Diss. ETH No. 16591

Investigations of Ligands for Cu-Catalyzed Conjugate Addition Reactions

A dissertation submitted to the

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Presented by

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Publications

(1) Knöpfel, T.F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. "Catalytic, Enantioselective, Conjugate Alkyne Addition" *J. Am. Chem. Soc.* **2005**, 127, 9682-9683.

Patents

(1) US Application No. 11/149,643

Poster Presentations

(1) Knöpfel, T. F.; Zarotti, P.; Carreira, E. M. "Enantioselective Conjugate Addition of Phenylacetylene Catalyzed by Cu in Water" ETH-Tag by Lonza, Visp, June 2005.

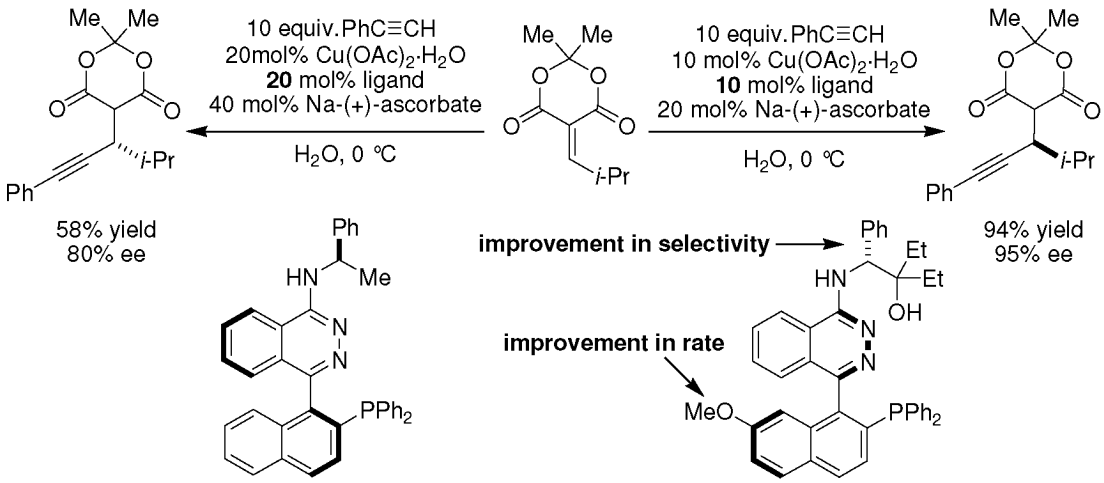
Table of Contents

Abstract

Chapter 1

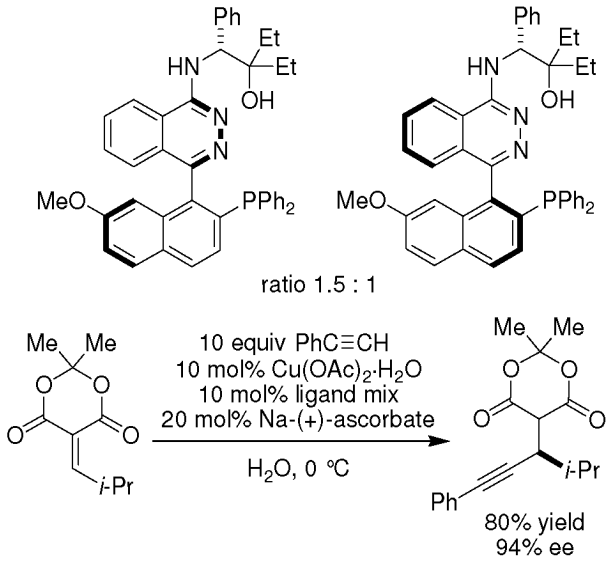
In order to improve the rate and enantioselectivity of the Cu-catalyzed conjugate addition of alkynes to *Meldrum`s* acid derived acceptors, a number of modified PINAP ligands were prepared. Variation of the phosphine did not result in any improvements, while the modifications at the amine moiety led to improved enantioselectivities albeit in lower isolated yields. Surprisingly, the incorporation of a methoxy group at the 7-position of the naphthalene led to an increase in reaction rate (Scheme I). The combination of these two substituents resulted in an efficient catalyst for the conjugate addition leading to the desired products in up to 94% yield and 95% ee.

Scheme I



During the final step in the preparation of the N-PINAP ligands a mixture of diastereomers is formed (ratio 1.5:1). Employing this mixture as catalyst for the conjugate addition reaction afforded the corresponding product in 80% yield and 94% ee (Scheme II). This surprising result is indicative of a positive nonlinear effect. In a practical sense, this phenomenon can potentially obviate the need for the separation of the two diastereomers.

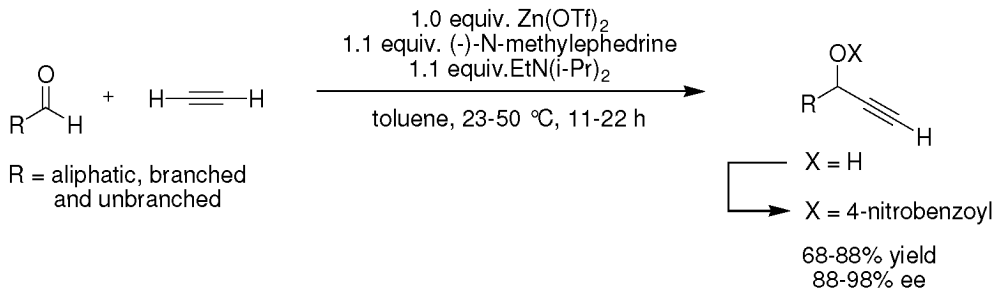
Scheme II



Chapter 2

Improved reaction conditions for the Zn-mediated enantioselective addition of acetylene to aldehydes to decrease the reaction times have been developed. This was achieved by saturation of the solvent with acetylene at -78 °C followed by elevated reaction temperatures (Equation I). Even at these temperatures, there is no erosion in enantioselectivity (88-98%).

Equation I



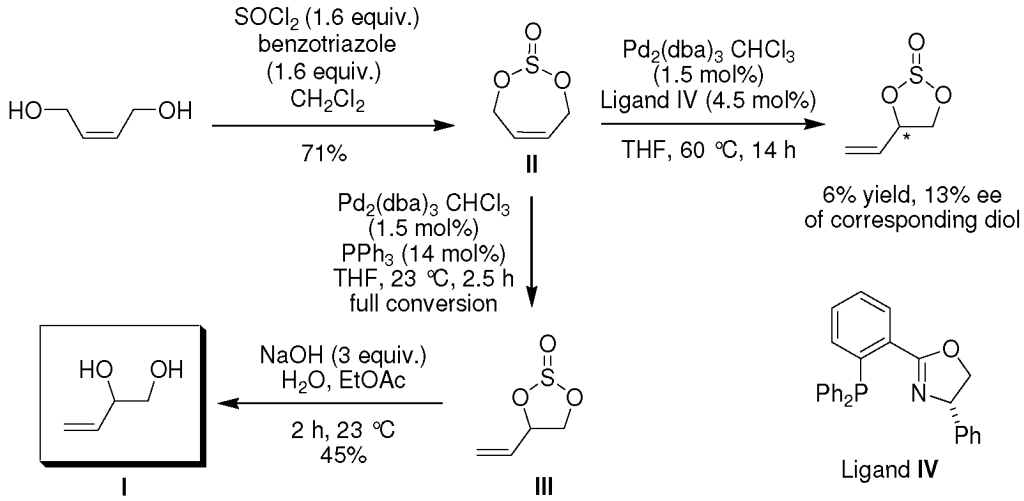
A racemic version of this process was also developed, employing one equivalent potassium-*tert*-butoxide as a base. Addition of acetylene to cyclohexanecarboxaldehyde employing potassium-*tert*-butoxide in toluene at 50 °C furnished 67% of the corresponding propargyl alcohol.

Chapter 3

3-Butene-1,2-diol (**I**) is a versatile, polyfunctional chiral synthon that can be manipulated into more complex structure in a highly stereo- and chemoselective manner. The utility of diol **I** has been demonstrated in the synthesis of a wide range natural and unnatural products with interesting biological properties. 3-Butene-1,2-diol can be obtained in enantiomerically enriched form via enzymatic resolution, multi-step synthesis starting from D-mannitol, L-ascorbic acid and tartaric acid or by hydrolytic kinetic- and dynamic kinetic resolution of 2-vinyloxirane.

Our approach to the diol **I** began with the cyclic seven-member sulfite **II,** a known compound which can be obtained in one step from inexpensive starting materials. Palladium catalyzed ring-contraction to the 5-member sulfite **III** proceeded in full conversion. Sulfite **III** was directly converted to 3-butene-1,2-diol **I** in an unoptimized yield of 45% (Scheme III).

Scheme III



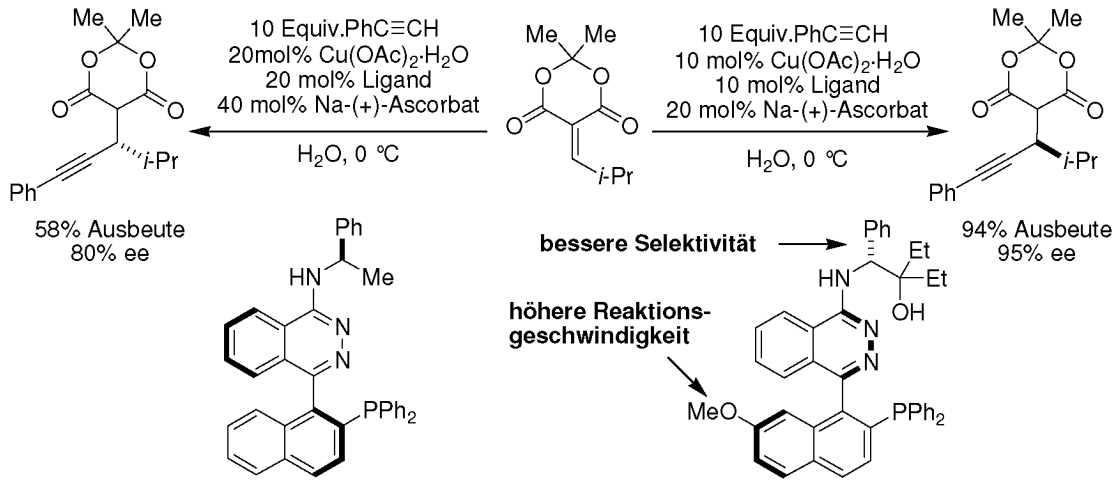
To obtain 3-butene-1,2-diol in enantiomeric enriched form, several ligands were employed in the ring contraction. Among all the ligands screened, phosphinooxazoline **IV** gave the highest enantiomeric excess (13%).

Zusammenfassung

Kapitel 1

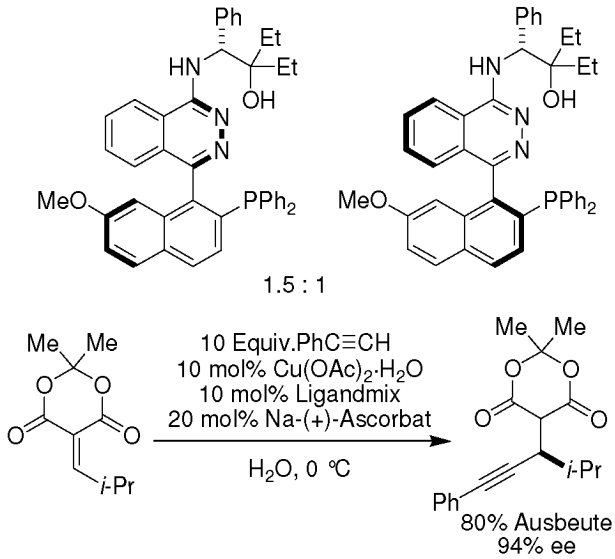
Zahlreiche Modifikationen des N-PINAP Liganden wurden mit dem Ziel synthetisiert, ihre Selektivität sowie Reaktivität in der enantioselektiven, konjugierten Addition von terminalen Alkinen an von Meldrumsäure abgeleitete Akzeptoren zu verbessern. Dabei brachten Variationen des Phosphins keine Verbesserungen, währenddessen Modifikationen des Amins höhere Selektivitäten lieferte, wenn auch in niedrigeren Ausbeuten. Zu unserer Ueberraschung resultierte die Einfügung einer Methoxygruppe in der 7-Position des Naphthalens zu einer markanten Steigerung der Reaktionsgeschwindigkeit (Schema I). Dadurch wurde es möglich, für bestimmte Substrate die Menge an Ligand auf 10 mol% zu senken bei gleich bleibenden hohen Ausbeuten von bis zu 94% und Enantioselektivitäten von 95%. Die konjugierte Addition war dabei für aliphatische sowie aromatische Akzeptoren erfolgreich.

Schema I



In der Synthese des Liganden werden die beiden Diastereomere nach der abschliessenden Phosphinierung in einem Verhältnis von 1.5:1 erhalten. Werden die Liganden in diesem Verhältnis in der konjugierten Addition eingesetzt, wird das Produkt immer noch in 80% Ausbeute und mit einer Enantioselektivität von 94% erhalten (Schema II). Dieses überraschende Resultat kann mit einem positiven nichtlinearen Effekt erklärt werden. Daher kann für bestimmte Substrate die Trennung der Diastereomeren für die konjugierte Addition entfallen.

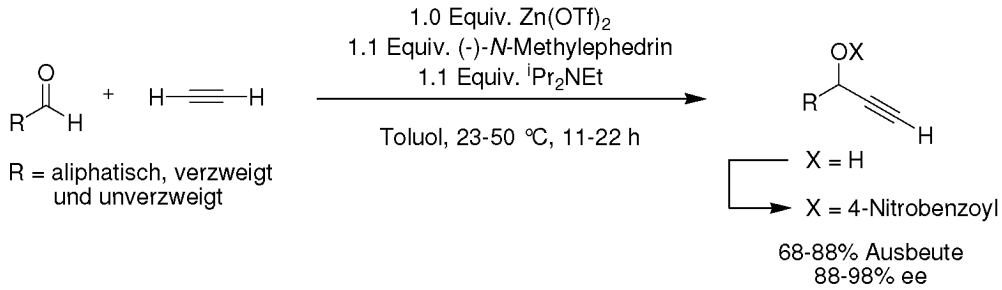
Schema II



Kapitel 2

Die Reaktionszeit in der enantioselektiven Addition von Acetylen an Aldehyde konnte von 7-14 Tagen auf 11-22 Stunden verringert werden. Dies gelang durch Sättigen des Lösungsmittels mit Acetylen bei -74 °C anstelle von -40 °C sowie erhöhten Reaktionstemperaturen (Gleichung I). Dabei blieb die Enantioselektivität auch bei erhöhten Temperaturen hoch.

Gleichung I



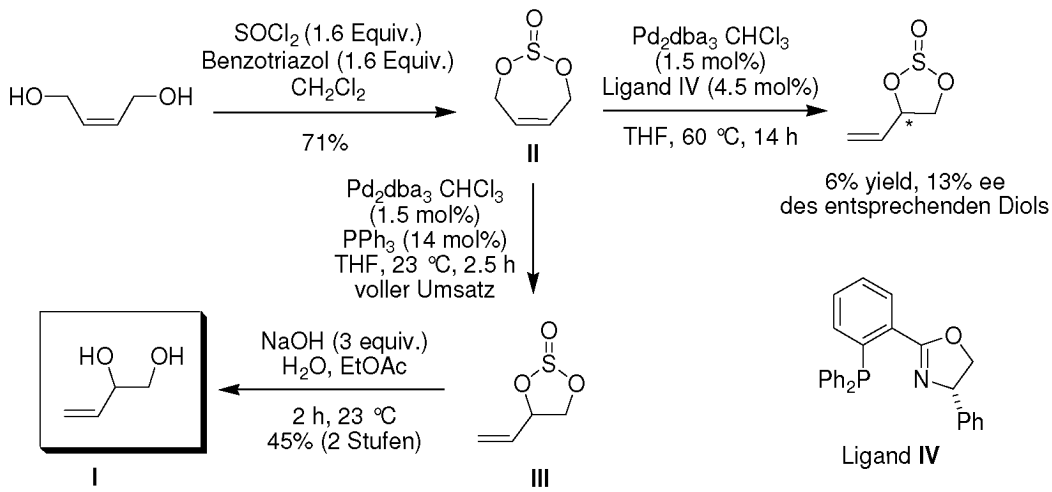
Eine nicht enantioselective Version dieser Reaktion unter Verwendung von Kaliumtertbutoxid als Base wurde ebenfalls entwickelt. Unter diesen Bedingungen lieferte die Addition von Acetylen an Cyclohexanal das Produkt in einer Ausbeute von 67%.

Kapitel 3

3-Buten-1,2-diol (**I**) ist ein vielseitig einsetzbarer, polyfunktionaler chiraler Baustein der stereo- und chemoselektiv verändert werden kann. Die Nützlichkeit des Diols **I** wurde durch die Synthese einer Vielzahl chiraler Verbindungen sowie durch zahlreiche Synthesen von Naturstoffen demonstriert. Das Diol **I** kann in seiner enantiomerenreinen Form durch enzymatische Racematspaltung, durch mehrstufige Synthesen ausgehend von D-Mannitol, L-Ascorbatsäure und Weinsäure oder durch hydrolytische kinetische oder dynamische kinetische Racematspaltung erhalten werden.

Unser Ansatz zur Synthese des diols **I** ging vom bekannten 7-Ring Sulfit **II** aus, das in einem Schritt ausgehend von 1,4-Butendiol erhalten werden kann. Die Pd-katalysierte Ringkontraktion vom 7-Ring Sulfit zum 5-Ring Sulfit erfolgte mit vollständigem Umsatz. Da das 5-Ring Sulfit **III** nicht stabil war, wurde es ohne Reinigung in 45% Ausbeute zum 3-Buten-1,2-diol umgesetzt (Schema III).

Schema III



Um 3-Buten-1,2-diol in enantiomeren angereicherter Form zu erhalten, wurden zahlreiche Liganden in der Umlagerung eingesetzt. Unter all den getesteten Liganden ergab das Phosphinoxazolin **IV** mit 13% die höchste Enantioselektivität.

List of Abbreviations and Acronyms

Å	Ångstrøm	FC	flash chromatography
°C	degree celsius		on silica gel
Ac	acetyl	g	gram
AcOEt	ethyl acetate	GC	gas chromatography
Anal.	elemental analysis	h	hour
Ar	aryl	HPLC	high pressure liquid
Bn	benzyl		chromatography
bp	boiling point	HIRES	high resolution
Bu	butyl	Hz	Herz
c-	cyclo	IR	infra-red
cat.	Catalyst	*i*	*iso*
conc.	concentrated	*J*	coupling constant in Hz
conv.	Conversion	K	degree Kelvin
Cy	cyclohexyl	LDA	lithium di*iso*propylamide
d	doublet	MALDI	matrix-assisted laser
δ	chemical shift in ppm		desorbtion ionization
DABCO	1,4-diazabicyclo[2.2.2]octane	Ms	methanesulfonyl
DCE	1,2-dichloroethane	NMR	nuclear magnetic resonance
DMAP	4-(*N*,*N*-dimethylamino)pyridine	kJ	kilojoule
DMF	*N*,*N*-dimethylformamide	m	multiplet
DMSO	dimethylsulfoxide	*m-*	*meta*
Dppe	diphenylphosphinoethane	M	molar
Diglyme	2-methoxyethylether	mbar	millibar
EDDA	ethylenediamoniumdiacetate	Me	methyl
dr	diastereomeric ratio	mg	milligram
ee	enantiomeric excess	MHz	Megaherz
equiv	equivalent	min	minute
EI	electron impact ionization	ml	milliliter
ESI	electron-spray ionization	mmol	millimol

Et	Ethyl	mp	melting point
MS	mass spectrometry	Ts	tosyl, *p*-toluenesulfonyl
Ms	methanesulfonyl	UV	ultra-violet
nd	not determined	w	weak
μ	micro	Tol	tolyl
ν	vibration frequency in cm^{-1}	t_R	resolution time
p-	*para*		
p.	page		
Ph	phenyl		
ppm	part per million		
Pr	propyl		
q	quartet		
quant.	quantitative		
recryst.	recrystallized		
rt	room temperature		
sat.	saturated		
soln.	solution		
t	time		
t	triplet		
t	*tert*		
T	temperature		
TBS	*tert*-butyldimethylsilyl		
TBDPS	*tert*-butyldiphenylsilyl		
TES	triethylsilyl		
TBDPS	*tert*- buthyldiphenylsilyl		
Tf	trifluoromethanesulfonyl		
TFA	trifluoro acetic acid		
THF	tetrahydrofuran		
TLC	thin layer chromatography		
TMS	trimethylsily		

Chapter 1

Modifications of the PINAP Ligand for Optimum Performance in the Cu-Catalyzed Conjugate Addition of Alkynes to *Meldrum`s* Acid Derived Acceptors

1.1 Introduction

One of the most useful methods for C-C bond formation is the conjugate addition reaction of carbon nucleophiles.[1] This introduction deals with the conjugate addition reactions of alkynyl nucleophiles. In contrary to other carbon nucleophiles only a few examples of conjugate additions of alkynes are known.[2] First racemic additions ar presented employing different metals, followed by enantioselective variants. The presentation of the synthesis of QUINAP and PINAP, two chiral P,N-ligands completes this introduction.

1.1.1 Conjugate Additions Employing Metal Alkynylides

Conjugate addition of carbon nucleophiles to *a,β*-unsaturated electrophiles is an essential carbon-carbon bond forming process in synthetic organic chemistry. Organocuprates are the most commonly used nucleophiles for this transformation to ensure high regioselectivity. The use of Cu(I) reagents has been thwarted by the inertness of Cu(I)-alkynylides towards conjugate addition reactions.[2] Moreover, alkynes are used as dummy ligands in mixed organocuprates, ensuring that only one equivalent of the more precious ligand is needed or increasing the solubility of the cuprate to achieve high conversions (Equation 1).[3]

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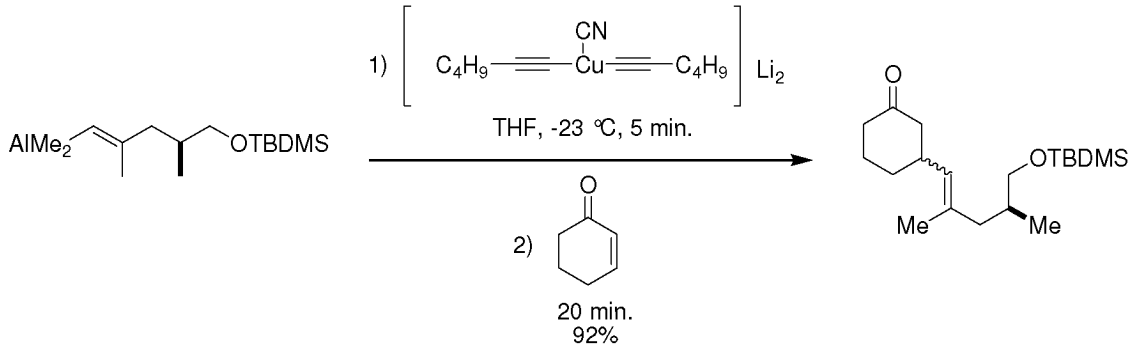
[1] Perlmutter, P. Conjugate Addition *Reactions in Organic Synthesis*, Pergamon: Oxford, 1992

[2] Reviews: (a) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 569-592. (b) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*, Krause, N., Ed.; Wiley-VCH: Weinheim, 2002, pp 224-258. (c) Sibi, M. P.; Manyem, S. Tetrahedron, **2000**, *56*, 8033.

[3] Wipf, P.; Smitrovich, J. H.; Moon, C. W. *J. Org. Chem.* **1992**, *57*, 3178.

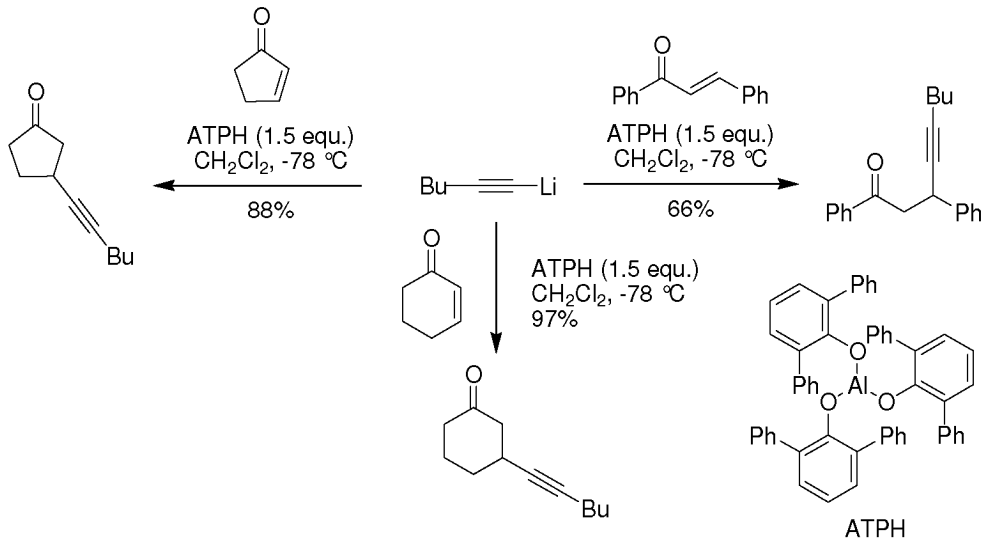
Equation 1



1.1.1.1 Conjugate Addition of Lithium and Grignard Alkynylides

Normally, the hard lithium alkynylides add in a 1,2-fashion to *a,β*-unsaturated carbonyls. But when the carbonyl is complexed to a very bulky *Lewis acid*, the carbonyl is blocked and 1,4 addition can be achieved (Scheme 1).[4] *Yamamoto* employed the bulky aluminiumtris(2,6-diphenoxide) and achieved 1,4-addition to cyclic and noncyclic *a,β*-unsaturated carbonyls in good yields.

Scheme 1

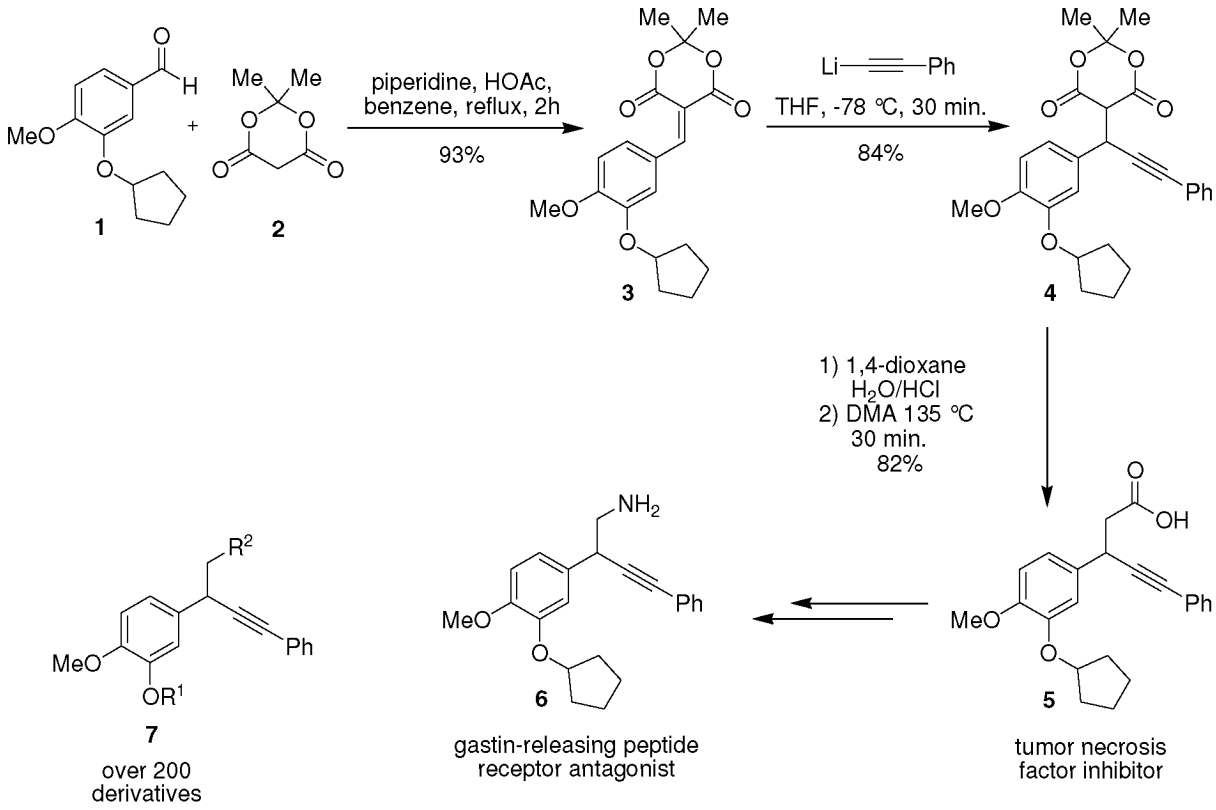


In a *Meldrum's* acid derived acceptor two π-acceptors activate the olefin and therefore it is more reactive towards 1,4-addition. These acceptors can be obtained in one step by the *Knoevenagel* condensation of an aldehyde and *Meldrum's* acid (Scheme 2).[5] Conjugate addition

[4] Maruoka, K.; Shimada, I.; Imoto, H.; Yamamoto, H. *Synlett*, **1994**, *7*, 519.
[5] Tietze, L. F.; Eicher, T. *Reaktionen und Synhesen im organisch-chemischen Praktikum*. Thieme: Stuttgart; 1981

of lithium phenylalkynylide to acceptor **3** furnished the racemic product **4** in good yield.[6] Decarboxylation to the carboxylic acid furnished the tumor necrosis factor (TNF) inhibitor **5**. TNF, a cytokine, is produced by activated white cells, vascular endothelium, fibroblasts and many other cells and mediates numerous pro-inflammatory processes. Most important diseases are rheumatoid arthritis, bronchial asthma and *Crohn's* disease.[6] From compound **7** over 200 derivatives were made for pharmacological studies. One of them is compound **6**, which is obtained from the acid **5** after *Curtius* rearrangement. Separation of the enantiomers for these compounds was either carried out by preparative chiral HPLC or by crystallisation.

Scheme 2



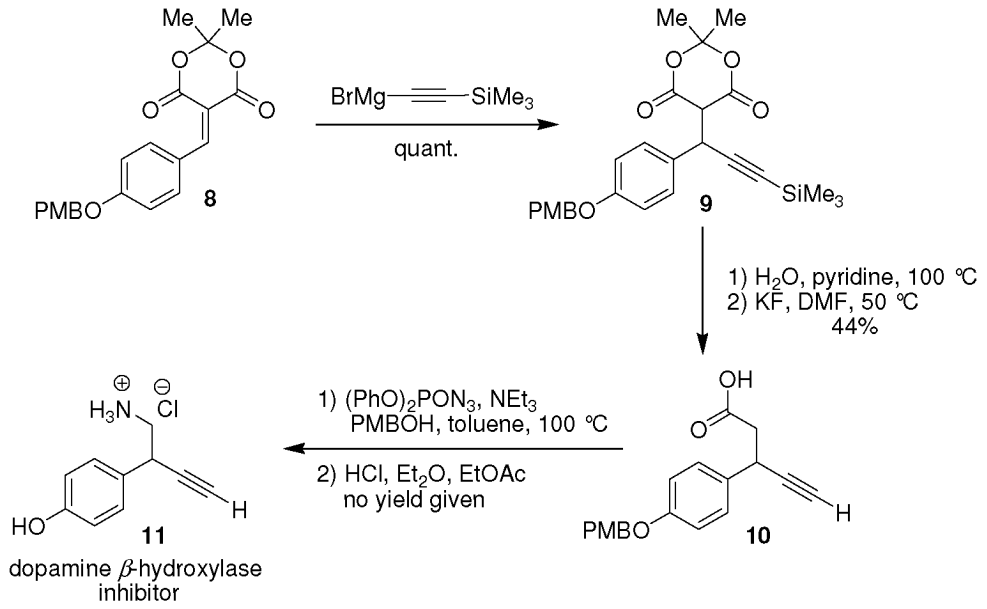
Reaction of trimethylsilylethynyl magnesium bromide to the very similar acceptor **8** furnished the conjugate addition product in 100% yield (Scheme 3).[7] Subsequent saponification and decarboxylation, followed by removal of the TMS-group provided acid **10**. Modified *Curtius*

[6] (a) Xiang, J. N.; Karpinski, J. M.; Christensen, S. B., IV. Int. Appl. PCT, WO 0009116, 2000. (b) Xiang, J. N.; Osifo, I. K.; Karpinski, J. M.; Christensen, S. B., IV. Int. Appl. PCT, WO 0009115, 2000. (c) Christensen, S. B., IV; Karpinski, J. M.; Frazee, J. S. Int. Appl. PCT, WO 9703945, 1997.

[7] Kruse, L. I.; Kaiser, W. E. D.; Chambers, P. A.; Goodhart, P. J.; Ezekiel, M.; Ohlstein. *J. Med. Chem.* **1988**, *31*, 704.

rearrangement followed by deprotection with HCl in ether/EtOAc provided compound **11**, which shows activity against the dopamineβ-hydroxylase.

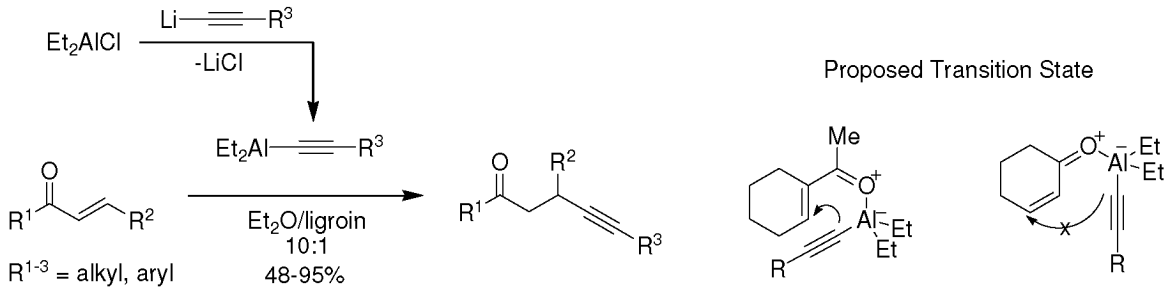
Scheme 3



1.1.1.2 Conjugate Addition of Aluminium Alkynylides

In 1971, *Hooz* reported the first conjugate addition of aluminium alkynes.[8] Aluminium alkynylides are prepared from corresponding lithium alkynylides using diethyl aluminiumchloride. However, under these conditions these alkynylides react only with *a,β*-unsaturated ketones that can adopt an *s-cis* conformation (Scheme 4). This problem can be overcome by using either a γ-hydroxyl directing group on the acceptor or by addition of TBSOTf to the reaction.[9,10]

Scheme 4

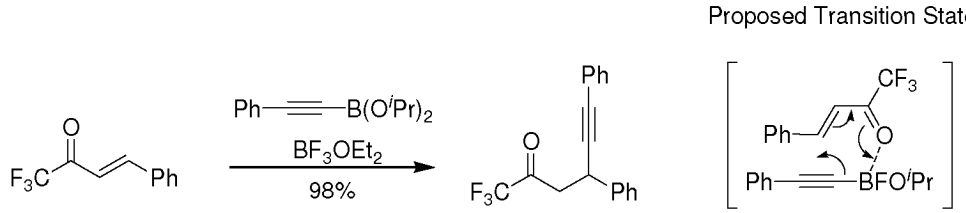


[8] Hooz, J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320.
[9] Pappo, R.; Collins, P. W. *Tetrahedron Lett.* **1972**, *13*, 2627.
[10] Sunggak, K.; Park, J. H. *Synlett* **1995**, 163.

1.1.1.3 Conjugate Addition of Boron Alkynylides

In 1972 the first example of a conjugate addition of trialkynylboron reagents was reported by *Pappo.*[11] However, synthetically useful methods, employing one equivalent of alkyne, have been discovered more recently. *Brown* used a preformed *B*-1-alkynyl-9-BBN reagent and *Suzuki* employed 1-alkynyl-diisopropoxyboranes for the addition to *a,β*-unsaturated ketones (Equation 2).[12,13] These reagents also only react with *a,β*-unsaturated ketones that can adopt *s-cis* conformation. A cyclic transition state has been proposed for the alkyne transfer process.

Equation 2



1.1.1.4 Conjugate Addition of Copper Alkynylides

Copper in the oxidation states 0, 1 or 2 can be used to form copper alkynylides. Oxidation of copper(0) in the presence of phenylacetylene forms the copper acetylide. On the other hand, oxygen has to be excluded when Cu(I) is used as precursor to avoid *Glaser* coupling.[14] This can be overcome by reducing Cu(II) in situ to Cu(I) by a reductant. Copper alkynylides are insoluble solids, likely due to their tendency to form aggregates. This seems reasonable, because Cu binds both end- and side-on to acetylenes (Figure 1).[15] These oligomeric structures can be broken by adding diamines or phosphines to a suspension of the aggregate.

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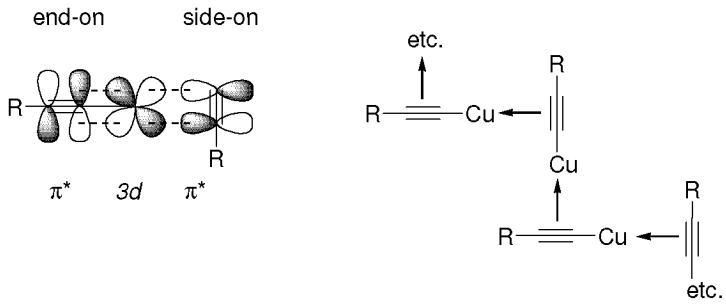
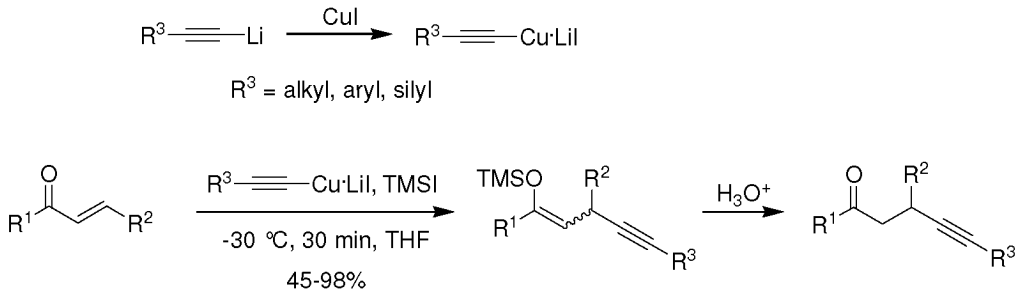
[11] Pappo, R.; Collins, P.W. *Tetrahedron Lett.* **1972**, *13*, 2627.
[12] Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954.
[13] Takada, E.; Hara, S.; Suzuki, A. *Heteroatom Chemistry*, **1992**, *3*, 483.
[14] Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.
[15] Blake, D.; Calvin, G.; Coates, G. E. *Proc. Chem. Soc.* **1959**, 396.

Figure 1 *Suggested structures of polymeric alkynylides*



As previously mentioned, copper alkynylides are in general not reactive toward *a,β*-unsaturated carbonyl compounds. However, when the electrophile is activated with TMSCl, copper acetylides can undergo conjugate addition (Scheme 5).[16]

Scheme 5

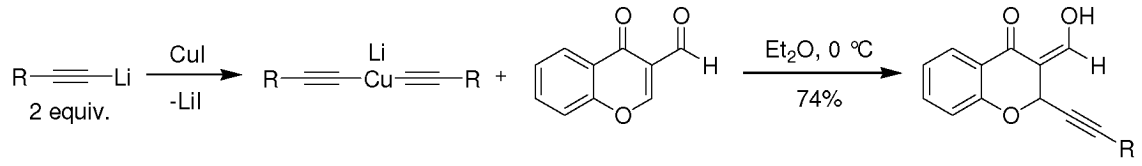


More recently, *Gabbutt* described the addition of lithium dialkynylcuprates to activated chromones (Scheme 6).[17] The dialkynylcuprates are easily generated by the addition of 2 equivalent of lithiumalkyne to CuI. The *in situ* generated cuprates react smoothly with substituted chromones to give the product in good yields.

[16] TMSCl is known to greatly accelerate the conjugate addition of dialkylorganocuprates to enones and enals, see: (a) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305. (b) Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1981**, *37*, 1385. (c) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (e) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. (f) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. (g) Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238. (h) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182.(i) Kim, S.; Park, J. H.; Jon, S. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 783.

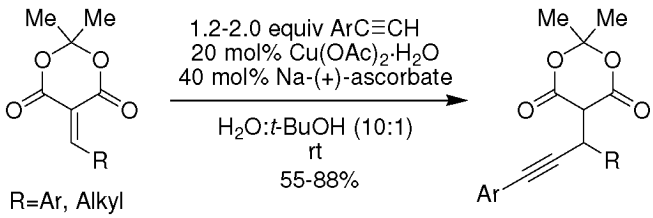
[17] Daia, D. E.; Gabbutt, C., D.; Heron, B. M.; Hepworth, J. D.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **2003**, *44*, 1461.

Scheme 6



The *Carreira* group has disclosed a more practical protocol for the conjugate addition of copper alkynylides.[18] The reaction employed *in situ* generated copper alkynylides and *Meldrum`s* acid derived acceptors as electrophiles. To avoid the handling of sensitive Cu(I) salts, Cu(I) is generated from more stable Cu(II) and reduced *in situ* in the presence of sodium ascorbate.[19] Using a 10:1 mixture of H_2O:*t*-BuOH, 0.2 equivalent $Cu(OAc)_2$ and 0.4 equivalent of sodium ascorbate aromatic alkynes undergo conjugate addition in good yields (Equation 3). The reaction is catalytic in copper and no preformed alkynylides are used, which further increase the synthetic utility of the process.

Equation 3

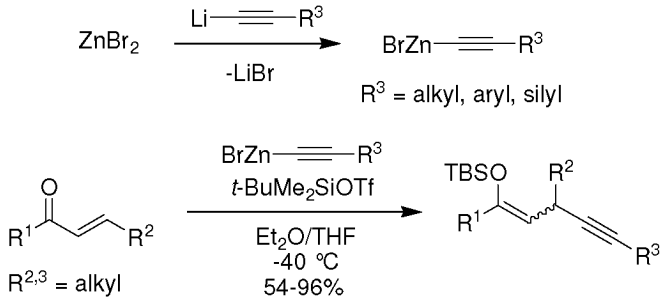


1.1.1.5 Conjugate Addition of Zinc Alkynylides

Activation of electrophiles with a silating reagent is also possible for the conjugate addition of zinc alkynylides. *Kim* reported conjugate addition of zinc alkynylides to various *a,β*-unsaturated ketones.[20] Zink alkynylides are prepared from the corresponding lithium alkynylides. In the presence of TBSOTf zinc alkynylides add to enones to give the TBS enol ethers as mixtures of *E* and *Z* isomers (Scheme 7).

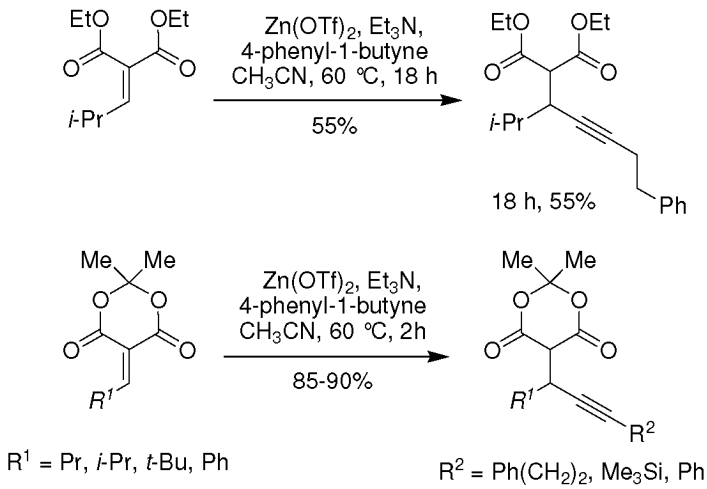
[18] Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054.
[19] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
[20] Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627.

Scheme 7



Zinc alkynylides are more conveniently prepared using the method developed by the *Carreira* group (Section 2.1.1.3).[21] This method was used for addition to aldehydes and imines; however, the same protocol can also be employed in the conjugate addition (Scheme 8). Again, *Meldrum`s* acid derived acceptors are suitable for this process. In this reaction, Zn salt must be used stoichiometrically.

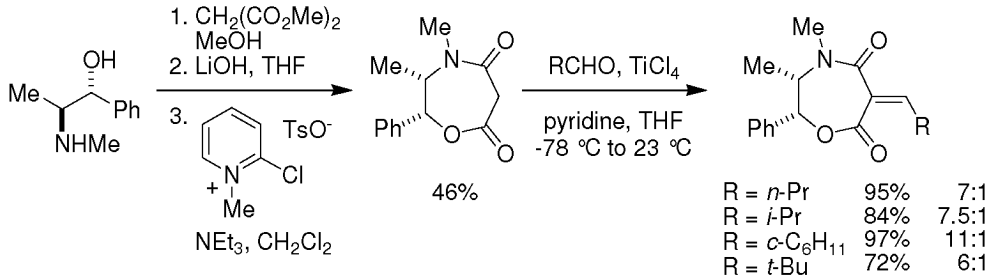
Scheme 8



To make this reaction enantioselective, *N*-methylephedrine was employed as a chiral ligand, however the result was not encouraging. Alternatively, a diastereoselective conjugate addition has been achieved employing *N*-metylephedrine as a chiral auxiliary. The chiral acceptors were prepared in four steps furnishing predominantly the (Z)-alkylidene products (Scheme 9).

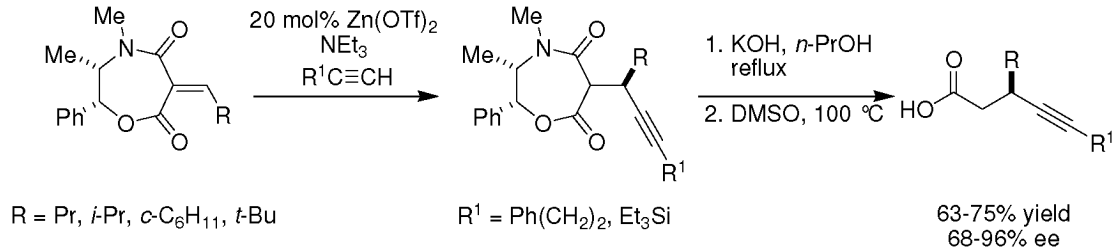
[21] Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.

Scheme 9



Gratifyingly, the additions could be conducted in a catalytic manner using only 20 mol% of $Zn(OTf)_2$. Furthermore, cleavage of the auxiliary provides useful chiral building blocks for organic synthesis (Scheme 10).

Scheme 10

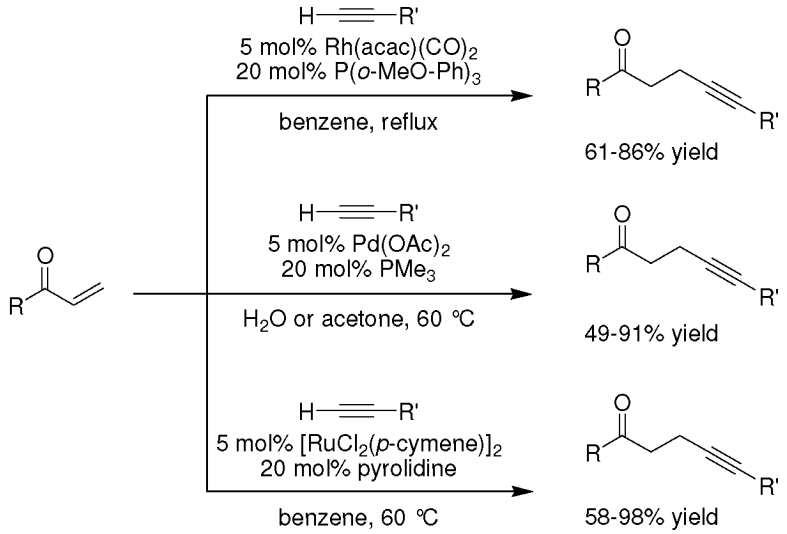


1.1.1.6 Conjugate Addition of Alkynes Involving Pd-, Rh- and Ru- Catalysis

There are very few reports describing catalytic conjugate alkyne addition. Besides the two cases discussed above (Equation 3, Scheme 10), these are examples which involve Pd(II)-, Rh(I)- and Ru(II)-catalysis.[22,23,24,25] Although these reactions can employ a wide range of alkynes the additions occur only with β-unsubstituted vinyl ketones or acrylates (Scheme 11).

[22] Chen, L.; Li, C.- J. *Chem. Commun.* **2004**, *20*, 2362.
[23] (a) Kovalev, I. P.; Nikishin,G. I. *Tetrahedron Lett.* **1990**, *31*, 7063. (b) Lerum, R. V.; Chisholm, J. D. *Tetrahedron Lett.* **2004**, *45*, 6591.
[24] Chang, S.; Na, Y.; Choi, E.; Kim, S. *Org. Lett.* **2001**, *3*, 2089.
[25] Nishimura, T.; Washitake, Y.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2004**, *11*, 1312.

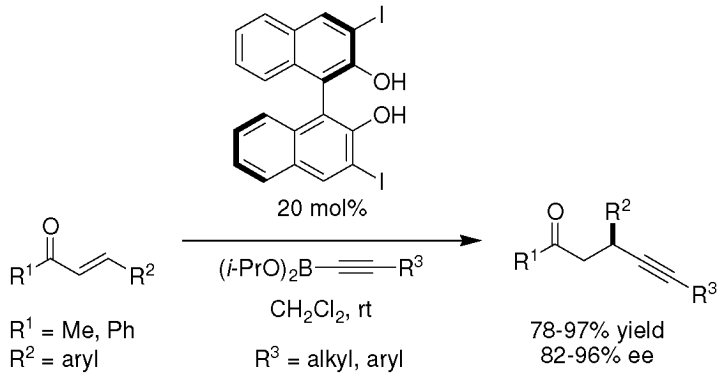
Scheme 11



1.1.2 Enantioselective Conjugate Additions of Alkynes

Chong reported that preformed alkynyl boronates derived from 3,3'-diphenyl-BINOL participate in conjugate addition to aryl-enones.[26] Recently, an improved procedure has been developed using a catalytic amount of 3,3'-diiodo-BINOL (Equation 4).[27]

Equation 4

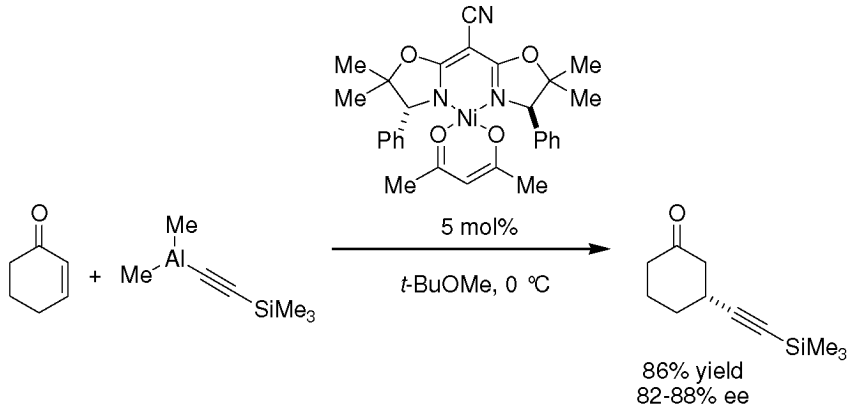


Another catalytic enantioselective conjugate addition of alkynylides has been developed by *Corey.*[28] The addition of an aluminium alkynylide is catalyzed by a chiral bisoxazoline-Ni

[26] Chong, J. M.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 1822.
[27] Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244.
[28] Kwak, Y. S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385.

complex, and the reaction with cyclohexanone proceeds in good yields. The report describes only one example and the substrate scope is yet to be explored. Furthermore the enantiomeric excess of the product was not consistent, varying from 82-88% ee (Equation 5).

Equation 5



1.1.3 QUINAP

To date, a large number of chiral P,N-ligands, having both nitrogen and phosphorus functional moieties, has been prepared and their applications in asymmetric reactions have been investigated.[29] The success in metal-catalysed asymmetric reactions of these mixed donor ligands may be due to the fact that they are a class of hemilabile ligands possessing a combination of hard and soft donor atoms. Therefore, the different features associated with each donor atom provide a unique reactivity to their metal complexes.[30]

One successful example of such a P,N-ligand is QUINAP (**12**, 1-(2-diphenylphosphino-1-naphthyl)isoquinoline). Its synthesis was reported in 1993 by *Brown*.[31] Since then it has been used as a ligand in Rh-catalyzed asymmetric hydroboration, Ag-catalyzed asymmetric [3+2] cycloaddition of azomethine ylides and electron deficient alkenes to give pyrrolidines, Pd-catalyzed allylic substitution, Ru-catalyzed Diels-Alder reaction, Rh-catalyzed diboration/oxidation and Cu-catalyzed addition of alkynes to enamines.[32,33,34,35,36] QUINAP is commercially available but rather expensive.[37] Racemic QUINAP can be obtained in seven steps starting from 1-chloroquinoline (**13**) and 2- methoxynaphthalene (**14**). However, resolution of QUINAP was only achieved by the use of a chiral palladium complex.

1.1.3.1 Synthesis of QUINAP

Although 1-chloroquinoline (**13**) is commercially available, it is rather expensive (1 g/53 CHF, Aldrich). However, it can be synthesized in two steps from isoquinoline in 92 % yield.[38]

---

[29] (a) Fache, F.; Schulz, E.; Tammasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159. (b) Tonks, L.; Williams, J. M. J. *Contemp. Org. Synth.* **1997**, *4*, 353. (c) Togni, A.; Veneziani, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497

[30] (a) Espinet, P.; Soulantica, K. Coord. *Chem. Rev.* **1999**, *193-195*, 499. (b) Molina, P:; Arques, A.; Garcia, A.; Ramriez de Arellano, M. C. *Eur. J. Inorg. Chem.* **1988**, *1359*. (c) P. J. Guiry, C. P. Saunders, *Adv. Synth. Cat.* **2004**, *346*, 497. (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (e) For a review about P,N-ligands with a pyridine as N-donor see: Chelucci, G.; Orru, G.; Pinna, G. A.; *Tetrahedron* **2003**, *59*, 9471.

[31] Alock, N. W.; Brown, J. M.;. Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743.

[32] Doucet, H.; Fernandez, E.; Layzell, T. P.; Brown, J. M. *Chem. Eur. J.* **1999**, *5*, 1320.

[33] Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.

[34] Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.

[35] Faller, J. W.; Grimmond, B. J. *Organometallics* **2001**, *20*, 2454.

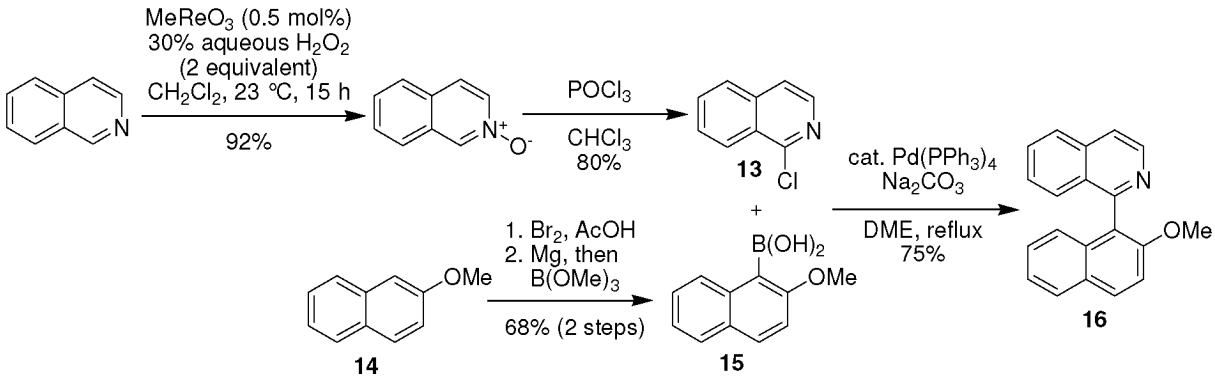
[36] Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702.

[37] 100 mg (*S*)-or (*R*)-QUINAP cost 306 CHF (Acros).

[38] Copéret, C.; Adolfsson, H.; Khuong, T-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740.

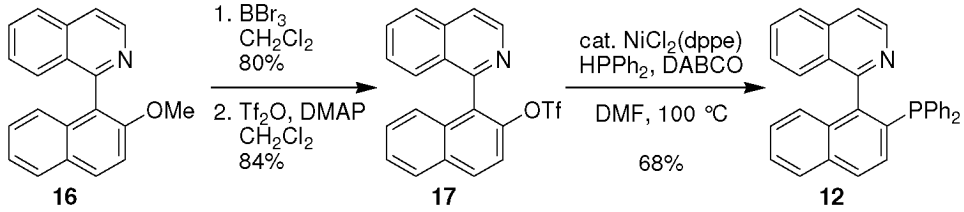
Subsequent *Suzuki*-coupling with boronic acid **15**, in a two step sequence from 2-methoxynaphthalene (**14**) affords the biaryl **16** in 75% yield (Scheme 12).[39]

Scheme 12



Demethylation of the methylarylether **16** with BBr_3 and triflation of the resulted naphthol with triflic anhydride furnishes compound **17** in 67% over 2 steps. Phosphination of the triflate gives racemic QUINAP in 68% yield (Scheme 13).

Scheme 13

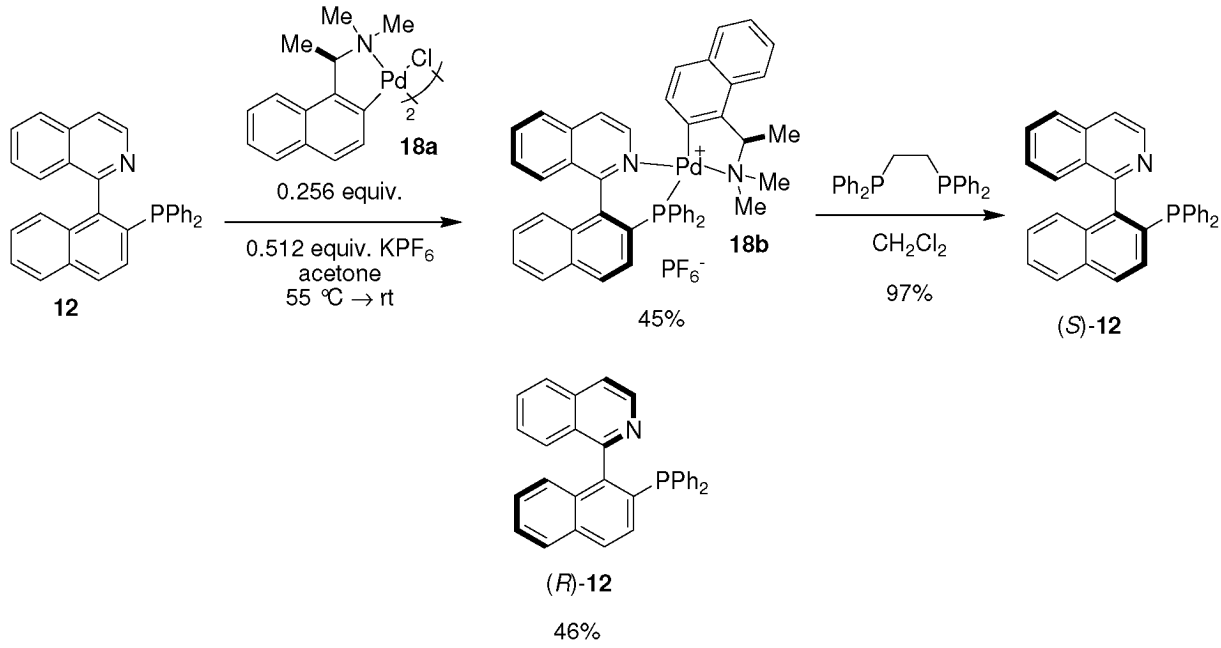


Resolution was achieved with the chiral palladium complex **18a**. One enantiomer of QUINAP preferentially forms a cationic complex **18b** with the palladium. After the isolation of the diasteromerically pure complex, (*S*)-QUINAP can be obtained by decomplexation with dppe. While enantioenriched (*R*)-QUINAP can be obtained from the mother liquor (Scheme 14). This resolution is rather costly because the chiral palladium complex is expensive.

---

[39] Lim, C. W.; Tissot, O.; Mattison, A.; Hooper, M. W.; Brown, J. M.; Cowley, A. R; Hulmes, D. I.;. Blacker, A. J *Org. Process Res. Dev.* **2003**, *7*, 379.

Scheme 14



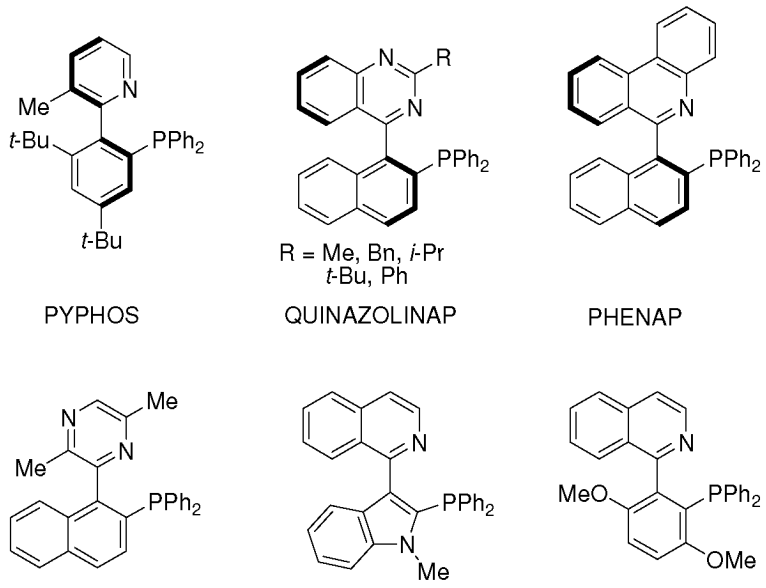
1.1.3.2 Analogues of QUINAP

To improve enantioselectivities in QUINAP-catalyzed processes, the structure of QUINAP has been modified. Apart from modifications of the phosphine moiety by *Brown* modifications of the backbone were also investigated.[40] Replacement of the isoquinoline by phenanthroline led to PHENAP.[41] Different substituents in the 2-position of quinazoline were reported by *Guiry* and a pyridine analogue was reported by Chan.[42,43] These ligands are synthesized via a *Suzuki*-coupling to install the biaryl moiety. The enantiomers were separated by the chiral palladium amine complex. Some modifications of the biaryl core lead to configurationally unstable ligands, as can be seen in Figure 2.

[40] Doucet, H.; Brown, J. M. *Tetrahedron: Asymmetry* **1997**, *8*, 3775.
[41] Valk, J. M.; Claridge, T. D. W.; Brown, J. M.; Hibbs, D.; Hursthouse, M. B. *Tetrahedron: Asymmetry* **1995**, *6*, 2597.
[42] Connolly, D.J.; Lacey, P. M.; McCarthy, M.; Saunders, C. P.; Carroll, A.-M.; Goddard, R.; Guiry, P. J. *J. Org. Chem.* **2004**, *69*, 6572.
[43] Kwong, F. Y.; Yang, Q.; Mak, T. C. W.; Chan, A. S. C.; Chan, K. S. *J. Org. Chem.* **2002**, *67*, 2769.

Figure 2

Separable and configurationally stable at room temperature



Separable but not configurationally stable at room temperature

1.1.4 PINAP

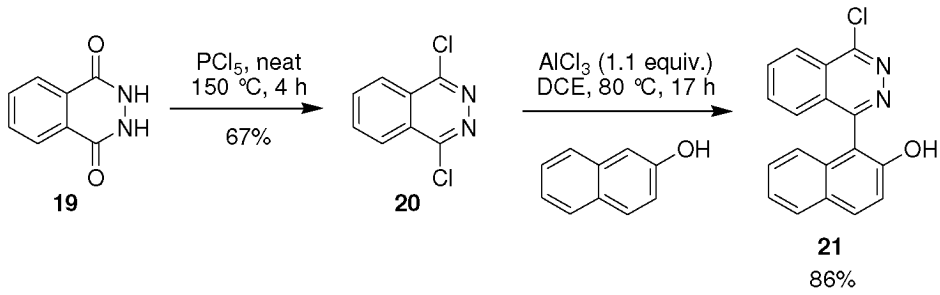
In a screening of ligands for the copper catalyzed alkyne addition to the *Meldrum`s* acceptors (Equation 3), QUINAP showed the highest enantioselectivity (42% ee).[44] Instead of modifying the structure of QUINAP, which can lead to resolution problems and configurationally unstable compounds, a new ligand class has been developed, which resembles the skeleton of QUINAP. The key feature of this new ligand, which was named PINAP, is the incorporation of a second stereogenic center. Because of the stereogenic center, the diastereomeric ligands can be separated by chromatography or crystallization, and the expensive resolution using the palladium complex can be avoided.

[44] Work of *T. Knöpfel* in the *Carreira* group

1.1.4.1 Synthesis of PINAP

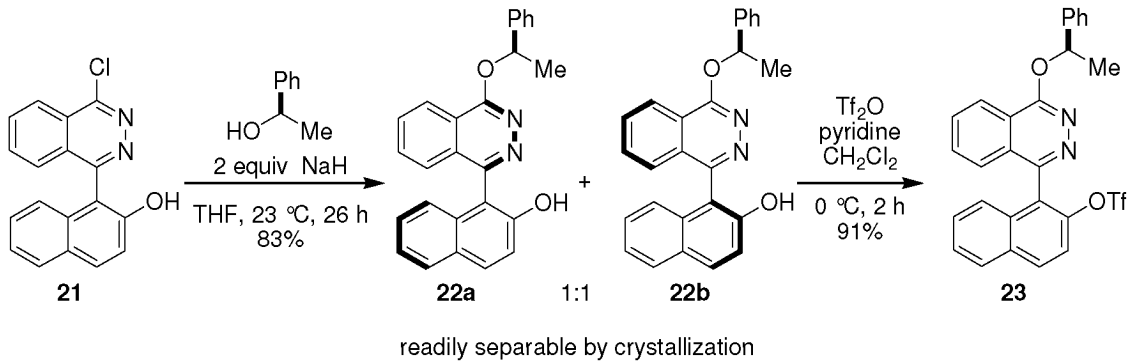
The synthesis of PINAP starts from preparation of 1,4-dichlorophthalazine (**20**). It can be prepared on a 100 g scale from inexpensive phthalhydrazide (**19**) and PCl_5.[45] *Friedel-Craft`s* Coupling with 2-naphtol using $AlCl_3$ furnished the monochlorophthalazine **21** in 86% yield (Scheme 15).[46]

Scheme 15



At this stage the modular synthesis allowed either the use of a chiral alcohol or amine to introduce the second stereogenic center.[47] Addition of naphthol **21** to a mixture of NaH and (*R*)-phenylethanol led to the diastereomeric aryl ether **22**. These diastereomers could easily be separated by crystallization, however it was found that these naphthols undergo epimerization in the subsequent phosphination reaction at 100 °C. Therefore, the mixture of the naphthols was converted to the corresponding triflate **23** (Scheme 16).

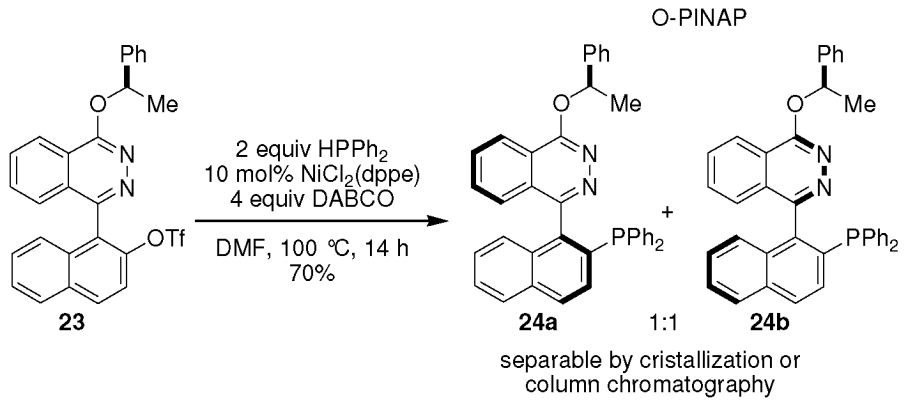
Scheme 16



[45] Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, B. K. *J. Org. Chem.* **1993**, *58*, 844.
[46] M. Pal, V. R. Batchu, K. Parasuraman, K. Yeleswarapu, *J. Org. Chem.* **2003**, *68*, 6806.
[47] Knöpfel, T. F.; Aschwanden, O.; Ichikawa, T.; Carreira, E.M. *Angew. Cem. Int. Ed.* **2004**, *43*, 5971.

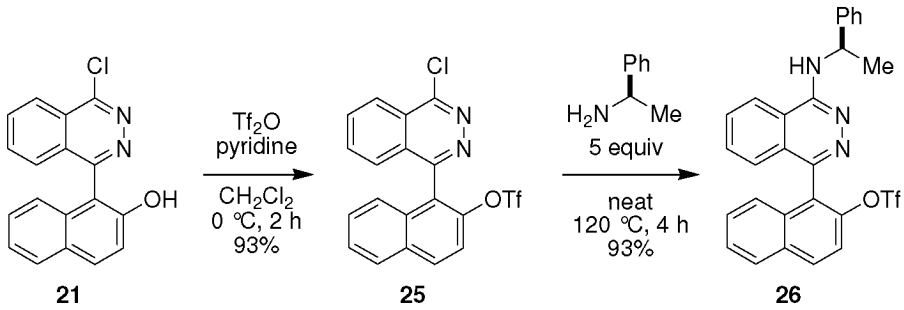
The Ni-catalyzed phosphination affords a 1:1 mixture of the diastereomers of **24**, which are termed O-PINAP (Equation 6). The separation of the two diastereomers is possible either by chromatography on silica gel or by crystallization. The configurationally stability of O-PINAP has been investigated by heating one diastereomer in *p*-xylene at different temperatures. For O-PINAP, the rotation barrier is calculated to be 27.6 kcal/mol, which corresponds to the half life $t_{1/2}$ at 65 °C of greater than 25 days.

Equation 6



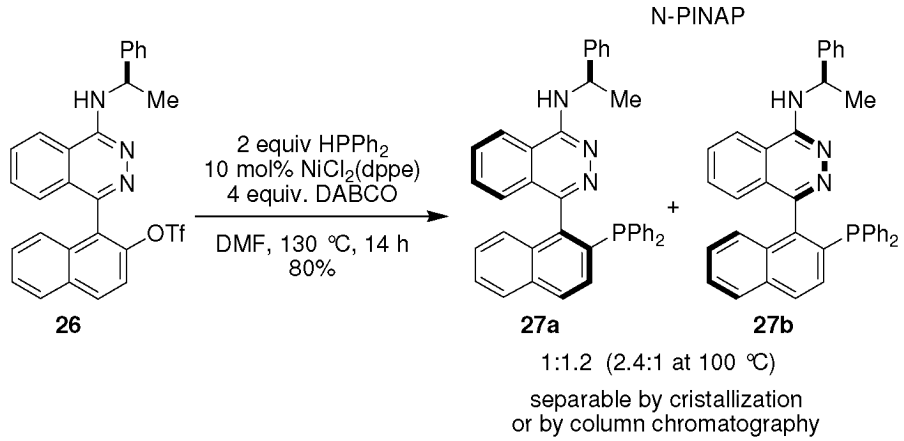
For the synthesis of the analogous ligand incorporating a chiral amine, naphthol **21** was first converted to the corresponding triflate (Scheme 17). Heating the triflate **25** in 5 equivalents (*R*) α-phenethylamine at 120 °C afforded compound **26** in 93% yield.

Scheme 17



In the final phosphination the ratio of diastereomers could be tuned by the reaction temperature (Equation 7). Separation of the two diastereomers was possible either by chromatography on silica gel or by crystallization. These ligands were termed N-PINAP. Unambiguous stereochemical assignment was achieved by X-ray crystallography for both O-PINAP and N-PINAP.

Equation 7

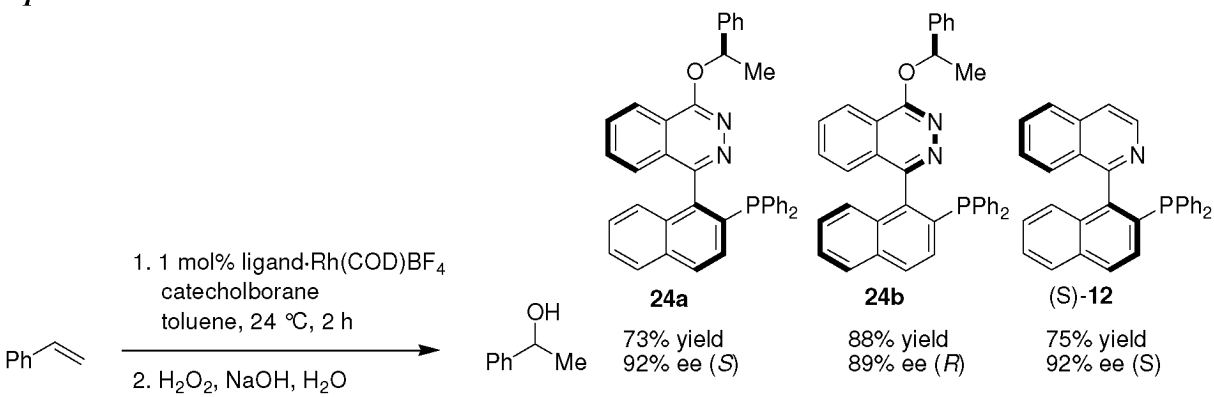


The synthesis of PINAP ligands is shorter than the synthesis of QUINAP. Furthermore, the additional stereogenic center in PINAP makes it possible to separate the two diastereomers by chromatography or crystallization, whereas in the resolution of QUINAP a chiral palladium complex needs to be employed.

1.1.4.2 Applications of PINAP

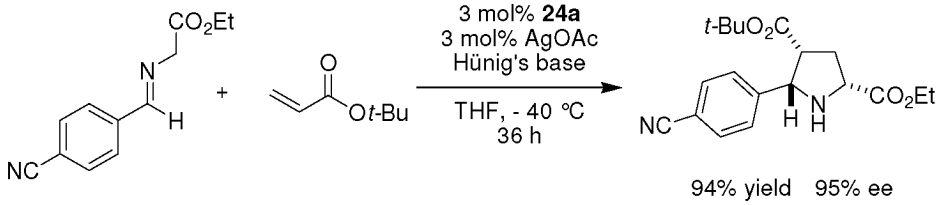
To demonstrate the utility of these new classes of ligands, they were tested in reactions that were known to give good enantioselectivities employing QUINAP as ligand.[47] In the Rh-catalyzed hydroboration of styrene derivatives O-PINAP gave similar results as QUINAP, except that the enantiomeric excess using **24a** was higher for *para*-substiteted styrenes. The axial chirality of the ligand determined the absolute configuration of the product; the second chiral center had little influence. Thus, compound **24a** furnished the product in 73% yield and 92% ee, whereas its diastereomer **24b** gave 88% yield and 89% ee (Equation 8).

Equation 8



In the Ag-catalyzed azomethine cycloaddition ligand **24a** also furnished comparable results to QUINAP. At –40 °C using 3 mol% of both AgOAc and O-PINAP **24a**, pyrrolidines were formed in 95% ee and 94% yield (Equation 9). Again, the diastereomer **24b** gave a similar result, namely 94% ee with the opposite absolute configuration.

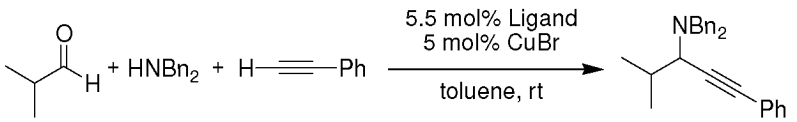
Equation 9

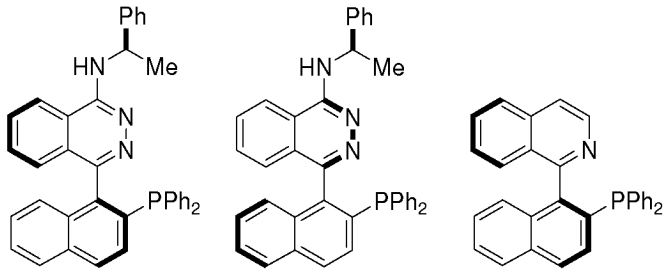


94% yield 95% ee
(QUINAP: 96% ee)

In the addition of copper alkynylides to imines (Equation 10), N-PINAP performed superior to QUINAP. The propargylic amines were formed in 90-99% ee, in 74-88% yields. The two diastereomers give similar enantioselectivity.

Equation 10





27a
88% yield
90% ee (*R*)

27b
82% yield
95% ee (*S*)

(S)-**12**
60% yield
84% ee (*R*)

Interestingly, in this reaction the diastereomer bearing the (*R*,*M*) configuration gives consistently higher ee`s than the (*R*,*P*)-configured N-PINAP. This result contrasts to the two reactions discussed above, where the (*R*,*P*) configuration gave the higher enantiomeric excesses. However, the axial chirality of the ligand always dictates the stereochemical outcome of the

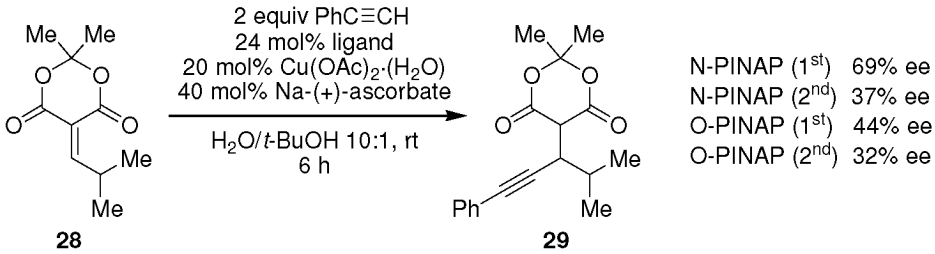
reaction; the stereogenic center has only little effect. In general the performance of the PINAP ligands is similar to QUINAP.

1.2 Results

1.2.1 Synthesis of PINAP Analogues

As mentioned before, *Knöpfel* in the *Carreira* group developed the PINAP ligand class while studying the conjugate addition of copper alkynylides to *Meldrum's* acid derived acceptors. Initial results were promising; N-PINAP gave ee`s of 69 % (1st diastereomer) and 37 % (2nd diastereomer) whereas O-PINAP gave similar results as QUINAP, 44 % (1st diastereomer) and 32 % (2nd diastereomer) for the O-PINAP diastereomers compared with 42% for QUINAP (Equation 11).[48]

Equation 11

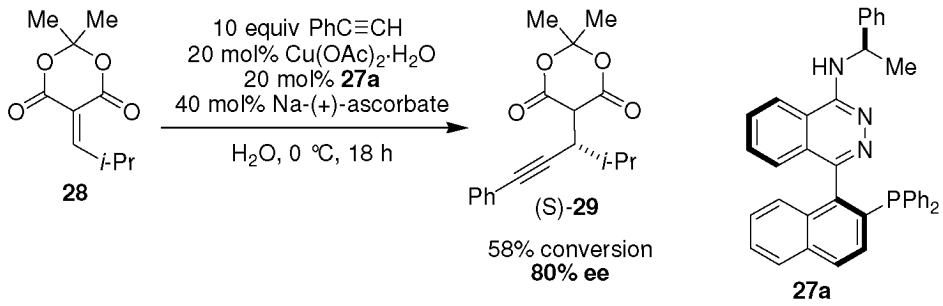


To further improve the enantiomeric excess the reaction was performed at 0 °C. Stirring the heterogeneous reaction mixture was difficult; therefore the amount of phenylacetylene was increased from 2 to 10 equivalents. Additionally, a copper/ligand ratio of 1:1 proved to be optimal. Thus, 20 mol% $Cu(OAc)_2 \cdot H_2O$ was dissolved in a minimal amount of water and then reduced in situ by Na-(+)-ascorbate, treated with ligand **27a** and 10 mol% of phenylacetylene and cooled to 0 °C.[49] To this suspension the acceptor **28** was added and the reaction was stirred for 18 h, furnishing the corresponding adduct **29** in 58% conversion and 80% ee (Equation 12).

[48] The enantiomeric excess was always determined by chiral HPLC of the corresponding anilide after decarboxylation in DMF/aniline at 100 °C.

[49] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

Equation 12

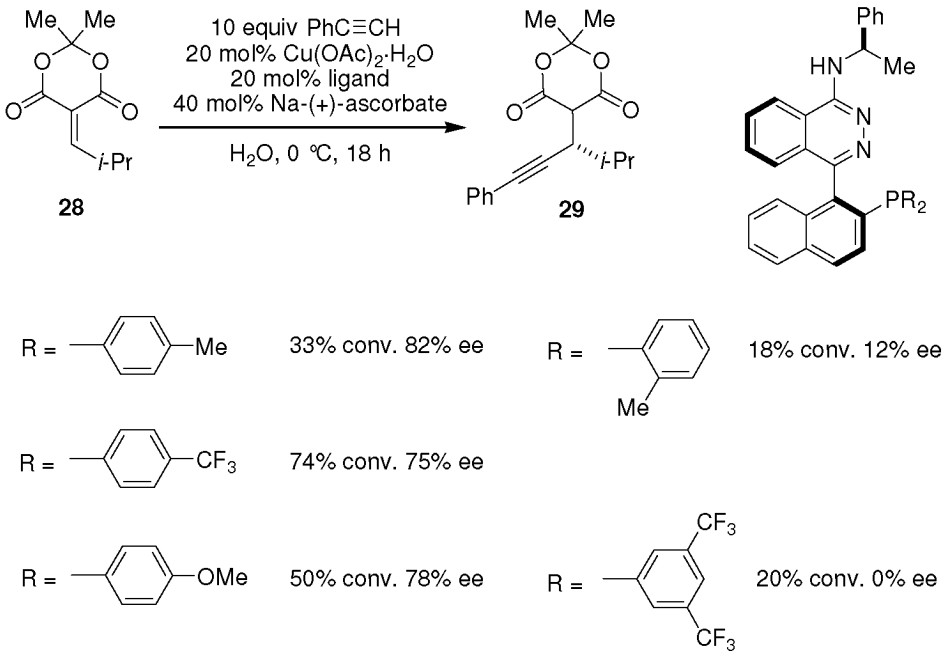


With the aim to further increase the enantioselectivity in the conjugate addition the reaction was cooled to temperatures below 0 °C. Performing the reaction at -5 °C resulted in the formation of a suspension and no conversion to product could be obtained any more. Since water is essential for this reaction to generate the reactive copper (I) species the reaction could not be run below 0 °C. Addition of cosolvents let always to a diminished yield. Therefore we decided to attempt modification of the ligand structure for further improvement in the enantiomeric excess of the conjugate addition reaction.

1.2.2 Modifications of the Phosphine

In the synthesis of the PINAP ligands, phosphination is the last step. Therefore modifications on the phosphine are accessible in a short way. *Ichikawa* in the *Carreira* group prepared some N-PINAP ligands bearing different phosphines and tested them in the conjugate addition reaction using the standard conditions (*Scheme 18*).

Scheme 18

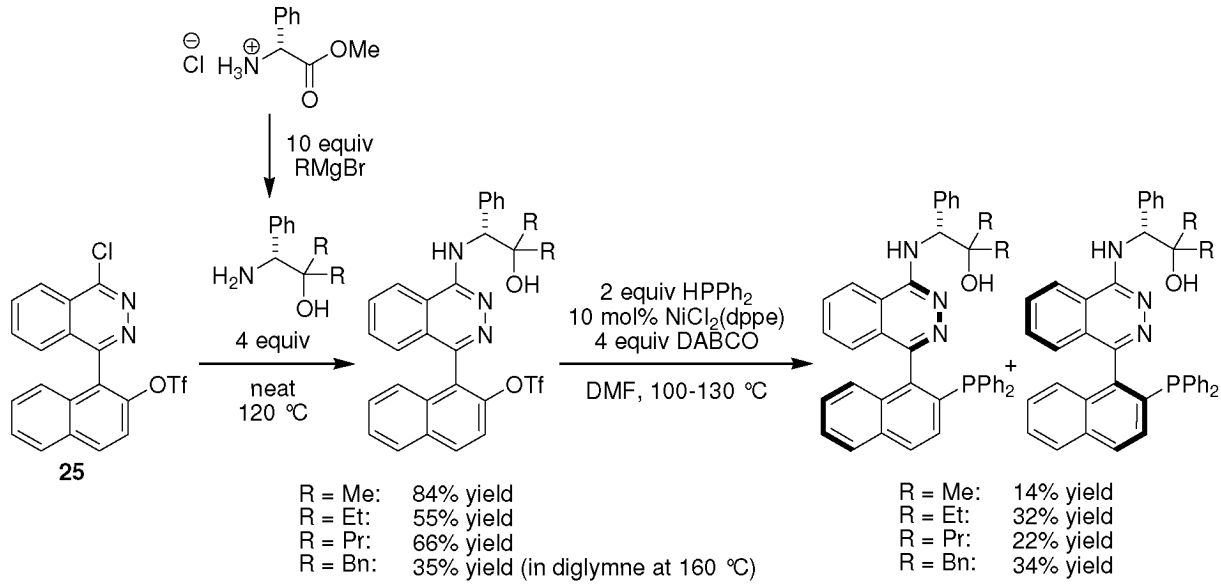


The *p*-tolyl substituted phosphine showed a slight increase in enantiomeric excess of the addition, but also a diminished yield. Other electron-withdrawing or electron-donating substituents on the phenyl showed no advantage over diphenylphosphine. Therefore we focused on modifications to other sections of the PINAP skeleton.

1.2.3 Modifications of the Amine

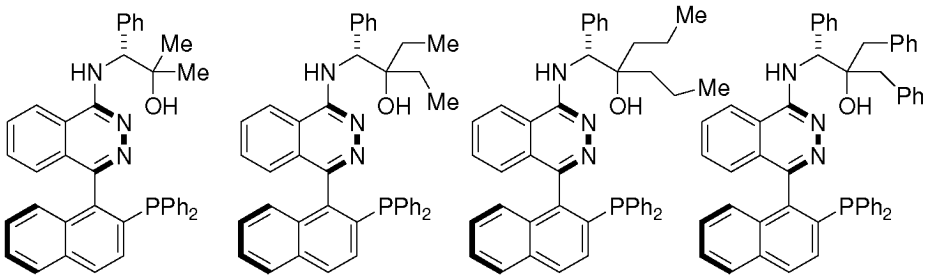
As mentioned before (Section 1.1.4.2), the two diastereomers of PINAP provided similar selectivity in the Rh-catalyzed hydroboration of styrene derivatives, the Ag-catalyzed azomethine cycloaddition and the Cu-catalyzed addition of alkynes to imines. In all cases, the sense of asymmetric induction was determined by the chirality of the biaryl. We were surprised; therefore, to find that in the Cu-catalyzed addition of phenylacetylene to acceptor **28**, the diastereomers displayed different selectivities (Equation 11). We reasoned that the chiral amino group plays an important role in determining the enantioselectivity. If that was true, then variation of the amine could lead to enhanced enantioselectivity. *Ichikawa* in the *Carreira* group synthesized some different amines by double addition of Grignard reagents to the inexpensive phenylglycine methyl ester hydrochloride (Scheme 19).

Scheme 19



Amination of compound **25** at 120 °C in a neat reaction gave the products in 35-84% yield.[50] Subsequent Ni-catalyzed phosphination furnished the desired ligands in unoptimized 14-34% yield. Separation of the diastereomers by flash chromatography was possible for all ligands. To test the ligands the standard conditions outlined in Scheme 20 were applied.

