New Methodologies in Organic Chemistry: Applications to the Synthesis of α-Amino Acids and Natural Products

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Abstract

This thesis deals with the development and application of new synthetic methodology in organic chemistry.

The first part describes the development of a new protocol for the synthesis of 3-pyrrolines by means of a microwave-assisted ring-expansion reaction of 2-vinylaziridines. In addition, this methodology is implemented as a key-step in a formal total synthesis of the antibiotic (–)-anisomycin.

In the second part, a new methodology for the synthesis of arylglycines from Weinreb amides is described. In this procedure, a Grignard reagent is added to the iminium ion formed from the Weinreb amide upon treatment with a base. When a chiral amide is used, the nucleophilic addition proceeds with high diastereoselectivity.

Finally, an easy and straightforward synthesis of α-amino amides via a base-mediated rearrangement of modified Weinreb amides into *N,O*-acetals is presented. Subsequent arylation, alkylation, alkenylation or alkynylation of this intermediate affords the corresponding α-amino amides in excellent yields. Furthermore, a more generalized protocol for the α-arylation of Weinreb amides lacking an α-amino moiety is also discussed.

Keywords: Organic synthesis, 2-Vinylaziridines, 3-Pyrrolines, Ring-expansion, Rearrangement, Anisomycin, Total synthesis, α-Amino acids, Arylglycines, Weinreb amides, α-Arylation, Grignard reagents, Umpolung, *N,O*-Acetals.

Abbreviations

Ac	acetyl
BuLi	butyl lithium
cat	catalyst
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent(s)
Et	ethyl
hfacac	hexafluoroacetylacetonate
i-Pr	isopropyl
LHMDS	lithium hexamethyldisilazide
LDA	lithium diisopropylamide
MAO	monoamine oxidase
Me	methyl
Ms	methanesulfonyl
NDMBA	*N*,*N*'-dimethylbarbituric acid
NMDA	*N*-methyl-D-aspartate
n.d.	not determined
n-Hex	*n*-hexyl
t	time
T	temperature
t-Bu	*tert*-butyl
THF	tetrahydrofuranes
TMP	2,2,6,6-tetramethylpiperidine
tol	toluene
Ts	*p*-toluenesulfonyl

List of Publications

This thesis is based on the following papers, referred to in the text by their Roman numerals **I**-**IV**:

I. **Microwave Assisted Rearrangement of Vinylaziridines to 3-Pyrrolines: Formal Total Synthesis of (–)-Anisomycin**
Sebastian Hirner and Peter Somfai
Synlett **2005**, *20*, 3099.

II. **Synthesis of Arylglycines by the α-Arylation of Weinreb Amides**
Sebastian Hirner, Olaf Panknin, Magnus Edefuhr and Peter Somfai
Angew. Chem. Int. Ed. **2008**, *47*, 1907.

III. **Synthesis of α-Amino Acids via Umpolung of Weinreb Amide Enolates**
Sebastian Hirner, Donata K. Kirchner and Peter Somfai
Eur. J. Org. Chem. **2008**, *33*, 5583.

IV. **Synthesis of α-Amino Amides via *N,O*-Acetals Derived from Weinreb Amides**
Sebastian Hirner and Peter Somfai
J. Org. Chem. **2009**, *accepted*.

Paper not included in this thesis:

V. **Total Synthesis of the Potent Anticancer Aglaia Metabolites (–)-Silvestrol and (–)-Episilvestrol and the Active Analogue (–)-4'-Desmethoxyepisilvestrol**
Tim E. Adams, Mariana El Sous, Bill C. Hawkins, Sebastian Hirner, Georgina Holloway, Mui Ling Khoo, David J. Owen, G. Paul Savage, Peter J. Scammells and Mark A. Rizzacasa
J. Am. Chem. Soc. **2009**, *131*, 1607.

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Für Antje

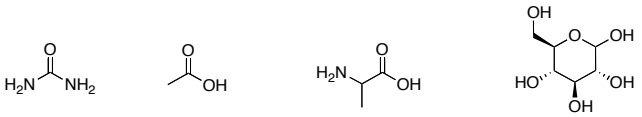
1. Introduction

1.1. Organic synthesis

"First and foremost, synthesis has to be viewed as an art and a science that needs to be advanced for its own sake." [1]

The term *total synthesis* describes the complete chemical synthesis of organic molecules from simple, commercially available or natural precursors. Although this broad definition is sometimes confined to complex molecules such as alkaloids or steroids,[2] the first conscious total synthesis of an organic compound is commonly considered to be that of urea (**1**) by Friedrich Wöhler in 1828.[3] Accidentally prepared in an attempt to make ammonium cyanate,[4] the synthesis of urea marks the beginning of organic chemistry, disproving *vital force* theory by showing that organic compounds can be synthesized from inorganic materials. However, the idea of *vitalism* in chemistry, which was believed for centuries, was not completely abandoned until 1845, when Herrmann Kolbe, a student of Wöhler, achieved the synthesis of acetic acid (**2**) from its elements.[5] Remarkably, Kolbe used the word *synthesis* for the first time when describing the process of assembling chemical compounds.[6]

