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Kinetic Resolution of Cyclic Amines and Automated Synthesis of N-Heterocycles

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presented by

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Abstract

N-Heterocycles are highly prevalent compounds featured in all areas of chemistry. In the development of new pharmaceuticals, these scaffolds are becoming more and more desirable. Of all small molecule drugs approved by the United States Food and Drug Administration, 59% contain at least one N-heterocyclic structure.

Their preparation still remains challenging. To address this issue the Bode group has developed technologies for the preparation of N-heterocycles and to obtain these in their enantiomeric forms. First, the Stannyl (**Sn**) **A**mine **P**rotocol (SnAP) allows rapid access, in one-pot, to saturated N-heterocycles. These products vary in ring size and are prepared from commercially accessible, stable SnAP reagents and a variety of structurally diverse aldehydes. Second, a kinetic resolution protocol was developed based on an achiral N-heterocyclic carbene and a chiral hydroxamic acid co-catalyst. This enables the separation of racemic mixture of secondary cyclic amines and can provide enantioenriched N-heterocycles with high selectivities (s up to 127). In this dissertation future developments of these two methods are discussed.

In Chapter 2, we disclose efforts towards identifying a new chiral hydroxamic acid co-catalyst to further enhance selectivities for the kinetic resolution. Furthermore, the effect of the substitution patterns of disubstituted piperidines in the kinetic resolution is also described, where practical selectivity factors (s up to 52) can be obtained (Chapter 3). Detailed experimental and computational studies of the kinetic resolution of various disubstituted piperidines uncovered an unexpected and pronounced conformational effect resulting in disparate reactivity and selectivity between the *cis*- and *trans*-substituted piperidine isomers. This work provides further support for the concerted 7-member transition state model for acyl transfer reagents and expands the substrate scope and functional group tolerance of the kinetic resolution of secondary amines.

Chapter 4 outlines the work conducted at the interface of chemistry, engineering and computer science to create and develop a fully automatic synthesizer for the generation of N-heterocycle compounds on the basis of novel polymer supported SnAP reagents. This enables non-specialized researchers to conduct “SnAP chemistry” without any drawbacks. The machine utilizes disposable cartridges containing the all reagents and requires no user involvement for the rapid access to *N*-unprotected N-heterocycles, in a fully automated fashion, with no exposure to toxic reagents. Initial tests of an assembled prototype are encouraging and future commercialization of this technology is planned.

Zusammenfassung

N-Heterocyclische Verbindungen sind weit verbreitet in allen Bereichen der Chemie. Für die Entwicklung neuer Arzneimittel gewinnen diese Strukturen vermehrt Bedeutung. Von allen von der „United States Food and Drug Administration“ zugelassenen Arzneistoffe mit geringem Molekulargewicht enthalten 59% mindestens eine N-heterocyclische Struktur.

Allerdings ist deren Herstellung nach wie vor eine Herausforderung. Die Bode Gruppe hat sich dieser Herrausforderun angenommen und Technologien für die Synthese von N-Heterocyclen entwickelt und außerdem diese als reine Enantiomere zu erhalten. Das „Stannyl (**Sn**) **A**mine **P**rotokoll“ (SNAP) erlaubt den schnellen Zugang zu gesättigte N-Heterocyclen. Die Produkte variieren in Ringgröße und können aus den kommerziell erhältlichen, stabilen SnAP Reagenzien und einer Vielzahl von strukturell unterschiedlichen Aldehyden in einem Schritt hergestellt werden. Außerdem wurde die kinetische Racematspaltung von Aminen entwickelt auf der Grundlage eines N-heterocyclischen Carbens und eines chiralen Hydroxamsäure Co-katalysators. Dadurch wird die Trennung von Razematen von sekundären cyclischen Aminen ermöglicht und liefert deren reine Enantiomere mit hohen Selektivitäten (s bis zu 127). In dieser Dissertation werden unter anderem weitere Entwicklungen dieser beiden Methoden diskutiert.

In Kapitel 2, legen wir Anstrengungen zur Identifizierung eines neuen chiralen Hydroxamsäure co-Katalysators dar um verbesserte Selektivitäten in der kinetische Racematspaltung zu erhalten. Darüber hinaus wurde der Effekt unterschiedlicher Substitutionsmuster von disubstituierten Piperidinen in der kinetischen Racematspaltung untersucht und wertvolle Selektivitäten (s bis zu 52) (Kapitel 3) wurden beobachtet. Detaillierte Experimente und Berechnungen der kinetischen Racematspaltung ergaben eine unerwartete und ausgeprägte Wirkung der unterschiedlichen Konformationen von *cis*- und *trans*-substituierten Piperidinen auf Reaktivität und Selektivität. Unsere Untersuchungen liefern weitere Belege für den konzertierten 7-gliedrigen Übergangszustand von Acyltransfer Reagenzien und erweitern die Bandbreite und Toleranz funktioneller Gruppen in der kinetischen Racematspaltung von sekundären Aminen.

Kapitel 4 beschreibt ein Projekt an der Schnittstelle von Chemie, Ingenieurwissenschaften und Informatik für die Entwicklung eines vollautomatisierten Synthesizers zur Herstellung von N-Heterozyklischen Verbindungen auf der Basis neuer immobilisierter SnAP Reagenzien. Dies ermöglicht nicht-spezialisierten Forschern "SnAP Chemie" ohne Schwierigkeiten durchzuführen. Der Automat nutzt Kartuschen, die alle Reagenzien enthalten, und erfordert keine menschliche Beteiligung um den schnellen Zugang zu *N*-ungeschützten N-Heterozyklen ohne Kontakt zu toxischen Reagenzien zu gewährleisten. Erste Tests mit einem Prototyp zeigen derart vielversprechende Ergebnisse, dass von einer Vermarktung dieser Technologie in naher Zukunft auszugehen ist.

Acknowledgements

I would like to thank Prof. Dr. Jeffrey Bode for accepting me into his group and allowing me to take part in fantastic research projects. It was a great experience since I visited the research group the first time in 2008 in Philadelphia. His input was always a valuable support and I looking forward to continuing this partnership on the next challenges.
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List of Publications and copyright permission notes

Hsieh, S.-Y.; Wanner, B.; Wheeler, P.; Beauchemin, A. M.; Rovis, T.; Bode J. W.: Stereoelectronic Basis for the Kinetic Resolution of N-Heterocycles with Chiral Acylating Reagents. *Chem. Eur. J.* **2014**, *20*, 7228–7231.

Bode, J. W.; Wanner, B.; Chen, K.-Y.; Pattabiraman, V.; Nichols, P. L. (ETH Zürich). Apparatus and process for the automated chemical synthesis of compounds. European Patent EP16150878.3, submitted: January 12, 2016.

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Wanner, B.; Kreituss, I.; Gutierrez, O.; Kozlowski, M. C.; Bode, J. W.: Catalytic Kinetic Resolution of Disubstituted Piperidines by Enantioselective Acylation: Synthetic Utility and Mechanistic Insights. *J. Am. Chem. Soc.* **2015**, *137*, 11491–11497.

Symbols and abbreviations

$[\alpha]_D$	specific optical rotation at wavelength of sodium D line
δ	chemical shift
ν	wave number
Ac	acetyl
aq	aqueous
Ar	aryl
Boc	*tert*-butoxycarbonyl
Bn	benzyl
br	broad (NMR)
Bz	benzoyl
Cbz	carboxybenzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DMAP	4-(dimethylamino)-pyridin
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
E	*entgegen* (olefin geometry)
ee	enantiomeric excess
equiv	equivalent
er	enantiomeric ratio
Et	ethyl
Fmoc	fluorenylmethyloxycarbonyl
HPLC	high performance liquid chromatography
HFIP	Hexafluorisopropanol
i	iso
IR	infra-red
J	coupling constant
m	multiplet (NMR), milli
m	meta
M	molarity (mol/L)
MALDI	matrix-assisted laser desorption/ionization
Me	methyl

MS	mass spectrometry (or molecular sieves)
m/z	mass to charge ratio
NEt_3	triethylamine
NMR	nuclear magnetic resonance
o	ortho
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
i-Pr	*iso*-propyl
R	general substituent
R	*rectus* (configuration)
RMesCl	(2,4,6-trimethylphenyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c] [1,2,4]triazol-4-ylium perchlorate
rt	room temperature
s	selectivity (or singlet)
S	*sinister* (configuration)
SFC	supercritical fluid chromatography
t	triplet
TBS	*tert*-butyldimethylsilyl
TFA	trifluoracetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N,N,N'N'*-tetramethylethylenediamine
Ts	*p*-toluenesulfonyl or *p*-toluenesulfonic
t_R	retention time
UV	ultraviolet
Z	*zusammen* (olefin geometry)

1

Introduction

CHAPTER 1. Introduction

1.1 Introductory Remarks

A heterocycle is defined as a cyclic structure with at least two different elements contained within the ring. The most predominant heterocycles in organic chemistry and biological systems are carbon-based heterocycles, five- and six-membered systems, such as pyrrolidine and piperidine. Also prominent are structures containing two heteroatoms within the carbocyclic ring, such as morpholines, thiomorpholines and piperazines (Figure 1).

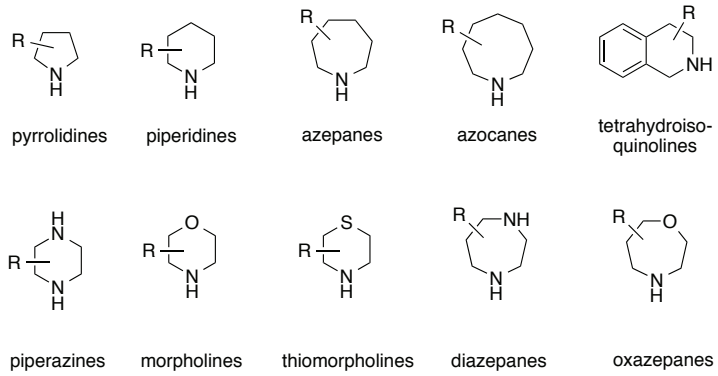


Figure 1. Common saturated N-heterocycles.

Nitrogen heterocyclic structures are increasingly desirable scaffolds for drug discovery.[1] In recent years a trend could be observed in the development of new drugs, by moving away from aromatic motifs as key structural elements. It has been suggested that a high aromatic-ring count in new drug candidates often leads to problems, such as poor pharmacokinetics and solubility.[2] The advantages of incorporating one or more saturated N-heterocycles into a drug include solubilizing features, such as ionizable moieties, and access to greater chemical space while remaining low in molecular weight. The precise placement of substituents on the ring, including chiral elements, offers highly diverse, three-dimensional entities that are ideally suited for structure-activity relationship studies. Figure 2 shows examples of a variety of drugs based on these structural entities. In 2010, the top 200 prescription list of drugs featured 11 pyrrolidine and 22 piperidine derivatives, including bicyclic species.[3]

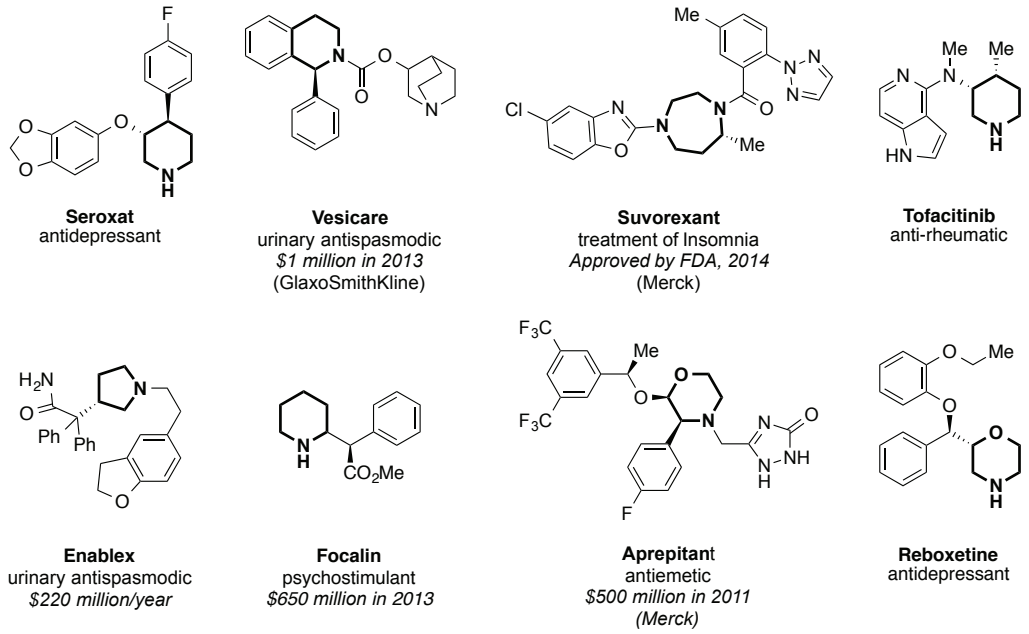


Figure 2. Examples of drugs containing N-heterocycles.

1.2 Saturated N-Heterocycle Synthesis

The synthesis of saturated N-heterocycles received much attention within the last years, yet their construction still remains a challenge.[4] While access to aromatic heterocycles is well established, the supply of saturated N-heterocyclic frameworks is quite limited. Unlike their aromatic counterparts, saturated N-heterocycles cannot yet be easily derivatized by cross-coupling reactions yet. Strategies for facile construction of substituted saturated N-heterocycles are consequently in demand. Methods developed to this date can be generally divided into four classes (Figure 3).

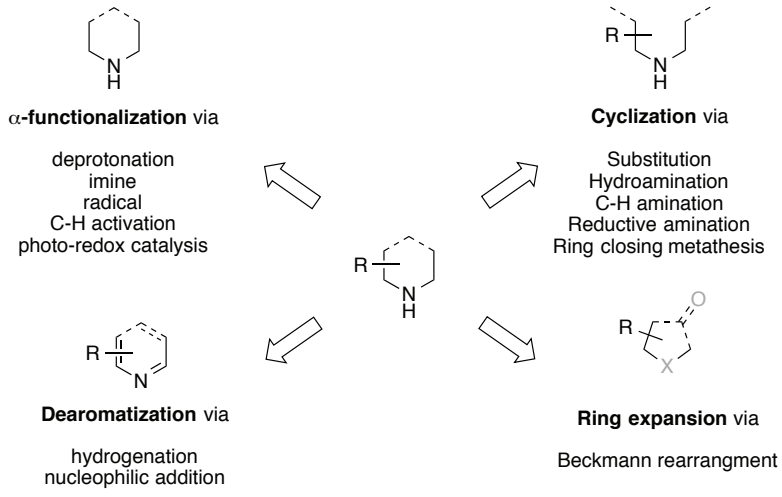
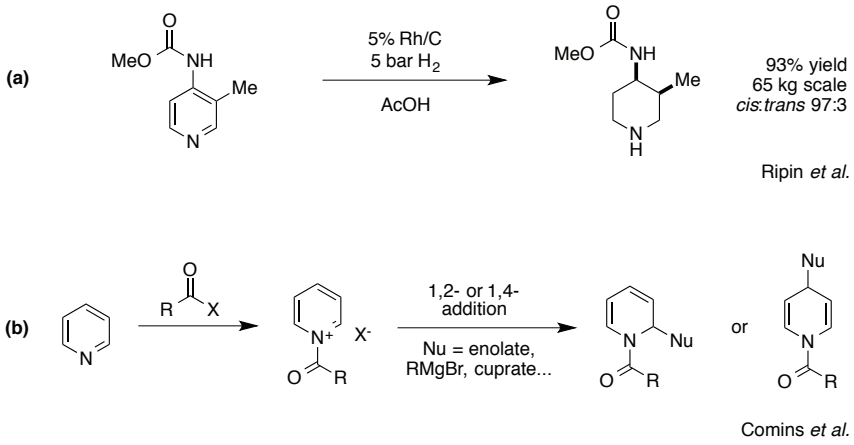


Figure 3. The four main methods to generate N-heterocycles.

1.2.1 Saturated N-Heterocycles by Dearomatization

The two most popular methods for the generation of N-heterocycles are dearomatization and α–functionalization. The first approach, dearomatization, is very popular for the synthesis of piperidines, tetrahydroquinolines and tetrahydroisoquinolines and many of the corresponding aromatic precursors are widely available.[5] Direct hydrogenation of pyridines usually proceeds via a clean transformation leading to little or no byproducts and is popular for production on an industrial scale using various transition metal catalysts (e.g. Pd/C, PtO_2, Rh/Al_2O_3) and hydrogen gas in a pressured reactor. With the use of acidic solvents, like acetic acid, protonated substrates can be hydrogenated more easily and catalyst poisoning by the amine product can be avoided. For these kind of heterogeneous reactions mainly the *cis*-product is obtained. An example shows the preparation of disubstituted piperidines from the corresponding pyridine, which was done on kilogram scale (Scheme 1a).[6]

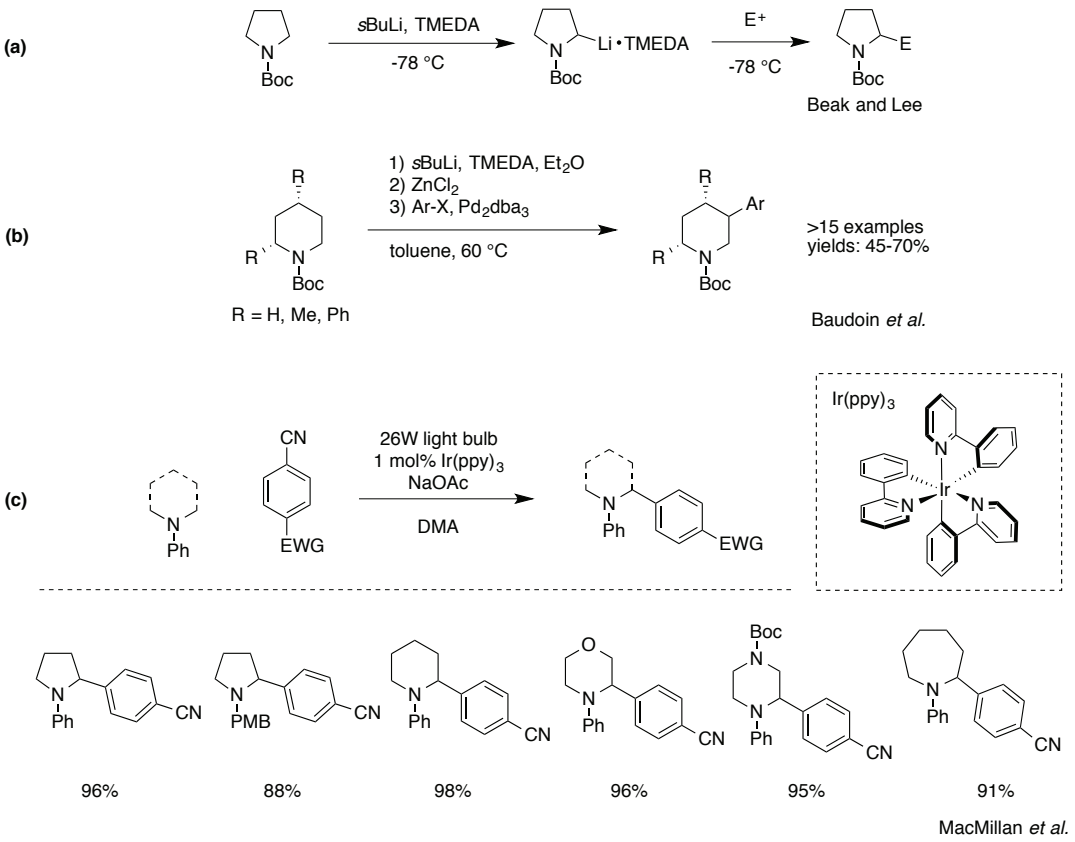


Scheme 1. Examples of N-heterocycle synthesis via dearomatization approaches.

Another example of a dearomatization approach was pioneered by Comins *et al.,* where functionalities were introduced into an existing pyridine ring by acylating the pyridine. With this method the aromatic character is lowered and an acyl pyridinium ion can be formed. Upon reaction with a nucleophile (enolate, Grignard reagent, organo-cuprate etc.) a partially saturated pyridine is formed and further functionalization is possible. The regioselectivity of this reaction, 1,2- vs. 1,4-addition, was examined and found to depend on the structures of the nucleophile and the identity of the acyl group (Scheme 1b). This scalable method was demonstrated in a variety of natural product syntheses.[7] Unfortunately, neither of these methods can provide access to morpholines or azepanes since the corresponding aromatic starting materials do not exist.

1.2.2 Saturated N-Heterocycles by Direct α-Functionalization

The direct α-functionalization strategy of saturated N-heterocycles has received far more attention.[8] This method allows access to a variety of functionalization of N-heterocycles (Scheme 2).



Scheme 2. Examples of N-heterocycle synthesis via direct functionalization approaches.

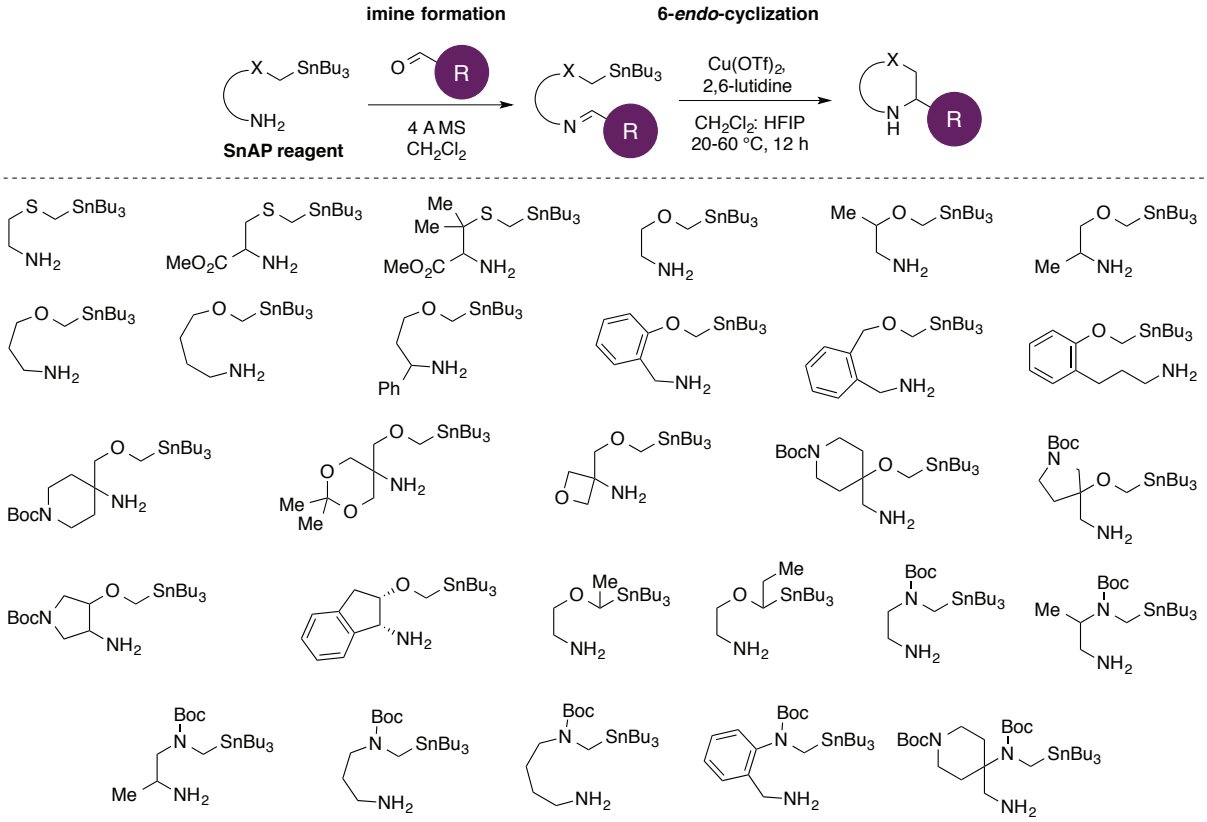
In the first report from Beak and Lee in 1989, pyrrolidines were α-lithiated using alkyllithium/diamine complexes, followed by quenching with an electrophile. In the following years extensive work expanded the scope of this method. Baudoin demonstrated a cross-coupling version utilizing α-lithiated *N*-Boc-piperidines followed by transmetallation, to provide substituted β-aryl-piperidines with good yields (45-70%).[9] A similar strategy was reported by the research group of Fu describing Negishi cross-couplings of racemic α-zincated *N*-Boc-pyrrolidine with unactivated secondary halides to generate enantiomerically enriched 2-alkylpyrrolidines.[10]

In a recent report, MacMillan describes a photoredox Ir-catalyzed C-H arylation reaction for the synthesis of *N*-aryl protected α-aryl-pyrrolidines, -piperidines, -morpholines, and -azepanes. A variety of electron deficient cyano-arenes are used as reagents to produce a large number of functionalized N-heterocycles in very high yields.[11]

The major drawback of these strategies is the use of nitrogen-protected substrates, which remain in the product and are generally difficult to remove later on. In addition the conditions required for the transformation are often harsh and would not be suitable for library synthesis. For example, the use of the α–lithiation/Negishi strategy in a library would require a laborious deprotonation at -78°C followed transmetallation followed by functionalization. A reliable, robust and easy method for the preparation of substituted saturated N-heterocycles would bring these exotic building blocks into the mainstream. [12]

1.2.3 SnAP Chemistry

In 2013 the Bode group reported a new technology that addresses the issue of the synthesis of substituted saturated N-heterocycles. The so-called SnAP (Stannyl (**Sn**)) **A**mine **P**rotocol) reaction provides a cross-coupling approach for substituted nitrogen heterocycles (Scheme 3). This technology gives rapid access to *N*-unprotected building blocks suitable for further functionalization.

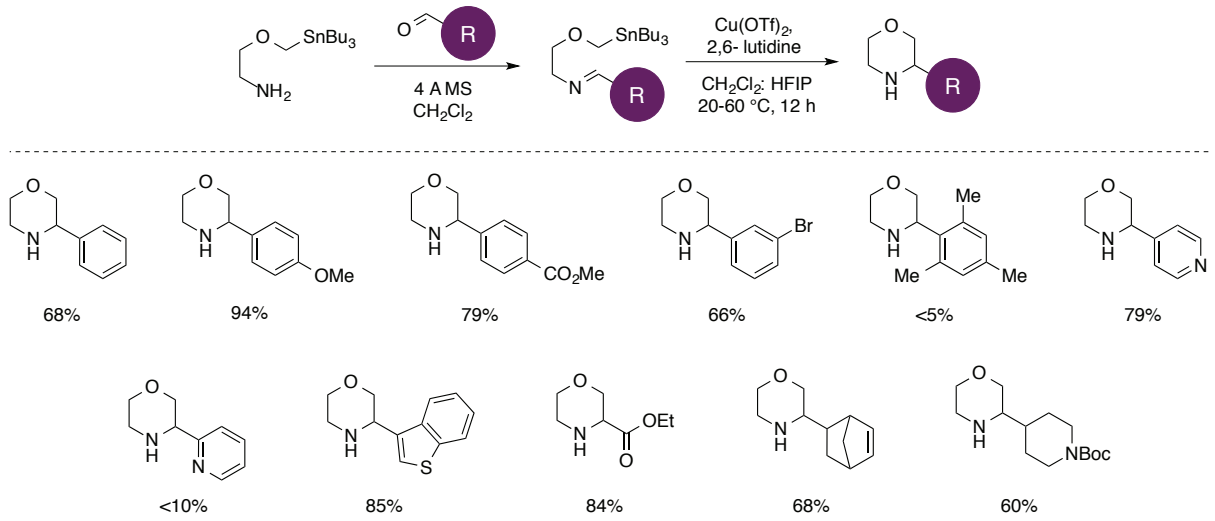


Scheme 3. Synthesis of N-heterocycles with SnAP reagents. At least 28 SnAP reagents have been prepared.

The SnAP reagent is first condensed with a carbonyl compound (widely available aliphatic, aromatic and heteroaromatic aldehydes/ketones) to generate an imine. Cyclization of the imine is induced by the presence of Cu(II) and lutidine to provide the unprotected N-heterocyclic product. The first report of this SnAP method was demonstrated for the synthesis of thiomorpholines.[13] Continuous efforts expanded the range of possible products to many other N-heterocycles, including morpholines and piperazines[14] in a variety of different ring sizes,[15] including more complex reagents for spirocycle and bicycle synthesis.[16]

To date, as many as 28 SnAP reagents have been synthesized (Scheme 3), with 12 of these reagents commercialized so far and the initial sales show a high interest in these kinds of reagents. The synthesis of these air and moisture stable reagents can be carried out on multigram scale by employing a straightforward synthetic sequence. The starting materials are inexpensive and readily available, the (protected) diamines or aminoalcohols (depending on the desired substitution pattern) are alkylated with Bu_3SnCH_2I to provide the desired SnAP reagent.

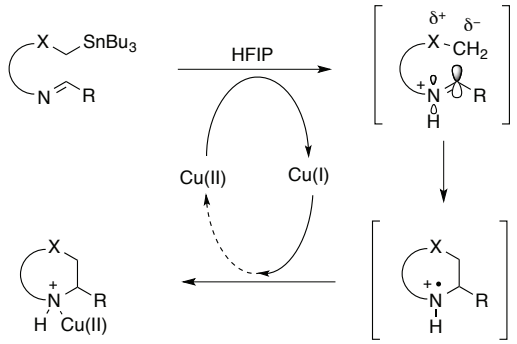
The scope of SnAP morpholine is shown in Scheme 4. The reaction is tolerant to a wide variety of functional groups and compatible with a broad range of aldehydes including aromatic, heteroaromatic and aliphatic ones to generate N-heterocycles in high yields. However, the product from bulky aldehydes or Cu(II) chelating aldehydes can only obtained in very low yields.



Scheme 4. The scope of the SnAP reaction with the SnAP morpholine reagent and variety of aldehydes.

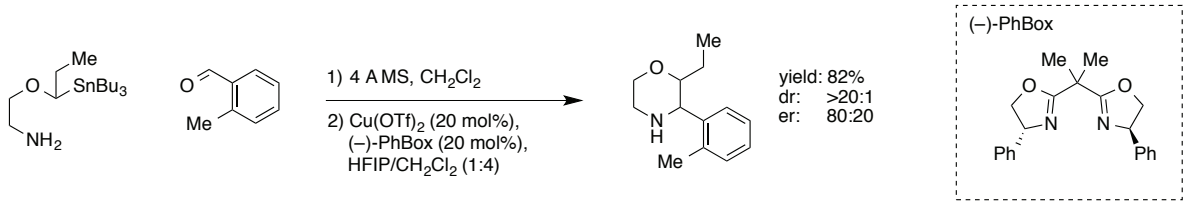
In further studies the methodology was expanded to couple ketones together with SnAP reagents to the corresponding spirocyclic nitrogen heterocycles.[17]

Mechanistic investigations speculate a Cu(II)-mediated 1-electron oxidation of the carbon-tin bond (Scheme 5). The carbon-centered radical of the SnAP reagents undergoes cyclization to form the cyclic product. Substrate inhibition is thought to make this process stoichiometric in copper. However, recent efforts within the group have rendered this process catalytic. [18]



Scheme 5. Proposed catalytic cycle of the cyclization step.

An enantioselective variant of the SnAP cyclization was attempted with the use of chiral ligands. However, the best ligand in the screening (–)PhBox could only generate low enantiomeric enrichment of 60% ee for a selected substrate (Scheme 6).



Scheme 6. Enantioselective variant of the SnAP chemistry.

1.3 Chiral Saturated N-Heterocycles

Due to the chiral nature of biomolecules, enantiomerically pure compounds are of great importance. An important consideration is the preparation of chiral N-heterocycles in their enantiomeric forms. Growing demand for these enantiomerically pure compounds are noticed for uses in pharmaceuticals, agricultural chemicals or in electronical and optical systems.

For obtaining enantiomerically pure compounds, the available methods can be sorted into three main categories (Figure 4):[19] 1) The desired enantiomerically pure compound can be synthesized from a chiral pool starting material with efforts to avoid racemization; 2)

Methods of stereoselective synthesis can be applied to prochiral substrates to induce a stereochemical outcome in order to obtain the desired enantiomerically pure compound; 3) starting from a racemate, it can be separated into the individual enantiomers using recrystallization or chromatographic techniques, widely used on industrial scale. The separation of enantiomers using chromatographic techniques can be found on anywhere from small to medium scale. Although chiral stationary phases are very expensive they allow separation with relatively little and fast optimization and can be reused for many cycles. Another powerful tool is kinetic resolution, which can be achieved by both chemical and enzymatic approaches.

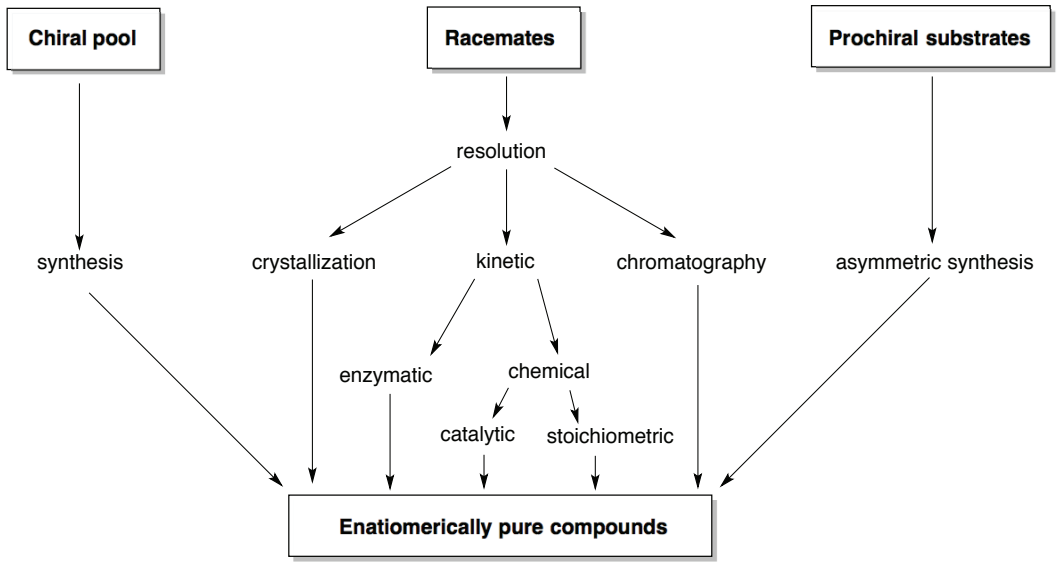


Figure 4. All general methods to obtain enantiomerically pure compounds.

For the preparation of substituted N-heterocycles, most of the available methods deliver racemic products and enantioselective preparation of the desired products is usually challenging, since many substitution patterns in enantioselective synthesis approaches are limited.[20,21] For such challenging cases, kinetic resolution can be an efficient and powerful alternative to the enantioselective synthesis of chiral N-heterocycles.[22]

1.4 Kinetic Resolution

1.4.1 Concept of Kinetic Resolution

Kinetic resolution[23] (Figure 5) is often a valuable alternative for preparing important chiral compounds.[24] Practical kinetic resolutions offer many advantages.[25] One needs to differentiate kinetic resolution with stoichiometric reagents from catalytic kinetic resolution

techniques. Many procedures based on non-enzymatic kinetic resolution using chiral stoichiometric reagents have been developed. However, catalytic variants offer several advantages over stoichiometric reagents. Low chiral catalyst loadings optimize atom economy aspects and cost factors since these compounds are typically expensive and difficult to prepare. High enantioselectivity and yields can be obtained to reliably deliver enantiopure materials.

In kinetic resolutions a chiral catalyst or chiral reagent is employed to react with an enantiomeric mixture that is difficult to separate. Ideally, only one enantiomer reacts towards the product. Due to the resulting different physical properties of the two products they can be separated easily with common methods.

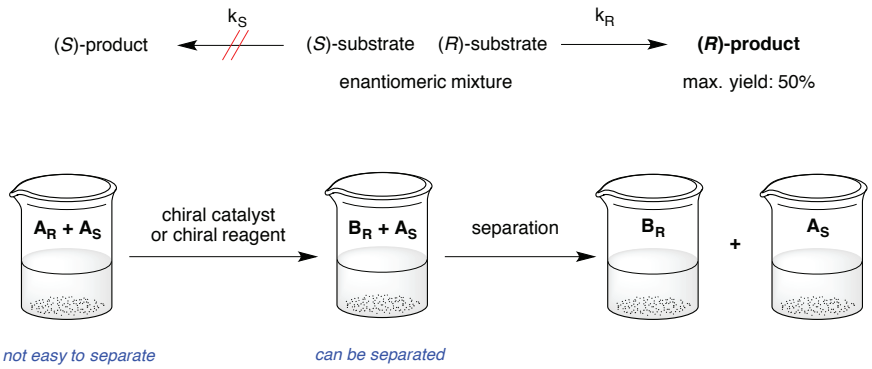
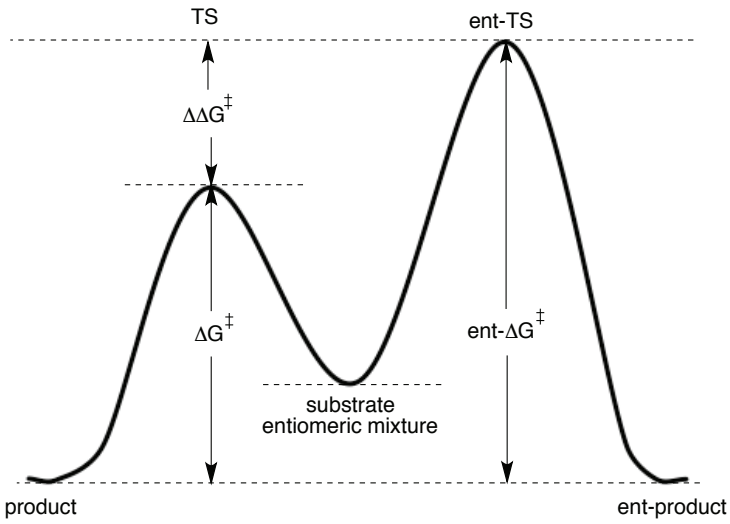


Figure 5. Concept of classical kinetic resolution.

The success of this method depends on the fact that the two enantiomers react at different rates with a chiral entity, so one of the two transition states is lower than the other one. The chiral entity can be present in catalytic or stoichiometric amounts; it may be a biocatalyst (enzyme or microorganism) or a chemo-catalyst (chiral acid or base or even a chiral metal complex).

Kinetic resolution occurs when the reaction rate of one enantiomer differs from the reaction rate of the other enantiomer ($k_R \neq k_S$) and the reaction is stopped somewhere between 0 and 100% conversion. Ideally, one enantiomer reacts much faster than the other; for example, if the reactant with the absolute configuration *R* is the only reacting enantiomer ($k_S = 0$). In this case, 50% conversion of the initial 50/50 mixture leads to a final mixture of 50% reactant (*S*) and 50% product (P).

The quality of the kinetic resolution is typically expressed with the selectivity s. It is calculated by the fraction of the rate constant for one enantiomer k_R by the rate constant for the other enantiomer k_S (Figure 6).



$$s = \frac{k_R}{k_S} = e^{\Delta\Delta G^{\ddagger}/RT}$$

Figure 6. Typical Energy diagram for a kinetic resolution reaction (left). Equation for the determination of the selectivity factor s (right).

The selectivity has an exponential relationship with the energetic difference of the two transition state $\Delta G^{\ddagger}$ and ent-$\Delta G^{\ddagger}$, typically referred to as $\Delta\Delta G^{\ddagger}$ and the temperature of the reaction. Table 1 shows that for $\Delta\Delta G^{\ddagger}$ values above 1.5 kcal/mol useful selectivities can be obtained. In many cases reducing the temperature can further boost the s-factor.

$\Delta\Delta G^{\ddagger}$ (kcal/mol)	Temperature (°C)	s
0.5	25	2
1.0	25	5
1.5	25	13
2.0	25	29
2.0	0	40

Table 1. Selectivities obtained at from different $\Delta\Delta G^{\ddagger}$ at various temperatures.

The enantiomeric ratios of the product and the recovered starting materials after the resolution are dependent on both the s-factor and the conversion (Figure 7). In an optimal kinetic resolution (high s-factors) enantiopure products can be obtained at 50% conversion. This represents as well the maximum possible yield in classical kinetic resolutions. Despite this disadvantage it can be a reliable, effective, and easily implemented tool for early stage applications for the production of enantiopure material.

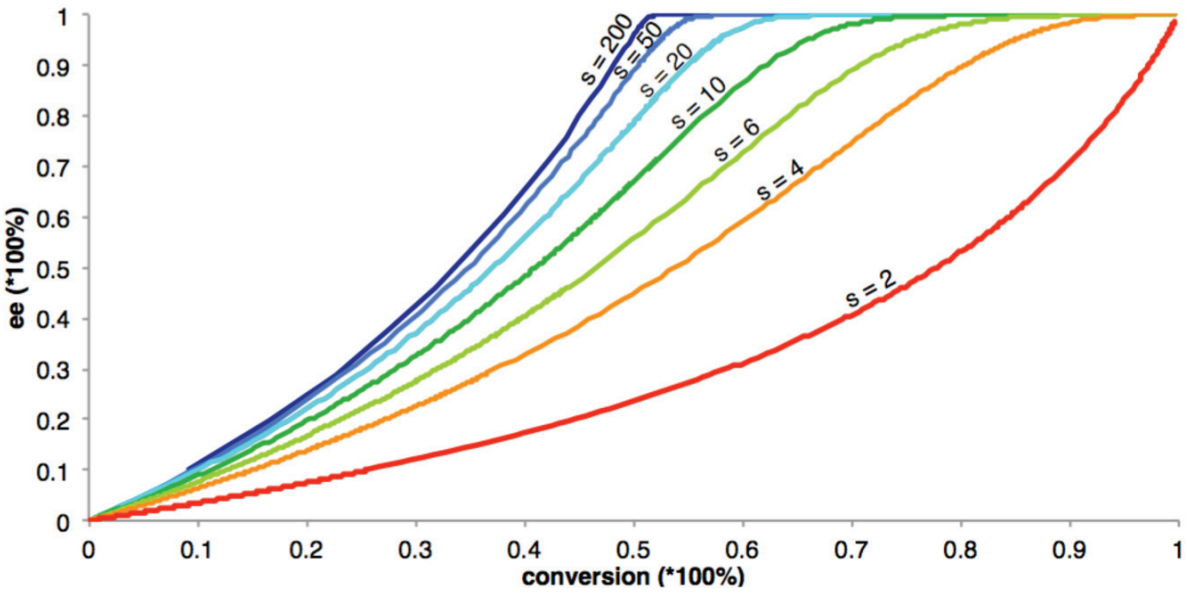


Figure 7. Progress of the enantiomeric excess obtained with the conversion at different selectivities.

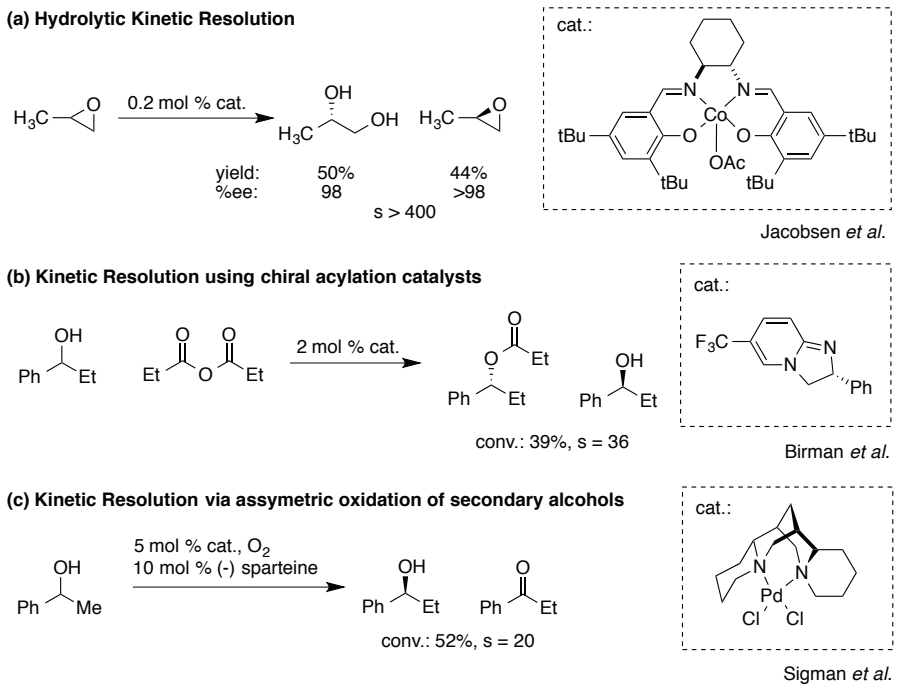
Generally any kinetic resolution with a reasonable selectivity (>20) can deliver 99% ee with in useful yields (Table 2). Because of the exponential relationship of the selectivity higher values will only enhance the reaction slightly. When having optimized a reaction to s > 50 no further optimization is necessary, as nearly perfect recovery of the pure enantiomer can be obtained. Provided that selectivity factors greater than 20 can be obtained, kinetic resolution can be used to separate enantiomers with acceptable yield and outstanding enantiopurity.[25,26]

s	conversion	yield recovered amine (max 50%)	% ee recovered amine
2	99%	1%	95%
10	65%	35%	95%
5	87%	13%	99%
10	72%	28%	99%
20	62%	38%	99%
50	55%	45%	99%
100	52%	48%	99%

Table 2. Selectivities and conversions needed to obtain high enantiomeric excess.

1.4.2 Successful Examples of Kinetic Resolution

Kinetic resolution has received much attention mainly for the resolution of alcohols, epoxides and carboxylic acids[27] with a multitude of approaches (Scheme 7). Three important non-enzymatic[28] examples include the kinetic resolution of the hydrolytic opening of epoxides developed by Jacobsen.[29] Terminal epoxides are key chiral building blocks and can be generated easily from racemic terminal epoxides with the method developed by Jacobsen and coworkers for the kinetic resolution of epoxides *via* nucleophilic ring opening with attack by an azide anion or water involving a cobald-salen complex. The nucleophile could effectively open the epoxide at the terminal position enantioselectively, with low catalyst loadings yielding enantiomerically enriched epoxide starting material and azido alcohols or diols. Yields are nearly quantitative and excellent ee's are obtained (>95% in nearly all cases).



Scheme 7. Examples of kinetic resolutions producing enantio-enriched alcohols.

Another example is presented by the kinetic resolution using a chiral acylation catalyst. Birman developed an effective method, where an anhydride reacts with the catalyst, which transfers the acyl group selectively on to one enantiomer of a racemic mixture of secondary alcohols.[30]

In a third example, Sigman reported a Pd(II)-catalyzed oxidative kinetic resolution of different secondary racemic aryl alcohols using (–)-sparteine as a chiral ligand to obtain a ketone and the enantio-enriched alcohol.[31] High selectivities of up to 20 could be obtained.

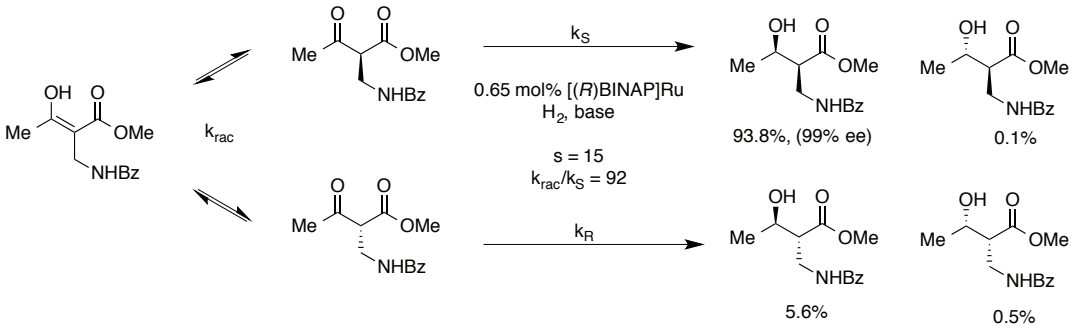
1.4.3 Dynamic Kinetic Resolution

The limitation of classical kinetic resolution to give only 50% yield can be overcome in several ways: 1) use of meso compounds or prochiral substrates,[32] 2) inversion of the stereochemistry of the unwanted, remaining enantiomer after initial classical resolution,[33] 3) recycling and racemization of the unwanted enantiomer 4) and the use of dynamic kinetic resolution.[34] In both classical and dynamic kinetic resolution (DKR), one enantiomer (e.g. (*R*)-substrate) is transformed to the product faster than the other enantiomer (e.g. (*S*)-substrate ($k_R > k_S$). The only difference is that in classical kinetic resolution one enantiomer is left behind as unreacted starting material, while in DKR the substrate is continuously isomerized during the resolution process. Because both enantiomers of the racemic mixture are in equilibrium it will not lead to a build up of the unwanted enantiomer.

If the rate of substrate racemization is significantly greater than the rate of formation of products ($k_{rac} \geq k_R$), and if the selectivity level is sufficient, dynamic resolution allows consequently the conversion of all starting materials into the product with the desired induction of stereochemistry. However, in order to be a practical method, it needs to fulfill certain requirements: in classical kinetic resolution even for low selectivities, highly enriched substrates can be recovered at higher conversions. In dynamic kinetic resolutions the enantio-enrichment cannot be controlled by the conversion and very high selectivities (s > 100) are necessary to obtain useful enantiomeric excess. An additional limitation in dynamic kinetic amine resolution is, that the substrate is typically *N*-functionalized in the course of the resolution. This group has to be removed again for the usage as chiral amine building block.

Figure 8. Concept of dynamic kinetic resolution.

The Noyori asymmetric hydrogenation of ketones constitutes an excellent example of dynamic kinetic resolution at work (Scheme 8).[35] The enantiomeric β-ketoesters can undergo epimerization by interconverting through their common enolic form, and the choice of the chiral [(*R*)-BINAP]Ru catalyst leads to one of the enantiomers reacting preferentially faster. The epimerization intermediate is lower in free energy than the transition states for hydrogenation, resulting in rapid racemization and high yields of a single enantiomer of the product.

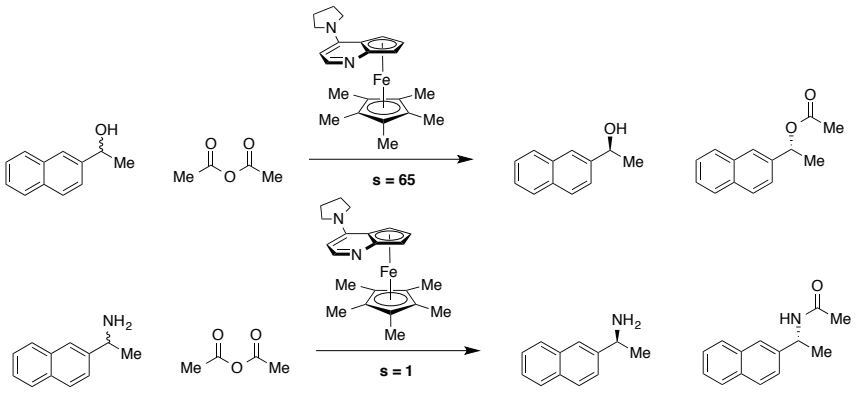


Scheme 8. Noyori's asymmetric hydrogenation; an example of dynamic kinetic resolution.

In another example for the synthesis of *O*-(α-bromoacyl) cyanohydrins Moberg solves the problem of the build up of the unwanted enantiomer by recycling it to regenerate the starting material, which can than participate in the kinetic resolution again. In the biphasic system the organic layer accommodates a chiral titanium catalyst, whereas the aqueous layer contains a lipase for the recycling. High yields and enantioselectivities are obtained (ee > 95%).[36]

1.5 Kinetic Resolution of Amines

Enantiomerically pure amines constitute an important class of building blocks for drugs discovery.[37] Compared to other important chiral compounds, such as alcohols and carboxylic acids, chiral amines are difficult to prepare.[38] The strategies of catalytic, enantioselective hydrogenations, reductions or oxidations, which have been broadly applied to these chiral compounds, are not generally useful in the preparation of chiral amines.

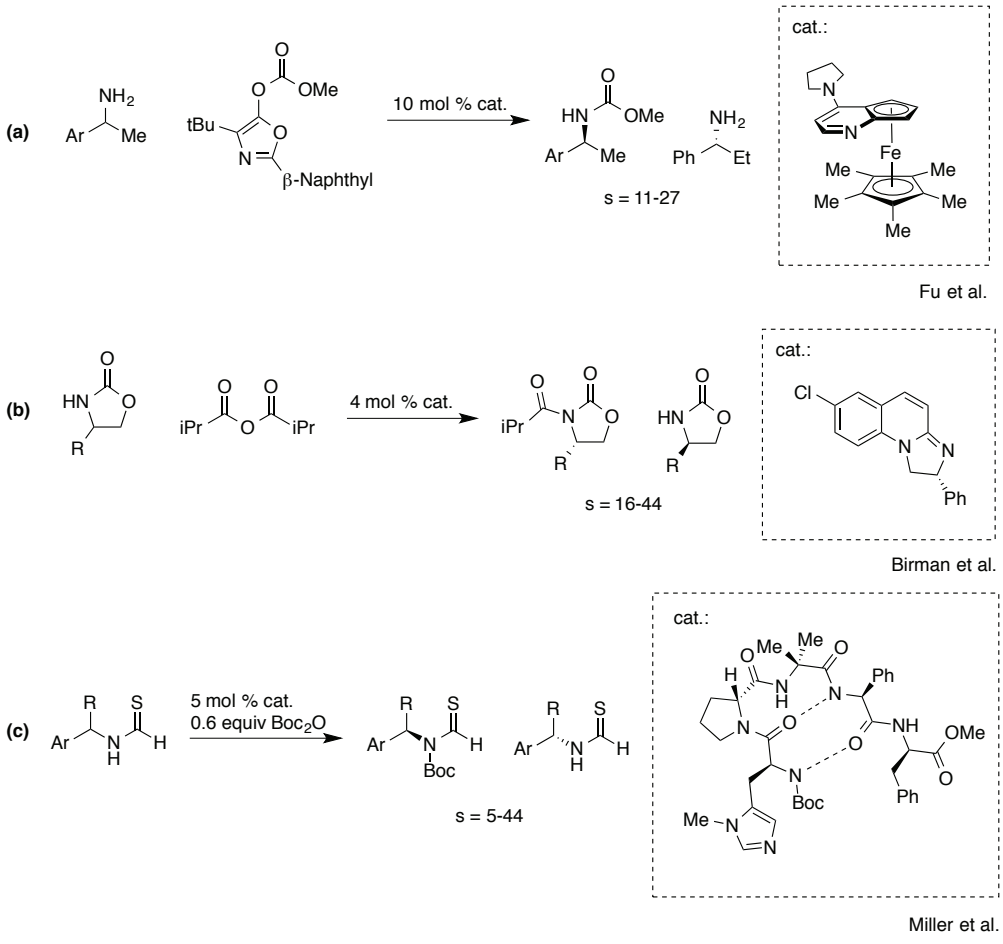


Scheme 9. Comparison of the kinetic resolution of alcohols and amines with a chiral DMAP-catalyst.

The main strategies used in industry used to obtain chiral amines are chromatography on a chiral support and classical resolution by formation of diastereomeric salts. The latter requires an intensive screening work to determine suitable counter-ions and

crystallization conditions (e.g. solvent, temperature, etc.); it is not guaranteed to successfully obtain the pure chiral amine.[39] Consequently these methods are not general.

Kinetic resolution of amines can provide a solution but catalytic nonenzymatic methodologies for the kinetic resolution of amines and their derivatives are much less developed than those of alcohols. Several challenges have to be mastered, since the resolution of amines is much more difficult than for alcohol substrates. The high reactivity of amines makes it difficult for the chiral reagent to discriminate between the two enantiomers to obtain reasonable selectivities. The increased background rate of the amine with the acyl carrier erodes the selectivity by reacting without any involvement of the chiral catalyst. Fu *et al.* had developed a kinetic resolution involving a chiral version of DMAP to successfully acylate and resolve a large number of secondary alcohols with high selectivities.[40] When changing the substrate to its amine analog only racemic product could be obtained (Scheme 9).[41]



Scheme 10. Examples for the kinetic resolution of amines.

Especially in catalytic kinetic resolution the background rate creates a challenge since the reaction rate of amines with simple derivatization agents (e.g., anhydrides) is competitive with catalytic rates, leading to low levels of selectivity. Therefore, many approaches to the kinetic resolution of amines involve stoichiometric amount of chiral acylating agents.[42] Effective catalytic methods for amine resolution using hindered acylation reagents have been reported by Fu.[43] Furthermore low-reactivity amines such as indolines or reduced-activity electrophiles (e.g., oxazolidinones[44] and thioformylamides have been resolved with excellent selectivities by Birman and Miller (Scheme 10). Alternatively, low reaction temperatures and extremely dilute condition can suppress the background acylation for kinetic resolution of primary amines by using standard acylating reagents and chiral co-catalysts. This strategy however cannot be applied to secondary amines, which fail to react under these conditions.[45]

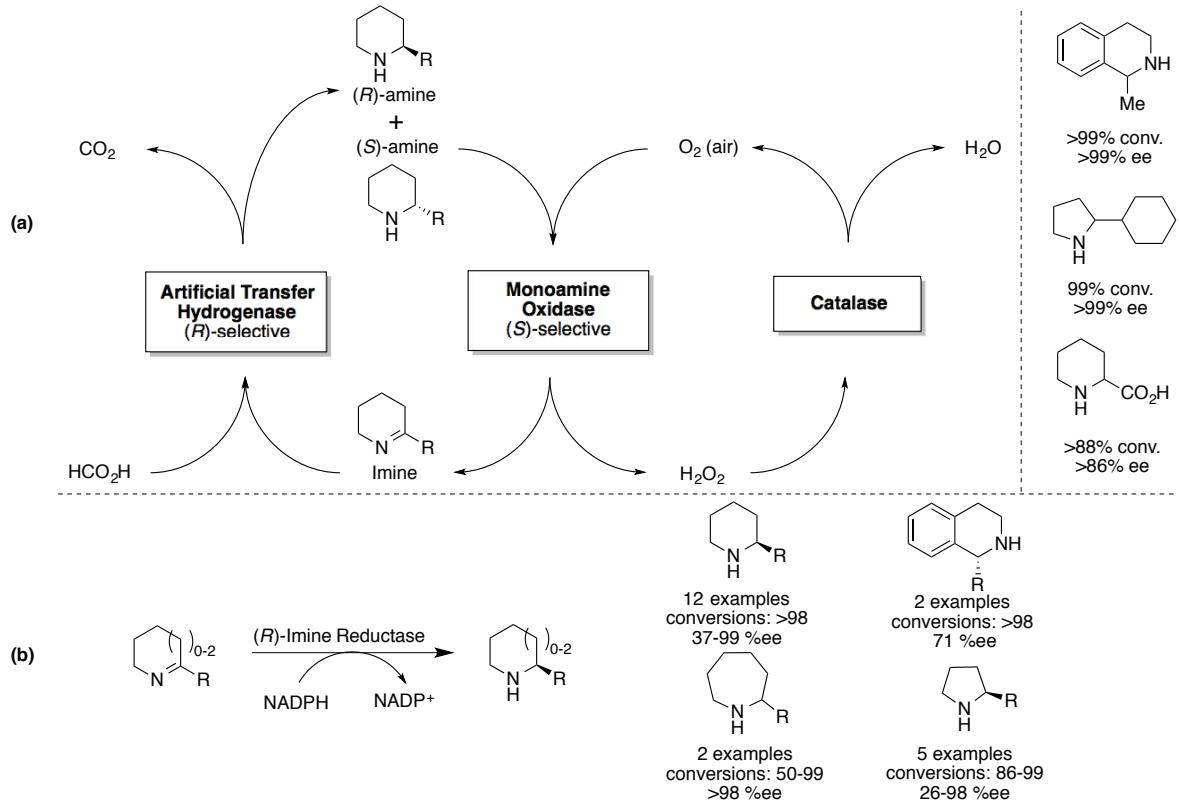
1.6 Enzymatic Kinetic Resolution

Kinetic resolution reactions utilizing purely synthetic reagents and catalysts are less common than the use of enzymatic kinetic resolution in application towards organic synthesis. Enzymes offer the advantage to be relatively low cost and to be highly selective. Lipases are frequently used for the kinetic resolution of alcohols and carboxylic acids.[46]

Enormous efforts on enzymatic deracemization of amines have been made in the Turner group. In the process they have reported a monoamine oxidase that selectively oxidizes only one enantiomer of a racemic amine mixture to successfully generate enantio-enriched secondary cyclic amine. Scheme 11a depicts an enzyme selectively oxidizing the *S*-enantiomer to the corresponding imine, which is subsequently reduced in situ by $NH_3 \bullet BH_3$ to the racemic amine. Repeated cycles eventually will lead to the accumulation of the *R*-enantiomer. By directed evolution screening they were able to obtain several variants of monoamine oxidases for the deracemization of primary, secondary and tertiary amines.[47] Furthermore, they combined this enzyme with an artificial metalloenzyme (transfer hydrogenase) to create a double stereoselective deracemization (Scheme 11b). The artificial enzyme reduces selectively the obtained imine to the *R*-enantiomer of the imine. By this process they can increase the efficiency of the catalytic cycle dramatically. A few examples, including cyclic secondary amines, were shown to give enantiopure products in very high yields.[48]

In their most recent version reported in 2015, the group developed an imine reductase selectively reducing only one enantiomer. A large substrate scope containing

mostly secondary cyclic amines was investigated and high enantioselectivity could be reached.[49]



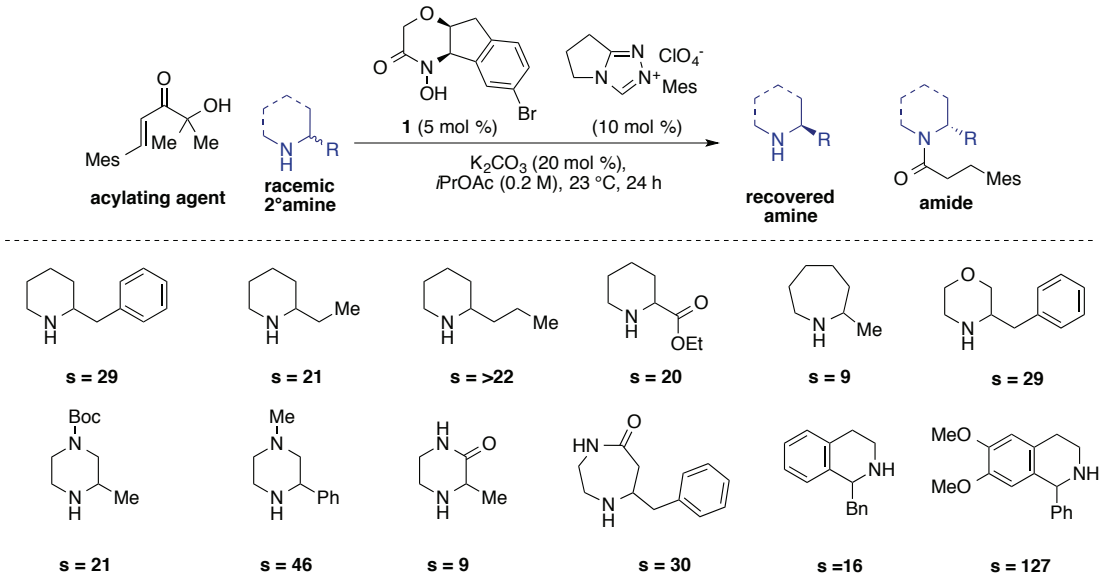
Scheme 11. Examples of the generating enantiomerically enriched amine by the Turner group via a desymmetrization.

Despite the very high selectivities obtained, this method is limited by its rather narrow substrate scope. Further directed evolution of the enzymes to expand the substrate scope typically requires extensive research and development. A method widely applicable to a large number of different cyclic secondary amines is desired.

1.7 Kinetic Resolution of Cyclic Secondary Amines

Important approaches, including enantioselective carbamate formation,[50] amide-formation,[51] deracemization[52] and dynamic kinetic resolution,[53] are mostly unsuccessful for the resolution of cyclic amines including piperidines, morpholines, and piperazines. To address this long-standing challenge, our research established a method for the catalytic kinetic resolution of cyclic amines before even any enzymatic method was known. In 2011, the Bode group published a powerful technique to obtain enantiopure cyclic secondary

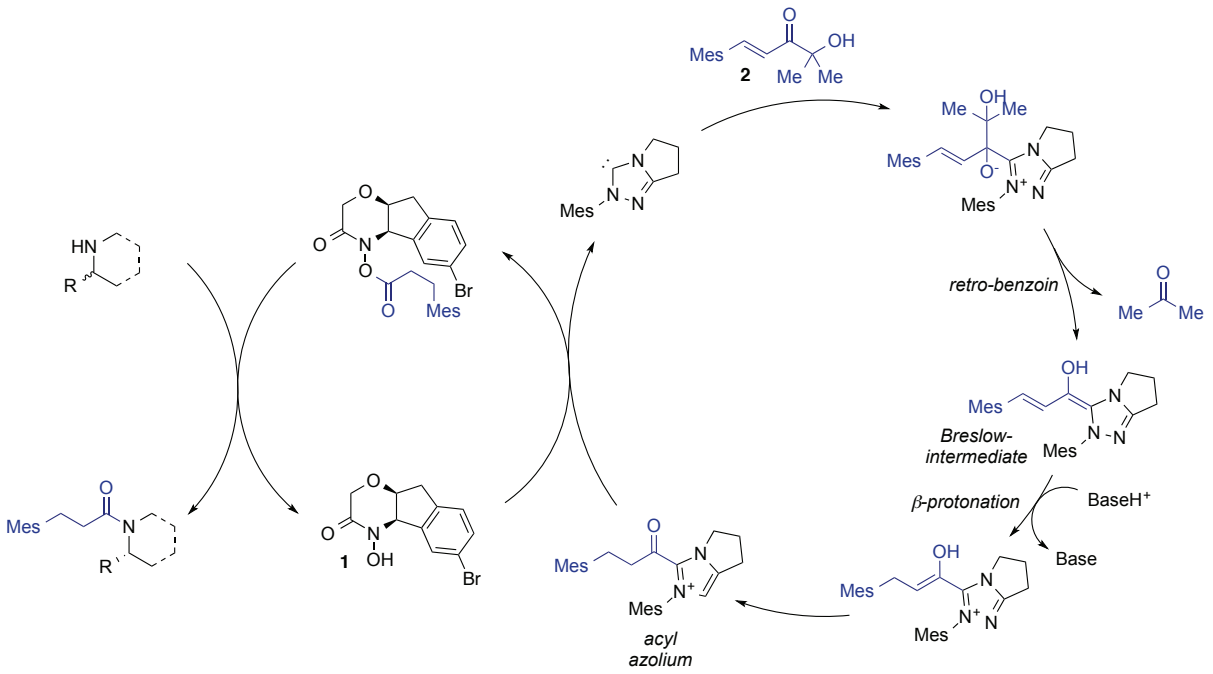
amines. The kinetic resolution of saturated N-heterocycles consists of two catalysts working synergistically.[54] Our key advance was the use of a chiral hydroxamic acid (**1**), employed in either catalytic or stoichiometric amounts, as highly enantio- and chemoselective acylating agent.



Scheme 12. Catalytic kinetic resolution of secondary cyclic alcohols.

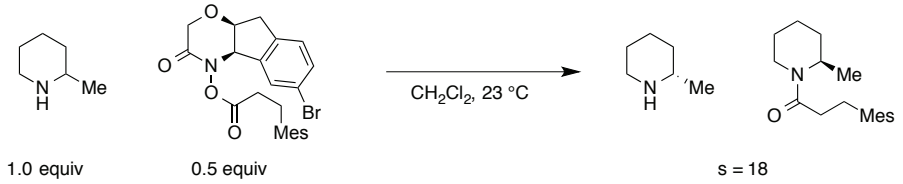
A wide array of substrates was investigated including piperidines, morpholines, piperazines, azepanes and tetrahydroisoquinolines. The enantiomerically enriched amines and amides were generated with high to very high selectivity factors (s up to 127).

The basis of this method is the catalytic amidation of amines using α-functionalized aldehydes or hydroxyenones.[55] This reaction relies on the combination of a catalytic N-heterocyclic carbene (NHC) and an essential co-catalyst like imidazole.[56] The key step is the generation of acyl azolium species as catalytically generated activated carboxylates.[57] These species undergo rapid acylation with water, alcohols, and thiols but not amines.[58] Upon addition of a co-catalyst, a secondary activated species that acylates the amine is generated. This suggested that the use of a chiral co-catalyst enables the kinetic resolution of amines by reacting with the acyl-azolium through the formation of a chiral amidation reagent. Chiral co-catalyst such as triazoles or imidazoles can generate the active species but display no enantioselectivity. A *cis*-(1*R*,2*S*)-aminoindanol-derived hydroxamic acid (**1**) has been demonstrated to be a competent co-catalyst for the kinetic resolution of racemic amines.[59] Notably both enantiomers of this co-catalyst are available. The opposite sense of induction of the amine can be obtained if the other enantiomer is used in the kinetic resolution.



Scheme 13. Proposed catalytic cycle of the kinetic resolution.

A catalytic cycle was proposed where the NHC-catalyst first attacks the α-hydroxyenone (**2**). Acetone is lost in a retro-benzoin reaction to generate the Breslow-intermediate. After β-protonation, the enol is formed, which rearranges to the acyl azolium. This intermediate transfers the acyl-group onto the chiral hydroxamic acid co-catalyst. In the last step, the acylated hydroxamate transfers the acyl group selectively to one enantiomer of the racemic amine mixture (Scheme 13).



Scheme 14. Acylated hydroxamic acid as stoichiometric reagent.

The acylated hydroxamic acid can be isolated and is stable for a long period. It can be prepared as well from the hydroxamic acid and another acylating reagent such as acid chloride or anhydride. This can be used as a stoichiometric reagent for the kinetic resolution, where equally high selectivities are obtained (Scheme 14).

Figure 9. 7-membered transition state of the chiral acylating agent and the secondary amine.

Detailed DFT calculations of the kinetic resolution of secondary amines have been reported in order to identify precise details of the reaction mechanism. These data revealed, that the reaction proceeds through a concerted acyl and proton transfer acyl transfer to the amine by aminolysis via a 7-membered transition state (Figure 9). More surprising was information about the reactive conformation of the piperidine substrate. Studies of 2-alkylpiperidine conformations have shown that the lowest energy conformation features an axial lone pair and equatorial substitution at the α-position. However, in the kinetic resolution the piperidine displays the α-substituent in the axial position for the lowest energy transition state.[60]

1.8 Conclusion

In this introduction two major issues have been highlighted. First, the need for a reliable and rapid method for the construction of substituted N-heterocyclic scaffolds, for their use in drug discovery and development. This problem was addressed with the development of the SnAP protocol developed by the Bode group. Chapter 4 in particular discusses our plans to revolutionize this SnAP technology.

Second, a method for the resolution of these cyclic amines into their enantiomeric counterparts is an additional and equally important challenge. Again, our efforts on the kinetic resolution of such cyclic amines aim to address this issue (described in Chapter 2 and 3).

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2

Design and Development of New Hydroxamic Acid Co-catalysts

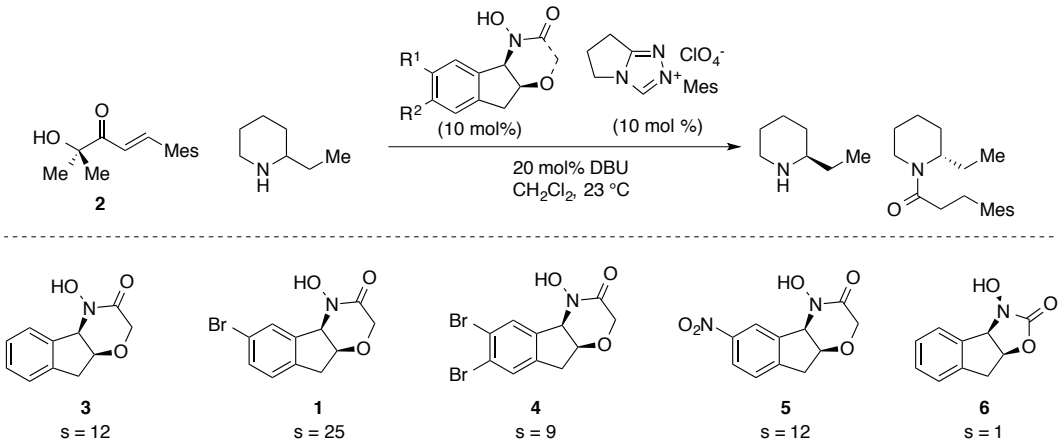
CHAPTER 2. Design and Development of New Hydroxamic Acid Co-Catalysts

2.1 Introductory Remarks

This chapter presents a study towards the discovery of a new hydroxamic acid co-catalyst for the catalytic kinetic resolution of cyclic secondary amines. A novel approach utilizing combinatorial chemistry provided rapid access to a new library of co-catalysts (>30 compounds), and their selectivity in the kinetic resolution of N-heterocycles was assessed.

2.2 Chiral Acyl-Transfer Co-Catalyst

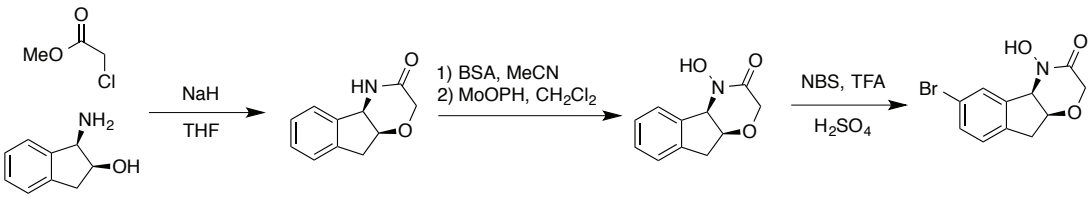
At the outset of our study only a limited number of co-catalysts had been examined. Structures based on an aminoindanol core showed promising results and five examples were synthesized and tested (Scheme 15).[61] These co-catalysts contained both 5- and 6-membered heterocyclic structures. Compound **1** displayed a significant improvement (s = 25) compared with the standard hydroxamic acid **3** (s = 12).



Scheme 15. Investigated hydroxamic acid co-catalyst based on aminoindanol.

Still a large number of N-heterocyclic substrates showed no acceptable selectivity or reactivity. A large screening for a suitable catalyst for a given substrate would result in an important insight in the mechanism of this reaction. If this goal would be reached, we could predict *a priori* which catalyst is most suitable for a given substrate, basically achieving a "custom-made" catalyst.

Unfortunately, to conduct a bigger study of optimization of the catalyst scaffold would be very laborious because of the linear synthetic path used for accessing these compounds (Scheme 16). The oxidation step was particularly challenging.



Scheme 16. Synthesis of the aminoindanol-based hydroxamic acid co-catalyst. (BSA = N,O-bis(trimethylsilyl)acetamide; MoOPH = MoO_5·Py·HMPA)

The synthesis requires introduction of the functional group modifications at the beginning of the synthetic sequence requiring many similar steps for preparing a larger number of catalysts. Also, variants of the aminoindanol-derived hydroxamic acids are difficult to prepare and are often expensive. Furthermore, the scaffold initially studied is very rigid and does not exhibit many sites for modifications. Therefore the aim of the project was to develop a more divergent and rapid approach to the synthesis of structurally diverse hydroxamic acid co-catalysts, preparing a large library in order to find a superior new co-catalyst.

For this study, several criteria had to be taken into consideration:

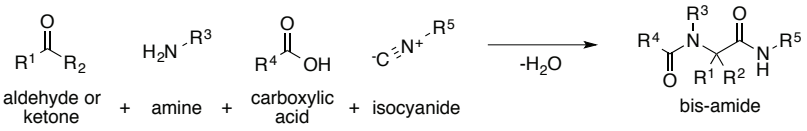
1) An enantioselective synthesis or chiral pool approach would have to be utilized to obtain the chiral hydroxamic acids. The latter proved to be the preferred approach, since high enantiopurity is required (>99% ee) and are typically more easily scaled up compared to enantioselective reactions;
2) The combinatorial synthetic approach must tolerate the use of a variety of functional groups e.g. aryl, aliphatic, heteroaromatic;
3) A more divergent synthesis towards the library must be achieved;
4) Complexity should be introduced late in the synthesis to minimize the total number of reactions.

2.3 Combinatorial Chemistry

The use of *combinatorial chemistry* has increased significantly in the last two decades as a way of rapidly creating tens of thousands of structurally diverse compounds. Especially utilized in pharmaceutical companies, with the help of automated robots used to prepare

huge libraries for compounds screenings.[62] This method allows to screen libraries in search of potential new drug candidates in months instead of years. The simple fact that these libraries can be created and screened in days makes this a very seductive approach for drug discovery.[63]

Particularly suitable in this area are multicomponent reactions.[64] One of the first examples was discovered in 1959, named after Ivar Karl Ugi, where 4 components (a carbonyl compound, an amine, a carboxylic acid and an isocyanate) react to form a bis-amide (Scheme 17).[65] Since then numerous attempts were made to utilize and combine this reaction with other types of reactions to create structurally diverse libraries. Prominent examples include the Ugi-Smiles-,[66] Ugi-Diels-Alder-,[67] and the Ugi-Heck-reaction.[68]



Scheme 17. The Ugi-Reaction.

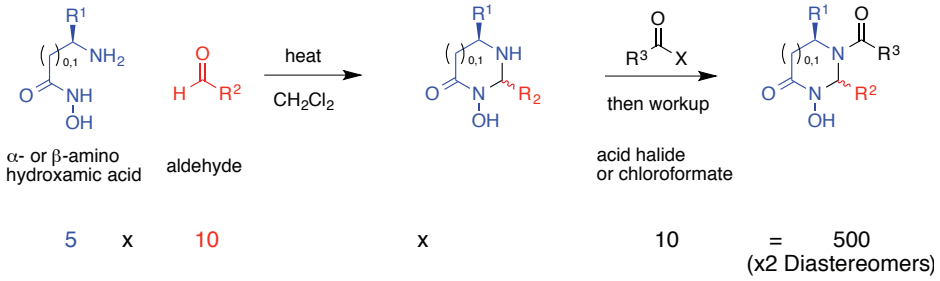
The beauty of this 4-component Ugi-reaction is, that the reagents can be permuted to form a wide range of structurally different compounds. For example, just by using five different starting materials of each component, the total number of 5^4 = 625 distinctive molecules can in theory be obtained.

This basic principle of combinatorial chemistry is being applied in many different ways. First, several compounds can be generated by permutation of the different starting materials in a single flask or several ones with a single product in each flask. This makes the separation and purification of the individual components much easier. Producing many compounds in a single flask requires more complicated purification methods or deconvolution approaches. Typically this is applied when only small amounts of compounds are synthesized.

The second consideration of this concept is whether to use solution phase or solid phase synthesis. Because of the resins and linkers required, solid phase synthesis is typically more expensive and due to the large molecular weight of the resin more suitable for smaller amounts of synthesized product. Therefore, solution phase synthesis is the method of choice for generating larger amounts of materials, although there are more difficulties associated with purification.

2.4 Design of Synthetic Strategy

Inspired by these approaches to structurally diverse compounds that could be obtained rapidly, we sought a combinatorial method for the generation of new hydroxamic acid co-catalysts. A wide range of available amino acids would serve as the chiral building blocks. Their derivatives (**blue**) can be condensed with aldehydes (**red**), and afterwards acyl donors to potentially generate a large library of catalysts (Scheme 18). The Vystorop research group showed that different variations of these N-heterocyclic compounds could be prepared.[69]

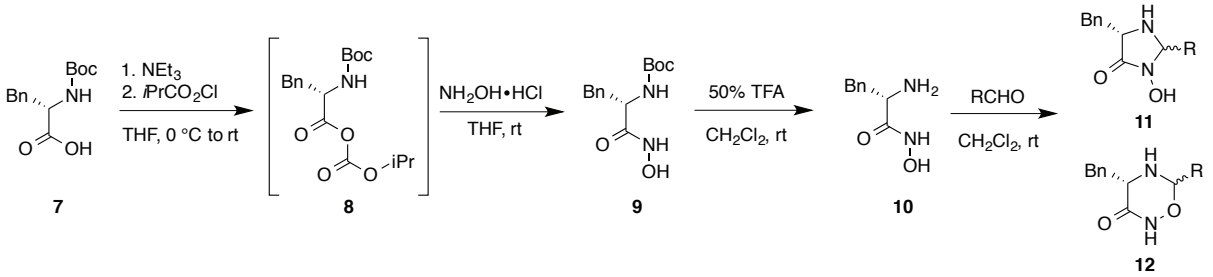


Scheme 18. Concept of the generation of a hydroxamic acid co-catalyst library.

Theoretically, using this approach and starting from five different amino hydroxamic acids, ten aldehydes, and ten acyl-donors a total number of 500 different catalysts could be generated with two diastereomers each.

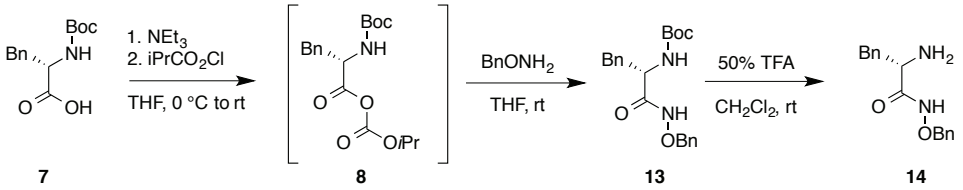
2.5 Development of the Synthetic Strategy

The first task was the development of a facile synthetic route for the preparation of chiral cyclic hydroxamic acids from commercially available amino acids. Accessing different heterocyclic ring sizes (5- or 6-membered) can be achieved using α- or β- amino acids. We began the study starting with inexpensive and commercially available Boc-protected amino acid Boc-L-phenylalanine (**7**).[70] Activation of the carboxylic acid to form the mixed anhydride **8** followed by the addition of hydroxylamine provided amide **9**. This material was treated with TFA to provide a free amine **10**, which could be condensed with aldehyde coupling partners, which cyclizes to provide the hydroxamic acid **11** (Scheme 19).[71]



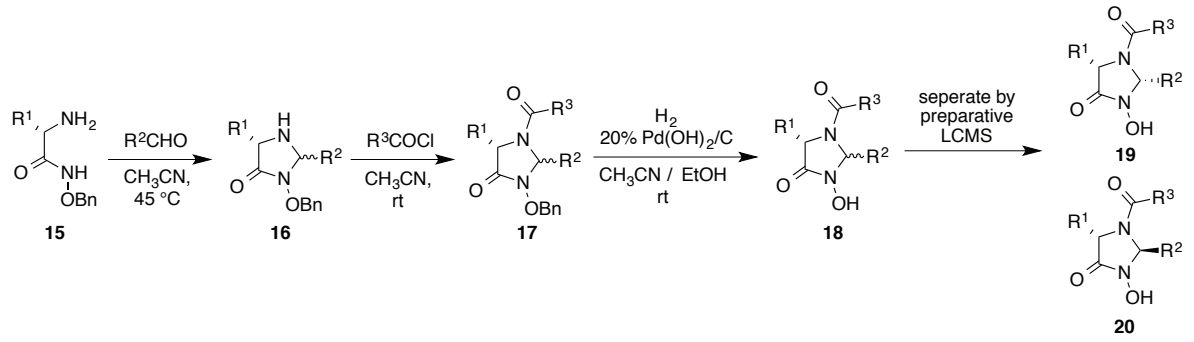
Scheme 19. First synthetic strategy for the synthesis of hydroxamic acids co-catalysts. The 6-membered side product is obtained as well.

However, this route was not without problems. The reaction of hydroxylamine with Boc-L-phenylalanine produced an insoluble product in low yields. The condensation of the hydroxamic acid **10** with aldehydes led to the desired kinetically favored five membered ring (aminal **11**) along with the thermodynamically favored six membered ring (hemiaminal **12**).



Scheme 20. Synthetic route towards the starting material backbone for the hydroxamic acid co-catalyst synthesis.

To overcome this problematic, competitive side reaction, *O*-benzyl-hydroxylamine was used to prepare the protected hydroxamic acid **14** (Scheme 20). This material readily formed the aminal **16** when coupled to an aldehyde in the presence of a base. Due to an equilibrium, the aminal proved to be configurationally unstable. By adding an acyl donor directly after the aminal formation the backward reaction is rendered impossible and the configuration is locked, forming the product in a mixture of two diastereomers **19** and **20** (Scheme 21). These were stereochemically stable over to whole period of investigation.



Scheme 21. Synthesis route to obtain both diastereomers of the hydroxamic acid co-catalyst.

This strategy was successfully applied to other amino acids, employing different aldehydes and acyl groups furnished access to a large variety of catalysts prepared in a combinatorial fashion. The diastereomeric mixtures could be separated using a preparative liquid chromatography mass spectrometer (LCMS). After full optimization of the sequence acetonitrile was chosen as solvent to simplify the compatibility with the preparative LCMS. The desired catalyst was obtained after hydrogenolysis of the benzyl group. The sequence to synthesize the catalyst could also be carried out in one-pot: after filtration the crude reaction mixture was directly injected into the LCMS for purification, providing diastereomerically pure products, by-passing an additional work-up step. In total over 30 compounds were prepared (Figure 10), most as separable mixtures of two diastereomers.

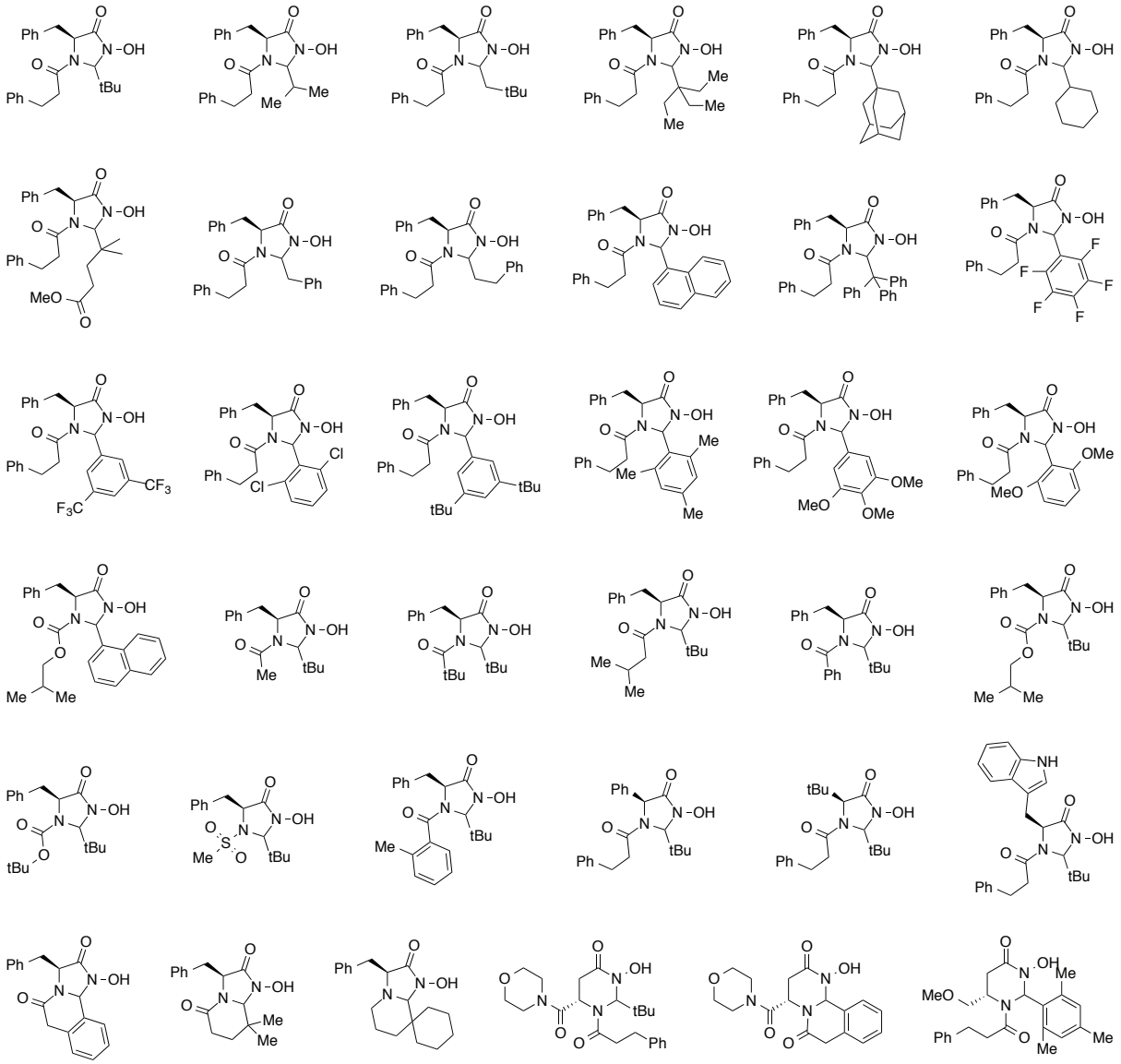


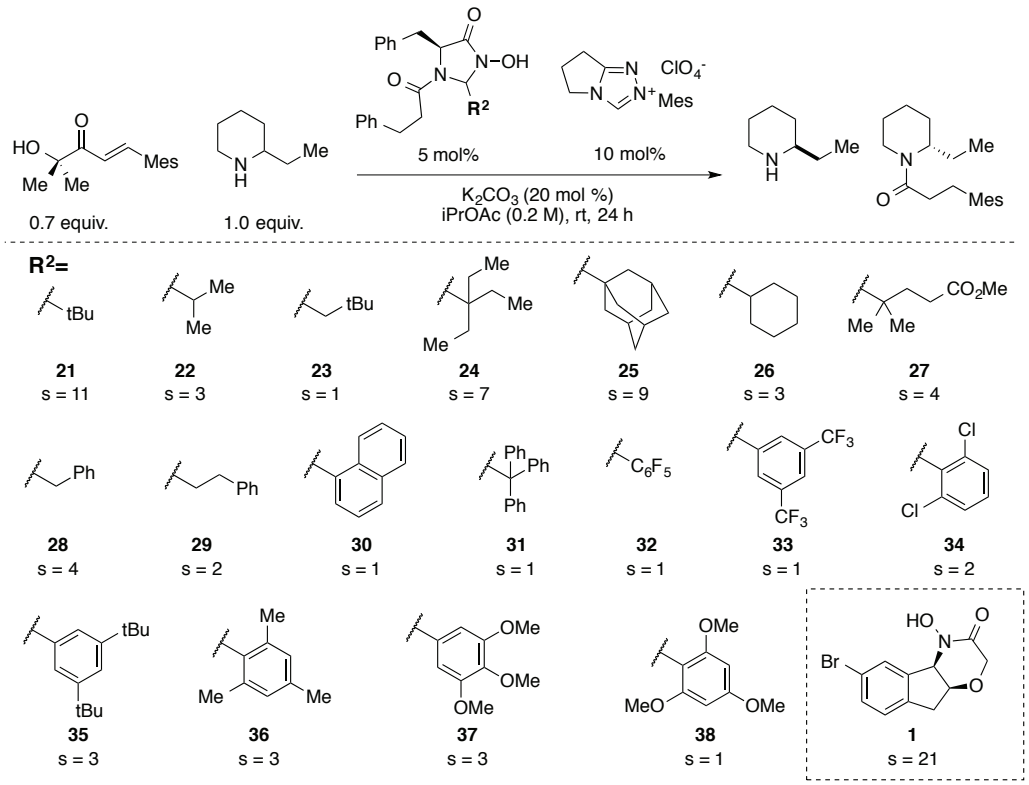
Figure 10. All hydroxamic acid co-catalysts prepared in this study.

2.6 Catalyst Library

For the screening of the new hydroxamic acid co-catalyst library, 2-ethyl-piperidine was chosen as a model substrate. This commercially available amine was used as a substrate in previous studies and offered reasonable selectivity but there was still room for improvement. Its relatively low polarity compared to other substrate made it easier to isolate the reaction products after the catalytic kinetic resolution protocol. Typically the reaction was complete within 24 h and the reaction quenched with CbzCl. The enantiomerically pure amine was isolated as the Cbz-protected product. For this initial screening we decided to screen one diastereomer of the catalyst out of the possible two, to get an indication of how the new catalysts perform in the kinetic resolution.

2.6.1 Effect of R^2 on the Selectivity

To compare the effect of R^2 on the selectivity only this parameter was varied in this set of compounds. The L-phenylalanine hydroxamic acid and hydrocinnamoyl chloride were chosen as the basic scaffold. Scheme 22 shows the result from 18 different hydroxamic acid co-catalysts where R^2 = aliphatic and aryl functional groups including sterically hindered analogues.

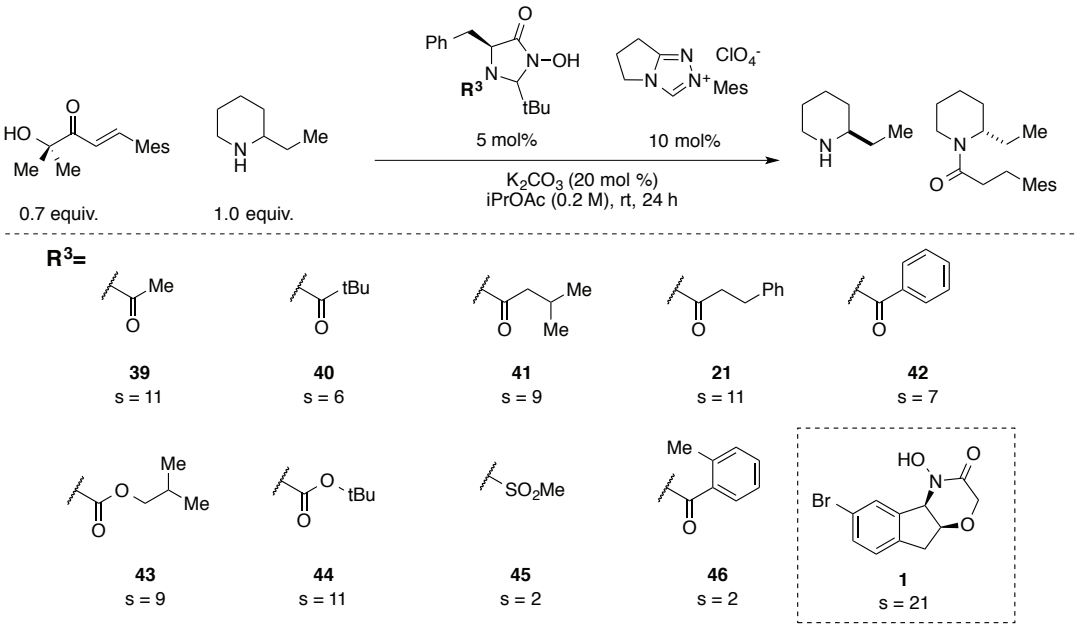


Scheme 22. Kinetic resolution with co-catalysts with varied R^2. Only one diastereomer could be isolated. The individual relative configuration was not assigned.

In the kinetic resolution of 2-ethyl piperidine all catalysts showed lower selectivity towards ethyl piperidine than the aminoindanol-derived compound **1** (s = 21). The best selectivity could be obtained for R^2 = *t*Bu (**21**, s = 11). Typically alkyl substituents performed better than their aromatic analogues (adamantyl **25** (s = 9) or triethyl **24** (s = 7)), aryl substitutions resulted in a maximum selectivity of three (s = 3).

2.6.2 Effect of R^3 on the Selectivity

We next examined the derivatization of R^3 while fixing the *t*Bu-group in the R^1 position (Scheme 23).



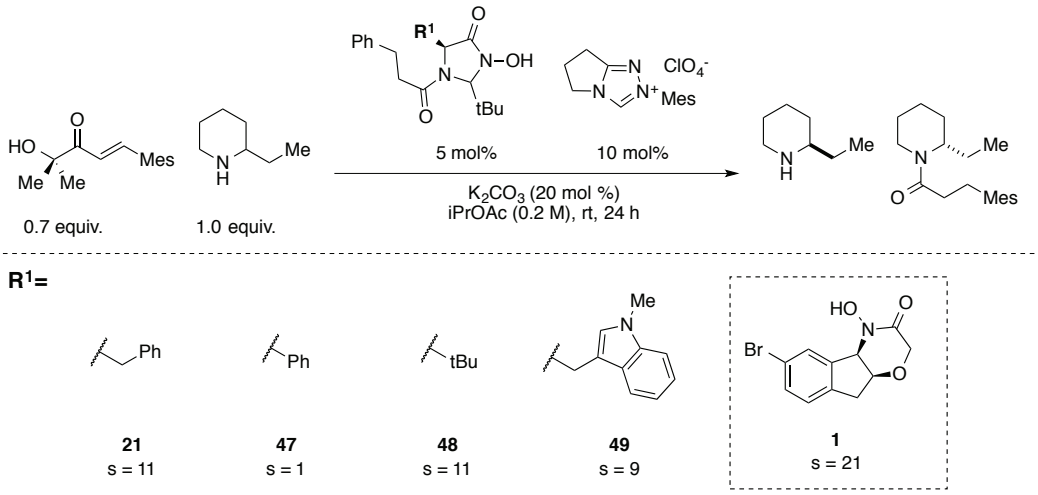
Scheme 23. Kinetic resolution with co-catalysts with varied R^3. Only one diastereomer could be isolated. The individual relative configuration was not assigned.

The synthetic sequence for the catalyst library was based on the protected phenylalanine hydroxamic acid and pivaldehyde from which the best hit was obtained so far. Several common commercially available acyl donors were chosen to produce in total 9 hydroxamic acid co-catalysts. The best selectivity in this series was s = 11 observed for three of the co-catalysts, however, they still do not rival the benchmark hydroxamic acid **1**.

From the results obtained from the kinetic resolution no increase in selectivity can be noted. It was decided that the R^3 site is too far away from the active site to have any significant influence.

2.6.3 Effect of R^1 on the Selectivity

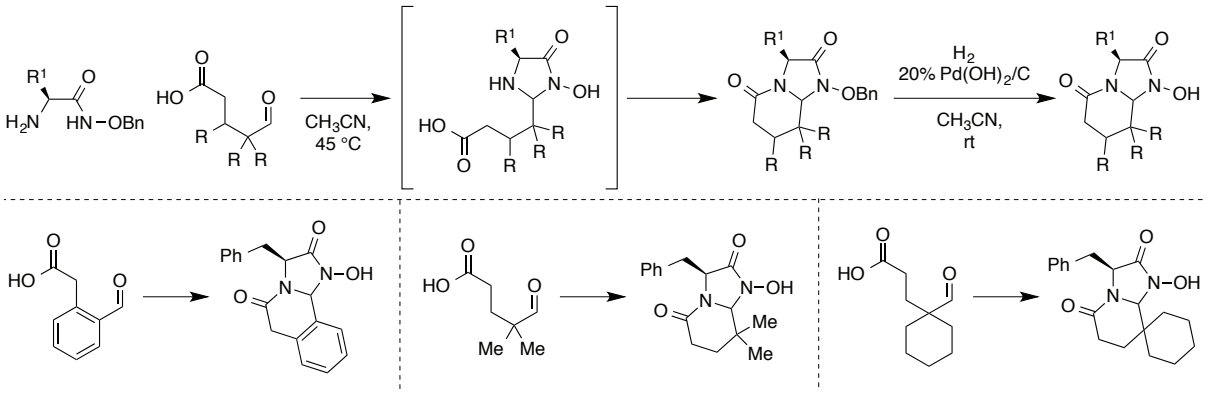
With R^2 and R^3 fixed we prepared three additional co-catalysts but the different functionalizations at this position had no significant influence on the selectivity (Scheme 24). All co-catalyst provided the same selectivity within the range of error. Unfortunately, epimerization was observed with the phenylglycine based catalysts in the α-position, resulting in both enantiomers being present, yielding no selectivity. In spite of this, this position would still be a convenient handle to influence the properties of the catalyst. Since some of the L-Phe based catalysts tended to be oils, all L-Trp based catalyst were solids making them easier to handle and store.



Scheme 24. Kinetic resolution with co-catalysts with varied R^1. Only one diastereomer could be isolated. The individual relative configuration was not assigned.

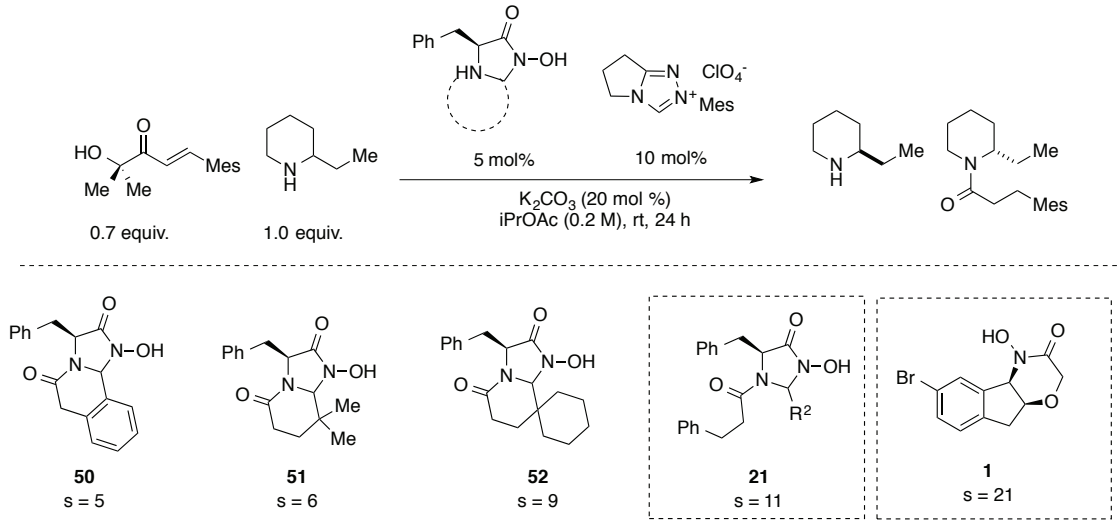
2.6.4 Synthesis of a More Rigid Core Structure

After investigating the effect of all the three positions of the core structure and a superior selectivity (s > 11) could not be obtained for our test substrate, we decided to take inspiration from the rigid structure observed in the aminoindanol-based skeleton of the gold standard hydroxamic acid catalyst **1**. Based on this, three more catalyst derivatives were designed that included a more rigid framework. For their preparation three aldehydes were utilized that also contain a carboxylic acid in a distance of five carbons. After formation of the aminal, the intermediate undergoes intramolecular cyclization to provide the hydroxamic acid catalysts (Scheme 26).



Schemes 26. Synthesis of catalyst with a more rigid core structure.

Unfortunately, these more rigid co-catalysts also led to no improvement of the selectivity, with a maximum selectivity observed at 9 (Scheme 26). At this point, having synthesized and screened over 30 co-catalysts, reaching a maximum selectivity of 11, further development and design of the 5-membered analogues were abandoned.

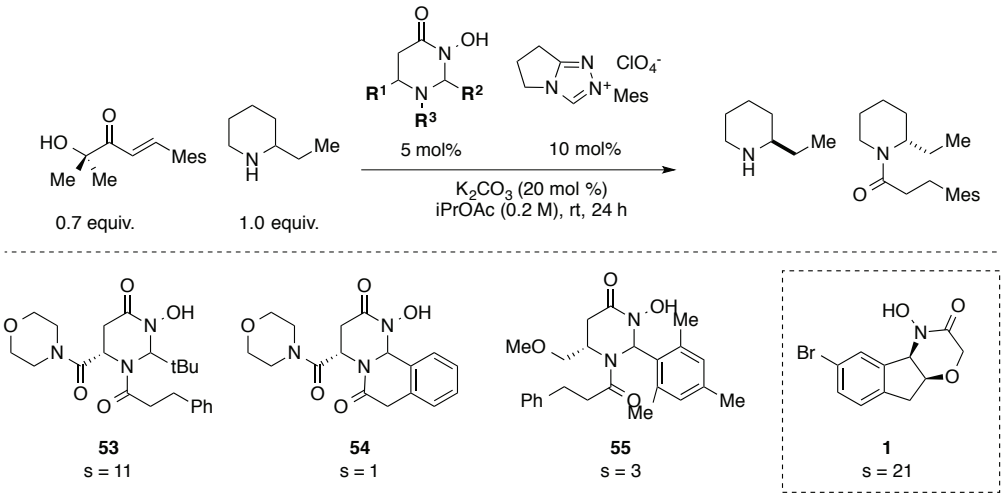


Scheme 24. Kinetic resolution with more rigid co-catalysts. Only one diastereomer could be isolated. The individual relative configuration was not assigned.

2.6.5 Accessing a 6-Membered Co-Catalyst Structure

For accessing the 6-membered series of co-catalysts the same synthetic procedure was used, starting from β-amino acids. However, these products proved to be unstable and characterization was difficult. Also, preliminary results of their selectivity in the kinetic resolution showed that they were inferior to the 5-membered analogues. Due to the synthetic difficulties and discouraged by the poor selectivities observed, we decided not to further

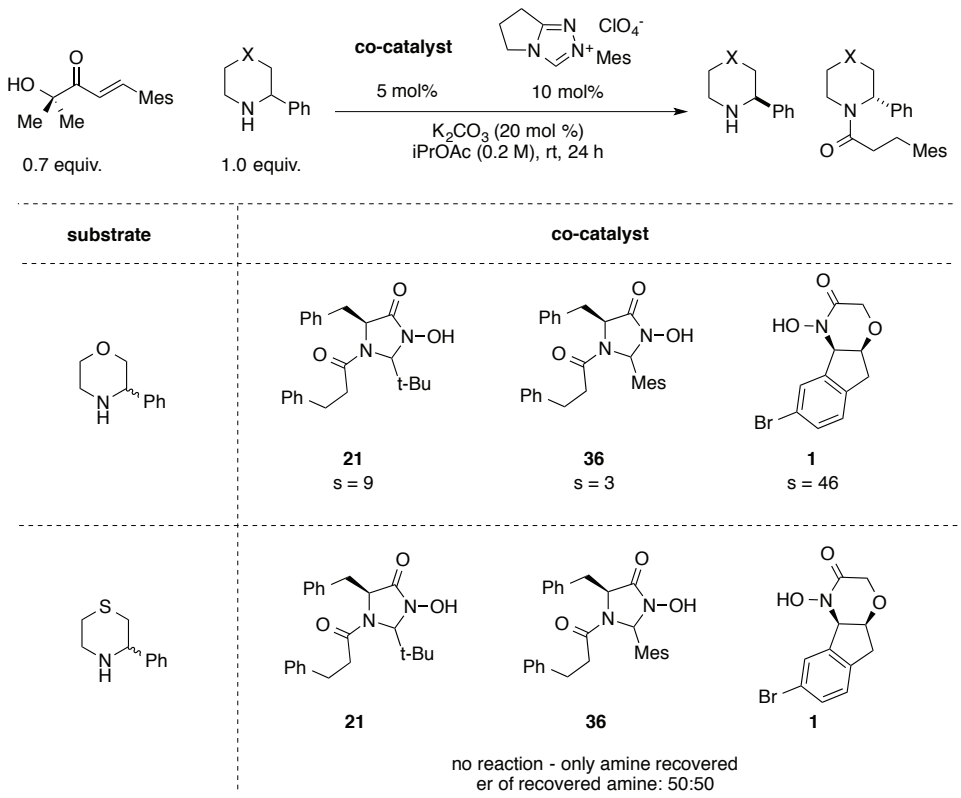
pursue these 6-membered analogues. Again there was no catalyst identified that rivaled the benchmark aminoindanol-derived hydroxamic acid **1**.



Scheme 27. Preliminary results of the kinetic resolution with 6-membered co-catalyst structure.

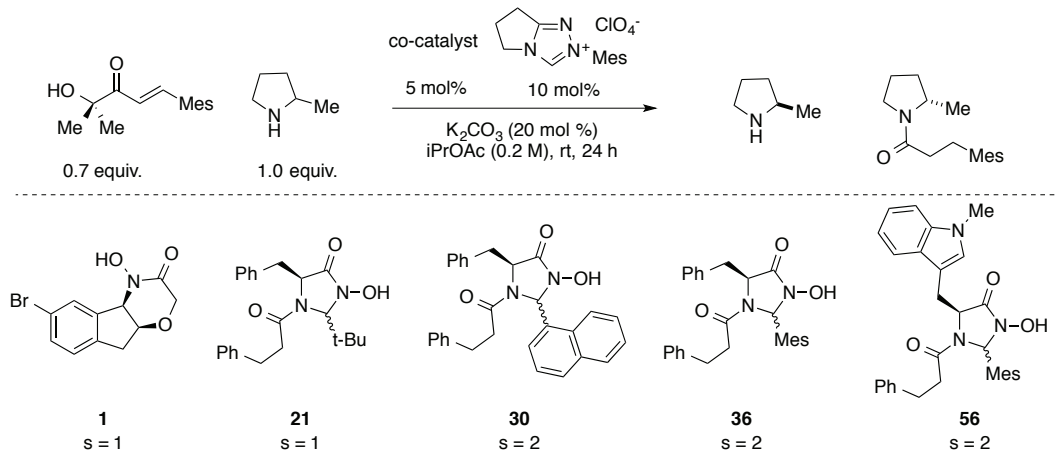
2.7 Screening of More Challenging Substrates

Additionally, 2-phenylmorpholine and 2-phenythiomorpholine were investigated as test substrates and screened against the 5-membered hydroxamic acid co-catalysts **21** and **36**. The previously published benchmark co-catalyst **1** gives s = 46 for morpholine, while no reaction was observed for the thiomorpholine. Compared with **1**, low selectivities were observed with co-catalysts **21** and **36**.



Scheme 28. Kinetic resolution of morpholine and thiomorpholine with hydroxamic acid co-catalysts.

Previously, the kinetic resolution of pyrrolidines using the aminoindanol-based co-catalyst **1** resulted in no selectivity. (s = 1). 2-Methyl pyrrolidine was screened against 4 co-catalysts (**21, 36, 56, 30**). Surprisingly, a slight increase in selectivity was observed with co-catalysts **36, 56** and **30** (s = 2) (Scheme 29). Although such low selectivity is of no real synthetic value, it presents an example where the new catalyst design surpasses the limitations of the previous design. Discouraged by these poor selectivities, we decided to not continue this study.



Scheme 29. Kinetic resolution of pyrrolidine with several new hydroxamic acid co-catalysts.

2.8 Stereochemical Outcome

After investigations of the new hydroxamic acid co-catalyst a trend in the induction of stereochemistry on ethyl piperidine was not observed. Attempts were made for the assignment of the relative configuration of the individual co-catalysts. However, this was not trivial due to the dynamic compounds at NMR timescale (acyl group rotation) and the large variety co-catalysts prepared. It was also shown that the aminal stereocenter was stereochemically stable over the total time of this project.

For cases where both diastereomers of the hydroxamic acid co catalyst could be obtained, it could be observed that the sense of induction for the amine substrate can be dictated by the choice of the diastereomer. Selectivities obtained for a set of diastereomers are compared in Table 3.

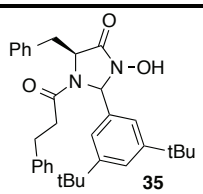
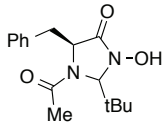
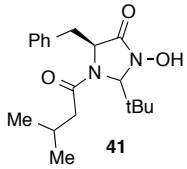
Co-catalyst	er of recovered amine (*R*:*S*)		er of acylated product (*R*:*S*)		s
	Diastereomer 1	Diastereomer 2	Diastereomer 1	Diastereomer 2	D1/D2
 **35**	22:78	71:29	66:34	33:67	3/3
 **39**	71:29	19:81	16:84	85:15	8/11
 **41**	13:87	71:29	81:19	16:84	9/8

Table 3. Effect of the two diastereomers on the selectivity (diastereomers could not be assigned).

2.9 Conclusion

In this project we established a new platform for the rapid and highly efficient synthesis of a library of chiral hydroxamic acids. Over 30 compounds were prepared and tested in the catalytic kinetic resolution of cyclic secondary amines. We hoped to find an improved co-catalysts or a library of catalysts for the kinetic resolution of N-heterocycles and obtain knowledge about the factors influencing the selectivity and reactivity. Unfortunately attempts failed to develop one or several catalyst, that can surpass the limits of the previously developed aminoindanol-based catalyst.

2.10 References

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3

Kinetic Resolution of Disubstituted Piperidines

The DFT calculations of the project were realized in cooperation with Prof. Marisa Kozlowski of the University of Pennsylvania.

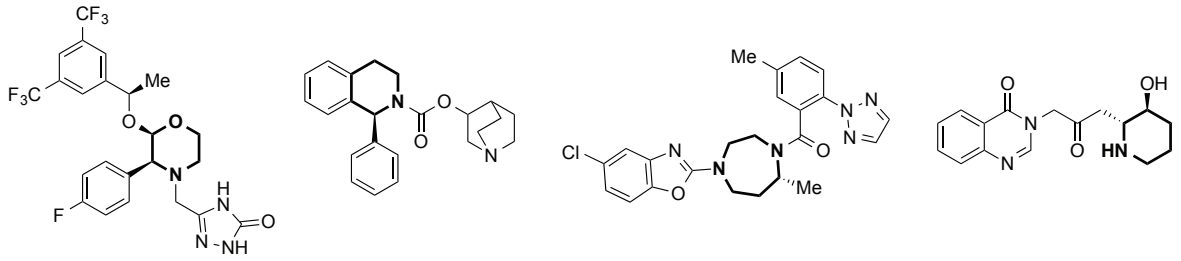
CHAPTER 3. Kinetic Resolution of Disubstituted Piperidines

3.1 Introductory Remarks

This chapter presents an in-depth analysis of the performance of disubstituted piperidines with the kinetic resolution, already introduced in Chapter 1. The catalytic kinetic resolution of disubstituted piperdines is described with practical selectivity factors (s up to 52) in which we uncovered an unexpected and pronounced conformational effect resulting in disparate reactivity and selectivity between *cis* and *trans*-substituted piperidine isomers. Detailed experimental and computational (DFT) studies of the kinetic resolution of various disubstituted piperidines revealed a strong preference for the acylation of conformers in which the α-substituent occupies the axial position. This work also provides experimental and computational data that further supports a concerted 7-membered transition state model for acyl transfer reagents. This study expanded the scope and functional group tolerance of the kinetic resolution of secondary amines, featuring a wide array of functional groups that could be further elaborated after the resolution.

3.2 Kinetic Resolution of Polysubstituted Cyclic Amines

The Bode group's study of the kinetic resolution of cyclic secondary amines has been limited to monosubstituted N-heterocycles. Since many biologically active and top selling pharmaceuticals incorporate more than one substitution on the heterocycle, limiting the studies on compounds bearing a single substitution seems to be an incomplete process. Aprepitant, Vesicare and Suvorexant are just a few examples of top selling drugs on the market with several substitutions on the N-heterocycle (Figure 11). Febrifugine[72] is currently being assessed because of its potent antimalarial activity. The piperidine ring constitutes a key structural element in various biologically relevant molecules and natural products.[73] Furthermore, they are increasingly attractive scaffolds for drug development, as the precise placement of substituents on basic, low-molecular weight, three-dimensional scaffolds is ideally suited for structure-activity relationship studies.[74] In order to assess whether this technology can become a standard tool for separating enantiomeric mixtures of cyclic amines this study was indispensable.



Aprepitant

Antiemetic
$500 million in 2011
(Merck)

Vesicare

Urinary antispasmodic
$1 million in 2013
(GlaxoSmithKline)

Suvorexant

Treatment of Insomnia
Approved by FDA, 2014
(Merck)

Febrifugine

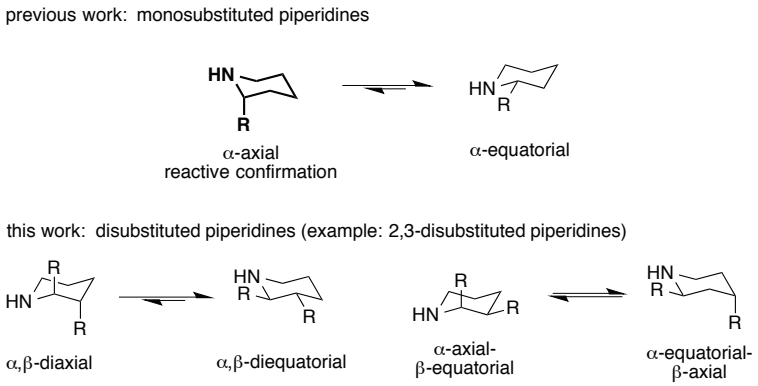
antimalarial drug
candidate

Figure 11. Examples of drugs containing polysubstituted N-heterocycles

3.3 Kinetic Resolution of Disubstituted Piperidines

We decided to prepare a series of disubstituted piperidines and subject them to our kinetic resolution method to examine, if the difference in the substitution pattern on heterocycle had an effect on both the selectivity and reaction rate. In addition to this we also investigated, if there was a significant effect in the reactivity of the *cis* and the *trans* isomers.

To date, our studies on the kinetic resolution of chiral N-heterocycles using chiral hydroxamic acids had been limited to mono-, α-substituted N-heterocyclic substrates (Chapter 1). Previous DFT calculations with an α-substituted piperidine substrate have uncovered a surprising feature of the kinetic resolution where the α-substituted is in the axial position in the lowest energy transition state.



Scheme 30. Conformers of mono- and disubstituted piperidines.

In contrast to the resolution of α-monosubstituted N-heterocycles, for which only a single enantiomeric pair with two conformations each exists, the resolution of disubstituted piperidines requires an enantioselective catalyst to discriminate among several different ring conformations (α,β-diaxial, α-axial-β-equatorial and α,β-diequatorial). From the results of

these substrates in the kinetic resolution we hoped to obtain experimental insight for the validation of the previously developed theory based on the DFT calculations.

For a disubstituted system where each site carries only one substituent there would be a total number of six substitution patterns each *cis* or *trans* as depicted in Figure 12. Piperidines without α-substituents, such as 3,5-disubstituted piperidines, undergo acylation in an unselective manner. In addition, 2,6-disubstituted substrates were found to be too sterically hindered, therefore unreactive and were excluded from further studies. The work therefore targeted the six isomers arising from 2,3-, 2,4-, and 2,5-disubstituted piperidines.

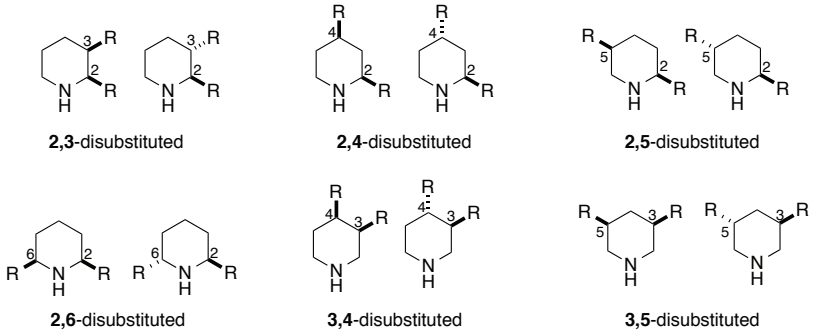
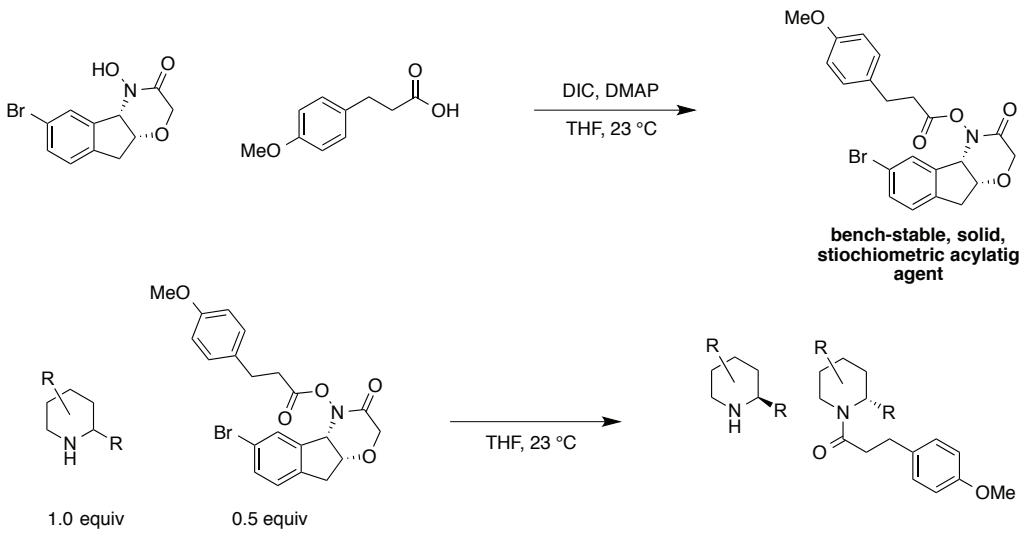


Figure 12. All possible isomers of a disubstituted piperidine.

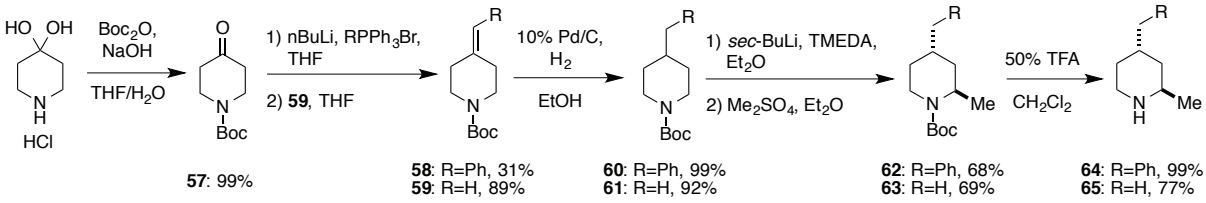
To rule out selectivity arising from the NHC-catalyst in the kinetic resolution, we used our previously reported stoichiometric variant in the resolution of these N-heterocycles.[54] Slightly higher reaction rates and selectivities are observed with this reagent and a recyclable, resin supported variant makes it an attractive option for practical amine resolution.[75] The 4-methoxyhydrocinnamoyl residue as the acyl transfer group proved to be suitable previously. With this the properties of the stoichiometric reagent are changed to become a bench-stable solid, which simplifies handling (Scheme 31). The kinetic resolution reactions were stopped once the stoichiometric reagent was fully consumed.[76] This could happen in several ways. Most of the stoichiometric reagent is consumed by the acylation reaction itself although at longer reaction times, the hydroxyenone and stoichiometric reagent can undergo side reactions such as hydrolysis or cycloadditions.[77] This protocol explains the low conversion even with full consumption of the reagent with slow-reacting substrates. For preparative work, the resolutions would be allowed to proceed to higher conversion, which affords virtually enantiopure recovered amines. As a guideline, s = 20 can deliver >99% ee at 62% conversion. For the purposes of method development and study, we performed the kinetic resolutions under conditions that allow for accurate calculations of the relative rates.



Scheme 31. Synthesis of a bench-stable solid

3.4 Design and Development of the Study

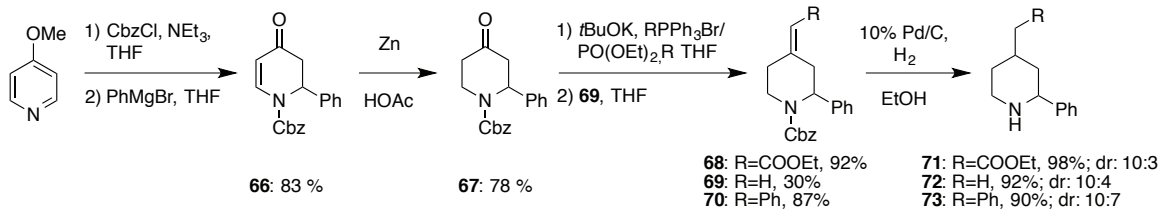
To begin our investigations on the effect of the different substitution pattern we first prepared 2,4-disubstituted piperidine substrates for our studies. The synthesis began with *N*-Boc-protected 4-piperidinone and Wittig reactions were employed to generate **58** and **59**, and each compound was subjected to hydrogenation conditions to reduce the double bonds. The key step in this synthetic sequence was the α-lithiation facilitated by the Boc-protected nitrogen. This extraordinary technology allowed regioselective α-substitution of the piperidine substrates, necessary to access 2,4-disubstituted cyclic amines.



Scheme 32. Synthesis of *trans*-2,4-disubstituted piperidines substrates.

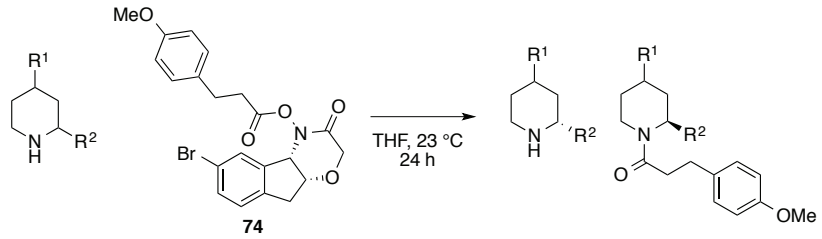
Unfortunately, the final products were isolated as only the diastereomerically pure *trans* forms **64** and **65** (Scheme 32). For our studies it is vital to have access to both *cis* and *trans* material. In an alternative route (Scheme 33), starting from 4-methoxypyridine, **66** was obtained by adding CbzCl and quenching the intermediate with a phenylmagnesium bromide reagent. In this synthesis, we decided to incorporate a chromophore into the amine product (PhMgBr) to aid our analysis (TLC, HPLC etc.). After alkene reduction with Zn in AcOH,

Wittig reactions provided material to **69** (30%) and **70** (87%), while a Horner Wadsworth Emmons olefination provided **68** in 92% yield. The resulting olefins could be reduced by H_2 catalyzed by Pd/C to furnish **71**, **72** and **73** in near quantitative yield. Notably this approach delivered the required mixture of both diastereomers (*cis*/*trans*) for each compound, albeit, these products proved inseparable on preparative scale.



Scheme 33. Synthesis of three diastereomeric mixtures of 2,4-disubstituted piperidines.

However, still optimistic with material in hand, and with the diastereomers somewhat clearly diagnostic on the SFC trace, we proceeded with the kinetic resolution. The two trans isomers **64** and **65**, along with diastereomeric mixtures **71**-**73** were examined in the kinetic resolution with the stoichiometric reagent **74**. Compound **64** and **65** (Table 4, Entry 1,2) showed good resolutions with s-factor of s=10 and s=7, respectively. Unsurprisingly, the results from the kinetic resolution of the diastereomeric mixtures **71**-**73** were not easy to interpret. However, by SFC, it was evident that one of the diastereomers reacted faster than the other (Table 4, Entry 3, 4, 5) but the identity of this diastereomer could not be clearly determined, as the peaks in the SFC spectra could not be assigned to the corresponding diastereomers because of overlapping peaks.



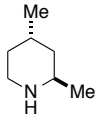
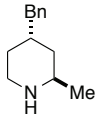
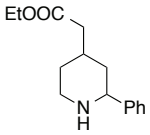
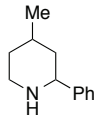
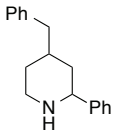
entry	substrate	dr	er amine 1	er amine 2	er amide 1	er amide 2
1		1:0	83:17	18:82	---	---
2		1:0	78:22	79:21	---	---
3		10:3	1:99	98:2	1:99	86:14
4		10:4	34:66	47:53	39:58	---
5		10:7	52:48	28:72	---	5:95

Table 4. Kinetic resolution of the first five substrates. No conclusive results could be obtained.

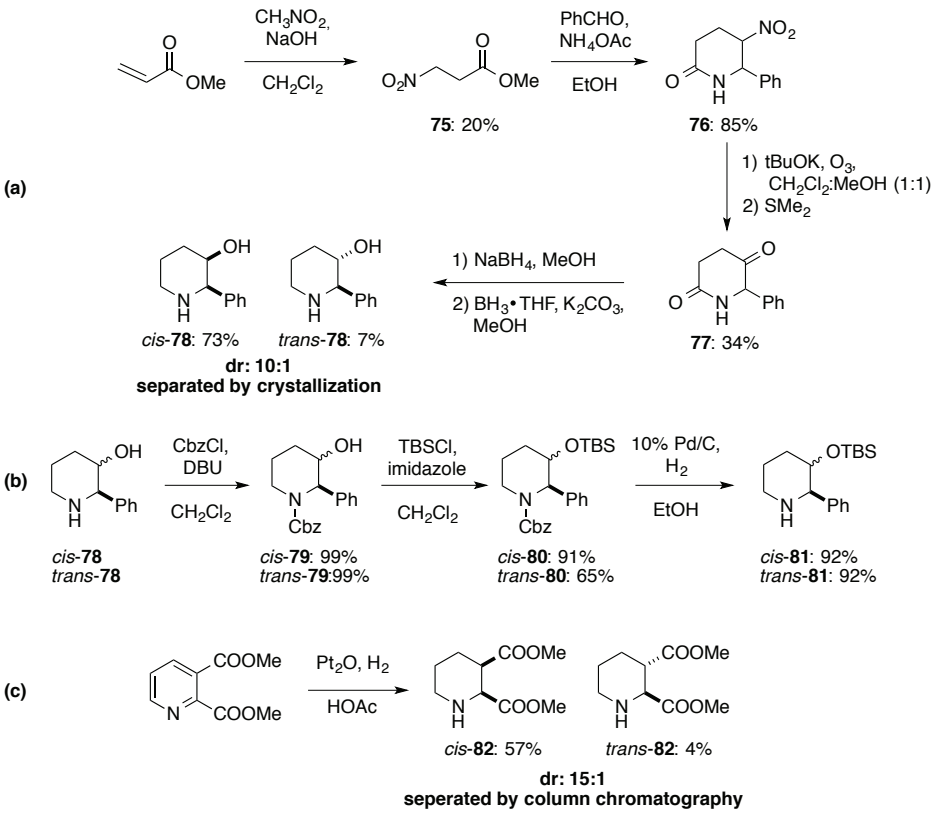
From this study we gained confidence that there would be an observable rate difference between the *cis* and *trans* isomers during the kinetic resolution. But it also highlighted a major flaw in our initial design. To facilitate the study, material of both *cis* and *trans* isomers had to be independently synthesized. We could not rely solely on separation of racemates. Our goal was to generate data that would provide a model for reliably predicting whether a given substrate would undergo a selective kinetic resolution. For this evaluation, we elected at least three substrate pairs (*cis/trans*) for each of the three positional isomers, giving 20 substrates in total. Considerations for compound selection included ease of synthesis, incorporation of functional handles for further functionalization, and ready access to diastereomerically pure forms of the targets.

3.5 2,3-Disubstituted Piperidines

The first substrate prepared was 2-phenyl-3-piperidinol (**78**), synthesized from methyl acrylate. A Henry reaction provided **77**,[78] followed by cyclization to the requisite lactam **76** with benzaldehyde via a Mannich type reaction. This material was subjected to ozonolysis to yield ketone **77**. The following two step, reduction with $NaBH_4$ and BH_3•THF produced a mixture of *separable* diastereomers (*cis*-**78**/*trans*-**78**) of the desired substrate, separated by crystallization from MeOH as the pTsOH salt.

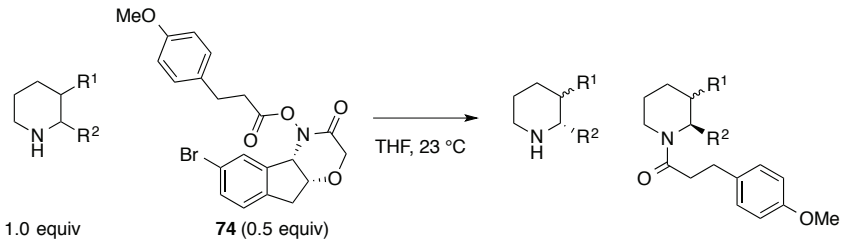
A bulkier analogue of **78** was prepared by attaching a *tert*-butyl silyl protecting group to the hydroxyl unit of the molecule. Compounds *cis*-**81**/*trans*-**81** were generated by protecting the previously obtained diastereomerically pure **78** with CbzCl yielding **79**, followed by subsequent TBS protection of the alcohol and removal of the protecting group to provide substrate *cis*-**81**. This sequence was repeated for accessing the other diastereomer, *trans*-**81**.

The final substrate prepared was by hydrogenation of the quinolic methyl ester to the corresponding disubstituted piperidine with Adams catalyst (PtO_2) providing the saturated piperidine as a mixture of diastereomers *cis*-**82**/*trans*-**82** (*cis/trans*: 15/1), which could be separated by repeated purifications by column chromatography.



Scheme 34. Synthesis of 2,3-disubstituted piperidines.

With the appropriate substrates in hand the kinetic resolution of the 2,3-disubstitution series was examined (Table 4) with the stoichiometric reagent **74**.



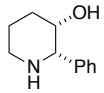
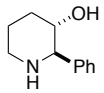
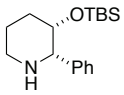
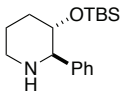
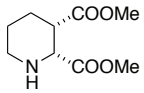
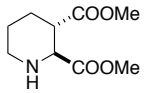
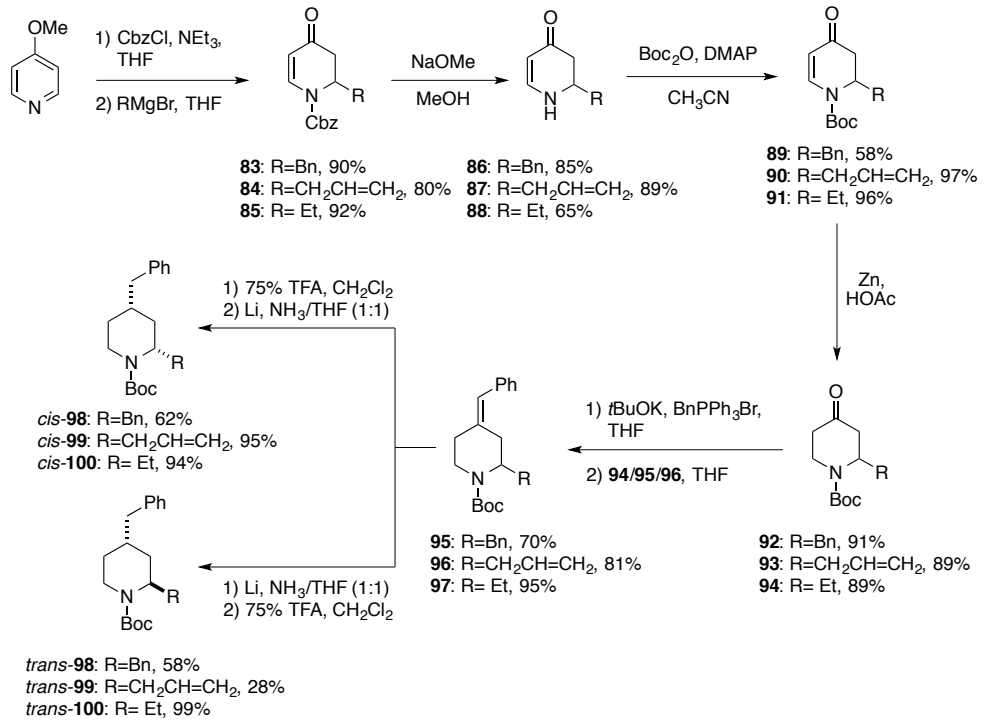
entry	substrate	s[a]	conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e,f] (%)	er amide[d] yield[f] (%)
1		24	33	48	72:28 (31)	94:6 (30)
2		1	14	72	51:49 (32)	56:44 (5)
3		19	31	72	69:31 (34)	93:7 (28)
4		2	46	96	56:44 (39)	57:43 (7)
5		23	50	72	90:10 (39)	91:9 (50)
6		4	26	96	59:41 (40)	75:25 (21)

Table 5. Results of the kinetic resolution of 2,3-disubstituted piperidines.
[a] Calculated selectivity. [b] Calculated conversion. [c] Reaction time until the stoichiometric reagent is fully consumed. [d] Determined by SFC or HPLC on a chiral support. [e] Isolated as the Cbz-derivative. [f] Yield after column chromatography.

A significant difference in selectivity and reactivity could be observed between each diastereomeric pair. With *cis*-2-phenylpiperidin-3-ol (Table 5, entry 1) an s-factor of 24 and a conversion of 33% could be obtained after 48 hours, whereas the *trans* diastereomer (Table 5, entry 2) reached only 14% conversion after 72 hours with essentially no selectivity. This *cis*-selective trend could also be observed for the other two sets of substrates (Table 5, entries 3 and 4, entries 5 and 6). It is noteworthy that the TBS-group had no real effect on the outcome of the kinetic resolution, except that the time for conversion was longer.

3.6 2,4-Disubstituted Piperidines

For the synthesis of the 2,4-disubstituted substrates,[79] the previously employed synthetic pathway was used. For accessing each substrate, **98**, **99** and **100**, several Grignard reagents (BnMgBr, AllylMgBr and EtMgBr) were added to the acylpyridinium salt intermediates (obtained from 4-methoxypyridine by adding phenyl chloroformate).[80] The Cbz-protected group would not be stable under Birch conditions later on in the synthesis and attempts to generate an acylpyridinium salt using Boc_2O instead of CbzCl failed. Therefore the protecting group had to be switched, which was accomplished by removal of the Cbz by MeONa and protection of **86**/**87**/**88** with Boc_2O. After conjugate reduction with Zn in AcOH the piperidinone **92**/**93**/**94** was obtained. A Wittig olefination reaction with benzyl triphenylphosponium bromide generated **95**/**96**/**97** as a 1:1 mixture of diastereomers.



Scheme 35. Synthesis of 2,4-disubstituted piperidines.

The key step of this synthesis was a sequence of Birch reduction and Boc removal, using TFA. By first deprotection of the amine in 75% TFA in CH_2Cl_2 and subsequent alkene reduction under Birch-type conditions (>50 equiv of Li, NH_3, THF, –78 °C) the *cis*-piperidine could be obtained in good overall yield. By reversing the order of the two steps (dissolved metal reduction conditions followed by TFA), the selectivity was reversed to provide exclusively the *trans*-piperidine in good overall yield and high diastereoselectivity. This difference of selectivity observed can be accounted by the favored generation of the

thermodynamic product in dissolved metal reductions[81] and to a special property of N-acylpiperidines (Figure 13).

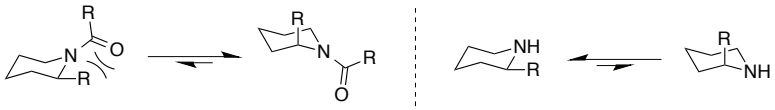
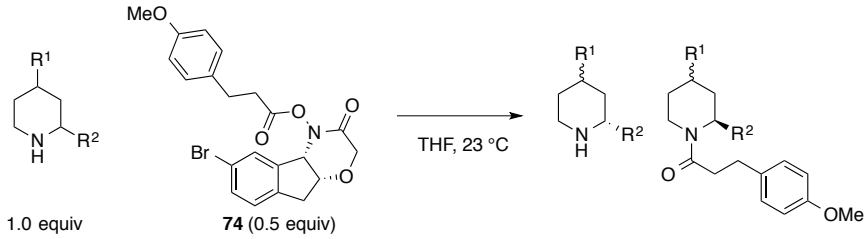


Figure 13. Comparison of stereochemical outcome between *N*-acylated and non-*N*-protected α-substituted piperdines in the Birch-type reaction.

In unprotected piperidines the preferred conformation has the α-substituent in an equatorial position; it is the opposite scenario for *N*-acylated piperidines (which is due to a *pseudo* allylic strain ($A^{1,3}$) known as the Paulsen effect).[82] This changes the ground state and therefore the thermodynamically favored product. With this pathway three 2,4-disubstituted substrate could be obtained, each in their diastereomerically pure *cis* and *trans* form.

Subjecting the compounds to the kinetic resolution revealed a reversed trend in comparison to that observed for the 2,3-disubstituted examples shown in Table 6. For this series, the *cis*-diastereomers exhibit poor selectivities (s = 3–7) and low reactivity with reaction times between 72 and 120 hours (Table 6, entries 1, 3, and 5). In contrast, the *trans*-diastereomers reached full conversion in 20 hours or less with high selectivities (s = 10–29) (Table 6, entries 2, 4, and 6).



1.0 equiv **74** (0.5 equiv)

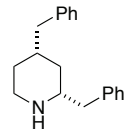
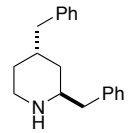
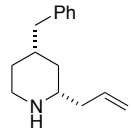
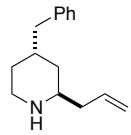
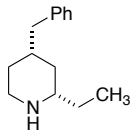
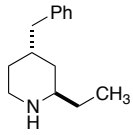
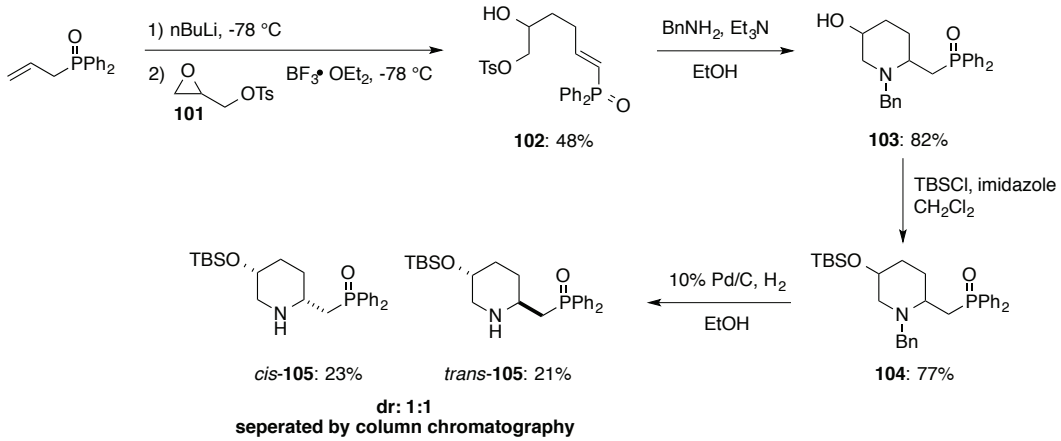
entry	substrate	s[a]	conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e,f] (%)	er amide[d] yield[f] (%)
1		3	22	120	57:43 (39)	78:22 (4)
2		10	65	20	97:3 (15)	75:25 (43)
3		7	32	72	66:34 (56)	84:16 (29)
4		29	52	20	94:6 (46)	91:9 (45)
5		6	38	96	68:32 (46)	80:20 (34)
6		15	62	20	98:2 (19)	80:20 (40)

Table 6. Results of the kinetic resolution of 2,4-disubstituted piperidines.
[a] Calculated selectivity. [b] Calculated conversion. [c] Reaction time until the stoichiometric reagent is fully consumed. [d] Determined by SFC or HPLC on a chiral support. [e] Isolated as the Cbz-derivative. [f] Yield after column chromatography.

3.7 2,5-Disubstituted Piperidines

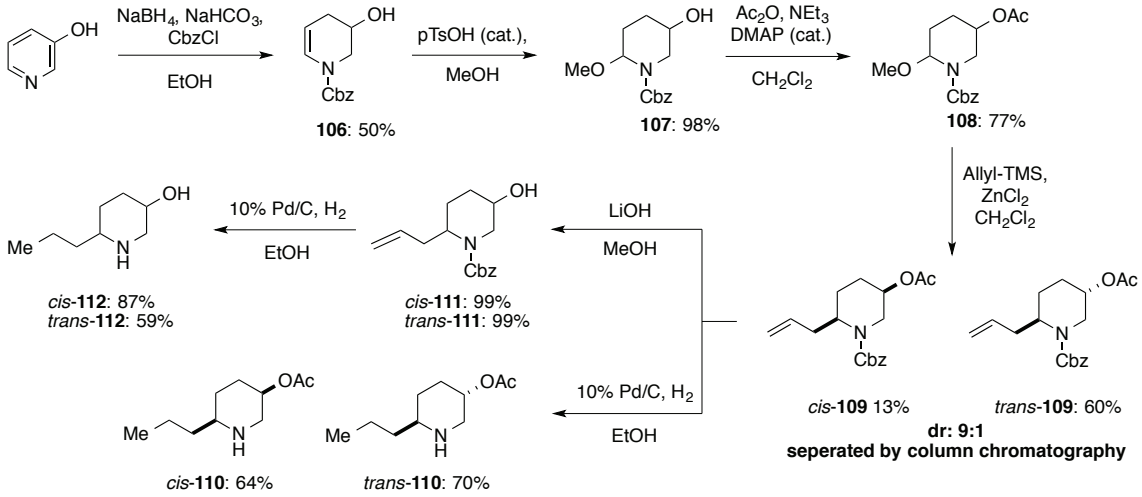
For the 2,5-disubstitutied piperidines, 3-hydroxypiperidines were chosen as substrates. Several methods for making these compounds have been developed since these scaffolds can be found frequently in alkaloids[83] making them attractive in the development of new pharmaceuticals.

For the preparation of 2,5-disubstituted substrates, two synthetic pathways were employed. In the first (Scheme 36), epoxide **101** was opened in the presence of BF_3•OEt_2 with lithiated allyldiphenylphosphane oxide to generate bis-homoallyl alcohol **102** in 48% yield.[84] Addition of a benzyl amine in the presence of a NEt_3 at elevated temperature triggered a domino reaction. First an S_N2 reaction of the tosylate, followed by cyclization *via* Michael-type addition to the vinyl-phosphine, formed the benzyl protected 3-hydroxypiperidine **103** as a 1:1 mixture of diastereomers. After TBS-protection of the alcohol and hydrogenation of the benzyl group, the mixture of diastereomers was separated by column chromatography to furnish one set of substrates *cis*-**105**/*trans*-**105**.



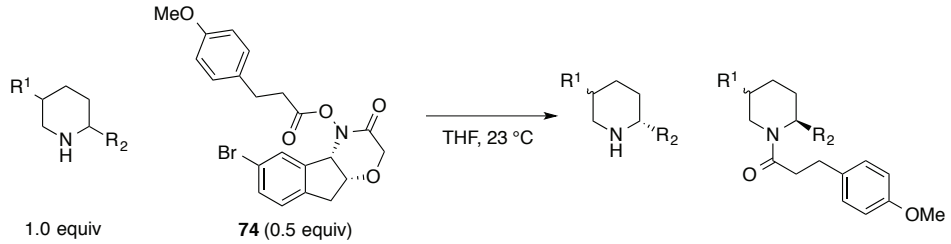
Scheme 36. Synthesis of 2,5-disubstituted piperidines (1/2).

In the second synthetic path (Scheme 37), 3-hydroxypyridine was converted to the homoallylic alcohol **106** *via* reductive carbamoylation.[85] After the addition of MeOH in pTsOH, the alcohol was acetylated to yield **108**. Intermediates **107** and **108** were both rather unstable and readily eliminated MeOH within a few hours at room temperature. This was not an issue when the products were allylated quickly. A Zn-mediated allylation generated **109** in a 9:1 mixture of stable diastereomers. This intermediate was used to generate two sets of substrates. After hydrogenation using Pd/C one set could be obtained (*cis*-**110**/*trans*-**110**). Another two compounds could be generated by hydrolysis of the ester followed by hydrogenation with Pd/C. This sequence yielded the aminoalcohol **112** known as pseudoconhydrine;[86] one enantiomer can be extracted from several plants as well.



Scheme 37. Synthesis of 2,5-disubstituted piperidines (2/2).

When subjecting the 2,5-disubstituted piperidines (Table 7) to the kinetic resolution we observed a similar *cis*-selective trend as with the 2,3-disubstituted substrates. Namely, higher s-factors were observed for the *cis* diastereomers as well as higher reaction rates compared to the corresponding *trans* diastereomers. The biggest contrast with regards to s-factors can be noticed in entry 5; for *cis*-6-propylpiperidin-3-ol an s-factor of 52 was obtained while the *trans*-isomer (Table 7, entry 6) afforded an s-factor of only 4. Such large differences in selectivity were not evident in entries 1-4; however, the data supports the conjecture that *cis* isomers in this series are superior to the *trans* isomers. These substrates also demonstrate the chemoselectivity of the kinetic resolution for N-heterocycles bearing a variety of functional groups suitable for further functionalization.



1.0 equiv **74** (0.5 equiv)

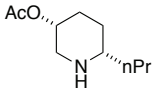
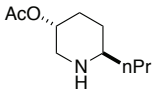
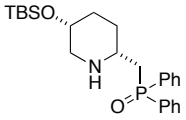
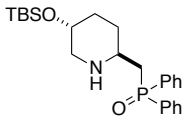
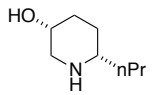
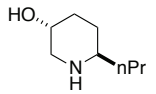
entry	substrate	s[a]	conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e,f] (%)	er amide[d] yield[f] (%)
1		22	42	24	81:19 (44)	92:8 (33)
2		20	40	96	78:22 (47)	92:8 (33)
3		13	54	72	90:10 (22)	84:16 (28)
4		9	29	72	65:35 (45)	87:13 (19)
5		52	54	20	99:1 (25)	92:2 (38)
6		4	53	48	74:26 (29)	71:29(51)

Table 7. Results of the kinetic resolution of 2,5-disubstituted piperidines.
[a] Calculated selectivity. [b] Calculated conversion. [c] Reaction time until the stoichiometric reagent is fully consumed. [d] Determined by SFC or HPLC on a chiral support. [e] Isolated as the Cbz-derivative. [f] Yield after column chromatography.

3.8 Model and DFT Calculations

Surprisingly, when summarizing the three cases substantial differences in the reactivity and selectivity between the *cis* and *trans* isomers of the otherwise identical positional isomers were observed. For the 2,3- (Table 5, entries 1 and 2, entries 7 and 8) and 2,5-disubstituted (Table 7, entries 5 and 6) piperidines the *cis* isomer underwent faster reactions with higher selectivity, while the *trans* isomer gave rise to superior outcomes for the 2,4-disubstituted compounds (Table 6, entries 3 and 4). These results already hinted at strict conformational requirements for effective enantioselective acylation.

In light of these initially confusing results, we undertook a computational study to assess the role of the positional isomers and their stereoisomers. The goal was to create a model for reliable prediction whether a given substrate would undergo a selective kinetic resolution.

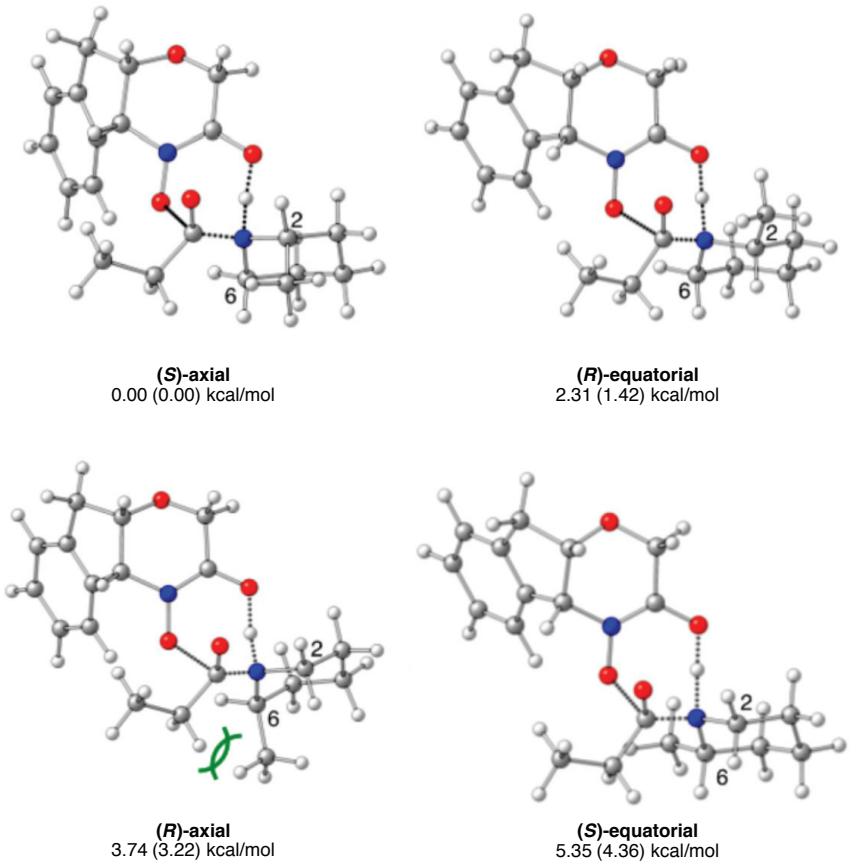


Figure 14. Four possible transition states obtained for the kinetic resolution of 2-methyl piperidine from previous calculations. In the lowest energy transition state α-substituent is in an axial position. Relatives values are solvated relative enthalpies (kcal/mol) compared to the lowest energy transition state. Parenthetical values are the corresponding gas phase values.

The divergent reactivity of the diastereomeric pairs in the different series can be rationalized on the basis of recent DFT calculations of the transition states of α-methyl piperidine reacting with the chiral acylating agent (Figure 14).[87] These studies concluded that acylation occurred via a concerted 7-membered transition state with concomitant proton transfer guided by the hydroxamic acid and with the α-substituent placed in the axial position. In contrast, other work from the Bode group on the resolution of morpholines with stoichiometric chiral acyl donors and achiral hydroxamic acids was most consistent with a stereochemical model featuring an equatorial substituent of a morpholine.[88] However, no computational studies were performed on this system and significant conformational

differences between morpholine and piperidines can be expected. Both models suggest that the stereoselective step involves a seven-membered transition state with the lone pair of the nitrogen in the equatorial position. This mechanism of acyl transfer was found to be general for a variety of widely used acyl transfer reagents including *N*-hydroxysuccinimide, and HOAt.

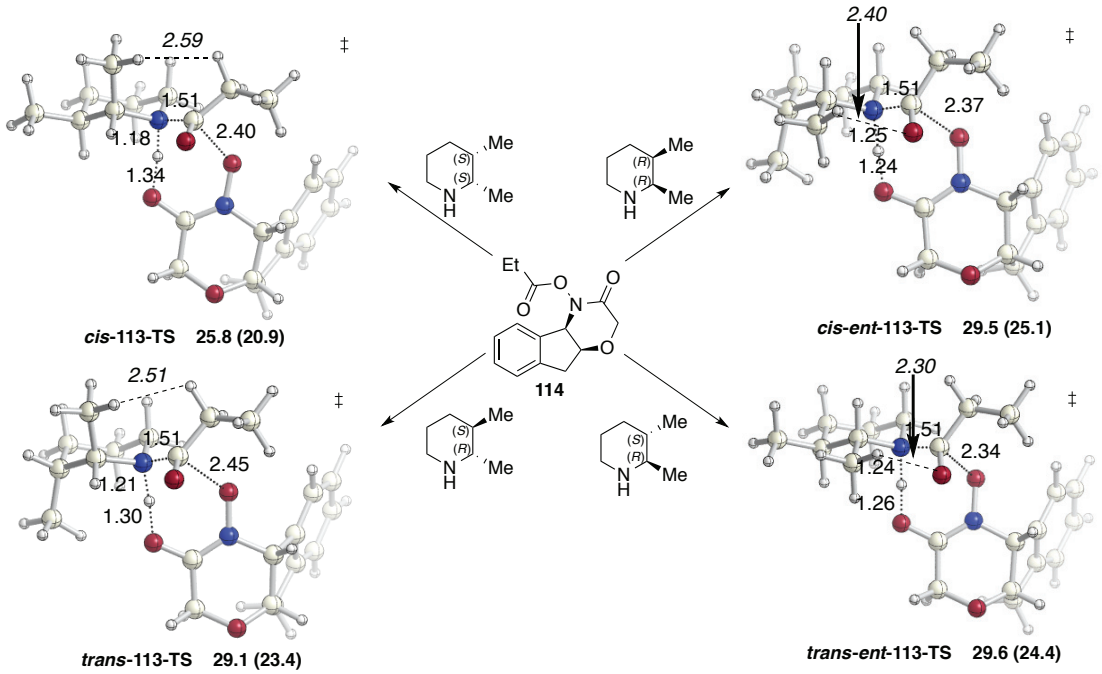


Figure 15. Four lowest energy transition states of the chiral acylating agent **114** with 2,3-dimethylpiperidine (**113**). In the lowest energy transition state (top left) the α-methyl-group is in the axial position. Values are free energies in kcal/mol relative to the piperidine ground state; gas phase energetics calculated using B3LYP/6-31G(d,p)//(in parentheses IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)).

In order to reconcile these two models with the results obtained for the resolution of disubstituted piperidines, we undertook detailed DFT studies on the relevant transition states using the *cis* and *trans* geometric isomers of 2,3-dimethylpiperidine (**113**) as a model system and the chiral hydroxamic acid.[89] *These calculations were performed with our collaborator Prof. Marisa Kozlowski from the University of Pennsylvania.* Notably the opposite enantiomer of the stoichiometric reagent **114** was employed in the calculation model. All calculations were carried out using the same computational methods previously employed in related systems using Gaussian 09.[90] Structures were optimized with B3LYP/6-31G(d).[91,92] Single-point energy calculations in the condensed phase (CH_2Cl_2; e = 8.93) were undertaken using the IEPCM solvation model with M06-2X/6-311+G(d,p).[93]

As a result of the calculations, Figure 15 shows the four lowest energy transition states for the acyl transfer to each enantiomer of *cis* and *trans* 2,3-dimethyl piperidine. As

anticipated from previous work, the concerted 7-membered transition states feature an intramolecular proton shuttle between the secondary amine and the hydroxamate carbonyl.

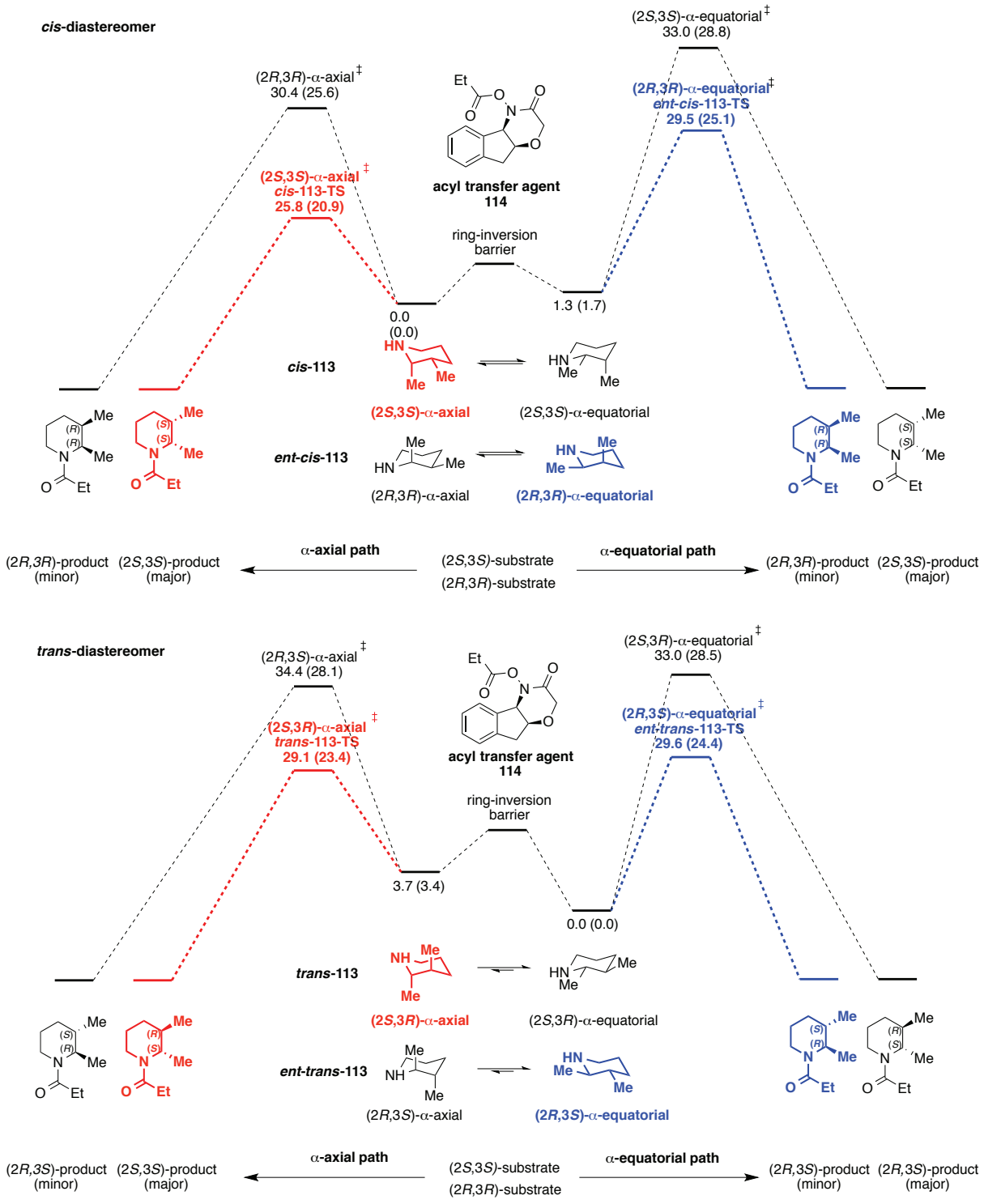


Figure 16. Calculated energy diagrams for the kinetic resolution of *cis*-2,3-dimethylpiperidine (top) and *trans*-2,3-dimethylpiperidine (bottom) with the chiral acylating agent. The lowest energy transistion state is highlighted in **red**, the second lowest one in **blue**. Values are free energies in kcal/mol; gas phase energetics calculated using B3LYP/6-31G(d,p)//(in parentheses IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)).

In total there are four possible transition states for each *cis*- and *trans*- substrate possible, since each enantiomer can react in two possible conformations. One conformation places the α-substituent in axial position, the other one in equatorial position. Notably the lowest energy transition state (**red**) for each *cis* and *trans* diastereomer places the α-substituent in axial position to result in the α-(*S*)-product. From the competing second lowest energy state (**blue**) placing the α-substituent in equatorial position the α-(*R*)-product can be obtained.

The data is also in agreement with experimental rates and selectivity trends listed in Table 52 (entries 1-6) in which the *cis* 2,3-disubstituted piperidines showed significantly faster rates and superior s-factors (s = up to 24) in comparison to the *trans* 2,3-disubstituted piperidines. For example, the lowest transition state free energy for the ***cis*-113** (25.8 kcal/mol gas phase) is approximately 3 kcal/mol lower in energy than the lowest for ***trans*-113 (**29.1 kcal/mol gas phase), which is consistent with the relative rates of these two amine diastereomers.

This finding is in line with our postulate that the lower energy transition states for acyl transfer feature an axial α-substituent, which requires the *trans*-2,3-dimethyl piperidine to adopt an unfavorable diaxial conformation. In contrast, the chair conformation of the *cis*-2,3-dimethylpiperidine with an α-axial substituent is the preferred ground state conformation. Further, our calculations correctly predict the fastest reacting enantiomer via ***trans*-113-TS** and ***cis*-113-TS,** respectively. For kinetic resolution, the energy difference between the diastereomeric acylation transition states determines the selectivity. In agreement with experiment, the quantum mechanical calculations indicate a larger gap between the *cis*-1,2-disubsituted systems (here modeled as 2,3-dimethyl piperidine ***cis*-113** and ***ent*-*cis*-113**) than the *trans*-1,2-disubsituted systems, which reflects the significant difference in selectivity between *cis* and *trans* diastereomers. Notably, the lowest energy diastereomeric transition states place the α-substituent away from both the aromatic ring of the acyl transfer agent and the acyl chain. Exhaustive conformational analysis, including other chair conformations, revealed that all other transition states are much higher in energy. As shown in Figure 16, the significant energy difference (3.7 kcal/mol, *s* = 19–24) between ***cis*-113-TS** and ***ent-cis*-113-TS** arises from the additional unfavorable *gauche* interactions between α-substituent in the equatorial position and the carbonyl group. In addition, ***ent-cis*-113-TS** has an further interaction between the axial β-methyl group and the hydroxamate carbonyl.

In contrast, the energy difference between ***trans*-113-TS** and ***ent-trans*-113-TS** is small at 0.5 kcal/mol, which is consistent with the poor s-factors (s = 1–4) observed for the *trans* substituted systems. It is remarkable, however, that the preferred conformation for the

lowest energy transition state is the *trans*-2,3-*bis*-axial, which demonstrates again the strong preference for α-axial substituents in the acylation step and offers an excellent example of the Curtin-Hammett principle (Figure 16, bottom). The dimethyl groups are in the axial position in ***trans*-113-TS** and in the equatorial position in ***ent-trans*-113-TS**; in this case, the additional 1,3-diaxial interactions in ***trans*-113-TS** raise its energy leading to a smaller energy gap between the two enantiomers and smaller selectivity values.

Another possible explanation for the different selectivities and reaction rates instead of the transition state effect are ground state effects. This explanation would be based on the fact that the selectivities would arise from the energy difference of the individual conformer and not necessarily the lowest energy conformer with its transition state. Table 8 summarizes the values leading to the different selectivities and compares the predicted outcome of the transition state effect model with the ground state effect model. It can be clearly seen that only the transition state effect model is good agreement with the experimental observations, whereas the ground state effect model would predict

	cis		*trans*	
	(2*R*,3*R*)-Product	(2*S*,3*S*)-Product	(2*R*,3*S*)-Product	(2*S*,3*R*)-Product
Transition state effect	25.8 kcal/mol	29.5 kcal/mol	29.1 kcal/mol	29.6 kcal/mol
	ΔΔG = 3.7 kcal/mol		ΔΔG = 0.5 kcal/mol	
Predicted outcome	*high selectivity*		*low selectivity*	
Ground state effect	25.8 kcal/mol	28.2 kcal/mol	25.4 kcal/mol	29.6 kcal/mol
	ΔΔG = 2.4 kcal/mol		ΔΔG = 4.2 kcal/mol	
Predicted outcome	*high selectivity*		*high selectivity*	
Experimental outcome	*high selectivity*		*low selectivity*	

Table 8. Comparison of a transition state effect model and Ground state effect model to the experimental outcome. The transition state effect model is in agreement with experimentally observed values.

To show that this model can be applied to the substrates tested experimentally, additional calculations using *cis*- and *trans*-2-phenyl-3-hydroxypiperidine (Table 9) showed a similar trend as the model, *cis*- and *trans*-2,3-dimethylpiperidine.

$s = e^{\frac{\Delta\Delta G^{\ddagger}}{RT}}$	calculated		experimental	
	cis	trans	cis	trans
$\Delta\Delta G^{\ddagger}$ (kcal/mol)	1.7	0.4	1.9	0.0-0.2
s	18	2	24	1

Table 9. Comparison of the experimental and calculated values of $\Delta\Delta G^{\ddagger}$ of the kinetic resolution of *cis*- and *trans*-2-phenylpiperidinol at 21°C.

The enthalpic energy difference (in solvent) between the two enantiomeric transition states of *cis*-2-phenylpiperidin-3-ol was computed to be 1.7 kcal/mol vs. only 0.4 kcal/mol for the corresponding *trans* diastereomer. This calculation is in excellent agreement with experiment for kinetic resolution of the *cis*- and *trans*-2-phenylpiperidin-3-ol systems (Table 5, entries 1 and 2), which exhibited s-values of 24 and 1, respectively.

3.9 Application of the Model to 2,4- and 2,5-Disubstituted Substrates

The results calculated for the 2,3-disbustituted piperidines could be assumed for the to 2,5-disubstituted piperidines as well. Just as with the 2,3-disubstituted compounds, the *cis*-diastereomer consists of two conformers that differ only slightly in energy whereas the *trans*-diastereomer exists primarily in the diequatorial conformer rather than the higher energy diaxial conformation (Figure 16). An analogous situation occurs for the 2,4-disubstituted compounds; however, it is reversed so that the *trans* isomer always has one axial substituent and the other substituent in an equatorial position, which both represent the lowest energy conformations, and make one conformer more selective. The *cis*-2,4-disubstituted isomers, in contrast, exist almost exclusively in the more favorable diequatorial conformation and gives rise to lower selectivity.

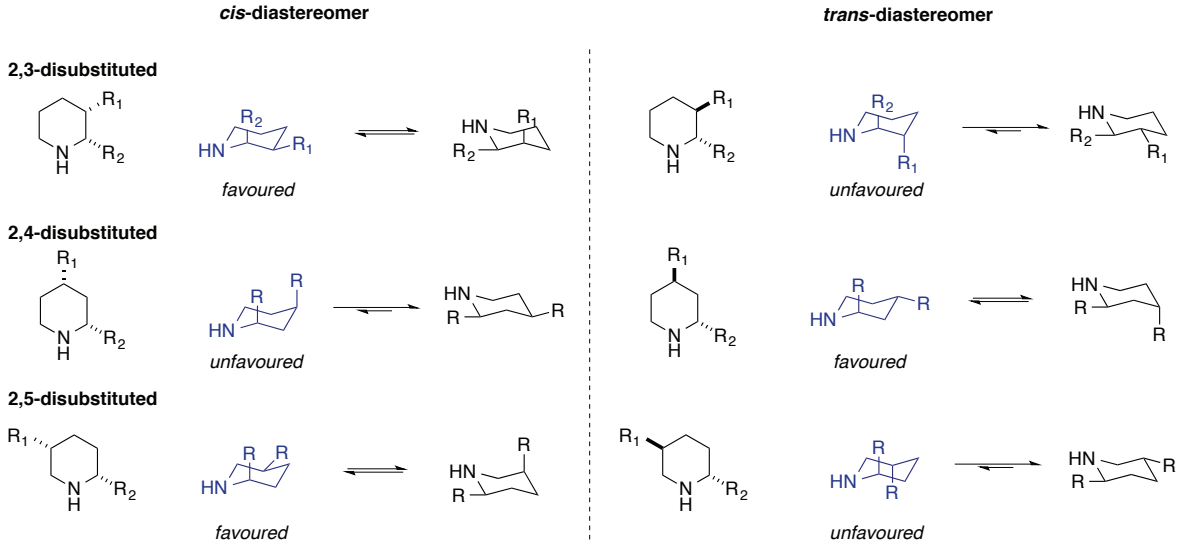
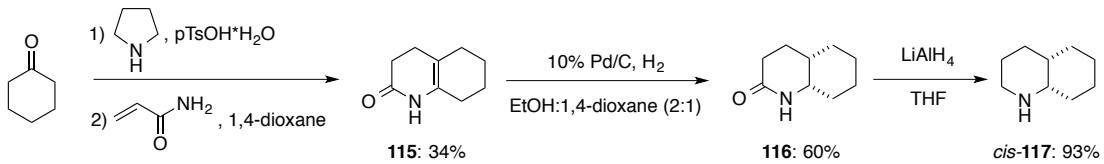


Figure 17. Conformers of the *cis*- and *trans*-disubstituted piperidines investigated. The conformer placing the α-substituent in axial position is highlighted in **blue**. For 2,4-disubstituted substrates and opposite behavior than for 2,3- and 2,5- disubstituted substrates can be observed.

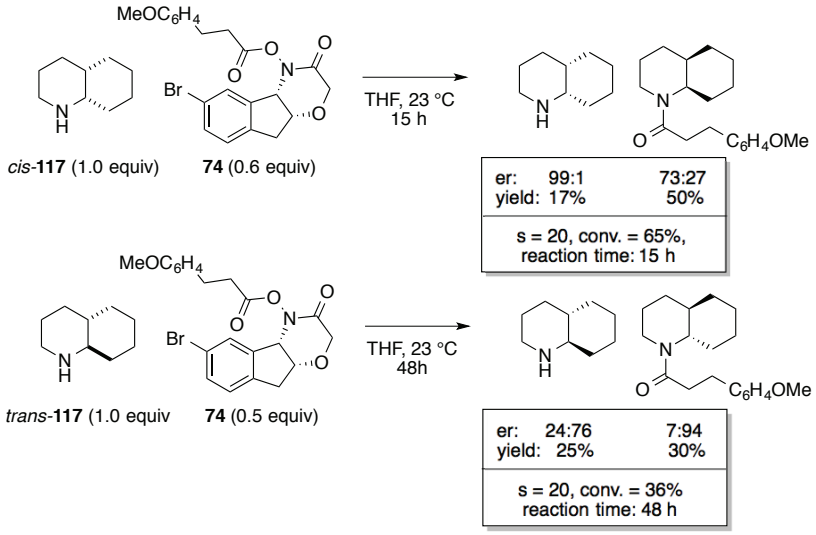
3.10 Calculation Model Tested with Locked Substrate

Decalin scaffolds are particularly interesting for this finding since the *trans*-decalin system cannot undergo ring-inversion.[94] The two diastereomers of decahydroquinoline were examined. For *trans*-decahydroquinoline, the enantiomers are locked in the diequatorial conformation and hypothetically could not populate the lower energy α-axial transition state. This would lead to a different stereochemical outcome of the kinetic resolution. Since the *cis*-diastereomer was not commercially available, it was prepared by reaction of cyclohexanone and acrylamide in the presence of pyrrolidine. This intermediate immediately cyclized to the lactam **115**, which was reduced by a sequence of hydrogenation and $LiAlH_4$, to generate the desired decahydroquinoline **117** as a single diastereomer in good yield (Scheme 38).



Scheme 38. Synthesis of *cis*-decahydroquinoline.

When subjecting both decahydroquinolines to the kinetic resolution the *cis*-isomer fully consumed the stoichiometric reagent within 15 hours whereas the *trans*-isomer showed 36% conversion only after 48 h (Scheme 39).



Scheme 39. Kinetic resolution of *cis*- and *trans*-decahydroquinoline.

Surprisingly, acceptable selectivity was obtained in both cases. The opposite sense of induction relative to the *cis*-decahydroquinoline was obtained, even though the same configuration of the chiral acylating reagent is employed. Since the *trans*-decahydroquinoline cannot react in the conformation where the α-substituent is axial, the only transition states that are accessible for the *trans*-diastereomer have the α-substituent in equatorial position ((2R,3S)-α-equatorial‡ and (2S,3R)-α-equatorial‡) (Figure 18). When only these two transition states are considered, equally high selectivity is expected for the *opposite enantiomer* due to the large calculated energy gap. Furthermore, the reaction rate of *trans*-decahydroquinoline is expected to be slower, as observed experimentally, since the overall, energy of this pathway is higher. This outcome is in good agreement with the calculated data and serves to confirm the previously proposed model to be correct.

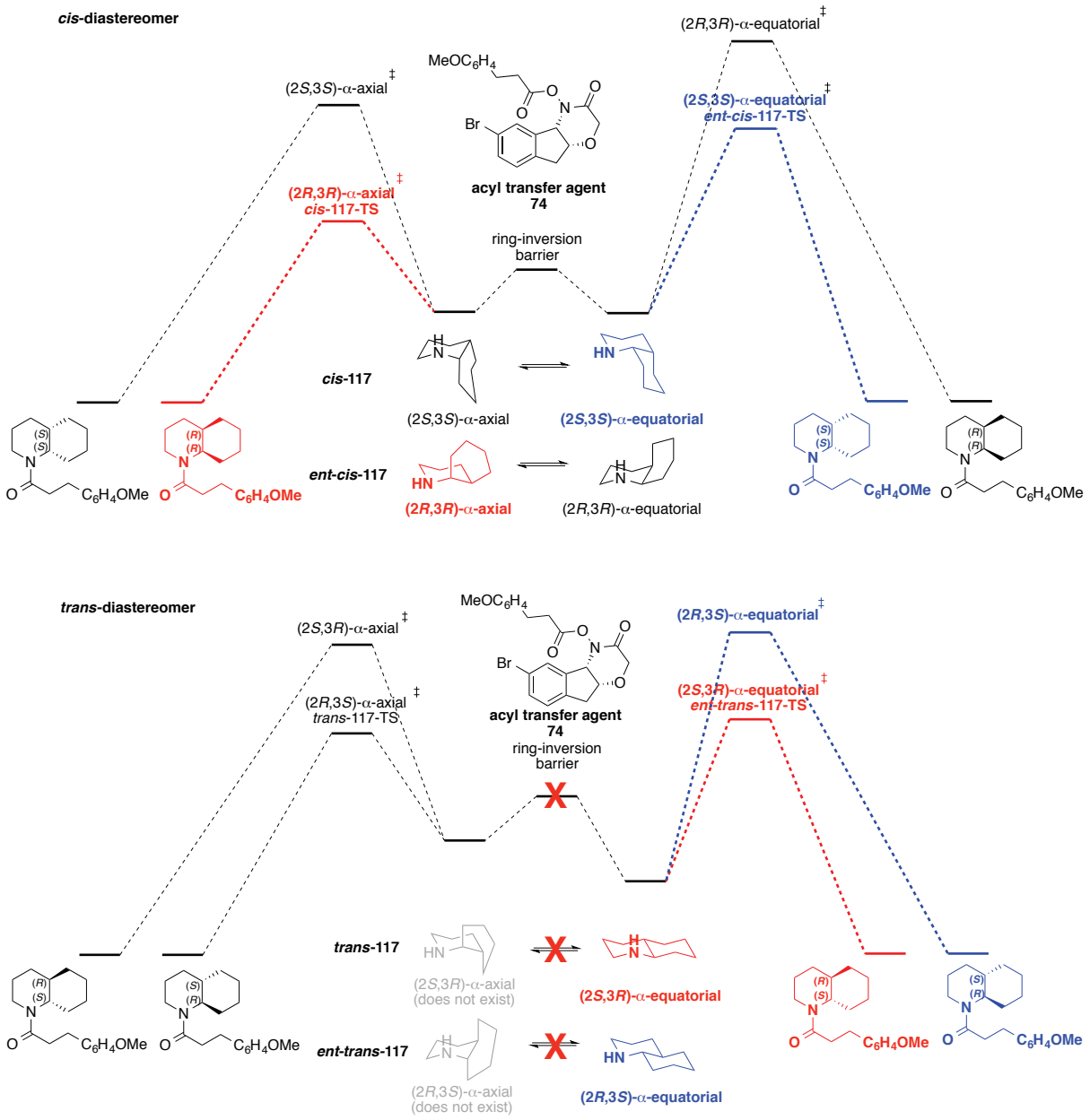
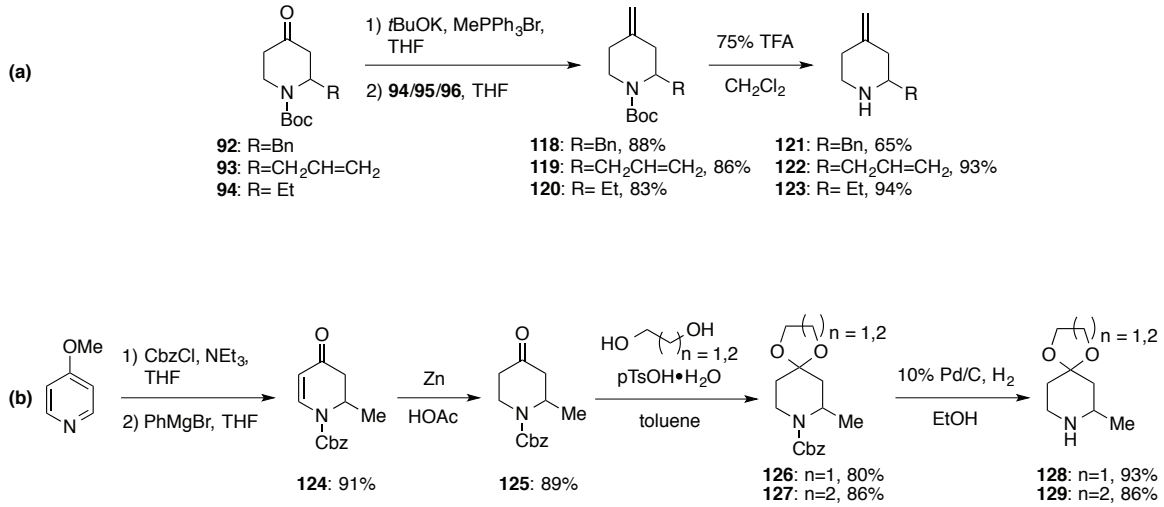


Figure 18. Proposed energy diagrams for the kinetic resolution of *cis*-decahydroquinoline (top) and *trans*-decahydroquinoline (bottom) with the chiral acylating agent. The lowest energy transistion state is highlighted in **red**, the second lowest one in **blue**.

3.11 2,4,4-Tribsubstituted Piperidines

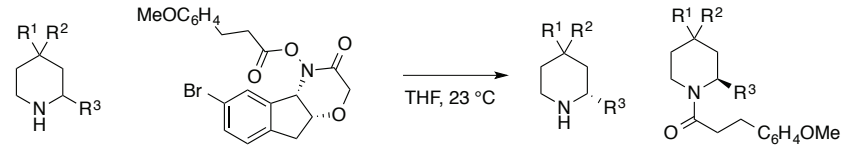
In addition, the model suggests that disubstituted piperdines with a single chiral center and no large conformational preferences between the axial and equatorial α-substituents should be good substrates for the kinetic resolution. To test this hypothesis five structures were prepared (Scheme 40) and subjected to the kinetic resolution. For their preparation similar routes were employed as for the preparation of 2,4-disubstituted

piperidines. The previously obtained intermediates **92**/**93**/**94** (Scheme 35) underwent Wittig olefination and acid catalyzed *N*-deprotection yielding three substrates **121**/**122**/**123** bearing a methylene group at position 4. In another analogue MeMgBr was added to the acylpyridinium salt obtained from 4-methoxypyridine and phenyl chloroformate. After conjugate reduction with Zn in AcOH acid the piperidinone **125** was obtained. Acid catalyzed acetal formation with either ethylene glycol or propylene glycol generated **126** and **127**. After deprotection *via* hydrogenation with Pd/C two piperidines **128** and **129** could be obtained in good overall yield.



Scheme 40. Synthesis of 2,4,4-trisubstituted piperidines.

Subjecting the prepared compounds to the kinetic resolution, the hypothesis was confirmed by the excellent results obtained with substrates bearing an exocyclic 4-methylene and a single α-substituent (Table 10, entries 1–3). In addition 2,4,4-trisubstituted spiro-piperidines containing a cyclic ketal were also resolved with modest selectivity (Table 10, entries 4 and 5).



1.0 equiv **74** (0.5 equiv)

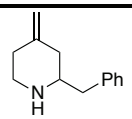
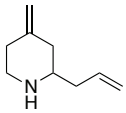
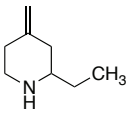
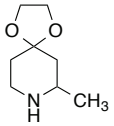
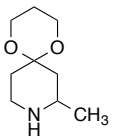
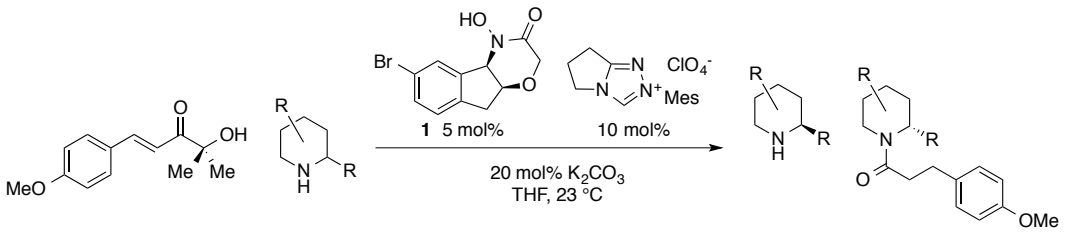
entry	substrate	s[a]	conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e,f] (%)	er amide[d] yield[f] (%)
1		27	51	20	92:8 (45)	91:9 (43)
2		18	49	20	88:12 (46)	89:11 (43)
3		18	56	20	95: 5 (39)	86:14 (54)
4		8	48	20	79:21 (25)	81:19 (44)
5		9	64	20	94:6 (23)	75:25 (21)

Table 10. Results of the kinetic resolution of 2,4,4-trisubstituted piperidines.
[a] Calculated selectivity. [b] Calculated conversion. [c] Reaction time until the stoichiometric reagent is fully consumed. [d] Determined by SFC or HPLC on a chiral support. [e] Isolated as the Cbz-derivative. [f] Yield after column chromatography.

All five substrates evaluated show fast reaction rates and useful selectivity, indicating no adverse affect on the resolution of substrates containing additional achiral substitution. The alkene or protected carbonyl in the products provide a means for post-resolution derivatization.

3.12 Catalytic Kinetic Resolution of Multisubstituted Piperidines

To test whether the obtained results and proposed model for all substrates can be reproduced and is valid also for the catalytic kinetic resolution, one substrate of each section was tested in addition to the decahydroquinolines and three substrates bearing an exocyclic methylene group (Table 11).



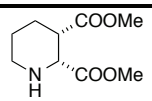
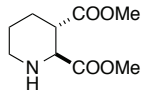
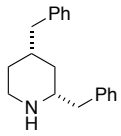
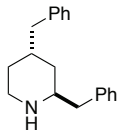
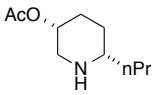
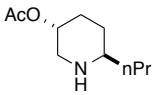
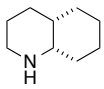
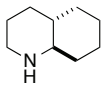
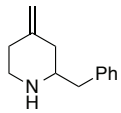
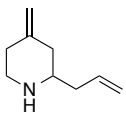
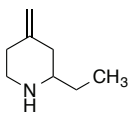
entry	substrate	s[a]	conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e,f] (%)	er amide[d] yield[f] (%)
1		11	28	72	64:36 (43)	89:11 (25)
2		2	3	72	51:49 (58)	67:33 (5)
3		3	4	48	51:49 (43)	78:22 (4)
4		21	59	20	99:1 (28)	83:17 (26)
5		19	17	20	59:41 (35)	94:6 (20)
6		8	5	48	52:48 (54)	89:11 (9)
7		18	63	48	99:1 (20)	79:21 (40)
8[g]		9	11	65	45:55 (61)	10:90 (9)
9		19	43	20	81:19 (40)	91:9 (42)
10		14	41	20	77:23 (43)	89:11 (40)
11		21	55	20	96:4 (42)	87:13 (43)

Table 11. Results of the catalytic kinetic resolution of disubstituted piperidines.

[a] Calculated selectivity. [b] Calculated conversion. [c] Reaction time until the α-hydroxyenone is fully consumed. [d] Determined by SFC or HPLC on a chiral support. [e] Isolated as the Cbz-derivative. [f] Yield after column chromatography. [g] Opposite sense of induction observed.

For the 2,3-, 2,4- and 2,5-disubstituted piperidines (Table 11, entries 1-6) the results where in good agreement with the data obtained with the stoichiometric kinetic resolution reagent. In general slightly lower conversion and selectivities where observed. The resolution of *trans*-decahydroquinoline (Table 11, entry 8) showed the same effect of inversed sense of induction proving the model also valid for the catalytic version of the kinetic resolution. Substrates bearing an exocyclic methylene group showed also similar fast reaction times and good selectivities.

3.13 Conclusion

In summary a series of disubstituted piperidines were prepared and the reactivity and selectivity of disubstituted piperidines in the kinetic resolution was examined by means of enantioselective acylation with a chiral hydroxamic acid. For most cases, synthetically useful relative rates and outstanding functional group tolerance were observed. Kinetic resolution studies and density functional theory (DFT) calculations exposed remarkable conformational preferences in both reactivity and selectivity, revealing a requirement for an axial-α-substitution on the reactive form of the N-heterocycle for effective resolution. This preference extends even to substitution patterns where the substituents must occupy bis-axial positions. This work provides, 1) access to valuable enantiomerically enriched disubstituted piperidines, 2) general guidelines for selecting suitable N-heterocycles as substrates for the kinetic resolution via chiral hydroxamic acids, and 3) affirmation of the transition state model involving a high energy conformation of the substrate that the Bode group had previously developed on the basis of DFT calculations.

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4

Automated Synthesis of N-Heterocycles

This project was realized in cooperation with Dr. Kuang-Yen Chen, Olivier Gröninger and Leran Zhang at the ETH Zürich.

CHAPTER 4. Automated Synthesis of Saturated N-Heterocycles

4.1 Introductory Remarks

This chapter presents the development of a device for the fully automated synthesis of saturated N-Heterocycles. The project is based on the SnAP (Stannyl (tin) Amine Protocol) chemistry developed by the Bode group and combines innovations in chemistry, engineering and computer science.

A fully automated, cartridge-based machine was developed, that enables researchers to conduct “SnAP chemistry” easily. This machine utilizes immobilized reagents in cartridges and requires no user involvement for the intermediate steps, enabling rapid production of N-heterocycles without exposure to toxic reagents (e.g. organostannanes), in a fully automated fashion. A prototype has been assembled and preliminary tests demonstrated that they key development goals of automation, broad scope, and construction from readily available components can be met.

4.2 Chemistry Research Today

In the last decades chemistry has evolved greatly with new technologies and reactions discovered faster than ever before.[95] However, the key processes in organic chemistry have not changed substantially. Even today, many chemical compounds for basic research are still synthesized using laborious and resource-inefficient processes, and in practice, synthetic chemistry still requires highly trained chemists. The process of conducting a reaction is time consuming. Careful weighing of chemicals and the addition of solvents, and a tedious workup and purification after completion of the reaction have to be conducted.[96] Slow reacting compounds cause further problems in organic synthesis and excess reagents or harsh conditions are often required to push the reactions to higher conversions within a reasonable time frame, which in return can cause problems in the purification step. Many of these problems have been addressed in the large-scale production of chemicals since even a small change in efficiency can render a process profitable or not. Therefore, every detail in the design of a production process is investigated and optimized. As a result, there is a great demand for automation and simplification of such chemical processes also on the laboratory scale for the quick production of research samples. In the research laboratory scale many

devices to simplify analysis of produced compounds were introduced over the past decades (e.g. autosampler for LC, GC or NMR). Another innovation is the development of synthesis robots for the production of large compound libraries. However, these require tedious reaction design and are aimed at parallel synthesizers. To our knowledge there is only a very limited number of easy to use reactor devices for the transformation of a certain functional group to another.

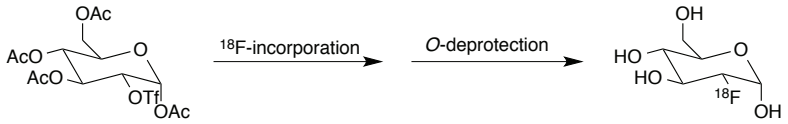
One object of the present project is to address these limitations of organic synthesis by enabling an unskilled user to rapidly synthesize organic compounds in a fully automated manner. It should obviate the need to weigh and measure all but one of the reaction components, avoid the use of excess reagents, eliminate tedious reaction workups, and ultimately allow faster reaction times. Another object is aimed mainly at aiding chemical research and development organizations, as it can greatly simplify the way in which key scaffolds are produced for research.

4.3 Automated Synthesis of Chemical Compounds

Automated synthesis in combination with solid phase synthesis has been introduced in many laboratories in the last few decades.[97] Usually these apparatuses are specific to one reaction as well as the substrate class (e.g. solid phase peptide synthesis; SPPS). Today, peptide and oligonucleotide[98] assembly is routinely carried out using commercially available automated synthesizers that sequentially combine monomeric building blocks. Even non-experts can synthesize most sequences within one day or just order them from service companies that rapidly deliver the desired molecules for all types of biological experiments.

Especially useful are robots for solid phase peptide synthesis and are the state of art for synthesizing peptides in small to medium scale. Synthetic steps in SPPS are mainly composed of a repeating set of standardized reactions and a set of typically all natural amino acids. [99]

Another application of automated synthesizers is found regularly in radiochemistry, especially for ^{18}F containing compounds. [100] These compounds are frequently used in positron emission tomography (PET) devices as a tracer but would be valuable in other spectroscopic technologies too. The most prominent example, Fludesoxyglucose F^{18} is made in two steps (Scheme 41).



Scheme 41. Preparation of Fludesoxyglucose F^{18} over two steps.

The short half-life of ^{18}F of only 110 minutes limits its use. The time from its production in a cyclotron to the final use is valuable and the activity decays fast. Synthetic routes and purification have to be fast and quick application to the patient is necessary. Also the radioactivity makes it difficult to work with for the technician or chemists. In order to reduce these problems, automatic synthesizers have been developed, that can produce the tracer molecule quickly, directly after delivery from the cyclotron and without the involvement or radioactive contamination of a human. Typically the synthesizers are optimized for only a single substrate and product, on microgram scale.

Automatic synthesis will begin to become difficult once a general automatic process for a large number of unknown substrates has to be developed. With the exception of a hydrogenation device[101] no other synthesizers have been developed that provide simple transformations of functional groups without previous optimization. A machine or a set of machines that carryout simple chemical reactions would revolutionize research in chemical laboratories. Therefore, there is a great demand for novel, automated methods that enable the synthesis of key compounds in a simple, rapid, and highly efficient manner.

4.4 Flow Chemistry

Organic synthesis has traditionally been performed in batch conditions, which means in round-bottomed flasks, test tubes, or closed vessels. Compared to this, continuous flow chemistry offers many advantages. Better mixing of components and easier control of reaction temperature allow faster and cleaner reactions. Reaction times in flow can be precisely controlled, down to a few seconds or less (impossible in batch conditions), allowing the rapid generation of reactive intermediates to be used immediately in another reaction step. Multistep, telescoped reactions provide a route to complex organic transformations avoiding the steps of isolating intermediates. Also difficulties of scaling up batch reactions are well documented. Flow reactions can be scaled up more easily, simply by running for longer or by using higher flow rates and correspondingly larger reactors. However, the requirements for mass transfer and heat transfer in the larger reactors must be considered.

Recent advances in continuous flow methodologies have gained much attention from synthetic organic chemists. New developments include downstream processes, work-up and analysis that can be integrated into the flow process. Operations such as aqueous work up, metal scavenging columns or ion exchange resins can be added into the flowing process. On-line analytical techniques of UV, conductivity, pH and even FTIR can be easily implemented. Offline techniques such as LC/MS can be integrated either through automated fraction collection or using a sampling valve / dilutor for approaching real time analysis. This had led many research groups to reconsider well-known chemical reactions and to develop versions compatible with flow chemistry conditions.[102] More and more flow chemistry devices are combined with intelligent hard- and software to create automatic synthesis devices.[103] A number of continuous flow chemistry equipment manufacturers like Uniqsis, Vapourtec and Syrris commercialized a range flow chemistry modules, which are commonly used in chemical research groups (Figure 19).[104] Their products are not specific to any particular reaction. Therefore any reaction to be run on the flow machine has to be specially developed and optimized for the type of flow reactor, which represents a laborious process with an uncertain outcome.[105]

Figure 19. Uniqsis and Vapourtec flow chemistry reactors.

Although the technology constitutes a big step in the general development of how organic chemistry is done, certain problems still remain. A fully optimized flow chemistry process can deliver high amounts of the desired product but the reactor setup and optimization for a specific product can consume a lot of human working hours. Although self-

optimizing systems have been investigated, the complexity of the system is limited.[106] More complex or flexible systems continue to be dependent on a skilled bench chemist. Therefore, we see a great demand in automatic synthesis system that can generate large numbers of different products without the input of a lot of work.

For this reasons we believe it is disadvantageous to develop an “all-rounder”, and instead see advantages in focusing on a high performing, targeted device. Flow chemistry in combination with a special cartridge, which can be easily inserted into a device would meet this demand. The cartridge contains all reagents necessary for producing a specific class of chemical compound.

So far, only one other reagent containing cartridge-based approach is currently available on the market – the H-cube from Thales Nano (Figure 20).[101] A user can select one of many different catalyst containing reagent cartridges to insert into the device. The substrate, chosen to be transformed, is pumped through the cartridge and reacts with hydrogen directly produced inside the device at a broad range of pressures and temperatures. Research companies are highly interested in these very successful machines (over 800 units sold to date), and are willing to pay 50-150 CHF for disposable reagent cartridges, if handling is simple and the quality of the product is high.

Figure 20. Thales Nano H-cube. Flow chemistry device for hydrogenation reactions.

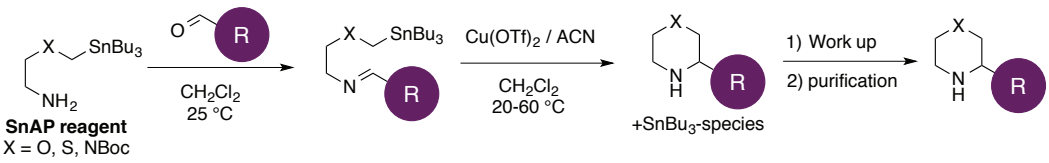
4.5 Background: SnAP Chemistry

Saturated N-heterocycles are an important class of compounds in all areas of chemistry, especially in the development of new pharmaceuticals where they are becoming increasingly attractive scaffolds. Unlike their aromatic counterparts, there are limited strategies for facile construction of substituted saturated N-heterocycles by convergent,

predictable methods. Currently long and laborious synthetic routes, with difficult to handle or toxic reagents, are employed. This limits the accessibility and variability of these compounds.

In the Bode Group we have developed so called “SnAP reagents” (Stannyl (**Sn**) **A**mine **P**rotocol). This rapidly expanding class of reagents has an outstanding substrate scope, and their coupling with widely available aliphatic, aromatic, heteroaromatic aldehydes, and ketones provides access to a large variety of N-heterocycles that are challenging to prepare using existing synthetic methods. The use of SnAP Reagents alleviates previous synthetic challenges and provides a direct route to saturated N-heterocycles. This methodology and the resulting products are of great interest in drug discovery, since it provides ready access to differentially substituted analogues for structure–activity relationship (SAR) studies, and greatly expands the availability of saturated N-heterocycles.

Recently these reagents were commercialized, in collaboration with Sigma-Aldrich. The consumer demand is high and initial sales are promising, indicating that there is significant interest in these products. This is despite the disadvantages associated with this methodology, including the use of toxic materials, long reaction times, and relatively complicated reaction setups and workups. Unfortunately, low profit margins and intense competition in the fine chemicals arena make further investment in the “reagent model” unattractive for further business development as a spin out. We have sought instead to generate a new concept that addresses both the limitations in the use of SnAP reagents, and creates new opportunity for creating a sustainable business model.



Scheme 42. Work sequence to generate N-heterocycles from SnAP reagents.

These limitations include the use of toxic material like tributyl-tin species. Furthermore the protocol is rather work intensive and can take up to two full working days to obtain a single compound. This arises from the time for weighing chemicals, reaction setup, catalyst formation, for the reaction to proceed and finally an aqueous workup and tedious purification by column chromatography. If several compounds need to be produced, this methodology is too time consuming to find a way into chemistry laboratories as a standard method.

4.6 Concept of Automated N-Heterocycle Synthesis

4.6.1 Key Advantages

The objective of this project was to develop a fully automated, cartridge-based machine that enables researchers to conduct SnAP chemistry without any of the drawbacks in batch synthesis or continuous flow chemistry. For this purpose we are developing single use disposable cartridges, which contain all the reagents and compounds necessary for the generation of N-heterocycles. The machine can use these cartridges together with the chosen aldehyde substrate. A programmed fully automatic sequence in combination with pumps and valves allows the machine to synthesize and provide N-heterocycles and does not require user involvement for the intermediate steps, thus enabling rapid incorporation of N-heterocycles without exposure to toxic reagents.

The key advantage for users include:

1) Fully automated, rapid synthesis
2) Synthesis without specialist training
3) Broad substrate scope
4) Disposable cartridge system
5) High purity products
6) Safe, enclosed system minimizing chemical exposure.

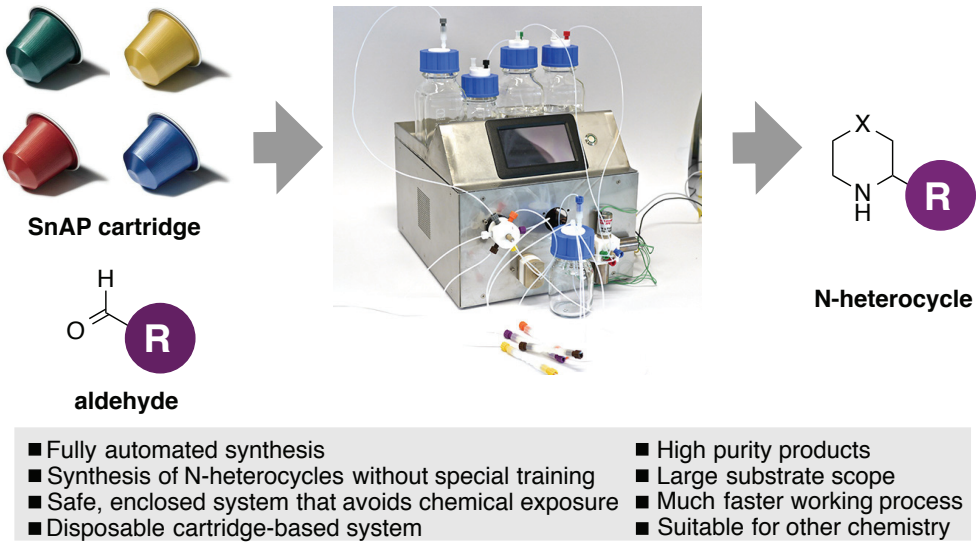


Figure 21. Concept and user advantages of the automated synthesizer for N-Heterocycles.

As shown previously there are many flow reactors and accessories already available on the market. These components are greatly used by research groups working in flow

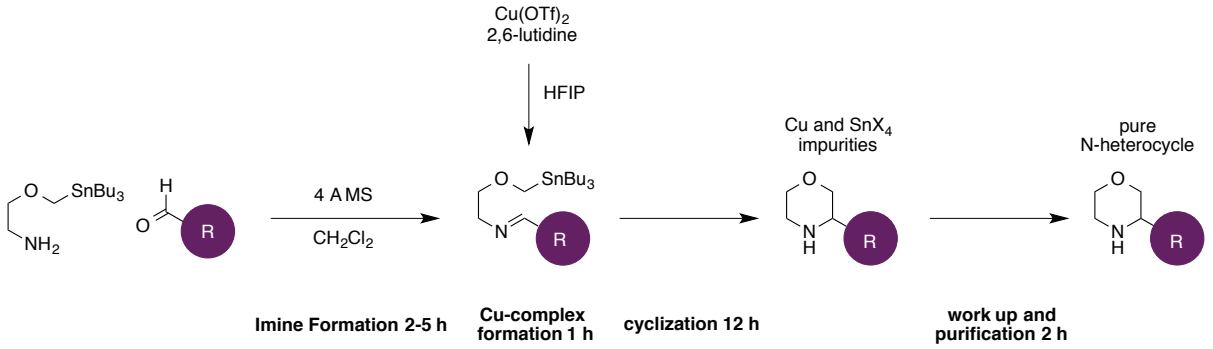
chemistry. Although our concept differs from these continuous flow devices (Table 12). Technically our concept is based on batch synthesis however we will be using flow chemistry technology. Only small research samples are produced one at a time, but this offers the possibility of generating a large number of highly important specialist compounds without any specialist training in a short time.

Generic flow chemistry devices	**VS.**	Synthesizer for N-heterocycles
Continuous flow synthesizer		Batch flow condition synthesizer
Limited to optimized substrates		Wide substrate scope
Laborious reaction tuning		No optimization
Scale production, mg – ton		Fixed mg scale
Production samples		R&D samples

Table 12. Comparison of generic flow chemistry devices and our automated N-heterocycle synthesizer.

4.6.2 Classical setup of SnAP reactions

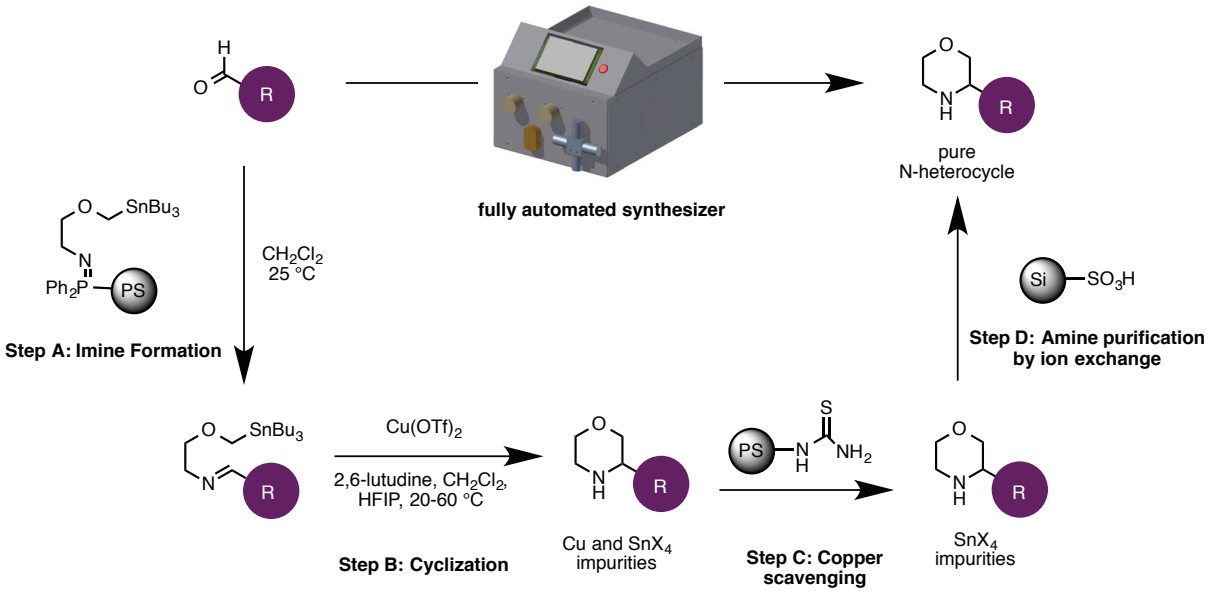
Carrying out a typical SnAP reaction is a time consuming and labor intensive process that requires a specially trained chemist to efficiently generate the wanted N-heterocycle (Scheme 43). A typical SnAP reaction starts with the preparation and weighing of the necessary reagents. The SnAP reagent and aldehyde are reacted within 2-5 hours to form the imine. For the next step the Cu-complex has to be prepared. The correct handling and generation of the complex is crucial in order to form the active complex during one hour. This can then cyclize the imine to the N-heterocycle during 12 h. Upon completion of the reaction the chemists has to spend another 2 hours for an aqueous work up and purification step to obtain the pure N-heterocycle. Overall the procedure can generate the wanted N-heterocycle after a minimum of 20 hours, which represents two working days. An automatic synthesizer producing the desired scaffold without any user involvement in only one hour would be a great advantage.



