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THE FRIEDEL-CRAFTS BENZYLATION OF ARENES AND THE SYNTHESIS OF STERICALLY HINDERED AMIDES

A thesis submitted to attain the degree of
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presented by
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Prof. Dr. Karl-Heinz Altmann, co-examiner

2014

Abstract

The Friedel-Crafts alkylation of aromatic compounds is among the oldest reactions for C–C bond formation. The power of this reaction lies in its capability of functionalizing unbiased arenes with unactivated C–H bonds. However, the harsh reaction conditions, the generation of stoichiometric metal waste (e.g. aluminum) and the poor reactivity with electron-poor substrates dramatically limit the use of Friedel-Crafts processes. We wanted to address these limitations and developed the Friedel-Crafts benzylation of activated and deactivated arenes. The key to our successful improvement of the Friedel-Crafts benzylation was the selective activation of a *N*-methyl hydroxamic acid leaving group with BF_3•OEt_2; an activation most likely proceeding in a reversible manner that avoids build up of highly reactive carbocations. This new Friedel-Crafts approach is therefore cleaner, more selective, and more easily executed than traditional methods. The reaction only produces nontoxic, metal-free by-products and the employed Lewis acid is inexpensive and easily handled.

The second part of this Dissertation deals with amide bond synthesis. Amide bonds are routinely formed in every organic laboratory via the coupling reagent-based dehydrative condensation of amines with carboxylic acids. However, the formation of sterically hindered amides is notoriously difficult with this approach and the development of alternative methodologies for the synthesis of these challenging substrates is a longtime unmet need. The addition of Grignard reagents to isocyanates – a reaction developed over 90 years ago by Henry Gilman – provides a facile and robust solution for the synthesis of sterically hindered amides and allows for their preparation with ease and in high yields. The introduction of this isocyanate/Grignard methodology paved the way for the synthesis of many other interesting substance classes, including sterically hindered *N*-acyl, *gem*-disubstituted amino acids and *N,N'*-bisamides.

Zusammenfassung

Die Friedel-Crafts Alkylierung von aromatischen Verbindungen ist eine der ältesten Reaktionen für die Knüpfung von C-C-Bindungen. Das enorme Potenzial dieser Reaktion liegt in ihrer Fähigkeit neutrale Aromaten mit unaktivierten C-H-Bindungen zu funktionalisieren. Die drastischen Reaktionsbedingungen, die Generierung von stöchiometrischem Metallabfall (e.g. Aluminium) und die schlechte Reaktivität mit elektronenarmen Substraten schränkt die Anwendung von Friedel-Crafts-Prozessen jedoch dramatisch ein. Wir wollten uns dieser Einschränkungen annehmen und entwickelten die Friedel-Crafts-Benzylierung von aktivierten und desaktivierten Aromaten. Der Schlüssel zu unserer erfolgreichen Verbesserung der Friedel-Crafts Benzylierung war die selektive Aktivierung einer *N*-methyl Hydroxamsäure-basierten Abgangsgruppe mit BF_3•OEt_2; ein Aktivierungsvorgang, der mit grösster Wahrscheinlichkeit in einer reversible Weise erfolgt und so die Ansammlung hochreaktiver Carbokationen verhindert. Dieser neuartige Friedel-Crafts-Ansatz ist deshalb sauberer, selektiver und einfacher anzuwenden als traditionelle Methoden. Während der Reaktion werden nur nichttoxische, metallfreie Nebenprodukte gebildet und die verwendete Lewissäure ist kostengünstig und einfach zu handhaben.

Im zweiten Teil dieser Dissertation geht es um die Synthese von Amidbindungen. Amidbindungen werden routinemässig in jedem organischen Labor mittels Kupplungsreagenz basierender, dehydrativer Kondensation von Aminen mit Carbonsäuren hergestellt. Die Anwendung dieses Zugangs auf die Synthese von sterisch gehinderten Amiden ist jedoch bekanntermassen schwierig und die Entwicklung alternativer Methoden für die Synthese dieser schwer herzustellenden Substrate ist ein seit langer Zeit ungedeckter Bedarf. Die Addition von Grignard-Reagenzien an Isocyanate, welche vor über 90 Jahren von Henry Gilman entwickelt wurde, liefert eine einfache und robuste Lösung für die Synthese sterisch gehinderter Amide und ermöglicht ihre Darstellung mit Leichtigkeit und in hohen Ausbeuten. Die Einführung dieser Isocyanat-Grignard-Methode ebnete den Weg für die Synthese zahlreicher anderer interessanter Substanzklassen wie sterisch gehinderte *N*-acyl, *gem*-disubstituierte Aminosäuren und *N,N'*-Bisamiden.

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1. G. Schäfer, J. W. Bode, Synthesis of sterically hindered *N*-Acylated Amino Acids from *N*-Carboxyanhydrides, *Org. Lett*. **2014**, *16*, 1526–1529.
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2. G. Schäfer, C. Matthey, J. W. Bode, Facile Synthesis of Sterically Hindered and Electron-Deficient Secondary Amides from Isocyanates, *Angew. Chem*. **2012**, *124*, 9307–9310; *Angew. Chem. Int. Ed.* **2012**, *51*, 9173–9175.
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3. G. Schäfer, J. W. Bode, Friedel-Crafts Benzylation of Activated and Deactivated Arenes, *Angew. Chem*. **2011**, *123*, 11105–1108; *Angew. Chem. Int. Ed.* **2011**, *50*, 10913–10916.
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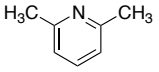
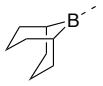
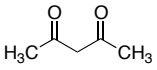
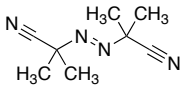
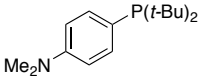
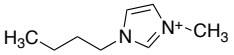
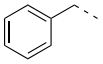
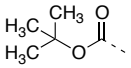
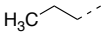
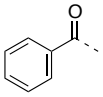
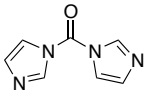
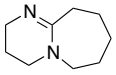
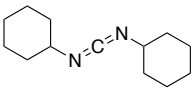
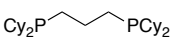
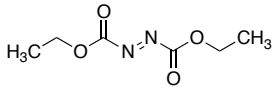
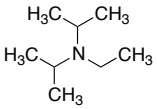
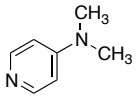
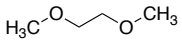
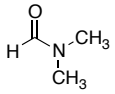
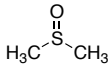
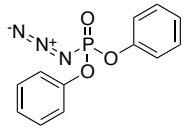
List of Abbreviations – Structures

Abbreviation	Name	Chemical Structure
2,6-Lutidine	2,6-dimethylpyridine	
9-BBN	9-borabicyclo[3.3.1]nonane	
Ac	acetyl	
acac	acetylacetonate	
Ad	adamantyl	
AIBN	azobisisobutyronitrile	
Amphos	4-(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline	
Ar	aryl	any aromatic ring
BMIM	1-butyl-3-methylimidazolium	
Bn	benzyl	
Boc	*tert*-butoxycarbonyl	
Bu	butyl	
Bz	benzoyl	
CDI	1,1'-carbonyldiimidazole	
Cy	cyclohexyl	
DBU	1,8-diazabicycloundec-7-ene	
DCC	*N,N'*-dicyclohexylcarbodiimide	
dcpp	1,3-bis(dicyclohexylphosphino)propane	

DEAD	diethyl diazenedicarboxylate	
DIPEA	*N,N*-diisopropylethylamine	
DMAP	4-dimethylaminopyridine	
DME	1,2-dimethoxyethane	
DMF	*N,N*-dimethylformamide	
DMSO	dimethyl sulfoxide	
DPPA	diphenylphosphoryl azide	
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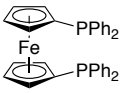
dppf	1,1'-bis(diphenylphosphino)ferrocene	
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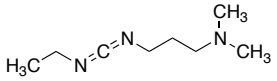
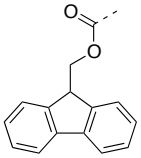
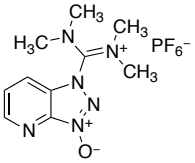
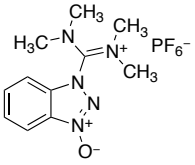
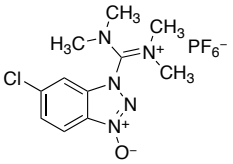
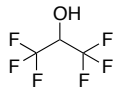
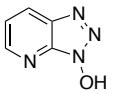
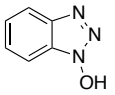
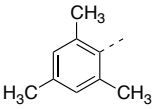
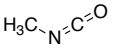
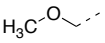
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide	
Et	ethyl	
Fmoc	fluorenylmethyloxycarbonyl	
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate	
HBTU	*N,N,N',N'*-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate	

HCTU	1-[bis(dimethylamino)methylen]-5-chlorobenzotriazolium 3-oxide hexafluorophosphate	
HFIP	hexafluoroisopropanol	
HOAt	1-hydroxy-7-azabenzotriazole	
HOBt	1-hydroxybenzotriazole	
iPr	isopropyl	
Me	methyl	
Mes	mesityl	
MIC	methyl isocyanate	
MOM	methoxy methyl	
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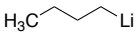
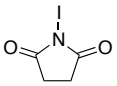
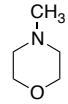
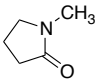
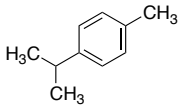
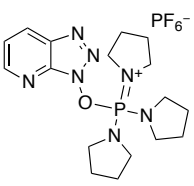
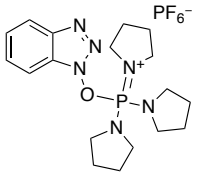
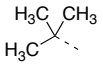
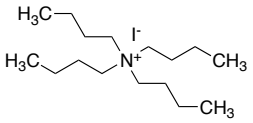
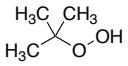
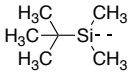
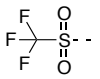
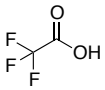
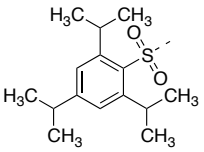
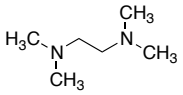
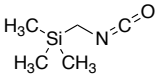
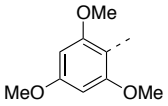
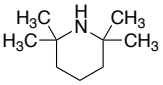
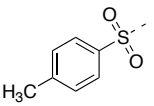
n-BuLi	*n*-butyllithium	
NIS	*N*-iodosuccinimide	
NMM	*N*-methylmorpholine	
NMP	*N*-methyl-2-pyrrolidone	
p-Cymene	1-methyl-4-(1-methylethyl)benzene	
Ph	phenyl	
PyAOP	(3-hydroxy-3H-1,2,3-triazolo[4,5-b]pyridinato-O)tri-1-pyrrolidinyl-phosphorous hexafluorophosphate	

PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate	
t-Bu	*tert*-butyl	
TBAI	tetrabutylammonium iodide	
TBHP	*tert*-butyl hydroperoxide	
TBS	*tert*-butyldimethylsilyl	
Tf	trifluoromethanesulfonyl	
TFA	trifluoroacetic acid	
THF	tetrahydrofuran	
TIPBS	2,4,6-triisopropylbenzenesulfonyl	
TMEDA	*N,N,N',N'*-tetramethylethylenediamine	
TMIC	(isocyanatomethyl)trimethylsilane	
Tmob	2,4,6-trimethoxyphenyl	
TMP	2,2,6,6-tetramethylpiperidine	
TMS	trimethylsilyl	
Ts	4-toluenesulfonyl	

List of Abbreviations – Terms

Abbreviation	Name
[α]	specific optical rotation
^{13}C NMR	carbon-13 nuclear magnetic resonance
^{19}F NMR	fluorine-19 nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
aq	aqueous
Ar-S_E	electrophilic aromatic substitutions
ATR	attenuated total reflectance
br	broad
cacld	calculated
cm^{-1}	SI unit for wavenumber
CMD	concerted cyclometalation/deprotonation
conv	conversion
d	doublet
D	sodium D line (589 nm)
EDG	electron-donating group
ee	enantiomeric excess
EI	electron ionization
eq	equation
equiv	equivalent(s)
ESI	electrospray ionization
et al.	*et alia* (“and others”)
EWG	electron-withdrawing group
FT	Fourier-transform
g	gram
GC	gas chromatography
gem	*geminal*
h	hour(s)
HR	high resolution
Hz	hertz
i	iso
IR	infrared
J	coupling constant

KAHA	ketoacid-hydroxylamine
L	liter
LC	liquid chromatography
LG	leaving group
m	*meta*
M	molar concentration
m	NMR: multiplet; IR: medium
m.p.	melting point
m/z	mass/charge
mg	milligram
MHz	megahertz
min	minute(s)
mL	milliliter
mmol	millimole
mol	mole
mol%	mole percent
MS	mass spectrometry
MW	micro wave
n.d.	not determined
n.r.	no reaction
NCA	*N*-carboxyanhydride
NHC	N-heterocyclic carbene
nm	nanometer
o	*ortho*
°C	degree Celsius
p	*para*
PG	protecting group
pK_a	acid dissociation constant (negative log)
ppm	parts per million
PTLC	preparative thin layer chromatography
q	quartet
quant	quantitative
rt	room temperature
s	NMR: singlet; IR: strong
sat.	saturated

SFC	supercritical fluid chromatography
S_N2	bimolecular nucleophilic substitution
SPPS	solid-phase peptide synthesis
t	triplet
t	*tert*
temp	temperature
TLC	thin layer chromatography
UV	ultraviolet
w	weak
η	hapticity
μ	micro
ν	wavenumber

“I have told you these things, so that in me you may have peace. In this world you will have trouble. But take heart! I have overcome the world.”

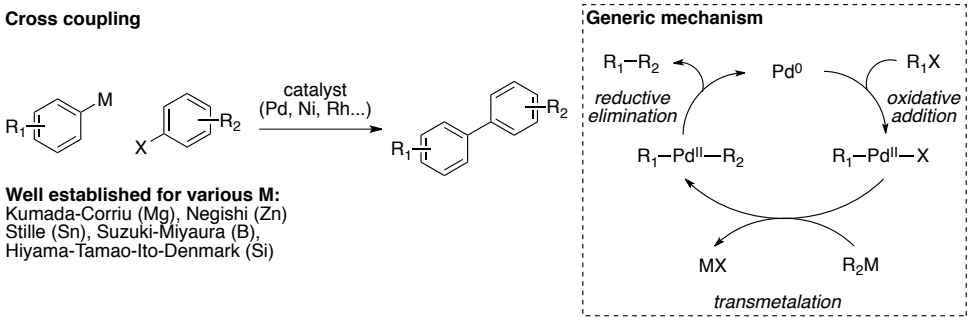
Dedicated to my family

PART I

FRIEDEL-CRAFTS BENZYLATION OF ACTIVATED AND DEACTIVATED ARENES

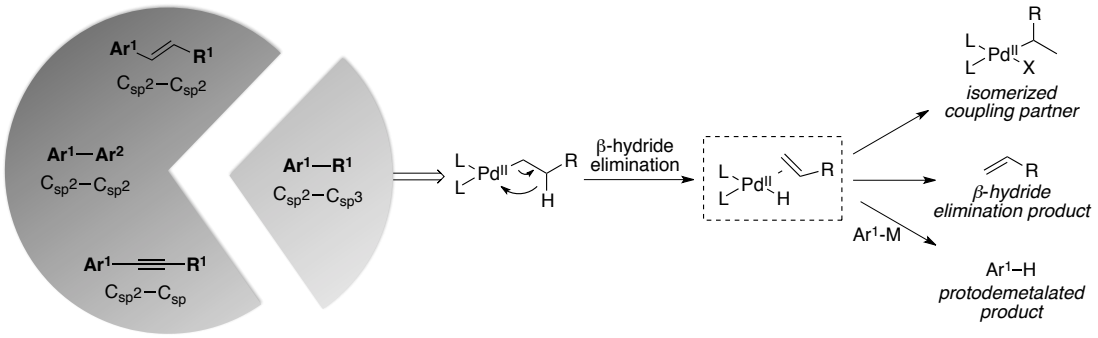
1. Background and Introduction

The last two decades in synthetic organic chemistry were dominated by the rise of transition metal-catalyzed cross-coupling reactions for the formation of C–C bonds from stable, prefunctionalized starting materials.[1] These cross-coupling reactions paved chemists the way for accessing completely new routes to carbon-rich molecules and had a paradigm-changing effect on the discovery and manufacture of pharmaceuticals and agrochemicals (Scheme 1).



Scheme 1: Common cross-coupling reactions and generic mechanism.

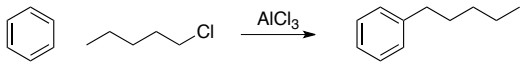
Despite the enormous efficacy of cross-coupling reactions in the formation of C_{sp}^2–C_{sp}^2 (e.g. biaryls, diphenylethenes) and C_{sp}^2–C_{sp} (e.g. phenylacetylenes) bonds, the direct alkylation of arenes and heteroarenes (C_{sp}^2–C_{sp}^3) is a far more delicate task when employing transition-metal catalysts. The reason for this is the affinity of transition metal catalysts towards β-hydride elimination and the sluggish reductive elimination of alkyl groups (Scheme 2).[2]



Scheme 2: Different type of cross-coupling reactions and β-hydride elimination with alkyl groups.

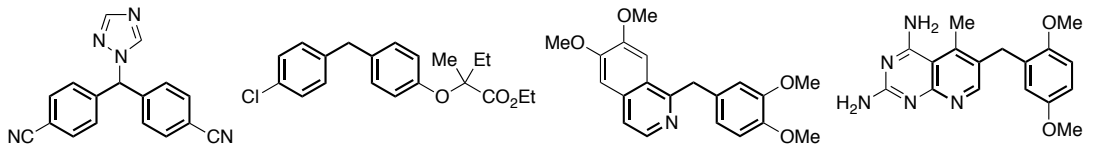
Great efforts have been made to overcome these difficulties in cross-coupling reactions[3] – however, neglecting that there is already a well-established method for the

aliphatic functionalization of arenes: the Friedel-Crafts alkylation. Over 120 years ago, Charles Friedel and James Mason Crafts reported the isolation of pentylbenzene after the reaction of 1-chloropentane and benzene using a stoichiometric amount of a Lewis acid promoter ($AlCl_3$) (eq 1).[4] Over the years many other Lewis acids have been tested in Friedel-Crafts alkylation processes in order to broaden the synthetic utility of this transformation.[5]



(1)

Diarylmethanes can be viewed as an exception, because they can be constructed via cross-coupling and Friedel-Crafts chemistry. They are amenable towards cross-coupling methods, due to the lack of a beta-hydride in the C_{sp}^3-coupling partner. On the other hand, diarylmethanes can be synthesized via Friedel-Crafts processes using benzyl donors (e.g. benzyl halides) and activated arenes as nucleophiles. The research in finding more efficient and sustainable routes to diarylmethanes is still ongoing, because they are key fragments in many pharmaceuticals, agro- and fine chemicals (Figure 1).



Letrozole
aromatase inhibitor

Beclobrate
lipoprotein regulator

Papaverin
against erectile dysfunction

Piritrexim
dihydrofolate redcutase inhibitor

Figure 1: Diarylmethane containing biological active compounds.

2. Formation of Diarylmethanes from Organometallic Reagents

2.1. Suzuki-Miyaura Coupling Reactions

The palladium-catalyzed C–C bond forming reaction between a boronic acid and an organohalide is commonly referred to as the Suzuki-Miyaura reaction. Since its introduction by Suzuki and Miyaura in 1979,[6] the reaction has gone from nearly unknown to one of the most used processes in drug discovery today[7] – owing to its robustness and practicality in the synthesis of substituted biaryls, styrenes and olefins (Figure 2).

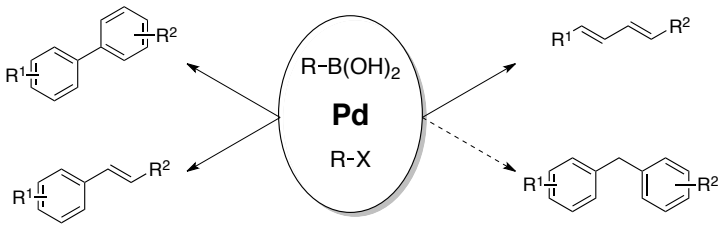
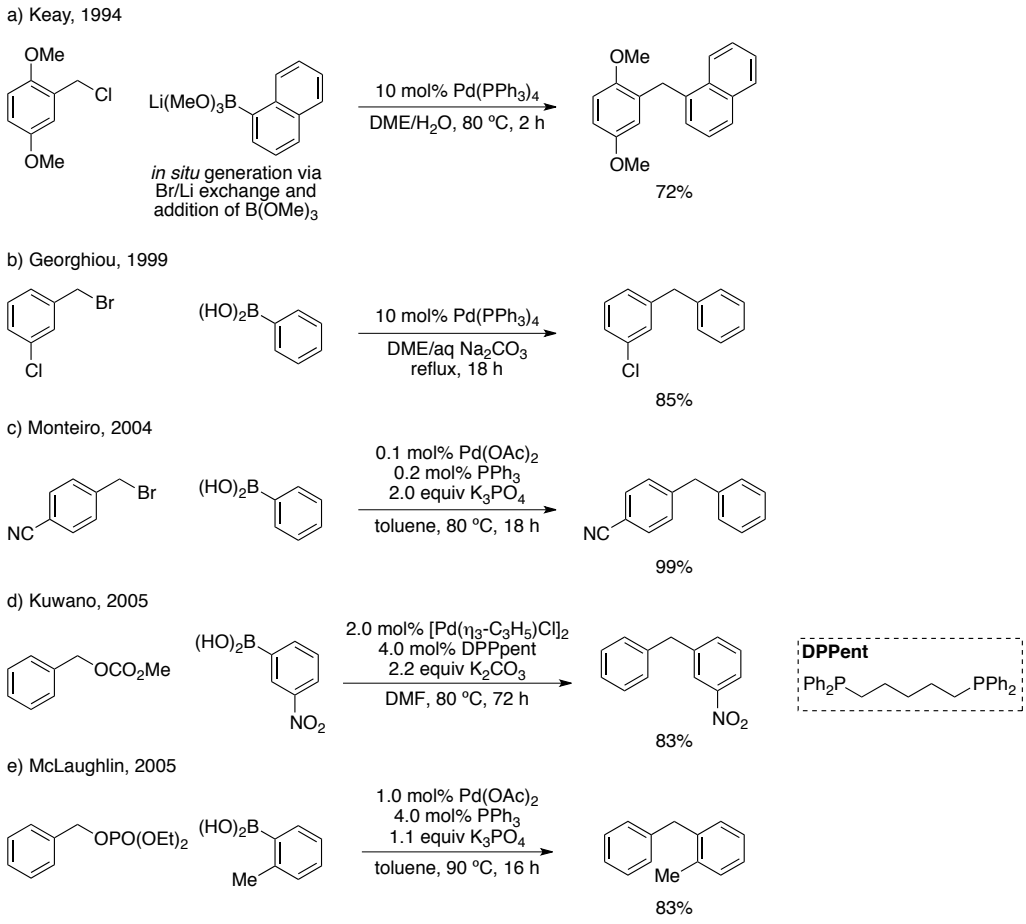


Figure 2: Suzuki-Miyaura coupling.

The development of suitable Suzuki-Miyaura cross-coupling conditions for the synthesis of diarylmethanes was lacking in the beginning, but has gained increased attention over the last 15 years. Two combinations of coupling partners can be envisioned: 1) the reaction between an arylboronic acid and a benzyl halide and 2) the coupling of a benzylboronic acid derivative with an aryl halide. The first combination has gained much more attention and has become a cornerstone in diarylmethane synthesis.

In 1994, Keay *et al*. reported the cross-coupling reaction of *in situ* generated organoboronates with organohalides. In their communication, the coupling of 2,4-dimethoxybenzyl chloride with 1-napthylboronate was described, which is the first successful employment of a benzyl halide under Suzuki-Miyaura-type reaction conditions (Scheme 3a).[8] Nevertheless, the practicality of this approach was limited, because the organoboron species had to be generated every time from scratch via Li/Br exchange at –90 ºC before the actual cross-coupling event. Five years later, Georghiou and coworkers were the first ones to explore the use of shelf-stable phenylboronic acids in the reaction with benzylic bromides (Scheme 3b).[9] Several unsymmetrical diarylmethanes could be obtained in good yields, although under relatively harsh conditions (10 mol% $Pd(PPh_3)_4$ in refluxing DME/aqueous Na_2CO_3 mixture). In 2004, Nobre and Monteiro reported a dramatically improved protocol for

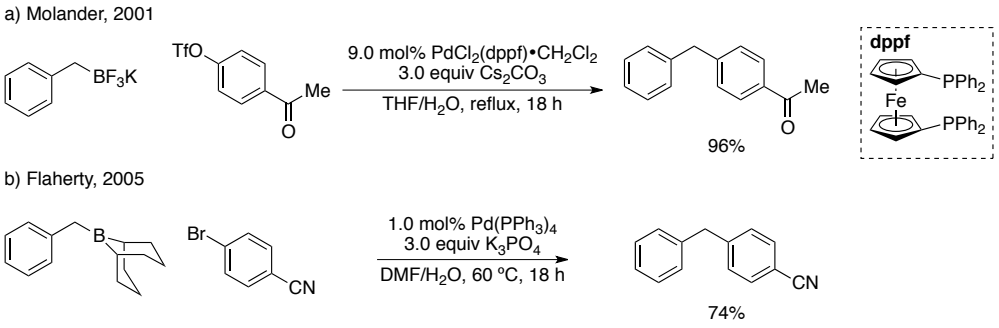
the coupling of benzylic bromides and chlorides with arylboronic acids. Their system allowed for the use of low catalyst loadings (0.1 mol%) under mild reaction conditions and a wide range of diarylmethanes could be synthesized in high yields (Scheme 3c).[10] The introduction of alternative coupling partners such as benzyl carbonates or benzyl phosphates further broadened the synthetic versatility of the Suzuki-Miyaura coupling approach to diarylmethanes (Scheme 3d and 3e).[11]



Scheme 3: Synthesis of diarylmethanes via Suzuki-Miyaura coupling.

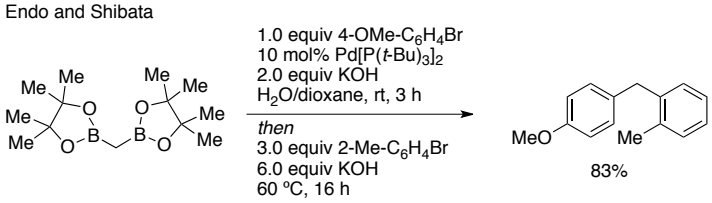
As mentioned before, the reverse case – the use of benzylboronic acids and aryl halides or other aryl coupling partners – is far less common. This can be contributed to the poor commercial availability of benzyl substituted boronic acids. In 2001, Molander *et al.* described the preparation of potassium benzyltrifluoroborates and their application in cross-coupling reactions with aryl trifluoromethanesulfonates (Scheme 4a).[12] A wide range of functional groups was tolerated and the diarylmethane products were isolated in high yields; however, the process employed a high loading of palladium catalyst. Flaherty and coworkers investigated the palladium-catalyzed arylation of (1*s*,5*s*)-9-benzyl-9-borabicyclo[3.3.1]nonane

(*B*-benzyl-9-BBN, Scheme 4b).[13] Despite the successful coupling of the benzylborane to many different aryl bromides, this rather unusual boron species cannot be isolated and has to be used as a THF solution.



Scheme 4: Synthesis of diarylmethanes from benzylboronic acids.

Recently, Shibata and Endo have disclosed the elegant one-pot synthesis of symmetrical and unsymmetrical diarylmethanes from bis[(pinacolato)boryl]methane (Scheme 5).[14] Their procedure circumvents the preparation of the individual benzyl halides and arylboronic acids, and simple aryl halide starting materials can be used. The reaction proceeds via initial formation of a benzylboronate, which subsequently undergoes a Suzuki-Miyaura coupling with a second aryl bromide at elevated temperature. Despite the elegance of this approach, the high price of the diborylmethane reagent (100 mg = 1500 CHF) and the expensive nature of the palladium catalyst make this reaction unsuitable on bigger scale.

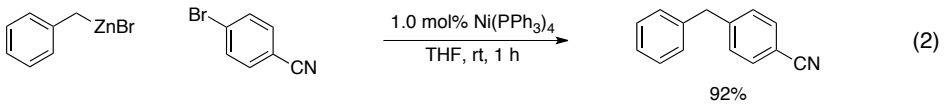


Scheme 5: Suzuki-Miyaura coupling using bis[(pinacolato)boryl]methane.

2.2. Negishi Cross-Coupling Reactions

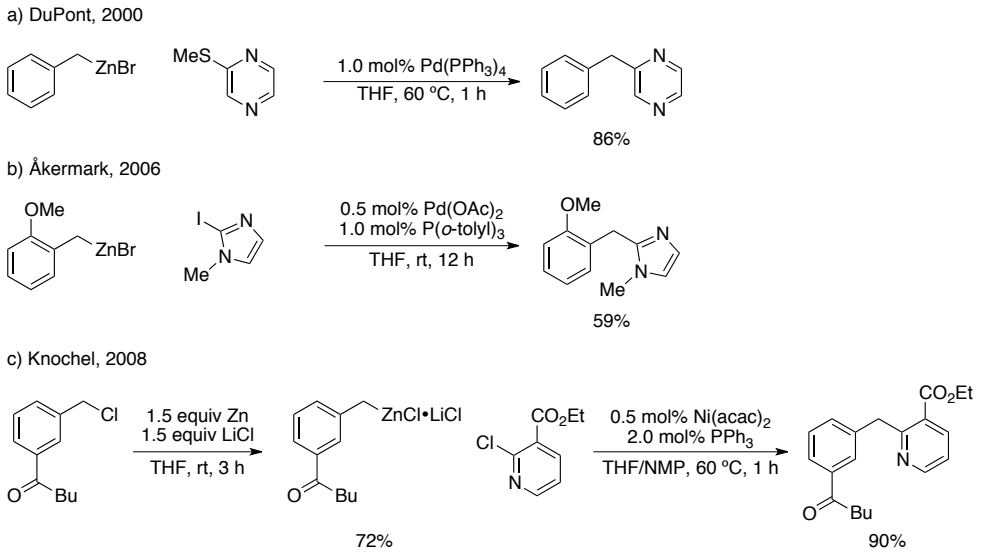
Negishi couplings involve the reaction of organozinc reagents with organohalides under the action of a palladium- or nickel-catalyst to form a new C–C bond. Already in their first publication, Negishi and coworkers described the synthesis of diarylmethanes from

benzylic organozinc reagents and aryl bromides.[15] The reactions proceeded under mild and simple conditions and the corresponding products could be isolated in high yields on an impressive 15 mmol scale (eq 2).



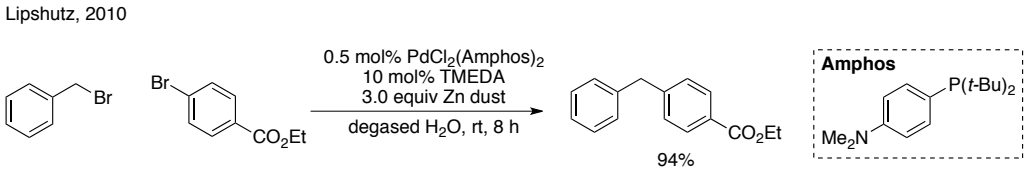
(2)

The seminal work by Negishi *et al*. set the bar high for further improvements. Nevertheless, several other research groups worked on Negishi-type transformations for the synthesis of diarylmethanes, particularly on the expansion of the substrate scope. In 2000, chemists at DuPont developed the cross-coupling reaction of benzylzinc reagents with heterocyclic methylthiol derivatives (Scheme 6a). This Pd-catalyzed methylthio-displacement allowed for the synthesis of a wide range of different heterocyclic diarylmethanes.[16] Using similar reaction conditions, Åkermark and coworkers efficiently coupled 2-iodo-imidazoles to benzylzinc reagents (Scheme 6b).[17] Knochel, one of the pioneers in the field of organozinc chemistry, investigated new routes for the preparation of benzylic zinc reagents.[18] The treatment of benzyl chlorides with Zn dust and LiCl allowed for the streamlined preparation of highly functionalized organometallic reagents, which underwent smooth Ni-catalyzed cross-coupling reactions with aromatic chlorides, bromides and tosylates (Scheme 6c).[19] In the same year, the group of Knochel also reported the Pd-catalyzed Negishi cross-coupling version of benzylic zinc reagent with different heterocyclic arylbromides.[20]



Scheme 6: Synthesis of diarylmethanes via Negishi coupling.

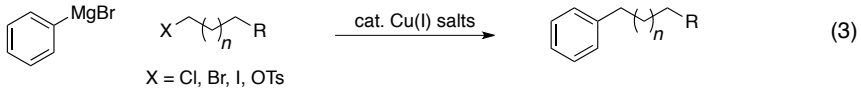
The major disadvantage of the Negishi coupling (e.g. compared to the Suzuki-Miyaura reaction) is that organozinc reagents are not commercially available and have to be prepared in a separate step. Lipshutz and coworkers found a practical solution that renders the preparation of the organometallic reagent unnecessary (Scheme 7). In their approach, two organic halides could be directly coupled, using palladium-catalysis and stoichiometric amount of Zn dust. Even more impressively, the reaction was performed in water at room temperature.[21]



Scheme 7: Synthesis of diarylmethanes via Negishi coupling.

2.3. Synthesis of Diarylmethanes from Grignard Reagents

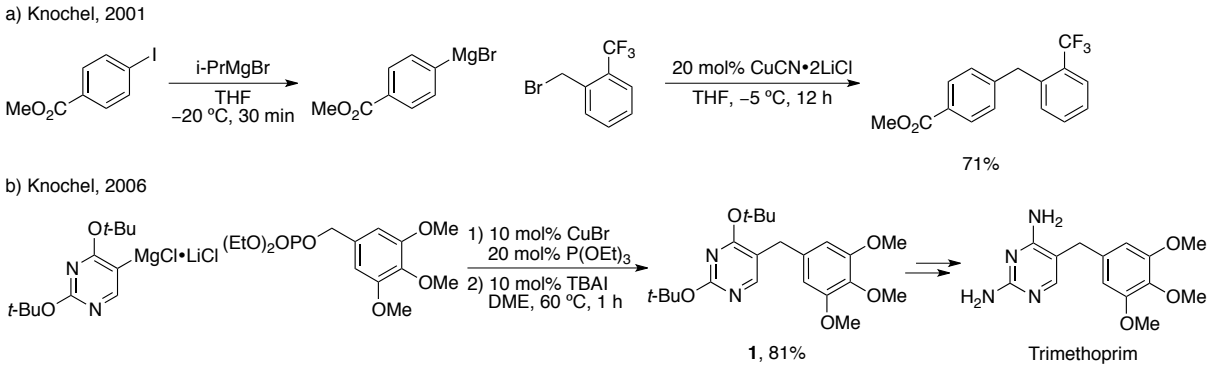
The sluggishness of Grignard reagents in S_N2-type reactions with alkyl halides is well documented. Already in the early 1970s, several research groups worked on rendering this synthetic transformation possible. Normant, Schlosser and others found that the addition of copper salts catalyzed the nucleophilic displacement of alkyl halides with Grignard reagents (eq 3).[22] This approach was also used in the synthesis of diarylmethanes by employing benzyl halides – however, the synthetic value was rather small, because at that time only unfunctionalized Grignard reagents were accessible.



(3)

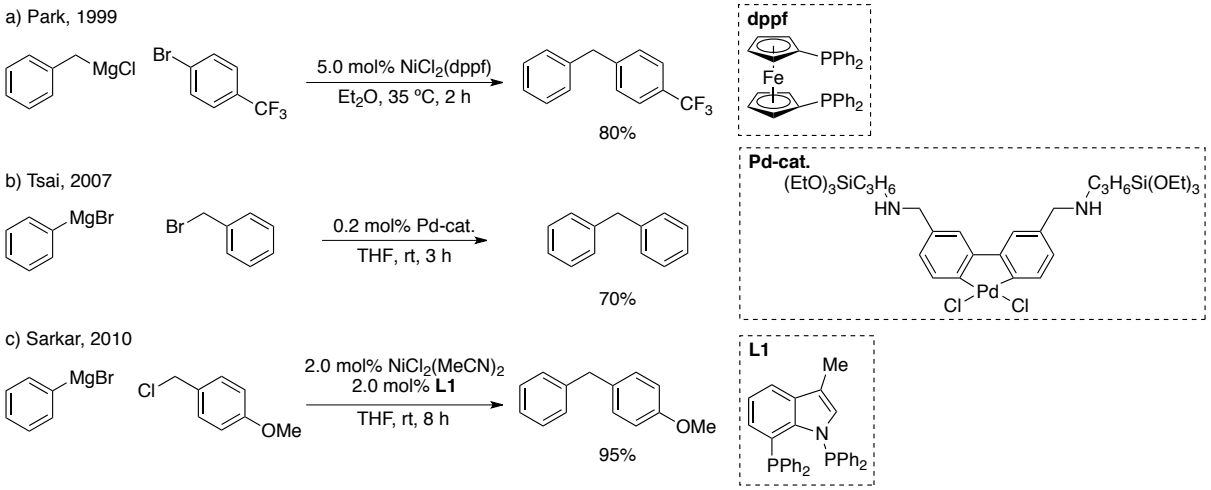
Between 2000–2006, Knochel introduced several new synthetic routes to Grignard reagents bearing sensitive functional groups including esters, nitro, aldehydes or nitriles.[23] These reports resulted in an increased attention of using organomagnesium reagents in copper-catalyzed transformations. Not surprisingly, Knochel was the first to report the Cu-catalyzed synthesis of diarylmethanes from highly functionalized Grignard reagents, prepared at low temperature via Mg/I exchange, and benzylic bromides (Scheme 8a).[24] The same research group later introduced an improved protocol using benzylic phosphates

instead of bromides. Several heterocyclic diarylmethanes could be prepared with ease; including pyrimidine derivative **1**, a valuable precursor to the bacteriostatic antibiotic trimethoprim (Scheme 8b).[25]



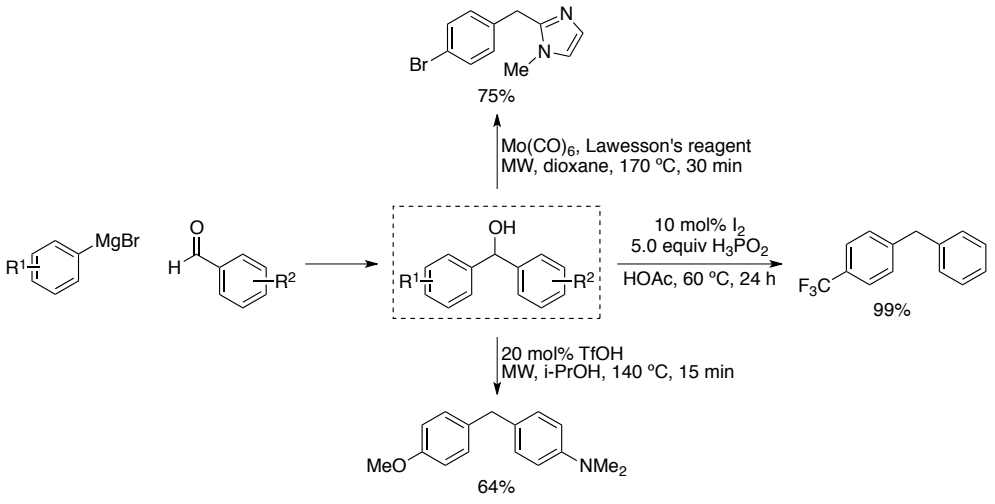
Scheme 8: Synthesis of diarylmethanes from highly functionalized Grignard reagents.

The nickel-catalyzed cross-coupling of Grignard reagents with aryl halides was independently discovered by Kumada and Corriu in 1972.[26] With the introduction of palladium catalysts in 1975 by the Murahashi group, the scope of the reaction was further broadened.[27] However, the application of the Kumada-Corriu reaction for the synthesis of diarylmethanes has been rarely reported. In 1999, Park *et al*. described the first nickel-catalyzed cross-coupling of benzylmagnesium chlorides and aryl bromides. The practicality of this approach was limited due to the use of benzylic Grignard reagents, which can be troublesome to prepare, and the use of 5 mol% of an expensive nickel catalyst (Scheme 9a).[28] Tsai and coworkers disclosed the coupling of phenylmagnesium bromide with benzyl bromide using an immobilized palladium-catalyst, which could be recycled and reused without loss of catalytic activity. Unfortunately, only a single diarylmethane example was synthesized (Scheme 9b).[29] Sarkar used a bidentate P,N-ligand for the nickel-catalyzed cross-coupling of benzyl chlorides with aryl Grignard reagents (Scheme 9c).[30] All described palladium- or nickel-catalyzed protocols suffered from a narrow substrate scope due to the instability of highly functionalized Grignard reagents under the coupling conditions. Recently, several research groups (Buchwald, Knochel, Hu) have reported improved Kumada-Corriu cross-coupling procedures that are effective at low temperature (below 0 °C), allowing the employment of functionalized Grignard reagents (including alkyl Grignard reagents) and alkyl halides.[31] Surprisingly, in none of the above-mentioned publications can an example of using benzyl halides or benzyl Grignard reagents be found, and therefore the synthesis of highly functionalized diarylmethane derivatives via the Kumada-Corriu reaction remains elusive.



Scheme 9: Synthesis of diarylmethanes via Kumada-Corriu coupling.

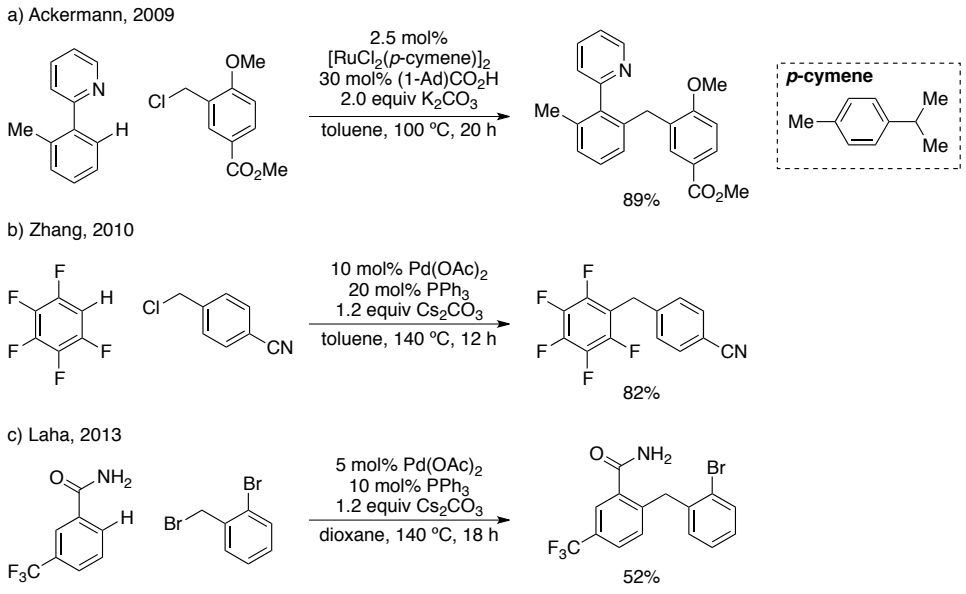
One of the most popular approaches to diarylmethanes is the addition of Grignard reagents to benzaldehydes and subsequent reduction of the benzylic alcohols. As nearly every Grignard reagent can be added to an aldehyde the substrate scope of this two-step procedure should be virtually limitless. However, this is not the case, because the conditions used in the second step are normally harsh and elevated temperatures have to be used for the deoxygenation (Scheme 10).[32]



Scheme 10: Synthesis of diarylmethanes via benzhydrol reduction.

2.4. Synthesis of Diarylmethanes via C-H activation

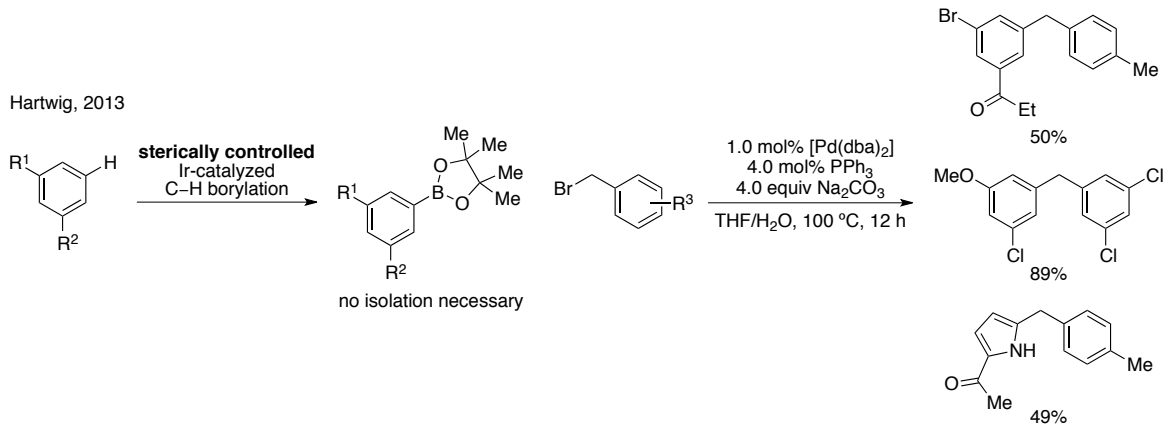
During recent years, C-H bond functionalization has become one of the highlight topics in organic chemistry and matured to be a viable alternative to traditional cross-coupling reactions.[33] The main advantage is the redundancy of prefunctionalizing starting materials, and therefore the use of organometallic reagents in stoichiometric fashion can be avoided. Several groups reported the direct benzylation of arenes under transition metal-catalysis. In 2009, the group of Ackermann developed the direct benzylation of arenes bearing a pyridine directing group that determined the regioselective outcome of the reaction (Scheme 11a). [34] Experimental observations led to the proposal of a concerted cyclometalation/deprotonation mechanism (CMD). Zhang and coworkers described the Pd-catalyzed benzylation of highly electron-deficient perfluorinated arenes. Several functional groups such as ester, methyl ketone, amide, nitro and nitrile were compatible with the reaction conditions (Scheme 11b).[35] Similar to Ackermann *et al.*, Zhang also suggested a mechanism in which after oxidative addition of the benzyl chloride, the resulting Pd-benzyl intermediate undergoes a CMD process. Recently, Laha used a primary amide directing group for C-H *ortho*-benzylation, leaving aryl bromides completely untouched to provide a synthetic anchor for further transformations (Scheme 11c).[36]



Scheme 11: Synthesis of diarylmethanes via C-H benzylation.

The regioselectivity in C-H activation processes is normally governed by the directing group or the electronic nature of the substrates (e.g. basicity). In contrast, Hartwig reported

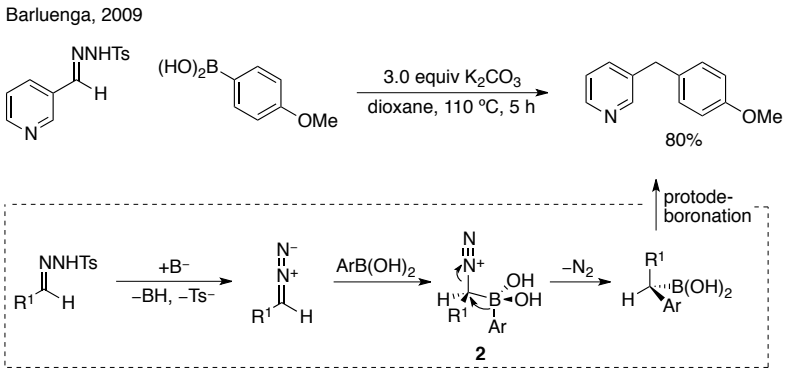
the iridium-catalyzed C-H borylation of arenes, in which the site-selectivity is predominantly controlled by steric factors.[37] The generated pinacol boranate esters can either be isolated, or directly transformed into diarylmethanes via a one-pot borylation/benzylation sequence (Scheme 12).[38] The synthetic utility of this approach is extremely high, because completely unbiased arenes can be used as starting materials. However, these reactions have to be performed in an inert glovebox using an expensive iridium-catalyst.



Scheme 12: Synthesis of diarylmethanes via one-pot C-H borylation/Suzuki-Miyaura coupling sequence.

2.5. Metal-Free Synthesis of Diarylmethanes

Chemical connections amenable to transition metal-catalyzed cross-coupling reactions have largely replaced constructions that require less predictable or more difficult reactions. However, the expensive nature of the catalysts, the need for separate disposal and the difficult elimination of trace metal impurities from final compounds makes the discovery of metal-free cross-coupling reactions necessary and compelling. Examples for metal-free diarylmethane synthesis are extremely rare. In 2009, Barluenga reported the metal-free reductive coupling between boronic acids and tosylhydrazones.[39] Under the basic reaction conditions, the hydrazone collapses to a diazo compound (Bamford-Stevens reaction), which attacks the boronic acid to form intermediate **2**. Subsequent 1,2-migration of the aryl group, followed by protodeboronation delivers the diarylmethane product (Scheme 11). The group of Zou reported a follow up on Barluenga's chemistry, in which they coupled different diarylborinic acids to tosylhydrazones, under otherwise identical reaction conditions.[40]



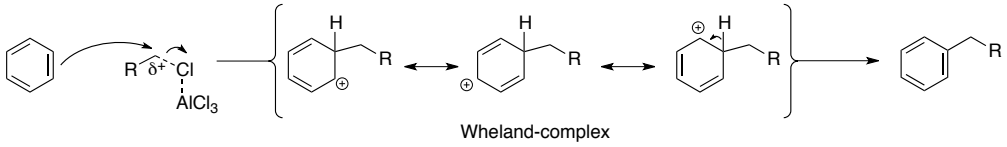
Scheme 13: Metal-free synthesis of diarylmethanes from boronic acids and tosylhydrazones.

2.6. Conclusions

The introduction of transition metal-catalyzed cross-coupling reactions revolutionized the field of C-C bond formation. The application of this new approach towards diarylmethanes has been intensively investigated. The Suzuki-Miyaura reaction of commercially available benzyl halides and arylboronic acids is by far the most widespread approach and can be considered as state-of-the-art. However, Negishi-type couplings have the advantage of simpler catalyst systems and more recently also a broad substrate scope due to improved protocols for organozinc reagent preparation. Regardless of these achievements, the metal-free synthesis of diarylmethanes is still a challenging task. The chemistry by Barleunga is an exception, but should guide the chemical community towards more sustainable reactions, particularly as the synthesis of diarylmethanes from cheap, non-prefunctionalized starting materials is still elusive.

3. Friedel-Crafts Benzylation

Electrophilic aromatic substitutions (Ar-S_E) are among the most important reactions for the preparation of highly functionalized arenes. The Friedel-Crafts alkylation is one of the most studied examples of an Ar-S_E reaction. Such transformations start with the initial nucleophilic attack of the arene onto the electrophile (e.g. alkyl halide) and the so-called *Wheland-complex* is formed. This highly energetic intermediate then collapses via extrusion of a proton to the final product (eq 4).[41]



(4)

As straightforward as the reaction seems to be according to eq 4, the process becomes less trivial when substituted aromatic nucleophiles are used, due to the possible formation of regioisomers. The regioisomeric outcome of Ar-S_E reactions is mainly governed by electronic factors. The charge distribution in the Wheland-complex is unequal and the highest partial positive charges are located in the *para*- and *ortho*-position (relative to the attacked carbon atom), the lowest in *meta*-position (Figure 3).[41] This means that arenes bearing electron-donating groups (EDG) are predominantly functionalized in the *para*- and *ortho*-position, because the highest stabilization of the Wheland-complex can be achieved this way. For the same reasons, arenes with electron-withdrawing groups (EWG) attack the electrophile in *meta*-position (relative to the EWG) so that the least destabilized Wheland-complex is formed. These are of course simplified rules – and several substituents cannot be clearly assigned to one of two categories (EDG or EWG). Representatives of such a borderline case are the halogens: they lower the reactivity of a specific arene towards an electrophile due to their high electronegativity, but normally deliver *para*- and *ortho*-substituted products due to their mesomeric stabilization of the Wheland-complex.[42] Halogens are therefore commonly referred as having *chameleon-like* character. In the following paragraphs of this thesis, the terms “activated” (bearing EDGs) and “deactivated” (bearing EWGs) will be used to refer to the relative nucleophilicity of an arene compared to that of benzene, which is considered “non-activated”.[42] The Friedel-Crafts benzylation (R^1 = Ph) can be seen as a sub-category of the correspondent alkylation process and has been intensively studied over the last 120 years.[5c]

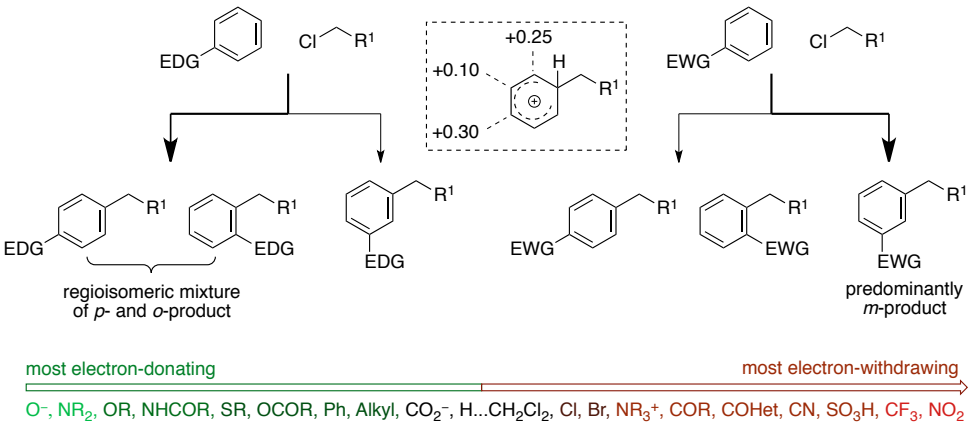
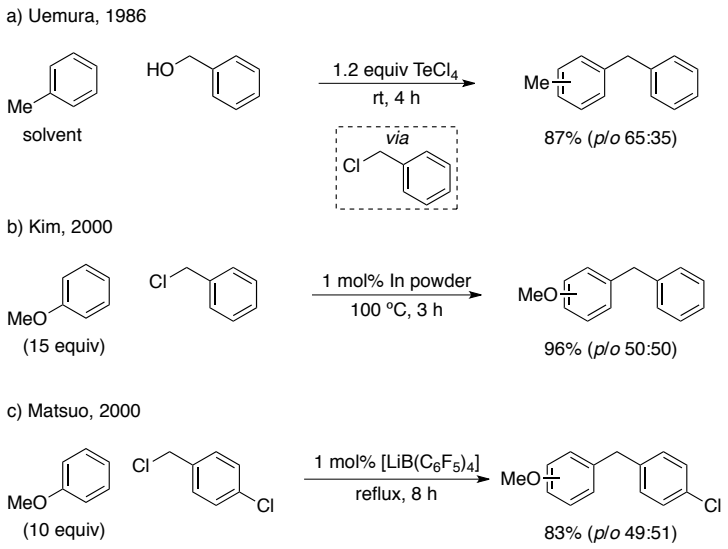


Figure 3: Friedel-Crafts reactions with substituted aromatic nucleophiles.

3.1. Synthesis of Diarylmethanes from Benzyl Halides

The synthesis of diarylmethanes from benzyl halides and arenes using catalytic or stoichiometric amounts of $AlCl_3$ can be seen as a textbook application of Friedel-Crafts-type conditions. However, the toxicity and complications associated with the separation of aluminum by-products have encouraged the development of improved benzylation protocols.[5c] Olah was the first one to report an extensive study on Friedel-Crafts benzylations. His pioneering work on the benzylation of toluene and benzene with various Lewis acid catalysts is impressively detailed, but lacks the deeper investigation of the substrate scope.[43] In 1986, Uemura *et al*. investigated the conversion of benzyl alcohols to benzyl chloride using $TeCl_4$.[44] When this reaction was performed in toluene, they found that the initially formed benzyl chloride further reacted with the solvent to produce a regioisomeric mixture of 1-methyl-2-methylbenzene (Scheme 14a). They could even increase the yield of this reaction by using only a catalytic amount of $TeCl_4$. Chung and coworkers reported the use of indium powder as an effective catalyst for the Friedel-Crafts benzylation of activated arenes, which were employed as solvents (30 equiv) (Scheme 14b).[45] In the same year, Matsuo described the lithium tetrakis(pentafluorophenyl)borate-promoted reaction of benzyl chlorides with electron-rich arenes (Scheme 14c).[46] The major limitations of these early examples are the strict reliance on activated arene nucleophiles such as toluene or anisole, and the high reaction temperatures. Furthermore, benzyl halides are known to be toxic and therefore the use of alternatives has gained increased attention in the last 10 years.

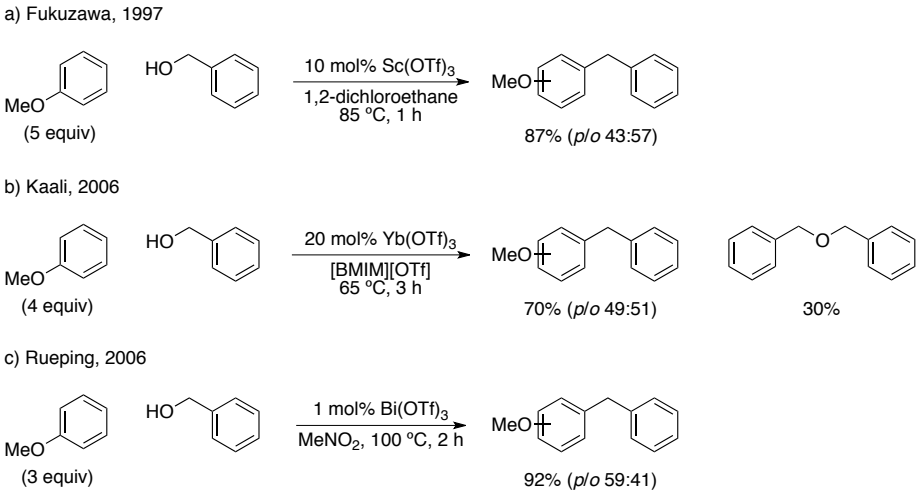


Scheme 14: Synthesis of diarylmethanes via Friedel-Crafts benzylation using benzyl halides.

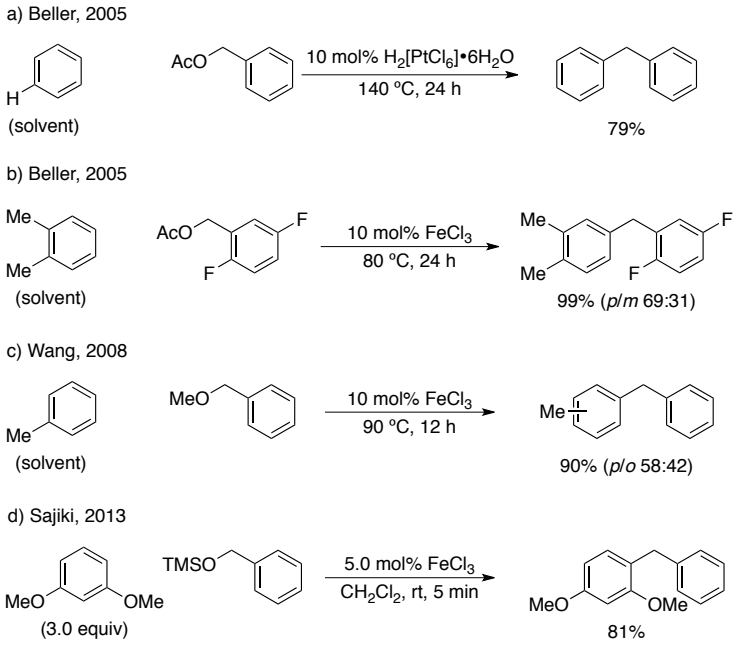
3.2. Synthesis of Diarylmethanes from Benzyl Alcohols and Derivatives

Benzyl alcohols have been established as a powerful alternative to benzyl halides in the synthesis of diarylmethanes, especially as only stoichiometric amounts of water are generated as the by-product. However, the formation of water is not only advantageous, since it has the potential to deactivate the active catalytic species. The first systematic investigation of catalytic Friedel-Crafts benzylations using benzyl aclohols was performed by the group of Fukuzawa (Scheme 15a).[47] They were intrigued by the use of rare earth(III) triflates, because they are commonly prepared in aqueous solution and should therefore be less prone to aqueous deactivation.[48] They found that $Sc(OTf)_3$ is an active catalyst in the benzylation of various activated arenes. In some cases, the amount of arene could be reduced to 5.0 equivalents using 1,2-dichloromethane as a solvent. Inspired by the report of Fukuzawa, Laali and coworkers performed Friedel-Crafts benzylations in ionic liquids with rare earth triflate catalysts (Scheme 15b).[49] The best performance was found for $Yb(OTf)_3$. Unfortunately, the formation of dibenzyl ether and the high catalyst loading rendered this approach difficult to perform on bigger scale. Rueping *et al*. developed an efficient $Bi(OTf)_3$-catalyzed Friedel-Crafts benzylation of several arenes (Scheme 15c).[50] Compared to other methods, their protocol required only a small amount of the highly reactive catalyst. During recent years, many different Friedel-Crafts benzylation using benzyl alcohols have been reported, utilizing a wide range of different catalysts.[51] Common limitations of all the above-

mentioned reactions are the formation of regioisomeric product mixtures and the poor reactivity of deactivated aromatic compounds.



Scheme 15: Synthesis of diarylmethanes via Friedel-Crafts benzylation using benzyl alcohols.



Scheme 16: Synthesis of diarylmethanes via Friedel-Crafts benzylation using benzyl alcohol derivatives.

In 2005, Beller *et al*. reported the systematic screening of active Lewis- and Brønsted acid catalysts in Friedel-Crafts benzylations using benzyl acetates.[52] They found that transition metal complexes such as $H_2[PtCl_6]•6H_2O$, $IrCl_3•nH_2O$ or $HAuCl_4$ were the most effective catalysts in the benzylation of various arenes (Scheme 16a). The substrate scope was found

to be slightly broader than for previously reported methods as non-activated arenes (e.g. benzene) could be used as nucleophiles. In the same year, Beller also reported the use of cheap and non-toxic $FeCl_3$ in Friedel-Crafts benzylations (Scheme 16b).[53] Benzyl acetates bearing weak EWGs could be employed in the reaction with highly reactive *o*-xylene, even though the nucleophile had to be used as solvent and poor regioselectivity was obtained. Wang and Sawana used the same iron catalyst in the benzylation of different arenes with benzyl methyl ethers resp. benzyl TMS ethers (Scheme 16c and 16d).[54] However, in both cases only highly electron-rich aromatic nucleophiles could be employed.

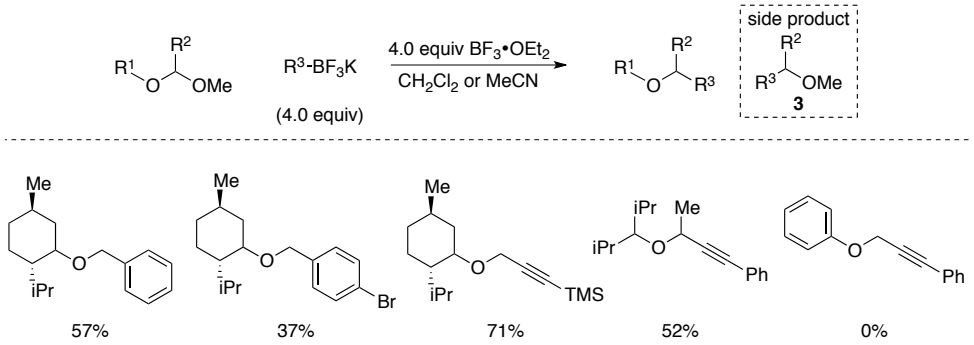
3.3. Conclusions

The Friedel-Crafts benzylation is a versatile method for the synthesis of diarylmethanes. The major advantage of Friedel-Crafts benzylations compared to cross-coupling methods is the direct use of completely unfunctionalized arenes – one of the most abundant organic feedstock. The discovery of several metal salts as active catalysts in the Friedel-Crafts benzylation with benzyl halides or alcohols have reduced the reliance on toxic aluminum Lewis acids and decreased the environmental impact of these transformations. In most cases, however, these advances are limited to highly activated benzylic substrates and the use of electron-rich nucleophiles. The textbook Friedel-Crafts benzylation of even slightly deactivated arenes, such as chlorobenzene or benzoic esters, has seen little improvement in its 135 years history. Furthermore, there remains an unmet synthetic need for metal-free, sustainable Friedel-Crafts processes.[55] Only with these improvements Friedel-Crafts benzylations can be a viable alternative to the omnipresent transition metal-catalyzed cross-coupling reactions.

4. Friedel-Crafts Benzylation of Activated and Deactivated Arenes

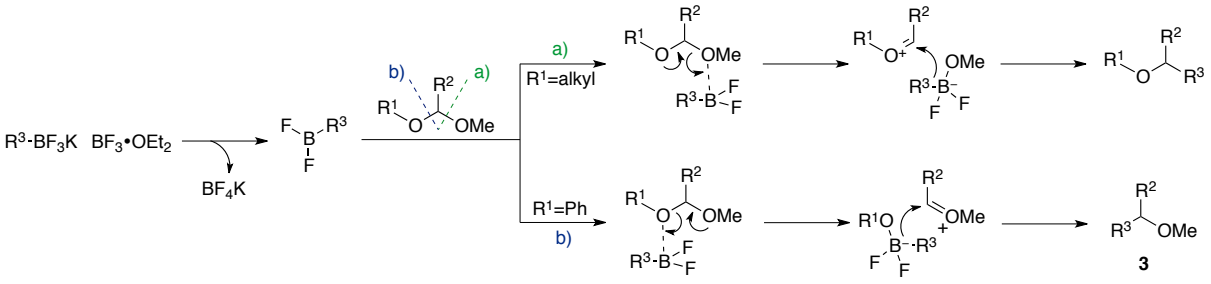
4.1. Initial results

In 2009, our group reported the BF_3•OEt_2-promoted synthesis of dialkylethers from potassium trifluoroborates and *O*-MOM acetals (Scheme 17).[56] The reaction was quite general in respect of substrate scope and a wide range of different ethers could be formed, including sterically hindered examples, which are known to be extremely hard to prepare via traditional methods (e.g. Williamson ether synthesis).