Figure 1. *Some of the first synthetically prepared organic compounds.*



Urea (**1**) *Acetic acid* (**2**) *Alanine* (**3**) *(+)-Glucose* (**4**)

In 1850, Adolph Strecker accomplished the first synthesis of an α-amino acid, preparing alanine (**3**) by the condensation of acetaldehyde with ammonia and hydrogen cyanide.[7] As trivial as it may seem by today's standards, the Strecker synthesis remains, more than 150 years after its initial appearance, the most important method for the synthesis of α-amino acids (see chapter 3 and 4).[8] Also many other reactions, which still constitute the indispensable synthetic foundation of any organic chemist, were discovered during that era, including

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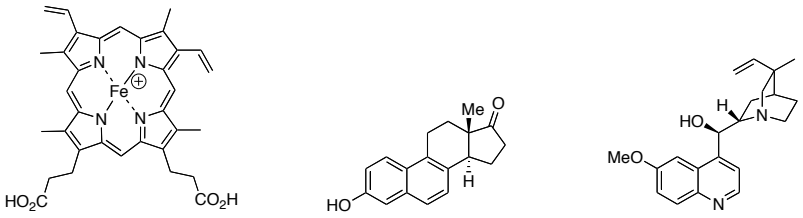
1 Nicolaou, K. C. *J. Org. Chem.* **2009**, *74*, 951.
2 Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim, 2007, p. 921.
3 Alternatively, the contemporary synthesis of ethanol from ethylene and sulfuric acid by Henry Hennell could be argued as the first organic synthesis: Hennell, H. *Phil. Trans.* **1828**, *118*, 365.
4 Wöhler, F. *Ann. Phys. Chem.* **1828**, *12*, 253.
5 Kolbe, H. *Ann. Chem. Pharm.* **1845**, *54*, 145.
6 Ancient Greek: συντιθέναι = to put together.
7 Strecker, A. *Ann.* **1850**, *75*, 27; **1854**, *91*, 349.
8 For a recent review, see: Yet, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 875.

the aldol reaction (1872),[9] the Friedel-Crafts alkylation (1877)[10] and the Michael reaction (1887).[11] In 1890, Emil Fischer completed the total synthesis of (+)-glucose (**4**), which stands as another milestone in organic synthesis, due to the complexity of the target molecule, which for the first time included stereochemical elements.[12] Also the birth of asymmetric synthesis dates from Fischer's work on carbohydrates in 1894, when he recognized that the addition of hydrogen cyanide to L-arabinose afforded one of the two possible diastereomeric cyanohydrins preferentially.[13]

During the first part of the twentieth century, the molecular complexity of natural products that could be synthesized was slowly but surely increasing, some of the most prominent examples being the syntheses of haemin (**5**),[14] the red pigment of blood (H. Fischer, 1929) and the sex hormone equilenin (**6**, Bachmann, 1939).[15] Perhaps most important, the discovery of new synthetic tools, such as the Grignard reaction (1900),[16] the Claisen rearrangement[17] (1912) and the Diels-Alder reaction[18] (1928) conferred a deeper understanding of reaction mechanisms and the electronic nature of molecules and chemical bonding, constituting a great leap forward in terms of explaining and predicting chemical reactivity.

Figure 2. *Target molecules during the first half of the 20th century.*



Haemin (**5**) *Equilenine* (**6**) *Quinine* (**7**)

One of the first organic chemists, who in a consequent manner applied these new concepts and ideas in organic synthesis, was Robert Burns Woodward. His total synthesis of quinine (**7**) in 1944 is often considered to mark the beginning

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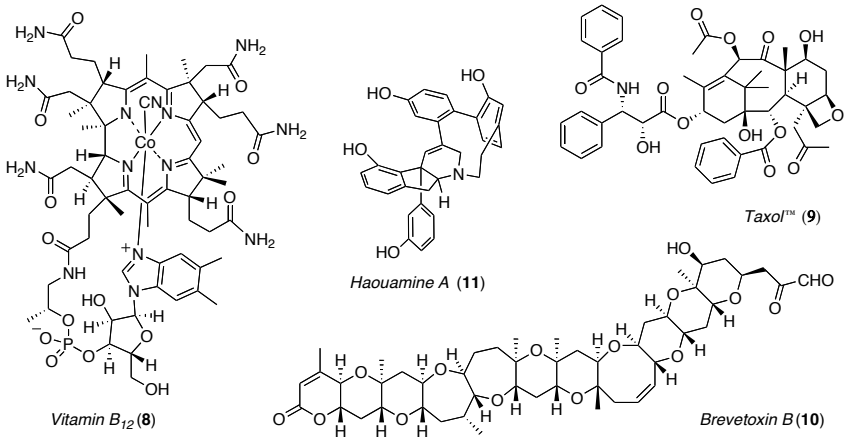
[9] Wurtz, M. A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436.
[10] Friedel, C.; Crafts, J. M. *J. Chem. Soc.* **1877**, *32*, 725.
[11] Michael, A. *J. Prakt. Chem.* **1887**, *36*, 113.
[12] Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 2611.
[13] Fischer, E. *Chem. Ber.* **1894**, *27*, 3189.
[14] Fischer, H.; Zeile, K. *Justus Liebigs Ann. Chem.* **1929**, *468*, 98.
[15] Bachmann, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 974.
[16] Grignard. V. *C. R. Acad. Sci.* **1900**, *130*, 1322.
[17] Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157.
[18] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