Scheme 20 *Performance of N-Modified PINAP Ligands in the Conjugate Addition* (Equation 12)



Indeed, the sterically more demanding ligands **30-33**, with sterically more demanding amino groups than in **26**, proved to provide better enantioselectivities than **26**. Diethyl derivative

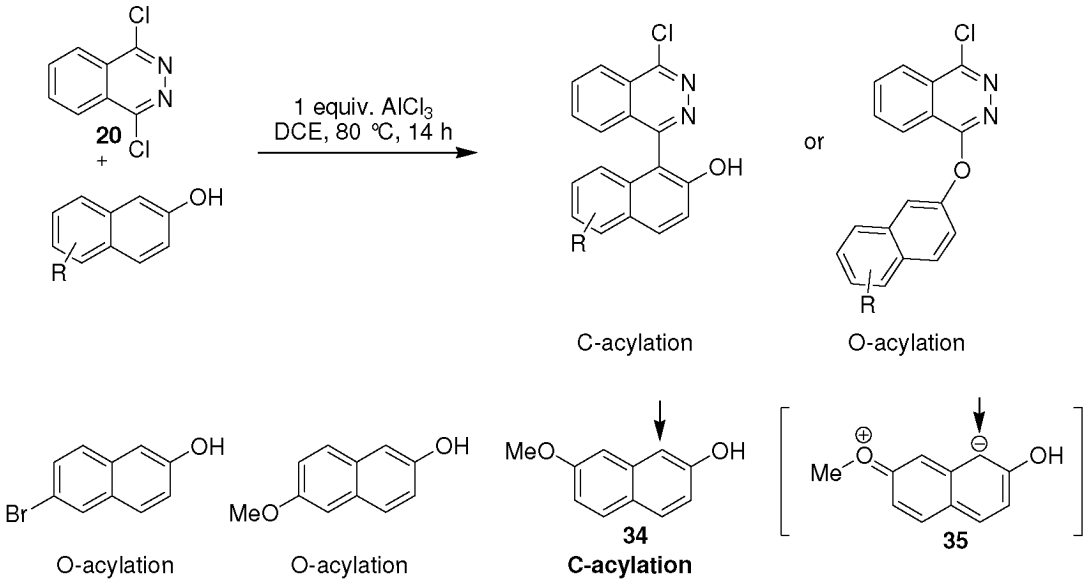
[50] The coupling with 2-((*R*)-amino(phenyl)methyl)-1,3-diphenylpropan-2-ol (R = Bn) was performed at 160 °C in diglyme.

31a proved to be optimal for stereoinduction, furnishing adduct **29** in 94% ee, although the yield dropped to 40%. Bulkier amines such as compounds **32a** and **33a** showed a slightly decreased selectivity compared to **30a**. Also, the less bulky dimethyl derivative **30a** (86% ee) was less selective. Having identified a ligand (**31a**) which furnished the desired product in high enantiomeric excess, we next turned our attention to the improvement of the reaction rate.

1.2.4 Modifications of the Naphthol

Having identified a chiral framework capable of inducing high enantiomeric excess, we next decided to modify the backbone of the ligand. With this in mind, we coupled various substituted naphthols to dichlorophthalazine (**20**, Scheme 21). Addition of 1 equivalent of a substituted naphthalene-2-ol to a solution of 1 equivalent $AlCl_3$ and 1 equivalent dichlorophthalazine **20** in 1,2-dichloroethane at 80 °C afforded the coupling product. We found that electron deficient β-naphthols underwent O-acylation instead of C-acylation. Only 7-methoxynaphthalen-2-ol (**34**) underwent the desired C-acylation, because it can activate the naphthol towards C-acylation as a π donor (see structure **35**).[51]

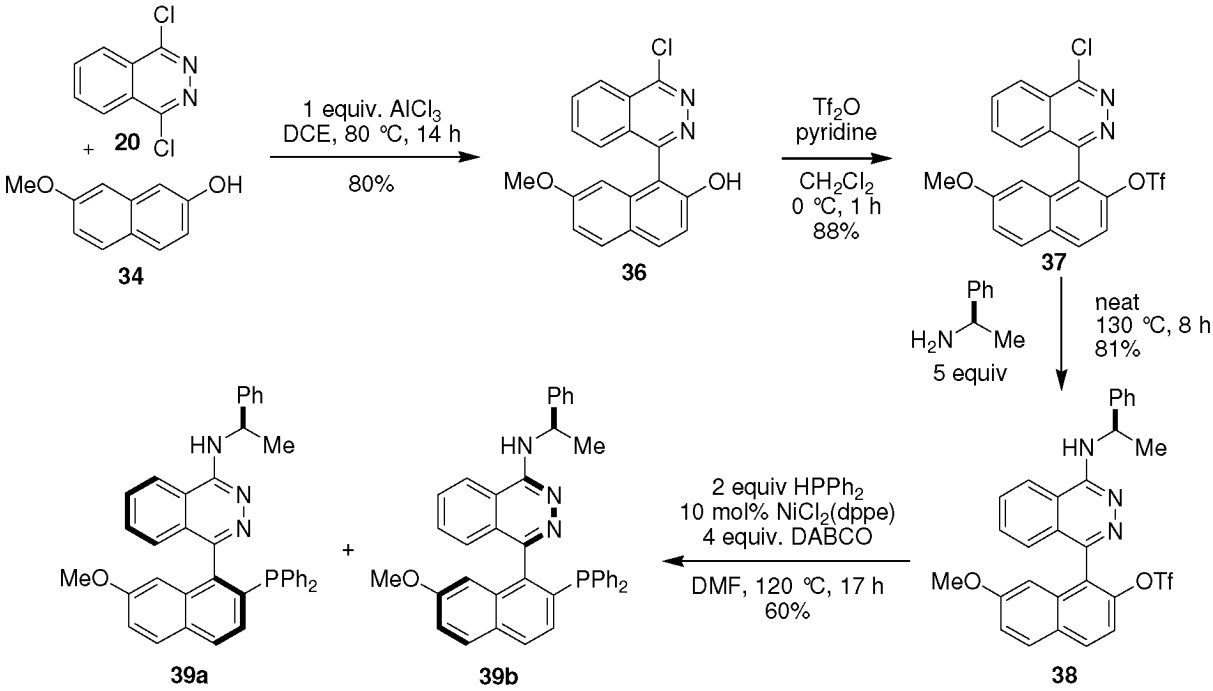
Scheme 21



[51] Davis, H. M. L.; Gilliatt, V.; Kuhn, L. A.; Saikali, E.; Ren, P.; Hammond, P, S.; Sexton, T.; Childers, S, R. *J. Med. Chem.* **2001**, *44*, 1509.

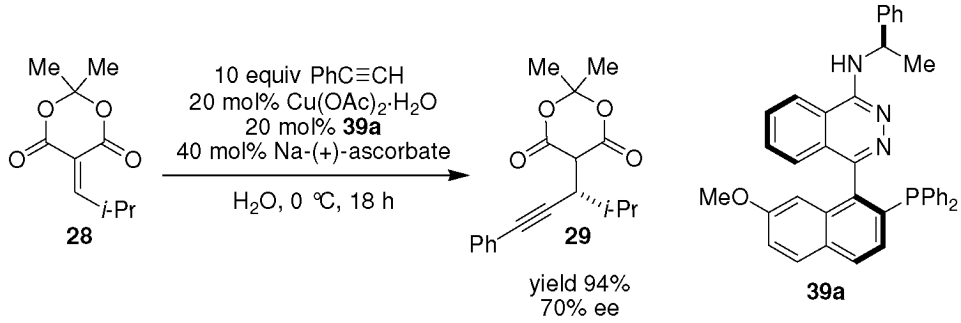
Friedel-Crafts acylation of 7-methoxynaphthalen-2-ol furnished product **36** in 80% yield. Reaction of naphthol **36** with triflic anhydride furnished the corresponding aryl triflate **37** in 88% yield. Subsequent amination with 5 equivalents of 3-((*R*)-aminophenyl-methyl)pentan-3-ol at 130 °C led to compound **38** in 81 % yield (Scheme 22).

Scheme 22



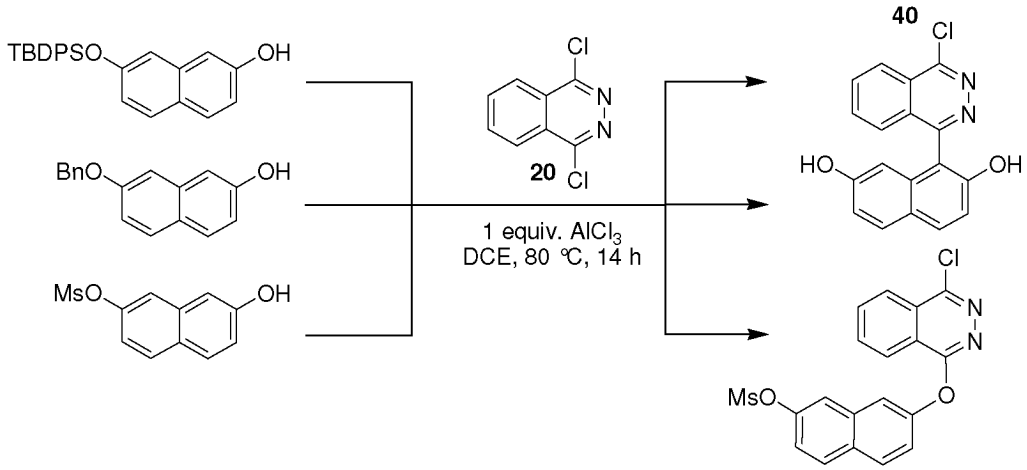
Finally, Ni-catalyzed phosphination provided ligand **39** in 60% yield. The two diastereomers of the ligand were then separated by column chromatography. Employing diastereomer **39a** in the standard test reaction, ie. 20 mol% copper and ligand with 10 equivalents of phenylacetylene in water at 0 °C, conjugate addition product **29** was isolated in 94% yield and 70% ee (Equation 13). This was by far the highest yield obtained so far, although the enantiomeric excess was a bit lower than that for ligand **27a**. Because the presence of the methoxy substituent had such a dramatic effect we wanted to explore the effect of other substituents at the same position.

Equation 13



Unfortunately, subjection of ligand **39** to BBr_3 with the interest of removing the methyl group to access the free naphthol led to decomposition of the ligand. Therefore, we started a new approach to the introduction of different functional groups (Scheme 23).

Scheme 23

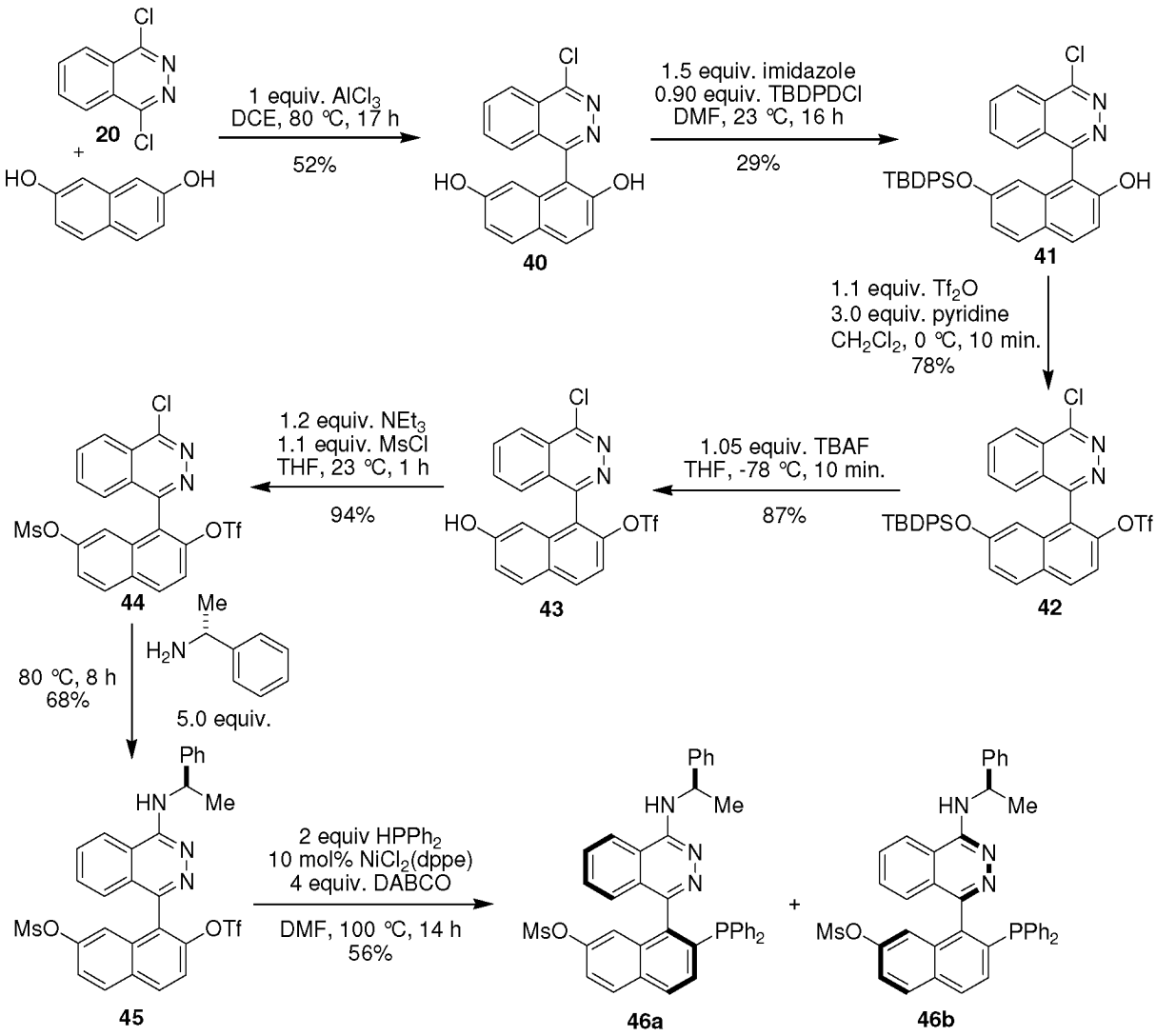


Finding a protecting group for 2,7-dihydroxynaphthalene that is stable to the *Friedel-Crafts* acylation conditions proved difficult. As seen before, the presence of an electron-withdrawing protecting group such as mesylate led to O-acylation. Silyl ether and benzyl protecting groups were cleaved during acylation. Therefore, we decided to perform acylation with 2,7-dihydroxynaphthalene first and then differentiate the two naphthol groups.

Coupling of 7-hydroxynaphthalene-2-ol with dichlorophthalazine in the presence of 1 equivalent of $AlCl_3$ in 1,2-dichloroethane at 80 °C furnished the desired product **40** in 52 % yield (Scheme 24). Attempted protection with 0.90 equivalent TBDPSCl was not regioselective,

furnishing a mixture of products which could be separated by column chromatography. Attempted protection with MsCl provided an inseparable mixture.

Scheme 24



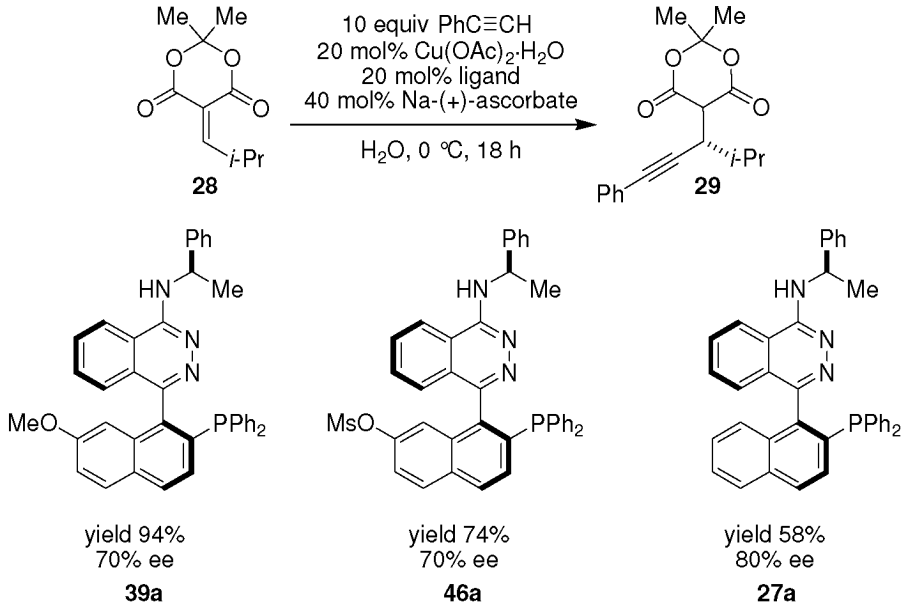
Treating naphthol **41** with 1.1 equivalent of triflic anhydride in the presence of 3 equivalent of pyridine compound **42** could be isolated in 78% yield. Subsequent deprotection and mesylation furnished compound **44** in 82% yield over two steps. Amination with 5 equivalents of 3-((*R*)-aminophenyl-methyl)pentan-3-ol at 80 °C led to precursor **45** in 64% yield. Ni-catalyzed phosphination furnished ligands **46a** and **46b,** which could be separated, in 56% combined yield.

Subjecting ligand **46a** to the standard test reaction the conjugate addition product was obtained in 74% yield and 70 % enantiomeric excess (Scheme 25).

In comparing the results obtained using ligands **27a**, **39a** and **46a**, no obvious trends are apparent (Scheme 25). The original ligand **27a** furnished the product in higher enantiomeric excess (80% ee) than the 7-methoxy (70% ee) and 7-methanesulfonate (70% ee) substituted ones. Since the same selectivity is observed employing the ligands with electron withdrawing substituents (compound **46a**) and electron donating substituents (compound **39a**), electronic factors should not play an important role. Although the substitution is distant from the chiral pocket it is still possible that steric repulsions can play a role in the transition state. Furthermore the difference in enantioselectivity is not so big, ie. 80% ee compared to 70% ee.

As already mentioned, the reaction is heterogeneous. However, the solubility of the ligand in phenylacetylene may still influence the outcome of the reaction. Therefore, the yields obtained in the conjugate addition reactions could be related to the solubility of the ligands employed. The additional polar substituent makes the ligands **39a** and **46a** more soluble in phenylacetylene than **27a** and thus the obtained yield is higher.

Scheme 25



1.2.5 Combination of the Best

To get good yield and high enantioselectivity, we next decided to synthesize a ligand that featured the best qualities of previously successful ligands **31** and **39**. Namely the high reactivity provided by ligand **39** and the high enantioselectivity provided by ligand **31**. Heating compound **37** with 5 equivalents of 3-((*R*)-aminophenyl-methyl)pentan-3-ol at 120 °C for 18 h furnished product **47** in 70% yield (Scheme 26). From here, Ni-catalyzed phosphination produced the two diastereomers **48a** and **48b** in a ratio of 1.5:1 which was determined by integration of the methoxy signals (δ 3.30 ppm for **48a**, respectively δ 3.50 ppm for **48b** in $CHCl_3$) in the 1H-NMR. The two diastereomers were separated by column chromatography or crystallization. The absolute configuration was determined by an X-ray of compound **48a** (Figure 3).

Scheme 26

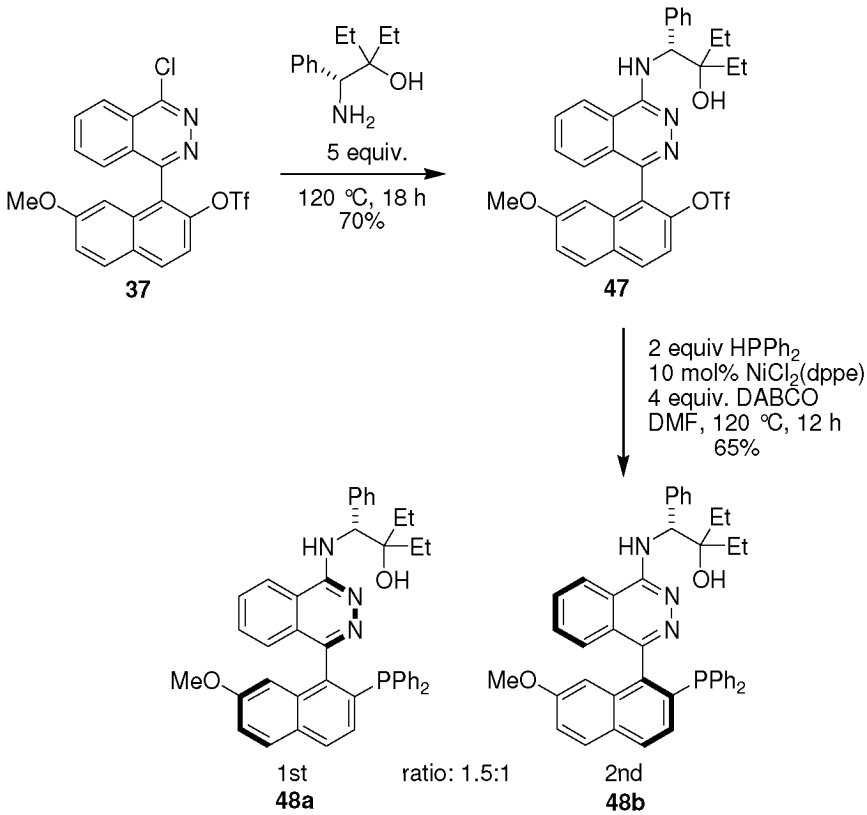
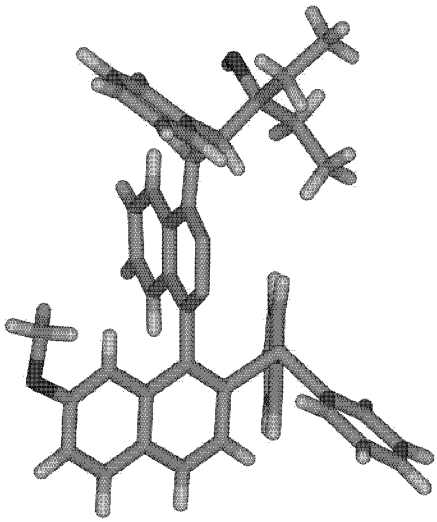
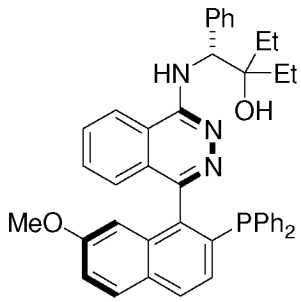


Figure 3 *X-ray structure of* ***48a***



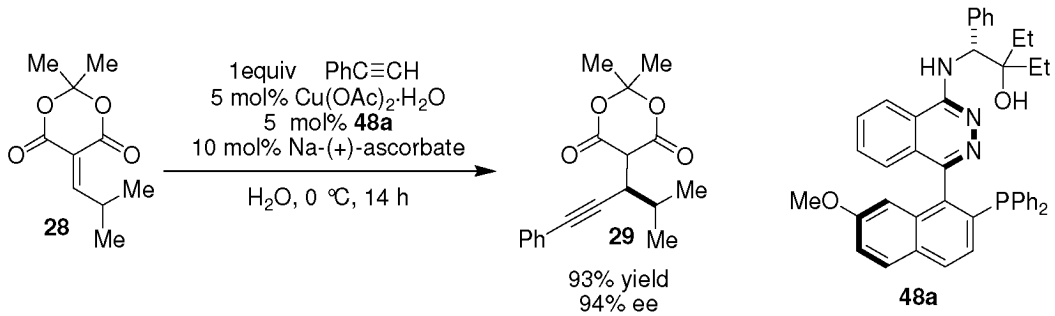


48a

Testing the diastereomer **48a** under standard conditions (Scheme 25) the corresponding product was isolated in 94% yield with an enantiomeric excess of 95%. Upon lowering the catalyst loading to 10%, we were pleased to find that the reactivity was still high, yielding 94% product with 95% ee (Scheme 27).

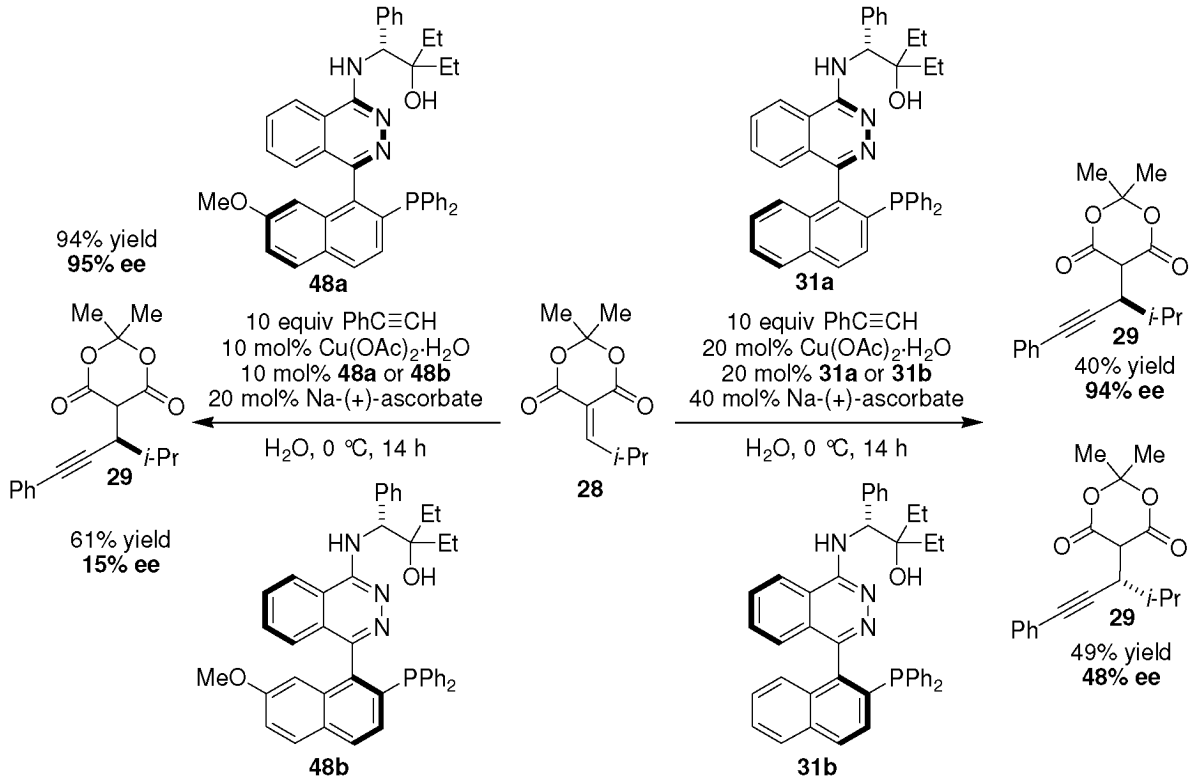
To ensure efficient stirring of the heterogeneous reaction mixture 10 equivalents phenylacetylene had to be used at a 0.25 mmol scale. It is likely that water just serves as the medium in which the reactive copper (I) species is generated and that the conjugate addition takes place in the organic layer, namely phenylacetylene. When the reaction was scaled up to 1.25 mmol and a catalyst loading of only 5 mol% was used the reaction could be performed employing only one equivalent of phenylacetylene, without a change in selectivity or yield (Equation 14).

Equation 14



In comparison, the use of ligand **31a**, which differs from ligand **48a** only in the absence of a 7-methoxy group, furnished the product in only 40% yield at a loading of 20 mol% (Scheme 27). Even more striking was the outcome of the conjugate addition when diastereomer **48b** was employed. In this reaction, the product was obtained in only 15% ee and 61% yield, with the same sense of enantiomeric induction. This means that in this case, the axial chirality no longer determines the absolute configuration of the product. Although the modification, ie. the additional methoxy group, is located in the naphthol part, the chirality of the amine becomes dominate over the axial chirality. Therefore it is likely that the additional 7-methoxy group is responsible for a major change in the active transition state in the conjugate addition reaction.

Scheme 27

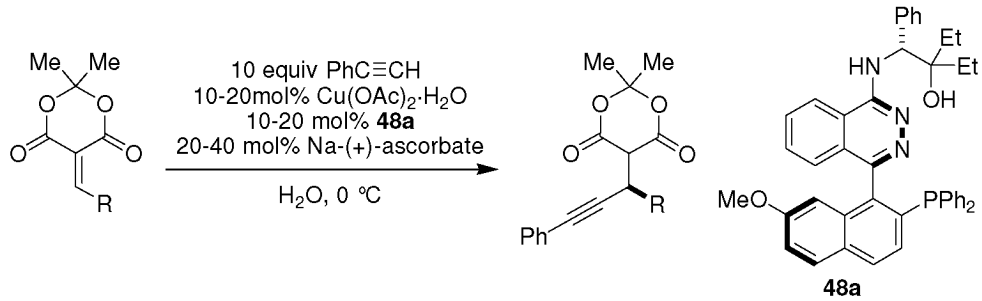


1.2.6 Scope of the Conjugate Addition Reaction Employing PINAP

The scope of the conjugate addition was examined next. Conjugate addition of phenylacetylene to γ-branched aliphatic acceptors could be conducted with 10 mol% catalyst (entries 1-3, Table 1). Performing the reaction with 10 equivalents phenylacetylene at 0 °C furnished good yields (79-94%) and excellent enantiomeric excesses (94-97%). Substrates

without γ-branching required the use of 20 mol% catalyst and provided the product in 83-85% yield and 82%-90% ee. Aromatic substituted acceptors required 20 mol% catalyst loading as well and furnished the corresponding adducts in 64-87% yield and 83-90% ee (entries 6 and 7). It is important to note that all the products are crystalline solids and therefore an increase in enantiomeric excess is possible by crystallization (entry 7).

Table 1



entry	acceptor (R)	t (h)	48a (mol%)	product	yield (%)[a]	ee (%)[b]
1	*i*-Pr	14	10	**29**	94	95
2	*c*-C_6H_{11}	14	10	**49**	81	94
3	*c*-Pr	51	10	**50**	79	97
4	*i*-Bu	24	20	**51**	85	90
5	Et	24	20	**52**	83	82
6	Ph	66	20	**53**	64	83
7	*m*-tol	66	20	**54**	83 (60)	90 (98)[c]

[a] Reactions were run on 0.25 mmol scale, except for entries 6 and 7 which were run at 0.50 mmol scale. [b] The enantioselectivity was determined by chiral HPLC analysis, after conversion of the product into the corresponding anilides by heating in aniline /DMF. [c] After one recrystallization from EtOAc.

As already mentioned the two diastereomers **48a** and **48b** can be separated either by chromatography on silica gel or by crystallization. Employing either the amorphous or the crystalline ligand in the conjugate addition of phenylacetylene to aliphatic acceptors, consistent enantioselectivities and yields were always obtained. This was not the case when aromatic acceptors were employed. In this, lower ee`s were obtained when diastereomer **48a** was purified

by crystallization from toluene/hexane. Dissolving this crystalline ligand and passing it through a plug of silica gel afforded an amorphous solid that gave consistent results.

For the three compounds **49**, **29**[52] and **53**[52] the absolute configuration was determined. Compound **55** was obtained in 92% yield by heating the conjugate addition product **49** with 2.0 equivalents of 4-bromoaniline in DMF (Equation 15). Recrystallization from hexane/toluene afforded crystals suitable for X-ray (Figure 4). The crystal structure proved the absolute configuration to be *S*.[53]

Equation 15

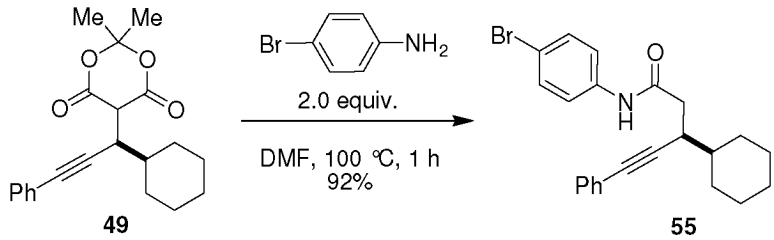
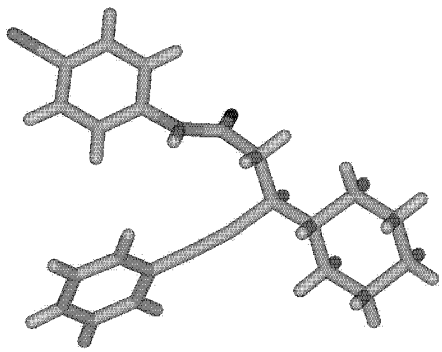


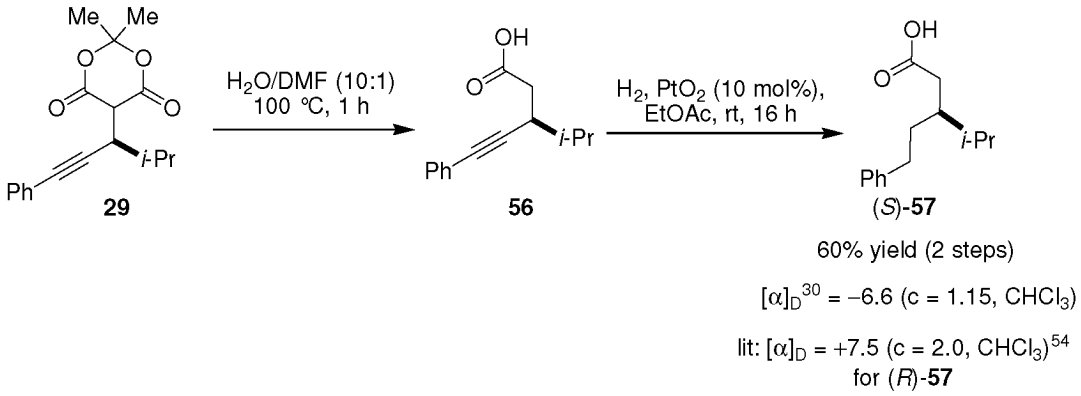
Figure 4 *Crystal structure of compound* ***55***



Compound **29** was decarboxylated in DMF/H_2O at 100 °C to the corresponding acid **56** and subsequently reduced with H_2 and 10 mol% PtO_2 in EtOAc at room temperature to afford acid **57** in 60% yield over two steps (Equation 16). The optical rotation of compound **57** ($[\alpha]_D^{30}$ = -6.6 (c=1.15, $CHCl_3$)) was compared to the value reported in the literature ($[\alpha]_D^{30}$ = 7.5 (c=1.15, $CHCl_3$) for (*R*)-**57**).[54] Therefore the absolute configuration was established to be *S*.

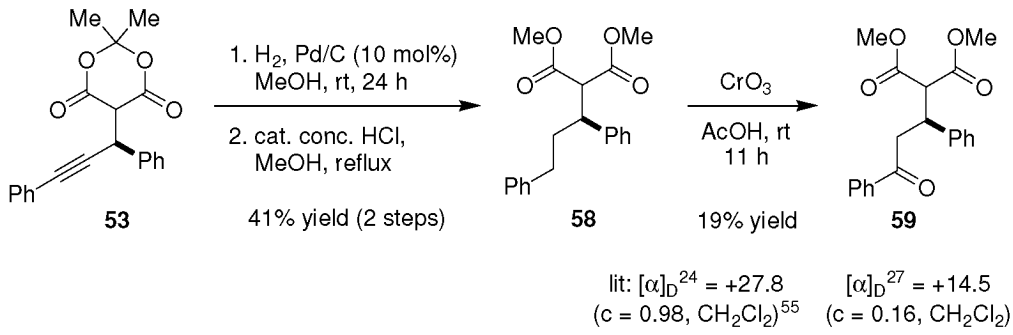
[52] Work of T. Knöpfel
[53] Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682.
[54] Nelson, S. G.; Wan, Z.; Stan, M. A. *J. Org. Chem.* **2002**, *67*, 4680

Equation 16



Reduction of the alkyne in adduct **53** to the alkane with H_2 and 10 mol% palladium on charcoal followed by transesterification with MeOH gave malonate **58** in 41% yield over two steps (Equation 17). CrO_3 mediated benzylic oxidation furnished the known compound **59** in 19% yield. The optical rotation of compound **59** ($[\alpha]_D^{27}$ = +14.5 (c=0.16, CH_2Cl_2)) was compared to the value ($[\alpha]_D^{24}$ = +27.8 (c=0.98, CH_2Cl_2) for (*S*)-**59**) reported in the literature.[55] Therefore the absolute configuration was established to be *S*.

Equation 17

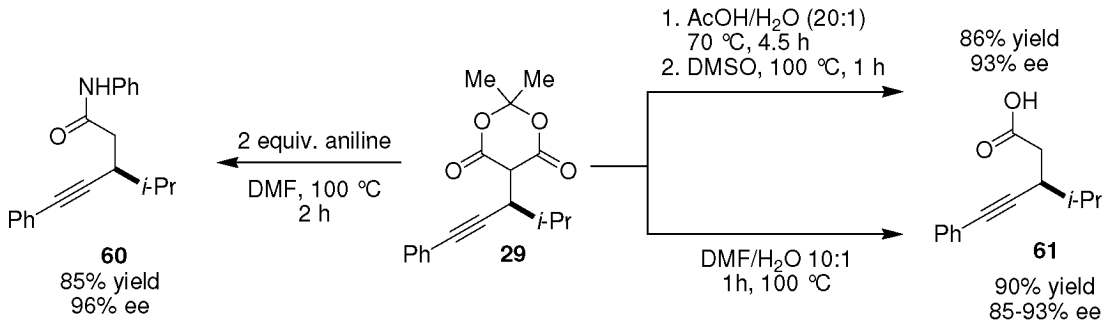


As mentioned above, the ee of the conjugate addition products were determined after conversion to the corresponding anilide. In fact, this chiral anilide can be a useful building block for natural product synthesis. In an optimized procedure compound **29** was heated in DMF at 100 °C with 2 equivalents of aniline for 2 h to furnish anilide **60** in 85% yield and 95% ee

[55] Hiroaki, S.; Arai,T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194

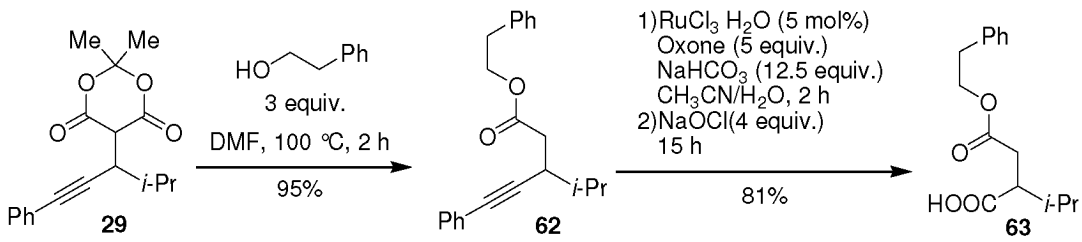
(Scheme 28). Similarly, the corresponding acid could be made, first hydrolysis of the acetal in AcOH/H_2O 20:1 at 70 °C furnished the dicarboxylic acid. Subsequent decarboxylation in DMSO at 100 °C provided acid **61** in 86% yield over two steps and 93% ee.[56] Heating compound **29** in DMF/H_2O 10:1 produced the corresponding acid **61** in good yields, but the enantiomeric excess ranged from 85-94%.

Scheme 28



As another example of derivatization of product **29**, *Fujimori* in the *Carreira* group decarboxylated compound **29** to the ester **62** by heating it in DMF in the presence of an alcohol (Scheme 29). Subsequent oxidative cleavage with 5 mol% $RuCl_3$ and oxone, followed by NaOCl furnished acid **63** in 81% yield over two steps. This product could be a useful building block, since the acid and ester allow numerous further elaborations like reduction, transesterification or condensation to amides.

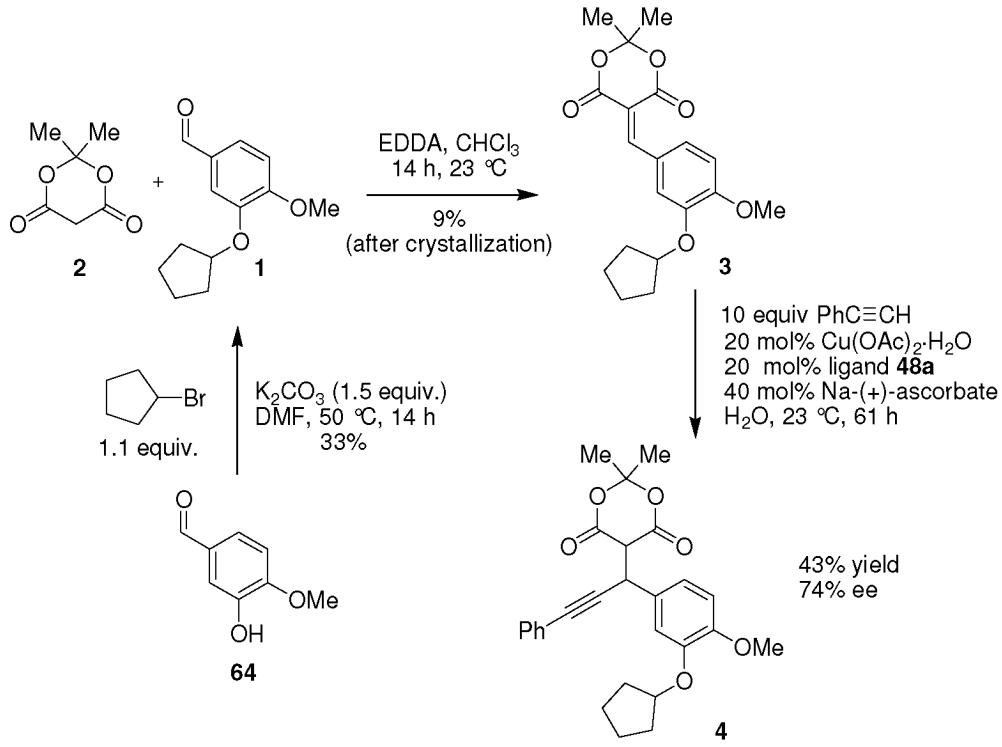
Scheme 29



[56] The enantiomeric excess was determined after conversion to the corresponding methyl ester with diazomethane.

Finally, the reaction conditions for the conjugate addition to the acceptor **3** described in Section 1.1.1.1 were optimized. As mentioned there, over 200 derivatives of this compound were prepared and tested for activity as TNF inhibitors.[6] Alkylation of commercially available phenol **64** with cyclopentyl bromide in DMF furnished aldehyde **1** in 33% yield (Scheme 30).[57] Condensation of aldehyde **1** with *Meldrum`s* acid (**2**) afforded **3** which could be purified by crystallization. At 0 °C, the conjugate addition of phenylacetylene to **3** did not proceed, however upon warming to room temperature the product **4** could be isolated in 43% yield and 74% ee after 61 h. The low conversion and extended reaction time was not surprising on the basis of our previous studies which indicated a marked decrease in reactivity of electron-rich acceptors.

Scheme 30

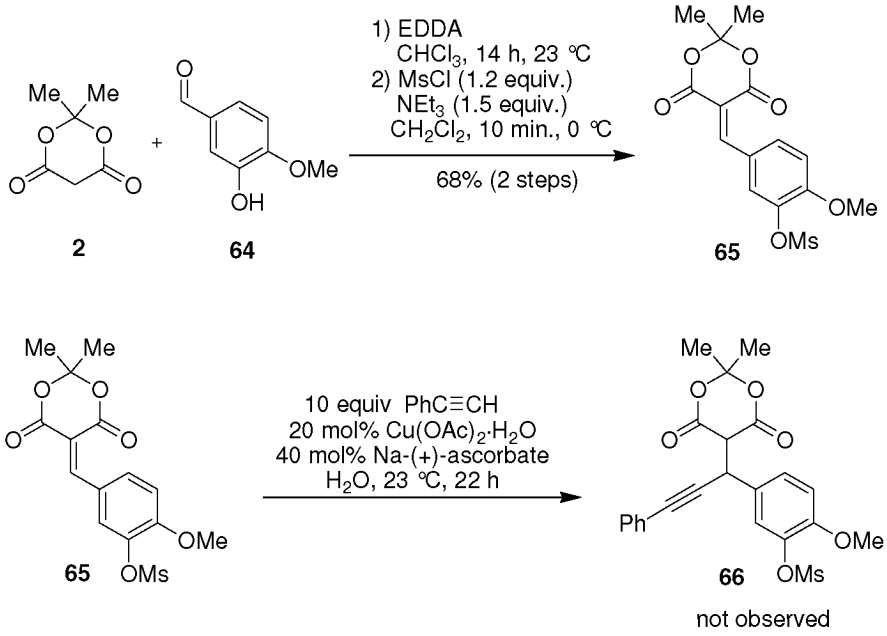


We believed that modification of the electronic properties of acceptor **3** could lead to improved reaction rate. Therefore we decided to use a protected version, replacing the cyclopropyl moiety with an electron withdrawing group. Previously in the group, it was shown that mesylates function as effective protecting groups for phenols and we reasoned that it might

[57] Unoptimized yield

electronically improve our acceptor.[58,59,60] Furthermore, this convergent approach would provide access to an advanced intermediate which would serve for subsequent diversification.[6]

Scheme 31



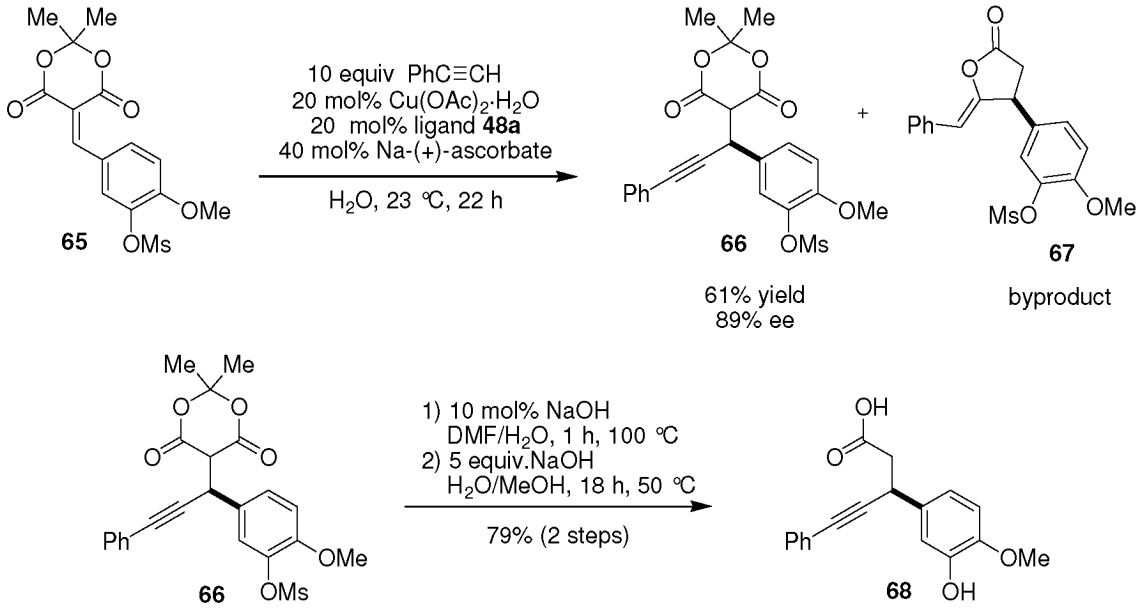
Knoevenagel condensation followed by mesylation of the phenol furnished acceptor **65** in 68% yield over two steps (Scheme 31). To test the reactivity of this new acceptor we first performed the addition without ligand. However, no conversion to the desired product was observed. In the conjugate addition of phenylacetylene to γ-branched aliphatic acceptors no background reaction could be detected at 0 °C. This suggests that the reaction is ligand accelerated and therefore we attempted the enantioselective addition anyway. Thus, in the presence of 20 mol% Cu-PINAP complex in 10 equivalent phenylacetylene at 23 °C, 75% conversion to the desired product **66** was observed after 22 h (Scheme 32). An unexpected byproduct **67** was observed in the conjugate addition at room temperature which resulted from cyclization, expulsion of acetone and decarboxylation. Our efforts to curtail this process by carrying out the conjugate addition at 0 °C resulted in less than 10% conversion. In addition, attempts to purify the mixture of **66** and **67** using SiO_2 chromatography resulted in decomposition.

---

[58] Ritter, T.; Stanek, K.; Larossa, I.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1513.
[59] Ritter, T.; Kvaerno, L.; Werder, M.; Hauser, H.; Carreira, E. M. *Organic and Biomolecular Chemistry* **2005**, *19*, 3514.
[60] Kvaerno, L.; Werder, M.; Hauser, H.; Carreira, E. M. *Journal of Medicinal Chemistry* **2005**, *19*, 6035.

However, crystallization of the crude from $CHCl_3$/hexane afforded **66** in 61% yield and 89% ee. Since the reaction was performed at 23 °C the ee was unexpectedly high, however chiral HPLC analysis of the crude mixture verified that the optical purity of the product was not enriched in the crystallization process.

Scheme 32

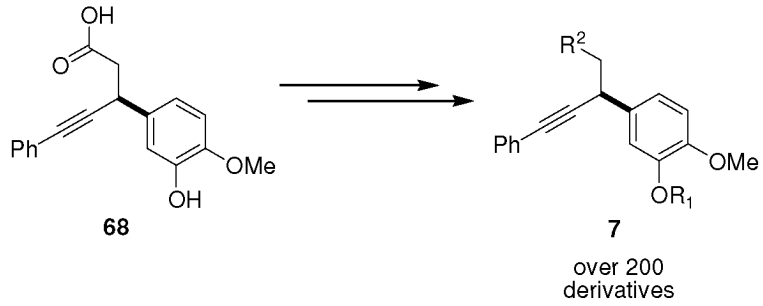


Decarboxylation and mesylate deprotection had to be carried out in two steps since a one-pot protocol where compound **66** was stirred in MeOH/H_2O with 5 equivalents of NaOH at 50 °C afforded several products. Decarboxylation (DMF/H_2O at 100 °C) also resulted in the formation of several compounds. However, decarboxylation in DMF/H_2O with 10 mol% NaOH and subsequent deprotection afforded compound **68** in 79% (2 steps).

The carboxylic acid and the phenol in compound **68** provide possible sites for further elaboration for the preparation of a structurally diverse library of derivatives. Over 200 derivatives of this compound are known and some of them are pharmacologically active as TNF inhibitors or GRP receptor antagonists (Figure 5). To obtain these active compounds the racemates had to be resolved by several crystallizations or by preparative chiral HPLC. To the

best of our knowledge, the enantioselective conjugate addition presented herein represents the only way to access these compounds in an enantiomerically enriched form.

Figure 5

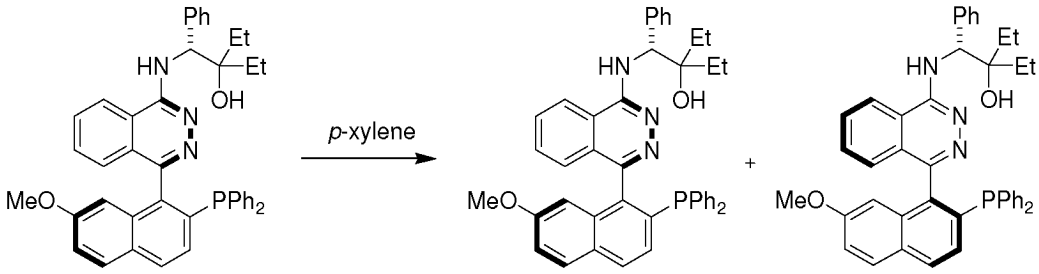


1.2.7 Determination of the Rotation Barrier of Ligand 48a

Biaryl structures analogous to QUINAP are known to undergo racemization at room temperature (Figure 2). Therefore we decided to determine the exact rotation barrier of compound **48a**. Thus, degassed *p*-xylene (5 ml) was placed in a two necked flask equipped with a reflux condenser. The flask was placed into a thermostat (Huber Polystat cc3) and heated. The temperatures (107.0 °C, 116.5 C°, 124.5 °C and 135.5 °C) were measured inside the flask by a digital thermometer (accuracy +/- 0.1 °C). When the temperature was constant, 20 mg (0.030 mmol) **48a** were added. After the indicated time aliquots (0.2 ml) were taken by syringe. The samples were concentrated at reduced pressure and dried in vacuo. The ratio of the diastereomers was determined by ^{1}H-NMR comparing the singlets of the methoxy group (1st diastereomer δ 3.30 ppm, 2nd diastereomer δ 3.50 ppm in $CHCl_3$, Figure 6). The rate constants for rotation, which correspond to the slopes in, were determined at 107.0, 116.5, 124.5 and 135.5 °C by plotting ln (de_0/de) against the time (Figure 7).[61]

[61] The rate law can be derived from: v = k_{epi}[**48a**]-k_{epi} [**48b**], which gives: ln (de_0/de) = k_{epi}t. The following assumption was made: the rate constants are the same for **48a** and **48b**.

Figure 6



48a **48a** **48b**

107.0 °C (380.2 K)

t (min)	**48a**	**48b**	de[a)]
0	100	0	100
60	95.0	5.0	90.0
124	92.4	7.6	84.8
183	89.3	10.7	78.6
245	85.9	14.1	71.8
303	84.0	16.0	68.0
362	81.6	18.4	63.2
425	79.2	20.8	58.4

k_{epi} (107.0 °C) = $2.14 \cdot 10^{-5}$ s^{-1}

116.5 °C (389.7 K)

t (min)	**48a**	**48b**	de[a)]
0	100	0	100
50	91.2	8.8	82.4
100	86.4	13.6	72.8
161	80.1	19.9	60.2
210	76.9	23.1	53.8
270	74.2	25.8	48.4
342	70.1	29.9	40.2
395	67.8	32.2	35.6

k_{epi} (116.5 °C) = $5.11 \cdot 10^{-5}$ s^{-1}

124.5 °C (397.7 K)

t (min)	**48a**	**48b**	de[a)]
0	100	0	100
30	91.0	9.0	82.0
60	83.9	16.1	67.8
120	74.0	26.0	48.0
180	67.0	33.0	34.0
240	63.1	36.9	26.2
300	60.0	40.0	20.0
360	58.2	41.8	16.4

k_{epi} (124.5 °C) = $9.71 \cdot 10^{-5}$ s^{-1}

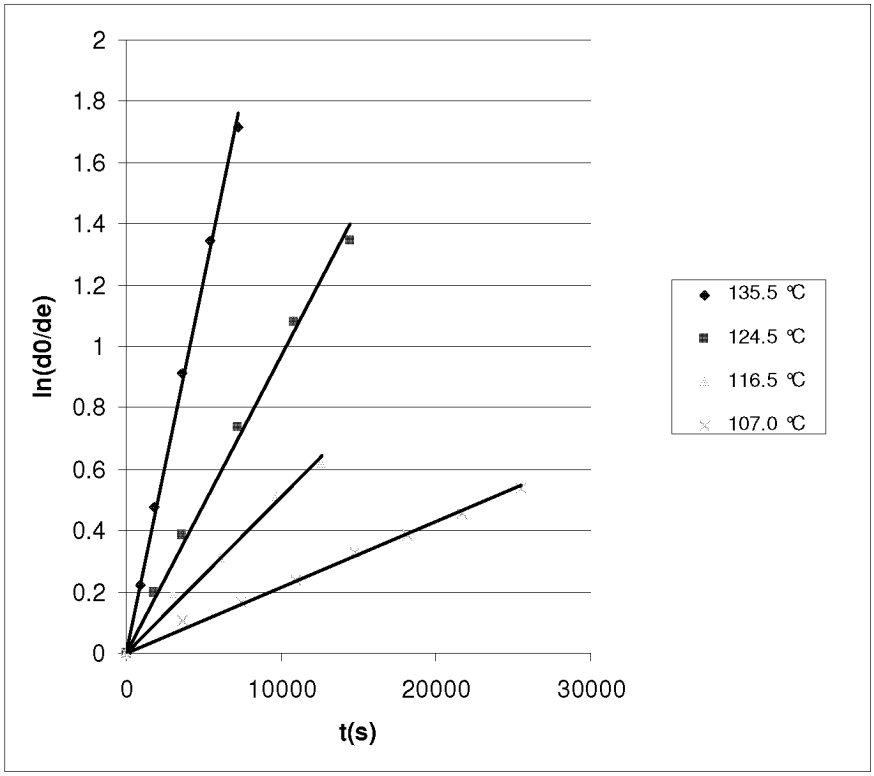
135.5 °C (408.7 K)

t (min)	**48a**	**48b**	de[a)]
0	100	0	100
15	90.1	9.9	80.2
30	81.0	19.0	62.0
60	68.8	31.2	37.6
90	63.0	37.0	26.0
120	59.0	41.0	18.0
150	57.1	42.9	14.2

k_{epi} (135.5 °C) = $2.45 \cdot 10^{-4}$ s^{-1}

[a)]The de was determined by ^{1}H-NMR comparing the singlets of the methoxy group:
(1st diastereomer δ 3.30 ppm, 2nd diastereomer δ 3.50 ppm in $CHCl_3$).

Figure 7 *Plot of ln(de_0/de) against the time at different temperatures for compound* ***48a***[a]



[a] in p-xylene

The rate constants of rotation, which correspond to the slopes in Figure 7, were determined at 107.0, 116.5, 124.5 and 135.5 °C by plotting ln (de_0/de) against the time (Figure 7). The slopes in Figure 7 correspond to the rate of axial epimerization (k_{epi}). The half-life of epimerization ($t_{1/2}$) can be calculated with the equation:

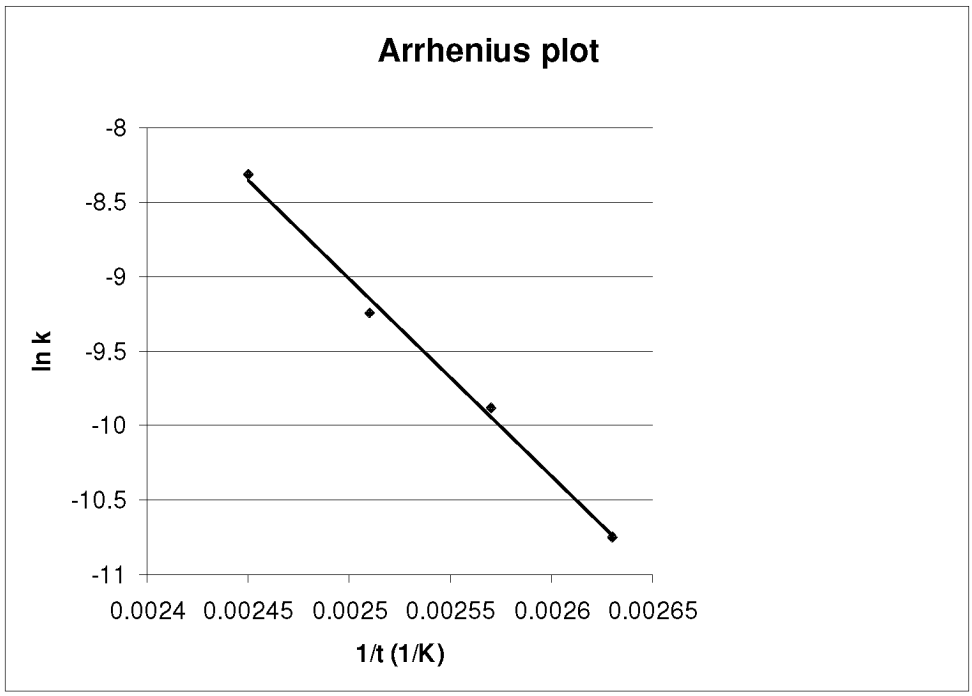
$$t_{1/2}(s) = (\ln 2)/(k_{epi})$$

Table 2 *Rate constants of epimerization of compound* ***48a*** *at different temperatures*

temperature[a)]	k_{epi}	$t_{1/2}$
107.0	$2.14 \cdot 10^{-5}$ s^{-1}	9.0 h
116.5	$5.11 \cdot 10^{-5}$ s^{-1}	3.8 h
124.5	$9.71 \cdot 10^{-5}$ s^{-1}	2.0 h
135.5	$2.45 \cdot 10^{-4}$ s^{-1}	0.8 h

a) in *p*-xylene

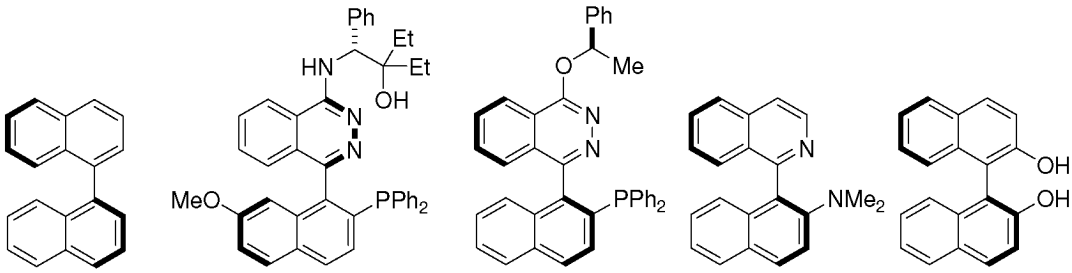
Figure 8 *Determination of the energy of activation* E_a *for the epimerization of* ***48a***



The energy of activation (E_a) for rotation about the biaryl bond in **48a** can be derived from an *Arrhenius* plot of ln k_{epi} vs. 1/T. The slope m in Figure 8 corresponds to $-E_a/R$.[62] Therefore E_A = –m*R furnishes the value for the energy of activation. For ligand **48a**, a value of 26.3 kcal/mol in *p*-xylene was found, which is very close to the value of O-PINAP (Figure 9). The calculated half life $t_{1/2}$ of **48a** at 65 °C is more than 25 days. Thus, no epimerization occurs under the reaction conditions fur Cu-catalyzed conjugate addition.

[62] R = 8.3145 J / molK

Figure 9



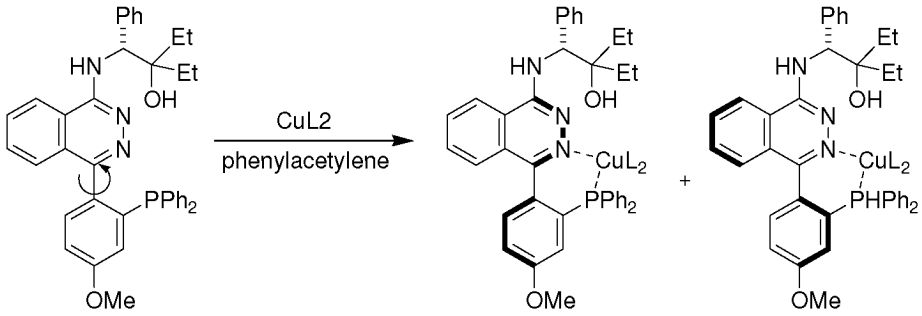
48a **24a**

$\Delta G^{\ddagger}$	24.1 kcal/mol	26.3 kcal/mol	27.6 kcal/mol	29.8 kcal/mol	37.2 kcal/mol
solvent	benzene	*p*-xylene	*p*-xylene	toluene	naphthalene

1.2.8 Is a Defined Axial Chirality Necessary ?

Since the axial chirality of ligand **48b** clearly does not determine the stereochemical outcome of the reaction when it was used in the conjugate addition reaction, we wondered if a ligand without defined axial chirality could also provide high stereoselectivity. When there is free rotation around the biaryl bond of the ligand no diastereomers would exist at room temperature. Only after the addition of copper, the bidentate ligand would form two diastereomers (Figure 10).

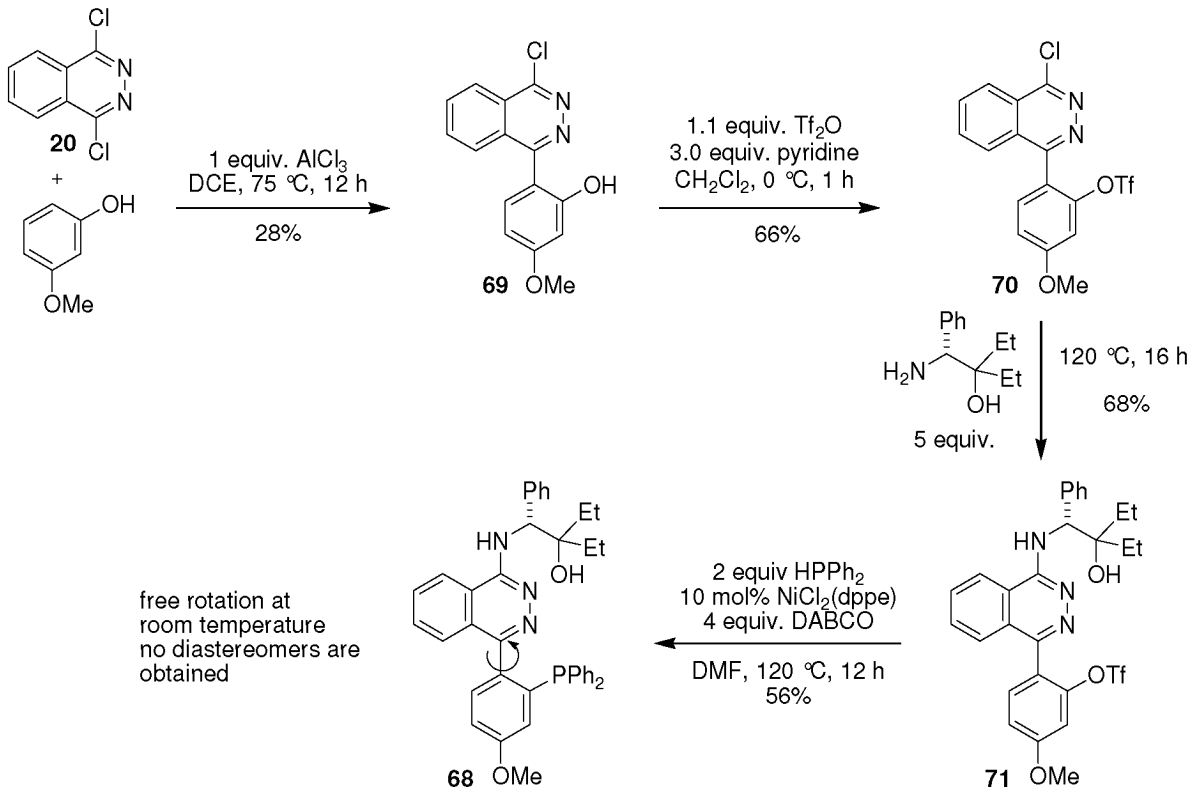
Figure 10



68

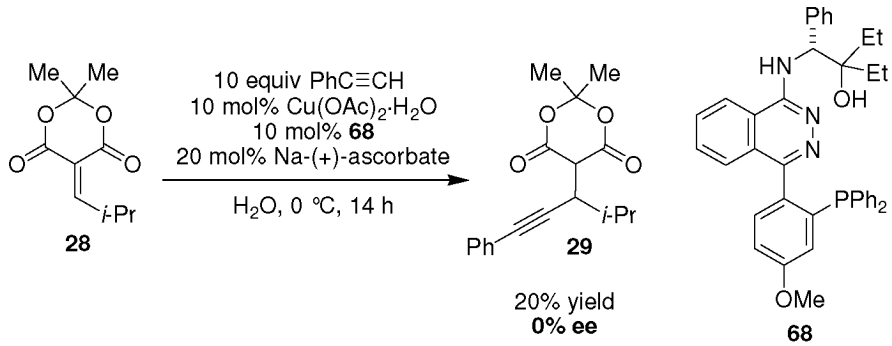
If one diastereomer would be more stable than the other, it would be possible that only one gets formed after the addition of copper. Therefore its employment in the conjugate addition reaction could result in high ee of the product with the benefit that no separation of diastereomers had to be carried out in the case of ligand preparation. To test this hypothesis *Waltman* in the *Carreira* group synthesized ligand **68**.

Scheme 33



Friedel-Crafts acylation proceeded in only 28% yield of the desired product because acylation *ortho* to the methoxy group was predominant. Reaction of phenol **69** with triflic anhydride in the presence of pyridine furnished compound **70** in 66% yield (Scheme 33). Heating compound **70** in 5 equivalents of 3-((*R*)-aminophenyl-methyl)pentan-3-ol at 120 °C for 16 h furnished product **71** in 68% yield. Ni-catalyzed phosphination of triflate **71** proceeded in 56% yield. Because there is free rotation around the biaryl bond at room temperature, compound **68** does not exist as a mixture of diastereomers; therefore only one compound was observed in the ^{1}H-NMR. Employing 10 mol% ligand **68** in the standard reaction the product was obtained in 20% yield as a racemate (Scheme 34). Since the background, ie. non-ligated, reaction is almost negligible under the conditions outlined in Scheme 34, ligand **68** has an accelerating effect on the conjugate addition reaction but in a non selective way. Therefore, the nature of the interaction between ligand **68** and the copper atom must be different than that of the original ligand **48a** and copper.

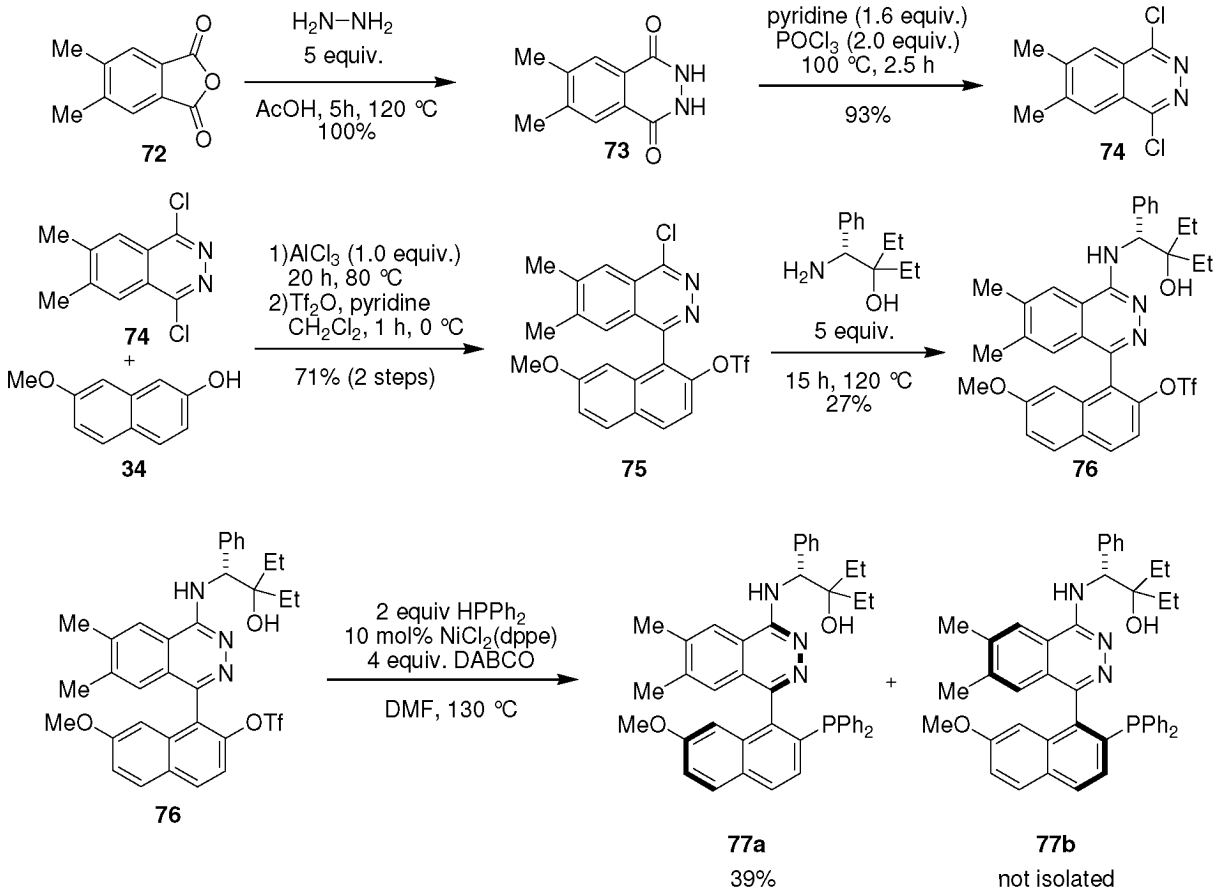
Scheme 34



1.2.9 Other Modifications

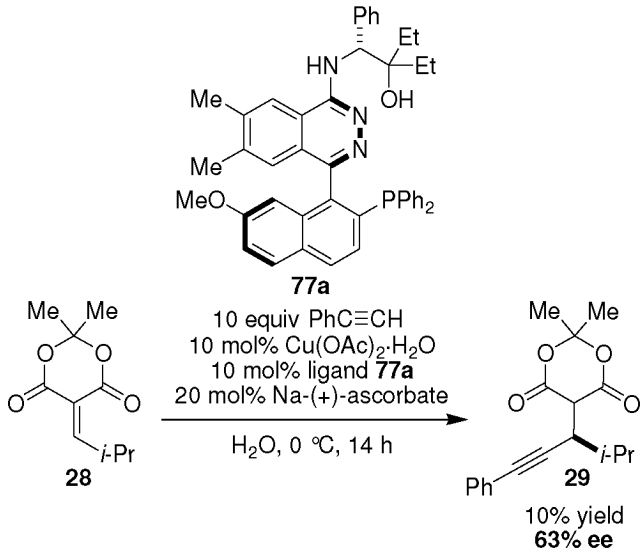
The last part of the PINAP framework to be modified was the phthalazine core. Again, since this modification is distant from the chiral pocket, we anticipated that this change would have larger effect on the rate of the conjugate addition than of the enantioselectivity. Thus, *Ogawa* in the *Carreira* group synthesized ligand **77a**. Dichlorophthalazine **74** was synthesized in 93% yield by reacting anhydride **72** with hydrazine, followed by chlorination with $POCl_3$. *Friedel-Crafts* acylation and subsequent reaction with triflic anhydride in the presence of pyridine furnished compound **75** in 71% yield over two steps. Amination with 5 equivalents 3-((*R*)-aminophenyl-methyl)pentan-3-ol at 120 °C proceeded in 27% yield. Ni-catalyzed phosphination furnished the two diastereomers **77** (Scheme 35).

Scheme 35



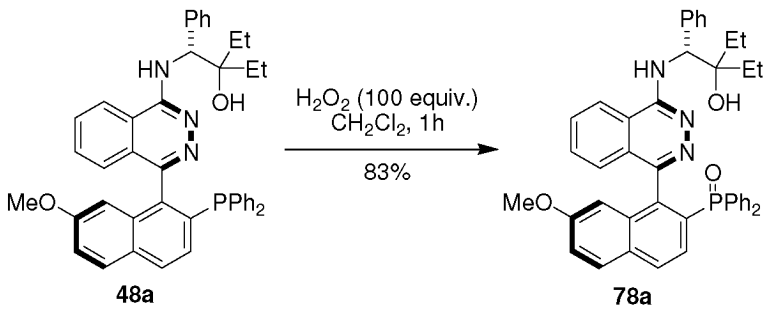
Employment of 10 mol% of the phthalazine-modified ligand **77a** in the standard conjugate addition reaction provided the product in only 10% yield and 63% ee (Scheme 36). The decrease in reactivity from 94% to only 10% yield due simply to the addition of two methyl groups to the phthalazine core is remarkable. A possible explanation is that ligand **77a** is less soluble than ligand **48a**. When ligand **77a** was stirred in 100 equivalents phenylacetylene, which corresponds to the ratio in the conjugate addition reaction, a suspension was obtained, whereas in the case of ligand **48a** a solution was obtained.

Scheme 36



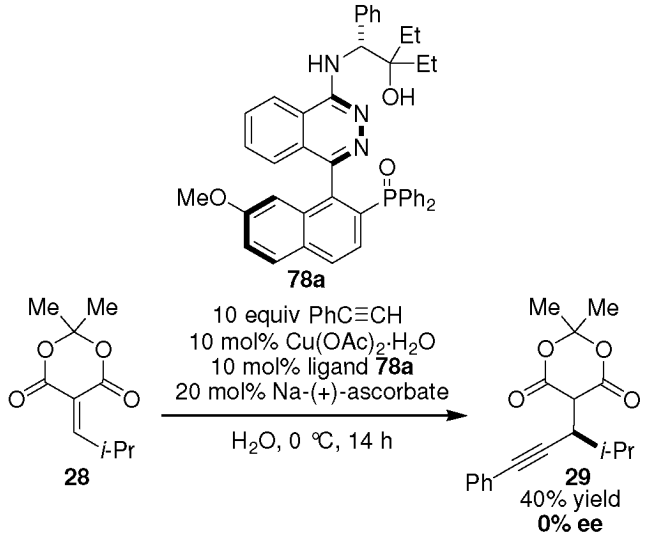
Another potential explanation for the behavior of the diastereomers of ligand **48** is that the phosphine does not bind to the metal. Instead, the alcohol and phthalazine moieties act as the donors. To test this we oxidized the phosphine, thus makes it unable to bind to copper (Equation 18). Treating diastereomer **48a** with H_2O_2 furnished the phosphine oxide **78a** in 83% yield.

Equation 18



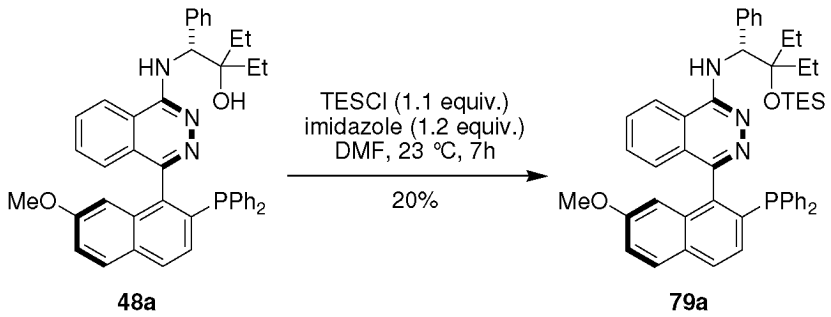
However, the fact that, racemic product is obtained in the conjugate addition with phosphine oxide **78a** as ligand suggests that the phosphine is crucial for selectivity in the reaction (Equation 19). Although the axial chirality does not always seem to determine the sense of chiral induction in the conjugate addition, the ligand does not serve only as an aminoalcohol.

Equation 19



We chose to protect the free hydroxyl group of ligand **48a** with TES to determine whether the hydroxyl group plays a role in selectivity, perhaps via coordination to copper. If this coordination does occur, protection of the alcohol with a bulky silyl ether would prevent this additional coordination. Thus treating ligand **48a** with TESCl furnished protected ligand **79a** in 20% yield (Equation 20). However, most of the unreacted ligand **48a** could be recovered.

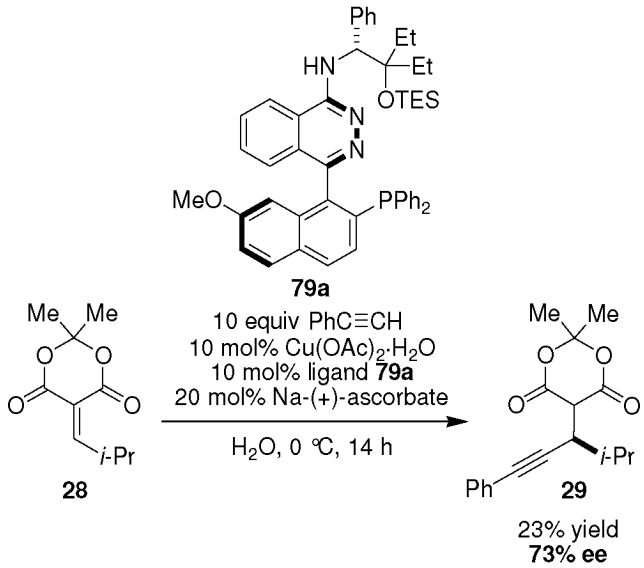
Equation 20



Indeed the selectivity decreased when silyl protected ligand **79a** was used in the conjugate addition (Equation 21). This suggests that the free hydroxy group may play a role in the determination of the enantioselectivity. More remarkable was the decrease in activity. The TES protected ligand **79a** furnished the product in the conjugate addition reaction in only 23% yield, comparing to 94% yield of the ligand **48a**. It is possible that the additional bulk of the protecting

group blocks' the chiral pocket and hinders substrate binding and therefore a diminished conversion is obtained.

Equation 21

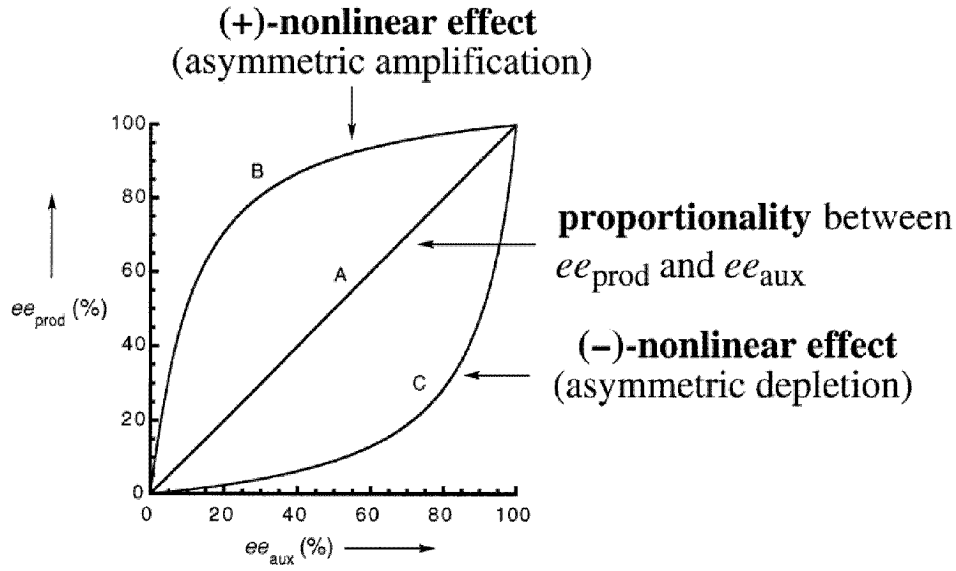


1.2.10 Observation of a Strong Nonlinear Effect

In 1986 *Kagan* discovered that in a metal catalyzed process involving the use of a chiral ligand the ee value of the ligand can deviate from the ee value of the product, a phenomena known as the nonlinear effect (NLE).[63] Nonlinear effects reflect the fact that molecular interactions can complicate the reaction mechanisms of asymmetric synthesis. A positive non linear effect can be used to generate products with high ee`s from enantiomerically impure, chiral auxiliaries or ligands which can be more economical to prepare (Figure 11). Furthermore, NLEs can also act as a probe to obtain information on the sometimes subtle mechanisms by which enantioselectivity is generated during catalysis.[64]

[63] Puchot, C.; Samuel, O.; Dunach,, E.; Zhao, S.; Agami, C.;Kagan, H. B.; *J. Am. Chem. Soc.* **1986**, *108*, 2353.
[64] Girart, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922.

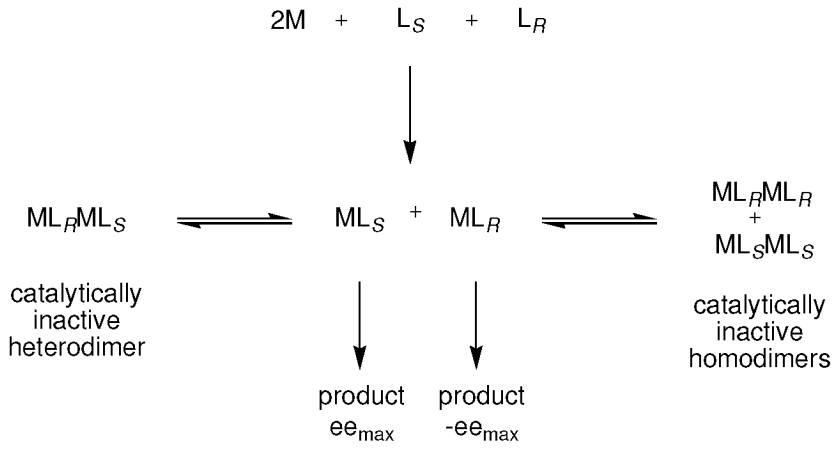
Figure 11 *(taken from reference [64])*



1.2.10.1 Models and Principles

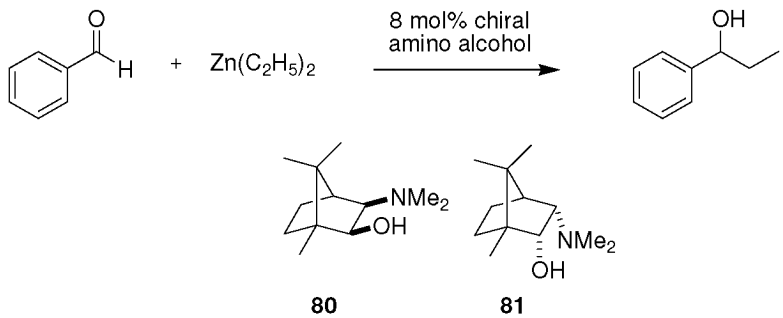
The model that explains most nonlinear effects is the so called *reservoir effect*. This postulates that several different metal-ligand complexes exist in equilibrium in solution, and that not all of them are active in the catalytic cycle.[64] Therefore an impurity, namely the other enantiomer of the ligand, may be stored in the reservoir as a non reactive complex. For instance, it is reasonable that the heterodimer and the homodimer of a metal/ligand complex have different thermodynamic stabilities, since the heterodimer has a diastereomeric relationship to the homodimer. If the heterodimer is thermodynamically more stable than the homodimer a positive nonlinear effect is observed. The heterodimer takes up the less abundant enantiomer of ligand leaving the excess of the more abundant ligand to afford catalysis (Figure 12).

Figure 12 *Modell for the reservoir effect*



In 1995 *Noyori* reported the only nonlinear effect in catalysis with a diastereomeric mixture of ligands so far observed. [65] During extensive studies in the amino-alcohol promoted enantioselective addition of dialky zincs to aldehydes, the two diastereomers **80** and **81** of dimethylaminoisoborneol were mixed to study the nonlinear effects (Equation 22).

Equation 22



Catalysis using diastereomer **80** gave the product in 98% ee, whereas the use of diastereomer **81** furnished the alcohol in 94% ee in the opposite configuration. A strong positive nonlinear effect was observed. Even at a ratio of 55:45 (10% de) of **80** to **81**, the product had an enantiomeric excess of 91%. Not only was the ee of the product different employing the two diastereomers, also the reaction rates differed. The complex of ligand **81** is 2.6 times more reactive than its diastereomer **80**. The lowest reactivity was observed when the diastereomers were mixed in equimolar amounts. This suggests that most of the ligand–Zn complex formed a

[65] Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832.

non reactive heterodimer. Further evidence for this scenario was obtained by reacting dimethylzinc and the aminoalcohols **80** and **81** (2:1:1 mole ratio) in toluene to afford selectively the crystalline mixed dimer. Therefore, *Noyori* suggested that the *reservoir effect* is operative in this case.

1.2.10.2 NLE Studies Employing Ligand **48a** in the Conjugate Addition Reaction

To gain more information about the active complex in solution we tested the conjugate addition reaction for the presence of a nonlinear effect. Ligand **48a** was either mixed with its diastereomer **48b** or with its enantiomer (ent-**48a,** synthesis see page 55) (Scheme 37).