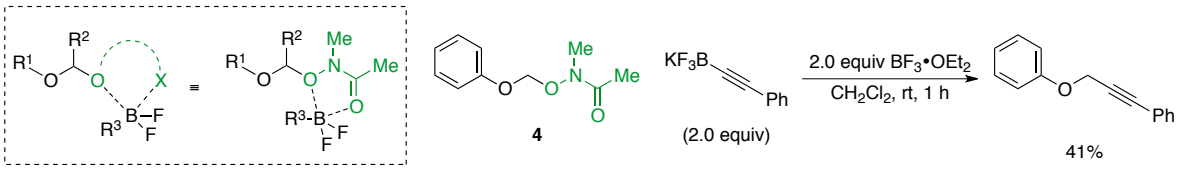
Scheme 17: Synthesis of dialkyl ethers from potassium trifluoroborates and *O*-MOM acetals.

However, the major limitation of this approach was the undesired formation of methyl ether **3**, whose formation can be explained by having a closer look at the reaction mechanism (Scheme 18). The reaction starts with the abstraction of a fluoride from the potassium trifluoroborate salt by BF_3•OEt_2, which results in the formation of the active nucleophilic R^3BF_2-species and BF_4K. The difluoroborane is a strong Lewis-acid and can coordinate to both of the oxygens in the starting acetal. Normally, the coordination to the OMe-group is favored, especially when R_1 is a bulky alkyl group. However, in the case of R_1=Ph the regioselectivity changes, due to the better leaving group ability of a phenoxy group (OPh) compared to a methoxy group. This leads to extrusion of the phenoxide and the formation of an oxonium intermediate, which is finally captured by the transfer of the R^3-group from the boron to the oxonium carbon to form side product **3**.



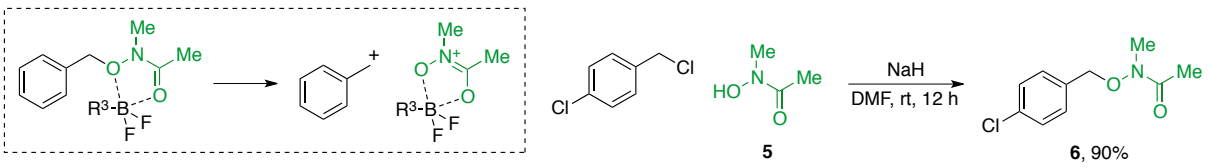
Scheme 18: Proposed reaction mechanism of BF_3•OEt_2-promoted ether synthesis.

In order to overcome this intrinsic limitation the design of a better leaving group – compared to methoxide – was envisioned. The main focus was laid on improving the chelation ability of the leaving group towards the active R^3BF_2 species. After an intense screening, *N*-methyl hydroxamate **5** was found to be the leaving group of choice, because it provided superior results in terms of reactivity, chemical yield and most importantly regioselectivity compared to the *O*-MOM acetals (Scheme 19). Using hydroxamic acid-derived acetal **4**, the before non-accessible phenyl ether could be synthesized in moderate yield.[57]



Scheme 19: *N*-Methyl hydroxamate as novel powerful leaving group.

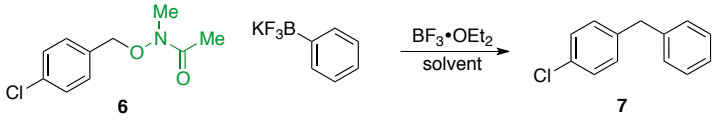
To build on this result, we sought new substrates suitable for our *N*-methyl hydroxamate leaving group. A substrate class that came to mind was the diarylmethanes, because the formation of an intermediate benzylic carbocation should be feasible using a benzyl hydroxamate. As a model substrate we chose *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (**6**), which was synthesized in 90% yield from 4-chloro benzyl chloride and *N*-hydroxy-*N*-methylacetamide (**5**) (Scheme 20).



Scheme 20: Preparation of *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (**6**).

The novel benzyl hydroxamate **6** was tested in the BF_3•OEt_2-promoted reaction with potassium phenyltrifluoroborate. After substantial optimization, the desired diarylmethane product **7** could be obtained in 77% yield – however, 4.0 equivalents of both boron reagents had to be used. The use of a lower amount of potassium trifluoroborate led to diminished yield or incomplete conversion of the benzyl hydroxamate **6**. The best results were obtained in chlorinated solvents; the reaction was completely shut down when coordinating solvents were used (e.g. Et_2O or EtOAc), most likely due to deactivation of the BF_3 by chelation to the solvent.

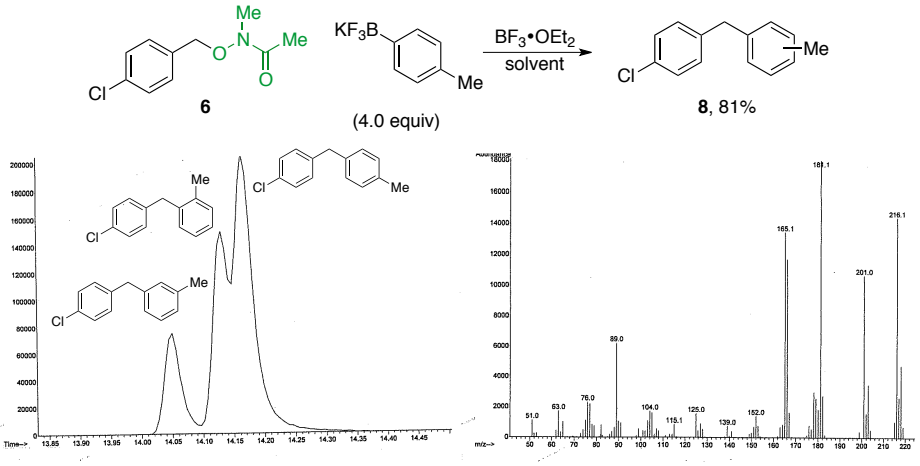
Table 1. Optimization of reaction conditions



6 **7**

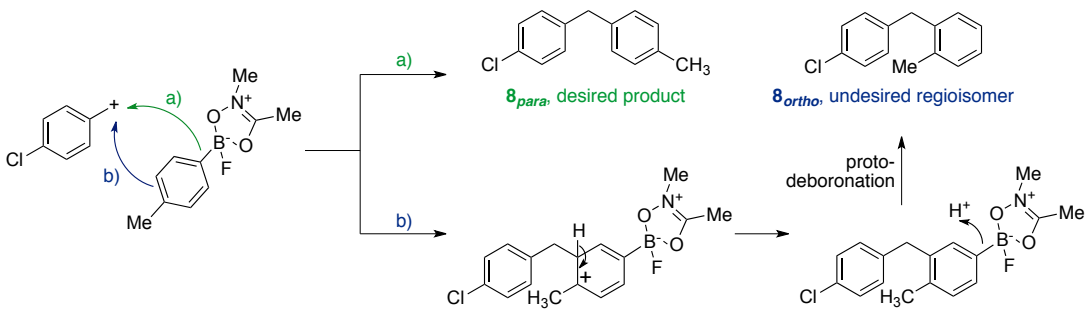
Entry	Equiv of $PhBF_3K$/ BF_3•OEt_2	Temperature	Solvent	Yield of 7
1	4/4	0 °C to 25 °C	CH_2Cl_2	77%
2	4/4	0 °C	CH_2Cl_2	20% (conv.)
3	4/4	0 °C to 25 °C	MeCN	17%
4	4/4	0 °C to 25 °C	Et_2O	0% (conv.)
5	4/4	0 °C to 25 °C	EtOAc	0% (conv.)
6	4/4	0 °C to 25 °C	$C_2H_4Cl_2$	74%
7	1/1	0 °C to 25 °C	CH_2Cl_2	30% (conv.)
8	2/2	0 °C to 25 °C	CH_2Cl_2	55%
9	4/4	25 °C to 45 °C	$C_2H_4Cl_2$	traces

Encouraged by this initial result, we turned our attention on the exploration of the substrate scope. Using our optimized conditions, potassium *p*-tolyltrifluoroborate provided the product in high yield. However, ^{1}H- and ^{13}C-NMR analysis showed a major impurity, and the ratio of *product:side-product* remained constant even after multiple chromatographic purification of the product mixture. When this mixture was consequently subjected to gas-chromatographic analysis (GC/MS), three peaks with very similar retention times were found. Surprisingly, all of these peaks showed the same fragmentation pattern and identical molecular mass, in accordance with the formation of all three possible regioisomers of product **8** (Scheme 21).



Scheme 21: Reaction of benzyl hydroxamate **6** with *p*-tolyltrifluoroborate.

We believe that after the formation of the initial benzylic carbocation, two different mechanisms operate in this reaction (Scheme 22). The first one is the expected migration of the aryl-group from the boron to the carbon electrophile, which leads to the desired product **8*para***. The second, undesired pathway is the Friedel-Crafts-type attack of the aromatic moiety of the borate-complex onto the benzylic cation. After formation of the Wheland-complex and protodeboronation the undesired *ortho*-regioisomer **8*ortho*** is generated (along with a small amount of *meta*-isomer, see Scheme 22). The fact that this regioisomeric scrambling could not be observed in the ether-forming project suggests that the benzylic cation is a more reactive intermediate than the corresponding oxonium ion – and therefore a Friedel-Crafts-type process can operate. At this point, the use of potassium aryltrifluoroborate salts was dismissed, especially as the same regioisomeric scrambling was also observed for other nucleophiles, e.g. potassium (4-acetylphenyl)trifluoroborate provided a 77:23-mixture of regioisomers (41% yield).

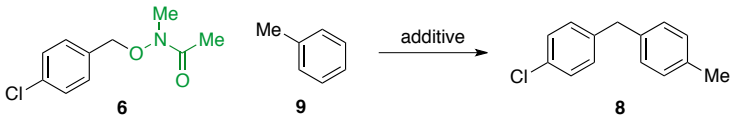


Scheme 22: Two possible mechanisms after formation of benzylic carbocation.

4.2. The Identification of Arenes as New Reaction Partners

The initial results described in the previous chapter led us to examine other nucleophilic species in the reaction with benzyl hydroxamate **6**. The possibility of using simple arenes as nucleophiles seemed particularly intriguing, because they are among the most abundant organic feedstocks. Furthermore, no prefunctionalization of the aromatic unit, e.g. via formation of a boronic acid derivative, would be necessary making this Friedel-Crafts benzylation approach more sustainable and economical. We already knew that *p*-tolyltrifluoroborate participates in a Friedel-Crafts-type reaction, and based on that the use of toluene (**9**) as a nucleophile in the reaction with benzyl hydroxamate **6** (Table 2) was investigated.*

Table 2. Additive screening of Friedel-Crafts benzylation[a]



Entry	Additive	Equiv	*T* [°C], (*t* [h])	Yield 8 [%][b], (ratio)[c]
1	BF_3•OEt_2	4	25 (13)	99 (55:43:2)
2	BF_3•OEt_2	2	25 (22)	99 (55:43:2)
3	BF_3•OEt_2	0.1	25 (24)	n.r.
4[d]	BF_3•OEt_2	4	40 (18)	80 (54:43:3)
5	HBF_4•OEt_2	4	25 (24)	traces (n.d.)
6	$B(OH)_3$	4	50 (24)	n.r.
7	$ZnCl_2$	4	50 (24)	n.r.
8	$Mg(acac)_2$	4	50 (24)	n.r.
9	TMSCl	4	25 (24)	n.r.
10	$Cu(OAc)_2$	4	50 (24)	n.r.
11	$AlCl_3$	1	25 (5)	83 (48:45:7)
12	$FeCl_3$	4	25 (12)	75 (50:45:5)
13	$FeCl_3$	0.1	80 (24)	n.r.
14	(no additive)	-	50 (24)	n.r.

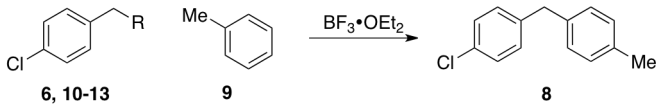
[a] Conditions: *para*-chlorobenzyl hydroxamate **6** (0.4 mmol), toluene **9** (4 mL) and additive. [b] Isolated yields [c] ratio of regioisomers (*p*:*o*:*m*) determined by GC/MS. [d] toluene (1.6 mmol), CH_2Cl_2 (4 mL).

* In this chapter, only the major regioisomer is shown in all schemes and tables. The regioisomeric ratio is indicated in the corresponding tables and was determined by gas chromatography (GC/MS).

To our delight, the use of BF_3•OEt_2 (4.0 equiv) at room temperature gave the benzylation product **8** as a mixture of regioisomers in excellent isolated yield. Similar results were obtained using only 2 equivalent of BF_3•OEt_2. As expected, catalytic reactions were not effective; likely due to chelation of the BF_3•OEt_2 by the released hydroxamate, an effect that sequesters the BF_3•OEt_2 after the reaction. This is beneficial under non-catalytic conditions, as it prevents the formation of side products. In contrast to BF_3•OEt_2 a number of other Lewis or Brønsted acids including HBF_4 (entry 5), $B(OH)_3$ (entry 6), $ZnCl_2$ (entry 7), $Mg(acac)_2$ (entry 8), and $Cu(OAc)_2$ (entry 10) proved ineffective. $FeCl_3$ and $AlCl_3$ were viable reagents but led to more complicated workup and the formation of side products (entries 11 and 12). Experiments in the absence of additive (entry 14) and 0.1 equiv $FeCl_3$ (entry 13) did not afford any product and confirmed that the reaction was not promoted by trace metal impurities. The reactions could also be performed with only 4 equivalents of toluene in CH_2Cl_2 by raising the temperature to 40 °C (entry 4).

The BF_3•OEt_2-promoted Friedel-Crafts benzylation using benzyl hydroxamates is remarkable for several reasons: 1) The benzylation takes place at room temperature and the diarylmethane product is formed in quantitative yield. This is even more impressive considering that hydroxamate **6** is substituted with an EWG. 2) It was possible to use only 4.0 equivalents of the nucleophile without significant erosion of isolated yield. 3) Other Lewis acids failed completely to provide any product. The unique ability of the hydroxamate leaving group to be activated by BF_3•OEt_2 was further confirmed by examining other benzylating agents (Table 3). Only trace amounts of product could be observed with benzyl alcohol **10** or acetate **11**, and no reaction occurred with benzyl methyl ether **12** or *para*-chlorobenzyl chloride **13** at room temperature.

Table 3. Comparison of different leaving groups.[a]



6, 10-13 **9** **8**

Entry	R =	*T* [°C]	Conversion [%] (ratio)[b]
1	 (**6**)	25	100 (55:43:2)
2	OH (**10**)	25	5% (n.d.)
3	OAc (**11**)	25	<5% (n.d.)
4	OCH_3 (**12**)	25	n.r. (-)
5	Cl (**13**)	25	n.r. (-)

[a] Conditions: benzylic substrate (0.4 mmol), BF_3•OEt_2 (1.6 mmol), toluene **9** (4 mL), 24h [b] Conversion and ratio of regioisomers determined by GC/MS with *n*-dodecane as internal standard.

The promising results obtained for benzyl hydroxamate **6** led us to investigate the full substrate scope. The optimized conditions were applied to three different classes of aromatic nucleophiles: arenes bearing an activating *ortho*/*para*-directing group, arenes bearing a deactivating *ortho*/*para*-directing group, and arenes bearing a deactivating *meta*-directing group.[42] Two conditions were screened for each substrate combination: A) the use of the nucleophile as the solvent and B) 4 equivalents of nucleophile relative to the benzylic hydroxamate using dichloromethane or 1,2-dichloroethane as a solvent.

As expected from the results with toluene (**9**), benzylation of electron-rich arenes (used as solvent or only 4 equivalents) all proceeded smoothly to give the diarylmethane products in excellent yields and with regioselectivities typically observed in a Friedel-Crafts process (Table 4, **7**, **14**–**16**). The reaction also worked with *para*-anisaldehyde and acetanisole, which bear unprotected aldehyde and ketone functionalities, to provide the desired products **17** and **18** as single regioisomers in good yields. The benzylation of trifluoromethoxybenzene and an electron-rich pyridine derivative was also feasible under our standard reaction conditions. The use of other benzyl hydroxamates in the reaction with toluene (**9**) was also investigated. Electron-rich and halogenated electrophiles with different substitution patterns reacted at room temperature with toluene (**9**) to provide the corresponding products in quantitative yields (Table 5, **22**–**25**). These electrophiles were also compatible with using only 4.0 equivalents of arene.

The attention was turned to the use of highly deactivated benzyl hydroxamates, because the formation of the intermediate benzylic carbocation from such substrates can normally not be easily achieved under Friedel-Crafts-type conditions. This is not the case when our Friedel-Crafts benzylation protocol was used. Several benzyl hydroxamates containing CF_3-, CN-, CO_2Me- and NO_2-groups (strong EWGs) were viable substrates, although higher temperatures were required (entries 5–9). Unfortunately, in most cases inseparable mixtures of regioisomers were obtained, most notably when toluene was used as the nucleophile. The regioisomeric ratio does not depend on the amount of nucleophilic species, 4.0 equivalents or used as solvent, because nearly identical mixtures were obtained in both cases. However, for some arenes a strong innate bias towards a specific substitution pattern exists and their use renders it possible to obtain single regioisomeric products, proven by the formation of **18** and **19**. We envisioned that the use of arenes bearing EWGs would induce a more accentuated directing effect leading to regioisomerically enriched or pure diarylmethane products.

Table 4. Benzylation of activated, *ortho*/*para*-directing nucleophiles with *para*-chlorobenzyl hydroxamate **6**.[a]

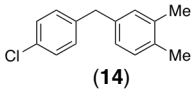
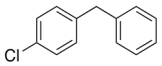
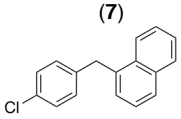
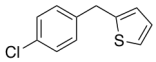
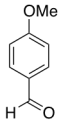
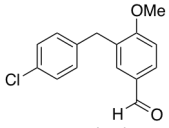
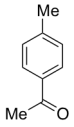
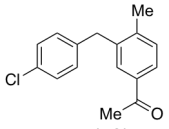
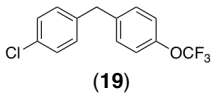
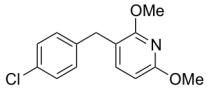
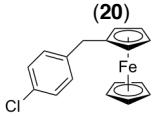
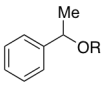
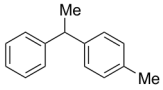
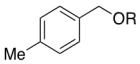
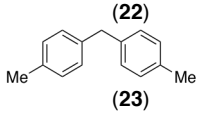
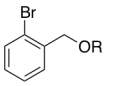
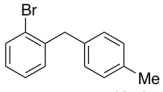
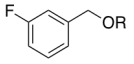
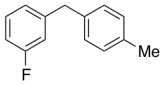
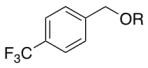
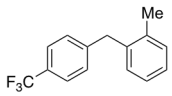
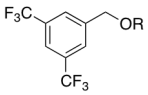
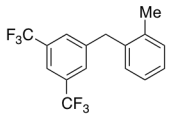
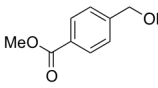
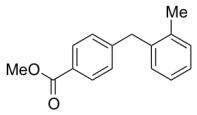
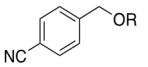
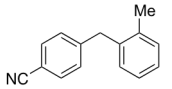
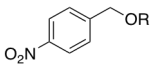
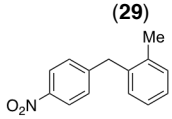
Entry	Arene	Major product	*T* [ºC]	Yield [%][b] (ratio)[c]
1a[d]		 (**14**)	25	99 (65:35)
1b			35	90 (53:47)
2a[d]		 (**7**)	25	99 (-)
2b			40	77 (-)
3		 (**15**)	40	87 (70:30)
4		 (**16**)	40	89 (65:35)
5		 (**17**)	50	52 (99:1)
6		 (**18**)	45	50 (99:1)
7		 (**19**)	40	63 (93:7)
8		 (**20**)	45	83 (97:3)
9		 (**21**)	35	89 (-)

Table 5. Benzylation of toluene (**9**) with various benzyl hydroxamates.[a]

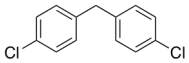
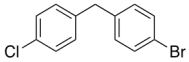
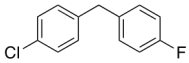
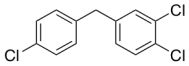
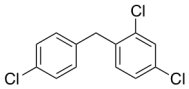
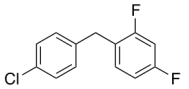
Entry	Benzylating agent	Major product	*T* [ºC]	Yield [%][b] (ratio)[c]
1a[d]		 (**22**)	25	99 (93:7)
1b			25	90 (93:7)
2a[d]		 (**23**)	25	99 (70:30)
2b			25	89 (77:23)
3a[d]		 (**24**)	25	99 (64:32:4)
3b			50	75 (64:33:3)
4a[d]		 (**25**)	25	99 (50:43:7)
4b			50	74 (50:43:7)
5a[d]		 (**26**)	70	99 (60:35:5)
5b[e]			85	70 (60:34:6)
6[d]		 (**27**)	85	90 (50:41:9)
7a[d]		 (**28**)	45	99 (49:38:13)
7b[e]			65	73 (50:37:12)
8a[d]		 (**29**)	65	99 (53:37:10)
8b[e]			85	65 (53:38:9)
9[d]		 (**30**)	80	93 (55:40:5)

[a] Reaction conditions: benzylic hydroxamate (0.4 mmol), BF_3•OEt_2 (1.6 mmol), arene (1.6 mmol), CH_2Cl_2 (4 mL), 24h [b] Isolated yields [c] ratio of regioisomers determined by GC/MS [d] arene (4 mL), no solvent [e] 1,2-dichloroethane (4 mL) was used as solvent. R=[$N(CH_3)(Ac)$].

We began our survey of electron-poor arenes with the use of aryl halides, because they are considered as prototypical deactivated nucleophiles in classical Friedel-Crafts reactions (Table 6).[42,58] Chloro-, bromo- and fluorobenzene were excellent substrates and provided the diarylmethane products **31**–**33** in quantitative yield. The use of the arene as solvent could also be avoided and good yields were obtained with only 4.0 equivalents of arene at 40 ºC (entries 1b–3b). The dihalogenated nucleophiles 1,3-dichlorobenzene and 1,3-difluorobenzene (entries 5 and 6) delivered the corresponding products **35** and **36** with excellent yield and perfect regioselectivity. The mildness of the reaction condition, under which normally inert aryl halides reacted with the benzyl hydroxamate, is remarkable and

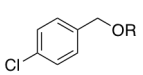
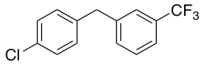
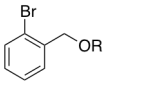
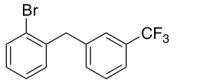
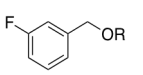
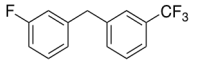
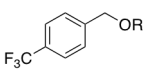
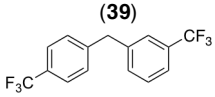
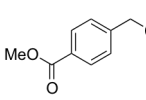
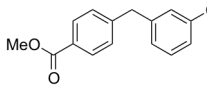
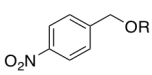
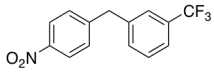
paved the way to test even more electron-poor arenes. For instance, the benzylation of highly deactivated trifluoromethylbenzene could be achieved using *p*-chlorobenzyl hydroxamate **6** (Table 7). Other halogen-substituted benzyl hydroxamates also participated in the reaction with trifluoromethylbenzene, although the arene had to be used as solvent (entries 2 and 3). All products were obtained as single regioisomers. The coupling of two electron-deficient substrates was also possible at elevated temperatures, including the *meta*-selective trifluoromethylarylation of *para*-trifluoromethyl- and *para*-nitro hydroxamates (entries 4 and 6). These are the first examples of acceptor-acceptor substituted diarylmethanes that were synthesized via a Friedel-Crafts benzylation process. In light of the recent interest in *meta*-selective C-H functionalization, [59] our method is an attractive, inexpensive and complementary approach to these transition metal-catalyzed arene functionalization.

Table 6. Benzylation of deactivated, *ortho*/*para*-directing nucleophiles with *para*-chlorobenzyl hydroxamate **6**.[a]

Entry	Arene	Major Product	*T* [ºC]	Yield [%][b] (ratio) [c]
1a[d] 1b		 (**31**)	25 40	99 (77:23) 76 (70:30)
2a[d] 2b		 (**32**)	25 40	99 (78:22) 75 (70:30)
3a[d] 3b		 (**33**)	25 40	99 (88:12) 77 (87:13)
4		 (**34**)	45	53 (79:21)
5		 (**35**)	45	63 (98:2)
6		 (**36**)	45	62 (99:1)

[a] Reaction conditions: *para*-chlorobenzyl hydroxamate **6** (0.4 mmol), BF_3•OEt_2 (1.6 mmol), arene (1.6 mmol), CH_2Cl_2 (4 mL), 24h [b] Isolated yields [c] ratio of regioisomers determined by GC/MS [d] arene (4 mL), no solvent.

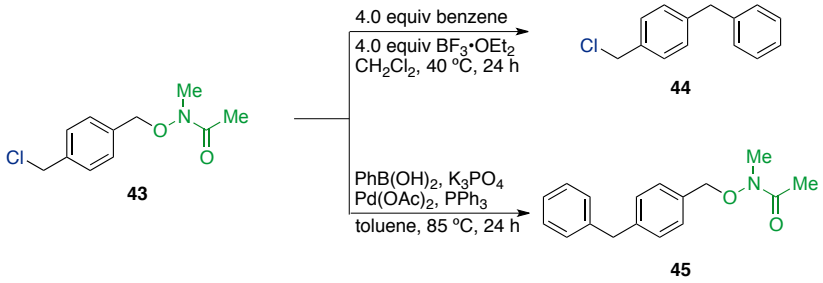
Table 7. Benzylations of deactivated, *meta*-directing trifluoromethylbenzene with various benzyl hydroxamates.[a]

Entry	Benzylating agent	Major Product	*T* [ºC]	Yield [%][b] (ratio) [c]
1[d]		 (**37**)	45	53 (99:1)
2[e]		 (**38**)	50	65 (99:1)
3[e]		 (**39**)	50	73 (98:2)
4[e]		 (**40**)	85	90 (97:3)
5[e]		 (**41**)	65	73 (97:3)
6[e]		 (**42**)	95	55 (95:5)

[a] Reaction conditions: Benzyl hydroxamate (0.4 mmol), BF_3•OEt_2 (1.6 mmol), arene (1.6 mmol), CH_2Cl_2 (4 mL), 24h [b] Isolated yields [c] ratio of regioisomers determined by GC/MS [d] arene (8 mL), no solvent, 24h [e] arene (4 mL), no solvent, 24h. R=[N(CH_3)(Ac)].

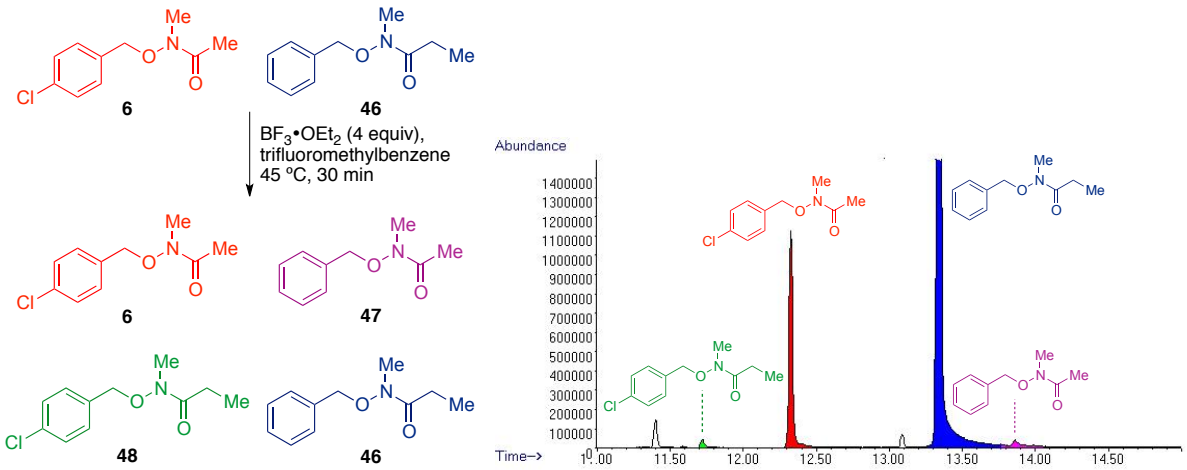
The advantage of the hydroxamate leaving group is its chemical stability towards a range of reagents and conditions, but can be selectively activated by the addition of BF_3•OEt_2 (as shown in Table 2). To demonstrate this, the selective functionalization of *para*-chloromethylbenzyl hydroxamate **43** was examined (Scheme 23). First, we carried out our BF_3•OEt_2-promoted Friedel-Crafts benzylation using benzene as a nucleophile (4.0 equiv). A

selective displacement of the hydroxamate leaving group over the chloride was observed and 1-benzyl-4-(chloromethyl)benzene (**44**) was obtained in high yield. In contrast, the benzylic halide was selectively arylated by using a Suzuki-Miyaura cross-coupling reaction with phenylboronic acid. In the second case, the benzylic halide is exclusively functionalized while the hydroxamate remains unchanged. This is quite remarkable knowing the lability of O–N- and O–C_{benzyl}-bonds under standard Pd-catalyzed conditions. The selective functionalization of *para*-chloromethylbenzyl hydroxamate **43** underlines the usefulness of the hydroxamate leaving group, which enables novel chemoselective functionalizations.



Scheme 23: Chemoselective functionalization of **43** by Friedel-Crafts or Suzuki-Miyaura reactions.

The improved performance of hydroxamates compared to standard leaving groups (see Table 3) is believed to lie in the ability of the boron-chelated hydroxamate to serve as a reversible leaving group – a process that allows the controlled generation of highly reactive benzylic carbocations. To confirm this hypothesis that the selective activation of the hydroxamate by BF_3•OEt_2 and reversible formation of the benzylic cation is responsible for the success of this reaction, the following cross-over experiment was performed: hydroxamates **6** and **46** were combined and treated with BF_3•OEt_3 in the presence of trifluoromethylbenzene (Scheme 24). After 30 minutes at 45 °C, the reaction was quenched prior to completion and analyzed by GC/MS. The chromatogram revealed the formation of benzyl hydroxamates **47** and **48** arising from cross-over of the two starting materials, indicating that the dissociation from the hydroxamate leaving group to form the benzyl cation is reversible.



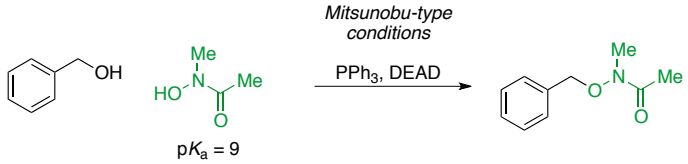
Scheme 24: Cross-over experiment with benzyl hydroxamates **6** and **46**.

5. Conclusions and Outlook

In 2007, the ACS Green Chemistry Institute (GCI) developed a pharmaceutical manufacturer roundtable to encourage the integration of green chemistry and engineering into the pharmaceutical industry. This roundtable identified several reactions that are commonly used on industrial scale, but would need better and greener reagents. One of these reactions was the "*Friedel-Crafts reaction on unactivated systems*", showing the necessity of improved protocols for this 135-year old transformation.[55] Inspired by this unmet synthetic need, we developed the Friedel-Crafts benzylation of activated and deactivated systems using benzyl hydroxamates.[60] The key to our successful improvement of the Friedel-Crafts benzylation was the selective activation of the *N*-methyl hydroxamic acid leaving group with BF_3•OEt_2; an activation most likely proceeding in a reversible manner that avoids build up of highly reactive carbocations. Friedel-Crafts reactions using this approach are therefore cleaner, more selective, and more easily executed than traditional methods. The implementation of deactivated arenes is not only of great interest from a reactivity point of view, but also from a regioselective one, because electron-poor arenes provide synthetically useful *meta*-substituted diarylmethanes with high selectivity. Even though the use of an excess of BF_3•OEt_2 is necessary, this Lewis acid is inexpensive, easily handled and forms only nontoxic, metal-free by-products.

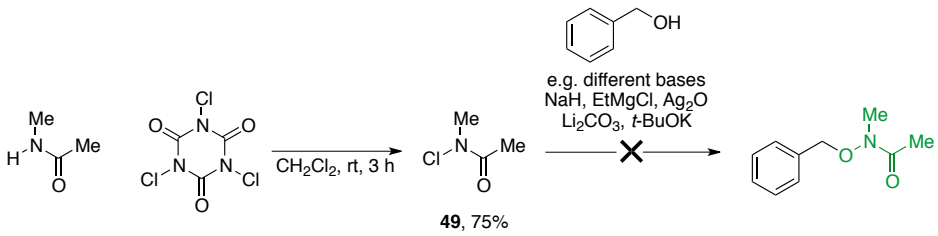
Outlook: Synthesis of Benzyl Hydroxamates

Despite the elegance of our Friedel-Crafts benzylation approach, a minor drawback of this chemistry is that the synthesis of the *O*-benzyl hydroxamic acids starts from benzyl chlorides, a substance class known to be toxic. Therefore, the replacement of benzyl chlorides by environmentally benign benzylic alcohols would be of great interest. Hydroxamic acids are known to have an accentuated lower pK_a (~ 9) than normal alcohols and their participation as nucleophilic species in a Mitsunobu reaction should be feasible (Scheme 25).



Scheme 25: Benzyl hydroxamate synthesis via Mitsunobu reaction.

Another attractive approach would be the use of *N*-chloro-*N*-methylacetamide (**49**), which could react via Cl-displacement with a benzylic alcoholate (Scheme 26). Even though the *N*-chlorinated starting material was easily prepared from *N*-methylacetamide and trichloroisocyanuric acid (TCCA),[61] the S_N2 reaction at the nitrogen with benzyl alcohol was not successful under a wide range of different conditions. However, given the recent advances in using *N*-chloro amines as electrophilic cross-coupling partners,[62] this approach should definitely be revisited under transition metal-catalysis.

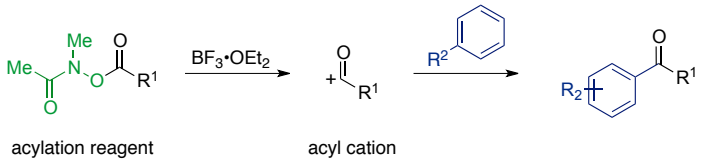


Scheme 26: Benzyl hydroxamate synthesis from *N*-chloro-*N*-methylacetamide (**49**).

Outlook: New Hydroxamate Electrophiles

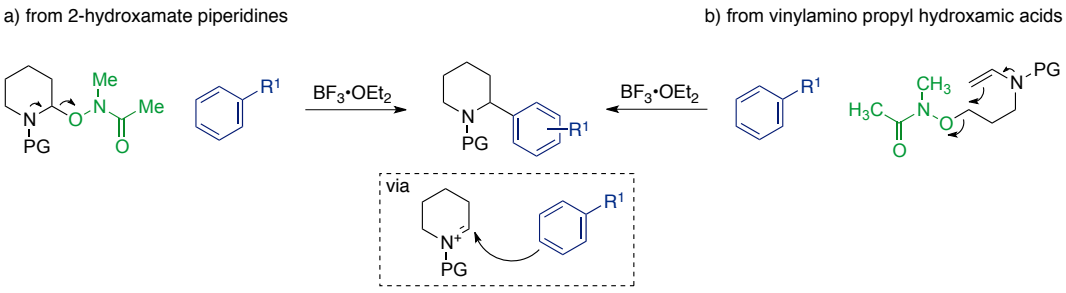
The acylation of aromatic compounds is normally performed via Friedel-Crafts acylation processes using acid chlorides as acylating reagents and a strong Lewis acid catalyst (e.g. $AlCl_3$). The two major drawbacks of this chemistry are the generation of

stoichiometric amount of HCl, the limitation to activated arenes and high reaction temperatures.[58] However, the use of an acylated version of our hydroxamate leaving group could provide an attractive alternative and probably overcome the inherent limitations of standard Friedel-Crafts acylation protocols (Scheme 27).



Scheme 27: Friedel-Crafts acylation using hydroxamate leaving group.

2-phenylpiperidines are interesting structural motifs in medicinal chemistry,[63] but only few methods are available for their synthesis.[64] We envision that starting from a suitable 2-hydroxamate piperidine precursor, a reactive iminium intermediate – similar to the oxonium ion in the ether synthesis project – could be formed which would be subsequently attacked by the arene in a Friedel-Crafts-type reaction (Scheme 28a). An alternative approach towards 2-phenylpiperidines would be the use of vinylamino propyl hydroxamic acid derivatives. The BF_3•OEt_2-induced cyclization of this substrate class would lead to the identical iminium intermediate that could then be attacked by aromatic nucleophiles (Scheme 28b).



Scheme 28: Synthesis of 2-phenylpiperidines using hydroxamate leaving group.

The implementation of our powerful hydroxamate leaving group could also be attractive in other substrates classes. Similar to benzylic substrates, allylic systems are known to form resonance-stabilized carbocations with relative ease. The use of such allylic hydroxamates would lead to skipped diene-like products. Furthermore, the formation of an intermediate cyclopropyl methyl- or β-silicon stabilized carbocation from the corresponding *N*-methyl hydroxamic acid could also be envisioned (Figure 4).

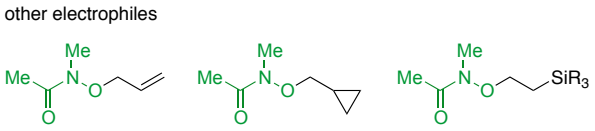
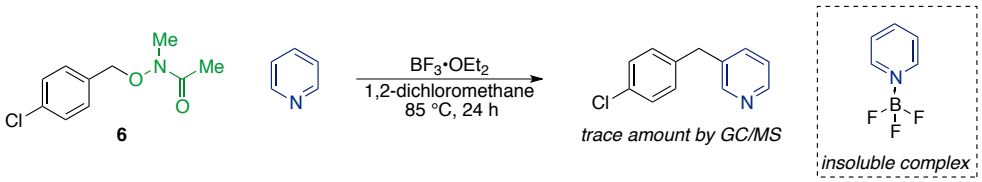


Figure 4: Envisioned hydroxamate-containing electrophiles.

Outlook: New Nucleophilic Coupling Partners

The use of pyridines in our Friedel-Crafts benzylation would be of particular synthetic interest due to the importance of these heterocycles in pharmaceutical applications,[65] and also because the benzylation event should occur with high *meta*-selectivity. In the first attempt to use simple pyridine as the nucleophile in our Friedel-Crafts benzylation, only trace amount of the desired product was observed (Scheme 29). In our opinion, the major problem was not the electron-deficiency of the heterocyclic substrate, but the formation of an insoluble pyridine-BF_3 adduct that prevented the participation of the nucleophile in the reaction.



Scheme 29: Suzuki-Miyaura coupling.

Three possible solutions to this problem can be anticipated. 1) The use of a more polar solvent than dichloromethane or 1,2-dichloroethane, e.g. a mixture of 1,2-dichloroethane and hexafluoroisopropanol, a solvent known to exhibit strong hydrogen bonding properties enabling it to dissolve substances that serve as hydrogen-bond acceptors (e.g. pyridines). This hydrogen bonding interaction to the pyridine moiety should break up the boron-nitrogen complex. 2) The use of a more oxophilic Lewis acid than BF_3•OEt_2 should favor the binding of the Lewis acid to the hydroxamate over the pyridine scaffold. Titanium based Lewis acids are known to be highly oxophilic. $Ti(OiPr)_4$ (titanium isopropoxide) could be an attractive solution, as it is cheap and easily handled. 3) The slow addition of BF_3•OEt_2 over several hours (e.g. via syringe pump) would keep the active concentration of the Lewis acid low and could prevent precipitation or formation of the pyridine adduct.

As previously discussed, the use of boronic acid derivatives was successful in the "ether project",[57] but could not be employed in the Friedel-Crafts benzylation chemistry due to the formation of regioisomers (see Chapter 4.1). For potassium alkyl-, alkenyl- or alkynyltrifluoroborates the problem of regioisomer formation does not exist and the use of these coupling partners could be an attractive alternative to traditional Friedel-Crafts alkylation reactions. Another highly interesting coupling partner is potassium trifluoro(trifluoromethyl)borate, which would open a new way for benzylic trifluoromethylations without the use of expensive metal-catalysts or electrophilic trifluoromethylating reagents (Figure 5).

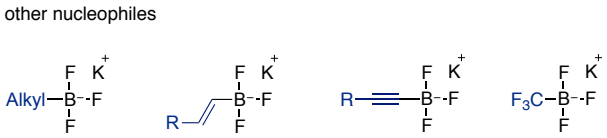


Figure 5: Alternative trifluoroborate reagents.

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PART II

THE ADDITION OF GRIGNARD REAGENTS TO ISOCYANATES

1. Background and Introduction

Amides are an integral part of our daily life, because they play a key role in the composition of biological systems.[1] Proteins are assembled of a specific setting of amino acids that are all linked together by amide bonds.[2] These amide linkages not only hold the amino acids together, but also define the secondary structure of the protein due to the hydrogen bonding ability of the amide functional group (Figure 1a). Amide bonds are not only present in biological systems, but have become a ubiquitous structural motif in a huge array of pharmaceuticals and biologically active compounds. An impressive example is Atorvastatin, a cholesterol production blocker developed by Pfizer and one of the top selling drugs worldwide, which consists of an essential *N*-phenyl amide bond (Figure 1b).[3] Furthermore, several structural materials and synthetic fibers are polyamides, such as Nylon or Aramid; the latter one being used in aerospace and in bulletproof vests, highlighting the strength of this synthetic material (Figure 1c).[4]

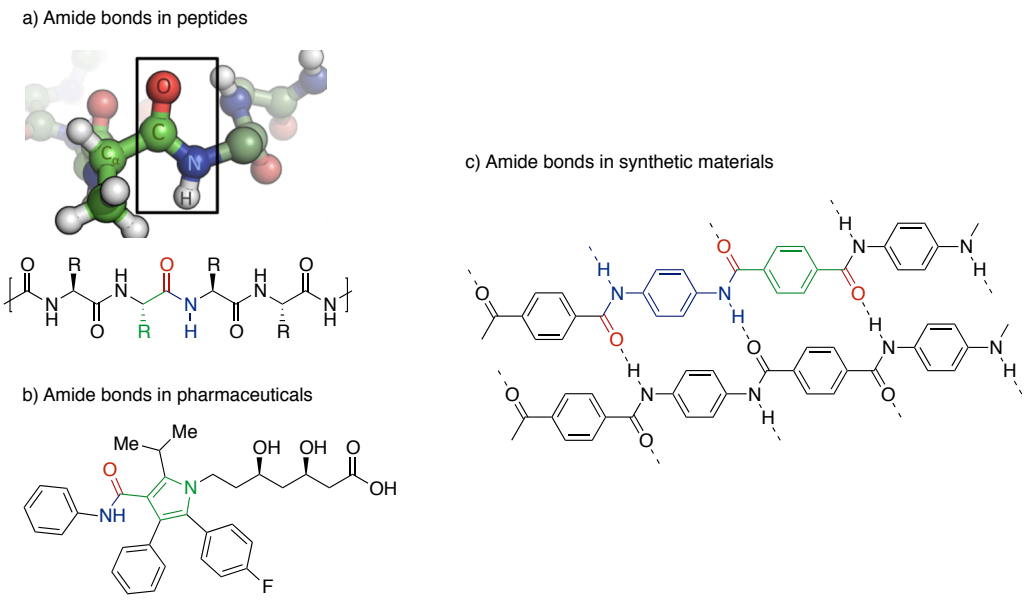


Figure 1: Amide bonds as integral part of daily life.

The widespread use of the amide functionality can be attributed to its special chemical properties (Figure 2). The amide functionality induces a structural rigidity to a certain compound due to its restricted C–N bond rotation. The high rotation barrier of amides arises from the partial double bond character, contributing to both of the amide resonance forms **A** and **B**. Furthermore, amides act as both hydrogen donors and acceptors, which can result in a very specific drug-protein interaction. The amide bond is highly inert towards

nucleophilic attacks and is resistant to hydrolysis, which is reflected in the high stability of our proteins.[5]

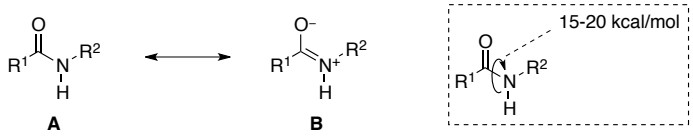
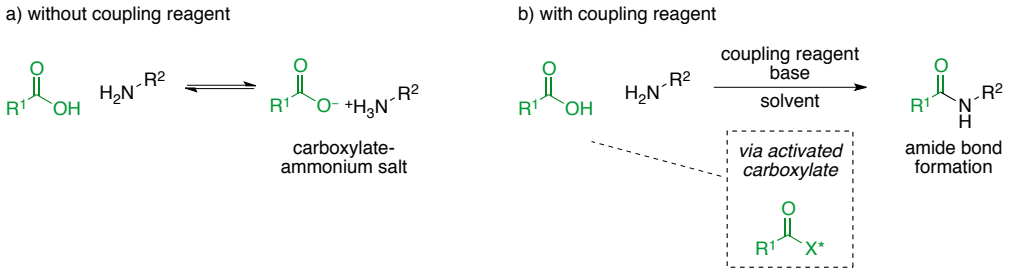


Figure 2: Amide resonance structures.

In living systems, the majority of amides are formed by ribosomes. These large, sophisticated molecular machines assemble complex proteins amino acid by amino acid in the order specified by the messenger RNA.[6] The efficacy of this templated polypeptide synthesis is remarkable, however, synthetic chemists do not have the privilege to work on such a single-molecule scale and therefore have to create an alternative approach. The most common method to prepare amides in a chemical laboratory is the condensation of an amine with a carboxylic acid. Nonetheless, this is not a trivial reaction due to its unfavorable thermodynamics, and the two functional groups simply form a carboxylate-ammonium salt instead of an amide bond (Scheme 1a). For a successful amide bond-forming reaction, a coupling reagent has to be used. The role of the coupling reagent is the transformation of the carboxylic acid moiety into an activated carboxylate, which is then attacked by the amine to generate a new amide bond (Scheme 1b).[7]



Scheme 1: Amide bond formation with coupling reagents.

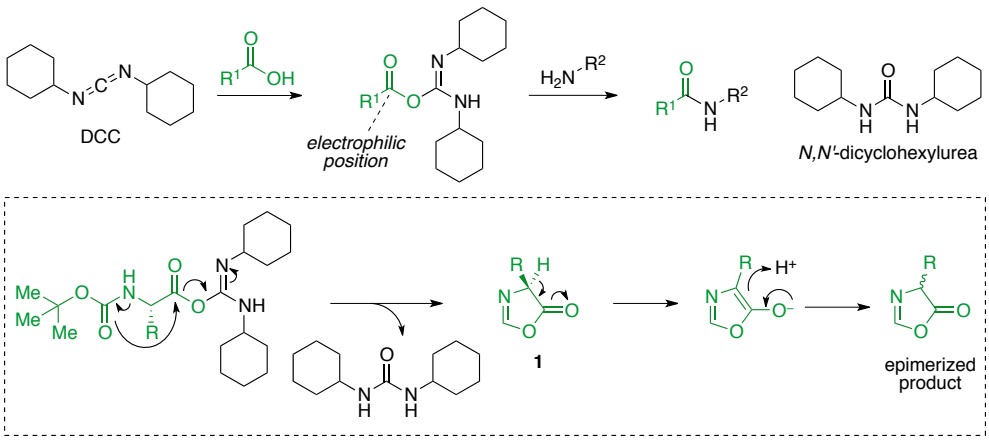
In the following chapters a brief overview will be given over recent advances in amide bond formation, primarily focusing on the solution-phase synthesis of secondary amides. Solid-phase peptide synthesis (SPPS) and other peptide-forming ligation reactions will not be discussed in the scope of this doctoral thesis.

2. Amide Bond Formation

2.1. Coupling Reagent-Based Amide Bond Formation

In a recently published study, Roughley and Jordan analyzed a wide range of medicinal chemistry campaigns and found that coupling-reagent based amide bond formation is the most used chemical reaction in drug discovery, accounting for 16% of all reactions.[8] The choice of the coupling reagent is critical, because in a medicinal chemistry library the corresponding amides are often generated from a broad range of substrates with varying reactivities. Therefore, many different coupling reagents are now commercially available, giving the customer the opportunity to screen for the most suitable reagent for a specific chemical transformation if standard conditions fail to provide the product.[7]

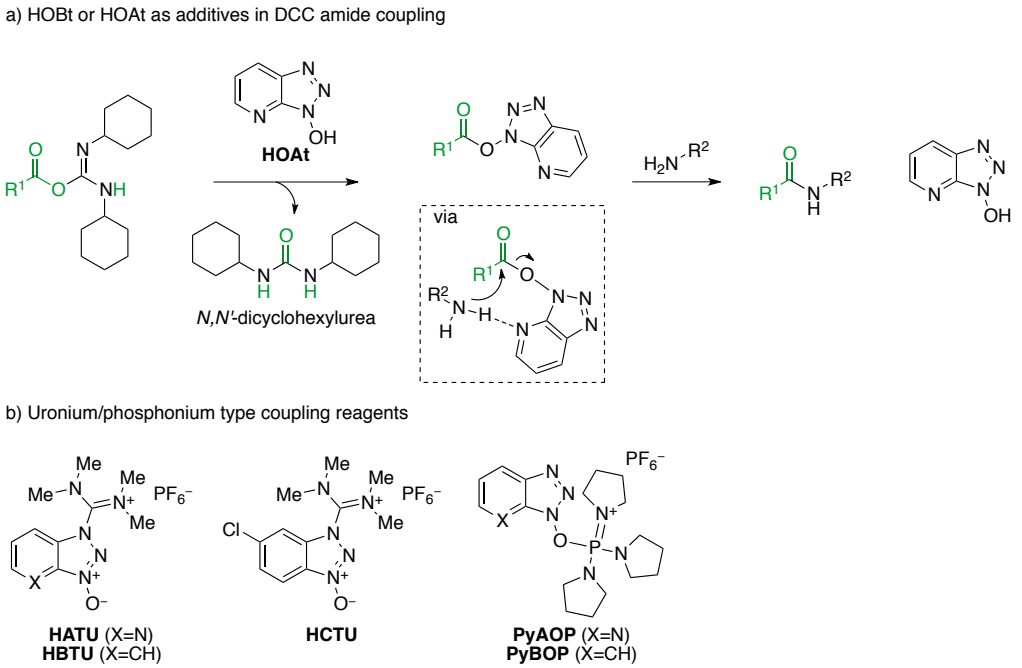
The simplest activation of a carboxylic acid is the conversion into the corresponding acid chloride, which can react with an amine to form an amide bond. This is known as the Schotten-Baumann reaction and was described as early as 1883.[9] Over 70 years later, *N,N'*-dicyclohexylcarbodiimide (DCC) was introduced as the first coupling reagent by Hess and Sheehan (Scheme 2).[10] DCC and other carbodiimides convert the amino acid *in situ* into an activated *O*-acylurea, which undergoes a nucleophilic attack of the amine to provide the desired amide and dicyclourea as a by-product. This approach has several limitations, such as the formation of unwanted by-products, the most problematic one being oxazolone **1**, which leads to epimerization of the α-position of the amide product.



Scheme 2: *N,N'*-dicyclohexylcarbodiimide (DCC)-activation mode.

To solve this problem, several additives were introduced to lower racemization levels. Koenig (1970)[11] and Carpino (1993)[12] introduced 2-hydroxy-1*H*-benzotriazole (HOBt) and 1-hydroxy-7-aza-benzotriazole (HOAt). These additives react with the *O*-acylurea to form a

new activated ester, which is less reactive, but stabilizes the approach of the nucleophilic amine via hydrogen bonding interactions (Scheme 3a). Despite the widespread use of carbodiimide-based approaches in process chemistry, the recent development of novel coupling reagents opened the door for alternative strategies. Uronium (HATU, HBTU and HCTU)[13] and phosphonium salts (PyAOP and PyBOP)[14] represent the widest class of such novel coupling reagents and are now commonly used in SPPS without the problem of potential peptide epimerization (Scheme 3b). The mode-of-action of these reagents is the release of a molecule of hydroxybenzotriazole after the initial attack of the carboxylic acid onto the uronium/phosphonium moiety, and then undergo the same type of mechanism as described in Scheme 2.



Scheme 3: HOBt and HOAt as additives for DCC-promoted couplings and novel coupling reagents.

The literature on coupling reagents is almost endless, and several reviews have been dedicated to this topic.[7,15] Despite the success and remarkable generality of the coupling reagent-based dehydrative coupling of amines with carboxylic acids, the use of these coupling reagents on an industrial scale is seen rather critically, due to their expensive nature and poor atom-economy.[16] While the cost of goods can be justified for the synthesis of therapeutic peptides in order to avoid potential epimerization, the synthesis of small achiral amide products with coupling reagent is often not cost-effective. Therefore, the development of more elegant and sustainable amide bond-forming reactions has become one of the most active research fields in organic chemistry.

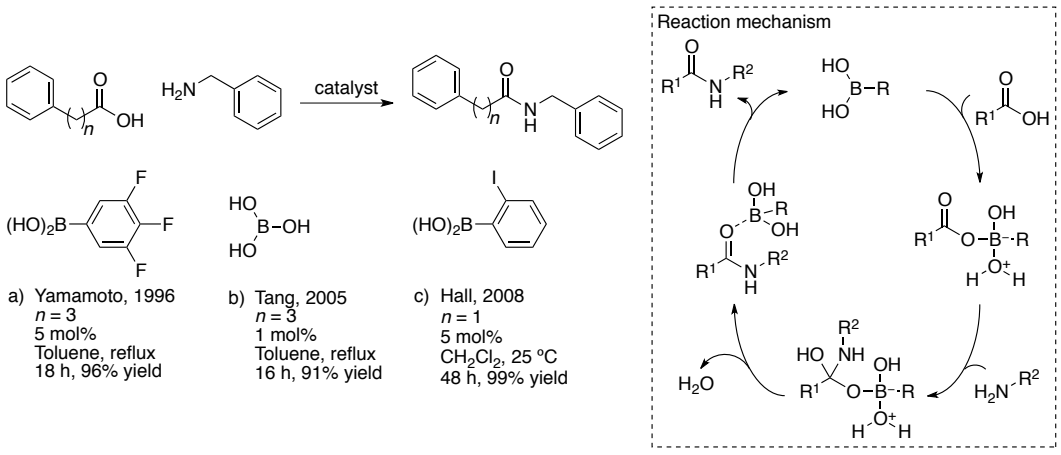
2.2. Coupling Reagent-Free Amide Bond Formation

2.2.1. Catalytic Generation of Activated Carboxylate

Traditional amide bond formation is based on the stoichiometric generation of the activated carboxylate from a carboxylic acid and a coupling reagent. As previously discussed, the major disadvantages of this approach are the poor atom-economy and the high costs. Several research groups have worked on circumventing the use of coupling reagents and developed many different catalysts that allowed for the catalytic generation of the activated carboxylate.

Catalytic Generation of Activated Carboxylate from Carboxylic Acids

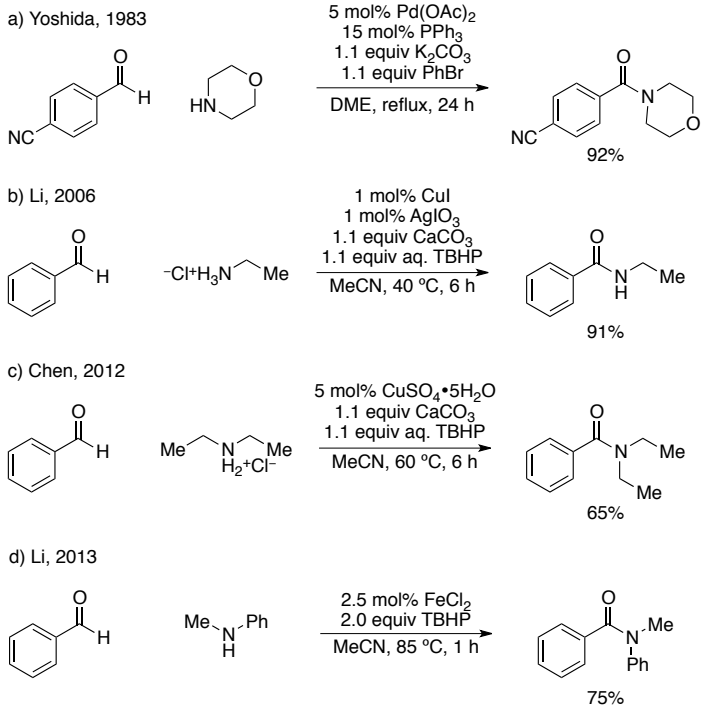
In 1996, Yamamoto and coworkers investigated the use of different boronic acids as amidation catalysts.[17] The best catalytic activity in the reaction of 4-phenylbutyric acid with phenethylamine was found for 3,4,5-trifluorobenzeneboronic acid (Scheme 4a). Tang reported the successful use of catalytic amounts of simple boric acid in the same reaction (Scheme 4b).[18] Recently, Hall *et al*. found that phenylboronic acids bearing *ortho*-halogens were superior catalysts, and the coupling reaction could be carried out at room temperature and the amide product was obtained in quantitative yield (Scheme 4c).[19] Marcelli intensively studied the mechanism of this reaction.[20] He proposed a catalytic cycle, in which the boronic acid is initially attacked by the carboxylic acid to form a tetracoordinated monoacyl boronate. This activated carboxylate reacts further with the amine and the resulting hemiaminal collapses under elimination of H_2O to the amide product.



Scheme 4: Boronic acid-catalyzed amidation.

Catalytic Generation of Activated Carboxylate from Aldehydes

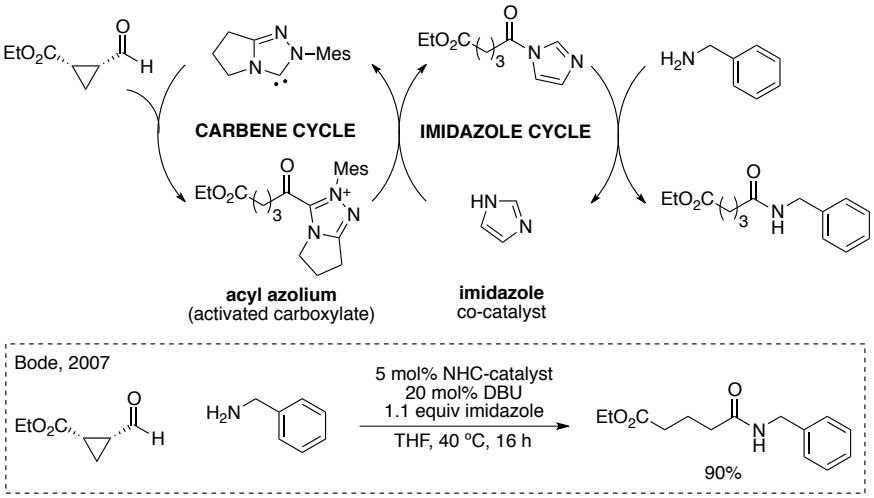
The oxidative transformation of aldehydes to amides is an attractive alternative to carboxylic acid based approaches. The requirement of such a reaction is that after nucleophilic attack of the amine onto the aldehyde, the formed hemiaminal can be efficiently oxidized to the corresponding amide by a sacrificial oxidant. In 1983, Yoshida reported the palladium-catalyzed oxidative transformation of aldehydes to amides using phenyl bromide as sacrificial oxidant (Scheme 5a).[21] The mechanistic proposal involves oxidative addition of the aromatic bromide to Pd(0), followed by ligand exchange with the deprotonated hemiaminal. The alkoxypalladium species then undergoes β-hydride elimination to form the desired amide and benzene as by-product. Based on the same concept, Li reported a copper-catalyzed oxidative amidation reaction employing *tert*-butyl hydroperoxide (TBHP) as stoichiometric oxidizing agent (Scheme 5b).[22] Chen and coworkers expanded the substrate scope of Li's reaction to primary and tertiary amides (Scheme 5c).[23] The iron-catalyzed version of this reaction was also recently developed (Scheme 5d).[24]



Scheme 5: Transition metal-catalyzed oxidative amidations.

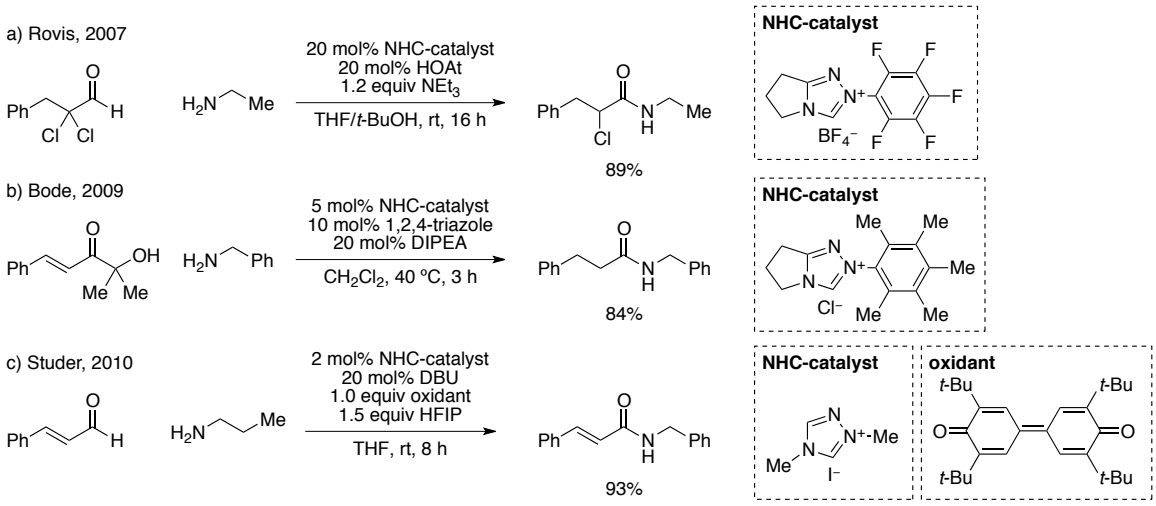
Our group also contributed in the field of catalytic generation of activated carboxylates via N-heterocyclic carbene (NHC)-catalyzed internal redox reactions of α-functionalized aldehydes (Scheme 6).[25] A common intermediate of these internal redox reactions is the acyl

azolium species (activated carboxylate), which normally gets readily attacked by the nucleophile to form the desired product and regeneration of the NHC-catalyst. However, this acyl azolium does not undergo nucleophilic displacement with amines. The finding that imidazole was able to act as a relay shuttle to form a second activated ester that was prone to the nucleophilic attack of amines, paved the way for new NHC-catalyzed amidation reactions.



Scheme 6: NHC-Catalyzed internal redox amidation.

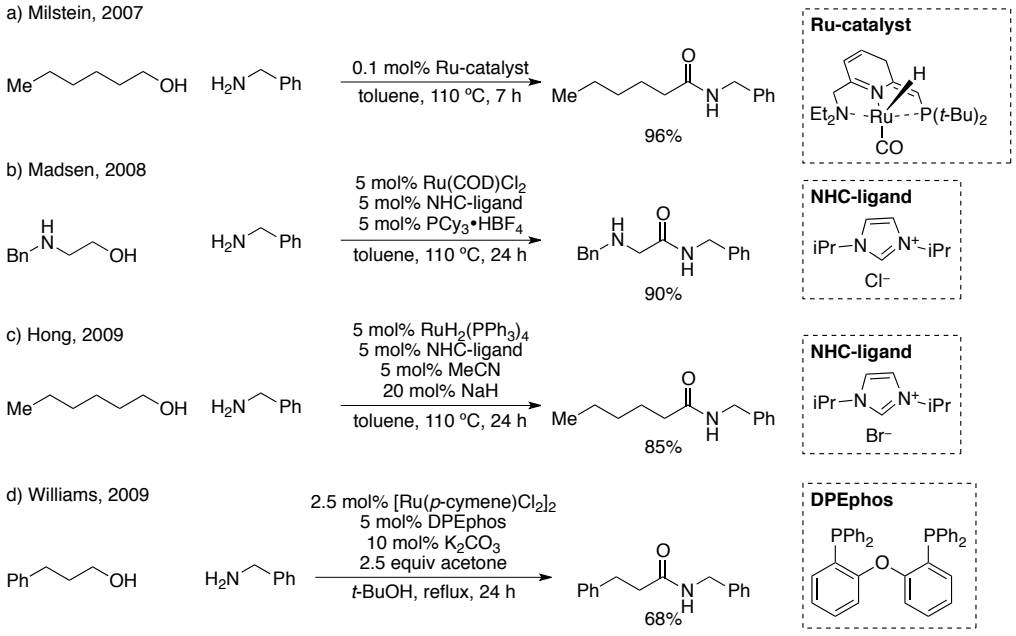
Several other α-functionalized aldehydes were introduced for NHC-catalyzed amidations, including α,α-dichlorinated aldehydes using HOAt as relay catalyst (Scheme 7a),[26] α'-hydroxyenones using 1,2,4-triazole as co-catalyst (Scheme 7b)[27] and simple aldehydes in combination with a stoichiometric oxidant (Scheme 7c).[28]



Scheme 7: NHC-Catalyzed internal redox amidations.