of a new era in chemistry,[19] elevating the science of organic synthesis into an intellectual and, even more importantly, an artistic process. Perhaps his most spectacular synthetic achievement was the synthesis of Vitamin B_{12} (**8**, 1974, with Albert Eschenmoser),[20] illustrating that organic chemists in principal are capable of synthesizing any compound imaginable, given enough money, time and manpower.[21] Furthermore, it exemplified the impact organic synthesis has on the progress of organic chemistry itself: Woodward's analysis of a reaction problem during the synthesis of **8** led in 1965 to the formulation of what are now known as the Woodward-Hoffmann rules. These represented a breakthrough for quantum mechanical models of structures and predictive reactivity in organic chemistry.[22]

Figure 3. *Target molecules in modern organic synthesis.*



During the second half of the twentieth century, organic chemistry and, in particular, natural product synthesis underwent an explosive growth as evidenced by inspection of the primary chemical literature. Furthermore, the original goal of total synthesis to confirm the structure of a natural product was more and more replaced with objectives related to the exploration of new technologies along the pathway. The discovery and invention of powerful new methodologies such as the Wittig reaction (1953),[23] palladium-catalyzed cross coupling reactions[24] and olefin metathesis[25] tremendously expanded the

[19] Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 849.
[20] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996.
[21] Eschenmoser, A. *Naturwissenschaften* **1974**, *61*, 513.
[22] For a controversial debate about the authorship of the Woodward-Hofmann rules, see: Hofmann, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 6586.
[23] Wittig, G.; Geissler, G. *Justus Liebigs Ann. Chem.* **1953**, *580*, 44.
[24] *Palladium Reagents and Catalysts*; Tsuji, J., Ed.; Wiley: New York, 1996.
[25] Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995,** *28*, 46.

available synthetic tools. At the same time, the advances in chromatographic and spectroscopic techniques allowed the rapid purification and characterization of organic compounds with unparalleled facility and speed. Furthermore, the development of new synthetic strategies, models and theories led to an unprecedented degree of predictability, making organic synthesis into the precise science which it is today. One of the most important achievements in this field was the introduction of retrosynthetic analysis by E. J. Corey in the early 1960's,[26] allowing synthetic chemists to analyze complex target molecules and to systematically devise possible synthetic strategies for their construction.

During the last two decades, organic chemists were able to accomplish the synthesis of entirely new types of complex and densely functionalized structures, such as the powerful anti-cancer agent Taxol™ (**9**) and polyether neurotoxins including brevetoxin A and B (**10**).[27] A more recent example is the synthesis of haouamine[28] (**11**) by Baran et al., which nicely illustrates the continuing necessity for the development of new methodology. Even though the quest for the synthesis of molecules with a steadily increasing size and complexity has not found its end,[29] the challenge in organic synthesis today lies less in the synthesis of monstrous natural products, than in the development of efficient, selective and environmentally benign transformations. Despite the immense number of organic transformations that have been developed since the days of Wöhler, organic synthesis is still in its early stages of development, compared to the powerful and selective synthetic tools available in nature.

1.2. Chirality

"L'univers est dissymétrique."[30]

First used by Lord Kelvin in 1873,[31] the term *chiral*[32] describes an object that is non-superposable on its mirror image. The principal of molecular chirality was established in 1874, when van't Hoff and Le Bel independently accounted for the phenomenon of optical activity by assuming that the chemical bonds between carbon atoms and their neighbors were directed towards the corners of

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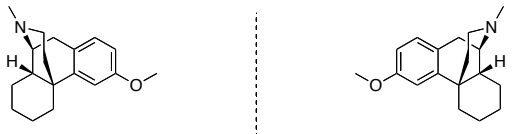
[26] Corey, E. J.; Ohno, M.; Vatakenchery, P. A.; Mitra, R. B. *J. Am. Chem. Soc.* **1961,** *83*, 1251.
[27] For a review, see: Nicolaou, K. C. *J. Org. Chem.* **2009**, *74*, 951.
[28] Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908.
[29] For example, see the unfinished synthesis of maitotoxin: Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182.
[30] Pasteur, L. *Ann Chim. Physique* **1848**, *24*, 442.
[31] Lord Kelvin *Baltimore Lectures* (Clay, London, 1904).
[32] Greek: $\chi\varepsilon\iota\rho$ = hand

a regular tetrahedron.[33] On a molecular level, chirality gives rise to enantiomers that can, in a chiral environment, exhibit strikingly different chemical and physical properties. Human enzymes, hormones and cell receptors are chiral, thus the pharmacological activity of two enantiomers of a chiral molecule can be extremely different. Most frequently, only one enantiomer of a chiral molecule displays the desired effect, whereas the other is either inactive or antagonist or is endowed with a different pharmacological profile. An interesting example is the drug metorphan (**12**, Figure 4): the (+)-isomer, dextromethorphan, is a widely used nonprescription antitussive, whereas the (–)-isomer, levomethorphan, is a strong opioid analgesic.