Scheme 37

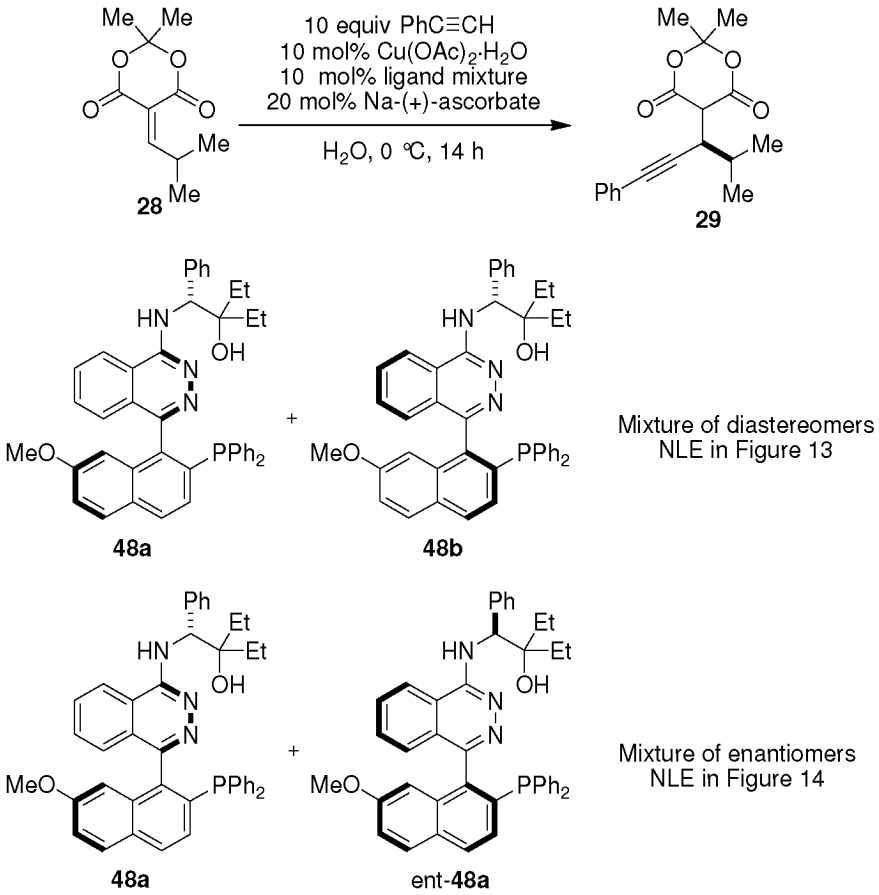
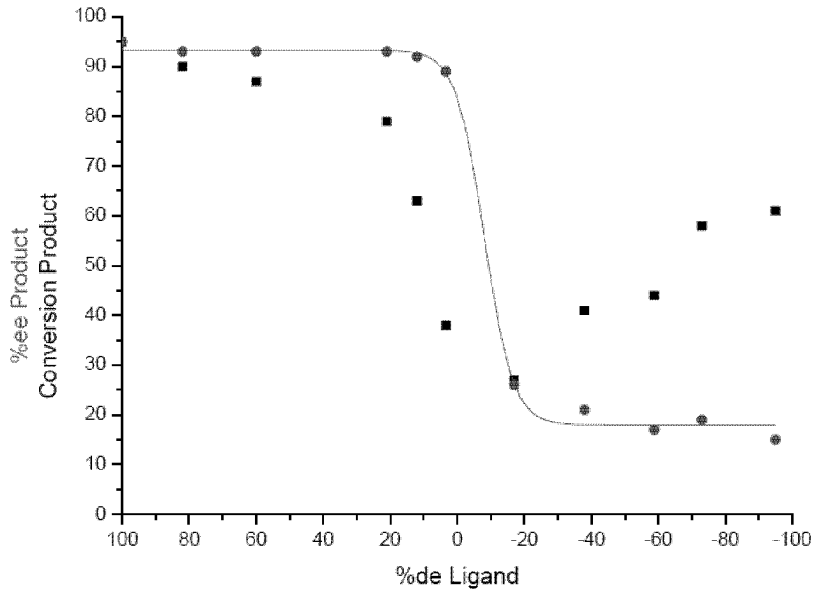
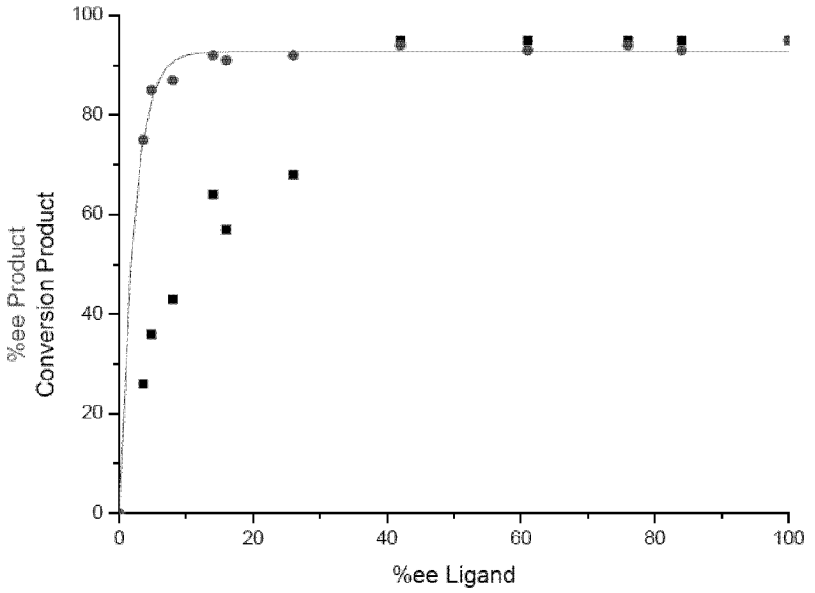


Figure 13 *Nonlinear Effect in the Conjugate Addition (Scheme 37) with Diastereomers* [a)]



[a)] ■corresponds to conversion, ● corresponds to enantioselectivity in the conjugate addition (Scheme 37).
100% de ligand corresponds to 100% diastereomer **48a**
-100% de ligand corresponds to 100% diastereomer **48b**

Figure 14 *Nonlinear Effect in the Conjugate Addition (Scheme 37) with Enantiomers* [a)]



a) ■corresponds to conversion, ● corresponds to enantioselectivity in the conjugate addition (Scheme 37).
100% ee ligand corresponds to 100% diastereomer **48a**
0% ee corresponds to 50% distereomer. **48a**, 50% ent-**48a**

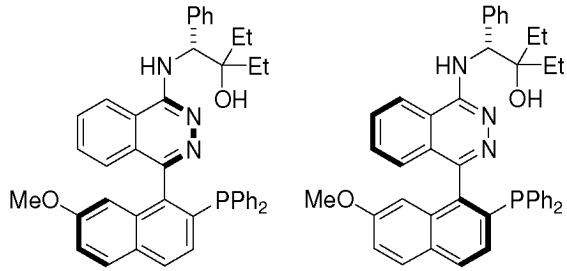
In both cases a strong nonlinear effect was observed.[66] In general, as ee or de of the ligands used approached 0%, the conversion diminished. This observation could be explained by invocing the *reservoir effect*, ie. the formation of thermodynamically stable heterodimers. Thus, when the two ligands are employed in equal ratios almost all of the ligand is bond in an inactive heterodimer, which explains the diminished conversion. This is in agreement with the model proposed by *Noyori* for diastereomeric ligands. Similar to our observation, *Knochel* reports a strong positive nonlinear effect in the copper/QUINAP catalyzed three-component coupling of alkynes, amines and aldehydes to propargylamines.[117] In that case, a lower reaction rate and product yield was also observed with the use of a ligand with low ee`s. This was also attributed to inactive heterodimers.

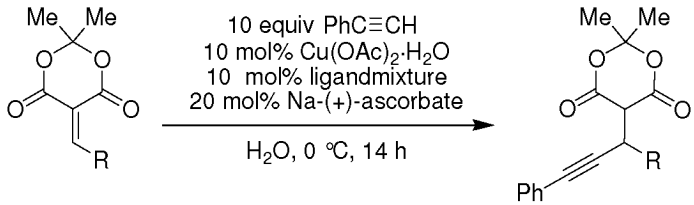
Applying the unpurified mixture of **48**, conjugate addition proceeds in 80% yield and 93% ee (Table 3). The nonlinear effect observed with diastereomer **48** is such that separation of the 1.5:1 mixture of diastereomers obtained in the synthesis of **48** in unnecessary.

This ratio of diastereomers was also employed for other substrates (Table 3). In all cases, a strong nonlinear effect was observed, although not as strong as for *i*-Pr acceptor. Very interestingly, for the aromatic acceptors the diastereomer **48b** furnished the *R* configuration whereas for the aliphatic acceptors the product had *S* configuration. Therefore, depending on the substrate either the axial chirality or the additional chiral center determines the absolute configuration of the product (Table 3).

[66] A Bolzmann fit was used for the graph. Software: Origin

Table 3





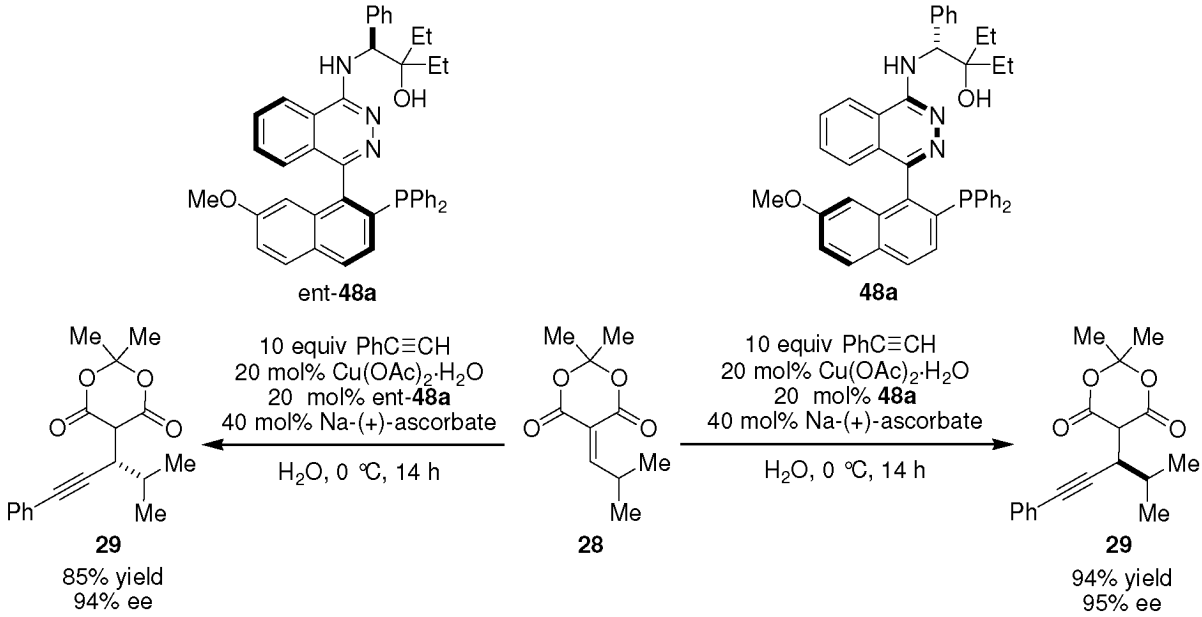
entry	acceptor (R)		100% de (48a)	20% de	-100% de (48b)
1	*i*-Pr	yield	94	80	65
		ee[b]	95 (*S*)	94 (*S*)	15 (*S*)
2	C_6H_{11}	yield	81	80	44
		ee[b]	94 (*S*)	84 (*S*)	24 (*S*)
3	*m*-tol	yield	87	24	44
		ee[b]	90 (*S*)	63 (*S*)	-6 (*R*)
4	*o*-methoxy-*m*-methanesulfonate phenyl (acceptor **65**)	yield	60	15	18
		ee[b]	89 (*S*)	59 (*S*)	-33 (*R*)

[a] Reactions were run using 10 equiv phenylacetylene with a ratio of **48**/$Cu(OAc)_2 \cdot H_2O$/ascorbate = 1:1:2 at 0 °C on 0.25 mmol scale, except for entry 4 which was run at 23 °C [b] The enantioselectivity was determined by chiral HPLC analysis, after conversion of the products into the corresponding anilides by heating in aniline/DMF

We next sought to rule out the chirality of sodium ascorbate as a factor in the enantioselectivity in the conjugate addition. Because only a single enantiomer of ascorbic acid is commercially available, *ent*-**48a** was synthesized. This was synthesized in the same way as ligand **48**, with the amine derived from (*S*)-phenylglycinemethyl ester, the enantiomer of the ester used before (Scheme 26).

It was found that in the conjugate addition, the two enantiomers provided essentially equal enantioselectivities (94 and 95%, Scheme 38), suggesting that the chirality of ascorbate plays no role in the selectivity.

Scheme 38

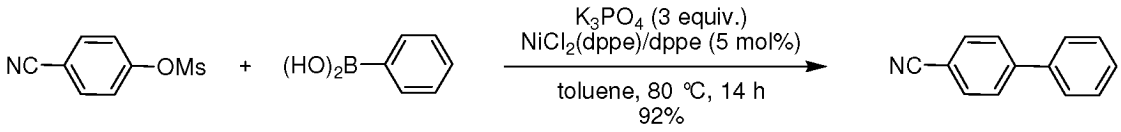


1.2.11 Phosphination Reaction of Aryl Mesylates

Structurally diverse PINAP analogues can be prepared by the Ni-catalyzed phosphination of aryl triflates. Although this reaction is general to various substrates, the phosphination of mesylates would offer more cost effective synthesis of PINAP analogs.[67] Moreover, there are no reports of phosphination of mesylates. Therefore we decided to investigate the scope and utility of mesylate phosphination in the context of PINAP preparation.

Aryl sulfonates have been used as substrates in Pd-catalyzed cross coupling reactions.[68,69] A Ni catalyzed Suzuki coupling of arylmesylates was also reported in 2004 by *Percec* (Equation 23).[70] Thus aryl sulfonates participate in transition metal catalyzed coupling reactions.

Equation 23

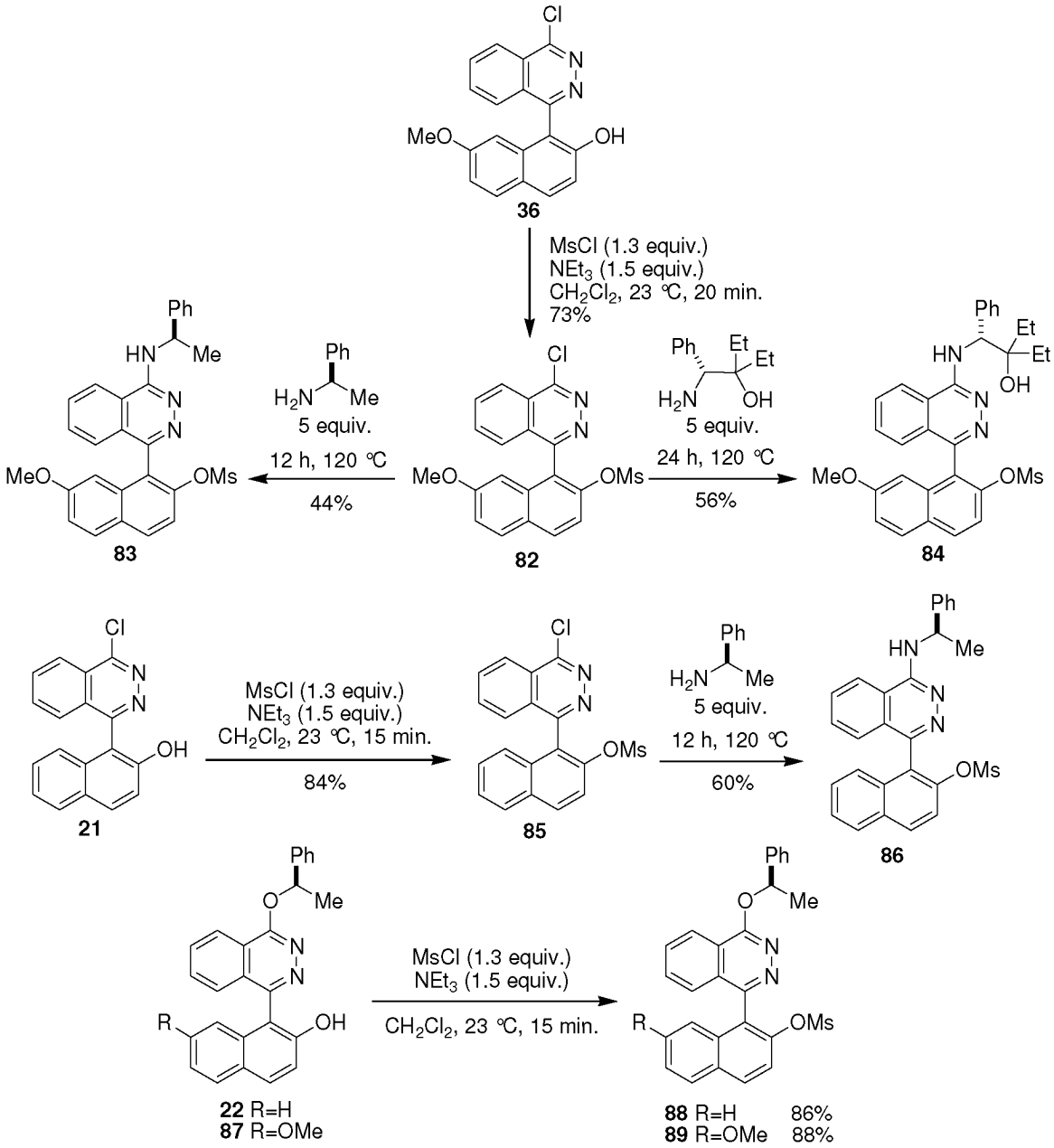


The aryl sulfonates were prepared from the corresponding naphthols using mesyl chloride. The mesylations proceeded smoothly employing NEt_3 as a base instead of pyridine, which had to be used in the triflations, to give the products in 73-88% yield (Scheme 39).

---

[67] 50 g Triflicanhydride cost 145 CHF.
[68] Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910.
[69] Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.
[70] Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447.

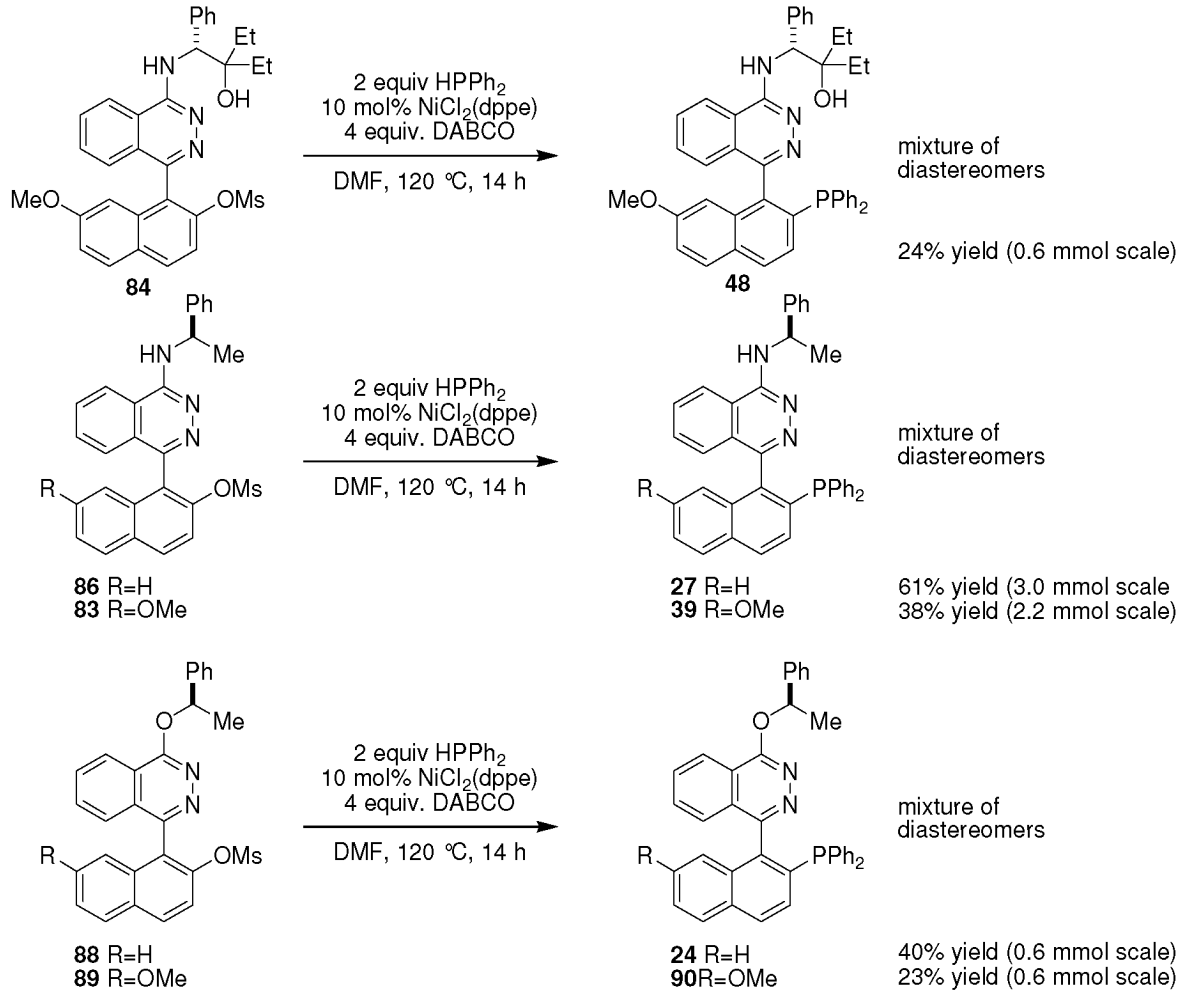
Scheme 39



With the mesylates in hand we turned our attention to the phosphination reaction. The reaction conditions are 10 mol% $NiCl_2$(dppe), 2 equivalent $HPPh_2$ and 4 equivalents of DABCO in DMF at 120 °C for 14 h. Under these conditions, the phosphines were obtained in 23-61% yield (Scheme 40). Unfortunately, the yields are lower than the phosphination of corresponding triflates. However, we have successfully demonstrated the first phosphination reaction of

arylmesylates. These yields are not optimized and further improvement could be achieved by careful optimization of reaction conditions such as solvent, temperature and/or other catalysts.

Scheme 40



1.3 Conclusion

The herein presented modifications of N-PINAP dramatically improved the yield and enantioselectivity in the conjugate addition of phenylacetylene to *Meldrum`s* acid derived acceptors. With a ligand loading of only 10 mol% the corresponding conjugate addition products could be isolated in up to 94% yield and 97% ee performing the reaction at 0 °C in 10 equivalents

of phenylacetylene. One of the conjugate addition products was further elaborated to an intermediate of which over 200 derivatives are known that act as TNF inhibitors or GRP receptor antagonists. These compounds could only be synthesized as a racemate and had to be resolved by several crystallizations or by preparative chiral HPLC. During the final step in the preparation of the PINAP ligands a mixture of diastereomers is formed. Employing this mixture (20% de) in the conjugate addition reaction of phenylacetylene to the acceptor derived from the condensation of *Meldrum`s* acid and *iso*-butyraldehyde afforded the corresponding product in 80% yield and 94% ee. This surprising result can be explained by a strong positive nonlinear effect. Therefore, separation of the two diastereomers becomes unnecessary for certain substrates in the conjugate addition reaction. Finally, the first phosphination of arylmesylates is reported in the context of PINAP preparation.

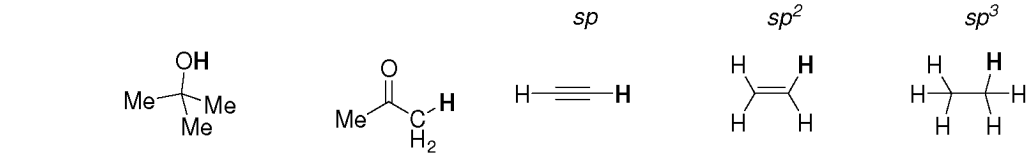
Chapter 2

Addition of Alkynes to Carbonyls and Iminiums

2.1 Introduction

Terminal acetylenes are exceptionally acidic compared to other hydrocarbons and therefore they can be easily functionalized. The reason for the enhanced acidity is the high percentage of *s*-character associated with the terminal carbon atom (Figure 15). [71]

Figure 15 *pK_a-Values of tert-butanol, acetone and C_2 hydrocarbons.*[72]



Usual bases for the deprotonation of terminal alkynes are *Grignard* reagents, [73] lithium amides[74] and organolithiums[75]. However, in 1900 *Favorsky* and *Skosarevsky*[76] discovered that ethyne can be deprotonated in the presence of KOH and added to ketones (Equation 24). Low temperature (5 °C) and a large excess of acetylene prevented the formation of the 1,4-diol and ensured that the acetylene reacts only once.

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[71] Simandi, L. I. In *The Chemistry of Functional Groups, Supplement C, pt 1*: Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1983, pp 529-534.

[72] (a) Streitwieser, A.; Brauman, J. I.; Hammons, J. H.; Pudjaatm.Ah *J. Am. Chem. Soc.* **1965**, *87*, 384. (b) Dessy, R. E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* **1966**, *88*, 460. (c) Streitwieser, A; Scannon, P. J.; Niemeyer, H. M. *J. Am. Chem. Soc.* **1972**, *94*, 7936 (d) Streitwieser, A.; Boerth, D. W. *J. Am. Chem. Soc.* **1978**, *100*, 755. (e) Bartmess, J. E.; Scott, J. A.; McIver, R. T. *J. Am. Chem. Soc.* **1979**, *101*, 6046.

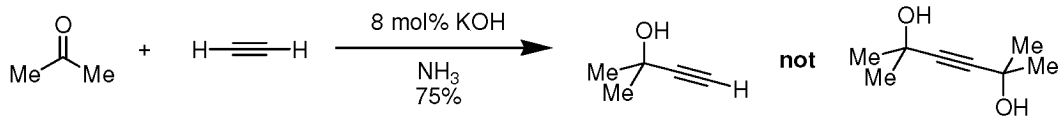
[73] Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*, Academic Press: London, **1995**, pp 46-48.

[74] Brandsma, L. *Preparative Acetylene Chemistry*, 2nd ed., Elsevier: Amsterdam, 1988.

[75] Wakefield, B. J. *Organolithium Methods*, Academic Press: London, 1988, Ch. 3, p 32.

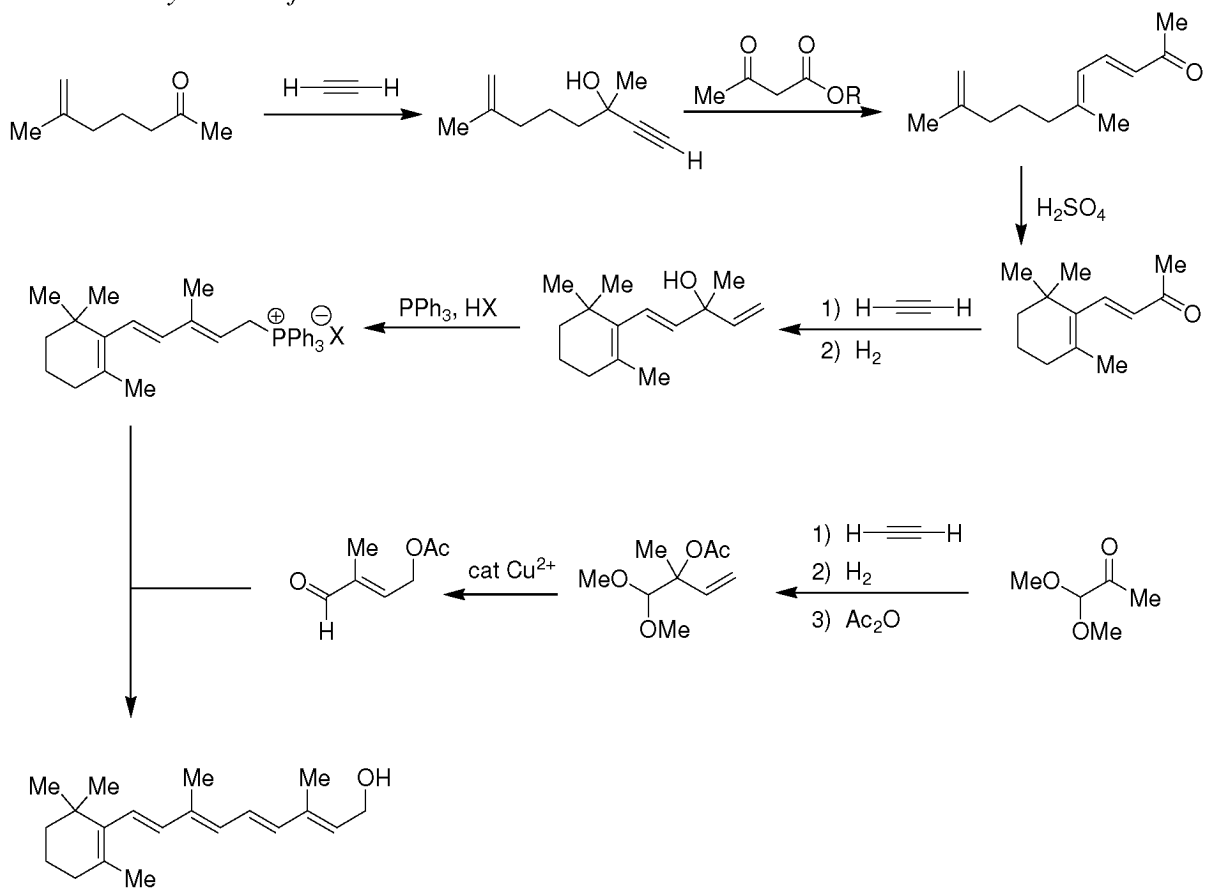
[76] (a) Favorsky, A. E.; Skosarevsky, M. *Russ. J. Phys. Chem. Soc.* **1900**, *32*, 652. (b) Favorsky, A. E.; Skosarevsky, M. *Bull. Soc. Chim. Fr.* **1901**, *26*, 284.

Equation 24



The synthesis of Vitamin A was reported by BASF incorporating the addition of acetylene to ketones without any base, albeit at high pressure.[77] The addition of acetylene is used three times in the synthesis on large scale processes (Scheme 41).[78]

Scheme 41 *Synthesis of Vitamin A*

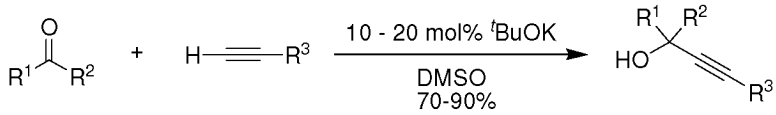


Babler developed a procedure for the addition of terminal alkynes to ketones in DMSO employing potassium *tert*-butoxide as a base (Equation 25).[79] In water *tert*-butanol has a pK_a of

[77] Reif, W.; Grassner, H. *Chem. Ing. Tech.* **1973**, *45*, 646.
[78] In 1997 BASF produced 600 t Vitamin A in a year.

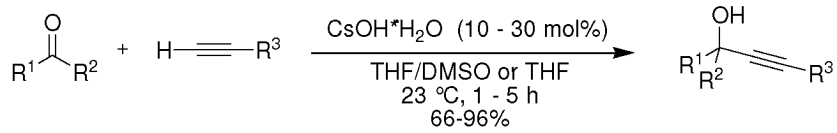
17, but in DMSO the pK_a is 30-32. The increase in pKa is due to the poor ability of DMSO to stabilize anions when its charge is localized on a single atom. Since the product is a tertiary alcohol as well the potassium *tert*-butoxide can be used in catalytic quantities.

Equation 25



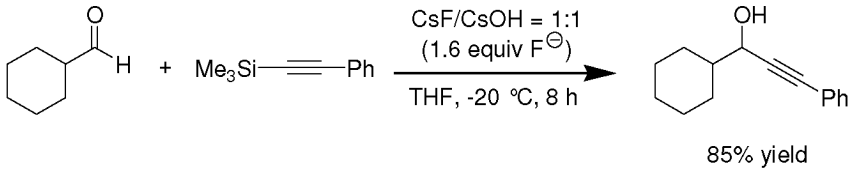
In a similar report by *Knochel* 10-30 mmol% of CsOH was employed as a base in a THF/DMSO mixture to promote the addition of terminal alkynes to ketones and aldehydes (Equation 26). [80]

Equation 26



Instead of deprotonation of a terminal alkyne *Corey* demonstrated that cesium salts are effective for the conversion of trimethylsilyl acetylene to the corresponding cesium acetylides.[81] Addition of these to aldehydes proceeded in good yields (Equation 27).

Equation 27



Despite the practical aspects of the deprotonation of terminal alkynes with alkali metal hydroxides and alkali metal alkoxides, none of the reported methods are enantioselective. Although a few processes have been described involving the use of organo-cesium reagents in asymmetric synthesis there is not as much known for these as is for other metal alkynylides

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[79] Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, *61*, 416.
[80] Tzalis, D.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 1463.
[81] Busch-Petersen, J.; Bo, Y. X.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 2065.

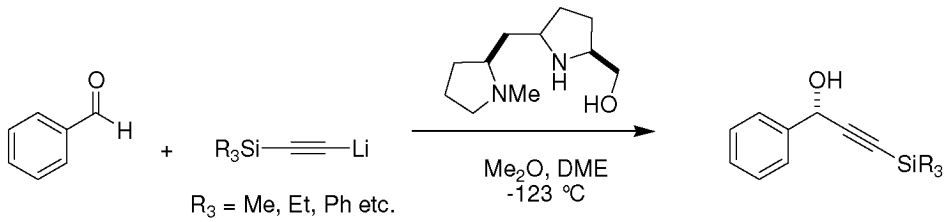
concerning their interaction with chiral ligands.[82] Therefore, the next section deals with metal alkynylides that give rice to enantiomeric enriched products.

2.1.1 Enantioselective Addition of Metal Acetylides to Carbonyls and Iminiums

2.1.1.1 Lithium Alkynylides

The first asymmetric addition of metal alkynylides to aldehydes was achieved by *Mukaiyama* using lithium acetylides and a chiral aminoalcohol as a ligand. [83] Good enantioselectivities (54-92% ee) were only achieved employing bulky trialkylsilylacetylenes and low reaction temperatures (Equation 28).

Equation 28



A well known example of the addition of lithium alkynylides to ketones is the report of *Merck* in their synthesis of *Efavirenz* (Scheme 42). [84] The key step in the synthesis of this HIV reverse transcripase inhibitor is the highly enantioselective (up to 98% ee) addition of lithium cyclopropyl acetylide to an *N*-protected trifluoromethyl ketoanilide. Careful mechanistic studies showed that the preformed ligand lithium alkynylide complex is not a monomer, but a dimer. [85] Subsequently zinc acetylides derived from transmetallation of the corresponding *Grignard* alkyne, were successfully employed in this transformation.[86]

---

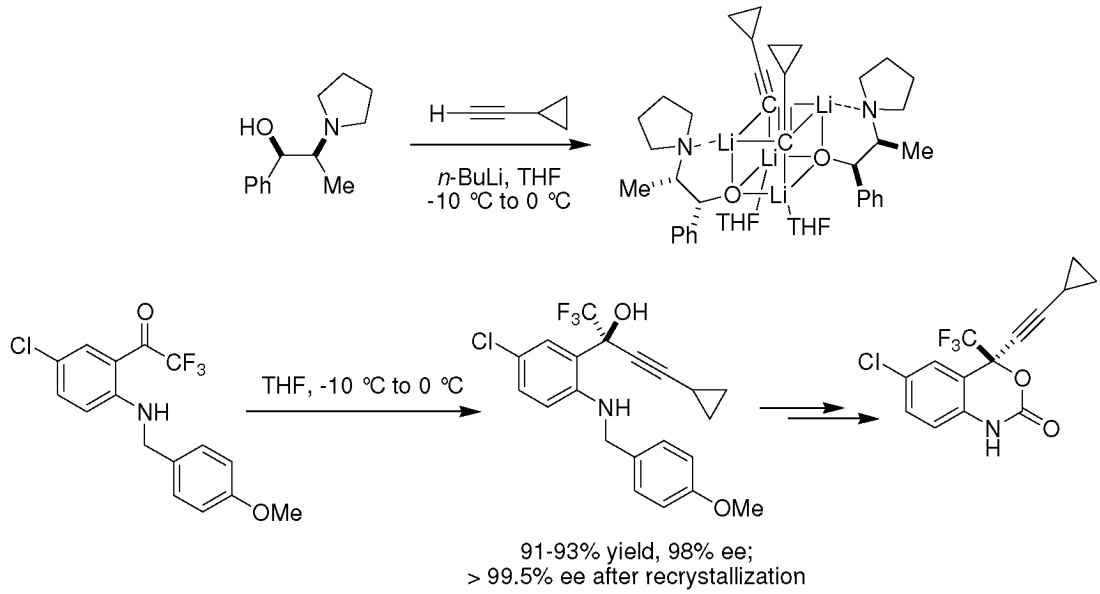
[82] (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**; *119*, 12414. (b) Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357. (c) Denmark, S. E.; Ober, M. H. *Adv. Syn. Catal.* **2004**, *346*, 1703.

[83] Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, 447. Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255.

[84] Pierce, M. E.; Parsons, R. L.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C. Y.; Tillyer, R. D.; Frey, L.; Tan, L. S.; Xu, F.; Zhao, D. ; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536.

[85] (a) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212. (b) Parsons, R. L.; Fortunak, J. M.; Dorow, R. L.; Harris, G. D.; Kauffman,

Scheme 42 *Efavirenz Synthesis by Merck Using a Chiral Lithium-Cyclopropyl Acetylide Complex*



2.1.1.2 Boryl Alkynylides

The use of boryl acetylides in enantioselective aldehyde addition reactions was reported by *Corey.* [87] The boron acetylides were prepared from the corresponding stannyl acetylenes (Equation 29). Using a chiral oxazaborolidene the desired propargylic alcohols were isolated in good yields (70-86%) and enantioselectivities (85-96%).[88] In the proposed transition state model the complex activates both acetylide and aldehyde, a concept that is known as dual activation.

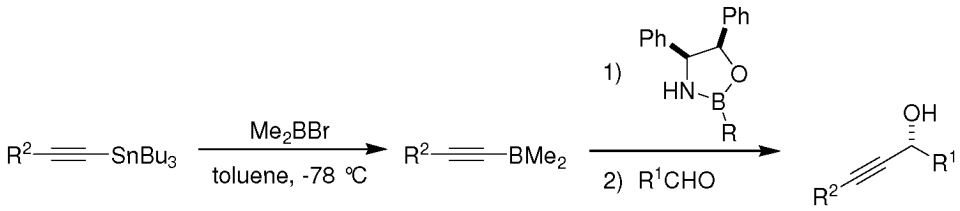
G. S.; Nugent, W. A.; Winemiller, M. D.; Briggs, T. F.; Xiang, B. S.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 9135.

[86] (a) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1999**, 1453. (b) Jiang, B.; Feng, Y. *Tetrahedron Lett.* **2002**, *43*, 2975.

[87] Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.

[88] (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880. (c) Corey, E. J.; Guzman Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769. (d) Singh, V. K. *Synthesis* **1992**, 605. (e) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. (f) Corey, E. J.; Helal, C. J. *Angew Chem. Int. Ed.* **1998**, *37*, 1986.

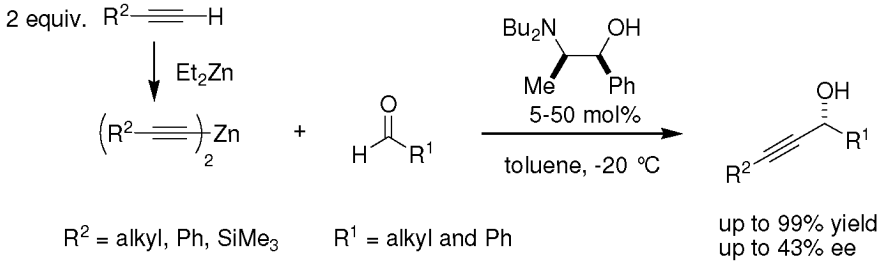
Equation 29



2.1.1.3 Zinc Alkynylides

Zinc alkynylides are widely used in asymmetric synthesis.[89] In the first report by *Soai* the dialkynyl zinc was prepared by reacting two equivalents of alkyne with one equivalent of dialkylzinc. [90] Treatment of an aldehyde with dialkynyl zinc in the of presence (+) *N,N*-dibutylnorephedrine as ligand furnished the corresponding propargylic alcohols in 99% yield and in up to 43% ee (Equation 30).

Equation 30



In the synthesis of the insecticide **91** an alternative zinc precursor was used (Scheme 43). Lithium phenylacetylide was transmetallated to $ZnBr_2$ and treated with the lithium alkoxide salt of (-)-*N*-methylephedrine and added to an aldehyde. [91] The propargyl alcohol was formed in 80% yield and 88% ee.

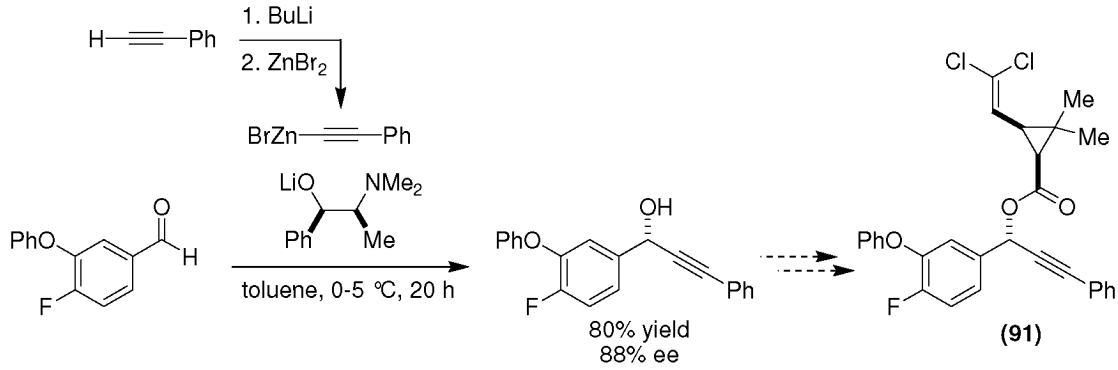
---

[89] Reviews: (a) Aschwanden, P.; Carreira, E. M. In *Acetylene Chemistry*, Diederich, F.; Stang, P.J.; Tykwinski, R. R., Eds.; WILEY-VCH: Weinheim, 2005; pp 101-138. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095. (c) Pu, L. *Tetrahedron* **2003**, *59*, 9876.

[90] Niwa, S.; Soai, K. *J. Chem. Soc. Perkin Trans. 1* **1990**, 937.

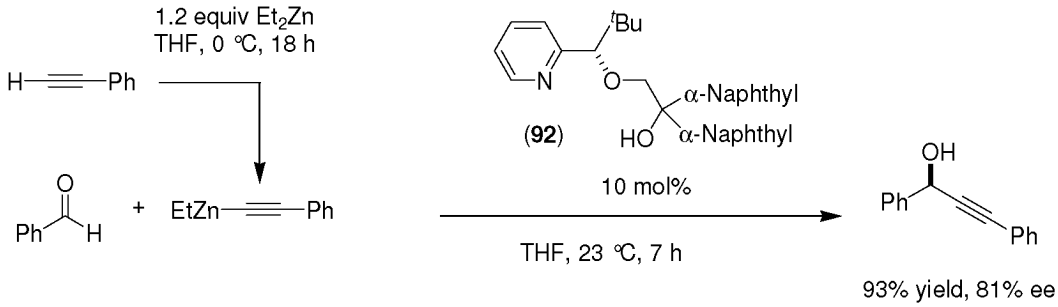
[91] Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547.

Scheme 43



When the ratio of mixed alkyne to dialkylzinc is 1 to 1.2, mixed organozinc compounds are obtained (Scheme 44).[92] The addition of such species to aldehydes was examined in the presence of ligand **92**.

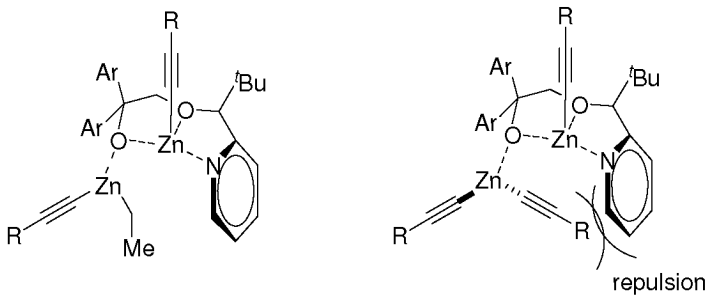
Scheme 44



In contrast to the dialkynyl zinc compounds higher enantioselectivities were obtained. The authors rationalized the outcome of this reaction by the presence of an unfavorable steric interaction in the reaction of the dialkylzinc (Figure 16). In contrast, the mixed diorganozinc reagent places the alkyl group towards the pyridine affording the product with increased enantioselectivity.

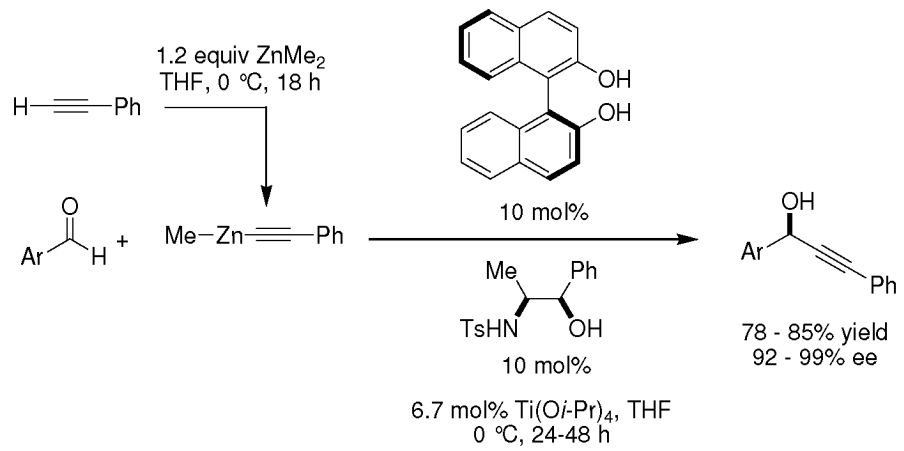
[92] Ishizaki, M.; Hoshino, O. *Tertrahedron Asym.* **1994**, *5*, 1901.

Figure 16



These mixed organozinc compounds R^1ZnR^2 (R^1 = alkyl, R^2 = alkynyl) have also been used successfully with other ligands in the addition to aldehydes, showing in general higher enantioselectivities than the dialkynylzinc compounds.[93] An interesting report by *Chan* combined the use of a Ti(IV)-BINOL complex, acting as a *Lewis* acid to activate the aldehyde, and *N*-tosylnorephedrine in the addition of a mixed alkyl alkynyl zinc reagent to aldehydes (Scheme 45).[94] The reported yields (78-85%) and enantiomeric excesses (92-99%) were impressive. Unfortunately only aromatic aldehydes afforded the desired propargylic alcohols.

Scheme 45



Although the chiral ligands can usually be used in substoichiometric quantities, those which have been reported thus far for enantioselective additions are not catalytic in metal. Moreover, the formation of the zinc alkynylides has to be performed in a separate step (Figure 17). This is

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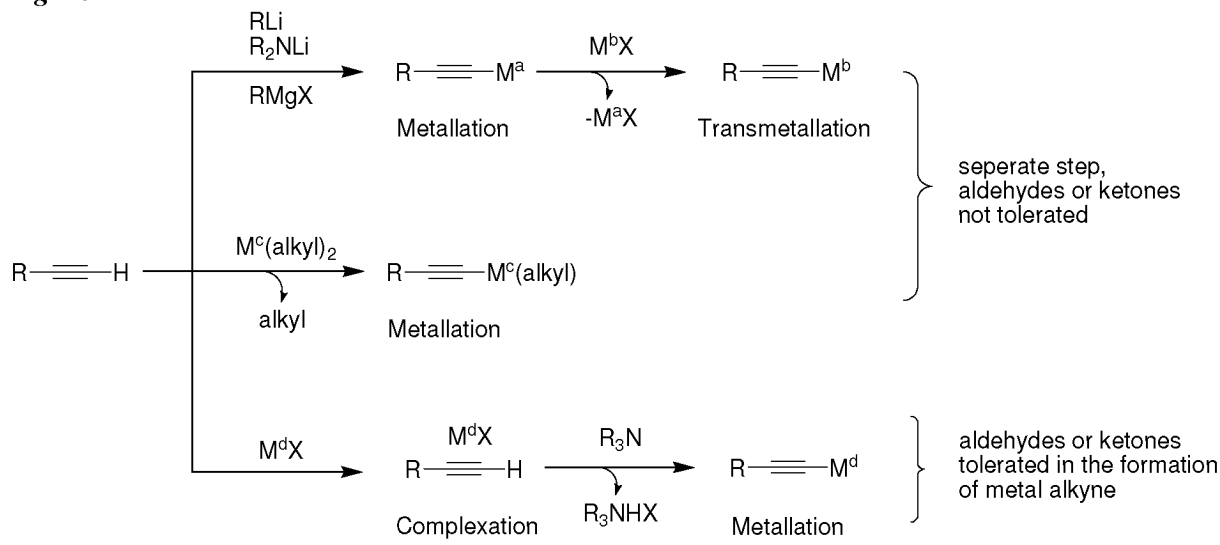
[93] (a) Ishizaki, M. Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1901. (b) Lu, G.; Li, X.; Zhou, Z.; Chan, W. L.; Chan, A. S. *Tetrahedron: Asymmetry* **2001**, *12*, 2147. (c) Xu, M.-H.; Pu, Li *Org. Lett.* **2002**, *4*, 4555. (d) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855. (e) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143. (f) Lu, G.; Li, X.; Chen, G.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 449.

[94] Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J Am. Chem. Soc.* **2002**, *124*, 12636.

due to the highly basic and/or nucleophilic character of the strong bases or the dialkylzinc that have to be used to form the zinc alkynylide.

Figure 17



A milder method was developed in the *Carreira* group (Figure 17).[21] Activation of the terminal alkyne by π-coordination with $Zn(OTf)_2$ allowed the use of a mild base, namely triethylamine, to deprotonate the alkyne in the presence of aldehydes and ketones.

To gain more insight into this new process *in situ* IR-studies were carried out (Figure 5).[95] Using a ReactIR the alkyne C-H stretch was monitored during the addition of amine and $Zn(OTf)_2$. When triethylamine was added to the terminal alkyne the absorbance of the terminal C-H stretch decreased slightly, but deprotonation was not detected. After the addition of $Zn(OTf)_2$ the C-H stretch immediately disappeared. In contrast, when the zinc alkynylide was treated with triflic acid the terminal C-H stretch reappeared immediately. These zinc alkynylides were demonstrated to react with nitrones, aldehydes, ketones and *N*-acylimminium ions, affording racemic products (Scheme 46).[96,97]

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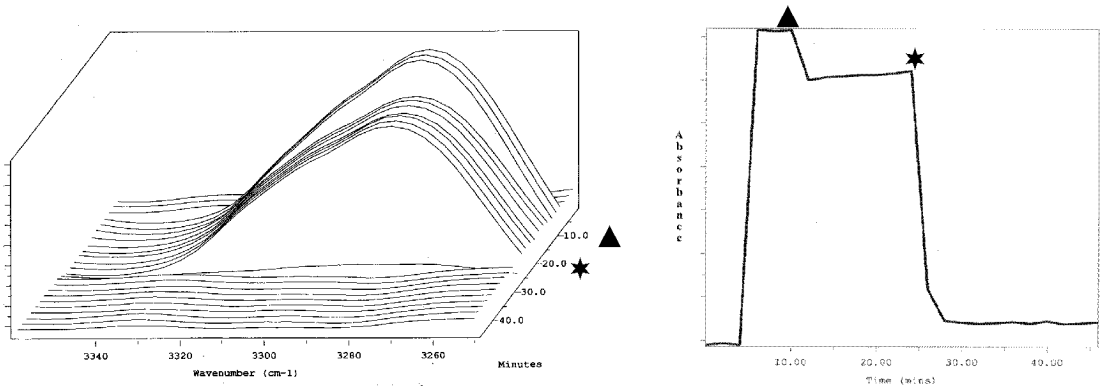
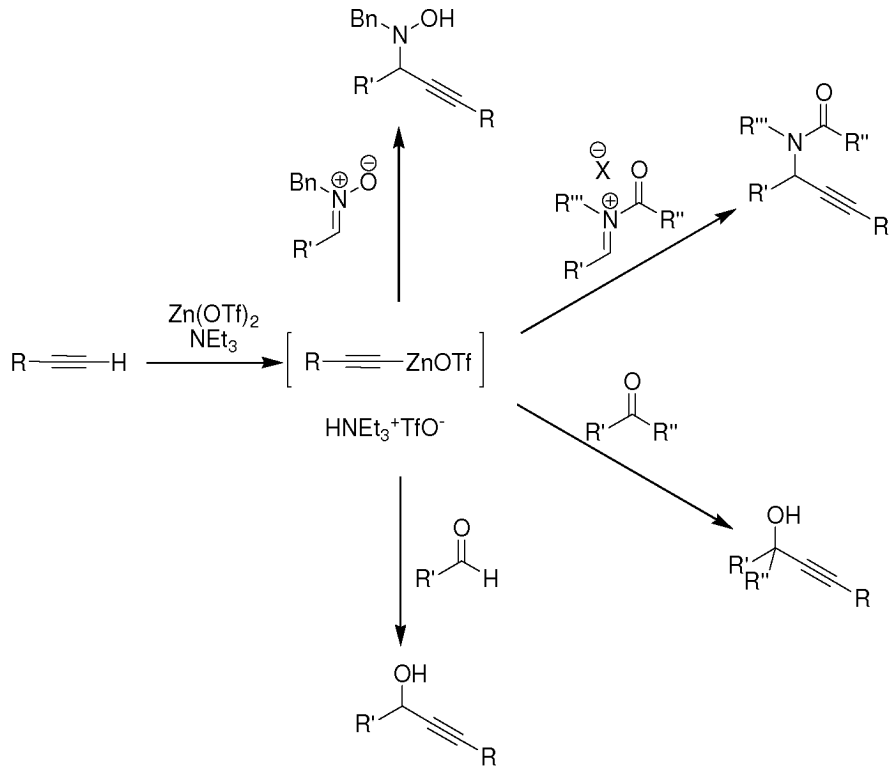
[95] Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843.
[96] Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373.
[97] Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497.

Figure 5 *ReactIR spectra of the C-H stretch resonance signal of phenylacetylene in CH_3CN. At 10 min (▲) Et_3N was added and subsequently at 20 min (★) $Zn(OTf)_2$. In the presence of both components the IR band corresponding to the terminal C-H completely disappears within 4 minutes.*[95]

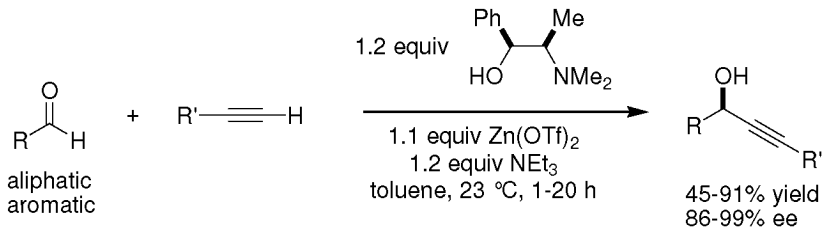


Scheme 46



For aldehydes the addition of cheap *N*-methylephedrine turns this process into an enantioselective one (Equation 31), furnishing the corresponding propargyl alcohols at ambient temperature in good yields and up to 99% ee. The addition works best for α-branched aldehydes, while unbranched or aromatic aldehydes also react, albeit with diminished yield.

Equation 31



A wide range of alkynes can be employed, including acetylene (Equation 32).[98] The utility of this new and mild method for the *in situ* generated zinc alkynylides has been demonstrated in numerous applications in natural product syntheses, namely epothilone A and B, leucascandrolide A, murisolin, oximidine II, (+)-gigantecin, epoxomicin, brefeldin C, and strongylodiols A and B.[99,100,101,102,103,104,105,106]

Ethyne is available as a solution in acetone and is used in industrial scale processes. Its use would be optimal because subsequent derivatization of the terminal alkyne (alkylation, acylation, or *Sonogashira* coupling) would provide access to a broad range of optically active, secondary propargylic alcohols.[107]

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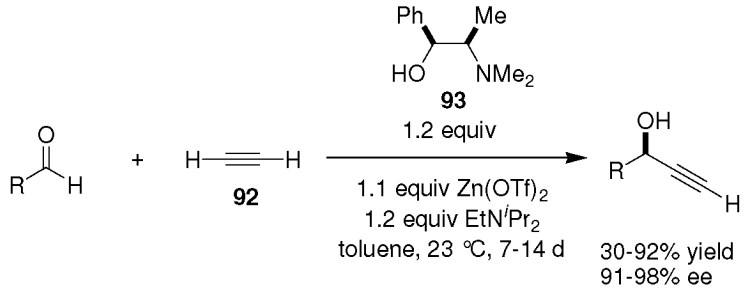
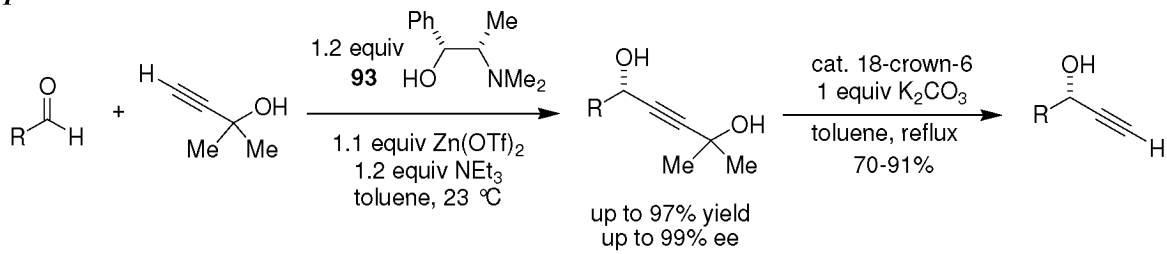
[98] Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964.
[99] (a) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611. (b) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410.
[100] (a) Fettes, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4098. (b) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274.
[101] Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Commun.* **2004**, 406.
[102] Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313.
[103] Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790.
[104] Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348.
[105] Archambaud, S.; Aphecetche-Julienne, K.; Guingant, A. *Synlett* **2005**, 139.
[106] Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813.
[107] *The Chemistry of Triple Bonded Functional Groups;* Patai, S.; Rappoport, Z., Eds.; Wiley: New York, **1983**; Parts 1 and 2.

Equation 32



The disadvantage of using acetylene as a nucleophile is that it has the potential to react twice. To prevent this, ethyne is usually used in a large excess and removed after the reaction upon evaporation. Unfortunately, prolonged reaction times are necessary when ethyne is used. Normally the reaction is complete in a few hours for terminal alkynes; however, for ethyne the reaction times range from 7 to 14 days. As an alternative to ethyne, 2-methyl-3-butyn-2-ol was used (Equation 33). The acetone protecting group can be removed by potassium carbonate and 18-crown-6 in refluxing toluene after the addition. The corresponding terminal alkyne can be use in a subsequent addition to aldehydes to give unsymmetrical 1,4-alkynyldiols.

Equation 33



In 2001, *Carreira* reported a catalytic version of the addition of zinc alkynes to aldehydes.[108] This was the first truly catalytic process (Equation 34) reported. Simply be heating the reaction to 60 °C in toluene catalytic turnover was achieved. Notably the enantiomeric excesses remain high. Using a different aminoalcohol, the catalytic enantioselective addition takes also place with non-enolizable, activated ketones (Equation 35).[109]

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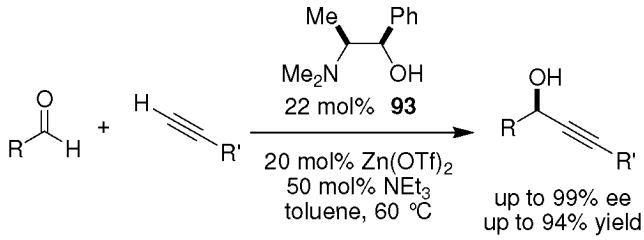
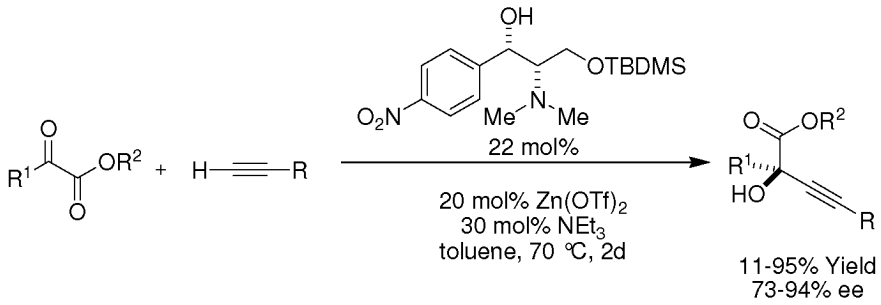
[108] Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
[109] Jiang, B; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.

Equation 34



Equation 35



2.1.1.4 Copper Alkynylides

The majority of applications of Cu-acetylides are for the formation of C-C bonds. The *Glaser* coupling was already reported in 1869 and an improved procedure employing pyridine was disclosed later by *Eglinton.*[110] Subsequently the formation of unsymmetrical diynes was achieved by *Cadiot* and *Chodkiewicz* by coupling a haloalkyne with a copper alkyne.[111] Further investigations by *Castro* and *Stephens* resulted in the coupling of copper alkynes with aryliodides.[112] Along the same lines *Sonogashira* achieved the same coupling using catalytic amounts of palladium together with copper.[113]

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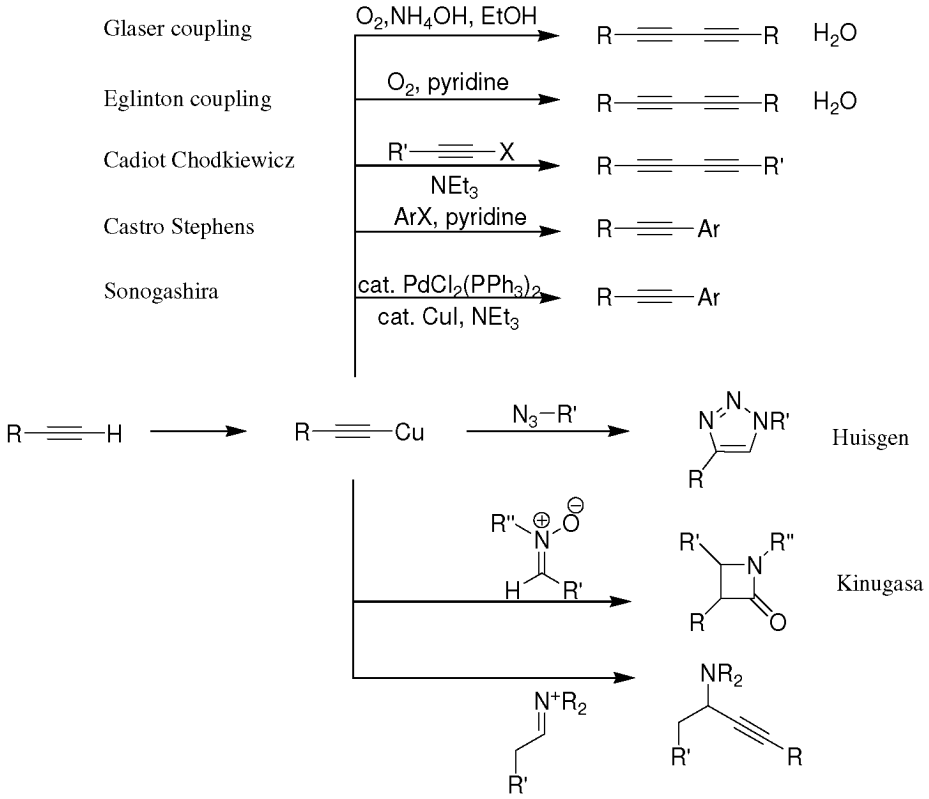
[110] Eglinton, G.; Galbraith, A. R. *Chem. Ind.* **1956**, 737.

[111] (a) Chodkiewicz, W. *Ann. Chim.* **1957**, *2*, 819. (b) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes* (Eds.: Viehe, H. G.) Decker, New York, **1969**, pp. 597-647. (c) Sevin, A.; Chodkiewicz, W.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1974**, 913.

[112] (a) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163. (b) Castro, C. E; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 3313.

[113] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. *J.Organomet. Chem.* **2002**, *653*, 46.

Scheme 47



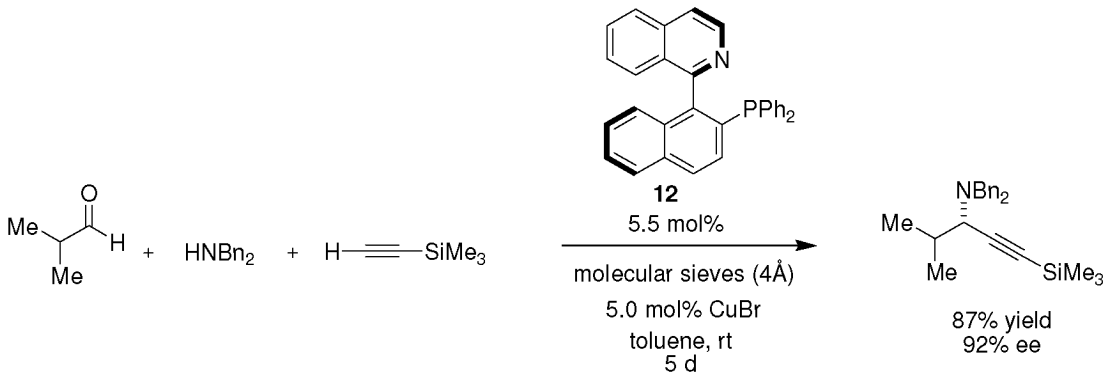
Apart from these coupling reactions copper alkynylides also participate in [3+2] cycloadditions with 1,3-dipoles. 1,2,3-triazoles are formed in the reaction with alkyl azides (*Huisgen* reaction) whereas nitrones undergo a rearrangement after cycloaddition to form *β*-lactams (*Kinugasa* reaction).[114,115]

Due to their stability and aggregation (see section 1.1.1.4), Cu-acetylides are unreactive compared to other organocooper species. In fact, alkynes are often used as dummy ligands (ie. placeholders) in higher order cuprates. Consequently, few reactions utilizing Cu-acetylides as nucleophiles have been reported. *Brannock* reported the CuCl catalyzed addition to iminium ions derived from enamines.[116] Using QUINAP as a ligand for copper, *Knochel* expanded this reaction to afford enantiomerically enriched products.[117] In addition a three component version where the iminium is generated from an aldehyde and an amine *in situ* has been reported recently (Equation

[114] Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry* Padwa A., Ed.; Wiley, New York, 1984; pp. 1-176.
[115] Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466.
[116] Brannock, K.; Burpitt, R. D.; Thweatt, J. G. *J.Org. Chem.* **1963**, *28*, 1462.
[117] (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2607. (b) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797. (c) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 5763.

36). The reaction is catalytic in copper as well as in ligand and good yields and high enantiomeric excess was achieved. A drawback is that only dibenzylamine can be used. In this case, deprotection to the free amine is only possible by reducing the alkyne as well. Recently, 2-phenallyl was reported as a protecting group of the amine that could be cleaved without the reduction of the alkyne.[118]

Equation 36

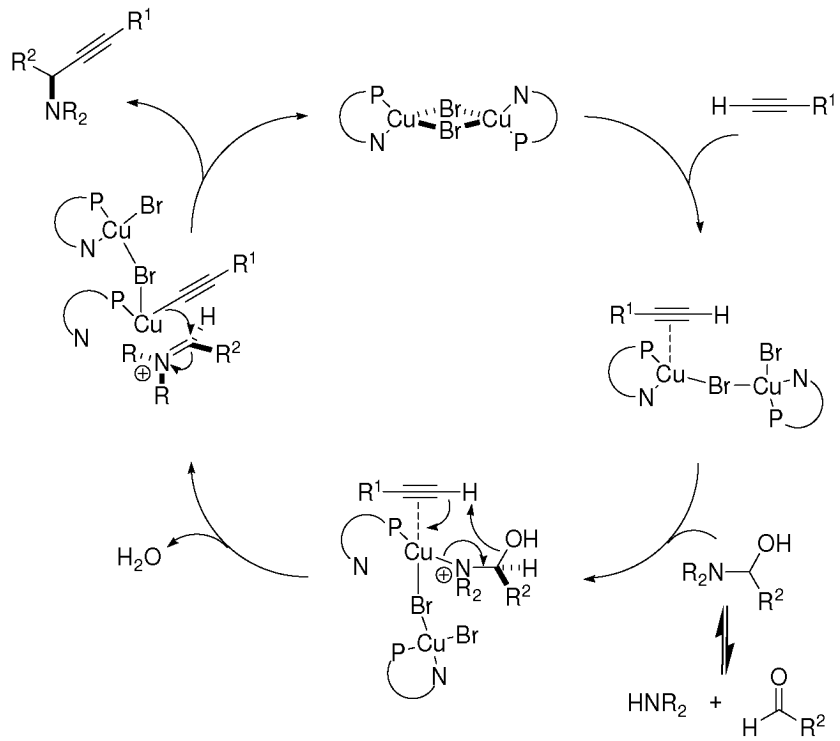


A dimeric Cu/QUINAP complex was suggested as the catalytically active species since a strong positive nonlinear effect was observed in the enantioselective addition (Scheme 48). This is also in agreement with the dimeric crystal structure reported of [CuBr{(*R*)-quinap}]$_2$.

In a very similar process starting with aromatic imines *Li* employed a PYBOX ligand and achieved good yields and enantioselectivities.[119] Although for both procedures the reaction is slow, taking several days for completion.

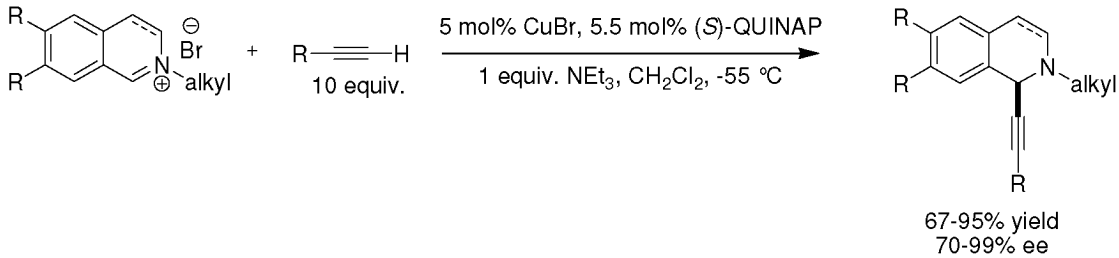
[118] Gommermann, N.; Knochel, P. *Chem. Comm.* **2005**, 4175.
[119] Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638.

Scheme 48 *Proposed mechanism for the Cu catalyzed three-component reaction*



Very recently, *Schreiber* reported the Cu/QUINAP catalyzed enantioselective addition to isolated alkylisoquinoliniums and alkyl-3,4-dihydroisoquinoliniums (Equation 37). [120] The reaction proceeds in high yield and high enantiomeric excess with a variety of substrates in solution and is also amenable to solid-phase synthesis.

Equation 37



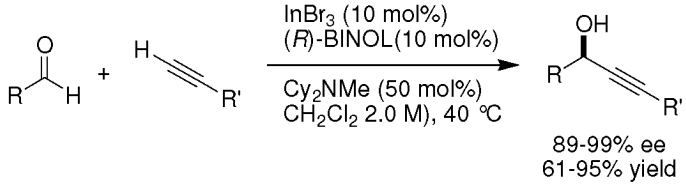
[120] Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143.

A fast but racemic process was developed by Arndtsen[121] using acyliminiums. *Gouge* reported the racemic addition of terminal alkynes to aldehydes employing CuOH.[122]

2.1.1.5 Indium Alkynylides

A second, truly catalytic enantioselective addition of alkynes to aldehydes was reported by *Shibasaki* employing $InBr_3$ (Equation 38).[123] A broad range of alkynes and aromatic as well as aliphatic aldehydes are suitable for the addition. The $InBr_3$ is believed to play a dual role, meaning that it activates the alkyne towards deprotonation by π-complexation and acts also as *Lewis* acid to activate the aldehyde.

Equation 38



2.2 Results

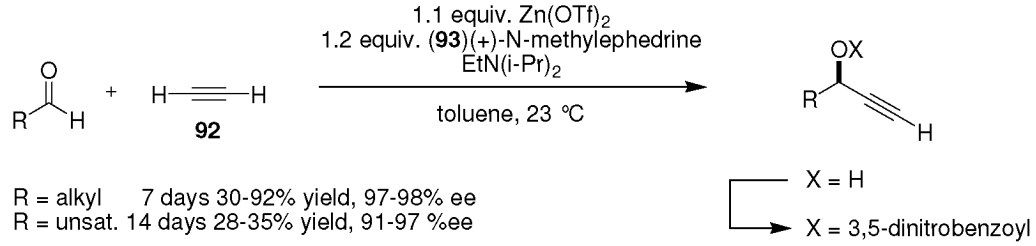
2.2.1 Enantioselective Addition of Acetylene to Aldehydes

Sasaki in the *Carreira* group investigated the Zn-catalyzed addition of acetylene to aldehydes, employing a procedure in which a Zn-acetylide is directly generated from a terminal alkyne *in situ*, under mild conditions.[95,96,97] In preliminary experiments, a solution of toluene was saturated with acetylene at 0 °C by bubbling for 10-15 min. This solution was subsequently treated with $Zn(OTf)_2$, $EtN(i\text{-}Pr)_2$, and (+)- or (-)-*N*-methylephedrine, followed by an aldehyde. Under these conditions, adducts were isolated as a 1:1 mixture of the desired alk-1-yn-3-ols and 1,4-diols, the products of double addition of C_2H_2 to 2 equiv. of aldehyde. By increasing the concentration of dissolved C_2H_2, minimization of the yield of 1,4-diol products was achieved.[98] In this regard, a mixture of aldehyde, $Zn(OTf)_2$, $EtN(i\text{-}Pr)_2$, and (+)- or (-)-*N*-methylephedrine in toluene was cooled to -40 °C and bubbled with C_2H_2 for 20 min, and then the reaction vessel was

[121] Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.
[122] Gouge, M. *Ann. Chim. (Paris)* **1951**, 648.
[123] Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760.

sealed and allowed to warm to 23 °C (Equation 39). This procedure furnished the propargylic alcohols in up to 98% ee. Since the propargylic alcohols are volatile, they were protected as their 3,5-dinitrobenzoates before isolation.

Equation 39



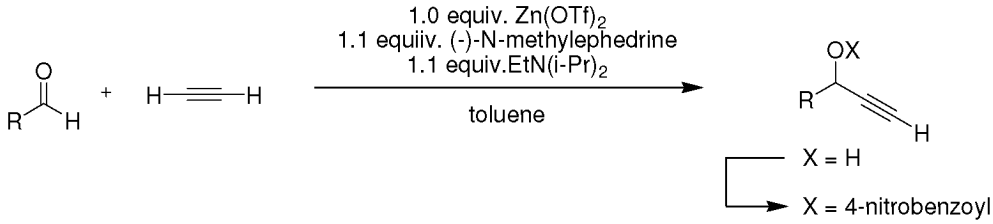
The ee was high for both aliphatic and α, β-unsaturated aldehydes. However, the yield was only good for α-branched aliphatic aldehydes; ranging in yield from 70-92%. For aromatic, conjugated aromatic and α-unbranched aldehydes the yields ranged from 28-35%. Another drawback is the typically long reaction time. For aliphatic aldehydes, the reactions required 7 days, while for aromatic and conjugated aromatic aldehydes, the reactions reached not more than 35% conversion after 14 days. As mentioned before, the reaction times of addition when terminal, substituted alkynes were employed were much shorter. This difference could result from the formation of unreactive aggregates of the sterically unhindered metallated species.

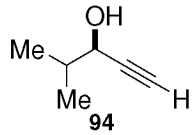
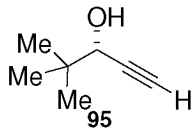
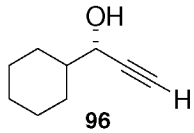
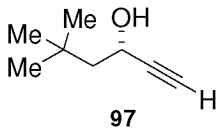
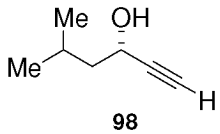
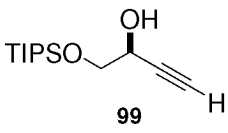
Because the reaction times of 7 to 14 days make this addition unattractive, we sought to increase the rates of this reaction. First, we turned our attention to the purity of the acetylene. Therefore, acetylene gas was passed through a cooling trap at -78 °C, then through concentrated H_2SO_4 and finally through a trap filled with KOH pellets. To enlarge the concentration of acetylene, the gas was bubbled through the solution at -78 °C instead of -40 °C. Thus, in a typical protocol, 0.55 mmol $EtN(i\text{-}Pr)_2$ and 0.50 mmol aldehyde were added to a solution of 0.50 mmol $Zn(OTf)_2$ and 0.55 mmol (+)-*N*-methylephedrine in 4.0 ml toluene. After stirring for 2 h at 23 °C, the reaction was cooled to -78 °C and C_2H_2 was bubbled through the solution for 10 min. The pressure tube was closed and the reaction was stirred at either 23 °C or 50 °C.

Employing this improved procedure, we were able to isolate α-branched as well as α-unbranched aldehydes in yields from 66-88% in up to 98% ee (Table 4). Importantly, the reaction times could be shortened from 7 days to 11/20 h. Increasing the reaction temperature from 23 °C

to 50 °C led only to a small diminution in the enantiomeric excess of the product from 93% ee to 89-91% ee. For aromatic or conjugated aromatic aldehydes this procedure could not be in practice applied, because the aldehydes decomposed at 50 °C; therefore the yields were never higher than 40 %.

Table 4



aldehyde (R)	product	time	temperature	yield[a)]	ee[c)]
i-Pr	 **94**	16 h	23 °C	88%	95%[d)]
t-Bu	 **95**	35 h 19 h	23 °C 50 °C	70% 86%	93% 89%
c-C_6H_{11}	 **96**	35 h 11 h	23 °C 50 °C	66% 75%	93% 91%
Me_3CCH_2	 **97**	18 h	50 °C	68%	98%
Me_2CHCH_2	 **98**	20 h	50 °C	71%	94%
$TIPSOCH_2$	 **99**	20 h	50 °C	70%[b)]	88%[d)]

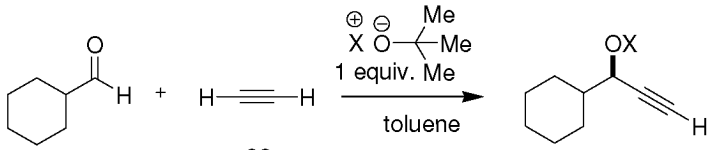
[a)] The products were isolated as their corresponding 4-nitrobenzoates. [b)] The propargylic alcohol was isolated
[c)] The ee was determined by chiral HPLC. [d)] (+)-NME was used.

2.2.2 Addition of Acetylene to Aldehydes Employing Alkali Metals

Based on the work of *Babler* and *Knochel* we wondered if it would be possible to substitute $Zn(OTf)_2$ in the addition of acetylene to aldehydes with cheaper metal sources, namely alkali

metals.[79,80] They presented the addition of terminal alkynes to ketones employing catalytic amounts of KO^{t}Bu, and CsOH. In these cases DMSO, THF, or a mixture of both were used as solvents. We wondered if the addition of acetylene to aldehydes would also be possible with a similar procedure. Following the example of *Babler* we chose to investigate the use of alkali metal-tert-butoxides because they are cheap and easy to handle.[124] We chose to study the reactions in toluene as solvent because it is removed easier than DMSO and worked well in the procedure employing $Zn(OTf)_2$. Thus, a solution of cyclohexylcarboxaldehyde in toluene was treated with one equivalent of alkalimetal *tert*-butoxide and the indicated amount of (+)-NME. The solution was cooled to -78 °C, saturated with acetylene and sealed (Table 5).

Table 5



92 96

alkoxide (X) 1 equivalent	(+)-NME	time	temperature	yield[a)]
K		18 h	50 °C	45%
K	1.1 equivalent	14 h	50 °C	67%
Na		14 h	23 °C	66%
Na	1.1 equivalent	14 h	23 °C	54%
Li		14 h	50 °C	0%
Li	1.1 equivalent	14 h	50 °C	0%

[a)] The products were isolated as their corresponding 4-nitrobenzoates

For potassium *tert*-butoxide the reaction had to be heated to 50 °C, or no addition took place. Interestingly, the product yield was higher when NME was added although analysis by chiral HPLC showed that the propargyl alcohol was obtained in racemic form. Employing sodium *tert*-butoxide, the reaction could be conducted at 23 °C, yielding 66% of propargylic alcohol. This time the addition of (+)-NME had a negative effect in reactivity, yielding only 54% product. Analysis by chiral HPLC showed again no stereoinduction. Lithium *tert*-butoxide could not effect the reaction - only starting material was isolated. It is known that monolithium

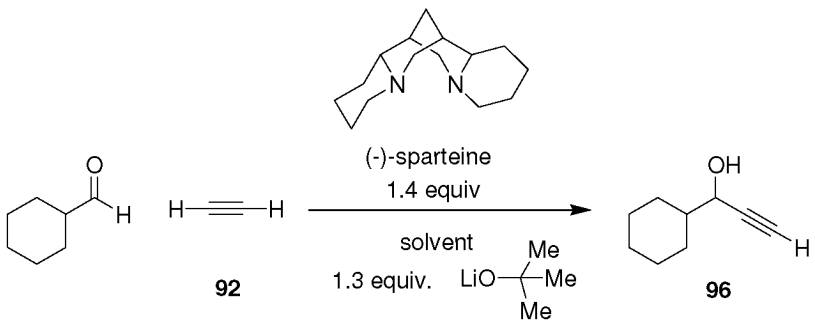
[124] KOC_4H_9 (1 kg 192 CHF, abcr), $NaOC_4H_9$ (1 kg 200 CHF, lancester), $LiOC_4H_9$ (100 g 285 CHF, abcr).

acetylide disproportionates readily above -25 °C into the more stable dilithium carbide and acetylene (Figure 18).[125]

Figure 18 *Disproportionation of Monolitium Acetylide into Dilithium Carbide and Acetylene*

This disproportionation can be prevented by complexation of a diamine to the monolithium acetylide.[126] With this in mind, we added (-) sparteine to the reaction mixture with the additional hope that it would induce enantioselectivity. Therefore, cyclohexylcarboxaldehyde in the indicated solvent was treated with 1.3 equivalent lithium *tert*-butoxide and 1.4 equivalent (-) sparteine (Equation 40). The solution was cooled to -78 °C, saturated with acetylene and sealed. In toluene and THF the reaction had to be heated to 50 °C in order to get addition whereas in CH_2Cl_2 the addition took place at 23 °C. The corresponding propargylic alcohols were isolated in 62-74 % yield. The reaction in toluene provided the highest ee: 13%.

Equation 40



solvent	time (h)	temperature	yield[a)]	ee[b)]
toluene	20	50 °C	62%	13%
THF	12	50 °C	64%	2%
CH_2Cl_2	5	23 °C	74%	10%

[a)] The products were isolated as their corresponding 4-nitrobenzoates
[b)] The ee was determined by chiral HPLC

[125] (a)Moissan, H. Compt. Rend. **1998**, *126*, 302. (b) Corbellini, M.; Turner, L. Chem. Ind. (Milan) **1960**, *42*, 251; Chem. Abstr. **1960**, *54*, 19250.
[126] Beumel, O. F.; Harris, R. F. *J. Org. Chem.* **1963**, *28*, 2775.

2.3 Conclusion

By saturation of toluene with acetylene at -78 °C and reaction temperatures of 50 °C the reaction time in the Zn-mediated enantioselective addition of acetylene to aldehydes could be decreased from 7-14 days to 11-22 h. Employing potassium-*tert*-butoxide instead of the combination of $Zn(OTf)_2$ and NEt_3 in toluene as a base furnished the corresponding propargylic alcohol as well. However, a catalytic or highly enantioselective reaction is not yet achieved employing alkali metal-*tert*-butoxides as bases.

Chapter 3

The Enantioselective Synthesis of 3-Butane-1,2-diol by Pd-Catalyzed Rearrangement

3.1 Introduction

3-Butene-1,2-diol (**100**) is a versatile polyfunctional chiral synthon that can be manipulated in a highly stereo- and chemoselective manner. The utility of diol **100** has been demonstrated in the synthesis of a wide range of chiral building blocks[127,128,129] as well as its application in total syntheses. These include a HIV protease inhibitor intermediate, [130] oscillatoxin A, [131] (-) bulgecinine, [132] D-allosamine, [133] (-)-bestatin, [134] cyclosporine, [135] (-)-tulipalin B, [136] (+/-)-blastmycinone, [137] and statine.[138] This introduction presents some approaches to the synthesis of enantiomerically enriched 3-butene-1,2-diol (**100**).

3.1.1 Preparation of 3-Butene-1,2-diol by Enzymatic Resolution

Racemic 3-butene-1,2-diol (**100**) is commercially available or can be obtained by isomerisation of the cheaper cis-2-butene-1,4-diol (**101**).[127] Treatment of diol **101** with 0.13 mol% $HgSO_4$ under acidic conditions furnishes racemic 3-butene-1,2-diol (**100**) in 62% yield (Equation 41).

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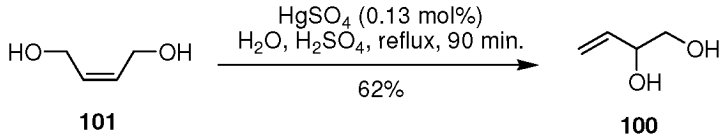
[127] Rama Rao, A. V.; Bose, D. S:; Gurjar, M. K.; Ravindranathan, T. *Tetrahedron* **1989**, *45*, 7031.
[128] Rama Rao, A. V.; Rajarathnam Reddy, E.; Joshi, B.V.; Yadav, J, S. *Tetrahedron Lett.* **1987**, *28*, 6497.
[129] Kozikowski, A.P.; Ghosh, A. K.; *J. Am. Chem. Soc.* **1982**, *104*, 5789.
[130] Gujar, M. K.; Devi, N.R. *Tetrahedron: Asymmetry* **1994**, *5*, 755.
[131] Walkup, R. D.; Cunningham, R. T: *Tetrahedron Lett.* **1987**, *28*, 4019.
[132] Maeda, M.; Okazaki, F.; Murayama, M.; a, Y.; Aoyagi, Y.; Ohta, A. *Chem. Pharm. Bull.* **1997**, *45*, 962.
[133] Jäger, V.; Schröter, D. *Synthesis*, **1990**, 556.
[134] Bergmeier, S. T.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852.
[135] Rama Rao, A. V.; Gurjar, M. K.; Bose, D. S.; Devi, R. R. *J. Org. Chem.* **1991**, *56*, 1320.
[136] Ohgiya, T.; Nishiyama, S. *Heterocycles*, **2004**, *63*, 2349.
[137] Kozikowski, A.P.; Ghosh, A. K.; *J. Org. Chem.* **1984**, *49*, 2762.
[138] Kang, S. H.; Ryu, D. H. *Bioorganic and Medicinal Chemistry Letters*, **1995**, *5*, 2959.

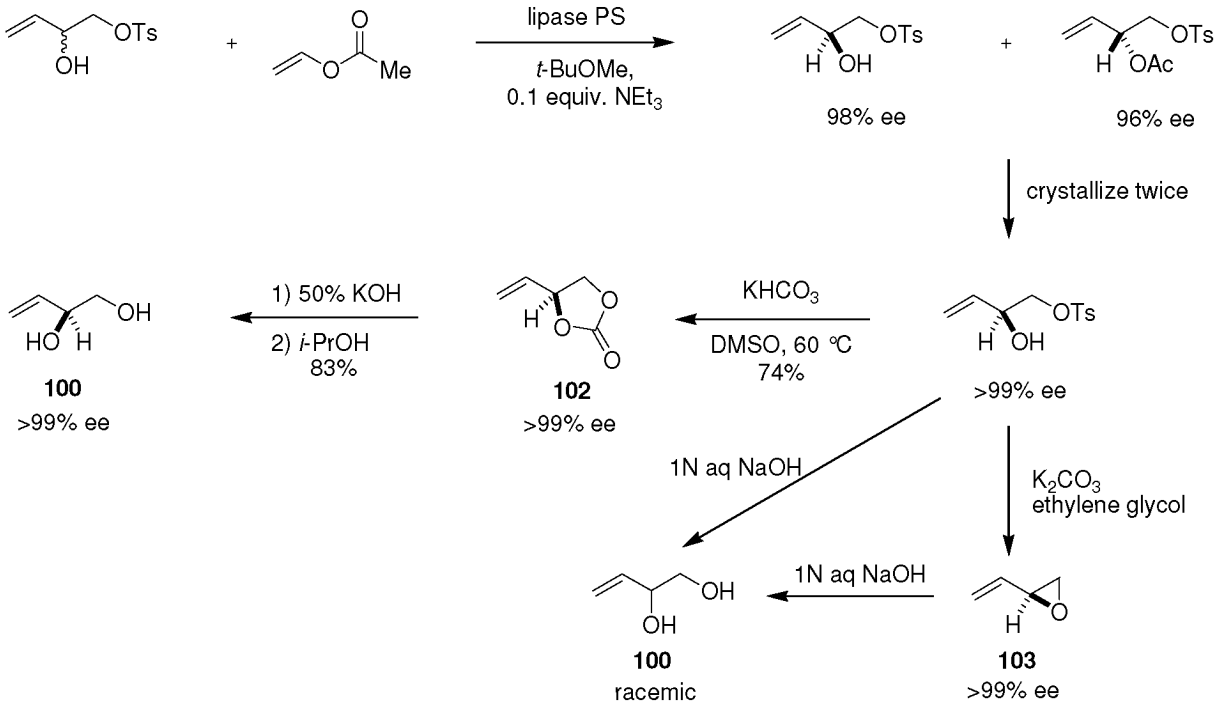
Equation 41



101 **100**

Enzymatic resolution by lipase PS[139] or by glycerol kinase[140] of the diol in the former or the primary monoprotected alcohol in the later[141,142,143,127,135] furnishes the enantiomerically enriched monoprotected tosylate. A practical procedure that provides the diol **100** on over 50-g scale is shown below (Scheme 49).[141]

Scheme 49



The monoprotected tosylate was used because it is a crystalline solid, and therefore an upgrade in enantiomeric excess is possible by crystallization. The attempted direct deprotection of the tosylate led to the formation of an intermediate epoxide. Unfortunately, the attack of hydroxide on the epoxide was not regioselective, leading to a total erosion of enantiomeric excess.