2.2.2. Oxidative Amide Bond Formation from Alcohols

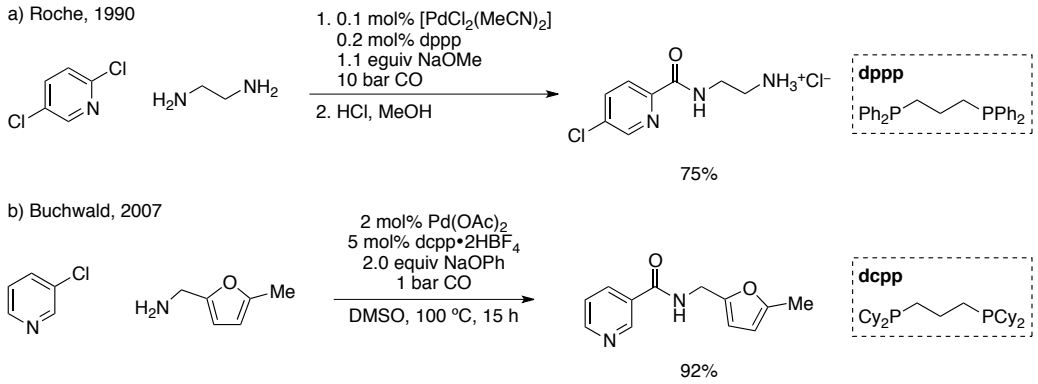
In 2007, Milstein reported the acylation of primary amines by an equimolar amount of alcohols to form amides and hydrogen gas using a highly active ruthenium pincer-complex catalyst (Scheme 8a). [29] This reaction proceeds via ruthenium-promoted dehydrogenation of the alcohol to the aldehyde, followed by its reaction with the amine. The formed hemiaminal is subsequently dehydrogenated to the amide under H_2 liberation. Several other research groups picked up the concept pioneered by Milstein. Madsen *et al.* used a ruthenium catalyst bearing a mixed NHC/phosphine ligand system for the oxidative amidation of amines and alcohols (Scheme 8b).[30] Hong and coworkers also reported the use of a ruthenium-NHC-system in the same reaction (Scheme 8c).[31] From an atom-economical point-of-view, the concept of Milstein is brilliant, because only hydrogen gas is produced as stoichiometric waste. From a reactivity standpoint, this transformation has several limitations, such as the sluggish reaction with aniline derivatives and the incompatibility of secondary amines. The catalyst systems developed by Madsen and Hong showed some minor improvements with these challenging substrates, but the complexity of their systems makes them problematic to use on bigger scale. Inspired by these limitations, Williams and coworkers developed the first commercially available catalyst system for the formation of amides from alcohols and amines, and therefore increased the attractiveness of this novel methodology.[32]



Scheme 8: Direct synthesis of amides from alcohols and amines.

2.2.3. Carbonylative Amide Bond Formation

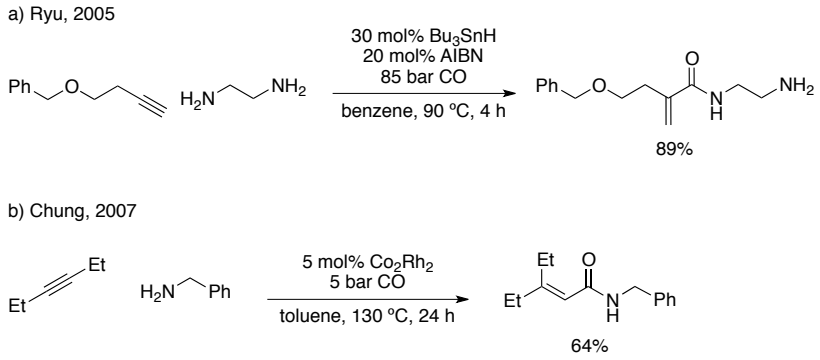
Since the introduction of palladium-catalyzed carbonylation reactions of aromatic halides in the presence of nucleophiles by Heck in 1974,[33] these transformations have undergone a rapid development.[34] Nowadays, a wide range of palladium catalysts is commercially available making these carbonylative processes particularly interesting. Already in 1990, Roche synthesized their monoamine oxidase B inhibitor Lazabemide via aminocarbonylation of 2,5-dichloropyridine with ethylendiamine (Scheme 9a).[35] The low catalyst loading used in this industrial application is remarkable. Many other research groups worked on the same type of transformations, but the first general protocol for the aminocarbonylation of (hetero)aryl halides was presented in 2007 by Buchwald (Scheme 9b).[36] Using a $Pd(OAc)_2$/dcpp catalyst system, several aryl and heteroaryl chlorides were successfully coupled to secondary amines under an atmospheric pressure of carbon monoxide.



Scheme 9: Carbonylative amide bond formation from aryl chlorides.

In 2005, Ryu and coworkers reported the synthesis of acrylamides via radical aminocarbonylation of alkynes with amines (Scheme 10a).[37] Mechanistically, this reaction proceeds via the addition of a tributyltin radical to the alkyne to form a vinyl radical, which then undergoes carbonylation to generate an α-ketenyl radical. Intermolecular trapping of this radical by the amine followed by 1,4-H migration leads to the desired α-methylene amide. However, the synthetic utility of this process is rather limited due to the necessity of a high carbon monoxide pressure and the use of a highly toxic organotin compound. An improved protocol for the synthesis of similar α,β-unsaturated amides from internal alkynes was disclosed by Chung *et al.*, which used a heterobimetallic cobalt-rhodium nanoparticle-catalyst

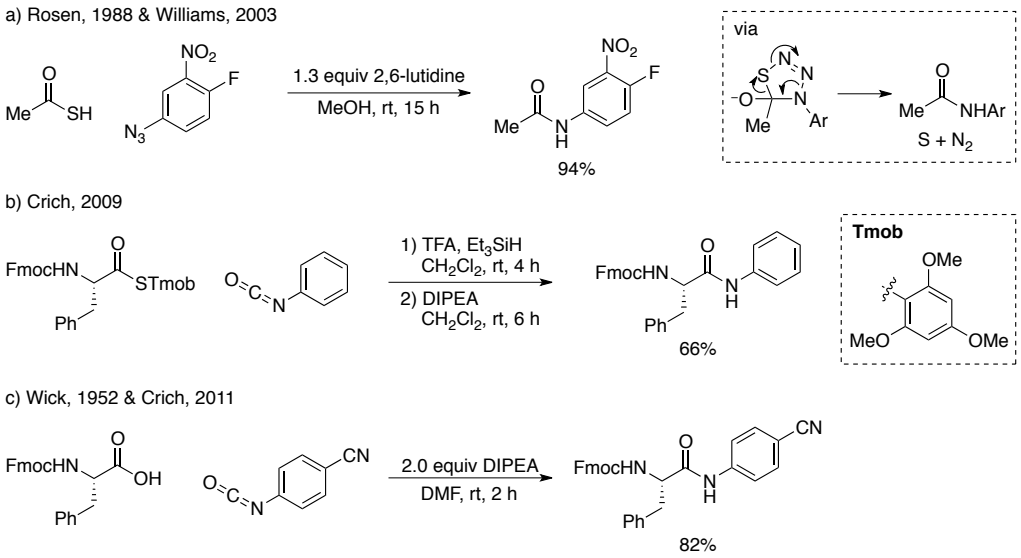
(Scheme 10b).[38] The reaction proceeded under mild conditions and also allowed for the synthesis of acetamides when the alkyne was omitted.



Scheme 10: Carbonylative amide bond formation from alkynes.

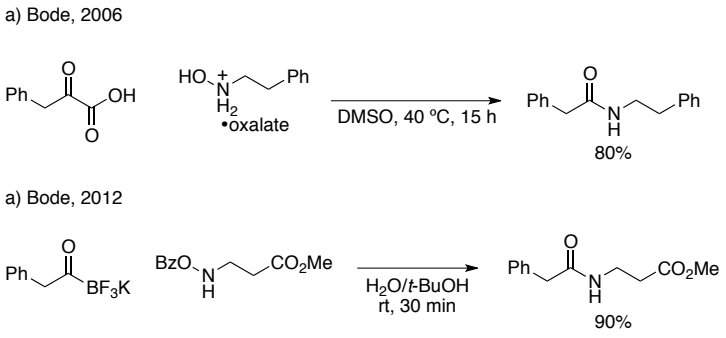
2.2.4. Amide Bond Formation with Amine Surrogates

The development of new substrates in amide-forming reactions was not only focused on the carboxylic acid part, but also in finding surrogates for the traditional amine reaction partner. Many of these newly developed transformations with amine surrogates are highly chemoselective and proceed without the need of expensive catalysts or additives. An early example is the reaction of thioacids with azides developed by Rosen.[39] Williams later investigated the mechanism of this reaction and expanded its substrate scope (Scheme 11a).[40] The reaction is believed to operate via a thiatriazoline intermediate that breaks down to the amide via a [2+3]-cycloaddition, extruding elemental sulfur and nitrogen. Crich reported the use of Tmob thioesters in the reaction with isocyanates.[41] The reaction proceeded at room temperature and allowed for the linkage of different sugar building blocks to aromatic and aliphatic isocyanates (Scheme 11b). Two years later, Crich reported the same reactivity of isocyanates in the reaction with carboxylic acids[42] – a reaction that was originally developed by Wick[43] and Steglich.[44] The protocol is user-friendly, simply mixing the isocyanate and carboxylic acid together in the presence of 2.0 equivalents of base at room temperature (Scheme 11c).



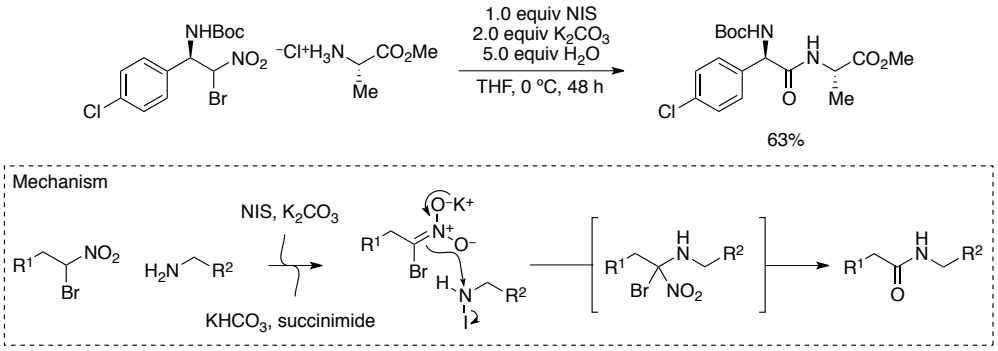
Scheme 11: Amide bond formation with azides and isocyanates.

During the last 10 years the Bode group has reported two new amide bond formation methods using amine surrogates. In 2006, we described the chemoselective, amide bond-forming ligation of hydroxylamines with α-ketoacids (KAHA ligation).[45] This reaction proceeds under mild reaction conditions, requires no reagents or additives and produces only water and CO_2 as by-products (Scheme 12a). Although the KAHA ligation can be used to form simple amide products, its major application lies in the synthesis of larger peptides using a C-terminal peptide α-ketoacid and an N-terminal hydroxylamine. In 2012, our group disclosed a new amide-forming ligation using acyltrifluoroborates and *O*-benzoyl hydroxylamines, without the need for additional promotors or catalysts (Scheme 12b).[46] In contrast to the KAHA ligation, this reaction was much slower in pure polar aprotic solvents such as DMSO or DMF. However, the addition of water, such as a 1:1-mixture of H_2O/*t*-BuOH, was beneficial and a wide range of different amides could be prepared in high yields.



Scheme 12: Amide bond-forming ligation reactions by Bode *et al.*

In 2010, Johnston and coworkers introduced a completely new approach to amide bond formation.[47] They reported the oxidative coupling of α-bromo nitroalkanes with amines in the presence of *N*-iodosuccinimide (NIS) and a base. In this conceptually new Umpolung-type reaction, the nitroalkane plays the role of an acyl anion equivalent, which reacts with the *in situ* formed electrophilic *N*-iodoamine to generate a tetrahedral intermediate, which collapses to the amide via hydrolysis. This method is particularly attractive for the preparation of arylglycine-containing peptides as the reaction proceeds without racemization.



Scheme 13: Umpolung-type amide bond formation.

2.3. Conclusions

The most common reaction for preparing amides is the coupling reagent-based dehydrative coupling of amines with carboxylic acids. A plethora of different coupling reagents are now commercially available, allowing the chemist to choose the most suitable agent for a specific chemical transformation. Despite the remarkable generality of this coupling reagent-based approach, the main disadvantages are its poor atom-economy and the high costs. Not surprisingly, the American Chemical Society Green Chemistry Institute described the *"amide formation avoiding poor atom economy reagents"* as one of the major challenges in synthetic organic chemistry.[16] In recent years, a number of mechanistically unique amide bond formation reactions have been reported that make the use of stoichiometric reagents redundant, such as boronic acid-catalyzed amidation reactions or the use of N-heterocyclic carbenes as effective catalysts in internal redox reactions of α-functionalized aldehydes. Our group has also developed new amide bond-forming ligation reactions that proceed without the addition of any additives or catalysts. These reactions

proceed under mild conditions and set a new standard in the matter of atom-economy and sustainability in the area of amide bond formation.

The improvements described in Chapter 2.2 make it look like there are no remaining challenges in amide bond synthesis. This is a false conclusion. By having a closer look at the substrate scope of most of the previously discussed amide bond-forming reactions, one will realize that a certain amide-class could not be prepared: sterically hindered amides. The synthesis of such sterically hindered amides cannot be easily solved, even with the best coupling reagent in hand or by using novel amide bond-forming reactions. In order to address the challenge of preparing sterically hindered amides, we sought to find a facile and reliable solution to this long-standing unmet synthetic need.

3. The Synthesis of Sterically Hindered Amides

Today, one of the biggest challenges in amide bond formation chemistry is the synthesis of sterically hindered amides – a challenge that cannot be easily solved and which was widely overlooked by synthetic organic chemists.[48] The difficulties associated with the formation of this class of amides stem from the slow nucleophilic attack of the amine onto the activated carboxylate in a sterically congested environment (Figure 3).

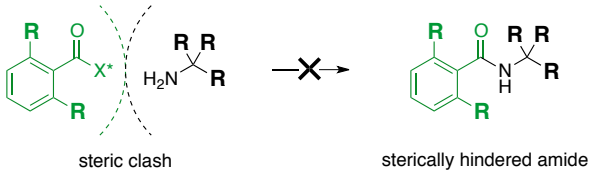
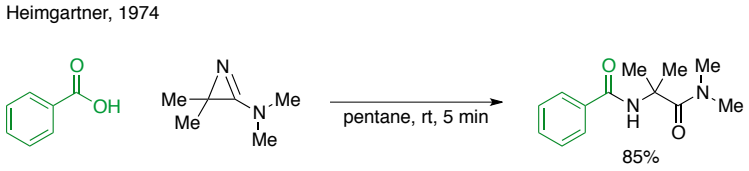


Figure 3: Synthesis of sterically hindered amides.

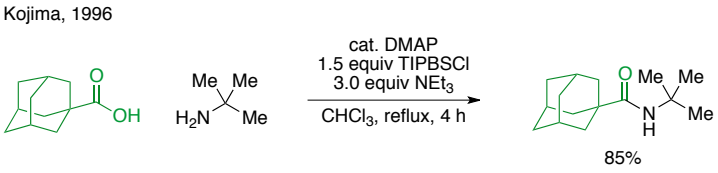
The use of acid chlorides as activated carboxylates in the reaction with amines under harsh reaction conditions (neat base, high temperatures) can be helpful in certain sterically hindered cases, but suffer from a narrow substrate scope and the generation of super-stoichiometric waste. Reports on alternative amide bond formation reactions that effectively generate sterically hindered amides from simple starting materials are scarce. In 1974, Heimgartner and Schmid described the addition of carboxylic acids to 2-dimethylamino-3,3-

dimethyl-1-azirine to form unique 2-amino-*N,N*-dimethylisobutyramides in good yields (Scheme 14).[49]



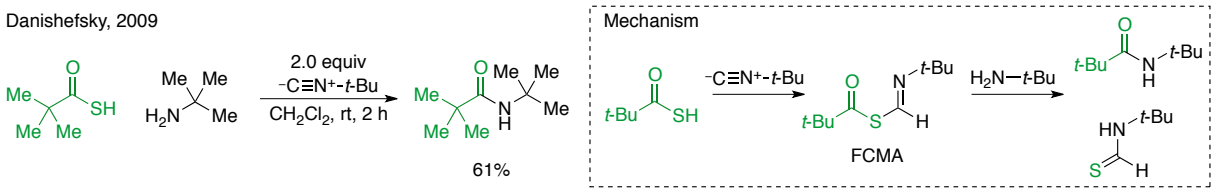
Scheme 14: Synthesis of sterically hindered 2-amino-*N,N*-dimethylisobutyramide.

In 1996, Kojima reported the condensation of adamantyl carboxylic acid with *tert*-butylamine in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride in refluxing chloroform to obtain the sterically hindered secondary amide in high yield (Scheme 15). Unfortunately, only this sole example bearing no functional groups was prepared and no conclusion can be drawn concerning the substrate scope of this approach.[50]



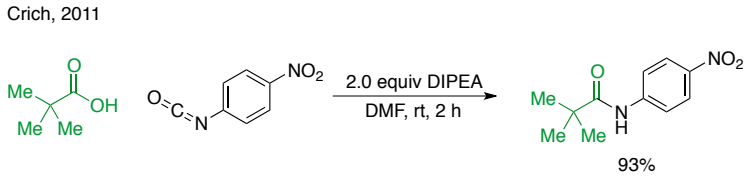
Scheme 15: Synthesis of sterically hindered amide using 2,4,6-triisopropylbenzenesulfonyl chloride .

More recently, Danishefsky and coworkers expanded their thio acid-isonitrile methodology towards the formation of sterically hindered amides (Scheme 16).[51] The combination of a thio acid with an isonitrile generates a formimidate thiocarboxylate anhydride intermediate (FCMA), which can be intercepted by the addition of a nucleophile to form a secondary amide. A small collection of bulky amides was prepared, but the formation of stoichiometric thioformamide by-product and the use of toxic and malodorous isonitriles make this approach unattractive on bigger scale.



Scheme 16: Synthesis of sterically hindered amides via FCMA intermediates.

In 2011, Crich and Sasaki disclosed the formation of amide bonds from carboxylic acids and isocyanates under mild conditions (Scheme 17).[44] Several sterically hindered carboxylic acids could be used in the reaction with sterically unbiased isocyanates. Unfortunately, all reactions were run on a very small scale (0.1 mmol) and it is difficult to predict if this reaction can provide a reliable solution for the synthesis of sterically hindered amides on an industrial scale.

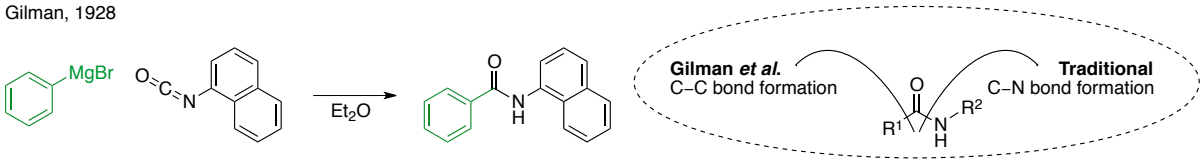


Scheme 17: Synthesis of sterically hindered amides from isocyanates.

The above-discussed reactions present the first improvements in the synthesis of sterically hindered amides. However, these are only small steps in the right direction considering that those reactions often fail in terms of generality, introduction of sensitive functional groups or atom-economy. Concerning this lack of a general protocol for sterically hindered amides, we sought to find a facile and reliable solution of this long-standing unmet synthetic need.

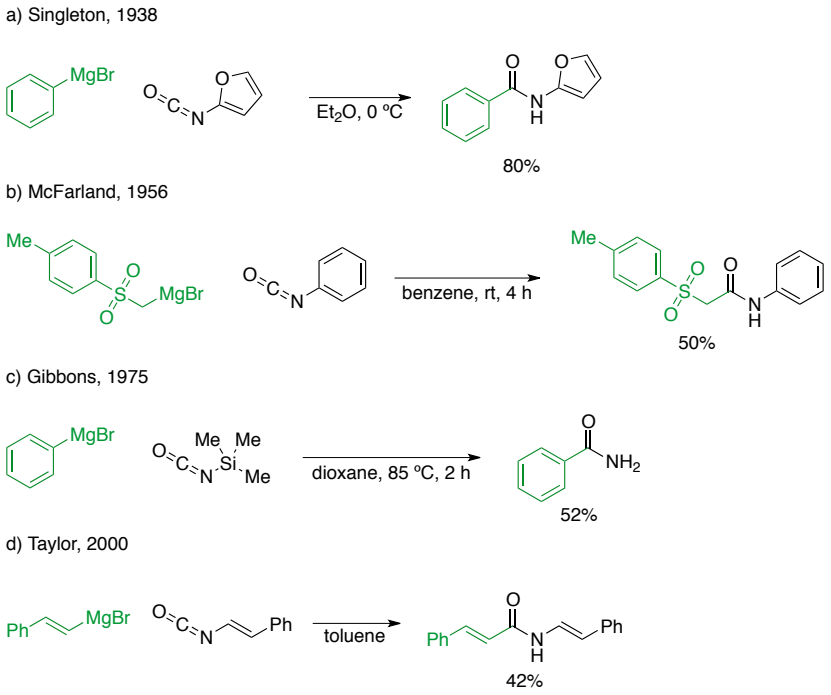
4. The Addition of Grignard Reagents to Isocyanates

In our own effort to find a practical method for the preparation of sterically hindered amides we performed an extensive literature survey and came across two interesting reports from Gilman, wherein he describes the addition of Grignard reagents to isocyanates to form amide bonds (Scheme 18).[52]



Scheme 18: Addition of Grignard reagents to isocyanates as described by Gilman *et al*.

Two factors about this reaction were intriguing to us: 1) Gilman described a C–C bond forming approach for amide synthesis, which is in contrast to the standard coupling reagent-based C–N bond formation process; and 2) since this seminal work of Gilman, only a few applications of this reaction have appeared in the literature in the last 85 years. In 1938, Singleton reported the synthesis of 2-aminofuran derivatives via the addition of Grignard reagents to 2-furyl isocyanate (Scheme 19a).[53] McFarland disclosed the use of more exotic sulfone-derived Grignard reagents and their addition to phenyl isocyanate to provide sulfonyl anilides (Scheme 19b).[54] Later, Gibbons synthesized primary amides from trimethylsilyl isocyanate and organomagnesium reagents,[55] and Taylor used the addition of vinylogous Grignard reagents to isocyanates in the synthesis of naturally occurring enamides (Scheme 19c and 19d).[56] We reasoned that the missing broader implementation of Gilman's chemistry into synthetic organic laboratories was due to the fact that Gilman and coworkers themselves were not interested in the amide products as such, but rather in finding a way to accurately identify and quantify their Grignard reagents. Even more intriguing, no literature reports on the synthesis of sterically hindered amides using the addition of Grignard reagents to isocyanates could be found.



Scheme 19: Amide bond formation via addition of Grignard reagents to isocyanates.

We were highly interested in Gilman's chemistry, because we had a strong belief that this reaction could be successfully used in the synthesis of sterically hindered amides. Bulky organomagnesium reagents are known to remain highly nucleophilic and they are commonly used in the synthesis of sterically demanding ligands for cross-coupling reactions (e.g. BrettPhos developed by Buchwald).[57] The electrophilic carbon-atom of the isocyanate moiety is not in close proximity to the steric bulk and should be easily attacked by the reactive Grignard reagent to form sterically congested amides. Furthermore, a wide range of both coupling partners is commercially available increasing the attractiveness of this approach (Figure 4).

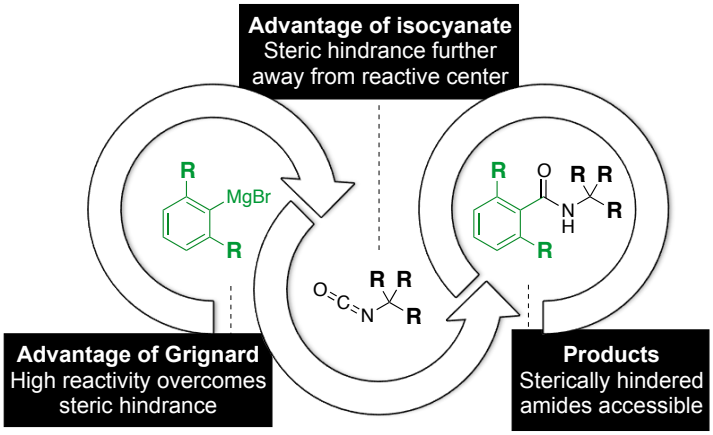
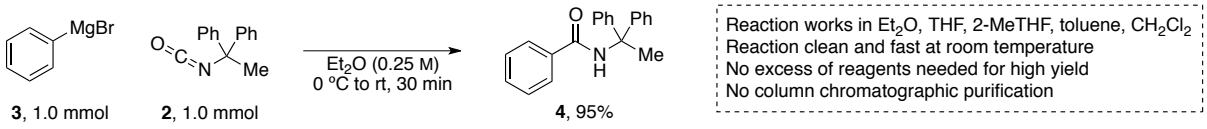


Figure 4: Envisioned synthesis of sterically hindered amides via addition of Grignard reagents to isocyanates.

4.1. Reaction Development and Substrate Scope

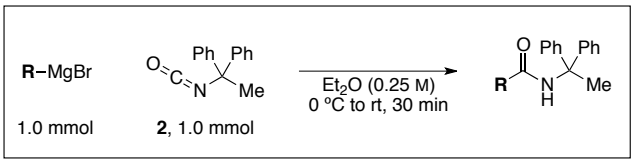
We began our investigation by using sterically hindered isocyanate **2** as a model substrate in the reaction with phenylmagnesium bromide (**3**). We found that the reaction could be successfully conducted under a variety of conditions, but found that the addition of the Grignard reagent (3.0 M in Et_2O, 1.0 equiv) to an ethereal solution of the isocyanate (0.25 M in Et_2O, 1.0 equiv) at 0 °C followed by warming to room temperature gave the best results, providing the desired amide **4** in nearly quantitative yield. The analytically pure product was obtained after aqueous workup and simple washing of the crude material with hexanes, without the need for further purification steps.

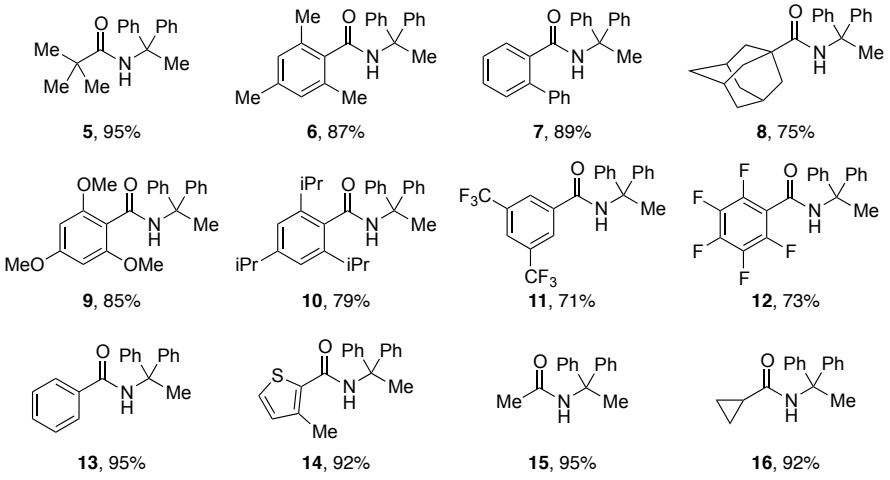


3, 1.0 mmol **2**, 1.0 mmol **4**, 95%

Scheme 20: Synthesis of sterically hindered amide **4**.

Driven by the success of the initial result with phenylmagnesium bromide (**3**) the addition of sterically hindered Grignard reagents to isocyanate **2** was explored (Scheme 21).

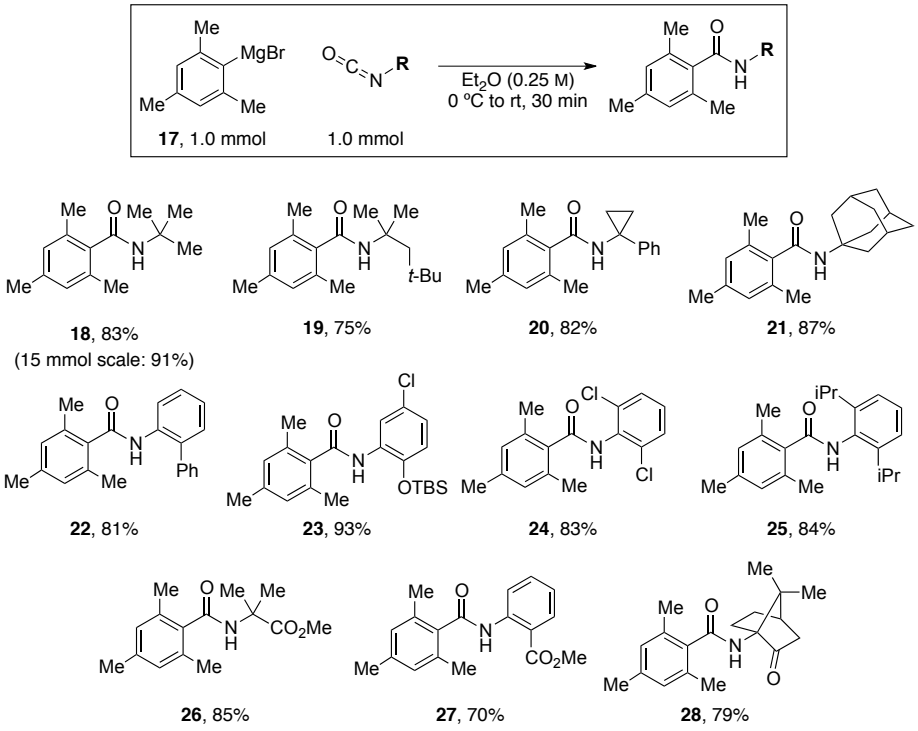




Scheme 21: Substrate scope of Grignard reagent.

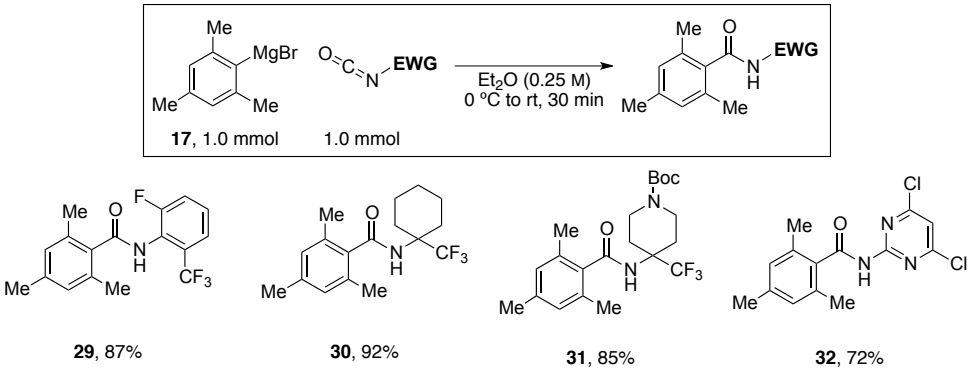
To our delight, hindered Grignard reagents including *tert*-butyl, mesityl and 2-biphenyl Grignard cleanly added to the isocyanate to give amide products **5**–**7** in excellent yields. Even the extremely bulky adamantyl, 2,4,6-trimethoxyphenyl and 2,4,6-triisopropylphenyl Grignard reagents provided desired products **8**–**10** in good yield, showing that the steric bulk of the organometallic reagents does not significantly influence the effectiveness of this reaction. The use of electron-poor Grignard reagents was also possible, as well as heterocyclic and sterically unbiased aliphatic organomagnesium reagents. In none of the examples over-reaction of the Grignard reagent with the resulting amide could be observed; this proved to be the case even when less hindered substrates were used.

To explore the versatility of our methodology, other sterically hindered isocyanates in the reaction with mesitylmagnesium bromide (**17**) were examined (Scheme 22). Sterically congested isocyanates such as *tert*-butyl, *tert*-octyl, 1-phenylcyclopropyl, or adamantyl isocyanate were excellent substrates and delivered amide products **18**–**21** in high yields. Amide **18** was synthesized on a 15 mmol scale using 2-methyl THF as a more industry-friendly solvent,[58] highlighting the potential of this reaction towards applications in pharmaceutical and agrochemical companies. The preparation of bulky, aromatic amides **24** and **25** was also feasible using the direct coupling of mesityl Grignard to 2,6-dichlorophenyl- and 2,6-diisopropylphenyl isocyanate. Furthermore, the chemoselective addition of Grignard reagents to isocyanates bearing ester or ketone functional groups could be achieved, and the corresponding amides **26**–**28** were obtained in good yield.



Scheme 22: Substrate scope of isocyanate.

Besides sterically hindered amides, a second class of amides is known to be very difficult to prepare via condensation chemistry: Amides derived from electron-deficient amines, particularly anilines. The reason for this lies in the poor nucleophilicity of electron-deficient amines, which renders their application in coupling reagent-based approaches challenging, because they will not easily attack the activated carboxylate. In contrast, isocyanates bearing electron-withdrawing groups are even more reactive than their electron-rich or neutral counterparts and should be readily attacked by Grignard reagents. In fact, when 2-fluoro-6-(trifluoromethyl)phenyl isocyanate was treated with mesitylmagnesium bromide (**17**) the desired amide **29** was isolated in excellent yield – an amide that would be very hard to prepare via condensation chemistry due to its steric hindrance and the use of an unreactive electron-poor aniline starting material (Scheme 23). Furthermore, our conditions were applicable to the synthesis of hindered, electron-deficient, aliphatic amides **30** and **31** derived from α-trifluoromethyl substituted isocyanates. These *alpha*-trifluoromethyl substituted amides could serve as promising building blocks in medicinal chemistry.[59] The use of a pyrimidyl isocyanate was also possible to obtain the interesting heterocyclic amide **32** in good yield.



Scheme 23: Synthesis of electron-deficient amides.

At the end of this project, we wanted to test the limits of the isocyanate/Grignard-methodology in terms of steric hindrance, and combined the most sterically hindered substrates from each reaction partner. Using our standard conditions, the exceptionally hindered amides **33** and **34** were prepared with ease and in good yields, setting a benchmark in the area of steric hindrance in amide bond synthesis (Figure 5).

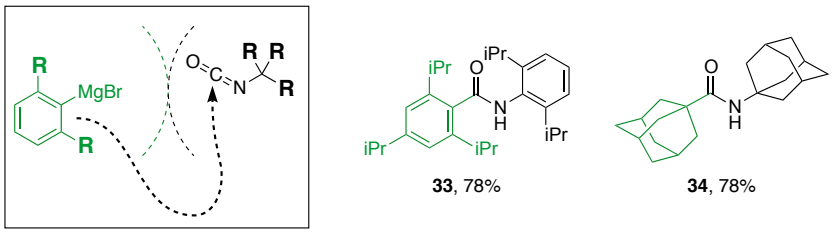
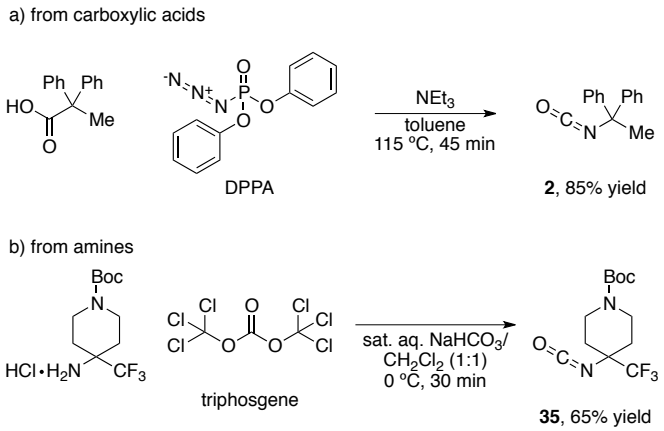


Figure 5: Synthesis of exceptionally hindered amides **33** and **34**.

The synthesis of sterically hindered and electron-deficient amides is considered as an unsolved challenge in the area of amide bond formation. The addition of Grignard reagents to isocyanates provides a general and robust solution to both of these challenging products and a wide range of sterically hindered and electron-deficient amides can be synthesized with ease and in high yields.[60] The isocyanate/Grignard-protocol does not need any excess amount of reagents, the reactions are finished within minutes at room temperature and the products are easily purified.

4.2. Synthesis of Isocyanates

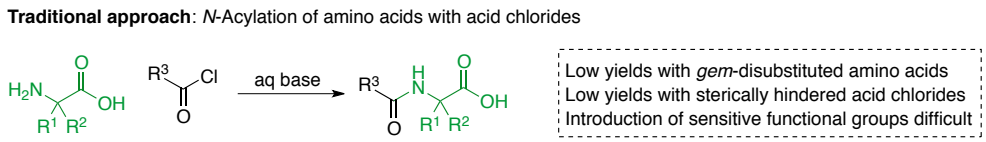
A criticism of our work is the use of isocyanates, a class of compounds that is biased with a poor reputation since the Bhopal accident with methyl isocyanate. It is important to note that isocyanates with a higher molecular mass, especially sterically hindered examples, can be handled without precautions and are completely stable compounds. A major advantage of the use of isocyanates is that they are highly appreciated starting materials in polymer chemistry and therefore many of them are commercially available[61] or can be readily prepared via well-established methods.[62] The most common method for isocyanate formation is the Curtius rearrangement starting from a carboxylic acid. This reaction proceeds via initial formation of an acyl azide, using an azide transfer reagent such as diphenylphosphoryl azide (DPPA), which rearranges under thermal conditions to the isocyanate. Another reliable method for isocyanate formation is the phosgenation of amines under basic conditions. The sterically hindered isocyanates prepared via both of these methods can be easily purified by column chromatography or distillation (Scheme 24).



Scheme 24: Synthesis of isocyanates.

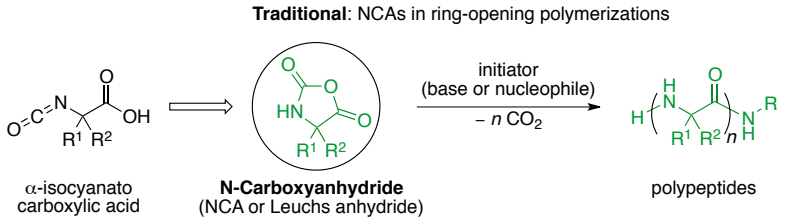
5. Synthesis of Sterically Hindered *N*-Acyl, *gem*-Disubstituted Amino Acids

The direct *N*-acylation of unprotected amino acids can be seen as a subcategory of amide bond formation. Traditionally, *N*-acyl amino acids are prepared from the corresponding amino acid and an acid chloride under basic conditions (Scheme 25).[63] Despite the generality of this approach for sterically unbiased starting materials, the reaction is usually low yielding for sterically hindered examples – comparable to traditional dehydrative amide bond-forming reactions – and is also not compatible with sensitive functional groups. Furthermore, the carboxylic acid by-product stemming from the unreacted acid chloride can render the purification of the desired *N*-acylated amino acid difficult.



Scheme 25: Acylation of amino acids.

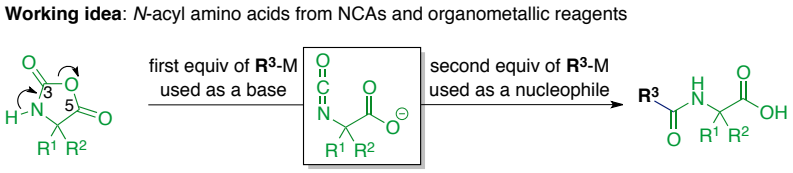
Despite the broad substrate scope of the isocyanate/Grignard-methodology,[60] the synthesis of sterically hindered, *N*-acylated amino acids was not possible. The reason for this was the lack of a suitable starting material, namely an α-isocyanatocarboxylic acid – a molecule possessing an electrophilic isocyanate moiety and a potentially nucleophilic carboxylate in close proximity. We wanted to find a solution for this limitation and were intrigued by the extensive literature on *N*-carboxyanhydrides (Leuchs anhydrides or NCAs);[64] a substrate class commonly used as starting materials in the preparation of polypeptides via ring-opening polymerization (Scheme 26).[65]



Scheme 26: *N*-Carboxyanhydrides in polymer chemistry.

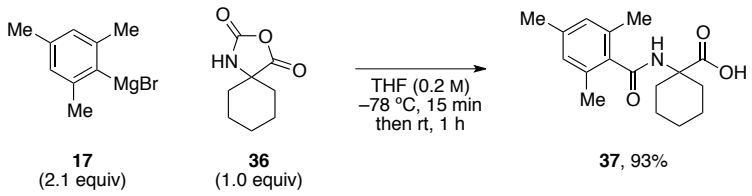
5.1. Reaction Discovery

We speculated that NCAs could serve as α-isocyanatocarboxylic acid surrogates in combination with two equivalents of a Grignard reagent. The first equivalent of Grignard reagent serves as a base and abstracts the N–H proton, upon which an α-isocyanatocarboxylate is released. This deprotonation event should be faster than the corresponding attack of the Grignard reagent at the electrophilic anhydride carbonyl C5. The reactive isocyanate intermediate is subsequently attacked by the second equivalent of organometallic reagent to form the desired amide bond (Scheme 27).



Scheme 27: *N*-Carboxyanhydrides as α-isocyanatocarboxylic acid surrogates.

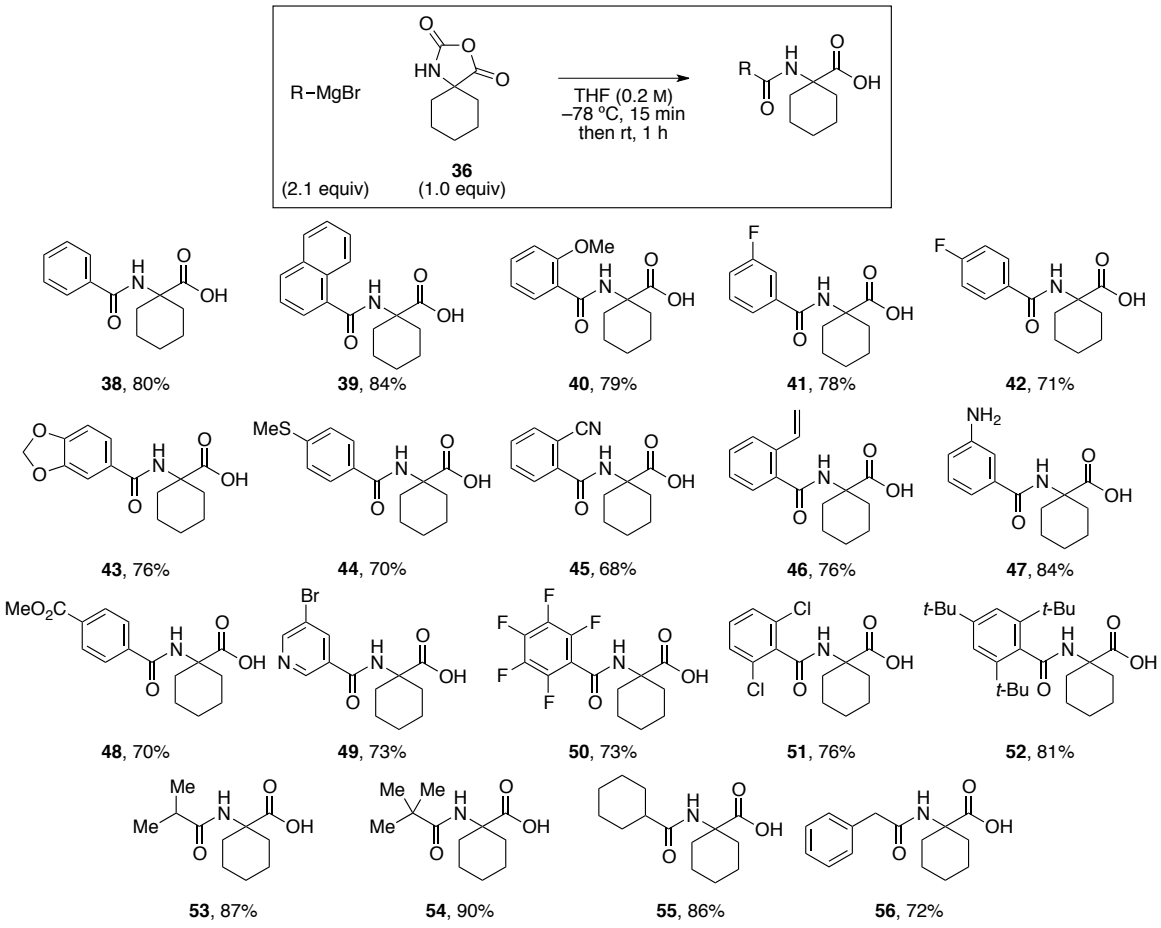
Sterically hindered 3-oxa-1-azaspiro[4.5]decane-2,4-dione (**36**, cyclohexyl-NCA) was chosen as a model substrate and the addition of mesitylmagnesium bromide (**17**, 2.1 equiv) to this NCA was investigated. Only a complex mixture of products could be obtained when the Grignard reagent was introduced at 0 °C, most likely due to polymerization of the NCA starting material **36**. However, when the temperature was lowered to −78 °C, the desired *N*-acylated, *gem*-disubstituted amino acid **37** was obtained in nearly quantitative yield (Scheme 28). The isolation of the product was simple; after aqueous workup, the crude material was washed with Et_2O to obtain the analytically pure *N*-acylated amino acid **37**.



Scheme 28: Diarylmethane containing biological active compounds.

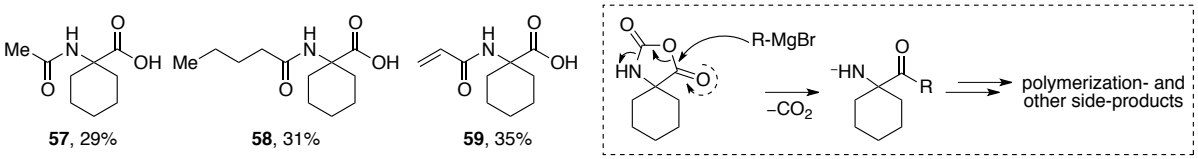
5.2. Substrate Scope

Having the optimized conditions in hand, the substrate scope of the Grignard reagent was evaluated (Scheme 29). As anticipated from the results with mesitylmagnesium bromide, the reaction worked well with standard aromatic Grignard reagents to provide the corresponding products **38**–**44** in high yields. The introduction of more sensitive functional groups was the next objective. Grignard reagents bearing cyano-, ester- or free amino-groups were easily prepared via magnesium-halogen exchange[66] (or were commercially available) and proved to be viable substrates in the reaction with NCA **36** and provided highly functionalized products **45**, **47**, and **48** in good yields. Products **46** and **49** derived from pyridinyl and styrenyl Grignard reagents were also accessible. Hindered Grignard reagents including pentafluorophenyl, 2,6-dichlorophenyl, isopropyl or *tert*-butyl Grignard also provided desired products **50**–**54**. Even the extremely bulky 2,4,6-tri-*tert*-butylphenyl Grignard reagent could be used to cleanly afford sterically congested amide **52** in good yield. Many of the examples shown in Scheme 29 would be difficult to synthesize via traditional acylation chemistry.



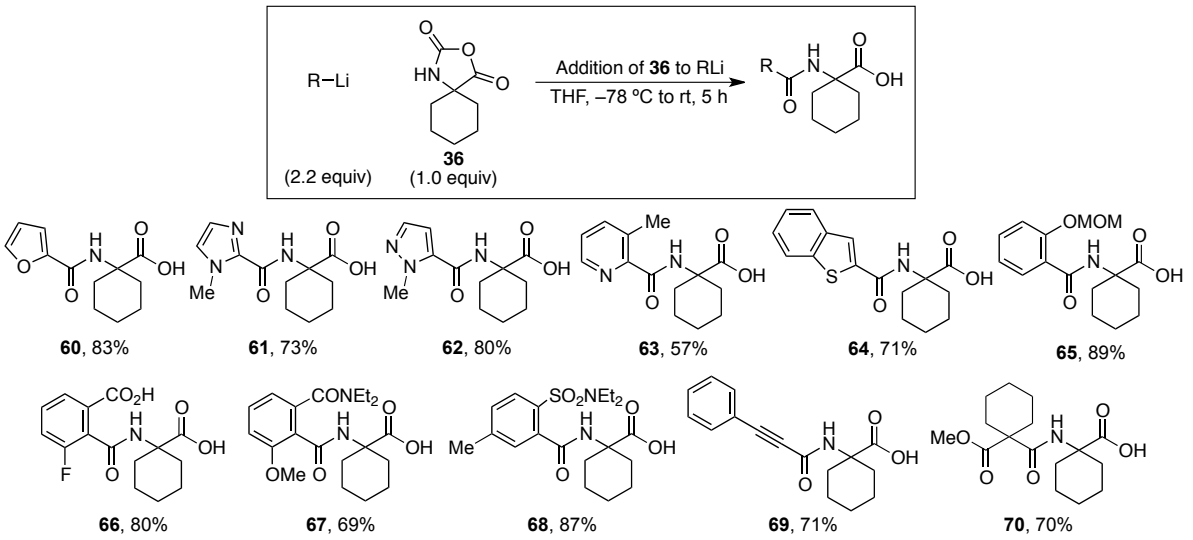
Scheme 29: Substrate scope of Grignard reagent.

Unfortunately, the reaction with two equivalents of sterically unbiased, aliphatic Grignard reagents was problematic. When methyl-, butyl- or vinylmagnesium bromide were used, the corresponding amide products **57**–**59** were isolated in low yields (Scheme 30). The low yield can be attributed to a competing nucleophilic attack of these unhindered Grignard reagents to anhydride carbonyl C5, which leads to ring-opening of the NCA followed by the formation of polymerized products or other side-products.



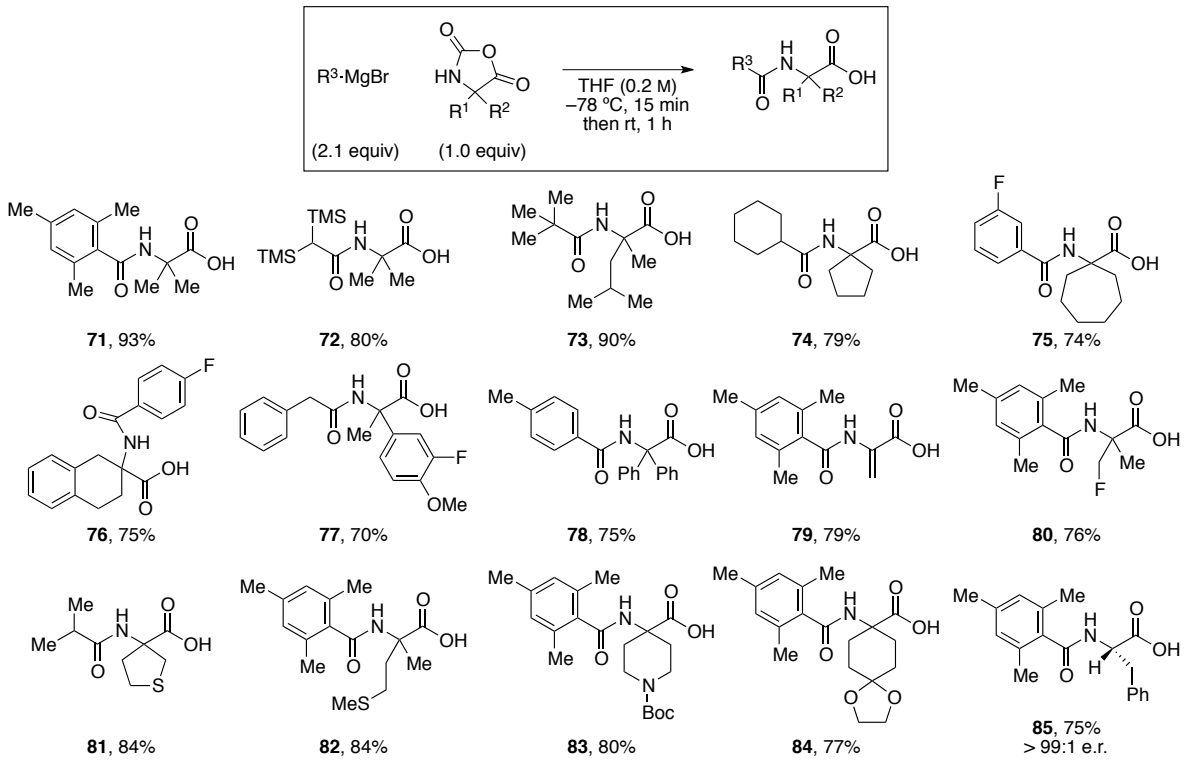
Scheme 30: Synthesis of *N*-acyl amino acids from sterically unbiased, aliphatic Grignard reagents.

The use of organolithium reagents in this amide-forming methodology would be of interest, because these reagents can be accessed via many different routes, such as simple deprotonation, *ortho*-lithiation or lithium-halogen exchange. Due to the instability of most organolithium reagents at room temperature, the addition sequence had to be modified: the organolithium species was generated at low temperature via one of the above-mentioned methods, followed by the addition of the NCA in THF at −78 ºC and slow warming to room temperature (Scheme 31). First, we tested the use of lithiated heterocycles, generated *in situ* at −78 ºC by deprotonation with *n*-butyllithium, in the addition to *N*-carboxyanhydride **36**. These reactions were remarkably clean and interesting heterocyclic amides **60**–**64** could be prepared in good yields. It was also possible to use *ortho*-lithiated arenes bearing protected alcohols, free acids, amides and sulfonamides as nucleophiles and the corresponding *N*-acyl amino acids **65**–**68** were isolated in high yields. In addition, products derived from lithium acetylide (**69**) and lithium enolate (**70**) were successfully prepared; the latter one possessing an aliphatic carboxylic acid and ester moiety amenable to further synthetic transformations. We imagine that other lithiated nucleophiles can also be used in this transformation, including enantioenriched organolithium species (e.g. using Sparteine), lithiated allenes or alkenes and lithiated heteroatoms. The use of milder organometallic reagents, such as cuprates or zincates, is probably more difficult, as they often display a characteristically lower basicity than their magnesium or lithium counterparts, and might be incapable of deprotonating the NCA starting material.



Scheme 31: Substrate scope of organolithium reagents.

Beside the substrate scope of the organometallic reagents, we were also interested in varying the aliphatic side chain of the *N*-carboxyanhydride starting material (Scheme 32). NCAs derived from 2-aminoisobutryic acid, α-methyl leucine or cyclic amino acids were excellent substrates and a wide range of different *N*-acyl, *gem*-disubstituted amino acids could be prepared (**71**–**76**). Products **77** and **78** containing aromatic side-chains were also accessible. Furthermore, our methodology allowed for the synthesis of *N*-acylated α,β-dehydroamino acid **79**. Heteroatom containing NCAs also cleanly reacted with Grignard reagents to provide the corresponding products **80**–**84** in high yields. Surprisingly, product **80** was prone to fluoride elimination via nucleophilic attack of the amide-oxygen. This side reaction was suppressed by the addition of TMSCl prior to the introduction of the Grignard reagent. Finally, the addition of mesitylmagnesium bromide to enantiopure phenylalanine *N*-carboxyanhydride was investigated. Addition of the sterically hindered Grignard reagent to this NCA, followed by slow warming of the reaction mixture to room temperature, provided the *N*-acylated amino acid **85** without racemization. The expansion of this amide bond-forming methodology to other natural amino acid-derived NCAs should be straightforward.

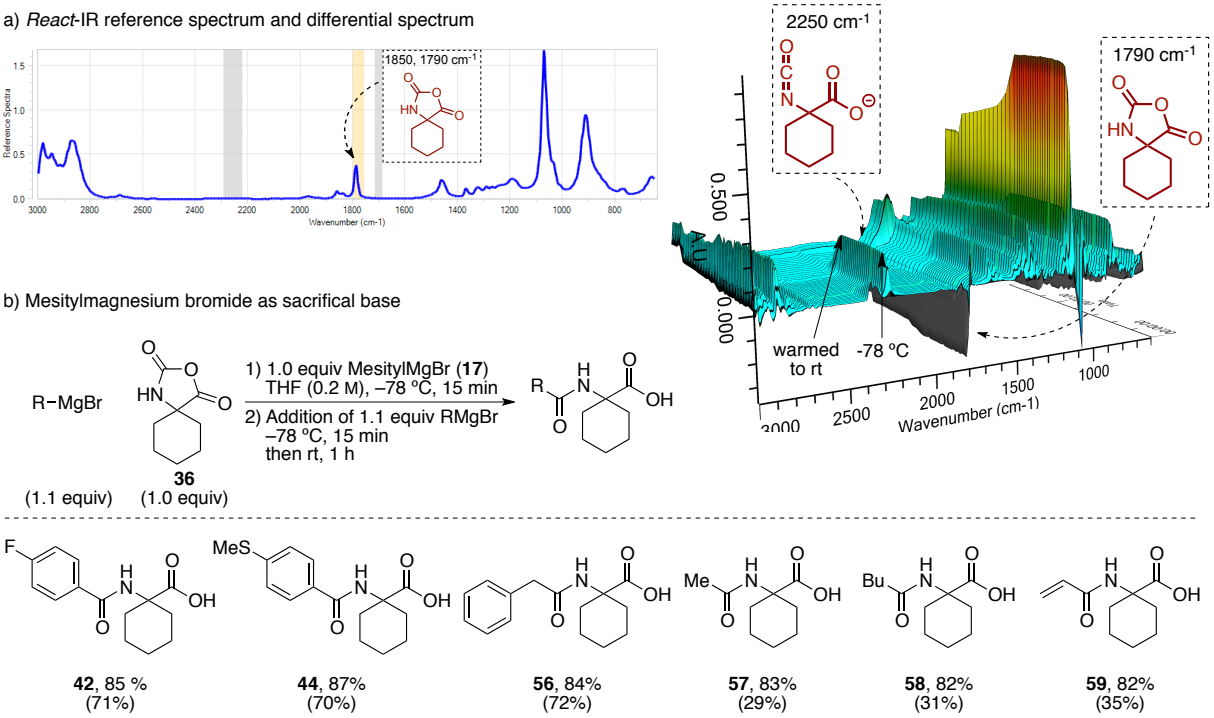


Scheme 32: Substrate scope of the *N*-carboxyanhydride.

5.3. Mechanistic Studies

In order to confirm the existence of an intermediate α-isocyanatocarboxylate in this amide bond-forming transformation, the reaction was followed by *react*-IR. Isocyanates are known to have a strong, isolated absorption band at 2250 cm^{-1}.[67] When mesitylmagnesium bromide (**17**, 2.1 equiv) was added to a solution of cyclohexyl-NCA (**36**, 1.0 equiv) at –78 °C, an absorption band at 2250 cm^{-1} appeared immediately, consistent with the formation of an intermediate isocyanate (Scheme 33a). Surprisingly, this isocyanate was stable at –78 °C, even in the presence of unreacted Grignard reagent. Only upon warming of the reaction mixture the isocyanate was consumed by the second equivalent of Grignard reagent to form the amide product. We concluded that mesitylmagnesium bromide (**17**) was too sterically hindered to attack the isocyanate at –78 °C and therefore, it should be possible to use this Grignard reagent as a sacrificial base for *in-situ* isocyanate release. As a matter of fact, when cyclohexyl-NCA **36** was treated with 1.0 equivalent of mesityl Grignard **17**, followed by addition of 1.1 equivalent of a second Grignard reagent, only the product stemming from the second Grignard reagent was observed. This modified procedure was applied to sterically

unbiased Grignard reagents, which were problematic substrates when using the standard protocol, and it was possible to significantly increase the yield of the corresponding unhindered amide products **57**–**59** (Scheme 33b, the yields obtained via the traditional protocol are shown in parantheses for comparison). From an economical point-of-view, this modified procedure is particularly interesting for valuable Grignard reagents, because their use in excess can be avoided by employing mesitylmagnesium bromide (**17**) as an inexpensive base.

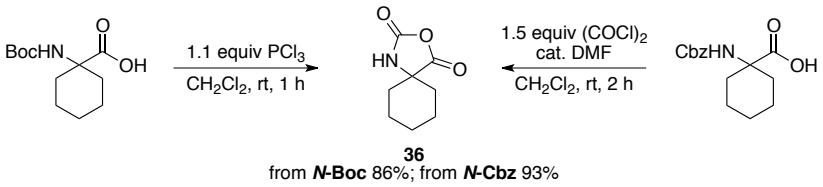


Scheme 33: *React*-IR studies and use of mesitylmagnesium bromide (**17**) as sacrificial base.

In summary, we have identified a new approach for the synthesis of sterically hindered *N*-acyl, *gem*-disubstituted amino acids by the addition of organometallic reagents to *N*-carboxyanhydrides.[68] This new methodology tolerates a wide range of functional groups and allows for the synthesis of amide products not readily accessible via traditional acylation chemistry. The reaction proceeds via an intermediate α-isocyanatocarboxylate, whose existence was demonstrated by *in situ* IR spectroscopy.

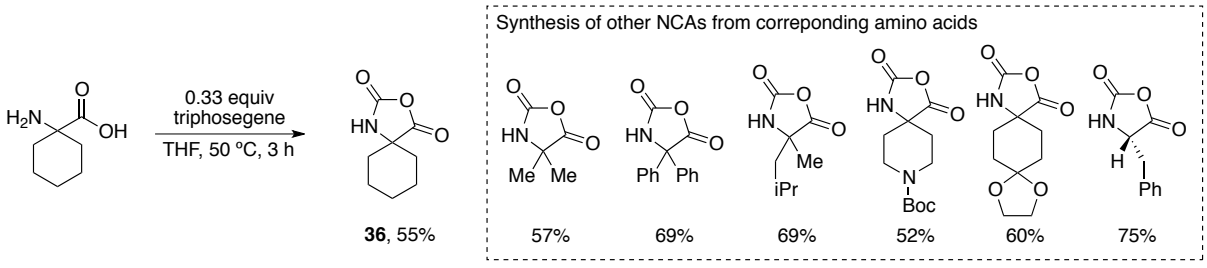
5.4. Synthesis of *N*-Carboxyanhydrides

In his seminal work, Leuchs discovered *N*-carboxyanhydrides by coincidence when he attempted to purify *N*-ethoxy- or *N*-methoxycarbonyl amino acid chlorides by distillation.[64] Using a similar approach, we synthesized 3-oxa-1-azaspiro[4.5]decane-2,4-dione (**36**) from the corresponding *N*-Boc amino acid and phosphorus trichloride. Furthermore, it was possible to use the Cbz-protected amino acid and convert it into NCA **36** via *in situ* formation of the acid chloride followed by ring-closure (Scheme 34).



Scheme 34: Synthesis of *N*-carboxyanhydride **36**.

In 1988, Daly and Poché discovered the direct conversion of unprotected natural amino acids into NCAs by treatment with triphosgene in THF.[69] When we followed their protocol, we could indeed obtain 3-oxa-1-azaspiro[4.5]decane-2,4-dione (**36**), but in relatively low yield compared to the above-described approaches (Scheme 35 in comparison to Scheme 34). The main problem was the poor solubility of the *gem*-disubstituted amino acid starting material in THF, which inhibited its reaction with triphosgene. Saturation of the reaction mixture with gaseous phosgene could potentially increase the yield of the NCA, however, due to safety concerns such a reaction was not performed. Nevertheless, the use of unprotected amino acids is convenient, because prefunctionalization can be avoided and many unnatural, *gem*-disubstituted amino acids are commercially available. All synthesized NCAs are easily handled compounds that can be stored for months at the benchtop without any sign of decomposition.

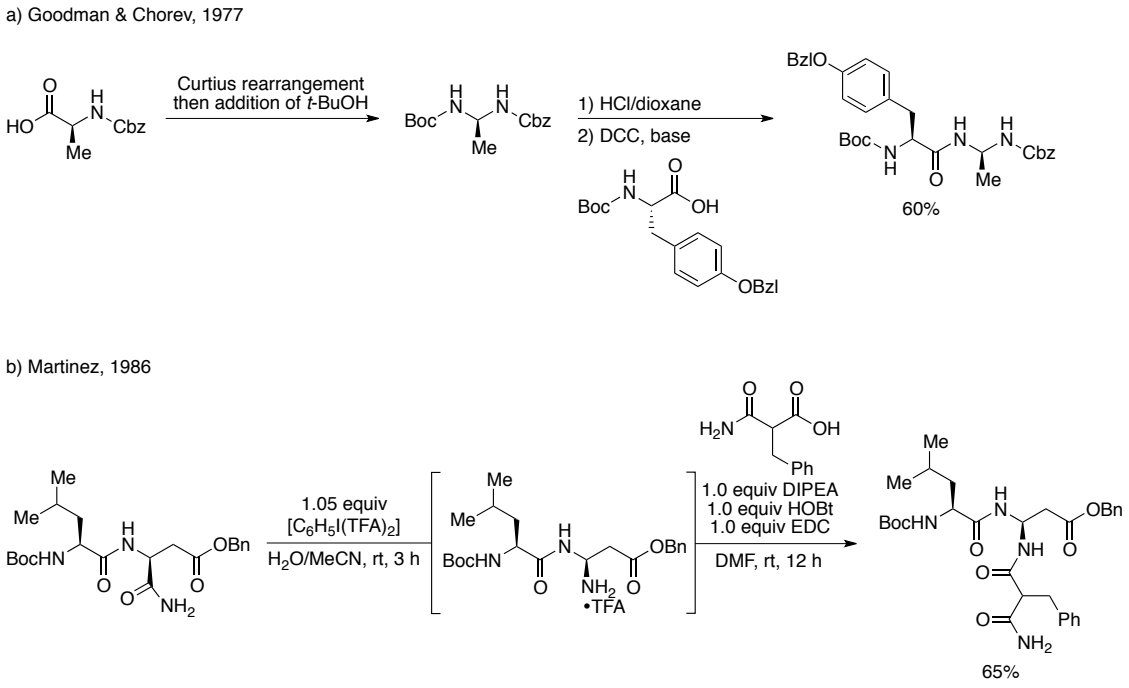


Scheme 35: Synthesis of NCA **36** from corresponding unprotected amino acid.