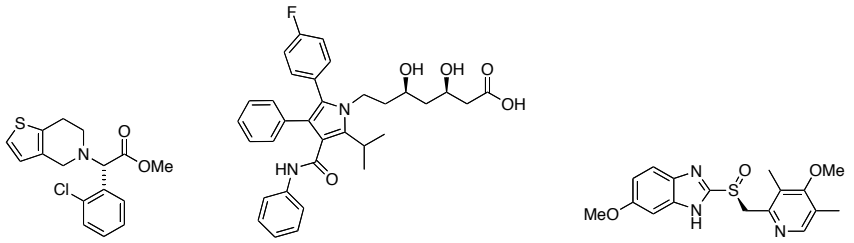
Figure 4. *The two enantiomers of metorphan.*



(+)-**12**, *Dextromethorphan* (–)-**12**, *Levomethorphan*

Within the last two decades, stunning advances have been achieved in the synthesis, analysis and separation of chiral molecules, and the awareness of their pharmalogical differences has been growing tremendously. Thus, drug stereochemistry has become an important issue, both for the pharmaceutical industry and the regulatory authorities, which increasingly demand the targeted synthesis of one stereoisomer.[34] As a consequence, already more than 50% of today's top-selling drugs, including blockbusters like Plavix™ (**13**), Lipitor™ (**14**) and Nexium™ (**15**), are sold as single enantiomers, and the trends for future drug development are evident (Figure 5).[35]

Figure 5. *Examples for blockbuster drugs sold as single enantiomers.*



Plavix™ (**13**) *Lipitor™* (**14**) *Nexium™* (**15**)

[33] (a) Le Bell, J. A. *Bull. Soc. Chim. Fr.* **1874**, *22*, 337. (b) Van't Hoff, J. H. *Arch. Neerl. Sci. Exactes Nat.* **1874**, *9*, 445.
[34] For a review, see: Hutt, A. J.; Valentova, J. *Acta Facult. Pharm. Univ. Comenianae* **2003**, *50*, 7.
[35] Shimazawa, R.; Nagai, N.; Toyoshima, S.; Okuda, H. *J. Health Science* **2008**, *54*, 23.

In broad outlines, enantiomerically pure compounds can be obtained in three different ways:

- *Chiral resolution,* the separation of a racemic mixture into its component enantiomers.
- *Chiral pool approach*, the use of readily available enantiopure building blocks, such as sugars and amino acids.
- *Asymmetric synthesis*, the intentional construction of enantiomers of a chiral compound by means of chemical reactions.

Asymmetric synthesis can be further divided into the following subgroups:

- *Reagent control*: The formation of a new stereogenic center is governed by a chiral reagent or catalyst not covalently bound to the substrate.
- *Substrate control*: The formation of a new stereogenic center is controlled by the inherent chirality of the substrate.
- *Auxiliary control*: The formation of a new stereogenic center is controlled by a stoichiometric amount of a chiral auxiliary covalently bound to the substrate but not part of the final structure.

1.3. Aim of this thesis

"Ultimately, the only real failure is recourse to tried and true methods." [36]

The aim of this doctoral thesis was to develop new synthetic methods for the stereoselective formation of carbon-carbon bonds and apply this methodology to tackle synthetic problems encountered in the synthesis of natural products and amino acids.

- ***Chapter 2*** deals with the development of an efficient synthesis of 3-pyrrolines from 2-vinyalziridines and its application in the formal total synthesis of the antibiotic (–)-anisomycin.
- ***Chapter 3*** describes our efforts to develop a protocol for the synthesis of arylglycines exploring the α-arylation of Weinreb amides with Grignard reagents.
- ***Chapter 4*** presents an improved protocol for the synthesis of α-amino acid derivatives from *N,O*-acetals, which is based on the methodology presented in chapter 3.

[36] Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530.

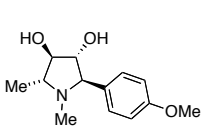
2. Ring-expansion of 2-vinylaziridines: Synthesis of 3-pyrrolines

(Paper I)

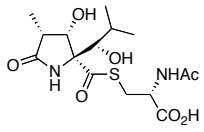
2.1. Introduction

3-Pyrrolines (2,5-dihydropyrroles) constitute an important class of heterocycles due to their broad biological activity such as NMDA receptor agonists,[37] MAO inhibitors,[38] κ-agonists[39] and tumor inhibitors.[40] Allowing ready access to pyrrolidines and pyrroles, 3-pyrrolines also represent versatile building blocks in organic synthesis and have frequently been used as intermediates for the synthesis of natural products,[41] including the antibiotic (–)-codonopsinine[42] (**16**, Figure 6) and the potent proteasome inhibitor (+)-lactacystin (**17**).