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[139] Suzuki, T.; Kasai, N.; Minamiura, N. *Tetrahedron: Asymmetry* **1994**, *5*, 239.
[140] Chenault, H. K.; Chafin, L. F.; Liehr, S. *J. Org. Chem.* **1998**, *63*, 4039.
[141] Boaz, N. W.; Falling, S.N.; Moore, M. K. *Synlett*, **2005**, *10*, 1615.
[142] Boaz, N. W.; Zimmermann, R. L. *Tetrahedron: Asymmetry* **1994**, *5*, 153.
[143] Ziegler, T.; Bien, F.; Jurisch, C. *Tetrahedron: Asymmetry* **1998**, *9*, 765.

The formation of the epoxide could be avoided by the use of potassium bicarbonate, which furnished the carbonate **102**. A possible mechanism involves the reaction of the secondary alcohol with in situ generated carbon dioxide followed by displacement of the tosylate with the thus generated carbonate anion. The cleavage of the carbonate with 50% aqueous potassium hydroxide afforded the diol **100** with retention of enantiomeric purity. The other enantiomer of diol **100** was obtained after deacylation and recrystallization.

3.1.2 Preparation of 3-Butene-1,2-diol by Synthesis from Chiral Pool

Early preparations of enantiomerically enriched diol **100** involved multi-step syntheses beginning with chiral pool materials such as D-mannitol,[144,145] L-ascorbic acid ,[146,147,148,149] or tartaric acid.[128,150] Some of them allow only the synthesis of one enantiomer of 3-butene-1,2-diol.

3.1.2.1 From D-Mannitol

In 1938, the oxidative cleavage of 1,2,5,6-diacetone D-mannitol to the corresponding aldehydes was reported.[144] From there *Wittig* reaction of the aldehyde with methyl triphenylphosphonium ylide, followed by deprotection afforded the (*S*)-diol **100** (Scheme 50).[151] A drawback of this method is that only a single isomer, namely D-mannitol, is readily available. L-Mannitol has to be prepared from L-mannose.

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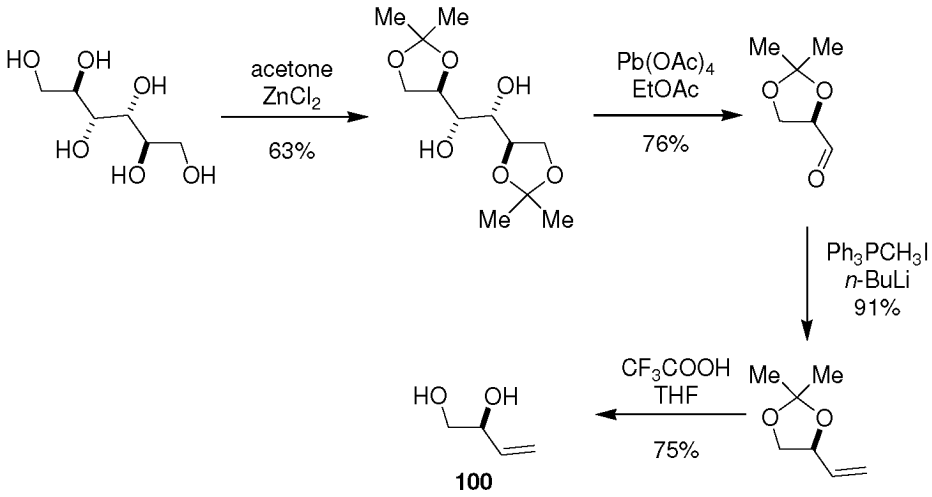
[144] Baer, E.; Fischer, H. O. *J. Biol. Chem.* **1939**, *128*, 463.
[145] Crawford, R. J.; Lutener, S. B.; Cockcroft, R. D. *Can J. Chem.* **1976**, *54*, 3364.
[146] Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.
[147] Marco, J. L.; Rodriguez, B. *Tetrahedron Lett.* **1988**, *29*, 1997.
[148] Takano, S.; Numata, H.; Ogasawara, K. *Heterocycles*, **1982**, *19*, 327.
[149] Hubschwerlen, C. *Synthesis*, **1986**, 962.
[150] Howes, D. A.; Brookes, M. H.; Coates, D.; Golding, B. T.; Hudson, A. T. *J. Chem. Res., Synop.* **1983**, 9.
[151] Kim, G.; Jeon, S. Y. *Bull. Korean Chem. Soc.* **2001**,*22*,1156.

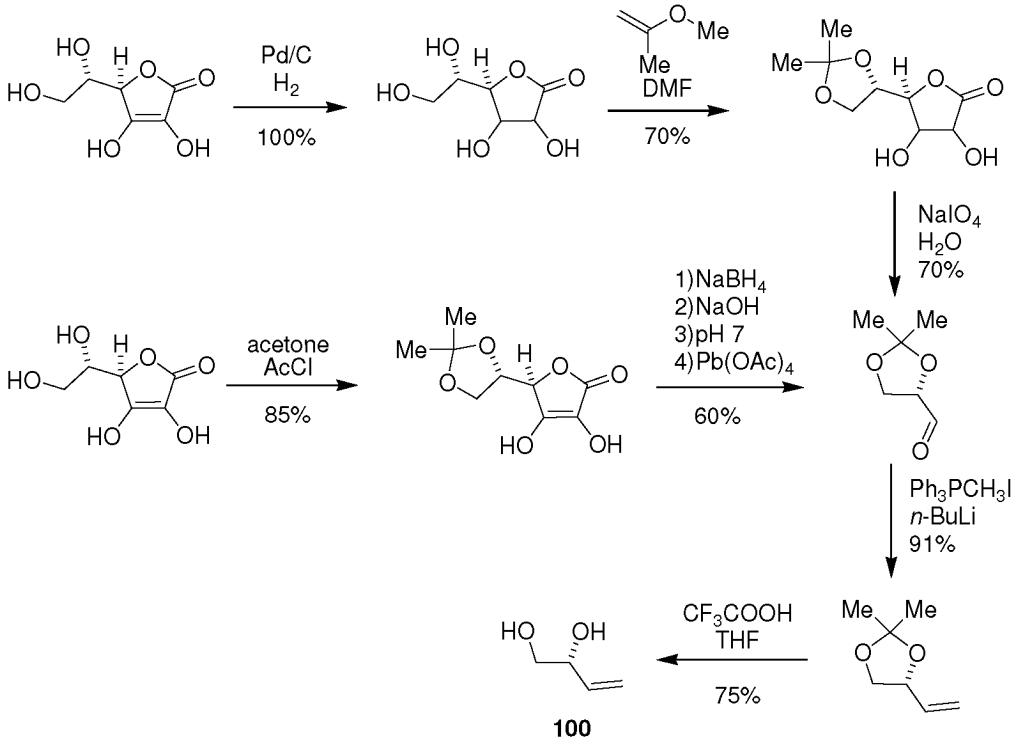
Scheme 50



3.1.2.2 From L-Ascorbic Acid

Two approaches to chiral diol **100** have used L-ascorbic acid as a starting material (Scheme 51). The first started with hydrogenation of L-ascorbic acid, followed by regioselective protection of one pair of the two diols.[149] Diol cleavage furnished the aldehyde. The second method began with protection of the saturated diol function of ascorbic acid.[146] Then, in a one-pot procedure the olefin was reduced with $NaBH_4$ and the lactone was cleaved with NaOH. After neutralization, cleavage with lead tetraacetate produced the aldehyde. *Wittig* olefination and acetonide deprotection, as before, gave (*R*)-diol **100**. Since the diastereomer of L-ascorbic acid, namely D-isoascorbic acid, is also commercially available, both enantiomers of alcohol **100** can be obtained.

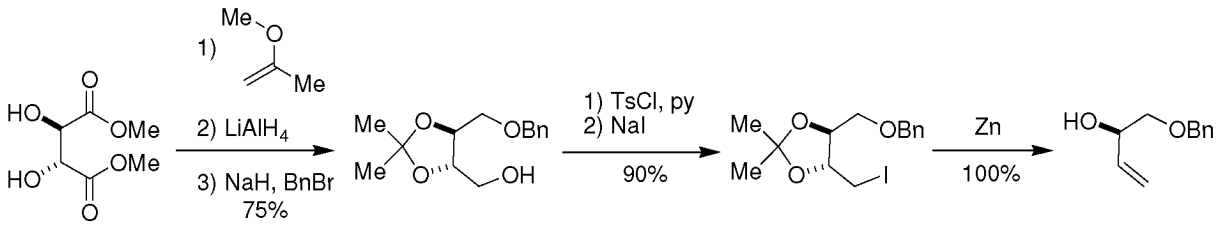
Scheme 51



3.1.2.3 From L-Tartaric Acid

A third procedure starts from the diethyl ester of L-tartaric acid[128] (Scheme 52). Diol protection followed by reduction and monoprotection of the resulting diol gave the monobenzyl ether. Iodination of the free alcohol and elimination gave (*R*)-1-benzyloxy-3-buten-2-ol in quantitive yield. Deprotection to the diol **100** was possible, but the yield was low. This method seems to be not as practical as the two discussed above; however tartaric acid is available as both L- and D-enantiomers.

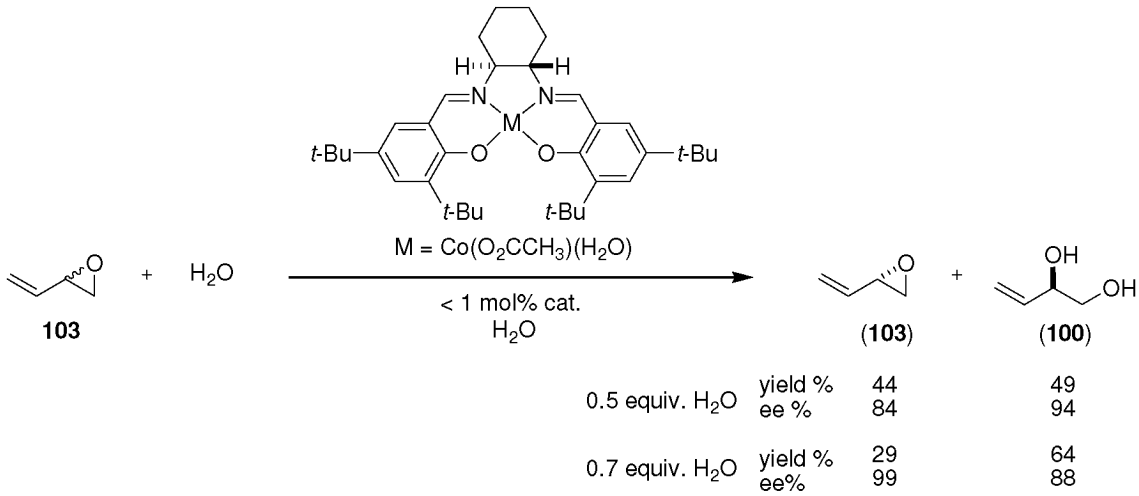
Scheme 52



3.1.3 Preparation of 3-Butene-1,2-diol by Hydrolytic Kinetic Resolution

A more recent preparative method developed by *Jacobsen*[152] is the hydrolytic kinetic resolution of racemic 3,4-epoxy-1-butene (**103**) (Scheme 53). The racemic epoxide **103** is produced by the *Eastman* process[153]-the Ag catalyzed aerobic epoxidation of butadiene. Although it is commercially available, it is not cheap or easily transported and handled because it tends to polymerize.

Scheme 53



		(103)	(100)
0.5 equiv. H_2O	yield %	44	49
	ee %	84	94
0.7 equiv. H_2O	yield %	29	64
	ee%	99	88

By varying the equivalents of water, the reaction can be tuned to give either good yield and moderate ee or lower yield and high ee. Both enantiomers of diol **100** can be obtained by this method because the ligand is available in both enantiomeric forms.

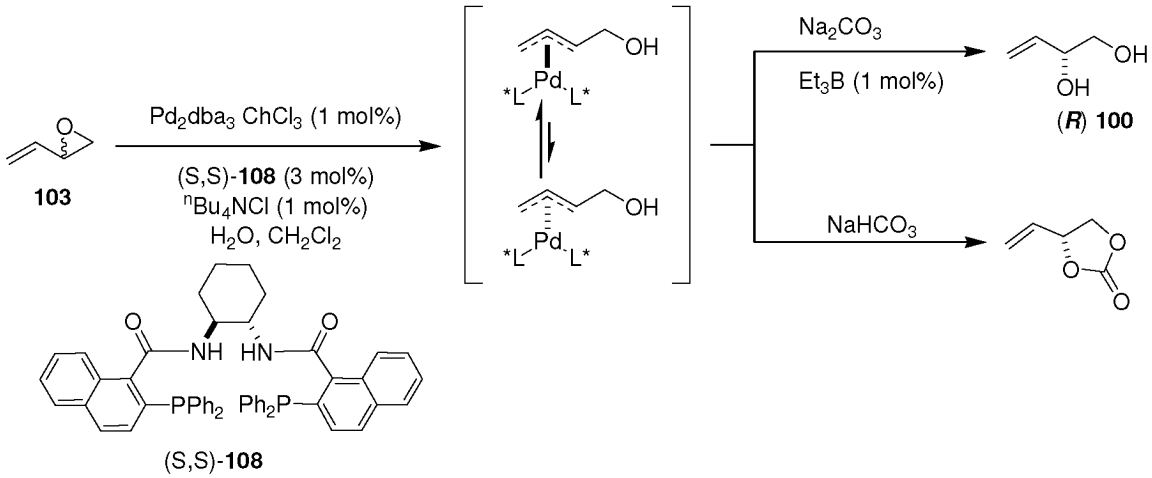
3.1.4 Preparation of 3-Butene-1,2-diol by Palladium-Catalyzed Dynamic Kinetic Resolution

Another approach is a palladium-catalyzed dynamic kinetic resolution presented by *Trost.* [154] Starting from racemic epoxide **103**, either the enantioenriched diol **100** or its corresponding carbonate could be obtained by palladium catalyzed allylic alkylation (Scheme 54). *Trost`s* initial procedure used Na_2CO_3 as the nucleophile and Et_3B to provide the diol **100** in

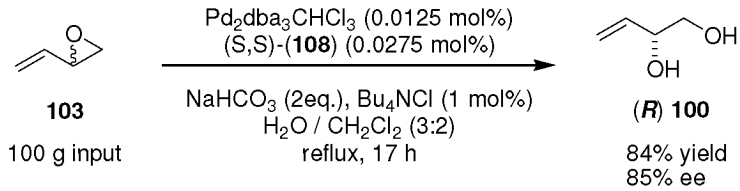
[152] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E.N. *Science*, **1997**, *277*, 936.
[153] Monnier, J. R. In *3rd World Congress on Oxidation Catalysis*, **1997**; Grasseli, R. K.; Oyama, S. T.; Gaffney, A. M.; Lyons, J. E., Eds.;Elsevier; New York, 1997; pp 135-149.
[154] Trost, B. M.; McEachern, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 8649.

yields of 70% and 86% ee. In an optimized procedure applicable to a 100 g-scale, the use of the alkylboron was avoided and $NaHCO_3$ was used as nucleophile (Scheme 55).[155] A catalyst loading of as low as 0.0275 mol% perhaps makes this the most practical synthesis of diol **100**, although the enantiomeric excess is not high (85%). A drawback is, as already mentioned above, that the starting material is not easy accessible in large quantities. Again, because the ligand is available in both enantiomeric forms, both enantiomers of diol **100** can be obtained by this method.

Scheme 54



Scheme 55



[155] Cheesman, N.; Fox, M.; Jackson, M.; Lennon, I. C.; Meek, G. *Proc. Natl. Acad. Sci. USA*, **2004**, 101, 5396.

3.2 Results

3.2.1 Background to Our Own Approach

Because diol **100** has been used in numerous natural products syntheses as a valuable building block its availability is highly desirable. Among the many routes to enantioenriched diol **100** described above none furnishes the desired diol **100** in over 50% yield with more than 90% ee in less than two steps. Therefore we started a project that would allow preparing diol **100** in good yields and high enantiomeric excess from easy and unexpensive starting materials. Similar to the work of *Trost*, our approach is based on a palladium catalyzed asymmetric allylic alkylation. Allylic monoacetates and monocarbonates are used extensively in palladium-catalyzed allylation of nucleophiles.[156,157] There are few reports on palladium-catalyzed reaction of bifunctional allylic diacetates and dicarbonates with nucleophiles featuring their bifunctionality (Scheme 56).[158,159] The bisacetates and biscarbonates starting materials are prepared in one step from achiral and unexpensive compounds (Scheme 57). Today's methods employing this double alkylation use dinucleophiles which are not easily cleaved to the corresponding diols, diamines and aminoalcohols.[160,161]

Terminal attack of the nucleophile leading to unbranched products is often a problem in palladium catalyzed allylic alkylations.[156] This is not a problem here since the formation of a six-member ring is favored over an eight-member one. Therefore, only the product resulting from six-member ring formation is obtained. Two chiral ligands were employed in this reaction. Using BINAP the yields and enantiomeric excesses were low to moderate.[158] Employing MeOBIPHEP higher yields were obtained but the enantiomeric excesses remained moderate.

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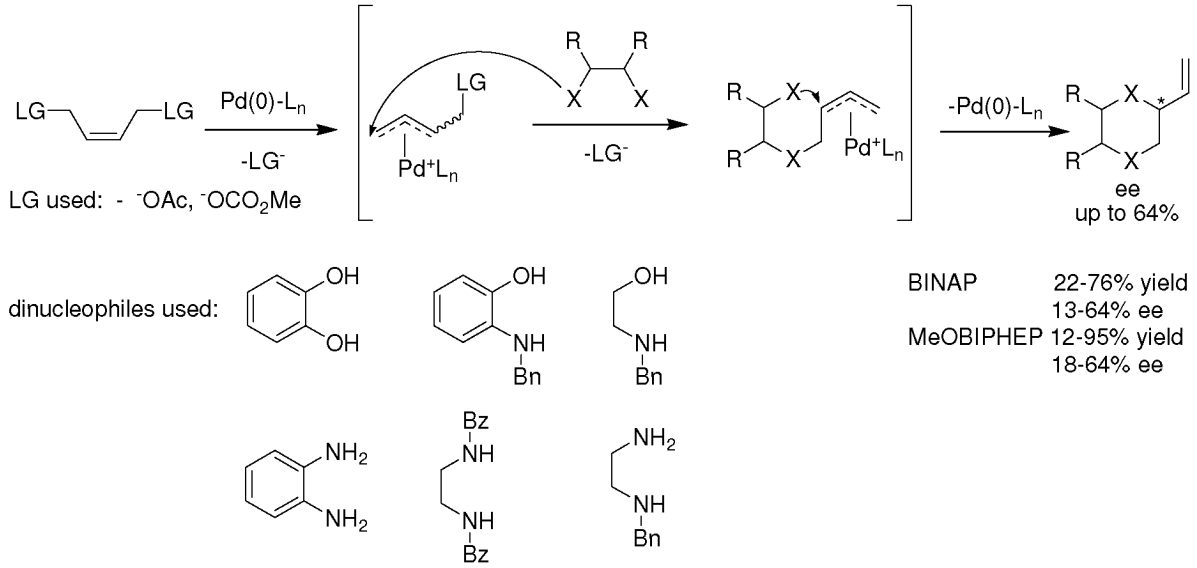
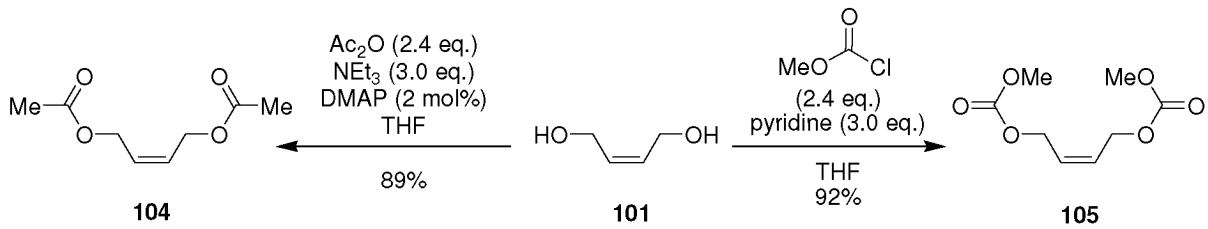
[156] Trost, B. M.; Van Vranken: D. Lv. *Chem. Rev.***1996**, *96*, 395.
[157] Pfaltz, A.; Lautens, M. *Comprehensive Asymmetric Catalysis I-III*, **1999**, 2, 833.
[158] Massacret, M.; Lakhmiri, R:; Lhoste, P:; Nguefack, C:;Abdelouahab, F. B. B.; Fadel, R.; Sinou, D: *Tetrahedron: Asymetry*, **2000**, *11*, 3561.
[159] Massacret, M.; Lhoste, P:; R.; Sinou, D: *Eur. J. Org. Chem.* **1999**, 129.
[160] Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826.
[161] Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 3388.

Scheme 56



Scheme 57



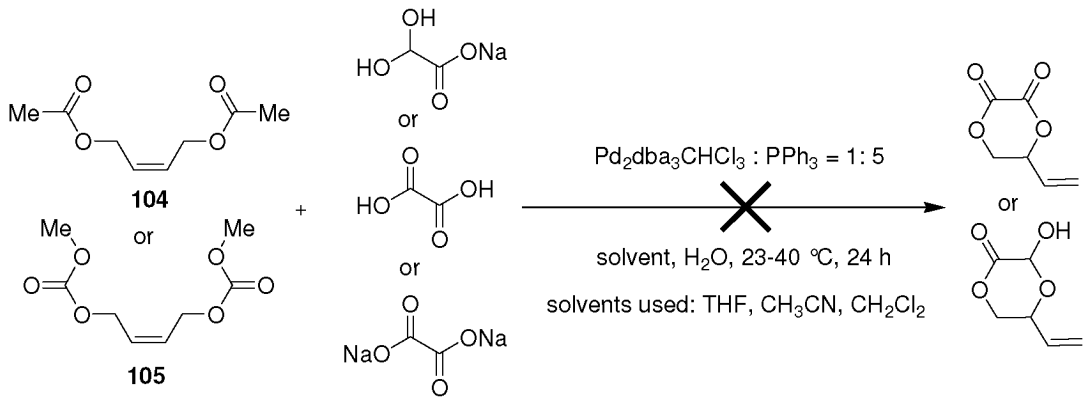
Our attempt to obtain 3-butene-1,2-diol (**100**) began with the same strategy, except we reasoned that the bisnucleophile should be easily cleaved after the addition. This would allow us to prepare the desired diol **100** in three steps from unexpensive and easy available starting materials.

3.2.2 Intermolecular Approach

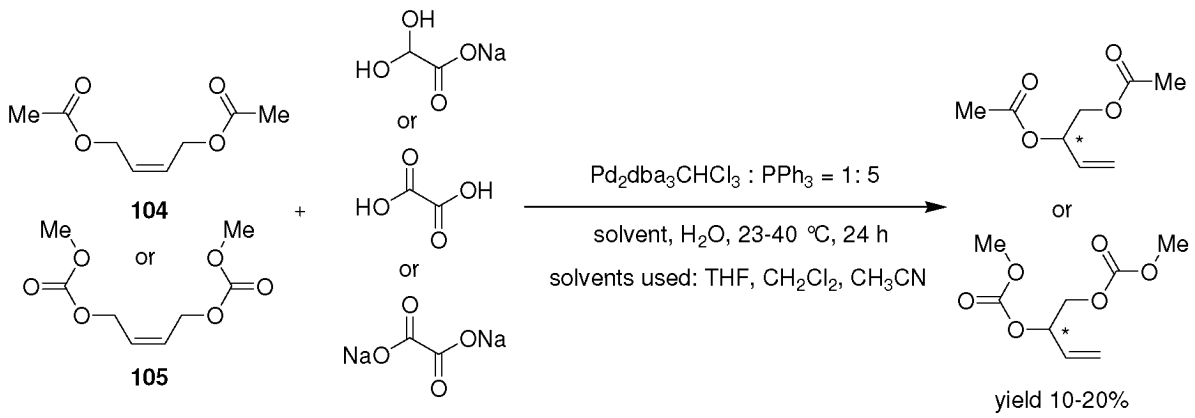
Starting from easily prepared bisacetates **104** and biscarbonates **105** (Scheme 57) our plan was to use commercially available bisnucleophiles, namely oxalic acid or its disodium salt and glyoxylic acid sodium salt monohydrate (Scheme 58). To a solution of $Pd(dba)_3CHCl_3$ and PPh_3 in THF under an argon atmosphere was added the biscarbonate **105** and oxalic acid. The solution was stirred at 40 °C for 24 h, but only starting material and rearranged compound could be isolated (Scheme 59). When the disodium salt of oxalic acid was added as nucleophile a

suspension was obtained, suggesting that the salt is not soluble in THF. Changing the solvent to acetonitrile or CH_2Cl_2 gave the same result. Glyoxylic acid sodium salt monohydrate was soluble in THF, but no reaction took place. To increase the probability of nucleophilic attack we next turned our attention to an intramolecular version of the reaction.

Scheme 58



Scheme 59



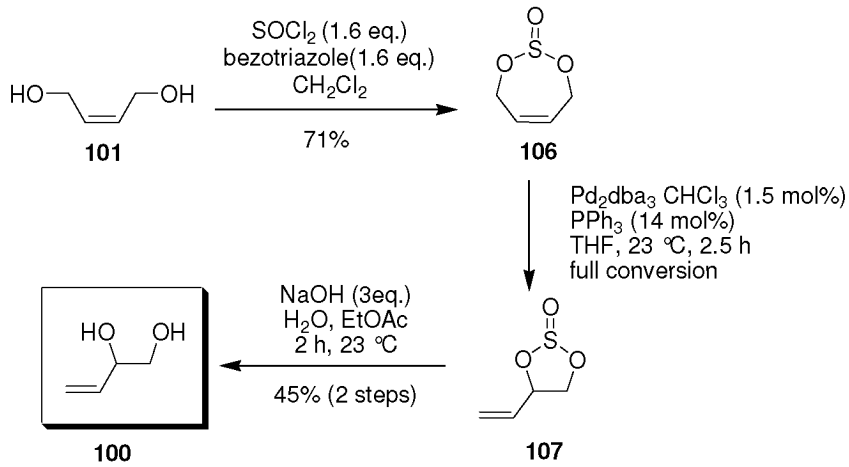
3.2.3 Intramolecular Approach

Because the attempts with external bisnucleophiles that would be easy to cleave after the addition were not successful, we turned our attention to an intramolecular approach. The cyclic seven-member sulfite **106** is a known compound that can be obtained from unexpensive starting materials in one step.[162] Therefore, *cis*-2-butene-1,4-diol (**101**) was treated with thionylchloride and benzotriazole in dichloromethane to give cyclic sulfite **106** in 71% yield on a 10 g-scale.

[162] Chaudhari, S. S.; Akamanchi, K. G. *Synlett*, **1999**, *11*, 1763.

To a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (1.5 mmol) and PPh_3 (14 mmol) in THF under an argon atmosphere was added the sulfite **106**. After stirring for 150 min. at 23 °C the solution was filtered over a short SiO_2-plug and concentrated (Scheme 60). Crude ^{1}H-NMR showed full conversion to the rearranged 5-member cyclic sulfite **107**. Purification of the 5-member cyclic sulfite **107** by flash chromatography on SiO_2 led to decomposition. Therefore, we decided to deprotect it and isolate the diol **100** instead (Scheme 60). Treatment of sulfite **107** with NaOH in a H_2O/EtOAc mixture and stirring at 23 °C for 2 h afforded the desired diol **100**. The reaction looked clean by TLC but isolation of the diol **100** proved to be difficult. This is mainly due to the extraction of the polar diol **100** from the water phase. Acidification of the water phase to pH 2 with HCl followed by the addition of NaCl until saturation and subsequent extraction with EtOAc (10 times) furnished 45% yield over 2 steps. This isolation procedure could likely be optimized to get a better yield, as the reaction looked very clean.

Scheme 60

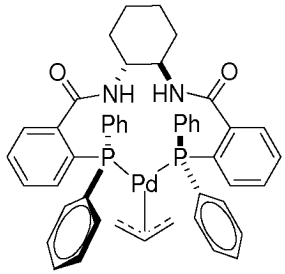


3.2.3.1 Enantioselective, Intramolecular Approach

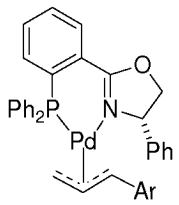
After the discovery of the rearrangement to afford the desired diol **100** we turned our attention to the identification of an enantioselective process. Special ligands have been developed for palladium catalyzed allylic alkylations, because the crucial bond-forming process, the nucleophilic addition to the allyl system, is taking place outside the coordination sphere of conventional ligands. One concept is to increase the bite angle and, as a consequence, create a chiral cavity in which the allyl system is embedded. In this case *trans*-1,2-diaminocyclohexanone

is used as a chiral scaffold to induce a specific chiral arrangement of the four P-phenyl groups.[156] Another concept to control the selectivity is based on electronic effects. In contrast to allyl complexes with C_2-symmetric ligands, complexation of the metal by P,N-ligands should result in electronic discrimination of the two allylic termini due to the different trans influence of phosphorus and nitrogen (Figure 19).[157] Otherwise chiral bidentate phosphines, bidentate nitrogen ligands and monodentate phosphines are also used, albeit their scope is more limited.

Figure 19 *Ligands developed for asymmetric allylic alkylation*



chiral cavity



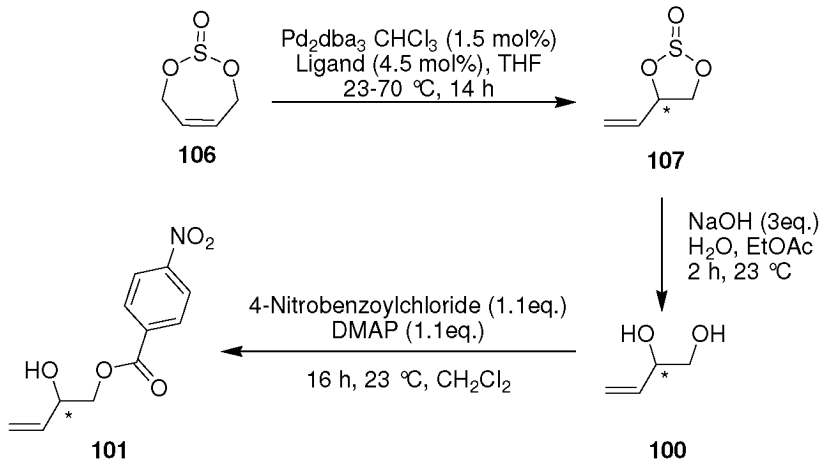
electronic discrimination
due to *trans* effect

For the ligand screen a ratio of Pd(0) to ligand of 2:3 was used to make sure that there is no background reaction that would lead to racemic product (Scheme 61). Determination of the ee for the diol **100** by GC was only possible qualitatively, since no complete separation of the two peaks was achieved. For ease of HPLC separation the diol was monoprotected with 4-nitro-benzoylchloride. Now complete separation of the two peaks by chiral HPLC was achieved and furnished exact ee values for alcohol **100**.

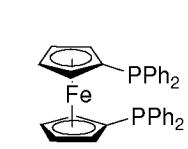
We first tried a series of commercially available diphosphines. Therefore, a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (1.5 mol%) and ligand (4.5 mol%) in THF under an argon atmosphere was treated with sulfite **106**. After stirring at 23 °C for 14 h the conversion was measured. If no conversion could be obtained the experiment was repeated at 60 °C. Employing diphosphines diol **100** was obtained in 0 to 31% yield, albeit as a racemate (Scheme 62). Using ligand **108**, which, as described above, forms a chiral cavity, furnished the diol in 2% yield and 5% ee. The phosphinooxazoline ligands **109** and **110** gave the highest enantiomeric excess (13%) in 5 to 6% yield. Since, apart from triphenylphosphine, all ligands gave low conversion we also tried the

monodentate phosphoramidite ligand **111** in order to get better conversion. The diol **100** was obtained in 5% yield as a racemate.

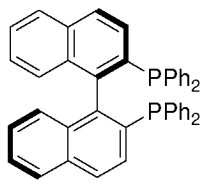
Scheme 61



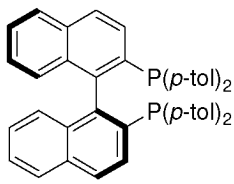
Scheme 62



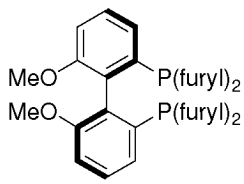
yield: 31% ee:0% 23 °C



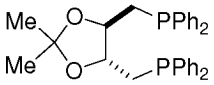
yield: 20% ee:0% 60 °C



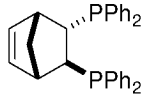
yield: 8% ee:0% 23 °C



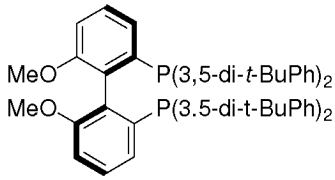
yield: 27% ee:0% 23 °C



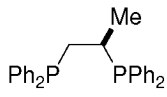
yield: 10% ee:0% 23 °C



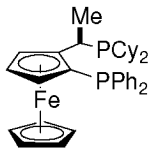
yield: 8% ee:0% 60 °C



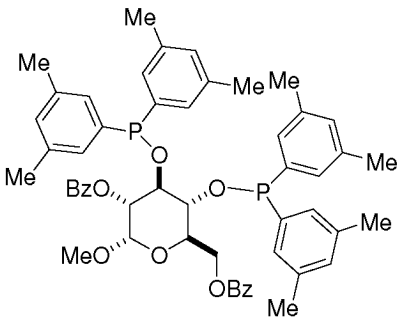
no conversion 60 °C



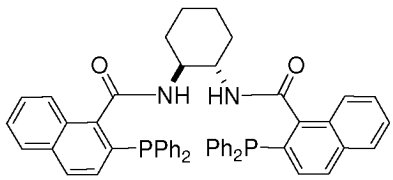
yield: 9% ee:0% 60 °C



no conversion 60 °C

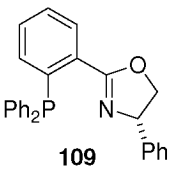


yield: 25% ee:0% 40 °C



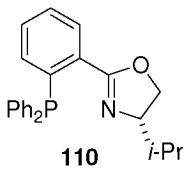
108

yield: 2% ee:5% 60 °C



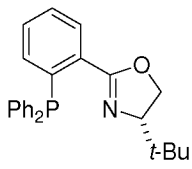
109

yield: 6% **ee:13%** 60 °C

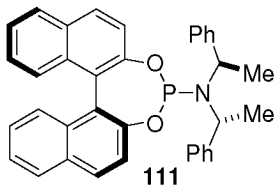


110

yield: 5% ee:13% 60 °C

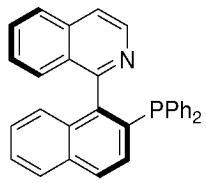


no conversion 60 °C



111

yield: 5% ee:0% 60 °C



12

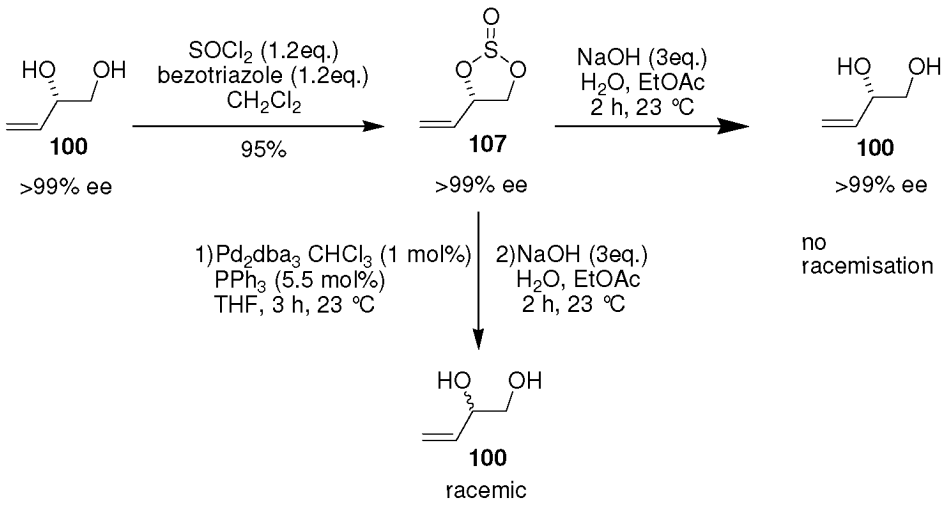
no conversion 60 °C

To make sure that the low enantiomeric excess was not due to racemization during the deprotection of 5-member cyclic sulfite **107** to the diol **100**, the enantiopure diol **100** was synthesized using D-mannitol as a starting material (Scheme 50). Treatment of the enantiopure diol **100** with $SOCl_2$ and benzotriazole in CH_2Cl_2 furnished the cyclic sulfite **107** in 95% yield (Scheme 63). Deprotection using exactly the same conditions as in the ligand screen, namely 3 equiv. of NaOH in a water/EtOAc mixture at 23 °C for 2 h furnished the enantiopure diol **100**. The enantiomeric excess was determined by chiral GC; both diols, the starting material and the

one after the protection/deprotection sequence showed an ee over 99%. This establishes that no racemisation occurs in the deprotection step from the cyclic sulfite **107** to the diol **100**.

Interestingly, when enantiopure sulfite **107** was treated with palladium and triphenylphosphine in THF at 23 °C for 3 h and subsequently deprotected to the diol **100** using the same conditions as before, complete racemisation occurred. Since we established that there is no racemisation during the deprotection, this suggests that the allyl-palladium complex was formed. Alternation of palladium between enantiofaces of the allylic fragment can then occur and, therefore, the enantiomeric purity is lost.

Scheme 63

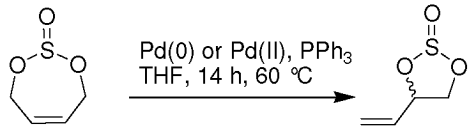


3.2.3.2 Screening of Different Pd Sources – Discovery of a Diastereoselective Rearrangement

To evaluate the effect of the palladium source in the outcome of the rearrangement we next employed Pd(0) and Pd(II) sources (Table 6). Full conversion was achieved using $Pd(PPh_3)_4$ and $Pd_2(dba)_3{\cdot}CHCl_3$ with 9.3 equiv. of PPh_3. When the ratio of $Pd_2(dba)_3{\cdot}CHCl_3$ to PPh_3 was 1 to 4, the conversion was only 29%. Non conversion was obtained when $Pd_2(dba)_3{\cdot}CHCl_3$ was used without additional PPh_3. Employing Pd(II) sources the highest conversion obtained was 40% using 5 mol% $PdCl_2(CH_3CN)$. $Pd(OAc)_2$ under identical conditions gave 20% yield. On the other hand the allyl-Pd(II)Cl-dimer (1.5 mol%) and $PdCl_2$ (5 mol%) gave no product. When PPh_3 was added to $PdCl_2(CH_3CN)$ diminished yields were obtained, namely 33% for a ratio of 2 to 1, 10% for 1 to 1 and no conversion at all for a ratio of $PdCl_2(CH_3CN)$ to PPh_3 equal 1 to 2. One could

speculate that the Pd(II) was reduced to Pd(0) by the oxidation of PPh_3 to $OPPh_3$. As already mentioned, Pd(0) does not catalyze the reaction without the addition of PPh_3.

Table 6



106 107

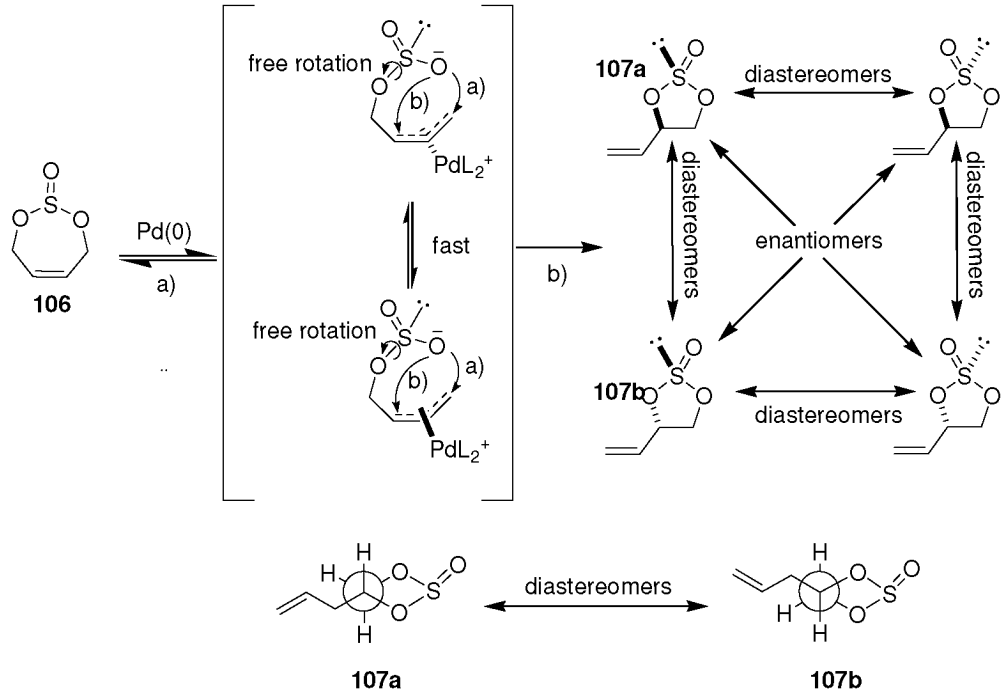
entry	Pd source	(mol%)	PPh_3 (mol%)	conversion (%)
1	$Pd(PPh_3)_4$	5.0	-	100
2	Pd_2dba_3 $CHCl_3$	1.5	14	100
3	Pd_2dba_3 $CHCl_3$	1.5	6	29
4	Pd_2dba_3 $CHCl_3$	3.0	-	-
5	Pd_2Cl_2 C_6H_{10}	1.5	-	-
6	$PdCl_2$	5.0	-	-
7	$PdCl_2$ $(CH_3CN)_2$	5.0	-	40[a)]
8	$Pd(OAc)_2$	5.0	-	20[a)]
9	$Pd(COD)Cl_2$	5.0	-	-
10	$PdCl_2$ $(CH_3CN)_2$	5.0	2.5	33[a)]
11	$PdCl_2$ $(CH_3CN)_2$	5.0	5.0	10[a)]
12	$PdCl_2$ $(CH_3CN)_2$	5.0	10.0	-

[a)] only a single set of diastereomers could be obtained in the ^{1}H-NMR

Interestingly, in the reactions with Pd(II) sources only a single set of enantiomers was detected in the ^{1}H-NMR. This was not the case when Pd(0) sources were used, there both sets of enantiomers were obtained in the ^{1}H-NMR . The 7-membered sulfite **106** is a *meso*-compound. On the other hand, the 5-membered sulfite **107**, obtained after ring contraction, contains two stereocenters (Scheme 64). Therefore four stereoisomers of the five-member cyclic sulfite **107** do exist (Scheme 64).

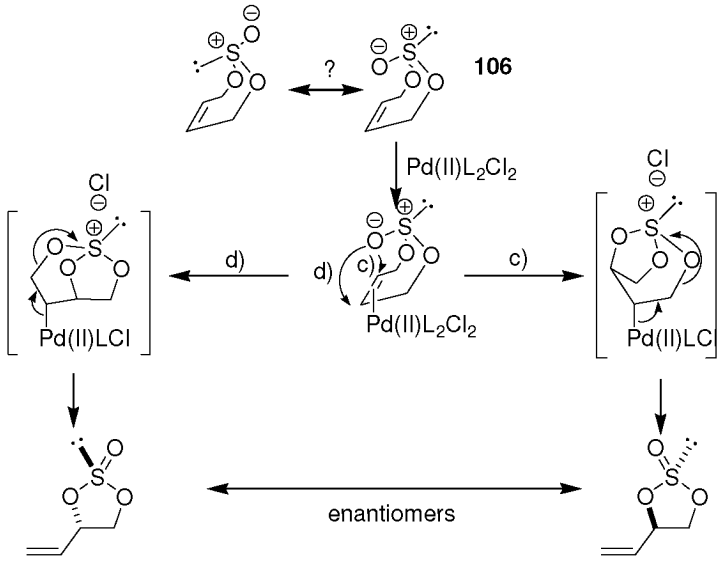
For Pd(0), as mentioned above, the palladium can switch between enantiofaces of the allylic fragment. This alternation should be fast since the chiral information in the experiment described above was completely lost. Thus, rotation of the sulfite around the S-O bond occurs before nucleophilic attack. Both diastereomers can adopt a stable half-chair conformation where the vinyl is in a *pseudo*-equatorial position. Therefore there is no preference of one over the other diastereomer and thus all four stereoisomers are obtained in the Pd(0) catalyzed rearrangement.

Scheme 64 Suggested mechanism for Pd(0)



For Pd(II) we propose a different mechanism (Scheme 65). After activation of the olefin by Pd(II) coordination a nucleophile can attack the olefin. The only nucleophile around is the oxygen of the sulfite. When the seven-member sulfite **106** adopts a *boat*-conformation, either the lone pair of the sulfur or the oxygen can be aligned to reach the olefin. If the oxygen is positioned on top of the olefin, nucleophilic attack on the olefin can occur. Since the seven-member sulfite **106** is a *meso*-compound, there is no preferential for one of the two carbons of the olefin to be attacked. In this process a bicyclic species is produced, containing a five- and a six-member ring. When the five-member ring gets opened, starting material is obtained. Opening of the six-member ring leads to the five-member sulfite **107** as a pair of enantiomers.

Scheme 65 Suggested mechanism for Pd(II)



3.3 Conclusion

The intermolecular approach to obtain 3-butene-1,2-diol (**100**) from easily prepared diacetates or dicarbonates furnished only rearranged product. This suggests that bisnucleophiles that could easily be cleaved after the addition are not nucleophilic enough.

In the intramolecular approach we identified the seven-member cyclic sulfite **106** as a substrate that underwent the desired rearrangement. It is obtained from inexpensive *cis*-butane-1,4-diol in one step in 71% yield. The racemic rearrangement was quantitative, employing a Pd(0) source with at least 4 equiv. of PPh_3. Deprotection of the rearranged product furnished the desired 3-butene-1,2-diol (**100**). Among the ligands tested so far (S)-2-(2-(diphenyl-phosphine)phenyl)-4-phenyl-4,5-dihydrooxazole (**109**) gave the best result, furnishing the product in 13% ee.

An interesting result was obtained when Pd(II) sources were employed in the reaction. Only one set of enantiomers were obtained, suggesting that two different mechanisms are operating, depending on the oxidation state of palladium.

4 Conclusion

The modifications of N-PINAP presented in *Part 1* dramatically improved the yield and enantioselectivity in the conjugate addition of phenylacetylene to *Meldrum`s* acid derived acceptors. With a ligand loading of only 10 mol% the corresponding conjugate addition products could be isolated in up to 94% yield and 97% ee performing the reaction at 0 °C in 10 equiv of phenylacetylene. The synthetic utility of this method has been demonstrated in the asymmetric synthesis of a key intermediate of TNF inhibitors and GRP receptor antagonists. A strong positive nonlinear effect was observed for the PINAP catalyzed conjugate addition. Employing a mixture of diastereomeric PINAP ligands (20% de) in the reaction the corresponding products were obtained in up to 80% yield and 94% ee. To determine the origin of this effect needs further experiments. Although the PINAP ligand can be obtained in diastereomerically pure form by chromatography, because of the strong positive nonlinear effect, high enantioselectivities can be obtained for certain substrates without the separation of the two diastereomers. The modular synthesis of PINAP allows preparation of various analogs. It would be possible to prepare and screen various PINAP ligands in a certain reaction for optimal performance. Therefore this new class of ligands should find wide applications in total synthesis as well as methodology in the future.

In *Part 2* enantioselective addition of acetylene to aldehydes was studied. Under the optimized conditions, the reaction time of the Zn-mediated enantioselective addition of acetylene to aldehydes was significantly decreased compared to the previously described conditions (from 7-14 days to 11-22 h). This improvement further enhanced the synthetic effectiveness of the process.

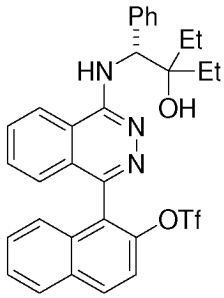
Finally, in *Part 3* a Pd-catalyzed rearrangement of cyclic sulfate was investigated. An easily available and stable seven-member cyclic sulfite underwent a Pd-catalyzed rearrangement to 3-Butane-1,2-diol, a valuable building block in natural product synthesis. Efforts were made to develop the enantioselective variant of the process, and various ligands on palladium were screened. Among the ligands tested, (*S*)-2-(2-(diphenyl-phosphine)phenyl)-4-phenyl-4,5-dihydrooxazole gave the best result, furnishing the product in 13% ee. The future work in this project involves examination of different types of ligands to improve the enantioselectivity.

5 Experimental Part

All non-aqueous reactions were carried out using oven-dried glassware under a positive pressure of argon unless otherwise noted. THF, acetonitrile, toluene, Et_2O and CH_2Cl_2 were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H_2O content < 30 ppm, Karl-Fischer titration).[163] Triethylamine, *Hünigs* base and pyridine were distilled from KOH. *N*-Buthyl lithium was titrated with *s*-BuOH/phenanthroline.[164] Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Merck Silica Gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain. Chromatografic purification of products was performed on E. Merck Silica Gel 60 (230-400 mesh) using a forced flow of eluant at 0.4 bar pressure.[165] Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Purified compounds were further dried under high vacuum (0.5-0.05 mbar). Yields refer to purified and spectroscopically pure compounds. Kugelrohr distillations were performed with a Büchi Glass Oven B-580. Melting points were measured on a Büchi 510 apparatus. All melting points were measured in open capillaries and are uncorrected. Optical rotaitions were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell. NMR spectra were recorde on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz for ^1H and ^{13}C acquisitions, respectively, or on a Bruker DRX500 spectrometer operating at 500 MHz and 125 MHz for ^1H and ^{13}C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, dt = double triplett, m = multiplet, br = broad signal, coupling constant(s) in Hz, integration). Infrared spectra were recorded on a Perkin Elmer Spectrum RX-I FT-IR spectrophotometer as thin films unless stated otherwise and are reported as cm^{-1} (w = weak, m = medium, s = strong).Gas chromatographic measurements were performed on a Varian 3300 gas chromatographer or a HP 6890 Series gas chromatographer using a Supelco fused silica column β-Dex 120 (length: 30 m, diameter: 0.25 cm, film thickness 0.25 μm), hydrogen as carrier gas and a FID detector. Mass spectrometric measurements were performed by the mass spectrometry service of the LOC at the ETHZ on a Finnigan TSQ 7000 ESI spectrometer for low resolution measurements and on an IONSPEC Ultima ESI-FT-ICR spectrometer at 4.7 Tesla, on an Ion Spec Ultima HR FT-ICR MS MALDI-FT-ICR MS using the DHB-tl (2,5-Dihydroxy-benzoic acid-two layers) method at 4.7 Tesla or on a EI-HIRES Micromass Autospel-ULTIMA spectrometer at 70 eV for high resolution measurements. Elemental analysis was performed by the Mikroelementaranalytisches

[163] Pangborn, A. B.; Girardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F, J. *Organometallics* **1996**, *15*, 1518.
[164] Watson, S. C.; Eastham, J. F. J. *Organomet. Chem.* **1967**, *9*, 165.
[165] Still, W. C.; Kahn, M.; Mitra, A."Rapid chromatographic technique for preparative separations with moderate resolution." *J. Org. Chem.* **1978**, *43*, 2923.

Laboratorium der ETHZ. Enantiomeric excesses were determined by chiral HPLC analysis with Merck-Hitachi D-7000 system. Solvent mixtures, conditions, retention times and columns used are given in parentheses.



Trifluoromethanesulfonic acid 1-[4-((*R*)-2-ethyl-2-hydroxy-1-phenylbutylamino) phthalazin-1-yl]-naphthalen-2-yl ester (112).

To 600 mg (1.37 mmol) of trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-naphthalen-2-yl (**25**) ester was added 1.06 g (5.49 mmol) of 3-((*R*)-aminophenyl-methyl)pentan-3-ol. The suspension was stirred for 24 h at 120 °C. FC (toluene/EtOAc 10:0 → 5:1) followed by crystallization from Et_2O afforded 451 mg (55%) of the title compound as a white powder as a mixture of diastereomers.

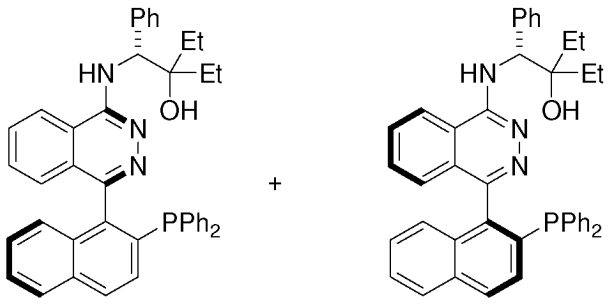
mp: 117-119 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-1.00 (m, 12H), 1.18-1.32 (m, 2H), 1.39-1.50 (m, 2H), 1.71-1.95 (m, 4H), 2.05-2.33 (m, 2H), 5.67 (d, J = 8.4, 1H), 5.73 (d, J = 8.5, 1H), 6.54-6.73 (m, 2H), 7.15-7.36 (m, 10 H), 7.43 (d, J = 3.4, 1H), 7.51-7.65 (m, 9H), 7.75-7.79 (m, 2H), 7.97-8.11 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.6, 7.8, 8.4, 8.5, 28.1, 28.2, 29.1, 29.1, 59.1, 59.7, 78.0, 78.1, 118.1, 118.3, 118.4(q, J_{CF} = 318), 118.7 (q, J_{CF}= 318), 119.9, 119.9, 121.1, 121.2, 126.2, 126.9, 127.0, 127.5, 127.6, 127.7, 127.8, 127.8, 128.2, 128.2, 128.4, 128.5, 128.6, 128.6, 129.0, 129.3, 131.7, 131.7, 131.8, 131.9, 133.0, 133.0, 133.9, 134.0, 140.6, 140.9, 145.8, 145.9, 146.5, 146.7, 153.3, 153.4.

FTIR (thin film, cm^{-1}): 3395 (w), 3052 (w), 2964 (w), 1508 (s), 1420 (s), 1544 (w), 1213 (s), 1138 (s).

MS (HiResMALDI, pos.) calcd for $C_{32}H_{31}N_3O_5F_3S^+$ ($M+H^+$) 596.1825, found 596.1828.



1st diastereomer 2nd diastereomer

(*R*,*M*)-[4-(2-Diphenylphosphanyl-naphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl} pentan-3-ol (1st diasteomer, 31a) and (*R*,*P*)-[4-(2-Diphenylphosphanyl-naphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (2nd diasteomer, 31b).

A solution of 37 mg (0.07 mmol) $Ni(dppe)Cl_2$ in 2.5 ml of DMF at 23 °C was treated with 0.244 ml (1.40 mmol) of diphenylphosphine. The resulting dark red solution was stirred at 120 °C for 30 min, treated with, a solution of 417 mg (0.70 mmol) of trifluoromethanesulfonic acid 1-[4-((*R*)-2-ethyl-2-hydroxy-1-phenyl-butylamino) phthalazin-1-yl]naphthalen-2-yl ester (**112**) and 449 mg (2.8 mmol) of DABCO in 2.5 ml of DMF via syringe. The resulting green solution was stirred at 120 °C for 12 h. The mixture was concentrated under reduced pressure (20 mbar, 70 °C bath temperature). The residue was purified by FC (toluene → toluene/EtOAc 5:1) to give 364 mg (82%) of the title compounds as an off white solid as a mixture of diastereomers.

Separation of the diastereomers was performed by FC (toluene → toluene/EtOAc 5:1)

(*R*,*P*)-[4-(2-Diphenylphosphanyl-naphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl} pentan-3-ol (1st diastereomer, **31a**)

mp: 162-164 °C.

$[\alpha]_D^{27}$ = 134.9 (c = 0.50, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.5, 3H), 0.93 (t, *J* = 7.6, 3H), 1.18-1.27 (m, 1H), 1.35-1.45 (m, 1H), 1.74-1.89 (m, 2H),1.99 (bs, 1 H), 5.64 (d, *J* = 8.4, 1H), 5.57 (d, *J* = 8.4, 1H), 7.02 (d, *J* = 8.0, 1H), 7.10 -7.45 (m, 17 H), 7.60-7.68 (m, 3H), 7.58-7.89 (m, 2H), 7.96 (d, *J* = 8.3, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 8.5, 28.2, 29.1, 59.2, 78.1, 118.1, 120.9, 126.8, 126.9, 127.2, 127.6, 128.3, 128.5, 128.5, 128.5, 128.6, 128.7, 128.7, 128.7, 129.1, 129.2, 130.4, 131.2, 131.4, 133.5, 133.5, 133.7, 133.8, 133.9, 134.0, 136.3, 136.5, 137.5, 137.6, 138.2, 138.3, 141.1, 142.1, 142.4, 152.6, 152.7, 152.9.

^{31}P NMR (121 MHz, $CDCl_3$) δ –12.58.

FTIR (KBr, cm^{-1}): 3365 (s), 3052 (m), 2965 (m), 2879 (m), 1576 (w), 1505 (s), 1478 (m), 1435 (m), 1392 (m), 1138 (w), 912 (s), 728 (s).

MS (HiResMALDI, pos.) calcd for $C_{42}H_{39}N_3O_2P^+$ ($M+H^+$) 632.2825, found 632.2814.

Anal. Calcd for $C_{42}H_{38}N_3O_2P$: C, 79.85; H, 6.06. Found: C, 80.06; H, 6.02.

(*R*,*M*)-[4-(2-Diphenylphosphanyl-naphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (2nd diastereomer, **31b**)

mp: ≥ 200 °C

$[\alpha]_D^{26}$ = -68.3 (c = 0.665, $CHCl_3$)

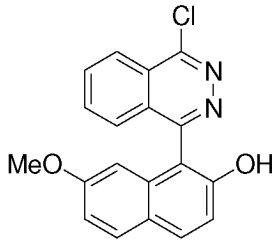
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.4, 3H), 0.98 (t, *J* = 7.5, 3H), 1.23-1.32 (m, 2H), 1.39-1.48 (m, 1H), 1.76-1.95 (m, 3H), 5.68 (bs, 1H), 6.52 (bs, 1H), 6.99-7.48 (m, 17H), 7.49-7.57 (m, 1H), 7.61-7.63 (m, 2H), 7.68-7.72 (m, 1H), 7.89-7.91 (m, 2H), 7.98 (d, *J* = 8.1, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 8.5, 28.2, 29.2, 59.5, 78.2, 118.2, 121.0, 126.9, 127.0, 127.2, 127.7, 128.4, 128.5, 128.6, 128.6, 128.7, 129.1, 129.1, 130.4, 131.3, 131.4, 133.6, 133.6, 133.8, 134.0, 134.0, 134.0, 136.7, 136.8, 137.4, 137.5, 137.9, 138.0, 140.9, 141.9, 142.2, 152.7, 153.0.

^{31}P NMR (121 MHz, $CDCl_3$) δ –11.74.

FTIR (KBr, cm^{-1}): 3354 (m), 3052 (m), 2954 (m), 2868 (w), 1581 (w), 1505 (s), 1435 (m), 1392 (m), 911 (s), 739 (s).

MS (HiResMALDI, pos.) calcd for $C_{42}H_{39}N_3O_2P^+$ ($M+H^+$) 632.2825, found 632.2830.



1-(4-Chlorophthalazin-1-yl)-7-methoxynaphthalen-2-ol (36).

In a oven dried 1 l flask under N_2 were mixed 11.4 g (57.3 mmol) of 1,4-dichlorophthalazine (**20**) with 10.0 g (57.5 mmol) of 7-methoxynaphthalen-2-ol (**34**). This mixture was suspended in 450 ml of 1,2-dichloroethane. After stirring for 10 min, 7.64 g (57.4 mmol) of $AlCl_3$ was added in one portion. The resulting suspension was stirred for 20 h at 80 °C. After cooling to room temperature the black suspension was poured on 500 ml ice-water and stirred for 1 h. The two phases were separated. The aq. phase was extracted with CH_2Cl_2 (3x200 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude solid was triturated with CH_2Cl_2 (35 ml) for 1 h. Filtration afforded 15.2 g (80%) of the pure product as a grey solid.

mp: >210 °C.

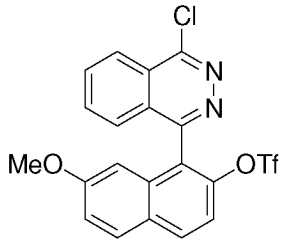
^{1}H NMR (300 MHz, DMSO) δ 3.50 (s, 3H), 6.33 (d, *J* = 2.4, 1H), 7.01 (dd, *J* = 2.4, *J* = 8.7, 1H), 7.20 (d, *J* = 8.7, 1H), 7.52 (d, *J* = 8.4, 1H), 7.86 (d, *J* = 9.0, 1H), 7.94 (d, *J* = 8.7, 1H), 7.96-8.02 (m, 1H), 8.13-8.18 (m, 1H), 8.40 (d, *J* = 8.4, 1H).

^{13}C NMR (75 MHz, DMSO) δ 55.6, 103.6, 113.9, 115.5, 116.2, 123.9, 125.6, 126.1, 127.4, 129.1, 130.5, 131.5, 134.9, 135.0, 135.5, 154.7, 154.8, 158.8, 159.2.

FTIR (thin film, cm^{-1}): 3017 (w), 1625 (m), 1513 (s), 1462 (w), 1342 (m), 1290 (m), 1221 (s), 772 (s).

MS (HiResESI, pos.) calcd for $C_{19}H_{14}N_2O_2Cl^+$ ($M+H^+$) 337.0738, found 337.0733.

Anal. Calcd for $C_{19}H_{13}N_2O_2Cl$: C, 67.76; H, 3.89. Found: C, 67.58; H, 4.13.



Trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl ester (37).

A suspension of 5.5 g (16 mmol) of 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-ol (**36**) and 4.2 ml (54 mmol) of pyridine in 500 ml of CH_2Cl_2 at 0 °C was treated dropwise over 40 min with 3.2 ml (19 mmol) of triflic anhydride and stirred at 0 °C for 1 h. The resulting solution was quenched with sat. aq. NH_4Cl soln. The organic phase was separated and the aq. phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and passed through a plug of SiO_2. The filtrate was concentrated under reduced pressure. Trituration with pentane afforded 6.3 g (88%) of the title compound as a grey powder.

mp: 140 °C.

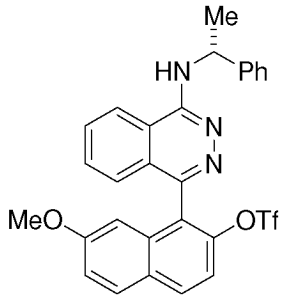
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (s, 3H), 6.50 (s, 1H), 7.22 (dd, J = 1.5, 9.0, 1H), 7.45 (d, J = 8.4, 1H), 7.47 (d, J = 8.4, 1H), 7.81-7.90 (m, 2H), 8.00-8.06 (m, 2H), 8.43 (d, J = 8.1, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 104.3, 116.7, 117.9 (q, J_{CF} = 315), 123.6, 125.5, 125.8, 126.2, 127.9, 128.2, 129.9, 131.9, 133.8, 134.0, 134.3, 145.8, 155.2, 155.5, 159.3.

FTIR (thin film, cm^{-1}): 3072 (w), 3008 (w), 2941 (w), 2835 (w), 1625 (s), 1508 (s), 1468 (s), 1422 (s), 1378 (s), 1344 (m), 1290 (s), 1229 (s), 1139 (s), 989 (s), 870 (s).

MS (HiResESI, pos.) calcd for $C_{20}H_{13}N_2O_2F_3SCl^+$ ($M+H^+$) 469.0231, found 469.0232.

Anal. Calcd for $C_{20}H_{12}N_2O_2F_3SCl$: C, 51.24; H, 2.58. Found: C, 51.47; H, 2.73.



7-methoxy-1-(4-((*R*)-1-phenylethylamino)phtalazin-1-yl)naphthyltrifluoromethane sulfonates (38).

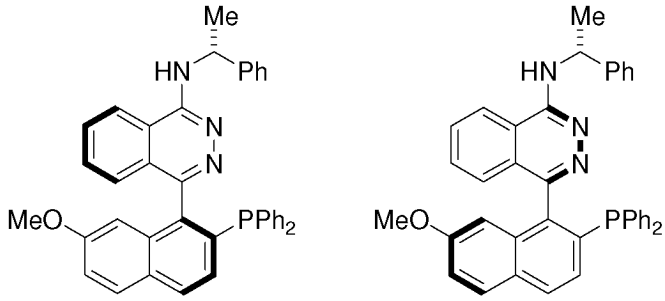
To 2.2 g (4.7 mmol) of trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl ester (**37**)was added 3.3 g (27 mmol) *D*-(+)-Methylbenzylamine. After stirring for 8 h at 130 °C the reaction mixture was purified by FC (toluene/EtOAc 5:1 to 3:1) to afford 2.1 g (81%) of the title compound as an off white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (d, *J* = 6.9, 3H), 1.77 (d, *J* = 6.9, 3H), 3.49 (s, 3H), 3.57 (s, 3H), 5.65-5.71 (m, 1H), 5.82-5.91 (m, 1H), 6.62 (d, *J* = 2.4, 1H), 6.72 (d, *J* = 2.1, 1H), 7.17-7.44 (m, 12H), 7.51-7.64 (m, 6H), 7.72-7.78 (m, 2H), 7.84 (d, *J* = 3.9, 1H), 7.87 (d, *J* = 3.9, 1H), 7.92-7.99 (m,4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 22.0, 50.7, 50.8, 55.2, 55.3, 76.6, 105.1, 105.2, 116.9, 117.1, 117.8, 117.8, 119.7, 119.9, 120.6, 125.8, 125.9, 126.2, 126.5, 126.7, 127.3, 127.4, 128.1, 128.6, 128.6, 129.8, 129.8, 130.9, 130.9, 131.4, 135.2, 144.1, 144.3, 146.3, 146.4, 146.8, 152.6, 152.7, 159.0.

FTIR (thin film, cm^{-1}): 3338 (m), 3062 (w), 3026 (w), 2970 (w), 2930 (w), 1625 (s), 1508 (s), 1418 (s), 1227 (s), 1137 (s).

MS (HiResMALDI, pos.) calcd for $C_{28}H_{22}F_3N_3O_4S^+$ ($M+H^+$) 554.1356, found: 554.1346.



(*R*,*P*)-4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-N-(1-phenylethyl)phthalazin-1-amine (39a) and (*R*,*M*)-4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-N-(-1-phenyl ethyl)phthalazin-1-amine (39b).

A solution of 220 mg (0.42 mmol) $Ni(dppe)Cl_2$ in 12 ml of DMF at 23 °C was treated with 1.5 ml (1.4 mmol) of diphenylphosphine. The resulting dark red solution was stirred at 120 °C for 30 min, treated with, a solution of 2.3 g (4.2 mmol) of 7-methoxy-1-(4-((*R*)-1-phenylethylamino)phtalazin-1-yl)naphthyltrifluoromethane sulfonate (**38**) and 1.9 g (17 mmol) of DABCO in 13 ml of DMF via syringe. The resulting green solution was stirred at 120 °C for 17 h. The mixture was concentrated under reduced pressure (20 mbar, 70 °C bath temperature). The residue was purified by FC (toluene → toluene/EtOAc 5:1) to give 1.5 g (60%) of the title compounds as an off white solid as a mixture of diastereomers.

Separation of the diastereomers was performed by FC (toluene → toluene/EtOAc 5:1)

(*R*,*P*)-4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-N-(1-phenylethyl)phthalazin-1-amine (1st diastereomer, **39a**)

mp: 194-195 °C.

$[\alpha]_D^{27}$ = -171.8 (c = 0.50, $CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (d, *J* = 5.2, 3H), 3.44 (s, 3H), 5.48 (s, 1H), 5.84 (quint, *J* = 5.6, 1H), 6.49 (d, *J* = 2.0, 1H), 7.13-7.15 (m, 2H), 7.19-7.28 (m, 12H), 7.31-7.34 (m, 2H), 7.39 (ddd, *J* = 6.4, *J* = 5.6, *J* = 0.8, 1H), 7.54-7.56 (m, 2H), 7.63 (ddd, *J* = 6.4, *J* = 5.6, *J* = 0.8, 1H), 7.77 (d, *J* = 7.2, 1H), 7.81 (d, *J* = 6.8, 1H), 7.84 (d, *J* = 6.4, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 50.5, 55.1, 58.5, 105.4, 105.4, 117.7, 119.3, 120.4, 126.6, 127.0, 128.0, 128.1, 128.2, 128.2, 128.2, 128.4, 128.5, 129.1, 129.2, 129.4, 130.8, 133.1, 133.3, 133.7, 133.9, 137.3, 137.4, 140.5, 144.6, 152.2, 152.5, 152.6, 157.9, 157.9.

^{31}P NMR (121 MHz, $CDCl_3$) δ –12.45.

FTIR (KBr, cm^{-1}): 3335 (m), 3051 (m), 2966 (m), 1620 (s), 1576 (w), 1504 (s), 1223 (s), 1435 (m), 1027 (m).

MS (HiResMALDI, pos.) calcd for $C_{39}H_{33}N_3OP^+$ ($M+H^+$) 590.2356, found 590.2348.

(*R*,*M*)-4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-N-(-1-phenylethyl)phthalazin-1-amine (2nd diastereomer, **39b**)

mp: 193-197 °C

$[\alpha]_D^{26}$ = 65.3 (c = 0.50, CD_2Cl_2)

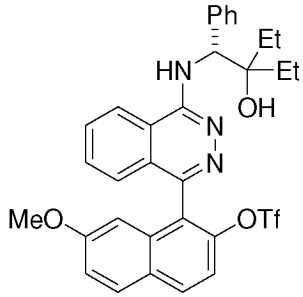
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (d, *J* = 6.8, 3H), 3.52 (s, 3H) , 5.32-5.61(m, 1H), 5.76 (d, *J* = 6.1, 1H), 6.52 (d, *J* = 2.5, 1H), 7.05-7.32 (m, 17H), 7.38-7.47 (m, 3H), 7.56-7.59 (m, 2H), 7.69-7.74 (m, 1H), 7.81-7.84 (m, 2H), 7.91 (d, *J* = 8.2, 1H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 22.8, 51.1, 55.5, 105.8, 105.8, 118.2, 119.4, 121.0, 126.9, 127.0, 127.6, 128.3, 128.4, 128.4, 128.5, 128.6, 128.7, 128.7, 128.8, 129.0, 129.5, 130.0, 131.4, 131.5, 133.8, 133.9, 134.0, 134.1, 134.7, 134.8, 137.3, 137.4, 137.5, 137.6, 138.1, 138.2, 140.4, 140.7, 145.0, 152.8, 153.1, 153.1, 158.6.

^{31}P NMR (121 MHz, CD_2Cl_2) δ –11.86.

FTIR (KBr, cm^{-1}): 3306 (m), 3050 (m), 2926 (m), 1618 (s)1579 (s), 1556 (s), 1504 (s), 1223 (s), 1026 (s).

MS (HiResMALDI, pos.) calcd for $C_{39}HN_3O_3P^+$ ($M+H^+$) 590.2356, found 590.2345.



Trifluoromethanesulfonic acid 1-[4-((*R*)-2-ethyl-2-hydroxy-1-phenylbutylamino)phthalazin-1-yl]-7-methoxynaphthalen-2-yl ester (47).

To 5.0 g (11 mmol) of trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl ester (**37**) was added 10 g (52 mmol) of 3-((*R*)-aminophenyl-methyl)pentan-3-ol. The suspension was stirred for 18 h at 120 °C. After cooling to 25 °C CH_2Cl_2 was added and the suspension was filtered. The filtrate was concentrated under reduced pressure. FC (toluene/EtOAc 10:1 → 5:1) afforded the title compound as a brown solid which was triturated with hexane/Et_2O to give 4.8 g (70%) of the title compound as a mixture of diastereomers.

mp: 175-177 °C.

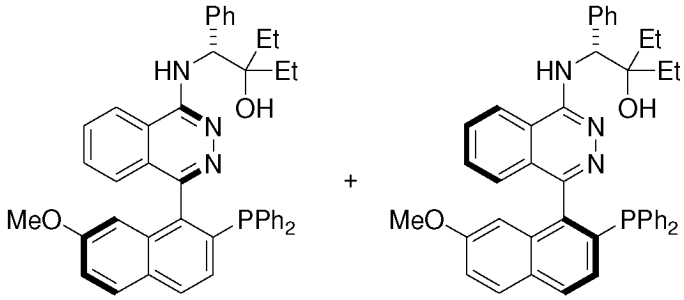
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88-1.02 (m, 12H), 1.21-1.40 (m, 2H), 1.41-1.49 (m, 2H), 1.72-1.97 (m, 4H), 3.41 (s, 3H), 3.60 (s, 3H), 5.71 (d, J = 8.7, 1H), 5.87 (d, J = 8.8, 1H), 6.52-6.58 (m, 3H), 6.74 (d, J = 2.4, 1H), 7.14-7.42 (m, 12H), 7.54-7.64 (m, 6H), 7.76-7.85 (m, 4H), 7.93-8.00 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.5, 7.6, 8.2, 8.3, 27.7, 27.7, 28.9, 28.9, 55.2, 55.2, 58.6, 59.4, 77.8, 78.2, 105.0, 105.2, 117.8 (q, J_{CF} = 319), 117.0, 117.1, 117.8, 118.0, 118.2 (q, J_{CF} = 318), 119.7, 119.9, 120.5, 125.4, 125.9, 126.1, 126.2, 127.3, 127.3, 128.0, 128.1, 128.2, 128.5, 128.9, 129.7, 129.7, 130.7, 130.8, 131.4, 131.4, 131.4, 135.1, 135.2, 140.0, 140.4, 146.1, 146.2, 146.3, 152.8, 152.9, 158.9, 159.0.

FTIR (thin film, cm^{-1}): 2996 (w), 1625 (w), 1579 (w), 1544 (w), 1508 (s), 1420(m), 1219 (s), 1139 (m), 772 (s).

MS (HiResMALDI, pos.) calcd for $C_{32}H_{31}N_3O_5F_3S^+$ ($M+H^+$) 626.1931, found 626.1918.

Anal. Calcd for $C_{32}H_{30}N_3O_5F_3S$: C, 61.43; H, 4.83. Found: C, 61.53; H, 4.74.



(*R*,*M*)-[4-(2-Diphenylphosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (48a, 1st diasteomer) and (*R*,*P*)-[4-(2-Diphenyl phosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (48b, 2nd diasteomer).

A solution of 0.61 g (1.2 mmol) $Ni(dppe)Cl_2$ in 30 ml of DMF at 23 °C was treated with 4.0 ml (23 mmol) of diphenylphosphine. The resulting dark red solution was stirred at 120 °C for 30 min, treated with, a solution of 7.3 g (12 mmol) of trifluoromethanesulfonic acid 1-[4-((*R*)-2-ethyl-2-hydroxy-1-phenyl-butylamino)phthalazin-1-yl]-7-methoxynaphthalen-2-yl ester (**47**) and 5.2 g (46 mmol) of DABCO in 65 ml of DMF via syringe, the flask was washed with 5 ml of DMF. The resulting green solution was stirred at 120 °C for 12 h. The mixture was concentrated under reduced pressure (20 mbar, 70 °C bath temperature). The residue was purified by FC (toluene → toluene/EtOAc 4:1) to give 5.2 g (65%) of the title compounds as an off white solid as a 1.7:1 (1st diasteomer : 2nd diasteomer) mixture of diastereomers.

Separation of the diastereomers was performed by FC (toluene → toluene/EtOAc 4:1).We observed that the use of amorphous ligand, obtained after FC from toluene/EtOAc gave consistent results. However, if the ligand is crystallized from toluene/hexane, irreproducible results were obtained, which we believe are due to crystal packing effects. If crystalline ligand is passed through a short plug of SiO_2 and concentrated form toluene/EtOAc, reproducible results are obtained again.

(1st diastereomer, **48a**)

mp: 180-181 °C.

$[\alpha]_D^{28}$ = 151.7 (c = 0.50, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 5.9, 3H), 0.97 (t, *J* = 6.0, 3H), 1.21-1.26 (m, 1H), 1.39-1.47 (m, 1H), 1.79-1.93 (m, 2H), 3.30 (s, 3H), 5.63 (d, *J* = 6.8, 1H), 6.31 (d, *J* = 1.8, 1H).

6.54 (d, *J* = 6.7, 1H), 7.08-7.42 (m, 11H), 7.46 (app t, *J* = 5.8, 1H), 7.58 (d, *J* = 5.7, 2H), 7.71 (app t, *J* = 6.2, 1H), 7.79 (dd, *J* = 7.2, 11.2 , 2H), 8.00 (d, *J* = 6.6, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 8.61, 28.1, 29.2, 55.4, 59.4, 78.1, 105.4, 105.4, 118.3, 119.7, 120.9, 126.8, 127.5, 128.2, 128.4, 128.5, 128.6, 128.6, 128.6, 128.7, 128.7, 129.2, 129.5, 129.8, 131.2, 131.4, 133.7, 133.8, 133.9, 134.0, 134.7, 134.7, 137.0, 137.1, 137.6, 137.7, 138.2, 138.3, 140.5, 140.8, 141.1, 152.6, 152.7, 153.0, 158.5.

^{31}P NMR (121 MHz, $CDCl_3$) δ –12.22.

FTIR (KBr, cm^{-1}): 3337 (s), 3048 (m), 2963 (m), 2936 (m), 2878 (m), 1619 (s), 1579 (s), 1552 (s), 1504 (s), 1405 (s), 1370 (s), 1225 (s), 1141 (m), 1028 (s), 838 (s) 696 (s).

MS (HiResMALDI, pos.) calcd for $C_{43}H_{41}N_3O_2P^+$ ($M+H^+$) 662.2931, found 662.2919.

Anal. Calcd for $C_{43}H_{40}N_3O_2P$: C, 78.04; H, 6.09. Found: C, 78.11; H, 6.02.

Crystallization of **48a** from a mixture of toluene/hexane afforded crystals (colorless plate) suitable for X-ray diffraction analysis. The axial stereochemistry was assigned to be *P*.

(2^{nd} diastereomer, **48b**)

mp: 143-145 °C

$[\alpha]_D^{29}$ = -41.5 (c = 0.50, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.96 (m, 6H), 1.23-1.30 (m, 1H), 1.41-1.45 (m, 1H), 1.78-1.82 (m, 1H), 1.87-1.92 (m, 1H), 3.50 (s, 3H), 5.68 (s, 1H), 6.49 (d, *J* = 1.9, 1H), 6.99-7.42 (m, 19H), 7.62-7.67 (m, 3H), 7.80-7.82 (m, 2H), 8.08 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 8.5, 28.1, 29.0, 55.4, 59.5, 78.0, 105.6, 119.4, 126.8, 127.6, 127.7, 128.1, 128.2, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.6, 128.7, 129.2, 129.4, 129.9, 130.0, 131.2, 131.3, 131.4, 133.8, 133.8, 133.9, 134.0, 134.7, 134.7, 137.4, 137.4, 137.5, 137.8, 137.9, 140.8, 152.5, 152.9, 158.5.

^{31}P NMR (121 MHz, $CDCl_3$) δ –11.13.

FTIR (KBr, cm^{-1}): 3389 (m), 3053 (m), 2961 (s), 2877 (m), 1619 (s), 1579 (m), 1504 (s), 1432 (s), 1262 (m), 1224 (s), 1092 (m), 1028 (m), 838 (s), 695 (s).

MS (HiResMALDI, pos.) calcd for $C_{43}H_{41}N_3O_2P^+$ ($M+H^+$) 662.1931, found 662.1940.

Determination of the rotation barrier of 48a

The rate constant of epimerization was determined at different temperatures:
Degassed *p*-xylene (5 ml) was placed in a two necked flask equipped with a reflux condenser. The flask was placed into a thermostat (Huber Polystat cc3) and heated to the indicated temperature. The temperature inside the flask was measured by a digital thermometer. When the temperature was constant, 20 mg (0.030 mmol) **48a** were added. After the indicated time aliquots (0.2 ml) were taken by syringe. The samples were concentrated at reduced pressure and dried in vacuo. The ratio of the diastereomers was determined by ^{1}H-NMR comparing the singlets of the methoxy group (1st diastereomer 3.30 ppm, 2nd diastereomer 3.50 ppm).

The rate constant at each temperature was determined by linear regression of plot of $\ln(de_0/de)$ vs. t

107.0 °C (380.2 K)

t (min)	**48a**	**48b**	de
0	100	0	100
60	95.0	5.0	90.0
124	92.4	7.6	84.8
183	89.3	10.7	78.6
245	85.9	14.1	71.8
303	84.0	16.0	68.0
362	81.6	18.4	63.2
425	79.2	20.8	58.4

$k\ (107.0\ °C) = 2.14 \cdot 10^{-5}\ s^{-1}$

116.5 °C (389.7 K)

t (min)	**48a**	**48b**	de
0	100	0	100
50	91.2	8.8	82.4
100	86.4	13.6	72.8
161	80.1	19.9	60.2
210	76.9	23.1	53.8
270	74.2	25.8	48.4
342	70.1	29.9	40.2
395	67.8	32.2	35.6

$k\ (116.5\ °C) = 5.11 \cdot 10^{-5}\ s^{-1}$

124.5 °C (397.7 K)

t (min)	**48a**	**48b**	de
0	100	0	100
30	91.0	9.0	82.0
60	83.9	16.1	67.8
120	74.0	26.0	48.0
180	67.0	33.0	34.0
240	63.1	36.9	26.2
300	60.0	40.0	20.0
360	58.2	41.8	16.4

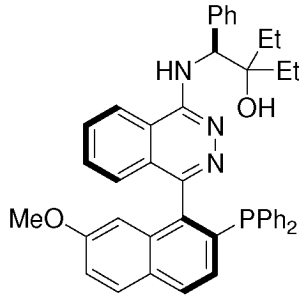
$k\ (124.5\ °C) = 9.71 \cdot 10^{-5}\ s^{-1}$

135.5 °C (408.7 K)

t (min)	**48a**	**48b**	de
0	100	0	100
15	90.1	9.9	80.2
30	81.0	19.0	62.0
60	68.8	31.2	37.6
90	63.0	37.0	26.0
120	59.0	41.0	18.0
150	57.1	42.9	14.2

$k\ (135.5\ °C) = 2.45 \cdot 10^{-4}\ s^{-1}$

An Arrhenius plot (ln k vs. 1/T) of the rate constants (Figure 8) was calculated. The slope of this graph corresponds to $-E_a/R$, therefore $E_a = \Delta G^{\ddagger}$ was determined to be 26.3 kcal/mol.



(*S*,*P*)-[4-(2-Diphenylphosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenyl-methyl}pentan-3-ol (*ent*-48a, 1st diasteomer).

Prepared like **48a**, from 3-((*S*)-amino-phenyl-methyl)-pentan-3-ol.

mp: 180-181 °C.

$[\alpha]_D^{25}$ = –160.0 (c = 0.50, $CHCl_3$).

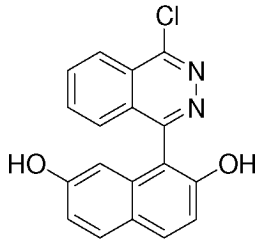
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 5.9, 3H), 0.97 (t, *J* = 6.0, 3H), 1.21-1.26 (m, 1H), 1.39-1.47 (m, 1H), 1.79-1.93 (m, 2H), 3.30 (s, 3H), 5.63 (d, *J* = 6.8, 1H), 6.31 (d, *J* = 1.8, 1H). 6.54 (d, *J* = 6.7, 1H), 7.08-7.42 (m, 11H), 7.46 (app t, *J* = 5.8, 1H), 7.58 (d, *J* = 5.7, 2H), 7.71 (app t, *J* = 6.2, 1H), 7.79 (dd, *J* = 11.2, 7.2, 2H), 8.00 (d, *J* = 6.6, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 8.61, 28.1, 29.2, 55.4, 59.4, 78.1, 105.4, 105.4, 118.3, 119.7, 120.9, 126.8, 127.5, 128.2, 128.4, 128.5, 128.6, 128.6, 128.6, 128.7, 128.7, 129.2, 129.5, 129.8, 131.2, 131.4, 133.7, 133.8, 133.9, 134.0, 134.7, 134.7, 137.0, 137.1, 137.6, 137.7, 138.2, 138.3, 140.5, 140.8, 141.1, 152.6, 152.7, 153.0, 158.5.

FTIR (KBr, cm^{-1}): 3337 (s), 3048 (m), 2963 (m), 2936 (m), 2878 (m), 1619 (s), 1579 (s), 1552 (s), 1504 (s), 1405 (s), 1370 (s), 1225 (s), 1141 (m), 1028 (s), 838 (s) 696 (s).

MS (HiResMALDI, pos.) calcd for $C_{43}H_{41}N_3O_2P^+$ ($M+H^+$) 662.2931, found 662.2919.

Anal. Calcd for $C_{43}H_{40}N_3O_2P$: C, 78.04; H, 6.09. Found: C, 77.78; H, 6.12.



1-(4-Chlorophthalazin-1-yl)-7-hydroxynaphthalen-2-ol (40).

In a oven dried 100 ml flask under N_2 were mixed 840 mg (4.20 mmol) of 1,4-dichlorophthalazine (**20**) with 668 mg (4.20 mmol) added in on of 2,7-Dihydroxynaphthalene. This mixture was suspended in 30.0 ml of 1,2-dichloroethane. After stirring for 10 min, 559 mg (4.20 mmol) of $AlCl_3$ was e portion. The resulting suspension was stirred for 17 h at 80 °C. After cooling to room temperature the black suspension was poured on 30.0 ml ice-water and stirred for 1 h. The suspension was filtered and the solid was washed with H_2O and CH_2Cl_2. FC (toluene/acetone 4:1) afforded 700 mg (52%) of the title compound as a yellow solid.

mp: >200 °C.

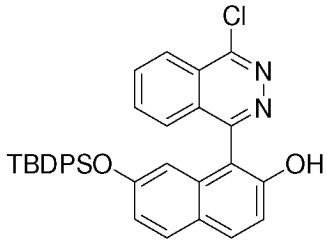
^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 6.04 (d, *J* = 2.4, 1H), 6.91 (dd, *J* = 2.1, *J* = 8.7, 1H), 7.17 (d, *J* = 9.0, 1H), 7.63 (d, *J* = 7.8, 1H), 7.75 (d, *J* = 9.0, 1H), 7.86 (d, *J* = 9.0, 1H), 7.97 (app t, *J* = 7.8, 1H), 8.13 (app t, *J* = 7.2, 1H), 8.39 (d, *J* = 7.8, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 106.5, 113.5, 115.5, 116.3, 124.0, 125.6, 126.5, 127.8, 129.6, 130.4, 131.7, 134.6, 134.8, 136.3, 154.3, 154.9, 157.2, 159.6.

FTIR (thin film, cm^{-1}): 3057 (w), 1702 (s), 1622 (s), 1365 (s), 1221 (s).

MS (HiResESI, pos.) calcd for $C_{18}H_{12}N_2O_2Cl^+$ ($M+H^+$) 323.0582, found 323.0589.

Anal. Calcd for $C_{18}H_{11}N_2O_2Cl$: C, 66.99; H, 3.44. Found: C, 66.78; H, 3.50.



7-(tert-Butyl-diphenyl-silanyloxy)-1-(4-chloro-phthalazin-1-yl)-naphthalen-2-ol (41).

To 2.70 g (8.39 mmol) 1-(4-Chlorophthalazin-1-yl)-7-hydroxynaphthalen-2-ol (**40**) in 25 ml DMF was added 830 mg (12.2 mmol) Imidazole and 2.00 ml (7.75 mmol) TBDPSCl. After stirring for 16 h at 23 °C the reaction was quenched with a saturated solution of NH_4Cl. Addition of Et_2O and phase separation. The aqueous phase was extracted with Et_2O twice. The combined organic layers were dried with Na_2SO_4 and concentrated at reduced pressure. FC (hexane/EtOAc 2:1) afforded 1.38g (29%) of the title compound as a yellow solid.

mp: 141 °C.