6. Synthesis of *N,N'*-Bisamides

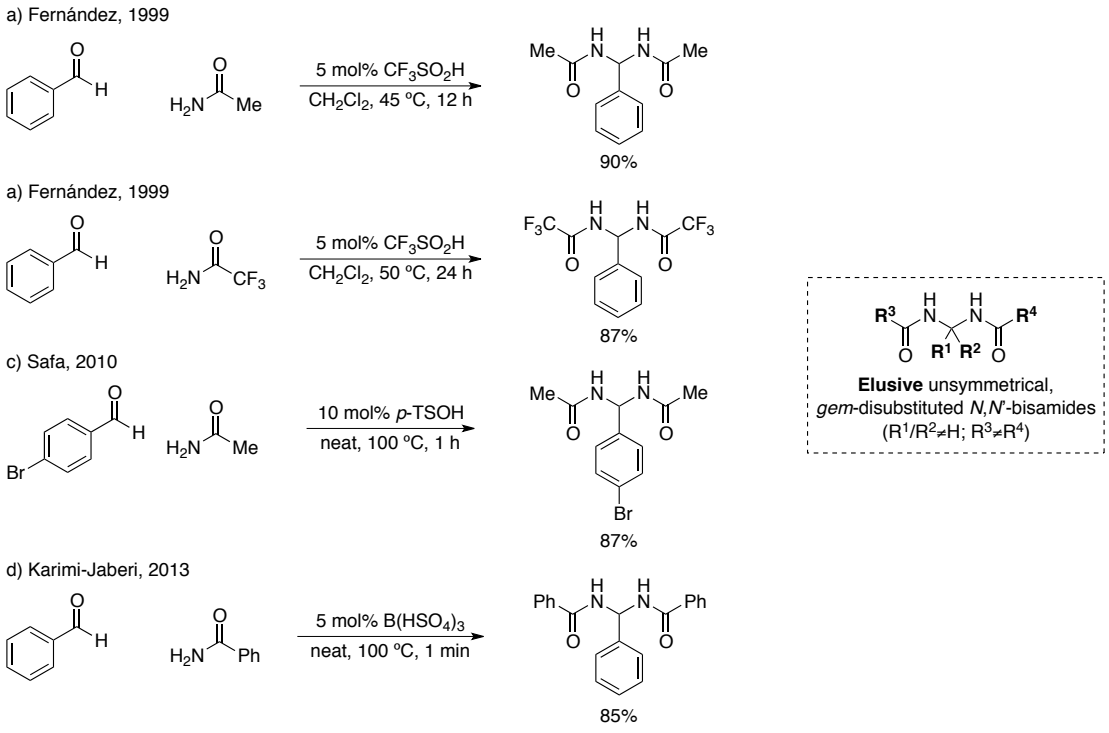
Peptidomimetics are compounds whose essential elements mimic a natural peptide or protein in three-dimensional space. Such peptidomimetics typically arise from natural modification of an existing peptide or via the introduction of unnatural amino acid residues such as *D*-amino acids, β-amino acids, *gem*-disubstituted amino acids or peptoids. The altered chemical structure is designed to improve certain molecular properties, such as stability or biological activity of the protein, and therefore this approach has an important role in the development of drug-like compounds from existing peptides.[70]

A relatively new category of peptidomimetics are *N,N'*-bisamides – a substrate class assembled of two amide functionalities connected to each other via a methylene bridge. Goodman and Chorev reported the first *N,N'*-bisamide-containing peptides in the late 1970s.[71] They synthesized the altered structure from *N*-Cbz natural amino acids, which were converted into *N,N'*-diprotected, *gem*-diamino compounds via Curtius rearrangement and trapping of the intermediate isocyanate with *tert*-butanol. This building block was coupled to the next fragment via standard coupling reagent-based amide bond formation. Martinez and coworkers used a similar approach and synthesized retro-inverso pseudopeptide derivatives of Gastrin from peptide primary amides, which were converted into the stable amine hydrochloride salt via Hofmann rearrangement.[72]



Scheme 36: Synthesis of *N,N'*-bisamide-containing peptides.

More recently, several research groups have investigated an alternative approach for the synthesis of *N,N'*-bisamides, which is the acid-catalyzed condensation of aldehydes with primary amides. In 1999, Fernández reported the triflic acid-catalyzed reaction of aldehydes with two equivalents of primary amides in refluxing CH_2Cl_2 (Scheme 37a).[73] In the same year, Zhu described the synthesis of fluorinated *N,N'*-bisamides using the reaction conditions developed by Fernández (Scheme 37b).[74] Later, Safa[75] and Karimi-Jaberi[76] introduced solvent-free approaches employing *p*-toluenesulfonic acid or tris(hydrogensulfato)boron as catalysts (Scheme 37c and 37d). All these approaches suffer from two major limitations: 1) only symmetrical *N,N'*-bisamides can be obtained and 2) the condensation only works with aldehydes, but *not* with ketones. For these reasons, the synthesis of unsymmetrical, *gem*-disubstituted *N,N'*-bisamides remains elusive. In our opinion the synthesis of these compounds would be highly attractive, because they could act as more soluble urea surrogates, and they would also allow pharmaceutical companies to circumvent excisting IP barriers.

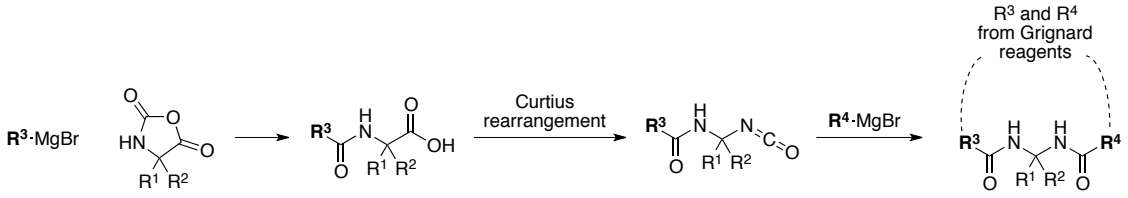


Scheme 37: Acid-catalyzed condensation of aldehydes with primary amides.

6.1. Synthesis of Unsymmetrical, *gem*-Disubstituted *N,N'*-Bisamides

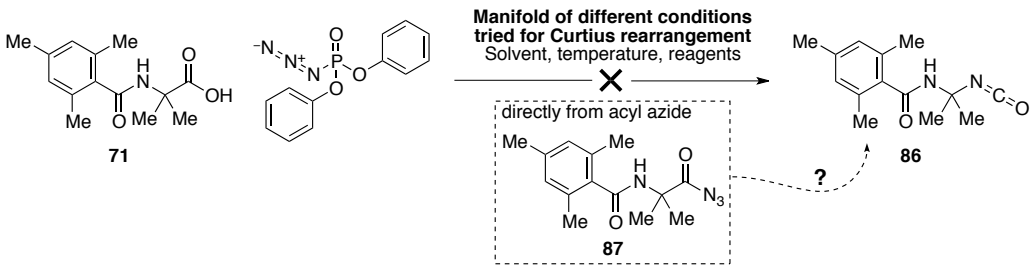
6.1.1. via Curtius Rearrangement

Our strategy was to use the isocyanate/Grignard-methodology for the synthesis of unsymmetrical, *gem*-disubstituted *N,N'*-bisamides. Retrosynthetically, we envisioned the use of *N*-acylated amino acids, prepared via the addition of Grignard reagents to NCAs, and convert them via Curtius rearrangement into the corresponding isocyanates. These crucial building blocks would then undergo addition reactions with organometallic reagents to form *N,N'*-bisamides. In summary, the acyl groups on both nitrogens would stem from Grignard reagents and completely avoid the use of acylation chemistry (Scheme 38).



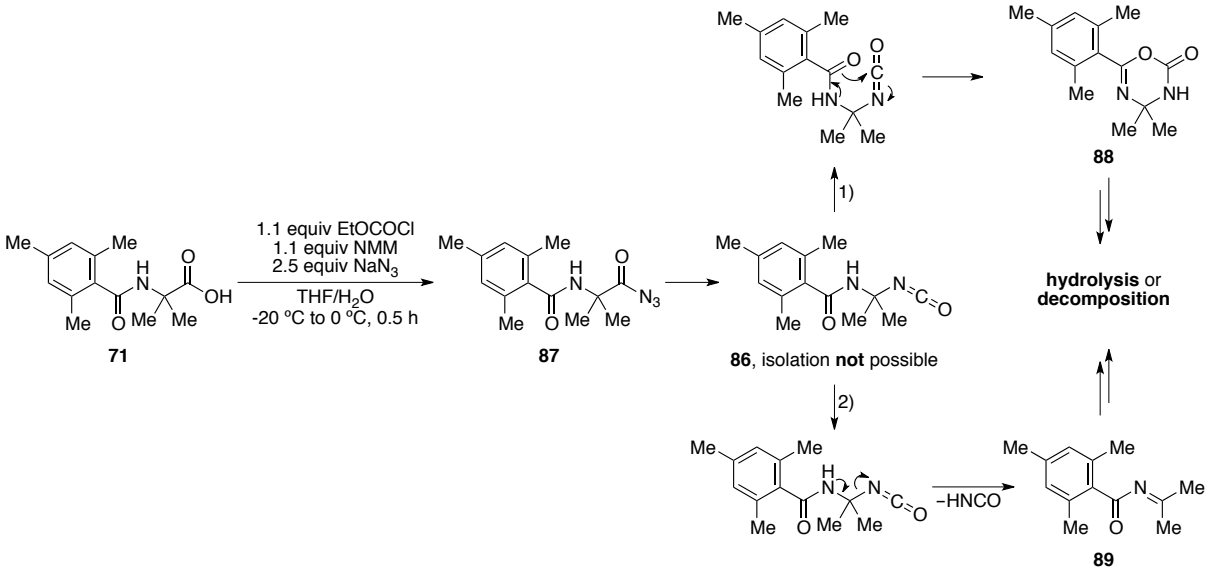
Scheme 38: Envisioned synthesis of *N,N'*-bisamides via isocyanate/Grignard-methodology.

2-methyl-2-(2,4,6-trimethylbenzamido)propanoic acid (**71**) was chosen as a model substrate and its transformation into the corresponding isocyanate **86** via Curtius rearrangements with diphenylphosphoryl azide (DPPA) was investigated (Scheme 39). Under the standard Curtius rearrangement conditions described in Chapter 4.2, only a complex mixture of products was obtained. Analysis of the crude product by IR showed no typical strong isocyanate absorption at 2250 cm^{-1}, and the NMR spectra were too unclean to draw further conclusions on the reaction outcome. Several other conditions, including different solvents (toluene, benzene, THF, 1,2-DCE or EtOAc), different bases and temperatures, were tried, however, we could never observe any isocyanate formation.



Scheme 39: Attempted synthesis of isocyanate **86**.

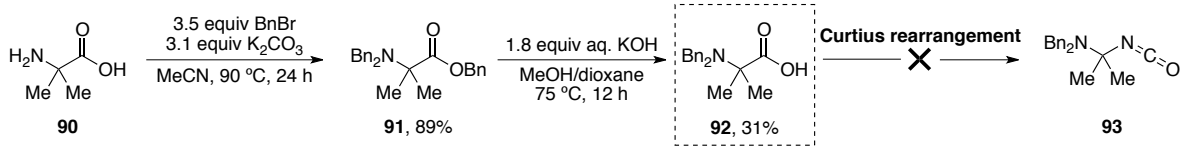
The formation of the intermediate acyl azide **87** with DPPA could be difficult due to the steric bulk of the starting material and also of the azide transfer agent itself. Therefore, acyl azide **87** was separately synthesized via a different route and isolated as a stable, colorless solid. According to textbooks, the critical temperature at which a rearrangement of an acyl azide to an isocyanate takes place is between 60–65 °C.[77] The rearrangement of acyl azide **87** was attempted in many different solvents, without the addition of any other reagents, but the desired isocyanate **86** could never be isolated, regardless of the applied temperature (between 60 °C and 115 °C). Nevertheless, during these reactions, vigorous gas evolution (N_2) was observed, which is in accordance with the event of a Curtius rearrangement. We now concluded that isocyanate **86** was actually formed in the reaction mixture, but that this compound was not stable at the high reaction temperature of the Curtius rearrangement.



Scheme 40: Possible decomposition pathways of isocyanate **86**.

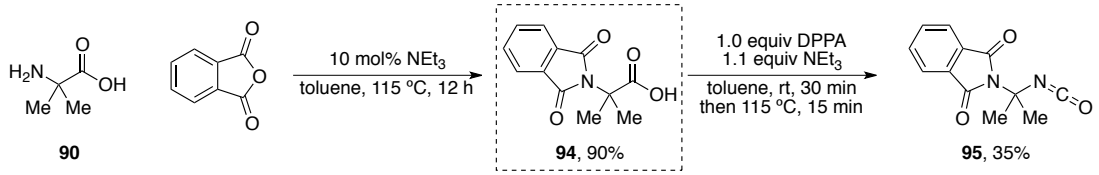
Two possible decomposition pathways of isocyanate **86** can be imagined (Scheme 40). 1) At elevated temperatures, isocyanate **86** could be prone to a nucleophilic attack of the amide-oxygen to form six-membered intermediate **88**, which finally decomposes. 2) At elevated temperatures, compound **86** could be prone to elimination of gaseous isocyanic acid, which would lead to intermediate acyl imine **89** that then decomposes as well. In order to examine which of the two decomposition pathways is more likely to operate, the use of two model compounds was envisoned. The first one being *N*-dibenzyl protected 2-aminoisobutyric acid **92**, lacking the possibility of amide-oxygen ring-closure (Scheme 41). In the second derivative **94**, the nitrogen will be protected as a

phthalimide, because the nitrogen lone pair is strongly delocalized into the imide-structure and therefore elimination of isocyanic acid should be less likely (Scheme 42). The synthesis of both starting materials were relatively straightforward. In the first case, 2-aminoisobutryric acid (**90**) was triply benzylated by using an excess of benzyl bromide in refluxing acetonitrile. The benzylic ester **91** was hydrolyzed under basic conditions in a mixture of methanol and dioxane, although in low yield due to the sterically congested environment around the ester carbonyl group. Once again, the conversion of carboxylic acid **92** into the corresponding isocyanate **93** via Curtius rearrangement failed completely. We reasoned that the elimination of the isocyanate group was the main problem of these labile systems – a problem that should reoccur several times in our journey towards the synthesis of unsymmetrical, *gem*-disubstituted *N*,*N'*-bisamides.



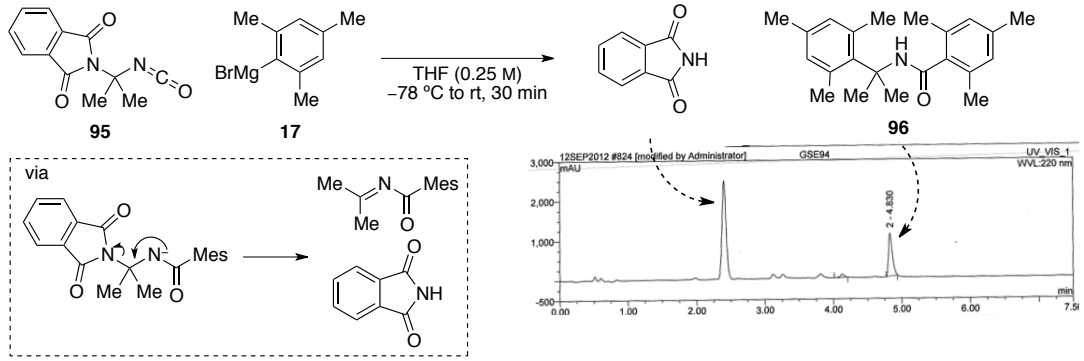
Scheme 41: Attempted synthesis of isocyanate **93**.

The attention was turned to the synthesis of the previously discussed *N*-phthalimidyl amino acid **94**. An equimolar amount of 2-aminoisobutyric acid (**90**) and phthalic anhydride was refluxed in toluene under base catalysis to provide the desired starting material **94** in nearly quantitative yield (Scheme 42). Using slightly modified Curtius rearrangement conditions, the conversion of *N*-phthalimidyl 2-aminoisobutyric acid **94** into the corresponding isocyanate **95** was successful. For the first time an appropriate starting material was in hand to elaborate the synthesis of unsymmetrical, *gem*-disubstituted *N*,*N'*-bisamides. The successful isolation of this isocyanate also suggests that the formation of six-membered intermediate **88**, as described in scheme 40, is most probably not a major decomposition pathway.



Scheme 42: Successful synthesis of isocyanate **95**.

The addition of mesitylmagnesium bromide (**17**, 1.0 equiv) to isocyanate **95** was investigated. The reaction was performed in different solvents (THF, Et_2O, dioxane) and temperatures (–78 ºC, 0 ºC, 25 ºC), but the formation of the desired *N,N'*-bisamide could never be observed. However, LC/MS analysis of the reaction mixture revealed the formation of phthalimide and a major product with mass $(M+H)^+$= 324.3, which could be assigned to compound **96** (Scheme 43). The formation of product **96** can be explained by the initial nucleophilic attack of the Grignard reagent onto the isocyanate. However, the intermediate amide anion is apparently not stable and prone to phthalimide elimination, and the so-formed acyl imine is attacked by a second equivalent of the Grignard reagent. The β-elimination of phthalimide must occur instantaneously, otherwise no Grignard reagent would be available for the second nucleophilic attack onto the imine.



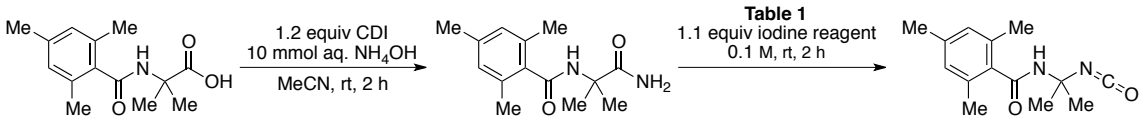
Scheme 43: Elimination of phthalimide and formation of **96**.

6.1.2. via Hofmann Rearrangement

At this point, the approach of protecting the nitrogen atom (benzyl or phthalimide) was discarded, because manipulation of the protecting groups after successful *N,N'*-bisamide formation was expected to be very difficult. Therefore, we went back to our original plan to use *N*-acyl, *gem*-disubstituted amino acids as starting materials. As previously discussed, the corresponding isocyanate could not be generated via Curtius rearrangement and we focused our attention on the investigation of milder isocyanate-forming reactions. One of the most well known examples of such a reaction is the Hofmann rearrangement, which is the conversion of a primary amide into an isocyanate.[78] The major problem is that this rearrangement is traditionally performed under strongly basic aqueous conditions, which hydrolyses the *in situ* generated isocyanate to the amine. Recently, several research groups used hypervalent iodine reagents for Hofmann-type rearrangements under mild conditions.[79]

The necessary primary amide **97** was synthesized in one step from carboxylic acid **71** and different hypervalent iodine reagents were screened for the Hofmann rearrangement (Table 1). Most of the hypervalent iodine reagents have a poor solubility in organic solvents, which hampered their reaction with the primary amide. The addition of water was also not beneficial in these processes (Entry 2). The use of Ph-I(TFA)$_2$ was promising, because primary amide **97** was completely consumed. However, IR spectroscopy of the crude reaction mixture showed no typical isocyanate absorbance band (Entry 4). We reasoned that the generated trifluoroacetic acid by-product possibly hydrolyzed the isocyanate. Switching to the milder Ph-I(OAc)$_2$ provided traces of the desired isocyanate **86** (Entry 5). The last reagent we wanted to test was tosylimino-λ^3-iodane (PhINTs), because the tosylamide by-product is not acidic and is also a poor nucleophile, which should leave the isocyanate moiety untouched (Entry 7). In fact, by using PhINTs the desired isocyanate **86** could be isolated for the first time and was fully characterized (HR/MS, NMR, IR). High dilution in this reaction was beneficial due to the poor solubility of the hypervalent iodine reagent in CH_2Cl_2 and allowed the isolation of isocyanate **86** in good yield (Entry 8). The mildness of the reaction conditions under which this transformation takes place is remarkable and highlights the utility of hypervalent reagents in synthetic chemistry.

Table 1. Optimization of Hofmann rearrangement with primary amide **97**.

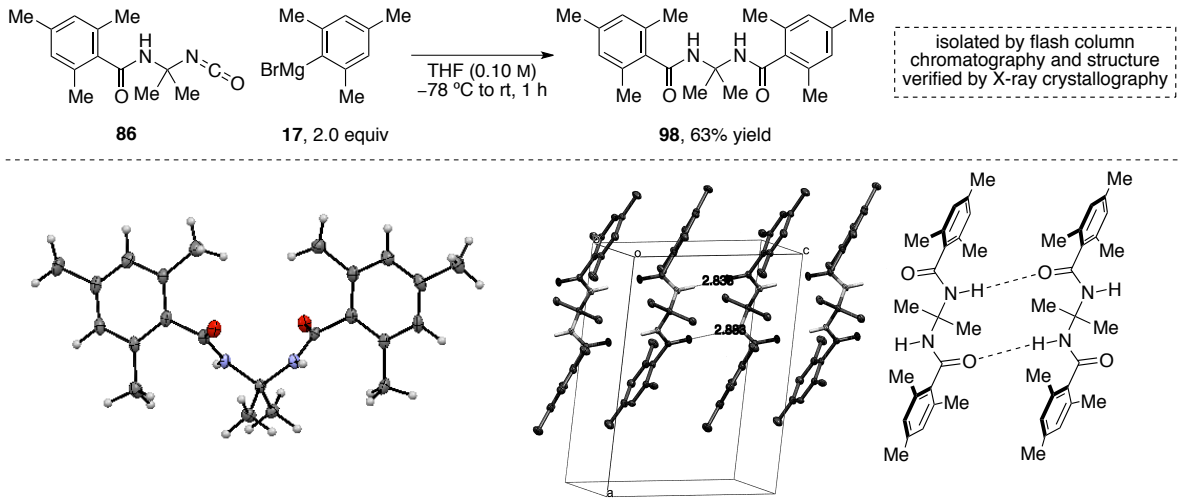


71 **97** **86**

Entry	Iodine reagent	Solvent	*T* [ºC]	Yield 86
1	PhI=O	CH_2Cl_2	25 ºC	n.r.
2	PhI=O	CH_2Cl_2/H_2O 95:5	25 ºC	-
3	PhI=O	MeCN	25 ºC	-
4	Ph-I(TFA)$_2$	CH_2Cl_2	25 ºC	-
5	Ph-I(OAc)$_2$	CH_2Cl_2	25 ºC	traces
6	PhI + Oxone	MeOH	25 ºC	-
7	Ph-I=NTs	CH_2Cl_2	25 ºC	43%
8	Ph-I=NTs	CH_2Cl_2 (0.05 M)	25 ºC	55%

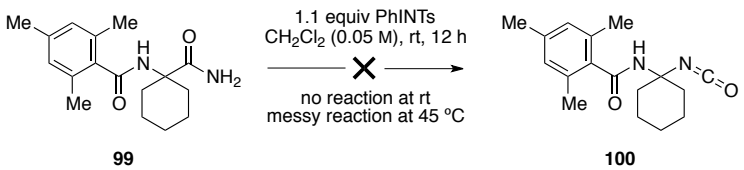
The addition of mesitylmagnesium bromide (**17**) to isocyanate **86** was surveyed. The use of 2.0 equivalents of the Grignard reagent was expected to be necessary, because the abstraction of the N–H proton should be faster than the corresponding nucleophilic attack. After a short optimization study, we could for the first time successfully isolate *gem*-dimethyl

N,N'-bisamide **98** in good yield after treatment of isocyanate **86** with 2.0 equivalents of mesityl Grignard **17** at –78 °C followed by warming to room temperature. The product proved to be a bench-stable colorless solid and its structure was confirmed by X-ray crystallography. The crystal structure revealed that the bisamide adapts a sheet-like orientation with intermolecular hydrogen-bonding interactions between the individual amide functionalities. According to the scale of Jeffrey, a donor-acceptor distance of 2.84 Å suggests a *"moderate, mostly electrostatic"* hydrogen bonding interaction.[80]



Scheme 44: Synthesis of *gem*-disubstituted *N,N'*-bisamide **98**.

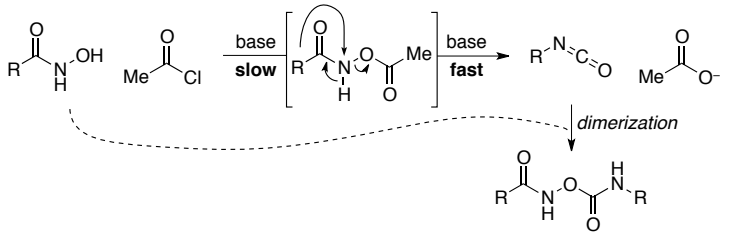
In light of the above result, the synthesis of other *N*-acyl isocyanates starting from *N*-acyl, *gem*-disubstituted amino acid primary amides was explored. However, using identical conditions as for the preparation of isocyanate **86**, primary amide **99** could not be converted into isocyanate **100** and only unreacted starting material was recovered (Scheme 45). A possible explanation for this observation could be the increased steric hindrance around the amide functionality in **99** compared to **97**. Warming of the reaction mixture led to full conversion of **99**, but isocyanate **100** could not be isolated. This result was disappointing, because this two step Hofmann rearrangement/Grignard addition approach towards *N,N'*-bisamides was the most promising one at the time.



Scheme 45: Attempted synthesis of isocyanate **100** via Hofmann rearrangement.

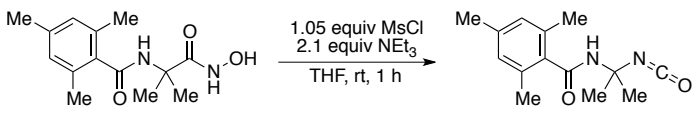
6.1.3. via Lossen rearrangement

The Lossen rearrangement is the conversion of a hydroxamic acid to an isocyanate via the formation of an *O*-acyl, -sulfonyl, or -phosphoryl hydroxamic acid intermediate.[81] The Lossen rearrangement is relatively underdeveloped compared to other rearrangements, mainly because of the inherent problem of competitive hydroxamic acid dimerization. This dimerization is a result of unfavorable reaction kinetics: the rate-limiting step of the Lossen rearrangement is the activation of the hydroxamic acid. As a consequence, there is an accumulation of isocyanate before complete consumption of the hydroxamic acid. Trapping of the isocyanate by the hydroxamic acid then results in the formation of dimerized products.[82]



Scheme 46: Lossen rearrangement of hydroxamic acids.

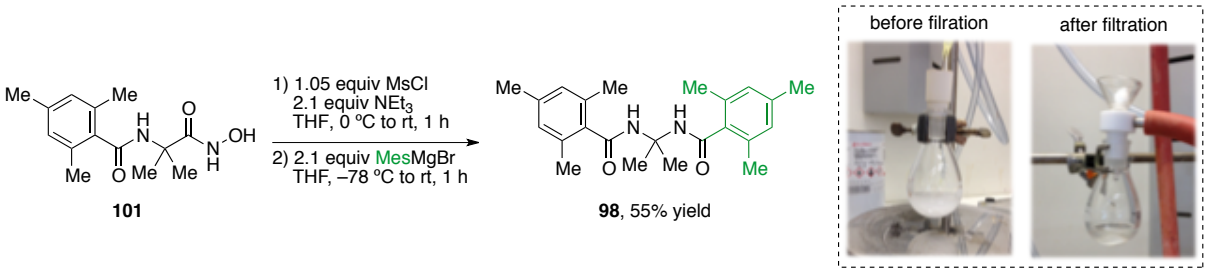
We came to the conclusion that we had to use a highly active reagent for hydroxamic acid activation in order to avoid the build up of unreacted starting material. Sulfonyl chlorides are highly reactive reagents for the formation of *O*-sulfonylated compounds. We were particularly intrigued by methanesulfonyl chloride (MsCl), because it is known to form a highly reactive sulfene intermediate upon treatment with a base. When hydroxamic acid **101**, prepared in one step from *N*-acyl, *gem*-disubstituted amino acid **71**, was treated with mesyl chloride and 2.1 equivalents of triethylamine, isocyanate **86** could be isolated in low yield after chromatographic purification (Scheme 47). Careful thin-layer chromatographic (TLC) analysis supported the assumption that partial decomposition of the relatively unstable isocyanate **86** occurred on the silica gel.



101 **86**, 35% yield

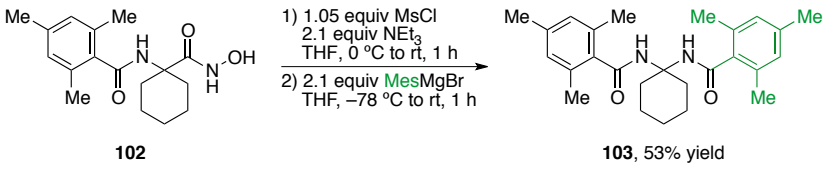
Scheme 47: Synthesis of isocyanate **86** via Lossen rearrangement.

During the methanesulfonyl chloride-promoted Lossen rearrangement, the formed triethylammonium chloride salt precipitated from the reaction mixture. We believed that a simple filtration of the reaction mixture after complete Lossen rearrangement would lead to a salt-free THF solution containing isocyanate **86**, which could be directly treated with a Grignard reagent to form the desired product. This filtration/addition protocol would also circumvent the isolation of unstable isocyanate **86**. The following reaction setup was developed: after complete Lossen rearrangement, the reaction mixture was filtered into a new round-bottom flask and the filter cake was rinsed with a small amount of dry THF. The clear, isocyanate solution was cooled to –78 °C and 2.1 equivalents of mesitylmagnesium bromide (**17**) were added (Scheme 48). This protocol allowed for the conversion of hydroxamic acid **101** into *gem*-dimethyl *N,N'*-bisamide **98** in an improved 55% yield, without isolation of the intermediate isocyanate.



Scheme 48: Synthesis of *N,N'*-bisamide **98** via quasi one-pot Lossen rearrangement/Grignard addition protocol.

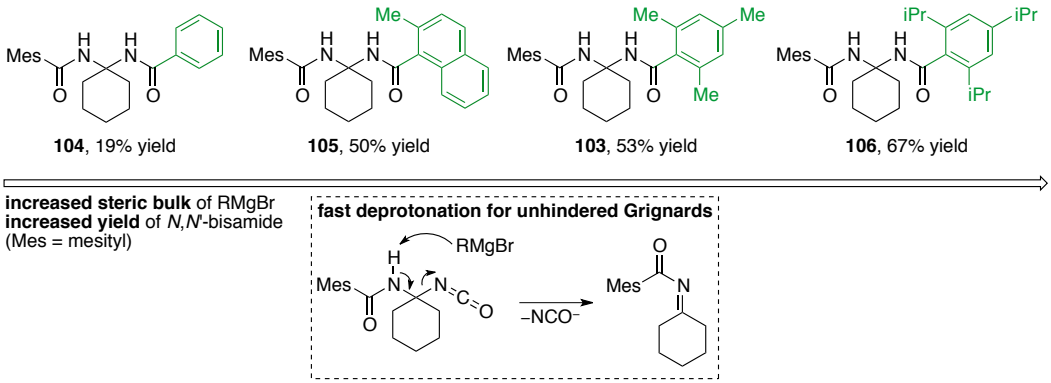
Compared to the Hofmann rearrangement, the formation of the isocyanate was also successful with cyclohexyl derivative **102**, providing the symmetrical *N,N'*-bisamides **103** in good yield (Scheme 49).



Scheme 49: Diarylmethane containing biological active compounds.

Driven by the success of the Lossen rearrangement, the preparation of unsymmetrical, *gem*-disubstituted *N,N'*-bisamides was investigated by using different Grignard reagents. We observed that the reaction with sterically unbiased organomagnesium reagents provided the bisamide in significantly lower yield than with the sterically hindered counterparts (Scheme 50). In addition, the bulkier the Grignard reagent was, the cleaner the

reactions became. We believe that sterically unbiased Grignard reagents deprotonate the N–H proton very rapidly, which leads to the previously discussed elimination of cyanate and formation of an intermediate imine (see Scheme 40). This elimination pathway can partly explain the 50% yield discrepancy between *N*-benzoyl bisamide **104** and *N*-2,4,6-triisopropylphenyl bisamide **106**. The full substrate scope of this reaction is currently under investigation.



Scheme 50: Synthesis of different *N,N'*-bisamides.

After a long journey towards the synthesis of elusive unsymmetrical, gem-disubstituted *N,N'*-bisamides, we could successfully report their synthesis via a quasi one-pot Lossen rearrangement/Grignard addition sequence, which avoids isolation of the intermediate isocyanate.[83] The full substrate scope of this reaction is currently being tested, but preliminary results suggest that the reaction works particularly well for sterically hindered substrates, but is prone to cyanate elimination with sterically unbiased Grignard reagents. The starting hydroxamic acid starting material is easily prepared in one step from the corresponding amino acid and aqueous hydroxylamine. The mildness of the mesyl chloride-promoted Lossen rearrangement would make this approach also attractive for the formation of conventional amide products, even more as the isocyanate can be generated without the use of potentially explosive azide transfer reagents or intermediate acyl azides.

7. Conclusions and Outlook

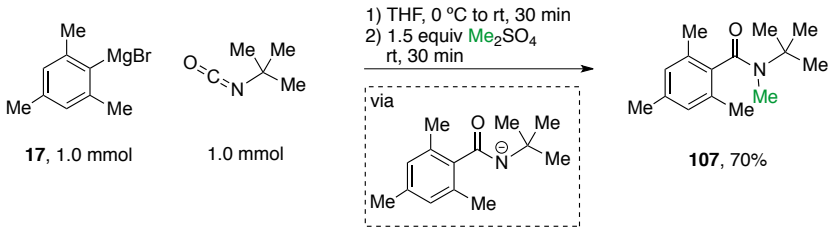
"A scientist has to work very hard to get to the point where he can be lucky". This famous quote by R. B. Woodward fits perfectly to the development of the addition of Grignard reagents to isocyanates. At the beginning there was an intensive literature review and reading a wide range of different papers about amide bond formation. That was when we came across the seminal work of Gilman on the synthesis of amides via the direct coupling of Grignard reagents to isocyanates and were immediately fascinated by this true piece of art of early organometallic chemistry. Our expansion of Gilman's chemistry towards sterically hindered amides provides the first reliable and robust solution for the synthesis of these challenging substrates. The majority of amide products described in this thesis would be very difficult to synthesize via traditional coupling reagent-based approaches. Additionally, the Grignard/isocyanate-protocol does not need any excess of reagents, the reactions are finished within minutes at room temperature and the products are easily purified.

After this initial success, we sought to find new interesting isocyanate substrates applicable to the addition of Grignard reagents. The discovery that *N*-carboxyanhydrides can serve as α-isocyanatocarboxylic acid surrogates upon addition of two equivalents of Grignard reagent at low temperature opened up a new way for the synthesis of sterically hindered, *N*-acylated amino acids. The existence of the intermediate α-isocyanatocarboxylate was established by *in situ* IR spectroscopy. In the last part of this thesis, our journey towards the synthesis of elusive unsymmetrical, *gem*-disubstituted *N*,*N'*-bisamides was described. The sensitivity of these compounds towards all kind of elimination reactions is remarkable and made their synthesis highly challenging. After many dead ends, the synthesis of *N*,*N'*-bisamides could finally be achieved via a quasi one-pot Lossen rearrangement/Grignard addition sequence from the corresponding hydroxamic acids. The isolation of the relatively unstable intermediate *N*-acyl isocyanate could be avoided, and the substrate scope of this reaction is currently under investigation.

We hope that the direct coupling of isocyanates with Grignard reagents will find a widespread use in the preparation of challenging amides, both in academic and industrial laboratories, and become an integral part of the everyday life of a synthetic organic chemist.

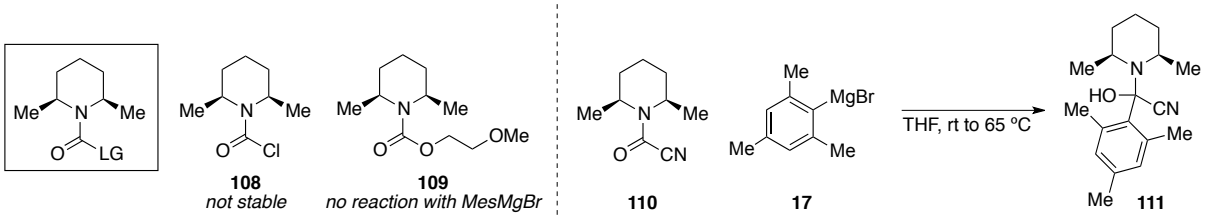
Outlook: Synthesis of Sterically Hindered, Tertiary Amides

The synthesis of sterically hindered, secondary amides was discussed in details in the previous chapters. The direct expansion of this methodology to tertiary amides is innately impossible, because the nitrogen of the isocyanate can only bear one substituent. However, as a preliminary result, it was possible to trap the intermediate amide anion, resulting from addition of the Grignard reagent to the isocyanate, with dimethyl sulfate to form sterically hindered tertiary amide **107** in good yield (Scheme 51). Surprisingly, the use of methyl iodide as alkylating reagent led to no formation of the desired tertiary amide. This suggests that the amide anion reacts more easily with hard electrophiles and the formation of other tertiary amides should be possible by using alkyl tosylates, triflates or mesylates.



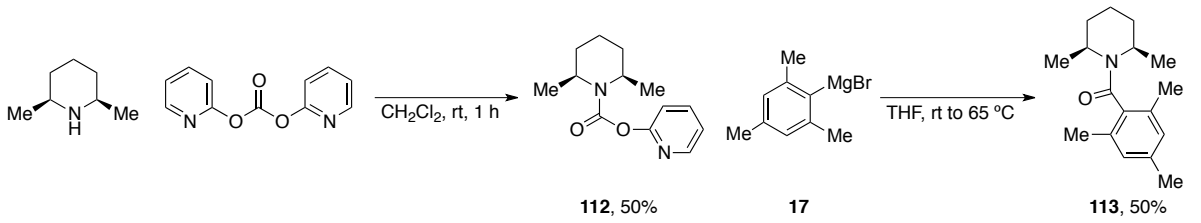
Scheme 51: Synthesis of sterically hindered, tertiary amide **107**.

The trapping of the intermediate amide anion with electrophiles could offer a solution for the synthesis of sterically hindered, tertiary amides. However, the generality of this approach is uncertain and it is possible that different conditions for every single electrophile have to be screened. Furthermore, cyclic tertiary amides cannot be accessed with this approach. We wanted to synthesize a common amino carbonyl starting material possessing a leaving group that will be replaced upon addition of a Grignard reagent. The simplest version of such a starting material is *cis*-2,6-dimethylpiperidine-1-carbonyl chloride (**108**), however, this compound proved to be unstable and also hard to purify (Scheme 52). Many other substrates with different leaving groups were tested, including **109** bearing a methoxyethoxy-group that is known to have a strong magnesium chelating ability, but no reaction with the Grignard reagent was observed. In contrast, carbonyl cyanide **110** underwent immediate reaction with mesitylmagnesium bromide (**17**). The product proved to not be the desired amide, but rather sterically congested cyanohydrin **111**. This compound was found to be completely stable, even at elevated temperature and with the addition of silver salts.



Scheme 52: Survey of different leaving groups for the synthesis of sterically hindered tertiary amides

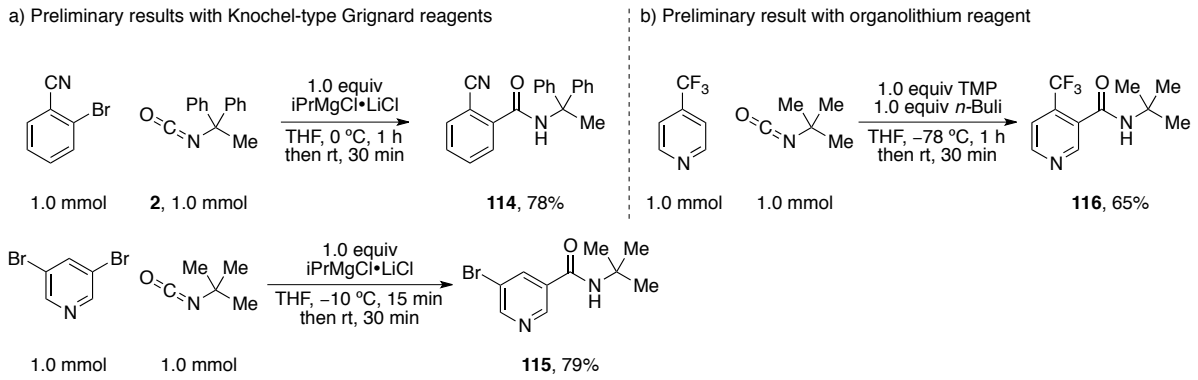
In order to favor the displacement of the leaving group by the Grignard reagent, we wanted to use a group that forms a very stable species when detached from the starting material. Furthermore, the group should facilitate the attack of the Grignard reagent by stabilization of the tetrahedral intermediate via Mg-chelation. Carbonate **112** was synthesized capable of forming highly stable 2-pyridone when attacked by the Grignard reagent. Indeed, by using this starting material highly sterically hindered amide **113** was formed in good yield (Scheme 53). Further optimization of the reaction conditions and the leaving group could provide a general route for the synthesis of sterically hindered, tertiary amides.



Scheme 53: Synthesis of sterically hindered, tertiary amide **113**.

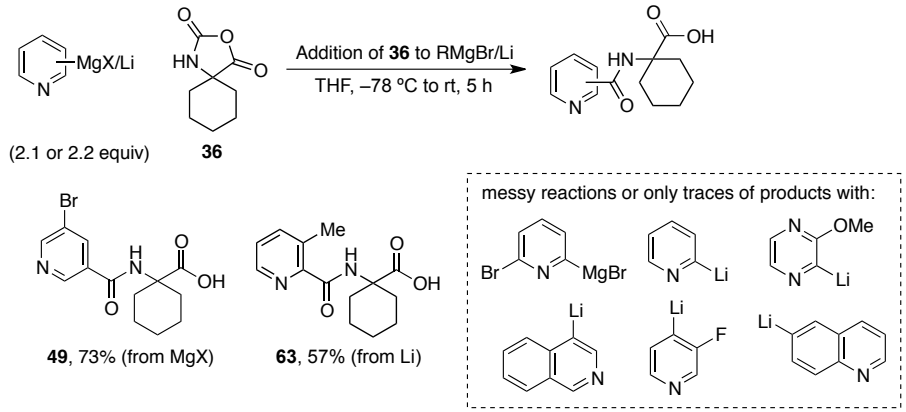
Outlook: Expansion of Nucleophilic Coupling Partners

In our seminal work on the synthesis of sterically hindered amides only standard Grignard reagents were employed.[60] The substrate scope could easily be expanded towards more functionalized amide products when Knochel-type organomagnesium reagents were used (Scheme 54a).[66] Furthermore, lithiated heterocycles were also feasible nucleophiles in the reaction with isocyanates (Scheme 54b). We believe that by employing both kinds of functionalized organometallic reagents highly valuable, sterically hindered amides can be accessed making this approach of specific interest for pharmaceutical and agrochemical companies. The use of other nucleophilic species such as cuprates or zincates, probably in combination with a catalyst, could also be envisioned.



Scheme 54: Use of Knochel-type Grignard and organolithium reagents.

The synthesis of sterically hindered *N*-acyl amino acids via the addition of organometallic reagents to isocyanates proved to be highly general in terms of functional group tolerance. Nevertheless, the employment of pyridine-derived nucleophiles resulted in lower product yields, and in certain cases to no product formation or unclean reaction profiles.



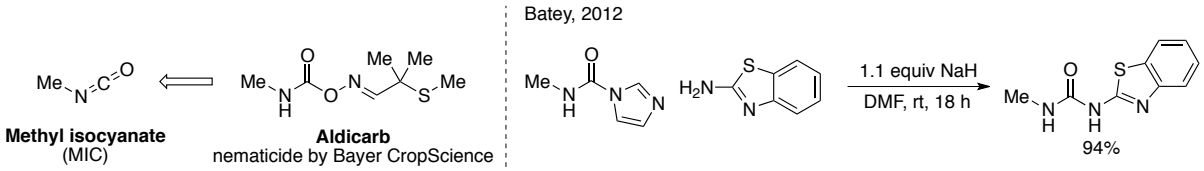
Scheme 55: The use of pyridinyl organometallic reagents in the reaction with NCA **36**.

In the addition of organometallic reagents to NCAs, one equivalent of the organometallic reagent always acts as a base to provide the corresponding proto-demetalated arene as a by-product. In most cases, the formation of this arene is unproblematic, but when pyridine-derived reagents are used the proto-demetalated pyridine itself is a potential electrophile and can possibly be attacked by the second equivalent of the organometallic reagent. This leads to the formation of side-products and a dramatic decrease in yield of the desired *N*-acyl amino acid. A possible solution could be the use of mesitylmagnesium bromide (**17**) as a sacrificial base to generate the isocyanate *in situ* at low temperature. The pyridyl-organolithium reagent could also be generated at –78 °C and then

added to the isocyanate via cannula transfer, diminishing the possibility of side-product generation from electrophilic pyridine-species.

Outlook: Expansion of Electrophilic Coupling Partners

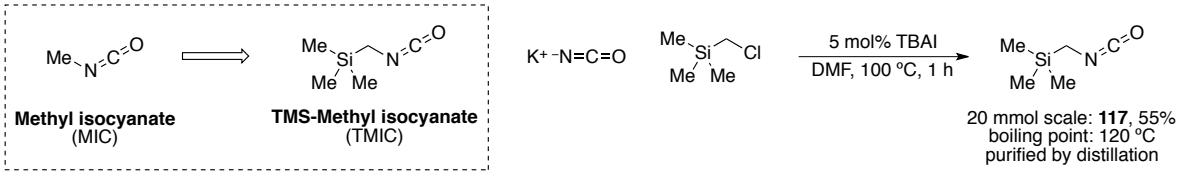
Methyl isocyanate (MIC) is an intermediate chemical in the production of different agrochemicals, such as Aldicarb, a methyl carbamate containing and highly effective nematacide (Scheme 56).[84] Methyl isocyanate is also used in the production of rubbers and adhesives. The use of MIC on bigger scale is problematic, because of its high toxicity that makes it extremely hazardous to human health. Furthermore, the handling of methyl isocyanate is difficult, because of its low boiling point (40 °C) and the rapid hydrolysis by atmospheric water. In 1984, the Union Carbide India Limited in Bhopal (India) improperly handled methyl isocyanate and around 30 metric tons of it escaped from a reaction tank into the atmosphere, leading to the death of nearly 30'000 people.[85] Finding safer methyl isocyanate replacements is one of the most important research topics in agrochemical and polymer chemical laboratories. Recently, Batey *et al*. introduced *N*-methyl carbamoylimidazole as a methyl isocyanate equivalent in the reaction of *N*-, *O*-, and *S*-nucleophiles (Scheme 56). The formation of *N*-methyl amides was not reported, but the nucleophilic displacement of the imidazole group by a Grignard reagent is expected to be difficult after initial deprotonation of the acidic NHMe proton.



Scheme 56: Methyl isocyanate and *N*-methyl carbamoylimidazole as its safe equivalent.

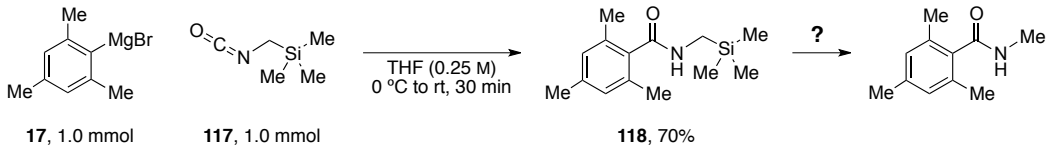
We wanted to find an isocyanate replacement for MIC bearing a *"protected"* methyl group, which can participate in the reaction with organometallic reagents and other nucleophiles. We envisioned that TMS-methyl isocyanate **117** (TMIC) could effectively replace MIC in many applications. TMIC was synthesized via a simple S_N2 reaction of potassium cyanate with (chloromethyl)trimethylsilane (Scheme 57). This isocyanate-forming reaction is interesting, because it does not involve the use of toxic phosgene derivatives or potentially explosive azide-containing intermediates. The development of further isocyanate-

forming reactions using inexpensive and safe potassium cyanate would be highly compelling. Isocyanate **117** has a significantly increased boiling point compared to methyl isocyanate, which simplifies its handling and was easily purified by distillation. Furthermore, TMS-methyl isocyanate **117** was also stable during an aqueous workup that was performed to remove residual DMF.



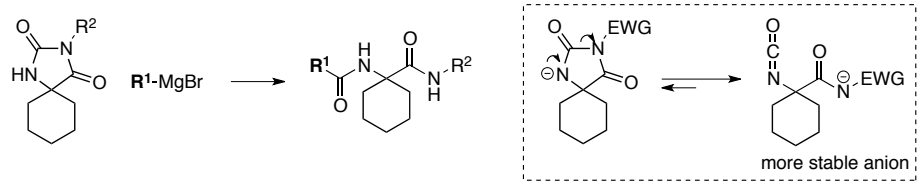
Scheme 57: Synthesis of TMS-methyl isocyanate **107**.

The addition of mesitylmagnesium bromide to isocyanate **117** proceeded without problem, providing amide **118** in good yield. The cleavage of the TMS-group was not investigated yet, but the successful deprotection of similar systems has already been reported.[86]



Scheme 58: Addition of mesitylmagnesium bromide (**17**) to TMS-methyl isocyanate **107**.

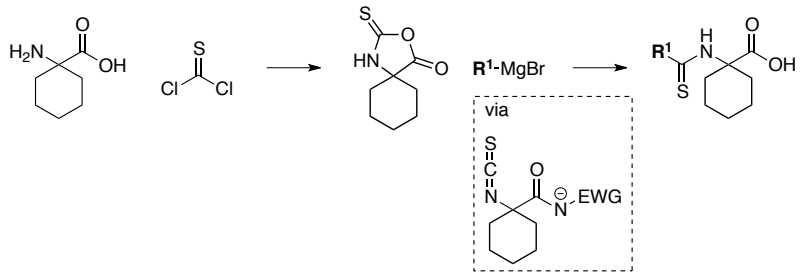
The deprotonative release of isocyanates from starting materials similar to *N*-carboxyanhydrides could be an attractive method for the generation of a wide range of amide products. The use of *N*3-substituted hydantoins would lead to the one-step formation of *N*-acyl carboxamides (Scheme 59). The ring-opening of the deprotonated hydantoin should be facilitated with electron-withdrawing R^2-groups due to the increased pK_a difference between the ring-closed and the ring-opened form.



Scheme 59: Synthesis of *N*-acyl carboxamides.

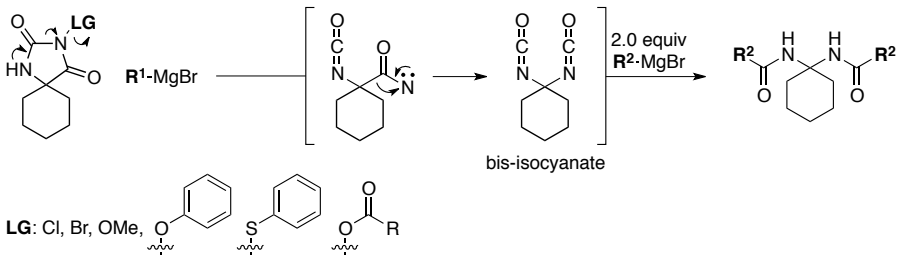
Other interesting coupling partners are 2-thioxo-oxazolidones. The addition of a Grignard reagent would provide in one step thioamidocarboxylic acids; a class of compounds

which is normally prepared from the corresponding amino acid and Lawesson's reagent (Scheme 60). Our approach would have the advantage of a common sulfur-containing building block and the avoidance of malodorous thiation agents. Despite the fact that there is no literature precedence for the preparation of 2-thioxo-oxazolidones, their synthesis from the corresponding amino acid and thiophosgene should be straightforward.



Scheme 60: Synthesis of thioamidocarboxylic acids.

In the last chapter of this thesis, the preparation of unsymmetrical, *gem*-disubstituted *N,N'*-bisamides was discussed. The *in situ* generation of the isocyanate via a Lossen rearrangement is the most promising approach so far and the substrate scope of the Grignard reagent is currently under investigation. Nevertheless, a more facile synthetic route would be advantageous, in particular the use of bis-isocyanates. These compounds have appeared in the literature,[87] but their synthesis from highly explosive bis-acyl azides makes their use problematic and less appealing. A solution could be the generation of the bis-isocyanate at low temperature from a stable and safe precursor. We envision that a hydantoin with an appropriate leaving group could rearrange to a bis-isocyanate upon addition of a Grignard reagent (Scheme 61). This highly reactive intermediate could then be intercepted by two equivalent of the same (or another) Grignard reagent. Most likely only symmetrical *N,N'*-bisamides will be accessible, but the ease of starting material preparation from available hydantoins would make this approach highly attractive.



Scheme 61: Synthesis of *N,N'*-bisamides via bis-isocyanate intermediate.

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PART III

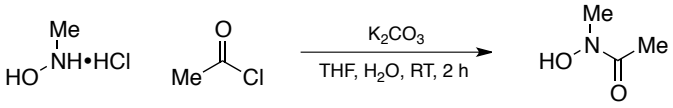
EXPERIMENTAL PROCEDURES AND ANALYTICAL DATA

1. General methods

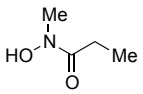
All reactions were carried out in oven-dried glassware under dry N_2 atmosphere. Tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF) and diethyl ether (Et_2O) were distilled from Na with benzophenone. Toluene, CH_2Cl_2 and 1,2-dichloroethane were distilled over CaH_2 and stored over 4Å molecular sieves. *N,N*-Dimethylformamide (DMF) was dried by passage over activated alumina under an Ar atmosphere and stored over 4Å molecular sieves. Boron trifluoride etherate (BF_3•OEt_2) was distilled under vacuum over CaH_2 and stored in a Schlenk-flask under N_2 atmosphere. Triethylamine (NEt_3) was distilled over CaH_2 and stored in a Schlenk-flask under N_2 atmosphere. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) was distilled over CaH_2 and stored in a Schlenk-flask under N_2 atmosphere. All other chemicals were used without further purification. Thin layer chromatography (TLC) was performed on Merck TLC plates pre-coated with silica gel 60 F254. Developed plates were visualized under a UV lamp (254 nm), or stained with potassium permanganate. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF254 (Art 7747). Column chromatography was performed on Silicycle SiliaFlash F60 (230–400 Mesh) using a forced flow of air at 0.5–1.0 bar. Purification by Kugelrohr was performed using a Büchi GKR-50 under reduced pressure (10 mbar). ^{1}H NMR and ^{13}C NMR were measured on VARIAN Mercury 300 MHz, 75 MHz or Bruker Avance 400 MHz, 101 MHz. ^{19}F NMR spectra were recorded with ^{1}H decoupling in $CDCl_3$ referenced to TFA (-76.53 ppm). Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported in Hertz (Hz). Splitting patterns are indicated as follows: app, apparent; br, broad; s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; m, multiplet. GC-MS chromatograms were recorded on an Agilent 7820A (GC) coupled with an Agilent 5975 MSD Series (MS). GC conditions: Agilent column 19091S-433 (30m × 250 µm × 0.25 µm); flow 0.5 mL/min; oven temperature 50 C to 300 ºC (ramp 15 ºC/min or 5 ºC/min). High-resolution mass spectrometric measurements were performed by the mass spectrometry service of the ETH Zürich on a Waters/Micromass AutoSpec Ultima (EI), a Varian IonSpec FT-ICR (ESI) or a Bruker maXis (ESI) spectrometer. IR spectra were obtained on a Varian 800 FT-IR (ATR) spectrometer. The wavenumbers of the bands are reported in cm^{-1}; the relative intensity of the bands is indicated by w (weak), m (medium), s (strong) and br (broad). Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries and are uncorrected. Chiral SFC (Supercritical Fluid Chromatography) was performed on *Jasco* liquid chromatography units using a *Daicel* Chiralpak column (0.46 x 25 cm). Details of chromatographic conditions are indicated below the measured compound. Optical rotation was measured on a *JASCO* P-1010 operating at the sodium D line with a 100 mm path length cell. *In-situ* FT-IR spectroscopy was carried out on a ReactIR R4000 (SiComb probe) with a spectral range of 4000–650 cm^{-1}.

2. Part I: Friedel-Crafts Benzylation of Activated and Deactivated Arenes

2.1. General Procedure: Synthesis of *N*-Methyl Hydroxamic Acids



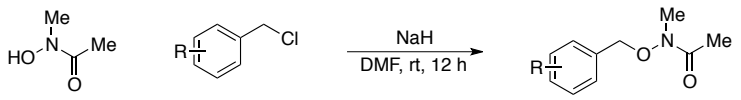
***N*-hydroxy-*N*-methylacetamide (5)** was synthesized by a modified literature procedure:[1] *N*-methyl hydroxylamine hydrochloride (5.0 g, 60 mmol) was dissolved in a mixture of THF (45 mL) and H_2O (45 mL). The solution was cooled to 0 ºC and K_2CO_3 (11 g, 78 mmol) was added. After stirring for 5 min at 0 ºC a solution of acetyl chloride (5.1 mL, 72 mmol) in THF (30 mL) was added dropwise over a period of 10 min. The reaction mixture was warmed to RT and stirred for 2 h. The reaction mixture was quenched with cold H_2O (200 mL) and extracted with EtOAc (4 x 250 mL). The aqueous layer was saturated with NaCl by using a sonication bath and extracted again with EtOAc (3 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to provide pure *N*-hydroxy-*N*-methylacetamide as a golden yellow oil (75%). **^{1}H NMR** (300 MHz, d^6-DMSO) 9.83 (s, 1H), 3.06 (s, 3H), 1.95 (s, 3H); **^{13}C NMR** (101 MHz, d_6-DMSO) 170.4, 35.5, 20.1; **IR** (ATR) ν 3190 (w, broad), 2990 (w), 1624 (s), 1390 (w), 1201 (m), 891 (w) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_3H_7NO_2Na$ ([M+Na)$^+$]): 112.0369. Found: 112.0371. Spectral data were consistent with previous report.[2]



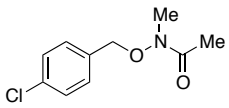
***N*-hydroxy-*N*-methylpropionamide** was prepared according to the general procedure using propionyl chloride as acylating agent (yield: 85%). **^{1}H NMR** (300 MHz, d^6-DMSO) 9.71 (s, 1H), 3.07 (s, 3H), 2.33 (q, *J* = 7.5, 2H), 0.96 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 173.7, 35.7, 24.8, 8.9; **IR** (ATR) ν 3181 (m, broad), 2980 (w), 2941 (w), 1618 (s), 1390 (m), 1199 (m), 1061 (w), 893 (w) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_4H_{10}NO_2$ ([M+H]$^+$): 104.0706. Found: 104.0705.

[1] Y. Endo, T. Uchida, S. Hizatate, K. Shudo, *Synthesis* **1994**, *10*, 1096-1105.
[2] P. G. Harrison, J. A. Richards, *J. Organomet. Chem.* **1980**, *185*, 9-51.

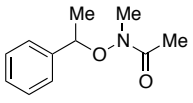
2.2. General Procedure: Synthesis of Benzyl Hydroxamates



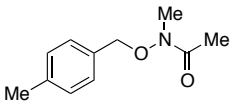
To a septum-capped round-bottom flask under N_2 atmosphere was added a solution of *N*-hydroxy-*N*-methylacetamide (5.6 mmol, 1.0 equiv) in DMF (25 mL). The solution was cooled to 0 ºC and sodium hydride (6.2 mmol, 1.1 equiv, 60% dispersion in mineral oil) was added in one portion. After stirring for 15 min, benzyl chloride (6.2 mmol, 1.1 equiv) was added in one portion. The reaction mixture was warmed to RT and stirred overnight. The reaction mixture was quenched with sat. NH_4Cl solution (15 mL) and stirred for 5 min. EtOAc (100 mL) was added and the layers were separated. The organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The corresponding products were purified by flash column chromatography.



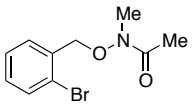
***N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (6)**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 1-chloro-4-(chloromethyl)benzene (0.99 g, 6.2 mmol). Purified by flash column chromatography (hexanes:EtOAc 1:1) and isolated as a colorless oil (1.1 g, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.37 (d br, *J* = 8.4 Hz, 2H), 7.31 (d br, *J* = 8.4 Hz, 2H), 4.80 (s, 2H), 3.18 (s, 3H), 2.07 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.7, 134.9, 133.0, 130.5, 128.9, 75.3, 33.4 (br), 20.2 (br); **IR** (ATR) ν 2928 (w), 2881 (w), 1663 (s), 1492 (m), 1409 (m), 1379 (s), 1179 (m), 1086 (m), 1015 (m), 851 (m), 811 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{10}H_{12}ClNO_2$ ($[M+H]^+$): 214.0629. Found: 214.0627.



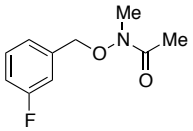
***N*-methyl-*N*-(1-phenylethoxy)acetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and (1-chloroethyl)benzene (0.87 g, 6.2 mmol). Purified by flash column chromatography (hexanes:EtOAc 1:1) and isolated as a colorless oil (0.97 g, 89%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.37 (s br, 5H), 4.87 (q, *J* = 6.3 Hz, 1H), 2.97 (s, 3H), 2.02 (s, 3H), 1.59 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 173.3 (br), 140.1, 128.6, 128.4, 127.2, 82.3, 34.8, 20.3 (br), 20.2; **IR** (ATR) ν 2979 (w), 1665 (s), 1378 (m), 762 (m), 703 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{16}NO_2$ ($[M+H]^+$): 194.1176. Found: 194.1180.



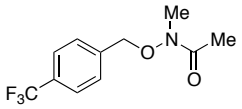
***N*-methyl-*N*-((4-methylbenzyl)oxy)acetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 1-(chloromethyl)-4-methylbenzene (0.87 g, 6.2 mmol). Purified by flash column chromatography (hexanes:EtOAc 1:1) and isolated as a colorless oil (1.0 g, 95%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.26 (d br, *J* = 8.1 Hz, 1H), 7.20 (d br, *J* = 8.1 Hz, 1H), 4.79 (s, 2H), 3.19 (s, 3H), 2.37 (s, 3H), 2.07 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.6, 139.0, 131.4, 129.4, 129.4, 76.0, 33.3 (br), 21.2, 20.2 (br); **IR** (ATR) ν 2927 (w), 1667 (s), 1380 (m), 840 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{16}NO_2$ ($[M+H]^+$): 194.1176. Found: 194.1178.



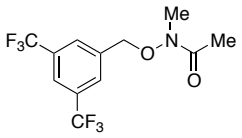
***N*-((2-bromobenzyl)oxy)-*N*-methylacetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 1-bromo-2-(chloromethyl)benzene (1.3 g, 6.2 mmol). Purified by flash column chromatography (hexanes:EtOAc 1:2) and isolated as a colorless oil (1.5 g, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.61 (ddd, *J* = 8.0 Hz, 3.2 Hz, 1.0 Hz, 1H), 7.41 (d br, *J* = 7.6 Hz, 1H), 7.34 (tdd, *J* = 7.6 Hz, 3.2 Hz, 1.6 Hz, 1H), 7.24 (tdd, *J* = 7.6 Hz, 3.2 Hz, 1.6 Hz, 1H), 4.94 (s, 2H), 3.22 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.8, 134.0, 133.0, 131.4, 130.5, 127.7, 124.5, 75.2, 33.4 (br), 20.2; **IR** (ATR) ν 2953 (w), 1668 (s), 1381 (m), 1028 (w), 762 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{10}H_{13}BrNO_2$ ($[M+H]^+$): 258.0124. Found: 258.0121.



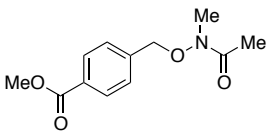
***N*-((3-fluorobenzyl)oxy)-*N*-methylacetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 1-(chloromethyl)-3-fluorobenzene (0.89 g, 6.2 mmol). Purified by flash column chromatography (hexanes:EtOAc 2:3) and isolated as a slightly yellow oil (1.0 g, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.35 (tdd, *J* = 7.7 Hz, 5.8 Hz, 0.8 Hz, 1H), 7.14 (d br, *J* = 7.6 Hz, 1H), 7.09-7.02 (m, 2H), 4.81 (s, 2H), 3.18 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.7, 162.8 (d, *J* = 247 Hz), 136.9 (d, *J* = 6.8 Hz), 130.3 (d, *J* = 8.2 Hz), 124.5 (d, *J* = 3.0 Hz), 115.9 (d, *J* = 21.7 Hz), 115.9 (d, *J* = 20.9 Hz), 75.3 (d, *J* = 1.5 Hz), 33.4 (br), 20.2; ^{19}F NMR (376 MHz, $CDCl_3$) –112.4; **IR** (ATR) ν 2941 (w), 1668 (s), 1382 (m), 1259 (m), 795 (w) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{10}H_{13}FNO_2$ ($[M+H]^+$): 198.0925. Found: 198.0928.



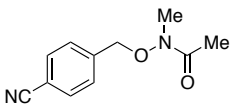
***N*-methyl-*N*-((4-(trifluoromethyl)benzyl)oxy)acetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 1-(chloromethyl)-4-(trifluoromethyl)benzene (1.2 g, 6.2 mmol). Purified by flash column chromatography (hexanes:EtOAc 1:1) and isolated as a colorless oil (1.3 g, 91%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.66 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 4.90 (s, 2H), 3.21 (s, 3H), 2.10 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.8, 138.5, 131.1 (q, *J* = 32.8 Hz), 129.1, 125.7 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 273 Hz), 75.5, 33.5, 20.3; ^{19}F NMR (376 MHz, $CDCl_3$) –62.7; **IR** (ATR) ν 2940 (w), 1668 (s), 1380 (w), 1325 (s), 1165 (m), 1124 (m), 1067 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{12}F_3NO_2$ ([M+H]$^+$): 248.0893. Found: 248.0894.