Scheme 43. Classical workflow of a typical SnAP morpholine reaction.

4.6.3 Automated Version of N-Heterocycle Synthesis

In order to generate the desired N-heterocycle using a synthesizer we had to alter the classical SnAP chemistry and adapt it to a version that can be fully automated. The synthetic sequence was then separated into four distinct steps A-D, each employing a different reagent. (Scheme 44)



Scheme 44. Synthetic scheme for the automated synthesis of N-heterocycles for the example of morpholine.

Step A – Imine Formation:

We began by looking at a way of speeding up the slow imine formation, which was achieved by their replacment with a Staudinger reaction. In previous work on the formation of spirocycles from SnAP reagents, it was demonstrated that ketimine formation is much faster

and cleaner with a Staudinger reaction than with our prior dehydration approach.[107] The use of a polymer support-PPh_3 reagent allowed access to a solid supported SnAP reagent. Another advantage of an immobilized SnAP reagent is that only the same amount of SnAP reagent as the aldehyde is released from the solid support. The rest will remain on the polymer support and will not contaminate the product in the end, simplifying the purification.

In the automated sequence the user provides the neat aldehyde in a reaction container and chooses one of the different cartridges containing the immobilized SnAP reagent of choice. The synthesizer adds solvent (CH_2Cl_2 or 1,2-dichloroethane) to the starting material from a solvent reservoir. Afterwards the solution is pumped through the first compartment of the cartridge containing the immobilized SnAP form the imine. The residual reagent in the first compartment is washed out with CH_2Cl_2 or 1,2-dichloroethane from the solvent reservoir to the reaction container.

Step B – Cyclization:

In the cyclization step HFIP and 2,6-lutidine are added to the solution in the reaction container from the solvent reservoirs. The mixture is pumped through the second compartment of the cartridge containing $Cu(OTf)_2$ at 60 °C to cyclize the ring. The residual reagent in the second compartment is washed out with CH_2Cl_2 or 1,2-dichloroethane from the solvent reservoir to the reaction container.

Step C – Cu-Scavenging:

In order to fully remove any Cu-complexes the product containing solution in the reaction container is pumped through the third compartment containing a Cu-scavenging resin at 60 °C. For the resin a polymer bound thiourea is used for this. The residual reagent in the third compartment is washed out with CH_2Cl_2 or 1,2-dichloroethane from the solvent reservoir to the reaction container.

Step D – Product Purification:

For purification of the product the mixture is pumped through the third compartment containing a polymer bound sulfonate (Isolute-HCX) - ion exchange resin at room temperature, where the product amine is captured. To remove all other impurities the solid support is washed with MeOH from the solvent reservoir. All the liquids are directed directly into the waste container. After a washing step of the reaction container the product is eluted from the ion exchange resin by a solution of NH_3 in MeOH to obtain the pure product in solution.

4.7 Setup of the Automated Synthesizer and Prototype

In order to perform all the four steps fully automatically, a number of key components were necessary. Several factors had to be taken into consideration when choosing the right equipment. For a later commercial production of the machine, costs of the components had to be kept low. Furthermore, the components of the machine have to be durable and should have a low maintenance cost. A central element included a pump suitable for working with chlorinated solvents or aggressive chemicals. In other flow chemistry machines HPLC pumps are typically used for this tasks. They can produce high pressures and flow rates, and the material stainless steel can withstand most chemicals used in a standard laboratory. However, these devices are relatively expensive (>2,000 CHF). Pump modules also come pre-assembled as a stand-alone device and individual parts from original equipment manufacturer are difficult to assemble and require higher engineering skill.

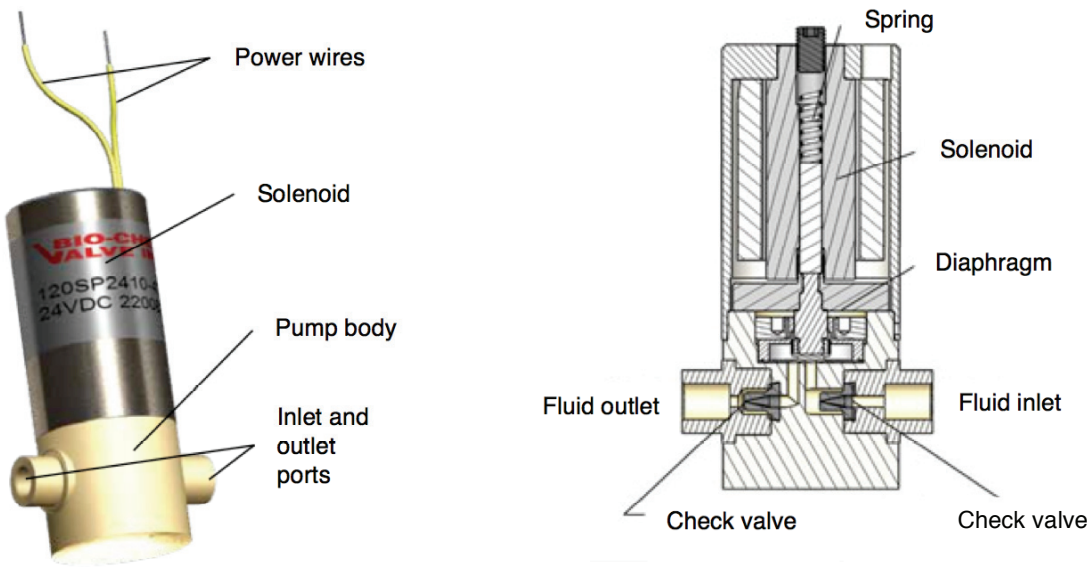


Figure 22. Illustration of Biochem fluidics solenoid pump.

Therefore, a solenoid pump was chosen for this project (approx. 600 CHF). Solenoid pumps use a little piston that can be moved back and forth *via* a solenoid (electro magnet) and a spring. Each time the solenoid moves back, the pumping chamber is flooded with the liquid. Upon moving the piston in the other direction, the liquid is pushed out towards the exit of the pump. Solenoid pumps are perfect for dosing of solvent since each stroke only pumps exactly the volume of the pump chamber. A product from Biochem fluidics was used, which has a 250 μL chamber. When running at a maximum cycle speed typical flows up to 25 ml/min can be obtained from this. The housing material of the pump is made out of PEEK (polyether ether ketone). It is highly resistant to aqueous and organic environments; it is not

perfectly suited for halogenated solvents since it can swell but this process is only observed at higher temperature (Figure 22).

The valves need to withstand the same chemicals as the pump. The requirement for this project is a solvent path selecting valve containing a common port and several selecting ports. The solvent should travel always from the common port to the selected port or vice versa. Several manufacturers offer a range of valves for example solenoid valves operating with the same principle as solenoid pumps. If the piston is moved with the electro-magnet it will open the port to allow the solvent to flow. These types of valves however, turned out to get blocked easily in our reaction setup. Once a solenoid piston could not completely close the port anymore unwanted solvent could flow unhindered. The second candidate was a rotary valve driven by a simple stepper motor. We obtained several valves with each a common port and eight selecting ports that could be selected by the motor rotating the valve. An electric encoder can also communicate the valve position to a controller. All the parts of the valve coming in contact with the chemicals are machined from Teflon to provide high resistance. Two of these devices were used for our prototype (Figure 23).

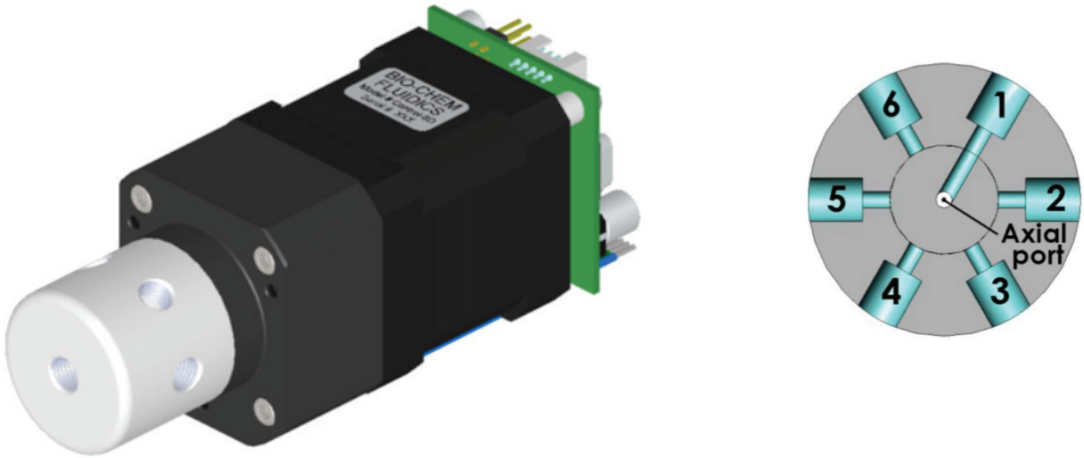


Figure 23. Illustration of the Biochem fluidics rotary valve (left). Port setup of the rotary valve (right).

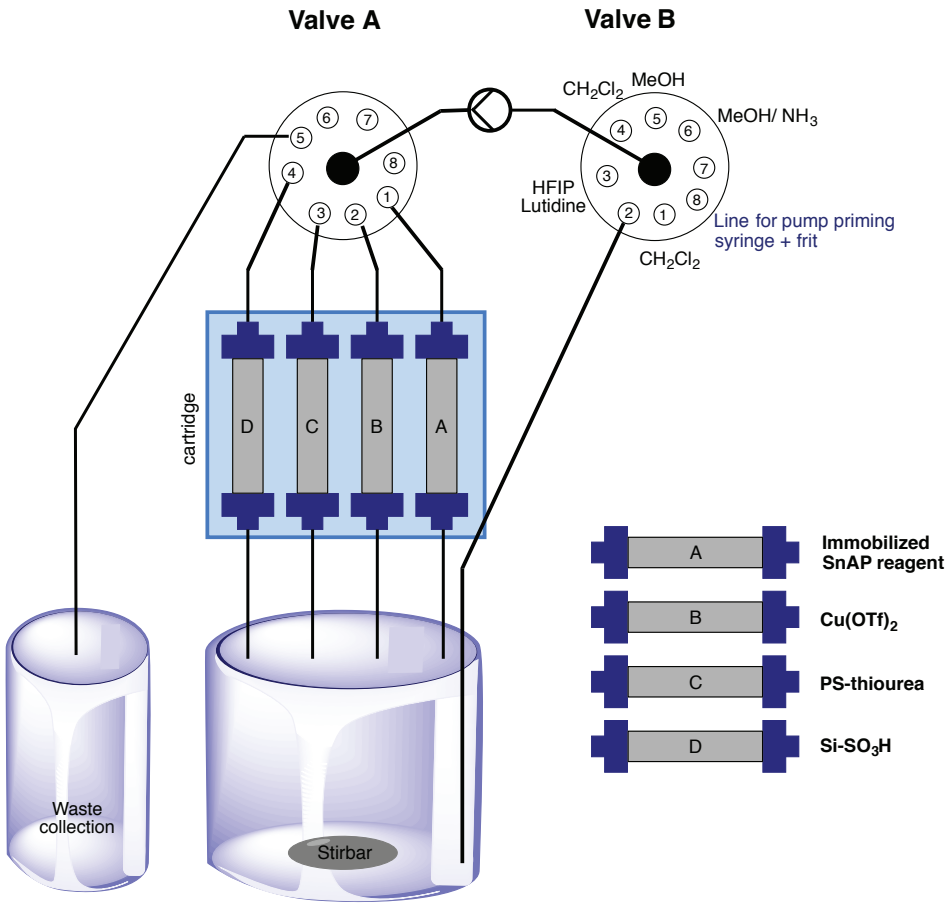


Figure 24. Setup and flow connetions of the automated N-heterocycle synthesizer.

Figure 24 depicts the general setup of the pumps and both valves. All the components are connected via Teflon tubing with 1 mm inner diameter, which is used also in common HPLC technology. Everything is connected in such a way that valve B selects the port from where the pump should draw the solvent from. This can be either the reaction container or one of the solvent reservoirs. Valve A selects the line where the liquid should be directed to; namely through one of the compartments A-D into the reaction reservoir or directly to the waste container.

Currently, we have not yet developed a single cartridge containing all four compartments itself. For each compartment containing the chemicals for Step A – D a syringe (Figure 25, top right) containing two frits was used for this purpose. In order to heat the compartment a cartridge holder was developed, which was machined from a block of aluminum to be able to house three reagent syringes. The block also contains four electric powered heating capsules to be able to raise the blocks temperature up to 80 °C. An attached polycarbonate block can hold two more syringes that do not need to be heated. In the final design all four compartments will be housed in a single cartridge and a fitting cartridge holder will be designed.

All of these essential components are attached on the outside front of the machine body. It is produced from six plates of stainless steel attached to an inner frame (Figure 25, left).

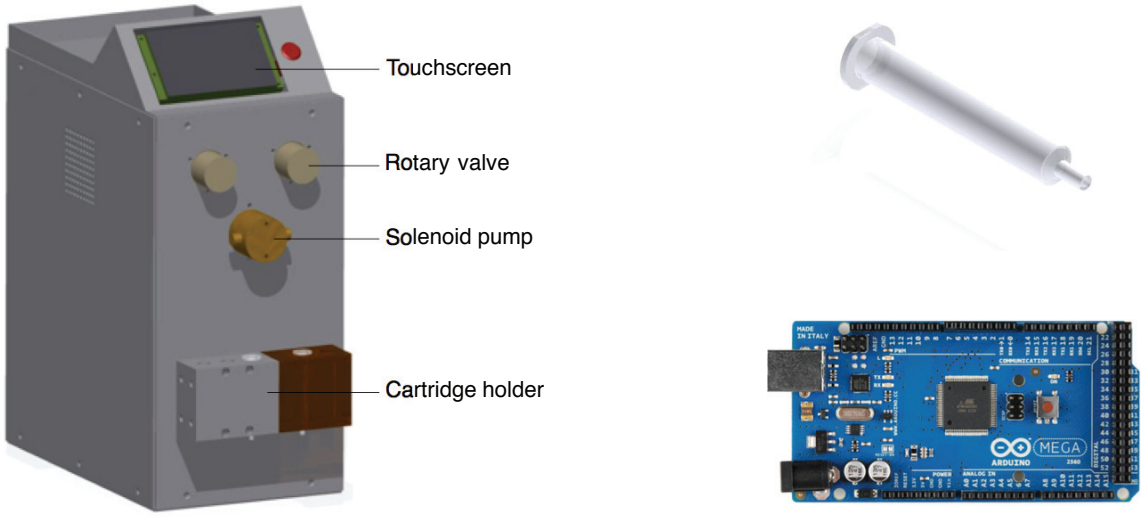


Figure 25. Prototype to the autmated synthesizer (left). Syringe used as compartment for the reagents (top right). Microcontroller Arduino MEGA 2560 (bottom right).

All of the outer components are controlled by an integrated internal microcontroller. In the beginning of the project, the ATmega328 in an Arduino Uno seemed to be the best choice. The open source platform of the Arduino offers plenty of code examples and the community developed several modules for this microcontroller to make projects like ours easier. However, soon with the development of the code the Arduino Uno reached its limitations both in terms of memory and number of interfaces. Its bigger brother the Arduino Mega (ATMega2560) offered the ideal upgrade (Figure 25, bottom right). The code was written in the open source Arduino IDE (integrated development environmen) that is based on the programming language C. The code with detailed explanations can be found in Experimental Part III. Two motor control modules for the Arduino that drives the two valves as well as the pump were obtained from Adafruit.

The machine itself takes its power from a regular 240 V socket. Inside the body the power is distributed to the heating pins in the aluminum block rail and their on/off state was controlled from the microcontroller via an opto-triac (electronic on/off switch for mains voltages). Also a common power supply converts 240 V to 12V and feeds power to the

central microcontroller board. The microcontroller handles the distribution of power to the other components.

As the central user interface a 4.3-inch touchscreen offers a simple, intuitive user interface. The solutions from 4D System offer a standalone touchscreen, which can be programmed by a specially developed IDE via a graphical interface. This greatly facilitates generated a user interface compared to the tedious manual programming. After the setup the touchscreen sends individual commands to the microcontroller to be processed over the serial interface (Figure 26).

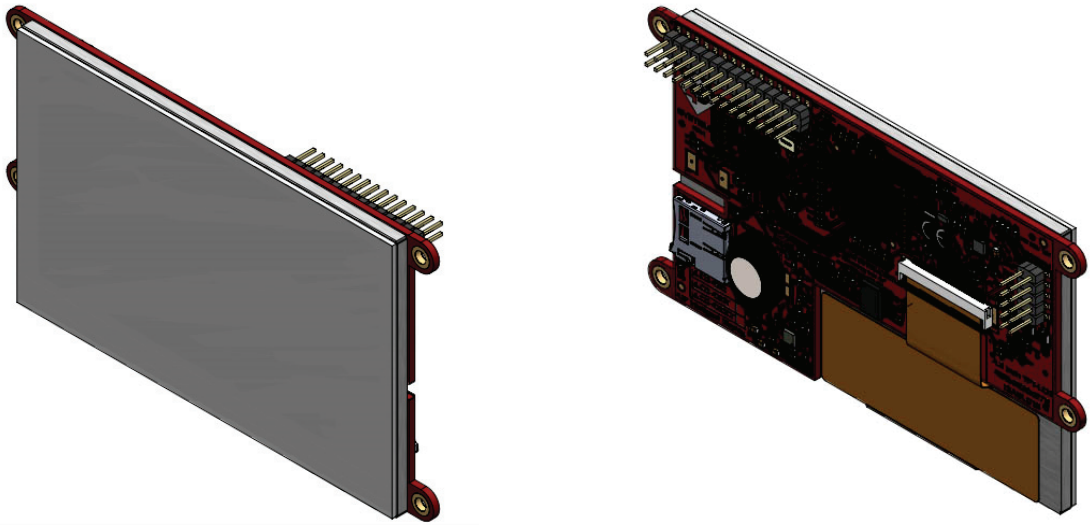


Figure 26. Illustration of the 4D Systems 4.3” touchscreen.

Further components include a manual main power switch on the back of the machine and a controller power button next to the touchscreen. A detailed circuit diagram can be found in the Experimental section III.

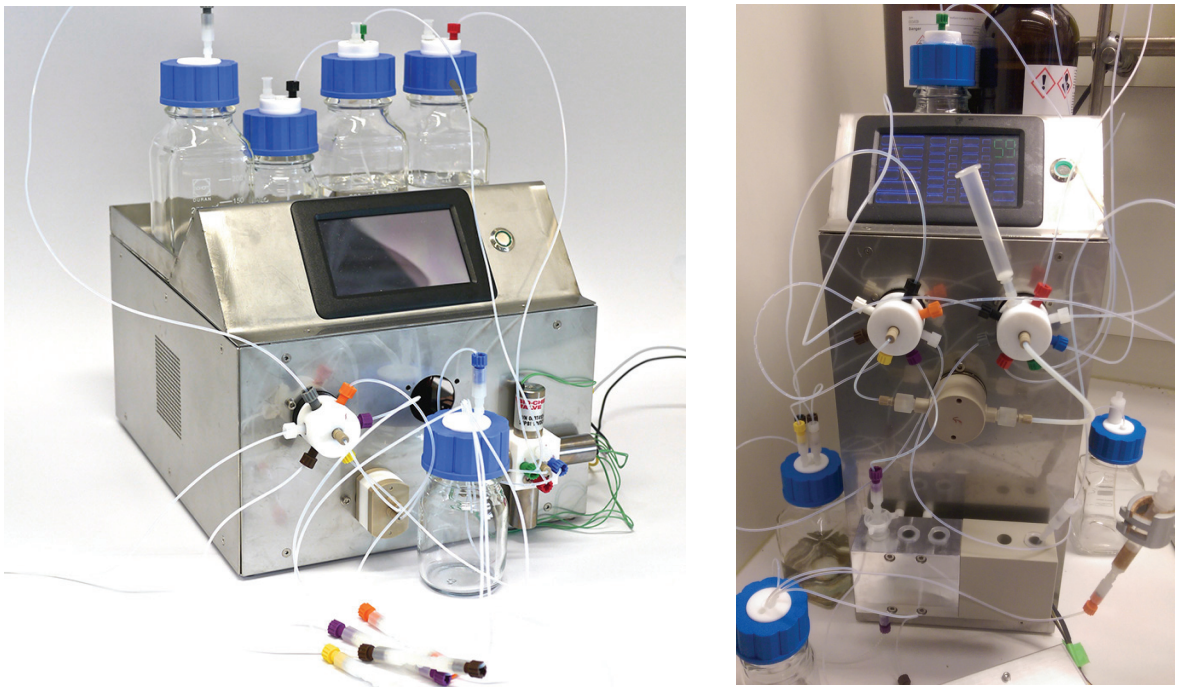
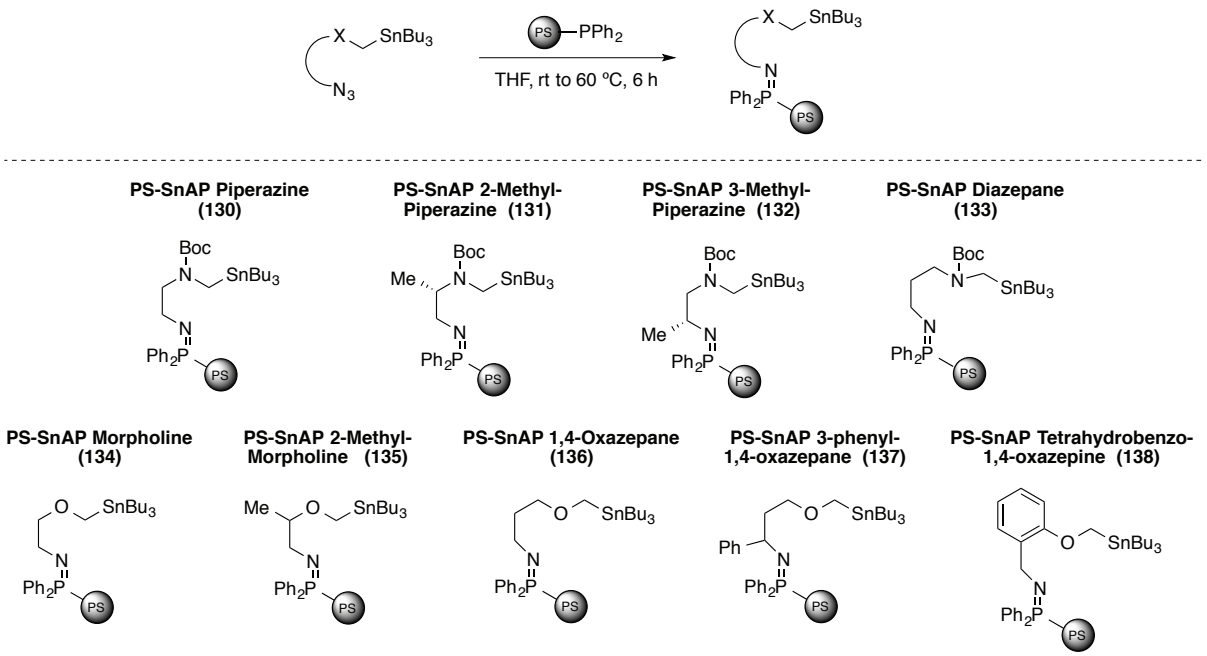


Figure 27. First and second prototype of the automatic N-heterocycle synthesizer.

4.8 Synthesis of Solid Supported SnAP Reagents

All polymer supported SnAP reagents were generated from their corresponding aza-SnAP reagents when treated with polymer-bound diphenylphospine *via* a Staudinger reaction. The two components were stirred until N_2 evolution ceased. After several washing steps the polymer supported SnAP reagents could be obtained with a typical loading of 1 mmol SnAP reagent per gram of polymer. Up to this point nine different polymer-bound SnAP reagents were prepared (Scheme 45). Aza-SnAP reagents were made according to literature procedures[108] and routes are shown in Experimental Part III.



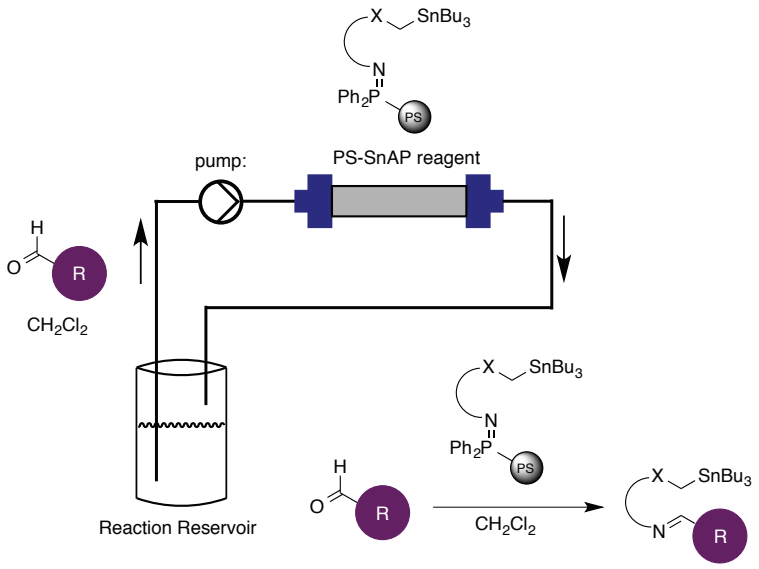
Scheme 45. Synthesis of the nine new polymer supported SnAP reagents.

4.9 Substrates for Automated Synthesis of N-Heterocycles

According to the previously detailed four step procedure (A – D) several N-heterocyclic products were obtained. These results were used to gain insight in the different reactivities of the SnAP reagents and to optimize and generate parameters for the different SnAP reagents. Parameters analyzed were temperature, flow rate, reaction time and concentration.

Step A: Imine Formation:

The prepared polymer-supported SnAP reagents were tested for imine formation with a number of different aldehydes. The aldehyde was first dissolved in a vial with CH_2Cl_2 or 1,2-dichloroethane (used for higher temperature reactions). And the solution was pumped through the fritted syringe containing the polymer-supported SnAP, resulting in imine formation. The solution exited the syringe on other side to flow back to the reaction reservoir. Since not all aldehyde reacts, the solution is cycled through this setup several time to gradually obtain full conversion in 1-2 h.



Scheme 47. Flow reaction for imine formation between the aldehyde and polymer-supported SnAP reagent.

The typical reaction scale was 0.2 mmol of aldehyde in 2 ml of CH_2Cl_2. To minimize the time to reach full conversion of the aldehyde three equivalents of polymer-supported SnAP reagent was used. Two equivalents of the reagent were remaining on the polymer after the reaction. However, theoretically the polymer could be washed and used again with longer reaction times.

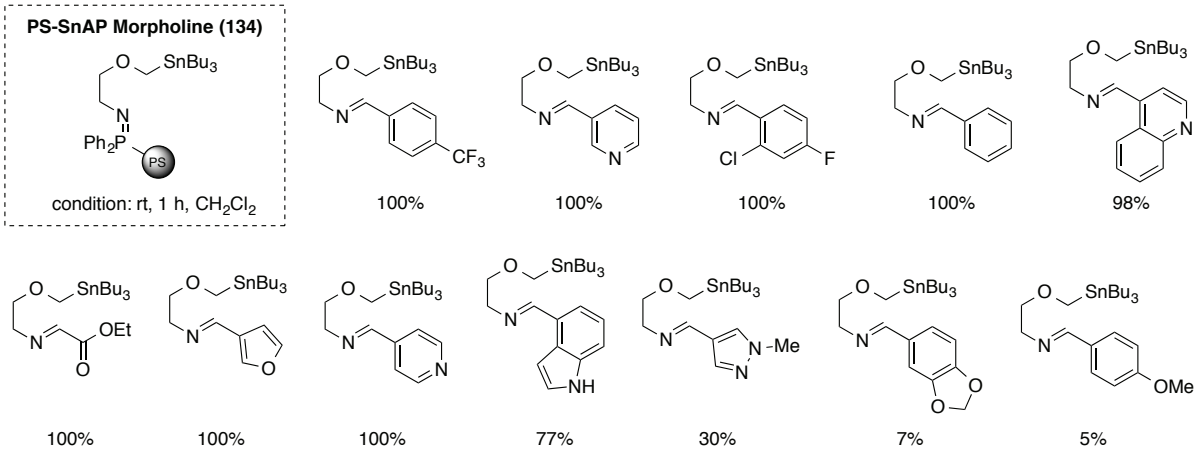


Figure 28. Scope of the imine formation of various aldehydes and the polymer supported SnAP morpholine reagent.

Polymer-supported SnAP Morpholine served as a test substrate to acquire a general aldehyde substrate scope. The efficiency of imine formation was affected by many parameters. A high concentration of the aldehyde would result in better conversion whereas

lower concentration required a prolonged reaction time to reach full conversion. Higher flow rates led to higher conversion in a fixed time as well. The different imines could be typically obtained in full conversion after one hour at room temperature. Only electron rich aldehydes required a prolonged reaction time because of the lower reactivity of the carbonyl group.

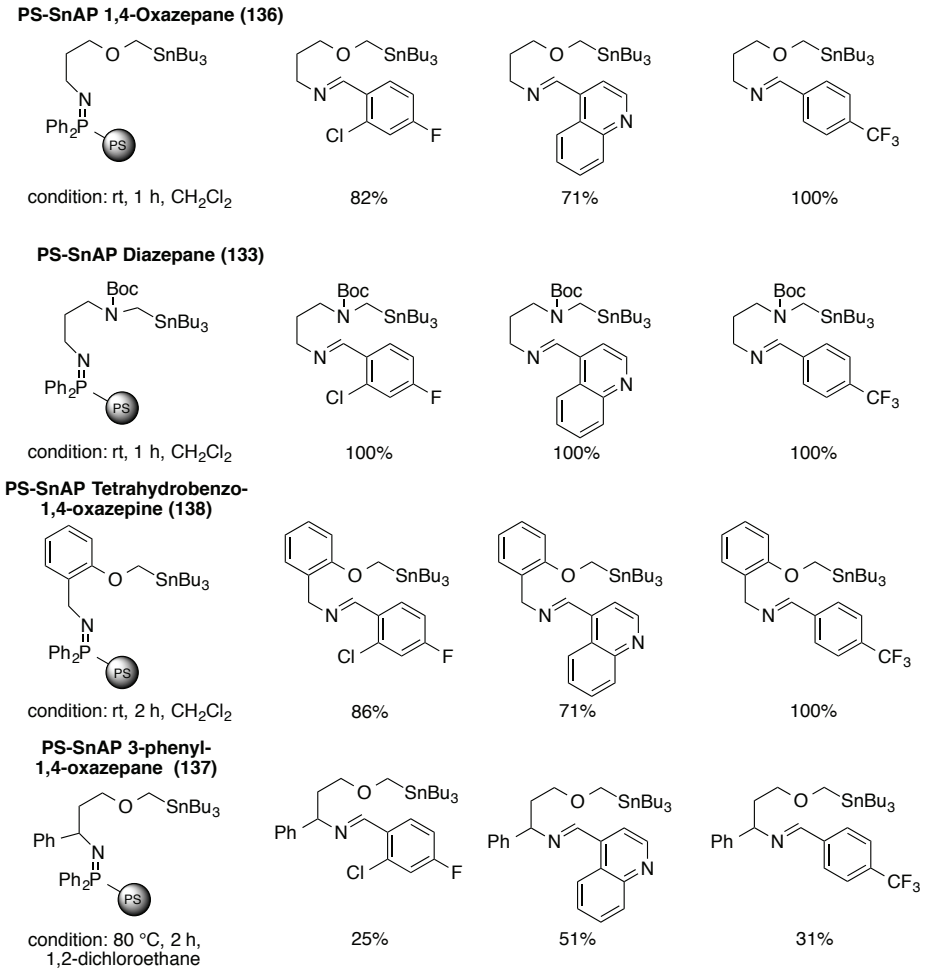


Figure 29. Investigation of the imine formation of three aldehydes with the polymer supported SnAP reagents.

In the next step different Polymer-Supported SnAP reagents were investigated towards their reactivity. Most of the reagents showed high reactivity with the previously identified conditions and could be converted into the imine in only one hour at room temperature (**136**, **133** and **135**). Unfortunately, reagents with a steric hindrance close to the phosphine imine moiety showed lower reactivity in the aza-Wittig imine formation depending on the size of the hindrance (**137** and **132**).

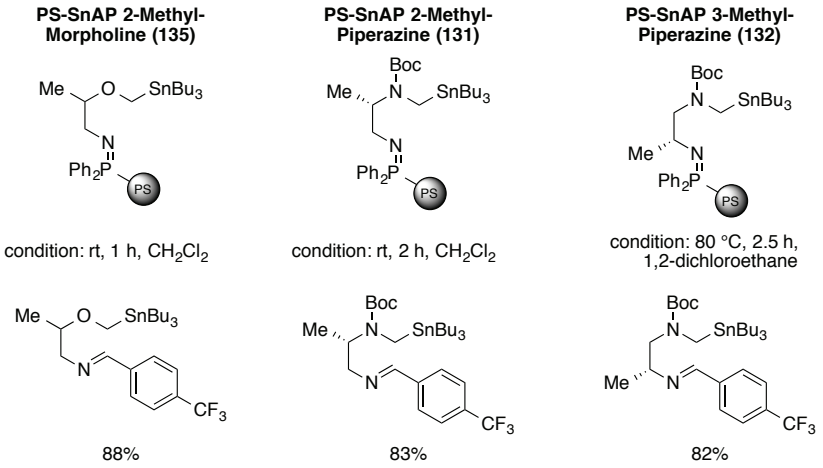
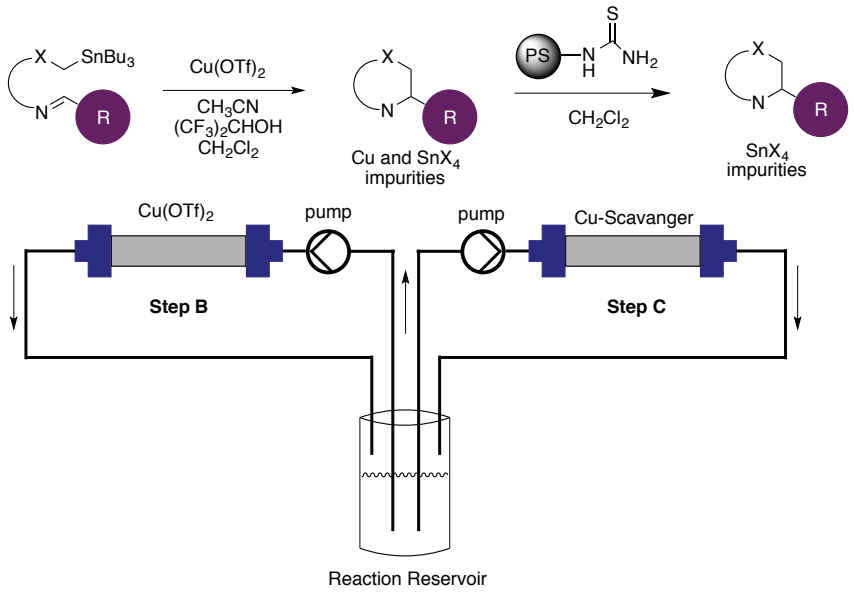


Figure 30. Investigation of the imine formation of the polymer supported SnAP reagents.

This effect could be overcome by heating the cartridge up to 80 °C. Since the boiling point of dichloromethane is lower than this the solvent had to be changed to 1,2-dichloroethane in these cases. With these optimized conditions a high conversion of 82% for **132** was reached only after 2.5 hours because it offers the largest steric hindrance of the prepared polymer supported SnAP reagents. This presents itself as difficult substrate and longer reaction times have to be anticipated.

Step B and C: Cyclization and Cu-Scavenging:

In the second step the previously formed imine is cyclized mediated by Cu(II), which is given from $Cu(OTf)_2$ in a second fritted syringe. The previously obtained solution containing the imine is pumped through the copper salt for one hour at room temperature. The resulting mixture contained the N-heterocycle, as well as copper and tin impurities that have to be removed. This happened in a two-step purification system. First, a commercial available metal scavenger (polymer support thiourea) was used to remove copper from the reaction mixture. The solution was pumped through a third fritted syringe containing the thiourea resin at room temperature for one hour. During this step the solution turned from blue or green to colorless as indication for the full removal of the copper complexes.



Scheme 48. Flow reaction for imine cyclization and cu-scavenging step.

Step D: Purification:

In order to remove impurities and side products in the reaction mixture a different approach than for the copper removal had to be taken. The crude mixture was passed through a fritted syringe filled with an Isolute-HCX (SO_3H support on silica), where the product N-heterocycle is captured.

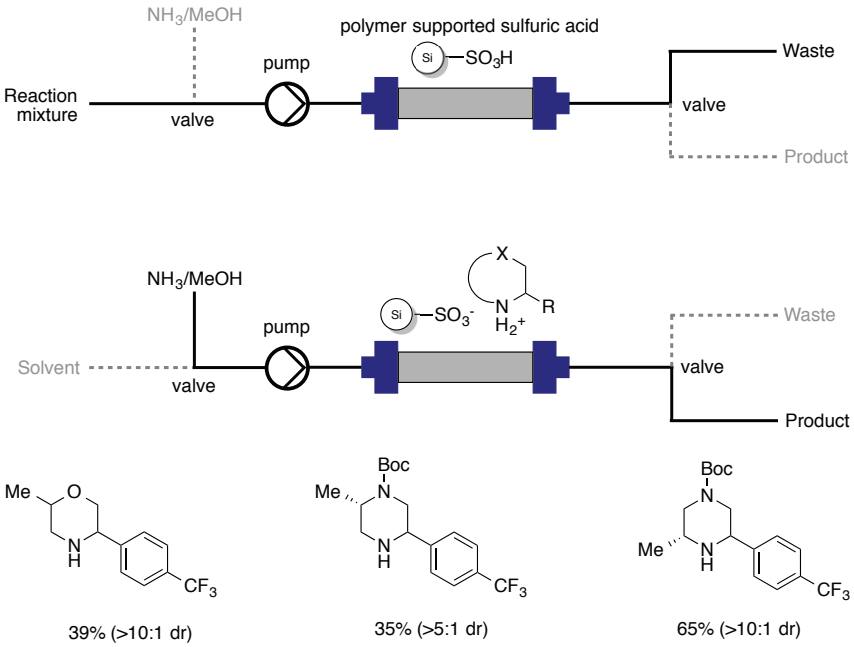


Figure 31. Purification of N-Heterocycle products with the catch and release resin.

All other compounds flowing through the resin were directed into the waste container. After few washing steps with MeOH and CH_2Cl_2, the pure product was released from the resin into a vial by flushing it with a solution of ammonia in methanol (Figure 31). By this method three N-heterocycles were generated from the corresponding imines in good yields.

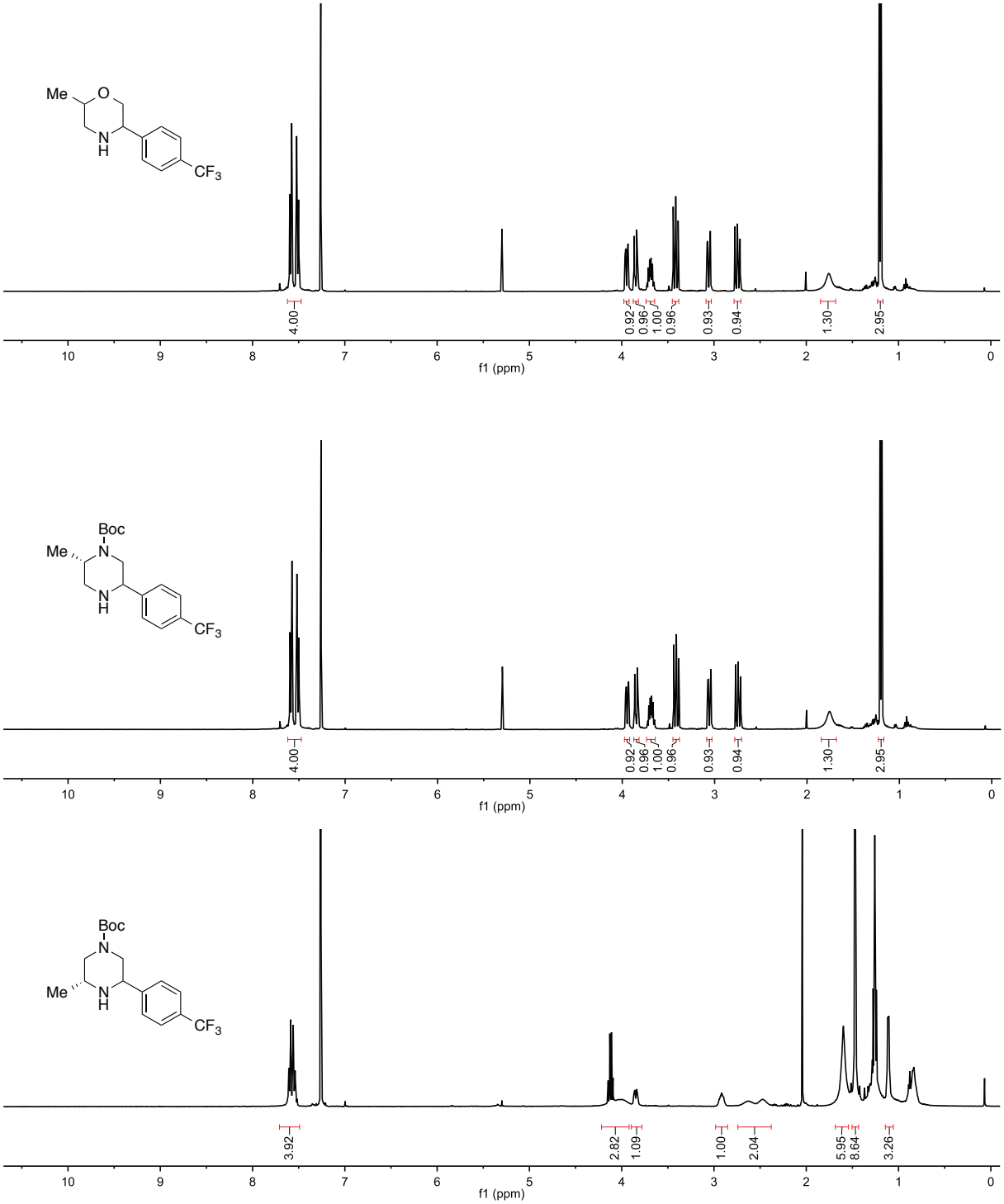


Figure 32. NMR-spectra of the pure N-heterocycle products obtained from the automated synthesizer.

4.10 Outlook

To reach the final goal of commercializing this technology a number of further development steps have to be taken. We are able to reduce the total time needed for N-heterocycle synthesis from almost 30 hours for classical batch conditions to 2 hours for our developed flow conditions. Further optimization and reduction of reaction time is necessary to create an attractive process. All previous results are encouraging, but still require further improvements, especially the design and fabrication of a user-friendly system for a single cartridge, and examination of the substrate scope is necessary to commercialize the machine and the technology. We plan to produce a total of 20 different polymer-supported SnAP reagents to provide a wide substrate scope for potential customers. In this study only three N-heterocycles were prepared to this date and more examples will be produced to assess all factors leading to high yields and high functional group tolerance.

Furthermore, we plan to develop a single use disposable cartridge, housing all of the four compartments with the individual reagents necessary for each step. Cartridges can eventually be purchased and be plugged in a partly heated cartridge holder. Depending on the wanted N-heterocycle the user can choose from a variety of different SnAP reagents in the cartridges. An asymmetric shape of the cartridge could prevent the wrong insertion.

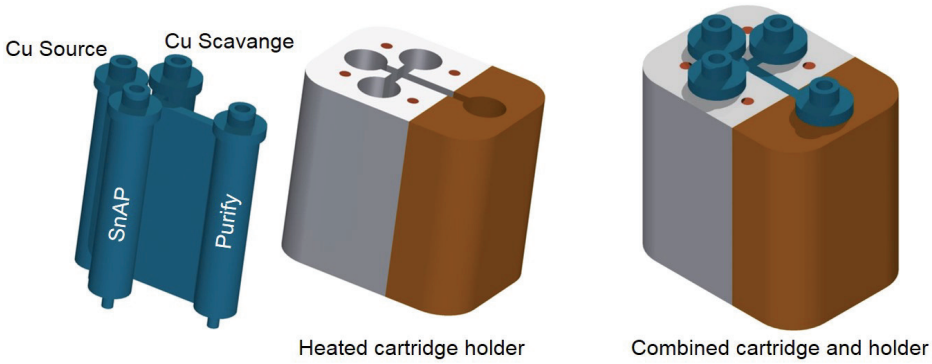


Figure 33. Preliminary draft of single cartridge and suitable heated cartridge holder constructed from aluminum with electronically controlled heating pins and plastics for a non heated part.

After finalizing the design of the machine itself and development of all of its components, production and distribution of a first production line can start.

4.11 Conclusion

We have described a new synthetic strategy for accessing N-heterocycles for drug discovery based on polymer-supported SnAP reagent. To achieve this, we have developed nine novel polymer-supported SnAP reagents and tested them for their ability to form imines. The imine-forming chemistry involved a Staudinger reaction of an iminophosphorane and the aldehyde is much faster and cleaner than our prior dehydration approach. Furthermore, the ability of the imines to cyclize under flow conditions was demonstrated by passage of the imine through a copper-catalyst compartment, which avoids the tedious, and sometimes capricious, formation of the copper-ligand complex necessary for the reaction. Finally, use of Cu-scavenging and an ion-exchange resin dramatically simplifies the reaction workup.

These key scientific discoveries enable our shift from a reagent-based to a machine-based flow chemistry approach. The development of a solid-supported delivery system for the SnAP reagents allows the delivery of the exact amount of SnAP reagent needed for a given amount of the aldehyde substrate. In comparison to batch condition, the need to carefully weigh and measure the reagents, handle the air- and water-sensitive imine, and exchange the solvent prior to cyclization is obviated in our new approach. Through this innovation and a prototype in hand, we are able to reduce the total time needed for N-heterocycle synthesis from almost 20 hours to 2 hours. This process does not require user involvement for the intermediate steps, thus enabling rapid preparation of N-heterocycles without exposure to toxic reagents, in a fully automated fashion.

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108 Full synthetic routes are displayed in Experimental Part III including references for spectral data and to synthesize starting materials.

5

Experimental Section I

CHAPTER 5. Experimental Section I on the Design and Development of New Hydroxamic Acid Co-Catalysts

5.1 General Remarks

All reactions were carried out in oven dried glassware under an atmosphere of dry N_2 using standard manifold techniques.[1] Chemicals were purchased from *Acros*, *Sigma-Aldrich*, *ABCR* or *TCI* and used without further purification unless otherwise stated. Dichloromethane was distilled from CaH_2 and THF from sodium, other solvents were dried by passage over two columns of anhydrous neutral A-2 alumina under an atmosphere of argon.[2]

Flash column chromatography was performed on silica gel (*Silicycle* SiliaFlash F60, 230-400 mesh). Thin layer chromatography was performed on glass-backed plates pre coated with silica gel (*Merck*, Silica Gel 60 F254).

NMR spectra were recorded on *Bruker* Avance III 400 MHz or *Varian* Mecury-VX 300 MHz spectrometers using $CDCl_3$ as the solvent unless indicated otherwise. ^{1}H NMR chemical shifts are expressed in parts per million (d) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.26 ppm or of CH_3OH at 3.31 used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (d) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.2 ppm or of CH_3OH at 49.0 used as a standard). All ^{13}C spectra were measured with complete proton decoupling. NMR coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; quint; quintet; sext, sextet; m, multiplet. Infrared (IR) spectra were recorded on a *JASCO* FT-IR-4100 spectrometer and reported as wavenumber (cm^{-1}) of the absorption maxima for the range between 4000 cm^{-1} and 750 cm^{-1} with only major peaks reported. Optical rotations were measured on *JASCO* P-1010 operating at the sodium D line with a 100 m path length cell. High resolution mass spectra were measured by the Mass Spectrometry Service Facility of Laboratorium für Organische Chemie at ETH Zürich on a *Bruker* Daltonics maXis for ESI-Q-TOF spectrometer (ESI-MS) or on a *Bruker* solariX (9.4T magnet) equipped with a dual ESI/MALDI-FT-ICR source using *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-

1 Leonard, J.; Lygo, B.; Procter, G.: Advanced Practical Organic Chemistry, Taylor & Fran*cis*, **1998**.
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propenylidene]malononitrile (DCTB) as matrix (MALDI-MS). Chiral HPLC (High-Performance Liquid Chromatography) and SFC (Supercritical Fluid Chromatography) were performed on *JASCO* liquid chromatography units. *Daicel* Chiralcel or Chiralpak columns (0.46 x 25 cm) were used. Liquid-chromatography/mass spectrometry was preformed using a Dionex UltiMate3000 RSLC (LC) coupled with a Surveyor MSQ Plus (MS). *Restek* Pinnacle II C18 columns (50 X 4.6 mm) with 5μm particle size were used. The standard gradient was 0% ACN in H_2O to 100% ACN over 4.5 min, hold for 2 min (both phases contain 0.01% formic acid). Details of chromatographic conditions are indicated under each compound. Hydroxamic acid co-catalysts were purified by reversed phase high performance liquid chromatography (RP-HPLC) on a Gilson preparative instrument on Shiseido Capcell Pak C4 or C18 columns (50 x 250 mm) at a flow rate of 40 ml/min. The mobile phase for RP-HPLC were Milipore-H_2O containing 0.1 % (v/v) TFA and HPLC grade CH_3CN containing 0.1 % (v/v) TFA.

5.2 Calculation of the s-Factor and Conversion

The s-factor (selectivity) was calculated using these equations:[3]

$$s = \frac{\ln[(1-C)(1-ee^{SM})]}{\ln[(1-C)(1+ee^{SM})]}$$

where ee^{SM} is the enantiomeric excess of the (acylated) recovered starting material amine or

$$s = \frac{\ln[(1-C)(1-ee^{PRODUCT})]}{\ln[(1-C)(1+ee^{PRODUCT})]}$$

where $ee^{PRODUCT}$ is the enantiomeric excess of the amide product.

The conversion was calculated using this equation:

$$conv = \frac{100 \cdot ee^{SM}}{ee^{SM} + ee^{PRODUCT}}$$

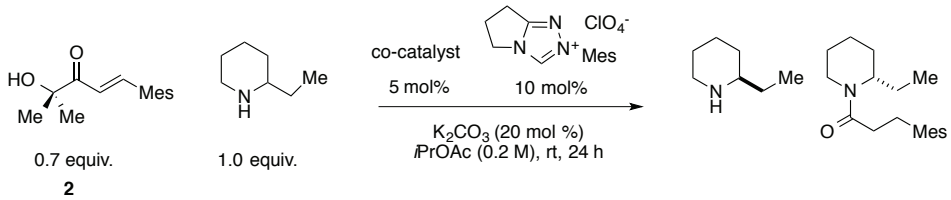
The enantiomeric ratios (ers) were determined by separation on HPLC or SCF columns with chiral support. Details of chromatographic conditions are indicated under each compound.

3 (a) Kagan, H. B.; Fiaud, J. C. Kinetic Resolution. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S. H.; Eds.; Wiley, New York, **1988**, *18*, 249-330–330. (b) Goodman, J. M.; Köhler, A.-K.; Alderton, S. C. M.: Interactive Analysis of Selectivity in Kinetic Resolutions. *Tetrahedron Lett.* **1999**, *40*, 8715–8718. (c) http://www-jmg.ch.cam.ac.uk/tools/magnus/KinRes.html (accessed February 2016).

5.3 Determination of Absolute Stereochemistry

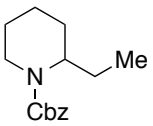
The relative stereochemistry could not be easily determined. When two diastereomers of a hydroxamic co-catalyst could be obtained, diastereomer 1 (eluted first) and diastereomer 2 (eluted second) were named according to the corresponding retention time in reverse phase HPLC. Enantiomeric ratios given for the recovered amine and acylated product after kinetic resolution reflect the ratio of the *R*-enantiomer over the *S*-enantiomer.

5.4 General Procedure for the Catalytic Kinetic Resolution of Ethyl Piperidine



Hydroxamic acid co-catalyst (0.013 mmol, 0.050 equiv), triazolium salt (8.2 mg, 0.025 mmol, 0.10 equiv), α'-hydroxyenone **2** (41 mg, 0.18 mmol, 0.70 equiv), K_2CO_3 (6.9 mg, 0.050 mmol, 0.20 equiv) and ethyl piperidine (32 mL, 0.25 mmol, 1.0 equiv) were mixed in *i*PrOAc (1.2 mL, 0.20 M). The reaction was allowed to stir for 24 h at rt and quenched by the addition of DBU (36 mL, 0.25 mmol, 1.0 equiv) and CbzCl (37 mL, 0.25 mmol, 1.0 equiv). The mixture was allowed to stir for 2 h at rt before sat aq $NaHCO_3$ solution (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by column chromatography (silica gel) to obtain the recovered amine as its Cbz-derivative and the amide.

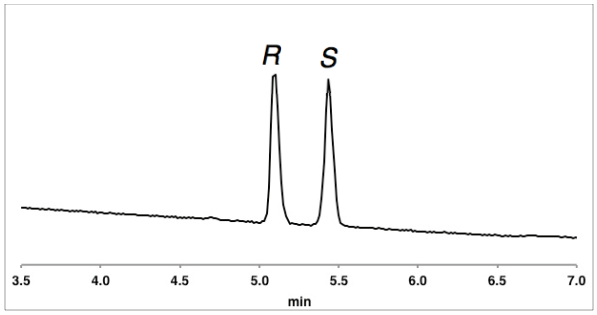
Benzyl 2-ethylpiperidine-1-carboxylate

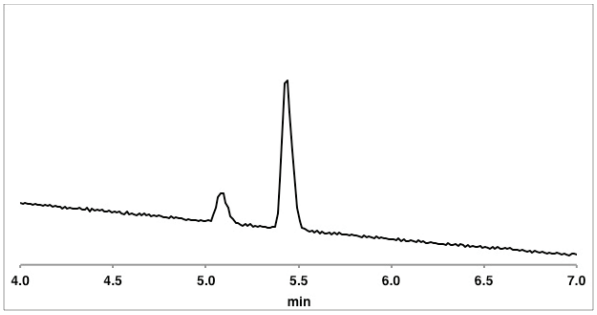


^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.38–7.26 (m, 5 H), 5.14 (d, *J* = 12.5 Hz, 1 H), 5.10 (d, *J* = 12.5 Hz, 1 H), 4.23–4.15 (m, 1 H), 4.04 (dd, *J* = 13.2, 1 H), 2.81 (td, *J* = 13.2, 2.6 Hz, 1 H), 1.76–1.33 (m, 8 H), 0.84 (t, *J* = 7.4 Hz, 3 H);[4] **HRMS** (ESI): calculated for $[C_{15}H_{22}NO_2]^+$: m/z = 248.1645, found: m/z = 248.1641; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in

4 spectral data is in accordance to: Aitken, S. J.; Grogan, G.; Chow, C. S.-Y.; Turner, N. J.; Flitsch, S. L.: Biohydroxylations of Cbz-protected Alkyl Substituted Piperidines by *Beauveria Bassiana* ATCC 7159. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3365–3370.

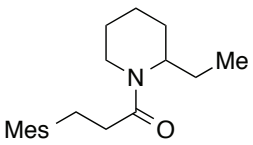
CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.1 min and 5.5 min.



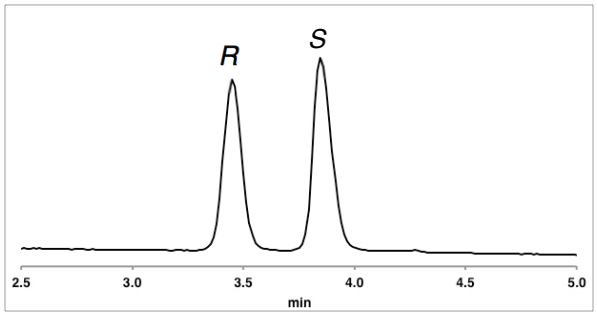


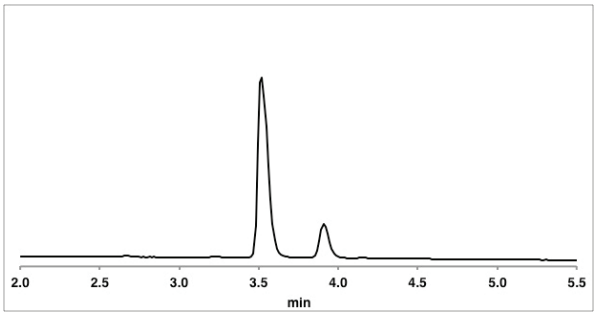
racemate enantiomerically enriched

1-(2-Ethylpiperidin-1-yl)-3-mesitylpropan-1-one



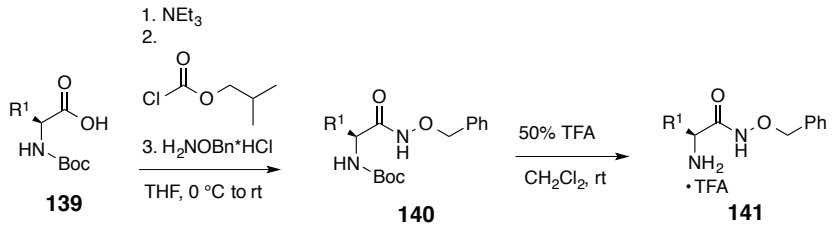
At room temperature the ratio of rotamers was 50:50 as determined by NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.82 (s, 2 H), 4.78–4.69 (m, 0.5 H), 4.59 (dd, *J* = 13.6, 3.1 Hz, 0.5 H), 3.74 (q, *J* = 6.7 Hz, 0.5 H), 3.57 (dd, *J* = 13.3, 2.8 Hz, 0.5 H), 3.06–2.89 (m, 2.5 H), 2.58 (dt, *J* = 13.3, 2.1 Hz, 0.5 Hz), 2.52–2.35 (m, 2 H), 2.30 (s, 6 H), 2.24 (s, 3 H),1.79–1.24 (m, 8 H), 0.86 (t, *J* = 7.5 Hz, 1.5 H), 0.84 (t, *J* = 7.5 Hz, 1.5 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.1, 171.0, 136.1, 135.0, 128.9, 54.2, 49.4, 40.9, 36.4, 32.8, 32.5, 28.6, 27.5, 26.2, 25.4, 25.2, 25.1, 22.9, 22.2, 20.7, 19.7, 19.0, 10.73, 10.71; **HRMS** (ESI): calculated for $[C_{19}H_{30}NO]^+$: m/z = 288.2322, found: m/z = 288.2317; **IR** (ν/cm^{-1}, neat) 2961, 2934, 2866, 1729, 1638, 1446, 1425, 1377, 1272, 1235, 1147, 1044; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.5 min and 3.9 min.





racemate enantiomerically enriched

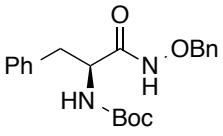
5.5 General Procedure for Starting Material Preparation



Commercially available Boc protected amino acid **139** (1.0 equiv) was added to a round bottom flask and suspended in dry THF (0.30 M) under N_2 atmosphere. The suspension was cooled to 0 °C and NEt_3 (2.3 equiv) was added. After 15 min ethyl chloroformate (1.2 equiv) was added dropwise and the solution was allowed to stir for an additional hour. $H_2NOBn•HCl$ (1.4 equiv) was in one portion to yield a suspension which was allowed to stir for 30 min at 0 °C and then 24 h at rt. The reaction was quenched with sat aq NH_4Cl solution and extracted three times with CH_2Cl_2. The combined organic layers were washed with sat aq $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica gel (hexanes:EtOAc).

140 was dissolved in 30% TFA in CH_2Cl_2 (0.10 M) and 1.5% H_2O was added. The mixture was allowed to stir for 1 h and the solvent was removed *in vacuo*. The oily residue was purified by column chromatography on silica gel (CH_2Cl_2:MeOH = 10:1) to yield the product **141**.

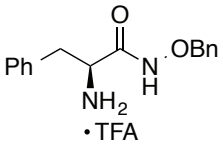
tert-Butyl (*S*)-(1-((benzyloxy)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (142)



tert-Butyl (*S*)-(1-((benzyloxy)amino)- 1-oxo- 3-phenylpropan-2-yl) carbamate (**142**) was prepared according to the General Procedure from Boc-L-Phenylalanine (4.26 g, 16.1 mmol). The product was obtained as a colorless solid in 79% yield (4.7 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.98 (s, 1H), 7.42–7.15 (m, 10H), 5.28–5.18 (m, 1H), 4.88–4.63 (m, 2H), 4.25 (q, *J* = 7.8 Hz, 1H), 3.17–2.95 (m, 2H), 1.40 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 169.0, 155.6, 136.5, 135.1, 129.6, 129.4, 128.87, 128.83, 128.6, 127.1, 80.6, 78.4, 53.7, 38.5, 28.4, 28.0; **LC/MS** (ESI): 371.2 for $[C_{21}H_{26}N_2O_4+H]$.[5]

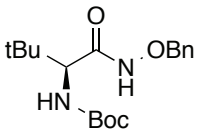
5 spectral data is in accordance to: Volonterio, A.; Bellosta, S.; Bravo, P.; Canavesi, M.; Corradi, E.; Meille, S. V.; Monetti, M.; Moussier, N.; Zanda, M.: Solution/Solid-Phase Synthesis of Partially Modified Retro- and Retro-Inverso-ψ[NHCH(CF_3)]-Peptidyl Hydroxamates and Their Evaluation as MMP-9 Inhibitors *Eur. J. Org. Chem.* **2002**, 428–438.

(*S*)-2-Amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (143)



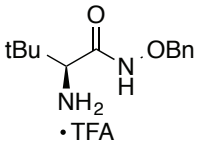
(*S*)-2-Amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) was prepared from **142** (4.83 g, 13.0 mmol) according to the General Procedure. The product was obtained as a colorless solid in quantitative yield (4.8 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.41–7.18 (m, 10H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 3.47 (dd, *J* = 8.0, 6.7 Hz, 1H), 3.02–2.86 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 169.8, 162.0 (q, *J* = 37.9 Hz), 137.2, 135.2, 129.7, 129.6, 128.95, 128.91, 128.6, 127.1, 116.0 (q, *J* = 289.7 Hz), 76.5, 51.6, 39.2; **LC/MS** (ESI): 271.2 for $[C_{16}H_{18}N_2O_2+H]$.[5]

***tert*-Butyl (*S*)-(1-((benzyloxy)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (144)**



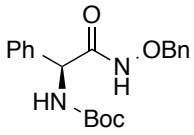
tert-Butyl (*S*)-(1-((benzyloxy)amino)- 3,3-dimethyl- 1-oxobutan-2-yl) carbamate (**144**) was prepared according to the General Procedure from (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (4.47 g, 19.3 mmol). The product was obtained as a colorless solid in 63% yield (4.1 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.96 (s, 1H), 7.45–7.29 (m, 5H), 5.35–5.20 (m, 1H), 4.96–4.78 (m, 2H), 3.71 (d, *J* = 9.7 Hz, 1H), 1.42 (s, 9H), 0.98 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 168.9, 156.1, 135.2, 129.4, 129.0, 128.7, 80.3, 78.5, 59.6, 34.6, 28.5, 26.6; **LC/MS** (ESI): 337.2 for $[C_{18}H_{28}N_2O_4+H]$.

(*S*)-2-Amino-*N*-(benzyloxy)-3,3-dimethylbutanamide trifluoroacetic acid salt (145)



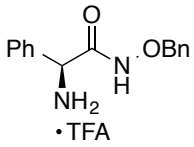
(*S*)-2-Amino-*N*-(benzyloxy)-3,3-dimethylbutanamide trifluoroacetic acid salt (**145**) was prepared from **144** (3.42 g, 10.2 mmol)according to the General Procedure. The product was obtained as a colorless solid in quantitative yield (3.4 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.95 (br, 1H), 7.34 (s, 5H), 4.98–4.67 (m, 2H), 3.78 (s, 1H), 0.97 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 165.9, 161.9 (q, *J* = 37.9 Hz), 134.6, 129.2, 129.2, 128.8, 115.9 (q, *J* = 289.7 Hz), 78.6, 59.9, 33.2, 31.2, 26.2, 26.0; **LC/MS** (ESI): 237.3 for $[C_{13}H_{20}N_2O_2+H]$.

tert-Butyl (*S*)-(2-((benzyloxy)amino)-2-oxo-1-phenylethyl)carbamate (146)



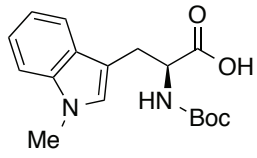
tert-Butyl (*S*)-(2-((benzyloxy)amino)-2-oxo-1-phenylethyl)carbamate (**146**) was prepared according to the General Procedure from (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetic acid (7.1 g, 28 mmol). The product was obtained as a colorless solid in 26% yield (2.6 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.66 (br, 1H), 7.42–7.16 (m, 10H), 5.73 (br, 1H), 5.10 (br, 1H), 4.82 (br, 2H), 1.40 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] =168.1, 155.3, 137.6, 129.6, 129.2, 129.0, 128.8, 128.7, 127.3, 78.5, 60.5, 56.2, 28.5; **LC/MS** (ESI): 357.2 for $[C_{20}H_{24}N_2O_4+H]$.

(*S*)-2-Amino-*N*-(benzyloxy)-2-phenylacetamide trifluoroacetic acid salt (147)



(*S*)-2-Amino-*N*-(benzyloxy)-2-phenylacetamide trifluoroacetic acid salt (**147**) was prepared from **146** (2.1 g, 5.9 mmol) according to the General Procedure. The product was obtained as a colorless solid in quantitative yield (2.1 g). At room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 11.15 (br, 1H), 8.48 (br, 1H), 7.43–7.16 (m, 6H), 7.14–7.06 (m, 2H), 7.06–6.97 (m, 2H), 5.29–5.20 (m, 1H), 4.61–4.51 (m, 2H), 4.29 (d, *J* = 10.3 Hz, 0.5H), 4.03 (d, *J* = 10.3 Hz, 0.5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 169.9, 165.8, 162.11 (q, *J* = 36.4 Hz), 134.0, 133.4, 132.0, 129.9, 129.3, 129.3, 129.1, 128.8, 128.5, 128.4, 127.5, 116.07 (q, *J* = 291.1 Hz), 78.9, 78.3, 55.4, 54.7; **LC/MS** (ESI): 257.1 for $[C_{15}H_{16}N_2O_2+H]$.

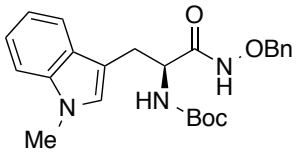
N^a-(*tert*-Butoxycarbonyl)-1-methyl-*L*-tryptophan (148)



Boc-L-Tryptophan (20.0 g, 65.8 mmol, 1.00 equiv) was dissolved in DMF (200 mL, 0.330 M) and cooled to 0 °C. A solution of KO^{t}Bu (14.1 g, 126 mmol, 1.90 equiv) in THF (126 mL, 1.00 M) was added slowly while stirring. The solution was allowed to stir for 15 min and a solution of MeI (6.10 mL, 99.0 mmol, 1.50 equiv) was added dropwise. The solution was allowed to stir for another 10 min and 100 mL of a 30% aqueous citric acid solution was added. The solution was adjusted to pH 4-5 by adding solid citric acid and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 30% aqueous citric acid solution (100 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to obtain the crude product, which was purified by column chromatography on silica gel (CH_2Cl_2:MeOH =

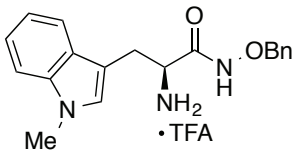
20:1). The product fractions were collected and the solvent removed. Diisopropyl ether (150 mL) was added and the product crystallized at 4 °C during 10 h to yield the product as colorless crystals (9.1 g, 43%). At room temperature the ratio of rotamers was 75:25 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.62 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.35–7.21 (m, 2H), 7.14 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 6.93 (s, 1H), 5.73 (s, 0.25H), 5.05 (s, 0.75H), 4.68 (s, 0.75H), 4.48 (s, 0.25H), 3.76 (s, 3H), 3.36 (d, *J* = 5.6 Hz, 2H), 1.46 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 176.4, 155.7, 136.9, 127.7, 121.8, 119.2, 118.8, 109.3, 108.3, 80.3, 54.2, 32.7, 28.3, 27.4; **LC/MS** (ESI): 319.3 for [$C_{17}H_{22}N_2O_4$+H].

tert-Butyl (*S*)-(1-((benzyloxy)amino)- 3-(1-methyl-1*H*-indol-3-yl)- 1-oxopropan-2-yl) carbamate (149)



tert-Butyl (*S*)-(1-((benzyloxy)amino)-3-(1-methyl-1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamate (**149**) was prepared according to the General Procedure from *N*$^{\alpha}$-(*tert*-butoxycarbonyl)-1-methyl-*L*-tryptophan (**148**) (6.00 g, 18.8 mmol). The product was obtained as a colorless solid in 74% yield (5.9 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.33 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.40–7.19 (m, 5H), 7.19–7.11 (m, 3H), 6.93 (s, 1H), 5.13 (br, 1H), 4.78 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.32 (q, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 3.23 (qd, *J* = 14.3, 6.8 Hz, 2H), 1.43 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 169.5, 155.6, 137.2, 135.1, 129.3, 128.9, 128.7, 128.2, 128.0, 122.1, 119.5, 119.1, 109.5, 108.8, 78.4, 32.9, 28.5, 28.1; **LC/MS** (ESI): 424.2 for [$C_{24}H_{29}N_3O_4$+H].

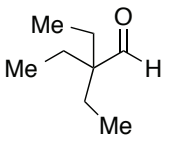
(*S*)-2-Amino-*N*-(benzyloxy)-3-(1-methyl-1*H*-indol-3-yl)propanamide trifluoroacetic acid salt (150)



(*S*)-2-Amino-*N*-(benzyloxy)-3-(1-methyl-1*H*-indol-3-yl)propanamide trifluoroacetic acid salt (**150**) was prepared from **149** (5.20 g, 12.4 mmol)according to the General Procedure. The product was obtained as a colorless solid in quantitative yield (5.2 g). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.55 (d, *J* = 8.0 Hz, 1H), 7.40–7.29 (m, 1H), 7.22–7.06 (m, 5H), 7.04–6.98 (m, 2H), 6.89 (s, 1H), 4.74 (br, 1H), 4.45–4.30 (m, 2H), 4.19 (t, *J* = 7.4 Hz, 1H), 3.61 (d, *J* = 4.7 Hz, 3H), 3.26–3.10 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 166.8, 162.05 (q, *J* = 36.4 Hz), 137.2, 134.5, 129.7, 129.3, 129.2, 129.0, 128.9, 128.6, 109.6, 106.0, 78.4, 52.3, 32.7, 27.3; **LC/MS** (ESI): 324.3 for [$C_{19}H_{21}N_3O_2$+H].

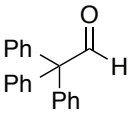
5.6 Aldehyde Preparation

2,2-Diethylbutanal (151)



NaH (60% in mineral oil, 2.2 g, 55 mmol, 1.1 equiv) was suspended in dry THF (40 mL) and cooled to 0 °C. A solution of 2-ethylbutanal (6.1 mL, 50 mmol, 1.0 equiv) in dry THF (15 mL) was added slowly within 1 h. The mixture was allowed to stir at 0 °C for 1 h and ethyl iodide (8.0 mL, 100 mmol, 2.0 equiv) was added dropwise. The mixture was allowed to stir for 30 min at 0 °C and 1 h at rt. The reaction was quenched with sat aq $NaHCO_3$ solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by fractional distillation at 30 mbar (bp. 65-70 °C) to obtain the desired compound as colorless liquid (3.8 g, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.43 (s, 1H), 1.54 (q, *J* = 7.6 Hz, 6H), 0.79 (t, *J* = 7.5 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 207.6, 52.6, 23.5, 7.8; **GC/MS** (EI): 128.0 for [$C_8H_{16}O^*$].

2,2,2-Triphenylacetaldehyde (152)

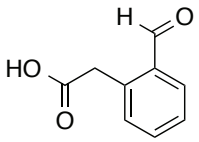


A suspension of $LiAlH_4$ (1.90 g, 52.0 mmol, 5.00 equiv) in dry THF (27 mL) was cooled to 0 °C and a solution of 2,2,2-triphenylacetic acid (3.00 g, 10.4 mmol, 1.00 equiv) was added dropwise. The mixture was heated to reflux for 1 h, cooled to 0 °C and quenched by the sequential addition of H_2O (4 mL) and 10% aq NaOH solution (3 mL). The mixture was allowed to stir for 1 h at rt and filtered over anhydrous Na_2SO_4. The solution was concentrated *in vacuo* and the crude product was crystallized by the addition of a mixture of 10:1 hexanes:EtOAc to afford the desired alcohol as colorless crystals (1.2 g, 44%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.40–7.09 (m, 15H), 5.57 (s, 1H), 4.66 (d, *J* = 6.9 Hz, 2H); **LC/MS** (ESI): 275.2 for [$C_{20}H_{18}O$+H].

A solution of oxalyl chloride (663 mg, 5.26 mmol, 1.20 equiv) in CH_2Cl_2 (50 mL) was cooled to -78 °C and dry DSMO (683 mg, 17.5 mmol, 2.00 equiv) was added dropwise. After 5 min a solution of 2,2,2-triphenylethan-1-ol (1.20 g, 4.38 mmol, 1.00 equiv) in CH_2Cl_2 (3 mL) was added and the mixture was allowed to stir for 30 min. Freshly distilled NEt_3 (1.77 g, 17.5 mmol, 4.00 equiv) was added and the mixture was allowed to warm to rt over 30 min. H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with 1% aq HCl, 5% aq $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 10:1) to afford the desired compound as

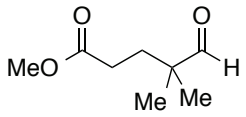
colorless solid (970 mg, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 10.30 (s, 1H), 7.54–6.96 (m, 15H).[6]

2-(2-Formylphenyl)acetic acid (153)



A solution of indene (5.8 g, 50 mmol, 1.0 equiv) and acetic acid (7.5 mL, 120 mmol, 2.4 equiv) in cyclohexane (50 mL) was cooled to 0 °C and ozone was bubbled through the solution for 4 h. To remove excess ozone, O_2 was bubbled through the solution for 15 min. The solvent was decanted. The viscous compound remaining was dissolved in acetic anhydride (10 mL). To this solution a mixture of NaOAc (5 g) in acetic acid (20 mL) was added in portions. The resulting suspension was allowed to stir for 30 min at rt and H_2O (25 mL) was added. The solution was heated to reflux for 30 min and the solvent was removed *in vacuo*. The residue was dissolved in H_2O (35 mL) and extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 10:1 → 2:1) to afford the desired compound as solid (690 mg, 9%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.77 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.54–7.40 (m, 2H), 7.27–7.22 (m, 1H), 4.00 (s, 2H); **HRMS** (ESI): calculated for $[C_9H_9O_3]^+$: m/z = 165.0646, found: m/z = 165.0547.

Methyl 4,4-dimethyl-5-oxopentanoate (154)

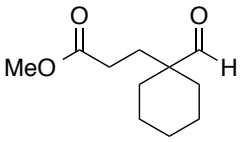


pTsOH (410 mg, 2.2 mmol, 0.020 equiv) was dissolved in benzene (120 mL) and isobutyraldehyde (9.8 mL, 110 mmol, 1.0 equiv) and benzyl amine (13 mL, 120 mmol, 1.1 equiv) were added. The mixture was heated to reflux for 20 h with a Dean-Stark trap. The solution was allowed to cool to rt, filtered and the solvent removed *in vacuo* to obtain the crude imine in quantitative yield (15.1 g, 96%). The imine (15 g, 100 mmol, 1.0 equiv) and methyl acrylate (10 mL, 110 mmol, 1.1 equiv) were stirred at rt for 60 h and a 10% aqueous AcOH solution was added (120 mL). The mixture was allowed to stir for 4 h and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 10:1

6 spectral data is in accordance to: Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carrol, P. J.: Asymmetric Synthesis and Properties of Sulfinimines (Thiooxime *S*-Oxides) *J Org. Chem.* **1997**, *62*, 2555–2563.

→ 6:1) to afford the desired compound as colorless liquid (1.46 g, 9%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 9.42 (d, *J* = 0.5 Hz, 1H), 3.65 (d, *J* = 0.4 Hz, 3H), 2.28–2.21 (m, 2H), 1.86–1.79 (m, 2H), 1.05 (s, 6H); **LC/MS** (ESI): 159.2 for $[C_8H_{14}O_3+H]$.[7]

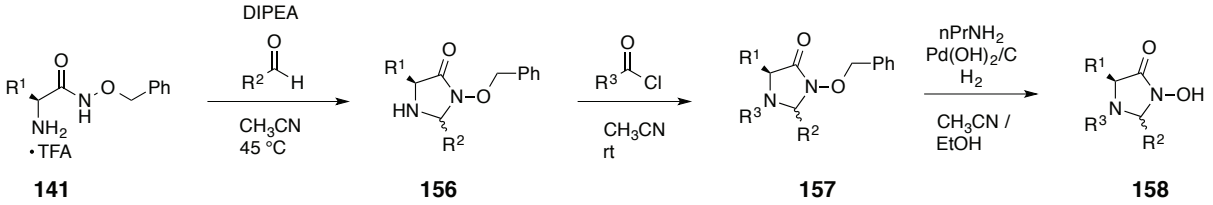
Methyl 3-(1-formylcyclohexyl)propanoate (155)



pTsOH (170 mg, 0.90 mmol, 0.020 equiv) was dissolved in benzene (50 mL) and cyclohexanecarbaldehyde (5.4 mL, 45 mmol, 1.0 equiv) and benzyl amine (5.3 mL, 50 mmol, 1.1 equiv) were added. The mixture was heated to reflux for 4 h with a Dean-Stark trap. The solution was allowed to cool to rt, filtered and the solvent removed *in vacuo* to obtain the crude imine in quantitative yield (9.0 g, 99%). The imine (9.4 g, 47 mmol, 1.0 equiv) and methyl acrylate (4.6 mL, 51 mmol, 1.1 equiv) were stirred at rt for 72 h and a 10% aqueous acetic acid solution was added (30 mL). The mixture was allowed to stir for 4 h and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 10:1 → 6:1) to afford the desired compound as colorless liquid (990 mg, 11%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.40 (s, 1H), 3.65 (s, 3H), 2.24–2.16 (m, 2H), 1.93–1.83 (m, 2H), 1.82–1.76 (m, 2H), 1.62–1.49 (m, 3H), 1.37–1.22 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 206.2, 173.7, 51.7, 49.1, 30.8, 30.6, 28.4, 25.6, 22.4; **HRMS** (ESI): calculated for $[C_{11}H_{19}O_3]^+$: m/z = 199.1329, found: m/z = 199.1326.

5.7 General Procedures for the Co-Catalyst Preparation

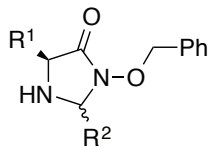
Remarks: This sequence can be run typically within 30 h in one pot to obtain the hydroxamic acid co-catalyst **160**. In order to give more detailed information about the sequence the "one pot" procedure is described as well as the procedure for carrying out the individual steps.



141 **156** **157** **158**

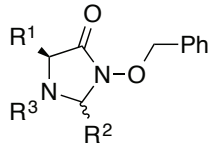
7 spectral data is in accordance to: Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C.: Regioselective Photochemical Rearrangement of *N*-Mesyloxylactams. *Eur. J. Org. Chem.* **2012**, *7*, 1328–1335.

Step 1:



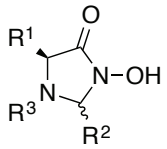
The protected hydroxamic acid **141** (1.0 equiv) was dissolved in dry CH_2Cl_2 (0.10 M) and DIPEA (2.0 equiv) was added, followed by the aldehyde (1.2 equiv). The reaction was allowed to stir for 5 h at 45 °C and cooled to rt. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (hexanes:EtOAc 9:1 → 2:1) to obtain the two diastereomers **156**.

Step 2:



The aminal **156** (1.0 equiv) was dissolved in dry CH_2Cl_2 (0.10 M) and DIPEA (2.1 equiv) was added followed by the acyl donor (2.0 equiv). The solution was allowed to stir at for 5–24 h until the reaction was complete. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (hexanes:EtOAc 9:1 → 2:1) to yield the two separated diastereomers **157**.

Step 3:



To a solution of a single diastereomer of **157** in EtOH (0.05 M) 5% $Pd(OH)_2/C$ was added and the flask purged with H_2. The reaction mixture was allowed to stir vigorously under H_2 atmosphere for 1–10 h until completion of the reaction. The mixture was filtered through a pad of Celite and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (CH_2Cl_2:MeOH 9:1 → 2:1) to yield the hydroxamic acid co-catalyst **158**.

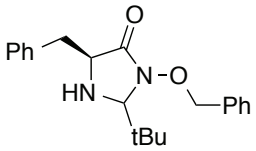
One-pot procedure:

The protected hydroxamic acid **141** (1.0 equiv) was dissolved in CH_3CN (0.10 M) and DIPEA (4.0 equiv) was added followed by the aldehyde (1.2 equiv). The reaction was allowed to stir for 5 h at 45 °C and cooled to rt. The acyl donor (2.5 equiv) was added and the mixture was allowed to stir overnight. The reaction was quenched with *n*-propyl amine and 5% $Pd(OH)_2$ was added and the atmosphere in the flask exchanged to H_2. The reaction mixture was allowed to stir vigorously under H_2 atmosphere for 1–10 h until completion of the reaction. The mixture was filtered through a pad of Celite and concentrated to a total volume of 5 mL. The crude mixture was injected into a preparative reversed phase liquid chromatography system for purification to obtain both diastereomers **158**.

5.8 Preparation of Hydroxamic Acid Co-Catalysts

5.8.1 Variations of R^2

(5*S*)-5-Benzyl-3-(benzyloxy)-2-(*tert*-butyl)imidazolidin-4-one (159)



(5*S*)- 5-Benzyl- 3-(benzyloxy)- 2-(*tert*-butyl)imidazolidin- 4-one (**159**) was prepared according to the stepwise General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (11 mg, 0.041 mmol , 1.0 equiv) and pivaldehyde (11 mg, 0.12 mmol, 3.0 equiv) to obtain two the two diastereomers.

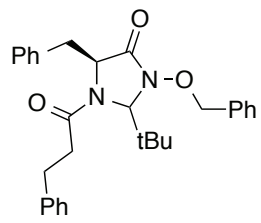
Diastereomer 1:

2.0 mg, 14%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.42–7.22 (m, 8H), 7.14 (dd, *J* = 7.9, 1.7 Hz, 2H), 4.84 (d, *J* = 10.6 Hz, 1H), 4.68 (d, *J* = 10.6 Hz, 1H), 3.82–3.72 (m, 1H), 3.53 (d, *J* = 1.6 Hz, 1H), 3.12–2.95 (m, 2H), 1.83 (s, 1H), 0.86 (s, 9H); **HRMS** (ESI): calculated for $[C_{21}H_{27}N_2O_2]^+$: m/z = 339.2067, found: m/z = 339.2069.

Diastereomer 2:

3.0 mg, 21%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.49–7.17 (m, 10H), 5.14 (d, *J* = 9.5 Hz, 1H), 4.92 (dd, *J* = 9.5, 0.4 Hz, 1H), 4.05 (s, 1H), 3.63 (s, 1H), 3.09 (dd, *J* = 5.4, 2.8 Hz, 2H), 0.80 (s, 9H).

(5*S*)-5-Benzyl-3-(benzyloxy)-2-(*tert*-butyl)-1-(3-phenylpropanoyl)imidazolidin-4-one (160)



(5*S*)- 5-Benzyl- 3-(benzyloxy)- 2-(*tert*-butyl)- 1-(3-phenylpropanoyl) imidazolidin-4-one (**160**) was prepared according to the stepwise General Procedure from **159** (300 mg, 0.780 mmol , 1.00 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to obtain two the two diastereomers.

Diastereomer 1:

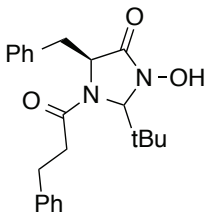
153 mg, 42%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.46–7.21 (m, 13H), 6.98 (d, *J* = 7.2 Hz, 2H), 5.42 (br, 1H), 4.98 (d, *J* = 1.7 Hz, 2H), 4.09 (br, 1H), 3.48–3.31 (m, 1H), 3.05–2.87 (m, 1H), 2.82–2.67 (m, 2H), 2.13 (br, 1H), 1.86 (br, 1H), 1.09 (s, 9H); **^{13}C NMR** (100 MHz,

$CDCl_3$): δ [ppm] = 175.9, 174.6, 140.4, 137.3, 133.8, 129.8, 129.4, 129.3, 129.0, 128.6, 128.6, 128.4, 128.3, 127.3, 126.4, 126.3, 59.4, 40.2, 36.9, 35.2, 30.9, 30.7, 26.7; **HRMS** (ESI): calculated for $[C_{30}H_{35}N_2O_3]^+$: m/z = 471.2642, found: m/z = 471.2638.

Diastereomer 2:

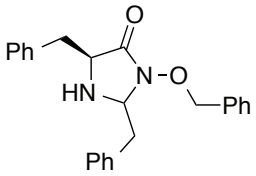
110 mg, 30%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.46–7.16 (m, 15H), 4.86 (d, *J* = 10.5 Hz, 1H), 4.71 (d, *J* = 10.6 Hz, 1H), 3.85–3.73 (m, 1H), 3.56 (d, *J* = 1.7 Hz, 1H), 3.10–2.97 (m, 3H), 2.78–2.60 (m, 1H), 1.28 (br, 1H), 1.15 (dd, *J* = 7.1, 4.9 Hz, 1H), 0.89 (s, 9H).

(5*S*)-5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (21)



(5*S*)- 5-Benzyl- 2-(*tert*-butyl)- 3-hydroxy- 1-(3-phenylpropanoyl) imidazolidin- 4-one (**21**) was prepared by hydrogenation according to the stepwise General Procedure from **160** (diastereomer 1, 126 mg, 0.260 mmol) to afford the product as a pale reddish solid (95.0 mg, 96%). **HRMS** (ESI): calculated for $[C_{23}H_{29}N_2O_3]^+$: m/z = 381.2173, found: m/z = 381.2177. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 83:17; acylated product: er = 85:15; calculated conversion: 49 %; **s = 11**.

(5*S*)-2,5-Dibenzyl-3-(benzyloxy)imidazolidin-4-one (161)



(5*S*)- 2,5-Dibenzyl- 3-(benzyloxy)imidazolidin- 4-one (**161**) was prepared according to the stepwise General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (292 mg, 0.760 mmol , 1.00 equiv) and 2-phenylacetaldehyde (274 mg, 2.28 mmol, 3.00 equiv) to obtain two the two diastereomers.

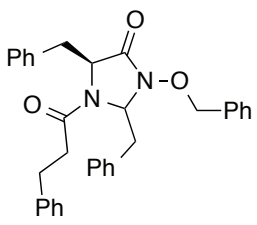
Diastereomer 1:

119 mg, 42%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.38–7.07 (m, 15H), 4.98 (d, *J* = 11.2 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 3.87–3.77 (m, 1H), 3.22–3.14 (m, 1H), 3.01 (dd, *J* = 14.1, 5.5 Hz, 1H), 2.85 (dd, *J* = 14.1, 4.7 Hz, 1H), 2.78–2.74 (m, 2H), 1.65 (br, 1H).

Diastereomer 2:

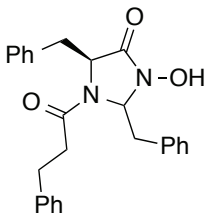
153 mg, 54%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.41–7.10 (m, 13H), 7.04 (dd, *J* = 7.6, 1.8 Hz, 2H), 5.12 (d, *J* = 10.7 Hz, 1H), 4.98 (d, *J* = 10.7 Hz, 1H), 4.33 (dd, *J* = 7.1, 3.4 Hz, 1H), 3.61 (dd, *J* = 6.8, 4.4 Hz, 1H), 2.97 (dd, *J* = 14.1, 4.4 Hz, 1H), 2.88–2.69 (m, 2H), 2.34 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.60 (br, 1H).

(5*S*)-2,5-Dibenzyl-3-(benzyloxy)-1-(3-phenylpropanoyl)imidazolidin-4-one (162)



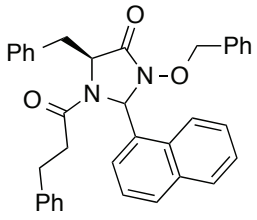
(5*S*)- 2,5-Dibenzyl- 3-(benzyloxy)- 1-(3-phenylpropanoyl)imidazolidin-4-one (**162**) was prepared according to the stepwise General Procedure from **161** (83 mg, 0.22 mmol , 1.0 equiv) and hydrocinnamoyl chloride (76 mg, 0.45 mmol, 2.0 equiv) to a 2:3 mixture of diastereomers a and b. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.45–6.88 (m, 40H, a+b), 4.95 (d, *J* = 11.4 Hz, 1H, a), 4.83 (dt, *J* = 3.5, 1.7 Hz, 1H, b), 4.78 (d, *J* = 11.0 Hz, 1H, b), 4.44 (d, *J* = 11.3 Hz, 1H, a), 4.23 (dt, *J* = 3.2, 1.7 Hz, 1H, a), 4.17 (d, *J* = 11.0 Hz, 1H, b), 3.68 (dd, *J* = 13.8, 4.9 Hz, 1H, a), 3.42 (td, *J* = 3.6, 1.7 Hz, 1H, b), 3.36–2.26 (m, 16H, a+b), 1.65 (br, 2H, a+b); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.6 (b), 169.7 (a), 166.8 (a), 164.5 (b), 140.7 (b), 140.6 (a), 135.7, 134.4, 134.1, 133.5, 131.8, 130.5, 130.4, 130.3, 130.2, 129.8, 129.2, 129.13, 129.12, 128.8, 128.75, 128.71, 128.67, 128.65, 128.56, 128.4, 128.2, 127.9, 127.4, 127.3, 126.9, 126.6, 126.5, 78.7 (a), 78.3 (b), 72.9 (a), 72.6 (b), 58.2 (a), 58.0 (b), 37.2, 37.0, 36.7, 36.5, 33.1, 32.6, 31.0, 30.9; **HRMS** (ESI): calculated for $[C_{33}H_{33}N_2O_3]^+$: m/z = 505.2486, found: m/z = 505.2477.

(5*S*)-2,5-Dibenzyl-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (28)



(5*S*)- 2,5-Dibenzyl- 3-hydroxy- 1-(3-phenylpropanoyl)imidazolidin- 4-one (**28**) was prepared by hydrogenation according to the stepwise General Procedure from **162** (diastereomer 2, 56 mg, 0.11 mmol) to afford the product as a pale reddish solid (39 mg, 85%). **HRMS** (ESI): calculated for $[C_{26}H_{27}N_2O_3]^+$: m/z = 415.2016, found: m/z = 415.2018. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 20:80; acylated product: er = 69:31; calculated conversion: 61 %; **s = 4**.

(5*S*)-5-Benzyl-3-(benzyloxy)-2-(naphthalen-1-yl)-1-(3-phenylpropanoyl)imidazolidin-4-one (163)



(5*S*)-5-Benzyl-3-(benzyloxy)-2-(naphthalen-1-yl)-1-(3-phenylpropanoyl) imidazolidin-4-one (**163**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol

, 1.00 equiv), 1-naphthaldehyde (243 mg, 1.56 mmol, 3.00 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to obtain two the two diastereomers.

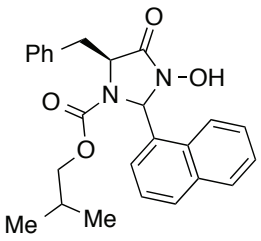
Diastereomer 1:

163 mg, 39%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.59–7.13 (m, 20H), 7.02–6.87 (m, 2H), 6.02 (d, *J* = 7.9 Hz, 1H), 5.53 (td, *J* = 8.1, 4.4 Hz, 1H), 5.13 (d, *J* = 9.3 Hz, 1H), 4.98 (d, *J* = 9.3 Hz, 1H), 3.18–2.78 (m, 5H), 2.57–2.38 (m, 1H).

Diastereomer 2:

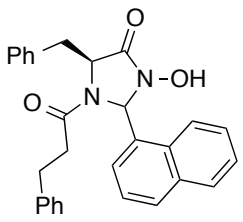
193 mg, 46%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.88 (dd, *J* = 31.0, 8.1 Hz, 2H), 7.63–7.49 (m, 2H), 7.21 (d, *J* = 42.7 Hz, 14H), 6.73–6.40 (m, 4H), 5.91 (br, 1H), 4.87–4.70 (m, 2H), 3.79 (d, *J* = 11.6 Hz, 1H), 3.58 (d, *J* = 13.6 Hz, 1H), 2.84–2.69 (m, 1H), 2.55 (br, 1H), 2.20–1.86 (m, 2H), 1.60 (br, 1H); **HRMS** (ESI): calculated for $[C_{36}H_{33}N_2O_3]^+$: m/z = 541.2486, found: m/z = 541.2484.

Isobutyl (5*S*)-5-benzyl-3-hydroxy-2-(naphthalen-1-yl)-4-oxoimidazolidine-1-carboxylate (164)



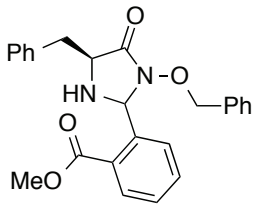
Isobutyl- (5*S*)- 5-benzyl-3-hydroxy-2-(naphthalen-1-yl)-4-oxoimidazolidine-1-carboxylate (**164**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), 1-naphthaldehyde (243 mg, 1.56 mmol, 3.00 equiv) and isobutyl chloroformate (213 mg, 1.57 mmol, 2.00 equiv) to afford a single diastereomer (118 mg, 36%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.34 (br, 1H), 7.91–7.81 (m, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.52–7.47 (m, 1H), 7.39–7.33 (m, 1H), 7.30–7.21 (m, 4H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.90 (s, 1H), 6.01 (br, 1H), 4.61 (dd, *J* = 6.4, 2.5 Hz, 1H), 3.94–3.30 (m, 4H), 1.06–0.02 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 165.0, 154.9, 136.1, 133.4, 132.3, 131.5, 130.6, 129.6, 128.8, 128.8, 127.2, 126.4, 125.5, 125.5, 125.0, 122.3, 72.3, 70.2, 60.0, 53.5, 36.0, 27.5, 18.4.

(5*S*)-5-Benzyl-3-hydroxy-2-(naphthalen-1-yl)-1-(3-phenylpropanoyl)imidazolidin-4-one (30)



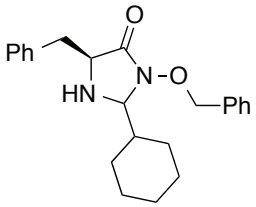
(5*S*)- 5-Benzyl- 3-hydroxy- 2-(naphthalen-1-yl)- 1-(3-phenylpropanoyl) imidazolidin-4-one (**30**) was prepared by hydrogenation according to the stepwise General Procedure from **163** (diastereomer 1, 206 mg, 0.380 mmol) to afford the product as a pale reddish solid (152 mg, 89%). **HRMS** (ESI): calculated for $[C_{29}H_{27}N_2O_3]^+$: m/z = 451.2016, found: m/z = 451.2015. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 49:50; acylated product: er = 47:53; calculated conversion: 25 %; **s = 1**.

Methyl 2-((4*S*)-4-benzyl-1-(benzyloxy)-5-oxoimidazolidin-2-yl)benzoate (165)



Methyl 2-((4*S*)-4-benzyl-1-(benzyloxy)-5-oxoimidazolidin-2-yl)benzoate (**165**) was prepared according to the stepwise General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (100 mg, 0.26 mmol , 1.0 equiv) and methyl 2-formylbenzoate (43 mg, 0.26 mmol, 1.0 equiv) to obtain a 5:4 mixture of diastereomers a and b (44 mg, 41 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.96–7.92 (m, 1H, b), 7.89–7.84 (m, 1H, a), 7.54 (td, *J* = 7.7, 1.5 Hz, 1H, b), 7.43–7.12 (m, 24H, a+b), 6.82 (dd, *J* = 7.7, 1.5 Hz, 1H, a), 6.04 (s, 1H, a), 5.82–5.74 (m, 1H, b), 4.99 (d, *J* = 10.5 Hz, 1H, a), 4.89 (d, *J* = 10.9 Hz, 1H, b), 4.82 (d, *J* = 10.9 Hz, 1H, b), 4.73 (d, *J* = 10.5 Hz, 1H, a), 3.93–3.85 (m, 4H, a), 3.85 (s, 3H, b), 3.79 (d, *J* = 1.6 Hz, 1H, b), 3.20 (dd, *J* = 14.0, 5.8 Hz, 1H, a), 3.14 (dd, *J* = 14.1, 6.2 Hz, 1H, b), 3.10 (dd, *J* = 4.6, 2.3 Hz, 1H, a), 3.06 (dd, *J* = 4.5, 2.3 Hz, 1H, b); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 172.4 (a), 171.4 (b), 167.2 (a), 167.1 (b), 139.4 (b), 139.2 (a), 136.5 (a), 136.3 (b), 134.9 (b), 134.8 (a), 132.5 (b), 132.5 (a), 131.2, 130.6, 130.3, 129.93, 129.91, 129.5, 129.33, 129.30, 128.80, 128.75, 128.71, 128.69, 128.5, 128.41, 128.38, 127.5 , 127.1, 126.9, 126.7, 77.5, 77.0, 71.3, 57.9, 56.0, 52.4 (a), 52.2 (b), 37.0 (a), 36.8 (b).

(5*S*)-5-Benzyl-3-(benzyloxy)-2-cyclohexylimidazolidin-4-one (166)



(5*S*)-5-Benzyl-3-(benzyloxy)-2-cyclohexylimidazolidin-4-one (**166**) was prepared according to the stepwise General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.78 mmol , 1.0 equiv) and cyclohexanecarbaldehyde (110 mg, 0.94 mmol, 1.2 equiv) to obtain two the two diastereomers.

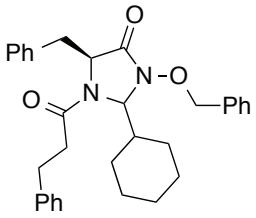
Diastereomer 1:

131 mg, 45%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.40–7.22 (m, 8H), 7.19–7.13 (m, 2H), 4.89 (d, *J* = 11.1 Hz, 1H), 4.73 (d, *J* = 11.1 Hz, 1H), 3.75–3.66 (m, 1H), 3.52 (dd, *J* = 2.8, 1.2 Hz, 1H), 3.10 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.98 (dd, *J* = 14.1, 4.6 Hz, 1H), 1.79–1.41 (m, 6H), 1.33–0.91 (m, 5H); **LC/MS** (ESI): 365.3 for $[C_{23}H_{28}N_2O_2+H]$.

Diastereomer 2:

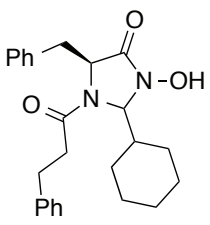
160 mg, 55%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.46–7.15 (m, 10H), 5.10 (d, *J* = 10.3 Hz, 1H), 4.89 (d, *J* = 10.3 Hz, 1H), 4.06 (s, 1H), 3.62 (s, 1H), 3.20–2.99 (m, 2H), 1.82–1.35 (m, 6H), 1.22–0.93 (m, 5H); **LC/MS** (ESI): 365.3 for $[C_{23}H_{28}N_2O_2+H]$.

(5*S*)-5-Benzyl-3-(benzyloxy)-2-cyclohexyl-1-(3-phenylpropanoyl)imidazolidin-4-one (167)



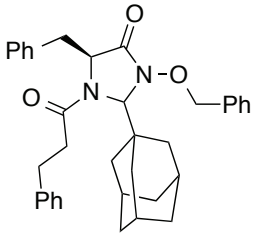
(5*S*)- 5-Benzyl- 3-(benzyloxy)- 2-cyclohexyl- 1-(3-phenylpropanoyl) imidazolidin-4-one (**167**) was prepared according to stepwise General Procedure from **166** (diastereomer 2, 44 mg, 0.12 mmol, 1.0 equiv) and hydrocinnamoyl chloride (41 mg, 0.24 mmol, 2.0 equiv) to obtain the product as a colorless oil (60 mg, 99%). In the identical reaction diastereomer 1 of **166** decomposed while attempting the acylation. At room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.46–6.99 (m, 15H), 5.17 (br, 0.6 H), 4.95 (s, 2H), 4.56 (s, 0.4H), 4.10 (br, 1H), 3.22 (dd, *J* = 14.2, 5.3 Hz, 1H), 3.04–2.62 (m, 3H), 2.37–1.91 (m, 2H), 1.86–1.31 (m, 6H), 1.22–0.88 (m, 5H); **LC/MS** (ESI): 497.3 for $[C_{32}H_{36}N_2O_3+H]$.

(5*S*)-5-Benzyl-2-cyclohexyl-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (26)



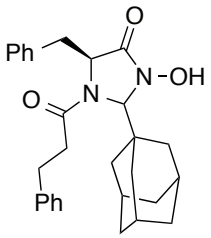
(5*S*)- 5-Benzyl- 2-cyclohexyl-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (**26**) was prepared by hydrogenation according to the stepwise General Procedure from **167** (diastereomer 2, 150 mg, 0.30 mmol) to afford the product as a pale reddish solid (120 mg, 99%). At room temperature the ratio of rotamers was 70:30 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 10.65 (br, 1H), 7.40–6.90 (m, 10H), 5.42 (br, 0.7H), 4.89 (br, 0.3H), 4.62 (br, 0.3H), 4.24 (br, 0.7H), 3.30–2.69 (m, 4H), 2.58 (br, 1H), 2.23 (br, 1H), 2.00 (br, 1H), 1.90–1.59 (m, 4H), 1.46–0.87 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 173.3, 165.2, 140.4, 136.2, 129.6, 128.9, 128.6, 128.5, 128.4, 128.3, 127.5, 126.3, 77.6, 60.1, 42.2, 39.9, 35.5, 35.3, 30.8, 30.7, 28.6, 28.0, 26.3, 26.1; **HRMS** (MALDI/ESI): calculated for $[C_{25}H_{31}N_2O_3Na]^+$: m/z = 407.2329, found: m/z = 407.2329. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 37:63; acylated product: er = 66:34; calculated conversion: 45 %; **s = 3**.

(5*S*)-2-((1*s*,3*R*)-Adamantan-1-yl)-5-benzyl-3-(benzyloxy)-1-(3-phenylpropanoyl) imidazolidin-4-one (168)



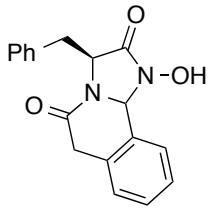
(5*S*)- 2-((1*s*,3*R*)-Adamantan-1-yl)- 5-benzyl- 3-(benzyloxy)- 1-(3-phenylpropanoyl) imidazolidin-4-one (**168**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), (3*r*,5*r*,7*r*)-adamantane-1-carbaldehyde (150 mg, 0.940 mmol, 1.20 equiv) and isobutyl chloroformate (330 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer (153 mg, 36%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.42–7.14 (m, 13H), 6.97 (d, *J* = 7.0 Hz, 2H), 5.22 (br, 1H), 5.00–4.88 (m, 2H), 4.11 (br, 1H), 3.33 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.95 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.81–2.62 (m, 2H), 2.17–1.45 (m, 17H).

(5*S*)-2-((1*s*,3*R*)-Adamantan-1-yl)-5-benzyl-3-hydroxy-1-(3-phenylpropanoyl) imidazolidin-4-one (25)



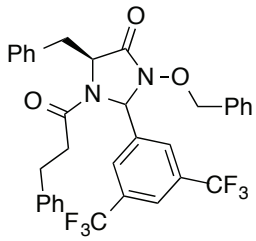
(5*S*)- 2-((1*s*,3*R*)-Adamantan-1-yl)- 5-benzyl- 3-hydroxy- 1-(3-phenylpropanoyl) imidazolidin-4-one (**25**) was prepared by hydrogenation according to the stepwise General Procedure from **168** (100 mg, 0.18 mmol) to afford the product as a pale reddish solid (75 mg, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 10.57 (s, 1H), 7.33–7.11 (m, 8H), 6.91 (d, *J* = 7.2 Hz, 2H), 5.43 (s, 1H), 4.19 (s, 1H), 3.28 (dd, *J* = 14.3, 4.9 Hz, 1H), 2.95 (dd, *J* = 14.3, 7.6 Hz, 1H), 2.72 (dt, *J* = 14.2, 7.1 Hz, 2H), 2.15–1.89 (m, 7H), 1.84–1.50 (m, 10H); **HRMS** (MALDI/ESI): calculated for $[C_{29}H_{35}N_2O_3Na]^+$: m/z = 459.2642, found: m/z = 459.2643. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 19:81; acylated product: er = 82:18; calculated conversion: 49 %; **s = 9**.

(3*S*)-3-Benzyl-1-hydroxy-6,10b-dihydroimidazo[2,1-*a*]isoquinoline-2,5(1*H*,3*H*)-dione (50)



(3*S*)- 3-Benzyl- 1-hydroxy- 6,10b-dihydroimidazo [2,1-*a*]isoquinoline-2,5(1*H*,3*H*)-dione (**50**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv) and 2-(2-formylphenyl)acetic acid (154 mg, 0.940, 1.20 equiv) to afford a single diastereomer (118 mg, 49%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.84 (dd, *J* = 5.6, 3.5 Hz, 1H), 7.39–7.13 (m, 8H), 4.81 (s, 1H), 4.73–4.64 (m, 1H), 3.64–3.47 (m, 3H), 3.31 (dd, *J* = 13.6, 2.0 Hz, 1H). With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 63:37; acylated product: er = 22:78; calculated conversion: 32 %; **s = 5**.

(5*S*)-5-Benzyl-3-(benzyloxy)-2-(3,5-bis(trifluoromethyl)phenyl)-1-(3-phenylpropanoyl) imidazolidin-4-one (169)



(5*S*)- 5-Benzyl- 3-(benzyloxy)- 2-(3,5-bis(trifluoromethyl)phenyl)- 1-(3-phenylpropanoyl)imidazolidin-4-one (**169**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol

, 1.00 equiv), 3,5-bis(trifluoromethyl)benzaldehyde (227 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford the two diastereomers as colorless solids.

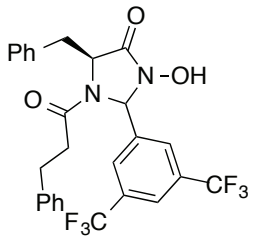
Diastereomer 1:

61 mg, 13%; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.89 (s, 0.5H), 7.82 (s, 0.5H), 7.49–7.17 (m, 11H), 7.16–7.08 (m, 2H), 7.08–7.02 (m, 1H), 6.90 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.75 (td, *J* = 7.8, 1.4 Hz, 2H), 5.16 (d, *J* = 1.9 Hz, 0.5H), 4.98 (dt, *J* = 4.6, 2.3 Hz, 0.5H), 4.87 (d, *J* = 1.9 Hz, 0.5H), 4.76 (dt, *J* = 4.6, 2.4 Hz, 0.5H), 4.72 (d, *J* = 11.6 Hz, 0.5H), 4.61 (d, *J* = 11.3 Hz, 0.5H), 4.41 (d, *J* = 11.5 Hz, 0.5H), 4.19 (d, *J* = 11.4 Hz, 0.5H), 3.88 (dd, *J* = 13.9, 4.9 Hz, 0.5H), 3.43–3.22 (m, 1.5H), 3.06–2.68 (m, 2.5H), 2.64–2.51 (m, 0.5H), 2.07 (dt, *J* = 15.4, 7.6 Hz, 0.5H), 1.83–1.71 (m, 0.5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.9, 170.6, 165.6, 164.7, 159.1, 158.6, 139.68, 139.65, 138.9, 138.1, 135.0, 134.2, 133.8, 133.3, 133.0, 132.7, 131.9, 131.6, 130.4, 130.3, 130.0, 129.8, 129.5, 129.45, 129.41, 129.2, 129.1, 128.9, 128.8, 128.73, 128.71, 128.66, 128.60, 128.3, 128.2, 128.1, 127.6, 127.5, 127.4, 126.8, 126.6, 124.3, 123.4, 79.4, 79.1, 74.3, 74.0, 58.7, 58.6, 37.9, 37.0, 36.5, 33.8, 30.7, 30.1.

Diastereomer 2:

227 mg, 47%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.86 (d, *J* = 18.0 Hz, 2H), 7.65–6.80 (m, 16H), 6.07 (s, 1H), 5.07–4.68 (m, 2H), 4.57–4.29 (m, 1H), 3.72–2.97 (m, 2H), 2.97–2.66 (m, 2H), 2.52–1.94 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 174.1, 166.1, 159.2, 158.8, 158.4, 157.9, 146.1, 139.8, 138.5, 133.9, 133.3, 132.1, 131.7, 129.73, 129.69, 129.5, 128.92, 128.86, 128.83, 128.79, 128.76, 128.3, 128.1, 127.8, 126.8, 124.2, 123.2, 121.5, 119.0, 116.1, 113.3, 110.5, 78.5, 72.5, 59.5, 38.8, 35.3, 30.8; **LC/MS** (ESI): 627.2 for $[C_{34}H_{28}F_6N_2O_3+H]$.

(5*S*)-5-Benzyl-2-(3,5-bis(trifluoromethyl)phenyl)-3-hydroxy-1-(3-phenylpropanoyl) imidazolidin-4-one (33)



Each diastereomer of (5*S*)- 5-benzyl-2- (3,5-bis(trifluoromethyl)phenyl)-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (**33**) was prepared separately by hydrogenation according to the stepwise General Procedure from **169** (diastereomer 1, 210 mg, 0.34 mmol; diastereomer 2, 61 mg, 0.097 mmol) to afford the two diastereomers as a pale reddish solids.

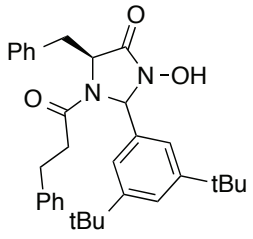
Diastereomer 1:

39 mg, 75%; **LC/MS** (ESI): t_R = 5.47 min; 578.1 for $[C_{27}H_{22}F_6N_2O_3+Na+H_2O]$.

Diastereomer 2:

141 mg, 77%; **LC/MS** (ESI): t_R = 5.77 min; 577.9 for $[C_{27}H_{22}F_6N_2O_3+Na+H_2O]$. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 46:54; acylated product: er = 52:48; calculated conversion: 67 %; **s = 1**.

(5*S*)-5-Benzyl-2-(3,5-di-*tert*-butylphenyl)-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (35)



(5*S*)- 5-Benzyl- 2-(3,5-di-*tert*-butylphenyl)- 3-hydroxy- 1-(3-phenylpropanoyl)imidazolidin-4-one (**35**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**3** (300 mg, 0.780 mmol , 1.00 equiv), 3,5-di-*tert*-butylbenzaldehyde (205 mg, 0.940 mmol, 1.20 equiv) and hyrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford the two diastereomers pale reddish solids.

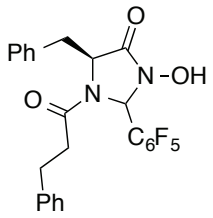
Diastereomer 1:

53 mg, 13%; **HRMS** (ESI): calculated for $[C_{33}H_{41}N_2O_3]^+$: m/z = 513.3112, found: m/z = 513.3112. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 22:78; acylated product: er = 66:34; calculated conversion: 64 %; **s = 3**.

Diastereomer 2:

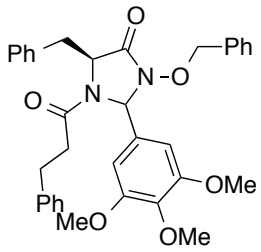
127 mg, 32%; **HRMS** (ESI): calculated for $[C_{33}H_{41}N_2O_3]^+$: m/z = 513.3112, found: m/z = 513.3114. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Opposite induction of stereochemistry was obtained compared to diastereomer 1. Recovered (Cbz-protected) amine: er = 71:29; acylated product: er = 33:67; calculated conversion: 55 %; **s = 3**.

(5*S*)-5-Benzyl-3-hydroxy-2-(perfluorophenyl)-1-(3-phenylpropanoyl)imidazolidin-4-one (32)



(5*S*)- 5-Benzyl- 3-hydroxy- 2-(perfluorophenyl)- 1-(3-phenylpropanoyl) imidazolidin-4-one (**32**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pentafluorobenzaldehyde (184 mg, 0.940 mmol, 1.20 equiv) and hyrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to a single diastereomer as a pale reddish solid (55 mg, 15%). **HRMS** (ESI): calculated for $[C_{25}H_{20}F_5N_2O_3]^+$: m/z = 491.1389, found: m/z = 491.1390. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 52:48; acylated product: er = 49:51; calculated conversion: 67 %; **s = 1**.

(5*S*)-5-Benzyl-3-(benzyloxy)-1-(3-phenylpropanoyl)-2-(3,4,5-trimethoxyphenyl) imidazolidin-4-one (170)



(5*S*)- 5-Benzyl- 3-(benzyloxy)- 1-(3-phenylpropanoyl)- 2-(3,4,5-trimethoxyphenyl)imidazolidin-4-one (**170**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), 3,4,5-trimethoxybenzaldehyde (184 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford the two diastereomers as colorless solids.

Diastereomer 1:

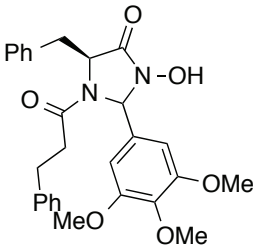
40 mg, 9%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.38–7.18 (m, 9H), 7.11–7.03 (m, 2H), 6.97–6.80 (m, 4H), 6.06 (s, 2H), 4.91 (dt, *J* = 4.8, 2.2 Hz, 1H), 4.75 (d, *J* = 2.0 Hz, 1H), 4.60–4.44 (m, 2H), 3.93–3.76 (m, 4H), 3.71 (s, 6H), 3.24 (dd, *J* = 13.8, 2.5 Hz, 1H), 2.79 (dd, *J* = 8.7, 6.7 Hz, 1H), 2.52 (ddd, *J* = 14.2, 8.7, 6.3 Hz, 1H), 2.19–1.90 (m, 2H); **LC/MS** (ESI): t_R = 5.79 min; 581.2 for $[C_{35}H_{36}N_2O_6+H]$.

Diastereomer 2:

227 mg, 58%; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.42–6.78 (m, 15H), 6.63 (br, 1H), 6.28–6.03 (m, 1H), 5.30 (br, 0.5H), 5.04–4.84 (m, 1.5H), 4.65 (br, 0.5H), 4.44–4.08 (m, 1H), 3.91–3.59 (m,

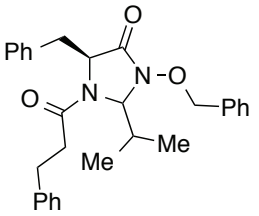
9.5H), 3.53–3.17 (m, 1.5H), 2.90–2.63 (m, 2.5H), 2.32–1.98 (m, 1.5H), 1.77 (br, 0.5H); **LC/MS** (ESI): t_R = 5.92 min; 581.2 for $[C_{35}H_{36}N_2O_6+H]$.

(5*S*)-5-Benzyl-3-hydroxy-1-(3-phenylpropanoyl)-2-(3,4,5-trimethoxyphenyl)imidazolidin-4-one (37)



(5*S*)- 5-Benzyl- 3-hydroxy- 1-(3-phenylpropanoyl)- 2-(3,4,5-trimethoxyphenyl)imidazolidin-4-one (**37**) was prepared by hydrogenation according to the stepwise General Procedure from **170** (diastereomer 2, 242 mg, 0.420 mmol) to afford the product as a pale reddish solid (199 mg, 97%). **HRMS** (ESI): calculated for $[C_{28}H_{31}N_2O_6]^+$: m/z = 491.2177, found: m/z = 491.2177. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 66:34; acylated product: er = 36:64; calculated conversion: 53 %; **s = 3**.

(5*S*)-5-Benzyl-3-(benzyloxy)-2-isopropyl-1-(3-phenylpropanoyl)imidazolidin-4-one (171)



(5*S*)- 5-Benzyl- 3-(benzyloxy)- 2-isopropyl- 1-(3-phenylpropanoyl) imidazolidin-4-one (**171**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), isobutyraldehyde (68.0 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford the two diastereomers as colorless solids.

Diastereomer 1:

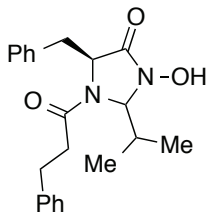
13 mg, 4%; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.32–7.06 (m, 11H), 7.08–6.93 (m, 3H), 6.82–6.72 (m, 1H), 4.69 (d, *J* = 2.3 Hz, 0.6H), 4.50–4.40 (m, 0.6H), 4.37–4.27 (m, 2x0.4H), 4.24 (d, *J* = 11.0 Hz, 0.6H), 4.12–4.04 (m, 0.4H), 3.94–3.76 (m, 1H), 3.19–2.67 (m, 4H), 2.37–2.09 (m, 2H), 1.86–1.61 (m, 1H), 0.76 (dd, *J* = 9.2, 7.3 Hz, 3H), 0.64 (d, *J* = 6.7 Hz, 2H), 0.41 (d, *J* = 6.9 Hz, 1H); **LC/MS** (ESI): t_R = 6.04 min; 457.2 for $[C_{29}H_{32}N_2O_3+H]$.

Diastereomer 2:

162 mg, 46%; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.38 (s, 5H), 7.31–7.16 (m, 8H), 7.01 (s, 2H),

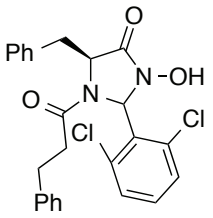
5.22 (s, 0.6H), 4.95 (s, 2H), 4.74 (s, 1.4H), 3.23 (s, 1H), 2.79 (s, 3H), 2.04 (d, *J* = 77.5 Hz, 3H), 0.96 (d, *J* = 7.3 Hz, 6H); **LC/MS** (ESI): t_R = 6.22 min; 457.2 for $[C_{29}H_{32}N_2O_3+H]$.

(5*S*)-5-Benzyl-3-hydroxy-2-isopropyl-1-(3-phenylpropanoyl)imidazolidin-4-one (22)



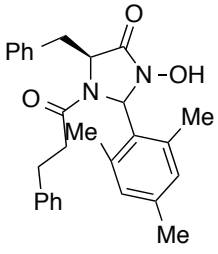
(5*S*)- 5-Benzyl- 3-hydroxy- 2-isopropyl- 1-(3-phenylpropanoyl)imidazolidin-4-one (**22**) was prepared by hydrogenation according to the stepwise General Procedure from **171** (diastereomer 2, 162 mg, 0.360 mmol) to afford the product as a pale reddish solid (110 mg, 84%). **HRMS** (ESI): calculated for $[C_{22}H_{27}N_2O_3]^+$: m/z = 367.2016, found: m/z = 367.2018. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 28:72; acylated product: er = 67:33; calculated conversion: 56 %; **s = 3**.

(5*S*)-5-Benzyl-2-(2,6-dichlorophenyl)-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (34)



(5*S*)- 5-Benzyl- 2-(2,6-dichlorophenyl)- 3-hydroxy- 1-(3-phenylpropanoyl) imidazolidin-4-one (**34**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), 2,6-dichlorobenzaldehyde (164 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (21.0 mg, 5%). **LC/MS** (ESI): t_R = 5.16 min; 469.1 for $[C_{25}H_{22}Cl_2N_2O_3+H]$. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 26:74; acylated product: er = 60:40; calculated conversion: 71 %; **s = 2**.

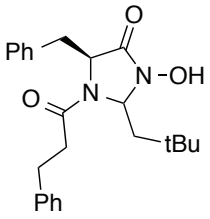
(5*S*)-5-Benzyl-3-hydroxy-2-mesityl-1-(3-phenylpropanoyl)imidazolidin-4-one (36)



(5*S*)- 5-Benzyl- 3-hydroxy- 2-mesityl- 1-(3-phenylpropanoyl) imidazolidin-4-one (**36**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), mesitaldehyde (139 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95

mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (63.0 mg, 18%). **LC/MS** (ESI): t_R = 5.46 min; 443.2 for [$C_{28}H_{30}N_2O_3$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 73:27; acylated product: er = 37:63; calculated conversion: 64 %; **s = 3**.

(5*S*)-5-Benzyl-3-hydroxy-2-neopentyl-1-(3-phenylpropanoyl)imidazolidin-4-one (23)



(5*S*)- 5-Benzyl- 3-hydroxy- 2-neopentyl- 1-(3-phenylpropanoyl)imidazolidin-4-one (**23**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), 3,3-dimethylbutanal (117 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford two diastereomers as colorless solids.

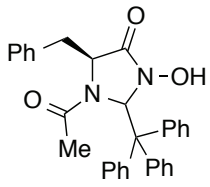
Diastereomer 1:

24 mg, 8%; **LC/MS** (ESI): t_R = 5.19 min; 395.2 for [$C_{24}H_{30}N_2O_3$+H].

Diastereomer 2:

83 mg, 27%; at room temperature the ratio of rotamers was 80:20 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 9.75 (br, 1H), 7.34–6.79 (m, 10H), 5.50 (t, *J* = 4.9 Hz, 0.8H), 4.85 (d, *J* = 8.2 Hz, 0.2H), 4.67 (br, 0.2H), 4.21 (t, *J* = 5.4 Hz, 0.8H), 3.29–2.69 (m, 3.2H), 2.51 (dd, *J* = 14.4, 7.1 Hz, 0.8H), 2.25 (dt, *J* = 15.4, 7.6 Hz, 1H), 2.07 (dt, *J* = 15.6, 7.7 Hz, 1H), 1.11–0.65 (m, 11H); **LC/MS** (ESI): t_R = 5.25 min; 395.1 for [$C_{24}H_{30}N_2O_3$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 41:59; acylated product: er = 55:45; calculated conversion: 64 %; **s = 1**.

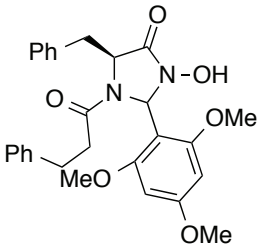
(5*S*)-1-Acetyl-5-benzyl-3-hydroxy-2-tritylimidazolidin-4-one (31)



(5*S*)-1-Acetyl-5-benzyl-3-hydroxy-2-tritylimidazolidin-4-one (**31**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (310 mg, 0.810 mmol , 1.00 equiv), 2,2,2-triphenylacetaldehyde (**152**) (220 mg, 0.810 mmol, 1.00 equiv) and acetyl chloride (159 mg, 2.03 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (17.0 mg, 4%). **HRMS** (ESI): calculated for $[C_{31}H_{29}N_2O_3]^+$: m/z = 477.2173, found: m/z = 477.2171. With this co-catalyst racemic ethyl

piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 49:51; acylated product: er = 49:51; calculated conversion: 50 %; **s = 1**.

(5*S*)-5-Benzyl-3-hydroxy-1-(3-phenylpropanoyl)-2-(2,4,6-trimethoxyphenyl)imidazolidin-4-one (38)



(5*S*)- 5-Benzyl- 3-hydroxy- 1-(3-phenylpropanoyl)- 2-(2,4,6-trimethoxyphenyl) imidazolidin-4-one (**38**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), 2,4,6-trimethoxybenzaldehyde (229 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford both diastereomers as colorless solids.

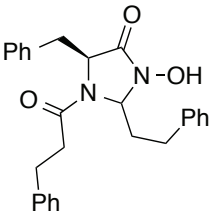
Diastereomer 1:

96 mg, 25%; **LC/MS** (ESI): t_R = 3.83 min; 491.3 for [$C_{28}H_{30}N_2O_6$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 61:39; acylated product: er = 45:55; calculated conversion: 69 %; **s = 1**.

Diastereomer 2:

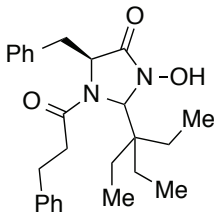
195 mg, 51%; **LC/MS** (ESI): t_R = 4.05 min; 491.4 for [$C_{28}H_{30}N_2O_6$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 44:56; acylated product: er = 51:49; calculated conversion: 86 %; **s = 1**.

(5*S*)-5-Benzyl-3-hydroxy-2-phenethyl-1-(3-phenylpropanoyl)imidazolidin-4-one (29)



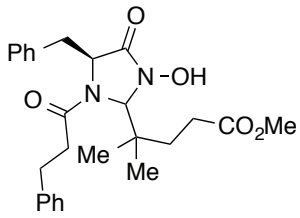
(5*S*)-5-Benzyl- 3-hydroxy- 2-phenethyl- 1-(3-phenylpropanoyl)imidazolidin-4-one (**29**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), hydrocinnamic aldehyde (157 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (104 mg, 31%). **LC/MS** (ESI): t_R = 4.21 min; 429.2 for [$C_{27}H_{28}N_2O_3$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 37:63; acylated product: er = 62:38; calculated conversion: 52 %; **s = 2**.

(5*S*)-5-Benzyl-2-(3-ethylpentan-3-yl)-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (24)



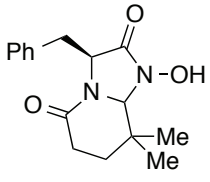
(5*S*)- 5-Benzyl- 2-(3-ethylpentan-3-yl)- 3-hydroxy- 1-(3-phenylpropanoyl) imidazolidin-4-one (**24**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), 2,2-diethylbutanal (**151**) (120 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (57.0 mg, 17%). **LC/MS** (ESI): t_R = 6.08 min; 423.1 for $[C_{26}H_{34}N_2O_3+H]$. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 21:79; acylated product: er = 80:20; calculated conversion: 51 %; **s = 7**.

Methyl 4-((4*S*)-4-benzyl-1-hydroxy-5-oxo-3-(3-phenylpropanoyl)imidazolidin-2-yl)-4-methylpentanoate (27)



Methyl 4-((4*S*)- 4-benzyl- 1-hydroxy- 5-oxo- 3-(3-phenylpropanoyl) imidazolidin-2-yl)- 4-methylpentanoate (**27**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), methyl 4,4-dimethyl-5-oxopentanoate (**156**) (148 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (23-0 mg, 7%). **HRMS** (ESI): calculated for $[C_{26}H_{33}N_2O_5]^+$: m/z = 453.2384, found: m/z = 453.2384. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 20:80; acylated product: er = 71:29; calculated conversion: 59 %; **s = 4**.

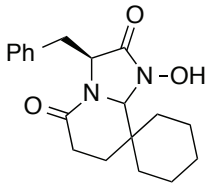
(3*S*)-3-Benzyl-1-hydroxy-8,8-dimethyltetrahydroimidazo[1,2-*a*]pyridine-2,5(1*H*,3*H*)-dione (51)



(3*S*)- 3-Benzyl- 1-hydroxy- 8,8-dimethyltetrahydroimidazo[1,2-*a*]pyridine-2,5(1*H*,3*H*)-dione (**51**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide

trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv) and 4,4-dimethyl-5-oxopentanoic acid (168 mg, 1.17 mmol, 1.50 equiv) to afford a single diastereomer as colorless solid (23.0 mg, 7%). **HRMS** (ESI): calculated for $[C_{16}H_{21}N_2O_3]^+$: m/z = 289.1547, found: m/z = 289.1544. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 14:86; acylated product: er = 75:25; calculated conversion: 59 %; **s = 6**.

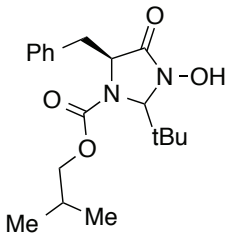
(3'*S*)-3'-Benzyl-1'-hydroxytetrahydro-5'*H*-spiro[cyclohexane-1,8'-imidazo[1,2-*a*]pyridine]-2',5'(3'*H*)-dione (52)



(3'*S*)- 3'-Benzyl- 1'-hydroxytetrahydro- 5'*H*-spiro[cyclohexane- 1,8'-imidazo[1,2-*a*]pyridine]-2',5'(3'*H*)-dione (**52**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv) and 3-(1-formylcyclohexyl)propanoic acid (215 mg, 1.17 mmol, 1.50 equiv) to afford a single diastereomer as colorless solid (23.0 mg, 7%). **LC/MS** (ESI): t_R = 3.33 min; 329.3 for $[C_{19}H_{24}N_2O_3+H]$. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 13:87; acylated product: er = 80:20; calculated conversion: 55 %; **s = 9**.

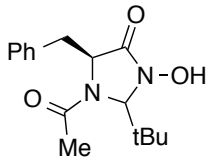
5.8.2 Variations of R^3

Isobutyl (5*S*)-5-benzyl-2-(*tert*-butyl)-3-hydroxy-4-oxoimidazolidine-1-carboxylate (43)



Isobutyl (5*S*)- 5-benzyl- 2-(*tert*-butyl)- 3-hydroxy- 4-oxoimidazolidine- 1-carboxylate (**43**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and isobutyl chloroformate (265 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (40.0 mg, 15%). **LC/MS** (ESI): t_R = 5.47 min; 349.2 for $[C_{19}H_{28}N_2O_4+H]$. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 21:79; acylated product: er = 84:16; calculated conversion: 46 %; **s = 9**.

(5*S*)-1-Acetyl-5-benzyl-2-(*tert*-butyl)-3-hydroxyimidazolidin-4-one (39)



(5*S*)- 1-Acetyl- 5-benzyl- 2-(*tert*-butyl)- 3-hydroxyimidazolidin- 4-one (**39**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and acetyl chloride (152 mg, 1.95 mmol, 2.50 equiv) to afford both diastereomers as colorless solids.

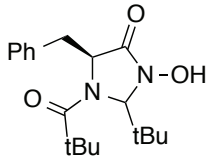
Diastereomer 1:

57 mg, 25%; **LC/MS** (ESI): t_R = 3.79 min; 291.2 for [$C_{16}H_{22}N_2O_3$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 71:29; acylated product: er = 16:84; calculated conversion: 38 %; **s = 8**.

Diastereomer 2:

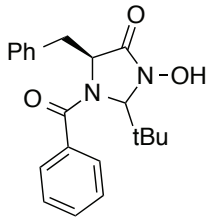
38 mg, 17%; **LC/MS** (ESI): t_R = 4.02 min; 291.2 for [$C_{16}H_{22}N_2O_3$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Opposite induction of stereochemistry was obtained compared to diastereomer 1. Recovered (Cbz-protected) amine: er = 19:81; acylated product: er = 85:15; calculated conversion: 47 %; **s = 11**.

(5*S*)-5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-pivaloylimidazolidin-4-one (40)



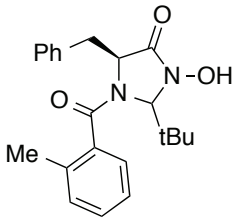
(5*S*)- 5-Benzyl- 2-(*tert*-butyl)- 3-hydroxy- 1-pivaloylimidazolidin- 4-one (**40**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and pivaloyl chloride (234 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (49.0 mg, 19%). **HRMS** (ESI): calculated for $[C_{19}H_{29}N_2O_3]^+$: m/z = 333.2173, found: m/z = 333.2175. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 25:75; acylated product: er = 78:22; calculated conversion: 47 %; **s = 6**.

(5*S*)-1-Benzoyl-5-benzyl-2-(*tert*-butyl)-3-hydroxyimidazolidin-4-one (42)



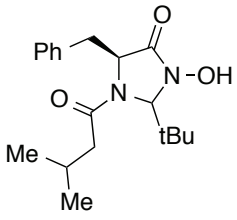
(5*S*)- 1-Benzoyl- 5-benzyl- 2-(*tert*-butyl)- 3-hydroxyimidazolidin- 4-one (**42**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and benzoyl chloride (273 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (29.0 mg, 11%). **LC/MS** (ESI): t_R = 3.85 min; 353.1 for $[C_{21}H_{24}N_2O_3+H]$. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 24:76; acylated product: er = 81:19; calculated conversion: 45 %; **s = 7**.

(5*S*)-5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-(2-methylbenzoyl)imidazolidin-4-one (46)



(5*S*)- 5-Benzyl- 2-(*tert*-butyl)- 3-hydroxy-1-(2-methylbenzoyl)imidazolidin-4-one (**46**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and 2-methylbenzoyl chloride (300 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (53.0 mg, 19%). **HRMS** (ESI): calculated for $[C_{22}H_{27}N_2O_3]^+$: m/z = 367.2016, found: m/z = 367.2016. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 34:66; acylated product: er = 64:36 calculated conversion: 53 %; **s = 2**.

(5*S*)-5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-(3-methylbutanoyl)imidazolidin-4-one (41)



(5*S*)- 5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-(3-methylbutanoyl)imidazolidin-4-one (**41**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and 3-methylbutanoyl chloride (234 mg, 1.95 mmol, 2.50 equiv) to afford both diastereomers as colorless solids.

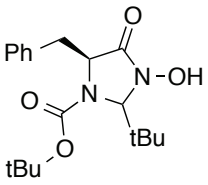
Diastereomer 1:

21 mg, 8%; **LC/MS** (ESI): t_R = 4.68 min; 333.2 for [$C_{19}H_{28}N_2O_3$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 13:87; acylated product: er = 81:19; calculated conversion: 54 %; **s = 9**.

Diastereomer 2:

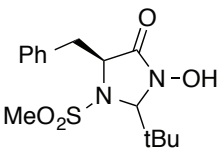
28 mg, 11%; **LC/MS** (ESI): t_R = 5.10 min; 333.2 for [$C_{19}H_{28}N_2O_3$+H]. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Opposite induction of stereochemistry was obtained compared to diastereomer 1. Recovered (Cbz-protected) amine: er = 71:29; acylated product: er = 16:84; calculated conversion: 38 %; **s = 8**.

tert-Butyl (5*S*)-5-benzyl-2-(*tert*-butyl)-3-hydroxy-4-oxoimidazolidine-1-carboxylate (44)



tert-Butyl (5*S*)- 5-benzyl- 2-(*tert*-butyl)- 3-hydroxy- 4-oxoimidazolidine- 1-carboxylate (**44**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and Boc anhydride (425 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (125 mg, 46%). **HRMS** (ESI): calculated for $[C_{19}H_{29}N_2O_4]^+$: m/z = 349.2122, found: m/z = 349.2120. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 8:92; acylated product: er = 81:19; calculated conversion: 58 %; **s = 11**.

(5*S*)-5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-(methylsulfonyl)imidazolidin-4-one (45)

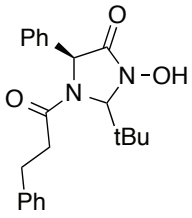


(5*S*)- 5-Benzyl- 2-(*tert*-butyl)- 3-hydroxy- 1-(methylsulfonyl)imidazolidin- 4-one (**45**) was prepared according to the one pot General Procedure from *(S)*-2-amino-*N*-(benzyloxy)-3-phenylpropanamide trifluoroacetic acid salt (**143**) (300 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and methanesulfonyl chloride (222 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (49.0 mg, 19%). **HRMS** (ESI): calculated for $[C_{15}H_{23}N_2SO_4]^+$: m/z = 327.1373, found: m/z = 327.1373. With this co-catalyst racemic ethyl piperidine was resolved according

to the General Procedure. Recovered (Cbz-protected) amine: er = 40:60; acylated product: er = 66:34; calculated conversion: 38 %; **s = 2**.

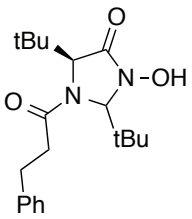
5.8.3 Variations of R^1

(5*S*)-2-(*tert*-Butyl)-3-hydroxy-5-phenyl-1-(3-phenylpropanoyl)imidazolidin-4-one (47)



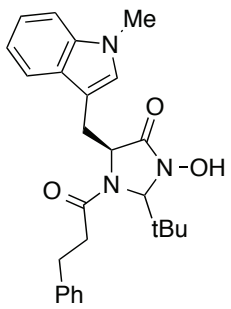
(5*S*)-2-(*tert*-Butyl)-3-hydroxy-5-phenyl-1-(3-phenylpropanoyl)imidazolidin-4-one (**47**) was prepared according to the one pot General Procedure from(*S*)-2-amino-*N*-(benzyloxy)-2-phenylacetamide trifluoroacetic acid salt (**147**) (300 mg, 0.850 mmol , 1.00 equiv), pivaldehyde (88.0 mg, 1.02 mmol, 1.20 equiv) and hydrocinnamoyl chloride (359 mg, 2.10 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (121 mg, 39%). **HRMS** (ESI): calculated for $[C_{20}H_{31}N_2O_3]^+$: m/z = 347.2329, found: m/z = 347.2330. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 17:83; acylated product: er = 85:15; calculated conversion: 49 %; **s = 11**.

(5*S*)-2,5-di-*tert*-Butyl-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (48)



(5*S*)- 2,5-di-*tert*-Butyl- 3-hydroxy- 1-(3-phenylpropanoyl) imidazolidin- 4-one (**48**) was prepared according to the one pot General Procedure from (*S*)-2-amino-*N*-(benzyloxy)-3,3-dimethylbutanamide trifluoroacetic acid salt (**145**) (300 mg, 0.900 mmol , 1.00 equiv), pivaldehyde (93.0 mg, 1.08 mmol, 1.20 equiv) and hydrocinnamoyl chloride (380 mg, 2.25 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (118 mg, 34%). **LC/MS** (ESI): t_R = 4.10 min; 367.2 for $[C_{22}H_{26}N_2O_3+H]$. With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 50:50; acylated product: er = 48:52; calculated conversion: 33 %; **s = 1**.

(5*S*)-2-(*tert*-Butyl)-3-hydroxy-5-((1-methyl-1*H*-indol-3-yl)methyl)-1-(3-phenylpropanoyl) imidazolidin-4-one (49)

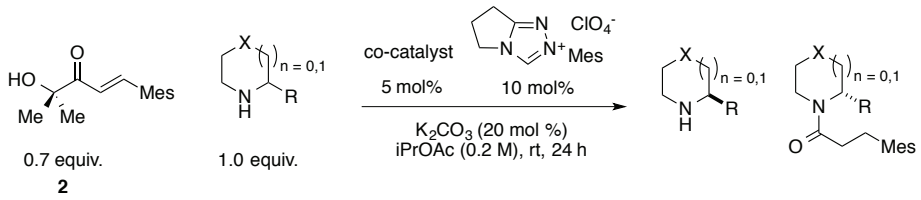


(5*S*)- 2-(*tert*-Butyl)- 3-hydroxy- 5-((1-methyl-1*H*-indol-3-yl)methyl)- 1-(3-phenylpropanoyl)imidazolidin-4-one (**49**) was prepared according to the one pot General Procedure from (*S*)-2-amino-*N*-(benzyloxy)-3-(1-methyl-1*H*-indol-3-yl)propanamide trifluoroacetic acid salt (**150**) (328 mg, 0.780 mmol , 1.00 equiv), pivaldehyde (81.0 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford a single diastereomer as colorless solid (100 mg, 30%). **LC/MS** (ESI): t_R = 4.26 min; 434.4 for $[C_{26}H_{31}N_3O_3+H]$.

With this co-catalyst racemic ethyl piperidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 18:82; acylated product: er = 82:18; calculated conversion: 50 %; **s = 9**.

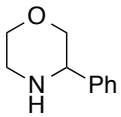
5.9 Kinetic Resolution of Other Secondary Cyclic Amines

General procedure for the catalytic kinetic resolution of secondary cyclic amines:



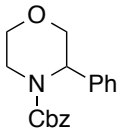
Hydroxamic acid co-catalyst (0.013 mmol, 0.050 equiv), triazolium salt (8.2 mg, 0.025 mmol, 0.10 equiv), α´-hydroxyenone **2** (41 mg, 0.18 mmol, 0.70 equiv), K_2CO_3 (6.9 mg, 0.050 mmol, 0.20 equiv) and the amine substrate (0.25 mmol, 1.0 equiv) were mixed in *i*PrOAc (1.3 mL, 0.20 M). The reaction was allowed to stir for the 24 h at rt and quenched by the addition of DBU (36 mL, 0.25 mmol, 1.0 equiv) and CbzCl (37 mL, 0.25 mmol, 1.0 equiv). The mixture was allowed to stir for 2 h at rt before sat aq $NaHCO_3$ solution (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by column chromatography on silica gel to obtain the recovered amine as its Cbz-derivative and the amide.

5.9.1 3-Phenylmorpholine

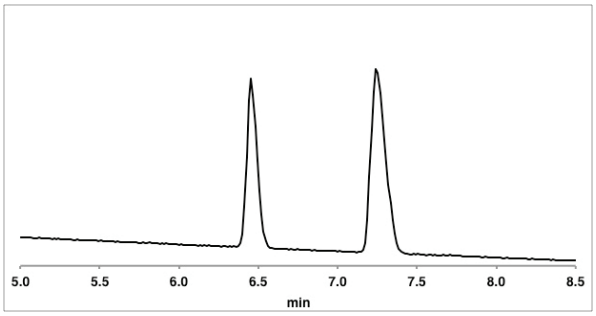


Racemic 3-phenylmorpholine (41.0 mg, 0.25 mmol) was resolved according to the General Procedure to generate the recovered amine and the amide.

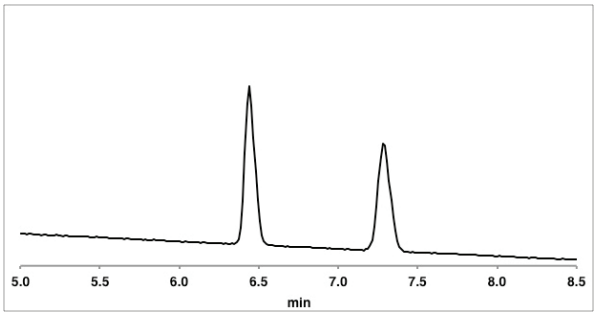
The recovered amine was obtained as its Cbz-derivative: **Benzyl 3-phenylmorpholine-4-carboxylate**



SFC: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.4 min and 7.3 min.

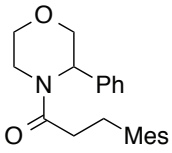


racemate

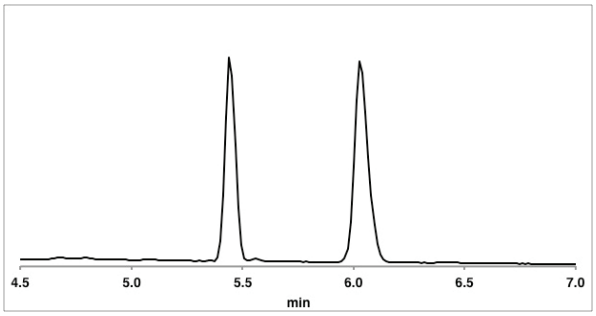


enantiomerically enriched

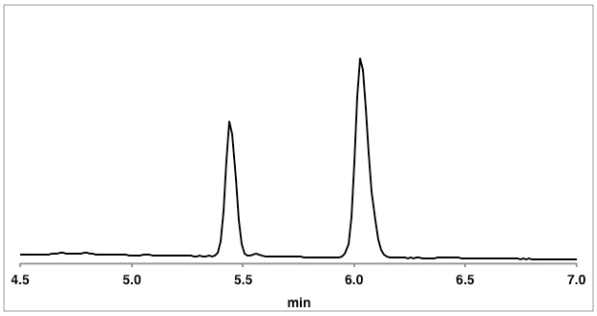
3-Mesityl-1-(3-phenylmorpholino)propan-1-one



SFC: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.4 min and 6.0 min.

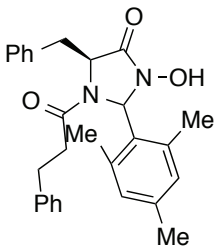


racemate



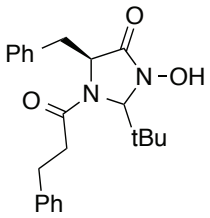
enantiomerically enriched

(5*S*)-5-Benzyl-3-hydroxy-2-mesityl-1-(3-phenylpropanoyl)imidazolidin-4-one (36)



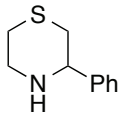
With this co-catalyst racemic phenyl morpholine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 39:61; acylated product: er = 33:67; calculated conversion: 39%; **s = 3**.

(5*S*)-5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (21)



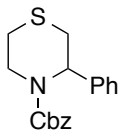
With this co-catalyst racemic phenyl morpholine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 54:46; acylated product: er = 89:11; calculated conversion: 9%; **s = 9**.

5.9.2 3-Phenylthiomorpholine

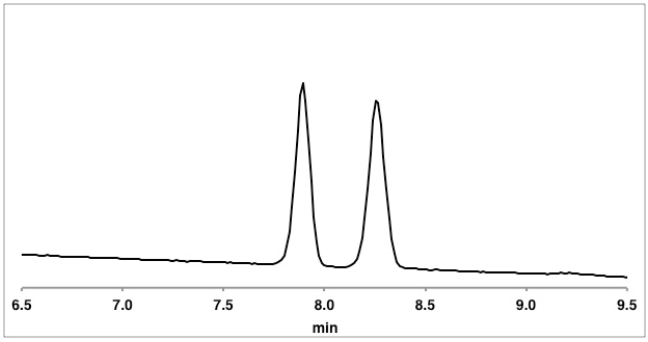


Racemic 3-phenylthiomorpholine (45.0 mg, 0.25 mmol) was resolved according to the General Procedure to generate only the recovered amine. The reactivity of the amine is very poor and no amide was obtained in the kinetic resolution.

The recovered amine was obtained as its Cbz-derivative: **Benzyl 3-phenylthiomorpholine-4-carboxylate**

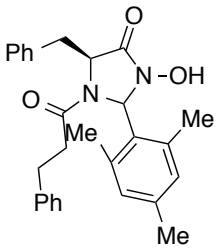


SFC: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.9 min and 8.3 min.



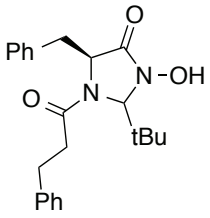
racemate

(5*S*)-5-Benzyl-3-hydroxy-2-mesityl-1-(3-phenylpropanoyl)imidazolidin-4-one (36)



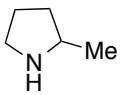
With this co-catalyst racemic phenyl thiomorpholine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 48:52.

(5*S*)-5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (21)



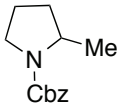
With this co-catalyst racemic phenyl thiomorpholine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 49:51.

5.9.3 2-Methylpyrrolidine

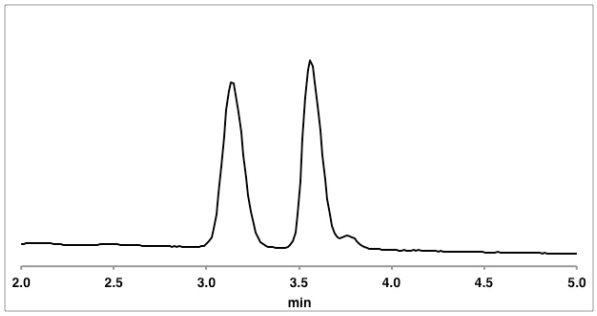


Racemic 2-methylpyrrolidin (21.0 mg, 0.25 mmol) was resolved according to the General Procedure to generate the recovered amine and the amide.

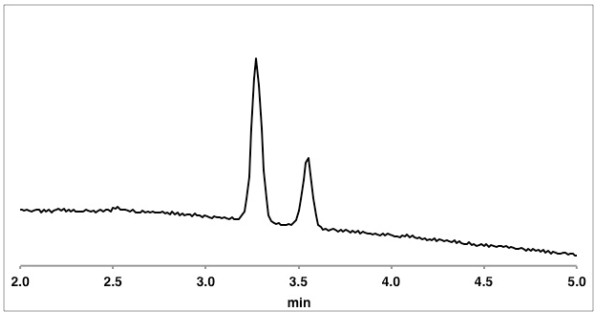
The recovered amine was obtained as its Cbz-derivative: **Benzyl 2-methylpyrrolidine-1-carboxylate**



SFC: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.2 min and 3.5 min.

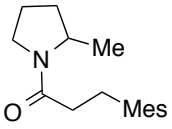


racemate

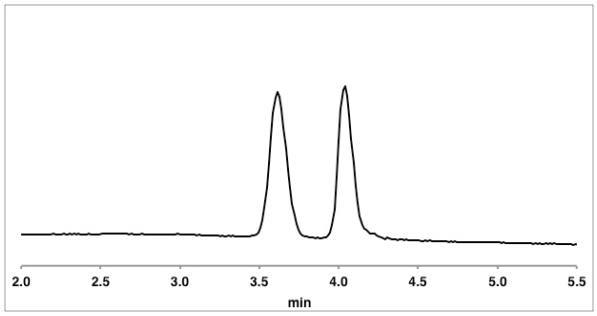


enantiomerically enriched

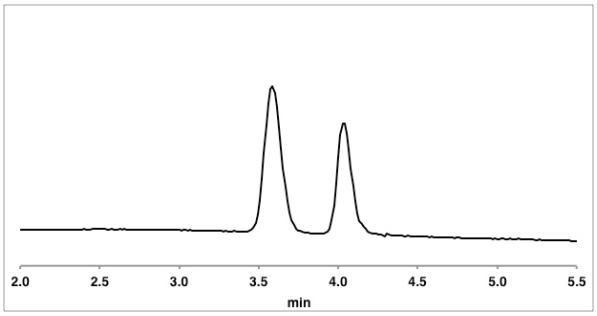
3-Mesityl-1-(2-methylpyrrolidin-1-yl)propan-1-one



SFC: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.6 min and 4.1 min.

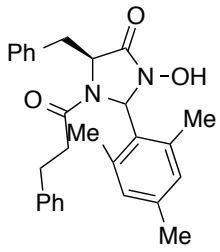


racemate



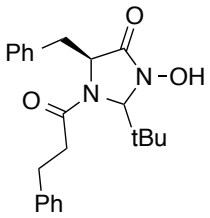
enantiomerically enriched

(5*S*)-5-Benzyl-3-hydroxy-2-mesityl-1-(3-phenylpropanoyl)imidazolidin-4-one (36)



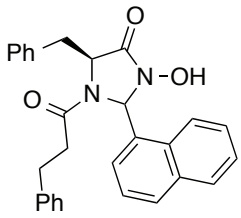
With this co-catalyst racemic methyl pyrrolidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 70:30; acylated product: er = 58:42; calculated conversion: 71%; **s = 2**.

(5*S*)-5-Benzyl-2-(*tert*-butyl)-3-hydroxy-1-(3-phenylpropanoyl)imidazolidin-4-one (21)



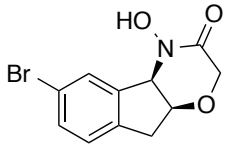
With this co-catalyst racemic methyl pyrrolidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 47:53; acylated product: er = 48:52; calculated conversion: 60 %; **s = 1**.

(5*S*)-5-Benzyl-3-hydroxy-2-(naphthalen-1-yl)-1-(3-phenylpropanoyl)imidazolidin-4-one (30)



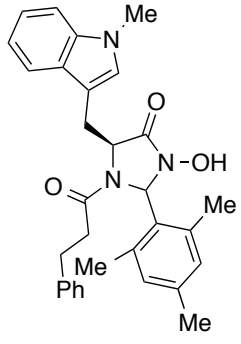
With this co-catalyst racemic methyl pyrrolidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 66:34; acylated product: er = 55:45; calculated conversion: 76 %; **s = 2**.

(4a*R*,9a*S*)-6-Bromo-4-hydroxy-4,4a,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one (1)



With this co-catalyst racemic methyl pyrrolidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 53:47; acylated product: er = 54:46; calculated conversion: 43 %; **s = 1**.

(5*S*)-3-Hydroxy-2-mesityl-5-((1-methyl-1*H*-indol-3-yl)methyl)-1-(3-phenylpropanoyl)imidazolidin-4-one (56)



(5*S*)- 3-Hydroxy- 2-mesityl- 5-((1-methyl-1*H*-indol-3-yl)methyl)- 1-(3-phenylpropanoyl)imidazolidin-4-one (**56**) was prepared according to the one pot General Procedure from (*S*)-2-amino-*N*-(benzyloxy)-3-(1-methyl-1*H*-indol-3-yl)propanamide trifluoroacetic acid salt (**150**) (328 mg, 0.780 mmol , 1.00 equiv), mesitaldehyde (139 mg, 0.940 mmol, 1.20 equiv) and hydrocinnamoyl chloride (330 mg, 1.95 mmol, 2.50 equiv) to afford both diastereomers as colorless solids.

Diastereomer 1:

76 mg, 20%; **LC/MS** (ESI): t_R = 4.38 min; 496.5 for [$C_{31}H_{33}N_3O_3$+H].

Diastereomer 2:

138 mg, 36%; **LC/MS** (ESI): t_R = 4.60 min; 496.5 for [$C_{31}H_{33}N_3O_3$+H]. With this co-catalyst racemic methyl pyrrolidine was resolved according to the General Procedure. Recovered (Cbz-protected) amine: er = 63:37; acylated product: er = 62:38; calculated conversion: 52 %; **s = 2**.

6

Experimental Section II

CHAPTER 6. Experimental Section II on the Kinetic Resolution of Disubstituted Piperidines

6.1 General Remarks

All reactions were carried out in oven dried glassware under an atmosphere of dry N_2 using standard manifold techniques.[8] Chemicals were purchased from *Acros*, *Sigma-Aldrich*, *ABCR* or *TCI* and used without further purification unless otherwise stated. Dichloromethane was distilled from CaH_2 and THF from sodium, other solvents were dried by passage over two columns of anhydrous neutral A-2 alumina under an atmosphere of argon.[9]

Flash column chromatography was performed on silica gel (*Silicycle* SiliaFlash F60, 230-400 mesh). Thin layer chromatography was performed on glass-backed plates pre coated with silica gel (*Merck*, Silica Gel 60 F254).

NMR spectra were recorded on *Bruker* Avance III 400 MHz or *Varian* Mecury-VX 300 MHz spectrometers using $CDCl_3$ as the solvent unless indicated otherwise. ^{1}H NMR chemical shifts are expressed in parts per million (d) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.26 ppm or of CH_3OH at 3.31 used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (d) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.2 ppm or of CH_3OH at 49.0 used as a standard). All ^{13}C spectra were measured with complete proton decoupling. NMR coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; quint; quintet; sext, sextet ; m, multiplet. Infrared (IR) spectra were recorded on a *JASCO* FT-IR-4100 spectrometer and reported as wavenumber (cm^{-1}) of the absorption maxima for the range between 4000 cm^{-1} and 750 cm^{-1} with only major peaks reported. Optical rotations were measured on *JASCO* P-1010 operating at the sodium D line with a 100 m path length cell. High resolution mass spectra were measured by the Mass Spectrometry Service Facility of Laboratorium für Organische Chemie at ETH Zürich on a *Bruker* Daltonics maXis for ESI-Q-TOF spectrometer (ESI-MS) or on a *Bruker* solariX (9.4T magnet) equipped with a dual ESI/MALDI-FT-ICR source using *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as matrix (MALDI-MS). Chiral HPLC (High-Performance

8 Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, Taylor & Fran*cis*, 1998.
9 Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J.: Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**,*15*, 1518.

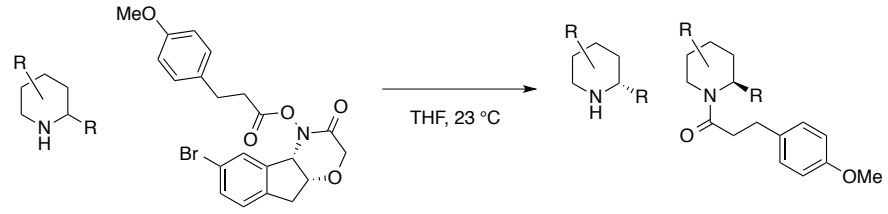
Liquid Chromatography) and SFC (Supercritical Fluid Chromatography) were performed on *JASCO* liquid chromatography units. *Daicel* Chiralcel or Chiralpak columns (0.46 x 25 cm) were used. Details of chromatographic conditions are indicated under each compound.

6.2 Determination of the Absolute Stereochemistry

The absolute stereochemistry of the products was assigned by comparison of optical rotation with compounds reported in the literature by X-ray crystallography or by analogy as indicated under each compound. All the amides and some carbamates obtained showed hindered rotation on the NMR timescale or were conformational isomers at room temperature. This has been studied extensively.[10]

6.3 General Procedure for the Kinetic Resolution of Disubstituted Piperidines and for the Preparation of Racemates

6.3.1 General Procedure A for the Kinetic Resolution of Disubstituted Piperidines



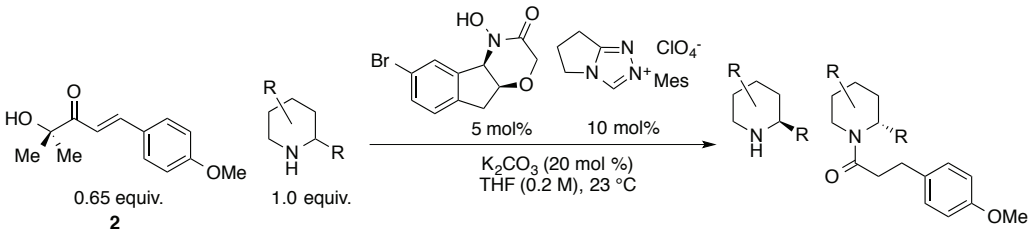
74

The racemic amine (1.0 equiv) was dissolved in THF (0.20 M) and acyl hydroxamate **74**[11] (0.50 equiv) was added. The mixture was allowed to stir for the indicated time (15 – 120 h) at 23 °C and quenched by the addition of DBU (1.0 equiv) and CbzCl (1.0 equiv). The mixture was allowed to stir for 2 h at rt before sat aq $NaHCO_3$ solution (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by column chromatography (silica gel).

10 (a) Chow, Y. L.; Colon, C. J.; Tam, J. N. S.: $A^{(1,3)}$ Interaction and Conformational Energy of Axial–Axial 1,3-Dimethyl Interaction. *Can. J. Chem.* **1968**, *46*, 2821–2825. (b) Rauk, A.; Tavares, D. F.; Khan, M. A.; Borkent, A. J.; Olson, J. F.: Conformational Analysis of Chiral Hindered Amides. *Can. J. Chem.* **1983**, *61*, 2572–2580.

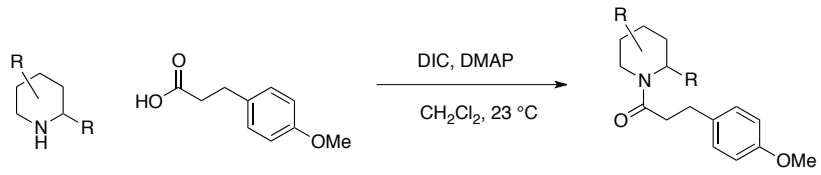
11 Allen, S. E.; Hsieh, S.-Y.; Gutierrez, O.; Bode, J. W.; Kozlowski, M. C.: Concerted Amidation of Activated Esters: Reaction Path and Origins of Selectivity in the Kinetic Resolution of Cyclic Amines via N-Heterocyclic Carbenes and Hydroxamic Acid Cocatalyzed Acyl Transfer. *J. Am. Chem. Soc.* **2014**, *136*, 11783–11791.

6.3.2 General Procedure B for the Catalytic Kinetic Resolution of Disubstituted Piperidines



Hydroxamic acid co-catalyst (5 mol%), triazolium salt (10 mol%), α'-hydroxyenone[12] **2** (0.65 equiv), K_2CO_3 (0.20 equiv) and the respective amine (1.0 equiv) were mixed in THF (0.20 M). The reaction was allowed to stir for the indicated time at rt and quenched by the addition of DBU (1.0 equiv) and CbzCl (1.0 equiv). The mixture was allowed to stir for 2 h at rt before sat aq $NaHCO_3$ solution (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by column chromatography (silica gel).

6.3.3 Racemic Amides



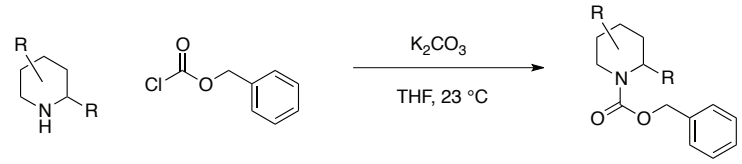
The amine (0.15 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.0 mL, 0.15 M) and 3-(4-methoxyphenyl)propionic acid (27 mg, 0.15 mmol, 1.0 equiv), *N,N'*-diisopropylcarbodiimide (23.2 µL, 0.150 mmol, 1.00 equiv) and DMAP (2.1 mg, 0.015 mmol, 0.10 equiv) were added. The reaction mixture was allowed to stir at 23 °C overnight. The resulting suspension was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel.

Note:

In some cases propylphosphoric anhydride (T3P) proved to be a more beneficial coupling agent.

12 Prepared according to: Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzales, A.; Arceo, E.: α'-Hydroxy Enones as Achiral Templates for Lewis Acid-Catalyzed Enantioselective Diels–Alder Reactions**.** *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

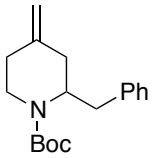
6.3.4 Racemic Carbamates



The amine (0.150 mmol, 1.00 equiv) was dissolved in THF (1.0 mL, 0.15 M) and K_2CO_3 (23.5 mg, 0.170 mmol, 1.10 equiv) and benzyl chloroformate (23.5 μL, 0.170 mmol, 1.10 equiv) were added. The reaction mixture was allowed to stir at 23 °C overnight. To the resulting suspension sat aq $NaHCO_3$ solution (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel.

6.4 Synthesis of Amines

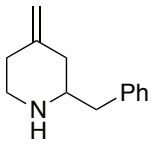
tert-Butyl 2-benzyl-4-methylenepiperidine-1-carboxylate (118)



To a slurry of $(Ph)_3PCH_3Br$ (2.68 g, 7.50 mmol, 1.80 equiv) in THF (9.4 mL) at 0 °C was added a solution of potassium *tert*-butoxide (7.5 mL, 1.0 M) in THF. After stirring the bright yellow solution for 30 min at 23 °C, a solution of *tert*-butyl 2-benzyl-4-oxopiperidine-1-carboxylate[13] (1.20 g, 4.20 mmol, 1.00 equiv) in THF (2.0 mL) was added and the reaction allowed to stir for 24 h. The reaction mixture was quenched by the addition of 1M aq HCl, partially concentrated and the residue extracted with methyl *tert*-butyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel (hexanes:EtOAc = 20:1) to afford the desired compound as a colorless oil (705 mg, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.39–7.09 (m, 5H), 4.96 (ap. q, J = 1.9 Hz, 1H), 4.82 (ap. q, J = 1.9 Hz, 1H), 4.55 (br, 1H), 4.18 (br, 1H), 2.99 (td, J = 12.8, 4.0 Hz, 1H), 2.84–2.69 (m, 2H), 2.42–2.09 (m, 4H), 1.39 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 154.9, 142.7, 139.2, 129.5, 128.5, 126.3, 111.4, 79.6, 53.9, 39.8, 36.7, 34.2, 28.5; **HRMS** (ESI): calculated for $[C_{18}H_{25}NO_2Na]^+$: m/z = 310.1777, found: m/z = 310.1778; **IR** (ν/cm^{-1}, neat) 3398, 2977, 2940, 1693, 1412, 1364, 1169, 1107, 1018, 892.

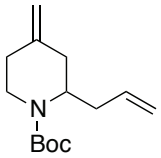
13 Prepared according to: Watson, P. S.; Jiang, B.; Scott, B.: A Diastereoselective Synthesis of 2,4-Disubstituted Piperidines: Scaffolds for Drug Discovery. *Org. Lett.* **2000**, 3679–3681.

2-Benzyl-4-methylenepiperidine (121)



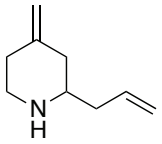
A solution of the carbamate **118** (350 mg, 1.20 mmol) in 75% TFA/CH_2Cl_2 (12 mL) was allowed to stir for 2 h at rt and concentrated *in vacuo*. Et_2O (20 mL) and 10% aq K_2CO_3 solution (20 mL) was added and the layers were separated. Following extraction with Et_2O (3 x 15 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a colorless liquid (144 mg, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.40–7.21 (m, 5H), 4.74–4.66 (m, 2H), 3.17–3.09 (m, 1H), 2.86–2.73 (m, 2H), 2.73–2.63 (m, 1H), 2.62–2.50 (m, 1H), 2.33 (dd, *J* = 13.0, 2.2 Hz, 1H), 2.27–2.17 (m, 2H), 2.03–1.91 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 146.5, 138.9, 129.4, 128.7, 126.5, 108.4, 59.3, 47.6, 43.4, 41.9, 35.3; **HRMS** (ESI): calculated for $[C_{13}H_{18}N]^+$: m/z = 188.1434, found: m/z = 188.1443; **IR** (ν/cm^{-1}, neat) 3026, 2938, 2819, 1651, 1494, 1454, 1443, 1310, 1127, 888.

***tert*-Butyl 2-allyl-4-methylenepiperidine-1-carboxylate (119)**



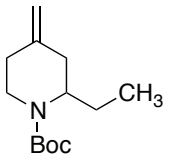
To a slurry of $(Ph)_3PCH_3Br$ (1.61 g, 4.50 mmol, 1.80 equiv) in THF (5.6 mL) at 0 °C was added a solution of potassium *tert*-butoxide (4.5 mL, 1.0 M) in THF. After stirring the bright yellow solution for 30 min at 23 °C, a solution of *tert*-butyl 2-allyl-4-oxopiperidine-1-carboxylate[13] (600 mg, 2.50 mmol, 1.00 equiv) in THF (1.5 mL) was added and the reaction allowed to stir for 24 h. The reaction mixture was quenched by the addition of 1M aq HCl, partially concentrated and the residue extracted with methyl *tert*-butyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel (hexanes:EtOAc = 10:1) to afford the desired compound as a colorless oil (509 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 5.81–5.61 (m, 1H), 5.08–4.96 (m, 2H), 4.84 (ap. q, *J* = 2.0 Hz, 1H), 4.73 (ap. q, *J* = 2.0 Hz, 1H), 4.38 (br, 1H), 4.06 (br, 1H), 2.79 (td, *J* = 12.8, 4.7 Hz, 1H), 2.42–2.03 (m, 6H), 1.45 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.1, 142.6, 135.3, 117.1, 111.1, 79.6, 51.2 (br.), 39.8 (br.), 37.4, 34.9, 34.2, 28.6; **HRMS** (MALDI/ESI): calculated for $[C_{14}H_{23}NO_2Na]^+$: m/z = 260.1621, found: m/z = 260.1621; **IR** (ν/cm^{-1}, neat) 3076, 2977, 2941, 2903, 1694, 1411, 1364, 1244, 1171, 1119, 1021, 997, 913, 893.

2-Allyl-4-methylenepiperidine (122)



A solution of the carbamate **119** (509 mg, 2.20 mmol) in 75% TFA/CH_2Cl_2 (24 mL) was allowed to stir for 2 h at rt and concentrated *in vacuo*. Et_2O (20 mL) and 10% aq K_2CO_3 solution (20 mL) was added and the layers were separated. Following extraction with Et_2O (3 x 15 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a colorless liquid (273 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 5.84–5.70 (m, 1H), 5.14–5.04 (m, 2H), 4.69–4.62 (m, 2H), 3.20–3.11 (m, 1H), 2.64–2.49 (m, 2H), 2.31–2.00 (m, 6H), 1.90–1.77 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 146.6, 135.2, 117.7, 108.2, 57.3, 47.6, 41.8, 41.4, 35.4; **HRMS** (ESI): calculated for $[C_9H_{16}N]^+$: m/z = 138.1277, found: m/z = 138.1278; **IR** (ν/cm^{-1}, neat) 2956, 2923, 2850, 1673, 1430, 1201, 1180, 1134.

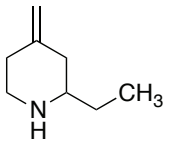
***tert*-Butyl 2-ethyl-4-methylenepiperidine-1-carboxylate (120)**



To a slurry of $(Ph)_3PCH_3Br$ (2.83 g, 7.90 mmol, 1.80 equiv) in THF (10.0 mL) at 0 °C was added a solution of potassium *tert*-butoxide (7.9 mL, 1.0 M) in THF. After stirring the bright yellow solution for 30 min at 23 °C, a solution of *tert*-butyl 2-benzyl-4-oxopiperidine-1-carboxylate[14] (1.00 g, 4.40 mmol, 1.00 equiv) in THF (2.0 mL) was added and the reaction allowed to stir for 24 h. The reaction mixture was quenched by the addition of 1M aq HCl, concentrated and the residue extracted with methyl *tert*-butyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel (hexanes:EtOAc = 10:1) to afford the desired compound as a colorless oil (822 mg, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.79 (s, 1H), 4.70 (s, 1H), 4.21 (br, 1H), 4.07 (br, 1H), 2.80–2.65 (m, 1H), 2.33 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.20–2.05 (m, 3H), 1.62–1.49 (m, 1H), 1.45 (s, 9H), 1.42–1.24 (m, 1H), 0.81 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.3, 143.1, 110.7, 79.4, 53.0 (br.), 39.5 (br.), 38.0, 34.3, 28.6, 23.1, 10.5; **HRMS** (MALDI/ESI): calculated for $[C_{13}H_{24}NO_2]^+$: m/z = 226.1802, found: m/z = 226.1806; **IR** (ν/cm^{-1}, neat) 2967, 2935, 2875, 1694, 1415, 1364, 1261, 1246, 1173, 1120, 1078, 996, 980, 890.

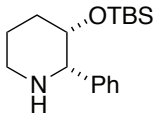
14 Prepared according to: Sebesta, R.; Pizzuti, M. G.; Boersma, A. J.; Minnaard, A. J.; Feringa, B. L.: Catalytic Enantioselective Conjugate Addition of Dialkylzinc Reagents to *N*-Substituted-2,3-Dehydro-4-piperidones. *Chem. Commun.* **2005**, 1711–1713.

2-Ethyl-4-methylenepiperidine (123)



A solution of the carbamate **120** (700 mg, 3.10 mmol) in 75% TFA/CH_2Cl_2 (24.0 mL was allowed to stir for 2 h at rt and concentrated *in vacuo*. Et_2O (20 mL) and 10% aq K_2CO_3 solution (20 mL) was added and the layers were separated. Following extraction with Et_2O (3 x 15 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a colorless liquid (363 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.66–4.62 (m, 2H), 3.18–3.11 (m, 1H), 2.60 (td, *J* = 11.8, 3.5 Hz, 1H), 2.45–2.24 (m, 3H), 2.24–2.06 (m, 2H), 1.84–1.71 (m, 1H), 1.48–1.37 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 146.6, 108.0, 59.7, 47.6, 41.5, 35.6, 29.6, 10.4; **HRMS** (ESI): calculated for $[C_8H_{16}N]^+$: m/z = 126.1277, found: m/z = 126.1275; **IR** (ν/cm^{-1}, neat) 2962, 2925, 2852, 1675, 1463, 1429, 1202, 1179, 1134, 834, 799.

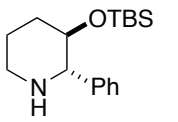
***cis*-3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpiperidine (*cis*-81)**



cis-Benzyl 3-hydroxy-2-phenylpiperidine-1-carboxylate (*cis*-**79**)[15] (526 mg, 1.69 mmol, 1.00 equiv) and imidazole (230 mg, 3.38 mmol, 2.00 equiv) were dissolved in dry CH_2Cl_2 (6.8 mL, 0.25 M). The reaction mixture was cooled to 0 °C and neat TBSCl (332 mg, 2.20 mmol, 1.30 equiv) was added in one portion. The solution was allowed to stir overnight and sat aq $NaHCO_3$ solution (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel (hexanes:EtOAc = 19:1). The solvent was removed and the residue dissolved in EtOH (7 mL). 10% Pd/C (60.0 mg) was added and the flask purged with H_2. The reaction mixture was allowed to stir vigorously under H_2 atmosphere for 5 h and filtered through a pad of Celite. The solvent was removed to obtain the desired compound as a colorless oil (376 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.36–7.18 (m, 5H), 3.97–3.89 (m, 1H), 3.82 (d, *J* = 1.5 Hz, 1H), 3.66 (br, 1H), 3.38–3.28 (m, 1H), 2.82 (td, *J* = 12.8, 3.1 Hz, 1H), 2.05–1.88 (m, 2H), 1.87–1.72 (m, 1H), 1.51–1.41 (m, 1H), 0.79 (s, 9H), -0.19 (s, 3H), -0.56 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 141.3, 128.0, 126.9, 126.8, 69.5, 64.3, 46.9, 32.7, 25.8, 20.0, 18.0, -5.3, -5.9; **HRMS** (ESI): calculated for $[C_{17}H_{30}NOSi]^+$: m/z = 292.2091, found: m/z = 292.2093; **IR** (ν/cm^{-1}, neat) 2929, 2893, 2855, 1460, 1254, 1080, 1025, 836.

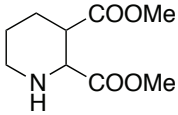
15 See General Procedure and section 6.5.2 for characterization.

trans-3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpiperidine (*trans*-81)



trans-3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpiperidine was prepared according to the above procedure from *trans*-benzyl 3-hydroxy-2-phenylpiperidine-1-carboxylate (*cis*-**79**)[16] (276 mg, 0.890 mmol) to afford the desired compound as a colorless oil (158 mg, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.52–7.41 (m, 2H), 7.34–7.25 (m, 3H), 3.68 (td, *J* = 10.2, 4.4 Hz, 1H), 3.45 (d, *J* = 9.1 Hz, 1H), 3.11–2.99 (m, 1H), 2.68 (td, *J* = 12.2, 3.1 Hz, 1H), 2.15–2.02 (m, 1H), 1.97–1.67 (m, 2H), 1.55–1.38 (m, 1H), 0.66 (s, 9H), -0.20 (s, 3H), -0.57 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 128.8, 128.4, 128.2, 72.7, 68.4, 46.2, 34.8, 25.7, 23.7, 17.9, -4.7, -5.7; **HRMS** (ESI): calculated for $[C_{17}H_{30}NOSi]^+$: m/z = 292.2091, found: m/z = 292.2091; **IR** (ν/cm^{-1}, neat) 2950, 2929, 2894, 2856, 1461, 1251, 1116, 1102, 836.

Dimethyl piperidine-2,3-dicarboxylate (82)



To a solution of 2,3-pyridinedicarboxylic acid dimethyl ester[17] (3.33 g, 17.1 mmol, 1.00 equiv) in AcOH (33 mL, 0.50 M) 0.05 wt% Pt_2O (170 mg) was added and the flask purged with H_2. The reaction mixture was allowed to stir vigorously under H_2 atmosphere for 6 h and filtered through a pad of Celite. The two diastereomers were separated by column chromatography on silica gel (CH_2Cl_2:MeOH = gradient 20:1 to 10:1) to afford *cis*-**82** (1.95 g, 57%) and *trans*-**82** (134 mg, 4%) both as a colorless oils.

cis-**82**:

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] =3.73 (s, 3H), 3.68 (s, 3H), 3.67–3.63 (m, 1H), 3.09–2.96 (m, 2H), 2.76–2.63 (m, 1H), 2.40 (s, 1H), 2.19–2.09 (m, 1H), 1.84–1.71 (m, 1H), 1.56–1.45 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 173.2, 172.4, 59.4, 52.2, 52.0, 45.3, 42.2, 26.0, 23.4; **HRMS** (ESI): calculated for $[C_9H_{15}NO_4Na]^+$: m/z = 224.0893, found: m/z = 224.0892; **IR** (ν/cm^{-1}, neat) 2952, 2856, 1732, 1437, 1362, 1340, 1255, 1226, 1205, 1132, 1036, 1003, 878.

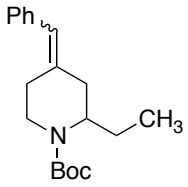
16 See General Procedure and section 6.5.2 for characterization.

17 Prepared according to: Wang, X.; Dacres, J. E.; Yang, X.; Broadus, K. M.; Lis, L.; Wang, L.; Kass, S. R.: Photodetachment of Zwitterions: Probing Intramolecular Coulomb Repulsion and Attraction in the Gas Phase Using Pyridinium Dicarboxylate Anions. *J. Am. Chem. Soc.* **2003**, *125*, 296–304.

trans-**82**:

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 3.72 (s, 3H), 3.69 (s, 3H), 3.66 (d, *J* = 9.3 Hz, 1H), 3.13–3.02 (m, 1H), 2.74–2.60 (m, 2H), 2.09–2.00 (m, 1H), 1.79 (s, 1H), 1.73–1.63 (m, 2H), 1.51–1.38 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 174.4, 172.5, 60.0, 52.4, 52.0, 45.5, 44.7, 27.4, 24.9; **HRMS** (ESI): calculated for $[C_9H_{15}NO_4Na]^+$: m/z = 224.0893, found: m/z = 224.0896; **IR** (ν/cm^{-1}, neat) 2951, 2859, 1736, 1438, 1360, 1262, 1206, 1159, 1038, 1016.

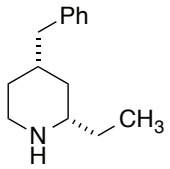
tert-Butyl 4-benzylidene-2-ethylpiperidine-1-carboxylate (97)



To a slurry of $(Ph)_3PCH_2PhBr$ (5.03 g, 11.6 mmol, 1.60 equiv) in THF (15 mL) was added a solution of potassium *tert*-butoxide (12 mL, 1.0 M) in THF. After stirring the bright orange solution for 30 min at 23 °C, a solution of *tert*-butyl 2-ethyl-4-oxopiperidine-1-carboxylate[18] (1.65 g, 7.25 mmol, 1.00 equiv) in THF (3 mL) was added and the reaction allowed to stir for 24 h. The reaction mixture was quenched by the addition of 1M aq HCl, concentrated and the residue extracted with methyl *tert*-butyl ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel (hexanes:EtOAc = 10:1) to afford the desired compound as a 1:1 mixture of E/Z-diastereomers as a colorless oil (2.08 g, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.35–7.28 (m, 4H), 7.24–7.14 (m, 6H), 6.45 (s, 1H), 6.32 (s, 1H), 4.32–3.94 (m, 4H), 2.98–2.65 (m, 4H), 2.62–2.50 (m, 1H), 2.36 (td, *J* = 13.0, 5.6 Hz, 1H), 2.30–2.04 (m, 4H), 1.69–1.51 (m, 3H), 1.46 (s, 9H), 1.47 (s, 9H), 1.38–1.20 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.71 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.31, 155.28, 137.8, 137.7, 136.5, 136.4, 129.0, 128.8, 128.31, 128.27, 126.40, 126.35, 126.2, 126.0, 79.50, 79.49, 53.5, 39.8, 36.1, 32.6, 29.0, 28.6, 23.8, 23.7, 10.6, 10.5; **HRMS** (ESI): calculated for $[C_{19}H_{27}NO_2Na]^+$: m/z = 324.1934, found: m/z = 324.1940; **IR** (ν/cm^{-1}, neat) 2967, 2932, 1692, 1415, 1364, 1254, 1170, 1118, 1076, 997, 979, 871.

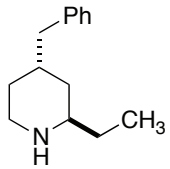
18 Prepared according to: Sebesta, R.; Pizzuti, M. G.; Boersma, A. J.; Minnaard, A. J.; Feringa, B. L.: Catalytic Enantioselective Conjugate Addition of Dialkylzinc Reagents to *N*-Substituted-2,3-Dehydro-4-piperidones. *Chem. Commun.* **2005**, 1711–1713.

cis-4-Benzyl-2-ethylpiperidine (_cis_-100)



A solution of the alkene **97** (900 mg, 3.00 mmol, 1.00 equiv) in 25 mL of 75% TFA/CH_2Cl_2 was allowed to stir for 2 h. The reaction mixture was concentrated, dissolved in THF (7 mL) and added dropwise to a –78 °C solution of THF (60 mL) and NH_3 (60 mL) containing lithium metal (1.32 g, 190 mmol, >50.0 equiv) which was previously allowed to stir for 30 min at –78 °C. The reaction mixture was allowed to stir for 30 min and was allowed to warm to –33 °C over 30 min. The mixture was quenched by the addition of sat aq NH_4Cl solution until the dark blue color disappeared. The colorless solution was allowed to warm to rt and the NH_3 to evaporate. The solvent was removed, H_2O (50 mL) was added and the aqueous layer extracted with methyl *tert*-butyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a colorless oil (570 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.34–7.25 (m, 2H), 7.24–7.13 (m, 3H), 3.15–3.05 (m, 1H), 2.66–2.50 (m, 3H), 2.41–2.31 (m, 1H), 1.88 (br, 1H), 1.76–1.59 (m, 3H), 1.39 (p, *J* = 7.4 Hz, 2H), 1.22–1.06 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.81 (dt, *J* = 12.5, 11.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 140.6, 129.2, 128.1, 125.7, 58.2, 46.8, 44.0, 39.1, 38.5, 33.0, 30.0, 10.4; **HRMS** (ESI): calculated for $[C_{14}H_{22}N]^+$: m/z = 204.1747, found: m/z = 204.1746; **IR** (ν/cm^{-1}, neat) 3026, 2958, 2920, 2849, 2804, 1496, 1454, 1325, 1115.

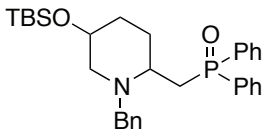
trans-4-Benzyl-2-ethylpiperidine (_trans_-100)



THF (60 mL) was cooled to –78 °C and gaseous NH_3 (60 mL) was condensed in it followed by lithium metal (819 mg, 117 mmol, 40.0 equiv). The dark blue mixture was allowed to stir for 30 min and a solution of the alkene **97** (900 mg, 3.00 mmol, 1.00 equiv) in THF (7 mL) was added dropwise. The reaction mixture was allowed to stir for 30 min and was allowed to warm to –33 °C over 30 min. The mixture was quenched by the addition of sat aq NH_4Cl solution until the dark blue color disappeared. The colorless solution was allowed to warm to rt and the NH_3 to evaporate. The solvent was removed, H_2O (50 mL) was added and the aqueous layer extracted with methyl *tert*-butyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in 25 mL of 75% TFA/CH_2Cl_2 and allowed to stir for 2 h. The reaction mixture was concentrated and methyl *tert*-butyl ether (20 mL) and H_2O (20 mL) were added. The aqueous layer was basified with solid K_2CO_3 and extracted with methyl *tert*-butyl ether (3 x 20 mL). The combined organic layers were dried

over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a colorless oil (605 mg, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.34–7.27 (m, 2H), 7.24–7.15 (m, 3H), 2.98–2.76 (m, 3H), 2.69 (d, *J* = 7.7 Hz, 2H), 2.13–2.01 (m, 1H), 1.83 (s, 1H), 1.73–1.60 (m, 1H), 1.58–1.32 (m, 5H), 0.91 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 141.3, 129.2, 128.3, 125.9, 53.1, 41.2, 40.2, 36.1, 33.6, 31.1, 28.0, 10.8; **HRMS** (ESI): calculated for $[C_{14}H_{22}N]^+$: m/z = 204.1747, found: m/z = 204.1752; **IR** (ν/cm^{-1}, neat) 3025, 2960, 2925, 2850, 1677, 1453, 1410, 1201, 1175, 1131.

((1-Benzyl-5-((*tert*-butyldimethylsilyl)oxy)piperidin-2-yl)methyl)diphenylphosphine oxide (104)

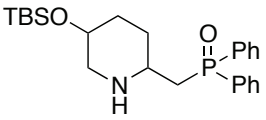


To a solution of ((1-benzyl- 5-hydroxypiperidin- 2-yl) methyl) diphenylphosphine oxide[19] (2.00 g, 4.94 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL, 0.25 M) was added imidazole (672 mg, 9.88 mmol, 2.00 equiv). The reaction mixture was cooled to 0 °C and neat TBSCl (970 mg, 6.42 mmol, 1.30 equiv) was added in one portion. After stirring overnight sat aq $NaHCO_3$ solution (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel (hexanes:EtOAc = 1:1) to afford the desired compound as a colorless oil as a 3:2 mixture of both cis and trans diastereomers which crystallizes upon standing (2.04 g, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$): 60:40 mixture of diastereomers a and b, δ [ppm] = 7.82–7.68 (m, 4H), 7.56–7.40 (m, 6H), 7.33–7.17 (m, 5H), 3.89 (d, *J* = 14.1 Hz, 0.4H, a), 3.67 (tt, *J* = 9.7, 4.6 Hz, 1H, ab), 3.58–3.45 (m, 1.2H, bb), 3.42–3.28 (m, 1H, ab), 2.87–2.71 (m, 1.2H, aaa), 2.68–2.62 (m, 0.6H, b), 2.61–2.55 (m, 0.6H, b), 2.50–2.41 (m, 0.6H, b), 2.35 (dt, *J* = 12.5, 2.9 Hz, 0.4H, a), 2.27 (dd, *J* = 11.6, 9.7 Hz, 0.6H, b), 2.20–2.13 (m, 0.4H, a), 2.06 (dd, *J* = 11.7, 8.2 Hz, 0.4H, a), 1.91–1.72 (m, 2.2H, abbb), 1.57–1.43 (m, 1H, ab), 1.37–1.27 (m, 0.4H, a), 0.84 (s, 5.4H), 0.83 (s, 3.6H), -0.03 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 139.6 (b), 139.1 (a), 134.4 (d, *J* = 98.5 Hz, b), 134.2 (d, *J* = 93.5 Hz, a), 133.2 (d, *J* = 93.2 Hz, a), 133.0 (d, *J* = 98.3 Hz, b), 131.76, 131.74, 131.71, 131.69, 130.88 (d, *J* = 9.1 Hz, b), 130.86 (d, *J* = 9.1 Hz, a), 130.7 (d, *J* = 9.4 Hz, a), 130.6 (d, *J* = 9.4 Hz, b), 126.93 (b), 126.85 (a), 68.3 (b), 67.3 (a), 58.6 (a), 58.5 (b), 58.1 (a), 55.5 (a), 53.2 (b), 51.8 (b), 32.5 (d, *J* = 34.8 Hz, a), 32.2 (d, *J* = 35.3 Hz), 29.6 (a) 29.2 (b),

19 Prepared according to: Scherner, C.; Ergüden, J.-K.; Adiwidjaja, G.; Schaumann, E.: A Novel Route to 6-Substituted Piperidin-3-ols via Domino Cyclization of 2-Hydroxy-6-phosphinyl-5-hexenyl Tosylates with Primary Amines: Synthesis of (±)-Pseudoconhydrine and (±)-*epi*-Pseudoconhydrine. *Synth*esis **2014**, *46*, 2506–2514.

28.0 (b), 25.93 (b), 25.91 (a), 24.7 (d, *J* = 69.0 Hz, b), 18.24 (b), 18.17 (a), -4.66, -4.70, -4.72; **HRMS** (ESI): calculated for $[C_{31}H_{47}NO_2PSi]^+$: m/z = 520.2795, found: m/z = 520.2793; **IR** (ν/cm^{-1}, neat) 3058, 2952, 2929, 2856, 1438, 1254, 1185, 1119, 1102, 1036, 855, 836.

((5-((*tert*-Butyldimethylsilyl)oxy)piperidin-2-yl)methyl)diphenylphosphine oxide (105)



To a solution of the benzylated amine **104** (1.98 g, 3.82 mmol, 1.00 equiv) in EtOH (19 mL, 0.20 M) 10% Pd/C (400 mg) was added and the flask purged with H_2. The reaction mixture was allowed to stir vigorously under H_2 atmosphere for 48 h and filtered through a pad of Celite. The solvent was removed to obtain a mixture of the two diastereomers and S17. The crude products were purified by column chromatography on silica gel (EtOAc:EtOH = 20:1 to elute **104** EtOAc:EtOH = 10:1 to elute *trans*-**105**, CH_2Cl_2:MeOH = 10:1 to elute *cis*-**105** to afford *trans*-**105** (347 mg, 21%, semi-solid), *cis*-**105** (369 mg, 23%, semi-solid) and **104** (760 mg, 38%, solid).

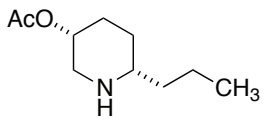
cis-**105**:

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] =7.79–7.67 (m, 4H), 7.58–7.42 (m, 6H), 3.63 (tt, *J* = 9.7, 4.6 Hz, 1H), 3.11–3.00 (m, 2H), 2.93–2.79 (m, 1H), 2.51–2.26 (m, 3H), 1.93–1.83 (m, 1H), 1.73–1.63 (m, 1H), 1.49–1.21 (m, 2H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 133.7 (d, *J* = 98.7 Hz), 132.6 (d, *J* = 98.5 Hz), 132.0 (d, *J* = 2.8 Hz), 132.0 (d, *J* = 2.8 Hz), 131.0 (d, *J* = 9.2 Hz), 130.6 (d, *J* = 9.5 Hz), 128.8 (d, *J* = 11.7 Hz), 128.8 (d, *J* = 11.7 Hz), 68.3, 54.1, 51.5 (d, *J* = 3.8 Hz), 36.1 (d, *J* = 71.1 Hz), 34.5 (d, *J* = 1.4 Hz), 33.5 (d, *J* = 12.4 Hz), 25.9, 18.2, -4.57, -4.61; **HRMS** (ESI): calculated for $[C_{24}H_{37}NO_2PSi]^+$: m/z = 430.2326, found: m/z = 430.2320; **IR** (ν/cm^{-1}, neat) 3317, 3058, 2952, 2930, 2898, 2930, 2898, 2856, 1471, 1438, 1254, 1187, 1177, 1120, 1103, 866, 837.

trans-**105**:

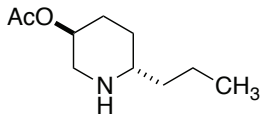
^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.91–7.81 (m, 2H), 7.78–7.70 (m, 2H), 7.61–7.41 (m, 6H), 6.28 (br, 1H), 3.94–3.84 (m, 1H), 3.48–3.27 (m, 1H), 3.08–2.88 (m, 3H), 2.76–2.60 (m, 1H), 1.99–1.78 (m, 1H), 1.74–1.49 (m, 3H), 0.93 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 133.1 (d, *J* = 101.0 Hz), 132.1 (d, *J* = 99.0 Hz),132.1 (d, *J* = 2.9 Hz), 132.1 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 9.4 Hz), 130.8 (d, *J* = 9.9 Hz), 128.8 (d, *J* = 11.8 Hz), 128.8 (d, *J* = 12.0 Hz), 63.5, 53.0, 51.0, 33.4 (d, *J* = 69.6 Hz), 30.5, 25.8, 18.0, -4.88, -4.91; **HRMS** (ESI): calculated for $[C_{24}H_{37}NO_2PSi]^+$: m/z = 430.2326, found: m/z = 430.2317; **IR** (ν/cm^{-1}, neat) 3411, 2952, 2929, 2885, 2855, 1471, 1438, 1254, 1177, 1119, 1102, 1062, 1029, 836

cis-6-Propylpiperidin-3-yl acetate (*cis*-110)



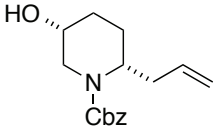
To a solution of *cis*-benzyl 5-acetoxy-2-allylpiperidine-1-carboxylate[20] (1.35 g, 4.26 mmol, 1.00 equiv) in EtOH (21 mL, 0.20 M) 10% Pd/C (135 mg) was added and the flask purged with H_2. The reaction mixture was allowed to stir vigorously under H_2 atmosphere for 5 h and filtered through a pad of Celite. The crude products were purified by column chromatography on silica gel (CH_2Cl_2:MeOH = 20:1) to afford the product as a colorless oil (547 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.84 (p, *J* = 2.7 Hz, 1H), 3.14 (dt, *J* = 13.8, 2.5 Hz, 1H), 2.83 (dd, *J* = 13.8, 2.1 Hz, 1H), 2.58–2.47 (m, 1H), 2.43–2.20 (m, 1H), 2.08 (s, 3H), 1.99–1.91 (m, 1H), 1.69–1.51 (m, 2H), 1.48–1.26 (m, 5H), 0.90 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.8, 67.9, 55.8, 49.6, 39.1, 28.5, 27.6, 21.6, 19.2, 14.3; **HRMS** (ESI): calculated for $[C_{10}H_{20}NO_2]^+$: m/z = 186.1489, found: m/z = 186.1489; **IR** (ν/cm^{-1}, neat) 2955, 2934, 2871, 1736, 1633, 1440, 1375, 1244, 1024, 959.

trans-6-Propylpiperidin-3-yl acetate (*trans*-110)



trans-6-Propylpiperidin-3-yl acetate was prepared according to the above procedure from *trans*-benzyl 5-acetoxy-2-allylpiperidine-1-carboxylate[20] (320 mg, 1.00 mmol, 1.00 equiv) to afford the desired compound as semi-solid (120 mg, 64%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.84–4.72 (m, 1H), 4.50 (s, 1H), 3.35–3.26 (m, 1H), 2.59 (dd, *J* = 11.8, 10.2 Hz, 2H), 2.14–2.06 (m, 1H), 2.01 (s, 3H), 1.91–1.80 (m, 1H), 1.59–1.29 (m, 6H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.3, 69.4, 55.8, 48.9, 37.2, 29.63, 29.61, 21.3, 19.4, 14.1; **HRMS** (ESI): calculated for $[C_{10}H_{19}NO_2Na]^+$: m/z = 208.1308, found: m/z = 208.1309; **IR** (ν/cm^{-1}, neat) 3346, 2956, 2934, 2971, 1735, 1620, 1455, 1439, 1372, 1245, 1045.

cis-Benzyl 2-allyl-5-hydroxypiperidine-1-carboxylate (*cis*-111)

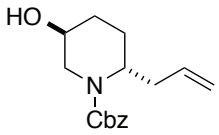


To a solution of *cis*-benzyl 5-acetoxy-2-allylpiperidine-1-carboxylate[20] (897 mg, 2.83 mmol, 1.00 equiv) in MeOH (11 mL, 0.25 M) LiOH (238 mg, 5.66 mmol, 2.00 equiv) was added and allowed to stir for 1.5 h. The reaction mixture was concentrated and sat aq $NaHCO_3$ solution (10 mL) was added. The aqueous

20 Prepared according to: Tanaka, H.; Sakagami, H.; Ogasawara, K.: Diastereoselective Synthesis of 3,5-*trans*-(+)-(3*R*,5*R*)-3-Carbomethoxycarbapenam from 3-Hydroxypyridine: Questioning the Stereochemical Assignment of the Natural Product**.** *Tetrahedron. Lett.* **2002**, *43*, 93–96.

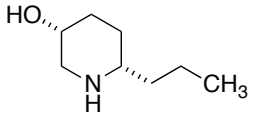
phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a colorless oil (769 mg, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.39–7.27 (m, 5H), 5.81–5.57 (m, 1H), 5.20–4.92 (m, 4H), 4.41–4.14 (m, 2H), 3.61 (tt, *J* = 10.4, 4.9 Hz, 1H), 2.65 (dd, *J* = 12.9, 10.8 Hz, 1H), 2.48–2.37 (m, 1H), 2.32–2.18 (m, 1H), 2.17–1.79 (m, 2H), 1.75–1.43 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.6, 136.8, 134.9, 128.6, 128.1, 128.0, 117.4, 67.3, 67.2, 49.5, 45.7, 34.2, 28.4, 26.2; **HRMS** (ESI): calculated for $[C_{16}H_{21}NO_3Na]^+$: m/z = 298.1414, found: m/z = 298.1411; **IR** (ν/cm^{-1}, neat) 3421, 2941, 1697, 1676, 1427, 1345, 1330, 1236, 1145, 1072, 1043, 1000, 963, 917.

trans-Benzyl 2-allyl-5-hydroxypiperidine-1-carboxylate (*trans*-111)



trans-Benzyl 2-allyl-5-hydroxypiperidine-1-carboxylate was prepared according the above procedure from *trans*-benzyl 5-acetoxy-2-allylpiperidine-1-carboxylate[20] (1.00 g, 3.15 mmol, 1.00 equiv) to afford the desired compound as a colorless oil (850 mg, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.43–7.27 (m, 5H), 5.71 (dd, *J* = 16.4, 8.5 Hz, 1H), 5.19–5.08 (m, 2H), 5.07–4.96 (m, 2H), 4.40 (d, *J* = 7.3 Hz, 1H), 4.10 (d, *J* = 14.4 Hz, 1H), 3.93 (s, 1H), 3.04 (d, *J* = 14.0 Hz, 1H), 2.47–2.33 (m, 1H), 2.23 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.17–1.98 (m, 2H), 1.83–1.64 (m, 2H), 1.42 (d, *J* = 13.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 156.7, 136.9, 135.1, 128.6, 128.0, 127.9, 117.2, 67.3, 64.4, 50.3, 45.2, 34.1, 25.5, 21.5; **HRMS** (ESI): calculated for $[C_{16}H_{21}NO_3Na]^+$: m/z = 298.1414, found: m/z = 298.1414; **IR** (ν/cm^{-1}, neat) 3438, 2938, 1693, 1682, 1429, 1346, 1323, 1242, 1144, 1107, 1023, 914.

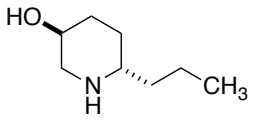
cis-6-Propylpiperidin-3-ol (*cis*-112)



To a solution of the carbamate *cis*-**111** (741 g, 2.69 mmol, 1.00 equiv) in EtOH (14 mL, 0.20 M) 10% Pd/C (74.0 mg) was added and the flask purged with H_2. The reaction mixture was allowed to stir vigorously under H_2 atmosphere for 5 h and filtered through a pad of Celite. The product was obtained as a colorless oil (334 mg, 87%). **^{1}H NMR** (400 MHz, CD_3OD): δ [ppm] = 3.74 (p, *J* = 3.0 Hz, 1H), 2.90 (dt, *J* = 13.5, 2.7 Hz, 1H), 2.74 (dd, *J* = 13.5, 2.1 Hz, 1H), 2.54–2.44 (m, 1H), 1.89–1.77 (m, 1H), 1.73–1.61 (m, 1H), 1.57–1.28 (m, 6H), 0.93 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, CD_3OD): δ [ppm] = 65.2, 56.6, 52.2, 39.7, 31.5, 27.5, 20.1, 14.6; **HRMS** (ESI):

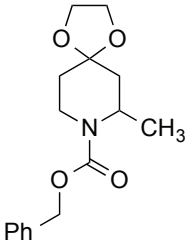
calculated for $[C_8H_{18}NO]^+$: m/z = 144.1383, found: m/z = 144.1383; **IR** (ν/cm^{-1}, neat) 3290, 2955, 2930, 2870, 1440, 1102, 1026, 980.

trans-6-Propylpiperidin-3-ol (*trans*-112)



trans-6-Propylpiperidin-3-ol was prepared according the above procedure from the carbamate *trans*-**111** (890 mg, 3.24 mmol, 1.00 equiv) to afford the desired compound as white solid (259 mg, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 3.59–3.47 (m, 1H), 3.13–3.03 (m, 1H), 2.44–2.29 (m, 2H), 2.05–1.95 (m, 1H), 1.77 (dq, *J* = 13.3, 3.2 Hz, 1H), 1.44–1.19 (m, 5H), 1.19–1.05 (m, 1H), 0.97–0.88 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 68.6, 56.8, 54.4, 39.5, 34.7, 31.9, 20.4, 14.6; **HRMS** (ESI): calculated for $[C_8H_{18}NO]^+$: m/z = 144.1383, found: m/z = 144.1381; **IR** (ν/cm^{-1}, neat) 3291, 3124, 2953, 2930, 2868, 2819, 1434, 1448, 1364, 1118, 1072, 1050, 1021, 989, 957.

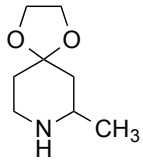
Benzyl 7-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (126)



In a 100 mL round bottom flask benzyl 2-methyl-4-oxopiperidine-1-carboxylate[21] (1.70 g, 6.90 mmol, 1.00 equiv), ethylene glycol (2.13 g, 34.3 mmol, 5.00 equiv) and pTsOH•H_2O (130 mg, 0.70 mmol, 0.10 equiv) were dissolved in toluene (30 mL). The flask was equipped with a Dean-Stark apparatus and a reflux condenser. The mixture was heated to reflux for 5 h and the water was distilled off. After the completion solvent was removed under reduced pressure, and crude product was purified via column chromatography (hexanes:EtOAc 2:1) to afford the product as a yellow oil (1.60 g, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.40–7.30 (m, 5H), 5.15, 5.11 (2d, *J* = 12.7Hz, 2H), 4.57 (m, 1H), 4.10 (m, 1H), 4.00–3.85 (m, 4H), 3.16 (m, 1H), 1.89 (dd, *J* = 13.6; 6.7Hz, 1H), 1.65 (m, 3H), 1.27 (d, *J* = 7.1Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.1, 136.9, 128.5, 128.0, 127.8, 107.2, 67.1, 64.7, 63.8, 46.9, 38.4, 37.1, 34.6, 17.6; **HRMS** (ESI): calculated for $[C_{16}H_{22}NO_4]^+$: m/z = 292.1543, found: m/z = 292.1543; **IR** (ν/cm^{-1}, neat) 2962, 2931, 2881, 1697, 1445, 1422, 1272, 1199, 1114, 1030.

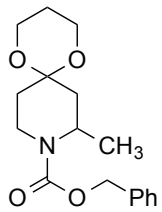
21 Prepared according to Kitagawa, H.; Ozawa, T.; Takahata, S.; Iida, M.; Saito, J.; Yamada, M.: Phenylimidazole Derivatives of 4-Pyridone as Dual Inhibitors of Bacterial Enoyl-Acyl Carrier Protein Reductases FabI and FabK**.** *J. Med. Chem.* **2007**, *50*, 4710.

7-Methyl-1,4-dioxa-8-azaspiro[4.5]decane (128)



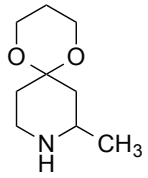
To a solution of benzyl 7-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**126**) (1.60 g, 5.50 mmol, 1.00 equiv) in MeOH (15 mL) was added (10 wt%) Pd/C (200mg). The system was purged with H_2 and left stirring overnight under one atmosphere of H_2 (balloon). After completion the reaction was purged with N_2 and filtered through a short pad of Celite. The Celite was washed with THF (2 x 20 mL). The solvent was removed under reduced pressure and resulting white solid was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure to yield the product as a yellow oil (800 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.05–3.90 (m, 4H), 3.50–3.30 (m, 2H), 3.07 (ddd, *J* = 11.1, 10.2, 3.6Hz, 1H), 2.19–2.07 (m, 1H), 1.97–1.76 (m, 3H), 1.49 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 105.4, 64.8, 64.6, 51.3, 42.3, 40.6, 32.0, 19.4; **HRMS** (ESI): calculated for $[C_8H_{16}NO_2]^+$: m/z = 158.1176, found: m/z = 158.1172; **IR** (ν/cm^{-1}, neat) 3409, 2944, 2844, 2755, 2365, 1451, 1374, 1192, 1134.

Benzyl 8-methyl-1,5-dioxa-9-azaspiro[5.5]undecane-9-carboxylate (127)



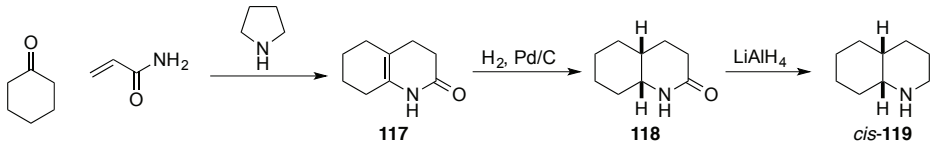
In a 100 mL round bottom flask benzyl 2-methyl-4-oxopiperidine-1-carboxylate (1.60 g, 6.50 mmol, 1.00 equiv), propane-1,3-diol (2.50 g, 32.9 mmol, 5.00 equiv) and pTsOH•H_2O (125 mg, 0.65 mmol, 0.10 equiv) were dissolved in toluene (30 mL). The flask was equipped with a Dean-Stark apparatus and a reflux condenser. The mixture was heated to reflux for 7 h and the water was distilled off. After the completion solvent was removed under reduced pressure, and crude product was purified via column chromatography (hexanes:EtOAc 2:1) to afford the product as a yellow oil (1.70 g, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.40 – 7.30 (m, 5H), 5.17, 5.14 (2d, *J* = 12.4 Hz, 2H), 4.52 (m, 1H), 4.05 (m, 1H), 4.00–3.85 (m, 4H), 3.15 (td, *J* = 13.4, 2.8 Hz, 1H), 2.28 (m, 1H), 2.13 (m, 1H), 1.85 (m, 1H), 1.70 (m, 2H), 1.56 (td, *J* = 13.4, 4.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.1, 136.9, 128.5, 128.0, 127.8, 96.5, 67.0, 59.5, 59.4, 46.5, 36.0, 35.2, 33.9, 25.4, 17.4; **HRMS** (ESI): calculated for $[C_{17}H_{23}NO_4Na]^+$: m/z = 328.1519, found: m/z = 328.1521; **IR** (ν/cm^{-1}, neat) 2965, 2871, 1697, 1423, 1337, 1206, 1110, 1090.

8-Methyl-1,5-dioxa-9-azaspiro[5.5]undecane (129)



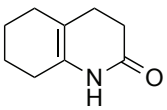
To a solution of benzyl 8-methyl-1,5-dioxa-9-azaspiro[5.5]undecane-9-carboxylate (**127**) (1.70 g, 5.60 mmol, 1.00 equiv) in MeOH (15 mL) was added (10 wt%) Pd/C (220 mg). The system was purged with H_2 and left stirring overnight under one atmosphere of H_2 (balloon). After completion the reaction was purged with N_2 and filtered through a short pad of Celite. The Celite was washed with THF (2 x 20 mL). The solvent was removed under reduced pressure and the resulting white solid was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure to yield the product as a yellow oil (820 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 3.93 (m, 2H), 3.87 (ap. t, *J* = 5.6 Hz, 2H), 3.40 (m, 2H), 3.05 (td, *J* = 13.3, 3.0 Hz, 1H), 2.43 (m, 1H), 2.33 (td, *J* = 14.1, 3.0 Hz, 1H), 2.05 (m, 1H), 1.90–1.65 (m, 3H), 1.53 (d, *J* = 6.6Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 94.6, 59.6, 59.5, 49.8, 40.8, 38.4, 28.7, 25.2, 18.9; **HRMS** (ESI): calculated for $[C_9H_{18}NO_2]^+$: m/z = 172.1332, found: m/z = 172.1333; **IR** (ν/cm^{-1}, neat) 3406, 2969, 2878, 1636, 1384, 1182, 1134, 1090.