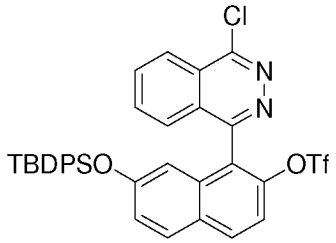
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 9H), 6.01 (d, *J* = 2.1, 1H), 6.96 (d, *J* = 9.0, 1H), 7.03-7.13 (m, 3H), 7.19-7.42 (m, 10H), 7.60 (d, *J* = 9.0, 1H), 7.67 (d, *J* = 8.7, 1H), 7.74-7.80 (m, 1 H), 8.24 (d, *J* = 8.4, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.3, 111.5, 112.6, 117.0, 119.1, 124.2, 125.0, 127.5, 127.5, 127.5, 128.0, 129.6, 129.8, 131.4, 132.4, 132.9, 133.3, 134.1, 134.9, 135.2, 154.1, 154.5, 154.6.

FTIR (thin film, cm^{-1}): 3070 (w), 2931 (w), 2857 (w), 1621 (m), 1510 (s), 1341 (m), 1222 (s), 896 (m).

MS (ESI, pos.) calcd for $C_{34}H_{30}N_2O_2SiCl^+$ ($M+H^+$) 561.2, found 561.2.

Anal. Calcd for $C_{34}H_{29}N_2O_2SiCl$: C, 72.77; H, 5.21. Found: C, 72.50; H, 5.27.



Trifluoro-methanesulfonic acid 7-(tert-butyl-diphenyl-silanyloxy)-1-(4-chloro-phthalazin-1-yl)-naphthalen-2-yl ester (42).

To 4.06 g (7.24 mmol) 7-(tert-Butyl-diphenyl-silanyloxy)-1-(4-chloro-phthalazin-1-yl)-naphthalen-2-ol (**41**) in 170 ml CH_2Cl_2 was added 1.70 ml (21.0 mmol) pyridine. The suspension was cooled to 0 °C and 1.30 ml (7.69 mmol) triflic anhydride was added by syringe over a period of 10 min. The solution was stirred for 10 min. at this temperature and then quenched with a saturated solution of NH_4Cl. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were dried with Na_2SO_4 and concentrated at reduced pressure. Traces of pyridine were removed under high vacuum to afford 3.90 g (78%) of the title compound as a colorless solid.

mp: 182 - 183 °C.

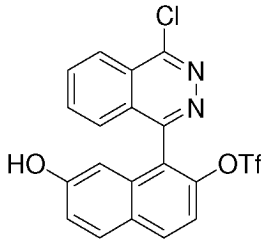
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 6.20 (d, J = 2.4, 1H), 7.1-7.19 (m, 5H), 7.29-7.41 (m, 8H), 7.48 (dt, J = 0.9, J = 7.2, 1H), 7.83-7.92 (m, 2H), 7.99 (d, J = 9.3, 1H), 8.33 (d, J = 7.8, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 26.5, 112.7, 117.0, 118.0 (q, J_{CF} = 319) 123.4, 123.8, 125.1, 125.5, 126.1, 127.5, 127.6, 127.8, 127.9, 129.7, 129.9, 130.1, 131.6, 131.7, 133.2, 133.4, 134.1, 134.8, 135.0, 145.6, 154.6, 155.0, 155.5.

FTIR (thin film, cm^{-1}): 3074 (w), 2967 (w), 2933 (w), 2862 (w), 1622 (m), 1503 (m), 1446 (m), 1418 (s), 1233 (s), 1201 (s), 1140 (s), 839 (s).

MS (ESI, pos.) calcd for $C_{35}H_{28}ClF_3N_2NaO_4SSi^+$ ($M+Na^+$) 715.1, found 715.1.

Anal. Calcd for $C_{35}H_{28}N_2O_4F_3SSiCl$: C, 60.64; H, 4.07. Found: C, 60.59; H, 4.11.



Trifluoro-methanesulfonic acid 1-(4-chloro-phthalazin-1-yl)-7-hydroxy-naphthalen-2-yl ester (43).

To 3.81 g (5.50 mmol) trifluoro-methanesulfonic acid 7-(tert-butyl-diphenyl-silanyloxy)-1-(4-chloro-phthalazin-1-yl)-naphthalen-2-yl ester (**42**) in 100 ml THF was added 5.78 ml (5.78 mmol, 1M in THF) TBAF at -78 °C dropwise over 10 min. The solution turned orange and stirring was continued for 10 min. The reaction was quenched with a saturated solution of NH_4Cl. The two phases were separated and the aqueous phase was extracted with Et_2O twice. The combined organic layers were dried with Na_2SO_4 and concentrated at reduced pressure. FC (hexane/EtOAc 2:1 to 1:1) afforded 2.18g (87%) of the title compound as a colorless solid.

mp: 180 - 182 °C.

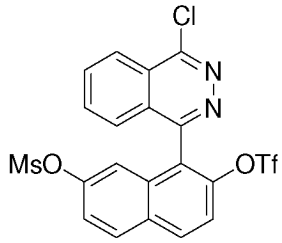
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.4, 1H), 6.99 (dd, *J* = 2.4, *J* = 6.6, 1H) 7.36 (d, *J* = 9.0 1H), 7.57 (d, *J* = 7.8, 1H), 7.71 (d, *J* = 9.1, 1H)7.93-7.99 (m, 2H), 8.13-8.18 (m, 1H), 8.40 (d, *J* = 8.1, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 107.3, 115.5, 116.0, 118 (q, J_{CF}= 315), 120.2, 120.7, 121.3, 125.7, 125.7, 127.1, 127.2, 128.6, 129.8, 132.5, 134.4, 134.7, 134.9, 145.5, 155.6, 156.3, 157.9.

FTIR (thin film, cm^{-1}): 3071 (w), 1625 (m), 1454 (m), 1421 (s), 1396 (s), 1203 (s), 1130 (s), 996 (s).

MS (ESI, pos.) calcd for $C_{19}H_{11}ClF_3N_2NaO_4S^+$ ($M+Na^+$) 455.0, found: 455.1.

Anal. Calcd for $C_{19}H_{10}ClF_3N_2NaO_4S$: C, 50.18; H, 2.22. Found: C, 49.97; H, 2.22.



Trifluoro-methanesulfonic acid 1-(4-chloro-phthalazin-1-yl)-7-methanesulfonyloxy-naphthalen-2-yl ester (44).

To 2.10 g (4.62 mmol) trifluoro-methanesulfonic acid 1-(4-chloro-phthalazin-1-yl)-7-hydroxy-naphthalen-2-yl ester (**43**) in 20 ml THF was added 0.766 ml (5.54 mmol) NEt_3. After cooling to 0 °C 0.377 ml (4.85 mmol) MsCl was added. The solution was stirred for 1h at 0 °C and 30 min at 23 °C. The reaction was quenched with a saturated solution of NH_4Cl. The two phases were separated and the aqueous phase was extracted with Et_2O twice. The combined organic layers were dried with Na_2SO_4 and concentrated at reduced pressure to give 2.30 g (94%) of the title compound as a colorless solid.

mp: 190 - 192 °C.

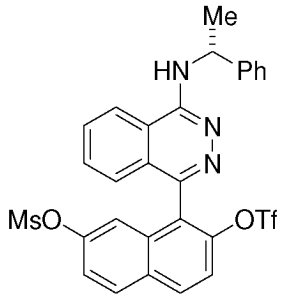
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 7.17 (d, J = 2.4, 1H), 7.46 (d, J = 8.4, 1H) 7.58 (dd, J = 2.1, J = 9.0, 1H), 7.66 (d, J = 9.0, 1H), 7.85-7.90 (m, 1H), 8.04-8.10 (m, 2H), 8.20 (d, J = 9.0, 1H), 8.47 (d, J = 8.4, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 37.8, 115.9, 117.9, 118.1 (q, J_{CF} = 318), 120.1, 122.8, 125.2, 125.7, 125.9, 127.0, 128.1, 130.8, 130.9, 132.1, 132.3, 133.5, 133.6, 134.0, 134.2, 146.0, 148.5, 154.3, 155.9.

FTIR (thin film, cm^{-1}): 3088 (w), 2939 (w), 1668 (w), 1509 (w), 1422 (s), 1372 (s), 1289 (s), 1220 (s), 1196 (s), 1131 (s).

MS (ESI, pos.) calcd for $C_{20}H_{12}ClF_3N_2NaO_6S_2^+$ ($M+Na^+$) 555.0, found: 555.0.

Anal. Calcd for $C_{20}H_{12}ClF_3N_2O_6S_2$: C, 45.08; H, 2.27. Found: C, 55.33; H, 2.35.



(*R*)Trifluoro-methanesulfonic acid 7-methanesulfonyloxy-1-[4-(1-phenyl-ethylamino)-phthalazin-1-yl]-naphthalen-2-yl ester (45).

To 2.22 g (4.17 mmol) trifluoro-methanesulfonic acid 1-(4-chloro-phthalazin-1-yl)-7-methanesulfonyloxy-naphthalen-2-yl ester (**44**) was added 2.52 g (20.8 mmol) (*R*)-1-phenylethylamine. The solution was stirred for 8 h at 80 °C, then cooled to 23 °C. The resulting viscous mixture was purified by FC (toluene/ EtOAc) to yield 1.76 g (68%) of the title compound as a 1:1 mixture of diastereomers as a light brown solid.

mp: 118 - 119 °C.

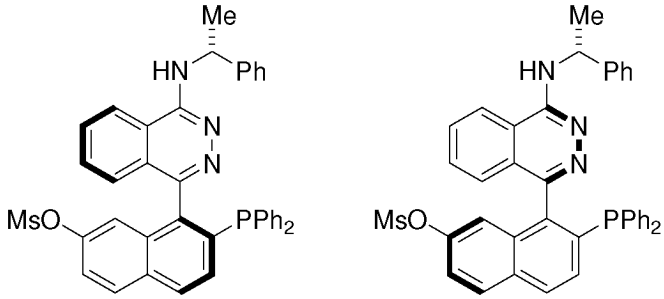
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, *J* = 6.9, 3H), 1.76 (d, *J* = 6.9, 3H), 2.90 (s, 3H), 3.00 (s, 3H), 5.71 (s, 1H), 5.73 (s, 1H), 5.84 (q, *J* = 6.9, 2H), 7.23-7.37 (m, 10 H), 7.50-7.57 (m, 6H), 7.60-7.66 (m, 4H), 7.72-7.79 (m, 2H), 7.93 (d, *J* = 5.1, 1H), 7.95 (d, *J* = 5.1, 1H), 8.00 (d, *J* = 3.6, 1H), 8.04 (d, *J* = 3.6, 1H), 8.08 (s, 1H9, 8.11 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 22.1, 37.4, 37.6, 50.8, 50.9, 116.0, 116.1, 117.8, 118.4, 118.6, 120.2, 120.3, 120.4, 120.9, 122.4, 122.5, 125.8, 126.5, 126.7, 126.8, 127.3, 127.6, 128.6, 128.7, 130.7, 130.7, 131.2, 131.2, 131.3, 131.7, 131.8, 134.3, 143.9, 144.2, 145.8, 145.8, 146.5, 148.4, 148.5, 152.8, 152.9.

FTIR (thin film, cm^{-1}): 3335 (w), 2975 (w), 1625 (w), 1506 (s), 1416 (s), 1361 (s), 1208 (s), 1134 (s).

MS (ESI, pos.) calcd for $C_{28}H_{23}F_3N_3O_6S_2^+$ ($M+H^+$) 618.1, found: 618.1.

Anal. Calcd for: $C_{28}H_{22}F_3N_3O_6S_2$. C, 54.45; H, 3.59. Found: C, 54.52; H, 3.71.



(*R,P*)-7-(diphenylphosphino)-8-(-4-(-1-phenylethylamino)phthalazin-1-yl)naphthalen-2-ylmethanesulfonate (46a) and (*R,M*)-7-(diphenylphosphino)-8-(-4-(-1-phenylethylamino) phthalazine-1-yl)naphthalen-2-yl methanesulfonate (46b).

A solution of 148 mg (0.28 mmol) $Ni(dppe)Cl_2$ in 14 ml of DMF at 23 °C was treated with 0.620 ml (3.51 mmol) of diphenylphosphine. The resulting dark red solution was stirred at 120 °C for 30 min, treated with a solution of 1.70 g (2.75 mmol) of (*R*)Trifluoro-methanesulfonic acid 7-methanesulfonyloxy-1-[4-(1-phenyl-ethylamino)-phthalazin-1-yl]-naphthalen-2-yl ester (**45**) and 1.20 g (11.0 mmol) of DABCO in 14 ml of DMF via syringe. The resulting green solution was stirred at 100 °C for 14 h. The mixture was concentrated under reduced pressure (20 mbar, 70 °C bath temperature). The residue was purified by FC (toluene → toluene/EtOAc 2:1) to give 1.00 mg (56%) of the title compounds as an yellow solid as a mixture of diastereomers.

Separation of the diastereomers was performed by FC (toluene → toluene/EtOAc 5:1)

(*R,P*)-7-(diphenylphosphino)-8-(-4-(-1-phenylethylamino)phthalazin-1-yl)naphthalen-2-ylmethanesulfonate (1st diastereomer, **46a**)

mp: 134 - 136 °C.

$[\alpha]_D^{27}$ = -102.0 (c = 0.50, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (d, *J* = 6.8, 3H), 2.82 (s, 3H), 5.59 (d, *J* = 6.2, 1H), 5.73 (q, *J* = 6.8, 1H), 7.02 (d, *J* = 2.2, 1H), 7.06 (d, *J* = 8.0, 1H), 7.12-7.49 (m, 19H), 7.54-7.57 (m, 2H), 7.74 (t, *J* = 7.1, 1H), 7.92-7.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 37.4, 51.1, 118.6, 118.7, 121.0, 122.5, 126.6, 126.8, 127.5, 128.3, 128.3, 128.7, 128.8, 128.8, 128.8, 128.9, 129.0, 129.0, 130.7, 131.3, 131.6, 131.6, 132.7, 133.6, 133.8, 133.9, 134.0, 134.2, 134.8, 135.0, 137.2, 137.3, 137.5, 137.6, 138.3, 138.4, 141.9, 142.2, 145.3, 148.1, 152.2, 152.2, 152.9.

FTIR (thin film, cm^{-1}): 3338 (w), 3040 (w), 2970 (w), 1549 (w), 1507 (s), 1434 (m), 1365 (s), 1219 (s), 1190 (s), 956 (m).

MS (HiResESI, pos.) calcd for $C_{39}H_{33}N_3O_3PS^+$ ($M+H^+$) 654.1975, found: 654.1964.

(*R*,*M*)-7-(diphenylphosphino)-8-(-4-(-1-phenylethylamino)phthalazine-1-yl)naphthalen-2-yl methanesulfonate (2nd diastereomer, **46b**)

mp: 136 - 138 °C.

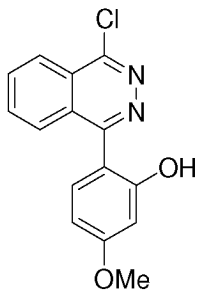
$[\alpha]_D^{26}$ = 50.1 (c = 0.50, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (d, *J* = 6.8, 3H), 2.92 (s, 3H), 5.62 (s, 1H), 5.75 (t, *J* = 6.2, 1H), 7.02-7.34 (m, 15H), 7.38-7.49 (m, 4H), 7.57 (d, *J* = 8.5, 2H), 7.73 (t, *J* = 5.1, 1H), 7.90-8.00 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 37.5, 51.2, 118.2, 118.7, 118.7, 121.1, 122.3, 126.6, 126.9, 127.2, 127.6, 128.3, 128.3, 128.6, 128.7, 128.7, 128.7, 128.8, 128.9, 128.9, 129.0, 129.4, 130.8, 131.2, 131.5, 131.6, 132.7, 133.8, 133.9, 134.0, 134.0, 134.1, 136.9, 137.1, 137.4, 137.5, 138.7, 138.9, 144.9, 148.0, 152.1, 152.1, 152.9.

FTIR (thin film, cm^{-1}): 3323 (w), 3020 (w), 2960 (w), 1549 (w), 1506 (s), 1429 (m), 1366 (s), 1219 (s), 1190 (s), 1150 (s), 960 (m).

MS (HiResESI, pos.) calcd for $C_{39}H_{33}N_3O_3PS^+$ ($M+H^+$) 654.1975, found: 654.1964.



2-(4-chlorophthalazin-1-yl)-5-methoxyphenol (69).

To 3.14 g (18.3 mmol) of 1,4-dichlorophthalazine (**20**) was added 25 ml dichloroethane and 2.26 g (18.3 mmol) of 3-methoxyphenol. After stirring for 10 min, 2.44 g (18.3 mmol) of $AlCl_3$ was added in one portion. The resulting suspension was stirred for 12 h at 75 °C. After cooling to room temperature water was added and a precipitate formed. The precipitate (O-Alkylation

product) was filter off and the two phases were separated. The organic phase was dried (Na_2SO_4) and concentrated to give 1.49 g (28%) of the title compound as a grey solid.

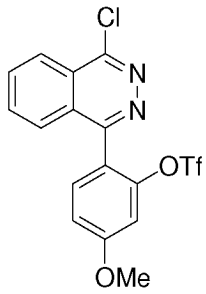
mp: >200 °C.

^{1}H NMR (300 MHz, DMSO) δ 3.80 (s, 3H), 6.58-6.63 (m, 2H), 7.29 (d, *J* = 8.1, 1H), 7.78 (d, *J* = 7.5, 1H), 8.02-8.15 (m, 2H), 8.31 (d, *J* = 8.1, 1H), 9.86 (s, 1H).

^{13}C NMR (100 MHz, DMSO) δ 55.1, 101.2, 105.2, 114.9, 124.3, 124.7, 127.4, 127.6, 131.9, 133.6, 133.8, 153.2, 156.1, 159.0, 161.4.

FTIR (thin film, cm^{-1}): 3058 (m), 2940 (m), 1612 (s), 1518 (w), 1362 (w), 1293 (s), 1214 (s), 1165 (w).

MS (HiRes EI+) calcd for $C_{15}H_{10}ClN_2O_2$ ($M-H^+$) 285.0426, found 285.0425.



2-(4-chlorophthalazin-1-yl)-5-methoxyphenyl trifluoromethanesulfonate (70).

A suspension of 1.03 g (3.60 mmol) 2-(4-chlorophthalazin-1-yl)-5-methoxyphenol (**69**) and 0.960 ml (11.9 mmol) of pyridine in 100 ml of CH_2Cl_2 at 0 °C was treated dropwise over 40 min with 0.670 ml (4.00 mmol) of triflic anhydride and stirred at 0 °C for 1 h. The resulting orange solution was quenched with sat. aq. NH_4Cl soln. The organic phase was separated and the aq. phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in EtOH and passed through a plug of SiO_2. The filtrate was concentrated under reduced pressure. Crystallization from hexane afforded 0.998 g (66%) of the title compound as a white solid. Recrystallization from acetone afforded a crystal of which an X-ray was obtained.

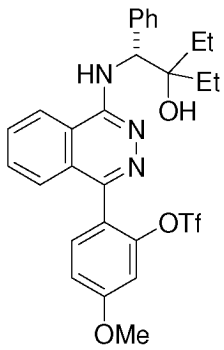
mp: 138-140 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.06 (d, *J* = 2.7, 1H), 7.13 (d, *J* = 9.0, 1H), 7.59 (d, *J* = 8.4, 1H), 7.76 (d, *J* = 7.8, 1H), 7.94 (ddd, *J* = 1.2, *J* = 7.2, *J* = 7.2, 1H), 8.03 (ddd, *J* = 1.2, *J* = 7.2, *J* = 7.2, 1H), 8.40 (d, *J* = 7.8, 1H).

^{13}C NMR (100 MHz, CDCl3) δ 56.1, 108.3, 114.1, 115.9, 120.9, 125.4, 125.9, 126.3, 127.6, 133.1, 133.4, 133.5, 147.6, 155.0, 155.8, 161.7.

FTIR (thin film, cm^{-1}): 3078 (w), 2950 (w), 2842 (w), 1620 (s), 1515 (m), 1423 (s), 1292 (s), 1219 (s), 1141 (s), 1080 (m).

MS (HiResMALDI, pos.) calcd for $C_{16}H_{11}ClF_3N_2O_4S^+$ ($M+H^+$) 419.0075, found 419.0069.



2-(4-((*R*)-2-ethyl-2-hydroxy-1-phenylbuthylamino)phthalazin-1-yl)-5-methoxy phenyltrifluoromethanesulfonate (71).

To 1.15 g (2.70 mmol) of 2-(4-chlorophthalazin-1-yl)-5-methoxyphenyl trifluoromethane sulfonate (**70**) was added 2.66 g (13.5 mmol) of 3-((*R*)-aminophenyl-methyl)pentan-3-ol. The suspension was stirred for 16 h at 120 °C. FC (toluene/EtOAc 4:1) afforded 1.07 g (68%) of the title compound as a white powder.

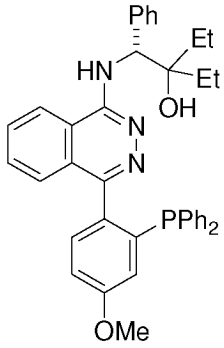
mp: 78-80 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85-0.97(m, 6H), 1.21-1.29 (m, 1H), 1.36-1.46 (m, 1H), 1.74-1.90 (m, 2H), 3.86 (s, 3H), 5.76 (d, *J* = 8.1, 1H), 6.54 (d, *J* = 8.7, 1H),6.98-7.02 (m, 2H), 7.16-7.28 (m, 4H), 7.47-7.71 (m, 6H), 7.89-7.92 (m, 1H).

^{13}C NMR (100 MHz, CDCl3) δ 7.7, 8.4, 27.7, 28.9, 55.9, 58.7, 107.9, 113.8, 117.8, 120.4, 126.0, 126.7, 127.1, 127.2, 128.1, 128.4, 128.6, 131.0, 131.2, 133.2, 140.0, 147.4, 147.9, 152.3, 160.7.

FTIR (thin film, cm^{-1}): 3401 (w), 2968 (w), 1620 (w), 1509 (s), 1421 (s), 1219 (s), 1139 (m).

MS (HiResMALDI, pos.) calcd for $C_{28}H_{29}F_3N_3O_5S^+$ ($M+H^+$) 576.1775, found 576.1784.



3-((*R*)-(4-(2-(diphenylphosphino)-4-methoxyphenyl)phthalazin-1-ylamino)(phenyl) methyl)pentan-3-ol (68).

A solution of 68.0 mg (0.128 mmol) of Ni(dppe)Cl_2 in 4.0 ml of DMF at 23 °C was treated with 0.970 ml (2.70 mmol) of diphenylphosphine. The resulting solution was stirred at 100 °C for 30 min. Then a solution of 738 mg (1.28 mmol) of 2-(4-((*R*)-2-ethyl-2-hydroxy-1-phenylbuthylamino) phthalazin-1-yl) -5-methoxy phenyltrifluoromethan sulfonate (**71**) and 575 mg (5.12 mmol) of DABCO in 4.0 ml of DMF was added via syringe, the flask was washed with 0.50 ml of DMF. The resulting solution was stirred at 120 °C for 12 h. The mixture was concentrated under reduced pressure (20 mbar, 60 °C bath temperature). The residue was purified by FC (SiO_2; toluene → toluene/EtOAc 4:1) and then FC (SiO_2; 1%% *iso*-Propanol in CH_2Cl_2) to give 78.4 mg (10%) of the title compound as an off white solid.

mp: 68-70 °C.

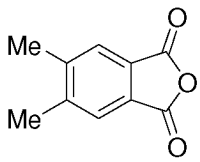
$[\alpha]_D^{23}$ = 16.0 (c = 0.520, $CDCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2, 3H), 0.96 (t, *J* = 7.5, 3H),1.20-1.44 (m, 2H), 1.73-1.90 (m, 2H), 3.70 (s, 3H), 5.73 (s, 1H), 6.24 (s, 1H), 6.73 (dd, *J* = 4.2, *J* = 5.4, 1H), 6.94 (dd, *J* = 2.7, *J* = 8.4, 1H), 7.09-7.79 (m, 20H).

^{13}C NMR (100 MHz, CDCl3) δ 7.8, 8.5, 27.8, 28.9, 55.2, 58.6, 78.0, 113.3, 117.7, 119.2, 120.0, 126.8, 127.1, 127.9, 128.0, 128.1, 128.3, 128.7, 130.2, 130.3, 131.1, 131.9, 131.9, 133.7, 133.8, 133.9, 134.1, 136.6, 136.8, 140.4, 140.6, 140.8, 151.9, 159.1.

FTIR (thin film, cm^{-1}): 3401 (w), 2966 (w), 1664 (m), 1508 (s), 1419 (m), 1220 (s), 1140 (m).

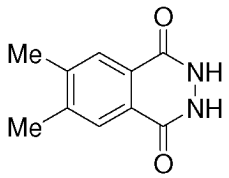
MS (HiResMALDI, pos.) calcd for $C_{39}H_{39}N_3O_2P^+$ ($M+H^+$) 612.2780, found 612.2763.



5,6-dimethylisobenzofuran-1,3-dione (72).

2,3-Dimethyl-1,3-butadiene 14.7 mL (130 mmol) was added to the suspension of maleic anhydride 9.8g (100 mmol) in benzene 220 mL. The mixture was heated for 1 h at 80°C. The solvent and excess volatile were removed under vacuum. The white solid obtained by Diels-Alder reaction was washed with hexane and dried under vacuum at room temperature. Sulfur 9.7g (297 mmol) was mixed with the white solid and heated 200~205°C for 2.5 h. The product was obtained quantitatively (17.6g, 100 mmol) after crystallization from toluene.

All spectroscopic data was in agreement with the data reported in the literature.[166]



2,3-dihydro-6,7-dimethylphthalazine-1,4-dione (73).

Hydrazine hydrate 8.9 mL (184.6 mmol) was added to 6.0 g (34.1 mmol) 5,6-dimethylisobenzofuran-1,3-dione (**72**) in acetic acid (170 mL). The mixture was stirred for 5 h at 120°C. The solution was cooled and the solid was collected and washed with water. The yellow-brown powder was dried under vacuum and 2,3-dihydro-6,7-dimethylphthalazine-1,4-dione was obtained quantitatively (6.5g, 34.1 mmol).

All spectroscopic data was in agreement with the data reported in the literature. [167]

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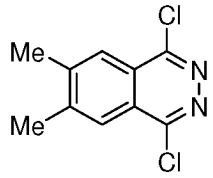
[166] Blanc, P. Y. *Helv. Chim. Acta.* **1961**, *44*, 1.

[167] Groud, K. J.; Hacker, N. P.; McOmie, J. F. W.; Perry, D. H. *J. C. S. Perkin 1.* **1979**, 1834.



1,4-dichloro-6,7-dimethylphthalazine (74).[168]

Dry pyridine 5.6 mL (70.0 mmol) was added slowly to the suspension of 8.3 g (43.6 mmol) 2,3-dihydro-6,7-dimethylphthalazine-1,4-dione (**73**) in 8.2 mL (88.0 mmol) $POCl_3$. The mixture was heated for 2.5 h at 100°C. The yellow solution obtained was allowed to be cooled to room temperature. Then volatiles were removed by evaporation. The dark brown solid was washed with diethylether 120 mL. Then the solid was transformed into ice water 120 mL with ethylacetate 120 mL. The precipitate was filtered and washed with water. The compound was dried under vacuum. The product 9.2 g (40.5 mmol) was obtained in 93% yield.

mp: >250 °C.

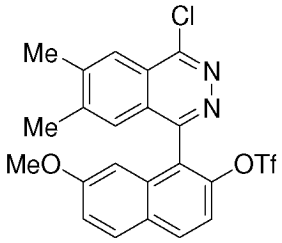
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 6H), 7.90 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 125.3, 145.6, 154.1.

FTIR (KBr thin film, cm^{-1}): 3163 (w), 1692 (s), 1541 (s), 972 (s), 679 (s).

MS (HiResESI, pos.) calcd for $C_{10}H_9N_2Cl_2^+$ ($M+H^+$) 227.0143, found 227.0119.

[168] Gandolfi, C. A.; Beggiolin, G.; Menta, E.; Palumbu, M.; Siss, C.; Spinell, S.; Johnson, F. *J. Med. Chem.* **1995**, *38*, 526.



1-(1-chloro-6,7-dimethylphthalazin-4-yl)-7-methoxynaphthalen-2-yl trifluoromethanesulfonate (75).

In a oven dried 200 mL flask under N_2 were mixed 1.80g (7.9 mmol) of 1,4-dichloro-6,7-dimethylphthalazine (**74**) with 1.38 g (7.9 mmol) of 7-methoxynaphthalen-2-ol (**34**). This mixture was suspended in 100 ml of 1,2-dichloroethane. After stirring for 10 min, 1.10 g (7.9 mmol) of $AlCl_3$ was added in one portion. The resulting suspension was stirred for 20 h at 80 °C. After cooling to room temperature the black suspension was poured on 100 mL ice-water and stirred for 1 h. The two phases were separated. The aq. phase was extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude solid was further dried under vacuum then dissolved in CH_2Cl_2 (80 mL). Then, 0.64 ml (7.9 mmol) of pyridine was added to the solution and the mixture was stirred at 0 °C. Finally, 1.3 mL (7.9 mmol) of triflic anhydride was added and the mixture was stirred for 1 h at 0°C. The resulting solution was quenched with sat. aq. NH_4Cl. The organic phase was separated and the aq. phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified with FC (Hexane/EtOAc = 5:1) to afford the title compound as a white powder in 71% yield (2.8 g, 5.6 mmol) in 2 steps.

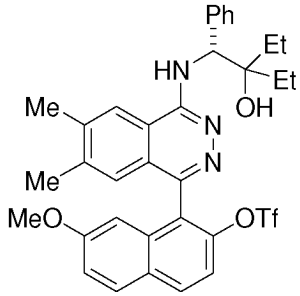
mp: 234 °C (decomposition).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (s, 3H), 6.33 (d, J = 2.4, 1H), 7.01 (dd, J = 2.4, J = 8.7, 1H), 7.20 (d, J = 8.7, 1H), 7.52 (d, J = 8.4, 1H), 7.86 (d, J = 9.0, 1H), 7.94 (d, J = 8.7, 1H), 7.96-8.02 (m, 1H), 8.13-8.18 (m, 1H), 8.40 (d, J = 8.4, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 20.7, 56.8, 107.8, 109.8, 113.4, 118.9 (q, J_{CF} = 315), 121.9, 126.2, 130.2, 134.4, 135.5, 136.4, 136.5, 139.9, 144.8, 150.0, 151.5, 156.3, 163.0, 166.0, 172.2.

FTIR (KBr thin film, cm^{-1}): 3142 (w), 1625 (m), 1513 (s), 1462 (w), 1341 (m), 778 (s).

MS (HiResESI, pos.) calcd for $C_{22}H_{16}ClF_s\ N_2O_4S^+$ ($M+H^+$) 497.0550, found 497.0537.



Trifluoromethanesulfonic acid 1-[4-((*R*)-2-ethyl-2-hydroxy-1-phenylbutylamino)-6,7-dimethylphthalazin-1-yl]-7-methoxynaphthalen-2-yl ester (76).

To 2.8 g (5.6 mmol) of trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl ester (**75**) was added 2.9 g (22.1 mmol) of 3-((*R*)-aminophenyl-methyl)pentan-3-ol. The suspension was stirred for 15 h at 120 °C. After cooling to 25 °C CH_2Cl_2 was added and the suspension was filtered. The filtrate was concentrated under reduced pressure. FC (Hexane/EtOAc = 5:1) afforded the title compound as a brown solid which was triturated with hexane/Et_2O to give 985.0 mg (27%) of the title compound as a single diastereomers.

mp: 243 °C (decomposition).

$[\alpha]_D^{35}$ = +89.7

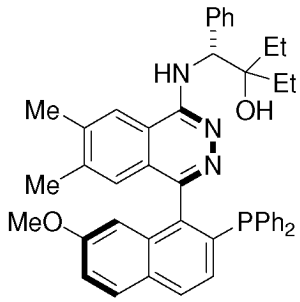
^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (app t, *J* = 7.5, 6H), 1.15-1.20 (m, 1H), 1.32-1.37 (m, 1H), 1.60-1.74 (m, 2H), 2.22 (s, 3H), 2.50 (s, 3H), 3.33 (s, 1H), 3.40 (s, 3H), 4.68 (br, 1H), 5.71 (d, *J* = 9.3, 1H), 6.42 (s, 1H), 6.86 (s, 1H), 7.18-7.33 (m, 5H), 7.54 (d, *J* = 9.0, 1H), 7.62 (d, *J* = 7.5, 1H), 8.09 (d, *J* = 9.3, 1H). 8.23 (d, *J* = 9.3, 1H), 8.36 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ7.8, 8.2, 19.2, 20.3, 28.1, 29.0, 55.5, 59.4, 78.0, 118.3 (q, J_{CF} = 315), 119.7, 120.9, 126.8, 127.5, 128.4, 128.7, 129.2, 129.5, 129.8, 131.2, 131.4, 133.7, 133.8, 134.0, 134.7, 137.0, 137.6, 138.3, 140.5, 140.8, 141.0, 152.6, 153.0, 158.6.

^{19}F NMR δ –74.19.

FTIR (KBr thin film, cm^{-1}): 3369 (w), 1625 (s), 1508 (s), 1419 (s), 1139 (s), 987 (s), 874 (s), 701 (w), 592 (s).

MS (HiResMALDI, pos.) calcd for $C_{34}H_{34}N_3F_3O_5S^+$ ($M+H^+$) 654.2250, found 654.2257.



(*R*,*M*)-[6,7-Dimethyl-4-(2-diphenylphosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (78a).

A solution of 53 mg (0.10 mmol) Ni(dppe)Cl_2 in 2.7 mL of dried DMF at 23 °C was treated with 0.35 mL (2.0 mmol) of diphenylphosphine. The resulting dark red solution was stirred at 120 °C for 30 min, treated with, a solution of 670 mg (1.0 mmol) of trifluoromethanesulfonic acid 1-[4-((*R*)-2-ethyl-2-hydroxy-1-phenylbutylamino)-6,7-dimethylphthalazin-1-yl]-7-methoxynaphthalen -2-yl ester (**76**) and 448.7 mg (4.0 mmol) of DABCO in 2.0 mL of DMF via syringe, the flask was washed with 0.7 mL of DMF. The resulting green solution was stirred at 120 °C for 18 h. The mixture was concentrated under reduced pressure (20 mbar, 70 °C bath temperature). The residue was purified by FC (toluene only) to remove nickel catalyst. The diastereomers were separated with FC (toluene/EtOAc = 10/1) give 270 mg (39%) of 1st diastereomer.

(1st diastereomer, 78a)

mp: >250 °C.

$[\alpha]_D^{35}$ = +172.2

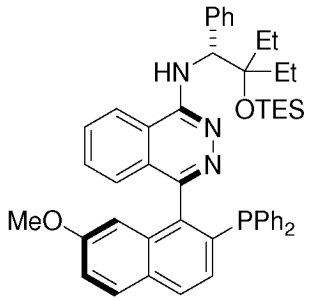
^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (t, *J* = 5.9, 3H), 0.83 (t, *J* = 6.0, 3H), 1.15-1.23 (m, 1H), 1.32-1.36 (m, 1H), 1.62-1.75 (m, 2H), 2.03 (s, 3H), 2.30 (s, 3H), 3.33 (s, 1H), 3.40 (s, 3H), 4.67 (s, 1H), 5.70 (d, *J* = 9.0, 1H), 6.42 (s, 1H). 6.85 (s, 1H), 7.17-7.32 (m, 14H), 7.51 (d, *J* = 5.6, 1H), 7.61 (d, *J* = 5.7, 1H), 7.71 (d, *J* = 6.2, 1H), 8.08 (dd, *J* = 7.2, 11.2 , 1H), 8.23 (d, *J* = 5.7, 1H), 8.36 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δδ7.8, 8.2, 19.2, 20.3, 28.1, 29.0, 54.7, 59.4, 76.3, 118.3, 119.7, 120.9, 126.8, 127.5, 128.2, 128.4, 128.5, 128.6, 128.6, 128.6, 128.7, 128.7, 129.2, 129.5, 129.8, 131.2, 131.4, 133.0, 133.8, 133.9, 134.0, 134.7, 136,6, 137.1, 137.6, 137.7, 138.2, 138.3, 140.5, 140.8, 141.4, 152.6, 152.7, 153.0, 158.5.

^{31}P NMR (DMSO-d_6) δ –13.75.

FTIR (KBr thin film cm^{-1}): 3392 (w), 2936 (m), 1620 (s), 1505 (s), 1223 (s), 839 (s), 743 (s), 698 (s).

MS (HiResMALDI, pos.) calcd for $C_{45}H_{44}N_3O_2P^+$ ($M+H^+$) 690.3249, found 690.3250.



(R,P)-4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-N-(2-ethyl-1-phenyl-2-((triethylsilyl)methyl)butyl)phthalazin-1-amine (79a).

To 130 mg (0.200 mmol) (*R,P*)-[4-(2-Diphenylphosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (**48a**) in 2.0 ml DMF was added 16.0 mg (0.240 mmol) Imidazole and 0.220 ml (0.220 mmol) triethylsilylchloride. After stirring for 7 h at 23 °C the solution was concentrated under reduced pressure. FC (SiO_2; toluene/EtOAc 5:1) afforded 31.0 mg (20 %) of the title compound as an oil.

$[\alpha]_D^{29}$ = 134.8 (c = 0.50, $CHCl_3$).

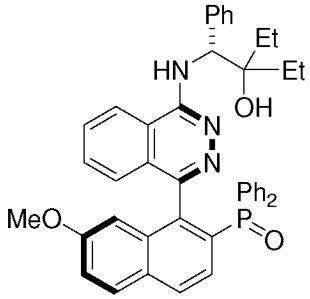
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73-1.11 (m, 21H), 1.35-1.51 (m, 2H), 1.89-2.37 (m, 2H), 3.29 (s, 3H), 5.74 (d, *J* = 8.7, 1H), 6.31 (d, *J* = 2.4, 1H), 6.43 (d, *J* = 9.0, 1H), 7.07-7.29 (m, 15H), 7.40 (t, *J* = 7.2, 1H), 7.61 (d, *J* = 6.9, 2H), 7.67-7.84 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4, 7.7, 8.8, 9.70, 27.0, 29.8, 30.7, 31.3, 31.5, 36.6, 55.1, 59.0, 82.5, 104.8, 117.8, 119.5, 119.9, 126.6, 127.4, 127.6, 127.9, 128.1, 128.1, 128.2, 129.0, 129.1, 129.3, 130.6, 132.4, 132.6, 133.1, 133.4, 133.6, 133.9, 134.4, 134.5, 136.3, 136.4, 137.1, 137.3, 137.6, 137.8, 139.9, 140.3, 140.9, 151.7, 152.0, 157.7, 162.4.

^{31}P NMR (121 MHz, $CDCl_3$) δ -12.2.

FTIR (thin film, cm^{-1}): 2956 (w), 2871 (w), 1621 (w), 1506 (m), 1220.

MS (HiResMALDI, pos.) calcd for $C_{49}H_{55}N_3O_2PSi^+$ ($M+H^+$) 776.3796, found 776.3806



3-((*R*)-(4-((*M*)-2-(diphenylphosphoryl)-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino)(phenyl)methyl)pentan-3-ol (78a).

To 50.0 mg (0.0760 mmol) (*R*,*P*)-[4-(2-Diphenylphosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (**48a**) in 2 ml CH_2Cl_2 was added 1.00 ml H_2O_2. Stirring at 23 °C for 10 min. The reaction was quenched with a saturated solution of NaS_2O_3H aqu. and diluted with CH_2Cl_2. After phase separation, the aqu. phase extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. FC (SiO_2; CH_2Cl_2/*iso*-PrOH 20:1) afforded 43.0 mg (83%) of the title compound as a white solid.

mp: 178-180 °C.

$[\alpha]_D^{27}$ = 298.9 (c = 0.50, $CHCl_3$).

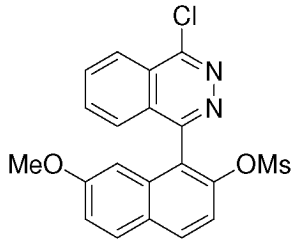
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.5, 3H), 1.06 (t, *J* = 7.6, 3H), 1.25-1.45 (m, 2H), 1.85-2.04 (m, 2H), 3.15 (s, 3H), 5.58 (d, *J* = 8.7, 1H), 6.02 (d, *J* = 2.1, 1H), 6.46 (d, *J* = 8.7, 1H), 6.72 -6.78 (m, 2 H), 6.92-6.98 (m, 2H), 7.05-7.52 (m, 14 H), 7.69 (d, *J* = 8.1, 1H), 7.79 (d, *J* = 9.0, 1H), 7.87-7.94 (m, 2H), 7.99 (dd, *J* = 2.1, *J* = 9.0, 1H), 8.13 (dd, *J* = 8.7, *J* = 11.1, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 8.7, 28.1, 28.6, 54.8, 59.4, 105.5, 117.3, 120.2, 120.5, 126.3, 126.4, 126.5, 126.8, 126.8, 126.9, 127.8, 127.9, 128.1, 128.3, 128.6, 128.8, 129.4, 129.9, 130.3, 130.6, 130.7, 131.3, 131.5, 132.0, 132.1, 132.5, 132.6, 133.5, 134.3, 134.5, 136.8, 137.0, 140.4, 150.8, 154.7, 158.0.

^{31}P NMR (121 MHz, $CDCl_3$) δ 31.5.

FTIR (KBr, cm^{-1}): 3369 (m), 2966 (m), 1621 (w), 1506 (s), 1437 (m), 1220 (s).

MS (HiResMALDI, pos.) calcd for $C_{43}H_{41}N_3O_3P^+$ ($M+H^+$) 678.2880, found 678.2868.



1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl methanesulfonate (82).

To a suspension of 3.30 g (9.80 mmol) 1-(4-Chlorophthalazin-1-yl)-7-methoxynaphthal en-2-ol (**40**) in 11.0 ml CH_2Cl_2 was added 2.00 ml (14.7 mmol) NEt_3. After cooling to 0 °C 0.950 ml (12.3 mmol) MsCl was added over a period of 10 min. Then the reaction was stirred at 23 °C for 20 min. and then quenched with sat. aq. NH_4Cl. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Filtration over short SiO_2 plug (EtOAc) and concentration afforded 2.95 g (73 %) of the title compound as an off white solid.

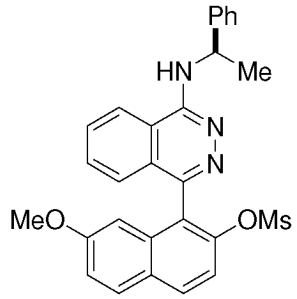
mp: 174-176 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (s, 3H), 3.56 (s, 3H), 6.41 (d, *J* = 2.4, 1H), 7.20 (dd, *J* = 2.4, *J* = 9.3, 1H), 7.44 (d, *J* = 8.4, 1H), 7.68 (d, *J* = 9.0, 1H), 7.83 (dt, *J* = 1.2, *J* = 8.1, 1H), 7.89 (d, *J* = 9.3, 1H),8.01-8.07 (m, 2H), 8.45 (d, *J* = 8.4, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 38.1, 55.4, 104.0, 118.4, 119.3, 122.4, 125.5, 125.9, 126.6, 127.5, 128.5, 129.9, 131.5, 133.9, 134.0, 134.3, 146.5, 155.7, 156.6, 159.0.

FTIR (thin film, cm^{-1}): 3005 (w), 2924 (w), 2832 (w), 1624 (m), 1506 (m), 1462 (m), 1355 (s), 1290 (s), 1232 (s), 1168 (s), 1140 (s), 1068 (m).

MS (HiResMALDI, pos.) calcd for $C_{20}H_{15}ClN_2O_4S^+$ (M^+) 414.0436, found 414.0433.



7-methoxy-1-(4-((R)-1-phenylethylamino)phthalazin-1-yl)naphthalene-2-yl methane sulfonate (83).

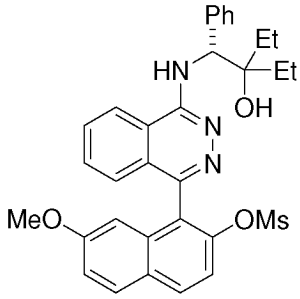
To 2.90 g (6.9 mmol) 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl methane sulfonate (**82**) was added 4.40 ml (34.5 mmol) (*R*)-(+)-alpha-methybenzylamine and the suspension was stirred for 12 h at 120 °C. The suspension was flashed directly (SiO_2; hexane/EtOAc 5:1 to 1:1) to give product together with demesylated product. Since it was not possible to separate the mixture it was dissolved in 10 ml CH_2Cl_2 and treated with 0.461 ml (3.39 mmol) NEt_3. After cooling to 0 °C 0.220 ml (2.83 mmol) MsCl was added over 10 min. After stirring for another 10 min., the reaction was quenched with sat. aq. NH_4Cl. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. FC (SiO_2; hexane/EtOAc 2:1 to 1:1) afforded 1.53 g (44 %) of the title compound as a 2:1 mixture of diastereomers as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (d, *J* = 6.3, 6H), 2.49 (s, 3H), 2.90 (s, 3H), 3.48 (s, 3H), 3.59 (s, 3H), 5.65-5.87 (m, 4H), 6.56 (d, *J* = 2.4, 1H), 6.69 (d, *J* = 2.4, 1H), 7.13-7.38 (m, 12H), 7.47-7.65 (m, 8H), 7.70-7.77 (m, 2H), 7.82-7.98 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 22.7, 37.9, 38.0, 50.8, 51.1, 55.1, 55.3, 104.9, 104.9, 118.0, 118.6, 119.1, 119.1, 121.1, 124.7, 124.8, 126.1, 126.4, 126.6, 127.0, 127.2, 127.5, 127.7, 127.8, 128.4, 128.6, 129.8, 129.8, 130.5, 130.6, 131.7, 135.0, 144.4, 144.7, 146.8, 146.9, 148.1, 153.0, 158.8.

FTIR (thin film, cm^{-1}): 3027 (w), 2933 (w), 1624 (m), 1580 (m), 1505 (s), 1359 (s), 1227 (s), 1210 (s), 1163 (s), 1137 (s), 1070 (m).

MS (HiResMALDI, pos.) calcd. for $C_{28}H_{26}N_3O_4S^+$ ($M+H^+$) 500.1639, found 500.1630.



1-(4-(*R*)-2-ethyl -2-hydroxy-1-phenylbuthylamino)phthalazin-1-yl)-7-methoxynaphthalen-2-yl methanesulfonate (84).

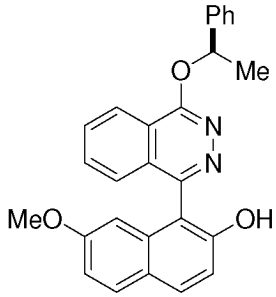
To 2.24 g (5.40 mmol) 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl methanesulfonate (**82**) was added 5.00 g (26 mmol) of 3-((*R*)-aminophenyl-methyl)pentan-3-ol. The suspension was stirred for 24 h at 120 °C. FC (toluene/EtOAc 10:0 → 5:1) afforded 1.73 g (56%) of the title compound as a white powder as a mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87-1.08 (m, 10H), 1.23-1.53 (m, 5H), 1.81-1.99 (m, 5H), 2.13 (s, 3H), 2.84 (s, 3H), 3.38 (s, 3H), 3.62 (s, 3H), 5.58 (d, *J* = 8.1, 1H), 5.78 (d, *J* = 8.1, 1H), 6.44 (d, *J* = 2.1, 1H), 6.56-6.64 (m, 2H), 6.72 (d, *J* = 2.1, 1H), 7.10-7.33 (m, 10H), 7.45-7.51 (m, 3H), 7.58-7.64 (m, 5H), 7.79-7.84 (m, 4H), 7.93 (d, *J* = 8.7, 2H), 8.03 (d, *J* = 8.7, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ7.7, 8.5, 27.8, 28.9, 29.0, 37.5, 37.9, 55.2, 55.3, 58.8, 59.7, 104.4, 104.6, 117.9, 118.1, 118.7, 119.0, 119.2, 119.3, 120.4, 124.5, 126.3, 126.5, 127.2, 127.4, 127.6, 128.0, 128.1, 128.5, 128.7, 129.0, 129.5, 129.6, 130.2, 130.4, 131.6, 131.7, 134.7, 135.0, 140.1, 146.5, 146.6, 147.8, 152.8, 158.5.

FTIR (thin film, cm^{-1}): 2965 (w), 2926 (w), 1626 (w), 1508 (m), 1368 (m), 1220 (s), 1165 (w),772 (s).

MS (HiResMALDI, pos.) calcd for $C_{32}H_{34}N_3O_5S^+$ ($M+H^+$) 572.2214, found 572.2205.



7-methoxy-1-(4-((*R*)-1-phenylethoxy)phthalazin-1-yl)naphthalen-2-ol (22).

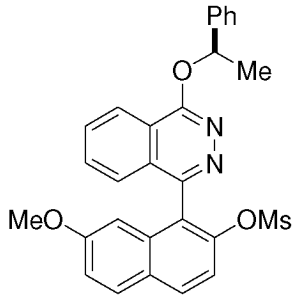
To a suspension of 797 mg (33.2 mmol) NaH in 80 ml THF at 23 °C was added cautiously over 10 min a solution of 2.03 (16.6 mmol) (*R*)-phenylethanol in 2 ml THF. The mixture was stirred for 15 min, then 5.07 g (15.1 mmol) 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-ol (**36**) were added portion wise. The resulting red suspension was stirred for 20 h at 23 °C, and then the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and poured into brine. The organic phase was separated and the water phase was extracted two more times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FC (hexane/EtOAc 4:1 to 1:1) to give 5.54 g (83 %) of the title compound as a 1:1 mixture of diastereomers, as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (d, *J* = 6.6, 3H), 1.90 (d, *J* = 6.6, 3H), 3.40 (s, 3H), 3.46 (s, 3H), 6.39 (d, *J* = 2.4, 1H), 6.47 (d, *J* = 2.1, 1H), 6.76-6.83 (m, 2H), 6.95-7.01 (m, 2H), 7.20-7.52 (m, 10H), 7.61-7.90 (m, 12H), 8.43 (d, *J* = 8.1, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 22.9, 55.0, 55.1, 74.8, 104.0, 104.3, 113.6, 113.8, 115.2, 115.3, 116.8, 116.9, 120.7, 120.7, 123.2, 124.0, 126.2, 126.3, 127.1, 127.8, 128.5, 128.5, 128.8, 128.9, 129.6, 129.7, 130.8, 130.8, 131.9, 132.2, 134.4, 142.2, 142.2, 154.2, 154.4, 157.9, 157.9, 159.4.

FTIR (thin film, cm^{-1}): 3059 (s), 1623 (s), 1587 (m), 1542 (m), 1513 (s), 1493 (m), 1462 (m), 1434 (m), 1404 (s), 1343 (s), 1225 (s), 1074 (s), 1057 (s).

MS (HiResESI, pos.) calcd for $C_{27}H_{23}N_2O_3^+$ ($M+H^+$) 423.1703, found 423.1710.



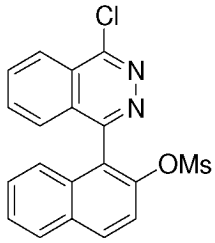
7-methoxy-1-(4-((*R*)-1phenylethoxy)phthalazin-1-yl)naphthalene-2-yl methanesulfonate (89). A solution of 1.08 g (2.56 mmol) of (1:1 mixture) 7-methoxy-1-(4-((*R*)-1-phenylethoxy)phthalazin-1-yl)naphthalen-2-ol (**22**) in 0.531 ml (3.84 mmol) of triethylamine and 5 ml of dichloromethane at 0 °C was treated drop wise with 0.248 ml (3.20 mmol) of MsCl. Then the reaction was stirred at 23 °C for 15 min. and quenched with sat. aq. NH_4Cl. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Filtration over short SiO_2 plug (EtOAc) and concentration afforded 1.13 g (88 %) of the title compound as an off white solid as a mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (t, *J* = 6.3, 6H), 2.40 (s, 3H), 2.91 (s, 3H), 3.45 (s, 3H), 3.60 (s, 3H), 6.40 (d, *J* = 2.7, 1H), 6.60 (d, *J* = 2.7, 1H), 6.73 (q., *J* = 6.6, 1H), 6.82 (q., *J* = 6.6, 1H), 7.14-7.42 (m, 10H), 7.54-7.72 (m, 8H), 7.83-8.01 (m, 6H), 8.46 (t, *J* = 6.9, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 23.0, 37.7, 38.0, 55.2, 55.3, 74.9, 75.0, 104.2, 104.5, 118.5, 119.0, 119.2, 119.9, 120.0, 123.2, 123.3, 123.8, 125.6, 125.7, 126.2, 126.3, 127.5, 127.6, 127.7, 128.4, 128.4, 129.0, 129.7, 129.7, 130.7, 130.8, 132.3, 132.3, 132.6, 134.5, 134.7, 142.2, 142.4, 146.4, 146.6, 152.0152.1, 158.7, 159.5, 159.6.

FTIR (thin film, cm^{-1}): 3028 (w), 2932 (w), 1623 (w), 1580 (w), 1509 (w), 1493 (w), 1396 (m), 1359 (s), 1209 (m), 1165 (s).

MS (HiResMALDI, pos.) calcd for $C_{28}H_{25}N_2O_5S^+$ ($M+H^+$) 501.1479, found 501.1470.



1-(4-chlorophthalazin-1-yl)naphthalene-2-yl methanesulfonate (85).

To a suspension of 3.00 g (9.80 mmol) 1-(4-Chlorophthalazin-1-yl) naphthalen-2-ol (**21**) in 15.0 ml CH_2Cl_2 was added 2.00 ml (14.7 mmol) NEt_3. After cooling to 0 °C 0.950 ml (12.3 mmol) MsCl was added over a period of 10 min. Then the reaction was stirred at 23 °C for 15 min. and then quenched with sat. aq. NH_4Cl. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Filtration over short SiO_2 plug (EtOAc) and concentration afforded 3.18 g (84 %) of the title compound as an off white solid.

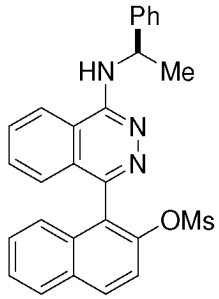
mp: 67-69 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (s, 3H), 7.16 (d, *J* = 8.4, 1H),7.36-7.41 (m, 2H), 7.55 (dt, *J* = 1.2, *J* = 8.1, 1H), 7.78-7.85 (m, 2H), 7.89-8.05 (m, 2H), 8.13 (d, *J* = 9.3, 1H), 8.44 (d, *J* = 8.4, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ38.2, 121.0, 123.8, 125.4, 125.8, 126.6, 126.7, 127.8, 128.3, 128.6, 131.7, 131.8, 132.7, 133.8, 133.9, 145.7, 155.7, 156.4.

FTIR (thin film, cm^{-1}): 3028 (w), 2933 (w), 1581 (w), 1510 (m), 1493 (m), 1361 (s), 1288 (s), 1208 (s), 1167 (s), 1072 (w).

MS (HiResMALDI) calcd for $C_{19}H_{14}ClN_2O_3S^+$ ($M+H^+$) 385.0408, found 385.0402.



1-(4-((*R*)-1-phenylethylamino)phthalazin-1-yl)naphthalene-2-yl methanesulfonate (86).

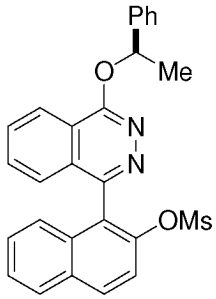
To 3.00 g (7.80 mmol) 1-(4-chlorophthalazin-1-yl)naphthalene-2-yl methanesulfonate (**85**)was added 5.00 ml (39.0 mmol) (*R*)-(+)-alpha-methybenzylamine and the suspension was stirred for 12 h at 120 °C. The suspension was flashed directly (SiO_2; hexane/EtOAc 2:1 to 1:1) to afforded 2.18 g (59 %) of the title compound as a mixture of diastereomers as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (d, J = 6.3, 6H), 2.55 (s, 3H), 2.94 (s, 3H), 5.58-5.86 (m, 4H), 7.18-8.07 (m, 30H).

^{13}C NMR (75 MHz, $CDCl_3$) δ22.0, 22.7, 37.9, 38.1, 50.7, 51.1, 117.8, 117.8, 120.4, 121.2, 121.3, 125.7, 125.8, 126.2, 126.2, 126.3, 126.4, 126.5, 126.6, 127.1, 127.3, 127.3, 127.4, 127.5, 127.6, 128.0, 128.2, 128.5, 128.7, 130.7, 130.8, 131.5, 131.6, 131.7, 131.7, 132.0, 133.4, 133.5, 143.9, 144.2, 145.9, 146.0, 147.9, 152.6, 152.7.

FTIR (thin film, cm^{-1}): 3027 (w), 2931 (w), 1615 (w), 1579 (m), 1555 (m), 1505 (s), 1359 (s), 1209 (m), 1166 (s), 1134 (s), 956 (s), 940 (s).

MS (HiResMALDI, pos.) calcd. for $C_{27}H_{24}N_3O_3S^+$ ($M+H^+$) 470.1533, found 470.1526.



1-(4-((R)-1-phenylethoxy)phthalazin-1-yl)naphthalene-2-yl methanesulfonate (88).

A solution of 1.50 g (3.83 mmol) of (1:1 mixture of diastereomers) (*R*)-1-[4-(1-phenylethoxy)-phthalazin-1-yl]-naphthalen-2-ol (**22**) in 0.794 ml (5.74 mmol) of triethylamine and 5 ml of dichloromethane at 0 °C was treated drop wise with 0.370 ml (4.78 mmol) of MsCl. Then the reaction was stirred at 23 °C for 15 min. and quenched with sat. aq. NH_4Cl. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Filtration over short SiO_2 plug (EtOAc) and concentration afforded 1.55 g (86 %) of the title compound as an off white solid as a mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (t, *J* = 6.0, 6H), 2.47 (s, 3H), 2.94 (s, 3H), 6.74 (q., *J* = 6.6, 1H), 6.84 (q, *J* = 6.6, 1H), 7.22-8.11 (m, 26H), 8.46 (t, *J* = 7.5, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ22.5, 22.7, 37.7, 37.9, 74.7, 75.0, 119.9, 119.9, 121.1, 121.6, 123.1, 123.3, 125.0, 125.6, 125.8, 125.9, 126.2, 126.3, 126.5, 127.4, 127.6, 127.8, 128.1, 128.3, 128.5, 129.1, 129.2, 131.0, 131.1, 131.9, 132.2, 132.3, 132.5, 132.6, 133.1, 133.2, 142.2, 142.3, 145.9, 151.9, 159.7, 159.8.

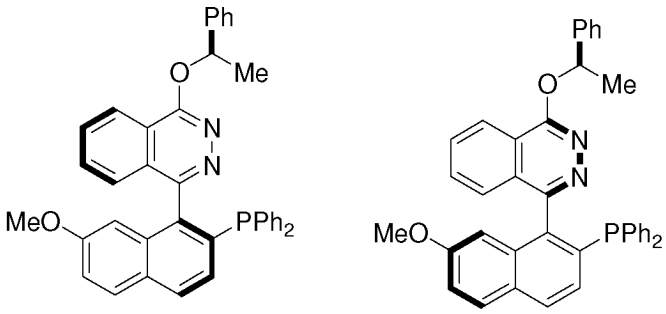
FTIR (thin film, cm^{-1}): 3029 (w), 2932 (w), 1580 (w), 1510 (w), 1493 (w), 1360 (m), 1325 (s), 1209 (m), 1166 (s), 1120(m), 956 (s).

MS (HiResMALDI, pos.) calcd for $C_{27}H_{23}N_2O_4S^+$ ($M+H^+$) 471.1373, found 471.1367.

General procedure for the phosphination reaction employing arylmesylates (GP 1):

A solution of 32.0 mg (0.060 mmol) Ni(dppe)Cl_2 in 2.0 ml of dried DMF at 23 °C was treated with 0.21 ml (1.2 mmol) of diphenylphosphine. The resulting dark red solution was stirred at 120 °C for 30 min, and then treated with a solution of 0.60 mmol arylmesylate and 269 mg (2.4 mmol) of DABCO in 2.0 ml of DMF via syringe, the flask was washed with 0.7 ml of DMF. The

resulting solution was stirred at 120 °C for 14 h. The mixture was concentrated under reduced pressure (20 mbar, 70 °C bath temperature). The residue was purified by FC (toluene only) to remove nickel catalyst.



(*R*,*P*)-1-(-2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-4-(-1-phenylethoxy) phthalazine (90a) and (*R*,*M*)-1-(-2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-4-(-1-phenylethoxy)phthalazine (90b).

Prepared according to GP1 employing 253 mg (0.60 mmol) 7-methoxy-1-(4-((*R*)-1phenylethoxy)phthalazin-1-yl)naphthalene-2-yl methanesulfonate as arylmesylate (**89**).

Purification by FC (toluene/EtOAc = 10/1) afforded 82 mg (23%) of the title compound as oil.

The two diastereomers were separated by FC (SiO_2; toluene /EtOAc 20:1→ toluene/EtOAc 10:1). The relative axial chirality was not established. However, the 1st diastereomer showed to have a negative rotation (-102.3) in the optical rotation measurement, similar to the 1st diastereomer of O-PINAP (-324.0).

(*R*,*P*)-1-(-2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-4-(-1-phenylethoxy) phthalazine (1st Diastereomer, **90a**)

$[\alpha]_D^{30}$ = -102.3 (c = 0.50, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (d, *J* = 6.0, 3H), 3.38 (s, 3H), 6.32 (d, *J* = 2.1, 1H), 6.83 (quart., *J* = 6.6, 1H), 7.11-7.37 (m, 13H), 7.47 (t, *J* = 8.7, 2H), 7.63 (t, *J* = 7.2, 2H), 7.75-7.84 (m, 4H), 8.37 (d, *J* = 8.1, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 55.0, 74.4, 104.8, 104.8, 119.4, 119.8, 123.0, 125.9, 126.4, 127.5, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 129.0, 129.3, 129.3, 131.4, 131.6, 133.0, 133.2, 133.6, 133.9, 134.0, 142.7, 157.9, 159.0.

^{31}P NMR (121 MHz, $CDCl_3$) δ -12.5.

FTIR (thin film, cm^{-1}): 3053 (w), 2978 (w), 2932 (w), 1620 (s), 1503 (m), 1433 (m), 1422 (m), 1398 (s), 1301 (m), 1225 (s), 1066 (m), 1028 (m).

MS (HiResMALDI, pos.) calcd for $C_{39}H_{32}N_2O_2P^+$ ($M+H^+$) 591.2196, found 591.2187.

(*R,M*)-1-(-2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-4-(-1-phenylethoxy)phthalazine (2nd Diastereomer, **90b**)

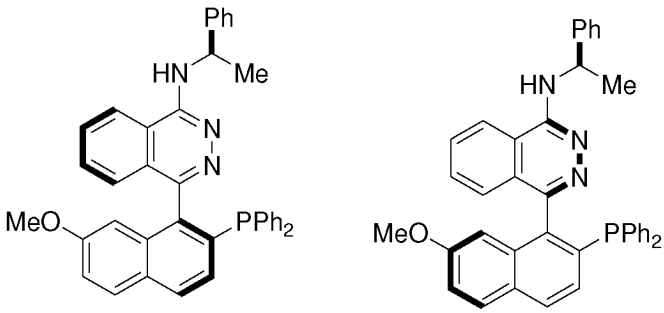
$[\alpha]_D^{29}$ = 16.9 (c = 0.50, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (d, *J* = 6.6, 3H), 3.54 (s, 3H), 6.51 (d, *J* = 2.7, 1H), 6.82 (quart., *J* = 6.6, 1H), 7.05-7.51 (m, 17H), 7.64-7.66 (m, 2H), 7.73-7.84 (m, 3H), 8.35 (d, *J* = 8.1, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ22.6, 55.2, 74.4, 105.2119.1, 119.7, 123.0, 125.9, 126.4, 127.6, 127.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 129.0, 129.4, 129.6, 131.3, 131.6, 133.3, 133.5, 133.8, 134.0, 134.1, 136.6, 136.8, 137.0, 137.0, 137.3, 138.9, 139.3, 142.5, 156.1, 156.2, 157.9, 159.0.

FTIR (thin film, cm^{-1}): 3060 (w), 2976 (w), 2931 (w), 1620 (s), 1504 (m), 1422 (m), 1398 (s), 1302 (m), 1225 (s), 1066 (m), 1028 (m).

MS (HiResMALDI, pos.) calcd for $C_{39}H_{32}N_2O_2P^+$ ($M+H^+$) 591.2196, found 591.2187.

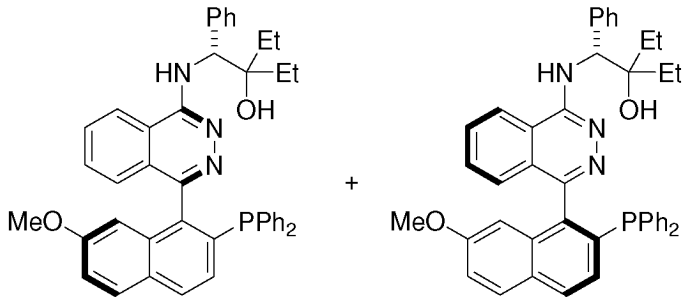


(*R,P*)-4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-N-(1-phenylethyl)phthalazin-1-amine (39a) and (*R,M*)-4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-N-(-1-phenyl ethyl)phthalazin-1-amine (39b).

Prepared according to GP 1 employing 300 mg (0.60 mmol) 7-methoxy-1-(4-((R)-1-phenylethylamino)phthalazin-1-yl)naphthalene-2-yl methane sulfonate (83).

Purification by FC (toluene/EtOAc = 10/1) afforded 135 mg (38%) of the title compound as oil.

All spectroscopic data was in agreement with the data reported earlier (page 109).

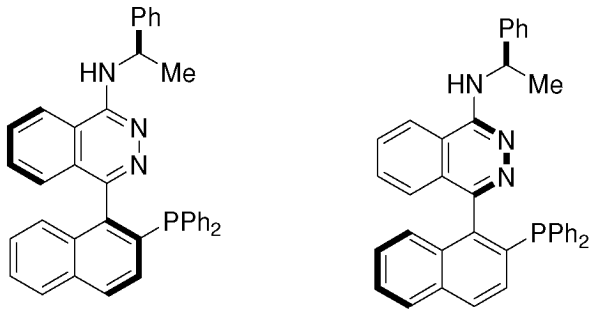


(*R*,*M*)-[4-(2-Diphenylphosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenyl methyl}pentan-3-ol (48a, 1st diasteomer) and (*R*,*P*)-[4-(2-Diphenylphosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (48b, 2nd diasteomer).

Prepared according to GP 1 employing 249 mg (0.60 mmol) 1-(4-(*R*)-2-ethyl -2-hydroxy-1-phenylbuthylamino)phthalazin-1-yl)-7-methoxynaphthalen-2-yl methanesulfonate (**84**).

Purification by FC (toluene/EtOAc = 10/1) afforded 95 mg (24%) of the title compound as a white solid.

All spectroscopic data was in agreement with the data reported earlier (page 112).

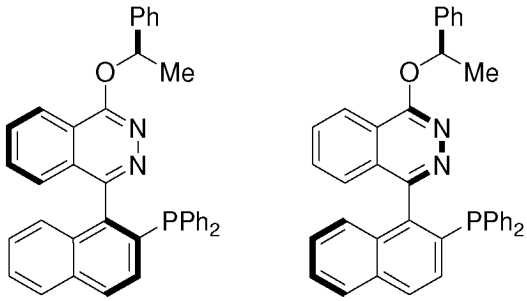


(*R*,*P*)-[4-(2-Diphenylphosphanylnaphthalen-1-yl)phthalazin-1-yl]-(1-phenylethyl)amine (27a) and (*R*,*M*)-[4-(2-Diphenylphosphanylnaphthalen-1-yl)phthalazin-1-yl]-(1-phenylethyl) amine (27b).

Prepared according to GP 1 employing 282 mg (0.60 mmol) 1-(4-((R)-1-phenylethylamino)phthalazin-1-yl)naphthalene-2-yl methanesulfonate (**86**).

Purification by FC (toluene/EtOAc = 10/1) afforded 205 mg (61%) of the title compound as a white solid.

All spectroscopic data was in agreement with the data reported in the literature.[47]

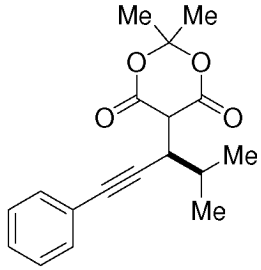


(*R,P*)-1-(2-Diphenylphosphanylnaphthalen-1-yl)-4-(1-phenylethoxy)phthalazine (24a) and (*R,M*)-1-(2-Diphenylphosphanylnaphthalen-1-yl)-4-(1-phenylethoxy)phthalazine (24b).

Prepared according to GP 1 employing 283 mg (0.60 mmol) 1-(4-((R)-1-phenylethoxy)phthalazin-1-yl)naphthalene-2-yl methanesulfonate (**88**).

Purification by FC (toluene/EtOAc = 10/1) afforded 134 mg (40%) of the title compound as a white solid.

All spectroscopic data was in agreement with the data reported in the literature.[47]



(*R*)-(+)-5-(1-Isopropyl-3-phenyl-prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (29).

In a test tube equipped with a stirring bar, a solution of 5.0 mg (0.025 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.2 ml of H_2O was treated with 10 mg (0.050 mmol) of sodium (*L*)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 16.5 mg (0.025 mmol) of **48a** and 0.275 ml (2.5 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C, cooled to 0 °C, stirred for 5 min and treated with 50 mg (0.25 mmol) of 2,2-dimethyl-5-(2-methylpropylidene)-1,3-dioxane-4,6-dione. The reaction mixture was stirred vigorously at 0 °C for 14 h, diluted with CH_2Cl_2 (2 ml) and subjected directly to FC (SiO_2, hexane/EtOAc 3:1) to yield 71 mg (94%) of the pure product as a white solid.

mp: 111-113 °C.

$[\alpha]_D^{25} = 7.93$ (c = 0.5, $CHCl_3$).

ee: determined after conversion into the corresponding anilide: 95% (Daicel Chiracel OD-H column 250 x 4.6 mm and Daicel Chiracel OD-H column 150 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min t_R (minor): 25.4 min, t_R (major): 27.5 min. detector: 254 nm).

The other spectroscopic data was in agreement with the data reported in the literature.[53]

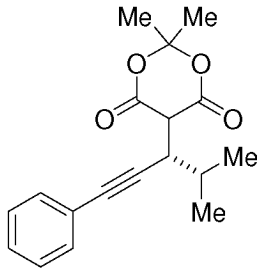
The reaction on 1.25 mmol scale (Equation 14) was run exactly like described above with the following amounts: $Cu(OAc)_2 \cdot H_2O$ (12.5 mg, 0.063 mmol), H_2O (1 ml), sodium (*L*)-ascorbate (25 mg, 0.126 mmol), **48a** (42 mg, 0.063 mmol), phenylacetylene (0.138 ml, 1.26 mmol) and **28** (250 mg, 1.26 mmol) to give **29** (354 mg, 93%).

ee: determined after conversion into the corresponding anilide: 94% (Daicel Chiracel OD-H column 250 x 4.6 mm and Daicel Chiracel OD-H column 150 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min t_R (minor): 25.4 min, t_R (major): 27.5 min. detector: 254 nm).

The other spectroscopic data was in agreement with the data reported in the literature.[53]

Absolute stereochemistry determination:

Determined by conversion into (*S*)-3-isopropyl-5-phenylpentanoic acid: a) H_2O, DMF, 100 °C b) H_2, PtO_2, EtOAc; and comparison with the reported optical rotation.



(*S*)-(–)-5-(1-Isopropyl-3-phenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (29).

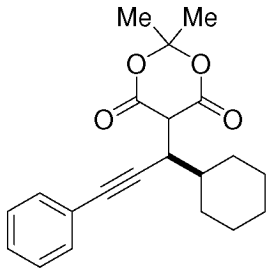
The product was obtained exactly like **28** using *ent*-**48a** as ligand in 85% yield.

mp: 110-112 °C.

$[\alpha]_D^{27} = -11.2$ (c = 0.5, $CHCl_3$).

ee: determined after conversion into the corresponding anilide: 94% (Daicel Chiracel OD-H column 250 x 4.6 mm and Daicel Chiracel OD-H column 150 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min t_R (major): 25.4 min, t_R (minor): 27.5 min. detector: 254 nm).

The other spectroscopic data was in agreement with the data reported in the literature.[53]



(*R*)-(+)-5-(1-Cyclohexyl-3-phenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (49).

In a test tube equipped with a stirring bar, a solution of 5.0 mg (0.025 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.2 ml of H_2O was treated with 10 mg (0.050 mmol) of sodium (*L*)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 16.5 mg (0.025 mmol) of **48a** and 0.275 ml (2.5 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C, cooled to 0 °C, stirred for 5 min and treated with 59 mg (0.25 mmol) of 5-(cyclohexylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione. The reaction mixture was stirred vigorously at 0 °C for 13 h, diluted with CH_2Cl_2 (2 ml) and subjected directly to FC (SiO_2, hexane/EtOAc 3:1) to yield 69 mg (81%) of the pure product as a white solid.

mp: 136-138 °C.

$[\alpha]_D^{31} = 8.93$ (c = 0.50, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98-1.40 (m, 5H), 1.55-1.81 (m, 10H), 2.11-2.24 (m. 1H), 2.32 (d, *J* = 12.6, 1H), 3.34 (dd, *J* = 2.7, 10.2, 1H), 3.78 (d, *J* = 2.7, 1H), 7.26-7.28 (m, 3H), 7.36-7.39 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 26.0, 26.2, 28.0, 28.6, 30.8, 32.4, 38.9, 39.4, 46.8, 84.3, 87.7, 105.2, 122.8, 128.0, 128.0, 131.6, 163.6, 165.5.

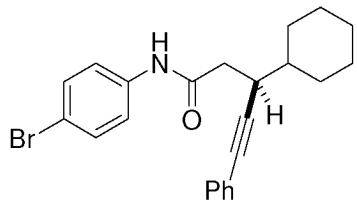
FTIR (thin film, cm^{-1}):3063 (w), 3000 (w), 2932 (m), 2848 (m), 1790 (m), 1750 (s), 1394 (m), 1384 (m), 1314 (m), 1207 (m), 1059 (m).

MS (ESI, pos.) calcd for $C_{21}H_{24}NaO_4^+$ ($M+Na^+$) 363.16 found 363.45.

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.85; H, 7.13.

ee: determined after conversion into the corresponding anilide: 94% (Daicel Chiracel OD-H column 250 x 4.6 mm and Daicel Chiracel OD-H column 150 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min t_R (major): 25.4 min, t_R (minor): 30.4 min. detector: 254 nm).

Absolute stereochemistry determination:



(*S*)-*N*-(4-bromophenyl)-3-cyclohexyl-5-phenylpent-4-ynamide (55).

69.0 mg (0.203 mmol) (*R*)-(+)-5-(1-Cyclohexyl-3-phenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**49**) was dissolved in 1.0 ml DMF. Addition of 100 mg (0.581 mmol) 4-bromoaniline and stirring at 100 °C for 1h. The reaction was quenched with a 1 M HCl aqu. and diluted with Et_2O. After phase separation, the aqu. phase extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated. FC (SiO_2; hexane/EtOAc 3:1) afforded 45.0 mg (54%) of the title compound as a white solid of which a crystal structure could be obtained (colourless needles obtained after crystallization from hexane/toluene).

$[\alpha]_D^{24}$ = -83.81 (c = 0.50, $CHCl_3$).

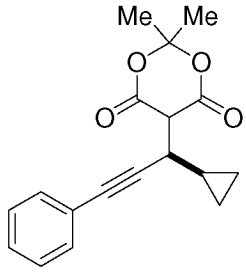
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17-1.52 (m, 5H), 1.53-1.56 (m,1H), 1.67-1.89 (m,5H), 2.58 (d, *J* = 7.2, 2H), 2.98-3.04 (q, *J* = 6.1, 1H), 7.26-7.35 (m, 6H), 7.36-7.42 (m, 3H), 7.70 (brs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.3, 29.3, 29.8, 31.4, 35.7, 41.1, 41.6, 84.4, 90.5, 116.7, 121.4, 123.0, 128.0, 128.2, 131.5, 131.8, 136.8, 169.7.

FTIR (thin film, cm^{-1}): 3280 (w), 2928 (m), 2849 (m), 1648 (s), 1591 (m), 1527 (s), 1489 (s), 1439 (m), 1396 (s), 1260 (m), 1072 (m), 1012 (m).

MS (HiResEI) calcd for $C_{23}H_{24}BrNO^+$ (M^+) 409.1036, found 409.1033.

Anal. Calcd for $C_{23}H_{24}BrNO$: C, 67.32; H, 5.89. Found: C, 67.21; H, 5.99.



(*R*)-(+)-5-(1-Cyclopropyl-3-phenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (50).

In a test tube equipped with a stirring bar, a solution of 5.0 mg (0.025 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.2 ml of H_2O was treated with 10 mg (0.050 mmol) of sodium (*L*)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 16.5 mg (0.025 mmol) of **48a** and 0.275 ml (2.5 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C, cooled to 0 °C, stirred for 5 min and treated with 49 mg (0.25 mmol) of 5-(cyclopropylmethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione. The reaction mixture was stirred vigorously at 0 °C for 51 h, diluted with CH_2Cl_2 (2 ml) and subjected directly to FC (SiO_2, hexane/CH_2Cl_2 1:3) to yield 59 mg (79%) of the pure product as a white solid.

mp: 96-97 °C

$[\alpha]_D^{25}$ = 105.4 (c = 0.505, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.30-0.37 (m, 1H), 0.51-0.65 (m, 2H), 0.70-0.79 (m, 1H), 1.66-1.76 (m, 1H), 1.80 (s, 6H), 2.98 (dd, *J* = 2.6, 9.5, 1H), 3.76 (d, *J* = 2.6, 1H), 7.25-7.29 (m, 3H), 7.37-7.42 (m, 2H).

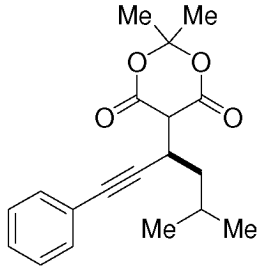
^{13}C NMR (75 MHz, $CDCl_3$) δ 4.9, 6.3, 14.7, 27.8, 28.5, 37.7, 50.7, 83.4, 86.9, 105.2, 122.7, 128.0, 131.7, 163.6, 164.5.

FTIR (thin film, cm^{-1}): 3003 (w), 2881 (w), 1785 (m), 1749 (s), 1490 (w), 1334 (m), 1298 (s), 1204 (m), 1005 (m), 758 (m), 693 (m).

MS (ESI, neg.) calcd for $C_{18}H_{17}O_4^-$ ($M\text{-}H^+$) 297.1 found 297.2.

Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.34; H, 6.11.

ee: determined after conversion into the corresponding anilide: 97%, (Daicel Chiralpak AD-H column 250 x 4.6 mm, hexane:*i*-PrOH 90:10, flow: 0.8 ml/min. t_R (minor): 14.5 min, t_R (major): 16.5 min. detector: 254 nm).



(*R*)-(+)-5-(1-Isobutyl-3-phenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (51).

In a test tube equipped with a stirring bar, a solution of 10 mg (0.050 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.2 ml of H_2O was treated with 20 mg (0.10 mmol) of sodium (*L*)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 33.1 mg (0.050 mmol) of **48a** and 0.275 ml (2.5 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C, cooled to 0 °C, stirred for 5 min and treated with 53 mg (0.25 mmol) of 2,2-dimethyl-5-(3-methylbutylidene)-1,3-dioxane-4,6-dione. The reaction mixture was stirred vigorously at 0 °C for 24 h, diluted with CH_2Cl_2 (2 ml) and subjected directly to FC (SiO_2, hexane/EtOAc 5:1) to yield 67 mg (85%) of the pure product as a white solid.

mp: 100-102 °C.

$[\alpha]_D^{27} = 18.1$ (c = 0.52, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, *J* = 2.5, 3H), 1.01 (d, *J* = 2.5, 3H), 1.35-1.44 (m, 1H), 1.78 (s, 6H), 1.87-2.00 (m, 1H), 2.10-2.20 (m, 1H), 3.65 (d, *J* = 2.7, 1H), 3.72-3.79 (m, 1H), 7.24-7.30 (m, 3H), 7.35-7.42 (m, 2H).

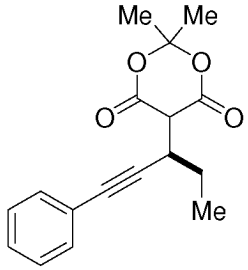
^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 23.3, 26.4, 27.7, 28.6, 30.4, 41.4, 50.3, 83.5, 88.0, 105.2, 122.9, 128.0, 128.1, 131.7, 163.5, 164.3.

FTIR (thin film, cm^{-1}): 2956 (m), 1791 (m), 1750 (s), 1384 (m), 1306 (s), 1206 (m), 1060 (m), 1006 (m), 884 (w), 756 (m).

MS (ESI, neg.) calcd for $C_{19}H_{21}O_4^-$ ($M\text{-}H^+$) 313.15 found 313.3.

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.52; H, 7.11.

ee: determined after conversion into the corresponding anilide: 90% (Daicel Chiracel OD-H column 250 x 4.6 mm and Daicel Chiracel OD-H column 150 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min. t_R (minor): 25.0 min, t_R (major): 26.8 min. detector: 254 nm).



(*R*)-(+)-5-(1-Ethyl-3-phenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (52).

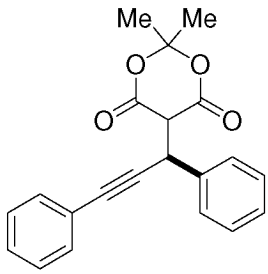
In a test tube equipped with a stirring bar, a solution of 10 mg (0.050 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.2 ml of H_2O was treated with 20 mg (0.10 mmol) of sodium (*L*)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 33.1 mg (0.050 mmol) of **48a** and 0.275 ml (2.5 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C, cooled to 0 °C, stirred for 5 min and treated with 46 mg (0.25 mmol) of 2,2-dimethyl-5-propylidene-1,3-dioxane-4,6-dione. The reaction mixture was stirred vigorously at 0 °C for 24 h, diluted with CH_2Cl_2 (2 ml) and subjected directly to FC (SiO_2, hexane/EtOAc 3:1 → 2:1) to yield 59 mg (83%) of the pure product as a white solid.

mp: 105-110 °C.

$[\alpha]_D^{25} = 20.5$ (c = 0.54, $CHCl_3$).

ee: determined after conversion into the corresponding anilide: 82%, (Daicel Chiracel OD-H column 250 x 4.6 mm and Daicel Chiracel OD-H column 150 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min t_R (major): 27.0 min, t_R (minor): 33.5 min. detector: 254 nm).

The other spectroscopic data was in agreement with the data reported in the literature.



(*S*)-(+)-5-(3-Phenyl-1-phenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (53).

In a test tube equipped with a stirring bar, a solution of 20 mg (0.10 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.4 ml of H_2O was treated with 40 mg (0.20 mmol) of sodium (*L*)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 66.2 mg (0.10 mmol) of **48a** and 0.55 ml

(5.0 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C, cooled to 0 °C, stirred for 5 min and treated with 116 mg (0.50 mmol) of 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione. The reaction mixture was stirred vigorously at 0 °C for 66 h, diluted with CH_2Cl_2 (2 ml) and subjected directly to FC (SiO_2, hexane/EtOAc 3:1 → 1:1) to yield 110 mg (64%) of the pure product as a white solid.

mp: 153-156 °C (decomp.).

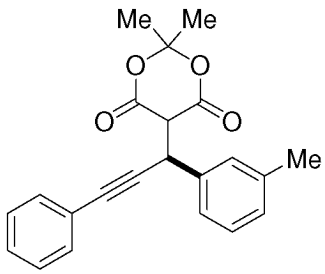
$[\alpha]_D^{27}$ = 59.5 (c = 0.31, $CHCl_3$).

ee: determined after conversion into the corresponding anilide: 83%, (Daicel Chiracel OD-H column 250 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min. t_R (minor): 21.5 min, t_R (major): 24.4 min. detector: 254 nm).

The other spectroscopic data was in agreement with the data reported in the literature.[53]

Absolute stereochemistry determination:

Determined by conversion into (*S*)-methyl-3,5-diphenyl-2-methoxycarbonyl-5-oxopentane: a) H_2, Pd/C, MeOH, rt, b) cat. HCl, MeOH, reflux, c) CrO_3, AcOH, rt; and comparison of the optical rotation with the reported value.



(*S*)-(+)-5-(3-Phenyl-1-*m*-tolylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (54).

In a test tube equipped with a stirring bar, a solution of 20 mg (0.10 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.4 ml of H_2O was treated with 40 mg (0.20 mmol) of sodium (*L*)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 66.2 mg (0.10 mmol) of **48a** and 0.55 ml (5.0 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C, cooled to 0 °C, stirred for 5 min and treated with 123 mg (0.50 mmol) of 2,2-dimethyl-5-(3-methylbenzylidene)-1,3-dioxane-4,6-dione. The reaction mixture was stirred vigorously at 0 °C

for 66 h, diluted with CH_2Cl_2 (2 ml) and subjected directly to FC (SiO_2, hexane/EtOAc 3:1 → 1:1) to yield 151 mg (87%) of the pure product as a white solid.

mp: 136-137 °C (decomp.).

$[\alpha]_D^{27}$ = 61.3 (c = 0.53, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.74 (s, 3H), 2.38 (s, 3H), 4.00 (d, *J* = 2.6, 1H), 5.12 (d, *J* = 2.6, 1H), 7.11 (d, *J* = 7.5, 1H), 7.26 (t, *J* = 7.5, 1H), 7.30-7.33 (m, 3H), 7.43 (d, *J* = 7.5, 2H), 7.46-7.51 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 27.9, 28.4, 37.1, 52.9, 85.4, 86.3, 105.2, 122.7, 125.6, 128.1. 128.2, 128.3 128.5. 129.1, 131.7, 136.9, 138.1, 162.9, 163.7.

FTIR (thin film, cm^{-1}): 3003 (w), 1786 (m), 1749 (s), 1607 (w), 1490 (m), 1296 (s), 1205 (m), 1006 (m), 758 (m), 692 (m).

MS (ESI, neg.) calcd for $C_{22}H_{19}O_4^-$ ($M\text{-}H^+$) 347.1 found 347.2.

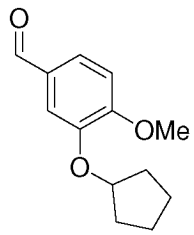
Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.66; H, 5.93.

ee: determined after conversion into the corresponding anilide: 90%, (Daicel Chiracel OD-H column 250 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min. t_R (minor): 19.8 min, t_R (major): 21.7 min. detector: 254 nm).

123 mg of adduct was recrystallized from warm (40 °C) EtOAc to give 85 mg white crystals (69% mass recovery), the ee was 98% (determined as described above).

$[\alpha]_D^{30}$ = 67.9 (c = 0.53, $CHCl_3$).

mp: 136-137 °C (decomp.).



3-(cyclopentyloxy)-4-methoxybenzaldehyde (1).

To 5.00 g (33.0 mmol) 3-hydroxy-4-methoxybenzaldehyde (**64**) in 50 ml DMF was added 6.90 g (50.0 mmol) K_2CO_3 and 3.50 ml (33.0 mmol) cyclopentylbromide. The reaction was heated to

50 °C and stirred for 14 h, and quenched with H_2O. The organic layer was separated and the water phase was extracted twice with pentane. The combined organic layers were dried over Na_2SO_4 and concentrated to give 2.40 g (33%) of the title compound as an oil.

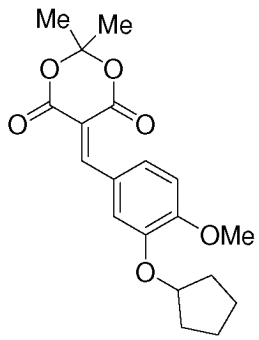
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59-2.03 (m, 8H), 3.91 (s, 3H), 4.81-4.86 (m, 1H), 6.95 (d, *J* = 8.1, 1H), 7.38-7.43 (m, 2H), 9.10 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 32.6, 56.0, 80.3, 110.6, 111.9, 126.2, 129.9, 148.1, 155.3.