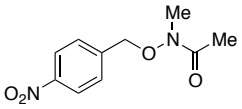
***N*-((3,5-bis(trifluoromethyl)benzyl)oxy)-*N*-methylacetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 1-(chloromethyl)-3,5-bis(trifluoromethyl)benzene (1.6 g, 6.2 mmol). Purified by flash column chromatography (hexanes:EtOAc 1:2) and isolated as a white solid (1.5 g, 85%). **m.p.** 77-78 ºC (EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.90 (s, 1H), 7.84 (s, 2H), 4.98 (s, 2H), 3.23 (s, 3H), 2.14 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.8, 137.2, 132.2 (q, *J* = 8.0 Hz), 128.6 (br), 123.0 (q, *J* = 274 Hz), 122.7 (app quin, *J* = 3.7 Hz), 74.4, 33.8 (br), 20.3; **^{19}F NMR** (376 MHz, $CDCl_3$) –63.0; **IR** (ATR) ν 2860 (w), 1665 (s), 1387 (m), 1361 (s), 1277 (s), 1167 (s), 1130 (s), 1111 (s), 889 (m), 841 (m), 704 (m), 680 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{12}F_6NO_2$ ([M+H]$^+$): 316.0767. Found: 316.0764.



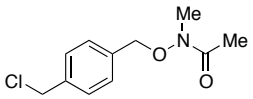
Methyl 4-(((*N*-methylacetamido)oxy)methyl)benzoate: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and methyl 4-(chloromethyl)benzoate (1.1 g, 6.2 mmol). Purified by flash column chromatography (gradient hexanes:EtOAc 1:1 to 1:4) and isolated as a colorless oil (1.1 g, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) 8.06 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 4.89 (s, 2H), 3.93 (s br, 3H), 3.19 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.7, 166.5, 139.4, 130.6, 129.9, 128.8, 75.5, 52.2, 33.5, 20.3; **IR** (ATR) ν 2954 (w), 1724 (s), 1668 (s), 1380 (m), 1281 (s), 1110 (m), 764 (w) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{12}F_6NO_2$ ([M+H]$^+$): 238.1074. Found: 238.1077.



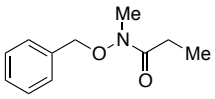
***N*-((4-cyanobenzyl)oxy)-*N*-methylacetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 4-(chloromethyl)benzonitrile (0.94 g, 6.2 mmol). Purified by flash column chromatography (gradient hexanes:EtOAc 1:1 to 0:1) and isolated as an off-white solid (0.84 g, 73%). **m.p.** 73-74 ºC (EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.68 (dd, *J* = 8.0 Hz, *J* = 1.4 Hz, 2H); 7.48 (d, *J* = 7.6 Hz, 2H); 4.89 (s, 2H), 3.20 (s, 3H), 2.09 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.6, 139.7, 132.4, 129.2, 118.3, 112.3, 75.0, 33.6 (br), 20.3; **IR** (ATR) ν 3043 (w), 2228 (m), 1662 (s), 1610 (m), 1386 (s), 1034 (s), 992 (s), 819 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{13}N_2O_2$ ($[M+H]^+$): 205.0972 Found: 205.0964.



***N*-methyl-*N*-((4-nitrobenzyl)oxy)acetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 1-(chloromethyl)-4-nitrobenzene (1.1 g, 6.2 mmol). Purified by flash column chromatography (EtOAc) and isolated as a yellow solid (1.0 g, 83%). **m.p.** over 250 ºC (ethyl acetate); **^{1}H NMR** (400 MHz, $CDCl_3$) 8.26 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 4.95 (s, 2H), 3.22 (s, 3H), 2.11 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$); 172.8, 148.1, 141.7, 129.3, 123.9, 74.7, 33.7 (br), 20.4; **IR** (ATR) ν 3110 (w), 3040 (w), 2827 (w), 1592 (s), 1501 (s), 1331 (s), 1109 (m), 957 (m), 849 (s), 754 (s), 691 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{10}H_{13}N_2O_4$ ($[M+H]^+$): 225.0870 Found: 225.0867.

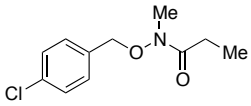


***N*-((4-(chloromethyl)benzyl)oxy)-*N*-methylacetamide**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylacetamide (0.50 g, 5.6 mmol) and 4-bis(chloromethyl)benzene (1.3 g, 7.3 mmol). Purified by flash column chromatography (hexanes:EtOAc 1:1) and isolated as a colorless oil (1.0 g, 79%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.42 (dd, *J* = 6.3 Hz, 2.1 Hz, 2H), 7.37 (d, *J* = 6.3 Hz, 2.1 Hz, 2H), 4.83 (s, 2H), 4.59 (s, 2H), 3.20 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.7, 138.3, 134.7, 129.5, 128.9, 75.7, 45.6, 33.4 (br), 20.3; **IR** (ATR) ν 2936 (w), 2877 (w), 1660 (s), 1419 (m), 1382 (s), 1268 (w), 1182 (w), 823 (w), 677 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{14}ClNO_2$ ($[M+H]^+$): 228.0786 Found: 228.0787.



***N*-(benzyloxy)-*N*-methylpropionamide (46)**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylpropionamide (0.50 g, 4.9

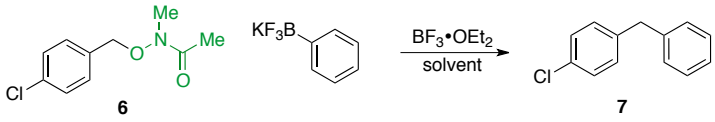
mmol) and benzyl chloride (0.68 g, 5.3 mmol). Purified by flash column chromatography (hexanes:EtOAc 3:1) and isolated as a colorless oil (0.91 g, 97%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.39 (s br, 5H), 4.82 (s, 2H), 3.20 (s, 3H), 2.42 (q, *J* = 7.5 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 176.0, 134.6, 129.1, 128.9, 128.6, 76.2, 33.6, 25.4, 8.7; **IR** (ATR) ν 2980 (w), 2940 (w), 1665 (s), 1377 (m), 896 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{16}NO_2$ ($[M+H]^+$): 194.1176 Found: 194.1176.



***N*-((4-chlorobenzyl)oxy)-*N*-methylpropionamide (48)**: Prepared according to the general procedure from *N*-hydroxy-*N*-methylpropionamide (0.50 g, 4.9 mmol) and 1-chloro-4-(chloromethyl)benzene (0.86 g, 5.3 mmol). Purified by flash column chromatography (hexanes:EtOAc 2:1) and isolated as a colorless solid (0.97 g, 88%). **m.p.** 49-50 ºC (ethyl acetate); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.36 (d br, *J* = 8.5 Hz, 2H), 7.30 (d br, *J* = 8.5 Hz, 2H), 4.78 (s, 2H), 3.18 (s, 3H), 2.40 (q, *J* = 7.5 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 176.1, 134.8, 133.1, 130.4, 128.9, 75.3, 33.8, 25.5, 8.6; **IR** (ATR) ν 2978 (w), 2941 (w), 1650 (s), 1421 (m), 1379 (m), 1194 (m), 1087 (s), 855 (s), 813 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{15}ClNO_2$ ($[M+H]^+$): 228.0786 Found: 228.0783.

2.3. Optimization of Reaction Conditions with Potassium Phenyltrifluoroborate

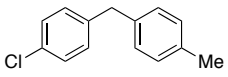
Table 1. Optimization of reaction conditions



6 **7**

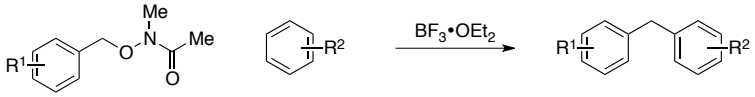
Entry	Equiv of $PhBF_3K$/ BF_3•OEt_2	Temperature	Solvent	Yield of 7
1	4/4	0 ºC to 25 ºC	CH_2Cl_2	77%
2	4/4	0 ºC	CH_2Cl_2	20% (conv.)
3	4/4	0 ºC to 25 ºC	MeCN	17%
4	4/4	0 ºC to 25 ºC	Et_2O	0% (conv.)
5	4/4	0 ºC to 25 ºC	EtOAc	0% (conv.)
6	4/4	0 ºC to 25 ºC	$C_2H_4Cl_2$	74%
7	1/1	0 ºC to 25 ºC	CH_2Cl_2	30% (conv.)
8	2/2	0 ºC to 25 ºC	CH_2Cl_2	55%
9	4/4	25 ºC to 45 ºC	$C_2H_4Cl_2$	traces

In a septum-capped round-bottom flask under N_2 *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (43 mg, 0.20 mmol) was dissolved in the solvent (2.0 mL) and potassium phenyltrifluoroborate (see Table 1) was added. The reaction mixture was cooled to 0 ºC and BF_3•OEt_2 (see Table 1) was added slowly. The reaction mixture was warmed to RT and stirred for 24 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and stirred for 5 min. The mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated under reduced and the crude material was purified by flash column chromatography (hexanes) to provide product **7** as a colorless oil.



In a septum-capped round-bottom flask under N_2 *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (43 mg, 0.20 mmol) was dissolved CH_2Cl_2 (2.0 mL) and potassium *p*-tolyltrifluoroborate (0.16 g, 0.80 mmol) was added. The reaction mixture was cooled to 0 ºC and BF_3•OEt_2 (0.10 mL, 0.80 mmol) was added slowly. The reaction mixture was warmed to RT and stirred for 14 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and stirred for 5 min. The mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated under reduced and the crude material was purified by flash column chromatography (hexanes) to provide product **8** as a colorless oil (35 mg, 0.16 mmol, 81%, 51:38:11 mixture of regioisomers).

2.4. General Procedure: Friedel-Crafts Benzylation of Arenes

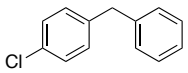


Method A: In a septum-capped round-bottom flask under N_2 the *N*-(benzyloxy)-*N*-methylacetamide derivative (0.4 mmol, 1.0 equiv) was dissolved in the arene (4.0 mL) and BF_3•OEt_2 (0.2 mL, 4.0 equiv) was added slowly. The reaction mixture was stirred at RT (or indicated temperature) for 24 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (15 mL) and stirred for 5 min. Hexanes (15 mL) was added and the phases were separated. The aqueous phase was extracted with hexanes (15 mL). The combined organic

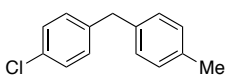
phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the pure diarylmethane product without further purification (if not otherwise indicated).

Method B: In a septum-capped round-bottom flask under N_2 the *N*-(benzyloxy)-*N*-methylacetamide derivative (0.4 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (4.0 mL). The arene (1.6 mmol, 4.0 equiv) was added, followed by slow addition of BF_3•OEt_2 (0.2 mL, 4.0 equiv). The flask was capped, sealed with parafilm and heated at the indicated temperature for 24 h. The reaction mixture was cooled to RT, quenched with sat. $NaHCO_3$ solution (15 mL), and stirred for 5 min. CH_2Cl_2 (15 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography to provide the product.

Only the structures of the major products are shown. Determination of the major product was performed by careful ^{1}H-NMR and ^{13}C-NMR analysis and comparison with literature data. For regioisomeric mixtures > 90:10 only peaks of the major product were assigned. The ratio of regioisomers was determined by GC/MS analysis.



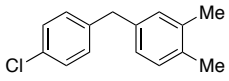
1-benzyl-4-chlorobenzene (7): Method A: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and benzene (4 mL) (81 mg, 99%). Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and benzene (0.14 mL, 1.6 mmol); reaction temperature 40 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (62 mg, 77%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.34-7.27 (m, 3H), 7.25-7.16 (m, 4H), 7.15-7.11 (m, 2H), 3.96 (s, 2H): **^{13}C NMR** (101 MHz, $CDCl_3$) 140.5, 139.6, 131.9, 130.2, 128.8, 128.5 (br), 126.3, 41.2; **MS** (EI) *m/z* calcd for $C_{13}H_{11}Cl$ (M^+): 202.1. Found: 202.1. Spectral data were consistent with previous report.[3]



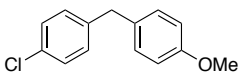
1-chloro-4-(4-methylbenzyl)benzene (8):[4] Method A: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and

[3] M. Armatore, C. Gosmini, *Chem. Commun.* **2008**, *40*, 5019-5021.
[4] Major isomer assigned by comparison with: J. R. Schmink, N. E. Leadbeater, *Org. Lett.* **2009**, *11*, 2575-2578.

toluene (4 mL) (86 mg, 99%, 55:43:2 mixture of regioisomers). Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and toluene (0.17 mL, 1.6 mmol); reaction temperature 40 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (69 mg, 80%, 54:43:3 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.26-7.17 (m, 5.8H), 7.13-7.00 (m, 8.2H), 3.96 (s, 1.3H, minor), 3.92 (s, 2H, major), 2.37 (s, 0.2H, major), 2.33 (s, 3H, major), 2.23 (s, 2.1H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 139.9, 138.9, 138.3, 138.2, 137.5, 136.6, 135.8, 131.7, 131.7, 130.4, 130.2, 130.2, 130.0, 129.7, 129.6, 129.2, 129.0, 128.7, 128.5, 128.5, 128.4, 128.2, 127.0, 126.7, 126.1, 125.9, 125.3, 41.2 (minor), 40.8 (major), 38.8 (minor), 21.4 (minor), 21.00 (major), 19.6 (minor); **MS** (EI) *m/z* calcd for $C_{14}H_{13}Cl$ (M^+): 216.1. Found: 216.1.



4-(4-chlorobenzyl)-1,2-dimethylbenzene (14):[5] Method A: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and *o*-xylene (4 mL) (92 mg, 99%, 65:35 mixture of regioisomers). Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and *o*-xylene (0.19 mL, 1.6 mmol); reaction temperature 35 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (83 mg, 90%, 53:47 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.26-7.22 (m, 3.2H), 7.13-7.03 (m, 5H), 6.99-6.90 (m, 2.6H), 3.99 (s, 1.1H, minor), 3.89 (s, 2H, major), 2.30 (s, 1.6H, minor), 2.24 (s br, 6H, major), 2.12 (s, 1.6H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 140.0 (major), 139.3 (minor), 138.1 (minor), 138.0 (major), 137.2 (minor), 136.7 (major), 135.1 (minor), 134.4 (major), 131.7 (major), 131.6 (minor), 130.2 (major), 130.2 (minor), 129.9 (major), 129.8 (major), 128.5 (major), 128.4 (br, minor), 128.0 (minor), 126.2 (major), 125.5 (minor), 40.8 (major), 39.4 (minor), 20.6 (minor), 19.7 (major), 19.3 (major), 15.4 (minor); **MS** (EI) *m/z* calcd for $C_{15}H_{15}Cl$ (M^+): 230.1. Found: 230.0.

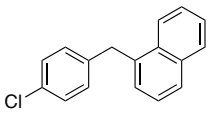


1-chloro-4-(4-methoxybenzyl)benzene:[6] Method A: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and anisole (4 mL) (93 mg, 99%, 54:46 mixture of regioisomers). Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and anisole (0.18 mL, 1.6 mmol);

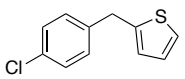
[5] Major isomer assigned by comparison with: K. Mertins, I. Iovel, J. Kischel, A. Zapf, M. Beller, *Adv. Syn. Cat.* **2006**, *348*, 691-695.

[6] Major isomer assigned by comparison with: R. Kuwano, M. Yokogi, *Org. Lett*, **2005**, *7*, 945-947.

reaction temperature 40 °C. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (88 mg, 95%, 57:43 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.27-7.20 (m, 4H), 7.17-7.06 (s, 6H), 6.92-6.82 (m, 3.4H), 3.94 (s, 1.5H, minor), 3.90 (s, 2H, major), 3.81 (s, 2H, minor), 3.80 (s, 3H, major); **^{13}C NMR** (101 MHz, $CDCl_3$) 158.1 (major), 157.3 (minor), 140.0 (major), 139.5 (minor), 132.6 (major), 131.8 (major), 131.5 (minor), 130.2 (minor), 130.2 (minor), 130.1 (major), 129.8 (major), 129.1 (minor), 128.5 (major), 128.3 (minor), 127.7 (minor), 120.5 (minor), 113.9 (major), 110.5 (minor), 55.3 (minor), 55.2 (major), 40.3 (major), 35.3 (minor); **MS** (EI) *m/z* calcd for $C_{14}H_{13}ClO$ (M^+): 232.1. Found: 232.0.



1-(4-chlorobenzyl)naphthalene (15):[7] Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and naphthalene (0.21 g, 1.6 mmol); reaction temperature 40 °C. Purified by flash column chromatography (gradient hexanes:Et_2O 100:0 to 100:3) and isolated as a colorless oil (88 mg, 87%, 70:30 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 8.00-7.81 (m, 4.2H), 7.67 (s, 0.45H), 7.55-7.46 (m, 3.7H), 7.35-7.26 (m, 4.7H), 7.21-7.14 (m, 3H), 4.45 (s, 2H, major), 4.15 (s, 0.9H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 139.4, 139.1, 138.0, 136.0, 133.9, 133.6, 132.1, 131.9, 131.8, 130.3, 130.0, 128.7, 128.6, 128.5, 128.2, 127.6, 127.5, 127.4, 127.3, 127.1, 126.1, 126.1, 125.6, 125.5, 125.5, 124.1, 41.3 (minor), 38.4 (major); **MS** (EI) *m/z* calcd for $C_{17}H_{13}Cl$ (M^+): 252.1. Found: 252.1.

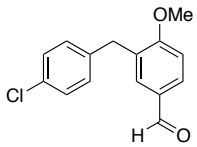


2-(4-chlorobenzyl)thiophene (16):[8] Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and thiophene (0.13 mL, 1.6 mmol); reaction temperature 40 °C. Purified by flash column chromatography (gradient hexanes:EtOAc 100:0 to 100:5) and isolated as a yellowish oil (75 mg, 89%, 65:35 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.30-7.25 (m, 3.5H), 7.20-7.12 (s, 4.0H), 6.95-6.91 (m, 1.5H), 6.88 (dd, J = 5.0 Hz, 1.5 Hz, 0.5H, minor), 6.80-6.78 (m, 1H), 4.13 (s, 2H, major), 3.95 (s, 1H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 143.3 (major), 140.9 (minor), 139.0 (major), 138.8 (minor), 132.3 (major), 132.0 (minor), 130.1 (minor), 129.9

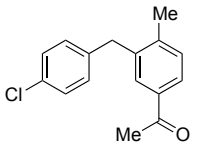
[7] Major isomer assigned by comparison with: H. P. J. Utley, G. G. Rozenberg, *Tetrahedron* **2002**, *59*, 5251-5265

[8] Major isomer assigned by comparison with: S. Zhang, D. Marshall, L. S. Liebeskind, *J. Org. Chem*. **1999**, *64*, 2796-2804.

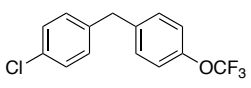
(major), 128.6 (major), 128.6 (minor), 128.2 (minor), 126.9 (major), 125.9 (minor), 125.3 (major), 124.2 (major), 121.4 (minor), 35.8 (minor), 35.4 (major); **MS** (EI) *m/z* calcd for $C_{11}H_9ClS$ (M^+): 208.0. Found: 208.0.



3-(4-chlorobenzyl)-4-methoxybenzaldehyde (17): Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and *para*-anisaldehyde (0.19 mL, 1.6 mmol); reaction temperature 50 ºC. Purified by flash column chromatography (gradient hexanes:Et_2O 100:0 to 100:5) and isolated as a colorless oil (54 mg, 52%, 99:1 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 9.84 (s, 1H), 7.76 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.26-7.21 (m, 2H), 7.13 (d br, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 2H), 3.90 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 190.9, 162.3, 138.4, 131.9, 131.3, 131.2, 130.2, 130.2, 129.7, 128.51, 110.4, 55.8, 35.3; **IR** (ATR) ν 3035 (w), 1686 (s), 1600 (s), 1491 (m), 1259 (s), 1112 (w), 813 (w), 734 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{15}H_{13}ClO_2$ (M^+): 260.0604. Found: 260.0602.

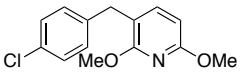


1-(3-(4-chlorobenzyl)-4-methylphenyl)ethanone (18): Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and 4'-methylacetophenone (0.21 mL, 1.6 mmol); reaction temperature 45 ºC. Purified by flash column chromatography (gradient hexanes:Et_2O 100:0 to 100:5) and then PTLC (hexanes:Et_2O 5:1) and isolated as a colorless oil (52 mg, 50%, 99:1 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.76 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.26-7.23 (m, 3H), 7.03 (d, *J* = 8.6 Hz, 2H), 4.00 (s, 2H), 2.56 (s, 3H), 2.26 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 197.9, 142.7, 138.8, 138.1, 135.4, 132.0, 130.7, 129.9, 129.7, 128.6, 127.0, 38.9, 26.6, 19.9; **IR** (ATR) ν 3049 (w), 2920 (w), 1597 (w), 1491 (s), 1091 (m), 1014 (m), 790 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{16}ClO$ ($[M+H]^+$): 259.0884. Found: 259.0877.

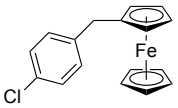


1-chloro-4-(4-(trifluoromethoxy)benzyl)benzene (19): Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and (trifluoromethoxy)benzene (0.21 mL, 1.6 mmol); reaction temperature 40 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (71 mg, 63%, 93:7 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.30-7.25 (m, 1.5H), 7.19-

7.13 (m, 3.7H), 7.12-7.11 (m, 1.6H), 7.10-7.08 (m, 1H), 4.00 (s, 0.2H, minor), 3.95 (s, 2H, major); **^{13}C NMR** (101 MHz, $CDCl_3$) 147.8 (q, *J* = 1.7 Hz, major), 139.3 (major), 138.9 (major), 138.0 (minor), 132.2 (major), 131.1 (minor), 130.3 (minor), 130.3 (major), 130.1 (major), 128.7 (major), 128.6 (minor), 127.9 (minor), 126.9 (minor), 121.1 (major), 120.5 (minor), 120.5 (q, *J* = 258 Hz, major), 40.5 (major), 35.1 (minor); **^{19}F NMR** (376 MHz, $CDCl_3$) –57.0 (minor), –57.9 (major); **IR** (ATR) ν 3041 (w), 2923 (w), 1508 (s), 1491 (s), 1250 (s), 1222 (s), 1161 (s), 1016 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{10}ClF_3O$ (M^+): 286.0372. Found: 286.0367.

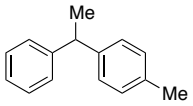


3-(4-chlorobenzyl)-2,6-dimethoxypyridine (20): Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and 2,6-dimethoxypyridine (0.21 mL, 1.6 mmol); reaction temperature 45 ºC. Purified by flash column chromatography (gradient hexanes:Et_2O 100:0 to 100:3) and isolated as a colorless oil (87 mg, 83%, 97:3 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.24-7.19 (m, 3H), 7.12-7.09 (m, 2H), 6.23 (d, *J* = 7.9 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.80 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 161.7, 160.2, 141.1, 139.2, 131.7, 130.1, 128.4, 113.8, 100.2, 53.5, 53.3, 34.1; **IR** (ATR) ν 2962 (w), 2918 (m), 2850 (m), 1736 (w), 1261 (m), 1020 (m), 795 (m), 721 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{15}ClNO_2$ ($[M+H]^+$): 264.0786. Found: 264.0789.

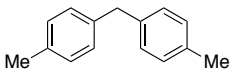


(4-chlorobenzyl)ferrocene (21): Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and ferrocene (0.30 g, 1.6 mmol); reaction temperature 35 ºC. Purified by flash column chromatography (hexanes) and isolated as a yellow solid (0.11 g, 89%). **m.p.** 73-74 ºC (hexane); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.23 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.12 (s, 5H), 4.09 (d, *J* = 1.5 Hz, 2H), 4.07 (d, *J* = 1.5 Hz, 2H), 3.66 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 140.0, 131.63, 129.7, 128.3, 87.4, 68.6, 68.5, 67.7, 35.4; **HRMS** (EI) *m/z* calcd for $C_{17}H_{16}ClFe$ (M^+): 310.0212. Found: 310.0207. Spectral data were consistent with previous report.[9]

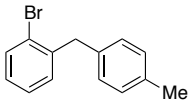
[9] H. Zhang, Z. Bian, *J. Organomet. Chem.* **2007**, *692*, 5687-5689.



1-methyl-4-(1-phenylethyl)benzene (22):[5] Method A: Prepared from *N*-methyl-*N*-(1-phenylethoxy)acetamide (77 mg, 0.40 mmol) and toluene (4 mL) (78 mg, 99%, 93:7 mixture of regioisomers). Method B: Prepared from *N*-methyl-*N*-(1-phenylethoxy)acetamide (77 mg, 0.40 mmol) and toluene (0.17 mL, 1.6 mmol); reaction temperature 25 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (71 mg, 90%, 93:7 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.33-7.11 (m, 9.9H), 4.35 (q, *J* = 7.2 Hz, 0.1H, minor), 4.15 (q, *J* = 7.2 Hz, 1H, major), 2.34 (s, 3H, major), 2.27 (s, 0.3H, minor), 1.66 (d, *J* = 7.2 Hz, 3H, major), 1.65 (d, *J* = 7.2 Hz, 0.3H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 146.6 (major), 146.2 (minor), 143.9 (minor), 143.4 (major), 136.1 (minor), 135.5 (major), 130.4 (minor), 129.0 (major), 128.3 (major), 128.3 (minor), 127.7 (minor), 127.6 (major), 127.5 (major), 126.7 (minor), 126.1 (minor), 126.0 (minor), 125.9 (major), 125.8 (minor), 44.4 (major), 41.0 (minor), 22.1 (minor), 21.9 (major), 21.0 (major), 19.7 (minor); **MS** (EI) *m/z* calcd for $C_{15}H_{16}$ (M^+): 196.1. Found: 196.1.



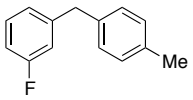
di-*p*-tolylmethane (23):[10] Method A: Prepared from *N*-methyl-*N*-((4-methylbenzyl)oxy)acetamide (77 mg, 0.40 mmol) and toluene (4 mL) (78 mg, 99%, 70:30 mixture of regioisomers). Method B: Prepared from *N*-methyl-*N*-((4-methylbenzyl)oxy)acetamide (77 mg, 0.40 mmol) and toluene (0.17 mL, 1.6 mmol); reaction temperature 25 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (70 mg, 89%, 77:23 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.17-7.15 (m, 1.7H, minor), 7.10 (s, 8H, major), 7.07-7.00 (m, 1.7H, minor), 3.96 (s, 0.8H, minor), 3.92 (s, 2H, major), 2.32 (s, 6H, major), 2.32 (s, 1.3H, minor), 2.62 (s, 1.3H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 139.2 (minor), 138.4 (major), 137.3 (minor), 136.6 (minor), 135.4 (major), 135.3 (minor), 130.2 (minor), 129.8 (minor), 129.1 (major), 129.1 (minor), 128.7 (major), 128.6 (minor), 126.3 (minor), 125.9 (minor), 41.1 (major), 39.0 (minor), 21.0 (major), 19.6 (minor); **MS** (EI) *m/z* calcd for $C_{15}H_{16}$ (M^+): 196.1. Found: 196.1.



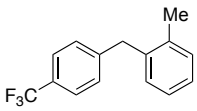
1-bromo-2-(4-methylbenzyl)benzene (24):[10] Method A: Prepared from *N*-((2-bromobenzyl)oxy)-*N*-methylacetamide (0.10 g, 0.40 mmol) and toluene (4 mL) (0.10 g, 99%, 64:32:4 mixture of regioisomers). Method B: Prepared from *N*-((2-

[10] Major isomer assigned by comparison with: R. B. Bedford, M. Huwe, C. Wilkinson, *Chem. Commun.* **2009**, *5*, 600-602.

bromobenzyl)oxy)-*N*-methylacetamide (0.10 g, 0.40 mmol) and toluene (0.17 mL, 1.6 mmol); reaction temperature 50 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (78 mg, 75%, 64:33:3 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.62-7.56 (s, 2H), 7.26-6.98 (m, 13H), 6.88 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 4.09 (s, 2H), 4.07 (s, 2H), 2.33 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 140.6, 140.5, 139.7, 139.4, 138.1, 137.5, 136.8, 136.4, 135.7, 132.8, 132.6, 131.1, 131.0, 130.3, 130.3, 129.8, 129.7, 129.2, 128.9, 128.3, 127.8, 127.8, 127.7, 127.4, 127.0, 126.6, 126.1, 126.0, 125.0, 124.9, 124.9, 41.6, 41.3, 39.5, 21.4, 21.0, 19.5; **MS** (EI) *m/z* calcd for $C_{14}H_{13}Br$ (M^+): 260.0. Found: 260.0.

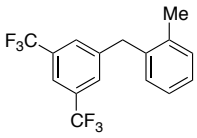


1-fluoro-3-(3-(trifluoromethyl)benzyl)benzene (25): Method A: Prepared from *N*-((3-fluorobenzyl)oxy)-*N*-methylacetamide (79 mg, 0.40 mmol) and toluene (4 mL) (80 mg, 99%, 50:43:7 mixture of regioisomers). Method B: Prepared from *N*-((3-fluorobenzyl)oxy)-*N*-methylacetamide (79 mg, 0.40 mmol) and toluene (0.17 mL, 1.6 mmol); reaction temperature 50 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (59 mg, 74%, 50:43:7 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.28-7.18 (m, 3.9H), 7.14-7.08 (m, 3.8H), 7.02-6.80 (m, 5.5H), 4.00 (s, 1.5H), 3.95 (s, 2H), 2.35 (s, 3H), 2.25 (s, 2.2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 163.0 (d, *J* = 246 Hz, minor), 163.0 (d, *J* = 246 Hz, major), 144.0 (d, *J* = 7.1 Hz), 143.8 (d, *J* = 7.1 Hz, minor), 143.1 (d, *J* = 7.1 Hz), 140.2 (minor), 138.2 (minor), 138.1 (major), 137.2 (minor), 136.6 (major), 135.9 (minor), 130.4 (minor), 130.0 (minor), 129.8 (d, *J* = 5.7 Hz), 129.7 (d, *J* = 5.7 Hz), 129.7 (app s), 129.3 (major), 128.8 (major), 128.5 (minor), 127.1 (minor), 126.7 (minor), 126.1 (minor), 125.9 (minor), 124.5 (d, *J* = 2.8 Hz, minor), 124.4 (d, *J* = 2.8 Hz), 124.3 (d, *J* = 2.8 Hz), 115.7 (d, *J* = 21.2 Hz, minor), 115.7 (d, *J* = 21.2 Hz), 115.5 (d, *J* = 21.3 Hz), 112.9 (d, *J* = 21.0 Hz, minor), 112.9 (d, *J* = 21.1 Hz), 112.8 (d, *J* = 21.1 Hz), 41.6 (d, *J* = 1.6 Hz, minor), 41.2 (d, *J* = 1.7 Hz), 39.2 (d, *J* = 1.7 Hz), 21.4 (minor), 21.0, 19.6; **^{19}F NMR** (376 MHz, $CDCl_3$), –113.6 (m, minor), –113.6 (m, minor), –113.6 (m, major); **IR** (ATR) v 2922 (w), 1614 (m), 1589 (s), 1486 (s), 1447 (m), 1248 (m), 1135 (w), 738 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{13}F$ (M^+): 200.1001. Found: 200.1001.

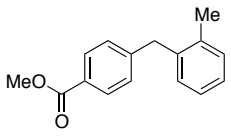


1-methyl-2-(4-(trifluoromethyl)benzyl)benzene (26):[10] Method A: Prepared from *N*-methyl-*N*-((4-(trifluoromethyl)benzyl)oxy)acetamide (99 mg, 0.40 mmol) and toluene (4 mL) (0.10 g, 99%, 60:35:5 mixture of regioisomers); reaction temperature 70 ºC. Method B: Prepared from *N*-methyl-*N*-((4-

(trifluoromethyl)benzyl)oxy)acetamide (99 mg, 0.40 mmol) and toluene (0.17 mL, 1.6 mmol); reaction temperature 85 ºC (in 1,2-dichloroethane). Purified by flash column chromatography (hexanes) and isolated as a colorless oil (70 mg, 70%, 60:34:6 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.54 (app d, *J* = 7.8 Hz, 3.7H), 7.30 (app d, *J* = 8.7 Hz, 2H), 7.25-6.98 (m, 8.6H), 4.06 (s, 1.5H, minor), 4.01 (s, 2H, major) 2.38 (s, 3H, major), 2.25 (s, 2.3H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 145.5 (minor), 145.3 (minor), 144.6 (major), 139.9, 138.3, 137.8, 136.9, 136.6, 136.0, 130.5, 130.0, 129.7, 129.3, 129.2, 129.1, 128.9, 128.8, 128.5, 128.5, 127.2, 126.9, 126.2, 126.0, 125.3 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 273 Hz), 41.7 (minor), 41.3 (minor), 39.3 (major), 21.4 (minor), 21.0 (minor), 19.6 (major); **^{19}F NMR** (376 MHz, $CDCl_3$) –62.3, –62.3 (br); **MS** (EI) *m/z* calcd for $C_{15}H_{13}F_3$ (M^+): 250.1. Found: 250.0.

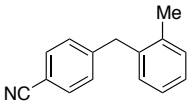


1-(2-methylbenzyl)-3,5-bis(trifluoromethyl)benzene (27): Method A: Prepared from *N*-((3,5-bis(trifluoromethyl)benzyl)oxy)-*N*-methylacetamide (0.13 g, 0.40 mmol) and toluene (4 mL); reaction temperature 85 ºC. Purified by flash column chromatography (gradient hexanes:Et_2O 100:0 to 100:1) and isolated as a colorless oil (0.11 g, 90%, 50:41:9 mixture of regioisomers) **^{1}H NMR** (300 MHz, $CDCl_3$) 7.73 (s, 1.6H), 7.64 (s, 2H), 7.58 (s, 1.2H), 7.23-7.00 (m, 6.5H), 4.12 (s, 1.2H, minor), 4.07 (s, 2H, major), 2.35 (s, 3H, major), 2.24 (s, 1.8H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 143.9 (minor), 143.7 (minor), 143.0 (major), 138.7, 138.6, 136.6, 136.5, 136.5, 135.7, 131.7 (q, *J* = 33.2 Hz), 132.2, 131.8, 131.5, 131.2, 130.7, 129.9, 129.6, 129.6, 128.9 (br), 128.8, 128.7, 127.7, 127.3, 126.5, 125.9, 123.4 (q, *J* = 274 Hz), 120.2 (q, *J* = 3.7 Hz), 41.5 (minor), 41.1 (minor), 39.1 (major), 21.4 (minor), 21.0 (minor), 19.6 (major); **^{19}F NMR** (376 MHz, $CDCl_3$) –62.8 (minor), –62.8 (minor), –62.8 (major); **IR** (ATR) ν 2925 (w), 2851 (w), 1506 (w), 1376 (m), 1278 (s), 1171 (m), 1135 (m), 747 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{16}H_{12}F_6$ (M^+): 318.0843. Found: 318.0835.

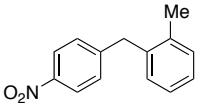


Methyl 4-(2-methylbenzyl)benzoate (28):[10] Method A: Prepared from methyl 4-(((*N*-methylacetamido)oxy)methyl)benzoate (95 mg, 0.40 mmol) and toluene (4 mL); reaction temperature 45 ºC (95 mg, 99%, 49:38:13 mixture of regioisomers). Method B: Prepared from methyl 4-(((*N*-methylacetamido)oxy)methyl)benzoate (95 mg, 0.40 mmol) and toluene (0.17 mL, 1.6 mmol); reaction temperature 65 ºC (in 1,2-dichloroethane). Purified by flash column chromatography (gradient hexanes:Et_2O 10:0 to 10:1) and isolated as a colorless oil (70 mg, 73%, 50:37:12

mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 8.00-7.93 (m, 4.4H), 7.28-7.26 (m, 1H), 7.25-7.15 (m, 6.6H), 7.13-7.00 (m, 5.4H), 4.04 (s, 2H), 3.99 (s, 2.6H), 3.90 (s br, 6.8H), 2.33 (s br, 3.6H), 2.22 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 167.1 (br), 146.8, 146.6, 145.9, 140.0, 138.2, 138.0, 137.1, 136.6, 135.9, 130.4, 130.0, 129.8, 129.7, 129.7, 129.3, 128.9, 128.9, 128.8, 128.7, 128.5, 128.0, 128.0, 128.0, 127.1, 126.8, 126.1, 126.0, 52.0 (br), 41.9 (minor), 41.5 (minor), 39.5 (major), 21.4 (minor), 21.0 (minor), 19.6 (major); **MS** (EI) *m/z* calcd for $C_{16}H_{16}O_2$ (M^+): 240.1. Found: 240.1.



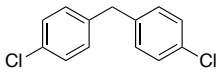
4-(2-methylbenzyl)benzonitrile (29):[11] Method A: Prepared from *N*-((4-cyanobenzyl)oxy)-*N*-methylacetamide (82 mg, 0.40 mmol) and toluene (4 mL) (82 mg, 99%, 53:37:10 mixture of regioisomers); reaction temperature 65 ºC. Method B: Prepared from *N*-((4-cyanobenzyl)oxy)-*N*-methylacetamide (82 mg, 0.40 mmol) and toluene (0.17 mL, 1.6 mmol); reaction temperature 85 ºC (in 1,2-dichloroethane). Purified by flash column chromatography (hexanes) and isolated as a colorless oil (54 mg, 65%, 53:38:9 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.59-7.54 (m, 3.5H), 7.30-7.26 (m, 2H), 7.23-6.95 (m, 9.0H), 4.04 (s, 1.5H, minor), 3.99 (s, 2H, major), 2.33 (s, 3H, major), 2.20 (s, 2.2H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 147.0 (minor), 146.9 (minor), 146.2 (major), 139.2, 138.4, 137.2, 136.5, 136.3, 136.2, 132.2, 132.2, 130.6, 130.0, 129.7, 129.6, 129.5, 129.4, 129.4, 128.8, 128.6, 127.4, 127.1, 126.3, 126.0, 119.0, 110.0, 109.9, 109.9, 41.9 (minor), 41.5 (minor), 39.6 (major), 21.4 (minor), 21.0 (minor), 19.6 (major); **MS** (EI) *m/z* calcd for $C_{15}H_{13}N$ (M^+): 207.1. Found: 207.0.



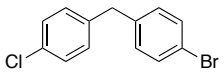
1-methyl-2-(4-nitrobenzyl)benzene (30): Method A: Prepared from *N*-methyl-*N*-((4-nitrobenzyl)oxy)acetamide (90 mg, 0.40 mmol) and toluene (4 mL); reaction temperature 80 ºC. Purified by flash column chromatography (gradient hexanes:Et_2O 100:0 to 100:5) and isolated as a yellowish oil (84 mg, 93%, 55:40:5 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 8.16-8.12 (m, 3.3H), 7.36-7.29 (m, 2.7H), 7.21-6.99 (m, 6.7H), 4.09 (s, 1.5H, minor), 4.04 (s, 2H, major), 2.34 (s, 3H, major), 2.22 (s, 2.2H, minor); **^{13}C NMR** (101 MHz, $CDCl_3$) 149.2 (minor), 149.0 (minor), 148.3 (major), 146.4, 139.1, 138.5, 137.1, 136.5, 136.3, 136.1, 130.6, 130.0, 129.7, 129.6, 129.5, 129.5, 129.4, 128.8, 128.7, 127.5, 127.2, 126.3, 126.0, 123.7, 123.6, 41.6 (minor), 41.3

[11] Major isomer assigned by comparison with: L. D. Frederick, J. R. Petisce, *Tetrahedron*, **1986**, *42*, 6207-6218.

(minor), 39.4 (major), 21.3 (minor), 21.0 (minor), 19.6 (major); **IR** (ATR) ν 2920 (w), 2850 (w), 1604 (w), 1517 (s), 1345 (s), 1261 (w), 1109 (w), 731 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{13}NO_2$ (M^+): 227.0946. Found: 227.0949.



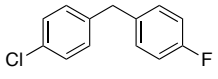
Bis(4-chlorophenyl)methane (31):[12] Method A: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and chlorobenzene (4 mL) (94 mg, 99%, 77:23 mixture of regioisomers). Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and chlorobenzene (0.16 mL, 1.6 mmol); reaction temperature 40 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (72 mg, 76%, 70:30 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.42-7.40 (m, 0.5H, minor), 7.28 (d, *J* = 8.4 Hz, 4H, major), 7.30-7.27 (m, 0.9H, minor), 7.23-7.15 (m, 2.4H, minor), 7.11 (d, *J* = 8.4 Hz, 4H, major), 4.10 (s, 0.9H, minor), 3.94 (s, 2H, major); **^{13}C NMR** (101 MHz, $CDCl_3$) 139.0 (major), 138.1 (minor), 138.0 (minor), 134.2 (minor), 132.1 (major), 132.1 (minor), 130.9 (minor), 130.2 (minor), 130.2 (major), 129.7 (minor), 128.7 (major), 128.6 (minor), 127.9 (minor), 126.9 (minor), 40.5 (major), 38.6 (minor); **MS** (EI) *m/z* calcd for $C_{13}H_{10}Cl_2$ (M^+): 236.0. Found: 236.0.



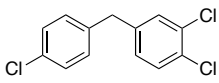
1-bromo-4-(4-chlorobenzyl)benzene (32): Method A: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and bromobenzene (4 mL) (0.11 g, 99%, 78:22 mixture of regioisomers). Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and bromobenzene (0.17 mL, 1.6 mmol) reaction temperature 40 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (84 mg, 75%, 70:30 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.60 (dd, *J* = 7.8 Hz, 1.0 Hz, 0.45H, minor), 7.44 (app dt, *J* = 8.4 Hz, 2.2 Hz, 2H, major), 7.28 (app dt, *J* = 8.4 Hz, 2.2 Hz, 2H, major), 7.30-7.25 (m, 1.6H), 7.17-7.12 (m, 1.9H), 7.11 (d br, *J* = 8.4 Hz, 2H, major), 7.06 (d, *J* = 8.4 Hz, 2H, major), 4.11 (s, 0.9H, minor), 3.92 (s, 2H, major); **^{13}C NMR** (101 MHz, $CDCl_3$) 139.8 (minor), 139.5 (major), 138.9 (major), 137.9 (minor), 133.0 (minor), 132.2 (major), 132.1 (minor), 131.6 (major), 131.0 (minor), 130.6 (major), 130.3 (minor), 130.2 (major), 128.7 (major), 128.6 (minor), 128.1 (minor), 127.6 (minor), 124.8 (minor), 120.2 (major), 41.1 (minor), 40.6 (major); IR

[12] Major isomer assigned by comparison with: M. Halpern, Z. Lysenko, *J. Org. Chem.* **1989**, *54*, 1201-1203.

(ATR) v 2921 (w), 1491 (s), 1407 (w), 1090 (m), 1014 (m), 897 (m) cm^{-1}; **MS** (EI) *m/z* calcd for $C_{13}H_{10}BrCl$ (M^+): 279.9654. Found: 279.9657.

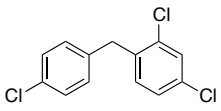


1-chloro-4-(4-fluorobenzyl)benzene (33):[4] Method A: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and fluorobenzene (4 mL) (87 mg, 99%, 88:12 mixture of regioisomers). Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and fluoroobenzene (0.15 mL, 1.6 mmol); reaction temperature 40 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (68 mg, 77%, 87:13 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.27-7.24 (m, 3H), 7.16-7.04 (m, 5H), 7.00-6.95 (m, 2H), 3.97 (s, 0.5H), 3.91 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 161.5 (d, *J* = 245 Hz, major), 160.9 (d, *J* = 247 Hz, minor), 139.4 (major), 138.3 (minor), 136.2 (d, *J* = 3.2 Hz, major), 132.0 (major), 130.9 (d, *J* = 4.5 Hz, minor), 130.2 (d, *J* = 7.9 Hz, major), 130.1 (major), 130.1 (minor), 128.6 (major), 128.6 (minor), 128.2 (d, *J* = 8.2 Hz, minor), 127.5 (d, *J* = 15.9 Hz, minor), 124.1 (d, *J* = 3.6 Hz, minor), 115.4 (d, *J* = 22.0 Hz, minor), 115.3 (d, *J* = 21.3 Hz, major), 40.4 (major), 34.2 (d, *J* = 3.0 Hz, minor); **^{19}F NMR** (376 MHz, $CDCl_3$) –116.9 (app t, *J* = 2.2 Hz, major), –117.8 (app t, *J* = 2.3 Hz, minor); **MS** (EI) *m/z* calcd for $C_{13}H_{10}ClF$ (M^+): 220.1. Found: 220.1.

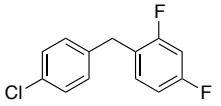


1,2-dichloro-4-(4-chlorobenzyl)benzene (34):[13] Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and 1,2-dichlorobenzene (0.18 mL, 1.6 mmol); reaction temperature 45 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (58 mg, 53%, 79:21 mixture of isomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.36 (d, *J* = 8.4 Hz, 0.25H, minor), 7.35 (d, *J* = 8.1 Hz, 1H, major), 7.29 (t, *J* = 2.4 Hz, 1H, major), 7.27-7.24 (m, 2.5H), 7.14-7.07 (m, 3H), 7.00-6.97 (m, 1H), 4.10 (s, 0.5H, minor), 3.90 (s, 2H, major); **^{13}C NMR** (101 MHz, $CDCl_3$) 140.8 (major), 140.5 (minor), 138.2 (major), 137.3 (minor), 133.4, 132.5, 132.4, 132.3, 130.7 (major), 130.5 (major), 130.4, 130.2, 130.2 (major), 129.0, 128.8 (major), 128.7, 128.7, 128.6, 128.2 (major), 127.2, 40.3 (major), 39.5 (minor); **HRMS** (EI) *m/z* calcd for $C_{13}H_9Cl_3$ (M^+): 269.9770. Found: 269.9767.

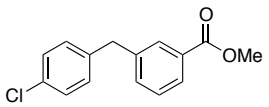
[13] Major isomer assigned by comparison with: R.-J. de Lang, M. J. C. M. van Hooijdonk, L. Brandsma, H. Kramer, W. Seinen, *Tetrahedron* **1998**, *54*, 2953-2966.



2,4-dichloro-1-(4-chlorobenzyl)benzene (35): Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and 1,3-dichlorobenzene (0.18 mL, 1.6 mmol); reaction temperature 45 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (68 mg, 63%, 98:2 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.40 (d, *J* = 2.1 Hz, 1H), 7.28 (t, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 2.4 Hz, 1H), 7.18 (dd, *J* = 8.1 Hz, 2.1 Hz, 1H), 7.11-7.04 (m, 3H), 4.02 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 137.4, 134.8, 132.9, 132.2, 131.6, 130.2, 129.4, 128.7, 127.2, 38.0; **IR** (ATR) ν 2930 (w), 1492 (s), 1471 (m), 1092 (m), 900 (w), 799 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{13}H_9Cl_3$ (M^+): 269.9770. Found: 269.9766.

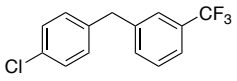


1-(4-chlorobenzyl)-2,4-difluorobenzene (36): Method B: Prepared from *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and 1,3-difluorobenzene (0.16 mL, 1.6 mmol); reaction temperature 45 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (59 mg, 62%, 99:1 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.27 (d, *J* = 2.5 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 7.14-7.04 (m, 3H), 6.80 (app tt, *J* = 8.1 Hz, 2.5 Hz, 2H), 3.92 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 162.5 (dd, *J* = 100.5 Hz, 11.8 Hz), 160.0 (dd, *J* = 101.5 Hz, 11.8 Hz), 138.0, 132.2, 131.3 (dd, *J* = 9.5 Hz, 6.2 Hz), 130.0, 128.7, 123.4 (dd, *J* = 16.2 Hz, 3.8 Hz), 111.2 (dd, *J* = 21.1 Hz, 3.8 Hz), 103.9 (t, *J* = 25.7 Hz) 33.7 (d, *J* = 2.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) –112.6 (app dt, *J* = 6.8 Hz, 1.9 Hz), –113.5 (app dt, *J* = 6.8 Hz, 1.5 Hz); **IR** (ATR) ν 3082 (w), 2928 (w), 1619 (m), 1603 (m), 1504 (s), 1495 (s), 1279 (m), 1137 (m), 1093 (m), 968 (m), 850 (m), 804 (w), 777 (w), 717 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{13}H_9ClF_2$ (M^+): 238.0361. Found: 238.0358.

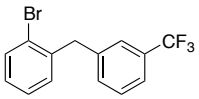


1-(4-chlorobenzyl)-3-(trifluoromethyl)benzene: Method B: *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and methyl benzoate (0.20 mL, 1.6 mmol); reaction temperature 50 ºC. Purified by flash column chromatography (gradient hexanes:Et_2O 100:0 to 100:5) and then PTLC (hexanes:Et_2O 5:1) and isolated as a colorless oil (52 mg, 50%, 91:9 mixture of isomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.90-7.87 (m, 2H), 7.39 (m, 2H), 7.27-7.25 (m, 2H), 7.12-7.07 (m, 2H), 3.99 (s, 2H), 3.90 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 167.0, 140.9, 138.9, 133.4, 132.2, 130.5, 130.2, 129.9, 128.7, 128.7, 127.6, 52.1, 41.0; **IR** (ATR) ν 2950 (w), 2927 (w), 1720 (s),

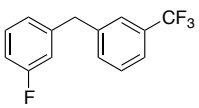
1491 (s), 1434 (m), 1283 (s), 1091 (m), 1015 (w), 739 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{15}H_{13}ClO_2$ (M^+): 260.0604. Found: 260.0602.



1-(4-chlorobenzyl)-3-(trifluoromethyl)benzene (37): Method A: *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (86 mg, 0.40 mmol) and trifluoromethylbenzene (8 mL); reaction temperature 45 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (57 mg, 53%, 99:1 mixture of isomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.48 (d, *J* = 7.8 Hz, 1H), 7.43 (s br, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.28 (dd, *J* = 8.2, 2.0 Hz, 2H), 7.11 (d br, *J* = 8.2 Hz, 2H), 4.00 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 144.4, 138.4, 132.4, 132.2 (app d, *J* = 1.2 Hz), 130.9 (q, *J* = 32.2 Hz), 130.2, 129.0, 128.8, 125.5 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 273 Hz), 123.3 (q, *J* = 3.8 Hz), 41.0; **^{19}F NMR** (376 MHz, $CDCl_3$) –62.6; **IR** (ATR) ν 2921 (w), 1597 (w), 1491 (s), 1330 (s), 1163 (s), 1123 (s), 1091 (s), 1074 (s), 1015 (m), 791 (m), 702 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{10}ClF_3$ (M^+): 270.0423. Found: 270.0417.

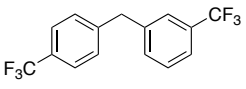


1-bromo-2-(3-(trifluoromethyl)benzyl)benzene (38): Method A: Prepared from *N*-((2-bromobenzyl)oxy)-*N*-methylacetamide (0.10 g, 0.40 mmol) and trifluoromethylbenzene (4 mL); reaction temperature 50 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (82 mg, 65%, 99:1 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.59 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.17 – 7.08 (m, 2H), 4.18 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 140.4, 139.3, 133.1, 132.3 (app d, *J* = 1.2 Hz), 131.1, 130.8 (q, *J* = 32.3 Hz), 128.9, 128.3, 127.7, 125.7 (q, *J* = 3.8 Hz), 124.9, 124.2 (q, *J* = 273 Hz), 123.2 (q, *J* = 3.8 Hz), 41.5; **^{19}F NMR** (376 MHz, $CDCl_3$) –62.6; **IR** (ATR) ν 3072 (w), 1440 (m), 1332 (s), 1163 (s), 1124 (s), 1073 (m), 1026 (m), 899 (m), 700 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{10}BrF_3$ (M^+): 313.9918. Found: 313.9910.

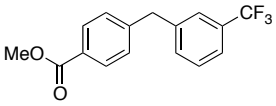


1-fluoro-3-(3-(trifluoromethyl)benzyl)benzene (39): Method A: Prepared from *N*-((3-fluorobenzyl)oxy)-*N*-methylacetamide (79 mg, 0.40 mmol) and trifluoromethylbenzene (4 mL); reaction temperature 50 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (74 mg, 73%, 98:2 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.50 (d br, *J* = 7.7 Hz, 1H), 7.46 (s br, 1H), 7.42

(t br, *J* = 7.6 Hz, 1H), 7.36 (d br, *J* = 7.6 Hz, 1H), 7.28 (td, *J* = 7.9, 6.1 Hz, 1H), 6.97 (d br, *J* = 7.6 Hz, 2H), 6.94 (td, *J* = 8.5, 2.4 Hz, 1H), 6.89 – 6.85 (m, 1H), 4.03 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 163.0 (d, *J* = 246 Hz), 142.5 (d, *J* = 7.2 Hz), 141.2, 132.3 (d, *J* = 1.1 Hz), 130.9 (q, *J* = 32.1 Hz), 130.1 (d, *J* = 8.3 Hz), 129.0, 125.6 (q, *J* = 3.8 Hz), 124.5 (d, *J* = 2.8 Hz), 124.1 (d, *J* = 274 Hz), 123.3 (q, *J* = 3.8 Hz), 115.8 (d, *J* = 21.3 Hz), 113.4 (d, *J* = 21.0 Hz), 41.3 (d, *J* = 1.6 Hz).; **^{19}F NMR** (376 MHz, $CDCl_3$) –62.5, –113.1; **IR** (ATR) ν 2927 (w), 1615 (m), 1590 (m), 1488 (m), 1447 (m), 1333 (s), 1164 (s), 1125 (s), 1073 (m), 889 (m), 783 (w), 745 (w), 703 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{10}F_4$ (M^+): 254.0719. Found: 254.0718.

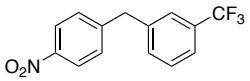


1-(trifluoromethyl)-3-(4-(trifluoromethyl)benzyl)benzene (40): Method A: Prepared from *N*-methyl-*N*-((4-(trifluoromethyl)benzyl)oxy)-acetamide (99 mg, 0.40 mmol) and trifluoromethylbenzene (4 mL); reaction temperature 85 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (0.11 g, 90%, 97:3 mixture of regioisomers) **^{1}H NMR** (300 MHz, $CDCl_3$) 7.56 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.34 (d br, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.09 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 144.0 (app d, *J* = 1.2 Hz), 140.9, 132.3 (app d, *J* = 1.2 Hz), 131.1 (q, *J* = 32.2 Hz), 129.2, 129.2, 129.1 (br), 128.8, 125.6 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 273 Hz), 124.1 (q, *J* = 273 Hz), 41.4; **^{19}F NMR** (376 MHz, $CDCl_3$) –62.5, –62.6; **IR** (ATR) ν 2925 (w), 1618 (w), 1450 (w), 1418 (w), 1326 (s), 1165 (s), 1125 (s), 1067 (m), 1019 (w), 763 (w), 751 (w), 703 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{15}H_{10}F_6$ (M^+): 304.0687. Found: 304.0681

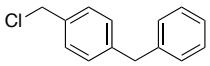


1-(trifluoromethyl)-3-(4-(trifluoromethyl)benzyl)benzene (41): Method A: Prepared from methyl 4-(((*N*-methylacetamido)oxy)-methyl)benzoate (95 mg, 0.40 mmol) and trifluoromethylbenzene (4 mL); reaction temperature 65 ºC. Purified by flash column chromatography (gradient hexanes:Et_2O 10:0 to 10:1) and isolated as a colorless oil (86 mg, 73%, 97:3 mixture of regioisomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.98 (d, *J* = 8.4 Hz, 2H), 7.49 (d br, *J* = 7.7 Hz, 1H), 7.44 (s br, 1H), 7.41 (t br, *J* = 8.0 Hz, 1H), 7.34 (d br, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.09 (s, 2H), 3.91 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 166.9, 145.3, 141.0, 132.2 (app d, *J* = 1.2 Hz), 131.0 (q, *J* = 32.1 Hz), 130.0, 129.1, 128.9, 128.5, 125.6 (q, *J* = 4.0 Hz), 124.1 (q, *J* = 273 Hz), 123.3 (q, *J* = 3.8 Hz), 52.1, 41.6; **^{19}F NMR** (376 MHz, $CDCl_3$) –62.6; **IR** (ATR) ν 2954 (w), 1723 (s), 1610 (w), 1437 (w), 1332 (s), 1282 (s), 1163 (m), 1121 (s), 1075

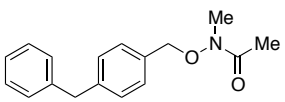
(m), 899 (w), 743 (w), 702 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{15}H_{10}F_6$ (M^+): 294.0868. Found: 294.0866.



1-(4-nitrobenzyl)-3-(trifluoromethyl)benzene (42): Method A: Prepared from *N*-methyl-*N*-((4-nitrobenzyl)oxy)acetamide (90 mg, 0.40 mmol) and trifluoromethylbenzene (4 mL); reaction temperature 95 ºC. Purified by flash column chromatography (gradient hexanes:Et_2O 100:0 to 100:5) and isolated as a yellowish oil (62 mg, 55%, 95:5 mixture of isomers). **^{1}H NMR** (300 MHz, $CDCl_3$) 8.17 (d br, *J* = 8.8 Hz, 2H), 7.60-7.42 (m, 3H), 7.36-7.32 (m, 3H), 4.15 (s br, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 147.6, 146.8, 140.1, 132.3 (app d, *J* = 1.1 Hz), 131.2 (q, *J* = 32.2 Hz), 129.7, 129.3, 125.6 (q, *J* = 3.8 Hz), 124.0, 124.0 (q, *J* = 274 Hz), 123.7 (q, *J* = 3.8 Hz), 41.4; **^{19}F NMR** (376 MHz, $CDCl_3$) –62.6; **IR** (ATR) ν 2917 (w), 2849 (w), 1597 (w), 1518 (s), 1347 (s), 1329 (s), 1259 (s), 1162 (m), 1093 (s), 1074 (s), 1016 (s), 791 (s), 705 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{10}F_3NO_2$ (M^+): 281.0664. Found: 281.0664.



1-benzyl-4-(chloromethyl)benzene (44): Method A: Prepared from *N*-((4-(chloromethyl)benzyl)oxy)-N-methylacetamide (91 mg, 0.40 mmol) and benzene (4 mL) (99%). Method B: Prepared from *N*-((4-(chloromethyl)benzyl)oxy)-N-methylacetamide (91 mg, 0.40 mmol) and benzene (0.14 mL, 1.6 mmol); reaction temperature 40 ºC. Purified by flash column chromatography (hexanes) and isolated as a colorless oil (69 mg, 80%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.34-7.28 (m, 4H), 7.25-7.18 (m, 5H), 4.58 (s, 2H), 4.00 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 141.5, 140.7, 135.3, 129.3, 128.9, 128.8, 128.5, 126.2, 46.1, 41.6. Spectral data were consistent with previous report.[14]

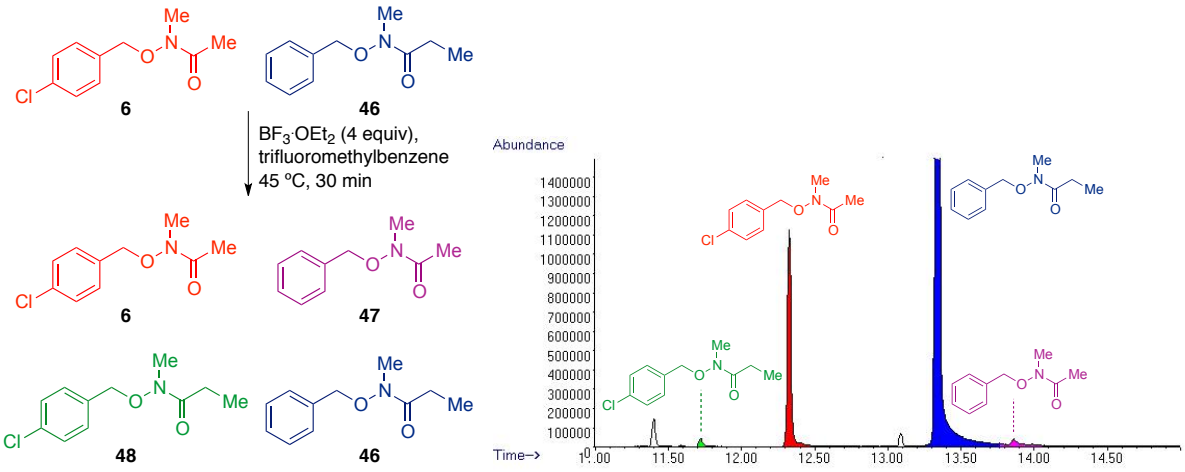


***N*-((4-benzylbenzyl)oxy)-*N*-methylacetamide (45):**[15] An oven-dried Schlenk flask was evacuated and backfilled with N_2 and $Pd(OAc)_2$ (2.0 mg, 8.0 µmol), PPh_3 (4.2 mg, 16 µmol), phenylboronic acid (0.15 g, 1.2 mmol) and K_3PO_4 (0.34 g, 1.6 mmol) were added. The flask was evacuated and backfilled with N_2, and *N*-((4-(chloromethyl)benzyl)oxy)-N-methylacetamide (0.18 g, 0.80 mmol) and toluene (3 mL)

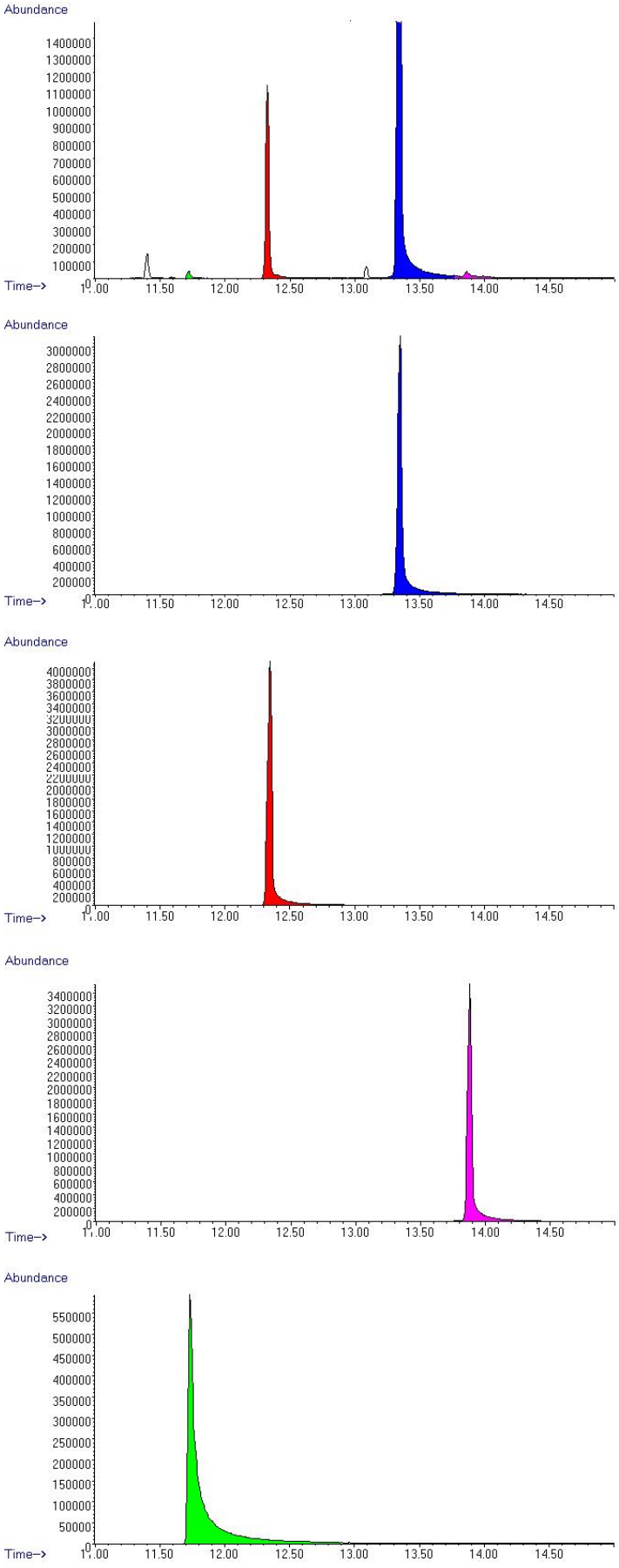
[14] H. W. G. Van Herwijnen, U. H. Brinker, *J. Org. Chem.* **2001**, *66*, 2874-2876.
[15] Reaction was performed according to: S. M. Nobre, A. L. Monteiro, *Tetrahedron Lett.* **2004**, *45*, 8225-8228.

were added. The reaction mixture was heated to 85 ºC for and stirred for 24 h. The reaction mixture was cooled to RT and Et_2O (30 mL) was added. The mixture was washed with 1 M NaOH (15 mL) and brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (gradient hexanes:EtOAc 5:1 to 1:1) obtained the desired product as a colorless oil (0.14 g, 63%). It was possible to recover unreacted starting material (60 mg). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.31-7.27 (m, 4H), 7.23-7.16 (m, 5H), 4.79 (s, 2H), 4.00 (s, 2H), 3.20 (s, 3H), 2.07 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.6, 142.1, 140.6, 132.1, 129.5, 129.2, 128.8, 128.5, 126.2, 75.9, 41.6, 33.2, 20.2; **IR** (ATR) ν 3027 (w), 2929 (w), 1660 (s), 1419 (w), 1265 (m), 1179 (m), 737 (s), 700 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{19}NO_2$ ($[M+H]^+$): 270.1489 Found: 270.1488.

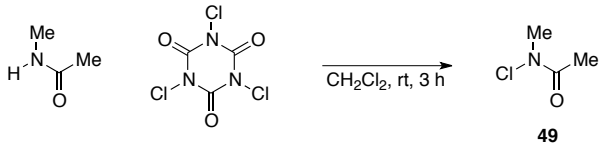
2.5. Cross-Over Experiment



In a septum-capped round-bottom flask under N_2 *N*-((4-chlorobenzyl)oxy)-*N*-methylacetamide (0.4 mmol) and *N*-(benzyloxy)-*N*-methylpropionamide (0.4 mmol) were dissolved in trifluoromethylbenzene (4.0 mL) and then BF_3•OEt_2 (1.6 mmol) was added slowly. The reaction mixture heated to 45 ºC and stirred for 30 min. The reaction mixture was allowed to reach RT and was quenched with sat. $NaHCO_3$ solution (15 mL) and stirred for 5 min. Then CH_2Cl_2 (15 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting mixture was analyzed by GC/MS.