Figure 6. *Natural products synthesized from 3-pyrrolines.*



(–)-Codonopsinine (**16**)



(+)-Lactacystin (**17**)

The importance of 3-pyrrolines has prompted the development of a multitude of methods for their racemic and asymmetric synthesis, including approaches based on the Birch reduction of pyrroles,[43] [3+2] dipolar cycloadditions of azomethine ylides,[44] ring closing metathesis,[45] McMurry coupling[46] and

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[37] Rondeau, D.; Gill, P.; Chan, M.; Curry, K.; Lubell, W. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 771.

[38] (a) Lee, Y.; Ling, K.-Q.; Lu, X.; Silverman, R. B.; Shepard, E. M.; Dooly, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2002**, *124*, 12135. (b) Williams, C. H.; Lawson, J. *Biochem. J.* **1998**, *336*, 63.

[39] Mou, Q.-Y.; Chen, J.; Zhu, Y.-C.; Zhou, D.-H.; Chi, Z.-Q.; Long, Y.-Q. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2287.

[40] Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1987**, *30*, 2144.

[41] Hayes, C. J.; Sherlock, A. E.; Green, M. P.; Wilson, C.; Blake, A. J.; Selby, M. D.; Prodger, J. C. *J. Org. Chem.* **2008**, *73*, 2041.

[42] Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039.

[43] Donohoe, T. J.; Guyo, P. M. *J. Org. Chem.* **1996**, *61*, 7664.

[44] (a) Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753. (b) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

[45] Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.

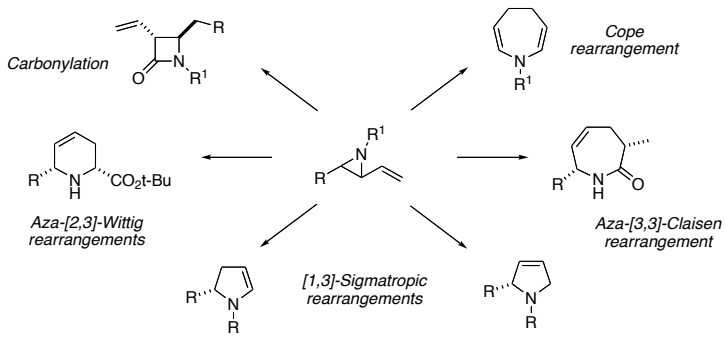
[46] Zeng, D. X.; Chen, Y. *Synlett* **2006**, 490.

carbene CH-insertion reactions.[47] More recently, much effort has focused on cyclizations of α-amino allenes.[48] Despite these and other creative approaches, there is a still need for simple and selective methods that allow ready access to enantiopure and structurally complex 3-pyrrolines.

2.2. 2-Vinylaziridines

Due to their highly functionalized nature and versatile reactivity, 2-vinylaziridines represent a tremendously valuable class of compounds, providing direct access to a host of structural motifs that are important in the synthesis of both natural and non-natural products.[49] In analogy to vinylepoxides[50] and vinylcyclopropanes[51], the relief of ring-strain provides a driving force for a variety of ring-opening and ring-expansion reactions, while the olefinic moiety allows for an efficient means of controlling the regioselectivity. For example, 2-vinylazirdines have been exploited as useful substrates for mild and selective ring-expansions to larger *N*-containing heterocycles, such as β-lactams, 2-pyrrolines, 3-pyrrolines, tetrahydropyridines, azepines and tetrahydroazepinones (Figure 7). [52]

Figure 7. *Ring-expansions of 2-vinylaziridines.*



[47] Green, M. P.; Prodger, J. C.; Sherlock, A. E.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3377.

[48] (a) Ohno, H.; Kadoh, Y.; Fujii, N.; Tanaka, T. *Org. Lett.* **2006**, 8, 947. (b) Dieter, R. K.; Chen, N.; Gore, V. K. *J. Org. Chem.* **2006**, *71*, 8755. (c) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (d) Horváth, A.; Benner, J.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **2004**, 3240.

[49] For recent examples, see: (a) Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823. (b) Dieter, R. K.; Chen, N.; Yu, H.; Nice, L. E.; Gore, V. K. *J. Org. Chem.* **2005**, *70*, 2109. (c) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121; (d) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855. (e) Green, M. P.; Prodger, J. C.; Sherlock, A. E.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3377.

[50] For a review on vinylepoxides, see: Olofsson, B.; Somfai, P. *Aziridines and Epoxides in Organic Synthesis*, Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; p 315.

[51] For a review, see; Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197.

[52] For a review, see: Somfai, P.; Åhman, J. *Targets Heterocycl. Syst.* **1999**, *3*, 341.

2.2.1. Synthesis of 2-vinylaziridines

2-Vinylaziridines are most commonly synthesized by one of the following methods: [53]

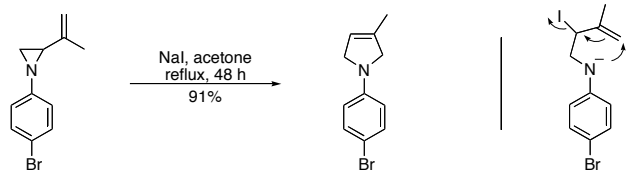
- Addition of nitrenes or nitrene equivalents to 1,3-dienes.
- Cyclization of α,β-unsaturated amino- or azido alcohols.
- Carbenoid additions to imines.