FTIR (thin film, cm^{-1}): 2960 (w), 1687 (s), 1585 (s), 1509 (s), 1434 (m), 1265 (s), 1239 (m), 1160 (w), 1132 (m), 1021(w).

MS (HiRes EI, pos.) calcd for $C_{13}H_{16}O_3^+$ (M^+) 220.1094, found 220.1095.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.67; H, 7.25.



5-(3-(cyclopentyloxy)-4-methoxybenzylidene)-2,2dimethyl-1,3-dioxane-4,6-dione (3).

To 1.56 g (10.9 mmol) *Meldrum`s* acid (**2**) and 2.40 g (10.9 mmol) 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**1**) in 20 ml $CHCl_3$ was added 25.0 mg (1.40 mmol) EDDA. After stirring for 14 h at 23 °C the reaction was quenched with sat. aq. NH_4Cl. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was recrystallized from EtOAc / hexane to give 340 mg (9.00 %) of the title compound as yellow crystals.

mp: 119-120 °C.

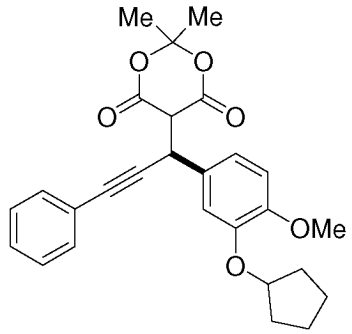
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56-2.13 (m, 15H), 3.95 (s, 3H), 4.82-4.88 (m, 1H), 6.93 (d, *J* = 8.4, 1H), 7.60 (dd, *J* = 2.1, *J* = 8.4, 1H), 8.31 (d, *J* = 2.1, 1H), 8.35 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 27.4, 32.7, 56.1, 56.1, 80.5, 104.0, 110.1, 110.7, 118.3, 124.9, 132.3, 147.4, 155.6, 158.5, 160.6, 164.2.

FTIR (thin film, cm^{-1}): 3130 (w), 3054 (w), 2940 (w), 2868 (w), 1747 (w), 1715 (s), 1538 (s), 1519 (s), 1461 (m), 1421 (s), 1393 (s), 1264 (s), 1219 (s), 1133 (s), 1050 (s).

MS (ESI, pos.) calcd for $C_{19}H_{22}NaO_6^+$ ($M+Na^+$) 396.1, found 368.9.

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.67; H, 6.55.



(*S*)-5-(1-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-phenylprop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4).

In a vial equipped with a stirring bar, a solution of 10.0 mg (0.050 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.2 ml of H_2O was treated with 20 mg (0.100 mmol) of sodium (L)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 34.0 mg (0.050 mmol) of **48a** and 0.275 ml (2.50 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C and treated with 87 mg (0.250 mmol) of 5-(3-(cyclopentyloxy)-4-methoxybenzylidene)-2,2dimethyl-1,3-dioxane-4,6-dione (**3**). The reaction mixture was stirred vigorously at 23 °C for 70 h, diluted with CH_2Cl_2 (2 ml) and subjected directly to FC (SiO_2, hexane/EtOAc 4:1 to 2:1) to yield 48 mg (43%) of the pure product as a yellow oil.

$[\alpha]_D^{27}$ = 34.11 (c = 0.50, $CHCl_3$).

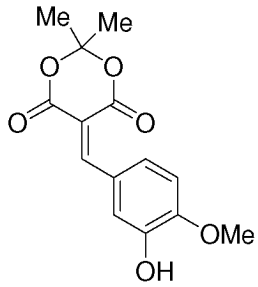
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56-2.00 (m, 14H), 3.83 (s, 3H), 3.97 (d, *J* = 3.0, 1H), 4.77-4.83 (m, 1H), 5.08 (d, *J* = 3.0, 1H), 6.82 (d, *J* = 8.4, 1H), 7.07 (dd, *J* = 2.4, *J* = 8.4, 1H), 7.19 (d, *J* = 2.1, 1H), 7.29-7.33 (m, 3H), 7.45-7.49 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 28.0, 28.5, 32.9, 32.9, 37.0, 53.0, 56.1, 80.4, 85.1, 87.0, 105.3, 111.5, 115.6, 120.7, 122.8, 128.2, 128.2, 129.1, 131.7, 147.3, 149.4, 163.5, 163.5.

FTIR (thin film, cm^{-1}): 2991 (w), 2952 (w), 1784 (m), 1750 (s), 1514 (m), 1365 (s), 1294 (m), 1259 (m), 1220 (s), 1137 (w), 773(s).

MS (HiResMALDI, pos.) calcd for $C_{27}H_{28}O_6Na^+$ ($M+Na^+$) 471.1784, found 471.1771.

ee: determined after conversion into the corresponding anilide: 74% (Daicel Chiracel OD-H column 250 x 4.6 mm and Daicel Chiracel OD-H column 150 x 4.6 mm, hexane:*i*-PrOH 87:13, flow: 0.7 ml/min t_R (minor): 36.5 min, t_R (major): 44.0 min. detector: 254 nm).



5-(3-hydroxy-4-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (113).

To 2.00 g (14.0 mmol) *Meldrum`s* acid (**2**) and 2.13 g (14.0 mmol) 3-(hydroxy)-4-methoxybenzaldehyde (**64**) in 20 ml $CHCl_3$ was added 25.0 mg (1.40 mmol) EDDA. After stirring for 14 h at 23 °C the reaction was quenched with H_2O. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was recrystallized from $CHCl_3$ / hexane to give 3.61 g (93 %) of the title compound as of white crystals.

mp: 132-134 °C.

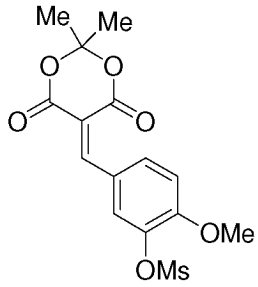
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 6H), 3.99 (s, 3H), 5.77 (s, 1H), 6.92 (d, J = 8.7, 1H), 7.70 (dd, J = 1.5, J = 8.4, 1H), 7.90 (d, J = 1.8, 1H), 8.30 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 56.2, 104.2, 110.2, 111.5, 119.5, 125.3, 130.1, 145.2, 151.7, 157.9, 160.1, 163.8.

FTIR (thin film, cm^{-1}): 3263 (w), 2989 (w), 1738 (w), 1694 (s), 1544 (s), 1408 (m), 1265 (s), 1190 (s), 1174 (s), 1126 (s), 1011 (s).

MS (ESI, neg.) calcd for $C_{14}H_{13}O_6^-$ ($M-H^-$) 277.1, found 277.1.

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.15; H, 5.03.



5-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)-2-methoxyphenylmethane sulfonate (65).

To 6.10 g (22.0 mmol) of 5-(3-hydroxy-4-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**113**) in 30 ml CH_2Cl_2 was added 4.60 ml (33.0 mmol) NEt_3 and the orange solution was cooled to 0 °C. Then 2.10 ml (27.4 mmol) MsCl was added by syringe over 15 min. After stirring for 10 min., the reaction was quenched with H_2O. The organic layer was separated and the water phase was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 / $CHCl_3$ (8 ml). After standing for 14 h the product precipitated (4.50 g). The mother liquor was concentrated. FC (SiO_2; hexane/EtOAc 3:1) afforded additional 1.20 g (total yield 73 %) of the title compound as a yellow solid.

mp: 148-150 °C.

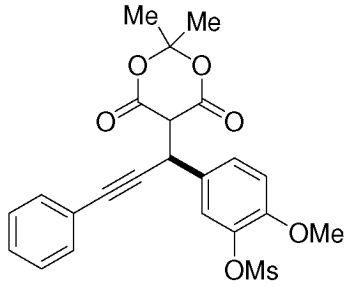
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (s, 6H), 3.27 (s, 3H), 4.01 (s, 3H), 7.09 (d, J = 8.7, 1H), 8.07 (dd, J = 2.1, J = 8.7, 1H), 8.34 (s, 1H), 8.36 (d, J = 2.1, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7, 38.7, 56.6, 104.5, 112.5, 112.7, 124.8, 129.4, 136.4, 137.9, 156.1, 156.4, 160.0, 163.2.

FTIR (thin film, cm^{-1}): 3024 (w), 1716 (s), 1591 (s), 1510 (m), 1372 (s), 1284 (s), 1268 (s), 1204 (s), 1178 (s), 1110 (s), 1007 (s), 992 (s).

MS (ESI, pos.) calcd for $C_{15}H_{16}NaO_8S^+$ ($M+Na^+$) 379.0, found 379.0.

Anal. Calcd for $C_{15}H_{16}O_8S$: C, 50.56; H, 4.53. Found: C, 50.27; H, 4.59.



(S)–(+)-5-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-phenylprop-2-ynyl)-2-methoxyphenylmethanesulfonate (66).

In a 5 ml flask equipped with a big stirring bar, a solution of 20.0 mg (0.100 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 0.4 ml of H_2O was treated with 40 mg (0.200 mmol) of sodium (L)-ascorbate, stirred until the mixture turned bright orange (3 min). Subsequently, 68.0 mg (0.100 mmol) of **48a** and 0.550 ml (5.00 mmol) of phenylacetylene were added, the resulting mixture was stirred 10 min at 23 °C and treated with 178 mg (0.500 mmol) of **65**. The reaction mixture was stirred vigorously at 23 °C for 22 h, diluted with CH_2Cl_2 (2 ml) and subjected to a plug of SiO_2. Crude NMR showed 80 % product, 15 % byproduct (**67**) and 5 % decomposition of starting material. Crystallization from $CHCl_3$ / hexane afforded 140 mg (61 %) of the title compound as yellow crystals.

FC (SiO_2; hexane/EtOAc 1:1) resulted in a diminished yield, since the title compound is not stable on the column.

mp: decomposition at 135 °C.

$[\alpha]_D^{26}$ = 42.47 (c = 0.50, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.76 (s, 3H), 3.20 (s, 3H), 3.89 (s, 3H), 3.96 (d, *J* = 3.0, 1H), 5.11 (d, *J* = 2.7, 1H), 6.99 (d, *J* = 8.4, 1H), 7.29-7.32 (m, 3H), 7.45-7.58 (m, 2H), 7.52 (d, *J* = 2.7, 1H), 7.61 (dd, *J* = 2.1, *J* = 8.7, 1H).

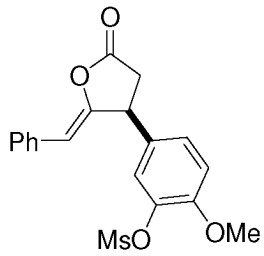
^{13}C NMR 75 MHz, $CDCl_3$) δ 27.7, 28.5, 35.9, 38.3, 52.8, 56.2, 85.6, 85.8, 105.4, 112.7, 122.4, 124.7, 128.2, 128.5, 128.9, 130.0, 131.8, 137.8, 151.0, 162.9, 163.4.

FTIR (thin film, cm^{-1}): 3009 (w), 2939 (w), 1785 (m), 1749 (s), 1512 (s), 1365 (s), 1294 (s), 1176 (s), 1110 (s), 1017 (m).

MS (HiResMALDI, pos.) calcd for $C_{23}H_{22}O_8SNa^+$ ($M+Na^+$) 481.0928, found 481.0919.

ee: Both the flashed and crystallized compound were decarboxylated in a mixture of DMF:Aniline = 10:1, (100 °C, 1h) to the corresponding anilide: 89 % (for both, Daicel Chiralpak

OD-H column 150 x 4.6 mm, hexane:*i*-PrOH 75:25, flow 0.5 ml/min. t_R (minor): 17.1 min, t_R (major): 19.5 min. detector: 254 nm)



(*S*, *Z*)-5-(2-benzylidene-5-oxo-tetrahydrofuran-3-yl)-2-methoxyphenyl methanesulfonate (67)

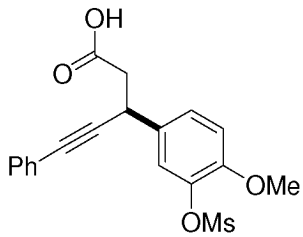
$[\alpha]_D^{25}$ = 40.66 (c = 0.54, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76 (dd, *J* = 8.1, *J* = 15.9, 1H), 3.01 (dd, *J* = 6.9, *J* = 15.9, 1H), 3.19 (s, 3H), 3.88-3.94 (m, 4H), 5.92 (d, *J* = 4.2, 1H), 6.97 (d, *J* = 8.4, 1H), 7.16 (dd, *J* = 2.1, *J* = 8.7, 1H), 7.21 (d, *J* = 2.1, 1H), 7.38-7.40 (m, 3H), 7.64-7.67 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ36.4, 37.0, 38.6, 56.2, 103.5, 113.4, 123.5, 124.7, 126.4, 128.5, 129.3, 131.9, 134.4, 138.4, 150.6, 151.0, 167.1.

FTIR (thin film, cm^{-1}): 3034 (w), 2934 (w), 1767 (s), 1512 (s), 1365 (s), 1275 (m), 1220 (s), 1178 (s), 1108 (s), 1021 (m).

MS (HiResMALDI, pos.) calcd for $C_{19}H_{18}O_6SNa^+$ ($M+Na^+$) 397.0716, found 397.0711.



(*S*)-3-(4-methoxy-3-(methylsulfonyloxy)phenyl)-5-phenylpent-4-ynoic acid (114).

To 40.0 mg (0.0870 mmol) (S)–(+)-5-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-phenylprop-2-ynyl)-2-methoxyphenylmethanesulfonate (**66**) in 1 ml DMF was added 0.40 mg NaOH in 0.100

ml H_2O. The solution was heated in a vial for 1 h at 100 °C. After cooling to RT, the solution was diluted with Et_2O and washed with 1 M HCl solution. After phase separation, the aqu. phase was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated. After evaporation of the DMF in HV 30.4 mg (93 %) of the pure title compound was isolated as a yellow oil.

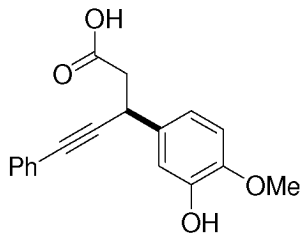
$[\alpha]_D^{22}$ = 12.22 (c = 0.50, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (dd, *J* = 6.9, *J* = 15.9, 1H), 2.96 (dd, *J* = 7.8, *J* = 15.9, 1H), 3.17 (s, 3H), 3.88 (s, 3H), 4.34 (t, *J* = 7.5, 1H), 6.97 (d, *J* = 8.4, 1H), 7.28-7.30 (m, 3H), 7.37-7.44 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 33.57, 38.4, 43.0, 56.2, 84.0, 89.0, 113.0, 122.8, 123.7, 127.1, 128.1, 128.2, 131.6, 133.3, 138.1, 150.5, 175.7.

FTIR (thin film, cm^{-1}): 3029 (w), 2931 (w), 2842 (w), 1712 (s), 1511 (s), 1365 (s), 1268 (m), 1220 (s), 1177 (s), 1109 (s), 772 (s).

MS (HiResMALDI) calcd for $C_{19}H_{18}NaO_6S^+$ ($M+Na^+$) 397.0716, found 397.0724.



(*S*)-3-(3-hydroxy-4-methoxyphenyl)-5-phenylpent-4-ynoic acid (68).

To 75.0 mg (0.200 mmol) (*S*)-3-(4-methoxy-3-(methylsulfonyloxy)phenyl)-5-phenylpent-4-ynoic acid (**114**)in 1.0 ml MeOH was added 42.0 mg (1.05 mmol) NaOH and 0.20 ml H_2O. The solution was stirred at 50 °C for 18 h. After cooling to 23 °C the reaction was quenched with 1M HCl and diluted with Et_2O. After phase separation, the aqu. phase was extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated to affored 50.0 mg (85%) of the title compound as beige oil.

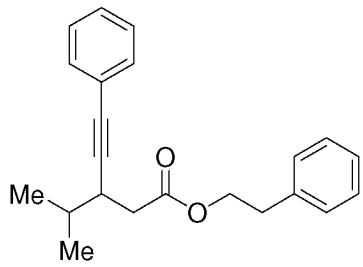
$[\alpha]_D^{28}$ = 9.93 (c = 0.50, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (dd, *J* = 6.9, *J* = 15.6, 1H), 2.94 (dd, *J* = 8.4, *J* = 15.6, 1H), 3.87 (s, 3H), 4.30 (t, *J* = 7.2, 1H), 6.81 (d, *J* = 8.4, 1H), 6.93 (dd, *J* = 2.4, *J* = 8.4, 1H), 7.06 (d, *J* = 2.1, 1H), 7.25-7.29 (m, 3H), 7.41-7.44 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 34.0, 43.2, 56.1, 83.6, 89.7, 110.7, 113.6, 118.9, 123.1, 127.9, 128.1, 131.6, 133.4, 145.6, 145.7, 176.7.

FTIR (thin film, cm^{-1}): 2962 (w),1701 (s), 1509 (s), 1270 (m), 1219 (s), 1129 (w).

MS (HiResEI) calcd for $C_{18}H_{16}O_4^+$ (M^+) 296.1044, found 296.1046.



Phenethyl 3-isopropyl-5-phenylpent-4-ynoate (62).

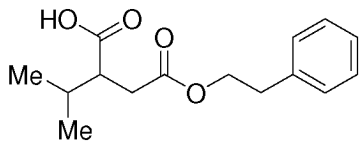
In a 25 mL round bottom flask was placed 0.83g (2.76 mmol) of **29** and DMF (10 mL). To the solution was added phenethyl alcohol (1.00 mL, 8.37 mmol, 3.0 equiv). The reaction mixture was heated to 100 °C for 2 h. The reaction mixture was cooled to rt, diluted with water (10 mL) and poured into pentane (50 mL). The phases were separated, and the organic layer was washed with brine (20 mL). The solution was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (Hexane/EtOAc, 9/1, SiO_2) to give 843 mg (95%) of the title compound as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.5, 3 H), 1.04 (d, *J* = 6.6, 3 H), 1.78 (m, 1 H), 2.55 (m, 2 H), 2.95 (t, *J* = 6.9, 2 H), 3.00 (m, 1 H), 4.34 (t, *J* = 7.0, 2 H), 7.21 – 7.39 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 17.99, 21.11, 31.19, 35.03, 35.60, 38.04, 64.90, 83.05, 89.61, 123.47, 126.28, 127.43, 127.91, 128.22, 128.61, 131.37, 137.50, 171.42.

FTIR (neat) 2961 (m), 1736 (s), 1598 (w), 1490 (m), 1454 (m), 1256 (m), 1163 (m).

HRMS (EI) Calcd for $C_{22}H_{24}O_2$ (M^+) 320.1771, found 320.1771.



2-Isopropyl-4-oxo-4-phenethoxybutanoic acid (63).

In a 50 mL round bottom flask were placed **62** (160 mg, 0.50 mmol), MeCN (10 mL) and water (6 mL). To the solution were added Oxone (1.54 g, 2.50 mmol, 5.0 equiv) and $NaHCO_3$ (525 mg, 6.25 mmol, 12.5 equiv). The reaction mixture was stirred for 5 min. To the reaction mixture was added $RuCl_3$-$3H_2O$ (6.5 mg, 0.025 mmol, 0.05 equiv). The reaction mixture was stirred for 2 h. To the reaction mixture was added aqueous 1 N NaOCl solution (2.0 mL, 2 mmol, 4 equiv). The reaction mixture was stirred for 15 h. The reaction mixture was acidified using 1 N HCl (8 mL) and extracted with EtOAc (30 mL). The layers were separated and the organic phase was washed with 10% aqueous $NaHSO_3$ (10 mL x 2) and with brine (10 mL). The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (Hexane/EtOAc, 1/1, SiO_2) to give the title compound and small amount of benzoic acid. The residual benzoic acid was removed by sublimation (ABT 100°C, 2mbar) for 2 h affording 107 mg (81%) of the title compound as clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 6.9, 3 H), 0.99 (d, J = 6.8, 3 H), 2.06 (m, 1 H), 2.38-2.83 (m, 2 H), 2.72 – 2.83 (m, 1 H), 2.94 (t, J = 7.1, 2 H), 4.31 (t, J = 7.1, 2 H), 7.21 – 7.34 (m, 5 H), 11.8 (s, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.36, 20.05, 29.87, 32.48, 34.98, 47.13, 65.17, 126.37, 128.30, 128.70, 137.45, 172.06, 180.41.

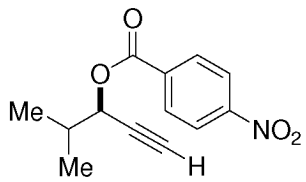
FTIR (neat) 3684 (w), 3620 (w), 3020 (s), 2968 (m), 1732 (s), 1709 (s), 1604 (w), 1498 (w), 1467 (w), 1455 (w), 1424 (w), 1393 (w), 1374 (w), 1345 (w), 1218 (s), 1173 (m), 1047 (w), 1012 (w).

General procedure for the addition of acetylene to aliphatic aldehydes (GP2).

182 mg (0.500 mmol) $Zn(OTf)_2$ and 98.0 mg (0.550 mmol) (+) or (-)-*N*-methylephedrine were placed in a pressure tube under an argon atmosphere. Then 4.0 ml toluene, 0.096 ml (0.550 mmol) Hünigs base and 0.500 mmol aldehyde was added. After stirring for 2 h at 23 °C, The solution was cooled to -78 °C and acetylene (see below) was bubbled through the solution for 10 min. The solution was warmed to 23 °C and stirred for the indicated amount of time and temperature. At 23 °C the reaction was quenched with sat. NH_4Cl aqu. and extracted with Et_2O. Concentration at reduced pressure (see below) and FC (SiO_2; hexane/EtOAc 9:1) afforded the propargylic alcohol.

-For volatile compounds the alcohol was directly protected as 4-Nitrobenzoate:
Concentration at 500 mbar and 40 °C, then addition of 280 mg (1.50 mmol) 4-Nitrobenzoylchloride and 0.200 ml (1.44 mmol) NEt_3 and a trace of DMAP. After stirring for 1 h at 23 °C the reaction was quenched with sat. NH_4Cl aqu. and extracted with CH_2Cl_2. Concentration at reduced pressure and FC (SiO_2; hexane/EtOAc 9:1) afforded the pure protected propargylic alcohol.

Acetylene gas was purified as follows: first it was passed through a cooling trap at -78 °C, then through a concentrated H_2SO_4 and finally through a trap filled with KOH pellets.



(R)-4-methylpent-1-yn-3-yl-4-nitrobenzoate (94).

Prepared according to GP 2 using 36 mg (0.50 mmol) isobutyraldehyde and (+)-NME. Stirring at 23 °C for 16 h. Protection as nitrobenzoate and purification by FC furnished 110 mg (88%) of the title compound as oil.

$[\alpha]_D^{28}$ = -1.9 (c = 0.195, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J* = 9.0, 1 H), 2.16-2.23 (m, 1H), 2.51 (d, *J* = 2.1, 1H), 5.47 (dd, *J* = 2.1, *J* = 9.0, 1H), 8.26-8.32 (m, 4H).

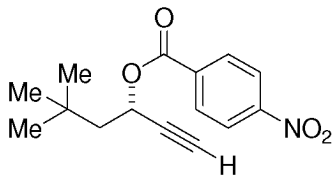
^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 18.2, 32.5, 70.3, 74.9, 79.2, 123.5, 130.8, 135.2, 150.5, 163.5.

FTIR (KBr, cm^{-1}): 3293 (w), 2923 (s), 1729 (m), 1530 (m), 1264 (m), 1220 (s), 1100 (m).

MS (ESI, pos.) calcd for $C_{13}H_{13}NO_4^+$ (M^+) 247.08, found 247.0

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30. Found: C, 63.00; H, 5.36.

ee: 95% (Daicel Chiracel OD-H column 250 x 4.6 mm, hexane:*i*-PrOH 98:2, flow: 1.0 ml/min t_R (minor): 17.11 min, t_R (mayor): 19.08 min. detector: 254 nm).



(*S*)-5,5-dimethylhex-1-yn-3-yl-4-nitrobenzoate (97).

Prepared according to GP 2 using 0.063 ml (0.50 mmol) 3-methylbutanal and (-)-NME. Stirring at 50 °C for 20 h. Protection as nitrobenzoate and purification by FC furnished 93 mg (68%) of the title compound as a white solid.

mp: 56-57 °C.

$[\alpha]_D^{30}$ = -31.8 (c = 0.26, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.92 (dd, *J* = 5.4, *J* = 14.4, 1H), 2.02 (dd, *J* = 5.4, *J* = 14.4, 1H), 2.53 (d, *J* = 2.1, 1H), 5.66-5.71 (m, 1H), 8.23 (d, *J* = 9.3, 2H), 8.30 (d, *J* = 9.3, 2H).

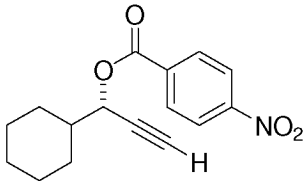
^{13}C NMR (125 MHz, $CDCl_3$) δ 29.9, 30.4, 48.3, 63.4, 74.2, 81.8, 123.5, 130.8, 135.1, 150.5, 163.5.

FTIR (KBr, cm^{-1}): 3293 (w), 2959 (m), 1728 (s), 1529 (s), 1343 (m), 1278 (s), 1101 (s).

MS (EI, pos.) calcd for $C_{15}H_{18}NO_4^+$ ($M+H^+$) 276.1, found 276.1.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22. Found: C, 65.28; H, 6.25.

ee: 95% (Daicel Chiracel OD-H column 250 x 4.6 mm, hexane:*i*-PrOH 99.5:0.5, flow: 0.5 ml/min t_R (minor): 31.55 min, t_R (mayor): 35.19 min. detector: 254 nm).



(R)-1-cyclohexylprop-2-ynyl-4-nitrobenzoate (96).

Prepared according to GP 2 using 0.063 ml (0.50 mmol) cyclohexylcarboxaldehyde and (-)-NME. Stirring at 50 °C for 11 h. Protection as nitrobenzoate and purification by FC furnished 107 mg (75%) of the title compound as a white solid.

mp: 86-87 °C.

$[\alpha]_D^{29}$ = -26.5 (c = 0.28, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18-1.38 (m, 5H), 1.65-1.98 (m, 6H), 2.52 (d, *J* = 2.1, 1H), 5.45-5.46 (m, 1H), 8.21-8.31 (m, 4H).

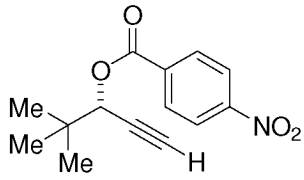
^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 25.8, 26.2, 28.2, 28.6, 41.8, 69.6, 75.0, 79.5, 123.5, 130.8, 135.2, 150.5, 163.5.

FTIR (KBr, cm^{-1}): 3294 (w), 2930 (m), 2856 (m), 1728 (m), 1529 (m), 1265 (m), 1220 (s), 1100 (m).

MS (EI, pos.) calcd for $C_{16}H_{17}NO_4^+$ (M^+) 287.12, found 287.2

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96. Found: C, 66.94; H, 6.22.

ee: 91% (Daicel Chiracel OD-H column 250 x 4.6 mm, hexane:*i*-PrOH 92:8, flow: 0.5 ml/min t_R (mayor): 21.4 min, t_R (minor): 25.6 min. detector: 254 nm).



(*S*)-4,4-dimethylpent-1-yn-3-yl-4-nitrobenzoate (95).

Prepared according to GP 2 using 0.054 ml (0.50 mmol) pivaldehyde and (-)-NME. Stirring at 50 °C for 19 h. Protection as nitrobenzoate and purification by FC furnished 113 mg (86%) of the title compound as a white solid.

mp: 72-73 °C.

$[\alpha]_D^{28}$ = -35.3 (c = 0.26, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 2.49 (d, *J* = 2.1, 1H), 5.34 (d, *J* = 2.1, 1H), 8.23 (d, *J* = 9.0, 2H), 8.31 (d, *J* = 9.0, 2H).

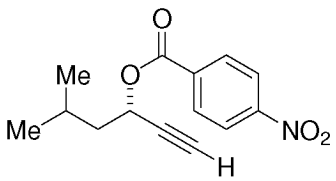
^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 35.4, 73.2, 74.9, 79.2, 123.5, 130.8, 135.2, 150.5, 163.5.

FTIR (KBr, cm^{-1}): 3294 (w), 2972 (m), 17 (m), 1530 (m), 1267 (m), 1220 (s), 1101 (m).

MS (EI, pos.) calcd for $C_{14}H_{16}NO_4^+$ ($M+H^+$) 262.1, found 246.1.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.41; H, 5.86.

ee: 89% (Daicel Chiracel OD-H column 250 x 4.6 mm, hexane:*i*-PrOH 92:8, flow: 1.0 ml/min t_R (minor): 15.58 min, t_R (mayor): 18.88 min. detector: 254 nm).



(*S*)-5-methylhex-1-yn-3-yl-4-nitrobenzoate (98).

Prepared according to GP 2 using 0.063 ml (0.50 mmol) 3-methylbutanal and (-)-NME. Stirring at 50 °C for 20 h. Protection as nitrobenzoate and purification by FC furnished 93 mg (71%) of the title compound as oil.

$[\alpha]_D^{30}$ = -3.1 (c = 0.25, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.0, 6H), 1.79-1.95 (m, 3H), 2.53 (d, *J* = 1.8, 1H), 5.66 (dt, *J* = 2.1, *J* = 6.9, 1H), 8.22-8.32 (m, 4H).

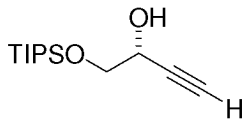
^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 22.6, 24.9, 43.4, 64.3, 74.4, 80.7, 123.5, 130.8, 135.1, 150.5, 163.5.

FTIR (KBr, cm^{-1}): 3293 (w), 2959 (m), 2925 (m), 1729 (m), 1529 (m), 1270 (m), 1220 (s), 1100 (m).

MS (EI, pos.) calcd for $C_{14}H_{16}NO_4^+$ ($M+H^+$) 262.1, found 262.1

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.28; H, 5.89.

ee: 95% (Daicel Chiracel OD-H column 250 x 4.6 mm, hexane:*i*-PrOH 99.5:0.5, flow: 0.5 ml/min t_R (mayor): 32.84 min, t_R (minor): 35.76 min. detector: 254 nm).



(S)-1-(triisopropylsilyloxy)but-3-yn-2-ol (99).

Prepared according to GP 2 using 107 mg (0.50 mmol) 2-(triisopropylsilyloxy)acetaldehyde and (+)-NME. Stirring at 50 °C for 20 h. Purification by FC furnished 86 mg (70%) of the title compound as oil.

$[\alpha]_D^{27}$ = 10.4 (c = 1.07, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01-1.25 (m, 21H), 2.53 (d, *J* = 2.1, 1H), 4.06-4.08 (m, 2H), 5.75-5.79 (m, 1H), 8.23-8.32 (m, 4H).

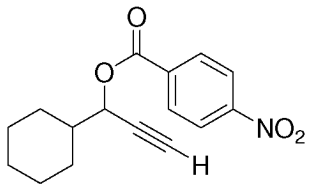
^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 18.0, 65.2, 66.3, 75.2, 78.2, 123.5, 130.8, 135.1, 150.5, 163.6.

FTIR (KBr, cm^{-1}): 3307 (w), 2924 (s), 2867 (m), 1735 (m), 1531 (m), 1268 (m), 1220 (s), 1100 (m).

MS (ESI, pos.) calcd for $C_{21}H_{33}NO_5SiNa^+$ ($M+Na^+$) 430.21, found 430.1

Anal. Calcd for $C_{21}H_{33}NO_5Si$: C, 61.88; H, 8.16. Found: C, 61.94; H, 8.22.

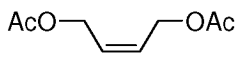
ee: 91% (Daicel Chiracel AD-H column 250 x 4.6 mm, hexane:*i*-PrOH 99.5:0.5, flow: 0.5 ml/min t_R (mayor): 15.1 min, t_R (minor): 18.5 min. detector: 254 nm).



1-cyclohexylprop-2-ynyl-4-nitrobenzoate (96, racemic version).

To 66 mg (0.55 mmol) potassium-*tert*-butoxide with or without 98.0 mg (0.550 mmol) (+)-*N*-methylephedrine a pressure tube under an argon atmosphere was added 4 ml toluene and 0.063 ml (0.50 mmol) cyclohexylcarboxaldehyde. The solution was cooled to -78 °C and acetylene was bubbled through the solution for 10 min. The solution was heated to 50 °C and stirred for 18 h or 14 h. At 23 °C the reaction was quenched with sat. NH_4Cl aqu. and extracted with Et_2O. Concentration at 500 mbar and 40 °C, then addition of 280 mg (1.50 mmol) 4-Nitrobenzoylchloride and 0.200 ml (1.44 mmol) NEt_3 and a trace of DMAP. After stirring for 1 h at 23 °C the reaction was quenched with sat. NH_4Cl aqu. and extracted with CH_2Cl_2. Concentration at reduced pressure and FC (SiO_2; hexane/EtOAc 9:1) afforded 31 mg (45%, reaction without (+)-NME) or 46 mg (67%, reaction with (+)-NME) of the title compound as a white solid.

All spectroscopic data was in agreement with the data reported earlier (page 168).

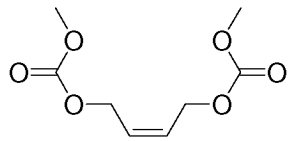


(*Z*)-but-2-ene-1,4-diyl diacetates (104).

(*Z*)-but-2-ene-1,4-diol was distilled before used (bp. 17 mbar, 136 °C). To a solution of 30.0 g (378 mmol) (*Z*)-but-2-ene-1,4-diol in 500 ml CH_2Cl_2 was added 100 ml (900 mmol) NEt_3 and 1.00 g (8.0 mmol) DMAP. After the solution was cooled to 0 °C, 90.0 ml (900 mmol) Ac_2O was added. The reaction was allowed to warm to 23 °C and additional 20.0 ml (142 mmol) NEt_3 was added. After stirring for 14 h, the reaction was quenched with 1 M HCl and diluted with EtOAc.

After phase separation the aqueous phase was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title compound as a colorless liquid.

All spectroscopic data was in agreement with the data reported in the literature.[169]



(Z)-but-2-ene-1,4-diyl dimethyl dicarbonates (105).

(Z)-but-2-ene-1,4-diol was distilled before used (bp. 17 mbar, 136 °C). To a solution of 3.00 g (38.0 mmol) (Z)-but-2-ene-1,4-diol in20 ml THF was added 9.2 ml (114 mmol) pyridine. After the solution was cooled to 0 °C, 7.0 ml (91.0 mmol) chloroformic acid methyl ester in 40 ml THF was added. The reaction was allowed to warm to 23 °C. After stirring for 20 h, the reaction was quenched with 1 M HCl and diluted with EtOAc. After phase separation the aqueous phase was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the title compound as a colorless liquid.

All spectroscopic data was in agreement with the data reported in the literature.[170]

General procedure for the attempted allylic alkylation employing oxalic acid, disodium salt of oxalic acid or glyoxylic acid sodium salt monohydrate as nucleophils:

To 20.0 mg (0.019 mmol) $Pd_2dba_3CHCl_3$ and 24.0 mg (0.39 mmol) PPh_3 in 1 ml solvent (THF, CH_3CN, CH_2Cl_2) was added 0.79 mmol (Z)-but-2-ene-1,4-diyl diacetates or (Z)-but-2-ene-1,4-diyl dimethyl dicarbonates under an argon atmosphere. After stirring for 18 h at 23 °C or 40 °C the crude reaction mixture was filtered over a SiO_2 plug and concentrated. Crude ^{1}H-NMR showed no product.

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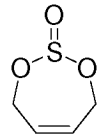
[169] Otaka, A.; Yukimasa, A.; Watanabe, J.; Sasaki, Y.; Oishi, S.; Tamamura, H.; Fujii, N. *Chem. Commun.* (Cambridge) **2003**, *15*, 1834.

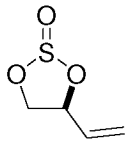
[170] Riesz, E.; Pollak, E.; Ziffer, R. *Monatsh. Chem.* **1931**, *58*, 147.



3-oxo-2,4,3-dioxathepin (106).

To a solution of 1.00 g (11.3 mmol) (*Z*)-2-butene-1,4-diol in 180 ml CH_2Cl_2 was added 2.23 g (18.5 mmol) benzotriazole and 1.37 ml (18.5 mmol) $SOCl_2$. The solution was stirred for 30 min. and then filtered and concentrated. FC (SiO_2; hexane/EtOAc 4:1) afforded 1.08 g (71%) of the title compound as a colorless liquid. For bigger scale reactions the product was distilled (95 °C, 12 Torr).

All spectroscopic data was in agreement with the data reported in the literature.[171]



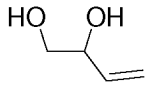
4-vinyl(1,3,3)dioxathiolane-2-oxide (107).

To 100 mg (1.1 mmol) (*S*)-3-butene-1,2-diol (**100**) in 15 ml CH_2Cl_2 was added 133 mg (1.1 mmol) benzotriazole and 0.081 ml (1.1 mmol) $SOCl_2$. The solution was stirred for 1 h and then filtered over celite and concentrated to afford 80 mg (0.60 mmol) of the title compound as oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (dd, *J* = 6.9, *J* = 8.4, 1H), 4.38 (t, *J* = 9.0, 1H), 4.55 (dd, *J* = 6.3, *J* = 8.7, 1H), 4.75 (dd, *J* = 6.3, *J* = 8.4, 1H),5.36-5.49, m, 4 H), 5.76-5.87 (m, 1H), 5.93-6.05 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 69.6, 71.5, 80.6, 84.5, 121.6, 122.3, 131.0, 132.3.

[171] Chaudari, S. S.; Akamanchi, K. G. *Synlett*, **1999**, *11*, 1763.



3-butene-1,2-diol (100).

To 24 mg (0.011 mmol) $Pd_2(dba)_3$ $CHCl_3$ and 55 mg (55 mmol) PPh_3 in 2 ml THF was added 200 mg (1.50 mmol) 3-oxo-2,4,3-dioxathepin (**106**) in 2 ml THF. Stirring for 150 min. at 23 °C. Filtration over a short plug of SiO_2 and concentration. Crude ^{1}H-NMR showed full conversion. Then the crude was dissolved in 2 ml EtOAc followed by the addition of 88 mg (2.2 mmol) NaOH in 0.5 ml H_2O. The resulting suspension was stirred for 2 h at 23 °C. Addition of 1M HCl till pH 1 and extraction with EtOAc (6 times). The combined organic layers were dried ($NaSO_4$) and concentrated under reduced pressure to afford the title compound as oil.

All spectroscopic data was in agreement with the data reported in the literature.[127]

General procedure for 3-butene-1,2-diol employing a ligand

12 mg (0.011 mmol) $Pd_2(dba)_3$ $CHCl_3$ and 0.033 mmol ligand were placed in a schlenk flask under an argon atmosphere. Addition of 1 ml THF and stirring at 23 °C for 1 h. Then 100 mg (0.75 mmol) 3-oxo-2,4,3-dioxathepin (**106**) in 1 ml THF was added. Stirring at either 23 °C or, if no conversion could be obtained by TLC, at 70 °C for the indicated amount of time. Filtration over a short plug of SiO_2 and concentration. The conversion was measured by ^{1}H-NMR. Then the crude was dissolved in 2 ml EtOAc followed by the addition of 88 mg (2.2 mmol) NaOH in 0.5 ml H_2O. The resulting suspension was stirred for 2 h at 23 °C. Addition of 1M HCl till pH 1 and extraction with EtOAc (6 times). The combined organic layers were dried ($NaSO_4$) and concentrated under reduced pressure to afforded the title compound as oil.

All spectroscopic data was in agreement with the data reported in the literature.[127]

For measurement of the ee by chiral HPLC the diol was monoprotected with 4-nitrobenzoylchloride (1.1eq.) and 4-DMAP (1.1eq.) in CH_2Cl_2. The crude was directly subjected to FC (SiO_2; hexane/EtOAc 2:1) to afford the monoprotected alcohol.

Determination of ee: (Daicel Chiracel OD-H column 250 x 4.6 mm, hexane:*i*-PrOH 90:10, flow: 0.7 ml/min t_R 16.11 min, and 19.7 min. detector: 254 nm).

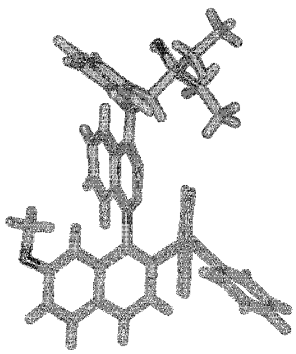
Procedure for a Pd(II) source

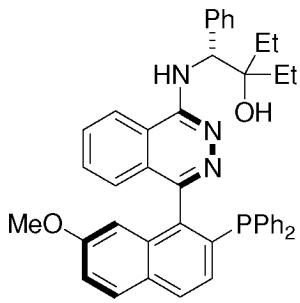
(0.038 mmol) Pd(II) were placed in a schlenk flask under an argon atmosphere. Addition of 1 ml THF and stirring at 23 °C for 2 h. Then 100 mg (0.75 mmol) 3-oxo-2,4,3-dioxathepin (**106**) in 1 ml THF was added. Stirring at 60 °C for 14 h. Filtration over a short plug of SiO_2 and concentration. The conversion was measured by ^{1}H-NMR. Then the crude was dissolved in 2 ml EtOAc followed by the addition of 88 mg (2.2 mmol) NaOH in 0.5 ml H_2O. The resulting suspension was stirred for 2 h at 23 °C. Addition of 1M HCl till pH 1 and extraction with EtOAc (6 times). The combined organic layers were dried ($NaSO_4$) and concentrated under reduced pressure to afforded the title compound as oil.

^{1}H NMR for crude 4-vinyl(1,3,3)dioxathiolane-2-oxide (300 MHz, $CDCl_3$) δ 4.40 (q, J = 9.0, 1H), 4.55 (dd, J = 6.6, J = 9.0, 1H), 4.85-4.93 (m, 1H), 5.43-5.54 (m, 2H), 5.93-6.04 (m, 1H).

All spectroscopic data was in agreement with the data reported in the literature.[127]

5.1 Crystallographic Data





48a

(*R*,*P*)-[4-(2-Diphenylphosphanyl-7-methoxynaphthalen-1-yl)phthalazin-1-ylamino]phenylmethyl}pentan-3-ol (48a).

Comment

The study of the titled structure was undertaken to establish its three dimensional structure. Geometries are tabulated below. All diagrams and calculations were performed using maXus (Bruker Nonius, Delft & MacScience, Japan).

Experimental

Crystal data

$C_{207}H_{200}N_{12}O_8P_4$
$C_{207}H_{200}N_{12}O_8P_4$
M_r = 3107.849
Monoclinic $P2_1$
a = 16.74110 (10)Å
b = 28.5619 (3)Å
c = 19.5010 (2)Å
α = 90.00°
β = 111.9746 (5)°
γ = 90.00°
V = 8647.12 (14)Å^3
Z = 2
D_x = 1.194 Mg m^{-3}
Density measured by: not measured
fine-focus sealed tube
Mo *K*α radiation λ = 0.71073
Cell parameters from 14681 refl.
θ = 0.998—25.028 °
μ = 0.107 mm^{-1}
T = 150 K
plate
0.26 x 0.14 x 0.06 mm
Colourless
Crystal source: Carreira laboratory

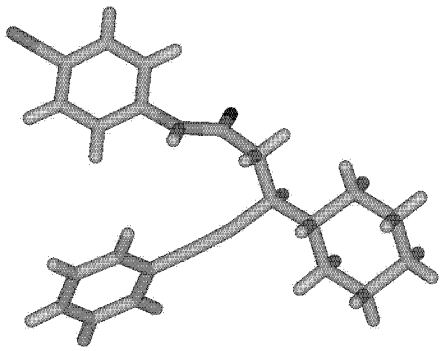
Data collection
KappaCCD CCD diffractometer
Absorption correction: none
27441 measured reflections
27420 independent reflections
23271 observed reflections
Criterion: >2sigma(I)
θ_{max} = 25.02 °
h = -19 →19
k = -33 →32
l = -23 →23

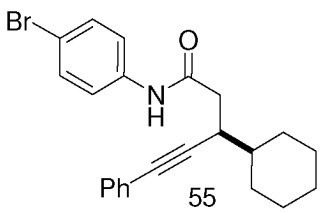
Refinement
Refinement on F^2
Full-matrix least squares refinement with fixed elements per cyclematrix least squares refinement
R(all) = 0.0880
R(gt) = 0.0718
wR(ref) = 0.2003
wR(gt)= 0.1850
S(ref) = 1.406

27420 reflections
1925 parameters
1 restraints
H positions constr
Calculated weights $1/[\sigma^2(I_o)+(I_o+I_c)^2/900]$
$\Delta/\sigma_{max} = 0.030$
$\Delta\rho_{max} = 0.822 e\text{Å}^3$
$\Delta\rho_{min} = -0.421 e\text{Å}^3$
Extinction correction: none
Atomic scattering factors from International Tables Vol C Tables 4.2.6.8 and 6.1.1.4
Flack parameter = -0.01 (8)
Flack H D (1983), *Acta Cryst.* A39, 876-881

Data collection: KappaCCD
Cell refinement: HKL Scalepack (Otwinowski & Minor 1997)
Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997)
Program(s) used to solve structure: *SIR*97(Cascarano al.,*Acta Cryst.*,1996,A52,C-79)
Program(s) used to refine structure: *SHELXL*-97 (Sheldrick, 1997)

CCDC 268030 contains the supplementary crystallographic data, which can be obtained online free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21 EZ, U.K.; Fax (+44) 1223-336-033; or deposit@cccd.cam.ac.uk).





(*S*)-*N*-(4-bromophenyl)-3-cyclohexyl-5-phenylpent-4-ynamide (55).

Comment

The study of the titled structure was undertaken to establish its three dimensional structure. Geometries are tabulated below. All diagrams and calculations were performed using maXus (Bruker Nonius, Delft & MacScience, Japan).

Experimental

Crystal data

$C_{23}H_{24}BrNO$

$C_{23}H_{24}BrNO$

$M_r = 410.360$

Triclinic

P1

a = 4.8551 (2)Å

b = 13.3330 (5)Å

c = 15.6798 (8)Å

α = 97.241 (2)°

β = 96.070 (2)°

γ = 95.031 (2)°

V = 996.00 (8)Å^3

Z = 2

$D_x = 1.368$ Mg m^{-3}

Density measured by: not measured

fine-focus sealed tube

Mo *K*α radiation λ = 0.71073

Cell parameters from 3457 refl.

θ = 2.910—25.350 °

μ = 2.075 mm^{-1}

T = 150 K

needle

0.32 x 0.04 x 0.03 mm

Colourless

Crystal source: Carreira group

Data collection

KappaCCD CCD diffractometer

Absorption correction: none

6738 measured reflections

6738 independent reflections

5390 observed reflections

Criterion: >2sigma(I)

θ_{max} = 25.33 °

h = -5 →5

k = -15 →15

l = -18 →18

Refinement

Refinement on F^2

fullmatrix least squares refinement

R(all) = 0.1272

R(gt) = 0.1008

wR(ref) = 0.2713

wR(gt)= 0.2500
S(ref) = 1.743
6738 reflections
418 parameters
3 restraints
H-atom parameters not refined
Calculated weights $1/[\sigma^2(I_o)+(I_o+I_c)^2/900]$
$\Delta/\sigma_{max} = 0.014$
$\Delta\rho_{max} = 3.163 e\text{Å}^3$
$\Delta\rho_{min} = -0.824 e\text{Å}^3$
Extinction correction: none
Atomic scattering factors from International Tables Vol C Tables 4.2.6.8 and 6.1.1.4
Flack parameter = 0.04 (2)
Flack H D (1983), *Acta Cryst.* A39, 876-881

Data collection: KappaCCD
Cell refinement: HKL Scalepack (Otwinowski & Minor 1997)
Data reduction: Denzo and Scalepak (Otwinowski & Minor, 1997)
Program(s) used to solve structure: *SIR*97(Cascarano al.,*Acta Cryst.*,1996,A52,C-79)
Program(s) used to refine structure: *SHELXL*-97 (Sheldrick, 1997)

CCDC 268029 contains the supplementary crystallographic data, which can be obtained online free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21 EZ, U.K.; Fax (+44) 1223-336-033; or deposit@cccd.cam.ac.uk).

Curriculum Vitae

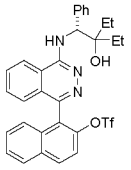
Born July 10, 1976 in Schaffhausen to Renato and Annemarie Zarotti

1983-1989	Primary School in Hallau, Schaffhausen
1989-1991	"Sekundarschule" in Hallau, Schaffhausen
1991-1996	High School in Schaffhausen, Schaffhausen
1996-2001	Studies at the ETH Zürich (Eidg. Dipl. Natw.): "Chemisch-biologische Studienrichtung mit Vertiefung in Chemie."
1999	Undergraduate internship in the group of Prof. Dr. A. Vasella
2000	Diploma thesis in the group of Prof. Dr. E. M. Carreira, under the supervision of T. Ritter at the ETH Zürich: "Studies Directed Towards the Total Synthesis of Resiniferatoxin"
2001-2006	Ph.D. thesis under the supervision of Prof. Dr. E. M. Carreira at the ETH Zürich: "Investigations of Ligands for Cu-Catalyzed Conjugate Addition Reactions"

- Supervision of a "SiROP"-student
- Teaching assistant for organic-chemistry laboratory courses as well as assistant for chemistry exercises.

Zürich, April 2006

Pablo Zarotti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OH
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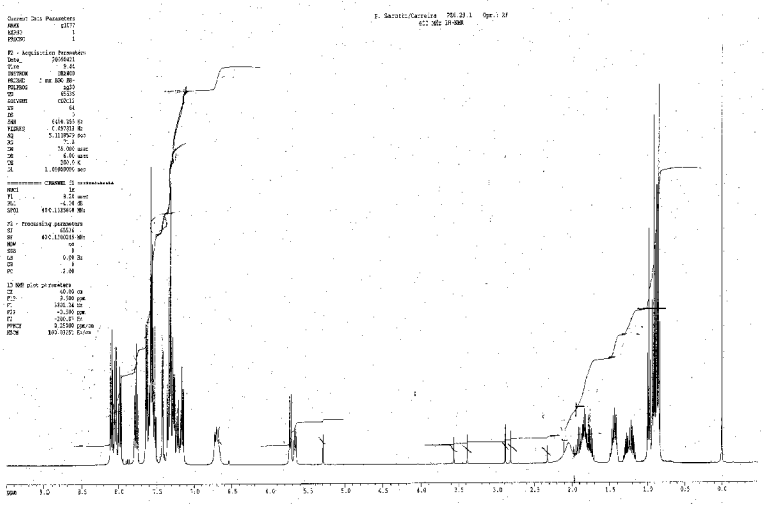

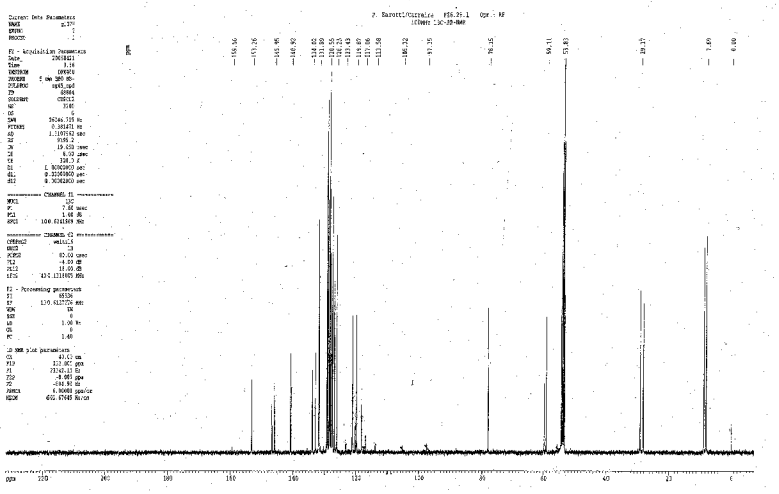

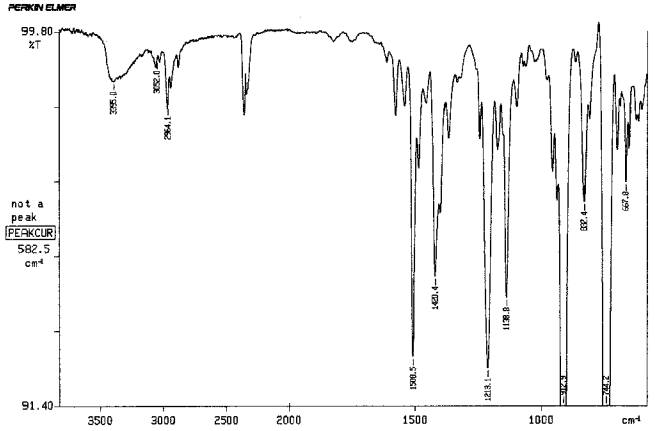
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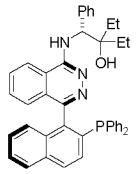

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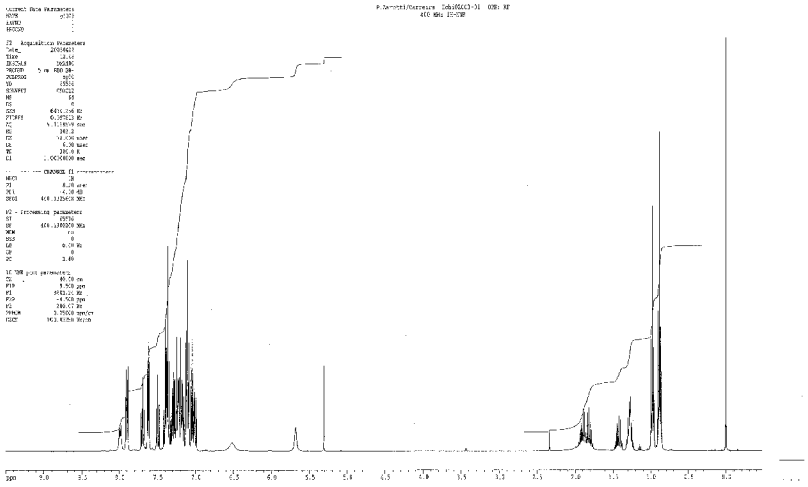
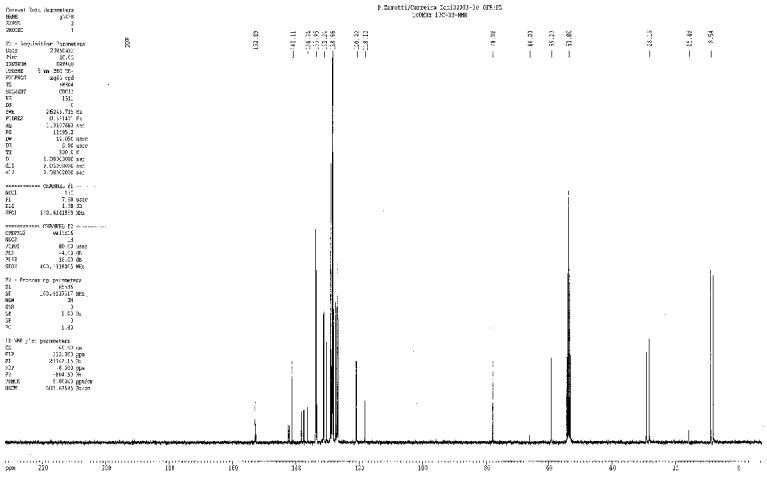
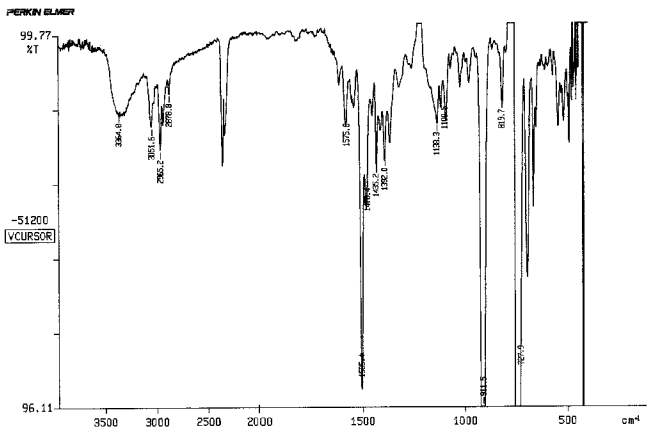
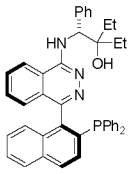
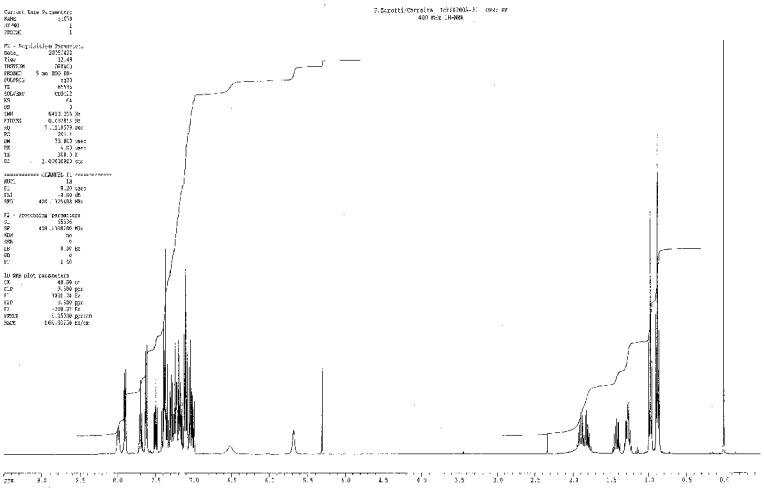


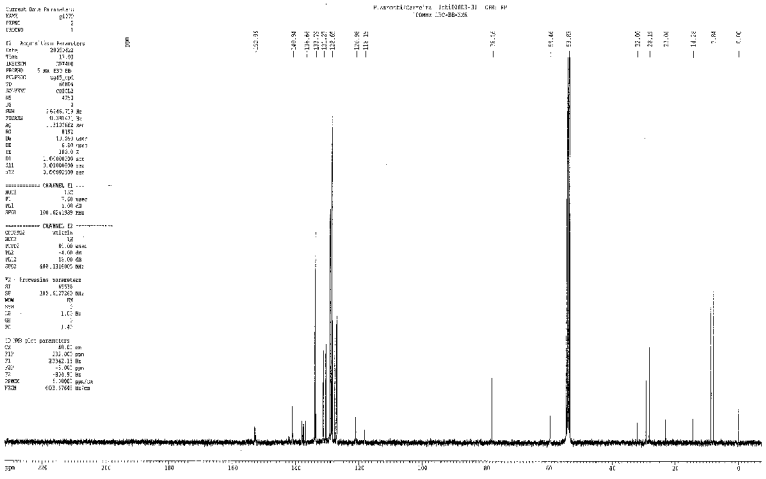


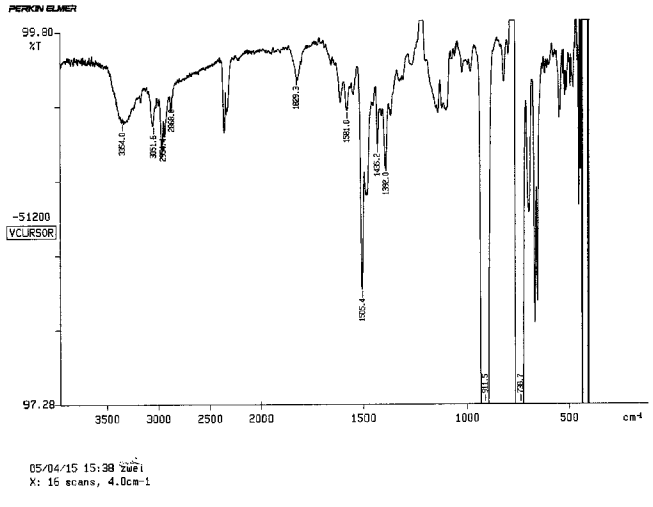


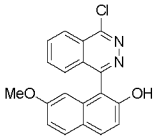


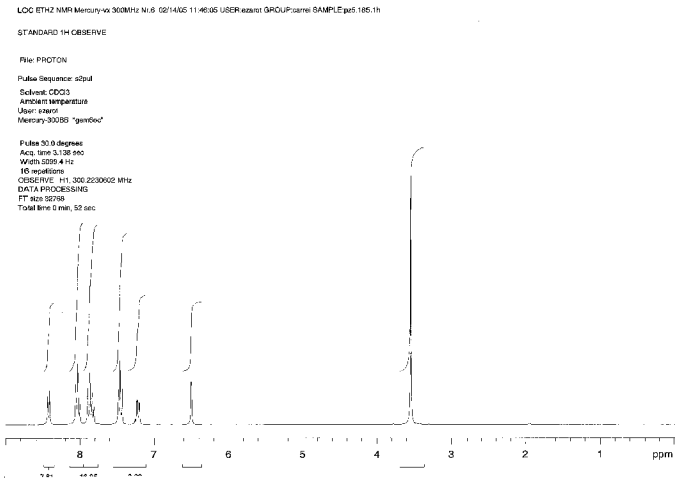
2nd diastereomer

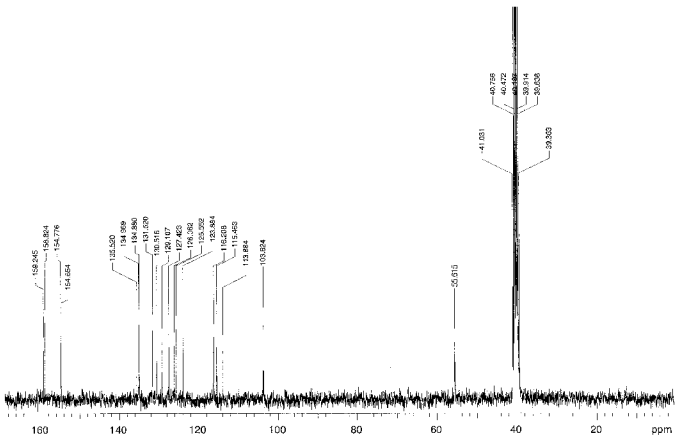


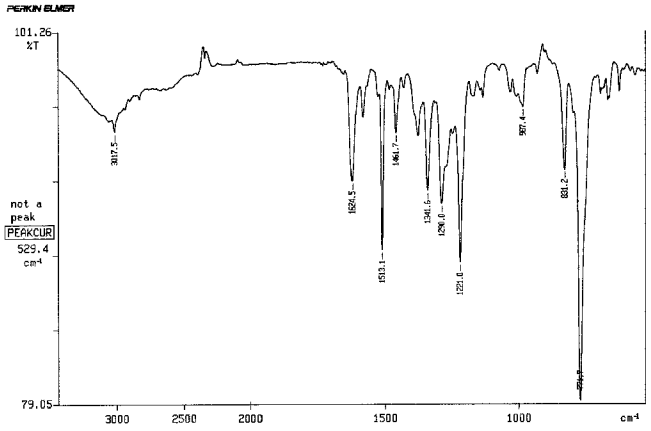












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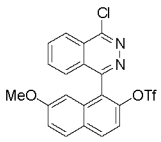
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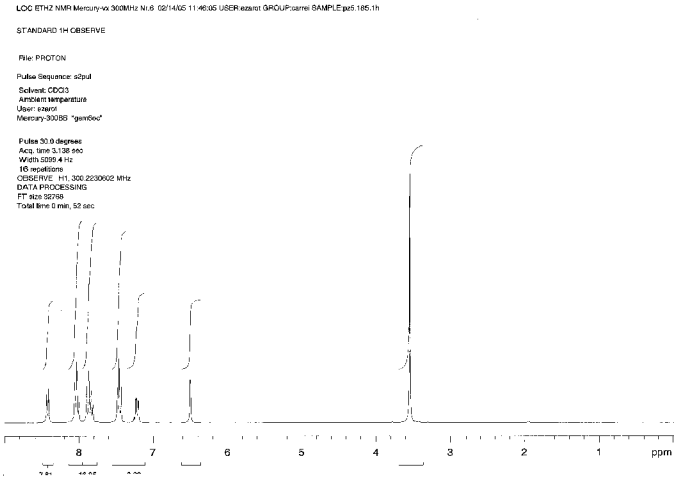
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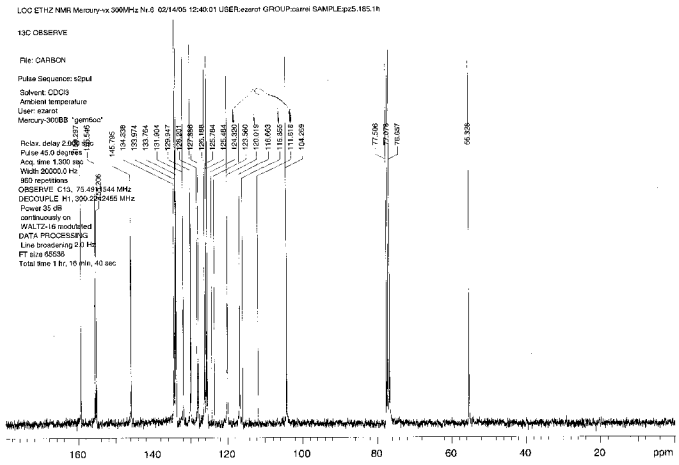
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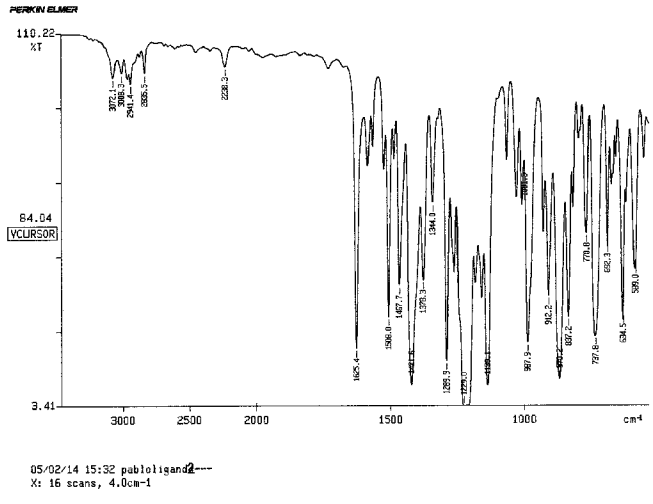
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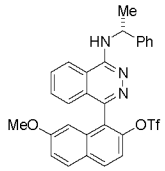

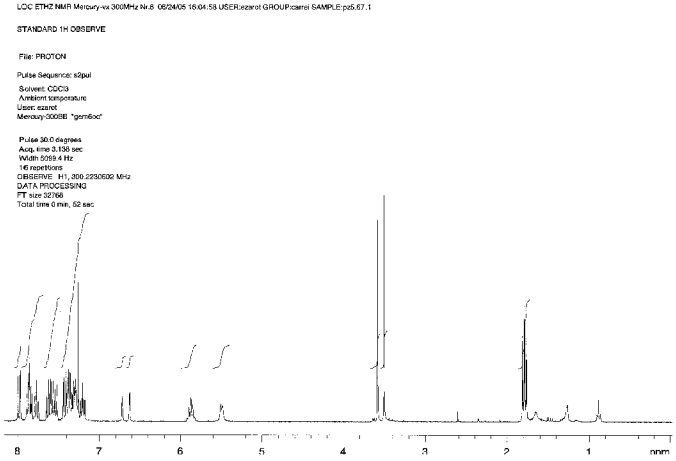

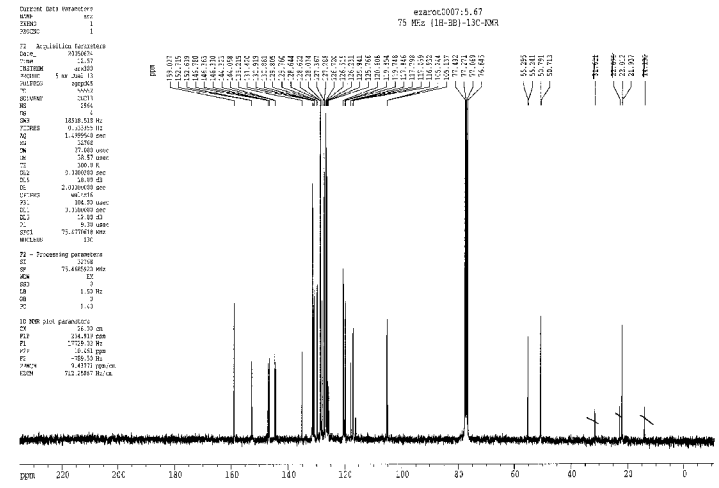

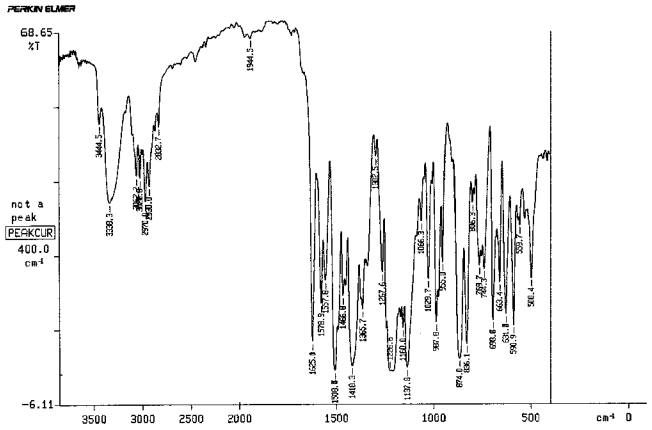

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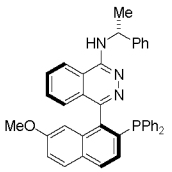

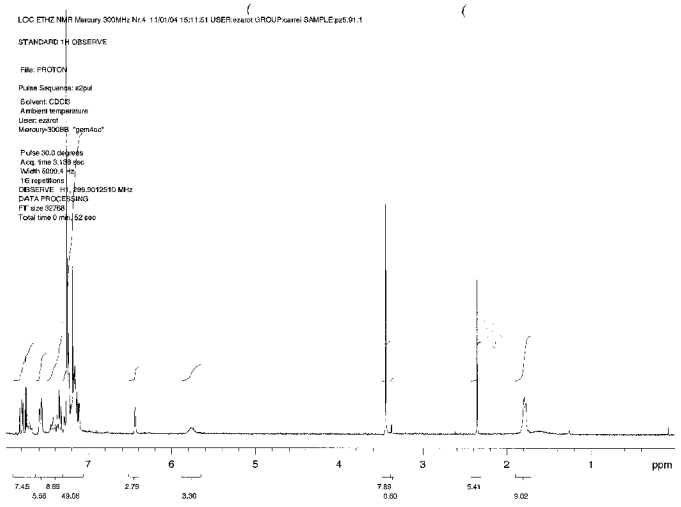

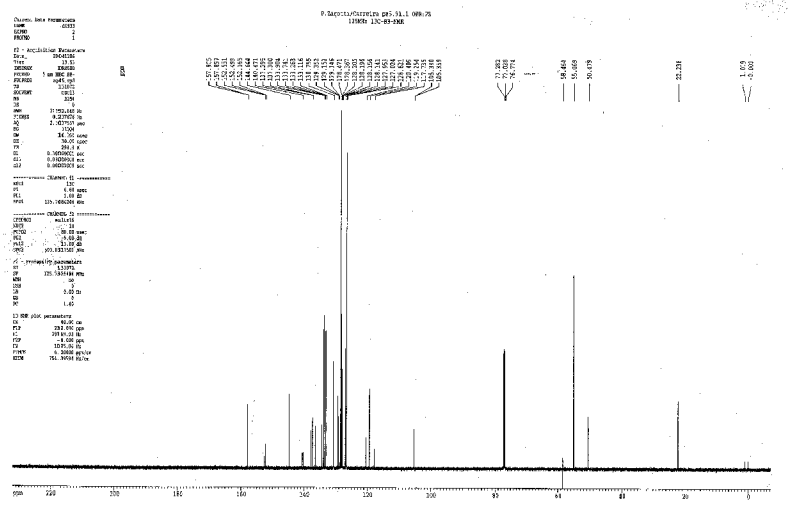

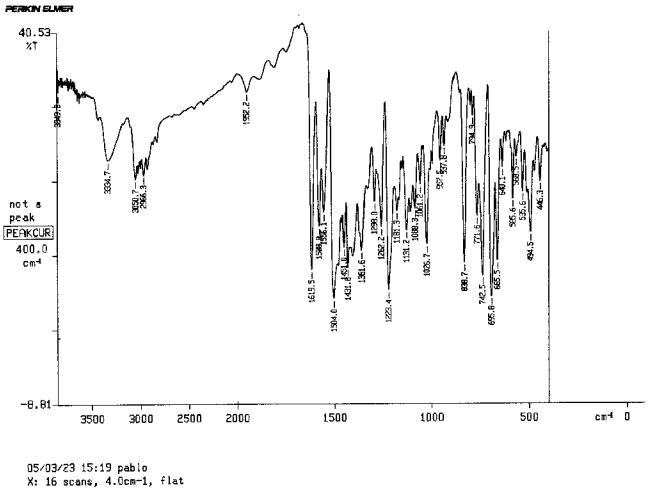

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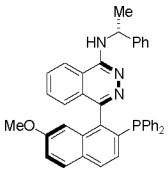

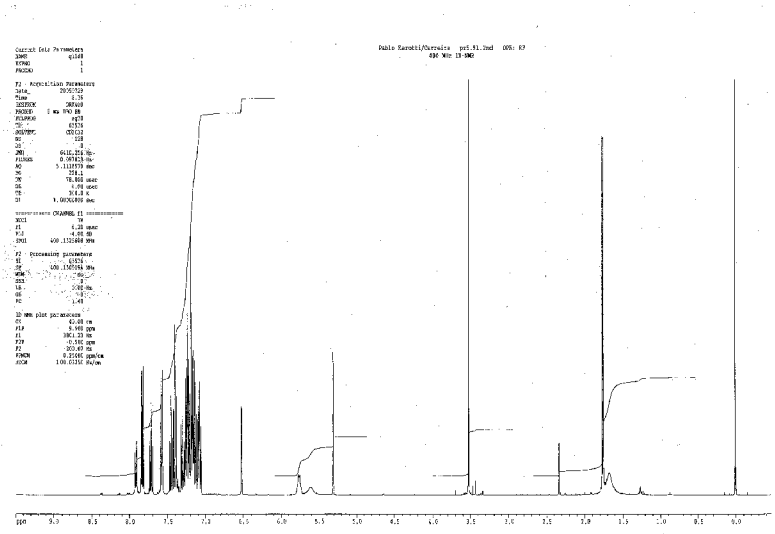

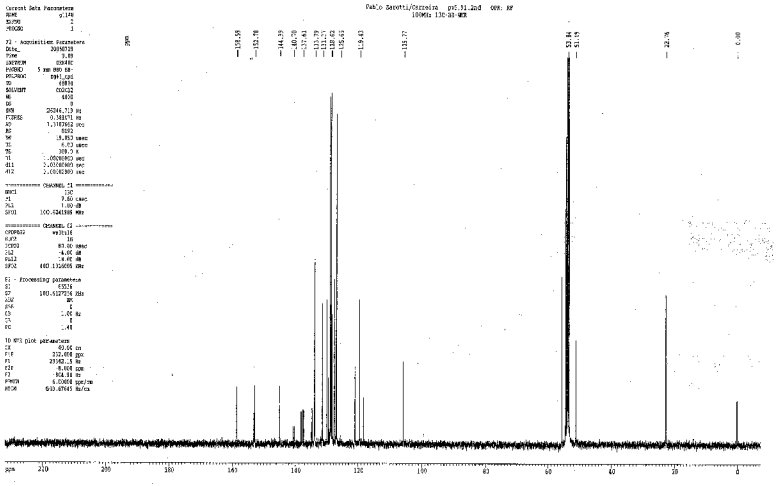

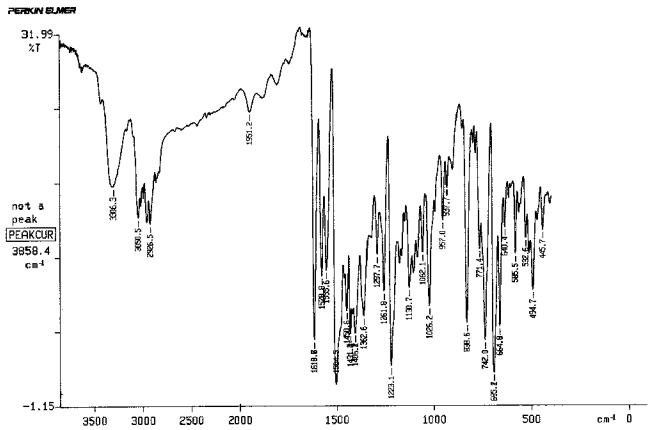

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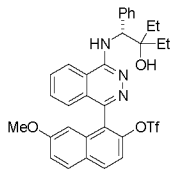

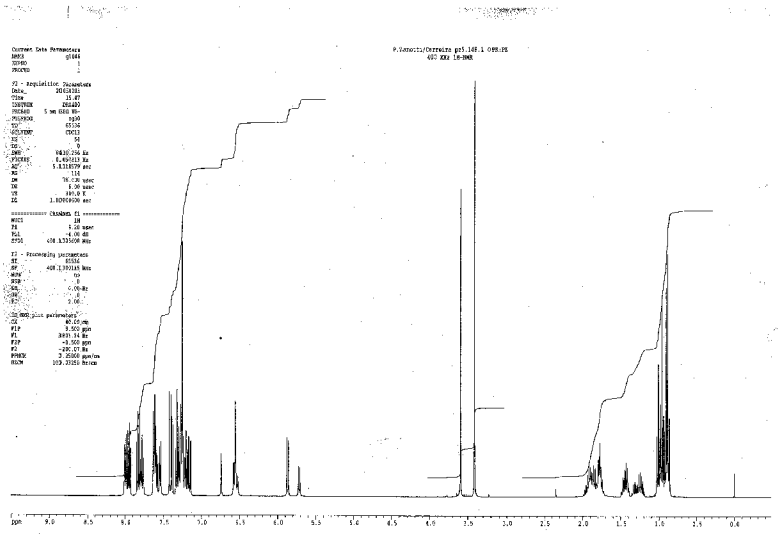

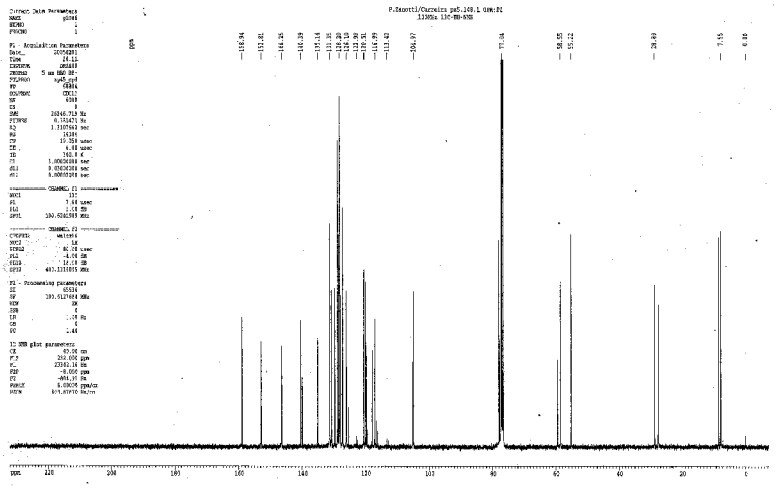

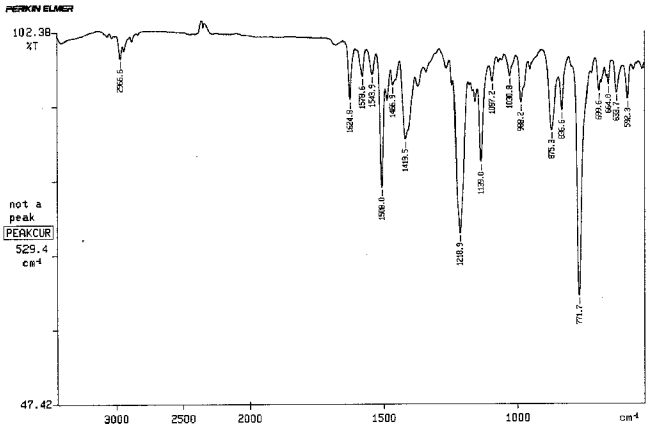

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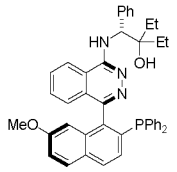

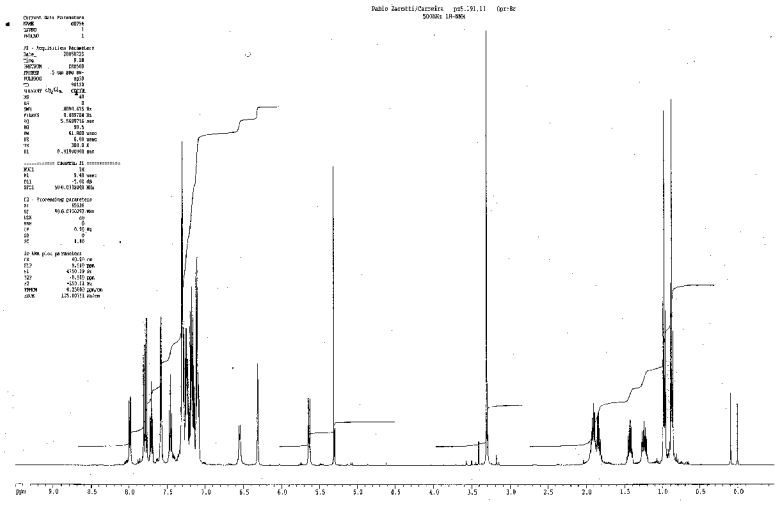

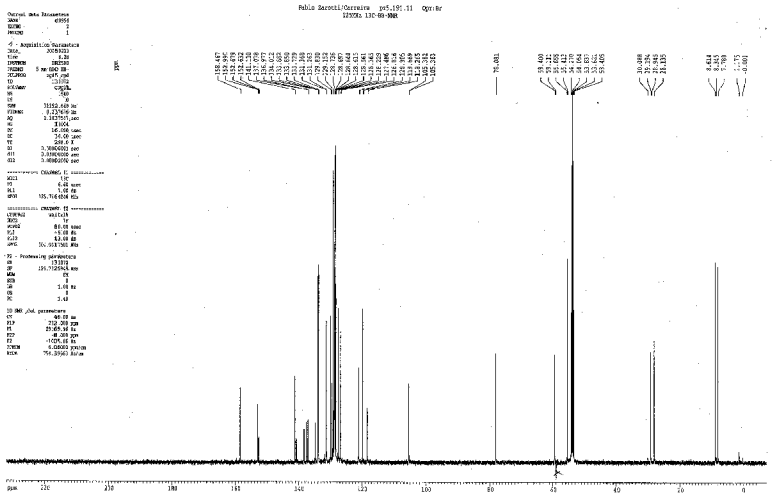

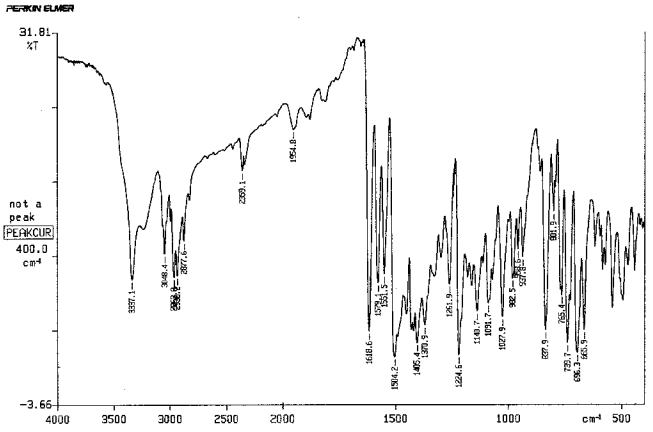

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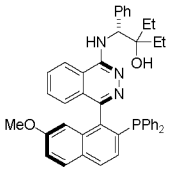
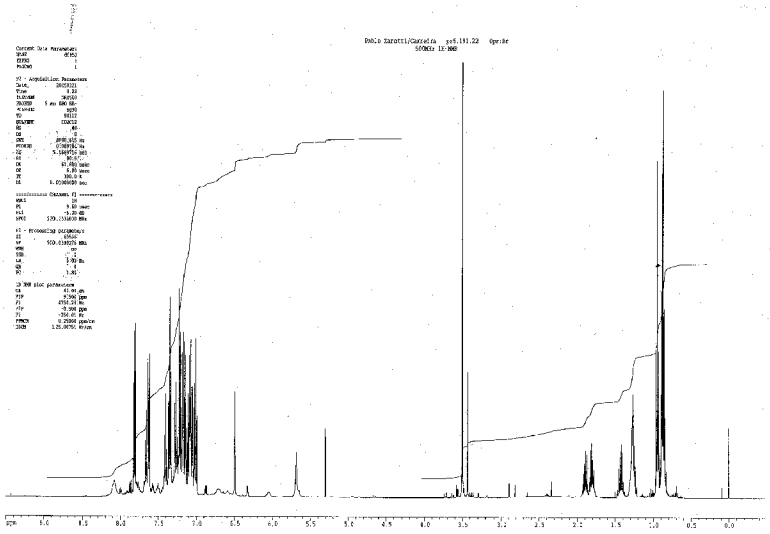
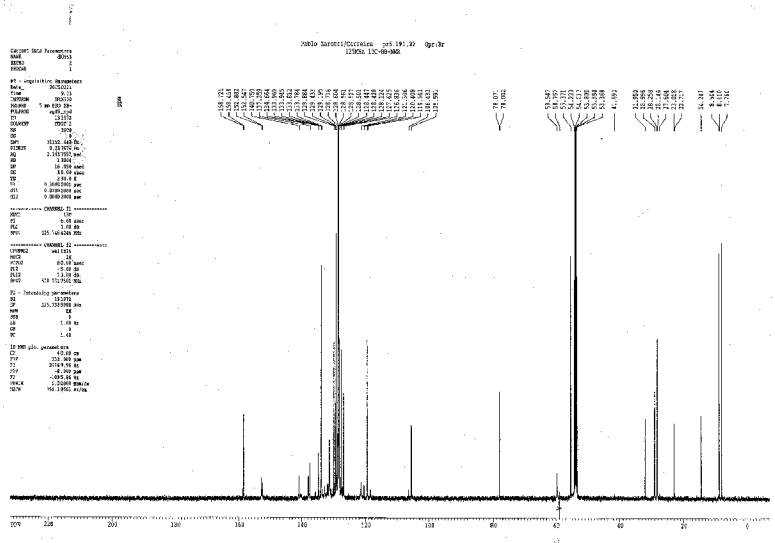
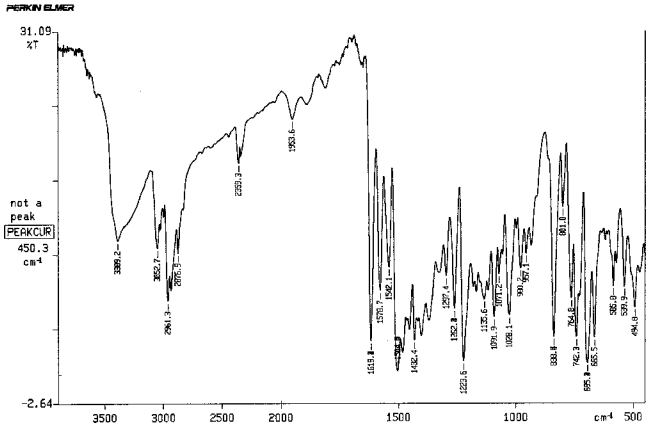
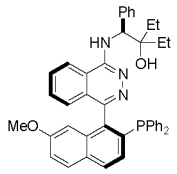