Abundance
Time-->
11.00
11.50
12.00
12.50
13.00
13.50
14.00
14.50

2.6. Synthesis of *N*-chloro-*N*-methylacetamide (49)



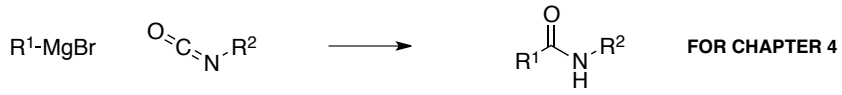
49

In a septum-capped round-bottom flask under N_2 *N*-methylacetamide (1.0 mL, 13 mmol) was dissolved in CH_2Cl_2 (80 mL) and cooled to 0 ºC. Trichloroisocyanuric acid (3.2 g, 14 mmol) was added and the reaction mixture warmed to RT and stirred for 3 h. was dissolved in the arene (4.0 mL) and BF_3•OEt_2 (0.2 mL, 4.0 equiv) was added slowly. The reaction mixture was placed into a fridge for 1 h and was filtered through Celite while still cold. The filtrate was concentrated under reduced pressure (35 ºC, 50 mBar) to obtain *N*-chloro-*N*-methylacetamide (49) as a colorless liquid (1.05 g, 9.8 mmol, 75%). **^{1}H NMR** (300 MHz, $CDCl_3$) 3.33 (s, 3H), 2.23 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.8, 40.8, 21.5. Spectral data were consistent with previous report.[16]

[16] L. De Luca, G. Giacomelli, G. Nieddu, *Synlett* **2005**, 223-226.

3. Part II: The Addition of Grignard Reagents to Isocyanates

3.1. General Procedure: Amide Formation from Isocyanates



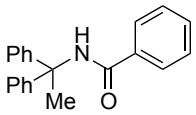
FOR CHAPTER 4

Method A from commercially available Grignard solutions: In a flame-dried Schlenk-flask under N_2 the isocyanate (1.0 mmol, 1.0 equiv) was dissolved in dry Et_2O (4.0 mL) and cooled to 0 ºC (for products **20**, **26**, **27**, **28** and **31** reaction was cooled to –78 ºC). The Grignard solution (1.0 mmol, 1.0 equiv) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and stirred for 1–2 min. EtOAc (25 mL) was added and the phases were separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was washed with hexanes (if not otherwise indicated) and the solid was collected by filtration and dried under high vacuum to obtain the pure product.

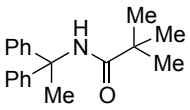
Method B from Grignard solutions prepared via Mg/Br insertion: To a flame-dried Schlenk-flask under N_2 magnesium turnings (29 mg, 1.2 mmol, 1.2 equiv) and dry Et_2O (1.0 mL) were added. The aryl bromide (1.20 mmol, 1.20 equiv) was added in one portion (if the aryl bromide was a liquid, it was added via micro syringe). When the Grignard formation started the reaction mixture was heated to 35 ºC and stirred for 15 min. The reaction mixture was cooled to 0 ºC and a solution of isocyanate (1.0 mmol, 1.0 equiv) in dry Et_2O (3 mL) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and stirred for 1–2 min. EtOAc (25 mL) was added and the phases were separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was washed with hexanes (if not otherwise indicated) and the solid was collected by filtration and dried under high vacuum to obtain the pure product.

Large scale procedure for (18): In a flame-dried 200 mL round-bottom flask under N_2 *tert*-butyl isocyanate (1.4 mL, 15 mmol) was dissolved in 2-MeTHF (60 mL) and cooled to 0 ºC. Mesitylmagnesium bromide (15 mL of 1 M solution in Et_2O, 15 mmol) was added dropwise

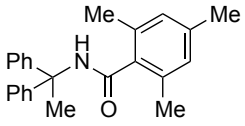
over 10 min via syringe pump. The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with sat. NH_4Cl solution (100 mL) and stirred for 1–2 min. The mixture was transferred into a separatory funnel and the reaction flask was rinsed with EtOAc (25 mL). The phases were separated and the organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was suspended in heptane (50 mL) and the flask placed in a fridge for 1 hour. The solid was collected by filtration and the filtrate was evaporated and the crude material was treated in the same way as described above. The solids were combined and dried under high vacuum to obtain the pure product (3.0 g, 91%).



***N*-(1,1-diphenylethyl)benzamide (4)**: Prepared according to method A from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and phenylmagnesium bromide (0.36 mL of 2.8 M solution in Et_2O) and isolated as a colorless solid (0.29 g, 0.95 mmol, 95%). **m.p.** 153 °C (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.80–7.77 (m, 2H), 7.54–7.40 (m, 3H), 7.36–7.24 (m, 10H), 6.79 (s, 1H), 2.36 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 166.4, 146.2, 135.5, 131.6, 128.8, 128.7, 127.3, 127.0, 126.6, 62.9, 27.5; **IR** (ATR) ν 3274 (br), 3067 (w), 1643 (s), 1535 (s), 1489 (s), 1443 (m), 1305 (s), 1027 (m), 762 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{20}NO$ ($[M+H]^+$): 302.1539. Found: 302.1535.

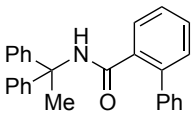


***N*-(1,1-diphenylethyl)pivalamide (5)**: Prepared according to method A from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and *tert*-butylmagnesium chloride (0.50 mL of 2.0 M solution in Et_2O) and isolated as a colorless solid (0.27 g, 0.95 mmol, 95%). **m.p.** 120 °C (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.34–7.22 (m, 10H), 6.30 (s, 1H), 2.20 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 177.2, 146.6, 128.5, 127.1, 126.4, 61.9, 39.3, 27.8, 27.6; **IR** (ATR) ν 3424 (w), 3063 (w), 2968 (w), 1670 (s), 1490 (s), 1447 (s), 1218 (m), 1182 (m), 753 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{23}NNaO$ ($[M+Na]^+$): 304.1672. Found: 304.1672.

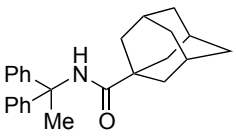


***N*-(1,1-diphenylethyl)-2,4,6-trimethylbenzamide (6)**: Prepared according to method A from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M

solution in Et_2O) and isolated as a colorless solid (0.30 g, 0.87 mmol, 87%). **m.p.** 127 ºC (hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.34–7.28 (m, 10H), 6.83 (s, 2H), 6.28 (s, 1H), 2.38 (s, 3H), 2.36 (s, 6H), 2.27 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.5, 146.4, 138.5, 135.5, 134.5, 128.5, 127.3, 126.8, 63.1, 27.3, 21.2, 19.5; **IR** (ATR) ν 3243 (br), 2970 (w), 1640 (s), 1525 (s), 1493 (s), 1445 (s), 1306 (m), 762 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{24}H_{26}NO$ ($[M+H]^+$): 344.2009. Found: 344.2004.



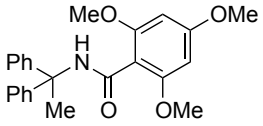
***N*-(1,1-diphenylethyl)-[1,1'-biphenyl]-2-carboxamide (7)**: Prepared according to method B from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and 2-bromo-1,1'-biphenyl (0.28 g, 1.2 mmol) and isolated as an off-white solid (0.36 g, 0.89 mmol, 89%). **m.p.** 150 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.70 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.53–7.49 (m, 5H), 7.46 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.21–7.18 (m, 6H), 6.84–6.82 (m, 4H), 5.93 (s, 1H), 2.07 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 168.1, 146.1, 140.7, 139.4, 136.7, 130.4, 130.1, 129.5, 129.2, 129.0, 128.3, 128.1, 127.9, 127.0, 126.4, 62.9, 26.4; **IR** (ATR) ν 3259 (br), 3053 (w), 1640 (s), 1536 (s), 1318 (m), 770 (w), 758 (m), 742 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{27}H_{24}NO$ ($[M+H]^+$): 378.1852. Found: 378.1853.



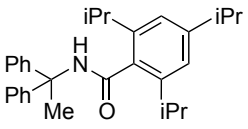
(3*r*,5*r*,7*r*)-*N*-(1,1-diphenylethyl)adamantane-1-carboxamide (8): Prepared according to method A from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and 1-adamantylmagnesium bromide[17] (1.3 mL of 0.66 M solution in Et_2O) and isolated as a colorless solid (0.27 g, 0.75 mmol, 75%). **m.p.** 159 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.33–7.22 (m, 10H), 6.26 (s, 1H), 2.19 (s, 3H), 2.05 (s br, 3H), 1.88 (d br, *J* = 2.2 Hz, 6H), 1.72 (q, *J* = 12.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 176.6, 146.7, 128.5, 127.1, 126.4, 61.8, 41.3, 39.6, 36.7, 28.4, 27.7;

[17] 1-Adamantylmagnesium bromide was prepared according to G. Molle, P. Bauer, J. E. Dubois, *J. Org. Chem.* **1982**, *47*, 4120–4128: In a 25 mL round-bottom flask under N2 1-bromoadamantane (2.15 g, 10.0 mmol) and Mg turnings (3.65 g, 150 mmol) were suspended in dry Et2O (15 mL) and 1,2-dibromoethane (40 µL) was added. The solution was heated to 35 ºC and heated overnight without mechanical stirring. Mg turned black. The Grignard solution was titrated using the phenanthroline/*sec*-butanol system and the concentration of the solution was determined to be 0.66 M. Aliquots of this Gringard solution were taken for the amidation reaction.

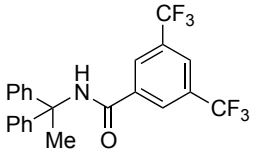
IR (ATR) ν 3320 (w), 2902 (w), 2875 (w), 1698 (s), 1644 (s), 1413 (m), 1280 (s), 1131 (s), 760 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{25}H_{30}NO$ ($[M+H]^+$): 360.2322. Found: 360.2318.



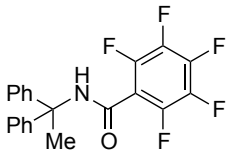
***N*-(1,1-diphenylethyl)-2,4,6-trimethoxybenzamide (9)**: 2,4,6-trimethoxy phenylmagnesium bromide was prepared according to the following procedure: To a flame-dried Schlenk-flask under N_2 magnesium turnings (34 mg, 1.4 mmol) and dry THF (1.0 mL) were added. Bromo-2,4,6-trimethoxy benzene (0.30 g, 1.2 mmol) was added in one portion, followed by addition of a small amount of iodine (~ 5 mg). The reaction mixture was heated to 70 ºC and stirred for 2 h. The reaction mixture was cooled to RT and then to 0 ºC and a solution of (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) in dry Et_2O (3.0 mL) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 30 min. The work up was performed according to method A. The crude material was suspended in MeOH (15 mL) and the flask placed in a freezer overnight. The solid was collected by filtration, washed with a small amount of cold MeOH and dried under high vacuum to obtain the pure product as a colorless solid (0.33 g, 0.85 mmol, 85%). **m.p.** 150 ºC (MeOH); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.41–7.39 (m, 4H), 7.36–7.34 (m, 4H), 7.25–7.20 (m, 2H), 6.30 (s, 1H), 6.10 (s, 2H), 3.83 (s, 6H), 3.81 (s, 3.81), 2.35 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 164.7, 162.0, 158.7, 146.5, 128.3, 126.9, 110.4, 90.9, 63.0, 56.2, 55.6, 27.4; **IR** (ATR) ν 3224 (br), 3041 (w), 1647 (s), 1585 (s), 1559 (s), 2181 (s), 1120 (s), 944 (m), 763 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{24}H_{26}NO_4$ ($[M+H]^+$): 392.1856. Found: 392.1852.



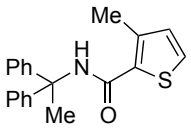
***N*-(1,1-diphenylethyl)-2,4,6-triisopropylbenzamide (10)**: Prepared according to method A from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and (2,4,6-triisopropylphenyl)magnesium bromide (2.0 mL of 0.50 M solution in THF) and isolated as a colorless solid (0.34 g, 0.79 mmol, 79%). **m.p.** 157 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.34–7.25 (m, 10H), 6.99 (s, 2H), 6.34 (s, 1H), 3.10 (sept, J = 6.8 Hz, 2H), 2.87 (sept, J = 6.8 Hz, 1H), 2.37 (s, 3H), 1.31 (d, J = 6.8, 6H), 1.24 (d, J = 6.8, 6H), 1.20 (d, J = 6.8, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.9, 149.8, 146.4, 145.3, 134.1, 128.4, 127.3, 126.9, 121.2, 63.3, 34.5, 30.7, 27.4, 24.8, 24.7, 24.1; **IR** (ATR) ν 3436 (w), 2962 (w), 1671 (s), 1483 (s), 1445 (s), 881 (m), 757 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{30}H_{38}NO$ ($[M+H]^+$): 428.2948. Found: 428.2942.



***N*-(1,1-diphenylethyl)-3,5-bis(trifluoromethyl)benzamide (11)**: Prepared according to method B from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and 1-bromo-3,5-bis(trifluoromethyl)benzene (0.21 mL, 1.2 mmol) and isolated as a tan solid (0.31 g, 0.71 mmol, 71%). **m.p.** 192 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 8.20 (s, 2H), 8.01 (s, 1H), 7.36–7.26 (m, 10H), 6.84 (s, 1H), 2.36 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 163.5, 145.4, 137.4, 132.4 (q, J = 33.9 Hz), 128.8, 127.7, 127.4 (br), 126.6, 125.2 (q, J = 7.5 Hz), 123.0 (q, J = 273 Hz), 63.5, 27.6; **^{19}F NMR** (376 MHz, $CDCl_3$) –62.9; **IR** (ATR) ν 3274 (br), 3046 (w), 1645 (s), 1532 (s), 1274 (s), 1123 (s), 898 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{23}H_{18}F_6NO$ ($[M+H]^+$): 438.1287. Found: 438.1291.

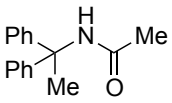


***N*-(1,1-diphenylethyl)-2,3,4,5,6-pentafluorobenzamide (12)**: Prepared according to method B from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and 1-bromo-2,3,4,5,6-pentafluorobenzene (0.15 mL, 1.20 mmol) and isolated as an off-white solid (0.29 g, 0.73 mmol, 73%). **m.p.** 143 ºC (hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.37–7.34 (m, 4H), 7.33–7.28 (m, 6H), 6.57 (s, 1H), 2.33 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) 156.2, 145.0, 143.4 (dddd, J = 256, 19.0, 9.5, 5.5 Hz), 142.3 (dtt, J = 258, 13.6, 5.0 Hz), 137.8 (dtdd, J = 255, 12.5, 6.7, 4.7 Hz), 128.8, 127.6, 126.5, 112.5 (t, J = 19.7 Hz), 64.2, 27.4; **^{19}F NMR** (376 MHz, $CDCl_3$) –140.8 (m), –151.1 (tt, J = 20.7, 2.6 Hz), –159.9 (m); **IR** (ATR) ν 3215 (w), 3041 (w), 1654 (s), 1493 (s), 1330 (m), 1105 (m), 990 (s), 765 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{15}F_5NO$ ($[M+H]^+$): 392.1068. Found: 392.1062.

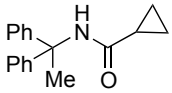


***N*-(1,1-diphenylethyl)-3-methylthiophene-2-carboxamide (14)**: Prepared according to method B from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and 2-bromo-3-methylthiophene (0.14 mL, 1.2 mmol). The crude oil was dissolved in small amount of Et_2O and hexanes (10 mL) were added and the flask placed in a freezer overnight. The precipitated solid was collected by filtration, washed with a small amount of cold hexanes and dried under high vacuum to obtain the pure product as slightly yellow needles (0.30 g, 0.92 mmol, 92%). **m.p.** 112 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.37–7.32 (m, 8H), 7.29–7.24 (m, 3H), 6.88 (d, J = 5.0 Hz, 1H), 6.52 (s, 1H), 2.47 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 162.2, 146.2, 141.1, 132.3, 132.0, 128.7, 127.3, 126.5, 126.3, 63.1, 27.7, 15.9; **IR** (ATR) ν 3303 (br), 3050 (w), 1626 (s), 1521 (s),

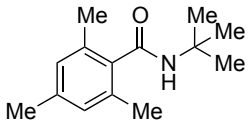
1494 (s), 1276 (s), 1028 (m), 756 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{20}H_{20}NOS$ ($[M+H]^+$): 322.1260. Found: 322.1261.



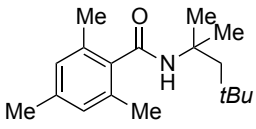
***N*-(1,1-diphenylethyl)acetamide (15)**: Prepared according to method A from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and methylmagnesium bromide (0.33 mL of 3.0 M solution in Et_2O) and isolated as a colorless solid (0.23 g, 0.95 mmol, 95%). **m.p.** 120 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.35–7.23 (m, 10H), 6.05 (s, 1H), 2.23 (s, 3H), 2.04 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.1, 146.2, 128.5, 127.2, 126.6, 62.6, 27.3, 24.6; **IR** (ATR) ν 3247 (br), 3055 (w), 1650 (s), 1522 (s), 1493 (s), 1364 (s), 1028 (m), 760 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{18}NO$ ($[M+H]^+$): 240.1383. Found: 240.1376.



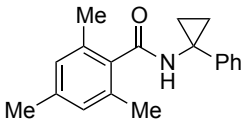
***N*-(1,1-diphenylethyl)cyclopropanecarboxamide (16)**: Prepared according to method A from (1-isocyanatoethane-1,1-diyl)dibenzene (0.22 g, 1.0 mmol) and cyclopropylmagnesium bromide (2.0 mL of 0.50 M solution in THF) and isolated as a colorless solid (0.25 g, 0.92 mmol, 92%). **m.p.** 132 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.34–7.24 (m, 10H), 6.22 (s, 1H), 2.23 (s, 3H), 1.43–1.37 (m, 1H), 0.93 (app dt, *J* = 6.6, 3.9 Hz, 2H), 0.70 (app dt, *J* = 7.1, 3.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.4, 146.5, 128.5, 127.1, 126.6, 62.5, 27.6, 15.6, 7.0; **IR** (ATR) ν 3301 (br), 3012 (w), 1646 (s), 1530 (s), 1492 (s), 1220 (s), 967 (m), 759 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{20}NO$ ($[M+H]^+$): 266.1539. Found: 266.1541.



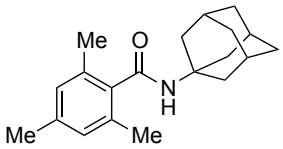
***N*-(*tert*-butyl)-2,4,6-trimethylbenzamide (18)**: Prepared according to method A from *tert*-butyl isocyanate (0.11 mL, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1 M solution in Et_2O) and isolated as a colorless solid (0.18 g, 0.83 mmol, 83%). **m.p.** 143 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 6.82 (s, 2H), 5.43 (s, 1H), 2.31 (s, 6H), 2.27 (s, 3H), 1.47 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.9, 138.2, 136.2, 134.1, 128.2, 51.8, 29.0, 21.2, 19.0; **IR** (ATR) ν 3238 (br), 2974 (w), 2958 (w), 1629 (s), 1613 (s), 1552 (s), 1453 (s), 1359 (s), 1320 (m), 1223 (s), 848 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{22}NO$ ($[M+H]^+$): 220.1696. Found: 220.1695.



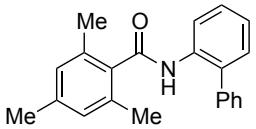
2,4,6-trimethyl-*N*-(2,4,4-trimethylpentan-2-yl)benzamide (19): Prepared according to method A from 2-isocyanato-2,4,4-trimethylpentane (0.16 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as a colorless solid (0.21 g, 0.75 mmol, 75%). **m.p.** 125 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 6.82 (s, 2H), 5.44 (s, 1H), 2.31 (s, 6H), 2.26 (s, 3H), 1.75 (s, 2H), 1.57 (s, 6H), 1.04 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.9, 138.1, 136.3, 134.1, 128.3, 56.3, 54.1, 31.8, 31.8, 28.5, 21.2, 19.2; **IR** (ATR) ν 3245 (w), 2950 (m), 1627 (s), 1549 (s), 1477 (m), 1311 (s), 1225 (s), 847 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{30}NO$ ($[M+H]^+$): 276.2322. Found: 276.2326.



2,4,6-trimethyl-*N*-(1-phenylcyclopropyl)benzamide (20): Prepared according to method A from (1-isocyanatocyclopropyl)benzene (0.16 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as an off-white solid (0.23 g, 0.82 mmol, 82%). **m.p.** 147 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.45–7.42 (m, 2H), 7.35–7.30 (m, 2H), 7.26–7.18 (m, 1H), 6.81 (s, 2H), 6.26 (s, 1H), 2.26 (s, 3H), 2.22 (s, 6H), 1.36 (s, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.8, 142.4, 138.6, 134.8, 134.4, 128.5, 128.4, 126.8, 126.6, 35.6, 21.2, 19.1, 17.2; **IR** (ATR) ν 3229 (br), 2907 (w), 1638 (s), 1613 (s), 1536 (s), 1453 (s), 1309 (s), 1018 (m), 847 (s), 755 (m), 697 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{22}NO$ ($[M+H]^+$): 280.1696. Found: 280.1697.

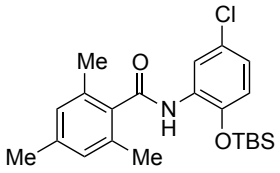


***N*-((3*s*,5*s*,7*s*)-adamantan-1-yl)-2,4,6-trimethylbenzamide (21)**: Prepared according to method A from 1-adamantyl isocyanate (0.18 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as a colorless solid (0.26 g, 0.87 mmol, 87%). **m.p.** over 225 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 6.82 (s, 2H), 5.30 (s, 1H), 2.32 (s, 6H), 2.27 (s, 3H), 2.12 (s, 9H), 1.73 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.9, 138.2, 136.3, 134.0, 128.2, 52.6, 41.9, 36.5, 29.6, 21.2, 19.1; **IR** (ATR) ν 3233 (br), 2905 (s), 2890 (s), 2848 (m), 1628 (s), 1613 (s), 1541 (s), 1307 (m), 849 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{20}H_{28}NO$ ($[M+H]^+$): 298.2165. Found: 298.2161.

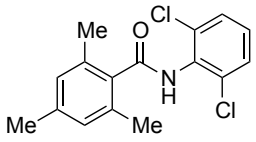


***N*-([1,1'-biphenyl]-2-yl)-2,4,6-trimethylbenzamide (22)**: Prepared according to method A from 2-biphenyl isocyanate (0.17 mL, 1.0 mmol)

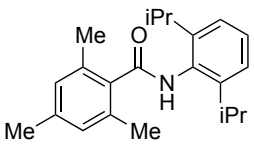
and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as a colorless solid (0.26 g, 0.81 mmol, 81%). **m.p.** 117 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 8.46 (d, *J* = 8.2 Hz, 1H), 7.47–7.20 (m, 10H), 6.80 (s, 2H), 2.26 (s, 6H), 2.24 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.0, 138.8, 138.2, 135.0, 134.8, 134.3, 133.1, 130.5, 129.5, 129.1, 128.6, 128.4, 128.2, 124.8, 122.3, 21.2, 19.2; **IR** (ATR) ν 3240 (w), 2917 (w), 1652 (s), 1521 (s), 1434 (s), 1305 (m), 744 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{22}H_{22}NO$ ($[M+H]^+$): 316.1696. Found: 316.1695.



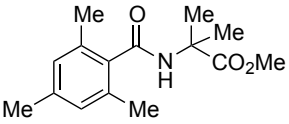
***N*-(2-((*tert*-butyldimethylsilyl)oxy)-5-chlorophenyl)-2,4,6-trimethylbenzamide (23)**: Prepared according to method A from *tert*-butyl(4-chloro-2-isocyanatophenoxy)dimethylsilane (0.28 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O). Purified by flash column chromatography (hexanes:EtOAc 10:1) and isolated as a colorless solid (0.38 g, 0.93 mmol, 93%). **m.p.** 80 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 8.63 (d, *J* = 2.6 Hz, 1H), 7.76 (s, 1H), 6.95 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.86 (s, 2H), 6.76 (d, *J* = 8.6 Hz, 1H), 2.33 (s, 6H), 2.30 (s, 3H), 0.85 (s, 9H), 0.21 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 168.7, 142.6, 139.0, 134.9, 134.0, 130.8, 128.5, 127.1, 123.5, 120.0, 118.4, 25.6, 21.3, 19.4, 18.2, 4.2; **IR** (ATR) ν 3424 (w), 3029 (w), 2858 (w), 1673 (m), 1506 (s), 1456 (s), 1414 (s), 1247 (s), 843 (s), 782 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{22}H_{31}ClNO_2Si$ ($[M+H]^+$): 404.1807. Found: 404.1817.



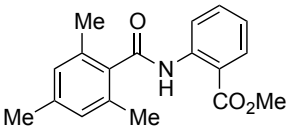
***N*-(2,6-dichlorophenyl)-2,4,6-trimethylbenzamide (24)**: Prepared according to method A from 2,6-dichlorophenyl isocyanate (0.19 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as an off-white solid (0.26 g, 0.83 mmol, 83%). **m.p.** 183 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.42 (d, *J* = 8.1 Hz, 2H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.18 (s, 1H), 6.91 (s, 2H), 2.50 (s, 6H), 2.31 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 168.6, 139.2, 135.1, 134.1, 133.6, 131.7, 128.9, 128.7, 128.6, 21.2, 19.9; **IR** (ATR) ν 3198 (br), 2967 (br), 1647 (s), 1495 (s), 1432 (s), 1304 (m), 1096 (m), 774 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{16}Cl_2NO$ ($[M+H]^+$): 308.0603. Found: 308.0595.



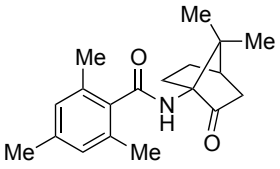
***N*-(2,6-diisopropylphenyl)-2,4,6-trimethylbenzamide (25)**: Prepared according to method A from 2,6-diisopropylphenyl isocyanate (0.21 mL, 1.00 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated a colorless solid (0.27 g, 0.84 mmol, 84%). **m.p.** 217 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.33 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.70 (br d, *J* = 7.4 Hz, 2H), 6.92 (s, 2H), 6.87 (s, 1H), 3.35 (sept, *J* = 6.9 Hz, 2H), 2.49 (s, 6H), 2.32 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.0, 146.3, 139.0, 135.0, 134.8, 130.5, 129.0, 128.6, 123.9, 28.8, 24.1, 21.2, 20.1; **IR** (ATR) ν 3218 (w), 2962 (m), 2867 (w), 1637 (s), 1502 (s), 1468 (s), 1299 (m), 794 (m), 738 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{22}H_{30}NO$ ($[M+H]^+$): 324.2322. Found: 324.2323.



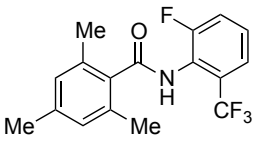
methyl 2-methyl-2-(2,4,6-trimethylbenzamido)propanoate (26): Prepared according to method A from methyl 2-isocyanato-2-methylpropanoate (0.14 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as colorless needles (0.22 g, 0.85 mmol, 85%). **m.p.** 98 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 6.82 (s, 2H), 6.12 (s, 1H), 3.78 (s, 3H), 2.31 (s, 6H), 2.27 (s, 3H), 1.66 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 175.0, 169.7, 138.6, 134.7, 134.5, 128.3, 56.7, 52.7, 25.0, 21.2, 19.0; **IR** (ATR) ν 3205 (br), 2988 (w), 1746 (s), 1624 (s), 1613 (s), 1541 (s), 1327 (m), 1142 (s), 920 (m), 852 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{22}NO_3$ ($[M+H]^+$): 264.1594. Found: 264.1586.



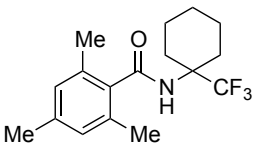
methyl 2-(2,4,6-trimethylbenzamido)benzoate (27): Prepared according to method A from methyl 2-isocyanatobenzoate (0.18 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as a colorless solid (0.21 g, 0.70 mmol, 70%). **m.p.** 125 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 11.07 (s, 1H), 8.96 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.07 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.68 (td, *J* = 15.8, 1.5 Hz, 1H), 7.14 (td, *J* = 15.3, 1.1 Hz, 1H), 6.88 (s, 2H), 3.87 (s, 3H), 2.35 (s, 6H), 2.30 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.7, 168.6, 141.6, 138.8, 135.4, 134.9, 134.2, 131.1, 128.6, 122.9, 120.7, 115.3, 52.4, 21.3, 19.5; **IR** (ATR) ν 3341 (w), 2954 (w), 1674 (s), 1507 (s), 1436 (s), 1273 (s), 1100 (m), 757 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{19}NNaO_3$ ($[M+Na]^+$): 320.1257. Found: 320.1265.



***N*-((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-2,4,6-trimethylbenzamide (28)**: Prepared according to method A from (1*R*,4*R*)-1-isocyanato-7,7-dimethylbicyclo[2.2.1]heptan-2-one (0.18 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O). Purified by flash column chromatography (hexanes:EtOAc 5:1) and isolated as a yellowish solid (0.24 g, 0.79 mmol, 79%). **m.p.** 103 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 6.84 (s, 2H), 6.01 (s, 1H), 3.47–3.39 (m, 1H), 2.50–2.41 (m, 1H), 2.31 (s, 6H), 2.28 (s, 3H), 2.28–2.21 (m, 1H), 2.11–2.02 (m, 2H), 1.57–1.42 (m, 2H), 1.39 (s, 3H), 0.92 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 213.8, 170.9, 138.4, 135.7, 134.0, 128.3, 73.5, 48.7, 41.5, 40.7, 26.9, 22.2, 22.0, 21.2, 19.7, 19.3; **IR** (ATR) ν 3255 (w), 2944 (m), 17753 (s), 1647 (s), 1540 (s), 1335 (m), 848 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{26}NO_2$ ($[M+H]^+$): 300.1958. Found: 300.1958.

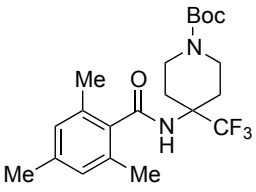


***N*-(2-fluoro-6-(trifluoromethyl)phenyl)-2,4,6-trimethylbenzamide (29)**: Prepared according to method A from 1-fluoro-2-isocyanato-3-(trifluoromethyl)benzene (0.21 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as a colorless solid (0.28 g, 0.87 mmol, 87%). **m.p.** 169 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.52 (dd, *J* = 5.9, 3.4 Hz, 1H), 7.46–7.42 (m, 2H), 7.07 (s, 1H), 6.91 (s, 2H), 2.42 (s, 6H), 2.32 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.0, 158.9 (q, *J* = 254 Hz), 139.3, 135.0, 133.9, 128.7 (d, *J* = 8.6 Hz), 128.6, 128.2 (qd, *J* = 30.3, 1.9 Hz), 123.1 (qd, *J* = 273, 3.6 Hz), 122.5 (app dd, *J* = 15.9, 1.6 Hz), 122.0 (app m), 120.7 (d, *J* = 21.1 Hz), 21.2, 19.2; **^{19}F NMR** (376 MHz, $CDCl_3$) –60.4, –111.9; **IR** (ATR) ν 3224 (br), 2971 (w), 1665 (s), 1505 (s), 1481 (s), 1323 (s), 1122 (s), 885 (s), 784 (m), 724 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{16}F_4NO$ ($[M+H]^+$): 326.1163. Found: 326.1164.

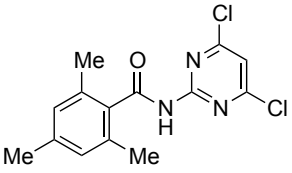


2,4,6-trimethyl-*N*-(1-(trifluoromethyl)cyclohexyl)benzamide (30): Prepared according to method A from methyl 1-isocyanato-1-(trifluoromethyl)cyclohexane (0.19 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as a colorless solid (0.29 g, 0.92 mmol, 92%). **m.p.** 197 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 6.85 (s, 2H), 5.17 (br s, 1H), 2.55 (br d, *J* = 10.0 Hz, 2H), 2.35 (s, 6H), 2.29 (s, 3H), 1.79–1.76 (m, 3H), 1.66–1.54 (m, 4H), 1.34–1.27 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.8, 138.7, 135.9, 134.2, 128.4, 126.8 (q, *J*

= 286 Hz), 60.2 (q, *J* = 27.1 Hz), 28.7, 24.9, 21.2, 20.9, 19.3; **^{19}F NMR** (376 MHz, $CDCl_3$) –80.3; **IR** (ATR) ν 3260 (br), 2943 (w), 1655 (s), 1540 (s), 1453 (m), 1292 (s), 1140 (s), 1027 (m), 847 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{23}F_3NO$ ($[M+H]^+$): 314.1726. Found: 314.1726.

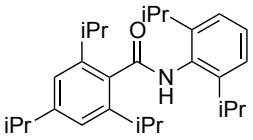


***tert*-butyl 4-(trifluoromethyl)-4-(2,4,6-trimethylbenzamido)-piperidine-1-carboxylate (31)**: Prepared according to method A from *tert*-butyl 4-isocyanato-4-(trifluoromethyl)piperidine-1-carboxylate (0.29 g, 1.0 mmol) and mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) and isolated as a colorless solid (0.35 g, 0.85 mmol, 85%). **m.p.** 210 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 6.86 (s, 2H), 5.32 (s br, 1H), 4.16 (br s, 2H), 2.98 (t, *J* = 10.9 Hz, 2H), 2.32 (s, 6H), 2.32 (s, 3H), 1.80 (t, *J* = 13.2 Hz, 2H), 1.48 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 171.3, 154.4, 138.9, 135.2, 133.9, 128.4, 126.0 (q, *J* = 285 Hz), 80.2, 58.9 (q, *J* = 28.0 Hz), 38.5 (br), 28.4, 21.1, 19.2; **^{19}F NMR** (376 MHz, $CDCl_3$) –80.3; **IR** (ATR) ν 3260 (w), 2983 (w), 1694 (s), 1655 (s), 1539 (m), 1159 (s), 1142 (s), 1042 (s), 868 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{29}F_3N_2NaO_3$ ($[M+Na]^+$): 437.2022. Found: 437.2012.

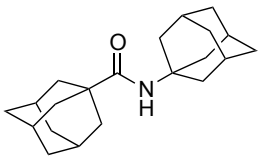


***N*-(4,6-dichloropyrimidin-2-yl)-2,4,6-trimethylbenzamide (32)**: In a flame-dried round-bottom flask with an attached reflux-condenser under N_2 4,6-dichloropyrimidin-2-amine (0.16 g, 1.0 mmol) was dissolved in benzene (10 mL). Oxalyl chloride (0.34 mL, 5.0 mmol) was added dropwise and the reaction mixture was heated to 80 ºC and stirred for 3 h. The reaction mixture was cooled to RT and the solvent and excess oxalyl chloride were removed under reduced pressure. The obtained residue was co-evaporated twice from hexanes (5.0 mL). The crude isocyanate was suspended in dry Et_2O (4.0 mL) and the solution cooled to –78 ºC. Mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 30 min. The work up was performed according to method A. The obtained crude material was titruated from Et_2O/hexanes. The solid was collected by filtration and dried under high vacuum to obtain the pure product as a tan solid (0.22 g, 0.72 mmol, 72%). **m.p.** 145 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 8.15 (s, 1H), 7.11 (s, 1H), 6.87 (s, 2H), 2.33 (s, 6H), 2.30 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 168.4, 162.7, 156.7, 139.6, 134.2, 133.7, 128.6, 116.5, 21.3, 19.4;

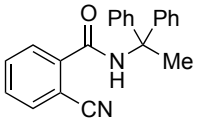
IR (ATR) ν 3121 (w), 3032 (w), 1699 (s), 1544 (s), 1490 (s), 1401 (s), 1227 (s), 1092 (s), 804 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{14}Cl_2N_3O$ ($[M+H]^+$): 310.0508. Found: 310.0517.



***N*-(2,6-diisopropylphenyl)-2,4,6-trimethylbenzamide (33)**: Prepared according to method A from 2,6-diisopropylphenyl isocyanate (0.21 mL, 1.0 mmol) and (2,4,6-triisopropylphenyl)magnesium bromide (2.0 mL of 0.50 M solution in THF). Crude material was suspended in hexanes and the flask placed in a freezer overnight. The colorless solid was collected by filtration, washed with a small amount of cold hexanes and dried under high vacuum to obtain the pure product (0.32 g, 0.78 mmol, 78%). **m.p.** 185 ºC (hexanes); **^{1}H NMR** (600 MHz, CD_3CN) 8.01 (s, 1H), 7.34 (td, *J* = 7.4, 0.3 Hz, 1H), 7.26 (d br, *J* = 7.4, 2H), 7.16 (s, 2H), 6.87 (s, 1H), 3.39 (sept, *J* = 6.9 Hz, 2H), 3.28 (sept, *J* = 6.9 Hz, 2H), 2.95 (sept, *J* = 6.9 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 6H), 1.27 (d, *J* = 6.9 Hz, 6H), 1.22 (br d, *J* = 6.9 Hz, 18H); **^{13}C NMR** (151 MHz, CD_3CN) 170.9, 150.6, 147.8, 146.3, 135.3, 132.5, 129.2, 124.5, 122.1, 35.1, 32.0, 29.4, 25.3, 24.2 (br), 24.1 (br); **IR** (ATR) ν 3263 (br), 2962 (s), 2868 (m), 1633 (s), 1490 (s), 1458 (s), 1362 (m), 877 (m), 796 (m), 738 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{42}NO$ ($[M+H]^+$): 408.3261. Found: 408.3258.



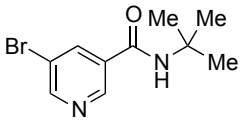
(3*R*,5*R*,7*R*)-*N*-((3*S*,5*S*,7*S*)-adamantan-1-yl)adamantane-1-carboxamide (34): Prepared according to method A from 1-adamantyl isocyanate (0.18 g, 1.0 mmol) and 1-adamantylmagnesium bromide (1.3 mL of 0.66 M solution in Et_2O). Purified by flash column chromatography (hexanes:EtOAc 4:1) and isolated as a colorless solid (0.24 g, 0.75 mmol, 75%). **m.p.** over 225 ºC (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 5.19 (s, 1H), 2.01 (br d, *J* = 15.7 Hz, 6H), 1.95 (d, *J* = 2.8 Hz, 6H), 1.77 (d, *J* = 2.6 Hz, 6H), 1.68–1.63 (m, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) 177.3, 51.3, 41.7, 40.9, 39.5, 36.7, 36.5, 29.6, 28.3. Spectral data were consistent with previous report.[18]



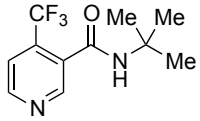
2-cyano-*N*-(1,1-diphenylethyl)benzamide (114): To a flame-dried Schlenk-flask under N_2 was added iPrMgCl•LiCl complex (0.77 mL of a 1.3

[18] C. E. Wagner, M. L. Mohler, G. S. Kang, D. D. Miller, E. E. Geisert, Y.–A. Chang, E. B. Fleischer, K. J. Shea, *J. Med. Chem.* **2003**, *46*, 2823-2833.

M solution in THF, 1.0 mmol) and THF (0.25 mL) and cooled to 0 ºC. 2-bromobenzonitrile (0.18 g, 1.0 mmol) was added in one portion and the reaction mixture stirred for 1 h at 0 ºC. A solution of (1-isocyanatoethane-1,1-diyl)dibenzene (**2**, 0.22 g, 1.0 mmol) in THF (3.0 mL) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred overnight. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and stirred for 1–2 min. EtOAc (25 mL) was added and the phases were separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (gradient hexanes:EtOAc 4:1 to 2:1) and the product isolated as a colorless solid (0.25 g, 0.78 mmol, 78%). **m.p.** 150 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.79 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.74 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.65 (td, *J* = 7.7, 1.4 Hz, 1H), 7.56 (td, *J* = 7.6, 1.3 Hz, 1H), 7.41 – 7.33 (m, 8H), 7.32 – 7.26 (m, 2H), 6.85 (br s, 1H), 2.38 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 164.4, 145.5, 139.8, 133.8, 133.2, 131.0, 129.3, 128.7, 127.5, 126.7, 117.8, 110.1, 63.8, 27.4; **IR** (ATR) ν 3285 (m), 1638 (s), 1527 (s), 1308 (m), 757 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{22}H_{19}N_2O$ ($[M+H]^+$): 327.1492. Found: 327.1491.



5-bromo-*N*-(*tert*-butyl)nicotinamide (115): To a flame-dried Schlenk-flask under N_2 was added iPrMgCl•LiCl complex (0.77 mL of a 1.3 M solution in THF, 1.1 mmol) and THF (0.25 mL) and cooled to –15 ºC. 3,5-dibromopyridine (0.26 g, 1.1 mmol) was added in one portion and the reaction mixture warmed to –10 ºC and stirred for 15 min. A solution of *tert*-butyl isocyanate (0.11 mL, 1.0 mmol) in THF (3.0 mL) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and stirred for 1–2 min. EtOAc (25 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (gradient hexanes:EtOAc 4:1 to 2:1) and the product isolated as a colorless solid (0.20 g, 0.79 mmol, 79%). **m.p.** 120 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.75 (d, *J* = 1.8 Hz, 1H), 8.67 (d, *J* = 2.2 Hz, 1H), 8.13 (t, *J* = 2.1 Hz, 1H), 6.21 (br s, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 163.7, 152.9, 145.9, 137.6, 132.9, 120.9, 52.4, 28.8; **IR** (ATR) ν 3286 (w), 2974 (w), 1636 (s), 1541 (s), 1313 (m), 1216 (m), 893 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{10}H_{14}BrN_2O$ ($[M+H]^+$): 257.0284. Found: 257.0289.

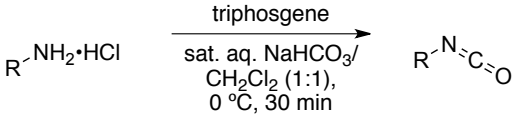


***N*-(*tert*-butyl)-4-(trifluoromethyl)nicotinamide (116)**: To a flame-dried Schlenk-flask under N_2 was added *n*-butyllithium (0.63 mL of a 1.6 M solution in hexanes, 1.0 mmol) and THF (1.0 mL) and cooled to –78 ºC. A solution of TMP (0.17 mL, 1.0 mmol) in THF (0.5 mL) was added dropwise over 2–3 min, followed by dropwise addition of a solution of 4-(trifluoromethyl)pyridine (0.12 mL, 1.0 mmol) in THF (0.5 mL) over 2–3 min. The reaction mixture was stirred at –78 ºC for 1 h and a solution of *tert*-butyl isocyanate (0.11 mL, 1.0 mmol) in THF (1.0 mL) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and stirred for 1–2 min. EtOAc (50 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 1:1 to 1:2) and the product isolated as a slightly yellow solid (0.16 g, 0.65 mmol, 65%). **m.p.** 117 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.83 – 8.78 (m, 2H), 7.54 (d, *J* = 5.2 Hz, 1H), 1.47 (s, 9H); **^{13}C NMR** (101 MHz, d^6- $CDCl_3$) 164.4, 151.5, 149.8, 134.8 (app d, *J* = 33.6 Hz), 131.2 (app d, *J* = 2.1 Hz), 122.6 (q, *J* = 274.7 Hz), 119.8 (q, *J* = 4.5 Hz), 52.9, 28.7; **^{19}F NMR** (376 MHz, $CDCl_3$) –61.1; **IR** (ATR) ν 3263 (w), 2976 (w), 1639 (s), 1555 (m), 1317 (s), 1280 (m), 1135 (s), 1069 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{14}F_3N_2O$ ($[M+H]^+$): 247.1053. Found: 247.1058.

3.2. General Procedure: Synthesis of Isocyanates

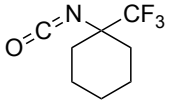
Tert-butyl isocyanate, *tert*-octyl isocyanate, 1-adamantyl isocyanate, 2-biphenylyl isocyanate, 2,6-dichlorophenyl isocyanate, 2,6-diisopropylphenyl isocyanates, methyl 2-isocyanatobenzoate and 1-fluoro-2-isocyanato-3-(trifluoromethyl)benzene are commercially available compounds and were purchased from Aldrich in the highest purity. *Tert*-butyl(4-chloro-2-isocyanatophenoxy)dimethylsilane was synthesized according to patent US2004/259885 A1, **2004**, p.10. (1-isocyanatoethane-1,1-diyl)dibenzene (**2**) and (1-isocyanatocyclopropyl)benzene were synthesized according to a published literature procedure.[19]

[19] C. Spino, M.-A. Joly, C. Godbout, M. Arbour, *J. Org. Chem.* **2005**, *70*, 6118-6121.

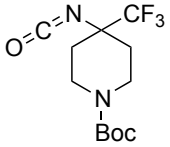


Isocyanates for products **26**, **30** and **31** were synthesized by a modified literature procedure:[20] To a septum-capped round-bottom flask under N_2 was added the amine hydrochloride salt (10 mmol) and dissolved in a 1:1 mixture of CH_2Cl_2 (40 mL) and sat. aq $NaHCO_3$ solution (40 mL). The biphasic mixture was cooled to 0 °C and under vigorous stirring triphosgene (1.0 g, 3.4 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 30 min and transferred into a separatory funnel. The phases were separated and the aqueous layer was extracted three times with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The corresponding products were purified by Kugelrohr distillation or flash column chromatography.

The carbon atom of the isocyanate functionality can normally not be observed by ^{13}C NMR. However, the existence of the isocyanate product was determined by IR (very intense band between 2275–2240 cm^{-1}) and high-resolution mass spectrometry.



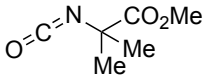
1-isocyanato-1-(trifluoromethyl)cyclohexane: Prepared according to the general procedure from 1-(trifluoromethyl)cyclohexanamine hydrochloride (1.02 g, 5.00 mmol) and triphosgene (504 mg, 1.70 mmol). Purified by Kugelrohr distillation and isolated as a colorless oil (676 mg, 3.50 mmol, 70%). **^{1}H NMR** (300 MHz, $CDCl_3$) 1.91 (br d, J = 9.7 Hz, 2H), 1.78 (app d, J = 10.5 Hz, 3H), 1.68–1.50 (m, 4H), 1.29–1.16 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 125.2 (q, J = 283 Hz), 62.9 (q, J = 28.5 Hz), 30.9 (app d, J = 1.2 Hz), 24.6, 20.7; **^{19}F NMR** (376 MHz, $CDCl_3$) –82.9; **IR** (ATR) ν 2946 (w), 2860 (w), 2273 (s), 1736 (m), 1305 (m), 1168 (s), 1137 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_7H_{10}NO$ ($[M–CF_3]^+$): 124.0757. Found: 124.0755.



***tert*-butyl 4-isocyanato-4-(trifluoromethyl)piperidine-1-carboxylate (35)**: Prepared according to the general procedure from *tert*-butyl 4-amino-4-(trifluoromethyl)piperidine-1-carboxylate hydrochloride (1.52 g, 5.00 mmol)

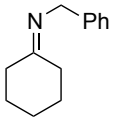
[20] J. H. Tsai, L. R. Takaoka, N. A. Powell, J. S. Nowick, *Org. Syn.* **2002**, *78*, 220-222.

and triphosgene (504 mg, 1.70 mmol). Purified by flash column chromatography (hexanes:EtOAc 10:1 to 5:1) and isolated as a colorless oil (956 mg, 3.25 mmol, 65%). **m.p.** 59 °C (hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) 4.18 (br s, 2H), 2.97 (br s, 2H), 1.83 (d, *J* = 4.5 Hz, 2H), 1.80 (d, *J* = 3.6 Hz, 2H), 1.47 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 154.4, 124.9 (d, *J* = 283 Hz), 80.5, 61.9 (q, *J* = 29.5 Hz), 38.7 (br), 30.7, 28.5; **^{19}F NMR** (376 MHz, $CDCl_3$) –82.7; **IR** (ATR) ν 2977 (w), 2946 (w), 2251 (s), 1681 (s), 1420 (s), 1160 (s), 1037 (s), 995 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{12}H_{17}F_3N_2O_3$ (M^+): 294.1191. Found: 294.1186.



methyl 2-isocyanato-2-methylpropanoate: Prepared according to the general procedure from methyl 2-amino-2-methylpropanoate hydrochloride[21] (1.54 g, 10.0 mmol) and triphosgene (1.00 g, 3.40 mmol). Purified by Kugelrohr distillation and isolated as a colorless oil (1.04 g, 7.30 mmol, 73%). **^{1}H NMR** (300 MHz, $CDCl_3$) 3.81 (s, 3H), 1.52 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 174.4, 60.8, 53.5, 28.2; **IR** (ATR) ν 2987 (w), 2958 (w), 2244 (s), 1743 (s), 1279 (m), 1145 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for C_4H_6NO ($[M–CO_2Me]^+$): 84.0444. Found: 84.0441.

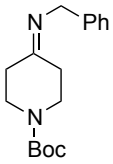
3.3. General Procedure: Synthesis of Starting Materials for Isocyanates



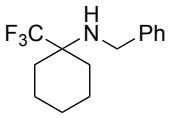
***N*-benzyl-1-(trifluoromethyl)cyclohexanamine**: To a 100 mL round-bottom flask with an attached Dean-Stark trap was added cyclohexanone (1.04 mL, 10.0 mmol) and benzene (50 mL). Benzylamine (**35**, 1.09 mL, 10.0 mmol) was added and the reaction mixture was heated to reflux and stirred for 5 h. The reaction mixture was cooled to RT and the solvent was evaporated under reduced pressure. The obtained yellow oil was

[21] Ø. Jacobsen, H. Maekawa, N.-H. Ge, C. H. Görbitz, P. Rongved, O. P. Ottersen, M. Amiry-Moghaddam, J. Klaveness, *J. Org. Chem.* **2011**, *76*, 1228–1238.

dried under high vacuum for several hours and used in the next step without further purification.

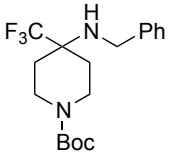


***tert*-butyl 4-(benzylamino)-4-(trifluoromethyl)piperidine-1-carboxylate**: Synthesized according to general procedure from *tert*-butyl 4-oxopiperidine-1-carboxylate (2.00 g, 10.0 mmol) and benzylamine (**35**, 1.09 mL, 10.0 mmol) and isolated as a yellow oil.

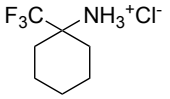


***N*-benzyl-1-(trifluoromethyl)cyclohexanamine**: Nucleophilic trifluoromethylation of imines was performed according to a published literature procedure:[22] Crude *N*-benzyl-1-(trifluoromethyl)cyclohexanamine (1.87 g, 10.0 mmol) was dissolved in a mixture of CH_3CN (20 mL) and DMF (2.32 mL, 30.0 mmol) and KHF_2 (590 mg, 7.50 mmol) was added. The reaction mixture was cooled to 0 ºC, TFA (1.00 mL, 12.5 mmol) was added slowly and the suspension was stirred for 5 min at 0 ºC. $TMSCF_3$ (2.21 mL, 15.0 mmol) was added and the reaction mixture was warmed to RT and stirred overnight. Saturated aqueous Na_2CO_3 solution (5 mL) was added dropwise and the mixture stirred for another 2 min and transferred into a separatory funnel containing H_2O (70 mL). The solution was extracted three times with 1:1 hexanes/Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes:EtOAc 100:1 to 50:1) and the product isolated as a colorless oil (1.80 g, 7.00 mmol, 70%). **^{1}H NMR** (300 MHz, $CDCl_3$) 7.43–7.40 (m, 2H), 7.38 (app tt, *J* = 7.0, 1.5 Hz, 2H), 7.28 (tt, *J* = 7.0, 1.5 Hz, 1H), 3.84 (br s, 2H), 1.83–1.53 (m, 9H), 1.30–1.17 (m, 1H), 1.10 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 141.3, 132.9, 128.5, 128.2, 127.1, 127.1 (d, *J* = 292 Hz), 58.4 (q, *J* = 23.9 Hz), 46.5 (app d, *J* = 1.5 Hz), 28.4 (app d, *J* = 1.3 Hz), 25.7, 20.4. **^{19}F NMR** (376 MHz, $CDCl_3$) –78.8; Spectral data were consistent with previous report.[22]

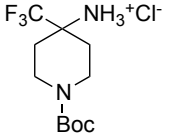
[22] V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova, V. A. Tartakovsky, *Eur. J. Org. Chem*. **2008**, 5226–5230.



***tert*-butyl 4-(benzylamino)-4-(trifluoromethyl)piperidine-1-carboxylate**: Synthesized according to general procedure from *tert*-butyl 4-(benzylamino)-4-(trifluoromethyl)piperidine-1-carboxylate (2.88 g, 10.0 mmol). Purified by column chromatography (hexanes:EtOAc 20:1 to 10:1) and isolated as colorless oil, which solidified upon standing (2.13 g, 5.90 mmol, 59%). **m.p.** 78 ºC (EtOAc); **^{1}H NMR** (300 MHz, $CDCl_3$) 7.38 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.37–7.32 (m, 2H), 7.28 (dt, *J* = 5.4, 2.2 Hz, 1H), 3.99 (br s, 2H), 3.85 (br s, 2H), 3.18 (br s, 2H), 1.79 (td, *J* = 13.2, 4.6 Hz, 2H), 1.70 (br d, *J* = 13.2 Hz, 2H), 1.47 (s, 9H), 1.18 (br s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 154.8, 140.4, 128.6, 128.2, 127.8 (d, *J* = 290 Hz), 127.4, 79.9, 57.4 (q, *J* = 24.9 Hz), 46.5, 38.3 (br), 28.6, 28.3; **^{19}F NMR** (376 MHz, $CDCl_3$) –78.5; **IR** (ATR) ν 2971 (w), 1695 (s), 1412 (s), 1282 (s), 1153 (s), 1129 (s), 1049 (m), 740 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{25}F_3N_2NaO_2$ ($[M+Na]^+$): 381.1760. Found: 381.1751.



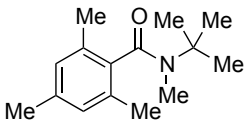
1-(trifluoromethyl)cyclohexanamine hydrochloride: In a 100 mL round-bottom flask *N*-benzyl-1-(trifluoromethyl)cyclohexanamine (1.70 g, 6.60 mmol) was dissolved in a mixture of MeOH (40 mL) and formic acid (1.00 mL, 26.4 mmol). Palladium (10%) on activated carbon (400 mg, 0.495 mmol) was added and a H_2 atmosphere (balloon pressure) was built up. The reaction mixture was heated to 45 ºC and stirred overnight. The reaction mixture was cooled to RT and a N_2 atmosphere was formed. The crude suspension was filtered through Celite and washed thoroughly with MeOH. The filtrate was concentrated under reduced pressure to obtain a residue that was taken up in Et_2O (20 mL). 2 M HCl in Et_2O (3.3 mL, 6.60 mmol) was added. Upon stirring a precipitate formed instantly. The colorless solid was collected by filtration, washed with a small amount of cold Et_2O and dried under high vacuum to obtain the pure product (1.22 g, 6.00 mmol, 91%). **m.p.** 207 ºC (Et_2O); **^{1}H NMR** (300 MHz, D_2O) 1.87 (app dd, *J* = 9.5, 4.5 Hz, 4H), 1.78–1.72 (m, 2H), 1.67 (ddd, *J* = 12.5, 7.8, 3.7 Hz, 1H), 1.55 (tdd, *J* = 16.8, 10.1, 4.8 Hz, 2H), 1.42–1.33 (m, 1H); **^{13}C NMR** (101 MHz, D_2O) 125.2 (q, *J* = 283 Hz), 58.5 (q, *J* = 28.2 Hz), 27.2 (app d, *J* = 1.3 Hz), 23.4, 19.1; **^{19}F NMR** (376 MHz, D_2O) –81.3; **IR** (ATR) ν 2856 (br s), 1738 (m), 1520 (s), 1318 (s), 1179 (s), 1144 (s), 1107 (s), 979 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_7H_{13}F_3N$ ($[M+H]^+$): 168.0995. Found: 168.1000.



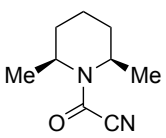
***tert*-butyl 4-amino-4-(trifluoromethyl)piperidine-1-carboxylate hydrochloride (41)**: Synthesized according to general procedure from *tert*-

butyl 4-(benzylamino)-4-(trifluoromethyl)piperidine-1-carboxylate (1.97 g, 5.50 mmol) and isolated as a colorless solid (1.59 g, 5.21 mmol, 95%). **m.p.** 175 ºC (Et_2O); **^{1}H NMR** (300 MHz, D_2O) 3.86 (br s, 2H), 3.37 (br s, 2H), 2.19 (br s, 2H), 2.01 (br s, 2H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, D_2O) 156.1, 124.6 (q, *J* = 283 Hz), 82.4, 57.1 (q, *J* = 28.8 Hz), 37.8 (br), 27.5, 26.9; **^{19}F NMR** (376 MHz, D_2O) –79.1; **IR** (ATR) ν 2823 (br s), 1702 (s), 1523 (s), 1422 (s), 1317 (s), 1241 (s), 1160 (s), 1116 (s), 1014 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{19}F_3N_2NaO_2$ ($[M+Na]^+$): 291.1291. Found: 291.1290.

3.4. Synthesis of Tertiary Amides and Corresponding Starting Materials

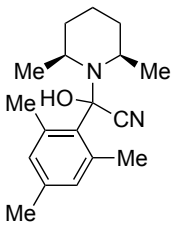


***N*-(*tert*-butyl)-*N*,2,4,6-tetramethylbenzamide (107)**: In a flame-dried Schlenk-flask under N_2 *tert*-butyl isocyanate (0.11 mL, 1.0 mmol) was dissolved in dry THF (4.0 mL) and cooled to 0 ºC. Mesitylmagnesium bromide (1.0 mL of 1.0 M solution in Et_2O, 1.0 mmol) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 30 min. Dimethyl sulfate (0.14 mL, 1.5 mmol) was added via micro syringe and the reaction mixture stirred at RT for 30 min. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and stirred for 1–2 minutes. EtOAc (25 mL) was added and the phases were separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (hexanes:EtOAc 7:1) and the product isolated as a colorless oil (0.16 g, 0.70 mmol, 70%). At room temperature the ratio of rotamers was 50:50 as determined by NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) 6.80 (br s, 4H), 2.72 (s, 3H), 2.29 (s, 6H), 2.25 (br s, 6H), 2.19 (s, 6H), 1.54 (s, 9H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 171.9, 169.8, 137.9, 137.0, 136.6, 136.1, 133.9, 132.8, 128.2, 128.1, 56.7, 51.7, 32.6, 28.8, 28.2, 21.1, 18.9, 18.7; **IR** (ATR) ν 3236 (br), 2958 (w), 2916 (w), 1627 (s), 1551 (m), 1453 (s), 1360 (s), 1223 (s), 1048 (m), 849 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{24}NO$ ($[M+H]^+$): 234.1852. Found: 234.1859.

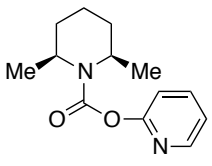


***cis*-2,6-dimethylpiperidine-1-carbonyl cyanide (110)**: To a flame-dried 50 mL round-bottom flask was added tetracyanoethylene oxide (0.87 g, 6 mmol),

and Et_2O (10 mL) and cooled to 0 ºC. Dimethyl sulfide (0.56 mL, 7.5 mmol) was added and the reaction mixture stirred for 1 h at 0 ºC. A solution of *cis*-2,6-dimethylpiperidine (0.68 mL, 5.0 mmol) in Et_2O (10 mL) was added in one portion and a dark precipitate formed instantaneously. The reaction mixture was warmed to RT and stirred for 12 h. The reaction mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (gradient hexanes:EtOAc 5:1 to 4:1) and the product isolated as a yellow oil (0.35 g, 2.2 mmol, 43%) **^{1}H NMR** (400 MHz, $CDCl_3$) 4.62 – 4.52 (m, 1H), 4.52 – 4.41 (m, 1H), 1.91 – 1.67 (m, 3H), 1.66 – 1.50 (m, 3H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.24 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 144.7, 110.9, 50.8, 45.8, 30.1, 29.3, 22.5, 20.0, 14.0; **IR** (ATR) ν 2944 (w), 1658 (s), 1417 (m), 1341 (m), 1059 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_9H_{14}N_2O$ (M^+): 166.1101. Found: 166.1102.

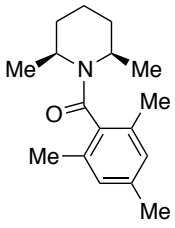


2-(*cis*-2,6-dimethylpiperidin-1-yl)-2-hydroxy-2-mesitylacetonitrile (111): In a flame-dried Schlenk-flask under N_2 *cis*-2,6-dimethylpiperidine-1-carbonyl cyanide (**110**, 83 mg, 0.50 mmol) was dissolved in dry THF (2.0 mL) and cooled to 0 ºC. Mesitylmagnesium bromide (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with H_2O (15 mL) and stirred for 1–2 min. EtOAc (25 mL) was added and the phases were separated. The organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (gradient hexanes:EtOAc 5:1 to 4:1) and the product isolated as a slightly yellow solid (0.11 g, 0.37 mmol, 75%). **m.p.** 85 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.85 (s, 2H), 4.85 (br s, 2H), 2.28 (s, 6H), 2.26 (s, 3H), 1.98 – 1.02 (m, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) 175.3, 166.9, 138.6, 134.6, 129.0, 48.8, 44.2, 30.4, 30.2, 22.3, 21.1, 20.7, 20.1, 14.3; **IR** (ATR) ν 2937 (w), 2865 (w), 1608 (s), 1434 (m), 1270 (m), 1124 (m), 1062 (m), 898 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{27}N_2O$ ($[M+H]^+$): 287.2118. Found: 287.2119.



***cis*-pyridin-2-yl 2,6-dimethylpiperidine-1-carboxylate (112)**: In a flame-dried Schlenk-flask under N_2 *cis*-2,6-dimethylpiperidine (0.68 mL, 5.0

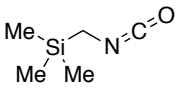
mmol) was dissolved in dry CH_2Cl_2 (15 mL) and cooled to 0 °C. Di(pyridin-2-yl) carbonate[23] (1.1 g, 5.0 mmol) was added in one portion. The reaction mixture was warmed to RT and stirred for 12 h. The reaction mixture was washed with sat. $NaHCO_3$ solution (30 mL). The aqueous layer was extracted three times with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (hexanes:EtOAc 3:2) and the product isolated as a colorless solid (0.70 g, 0.25 mmol, 50%). **m.p.** 83 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.39 (br s, 1H), 7.76 (ddd, *J* = 7.9, 5.1, 2.0 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.13 (br d, *J* = 8.2 Hz, 1H), 4.60 – 4.41 (m, 2H), 1.90 – 1.68 (m, 3H), 1.63 (br d, *J* = 12.3 Hz, 2H), 1.57 – 1.46 (m, 1H), 1.35 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 159.0, 153.5, 148.4, 139.3, 121.3, 116.6, 47.0, 30.1, 21.0, 13.7; **IR** (ATR) ν 2938 (w), 1699 (s), 1395 (m), 1342 (m), 1207 (s), 1061 (s), 748 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{18}N_2NaO_2$ ($[M+Na]^+$): 257.1260. Found: 257.1266.



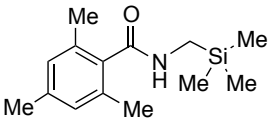
(*cis*-2,6-dimethylpiperidin-1-yl)(mesityl)methanone (113): In a flame-dried Schlenk-flask under N_2 *cis*-pyridin-2-yl 2,6-dimethylpiperidine-1-carboxylate (**112**, 0.12 g, 0.50 mmol) was dissolved in dry THF (2.0 mL) and mesitylmagnesium bromide (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) was added dropwise over 2–3 min. The reaction mixture was warmed to 50 °C and stirred for 7 h. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and stirred for 1–2 min. EtOAc (25 mL) was added and the phases were separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (hexanes:EtOAc 3:1) and the product isolated as a slightly yellow solid (50 mg, 0.25 mmol, 50%). **m.p.** 97 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.85 (s, 1H), 6.81 (s, 1H), 5.18 – 5.01 (m, 1H), 3.77 – 3.63 (m, 1H), 2.26 (s, 6H), 2.21 (s, 3H), 1.94 – 1.75 (m, 1H), 1.75 – 1.58 (m, 3H), 1.54 – 1.41 (m, 2H), 1.36 (d, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.6, 137.5, 134.5, 133.9, 133.0, 128.8, 128.0, 49.4, 43.4, 31.6, 30.1, 21.5, 21.2, 21.0, 19.6, 19.1, 14.3; **IR** (ATR) ν 2968 (w), 2935 (w), 2916 (w), 1613 (s), 1410 (m), 1361 (m), 1051 (m), 860 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{26}NO$ ($[M+H]^+$): 260.2009. Found: 260.2008.

[23] J. Q. Liu, G. Wulff, *J. Am. Soc. Chem.* **2004**, *126*, 7452-7453.