Synthetic route towards *cis*-decahydroquinoline (*cis*-117)



117 **118** ***cis*-119**

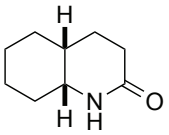
3,4,5,6,7,8-Hexahydroquinolin-2(1*H*)-one (115)



In a 100 mL round bottom flask cyclohexanone (4.75 g, 48.5 mmol, 1.00 equiv), pyrrolidine (6.90 g, 97.2 mmol, 2.00 equiv) and pTsOH•H_2O (180 mg, 1.00 mmol, 0.20 equiv) were dissolved in toluene (50 mL). The flask was equipped with a Dean-Stark apparatus and a reflux condenser. The mixture was heated to reflux for 4 h and the water was distilled off. After the completion solvent was removed under reduced pressure, and the residue was dissolved in anhydrous 1,4-dioxane (25 mL). To this solution acrylamide (3.40, 48.5 mmol, 1.00 equiv) was added neat in one portion. The flask was equipped with a reflux condenser and heated to reflux under an atmosphere of N_2 for 12 h. After completion solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (300 mL) and washed with saturated aqueous (1 M) HCl (2 x 30 mL) and brine (1 x

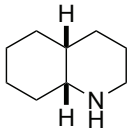
30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. Purification by column chromatography (hexanes:EtOAc 2:1 → 1:1) afforded the product as an amorphous colorless solid (2.50 g, 34%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.95 (br, 1H), 2.50 (t, *J* = 2.50, 2H), 2.25 (m, 2H), 2.02 (m, 4H), 1.68 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.3, 128.1, 109.7, 30.7, 27.8, 26.2, 25.8, 22.7, 22.2. **HRMS** (ESI): calculated for $[C_9H_{14}NO]^+$: m/z = 152.1070, found: m/z = 152.1071; **IR** (ν/cm^{-1}, neat) 3207, 3171, 3086, 2929, 2859, 2833, 1661, 1389, 1317.

cis-Octahydroquinolin-2(1*H*)-one (116)



To a solution of 3,4,5,6,7,8-hexahydroquinolin-2(1*H*)-one (1.50 g, 9.80 mmol, 1.00 equiv) in a 2:1 EtOH:1,4-dioxane mixture (20 mL) was added (10 wt%) Pd/C (300 mg). The system was purged with H_2 and left stirring under one atmosphere of H_2 (balloon) for 48 h. After completion the reaction was purged with N_2 and filtered through a short pad of Celite. The Celite was washed with THF (2 x 30 mL). The solvent was removed under reduced pressure and the resulting solid was recrystallized from a hexanes:EtOAc mixture to afford the product as a white solid (900 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 5.80 (br, 1H), 3.55 (m, 1H), 2.35 (m, 2H), 1.95 (m, 1H), 1.87 (m, 1H), 1.77–1.45 (m, 7H), 1.37 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 172.4, 52.2, 32.9, 31.5, 28.8, 26.4, 24.4, 23.4, 21.4. **HRMS** (ESI): calculated for $[C_9H_{16}NO]^+$: m/z = 154.1226, found: m/z = 154.1225; **IR** (ν/cm^{-1}, neat) 3178, 3048, 2928, 2855, 1660, 1408, 1325, 836, 714.

cis-Decahydroquinoline (*cis*-117)



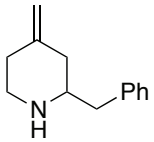
To a suspension of $LiAlH_4$ (380 mg, 10.0 mmol, 2.00 equiv) in THF (10 mL) was slowly added a solution of *cis*-octahydroquinolin-2(1*H*)-one (779 mg, 5.00 mmol, 1.00 equiv) in THF (10 mL) at 0 °C (vigorous gas evolution). After the addition the resulting mixture was heated to reflux for 5 h. Upon completion the reaction mixture was cooled to 0 °C and carefully quenched with water (0.38 mL) followed by 10% aqueous NaOH solution (0.76 mL) and finally water (1.2 mL). The resulting precipitate was filtered and washed with THF (30 mL). Filtrate was removed under reduced pressure to afford the product as a colorless oil (650 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 3.05 (m,1H), 2.85 (m, 1H), 2.67 (m, 1H). 1.85–1.45 (m, 9H), 1.40–1.20 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 55.0, 47.1 (br.), 35.8, 32.4 (br.), 32.1 (br.), 31.6 (br.), 30.1 (br.), 29.7 (br.),

26.4 (br.), 25.7 (br.), 22.7 (br.), 21.6 (br.). **HRMS** (ESI): calculated for $[C_9H_{18}N]^+$: m/z = 140.1434, found: m/z = 140.1434; **IR** (ν/cm^{-1}, neat) 3292, 2923, 2852, 2796, 1651, 1556, 1445, 1305, 769.[22]

6.5 Kinetic Resolution of Disubstituted Piperidines

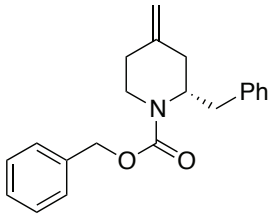
6.5.1 Kinetic Resolution of 2,4,4-Trisubstituted Piperidines

2-Benzyl-4-methylenepiperidine (121, Table 10, entry 1)



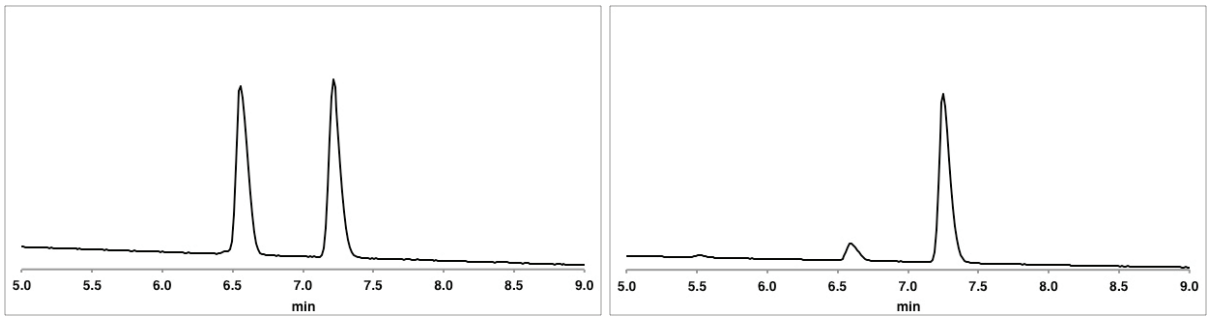
Racemic 2-benzyl-4-methylenepiperidine (37.4 mg, 0.200 mmol) was resolved according to the General Procedure A for 20 h. Recovered (Cbz-protected) amine: 29.0 mg (45 % yield, er = 8:92); acylated product: 30.0 mg (43 % yield, er = 91:9); calculated conversion: 51 %; **s = 27**

The recovered amine was characterized as its Cbz-derivative: **(*R*)-Benzyl 2-benzyl-4-methylenepiperidine-1-carboxylate**

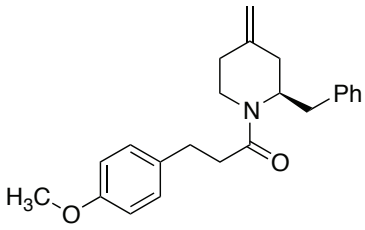


$[\alpha]^{28}_D$ (c = 1.0, CH_3Cl): -24.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.47–7.03 (m, 10H), 5.09 (br, 2H), 4.99 (d, *J* = 1.9 Hz, 1H), 4.85 (d, *J* = 1.9 Hz, 1H), 4.64 (br, 1H), 4.25 (br, 1H), 3.08 (td, *J* = 12.8, 4.0 Hz, 1H), 2.81 (d, *J* = 7.3 Hz, 2H), 2.38–2.12 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.5, 142.2, 138.8, 136.9, 129.4, 128.6, 128.5, 128.1, 128.0, 126.4, 111.8, 67.2, 53.8 (br.), 40.5, 36.8 (br.), 36.1 (br.), 34.1; **HRMS** (ESI): calculated for $[C_{21}H_{24}NO_2]^+$: m/z = 322.1802, found: m/z = 322.1806; **IR** (ν/cm^{-1}, neat) 3065, 3030, 2945, 1698, 1421, 1342, 1321, 1242, 1195, 1104, 1016; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.6 min (minor) and 7.2 min (major).

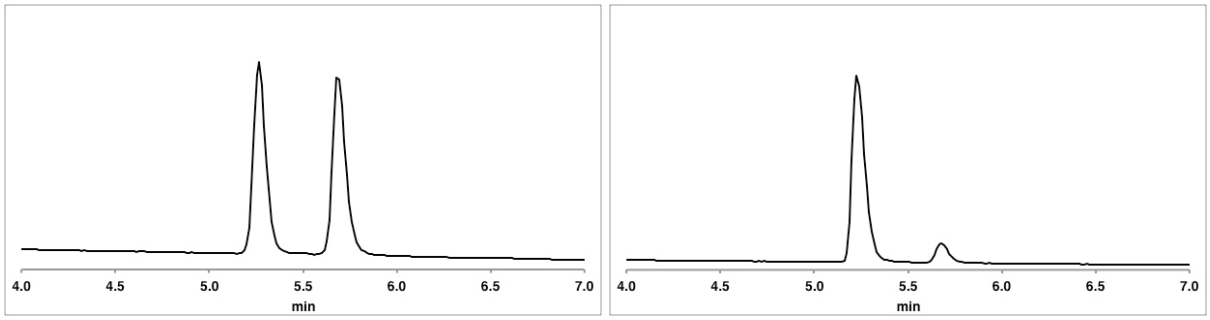
22 Spectral data matches Meyers, A. I.; Milot, G.: α-Alkylation and Stereochemistry of *cis*- and *trans*-Decahydroquinolines Mediated by the Formamidine and Boc Activating Groups. Synthesis of Pumiliotoxin C. *J. Am. Chem. Soc.* **1993**, *115*, 6652.



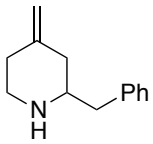
Acylated product: **(*S*)-1-(2-Benzyl-4-methylenepiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{28}_{D}$ (c = 1.0, CH_3Cl): +28.1; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.38–7.23 (m, 4H), 7.18–7.09 (m, 2H), 7.00–7.05 (m, 1H), 6.87–6.81 (m, 2H), 5.29–5.15 (m, 0.5H), 4.98 (s,1H) 4.85 (s, 1H), 4.84–4.76 (m, 0.5H), 4.20–4.12 (m, 0.5H), 3.81 (s, 1.5H), 3.80 (s, 1.5H), 3.73 (dd, *J* = 13.4, 4.9 Hz, 0.5H), 3.16 (td, *J* = 13.1, 3.3 Hz, 0.5H), 2.94–2.52 (m, 5.5H), 2.47–2.04 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.4, 171.1, 158.1, 158.0, 142.0, 141.9, 138.6, 138.5, 133.6, 133.5, 129.5, 129.41, 129.37, 129.3, 128.8, 128.5, 126.8, 126.4, 114.0, 113.9, 112.1, 111.7, 55.9, 55.4, 50.4, 42.0, 38.2, 37.7, 37.2, 36.3, 36.0, 35.8, 35.2, 34.6, 34.0, 30.72, 30.66; **HRMS** (ESI): calculated for $[C_{23}H_{28}NO_2]^+$: m/z = 350.2115, found: m/z = 350.2106; **IR** (ν/cm^{-1}, neat) 2942, 2906, 2835, 1643, 1513, 1425, 1246, 1178, 1034, 825; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.2 min (major) and 5.7 min (minor).

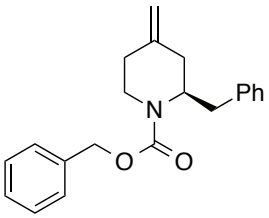


2-Benzyl-4-methylenepiperidine (121, Table 11, entry 9)

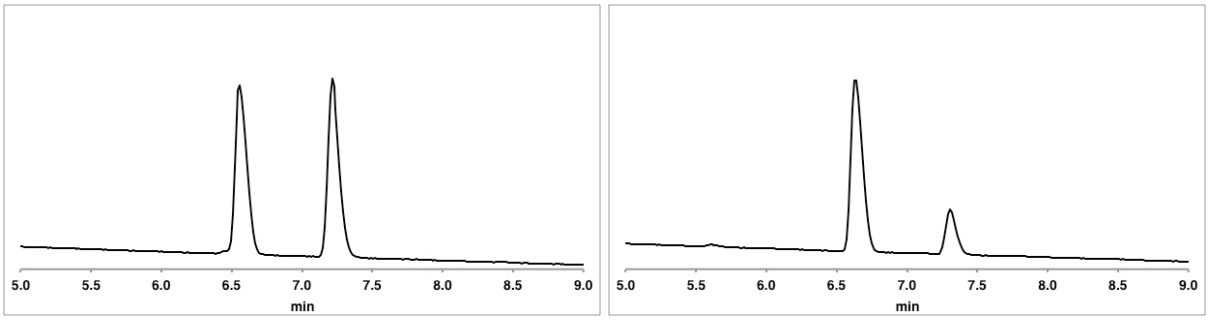


Racemic 2-benzyl-4-methylenepiperidine (46.8 mg, 0.250 mmol) was resolved according to the General Procedure B for 20 h. Recovered (Cbz-protected) amine: 32.0 mg (40 % yield, er = 81:19); acylated product: 37.0 mg (37 % yield, er = 9:91); calculated conversion: 43 %; **s = 19**

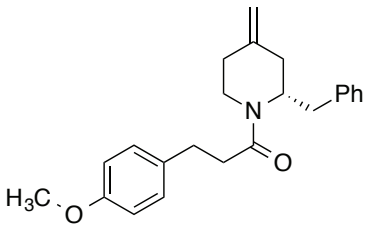
The recovered amine was characterized as its Cbz-derivative: **(*S*)-Benzyl 2-benzyl-4-methylenepiperidine-1-carboxylate**



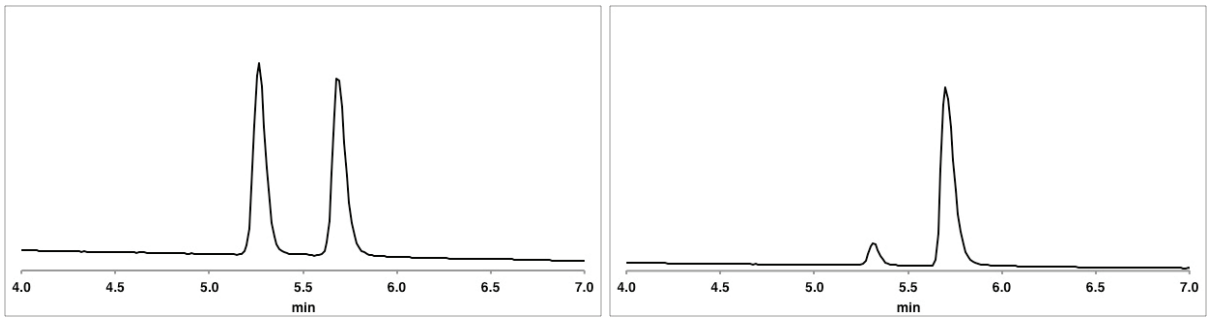
SFC: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.6 min (major) and 7.2 min (minor).



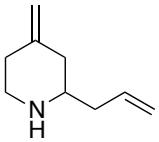
Acylated product: **(*R*)-1-(2-Benzyl-4-methylenepiperidin-1-yl)-3-(4-methoxyphenyl) propan-1-one**



SFC: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.2 min (minor) and 5.7 min (major).

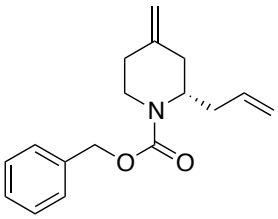


2-Allyl-4-methylenepiperidine (122, Table 10, entry 2)

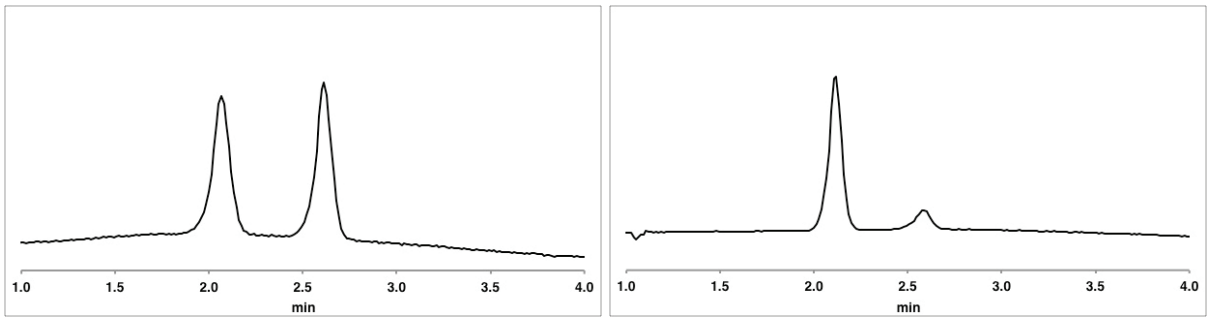


Racemic 2-allyl-4-methylenepiperidine (27.4 mg, 0.200 mmol) was resolved according to the General Procedure A for 20 h. Recovered (Cbz-protected) amine: 25.0 mg (46 % yield, er = 88:12); acylated product: 26.0 mg (43 % yield, er = 89:11); calculated conversion: 49 %; **s = 18**

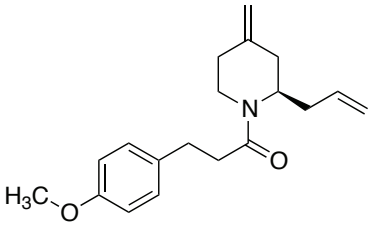
The recovered amine was characterized as its Cbz-derivative: **(*S*)-Benzyl 2-allyl-4-methylenepiperidine-1-carboxylate**



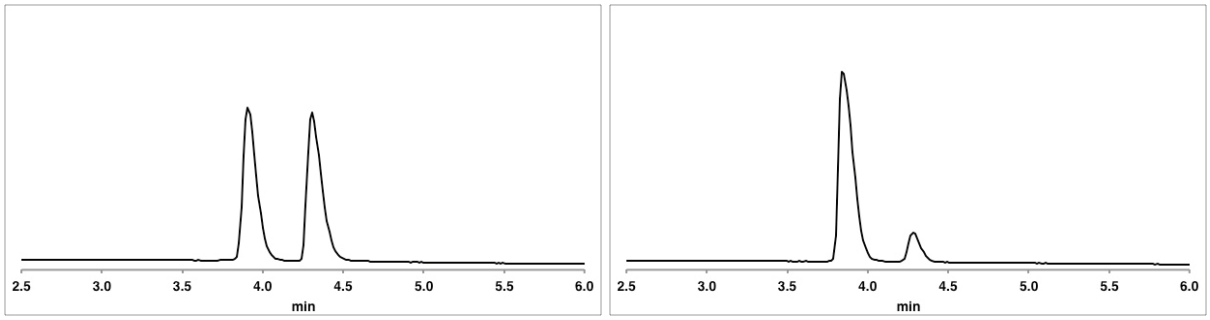
$[\alpha]^{29}_{D}$ (c = 1.0, CH_3Cl): +18.1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.39–7.28 (m, 5H), 5.69 (br, 1H), 5.20–5.09 (m, 2H), 5.07–4.96 (m, 2H), 4.81 (dd, *J* = 47.3, 1.8 Hz, 2H), 4.48 (br, 1H), 4.16 (br, 1H), 2.89 (td, *J* = 12.9, 4.7 Hz, 1H), 2.40–2.09 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.6, 142.1, 137.0, 134.9, 128.6, 128.1, 127.9, 117.4, 111.6, 67.2, 51.4, 40.2, 37.4, 34.9, 34.1; **HRMS** (ESI): calculated for $[C_{17}H_{22}NO_2]^+$: m/z = 272.1645, found: m/z = 272.1646; **IR** (ν/cm^{-1}, neat) 3072, 2944, 2900, 1697, 1421, 1340, 1321, 1239, 1191, 1118, 1095, 1018, 894; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 2.1 min (major) and 2.6 min (minor).



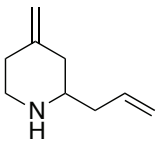
Acylated product: **(*R*)-1-(2-Allyl-4-methylenepiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -14.1; at room temperature the ratio of rotamers was 55:45 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.13 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.77–5.55 (m, 1H), 5.11–4.95 (m, 2.55H), 4.89–4.85 (m, 1H), 4.78–4.73 (m, 1H), 4.68 (dd, *J* = 13.3, 5.6 Hz, 0.45H), 4.01 (dt, *J* = 7.7, 3.9 Hz, 0.45H), 3.78 (s, 3H), 3.68 (dd, *J* = 13.4, 5.3 Hz, 0.55H), 3.02 (td, *J* = 13.2, 3.3 Hz, 0.55H), 2.91 (q, *J* = 7.4 Hz, 2H), 2.70–2.54 (m, 2.45H), 2.35–2.16 (m, 5H), 2.16–1.97 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.2, 171.1, 158.1, 141.8, 135.1, 134.1, 133.6, 133.5, 129.5, 118.3, 117.1, 114.02, 114.00, 111.7, 55.4, 53.5, 48.2, 41.7, 38.0, 37.5, 36.9, 36.0, 35.7, 35.1, 34.65, 34.58, 33.9, 30.9, 30.8; **HRMS** (ESI): calculated for $[C_{19}H_{26}NO_2]^+$: m/z = 300.1958, found: m/z = 300.1952; **IR** (ν/cm^{-1}, neat) 3072, 2940, 2905, 2833, 1644, 1513, 1427, 1247, 1179, 1036, 896, 825; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.9 min (major) and 4.3 min (minor).

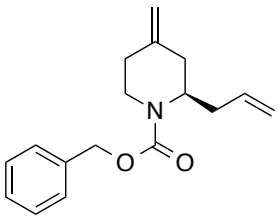


2-Allyl-4-methylenepiperidine (122, Table 11, entry 10)

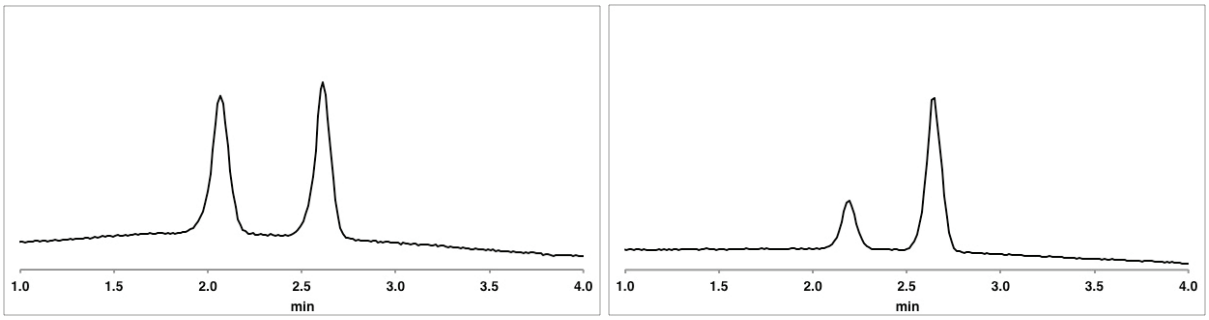


Racemic 2-allyl-4-methylenepiperidine (34.3 mg, 0.250 mmol) was resolved according to the General Procedure B for 20 h. Recovered (Cbz-protected) amine: 29.0 mg (43 % yield, er = 23:77); acylated product: 30.0 mg (40 % yield, er = 11:89); calculated conversion: 41 %; **s = 14**

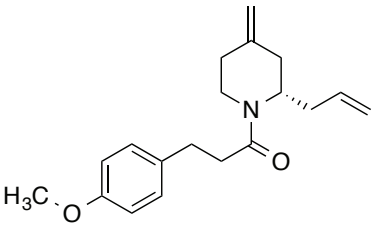
The recovered amine was characterized as its Cbz-derivative: **(*R*)-Benzyl 2-allyl-4-methylenepiperidine-1-carboxylate**



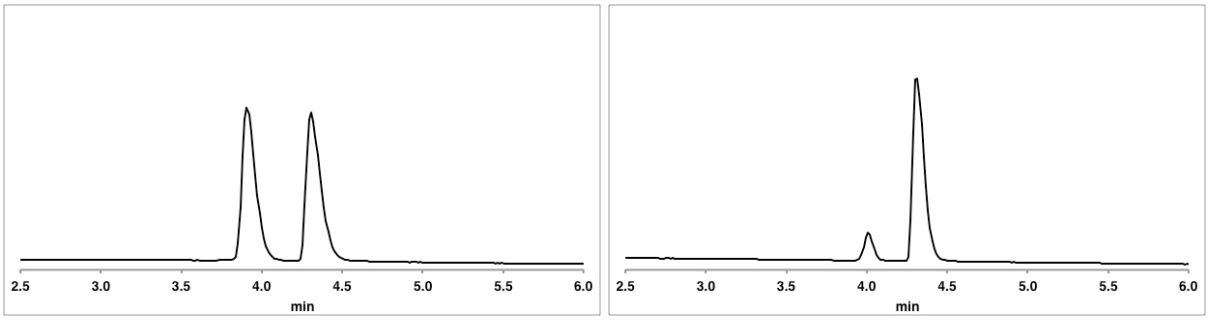
SFC: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 2.1 min (minor) and 2.6 min (major).



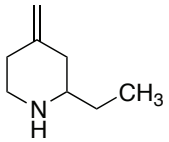
Acylated product: **(*S*)- 1-(2-Allyl-4-methylenepiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



SFC: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.9 min (minor) and 4.3 min (major).

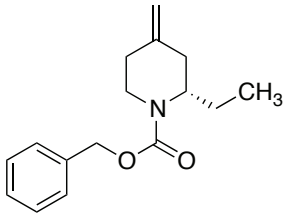


2-Ethyl-4-methylenepiperidine (123, Table 10, entry 3)

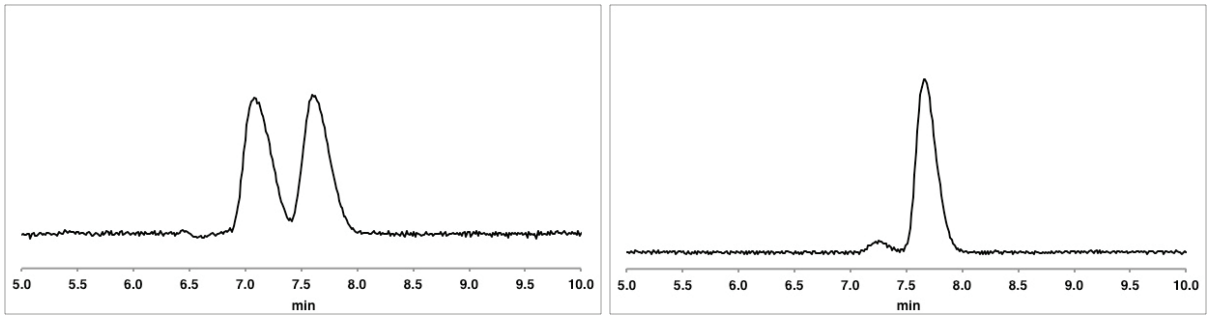


Racemic 2-ethyl-4-methylenepiperidine (25.0 mg, 0.200 mmol) was resolved according to the General Procedure A for 20 h. Recovered (Cbz-protected) amine: 20.0 mg (39 % yield, er = 5:95); acylated product: 31.0 mg (54 % yield, er = 86:14); calculated conversion: 56 %; **s = 18**

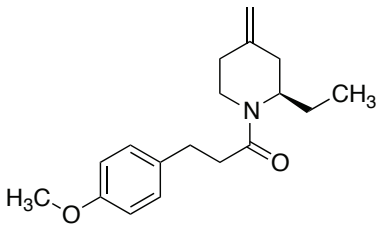
The recovered amine was characterized as its Cbz-derivative: **(*S*)-Benzyl 2-ethyl-4-methylenepiperidine-1-carboxylate**



[α]$^{29}_{D}$ (c = 1.0, CH_3Cl): +15.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.43–7.33 (m, 5H), 5.18–5.10 (m, 2H), 4.83 (s, 1H), 4.73 (s, 1H), 4.32 (br, 1H), 4.16 (br, 1H), 2.90–2.78 (m, 1H), 2.36 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.24–2.07 (m, 3H), 1.60–1.51 (m, 1H), 1.49–1.30 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.8, 155.2, 142.5, 137.1, 135.3, 128.72, 128.67, 128.60, 128.5, 128.0, 127.9, 111.1, 69.9, 67.2, 53.4, 39.9, 37.9, 34.3, 23.1, 10.4; **HRMS** (ESI): calculated for $[C_{16}H_{22}NO_2]^+$: m/z = 260.1645, found: m/z = 260.1641; **IR** (ν/cm^{-1}, neat) 2961, 2935, 1697, 1422, 1254, 1243, 1194, 1119; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); isocratic 5% *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.3 min (minor) and 7.7 min (major).

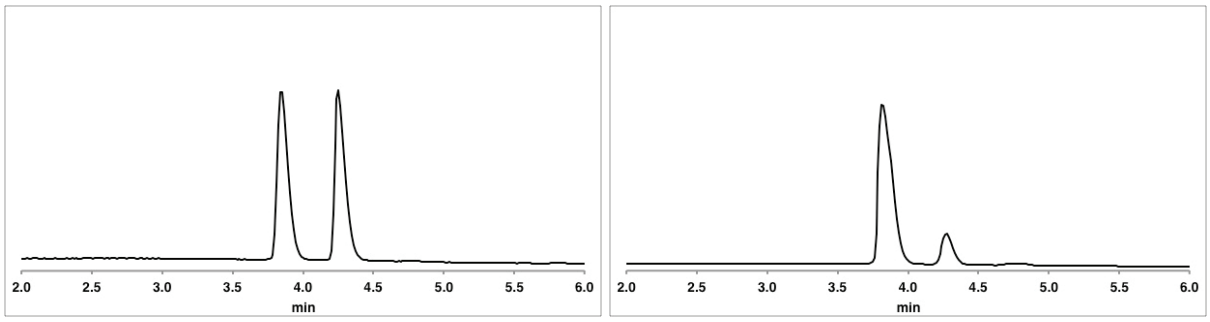


Acylated product: **(*R*)- 1-(2-Ethyl-4-methylenepiperidin-1-yl)-3-(4-methoxyphenyl) propan-1-one**

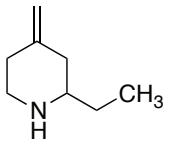


[α]$^{29}_{D}$ (c = 1.0, CH_3Cl): -27.5; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.14 (d, *J* = 8.6 Hz, 2H), 6.83 (m, 2H), 4.86–4.79 (m, 1.5H), 4.76–4.71 (m, 1H), 4.67 (dd, *J* =

13.2, 5.5 Hz, 0.5H), 3.85 (q, *J* = 6.6 Hz, 0.5H), 3.78 (s, 3H), 3.68 (dd, *J* = 13.6, 5.3 Hz, 0.5H), 3.05–2.89 (m, 2.5H), 2.73–2.52 (m, 2.5H), 2.32–1.95 (m, 4H), 1.65–1.36 (m, 2H), 0.81 (td, *J* = 7.4, 1.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.2, 171.1, 158.1, 142.2, 133.62, 133.59, 129.5, 114.05, 114.03, 111.3, 55.4, 55.2, 50.3, 41.6, 38.4, 37.4, 37.3, 36.0, 35.7, 34.7, 34.0, 31.0, 30.9, 23.5, 22.7, 10.6, 10.4; **HRMS** (ESI): calculated for $[C_{18}H_{26}NO_2]^+$: m/z = 288.1958, found: m/z = 288.1953; **IR** (ν/cm^{-1}, neat) 2960, 2935, 1637, 1513, 1427, 1246, 1179, 1036; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.8 min (major) and 4.3 min (minor).

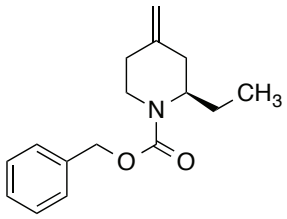


2-Ethyl-4-methylenepiperidine (123, Table 11, entry 11)

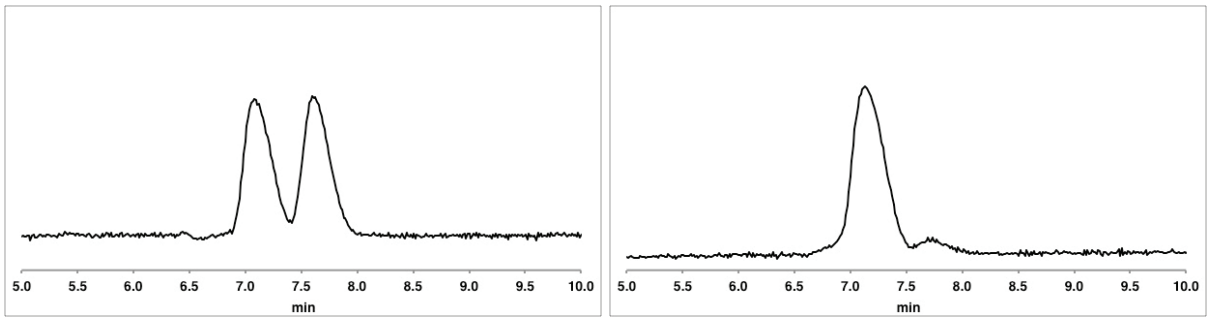


Racemic 2-ethyl-4-methylenepiperidine (31.0 mg, 0.250 mmol) was resolved according to the General Procedure B for 20 h. Recovered (Cbz-protected) amine: 27.0 mg (42 % yield, er = 96:4); acylated product: 31.0 mg (43 % yield, er = 13:87); calculated conversion: 55 %; **s = 21**

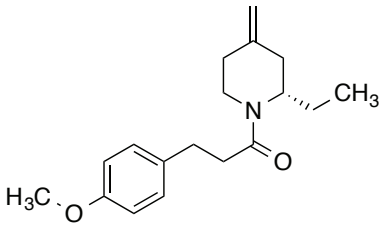
Cbz-derivative: **(*R*)-Benzyl 2-ethyl-4-methylenepiperidine-1-carboxylate**



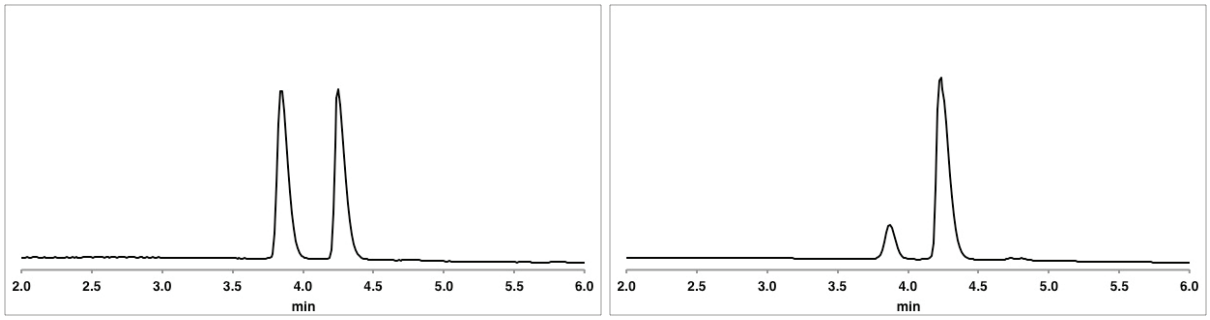
SFC: column: Daicel Chiralpak ADH (4.6 x 250 mm); isocratic 5% *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.3 min (major) and 7.7 min (minor).



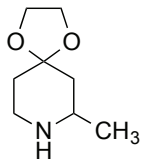
Acylated product: **(*S*)- 1-(2-Ethyl-4-methylenepiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



SFC: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.8 min (minor) and 4.3 min (major).

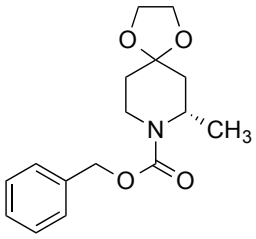


7-Methyl-1,4-dioxa-8-azaspiro[4.5]decane (128, Table 10, entry 4)

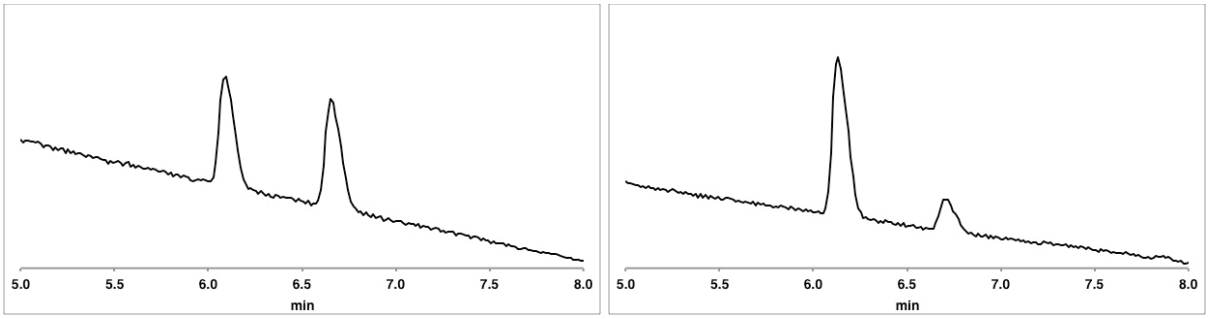


Racemic 7-methyl-1,4-dioxa-8-azaspiro[4.5]decane (90 mg, 0.57 mmol) was resolved according to the General Procedure A for 24 h. Recovered (Cbz-protected) amine: 42.0 mg (25 % yield, er = 84:16); acylated product: 80.0 mg (44 % yield, er = 81:19); calculated conversion: 52 %; **s = 8**

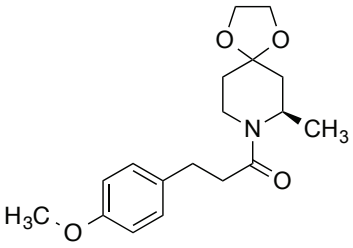
The recovered amine was characterized as its Cbz-derivative: **(*S*)-Benzyl 7-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate**



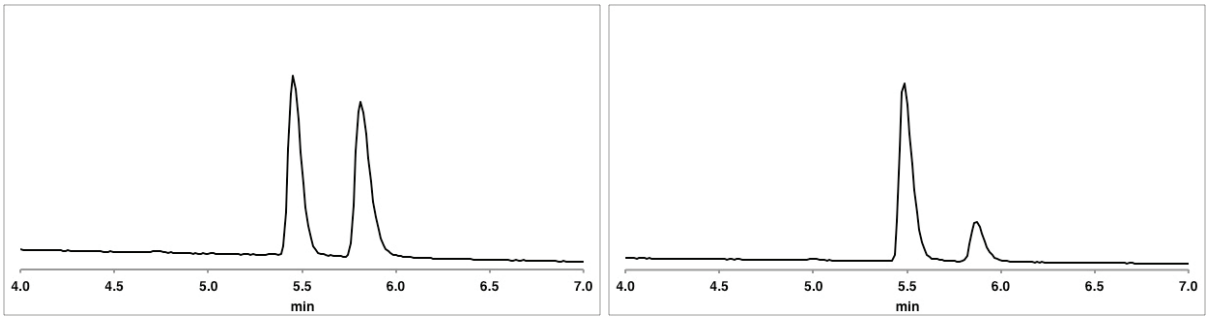
$[\alpha]^{26}_D$ (c = 2.0, CH_3Cl): +17.1. **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.1 min (major) and 6.7 min (minor). Other characterization data were identical to the racemic product described previously.



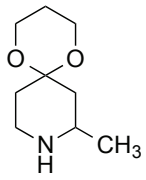
Acylated product: **(*R*)-3-(4-Methoxyphenyl)-1-(7-methyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)propan-1-one**



$[\alpha]^{26}_D$ (c = 3.5, CH_3Cl): -14.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.15 (m, 2H), 6.85 (m, 2H), 5.05 (br. 0.5H), 4.65 (br. 0.5H), 4.20 (br. 0.5H), 4.00–3.90 (m, 4H), 3.80 (s, 3H), 3.65 (br., 0.5H), 3.30 (br., 0.5H), 2.90 (m, 2H), 2.60 (br., 2H), 1.80–1.50 (br.m, 4.5H), 1.25 (br., 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.4, 158.0, 133.4, 129.4, 113.9, 107.1, 64.6, 63.9, 55.3, 48.5, 44.0, 38.8, 38.5, 38.2, 35.9, 35.2, 34.3, 30.8, 18.3, 17.0; **HRMS** (ESI): calculated for $[C_{18}H_{26}NO_4]^+$: m/z = 320.1858, found: m/z = 320.1861; **IR** (ν/cm^{-1}, neat) 2957, 2929, 2882, 1513, 1425, 1245, 1103, 1036, 827; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.4 min (major) and 5.9 min (minor).

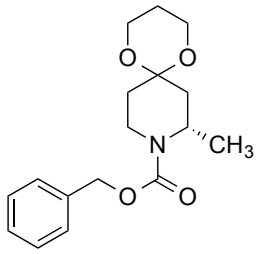


8-Methyl-1,5-dioxa-9-azaspiro[5.5]undecane (129, Table 10, entry 5)

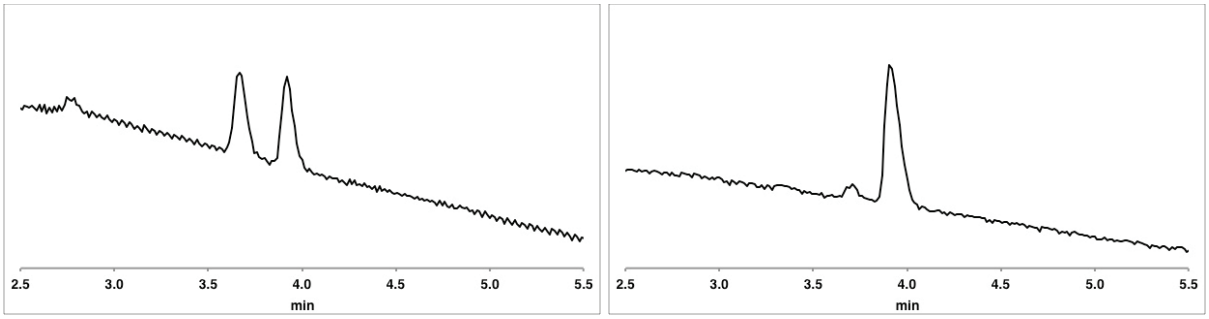


Racemic 8-methyl-1,5-dioxa-9-azaspiro[5.5]undecane (85.0 mg, 0.50 mmol) was resolved according to the General Procedure A for 24 h. Recovered (Cbz-protected) amine: 38.0 mg (23 % yield, er = 6:94); acylated product: 35.0 mg mg (21 % yield, er = 75:25); calculated conversion: 64 %; **s = 9**

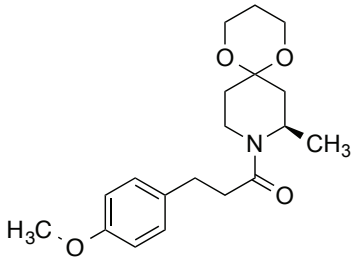
The recovered amine was characterized as its Cbz-derivative: **(*S*)-Benzyl 8-methyl-1,5-dioxa-9-azaspiro[5.5]undecane-9-carboxylate**



[α]$^{27}_{D}$ (c = 1.8, CH_3Cl): +14.0. **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.7 min (minor) and 3.9 min (major). Other characterization data were identical to the racemic product described previously.

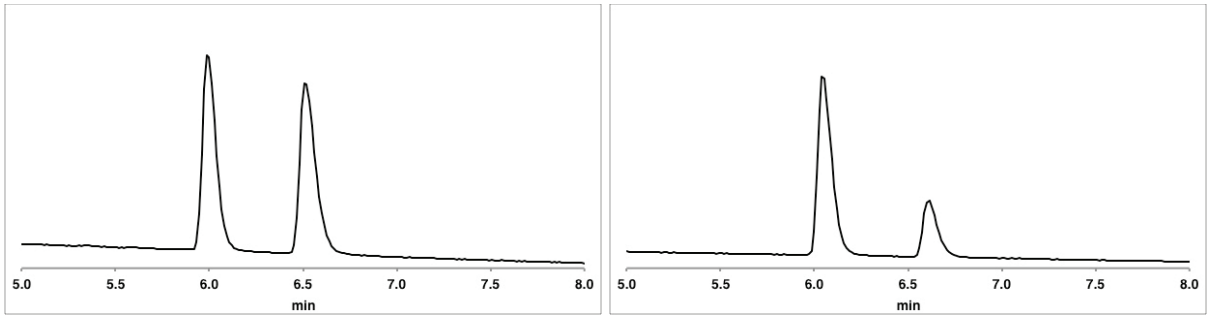


Acylated product: **(*R*)-3-(4-Methoxyphenyl)-1-(8-methyl-1,5-dioxa-9-azaspiro[5.5]undecan-9-yl)propan-1-one**



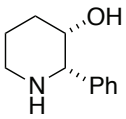
[α]$^{27}_{D}$ (c = 1.8, CH_3Cl): -15.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.15 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.95 (br., 0.5H), 4.55 (br., 0.5H), 4.15 (br., 0.5H), 3.95 (br., 4H), 3.78 (s, 3H), 3.55 (br., 0.5H), 3.30 (br., 0.5H), 2.90 (m, 2H.5), 2.60 (br., 2H), 2.35 (br, 0.5H), 2.20 (br., 1H), 2.05 (br. 0.5H), 1.80–1.40 (br, 3H), 1.50 (m, 1H), 1.20 (br., 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.6, 170.4, 158.0, 133.4, 129.4, 113.9, 96.4, 59.5, 59.4, 55.3, 48.0, 43.7, 37.6, 35.9, 35.3, 34.1, 33.3, 32.9, 30.8, 25.4; **HRMS** (ESI): calculated for $[C_{19}H_{28}NO_4]^+$: m/z = 334.2013, found: m/z = 334.2015; **IR** (ν/cm^{-1}, neat) 2963, 2931, 2871, 1638, 1513, 1428, 1245, 1146, 1110, 1033; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 %

*i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.0 min (major) and 6.6 min (minor).



6.5.2 Kinetic Resolution of 2,3-Disubstituted Piperidines

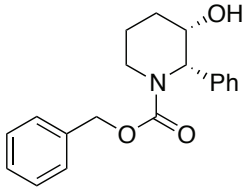
***cis*-2-Phenylpiperidin-3-ol (*cis*-78, Table 5, entry 1)**



Racemic *cis*-2-phenylpiperidin-3-ol [23] (35.4 mg, 0.200 mmol) was resolved according to the General Procedure A for 48 h. Recovered (Cbz-protected) amine: 19.0 mg (31 % yield, er = 72:28); acylated product: 20.0 mg (30 % yield, er = 6:94); calculated conversion: 33 %; **s = 24**

The absolute stereochemistry was assigned by recovering the amine after kinetic resolution by acid base extraction and with their optical rotation according to literature values. Recovered amine: **$[\alpha]^{25}_D$** (c = 1.0, $CHCl_3$): +47.3 (lit.,[24] : **$[\alpha]^{23}_D$** (c = 0.62, $CHCl_3$): +66.4).

The recovered amine was characterized as its Cbz-derivative: **(2*S*,3*R*)- Benzyl 3-hydroxy-2-phenylpiperidine-1-carboxylate**



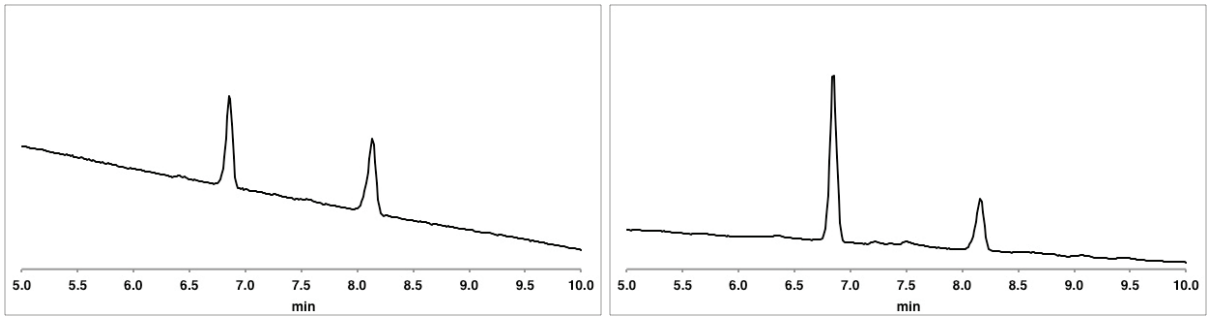
$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): +22.0 (lit. *2R,3S* enantiomer (opposite)[25] : **$[\alpha]^{25}_D$** (c = 1.0, $CHCl_3$): -66.4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.60–7.44 (m, 2H), 7.44–7.21 (m, 8H), 5.47 (d, *J* = 5.8 Hz, 1H), 5.20–5.06 (m, 2H), 4.21–4.02 (m, 2H), 3.17–3.06 (m, 1H), 1.90–1.69 (m, 5H); **^{13}C**

23 Prepared according to: Baker, R.; Swain, C.; Williams, B. J.: Azacyclic Compounds, Compositions Containing them and their Use as Tachykinin Antagonists. International Patent Publication Number WO 94/19232, September 01, 1994.

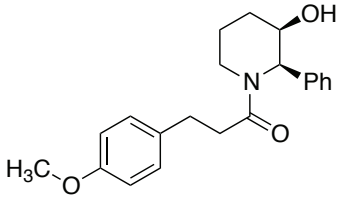
24 Pansare S. V.; Paul, E. K.: Synthesis of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-hydroxypipecolic acid: Application of an organocatalytic direct vinylogous aldol reaction. *Org. Biomol. Chem.* **2012**, *10*, 2119–2125.

25 Monterde, M. I.; Brieva, R.; Gotor, V.: Stereocontrolled Chemoenzymatic Synthesis of 2,3-Disubstituted Piperidines. *Tetrahedron: Asymmetry* **2001**, *12*, 525–528.

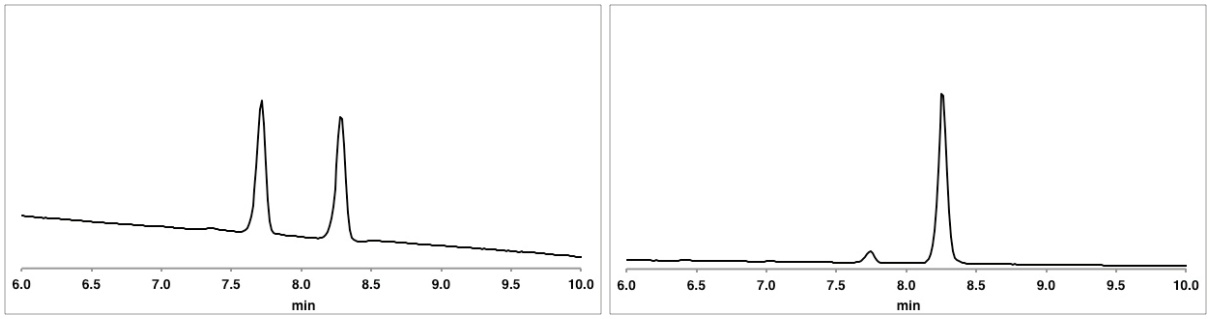
NMR (100 MHz, $CDCl_3$): δ [ppm] = 156.1, 137.9, 136.7, 128.63, 128.60, 128.56, 128.0, 127.8, 127.5, 70.1, 67.4, 59.4, 39.9, 27.8, 23.3; **HRMS** (ESI): calculated for $[C_{19}H_{21}NO_3Na]^+$: m/z = 334.1414, found: m/z = 334.1414; **IR** (ν/cm^{-1}, neat) 3435, 2945, 2870, 1694, 1675, 1447, 1424, 1256, 1148, 1082, 962; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.9 min (major) and 8.2 min (minor).



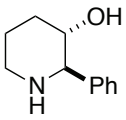
Acylated product: **1-((2*R*,3*R*)-3-Hydroxy-2-phenylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -64.4; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.61–7.27 (m, 5H), 7.20–6.98 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 5.98 (br, 0.6H), 5.00 (br, 0.4H), 4.56 (br, 0.4H), 4.02 (br, 1H), 3.78 (s, 3H), 3.59 (br, 0.6H), 3.17–2.73 (m, 3H), 2.73–2.37 (m, 2H), 2.01–1.46 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.6, 158.1, 137.5, 133.4, 129.5, 128.7, 114.0, 70.8, 70.2, 56.5, 55.4, 41.1, 35.7, 30.8, 27.6, 24.2; **HRMS** (ESI): calculated for $[C_{21}H_{26}NO_3]^+$: m/z = 340.1907, found: m/z = 340.1905; **IR** (ν/cm^{-1}, neat) 3340, 2967, 2936, 1617, 1573, 1513, 1463, 1441, 1247, 1170, 1035; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.8 min (minor) and 8.3 min (major).

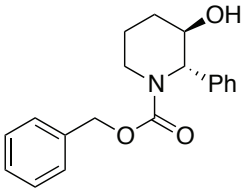


***trans*-2-Phenylpiperidin-3-ol (*trans*-78, Table 5, entry 2)**

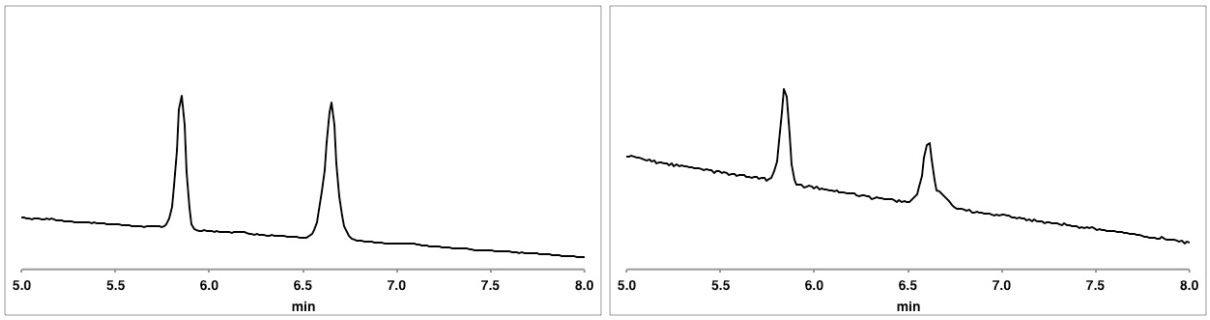


Racemic *trans*-2-phenylpiperidin-3-ol[23] (35.4 mg, 0.200 mmol) was resolved according to the General Procedure A for 72 h. Recovered (Cbz-protected) amine: 20.0 mg (32 % yield, er = 51:49); acylated product: 3.0 mg (5 % yield, er = 44:56); calculated conversion: 14 %; **s = 1.3**

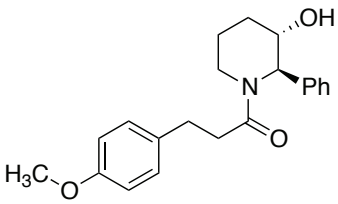
The recovered amine was characterized as its Cbz-derivative: **(2*S*,3*R*)- Benzyl 3-hydroxy-2-phenylpiperidine-1-carboxylate**



$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -0.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.41–7.21 (m, 10H), 5.50 (s, 1H), 5.22 (s, 2H), 4.61–4.55 (m, 1H), 4.26–4.16 (m, 1H), 2.97 (td, *J* = 13.3, 3.3 Hz, 1H), 2.00 (dt, *J* = 17.9, 4.9 Hz, 2H), 1.85–1.77 (m, 1H), 1.73–1.63 (m, 1H), 1.48–1.40 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 157.2, 137.6, 136.7, 128.8, 128.5, 128.0, 127.7, 127.1, 126.3, 67.4, 67.4, 60.4, 40.3, 25.9, 18.8, **HRMS** (ESI): calculated for $[C_{19}H_{21}NO_3Na]^+$: m/z = 334.1414, found: m/z = 334.1418; **IR** (ν/cm^{-1}, neat) 3437, 2943, 1693, 1675, 1424, 1258, 1125; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.8 min (major) and 6.6 min (minor).

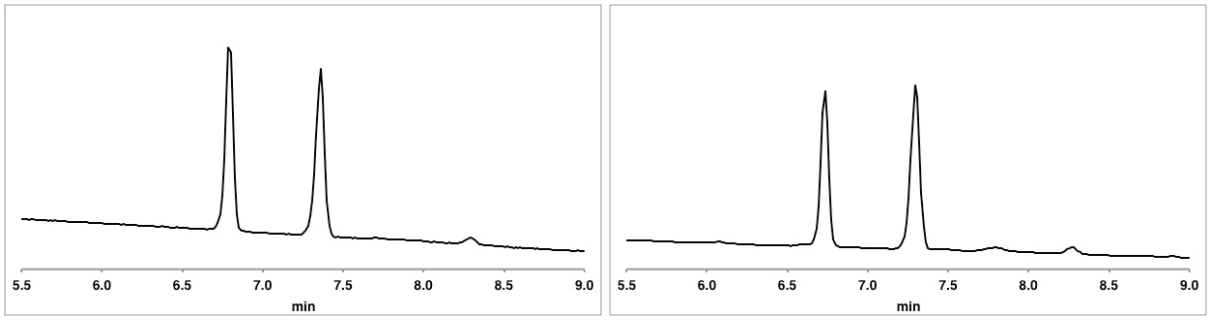


Acylated product: **1-((2*R*,3*S*)-3-Hydroxy-2-phenylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**

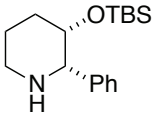


$[\alpha]^{29}_D$ (c = 0.3, CH_3Cl): -4.3; at room temperature the ratio of rotamers was 70:30 as determined by ^{1}H NMR; **^{1}H NMR** (600 MHz, $CDCl_3$): δ [ppm] = 7.41–7.29 (m, 2H), 7.29–7.19 (m, 2H), 7.21–7.02 (m, 3H), 6.93–6.72 (m, 2H), 6.00 (br, 0.7H), 5.09 (br, 0.6H), 4.62 (br, 1.7H), 3.88–3.66 (br, 3H), 3.08–2.86 (m, 2H), 2.84–2.61 (m, 2H), 2.61–2.35 (m, 1H), 2.32–2.12 (m, 1H), 1.92–1.63 (m, 3H), 1.50–1.32 (br, 1H); **^{13}C NMR** (150 MHz,

$CDCl_3$): δ [ppm] = 173.6, 158.1, 137.3, 133.5, 129.5, 129.2, 129.0, 127.4, 127.2, 126.6, 126.3, 114.0, 67.9, 67.1, 62.1, 57.5, 55.4, 42.1, 37.9, 35.5, 30.8, 26.4, 20.0, 18.8; **HRMS** (ESI): calculated for $[C_{21}H_{26}NO_3]^+$: m/z = 340.1907, found: m/z = 340.1907; **IR** (ν/cm^{-1}, neat) 3375, 2934, 1613, 1513, 1447, 1245, 1178, 1108, 1035, 985, 825; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.7 min (minor) and 7.3 min (major).

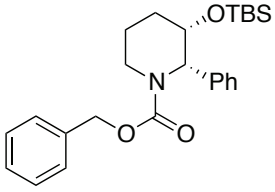


***cis*-3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpiperidine (*cis*-81, Table 5, entry 3)**

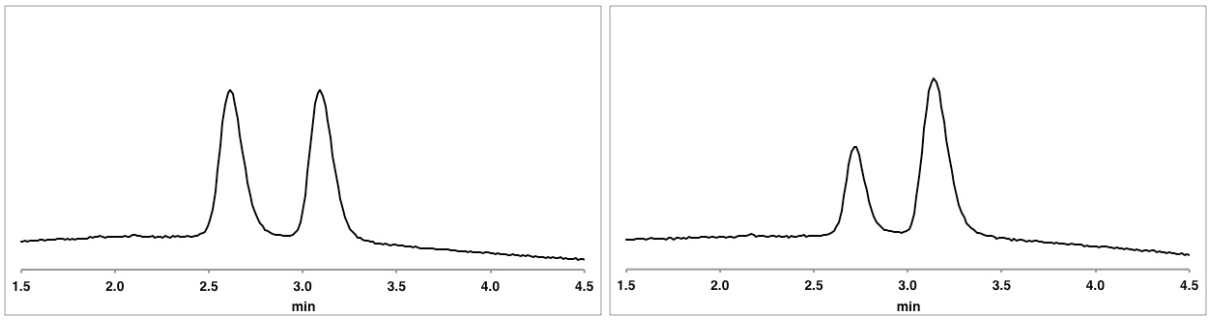


Racemic *cis*-3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpiperidine (58.2 mg, 0.200 mmol) was resolved according to the General Procedure A for 72 h. Recovered (Cbz-protected) amine: 29.0 mg (34 % yield, er = 31:69); acylated product: 25.0 mg (28 % yield, er = 7:93); calculated conversion: 31 %; **s = 19**

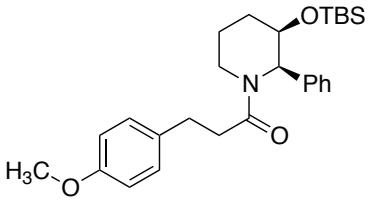
The recovered amine was characterized as its Cbz-derivative: **(2*S*,3*S*)-Benzyl 3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpiperidine-1-carboxylate**



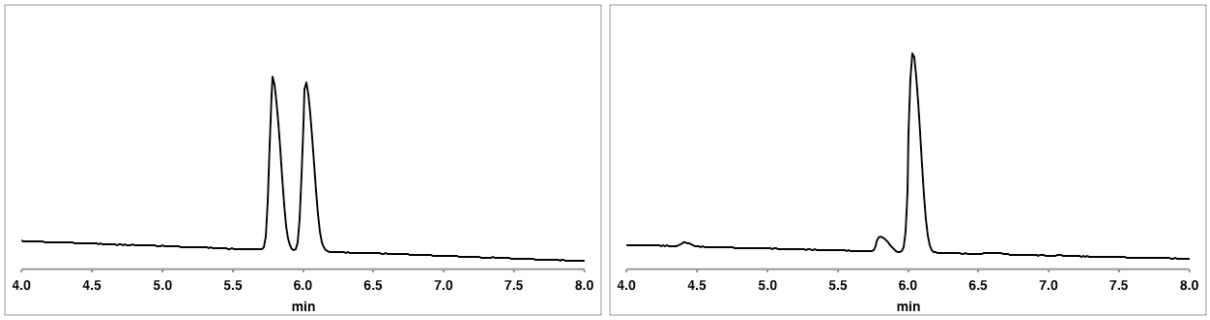
[α]$^{29}_D$ (c = 1.0, CH_3Cl): +16.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.58 (d, *J* = 7.7 Hz, 2H), 7.45–7.22 (m, 8H), 5.48 (s, 1H), 5.28–5.16 (m, 2H), 4.14–4.07 (m, 1H), 4.04 (d, *J* = 13.6 Hz, 1H), 2.91–2.74 (m, 1H), 1.95 (d, *J* = 8.5 Hz, 1H), 1.85–1.75 (m, 1H), 1.75–1.60 (m, 2H), 0.89 (s, 9H), 0.11 (a, 3H), -0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 156.0, 138.4, 136.9, 128.7, 128.6, 128.1, 128.0, 127.9, 126.8, 71.8, 67.4, 59.1, 39.3, 28.8, 25.9, 25.8, 24.1, 18.1, -4.8, -4.9; **HRMS** (ESI): calculated for $[C_{25}H_{36}NO_3Si]^+$: m/z = 426.2459, found: m/z = 426.2459; **IR** (ν/cm^{-1}, neat) 2952, 2930, 2857, 1703, 1470, 1420, 1257, 1128, 1113, 1092, 838, 776; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 2.6 min (minor) and 3.1 min (major).



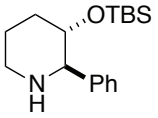
Acylated product: **1-((2*R*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{29}_{D}$ (c = 1.0, CH_3Cl): -50.1; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.50–7.40 (m, 2H), 7.36–7.02 (m, 5H), 6.93–6.76 (m, 2H), 5.99 (d, *J* = 5.3 Hz, 0.6H), 4.96 (d, *J* = 5.0 Hz, 0.4H), 4.52 (dd, *J* = 13.8, 4.9 Hz, 0.4H), 4.08–3.93 (m, 1H), 3.79 (s, 1.8H), 3,78 (s, 1.2H), 3.51 (dd, *J* = 14.1, 4.6 Hz, 0.6H), 3.05–2.81 (m, 2.6H), 2.78–2.48 (m, 2.4H), 2.02–1.61 (m, 3.4H), 1.54–1.33 (m, 0.6H), 0.86 (s, 5.4H), 0.85 (s, 3.6H), 0.10 (s, 1.8H), 0.06 (s, 1.2H), 0.02 (s, 1.8H), -0.06 (s, 1.2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 172.2, 171.3, 158.2, 158.1, 138.2, 138.0, 133.5, 133.4, 129.5, 129.4, 128.9, 128.5, 128.1, 128.0, 127.2, 126.6, 114.00, 113.99, 72.6, 71.3, 61.4, 56.0, 55.4, 40.9, 37.0, 35.6, 35.4, 30.9, 29.0, 28.3, 25.9, 24.9, 22.9, 18.1, -4.66, -4.76, -4.84, -5.0; **HRMS** (ESI): calculated for $[C_{27}H_{40}NO_3Si]^+$: m/z = 454.2772, found: m/z = 454.2768; **IR** (ν/cm^{-1}, neat) 2952, 2932, 2857, 1644, 1513, 1421, 1249, 1107, 1036, 867, 367, 777; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.7 min (minor) and 6.0 min (major).

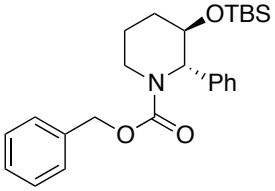


***trans*-3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpiperidine (*trans*-81, Table 5, entry 4)**

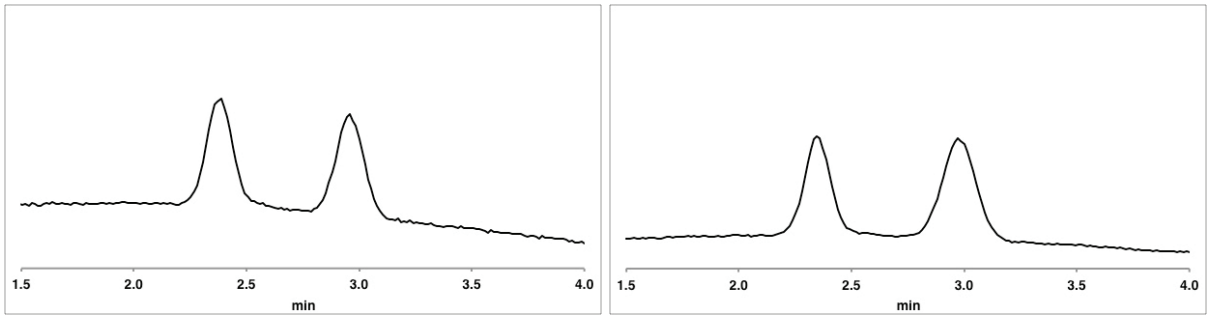


Racemic *trans*-3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpiperidine (58.2 mg, 0.200 mmol) was resolved according to the General Procedure A for 96 h. Recovered (Cbz-protected) amine: 33.0 mg (39 % yield, er = 44:56); acylated product: 6.0 mg (7 % yield, er = 43:57); calculated conversion: 46 %; **s = 2**

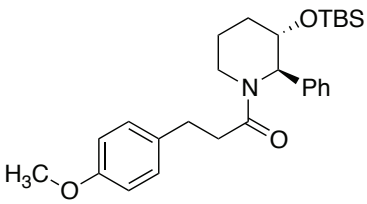
The recovered amine was characterized as its Cbz-derivative: **(2*S*,3*R*)-Benzyl 3-((*tert*-butyldimethylsilyl)oxy)-2-phenylpiperidine-1-carboxylate**



$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): +2.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.43–7.19 (m, 10H), 5.38 (s, 1H), 5.27–5.11 (m, 2H), 4.49 (q, *J* = 2.7 Hz, 1H), 4.23 (dt, *J* = 13.7, 3.0 Hz, 1H), 2.95 (td, *J* = 13.3, 3.3 Hz, 1H), 2.18–2.02 (m, 1H), 1.67–1.60 (m, 2H), 1.41–1.30 (m, 1H), 0.92 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 157.0, 138.7, 137.2, 128.8, 128.5, 127.9, 127.8, 127.0, 126.6, 68.0, 67.2, 60.9, 40.6, 27.1, 25.9, 19.0, 18.2, -4.7, -4.9; **HRMS** (ESI): calculated for $[C_{25}H_{36}NO_3Si]^+$: m/z = 426.2459, found: m/z = 426.2468; **IR** (ν/cm^{-1}, neat) 2951, 2927, 2855, 1701, 1425, 1254, 1125, 1026, 836; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 2.4 min (minor) and 3.0 min (major).

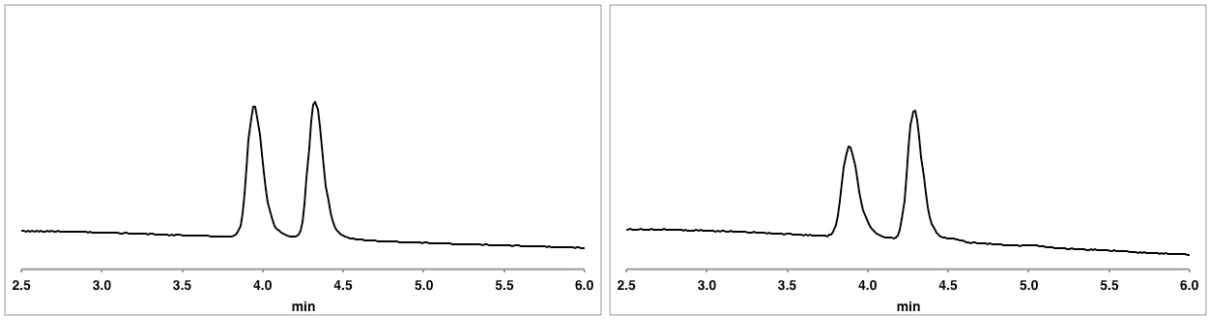


Acylated product: **1-((2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-phenylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**

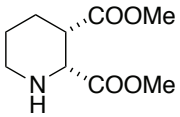


$[\alpha]^{29}_D$ (c = 0.6, CH_3Cl): +5.5; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.42–6.95 (m, 7H), 6.93–6.71 (m, 2H), 5.86 (br, 0.5H), 4.96 (br, 0.5H), 4.67 (br, 0.5H), 4.53 (q, *J* = 2.9 Hz, 1H), 3.78 (s, 3H), 3.70 (br, 0.5 s), 3.15–2.84 (m, 2.5H), 2.84–2.57 (m, 2H), 2.57–2.41

(m, 0.5H), 2.11–1.93 (m, 1H), 1.70–1.52 (m, 2H), 1.34 (dt, *J* = 13.0, 3.2 Hz, 1H), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 173.0, 172.3, 158.0, 137.8, 133.8, 129.4, 129.0, 127.3, 126.3, 114.0, 68.6, 67.7, 62.8, 57.9, 55.4, 42.1, 38.2, 35.4, 30.8, 29.8, 27.3, 25.9, 18.9, 18.2, -4.6, -4.8; **HRMS** (ESI): calculated for $[C_{27}H_{40}NO_3Si]^+$: m/z = 454.2772, found: m/z = 454.2777; **IR** (ν/cm^{-1}, neat) 2952, 2929, 2855, 1646, 1513, 1446, 1431, 1248, 1119, 1036, 836, 776; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.9 min (minor) and 4.3 min (major).

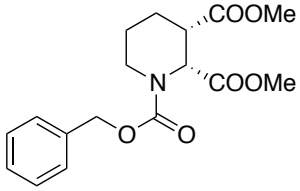


***cis*-Dimethyl piperidine-2,3-dicarboxylate (*cis*-82, Table 5, entry 5)**



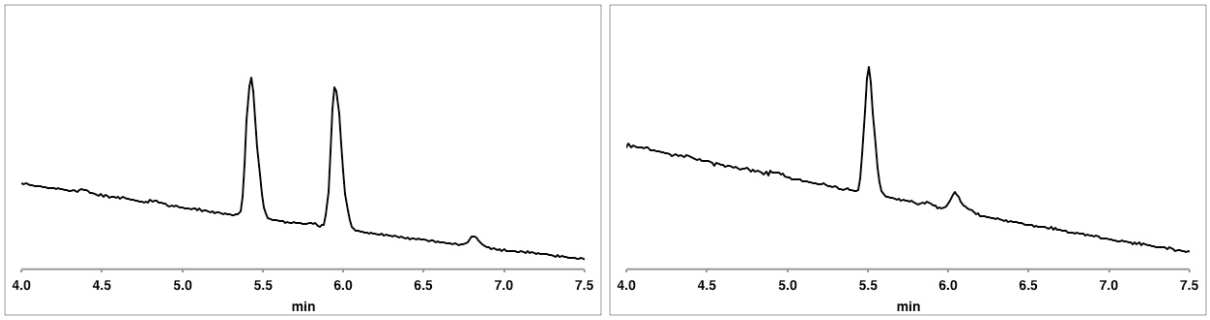
Racemic *cis*-dimethyl piperidine-2,3-dicarboxylate (40.2 mg, 0.200 mmol) was resolved according to the General Procedure A for 72 h. Recovered (Cbz-protected) amine: 26.0 mg (39 % yield, er = 90:10); acylated product: 36.0 mg (50 % yield, er = 9:91); calculated conversion: 50 %; **s = 23**

The recovered amine was characterized as its Cbz-derivative: **(2*R*,3*S*)-1-Benzyl 2,3-dimethyl piperidine-1,2,3-tricarboxylate**

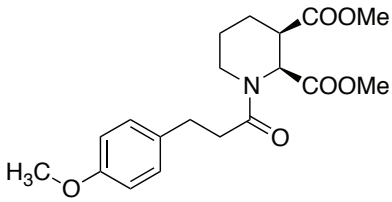


[α]$^{29}_D$ (c = 1.0, CH_3Cl): +63.7; at room temperature the ratio of rotamers was 55:45 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.41–7.28 (m, 5H), 5.56 (d, *J* = 4.8 Hz, 0.55H), 5.41 (d, *J* = 4.8 Hz, 0.45H), 5.26 (d, *J* = 12.5 Hz, 0.45H), 5.18 (s, 1.1H), 5.13 (d, *J* = 12.5 Hz, 0.45H), 4.19–4.04 (m, 1H), 3.74–3.63 (m, 6H), 2.86 (td, *J* = 13.3, 3.1 Hz, 0.55H), 2.73 (td, *J* = 13.3, 3.1 Hz, 0.45H), 2.67–2.57 (m, 1H), 2.09 (d, *J* = 13.8 Hz, 1H), 1.78–1.42 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.9, 170.2, 170.1, 156.1, 155.5, 136.7, 136.5, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 67.8, 67.6, 56.2, 56.0, 52.6, 52.1, 52.0, 43.3, 43.1, 41.6, 41.4, 24.4, 24.1, 22.5; **HRMS** (ESI): calculated for $[C_{17}H_{22}NO_6]^+$: m/z = 336.1441, found: m/z = 336.1442; **IR** (ν/cm^{-1}, neat) 2982, 2867, 1743, 1703, 1420,

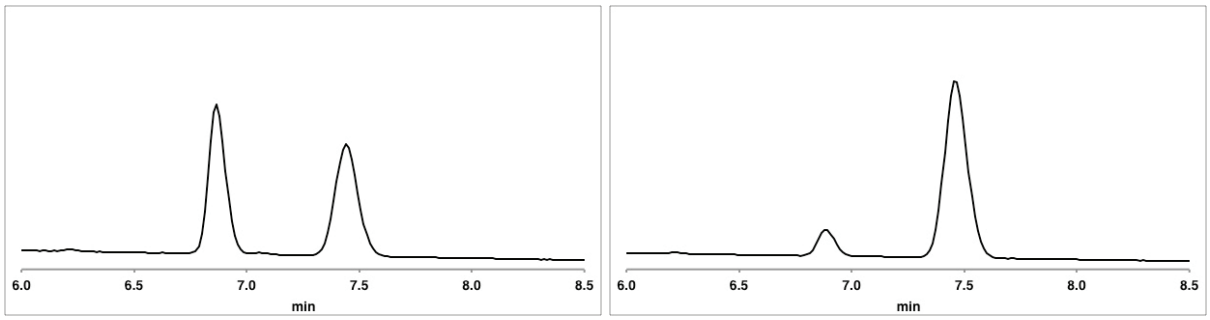
1289, 1257, 1212, 1157, 1137; **SFC**: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.5 min (major) and 6.0 min (minor).



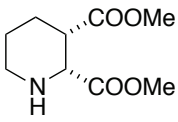
Acylated product: **(2*S*,3*R*)-Dimethyl 1-(3-(4-methoxyphenyl)propanoyl)piperidine-2,3-dicarboxylate**



$[\alpha]^{29}_D$ (c = 1.0 CH_3Cl): -68.8; at room temperature the ratio of rotamers was 70:30 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.21–7.09 (m, 2H), 6.88–6.77 (m, 2H), 6.01 (d, *J* = 4.9 Hz, 0.7H), 5.01 (d, *J* = 4.6 Hz, 0.3H), 4.64–4.54 (m, 0.3H), 3.80–3.75 (m, 3H), 3.74 (m, 0.7H), 3.72–3.64 (m, 6H), 3.05–2.87 (m, 2.7H), 2.74–2.60 (m, 2H), 2.56–2.46 (m, 0.7H), 2.42–2.27 (m, 0.6H), 2.15–2.02 (m, 1H), 1.80–1.60 (m, 2H), 1.41–1.24 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.9, 171.81, 171.79, 171.7, 170.1, 169.5, 158.2, 158.1, 133.2, 129.6, 129.5, 114.1, 114.0, 57.3, 55.4, 53.3, 52.8, 52.5, 52.1, 52.0, 43.3, 43.0, 42.9, 38.9, 35.5, 35.2, 30.7, 30.5, 24.8, 24.1, 22.6, 22.5; **HRMS** (ESI): calculated for $[C_{19}H_{26}NO_6]^+$: m/z = 364.1755, found: m/z = 364.1758; **IR** (ν/cm^{-1}, neat) 2952, 2870, 1743, 1651, 1513, 1434, 1302, 1246, 1152, 1032, 1002, 828; **SFC**: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.9 min (minor) and 7.5 min (major).

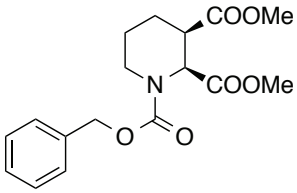


cis-Dimethyl piperidine-2,3-dicarboxylate (_cis_-82, Table 11, entry 1)

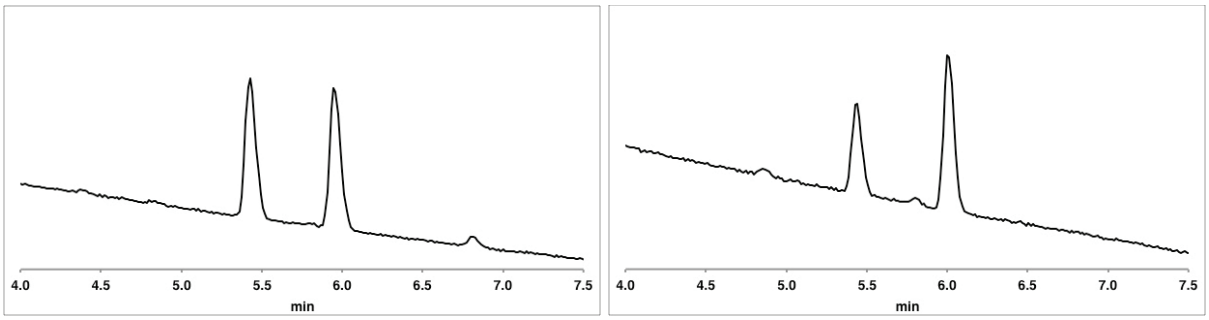


Racemic *cis*-dimethyl piperidine-2,3-dicarboxylate (50.3 mg, 0.250 mmol) was resolved according to the General Procedure B for 72 h. Recovered (Cbz-protected) amine: 36.0 mg (43 % yield, er = 36:64); acylated product: 23.0 mg (25 % yield, er = 89:11); calculated conversion: 28 %; **s = 11**

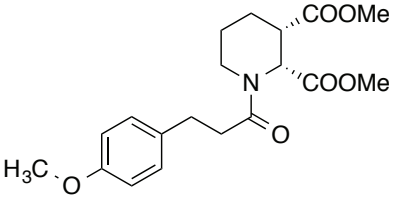
Cbz-derivative: **(2*S*,3*R*)-1-Benzyl 2,3-dimethyl piperidine-1,2,3-tricarboxylate**



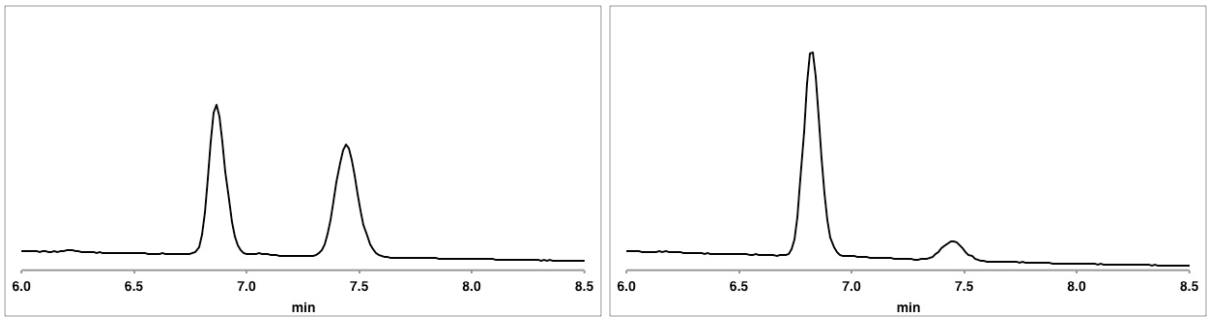
SFC: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.5 min (minor) and 6.0 min (major).



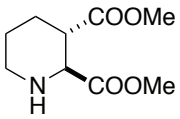
Acylated product: **(2*R*,3*S*)-Dimethyl 1-(3-(4-methoxyphenyl)propanoyl)piperidine-2,3-dicarboxylate**



SFC: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.9 min (minor) and 7.5 min (major).

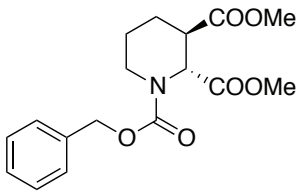


***trans*-Dimethyl piperidine-2,3-dicarboxylate (*trans*-82, Table 5, entry 6)**

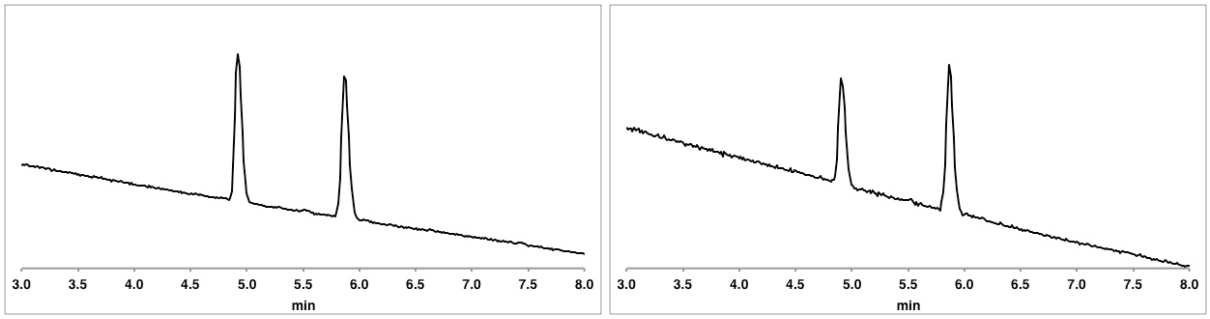


Racemic *trans*-dimethyl piperidine-2,3-dicarboxylate (40.2 mg, 0.200 mmol) was resolved according to the General Procedure A for 96 h. Recovered (Cbz-protected) amine: 27.0 mg (40 % yield, er = 41:59); acylated product: 15.0 mg (21 % yield, er = 75:25); calculated conversion: 26 %; **s = 4**

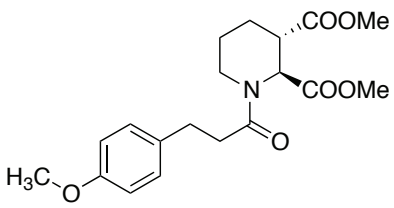
The recovered amine was characterized as its Cbz-derivative: **(2*R*,3*R*)-1-Benzyl 2,3-dimethyl piperidine-1,2,3-tricarboxylate**



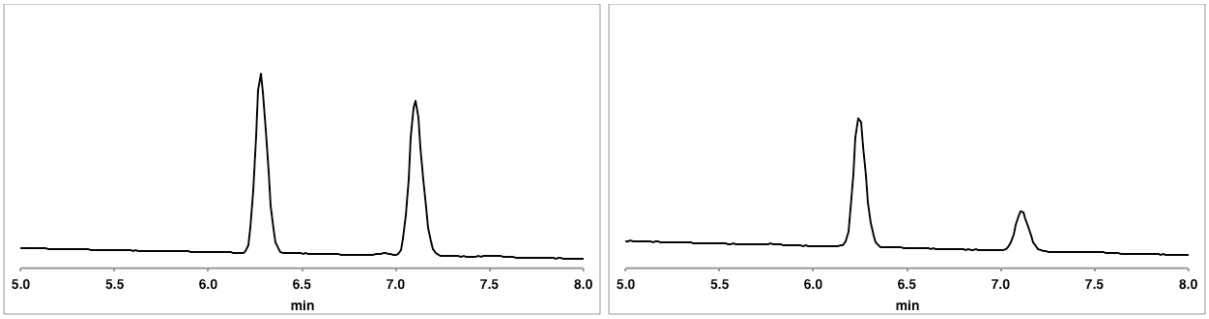
$[\alpha]^{29}_{D}$ (c = 1.0, CH_3Cl): +0.8; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.39–7.28 (m, 5H), 5.52 (s, 1H), 5.23–5.11 (m, 2H), 4.18–3.98 (m, 1H), 3.80–3.62 (m, 6H), 3.28 (d, *J* = 13.8 Hz, 1H), 3.07–2.92 (m, 0.5H), 2.92–2.80 (m, 0.5H), 2.21 (d, *J* = 12.8 Hz, 1H), 1.62–1.40 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 172.4, 171.0, 156.3, 155.8, 136.7, 136.6, 128.4, 127.9, 127.7, 67.5, 67.3, 55.7, 55.5, 52.6, 52.3, 41.6, 41.3, 40.7, 40.6, 22.5, 21.2; **HRMS** (ESI): calculated for $[C_{17}H_{21}NO_6Na]^+$: m/z = 358.1261, found: m/z = 358.1261; **IR** (ν/cm^{-1}, neat) 2953, 1738, 1706, 1424, 1342, 1320, 1253, 1212, 1187, 1120, 1043, 1010; **SFC**: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 4.9 min (minor) and 5.9 min (major).



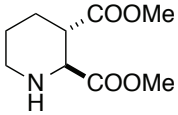
Acylated product: **(2*S*,3*S*)-Dimethyl 1-(3-(4-methoxyphenyl)propanoyl)piperidine-2,3-dicarboxylate**



$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -6.4; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.14 (m, 2H), 6.86–6.80 (m, 2H), 5.93 (s, 0.6H), 5.21 (s, 0.4H), 4.71–4.52 (m, 0.4H), 3.78 (s, 3H), 3.77–3.74 (m, 3H), 3.74–3.67 (m, 3.6H), 3.34 (m, 1H), 3.19–3.09 (m, 0.6H), 2.97–2.86 (m, 2.4H), 2.68–2.46 (m, 2H), 2.31–2.14 (m, 1H), 1.69–1.35 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 172.47, 172.45, 172.43, 172.37, 170.8, 170.5, 158.0, 133.6, 133.3, 129.3, 113.89, 113.87, 56.8, 55.3, 53.1, 52.9, 52.6, 52.4, 52.2, 43.0, 41.1, 40.4, 38.9, 35.5, 34.7, 30.2, 30.1, 22.8, 22.7, 21.6, 21.5; **HRMS** (ESI): calculated for $[C_{19}H_{26}NO_6]^+$: m/z = 364.1755, found: m/z = 364.1752; **IR** (ν/cm^{-1}, neat) 2952, 1737, 1654, 1514, 1435, 1247, 1178, 1147, 1010; **SFC**: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.2 min (major) and 7.1 min (minor).

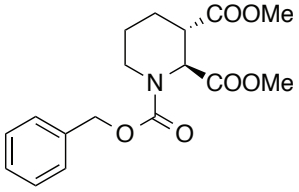


***trans*-Dimethyl piperidine-2,3-dicarboxylate (*trans*-82, Table 11, entry 2)**

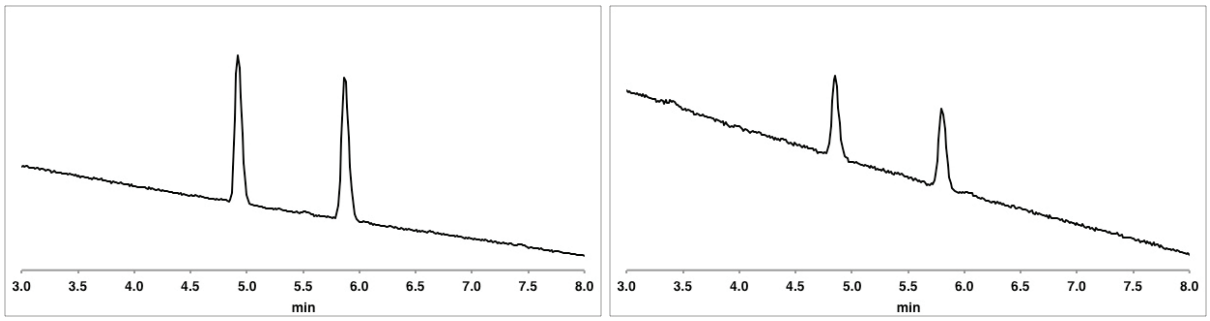


Racemic *trans*-dimethyl piperidine-2,3-dicarboxylate (50.3 mg, 0.250 mmol) was resolved according to the General Procedure B for 72 h. Recovered (Cbz-protected) amine: 48.0 mg (58 % yield, er = 50:50); acylated product: 5.00 mg (5 % yield, er = 33:67); calculated conversion: 3 %; **s = 2**

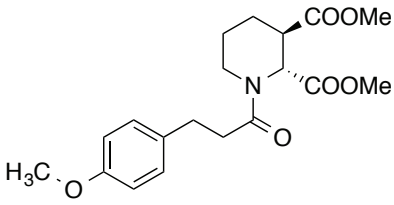
Cbz-derivative: **(2*S*,3*S*)-1-Benzyl 2,3-dimethyl piperidine-1,2,3-tricarboxylate**



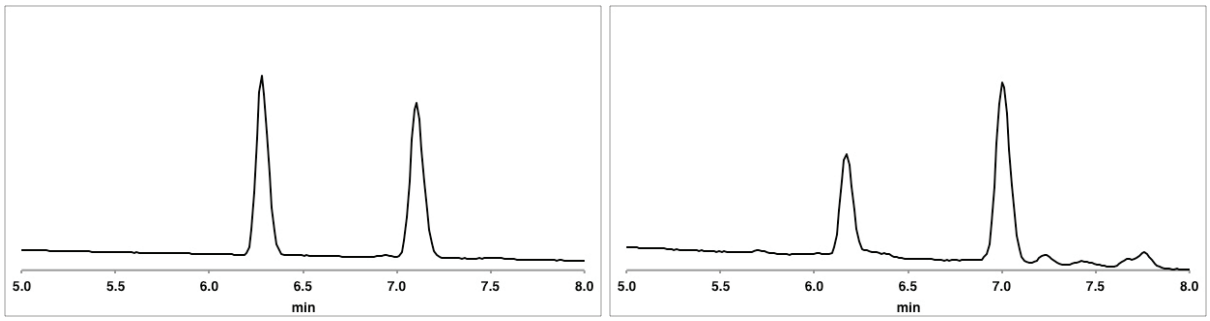
SFC: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 4.9 min and 5.9 min.



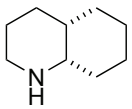
Acylated product: **(2*R*,3*R*)-Dimethyl 1-(3-(4-methoxyphenyl)propanoyl)piperidine-2,3-dicarboxylate**



SFC: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.2 min (minor) and 7.1 min (major).

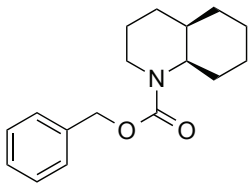


***cis*-Decahydroquinoline (*cis*-117, Table 11, entry 7)**



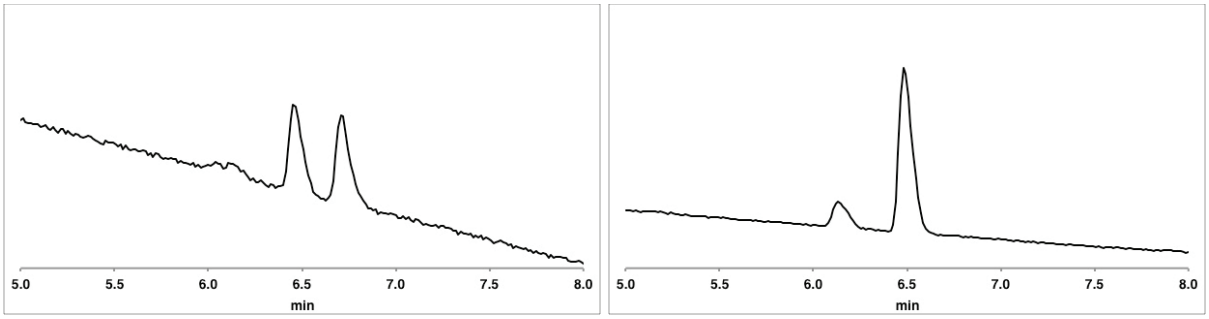
Racemic *cis*-decahydroquinoline (100 mg, 0.72 mmol) was resolved according to the General Procedure B for 48 h. Recovered (Cbz-protected) amine: 40.0 mg (20 % yield, er = 99:1); acylated product: 85.0 mg (40 % yield, er = 21:79); calculated conversion: 63 %; **s = 18**

The recovered amine was characterizes as it's Cbz derivative: **(4a*R*,8a*R*)-Benzyl octahydroquinoline-1(2*H*)-carboxylate**

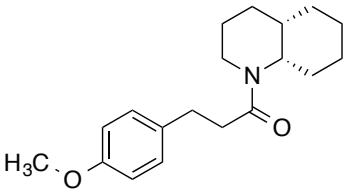


$[\alpha]^{28}_D$ (c = 1.3, CH_3Cl): -11.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.45–7.30 (m, 5H), 5.16 (m, 2H), 4.20 (br., 1H), 4.03 (br., 1H), 2.84

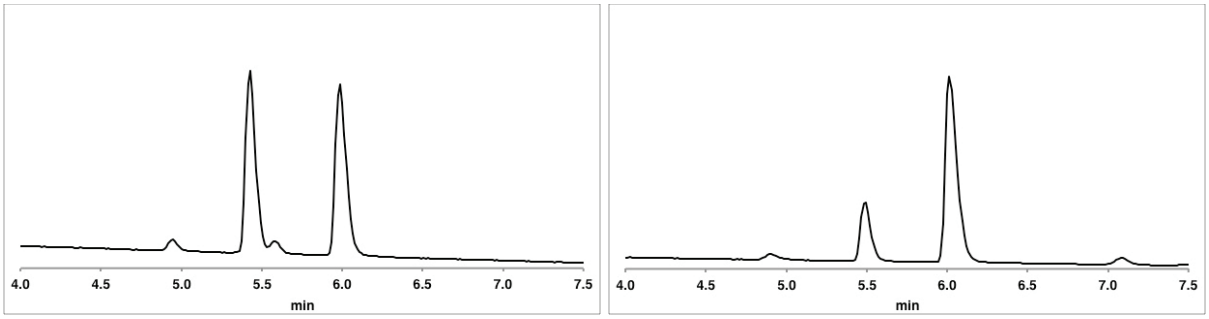
(br.m, 1H), 1.90–1.65 (m, 5H), 1.60 (m, 2H), 1.55–1.20 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.5, 137.2, 128.4, 127.8, 127.6, 66.8, 53.3, 39.1, 35.0, 31.4, 25.9, 25.6, 23.9, 20.3; **HRMS** (ESI): calculated for $[C_{17}H_{24}NO_2]^+$: m/z = 274.1802, found: m/z = 274.1803; **IR** (ν/cm^{-1}, neat) 2925, 2855, 1696, 1420, 1348, 1312, 1263, 1251, 1234, 1164; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.4 min (major) and 6.7 min (minor).



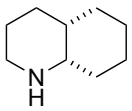
Acylated product: **3-(4-Methoxyphenyl)-1-((4a*S*,8a*S*)-octahydroquinolin-1(2*H*)-yl)propan-1-one**



[α]$^{27}_D$ (c = 1.3, CH_3Cl): +8.8; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.17 (m, 2H), 6.85 (m, 2H), 4.70 (m, 0.5H), 4.55 (m, 0.5H), 3.81 (s, 3H), 3.70 (m, 0.5H), 3.57 (m, 0.5H), 2.95 (m, 2.5H), 2.60 (m, 2.5H), 1.90–1.50 (m, 7H), 1.45–1.15 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.8, 170.6, 158.0, 157.9, 133.7, 133.6, 129.4, 129.4, 129.2, 113.9, 113.9, 55.6, 55.3, 55.3, 50.5, 40.9, 36.5, 36.0, 35.8, 35.5, 34.8, 31.4, 31.3, 30.9, 30.8, 26.5, 25.8, 25.7, 25.6, 25.0, 24.1, 23.9, 23.7, 20.3, 20.0; **HRMS** (ESI): calculated for $[C_{19}H_{28}NO_2]^+$: m/z = 302.2115, found: m/z = 302.2117; **IR** (ν/cm^{-1}, neat) 2925, 2858, 1637, 1612, 1512, 1454, 1427, 1245, 1033, 825; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.5 min (minor) and 6.0 min (major).

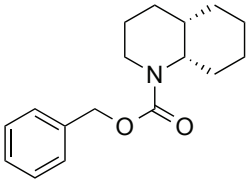


***cis*-Decahydroquinoline (*cis*-117, Scheme 39)**

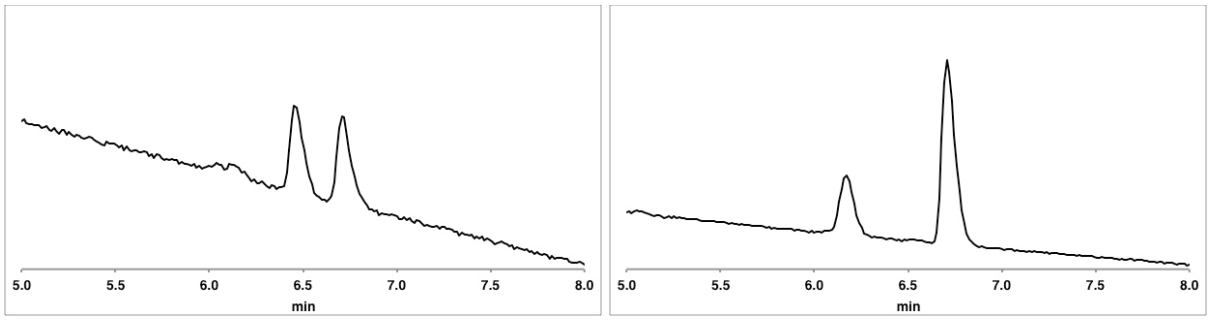


Racemic *cis*-decahydroquinoline (65.0 mg, 0.47 mmol) was resolved according to the General Procedure A (~ 0.7 equiv of acylating agent was used) for 15 h. Recovered (Cbz-protected) amine: 22.0 mg (17 % yield, er > 99:1); acylated product: 70.0 mg (50 % yield, er = 73:27); calculated conversion: 65 %; **s = 20**

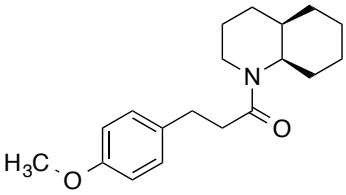
The recovered amine was characterizes as it's Cbz derivative: **(4a*S*,8a*S*)-Benzyl octahydroquinoline-1(2*H*)-carboxylate**



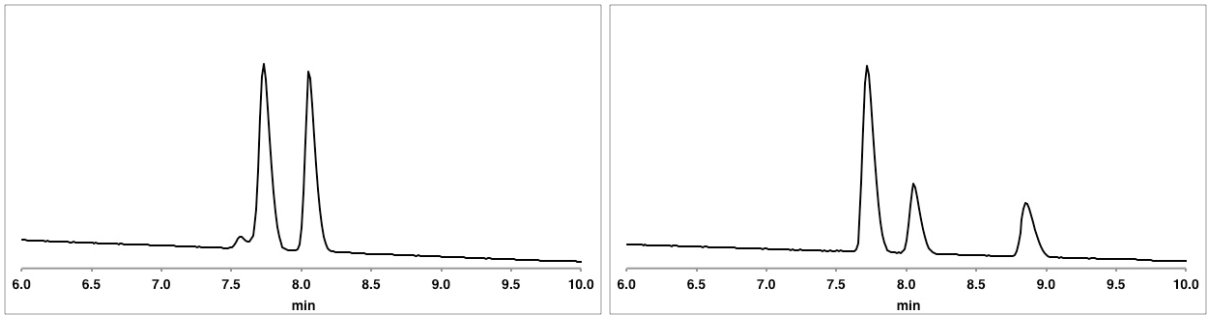
SFC: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.4 min (minor) and 6.7 min (major).



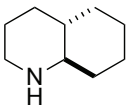
Acylated product: **3-(4-Methoxyphenyl)-1-((4a*R*,8a*R*)-octahydroquinolin-1(2*H*)-yl)propan-1-one**



SFC: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.7 min (major) and 8.1 min (minor).

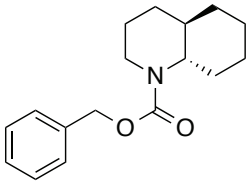


***trans*-Decahydroquinoline (*trans*-117, Table 11, entry 8)**

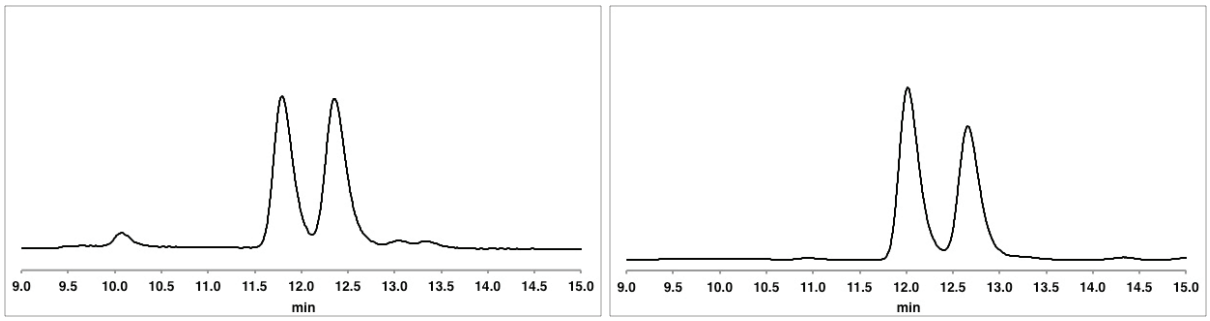


Racemic *trans*-decahydroquinoline (100 mg, 0.72 mmol) was resolved according to the General Procedure B for 65 h. Recovered (Cbz-protected) amine: 120 mg (61 % yield, er = 55:45); acylated product: 20.0 mg (9 % yield, er = 90:10); calculated conversion: 11 %; **s = 9**

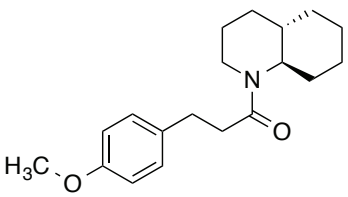
The recovered amine was characterized as it's Cbz derivative: (**4a*R*,8a*S*)-Benzyl octahydroquinoline-1(2*H*)-carboxylate**



$[\alpha]^{29}_D$ (c = 6.0, CH_3Cl) : +4.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.35 (m, 5H), 5.15 (2d, *J* = 12.7 Hz, 2H), 3.67 (m, 1H), 3.30 (m, 1H), 3.12 (td, *J* = 11.0, 3.3 Hz, 1H), 2.17 (m, 1H), 1.80–1.00 (m, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.9, 137.2, 128.4, 127.7, 127.6, 66.6, 62.3, 39.8, 38.4, 33.2, 31.4, 27.5, 26.1, 25.6, 23.1; **HRMS** (ESI): calculated for $[C_{17}H_{24}NO_2]^+$: m/z = 274.1802, found: m/z = 274.1802; **IR** (ν/cm^{-1}, neat) 2953, 2915, 2851, 1509, 1220, 1158, 1106, 1072, 946; **Chiral HPLC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); eluent: 10% *i*PrOH in hexanes; flow: 0.5 mL/min; detection: 254 nm; Retention time: t_R = 11.7 min (major) and 12.4 min (minor).

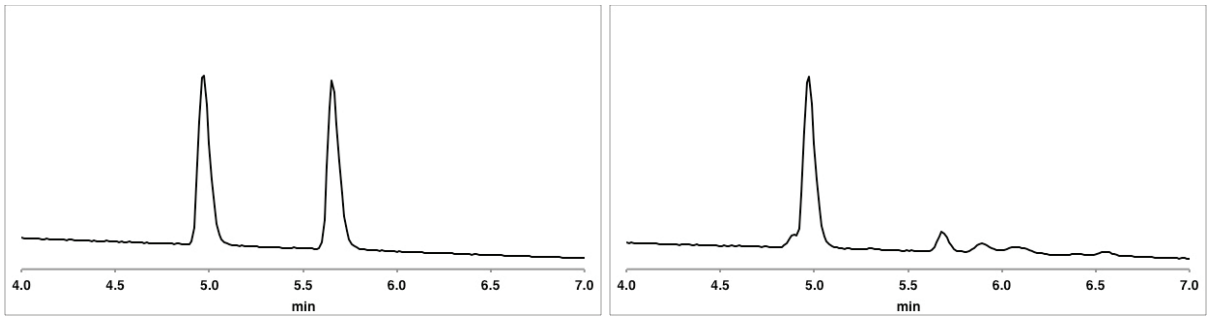


Acylated product: **3-(4-Methoxyphenyl)-1-((4a*S*,8a*R*)-octahydroquinolin-1(2*H*)-yl)propan-1-one**

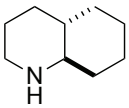


$[\alpha]^{28}_D$ (c = 1.0, CH_3Cl): -97.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.15 (m, 2H), 6.85 (m, 2H), 3.82 (s, 3H), 3.80–3.70 (br., 1H), 3.30 (br., 1H), 3.05 (br., 1H), 2.93 (ap.t, *J* = 7.8 Hz, 2H), 2.55 (m, 2H), 2.05 (br., 1H), 1.80–1.35 (m, 8H), 1.25 (m, 2H), 1.15 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.6, 158.0, 133.7, 129.4, 113.9, 61.4, 55.3, 38.4, 36.0, 33.0, 31.1, 30.9, 26.3, 25.8, 25.4, 22.8; **HRMS** (ESI): calculated for

$[C_{19}H_{28}NO_2]^+$: m/z = 302.2115, found: m/z = 302.2112; **IR** (ν/cm^{-1}, neat) 2927, 2855, 1636, 1613, 1513, 1430, 1246, 1175, 1028, 823; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.0 min (major) and 5.6 min (minor).



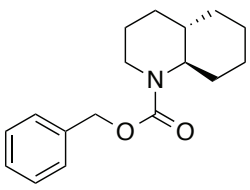
***trans*-Decahydroquinoline (*trans*-117, Scheme 39)**



Racemic *trans*-decahydroquinoline (95.0 mg, 0.68 mmol) was resolved according to the General Procedure A for 48 h. Recovered (Cbz-protected) amine: 45.0 mg (25 % yield, er = 24:76); acylated product: 60 mg (30 % yield, er = 7:93); calculated conversion: 36 %; **s = 21**

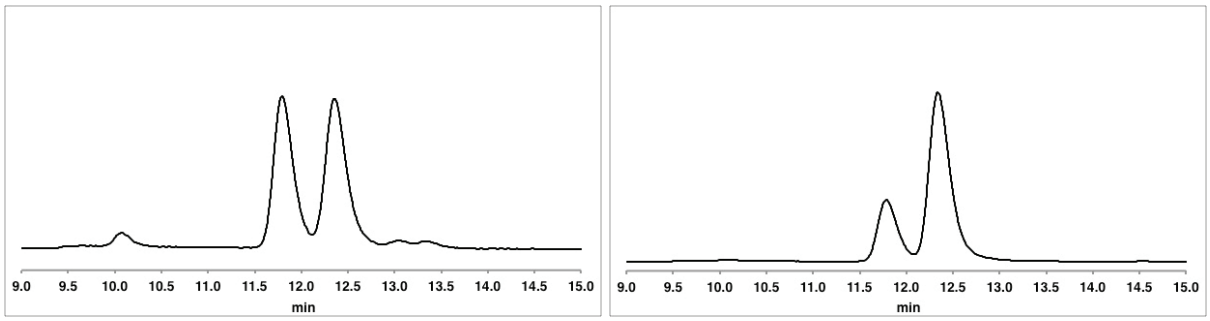
For this substrate opposite absolute configuration was noted. For explanation please see Chapter 3. The absolute stereochemistry was assigned by recovering the amine after kinetic resolution (43 %ee obtained) by acid base extraction and with their optical rotation according to literature values. Recovered amine: **[α]$^{25}_D$** (c = 3.5, EtOH): +1.1 (lit. *4aR,8aS* enantiomer (opposite)[26] : **[α]$^{25}_D$** (c = 3.48, EtOH): -4.6).

The recovered amine was characterized as it's Cbz derivative: **(4a*S*,8a*R*)-benzyl octahydroquinoline-1(2*H*)-carboxylate**

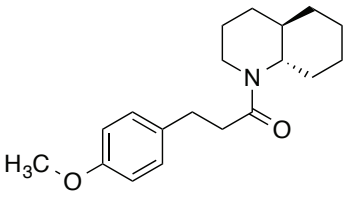


Chiral HPLC: column: Daicel Chiralpak ADH (4.6 x 250 mm); eluent: 10% *i*PrOH in hexanes; flow: 0.5 mL/min; detection: 254 nm; Retention time: t_R = 11.7 min (minor) and 12.4 min (major).

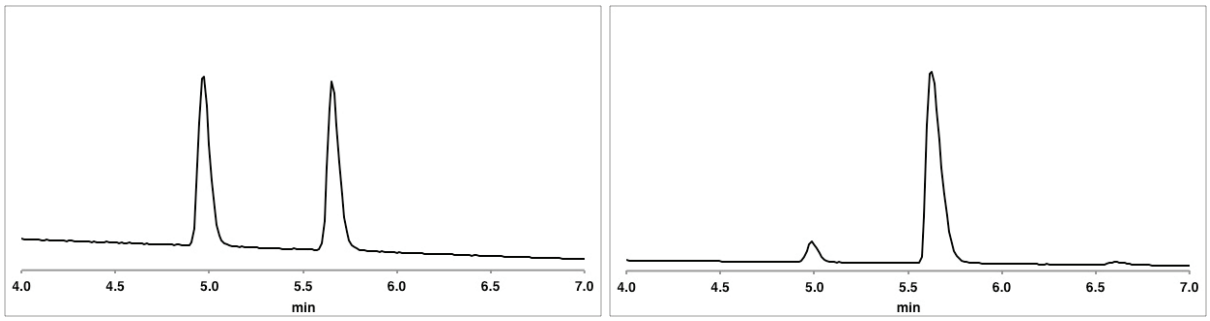
26 Ripperger, H.; Schreiber, K.: Untersuchungen zur Optischen Rotations-Dispersion und zum Circulardichroismus − XII : Zur Absoluten Konfiguration von (−)-*trans*-Dekahydrochinolin. *Tetrahedron* **1969**, *25*, 737–740.



Acylated product: **3-(4-Methoxyphenyl)-1-((4a*R*,8a*S*)-octahydroquinolin-1(2*H*)-yl)propan-1-one**

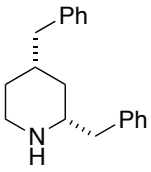


SFC: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.0 min (minor) and 5.6 min (major).



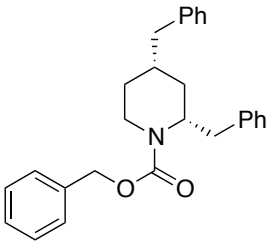
6.5.3 Kinetic Resolution of 2,4-Disubstituted Piperidines

***cis*-2,4-Dibenzylpiperidine (*cis*-98, Table 6, entry 1)**

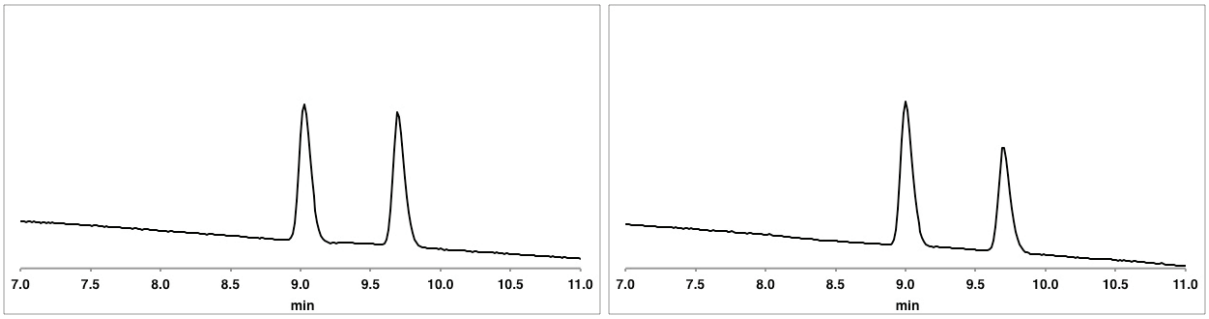


Racemic *cis*-2,4-dibenzylpiperidine (53.0 mg, 0.200 mmol) was resolved according to the General Procedure A for 120 h. Recovered (Cbz-protected) amine: 31.0 mg (39 % yield, er = 57:43); acylated product: 3.0 mg (4 % yield, er = 78:22); calculated conversion: 22 %; **s = 3**

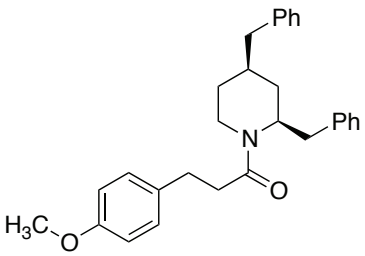
The recovered amine was characterized as its Cbz-derivative: **(2*R*,4*S*)-Benzyl 2,4-dibenzylpiperidine-1-carboxylate**



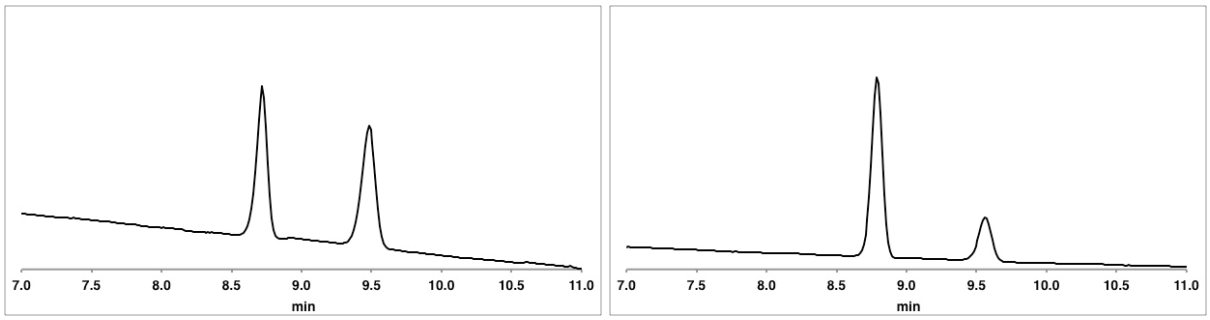
[α]$^{28}_{D}$ (c = 1.0, CH_3Cl): -5.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.46–7.07 (m, 15H), 5.20–5.00 (m, 2H), 4.17–4.06 (m, 1H), 3.93–3.79 (m, 1H), 3.10–2.94 (m, 2H), 2.81 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.60 (dd, *J* = 7.0, 3.3 Hz, 2H), 1.95–1.78 (m, 2H), 1.77–1.67 (m, 1H), 1.34–1.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.9, 140.4, 138.6, 137.0, 129.6, 129.1, 128.6, 128.4, 128.4, 128.0, 128.0, 126.3, 126.1, 67.0, 55.2, 42.7, 40.7, 38.0, 33.4, 32.8, 29.0; **HRMS** (ESI): calculated for $[C_{27}H_{29}NO_2Na]^+$: m/z = 422.2090, found: m/z = 422.2095; **IR** (ν/cm^{-1}, neat) 3027, 2921, 2856, 1695, 1454, 1421, 1246, 1172, 1120, 1084; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 9.0 min (minor) and 9.7 min (major).



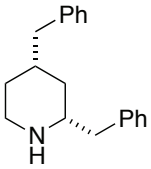
Acylated product: **1-((2*S*,4*R*)-2,4-Dibenzylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



[α]$^{28}_{D}$ (c = 0.27, CH_3Cl): +8.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.35–7.05 (m, 12H), 6.83 (d, *J* = 8.1 Hz, 2H), 4.46 (br, 1H), 3.80 (s, 3H), 3.43 (br, 1H), 3.01–2.81 (m, 3H), 2.76 (dd, *J* = 13.1, 7.5 Hz, 1H), 2.64–2.45 (m, 3H), 1.71 (br, 3H), 1.36–1.16 (m, 3H), 0.94–0.81 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 158.1, 140.3, 138.3, 133.6, 129.6, 129.5, 129.0, 128.4, 126.2, 114.0, 55.4, 42.7, 32.8, 30.8, 29.9; **HRMS** (ESI): calculated for $[C_{29}H_{33}NO_2Na]^+$: m/z = 450.2404, found: m/z = 450.2404; **IR** (ν/cm^{-1}, neat) 3025, 2920, 2854, 1634, 1512, 1453, 1246, 1177, 1033; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.8 min (major) and 9.6 min (minor).

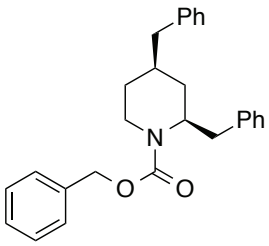


***cis*-2,4-Dibenzylpiperidine (*cis*-98, Table 11, entry 3)**

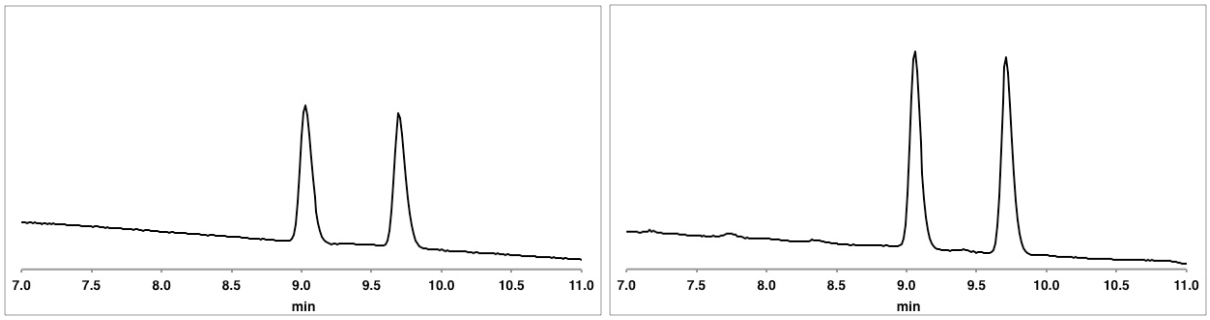


Racemic *cis*-2,4-dibenzylpiperidine (66.3 mg, 0.250 mmol) was resolved according to the General Procedure B for 48 h. Recovered (Cbz-protected) amine: 43.0 mg (43 % yield, er = 49:51); acylated product: 4.0 mg (4 % yield, er = 22:78); calculated conversion: 4 %; **s = 3**

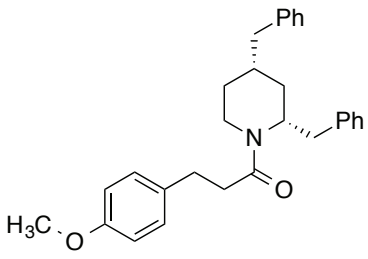
Cbz-derivative: **(2*S*,4*R*)-Benzyl 2,4-dibenzylpiperidine-1-carboxylate**



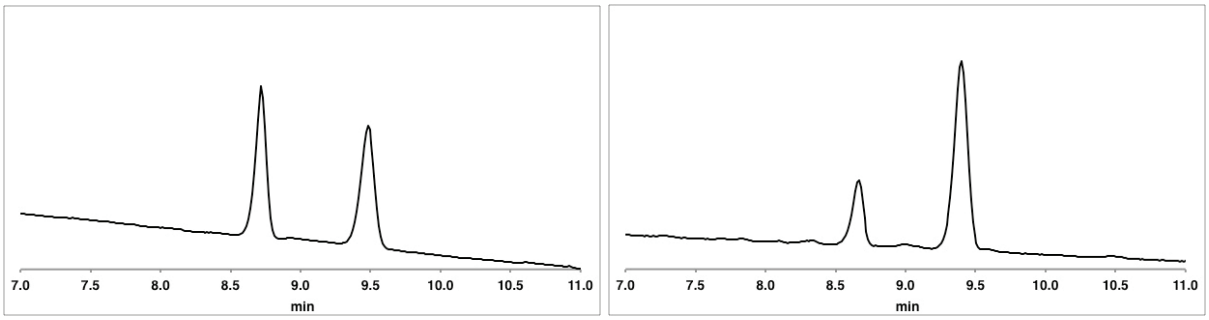
SFC: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 9.0 min (minor) and 9.7 min (major).



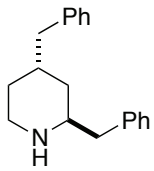
Acylated product: **1-((2*R*,4*S*)-2,4-Dibenzylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



SFC: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.8 min (minor) and 9.6 min (major).

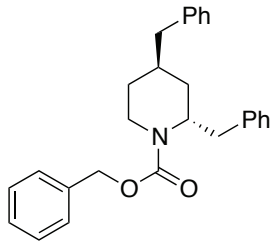


***trans*-2,4-Dibenzylpiperidine (*trans*-98, Table 6, entry 2)**



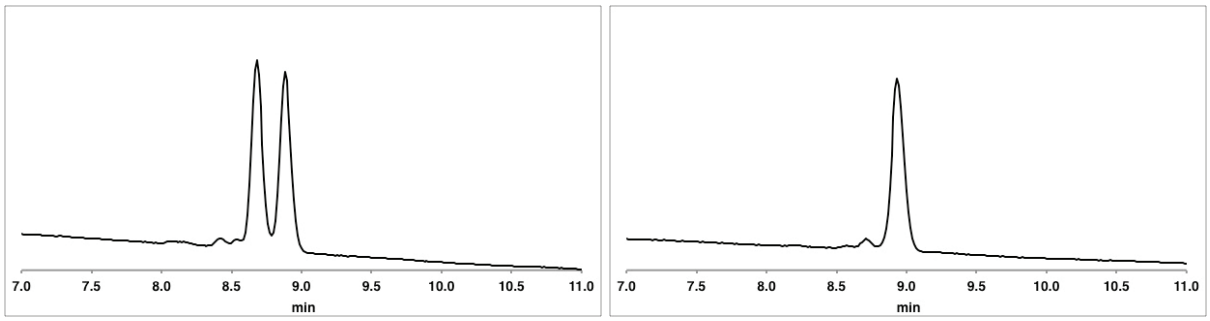
Racemic *trans*-2,4-dibenzylpiperidine (53.0 mg, 0.200 mmol) was resolved according to the General Procedure A for 20 h. Recovered (Cbz-protected) amine: 12.0 mg (15 % yield, er = 3:97); acylated product: 37.0 mg (43 % yield, er = 75:25); calculated conversion: 65 %; **s = 10**

The recovered amine was characterized as its Cbz-derivative: **(2*R*,4*R*)-Benzyl 2,4-dibenzylpiperidine-1-carboxylate**

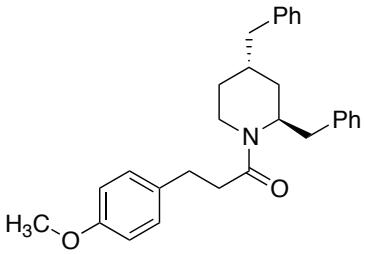


$[\alpha]^{28}_D$ (c = 0.64, CH_3Cl): -4.5; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.47–6.94 (m, 15H), 5.18–5.00 (m, 1.4H), 4.89 (d, *J* = 12.3 Hz, 0.6H), 4.66–4.43 (m, 1H), 4.29–4.07 (m, 1H), 3.03 (td, *J* = 13.4, 3.0 Hz, 1H), 2.94–2.70 (m, 2H), 2.66–2.45 (m, 2H), 2.14–1.99 (m, 1H), 1.86–1.62 (m, 2H), 1.37–1.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.6, 155.4, 140.1, 139.0, 138.8, 137.1, 136.9, 129.3, 129.2, 128.5, 128.45, 128.40, 128.0, 127.9, 126.3, 126.1, 67.1, 67.0, 53.3, 52.7, 43.4, 39.8, 39.6, 37.0, 36.4, 34.0, 32.9, 32.8, 32.2, 32.0; **HRMS** (ESI): calculated for $[C_{27}H_{30}NO_2]^+$: m/z = 400.2271, found: m/z = 400.2280; **IR** (ν/cm^{-1},

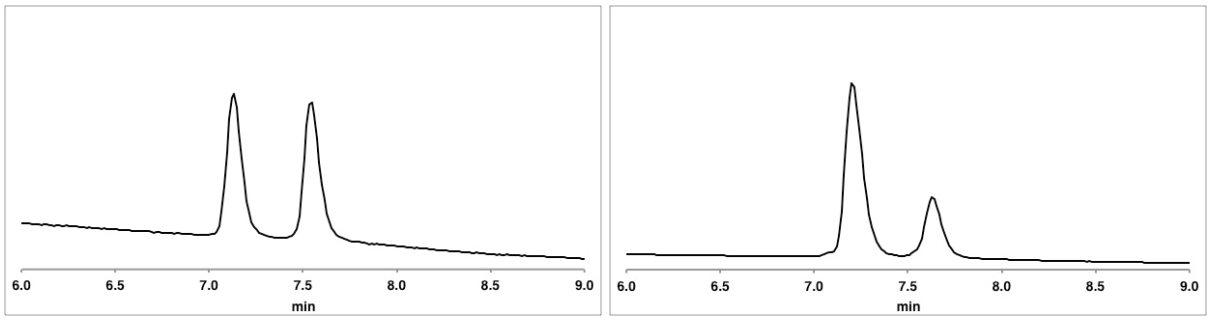
neat) 3026, 2920, 2849, 1723, 1452, 1421, 1328, 1247, 1173, 1088; **SFC**: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.7 min (minor) and 8.9 min (major).



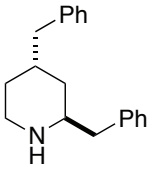
Acylated product: **1-((2*S*,4*S*)-2,4-Dibenzylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{28}_D$ (c = 1.0, CH_3Cl): +2.2; at room temperature the ratio of rotamers was 55:45 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.34–7.06 (m, 10H), 7.02–6.92 (m, 2H), 6.86–6.74 (m, 2H), 5.04 (q, *J* = 7.4 Hz, 0.45H), 4.74–4.68 (m, 0.55H), 4.07–3.97 (m, 0.55H), 3.79 (s, 1.35H), 3.78 (s, 1.65H), 3.65 (dt, *J* = 13.8, 3.9 Hz, 0.45H), 3.08 (td, *J* = 13.4, 2.8 Hz, 0.45H), 3.00–2.90 (m, 0.55H), 2.88–2.62 (m, 3.45H), 2.62–2.38 (m, 3.45H), 2.88–2.62 (m, 0.55H), 2.12–1.97 (m, 1H), 1.97–1.84 (m, 0.55H), 1.75 (dt, *J* = 13.3, 2.9 Hz, 0.55H), 1.69–1.57 (m, 1.45H), 1.18–0.92 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.3, 170.9, 158.1, 158.0, 140.04, 140.01, 138.74, 138.67, 133.7, 133.6, 129.5, 129.4, 129.3, 129.18, 129.16, 128.8, 128.5, 128.43, 128.42, 126.8, 126.3, 126.22, 126.19, 114.0, 113.9, 55.41, 55.39, 49.8, 43.4, 43.3, 41.4, 37.3, 36.7, 36.3, 36.0, 35.7, 35.0, 33.1, 32.9, 32.8, 32.5, 32.2, 30.81, 30.75; **HRMS** (ESI): calculated for $[C_{29}H_{33}NO_2Na]^+$: m/z = 450.2404, found: m/z = 450.2402; **IR** (ν/cm^{-1}, neat) 3025, 2919, 2849, 1637, 1512, 1452, 1425, 1246, 1177, 1035; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.2 min (major) and 7.6 min (minor).

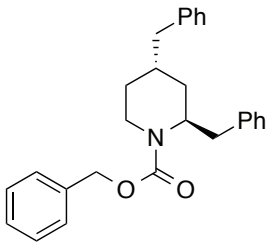


***trans*-2,4-Dibenzylpiperidine (*trans*-98, Table 11, entry 4)**

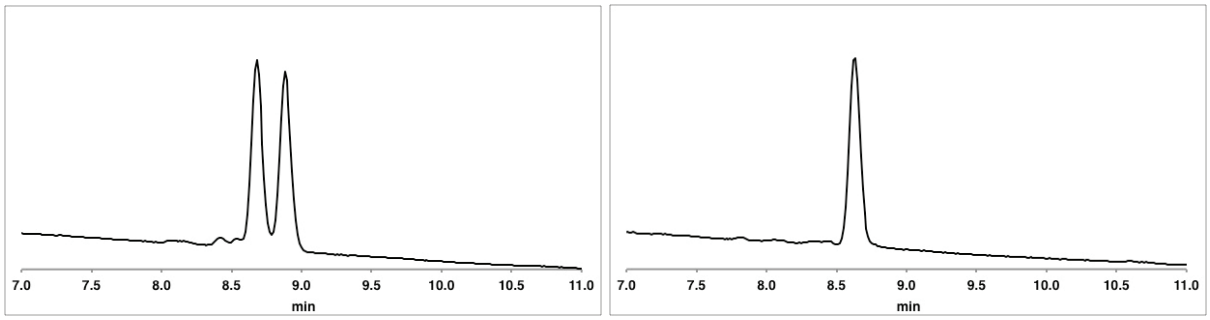


Racemic *trans*-2,4-dibenzylpiperidine (66.3 mg, 0.250 mmol) was resolved according to the General Procedure B for 20 h. Recovered (Cbz-protected) amine: 26.0 mg (26 % yield, er = 99:1); acylated product: 30.0 mg (28 % yield, er = 17:83); calculated conversion: 59 %; **s = 21**

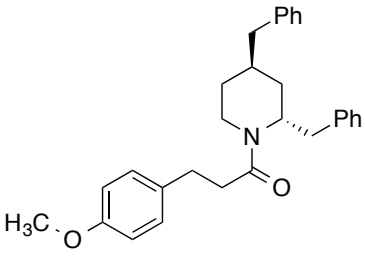
Cbz-derivative: **(2*S*,4*S*)-Benzyl 2,4-dibenzylpiperidine-1-carboxylate**



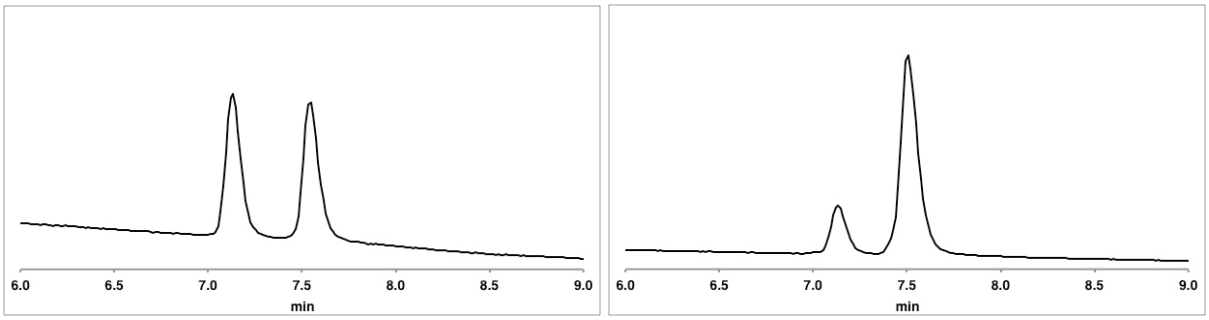
SFC: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.7 min (major) and 8.9 min (minor).



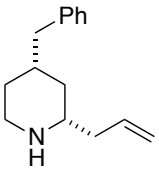
Acylated product: **1-((2*R*,4*R*)-2,4-Dibenzylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



SFC: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.2 min (minor) and 7.6 min (major).

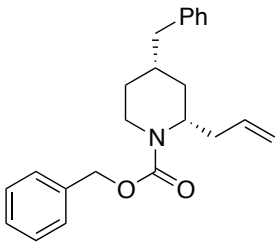


***cis*-2-Allyl-4-benzylpiperidine (*cis*-99, Table 6, entry 3)**



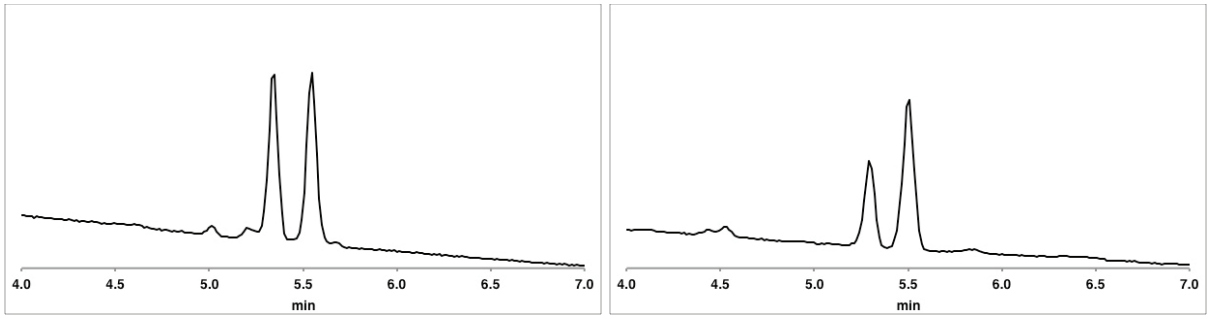
Racemic *cis*-2-allyl-4-benzylpiperidine (43.0 mg, 0.200 mmol) was resolved according to the General Procedure A for 72 h. Recovered (Cbz-protected) amine: 39.0 mg (56 % yield, er = 34:66); acylated product: 22.0 mg (29 % yield, er = 16:84); calculated conversion: 32 %; **s = 7**

The recovered amine was characterized as its Cbz-derivative: **(2*S*,4*S*)-Benzyl 2-allyl-4-benzylpiperidine-1-carboxylate**

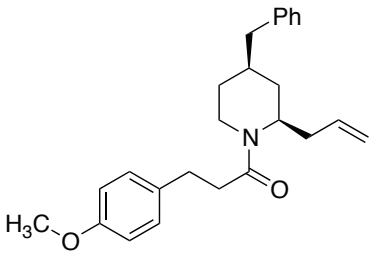


$[\alpha]^{28}_D$ (c = 1.0, CH_3Cl): -21.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.39–7.24 (m, 7H), 7.23–7.16 (m, 1H), 7.16–7.09 (m, 2H), 5.83–5.66 (m, 1H), 5.17–5.08 (m, 2H), 5.07–4.97 (m, 2H), 3.97–3.77 (m, 2H), 3.18–3.05 (m, 1H), 2.59 (qd, *J* = 13.5, 6.9 Hz, 2H), 2.47–2.37 (m, 1H), 2.34–2.24 (m, 1H), 1.94–1.72 (m, 3H), 1.33–1.17 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 156.0, 140.5, 137.1, 135.0, 129.1, 128.6, 128.42, 128.38, 128.0, 127.94, 127.87 126.1, 117.3, 66.9, 53.6, 42.7, 39.2, 38.2, 33.5, 32.9, 29.3; **HRMS** (ESI): calculated for $[C_{23}H_{28}NO_2]^+$: m/z = 350.2115, found: m/z = 350.2109; **IR** (ν/cm^{-1}, neat) 3027, 2918, 2856, 1698, 1421, 1342, 1245, 1130, 1083; **SFC**: column: Daicel Chiralpak OJH

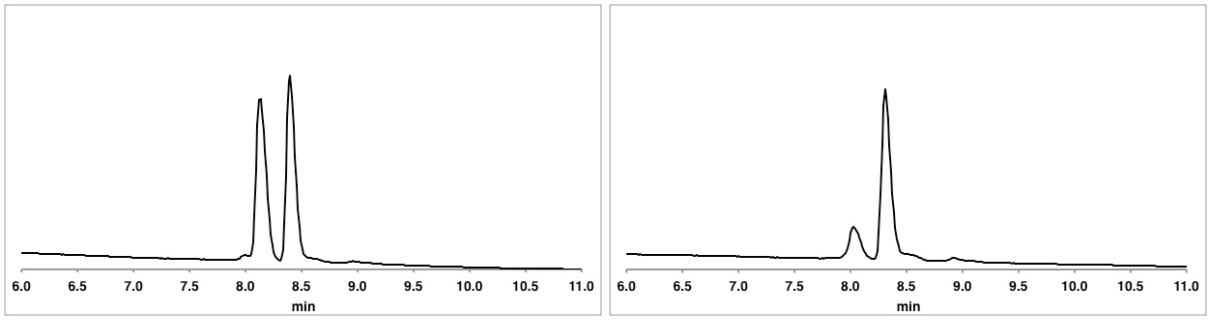
(4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.3 min (minor) and 5.5 min (major).



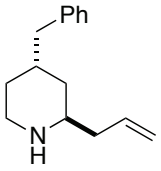
Acylated product: **1-((2*R*,4*R*)-2-Allyl-4-benzylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{28}_D$ (c = 1.0, CH_3Cl): +44.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.34–7.27 (m, 2H), 7.25–7.20 (m, 1H), 7.18–7.10 (m, 4H), 6.88–6.81 (m, 2H), 5.86–5.68 (m, 1H), 5.13–4.96 (m, 2H), 4.31 (br, 1H), 3.81 (s, 3H), 3.50 (br, 1H), 3.09 (br, 1H), 2.93 (t, *J* = 7.8 Hz, 2H), 2.69–2.50 (m, 4H), 2.42–2.18 (m, 2H), 1.82–1.67 (m, 3H), 1.31–1.16 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.6, 158.1, 140.4, 140.3, 134.7, 133.7, 133.6, 129.5, 129.0, 128.44, 128.42, 126.2, 126.1, 117.4, 114.0, 55.4, 51.7, 42.5, 38.8, 35.7, 32.8, 32.7, 30.9, 29.5; **HRMS** (ESI): calculated for $[C_{25}H_{32}NO_2]^+$: m/z = 378.2428, found: m/z = 378.2423; **IR** (ν/cm^{-1}, neat) 2930, 1637, 1512, 1453, 1440, 1246, 1177, 1034; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.0 min (major) and 8.3 min (minor).

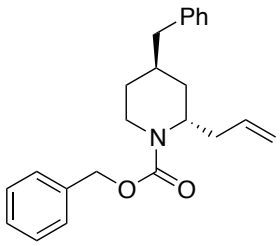


***trans*-2-Allyl-4-benzylpiperidine (*trans*-99, Table 6, entry 4)**

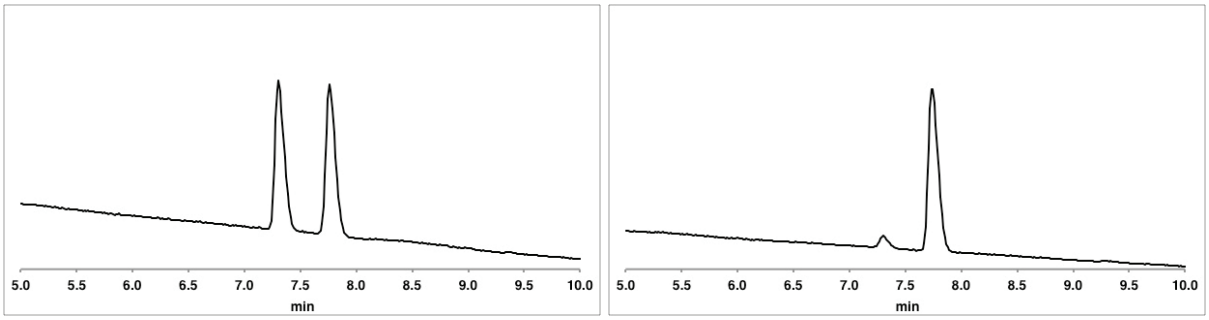


Racemic *trans*-2-allyl-4-benzylpiperidine (43.0 mg, 0.200 mmol) was resolved according to the General Procedure A for 20 h. Recovered (Cbz-protected) amine: 32.0 mg (46 % yield, er = 6:94); acylated product: 34.0 mg (45 % yield, er = 9:91); calculated conversion: 52 %; **s = 29**

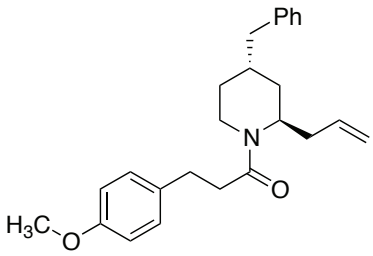
The recovered amine was characterized as its Cbz-derivative: **(2*S*,4*R*)-Benzyl 2-allyl-4-benzylpiperidine-1-carboxylate**



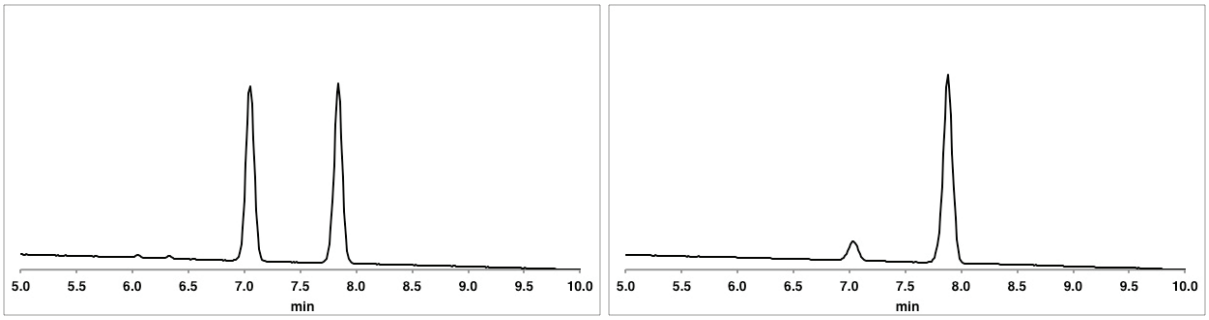
$[\alpha]^{28}_D$ (c = 1.0, CH_3Cl): +28.6; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.43–7.26 (m, 7H), 7.28–7.19 (m, 1H), 7.20–7.12 (m, 2H), 5.84–5.57 (m, 1H), 5.25–5.08 (m, 2H), 5.08–4.90 (m, 2H), 4.53–4.44 (m, 0.5H), 4.44–4.34 (m, 0.5H), 4.16 (d, *J* = 13.7 Hz, 0.5H), 4.07 (d, *J* = 13.9 Hz, 0.5H), 2.95–2.78 (m, 1H), 2.59–2.46 (m, 2H), 2.46–2.35 (m, 1H), 2.32–2.14 (m, 1H), 2.01–1.86 (m, 1H), 1.76–1.58 (m, 2H), 1.41–1.26 (m, 1H), 1.25–1.05 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.7, 155.5, 140.1, 137.1, 135.3, 135.1, 129.2, 128.5, 128.4, 128.0, 127.8, 126.1, 117.1, 117.0, 67.0, 50.8, 50.5, 43.5, 39.3, 39.2, 35.3, 35.0, 34.8, 34.4, 32.4, 32.1, 31.8; **HRMS** (ESI): calculated for $[C_{23}H_{28}NO_2]^+$: m/z = 350.2115, found: m/z = 350.2119; **IR** (ν/cm^{-1}, neat) 3029, 2919, 2848, 1696, 1447, 1424, 1326, 1248, 1226, 1174, 1076; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.3 min (minor) and 7.8 min (major).



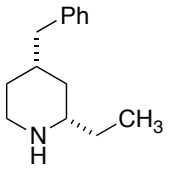
Acylated product: **1-((2*R*,4*S*)-2-Allyl-4-benzylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -19.8; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.34–7.27 (m, 2H), 7.27–7.19 (m, 1H), 7.19–7.10 (m, 4H), 6.89–6.82 (m, 2H), 5.78–5.55 (m, 1H), 5.08–4.91 (m, 2.5H), 4.67–4.60 (m, 0.5H), 4.01–3.92 (m, 0.5H), 3.81 (s, 1.5H), 3.82 (s, 1.5H), 3.66–3.58 (m, 0.5H), 3.05–2.87 (m, 2.5H), 2.70–2.29 (m, 5.5H), 2.29–2.18 (m, 1H), 2.02–1.89 (m, 1H), 1.73–1.58 (m, 2H), 1.32–1.20 (m, 0.5H), 1.16–0.89 (m, 1.5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.0, 170.9, 158.10, 158.09, 140.01, 139.96, 135.4, 134.3, 133.65, 133.63, 129.52, 129.49, 129.13, 129.11, 128.40, 128.39, 126.2, 118.0, 116.7, 114.02, 113.98, 55.4, 53.0, 47.6, 43.4, 40.9, 36.5, 35.9, 35.6, 35.4, 35.3, 34.9, 34.3, 32.6, 32.4, 31.9, 31.0, 30.9; **HRMS** (ESI): calculated for $[C_{25}H_{32}NO_2]^+$: m/z = 378.2428, found: m/z = 378.2427; **IR** (ν/cm^{-1}, neat) 2930, 2847, 1638, 1513, 1429, 1246, 1177, 1036, 825; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.0 min (major) and 7.9 min (minor).

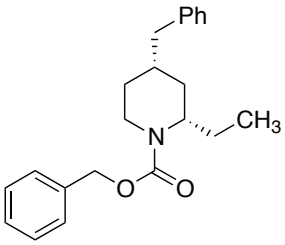


***cis*-4-Benzyl-2-ethylpiperidine (*cis*-100, Table 6, entry 5)**

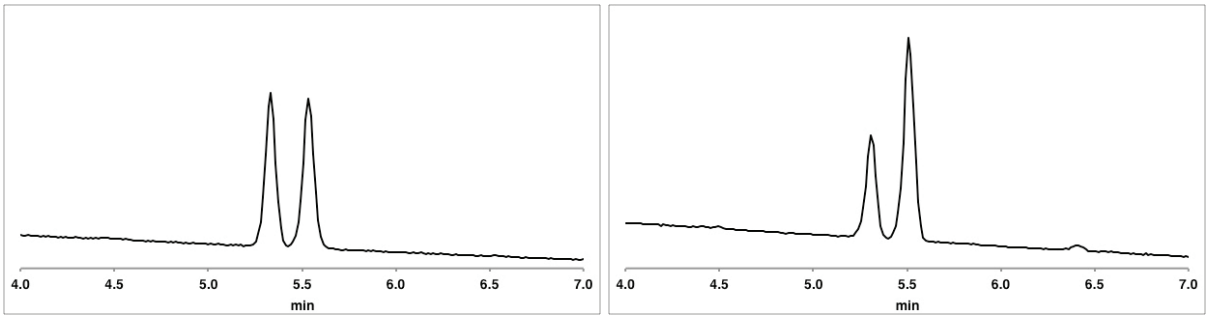


Racemic *cis*-2-ethyl-4-benzylpiperidine (40.6 mg, 0.200 mmol) was resolved according to the General Procedure A for 96 h. Recovered (Cbz-protected) amine: 31.0 mg (46 % yield, er = 32:68); acylated product: 25.0 mg (34 % yield, er = 20:80); calculated conversion: 38 %; **s = 6**

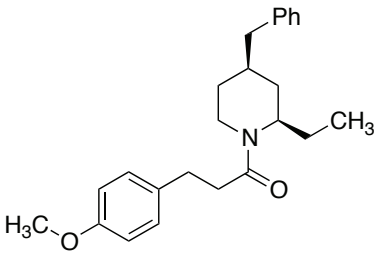
The recovered amine was characterized as its Cbz-derivative: **(2*S*,4*S*)-Benzyl 4-benzyl-2-ethylpiperidine-1-carboxylate**



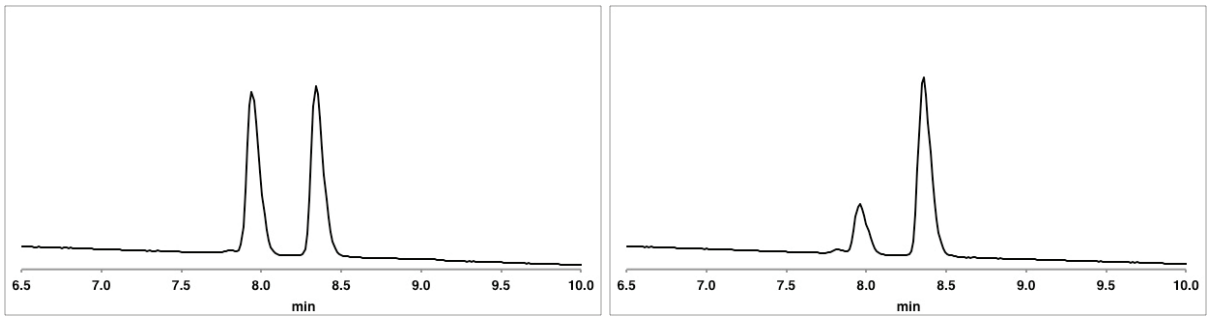
[α]$^{28}_{D}$ (c = 1.0, CH_3Cl): -23.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.44–7.26 (m, 7H), 7.26–7.19 (m, 1H), 7.19–7.13 (m, 2H), 5.15 (s, 2H), 3.88–3.78 (m, 2H), 3.19–3.07 (m, 1H), 2.71–2.53 (m, 2H), 1.94–1.78 (m, 3H), 1.78–1.67 (m, 1H), 1.62–1.47 (m, 1H), 1.32–1.14 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 156.2, 140.6, 137.2, 129.1, 128.5, 128.4, 127.9, 127.8, 126.1, 66.9, 55.3, 42.6, 38.0, 33.5, 33.1, 29.4, 27.6, 10.7; **HRMS** (ESI): calculated for $[C_{22}H_{28}NO_2]^+$: m/z = 338.2115, found: m/z = 338.2114; **IR** (ν/cm^{-1}, neat) 2919, 1697, 1456, 1419, 1245; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.3 min (minor) and 5.5 min (major).



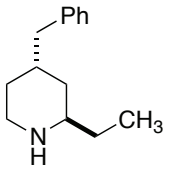
Acylated product: **1-((2*R*,4*R*)-4-Benzyl-2-ethylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



[α]$^{29}_{D}$ (c = 1.0, CH_3Cl): +43.0; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.34–7.28 (m, 2H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.18–7.11 (m, 4H), 6.91–6.80 (m, 2H), 4.20 (br, 1H), 3.81 (s, 3H), 3.47 (br, 1H), 3.11 (br, 1H), 2.94 (t, *J* = 7.8 Hz, 2H), 2.68–2.47 (m, 4H), 1.89–1.43 (m, 5H), 1.32–1.10 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.6, 158.1, 140.4, 133.7, 129.5, 129.5, 129.1, 128.4, 128.4, 126.1, 114.0, 55.4, 53.2, 42.5, 38.8, 35.7, 32.8, 30.9, 29.8, 27.2, 10.6; **HRMS** (ESI): calculated for $[C_{24}H_{32}NO_2]^+$: m/z = 366.2428, found: m/z = 366.2428; **IR** (ν/cm^{-1}, neat) 3279, 2970, 1699, 1655, 1638, 1616, 1513, 1456, 1247, 1177, 1036, 825; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.0 min (minor) and 8.4 min (major).



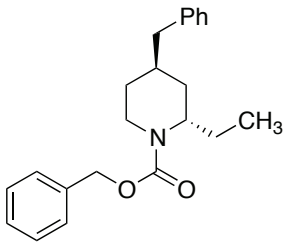
***trans*-4-Benzyl-2-ethylpiperidine (*trans*-100, Table 6, entry 6)**



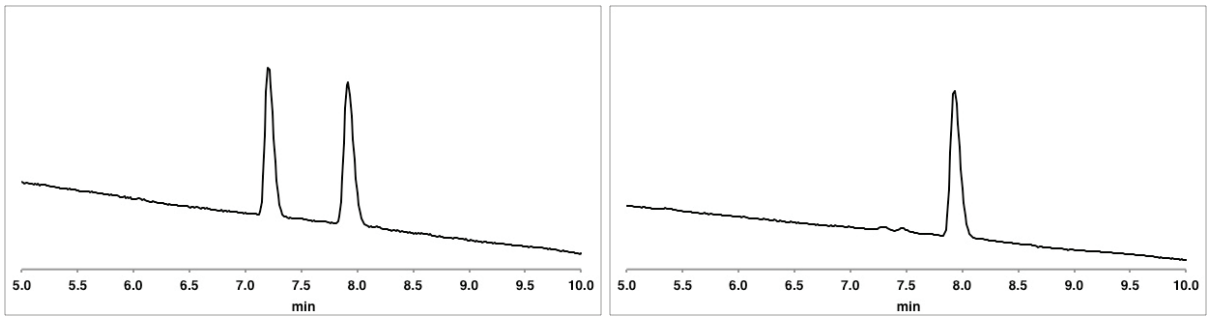
Racemic *trans*-2-ethyl-4-benzylpiperidine (40.6 mg, 0.200 mmol) was resolved according to the General Procedure A for 20 h. Recovered (Cbz-protected) amine: 13.0 mg (19 % yield, er = 2:98); acylated product: 29.0 mg (40 % yield, er = 80:20); calculated conversion: 62 %; **s = 15**

The absolute stereochemistry was assigned by recovering the amine after kinetic resolution by acid base extraction. This was converted to the 4-nitrophenylsulfonamide and crystallized to obtain a crystal for X-ray crystallography. See section 5.

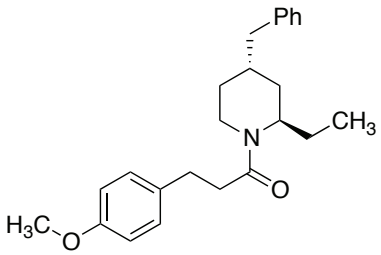
The recovered amine was characterized as its Cbz-derivative: **(2*S*,4*R*)-Benzyl 4-benzyl-2-ethylpiperidine-1-carboxylate**



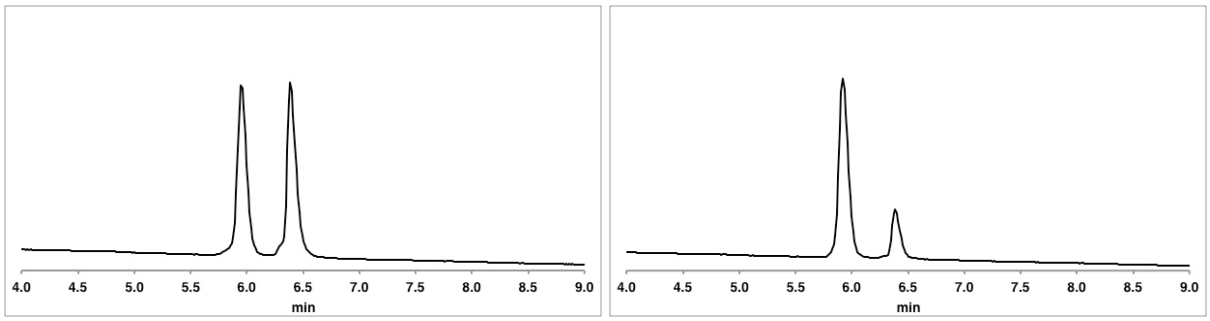
$[\alpha]^{29}_{D}$ (c = 0.73, CH_3Cl): +5.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.43–7.27 (m, 7H), 7.26–7.19 (m, 1H), 7.18–7.12 (m, 2H), 5.20–5.09 (m, 2H), 4.41–4.00 (m, 2H), 2.82 (q, *J* = 13.8 Hz, 1H), 2.60–2.42 (m, 2H), 1.99–1.84 (m, 1H), 1.71–1.58 (m, 3H), 1.53–1.27 (m, 2H), 1.23–1.04 (m, 1H), 0.93–0.77 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.7, 155.5, 140.1, 137.1, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 126.0, 66.9, 52.6, 52.4, 43.5, 39.0, 38.8, 35.2, 34.7, 32.5, 32.1, 31.9, 23.3, 23.0, 10.8; **HRMS** (ESI): calculated for $[C_{22}H_{28}NO_2]^+$: m/z = 338.2115, found: m/z = 338.2109; **IR** (ν/cm^{-1}, neat) 2962, 2929, 1696, 145, 1424, 1248, 1172, 1070; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.3 min (minor) and 7.9 min (major).



Acylated product: **1-((2*R*,4*S*)-4-Benzyl-2-ethylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**

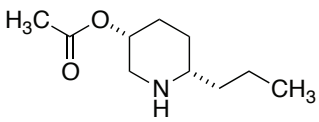


$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -6.4; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.34–7.27 (m, 2H), 7.26–7.19 (m, 1H), 7.19–7.11 (m, 4H), 6.86 (dd, *J* = 8.6, 3.9 Hz, 2H), 4.82–4.73 (m, 0.5H), 4.64–4.58 (m, 0.5H), 3.86–3.78 (m, 3.5H), 3.66–3.56 (m, 0.5H), 3.00–2.90 (m, 2.5H), 2.75–2.34 (m, 4.5H), 2.01–1.85 (m, 1H), 1.73–1.54 (m, 3H), 1.54–1.42 (m, 1H), 1.29–1.21 (m, 0.5H), 1.14–1.00 (m, 1H), 1.00–0.87 (m, 0.5H), 0.82 (ap. td, *J* = 7.4, 4.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.1, 170.9, 158.10, 158.08, 140.10, 140.07, 133.68, 133.67, 129.52, 129.50, 129.14, 129.12, 128.4, 126.1, 114.03, 113.99, 55.4, 54.7, 49.6, 43.5, 40.8, 36.3, 35.9, 35.6, 35.5, 34.7, 32.68, 32.65, 32.57, 32.0, 31.1, 31.0, 23.7, 23.0, 11.0, 10.8; **HRMS** (ESI): calculated for $[C_{24}H_{32}NO_2]^+$: m/z = 366.2428, found: m/z = 366.2423; **IR** (ν/cm^{-1}, neat) 2961, 2930, 1635, 1513, 1453, 1434, 1246, 1177, 1035, 825; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 5.9 min (major) and 6.4 min (minor).



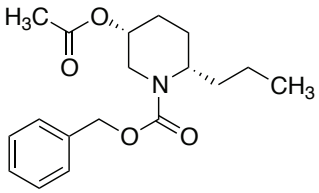
6.5.4 Kinetic Resolution of 2,5-Disubstituted Piperidines

***cis*-6-Propylpiperidin-3-yl acetate (*cis*-110, Table 7, entry 1)**

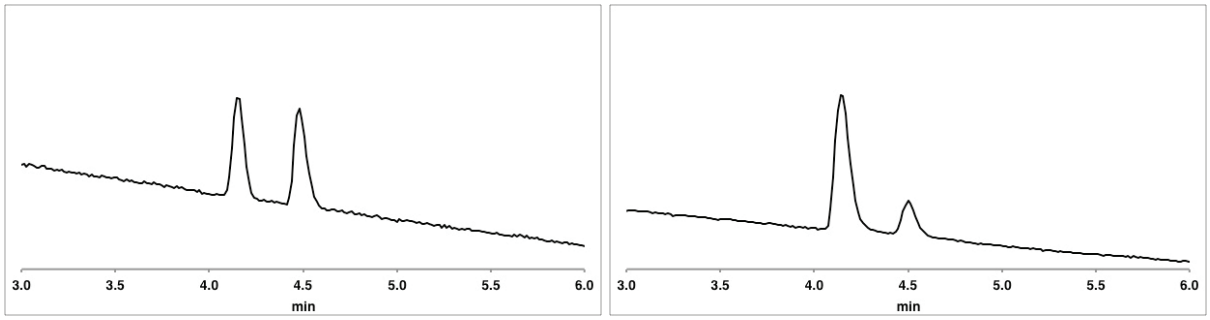


Racemic *cis*-6-propylpiperidin-3-yl acetate (37.0 mg, 0.200 mmol) was resolved according to the General Procedure A for 24 h. Recovered (Cbz-protected) amine: 28.0 mg (44 % yield, er = 81:19); acylated product: 23.0 mg (33 % yield, er = 92:8); calculated conversion: 42 %; **s = 22**

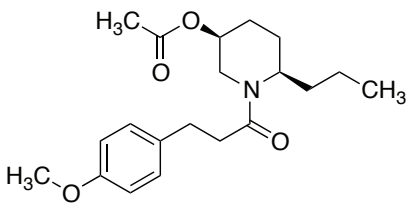
The recovered amine was characterized as its Cbz-derivative: **(2*S*,5*R*)-Benzyl 5-acetoxy-2-propylpiperidine-1-carboxylate**



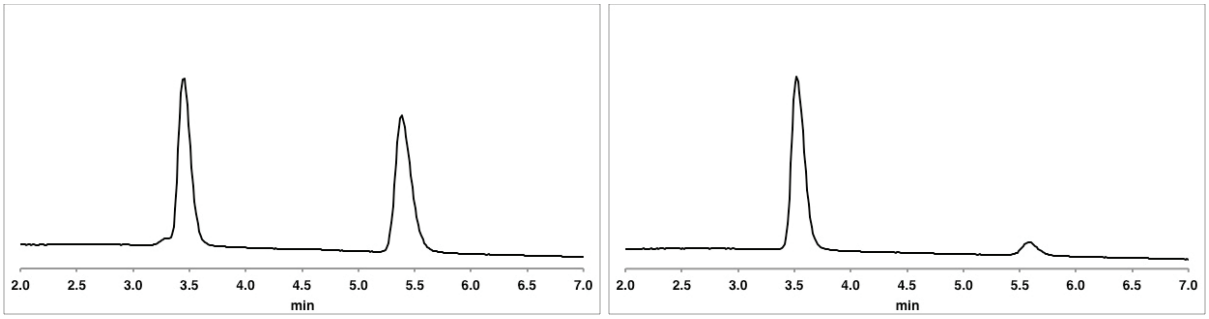
$[\alpha]^{29}_{D}$ (c = 1.0, CH_3Cl): +1.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.39–7.27 (m, 5H), 5.13 (s, 2H), 4.73–4.58 (m, 1H), 4.24 (br, 2H), 2.74 (t, *J* = 11.9 Hz, 1H), 2.03 (s, 3H), 1.98–1.89 (m, 1H), 1.78–1.52 (m, 4H), 1.49–1.17 (m, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.2, 155.5, 136.8, 128.6, 128.1, 128.0, 69.2, 67.3, 49.8, 42.1, 31.6, 26.7, 25.2, 21.3, 19.5, 14.1; **HRMS** (ESI): calculated for $[C_{18}H_{25}NO_4Na]^+$: m/z = 342.1676, found: m/z = 342.1676; **IR** (ν/cm^{-1}, neat) 2959, 2934, 2872, 1739, 1699, 1424, 1364, 1329, 1238, 1153, 1040; **SFC**: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 4.2 min (major) and 4.6 min (minor).



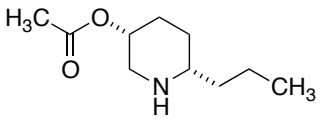
Acylated product: **(3*S*,6*R*)-1-(3-(4-Methoxyphenyl)propanoyl)-6-propylpiperidin-3-yl acetate**



$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -7.5; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.20–7.08 (m, 2H), 6.88–6.77 (m, 2H), 4.81–4.67 (m, 1H), 4.64–4.43 (m, 1H), 3.87–3.73 (m, 4H), 2.96–2.78 (m, 2.5H), 2.74–2.46 (m, 2.5H), 2.07–1.99 (m, 3H), 1.98–1.83 (m, 1H), 1.73–1.36 (m, 5H), 1.32–1.16 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.3, 170.4, 170.0, 158.14, 158.08, 133.41, 133.38, 129.50, 129.47, 114.1, 114.0, 69.8, 68.9, 55.40, 55.37, 52.0, 47.0, 43.9, 39.5, 35.9, 35.7, 32.2, 31.3, 30.9, 30.8, 27.1, 26.2, 25.3, 21.23, 21.21, 19.8, 19.5, 14.2, 14.1; **HRMS** (ESI): calculated for $[C_{20}H_{30}NO_4]^+$: m/z = 348.2169, found: m/z = 348.2174; **IR** (ν/cm^{-1}, neat) 2955, 2934, 2872, 1737, 1645, 1513, 1428, 1366, 1245, 1038, 826; **SFC**: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.5 min (major) and 5.6 min (minor).

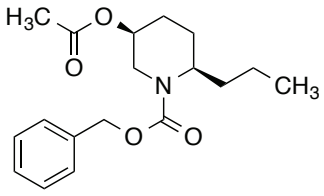


***cis*-6-Propylpiperidin-3-yl acetate (*cis*-110, Table 11, entry 5)**

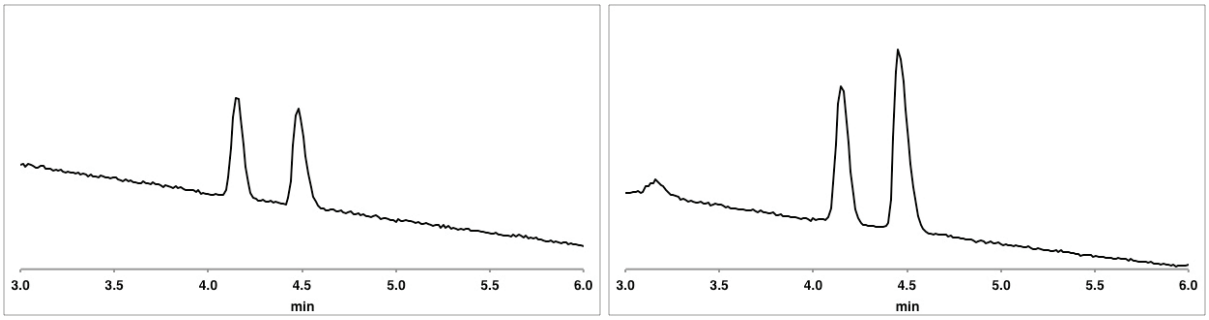


Racemic *cis*-6-propylpiperidin-3-yl acetate (46.3 mg, 0.250 mmol) was resolved according to the General Procedure B for 20 h. Recovered (Cbz-protected) amine: 28.0 mg (35 % yield, er = 41:59); acylated product: 17.0 mg (20 % yield, er = 6:94); calculated conversion: 17 %; **s = 19**

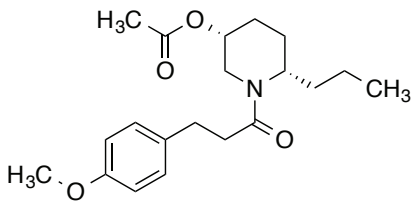
Cbz-derivative: **(2*R*,5*S*)-Benzyl 5-acetoxy-2-propylpiperidine-1-carboxylate**



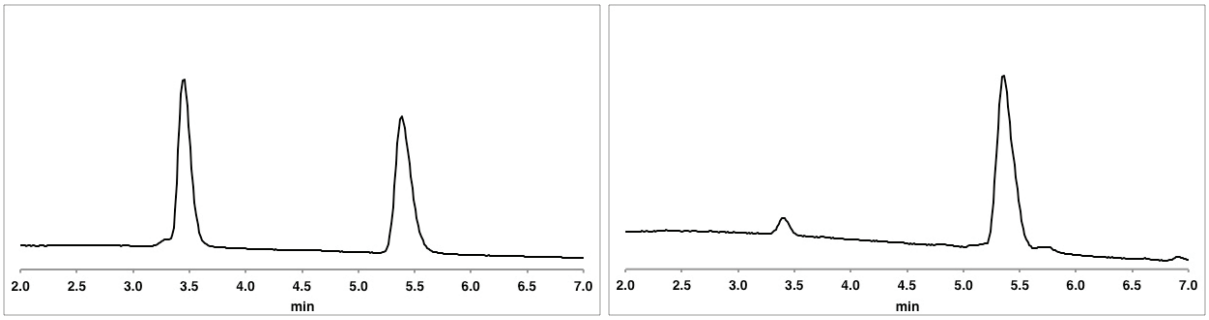
SFC: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 4.2 min (minor) and 4.6 min (major).



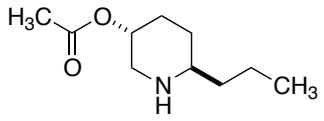
Acylated product: **(3*R*,6*S*)-1-(3-(4-Methoxyphenyl)propanoyl)-6-propylpiperidin-3-yl acetate**



SFC: column: Daicel Chiralpak ASH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.5 min (minor) and 5.6 min (major).

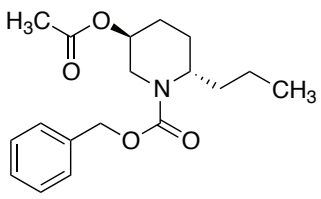


***trans*-6-Propylpiperidin-3-yl acetate (*trans*-110, Table 7, entry 2)**

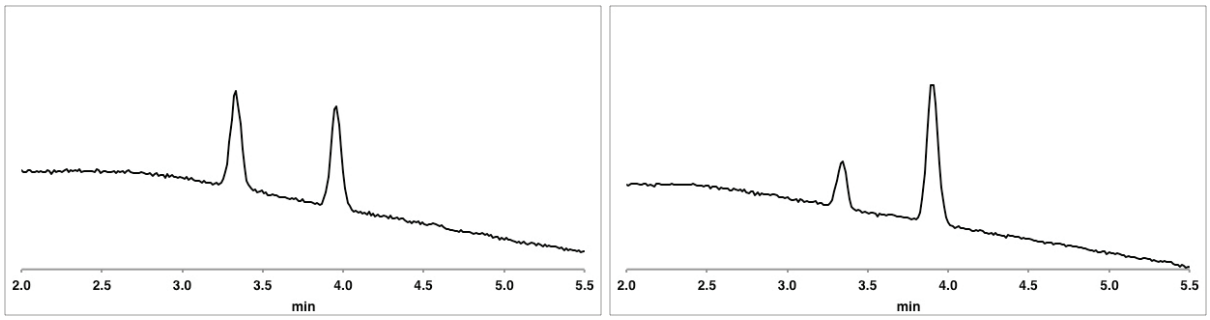


Racemic *trans*-6-propylpiperidin-3-yl acetate (37.0 mg, 0.200 mmol) was resolved according to the General Procedure A for 96 h. Recovered (Cbz-protected) amine: 30.0 mg (47 % yield, er = 22:78); acylated product: 23.0 mg (33 % yield, er = 8:92); calculated conversion: 40 %; **s = 20**

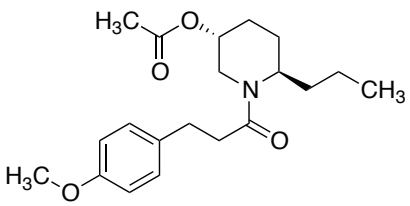
The recovered amine was characterized as its Cbz-derivative: **(2*S*,5*S*)-Benzyl 5-acetoxy-2-propylpiperidine-1-carboxylate**



$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -2.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.42–7.26 (m, 5H), 5.25–5.02 (m, 2H), 4.86 (br, 1H), 4.38 (br, 1H), 4.25 (d, *J* = 15.0 Hz, 1H), 3.00 (d, *J* = 14.8 Hz, 1H), 2.01–1.66 (m, 7H), 1.46–1.21 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 170.7, 156.2, 137.1, 128.6, 128.0, 127.8, 67.2, 67.1, 50.2, 42.0, 31.5, 23.4, 23.0, 21.2, 19.6, 14.1; **HRMS** (ESI): calculated for $[C_{18}H_{25}NO_4Na]^+$: m/z = 342.1676, found: m/z = 342.1678; **IR** (ν/cm^{-1}, neat) 2955, 2934, 2869, 1737, 1698, 1427, 1359, 1250, 1229, 1156, 1100, 1023; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.4 min (minor) and 3.9 min (major).

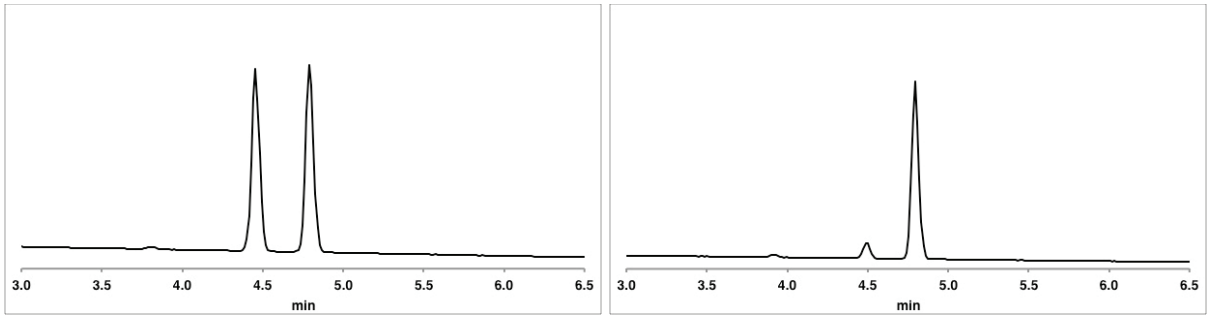


Acylated product: **(3*R*,6*R*)-1-(3-(4-Methoxyphenyl)propanoyl)-6-propylpiperidin-3-yl acetate**

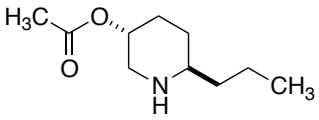


$[\alpha]^{29}_D$ (c = 1.0, CH_3Cl): -2.7; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.18–7.07 (m, 2H), 6.86–6.78 (m, 2H), 4.99–4.81 (m, 1.6H), 4.75 (d, *J* = 14.7 Hz, 0.4H), 3.91 (br, 0.4H), 3.81 (d, *J* = 14.6 Hz, 0.6H), 3.77 (s, 3H), 3.17 (dd, *J* = 15.0, 1.9 Hz, 0.6H), 2.97–2.84 (m, 2H), 2.79–2.42 (m, 2.4H), 2.00 (s, 1.2H), 1.99 (s, 1.8H), 1.96–1.69 (m, 3H), 1.67–1.34 (m, 3H), 1.33–1.14 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.9, 171.6, 170.6, 158.1, 133.6, 133.5, 129.41, 129.37, 114.0, 67.9, 67.1, 55.4, 52.4, 47.4, 43.7, 39.4, 35.6, 35.4, 32.1, 31.3, 30.8, 30.7, 23.6, 23.4, 22.7, 21.3, 21.2, 19.8, 19.6, 14.2, 14.1; **HRMS** (ESI): calculated for $[C_{20}H_{30}NO_4]^+$: m/z = 348.2169, found: m/z = 348.2165; **IR** (ν/cm^{-1}, neat) 2955, 2934, 2871, 1736, 1639, 1513, 1441, 1374, 1246, 1033, 1023, 826; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to

50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 4.5 min (minor) and 4.8 min (major).

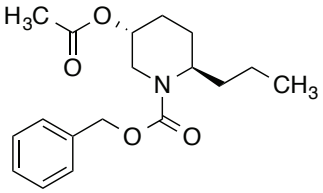


trans-6-Propylpiperidin-3-yl acetate (_trans_-110, Table 11, entry 6)

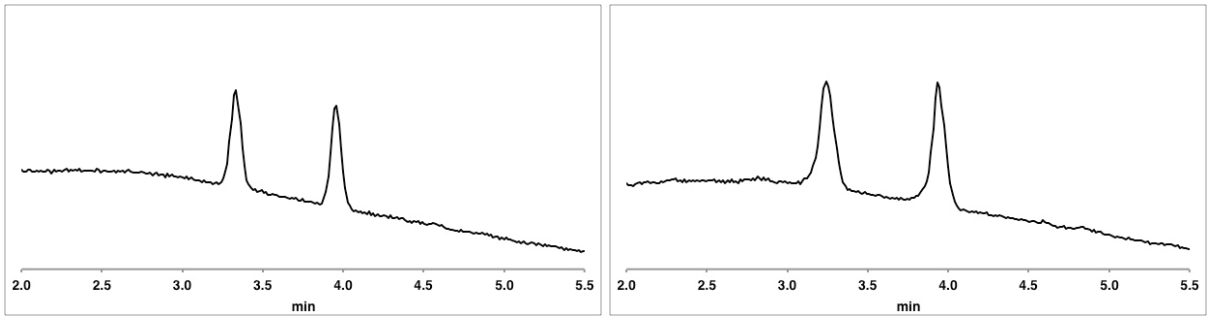


Racemic *trans*-6-propylpiperidin-3-yl acetate (46.3 mg, 0.250 mmol) was resolved according to the General Procedure B for 48 h. Recovered (Cbz-protected) amine: 43.0 mg (54 % yield, er = 52:48); acylated product: 8.0 mg (9 % yield, er = 89:11); calculated conversion: 5 %; **s = 8**

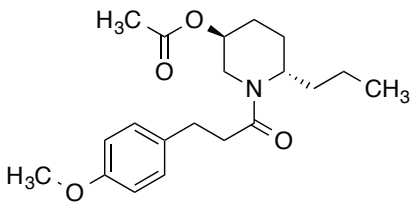
The recovered amine was characterized as its Cbz-derivative: **(2*R*,5*R*)-Benzyl 5-acetoxy-2-propylpiperidine-1-carboxylate**



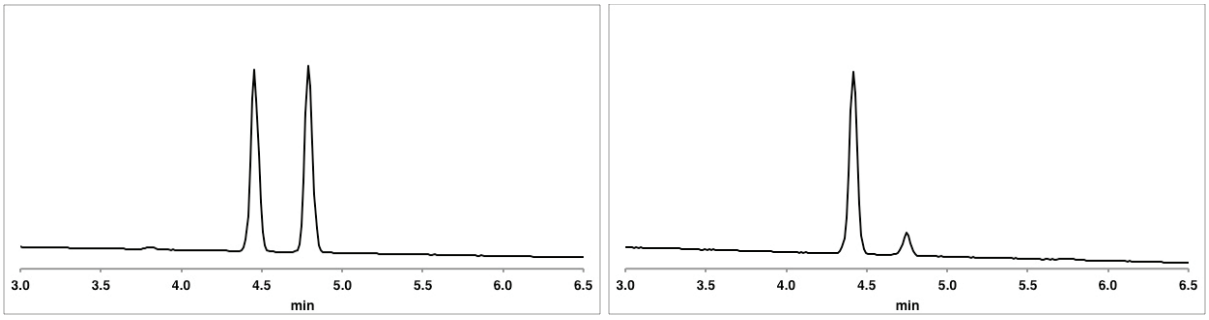
SFC: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 3.4 min (major) and 3.9 min (minor).



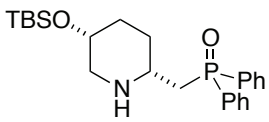
Acylated product: **(3*S*,6*S*)-1-(3-(4-Methoxyphenyl)propanoyl)-6-propylpiperidin-3-yl acetate**



SFC: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 4.5 min (major) and 4.8 min (minor).

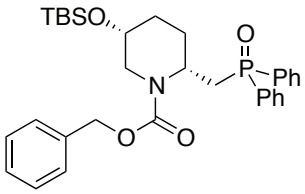


***cis*-((5-((*tert*-Butyldimethylsilyl)oxy)piperidin-2-yl)methyl)diphenylphosphine oxide (*cis*-105, Table 7, entry 3)**



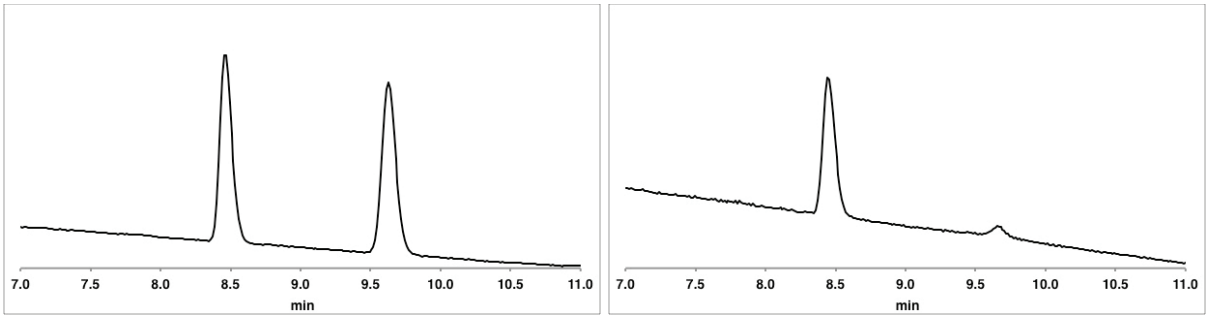
Racemic *cis*-((5-((*tert*-butyldimethylsilyl)oxy)piperidin-2-yl)methyl)diphenylphosphine oxide (85.8 mg, 0.200 mmol) was resolved according to the General Procedure A for 72 h. Recovered (Cbz-protected) amine: 25.0 mg (22 % yield, er = 90:10); acylated product: 33.0 mg (28 % yield, er = 84:16); calculated conversion: 54 %; **s = 13**

The recovered amine was characterized as its Cbz-derivative: **(2*R*,5*R*)-Benzyl 5-((*tert*-butyldimethylsilyl)oxy)-2-((diphenylphosphoryl)methyl)piperidine-1-carboxylate**

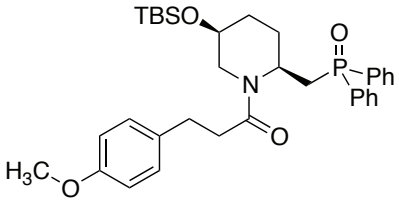


[α]$^{29}_{D}$ (c = 1.0, CH_3Cl): +10.1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.00–7.61 (m, 4H), 7.61–7.40 (m, 5H), 7.40–7.21 (m, 6H), 5.17–4.85 (m, 2H), 4.75–4.65 (m, 1H), 4.14–3.89 (m, 1H), 3.52 (br, 1H), 2.80–2.35 (m, 3H), 2.15–1.98 (m, 1H), 1.85–1.75 (m, 1H), 1.69–1.51 (m, 2H), 0.86 (s, 9H), 0.12– -0.07 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 154.7, 136.6, 134.7, 134.5, 133.7, 133.5, 132.3, 131.9, 131.2, 131.0, 130.9, 130.5, 130.4, 128.8, 128.7, 128.6, 128.1, 127.7, 67.8, 67.5, 67.3, 46.3, 46.0, 45.9, 45.8, 31.0, 30.6, 30.3, 30.0, 29.1, 27.8, 27.2, 25.9, 25.8, 18.2, -4.6, -4.7; **HRMS** (ESI): calculated for $[C_{32}H_{43}NO_4PSi]^+$: m/z

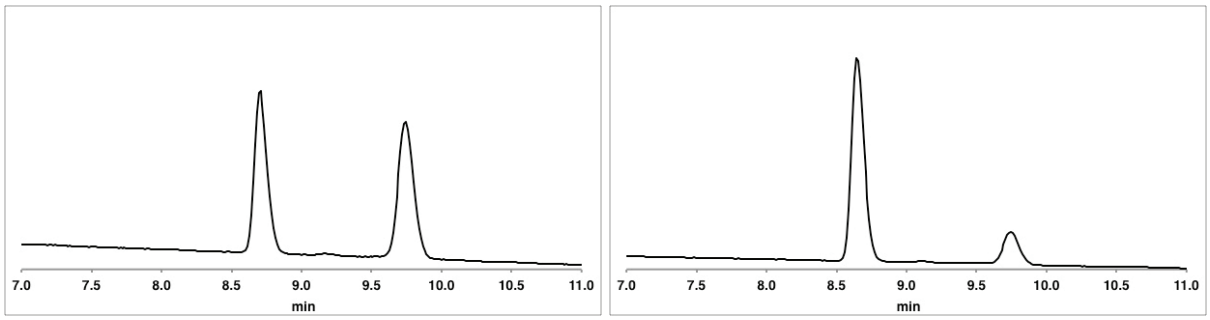
= 564.2693, found: m/z = 564.2690; **IR** (ν/cm^{-1}, neat) 3056, 2952, 2931, 2857, 1699, 1438, 1424, 1325, 1253, 1236, 1192, 1171, 1102, 855, 837; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.5 min (major) and 9.7 min (minor).



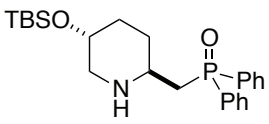
Acylated product: **1-((2*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-((diphenylphosphoryl)methyl)piperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



[α]$^{29}_{D}$ (c = 1.0, CH_3Cl): -9.1; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.98–7.86 (m, 1H), 7.78–7.63 (m, 3H), 7.57–7.36 (m, 6H), 7.11–6.98 (m, 2H), 6.81 (dd, *J* = 8.6, 3.4 Hz, 2H), 5.17–4.96 (m, 0.4H), 4.51–4.36 (m, 1.2H), 3.78 (s, 1.8H), 3.76 (s, 1.2H), 3.54 (dd, *J* = 13.2, 5.0 Hz, 0.4H), 3.49–3.29 (m, 1H), 2.88–2.53 (m, 3.4H), 2.54–2.35 (m, 3H), 2.23 (dd, *J* = 13.1, 10.6 Hz, 0.6H), 2.14 (dq, *J* = 14.0, 3.2 Hz, 0.4H), 1.84–1.71 (m, 1.6H), 1.68–1.37 (m, 2H), 0.87 (s, 5.4H), 0.86 (s, 3.6H), 0.07–0.02 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.0, 170.8, 158.2, 158.0, 134.9, 133.93, 133.90, 133.4, 133.1, 132.9, 132.4, 132.25, 132.23, 132.20, 132.17, 132.07, 132.05, 131.8, 131.7, 131.39, 131.36, 131.27, 131.22, 130.8, 130.7, 130.6, 130.53, 130.48, 130.43, 129.6, 129.4, 129.02, 128.97, 128.91, 128.85, 128.80, 128.77, 128.7, 114.0, 113.9, 68.1, 67.5, 55.43, 55.35, 48.1, 46.8, 43.7, 43.4, 35.8, 34.9, 31.7, 31.0, 30.8, 30.5, 30.3, 29.8, 29.7, 29.4, 29.23, 29.18, 26.5, 25.92, 25.87, 18.2, 18.1, -4.4, -4.60, -4.63, -4.65; **HRMS** (ESI): calculated for $[C_{34}H_{47}NO_4PSi]^+$: m/z = 592.3006, found: m/z = 592.3003; **IR** (ν/cm^{-1}, neat) 3339, 2957, 2932, 2857, 1616, 1568, 1513, 1464, 1438, 1248, 1175, 1119, 1103, 836; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.6 min (major) and 9.8 min (minor).

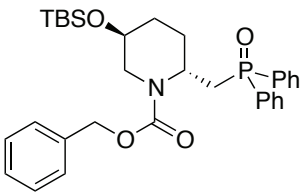


***trans*-((5-((*tert*-Butyldimethylsilyl)oxy)piperidin-2-yl)methyl)diphenylphosphine oxide (*trans*-105, Table 7 entry 4)**

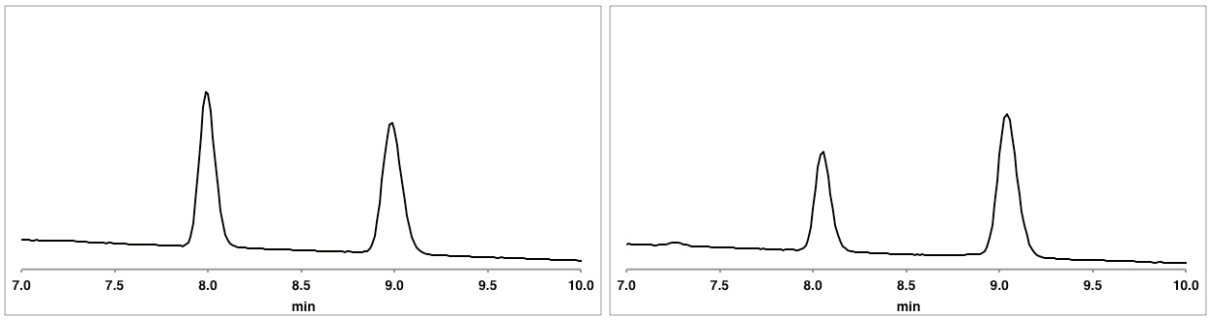


Racemic *trans*-((5-((*tert*-butyldimethylsilyl)oxy)piperidin-2-yl)methyl)diphenylphosphine oxide (85.8 mg, 0.200 mmol) was resolved according to the General Procedure A for 72 h. Recovered (Cbz-protected) amine: 51.0 mg (45 % yield, er = 35:65); acylated product: 22.0 mg (19 % yield, er = 87:13); calculated conversion: 29 %; **s = 9**

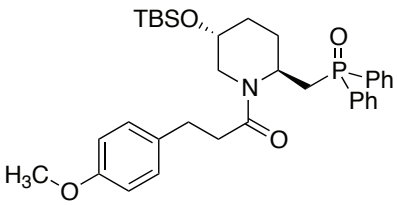
The recovered amine was characterized as its Cbz-derivative: **(2*R*,5*S*)-Benzyl 5-((*tert*-butyldimethylsilyl)oxy)-2-((diphenylphosphoryl)methyl)piperidine-1-carboxylate**



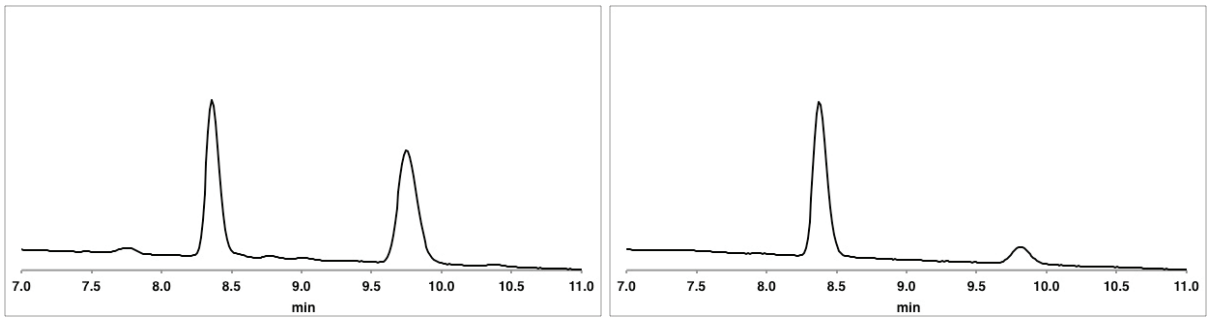
$[\alpha]^{29}_{D}$ (c = 1.0, CH_3Cl): +5.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.91–7.69 (m, 4H), 7.56–7.26 (m, 11H), 5.13–4.95 (m, 2H), 4.84–4.70 (m, 1H), 4.02–3.85 (m, 2H), 2.97 (d, *J* = 14.0 Hz, 1H), 2.67 (td, *J* = 15.1, 9.7 Hz, 1H), 2.58–2.45 (m, 1H), 2.20–2.07 (m, 1H), 1.85–1.73 (m, 2H), 1.64–1.54 (m, 1H), 0.82 (s, 9H), 0.00 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.5, 134.20 (d, *J* = 99.8 Hz), 131.91 (d, *J* = 2.8 Hz), 131.75 (d, *J* = 2.8 Hz), 131.74 (d, *J* = 98.6 Hz), 131.09 (d, *J* = 9.3 Hz), 130.50 (d, *J* = 9.3 Hz), 128.73 (d, *J* = 11.7 Hz), 128.70 (d, *J* = 11.7 Hz), 128.5, 127.9, 67.1, 64.6, 46.7, 45.9, 30.60 (d, *J* = 68.4 Hz), 26.7, 25.7, 22.7, 18.0, -4.9, -5.0; **HRMS** (ESI): calculated for $[C_{32}H_{43}NO_4PSi]^+$: m/z = 564.2693, found: m/z = 564.2691; **IR** (ν/cm^{-1}, neat) 3058, 2951, 2929, 2855, 1697, 1437, 1359, 1314, 1253, 1187, 1119, 1043, 889, 837; **SFC**: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.1 min (major) and 9.0 min (minor).



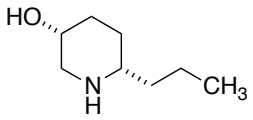
Acylated product: **1-((2*S*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-((diphenylphosphoryl)methyl)piperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{29}_{D}$ (c = 1.0, CH_3Cl): -18.2; at room temperature the ratio of rotamers was 70:30 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.00–7.85 (m, 1.3H), 7.79–7.63 (m, 2.7H), 7.61–7.35 (m, 6H), 7.14–7.00 (m, 2H), 6.86–6.75 (m, 2H), 5.09–4.98 (m, 0.7H), 4.53–4.38 (m, 0.6H), 3.97–3.85 (m, 1H), 3.79 (s, 0.9H), 3.77 (s, 2.1H), 3.44 (d, *J* = 14.3 Hz, 0.7H), 3.18 (dd, *J* = 14.3, 2.1 Hz, 0.7H), 2.85–2.25 (m, 6.3H), 1.96–1.47 (m, 4H), 0.82 (s, 9H), 0.08– -0.05 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 172.0, 171.2, 158.0, 134.8, 133.8, 133.6, 132.5, 132.2, 132.0, 131.7, 131.3, 131.2, 130.9, 130.8, 130.6, 130.5, 129.5, 129.4, 129.0, 128.8, 128.7, 128.6, 114.0, 65.8, 64.7, 55.4, 47.7, 45.4, 42.7, 35.7, 35.0, 31.8, 30.9, 30.5, 30.2, 27.5, 26.9, 25.8, 23.1, 18.1, -4.5, -4.9, -5.0; **HRMS** (ESI): calculated for $[C_{34}H_{47}NO_4PSi]^+$: m/z = 592.3006, found: m/z = 592.3005; **IR** (ν/cm^{-1}, neat) 3350, 2953, 2930, 2856, 1639, 1513, 1438, 1248, 1180, 1119, 1103, 1040, 836; **SFC**: column: Daicel Chiralpak ODH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 8.4 min (major) and 9.8 min (minor).



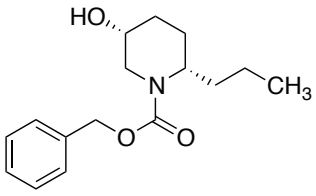
***cis*-6-Propylpiperidin-3-ol (*cis*-112, Table 7, entry 5)**



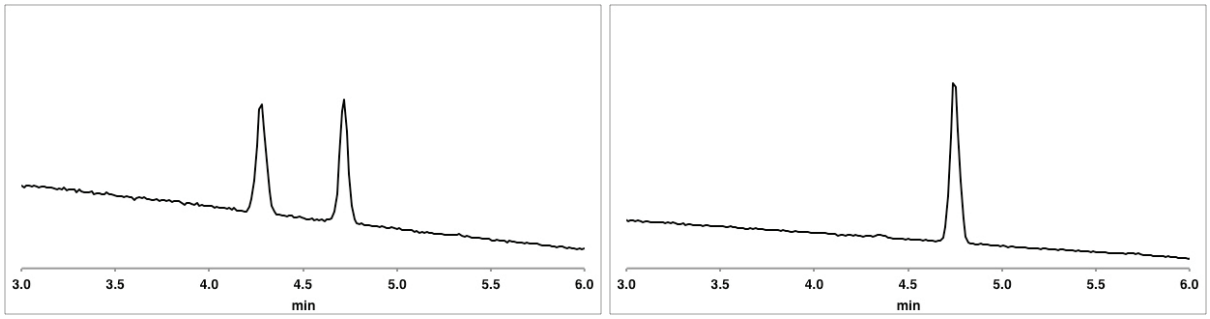
Racemic *cis*-6-propylpiperidin-3-ol (28.6 mg, 0.200 mmol) was resolved according to the General Procedure A for 20 h. Recovered (Cbz-protected) amine: 14.0 mg (25 % yield, er = 1:99); acylated product: 23.0 mg (38 % yield, er = 8:92); calculated conversion: 54 %; **s = 52**

The absolute stereochemistry was assigned by recovering the amine after kinetic resolution by acid base extraction and with their optical rotation according to literature values. Revovered amine hydrochloride salt: $[\alpha]^{26}_{D}$ (c = 1.0, MeOH): +13.0 (lit.,[27] : $[\alpha]^{20}_{D}$ (c = 1.0, MeOH): +9.4).

The recovered amine was characterized as its Cbz-derivative: **(2*S*,5*R*)-Benzyl 5-hydroxy-2-propylpiperidine-1-carboxylate**

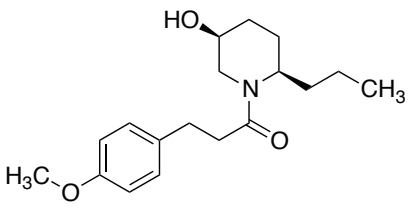


$[\alpha]^{26}_{D}$ (c = 0.8, CH_3Cl): +7.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.45–7.28 (m, 5H), 5.11 (2d, *J* = 3.6 Hz, 2H), 4.34–4.14 (m, 2H), 3.59 (tt, *J* = 10.4, 4.8 Hz, 1H), 2.63 (dd, *J* = 12.9, 10.8 Hz, 1H), 2.02 (br, 1H), 1.91–1.83 (m, 1H), 1.74–1.59 (m, 3H), 1.59–1.48 (m, 1H), 1.41–1.21 (m, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.7, 136.9, 128.6, 128.1, 128.0, 67.34, 67.31, 49.8, 45.5, 31.7, 28.7, 27.0, 19.6, 14.1; **HRMS** (ESI): calculated for $[C_{16}H_{23}NO_3Na]^+$: m/z = 300.1570, found: m/z = 300.1571; **IR** (ν/cm^{-1}, neat) 3421, 2953, 2934, 2871, 1697, 1674, 1427, 1344, 1237, 1159, 1147, 1071; **SFC**: column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 4.3 min (minor) and 4.7 min (major).

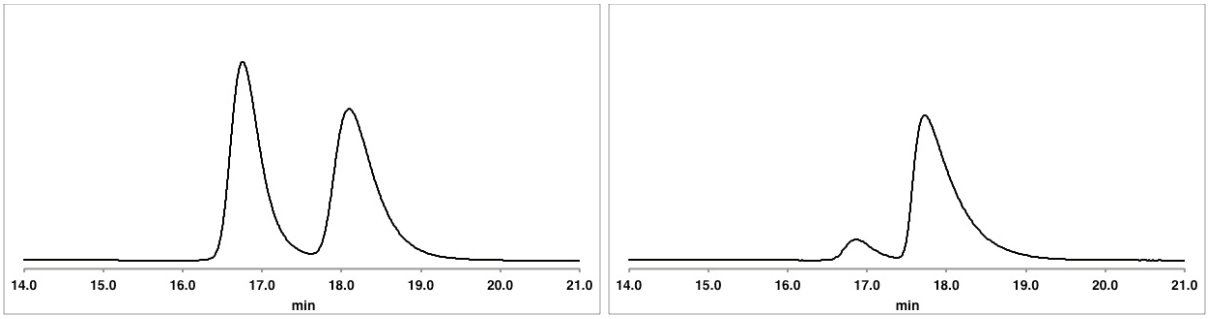


27 Khobare, S. R.; Gajare, V. S.; Jammula, S.; Kumar, U. K. S.; Murthy, Y. L. N.: Diastereoselective Total Synthesis of 3,6-Disubstituted Piperidine Alkaloids, (3*R*,6*S*)-*epi*-Pseudoconhydrine and (3*R*,6*R*)-Pseudoconhydrine. *Tetrahedron Lett.* **2013**, *54*, 2909–2912.

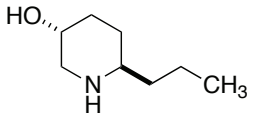
Acylated product: **1-((2*R*,5*S*)-5-Hydroxy-2-propylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



$[\alpha]^{26}_{D}$ (c = 1.0, CH_3Cl): -5.1; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.16–7.08 (m, 2H), 6.88–6.76 (m, 2H), 4.81–4.67 (m, 1H), 3.84–3.68 (m, 4H), 3.58–3.37 (m, 1H), 2.89 (t, *J* = 7.9 Hz, 2H), 2.80 (t, *J* = 12.0 Hz, 0.5H), 2.67–2.50 (m, 2H), 2.42 (t, *J* = 11.8 Hz, 0.5H), 1.95–1.82 (m, 1H), 1.71–1.34 (m, 5H), 1.34–1.10 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.3, 171.2, 158.1, 133.4, 129.5, 114.04, 114.01, 67.9, 67.0, 55.4, 52.1, 47.4, 46.8, 43.1, 35.9, 35.7, 32.2, 31.4, 30.94, 30.87, 29.2, 28.3, 27.5, 26.3, 19.8, 19.6, 14.2; **HRMS** (ESI): calculated for $[C_{18}H_{28}NO_3]^+$: m/z = 306.2064, found: m/z = 306.2067; **IR** (ν/cm^{-1}, neat) 3341, 2956, 2934, 2871, 1613, 1513, 14541247, 1177, 1081, 1036; **Chiral HPLC**: column: Daicel Chiralpak IB (4.6 x 250 mm); eluent: 10% *i*PrOH in hexanes; flow: 0.6 mL/min; detection: 254 nm; Retention time: t_R = 16.9 min (minor) and 18.0 min (major).



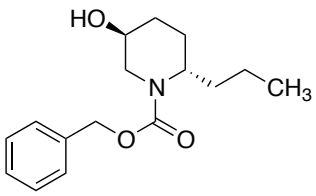
***trans*-6-Propylpiperidin-3-ol (*trans*-112, Table 7, entry 6)**



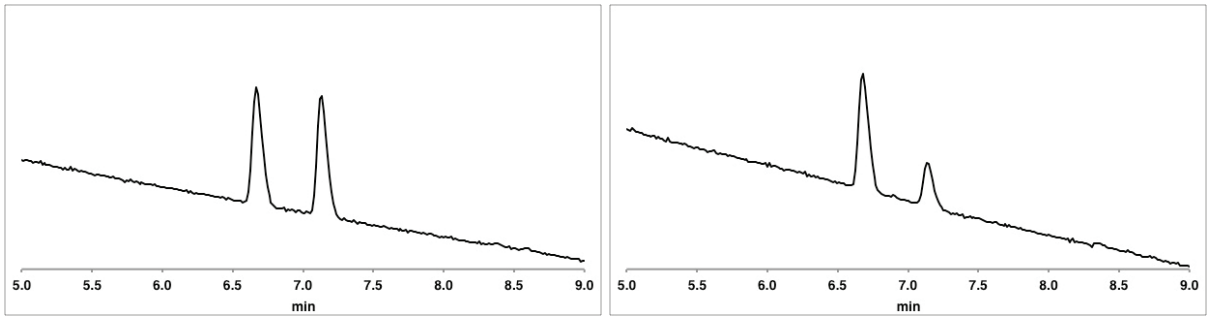
Racemic *trans*-6-propylpiperidin-3-ol (28.6 mg, 0.200 mmol) was resolved according to the General Procedure A for 48 h. Recovered (Cbz-protected) amine: 16.0 mg (29 % yield, er = 74:26); acylated product: 31.0 mg (51 % yield, er = 29:71); calculated conversion: 53 %; **s = 4**

The absolute stereochemistry was assigned by recovering the amine after kinetic resolution by acid base extraction and with their optical rotation according to literature values. Revovered amine: **[α]$^{25}_{D}$** (c = 1.0, CH_3Cl): +3.4 (lit.,[28] : **[α]$^{25}_{D}$** (c = 0.62, CH_3Cl): +17.4).

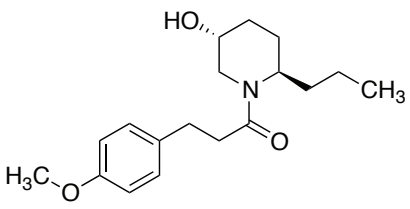
The recovered amine was characterized as its Cbz-derivative: **(2*S*,5*S*)-Benzyl 5-hydroxy-2-propylpiperidine-1-carboxylate**



[α]$^{27}_{D}$ (c = 1.0, CH_3Cl): +6.4 (lit.,[28] : **[α]$_{D}$** (c = 1.4, MeOH): +15.7); **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.38–7.27 (m, 5H), 5.13 (d, *J* = 6.9 Hz, 2H), 4.33 (br, 1H), 4.10 (d, *J* = 14.4 Hz, 1H), 3.91 (br, 1H), 3.03 (d, *J* = 14.0 Hz, 1H), 2.13–2.00 (m, 1H), 1.96 (s, 1H), 1.80–1.59 (m, 3H), 1.42–1.22 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 156.9, 137.0, 128.6, 128.0, 127.9, 67.3, 64.7, 50.6, 45.0, 31.5, 25.7, 22.3, 19.7, 14.1; **HRMS** (ESI): calculated for $[C_{16}H_{23}NO_3Na]^+$: m/z = 300.1570, found: m/z = 300.1571; **IR** (ν/cm^{-1}, neat) 3438, 2953, 2932, 2871, 1693, 1681, 1429, 1357, 1341, 1259, 1243, 1151, 1107, 1019; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 6.7 min (major) and 7.1 min (minor).