Other methods include the reduction[54] or alkylation[55] of α,β-unsaturated oximes, olefination of aziridines,[56] vinylation of azirines and the rearrangement of allylic sulfilimines. Despite the large number of synthetic procedures, most of the methods available require multi-step syntheses, lack substrate scope or afford the products as inseparable mixtures of *cis*- and *trans*-isomers. Since the pioneering work of Hou and Dai on the addition of ylides to activated imines,[57] this approach has probably become the most promising and general. However, the development of an efficient protocol, which allows the enantioselective synthesis of both *cis*- and *trans*-vinylaziridines, remains still elusive.

2.2.2. Ring-expansions to 3-pyrrolines: a short review

The ring-expansion of 2-vinylaziridines to 3-pyrrolines was first reported by Scheiner in 1967.[58] Treating *N*-aryl protected 2-vinylaziridine **18** with NaI in refluxing acetone, conditions that successfully had been applied in the related *N*-acylaziridine to oxazoline rearrangement,[59] 3-pyrroline **19** was formed in excellent yield (Scheme 1).

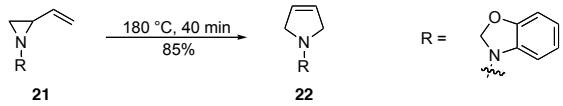
Scheme 1. *Ring-expansion of vinylaziridines using nucleophilic catalysis.*



[53] For a review, see: (a) Ohno, H., *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006; p 37.
[54] Ferrero, L.; Rouillard, M.; Decouzon, M.; Azzaro, M. *Tetrahedron Lett*. **1974**, *15*, 131.
[55] Chaabouni, R.; Laurent, A. *Synthesis*, **1975**, 464.
[56] Lindström, U. M; Somfai, P. *Synthesis* **1998**, 109.
[57] (a) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Chen, M.-B. *J. Org. Chem*. **1996**, *61*, 4641. (b) Li, A.-H.; Zhou, Y.-G.; Dai, L.-X.; Hou, X.-L.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem*. **1998**, *63*, 4338. (c) Hou, X.-L.; Yang, X.-F.; Dai, L.-X.; Chen, X.-F. *Chem. Commun*. **1998**, 747.
[58] Scheiner, P. *J. Org. Chem*. **1967**, *32*, 2628.
[59] Heine, H. W.; *Angew. Chem. Int. Ed*. **1962**, *1*, 528.

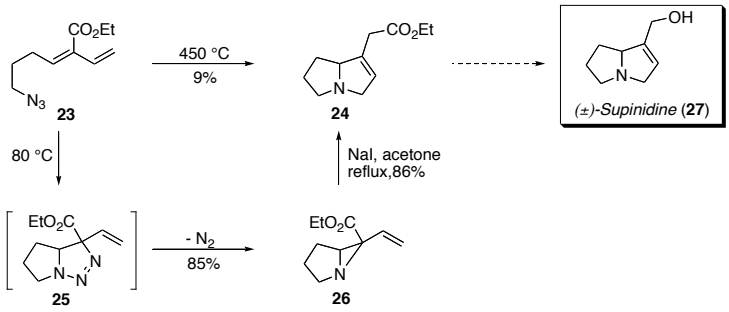
Mechanistically, the reaction was believed to proceed via a S_N2 attack of iodide on **18**, followed by an intramolecular S_N2' cyclization of the formed allylic iodide **20**. The same year, Rees and coworkers reported the thermolytic rearrangement of **21**, affording 3-pyrroline **22** in 85% yield (Scheme 2). [60] It was suggested that this rearrangement proceeds through a diradical intermediate, in analogy to the ring-expansion of vinylcyclopropanes,[61] although zwitterionic species could not be excluded. A similar thermolytic rearrangement was also observed by Lwowski and coworkers.[62]

Scheme 2. *Thermolytic ring-expansion of 2-vinylaziridines.*



Despite these promising initial results, only little effort was made to further explore the synthetic scope of this reaction.[63] First in 1985, the groups of Hudlicky and Pearson started to investigate the potential for the synthesis of pyrrolizidine alkaloids via an intramolecular [4+1]-pyrroline annulation reaction,[64] exemplified by the formal total synthesis of (±)-supinidine (**27**), which is depicted in Scheme 3.[65]

Scheme 3. *Synthesis of pyrrolizidine alkaloids.*

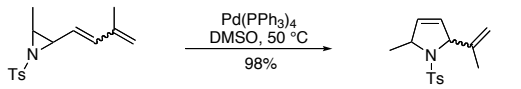


[60] Atkinson, R. S.; Rees, C. W. *Chem. Commun*. **1967**, 1230.
[61] Baldwin, J. E. *Chem. Rev*. **2003**, *103*, 1197.
[62] Mishra, A.; Rice, S. N.; Lwowski, W. *J. Org. Chem*. **1968**, *33*, 481.
[63] (a) Mente, P. G.; Heine, H. W.; Scharoubim, G. R. *J. Org. Chem*. **1968**, *33*, 4547. (b) Hoesch, L.; Dreiding, A. S. *Chimia* **1972**, *26*, 629. (c) Hortmann, A. G.; Koo, J.-Y. *J. Org. Chem*. **1974**, *39*, 3781.
[64] (a) Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K. C.; Poon, Y. F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem*. **1990**, *55*, 5719. (b) Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. *Synlett* **1990**, 433.
[65] Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc*. **1986**, *108*, 3755.