3.5. Synthesis of TMS-methyl isocyanate 117 and Amide 118



(isocyanatomethyl)trimethylsilane (117): To a flame-dried 100 mL round-bottom flask was added under N_2 potassium cyanate (2.4 g, 30 mmol), ammonium iodide (0.26 g, 1.0 mmol) and DMF (20 mL). (Chloromethyl)trimethylsilane (2.8 mL, 20 mmol) was added and the reaction mixture warmed to 100 ºC and stirred for 1 h. The reaction mixture was cooled to 0 ºC, diluted with cold Et_2O (75 mL) and washed with cold H_2O (50 mL) and cold brine (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure (30 ºC, 250 mBar). The obtained crude material was purified by Kugelrohr distillation (50 ºC, 20 mBar) and the product isolated as a colorless liquid (1.4 g, 11 mmol, 55%). The liquid was contaminated with ~10% Et_2O by NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) 2.72 (s, 2H), 0.13 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 32.3, 3.1; **IR** (ATR) ν 2959 (w), 2265 (s), 1251 (m), 837 (s) cm^{-1}. Spectral data were consistent with previous report.[24]

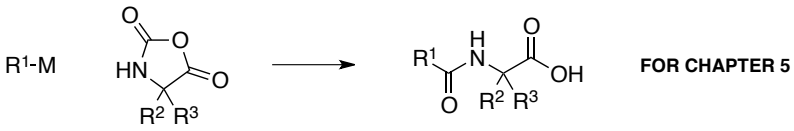


2,4,6-trimethyl-*N*-((trimethylsilyl)methyl)benzamide (118): In a flame-dried Schlenk-flask under N_2 (isocyanatomethyl)trimethylsilane (**117**, 65 mg, 0.50 mmol) was dissolved in dry THF (2 mL) and cooled to 0 ºC. Mesitylmagnesium bromide (0.50 mL of 1.0 M solution in Et_2O, 0.50 mmol) was added dropwise over 2–3 min. The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and stirred for 1–2 min. EtOAc (25 mL) was added and the phases were separated. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (cyclohexane:EtOAc 4:1) and the product isolated as a colorless solid (87 mg, 0.35 mmol, 70%). **m.p.** 100 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.84 (s, 2H), 5.43 (s, 1H), 2.97 (d, J = 5.7 Hz, 2H), 2.27 (s, 9H), 0.11 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.9, 138.5, 135.5, 134.4, 128.3, 29.8, 21.2, 19.4, -2.4; **IR** (ATR) ν 3269 (w), 2959 (w), 2918 (w), 1625 (m), 1610 (m), 1538 (m), 1246 (m), 885 (m), 835 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{24}NOSi$ ($[M+H]^+$): 250.1622. Found: 250.1625.

[24] Wang, Y. F.; Stevens, M. F. G.; Thomson, W. T.; Shutts, B. P. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2783-2787.

4. Part II: The Addition of Organometallic Reagents to *N*-Carboxyanhydrides (NCAs)

4.1. General Procedure: Amide Formation from NCAs



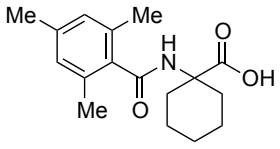
Method A from Grignard solutions (stable at RT): In a flame-dried Schlenk-flask under N_2 the *N*-carboxyanhydride (0.50 mmol, 1.0 equiv) was dissolved in dry THF (2.5 mL), cooled to –78 °C and stirred for at least 5 min. The Grignard solution (1.05 mmol, 2.1 equiv) was added dropwise over 5 min directly into the solution. The reaction mixture was stirred at –78 °C for 15 min, before the flask was removed from the cooling bath and the reaction mixture stirred at RT for 1 h. The reaction mixture was quenched with 1 M aq HCl (10 mL) and stirred for 1 min. EtOAc (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was washed with 2 x 5 mL of dry Et_2O (if not otherwise indicated) and the solid was collected by filtration and dried under high vacuum to obtain the pure product. A second crop of pure product can be obtained by evaporation of the etheral filtrate and washing the crude material once more with a small amount of Et_2O.

Method B from *in situ* generated Grignard or organolithium reagents (not stable at RT): In a flame-dried Schlenk-flask under N_2 the Grignard or organolithium reagent (1.1 mmol, 2.2 equiv) was prepared at low temperature according to the procedure indicated for each individual product. The solution containing the *in situ* generated Grignard or organolithium reagent was cooled to –78 °C and stirred for at least 5 min. A solution of the *N*-carboxyanhydride (0.50 mmol, 1.0 equiv) in dry THF (2.5 mL) was added dropwise over 10 min directly into the solution. The reaction mixture was slowly warmed to RT over the course of 5–12 h (CO_2 evaporation from the acetone/CO_2 cooling bath). The reaction mixture was quenched with 1 M aq HCl (10 mL) and stirred for 1 min. EtOAc (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified as described for method A or via column chromatography (slow gradient of MeOH in CH_2Cl_2 or EtOAc).

Method C from Grignard solutions (stable at RT) and mesitylmagnesium bromide as a base: In a flame-dried Schlenk-flask under N_2 the *N*-carboxyanhydride (0.50 mmol, 1.0 equiv) was dissolved in dry THF (2.5 mL), cooled to –78 °C and stirred for at least 5 min. Mesitylmagnesium bromide (0.50 mL of 1 M solution in Et_2O, 0.50 mmol, 1.0 equiv) was added dropwise over 2–3 min directly into the solution. The reaction mixture was stirred at –78 °C for 15 min and the second Grignard solution (0.55 mmol, 1.1 equiv) was added dropwise over 2–3 min. The reaction mixture was stirred at –78 °C for another 15 min, before the flask was removed from the cooling bath and the reaction mixture stirred at RT for 1 h. The reaction mixture was quenched with 1 M aq HCl (10 mL) and stirred for 1 min. EtOAc (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was washed with 2 x 5 mL of ambient Et_2O (if not otherwise indicated) and the solid was collected by filtration and dried under high vacuum to obtain the pure product. A second crop of pure product can be obtained by evaporation of the etheral filtrate and washing the crude material once more with a small amount of Et_2O.

Important notes:

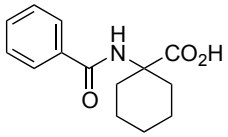
All Grignard reagents should be carefully titrated before use. We used a system based on benzoic acid and 4-(phenylazo)diphenylamine as an indicator, which was described by Knochel:[25] To an oven-dried 3 mL vial with Teflon cap was added benzoic acid (61 mg, 0.50 mmol) and 4-(phenylazo)diphenylamine (2–3 mg). The vial was evacuated and back-filled with N_2 and dry THF (1 mL) was added. A deep green solution was obtained. The solution was cooled to 0 °C and the Grignard reagent was added dropwise. During the course of the addition, the reaction becomes increasingly yellow. The sudden appearance of a dark purple color indicates the endpoint of the titration. The endpoint is easy to see and the concentration of the Grignard reagent can be determined very accurately. *The determination of the concentration is important otherwise the yield of the reactions can drop significantly*.



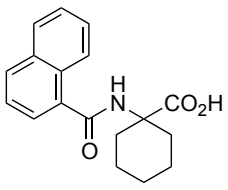
1-(2,4,6-trimethylbenzamido)cyclohexanecarboxylic acid (37): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and mesitylmagnesium bromide (1.05

[25] C. J. Rohbogner, A. J. Wagner, G. C. Clososki, P. Knochel, *Org. Synth.* **2009**, *86*, 374-384.

mL of a 1.0 M solution in Et_2O, 1.05 mmol) and isolated as a colorless solid (0.13 g, 0.47 mmol, 93%). **m.p.** 187 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.85 (s, 2H), 5.83 (s, 1H), 2.34 (s, 6H), 2.28 (s, 3H), 2.15 (d, *J* = 14.4 Hz, 2H), 2.07 – 1.96 (m, 2H), 1.79 – 1.68 (m, 2H), 1.67 – 1.57 (m, 1H), 1.56 – 1.31 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 177.0, 171.6, 139.1, 134.9, 133.9, 128.5, 59.7, 32.5, 25.2, 21.7, 21.1, 19.4; **IR** (ATR) ν 3238 (br), 2940 (w), 2859 (w), 1706 (s), 1632 (s), 1537 (s), 1250 (m), 852 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{24}NO_3$ ($[M+H]^+$): 290.1751. Found: 290.1751.



1-benzamidocyclohexanecarboxylic acid (38): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and phenylmagnesium bromide (0.42 mL of a 2.5 M solution in Et_2O, 1.05 mmol) and isolated as a colorless solid (93 mg, 0.38 mmol, 75%). **m.p.** 195 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.11 (s, 1H), 8.19 (s, 1H), 7.82 (dd, *J* = 6.9, 1.6 Hz, 2H), 7.56 – 7.39 (m, 3H), 2.12 (d, *J* = 13.4 Hz, 2H), 1.81 – 1.64 (m, 2H), 1.54 (s, 5H), 1.39 – 1.16 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.6, 166.5, 134.7, 131.1, 128.1, 127.6, 58.3, 31.7, 25.1, 21.3. Spectral data were consistent with previous report.[26]

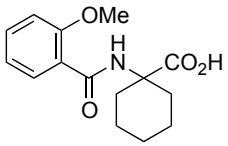


1-(1-naphthamido)cyclohexanecarboxylic acid (39): *Preparation of the Grignard reagent*: To a flame-dried Schlenk-flask were added Mg turnings (122 mg, 5 mmol) and THF (5.0 mL). 2–3 drops of 1,2-dibromoethane were added, followed by dropwise addition of a solution of 1-bromonaphthalene (0.70 mL, 5.0 mmol) in THF (5.0 mL) over 10 min at RT. The reaction mixture was stirred for 1 h at RT. LC/MS showed complete consumption of 1-bromonaphthalene. Concentration determined by titration: 0.40 M in THF.

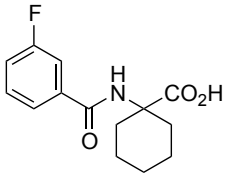
The product was prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and naphthalen-1-ylmagnesium bromide (2.6 mL of a 0.40 M solution in THF, 1.05 mmol) and isolated as a colorless solid (0.13 g, 0.42 mmol, 84%). **m.p.** 175 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.30 (s, 1H), 8.56 (s, 1H), 8.20 (dd, *J* = 6.2, 3.5 Hz, 1H), 8.07 – 7.87 (m, 2H), 7.67 – 7.44 (m, 4H), 2.16 (d, *J* = 13.1 Hz, 2H), 1.85 – 1.71 (m, 2H), 1.70 – 1.48 (m, 5H), 1.40 – 1.22 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.7, 168.8, 135.2, 133.0, 129.9, 129.3, 128.0, 126.4, 126.1, 125.5, 125.1, 125.0, 58.6, 31.8, 25.1, 21.3; **IR**

[26] C. Saavedra, R. Hernández, A. Boto, E. Álvarez, *J. Org. Chem.* **2009**, *74*, 4655-4665.

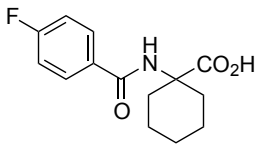
(ATR) ν 3273 (br), 2942 (m), 1704 (s), 1645 (s), 1525 (s), 1290 (m), 783 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{20}NO_3$ ($[M+H]^+$): 298.1438. Found: 298.1444.



1-(2-methoxybenzamido)cyclohexanecarboxylic acid (40): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and 2-methoxyphenylmagnesium bromide (1.05 mL of a 1.0 M solution in THF, 1.05 mmol) and isolated as a colorless solid (0.11 g, 0.39 mmol, 79%). **m.p.** 192 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.17 (s, 1H), 8.21 (s, 1H), 7.77 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.50 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.06 (td, *J* = 7.6, 0.9 Hz, 1H), 3.95 (s, 3H), 2.08 (d, *J* = 13.2 Hz, 2H), 1.71 (td, *J* = 13.1, 3.3 Hz, 2H), 1.60 (d, *J* = 10.1 Hz, 3H), 1.44 (td, *J* = 12.6, 3.1 Hz, 2H), 1.35 – 1.16 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.2, 163.7, 157.2, 132.6, 130.6, 122.3, 120.7, 112.3, 57.9, 56.3, 31.7, 24.9, 21.1; **IR** (ATR) ν 3366 (m), 2937 (m), 2857 (w), 1742 (s), 1538 (s), 1233 (s), 1233 (s), 1008 (m), 751 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{20}NO_4$ ($[M+H]^+$): 278.1387. Found: 278.1388.



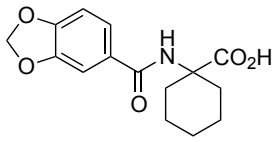
1-(3-fluorobenzamido)cyclohexanecarboxylic acid (41): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and 3-fluorophenylmagnesium bromide (1.05 mL of a 1.0 M solution in 2-MeTHF, 1.05 mmol) and isolated as a colorless solid (0.10 g, 0.39 mmol, 78%). **m.p.** 205 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.17 (s, 1H), 8.28 (s, 1H), 7.72 – 7.68 (m, 1H), 7.64 (ddd, *J* = 10.0, 2.5, 1.5 Hz, 1H), 7.52 (td, *J* = 8.0, 5.9 Hz, 1H), 7.42 – 7.35 (m, 1H), 2.12 (d, *J* = 13.3 Hz, 2H), 1.81 – 1.66 (m, 2H), 1.53 (s br, 5H), 1.28 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.4, 165.1 (d, *J* = 2.4 Hz), 161.8 (d, *J* = 244 Hz), 137.0 (d, *J* = 6.7 Hz), 130.3 (d, *J* = 8.0 Hz), 123.9 (d, *J* = 2.8 Hz), 118.0 (d, *J* = 21.1 Hz), 114.4 (d, *J* = 22.7 Hz), 58.6, 31.7, 25.1, 21.3; **^{19}F NMR** (376 MHz, d^6-DMSO) –113.1; **IR** (ATR) ν 3260 (br), 2974 (w), 2861 (w), 1702 (s), 1527 (s), 1267 (s), 760 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{16}FNNaO_3$ ($[M+Na]^+$): 288.1006. Found: 288.1012.



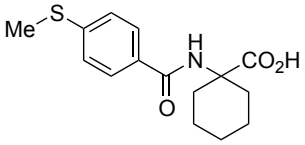
1-(4-fluorobenzamido)cyclohexanecarboxylic acid (42): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and 4-fluorophenylmagnesium bromide (1.3 mL of a

0.80 M solution in THF, 1.05 mmol) and isolated as a colorless solid (94 mg, 0.35 mmol, 71%).

Prepared according to method C from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol), mesitylmagnesium bromide (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) and 4-fluorophenylmagnesium bromide (0.69 mL of a 0.80 M solution in THF, 0.55 mmol) and isolated as a colorless solid (0.11 g, 0.43 mmol, 85%). **m.p.** 211 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.13 (s, 1H), 8.23 (s, 1H), 8.01 – 7.79 (m, 2H), 7.36 – 7.17 (m, 2H), 2.12 (d, *J* = 13.3 Hz, 1H), 1.83 – 1.66 (m, 2H), 1.53 (s br, 5H), 1.34 – 1.22 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.6, 165.5, 163.8 (d, *J* = 248.2 Hz), 131.1 (d, *J* = 2.9 Hz), 130.3 (d, *J* = 9.0 Hz), 115.0 (d, *J* = 21.7 Hz), 58.4, 31.7, 25.1, 21.3; **^{19}F NMR** (376 MHz, d^6-DMSO) –109.6; **IR** (ATR) ν 3288 (br), 2947 (w), 2862 (w), 1698 (s), 1531 (s), 1499 (s), 1237 (s), 1160 (m), 849 (s). 765 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{16}FNNaO_3$ ([M+Na]$^+$): 288.1006. Found: 288.1013.



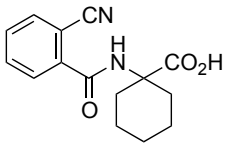
1-(benzo[*d*][1,3]dioxole-5-carboxamido)cyclohexanecarboxylic acid (43): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and 3,4-(methylenedioxy)-phenylmagnesium bromide (1.4 mL of a 0.75 M solution in THF/toluene 1:1, 1.05 mmol) and isolated as a colorless solid (0.11 g, 0.38 mmol, 76%). **m.p.** 209 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.06 (s, 1H), 8.01 (s, 1H), 7.45 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.39 (d, *J* = 1.6 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.09 (s, 2H), 2.10 (d, *J* = 13.3 Hz, 2H), 1.80 – 1.64 (m, 2H), 1.52 (s br, 5H), 1.32 – 1.20 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.7, 165.5, 149.6, 147.1, 128.6, 122.7, 107.7, 107.7, 101.6, 58.3, 31.8, 25.1, 21.3; **IR** (ATR) ν 3336 (w), 2934 (w), 1702 (s), 1478 (s), 1259 (s), 1039 (m), 761 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{18}NO_5$ ([M+H]$^+$): 292.1179. Found: 292.1183.



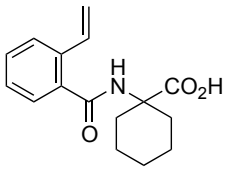
1-(4-(methylthio)benzamido)cyclohexanecarboxylic acid (44): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and 4-thioanisolemagnesium bromide (2.1 mL of a 0.50 M solution in THF, 1.05 mmol) and isolated as a colorless solid (0.10 g, 0.35 mmol, 70%).

Prepared according to method C from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol), mesitylmagnesium bromide (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) and 4-

thioanisolemagnesium bromide (1.1 mL of 0.50 M solution in THF, 0.55 mmol) and isolated as a colorless solid (0.13 g, 0.44 mmol, 87%) **m.p.** 207 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.09 (s, 1H), 8.13 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 2.51 (s, 3H), 2.11 (d, *J* = 13.2 Hz, 2H), 1.74 (dt, *J* = 13.6, 6.9 Hz, 2H), 1.53 (s br, 5H), 1.28 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.6, 165.9, 142.3, 130.7, 128.2, 124.7, 58.3, 31.8, 25.1, 21.3, 14.2; **IR** (ATR) ν 3220 (br), 2919 (w), 1710 (s), 1625 (s), 1539 (s), 840 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{20}NO_3S$ ([M+H]$^+$): 294.1158. Found: 294.1162.



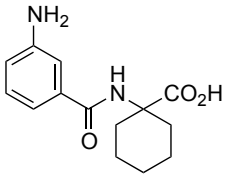
1-(2-cyanobenzamido)cyclohexanecarboxylic acid (45): *Preparation of the Grignard reagent*:[27] To a flame-dried Schlenk-flask was added *i*PrMgCl•LiCl complex (0.85 mL of a 1.3 M solution in THF, 1.1 mmol) and THF (0.25 mL) and cooled to 0 °C. 2-bromobenzonitrile (0.20 g, 1.1 mmol) was added in one portion and the reaction mixture stirred for 1 h at 0 °C. The *in situ* generated Grignard solution was cooled to –78 °C and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless solid (93 mg, 0.34 mmol, 68%). **m.p.** 157 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.30 (s, 1H), 8.65 (s, 1H), 7.91 (ddd, *J* = 7.6, 1.2, 0.4 Hz, 1H), 7.78 (td, *J* = 7.8, 1.3, 1H), 7.75 – 7.71 (m, 1H), 7.68 (td, *J* = 7.5, 1.5, 1H), 2.13 (d, *J* = 12.7 Hz, 2H), 1.80 – 1.49 (m, 7H), 1.32 – 1.20 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.3, 165.4, 139.4, 133.7, 132.8, 130.8, 128.9, 117.6, 110.1, 58.9, 31.6, 25.1, 21.0; **IR** (ATR) ν 3268 (w), 2927 (w), 2228 (w), 1702 (s), 1627 (s), 1539 (s), 1256 (m), 759 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{17}N_2O_3$ ([M+H]$^+$): 273.1234. Found: 273.1239.



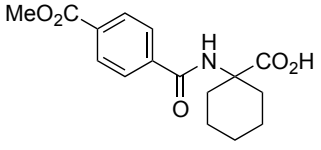
1-(2-vinylbenzamido)cyclohexanecarboxylic acid (46): *Preparation of the Grignard reagent*: To a flame-dried Schlenk-flask were added Mg turnings (53 mg, 2.2 mmol) and THF (2.0 mL). 2–3 drops of 1,2-dibromoethane were added, followed by dropwise addition of a solution of 2-bromostyrene (0.37 g, 2.0 mmol) in THF (2.0 mL) over 5 min at RT. The reaction mixture was heated to 45 °C and stirred for 30 min. LC/MS showed complete consumption of 2-bromostyrene. Concentration determined by titration: 0.45 M in THF.

[27] A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336.

The product was prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and (2-vinylphenyl)magnesium bromide (2.3 mL of a 0.45 M solution in THF, 1.05 mmol) and isolated as a colorless solid (0.10 g, 0.38 mmol, 76%). **m.p.** 140 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.22 (s, 1H), 8.39 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.41 (ddd, *J* = 5.8, 4.7, 3.0 Hz, 1H), 7.36 – 7.28 (m, 2H), 6.97 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.82 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.26 (dd, *J* = 11.1, 1.0 Hz, 1H), 2.08 (d, *J* = 13.3 Hz, 2H), 1.78 – 1.65 (m, 2H), 1.54 (s br, 5H), 1.36 – 1.21 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.6, 168.8, 136.7, 134.6, 134.1, 129.2, 127.6, 127.4, 124.7, 115.3, 58.5, 31.7, 25.0, 21.2; **IR** (ATR) ν 3267 (w), 2938 (w), 2855 (w), 1708 (s), 1642 (s), 1527 (s), 1289 (m), 914 (s), 772 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{20}NO_3$ ([M+H]$^+$): 274.1438. Found: 274.1441.



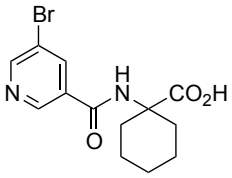
1-(3-aminobenzamido)cyclohexanecarboxylic acid (47): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and 3-[Bis(trimethylsilyl)amino]phenylmagnesium chloride (1.05 mL of a 1.0 M solution in THF, 1.05 mmol). *Workup*: The reaction mixture was quenched with MeOH (5 mL) and solvent removed under reduced pressure. The yellow crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:9) and the product isolated as a slightly yellow solid (0.11 g, 0.42 mmol, 84%). **m.p.** 203 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 11.78 (s, 1H), 7.95 (s, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.97 (s, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.68 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.20 (s br, 2H), 2.10 (d, *J* = 13.2 Hz, 2H), 1.78 – 1.64 (m, 2H), 1.52 (s br, 5H), 1.37 – 1.16 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.7, 167.3, 148.5, 135.8, 128.4, 116.3, 114.9, 113.0, 58.1, 31.7, 25.1, 21.3; **IR** (ATR) ν 3229 (br), 2931 (m), 2858 (w), 1621 (s), 1585 (s), 1531 (s), 1328 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{18}N_2NaO_3$ ([M+Na]$^+$): 285.1210. Found: 285.1214.



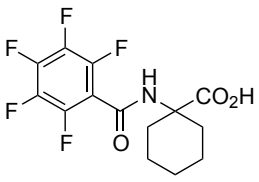
1-(4-(methoxycarbonyl)benzamido)cyclohexanecarboxylic acid (48): *Preparation of the Grignard reagent*:[28] To a flame-dried Schlenk-flask was added methyl 4-iodobenzoate (0.29 g, 1.1 mmol) and THF (2.2 mL) and cooled to –20 °C. Isopropylmagnesium chloride (0.65 mL of a 1.7 M solution in THF, 1.1 mmol) was added dropwise over 5 min and the reaction mixture

[28] E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis*, **2002**, 565-569.

stirred for 1 h at –20 ºC. The *in situ* generated Grignard solution was cooled to –78 ºC and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless solid (0.11 g, 0.35 mmol, 70%). **m.p.** 210 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.19 (s, 1H), 8.42 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 3H), 2.13 (d, *J* = 13.3 Hz, 2H), 1.83 – 1.68 (m, 2H), 1.54 (s br, 5H), 1.29 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.4, 165.8, 165.8, 138.9, 131.7, 128.9, 128.0, 58.6, 52.4, 31.7, 25.1, 21.3; **IR** (ATR) ν 3388 (w), 2941 (w), 1720 (s), 1531 (s), 1279 (s), 729 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{20}NO_5$ ([M+H]$^+$): 306.1336. Found: 306.1340.



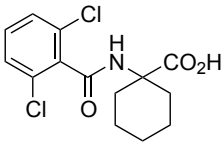
1-(5-bromonicotinamido)cyclohexanecarboxylic acid (49): *Preparation of the Grignard reagent*:[27] To a flame-dried Schlenk-flask was added *i*PrMgCl•LiCl complex (0.85 mL of a 1.3 M solution in THF, 1.1 mmol) and THF (0.25 mL) and cooled to –15 ºC. 3,5-dibromopyridine (0.26 g, 1.1 mmol) was added in one portion and the reaction mixture warmed to –10 ºC and stirred for 15 min. The *in situ* generated Grignard solution was cooled to –78 ºC and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). *Workup*: The reaction mixture was quenched with 5% aq citric acid (10 mL) instead of 1 M aq HCl. The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:5) and the obtained yellow solid was washed with Et_2O (2 x 5 mL) to isolate the product as a colorless solid (0.12 g, 0.37 mmol, 73%). **m.p.** 225 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.28 (s, 1H), 8.94 (d, *J* = 1.5 Hz, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.51 (s, 1H), 8.47 – 8.37 (m, 1H), 2.12 (d, *J* = 13.2 Hz, 2H), 1.83 – 1.67 (m, 2H), 1.55 (s br, 5H), 1.36 – 1.16 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.2, 163.6, 152.5, 147.4, 137.6, 131.6, 119.9, 58.9, 31.6, 25.0, 21.2; **IR** (ATR) ν 3394 (m), 2935 (m), 2853 (w), 1743 (s), 1619 (s), 1535 (s), 1193 (s), 1132 (s), 877 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{16}BrN_2O_3$ ([M+H]$^+$): 327.0339. Found: 327.0342.



1-(perfluorobenzamido)cyclohexanecarboxylic acid (50): *Preparation of the Grignard reagent*: To a flame-dried Schlenk-flask were added Mg turnings (73 mg, 3.0 mmol) and Et_2O (3.0 mL). 2–3 drops of 1,2-dibromoethane were added, followed by dropwise addition

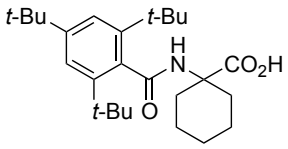
of a solution of 1-bromo-2,3,4,5,6-pentafluorobenzene (0.37 mL, 3.0 mmol) in Et_2O (3.0 mL) over 30 min at RT, using a syringe pump. The reaction mixture was stirred for 30 min at RT. LC/MS showed complete consumption of 1-bromo-2,3,4,5,6-pentafluorobenzene. Concentration determined by titration: 0.50 M in Et_2O.

The product was prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and (perfluorophenyl)magnesium bromide (2.1 mL of a 0.50 M solution in Et_2O, 1.05 mmol). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless solid (0.12 g, 0.36 mmol, 73%). **m.p.** 208 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.44 (s, 1H), 8.89 (s, 1H), 2.07 (d, *J* = 12.7 Hz, 2H), 1.70 (t, *J* = 11.0 Hz, 2H), 1.63 – 1.36 (m, 5H), 1.35 – 1.13 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 174.6, 156.2, 143.3 (d br, *J* = 248 Hz), 141.0 (d br, *J* = 252 Hz), 136.8 (d br, *J* = 251 Hz), 112.7 (s br), 59.2, 31.4, 24.8, 20.8; **^{19}F NMR** (376 MHz, d^6-DMSO) -141.9 (dd, *J* = 24.9, 8.2 Hz), -153.6 (t, *J* = 21.8 Hz), -161.7 – -161.9 (m); **IR** (ATR) ν 3289 (w), 2944 (w), 2869 (w), 1714 (s), 1661 (s), 1498 (s), 1110 (m), 991 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{13}F_5NO_3$ ([M+H]$^+$): 338.0810. Found: 338.0813.



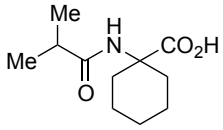
1-(2,6-dichlorobenzamido)cyclohexanecarboxylic acid (51): *Preparation of the Grignard reagent*:[27] To a flame-dried Schlenk-flask was added *i*PrMgCl•LiCl complex (2.4 mL of 1.3 M solution in THF) and THF (0.60 mL) and cooled to 0 ºC. 2-bromo-1,3-dichlorobenzene (0.68 g, 3.0 mmol) was added in one portion and the reaction mixture warmed to RT and stirred for 1 h. LC/MS showed complete consumption of 2-bromo-1,3-dichlorobenzene. Concentration determined by titration: 0.85 M in THF.

The product was prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and (2,6-dichlorophenyl)magnesium bromide LiCl complex (1.2 mL of a 0.85 M solution in THF, 1.05 mmol) and isolated as a colorless solid (0.12 g, 0.38 mmol, 76%). **m.p.** 195 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.17 (s, 1H), 8.70 (s, 1H), 7.50 – 7.45 (m, 2H), 7.40 (dd, *J* = 9.2, 6.6 Hz, 1H), 2.05 (d, *J* = 13.0 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.67 – 1.41 (m, 5H), 1.32 – 1.21 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 174.9, 163.0, 136.4, 131.5, 130.7, 128.1, 58.3, 31.7, 25.0, 21.0; **IR** (ATR) ν 3297 (br), 2925 (w), 1703 (s), 1650 (s), 1528 (s), 1428 (s), 803 (s), 770 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{16}Cl_2NO_3$ ([M+H]$^+$): 316.0502. Found: 316.0509.

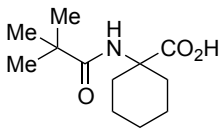


1-(2,4,6-tri-*tert*-butylbenzamido)cyclohexanecarboxylic acid (52): *Preparation of the Grignard reagent*:[29] 2-Bromo-1,3,5-tri-*tert*-butylbenzene (0.65 g, 2.0 mmol), Mg turnings (53 mg, 2.2 mmol) and THF (4.0 mL) were added to a flame-dried Schlenk-flask and heated to 65 ºC. 2–3 drops of 1,2-dibromoethane were added and the reaction mixture stirred for 2 h at 65 ºC. LC/MS showed complete consumption of 2-Bromo-1,3,5-tri-*tert*-butylbenzene. Concentration determined by titration: 0.40 M in THF.

The product was prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and (2,4,6-tri-*tert*-butylphenyl)magnesium bromide (2.6 mL of a 0.40 M solution in THF, 1.05 mmol). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:2) and the product isolated as a colorless solid (0.17 g, 0.40 mmol, 81%). **m.p.** over 225 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.41 (s, 1H), 7.93 (s, 1H), 7.35 (s, 2H), 2.33 (d, *J* = 11.3 Hz, 2H), 1.69 – 1.46 (m, 5H), 1.41 (s, 18H), 1.39 – 1.32 (m, 2H), 1.26 (s, 9H), 1.19 – 0.98 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 172.3, 169.9, 148.3, 146.4, 134.0, 121.7, 59.6, 37.1, 34.5, 33.9, 32.8, 31.1, 24.8, 22.6; **IR** (ATR) ν 3368 (w), 2934 (m), 2866 (w), 1773 (m), 1714 (s), 1585 (s), 1513 (s), 1224 (s), 914 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{26}H_{42}NO_3$ ([M+H]$^+$): 416.3159. Found: 416.3162.



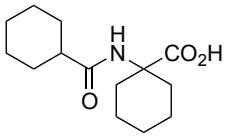
1-isobutyramidocyclohexanecarboxylic acid (53): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and isopropylmagnesium chloride (0.62 mL of a 1.7 M solution in THF, 1.05 mmol) and isolated as a colorless solid (93 mg, 0.44 mmol, 87%). **m.p.** 207 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 11.94 (s, 1H), 7.63 (s, 1H), 2.58 – 2.43 (m, 1H), 1.95 (d, *J* = 13.1 Hz, 2H), 1.67 – 1.56 (m, 2H), 1.56 – 1.38 (m, 5H), 1.28 – 1.12 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.8, 175.7, 57.3, 33.3, 31.7, 25.0, 21.1, 19.5; **IR** (ATR) ν 3298 (br), 2933 (m), 2867 (w), 1702 (s), 1650 (s), 1539 (s), 1285 (s), 1242 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{20}NO_3$ ([M+H]$^+$): 214.1438. Found: 214.1438.



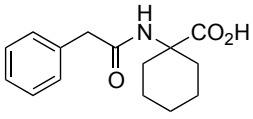
1-pivalamidocyclohexanecarboxylic acid (54): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50

[29] L. Salvi , N. R. Davis , S. Z. Ali, S. L. Buchwald, *Org. Lett.* **2012**, *14*, 170-173.

mmol) and *tert*-butylmagnesium chloride (1.05 mL of a 1.0 M solution in THF, 1.05 mmol) and isolated as a colorless solid (0.10 g, 0.45 mmol, 90%). **m.p.** 177 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 11.88 (s, 1H), 6.90 (s, 1H), 2.03 – 1.94 (m, 2H), 1.68 – 1.58 (m, 2H), 1.53 – 1.34 (m, 5H), 1.29 – 1.18 (m, 1H), 1.11 (s, 9H); **^{13}C NMR** (101 MHz, d^6-DMSO) 177.1, 175.7, 57.6, 38.1, 31.7, 27.2, 25.1, 21.3; **IR** (ATR) ν 3330 (br), 2933 (w), 2869 (w), 1707 (s), 1639 (s), 1519 (s), 1286 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{22}NO_3$ ([M+H]$^+$): 228.1594. Found: 228.1598.

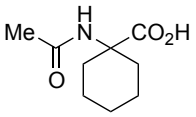


1-(cyclohexanecarboxamido)cyclohexanecarboxylic acid (55): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and cyclohexylmagnesium chloride (0.81 mL of a 1.3 M solution in THF/toluene 1:1, 1.05 mmol) and isolated as a colorless solid (0.11 g, 0.43 mmol, 86%). **m.p.** 178 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 11.91 (s, 1H), 7.58 (s, 1H), 2.28 – 2.18 (m, 1H), 1.93 (d, *J* = 13.1 Hz, 2H), 1.74 – 1.35 (m, 12H), 1.35 – 1.03 (m, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.8, 174.9, 57.3, 43.3, 31.7, 29.1, 25.5, 25.2, 25.0, 21.0; **IR** (ATR) ν 3350 (m), 2934 (s), 2861 (m), 1714 (s), 1617 (m), 1531 (s), 1221 (m), 1191 (m), 662 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{24}NO_3$ ([M+H]$^+$): 254.1751. Found: 254.1754.



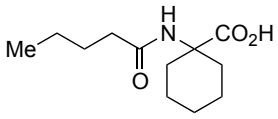
1-(2-phenylacetamido)cyclohexanecarboxylic acid (56): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and benzylmagnesium chloride (0.53 mL of a 2.0 M solution in THF, 1.05 mmol. *Attention: This Grignard tends to freeze inside the syringe*) and isolated as a colorless solid (94 mg, 0.36 mmol, 72%).

Prepared according to method C from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol), mesitylmagnesium bromide (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) and benzylmagnesium chloride (0.28 mL of a 2.0 M solution in THF, 0.55 mmol. *Attention: This Grignard tends to freeze inside the syringe*) and isolated as a colorless solid (0.11 g, 0.44 mmol, 87%). **m.p.** 185 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.05 (s, 1H), 8.02 (s, 1H), 7.31 – 7.23 (m, 4H), 7.23 – 7.16 (m, 1H), 3.47 (s, 2H), 1.94 (d, *J* = 13.2 Hz, 2H), 1.71 – 1.57 (m, 2H), 1.55 – 1.34 (m, 5H), 1.30 – 1.10 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.5, 169.7, 136.7, 128.9, 128.1, 126.2, 57.7, 42.0, 31.7, 25.0, 21.0; **IR** (ATR) ν 3336 (m), 2931 (m), 2857 (w), 1704 (s), 1615 (s), 1543 (s), 1208 (m), 723 (s), 693 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{20}NO_3$ ([M+H]$^+$): 262.1438. Found: 262.1441.



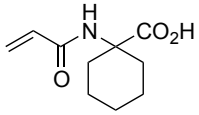
1-acetamidocyclohexanecarboxylic acid (57): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and methylmagnesium bromide (0.35 mL of a 3.0 M solution in Et_2O, 1.05 mmol) and isolated as a colorless solid (25 mg, 0.13 mmol, 27%).

Prepared according to method C from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol), mesitylmagnesium bromide (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) and methylmagnesium bromide (0.18 mL of 3.0 M solution in Et_2O, 0.55 mmol) and isolated as a colorless solid (77 mg, 0.42 mmol, 83%). **m.p.** 197 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.00 (s, 1H), 7.78 (s, 1H), 1.91 (d, *J* = 13.1 Hz, 2H), 1.82 (s, 3H), 1.67 – 1.55 (m, 2H), 1.54 – 1.38 (m, 5H), 1.28 – 1.11 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.7, 169.0, 57.6, 31.8, 25.0, 22.6, 21.0; **IR** (ATR) ν 3353 (m), 2938 (m), 2860 (m), 1712 (s), 1620 (s), 1543 (s), 1240 (m), 680 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_9H_{14}NO_3$ ([M–H]$^-$): 184.0979. Found: 184.0983.



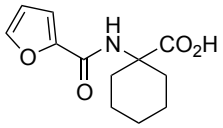
1-pentanamidocyclohexanecarboxylic acid (58): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and butylmagnesium bromide (0.95 mL of a 1.1 M solution in THF, 1.05 mmol) and isolated as a colorless solid (35 mg, 0.15 mmol, 31%).

Prepared according to method C from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol), mesitylmagnesium bromide (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) and butylmagnesium bromide (0.50 mL of a 1.1 M solution in THF, 0.55 mmol) and isolated as a colorless solid (93 mg, 0.41 mmol, 82%). **m.p.** 163 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 11.96 (s, 1H), 7.70 (s, 1H), 2.10 (t, *J* = 7.3 Hz, 2H), 1.92 (d, *J* = 13.3 Hz, 2H), 1.67 – 1.55 (m, 2H), 1.55 – 1.37 (m, 7H), 1.34 – 1.14 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.7, 172.0, 57.5, 34.8, 31.7, 27.5, 25.0, 21.7, 21.1, 13.8; **IR** (ATR) ν 3360 (m), 2933 (m), 2856 (w), 1709 (s), 1620 (s), 1539 (s), 1235 (s), 1196 (s), 823 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{21}NNaO_3$ ([M+Na]$^+$): 250.1414. Found: 250.1421.

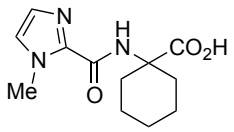


1-acrylamidocyclohexanecarboxylic acid (59): Prepared according to method A from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) and vinylmagnesium bromide (1.05 mL of a 1.0 M solution in THF, 1.05 mmol. *Attention: This Grignard tends to freeze inside the syringe*). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:5) and the product isolated as a colorless solid (35 mg, 0.18 mmol, 35%).

Prepared according to method C from 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol), mesitylmagnesium bromide (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) and vinylmagnesium bromide (0.55 mL of a 1.0 M solution in THF, 0.55 mmol. *Attention: This Grignard tends to freeze inside the syringe*) The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:5) and the product isolated as a colorless solid (81 mg, 0.41 mmol, 82%). **m.p.** 185 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.10 (s, 1H), 8.00 (s, 1H), 6.38 (dd, *J* = 17.1, 10.2 Hz, 1H), 6.04 (dd, *J* = 17.1, 2.3 Hz, 1H), 5.57 (dd, *J* = 10.2, 2.3 Hz, 1H), 1.98 (d, *J* = 13.2 Hz, 2H), 1.74 – 1.59 (m, 2H), 1.56 – 1.35 (m, 5H), 1.28 – 1.15 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.4, 164.1, 131.7, 125.1, 57.8, 31.7, 24.9, 21.1; **IR** (ATR) ν 3396 (w), 2942 (m), 2870 (m), 1730 (s), 1524 (s), 1229 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{10}H_{15}NNaO_3$ ([M+Na]$^+$): 220.0944. Found: 220.0951.

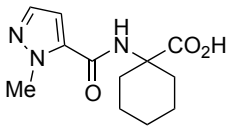


1-(furan-2-carboxamido)cyclohexanecarboxylic acid (60): *Preparation of the organolithium reagent*: To a flame-dried Schlenk-flask was added furan (80 µL, 1.1 mmol) and THF (2.2 mL) and cooled to –78 °C. *n*-Butyllithium (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol) was added dropwise over 2–3 min and the flask placed into an ice-bath (0 °C) and stirred for 1 h. The *in situ* generated organolithium reagent was cooled to –78 °C and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was washed with Et_2O (2 x 5 mL) and the product isolated as a colorless solid (99 mg, 0.42 mmol, 83%). **m.p.** 215 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.22 (s, 1H), 7.94 (s, 1H), 7.83 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.18 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.62 (dd, *J* = 3.5, 1.7 Hz, 1H), 2.09 (d, *J* = 13.5 Hz, 2H), 1.80 – 1.67 (m, 2H), 1.60 – 1.38 (m, 5H), 1.36 – 1.16 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.3, 157.6, 147.7, 145.0, 113.7, 111.7, 58.2, 31.8, 25.0, 21.2; **IR** (ATR) ν 3364 (m), 3129 (w), 2936 (w), 1720 (s), 1590 (s), 1531 (s), 1222 (m), 751 (s), cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{15}NNaO_4$ ([M+Na]$^+$): 260.0893. Found: 260.0897.

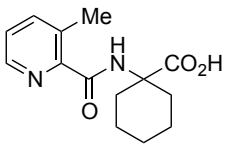


1-(1-methyl-1*H*-imidazole-2-carboxamido)cyclohexanecarboxylic acid (61): *Preparation of the organolithium reagent*: To a flame-dried Schlenk-flask was added 1-methylimidazole (88 µL, 1.1 mmol) and THF (2.2 mL) and cooled to –78 °C. *n*-Butyllithium (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol) was added dropwise over 2–3 min and the reaction mixture stirred at –78 °C for 1 h. The *in situ* generated organolithium reagent was kept at –78 °C and the product prepared

according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). *Workup*: The reaction mixture was quenched with MeOH (5 mL) and the solvent removed under reduced pressure. The yellow crude material was purified by flash column chromatography (gradient EtOAc:MeOH 100:0 to 100:15) and the obtained slightly yellow solid was washed with Et_2O (2 x 5 mL) to isolate the product as a colorless solid (92 mg, 0.37 mmol, 73%). **m.p.** 130 ºC (decomposition); **^{1}H NMR** (400 MHz, d^6-DMSO) 12.41 (s, 1H), 7.89 (s br, 1H), 7.34 (s br, 1H), 6.97 (d, *J* = 0.8 Hz, 1H), 3.91 (s, 3H), 2.11 (d, *J* = 13.4 Hz, 2H), 1.76 – 1.70 (m, 2H), 1.60 (s br, 2H), 1.55 – 1.18 (m, 4H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.2, 158.2, 138.5, 126.9, 126.2, 58.1, 35.0, 31.8, 24.9, 21.4; **IR** (ATR) ν 2934 (m), 2859 (w), 1660 (s), 1539 (s), 1280 (s), 1169 (m), 762 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{18}N_3O_3$ ([M+H]$^+$): 252.1343. Found: 252.1345.

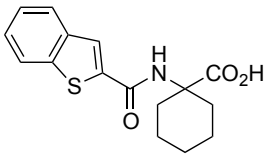


1-(1-methyl-1*H*-pyrazole-5-carboxamido)cyclohexanecarboxylic acid (62): *Preparation of the organolithium reagent*: To a flame-dried Schlenk-flask was added 1-methylpyrazole (91 µL, 1.1 mmol) and THF (2.2 mL) and cooled to –78 ºC. *n*-Butyllithium (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol) was added dropwise over 2–3 min and the reaction mixture was warmed to RT and stirred for 1 h. The *in situ* generated organolithium reagent was cooled to –78 ºC and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). *Workup*: The reaction mixture was quenched with MeOH (5 mL) and solvent removed under reduced pressure. The yellow crude material was purified by flash column chromatography (gradient EtOAc:MeOH 100:0 to 100:10) and the product isolated as a slightly tan solid (0.10 g, 0.40 mmol, 80%). **m.p.** 180 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.24 (s, 1H), 8.16 (s, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 3.98 (s, 3H), 2.09 (d, *J* = 13.5 Hz, 2H), 1.83 – 1.67 (m, 2H), 1.60 – 1.40 (m, 5H), 1.36 – 1.13 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.3, 159.5, 137.0, 135.4, 107.8, 58.6, 38.7, 31.7, 25.0, 21.3; **IR** (ATR) ν 3257 (w), 2929 (w), 2859 (w), 1717 (s), 1646 (s), 1549 (s), 1270 (s), 1236 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{18}N_3O_3$ ([M+H]$^+$): 252.1343. Found: 252.1345.

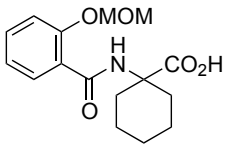


1-(3-methylpicolinamido)cyclohexanecarboxylic acid (63): *Preparation of the organolithium reagent*: To a flame-dried Schlenk-flask was added 2-bromo-3-methylpyridine (0.12 mL, 1.1 mmol) and THF (2.2 mL) and cooled to –78 ºC. *n*-Butyllithium (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol)

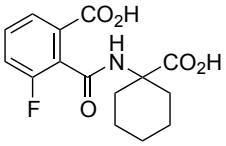
was added dropwise over 2–3 min and the reaction mixture stirred for 15 min at –78 ºC. The *in situ* generated organolithium reagent was kept –78 ºC and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). *Workup*: The reaction mixture was quenched with 5% aq citric acid (10 mL) instead of 1 M aq HCl. The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the obtained yellow solid washed with Et_2O (2 x 5 mL) to isolate the product as a colorless solid (75 mg, 0.29 mmol, 57%). **m.p.** 172 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.26 (s, 1H), 8.45 (dd, *J* = 4.6, 0.9 Hz, 1H), 8.41 (s, 1H), 7.73 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.45 (dd, *J* = 7.7, 4.7 Hz, 1H), 2.09 (d, *J* = 13.3 Hz, 2H), 1.84 – 1.67 (m, 2H), 1.65 – 1.40 (m, 5H), 1.38 – 1.17 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.2, 165.6, 149.5, 145.8, 140.0, 132.9, 125.4, 57.8, 31.8, 24.9, 21.2, 19.0; **IR** (ATR) ν 3275 (m), 2921 (w), 1707 (s), 1660 (s), 1544 (m), 1245 (m), 684 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{19}N_2O_3$ ([M+H]$^+$): 263.1390. Found: 263.1392.



1-(benzo[*b*]thiophene-2-carboxamido)cyclohexanecarboxylic acid (64): *Preparation of the organolithium reagent*: To a flame-dried Schlenk-flask was added benzo[*b*]thiophene (0.15 g, 1.1 mmol) and THF (2.2 mL) and cooled to –78 ºC. *n*-Butyllithium (0.69 mL of a 1.6 M solution in cyclohexane, 1.1 mmol) was added dropwise over 2–3 min and the reaction mixture stirred for 1 h –78 ºC. The *in situ* generated organolithium reagent was kept at –78 ºC and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was washed with Et_2O (3 x 5 mL) and the product isolated as a slightly yellow solid (0.11 g, 0.36 mmol, 71%). **m.p.** over 225 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.25 (s, 1H), 8.45 (s, 1H), 8.27 (s, 1H), 8.04 – 7.99 (m, 1H), 7.98 – 7.92 (m, 1H), 7.49 – 7.41 (m, 2H), 2.14 (d, *J* = 13.3 Hz, 2H), 1.84 – 1.67 (m, 2H), 1.56 (s br, 5H), 1.40 – 1.23 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.3, 161.6, 140.2, 139.9, 139.2, 126.2, 125.6, 125.2, 124.9, 122.8, 58.8, 31.8, 25.0, 21.3; **IR** (ATR) ν 3330 (m), 2919 (w), 2853 (w), 1702 (s), 1619 (s), 1540 (s), 1291 (s), 1249 (s), 1203 (s), 761 (s), 722 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{17}NNaO_3S$ ([M+Na]$^+$): 326.0821. Found: 326.0821.



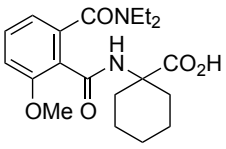
1-(2-(methoxymethoxy)benzamido)cyclohexanecarboxylic acid (65): *Preparation of the organolithium reagent*:[30] To a flame-dried Schlenk-flask was added (methoxymethoxy)benzene (0.15 g, 1.1 mmol), Et_2O (2.2 mL) and TMEDA (0.17 mL, 1.1 mmol) and cooled to 0 °C. *n*-Butyllithium (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol) was added dropwise over 2–3 min and the reaction mixture stirred for 30 min at 0 °C. The *in situ* generated organolithium reagent was cooled to –78 °C and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was washed with Et_2O (2 x 5 mL) and the product isolated as a colorless solid (0.14 g, 0.45 mmol, 89%). **m.p.** 160 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.17 (s, 1H), 8.24 (s, 1H), 7.72 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1H), 7.21 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.09 (td, *J* = 7.6, 1.0 Hz, 1H), 5.37 (s, 2H), 3.44 (s, 3H), 2.10 (d, *J* = 13.2 Hz, 2H), 1.71 (td, *J* = 13.0, 3.4 Hz, 2H), 1.65 – 1.40 (m, 5H), 1.35 – 1.17 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.3, 163.9, 154.4, 132.1, 130.5, 123.8, 121.6, 115.0, 94.8, 58.0, 56.2, 31.7, 24.9, 21.1; **IR** (ATR) ν 3388 (s), 2945 (w), 1699 (s), 1647 (s), 1514 (s), 943 (s), 923 (s), 753 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{21}NNaO_5$ ([M+Na]$^+$): 330.1312. Found: 330.1317.



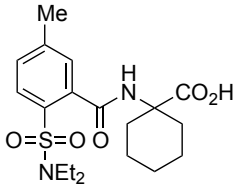
2-((1-carboxycyclohexyl)carbamoyl)-3-fluorobenzoic acid (66): *Preparation of the organolithium reagent*:[31] To a flame-dried Schlenk-flask was added TMEDA (0.33 mL, 2.2 mmol) and THF (1.1 mL) and cooled to –90 °C (N_2/acetone bath). *sec*-Butyllithium (1.6 mL of a 1.4 M solution in cyclohexane, 2.2 mmol) was added. Then a solution of 3-fluorobenzoic acid (0.15 g, 1.1 mmol) in THF (1.1 mL) was added dropwise over 5 min and the reaction mixture stirred for 1 h –90 °C. The *in situ* generated organolithium reagent was kept at –90 °C and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was washed with Et_2O (3 x 5 mL) and the product isolated as a colorless solid (0.12, 0.40 mmol, 80%). **m.p.** 207 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.61 (s br, 2H), 8.44 (s, 1H), 7.66 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.51 (td, *J* = 8.0, 5.5 Hz, 1H), 7.47 – 7.40 (m, 1H), 2.02 (d, *J* = 12.5 Hz, 2H), 1.78 – 1.54 (m, 4H), 1.47 (s br, 3H), 1.33 – 1.14 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.2 (s), 166.4 (d, *J* = 3.0 Hz), 162.9, 158.9 (d, *J* = 247 Hz), 131.6 (d, *J* = 3.7 Hz), 130.1 (d, *J* = 8.2 Hz), 127.0 (d, *J* = 20.6 Hz), 125.3 (d, *J* = 2.8 Hz), 119.3 (d, *J* = 22.3 Hz), 58.3, 31.7, 25.0, 21.0; **^{19}F NMR** (376 MHz,

[30] W. M. Seganish, P. DeShong, *J. Org. Chem.* **2004**, *69*, 6790-6795.
[31] J. Mortier, J. Moyroud, B. Bennetau, P. A. Cain, *J. Org. Chem.* **1994**, *59*, 4042-4044.

d^6-DMSO) –114.8; **IR** (ATR) ν 3363 (w), 2939 (w), 1683 (s), 1520 (s), 1276 (s), 1243 (s), 756 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{16}FNNaO_5$ ([M+Na]$^+$): 332.0905. Found: 332.0900.



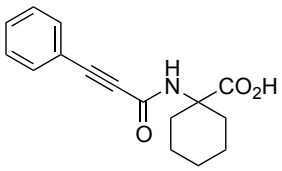
1-(2-(diethylcarbamoyl)-6-methoxybenzamido)cyclohexane-carboxylic acid (67): *Preparation of the organolithium reagent*:[32] To a flame-dried Schlenk-flask was added TMEDA (0.17 mL, 1.1 mmol) and THF (2.2 mL) and cooled to –78 ºC. *sec*-Butyllithium (0.80 mL of a 1.4 M solution in cyclohexane, 1.1 mmol) was added. A solution of *N*,*N*-diethyl-3-methoxybenzamide (0.23 g, 1.1 mmol) in THF (1.1 mL) was added dropwise over 5 min and the reaction mixture stirred for 1 h –78 ºC. The *in situ* generated organolithium reagent was kept at –78 ºC and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was washed with Et_2O (3 x 5 mL) and the product isolated as a colorless solid (0.13 g, 0.35 mmol, 69%). **m.p.** 188 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 11.92 (s, 1H), 7.99 (s, 1H), 7.41 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.77 (dd, *J* = 7.5, 0.8 Hz, 1H), 3.82 (s, 3H), 3.34 (q, *J* = 6.7 Hz, 3H), 3.07 (q, *J* = 7.0 Hz, 2H), 2.02 (d, *J* = 12.2 Hz, 2H), 1.71 – 1.39 (m, 8H), 1.34 – 1.15 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.2, 168.6, 163.9, 156.5, 138.4, 130.5, 123.0, 118.2, 111.8, 58.1, 56.0, 42.6, 38.2, 31.7, 25.1, 20.9, 13.6, 12.4; **IR** (ATR) ν 3274 (w), 2934 (w), 1695 (s), 1660 (s), 1575 (s), 1540 (s), 1273 (s), 1059 (s), 802 (m), 758 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{20}H_{28}N_2NaO_5$ ([M+Na]$^+$): 399.1890. Found: 399.1888.



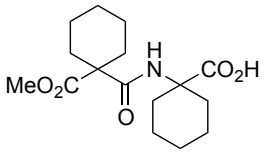
1-(2-(*N*,*N*-diethylsulfamoyl)-5-methylbenzamido)cyclohexane-carboxylic acid (68): *Preparation of the organolithium reagent*: To a flame-dried Schlenk-flask was added *N*,*N*-diethyl-4-methylbenzenesulfonamide[33] (0.25 g, 1.1 mmol) and THF (2.2 mL) and cooled to –78 ºC. *n*-Butyllithium (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol) was added dropwise over 2–3 min and the reaction mixture stirred for 1 h at –78 ºC. The *in situ* generated organolithium reagent was kept at –78 ºC and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was purified by flash column chromatography (slow gradient

[32] R. J. Mills , N. J. Taylor , V. Snieckus, *J. Org. Chem.* **1989**, *54*, 4372-4385.
[33] M. Inman, A. Carbone, C. J. Moody, *J. Org. Chem.* **2012**, *77*, 1217-1232.

CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless foam (0.17 g, 0.44 mmol, 87%). **m.p.** 90 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.14 (s, 1H), 8.31 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.39 (ddd, *J* = 8.2, 1.8, 0.7 Hz, 1H), 7.17 (d, *J* = 0.9 Hz, 1H), 3.23 (q, *J* = 7.1 Hz, 4H), 2.39 (s, 3H), 2.05 (d, *J* = 10.3 Hz, 2H), 1.76 – 1.56 (m, 4H), 1.48 (s br, 3H), 1.33 – 1.14 (m, 1H), 1.00 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.6, 167.2, 142.1, 137.0, 134.3, 129.6, 129.2, 128.4, 58.6, 41.1, 31.7, 25.0, 20.9, 20.8, 14.1; **IR** (ATR) ν 3332 (w), 2935 (m), 1711 (m), 1659 (m), 1319 (s), 1157 (s), 700 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{28}N_2NaO_5S$ ([M+Na]$^+$): 419.1611. Found: 419.1610.

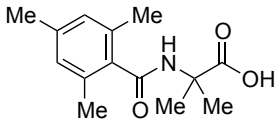


1-(3-phenylpropiolamido)cyclohexanecarboxylic acid (69): *Preparation of the organolithium reagent*: To a flame-dried Schlenk-flask was added ethynylbenzene (0.12 mL, 1.1 mmol) and THF (2.2 mL) and cooled to –78 °C. *n*-Butyllithium (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol) was added dropwise over 2–3 min and the reaction mixture stirred for 30 min at –78 °C. The *in situ* generated organolithium reagent was kept at –78 °C and the product prepared according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was washed with a 1:1-mixture of cyclohexane:Et_2O (2 x 10 mL) and the product isolated as a colorless solid (96 mg, 0.35 mmol, 71%). **m.p.** 163 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.35 (s, 1H), 8.80 (s, 1H), 7.60 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.54 – 7.42 (m, 3H), 1.99 (d, *J* = 13.3 Hz, 2H), 1.77 – 1.62 (m, 2H), 1.59 – 1.42 (m, 5H), 1.32 – 1.17 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 174.9, 152.0, 132.1, 130.2, 128.9, 120.0, 84.3, 82.8, 58.8, 31.5, 24.8, 21.1; **IR** (ATR) ν 3200 (w), 2929 (m), 2853 (m), 2214 (m), 1707 (s), 1616 (s), 1533 (s), 755 (s), 687 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{18}NO_3$ ([M+H]$^+$): 272.1281. Found: 272.1283.

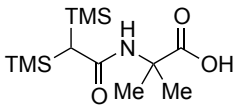


1-(1-(methoxycarbonyl)cyclohexanecarboxamido)cyclohexane-carboxylic acid (70): *Preparation of the organolithium reagent*: To a flame-dried Schlenk-flask was added diisopropylamine (0.16 mL, 1.2 mmol) and THF (1.1 mL) and cooled to –78 °C. *n*-Butyllithium (0.69 mL of a 1.6 M solution in hexanes, 1.1 mmol) was added dropwise over 2–3 min and the reaction mixture stirred for 30 min at –78 °C. A solution of methyl cyclohexanecarboxylate (0.16 g, 1.1 mmol) in THF (1.1 mL) was added dropwise over 2–3 min and the reaction mixture stirred for 30 min at –78 °C. The *in situ* generated organolithium reagent was kept at –78 °C and the product prepared

according to method B by adding 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) in THF (2.5 mL). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless solid (0.11 g, 0.35 mmol, 70%). **m.p.** 115 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.04 (s, 1H), 7.06 (s, 1H), 3.64 (s, 3H), 2.02 (d br, *J* = 13.2 Hz, 2H), 1.93 (s br, 4H), 1.69 – 1.46 (m, 7H), 1.44 – 1.24 (m, 7H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.3, 172.7, 170.0, 58.1, 54.9, 51.9, 31.5, 30.9, 25.0, 24.7, 22.6, 21.2; **IR** (ATR) ν 3388 (w), 2935 (m), 2860 (w), 1741 (s), 1706 (s), 1645 (s), 1520 (s), 1197 (s), 1063 (s), 906 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{24}NO_5$ ($[M–H]^-$): 310.1660. Found: 310.1660.



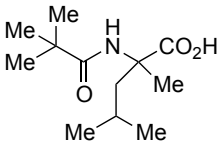
2-methyl-2-(2,4,6-trimethylbenzamido)propanoic acid (71): Prepared according to method A from 4,4-dimethyloxazolidine-2,5-dione (65 mg, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol) and isolated as a colorless solid (0.12 g, 0.47 mmol, 93%). **m.p.** 175 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.83 (s, 2H), 6.16 (s, 1H), 2.30 (s, 6H), 2.28 (s, 3H), 1.69 (s, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.5, 168.5, 137.0, 135.3, 133.9, 127.5, 54.8, 24.8, 20.6, 18.5; **IR** (ATR) ν 3228 (w), 2983 (w), 2918 (w), 1708 (s), 1633 (s), 1551 (s), 850 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{19}NNaO_3$ ($[M+Na]^+$): 272.1257. Found: 272.1261.



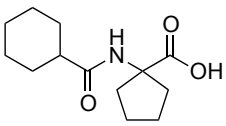
2-(2,2-bis(trimethylsilyl)acetamido)-2-methylpropanoic acid (72): *Preparation of the Grignard reagent*:[34] To a flame-dried Schlenk-flask was added LiCl (0.11 g, 2.5 mmol) and dried with a heat gun under high vacuum for 5 min. Mg turnings (73 mg, 3.0 mmol) were added under N_2 counterflow, followed by THF (1.5 mL). TMSCl and 1,2-dibromoethane (each 2–3 drops) were added and the mixture gently heated until ebullition occurred. The mixture was cooled to 0 °C and a solution of bis(trimethylsilyl)methylbromide (0.48 g, 2.0 mmol) in THF (0.5 mL) was added dropwise over 2–3 min. The reaction mixture was stirred for 30 min at 0 °C until the Grignard formation was complete. Concentration determined by titration: 0.65 M in THF. The product was prepared according to method A from 4,4-dimethyloxazolidine-2,5-dione (65 mg, 0.50 mmol) and (bis(trimethylsilyl)methyl)magnesium bromide LiCl complex (1.6 mL of a 0.65 M solution

[34] K. Groll, S. M. Manolikakes, X. M. du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell, P. Knochel, *Angew. Chem. Int. Ed.* **2013**, *52*, 6776-6780.

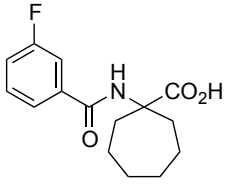
in THF, 1.05 mmol). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless solid (0.12 g, 0.40 mmol, 80%). **m.p.** 150 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 11.90 (s, 1H), 7.58 (s, 1H), 1.58 (s, 1H), 1.28 (s, 6H), 0.05 (s, 18H); **^{13}C NMR** (101 MHz, d^6-DMSO) 1759, 172.0, 54.5, 30.2, 25.1, 0.1; **IR** (ATR) ν 3388 (w), 1957 (w), 2891 (w), 1697 (m), 1509 (s), 1454 (s), 864 (s), 839 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{28}NO_3Si_2$ ([M+H]$^+$): 290.1602. Found: 290.1602.



2,4-dimethyl-2-pivalamidopentanoic acid (73): Prepared according to method A from 4-isobutyl-4-methyloxazolidine-2,5-dione (86 mg, 0.50 mmol) and *tert*-butylmagnesium chloride (1.05 mL of a 1.0 M solution in THF, 1.05 mmol). The crude material was washed with cyclohexane (3 x 5 mL) and the product isolated as a colorless solid (0.10 g, 0.45 mmol, 90%). **m.p.** 105 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.80 (s br, 1H), 7.13 (s, 1H), 1.95 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.70 (dd, *J* = 13.9, 6.6 Hz, 1H), 1.59 – 1.47 (m, 1H), 1.37 (s, 3H), 1.09 (s, 9H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 176.2, 176.0, 58.2, 43.7, 38.2, 27.3, 24.0, 24.0, 23.5, 23.4; **IR** (ATR) ν 3398 (w), 2961 (s), 1722 (m), 1628 (s), 1520 (s), 1447 (s), 1214 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{24}NO_3$ ([M+H]$^+$): 230.1751. Found: 230.1755.

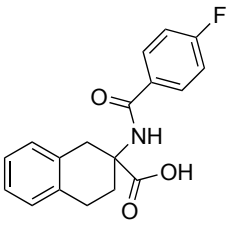


1-(cyclohexanecarboxamido)cyclopentanecarboxylic acid (74): Prepared according to method A from 3-oxa-1-azaspiro[4.4]nonane-2,4-dione (78 mg, 0.50 mmol) and cyclohexylmagnesium chloride (0.81 mL of a 1.3 M solution in THF/toluene 1:1, 1.05 mmol) and isolated as a colorless solid (95 mg, 0.40 mmol, 79%). **m.p.** 185 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 11.95 (s, 1H), 7.87 (s, 1H), 2.16 – 2.07 (m, 1H), 2.04 – 1.91 (m, 2H), 1.87 – 1.77 (m, 2H), 1.73 – 1.52 (m, 9H), 1.36 – 1.10 (m, 5H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.5, 175.0, 64.5, 43.4, 36.2, 29.0, 25.5, 25.2, 24.0; **IR** (ATR) ν 3275 (w), 2929 (w), 1699 (m), 1640 (s), 1544 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{21}NNaO_3$ ([M+Na]$^+$): 262.1414. Found: 262.1416.

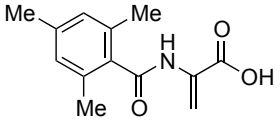


1-(3-fluorobenzamido)cycloheptanecarboxylic acid (75): Prepared according to method A from 3-oxa-1-azaspiro[4.6]undecane-2,4-dione (92 mg, 0.50 mmol) and 3-fluorophenylmagnesium bromide (1.05 mL of a

1.0 M solution in 2-MeTHF, 1.05 mmol) and isolated as a colorless solid (0.10 g, 0.37 mmol, 74%). **m.p.** 175 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.10 (s, 1H), 8.35 (s, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 9.5 Hz, 1H), 7.51 (dd, *J* = 13.9, 7.9 Hz, 1H), 7.38 (td, *J* = 8.4, 1.9 Hz, 1H), 2.09 (s br, 4H), 1.53 (s br, 8H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.6, 164.7 (d, *J* = 2.4 Hz), 161.8 (d, *J* = 244 Hz), 136.8 (d, *J* = 6.9 Hz), 130.3 (d, *J* = 8.0 Hz), 123.8 (d, *J* = 2.7 Hz), 118.0 (d, *J* = 21.2 Hz), 114.3 (d, *J* = 22.7 Hz), 62.1, 35.1, 29.6, 22.4; **^{19}F NMR** (376 MHz, d^6-DMSO) –113.1; **IR** (ATR) ν 3423 (w), 3070 (w), 2925 (m), 1734 (s), 1579 (s), 1523 (s), 1208 (m), 1181 (m), 755 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{19}FNO_3$ ([M+H]$^+$): 280.1343. Found: 280.1350.

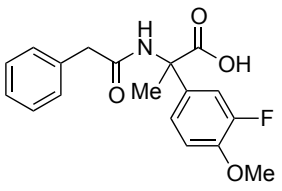


2-(4-fluorobenzamido)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (76): Prepared according to method A from 3,4-dihydro-1*H*-spiro[naphthalene-2,4'-oxazolidine]-2',5'-dione (0.11 g, 0.50 mmol) and 4-fluorophenylmagnesium bromide (1.3 mL of a 0.80 M solution in THF, 1.05 mmol). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless solid (0.12 g, 0.37 mmol, 75%). **m.p.** 185 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.41 (s, 1H), 8.47 (s, 1H), 7.87 – 7.80 (m, 2H), 7.30 – 7.21 (m, 2H), 7.08 (s br, 4H), 3.30 (d, *J* = 10.3 Hz, 1H), 3.18 (d, *J* = 16.8 Hz, 1H), 2.85 (ddd, *J* = 15.7, 9.7, 5.6 Hz, 1H), 2.73 (dt, *J* = 16.9, 5.3 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.05 (ddd, *J* = 13.3, 9.9, 5.7 Hz, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 174.9, 165.8, 163.9 (d, *J* = 248 Hz), 134.9, 133.9, 130.7 (d, *J* = 2.8 Hz), 130.2 (d, *J* = 9.0 Hz), 129.1, 128.2, 125.5 (d, *J* = 8.0 Hz), 115.0 (d, *J* = 21.7 Hz), 57.6, 36.4, 28.7, 25.0; **^{19}F NMR** (376 MHz, d^6-DMSO) –109.4; **IR** (ATR) ν 3257 (br), 2903 (br), 1703 (s), 1636 (s), 1605 (m), 1545 (s), 1505 (s), 849 (m), 745 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{16}FNNaO_3$ ([M+Na]$^+$): 336.1006. Found: 336.1014.