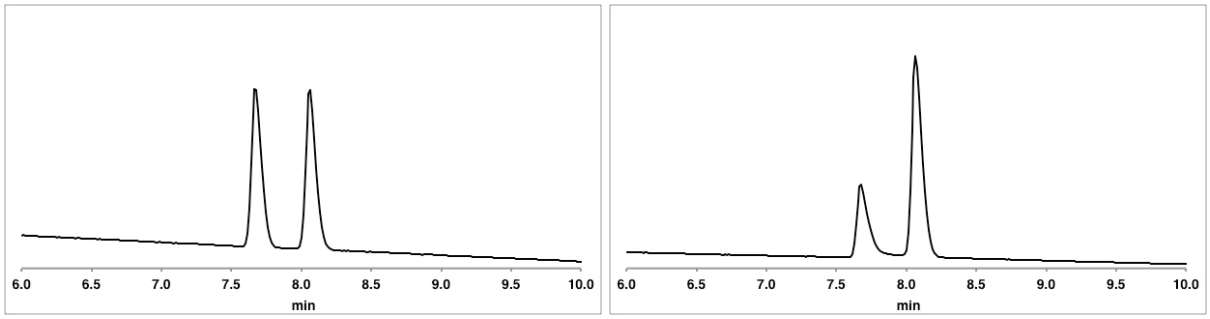
Acylated product: **1-((2*R*,5*R*)-5-Hydroxy-2-propylpiperidin-1-yl)-3-(4-methoxyphenyl)propan-1-one**



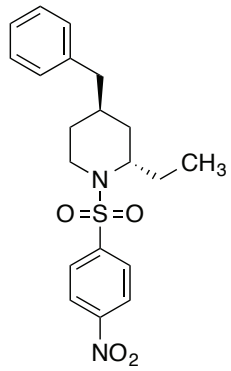
[α]$^{27}_{D}$ (c = 1.0, CH_3Cl): -25.7; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.19–7.08 (m, 2H), 6.82 (t, *J* = 8.0 Hz, 2H), 4.83 (q, *J* = 6.0, 5.6 Hz, 0.5H), 4.61 (d, *J* =

28 Moody, J. C.; Lightfoot, A. P., Gallagher, P. T.: Asymmetric Synthesis of 2-Substituted Piperidines. Synthesis of the Alkaloids (−)-Coniine and (+)-Pseudoconhydrine. *J. Org. Chem.* **1997**, *62*, 746–748.

14.4 Hz, 0.5H), 3.98 (br, 0.5H), 3.88 (br, 0.5H), 3.78 (s, 3H), 3.67 (d, *J* = 14.3 Hz, 0.5H), 3.16 (d, *J* = 14.2 Hz, 0.5H), 2.98–2.83 (m, 2H), 2.78 (d, *J* = 14.2 Hz, 1H), 2.75–2.51 (m, 2H), 1.96–1.35 (m, 7H), 1.32–1.16 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 173.1, 172.2, 158.0, 133.6, 133.4, 129.4, 129.3, 113.9, 113.8, 65.0, 64.9, 55.3, 53.0, 47.4, 46.3, 42.2, 35.6, 35.4, 31.9, 31.1, 30.8, 30.6, 26.2, 25.5, 23.0, 21.9, 19.8, 19.6, 14.1; **HRMS** (ESI): calculated for $[C_{18}H_{28}NO_3]^+$: m/z = 306.2064, found: m/z = 306.2070; **IR** (ν/cm $^{-1}$, neat) 3398, 2953, 2932, 2871, 1612, 1513, 1454, 1300, 1247, 1178, 1150, 1036, 825; **SFC**: column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient 5% *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; Retention time: t_R = 7.7 min (minor) and 8.1 min (minor).



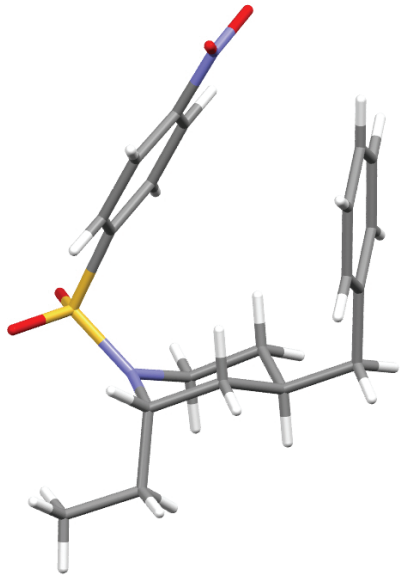
6.6 X-ray Crystallography of 4-Benzyl-2-ethyl-1-((4-nitrophenyl)sulfonyl) piperidine



A solution of (2*S*,4*R*)-4-benzyl-2-ethylpiperidine (35 mg, 0.17 mmol, 1.0 equiv) was dissolved in THF (1.1 mL, 0.15 M) and K_2CO_3 (26 mg, 0.19 mmol, 1.1 equiv) and 4-nitrobenzenesulfonyl chloride (42 mg, 0.19 mmol, 1.1 equiv) were added. The reaction mixture was allowed to stir at 23 °C overnight. To the resulting suspension sat aq $NaHCO_3$ solution (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel (hexanes:EtOAc 20:1) to afford the desired product as colorless crystals. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.32 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.32–7.14 (m, 3H), 7.08–6.98 (m, 2H), 4.08–3.97 (m, 1H), 3.91–3.80 (m, 1H), 3.10–2.95 (m, 1H), 2.49–2.34 (m, 2H), 1.96–1.82 (m, 1H), 1.72–1.42 (m, 4H), 1.14–1.03 (m, 1H), 0.84 (t, *J* = 7.4 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 149.8, 147.9, 139.1, 129.2, 128.3, 128.1, 126.3, 124.4, 55.5, 43.0, 40.9, 33.9, 31.7, 30.8, 23.4, 11.1; **HRMS** (ESI): calculated for $[C_{20}H_{25}N_2O_4S]^+$: m/z = 389.1530, found: m/z = 389.1530.

The compound was recrystallized from MeOH to obtain larger crystals for X-ray crystallography.

The X-ray data was collected to establish the relative stereochemistry CDCC number 1046811 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



(2*S*,4*R*)-4-Benzyl-2-ethyl-1-((4-nitrophenyl)sulfonyl)piperidine

Experimental

A suitable single crystal of $C_{19}H_{21}N_2O_4S$ [jb200115_1_1_0m] was selected and measured on a Bruker ApexII Duo (Mo) diffractometer. The crystal was kept at 100.02 K during data collection. Using Olex2, the structure was solved with the XS [SHELX, G.M. Sheldrick, Acta Cryst. (2008). A64, 112-122] structure solution program using Direct Methods and refined with the XL [SHELXL-97 (Sheldrick, 2008)] refinement package using Least Squares minimization.

Crystal Data:

orthorhombic, space group $P2_12_12_1$ (no. 19), a = 8.8603(7) Å, b = 11.6145(9) Å, c = 18.4379(14) Å, V = 1897.4(3) Å^3, Z = 4, T = 100.0(2) K, μ(MoKα) = 0.199 mm^{-1}, *Dcalc* = 1.360 g/cm^3, 32217 reflections measured (4.144° ≤ 2Θ ≤ 54.968°), 3747 unique (R_{int} = 0.0198, R_{sigma} = 0.0114) which were used in all calculations. The final R_1 was 0.0232 (I > 2σ(I)) and wR_2 was 0.0607

7

Experimental Section III

CHAPTER 7. Experimental Section III on the Automated Synthesis of N-Heterocycles

7.1 General Remarks

All reactions were carried out in oven dried glassware under an atmosphere of dry N_2 using standard manifold techniques.[29] Chemicals were purchased from *Acros*, *Sigma-Aldrich*, *ABCR* or *TCI* and used without further purification unless otherwise stated. Dichloromethane was distilled from CaH_2 and THF from sodium, other solvents were dried by passage over two columns of anhydrous neutral A-2 alumina under an atmosphere of argon.[30] Cu(OTf)2 was dried at 110 °C under high vacuum (ca. 0.1 mmHg) for 4 h and stored in desiccator.

Flash column chromatography was performed on silica gel (*Silicycle* SiliaFlash F60, 230-400 mesh). Thin layer chromatography was performed on glass-backed plates pre coated with silica gel (*Merck*, Silica Gel 60 F254).

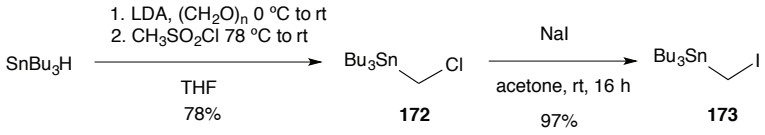
NMR spectra were recorded on *Bruker* Avance III 400 MHz or *Varian* Mecury-VX 300 MHz spectrometers using $CDCl_3$ as the solvent unless indicated otherwise. ^{1}H NMR chemical shifts are expressed in parts per million (d) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.26 ppm or of CH_3OH at 3.31 used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (d) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.2 ppm or of CH_3OH at 49.0 used as a standard). $^{117/119}$Sn-^{13}C couplings were not reported. All ^{13}C spectra were measured with complete proton decoupling. NMR coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; quint; quintet; sext, sextet ; m, multiplet. Infrared (IR) spectra were recorded on a *JASCO* FT-IR-4100 spectrometer and reported as wavenumber (cm^{-1}) of the absorption maxima for the range between 4000 cm^{-1} and 750 cm^{-1} with only major peaks reported. Optical rotations were measured on *JASCO* P-1010 operating at the sodium D line with a 100 m path length cell. High resolution mass spectra were measured by the Mass Spectrometry Service Facility of Laboratorium für Organische Chemie at ETH Zürich on a *Bruker* Daltonics maXis for ESI-Q-TOF spectrometer (ESI-MS) or on a *Bruker* solariX (9.4T magnet) equipped with a dual ESI/MALDI-FT-ICR source using *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as matrix (MALDI-MS).

29 Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, Taylor & Fran*cis*, 1998

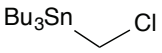
30 Pangborn, A.B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J.: Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**,*15*, 1518–1520.

7.2 Preparation of the Aza SnAP Reagents

7.2.1 Synthetic Route towards Tributyl(iodomethyl)stannane (173)

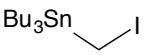


Tributyl(chloromethyl)stannane (172)



n-BuLi (1.6 M in hexanes, 42.3 mL, 67.6 mmol, 1.15 equiv) was added to a stirred solution of N,N-diisopropylamine (9.90 mL, 70.6 mmol, 1.20 equiv) in THF (130 mL) at 0 °C over 30 min. The solution was allowed to stir at 0 °C for 30 min before tributyltin hydride (15.8 mL, 58.8 mmol, 1.00 equiv) was added dropwise over 10 min. The solution was allowed to stir at rt for 30 min and cooled to 0 °C. Paraformaldehyde (1.86 g, 61.7 mmol, 1.05 equiv) was added and the reaction mixture was allowed to stir at rt for 3 h and cooled to -78 °C. Methanesulfonyl chloride (5.70 mL, 73.5 mmol, 1.25 equiv) was added dropwise over 10 min and the resulting mixture was allowed to stir at rt for 16 h. Water (80 mL) was added and the aqueous layer separated and washed with hexane (2 × 60 mL). The combined organic layers were washed with water (2 × 30 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes) to yield the product (15.6 g, 78%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 3.06 (s, $J(^{117/119}Sn\text{-}^1H)$ = 8.1 Hz, 2H), 1.61–1.45 (m, 6H), 1.30 (s, 6H), 1.13–0.83 (m, 15H).[31]

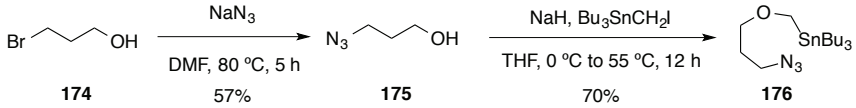
Tributyl(iodomethyl)stannane (173)



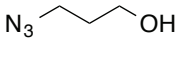
Sodium iodide (14.1 g, 94.3 mmol, 2.05 equiv) was added in one portion to a stirred solution of tributyl(chloromethyl)stannane (**172**) in acetone (230 mL). The resulting suspension was allowed to stir at rt for 16 h. The suspension was filtered through a short plug of silica (hexane rinse). The filtrate was concentrated *in vacuo*, resulting in the product (19.2 g, 97%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 1.94 (s, $J(^{117/119}Sn\text{-}^1H)$ = 9.1 Hz, 2H), 1.60–1.49 (m, 6H), 1.32 (sext, *J* = 7.1 Hz, 6H), 1.02–0.94 (m, 6H), 0.90 (t, *J* = 7.2 Hz, 9H).[31]

31 spectral data is in accordance to: Luescher, M. U.; Vo, C.-V T.; Bode, J. W.: SnAP Reagents for the Synthesis of Piperazines and Morpholines. *Org. Lett.*, **2014**, *16*, 1236–1239.

7.2.2 Synthetic Route towards SnAP 1,4-Oxazepane Azide (176)

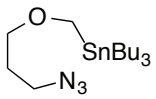


3-Azido-1-propanol (175)



3-bromo-1-propanol (40.0 g, 288 mmol, 1.00 equiv) was allowed to stir in DMF (72 mL). Sodium azide (26.7 g, 410 mmol, 1.40 equiv) was added in portions and the resulting suspension was allowed to stir for 30 min. The reaction mixture was heated to 80 °C for 5 h. Et_2O (100 mL) and water (75 mL) were added to the mixture. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined ethereal layers were washed with water (3 × 75 mL), dried over Na_2SO_4 and filtered. The solution was concentrated *in vacuo* to afford the desired azide **175** as colorless liquid (16.6 g, 57%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 3.73 (t, *J* = 6.2 Hz, 2H), 3.48 (t, *J* = 6.7 Hz, 2H), 1.82 (m, 2H).[32]

((3-Azidopropoxy)methyl)tributylstannane (176)

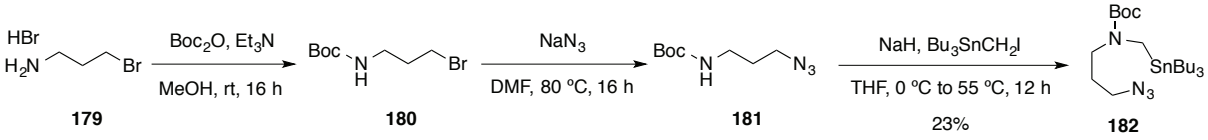


Sodium hydride (2.10 g of a 60% suspension in mineral oil, 51.9 mmol, 0.750 equiv) was washed with hexane and suspended in THF (45 mL). The suspension was cooled to 0 °C and azide **175** (6.90 g, 69.2 mmol, 1.00 equiv) was added dropwise over 10 min. The resulting suspension was allowed to stir at rt until no more gas formation was observed. The suspension was cooled to 0 °C and tributyl(iodomethyl)stannane (**173**) (14.9 g, 34.6 mmol, 0.5 equiv) was added dropwise over 10 min. The mixture was allowed to stir at 55 °C for 16 h. The reaction mixture was allowed to cool to rt and treated with water (15 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL) and the combined organic layers were washed with water (2 x 15 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 1:0 → 6:1) to afforded the desired the SnAP reagent **178** (9.8 g, 70). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 3.70 (s, $J(^{117/119}Sn$-$^1H)$ = 14.8 Hz, 2H), 3.41–3.31 (m, 4H), 1.85–1.77 (m, 2H), 1.56–1.45 (m, 6H), 1.36–1.25 (sext, *J* = 8 Hz, 6H), 0.99–0.81 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 72.2, 62.3,

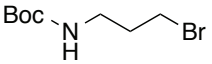
32 spectral data is in accordance to: Jin, J.; Wu, D.; Sun, P.; Liu, L.; Zhao, H.: Amphiphilic Triblock Copolymer Bioconjugates with Biotin Groups at the Junction Points: Synthesis, Self-Assembly, and Bioactivity. *Macromolecules,* **2011**, *44*, 2016–2024.

48.8, 29.4, 29.3, 27.5, 13.9, 9.2; **IR** (ν/cm $^{-1}$, neat) 2956, 2925, 2871, 2854, 2096, 1463, 1377, 1340, 1293, 1260, 1094, 1021, 874, 725.

7.2.3 Synthetic Route towards SnAP Diazepane Azide (180)

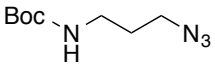


tert-Butyl (3-bromopropyl)carbamate (178)



3-Bromopropylamine hydrobromide (**177**) (24.8 g, 113 mmol, 1.00 equiv) in MeOH (95 mL) was treated with NEt_3 (14.0 mL, 100 mmol) and stirred for 5 min. The mixture was cooled to 0 °C and Boc_2O (46.6 g, 213 mmol, 1.90 equiv) was added. The mixture was allowed to stir for 16 h at rt. CH_2Cl_2 (100 mL) was added and the resulting solution was washed with 1 N $KHSO_4$ (3 × 100 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude dark red liquid was used without isolation. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.75 (br, 1H), 3.40 (t, J = 6.5 Hz, 2H), 3.22 (q, J = 6.4 Hz, 2H), 2.01 (quint, J = 6.6 Hz, 2H), 1.40 (s, 9H).[33]

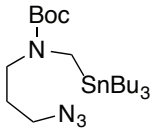
tert-Butyl (3-azidopropyl)carbamate (179)



tert-Butyl-(3-bromopropyl)carbamate **178** (27.0 g, 113 mmol, 1.00 equiv) and NaN_3 (14.7 g, 227 mmol, 2.00 equiv) were dissolved in DMF (300 mL) and stirred at 80 °C for 16 h. DMF was removed *in vacuo* and the residue was dissolved with CH_2Cl_2 (330 mL). The resulting solution was washed with 1 N $KHSO_4$ (3 × 100 mL) and brine (3 × 100ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was co-evaporated with toluene (2 × 100 mL). The resulting dark red liquid was used without isolation. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.63 (br, 1H), 3.36 (t, J = 6.7 Hz, 2H), 3.21 (q, J = 6.4 Hz, 2H), 1.77 (quint, J = 6.7 Hz, 2H), 1.44 (s, 9H).[33]

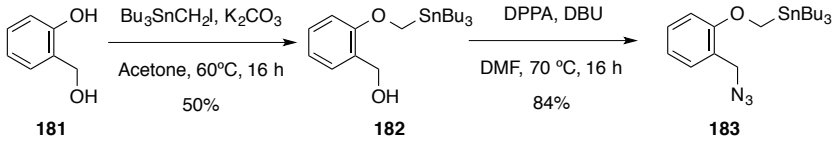
33 spectral data is in accordance to: Barnard, A.; Long, K.; Yeo, D. J.; Miles, J. A.; Azzarito, V.; Burslem, G. M.; Prabhakaran, P.; Edwards, T. A.; Wilson, A. J.: Orthogonal functionalisation of α-helix mimetics. *Org. Biomol. Chem.*, **2014**, *12*, 6794–6799.

***tert*-Butyl (3-azidopropyl)((tributylstannyl)methyl)carbamate (180)**

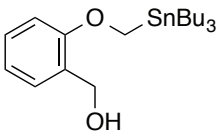


Sodium hydride (2.10 g of a 60% suspension in mineral oil, 52.2 mmol, 1.50 equiv) was washed with hexane and suspended in THF (45 mL). The suspension was cooled to 0 °C and azide **179** (13.9 g, 69.6 mmol, 2.00 equiv) was added dropwise over 10 min. The resulting suspension was allowed to stir at rt until no more gas formation was observed. The suspension was cooled to 0 °C and tributyl(iodomethyl)stannane (**173**) (15.0 g, 34.8 mmol, 1.00 equiv) was added dropwise over 3 min. The mixture was allowed to stir at 55 °C for 16 h. The reaction mixture was allowed to cool to rt and treated with water (15 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water (2 × 15 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 1:0 → 8:1) to afford the desired the SnAP reagent **180** (4.1 g, 23%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 3.35–3.17 (m, 4H), 2.85–2.74 (m, 2H), 1.87–1.74 (m, 2H), 1.59–1.39 (m, 15H), 1.35–1.21 (m, 6H) 0.97–0.79 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.4, 79.2, 49.0, 47.5, 33.6, 29.1, 28.4, 27.5, 13.7, 10.5; **HRMS** (ESI): calculated for $[C_{21}H_{44}N_4NaO_2Sn]^+$: m/z = 527.2384, found: m/z = 527.2386; **IR** (ν/cm $^{-1}$, neat) 2956, 2924, 2871, 2853, 2097, 1681, 1481, 1464, 1405, 1365, 1253, 1163.

7.2.4 Synthetic Route towards SnAP Tetrahydrobenzo-1,4-oxazepine Azide (183)



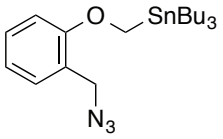
(2-((Tributylstannyl)methoxy)phenyl)methanol (182)



2-Hydroxybenzyl alcohol (**182**) (4.50 g, 36.2 mmol, 1.00 equiv) in acetone (180 mL) was treated with K_2CO_3 (6.00 g, 43.4 mmol, 1.20 equiv) and tributyl(iodomethyl)stannane (**173**) (17.2 g, 39.8 mmol, 1.10 equiv) at rt. The resulting mixture was allowed to stir at 60 °C for 16 h followed by 80 °C for 1 h. The reaction mixture was allowed to cool to rt and the residue was diluted with hexane (150 mL) and filtered through a short plug of silica. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 1:0 → 9:1) to yield the benzyl alcohol **182**

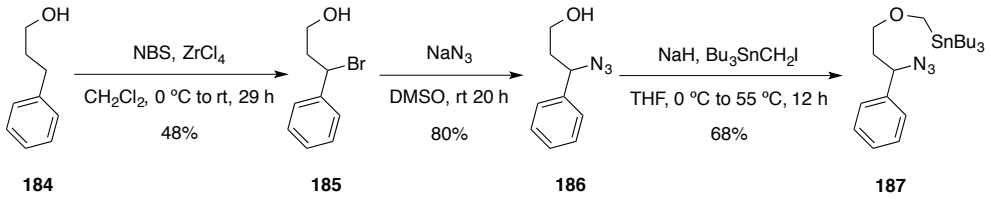
(7.7 g, 50%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.32–7.23 (m, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.95–6.89 (m, 1H), 4.66 (d, *J* = 6.6 Hz, 2H), 4.19 (s, *J*($^{117/119}$Sn-^{1}H) = 14.8 Hz, 2H), 2.26 (t, *J* = 6.6 Hz, 1H), 1.58–1.47 (m, 6H), 1.32 (sext, = 7.3 Hz, 6H), 1.03–0.96 (m, 6H), 0.90 (t, *J* = 7.3 Hz, 9H).[34]

((2-(Azidomethyl)phenoxy)methyl)tributylstannane (183)



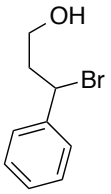
Benzyl alcohol **182** (7.60 g, 17.8 mmol, 1.00 equiv) and DMF (16 mL) were stirred at 70 °C. 1,8-diazabicyclo[5.4.0]undec-7-ene (4.00 mL, 26.7 mmol, 1.50 equiv) was added in one portion, followed by diphenylphosphoryl azide (7.70 mL, 35.6 mmol, 2.00 equiv) over 10 min. The solution was allowed to stir at 70 °C for 16 h. The reaction mixture was allowed to cool to rt, diluted with EtOAc (80 mL), washed with sat aq $NaHCO_3$ (2 × 25 mL), water (4 × 25 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel afforded the product **182** (6.8 g, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.36–7.30 (m, 1H), 7.26–7.23 (m, 1H), 7.08 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.93 (td, *J* = 7.4, 1.1 Hz, 1H), 4.33 (s, 2H), 4.17 (s, *J*($^{117/119}$Sn-^{1}H) = 14.8 Hz, 2H), 1.65–1.42 (m, 6H), 1.38–1.27 (sext, *J* = 7.3 Hz, 6H), 1.03–0.96 (m, 6H), 0.93-0.87 (t, *J* = 6.6 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 159.5, 129.73, 129.68, 123.6, 120.1, 110.6, 58.4, 50.0, 29.1, 27.4, 13.7, 9.2. **HRMS** (ESI): calculated for $[C_{25}H_{35}N_3NaOSn]^+$: m/z = 476.1698, found: m/z = 476.1700; **IR** (ν/cm^{-1}, neat) 2956, 2925, 2871, 2852, 2098, 1603, 1589, 1489, 1456, 1260, 1209, 999, 876, 751.

7.2.5 Synthetic Route towards SnAP 3-Phenyl-1,4-oxazepane Azide (187)



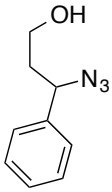
34 spectral data is in accordance to: Luescher, M. U.; Vo, C.-V T.; Bode, J. W.: SnAP reagents for the one-step synthesis of medium-ring saturated N-heterocycles from aldehydes. *Nature Chem.*, **2014**, *6*, 310–314.

3-Bromo-3-phenylpropan-1-ol (185)



A solution of N-bromosuccinimide (6.50 g, 36.7 mmol, 1.00 equiv) in CH_2Cl_2 (300 mL) was cooled to -78 °C. $ZrCl_4$ (0.43 g, 1.8 mmol, 0.050 equiv) and 3-phenylpropan-1-ol **184** (5.00 g, 36.7 mmol, 1.00 equiv) were added and the resulting mixture was allowed to stir at 0 °C for 5 h and at rt for 24 h. The reaction mixture was quenched with sat aq $NaHCO_3$ (60 mL). The organic phase was washed with brine (60 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 4:1 → 2:1) to yield the bromide **187** (3.78 g, 48%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.45–7.27 (m, 5H), 5.23 (dd, *J* = 5.75 Hz, 8.8 Hz, 1H), 3.90– 3.70 (m, 2H), 2.58–2.43 (m, 1H), 2.40–2.27 (m, 1H), 1.55 (br, 1H).[35]

3-Azido-3-phenylpropan-1-ol (186)

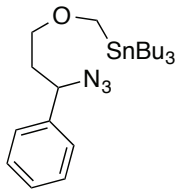


Sodium azide (1.30 g, 19.4 mmol, 1.10 equiv) was added to DMSO (350 mL) and was allowed to stir for 1 h until fully dissolved. Benzyl bromide **185** (3.80 g, 17.6 mmol, 1.00 equiv) was added and the resulting solution was allowed to stir at rt for 20 h. Water (350 mL) was added and the solution was cooled back to rt. The mixture was extracted with Et_2O (3 × 180 mL) and the organic phase was washed with water (2 × 90 mL) followed by brine (90 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 2:1) to afford the azide **186** (2.51 g, 80%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.44–7.27 (m, 5H), 4.72 (dd, *J* = 5.8 Hz, 9 Hz, 1H), 3.85–3.64 (m, 2H), 2.13–1.89 (m, 2H), 1.58 (br, 1H).[36]

35 spectral data is in accordance to: Isleyen, A.; Tanyeli, C.; Dogan, O.: Kinetic Resolution of Primary Alcohols having Remote Stereogenic Centers: Lipase Mediated Kinetic Resolution of (±)-3-Chloro-3-arylpropanols. *Tetrahedron Asymmetry,* **2006**, *17*, 1561–1567.

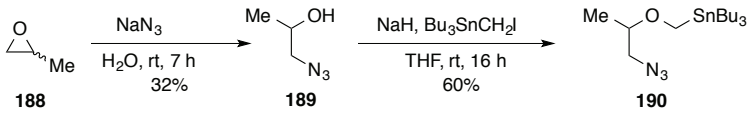
36 spectral data is in accordance to: Sawama, Y.; Nagata, S.; Yabe, Y.; Morita, K.; Monguchi, Y.; Sajiki, H.: Iron-Catalyzed Chemoselective Azidation of Benzylic Silyl Ethers *Chem. Eur. J.,* **2012**, *18*, 16608–16611.

((3-Azido-3-phenylpropoxy)methyl)tributylstannane (187)

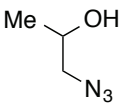


Sodium hydride (1.40 g of a 60% suspension in mineral oil, 35.4 mmol, 2.50 equiv) was washed with hexane (3 × 20 mL) and suspended in THF (35 mL). The suspension was cooled to 0 °C and azide **186** (2.51 g, 14.2 mmol, 1.00 equiv) was added dropwise over 1 min. The resulting suspension was allowed to stir at rt until no more gas formation was observed. The suspension was cooled to 0 °C and tributyl(iodomethyl)stannane (**173**) (9.20 g, 21.2 mmol, 1.50 equiv) was added dropwise over 3 min. The mixture was allowed to stir at 55 °C for 20 h. The reaction was allowed to cool to rt and water (15 mL) was added. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic phase was washed with water (2 × 15 mL), brine (20ml), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexanes:Et_2O = 1:0 → 15:1) afforded the desired the SnAP reagent **187** (4.6 g, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.43–7.30 (m, 5H), 4.66 (dd, *J* = 8.6 Hz, 6.2 Hz, 1H), 3.72 (s, *J*($^{117/119}$Sn-^{1}H) = 7.3 Hz, 2H), 3.49–3.42 (m, 1H), 3.31–3.25 (m, 1H), 2.10–1.90 (m, 2H), 1.66–1.44 (m, 6H), 1.40–1.29 (sext, *J* = 7.6 Hz, 6H), 1.03–0.85 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 139.8, 128.8, 128.2, 126.9, 71.5, 63.1, 62.2, 36.5, 29.2, 27.3, 13.7, 9.0; **HRMS** (ESI): calculated for $[C_{22}H_{39}N_3NaOSn]^+$: m/z = 504.2011, found: m/z = 504.2012; **IR** (ν/cm $^{-1}$, neat) 2955, 2925, 2871, 2853, 2097, 1455, 1377, 1246, 1092, 1070, 699.

7.2.6 Synthetic Route towards SnAP 2-Methyl-Morpholine Azide (190)



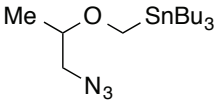
1-Azidopropan-2-ol (189)



Commercially available 2-methyloxirane (**188**) (35 mL, 0.50 mol, 1.0 equiv) was added dropwise over 10 min to a stirring sodium azide (50 g, 0.77 mol, 1.5 equiv) solution in water (125 mL) and stirred for 7 h at rt. The organic layer was separated and dried over anhydrous $MgSO_4$. Purification by Kugelrohr distillation (180 °C, 760 mmHg) afforded alcohol **189** (16.4 g, 32% yield) as a clear, yellow liquid. **^{1}H NMR** (300

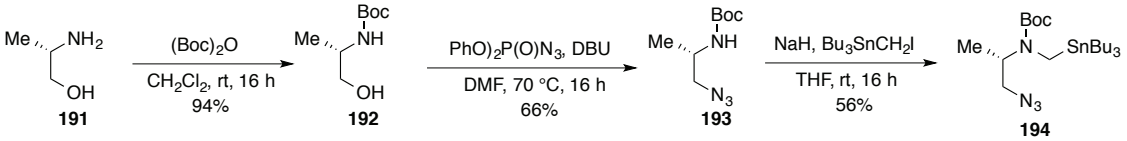
MHz, $CDCl_3$): δ [ppm] = 4.00–3.92 (m, 1H), 3.35 (dd, *J* = 12.3, 3.5 Hz, 1H), 3.22 (dd, *J* = 12.3, 7.4 Hz, 1H), 1.71 (br, OH), 1.22 (d, *J* = 6.3 Hz, 3H).[37]

(((1-Azidopropan-2-yl)oxy)methyl)tributylstannane (190)



Under N_2, sodium hydride (2.84 g of a 60% suspension in mineral oil, 71.4 mmol, 0.750 equiv) was washed with pentane (2 x 20 mL) and suspended in THF (60 mL). The suspension was cooled to 0 °C and 1-azidopropan-2-ol (**189**) (9.63 g, 95.2 mmol, 1.00 equiv) was added dropwise over 10 min. The resulting suspension was allowed to stir at rt until no further gas formation was observed. The reaction mixture was cooled to 0 °C and tributyl(iodomethyl)stannane (**173**) (20.5 g, 47.6 mmol, 0.500 equiv) was added dropwise over 10 min. The mixture was warmed to 55 °C and stirred for 16 h. The reaction was treated with H_2O (20 mL), the layers were separated and the water layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 20 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (hexanes:EtOAc = 1:0 → 3:1) afforded aza-SnAP reagent **190** (11.5 g, 60% yield) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 3.70 (dd, *J* = 69.1, 9.8 Hz, 2H), 3.42–3.31 (m, 1H), 3.22–3.08 (m, 2H), 1.61–1.41 (m, 6H), 1.37–1.24 (m, 6H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.00–0.80 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 79.1, 59.4, 55.6, 29.2, 27.4, 16.8, 13.9, 9.1; **IR** (ν/cm $^{-1}$, neat) 2956, 2925, 2871, 2853, 2099, 1463, 1458, 1418, 1376, 1340, 1274, 1137, 1085, 1037.[38]

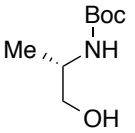
7.2.7 Synthetic Route towards SnAP 2-Methyl-Piperazine Azide (194)



37 spectral data is in accordance to: (a) Ingham, J.; Petty, W.; Nichols, P., Jr.: Notes- The Additon of Azide Ion to Epoxides. *J. Org. Chem.* **1956**, *21*, 373–375. (b) Mathieu-Pelta, I.; Evans, S. A., Jr.: Highly Regioselective and Stereospecific Functionalization of 1,2-Propanediol with Trimethyl(X)silanes Employing the 1,3,2λ^5-Dioxaphospholane Methodology. *J. Org. Chem.* **1992**, *57*, 3409–3413.

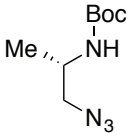
38 Siau, W.-Y.; Bode, J. W.: One-Step Synthesis of Saturated Spirocyclic N-Heterocycles with Stannyl Amine Protocol (SnAP) Reagents and Ketones. *J. Am. Chem. Soc.* **2014**, *136*, 17726–17729.

tert-Butyl (*S*)-(1-hydroxypropan-2-yl)carbamate (192)



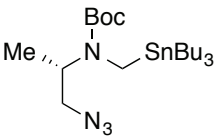
Commercially available (*S*)-2-aminopropan-1-ol (**191**) (2.00 g, 27.0 mmol, 1.10 equiv) in CH_2Cl_2 (10 mL) was added slowly to a solution of Boc_2O (5.25 g, 24.5 mmol, 1.00 equiv) in CH_2Cl_2 (18 mL) at 0 °C. The mixture was allowed to stir for 16 h at rt. The solution was diluted with CH_2Cl_2 (60 mL) and washed with sat aq NH_4Cl (2 x 10 mL), sat aq $NaHCO_3$ (2 x 10 mL), H_2O (2 x 10 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield pure carbamate **192** (4.03 g, 94% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 4.67 (br, 1H), 3.86–3.68 (m, 1H), 3.68–3.57 (m, 1H), 3.57–3.41 (m, 1H), 2.71 (b, 1H), 1.44 (s, 9H), 1.14 (d, *J* = 6.8 Hz, 3H).[39]

tert-Butyl (*S*)-(1-azidopropan-2-yl)carbamate (193)



tert-Butyl (*S*)-(1-hydroxypropan-2-yl)carbamate (**192**) (4.00 g, 22.8 mmol, 1.00 equiv) in DMF (20 mL) was heated to 70 °C and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (4.80 mL, 34.0 mmol, 1.50 equiv) was added in one portion and Diphenyl phosphorazidate (DPPA) (7.30 mL, 34.0 mmol, 1.50 equiv) was added dropwise over 10 min. The resulting solution was allowed to stir at 70 °C for 16 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc (100 mL) and washed with sat aq $NaHCO_3$ (2 x 30 mL), H_2O (4 x 30 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (hexanes:EtOAc = 4:1) afforded product **193** (3.0 g, 66% yield) as a colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 4.54 (br, 1H), 3.94–3.72 (m, 1H), 3.48–3.20 (m, 2H), 1.46 (s, 9H), 1.19 (d, *J* = 6.8 Hz, 3H).[38,40]

tert-Butyl (*S*)-(1-azidopropan-2-yl)((tributylstannyl)methyl)carbamate (194)



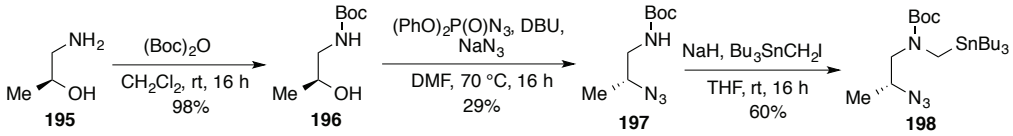
Sodium hydride (2.82 g of a 60% suspension in mineral oil, 70.5 mmol, 1.50 equiv) was washed with pentane (2 x 20 mL) and suspended in THF (60 mL). The suspension was cooled to 0 °C and tert-butyl (*S*)-(1-azidopropan-2-yl)carbamate (**193**) (9.40 g, 47.0 mmol, 1.00 equiv) was added dropwise over

39 spectral data is in accordance to: Luescher, M. U.; Vo, C.-V. T.; Bode, J. W.: SnAP Reagents for the Synthesis of Piperazines and Morpholines. *Org. Lett.* **2014**, *16*, 1236–1239.

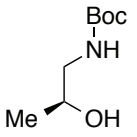
40 Pendem, N.; Douat, C.; Claudon, P.; Laguerre, M.; Castano, S.; Desbat, B.; Cavagnat, D.; Ennifar, E.; Kauffmann, B.; Guichard, G.: Helix-Forming Propensity of Aliphatic Urea Oligomers Incorporating Noncanonical Residue Substitution Patterns. *J. Am. Chem. Soc.* **2013**, *135*, 4884–4892.

10 min. The resulting suspension was allowed to stir at rt until no further gas formation was observed. The reaction mixture was cooled to 0 °C and tributyl(iodomethyl)stannane (**173**) (30.4 g, 70.5 mmol, 1.50 equiv) was added dropwise over 10 min. The reaction mixture was warmed to 55 °C and stirred for 16 h. The reaction was quenched with H_2O (20 mL). The layers were separated and the water layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 20 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (hexanes:EtOAc = 1:0 → 3:1) afforded aza-SnAP reagent **194** (13.2 g, 56% yield) as a colorless liquid. At temperature the ratio of rotamers was 75:25 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.27 (q, *J* = 7.1 Hz, 1H), 3.51–3.41 (m, 0.25H), 3.31 (dd, J = 12.5, 8.8 Hz, 0.75H), 3.17 (dd, *J* = 12.5, 5.6 Hz, 1H), 2.96–2.74 (m, 2x 0.25H), 2.51 (s, $J(^{117/119}Sn\text{-}^1H)$ = 30.7 Hz, 2x 0.75H), 1.53–1.43 (m, 15H), 1.30 (q, *J* = 7.3 Hz, 6H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.94 – 0.80 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.7, 79.8, 53.9, 51.9, 29.3, 28.6, 27.7, 26.9, 16.2, 13.9, 11.0; **HRMS** (ESI): calculated for $[C_{21}H_{44}N_4NaO_2Sn]^+$: m/z = 527.2385, found: m/z = 527.2369; **IR** (ν/cm $^{-1}$, neat) 2956, 2922 2871, 2853, 2099, 1675, 1455, 1396, 1365, 1355, 1266, 1157.

7.2.8 Synthetic Route towards SnAP 3-Methyl-Piperazine Azide (198)



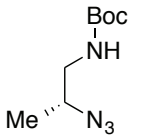
***tert*-Butyl (*S*)-(2-hydroxypropyl)carbamate (196)**



Commercially available (*S*)-1-aminopropan-2-ol (5.00 g, 66.6 mmol, 1.10 equiv) in CH_2Cl_2 (5 mL) was added slowly to a solution of Boc_2O (13.4 g, 61.4 mmol, 1.00 equiv) in CH_2Cl_2 (85 mL) at 0 °C. The reaction mixture was allowed to stir for 16 h at rt. The solution was diluted with CH_2Cl_2 (100 mL) and washed with sat aq NH_4Cl (2 x 35 mL), sat aq $NaHCO_3$ (2 x 35 mL), H_2O (2 x 35 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to yield pure carbamate **196** (10.6 g, 98% yield) as a liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.92 (br, 1H), 3.97–3.82 (m, 1H), 3.31–3.20 (m, 1H), 3.06–2.94 (m, 1H), 2.17 (br, 1H), 1.45 (s, 9H), 1.18 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 157.0, 79.8, 67.9, 48.2, 28.5, 20.9; **HRMS** (ESI): calculated for $[C_8H_{17}NNaO_3]^+$: m/z = 198.1101, found: m/z = 198.1105; **IR** (ν/cm $^{-1}$, neat) 3398, 2953, 2932, 2871, 1612, 1513,

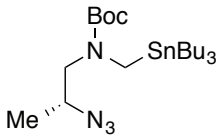
1454, 1300, 1247, 1178, 1150, 1036, 825 3360, 2977, 2932, 1693, 1523, 1456, 1392, 1367, 1277, 1253, 1173.[41]

tert-Butyl (*R*)-(2-azidopropyl)carbamate (197)



tert-Butyl (*S*)-(2-hydroxypropyl)-carbamate (**196**) (8.50 g, 48.6 mmol, 1.00 equiv) in DMF (40 mL) was heated to 70 °C and 1,8-Diazabicyclo[5.4.0]undec-7-ene (10.2 mL, 68.3 mmol, 1.40 equiv) was added in one portion and diphenyl phosphorazidate (DPPA) (11.0 mL, 51.0 mmol, 1.05 equiv) was added dropwise over 10 min. The resulting solution was allowed to stir at 70 °C for 16 h. Sodium azide (1.60 g, 24.0 mmol, 0.500 equiv) was added and the resulting suspension was allowed to stir for another 3 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with sat aq $NaHCO_3$ (2 x 50 mL), H_2O (4 x 50 mL), brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (hexanes:Et_2O = 4:1) afforded product **197** (2.8 g, 29% yield) as a liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 4.81 (s, 1H), 3.72–3.61 (m, 1H), 3.35–3.27 (m, 1H), 3.02–2.93 (m, 1H), 1.45 (s, 9H), 1.25 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 156.0, 79.9, 57.9, 45.8, 28.5, 16.9; **IR** (ν/cm $^{-1}$, neat) 3347, 2978, 2932, 2116, 1697, 1518, 1456, 1392, 1366, 1337, 1273, 1251, 1171, 1104.[42]

tert-Butyl (*R*)-(2-azidopropyl)((tributylstannyl)methyl)carbamate (198)



Sodium hydride (0.830 g of a 60% suspension in mineral oil, 21.0 mmol, 1.50 equiv) was washed with pentane (2 x 10 mL) and suspended in THF (18 mL). The suspension was cooled to 0 °C and *tert*-butyl (*R*)-(2-azidopropanyl)carbamate (2.80 g, 14.0 mmol, 1.00 equiv) was added dropwise over 10 min. The resulting suspension was stirred at rt until no gas formation was observed. The reaction mixture was cooled to 0 °C and tributyl(iodomethyl)stannane (**173**) (9.10 g, 21.0 mmol, 1.50 equiv) was added dropwise over 10 min. The reaction mixture was warmed to 55 °C and stirred for 16 h. The reaction was quenched with H_2O (10 mL). The layers were separated and the water layer was extracted with EtOAc (3 x 10 mL). The combined organic

41 Luescher, M. U.; Vo, C.-V. T.; Bode, J. W.: SnAP Reagents for the Synthesis of Piperazines and Morpholines. *Org. Lett.* **2014**, *16*, 1236–1239.

42 Pendem, N.; Douat, C.; Claudon, P.; Laguerre, M.; Castano, S.; Desbat, B.; Cavagnat, D.; Ennifar, E.; Kauffmann, B.; Guichard, G.: Helix-Forming Propensity of Aliphatic Urea Oligomers Incorporating Noncanonical Residue Substitution Patterns. *J. Am. Chem. Soc.* **2013**, *135*, 4884–4892.

layers were washed with H_2O (2 x 10 mL), brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (hexanes:EtOAc = 1:0 → 8:1) afforded aza-SnAP reagent **198** (4.2 g, 60% yield) as a colorless liquid. At temperature the ratio of rotamers was 75:25 as determined by ^{1}H NMR; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 3.87–3.80 (m, 2x 0.25H), 3.69 (h, *J* = 6.7 Hz, 2x 0.25H), 3.34 (dd, *J* = 14.0, 4.2 Hz, 2x 0.25H), 3.25–3.15 (m, 2x 0.75H), 3.09 (d, *J* = 13.6 Hz, 2x 0.25H), 2.96–2.89 (m, 2x 0.25H), 2.85 (s, $J(^{117/119}Sn\text{-}^1H)$ = 26.1 Hz, 1H), 1.54–1.41 (m, 15H), 1.29 (q, *J* = 7.3 Hz, 6H), 1.22 (d, *J* = 6.5 Hz, 3H), 0.93–0.82 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 155.4, 79.7, 56.7, 55.5, 35.0, 29.3, 28.6, 27.6, 17.3, 13.9, 10.7; **HRMS** (ESI): calculated for $[C_{21}H_{44}N_4NaO_2Sn]^+$: m/z = 527.2382, found: m/z = 527.2375; **IR** (ν/cm $^{-1}$, neat) 2956, 2924, 2871, 2853, 2114, 1683, 1479, 1456, 1400, 1380, 1365, 1338, 1247, 1162, 1134.

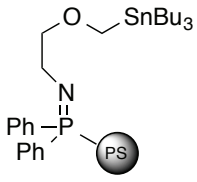
7.3 Preparation of Polymer Supported SnAP Reagents

The loading of the SnAP reagent was calculated according to the following formula:

$$m(loaded\ SnAP) = m(PS\ after\ rxn) - m(PS\ before\ rxn)$$

$$Loading = \frac{m(loaded\ SnAP)/MW(aza\ SnAP - N_2)}{m(PS\ after\ rxn)} \left[{}^{mol}/_{g}\right]$$

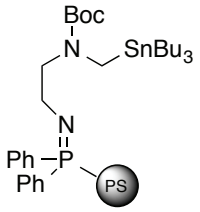
Polymer Supported SnAP Morpholine (134)



((2-Azidoethoxy)methyl)ributylstannane[43] (2.0 g, 5.1 mmol, 1.0 equiv) and polymer-bound diphenylphosphine (1.7 g, 5.1 mmol, 1.0 equiv) in THF (8 mL) was allowed to stir at rt for 1 h and at 60 ºC for 5 h. The resulting polymer was washed with THF (5 x 20 mL) and dried *in vacuo*. **Elemental analysis** found C 64.8%, H 7.2%, N 1.9%, P 4.8 % (Loading 1.34 mmol/g); Dry weight = 2.5 g.

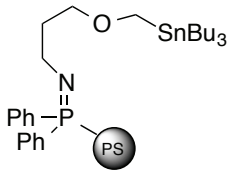
43 Prepared according to: Siau, W.-Y.; Bode, J. W.: One Step Synthesis of Saturated Spirocyclic N-Heterocycles with SnAP Reagents and Ketones *J. Am. Chem. Soc.* **2014**, *136*, 17726–17729.

Polymer Supported SnAP Piperazine (130)



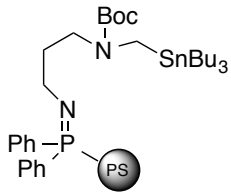
tert-Butyl (2-azidoethyl)((tributylstannyl)methyl)carbamate[43] (2.9 g, 6.0 mmol, 1.0 equiv) and polymer-bound diphenylphosphine (2.0 g, 6.0 mmol, 1.0 equiv) in THF (8 mL) was allowed to stir at rt for 1 h and at 60 ºC for 5 h. The resulting polymer was washed with THF (5 × 20 mL) and dried *in vacuo*. **Elemental analysis** found C 64.1%, H 7.3%, N 3.0%, O 5.1%, P 4.3 % (Loading 1.09 mmol/g); Dry weight = 3.1 g.

Polymer Supported SnAP 1,4-Oxazepane (136)



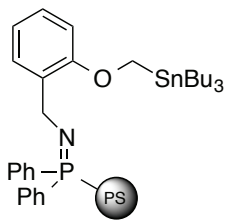
((3-Azidopropoxy)methyl)tributylstannane **176** (1.8 g, 4.5 mmol, 1.0 equiv) and polymer-bound diphenylphosphine (1.5 g, 4.5 mmol, 1.0 equiv) in THF (8 mL) was allowed to stir at rt for 1 h and at 60 ºC for 5 h. The resulting polymer was washed with THF (5 × 20 mL) and dried *in vacuo*. **Elemental analysis** found C 66%, H 7.2%, N 1.7%, O 3.0%, P 5.0% (Loading 1.23 mmol/g); Dry weight = 2.5 g.

Polymer Supported SnAP Diazepane (133)



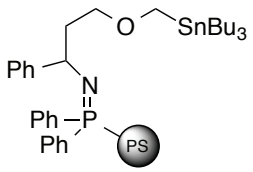
tert-Butyl (3-azidopropyl)((tributylstannyl)methyl)carbamate **180** (2.7 g, 5.4 mmol, 1.2 equiv) and polymer-bound diphenylphosphine (1.5 g, 4.5 mmol, 1.0 equiv) in THF (8 mL) was allowed to stir at rt for 1 h and at 60 ºC for 5 h. The resulting polymer was washed with THF (5 × 20 mL) and dried *in vacuo*. **Elemental analysis** found C 65.2%, H 7.6%, N 2.8%, O 4.9%, P 4.4 % (Loading 1.00 mmol/g); Dry weight = 2.7 g.

Polymer Supported SnAP Tetrahydrobenzo-1,4-oxazepine (138)



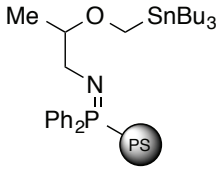
((2-(Azidomethyl)phenoxy)methyl)tributylstannane **183** (3.2 g, 7.0 mmol, 1.0 equiv) and polymer-bound diphenylphosphine (2.3 g, 7.0 mmol, 1.0 equiv) in THF (13 mL) was allowed to stir at rt for 1 h and at 60 °C for 5 h. The resulting polymer was washed with THF (5 × 20 mL) and dried *in vacuo*. **Elemental analysis** found C 67.1%, H 6.7%, N 1.5%, O 2.5%, P 4.6% (Loading 1.10 mmol/g); Dry weight = 4.3 g.

Polymer Supported SnAP 3-Phenyl-1,4-oxazepane (137)



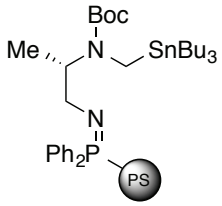
((3-Azido-3-phenylpropoxy)methyl)tributylstannane **187** (3.9 g, 8.0 mmol, 1.0 equiv) and polymer-bound diphenylphosphine (2.7 g, 8.0 mmol, 1.0 equiv) in THF (15 mL) was allowed to stir at rt for 1 h and at 60 °C for 5 h. The resulting polymer was washed with THF (5 x 20 mL) and dried *in vacuo*. **Elemental analysis** found C 68.7%, H 7.0%, N 1.4%, O 2.6%, P 4.2% (Loading 1.00 mmol/g); Dry weight = 5.0 g.

Polymer Supported SnAP 2-Methyl-Morpholine (135)



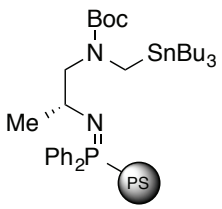
(((1-Azidopropan-2-yl)oxy)methyl)tributylstannane **190** (2.1 g, 5.2 mmol, 1.5 equiv) was added to polymer-bound triphenylphosphine (1.2 g, 3.5 mmol, 1.0 equiv) in THF (5 mL). The resulting mixture was allowed to stir at rt for 1 h and at 60 °C for another 4 h. The polymer was washed with THF (6 x 30 mL) and dried *in vacuo* affording polymer-bound iminophosphorane. **Elemental analysis** found C 65.1%, H 7.3%, N 1.5%, O 3.8%, P 5.0% (Loading 1.00 mmol/g); Dry weight = 1.9 g.

Polymer Supported SnAP 2-Methyl-Piperazine (131)



tert-Butyl (*S*)-(1-azidopropan-2-yl)((tributylstannyl)methyl)-carbamate **194** (2.2 g, 4.3 mmol, 1.2 equiv) was added to polymer-bound triphenylphosphine (1.2 g, 3.6 mmol, 1.0 equiv) in THF (5 mL). The resulting mixture was allowed to stir at rt for 1 h and at 60 °C for another 4 h. The polymer was washed with THF (6 x 30 mL) and dried *in vacuo* affording polymer-bound iminophosphorane. **Elemental analysis** found C 64.4%, H 7.6%, N 2.8%, O 4.8%, P 4.3% (Loading 1.03 mmol/g); Dry weight = 2.4 g.

Polymer Supported SnAP 3-Methyl-Piperazine (132)

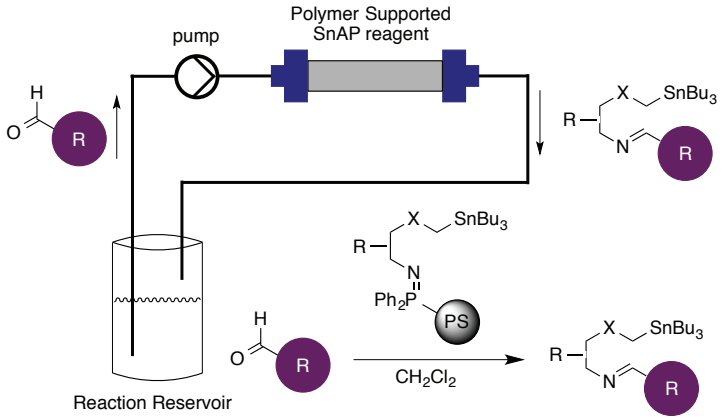


tert-Butyl (*R*)-(2-azidopropyl)-((tributylstannyl)methyl)carbamate **198** (3.0 g, 6.0 mmol, 1.1 equiv) was added to polymer-bound triphenylphosphine (1.8 g, 5.5 mmol, 1.0 equiv) in THF (10 mL). The resulting mixture was allowed to stir at rt for 1 h and at 60 °C for another

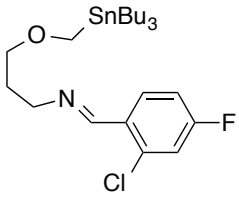
6 h. The polymer was washed with THF (6 x 30 mL) and dried *in vacuo* affording polymer-bound iminophosphorane. **Elemental analysis** found C 65.4%, H 7.4%, N 2.7%, O 4.2%, P 4.63% (Loading 0.99 mmol/g); Dry weight = 3.4 g.

7.4 Synthesis of Imines in Flow Conditions

Scheme of general reaction setup for imine-formation step:

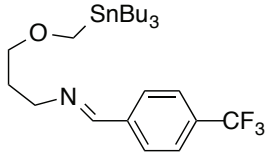


1-(2-Chloro-4-fluorophenyl)-*N*-(3-((tributylstannyl)methoxy)propyl)methanimine (199)



A solution of 4-chloro-2-fluorobenzaldehyde (32 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was pumped at 7 ml/min through polymer supported SnAP 1,4-oxazepane **136** (0.49 g, 0.60 mmol, 3.0 equiv) at rt for 1 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **199** (82%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.32 (s, 1H), 7.83 (d, *J* = 8.3Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 3.74–3.67 (m, 4H), 3.40 (t, *J* = 6.1 Hz, 2H), 1.95 (quint, *J* = 6.5 Hz, 2H), 1.63–1.40 (m, 6H), 1.30 (sext, *J* = 7.7 Hz, 6H), 1.01–0.78 (m, 15H).

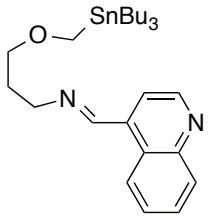
N-(3-((Tributylstannyl)methoxy)propyl)-1-(4-(trifluoromethyl)phenyl)methanimine (200)



A solution of 4-(trifluoromethyl)benzaldehyde (35 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was pumped at 7 ml/min through polymer supported SnAP 1,4-oxazepane **136** (0.49 g, 0.60 mmol, 3.0 equiv) at rt for 1 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **200** (71%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.64 (s, 1H), 8.03 (dd, *J* = 8.5 Hz, 6.3 Hz, 1H), 7.12 (dd, *J* = 8.5 Hz, 2.6 Hz, 1H), 7.05–6.98

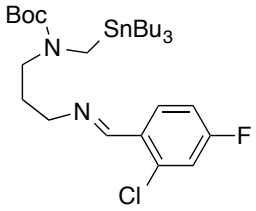
(m, 1H), 3.75–3.67 (m, 4H), 3.39 (t, *J* = 6.1 Hz, 2H), 1.94 (quint, *J* = 6.4 Hz, 2H), 1.65–1.41 (m, 6H), 1.30 (sext, *J* = 7.7 Hz, 6H), 1.02–0.78 (m, 15H).

1-(Quinolin-4-yl)-*N*-(3-((tributylstannyl)methoxy)propyl)methanimine (201)



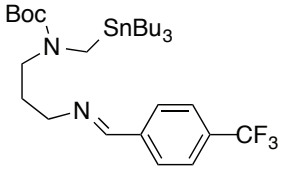
A solution of quinoline-4-carbaldehyde (31 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was pumped at 7 ml/min through polymer supported SnAP 1,4-oxazepane **136** (0.49 g, 0.60 mmol, 3 .0equiv) at rt for 1 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **201** (100%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.03–8.90 (m, 2H), 8.80–8.67 (m, 1H), 8.23–8.09 (m, 1H), 7.81–7.71 (m, 2H), 7.68–7.59 (m, 1H), 3.85 (td, *J* = 6.9, 1.4 Hz, 2H), 3.78–3.68 (m, 2H), 3.46 (t, *J* = 6.1 Hz, 2H), 2.10–1.98 (m, 2H), 1.63–1.39 (m, 6H), 1.38– 1.23 (m, 6H), 1.03–0.78 (m, 15H).

***tert*-Butyl (3-((2-chloro-4-fluorobenzylidene) amino)propyl)((tributylstannyl) methyl) carbamate (202)**



A solution of 4-chloro-2-fluorobenzaldehyde (32 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was pumped at 7 ml/min through polymer supported SnAP diazepane **133** (0.60 g, 0.60 mmol, 3.0 equiv) at rt for 1 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **202** (100%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.67 (s, 1H), 8.06 (dd, *J* = 8.7 Hz, 6.3 Hz, 1H), 7.18–7.10 (m, 1H), 7.08–6.98 (m, 1H), 3.72–3.61 (m, 2H), 3.37–2.78 (m, 5H), 2.03–1.89 (m, 2H), 1.63–1.21 (m, 21H), 1.01–0.75 (m, 15H).

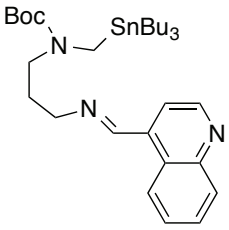
***tert*-Butyl ((tributylstannyl)methyl) (3-((4-(trifluoromethyl)benzylidene)amino)propyl) carbamate (203)**



A solution of 4-(trifluoromethyl)benzaldehyde (35 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was pumped at 7 ml/min through polymer supported SnAP diazepane **133** (0.60 g, 0.60 mmol, 3.0 equiv) at rt for 1 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **203** (100%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.33 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 3.70–3.60 (m, 2H), 3.34–3.20

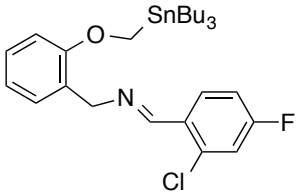
(m, 2H), 3.08 (s, 1H), 2.85 (s, 1H), 2.01–1.89 (m, 2H), 1.57–1.38 (m, 15H), 1.36–1.20 (sext, *J* = 7.7 Hz, 6H), 0.98–0.81 (m, 15H).

tert-Butyl (3-((quinolin-4-ylmethylene)amino)propyl)((tributylstannyl)methyl)carbamate (204)



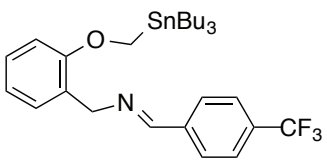
A solution of quinoline-4-carbaldehyde (31 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was pumped at 7 ml/min through polymer-supported SnAP diazepane **133** (0.60 g, 0.60 mmol, 3.0 equiv) at rt for 1 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **204** (100%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.04–8.92 (m, 2H), 8.76 (d, *J* = 8.3 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 7.82–7.70 (m, 2H), 7.68–7.59 (m, 1H), 3.79 (t, *J* = 6.9 Hz, 2H), 3.44–3.25 (m, 2H), 2.88 (s, 1H), 2.14–1.93 (m, 2H), 1.57–1.35 (m, 16H), 1.27 (sext, *J* = 7.2 Hz, 6H), 0.87 (t, *J* = 7.2 Hz, 15H).

1-(2-Chloro-4-fluorophenyl)-*N*-(2-((tributylstannyl)methoxy)benzyl)methanimine (205)



A solution of 4-chloro-2-fluorobenzaldehyde (32 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was pumped at 7 ml/min through polymer supported SnAP tetrahydrobenzo-1,4-oxazepine **138** (0.55 g, 0.60 mmol, 3.0 equiv) at rt for 2 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **205** (86%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.72–8.69 (m, 1H), 8.13 (dd, *J* = 8.6 Hz, 6.4 Hz, 1H), 7.31–6.89 (m, 5H), 4.83 (s, 2H), 4.16 (s, $J(^{117/119}Sn\text{-}^1H)$ = 7.8 Hz, 2H), 1.58–1.45 (m, 6H), 1.35–1.22 (m, 6H), 1.08–0.84 (m, 15H).

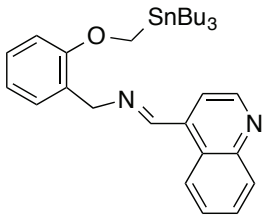
N-(2-((Tributylstannyl)methoxy)benzyl)-1-(4-(trifluoromethyl)phenyl)methanimine (206)



A solution of 4-(trifluoromethyl)benzaldehyde (35 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was pumped at 7 ml/min through polymer supported SnAP tetrahydrobenzo-1,4-oxazepine **138** (0.55 g, 0.60 mmol, 3.0 equiv) at rt for 2 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **206** (74%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.34 (m, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.32–7.23 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.96–6.89 (m, 1H), 4.85 (s, 2H),

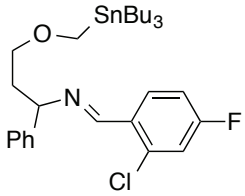
4.15 (s, $J(^{117/119}Sn\text{-}^{1}H)$ = 7.5 Hz, 2H), 1.56–1.36 (m, 6H), 1.28 (sext, *J* = 7.3 Hz, 6H), 1.07–0.83 (m, 15H).

1-(Quinolin-4-yl)-*N*-(2-((tributylstannyl)methoxy)benzyl)methanimine (207)



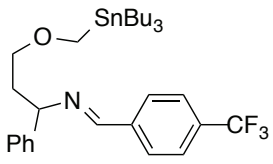
A solution of quinoline-4-carbaldehyde (31 mg, 0.2.0 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was pumped at 7 ml/min through polymer supported SnAP tetrahydrobenzo-1,4-oxazepine **138** (0.55 g, 0.60 mmol, 3.0 equiv) at rt for 2 h. The column was washed with CH_2Cl_2 (10 mL). The solution was concentrated *in vacuo*, yielding imine **207** (100%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.02–8.94 (m, 2H), 8.78–8.71 (m, 1H), 8.20–8.14 (m, 1H), 7.81–7.71 (m, 2H), 7.66–7.58 (m, 1H), 7.35–7.28 (m, 2H), 7.13–7.06 (m, 1H), 6.95 (m, 1H), 4.99 (d, *J* = 1.6 Hz, 2H), 4.19 (s, 2H), 1.59–1.38 (m, 6H), 1.36– 1.17 (m, 6H), 0.99–0.81 (m, 15H).

1-(2-Chloro-4-fluorophenyl)-*N*-(1-phenyl-3-((tributylstannyl)methoxy)propyl) methanimine (208)



A solution of 4-chloro-2-fluorobenzaldehyde (32 mg, 0.20 mmol, 1.0 equiv) in 1,2-dichloroethane (2 mL) was pumped at 7 ml/min through polymer-supported SnAP 3-phenyl-1,4-oxazepane **137** (0.57 g, 0.60 mmol, 3.0 equiv) at 80 °C for 2 h. The column was washed with 1,2-dichloroethane (10 mL). The solution was concentrated *in vacuo*, yielding imine **208** (25%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.69 (s, 1H), 8.14 (dd, *J* = 8.8, 6.4 Hz, 1H), 7.46–7.40 (m, 2H), 7.37–7.31 (m, 2H), 7.28–7.21 (m, 1H), 7.13–7.09 (m, 1H), 7.06–6.96 (m, 1H), 4.56 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.72–3.59 (m, 2H), 3.27 (dd, *J* = 6.7, 5.5 Hz, 2H), 2.23–2.03 (m, 2H), 1.56–1.44 (m, 6H), 1.39–1.23 (m, 6H), 0.99–0.78 (m, 15H).

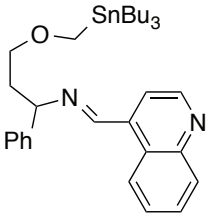
***N*-(1-Phenyl-3-((tributylstannyl)methoxy)propyl)-1-(4-(trifluoromethyl)phenyl) methanimin (209)**



A solution of 4-(trifluoromethyl)benzaldehyde (35 mg, 0.20 mmol, 1.0 equiv) in 1,2-dichloroethane (2 mL) was pumped at 7 ml/min through polymer-supported SnAP 3-phenyl-1,4-oxazepane **137** (0.57 g, 0.60 mmol, 3.0 equiv) at 80 °C for 2 h. The column was washed with 1,2-

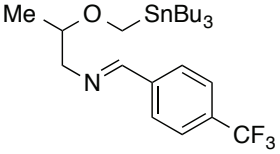
dichloroethane (10 mL). The solution was concentrated *in vacuo*, yielding imine **209** (51%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 8.38 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.49–7.42 (m, 2H), 7.40–7.33 (m, 2H), 7.28–7.23 (m, 1H), 4.56 (dd, *J* = 8.3, 5.8 Hz, 1H), 3.77–3.61 (m, 2H), 3.35–3.23 (m, 2H), 2.26–2.08 (m, 2H), 1.58–1.44 (m, 6H), 1.40–1.25 (m, 6H), 0.92 (m, 15H).

N-(1-Phenyl-3-((tributylstannyl)methoxy)propyl)-1-(quinolin-4-yl)methanimine (210)



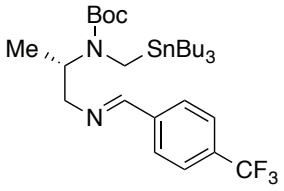
A solution of quinoline-4-carbaldehyde (31 mg, 0.20 mmol, 1.0 equiv) in 1,2-dichloroethane (2 mL) was pumped at 7 ml/min through polymer-supported SnAP 3-phenyl-1,4-oxazepane **137** (0.57 g, 0.60 mmol, 3.0 equiv) at 80 °C for 2 h. The column was washed with 1,2-dichloroethane (10 mL). The solution was concentrated *in vacuo*, yielding imine **210** (31%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ [ppm] = 9.0–8.96 (m, 2H), 8.84–8.79 (m, 1H), 8.19–8.14 (m, 1H), 7.79–7.73 (m, 1H), 7.68–7.60 (m, 1H), 7.53–7.47 (m, 2H), 7.42–7.27 (m, 4H), 4.66 (dd, *J* = 8.2, 5.8 Hz, 1H), 3.69 (d, *J* = 4.2 Hz, 2H), 3.36–3.28 (m, 2H), 2.23 (m, 2H), 1.58–1.43 (m, 6H), 1.38–1.22 (m, 6H), 1.01–0.81 (m, 15H).

N-(2-((Tributylstannyl)methoxy)propyl)-1-(4-(trifluoromethyl)phenyl)methanimine (211)



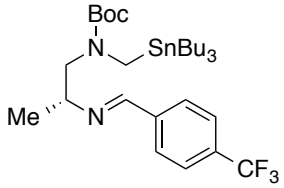
A solution of 4-(trifluoromethyl)benzaldehyde (55 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was pumped at 5 ml/min through polymer supported SnAP 2-methyl-morpholine **135** (0.50 g, 0.50 mmol, 1.5 equiv) at rt. After 1 h circular flow the column was purged with air and washed with CH_2Cl_2 (5 mL). The solution was concentrated *in vacuo*, yielding imine **211** (150 mg, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.27 (s, 1H), 7.75 (dd, *J* = 71.9, 8.1 Hz, 4H), 3.71 (dd, *J* = 83.1, 10.0 Hz, 2H), 3.72–3.60 (m, 2H), 3.58–3.50 (m, 1H), 1.48–1.39 (m, 6H), 1.28–1.17 (m, 9H), 0.92–0.80 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 160.87, 139.61, 128.66 (d, J = 12.5 Hz), 128.42, 125.64 (q, *J* = 3.7 Hz), 78.77, 67.06, 59.42, 29.24, 27.39, 17.71, 13.83, 9.07; **HRMS** (ESI): calculated for $[C_{24}H_{41}F_3NOSn]^+$: m/z = 536.2161, found: m/z = 536.2149; **IR** (ν/cm $^{-1}$, neat) 2957, 2926, 2871, 2853, 1650, 1458, 1415, 1376, 1325, 1310, 1168, 1131, 1105, 1088, 1066, 1043, 1018.

tert-Butyl (_S_)-((tributylstannyl)methyl) (1-((4-(trifluoromethyl)benzylidene)amino) propan-2-yl) carbamate (212)



A solution of 4-(trifluoromethyl)benzaldehyde (58 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was pumped at 5 ml/min through polymer supported SnAP 2-methyl-piperazine **131** (0.50 g, 0.50 mmol, 1.5 equiv) at rt. After 2 h circular flow the column was purged with air and washed with CH_2Cl_2 (5 mL). The solution was concentrated *in vacuo,* yielding imine **212** (170 mg, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.24 (s, 1H), 7.74 (dd, *J* = 68.3, 8.1 Hz, 4H), 4.47–4.40 (m, 1H), 3.71 (dd, *J* = 21.2, 7.4 Hz, 2H), 2.89 (q, *J* = 13.3 Hz, 2H x0.25), 2.58 (s, $J(^{117/119}Sn\text{-}^1H)$ = 29.0 Hz, 2H x0.75), 1.50–1.37 (m, 15H), 1.31–1.20 (m, 9H), 0.92–0.77 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 180.53, 160.39, 155.94, 139.39, 130.07, 128.46, 125.66 (q, *J* = 3.4 Hz), 79.19, 64.71, 53.19, 29.32, 28.66, 27.65, 16.89, 13.88, 10.95, 9.90; **HRMS** (ESI): calculated for $[C_{29}H_{50}F_3N_2O_2Sn]^+$: m/z = 635.2846, found: m/z = 635.2841; **IR** (ν/cm $^{-1}$, neat) 2956, 2924, 2871, 2852, 1671, 1651, 1456, 1415, 1393, 1366, 1356, 1325, 1310, 1254, 1165, 1132, 1105, 1066, 1018.

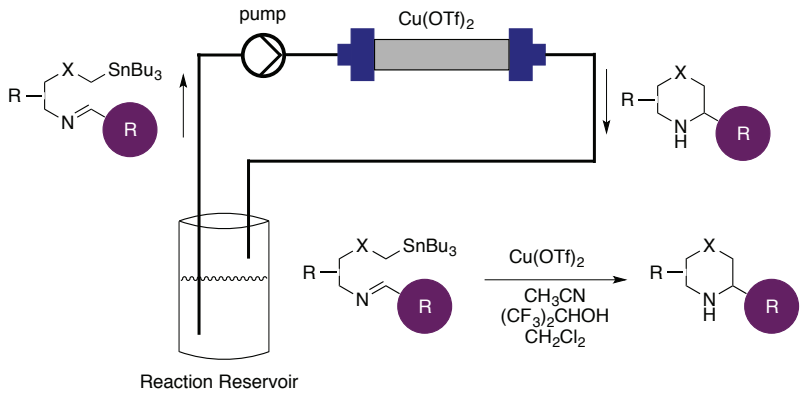
tert-Butyl (_R_)-((tributylstannyl)methyl)(2-((4-(trifluoromethyl)benzylidene)amino)propyl) carbamate (213)



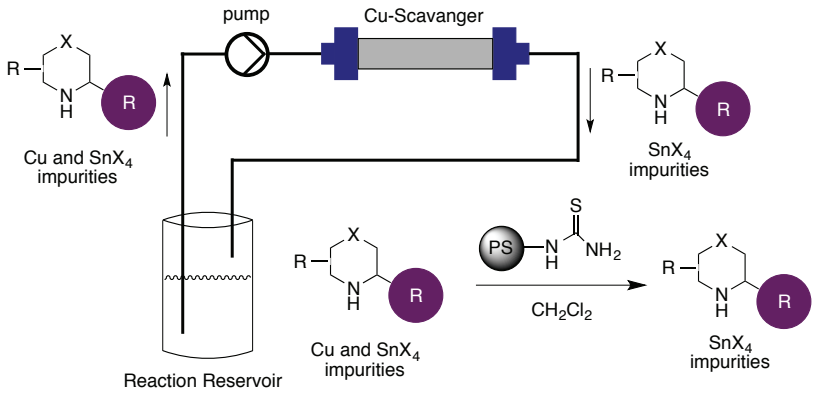
A solution of 4-(trifluoromethyl)benzaldehyde (260 mg, 1.5 mmol, 3.0 equiv) in 1,2-dichloroethane (5 mL) was pumped at 1 ml/min through polymer supported SnAP 3-methyl-piperazine **132** (0.50 g, 0.50 mmol, 1.0 equiv) at 80 °C. After 2.5 h circular flow the column was purged with air and washed with 1,2-dichloroethane (5 mL). The solution was concentrated *in vacuo*, yielding imine **213** (260 mg, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.28 (s, 1H), 7.77 (dd, *J* = 72.0, 8.1 Hz, 4H), 3.74–3.63 (m, 1H), 3.52–3.20 (m, 2H), 2.96–2.74 (m, 2H), 1.50–1.40 (m, 15H), 1.33–1.24 (m, 9H), 0.93–0.85 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 163.3, 158.6, 139.5, 135.6, 128.5, 125.7 (q, *J* = 3.4 Hz), 119.3, 79.2, 66.0, 57.0, 35.2, 29.3, 28.6, 27.6, 20.0, 13.9, 10.6; **HRMS** (ESI): calculated for $[C_{29}H_{50}F_3N_2O_2Sn]^+$: m/z = 635.2846, found: m/z = 635.2844; **IR** (ν/cm $^{-1}$, neat) 2956, 2925, 2871, 2853, 1677, 1648, 1480, 1457, 1394, 1376, 1365, 1324, 1308, 1249, 1166, 1132, 1105, 1065, 1018.

7.5 Cyclization in Flow Conditions

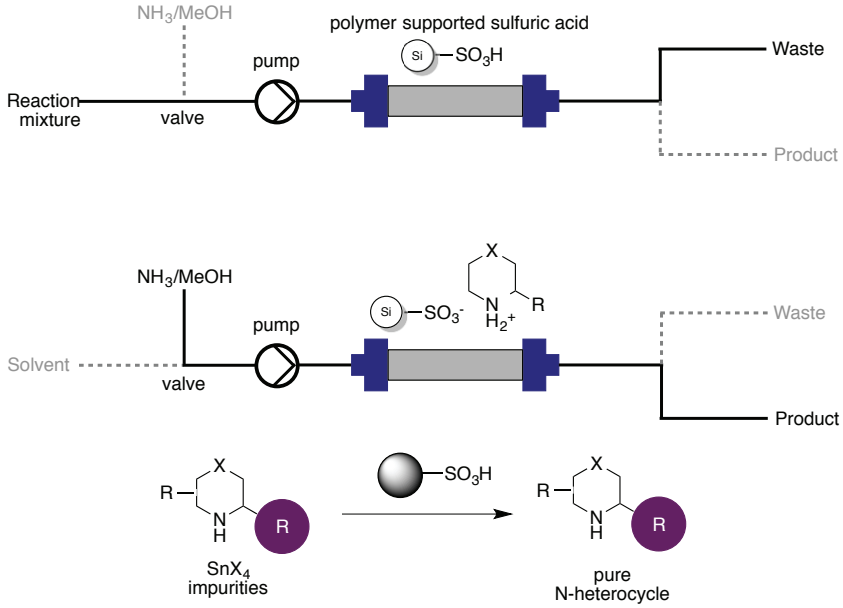
Scheme of general reaction setup for cyclization step:



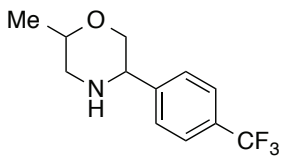
Scheme of general reaction setup for copper scavenging step:



Scheme of general reaction setup for purification scavenging step:



2-Methyl-5-(4-(trifluoromethyl)phenyl)morpholine (214)

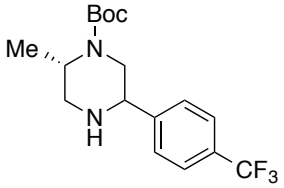


Cyclization step: A solution of imine **211** (49 mg, 0.10 mmol, 1.0 equiv) and CH_3CN (52 μl, 1.0 mmol, 10 equiv) in $(CF_3)_2CHOH$ (2 mL) and CH_2Cl_2 (8 mL) was pumped at 1 ml/min through dry $Cu(OTf)_2$ (360 mg, 1.0 mmol, 10 equiv) at rt. After 1 h circular flow the column was purged with air and washed with CH_2Cl_2 (5 mL).

Copper scavenging step: The reaction mixture was pumped at 1 ml/min through QP-TU (thiourea resin) (bed volume = 1.7 mL). After 20 min circular flow the column was purged with air and washed with CH_2Cl_2 (5 mL).

Purification step: The resulting mixture was loaded on a column of ISOLUTE® HCX (SO_3H support on silica) (bed volume = 2.4 mL). The system was washed with CH_2Cl_2 (50 mL) and MeOH (25 mL). The product was eluted with 2 N NH_3/Methanol (10 mL). Purification by column chromatography on silica (CH_2Cl_2:MeOH = 1:0 → 20:1) afforded morpholine **214** (8.8 mg, 39%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.55 (dd, *J* = 29.9, 8.2 Hz, 4H), 3.95 (dd, *J* = 10.2, 3.2 Hz, 1H), 3.85 (dd, *J* = 11.1, 3.2 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.42 (dd, *J* = 11.0, 10.3 Hz, 1H), 3.06 (dd, *J* = 11.6, 2.3 Hz, 1H), 2.74 (dd, *J* = 11.6, 10.2 Hz, 1H), 1.75 (br, 1H), 1.20 (d, *J* = 6.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 144.6, 130.1 (q, *J* = 32.4 Hz), 127.7, 125.6 (q, *J* = 3.8 Hz), 122.9, 73.7, 72.5, 59.8, 53.1, 19.1; **HRMS** (ESI): calculated for $[C_{12}H_{15}F_3NO]^+$: m/z = 246.1100, found: m/z = 246.1100; **IR** (ν/cm^{-1}, neat) 3304, 2977, 2892, 2868, 2853, 2817, 2895, 1618, 1444, 1414, 1392, 1331, 1165, 1116, 1068.

***tert*-Butyl (2*S*)-2-methyl-5-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (215)**



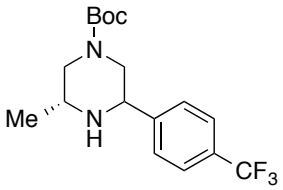
Cyclization step: A solution of imine **212** (63 mg, 0.1 mmol, 1.0 equiv) and CH_3CN (52 μl, 1.0 mmol, 10 equiv) in $(CF_3)_2CHOH$ (2 mL) and CH_2Cl_2 (8 mL) was pumped at 5 ml/min through dry $Cu(OTf)_2$ (180 mg, 0.50 mmol, 5.0 equiv) at rt. After 1 h circular flow the column was purged with air and washed with CH_2Cl_2 (5 mL).

Copper scavenging step: The reaction mixture was pumped at 2 ml/min through QP-TU (thiourea resin) (bed volume = 1.7 mL). After 10 min circular flow the system was purged with air and washed with CH_2Cl_2 (5 mL).

Purification step: The resulting mixture was loaded on a column of ISOLUTE® HCX (SO_3H support on silica) (bed volume = 2.5 mL). The system was washed with CH_2Cl_2 (20 mL) and MeOH (20 mL). The product was eluted with 2 N NH_3/Methanol (10 mL). Purification with

PTLC on silica (CH_2Cl_2:MeOH = 20:1) afforded piperazine **215** (11.7 mg, 35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.60 (q, *J* = 8.1, 7.6 Hz, 4H), 4.31 (d, *J* = 53.0 Hz, 1H), 4.13–3.82 (m, 1H), 3.78 (d, *J* = 8.6 Hz, 1H), 3.15–2.93 (m, 2H), 2.91–2.77 (m, 1H), 1.60 (br, 1H), 1.50 (s, 9H), 1.35 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 146.0, 143.7, 127.5, 125.6, 119.1, 115.8, 79.9, 60.3, 50.6, 46.9, 28.6, 15.4; **HRMS** (ESI): calculated for $[C_{17}H_{24}F_3N_2O_2]^+$: m/z = 345.1784, found: m/z = 345.1780; **IR** (ν/cm $^{-1}$, neat) 3323, 2963, 2926, 2864, 2814, 1687, 1618, 1451, 1410, 1366, 1326, 1292, 1244, 1234, 1166, 1125, 1067, 1017.

tert-Butyl (3*R*)-3-methyl-5-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (216)



Cyclization step: A solution of imine **213** (64.5 mg, 0.1 mmol, 1.0 equiv) and CH_3CN (52 μl, 1.0 mmol, 10 equiv) in $(CF_3)_2CHOH$ (2 mL) and CH_2Cl_2 (8 mL) was pumped at 2 ml/min through dry $Cu(OTf)_2$ (180 mg, 0.5 mmol, 5 equiv) at rt. After 1 h circular flow the column was purged with air and washed with CH_2Cl_2 (5 mL).

Copper scavenging step: The reaction mixture was pumped at 1 ml/min through QP-TU (thiourea resin) (bed volume = 1.7 mL). After 20 min circular flow the system was purged with air and washed with CH_2Cl_2 (5 mL).

Purification step: The resulting mixture was loaded on a column of ISOLUTE® HCX (SO_3H support on silica) (bed volume = 4 mL). The system was washed with CH_2Cl_2 (15 mL) and MeOH (15 mL). The product was eluted with 2 N NH_3/MeOH (6 mL) yielding piperazine **216** (22.8 mg, 65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.64–7.55 (m, 4H), 4.06 (s, 2H), 3.90–3.84 (m, 1H), 2.99–2.90 (m, 1H), 2.58 (d, *J* = 62.6 Hz, 2H), 1.62 (br, 1H), 1.50 (s, 9H), 1.14 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 167.4, 154.7, 127.7, 125.6 (q, *J* = 4.0 Hz), 110.5, 80.1, 60.6, 51.1, 45.3, 29.9, 28.6, 19.5; **HRMS** (ESI): calculated for $[C_{17}H_{24}F_3N_2O_2]^+$: m/z = 345.1784, found: m/z = 345; **IR** (ν/cm $^{-1}$, neat) 3305, 2963, 2925, 2853, 1693, 1621, 1456, 1417, 1393, 1366, 1325, 1310, 1266, 1240, 1166, 1128, 1067, 1018.

7.6 Source Code for the Automated Synthesizer

The following code was written in the Open Source Arduino IDE.

```
//---------------DECLARATION----------------------
//all variables, objects and libraries are declared
//------------------------------------------------

//all external libraries included:

#include <Wire.h> //library for the I2C interface
#include <genieArduino.h> //library for the touchscreen interface from 4D

//library for MotorShields powering the rotary valves:
#include <Adafruit_MotorShield.h> #include
"utility/Adafruit_PWMServoDriver.h"

//two libraries for the one-wire-interface and commands to temperature
sensor:
#include <OneWire.h>
#include <DallasTemperature.h>


//Setup of all classes and components:

//setup of the command handler of the touchscreen
Genie genie;

//Setup of both stepper motor for both rotary valves:
Adafruit_MotorShield AFMSa = Adafruit_MotorShield(0x62);
Adafruit_StepperMotor *rotvalve[3] = {AFMSa.getStepper(200,
1),AFMSa.getStepper(200, 2)};

//Setup of the temperature sensor
OneWire oneWire(ONE_WIRE_BUS);
DallasTemperature sensors(&oneWire);
//Device Adress of temperature sensor
DeviceAddress insideThermometer = {0x28, 0xF2, 0xCB, 0xB4, 0x6, 0x0, 0x0,
0x1E};


//definition of all global variables:

#define RESETLINE 10 //pin attached to reset transistor of touchscreen
#define ONE_WIRE_BUS 2 //pin attached to data line of temperature sensor

boolean stepdone=0;
boolean pumpswitch = LOW;
unsigned long previousMillis = 0;
unsigned long previousMillisTemp = 0;
unsigned long previousMillisHeat = 0;
boolean pumpstate =LOW;
boolean pumpcycle =LOW;
boolean heaterstate = LOW;
int pumpspeed = 2;
int currentportnr[3]={1,1};
int tempmenu;
byte speedcom = 13;
int tempset = 60;
int tempCc;
boolean heaterswitch = LOW;
```

```
int i;
unsigned long previousMillisAutoMode = 0;
unsigned long currentMillisAutoMode =0;
unsigned long pause = 0;

//following values represent time each step takes
unsigned long MillisStep1 = 960000;
unsigned long MillisStep2 = 1800000+MillisStep1;
unsigned long MillisStep3 = 960000+MillisStep2;
unsigned long MillisStep4 = 420000+MillisStep3;
unsigned long MillisStep5 = 100+MillisStep4;
unsigned long MillisStep6 = 100+MillisStep5;
unsigned long MillisStep7 = 100+MillisStep6;
unsigned long MillisStep8 = 100+MillisStep7;
unsigned long MillisStep9 = 100+MillisStep8;
unsigned long MillisStepTemp;

int manualdose=20;
int temp;
int counter = 0;
char keyvalue[10];
char StepTimes2[5][10]={"10","20","30","40","50"};
StepTimes2[5][10]={"10","20","30","40","50"};
int menuselector = 0;
int menucounter[6] = {2,2,2,2,2};
boolean automaticState = LOW;
boolean pauseState;
byte x = 0;

//----------------------LOOP-----------------------------------------------
//setup routine is executed one time when the microcontroller is started:
//variables, pins and objects are initialized
//-------------------------------------------------------------------------

void setup() {

  Serial.begin(115200); //begin serial interface to PC
  Serial3.begin(9600); //begin serial interface for stirrer communication
  sensors.begin(); //start temperature sensor

  //output pins connected to status LEDs
  pinMode(24, OUTPUT);
  pinMode(25, OUTPUT);
  pinMode(26, OUTPUT);
  pinMode(27, OUTPUT);
  pinMode(28, OUTPUT);
  pinMode(29, OUTPUT);
  pinMode(30, OUTPUT);
  pinMode(31, OUTPUT);

  pinMode(4, OUTPUT); //output pin for pump solenoid magnetization
  pinMode(3, OUTPUT); // output pin to heater – optotriac

  //input pins for rotary valve position sensor
  pinMode(7, INPUT);
  pinMode(6, INPUT);
  pinMode(8, INPUT);
  pinMode(9, INPUT);

  digitalWrite(3, LOW); //start heater as 'off'

  //start up stirrer as 'off'
  Serial3.write('i');
```

```
  Serial3.write(0);
  Serial3.write(speedcom);

  //start rotary valves stepper motor and set speed
  AFMSa.begin();
  for(i = 0; i<2; i++){
    rotvalve[i]->setSpeed(35);
  }

  //start the communication between the touchscreen and the microcontroller
  Serial2.begin(9600); //Serial2 to comminicate with LCD
  genie.Begin(Serial2);
  genie.AttachEventHandler(myGenieEventHandler);

  //send parameters for the temperature sensors
  sensors.setResolution(insideThermometer, 11);
  sensors.setWaitForConversion(false);

  //set both rotary valves to port nr 1
  homevalve(0);
  homevalve(1);

  //reset touchscreen to enable communication synchronization
  //pull reset line high for 0.1s to reset and wait 3.5s for a restart
  pinMode(RESETLINE, OUTPUT);
  digitalWrite(RESETLINE, 1);
  delay(100);
  digitalWrite(RESETLINE, 0);
  delay (3500);

  //set all start parameters on the touchscreen

genie.WriteContrast(15); //set display brightness

  genie.WriteObject(GENIE_OBJ_USER_LED,   0, 1);
  genie.WriteObject(GENIE_OBJ_USER_LED,   8, 1);
  genie.WriteObject(GENIE_OBJ_WINBUTTON,  2, 1);
  genie.WriteObject(GENIE_OBJ_WINBUTTON,  28, 1);
  genie.WriteObject(GENIE_OBJ_WINBUTTON,  36, 1);
  genie.WriteObject(GENIE_OBJ_SLIDER,     0, 9);
  genie.WriteObject(GENIE_OBJ_LED_DIGITS, 0, 9);
  genie.WriteObject(GENIE_OBJ_FORM,       2, 0);
  genie.WriteObject(GENIE_OBJ_SLIDER,     3, tempset);
  genie.WriteObject(GENIE_OBJ_LED_DIGITS, 3, tempset);
  genie.WriteObject(GENIE_OBJ_LED_DIGITS, 5, manualdose);
  genie.WriteObject(GENIE_OBJ_SLIDER,     1, speedcom);
  genie.WriteObject(GENIE_OBJ_LED_DIGITS, 1, speedcom);

  //request the first temperature data from the sensor
  sensors.requestTemperatures();
}


//-------------------------------------------------------------
//loop routine looped consecutively after the setup routine
//This runs the actual program
//-------------------------------------------------------------

void loop() {

  //four functions are called to control the basic machine functions
  pumpcontrol(pumpswitch, pumpspeed);
  tempcontrol();
```

```
heatercontrol();
genie.DoEvents();

//the following code is executed when the automatic synthesis is
//activated. Every if-loop represents one step.
if(automaticState){
  currentMillisAutoMode = millis();

  if ((currentMillisAutoMode - previousMillisAutoMode - pause) <
  MillisStep1){

    if (stepdone ==0) {
      genie.WriteObject(GENIE_OBJ_USER_LED, 22, 1);
      genie.WriteObject(GENIE_OBJ_USER_LED, 18, 1);
      pumpspeed = 10;
      pumpspeed = map(pumpspeed, 1, 10, 10, 1);
      pumpswitch=HIGH;
      valvepos(0,1);
      valvepos(1,1);
      dosing(60,8,0);
      valvepos(1,2);
      stepdone =1;
      genie.WriteObject(GENIE_OBJ_USER_LED, 22, 0);
    }
    digitalWrite(24, HIGH);
  }

  if ((currentMillisAutoMode - previousMillisAutoMode - pause) >
  MillisStep1 && (currentMillisAutoMode - previousMillisAutoMode - pause)
  < MillisStep2) {

    digitalWrite(24, LOW);
    digitalWrite(25, HIGH);

    if (stepdone == 1) {
      genie.WriteObject(GENIE_OBJ_USER_LED, 22, 1);
      genie.WriteObject(GENIE_OBJ_USER_LED, 18, 0);
      genie.WriteObject(GENIE_OBJ_USER_LED, 19, 1);
      valvepos(1,1);
      dosing(80,8,0);
      valvepos(0,2);
      valvepos(1,3);
      speedcom = 13;
      speedcom = map(speedcom,0,30,20,2);
      Serial3.write('i');
      Serial3.write(1);
      Serial3.write(speedcom);
      dosing(40,8,0);
      valvepos(1,2);
      stepdone =0;
      genie.WriteObject(GENIE_OBJ_USER_LED, 22, 0);
    }
  }

  if ((currentMillisAutoMode - previousMillisAutoMode - pause) >
  MillisStep2 && (currentMillisAutoMode - previousMillisAutoMode - pause)
  < MillisStep3) {

    digitalWrite(25, LOW);
    digitalWrite(26, HIGH);

    if(stepdone == 0) {
      genie.WriteObject(GENIE_OBJ_USER_LED, 22, 1);
```

```
    genie.WriteObject(GENIE_OBJ_USER_LED, 19, 0);
    genie.WriteObject(GENIE_OBJ_USER_LED, 20, 1);
    valvepos(1,4);
    dosing(80,8,1);
    Serial3.write('i');
    Serial3.write(0);
    Serial3.write(speedcom);
    valvepos(0,3);
    valvepos(1,2);
    stepdone=1;
    genie.WriteObject(GENIE_OBJ_USER_LED, 22, 0);
  }
}

if ((currentMillisAutoMode - previousMillisAutoMode - pause) >
MillisStep3 && (currentMillisAutoMode - previousMillisAutoMode - pause)
< MillisStep4) {

  digitalWrite(26, LOW);
  digitalWrite(27, HIGH);

  if(stepdone == 1) {
    genie.WriteObject(GENIE_OBJ_USER_LED, 22, 1);
    genie.WriteObject(GENIE_OBJ_USER_LED, 20, 0);
    genie.WriteObject(GENIE_OBJ_USER_LED, 21, 1);
    valvepos(1,4);
    dosing(80,8,1);
    valvepos(0,4);
    valvepos(1,2);
    stepdone=0;
    genie.WriteObject(GENIE_OBJ_USER_LED, 22, 0);
    }
  }

if ((currentMillisAutoMode - previousMillisAutoMode - pause) >
MillisStep4 && (currentMillisAutoMode - previousMillisAutoMode - pause)
< MillisStep5) {

  digitalWrite(27, LOW);
  digitalWrite(28, HIGH);

}

if ((currentMillisAutoMode - previousMillisAutoMode - pause) >
MillisStep5 && (currentMillisAutoMode - previousMillisAutoMode - pause)
< MillisStep6) {

  digitalWrite(28, LOW);
  digitalWrite(29, HIGH);

}

if ((currentMillisAutoMode - previousMillisAutoMode - pause) >
MillisStep6 && (currentMillisAutoMode - previousMillisAutoMode - pause)
< MillisStep7) {

  digitalWrite(29, LOW);
  digitalWrite(30, HIGH);

}

if ((currentMillisAutoMode - previousMillisAutoMode - pause) >
MillisStep7 && (currentMillisAutoMode - previousMillisAutoMode - pause)
```

```
    < MillisStep8) {

      digitalWrite(30, LOW);
      digitalWrite(31, HIGH);

    }

    if ((currentMillisAutoMode - previousMillisAutoMode - pause) >
    MillisStep8 && (currentMillisAutoMode – previousMillisAutoMode - pause)
    < MillisStep9) {

     digitalWrite(31, LOW);
     digitalWrite(24, HIGH);
     digitalWrite(25, HIGH);

    }
    if (currentMillisAutoMode - previousMillisAutoMode - pause >
    MillisStep9 ) {

      for (i=24;i<32;i++){
        digitalWrite(i, LOW);
      }
      genie.WriteObject(GENIE_OBJ_USER_LED, 22, 1);
      genie.WriteObject(GENIE_OBJ_USER_LED, 21, 0);
      valvepos(1,5);
      dosing(100,8,1);
      pumpswitch=LOW;
      genie.WriteObject(GENIE_OBJ_USER_LED, 22, 0);
      valvepos(0,1);
      valvepos(1,1);
      genie.WriteObject(GENIE_OBJ_USER_LED, 0, 1);
      genie.WriteObject(GENIE_OBJ_USER_LED, 8, 1);
      genie.WriteObject(GENIE_OBJ_FORM, 3, 0);
      automaticState = 0;
      stepdone=0;

    }
  }
}

//-----------------TOUCHSCREEN COMMANDS-----------------
//this routine is called by genie.DoEvents()
//All user inputs from the touchscreen are handled here
//------------------------------------------------------

void myGenieEventHandler(void) {

  genieFrame Event;
  genie.DequeueEvent(&Event);

  if (Event.reportObject.cmd == GENIE_REPORT_EVENT) {

    //all user inputs from buttons are handled here:
    if (Event.reportObject.object == GENIE_OBJ_WINBUTTON) {

      if (Event.reportObject.index >= 3 && Event.reportObject.index <= 8) {

        for (i = 0; i < 8; i++) {
          genie.WriteObject(GENIE_OBJ_USER_LED, i, 0);
        }
      }

      if (Event.reportObject.index >= 29 &&
```

```
Event.reportObject.index <= 34) {

  for (i = 8; i < 16; i++) {
    genie.WriteObject(GENIE_OBJ_USER_LED, i, 0);
  }
}

if(Event.reportObject.index == 3) {
  valvepos(0,1);
  genie.WriteObject(GENIE_OBJ_USER_LED, 0, 1);
  Serial.println("port1,1");
}

else if(Event.reportObject.index == 4) {
  valvepos(0,2);
  genie.WriteObject(GENIE_OBJ_USER_LED, 1, 1);
  Serial.println("port1,2");
}

else if(Event.reportObject.index == 5) {
  valvepos(0,3);
  genie.WriteObject(GENIE_OBJ_USER_LED, 2, 1);
}

else if(Event.reportObject.index == 6) {
  valvepos(0,4);
  genie.WriteObject(GENIE_OBJ_USER_LED, 3, 1);
}

else if(Event.reportObject.index == 7) {
  valvepos(0,5);
  genie.WriteObject(GENIE_OBJ_USER_LED, 4, 1);
}

else if(Event.reportObject.index == 8) {
  valvepos(0,6);
  genie.WriteObject(GENIE_OBJ_USER_LED, 5, 1);
}

else if(Event.reportObject.index == 37) {
  for (i = 0; i < 8; i++) {
    genie.WriteObject(GENIE_OBJ_USER_LED, i, 0);
  }
  valvepos(0,7);
  genie.WriteObject(GENIE_OBJ_USER_LED, 6, 1);
}

else if(Event.reportObject.index == 38) {
  for (i = 0; i < 8; i++) {
    genie.WriteObject(GENIE_OBJ_USER_LED, i, 0);
  }
  valvepos(0,8);
  genie.WriteObject(GENIE_OBJ_USER_LED, 7, 1);
}

else if(Event.reportObject.index == 29) {
  valvepos(1,1);
  genie.WriteObject(GENIE_OBJ_USER_LED, 8, 1);
}

else if(Event.reportObject.index == 30) {
  valvepos(1,2);
  genie.WriteObject(GENIE_OBJ_USER_LED, 9, 1);
```

```
}

else if(Event.reportObject.index == 31) {
  valvepos(1,3);
  genie.WriteObject(GENIE_OBJ_USER_LED, 10, 1);
}

else if(Event.reportObject.index == 32) {
  valvepos(1,4);
  genie.WriteObject(GENIE_OBJ_USER_LED, 11, 1);
}

else if(Event.reportObject.index == 33) {
  valvepos(1,5);
  genie.WriteObject(GENIE_OBJ_USER_LED, 12, 1);
}

else if(Event.reportObject.index == 34) {
  valvepos(1,6);
  genie.WriteObject(GENIE_OBJ_USER_LED, 13, 1);
}

else if(Event.reportObject.index == 39) {
  for (i = 8; i < 16; i++) {
    genie.WriteObject(GENIE_OBJ_USER_LED, i, 0);
  }
  valvepos(1,7);
  genie.WriteObject(GENIE_OBJ_USER_LED, 14, 1);
}

else if(Event.reportObject.index == 40) {
  for (i = 8; i < 16; i++) {
    genie.WriteObject(GENIE_OBJ_USER_LED, i, 0);
  }
  valvepos(1,8);
  genie.WriteObject(GENIE_OBJ_USER_LED, 15, 1);
}

else if(Event.reportObject.index == 27){
  Serial3.write('i');
  Serial3.write(1);
  Serial3.write(speedcom);
}

else if(Event.reportObject.index == 28){
  Serial3.write('i');
  Serial3.write(0);
  Serial3.write(speedcom);
}

else if(Event.reportObject.index == 43){
  manualdose++;
  genie.WriteObject(GENIE_OBJ_LED_DIGITS, 5, manualdose);
}

else if(Event.reportObject.index == 44){
  manualdose--;
  genie.WriteObject(GENIE_OBJ_LED_DIGITS, 5, manualdose);
}

else if(Event.reportObject.index == 45){
  dosing(manualdose,8,0);
}
```

```
else if(Event.reportObject.index == 47){
  genie.WriteObject(GENIE_OBJ_FORM, 11, 0);
  systemwash();
  genie.WriteObject(GENIE_OBJ_FORM, 3, 0);
}

else if(Event.reportObject.index == 51){
  tempmenu = 1;
  genie.WriteObject(GENIE_OBJ_FORM, 9, 0);
}

else if(Event.reportObject.index == 15){
  if(tempmenu == 1) {
    tempmenu = 0;
    genie.WriteObject(GENIE_OBJ_FORM, 6, 0);
  }
  else genie.WriteObject(GENIE_OBJ_FORM, 1, 0);
}

else if(Event.reportObject.index == 49){
  genie.WriteObject(GENIE_OBJ_FORM, 3, 0);
  automaticState = 0;
  stepdone=0;
  pumpswitch = LOW;
  Serial3.write('i');
  Serial3.write(0);
  Serial3.write(speedcom);
}

else if(Event.reportObject.index == 35){
  heaterswitch = HIGH;
}

else if(Event.reportObject.index == 36){
  heaterswitch = LOW;
}

else if(Event.reportObject.index == 41){
  genie.WriteObject(GENIE_OBJ_FORM, 8, 0);
  for(int i = 0; i < 5; i++){
    genie.WriteStr(i,StepTimes2[i]);
  }
}

else if(Event.reportObject.index == 1) {
  pumpswitch = HIGH;
  Serial.println("pump on");
}

else if (Event.reportObject.index == 2) pumpswitch = LOW;

else if (Event.reportObject.index == 14){
  Serial.println("pause");
  if (automaticState) {
    pauseState = 1;
    automaticState = 0;
    genie.WriteObject(GENIE_OBJ_USER_LED, 17, 1);
    pumpswitch=LOW;
  }
  else {
    pauseState = 0;
    automaticState = 1;
```

```
    pause = pause + millis() - currentMillisAutoMode;
    genie.WriteObject(GENIE_OBJ_USER_LED, 17, 0);
    pumpswitch=HIGH;
    Serial.println("unpuse");
    Serial.println(currentMillisAutoMode);
    Serial.println(pause);
  }
}

else if(Event.reportObject.index == 17) {
  currentMillisAutoMode = millis();
  previousMillisAutoMode = currentMillisAutoMode;
  automaticState = HIGH;
  pause = 0;
  genie.WriteObject(GENIE_OBJ_FORM, 6, 0);
  for (i = 10; i < 14; i++) {
    genie.WriteObject(GENIE_OBJ_USER_LED, i, 0);
  }
  genie.WriteObject(GENIE_OBJ_GAUGE, 0, 0);
  for (i=22;i<27;i++){
    digitalWrite(i, LOW);
  }
}

else if(Event.reportObject.index == 18) {
  Serial.println(Event.reportObject.index);
  genie.WriteObject(GENIE_OBJ_FORM, 7, 0);
  menuselector = 0;
  counter=menucounter[menuselector];
  strlcpy(keyvalue,StepTimes2[menuselector], 10);
  genie.WriteStr(6,keyvalue);
  Serial.println(keyvalue);
}

else if(Event.reportObject.index == 19) {
  genie.WriteObject(GENIE_OBJ_FORM, 7, 0);
  menuselector = 1;
  counter=menucounter[menuselector];
  strlcpy(keyvalue,StepTimes2[menuselector], 10);
  genie.WriteStr(6,keyvalue);
  Serial.println(keyvalue);
}

else if(Event.reportObject.index == 20) {
  genie.WriteObject(GENIE_OBJ_FORM, 7, 0);
  menuselector = 2;
  counter=menucounter[menuselector];
  strlcpy(keyvalue,StepTimes2[menuselector], 10);
  genie.WriteStr(6,keyvalue);
  Serial.println(keyvalue);
}

else if(Event.reportObject.index == 21) {
  genie.WriteObject(GENIE_OBJ_FORM, 7, 0);
  menuselector = 3;
  counter=menucounter[menuselector];
  strlcpy(keyvalue,StepTimes2[menuselector], 10);
  genie.WriteStr(6,keyvalue);
  Serial.println(keyvalue);
}

else if(Event.reportObject.index == 22) {
  genie.WriteObject(GENIE_OBJ_FORM, 7, 0);
```

```
      menuselector = 4;
      counter=menucounter[menuselector];
      strlcpy(keyvalue,StepTimes2[menuselector], 10);
      genie.WriteStr(6,keyvalue);
      Serial.println(keyvalue);
    }
  }

  //all user inputs from keyboard are handled here:
  if(Event.reportObject.object == GENIE_OBJ_KEYBOARD) {

    if (Event.reportObject.index == 0) {
      temp = genie.GetEventData(&Event); //get data from keyboard

      //process data obtained from keybaord
      if(temp >= 48 && temp <= 57 && counter <=9) {
        Serial.println(temp);
        Serial.println(counter);
        // Receive the event data from the keyboard
        keyvalue[counter] = temp;
        genie.WriteStr(6,keyvalue);
        counter = counter + 1; //increment array
        Serial.println(keyvalue);
      }

      else if(temp == 8) {
        if(counter >= 1) {
          counter--;
          keyvalue[counter] = 0;
          genie.WriteStr(6,keyvalue);
        }
      }

      else if(temp == 13)
      {
        genie.WriteObject(GENIE_OBJ_FORM,8,0);
        strlcpy(StepTimes2[menuselector], keyvalue, 10);
        menucounter[menuselector]=counter;
        MillisStepTemp = strtoul(StepTimes2[menuselector], NULL, 10);
        MillisStepTemp = MillisStepTemp *1000;
        for (int i = 0; i<10; i++) {
          keyvalue[i]=0;
          Serial.println(keyvalue[i]);
        }
        Serial.println(keyvalue);

        switch (menuselector) {
          case 0:
            MillisStep1 = MillisStepTemp;
            break;
          case 1:
            MillisStep2 = MillisStepTemp;
            break;
          case 2:
            MillisStep3 = MillisStepTemp;
            break;
          case 3:
            MillisStep4 = MillisStepTemp;
            break;
          case 4:
            MillisStep5 = MillisStepTemp;
            break;
          case 5:
```

```
              MillisStep6 = MillisStepTemp;
              break;
          }

          //Output received parameters to the PC
          Serial.println("Parameters:------------------------------- ");
          Serial.println(menuselector);
          Serial.println(MillisStepTemp);
          Serial.println(MillisStep1);
          Serial.println(MillisStep2);
          Serial.println(MillisStep3);
          Serial.println(MillisStep4);
          Serial.println(MillisStep5);
          Serial.println(MillisStep6);
          Serial.println("-------------------------------- ");

          for(i = 0; i < 5; i++){
            genie.WriteStr(i,StepTimes2[i]);
          }
        }
      }
    }

    //all user inputs from the slider values are handled here:
    if (Event.reportObject.object == GENIE_OBJ_SLIDER) {

      if(Event.reportObject.index == 0) {
        pumpspeed = genie.GetEventData(&Event);
        pumpspeed = map(pumpspeed, 1, 10, 10, 1);
      }

      else if (Event.reportObject.index == 1) {
        speedcom = genie.GetEventData(&Event);
        speedcom = map(speedcom,0,30,20,2);
        Serial3.write('i');
        Serial3.write(1);
        Serial3.write(speedcom);
        genie.WriteObject(GENIE_OBJ_WINBUTTON, 27, 1);
      }

      else if (Event.reportObject.index == 3) {
        tempset = genie.GetEventData(&Event) *10;
      }
    }
  }
}


//----------------ROTARY VALVE HOMING-------------------
//this routine can be called to home each rotary valve
//the argument can be 0 or 1 for the left or right valve
//------------------------------------------------------

void valvepos(int select, int gotoport) {

  boolean porttrigger;
  int nrofturns;

  if (gotoport > currentportnr[select]) {
    nrofturns = gotoport - currentportnr[select];
  }

  else if (gotoport < currentportnr[select]) {
```

```
    nrofturns = gotoport - currentportnr[select] + 8;
  }

  else nrofturns = 0;

  for (int i = 0; i < nrofturns; i++) {
    rotvalve[select]->step(10, BACKWARD, DOUBLE);
    if (select == 0)  porttrigger = digitalRead(7);
    else if (select == 1)  porttrigger = digitalRead(9);

    while(porttrigger) {
      rotvalve[select]->step(1, BACKWARD, DOUBLE);
      if (select == 0)  porttrigger = digitalRead(7);
      else if (select == 1)  porttrigger = digitalRead(9);
    }

    rotvalve[select]->release();
    currentportnr[select]++;
    if (currentportnr[select] == 9) currentportnr[select] = 1;
  }
}


//----------------ROTARY VALVE HOMING-------------------
//this routine can be called to home each rotary valve
//the argument can be 0 or 1 for the left or right valve
//------------------------------------------------------

void homevalve(int select) {

  boolean hometrigger;
  if (select == 0)  hometrigger = digitalRead(6);
  else if (select == 1)  hometrigger = digitalRead(8);

  while(hometrigger) {
    rotvalve[select]->step(1, BACKWARD, DOUBLE);
    if (select == 0)  hometrigger = digitalRead(6);
    else if (select == 1)  hometrigger = digitalRead(8);
  }
  rotvalve[select]->release();
  currentportnr[select]=1;
}


//----------------PUMP-----------------------------------------
//this routine is repeatedly called to drive the pump
//the argument pumpswitch represents the on/off state of pumping
//the argument pumpfreq sets the frequency of pump strokes
//pumpfreq can be any value from 1, with one the fastest
//-------------------------------------------------------------

void pumpcontrol(boolean pumpswitch, float pumpfreq) {

  unsigned long currentMillis = millis();
  long interval = pumpfreq*125;

  if (pumpswitch == HIGH) {
    if (pumpstate==LOW) {
      if(currentMillis - previousMillis > interval) {
        previousMillis = currentMillis;
        digitalWrite(4, HIGH);
        pumpstate = HIGH;
      }
```

```
    }
    else if (pumpstate==HIGH) {
      if(currentMillis - previousMillis > 200) {
        previousMillis = currentMillis;
        digitalWrite(4, LOW);
        pumpstate = LOW;
      }
    }
  }
  else {
    digitalWrite(4, LOW);
    pumpstate = LOW;
  }
}


//-----------------TEMPERATURE SENSOR-------------------------
//this routine is repeatedly called to drive the temperature
//sensor and to obtain new temperature values.
//it is executed every 600ms
//------------------------------------------------------------

void tempcontrol() {

  unsigned long currentMillis = millis();

  //rule for delay delayInMillis = 750 / (1 << (12 - resolution))
  if(currentMillis - previousMillisTemp > 600) {
    previousMillisTemp = currentMillis;
    float tempC = sensors.getTempC(insideThermometer);
    tempCc = tempC * 10;
    genie.WriteObject(GENIE_OBJ_LED_DIGITS, 4, tempCc);
    genie.WriteObject(GENIE_OBJ_LED_DIGITS, 2, tempC);
    sensors.requestTemperatures();
  }
}


//-----------------CARTRIDGE HEATER---------------------------
//this routine is repeatedly called to control the heating of
//the cartridge holder.
//the routine contains code to heat fast in the beginning and
//reduces the heating closer to the target value
//------------------------------------------------------------

void heatercontrol() {

  int intervaltemp=900; // calculate interval temp here
  unsigned long currentMillis = millis();

  if (heaterswitch == HIGH){
    //heating with full power
    if ((tempset - tempCc) > 80) {
      digitalWrite(3, HIGH);
      genie.WriteObject(GENIE_OBJ_USER_LED, 16, 1);
    }

    //between 0-8°C from target reduce heating power
    else if ((tempset > tempCc) && (tempset-tempCc <= 80)) {
      if ((tempset - tempCc) > 50) intervaltemp=400;
      else if ((tempset - tempCc) > 30) intervaltemp=600;
      else if ((tempset - tempCc) > 10) intervaltemp=700;
      else if ((tempset - tempCc) > 5) intervaltemp=850;
```

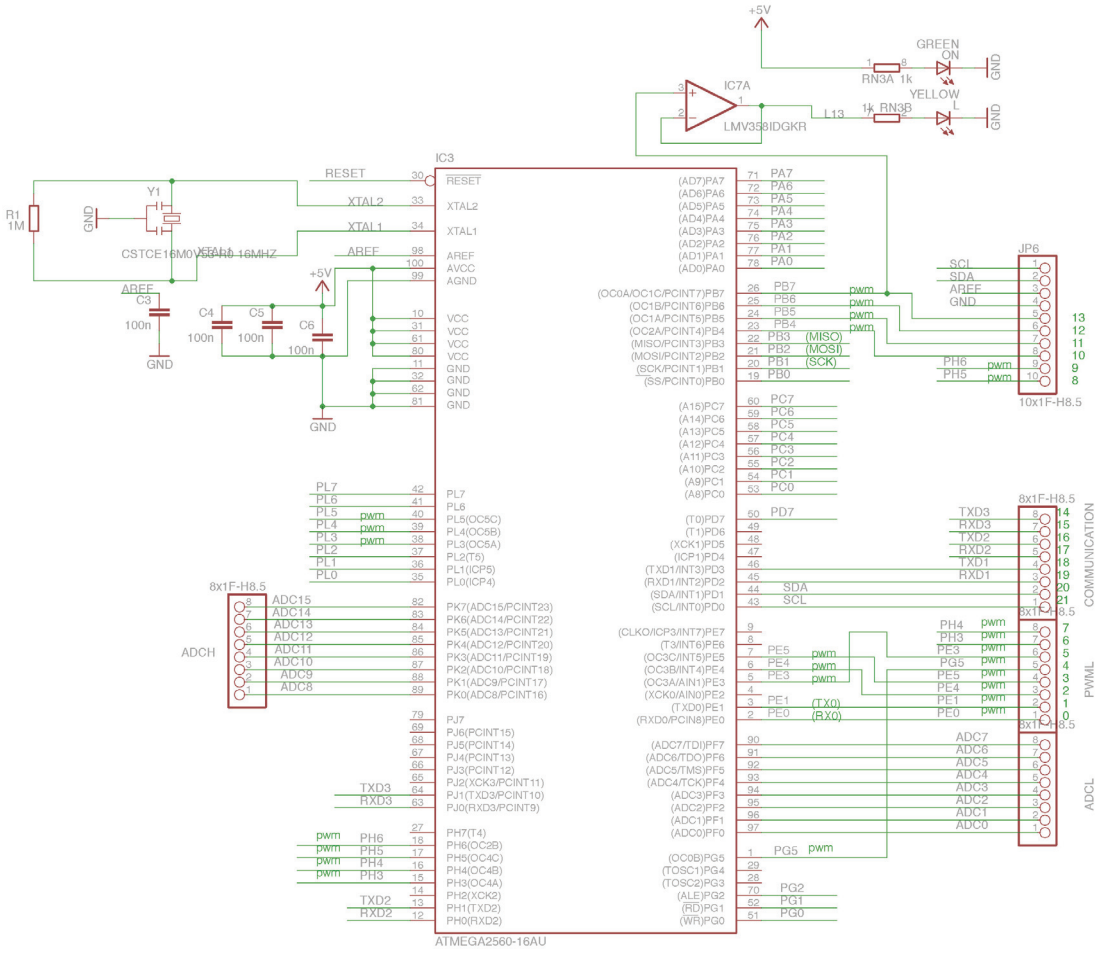
```
      else if ((tempset - tempCc) <= 5) intervaltemp=900;
      genie.WriteObject(GENIE_OBJ_USER_LED, 16, 1);

      if (heaterstate==LOW) {

        if(currentMillis - previousMillisHeat > intervaltemp) {
          previousMillisHeat = currentMillis;
          digitalWrite(3, HIGH);

          heaterstate = HIGH;
          Serial.print("abs. Temp.: ");
          Serial.print(tempCc);
          Serial.print("     diff. Temp.: ");
          Serial.print(tempset-tempCc);
          Serial.print("     Intervaltemp: ");
          Serial.println(intervaltemp);
        }
      }

      else if (heaterstate==HIGH) {

        if((currentMillis - previousMillisHeat) > (1000-intervaltemp)) {
          previousMillisHeat = currentMillis;
          digitalWrite(3, LOW);

          heaterstate = LOW;
          Serial.print("abs. Temp.: ");
          Serial.print(tempCc);
          Serial.print("     diff. Temp.: ");
          Serial.print(tempset-tempCc);
          Serial.print("     Intervaltemp: ");
          Serial.println(intervaltemp);
        }
      }
    }

    else {
      digitalWrite(3, LOW);
      genie.WriteObject(GENIE_OBJ_USER_LED, 16, 0);
    }
  }

  else {
    digitalWrite(3, LOW);
    genie.WriteObject(GENIE_OBJ_USER_LED, 16, 0);
  }
}

//------------------------DOSING---------------------------------------
//this routine is called to execute only a certain number of pump
//strokes for exact dosing.
//the argument strokes set the exact number of pump strokes
//the argument strokespeed sets the pump frequency (see void pump)
//the argument timecorrection enables the correction for the time
//taking for the dosing step in the automatic mode
//Since the main loop cannot be executed during the dosing the heater
//is turned off the prevent overheating and reset afterwards
//---------------------------------------------------------------------

void dosing(int strokes, int strokespeed, boolean timecorrection) {

  strokespeed = map(strokespeed, 1, 10, 10, 1);
  boolean previousheaterswitch = heaterswitch;
```

```
  heaterswitch = LOW;

  for(i=0; i<strokes; i++) {
    digitalWrite(4,HIGH);
    delay(200);
    digitalWrite(4,LOW);
    delay(strokespeed*125);
    Serial.print("Dosing: ");
    Serial.println(i);
  }

  if (timecorrection) {
    pause = pause + millis() - currentMillisAutoMode;
  }

  heaterswitch = previousheaterswitch;
}


//-----------------SYSTEM WASH----------------------------------------
//this routine can be called to execute a system wash.
//all lines are being washed and primed afterwards.
//Since the main loop cannot be executed during the dosing the heater
//is turned off the prevent overheating.
//--------------------------------------------------------------------

void systemwash() {

  digitalWrite(3, LOW);

  valvepos(0,2);
  valvepos(1,5);
  dosing(10,10,0);

  valvepos(1,1);
  dosing(10,10,0);

  valvepos(1,2);
  dosing(100,10,0);

  valvepos(1,3);
  dosing(10,10,0);

  valvepos(1,4);
  dosing(100,10,0);

  valvepos(0,3);
  valvepos(1,1);
  dosing(10,10,0);

  valvepos(0,4);
  dosing(10,10,0);

  valvepos(0,5);
  dosing(10,10,0);

  valvepos(0,6);
  dosing(10,10,0);

  valvepos(0,7);
  dosing(10,10,0);

  valvepos(0,1);
```

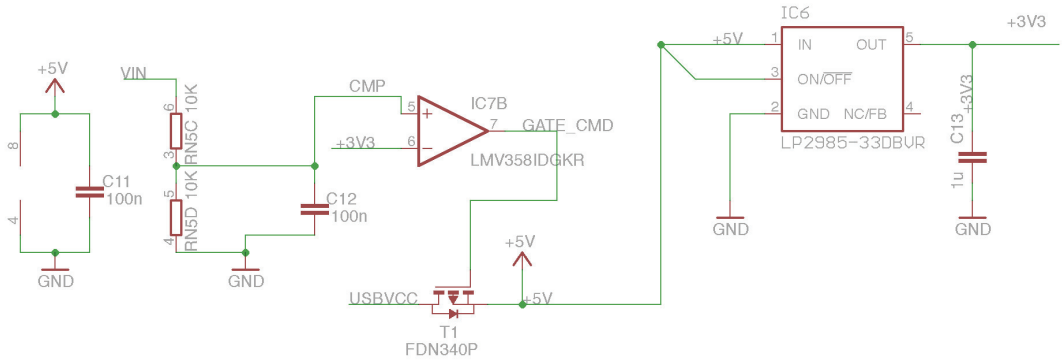
```
  valvepos(1,1);
  dosing(20,10,0);

  genie.WriteObject(GENIE_OBJ_USER_LED, 0, 1);
  genie.WriteObject(GENIE_OBJ_USER_LED, 8, 1);

}


//--------------------STIRRER-----------------------------------------
//this routine can be called to operate the external stirrer
//for sending a command to the stirrer three bytes are sent:
//for the first byte ‘i’ is sent to initialize the command
//the second byte can either be ‘0’ or ‘1’ to turn ‘on’ or ‘off’
//the third byte is a number between ‘0’ and ‘30’ to set the stir speed
//all numbers are transmitted as ASCII characters
//--------------------------------------------------------------------

void stirrer(boolean power, byte stirrspeed) {

  stirrspeed = map(stirrspeed,0,30,20,2);
  Serial3.write('i');
  Serial3.write(power);
  Serial3.write(speedcom);

}
```

7.7 Circuit Diagram for the Automated Synthesizer

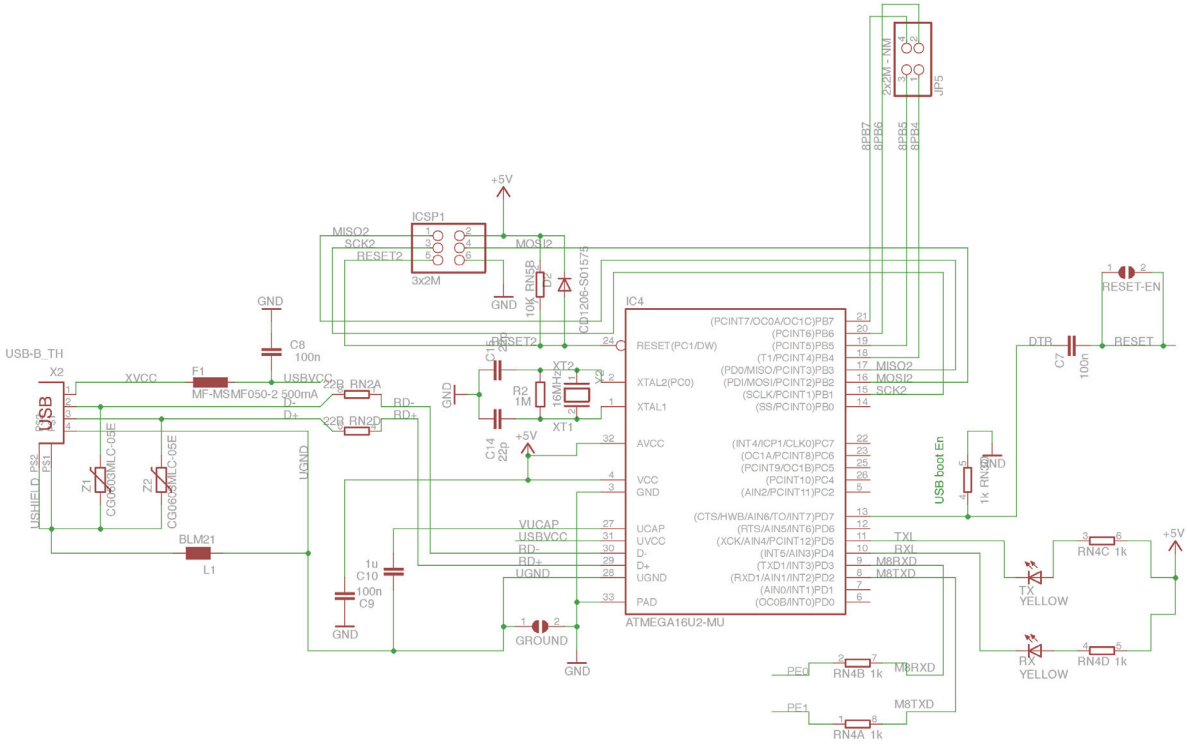
Arduino MEGA 2560: The automatic synthesizer is controlled by a ATmega2560. All its machines peripheral controlled with the microcontrollers data pins. The following circuit diagrams show all components of the Arduino board:



Microcontroller: An ATmega2560 is used as a microcontroller. It is clocked at 16Mhz and features 256 KB of memory. The pins possessing the same tasks are grouped into pin-headers: Power, Communication, Digital and Analog Pins (ADCL, ADCN)

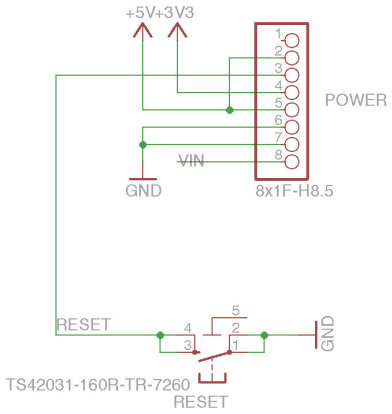


3.3V-Output regulator: The Arduino MEGA features an internal 3.3V regulator for generating a 3.3V sourcing from main power. It's header is located at power pin headers.

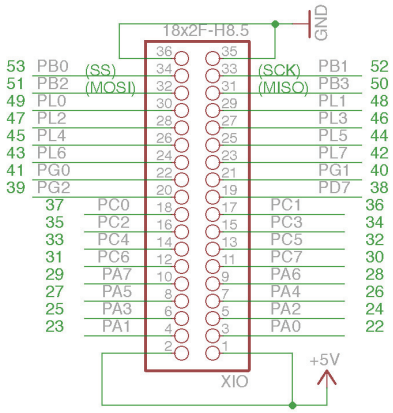


USB to TTL module: Since the ATmega chip expects signals on TTL-logic a ATmega16U2 USB-to-TTL converter chip is used to program the microcontroller via USB. Serial commands send from the microcontroller to the PC using this converter as well.

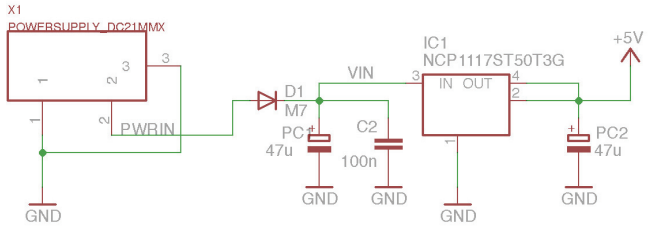
Additional components on Arduino MEGA 2560:



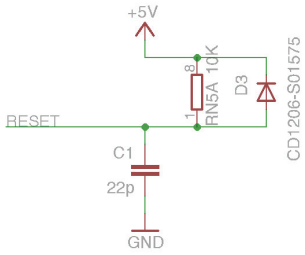
Main reset button of the Arduino Mega and power pin headers



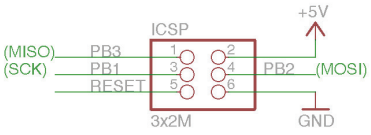
Header for the general Input/Output pins 22-53 of the Arduino Mega



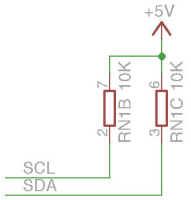
Power supply jack on the Arduino Mega. A NCP1117 power regulator generates 5V from any incoming 6-20V source



Pull-up resistor to keep the Chip-Reset on a 5V level to prevent accidental reset

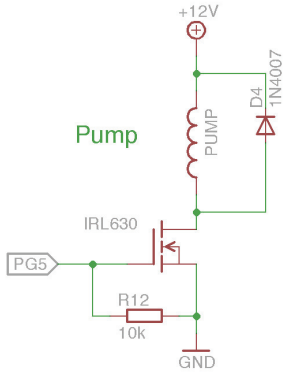


Header for the In-Circuit-Serial-Programming (ICSP) of the microcontroller.

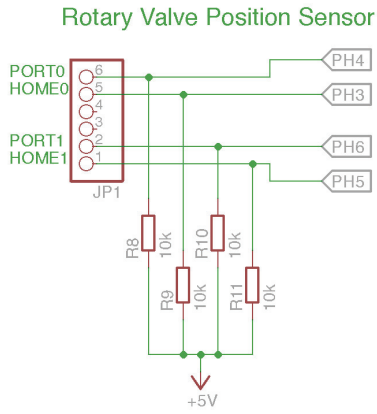


Pull-up resistors for the SCL and SDA line of the I^2C interface

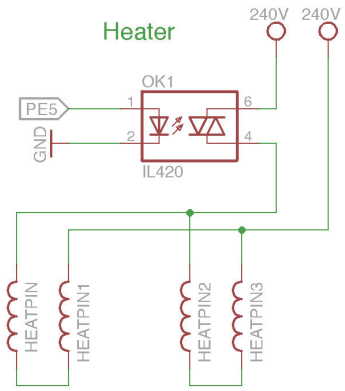
Modules of the automatic synthesizer:



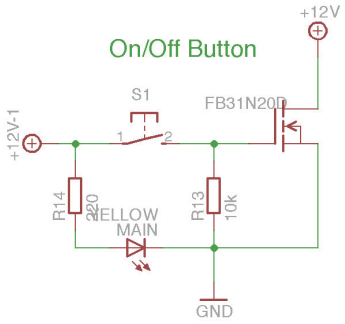
Pump: An IRL630 MOSFET closes the circuit to supply the solenoid of the pump with 12V. The MOSFET is controlled from Arduino digital pin 4. A pull-down resistor avoids uncontrolled activation by a floating line. Furthermore a flyback diode is used to eliminate the voltage spike across the inductive solenoid when the supply voltage is switched off.



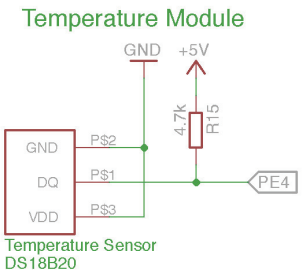
Rotary Valve Position Sensor: Each rotary valve includes two position sensors. One sensor reports the “Home”-position of the valve, the other one for the detection of a port position. Each sensor will report the position by dropping the voltage to 0V of the digital pins 6-9 of the microcontroller. Furthermore each sensor line requires a pull-up resistor to 5V. The position sensor also requires to be powered from 5V.



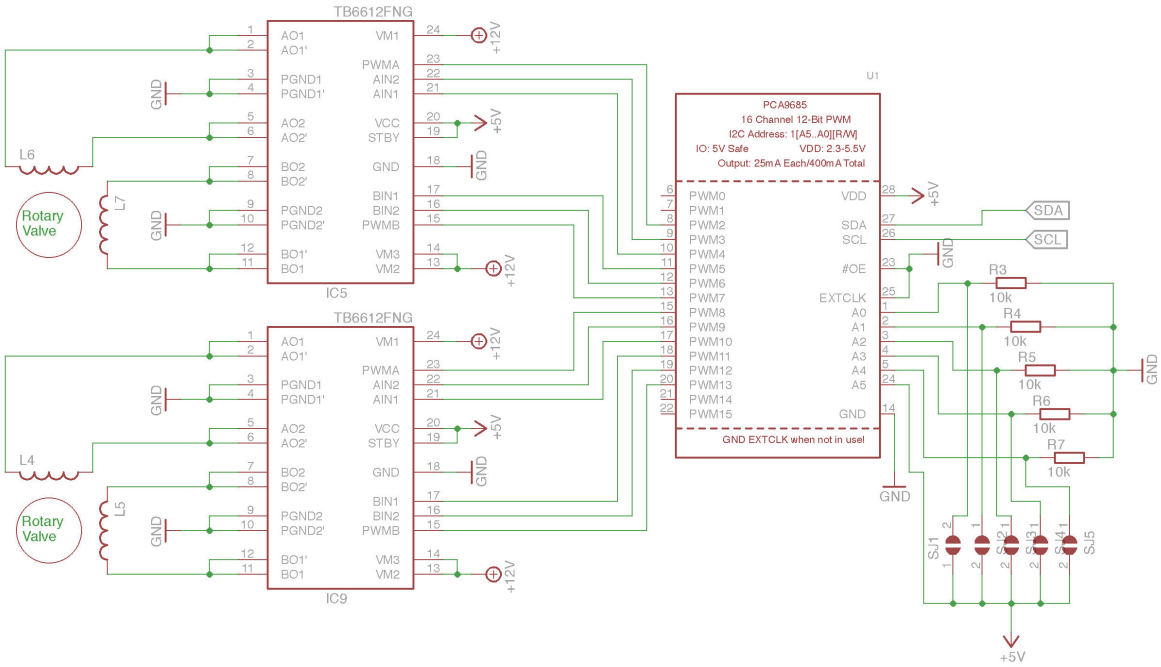
Heater: Four heating cartridges powered by 240V were used for the heating module. Two cartridges each were connected in series and controlled with a solid-state relay which is switched on/off by digital pin 3 of the microcontroller.



On/Off Button: For the main power of the microcontroller a MOSFET was switched on or off with a LED-lit push-button. A pull-down resistor avoids uncontrolled operation of the MOSFET.



Temperature Sensor: A DS18B20 temperature sensor was used to acquire the temperature from the cartridge heater. It is operated with the one-wire-protocol using parasite power mode on digital pin 2 of the microcontroller.



Rotary Valves: This module runs the two stepper motors of the rotary valves. Commands to move the motors are transmitted from the microcontroller over the I^2C interface (SDA and SCL) to a PCA9685 pulse-width-modulation controller. This chip controls two TB6612FNG motor drivers chips; one for each stepper motor. The PCA9685 is powered by the 5V rail, whereas the stepper motors are powered via the motor driver with 12V.

Appendix

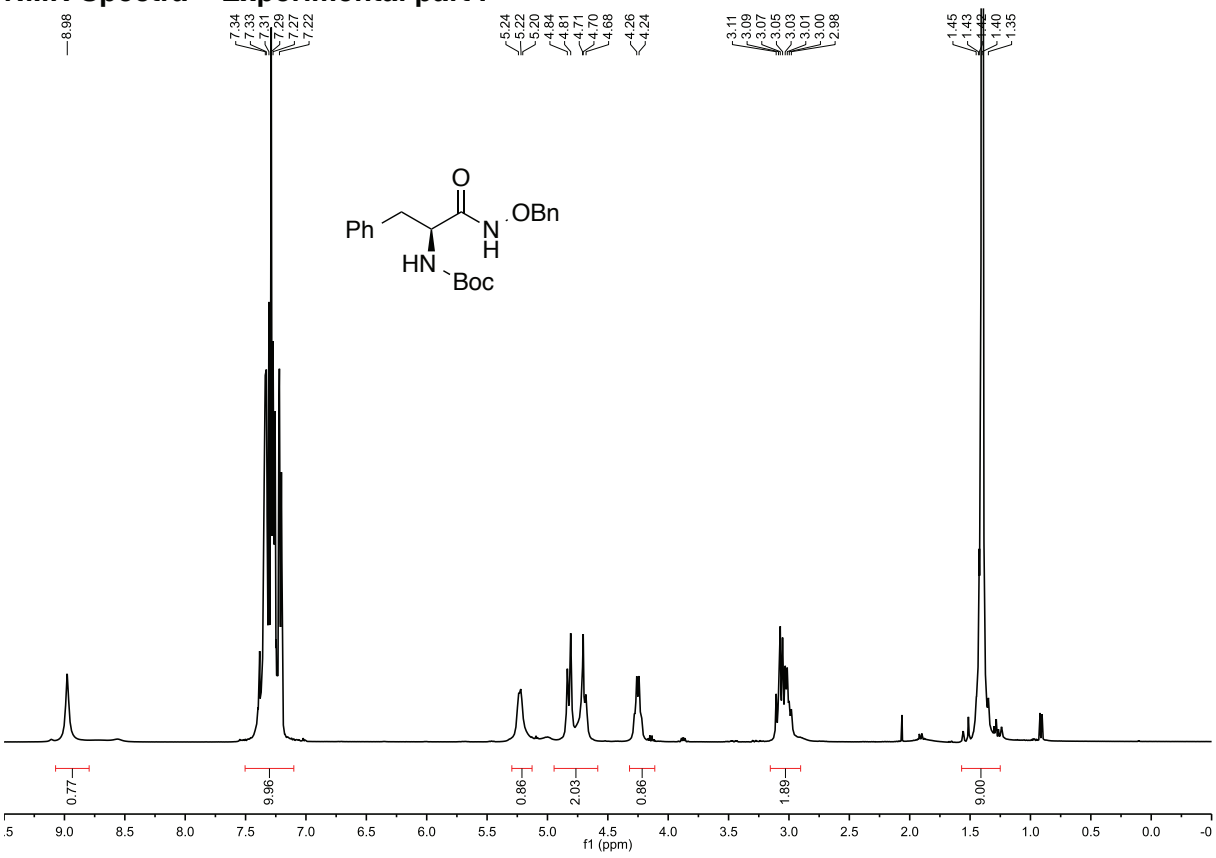
NMR-Spectra

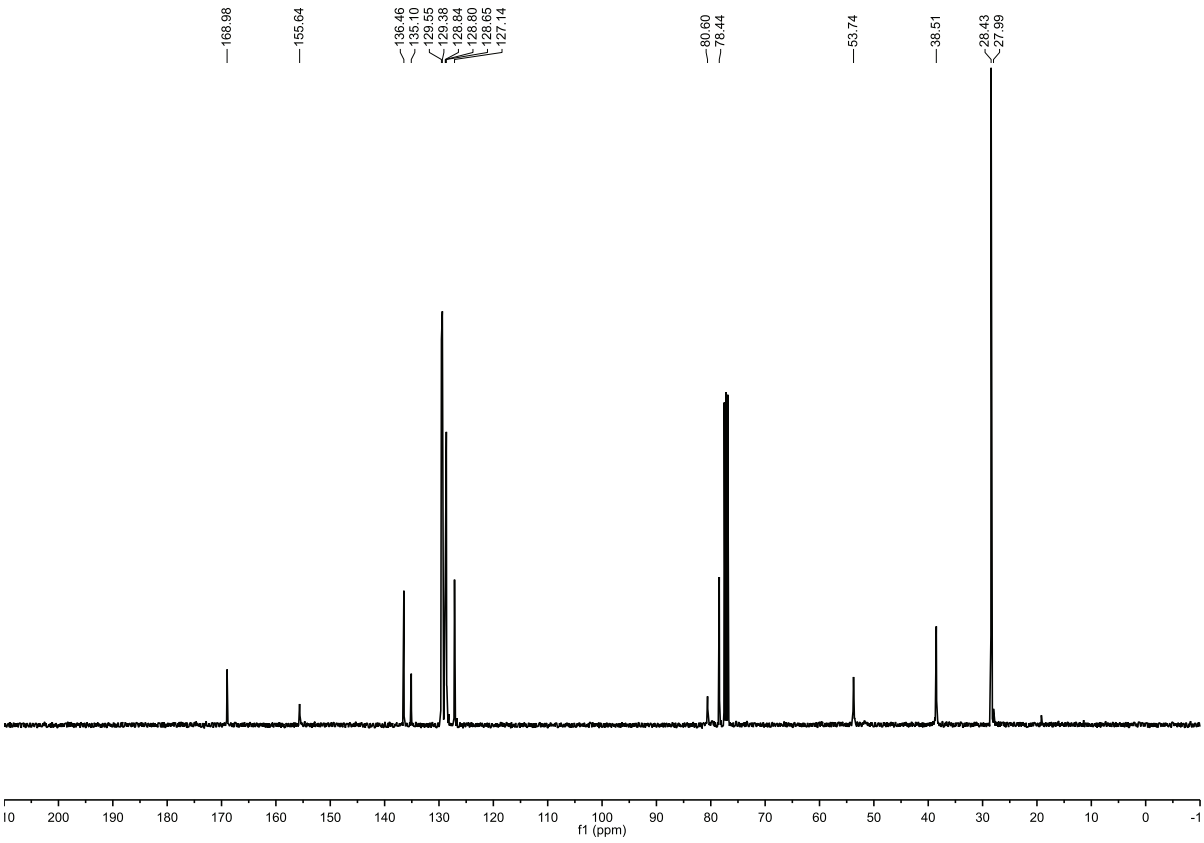
X-Ray spectroscopy

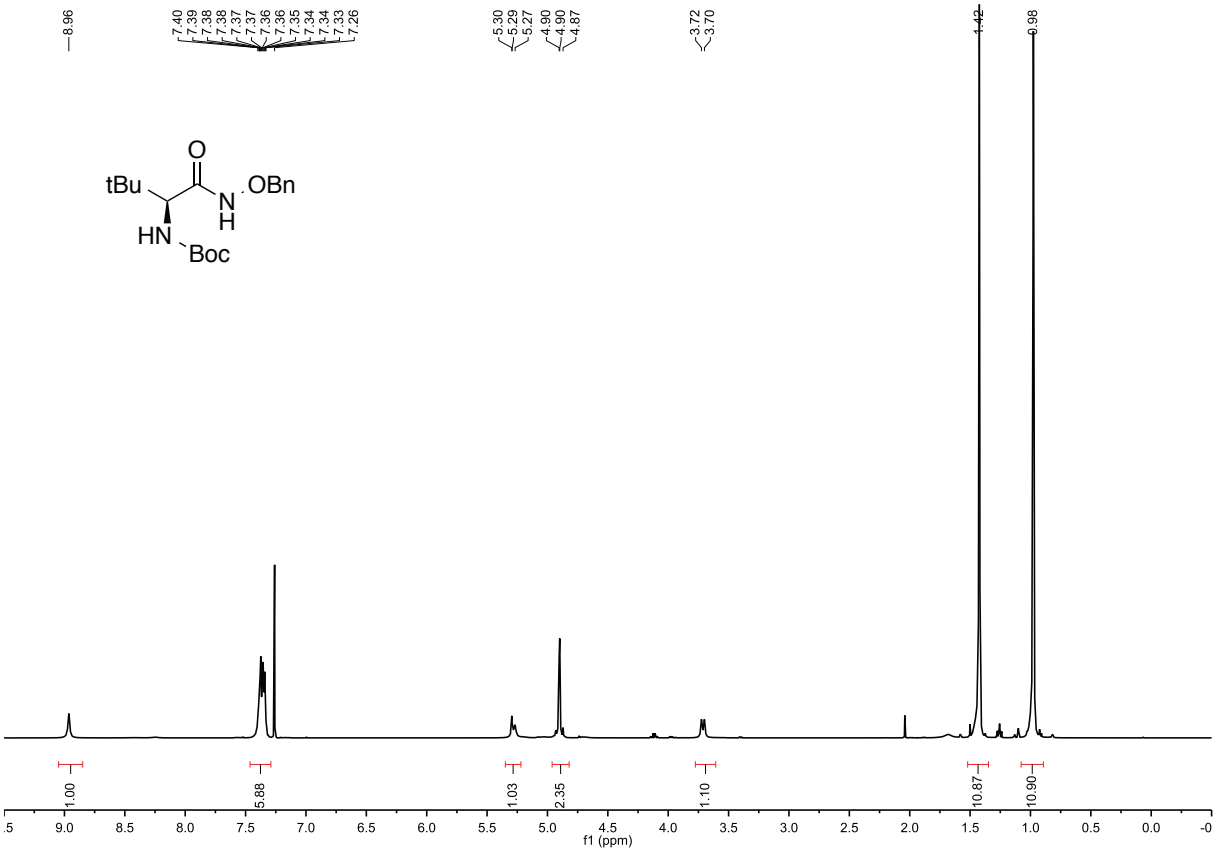
DFT-calculation

Curriculum Vitae

NMR-Spectra – Experimental part I



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7.26
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5.29
5.27
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4.90
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3.70
1.42
0.98
O
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N
H
HN
Boc
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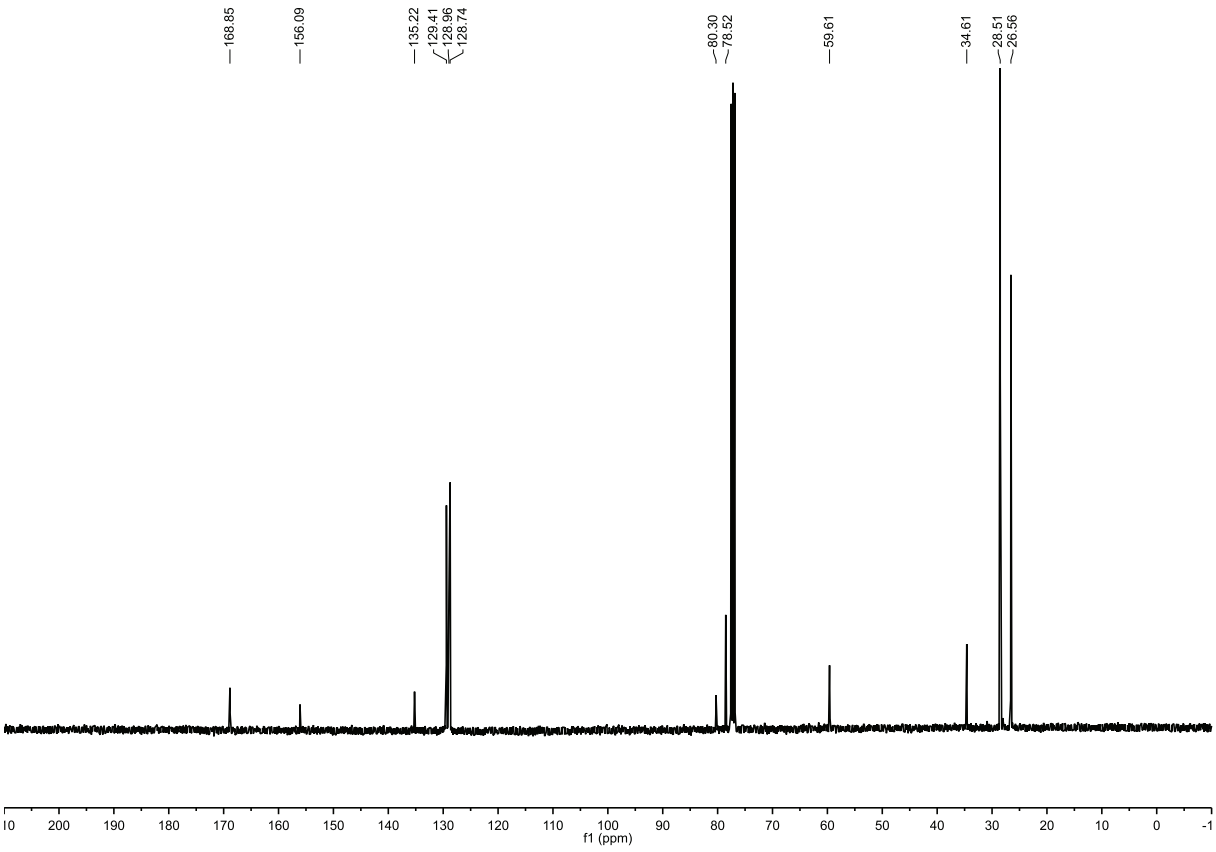
10.90
f1 (ppm)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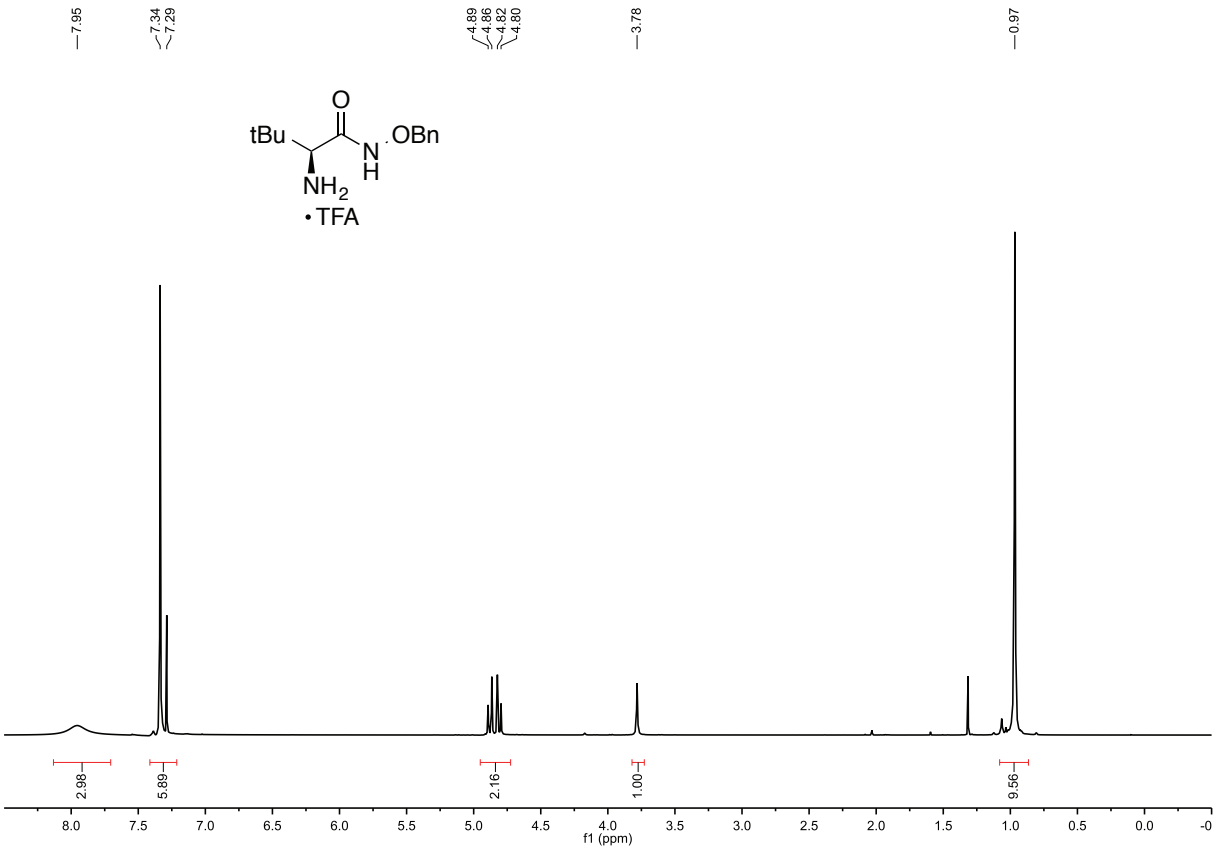
f1 (ppm)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OBn
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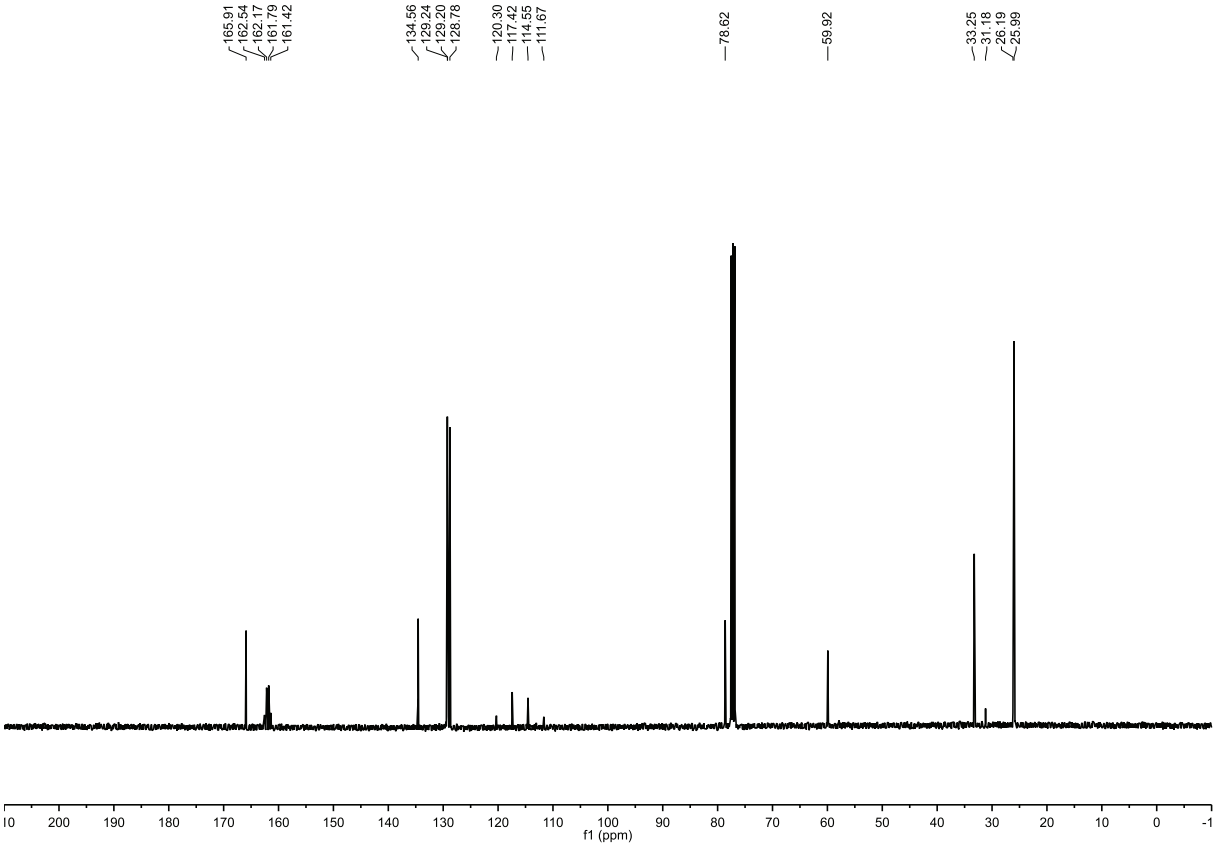
f1 (ppm)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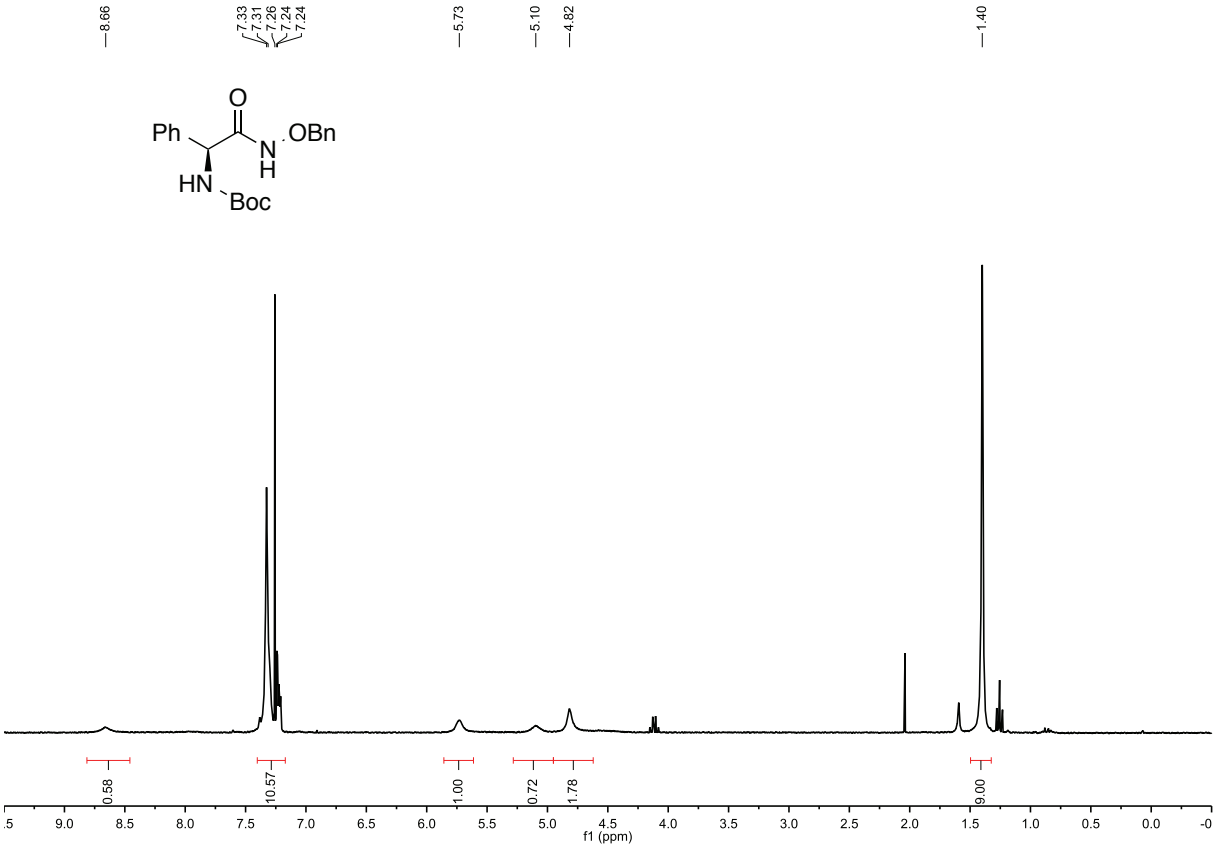
f1 (ppm)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OBn
HN
Boc
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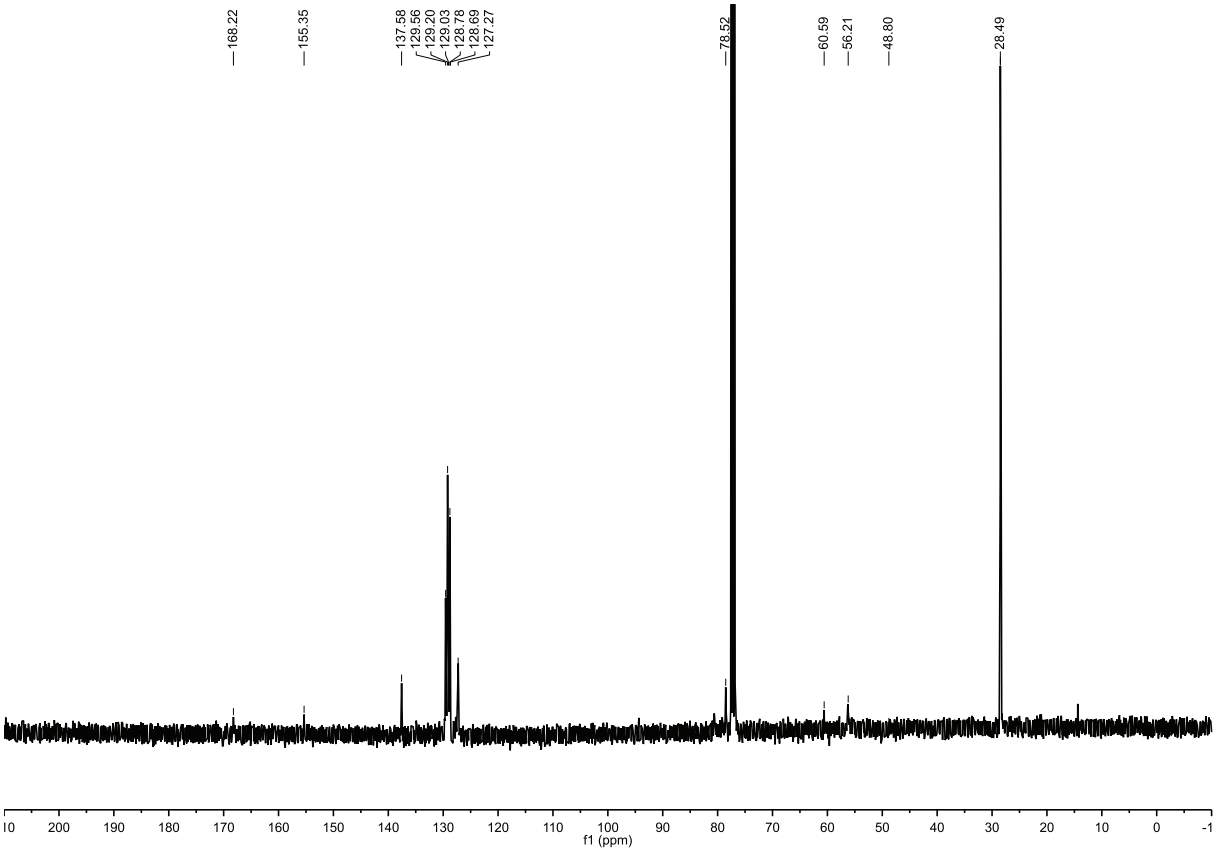
f1 (ppm)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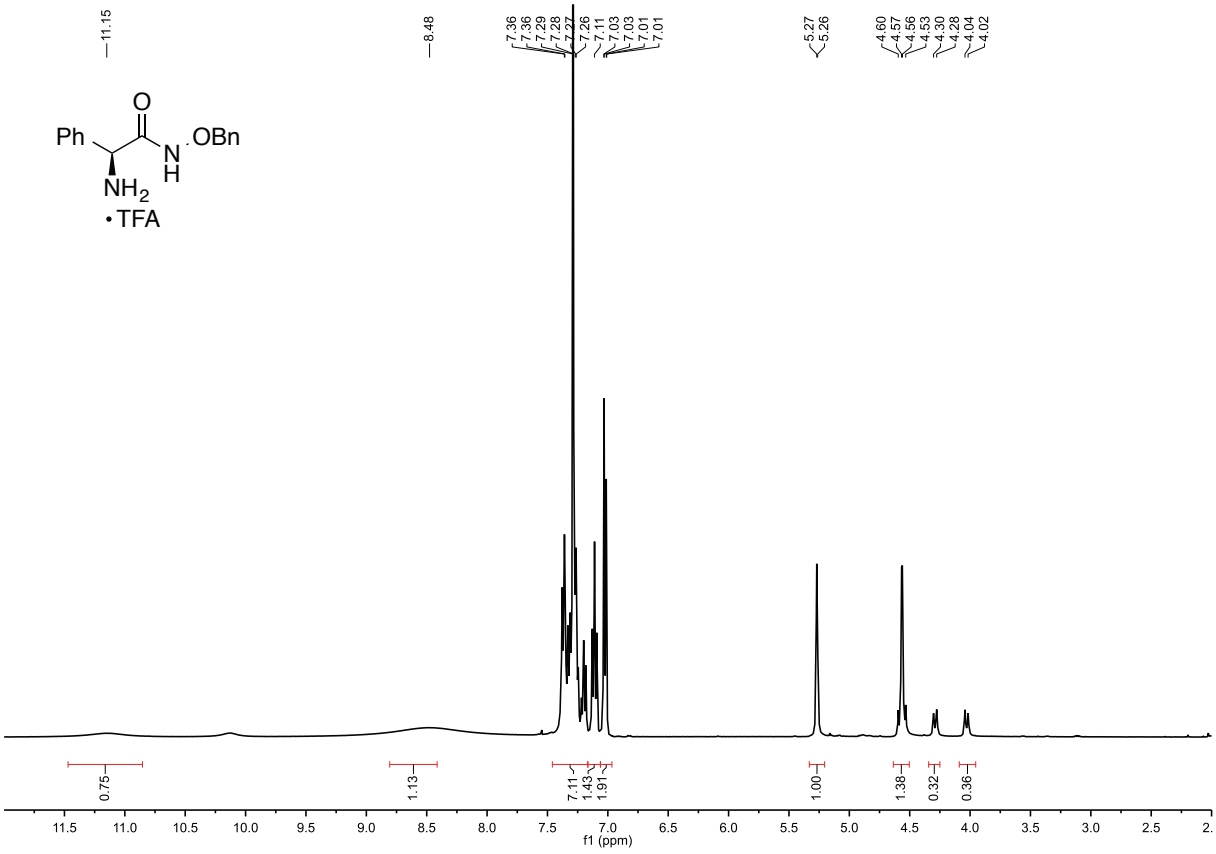
f1 (ppm)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7.01
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5.26
4.60
4.57
4.56
4.53
4.30
4.28
4.04
4.02
Ph
O
N
H
OBn
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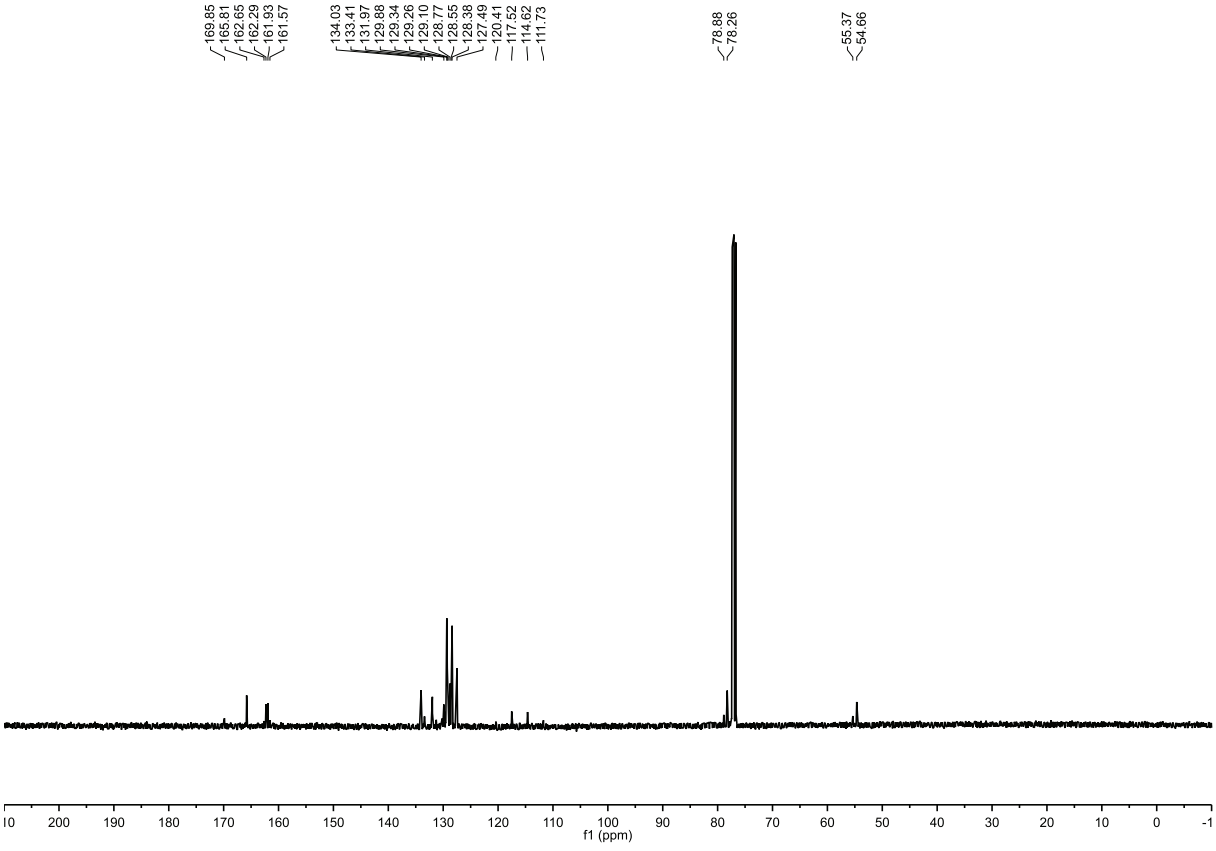
f1 (ppm)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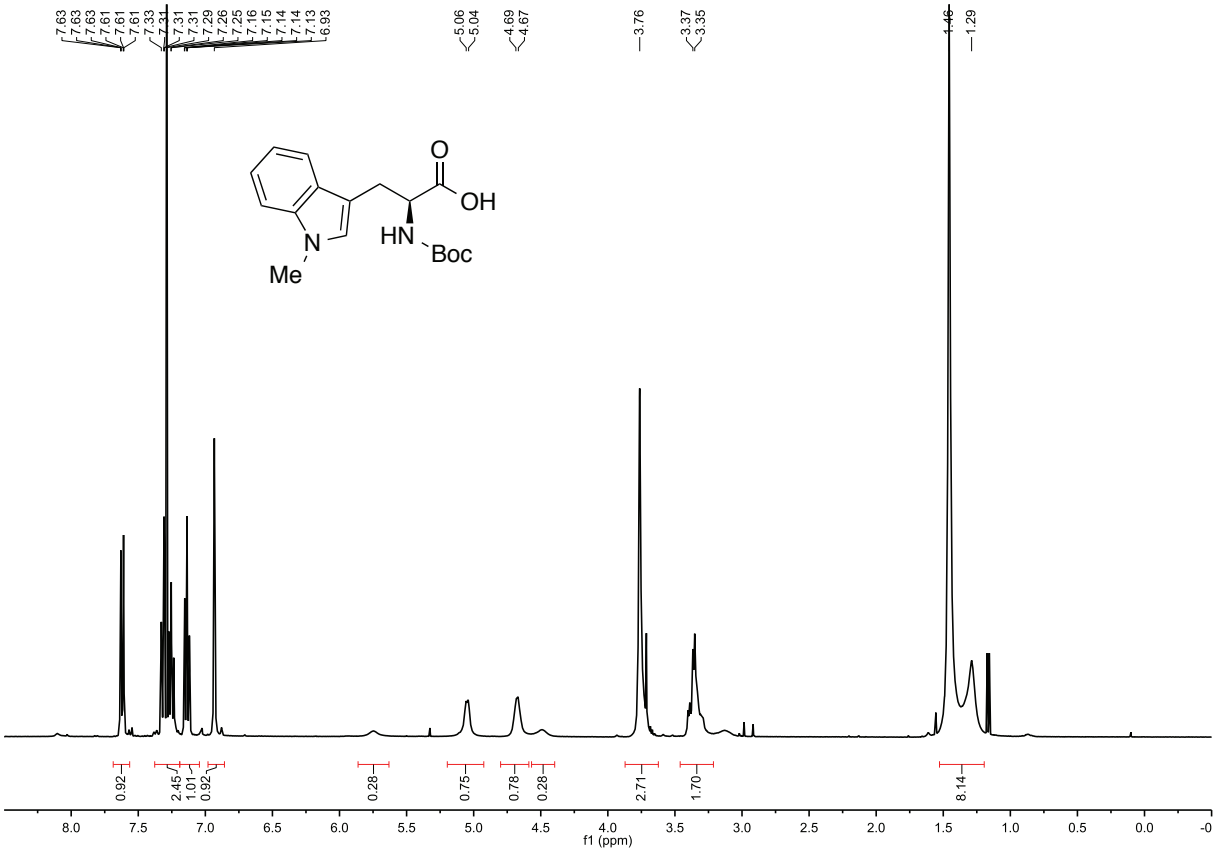
f1 (ppm)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7.13
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5.06
5.04
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3.37
3.35
1.46
1.29
O
OH
HN
Boc
N
Me
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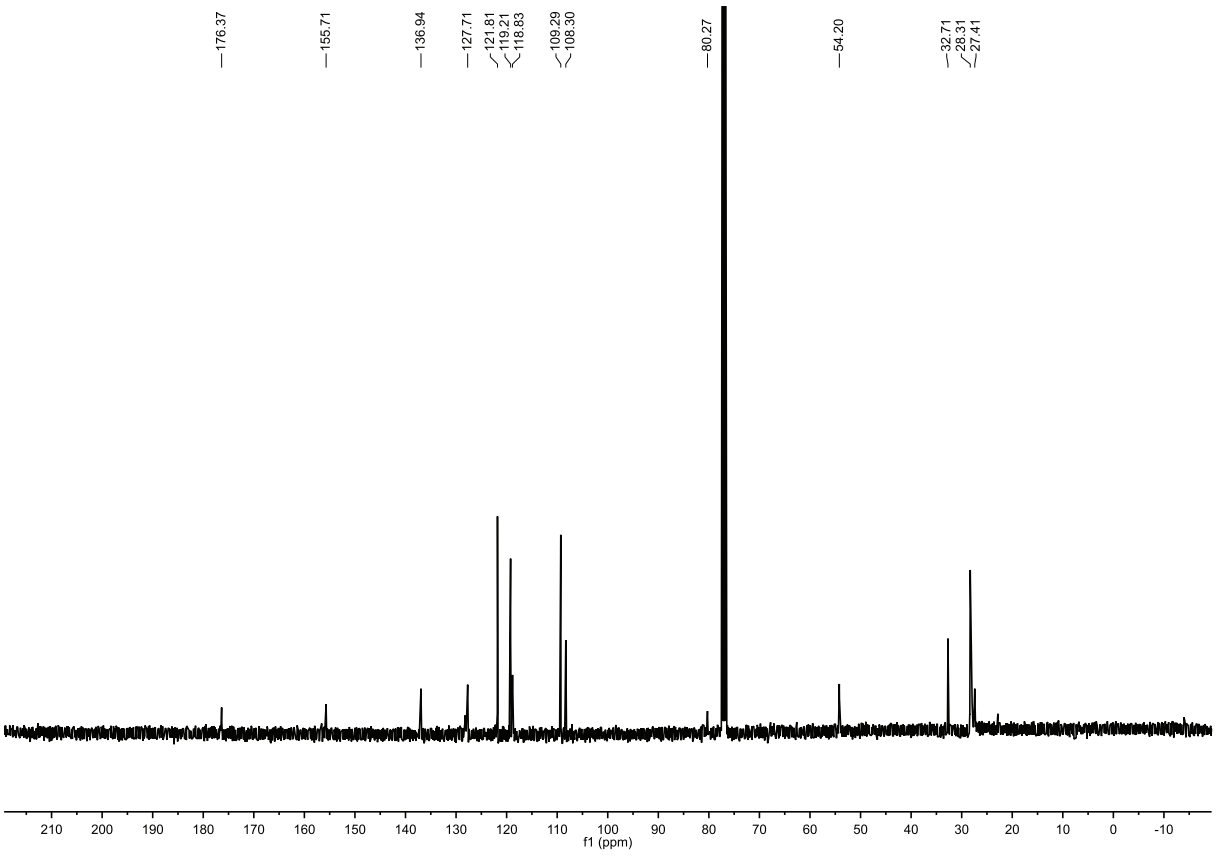
f1 (ppm)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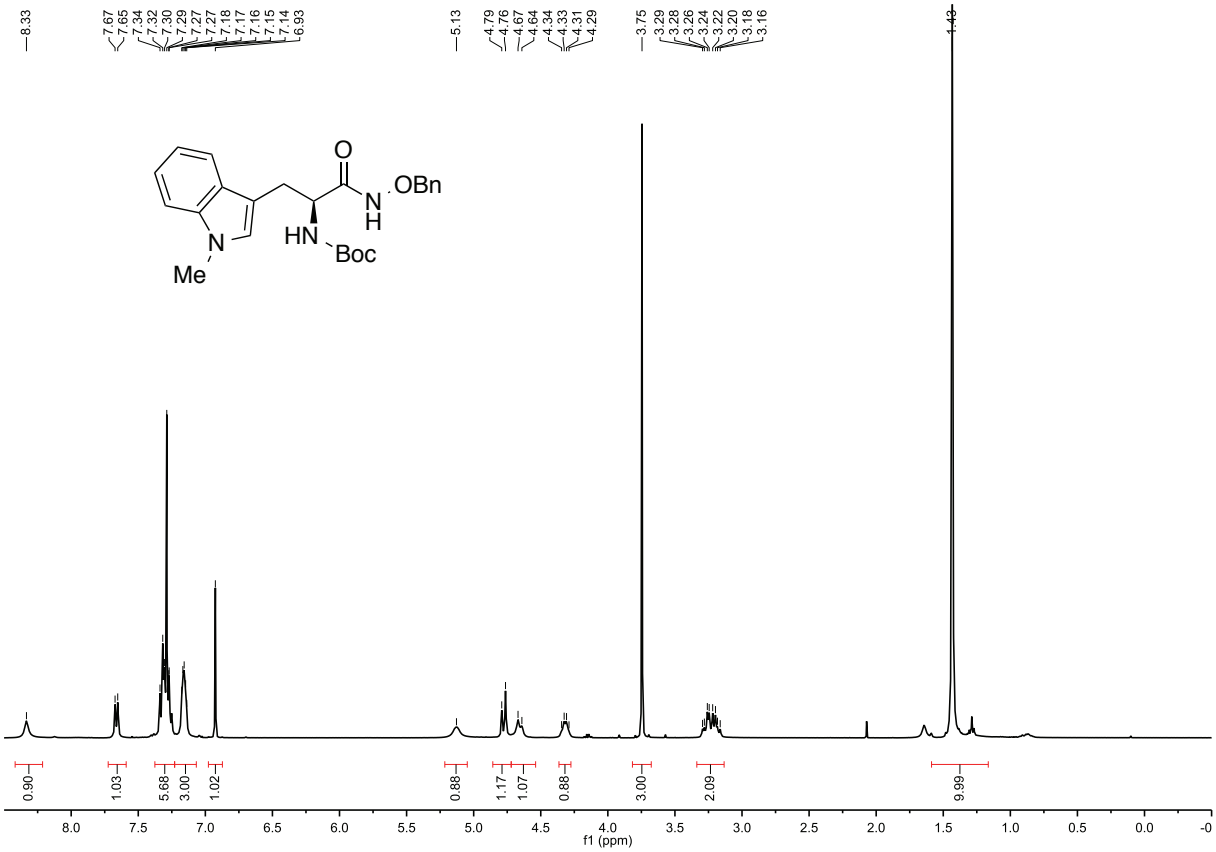
27.41
f1 (ppm)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7.14
6.93
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4.79
4.76
4.67
4.64
4.34
4.33
4.31
4.29
3.75
3.29
3.28
3.26
3.24
3.22
3.20
3.18
3.16
1.43
O
OBn
N
H
HN
Boc
N
Me
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1.02
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1.17
1.07
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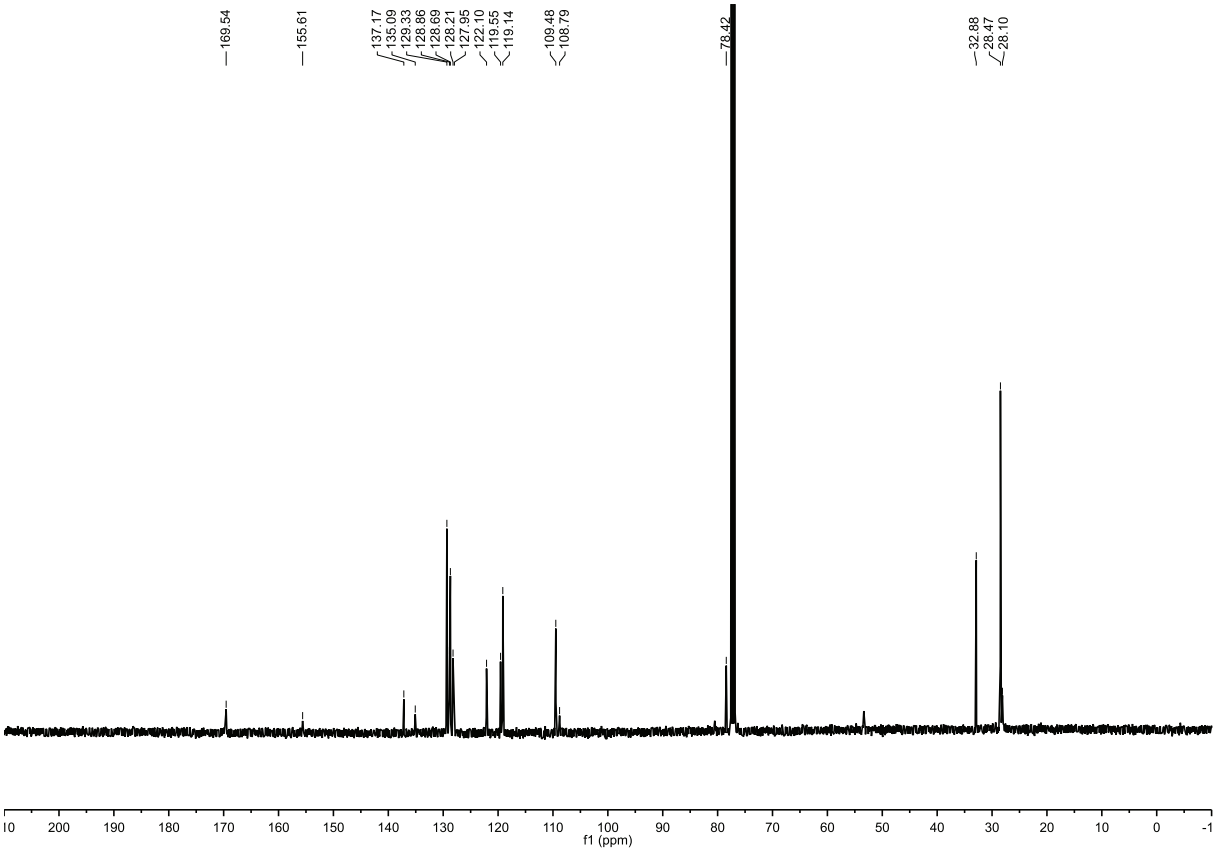
9.99
f1 (ppm)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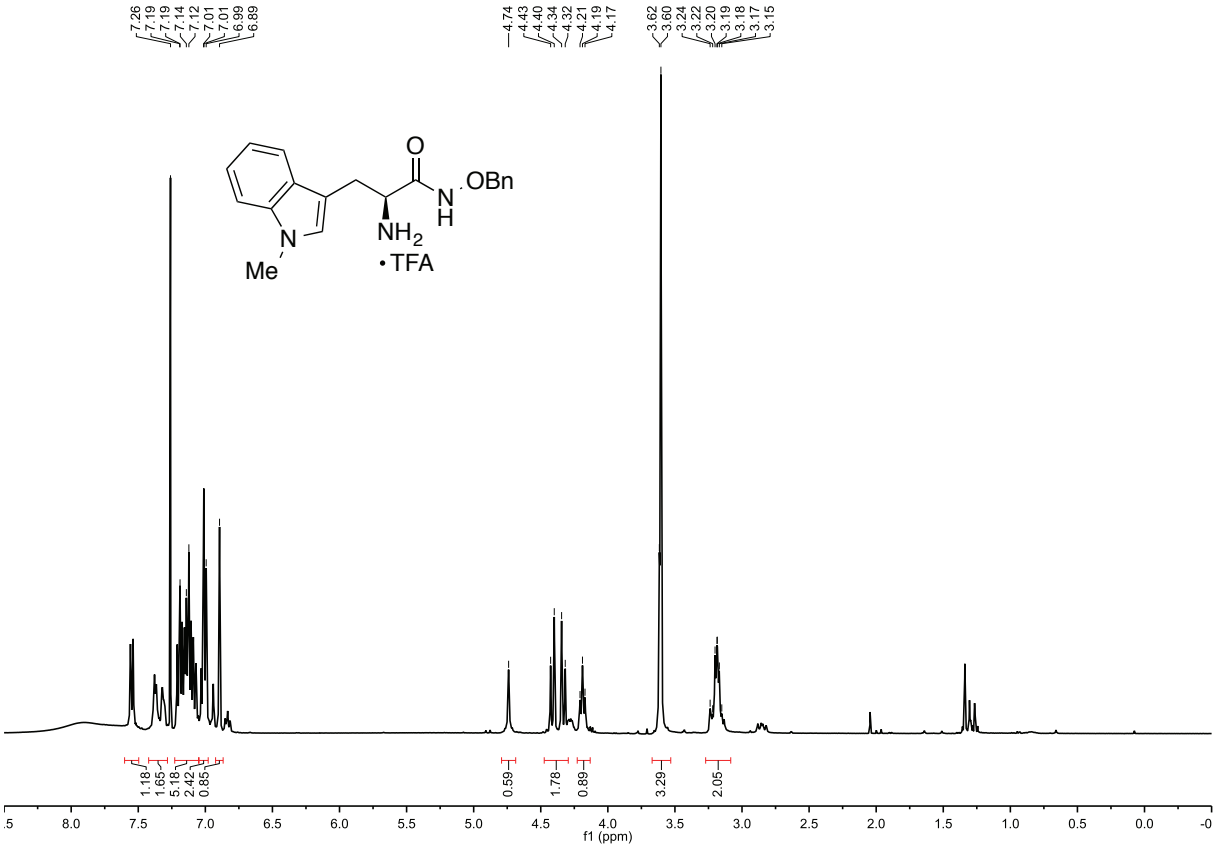
28.10
f1 (ppm)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7.01
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4.40
4.34
4.32
4.21
4.19
4.17
3.62
3.60
3.24
3.22
3.20
3.19
3.18
3.17
3.15
O
OBn
N
H
NH2
•TFA
N
Me
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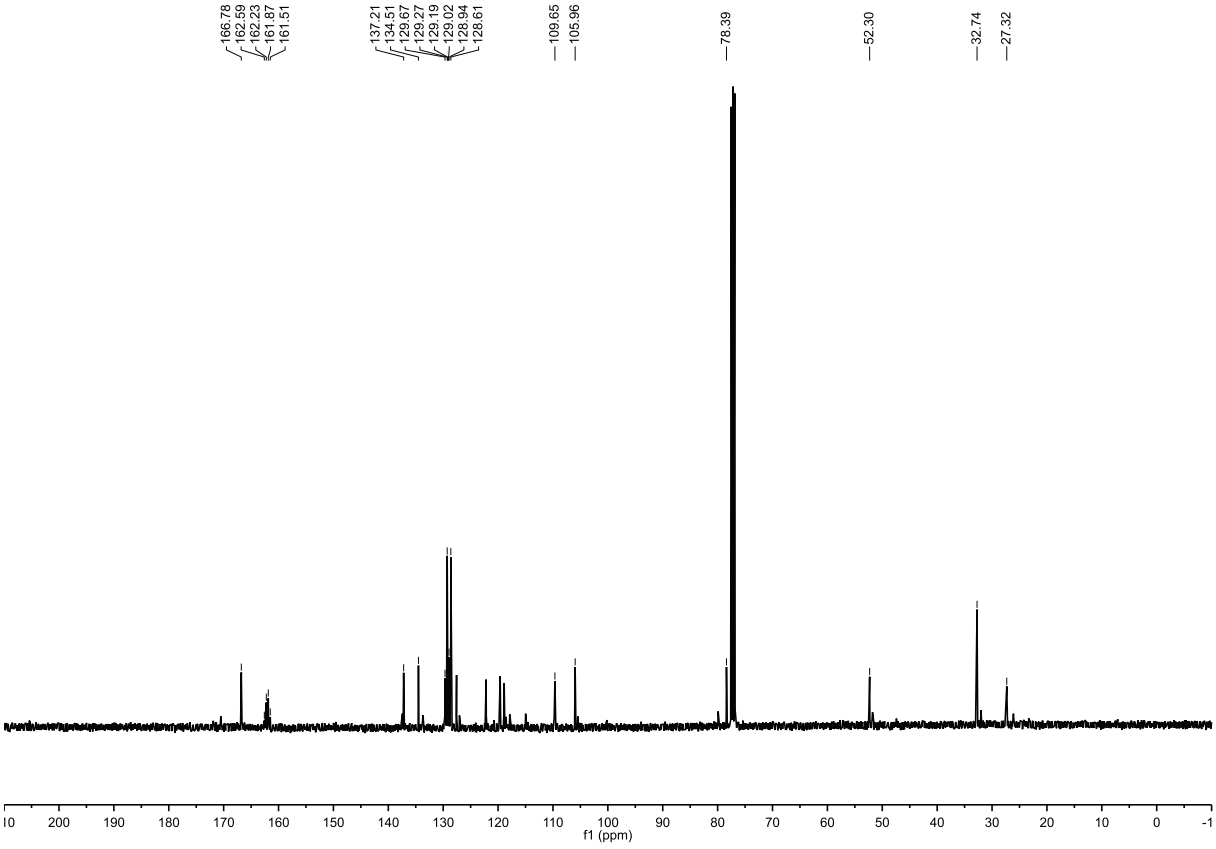
0.89
3.29
2.05
f1 (ppm)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109.65
105.96
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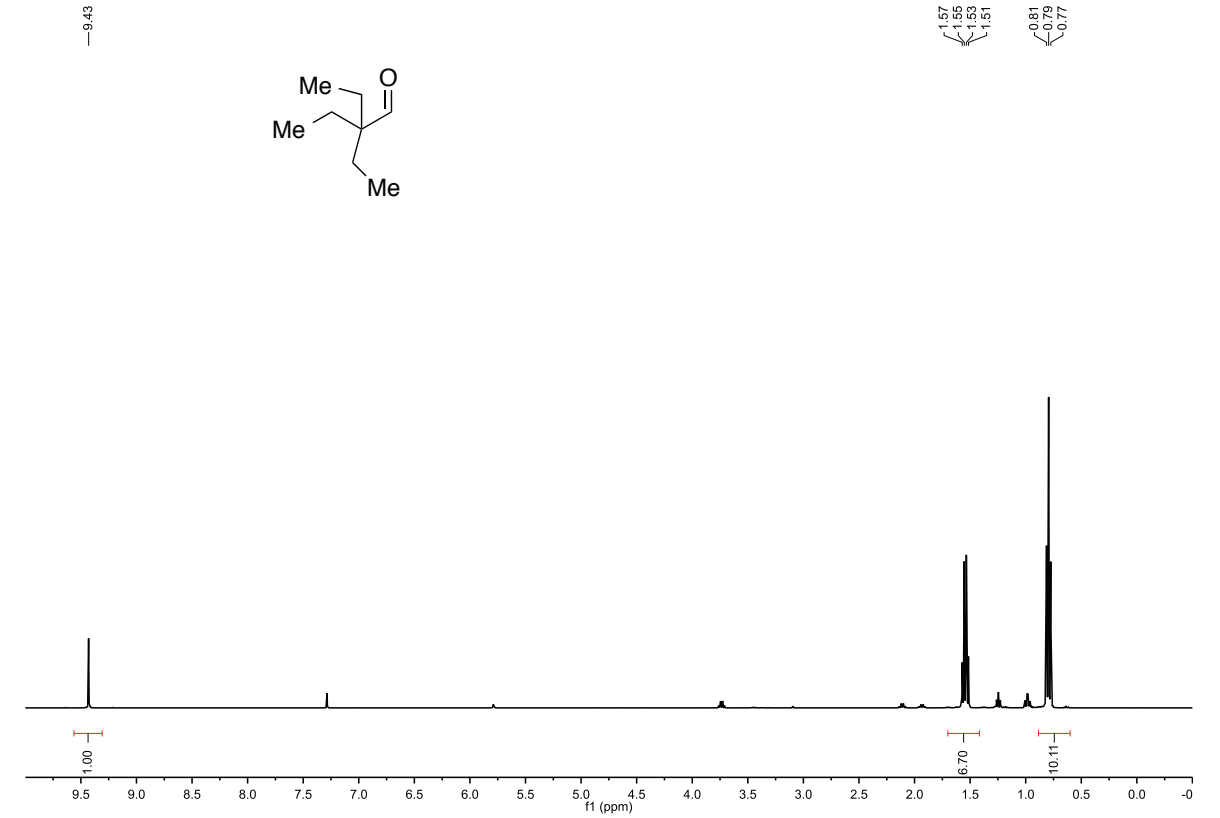
52.30
32.74
27.32
f1 (ppm)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Me
Me
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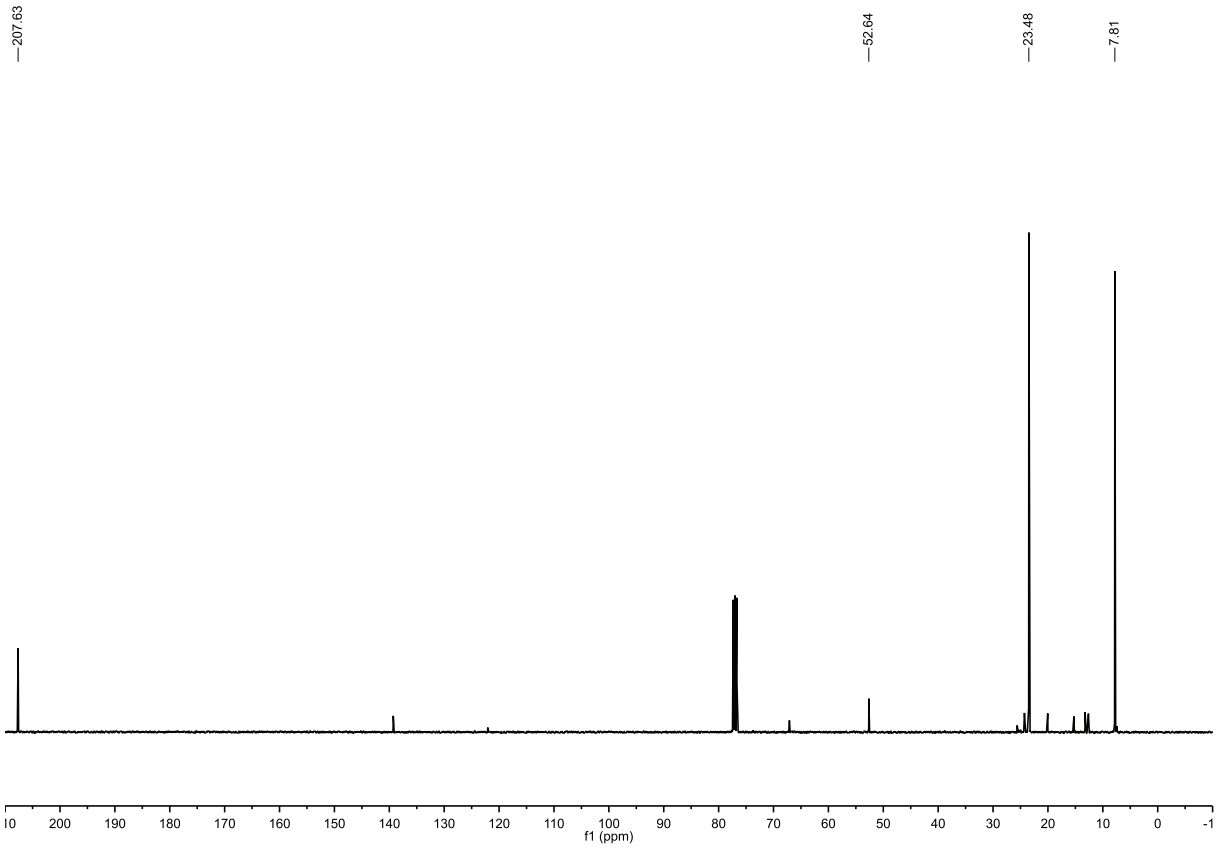
f1 (ppm)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7.81
f1 (ppm)


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2.17
1.81
1.80
1.79
1.77
1.56
1.29
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O
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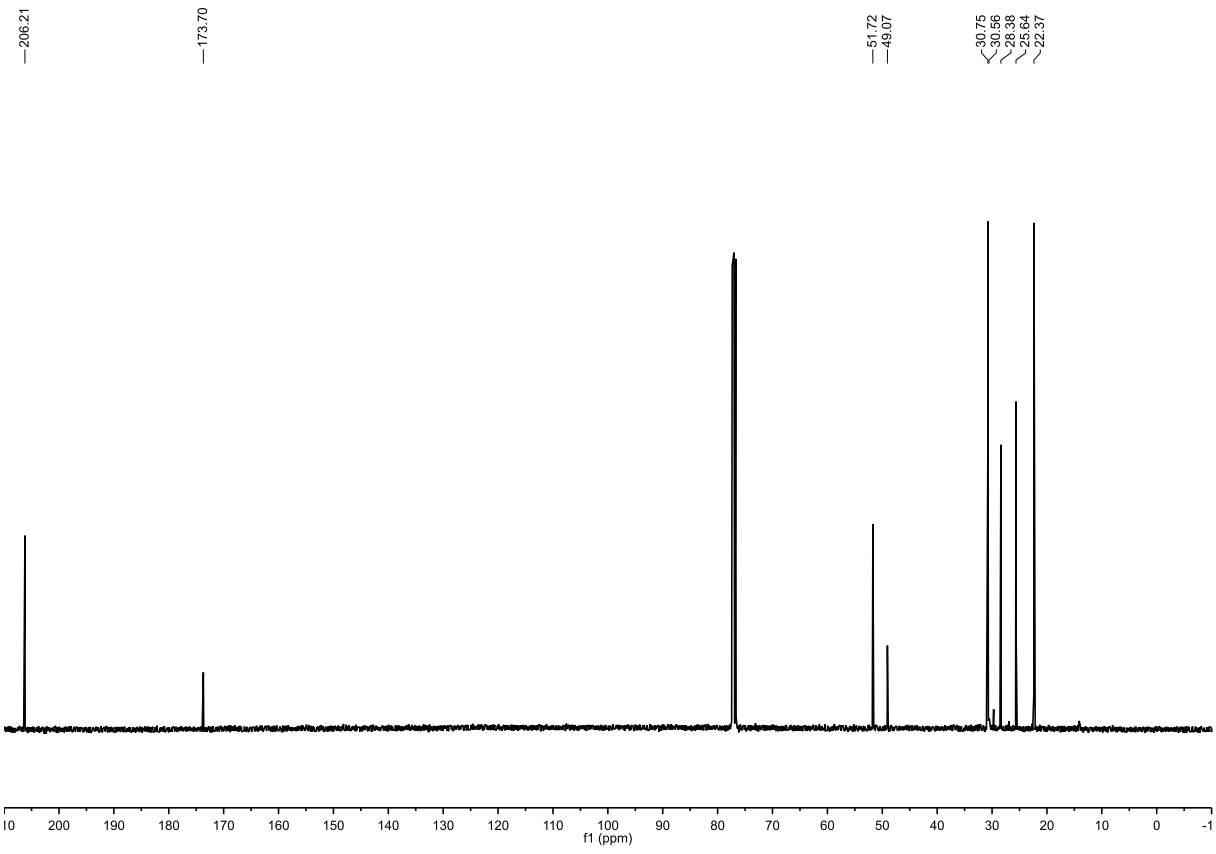
5.86
f1 (ppm)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25.64
22.37
f1 (ppm)

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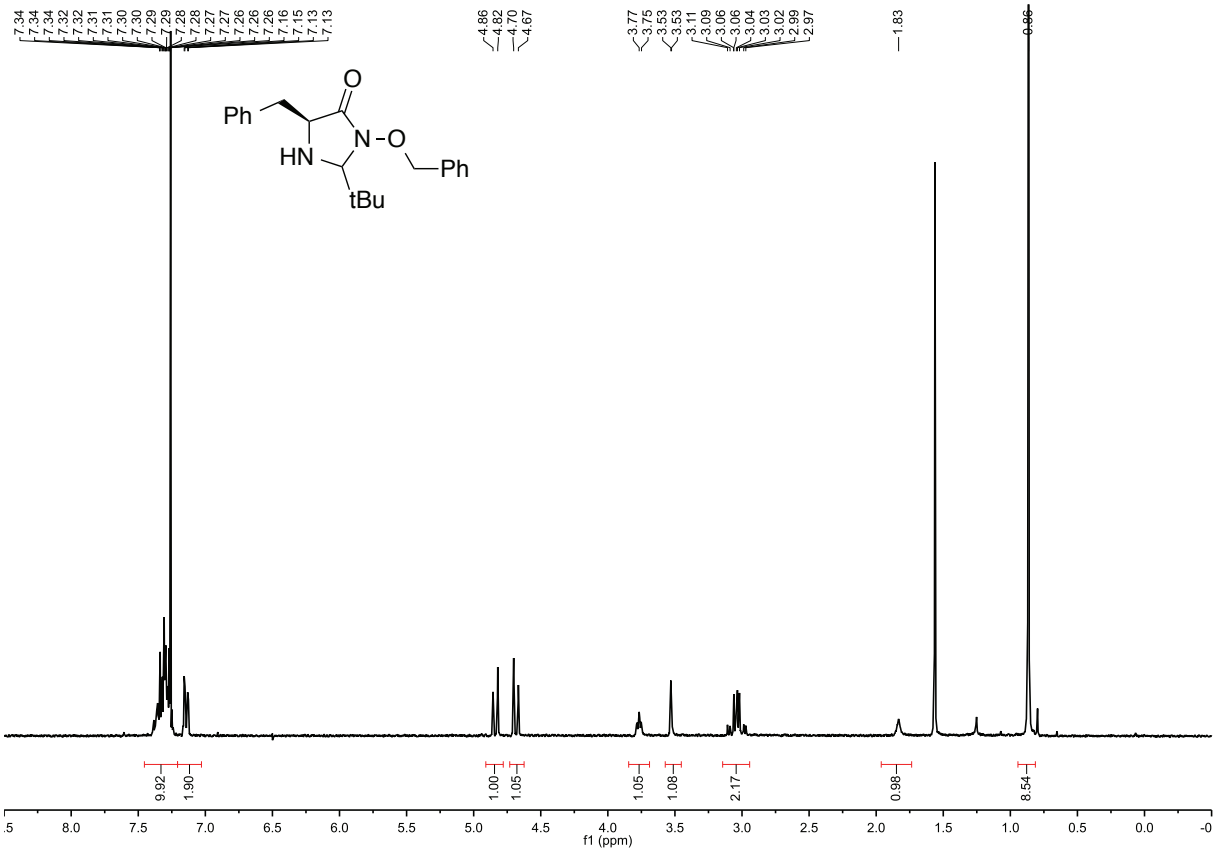

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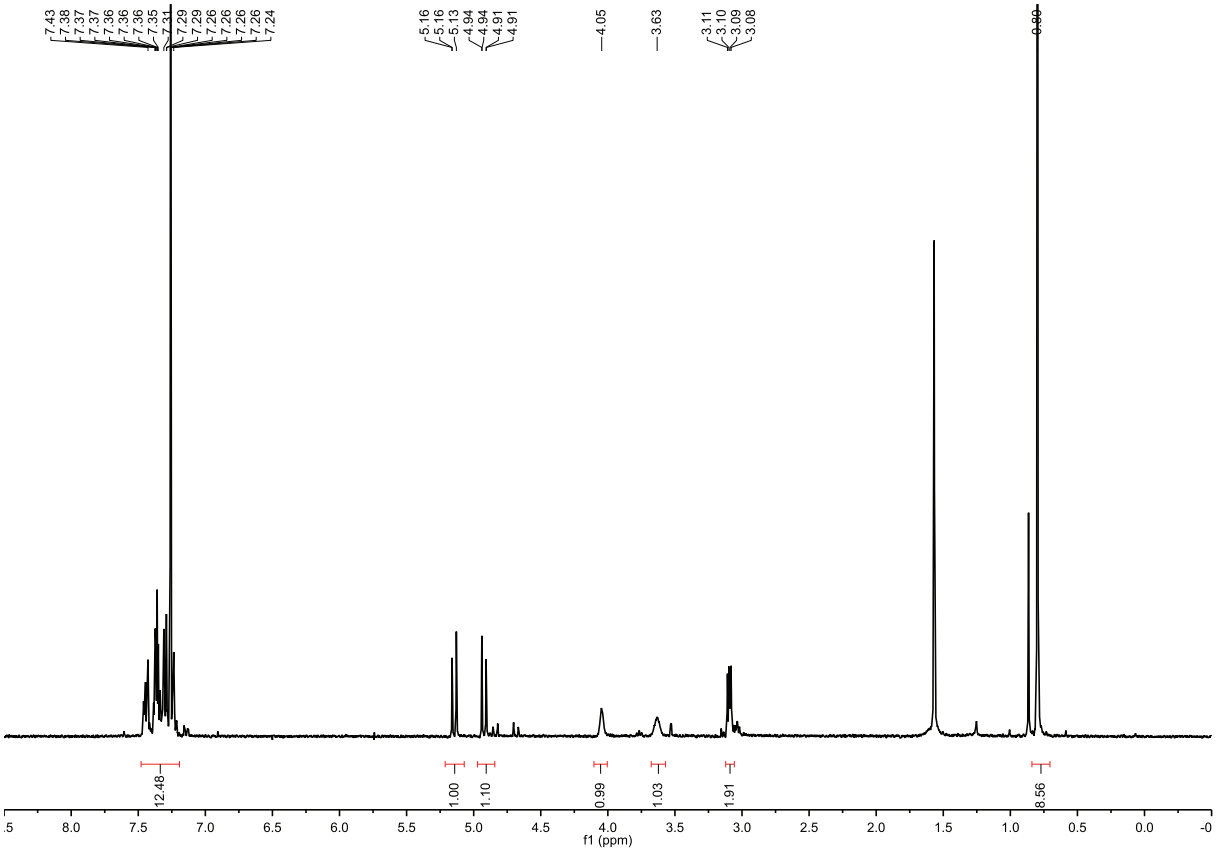

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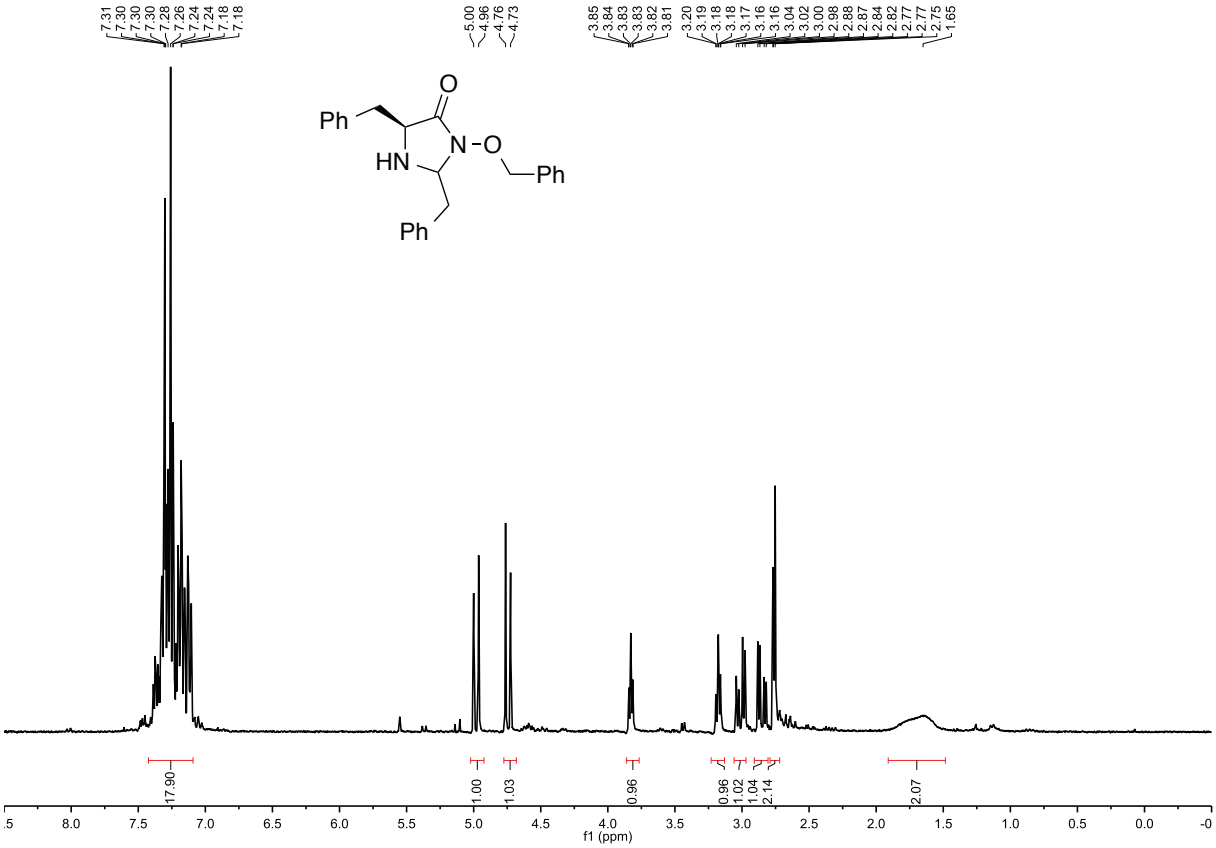