Starting from azidodiene **23**, the desired pyrrolizidine **24** can be obtained by thermolysis in only one step. The formation of **24** can be rationalized by an intramolecular 1,3-dipolar cycloaddition to give triazoline **25**, followed by the extrusion of N_2 affording 2-vinylaziridine **26**. Thermolysis of **26** gives then pyrrolizidine **24**. Alternatively, isolated **26** could be rearranged under nucleophilic catalysis with NaI in refluxing acetone to give **24** in good yield.

A completely new strategy for the preparation of 3-pyrrolines was introduced by Fugami and coworkers, employing a Pd(0)-catalyzed rearrangement of *N*-Ts dienylaziridines **28**.[66] A possible mechanism of this reaction is suggested to proceed by an attack of Pd(0) on the diene moiety in **28** to form a zwitterionic alkenyl π-allylpalladium intermediate which then cyclizes to **29**.

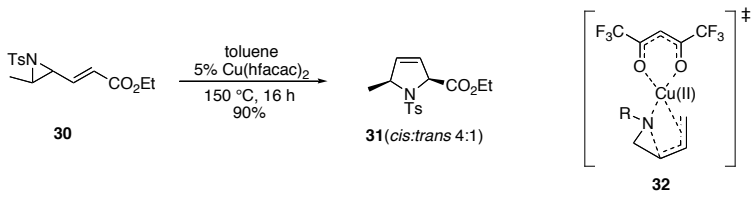
Scheme 4. *Pd(0)-catalyzed ring-expansion of 2-vinylaziridines.*



28 **29** (*cis*:*trans* 95:5)

In 2008, Njardarson and coworkers reported on a Cu(II)-catalyzed [1,3]-sigmatropic rearrangement of *N*-Ts and *N*-phthalimide protected 2-vinylaziridines to 3-pyrrolines.[67] Using $Cu(hfacac)_2$ as catalyst, this method gives the desired 3-pyrrolines in excellent yields and good diastereoselectivity (Scheme 5). To account for the observed diastereoselectivity, the reaction was suggested to proceed via an ordered transition state **32** without complete cleavage of the C-N-bond.

Scheme 5. *Cu(II)-catalyzed ring-expansion of 2-vinylaziridines.*



30 **31**(*cis*:*trans* 4:1) **32**

[66] (a) Fugami, K.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*, 857. (b) Fugami, K.; Miura, K.; Morizawa, Y.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1989**, *45*, 3089.

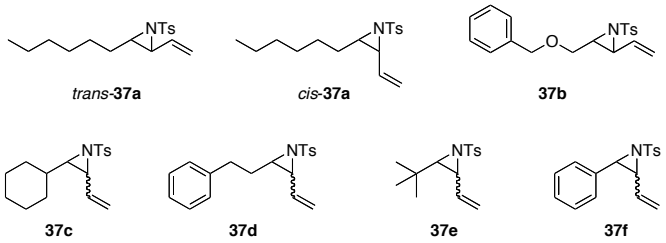
[67] Brichacek, M.; Lee, D.; Njardarson, J. T. *Org. Lett*. **2008**, *10*, 5023.

2.3. Ring-expansion of 2-vinylaziridines to 3-pyrrolines

*2.3.1. Synthesis of 2-vinylaziridines **37***

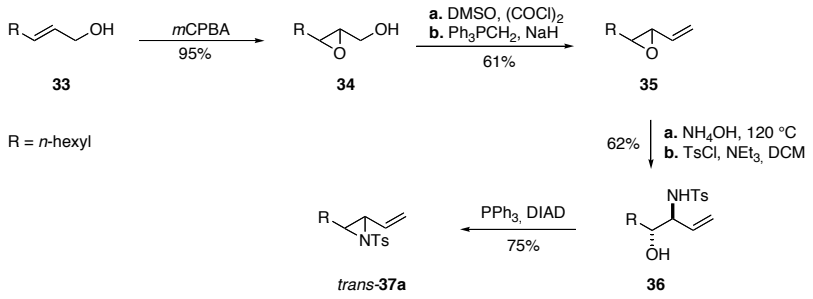
For the present study, activated[68] *N*-Ts-2-vinylaziridines were chosen as suitable starting materials, and six substrates were synthesized to represent variations in steric and electronic properties (Figure 8).