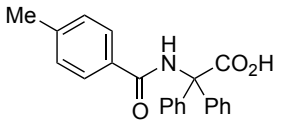


2-(2,4,6-trimethylbenzamido)acrylic acid (77): Prepared according to method A from 4-methyleneoxazolidine-2,5-dione (57 mg, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol) and isolated as a colorless solid (92 mg, 0.39 mmol, 79%). **m.p.** 155 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 13.13 (s, 1H), 9.34 (s, 1H), 6.87 (s, 2H), 6.05 (s, 1H), 5.74 (s, 1H), 2.25 (s, 3H), 2.20 (s, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 168.6, 165.0, 137.7, 135.0, 134.0, 133.7, 127.7, 110.4, 20.7, 18.8; **IR** (ATR) ν 3371 (w), 2921 (br), 1707 (m), 1635 (s),

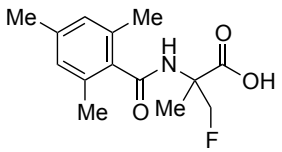
1508 (s), 1431 (m), 897 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{16}NO_3$ ($[M+H]^+$): 234.1125. Found: 234.1125.



2-(3-fluoro-4-methoxyphenyl)-2-(2-phenylacetamido)propanoic acid (77): Prepared according to method A from 4-(3-fluoro-4-methoxyphenyl)-4-methyloxazolidine-2,5-dione (0.12 g, 0.50 mmol) benzylmagnesium chloride (0.53 mL of a 2.0 M solution in THF, 1.05 mmol. *Attention: This Grignard tends to freeze inside the syringe*) and isolated as a colorless solid (0.12 g, 0.35 mmol, 70%). **m.p.** 200 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.63 (s, 1H), 8.46 (s, 1H), 7.33 – 7.25 (m, 5H), 7.23 (dd, *J* = 5.5, 3.1 Hz, 1H), 7.19 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.12 (t, *J* = 8.8 Hz, 1H), 3.82 (s, 3H), 3.53 (s, 2H), 1.74 (s, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 173.2, 169.7, 150.9 (d, *J* = 243 Hz), 146.3 (d, *J* = 10.5 Hz), 136.3, 133.9 (d, *J* = 5.7 Hz), 129.0, 128.2, 126.3, 122.5 (d, *J* = 3.3 Hz), 114.3 (d, *J* = 19.6 Hz), 113.2 (d, *J* = 1.7 Hz), 60.4, 56.0, 42.0, 23.2; **^{19}F NMR** (376 MHz, d^6-DMSO) –135.6; **IR** (ATR) ν 3349 (m), 1171 (m), 1602 (s), 1516 (s), 1229 (s), 1139 (m), 699 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{19}FNO_4$ ($[M+H]^+$): 332.1293. Found: 332.1298.

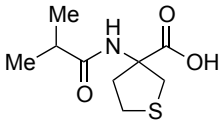


2-(4-methylbenzamido)-2,2-diphenylacetic acid (78): Prepared according to method A from 4,4-diphenyloxazolidine-2,5-dione (0.13 g, 0.50 mmol) and *p*-tolylmagnesium bromide (1.1 mL of a 0.95 M solution in THF, 1.05 mmol). The crude material was washed with a 1:1-mixture of cyclohexane:Et_2O (3 x 5 mL) and the product isolated as a colorless solid (0.13 g, 0.38 mmol, 75%). **m.p.** 210 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 13.04 (s, 1H), 8.96 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.3 Hz, 4H), 7.39 – 7.21 (m, 8H), 2.36 (s, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 172.0, 165.9, 141.4, 140.9, 131.3, 128.8, 128.4, 127.7, 127.5, 127.1, 68.4, 21.0; **IR** (ATR) ν 3367 (w), 2792 (br), 1713 (m), 1628 (m), 1488 (s), 1240 (m), 695 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{22}H_{19}NNaO_3$ ($[M+Na]^+$): 368.1257. Found: 368.1258.

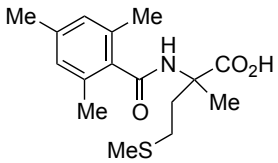


3-fluoro-2-methyl-2-(2,4,6-trimethylbenzamido)propanoic acid (80): *Prepared according to a slightly modified version of method A*: 4-(fluoromethyl)-4-methyloxazolidine-2,5-dione (74 mg, 0.50 mmol) and THF (2.5 mL) were added to a flame-dried Schlenk-flask. TMSCl (0.13 mL, 1.05 mmol)

was added and the reaction mixture cooled to –78 °C and stirred for at least 5 min. Mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol) was added dropwise over 5 min directly into the solution. The reaction mixture was slowly warmed to RT over the course of 5 h. Workup was performed according to method A. The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless foam (0.10 g, 0.38 mmol, 76%). **m.p.** 175 °C (decomposition); **^{1}H NMR** (400 MHz, d^6-DMSO) 12.80 (s, 1H), 8.61 (s, 1H), 6.83 (s, 2H), 4.92 (dd, *J* = 48.4, 9.0 Hz, 1H), 4.58 (dd, *J* = 47.2, 8.9 Hz, 1H), 2.23 (s, 3H), 2.20 (s, 6H), 1.40 (s, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 172.9 (d, *J* = 7.2 Hz), 169.1 (s), 137.3 (s), 134.8 (s), 134.0 (s), 127.6 (s), 83.5 (d, *J* = 170 Hz), 57.6 (d, *J* = 18.7 Hz), 20.6 (s), 20.0 (d, *J* = 4.6 Hz), 18.5 (s); **^{19}F NMR** (376 MHz, d^6-DMSO) –230.9; **IR** (ATR) ν 3226 (br), 1719 (m), 1633 (s), 1024 (s), 855 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{18}FNNaO_3$ ([M+Na]$^+$): 290.1163. Found: 290.1169.

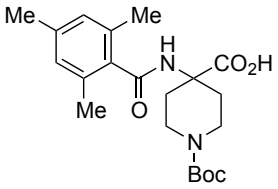


3-isobutyramidotetrahydrothiophene-3-carboxylic acid (81): Prepared according to method A from 3-oxa-7-thia-1-azaspiro[4.4]nonane-2,4-dione (87 mg, 0.50 mmol) and isopropylmagnesium chloride (0.62 mL of a 1.7 M solution in THF, 1.05 mmol) and isolated as a colorless solid (91 mg, 0.42 mmol, 84%). **m.p.** 127 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.48 (s, 1H), 8.09 (s, 1H), 3.23 (d, *J* = 11.3 Hz, 1H), 3.04 (dd, *J* = 11.3, 0.8 Hz, 1H), 2.93 – 2.82 (m, 2H), 2.46 – 2.35 (m, 2H), 2.21 – 2.07 (m, 1H), 0.99 (d, *J* = 4.2 Hz, 3H), 0.97 (d, *J* = 4.2 Hz, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 176.4, 172.9, 67.2, 38.2, 33.4, 28.8, 19.4, 19.2; **IR** (ATR) ν 3341 (w), 3153 (br), 2978 (w), 1747 (s), 1608 (m), 1523 (s), 1209 (s), 1101 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_9H_{15}NNaO_3S$ ([M+Na]$^+$): 240.0665. Found: 240.0669.

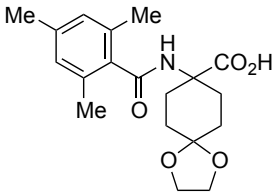


2-methyl-4-(methylthio)-2-(2,4,6-trimethylbenzamido)butanoic acid (82): Prepared according to method A from 4-methyl-4-(2-(methylthio)ethyl)oxazolidine-2,5-dione (95 mg, 0.5 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol) and isolated as a colorless solid (0.13 g, 0.42 mmol, 84%). **m.p.** 180 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.38 (s, 1H), 8.41 (s, 1H), 6.83 (s, 2H), 2.46 (d, *J* = 8.6 Hz, 1H), 2.22 (s, 3H), 2.21 (s, 6H), 2.19 – 2.08 (m, 2H), 2.02 – 1.93 (m, 1H), 1.40 (s, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.1, 169.2, 137.6, 135.7, 134.5, 128.1, 58.3, 37.1, 28.2, 22.6, 21.1, 19.2, 15.1;

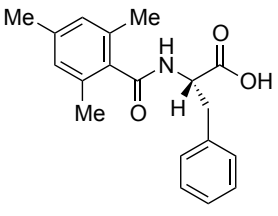
IR (ATR) ν 3228 (w), 2917 (w), 1704 (s), 1629 (s), 1537 (s), 1286 (s), 1216 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{16}H_{23}NNaO_3S$ ($[M+Na]^+$): 332.1291. Found: 332.1294.



1-(*tert*-1-(*tert*-butoxycarbonyl)-4-(2,4,6-trimethylbenzamido) piperidine-4-carboxylic acid (83): Prepared according to method A from *tert*-butyl 2,4-dioxo-3-oxa-1,8-diazaspiro[4.5]decane-8-carboxylate (0.14 g, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:2) and the product isolated as a colorless solid (0.16 g, 0.40 mmol, 80%). **m.p.** 145 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.47 (s, 1H), 8.56 (s, 1H), 6.84 (s, 2H), 3.68 (d, *J* = 13.6 Hz, 2H), 3.13 (s br, 2H), 2.22 (s br, 9H), 2.02 (d, *J* = 13.8 Hz, 2H), 1.91 – 1.74 (m, 2H), 1.40 (s, 9H); **^{13}C NMR** (101 MHz, d^6-DMSO) 174.6, 169.5, 153.8, 137.2, 135.2, 134.1, 127.6, 78.7, 56.5, 31.3, 28.1, 20.6, 18.9; **IR** (ATR) ν 3279 (br), 2975 (w), 2929 (w), 1738 (m), 1639 (s), 1426 (s), 1154 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{30}N_2NaO_5$ ($[M+Na]^+$): 413.2047. Found: 413.2050.



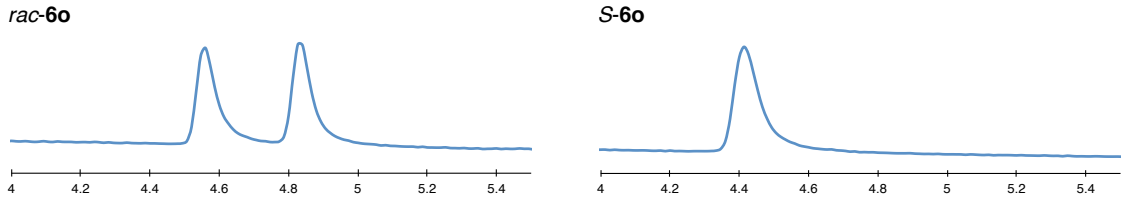
8-(2,4,6-trimethylbenzamido)-1,4-dioxaspiro[4.5]decane-8-carboxylic acid (84): Prepared according to method A from ethylene glycol protected 8-oxo-3-oxa-1-azaspiro[4.5]decane-2,4-dione (0.11 g, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol). The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless solid (0.13 g, 0.39 mmol, 77%). **m.p.** 207 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.30 (s, 1H), 8.45 (s, 1H), 6.83 (s, 2H), 3.85 (s, 4H), 2.22 (s br, 9H), 2.17 – 2.06 (m, 2H), 2.04 – 1.89 (m, 2H), 1.73 (td, *J* = 13.0, 3.9 Hz, 2H), 1.65 – 1.51 (m, 2H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.2, 169.5, 137.0, 135.4, 134.0, 127.6, 107.3, 63.6, 57.2, 30.1, 29.1, 20.6, 18.9; **IR** (ATR) ν 3276 (br), 2956 (br), 1702 (m), 1638 (m), 1508 (m), 1094 (s), 894 (m), 850 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{25}NNaO_5$ ($[M+Na]^+$): 370.1625. Found: 370.1626.



(*S*)-3-phenyl-2-(2,4,6-trimethylbenzamido)propanoic acid (85): Prepared according to method A from (*S*)-4-benzyloxazolidine-2,5-dione (96 mg, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL

of a 1.0 M solution in Et_2O, 1.05 mmol). After the addition of the Grignard reagent the reaction mixture was slowly warmed to RT over the course of 5 h. Workup was performed according to method A. The crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 100:0 to 100:3) and the product isolated as a colorless solid (0.12 g, 0.38 mmol, 75%). **$[\alpha]^{25}_D$** (c = 0.5, MeOH): –47.2; **m.p.** 80 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 12.71 (s, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.25 (m, 4H), 7.24 – 7.15 (m, 1H), 6.76 (s, 2H), 4.69 (ddd, *J* = 12.0, 8.4, 4.0 Hz, 1H), 3.18 (dd, *J* = 13.9, 4.0 Hz, 1H), 2.85 (dd, *J* = 13.9, 11.5 Hz, 1H), 2.19 (s, 3H), 1.91 (s, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 173.2, 169.2, 138.0, 137.0, 135.4, 133.8, 129.1, 128.1, 127.4, 126.3, 53.2, 36.2, 20.6, 18.4; **IR** (ATR) ν 2921 (br), 1719 (m), 1610 (s), 1517 (s), 1180 (s), 848 (s), 697 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{22}NO_3$ ($[M+H]^+$): 312.1594. Found: 312.1595; **SFC** column: Daicel Chiralpak OJH (4.6 x 250 mm); gradient: 5% *i*PrOH in CO_2 to 50% *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm.

The racemate was prepared according to the same procedure from 4-benzyloxazolidine-2,5-dione (96 mg, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of 1.0 M solution in Et_2O) and isolated as a colorless solid after column chromatography (0.11 g, 0.37 mmol, 73%).



4.2. General Procedure: Synthesis of *N*-Carboxyanhydrides (NCAs)

Attention: All reactions (including evaporation of solvents) were performed in a ventilated hood due to possible formation of toxic phosgene and/or HCl vapors.

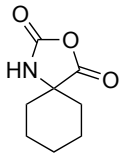
Method A from amino acid:
Apparature: Flame-dried three-necked flask with an attached reflux condenser and an N_2 inlet on the side. On top of the reflux condenser a gas outlet, which is passed into a 1 M NaOH solution, was attached to quench formed HCl vapors. *Reaction procedure*: Under N_2 to the three-necked flask was added the amino acid (1.0 equiv) and suspended in dry THF (0.25 M) and heated to 50 °C. Triphosgene (0.33 equiv) was added in one portion and the reaction mixture stirred at 50 °C for 1 h. If the reaction mixture was homogeneous at this point, no further triphosgene was added and the reaction mixture directly cooled to RT. If the reaction mixture was heterogeneous at this point, a second portion of triphosgene (0.033 equiv) was added and the reaction mixture stirred for another 2 h at 50 °C, and then cooled to RT. The reaction mixture was filtered and the filtrate concentrated under reduced pressure at 35 °C. The obtained crude material was purified by flash column chromatography or trituration from THF/pentane.

Method B from *N*-Boc protected amino acid
In a flame-dried round-bottom flask under N_2 the *N*-Boc amino acid (1.0 equiv) was dissolved in dry CH_2Cl_2 (0.2 M) and cooled to 0 °C. Phosphorus trichloride (1.1 equiv) was added in one portion and the reaction mixture warmed to RT and stirred until TLC showed disappearance of the *N*-Boc amino acid. The reaction mixture was filtered, the filtrate concentrated under reduced pressure at 35 °C and the obtained crude material was purified by flash column chromatography.

Method C from *N*-Cbz protected amino acid
In a flame-dried round-bottom flask under N_2 the *N*-Cbz amino acid (1.0 equiv) was dissolved in dry CH_2Cl_2 (0.2 M). Oxalyl chloride (1.5 equiv) was added, followed by a few drops of DMF and the reaction mixture stirred at RT until TLC showed disappearance of the *N*-Cbz amino acid. The reaction mixture was concentrated under reduced pressure at 35 °C and the obtained crude material was purified by flash column chromatography.

Important Notes:

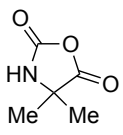
For method A, the amino acid should be grinded to a fine powder and vigorously dried at elevated temperature under high vacuum for several hours before use. We think that the yields could be further improved by using phosgene instead of triphosgene, but due to safety concerns we did not perform such reactions.



3-oxa-1-azaspiro[4.5]decane-2,4-dione (36): Prepared according to method A from 1-aminocyclohexanecarboxylic acid (1.4 g, 10 mmol) and triphosgene (0.99 g, 3.3 mmol + 99 mg, 0.33 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 1:1) and the product isolated as a colorless solid (0.93 g, 5.5 mmol, 55%)

Prepared according to method B from 1-((*tert*-butoxycarbonyl)amino)cyclohexanecarboxylic acid (1.2 g, 5.0 mmol) and phosphorus trichloride (0.48 mL, 5.5 mmol). Reaction was complete after 1 h at RT. The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 1:1) and the product isolated as a colorless solid (0.73 g, 4.3 mmol, 86%)

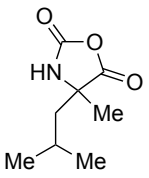
Prepared according to method C from 1-(((benzyloxy)carbonyl)amino)cyclohexanecarboxylic acid (1.4 g, 5.0 mmol) and oxalyl chloride (0.64 mL, 7.5 mmol). Reaction was complete after 2 h at RT. The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 1:1) and the product isolated as a colorless solid (0.79 g, 4.7 mmol, 93%). **^{1}H NMR** (400 MHz, d^{6}-DMSO) 9.47 (s, 1H), 1.76 – 1.70 (m, 4H), 1.69 – 1.60 (m, 2H), 1.57 – 1.43 (m, 3H), 1.41 – 1.27 (m, 1H); **^{13}C NMR** (101 MHz, d^{6}-DMSO) 173.7, 150.8, 62.3, 33.2, 24.1, 20.7; **IR** (ATR) ν 3348 (m), 2938 (m), 1855 (m), 1788 (s), 911 (s), 770 (s) cm^{-1}. Spectral data were consistent with previous report.[35]



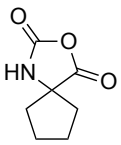
4,4-dimethyloxazolidine-2,5-dione: Prepared according to method A from 2-amino-2-methylpropanoic acid (1.0 g, 10 mmol) and triphosgene (0.99 g, 3.3 mmol + 99 mg, 0.33 mmol). The crude material was dissolved in a minimal amount of THF (3-5 mL), pentane (25 mL) was added and the flask placed into a freezer overnight. The formed precipitate was filtered off, washed with a small amount of pentane and dried under high vacuum (0.73 g, 5.7 mmol, 57%). **m.p.** 95 ºC; **^{1}H NMR** (400 MHz, d^{6}-

[35] M. Frizler, F. Lohr, M. Lülsdorff, M. Gütschow, *Chem. Eur. J.* **2011**, *17*, 11419-11423.

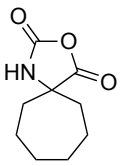
DMSO) 9.13 (s, 1H), 1.42 (s br, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 174.6, 150.4, 59.3, 24.7; **IR** (ATR) ν 3296 (br), 1839 (m), 1757 (s), 1257 (m), 906 (s), 762 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_5H_7NO_3$ (M^+): 129.0420. Found: 129.0419.



4-isobutyl-4-methyloxazolidine-2,5-dione: Prepared according to method A from 2-amino-2,4-dimethylpentanoic acid (0.73 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 2:1) and the product isolated as a colorless solid (0.59 g, 3.4 mmol, 69%). **m.p.** 40 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.80 (s, 1H), 1.90 – 1.67 (m, 3H), 1.54 (s, 3H), 0.97 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 173.2, 152.3, 63.3, 46.3, 25.6, 24.7, 24.1, 22.9; **IR** (ATR) ν 3271 (s), 2965 (m), 1838 (m), 1759 (s), 1334 (m), 923 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_4H_5NO_3$ ($[M–C_4H_8]^+$): 115.0264. Found: 115.0264.

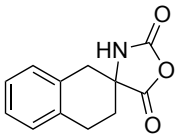


3-oxa-1-azaspiro[4.4]nonane-2,4-dione: Prepared according to method A from 1-aminocyclopentanecarboxylic acid (0.65 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol + 50 mg, 0.17 mmol). The crude material was dissolved in a minimal amount of THF (2–3 mL), pentane (10 mL) was added and the flask placed into a freezer overnight. The formed precipitate was filtered off, washed with a small amount of pentane and dried under high vacuum (0.39 g, 2.5 mmol, 50%). **m.p.** 130 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 9.28 (s, 1H), 2.15 – 2.00 (m, 2H), 1.91 – 1.81 (m, 2H), 1.79 – 1.65 (m, 4H); **^{13}C NMR** (101 MHz, d^6-DMSO) 175.3, 150.8, 68.1, 37.7, 24.4; **IR** (ATR) ν 3221 (br), 2971 (w), 1838 (m), 1769 (s), 1743 (s), 933 (s), 758 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_7H_9NO_3$ (M^+): 155.0582. Found: 155.0576.

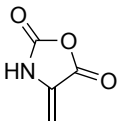


3-oxa-1-azaspiro[4.6]undecane-2,4-dione: Prepared according to method A from 1-aminocycloheptanecarboxylic acid (0.79 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol + 50 mg, 0.17 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 2:1) and the product isolated as a colorless solid (0.47 g, 2.6 mmol, 51%). **m.p.** 147 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.21 (s br, 1H), 2.11 (ddd, *J* = 14.0, 10.5, 1.8 Hz, 2H), 1.90 (ddd, *J* = 13.9, 7.9, 1.3 Hz, 2H), 1.88 – 1.76 (m, 2H), 1.71 – 1.61 (m, 4H), 1.60 – 1.47 (m, 2H); **^{13}C NMR** (101 MHz,

$CDCl_3$) 173.5, 152.6, 66.1, 37.6, 28.7, 22.9; **IR** (ATR) ν 3293 (m), 2930 (m), 2861 (w), 1834 (m), 1746 (s), 1338 (m), 918 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_8H_{12}NO$ ($[M–CO_2H]^+$): 138.0913. Found: 138.0915.

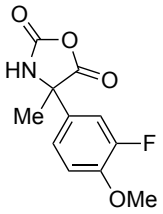


3,4-dihydro-1*H*-spiro[naphthalene-2,4'-oxazolidine]-2',5'-dione: Prepared according to method A from 2-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid hydrate (0.25 g, 1.3 mmol, the exact degree of hydration was not stated on the commercially available product) and triphosgene (0.13 g, 0.44 mmol + 13 mg, 0.044 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 2:1) and the product isolated as a colorless solid (0.13 g, 0.52 mmol, 40%). **m.p.** 150 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 9.43 (s, 1H), 7.19 – 7.12 (m, 3H), 7.11 – 7.05 (m, 1H), 3.23 (d, *J* = 16.9 Hz, 1H), 3.05 (d, *J* = 17.0 Hz, 1H), 2.97 – 2.84 (m, 2H), 2.09 (t, *J* = 6.9 Hz, 2H); **^{13}C NMR** (101 MHz, d^6-DMSO) 173.5, 150.8, 134.4, 131.6, 128.9, 128.6, 126.3, 126.1, 61.1, 36.7, 30.0, 24.5; **IR** (ATR) ν 3267 (br), 1840 (m), 1785 (s), 1337 (m), 929 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{12}H_{11}NO_3$ (M^+): 217.0733. Found: 217.0730.



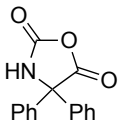
4-methyleneoxazolidine-2,5-dione: Prepared according to method C from 2-(((benzyloxy)carbonyl)amino)acrylic acid[36] (0.33 g, 1.5 mmol) and oxalyl chloride (0.19 mL, 2.3 mmol). Reaction was complete after 2 h at RT. The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 2:1 to 1:1) and the product isolated as a colorless solid (0.11 g, 1.0 mmol, 65%). **m.p.** 100 ºC (decomposition); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.62 (s, 1H), 5.59 (d, *J* = 2.9 Hz, 1H), 5.17 (d, *J* = 2.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 159.2, 149.4, 131.1, 100.2; **IR** (ATR) ν 3254 (br), 1833 (m), 1753 (s), 1672 (s), 1297 (s), 919 (s), 790 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_4H_3NO_3$ (M^+): 113.0107. Found: 113.0107. *Important: This compound decomposed after several weeks at room temperature.*

[36] M. Ihara, Y. Haga, M. Yonekura, T. Ohsawa, K. Fukumoto, T. Kametani, *J. Am. Chem. Soc.* **1983**, *105*, 7345-7352.

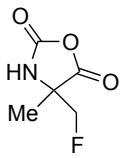


4-(3-fluoro-4-methoxyphenyl)-4-methyloxazolidine-2,5-dione: *Amino acid prepared via Bucherer-Bergs reaction*: To a 100 mL round-bottom flask was added 1-(3-fluoro-4-methoxyphenyl)ethanone 2.52 g, 15.0 mmol), EtOH (15 mL) and H_2O (15 mL). Then $(NH_4)_2CO_3$ (5.76 g, 60 mmol) and KCN (1.95 g, 30 mmol) were added an the reaction mixture heated to 55 ºC and stirred for 2 days. The reaction mixture was cooled to RT and then placed into a fridge overnight. The precipitated hydantoin was collected by filtration, washed with cold H_2O (2 x 15 mL) and dried under high vacuum at elevated temperature for several hours (62%). The hydantoin was dissolved in 3 M aq KOH (45 mL) and refluxed (oil bath 130 ºC) for 2 days. The reaction mixture was cooled to RT and then to 0 ºC and the pH of the solution was adjusted to 7 by careful addition of conc. HCl under vigorous stirring. The precipitated, colorless amino acid was collected by filtration, washed with cold H_2O (2 x 15 mL) and dried under high vacuum at elevated temperature for several hours (89% from hydantoin). The amino acid (1.07 g, 5.00 mmol) was suspended in H_2O (20 mL) and dioxane (5 mL), Na_2CO_3 (1.59 g, 15 mmol) was added and the suspension cooled to 0 ºC. Then benzyl chloroformate (0.785 mL, 5.50 mmol) was added dropwise over 5 min and the reaction mixture was warmed to RT and stirred vigorously overnight. MTBE (50 mL) and H_2O (40 mL) were added and the phases separated. The aqueous phase was acidified to pH 1 with 3 M aq HCl and extracted with CH_2Cl_2 (3 x 100 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the Cbz-protected amino acid as a colorless solid (30%).

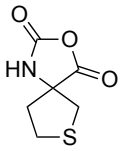
NCA prepared according to method C from 2-(((benzyloxy)carbonyl)amino)-2-(3-fluoro-4-methoxyphenyl)propanoic acid (347 mg, 1.0 mmol) and oxalyl chloride (129 µL, 1.5 mmol). Reaction was complete after 2 h at RT. The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 4:1 to 2:1) and the product isolated as a colorless solid (208 mg, 0.870 mmol, 87%) **m.p.** 122 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 9.81 (s, 1H), 7.36 (dd, *J* = 12.7, 2.1 Hz, 1H), 7.27 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.23 (t, *J* = 8.6 Hz, 1H), 3.85 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (101 MHz, d^6-DMSO) 172.3, 151.3 (d, *J* = 245 Hz), 150.4, 147.3 (d, *J* = 10.4 Hz), 130.7 (d, *J* = 5.9 Hz), 121.6 (d, *J* = 3.5 Hz), 114.0 (d, *J* = 1.7 Hz), 113.3 (d, *J* = 20.1 Hz), 63.8 (d, *J* = 1.4 Hz), 56.1, 24.9; **IR** (ATR) ν 3152 (br), 1841 (w), 1784 (s), 1520 (m), 1273 (m), 923 (s), 755 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{11}H_{10}FNO_4$ (M^+): 239.0588. Found: 239.0590.



4,4-diphenyloxazolidine-2,5-dione: Prepared according to method A from 2-amino-2,2-diphenylacetic acid (1.1 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol + 50 mg, 0.17 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 4:1 to 2:1) and the product isolated as a colorless solid (0.87 g, 3.4 mmol, 69%). **m.p.** 167 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.53 (s, 1H), 7.44 – 7.39 (m, 6H), 7.39 – 7.35 (m, 4H), 7.36 (d, *J* = 2.3 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.0, 152.0, 137.5, 129.5, 129.3, 126.6, 71.9; **IR** (ATR) ν 3218 (w), 3148 (m), 1843 (m), 1765 (s), 1349 (m), 950 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{15}H_{11}NO_3$ (M^+): 253.0733. Found: 253.0728.



4-(fluoromethyl)-4-methyloxazolidine-2,5-dione: Prepared according to method B from 2-((*tert*-butoxycarbonyl)amino)-3-fluoro-2-methylpropanoic acid[37] (0.55 g, 2.5 mmol) and phosphorus trichloride (0.24 mL, 2.8 mmol). Reaction was complete after stirring overnight at RT. The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 1:1) and the product isolated as a colorless solid (0.30 g, 2.0 mmol, 82%). **m.p.** 80 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.61 (s, 1H), 4.64 (dd, *J* = 45.9, 9.8 Hz, 1H), 4.42 (dd, *J* = 46.9, 9.8 Hz, 1H), 1.55 (d, *J* = 2.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 169.8 (d, *J* = 4.2 Hz), 151.6 (s), 83.9 (d, *J* = 181.7 Hz), 64.0 (d, *J* = 19.1 Hz), 18.9 (d, *J* = 4.1 Hz); **IR** (ATR) ν 3310 (br), 1836 (w), 1793 (s), 1754 (s), 1287 (m), 918 (s) cm^{-1}; **^{19}F NMR** (376 MHz, d^6-DMSO) –223.7; **HRMS** (EI) *m/z* calcd for $C_5H_6FNO_3$ (M^+): 147.0326. Found: 147.0329.

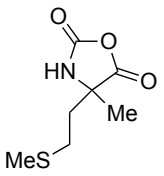


3-oxa-7-thia-1-azaspiro[4.4]nonane-2,4-dione: *Amino acid prepared via Bucherer-Bergs reaction*: To a 100 mL round-bottom flask was added dihydrothiophen-3(2*H*)-one (1.71 mL, 20.0 mmol), EtOH (20 mL) and H_2O (20 mL). Then $(NH_4)_2CO_3$ (5.76 g, 60 mmol) and KCN (1.95 g, 30 mmol) were added an the reaction mixture heated to 55 ºC and stirred for 24 h. The reaction mixture was cooled to RT and then placed into a fridge overnight. The precipitated hydantoin was collected by filtration, washed with cold H_2O (2 x 15 mL) and dried under high vacuum at elevated temperature for several hours (53%). The hydantoin was dissolved in 3 M aq KOH (53 mL) and refluxed (oil bath 130 ºC) for 24 h. The reaction mixture was cooled to RT and then to 0 ºC and the pH of

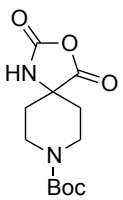
[37] J. McConathy, L. Martarello, E. J. Malveaux, V. M. Camp, N. E. Simpson, C. P. Simpson, G. D. Bowers, J. J. Olson, M. M. Goodman, *J. Med. Chem.* **2002**, *45*, 2240-2249.

the solution was adjusted to 7 by careful addition of conc. HCl under vigorous stirring. The precipitated, colorless amino acid was collected by filtration, washed with cold H_2O (2 x 15 mL) and dried under high vacuum at elevated temperature for several hours (73% from hydantoin). Spectral data were consistent with previous report.[38]

Prepared according to method A from 3-aminotetrahydrothiophene-3-carboxylic acid (0.74 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol + 50 mg, 0.17 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 1:1) and the product isolated as a colorless solid (0.37 g, 2.1 mmol, 43%). **m.p.** 137 °C; **^{1}H NMR** (400 MHz, d^6-DMSO) 9.56 (s, 1H), 3.20 (d, *J* = 11.7 Hz, 1H), 3.10 (dd, *J* = 11.8, 0.9 Hz, 1H), 3.05 (ddd, *J* = 11.1, 7.7, 3.6 Hz, 1H), 2.95 (td, *J* = 10.3, 6.1 Hz, 1H), 2.42 (ddd, *J* = 9.7, 5.1, 3.7 Hz, 1H), 2.22 (ddd, *J* = 13.0, 9.9, 7.7 Hz, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 172.0, 150.5, 70.3, 40.3, 29.0; **IR** (ATR) ν 3238 (w), 3147 (w), 2946 (w), 1797 (s), 1288 (m), 935 (s), 751 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_6H_7NO_3S$ (M^+): 173.0141. Found: 173.0144.



4-methyl-4-(2-(methylthio)ethyl)oxazolidine-2,5-dione: Prepared according to method A from 2-amino-2-methyl-4-(methylthio)butanoic acid (0.82 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 3:1 to 1:1) and the product isolated as a slightly yellow, sticky solid (0.52 g, 2.7 mmol, 55%). **m.p.** 175 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.50 (s, 1H), 2.63 (ddd, *J* = 13.0, 8.3, 4.6 Hz, 1H), 2.51 (dt, *J* = 13.4, 8.2 Hz, 1H), 2.24 (dt, *J* = 14.7, 8.2 Hz, 1H), 2.09 (s, 3H), 2.05 (ddd, *J* = 14.7, 8.3, 4.6 Hz, 1H), 1.57 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 172.5, 151.7, 63.0, 36.2, 28.6, 24.4, 15.4; **IR** (ATR) ν 3284 (br), 2951 (w), 1778 (w), 1649 (s), 1527 (s), 1438 (s), 1218 (m), 911 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_7H_{11}NO_3S$ (M^+): 189.0454. Found: 189.0454.

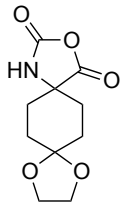


***tert*-butyl 2,4-dioxo-3-oxa-1,8-diazaspiro[4.5]decane-8-carboxylate**: Prepared according to method A from 4-amino-1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid[39] (1.2 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol + 50 mg, 0.17 mmol). The crude material was purified by flash column chromatography

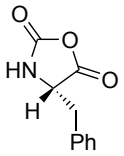
[38] M. Obaa, A. Shimabukuroa, M. Onoa, M. Doib, M. Tanaka, *Tetrahedron Asymm.* **2013**, *24*, 464-467.

[39] L. G. J. Hammarström, Y. Fu, S. Vail, R. P. Hammer, M. L. McLaughlin, *Org. Synth.* **2005**, *81*, 213-224.

(gradient cyclohexane:EtOAc 2:1 to 1:1) and the product isolated as a colorless solid (0.70 g, 2.6 mmol, 52%). **m.p.** 200 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.83 (s, 1H), 3.83 (dd, *J* = 12.7, 7.7 Hz, 2H), 3.48 – 3.32 (m, 2H), 2.15 – 1.99 (m, 2H), 1.87 – 1.70 (m, 2H), 1.47 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) 171.0, 154.5, 151.6, 80.8, 61.1, 39.5, 33.7, 28.5; **IR** (ATR) ν 3229 (br), 1833 (w), 1777 (s), 1651 (s), 1427 (s), 1162 (s), 925 (s), 755 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{12}H_{18}N_2O_5$ (M^+): 270.1210. Found: 270.1217.



8-oxo-3-oxa-1-azaspiro[4.5]decane-2,4-dione ethylene glycol acetale: Prepared according to method A from 8-amino-1,4-dioxaspiro[4.5]decane-8-carboxylic acid (0.28 g, 1.4 mmol) and triphosgene (0.14 g, 0.47 mmol + 14 mg, 0.047 mmol). The crude material was dissolved in a minimal amount of THF (1-2 mL), pentane (7 mL) was added and the flask placed into a freezer overnight. The formed precipitate was filtered off, washed with a small amount of pentane and dried under high vacuum (0.19 g, 0.83 mmol, 60%). **m.p.** 190 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 9.53 (s, 1H), 3.88 (s, 4H), 2.01 – 1.83 (m, 4H), 1.81 – 1.58 (m, 4H); **^{13}C NMR** (101 MHz, d^6-DMSO) 173.6, 150.8, 106.3, 63.8, 63.8, 61.3, 31.4, 29.7; **IR** (ATR) ν 3322 (m), 2953 (w), 1837 (m), 1771 (s), 1320 (m), 1265 (m), 1094 (m), 926 (s), 894 (s) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_8H_9NO_5$ ($[M-C_2H_4]^+$): 199.0475. Found: 199.0478.

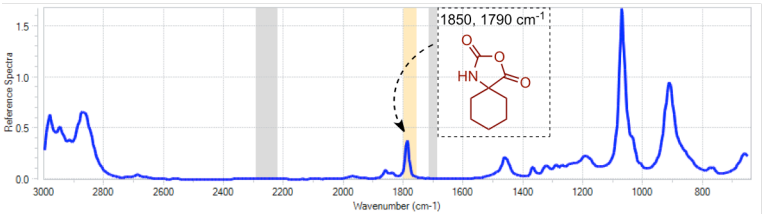


***(S)*-4-benzyloxazolidine-2,5-dione**: Prepared according to method A from L-phenylalanine (0.83 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol + 50 mg, 0.17 mmol). The crude material was dissolved in a minimal amount of THF (3-5 mL), pentane (25 mL) was added and the flask placed into a freezer overnight. The formed precipitate was filtered off, washed with a small amount of pentane and dried under high vacuum (0.72 g, 3.7 mmol, 75%).

Racemic **4-benzyloxazolidine-2,5-dione** was prepared from DL-phenylalanine (0.83 g, 5.0 mmol) and triphosgene (0.50 g, 1.7 mmol + 50 mg, 0.17 mmol). The crude material was dissolved in a minimal amount of THF (3-5 mL), pentane (25 mL) was added and the flask placed into a freezer overnight. The formed precipitate was filtered off, washed with a small amount of pentane and dried under high vacuum (0.77 g, 4.0 mmol, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.42 – 7.30 (m, 3H), 7.23 – 7.11 (m, 2H), 5.97 (s, 1H), 4.53 (ddd, *J* = 8.5, 4.1, 0.7 Hz, 1H), 3.29 (dd, *J* = 14.1, 4.1 Hz, 1H), 3.00 (dd, *J* = 14.1, 8.5 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) 168.7, 151.8, 134.1, 129.4, 129.3, 128.2, 59.0, 38.0.

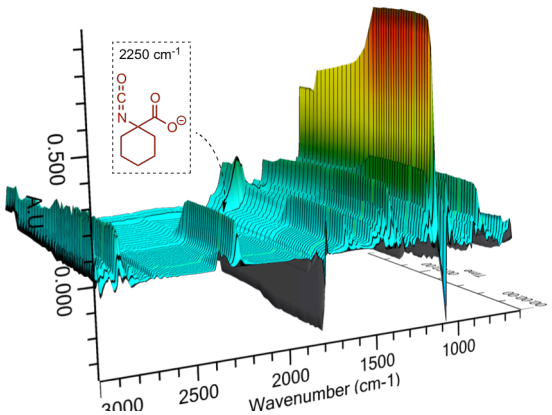
4.3. *React*-IR Experiment

In a flame-dried Schlenk-flask 3-oxa-1-azaspiro[4.5]decane-2,4-dione (85 mg, 0.50 mmol) was dissolved in dry THF (2.5 mL). The IR probe was penetrated through the septum and placed directly into the reaction mixture under N_2 atmosphere. The reaction mixture was cooled to –78 °C and stirred for 5 min. At this point the IR measurement was started (reference spectrum). The reaction progress was monitored by following the appearance of the expected strong isocyanate IR-absorption at 2250 cm^{-1} and the disappearance of the strong C=O absorption (1790 cm^{-1}) of the starting anhydride. Mesitylmagnesium bromide (1.05 mL of 1.0 M solution in Et_2O) was added dropwise over 2–3 min. Spectra were collected every 15 seconds for the first 30 min at –78 °C. The reaction mixture was warmed to RT by removing the flask from the cooling bath. Spectra were now collected every 30 seconds for further 30 min at RT.



Reference spectrum before addition of Grignard reagent

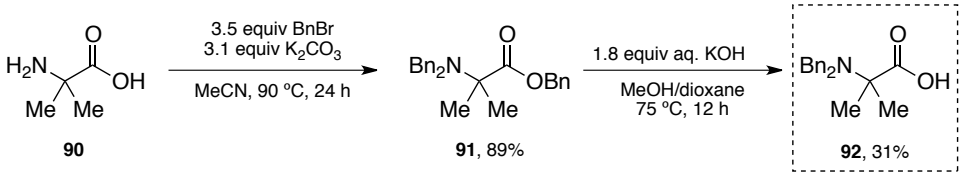
The appearance of an intense band 2250 cm^{-1} is consistent with the existence of an intermediate isocyanate. The isocyanate is stable at –78 °C and is not attacked by the second equivalent of Grignard reagent. Upon warming of the reaction mixture, the isocyanate is rapidly consumed to form the desired amide.

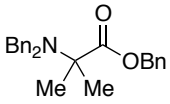


Reaction progress monitored by *react*-IR
(positive value = appearance of absorption band;
negative value = disappearance of absorption band)

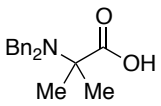
5. Part II: Synthesis of *N,N'*-Bisamides

5.1. Synthesis of 2-(dibenzylamino)-2-methylpropanoic acid (92)



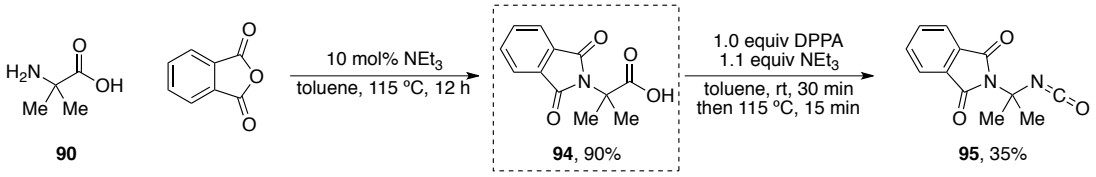


benzyl 2-(dibenzylamino)-2-methylpropanoate (91): To a 100 mL round-bottom flask with attached reflux condenser was added 2-aminoisobutyric acid (1.7 g, 17 mmol), potassium carbonate (7.1 g, 51 mmol) and MeCN (30 mL) under N_2 atmosphere and the reaction mixture was heated to reflux. A solution of benzyl bromide (7.0 mL, 59 mmol) in MeCN (15 mL) was added dropwise over 10 min through the reflux condenser. The reaction mixture was stirred at reflux for 24 h, cooled to RT and filtered. The filtrate was concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (hexanes:EtOAc 40:1 to remove excess benzyl bromide, then hexanes:EtOAc 10:1) and the product isolated as a colorless oil (5.6 g, 15 mmol, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.45 – 7.31 (m, 5H), 7.29 – 7.24 (m, 4H), 7.18 (t, J = 7.2 Hz, 4H), 7.15 – 7.08 (m, 2H), 5.16 (s, 2H), 3.83 (s, 4H), 1.42 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 175.9, 141.7, 136.4, 128.7, 128.4, 128.3, 128.0, 126.51, 66.4, 64.4, 55.4, 25.5.

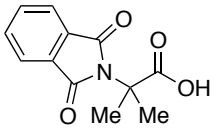


2-(dibenzylamino)-2-methylpropanoic acid (92): To a 100 mL round-bottom flask was added benzyl 2-(dibenzylamino)-2-methylpropanoate (91, 5.5 g, 14.7 mmol) and dissolved in a mixture of dioxane (28 mL) and MeOH (5.0 mL). 2 M aq KOH (13 mL, 26 mmol) was added and the reaction mixture warmed to 75 °C and stirred for 12 h. The aqueous mixture was extracted with Et_2O (30 mL) and the organic phase discarded. The aqueous phase was acidified with 6 M aq HCl and extracted with EtOAc (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (slow gradient CH_2Cl_2:MeOH 20:1 to 10:1) and the product isolated as a slightly yellow solid (1.3 g, 4.6 mmol, 31%). **m.p.** 117 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.28 – 7.14 (m, 10H), 3.86 (br s, 4H), 1.40 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 177.0, 138.3, 128.8, 128.7, 127.8, 68.1, 55.1, 22.7; **IR** (ATR) ν 2841 (br), 1698 (m), 1599 (m), 1353 (m), 1148 (s) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{20}NO_2$ ($[M+Na]^+$): 282.1500. Found: 282.1499.

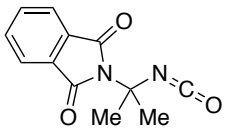
5.2. Synthesis of 2-(2-isocyanatopropan-2-yl)isoindoline-1,3-dione (95)



90 **94**, 90% **95**, 35%



2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoic acid (94): To a 100 mL round-bottom flask with attached reflux condenser under N_2 was added 2-aminoisobutyric acid (1.75 g, 17 mmol) and toluene (50 mL). Triethylamine (0.24 mL, 1.7 mmol) and phthalic anhydride (2.5 g, 17 mmol) were added and the reaction mixture was heated to reflux and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the obtained solid was taken up in EtOAc (50 mL). The organic phase was washed with 1 M aq HCl (25 mL). The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was washed with Et_2O (50 mL) and the product isolated as a colorless solid (3.6 g, 15 mmol, 90%). At room temperature the ratio of rotamers was 65:35 as determined by NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) 8.03 (dd, *J* = 5.6, 3.0 Hz, 3H), 7.92 (dd, *J* = 5.6, 3.1 Hz, 3H), 7.81 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.1 Hz, 2H), 1.88 (br s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 168.4, 162.9, 136.2, 134.3, 131.9, 131.5, 125.9, 123.4, 60.3, 24.5. Spectral data were consistent with previous report.[40]

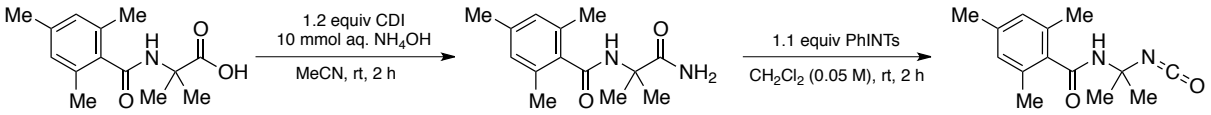


2-(2-isocyanatopropan-2-yl)isoindoline-1,3-dione (95): To a 25 mL round-bottom flask with attached reflux condenser under N_2 was added 2-(1,3-dioxoisoindolin-2-yl)-2-methylpropanoic acid (**94**, 0.23 g, 1.0 mmol) and toluene (5.0 mL). Triethylamine (0.15 mL, 1.1 mmol) and DPPA (0.22 mL, 1.0 mmol) were added and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture heated to 115 °C and stirred for 15 min. The reaction mixture was cooled to RT, EtOAc (15 mL) was added and the organic phase washed with sat. NH_4Cl solution (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced

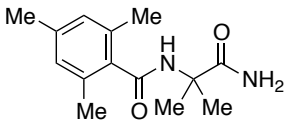
[40] J. R. Casimir, G. Guichard, J. P. Briand, *J. Org. Chem.* **2002**, *67*, 3764-3768.

pressure. The obtained crude material was purified by flash column chromatography (slow gradient hexanes:EtOAc 5:1 to 2:1) and the product isolated as a colorless solid (81 mg, 0.35 mmol, 35%). At room temperature the ratio of rotamers was 65:35 as determined by NMR. **^{1}H NMR** (300 MHz, $CDCl_3$) 7.90 – 7.86 (m, 3H), 7.82 – 7.74 (m, 5H), 7.72 – 7.67 (m, 2H), 2.03 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 168.0, 134.5, 134.4, 131.7, 130.2, 130.2, 123.5, 73.0, 30.8; **IR** (ATR) ν 2253 (s), 1715 (s), 1314 (m), 961 (w), 718 (w) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{18}H_{20}NO_2$ ($[M–NCO]^+$): 188.0706. Found: 188.0701.

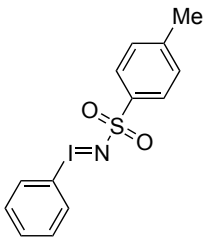
5.3. Synthesis of *N*-(2-isocyanatopropan-2-yl)-2,4,6-trimethylbenzamide (86)



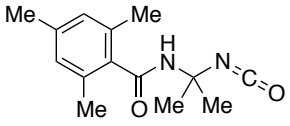
71 97 86



***N*-(1-amino-2-methyl-1-oxopropan-2-yl)-2,4,6-trimethylbenzamide (97)**: In a 25 mL round-bottom flask under N_2 2-methyl-2-(2,4,6-trimethylbenzamido)propanoic acid (**71**, 0.25 g, 1.0 mmol) was dissolved in MeCN (3.5 mL) and CDI (0.20 g, 1.2 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. A 25% aq NH_4OH solution (1.0 mL, 9.0 mmol) was added in one portion and the reaction mixture stirred at room temperature for 1 h. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and extracted with EtOAC (50 mL). The organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The yellowish solid was washed with Et_2O (2 x 5 mL) and the product isolated as a colorless solid (0.23 g, 0.93 mmol, 93%). **m.p.** 188 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.84 (br s, 3H), 6.15 (s, 1H), 5.38 (s, 1H), 2.30 (s, 6H), 2.27 (s, 3H), 1.70 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 176.7, 171.1, 138.9, 134.7, 134.2, 128.45, 58.0, 25.4, 21.2, 19.1; **IR** (ATR) ν 3554 (w), 3432 (w), 3252 (m), 1639 (s), 1533 (s), 1453 (m), 1221 (m), 848 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{21}N_2O_2$ ($[M+H]^+$): 249.1598. Found: 249.1601.



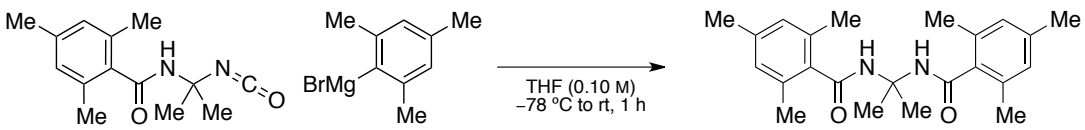
***N*-tosyliminobenzyliodinane**: In a 100 mL round-bottom flask under N_2 4-toluenesulfonamide (1.4 g, 8.0 mmol) was dissolved in MeOH (30 mL) and potassium hydroxide (1.1 g, 20 mmol) was added in one portion. The reaction mixture was stirred at room temperature until all potassium hydroxide was dissolved and then cooled to 0 ºC. (Diacetoxyiodo)benzene (2.6 g, 8.0 mmol) was added in one portion and the reaction mixture warmed to RT and stirred for 3 h. The reaction mixture was poured into H_2O (50 mL) and stirred at room temperature for 12 h. The solid was filtered off, recrystallized from MeOH and crystallization was completed by storage at –20 ºC for 12 h. The solid was filtered off and the product isolated as a light yellow solid (2.1 g, 5.6 mmol, 70%). **^{1}H NMR** (400 MHz, d^6-DMSO) 7.71 – 7.62 (m, 2H), 7.48 – 7.35 (m, 3H), 7.34 – 7.22 (m, 2H), 7.05 (br d, *J* = 8.4 Hz, 2H), 2.27 (s, 3H). Spectral data were consistent with previous report.[41]



***N*-(2-isocyanatopropan-2-yl)-2,4,6-trimethylbenzamide (86)**: In a 25 mL flame-dried round-bottom flask under N_2 *N*-(1-amino-2-methyl-1-oxopropan-2-yl)-2,4,6-trimethyl-benzamide (**97**, 0.12 g, 0.50 mmol) was suspended in CH_2Cl_2 (10 mL) and *N*-tosyliminobenzyliodinane (0.22 g, 0.60 mmol) was added in one portion. The reaction mixture was stirred at RT for 2 h and was concentrated under reduced pressure at 25 ºC. The obtained crude material was purified by flash column chromatography (pentane:EtOAc 4:1) and the product isolated as a colorless solid (68 mg, 0.28 mmol, 55%). **m.p.** 84 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.84 (s, 2H), 6.00 (s, 1H), 2.31 (s, 6H), 2.28 (s, 3H), 1.80 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.5, 139.0, 136.1, 134.3, 128.4, 69.2, 30.5, 21.2, 19.1; **IR** (ATR) ν 3260 (br), 2919 (w), 2249 (s), 1635 (m), 1539 (s), 1211 (m), 1151 (s), 844 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{18}N_2O_2$ (M^+): 246.1368. Found: 246.1366.

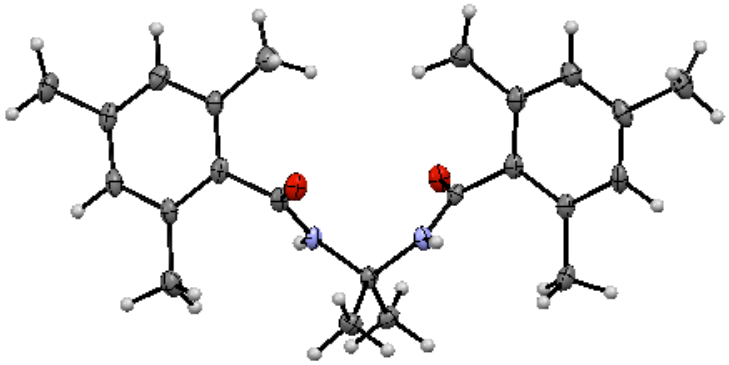
[41] A. Yoshimura, M. W. Luedtke, V. V. Zhdankin, *J. Org. Chem.* **2012**, *77*, 2087-2091.

5.4. Synthesis of *N,N'*-(propane-2,2-diyl)bis(2,4,6-trimethylbenzamide) (98)

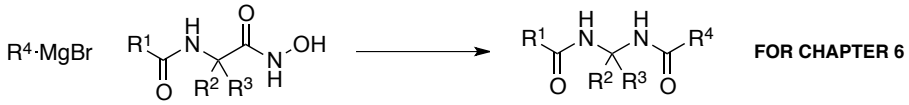


86 **17**, 2.0 equiv **98**, 63% yield

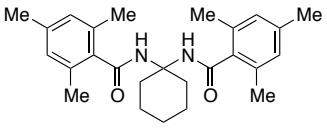
In a flame-dried 10 mL Schlenk-flask under N_2 *N*-(2-isocyanatopropan-2-yl)-2,4,6-trimethylbenzamide (**86**, 25 mg, 0.10 mmol) was dissolved in dry THF (1.0 mL) and cooled to –78 °C. Mesitylmagnesium bromide (0.20 mL of 1.0 M solution in Et_2O, 0.20 mmol) was added dropwise over 1 min. The reaction mixture was stirred at –78 °C for 15 min, followed by warming to RT and stirring for 45 min. The reaction mixture was quenched with sat. NH_4Cl solution (5 mL) and stirred for 1–2 min. EtOAc (15 mL) was added and the phases were separated. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by flash column chromatography (gradient pentane:EtOAc 4:1 to 2:1) and the product isolated as a colorless solid (23 mg, 0.063 mmol, 63%). **m.p.** over 225 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.83 (s, 4H), 6.45 (s, 2H), 2.35 (s, 12H), 2.28 (s, 6H), 1.91 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.3, 138.6, 135.1, 134.3, 128.4, 66.7, 60.5, 27.5, 21.2, 21.2, 19.3, 14.3; **IR** (ATR) ν 3273 (m), 2920 (w), 1645 (s), 1543 (s), 1308 (m), 1215 (m), 844 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{23}H_{31}N_2O_2$ ($[M+H]^+$): 367.2380. Found: 367.2387.



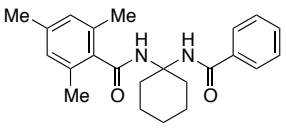
5.5. General Procedure: Synthesis of *N,N'*-Bisamides via Lossen Rearrangement



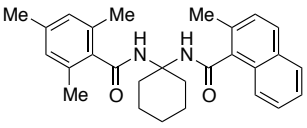
In a flame-dried round-bottom flask under N_2 the hydroxamic acid (0.50 mmol, 1.0 equiv) was dissolved in dry THF (5.0 mL) and NEt_3 (0.15 mL, 1.05 mmol, 2.1 equiv) was added. The solution was cooled to 0 °C and mesyl chloride (41 µL, 0.53 mmol, 1.05 equiv) was slowly added. The reaction mixture was warmed to RT and stirred for 1 h. The reaction mixture was quickly filtered through a glass filter (medium porosity) into a second, flame-dried round-bottom flask and the filter cake rinsed with dry THF (1.0 mL). The second round-bottom flask was placed under N_2 and cooled to –78 °C. The Grignard solution (1.05 mmol, 2.1 equiv) was added dropwise over 2–3 min directly into the solution. The reaction mixture was stirred at –78 °C for 15 min, before the flask was removed from the cooling bath and the reaction mixture stirred at RT for 1 h. The reaction mixture was quenched with 1 M aq HCl (10 mL) and stirred for 1 min. EtOAc (15 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by washing with 2 x 5 mL of dry Et_2O or via flash column chromatography (slow gradient of cyclohexane:EtOAc) and the *N,N'*-bisamide isolated as a bench-stable, colorless solid.



***N,N'*-(cyclohexane-1,1-diyl)bis(2,4,6-trimethylbenzamide) (103)**: Prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol). The crude material was washed with Et_2O (2 x 5 mL) and the product isolated as a colorless solid (0.11 g, 0.27 mmol, 53%). **m.p.** 221 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.84 (s, 4H), 6.25 (s, 2H), 2.38 (br s, 16H), 2.27 (s, 6H), 1.67 – 1.57 (m, 4H), 1.55 – 1.47 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.3, 138.6, 135.2, 134.5, 128.5, 68.5, 35.0, 35.0, 25.3, 22.2, 21.2, 19.7; **IR** (ATR) ν 3287 (m), 2922 (w), 2854 (w), 1643 (s), 1531 (s), 1301 (m), 845 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{26}H_{35}N_2O_2$ ($[M+H]^+$): 407.2693. Found: 407.2693.

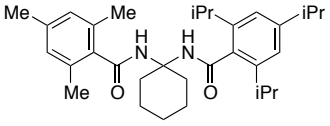


***N*-(1-benzamidocyclohexyl)-2,4,6-trimethylbenzamide (104)**: Prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and phenylmagnesium bromide (0.35 mL of a 3.0 M solution in Et_2O, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 9:1 to 5:1) and the product isolated as a colorless solid (32 mg, 0.088 mmol, 18%). **m.p.** 197 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.80 – 7.75 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.39 (m, 2H), 6.90 (s, 1H), 6.81 (s, 2H), 6.32 (s, 1H), 2.56 – 2.32 (m, 4H), 2.27 (s, 6H), 2.25 (s, 3H), 1.71 – 1.49 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 171.0, 168.1, 138.5, 135.7, 135.2, 134.3, 131.6, 128.8, 128.3, 127.1, 68.9, 35.3, 25.5, 22.4, 21.2, 19.2; **IR** (ATR) ν 3279 (br), 2929 (w), 1642 (s), 1538 (s), 1451 (m), 850 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{23}H_{29}N_2O_2$ ($[M+H]^+$): 365.2224. Found: 365.2225.



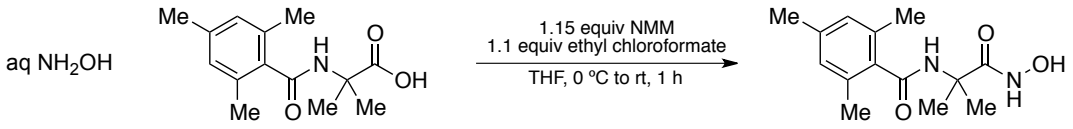
2-methyl-*N*-(1-(2,4,6-trimethylbenzamido)cyclohexyl)-1-naphthamide (105): *Grignard reagent*: To a flame-dried Schlenk-flask were added Mg turnings (107 mg, 4.4 mmol) and THF (2.0 mL). 2–3 drops of 1,2-dibromoethane were added, followed by dropwise addition of a solution of 1-bromo-2-methylnaphthalene (0.49 g, 2.0 mmol) in toluene (2.0 mL) over 5 min at RT. The reaction mixture was heated to 50 °C and stirred for 1 h. LC/MS showed complete consumption of 1-bromo-2-methylnaphthalene. Concentration determined by titration: 0.40 M in THF/toluene 1:1.

The product was prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and (2-methylnaphthalen-1-yl)magnesium bromide (2.3 mL of a 0.45 M solution in THF/toluene 1:1, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 9:1 to 5:1) and the product isolated as a colorless solid (0.11 g, 0.26 mmol, 53%). **m.p.** 220 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.13 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.52 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.44 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 2H), 6.47 (s, 1H), 6.38 (s, 1H), 2.60 (s, 3H), 2.54 – 2.46 (m, 3H), 2.42 (s, 6H), 2.29 (s, 3H), 1.73 – 1.48 (m, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.6, 169.6, 138.7, 135.3, 134.5, 134.0, 132.6, 131.9, 130.3, 129.1, 128.7, 128.5, 128.1, 127.1, 125.6, 125.0, 68.7, 35.1, 25.4, 22.3, 21.2, 20.1, 19.8; **IR** (ATR) ν 3282 (m), 2927 (w), 1641 (s), 1532 (s), 1451 (w), 1258 (m), 808 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{33}N_2O_2$ ($[M+H]^+$): 429.2537. Found: 429.2540.

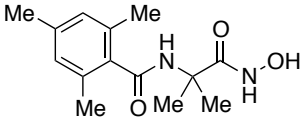


2,4,6-triisopropyl-*N*-(1-(2,4,6-trimethylbenzamido)cyclohexyl)benzamide (106): Prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and 2,4,6-triisopropylphenylmagnesium bromide (2.1 mL of a 0.5 M solution in THF, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 10:1 to 7:1) and the product isolated as a colorless solid (0.17 g, 0.34 mmol, 67%). **m.p.** 165 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.01 (s, 2H), 6.84 (s, 2H), 6.25 (s, 1H), 6.23 (s, 1H), 3.16 (hept, *J* = 6.7 Hz, 1H), 2.88 (hept, *J* = 6.7 Hz, 1H), 2.51 – 2.41 (m, 2H), 2.38 (s, 6H), 2.35 – 2.29 (m, 2H), 2.28 (s, 3H), 1.66 – 1.47 (m, 6H), 1.30 (d, *J* = 6.4 Hz, 6H), 1.25 (d, *J* = 6.9 Hz, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.5, 170.2, 149.9, 145.2, 138.5, 135.5, 134.4, 133.7, 128.4, 121.3, 68.7, 35.0, 34.5, 30.9, 27.1, 25.3, 24.9, 24.8, 24.1, 22.2, 21.2, 19.6; **IR** (ATR) ν 3280 (br), 2958 (m), 2931 (m), 2866 (w), 1634 (s), 1530 (s), 1454 (m), 1298 (m), 873 (w), 850 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{32}H_{47}N_2O_2$ ($[M+H]^+$): 491.3632. Found: 491.3628.

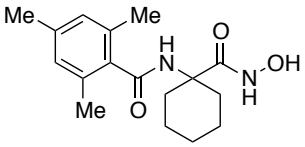
5.6. General Procedure: Synthesis of Hydroxamic Acids



In a flame-dried round-bottom flask under N_2 the *N*-acyl amino acid (1.0 mmol, 1.0 equiv) was dissolved in dry THF (5.0 mL) and NMM (0.13 mL, 1.15 mmol) was added. The solution was cooled to 0 ºC and ethyl chloroformate (0.10 mL, 1.1 mmol) was added slowly via micro syringe. The reaction mixture was stirred at 0 ºC for 15 min and a 50% aq hydroxylamine solution (0.5 mL, ca. 10 mmol) was added in one portion. The reaction mixture was warmed to RT and stirred for 30 min. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was washed with Et_2O (2 x 5 mL) and the hydroxamic acid isolated as a colorless solid.



***N*-(1-(hydroxyamino)-2-methyl-1-oxopropan-2-yl)-2,4,6-trimethylbenzamide (101)**: Prepared according to the general procedure from 2-methyl-2-(2,4,6-trimethylbenzamido)propanoic acid (0.25 g, 1.0 mmol) and the product isolated as a colorless solid (0.23 g, 0.91 mmol, 91%). **m.p.** 168 ºC; **^{1}H NMR** (400 MHz, d^{6}-DMSO) 10.29 (s, 1H), 8.69 (s, 1H), 8.15 (s, 1H), 6.81 (s, 2H), 2.20 (s, 9H), 1.42 (s, 6H); **^{13}C NMR** (101 MHz, d^{6}-DMSO) 171.4, 168.7, 136.9, 135.6, 133.9, 127.5, 55.1, 26.8, 25.0, 20.6, 18.7; **IR** (ATR) ν 3253 (br), 1637 (s), 1530 (s), 1454 (m), 1314 (m), 1220 (m), 896 (w) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{20}N_2NaO_3$ ([M+Na]$^{+}$): 287.1366. Found: 287.1372.



***N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (102)**: Prepared according to the general procedure from 1-(2,4,6-trimethylbenzamido)cyclohexanecarboxylic acid (0.29 g, 1.0 mmol) and the product isolated as a colorless solid (0.26 g, 0.87 mmol, 87%). **m.p.** 200 ºC; **^{1}H NMR** (400 MHz, d^{6}-DMSO) 10.19 (s, 1H), 8.63 (s, 1H), 7.99 (s, 1H), 6.81 (s, 2H), 2.25 (s, 6H), 2.22 (s, 3H), 2.17 (d, *J* = 13.1 Hz, 2H), 1.74 – 1.59 (m, 2H), 1.59 – 1.40 (m, 5H), 1.32 – 1.09 (m, 1H); **^{13}C NMR** (101 MHz, d^{6}-DMSO) 171.7, 169.6, 136.8, 135.9, 134.0, 127.6, 58.6, 31.9, 25.1, 21.3, 20.6, 19.2; **IR** (ATR) ν 3255 (br), 1638 (s), 1531 (s), 1453 (m), 1311 (m), 848 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{24}N_2NaO_3$ ([M+Na]$^{+}$): 327.1679. Found: 327.1683.