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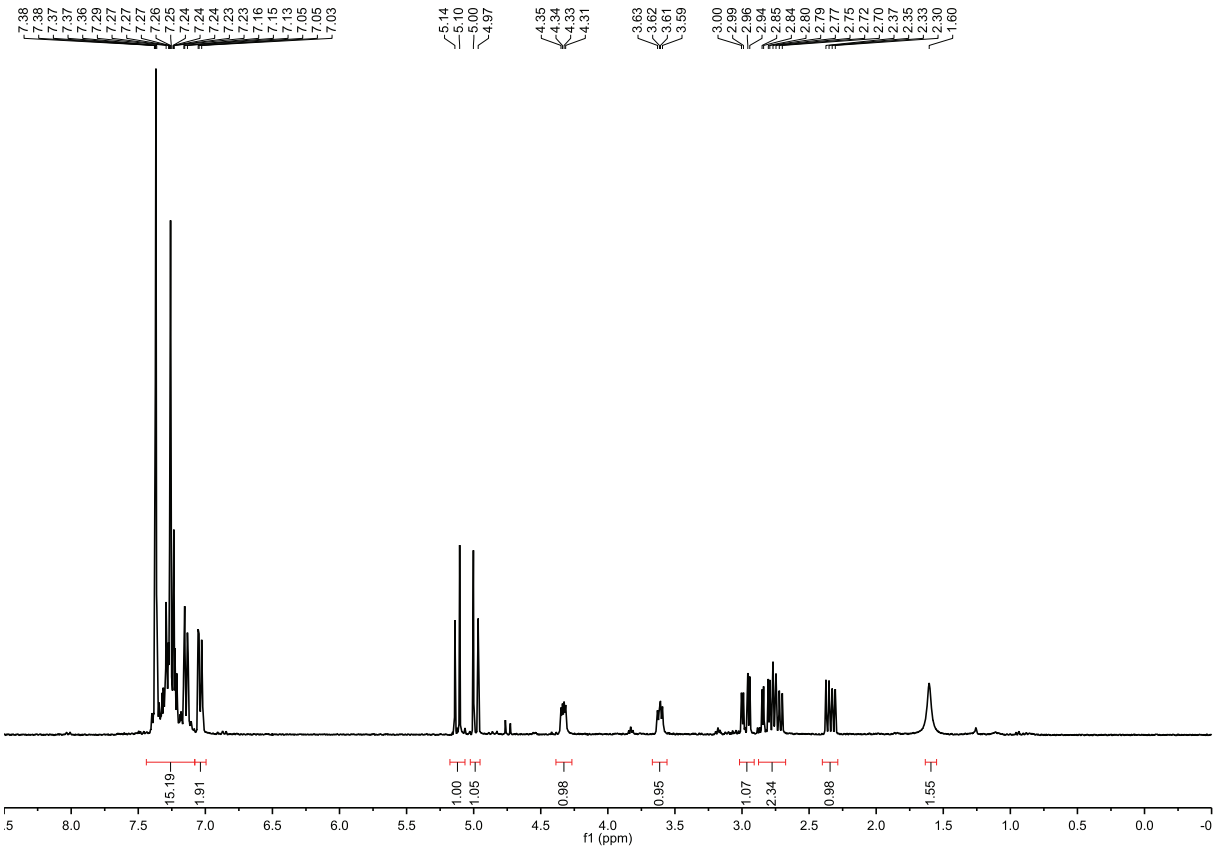

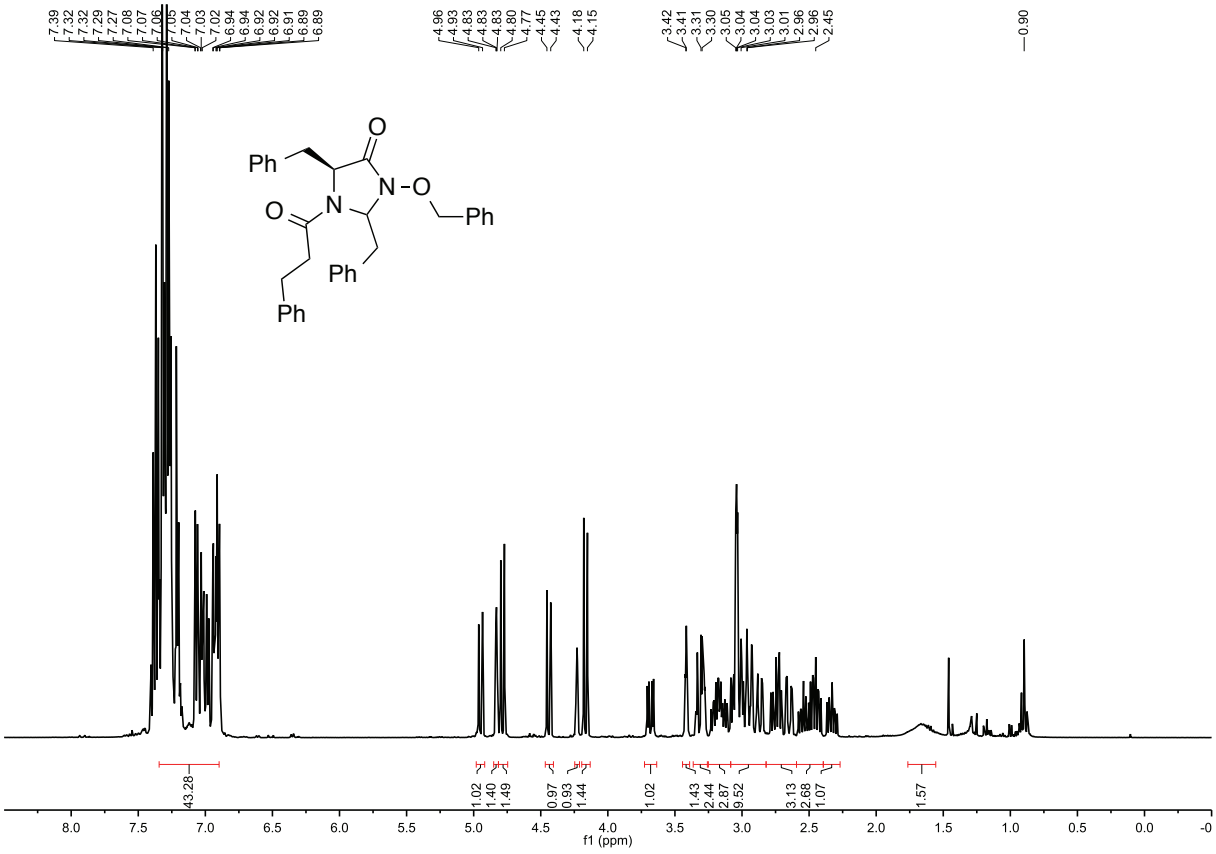
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3.04
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Ph
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O
N-O
Ph
Ph
Ph
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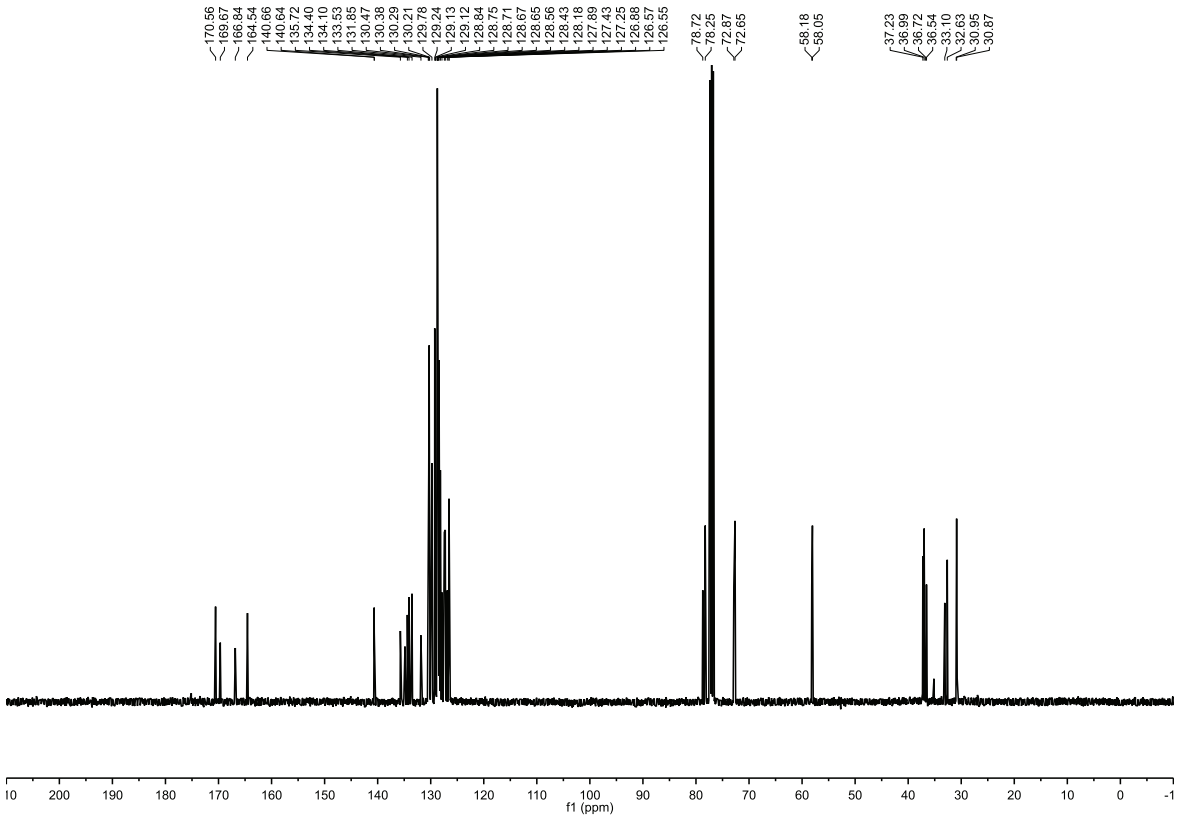
f1 (ppm)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f1 (ppm)

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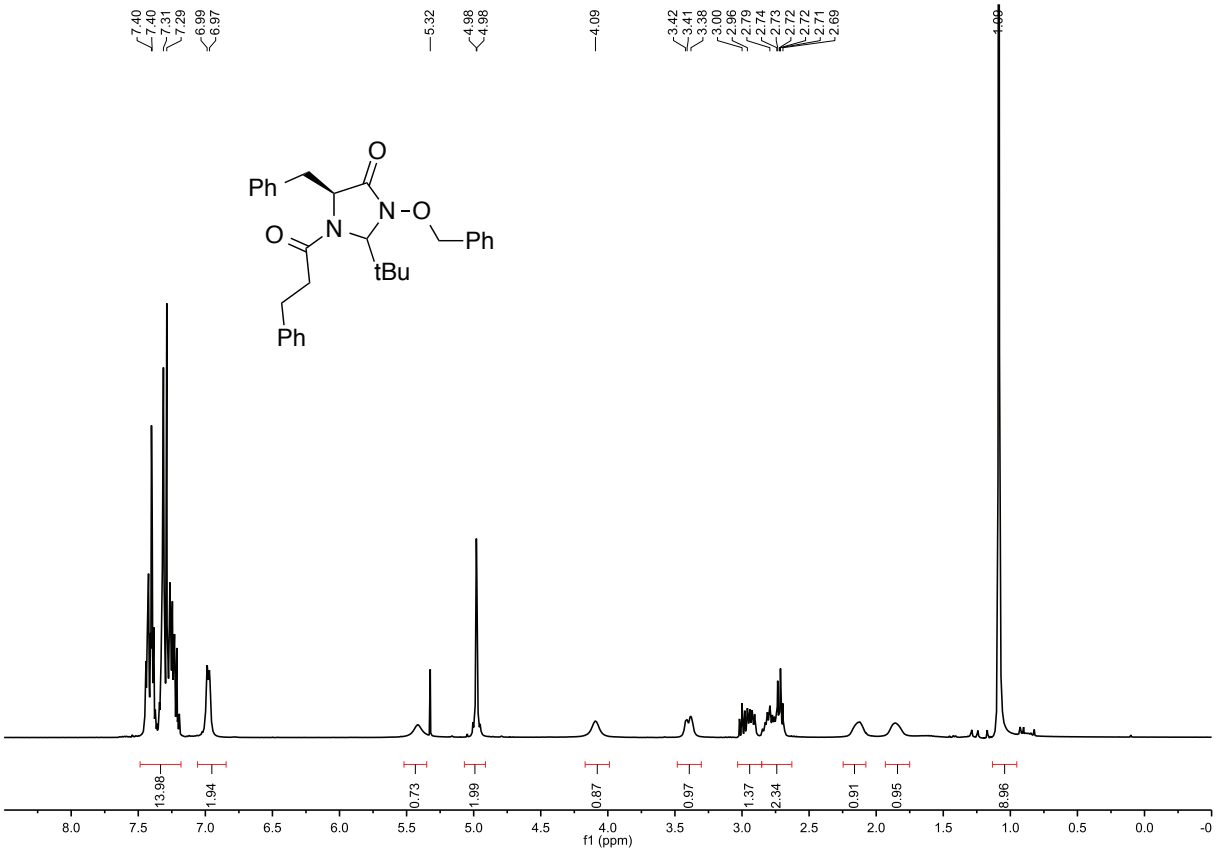

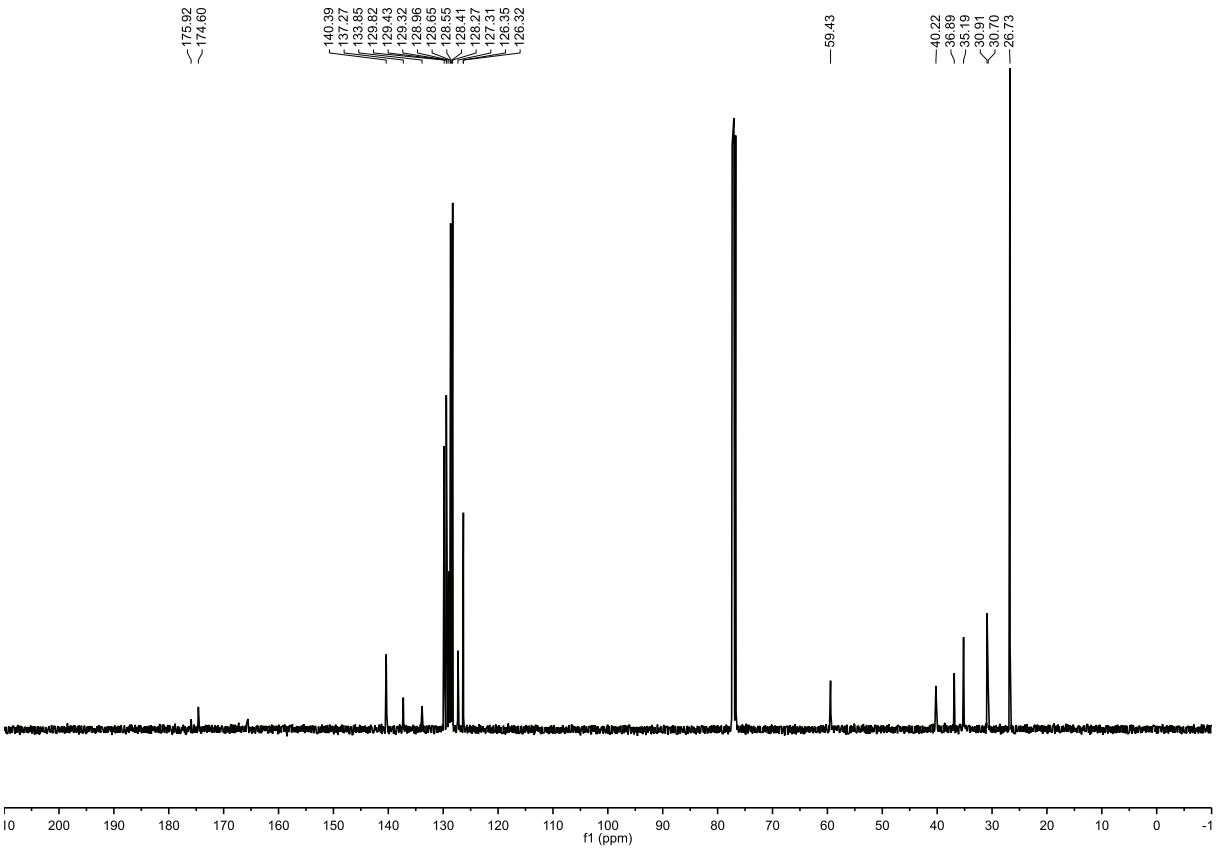

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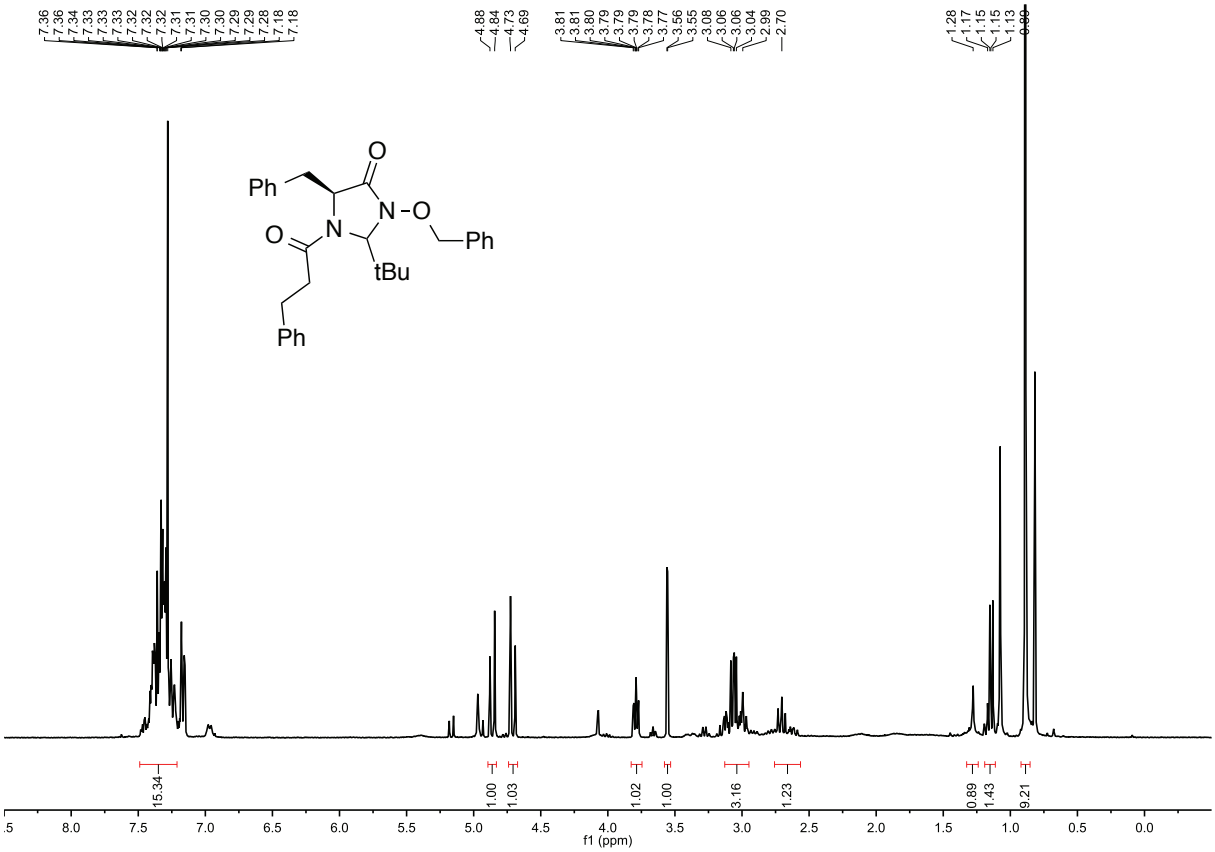

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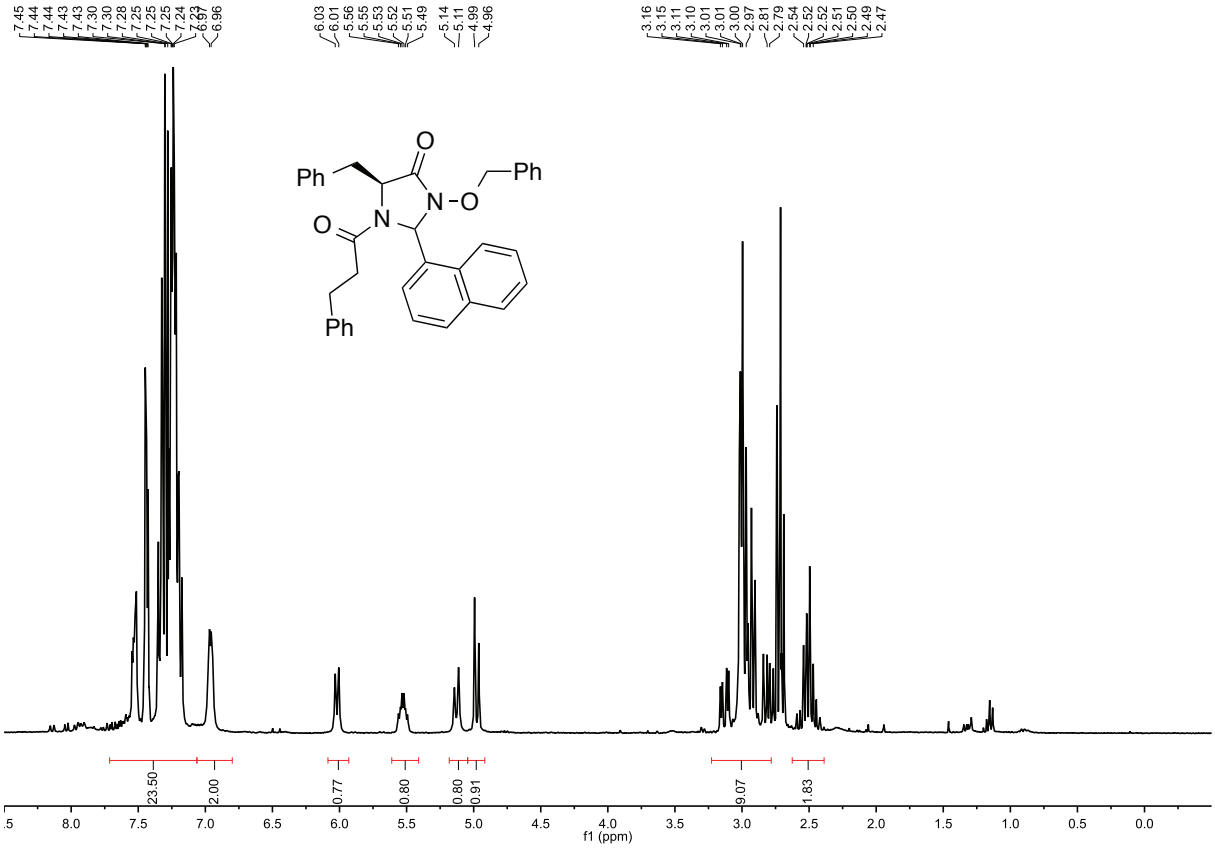

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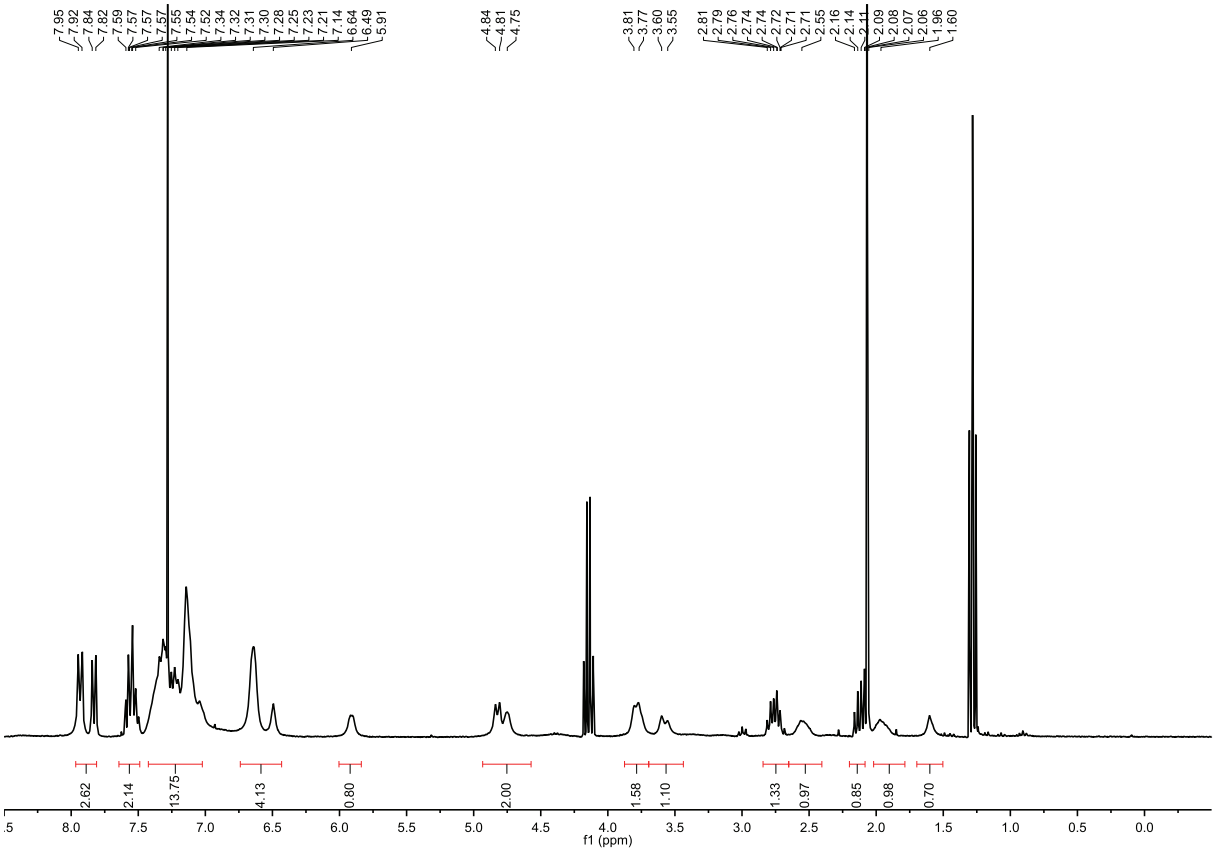

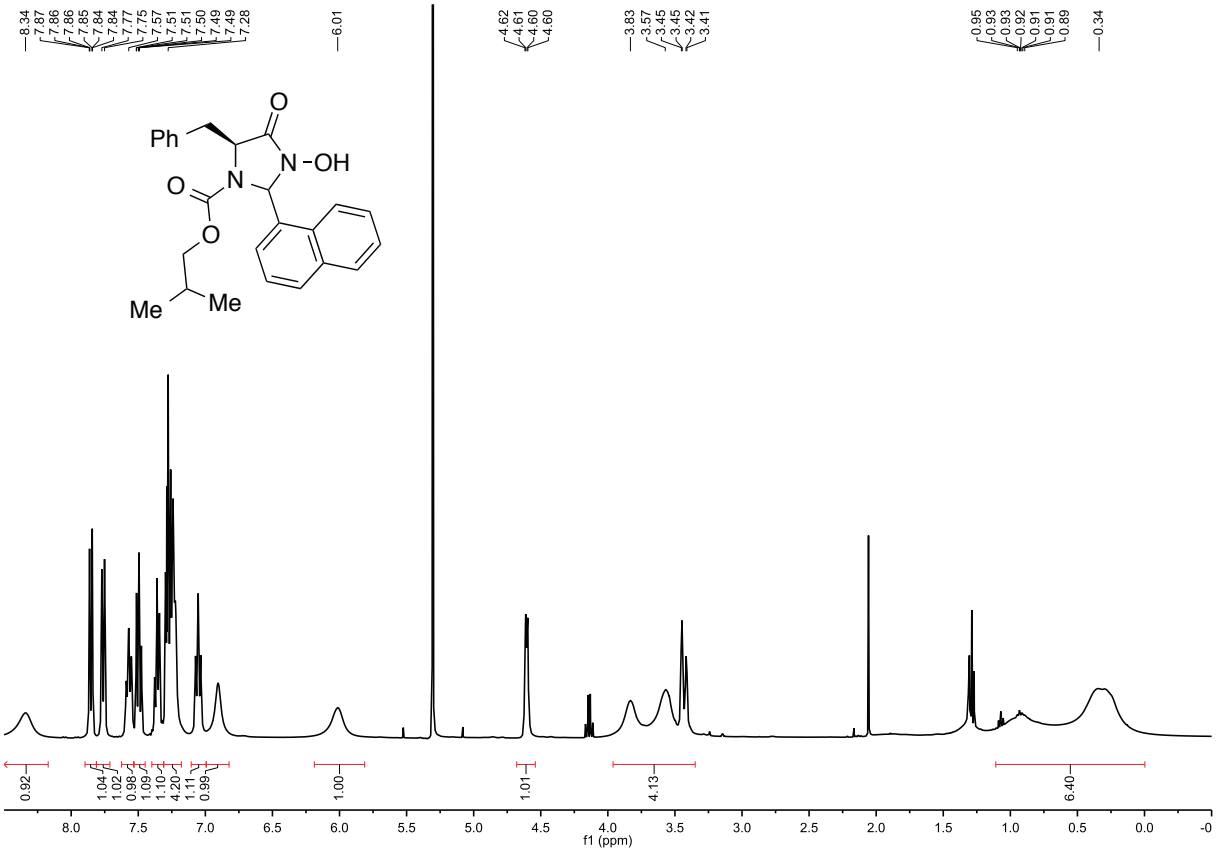
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7.49
7.28
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4.60
4.60
3.83
3.57
3.45
3.45
3.42
3.41
0.95
0.93
0.93
0.92
0.91
0.91
0.89
0.34
Ph
O
N
N-OH
O
O
Me
Me
0.92
1.04
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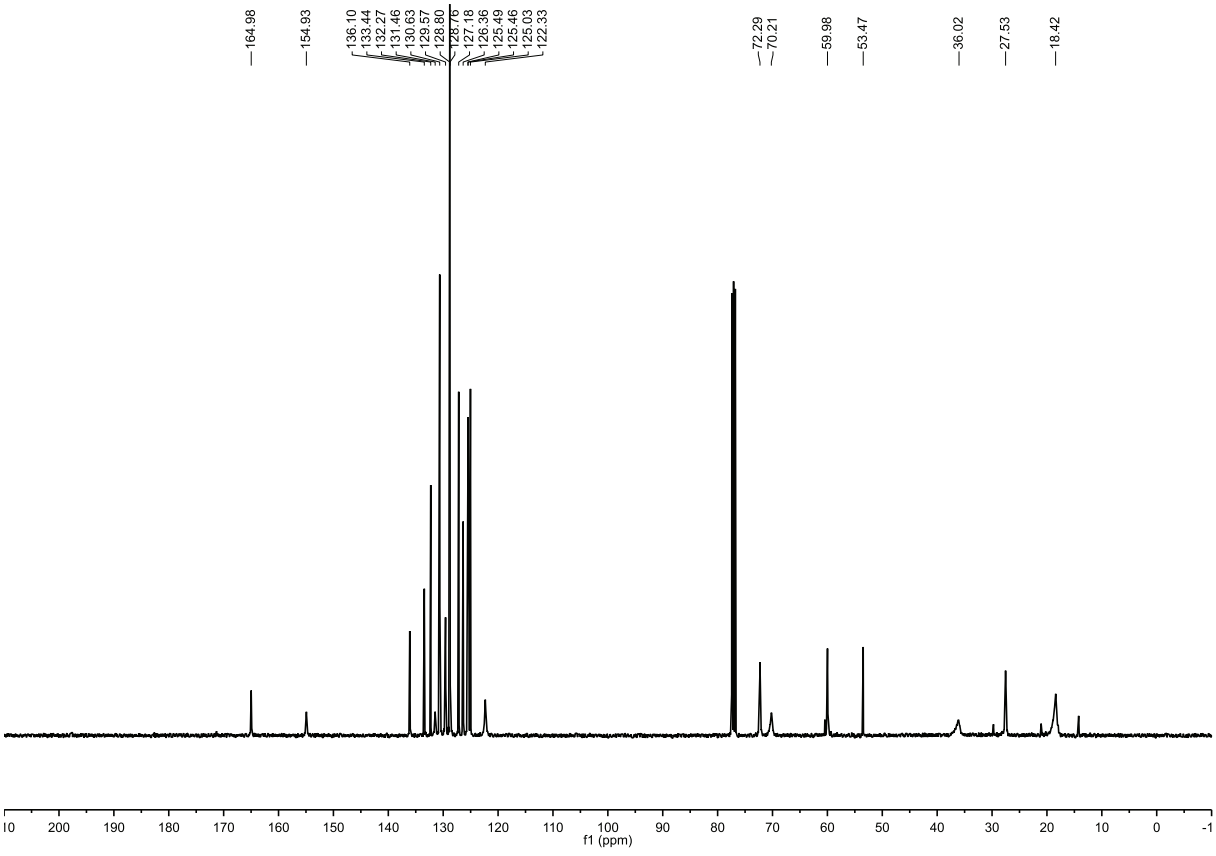
6.40
f1 (ppm)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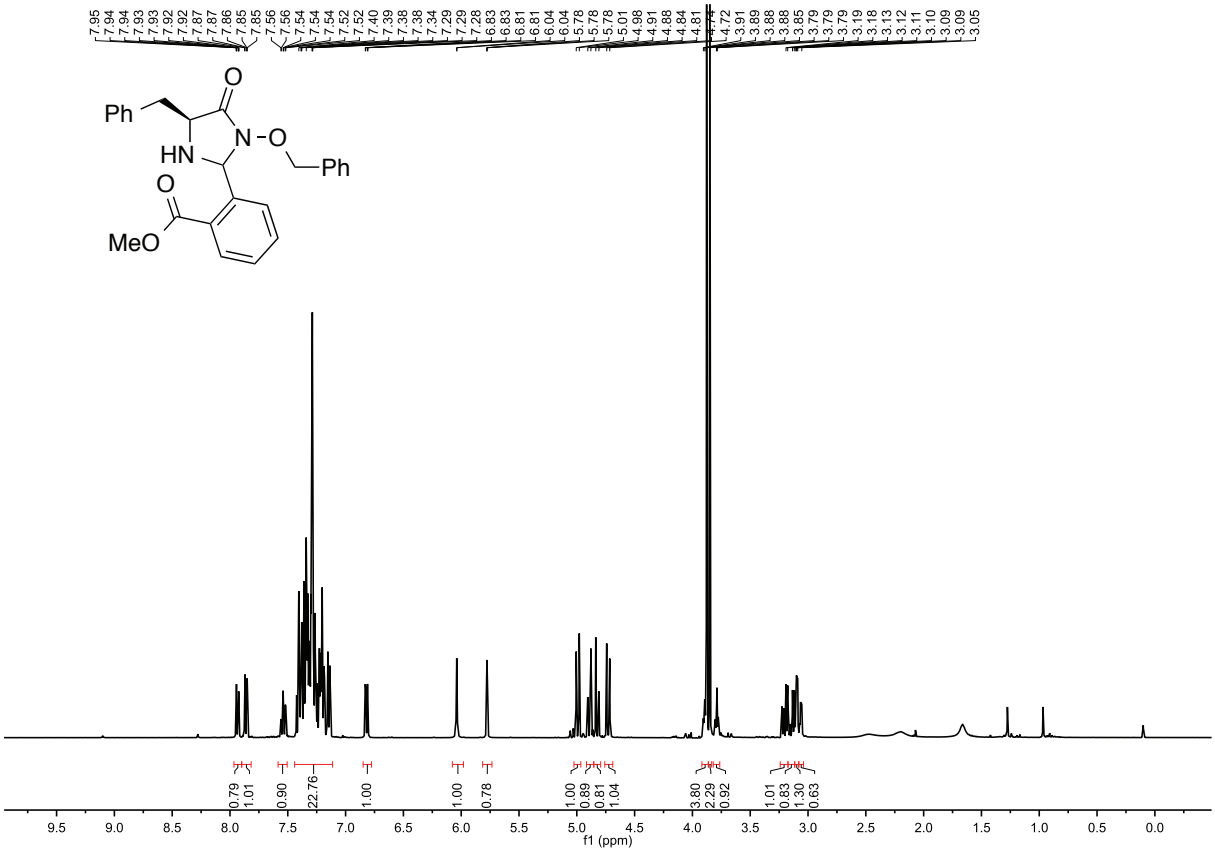
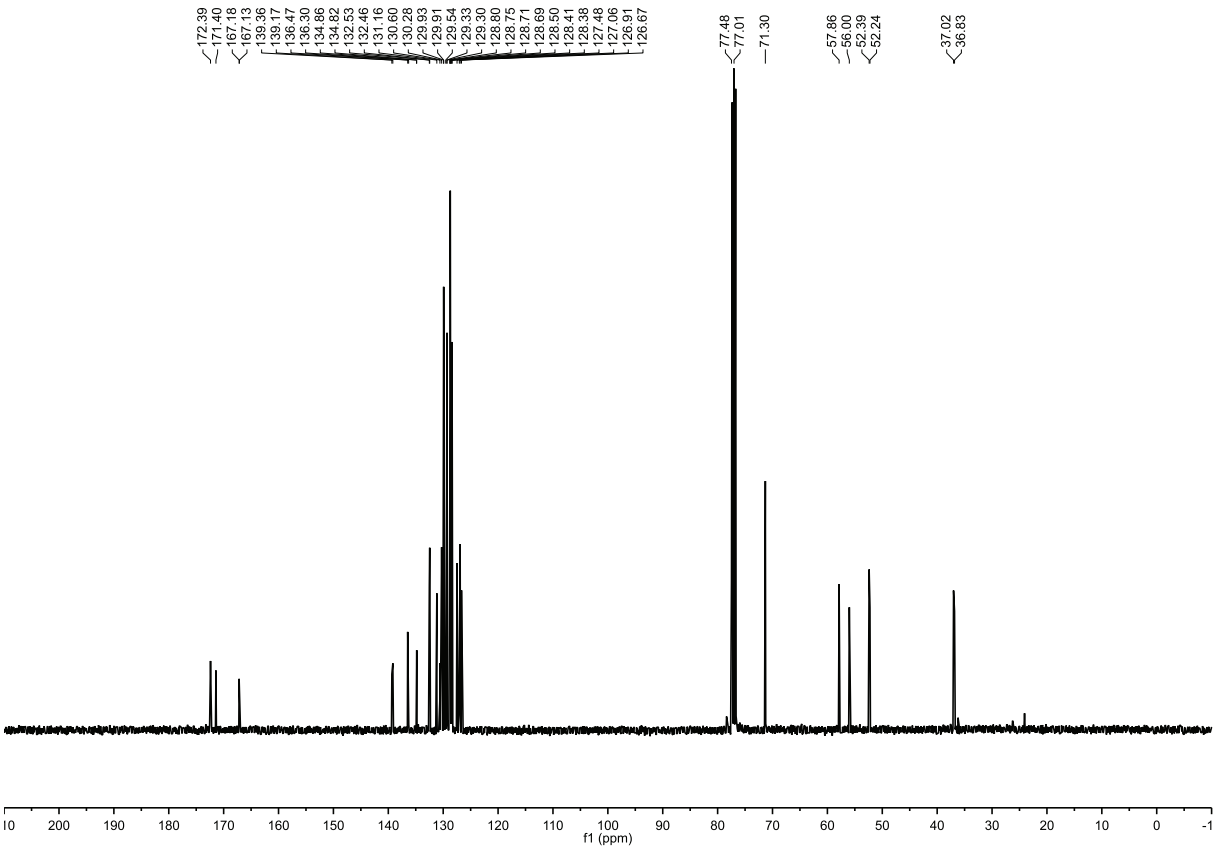
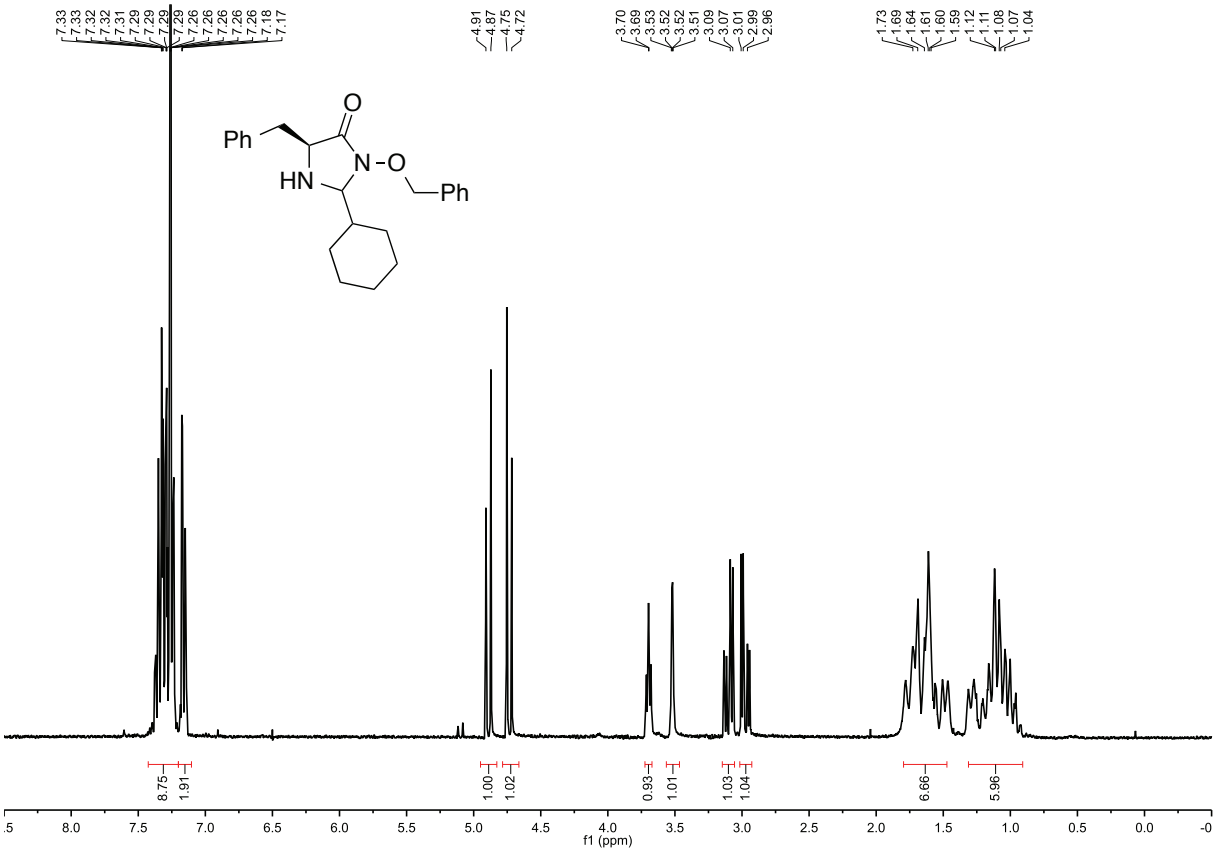
127.18
126.36
125.49
125.46
125.03
122.33
72.29
70.21
59.98
53.47
36.02
27.53
18.42
f1 (ppm)


Ph
O
N-O
HN
Ph
O
MeO
f1 (ppm)


f1 (ppm)

Diastereomer 1:



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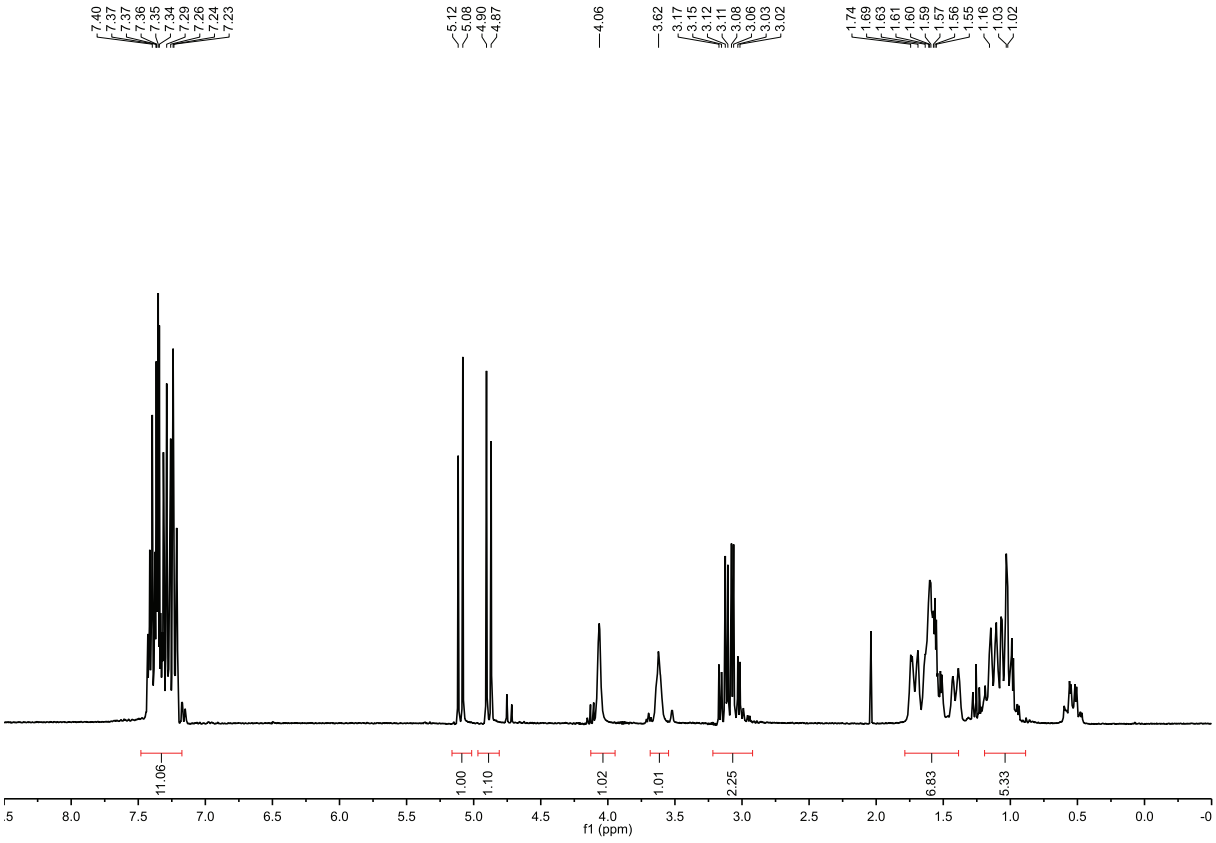

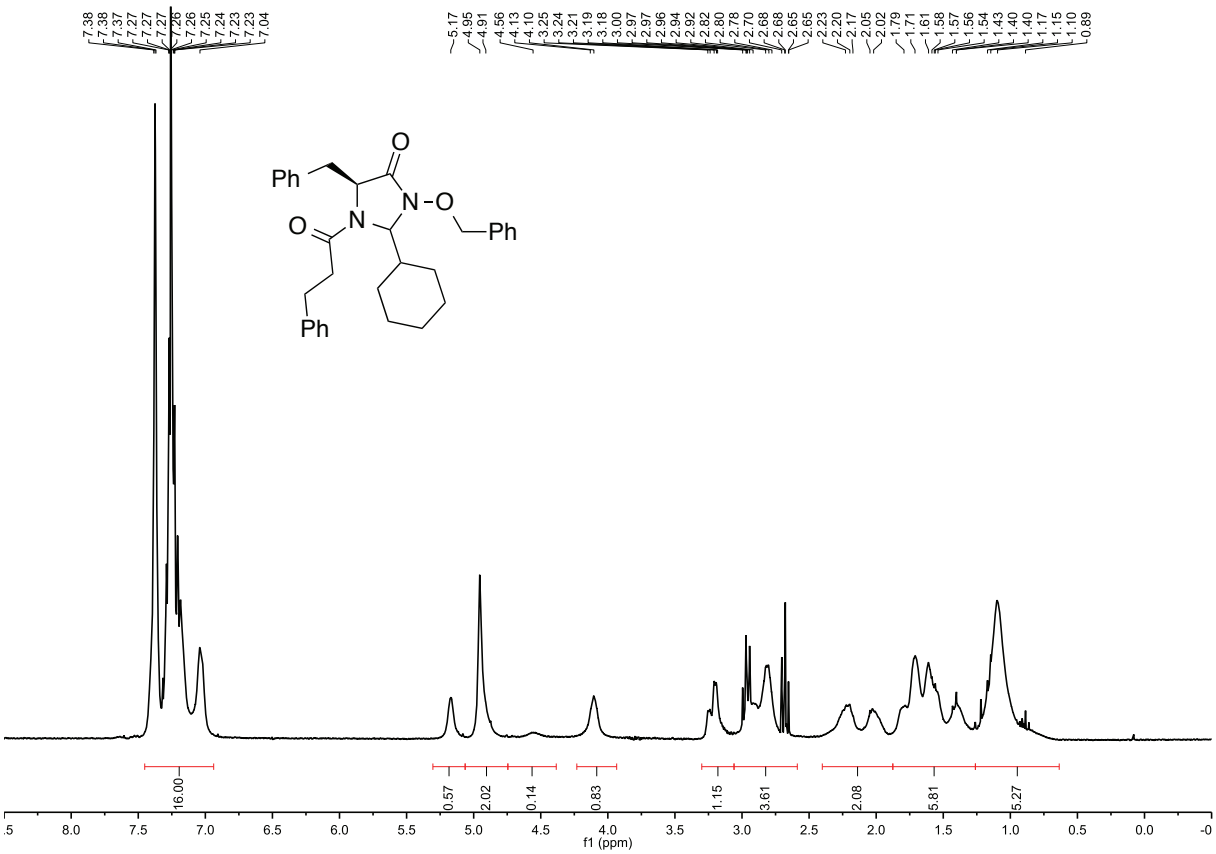
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7.27
7.27
7.26
7.26
7.25
7.24
7.23
7.23
7.04
5.17
4.95
4.91
4.56
4.13
4.10
3.25
3.24
3.21
3.19
3.18
3.00
2.97
2.97
2.96
2.94
2.92
2.82
2.80
2.78
2.70
2.68
2.68
2.65
2.65
2.23
2.20
2.17
2.05
2.02
1.79
1.71
1.61
1.58
1.57
1.56
1.54
1.43
1.40
1.40
1.17
1.15
1.10
0.89
Ph
O
N
N-O
O
Ph
Ph
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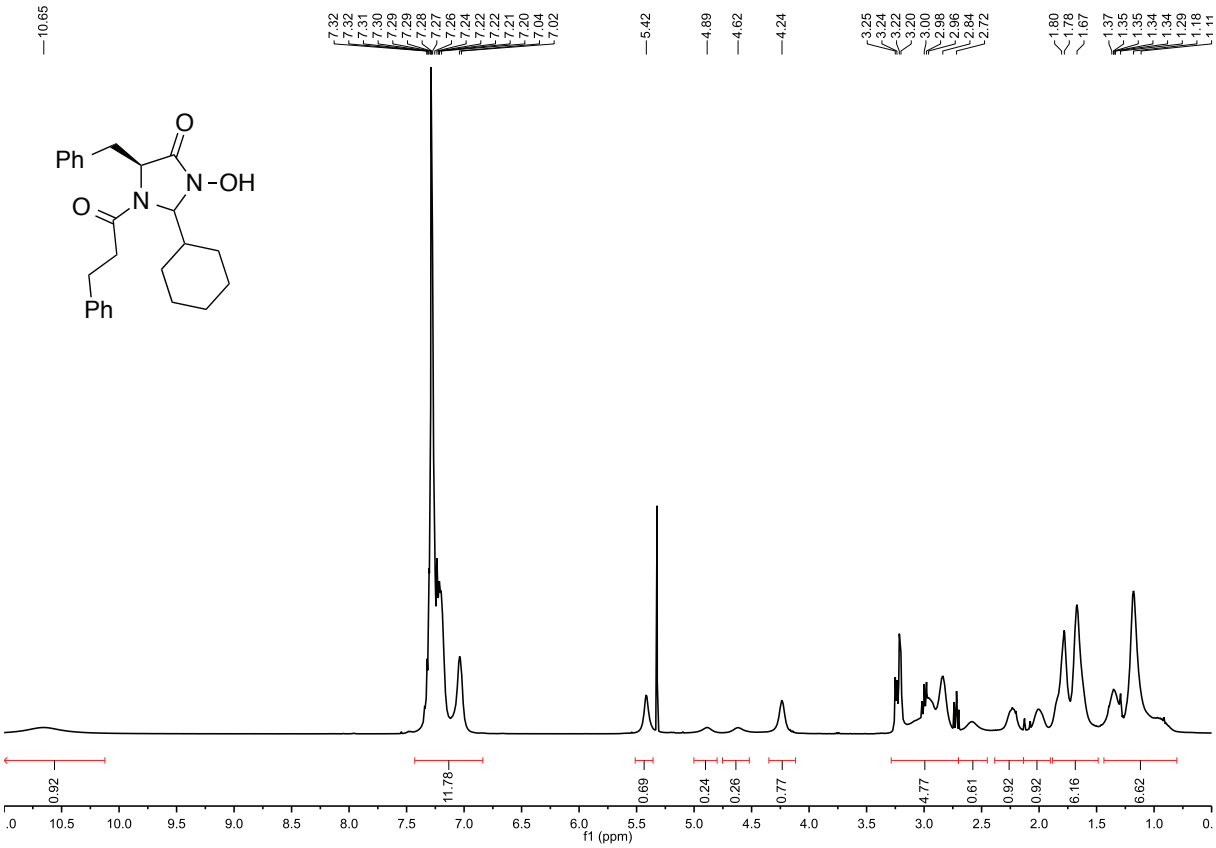
2.02
0.14
0.83
1.15
3.61
2.08
5.81
5.27
f1 (ppm)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7.32
7.32
7.31
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7.29
7.29
7.28
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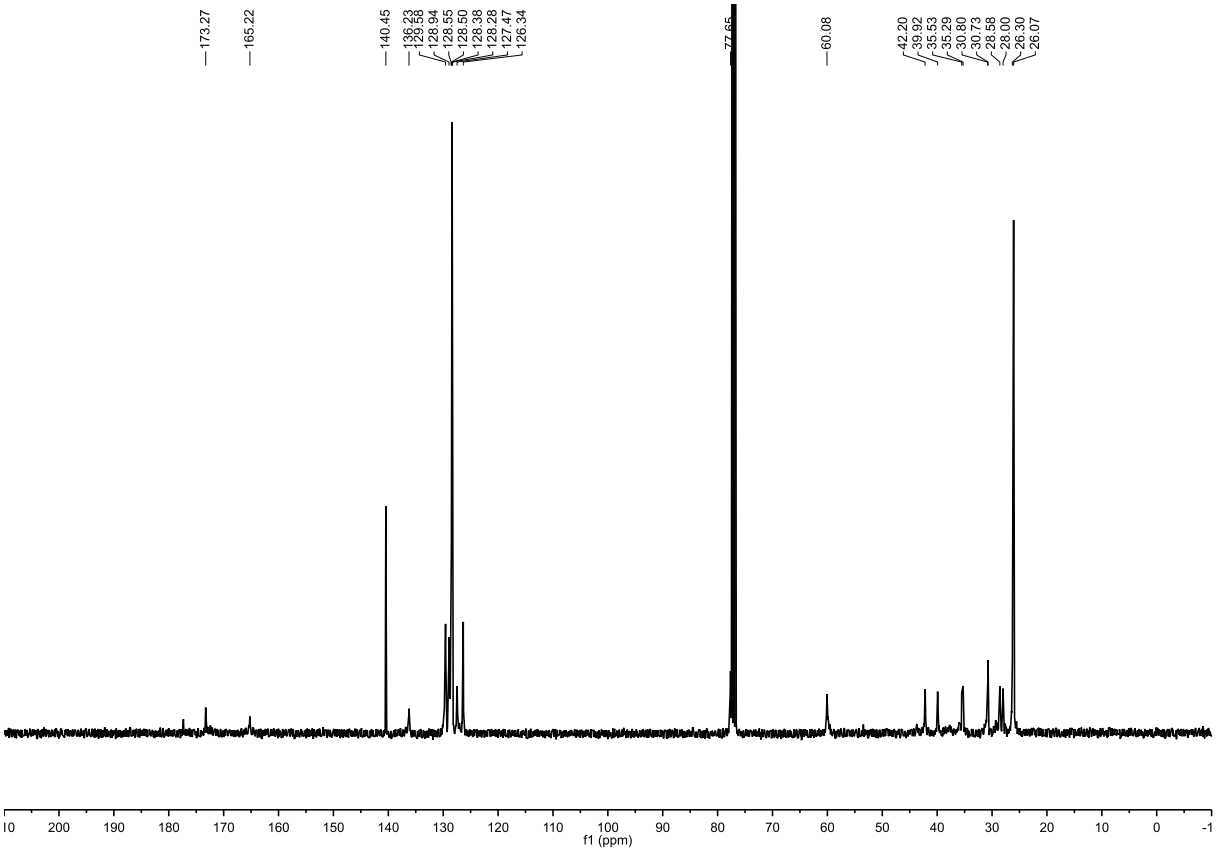
7.26
7.24
7.22
7.22
7.21
7.20
7.04
7.02
5.42
4.89
4.62
4.24
3.25
3.24
3.22
3.20
3.00
2.98
2.96
2.84
2.72
1.80
1.78
1.67
1.37
1.35
1.35
1.34
1.34
1.29
1.18
1.11
Ph
O
N-OH
O
N
Ph
0.92
11.78
0.69
0.24
0.26
0.77
4.77
0.61
0.92
0.92
6.16
6.62
f1 (ppm)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128.50
128.38
128.28
127.47
126.34
77.65
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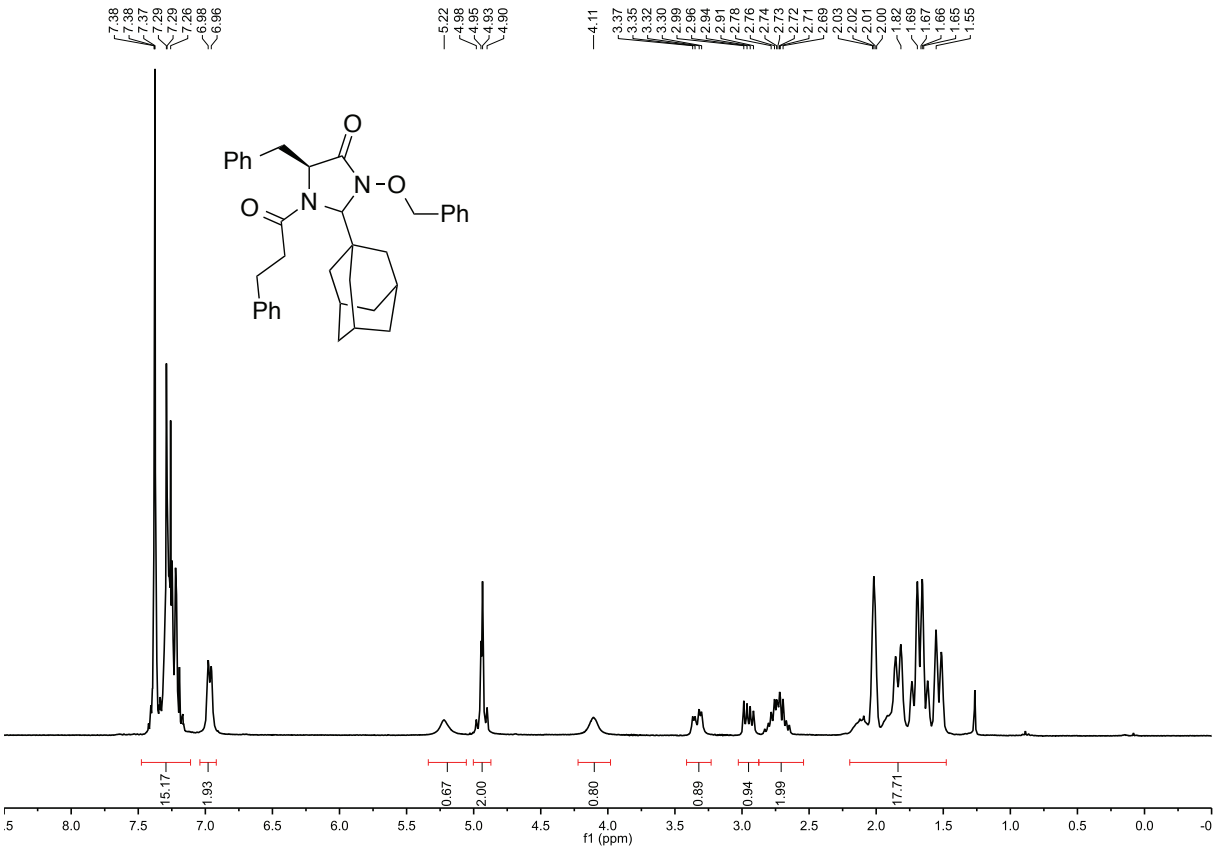
35.53
35.29
30.80
30.73
28.58
28.00
26.30
26.07
f1 (ppm)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7.38
7.37
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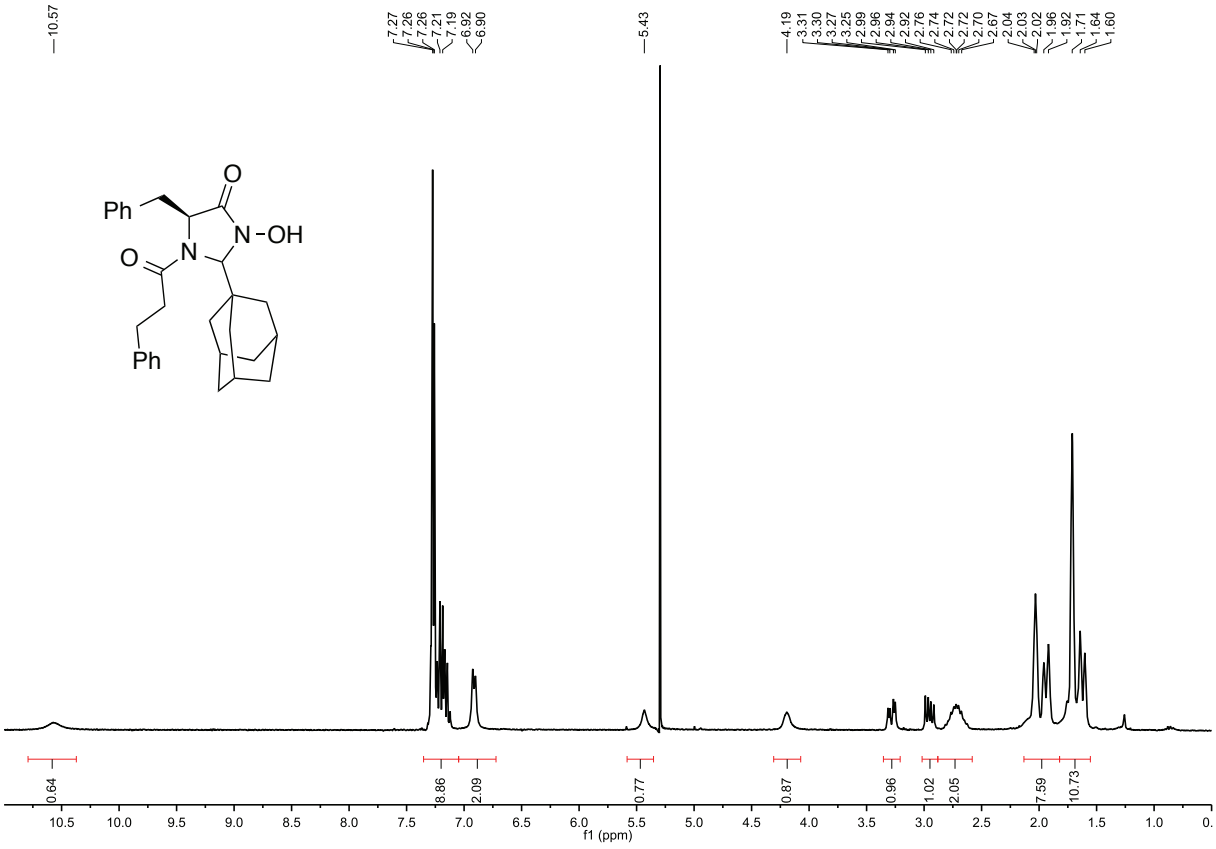
7.29
7.26
6.98
6.96
5.22
4.98
4.95
4.93
4.90
4.11
3.37
3.35
3.32
3.30
2.99
2.96
2.94
2.91
2.78
2.76
2.74
2.73
2.72
2.71
2.69
2.03
2.02
2.01
2.00
1.82
1.69
1.67
1.66
1.65
1.55
Ph
O
N-O
Ph
O
N
Ph
15.17
1.93
0.67
2.00
0.80
0.89
0.94
1.99
17.71
f1 (ppm)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7.27
7.26
7.26
7.21
7.19
6.92
6.90
5.43
4.19
3.31
3.30
3.27
3.25
2.99
2.96
2.94
2.92
2.76
2.74
2.72
2.72
2.70
2.67
2.04
2.03
2.02
1.96
1.92
1.71
1.64
1.60
Ph
O
N-OH
O
N
Ph
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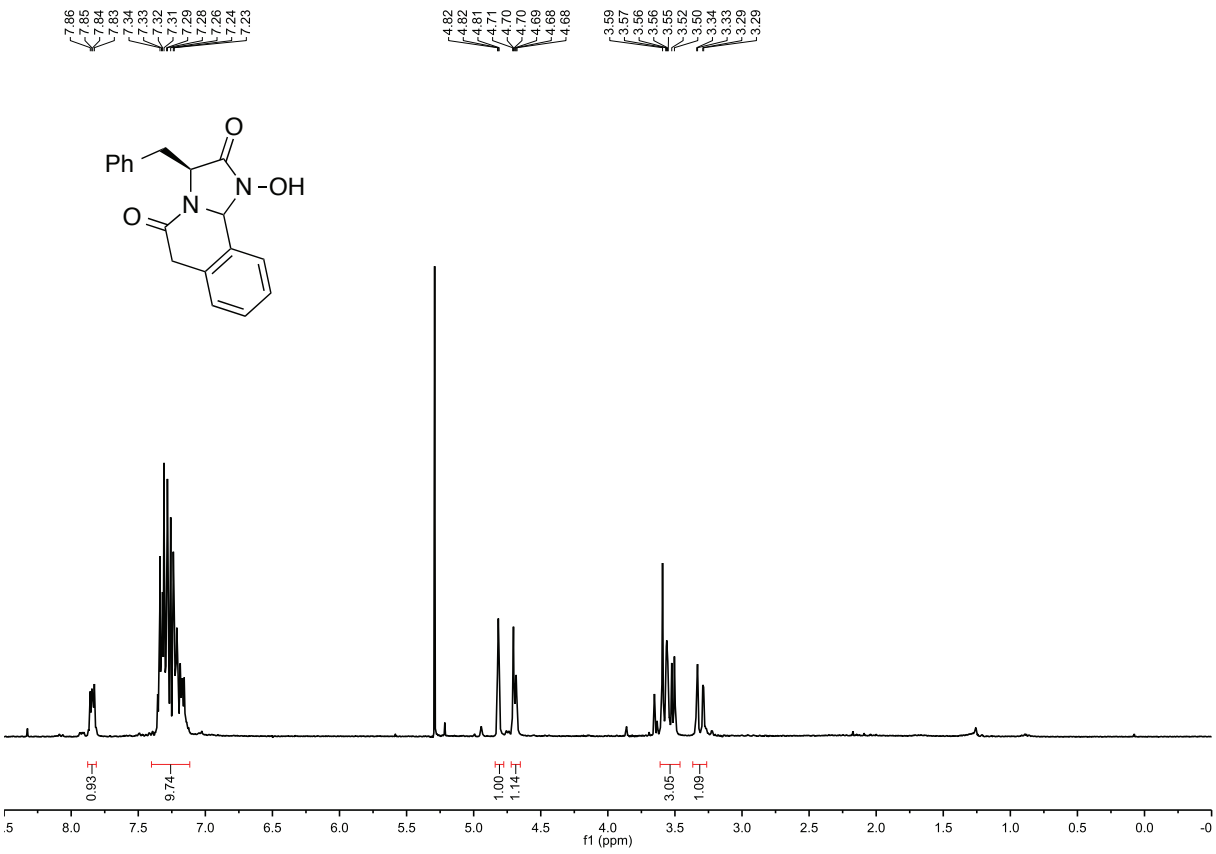
8.86
2.09
0.77
0.87
0.96
1.02
2.05
7.59
10.73
f1 (ppm)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7.85
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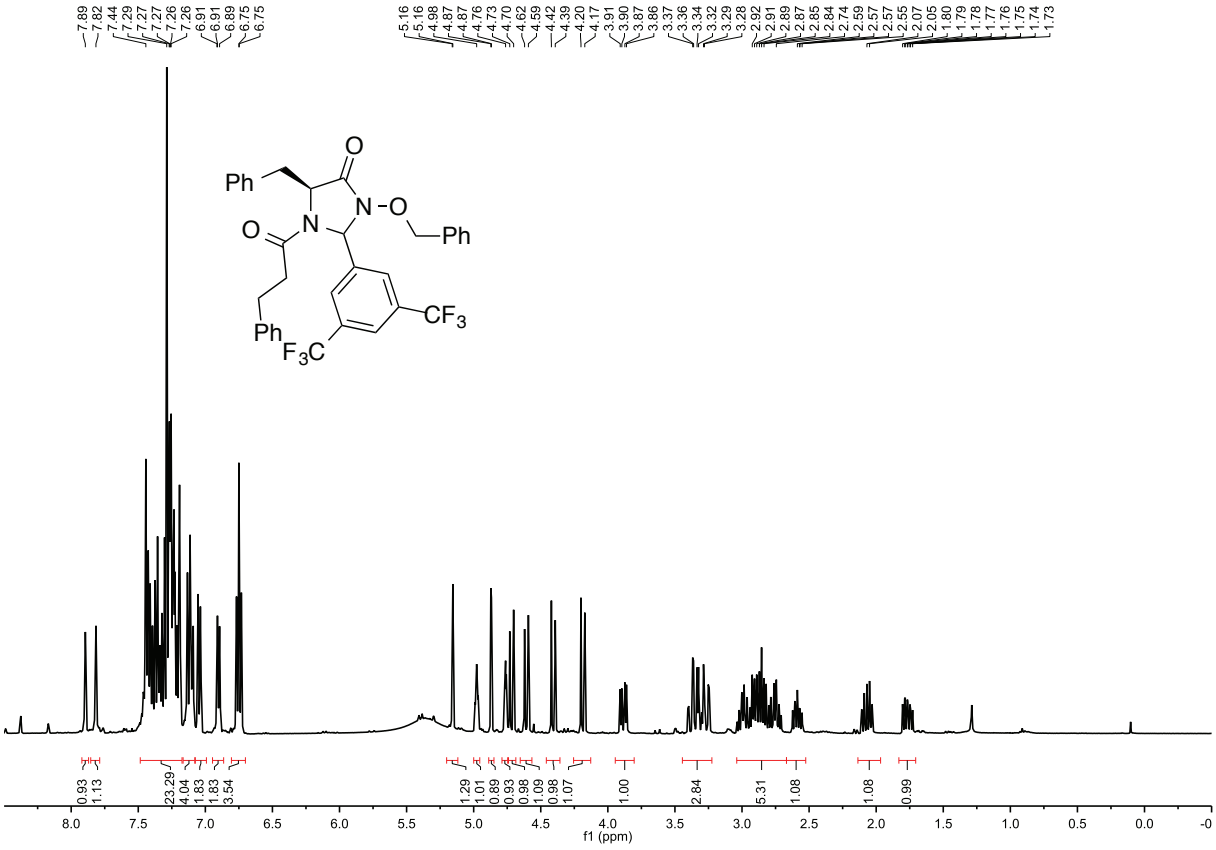
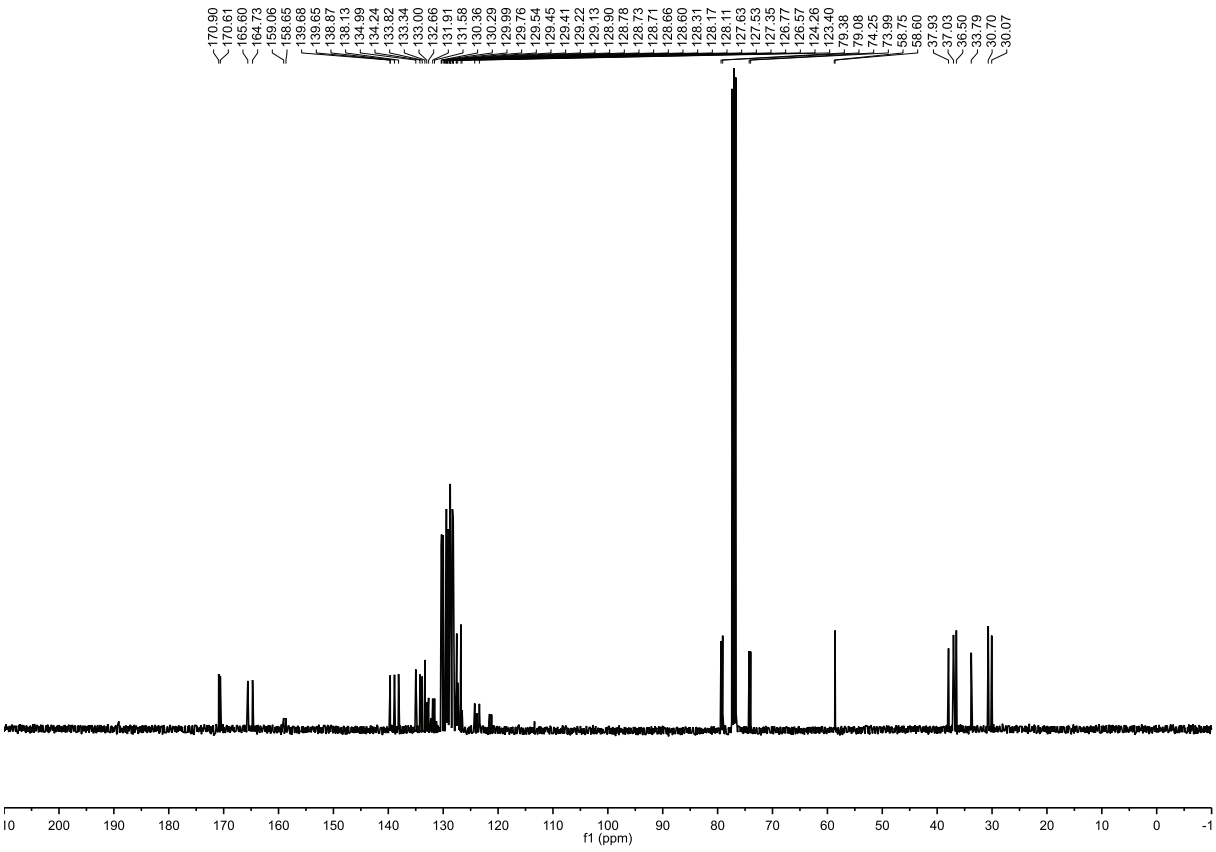
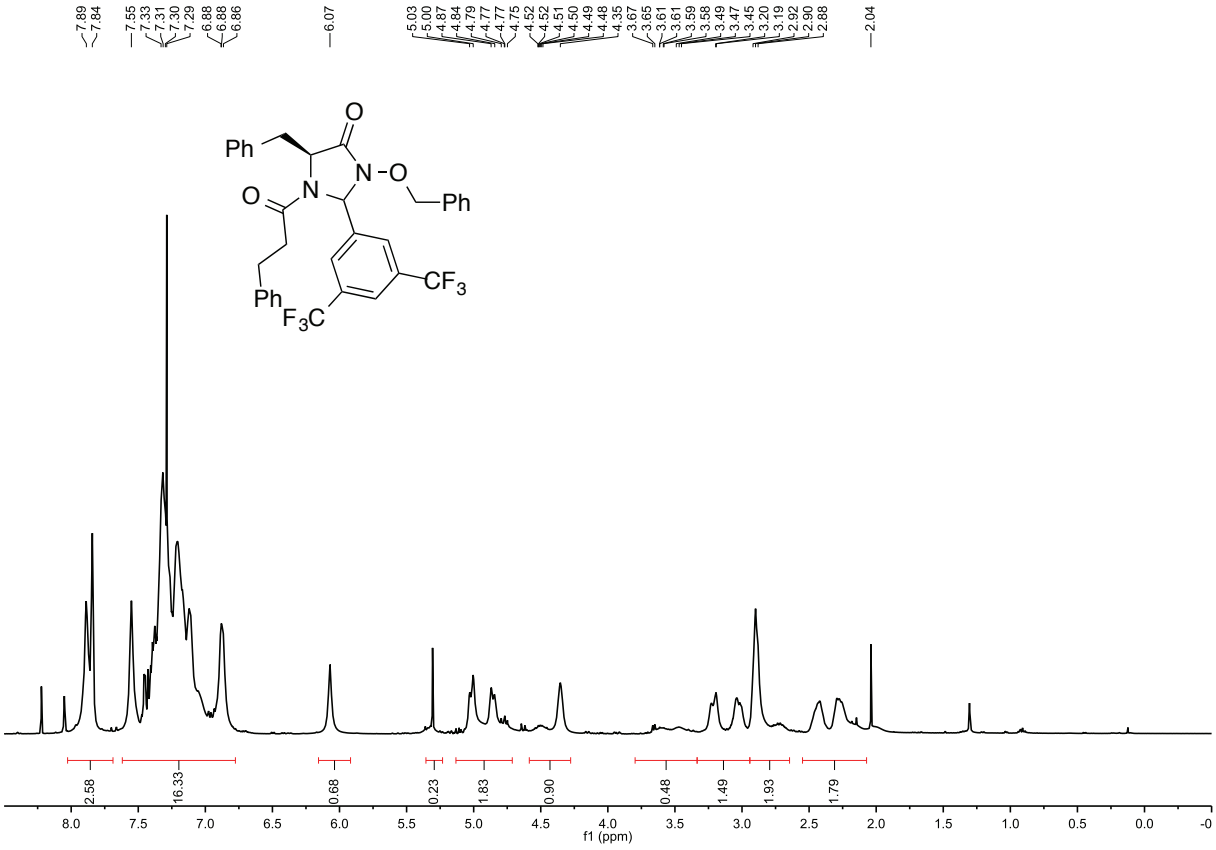
7.83
7.34
7.33
7.32
7.31
7.29
7.28
7.26
7.24
7.23
4.82
4.82
4.81
4.71
4.70
4.69
4.68
4.68
3.59
3.57
3.56
3.56
3.55
3.52
3.50
3.34
3.33
3.29
3.29
Ph
O
N
N-OH
O
0.93
9.74
1.00
1.14
3.05
1.09
f1 (ppm)

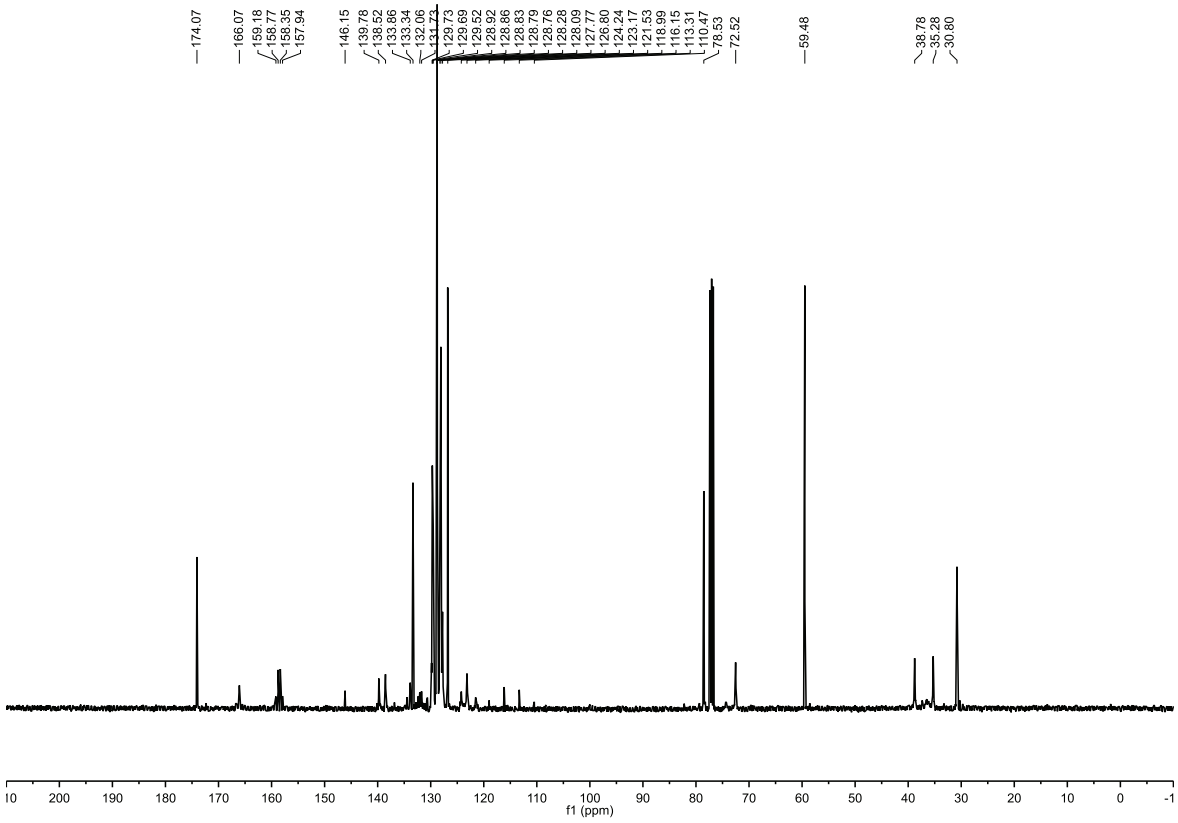
Diastereomer 1:



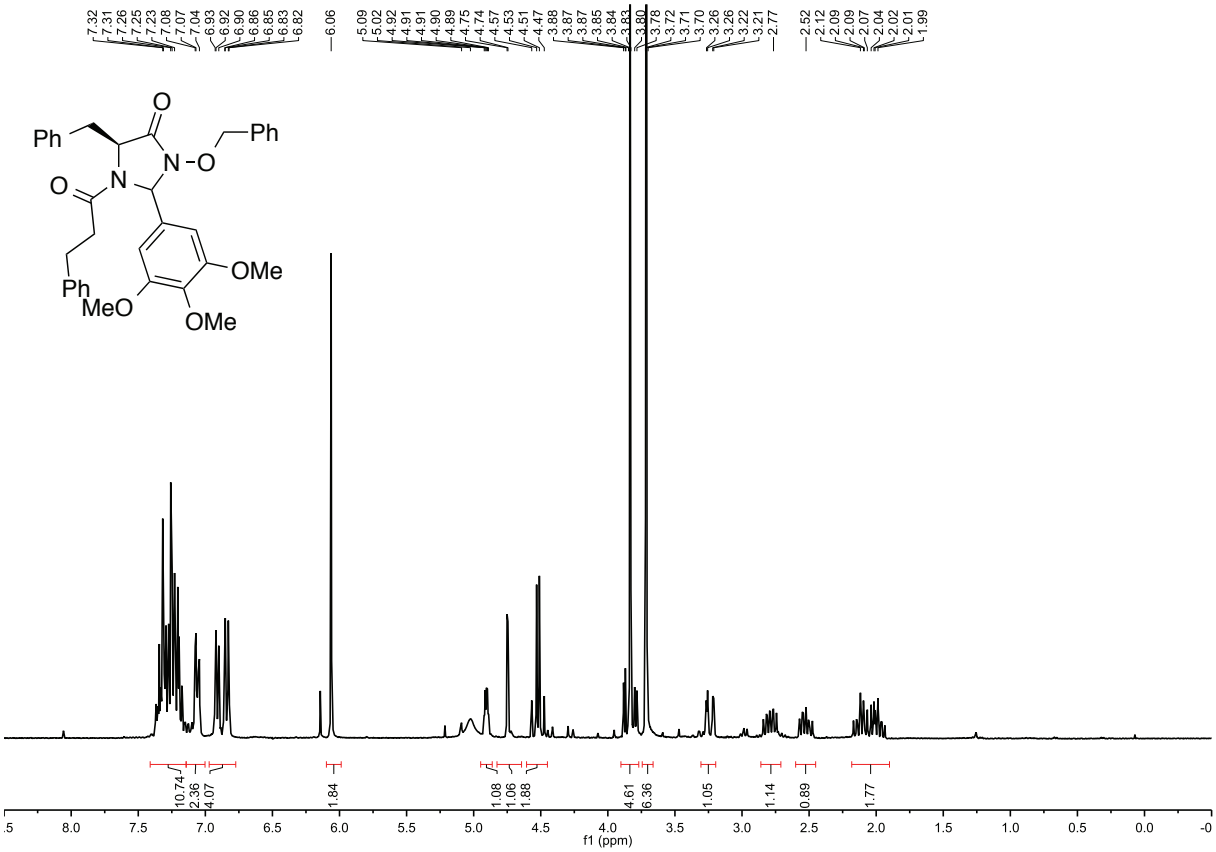


Diastereomer 2:

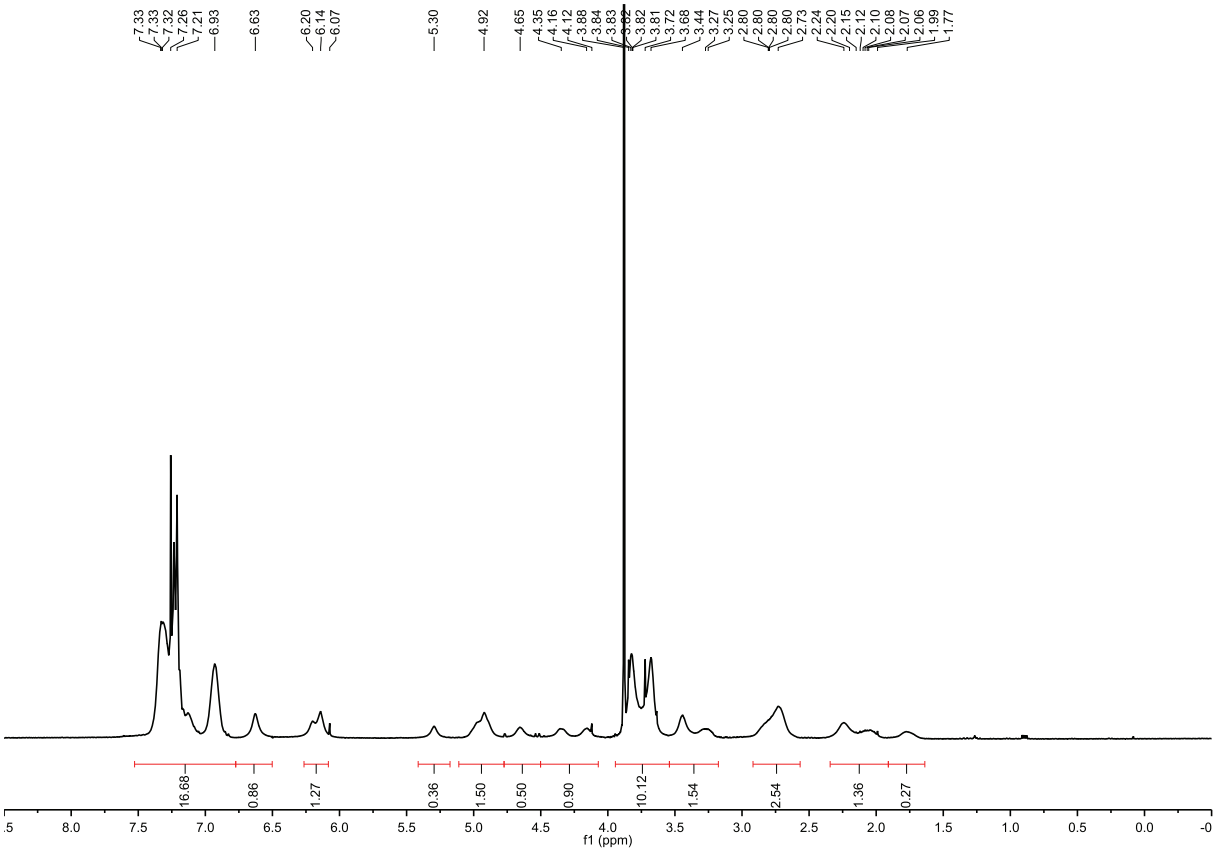




Diastereomer 1:



Diastereomer 2:



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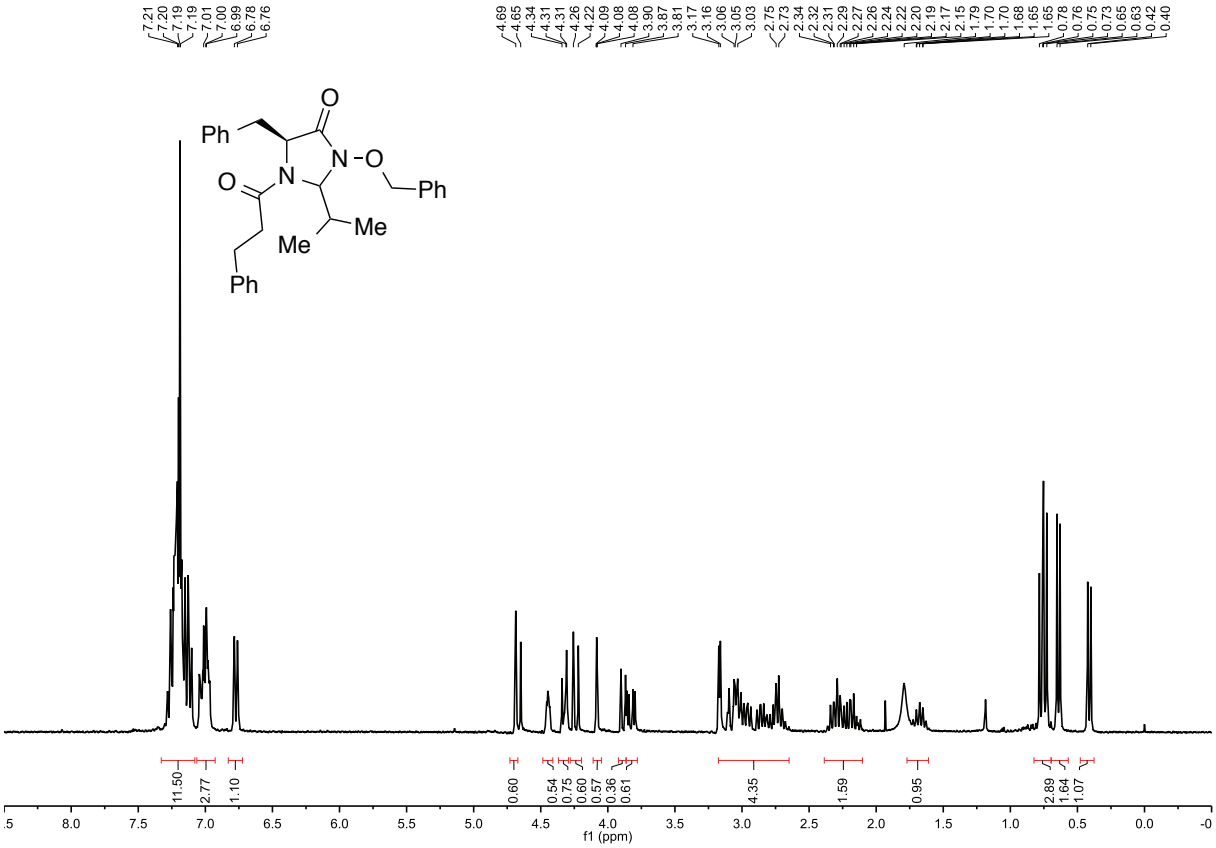

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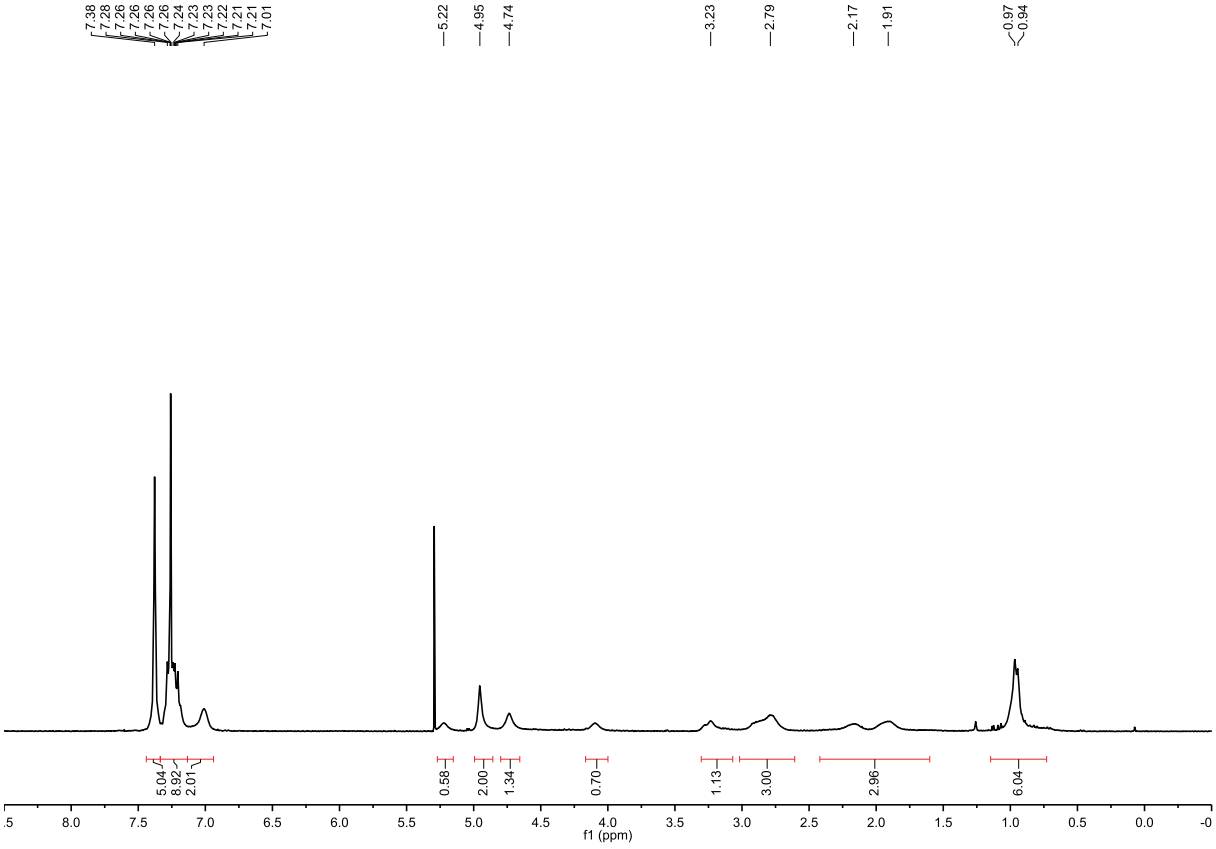
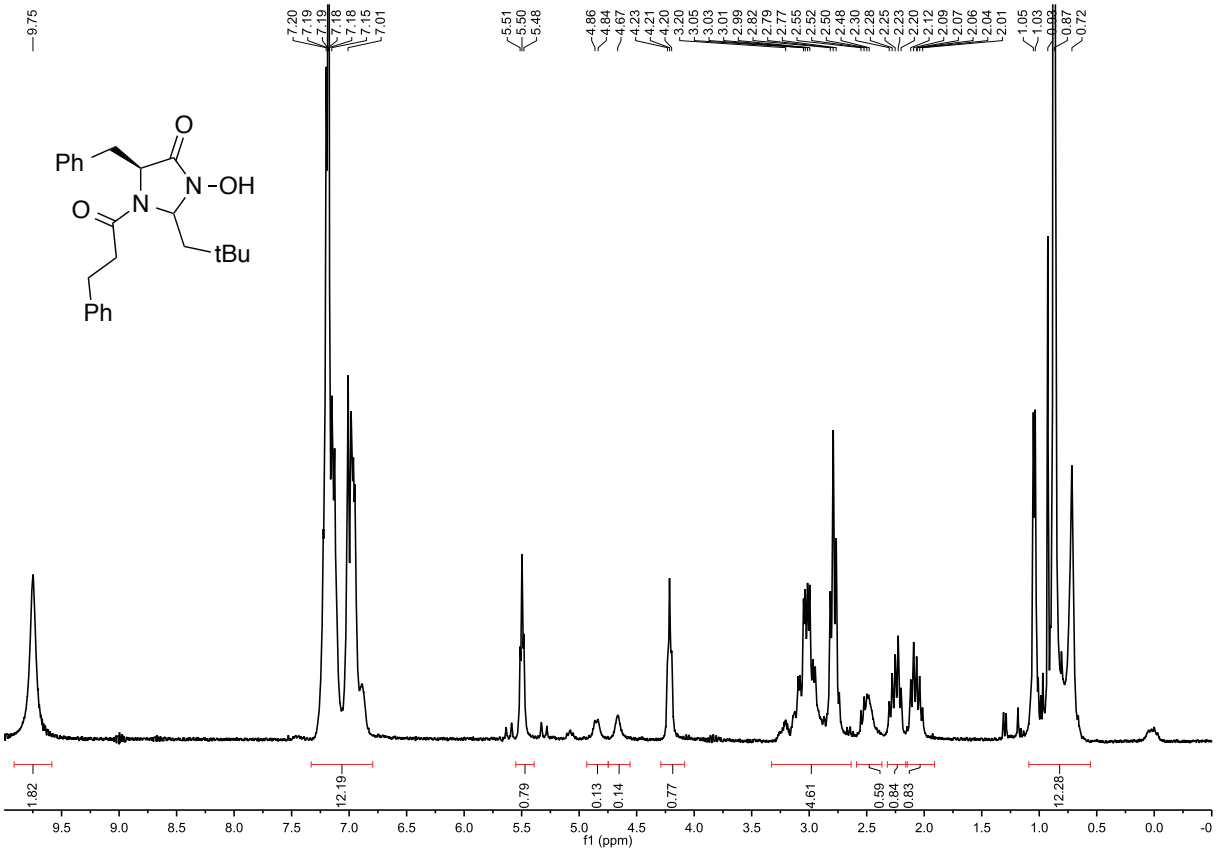
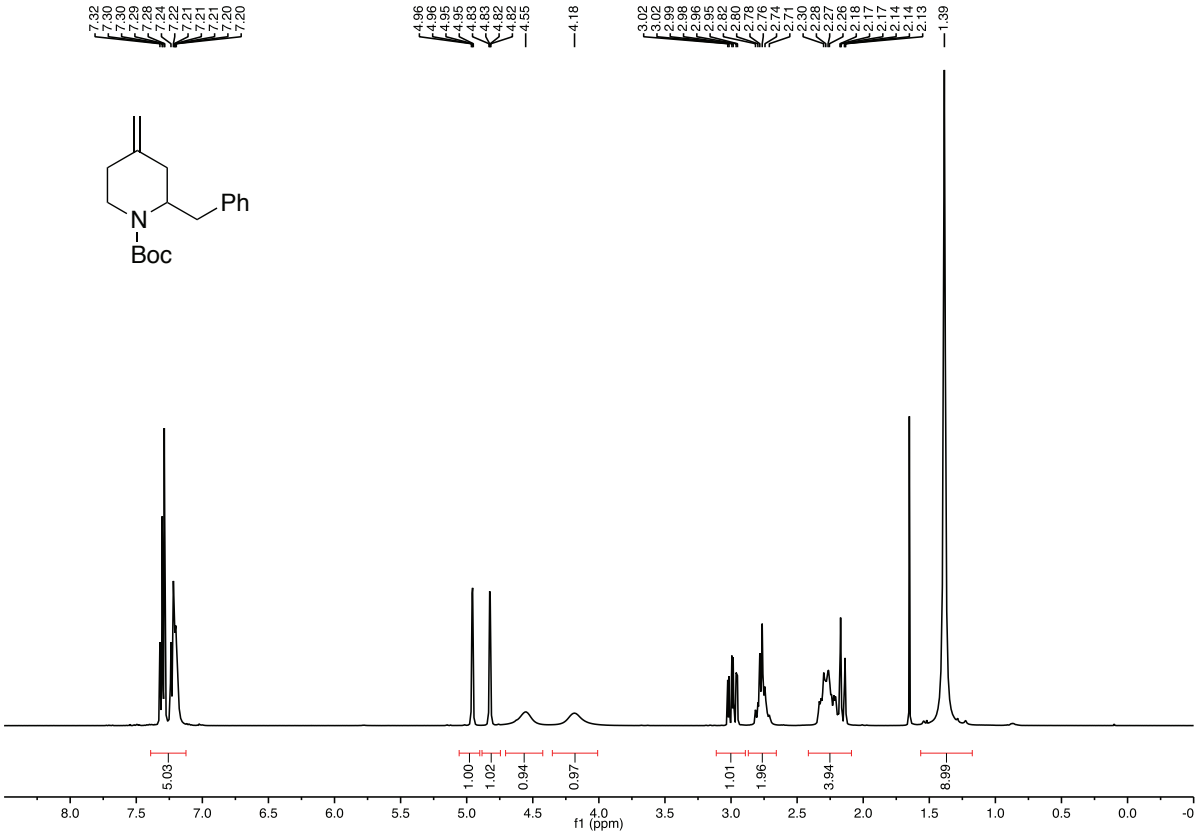
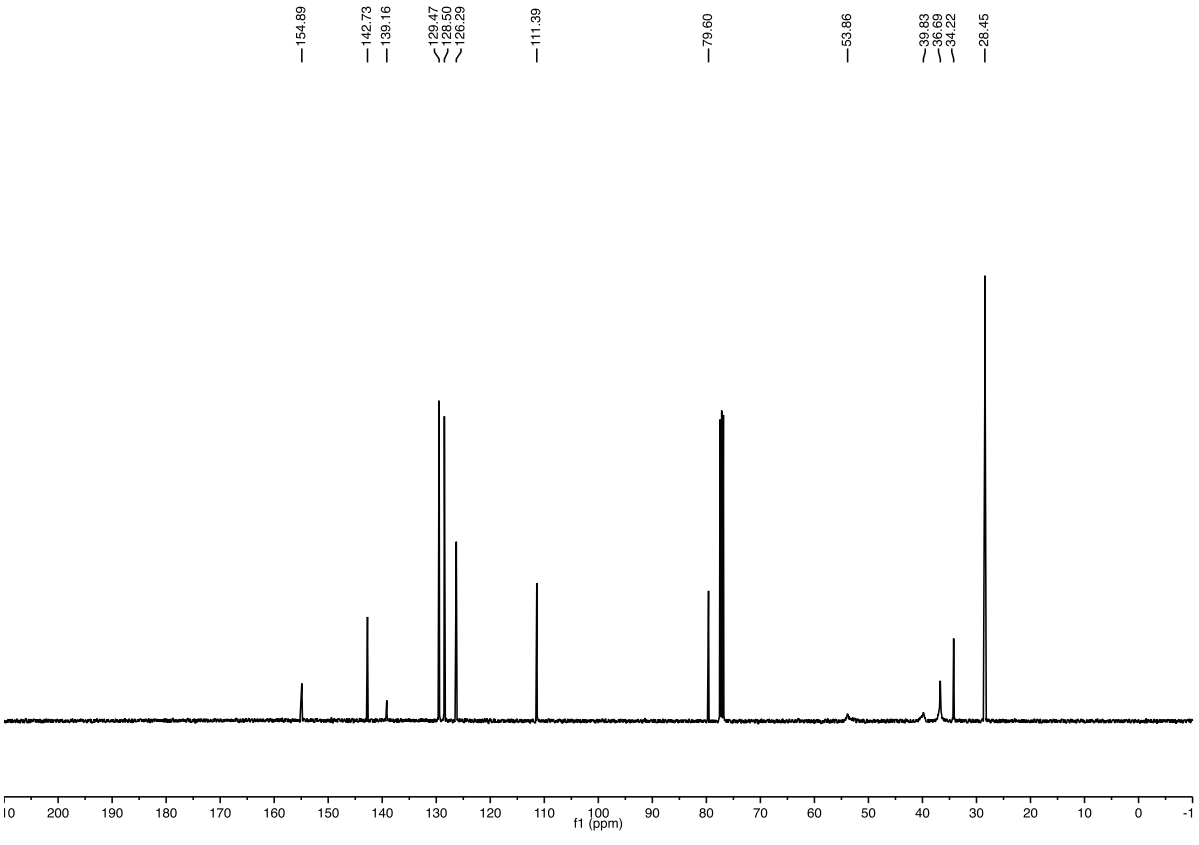
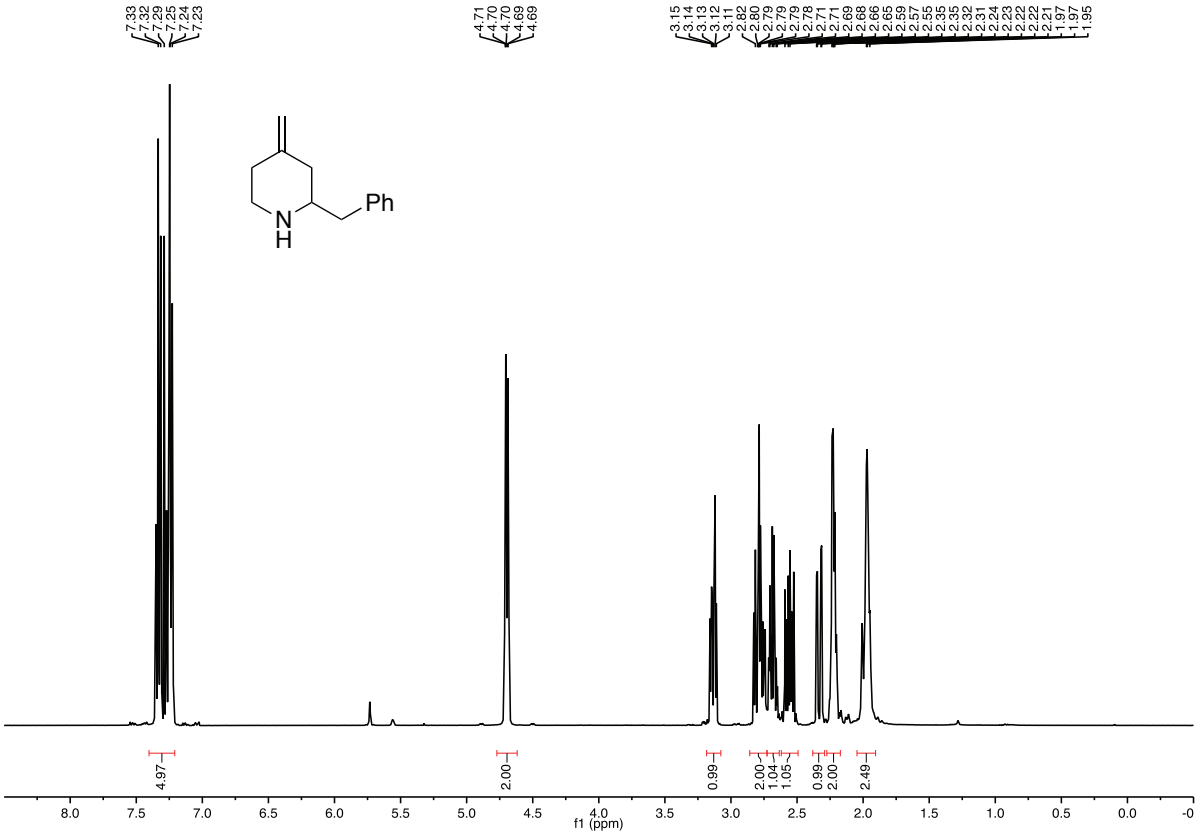


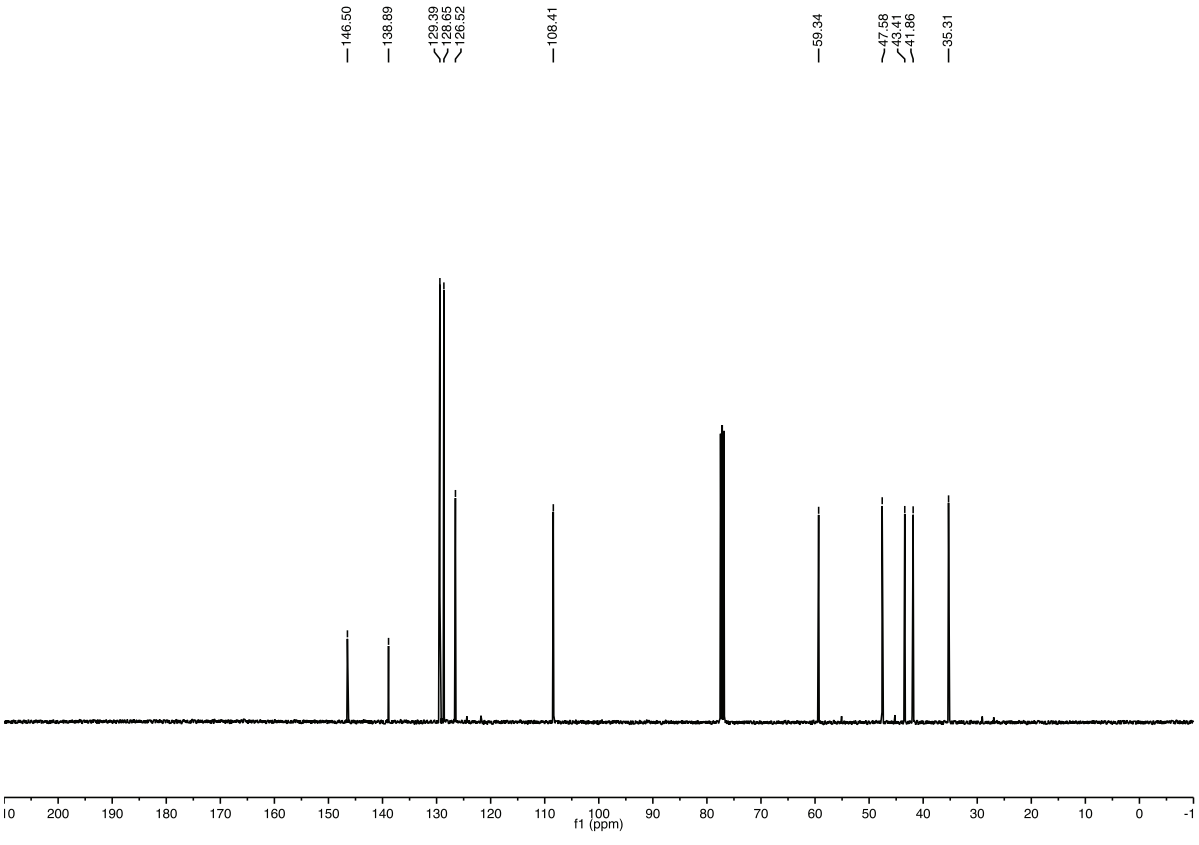

9.75
7.20
7.19
7.19
7.18
7.18
7.15
7.01
5.51
5.50
5.48
4.86
4.84
4.67
4.23
4.21
4.20
3.20
3.05
3.03
3.01
2.99
2.82
2.79
2.77
2.55
2.52
2.50
2.48
2.30
2.28
2.25
2.23
2.20
2.12
2.09
2.07
2.06
2.04
2.01
1.05
1.03
0.87
0.72
Ph
O
N
OH
O
N
tBu
Ph
1.82
12.19
0.79
0.13
0.14
0.77
4.61
0.59
0.84
0.83
12.28
f1 (ppm)

NMR-Spectra – Experimental part II






7.33
7.32
7.29
7.25
7.24
7.23
4.71
4.70
4.70
4.69
4.69
3.15
3.14
3.13
3.12
3.11
2.82
2.80
2.79
2.79
2.78
2.78
2.71
2.71
2.69
2.68
2.66
2.65
2.59
2.57
2.55
2.35
2.35
2.32
2.31
2.24
2.23
2.22
2.22
2.21
1.97
1.95
Ph
N
H
4.97
2.00
0.99
2.00
1.04
1.05
0.99
2.00
2.49
f1 (ppm)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138.89
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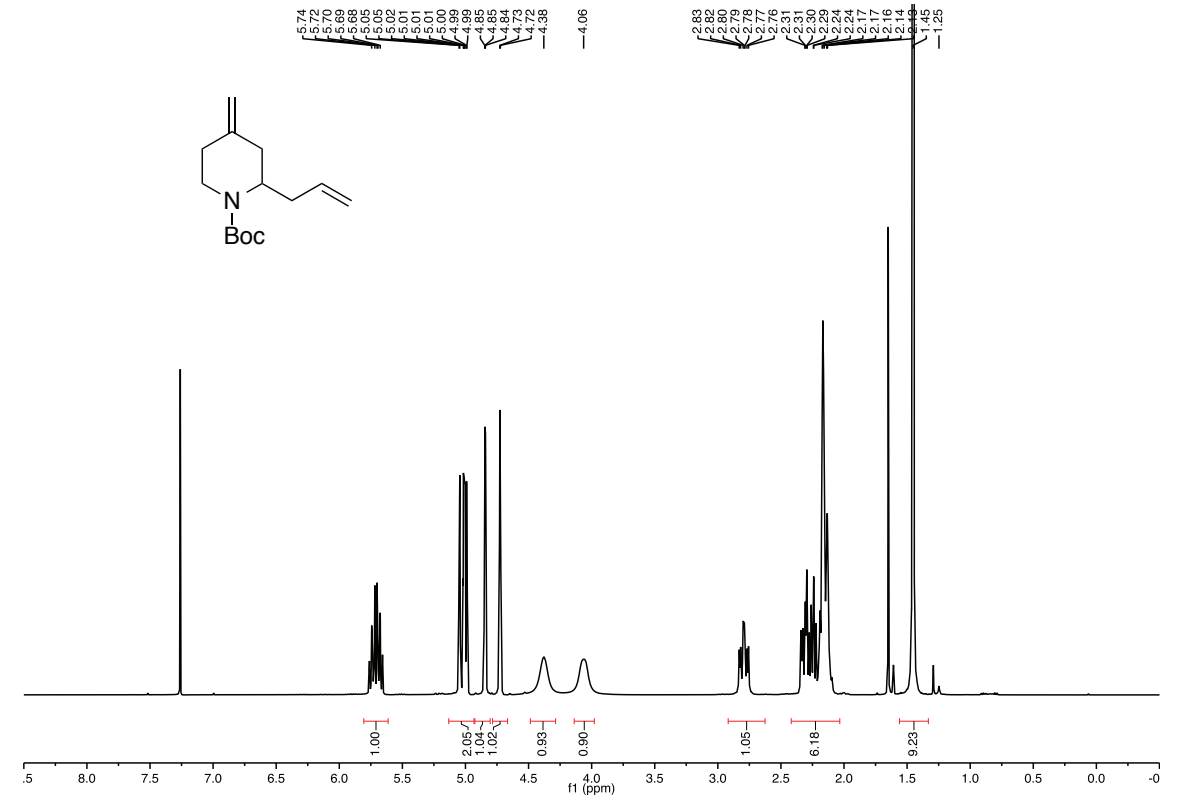
128.65
126.52
108.41
59.34
47.58
43.41
41.86
35.31
f1 (ppm)


5.74
5.72
5.70
5.69
5.68
5.05
5.05
5.02
5.01
5.01
5.01
5.00
4.99
4.99
4.85
4.85
4.84
4.73
4.72
4.38
4.06
2.83
2.82
2.80
2.79
2.78
2.77
2.76
2.31
2.31
2.30
2.29
2.24
2.17
2.17
2.16
2.14
1.45
1.25
N
Boc
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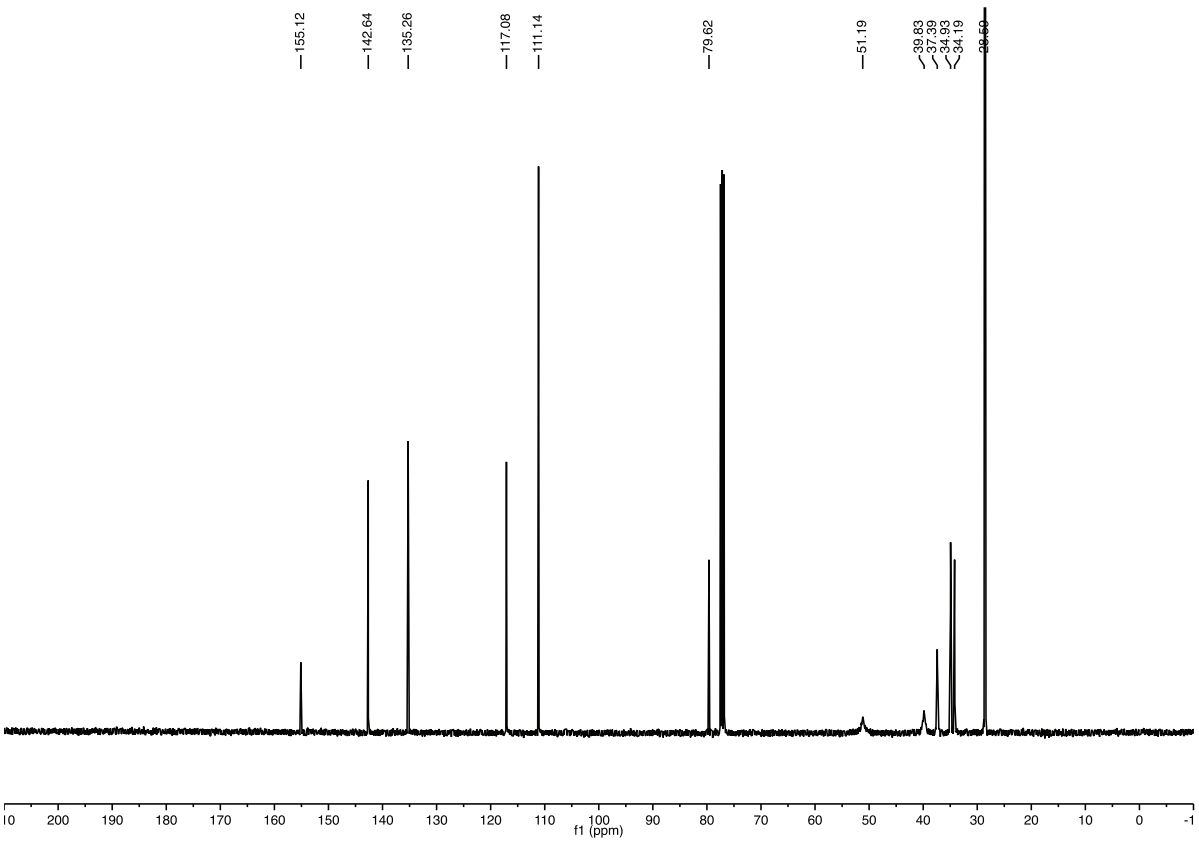
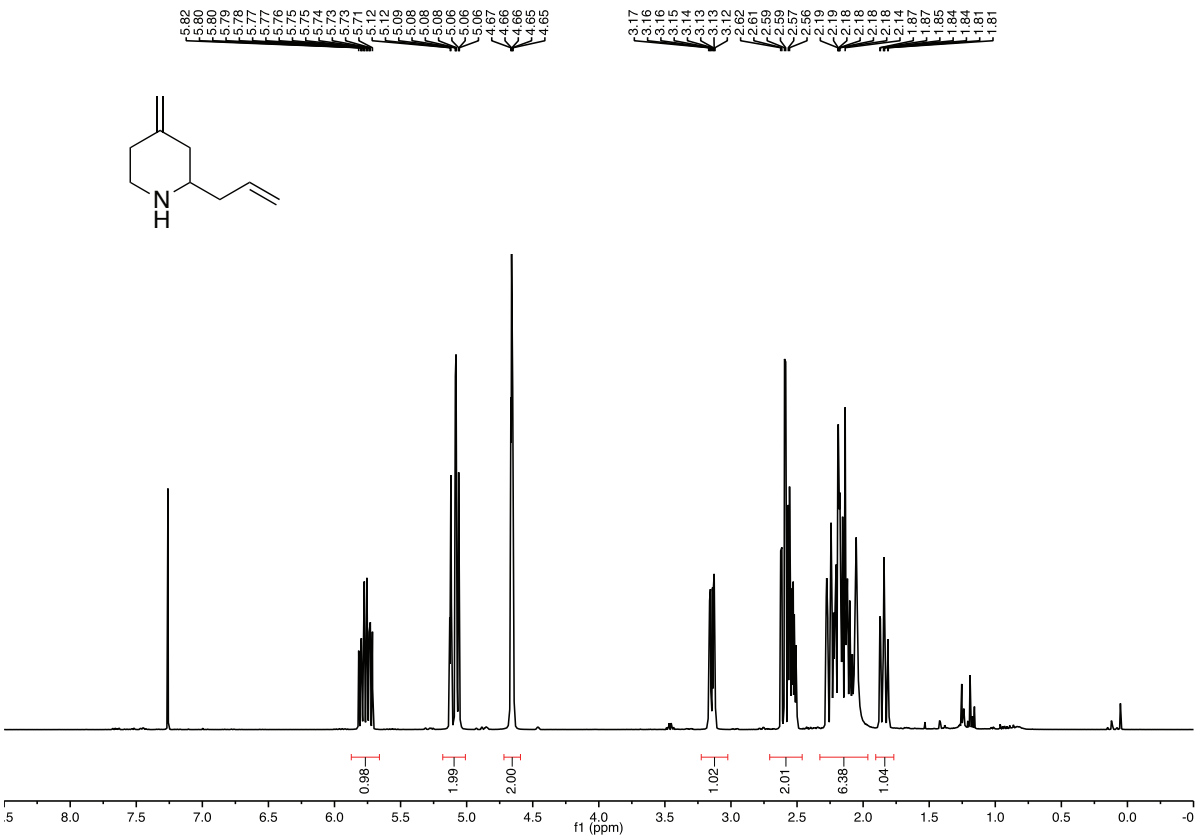
2.05
1.04
1.02
0.93
0.90
1.05
6.18
9.23
f1 (ppm)


155.12
142.64
135.26
117.08
111.14
79.62
51.19
39.83
37.39
34.93
34.19
28.60
f1 (ppm)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5.80
5.80
5.79
5.78
5.77
5.77
5.76
5.75
5.75
5.74
5.73
5.73
5.71
5.12
5.12
5.09
5.08
5.08
5.08
5.06
5.06
5.06
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4.66
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4.65
3.17
3.16
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3.14
3.13
3.13
3.12
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2.57
2.56
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2.19
2.18
2.18
2.18
2.18
2.14
1.87
1.87
1.85
1.84
1.84
1.81
1.81
N
H
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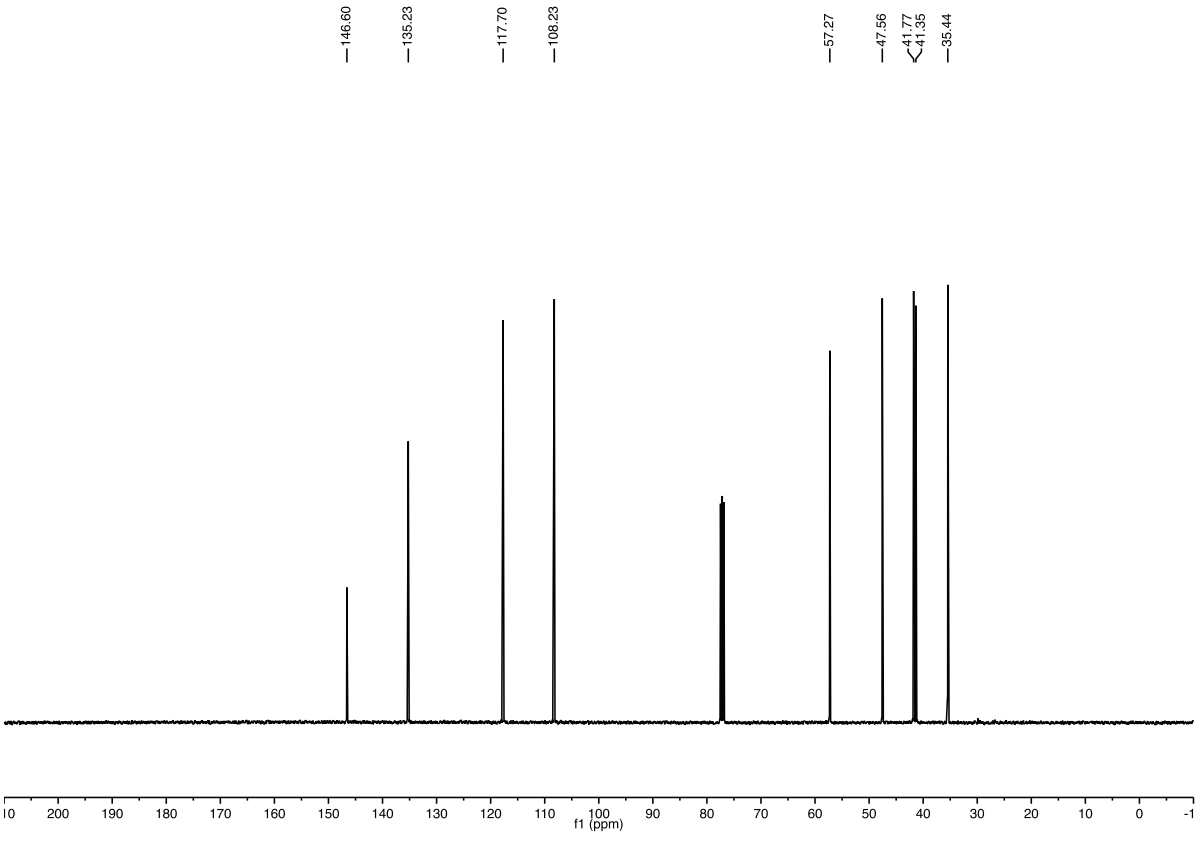
1.99
2.00
1.02
2.01
6.38
1.04
f1 (ppm)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135.23
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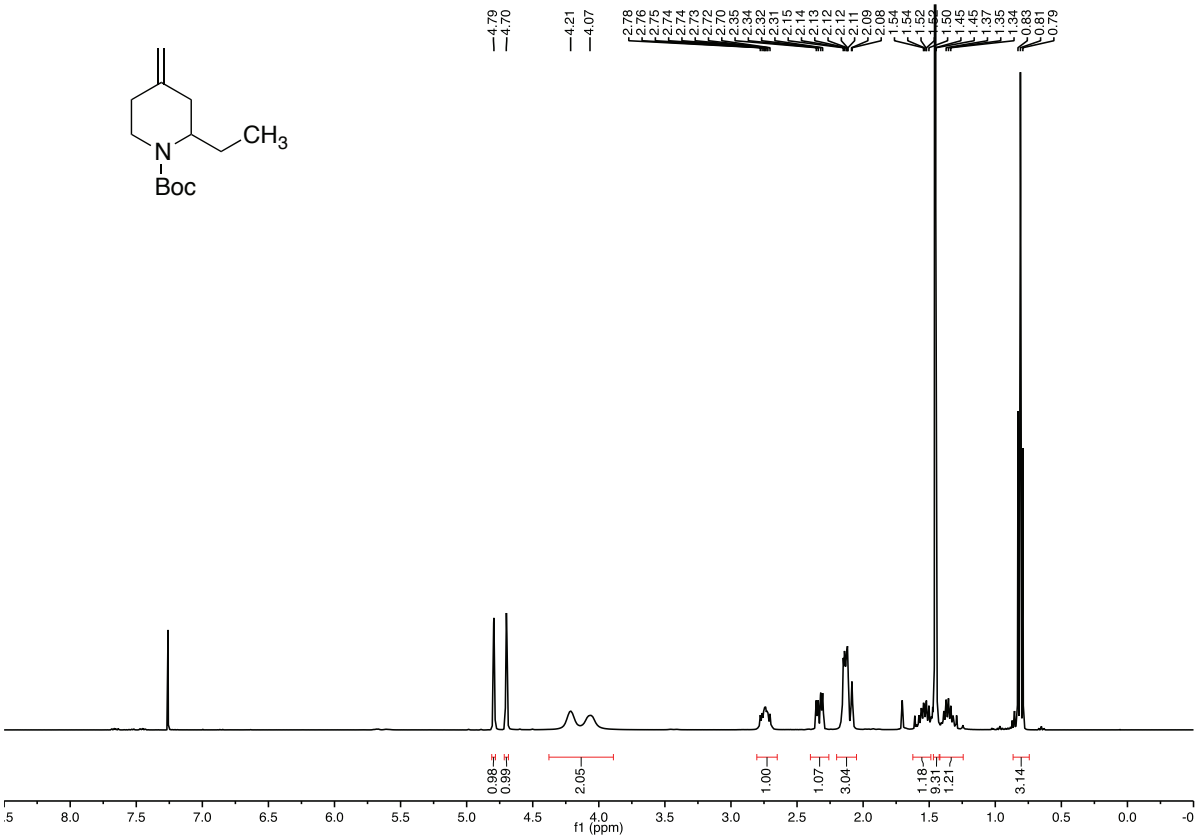
108.23
57.27
47.56
41.77
41.35
35.44
f1 (ppm)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N
Boc
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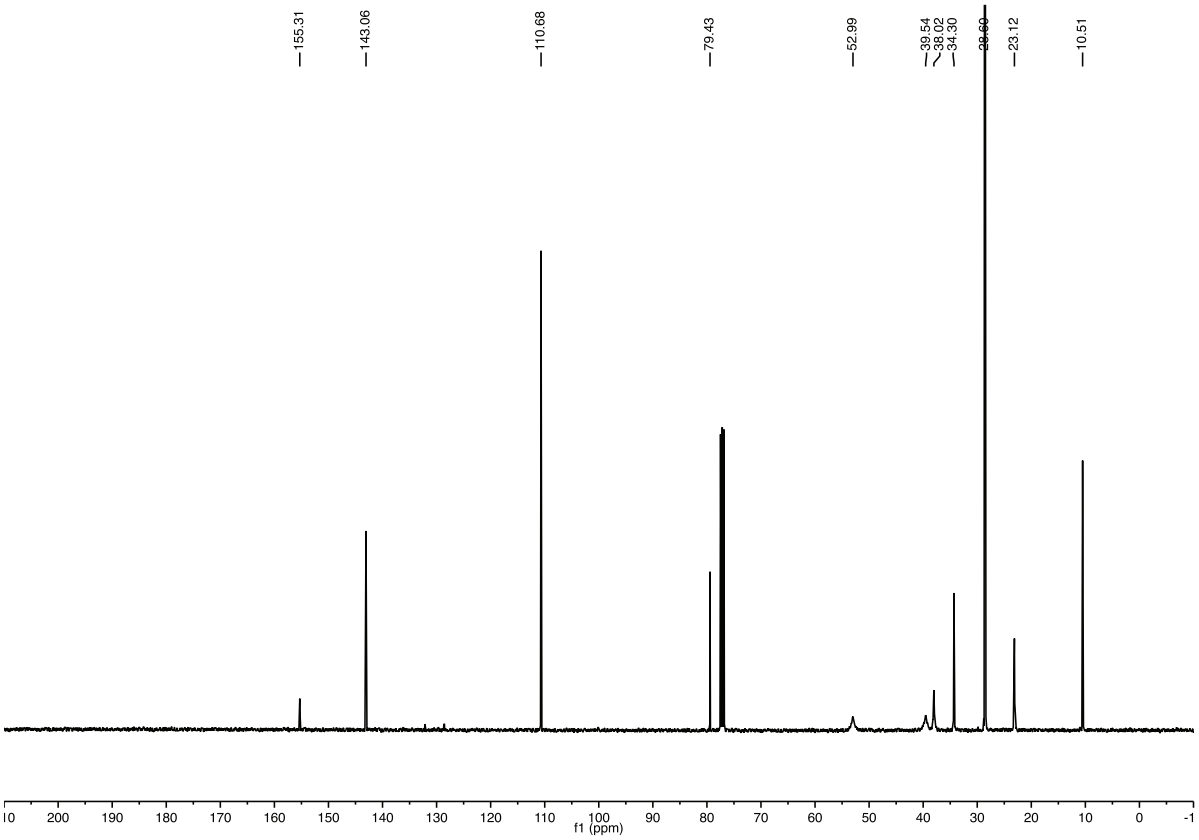
2.75
2.74
2.73
2.72
2.70
2.35
2.34
2.32
2.31
2.15
2.14
2.13
2.12
2.12
2.11
2.09
2.08
1.54
1.54
1.52
1.50
1.45
1.45
1.37
1.35
1.34
0.83
0.81
0.79
0.98
0.99
2.05
1.00
1.07
3.04
1.18
9.31
1.21
3.14
f1 (ppm)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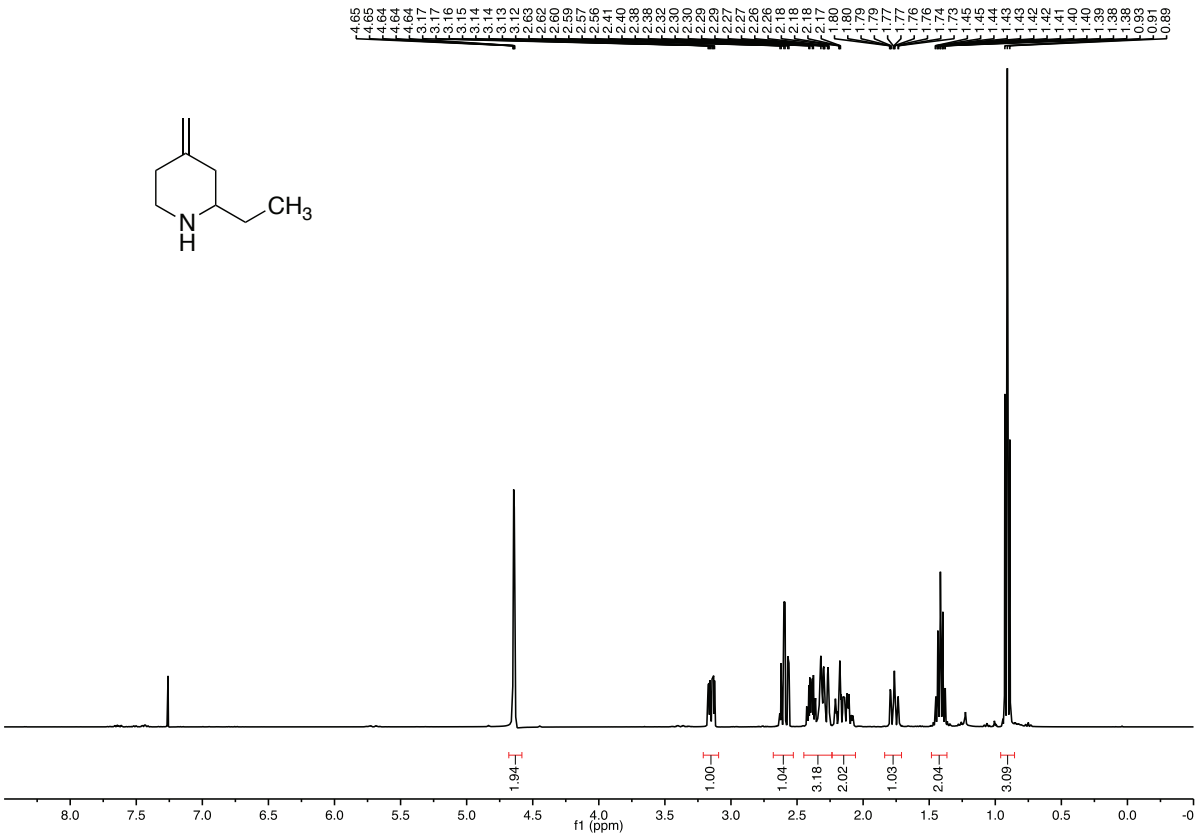
38.02
34.30
28.60
23.12
10.51
f1 (ppm)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4.64
4.64
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3.17
3.16
3.15
3.14
3.14
3.13
3.12
2.63
2.62
2.60
2.59
2.57
2.56
2.41
2.40
2.38
2.38
2.32
2.30
2.30
2.29
2.29
2.27
2.27
2.26
2.26
2.18
2.18
2.17
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1.80
1.79
1.79
1.77
1.77
1.76
1.76
1.74
1.73
1.45
1.45
1.44
1.43
1.43
1.42
1.42
1.41
1.40
1.40
1.39
1.38
1.38
0.93
0.91
0.89
N
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CH3
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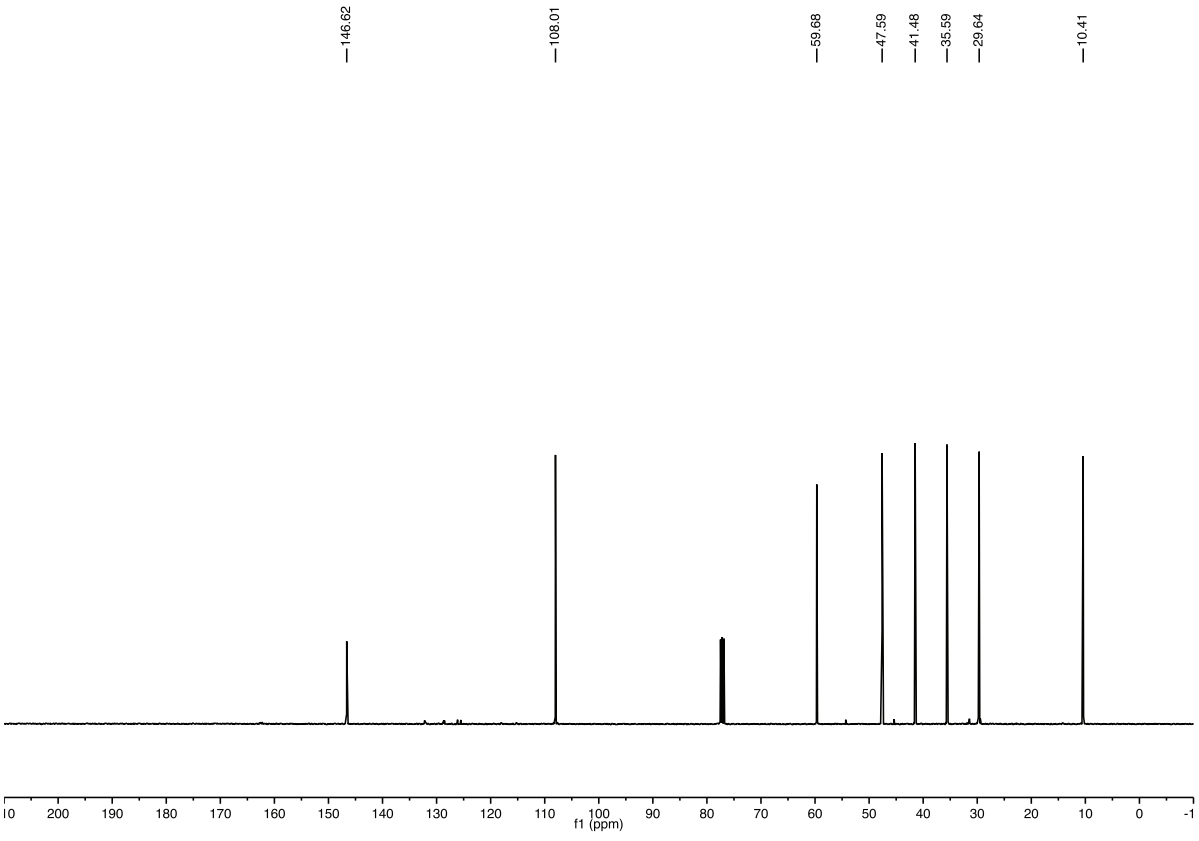
1.04
3.18
2.02
1.03
2.04
3.09
f1 (ppm)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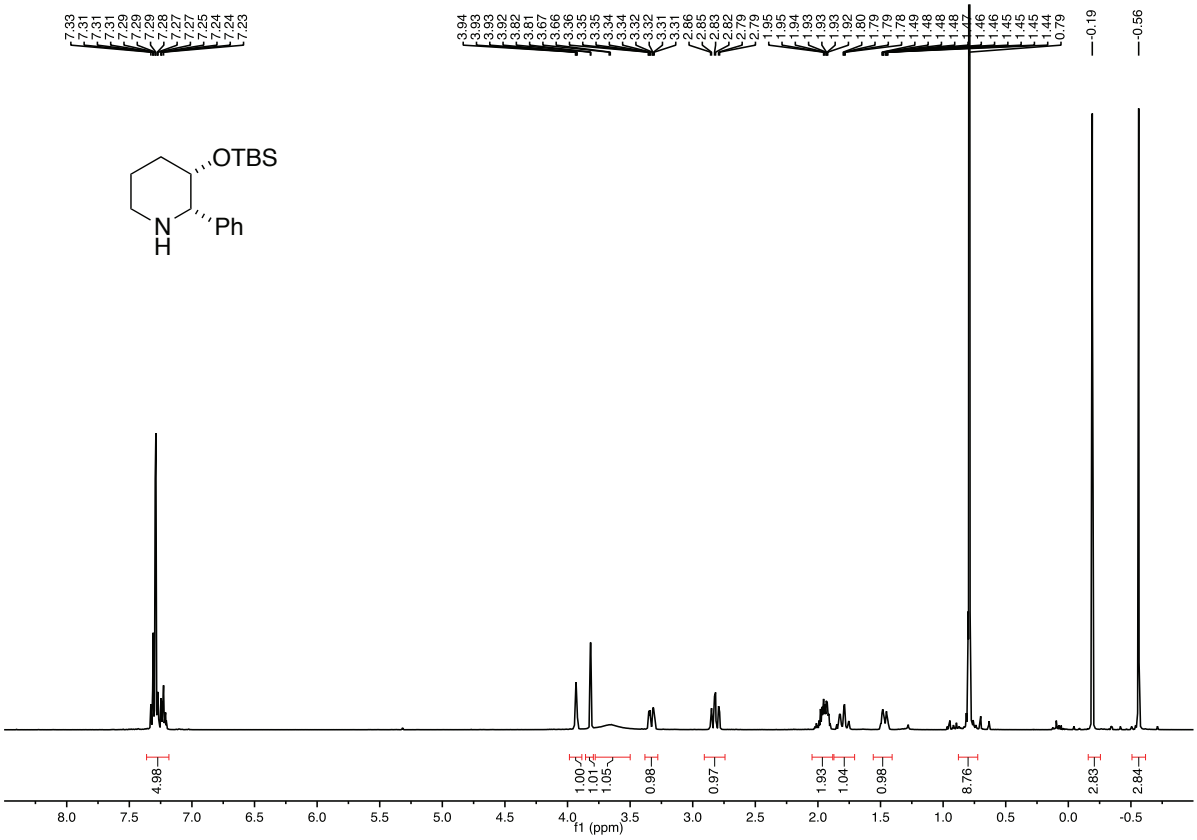
10.41
f1 (ppm)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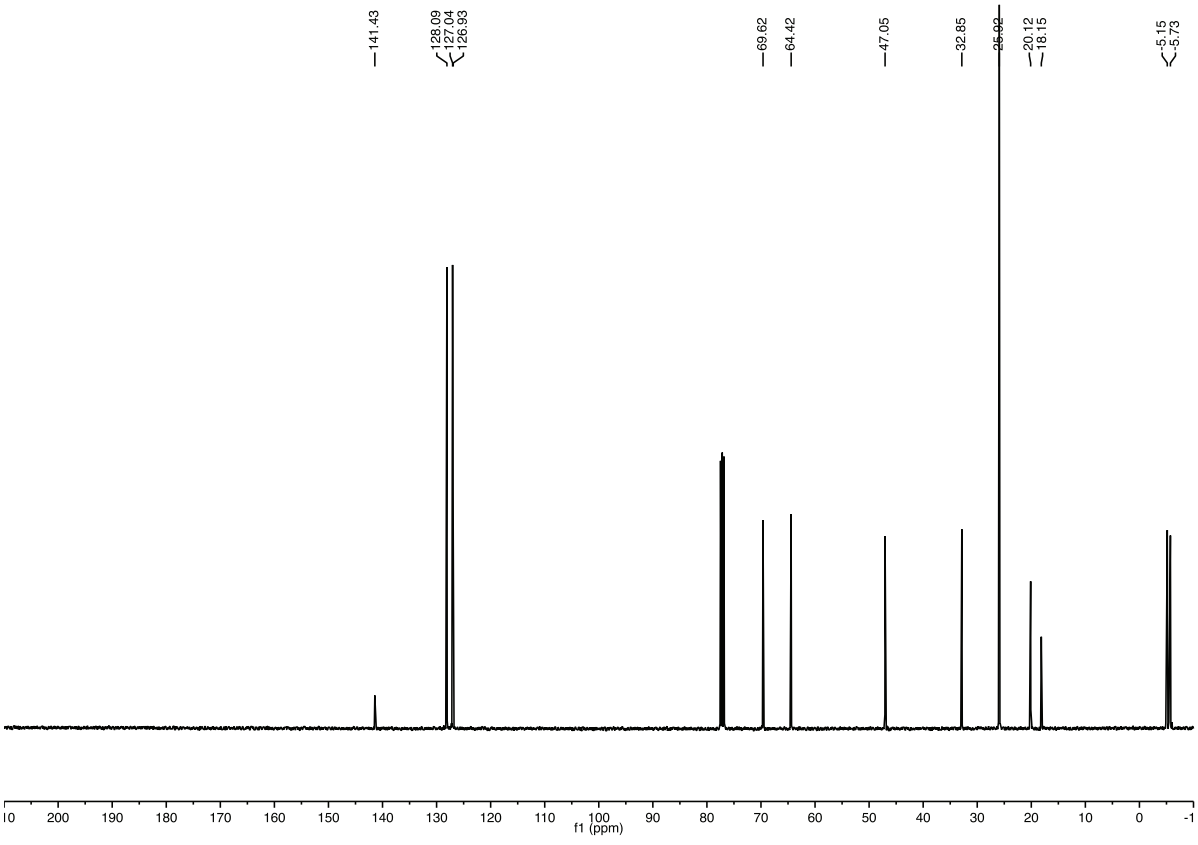
Ph
N
H
f1 (ppm)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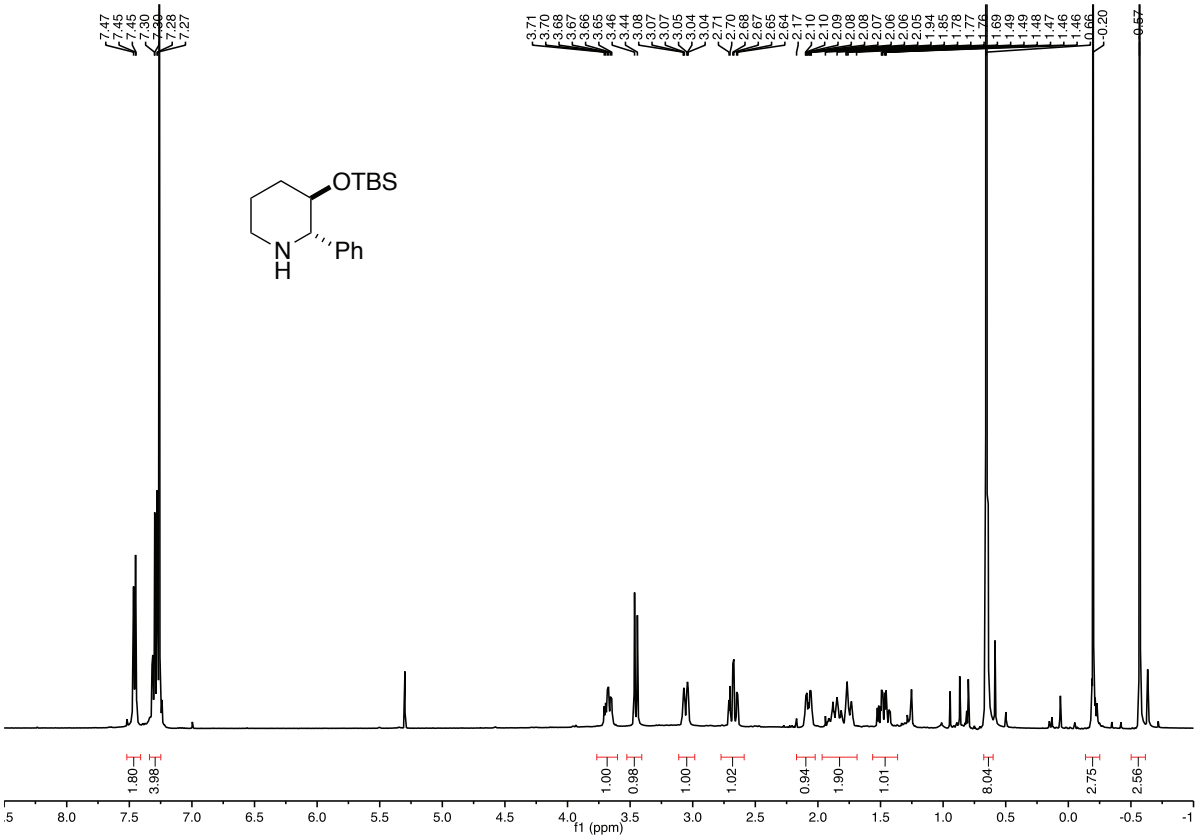
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3.66
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3.46
3.44
3.08
3.07
3.07
3.05
3.04
3.04
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2.64
2.17
2.10
2.10
2.09
2.08
2.08
2.07
2.06
2.06
2.05
1.94
1.85
1.78
1.77
1.76
1.69
1.49
1.49
1.48
1.47
1.46
1.46
0.20
0.67
OTBS
N
H
Ph
1.80
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1.01
8.04
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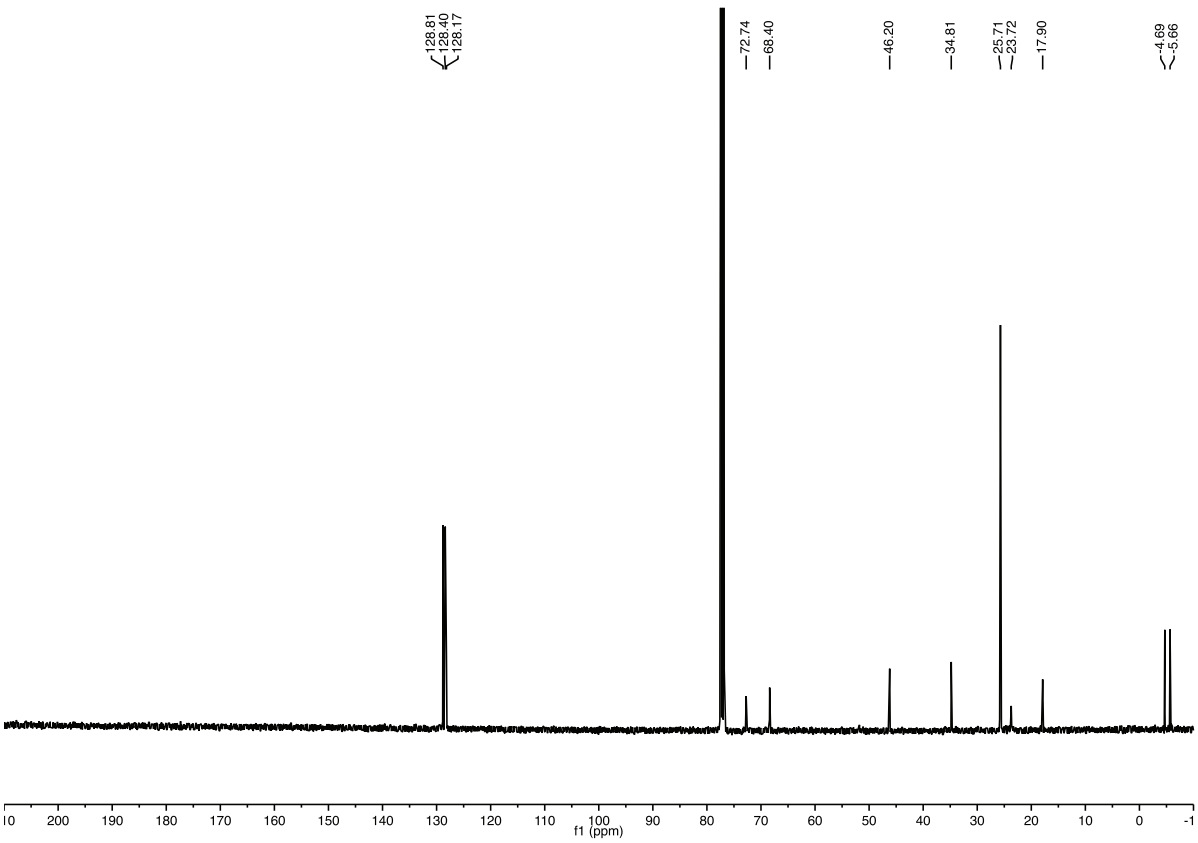
2.56
f1 (ppm)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25.71
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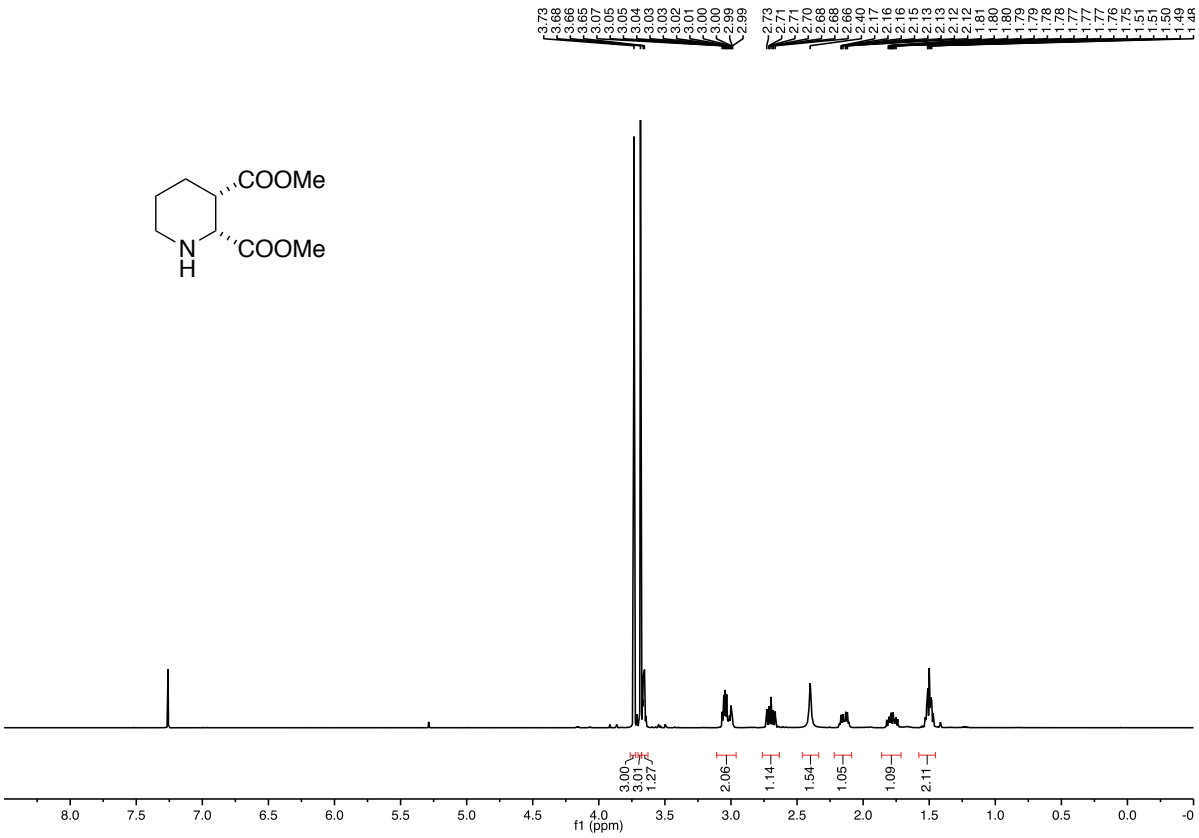
17.90
-4.69
-5.66
f1 (ppm)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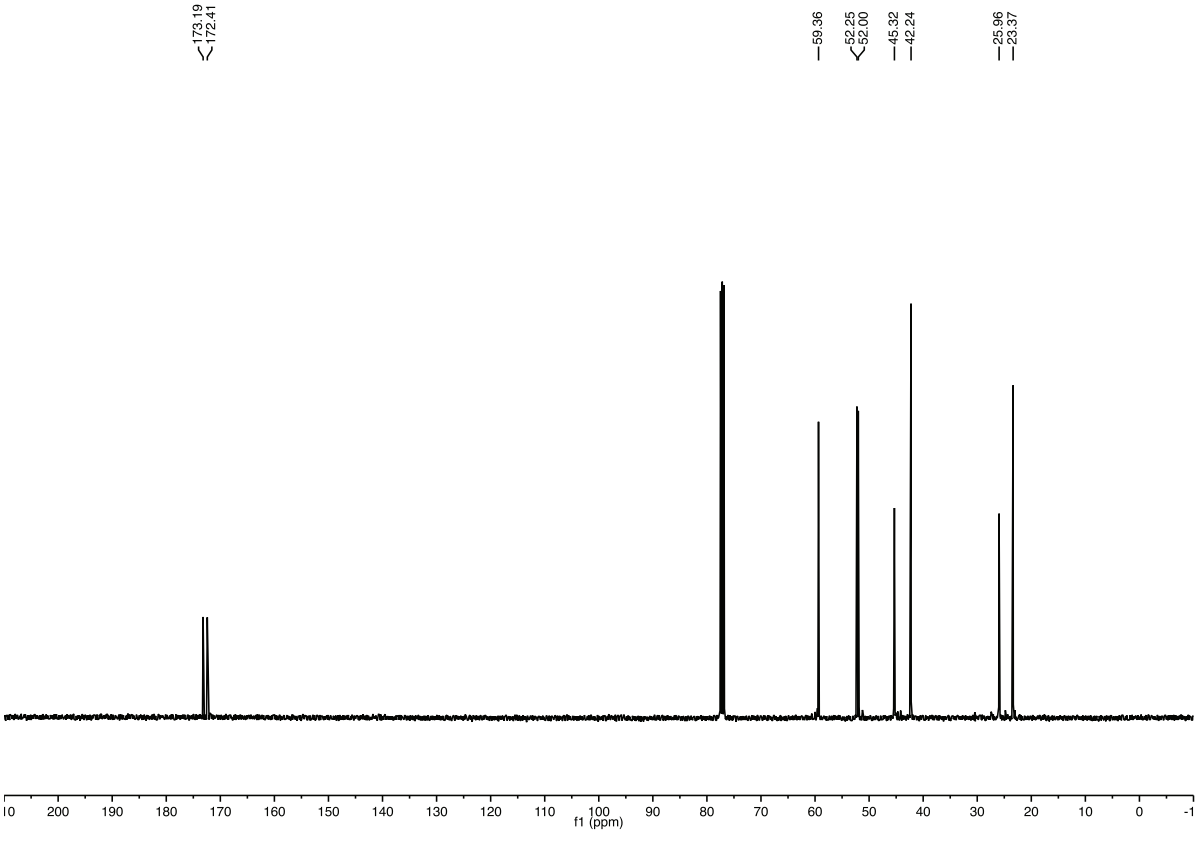
COOMe
N
H
f1 (ppm)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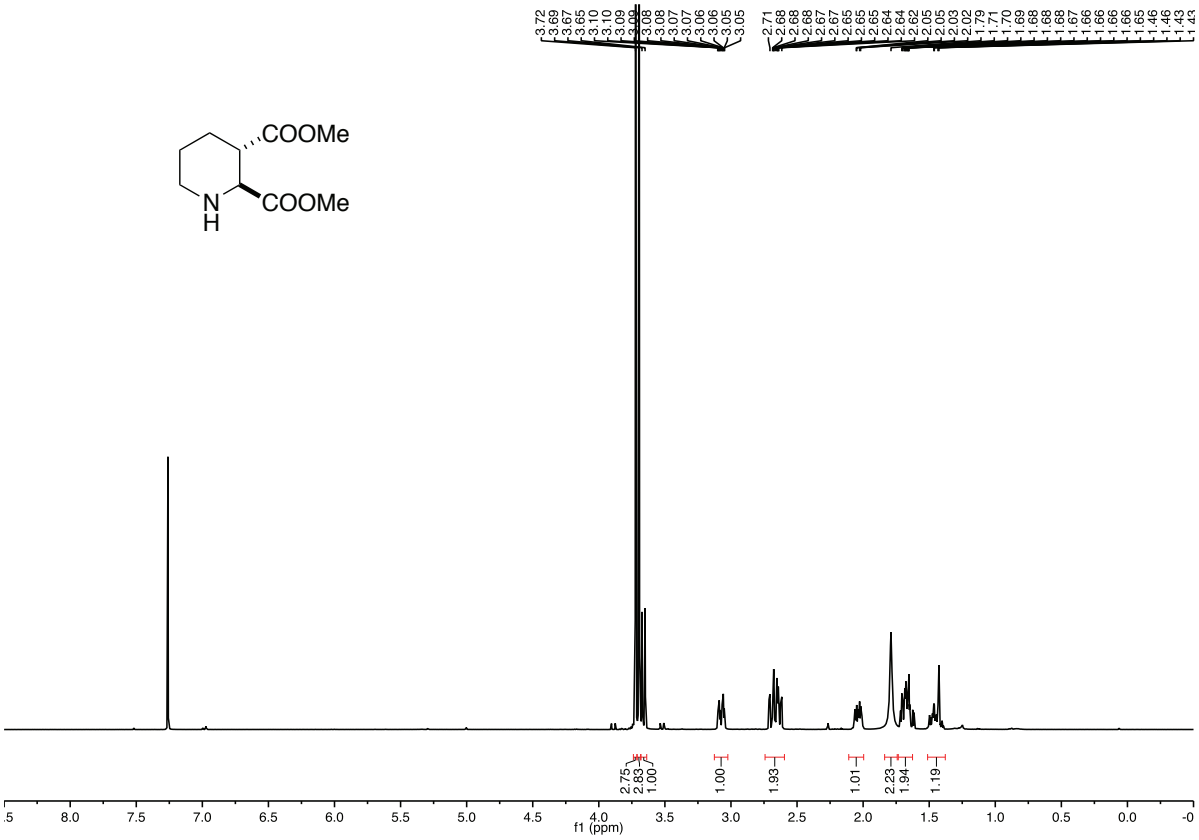
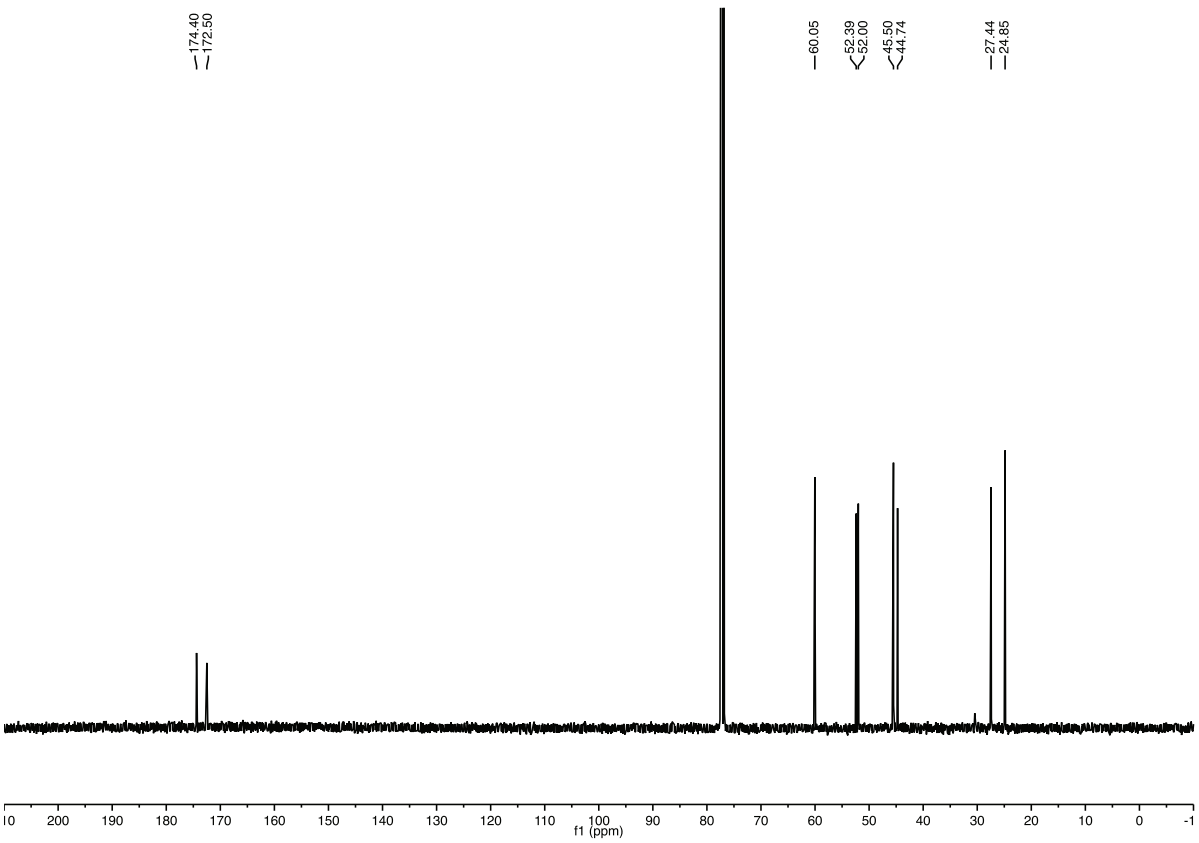

COOMe
COOMe
N
H
f1 (ppm)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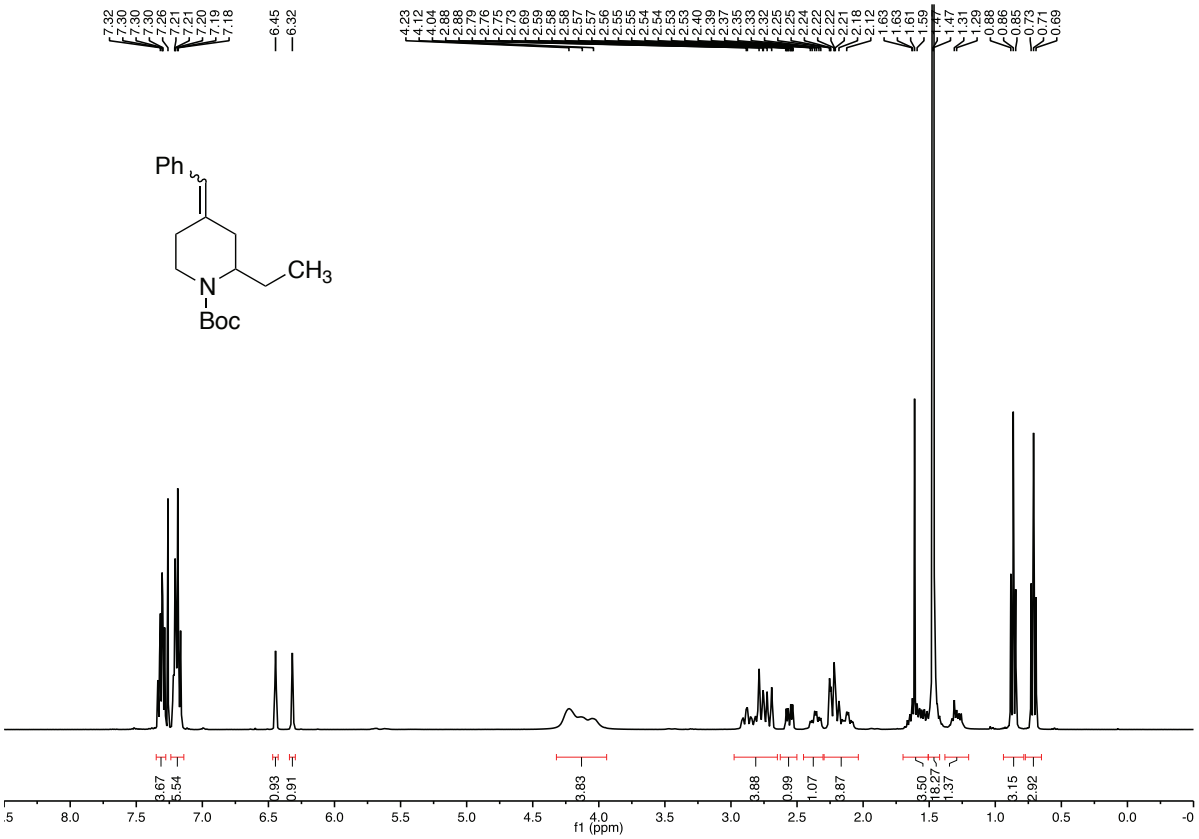
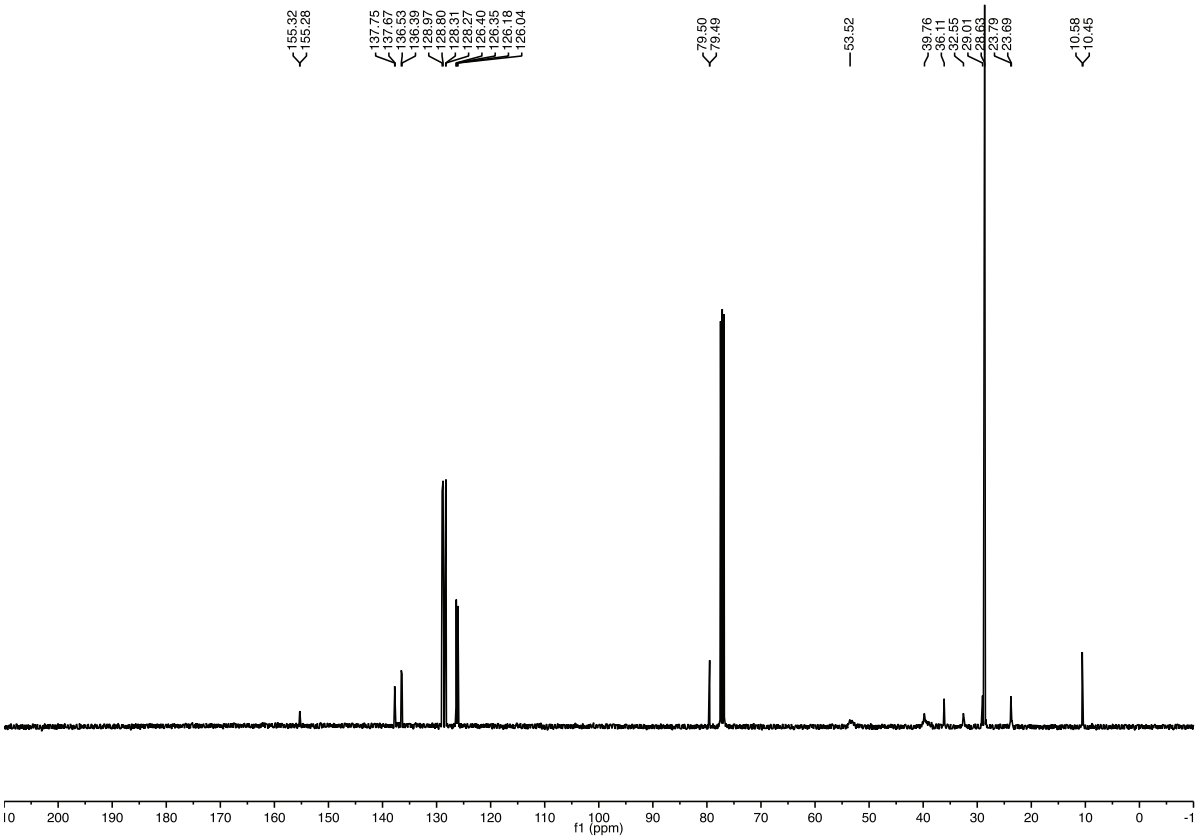
24.85
f1 (ppm)


Ph
CH3
N
Boc
f1 (ppm)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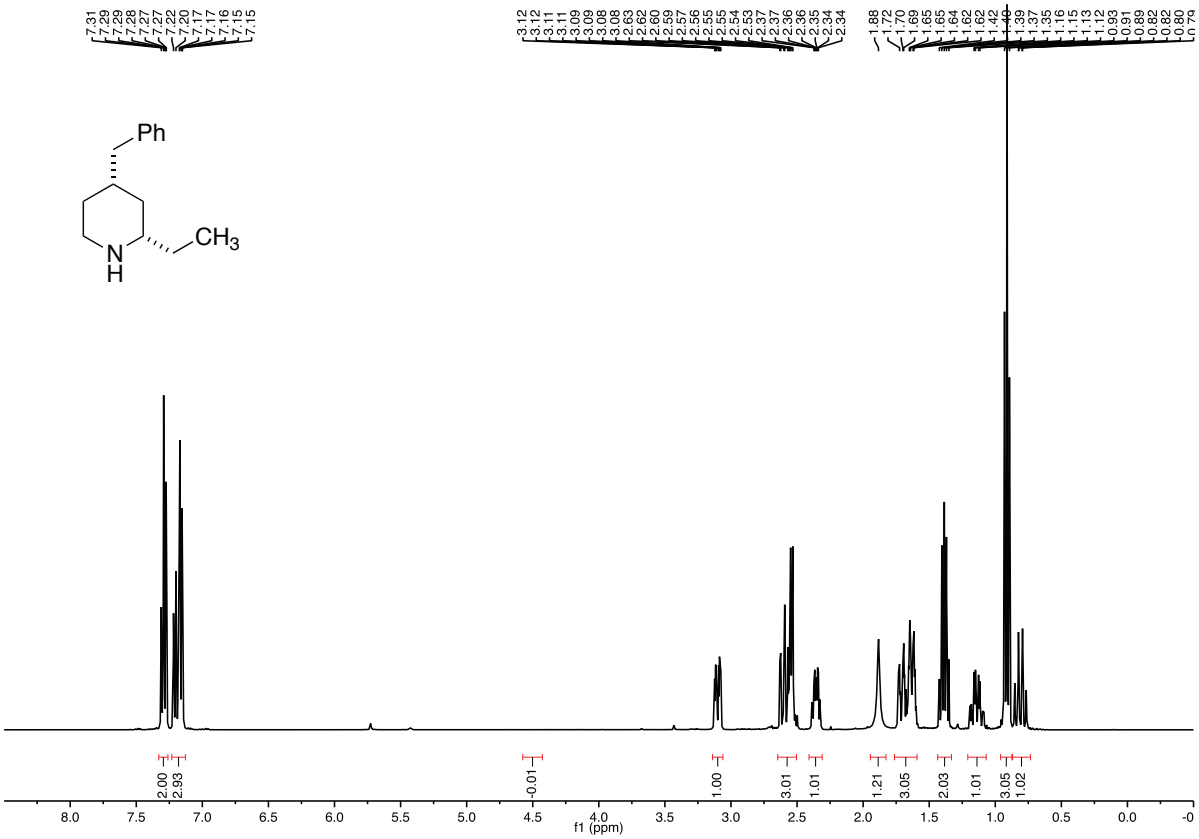
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7.16
7.15
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3.12
3.11
3.11
3.09
3.09
3.08
3.08
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2.62
2.60
2.59
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2.56
2.55
2.55
2.54
2.53
2.37
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2.35
2.34
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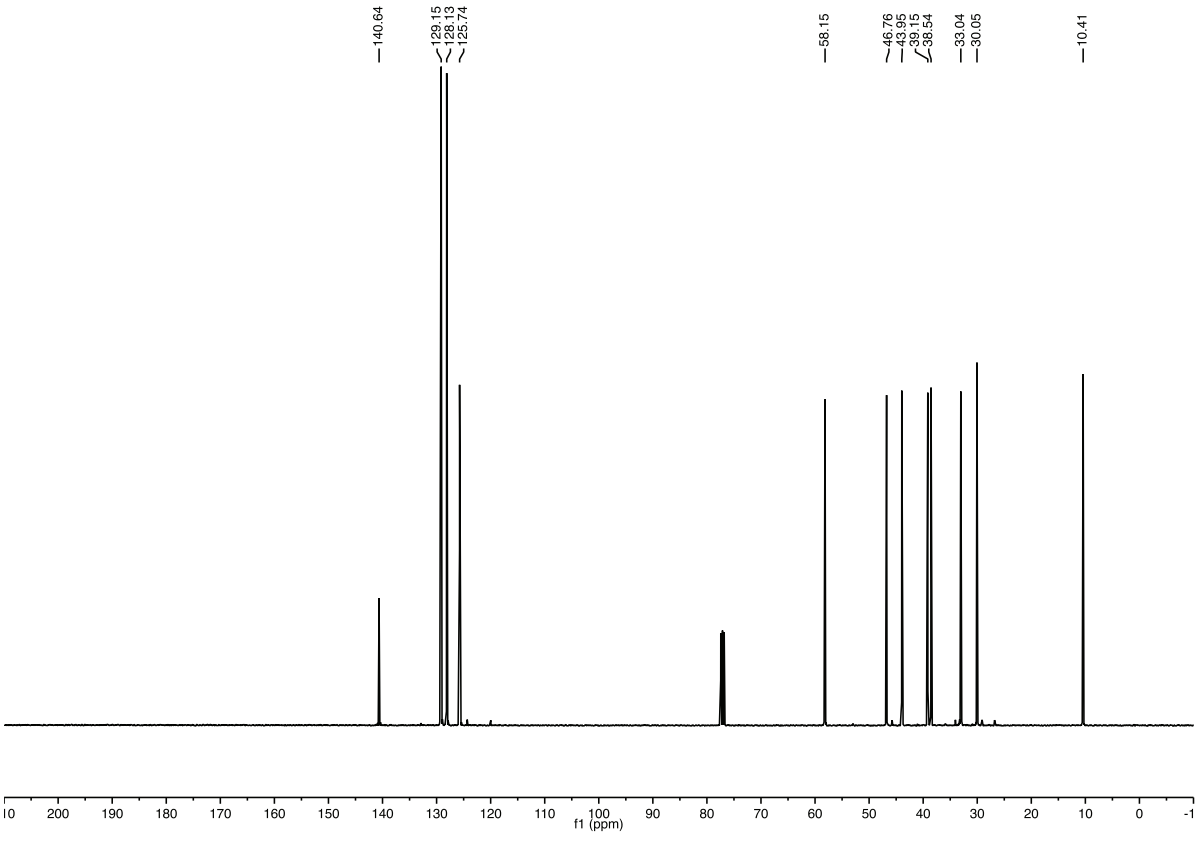
1.65
1.64
1.62
1.62
1.42
1.40
1.39
1.37
1.35
1.16
1.15
1.13
1.12
0.93
0.91
0.89
0.82
0.82
0.80
Ph
CH3
N
H
2.00
2.93
0.01
1.00
3.01
1.01
1.21
3.05
2.03
1.01
3.05
1.02
f1 (ppm)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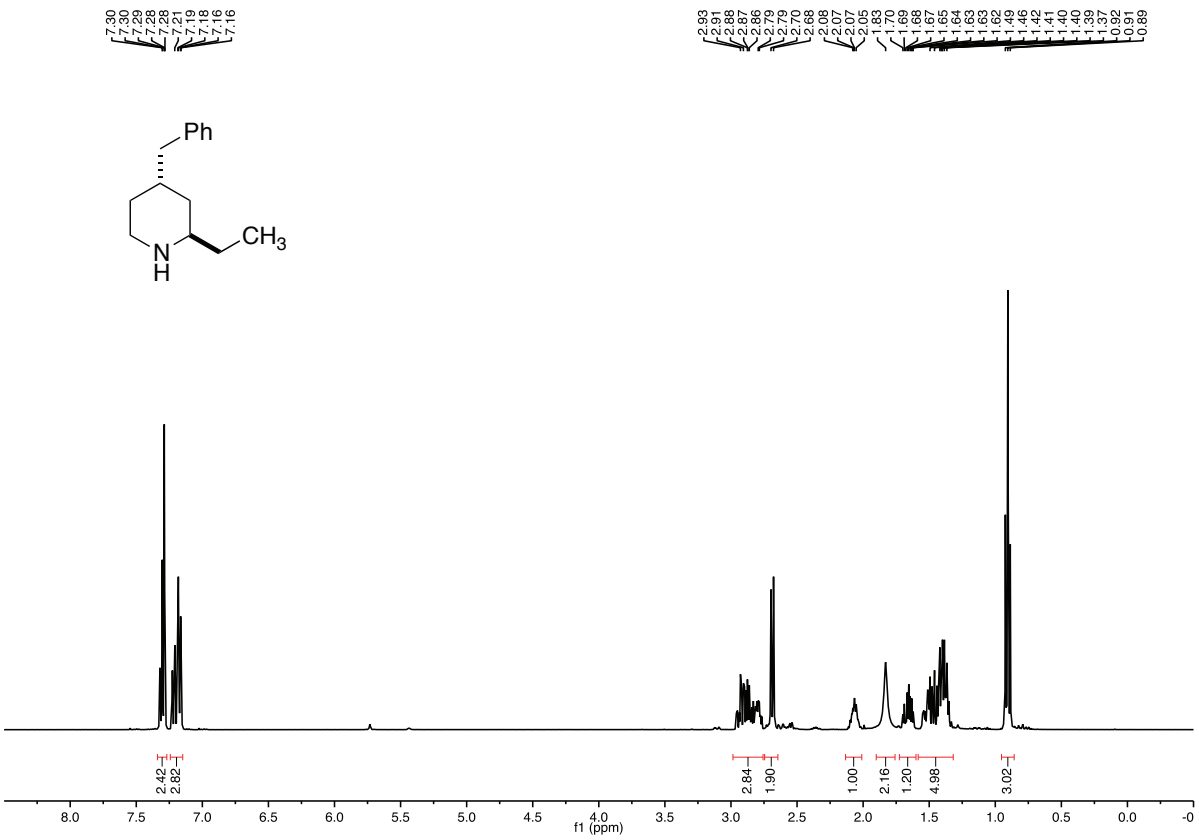
38.54
33.04
30.05
10.41
f1 (ppm)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7.29
7.28
7.28
7.21
7.19
7.18
7.16
7.16
2.93
2.91
2.88
2.87
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2.79
2.79
2.70
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2.07
2.05
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1.64
1.63
1.63
1.62
1.49
1.46
1.42
1.41
1.40
1.40
1.39
1.37
0.92
0.91
0.89
Ph
CH3
N
H
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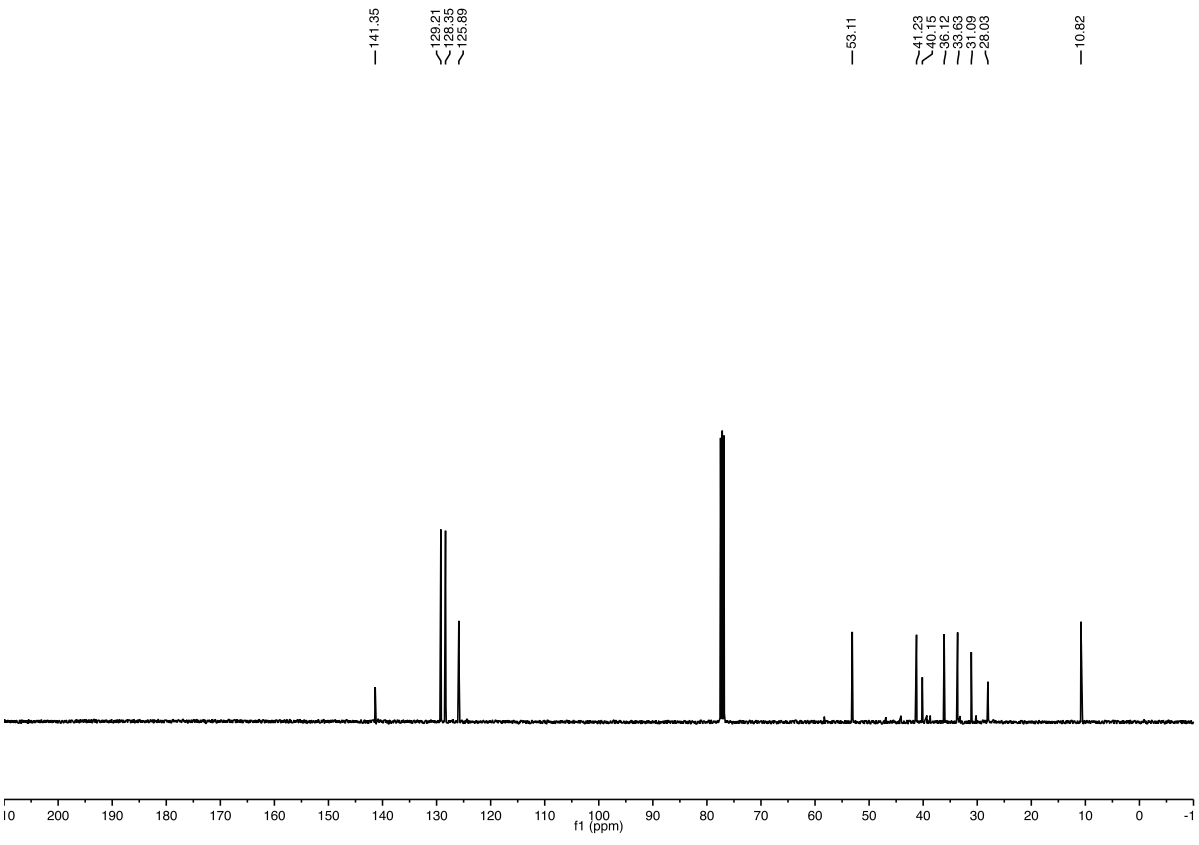
1.90
1.00
2.16
1.20
4.98
3.02
f1 (ppm)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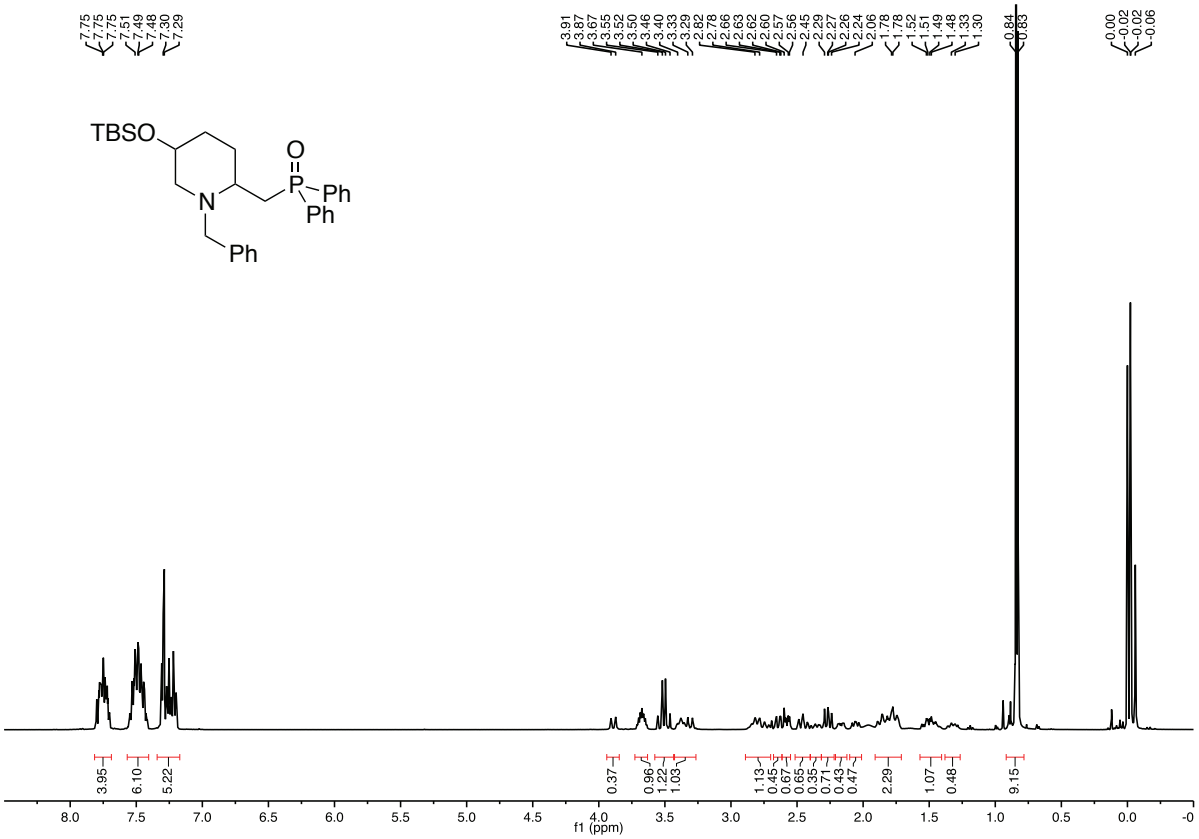
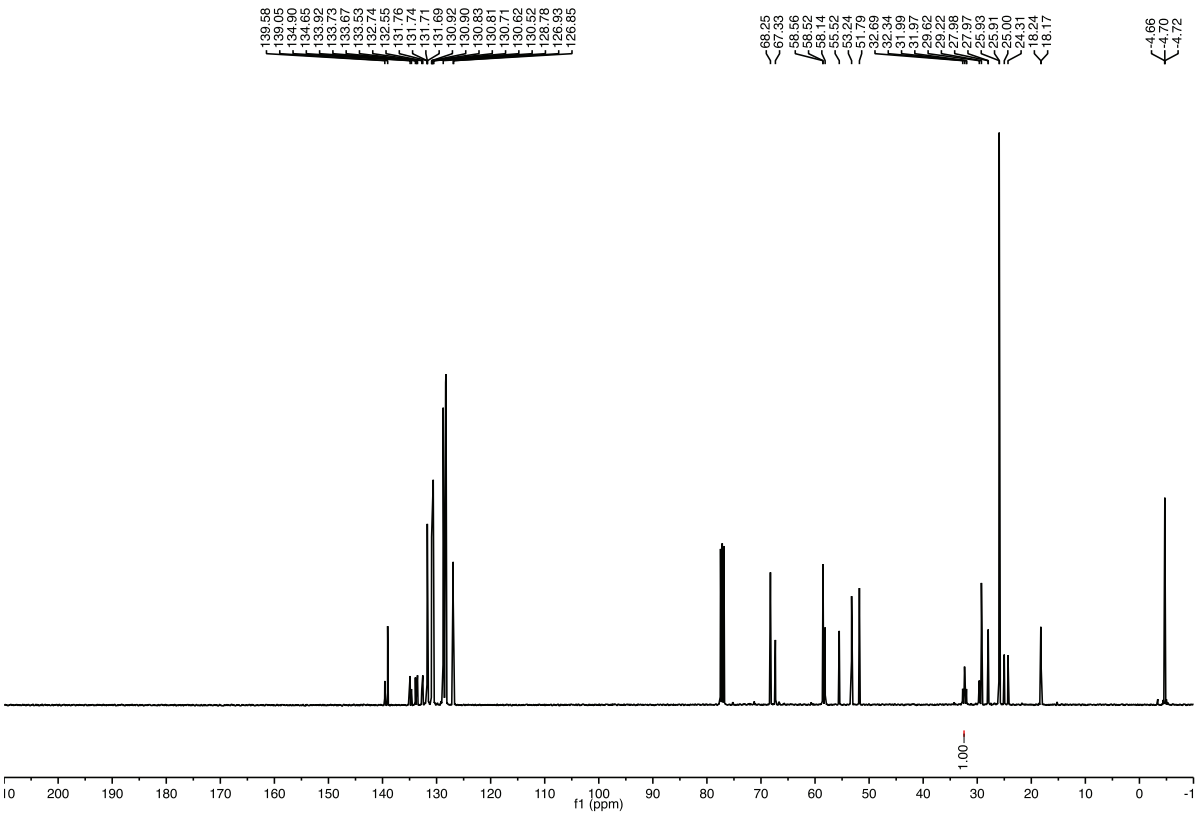
129.21
128.35
125.89
53.11
41.23
40.15
36.12
33.63
31.09
28.03
10.82
f1 (ppm)


TBSO
O
P
Ph
Ph
N
Ph
f1 (ppm)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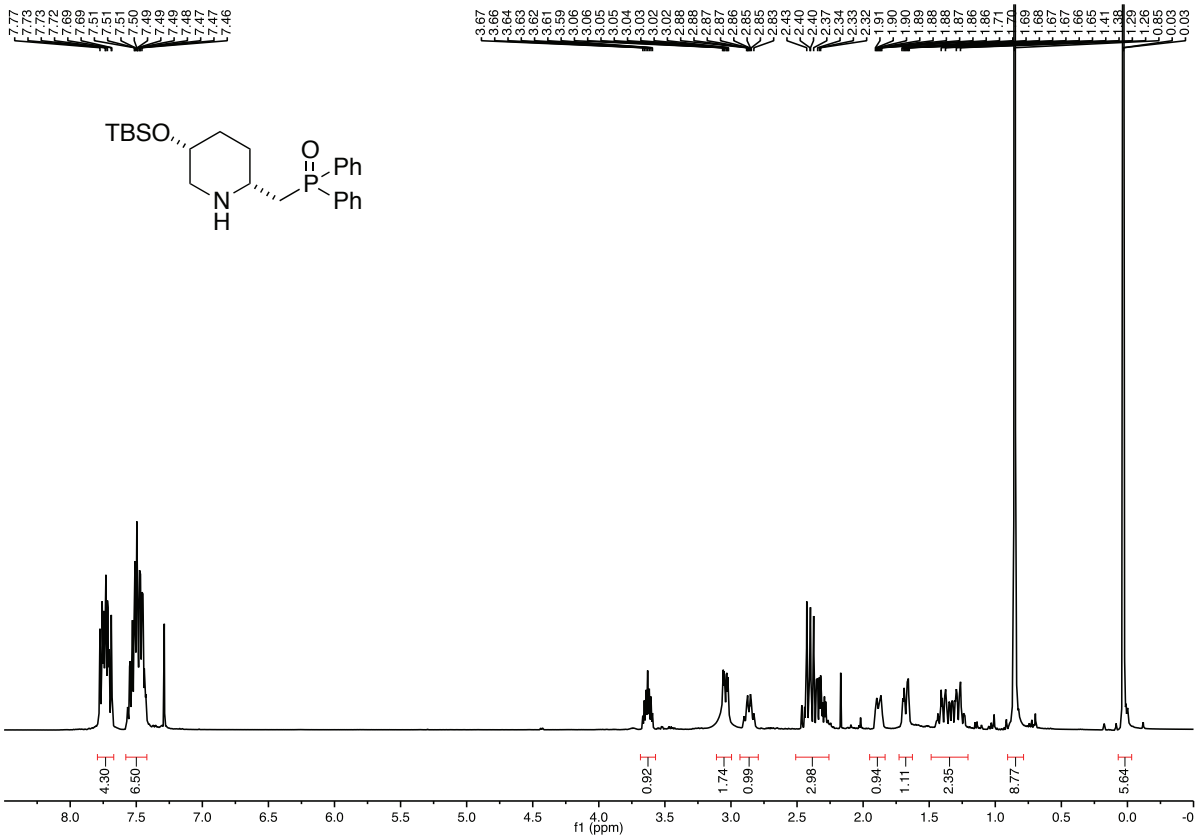
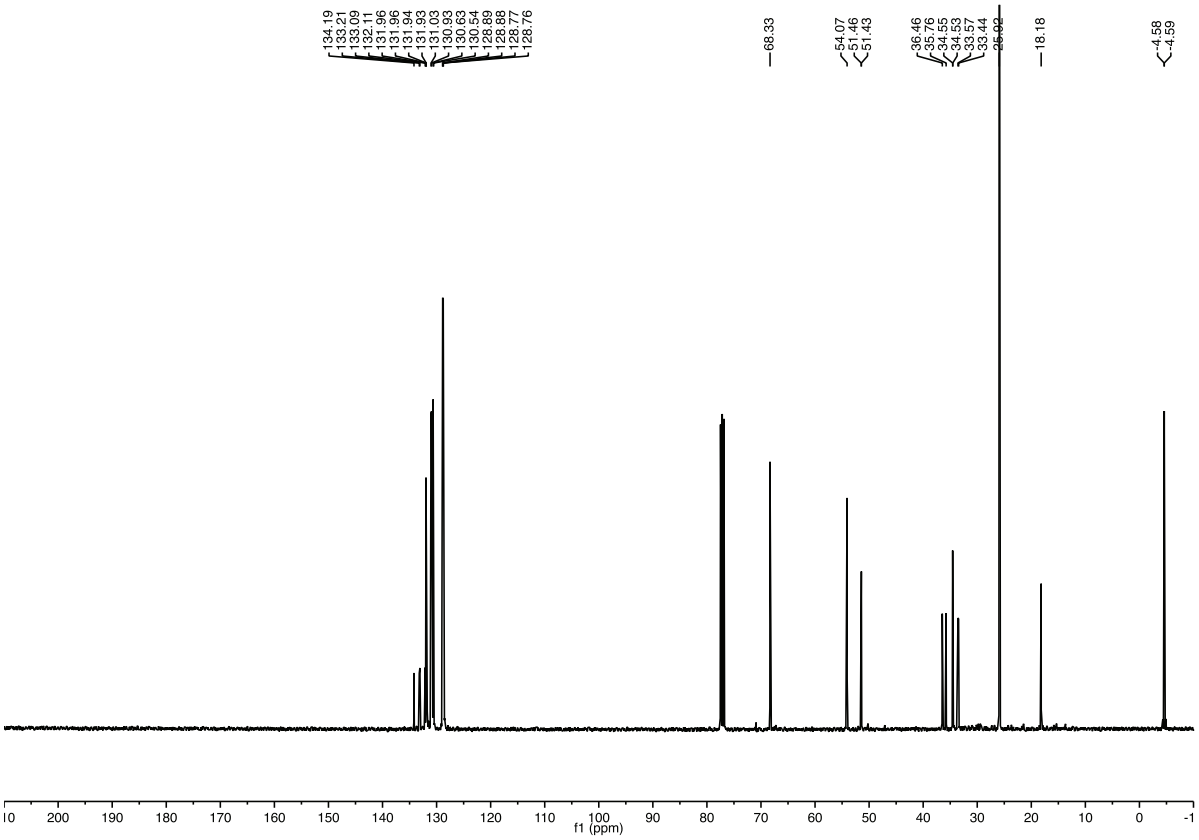

TBSO
O
P
Ph
Ph
N
H
f1 (ppm)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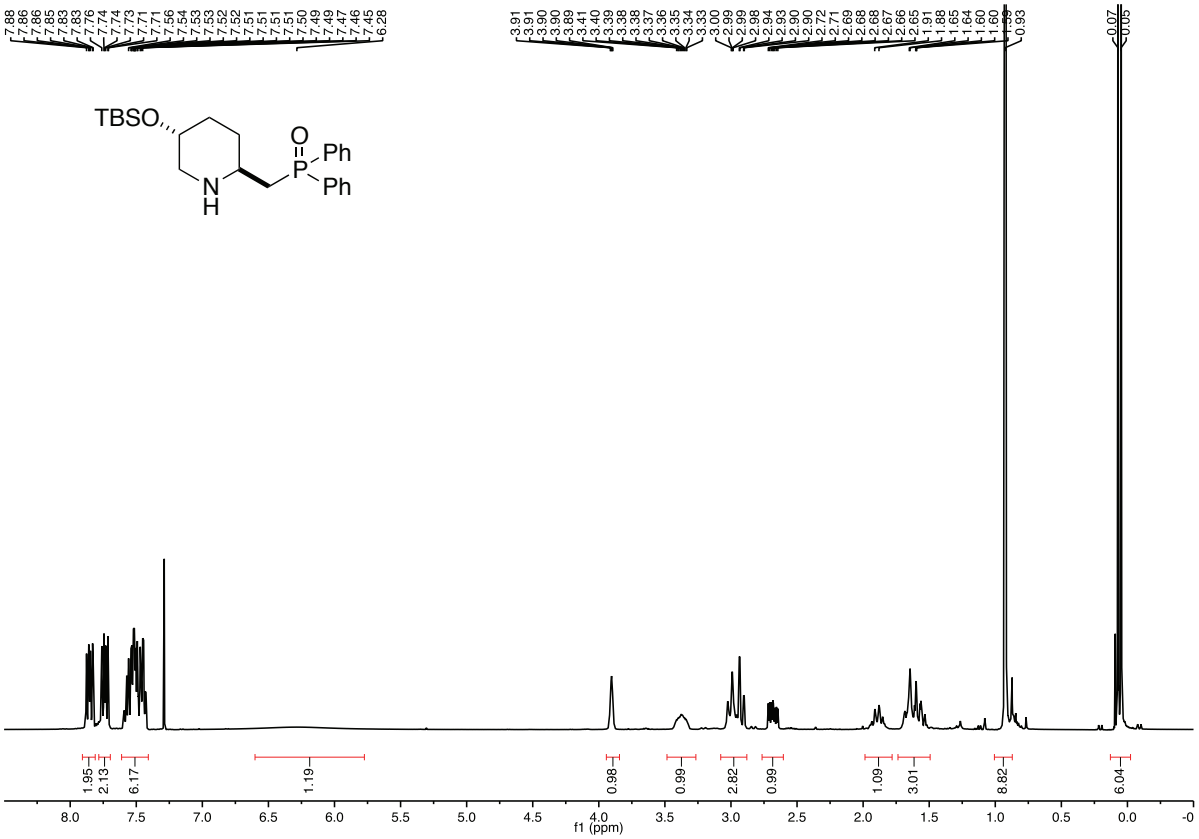
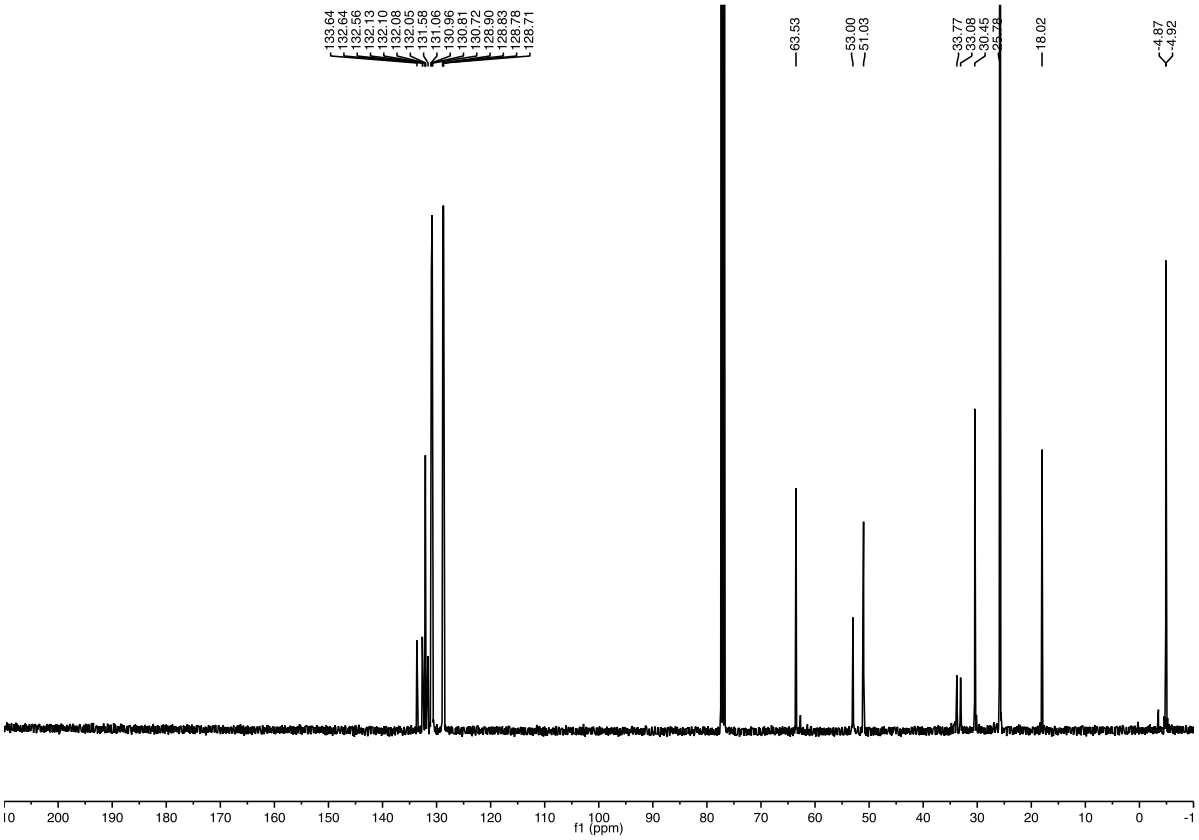