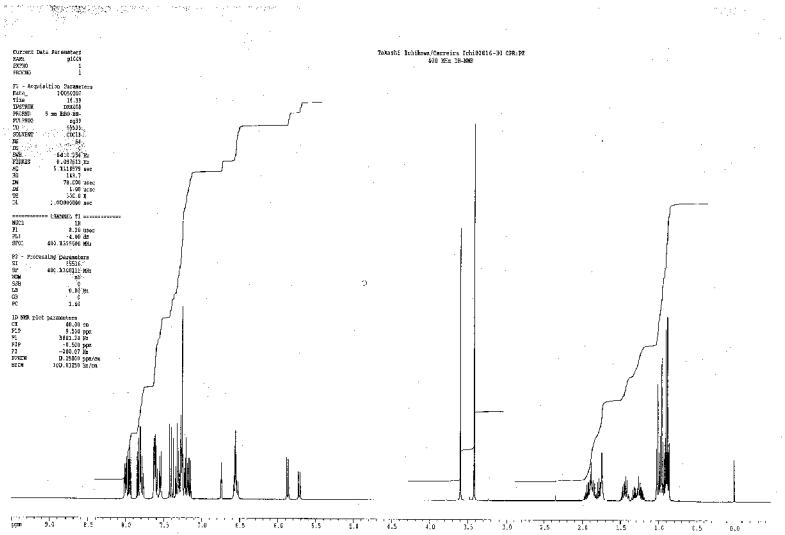


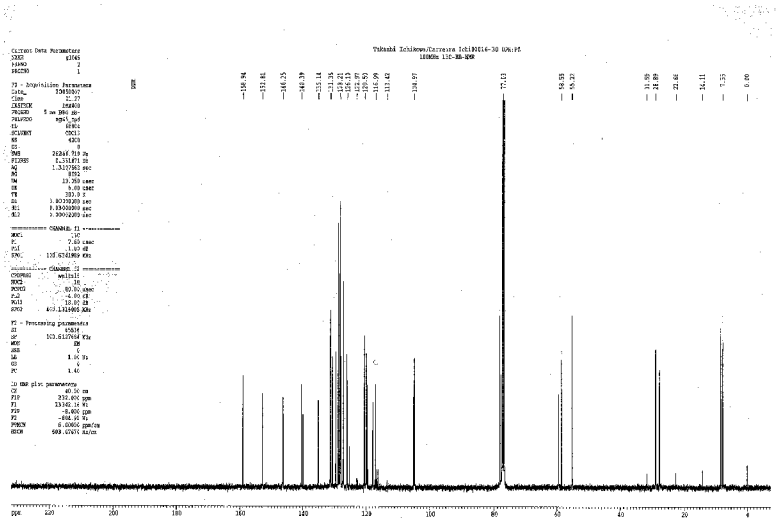


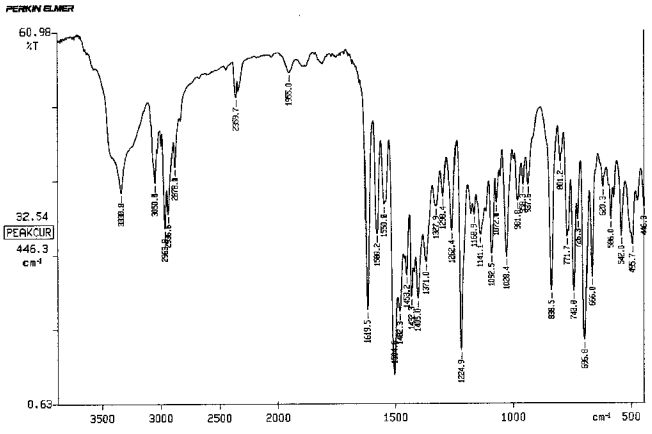


05/03/21 14:59 pablo
X: 16 scans, 4.0cm-1, flat

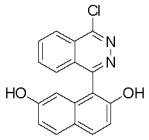


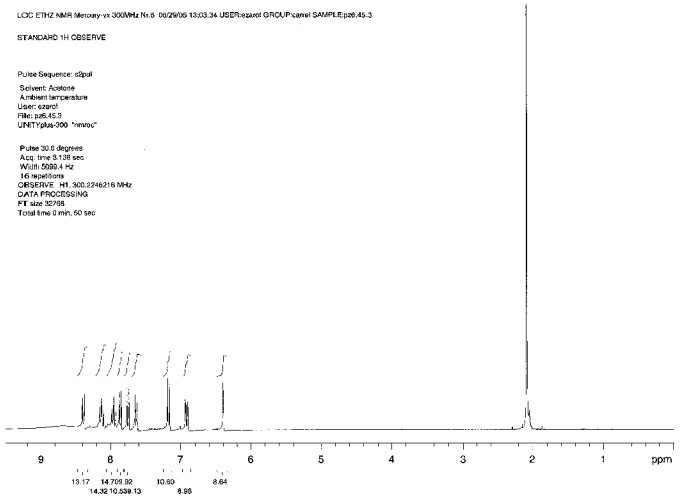


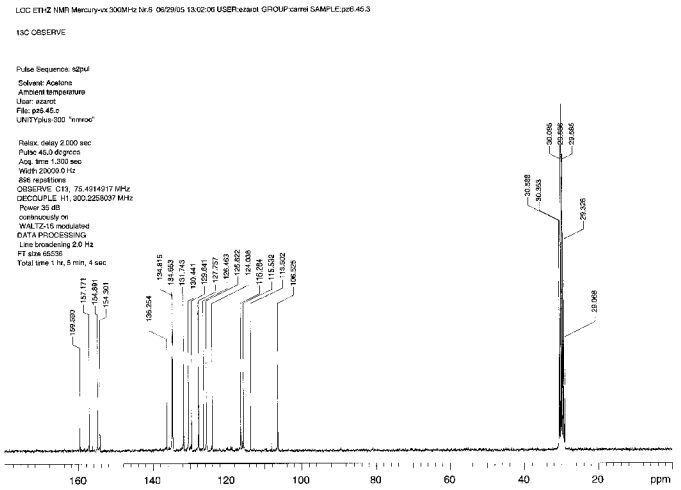


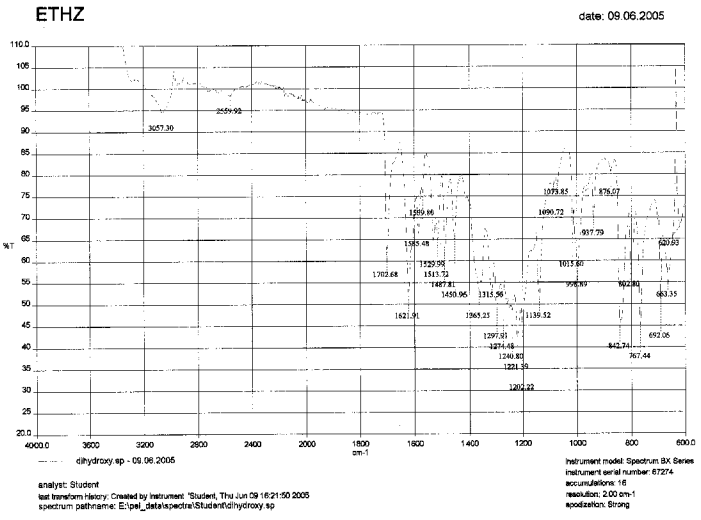


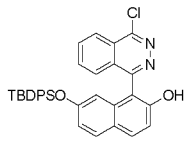
05/03/21 15:52 pablo
X: 16 scans, 4.0cm-1, flat

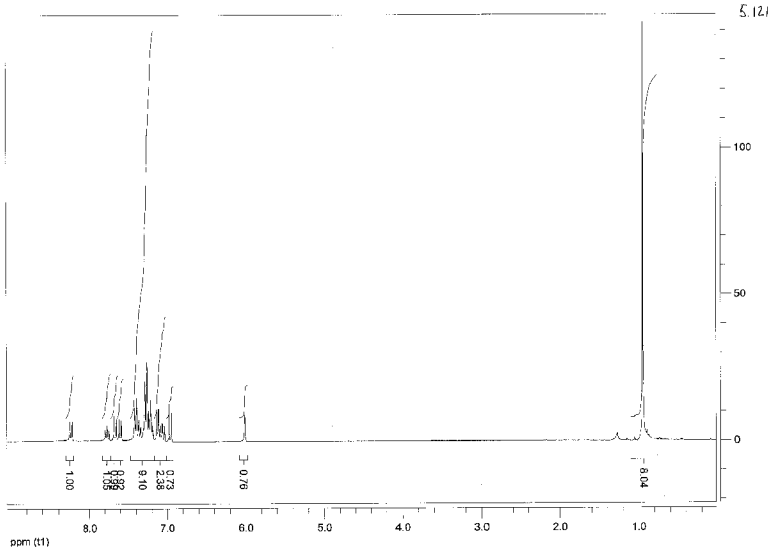

Cl
N
N
HO
OH

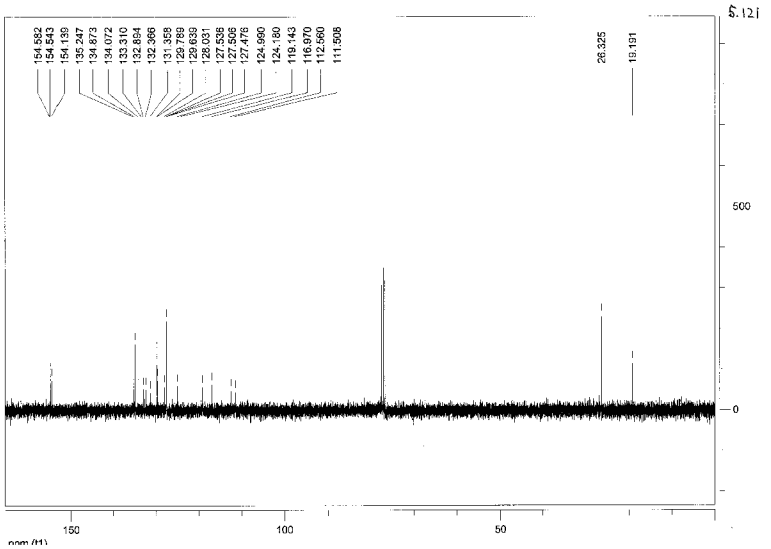

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 09/29/05 13:03:34 USER:ezarot GROUP:camrel SAMPLE:pz6.45.3
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: Acetone
Ambient temperature
User: ezarot
File: pz6.45.3
UNITYplus-300 "nmroc"
Pulse 30.0 degrees
Acq. time 8.138 sec
Width 5998.4 Hz
16 repetitions
OBSERVE H1, 300.2246216 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 50 sec
9
8
7
6
5
4
3
2
1
ppm
13.17
14.709.92
14.32 10.539.13
10.80
8.98
8.64

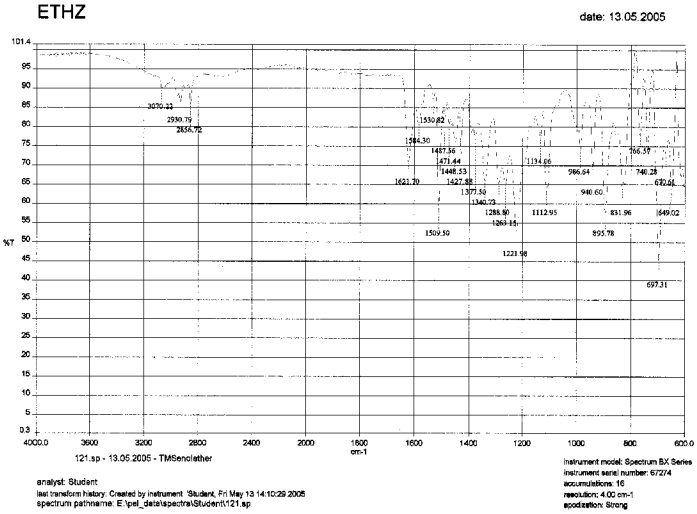

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 09/29/05 13:02:06 USER:ezarot GROUP:camrel SAMPLE:pz6.45.3
13C OBSERVE
Pulse Sequence: s2pul
Solvent: Acetone
Ambient temperature
User: ezarot
File: pz6.45.c
UNITYplus-300 "nmroc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.360 sec
Width 20000.0 Hz
896 repetitions
OBSERVE C13, 75.4914917 MHz
DECOUPLE H1, 300.2258037 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 hr, 5 min, 4 sec
160
140
120
100
80
60
40
20
ppm

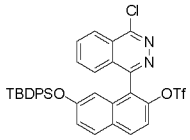

ETHZ
date: 09.06.2005
%T
cm-1
dihydroxy.sp - 09.06.2005
analyst: Student
fast transform history: Created by instrument: 'Student, Thu Jun 09 16:21:50 2005
spectrum pathname: E:\psi_data\spectra\Student\dihydroxy.sp
instrument model: Spectrum BX Series
instrument serial number: 67274
accumulations: 16
resolution: 2.00 cm-1
apodization: Strong

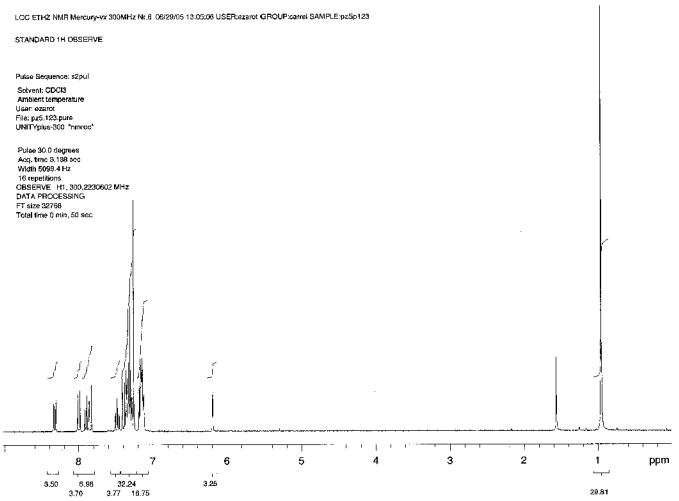

Cl
N
N
TBDPSO
OH

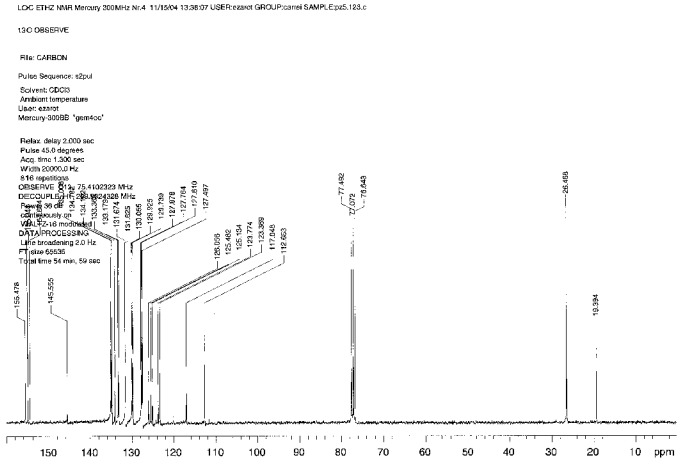

5.121
100
50
0
1.00
2.01
2.00
2.00
9.10
2.38
2.00
9.76
6.04
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

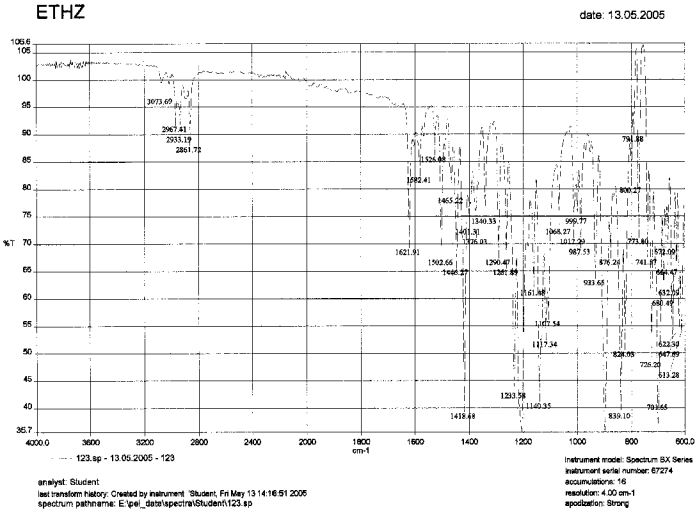

5.121
154.582
154.543
154.139
135.247
134.873
134.072
133.310
132.854
132.366
131.358
129.789
129.639
128.031
127.536
127.506
127.476
124.990
124.180
119.143
116.870
112.560
111.508
26.325
18.191
500
0
150
100
50

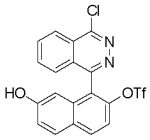

ETHZ
date: 13.05.2005
%T
3070.33
2930.79
2856.72
1530.82
1584.30
1487.56
1471.64
1448.53
1427.88
1621.70
1377.50
1340.78
1288.90
1263.15
1509.50
1112.95
1134.06
986.64
940.60
831.96
895.78
1221.98
766.39
746.28
697.31
649.02
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1
121.sp - 13.05.2005 - TMSendather
analyst: Student
last transform history: Created by instrument 'Student, Fri May 13 14:10:29 2005
spectrum pathname: E:\pel_data\spectra\Student\121.sp
instrument model: Spectrum BX Series
instrument serial number: 67274
accumulations: 16
resolution: 4.00 cm-1
apodization: Strong

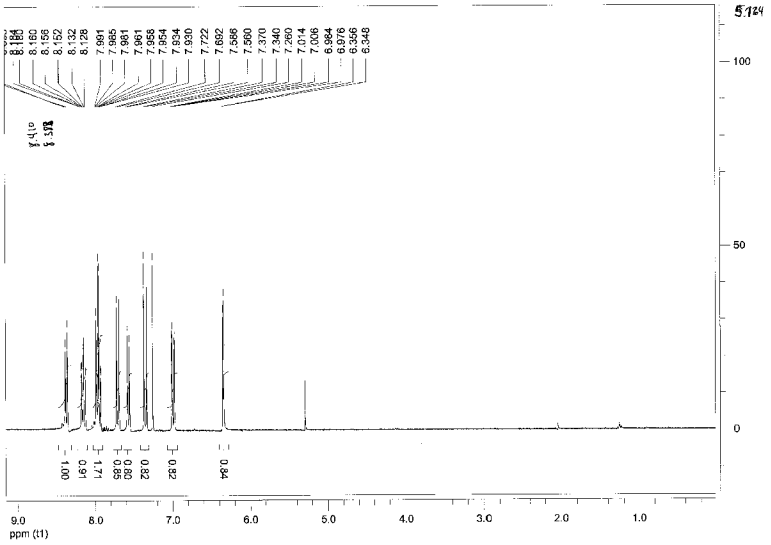

Cl
N
N
TBDPSO
OTf

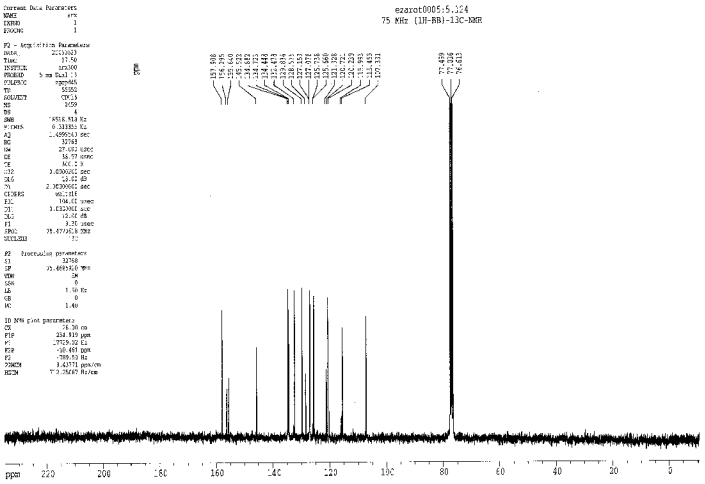

LOC ETHZ NMR Mercury-vx 300MHz Nr.8 06/28/05 13:05:06 USER:ezarot GROUP:camel SAMPLE:pz5p123
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
File: pz5.123.pure
UNITY-plus-300 "nmrec"
Pulse 30.0 degrees
Acq. time 3.198 sec
Width 5988.4 Hz
16 repetitions
OBSERVE H1, 300.2230602 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 50 sec
8
7
6
5
4
3
2
1
ppm
3.50
6.88
3.76
32.24
3.77
18.75
3.25
29.81

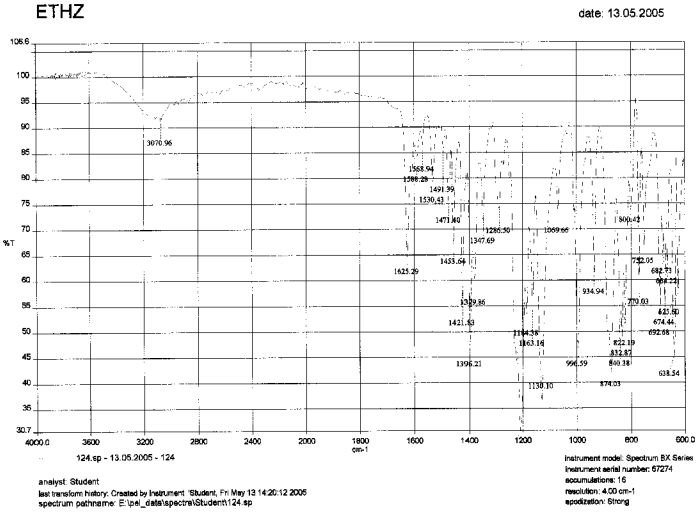

LOC ETHZ NMR Mercury 300MHz Nr.4 11/15/04 13:36:07 USER:ezarot GROUP:camel SAMPLE:pz5.123.c
13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gsm4oc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
616 repetitions
OBSERVE C13, 75.4132332 MHz
DECOUPLE H1, 299.9624326 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 54 min, 59 sec
154.476
145.525
77.492
77.072
76.643
26.469
19.394
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

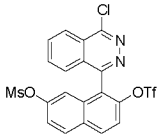

ETHZ
date: 13.05.2005
%T
105.6
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35.7
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1
3073.69
2967.41
2933.19
2861.72
1621.91
1526.68
1492.41
1463.22
1340.33
1290.47
1233.58
1140.35
1068.27
987.53
933.65
876.24
839.10
791.88
741.87
632.04
680.49
622.39
613.28
1418.68
123.sp - 13.05.2005 - 123
analyst: Student
last transform history: Created by instrument 'Student, Fri May 13 14:16:51 2005
spectrum pathname: E:\pel_data\spectra\Student\123.sp
instrument model: Spectrum BX Series
instrument serial number: 67274
accumulations: 16
resolution: 4.00 cm-1
apodization: Strong

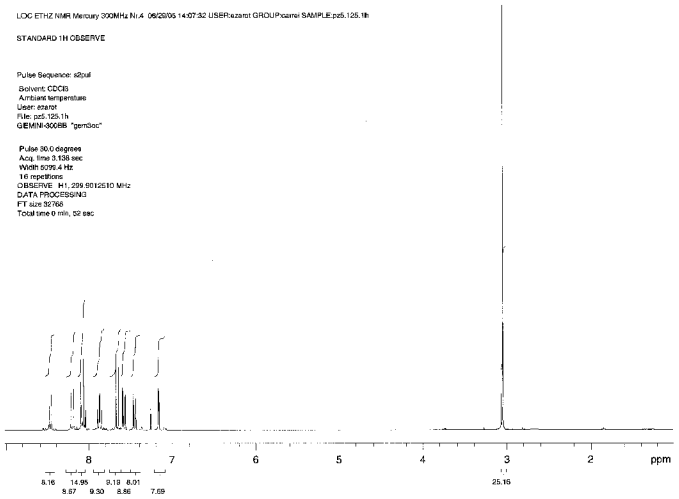

Cl
N
N
HO
OTf

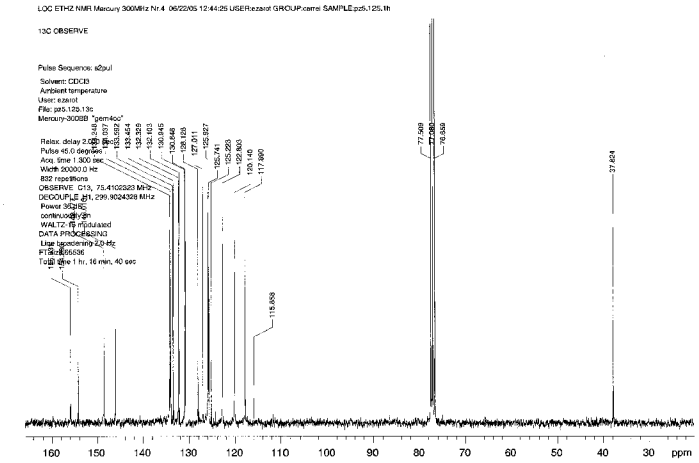

8.160
8.156
8.152
8.132
8.128
7.991
7.985
7.961
7.955
7.954
7.934
7.930
7.722
7.692
7.586
7.560
7.370
7.340
7.290
7.014
7.006
6.984
6.976
6.356
6.348
1.00
0.91
1.71
0.80
2.82
0.82
9.84
ppm (t1)

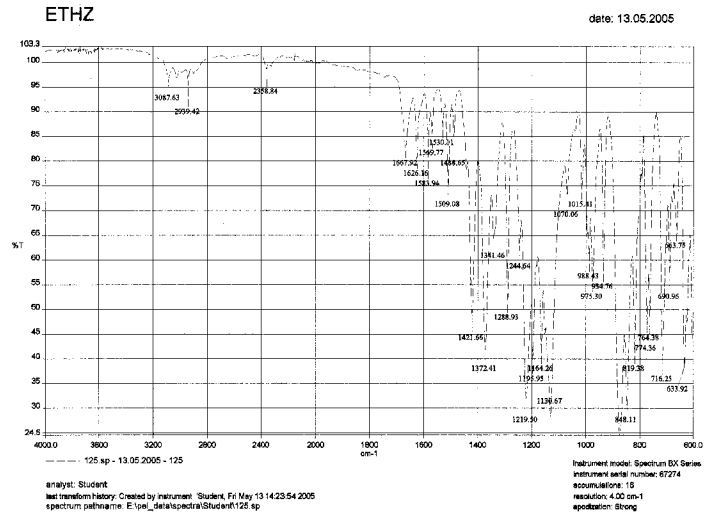

ezazat0005:5.124
75 MHz (1H-BB)-13C-NMR
ppm

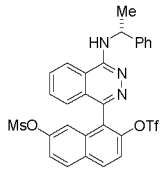

ETHZ
date: 13.05.2005
%T
3070.96
1568.94
1588.25
1491.39
1530.43
1471.10
1286.50
1347.69
1069.66
800.42
1455.04
1625.29
752.05
682.71
934.94
770.03
1329.86
1421.53
674.44
692.08
1194.58
1363.16
822.19
832.87
1396.21
996.59
860.38
638.54
1130.10
874.03
cm-1
124.sp - 13.05.2005 - 124
analyst: Student
last transform history: Created by Instrument 'Student, Fri May 13 14:20:12 2005
spectrum pathname: E:\pel_data\spectra\Student\124.sp
Instrument model: Spectrum BX Series
Instrument serial number: 67274
accumulations: 16
resolution: 4.00 cm-1
apodization: Strong

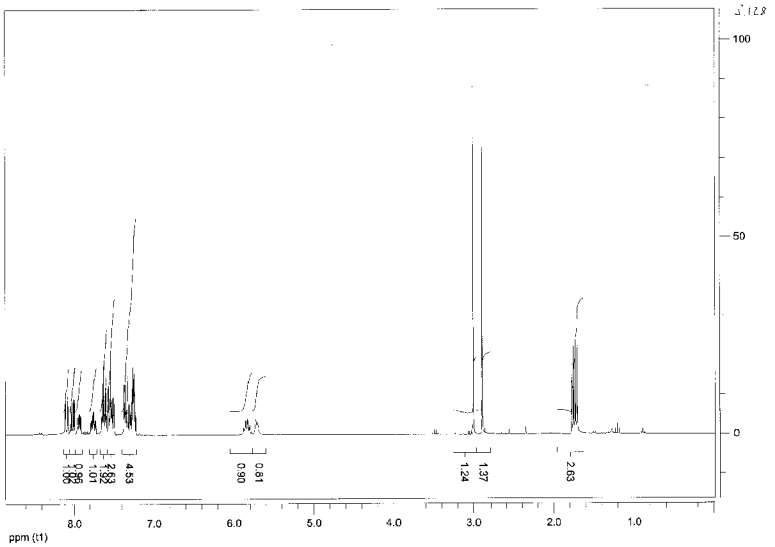

Cl
N
N
MsO
OTf

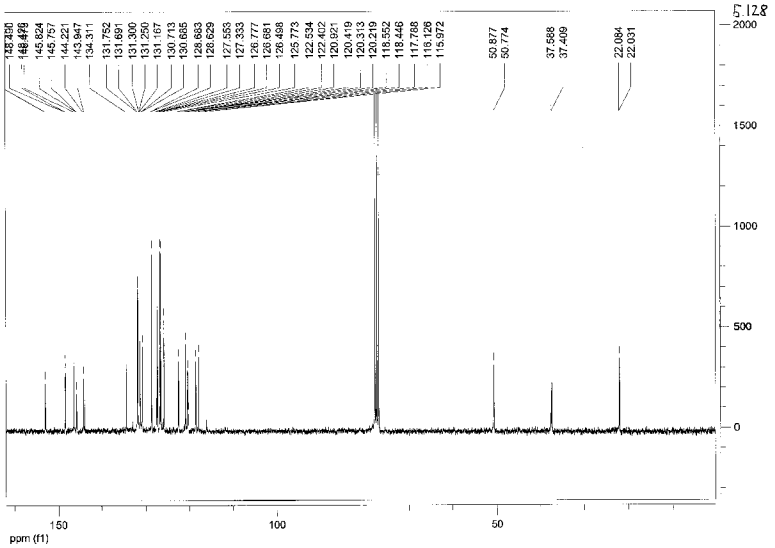

LOC ETHZ NMR Mercury 300MHz Nr.4 06/29/05 14:07:32 USER:ezarot GROUP:ezarot SAMPLE:pz5.125.1h
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
File: pz5.125.1h
GEMINI-300BB "gem3oc"
Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5299.4 Hz
16 repetitions
OBSERVE H1, 299.9012510 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec
8
7
6
5
4
3
2
ppm
8.16
14.95
8.19
8.01
8.67
9.30
8.86
7.69
25.15

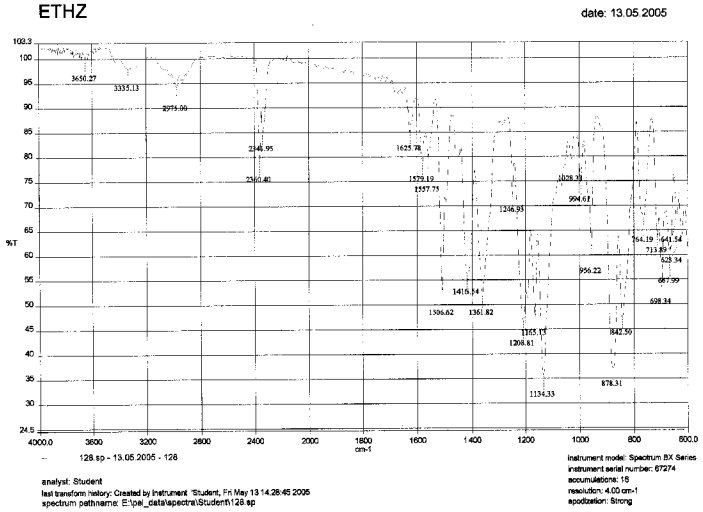

LOC ETHZ NMR Mercury 300MHz Nr.4 06/22/05 12:44:25 USER:ezarot GROUP:ezarot SAMPLE:pz5.125.1h
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
File: pz5.125.13c
Mercury-300BB "gem4oc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 30000.0 Hz
832 repetitions
OBSERVE C13, 75.4102823 MHz
DECOUPLE H1, 299.9024328 MHz
Power 35dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 hr, 16 min, 40 sec
152.248
147.697
143.357
133.454
132.328
132.103
130.445
130.046
128.125
127.511
125.827
125.574
125.293
122.803
120.140
117.990
77.569
77.060
76.559
27.824
115.858
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

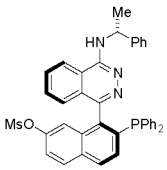

ETHZ
date: 13.05.2005
103.3
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
24.5
%T
3067.63
2959.42
2358.84
1530.31
1549.77
1597.52
1626.36
1583.96
1498.65
1509.08
1015.83
1078.06
963.78
1381.46
1244.64
988.43
934.76
975.39
690.95
1288.93
1431.66
764.36
774.36
1372.41
1394.26
1192.95
819.38
716.25
633.92
1139.67
1219.50
848.11
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1
125.sp - 13.05.2005 - 125
analyst: Student
last transform history: Created by instrument: Student, Fri May 13 14:23:54 2005
spectrum pathname: E:\pei_data\spectra\Student\125.sp
Instrument model: Spectrum BX Series
instrument serial number: 67274
accumulations: 16
resolution: 4.00 cm-1
apodization: Strong

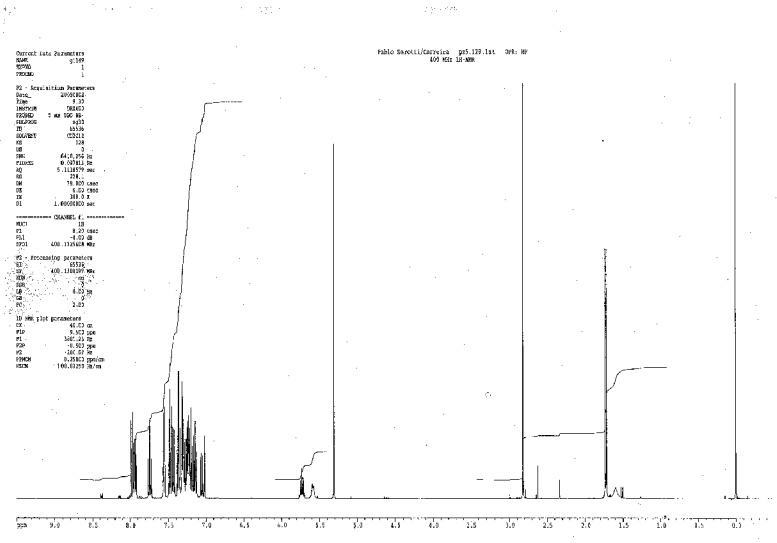

Me
HN
Ph
N
N
MsO
OTf

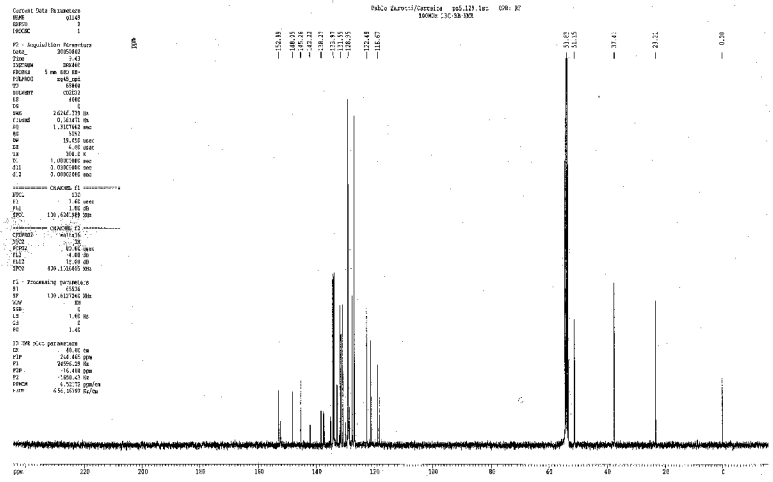

5.12.8
100
50
0
0.90
0.81
1.24
1.37
2.63
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

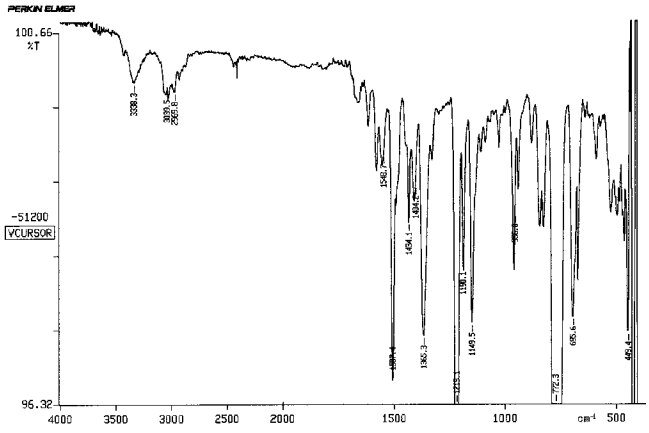

5.12.8
2000
1500
1000
500
0
50.877
50.774
37.588
37.409
22.084
22.031
150
100
50
ppm (f1)


ETHZ
date: 13.05.2005
%T
3650.27
3335.13
2975.99
2348.95
2320.40
1625.78
1579.19
1557.75
1496.54
1416.14
1396.62
1361.82
1246.93
1208.81
1134.33
1028.39
994.61
956.22
878.31
842.50
764.19
713.87
698.34
cm-1
128.sp - 13.05.2005 - 128
analyst: Student
last transform history: Created by Instrument 'Student, Fri May 13 14:26:45 2005
spectrum pathname: E:\pe_data\spectra\Student\128.sp
instrument model: Spectrum BX Series
instrument serial number: 67274
accumulations: 16
resolution: 4.00 cm-1
apodization: Strong

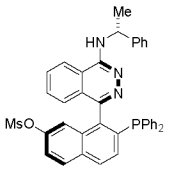


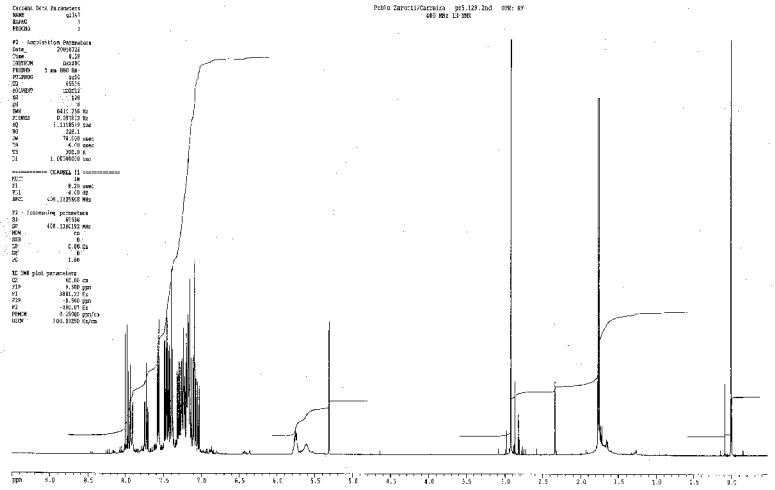


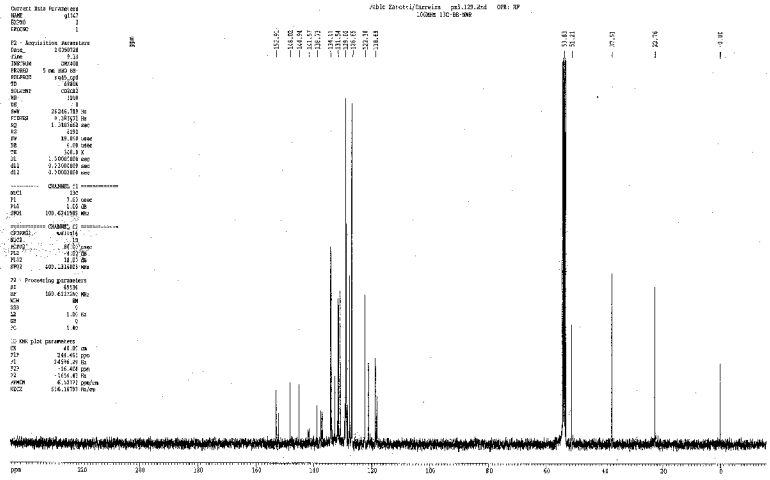


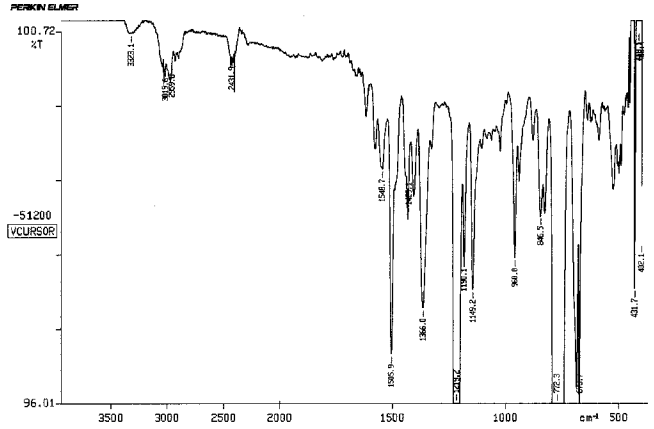


05/08/08 12:52 pablems1
X: 16 scans, 4.0cm-1

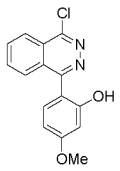


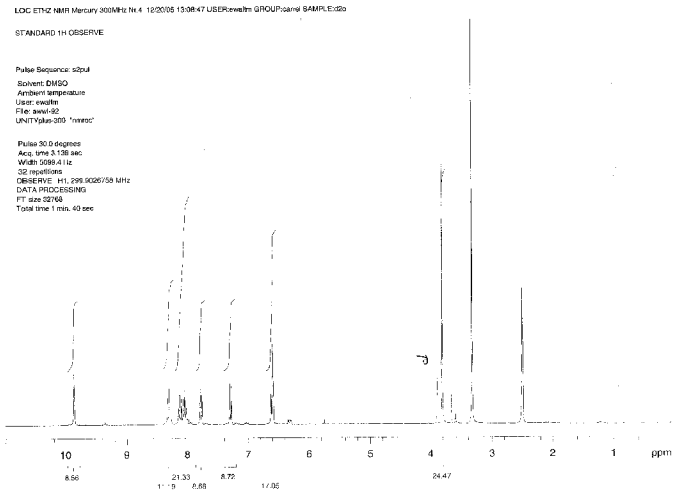


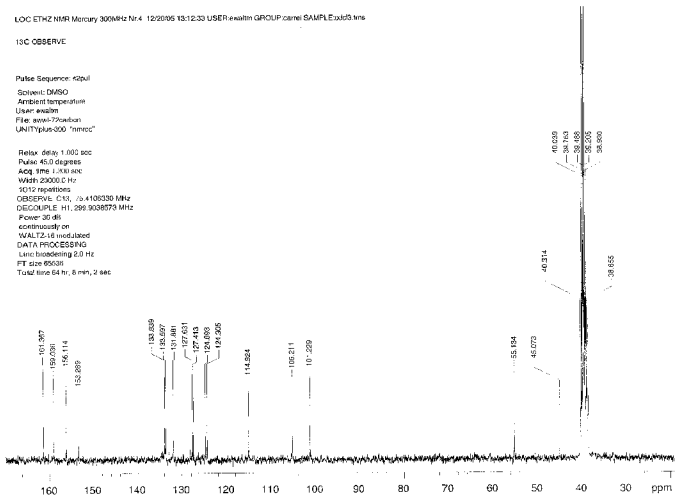


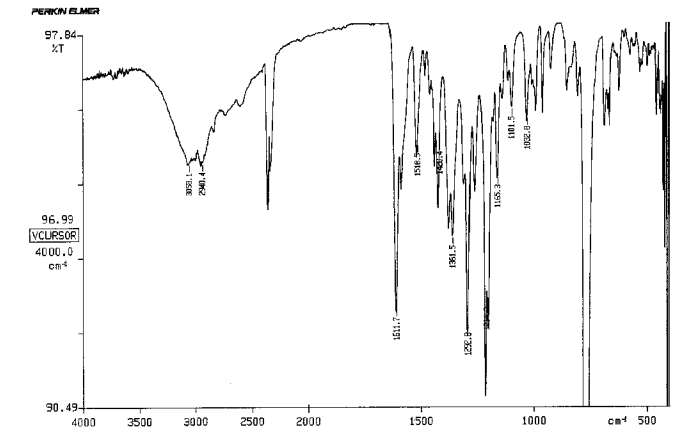


05/08/08 13:00 pablom1
X: 16 scans, 4.0cm-1

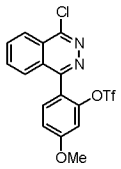


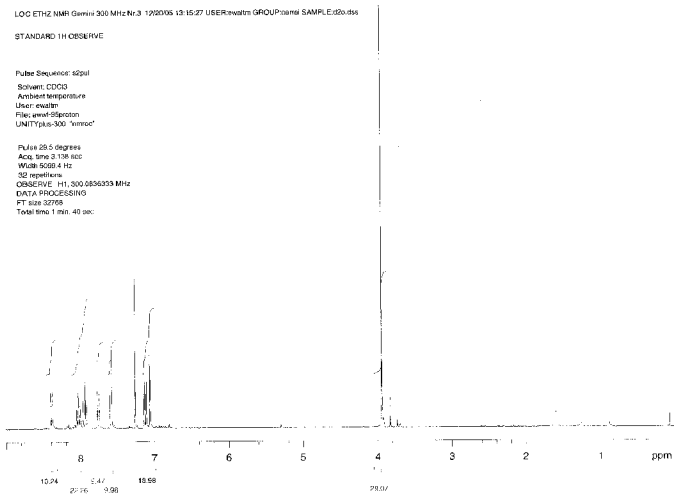


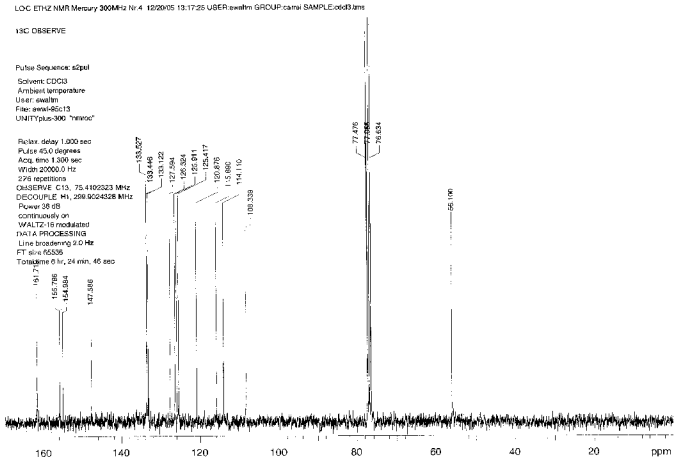


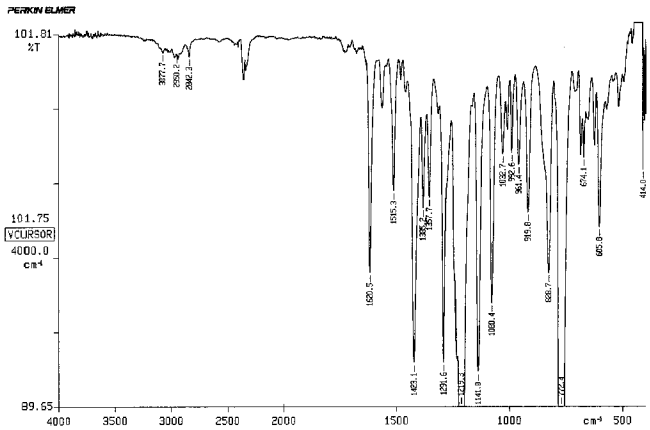


05/12/16 12:56 andrew1
X: 16 scans, 4.0cm-1, flat

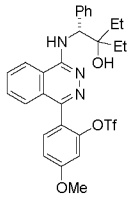


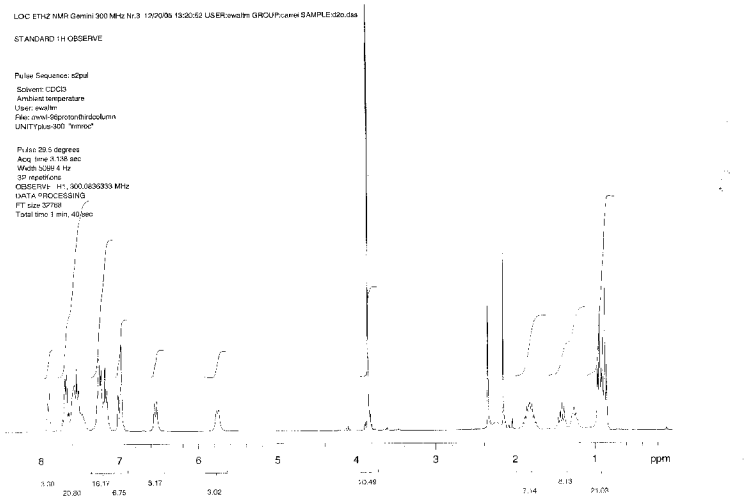


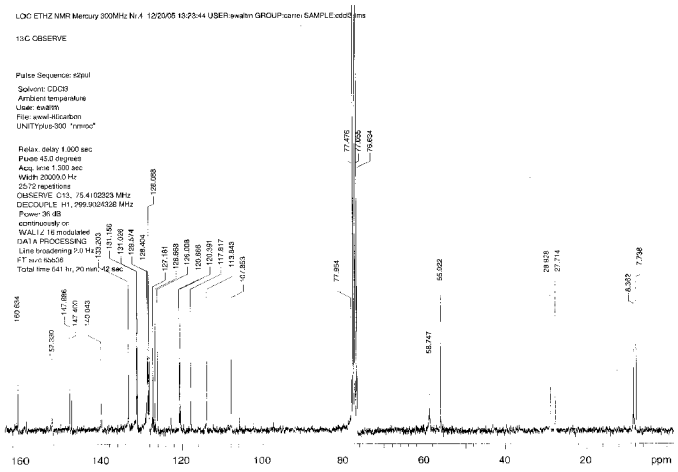


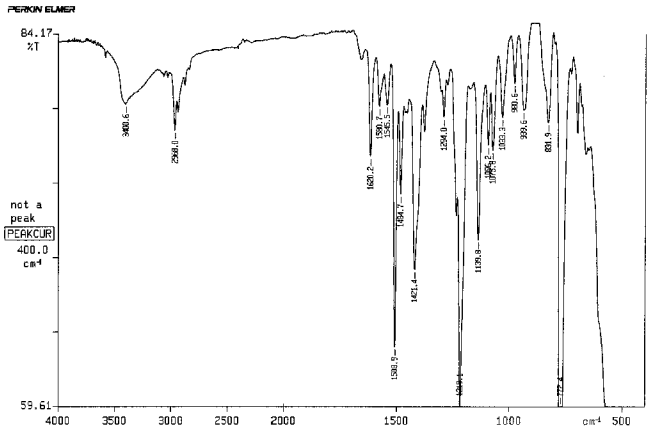


05/12/16 13:06 andrew2
X: 16 scans, 4.0cm-1, flat

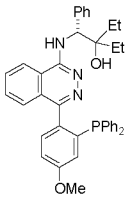


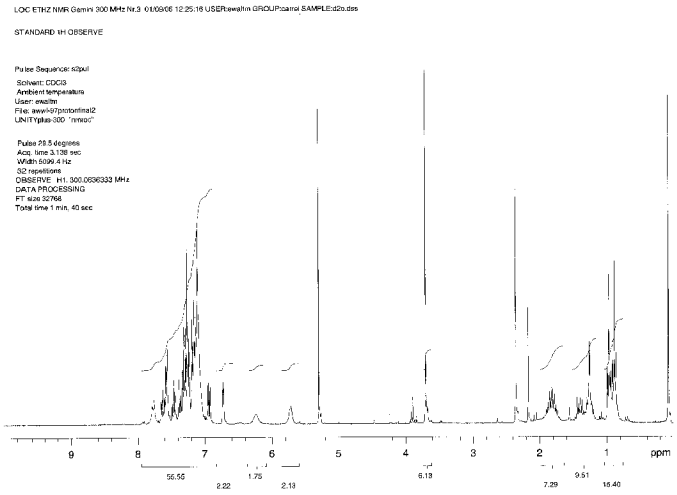


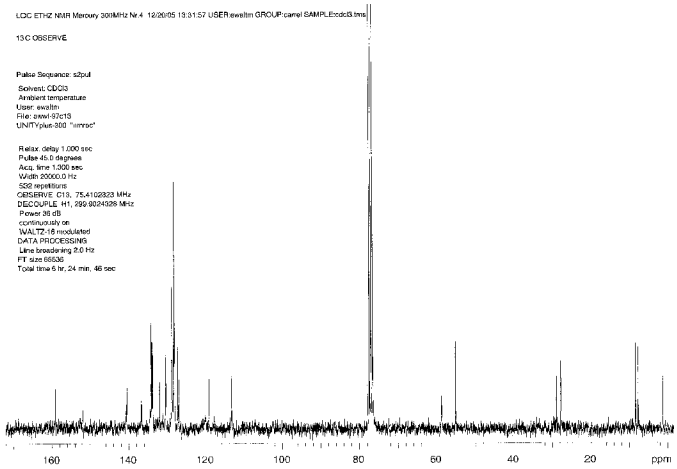


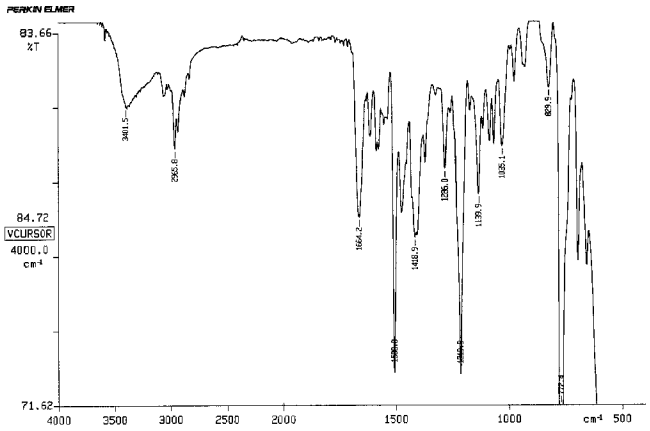


05/12/15 13:16 andrewß
X: 16 scans, 4.0cm-1, flat

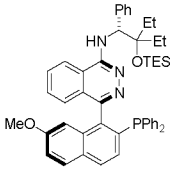


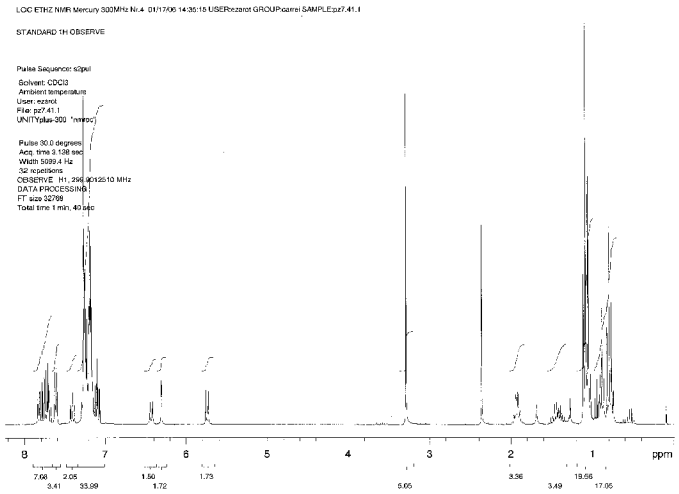


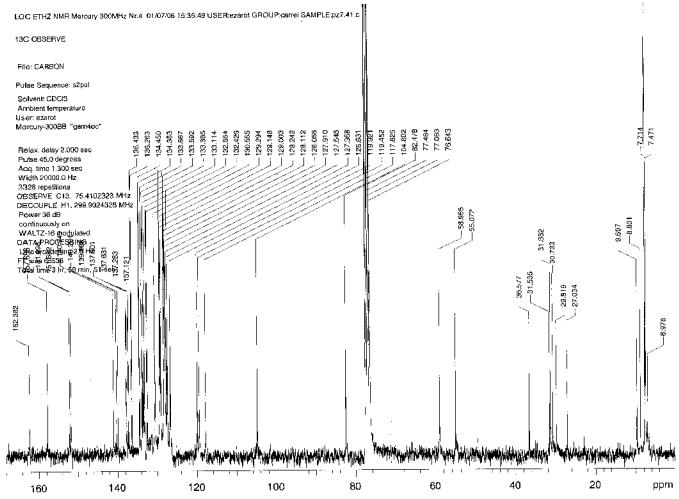


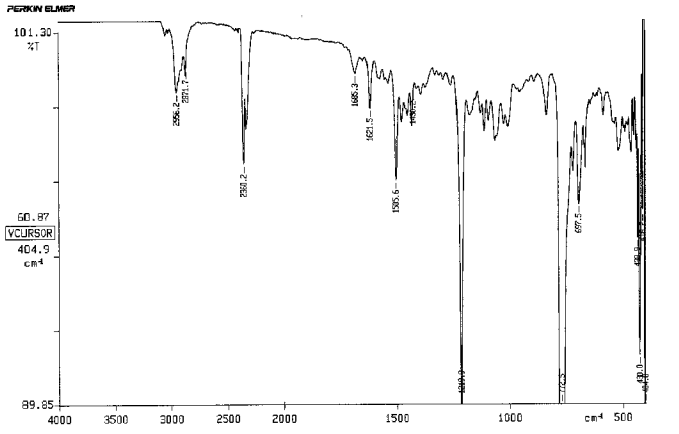


05/12/16 13:25 andrewH
X: 16 scans, 4.0cm-1, flat

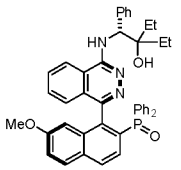


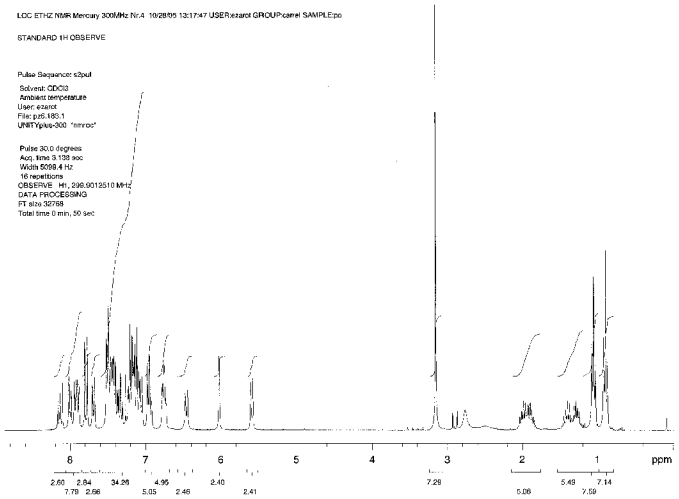


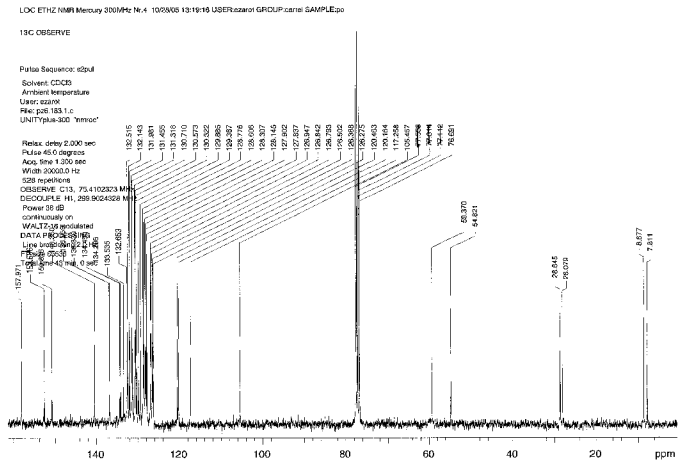


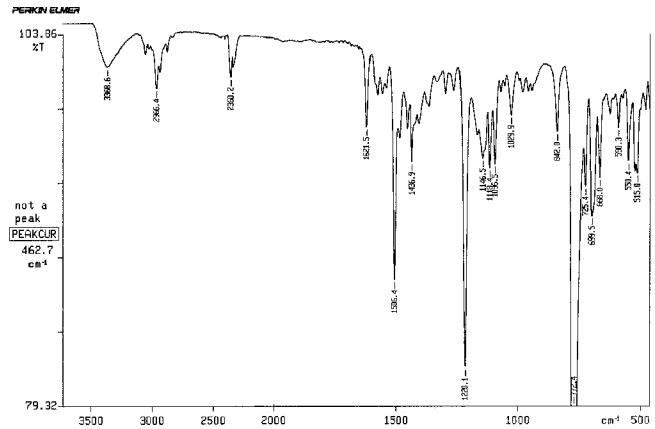


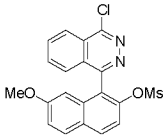
06/01/17 16:50 cs-367
X: 16 scans, 4.0cm-1


Ph
Et
HN
Et
OH
N
N
Ph2
P
O
MeO


LOC ETHZ NMR Mercury 300MHz Nr.4 10/28/05 13:17:47 USER:ezarot GROUP:camel SAMPLE:po
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
File: pz5.183.1
UNITYplus-300 "nmroo"
Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5098.4 Hz
16 repetitions
OBSERVE H1, 299.9012510 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 50 sec
8
7
6
5
4
3
2
1
ppm
2.60
2.84
34.26
4.95
2.40
7.29
5.49
7.14
7.79
2.66
5.05
2.46
2.41
5.06
7.59


LOC ETHZ NMR Mercury 300MHz Nr.4 10/28/05 13:19:16 USER:ezarot GROUP:camel SAMPLE:po
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
File: pz5.183.1.c
UNITYplus-300 "nmroo"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
528 repetitions
OBSERVE C13, 75.4102323 MHz
DECOUPLE H1, 299.9024928 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 42 min, 0 sec
132.515
132.143
131.881
131.495
131.315
130.710
130.573
130.322
130.086
129.982
129.776
129.606
129.307
129.145
127.992
127.837
126.947
126.842
126.702
125.502
85.368
85.275
77.581
58.370
54.601
28.845
28.529
8.677
7.811
140
120
100
80
60
40
20
ppm


PERKIN ELMER
103.86
%T
not a
peak
PEAKCUR
462.7
cm-1
79.32
3366.6
2966.4
2360.2
1621.5
1496.9
1366.4
1236.1
1146.5
1126.3
1029.9
940.8
756.4
699.5
666.0
596.3
539.4
515.6
3500
3000
2500
2000
1500
1000
cm-1
500
05/10/31 13:41 pablopoxide
X: 16 scans, 4.0cm-1, flat



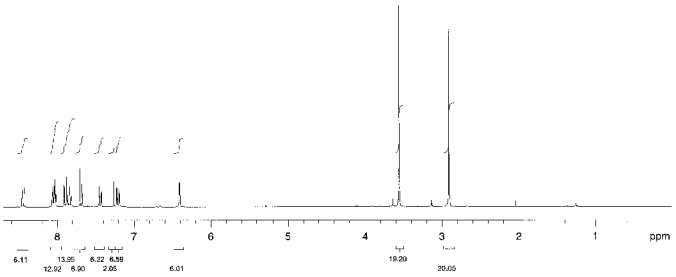
LOC ETHZ NMR Mercury 300MHz Nr.4 12/03/05 12:38:56 USER:ezarot GROUP:carrel SAMPLE:pz7.13.11

STANDARD 1H OBSERVE

File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"

Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5999.4 Hz
16 repetitions
OBSERVE H1, 299.9012510 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec

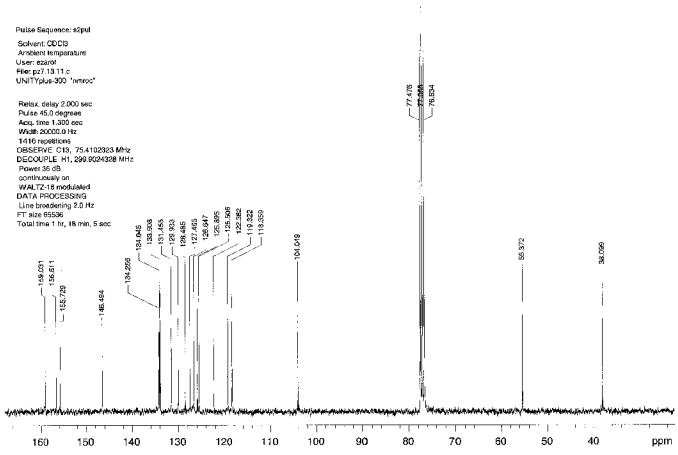


LOC ETHZ NMR Mercury 300MHz Nr.4 12/03/05 14:26:19 USER:ezarot GROUP:carrel SAMPLE:pz7.13.11

13C OBSERVE

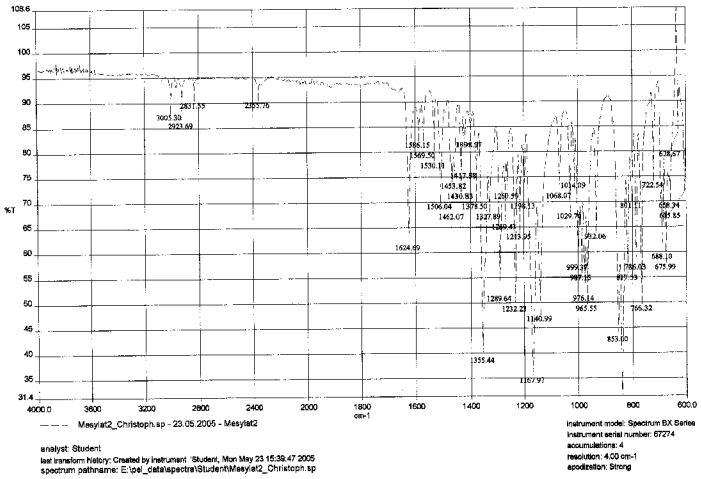
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
File: pz7.13.11.c
UNITYplus-300 "nmroc"

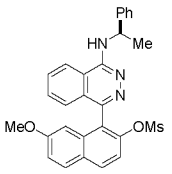
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
1416 repetitions
OBSERVE C13, 75.4102923 MHz
DECOUPLE H1, 299.9024328 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 hr, 15 min, 5 sec



ETHZ

date: 23.05.2005





LOC ETHZ NMR Mercury-vx 300MHz Nr:6 06/24/05 16:00:52 USER:azarot GROUP:azarot SAMPLE:pa6.74.1h

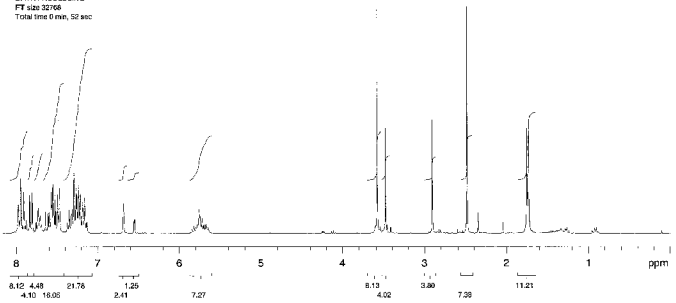
STANDARD 1H OBSERVE

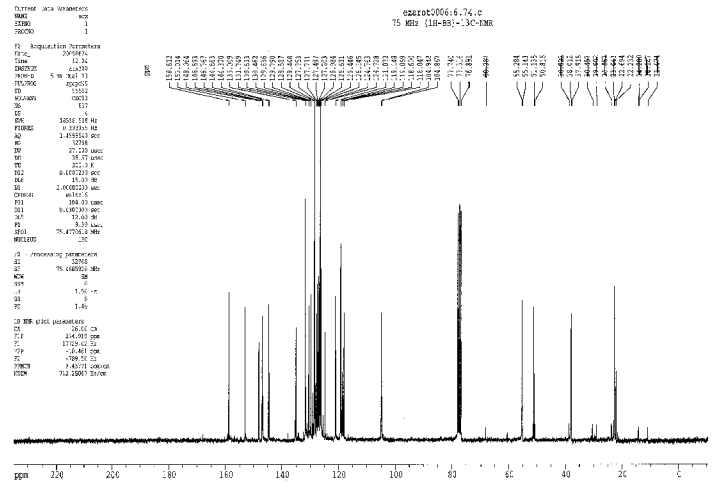
File: PROTON

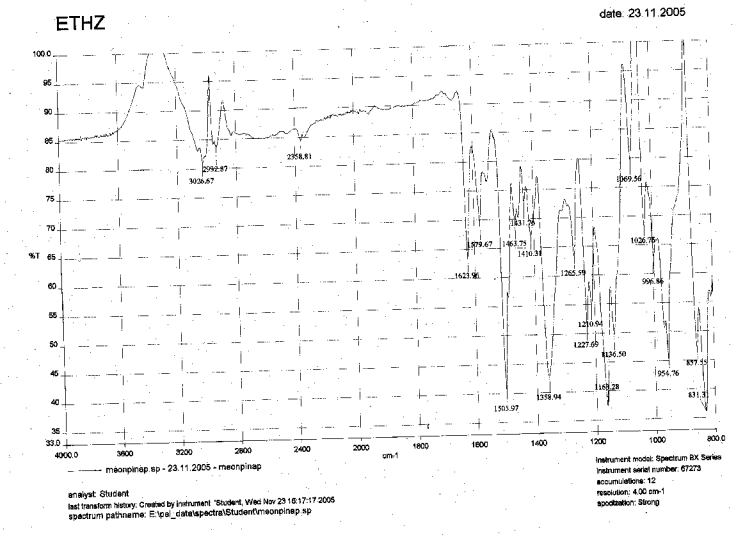
Pulse Sequence: s2pul

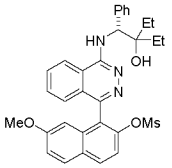
Solvent: CDCl3
Ambient temperature
User: azarot
Mercury-300BB "gem6ac"

Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5099.4 Hz
16 repetitions
OBSERVE H1, 300.2230602 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec









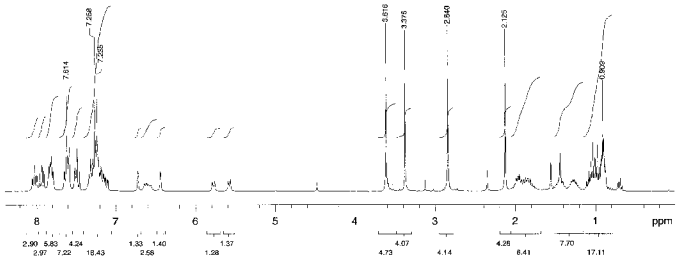
LOC ETHZ NMR Mercury 300MHz Nr.4 12/03/05 10:09:16 USER ezarot GROUP:carrel SAMPLE:pz7.15.11

STANDARD 1H OBSERVE

File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"

Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5099.4 Hz
32 repetitions
OBSERVE H1, 299.9012510 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 45 sec



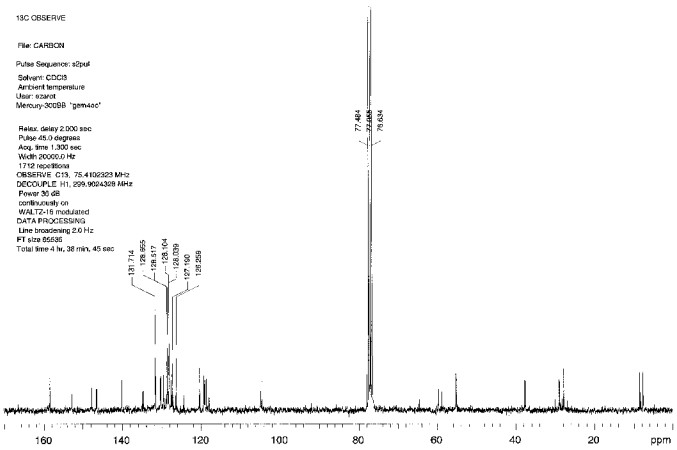
LOC ETHZ NMR Mercury 300MHz Nr.4 12/03/05 11:52:23 USER:ezarot GROUP:carrel SAMPLE:pz7.15.11

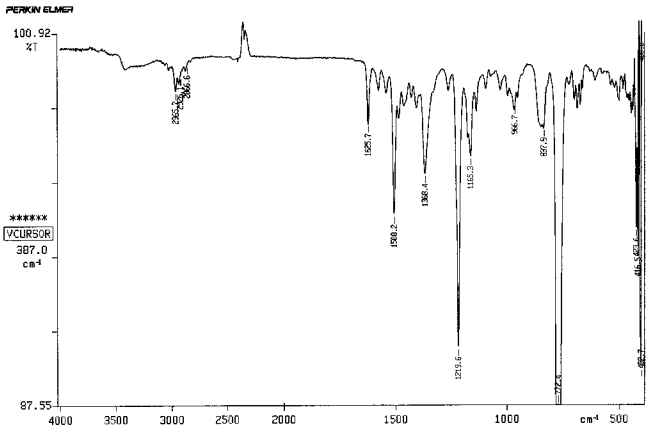
13C OBSERVE

File: CARBON

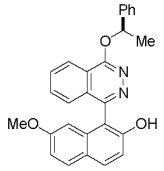
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"

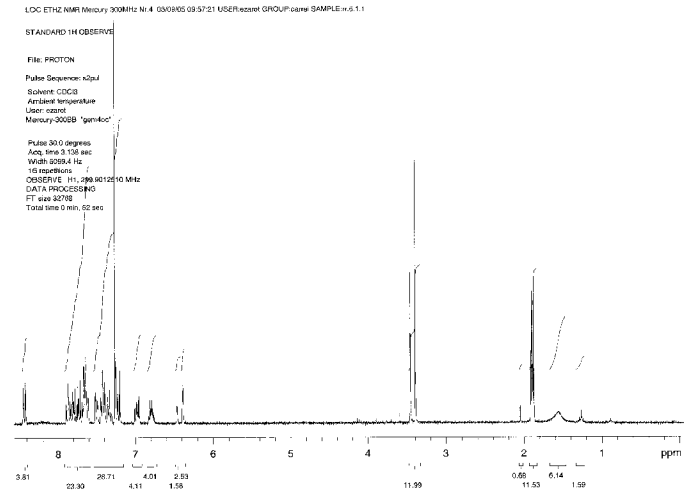
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
1712 repetitions
OBSERVE C13, 75.4102323 MHz
DECOUPLE H1, 299.9024328 MHz
Power 30 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 38 min, 45 sec

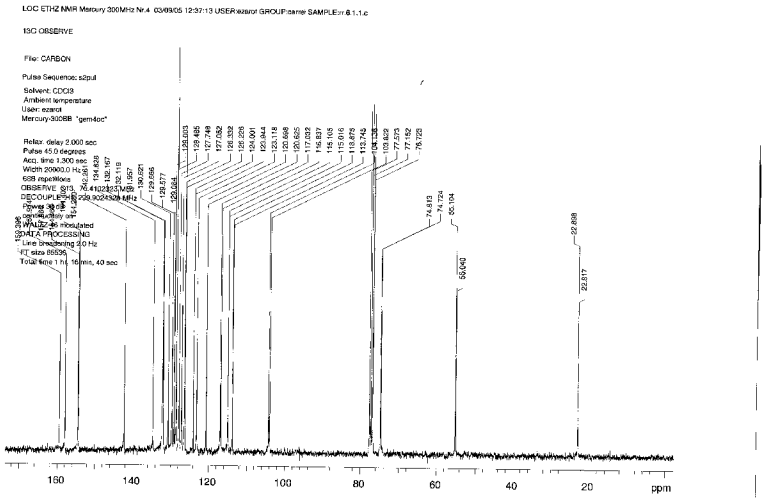


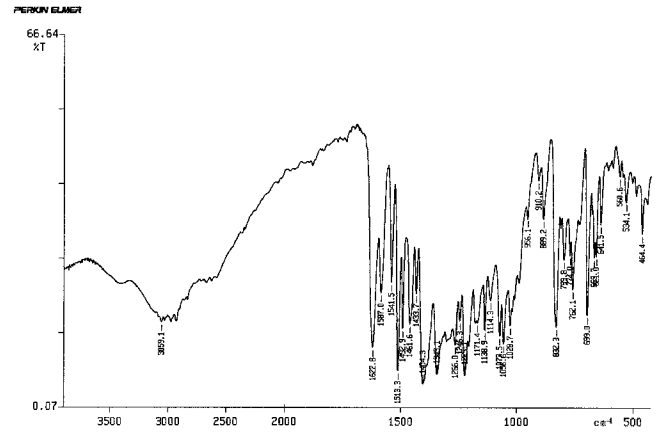


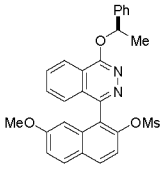
05/12/08 16:37 mesgoodlig
X: 16 scans, 4.0cm-1

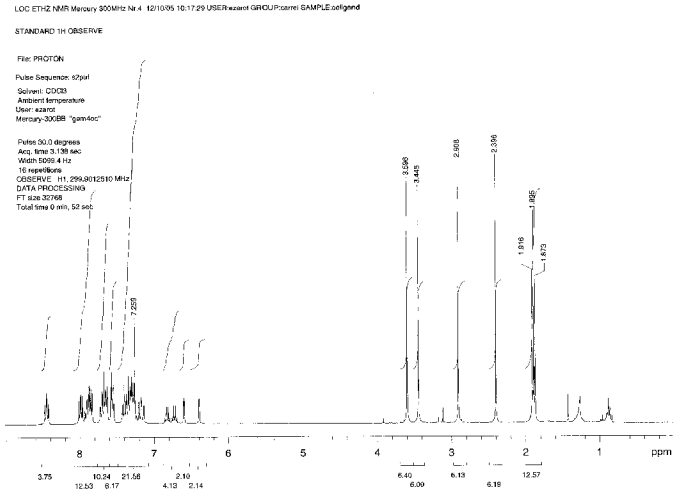

Ph
O
Me
N
N
MeO
OH

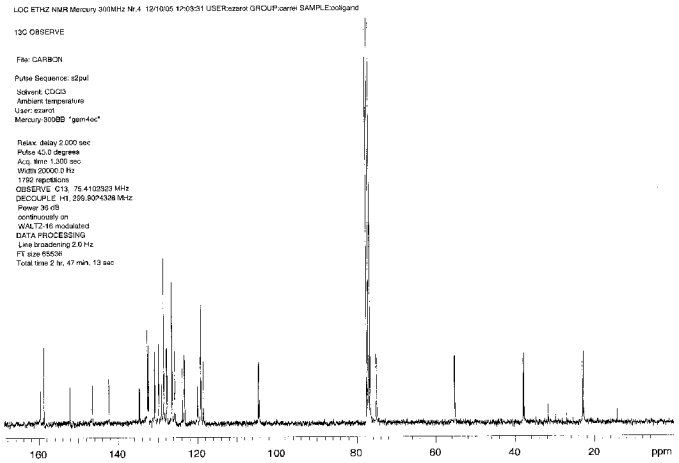

LOC ETHZ NMR Mercury 300MHz Nr.4 03/09/05 09:57:21 USER:ezarot GROUP:camel SAMPLE:rr.6.1.1
STANDARD 1H OBSERVE
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"
Pulse 30.0 degrees
Acq. time 3.138 sec
Width 6099.4 Hz
16 repetitions
OBSERVE H1, 299.9012510 MHz
DATA PROCESSING
FT size 92768
Total time 0 min, 52 sec
8
7
6
5
4
3
2
1
ppm
3.81
22.30
28.71
4.01
4.11
2.53
1.58
11.99
0.68
11.53
6.14
1.59

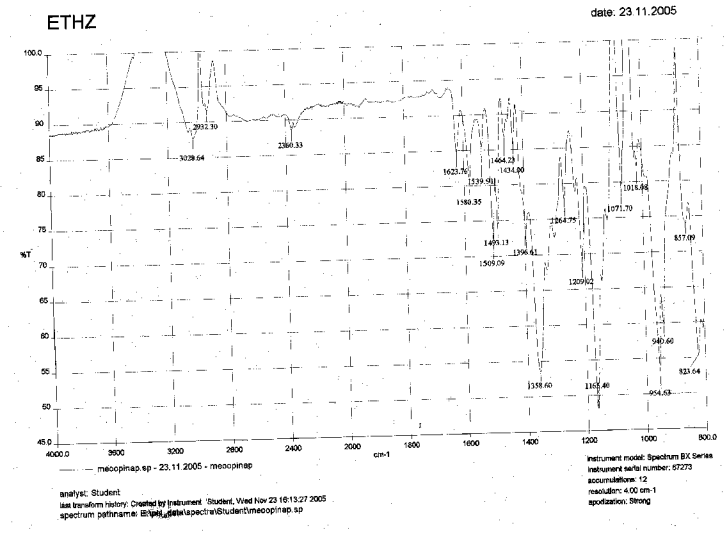

LOC ETHZ NMR Mercury 300MHz Nr.4 03/09/05 12:37:13 USER:ezarot GROUP:camel SAMPLE:rr.6.1.1.c
13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
608 repetitions
OBSERVE C13, 75.4102353 MHz
DECOUPLER H1, 299.9024329 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
EXPONENTIAL PROCESSING
Line broadening 2.0 Hz
FT size 86936
Total time 1 hr, 16 min, 40 sec
160
140
120
100
80
60
40
20
ppm
77.000
76.728
74.418
74.104
55.104
55.040
22.817
22.698

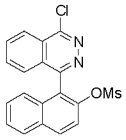

PERKIN ELMER
66.64
%T
0.07
3500
3000
2500
2000
1500
1000
cm-1
500
3055.1
1622.8
1597.6
1541.5
1513.3
1496.3
1456.1
1371.4
1114.3
1026.7
956.1
889.2
832.3
762.1
699.3
664.3
534.1
464.4
05/03/15 16:17 ezarot
X: 16 scans, 4.0cm-1

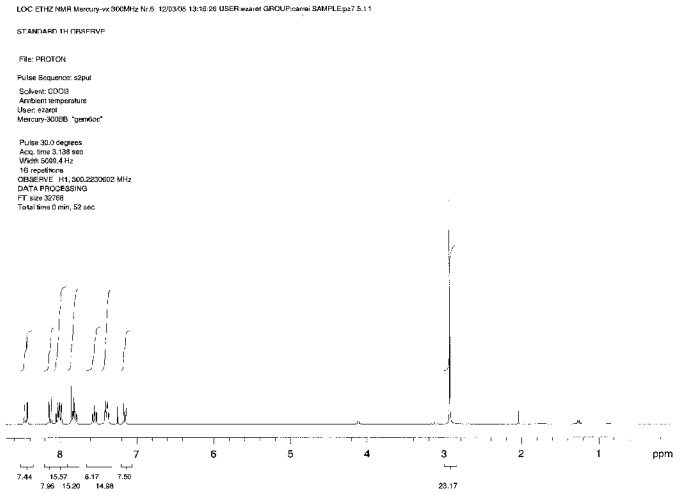

Ph
O
Me
N
N
MeO
OMs

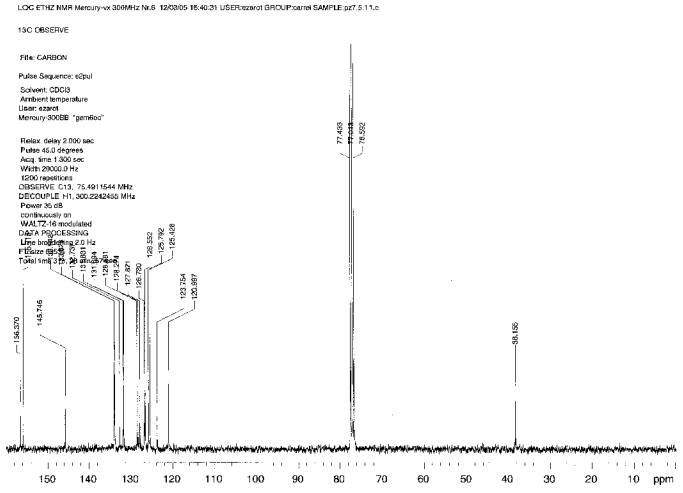

LOC ETHZ NMR Mercury 300MHz Nr.4 12/10/05 10:17:29 USER:ezarot GROUP:cantel SAMPLE:oligand
STANDARD 1H OBSERVE
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"
Pulse 30.0 degrees
Acq. time 3.139 sec
Width 5099.4 Hz
16 repetitions
OBSERVE H1, 299.9012510 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec
7.259
3.596
3.445
2.605
2.396
1.916
1.873
1.695
8
7
6
5
4
3
2
1
ppm
3.75
10.24
21.58
2.10
6.40
6.13
12.57
12.53
8.17
4.13
2.14
6.00
6.19

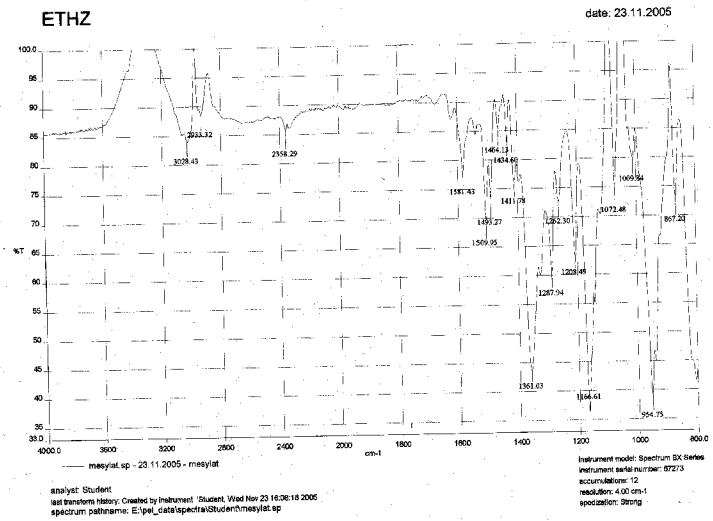

LOC ETHZ NMR Mercury 300MHz Nr.4 12/10/05 12:03:31 USER:ezarot GROUP:cantel SAMPLE:oodigand
13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"
Relax. delay 2.000 sec
Pulse 42.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
1792 repetitions
OBSERVE C13, 75.4102323 MHz
DECOUPLE H1, 299.9074328 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 2 hr, 47 min, 13 sec
160
140
120
100
80
60
40
20
ppm

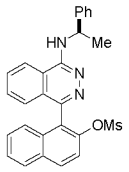

ETHZ
date: 23.11.2005
100.0
95
90
85
80
75
%T
70
65
60
55
50
45.0
4000.0
3500
3000
2500
2000
1800
1600
1400
1200
1000
800.0
cm-1
3028.64
2992.30
2860.33
1623.76
1539.91
1464.23
1434.80
1380.35
1493.13
1509.09
1396.41
1264.75
1220.92
1071.70
1016.84
857.09
940.66
923.64
1358.60
1165.46
954.63
meopinap.sp - 23.11.2005 - meopinap
analyst: Student
last transform history: Created by Instrument 'Student, Wed Nov 23 16:13:27 2005
spectrum pathname: E:\data\spectra\Student\meopinap.sp
instrument model: Spectrum BX Series
instrument serial number: 57273
accumulations: 12
resolution: 4.00 cm-1
apodization: Strong


Cl
N
N
OMs


LOC ETHZ NMR Mercury-vx 300MHz Nr.6 12/03/05 13:16:26 USER:ezarot GROUP:csarel SAMPLE:pz7.5.1.1
STANDARD 1H OBSERVE
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem6oc"
Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5088.4 Hz
16 repetitions
OBSERVE H1, 300.2230602 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec
8
7
6
5
4
3
2
1
ppm
7.44
15.57
8.17
7.50
7.96
15.20
14.98
23.17


LOC ETHZ NMR Mercury-vx 300MHz Nr.6 12/03/05 16:40:31 USER:ezarot GROUP:csarel SAMPLE:pz7.5.1.1.c
13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem6oc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 29000.0 Hz
1200 repetitions
OBSERVE C13, 75.4911544 MHz
DECOUPLE H1, 300.2242468 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 3 hr, 20 min
77.468
77.048
76.592
156.370
148.746
136.532
135.792
135.408
133.754
133.697
127.827
126.750
38.185
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


ETHZ
date: 23.11.2005
%T
100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30.0
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800.0
cm-1
3333.32
3028.45
2358.29
1581.43
1484.13
1434.60
1411.78
1493.27
1509.95
1262.30
1208.49
1287.04
1361.03
1164.61
1069.94
1072.48
867.23
954.75
mesylat.sp - 23.11.2005 - mesylat
analyst: Student
last transform history: Created by Instrument 'Student, Wed Nov 23 16:06:18 2005
spectrum pathname: E:\pel_data\spectra\Student\mesylat.sp
Instrument model: Spectrum BX Series
instrument serial number: 67273
accumulations: 12
resolution: 4.00 cm-1
apodization: Strong



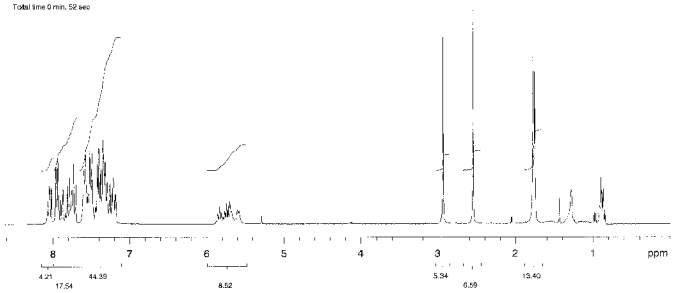
LOC ETHZ NMR Mercury 300MHz Nr.4 12/10/05 12:09:06 USER:ezarot GROUP:carrel SAMPLE:pz7.8.h

STANDARD 1H OBSERVE

File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4ac"

Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5999.4 Hz
16 repetitions
OBSERVE H1, 299.9012510 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec

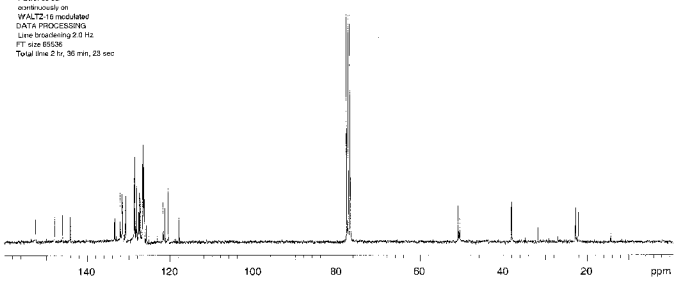


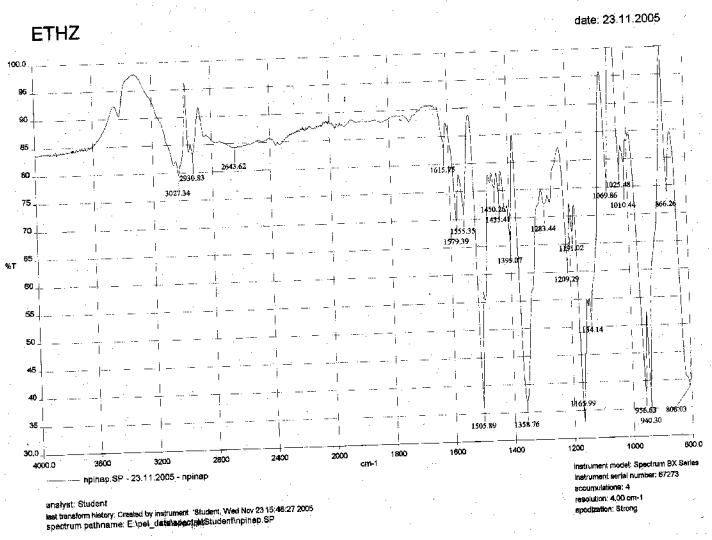
LOC ETHZ NMR Mercury 300MHz Nr.4 12/10/05 14:22:51 USER:ezarot GROUP:carrel SAMPLE:pz7.8.h

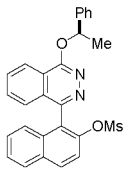
13C OBSERVE

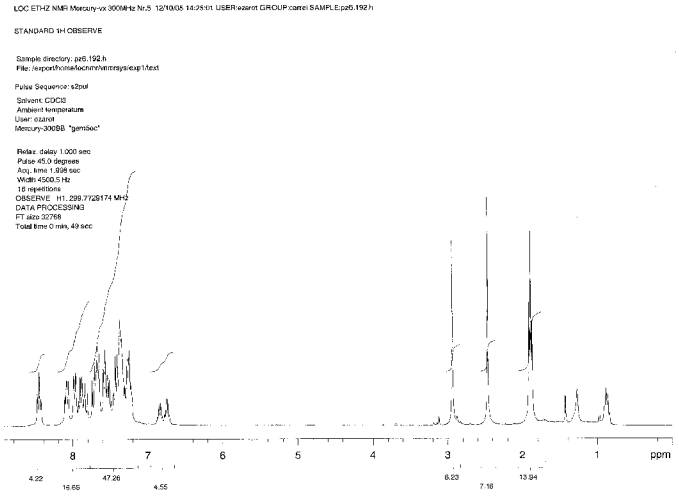
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
File: pz7.8.c
UNITYplus-300 "nmrod"

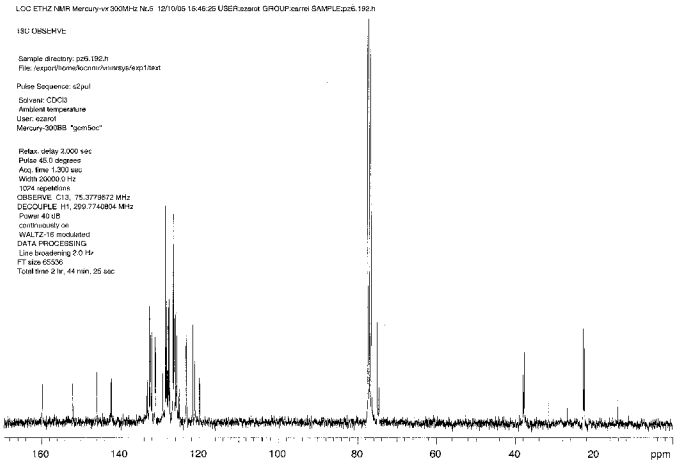
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
1955 repetitions
OBSERVE C13, 75.4102223 MHz
DECOUPLE H1, 299.9024528 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 2 hr, 36 min, 23 sec

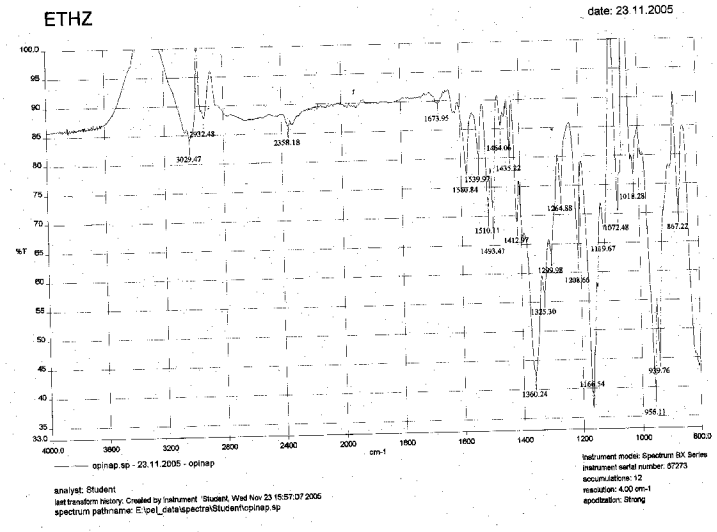


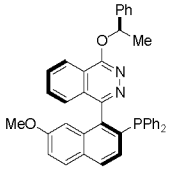


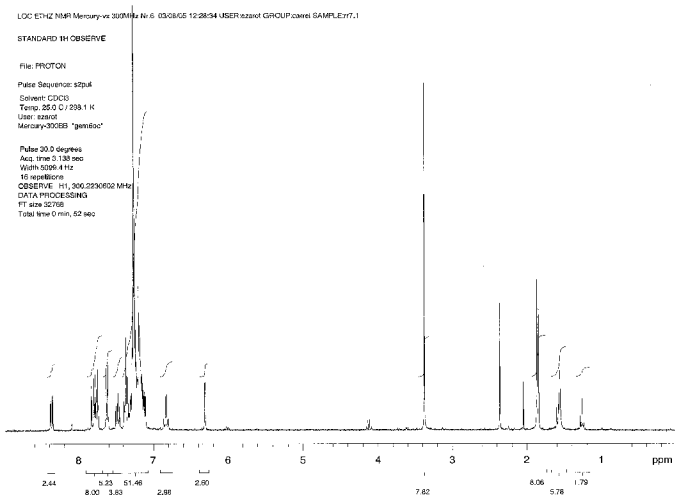

Ph
O
Me
N
N
OMs

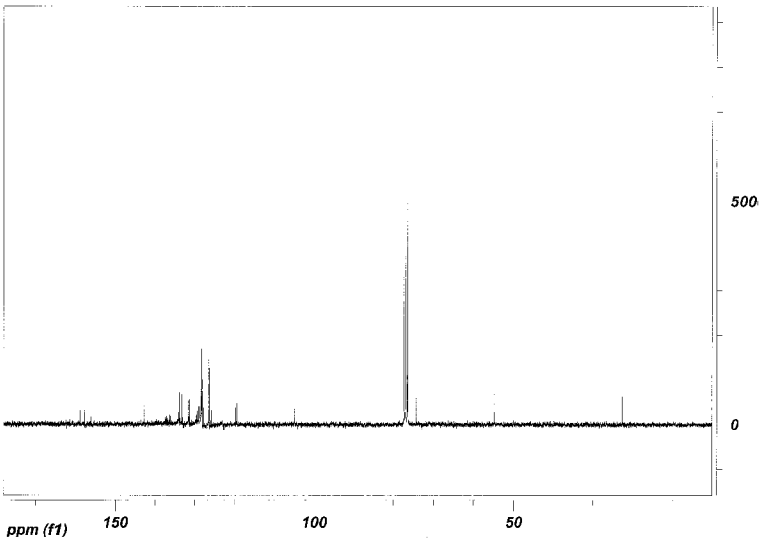

LOC ETHZ NMR Mercury-vx 300MHz Nr.5 12/10/05 14:28:01 USER:ezarot GROUP:carrel SAMPLE:pz5.192.h
STANDARD 1H OBSERVE
Sample directory: pz5.192.h
File: /export/home/locnmr/vnmrsys/exp1/fext
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem5oc"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.898 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 299.7729174 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec
8
7
6
5
4
3
2
1
ppm
4.22
16.65
47.26
4.55
6.23
7.18
13.94

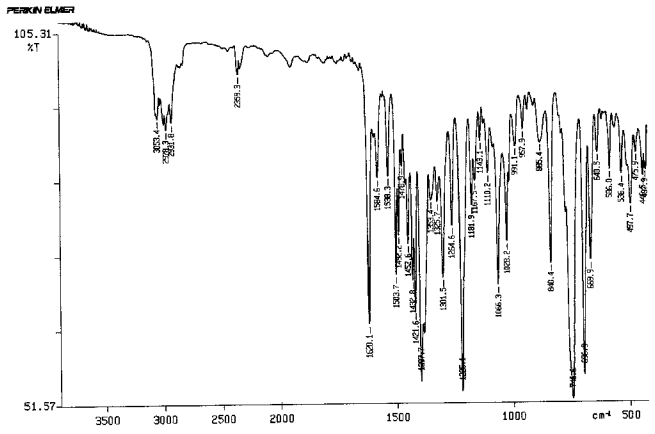

LOC ETHZ NMR Mercury-vx 300MHz Nr.5 12/10/05 15:46:25 USER:ezarot GROUP:carrel SAMPLE:pz5.192.h
13C OBSERVE
Sample directory: pz5.192.h
File: /export/home/locnmr/vnmrsys/exp1/fext
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem5oc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
1074 repetitions
OBSERVE C13, 75.3779872 MHz
DECOUPLE H1, 299.7740894 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 2 hr, 44 min, 25 sec
160
140
120
100
80
60
40
20
ppm


ETHZ
date: 23.11.2005
100.0
95
90
85
80
75
70
%T
65
60
55
50
45
40
35
33.0
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800.0
cm-1
3029.47
2912.43
2358.18
1673.95
1494.06
1433.22
1539.97
1580.84
1510.11
1412.97
1493.47
1264.88
1072.48
1018.28
867.22
1119.67
1299.08
1238.86
1225.36
1360.24
1168.54
959.76
956.11
opinap.sp - 23.11.2005 - opinap
analyst: Student
last transform history: Created by instrument `Student, Wed Nov 23 15:57:07 2005
spectrum pathname: E:\pel_data\spectra\Student\opinap.sp
instrument model: Spectrum BX Series
instrument serial number: 57273
accumulations: 12
resolution: 4.00 cm-1
apodization: Strong

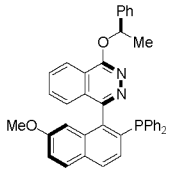


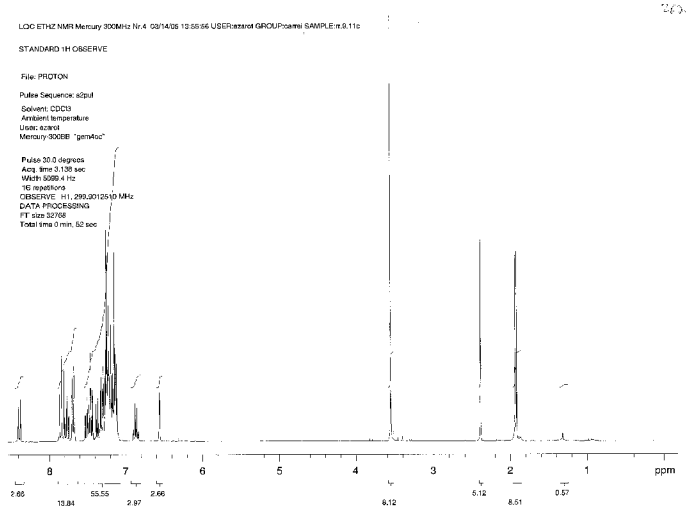


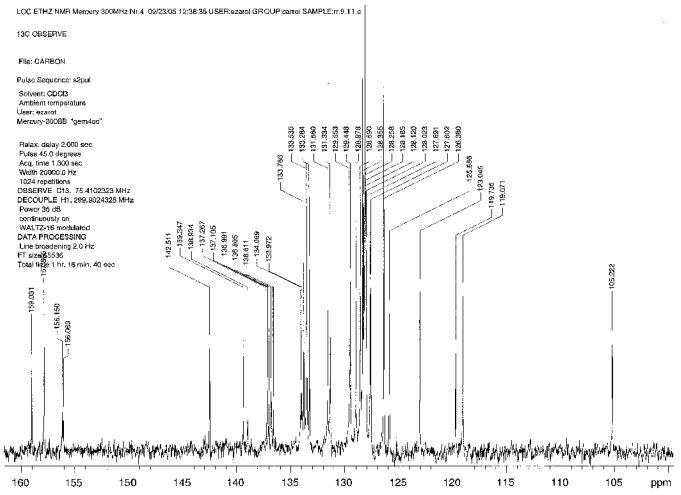


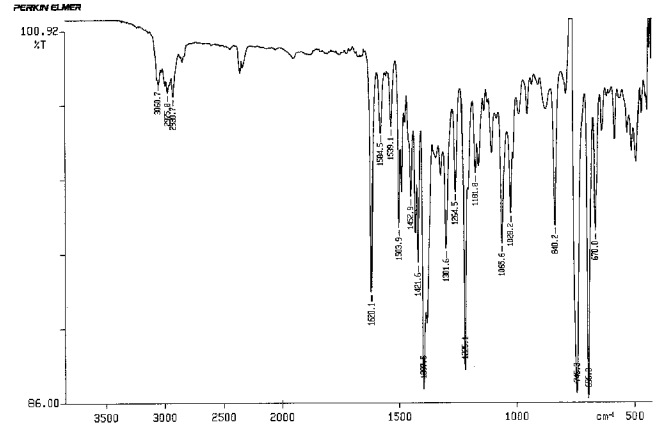


05/03/16 12:37 ezarot
X: 16 scans, 4.0cm-1

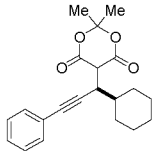


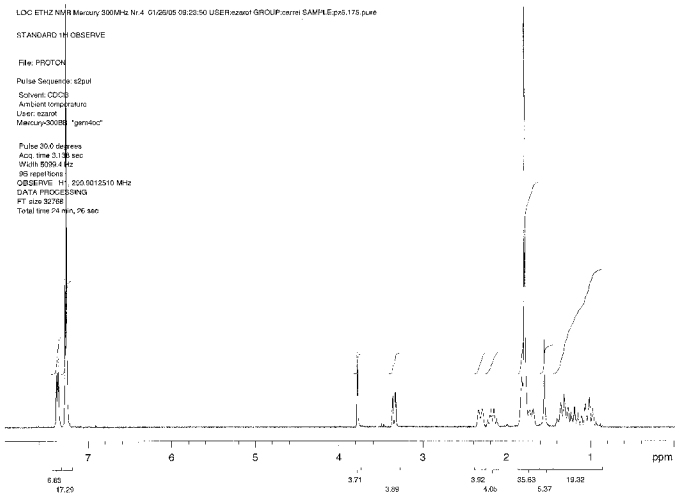


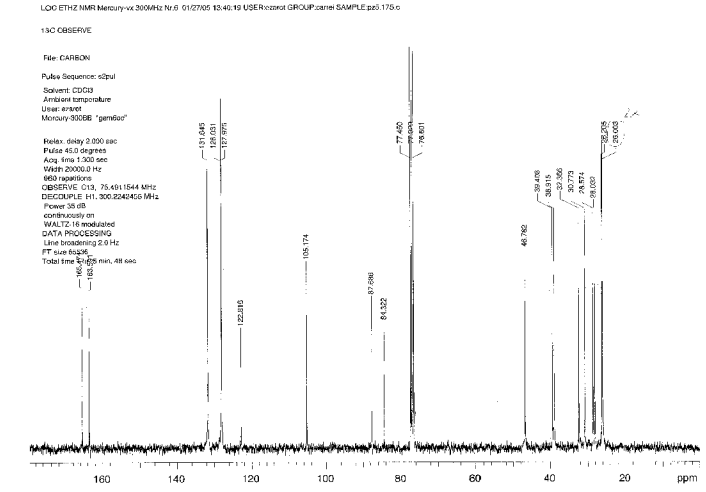


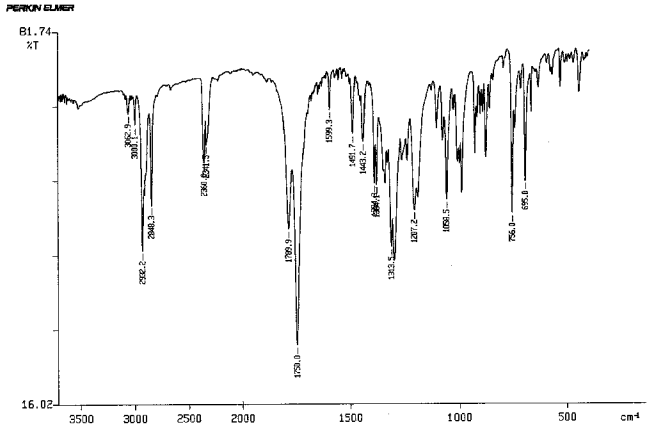


05/12/05 12:53 pablorr9.11.c
X: 16 scans, 4.0cm-1

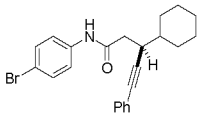


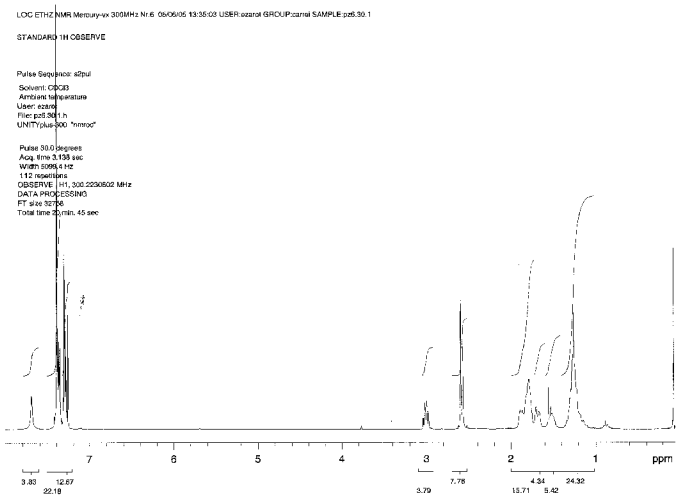


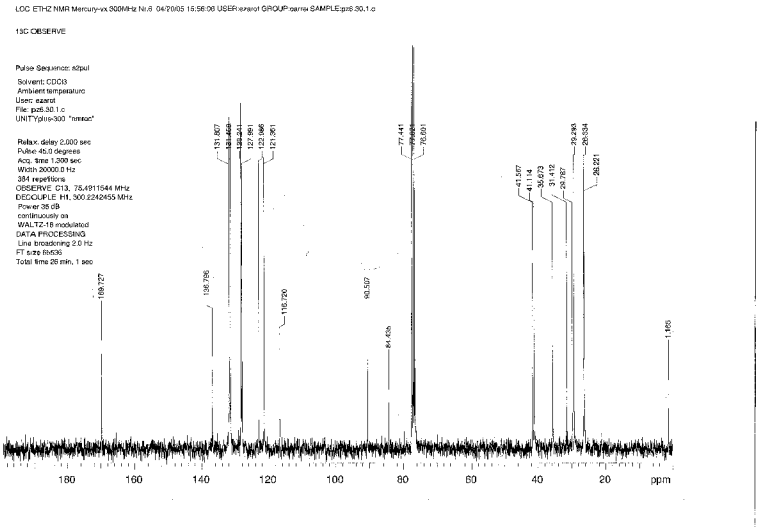


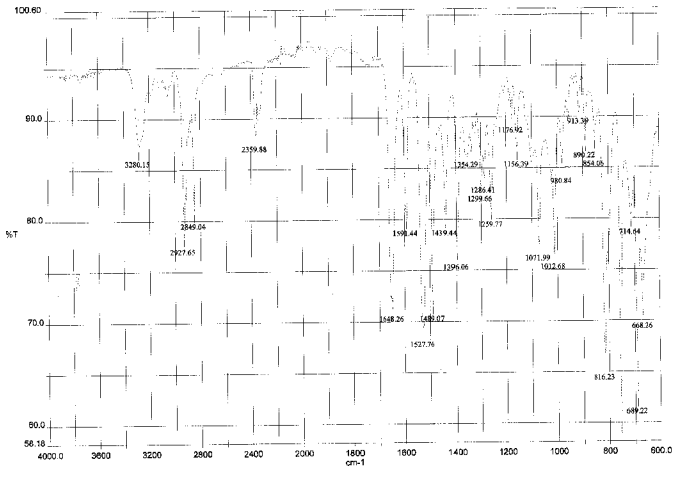


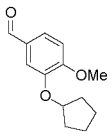
05/01/27 16:06 pablo..
X: 16 scans, 4.0cm-1

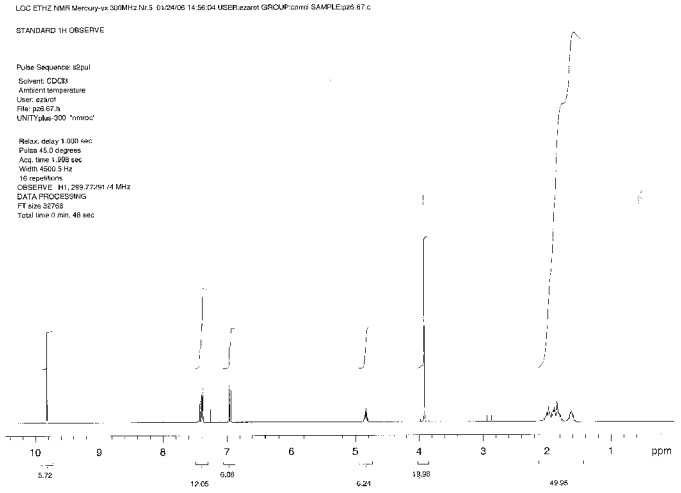

H
N
O
H
Br
Ph

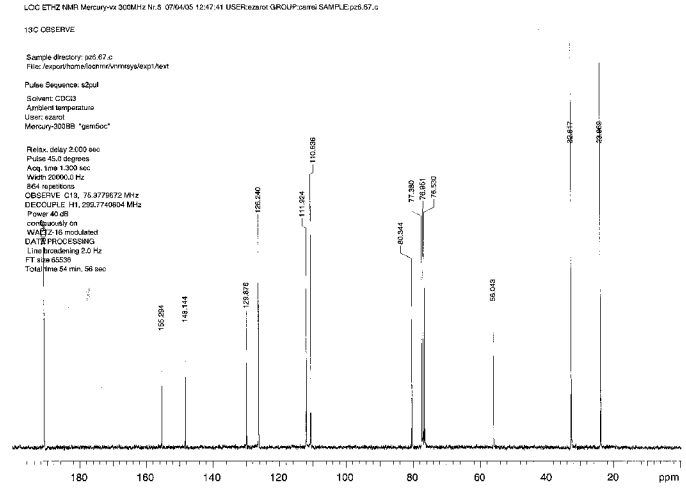

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 05/06/05 13:35:03 USER:ezarol GROUP:camil SAMPLE:pz6.30.1
STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarol
File: pz6.30.1.fi
UNITYplus-300 "nmroc"
Pulse 30.0 degrees
Acq. time 3.135 sec
Width 5099.4 Hz
112 repetitions
OBSERVE H1, 300.2230502 MHz
DATA PROCESSING
FT size 32768
Total time 20 min, 45 sec
7
6
5
4
3
2
1
ppm
3.83
12.67
22.18
3.79
7.78
15.71
4.34
5.42
24.32

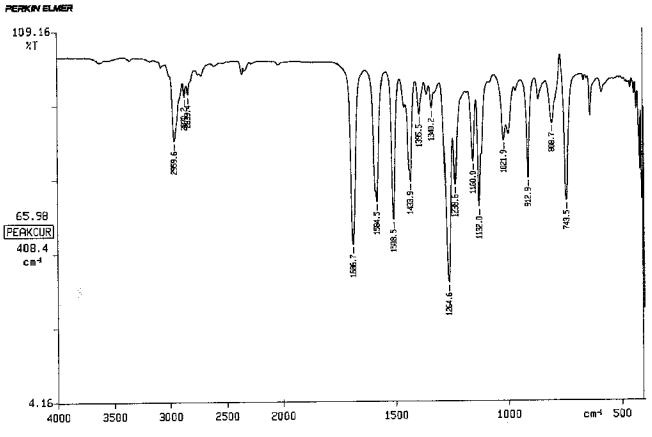

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 04/20/05 16:56:06 USER:ezarol GROUP:camil SAMPLE:pz6.30.1.c
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarol
File: pz6.30.1.c
UNITYplus-300 "nmroc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.200 sec
Width 20000.0 Hz
351 repetitions
OBSERVE C13, 75.4911644 MHz
DECOUPLE H1, 300.2242455 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 26 min, 1 sec
169.727
136.786
131.807
129.241
127.991
121.966
121.761
116.720
83.597
84.405
77.441
76.801
61.567
41.114
30.973
29.787
29.295
26.534
26.221
1.165
180
160
140
120
100
80
60
40
20
ppm


100.60
90.0
80.0
70.0
60.0
56.18
%T
3280.15
2359.58
2927.65
2849.04
1598.44
1439.44
1396.06
1648.26
1481.07
1527.76
1176.92
913.39
1254.29
1156.79
890.22
854.05
980.84
1286.41
1299.65
1256.77
714.64
1071.99
1012.68
668.26
816.23
689.22
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1
s:\pel_data\spectra\student\pz6.30.sc - sample

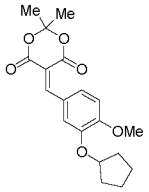


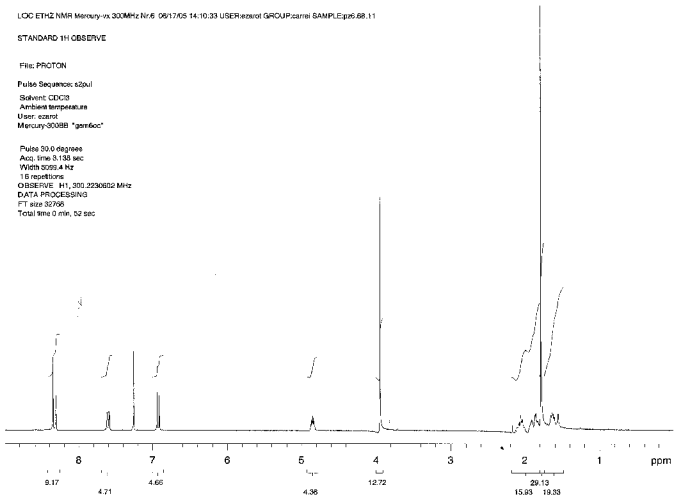


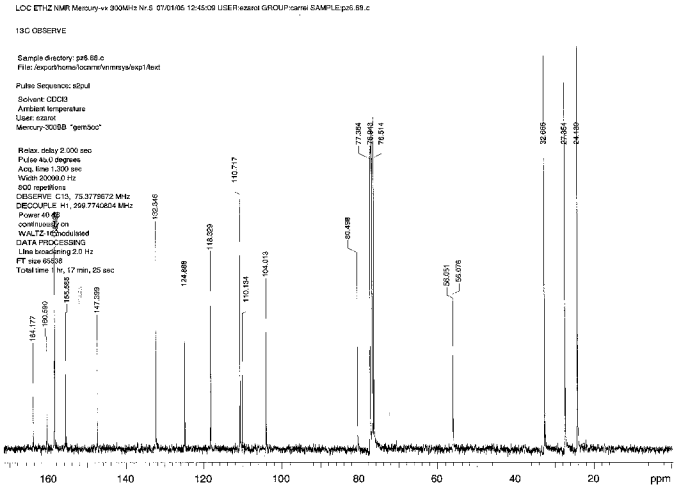


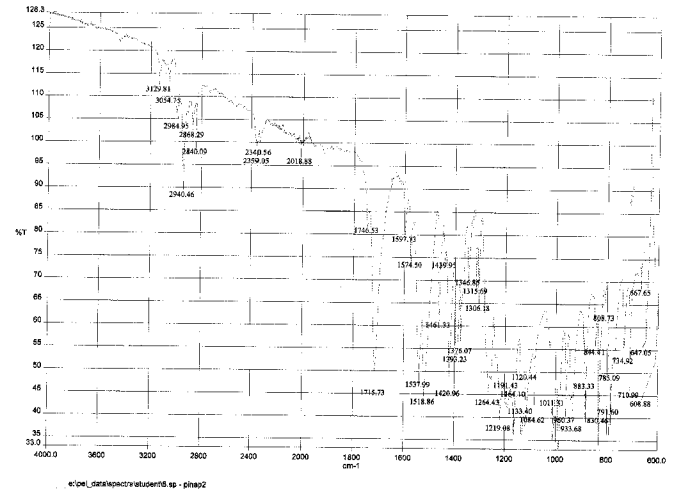


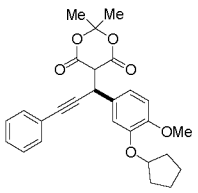
05/07/04 12:38 PABLO
X: 16 scans, 4.0cm-1

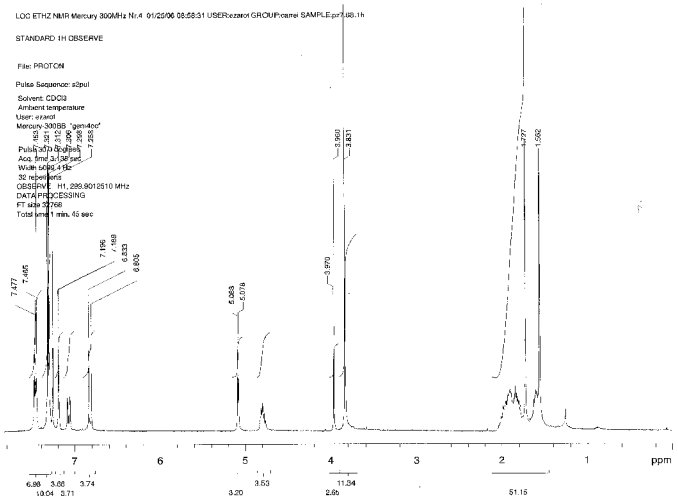

Me
Me
O
O
O
O
OMe
O

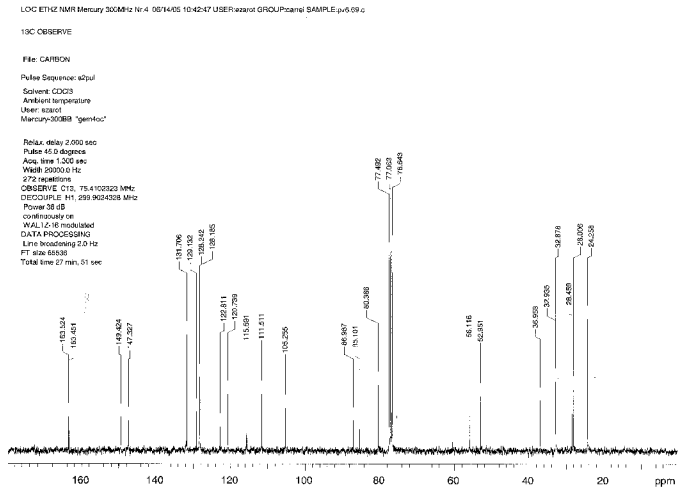

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 06/17/05 14:10:33 USER:ezarot GROUP:camsi SAMPLE:pa5.68.11
STANDARD 1H OBSERVE
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem5oc"
Pulse 30.0 degree
Acq. time 8.138 sec
Width 3099.4 Hz
16 repetitions
OBSERVE H1, 300.2230652 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec
8
7
6
5
4
3
2
1
ppm
9.17
4.71
4.66
4.36
12.72
29.13
15.93
19.33

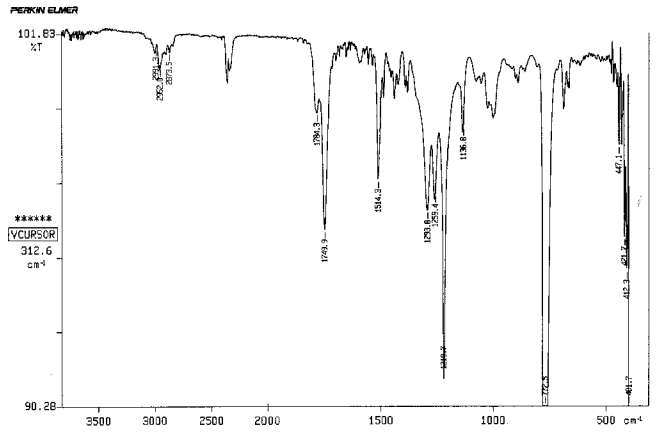

LOC ETHZ NMR Mercury-vx 300MHz Nr.5 07/01/05 12:45:09 USER:ezarot GROUP:camsi SAMPLE:pa5.68.c
13C OBSERVE
Sample directory: pa5.68.c
File: /export/home/ocamr/vnmrsys/exp1/fext
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem5oc"
Relax. delay 2.000 sec
Pulse 40.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
500 repetitions
OBSERVE C13, 75.3779572 MHz
DECOUPLE H1, 299.7740604 MHz
Power 40 dB
continuously on
WALTZ16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 hr, 17 min, 25 sec
164.177
159.580
155.889
147.099
133.946
124.889
118.329
110.717
110.154
104.013
85.498
77.264
76.840
76.514
56.051
55.076
32.695
27.364
24.189
160
140
120
100
80
60
40
20
ppm


%T
128.3
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
33.0
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1
3129.81
3054.75
2964.95
2868.29
2840.09
2340.56
2359.05
2018.88
2940.46
1746.53
1597.33
1574.50
1439.95
1344.85
1315.69
1306.18
1461.33
1376.07
1290.23
1516.73
1537.99
1420.96
1518.86
1264.43
1133.40
1064.62
1219.08
1120.44
1198.43
1164.18
1011.31
983.33
933.68
960.37
910.50
897.46
784.05
710.09
608.88
667.63
808.73
884.81
847.05
734.92
c:\pe_data\epactra\student6.sp - pinap2

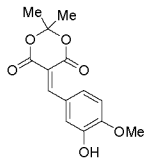


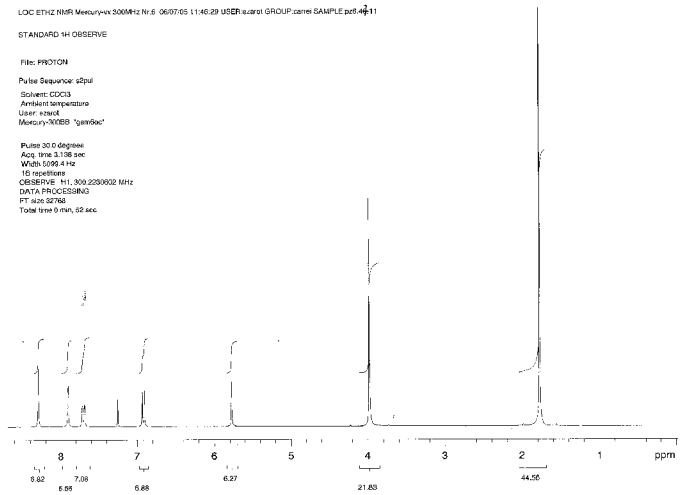


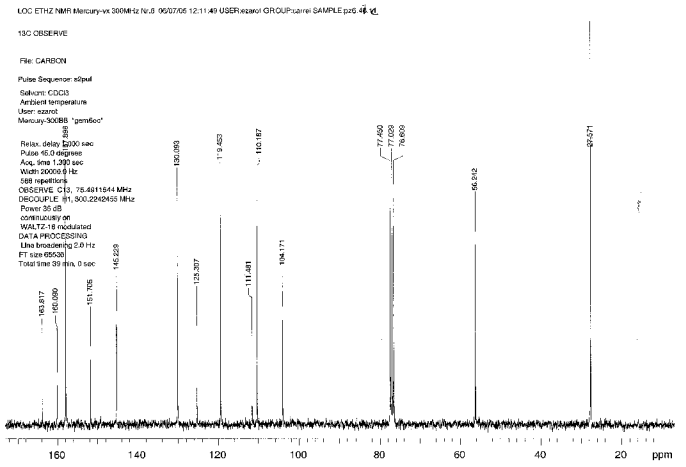


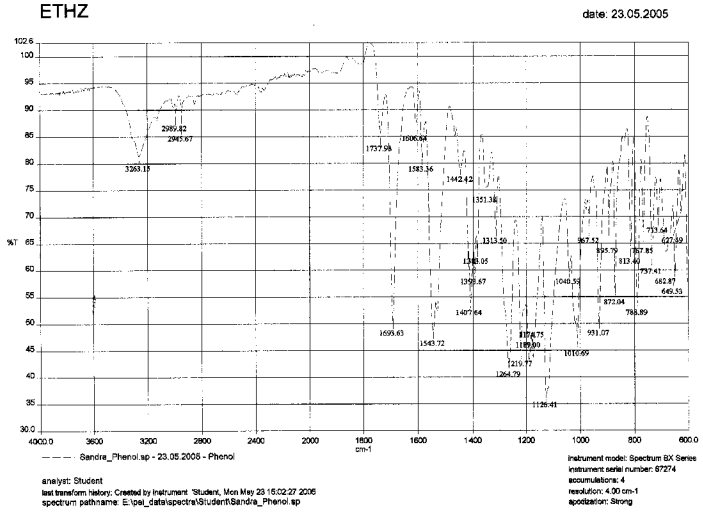


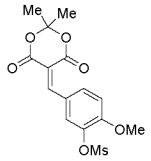
06/01/24 16:21 jc-215
X: 16 scans, 4.0cm-1, flat

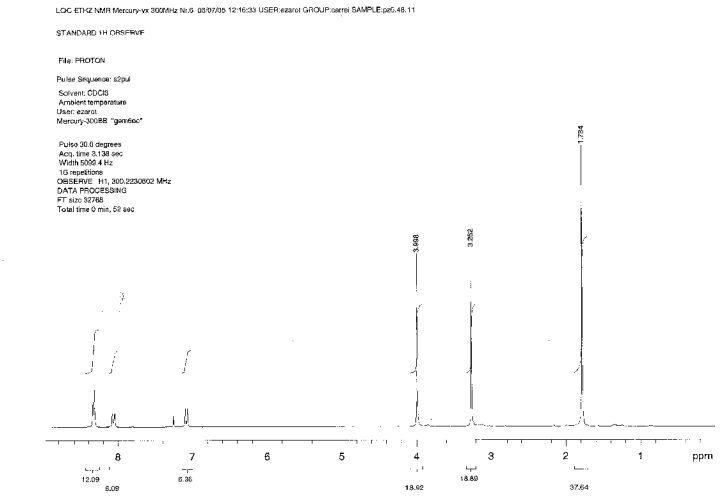

Me
Me
O
O
O
O
OMe
OH

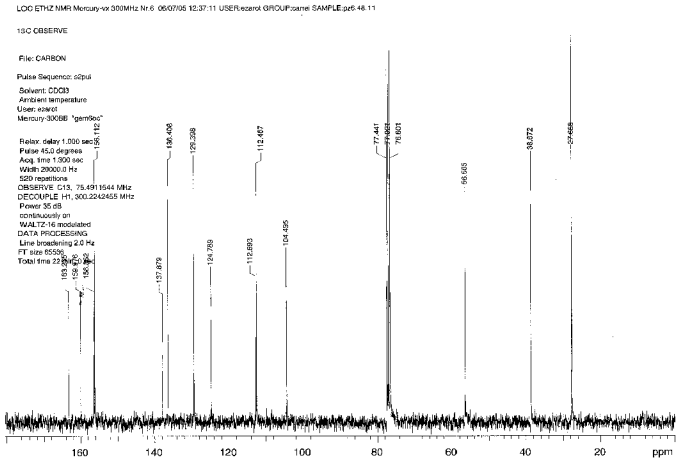

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 06/07/05 11:46:29 USER:ezarot GROUP:zarrel SAMPLE:pz6.46.11
STANDARD 1H OBSERVE
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gsm6oc"
Pulse 30.0 degrees
Acq. time 3.136 sec
Width 5099.4 Hz
16 repetitions
OBSERVE H1, 300.2230602 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec
8
7
6
5
4
3
2
1
ppm
6.82
7.08
6.66
6.88
6.27
21.83
44.56

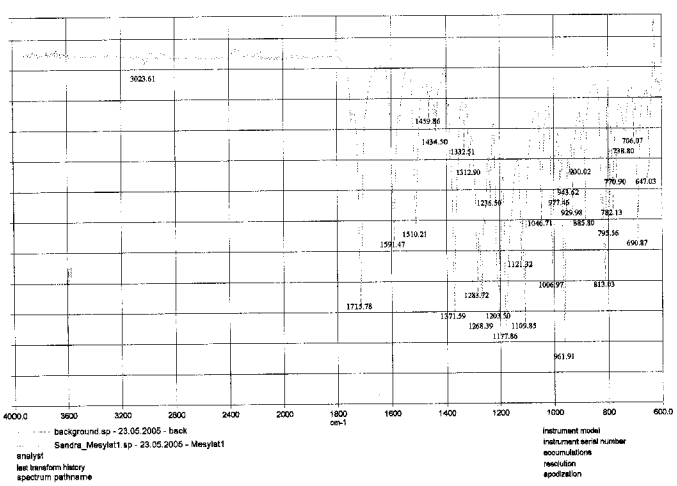

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 06/07/05 12:11:49 USER:ezarot GROUP:zarrel SAMPLE:pz6.46.11
13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gsm6oc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.360 sec
Width 20000.0 Hz
588 repetitions
OBSERVE C13, 75.4811544 MHz
DECOUPLE H1, 300.2242453 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 39 min, 0 sec
163.817
160.099
151.765
145.223
130.093
125.307
119.453
111.481
110.187
104.171
77.450
77.039
76.629
56.242
97.571
160
140
120
100
80
60
40
20
ppm

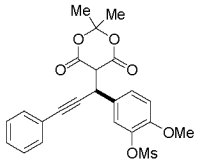

ETHZ
date: 23.05.2005
%T
cm-1
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
2989.42
2945.67
3263.15
1737.98
1606.64
1583.16
1442.42
1351.38
1313.59
1288.05
1268.67
1407.64
1699.63
1543.72
1219.77
1264.79
1126.41
1040.53
1010.69
931.07
872.04
783.89
733.64
627.39
Sandra_Phenol.sp - 23.05.2005 - Phenol
analyst: Student
last transform history: Created by instrument 'Student, Mon May 23 15:02:27 2005
spectrum pathname: E:\pel_data\spectra\Student\Sandra_Phenol.sp
instrument model: Spectrum BX Series
instrument serial number: 67274
accumulations: 4
resolution: 4.00 cm-1
apodization: Strong

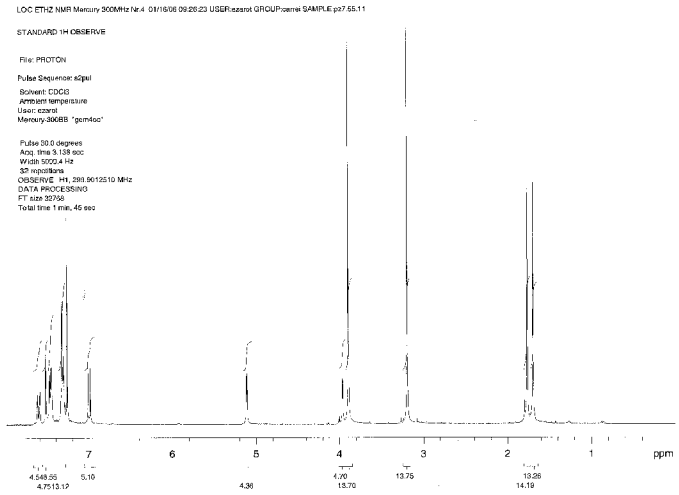

Me
Me
O
O
O
O
OMe
OMs

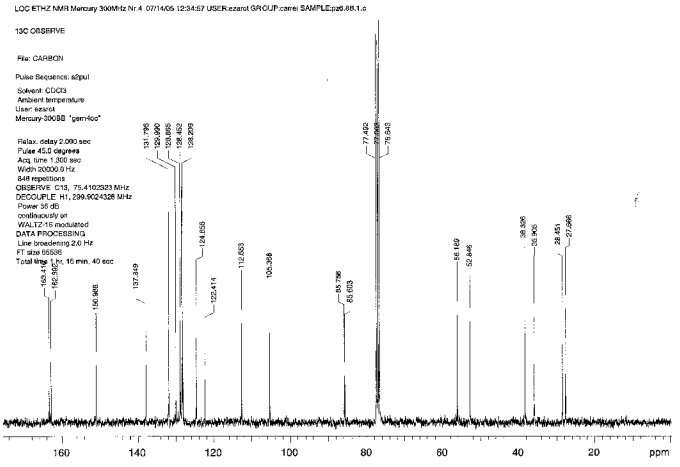

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 06/07/05 12:16:33 USER:ezarot GROUP:csmsl SAMPLE:pc5.48.11
STANDARD 1H OBSERVE
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem5ec"
Pulse 30.0 degrees
Acq. time 3.138 sec
Width 5000.4 Hz
16 repetitions
OBSERVE H1, 300.0230802 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec
1.784
3.666
3.852
8
7
6
5
4
3
2
1
ppm
12.09
6.09
6.36
18.92
18.89
37.64

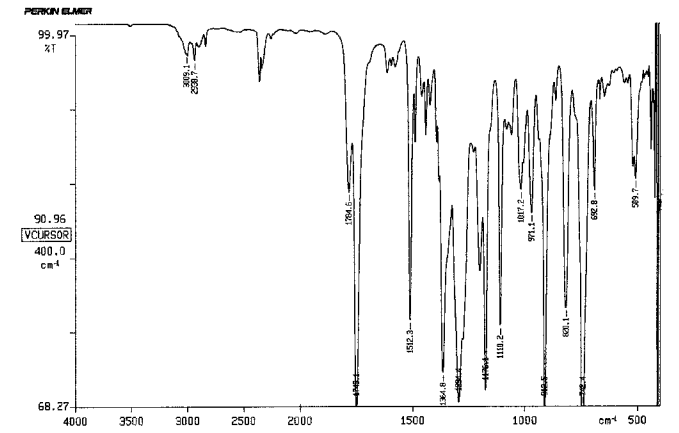

LOC ETHZ NMR Mercury-vx 300MHz Nr.6 06/07/05 12:37:11 USER:ezarot GROUP:csmsl SAMPLE:pc5.48.11
13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem9ec"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.900 sec
Width 29000.0 Hz
520 repetitions
OBSERVE C13, 75.4911644 MHz
DECOUPLE H1, 300.2242455 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 22 min, 52 sec
159.112
158.406
129.298
112.467
77.441
77.025
76.601
66.655
59.872
27.469
157.879
124.769
110.893
104.495
160
140
120
100
80
60
40
20
ppm


ETHZ
date: 23.05.2005
3023.61
1459.86
1434.50
1332.51
1312.90
1236.59
1046.71
1510.21
1591.47
1715.78
1391.59
1268.39
1177.86
1121.32
1283.72
1269.50
1109.85
963.91
706.97
738.80
800.02
770.90
647.03
943.62
977.46
926.98
782.13
885.80
795.56
690.87
1066.97
813.03
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1
background.sp - 23.05.2005 - back
Sandra_Mesylat1.sp - 23.05.2005 - Mesylat1
analyst
last transform history
spectrum pathname
instrument model
instrument serial number
accumulations
resolution
apodization

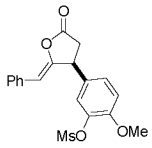


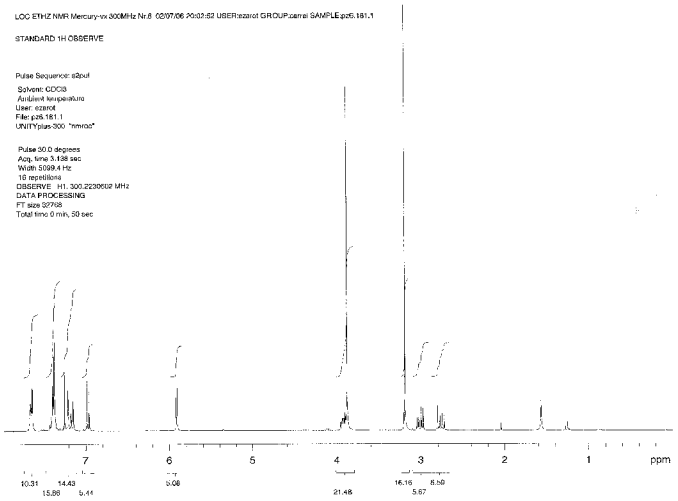


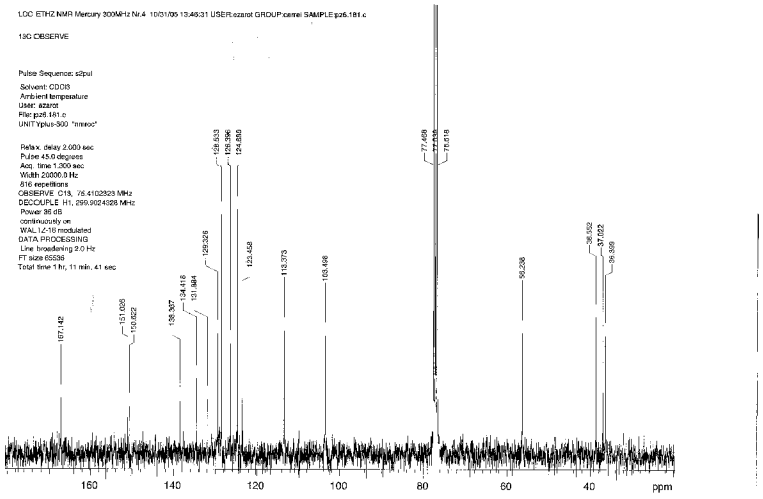


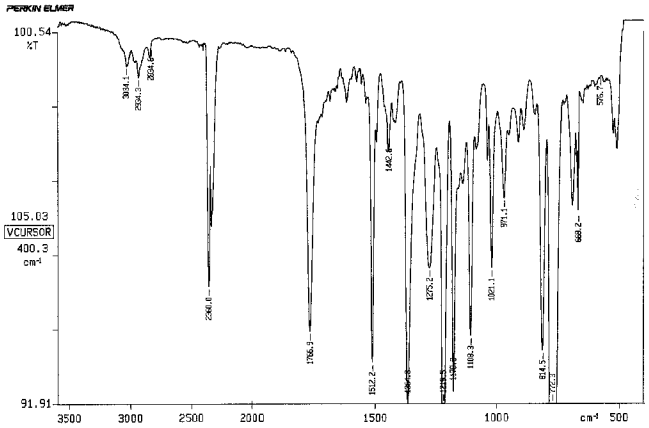


05/07/14 12:01 PABL06.81
X: 16 scans, 4.0cm-1

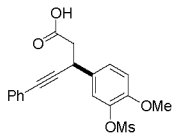


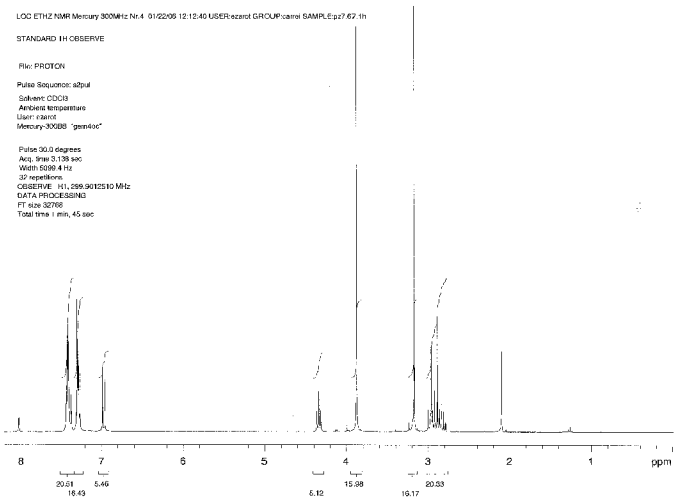


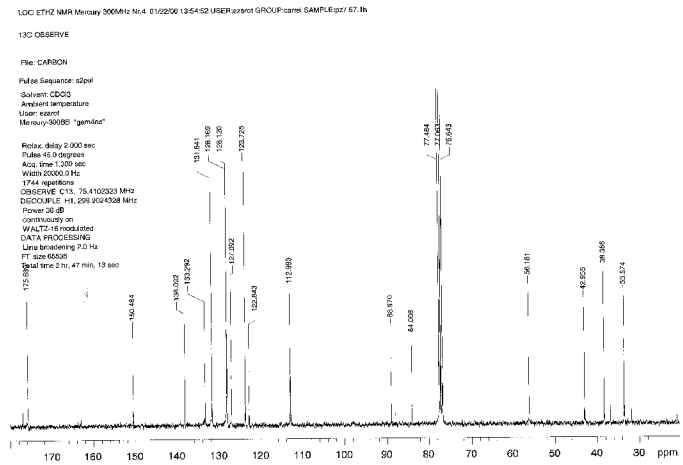


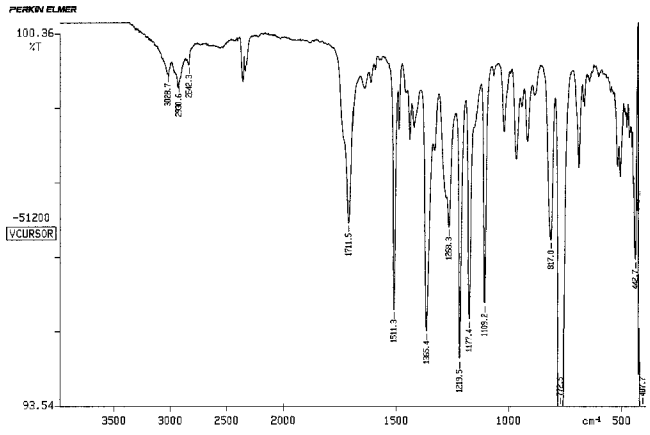


05/11/03 15:10 pablolactoneBACKGSCB
X: 16 scans, 4.0cm-1

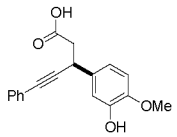


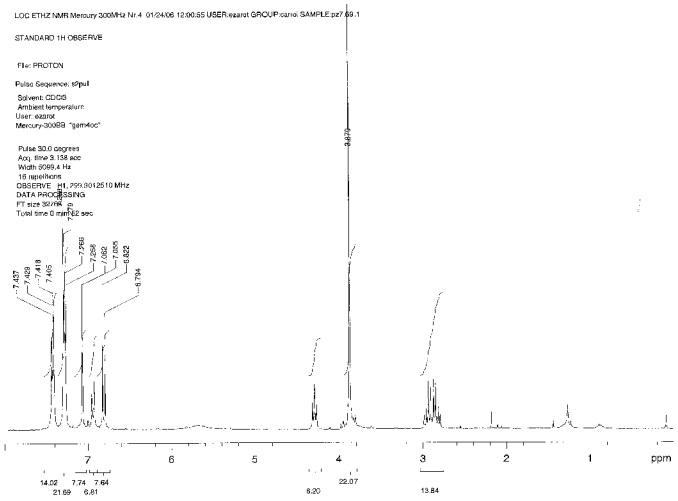


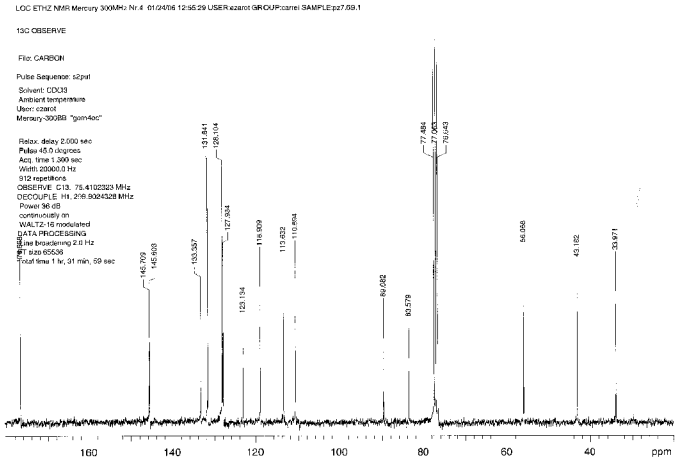


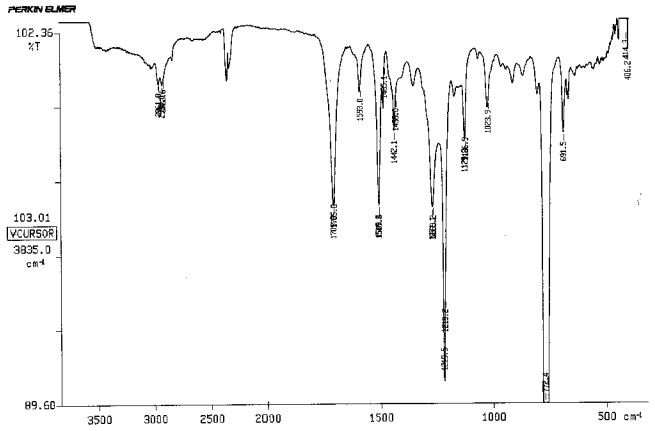


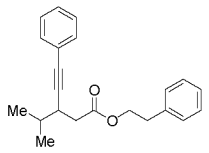
06/01/22 16:01 xin
%: 16 scans, 4.0cm-1

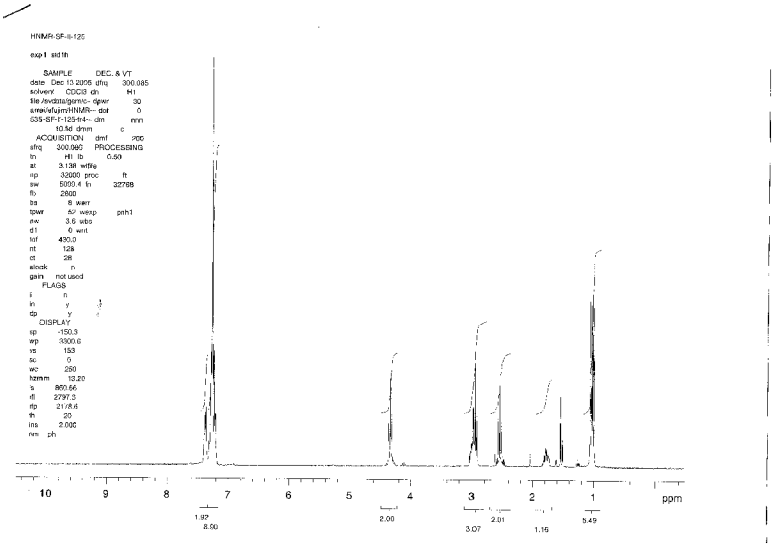

OH
O
Ph
OMe
OH

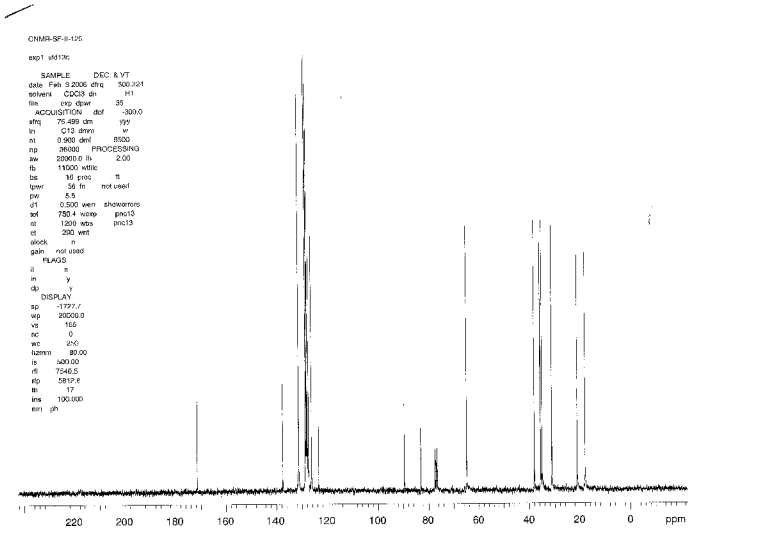

LOC ETHZ NMR Mercury 300MHz Nr.4 01/24/06 12:00:55 USER:ezarot GROUP:carrei SAMPLE:pz7.69.1
STANDARD 1H OBSERVE
File: PROTON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"
Pulse 30.0 degrees
Acq. time 3.138 sec
Width 3099.4 Hz
16 repetitions
OBSERVE H1, 299.8012510 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 52 sec
7.457
7.439
7.418
7.405
7.255
7.252
7.055
6.822
6.794
3.670
14.02
7.74
7.64
21.69
6.81
6.20
22.07
13.84
7
6
5
4
3
2
1
ppm

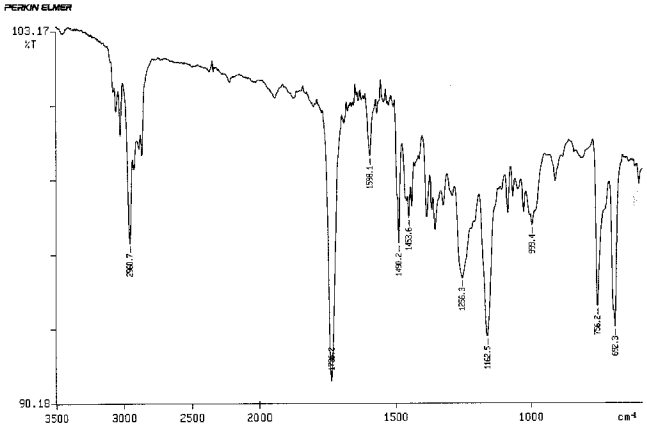

LOC ETHZ NMR Mercury 300MHz Nr.4 01/24/06 12:55:29 USER:ezarot GROUP:carrei SAMPLE:pz7.69.1
13C OBSERVE
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: ezarot
Mercury-300BB "gem4oc"
Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 20000.0 Hz
912 repetitions
OBSERVE C13, 75.4102323 MHz
DECOUPLE H1, 216.9024328 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 hr, 31 min, 59 sec
145.709
145.608
133.587
131.841
128.104
127.884
123.134
118.909
113.632
110.894
89.082
80.579
77.484
77.063
76.453
56.056
43.182
33.671
160
140
120
100
80
60
40
ppm


PERKIN ELMER
102.36
%T
103.01
VCURSOR
3835.0
cm-1
89.60
3500
3000
2500
2000
1500
1000
500 cm-1
06/01/24 16:33 jo-215
X: 16 scans, 4.0cm-1, flat

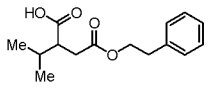


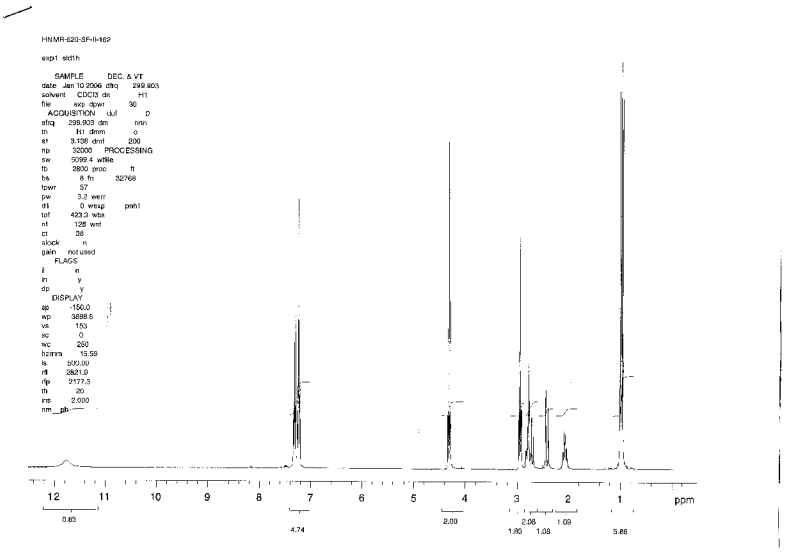


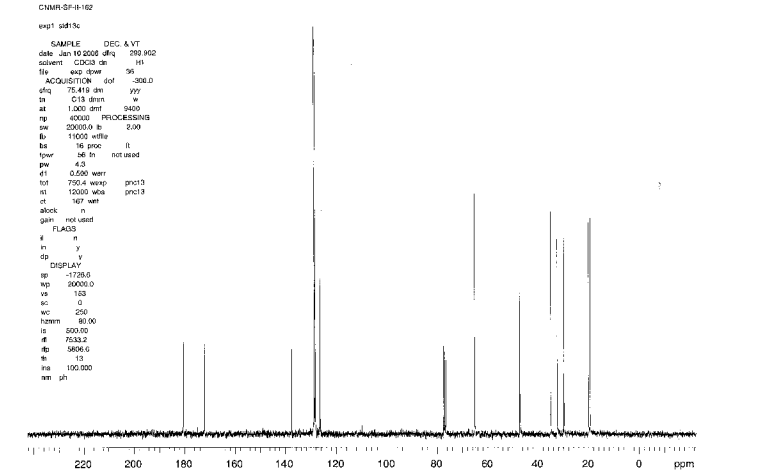


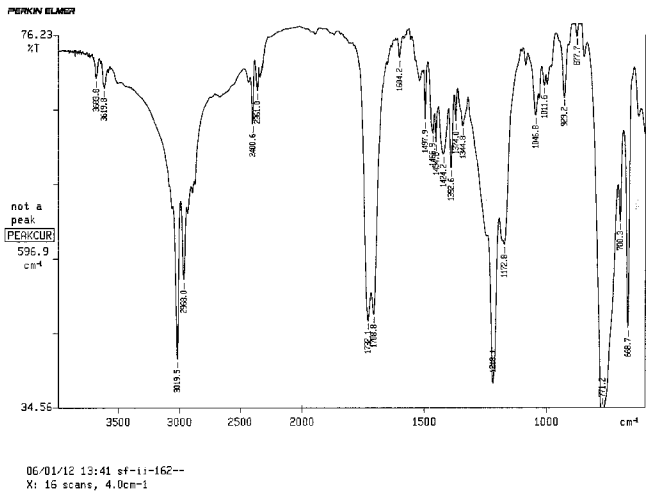


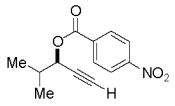
06/01/12 13:57 sf-ii-125
X: 16 scans, 4.0cm-1

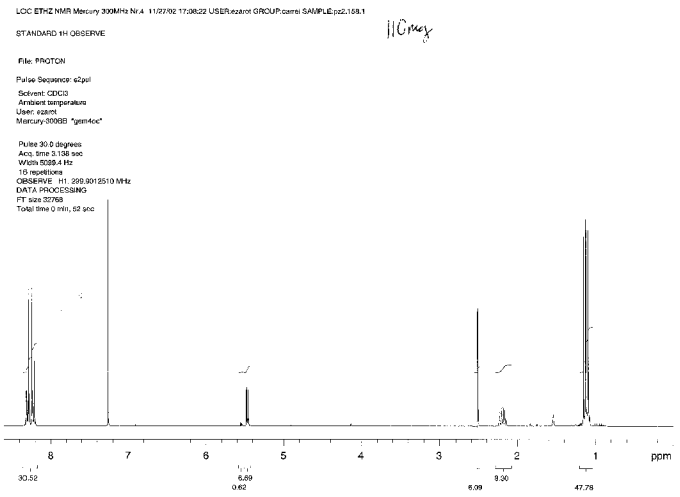


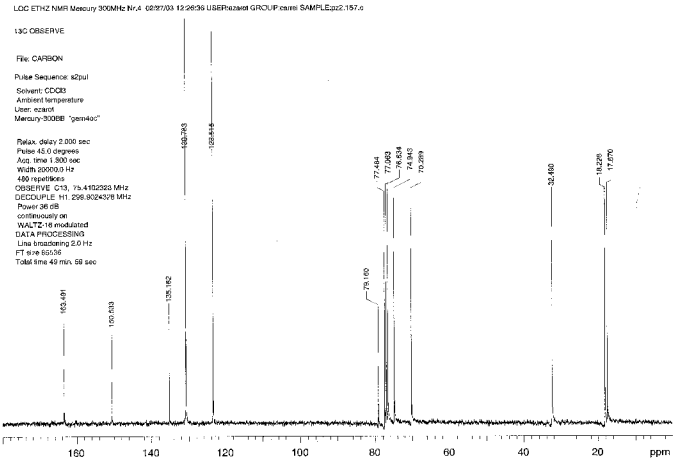

HNMR-620-SF-II-162
exp1 std1h
SAMPLE DEC. & VT
date Jan 10 2006 dfrq 299.803
solvent CDCl3 dn H1
file exp dpwr 90
ACQUISITION dof 0
sfrq 299.803 dm nnn
tn H1 dmm c
at 9.136 dmf 200
np 32000 PROCESSING
sw 5099.4 wtfile
fb 2800 proc lb
bs 8 fn 32768
tpwr 57
pw 3.2 werr
d1 0 wexp pch1
tof 423.3 wba
nt 128 wnt
ct 38
alock n
gain not used
FLAGS
il n
in y
dp y
DISPLAY
sp 150.0
wp 3898.6
vs 153
sc 0
wc 250
hzmm 15.59
is 500.00
rfl 2821.9
rfp 2177.3
th 20
ins 2.000
nm ph
12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.85 4.74 2.00 2.06 1.09 1.89 1.08 5.86

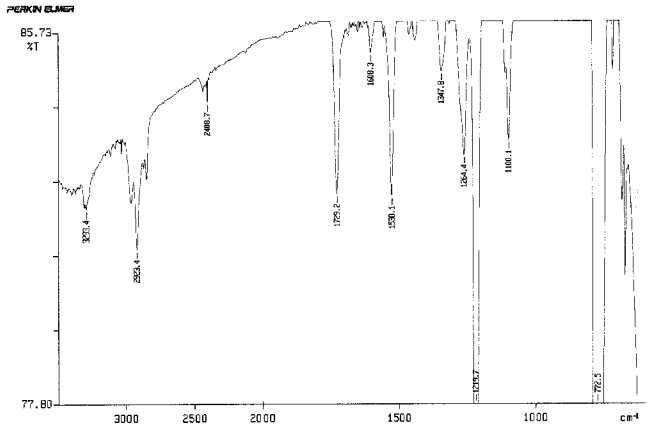

CNMR-SF-II-162
exp1 std13c
SAMPLE DEC. & VT
date Jan 10 2006 dfrq 282.962
solvent CDCl3 dn H1
file exp dpwr 96
ACQUISITION dof -300.0
sfrq 75.419 dm yyy
tn C13 dmm w
at 1.000 dmf 9400
np 40000 PROCESSING
sw 20000.0 lb 2.00
fb 11000 wtfile
bs 16 proc lt
tpwr 56 fn not used
pw 4.3
d1 0.500 werr
tof 750.4 wexp pnc13
nt 12000 wba pnc13
ct 167 wnt
alock n
gain not used
FLAGS
il n
in y
dp y
DISPLAY
sp -1729.6
wp 20000.0
vs 163
sc 0
wc 250
hzmm 80.00
is 500.00
rfl 7533.2
rfp 5806.6
th 13
ins 100.000
nm ph
220 200 180 160 140 120 100 80 60 40 20 0 ppm


PERKIN ELMER
76.23
%T
not a peak
PEAKCUR
596.9
cm-1
34.56
3500 3000 2500 2000 1500 1000 cm-1
06/01/12 13:41 sf-ii-162--
X: 16 scans, 4.0cm-1

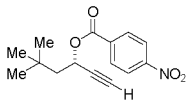


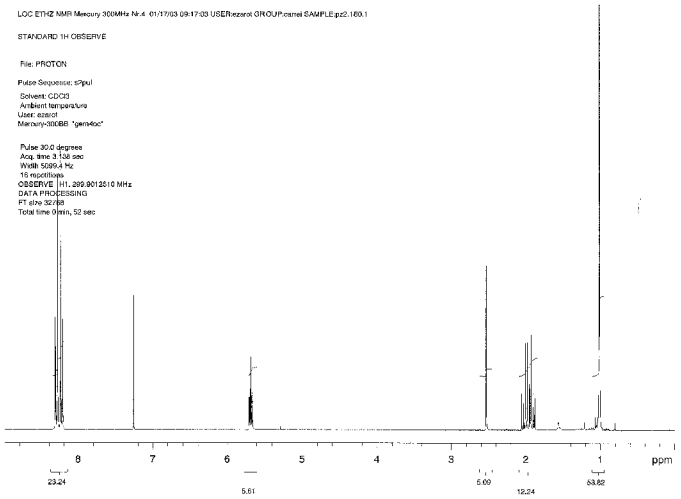


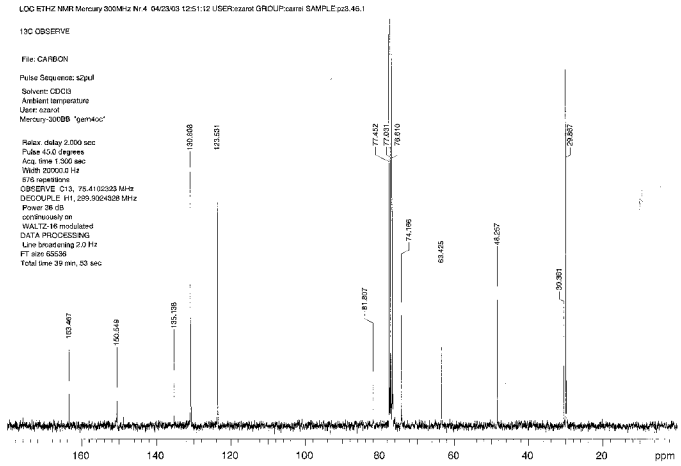


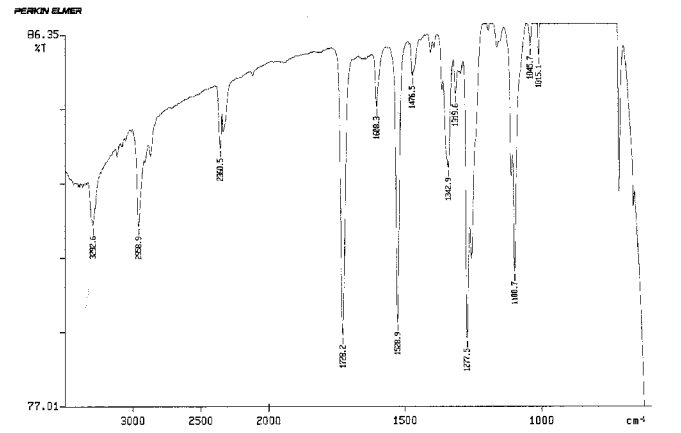


03/07/10 14:04 PABLO 157
X: 16 scans, 4.0cm-1

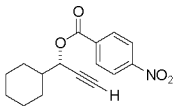


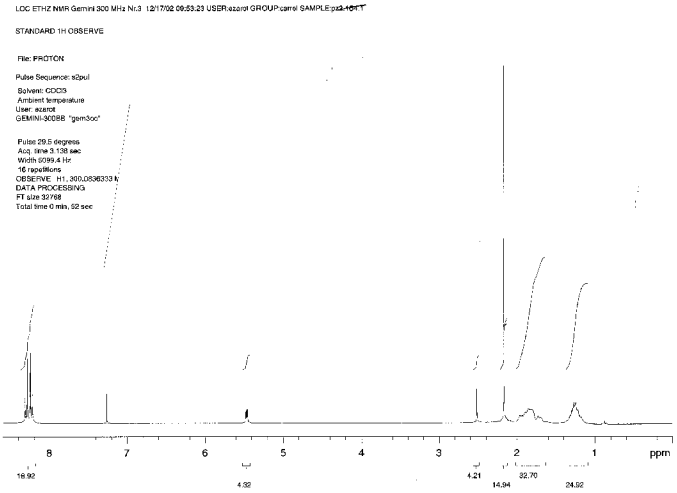


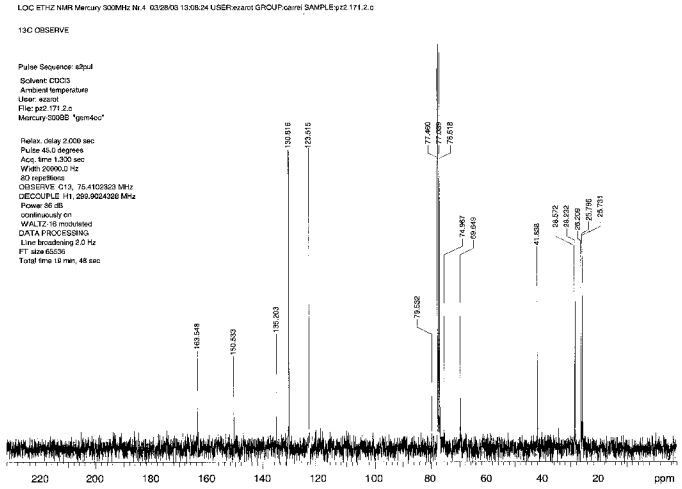


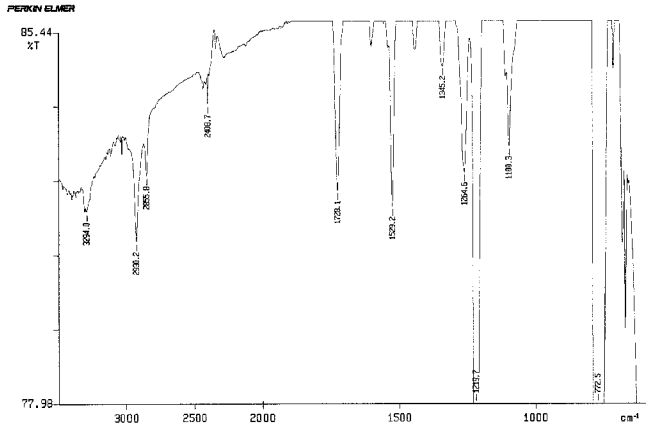


03/07/10 13:36 PABLO 162
X: 16 scans, 4.0cm-1

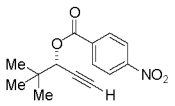


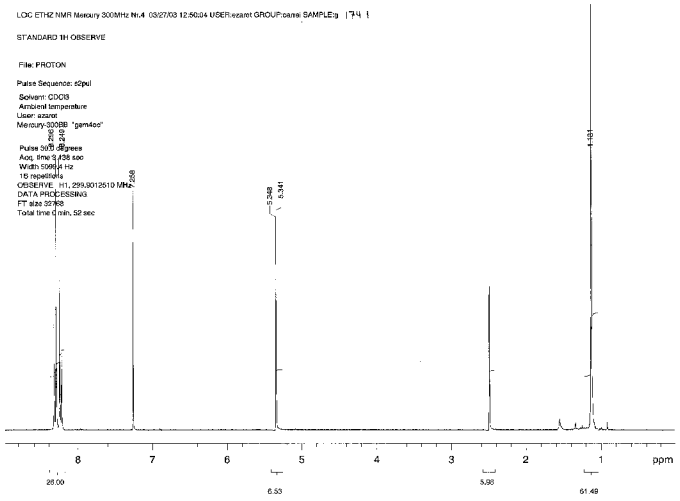


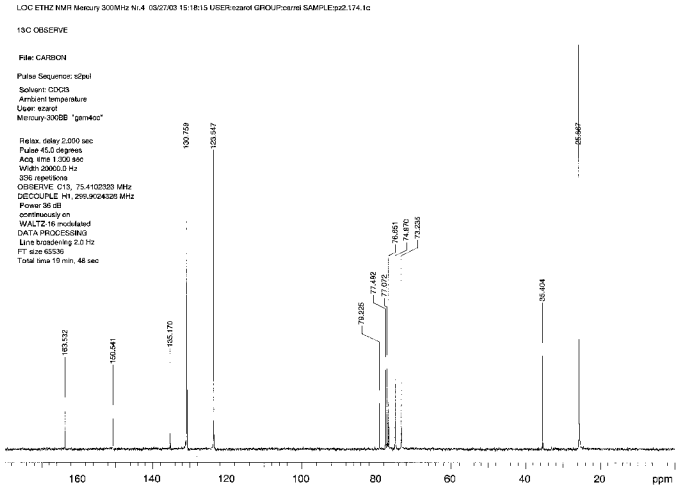


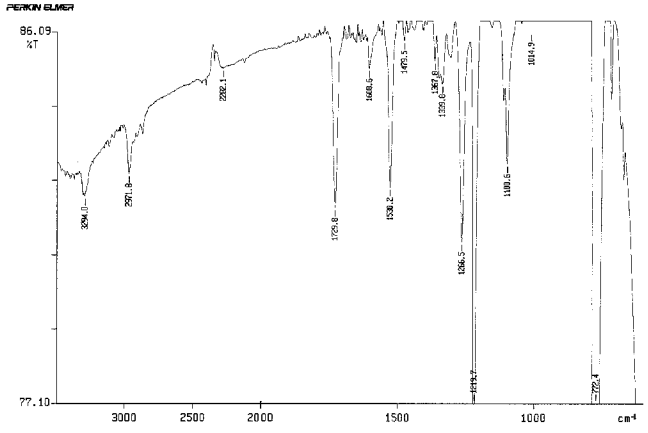


03/07/10 13:52 PABLO 171
X: 16 scans, 4.0cm-1

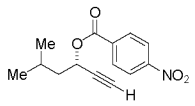


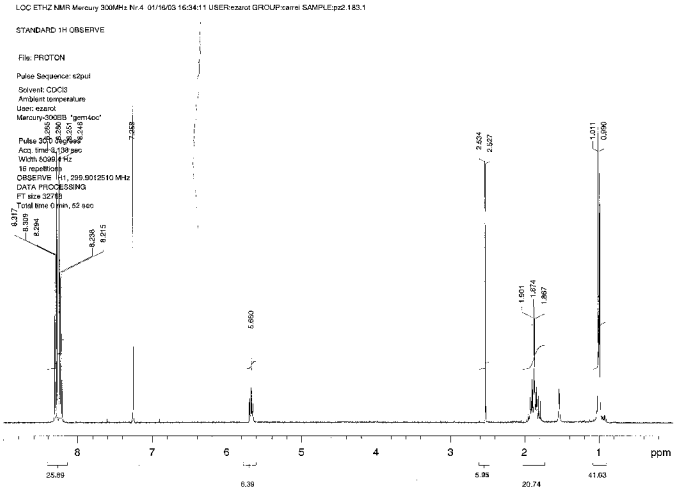


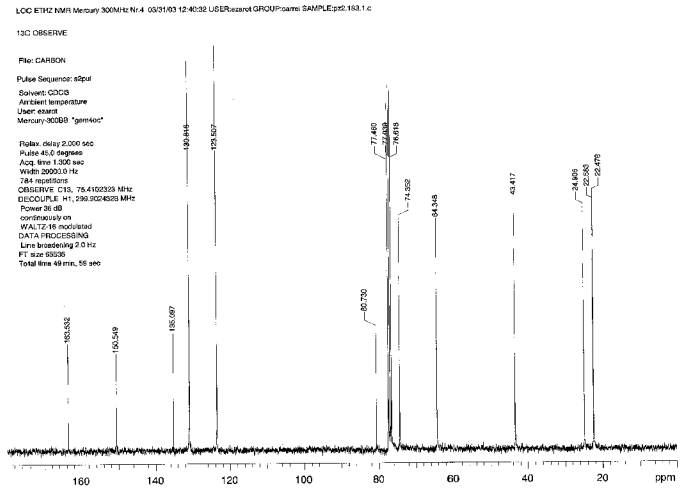


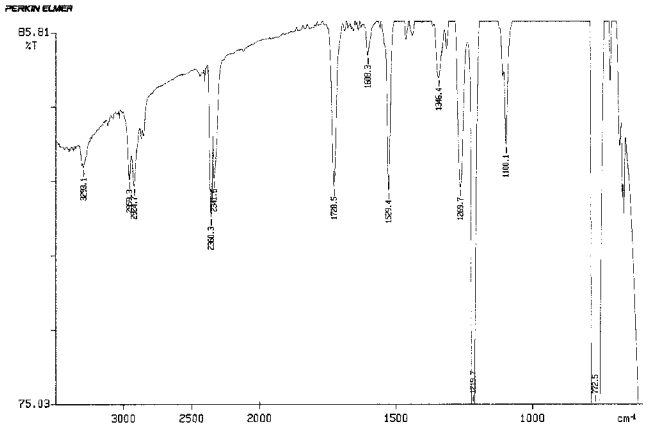


03/07/10 13:48 PABLO 174
X: 16 scans, 4.0cm-1

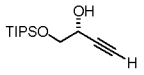


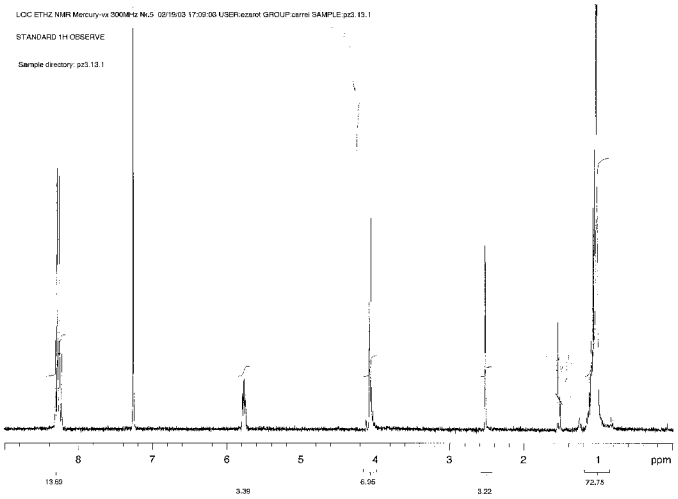


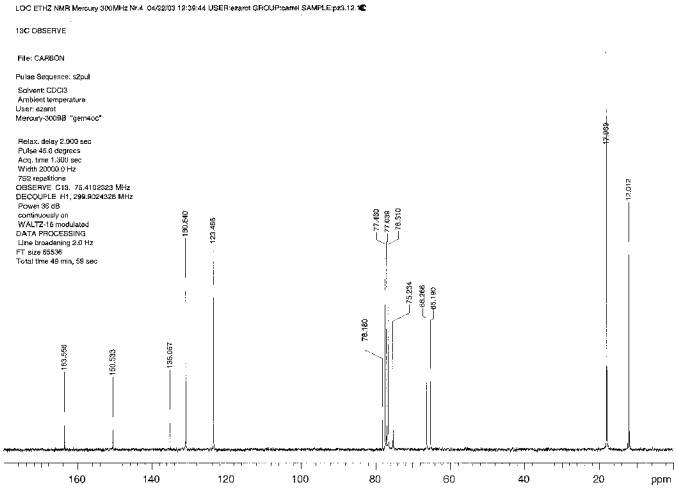


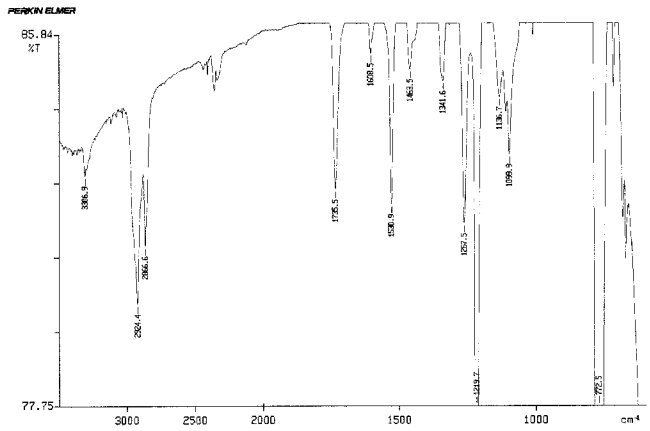


03/07/10 13:59 PABLO 183.1SCANBACKG
X: 16 scans, 4.0cm-1









03/07/10 14:10 PABLO 12.1
X: 16 scans, 4.0cm-1