TBSO
O
Ph
P
Ph
N
H
f1 (ppm)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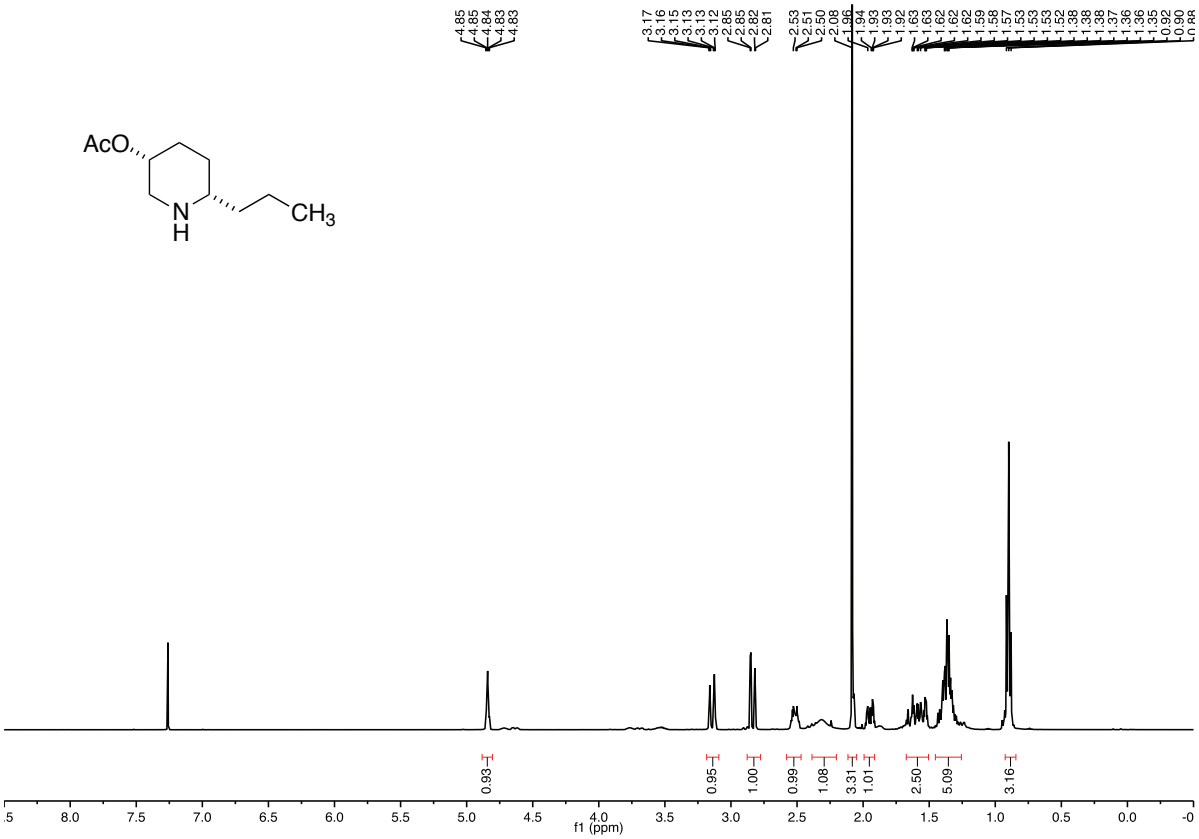
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N
H
CH3
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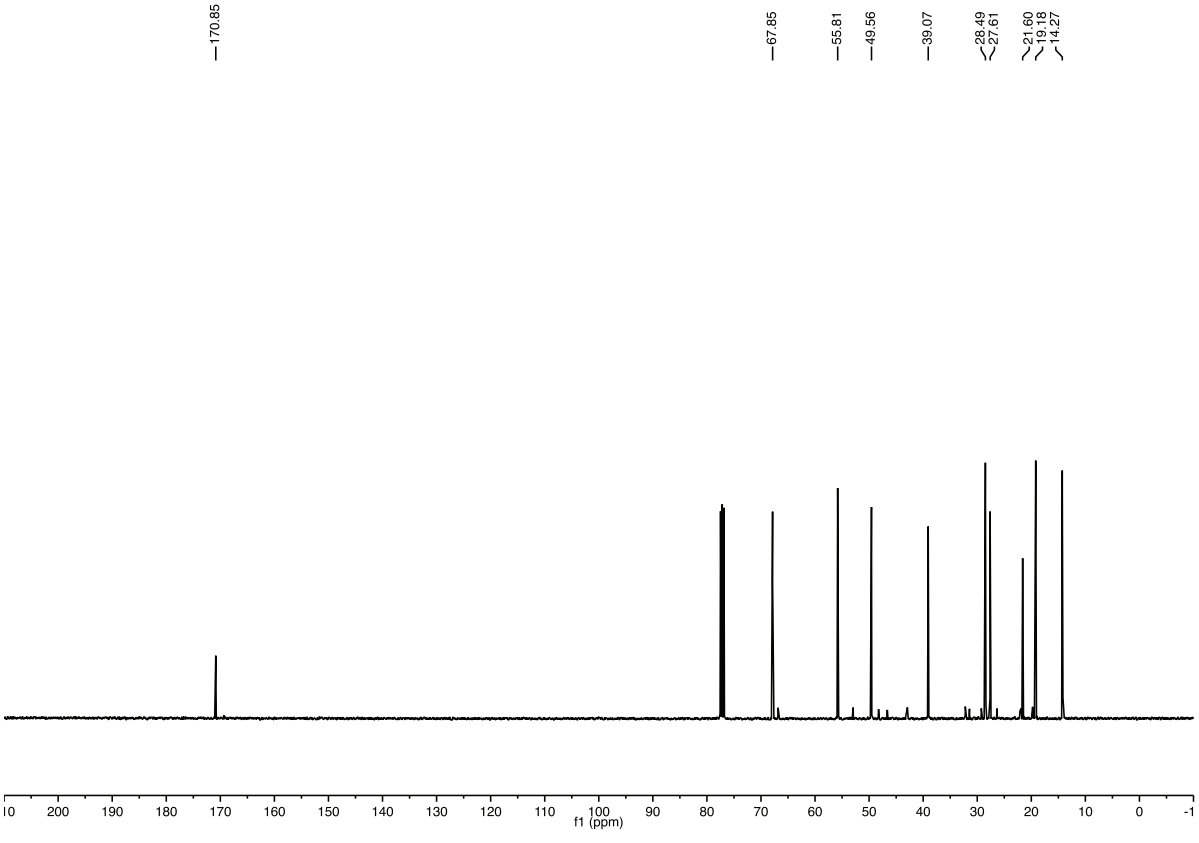
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28.49
27.61
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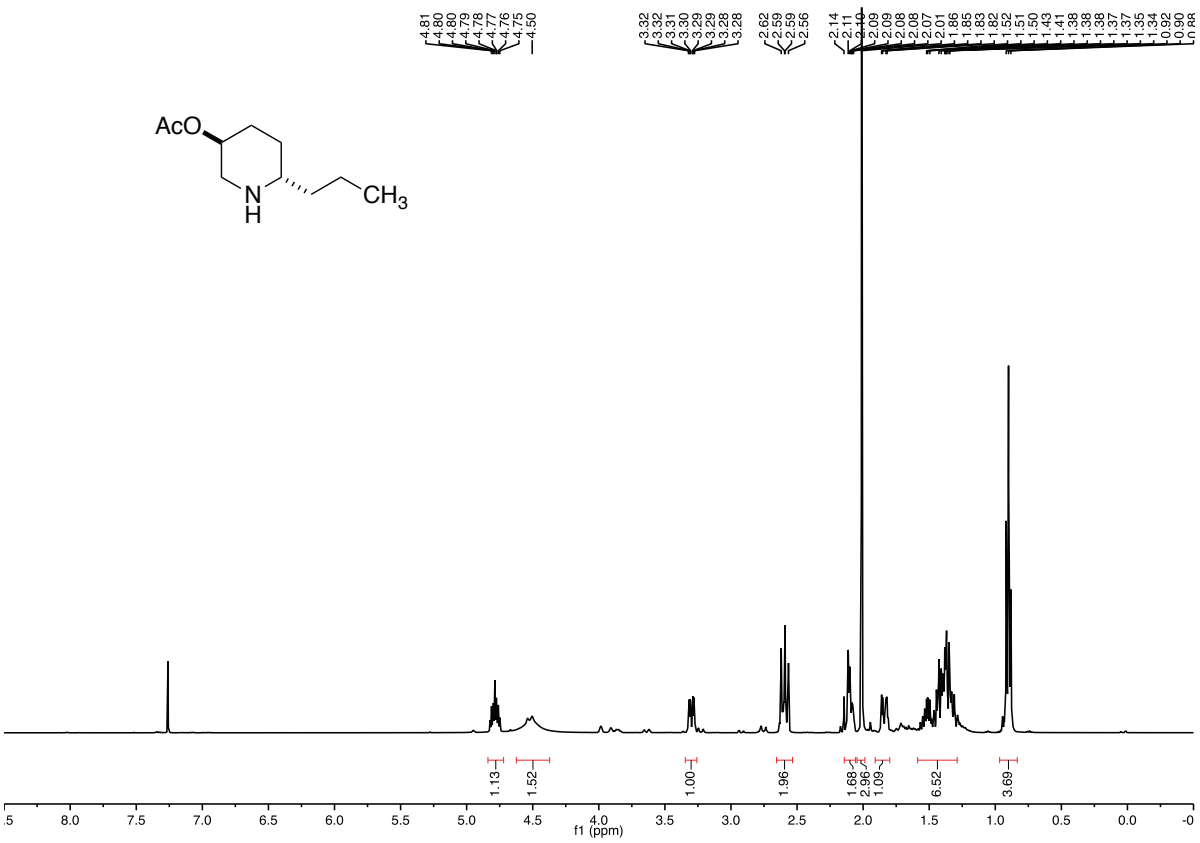
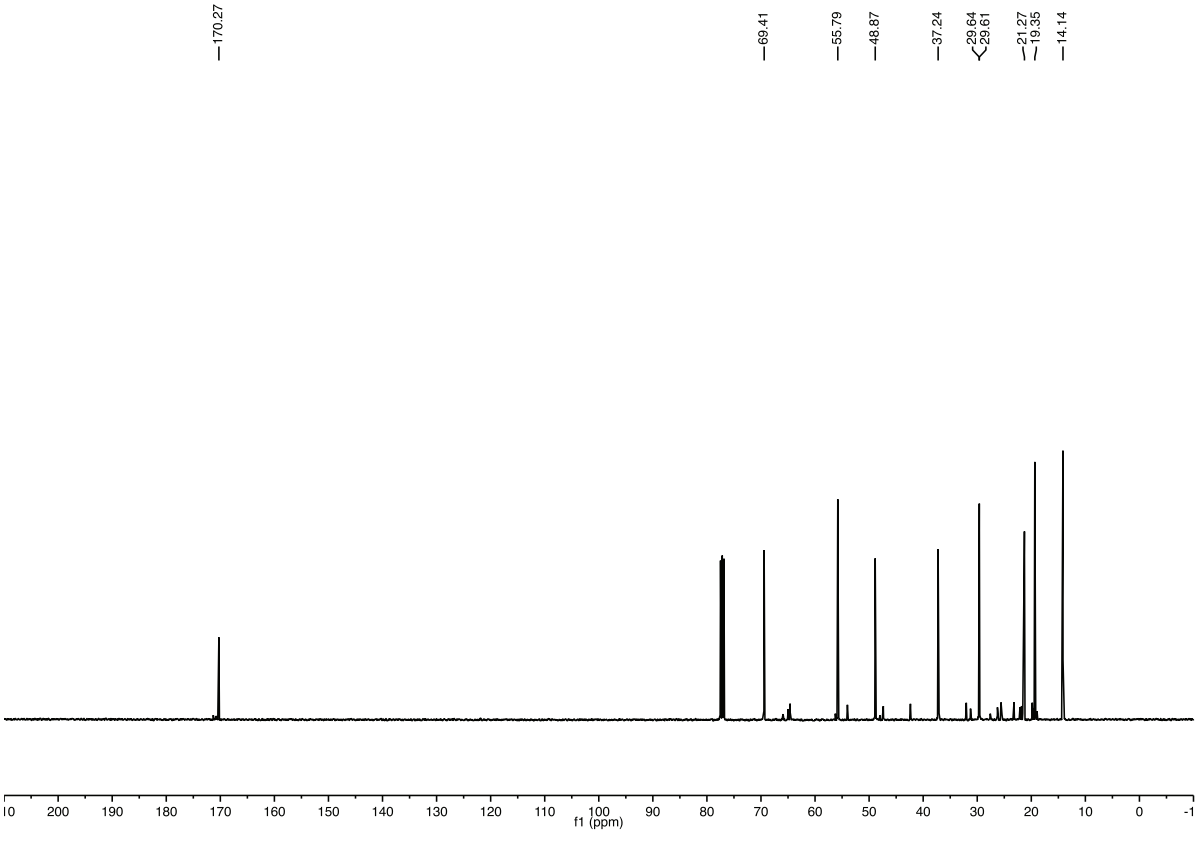
19.18
14.27
f1 (ppm)


AcO
N
H
CH3
f1 (ppm)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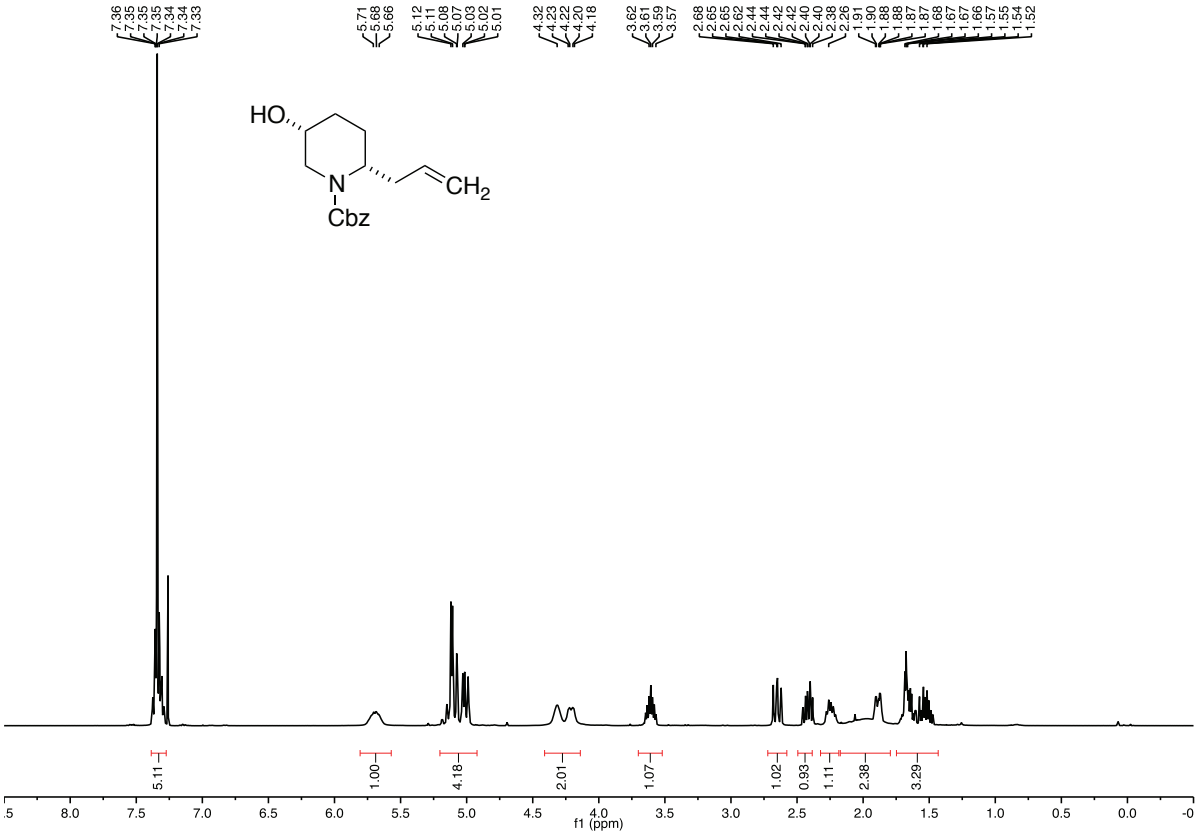
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5.66
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5.11
5.08
5.07
5.03
5.02
5.01
4.32
4.23
4.22
4.20
4.18
3.62
3.61
3.59
3.57
2.68
2.65
2.65
2.62
2.44
2.44
2.42
2.42
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1.88
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1.57
1.55
1.54
1.52
HO
N
Cbz
CH2
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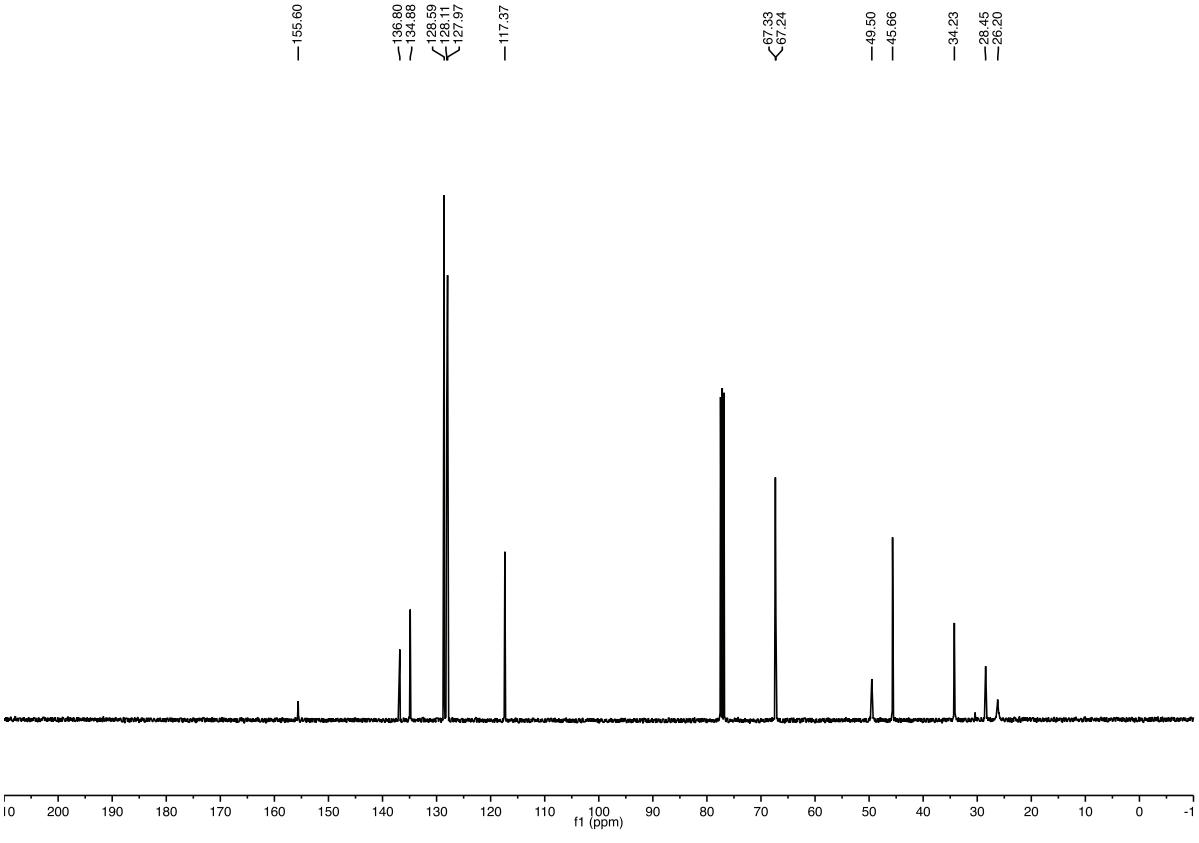
1.07
1.02
0.93
1.11
2.38
3.29
f1 (ppm)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49.50
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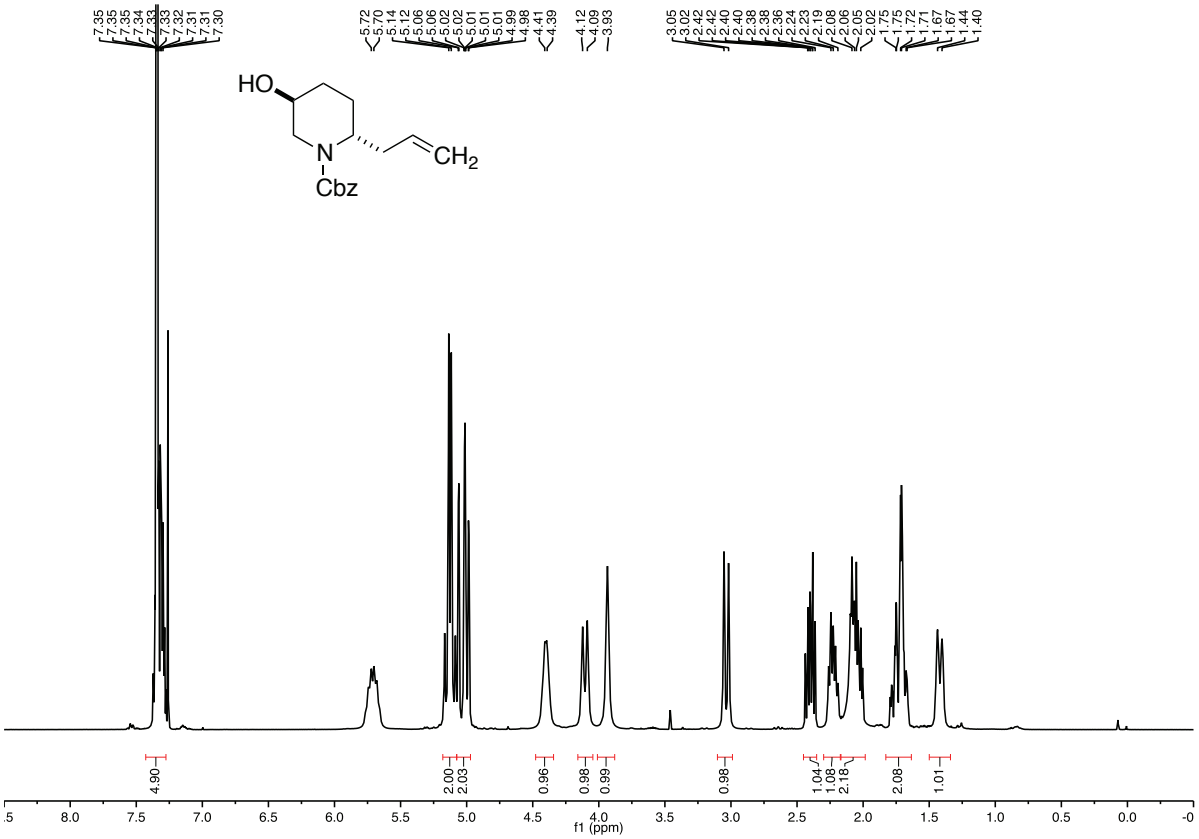
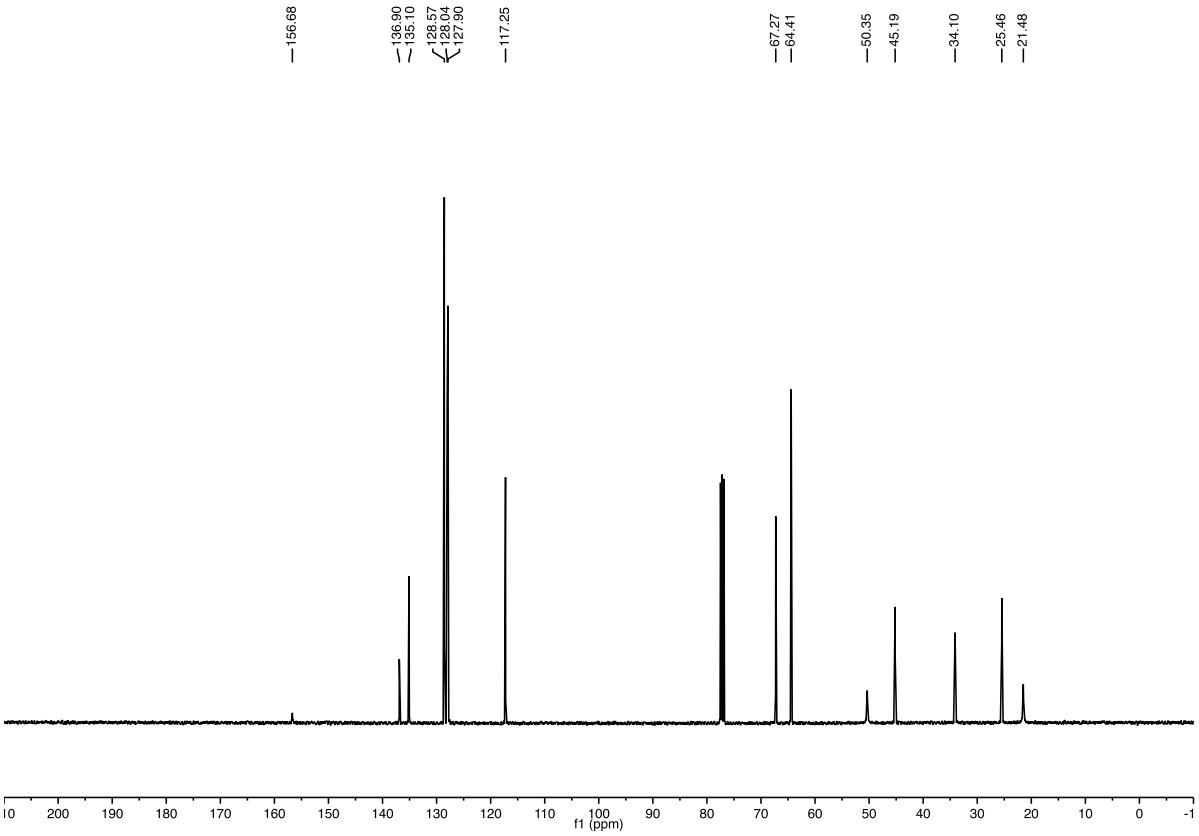
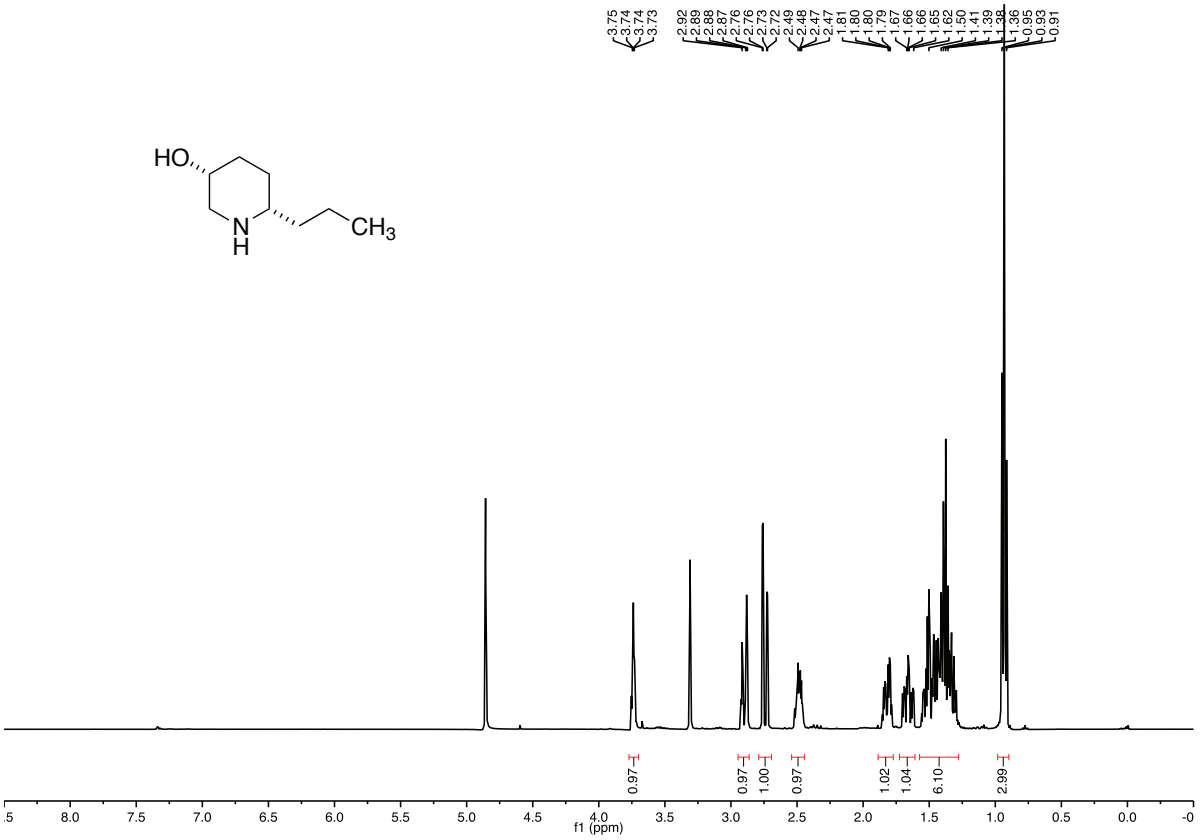
34.23
28.45
26.20
f1 (ppm)


HO
N
Cbz
CH2
f1 (ppm)


f1 (ppm)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2.73
2.72
2.49
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2.47
2.47
1.81
1.80
1.80
1.79
1.67
1.66
1.65
1.62
1.50
1.41
1.39
1.38
1.36
0.95
0.93
0.91
HO
N
H
CH3
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0.97
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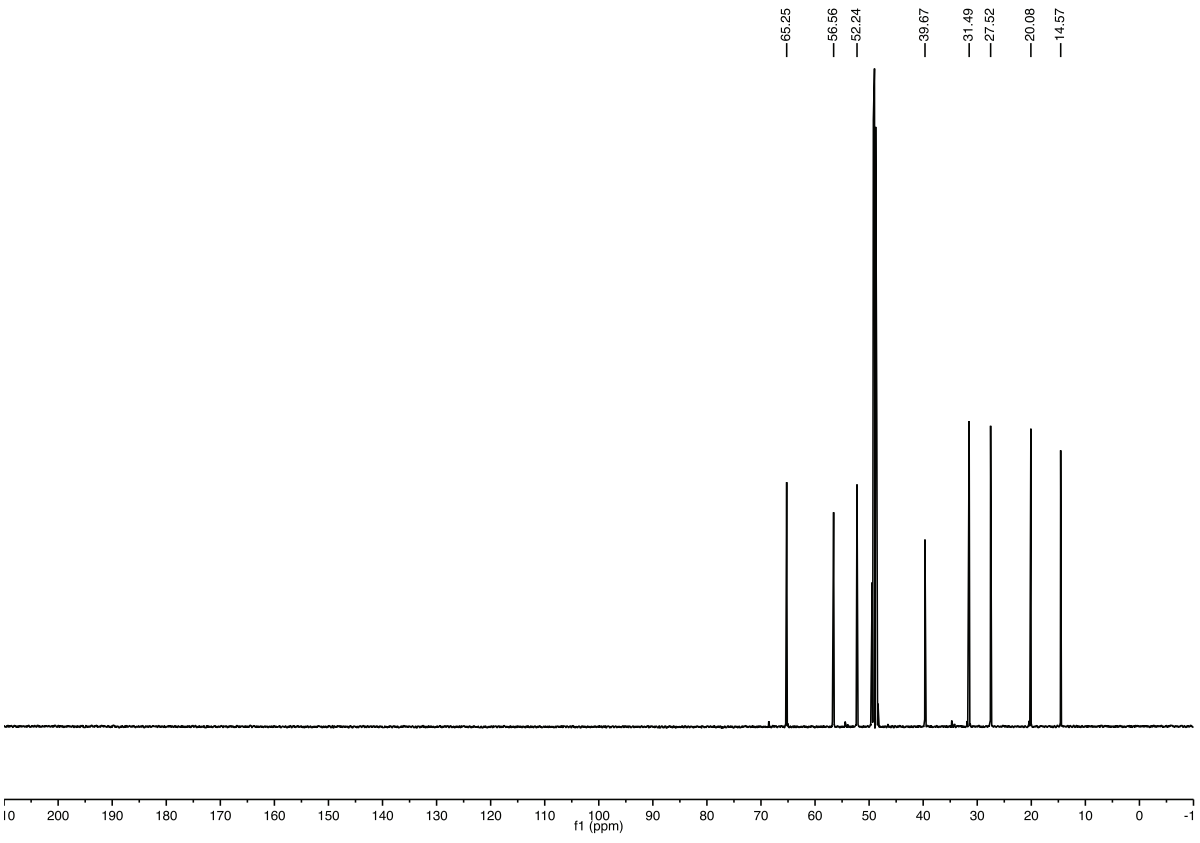
0.97
1.02
1.04
6.10
2.99
f1 (ppm)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39.67
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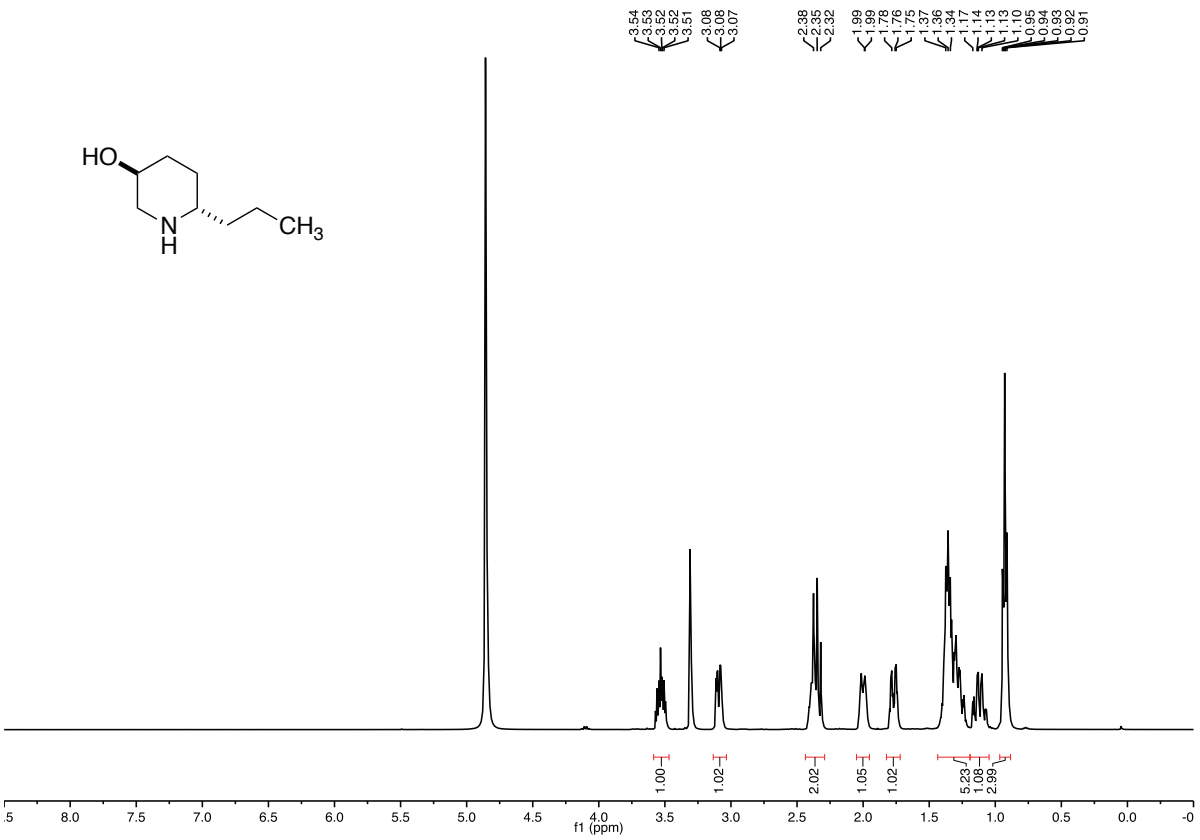
27.52
20.08
14.57
f1 (ppm)


HO
N
H
CH3
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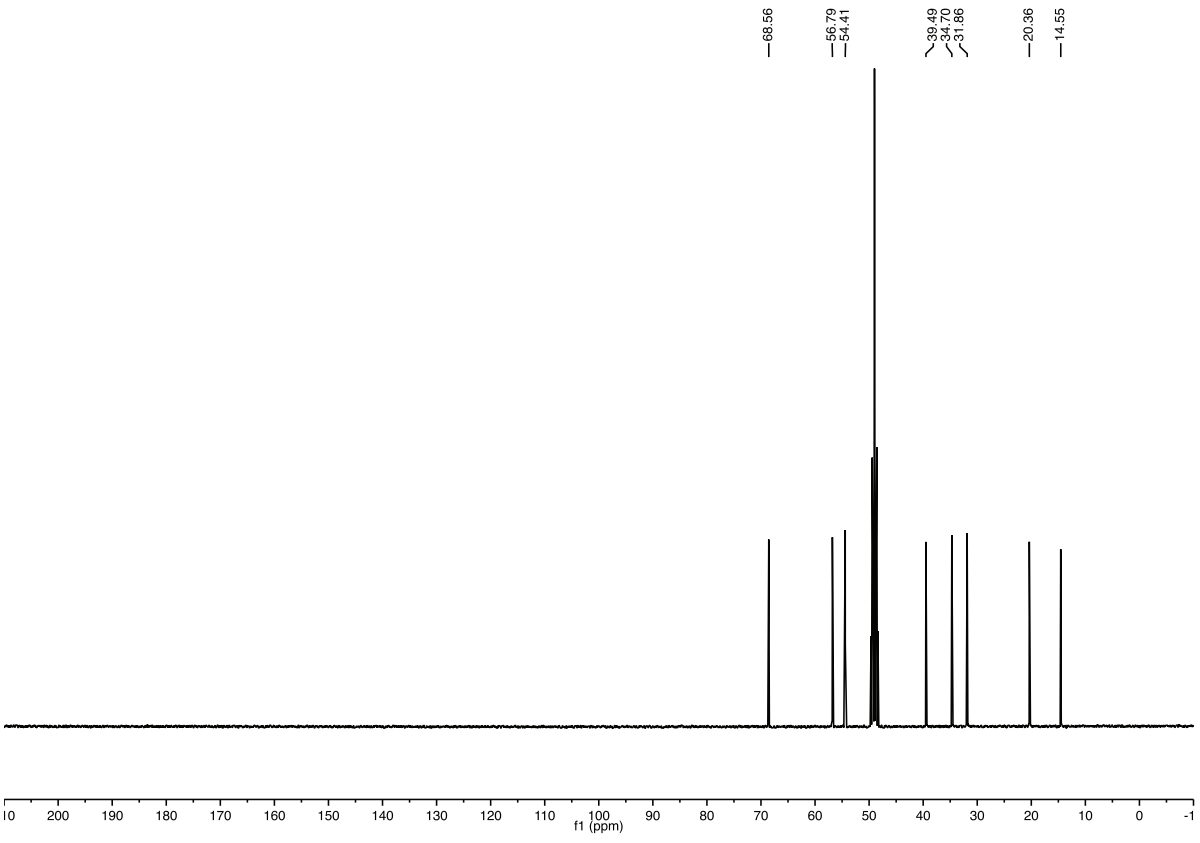
3.52
3.51
3.08
3.08
3.07
2.38
2.35
2.32
1.99
1.99
1.78
1.76
1.75
1.37
1.36
1.34
1.17
1.14
1.13
1.10
0.95
0.94
0.93
0.92
0.91
1.00
1.02
2.02
1.05
1.02
5.23
1.08
2.99
f1 (ppm)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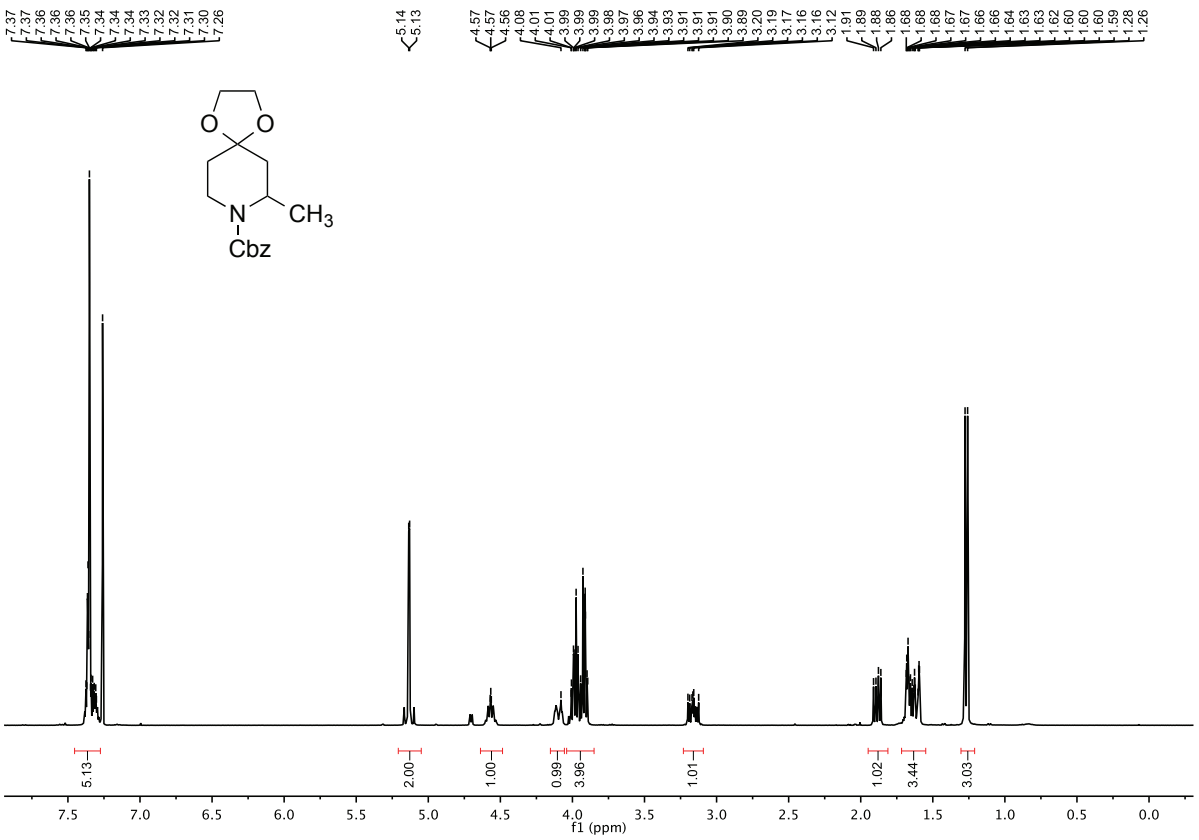
14.55
f1 (ppm)


7.37 7.37 7.36 7.36 7.36 7.35 7.34 7.34 7.34 7.33 7.32 7.32 7.31 7.30 7.26
5.14 5.13
4.57 4.57 4.56 4.08 4.01 4.01 3.99 3.99 3.99 3.98 3.97 3.96 3.94 3.93 3.91 3.91 3.90 3.89 3.20 3.19 3.17 3.16 3.16 3.12 1.91 1.89 1.88 1.86 1.68 1.68 1.68 1.67 1.67 1.66 1.66 1.64 1.63 1.63 1.62 1.60 1.60 1.60 1.59 1.28 1.26
O
O
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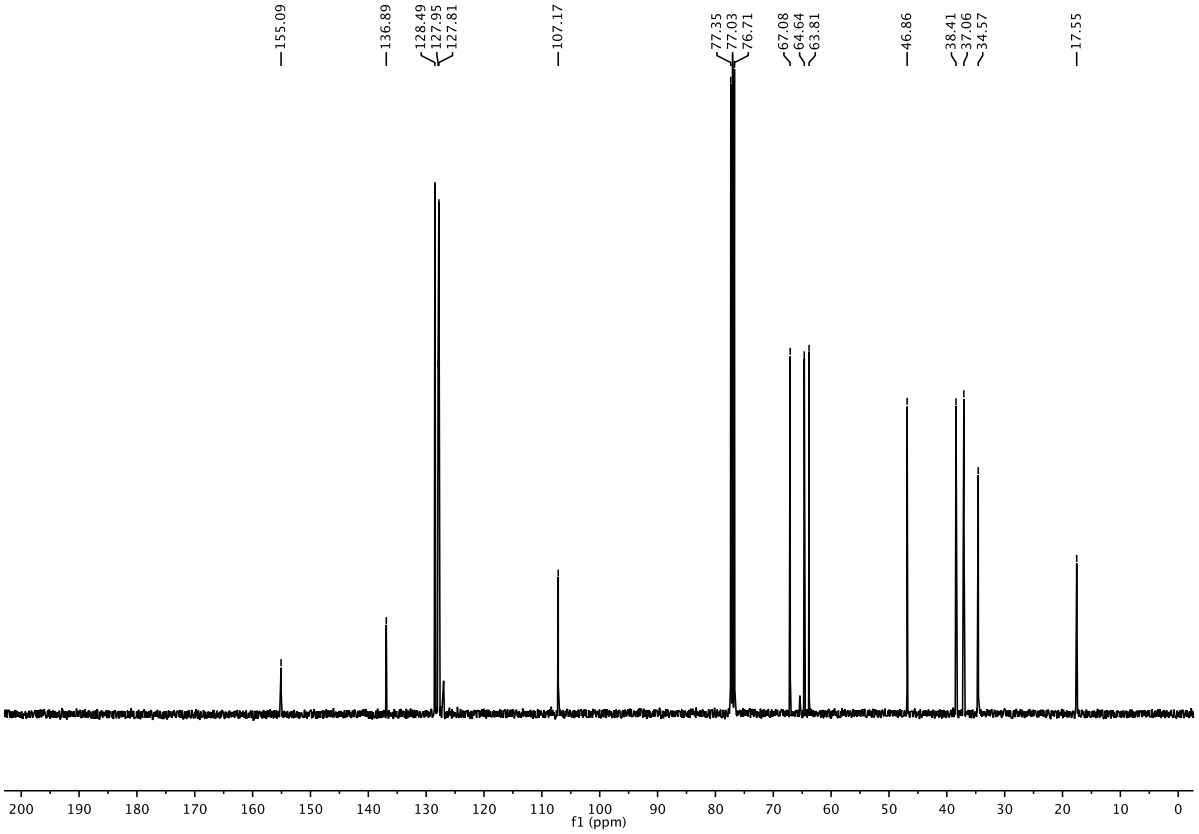
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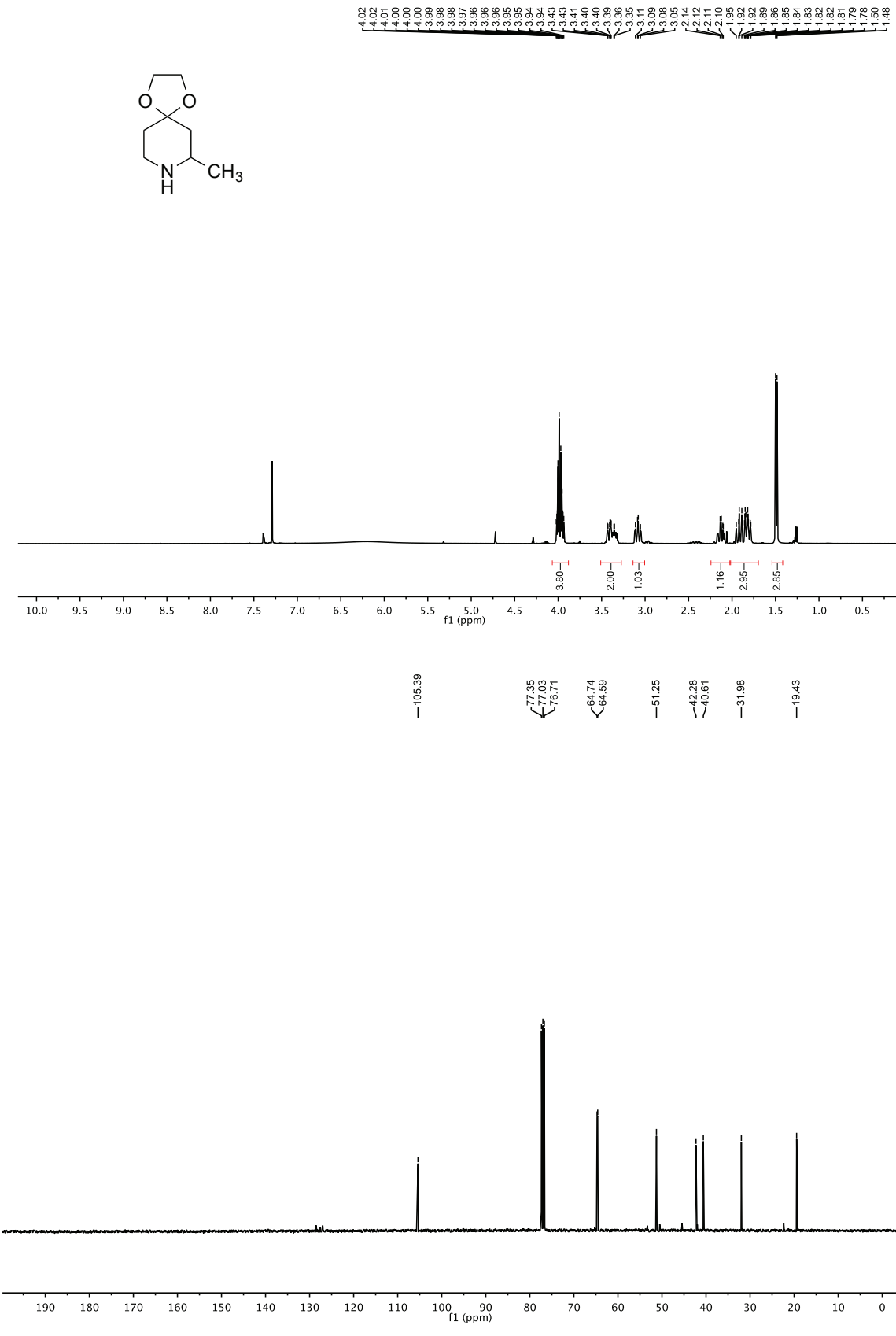
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3.94
3.43
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3.41
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1.50
1.48
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O
N
H
CH3
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1.03
1.16
2.95
2.85
f1 (ppm)
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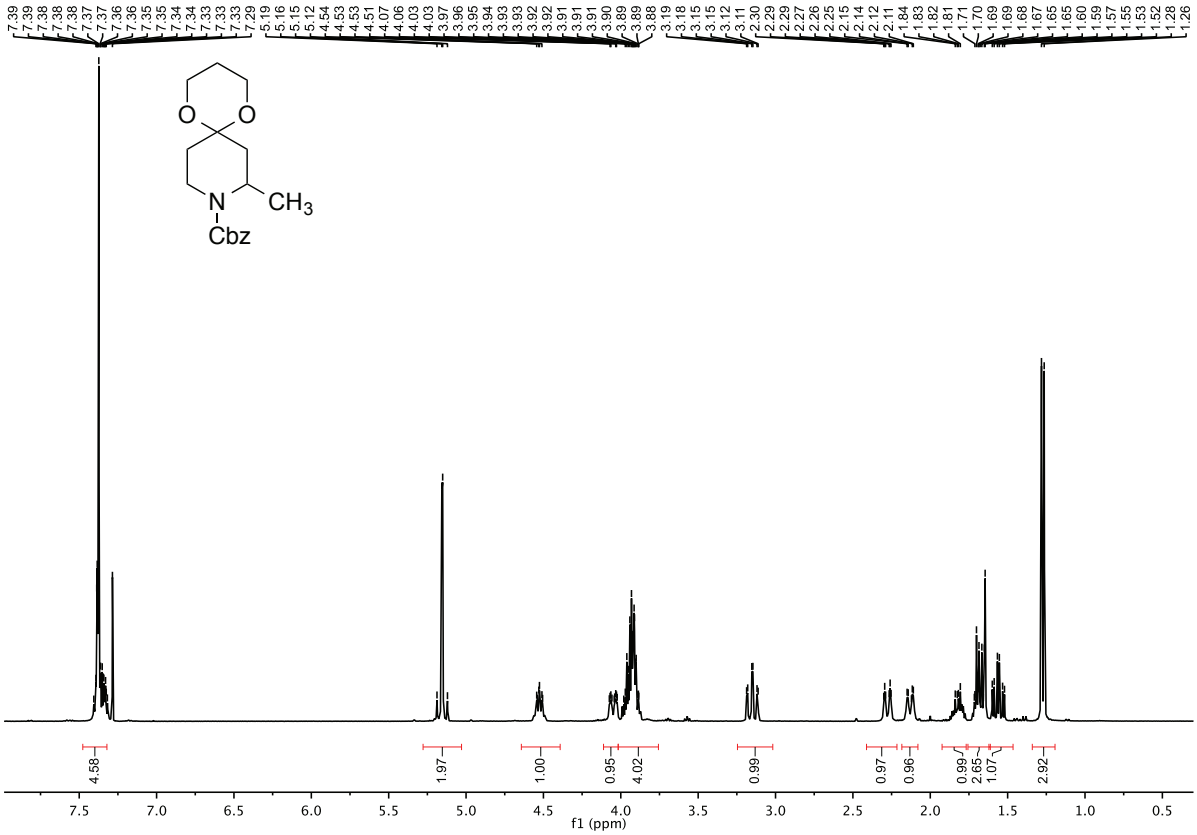
f1 (ppm)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O
O
N
CH3
Cbz
4.58
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1.00
0.95
4.02
0.99
0.97
0.96
0.99
2.65
1.07
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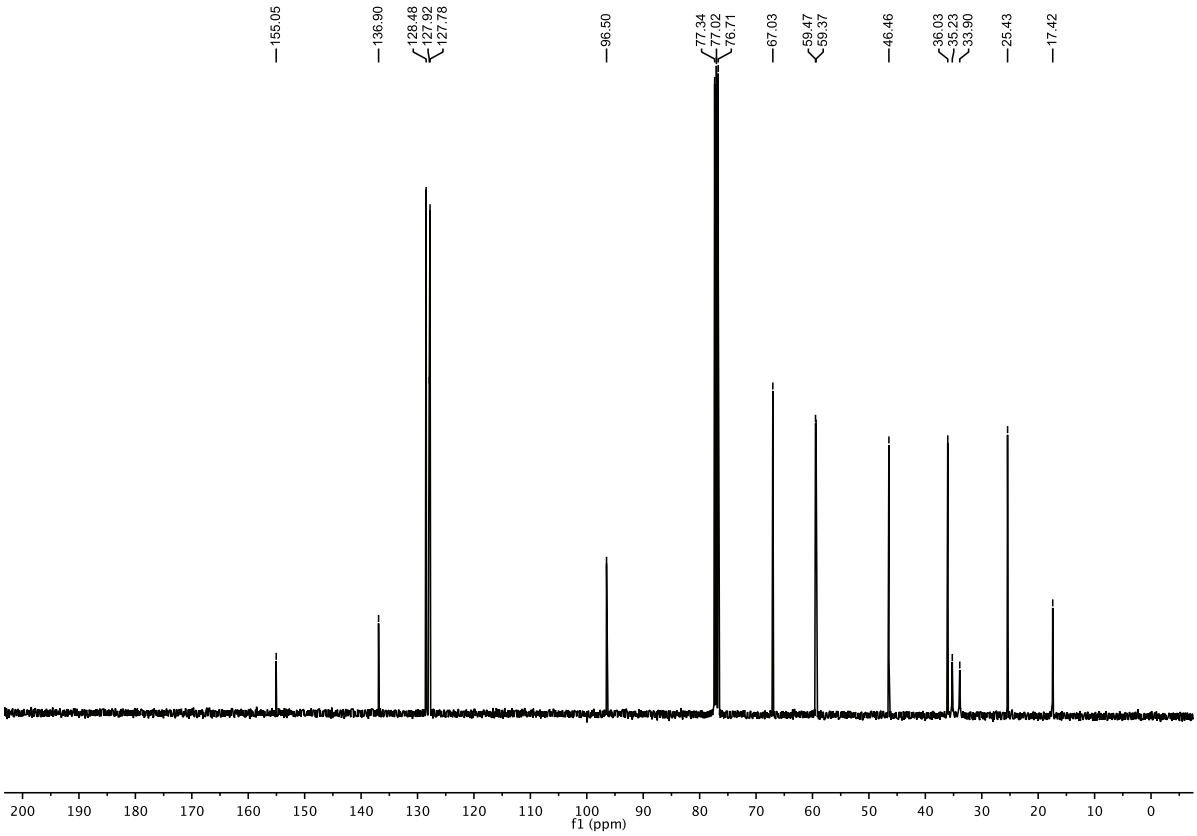
f1 (ppm)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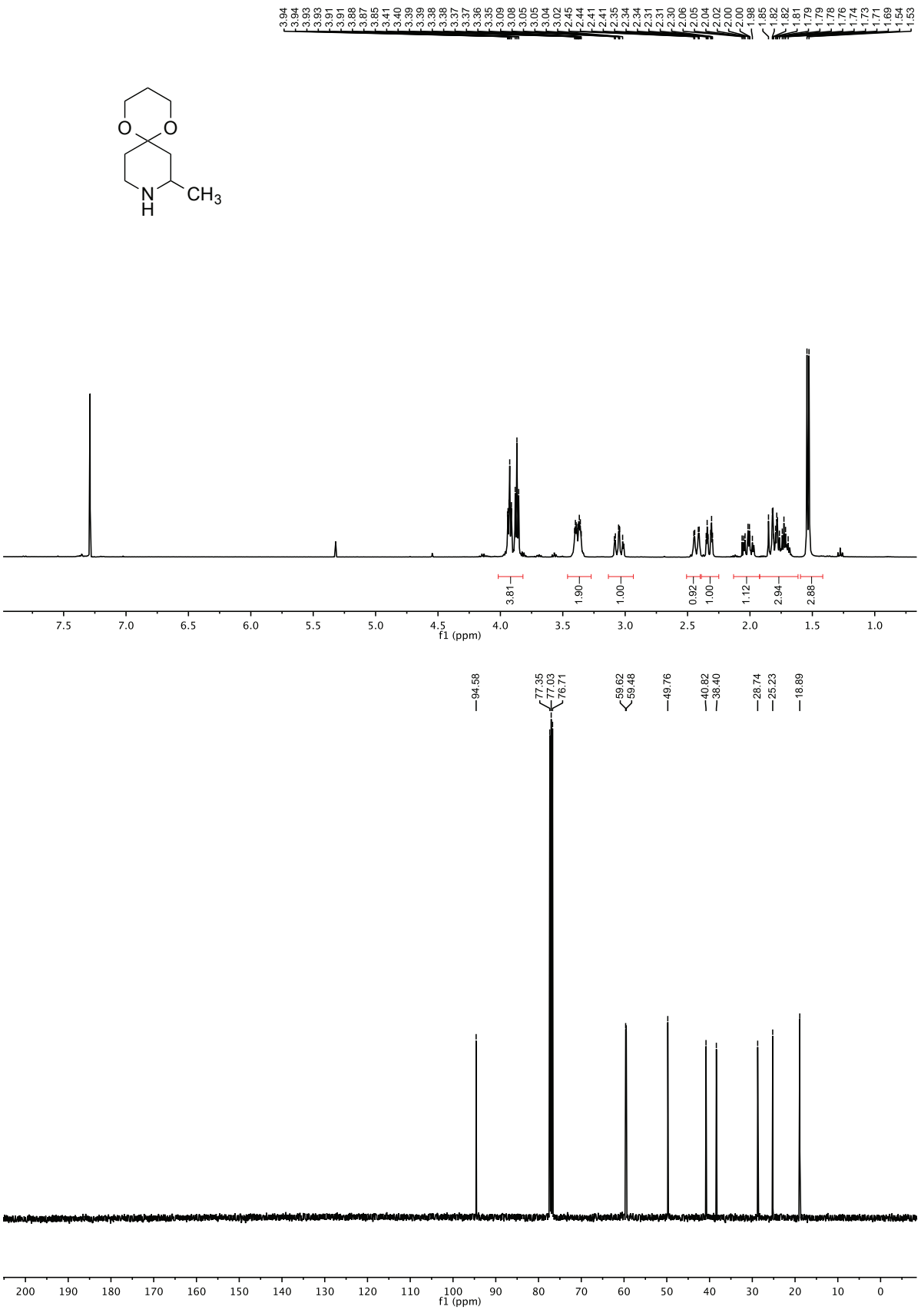
f1 (ppm)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3.08
3.05
3.05
3.04
3.02
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2.31
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2.06
2.05
2.04
2.02
2.00
2.00
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1.82
1.81
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1.74
1.73
1.71
1.69
1.54
1.53
O
O
N
H
CH3
3.81
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1.00
0.92
1.00
1.12
2.94
2.88
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
94.58
77.35
77.03
76.71
59.62
59.48
49.76
40.82
38.40
28.74
25.23
18.89
200
190
180
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120
110
100
90
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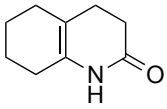
50
40
30
20
10
0
f1 (ppm)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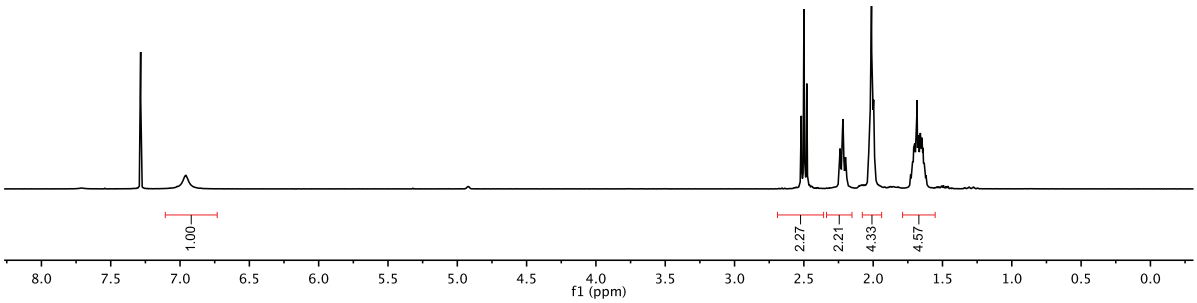
H
O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7.0
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6.0
5.5
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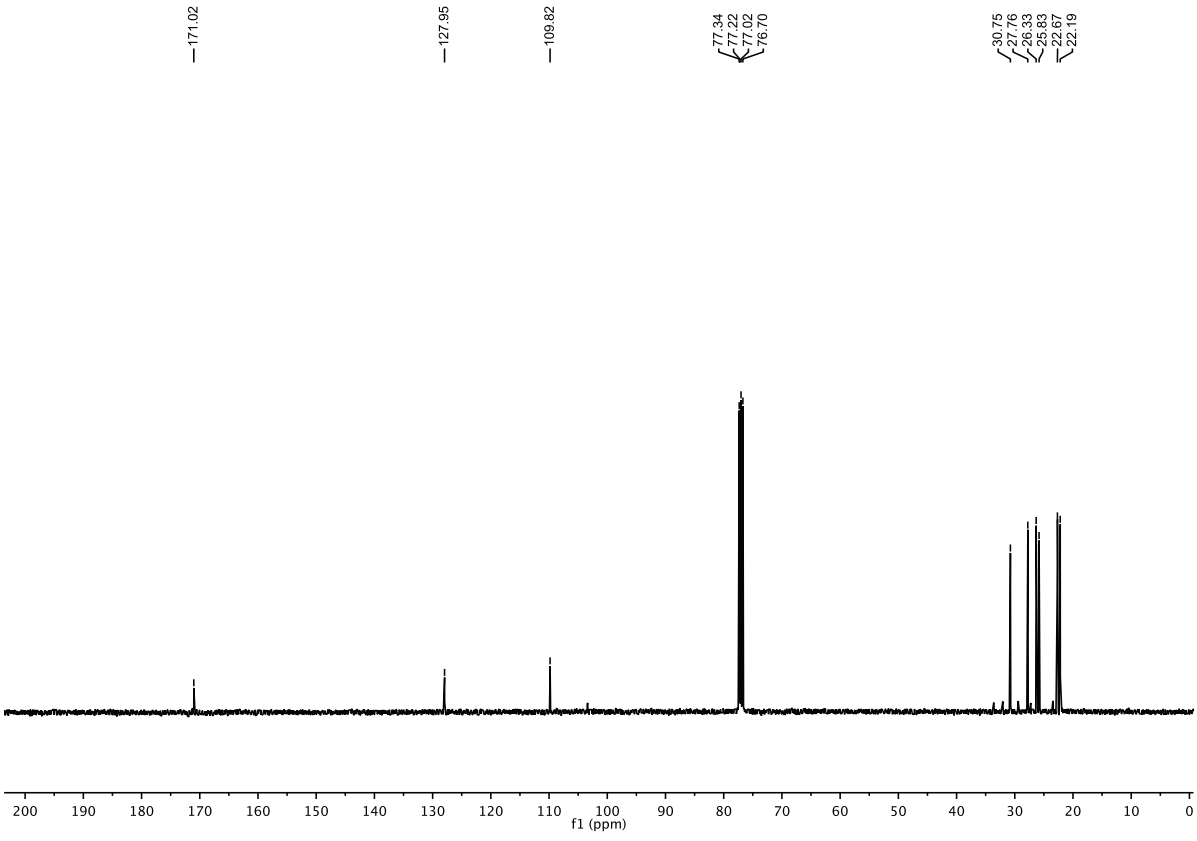
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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127.95
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30.75
27.76
26.33
25.83
22.67
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200
190
180
170
160
150
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130
120
110
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90
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50
40
30
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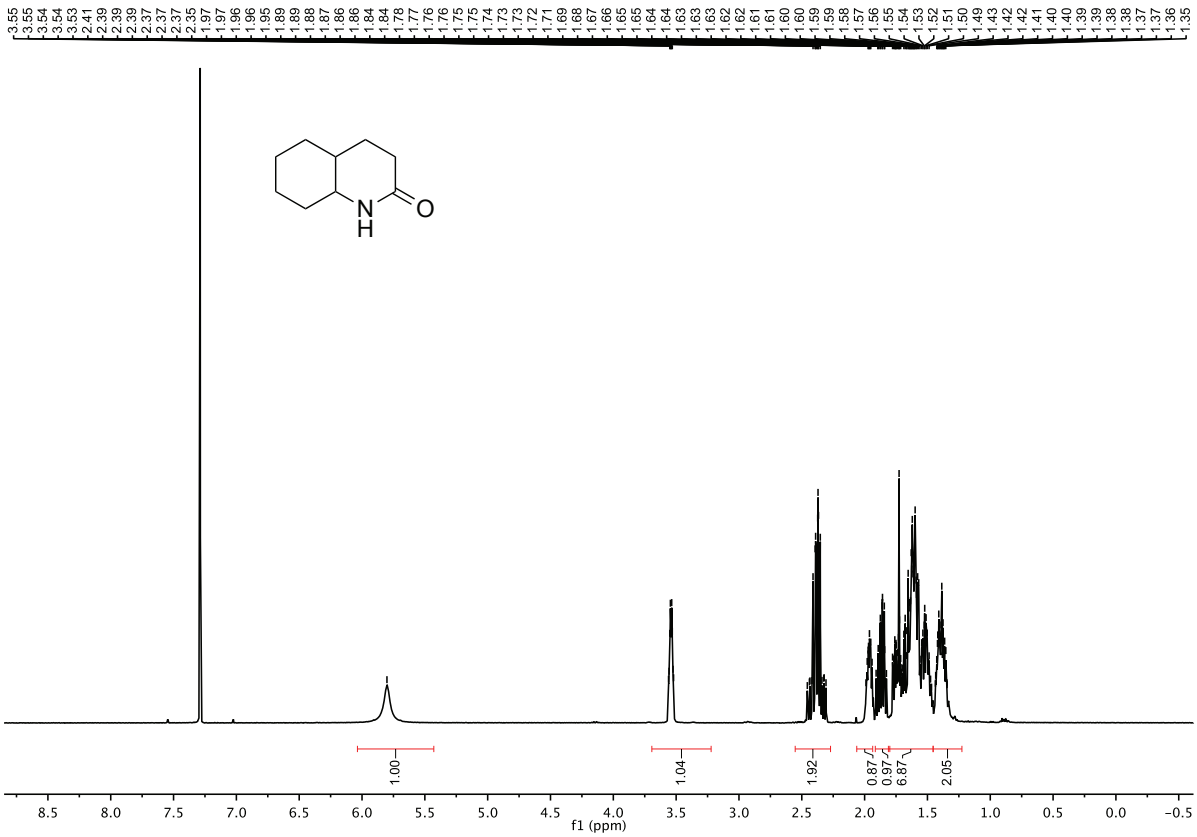
10
0
f1 (ppm)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H
O
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1.92
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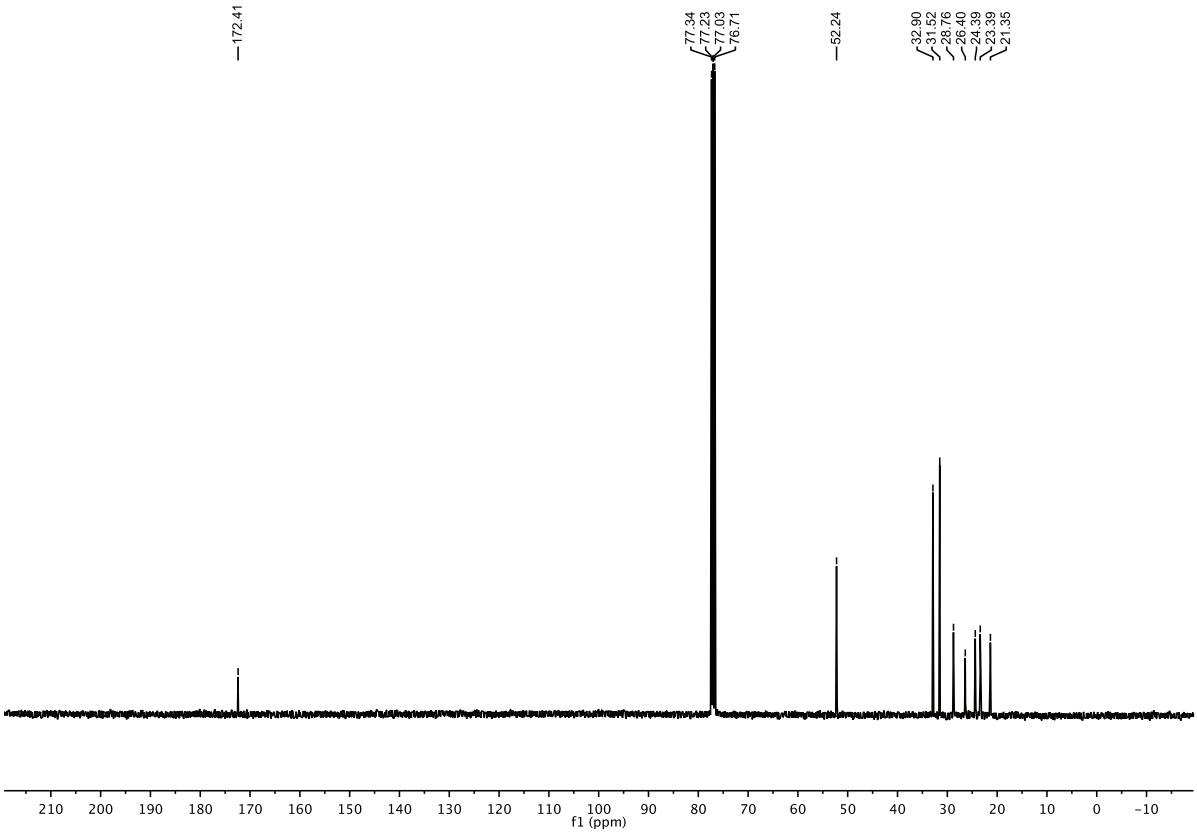
0.97
6.87
2.05
f1 (ppm)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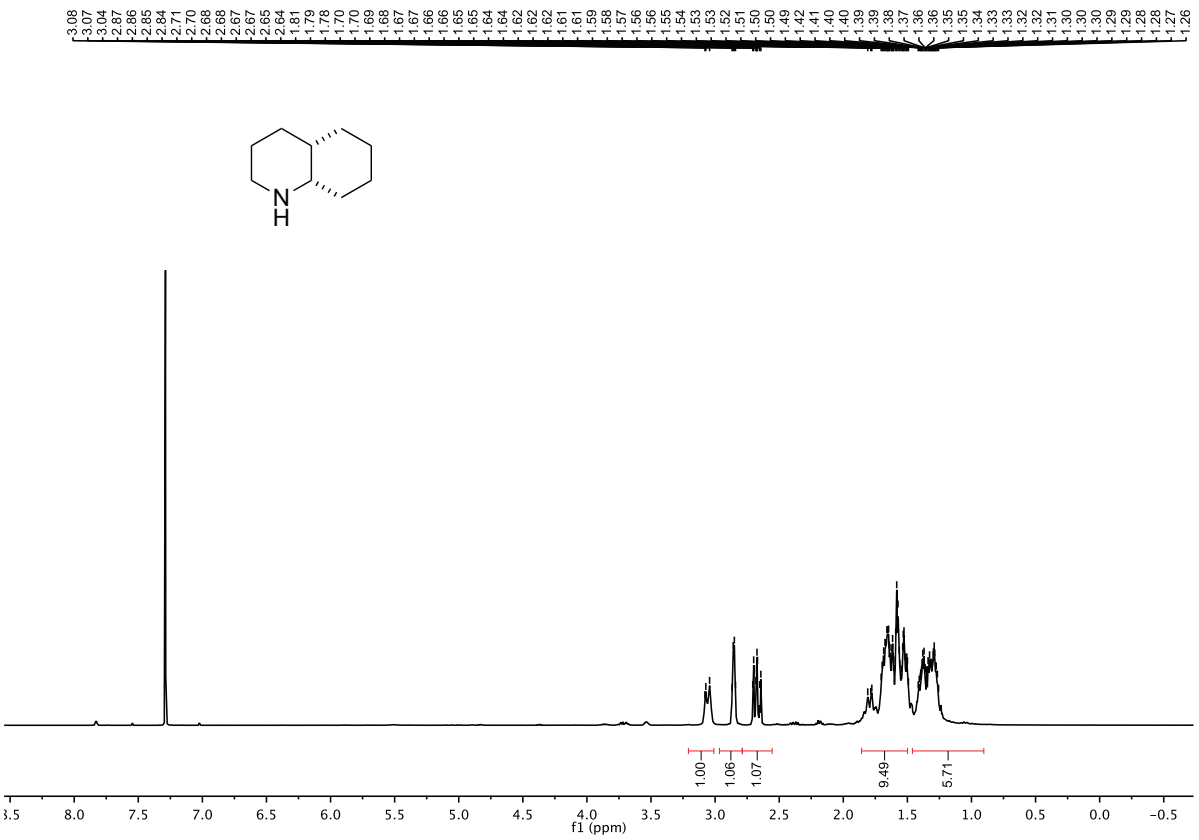
31.52
28.76
26.40
24.39
23.39
21.35
f1 (ppm)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N
H
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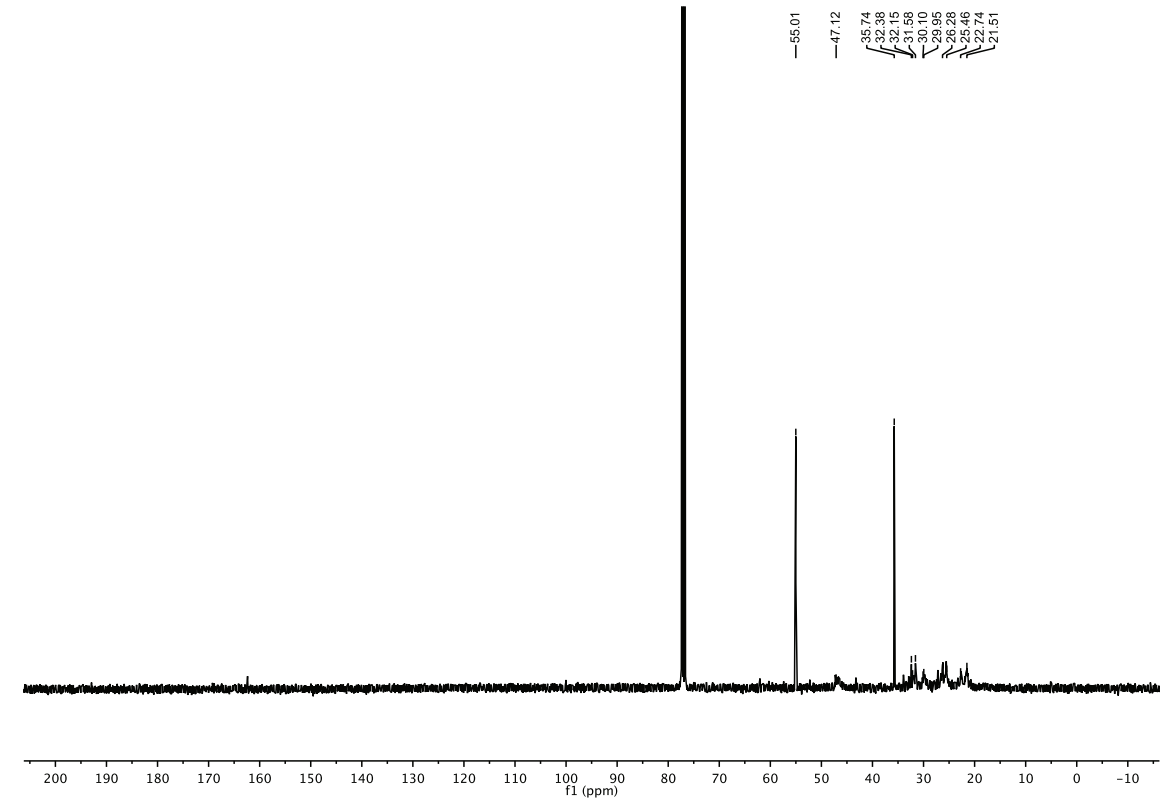
1.06
1.07
9.49
5.71
f1 (ppm)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26.28
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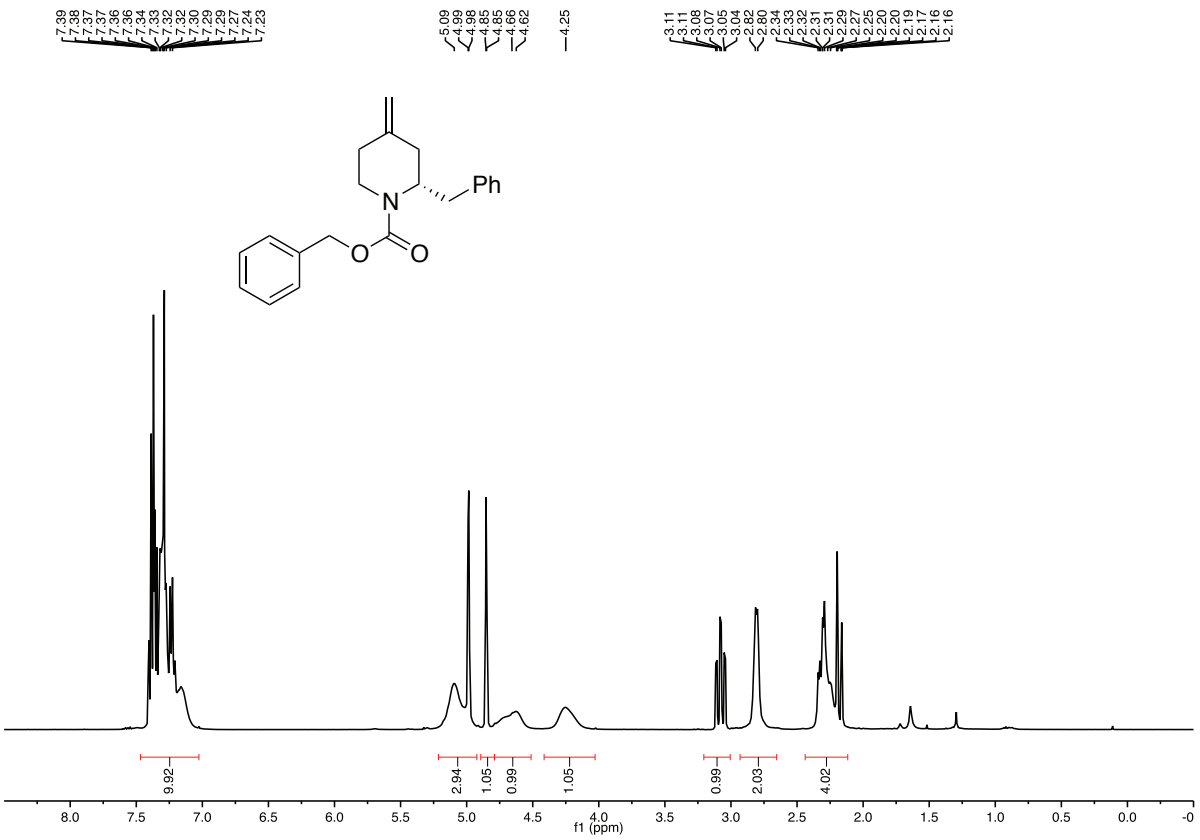
22.74
21.51
f1 (ppm)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7.27
7.24
7.23
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4.98
4.85
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4.62
4.25
3.11
3.11
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2.80
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2.31
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2.27
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2.20
2.20
2.19
2.17
2.16
2.16
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O
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0.99
1.05
0.99
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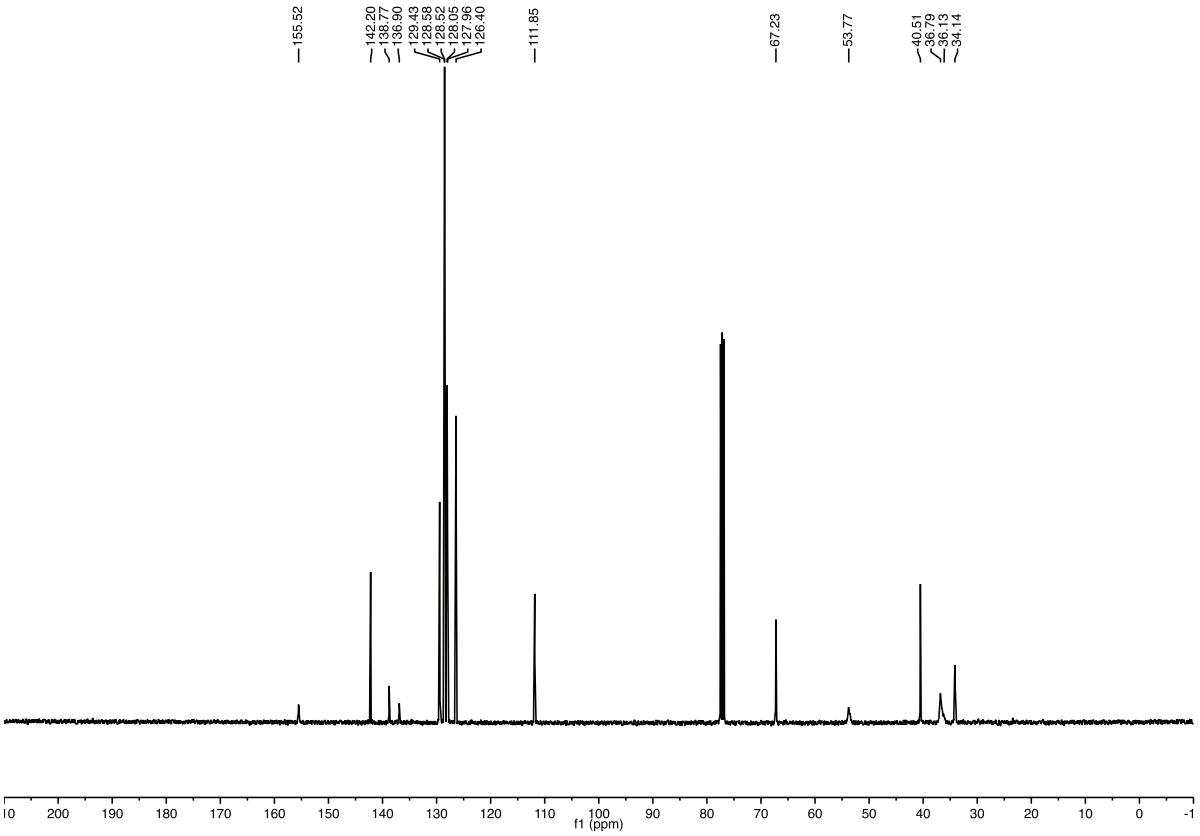
f1 (ppm)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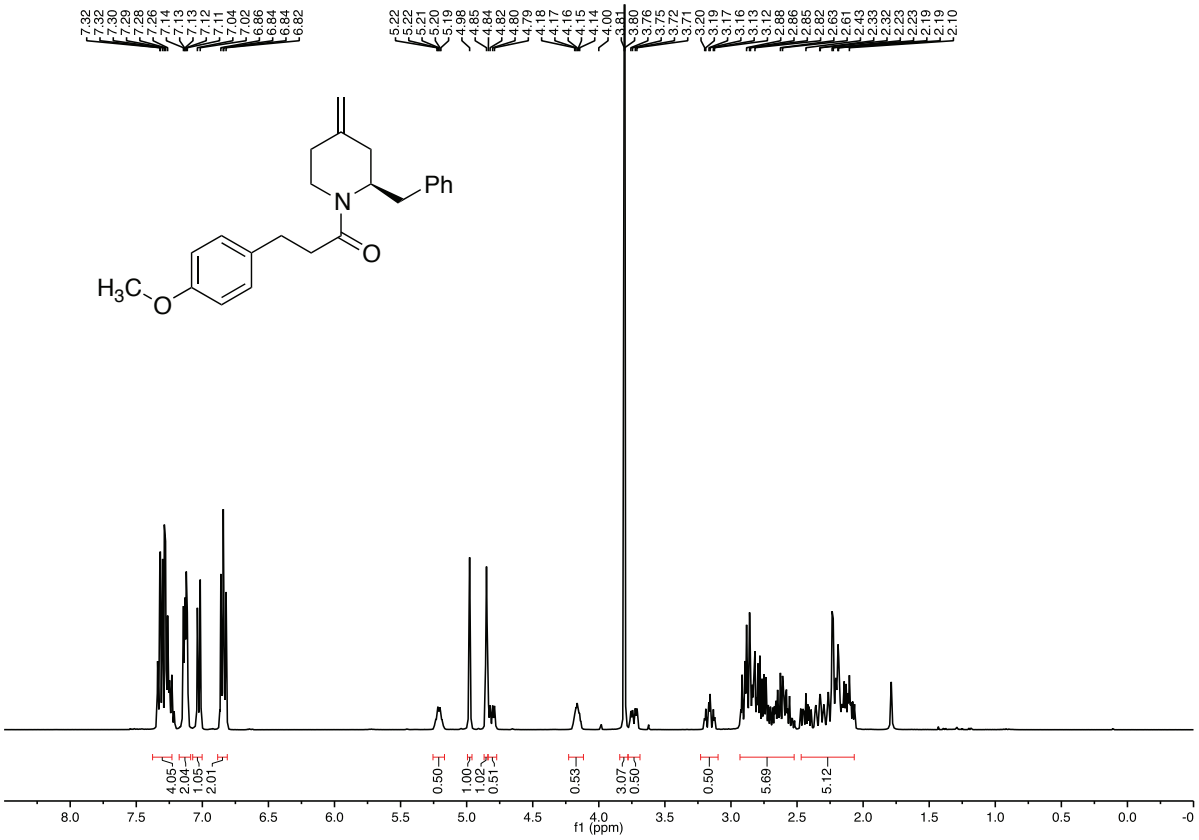
36.13
34.14
f1 (ppm)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7.02
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6.84
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6.82
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5.19
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4.82
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4.14
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3.75
3.72
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3.19
3.17
3.16
3.13
3.12
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2.85
2.82
2.63
2.61
2.43
2.33
2.32
2.23
2.19
2.19
2.10
Ph
N
O
H3C
O
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2.04
1.05
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1.02
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0.53
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0.50
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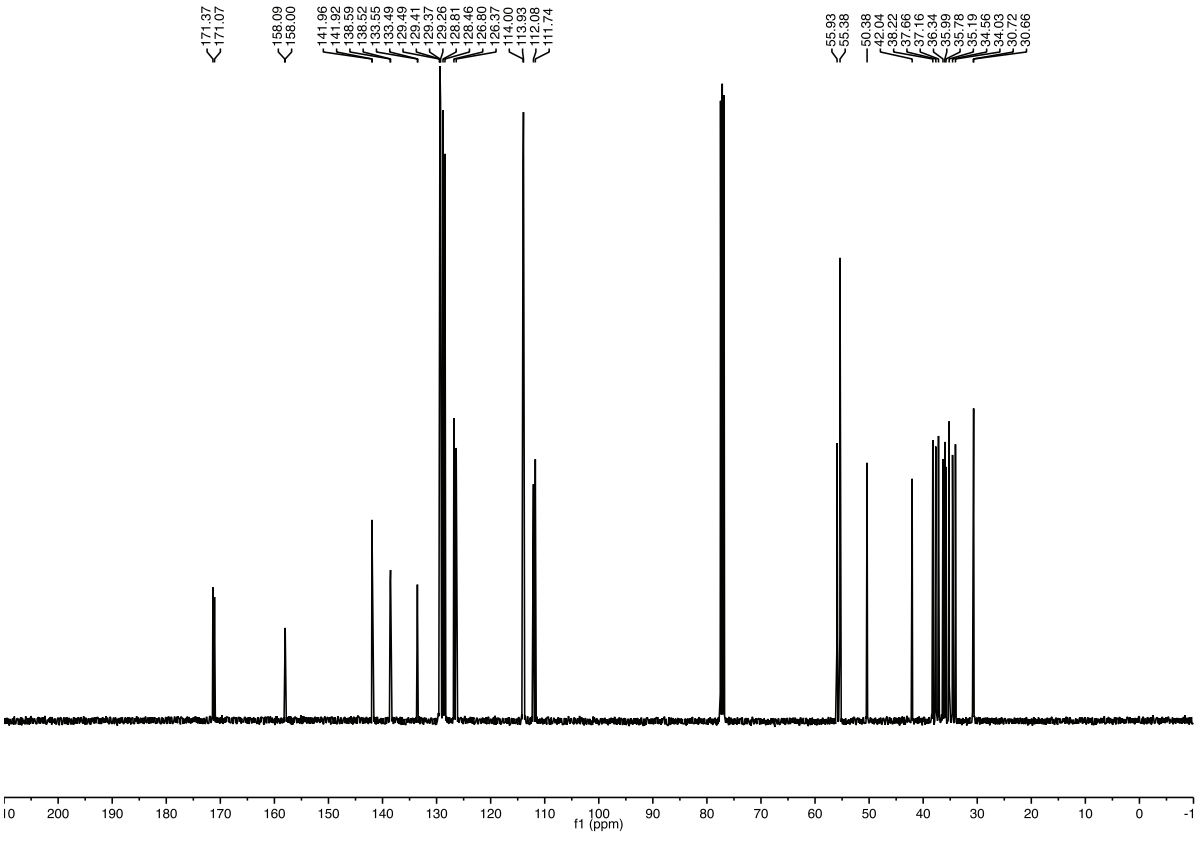
f1 (ppm)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129.49
129.41
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128.81
128.46
126.80
126.37
114.00
113.93
112.08
111.74
55.93
55.38
50.38
42.04
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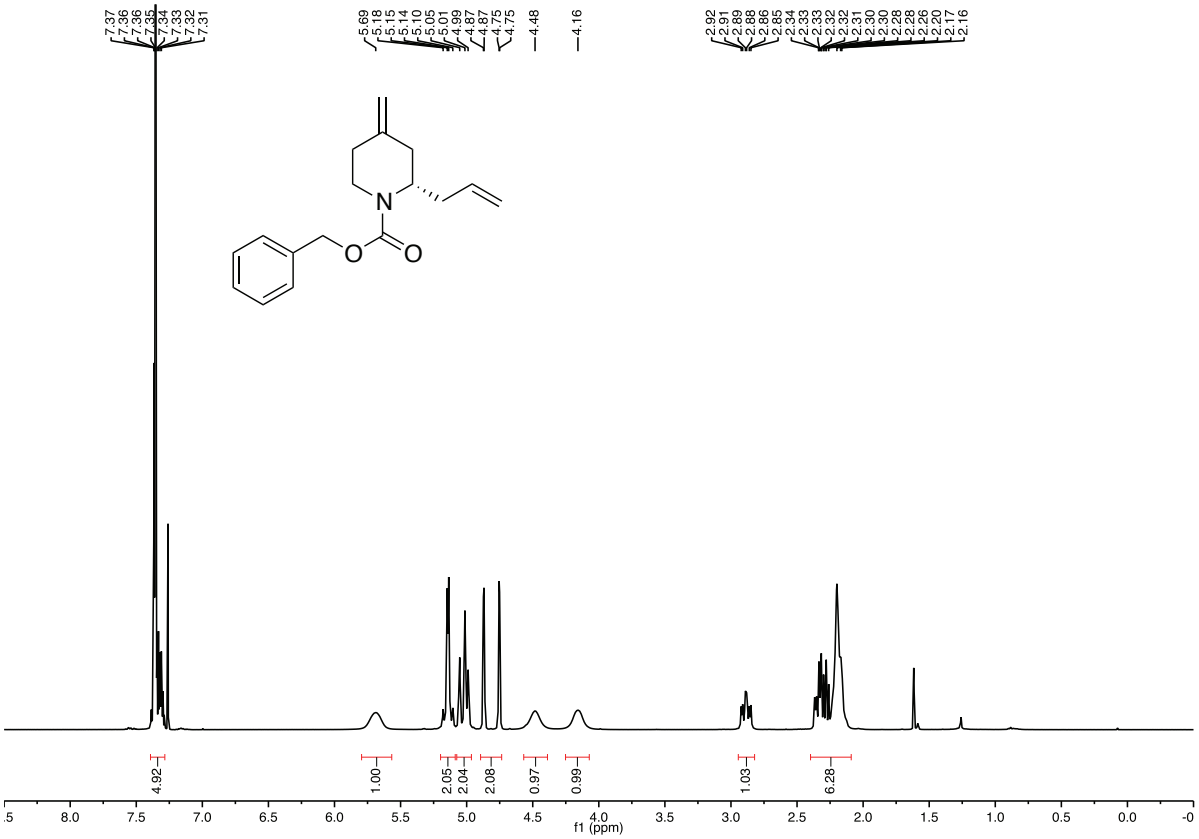
30.66
f1 (ppm)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2.20
2.17
2.16
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2.08
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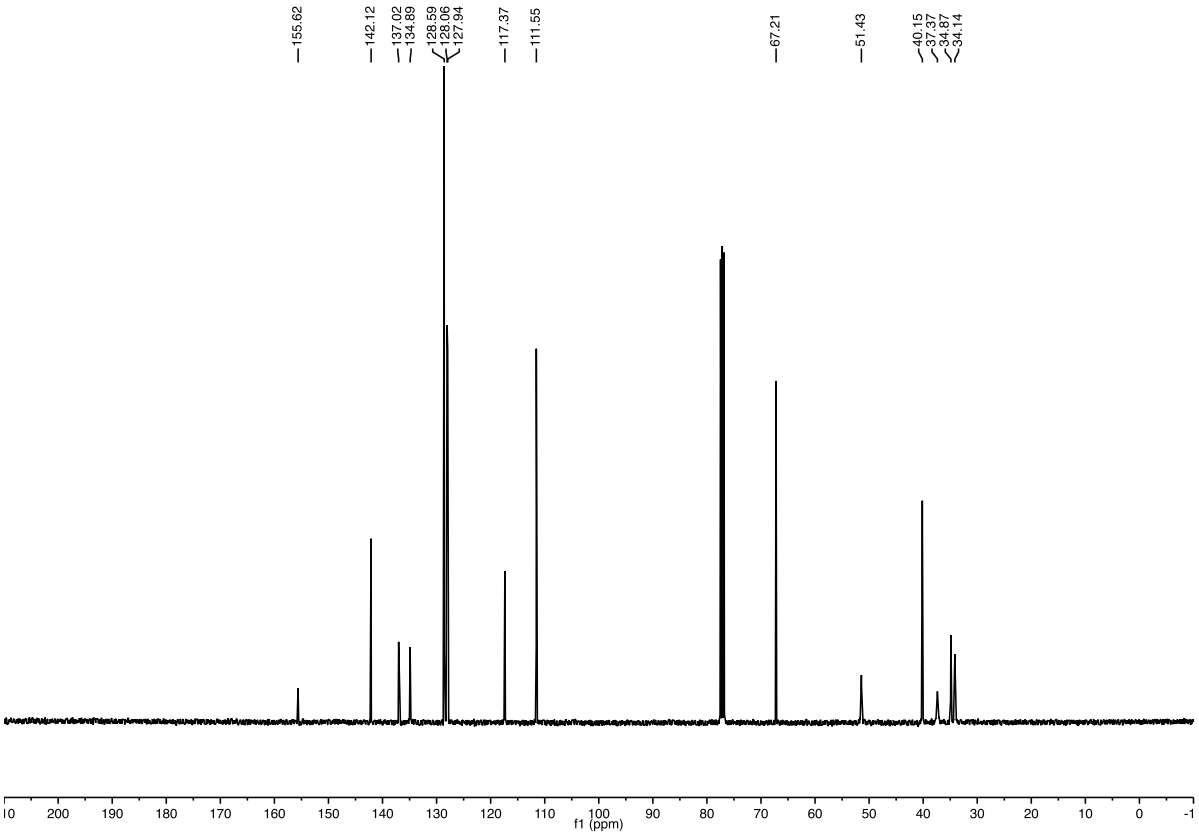
0.99
1.03
6.28
f1 (ppm)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37.37
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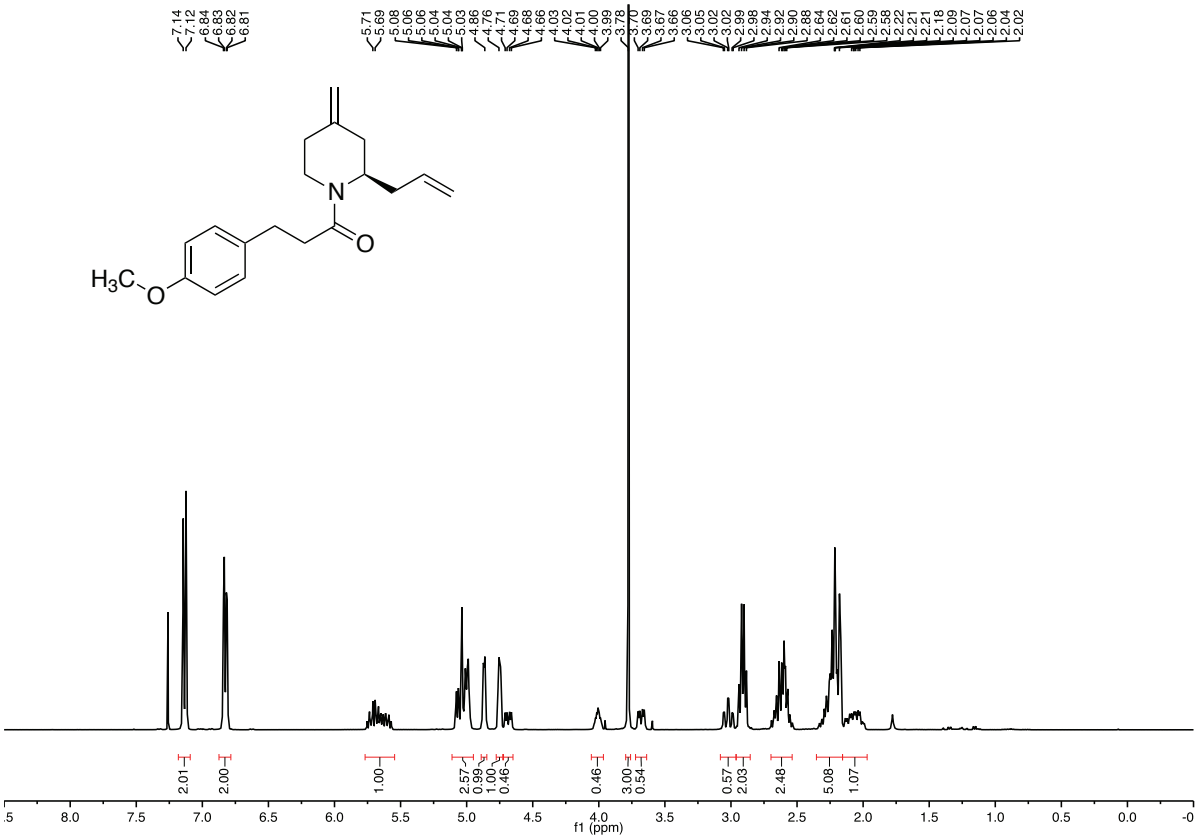
34.14
f1 (ppm)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2.07
2.07
2.06
2.04
2.02
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H3C
O
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2.00
1.00
2.57
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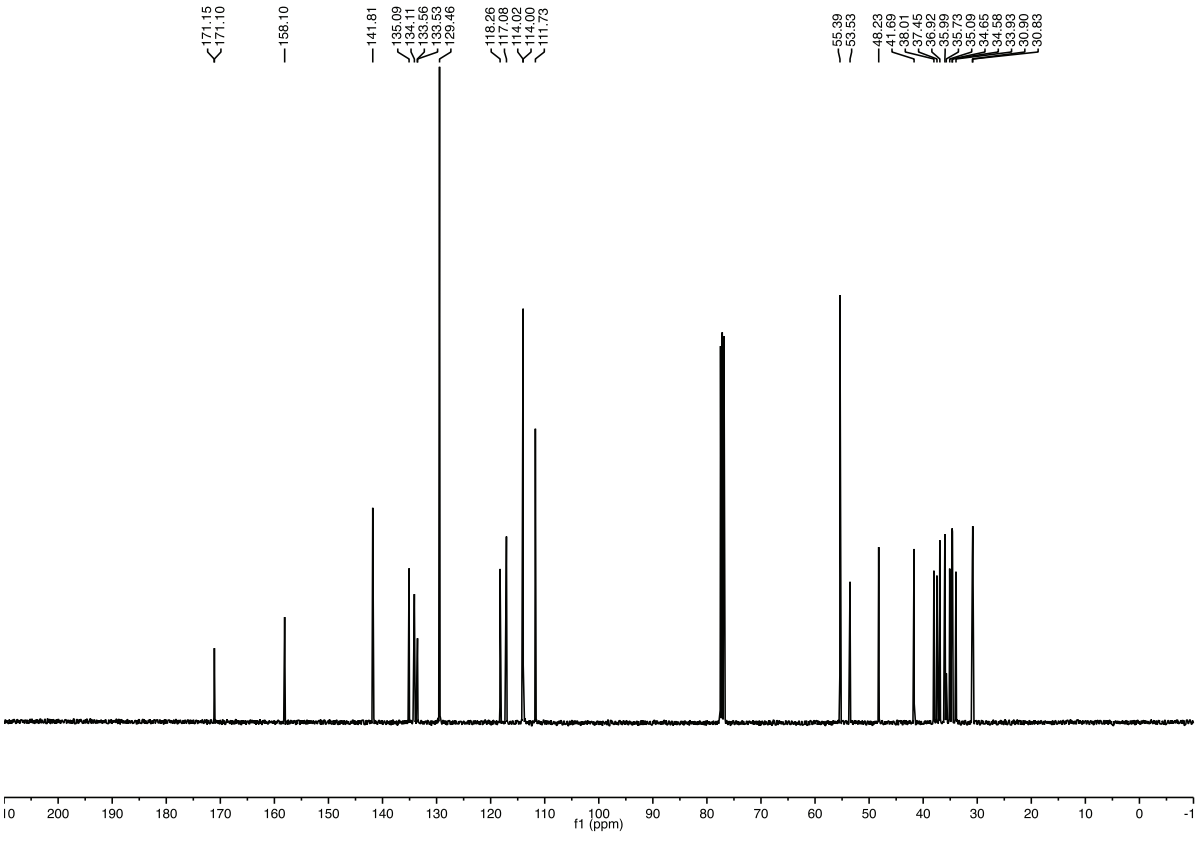
1.07
f1 (ppm)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53.53
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41.69
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33.93
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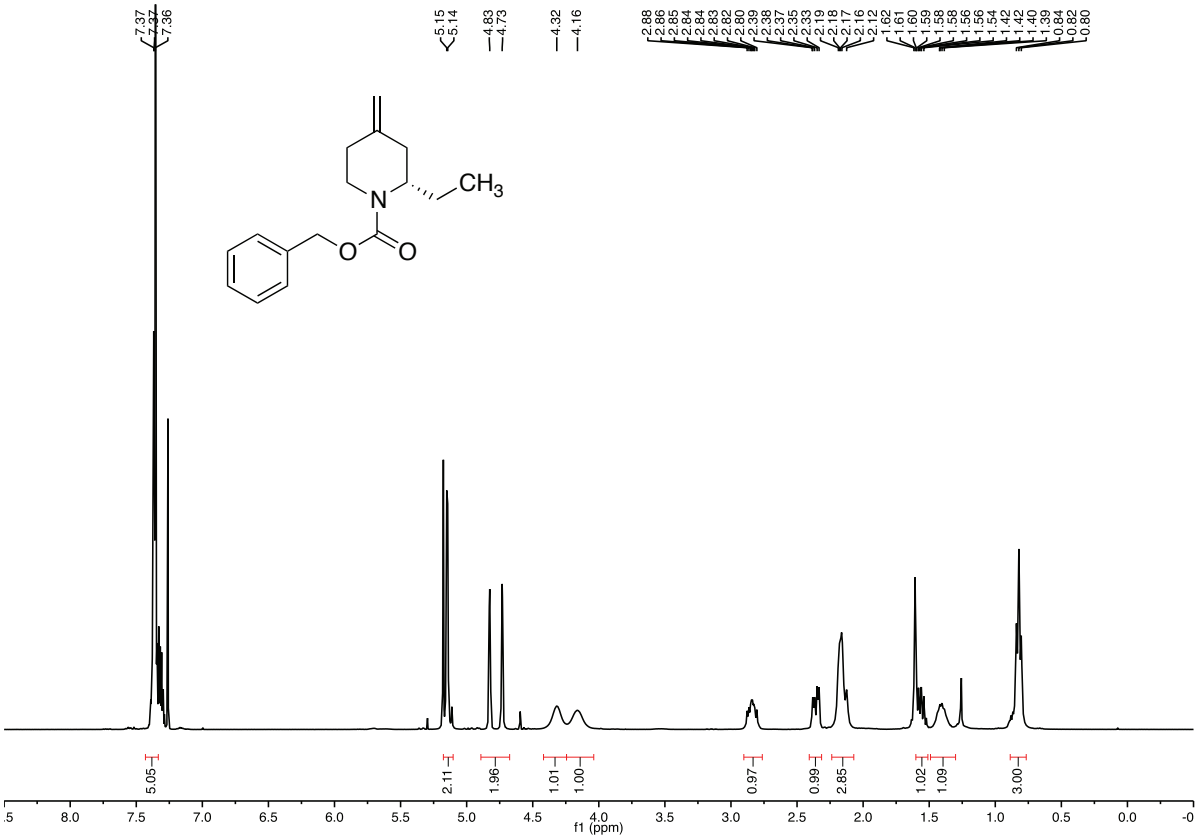
30.83
f1 (ppm)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0.82
0.80
CH3
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O
O
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2.11
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1.01
1.00
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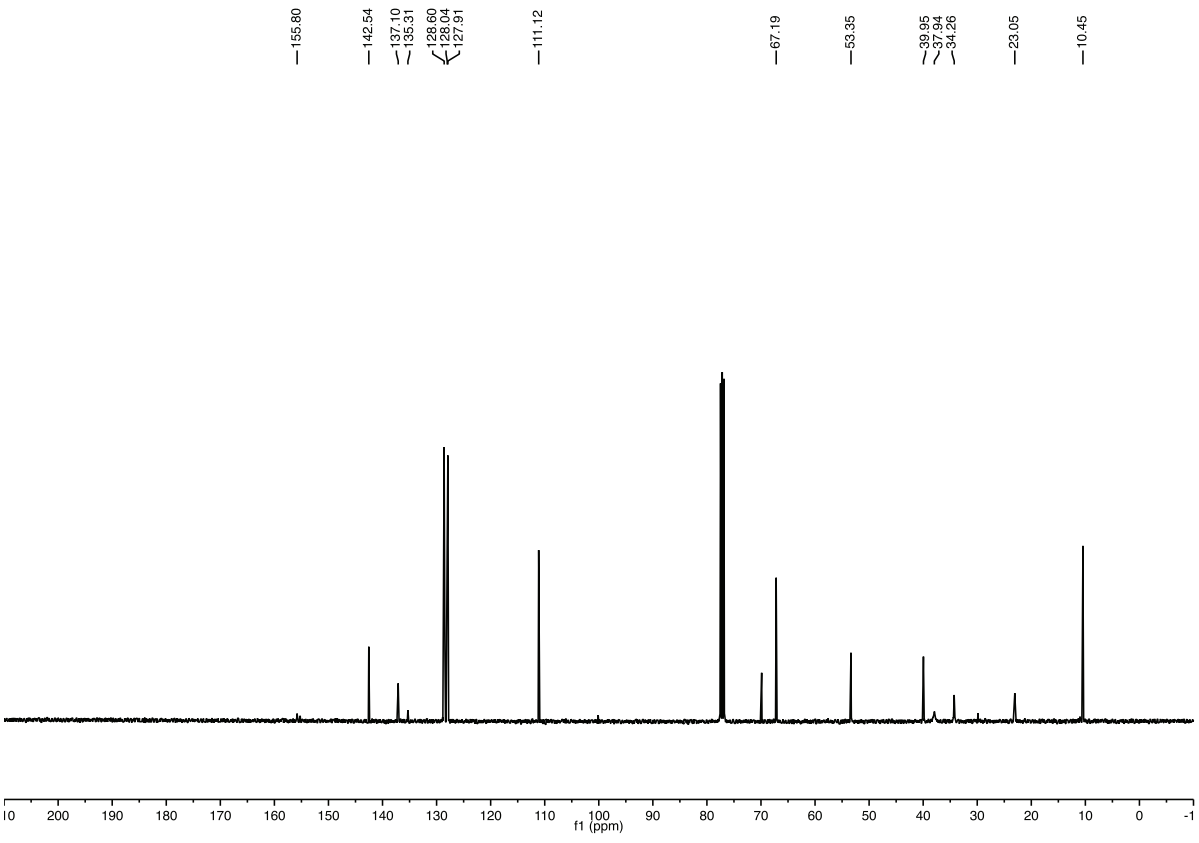
0.99
2.85
1.02
1.09
3.00
f1 (ppm)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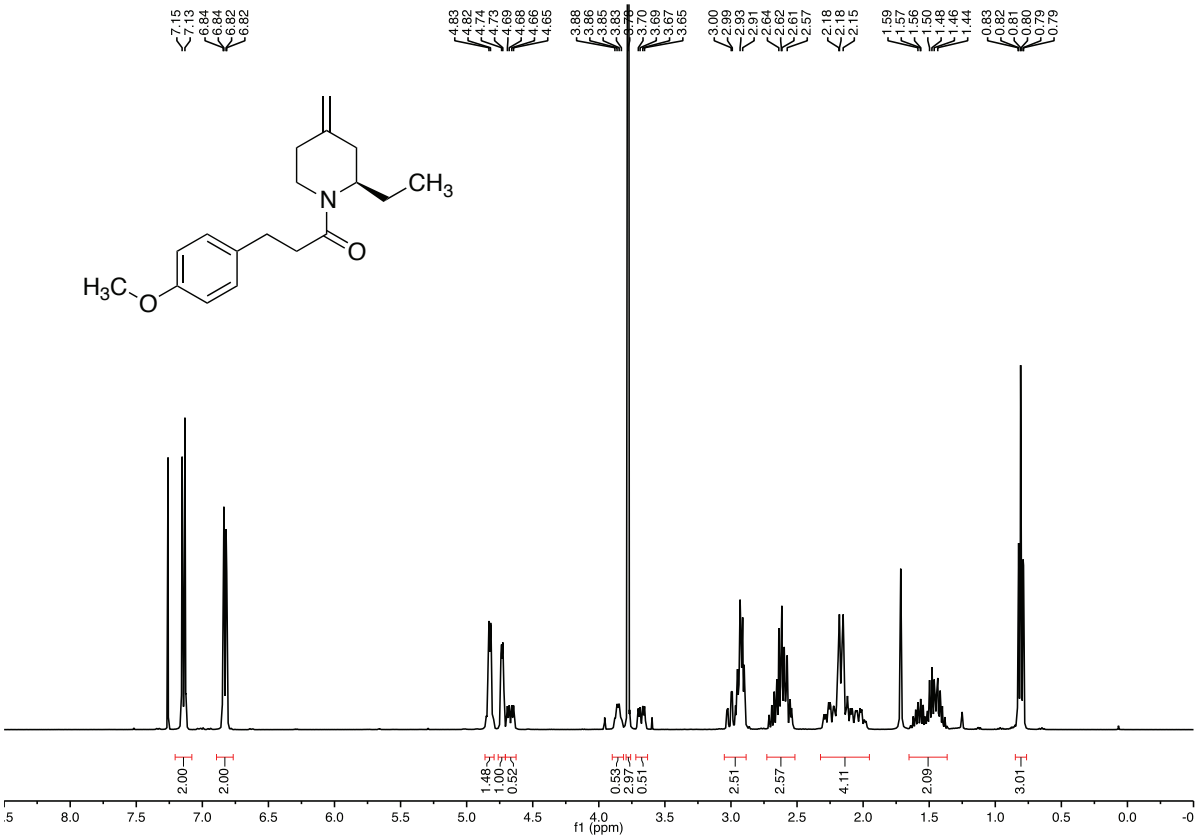
f1 (ppm)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4.65
3.88
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3.85
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2.64
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2.61
2.57
2.18
2.18
2.15
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1.57
1.56
1.50
1.48
1.46
1.44
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0.82
0.81
0.80
0.79
0.79
CH3
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O
H3C
O
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2.00
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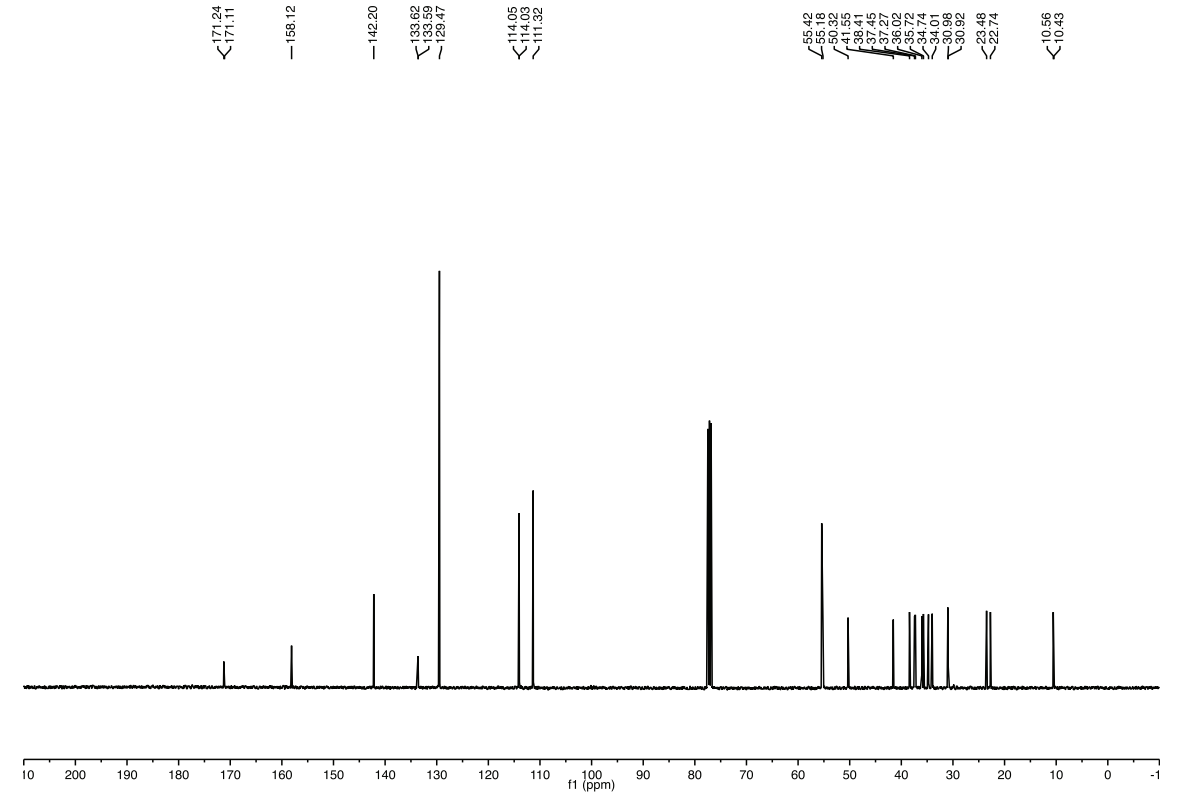
f1 (ppm)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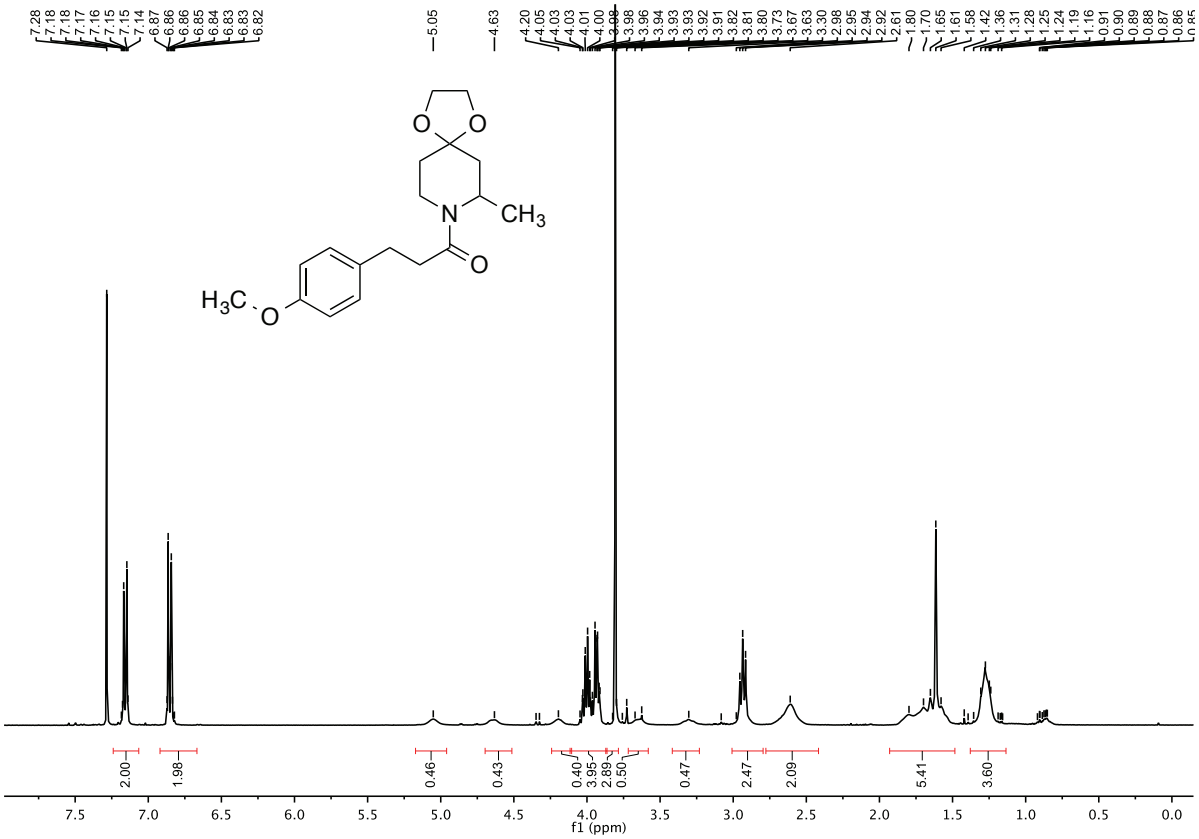
f1 (ppm)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6.83
6.82
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3.91
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3.80
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3.67
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2.94
2.92
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O
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CH3
O
H3C
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3.95
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3.60
7.5
7.0
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6.0
5.5
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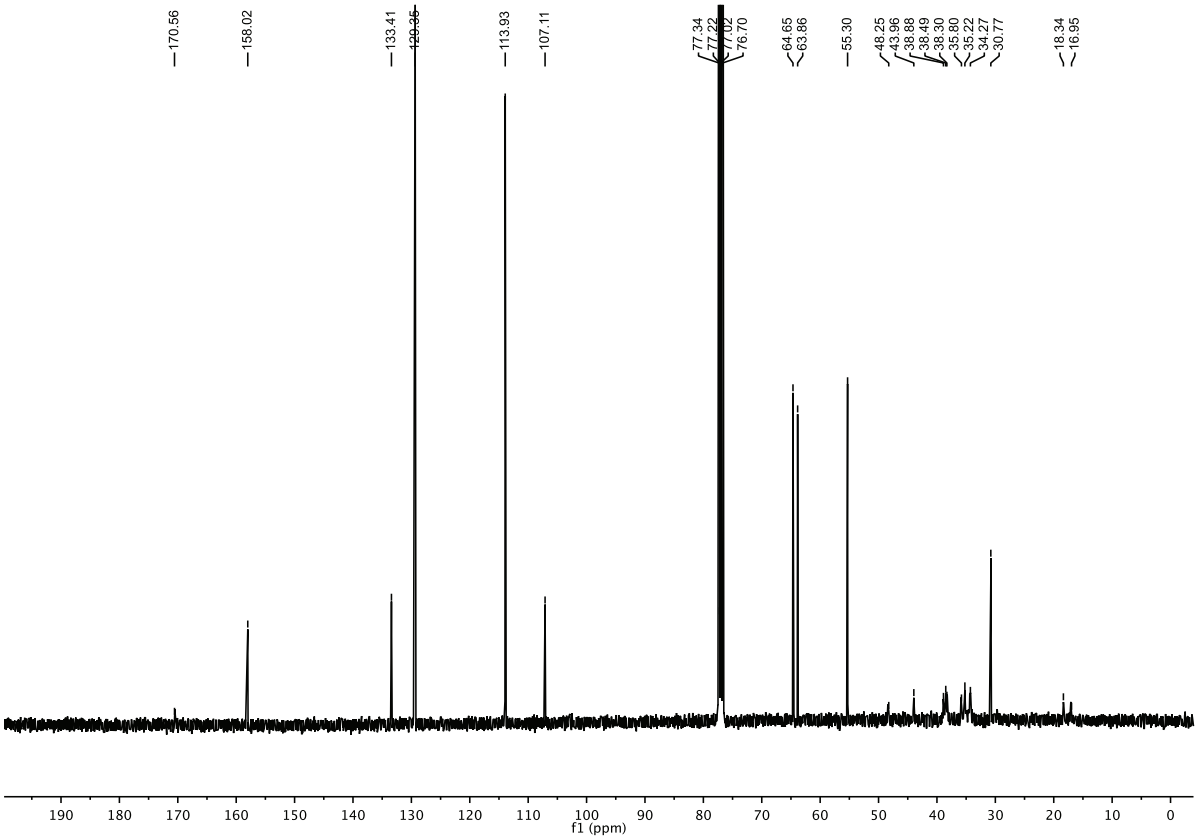
f1 (ppm)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180
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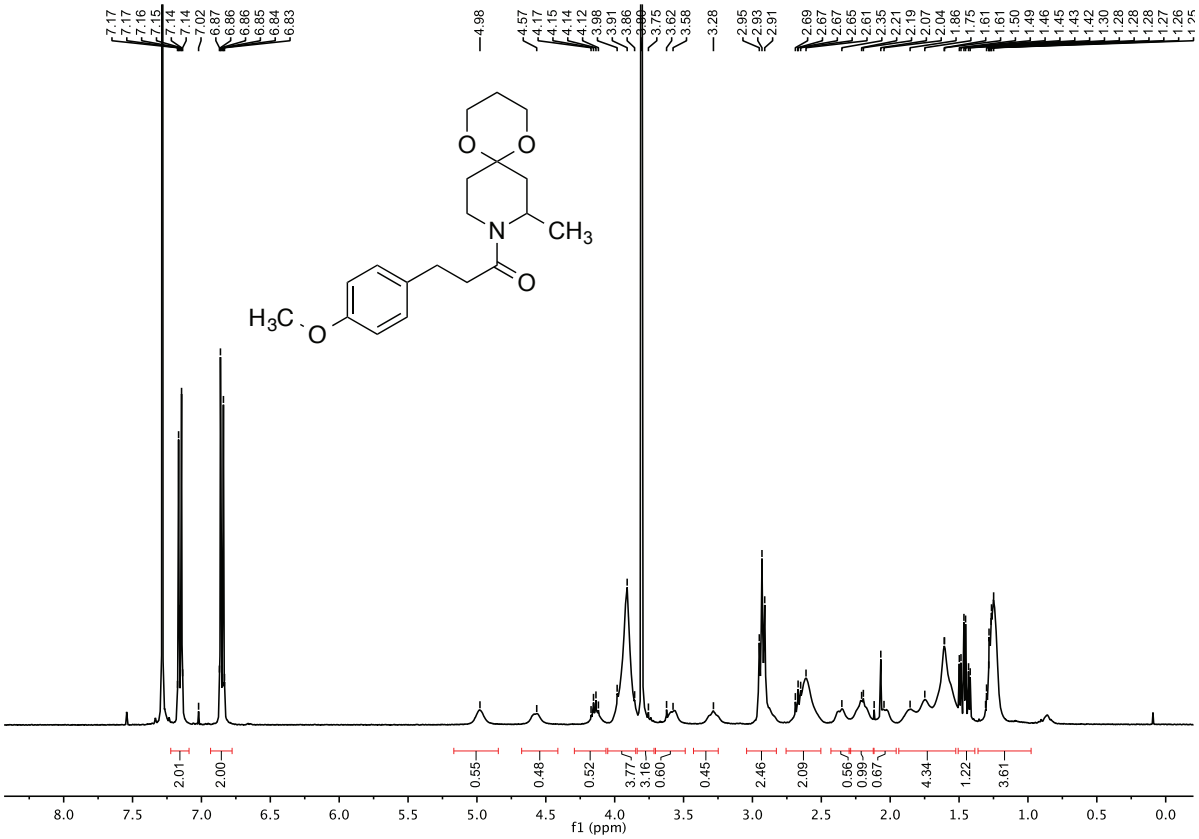
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6.83
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4.15
4.14
4.12
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1.45
1.43
1.42
1.30
1.28
1.28
1.27
1.26
O
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CH3
O
H3C
O
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3.77
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0.45
2.46
2.09
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1.22
3.61
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6.0
5.5
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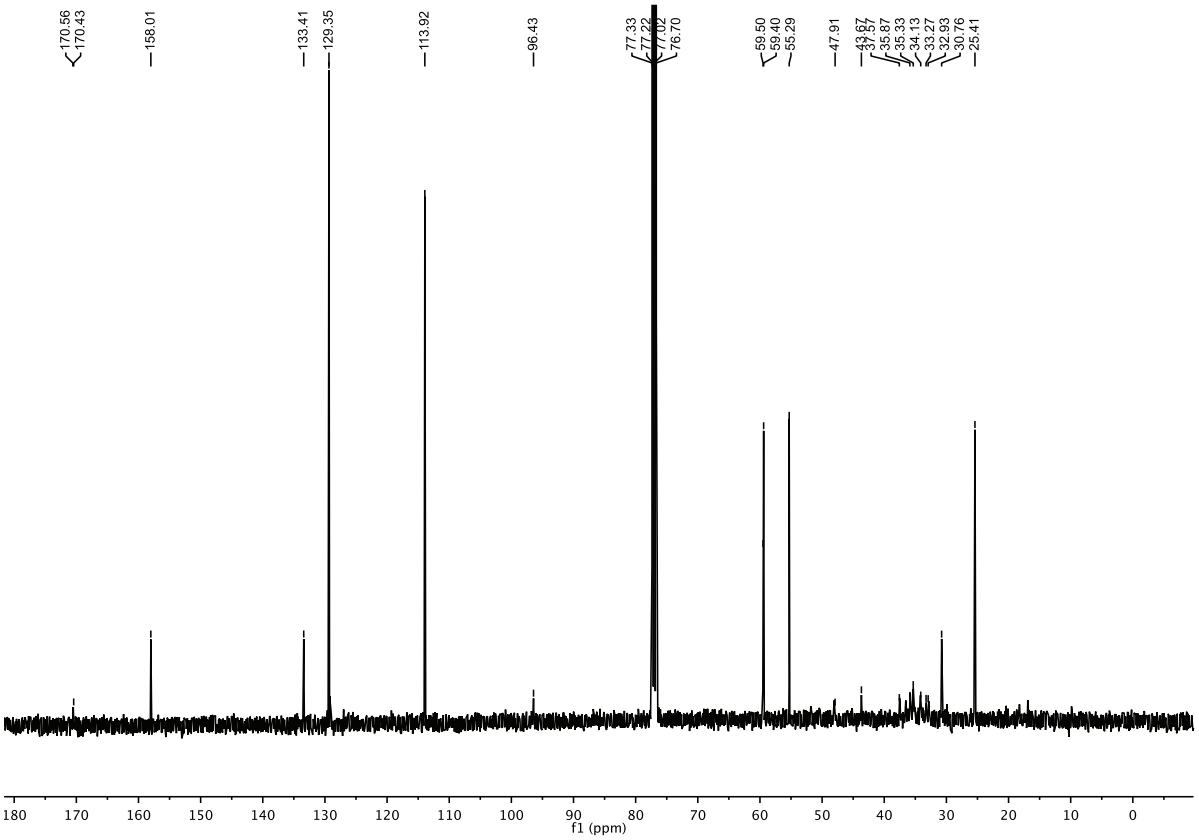
0.0
f1 (ppm)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35.87
35.33
34.13
33.27
32.93
30.76
25.41
180
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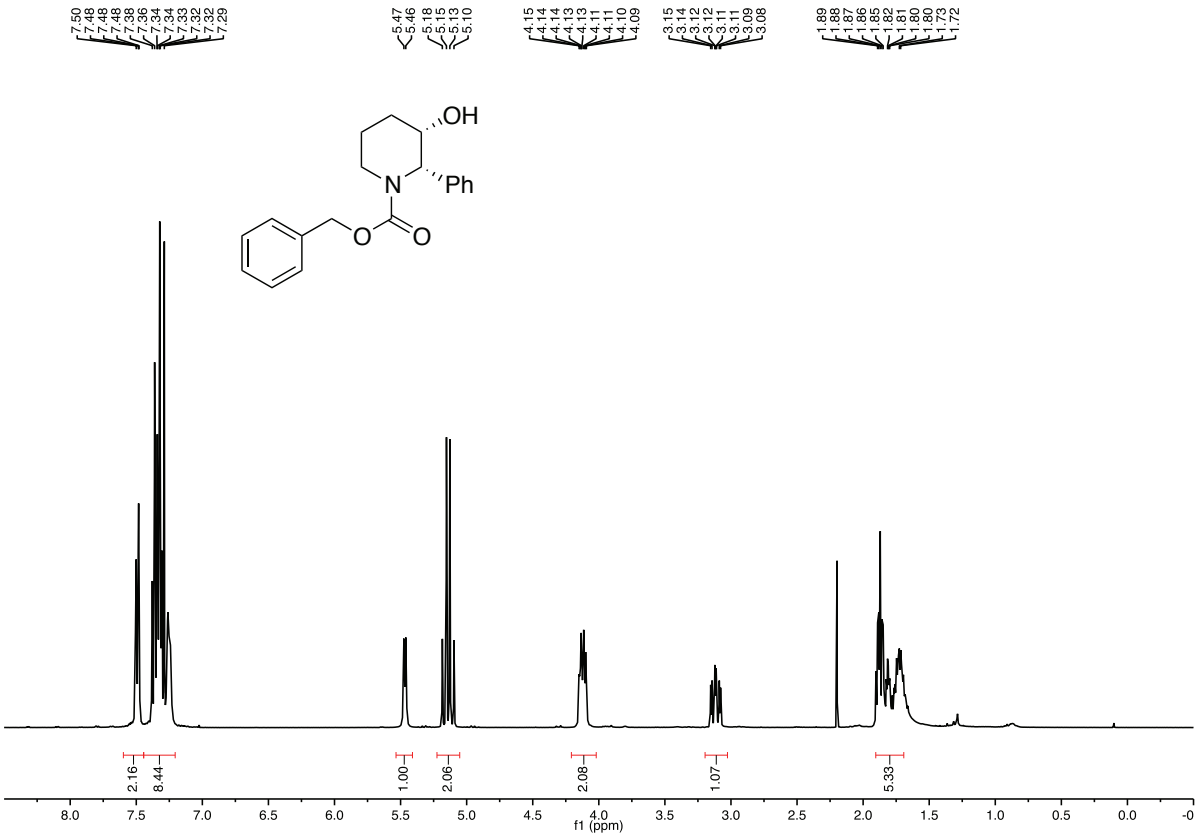
f1 (ppm)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5.46
5.18
5.15
5.13
5.10
4.15
4.14
4.14
4.13
4.11
4.11
4.10
4.09
3.15
3.14
3.12
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1.88
1.87
1.86
1.85
1.82
1.81
1.80
1.80
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2.08
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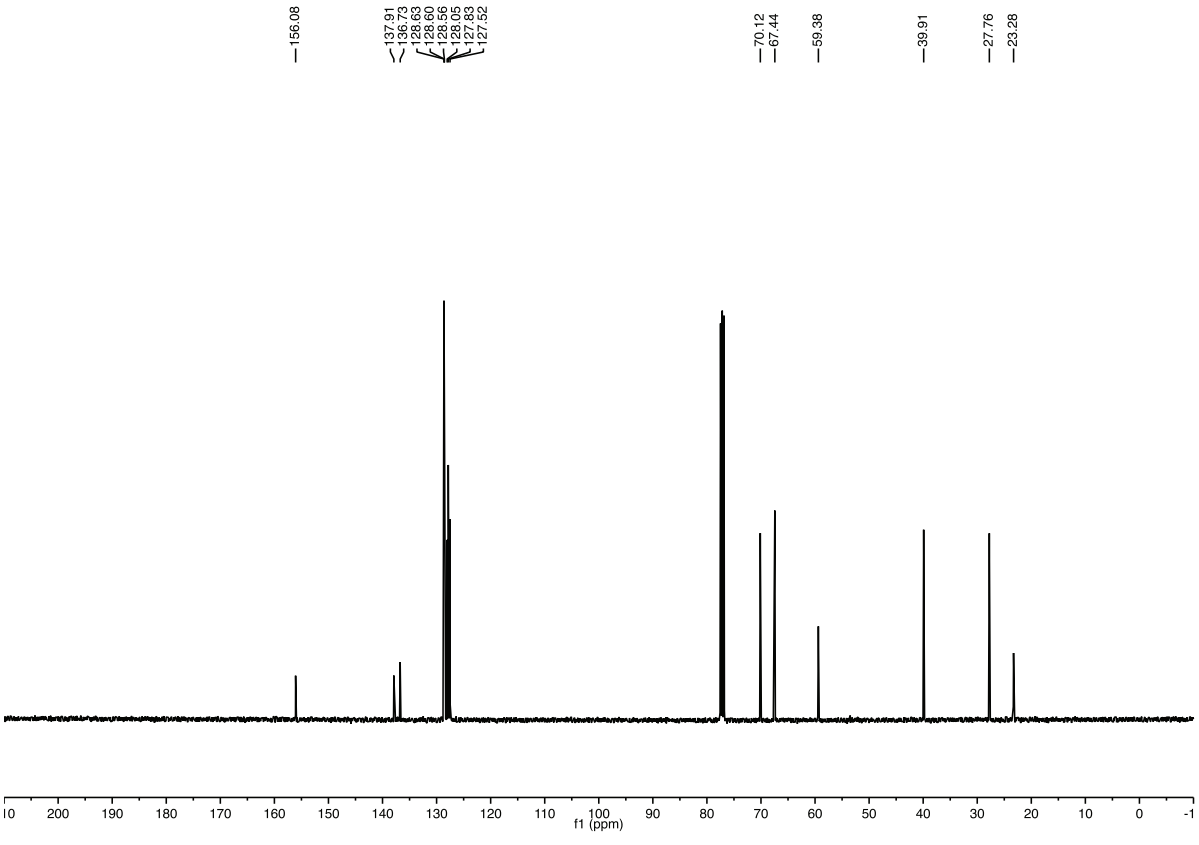
5.33
f1 (ppm)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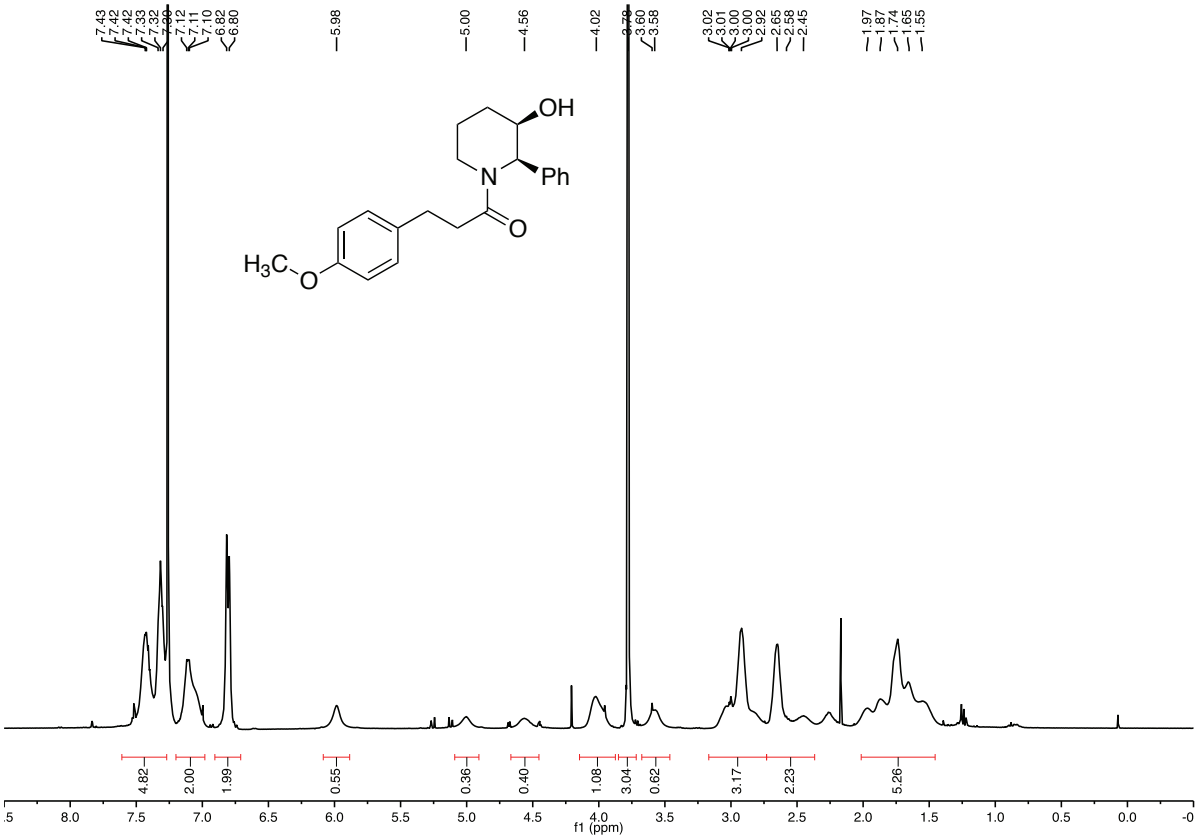
23.28
f1 (ppm)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5.00
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4.02
3.78
3.60
3.58
3.02
3.01
3.00
3.00
2.92
2.65
2.58
2.45
1.97
1.87
1.74
1.65
1.55
OH
Ph
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O
H3C
O
4.82
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0.40
1.08
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0.62
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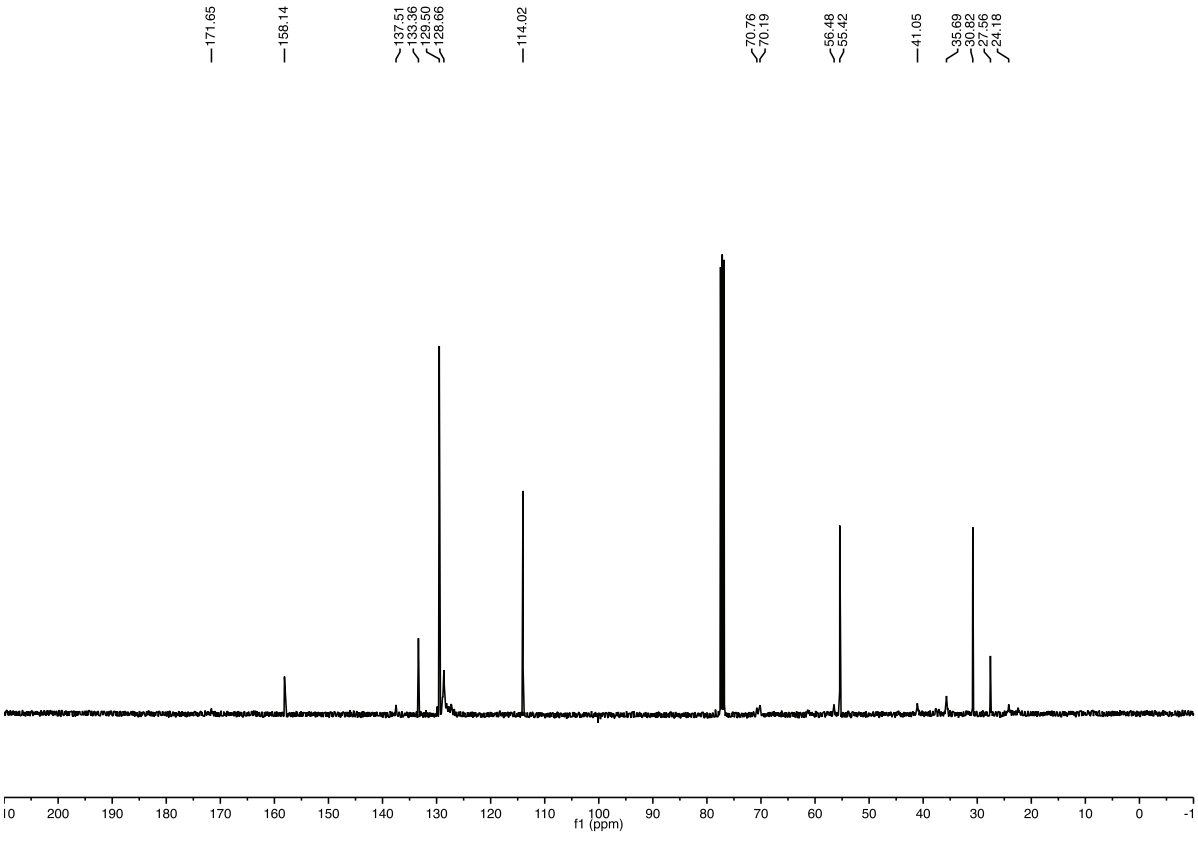
2.23
5.26
f1 (ppm)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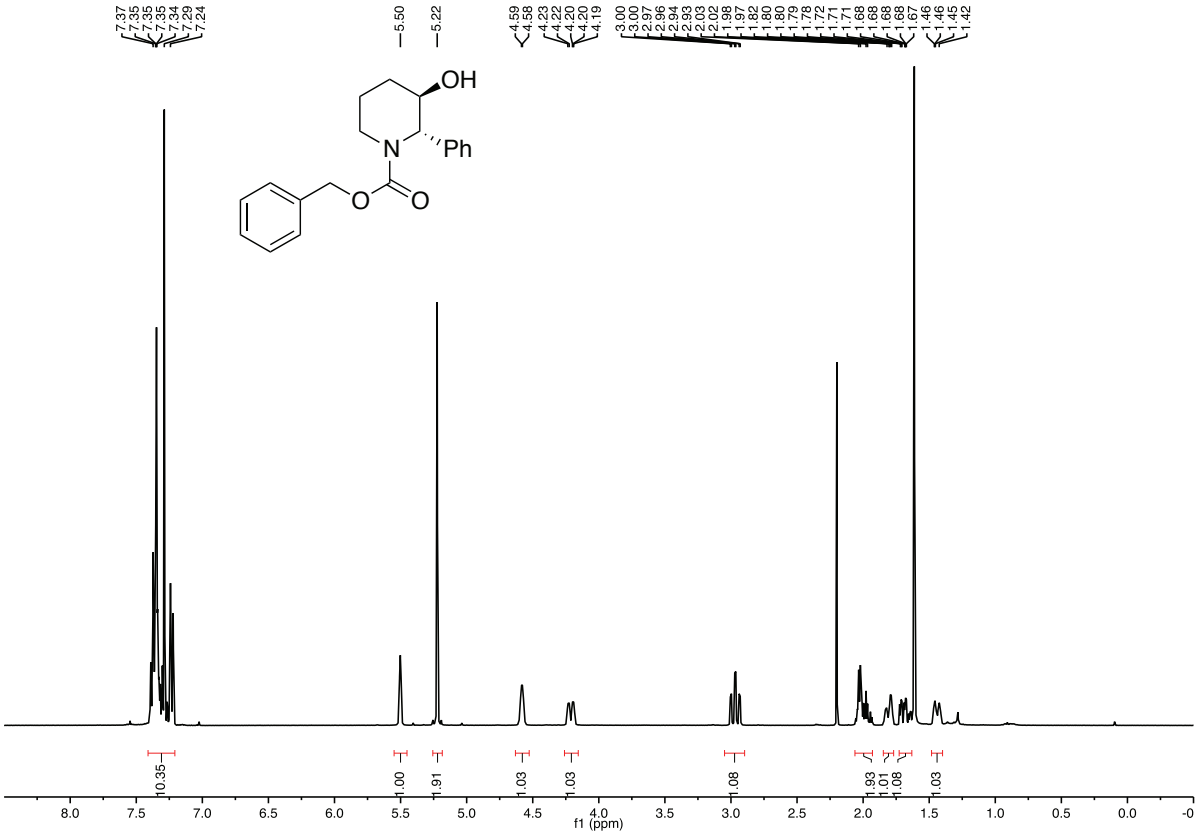
41.05
35.69
30.82
27.56
24.18
f1 (ppm)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4.23
4.22
4.20
4.19
3.00
3.00
2.97
2.96
2.94
2.93
2.03
2.02
1.98
1.97
1.82
1.80
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1.72
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1.71
1.68
1.68
1.68
1.68
1.67
1.46
1.45
1.42
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Ph
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1.03
1.03
1.08
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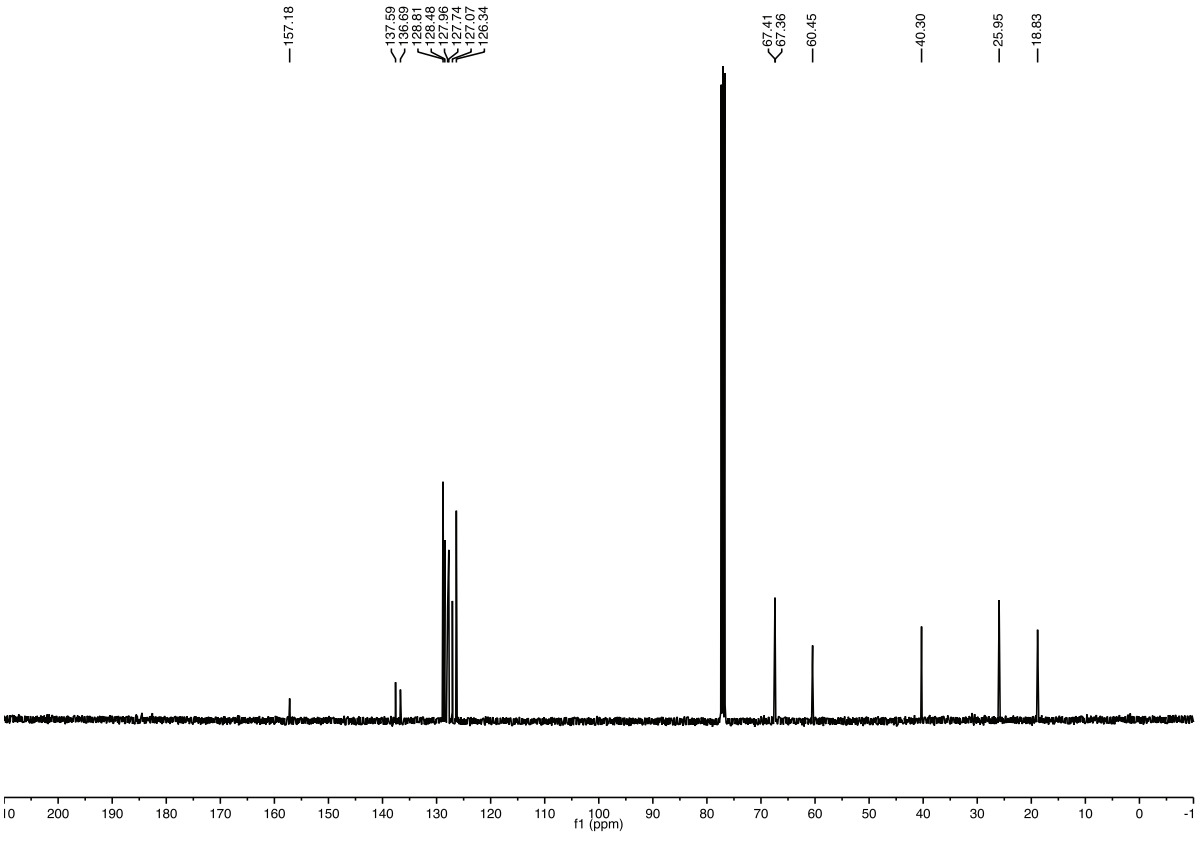
1.01
1.08
1.03
f1 (ppm)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40.30
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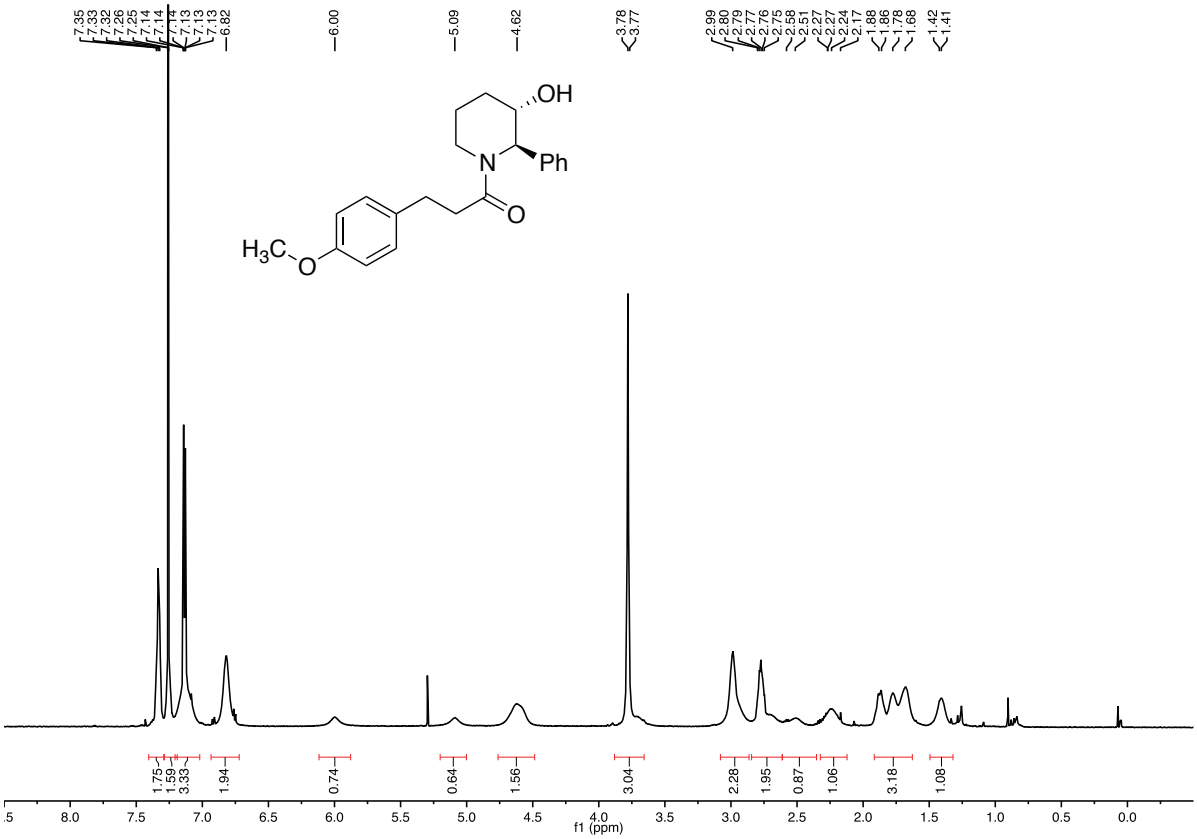
18.83
f1 (ppm)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7.13
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6.00
5.09
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2.79
2.77
2.76
2.75
2.58
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2.27
2.27
2.24
2.17
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1.86
1.78
1.68
1.42
1.41
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Ph
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H3C
O
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3.33
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1.06
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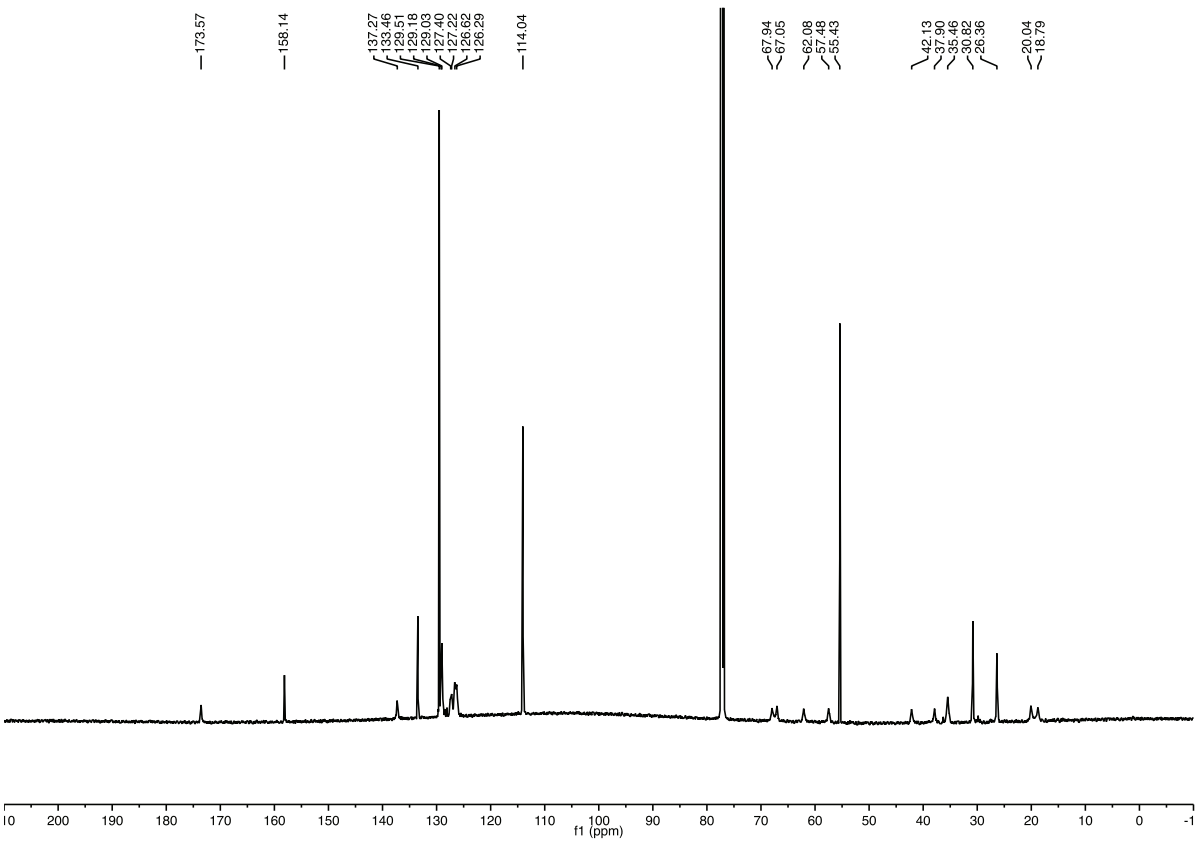
1.08
f1 (ppm)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126.29
114.04
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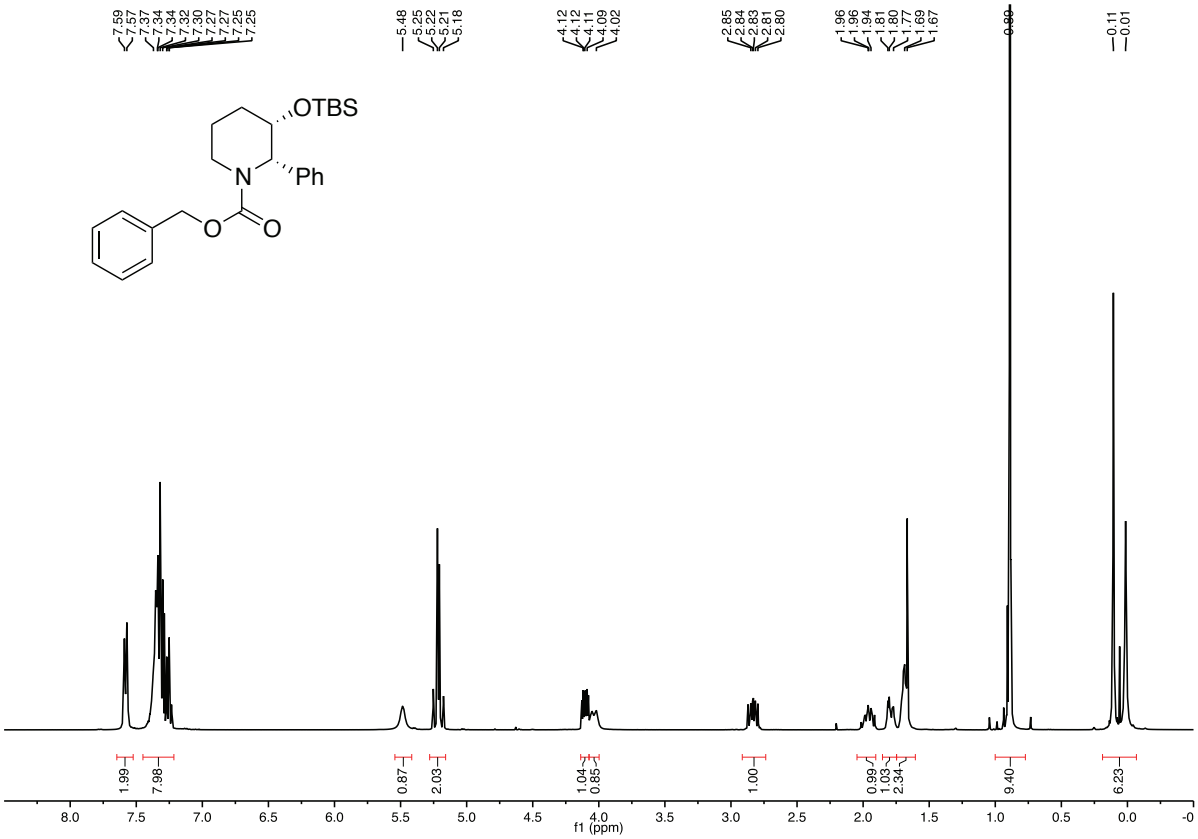
30.82
26.36
20.04
18.79
f1 (ppm)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5.25
5.22
5.21
5.18
4.12
4.12
4.11
4.09
4.02
2.85
2.84
2.83
2.81
2.80
1.96
1.96
1.94
1.81
1.80
1.77
1.69
1.67
0.89
0.11
0.01
OTBS
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Ph
O
O
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0.85
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0.99
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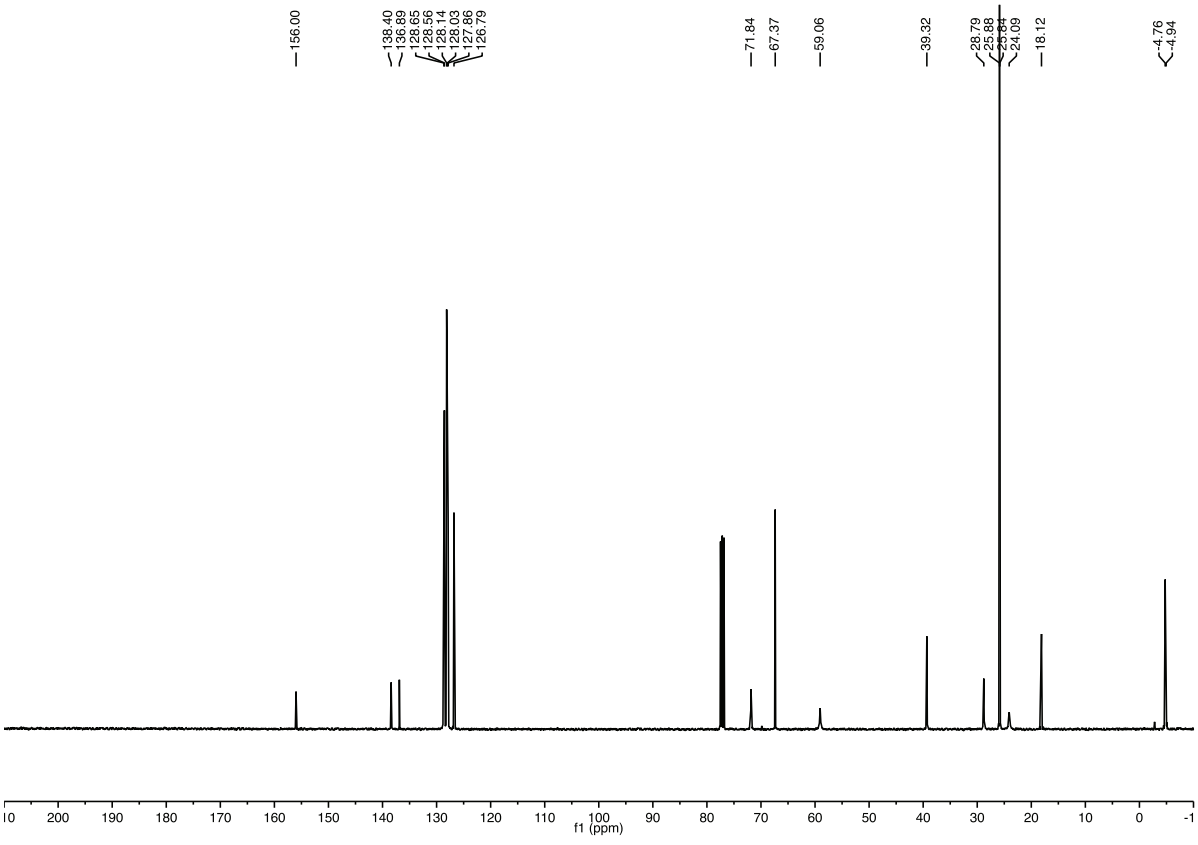
6.23
f1 (ppm)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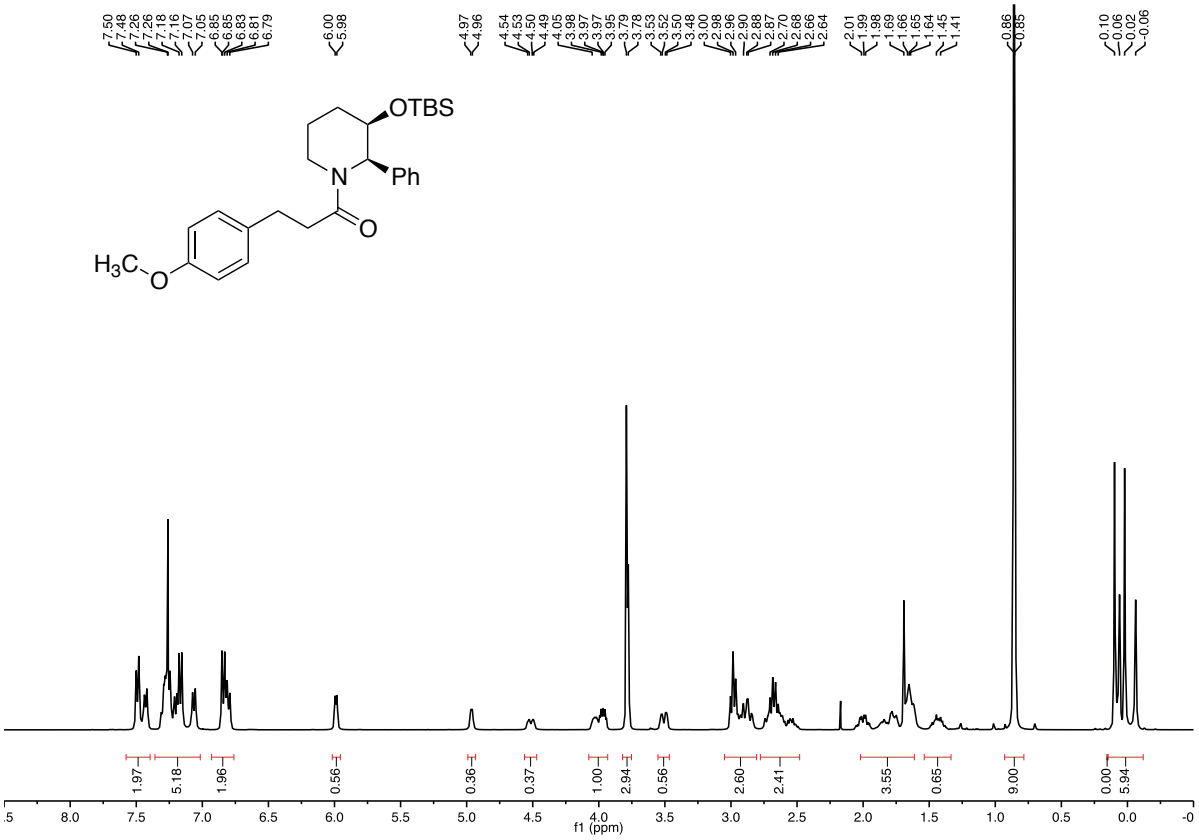
25.88
25.84
24.09
18.12
4.76
4.94
f1 (ppm)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Ph
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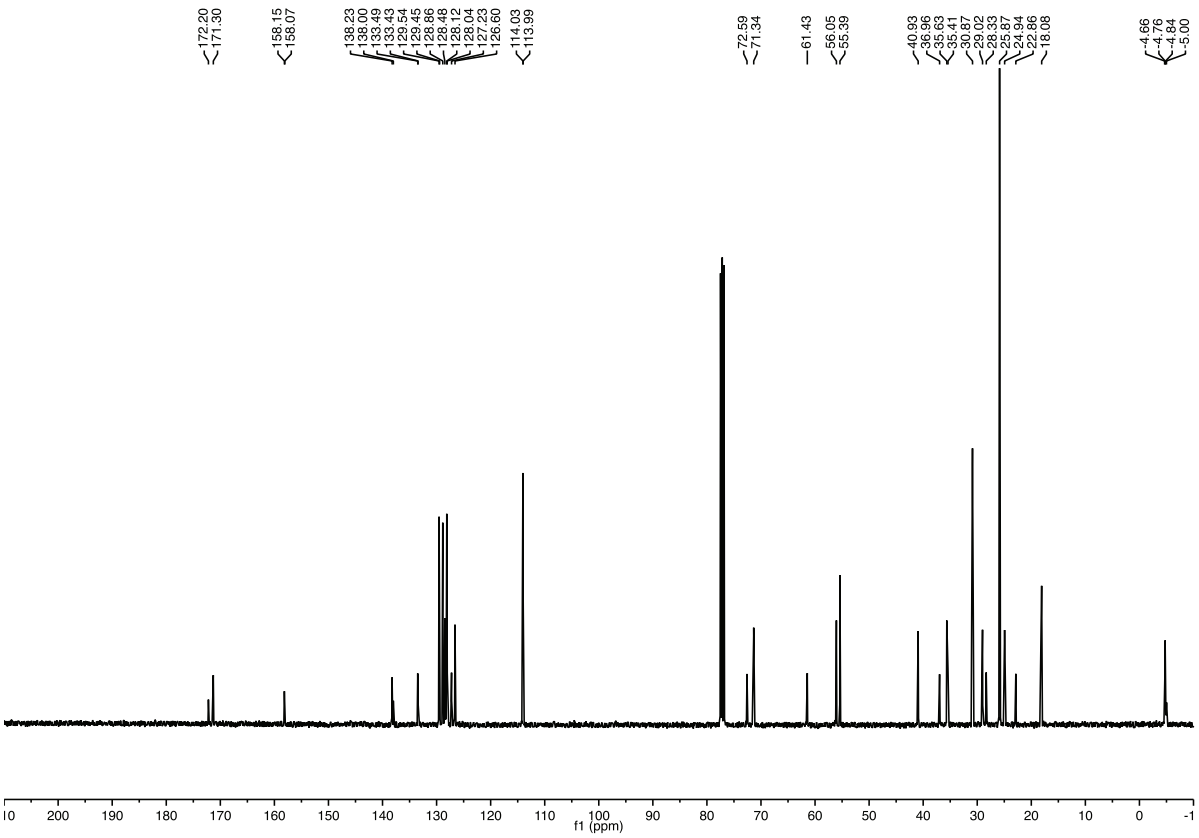
H3C
O
f1 (ppm)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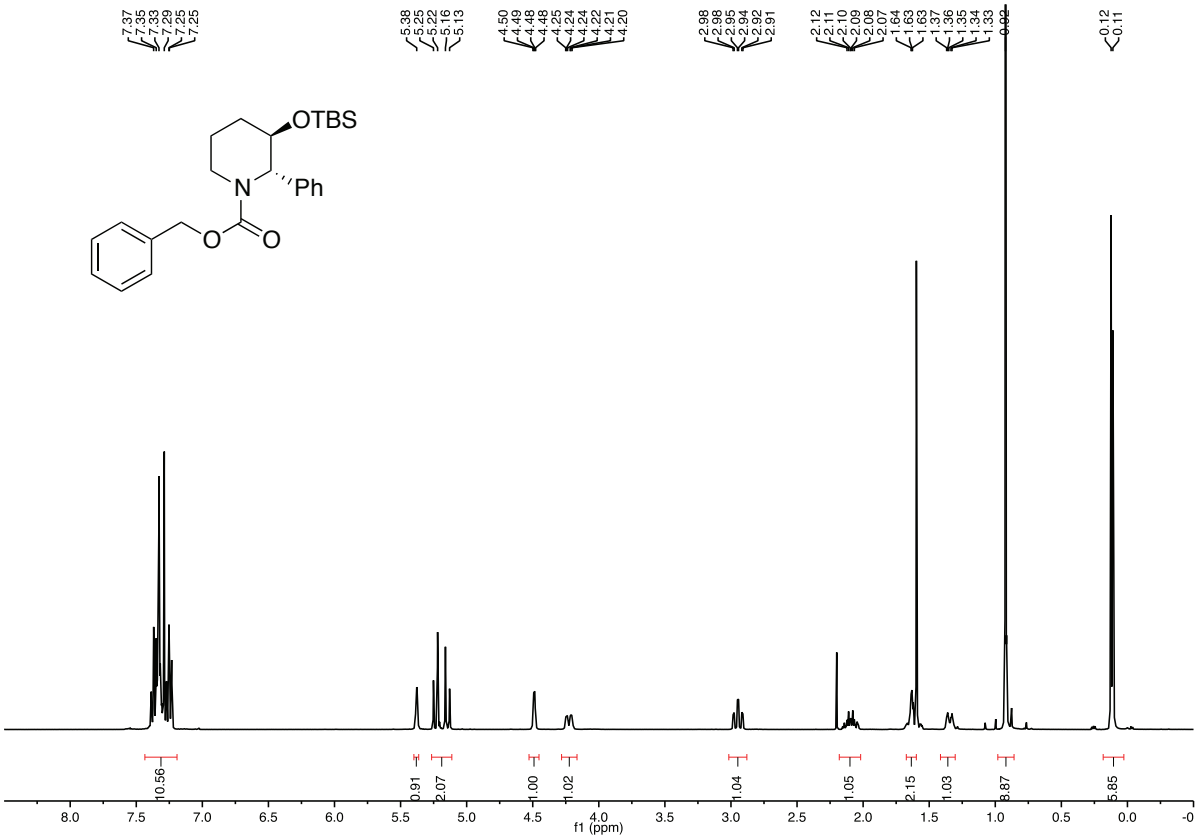
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4.48
4.48
4.25
4.24
4.22
4.21
4.20
2.98
2.98
2.95
2.94
2.92
2.91
2.12
2.11
2.10
2.09
2.08
2.07
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1.63
1.63
1.37
1.36
1.35
1.34
1.33
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0.11
OTBS
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Ph
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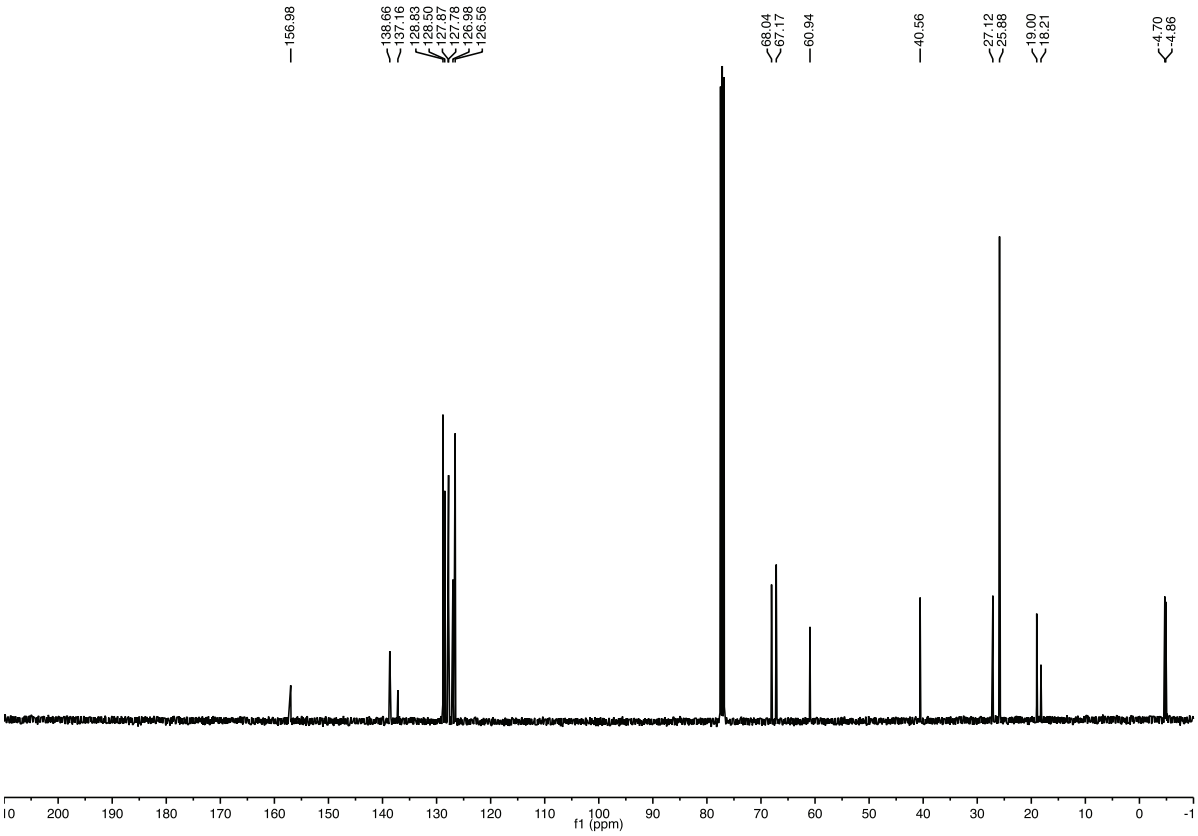
f1 (ppm)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126.56
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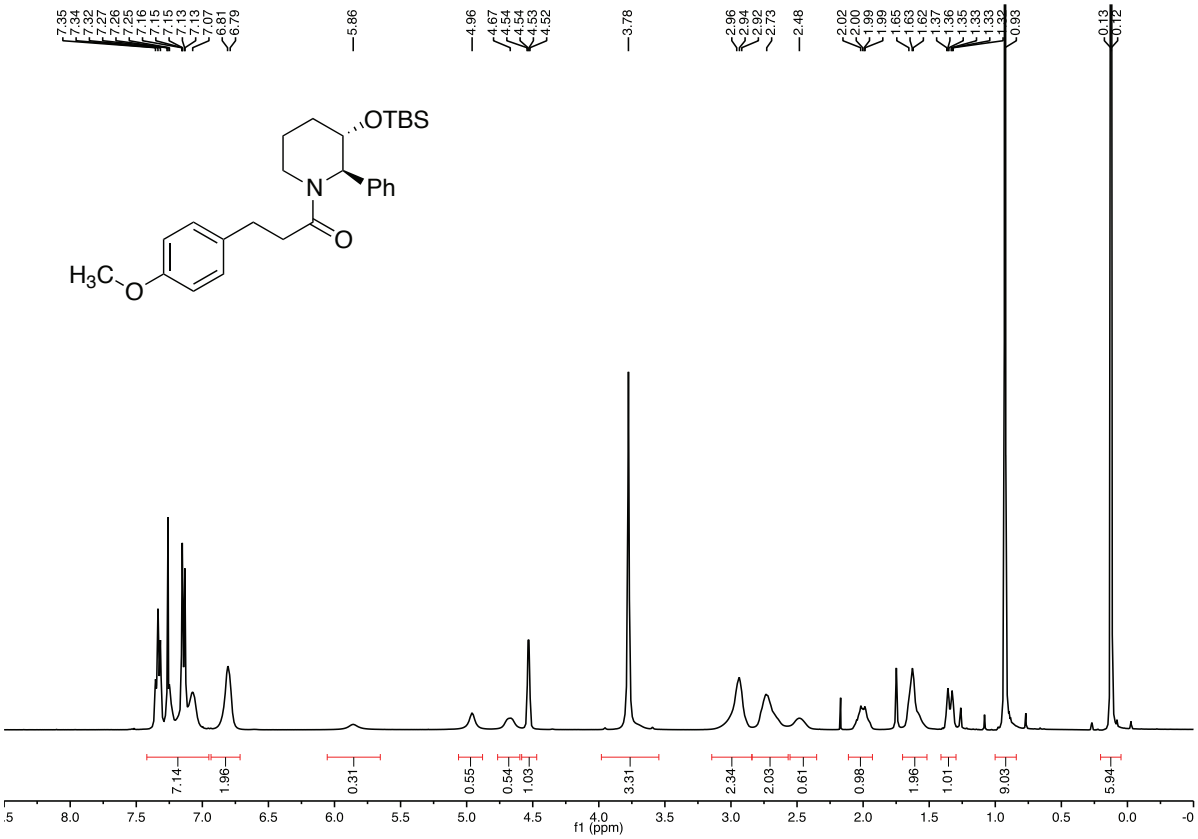
40.56
27.12
25.88
19.00
18.21
-4.70
-4.86
f1 (ppm)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7.07
6.81
6.79
5.86
4.96
4.67
4.54
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4.53
4.52
3.78
2.96
2.94
2.92
2.73
2.48
2.02
2.00
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1.99
1.65
1.63
1.62
1.37
1.36
1.35
1.33
1.33
1.32
0.93
0.13
0.12
OTBS
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H3C
O
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0.55
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2.03
0.61
0.98
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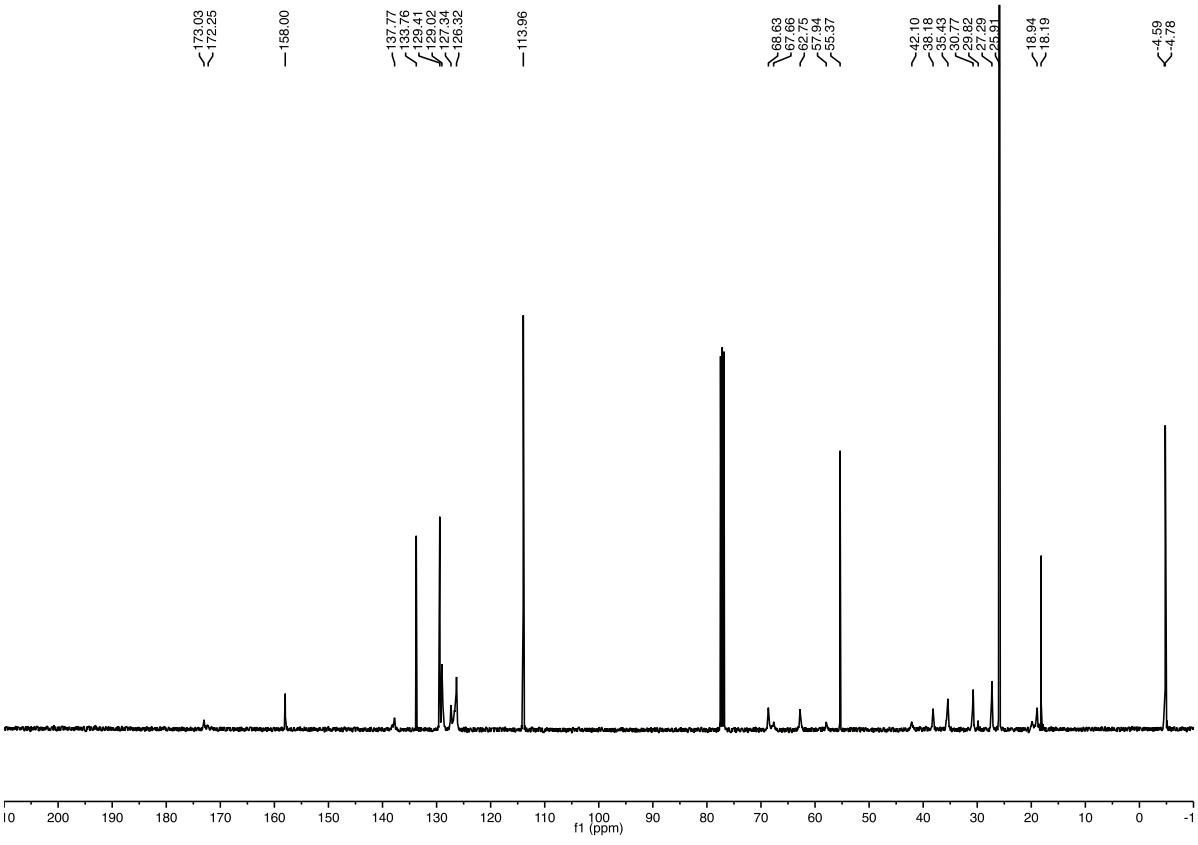
5.94
f1 (ppm)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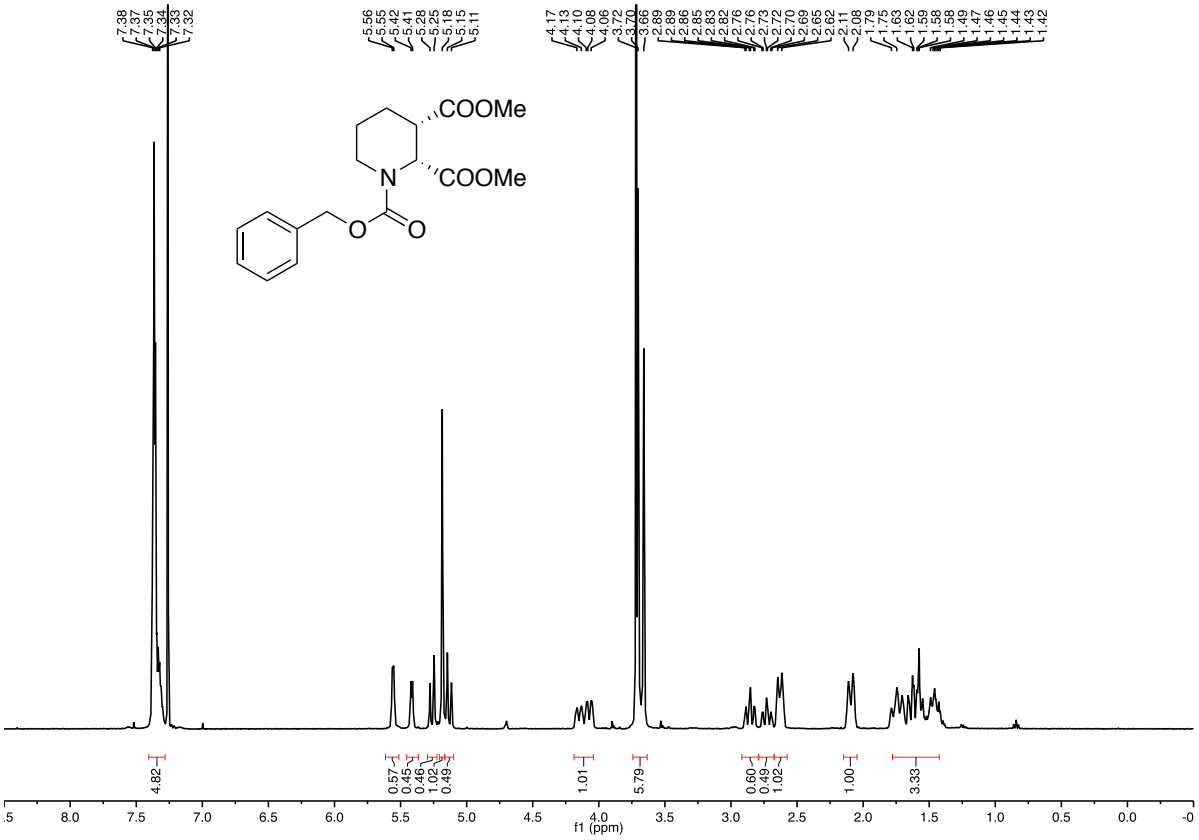
67.66
62.75
57.94
55.37
42.10
38.18
35.43
30.77
29.82
27.29
25.91
18.94
18.19
-4.59
-4.78
f1 (ppm)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4.08
4.06
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2.89
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2.82
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2.73
2.72
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2.69
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2.62
2.11
2.08
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1.45
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1.43
1.42
COOMe
COOMe
N
O
O
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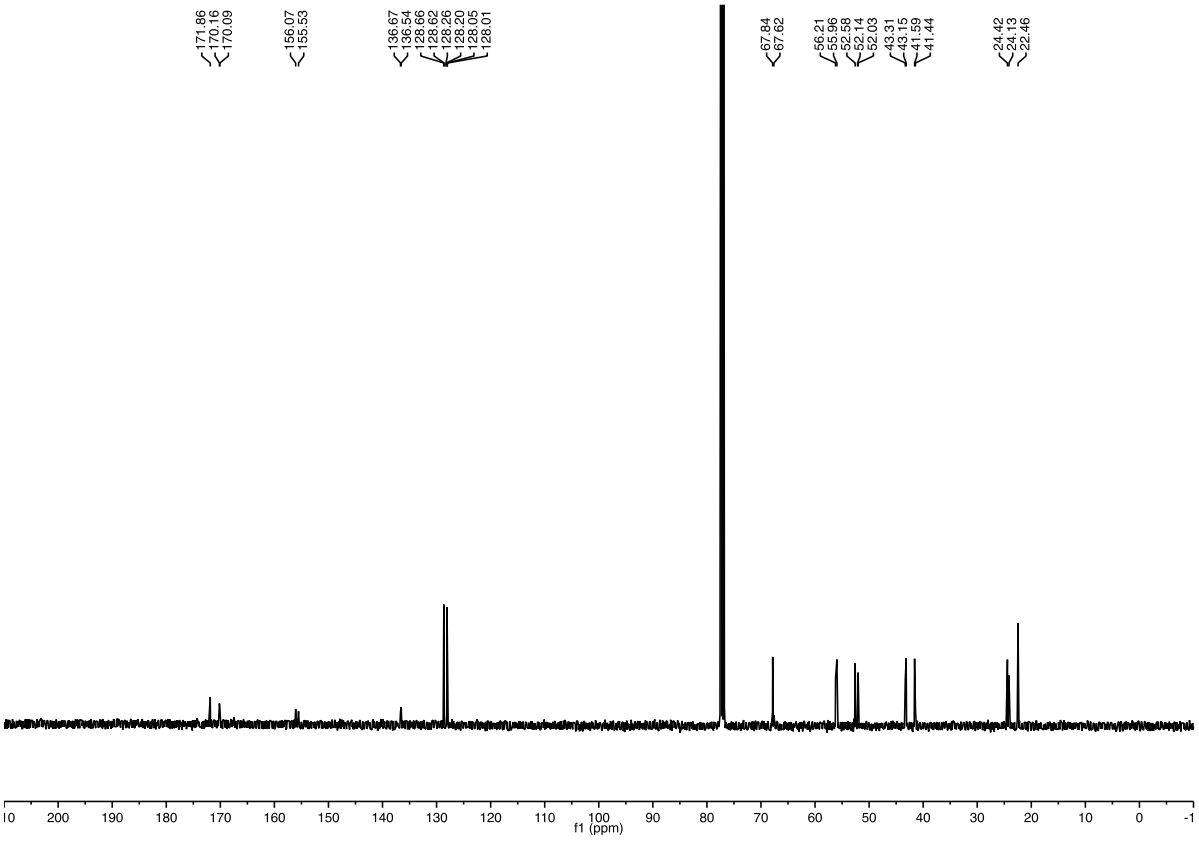
f1 (ppm)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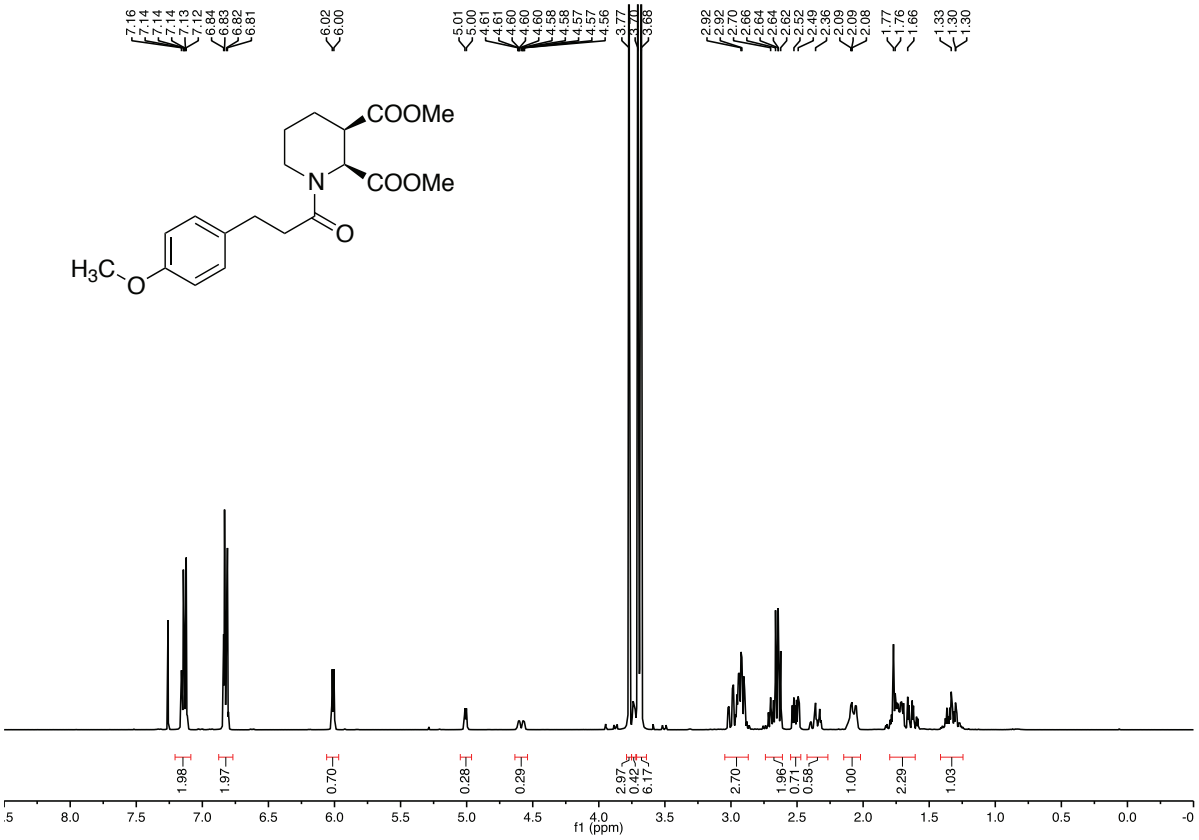
f1 (ppm)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COOMe
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O
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O
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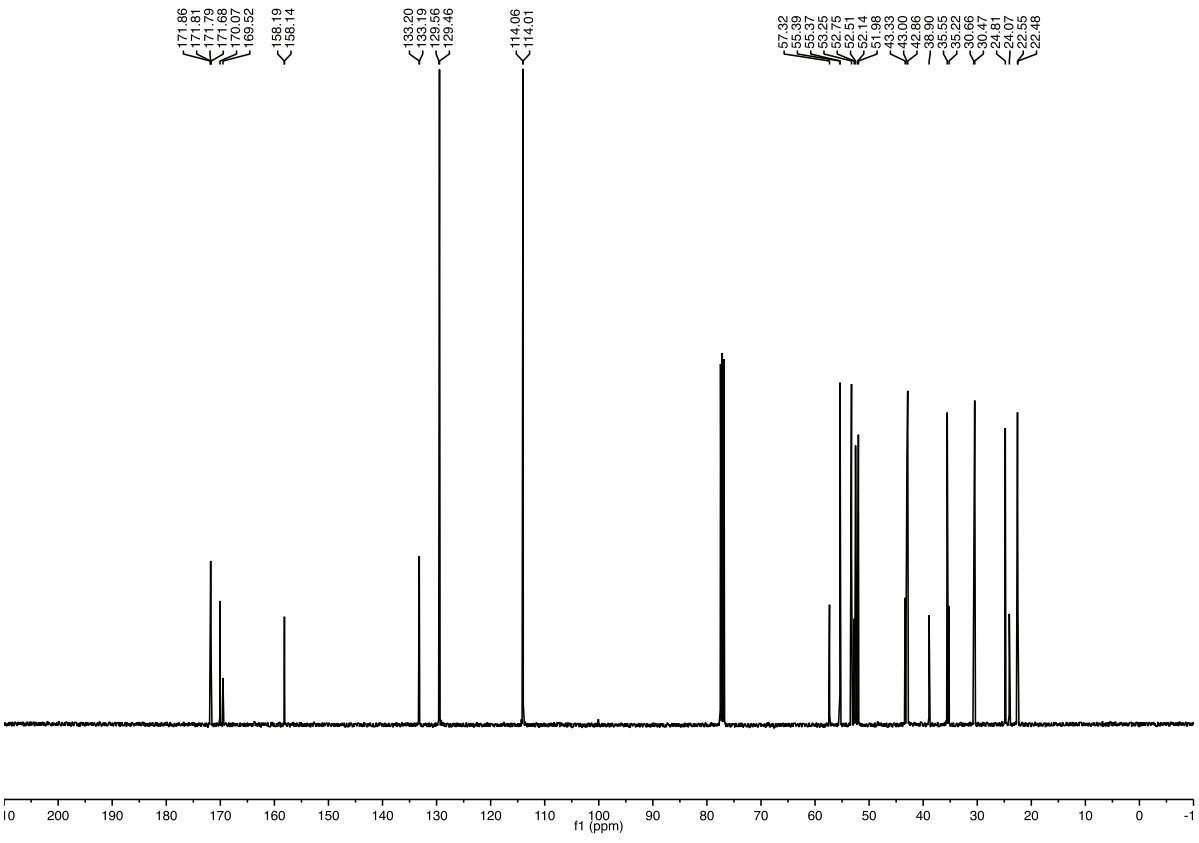
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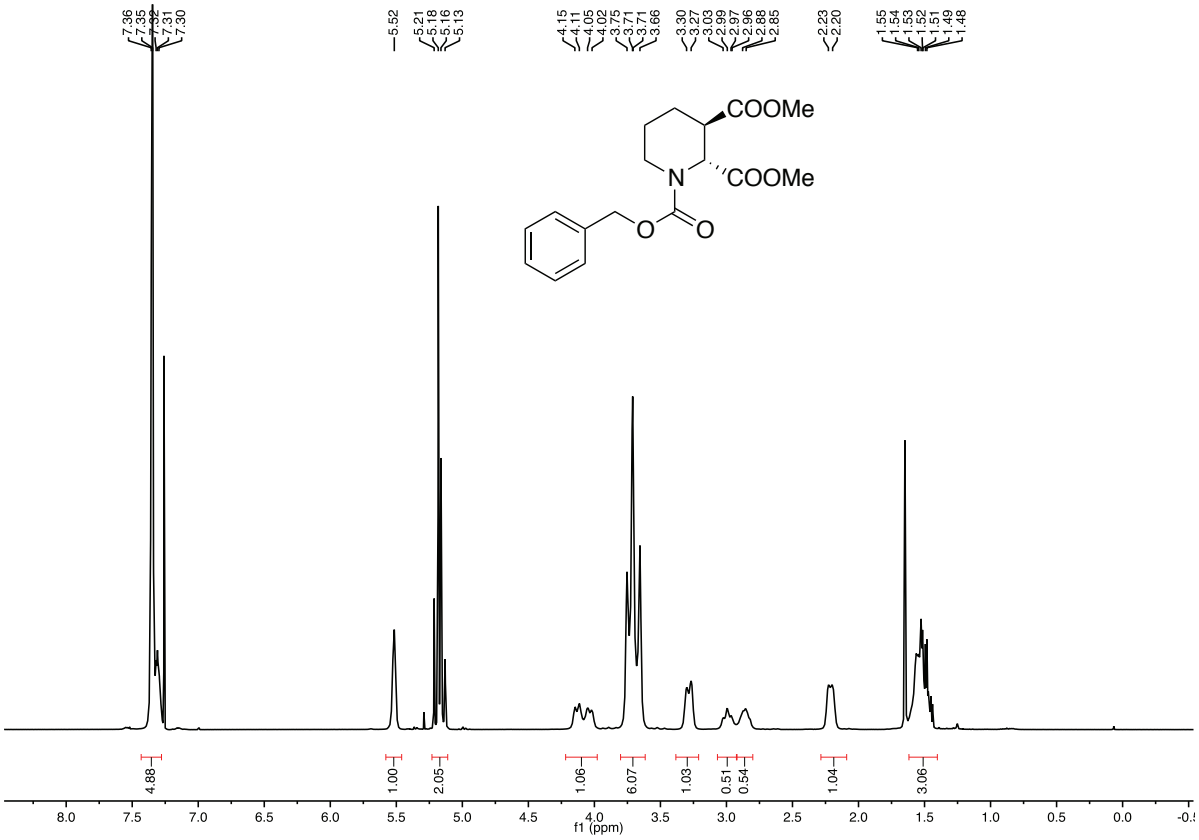
22.48
f1 (ppm)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2.85
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1.51
1.49
1.48
COOMe
COOMe
N
O
O
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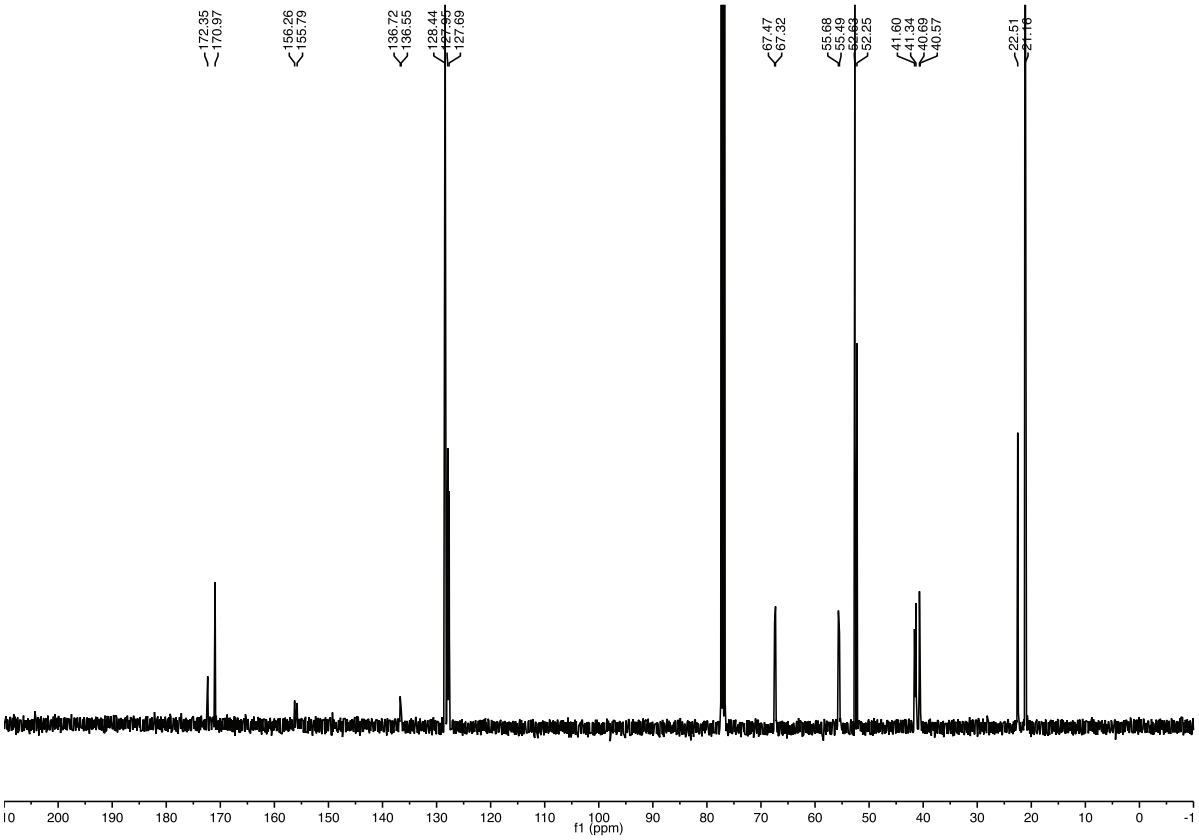
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52.63
52.25
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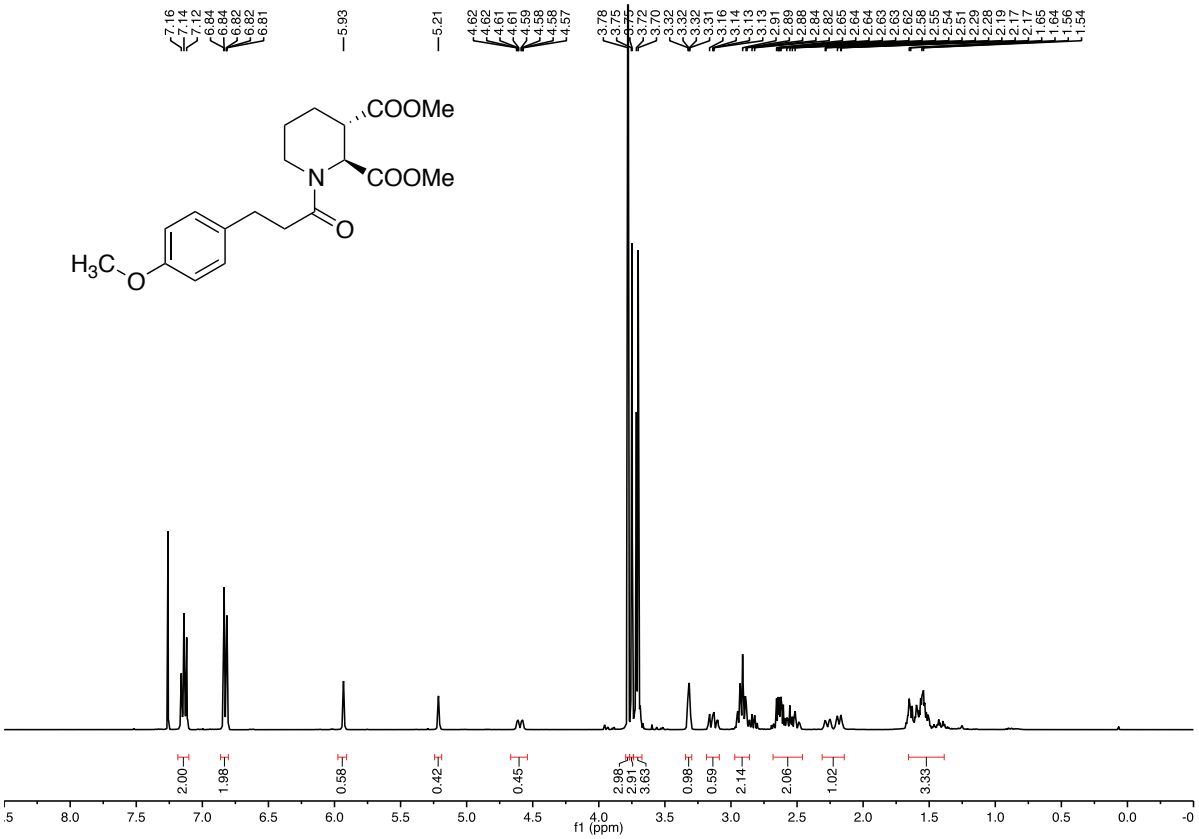
41.34
40.69
40.57
22.51
21.16
f1 (ppm)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4.59
4.58
4.58
4.57
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2.55
2.54
2.51
2.29
2.28
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1.64
1.56
1.54
COOMe
COOMe
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O
H3C
O
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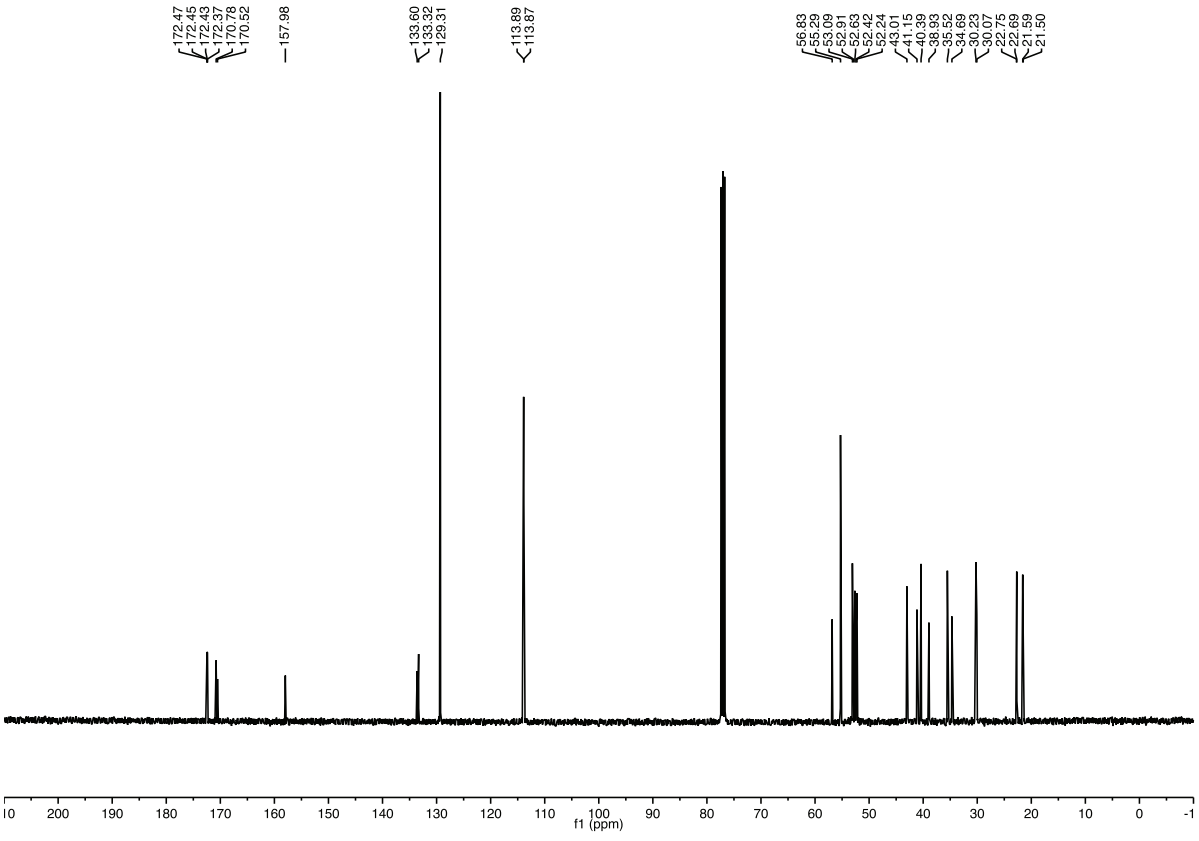
2.06
1.02
3.33
f1 (ppm)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133.60
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129.31
113.89
113.87
56.83
55.29
53.09
52.91
52.63
52.42
52.24
43.01
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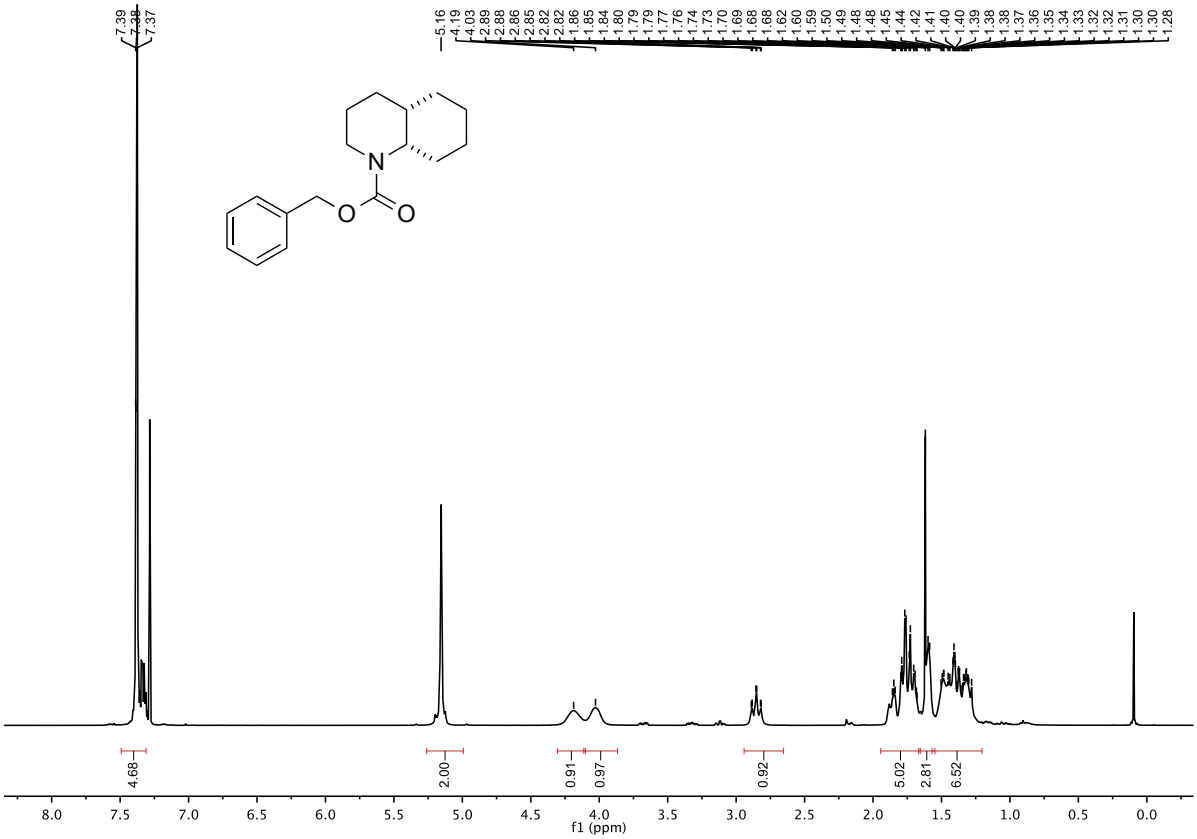
21.50
f1 (ppm)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1.34
1.33
1.32
1.32
1.31
1.30
1.30
1.28
N
O
O
4.68
2.00
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0.97
0.92
5.02
2.81
6.52
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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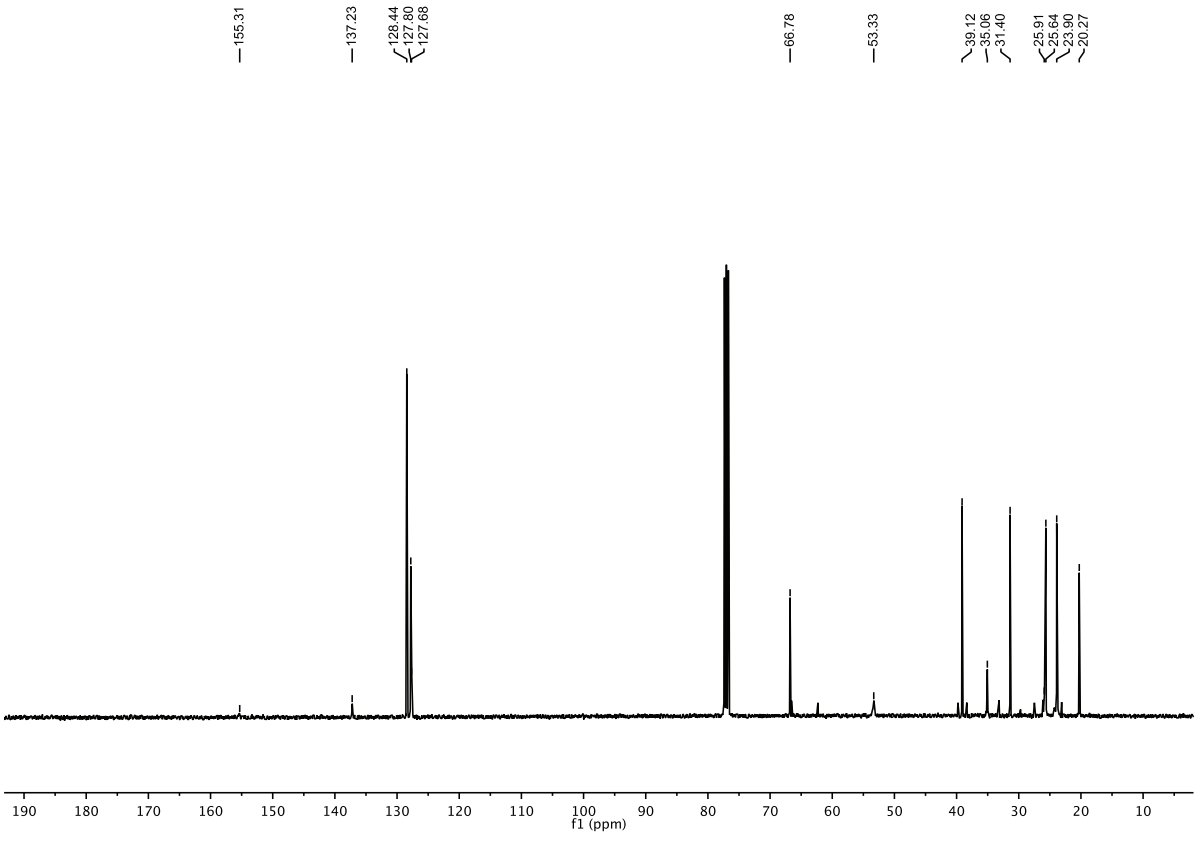
0.0
f1 (ppm)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127.68
66.78
53.33
39.12
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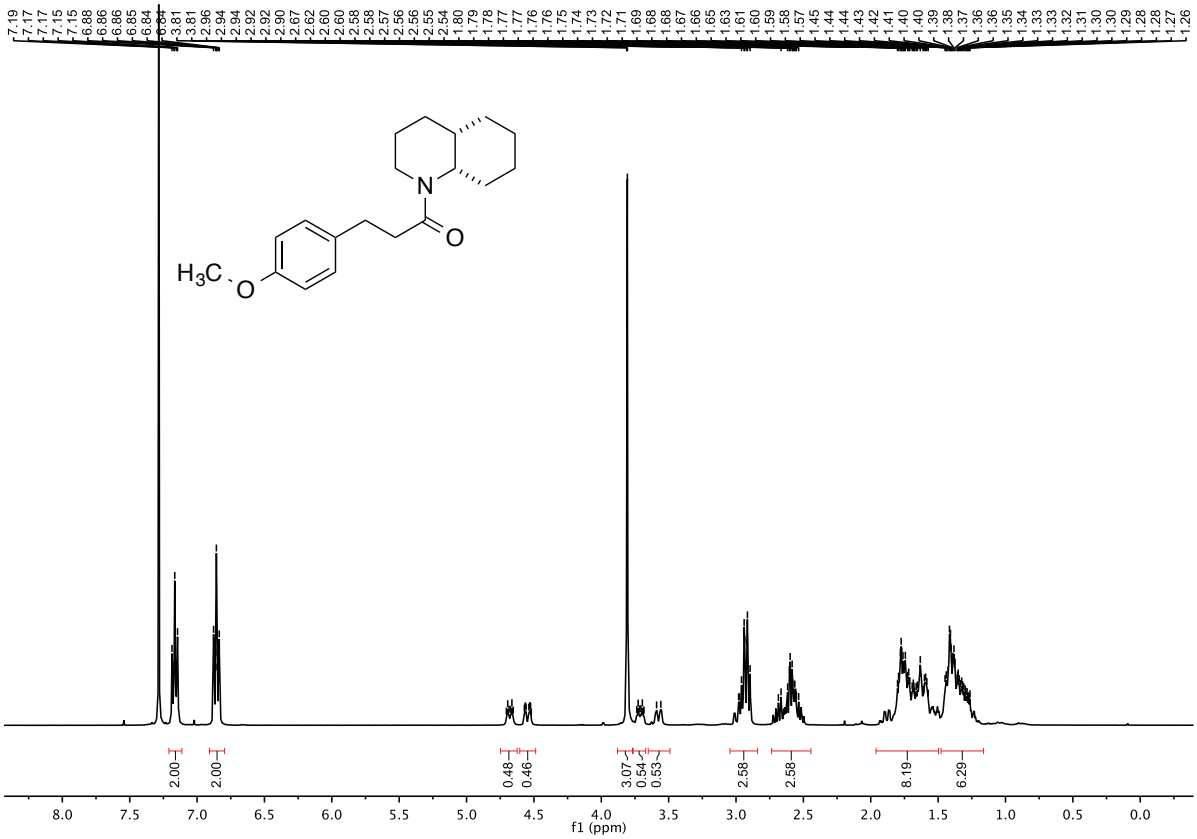
31.40
25.91
25.64
23.90
20.27
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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N
O
H3C
O
2.00 2.00 0.48 0.46 3.07 0.54 0.53 2.58 2.58 8.19 6.29
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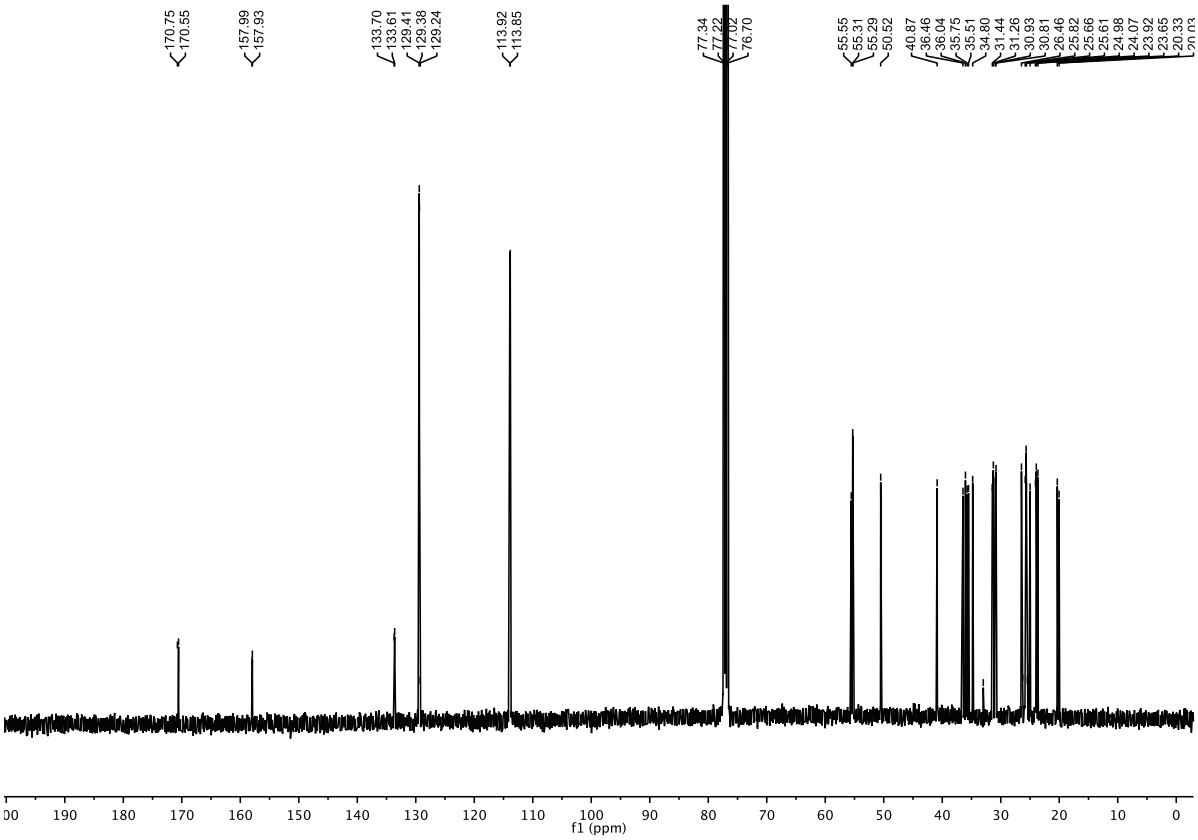
f1 (ppm)


170.75 170.55 157.99 157.93 133.70 133.61 129.41 129.38 129.24 113.92 113.85 77.34 77.22 77.02 76.70 55.55 55.31 55.29 50.52 40.87 36.46 36.04 35.75 35.51 34.80 31.44 31.26 30.93 30.81 26.46 25.82 25.66 25.61 24.98 24.07 23.92 23.65 20.33
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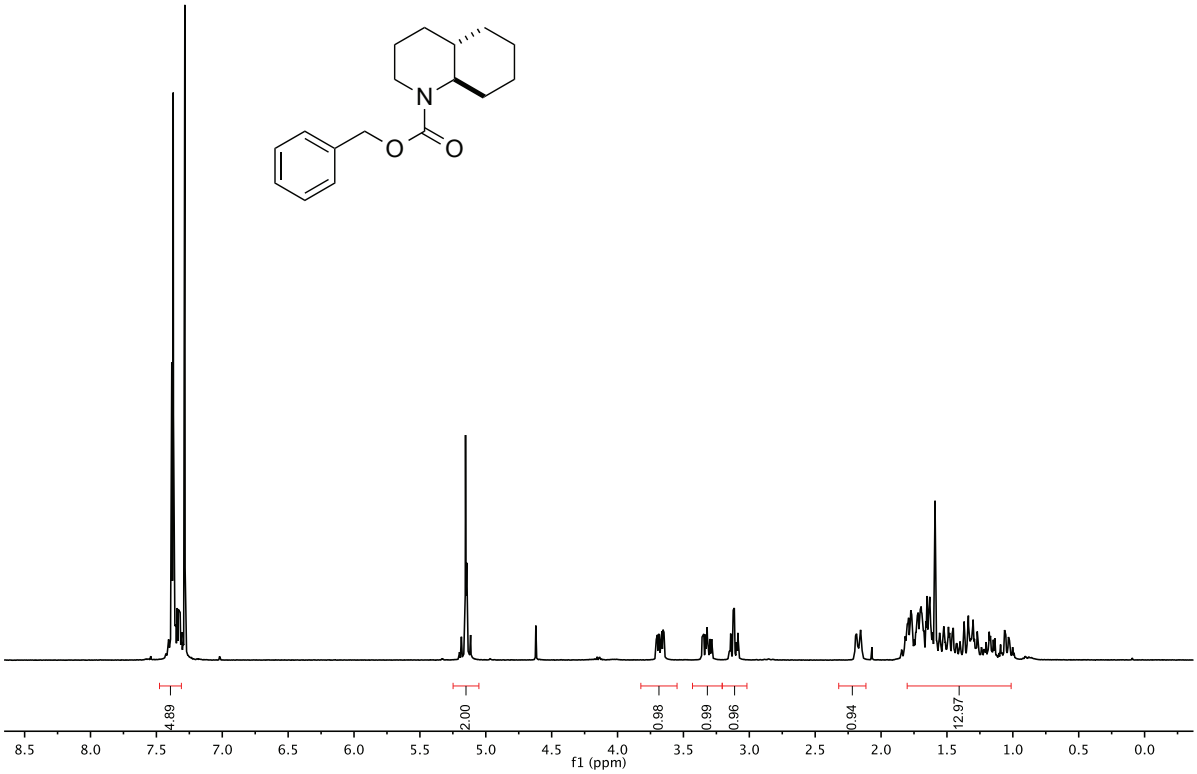
f1 (ppm)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O
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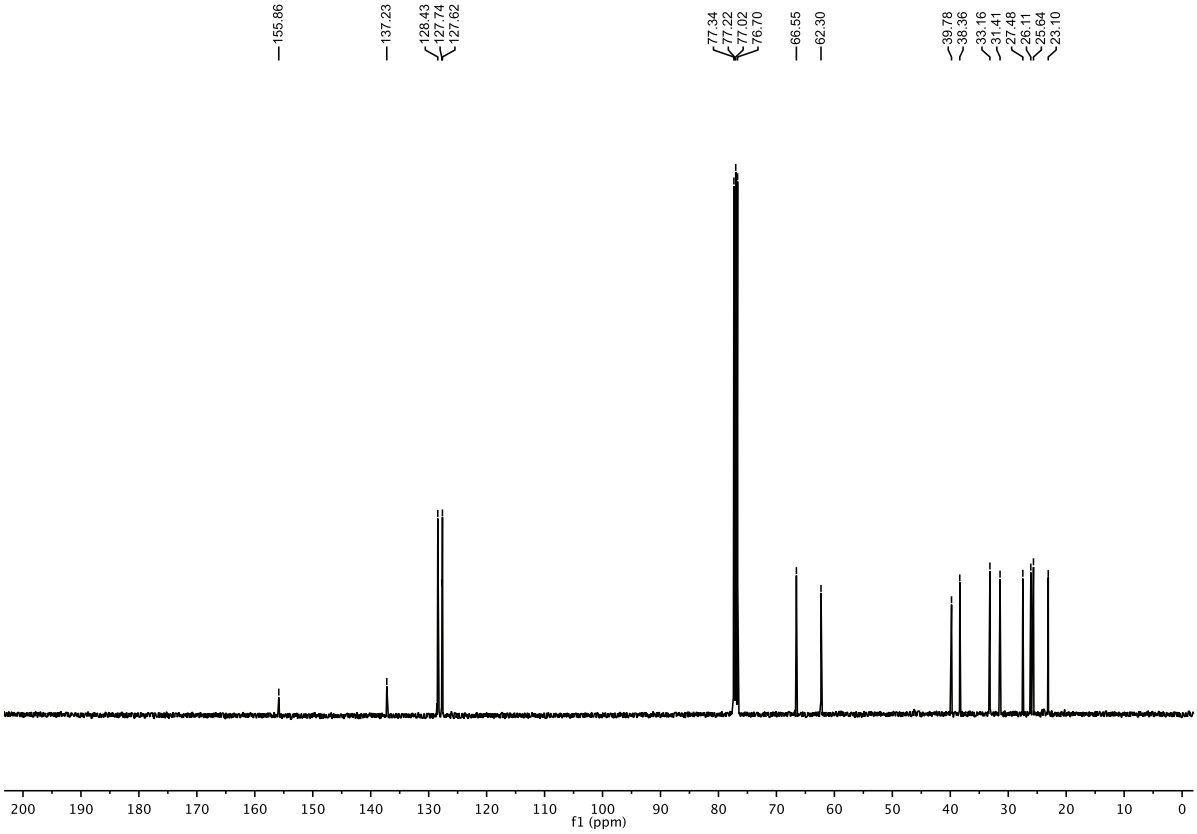
0.99
0.96
0.94
12.97
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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127.74
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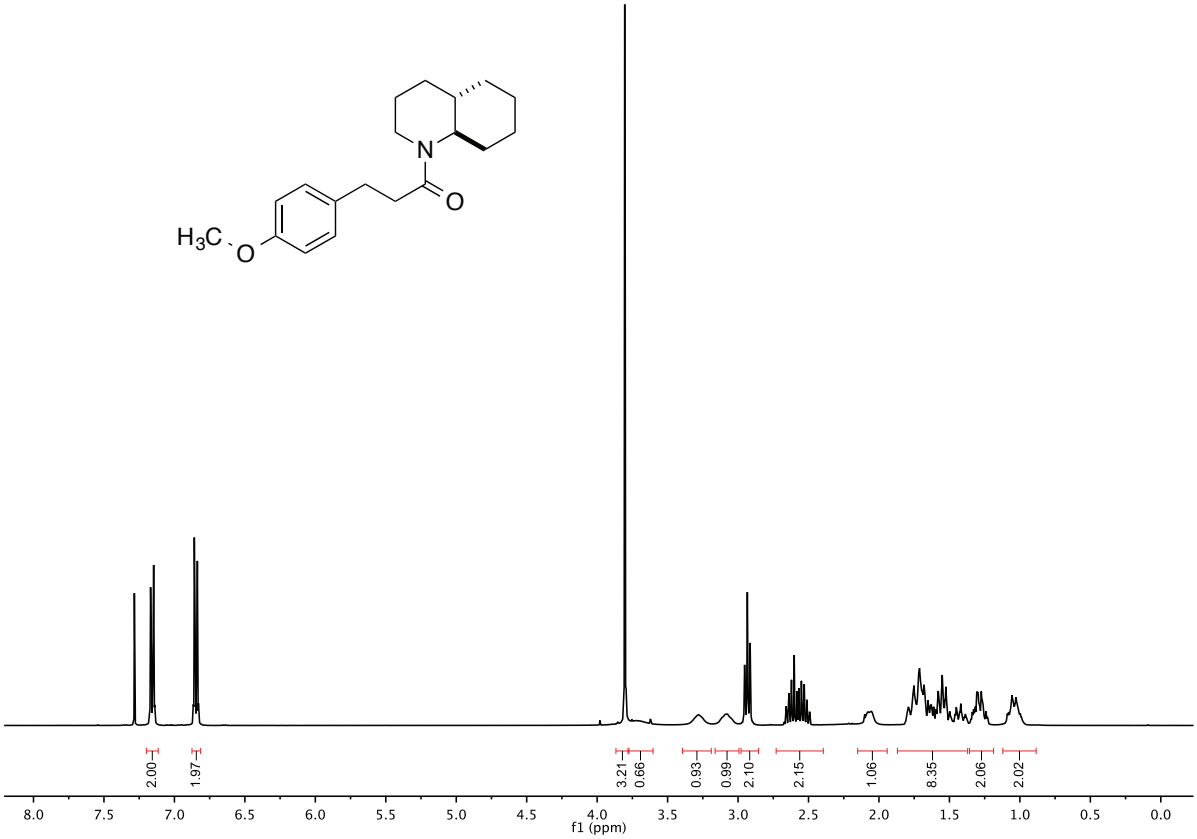
77.02
76.70
66.55
62.30
39.78
38.36
33.16
31.41
27.48
26.11
25.64
23.10
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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O
H3C
O
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3.21
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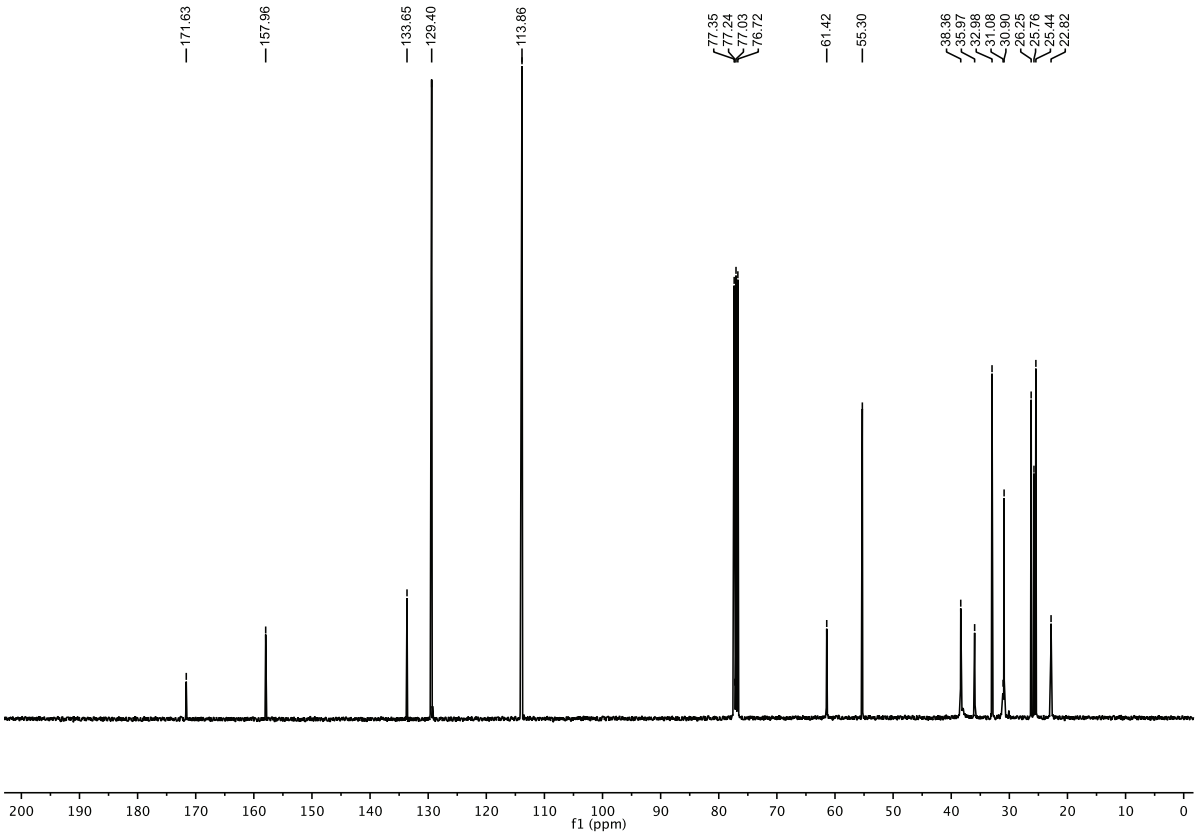
0.93
0.99
2.10
2.15
1.06
8.35
2.06
2.02
f1 (ppm)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25.76
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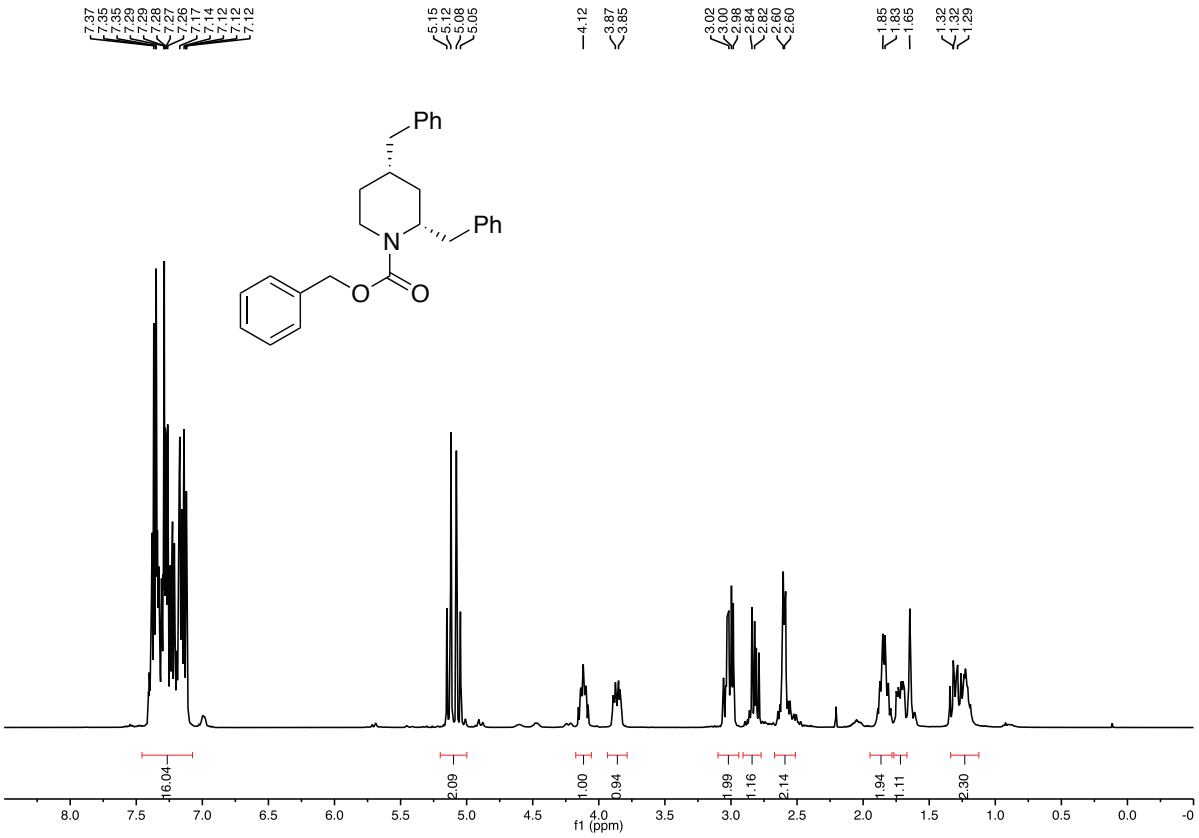
22.82
f1 (ppm)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7.12
5.15
5.12
5.08
5.05
4.12
3.87
3.85
3.02
3.00
2.98
2.84
2.82
2.60
2.60
1.85
1.83
1.65
1.32
1.32
1.29
Ph
Ph
N
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1.99
1.16
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1.94
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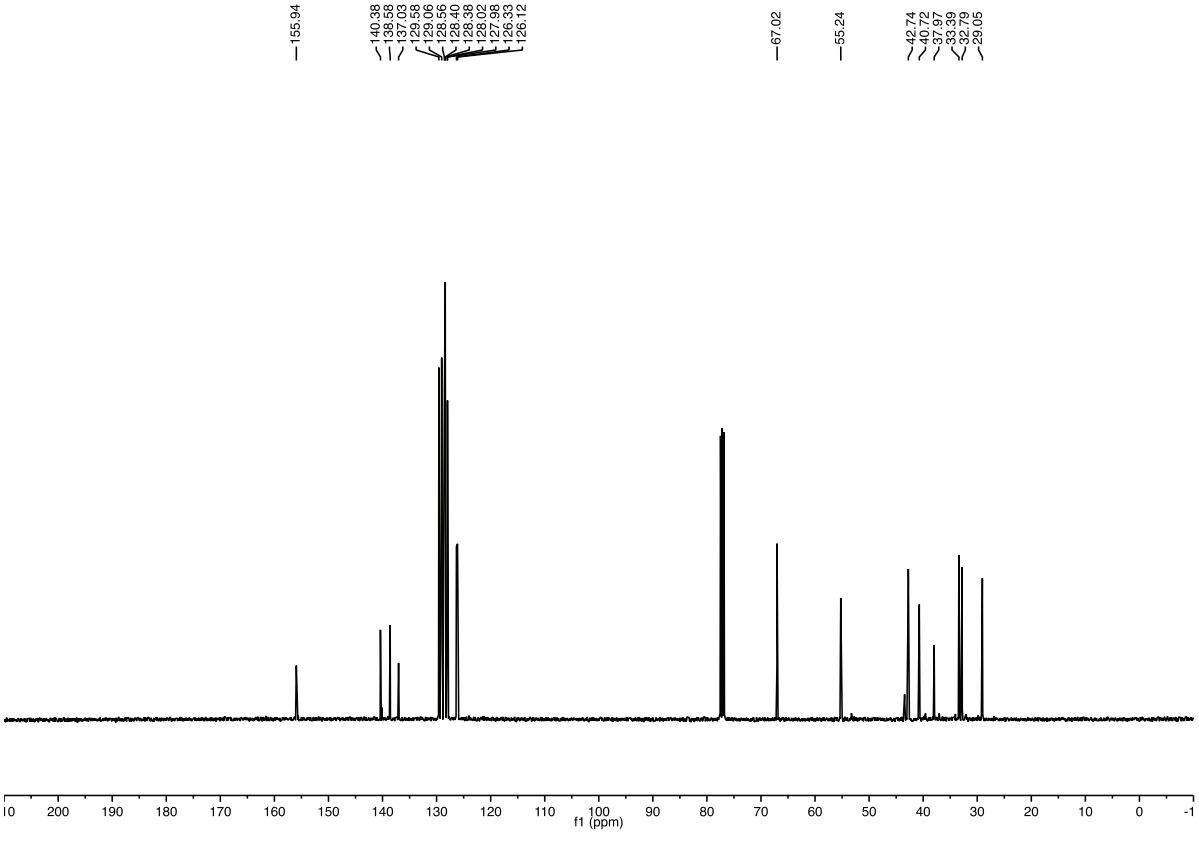
2.30
f1 (ppm)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128.02
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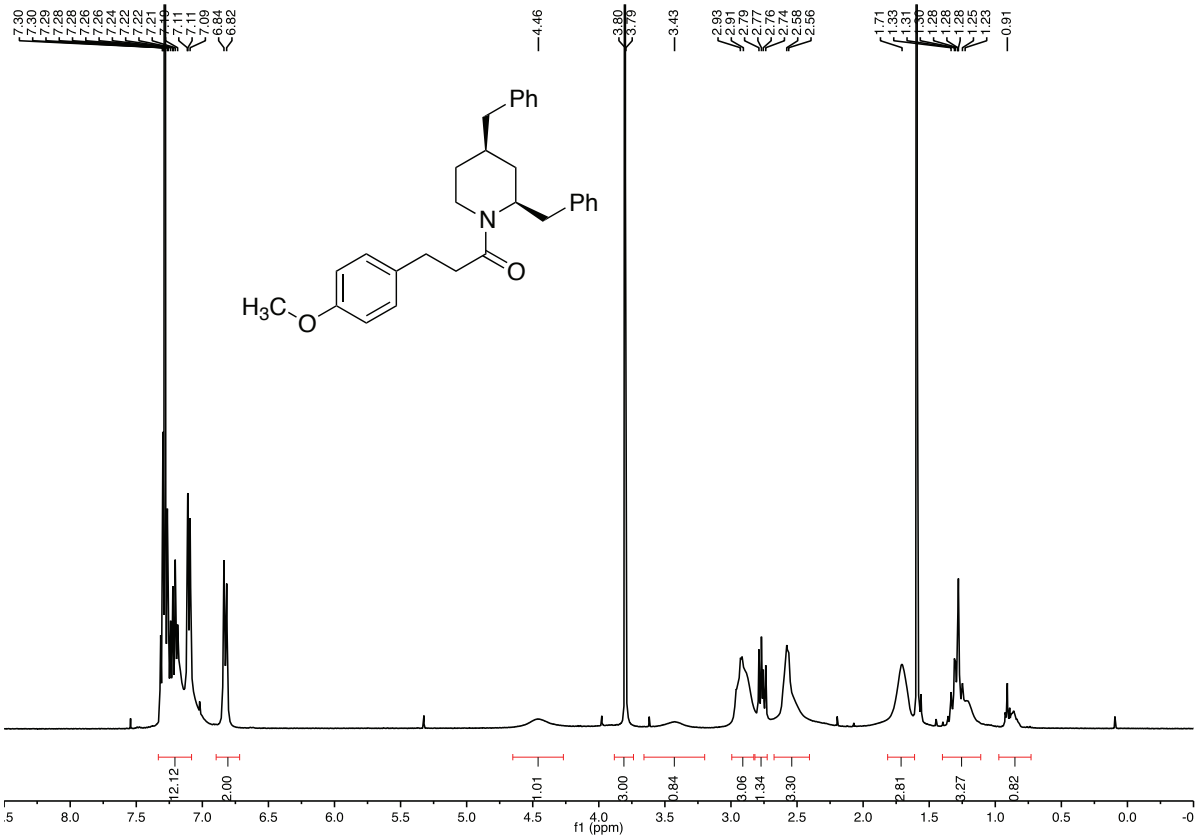
67.02
55.24
42.74
40.72
37.97
33.39
32.79
29.05
f1 (ppm)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7.11
7.11
7.09
6.84
6.82
4.46
3.80
3.79
3.43
2.93
2.91
2.79
2.77
2.76
2.74
2.58
2.56
1.71
1.33
1.31
1.28
1.28
1.25
1.23
0.91
Ph
Ph
N
O
H3C
O
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3.00
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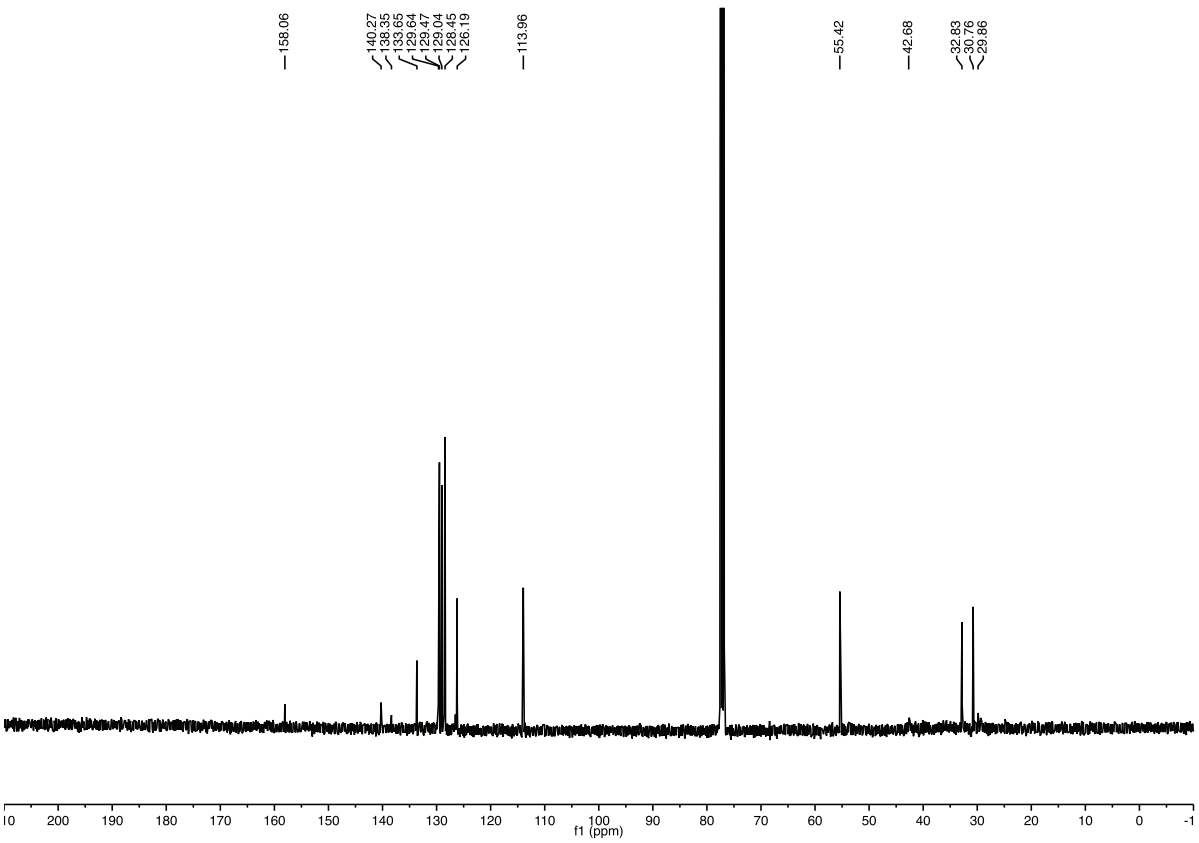
3.06
1.34
3.30
2.81
3.27
0.82
f1 (ppm)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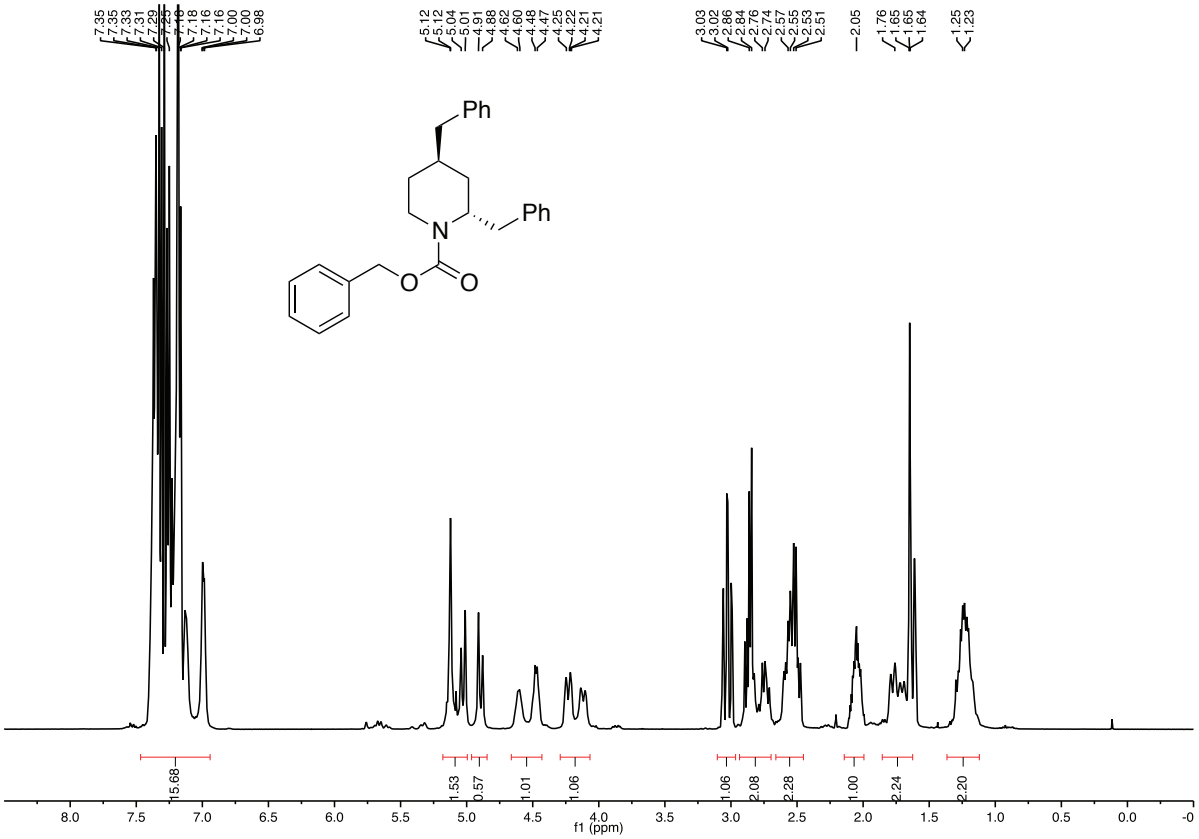
113.96
55.42
42.68
32.83
30.76
29.86
f1 (ppm)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7.00
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5.12
5.12
5.04
5.01
4.91
4.88
4.62
4.60
4.48
4.47
4.25
4.22
4.21
4.21
3.03
3.02
2.86
2.84
2.76
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2.55
2.53
2.51
2.05
1.76
1.65
1.65
1.64
1.25
1.23
Ph
Ph
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O
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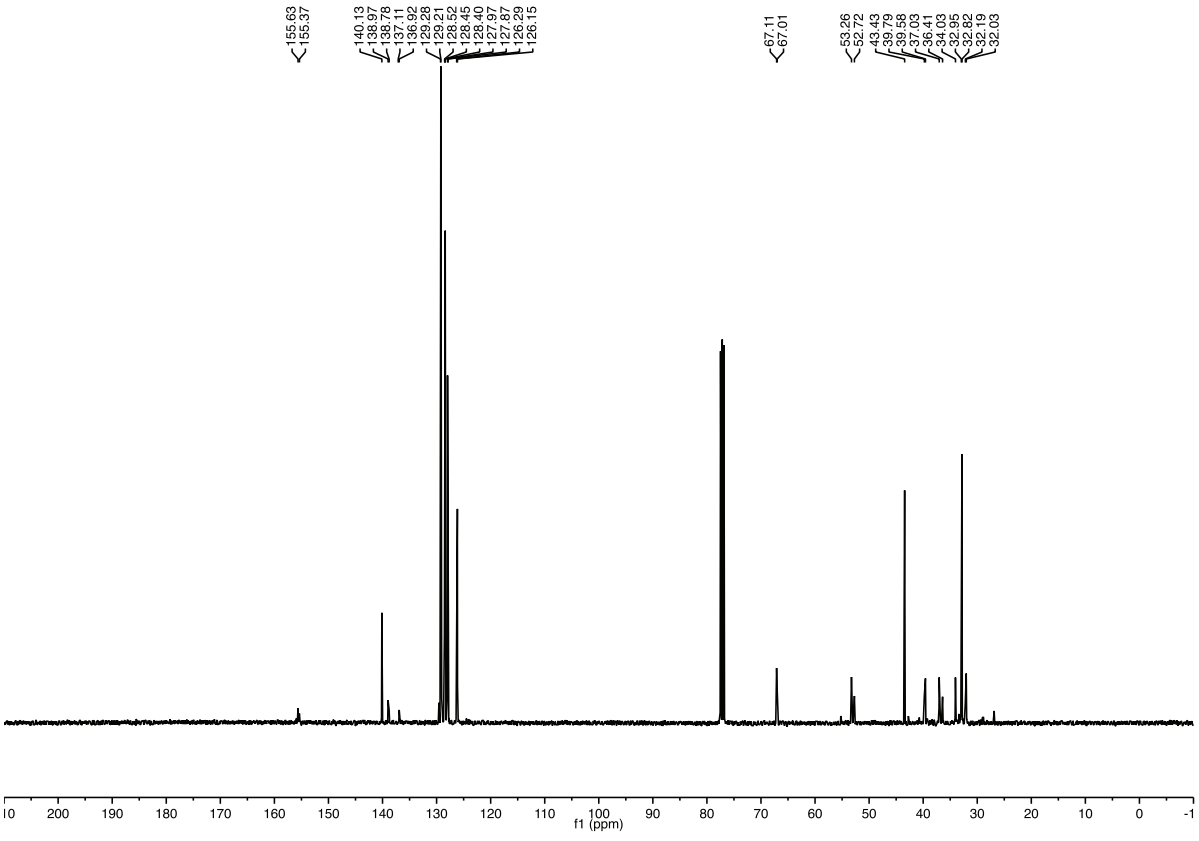
2.20
f1 (ppm)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126.29
126.15
67.11
67.01
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34.03
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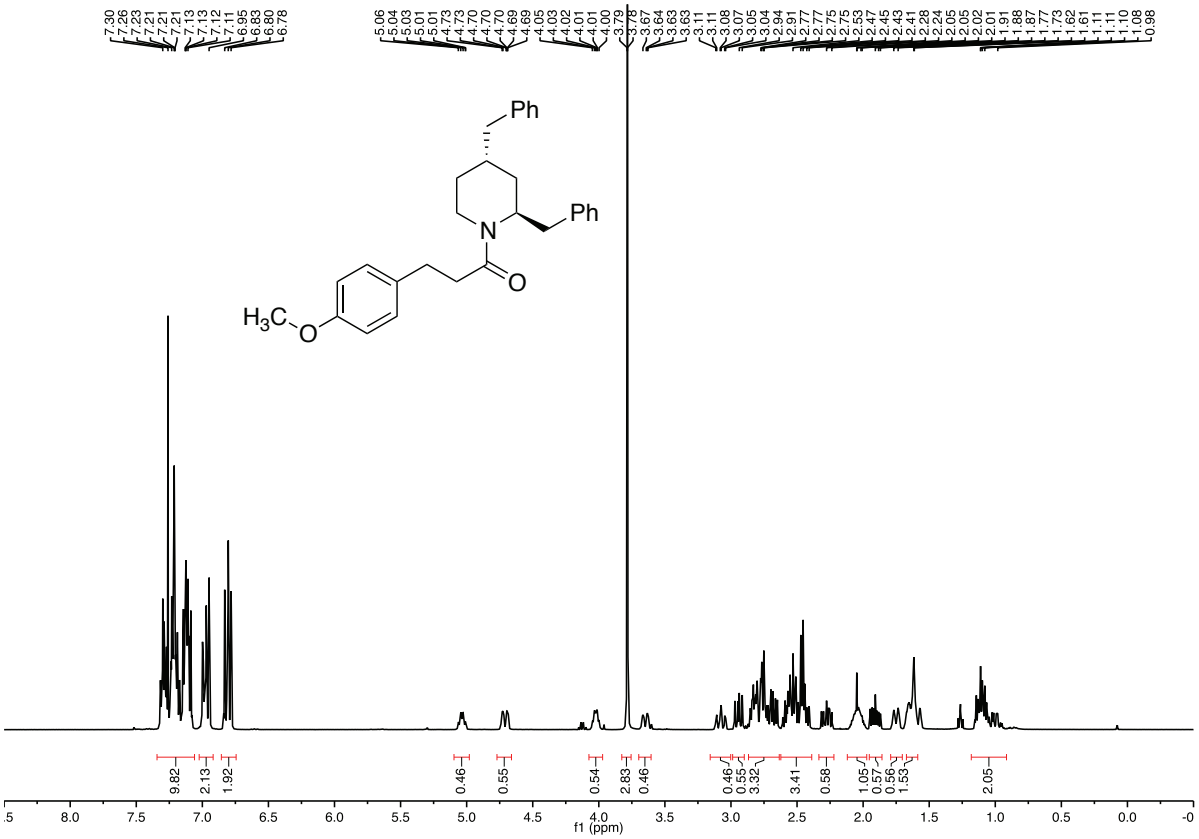
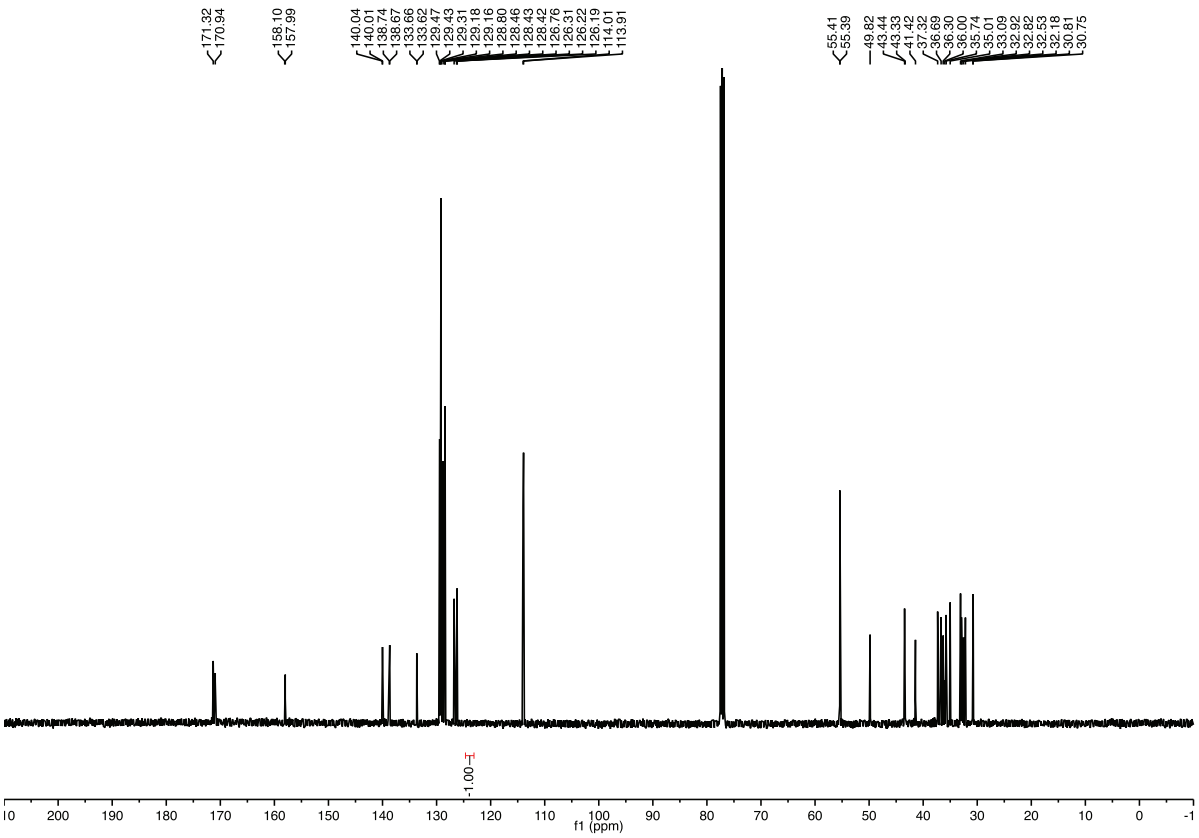
32.82
32.19
32.03
f1 (ppm)


Ph
Ph
N
O
H3C
O
f1 (ppm)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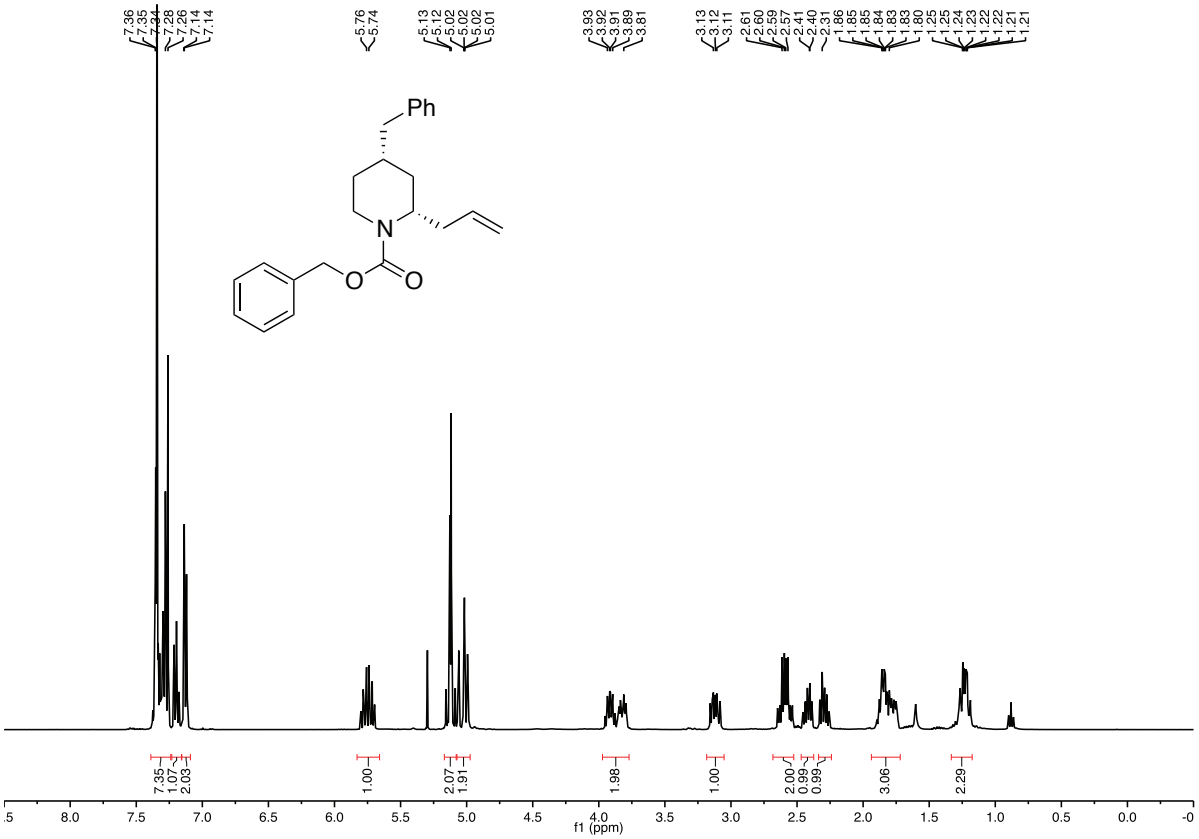
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1.83
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1.25
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1.21
1.21
Ph
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O
O
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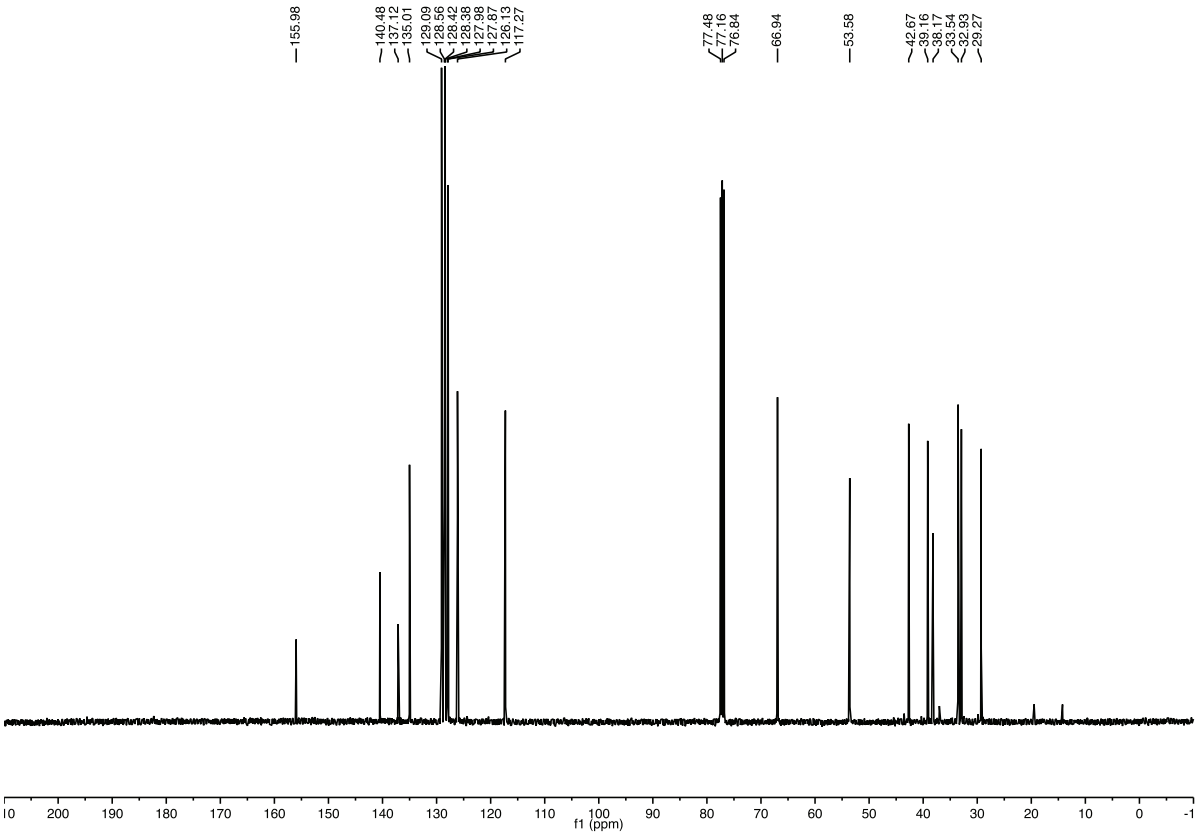
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32.93
29.27
f1 (ppm)


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5.75
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5.73
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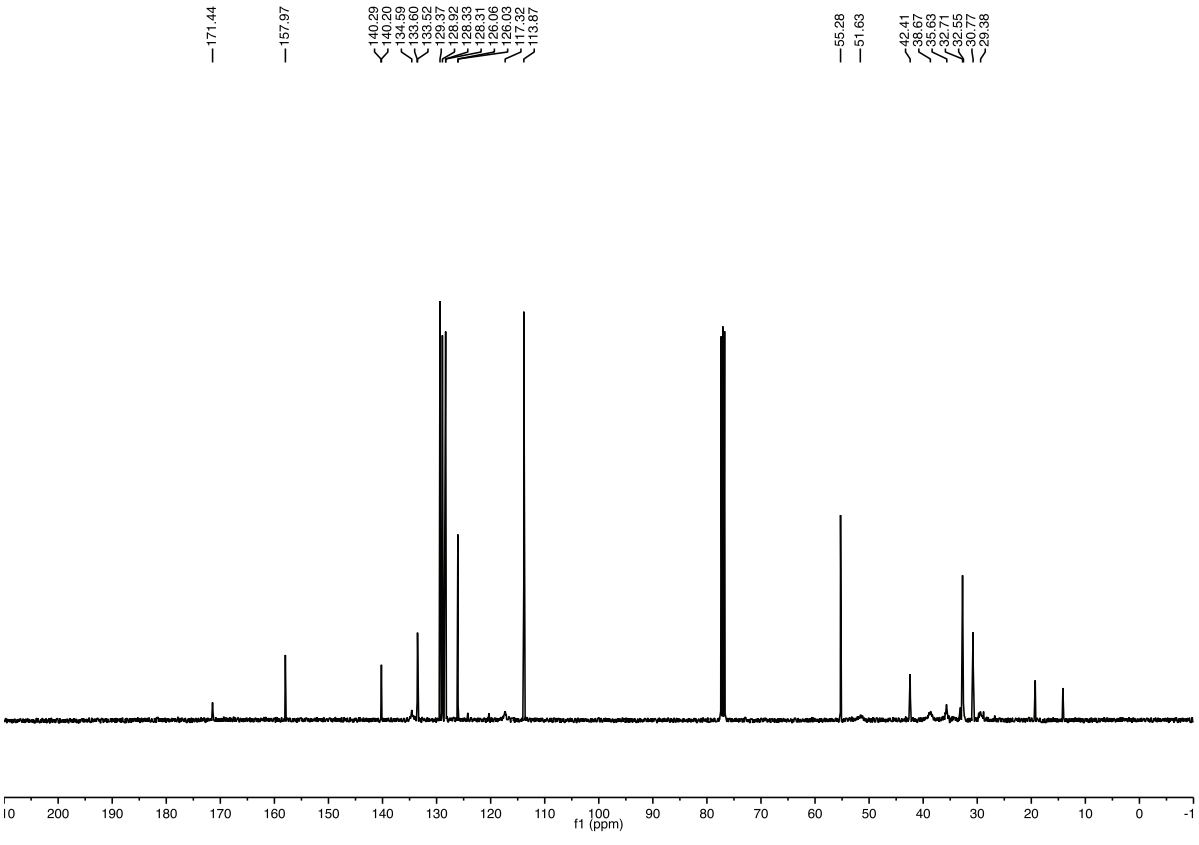
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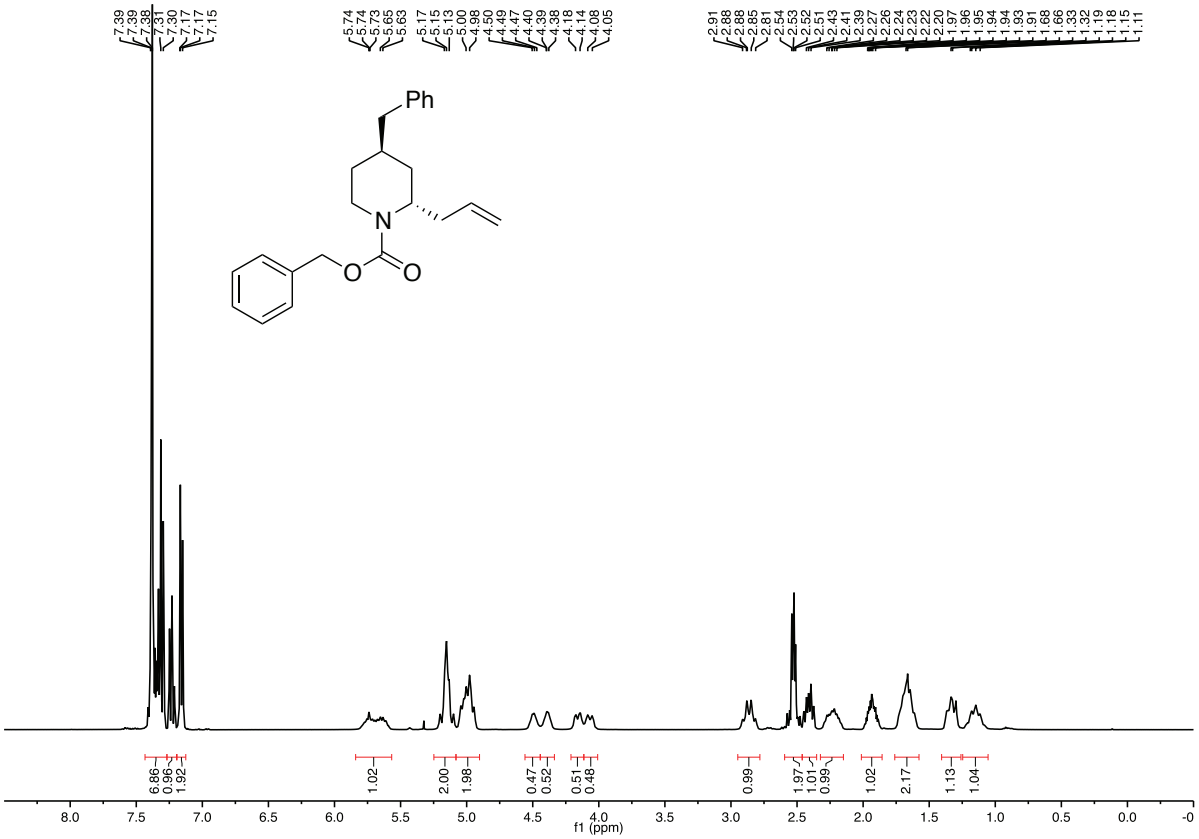
f1 (ppm)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2.20
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1.95
1.94
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1.93
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1.32
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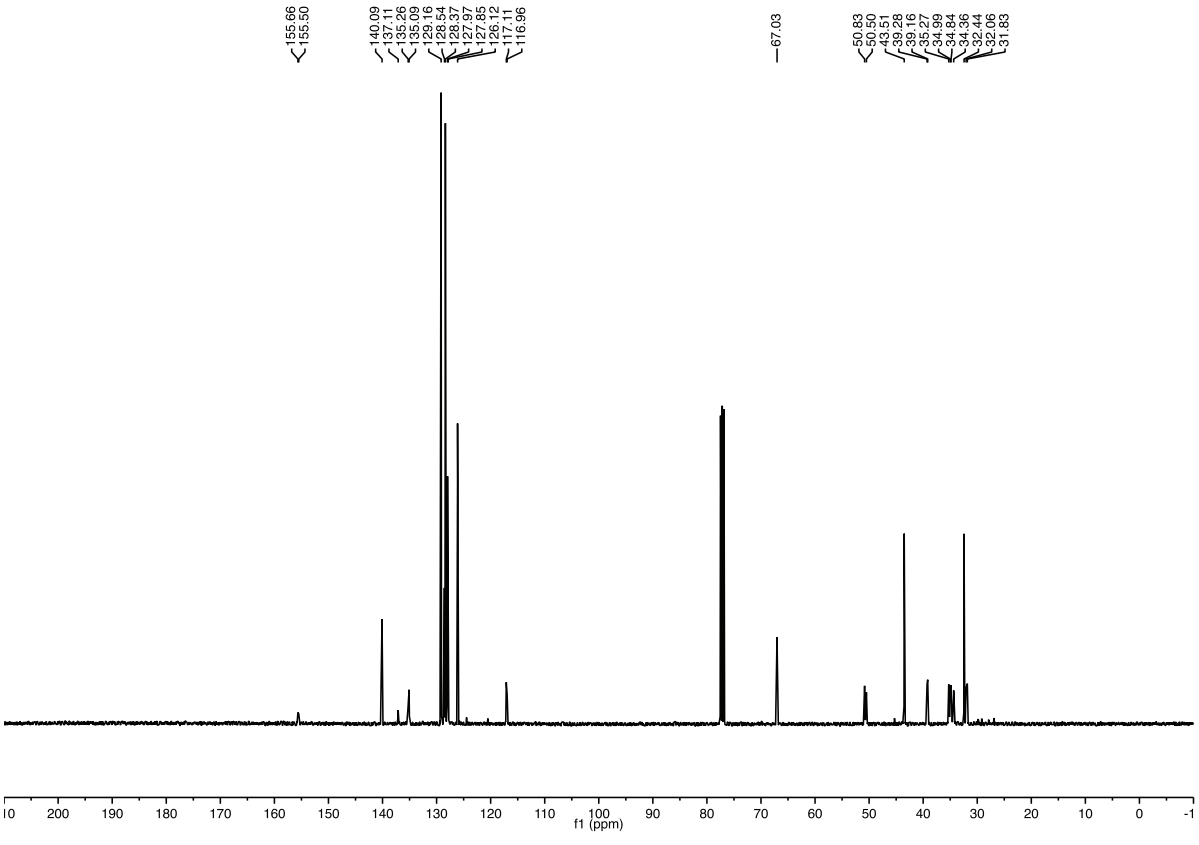
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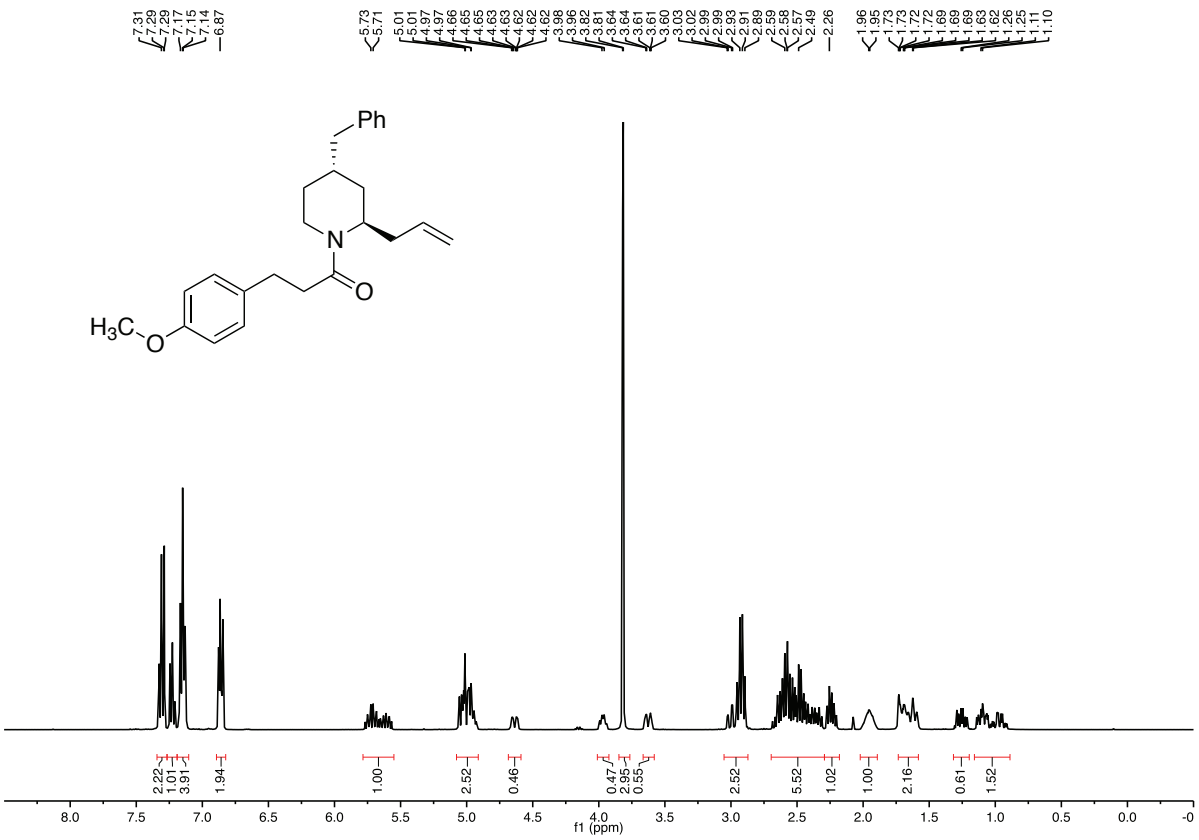
31.83
f1 (ppm)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3.60
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1.62
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1.25
1.11
1.10
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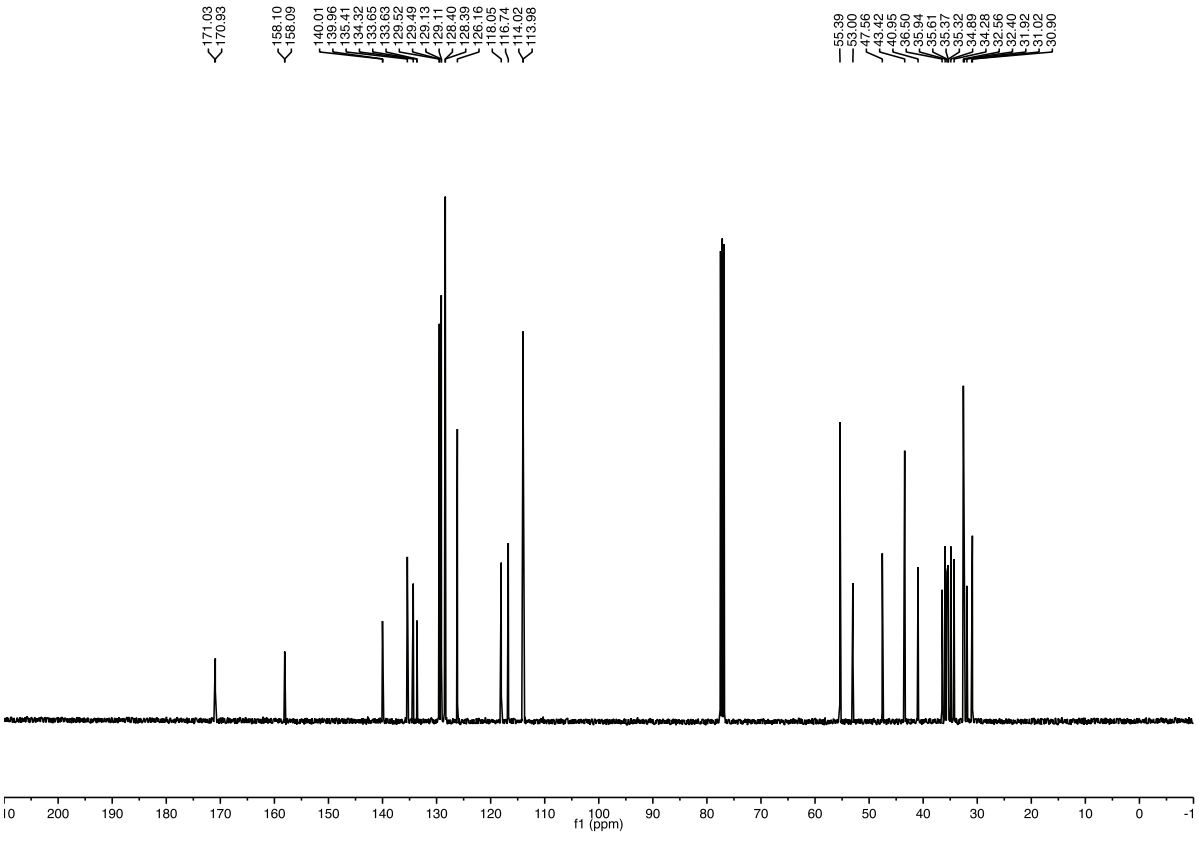
f1 (ppm)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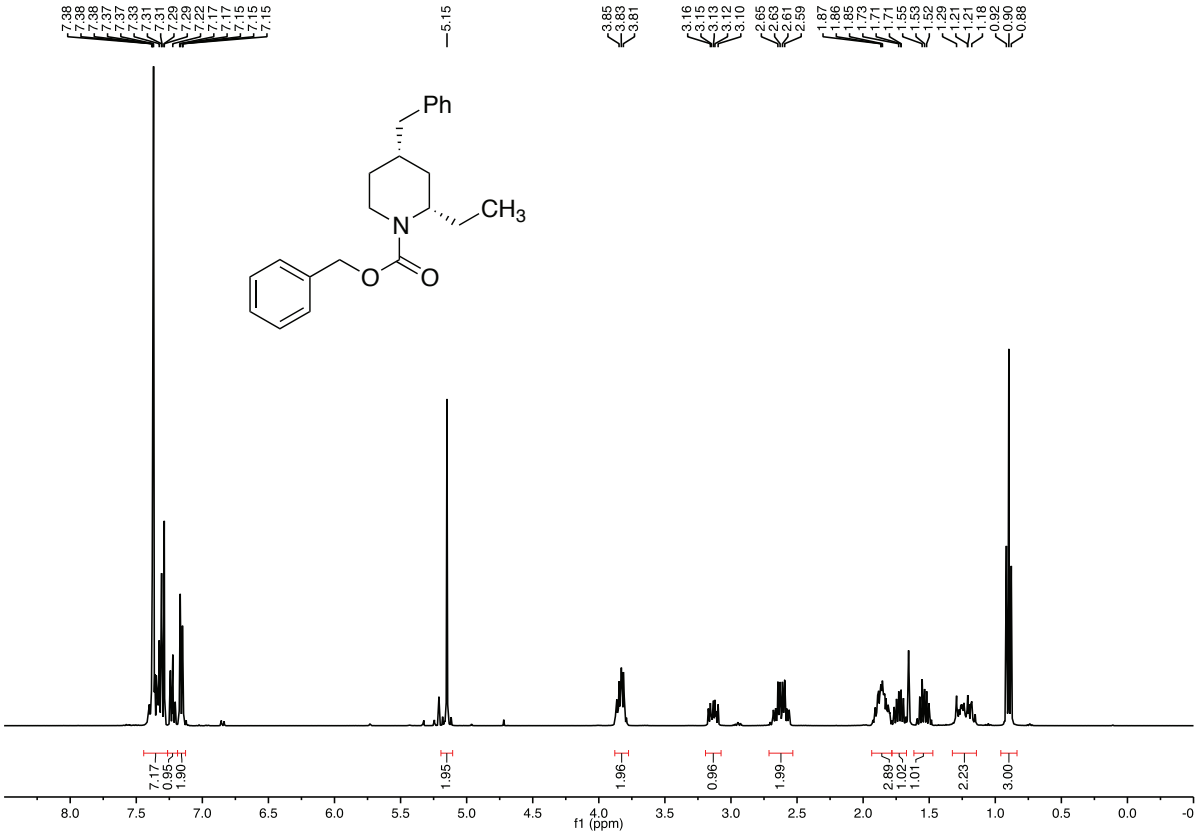
30.90
f1 (ppm)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3.13
3.12
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1.85
1.73
1.71
1.71
1.55
1.53
1.52
1.29
1.21
1.21
1.18
0.92
0.90
0.88
Ph
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O
O
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1.95
1.96
0.96
1.99
2.89
1.02
1.01
2.23
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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2.0
1.5
1.0
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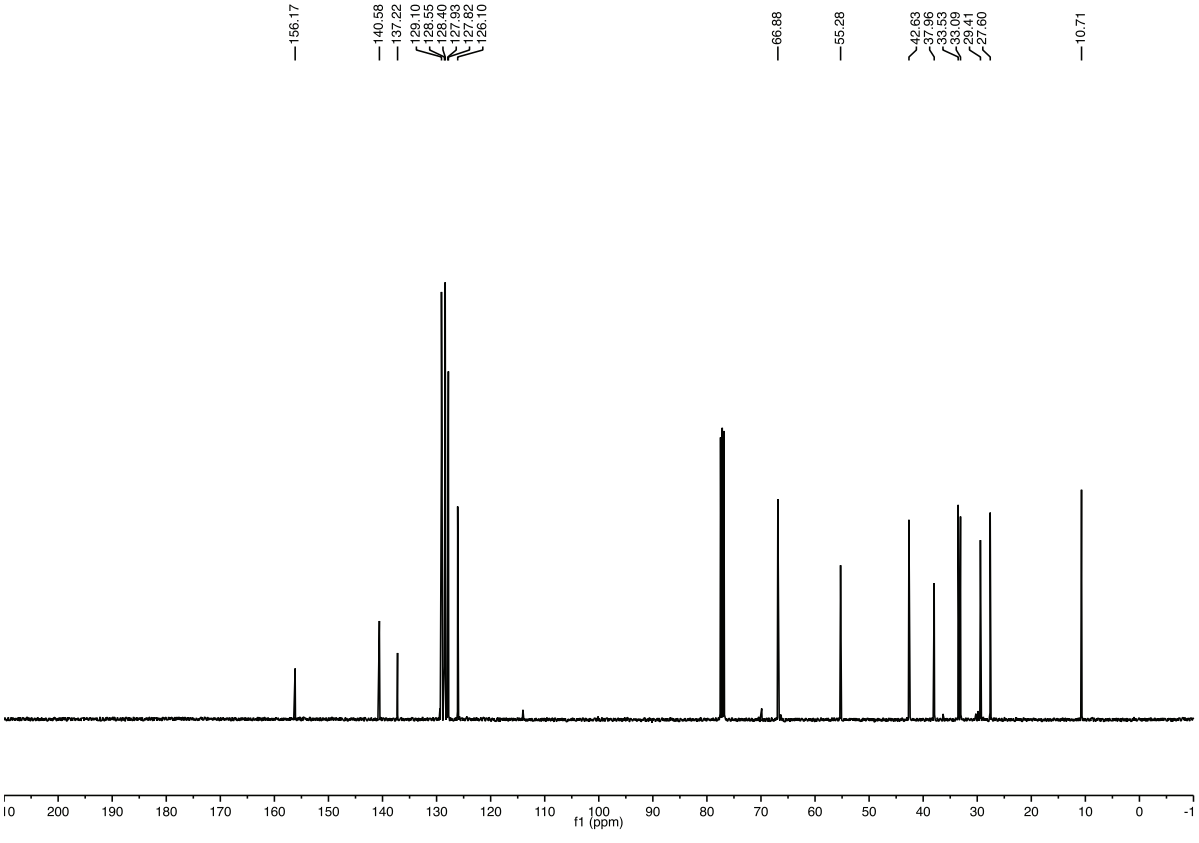
-0
f1 (ppm)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66.88
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37.96
33.53
33.09
29.41
27.60
10.71
10
200
190
180
170
160
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120
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100
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80
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30
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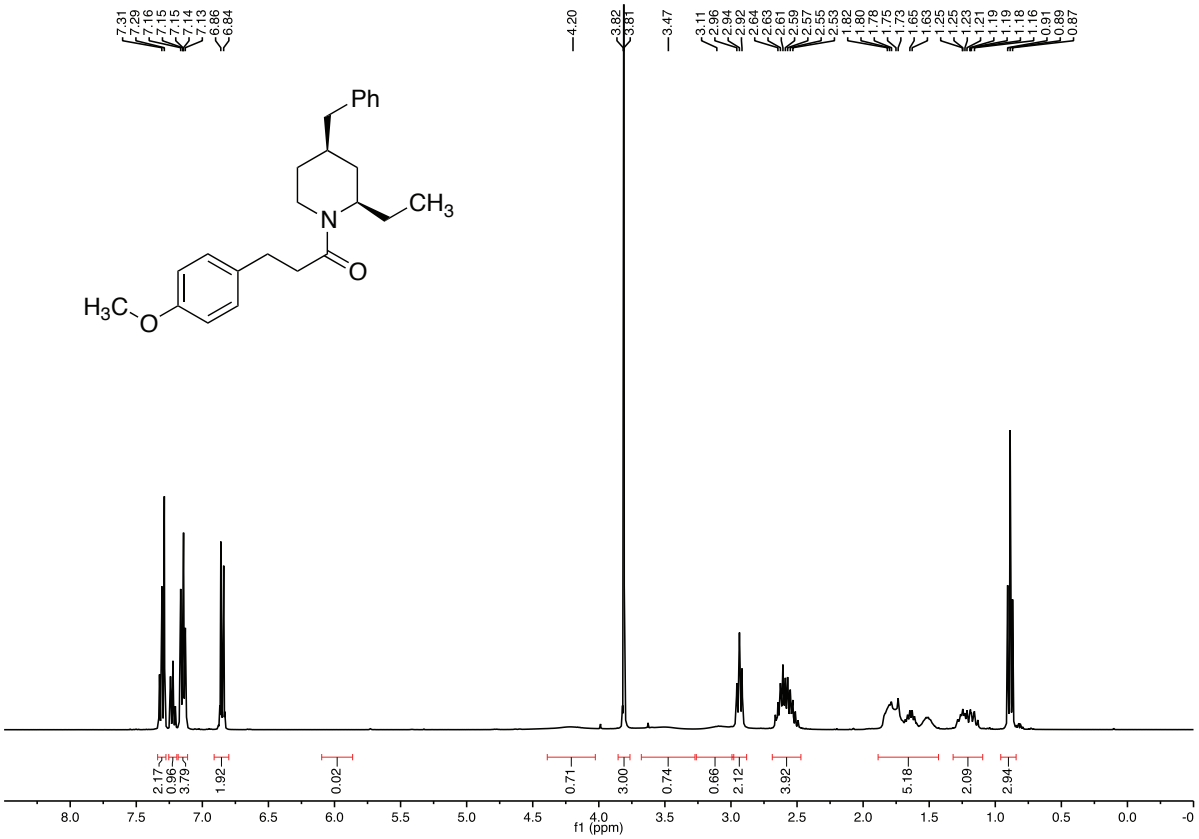
f1 (ppm)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3.47
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2.92
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2.59
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1.75
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1.63
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1.25
1.23
1.21
1.19
1.19
1.18
1.16
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0.89
0.87
Ph
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O
H3C
O
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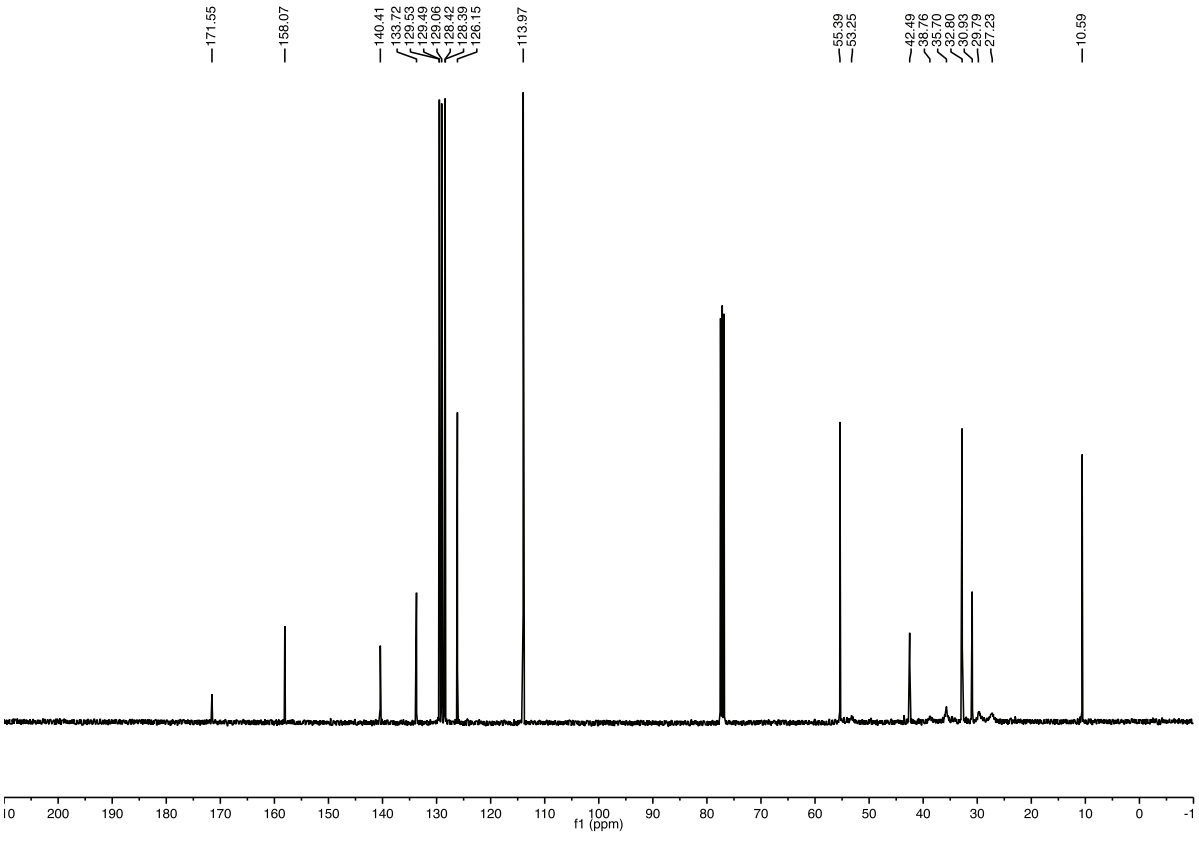
f1 (ppm)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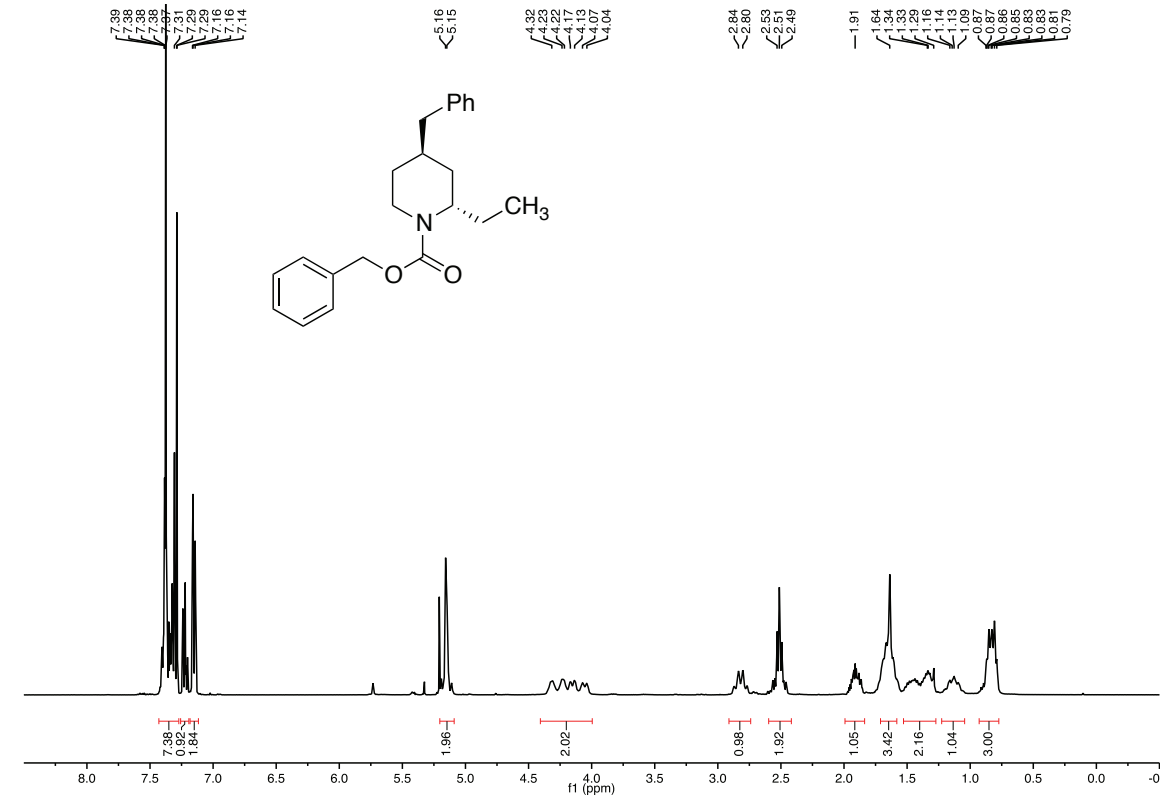
32.80
30.93
29.79
27.23
10.59
f1 (ppm)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5.15
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4.23
4.22
4.17
4.13
4.07
4.04
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2.80
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2.51
2.49
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1.64
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1.29
1.16
1.14
1.13
1.09
0.87
0.86
0.86
0.85
0.83
0.83
0.81
0.79
Ph
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CH3
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O
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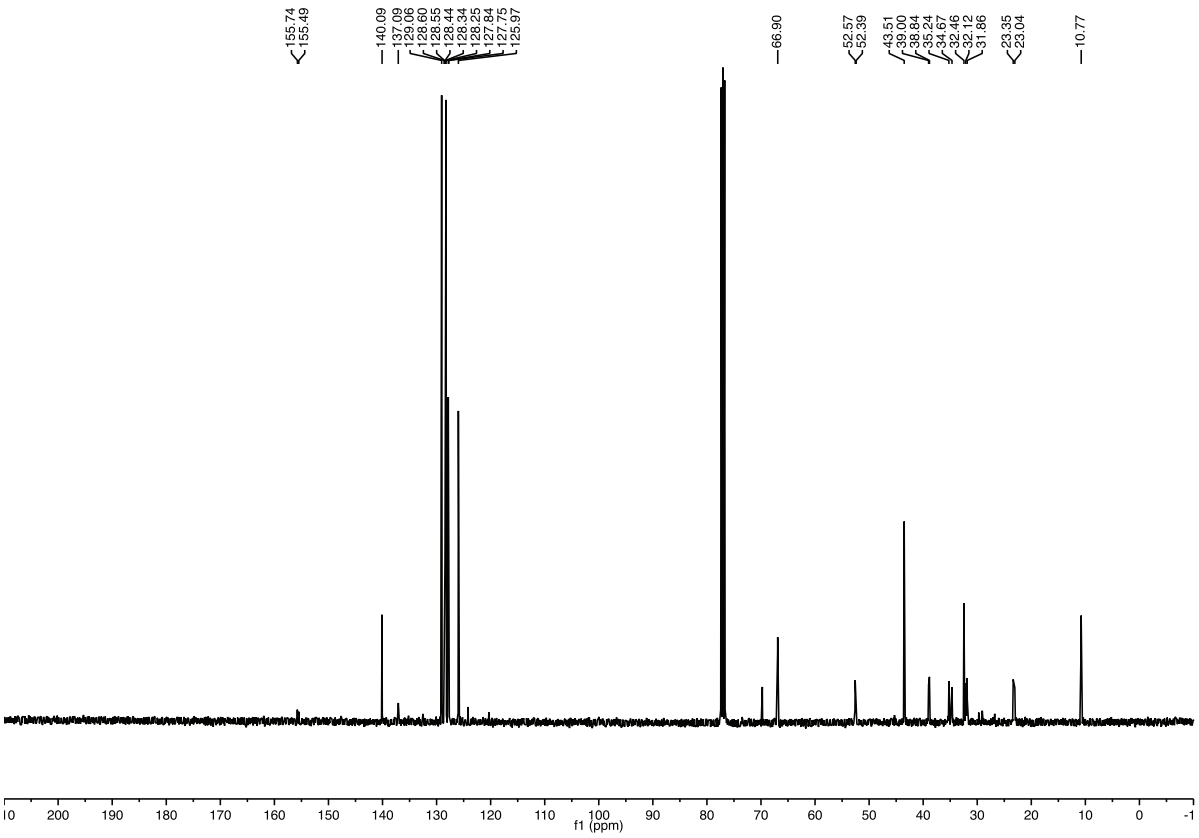
f1 (ppm)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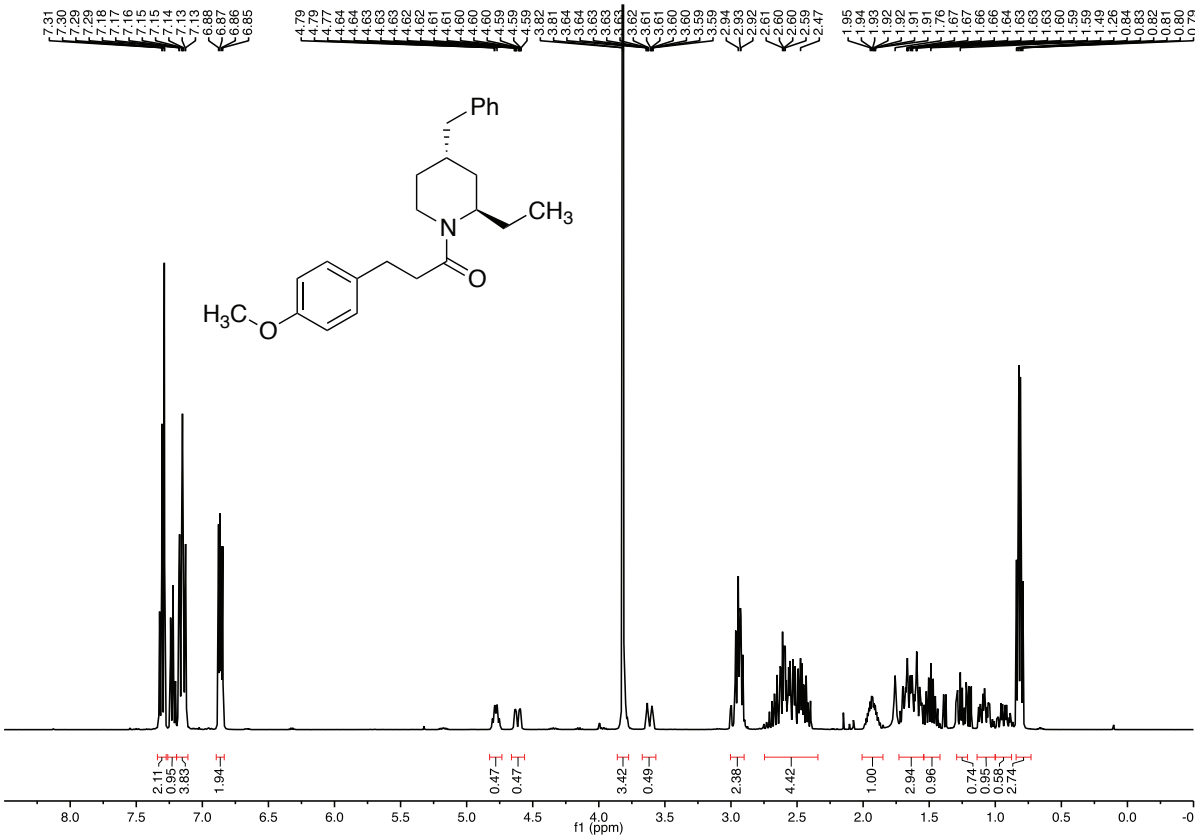
31.86
23.35
23.04
10.77
f1 (ppm)


Ph
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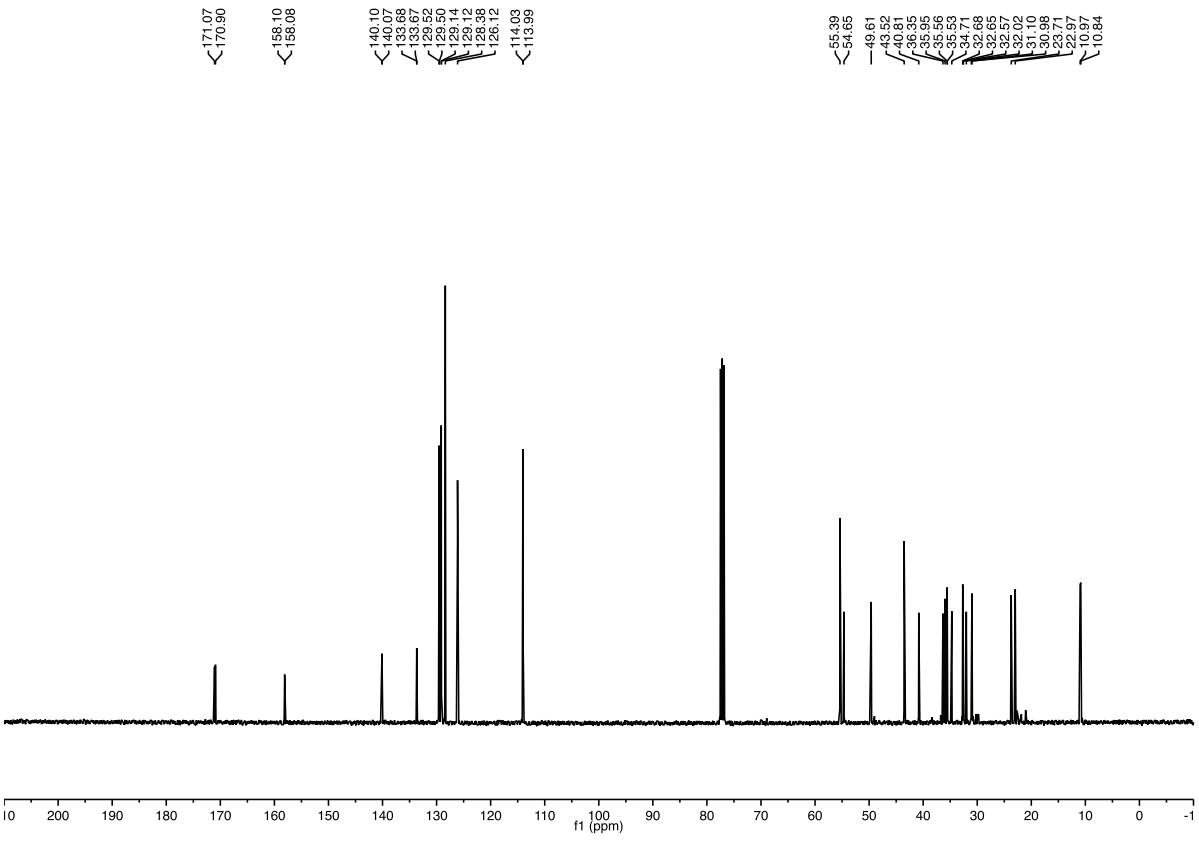
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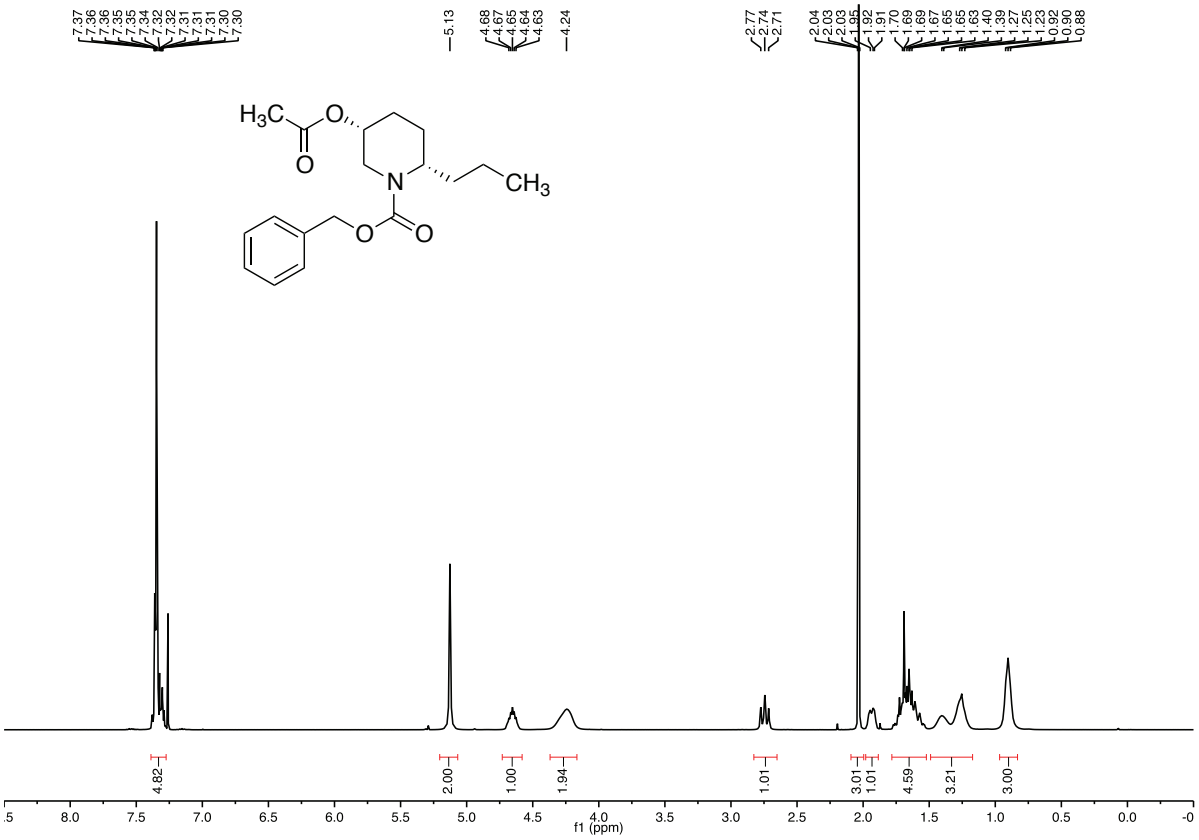
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1.27
1.25
1.23
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0.88
H3C
O
O
N
CH3
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3.01
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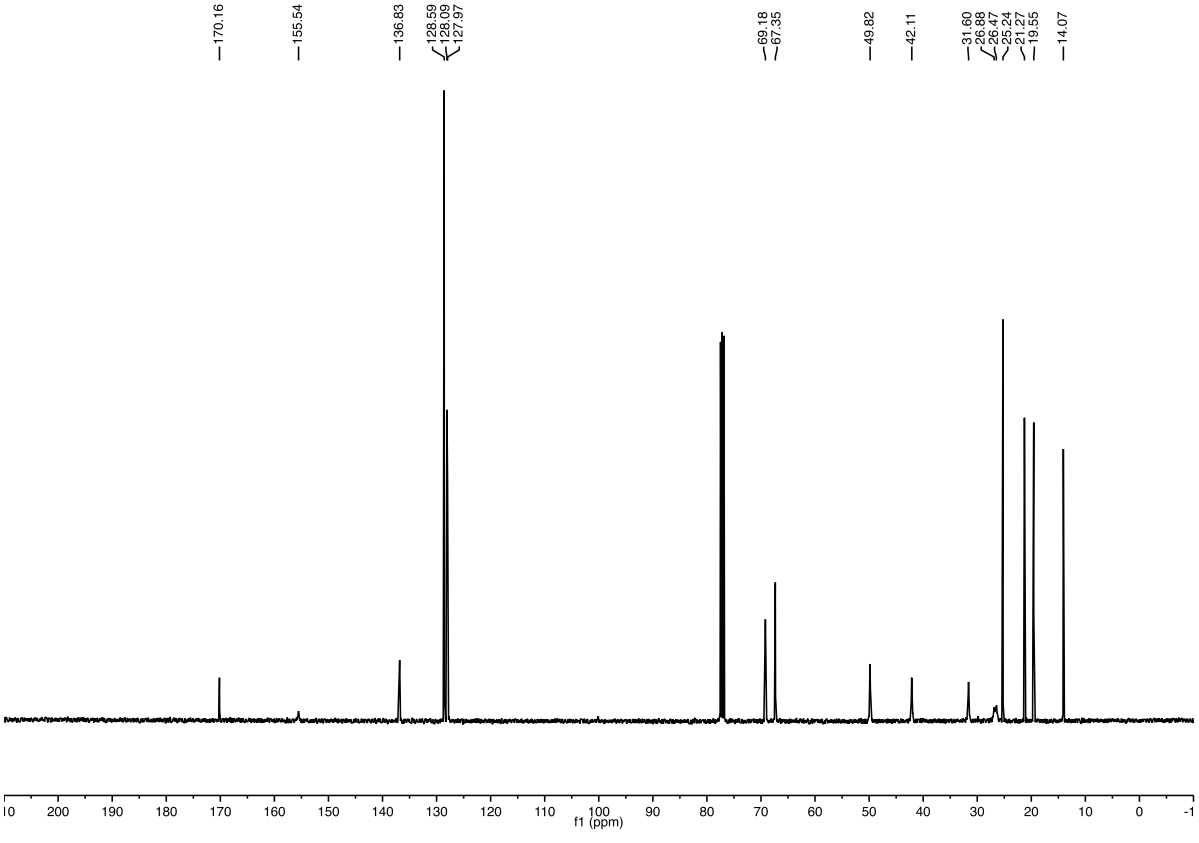
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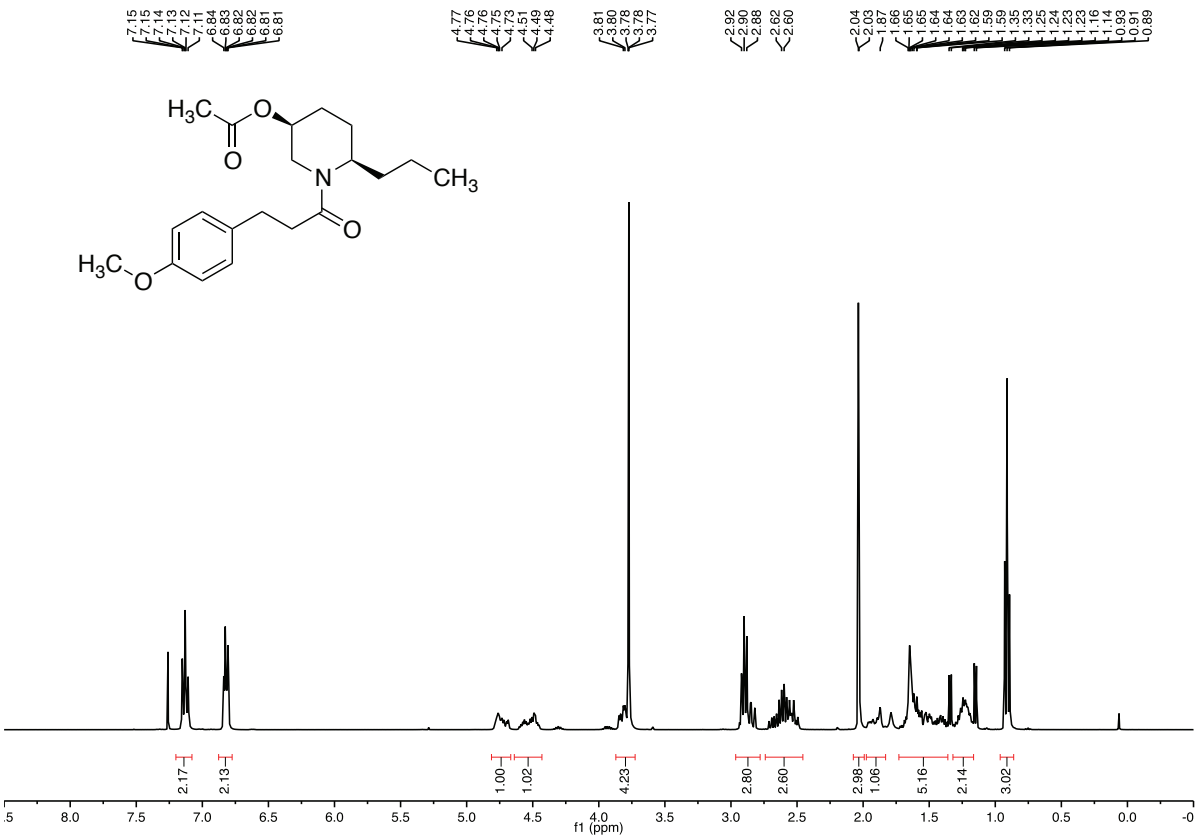
26.47
25.24
21.27
19.55
14.07
f1 (ppm)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1.25
1.24
1.23
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1.16
1.14
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0.91
0.89
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O
O
N
CH3
O
H3C
O
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3.02
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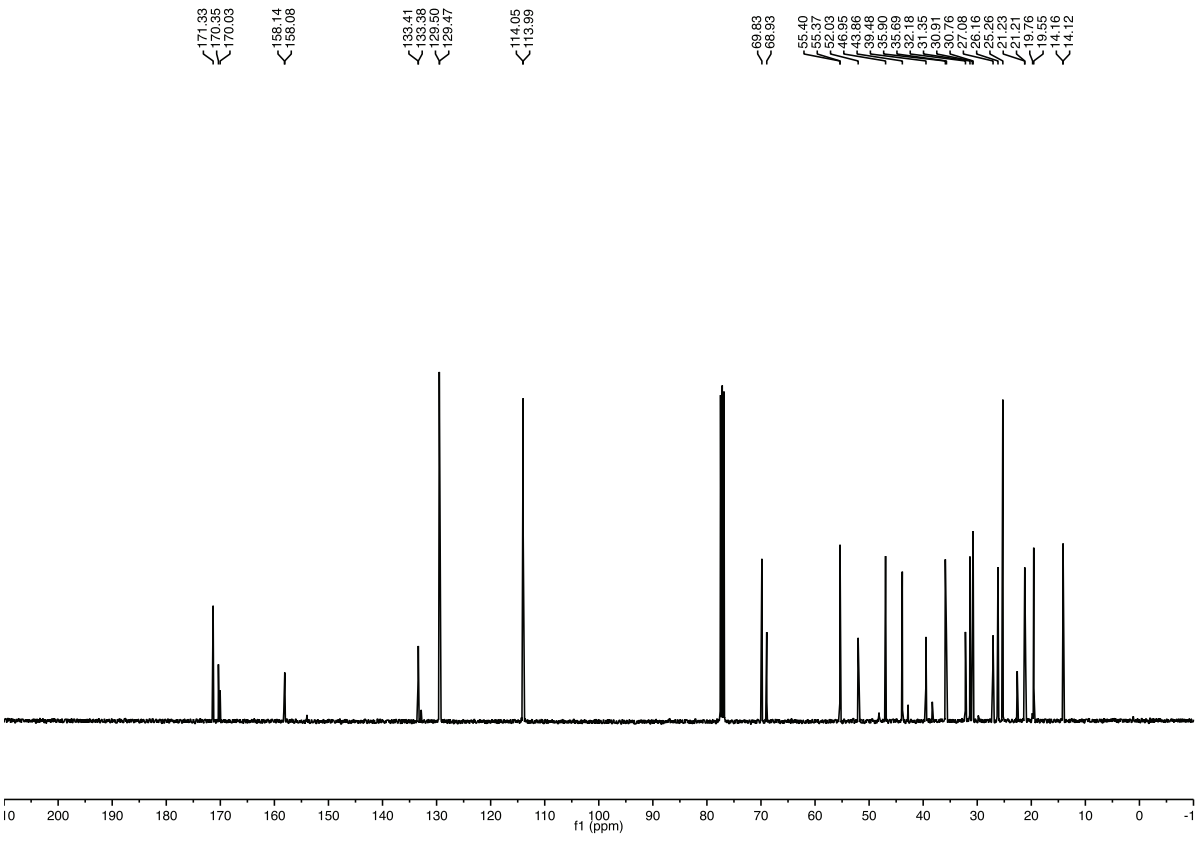
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68.93
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43.86
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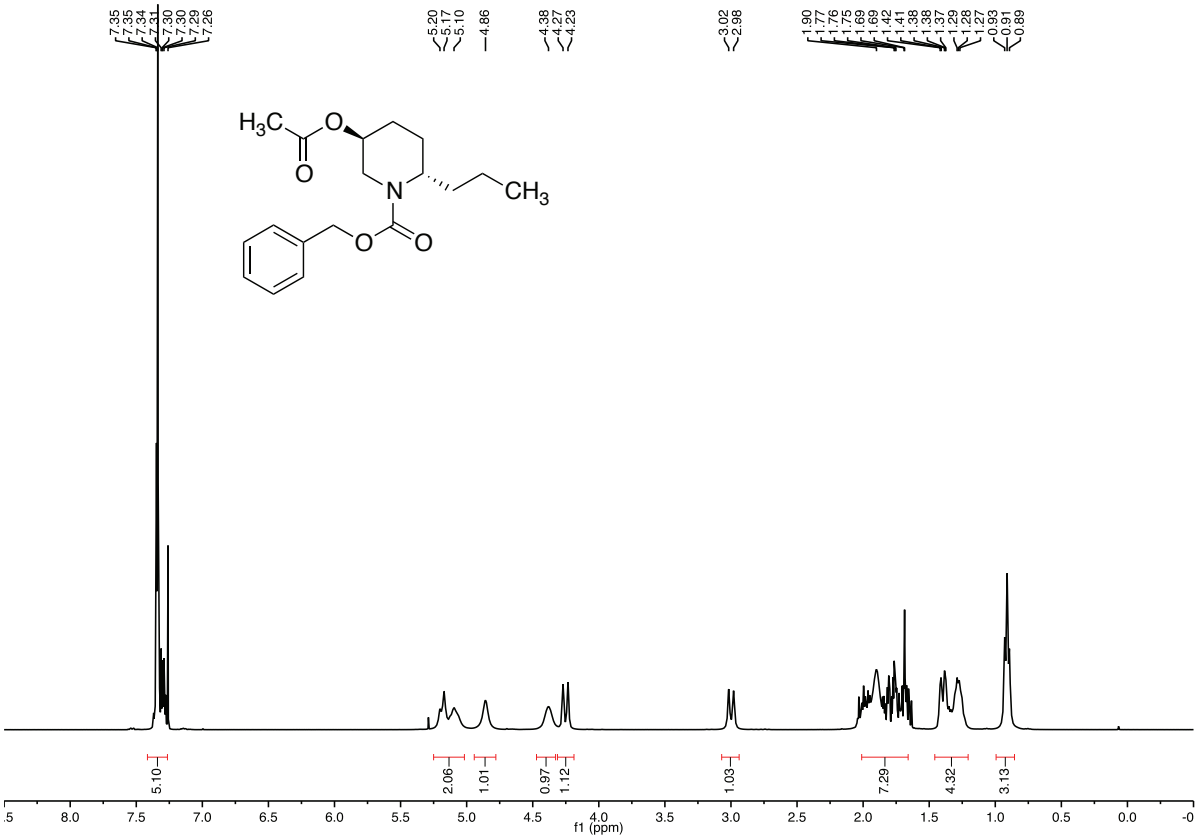
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4.38
4.27
4.23
3.02
2.98
1.90
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1.69
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1.41
1.38
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1.37
1.29
1.28
1.27
0.93
0.91
0.89
H3C
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O
N
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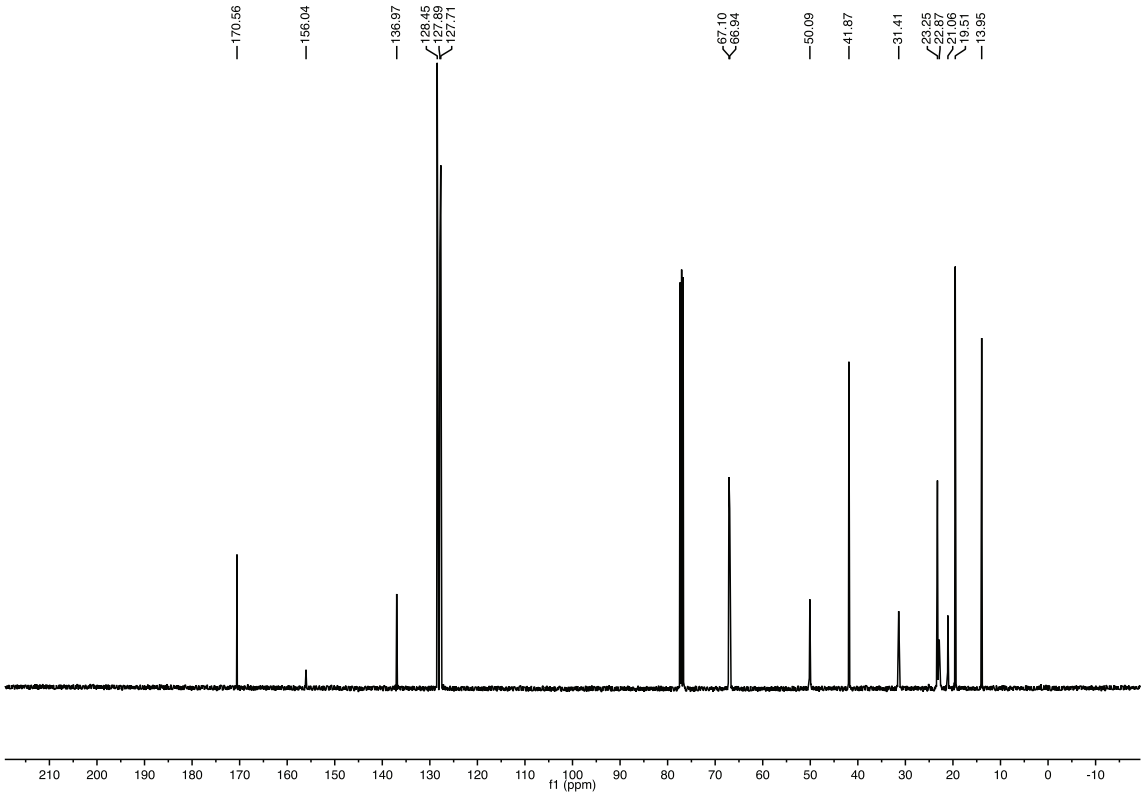
2.06
1.01
0.97
1.12
1.03
7.29
4.32
3.13
f1 (ppm)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41.87
31.41
23.25
22.87
21.06
19.51
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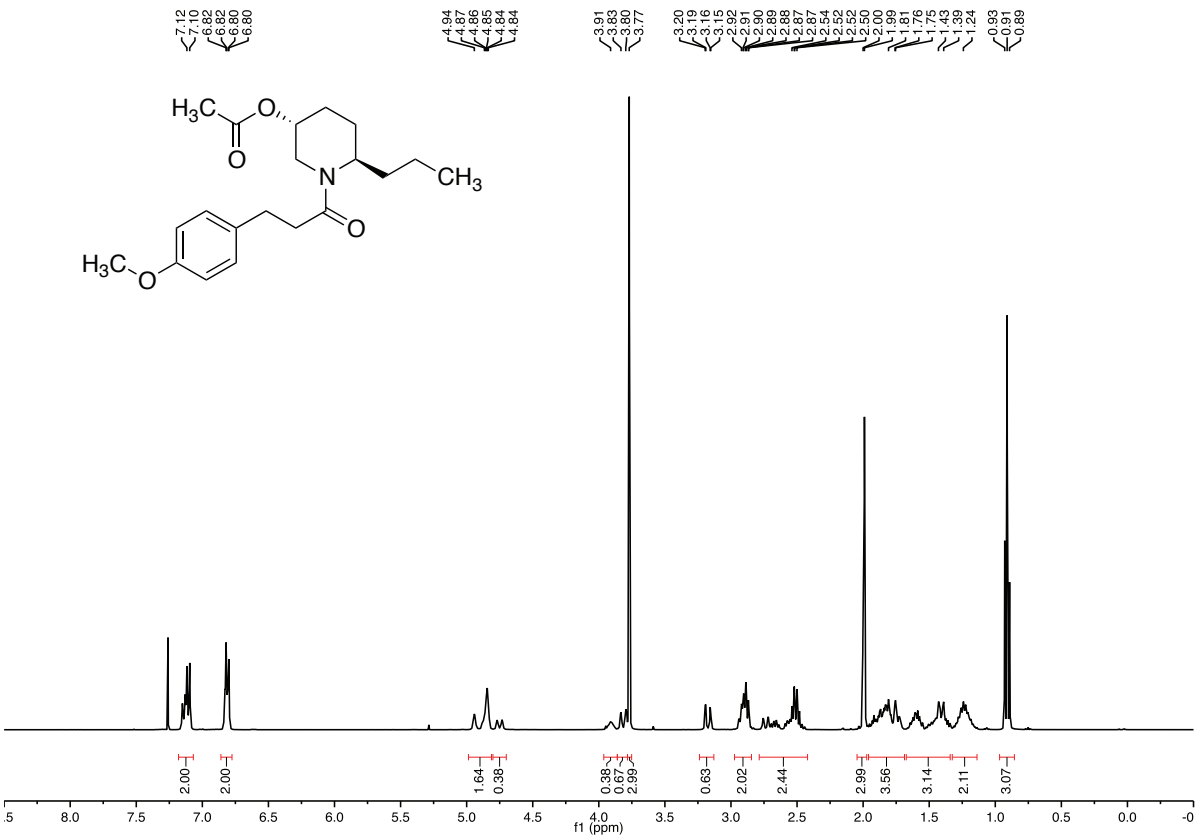
f1 (ppm)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0.91
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CH3
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H3C
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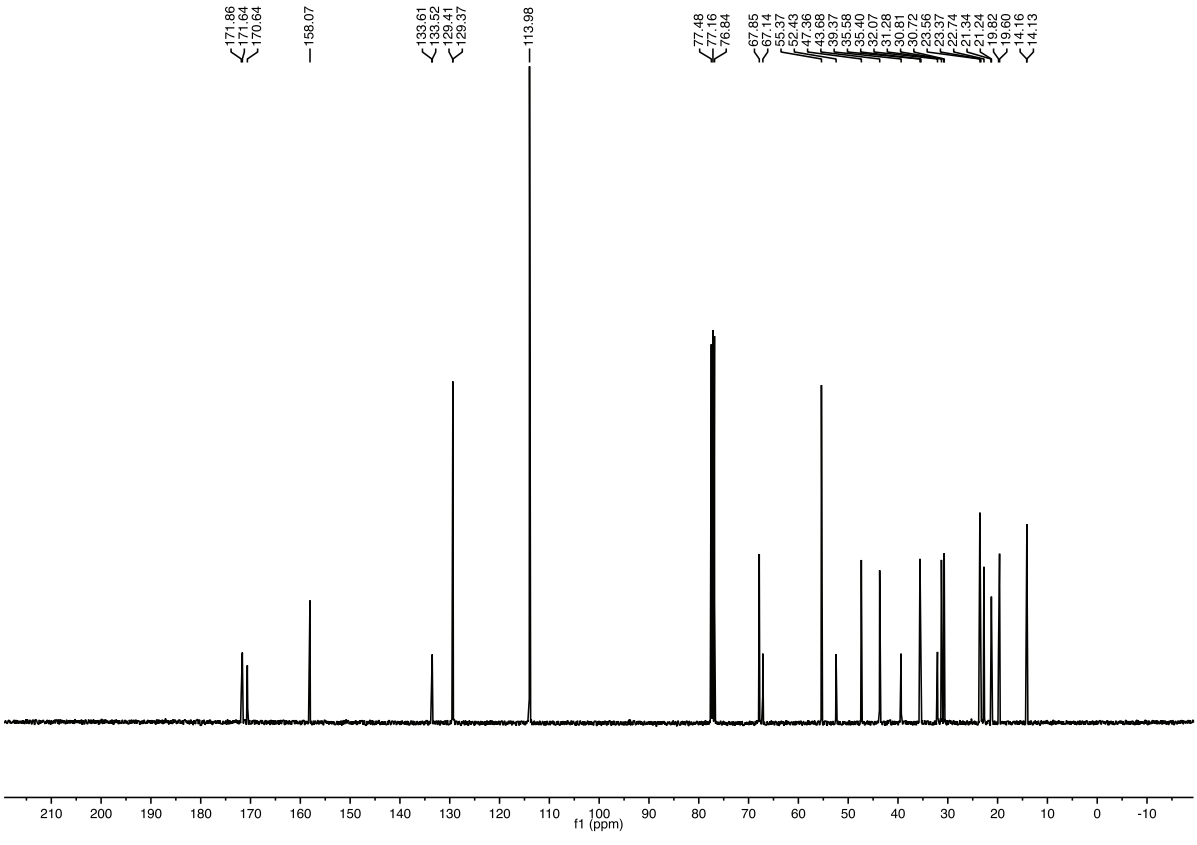
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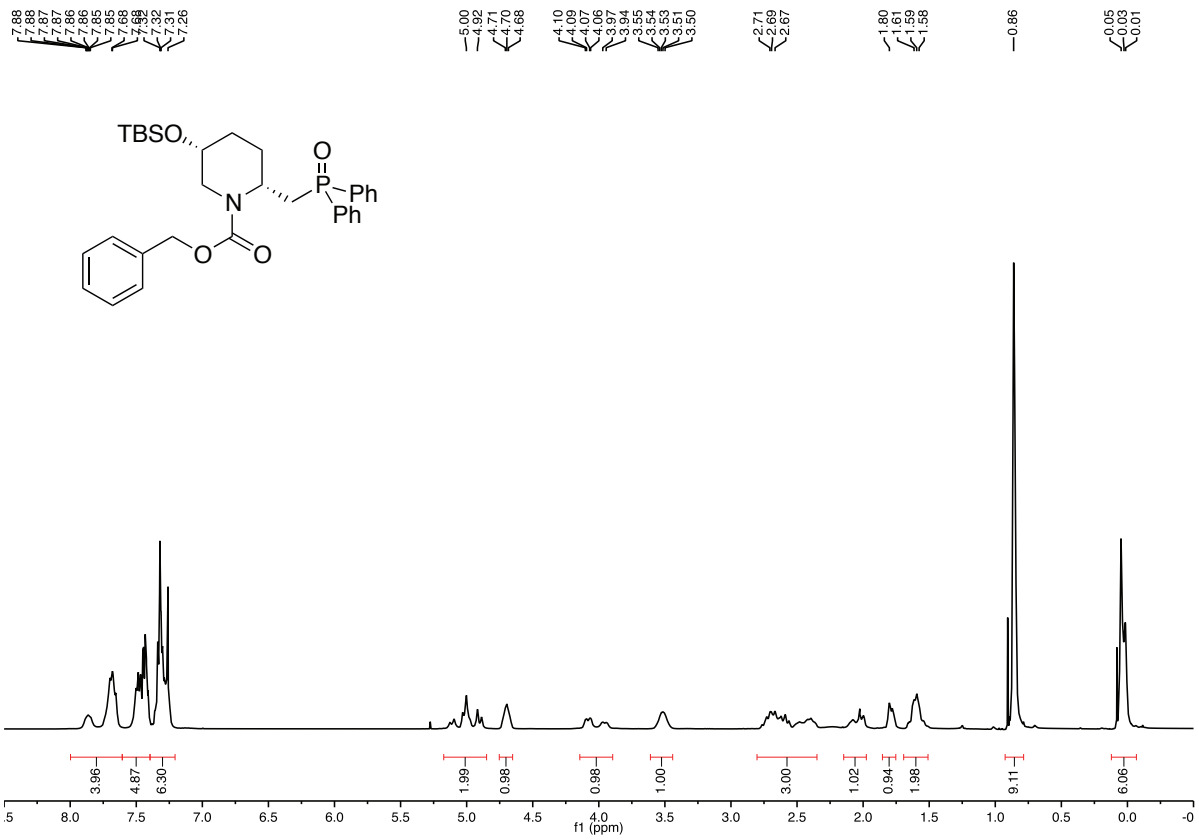
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P
Ph
Ph
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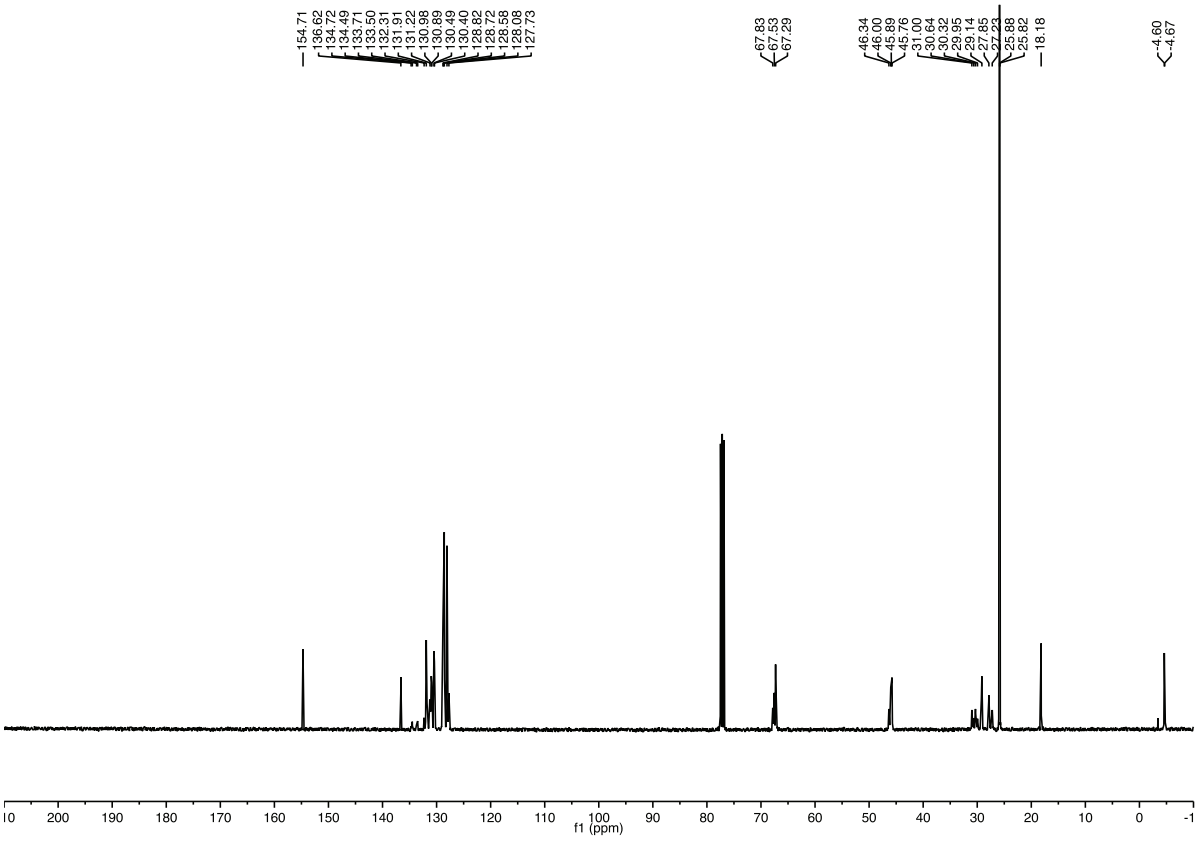
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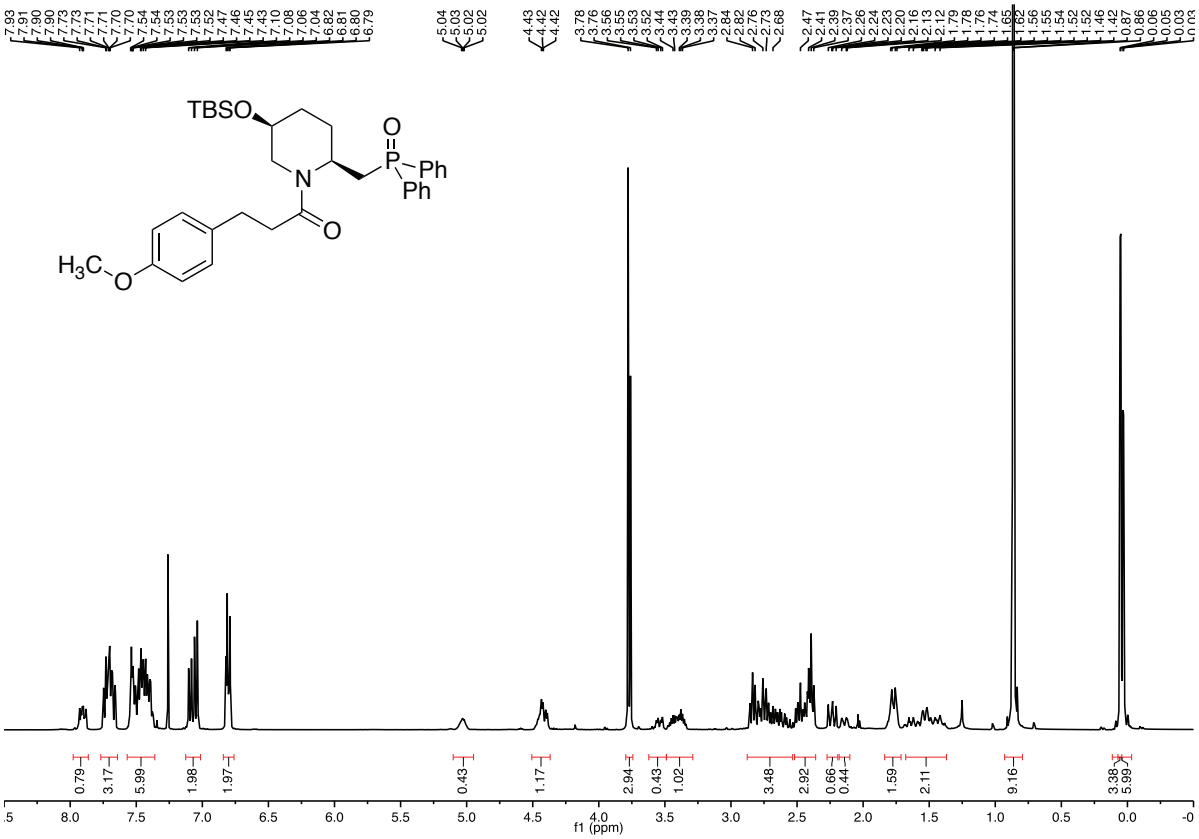
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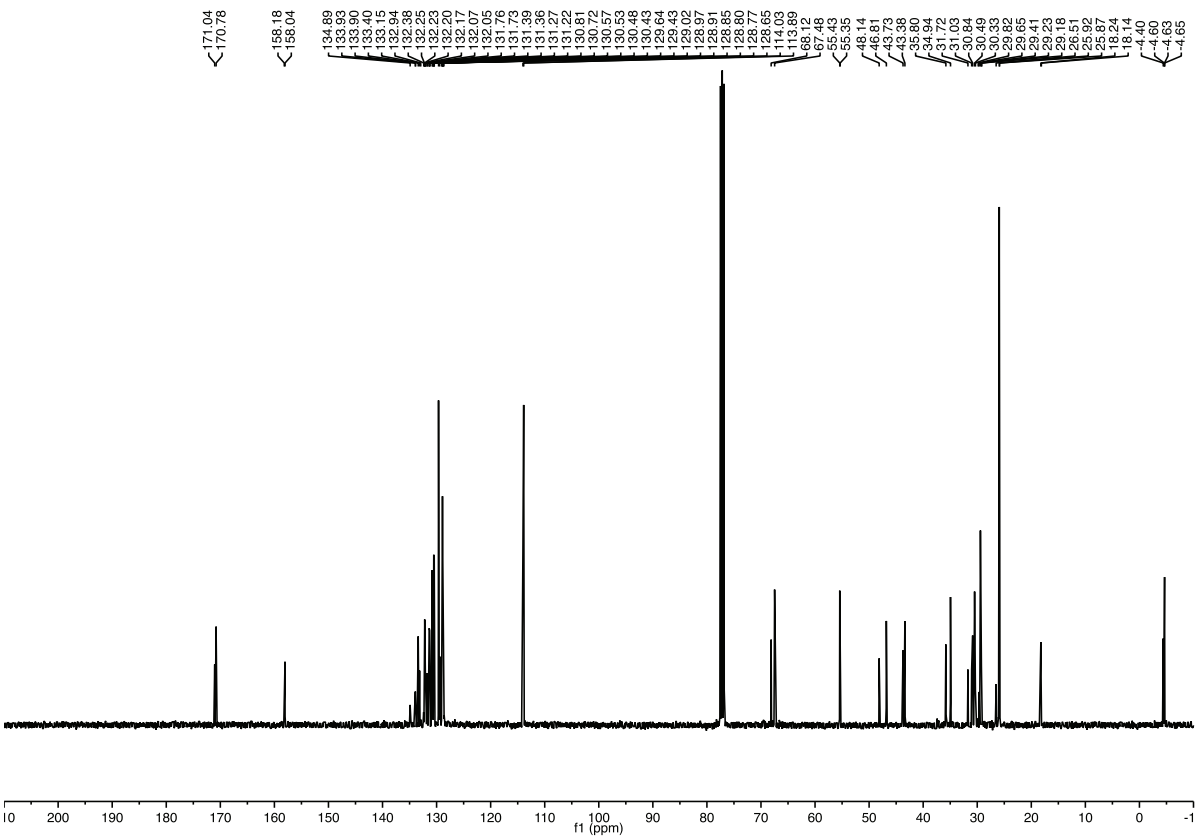
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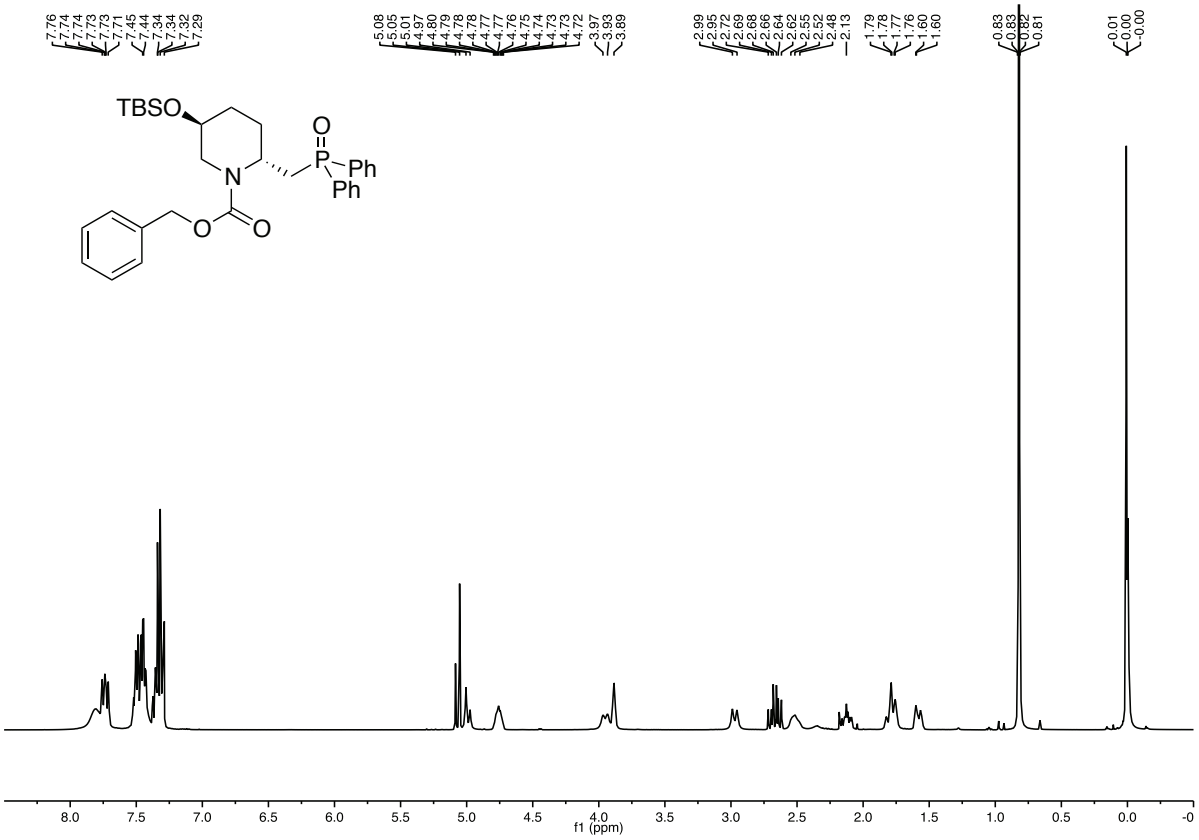
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P
Ph
Ph
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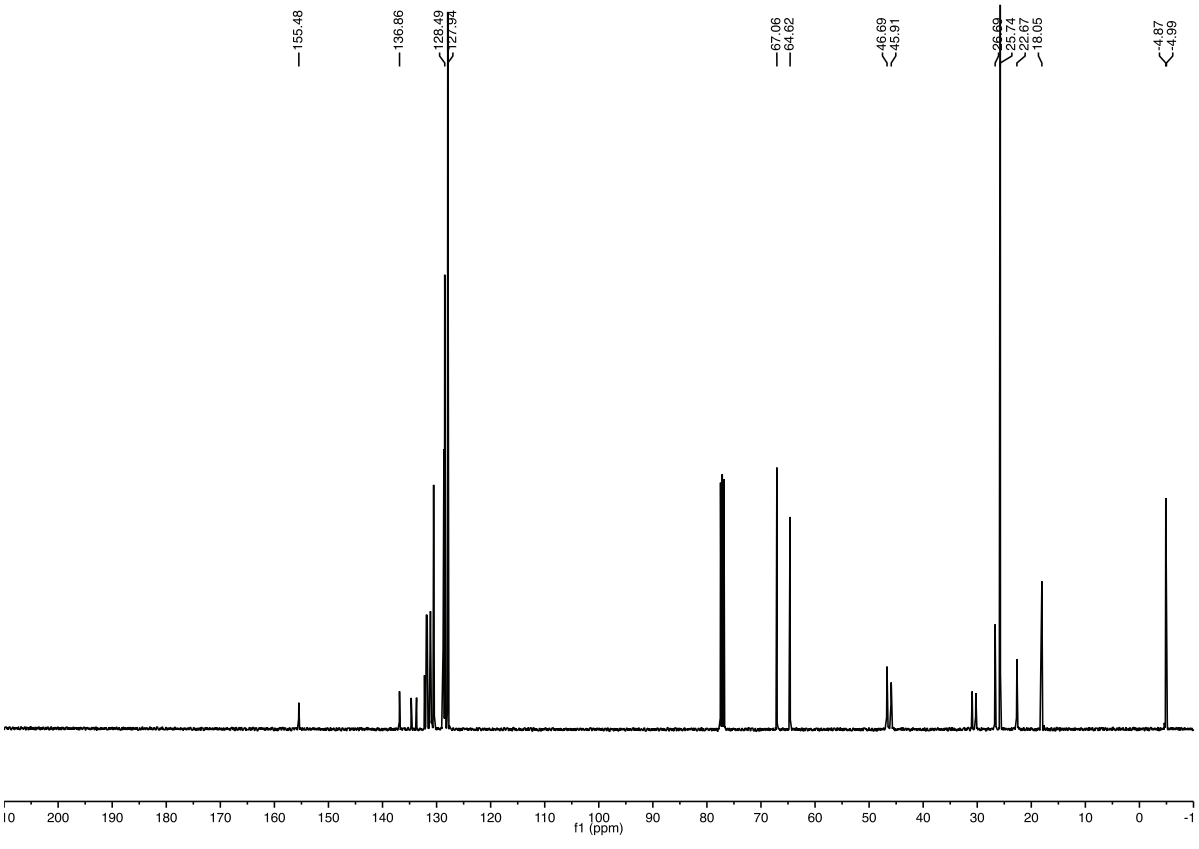
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180
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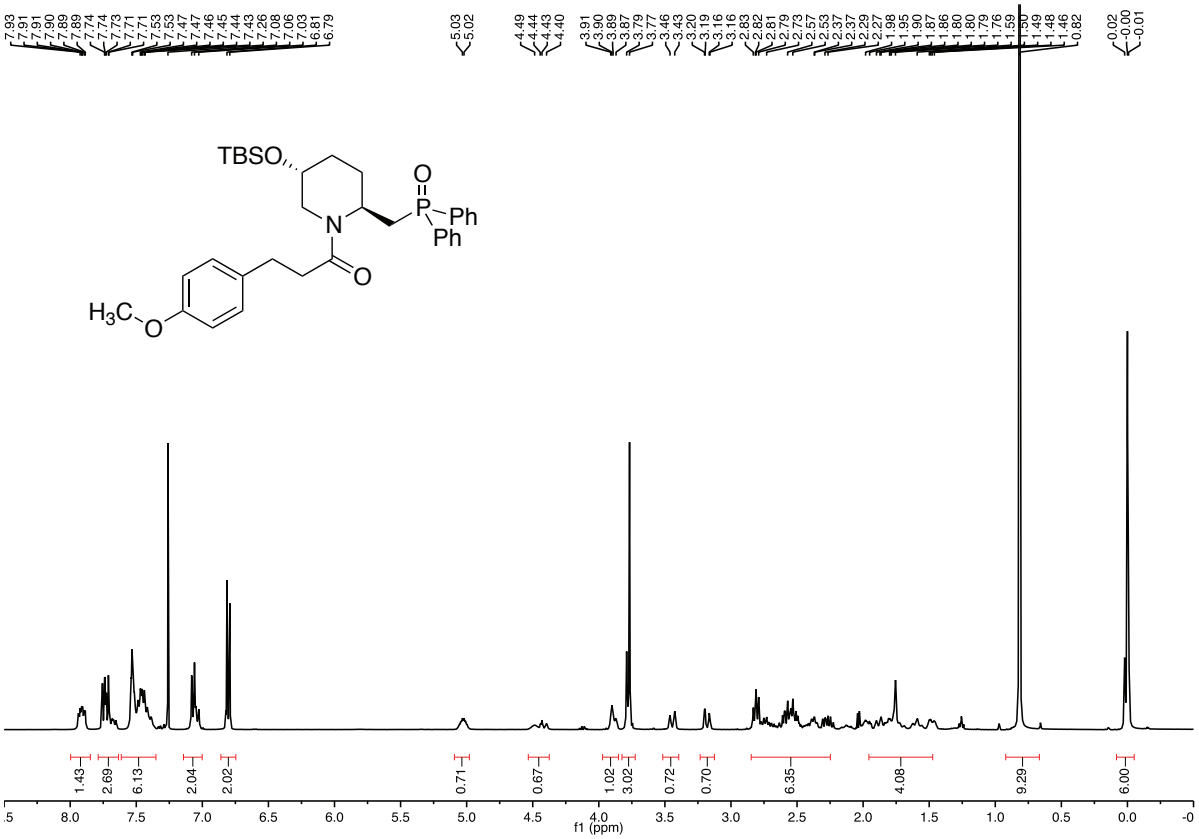
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Ph
Ph
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H3C
O
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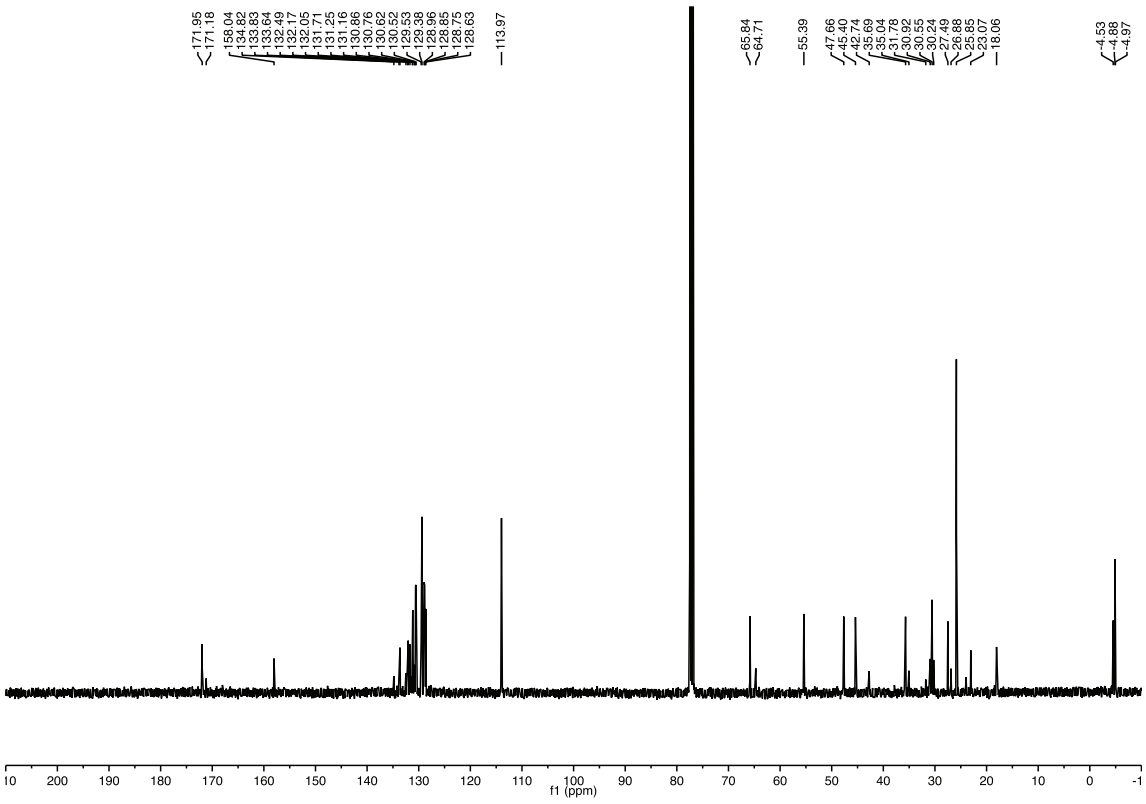
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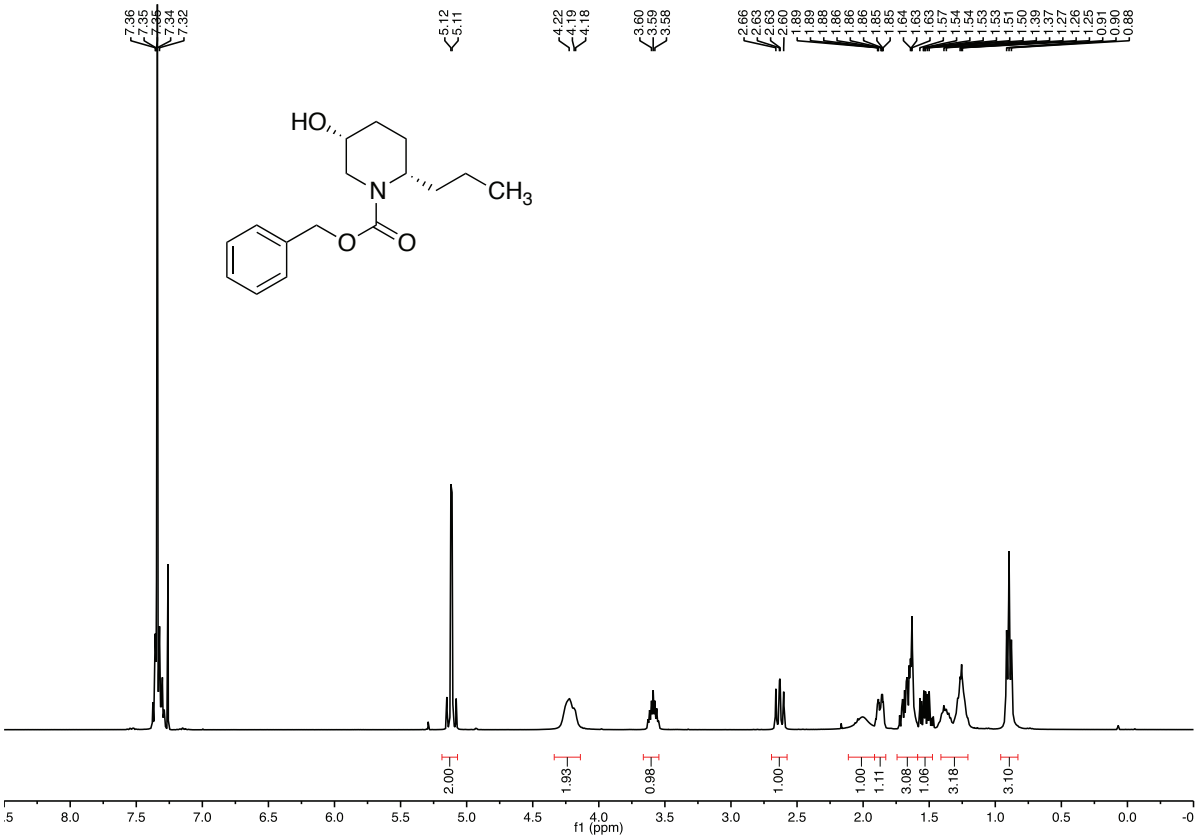
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0.88
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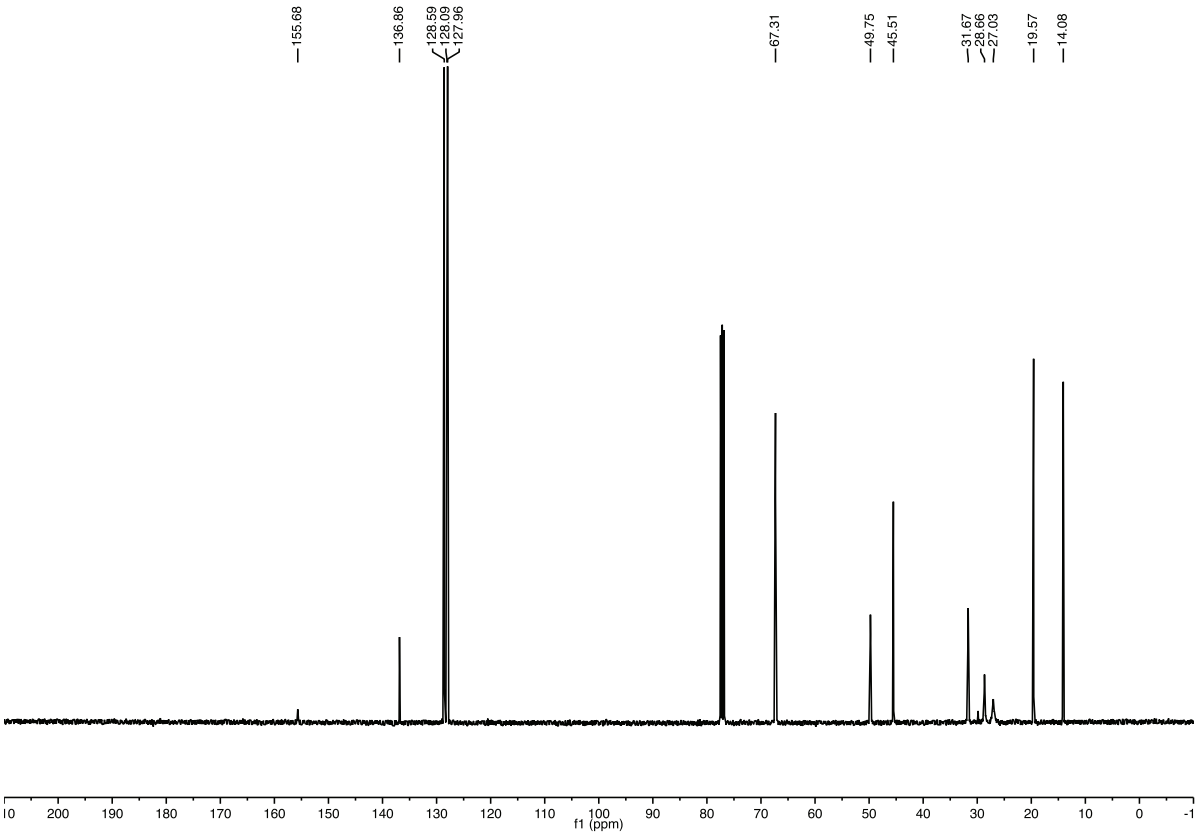
f1 (ppm)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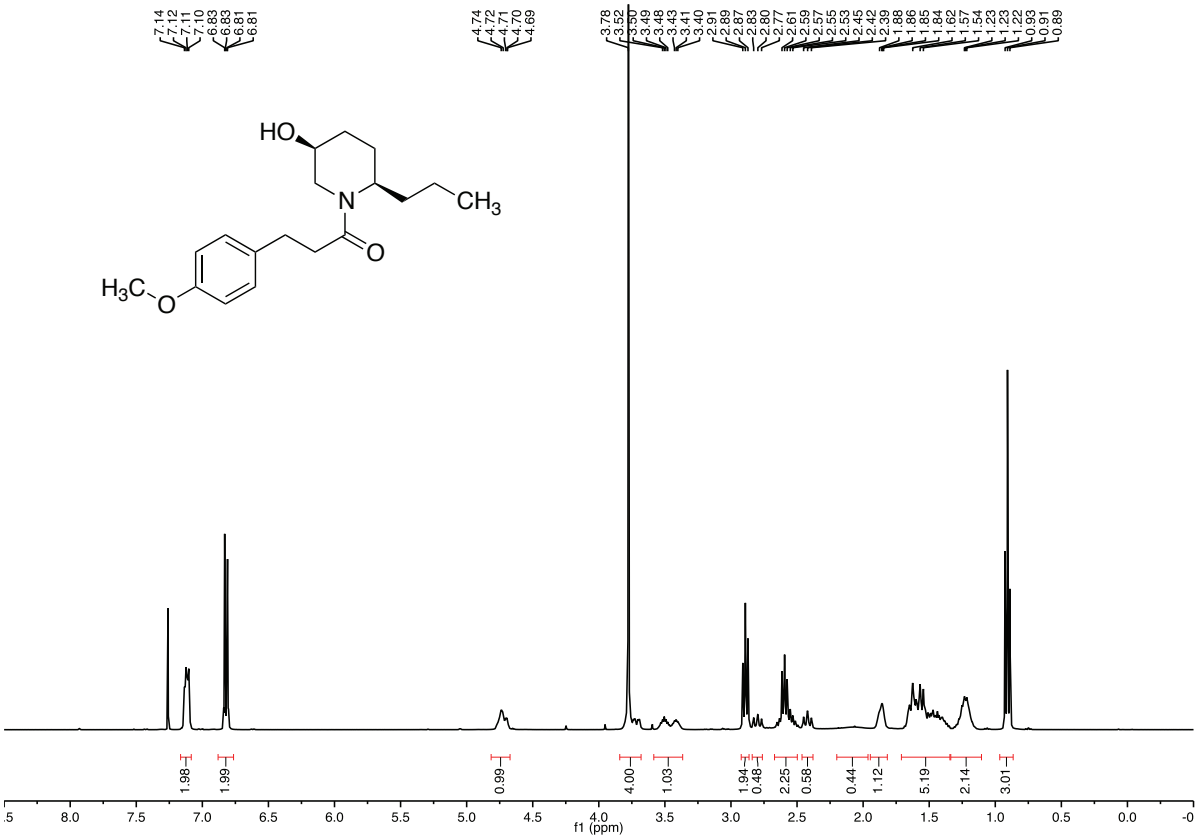
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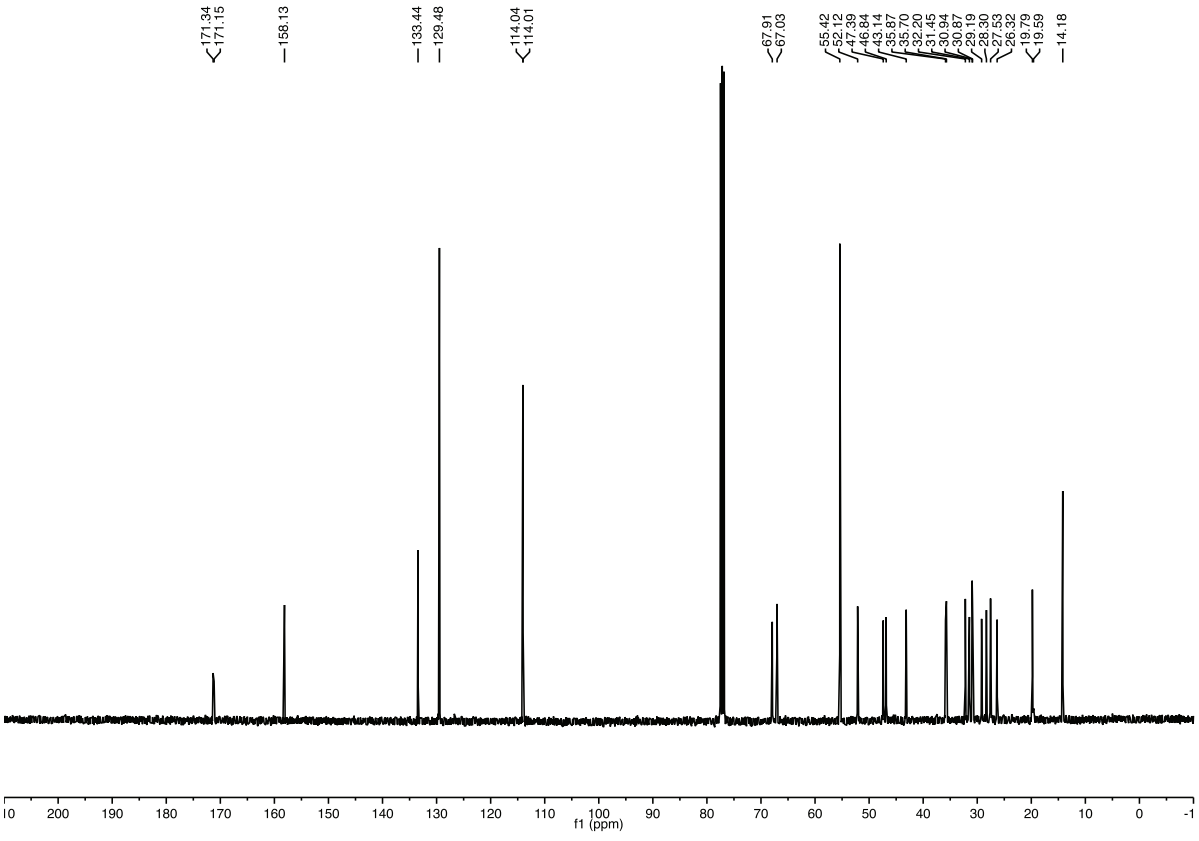
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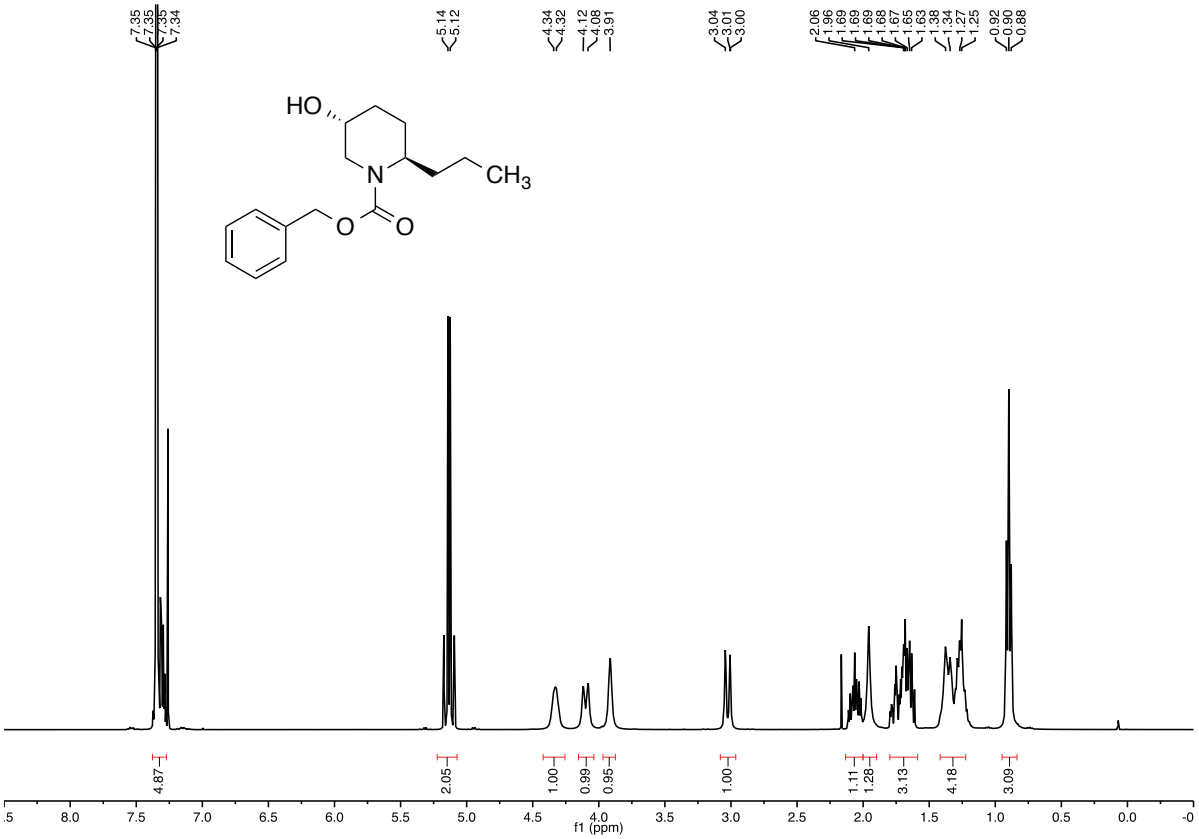
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CH3
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O
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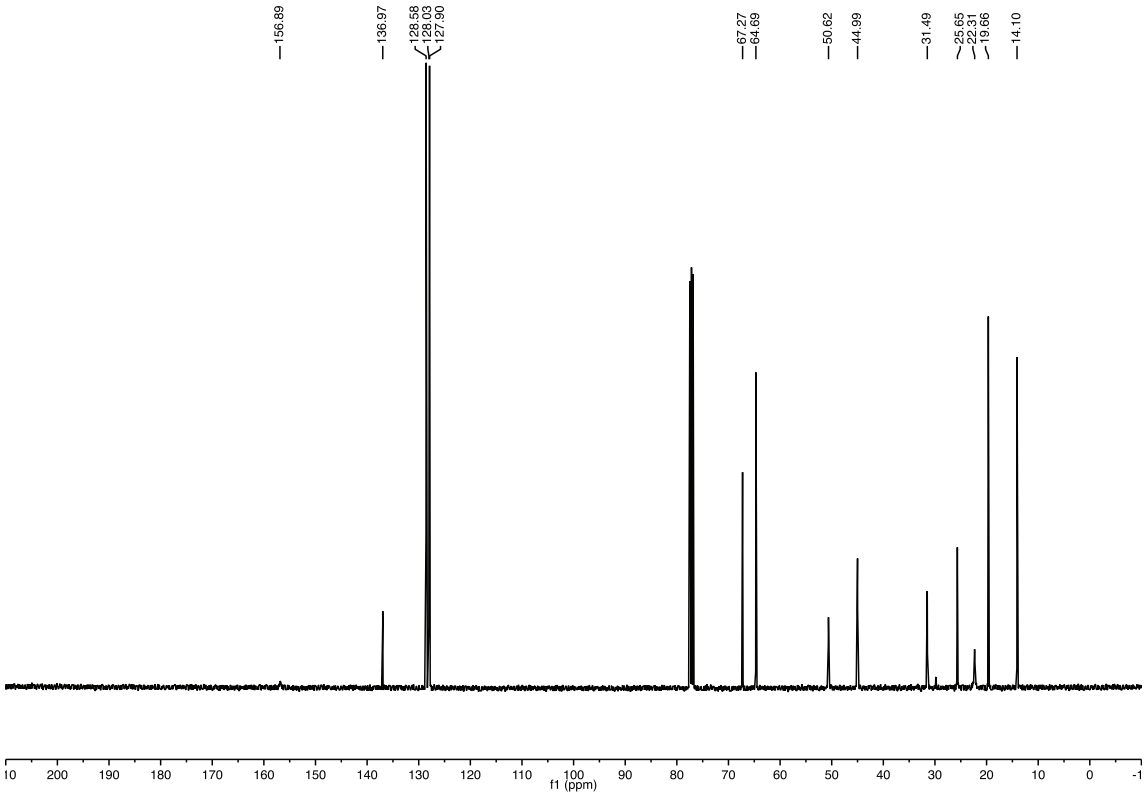
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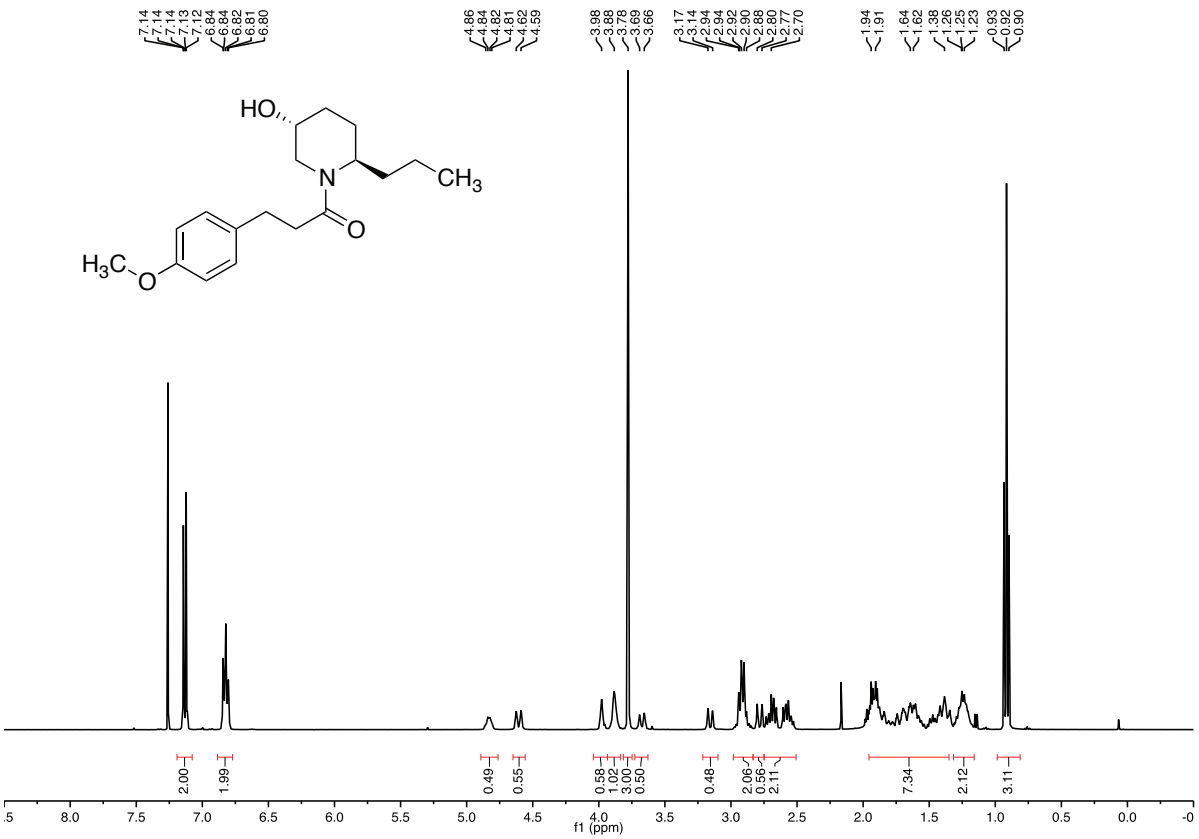
f1 (ppm)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H3C
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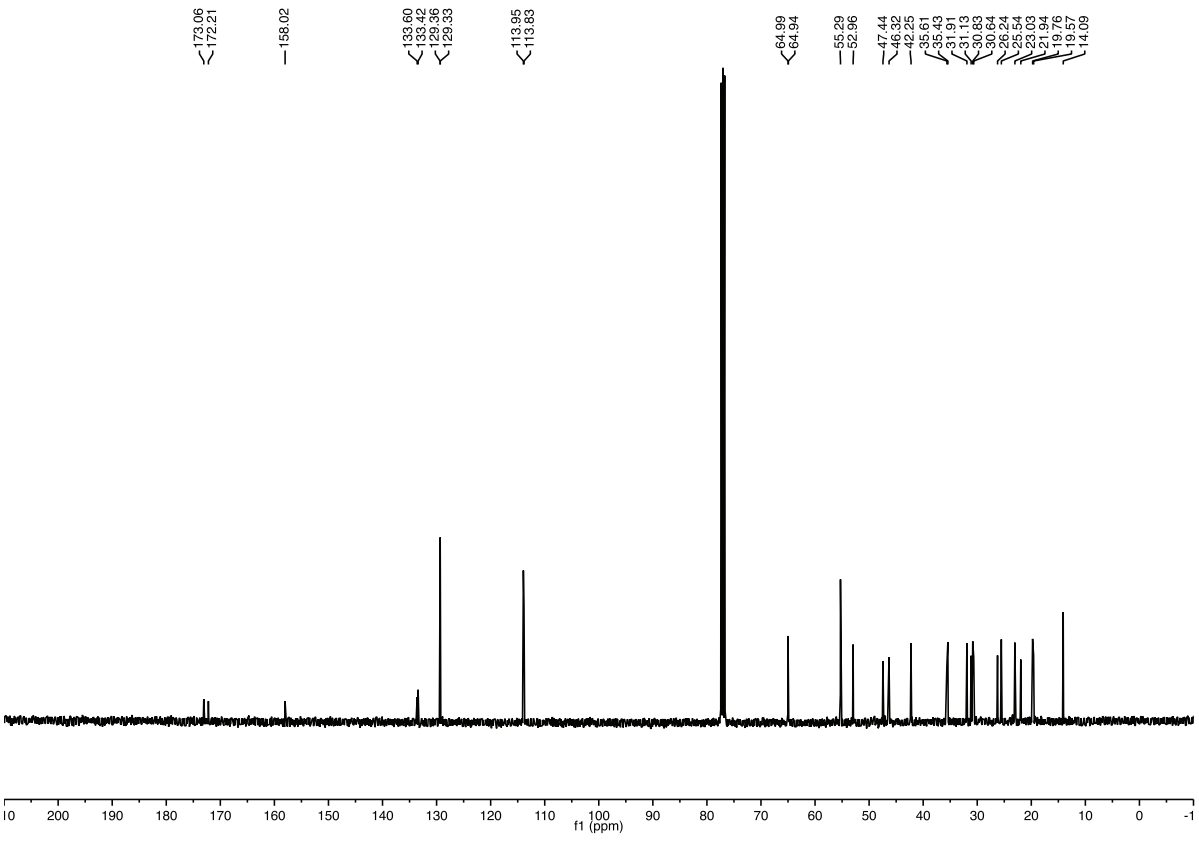
f1 (ppm)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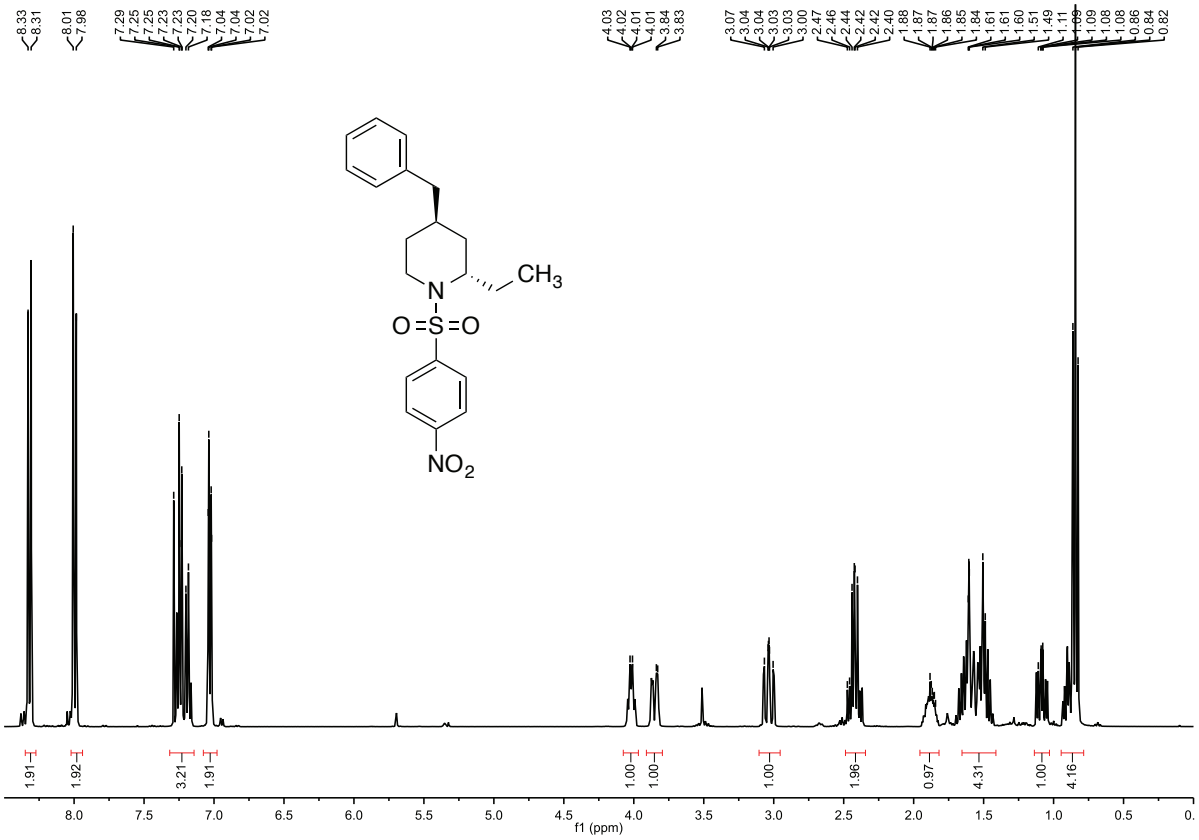
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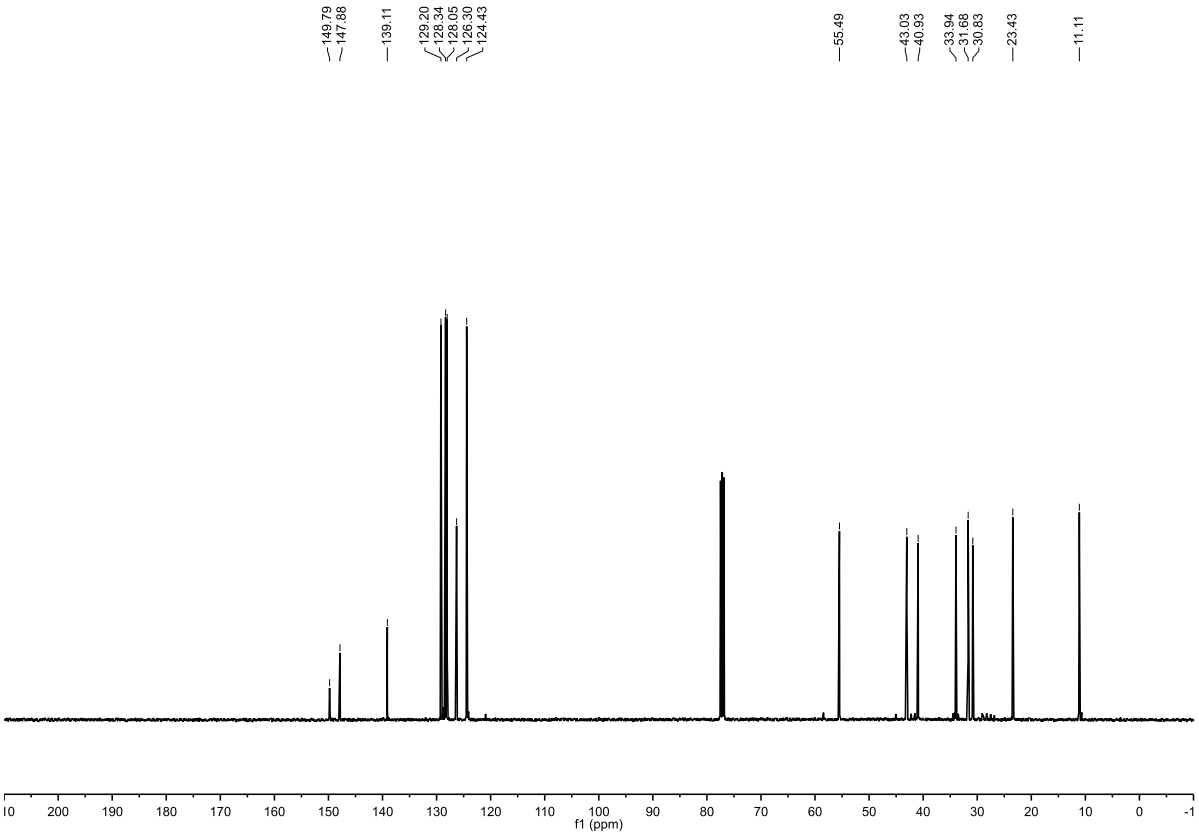
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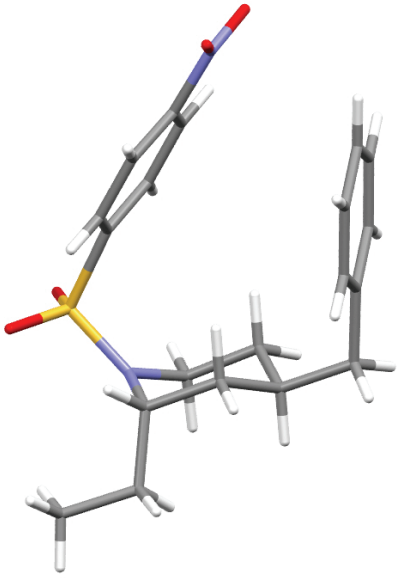
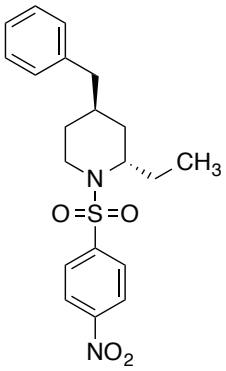
f1 (ppm)

X-Ray crystallography data – Experimental part II





Crystal Data:

orthorhombic, space group $P2_12_12_1$ (no. 19), a = 8.8603(7) Å, b = 11.6145(9) Å, c = 18.4379(14) Å, V = 1897.4(3) Å^3, Z = 4, T = 100.0(2) K, μ(MoKα) = 0.199 mm^{-1}, *Dcalc* = 1.360 g/cm^3, 32217 reflections measured (4.144° ≤ 2Θ ≤ 54.968°), 3747 unique (R_{int} = 0.0198, R_{sigma} = 0.0114) which were used in all calculations. The final R_1 was 0.0232 (I > 2σ(I)) and wR_2 was 0.0607

Table S1. Crystal data and structure refinement

Identification code	mo_jb200115_1_1_0m
Empirical formula	$C_{20}H_{24}N_2O_4S$
Formula weight	388.47
Temperature/K	100.0(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.8603(7)
b/Å	11.6145(9)
c/Å	18.4379(14)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1897.4(3)
Z	4

ρ_{calc}g/cm^3	1.360
μ/mm^{-1}	0.199
F(000)	824.0
Crystal size/mm^3	0.28 × 0.24 × 0.06
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.144 to 54.968
Index ranges	-11 ≤ h ≤ 5, -15 ≤ k ≤ 14, -16 ≤ l ≤ 16
Reflections collected	32217
Independent reflections	3747 [R_{int} = 0.0198, R_{sigma} = 0.0114]
Data/restraints/parameters	3747/0/245
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0232, wR_2 = 0.0601
Final R indexes [all data]	R_1 = 0.0241, wR_2 = 0.0607
Largest diff. peak/hole / e Å^{-3}	0.21/-0.26
Flack parameter	0.029(11)

Table S2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for mo_jb200115_1_1_0m. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(equiv)**
S1	5120.2(4)	2114.2(3)	8204.5(2)	15.91(11)
O1	1832.0(17)	2228.6(15)	4977.4(8)	35.1(4)
O2	3229.3(19)	3743.9(13)	4875.1(8)	34.5(4)
O3	6552.0(12)	2684.6(11)	8266.9(7)	21.7(3)
O4	5004.1(15)	905.6(10)	8349.2(8)	23.7(3)
N1	3954.7(14)	2768.3(12)	8736.7(8)	14.8(3)
N2	2786.7(17)	2899.1(15)	5209.9(9)	24.5(4)
C1	-22(2)	4397.9(18)	5873.3(12)	29.5(5)
C2	926(2)	5225.0(18)	6161.4(12)	28.7(5)
C3	969.3(19)	5418.2(15)	6901.5(12)	22.3(4)
C4	65.5(19)	4776.0(14)	7375.0(11)	18.8(4)
C5	117.4(18)	4959.7(14)	8180.8(11)	19.6(4)
C6	1350.5(18)	4283.3(14)	8590.2(10)	15.6(4)
C7	1240.1(18)	2991.1(14)	8441.9(10)	15.4(4)
C8	2416.6(17)	2273.7(14)	8853.7(10)	15.1(4)
C9	4499.3(18)	2306.7(13)	7297.8(10)	14.7(4)
C10	3502(2)	1516.8(15)	6991.6(11)	20.1(4)
C11	2954(2)	1704.0(15)	6303.4(11)	21.8(4)
C12	3415.4(19)	2682.1(15)	5932.9(10)	17.4(4)
C13	-934(2)	3750.0(19)	6335.8(12)	30.1(5)
C14	-876(2)	3942.0(17)	7074.5(11)	23.1(5)
C15	2947.2(18)	4705.5(14)	8417.6(11)	16.7(4)

C16	4101.8(19)	4024.6(14)	8850.9(11)	17.7(4)
C17	2102.6(19)	2149.6(16)	9661.1(10)	20.3(4)
C18	3114(2)	1261.8(18)	10029.1(12)	26.2(4)
C19	4964.4(19)	3275.4(13)	6912.3(10)	16.5(4)
C20	4423.2(19)	3468.3(14)	6222.3(11)	17.4(4)

Table S3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for mo_jb200115_1_1_0m. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
S1	14.80(17)	15.71(18)	17.2(3)	3.15(16)	1.55(16)	4.23(14)
O1	34.1(8)	48.4(10)	22.8(9)	-6.9(7)	-6.1(6)	-12.4(7)
O2	45.0(9)	37.6(8)	20.9(9)	10.0(6)	-4.9(7)	-6.1(7)
O3	13.6(5)	29.7(7)	21.8(9)	2.5(6)	-0.4(5)	3.0(5)
O4	28.3(6)	17.8(6)	25.0(8)	6.4(5)	4.1(6)	9.0(5)
N1	14.5(6)	15.0(6)	14.8(9)	0.6(6)	1.3(5)	0.3(5)
N2	24.7(7)	31.1(8)	17.5(10)	-2.9(7)	0.0(6)	0.5(7)
C1	26.4(9)	41.7(11)	20.3(12)	7.0(9)	-0.6(8)	10.0(9)
C2	20.4(9)	34.8(11)	31.0(16)	16.1(9)	4.9(8)	4.7(8)
C3	17.0(7)	20.9(8)	29.1(14)	8.6(8)	1.4(7)	1.8(6)
C4	12.9(7)	16.8(7)	26.5(13)	6.7(7)	2.0(7)	5.2(7)
C5	15.9(7)	16.5(7)	26.5(13)	0.9(7)	5.6(7)	3.6(6)
C6	17.0(7)	15.3(7)	14.4(11)	-1.6(7)	2.5(6)	1.5(6)
C7	15.2(7)	15.4(7)	15.4(11)	-0.5(7)	0.5(6)	0.1(6)
C8	13.9(7)	15.2(7)	16.1(11)	0.5(7)	0.1(6)	-1.5(6)
C9	15.1(7)	13.3(7)	15.7(11)	-1.4(6)	4.8(6)	2.6(6)
C10	24.8(8)	16.2(8)	19.3(12)	0.7(7)	5.4(7)	-6.2(7)
C11	23.8(9)	23.5(9)	18.0(12)	-3.7(8)	3.3(8)	-9.9(7)
C12	19.1(8)	20.3(8)	12.7(11)	-2.6(7)	2.7(6)	-0.2(6)
C13	26.4(10)	34.9(11)	29.0(15)	3.8(9)	-6.1(9)	-2.7(8)
C14	16.8(8)	26.1(9)	26.3(14)	8.2(8)	-0.8(7)	-2.1(7)
C15	17.8(7)	12.9(7)	19.5(11)	-1.9(7)	3.2(6)	0.1(6)
C16	17.0(8)	17.4(8)	18.8(12)	-1.7(7)	0.7(7)	-2.6(6)
C17	20.4(8)	22.3(8)	18.1(12)	0.8(8)	0.9(7)	-3.0(7)
C18	24.3(9)	34.3(11)	20.0(13)	10.3(8)	-2.0(8)	-3.0(8)
C19	17.8(7)	13.7(7)	17.9(11)	-2.2(6)	1.5(7)	-2.4(6)
C20	22.5(8)	13.0(7)	16.7(12)	0.4(7)	3.1(7)	-0.7(6)

Table S4. Bond Lengths for mo_jb200115_1_1_0m.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O3	1.4358(12)	C5	C6	1.543(2)
S1	O4	1.4325(12)	C6	C7	1.529(2)
S1	N1	1.6144(15)	C6	C15	1.531(2)
S1	C9	1.7740(19)	C7	C8	1.535(2)
O1	N2	1.227(2)	C8	C17	1.521(3)
O2	N2	1.224(2)	C9	C10	1.393(2)
N1	C8	1.495(2)	C9	C19	1.393(2)
N1	C16	1.480(2)	C10	C11	1.376(3)
N2	C12	1.467(3)	C11	C12	1.387(2)
C1	C2	1.382(3)	C12	C20	1.384(2)
C1	C13	1.395(3)	C13	C14	1.381(3)
C2	C3	1.384(3)	C15	C16	1.520(2)
C3	C4	1.400(2)	C17	C18	1.525(3)
C4	C5	1.502(3)	C19	C20	1.378(3)
C4	C14	1.393(3)			

Table S5. Bond Angles for mo_jb200115_1_1_0m.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O3	S1	N1	107.42(7)	C15	C6	C5	112.94(14)
O3	S1	C9	106.94(8)	C6	C7	C8	113.64(14)
O4	S1	O3	120.04(8)	N1	C8	C7	109.82(13)
O4	S1	N1	107.57(8)	N1	C8	C17	110.15(14)
O4	S1	C9	106.07(8)	C17	C8	C7	114.27(14)
N1	S1	C9	108.37(7)	C10	C9	S1	119.70(13)
C8	N1	S1	119.35(12)	C10	C9	C19	120.84(17)
C16	N1	S1	119.61(11)	C19	C9	S1	119.40(13)
C16	N1	C8	116.02(13)	C11	C10	C9	119.57(16)
O1	N2	C12	118.05(16)	C10	C11	C12	118.66(17)
O2	N2	O1	123.61(18)	C11	C12	N2	118.45(16)
O2	N2	C12	118.33(16)	C20	C12	N2	118.81(16)
C2	C1	C13	119.5(2)	C20	C12	C11	122.73(18)
C1	C2	C3	120.57(19)	C14	C13	C1	119.6(2)
C2	C3	C4	120.86(18)	C13	C14	C4	121.78(18)
C3	C4	C5	121.59(17)	C16	C15	C6	110.25(14)
C14	C4	C3	117.71(19)	N1	C16	C15	112.27(14)
C14	C4	C5	120.70(16)	C8	C17	C18	113.07(15)
C4	C5	C6	115.68(14)	C20	C19	C9	119.97(16)
C7	C6	C5	111.54(14)	C19	C20	C12	118.23(16)

C7 C6 C15 109.66(13)

Table S6. Torsion Angles for mo_jb200115_1_1_0m.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	N1	C8	C7	-105.77(14)	C3	C4	C14	C13	-0.3(3)
S1	N1	C8	C17	127.52(14)	C4	C5	C6	C7	-55.28(19)
S1	N1	C16	C15	102.10(15)	C4	C5	C6	C15	68.76(19)
S1	C9	C10	C11	176.25(13)	C5	C4	C14	C13	-179.43(17)
S1	C9	C19	C20	-176.37(13)	C5	C6	C7	C8	-178.40(14)
O1	N2	C12	C11	2.9(2)	C5	C6	C15	C16	178.64(15)
O1	N2	C12	C20	-176.03(17)	C6	C7	C8	N1	-50.7(2)
O2	N2	C12	C11	-177.83(17)	C6	C7	C8	C17	73.65(18)
O2	N2	C12	C20	3.2(2)	C6	C15	C16	N1	54.94(19)
O3	S1	N1	C8	-172.57(12)	C7	C6	C15	C16	-56.3(2)
O3	S1	N1	C16	33.47(15)	C7	C8	C17	C18	169.48(15)
O3	S1	C9	C10	154.87(13)	C8	N1	C16	C15	-52.7(2)
O3	S1	C9	C19	-27.97(15)	C9	S1	N1	C8	72.21(14)
O4	S1	N1	C8	-42.06(15)	C9	S1	N1	C16	-81.74(14)
O4	S1	N1	C16	163.99(13)	C9	C10	C11	C12	0.0(3)
O4	S1	C9	C10	25.64(15)	C9	C19	C20	C12	0.3(2)
O4	S1	C9	C19	-157.20(13)	C10	C9	C19	C20	0.8(2)
N1	S1	C9	C10	-89.61(15)	C10	C11	C12	N2	-177.85(16)
N1	S1	C9	C19	87.55(14)	C10	C11	C12	C20	1.1(3)
N1	C8	C17	C18	-66.34(18)	C11	C12	C20	C19	-1.2(3)
N2	C12	C20	C19	177.74(15)	C13	C1	C2	C3	-0.4(3)
C1	C2	C3	C4	0.5(3)	C14	C4	C5	C6	93.21(19)
C1	C13	C14	C4	0.5(3)	C15	C6	C7	C8	55.7(2)
C2	C1	C13	C14	-0.1(3)	C16	N1	C8	C7	49.1(2)
C2	C3	C4	C5	178.93(16)	C16	N1	C8	C17	-77.62(18)
C2	C3	C4	C14	-0.2(3)	C19	C9	C10	C11	-0.9(3)
C3	C4	C5	C6	-85.84(19)					

Table S7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for mo_jb200115_1_1_0m.

Atom	*x*	*y*	*z*	U(equiv)
H1	-52	4271	5364	35
H2	1553	5665	5848	34
H3	1621	5994	7091	27
H5A	-876	4746	8386	24
H5B	269	5791	8274	24

H6	1178	4402	9121	19
H7A	1366	2857	7915	18
H7B	219	2722	8579	18
H8	2412	1483	8639	18
H10	3202	853	7256	24
H11	2274	1174	6086	26
H13	-1592	3180	6144	36
H14	-1495	3493	7386	28
H15A	3149	4613	7893	20
H15B	3033	5533	8538	20
H16A	5129	4271	8708	21
H16B	3973	4197	9373	21
H17A	1035	1923	9730	24
H17B	2250	2906	9899	24
H18A	2908	498	9827	39
H18B	2909	1256	10551	39
H18C	4174	1462	9946	39
H19	5654	3803	7125	20
H20	4734	4124	5952	21

DFT calculation data – Experimental part II

Cartesian coordinates transistion state DFT calculations

***trans*-113-*TS*(α*axial*-β*axial*)**

Zero-point correction=	0.487740 (Hartree/Particle)
Thermal correction to Energy=	0.512993
Thermal correction to Enthalpy=	0.513937
Thermal correction to Gibbs Free Energy=	0.432770
Sum of electronic and zero-point Energies=	-1228.197123
Sum of electronic and thermal Energies=	-1228.171870
Sum of electronic and thermal Enthalpies=	-1228.170926
Sum of electronic and thermal Free Energies=	-1228.252093

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4873021 *(ΔGrel-solv = 0.0 kcal/mol*)

C	2.10206600	-0.67989600	1.58461800
H	1.76653700	0.32312300	-0.22346600
O	2.31653800	0.29329500	2.26584600
C	1.70834800	-2.03499700	2.13169500
H	2.62725700	-2.64104900	2.16661700
H	1.02318900	-2.53370800	1.44708600
C	3.94916700	-0.11203700	0.02358900
C	2.15307500	-1.72927900	-0.74865300
C	2.48092100	-1.39344400	-2.20306000
C	3.95886800	-1.02692000	-2.36712900
C	4.36606900	0.14487600	-1.44886300
H	4.17668600	-0.76417600	-3.40847400
H	4.57203100	-1.90855000	-2.13751100
N	2.49916600	-0.57182000	0.13259300
O	-0.20820400	-0.64723300	0.78293300
N	-0.81066700	0.48437500	0.40854400
C	-0.18071800	1.42442900	-0.26151300
O	1.04544200	1.32371700	-0.63776900
O	-2.06764100	2.96302300	0.12544600
H	-1.11105300	2.69077700	-1.71669100
H	-0.21377300	3.53075300	-0.44866000
C	-0.90191200	2.70186500	-0.63409800
C	-2.22709700	0.58323700	0.81574600
H	-2.21718300	0.56759900	1.91100800
H	-3.68547500	2.15742000	0.97687300
C	-2.92951100	1.84824500	0.24886600
H	-2.40250000	-2.22908500	1.39998600
C	-3.05620400	-1.88612800	0.60613700
C	-4.71486900	-0.96458900	-1.47871700
C	-3.04811800	-0.54492200	0.22911400
C	-3.90385800	-2.76807100	-0.06759300
C	-4.72901900	-2.30940200	-1.10034500
C	-3.86488800	-0.08326100	-0.81104700
H	-3.92619600	-3.81719300	0.21329300
H	-5.38907600	-3.00493400	-1.61125700
C	-3.65387600	1.39352100	-1.04768500
H	-5.35858600	-0.61347600	-2.28099500
H	-3.02402400	1.56259300	-1.93071600
H	-4.58156300	1.95131800	-1.20967700
H	3.96232900	0.83487700	0.56721500
H	2.69842000	-2.62342000	-0.42635000

H	2.22612300	-2.25893500	-2.82475900
C	4.90385800	-1.08461500	0.72945200
H	5.92126000	-0.68573300	0.68082900
H	4.65164500	-1.19845000	1.78653100
H	4.91681600	-2.07523100	0.26528000
H	1.08216300	-1.88519100	-0.61503400
H	1.83932100	-0.56677100	-2.52699000
H	5.46347000	0.17752900	-1.42946600
C	3.89818300	1.50832400	-1.98477000
H	4.28281400	2.31858700	-1.35596000
H	4.28575700	1.66344900	-2.99762200
H	2.81200000	1.60741600	-2.00886500
C	1.08432300	-1.91568700	3.52054400
H	0.85180800	-2.90707400	3.92050900
H	1.75479500	-1.40464100	4.21530900
H	0.16075100	-1.33749700	3.44770000

trans-113-TS-CO-conformer(α axial-β axial)

Zero-point correction= 0.492214 (Hartree/Particle)
Thermal correction to Energy= 0.517147
Thermal correction to Enthalpy= 0.518091
Thermal correction to Gibbs Free Energy= 0.438073
Sum of electronic and zero-point Energies= -1228.192950
Sum of electronic and thermal Energies= -1228.168017
Sum of electronic and thermal Enthalpies= -1228.167073
Sum of electronic and thermal Free Energies= -1228.247091

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4887122 *(ΔGrel-solv = 2.4 kcal/mol*)

C	1.90954600	-0.77099300	1.88781200
H	1.75821400	0.22436900	-0.04379300
C	3.81033600	-0.22963600	0.02304500
C	1.91538600	-1.77185100	-0.50639900
C	2.12183900	-1.55896700	-2.00583000
C	3.57950700	-1.20340100	-2.32677000
C	4.08196000	-0.00667100	-1.49027600
H	3.69263000	-0.97521600	-3.39281100
H	4.21177600	-2.07852000	-2.13171200
N	2.36095700	-0.56955500	0.25786100
O	0.22913500	-0.62506400	1.53578700
N	-0.46447200	0.56640000	1.59229400
C	-0.29528100	1.51111100	0.65466600
O	0.55527000	1.45842000	-0.25608800
O	-1.84218400	2.92362200	1.98953000
H	-1.87940300	2.72668000	-0.09661600
H	-0.53149800	3.61834700	0.61382000
C	-1.17869200	2.74912900	0.75265100
C	-1.55842900	0.52972400	2.58070900
H	-1.08581100	0.49420200	3.56735600
H	-2.85280800	2.01190800	3.45178200
C	-2.50354500	1.75884500	2.44681500
H	-1.29664200	-2.30920600	3.00675600
C	-2.26258600	-1.98851100	2.63227400
C	-4.74220400	-1.13081000	1.59627800
C	-2.49739500	-0.64068800	2.36376400
C	-3.28213600	-2.90814400	2.37866600

C	-4.51346700	-2.48160800	1.86868600
C	-3.72364800	-0.21038300	1.84197600
H	-3.11894300	-3.96275200	2.58040600
H	-5.29990500	-3.20791700	1.68344100
C	-3.72101700	1.28189100	1.60983700
H	-5.70039900	-0.80510900	1.20008300
H	-3.58574600	1.51112000	0.54515000
H	-4.64390600	1.77910300	1.92432100
H	2.46933700	-2.63217400	-0.12616000
H	1.44903100	-0.76408500	-2.34947300
H	3.96519600	0.72878200	0.52800900
H	5.17454400	0.03821100	-1.59323800
C	2.32849700	0.47168400	2.67030100
H	3.41782800	0.55453100	2.58671600
H	1.90690300	1.38039500	2.23274500
C	1.97002300	0.33762400	4.15263300
H	0.89006100	0.26263900	4.30001500
H	2.42054200	-0.56795600	4.56504100
H	2.33144000	1.20288700	4.71634400
O	2.09420600	-1.90803900	2.28996100
C	4.75325000	-1.26473300	0.64942500
H	5.77242900	-0.86662000	0.64010900
H	4.47096500	-1.49687100	1.67731600
H	4.76242400	-2.20580100	0.09376900
C	3.52457600	1.33904600	-1.98666500
H	3.98754500	2.17098400	-1.44440700
H	3.74793100	1.47397600	-3.05021700
H	2.44312700	1.43137700	-1.85544500
H	1.82557100	-2.47080900	-2.53672800
H	0.86539000	-1.91592400	-0.25625400

***trans*-113-*TS-ring-conformer* (α*equitorial*-β*equitorial*)**

Zero-point correction= 0.487508 (Hartree/Particle)
Thermal correction to Energy= 0.512812
Thermal correction to Enthalpy= 0.513757
Thermal correction to Gibbs Free Energy= 0.432230
Sum of electronic and zero-point Energies= -1228.190735
Sum of electronic and thermal Energies= -1228.165430
Sum of electronic and thermal Enthalpies= -1228.164486
Sum of electronic and thermal Free Energies= -1228.246012

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4787461 *(ΔGrel-solv = 5.0 kcal/mol*)

C	1.91609400	-0.62134400	1.57615000
H	1.62197200	0.06599000	-0.42866700
O	2.03131700	0.42391100	2.16754700
C	1.62582000	-1.93993300	2.25849900
H	2.59086000	-2.46074900	2.36252000
H	0.99518300	-2.56777900	1.63262800
C	3.71207800	0.15673700	0.13805100
C	2.52602000	-1.96369500	-0.59975800
C	3.25589200	-1.81917500	-1.96417100
C	4.55211300	-1.00603300	-1.89739800
C	4.28644600	0.35084700	-1.25448800
H	4.96027400	-0.89117400	-2.90818900
H	5.30805800	-1.55181700	-1.31363500

N	2.42479700	-0.63106500	0.12989300
O	-0.34798700	-0.56614000	0.86802100
N	-0.85899900	0.56202700	0.36037900
C	-0.22716500	1.28641400	-0.54085500
O	0.91418200	0.97178800	-1.04014400
O	-1.85294400	3.11096800	-0.20451700
H	-1.23852000	2.39208100	-2.07199600
H	-0.06465900	3.31205400	-1.12611900
C	-0.85910800	2.56522200	-1.05132400
C	-2.18399200	0.91717200	0.91059700
H	-2.01904200	1.07088600	1.98241800
H	-3.40403600	2.68833300	0.98228700
C	-2.81121500	2.16429400	0.22672200
H	-2.59048400	-1.72529400	1.97922400
C	-3.31340300	-1.41889200	1.23195800
C	-5.15347400	-0.60375100	-0.74133300
C	-3.20755400	-0.16446600	0.63453000
C	-4.34987500	-2.26689200	0.83585000
C	-5.26490400	-1.86044100	-0.14144500
C	-4.11516800	0.24197400	-0.35180800
H	-4.44922500	-3.24805100	1.29136200
H	-6.07108200	-2.52716600	-0.43476200
C	-3.77436300	1.62113900	-0.86355100
H	-5.86749300	-0.29232400	-1.49931000
H	-3.27369100	1.56329700	-1.83865200
H	-4.64520800	2.27131300	-0.99378600
H	3.13595600	-2.61559000	0.03974000
H	2.56556100	-1.27716800	-2.62632900
H	3.47714100	1.10434100	0.61690400
H	5.20639700	0.93997900	-1.16670100
C	1.12965900	-2.58599500	-0.83775700
H	0.85577100	-2.50518000	-1.89389100
H	1.12751200	-3.64811400	-0.57788300
H	0.35019700	-2.06651200	-0.27485500
C	3.52190700	-3.20662000	-2.56784000
H	2.60648200	-3.78503000	-2.71306700
H	4.00960000	-3.10666800	-3.54268300
H	4.19006300	-3.79011200	-1.92280900
H	4.43247800	-0.37501300	0.77411900
H	3.58353600	0.93373300	-1.86129700
C	0.98272700	-1.72228300	3.62731400
H	0.79027500	-2.68305100	4.11388700
H	1.62400700	-1.12173500	4.27621800
H	0.03759400	-1.19121500	3.49762400

trans*-113-*TS-ring-CO-conformer (α equitorial-β equitorial)

Zero-point correction= 0.491833 (Hartree/Particle)
Thermal correction to Energy= 0.516718
Thermal correction to Enthalpy= 0.517662
Thermal correction to Gibbs Free Energy= 0.437625
Sum of electronic and zero-point Energies= -1228.190672
Sum of electronic and thermal Energies= -1228.165787
Sum of electronic and thermal Enthalpies= -1228.164843
Sum of electronic and thermal Free Energies= -1228.244880

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4853201 *(ΔGrel-solv = 4.3 kcal/mol*)

C	1.90828500	-1.00455200	1.74836700
H	1.52209300	-0.09746100	-0.19412500
C	3.57843400	0.01641600	0.03940600
C	2.27426600	-2.03288300	-0.63775600
C	2.78797600	-1.83245200	-2.08992100
C	4.11126000	-1.05645900	-2.15236100
C	3.99456600	0.26576900	-1.40407300
H	4.38641300	-0.88672700	-3.19962200
H	4.91553500	-1.66253800	-1.71023400
N	2.28939900	-0.73187000	0.14659800
O	0.10102000	-0.75200600	1.46827600
N	-0.51067800	0.47491100	1.47619900
C	-0.30467800	1.35922400	0.49139200
O	0.49884300	1.18914600	-0.45388800
O	-1.64450800	2.98020000	1.80962900
H	-1.82718900	2.65880300	-0.25299800
H	-0.36833500	3.47143300	0.31847500
C	-1.07512600	2.67152300	0.55158200
C	-1.53164200	0.60794600	2.53213600
H	-0.99491100	0.59273100	3.48608400
H	-2.63634300	2.24748600	3.38197100
C	-2.37315000	1.90752100	2.37621500
H	-1.50446400	-2.20886800	3.15363700
C	-2.45735500	-1.82334900	2.80849800
C	-4.90906600	-0.80676200	1.85604800
C	-2.58448900	-0.48042000	2.45733500
C	-3.56948300	-2.65789700	2.68017000
C	-4.78670200	-2.15223700	2.21070000
C	-3.79831600	0.02760800	1.97730900
H	-3.48976300	-3.70730900	2.94841600
H	-5.64554100	-2.81176200	2.12266600
C	-3.67707900	1.49502900	1.64188100
H	-5.85703000	-0.41870100	1.49271800
H	-3.58578400	1.64198300	0.55813300
H	-4.53121300	2.09509300	1.97095900
H	2.95613200	-2.69533900	-0.09284400
H	2.03054800	-1.23572000	-2.61996000
H	3.44419500	0.96563800	0.55752700
H	4.94497200	0.81182600	-1.40336100
C	0.86899700	-2.64350100	-0.63401200
H	0.16433700	-1.99933300	-1.16907900
H	0.89899800	-3.61438800	-1.13359700
H	0.49983000	-2.78680200	0.37678100
C	2.93527100	-3.17675100	-2.82077900
H	1.98038400	-3.68631200	-2.96576200
H	3.37511500	-3.01729400	-3.81065900
H	3.59890300	-3.85331700	-2.26915800
H	4.34407200	-0.56332800	0.56794300
H	3.25148800	0.91336800	-1.88582000
C	2.27194800	0.17214100	2.65038200
H	3.35725600	0.31560300	2.60955300
H	1.80925200	1.09956100	2.30195000
C	1.88627900	-0.13553200	4.09997100
H	0.81801700	-0.34357000	4.18792000
H	2.42092000	-1.02048900	4.45159000
H	2.13356700	0.70958200	4.74951700
O	2.05383500	-2.15990000	2.09514400

ent-trans*-113-*TS*-(α *equitorial*-β *equitorial)

Zero-point correction= 0.487284 (Hartree/Particle)
Thermal correction to Energy= 0.512590
Thermal correction to Enthalpy= 0.513534
Thermal correction to Gibbs Free Energy= 0.431939
Sum of electronic and zero-point Energies= -1228.196057
Sum of electronic and thermal Energies= -1228.170751
Sum of electronic and thermal Enthalpies= -1228.169807
Sum of electronic and thermal Free Energies= -1228.251402

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4849694 *(ΔGrel-solv = 0.9 kcal/mol*)

C	1.99613800	-0.30555900	1.66332300
H	1.83095800	0.37907800	-0.32292300
O	1.87225700	0.80309100	2.12876900
C	1.88198800	-1.57840200	2.47875100
H	2.90923600	-1.92506000	2.67632300
H	1.39549900	-2.36120300	1.89641700
C	4.02388000	0.05838200	0.14179100
C	2.38079100	-1.74645300	-0.38161100
C	2.69614200	-1.66412400	-1.87111000
C	4.12065400	-1.16549400	-2.09885600
C	4.37812100	0.16211600	-1.36849900
H	4.31735700	-1.03617000	-3.16941600
H	4.83835500	-1.91783400	-1.73865900
N	2.57613900	-0.41242300	0.26876100
O	-0.10382500	-0.66469500	0.68474300
N	-0.68090200	0.48637900	0.32911700
C	-0.07230500	1.39073500	-0.40994500
O	1.11590800	1.24465600	-0.88806900
O	-1.86253100	3.01385400	0.08486800
H	-1.08779000	2.63737400	-1.82280800
H	-0.04945500	3.48707800	-0.67373200
C	-0.78116700	2.68043100	-0.76452900
C	-2.04736900	0.66392000	0.86561200
H	-1.93006100	0.68583100	1.95423600
H	-3.42240000	2.29956100	1.10855900
C	-2.75014600	1.93956500	0.32394300
H	-2.28930600	-2.11745000	1.56912800
C	-3.00335500	-1.76890200	0.83175300
C	-4.81832300	-0.83772900	-1.11351400
C	-2.97033300	-0.44363000	0.40333600
C	-3.95484800	-2.62976800	0.28075100
C	-4.85765000	-2.16594900	-0.68234500
C	-3.86484400	0.02201700	-0.56895700
H	-3.99744500	-3.66609800	0.60350200
H	-5.59787100	-2.84438900	-1.09738100
C	-3.60975400	1.47690100	-0.88326900
H	-5.52264100	-0.48254800	-1.86123800
H	-3.05555400	1.58176200	-1.82508900
H	-4.52128900	2.07426800	-0.98378600
H	3.02921600	-2.48597200	0.10656700
H	2.54902600	-2.65473100	-2.31615500
H	1.33495300	-2.00645300	-0.22951400
H	1.97700100	-0.98628800	-2.34514500

C	4.29283800	1.37478500	0.87602800
H	3.65729000	2.17447000	0.48758600
H	4.11360700	1.30001200	1.94664700
H	5.33913000	1.65115800	0.73037000
C	5.83208400	0.60477200	-1.59678700
H	6.07617600	0.53974500	-2.66203400
H	6.01604900	1.63466900	-1.28360500
H	6.53464400	-0.04449000	-1.05987400
H	4.64773100	-0.73364800	0.58581100
H	3.71081300	0.92347800	-1.79596700
C	1.13020400	-1.33998500	3.78604600
H	0.11047900	-1.01850200	3.56192300
H	1.08895500	-2.25868100	4.37863000
H	1.60773100	-0.55794100	4.38054400

ent-trans*-113-*TS-CO-conformer-(α equitorial-β equitorial)

Zero-point correction= 0.491712 (Hartree/Particle)
Thermal correction to Energy= 0.516886
Thermal correction to Enthalpy= 0.517831
Thermal correction to Gibbs Free Energy= 0.436640
Sum of electronic and zero-point Energies= -1228.186617
Sum of electronic and thermal Energies= -1228.161443
Sum of electronic and thermal Enthalpies= -1228.160499
Sum of electronic and thermal Free Energies= -1228.241689

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4783503 *(ΔGrel-solv = 8.0 kcal/mol*)

C	2.02448200	-0.71940900	1.94295300
H	1.70488700	0.33822400	0.03100700
C	3.78452000	-0.03924800	-0.06604200
C	1.88691100	-1.68726200	-0.39612700
C	2.10247200	-1.66686900	-1.90009800
C	3.58982300	-1.51864300	-2.19437200
C	4.14470900	-0.23056300	-1.57266400
H	3.78510700	-1.50632700	-3.27309600
H	4.12758600	-2.38716400	-1.78768100
N	2.36282900	-0.43636200	0.27358900
O	0.24222500	-0.56068300	1.63486800
N	-0.46668200	0.61397100	1.72995800
C	-0.26973500	1.62688300	0.87467400
O	0.60434800	1.64461400	-0.01935700
O	-1.86655200	2.93798300	2.25747900
H	-1.80631200	2.92545500	0.16305400
H	-0.48532500	3.73151500	1.01060300
C	-1.14649600	2.86198400	1.04223800
C	-1.60307600	0.50543300	2.66383700
H	-1.17447400	0.39118400	3.66472200
H	-2.94496300	1.91027300	3.58916800
C	-2.54545600	1.74088100	2.58520600
H	-1.36133800	-2.35907700	2.88707400
C	-2.30637500	-2.00840400	2.48743700
C	-4.73178000	-1.06848500	1.39789700
C	-2.52901900	-0.64327700	2.31327900
C	-3.30950000	-2.90398800	2.11146400
C	-4.51425400	-2.43695800	1.57435400
C	-3.72899800	-0.17187200	1.76615600

H	-3.15452800	-3.97146400	2.23852200
H	-5.28857900	-3.14517600	1.29290100
C	-3.71874500	1.33400300	1.65311000
H	-5.66952500	-0.71092600	0.98070000
H	-3.53106400	1.64626600	0.61791300
H	-4.65765400	1.80580900	1.95936700
H	2.42354300	-2.51844300	0.06763900
H	1.53424200	-0.84616600	-2.35751000
C	2.36543600	0.45640700	2.84141400
H	3.45701000	0.53609200	2.85776200
H	1.97086400	1.39341400	2.44434300
C	1.88778000	0.19691600	4.27361600
H	0.80499600	0.06553000	4.31398400
H	2.34495700	-0.71545300	4.66279200
H	2.15988000	1.03406800	4.92338400
O	2.22537100	-1.87092500	2.26029500
H	1.70793700	-2.59923100	-2.31980000
H	0.83646500	-1.77845000	-0.12627300
C	5.66772200	-0.17597800	-1.78019200
H	5.90496300	-0.29274400	-2.84246600
H	6.11811300	0.76313700	-1.44898200
H	6.16125700	-0.99256100	-1.24020000
H	3.69005200	0.61368900	-2.11246000
C	4.01729200	1.43754300	0.30566400
H	4.14850800	1.60035200	1.37315300
H	4.91683800	1.81064000	-0.18598600
H	3.17260600	2.04641200	-0.03042400
H	4.42538000	-0.70322300	0.52890300

ent-trans*-113-*TS-ring-conformer-(*α*axial-*β*axial)

Zero-point correction= 0.489820 (Hartree/Particle)
Thermal correction to Energy= 0.514565
Thermal correction to Enthalpy= 0.515510
Thermal correction to Gibbs Free Energy= 0.436476
Sum of electronic and zero-point Energies= -1228.190320
Sum of electronic and thermal Energies= -1228.165574
Sum of electronic and thermal Enthalpies= -1228.164630
Sum of electronic and thermal Free Energies= -1228.243664

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4835693 *(ΔGrel-solv = 4.0 kcal/mol*)

C	2.25106200	-0.41203700	1.84540300
H	1.84153400	0.22238800	-0.04840800
O	2.52959000	0.64736100	2.34731000
C	1.75998500	-1.60224600	2.64113300
H	2.65900200	-2.12872100	2.99465100
H	1.19616200	-2.29053300	2.01377400
C	3.92698400	0.08547800	0.05124600
C	2.39598000	-1.87734700	-0.32493500
C	2.53614500	-1.71768000	-1.86591200
C	3.85744700	-1.00711600	-2.23778900
C	4.05801000	0.29942300	-1.45666200
H	3.87014500	-0.80753500	-3.31511200
H	4.70572300	-1.67511400	-2.04183600
N	2.59502100	-0.54310800	0.36301100
O	-0.08219900	-0.51042000	0.92917200

N	-0.67968600	0.61761800	0.52284900
C	-0.01977500	1.54277800	-0.14697900
O	1.20724000	1.40767000	-0.48370300
O	-1.91145100	3.09485200	0.16787100
H	-0.90220300	2.79746200	-1.64215400
H	-0.03849800	3.64885300	-0.35888600
C	-0.72402000	2.81997600	-0.55417700
C	-2.10571700	0.72268500	0.87901200
H	-2.14091800	0.71869600	1.97447900
H	-3.55989800	2.30714900	0.97554700
C	-2.78254800	1.98573700	0.27577400
H	-2.30608000	-2.08450400	1.47722900
C	-2.93392400	-1.74647900	0.66065800
C	-4.52101900	-0.83831800	-1.48439300
C	-2.91126500	-0.40795800	0.27468800
C	-3.76079500	-2.63232500	-0.03370800
C	-4.55092000	-2.18013600	-1.09623700
C	-3.69172000	0.04677000	-0.79591600
H	-3.79438400	-3.67929900	0.25425400
H	-5.19555300	-2.87830400	-1.62305500
C	-3.46858700	1.52086100	-1.03828200
H	-5.13690300	-0.49234200	-2.31044200
H	-2.81198300	1.68028600	-1.90334200
H	-4.38933800	2.07967900	-1.23350500
H	2.59910500	-2.74562800	-2.24694300
H	1.35989700	-2.13672700	-0.10059800
H	4.72238100	-0.55976900	0.43949700
H	3.32512500	1.05138900	-1.76381700
H	3.95117800	1.02943500	0.59273200
H	5.05086900	0.71626000	-1.66044400
C	3.34868700	-2.96964500	0.18452600
H	3.32476400	-3.09048100	1.26720000
H	3.04755600	-3.92490300	-0.25562100
H	4.38577100	-2.79001000	-0.11053200
C	1.30925200	-1.07465100	-2.53310300
H	1.40270200	-1.14456600	-3.62240500
H	0.39119200	-1.59262900	-2.23796400
H	1.19219800	-0.02380300	-2.26316700
C	0.92254300	-1.15788500	3.84165300
H	0.64965600	-2.02431200	4.45150300
H	1.47355500	-0.44953800	4.46394900
H	0.01512900	-0.67568700	3.47485700

ent-trans*-113-*TS-ring-CO-conformer-(*α*axial-*β*axial)

Zero-point correction= 0.492298 (Hartree/Particle)
Thermal correction to Energy= 0.517164
Thermal correction to Enthalpy= 0.518108
Thermal correction to Gibbs Free Energy= 0.438791
Sum of electronic and zero-point Energies= -1228.188486
Sum of electronic and thermal Energies= -1228.163619
Sum of electronic and thermal Enthalpies= -1228.162675
Sum of electronic and thermal Free Energies= -1228.241993

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4831346 *(ΔGrel-solv = 6.4 kcal/mol*)

C	2.04333400	-0.84302600	2.01177900

H	1.76790400	-0.05371400	0.05789700
C	3.80609000	-0.11702200	0.05067500
C	2.26754500	-2.04302500	-0.34857200
C	2.29135200	-1.79638900	-1.87986000
C	3.60063400	-1.08544900	-2.29613200
C	3.88236700	0.16828000	-1.45511300
H	3.55084400	-0.81768500	-3.35769700
H	4.44250400	-1.78112700	-2.19618400
N	2.48852200	-0.73484600	0.37745400
O	0.31108000	-0.65505800	1.56448700
N	-0.36077300	0.54279500	1.59213400
C	-0.07507800	1.51453700	0.71747300
O	0.85489200	1.45077000	-0.11742600
O	-1.66276100	2.95055900	1.97280800
H	-1.54936300	2.81426700	-0.11533800
H	-0.22606100	3.63035200	0.72055200
C	-0.91391300	2.78370800	0.78364500
C	-1.51113100	0.53127400	2.51159300
H	-1.10148800	0.45250900	3.52417000
H	-2.80689600	2.04011200	3.33391100
C	-2.39685700	1.80035600	2.34872800
H	-1.39737700	-2.32088000	2.90005700
C	-2.32090400	-1.95429900	2.46554200
C	-4.68685600	-0.97367500	1.28311300
C	-2.48086100	-0.59359700	2.20913100
C	-3.35830000	-2.82514200	2.12604000
C	-4.53335900	-2.33759200	1.54316700
C	-3.65002500	-0.10211400	1.61505600
H	-3.25383800	-3.88905300	2.31793100
H	-5.33507600	-3.02626500	1.29150500
C	-3.56919000	1.39294700	1.41583200
H	-5.60182700	-0.60056100	0.83051600
H	-3.34675000	1.63566200	0.36885200
H	-4.49122300	1.92323900	1.67365600
H	3.88828500	0.81558000	0.60902200
H	4.87419500	0.57172700	-1.68962800
H	4.60366400	-0.78640600	0.38413600
H	3.15720300	0.95586000	-1.68842500
C	2.46022600	0.43213400	2.73403500
H	3.55691100	0.45234000	2.72473800
H	2.11816900	1.32222300	2.20150500
C	1.99100500	0.42222800	4.19063200
H	0.90099700	0.41561600	4.26034200
H	2.35979200	-0.47227400	4.69732600
H	2.36112100	1.30642200	4.71800000
O	2.13907700	-1.94886600	2.50290500
C	1.03293000	-1.07745700	-2.39493900
H	1.06591500	-0.99544900	-3.48686700
H	0.13320400	-1.64301800	-2.13035400
H	0.91511900	-0.07076100	-1.98505600
H	2.29984100	-2.79417400	-2.33848700
C	3.26117400	-3.13500000	0.06967000
H	3.26161800	-3.26149000	1.15024200
H	2.94543700	-4.07668100	-0.39057300
H	4.28114000	-2.93645900	-0.27204200
H	1.26486400	-2.34659600	-0.03917100

cis*-113-*TS* (α*axial*-β*aquitorial)

Zero-point correction=	0.488331 (Hartree/Particle)
Thermal correction to Energy=	0.513460
Thermal correction to Enthalpy=	0.514405
Thermal correction to Gibbs Free Energy=	0.433637
Sum of electronic and zero-point Energies=	-1228.199972
Sum of electronic and thermal Energies=	-1228.174842
Sum of electronic and thermal Enthalpies=	-1228.173898
Sum of electronic and thermal Free Energies=	-1228.254666

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4909118 *(ΔGrel-solv = 0.0 kcal/mol*)

C	2.05874000	-0.79981900	1.62844400
H	1.81482800	0.11662700	-0.23249800
O	2.26510800	0.18953800	2.28927200
C	1.64652600	-2.13838800	2.20095300
H	2.56462300	-2.74076900	2.28925500
H	0.98781500	-2.66041700	1.50770000
C	3.93010000	-0.20763700	0.08157800
C	2.24055400	-1.93649600	-0.66683700
C	2.55779600	-1.62211300	-2.13043000
C	3.98147700	-1.08439100	-2.31163400
C	4.22135000	0.13079400	-1.39960300
H	4.14368300	-0.79461800	-3.35639100
H	4.71535200	-1.87266800	-2.09328300
N	2.51028900	-0.73890400	0.18632900
O	-0.16204700	-0.73500400	0.72084700
N	-0.71814100	0.42538800	0.35004300
C	-0.05365300	1.33198800	-0.33821800
O	1.15789100	1.17103500	-0.72830200
O	-1.86170600	2.95749000	0.07750800
H	-0.96344600	2.62498600	-1.78413600
H	0.00106000	3.43603400	-0.54684200
C	-0.72751500	2.63715900	-0.70716300
C	-2.12045400	0.58921600	0.77933300
H	-2.09486200	0.57409300	1.87455100
H	-3.49757900	2.23272700	0.96683200
C	-2.77340100	1.88599500	0.22359700
H	-2.41357900	-2.21302700	1.36596700
C	-3.06720500	-1.83939500	0.58607000
C	-4.72509200	-0.84040000	-1.46311400
C	-3.00471100	-0.49957100	0.20914800
C	-3.96863900	-2.68063600	-0.06968700
C	-4.79351400	-2.18350000	-1.08469200
C	-3.82117400	-0.00007900	-0.81357700
H	-4.03341400	-3.72792500	0.21157700
H	-5.49563300	-2.84735700	-1.58149800
C	-3.54664300	1.46515600	-1.05590600
H	-5.36859500	-0.45876700	-2.25151900
H	-2.92911500	1.60435100	-1.95273800
H	-4.45039700	2.06601200	-1.19811300
H	3.90058300	0.72464800	0.64967100
H	2.83016300	-2.78790100	-0.30969000
H	2.40138600	-2.53130800	-2.72146200
C	4.93956800	-1.14734800	0.74902200
H	5.93162000	-0.68948100	0.74220000

H	4.67448500	-1.31966700	1.79553800
H	5.01898100	-2.11609200	0.24786000
H	1.17817100	-2.14821800	-0.54746400
H	1.83801900	-0.87614500	-2.48621100
C	0.97197500	-1.97705500	3.56165300
H	0.72104500	-2.95534200	3.98208900
H	1.61845000	-1.44700800	4.26478700
H	0.05414500	-1.39832400	3.43786100
H	3.48743700	0.89749800	-1.67802200
C	5.61867500	0.73388300	-1.58772700
H	5.73152100	1.10977700	-2.60956400
H	5.78887300	1.57384500	-0.90534200
H	6.41166900	-0.00283500	-1.42117000

cis*-113-*TS-CO-conformer-(α axial-β equitorial)

Zero-point correction= 0.492191 (Hartree/Particle)
Thermal correction to Energy= 0.517078
Thermal correction to Enthalpy= 0.518022
Thermal correction to Gibbs Free Energy= 0.438278
Sum of electronic and zero-point Energies= -1228.194308
Sum of electronic and thermal Energies= -1228.169420
Sum of electronic and thermal Enthalpies= -1228.168476
Sum of electronic and thermal Free Energies= -1228.248221

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4901665 *(ΔGrel-solv = 3.4 kcal/mol*)

C	1.90217200	-0.82037900	1.94822800
H	1.76843100	0.12906100	-0.01426600
C	3.80980500	-0.30234000	0.05772500
C	1.94327300	-1.88428400	-0.42554500
C	2.13347100	-1.70295700	-1.93209100
C	3.56898600	-1.29017500	-2.28300800
C	4.00919500	-0.06501300	-1.46280100
H	3.64696700	-1.05921700	-3.35196600
H	4.25469300	-2.12800800	-2.09924300
N	2.37028200	-0.65827600	0.30755900
O	0.25020800	-0.65378600	1.57558000
N	-0.42117100	0.55310200	1.62364700
C	-0.21576100	1.49934700	0.69304000
O	0.65038500	1.43898300	-0.20138300
O	-1.76921000	2.92786100	2.00584800
H	-1.75558700	2.75492400	-0.08268800
H	-0.40948800	3.61117400	0.67272600
C	-1.07726300	2.75371600	0.78464000
C	-1.54041400	0.52516400	2.58338100
H	-1.09433800	0.47347200	3.58159900
H	-2.83415000	2.02080700	3.43199700
C	-2.46170200	1.77054800	2.43469900
H	-1.33914900	-2.32058000	2.99931500
C	-2.28868800	-1.98102900	2.60021600
C	-4.72466500	-1.07457900	1.50384800
C	-2.49279500	-0.62787200	2.33330100
C	-3.31679600	-2.88136000	2.31397100
C	-4.52646700	-2.43067600	1.77380800
C	-3.69733400	-0.17337500	1.78215400
H	-3.17740000	-3.93971800	2.51392200

H	-5.32004300	-3.14218100	1.56327600
C	-3.66353400	1.32018400	1.56094500
H	-5.66638100	-0.73005300	1.08472500
H	-3.49563300	1.55415700	0.50197900
H	-4.58629100	1.83060600	1.85387900
H	2.51442200	-2.72586900	-0.02914000
H	1.43407200	-0.93431300	-2.28593700
H	3.95989200	0.66068200	0.55569900
C	2.35532400	0.42738000	2.70482200
H	3.44837800	0.46061600	2.63823500
H	1.98053900	1.34048000	2.23545800
C	1.96861500	0.34965700	4.18420200
H	0.88433900	0.34585600	4.31855100
H	2.35824900	-0.57190100	4.62242000
H	2.37480400	1.20406800	4.73388200
O	2.07216100	-1.95284800	2.37250800
C	4.76693400	-1.32581600	0.68246400
H	5.77434500	-0.90490100	0.73314700
H	4.44595000	-1.59265600	1.69090300
H	4.82404900	-2.25141400	0.10381700
H	1.86187500	-2.63554600	-2.43965300
H	0.89733000	-2.04456700	-0.16728600
C	5.43983200	0.37409100	-1.79618800
H	5.51346100	0.66215300	-2.84976800
H	5.74693800	1.23710900	-1.19470900
H	6.16238000	-0.43025200	-1.62399000
H	3.33636900	0.76394400	-1.72751200

cis*-113-*TS-ring-conformer-(α equitorial-β axial)

Zero-point correction= 0.487899 (Hartree/Particle)
Thermal correction to Energy= 0.513028
Thermal correction to Enthalpy= 0.513972
Thermal correction to Gibbs Free Energy= 0.433085
Sum of electronic and zero-point Energies= -1228.188360
Sum of electronic and thermal Energies= -1228.163231
Sum of electronic and thermal Enthalpies= -1228.162287
Sum of electronic and thermal Free Energies= -1228.243174

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4777576 *(ΔGrel-solv = 7.9 kcal/mol*)

C	1.85731100	-0.56919600	1.57453200
H	1.58154200	0.10200400	-0.41223600
O	1.88896800	0.52225600	2.09140200
C	1.59878600	-1.84469200	2.34853300
H	2.46988600	-2.50567600	2.23472000
H	0.74443400	-2.35303600	1.90505600
C	3.68231500	0.14882300	0.13281300
C	2.56080900	-1.97301300	-0.56045800
C	3.10280400	-1.76621700	-2.00718500
C	4.40114600	-0.94326000	-2.00497200
C	4.20080300	0.38643000	-1.27862100
H	4.74230600	-0.78107700	-3.03363500
H	5.19200500	-1.51268000	-1.49673500
N	2.39004700	-0.63572900	0.14595500
O	-0.37123800	-0.66274700	0.70202000
N	-0.87691500	0.51916700	0.34556700

C	-0.21820100	1.35377700	-0.42885900
O	0.94136200	1.08727300	-0.92311800
O	-1.85817100	3.12362300	0.07107800
H	-1.15902600	2.65450300	-1.84542600
H	-0.03084700	3.43856100	-0.73547800
C	-0.82564400	2.69047800	-0.79491200
C	-2.20889700	0.81400900	0.91333800
H	-2.06127200	0.85034100	1.99803900
H	-3.44513700	2.55888100	1.14426700
C	-2.82145100	2.12798800	0.35524000
H	-2.65073000	-1.91925100	1.69704900
C	-3.35249700	-1.53489500	0.96563600
C	-5.13479900	-0.51201900	-0.96391500
C	-3.22677300	-0.22749300	0.50151700
C	-4.38127700	-2.33161100	0.45868000
C	-5.26760300	-1.82193400	-0.49650000
C	-4.10442600	0.28327900	-0.46333700
H	-4.49707000	-3.35307200	0.80959900
H	-6.06832900	-2.45000800	-0.87704200
C	-3.74301300	1.70550900	-0.82106100
H	-5.82672400	-0.12141200	-1.70550400
H	-3.20475900	1.74358300	-1.77705100
H	-4.60703800	2.37039700	-0.91756900
H	3.35080500	-2.50198000	-0.00784900
H	3.47122000	1.08572500	0.64299500
H	5.14457100	0.93916300	-1.20583500
C	1.28994400	-2.83677900	-0.59008600
H	1.33545800	-3.50742800	-1.45305900
H	1.20269000	-3.46781600	0.29412600
H	0.39152300	-2.21873200	-0.65050900
H	4.42260700	-0.40845800	0.72364700
H	3.49605900	1.02744700	-1.81796700
C	1.32427100	-1.55107500	3.82314900
H	1.14841500	-2.48437800	4.36627300
H	2.15979500	-1.02571100	4.29229500
H	0.43876200	-0.91890700	3.91912200
H	3.35724000	-2.78201600	-2.33914200
C	2.06826200	-1.20972100	-3.00264000
H	2.52385700	-1.12984300	-3.99552500
H	1.20289000	-1.87148000	-3.09304700
H	1.69480100	-0.22419200	-2.71690200

cis*-113-*TS-ring-CO-conformer-(α equitorial-β axial)

Zero-point correction= 0.492324 (Hartree/Particle)
Thermal correction to Energy= 0.517010
Thermal correction to Enthalpy= 0.517954
Thermal correction to Gibbs Free Energy= 0.438823
Sum of electronic and zero-point Energies= -1228.188935
Sum of electronic and thermal Energies= -1228.164249
Sum of electronic and thermal Enthalpies= -1228.163305
Sum of electronic and thermal Free Energies= -1228.242436

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4856306 *(ΔGrel-solv = 6.6 kcal/mol*)

C	1.92308800	-0.90880800	1.81368200
H	1.58556400	0.01671800	-0.12847400

C	3.66042400	-0.09320100	0.03906900
C	2.15652900	-1.98291600	-0.58929100
C	2.55883900	-1.79170900	-2.07678100
C	3.97751600	-1.20916400	-2.19099600
C	4.08420200	0.10318300	-1.41470200
H	4.24075700	-1.05879100	-3.24415600
H	4.70038600	-1.92901800	-1.78331800
N	2.29521300	-0.68640500	0.18485000
O	0.16914500	-0.66903900	1.54633600
N	-0.46101300	0.55297300	1.59388900
C	-0.24841500	1.48265200	0.65256100
O	0.58906000	1.37723200	-0.27067700
O	-1.70657600	2.99073500	1.98400400
H	-1.74713800	2.79929900	-0.10208100
H	-0.34795800	3.60075700	0.61474900
C	-1.05005200	2.77438800	0.74997800
C	-1.54896700	0.58993500	2.58995900
H	-1.07345500	0.54319500	3.57480500
H	-2.77304700	2.13991200	3.44389400
C	-2.42946900	1.86421900	2.44280600
H	-1.45334900	-2.25093900	3.07954100
C	-2.39511900	-1.88390300	2.68691300
C	-4.81533500	-0.90953200	1.61650000
C	-2.55089500	-0.53060100	2.39103200
C	-3.46234200	-2.75040000	2.44226600
C	-4.66399500	-2.26590600	1.91387100
C	-3.74885500	-0.04277500	1.85387300
H	-3.35976500	-3.80837700	2.66524900
H	-5.48814100	-2.95080100	1.73489700
C	-3.66353600	1.44344100	1.59993800
H	-5.75149100	-0.53818100	1.20794400
H	-3.50601600	1.64881400	0.53349300
H	-4.56105500	1.99421700	1.89817400
H	2.87942000	-2.65624200	-0.11533000
H	3.65510300	0.86624400	0.55585400
H	5.11148200	0.48560800	-1.42344600
C	0.76679800	-2.61072500	-0.46330600
H	-0.02400500	-1.92165800	-0.76203600
H	0.73288700	-3.48822600	-1.11931200
H	0.57154200	-2.92291300	0.55894400
H	4.35750300	-0.76144200	0.55813500
H	3.45706500	0.87580800	-1.87368900
C	2.35100500	0.29361900	2.65320000
H	3.44322600	0.36021900	2.60819300
H	1.95252500	1.22808900	2.24937300
C	1.94804300	0.09441300	4.11686100
H	0.86671600	-0.01564500	4.22092800
H	2.40858100	-0.81407100	4.51099600
H	2.26962600	0.94690200	4.72265600
O	2.08505000	-2.05478000	2.19015100
C	1.53401600	-0.98457700	-2.89684900
H	1.91049300	-0.82347200	-3.91270600
H	0.58427500	-1.51852400	-2.98041400
H	1.31595400	-0.00513100	-2.46031500
H	2.58283300	-2.80760200	-2.49338700

ent-cis*-113-*TS-(α equitorial-β axial)

Zero-point correction= 0.487557 (Hartree/Particle)
Thermal correction to Energy= 0.512718
Thermal correction to Enthalpy= 0.513663
Thermal correction to Gibbs Free Energy= 0.432593
Sum of electronic and zero-point Energies= -1228.193809
Sum of electronic and thermal Energies= -1228.168647
Sum of electronic and thermal Enthalpies= -1228.167703
Sum of electronic and thermal Free Energies= -1228.248772

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4832668 *(ΔGrel-solv = 4.1 kcal/mol*)

C	1.89833400	-0.52310100	1.47525700
H	1.69148900	0.41952400	-0.40318400
O	1.78836500	0.51740200	2.07950500
C	1.77902400	-1.88988300	2.11978400
H	2.80185600	-2.28363400	2.23318700
H	1.25167000	-2.57409100	1.45462200
C	3.92686600	-0.03429500	0.04584900
C	2.23711200	-1.68914200	-0.74341700
C	2.66162900	-1.47574800	-2.19254200
C	4.14039800	-1.09366200	-2.26443700
C	4.43384800	0.15457900	-1.41272400
H	4.45238300	-0.91863400	-3.30028600
H	4.74186000	-1.93548400	-1.89318600
N	2.45840200	-0.45018500	0.07113400
O	-0.24581800	-0.78646900	0.50853600
N	-0.84904200	0.37905200	0.26787000
C	-0.25887800	1.37105700	-0.36249900
O	0.93859000	1.30816300	-0.83970100
O	-2.08977100	2.88738200	0.28690700
H	-1.29644400	2.73688900	-1.64430900
H	-0.28562300	3.48350000	-0.40267400
C	-0.99643300	2.67364800	-0.58508300
C	-2.22861900	0.46091100	0.79558400
H	-2.12692200	0.35628500	1.88093100
H	-3.63896300	2.03061500	1.21241800
C	-2.95614800	1.77503900	0.39670800
H	-2.39205900	-2.39052900	1.15233500
C	-3.11056000	-1.97572700	0.45471000
C	-4.93689900	-0.86704800	-1.38437100
C	-3.11431100	-0.60752200	0.19128600
C	-4.03083900	-2.78992500	-0.20869500
C	-4.93959600	-2.23851600	-1.11862300
C	-4.01432100	-0.05297900	-0.72776400
H	-4.04443800	-3.85877300	-0.01543400
H	-5.65523900	-2.88259500	-1.62205700
C	-3.80012100	1.43602500	-0.86196600
H	-5.64468800	-0.44362300	-2.09218000
H	-3.24850600	1.67058400	-1.78162900
H	-4.72858300	2.01467100	-0.89400900
H	2.81465000	-2.51480100	-0.30755800
H	2.47074400	-2.40118100	-2.74767600
H	1.17149000	-1.90375400	-0.67336800
H	2.03295800	-0.69994200	-2.64317000
H	5.52506000	0.23201200	-1.30848300

C	3.95388000	1.44788100	-2.09625500
H	4.31230400	2.33554700	-1.56830700
H	4.35427100	1.49165200	-3.11476200
H	2.86605000	1.52075300	-2.15365000
C	1.07454500	-1.81212100	3.47196200
H	1.02863100	-2.80105300	3.93754000
H	1.58943900	-1.12740600	4.14961900
H	0.05663400	-1.44262700	3.32798700
H	4.48041300	-0.89097000	0.46039900
C	4.22795700	1.20029000	0.90128800
H	3.55776600	2.02669000	0.66035700
H	4.13341400	1.00137700	1.96786100
H	5.25862500	1.51145000	0.70018100

***ent-cis*-113 -TS-CO-conformer-(α*equitorial*-β*axial*)**

Zero-point correction= 0.492176 (Hartree/Particle)
Thermal correction to Energy= 0.517142
Thermal correction to Enthalpy= 0.518086
Thermal correction to Gibbs Free Energy= 0.437996
Sum of electronic and zero-point Energies= -1228.184787
Sum of electronic and thermal Energies= -1228.159821
Sum of electronic and thermal Enthalpies= -1228.158877
Sum of electronic and thermal Free Energies= -1228.238967

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4784733 *(ΔGrel-solv = 10.5 kcal/mol*)

C	2.04447300	-0.67675200	2.03740400
H	1.74556000	0.30032100	0.06952200
C	3.80509700	-0.12785500	-0.11724100
C	1.93350400	-1.75541500	-0.28279000
C	2.02383500	-1.77667200	-1.80455400
C	3.44802400	-1.46059600	-2.26172300
C	3.92151600	-0.12261400	-1.67168500
H	3.51468000	-1.43108100	-3.35545100
H	4.11867500	-2.26309300	-1.92524700
N	2.40225900	-0.46764600	0.32251800
O	0.28819700	-0.54699300	1.69128800
N	-0.43752500	0.62115900	1.76089600
C	-0.22777600	1.63348200	0.90744800
O	0.67376500	1.66008200	0.04258100
O	-1.87263000	2.92783700	2.24743600
H	-1.75901000	2.91638900	0.15488900
H	-0.46810200	3.73532700	1.03593000
C	-1.12149700	2.85951900	1.05082200
C	-1.60538200	0.49463100	2.65240300
H	-1.21087600	0.37193100	3.66611100
H	-2.97821000	1.88971900	3.54816700
C	-2.55275500	1.72578700	2.55410500
H	-1.34746400	-2.36932700	2.85387700
C	-2.28257000	-2.02222500	2.42846400
C	-4.68317300	-1.09018900	1.27887600
C	-2.51104300	-0.65710100	2.26119100
C	-3.26693500	-2.92172800	2.01420400
C	-4.45940200	-2.45865400	1.44701400
C	-3.69896400	-0.18950300	1.68538600
H	-3.10731500	-3.98917600	2.13549800

H	-5.21948500	-3.16994800	1.13611400
C	-3.69964200	1.31752700	1.59005700
H	-5.61164000	-0.73556900	0.83904800
H	-3.49154200	1.64437100	0.56331200
H	-4.64995900	1.77680900	1.87975400
H	2.54710600	-2.54467900	0.15967700
H	1.31224200	-1.06138700	-2.23377900
C	2.38011300	0.55110200	2.86505100
H	3.47002900	0.60588000	2.91602600
H	2.02605500	1.46626900	2.38821800
C	1.85099200	0.40599200	4.29594300
H	0.76211900	0.33972900	4.31939600
H	2.24890200	-0.50334400	4.75210800
H	2.15521300	1.26567600	4.90057900
O	2.25480700	-1.81017800	2.40149500
H	1.71442400	-2.76939400	-2.15138000
H	0.91180500	-1.89682900	0.06344900
C	4.30949700	1.20572700	0.45031500
H	4.64217500	1.12369200	1.48394400
H	5.16991500	1.53927900	-0.13754700
H	3.54175300	1.98152500	0.39249000
H	4.43213900	-0.94515700	0.26103300
H	4.99740100	-0.02868900	-1.87417300
C	3.22039500	1.07911200	-2.33388600
H	3.69283000	2.02452700	-2.05468000
H	3.28411900	0.99163100	-3.42354200
H	2.16365100	1.15680500	-2.06368100

***ent-cis*-113-TS-ring-conformer-(α*axial*-β*equitorial*)**

Zero-point correction= 0.489941 (Hartree/Particle)
Thermal correction to Energy= 0.514706
Thermal correction to Enthalpy= 0.515650
Thermal correction to Gibbs Free Energy= 0.436699
Sum of electronic and zero-point Energies= -1228.194058
Sum of electronic and thermal Energies= -1228.169293
Sum of electronic and thermal Enthalpies= -1228.168349
Sum of electronic and thermal Free Energies= -1228.247301

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4865416 *(ΔGrel-solv = 10.5 kcal/mol*)

C	2.18057400	-0.38265400	1.84086800
H	1.90395400	0.17252700	-0.11539800
O	2.40604200	0.70642600	2.30725800
C	1.73026900	-1.57016900	2.66193300
H	2.64494800	-2.07721700	3.00429500
H	1.17096100	-2.27569900	2.04858700
C	3.98883400	-0.00144600	0.14540500
C	2.39490400	-1.89162500	-0.31307100
C	2.53423200	-1.62670400	-1.83724800
C	3.91253900	-1.03143900	-2.18115300
C	4.20084800	0.22830900	-1.35205700
H	4.73256200	-0.69050500	0.55976000
H	1.77971100	-0.86734800	-2.07492700
H	3.94547300	-0.78747800	-3.24929100
H	4.69792100	-1.78148400	-2.01599000
H	5.23104900	0.56848000	-1.50728200

N	2.61647900	-0.56776000	0.38813100
H	1.34689900	-2.12179500	-0.10915400
O	-0.04672200	-0.51161300	0.90959600
N	-0.63569600	0.58358500	0.40629500
C	0.01009800	1.40935700	-0.39605800
O	1.21780600	1.21538200	-0.76687900
O	-1.83322800	3.03640900	-0.17454300
H	-0.92839100	2.49907100	-1.98423700
H	0.01940900	3.47458200	-0.85770400
C	-0.69198900	2.64689100	-0.91752500
C	-2.03689600	0.77076200	0.82277300
H	-2.00967800	0.90041200	1.91075300
H	-3.45335900	2.39119900	0.80042300
C	-2.71874500	1.97066500	0.10707200
H	-2.28453200	-1.93380600	1.77886800
C	-2.94522300	-1.67711700	0.95861400
C	-4.62306900	-0.98600900	-1.19784800
C	-2.90355800	-0.39910900	0.40556200
C	-3.83629700	-2.61167200	0.42641800
C	-4.67119200	-2.26692300	-0.64205100
C	-3.72998500	-0.05325900	-0.67130800
H	-3.88537500	-3.61228600	0.84654600
H	-5.36554300	-3.00095600	-1.04154400
C	-3.47917900	1.37069600	-1.10710500
H	-5.27490700	-0.72299700	-2.02691100
H	-2.85955800	1.39872700	-2.01282600
H	-4.39225500	1.93136600	-1.33082900
C	3.30324200	-3.01930000	0.19157800
H	2.97571200	-3.96438100	-0.24903800
H	4.35088100	-2.87700600	-0.08575200
H	3.25694600	-3.13846100	1.27410000
C	2.22019600	-2.87534700	-2.66971400
H	1.25634100	-3.31258800	-2.38743300
H	2.16718000	-2.61562700	-3.73179200
H	2.98830900	-3.64852400	-2.56163200
H	4.03626700	0.93400200	0.70099600
H	3.53754800	1.03796200	-1.67215000
C	0.90289600	-1.12677100	3.86876400
H	0.63830900	-1.99132300	4.48486100
H	1.45621500	-0.41337800	4.48341000
H	-0.01004600	-0.64634400	3.51295200

***ent-cis*-113-TS-CO-ring-conformer-(α*axial*-β*equitorial*)**

Zero-point correction= 0.491959 (Hartree/Particle)
Thermal correction to Energy= 0.516999
Thermal correction to Enthalpy= 0.517943
Thermal correction to Gibbs Free Energy= 0.437359
Sum of electronic and zero-point Energies= -1228.190698
Sum of electronic and thermal Energies= -1228.165659
Sum of electronic and thermal Enthalpies= -1228.164714
Sum of electronic and thermal Free Energies= -1228.245299

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1228.4843378 *(ΔGrel-solv = 6.5 kcal/mol*)

C	2.08006200	-0.75285200	2.09103400
H	1.95842700	0.05866000	0.10104400

C	3.98869600	-0.30495800	0.19210000
C	2.18671000	-1.94730200	-0.31397800
C	2.27745000	-1.60396200	-1.82319800
C	3.70315700	-1.15634600	-2.19758200
C	4.18580600	-0.00713200	-1.30077100
H	3.72701200	-0.84072400	-3.24725800
H	4.39148300	-2.00746300	-2.11773600
N	2.57824200	-0.70284100	0.45419200
O	0.41112900	-0.65775700	1.63276800
N	-0.30049200	0.52264400	1.58270800
C	-0.06239100	1.43775000	0.63209700
O	0.86253700	1.36424100	-0.20373700
O	-1.71087700	2.87887200	1.80171000
H	-1.59280800	2.61798500	-0.27480300
H	-0.30547200	3.54020900	0.50524700
C	-0.95702500	2.67109200	0.62274900
C	-1.47222300	0.50102200	2.47568300
H	-1.08213800	0.48233800	3.49841500
H	-2.82306000	2.00660800	3.21309500
C	-2.40419400	1.72618000	2.24266800
H	-1.23649000	-2.32681800	2.97076400
C	-2.17055400	-2.01848300	2.51410700
C	-4.56562200	-1.18999900	1.27572500
C	-2.38860700	-0.67634900	2.20554400
C	-3.16345900	-2.94741000	2.19670000
C	-4.35295300	-2.53533000	1.58545000
C	-3.57303300	-0.26026900	1.58512400
H	-3.01287000	-3.99776600	2.42838400
H	-5.11965600	-3.26852900	1.35107300
C	-3.56079000	1.22877100	1.33289300
H	-5.49198700	-0.87556000	0.80222500
H	-3.35756800	1.44521800	0.27636900
H	-4.50515100	1.72437300	1.57883500
H	4.20726100	0.58866000	0.77806700
H	5.24379800	0.21402700	-1.48336600
H	4.64583800	-1.10450600	0.54432200
H	3.62405200	0.90380800	-1.54305300
C	2.47126700	0.57355500	2.74219600
H	3.56679300	0.59375300	2.76774300
H	2.14769000	1.42891200	2.14400200
C	1.96315100	0.65994500	4.18343000
H	0.87249700	0.69796000	4.22632500
H	2.28875600	-0.21805500	4.74567400
H	2.35122500	1.55820300	4.67299900
O	2.24205400	-1.82542000	2.64368600
C	2.98377400	-3.18818100	0.10428300
H	2.94886200	-3.30164000	1.18635600
H	2.52595400	-4.07047600	-0.35122100
H	4.02807200	-3.16054700	-0.22050000
H	1.13940900	-2.09894200	-0.04543400
C	1.78166900	-2.74961500	-2.71288500
H	0.77875500	-3.07728700	-2.41859400
H	1.73338200	-2.42684200	-3.75808300
H	2.44618800	-3.61852100	-2.66749500
H	1.60751900	-0.74659000	-1.98105900

cis-2-phenylpiperidin-3-ol-TS

Zero-point correction= 0.517414 (Hartree/Particle)
Thermal correction to Energy= 0.545612
Thermal correction to Enthalpy= 0.546556
Thermal correction to Gibbs Free Energy= 0.457807
Sum of electronic and zero-point Energies= -1455.799044
Sum of electronic and thermal Energies= -1455.770846
Sum of electronic and thermal Enthalpies= -1455.769902
Sum of electronic and thermal Free Energies= -1455.858651

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1456.1112825

C	0.00000000	0.00000000	0.00000000
H	0.00000000	0.00000000	2.09045442
O	1.19897569	0.00000000	-0.14170068
C	-0.99798347	-0.33861057	-1.08177345
H	-1.32415801	0.62274686	-1.50767618
H	-1.87853164	-0.81507247	-0.65049059
C	0.10100931	2.05495559	1.40680085
C	-1.97904022	0.60116925	1.54099682
C	-2.25546128	1.09635754	2.96427863
C	-1.69147746	2.50151301	3.21549021
C	-0.20847659	2.56482927	2.83399103
H	-1.79726777	2.76158816	4.27665587
H	-2.24497188	3.26118914	2.65508078
N	-0.51409042	0.67393453	1.25863698
O	-0.62176025	-2.02488597	1.05793775
N	0.24552462	-2.58622047	1.90921420
C	0.85427383	-1.89369572	2.85078353
O	0.65092733	-0.64070059	3.04805150
O	2.34707694	-3.80859869	3.28651941
H	1.37590866	-2.69232562	4.76738849
H	2.69539873	-1.91109248	3.89140576
C	1.83932490	-2.58037290	3.77322247
C	0.45678591	-4.03165259	1.69228548
H	0.89592664	-4.11679637	0.69229956
H	1.90457387	-5.49667935	2.31435636
C	1.35137525	-4.67893655	2.78591971
H	-1.86585408	-4.27558731	0.00918358
C	-1.90161153	-4.85606191	0.92399652
C	-1.97659153	-6.32232715	3.33000954
C	-0.83821722	-4.80482885	1.82257266
C	-3.00746481	-5.64978547	1.23589544
C	-3.04277506	-6.37980080	2.42900249
C	-0.87373393	-5.52583591	3.02286989
H	-3.84521388	-5.70433969	0.54651484
H	-3.90596233	-6.99945462	2.65572120
C	0.37817923	-5.28609541	3.83318331
H	-2.00834830	-6.89264294	4.25470246
H	0.18630762	-4.57877380	4.65046492
H	0.78877901	-6.19235738	4.28935221
H	1.17324612	1.85979051	1.38074605
H	-2.53216725	1.17981451	0.79547073
H	-3.33619525	1.07459578	3.14015547
H	-2.23779877	-0.45404524	1.45524047
H	-1.80009303	0.38775432	3.66507795

C	-0.37682752	-1.22836662	-2.15611983
H	-1.09906451	-1.42630218	-2.95353851
H	0.50866277	-0.76066010	-2.59243771
H	-0.07583808	-2.17747765	-1.70696555
H	0.34135036	1.89282738	3.51003293
C	-0.19811171	2.99708568	0.24646680
C	0.85677736	3.28817780	-0.63268241
C	-1.44723321	3.58480332	-0.01311632
C	0.67875145	4.13450466	-1.72614254
H	1.82771213	2.83497353	-0.45889643
C	-1.62928392	4.43009803	-1.10850125
H	-2.29204841	3.40088556	0.63829211
C	-0.56801255	4.70996176	-1.96896537
H	1.51507326	4.34131910	-2.38735829
H	-2.60488041	4.87420727	-1.28405147
H	-0.71193232	5.37018243	-2.81916885
O	0.32011246	3.88318587	2.90305622
H	0.31372402	4.15266874	3.83059630

ent-cis-2-phenylpiperidin-3-ol-TS

Zero-point correction= 0.515792 (Hartree/Particle)
Thermal correction to Energy= 0.544089
Thermal correction to Enthalpy= 0.545033
Thermal correction to Gibbs Free Energy= 0.456409
Sum of electronic and zero-point Energies= -1455.796031
Sum of electronic and thermal Energies= -1455.767734
Sum of electronic and thermal Enthalpies= -1455.766790
Sum of electronic and thermal Free Energies= -1455.855414

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1456.107093

C	0.04294400	-0.10754400	0.10780400
H	0.01390900	-0.01169800	2.23217500
O	1.24802400	-0.15390000	0.07061800
C	-0.85744900	-0.37283600	-1.08366800
H	-1.19099100	0.60578200	-1.46458300
H	-1.75199500	-0.91053700	-0.76743400
C	-0.35317600	2.09047500	1.28182500
C	-2.03990200	0.28626000	1.51077200
C	-2.56083200	0.88771300	2.81273100
C	-2.37940400	2.40565800	2.80727700
C	-0.90444000	2.74941000	2.57174800
H	-2.71193500	2.85386700	3.75257200
H	-2.98945300	2.85986000	2.01461400
N	-0.58263500	0.58722400	1.31539100
O	-0.52484500	-2.12192600	1.05393700
N	0.47376000	-2.57780700	1.81684400
C	1.02566600	-1.85624700	2.77109700
O	0.64340600	-0.67048500	3.09333900
O	2.83058400	-3.52766000	2.99760000
H	1.77143000	-2.68709700	4.59501500
H	2.90047600	-1.64334700	3.72510400
C	2.15854700	-2.43476600	3.59382200
C	0.92545000	-3.94020700	1.46216700
H	1.32940100	-3.85978200	0.44740200

H	2.61504200	-5.19073700	1.91168900
C	1.96346200	-4.50922600	2.46685700
H	-1.38097800	-4.47090900	-0.18050300
C	-1.27751600	-5.11460800	0.68563400
C	-0.99983100	-6.74641600	2.96729700
C	-0.20754200	-4.93960000	1.56018200
C	-2.21150200	-6.11641800	0.95823400
C	-2.07136100	-6.92789000	2.08933400
C	-0.06910100	-5.74292400	2.69965300
H	-3.05145500	-6.26961100	0.28668000
H	-2.80120700	-7.70844700	2.28566200
C	1.15013900	-5.34076700	3.49527100
H	-0.89502600	-7.38032700	3.84389600
H	0.86688700	-4.72825900	4.36117200
H	1.72714200	-6.18753300	3.87982700
H	-2.60715600	0.69192500	0.66281400
H	-3.61644400	0.61758100	2.92450900
H	-2.11537900	-0.80035900	1.51774700
H	-2.01658100	0.45034400	3.65549800
H	-0.79189900	3.83416100	2.41925100
C	-0.12283000	-1.14919600	-2.17410900
H	-0.77265600	-1.30287200	-3.04079700
H	0.77695700	-0.62052300	-2.49629600
H	0.18032800	-2.12366500	-1.78429600
H	-0.98152300	2.47347700	0.46526000
C	1.07229600	2.54058300	1.00706400
C	1.28760200	3.45575700	-0.02914800
C	2.15900500	2.15225100	1.80494600
C	2.55766900	3.98459800	-0.26914800
H	0.45445900	3.76166700	-0.65841600
C	3.42543000	2.67716500	1.56225400
H	2.00857200	1.43021400	2.59749100
C	3.63083100	3.59616600	0.52938400
H	2.70387100	4.69251100	-1.07989300
H	4.26085100	2.36362900	2.18176000
H	4.62252200	4.00020100	0.34682100
O	-0.10208600	2.31123400	3.65926500
H	-0.39478300	2.77167800	4.45593400

trans-2-phenylpiperidin-3-ol-TS

Zero-point correction= 0.516528 (Hartree/Particle)
Thermal correction to Energy= 0.544756
Thermal correction to Enthalpy= 0.545701
Thermal correction to Gibbs Free Energy= 0.457209
Sum of electronic and zero-point Energies= -1455.797119
Sum of electronic and thermal Energies= -1455.768890
Sum of electronic and thermal Enthalpies= -1455.767946
Sum of electronic and thermal Free Energies= -1455.856438

IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1456.1094842

C	-0.22965000	-0.07016500	0.21638200
H	-0.23648800	0.10147100	2.31178300
O	0.97401700	-0.17074400	0.13123000
C	-1.19865000	-0.34039600	-0.91510300

H	-1.40127400	0.63157200	-1.38880100
H	-2.14575700	-0.71192700	-0.52241300
C	-0.09484500	2.12697400	1.38318000
C	-2.20034900	0.74231800	1.65797700
C	-2.47983500	1.40540600	3.00764100
C	-1.96658600	2.84834000	3.02994100
C	-0.47955700	2.92723000	2.65021000
H	-2.09662300	3.29428300	4.02534800
H	-2.55706700	3.47114700	2.34888600
N	-0.73188100	0.74604800	1.39975500
O	-1.01266300	-1.92415700	1.25270400
N	-0.13325100	-2.51361400	2.07592100
C	0.50845700	-1.83872600	3.00920000
O	0.33422700	-0.58992300	3.23331500
O	1.97646700	-3.78644800	3.38735400
H	1.06728100	-2.66365200	4.90309300
H	2.37626000	-1.89946900	3.99620500
C	1.50583500	-2.55270100	3.89792000
C	0.04466300	-3.95892500	1.83754900
H	0.45958600	-4.04437100	0.82728200
H	1.47620200	-5.45784600	2.41441300
C	0.95191500	-4.63226900	2.90506000
H	-2.32389200	-4.14888200	0.20820900
C	-2.34783800	-4.73381000	1.12061600
C	-2.39421500	-6.21269100	3.51924400
C	-1.26194700	-4.70892700	1.99307100
C	-3.46171100	-5.50701400	1.45495200
C	-3.48302200	-6.24331100	2.64443700
C	-1.28327900	-5.43670800	3.18973700
H	-4.31700200	-5.54007700	0.78604000
H	-4.35304600	-6.84641400	2.88903400
C	-0.00823800	-5.22689600	3.97142100
H	-2.41496900	-6.78748200	4.44150200
H	-0.16681800	-4.52081300	4.79681500
H	0.39487000	-6.14390300	4.41260600
H	0.97024900	1.91736700	1.48881300
H	-2.72980400	1.25604100	0.84793400
H	-3.55689800	1.37628000	3.20413300
H	-2.49003100	-0.30827800	1.67460600
H	-1.98639400	0.82161100	3.79141300
H	-0.20948100	3.97640700	2.45340700
C	-0.61515300	-1.32020000	-1.93055600
H	-1.30901400	-1.46768900	-2.76364100
H	0.33566000	-0.95556100	-2.32605300
H	-0.43558100	-2.28223500	-1.44554300
O	0.34131600	2.39511000	3.68521300
H	0.04778800	2.76417400	4.52829200
C	-0.27826600	2.88194500	0.07025200
C	0.81266200	2.93432900	-0.81242700
C	-1.46114300	3.53774100	-0.30752300
C	0.72868400	3.61595600	-2.02588500
H	1.72916700	2.41684400	-0.54775500
C	-1.54831000	4.21927800	-1.52283500
H	-2.32888100	3.52684000	0.34106700
C	-0.45393400	4.26224400	-2.38620500
H	1.58812700	3.63934000	-2.68936100
H	-2.47451100	4.71928300	-1.79098700
H	-0.52257400	4.79435100	-3.33041200

ent-trans-2-phenylpiperidin-3-ol-TS

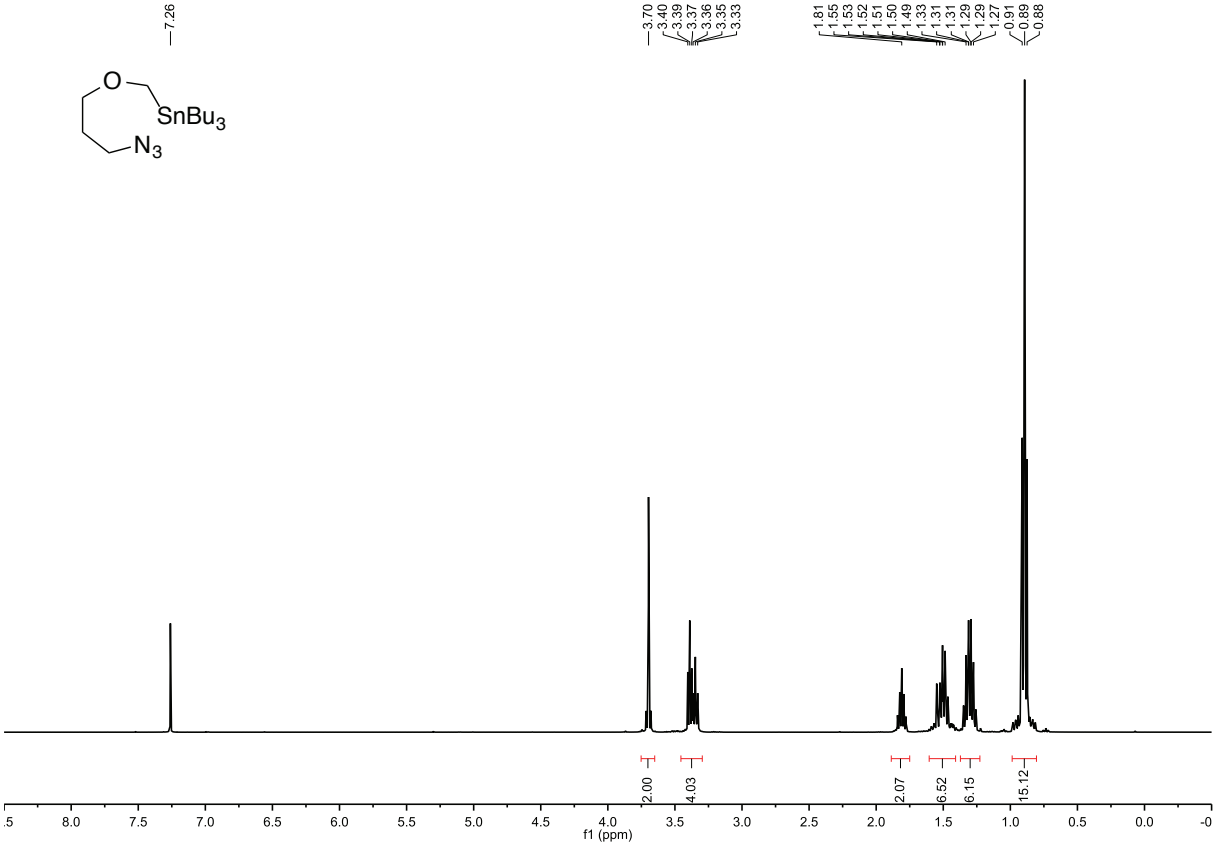
Zero-point correction= 0.515633 (Hartree/Particle)
Thermal correction to Energy= 0.544193
Thermal correction to Enthalpy= 0.545137
Thermal correction to Gibbs Free Energy= 0.455122
Sum of electronic and zero-point Energies= -1455.799163
Sum of electronic and thermal Energies= -1455.770604
Sum of electronic and thermal Enthalpies= -1455.769659
Sum of electronic and thermal Free Energies= -1455.859675

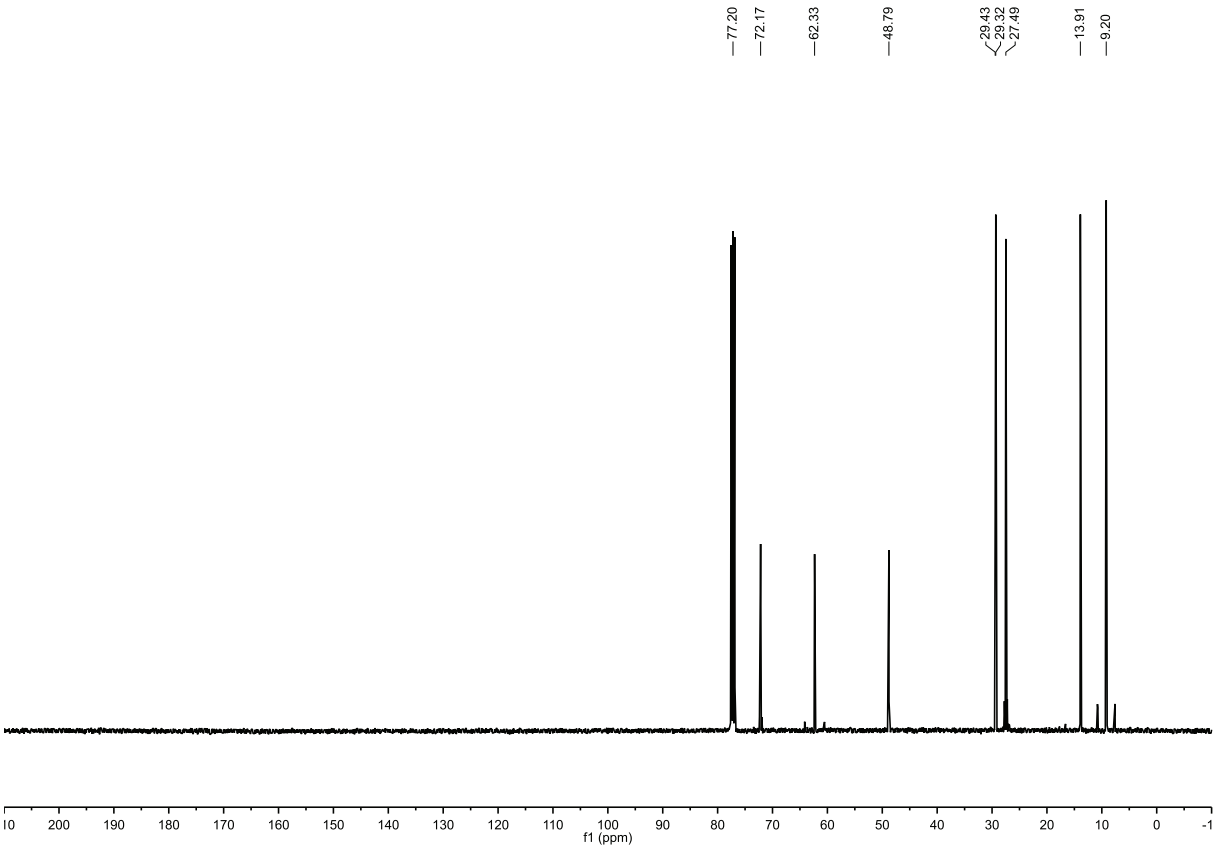
IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)//B3LYP/6-31G(d,p)
E= -1456.1095143

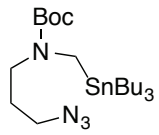
C	0.07446700	0.01889400	-0.08124400
H	0.14988700	-0.05448500	2.03865800
O	1.26814900	0.07795500	-0.21699100
C	-0.89309100	-0.34243100	-1.18859200
H	-1.36715000	0.59399800	-1.52302300
H	-1.68930300	-0.97674500	-0.79832500
C	-0.32409100	2.06968600	1.35445900
C	-1.92654100	0.15927000	1.48381200
C	-2.32838200	0.53671200	2.90596100
C	-2.17555300	2.04074700	3.12684900
C	-0.75930900	2.49964400	2.77833700
H	-2.40263200	2.31143900	4.16588200
H	-2.87755600	2.59528500	2.49046100
N	-0.50515300	0.56072200	1.21336800
O	-0.26664900	-2.17635000	0.90201300
N	0.68325300	-2.61536600	1.72902200
C	1.20216600	-1.87362500	2.68429000
O	0.82394300	-0.66529200	2.93969600
O	2.96465800	-3.56182600	3.05302100
H	1.85413400	-2.64521700	4.57102000
H	3.03736900	-1.65347000	3.71323100
C	2.28683500	-2.43669500	3.57816500
C	1.11499500	-4.00516700	1.45959000
H	1.55566600	-3.98130300	0.45734300
H	2.76331700	-5.26436100	2.02658500
C	2.10179700	-4.55082000	2.52696000
H	-1.14604600	-4.54246900	-0.23776400
C	-1.09016400	-5.15389400	0.65562500
C	-0.93209600	-6.69873800	3.00858500
C	-0.04588000	-4.97104700	1.55923000
C	-2.05888500	-6.12007800	0.93542100
C	-1.97805400	-6.88844900	2.10196100
C	0.03329100	-5.73043900	2.73375600
H	-2.87959600	-6.27952100	0.24189000
H	-2.73432800	-7.64201500	2.30360300
C	1.23432200	-5.32566500	3.55549900
H	-0.87360600	-7.29925500	3.91258200
H	0.93597400	-4.67515300	4.38799900
H	1.77800900	-6.16979500	3.99096200
H	-2.58521000	0.65094000	0.75726400
H	-3.36365300	0.22018400	3.07232900
H	-1.95359500	-0.92158500	1.35082300

H	-1.70155100	-0.02165400	3.61021300
H	-1.02634600	2.53575300	0.65037700
H	-0.04586300	2.05692300	3.48973400
C	-0.17725100	-1.03500400	-2.34622600
H	0.26168800	-1.97016900	-1.99098000
H	-0.88180900	-1.25854500	-3.15259300
H	0.62788700	-0.41291700	-2.74319800
C	1.07103000	2.58846900	1.05070100
C	1.22932200	3.56949900	0.06860500
C	2.19084700	2.18122500	1.78954800
C	2.47946700	4.13951400	-0.17821500
H	0.36582800	3.90097000	-0.50245000
C	3.43806400	2.74837500	1.54294500
H	2.09232300	1.39430100	2.53080500
C	3.58779500	3.73094200	0.56063200
H	2.58297700	4.90181100	-0.94500800
H	4.30008400	2.41747100	2.11518000
H	4.56309000	4.17036300	0.37202200
O	-0.66768500	3.91975800	2.78409100
H	-0.76999700	4.21751100	3.69688900

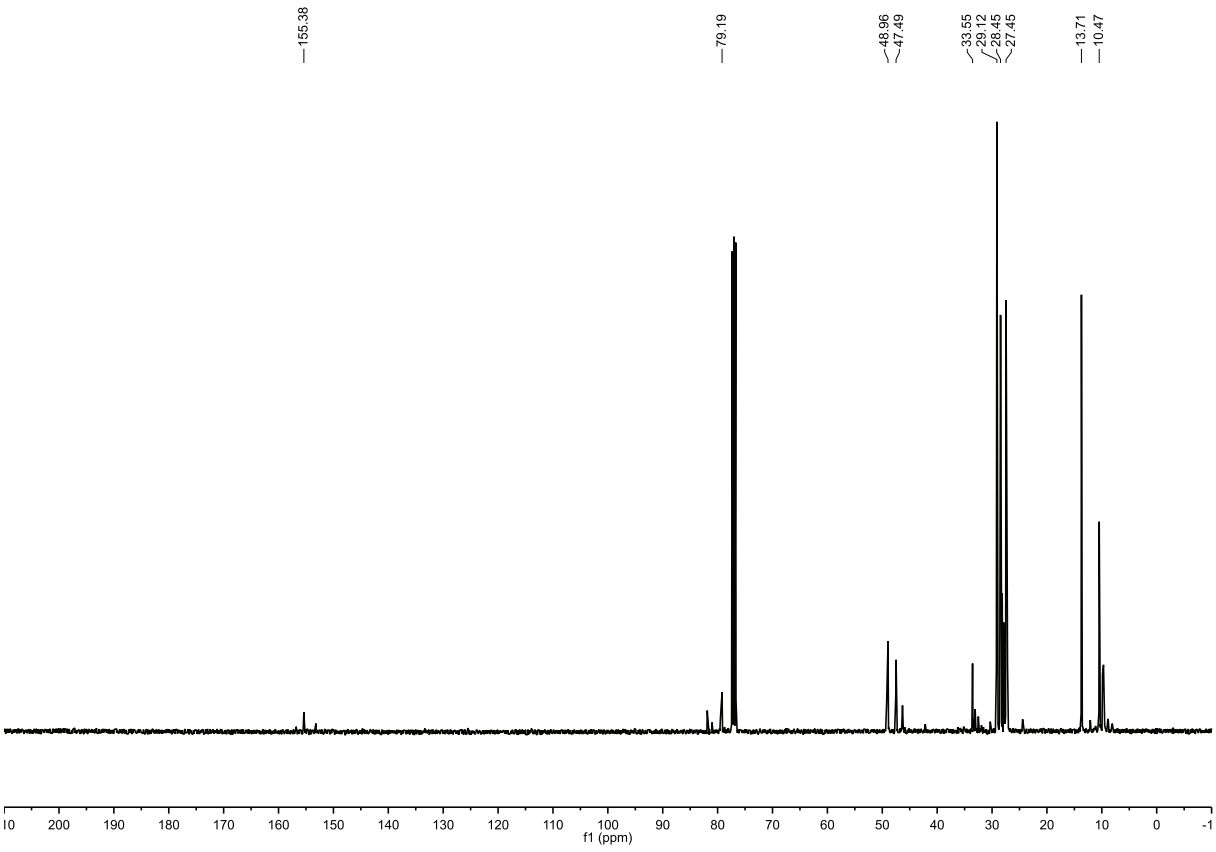
NMR-Spectra – Experimental part III






Boc
N
SnBu3
N3

3.28
3.03
2.79
1.80
1.47
1.28
0.89
3.52
1.38
1.65
17.64
6.90
16.40
f1 (ppm)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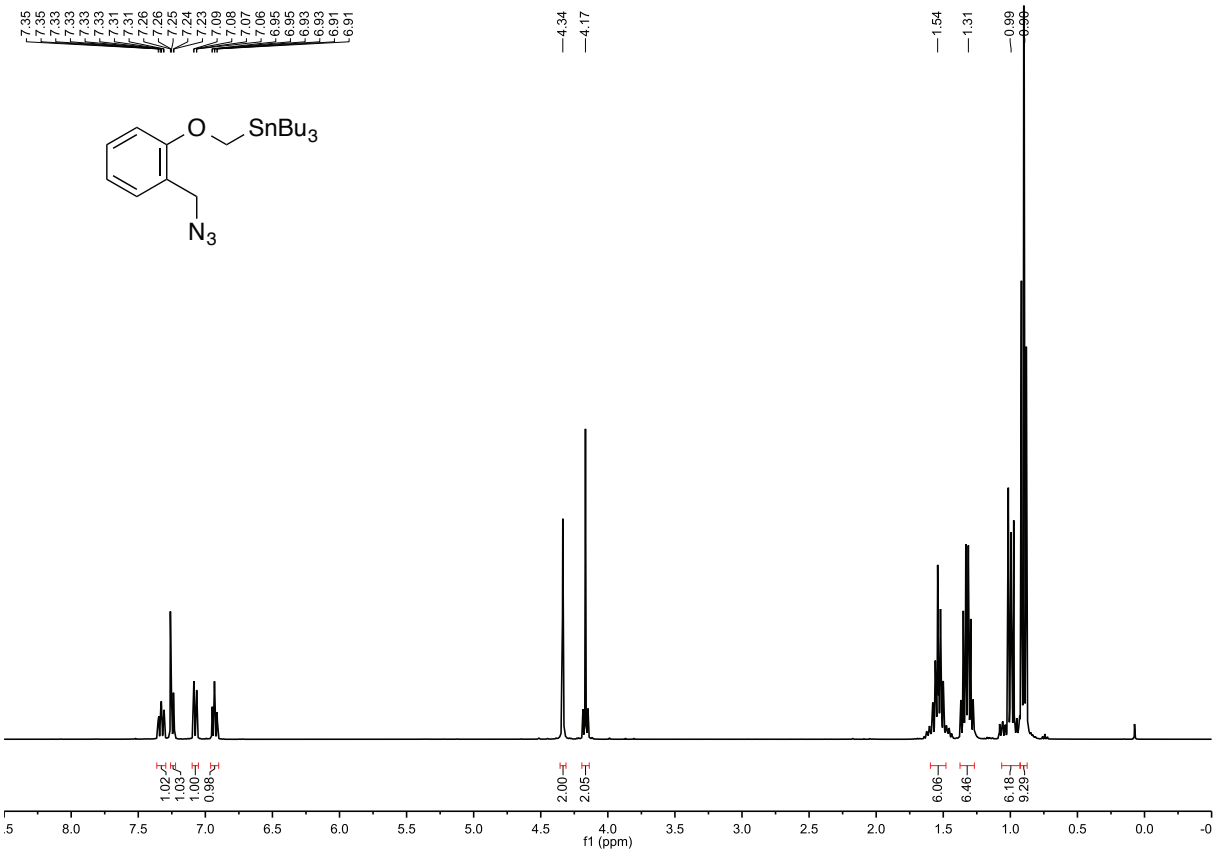
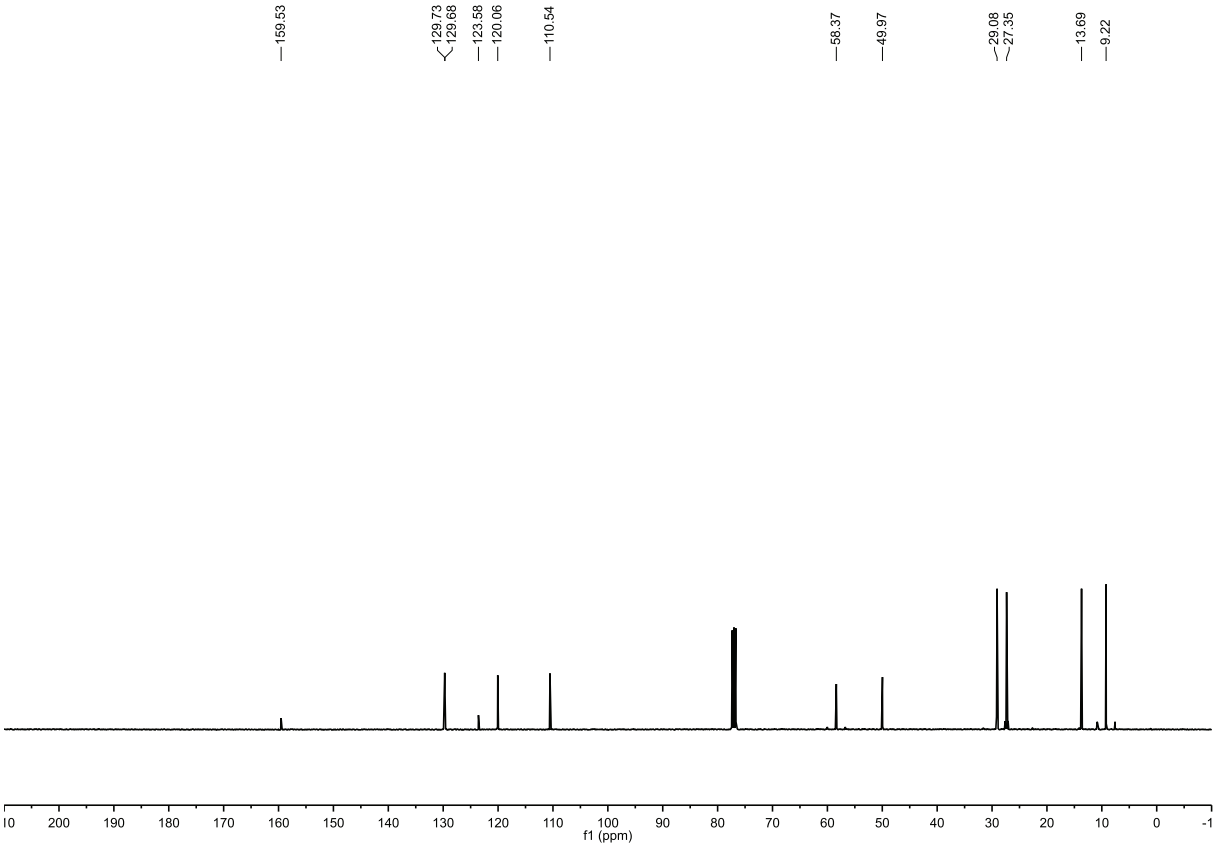
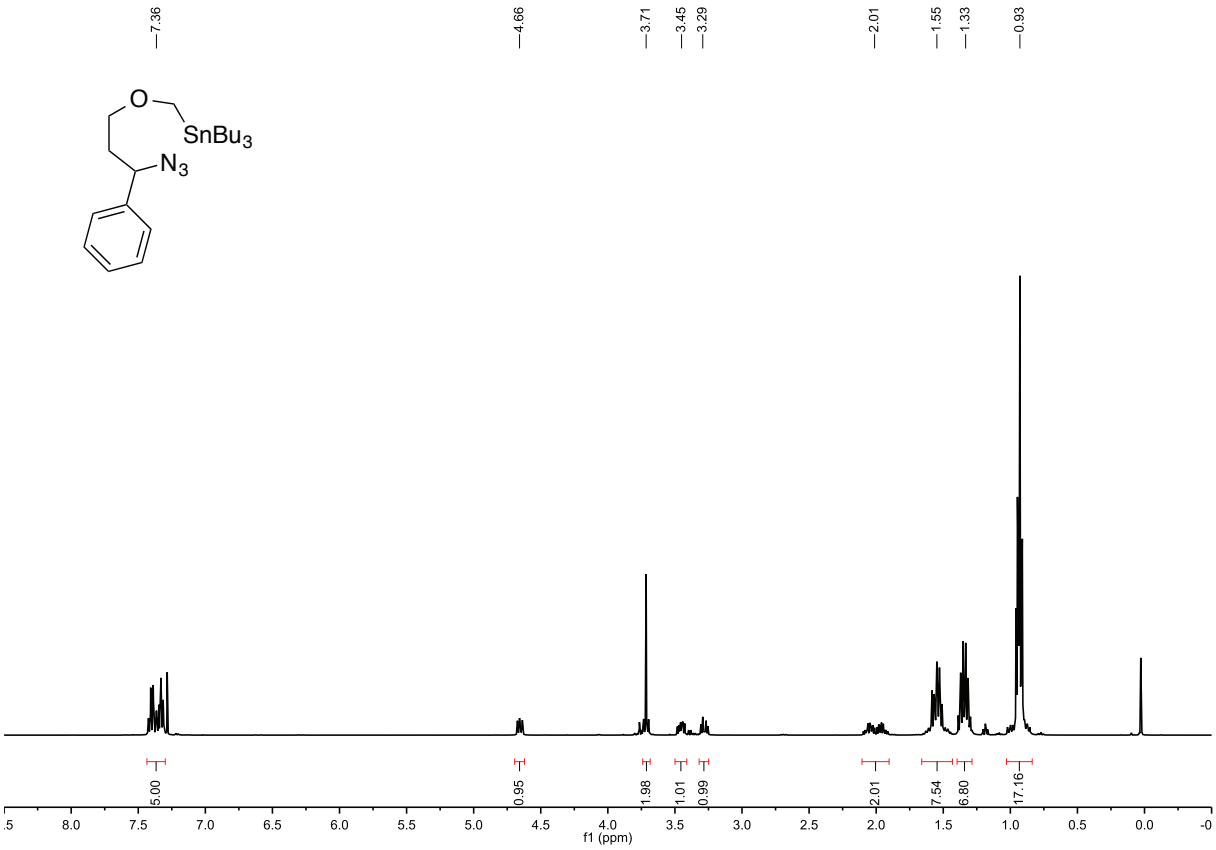
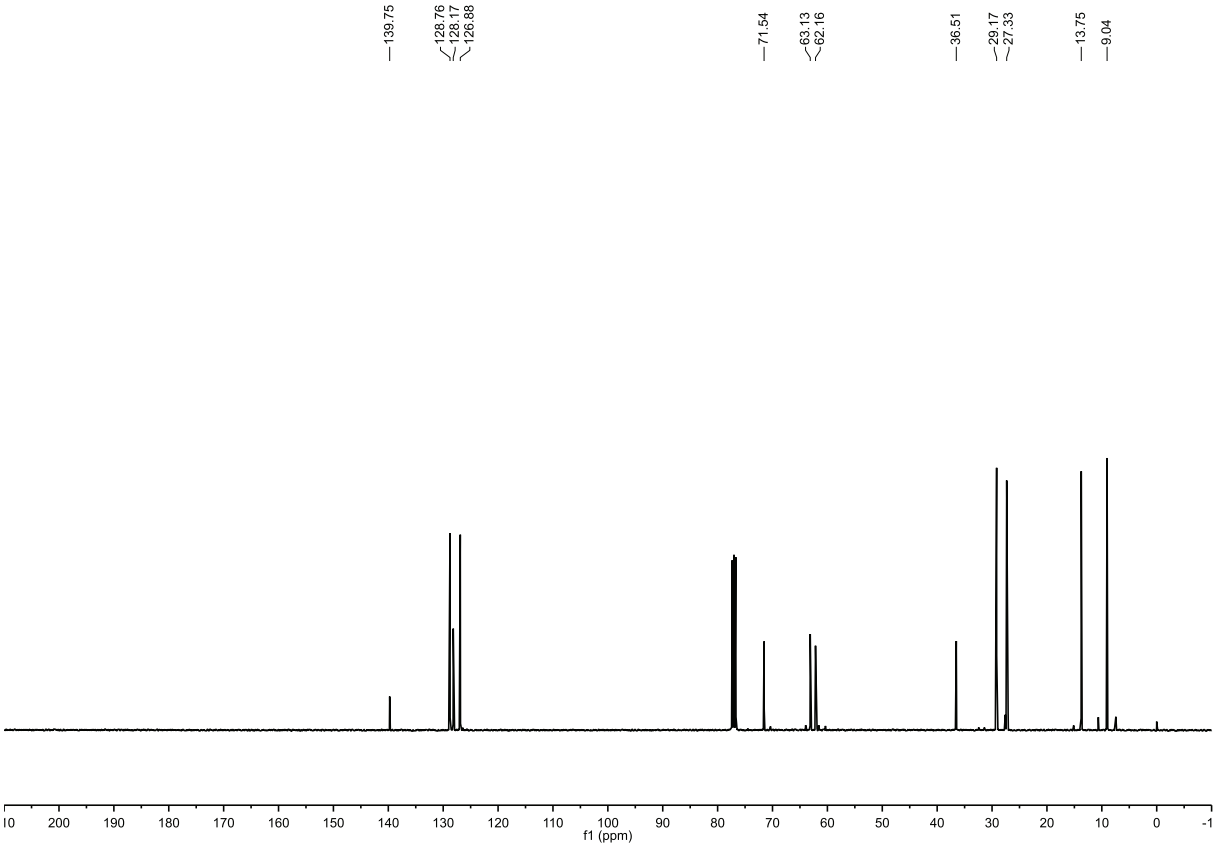
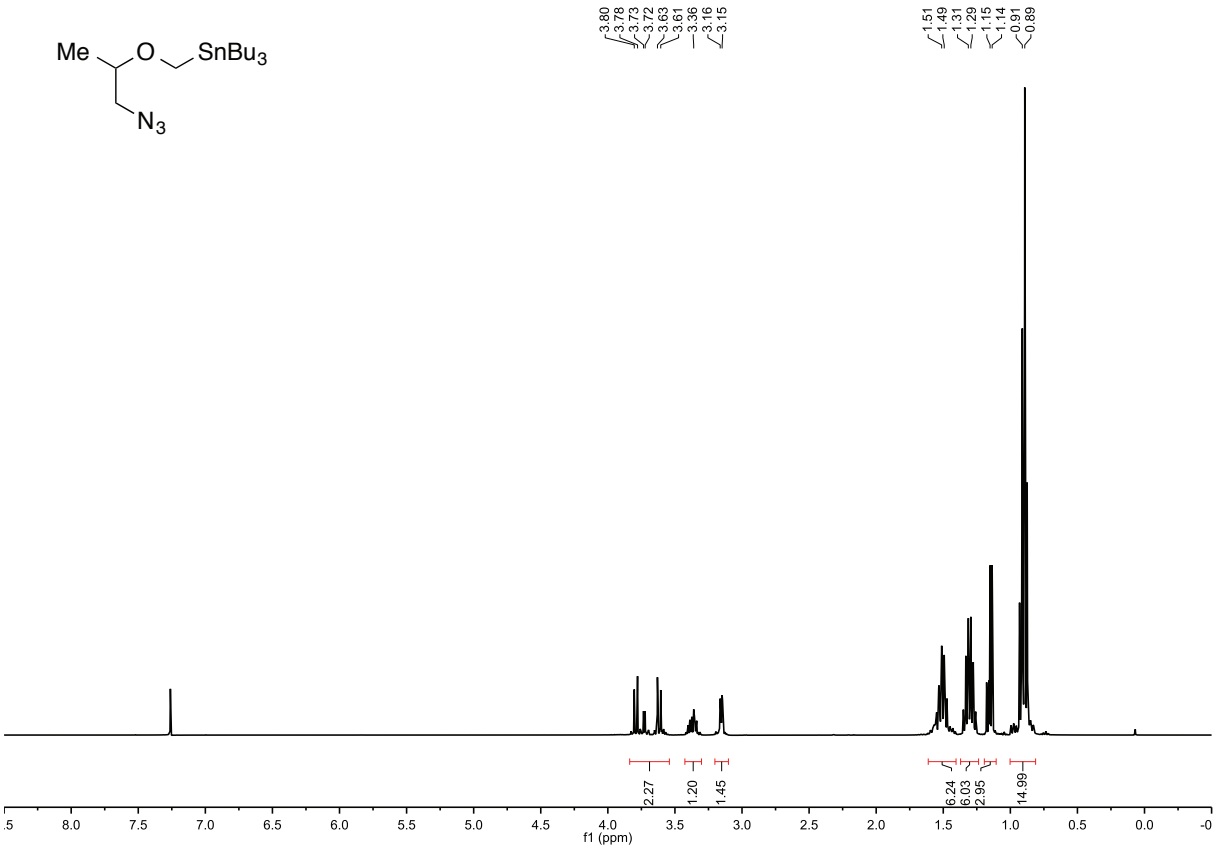
79.19
48.96
47.49
33.55
29.12
28.45
27.45
13.71
10.47
f1 (ppm)

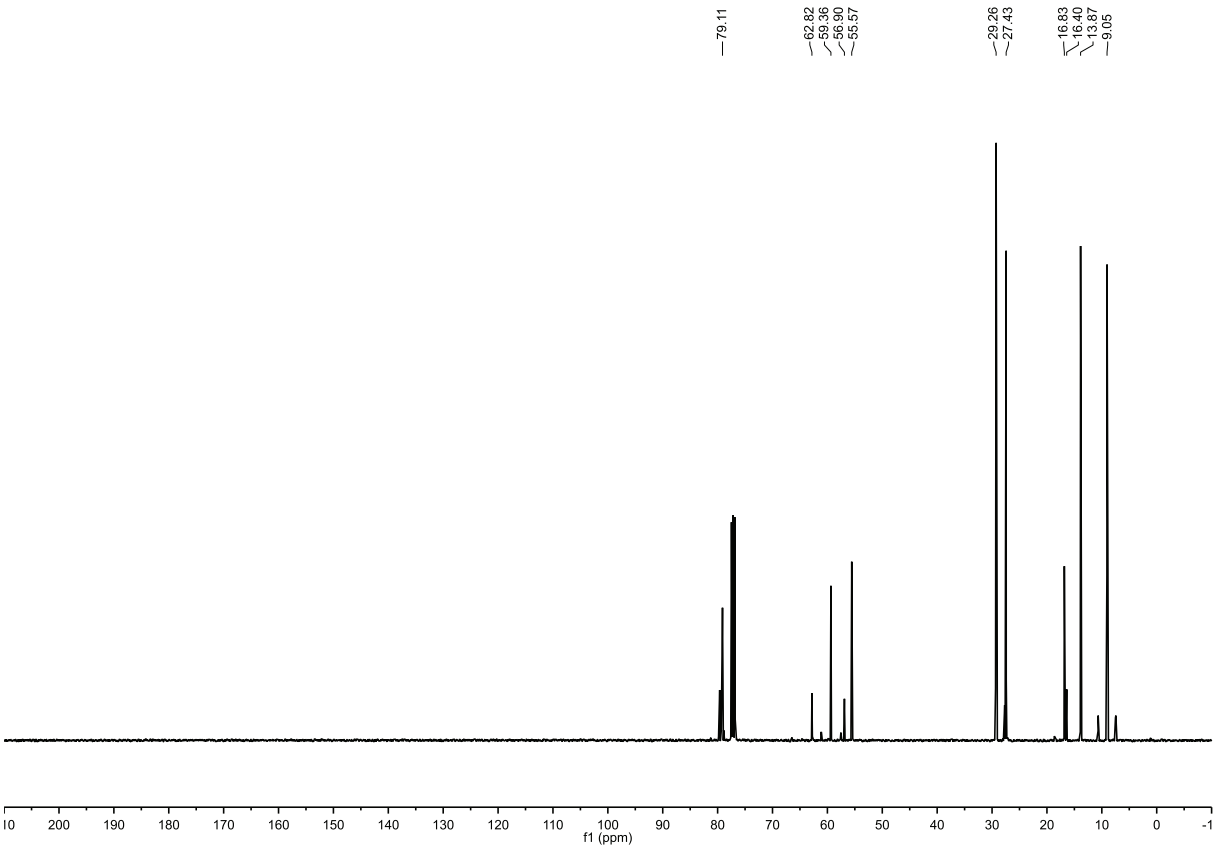

7.35
7.35
7.33
7.33
7.33
7.33
7.31
7.31
7.26
7.26
7.25
7.24
7.23
7.09
7.08
7.07
7.06
6.95
6.95
6.93
6.93
6.91
6.91
4.34
4.17
1.54
1.31
0.99
0.90
O
SnBu3
N3
1.02
1.03
1.00
0.98
2.00
2.05
6.06
6.46
6.18
9.29
f1 (ppm)

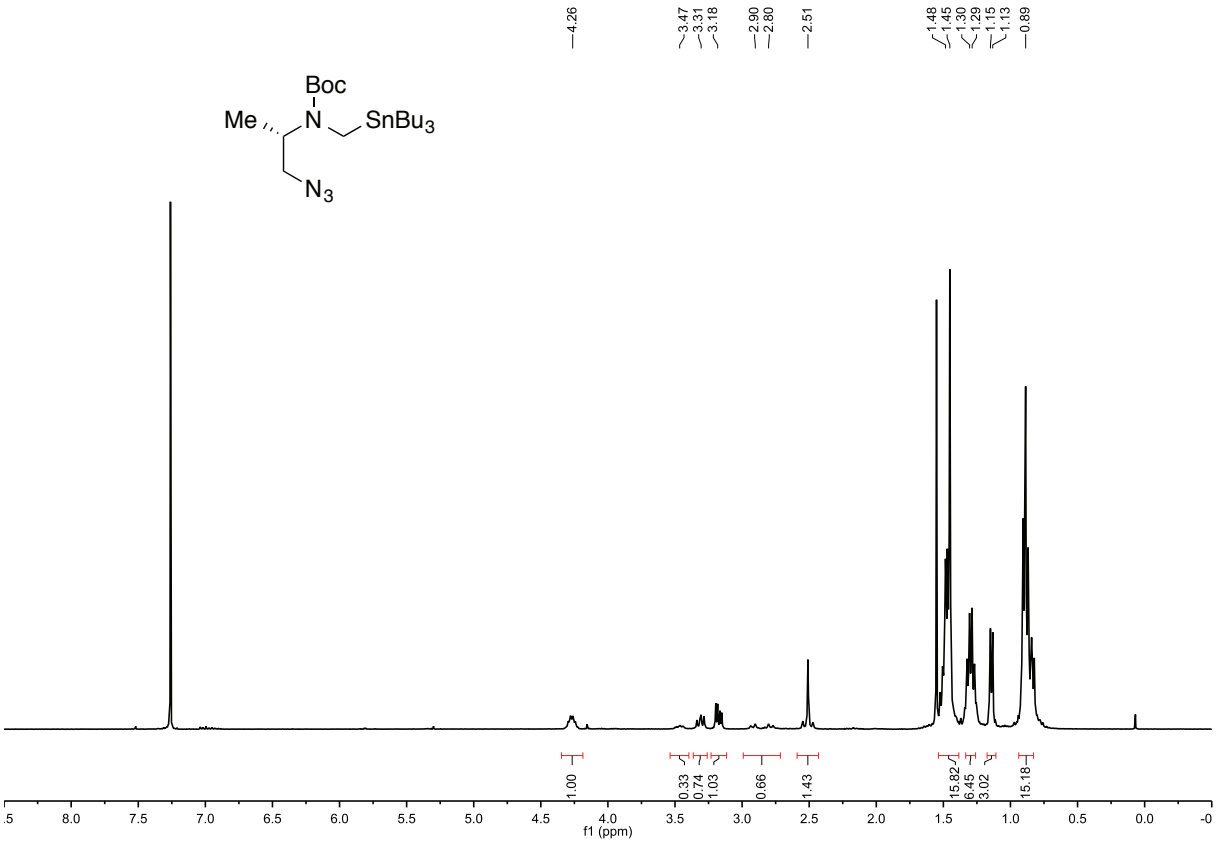

159.53
129.73
129.68
123.58
120.06
110.54
58.37
49.97
29.08
27.35
13.69
9.22
f1 (ppm)

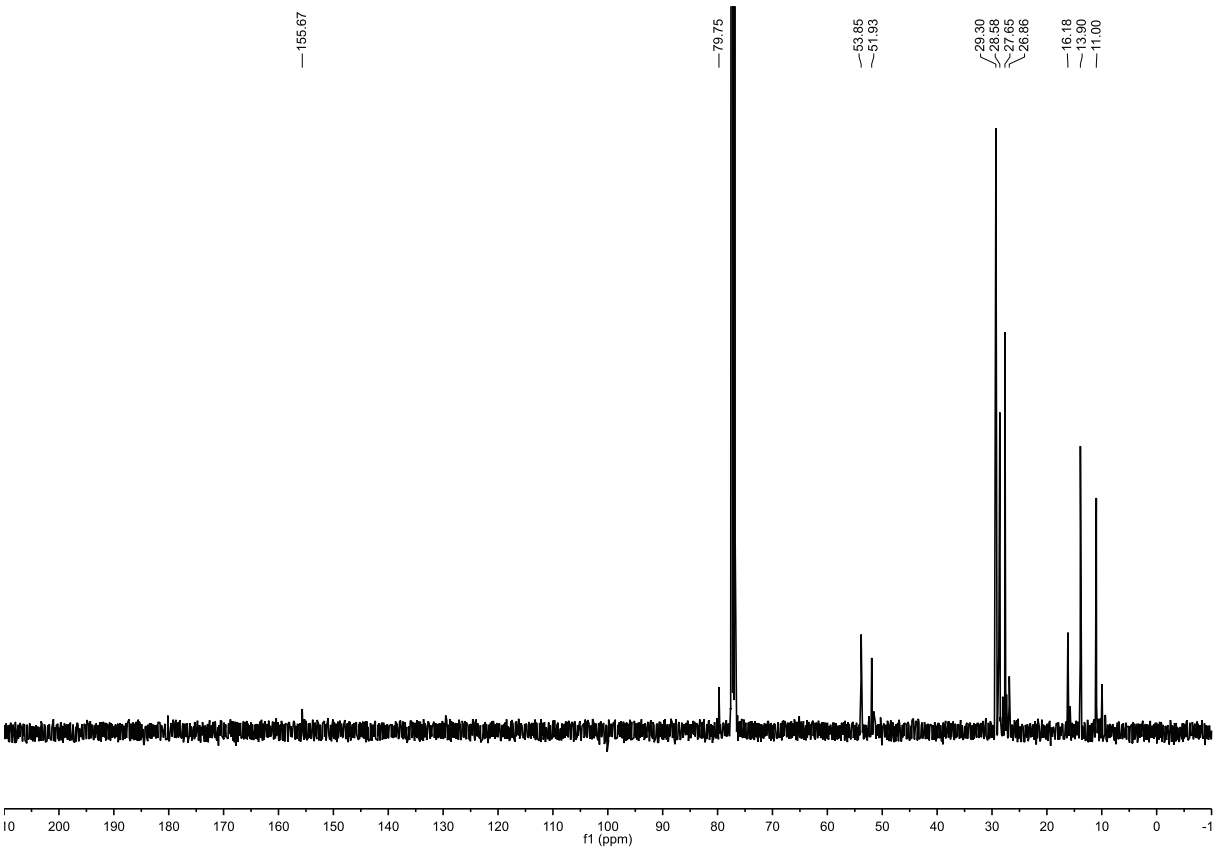

7.36
4.66
3.71
3.45
3.29
2.01
1.55
1.33
0.93
O
SnBu3
N3
5.00
0.95
1.98
1.01
0.99
2.01
7.54
6.80
17.16
f1 (ppm)


139.75
128.76
128.17
126.88
71.54
63.13
62.16
36.51
29.17
27.33
13.75
9.04
f1 (ppm)


Me
O
SnBu3
N3
3.80
3.78
3.73
3.72
3.63
3.61
3.36
3.16
3.15
1.51
1.49
1.31
1.29
1.15
1.14
0.91
0.89
2.27
1.20
1.45
6.24
6.03
2.95
14.99
f1 (ppm)


79.11
62.82
59.36
56.90
55.57
29.26
27.43
16.83
16.40
13.87
9.05
f1 (ppm)


4.26
3.47
3.31
3.18
2.90
2.80
2.51
1.48
1.45
1.30
1.29
1.15
1.13
0.89
Boc
N
SnBu3
Me
N3
1.00
0.33
0.74
1.03
0.66
1.43
15.82
6.45
3.02
15.18
f1 (ppm)


155.67
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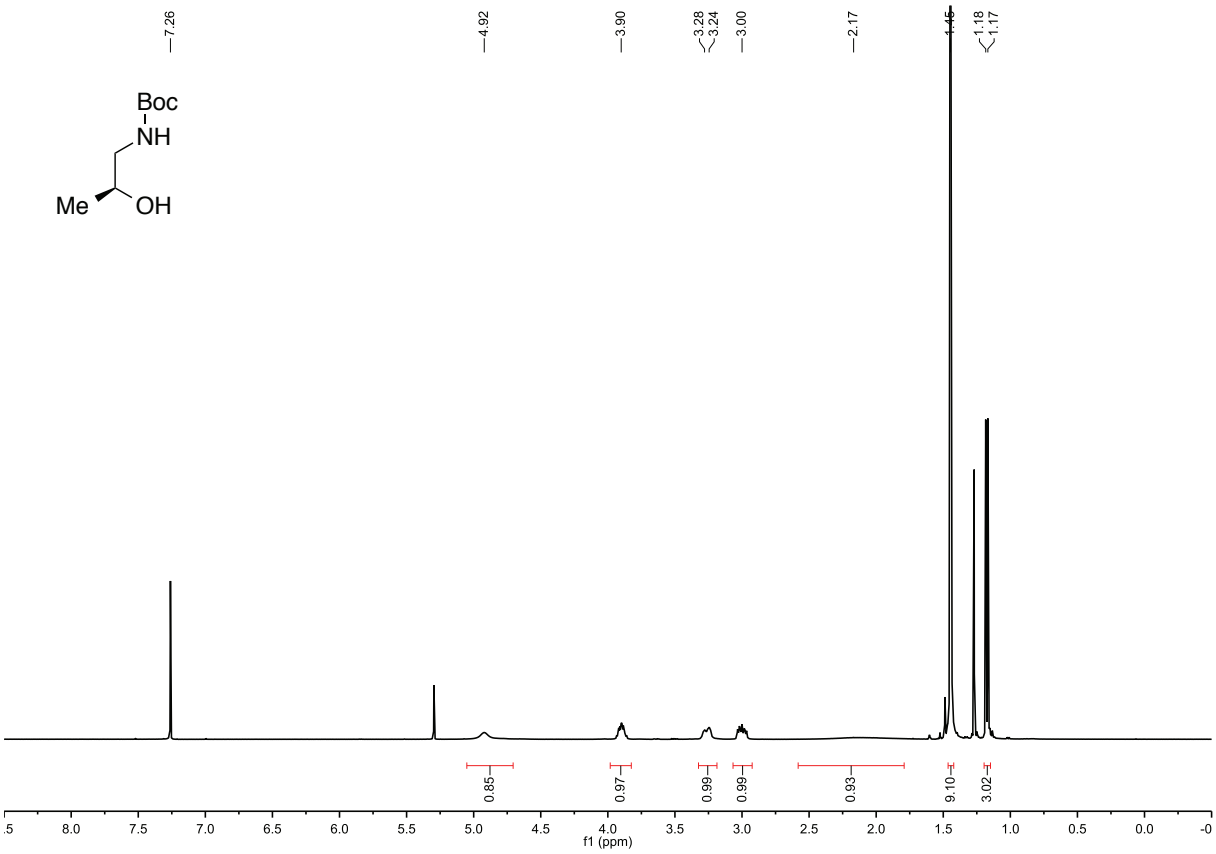
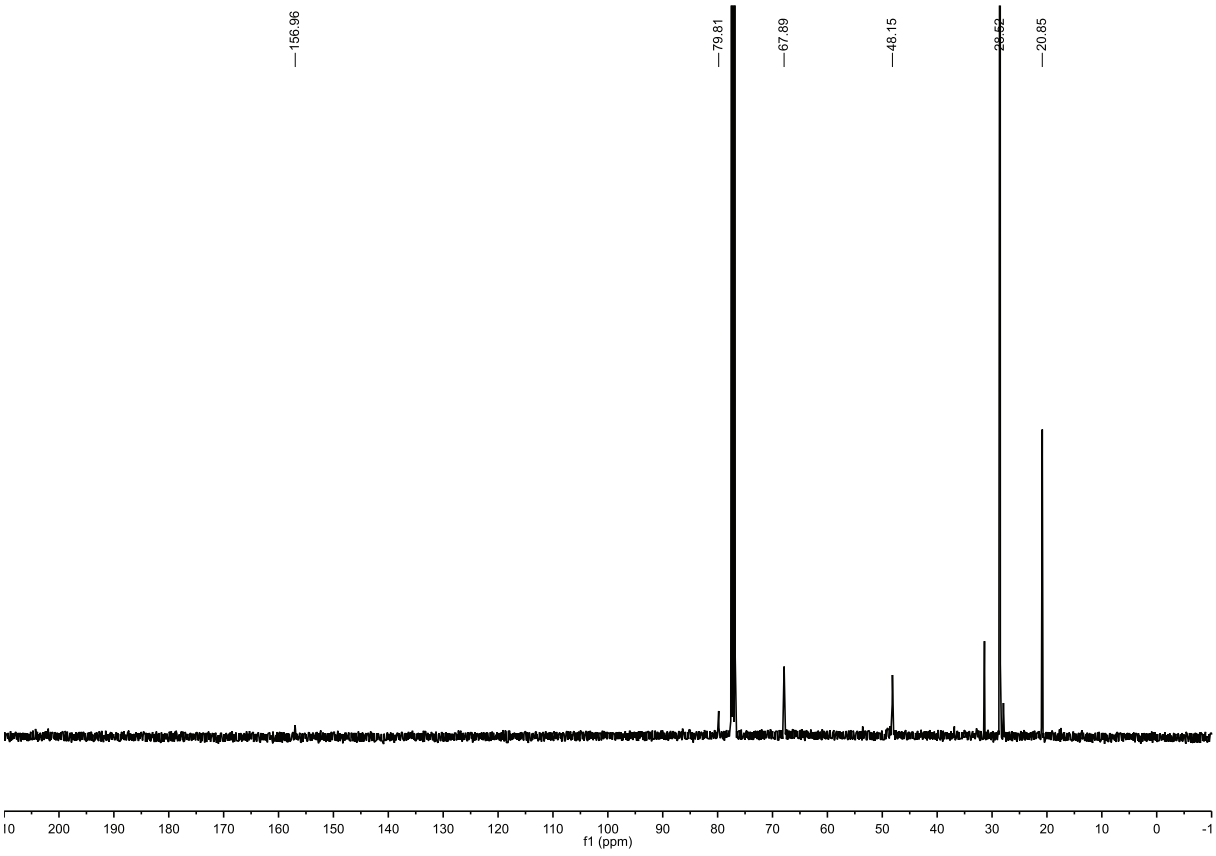
53.85
51.93
29.30
28.58
27.65
26.86
16.18
13.90
11.00
f1 (ppm)


7.26
4.92
3.90
3.28
3.24
3.00
2.17
1.45
1.18
1.17
Boc
NH
Me
OH
0.85
0.97
0.99
0.99
0.93
9.10
3.02
f1 (ppm)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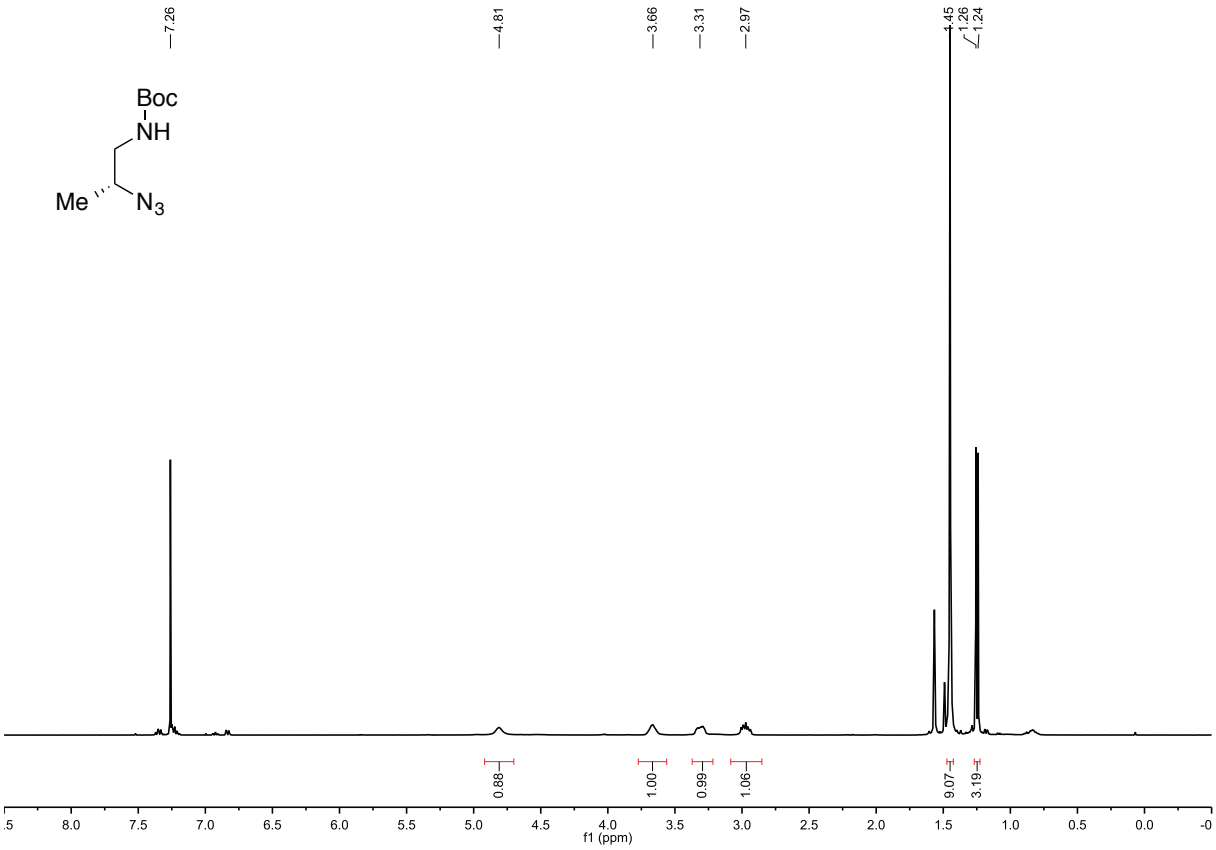
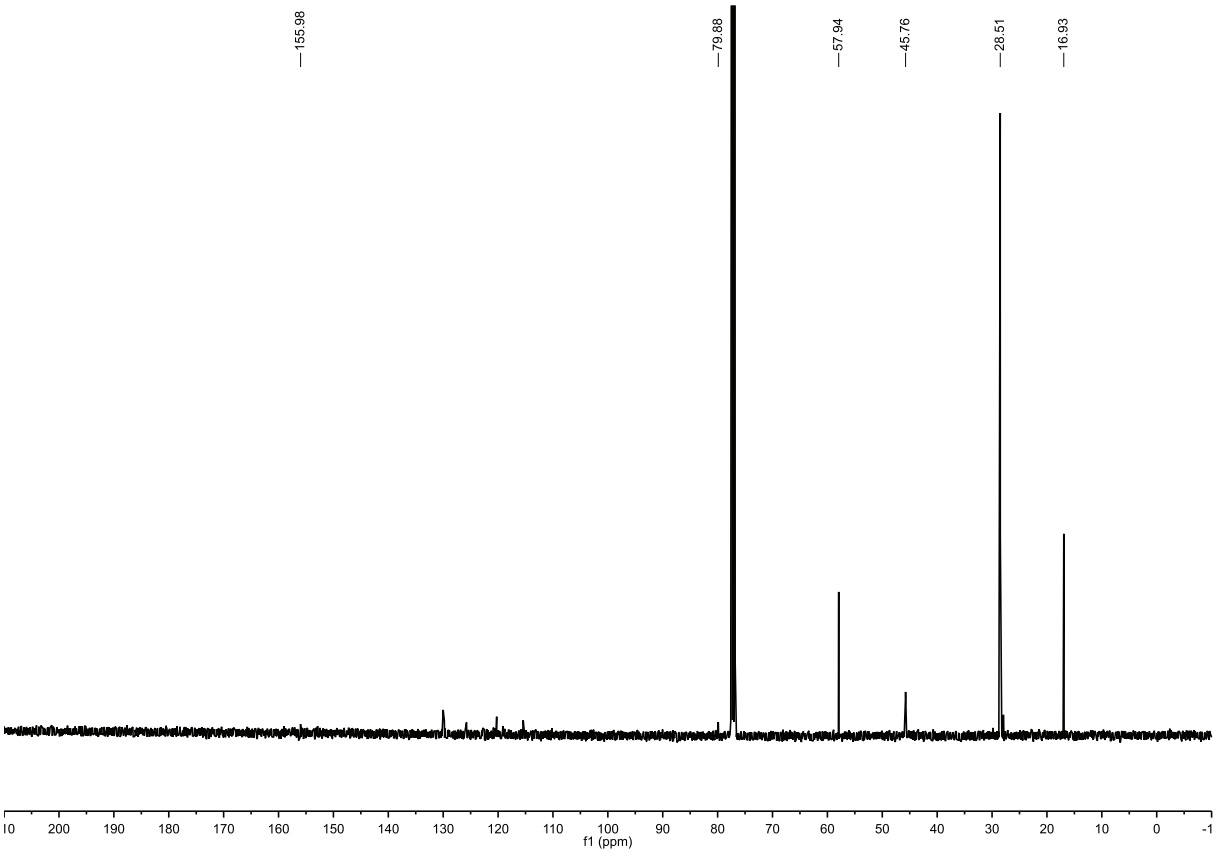
79.81
67.89
48.15
28.52
20.85
f1 (ppm)


7.26
4.81
3.66
3.31
2.97
1.45
1.26
1.24
Boc
NH
Me
N3
0.88
1.00
0.99
1.06
9.07
3.19
f1 (ppm)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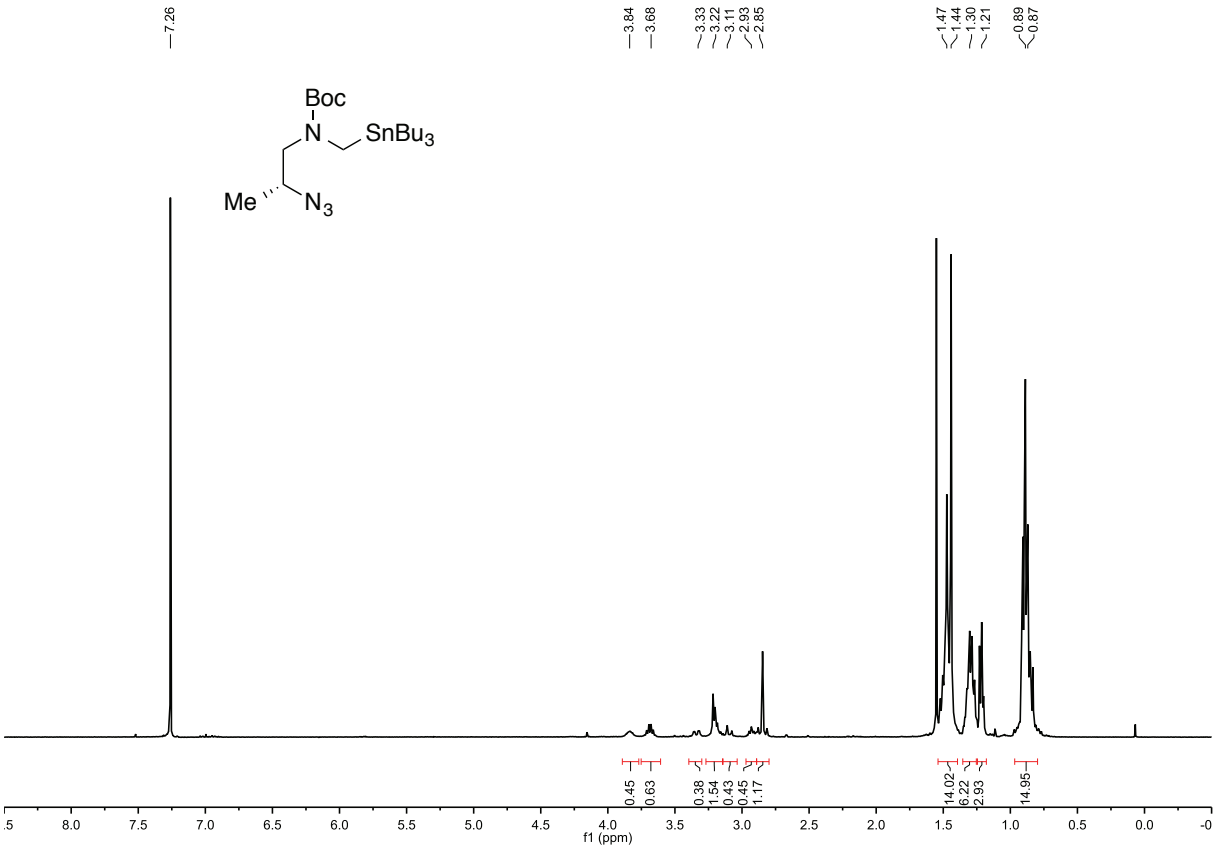
79.88
57.94
45.76
28.51
16.93
f1 (ppm)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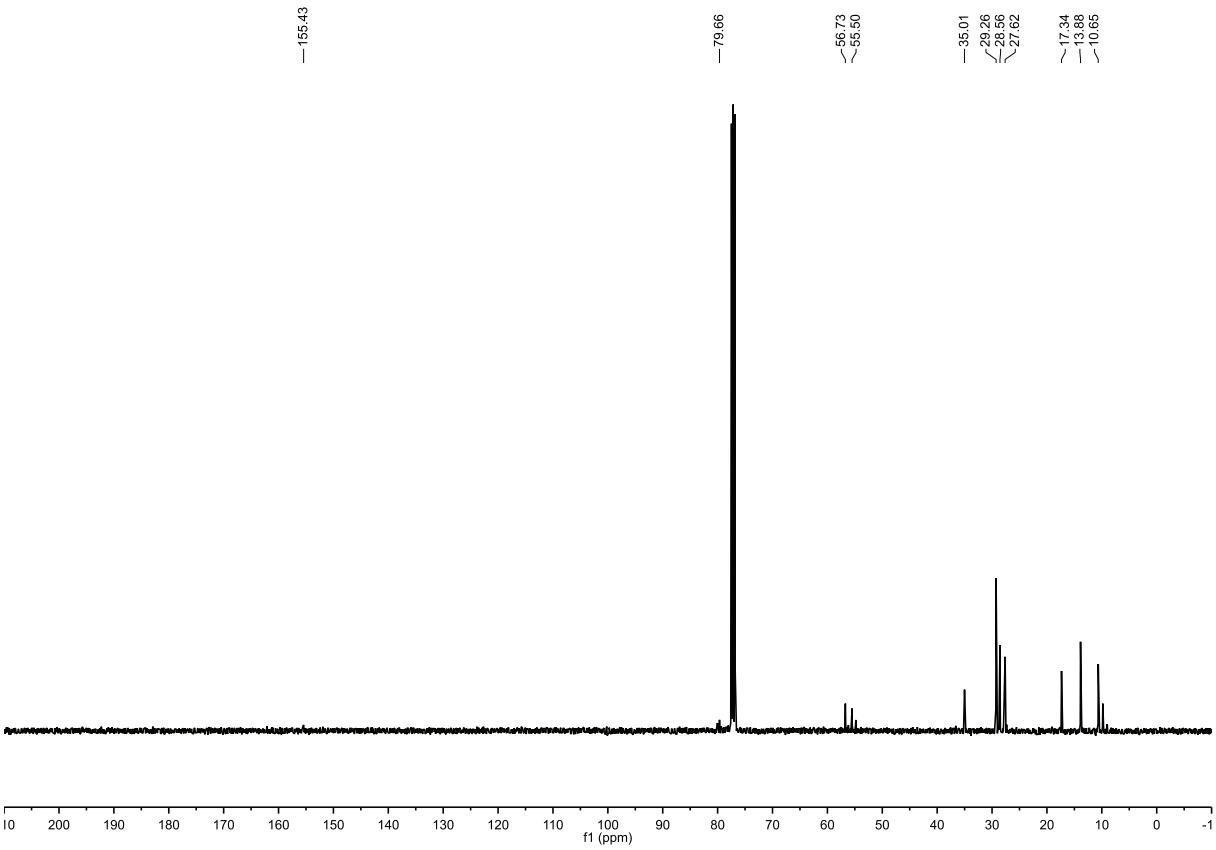
3.84
3.68
3.33
3.22
3.11
2.93
2.85
1.47
1.44
1.30
1.21
0.89
0.87
Boc
N
SnBu3
Me
N3
0.45
0.63
0.38
1.54
0.43
0.45
1.17
14.02
6.22
2.93
14.95
f1 (ppm)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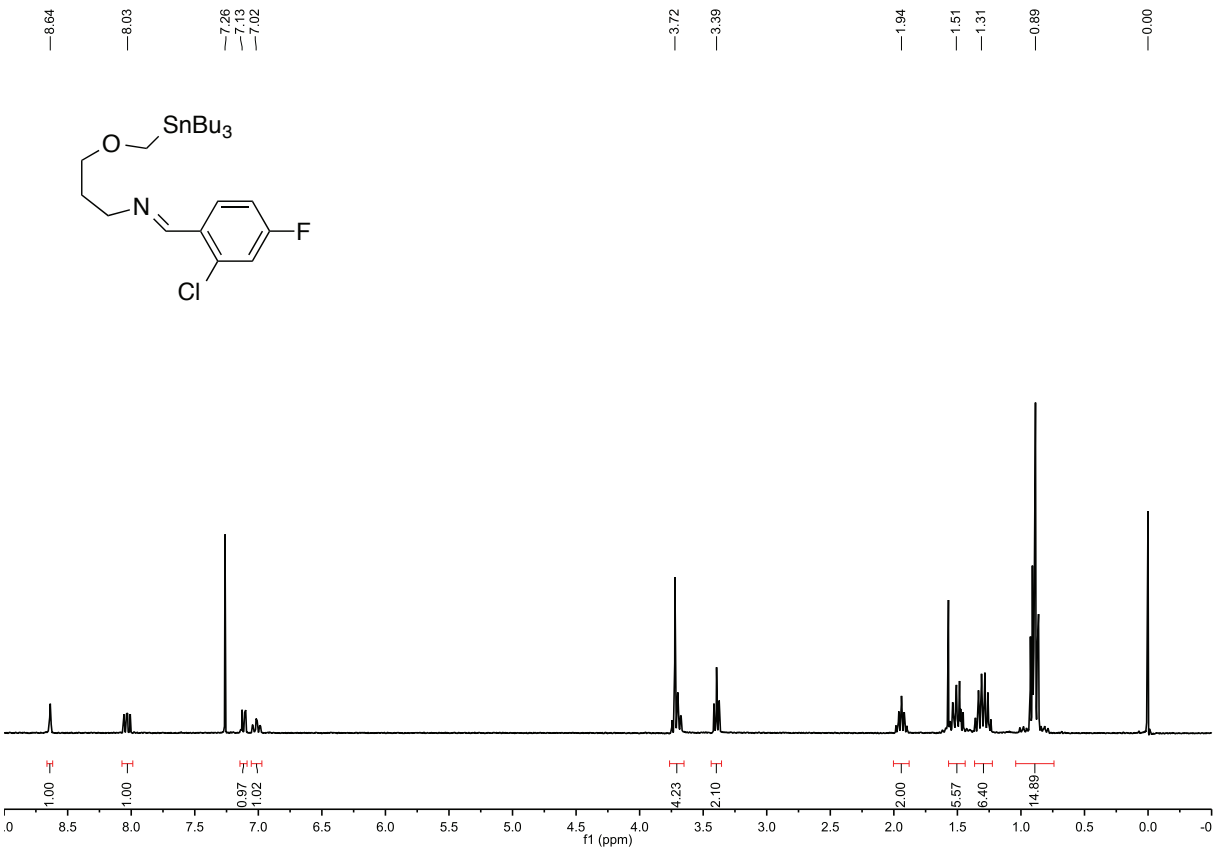
29.26
28.56
27.62
17.34
13.88
10.65
f1 (ppm)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8.03
7.26
7.13
7.02
3.72
3.39
1.94
1.51
1.31
0.89
0.00
SnBu3
O
N
F
Cl
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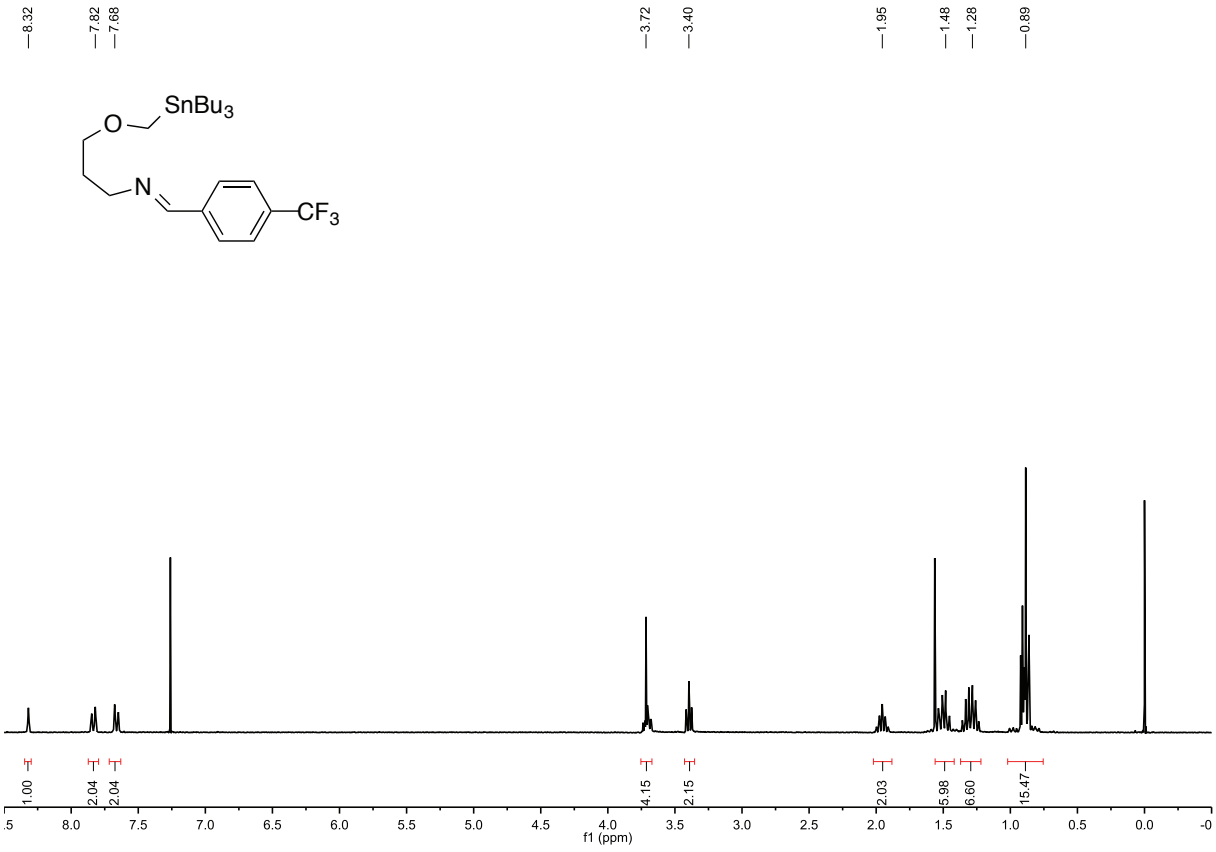
1.00
0.97
1.02
4.23
2.10
2.00
5.57
6.40
14.89
f1 (ppm)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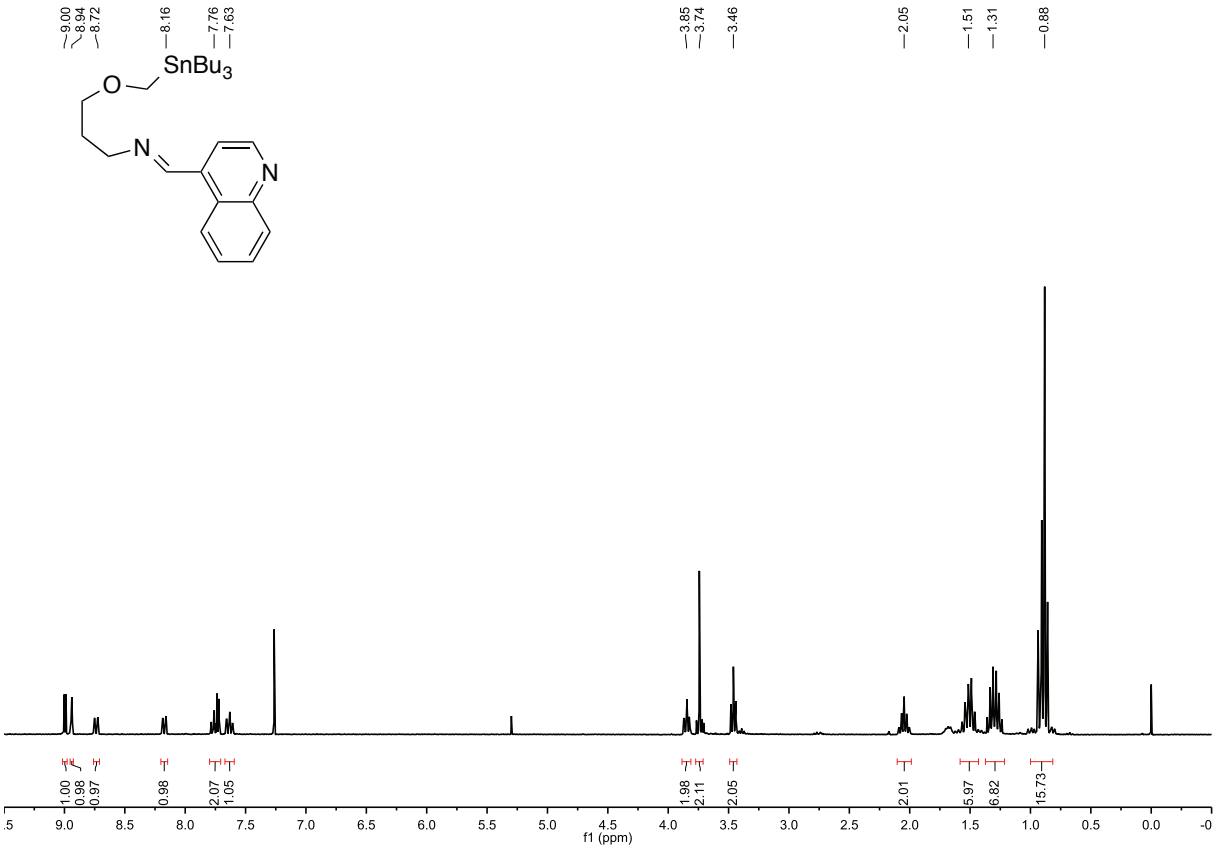
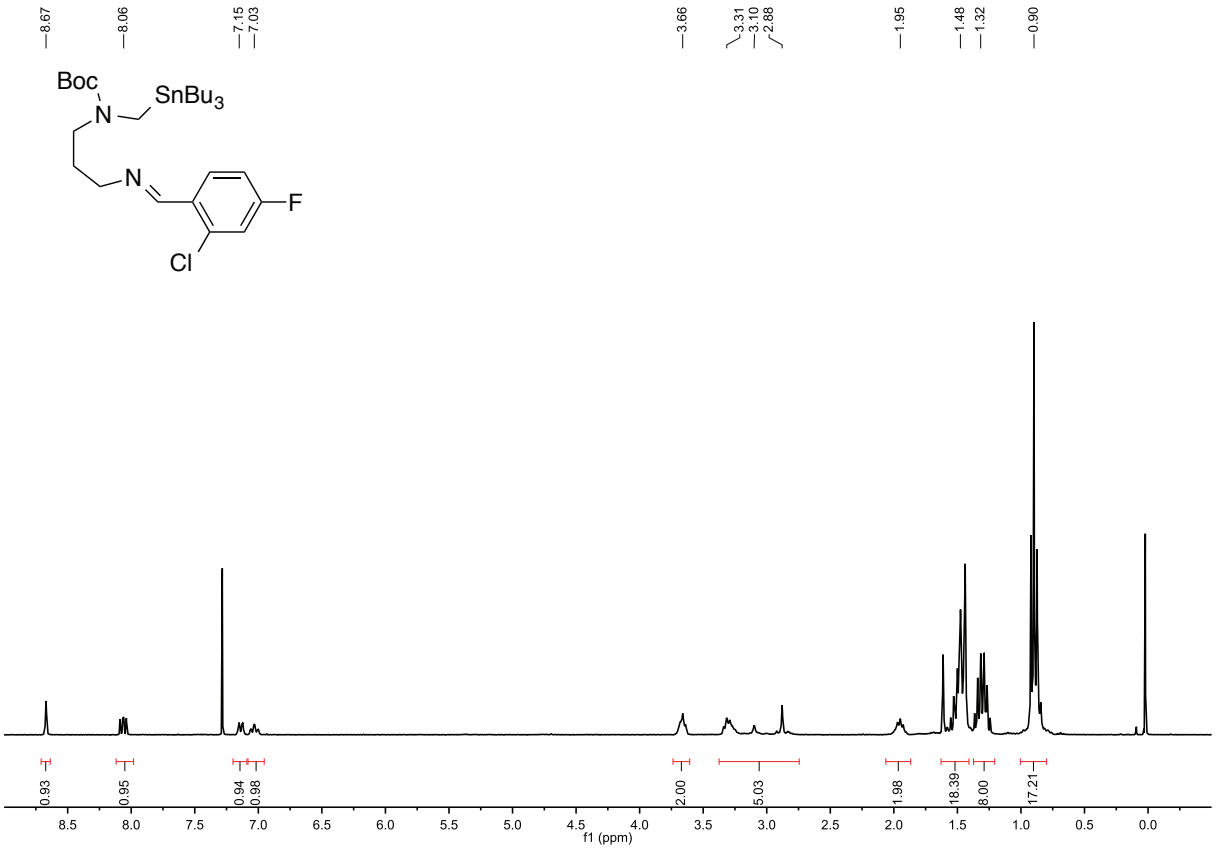
7.82
7.68
3.72
3.40
1.95
1.48
1.28
0.89
SnBu3
O
N
CF3
1.00
2.04
2.04
4.15
2.15
2.03
5.98
6.60
15.47
f1 (ppm)


9.00
8.94
8.72
8.16
7.76
7.63
3.85
3.74
3.46
2.05
1.51
1.31
0.88
SnBu3
O
N
N
1.00
0.98
0.97
0.98
2.07
1.05
1.98
2.11
2.05
2.01
5.97
6.82
15.73
f1 (ppm)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8.06
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3.10
2.88
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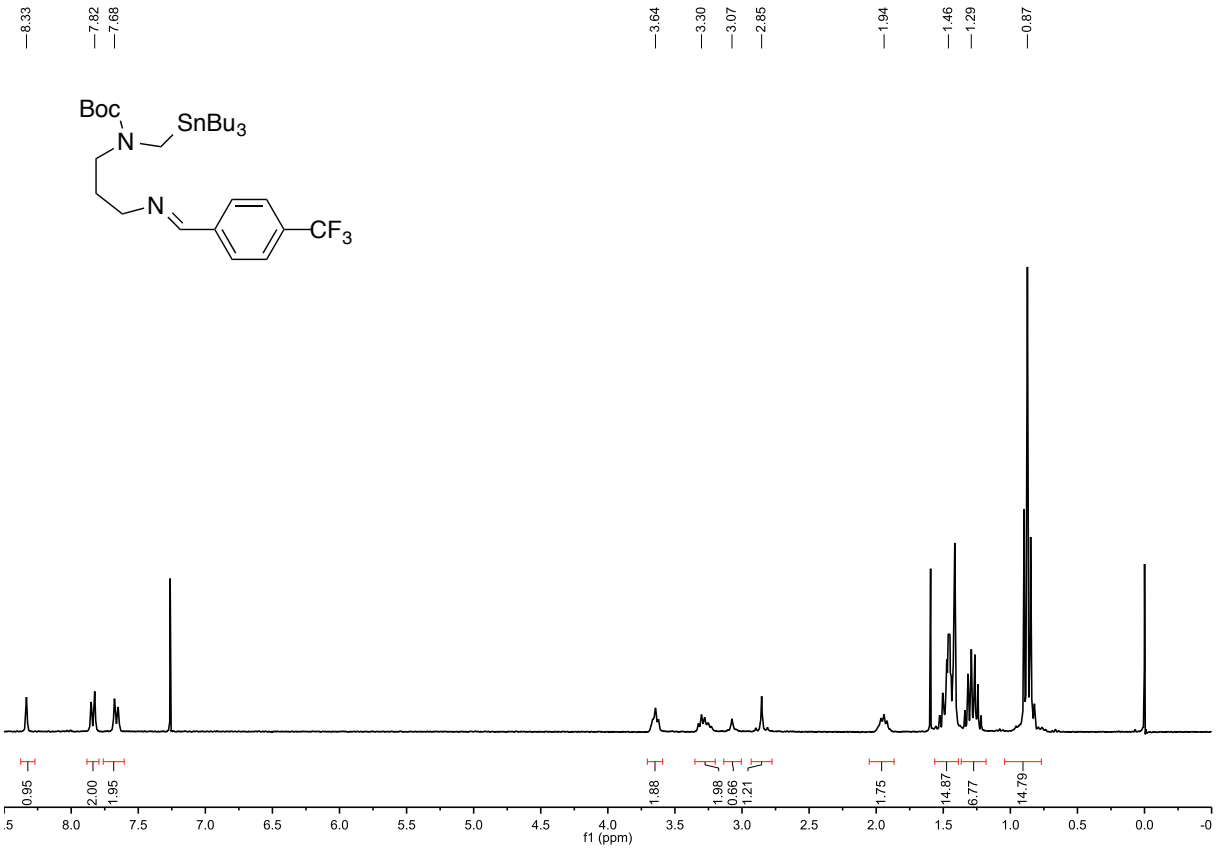
1.48
1.32
0.90
Boc
N
SnBu3
N
F
Cl
0.93
0.95
0.94
0.98
2.00
5.03
1.98
18.39
8.00
17.21
f1 (ppm)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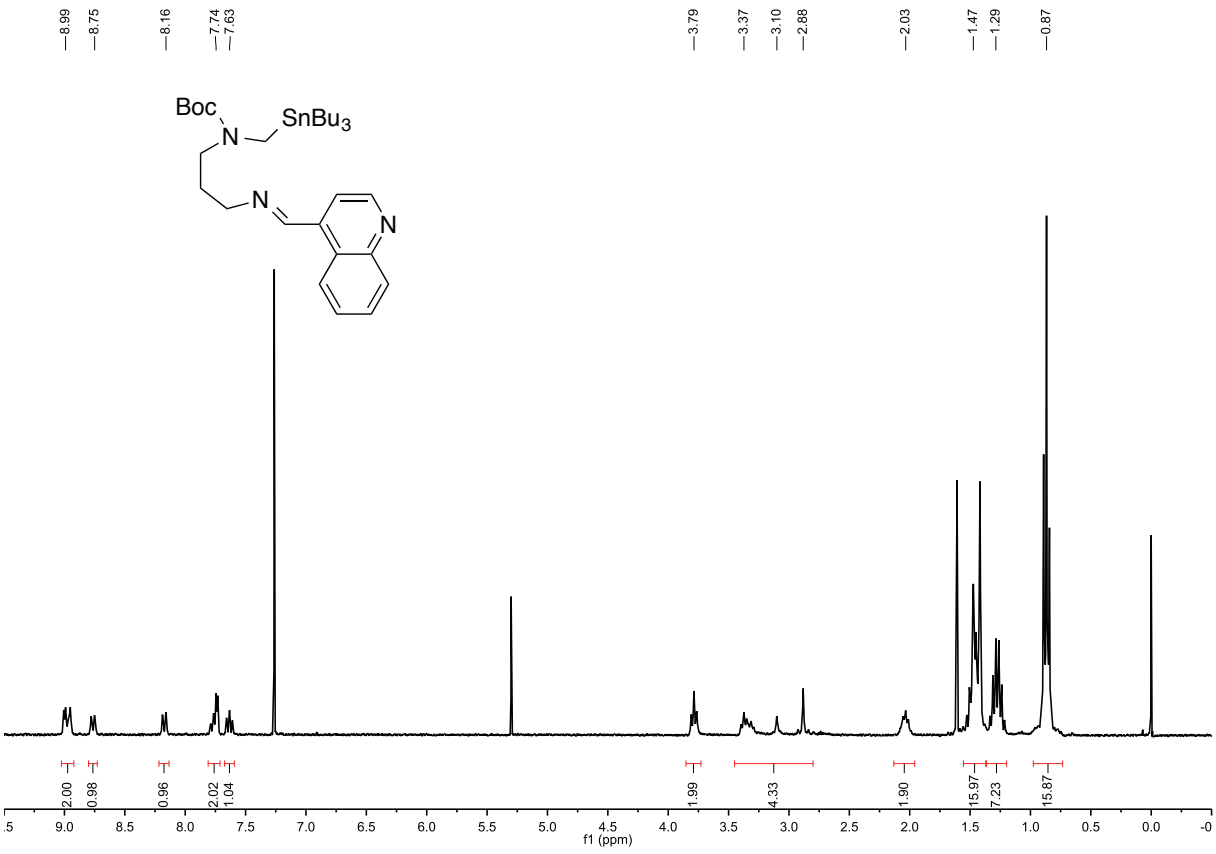
7.82
7.68
3.64
3.30
3.07
2.85
1.94
1.46
1.29
0.87
Boc
N
SnBu3
N
CF3
0.95
2.00
1.95
1.88
1.98
0.66
1.21
1.75
14.87
6.77
14.79
f1 (ppm)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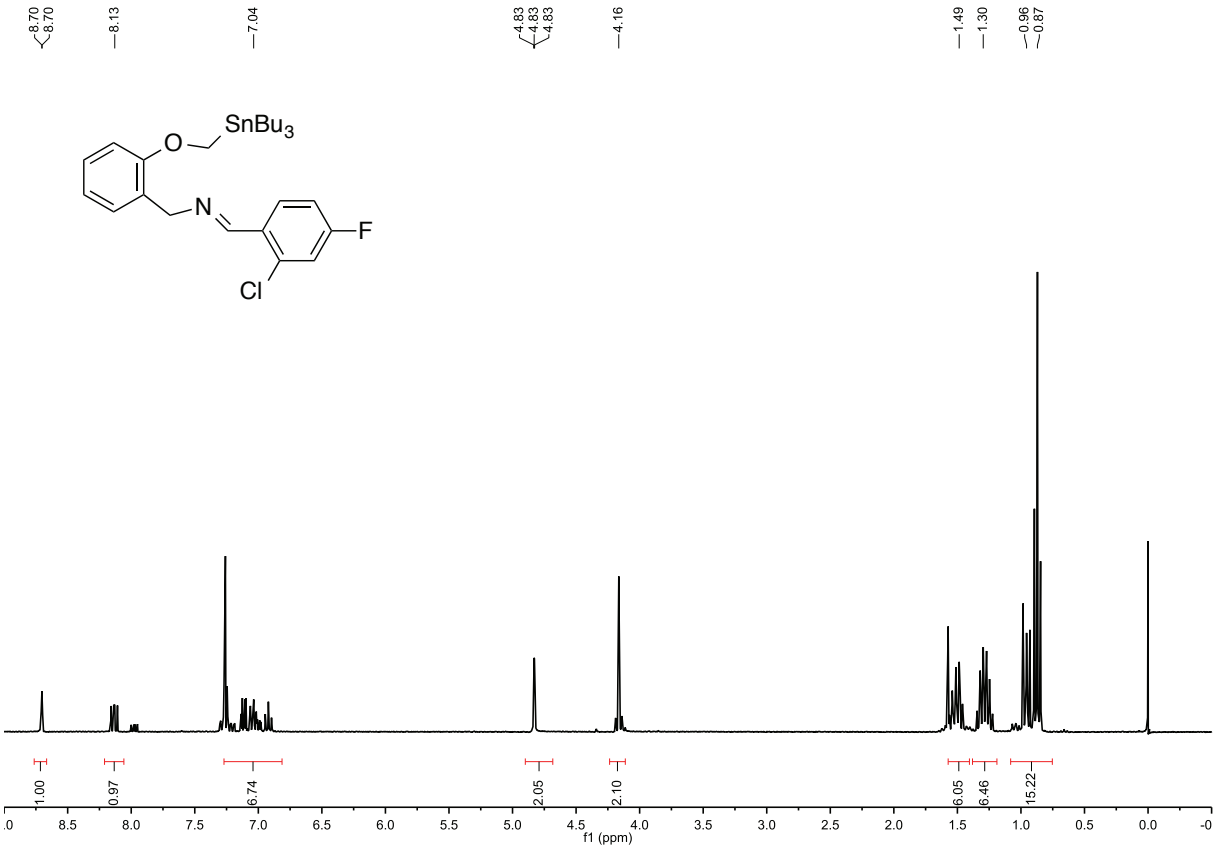
8.75
8.16
7.74
7.63
3.79
3.37
3.10
2.88
2.03
1.47
1.29
0.87
Boc
N
SnBu3
N
N
2.00
0.98
0.96
2.02
1.04
1.99
4.33
1.90
15.97
7.23
15.87
f1 (ppm)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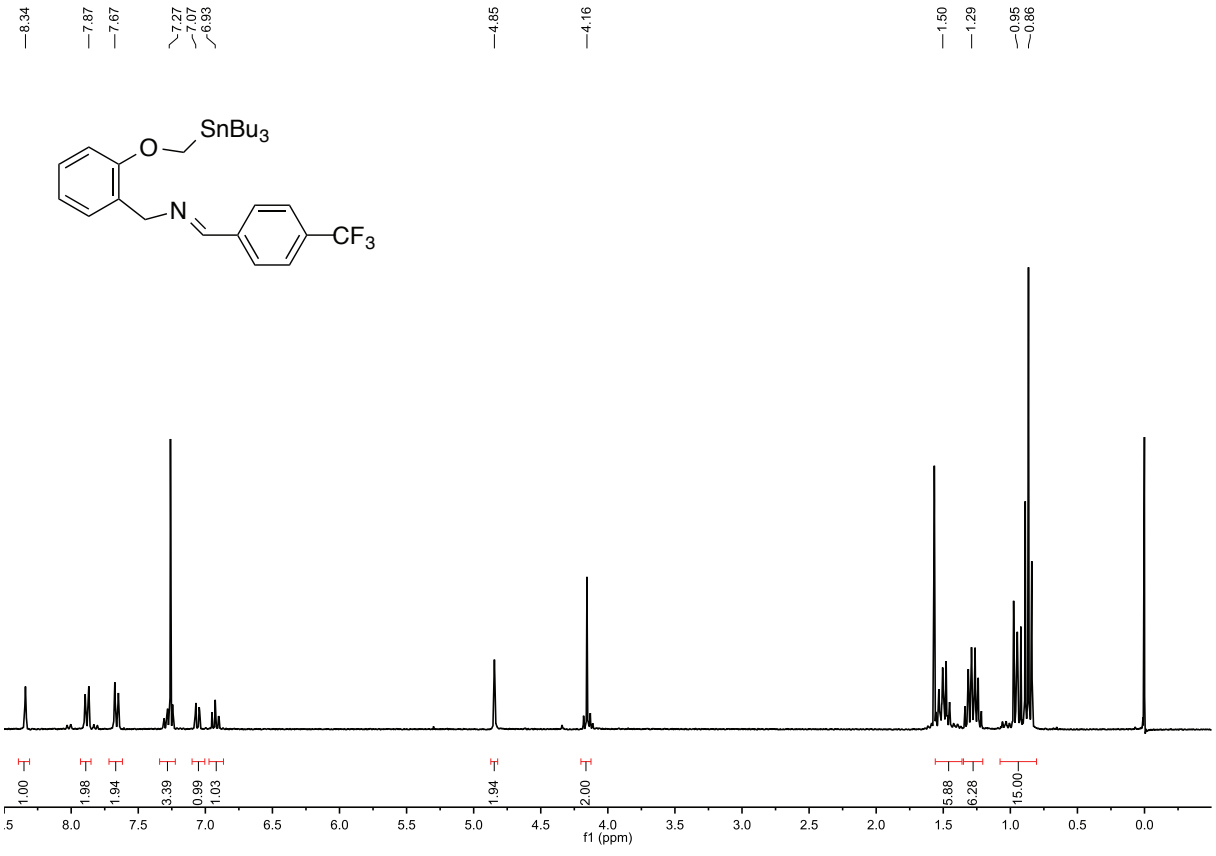
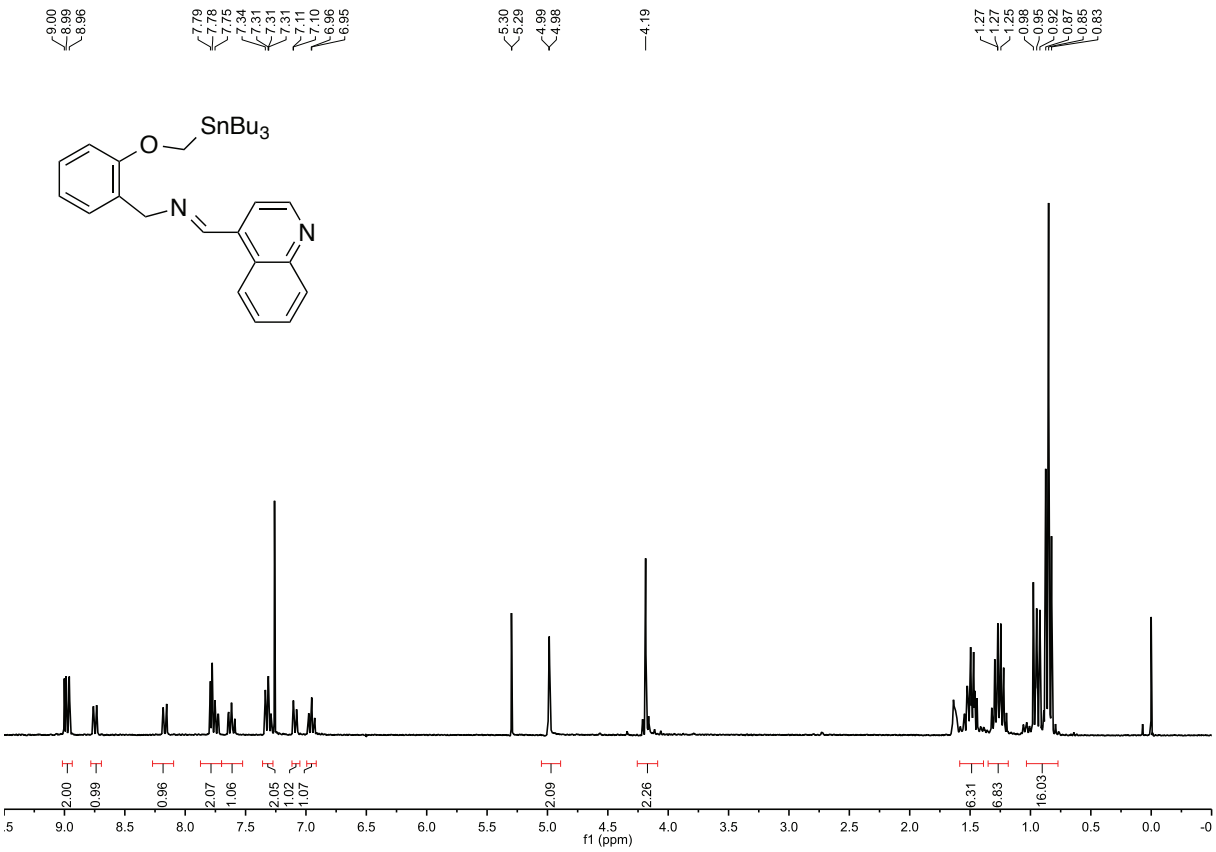
8.70
8.13
7.04
4.83
4.83
4.83
4.16
1.49
1.30
0.96
0.87
SnBu3
O
N
F
Cl
1.00
0.97
6.74
2.05
2.10
6.05
6.46
15.22
f1 (ppm)


8.34
7.87
7.67
7.27
7.07
6.93
4.85
4.16
1.50
1.29
0.95
0.86
SnBu3
O
N
CF3
1.00
1.98
1.94
3.39
0.99
1.03
1.94
2.00
5.88
6.28
15.00
f1 (ppm)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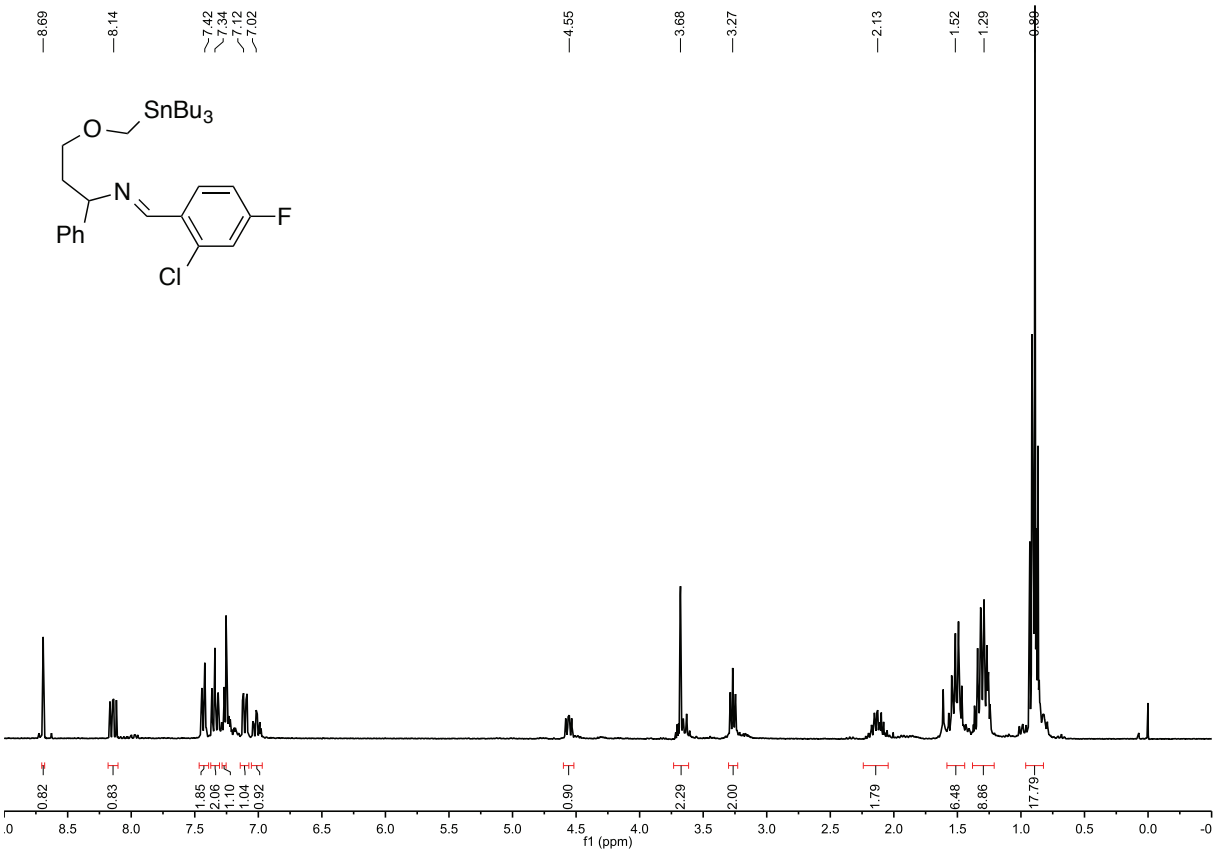
8.99
8.96
7.79
7.78
7.75
7.34
7.31
7.31
7.31
7.11
7.10
6.96
6.95
5.30
5.29
4.99
4.98
4.19
1.27
1.27
1.25
0.98
0.95
0.92
0.87
0.85
0.83
SnBu3
O
N
N
2.00
0.99
0.96
2.07
1.06
2.05
1.02
1.07
2.09
2.26
6.31
6.83
16.03
f1 (ppm)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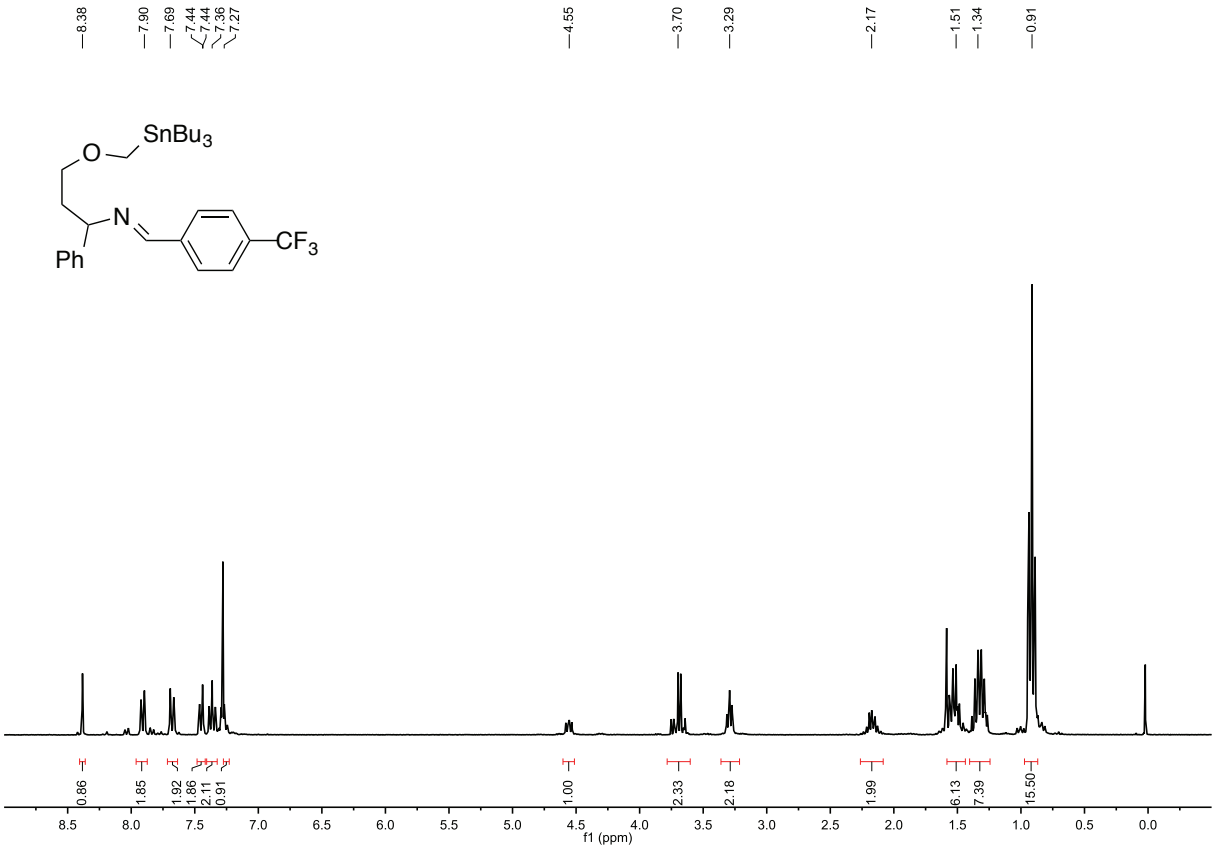
8.14
7.42
7.34
7.12
7.02
4.55
3.68
3.27
2.13
1.52
1.29
0.89
SnBu3
O
N
Ph
F
Cl
0.82
0.83
1.85
2.06
1.10
1.04
0.92
0.90
2.29
2.00
1.79
6.48
8.86
17.79
f1 (ppm)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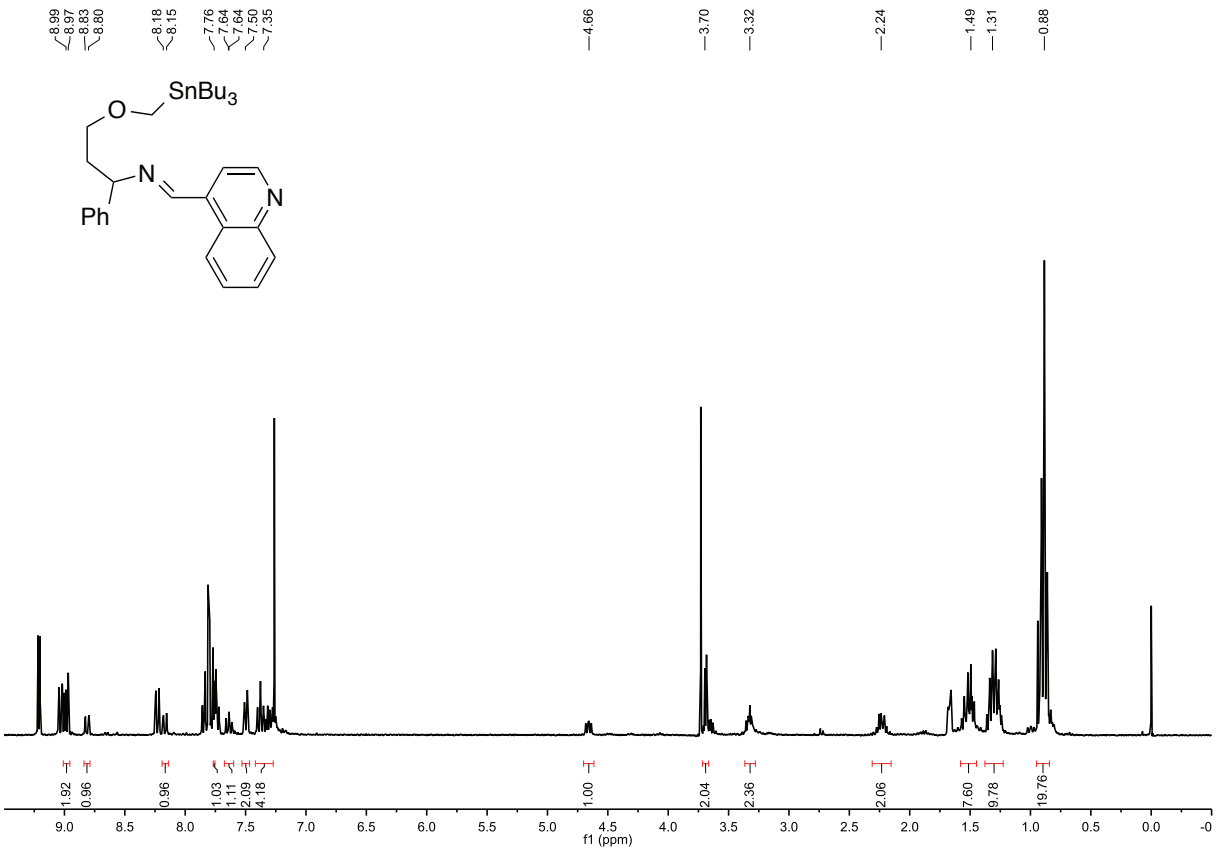
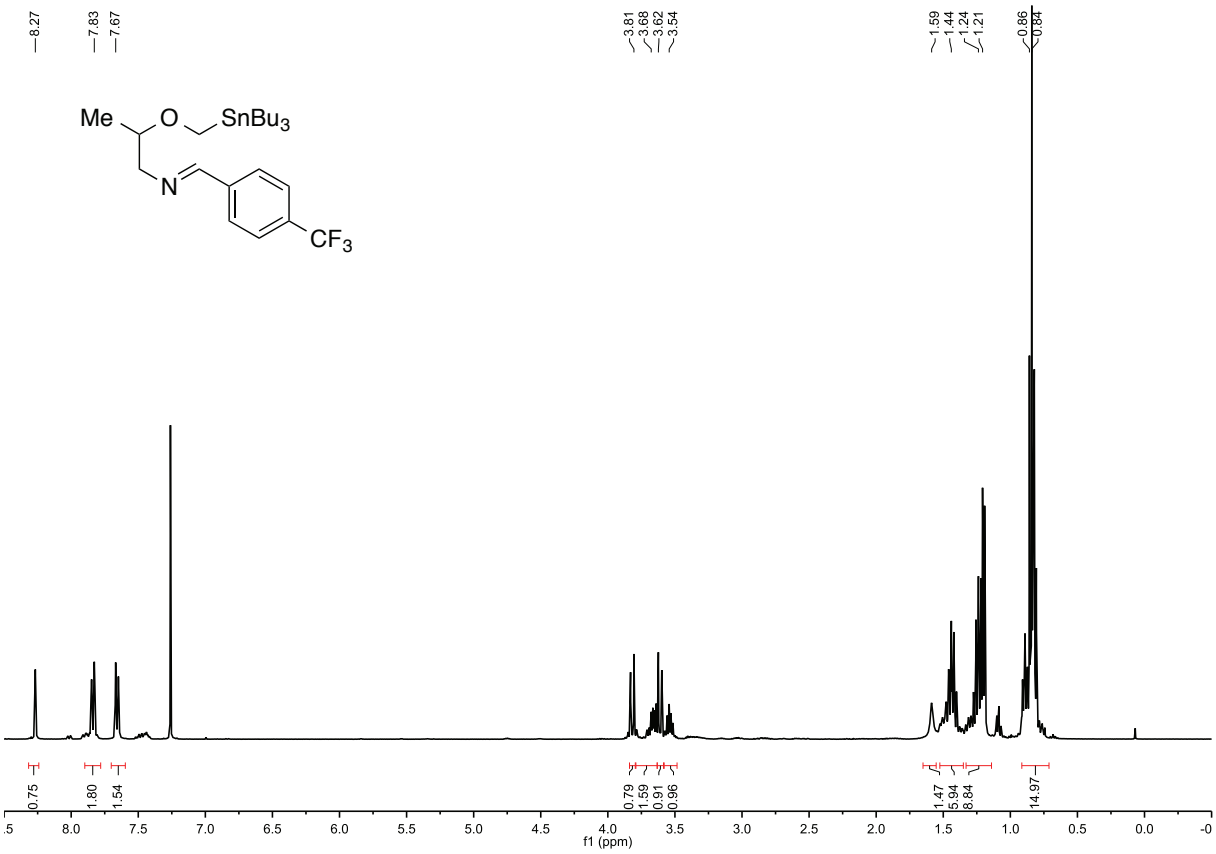
7.90
7.69
7.44
7.44
7.36
7.27
4.55
3.70
3.29
2.17
1.51
1.34
0.91
SnBu3
O
N
Ph
CF3
0.86
1.85
1.92
1.86
2.11
0.91
1.00
2.33
2.18
1.99
6.13
7.39
15.50
f1 (ppm)


8.99
8.97
8.83
8.80
8.18
8.15
7.76
7.64
7.64
7.50
7.35
4.66
3.70
3.32
2.24
1.49
1.31
0.88
SnBu3
O
N
Ph
N
1.92
0.96
0.96
1.03
1.11
2.09
4.18
1.00
2.04
2.36
2.06
7.60
9.78
19.76
f1 (ppm)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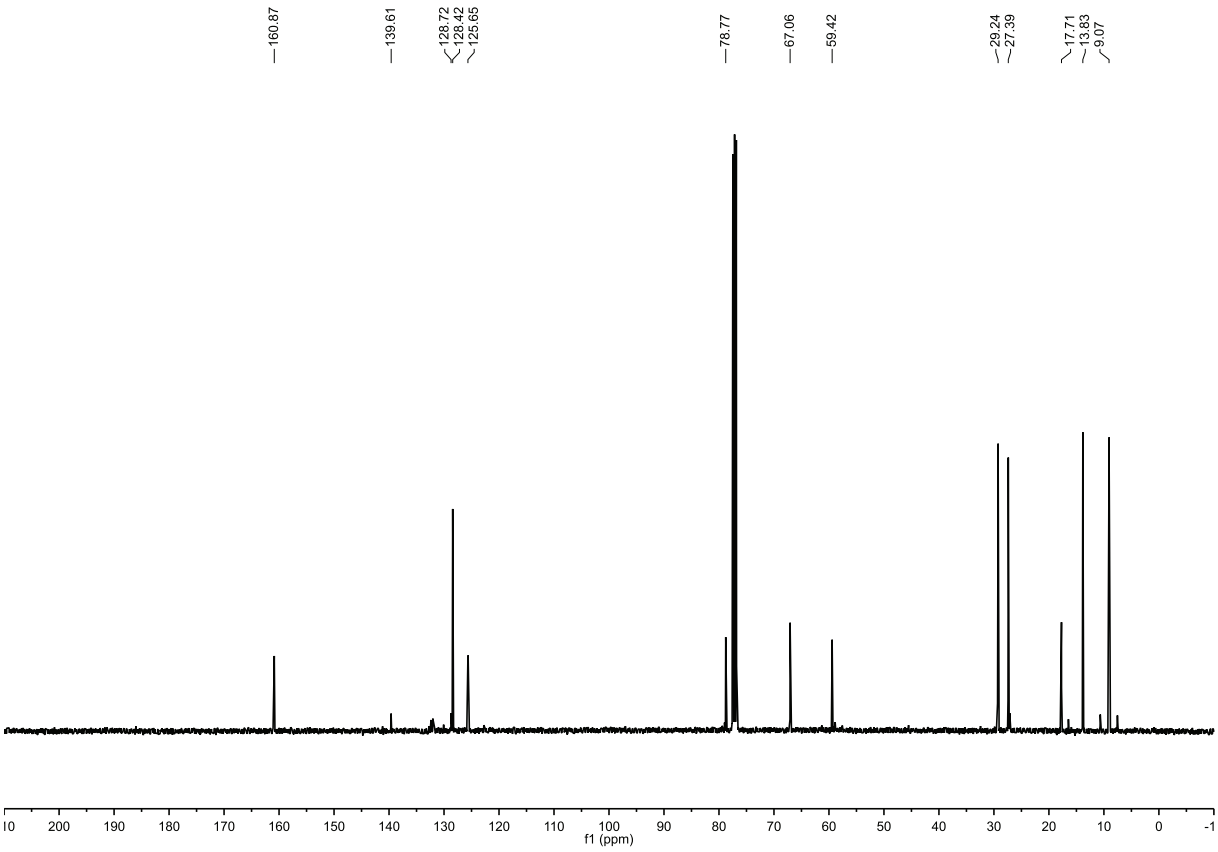
7.83
7.67
3.81
3.68
3.62
3.54
1.59
1.44
1.24
1.21
0.86
0.84
Me
O
SnBu3
N
CF3
0.75
1.80
1.54
0.79
1.59
0.91
0.96
1.47
5.94
8.84
14.97
f1 (ppm)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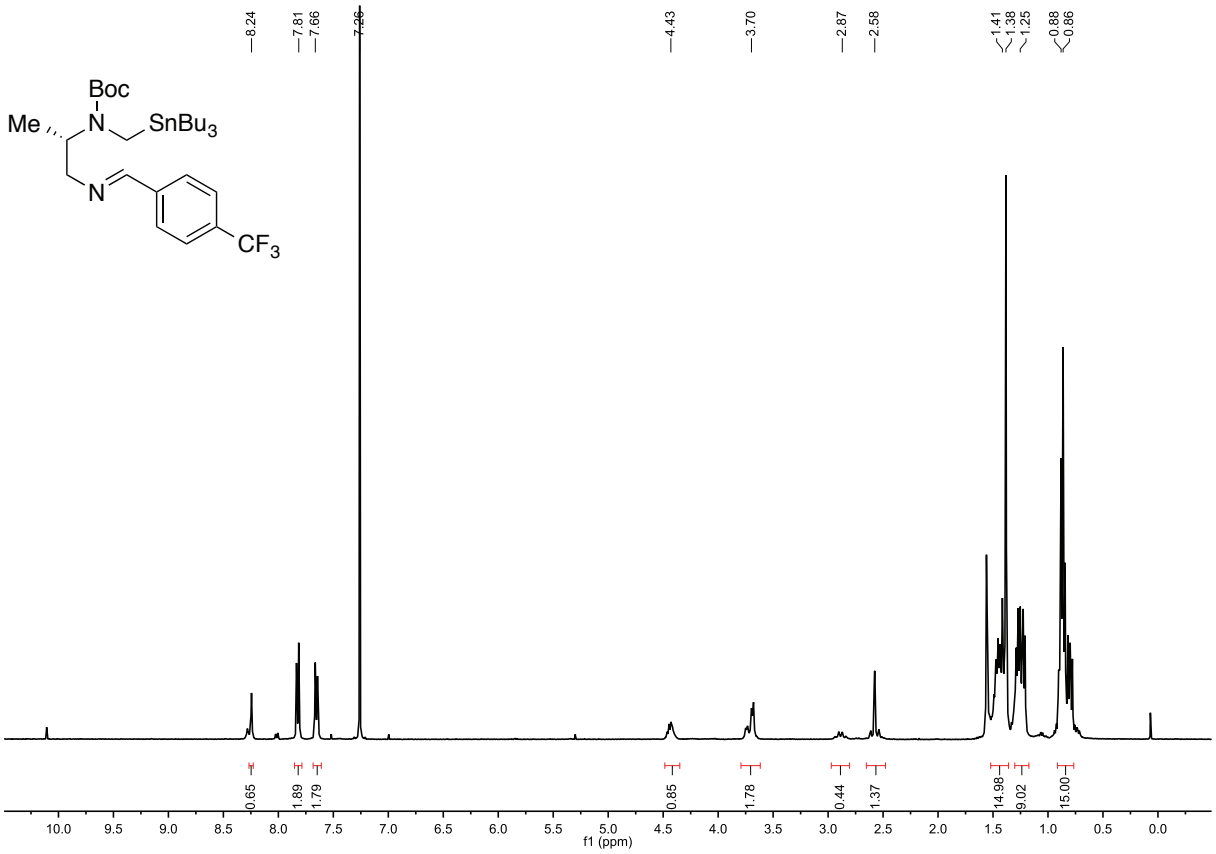
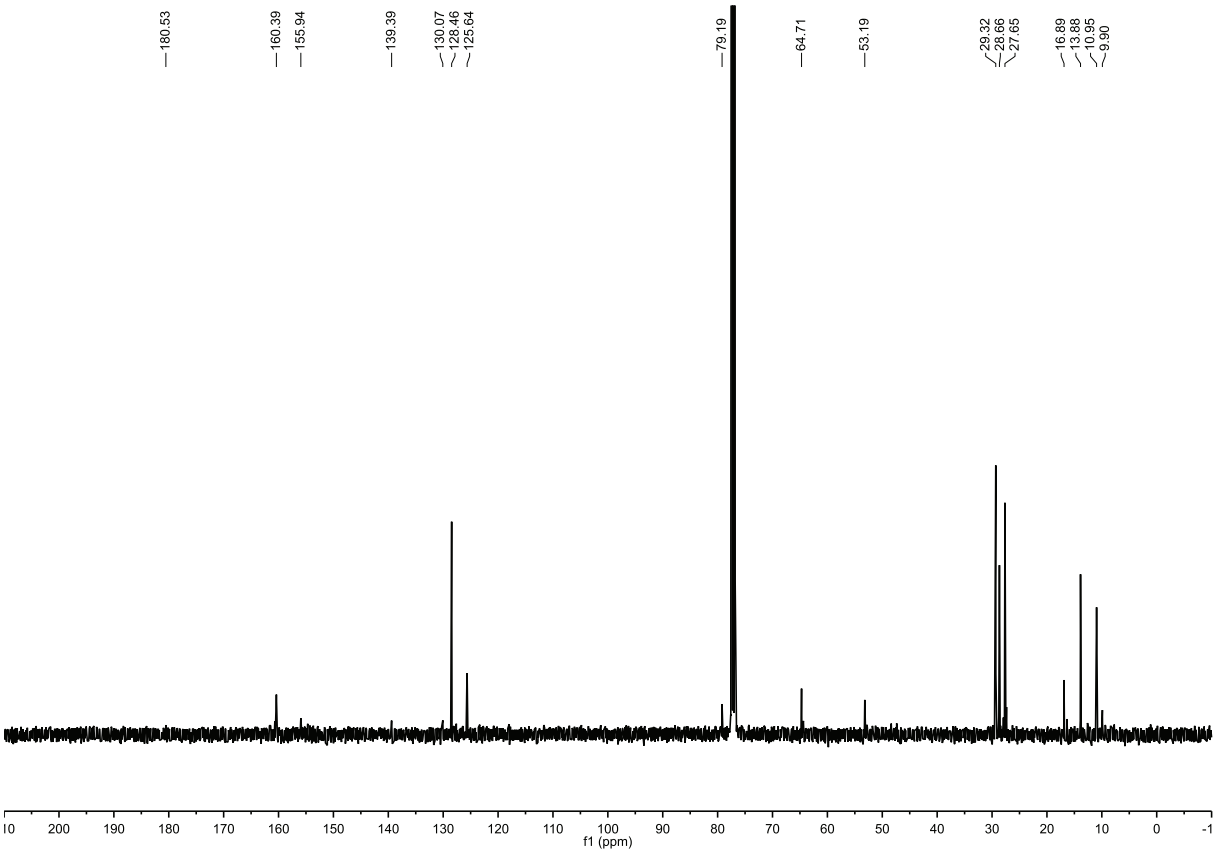
139.61
128.72
128.42
125.65
78.77
67.06
59.42
29.24
27.39
17.71
13.83
9.07
f1 (ppm)


Boc
N
Me
SnBu3
N
CF3
8.24
7.81
7.66
7.26
4.43
3.70
2.87
2.58
1.41
1.38
1.25
0.88
0.86
0.65
1.89
1.79
0.85
1.78
0.44
1.37
14.98
9.02
15.00
f1 (ppm)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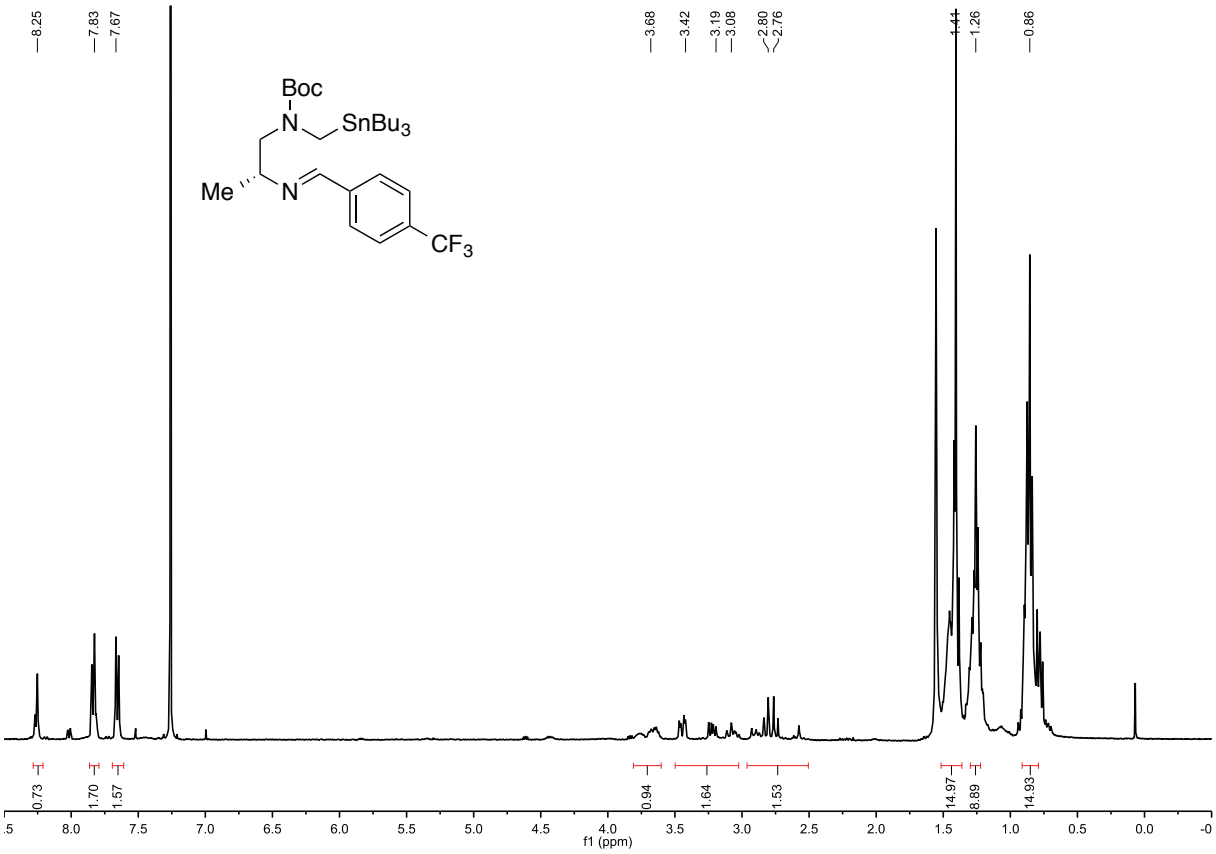
160.39
155.94
139.39
130.07
128.46
125.64
79.19
64.71
53.19
29.32
28.66
27.65
16.89
13.88
10.95
9.90
f1 (ppm)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7.83
7.67
3.68
3.42
3.19
3.08
2.80
2.76
1.44
1.26
0.86
Boc
N
SnBu3
Me
N
CF3
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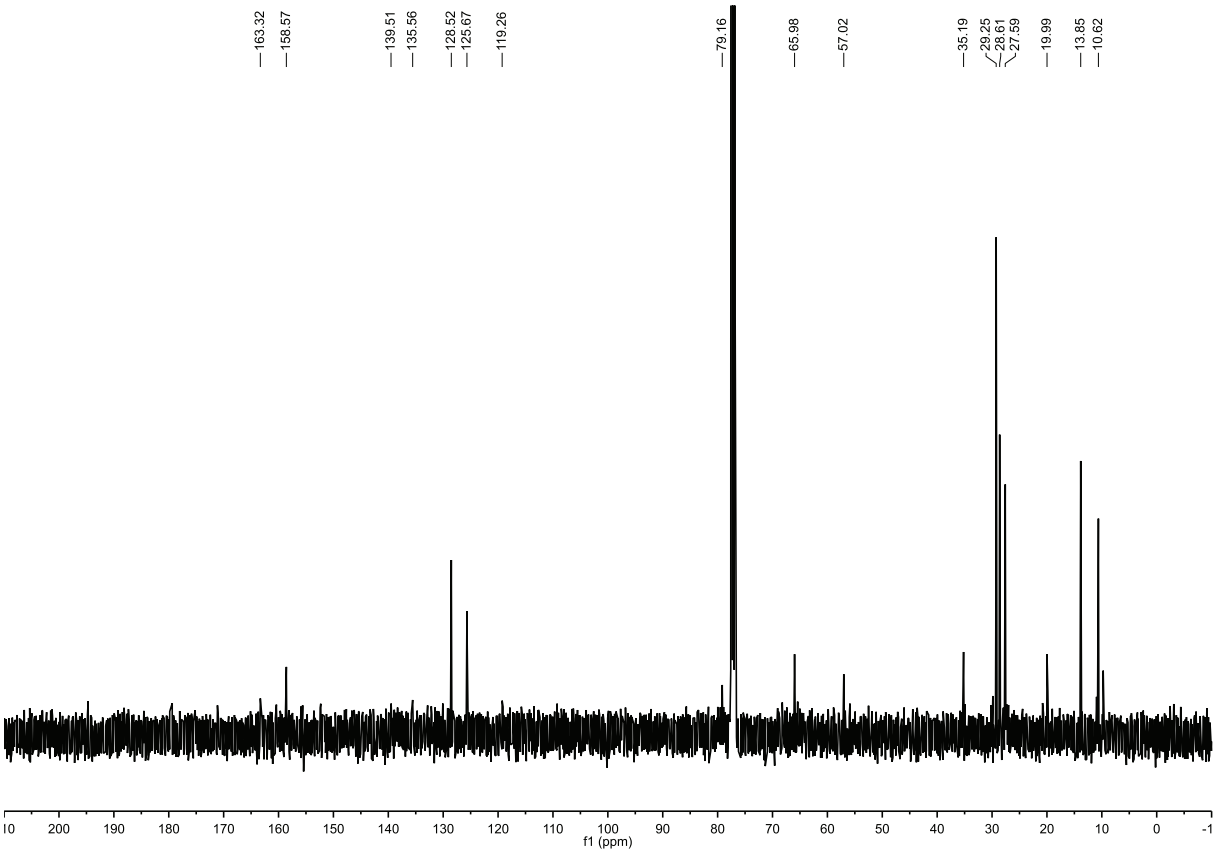
1.70
1.57
0.94
1.64
1.53
14.97
8.89
14.93
f1 (ppm)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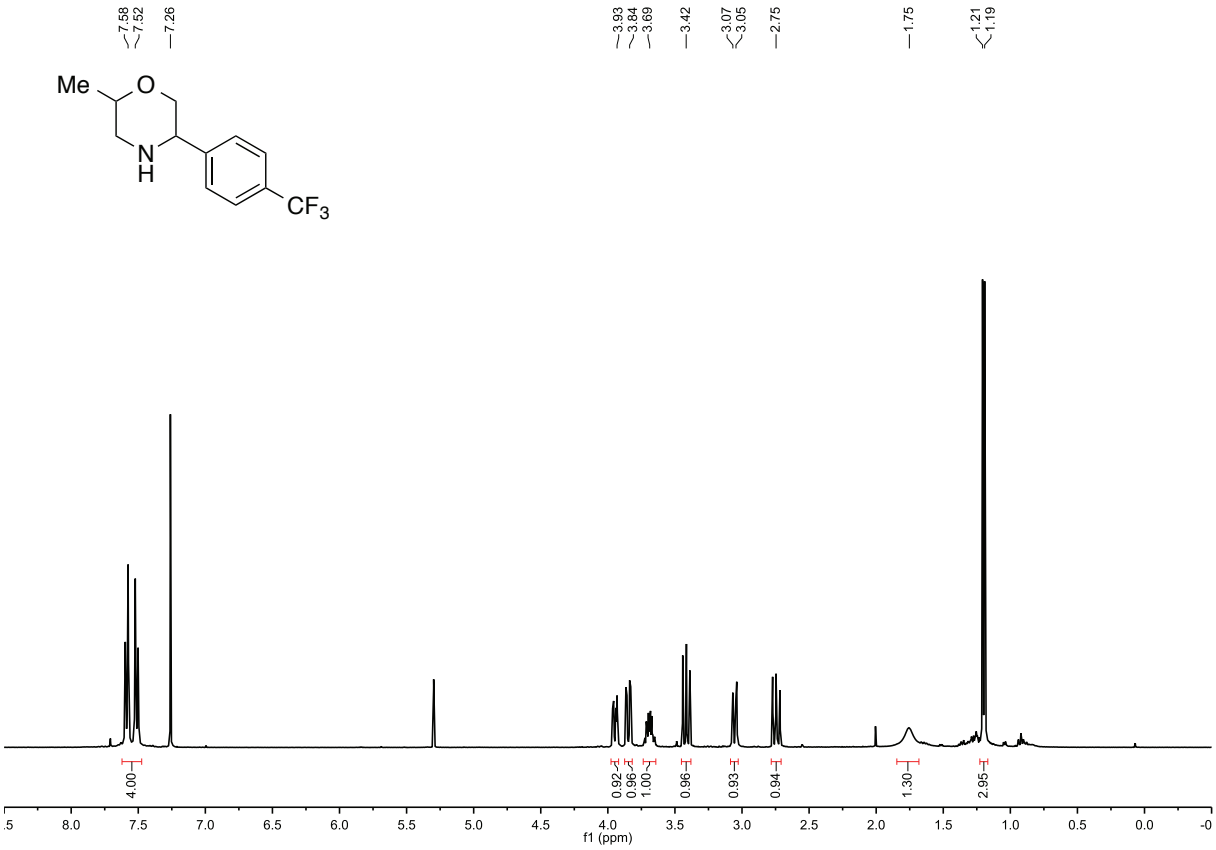
139.51
135.56
128.52
125.67
119.26
79.16
65.98
57.02
35.19
29.25
28.61
27.59
19.99
13.85
10.62
f1 (ppm)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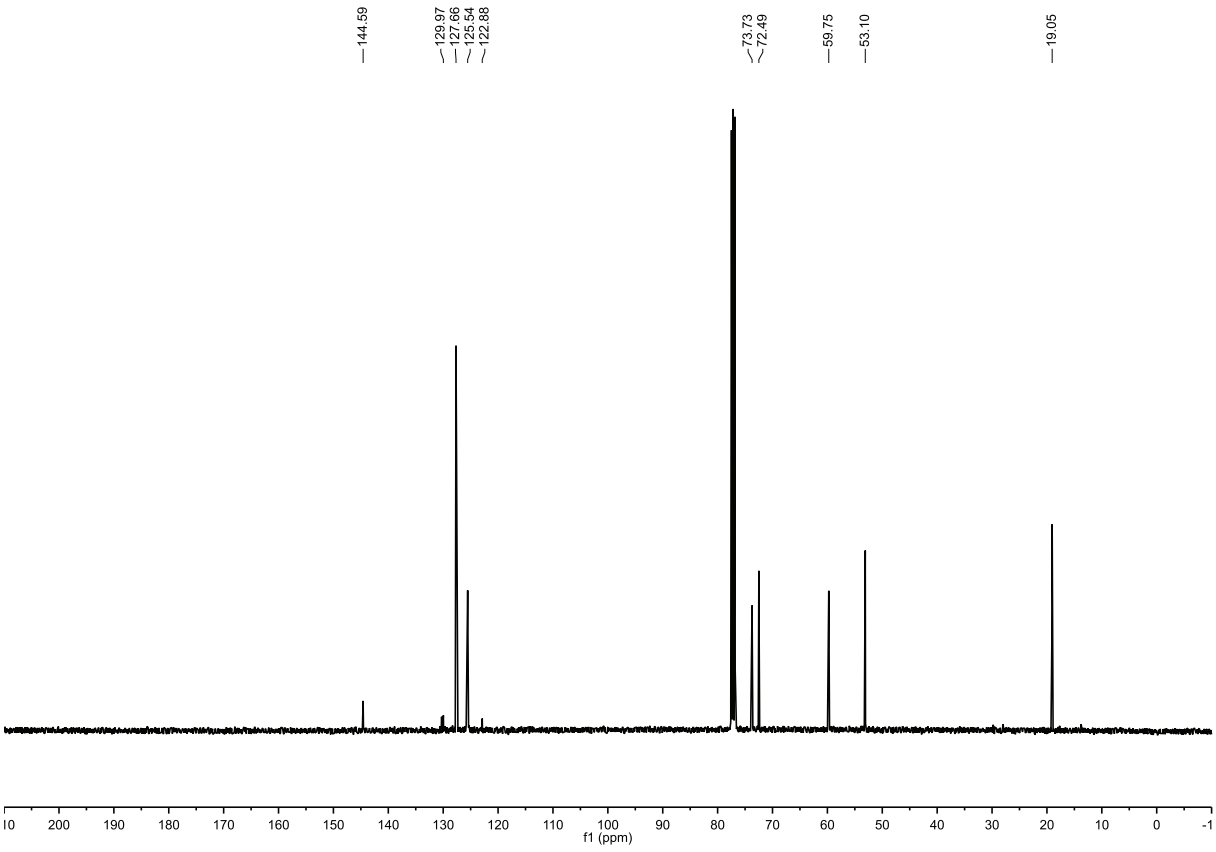
7.26
3.93
3.84
3.69
3.42
3.07
3.05
2.75
1.75
1.21
1.19
Me
O
N
H
CF3
4.00
0.92
0.96
1.00
0.96
0.93
0.94
1.30
2.95
f1 (ppm)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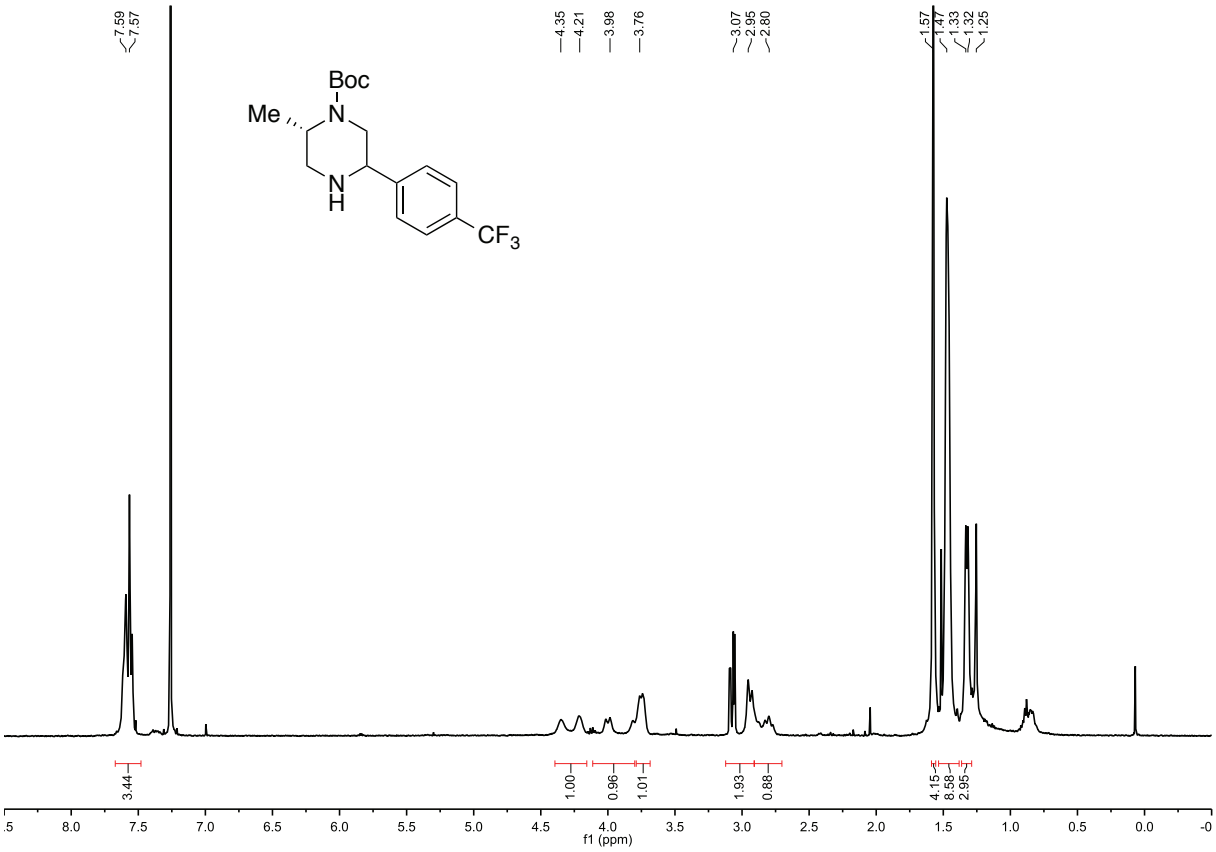
122.88
73.73
72.49
59.75
53.10
19.05
f1 (ppm)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7.57
4.35
4.21
3.98
3.76
3.07
2.95
2.80
1.57
1.47
1.33
1.32
1.25
Boc
Me
N
N
H
CF3
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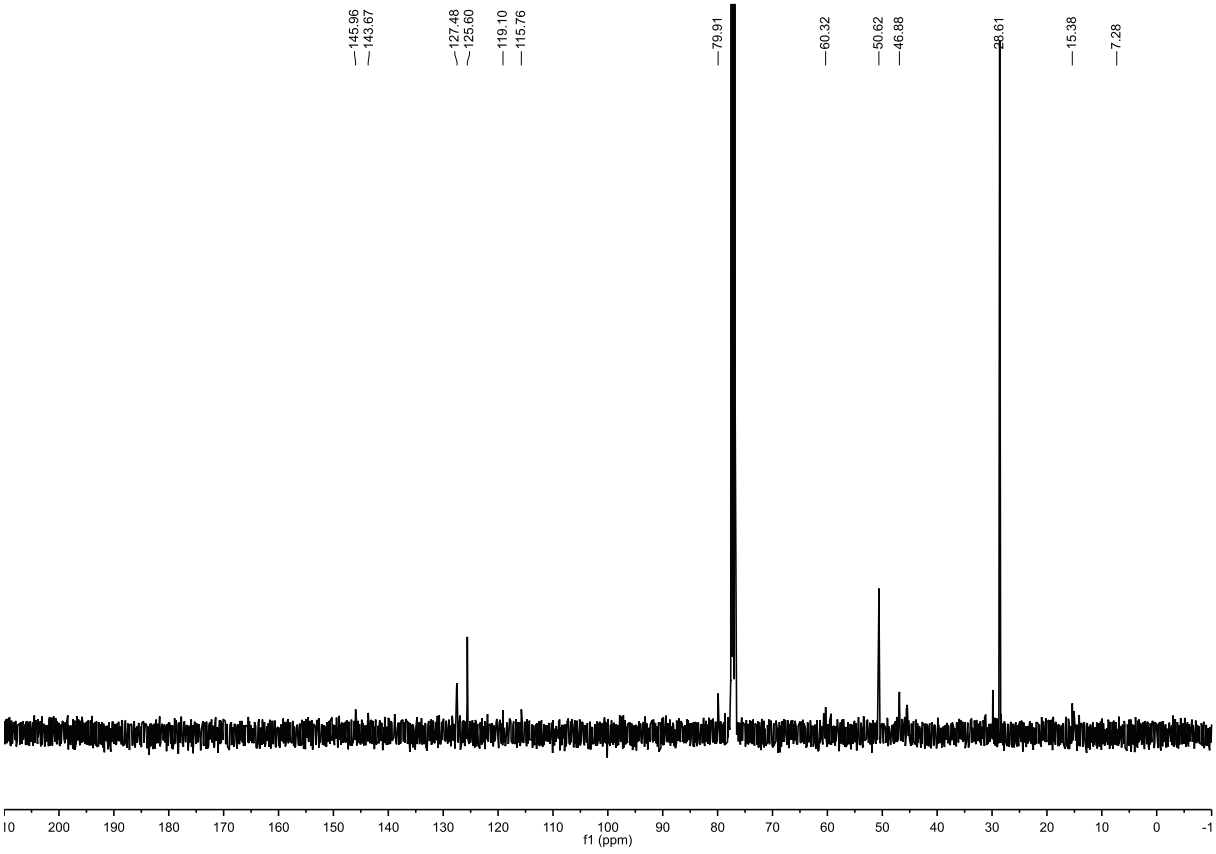
1.00
0.96
1.01
1.93
0.88
4.15
8.58
2.95
f1 (ppm)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115.76
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60.32
50.62
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28.61
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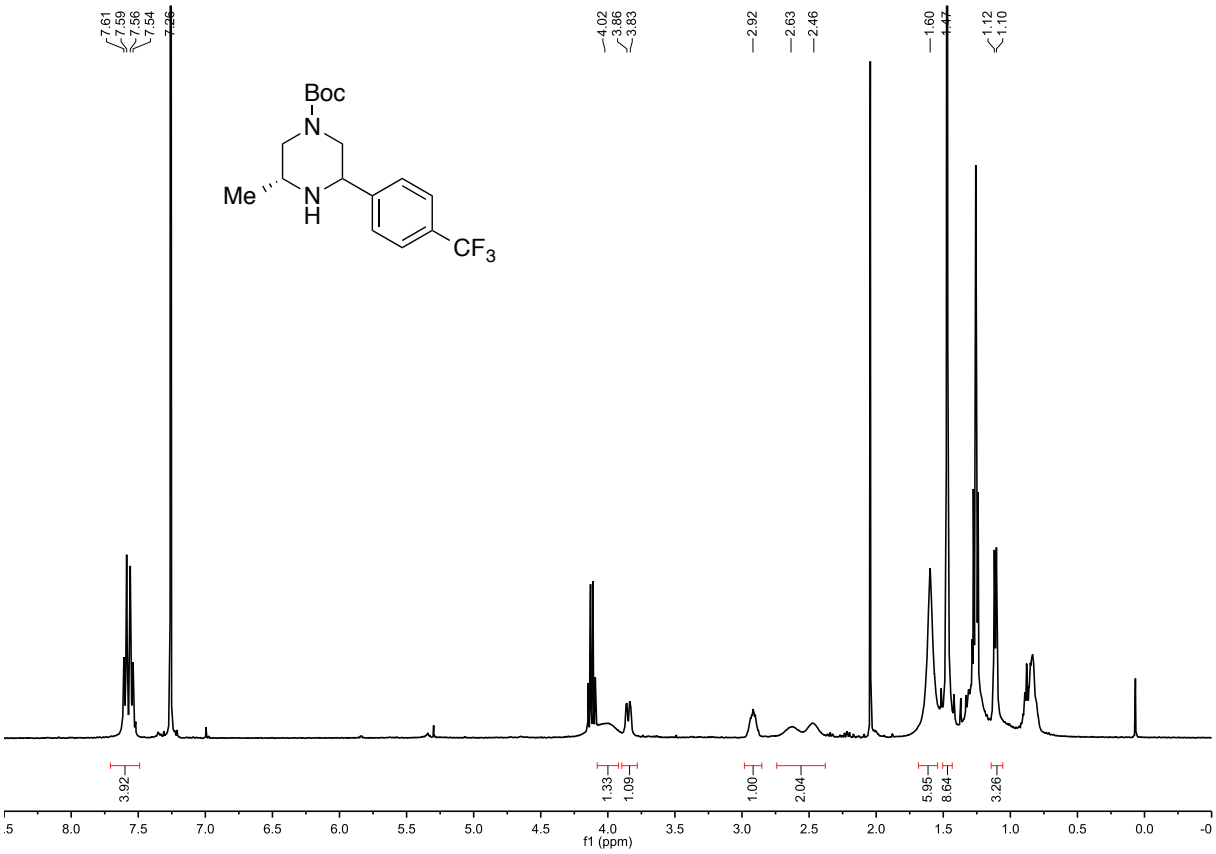
7.28
f1 (ppm)


7.61
7.59
7.56
7.54
7.26
4.02
3.86
3.83
2.92
2.63
2.46
1.60
1.47
1.12
1.10
Boc
N
Me
N
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CF3
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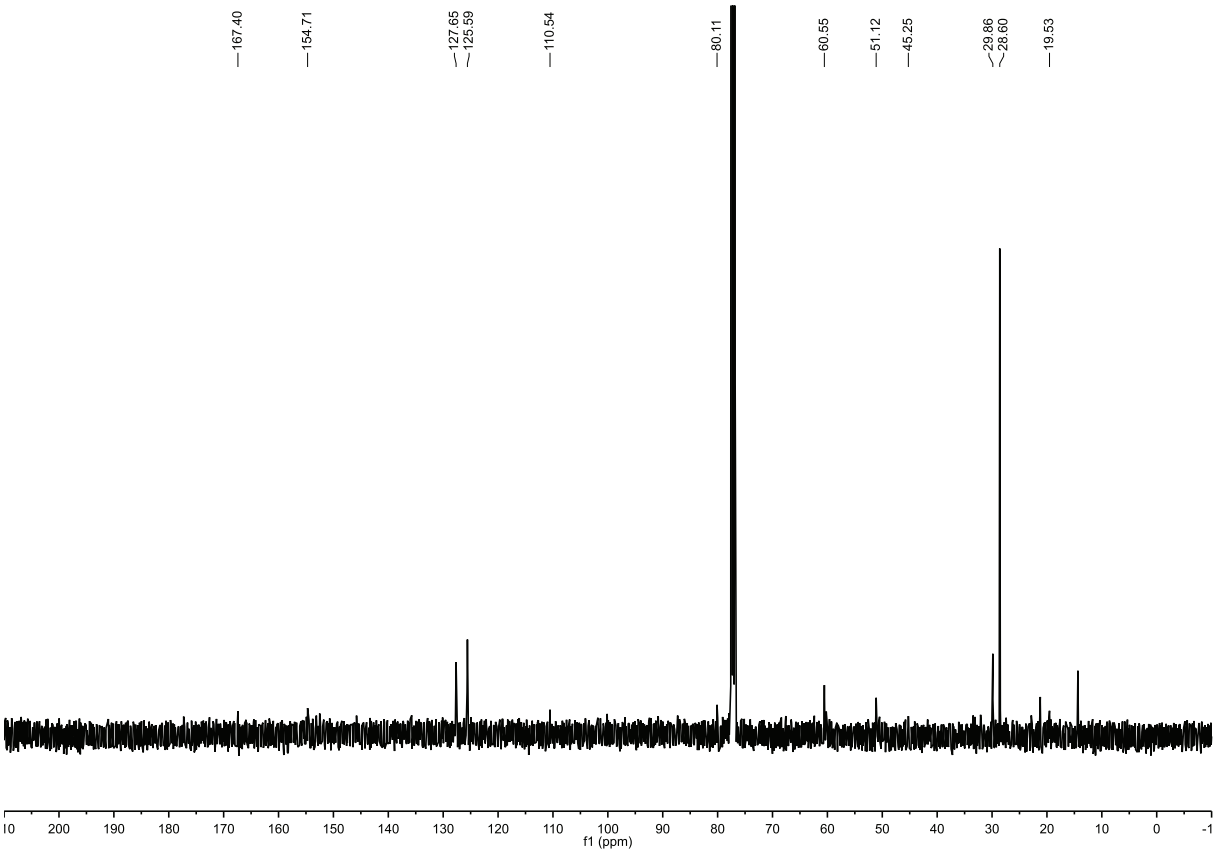
1.33
1.09
1.00
2.04
5.95
8.64
3.26
f1 (ppm)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154.71
127.65
125.59
110.54
80.11
60.55
51.12
45.25
29.86
28.60
19.53
f1 (ppm)