***Figure 8.** Structures of 2-vinylaziridines **37a-f**.*



Compound *trans*-**37a** was prepared from commercially available (*E*)-non-2-en-1-ol (**33**, Scheme 6). Epoxidation with *m*CPBA, followed by a Swern/Wittig sequence[56] gave vinylepoxide **35** in good overall yield. Aminolysis and subsequent *N*-tosylation afforded protected amino alcohol **36**, which was cyclized under Mitsunobu conditions to give the desired product. In analogy, *cis*-**37a** was prepared from (*Z*)-non-2-en-1-ol, and **37b** from the corresponding *syn*-amino alcohol[69]. Vinylaziridines **37c-e**,**g** were prepared as *cis*/*trans* mixtures in one step from the corresponding *N*-Ts-imines.[70,71]

***Scheme 6.** Synthesis of trans-**37a**.*

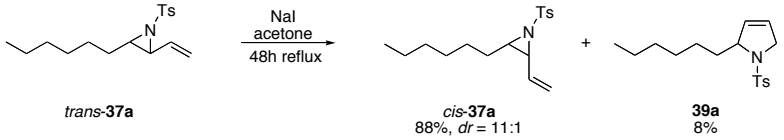


[68] For a definition, see: Ham, G. E. *J. Org. Chem.* **1964**, *29*, 3052.
[69] Lindström, U. M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* **1999**, *40*, 9273.
[70] Arini, L. G.; Sinclair, A.; Szeto, P.; Stockman, R. A. *Tetrahedron Lett.* **2004**, *45*, 1589.
[71] (a) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75; (b) MacKay, W. R.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2435.

2.3.2. Cis/trans-equilibration of 2-vinylaziridines

Our investigations commenced with reaction conditions similar to those reported by Scheiner in 1967. To our delight, when *trans*-**37a** was refluxed in acetone with an excess of NaI, the desired product **39a** was formed, albeit in poor yield (Scheme 7). Surprisingly, the main reaction was an equilibration of *trans*-**37a**, affording the isomer *cis*-**37a** in excellent selectivity (*dr* = 11:1).

Scheme 7. *NaI-mediated equilibration of trans-**37a**.*[72]



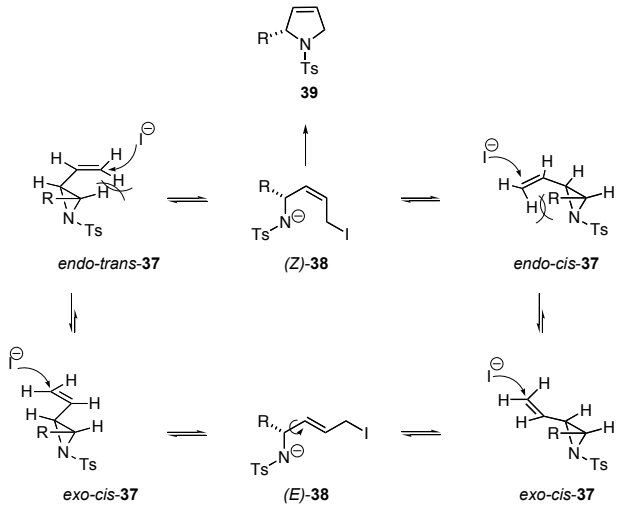
trans-**37a**

cis-**37a**
88%, *dr* = 11:1

39a
8%

The proposed mechanism for the iodide-mediated equilibration between vinylaziridines *cis*-**37** and *trans*-**37** and the formation of pyrroline **39** is depicted in Scheme 8. Assuming a S_N2' attack of the iodide as initial step, only ring-opening in the thermodynamically less favored *endo-trans*-**37** conformation will give the *Z*-configured allylic iodide **38**, which can cyclize to the desired pyrroline **39**. Alternatively, **38** can reform the aziridine moiety, leading to the corresponding *cis*-isomer. However, without further mechanistical studies, an S_N2-mechanism (Scheme 1) cannot be excluded.

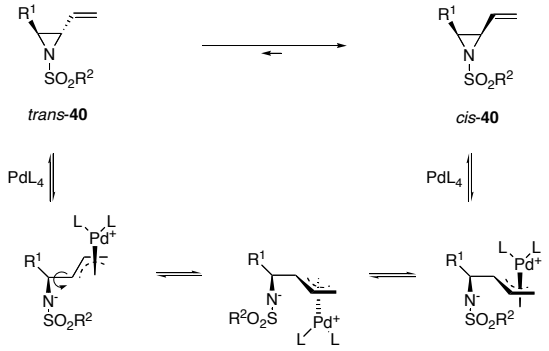
Scheme 8. *Proposed mechanism for the formation of **39**.*



[72] Yields determined by ^{1}H NMR of the crude reaction mixture.

A similar, Pd(0)-catalyzed equilibration reaction of *N*-sulfonylated 2-vinylaziridines **40** was reported in 1997 by the Ibuka group.[73] Mechanistically, this reaction is suggested to proceed via π-allyl palladium complexes as depicted in Scheme 9.

Scheme 9. *Pd(0)-catalyzed equilibration of 2-vinylaziridines (Ibuka et al.)*



It was found, that the thermodynamic stabilities of *cis*- and *trans*-vinylaziridines strongly depend on the *N*-protective group. *Ab initio* calculations revealed that for the unprotected case the *trans*-isomer is the thermodynamically more stable compound. However, the calculations showed that when introducing an *N*-methyl or *N*-mesyl group, the *cis*-isomer becomes more stable.[73]

Since many protocols for the synthesis of 2-vinylaziridens yield mixtures of *cis*- and *trans*-isomers, equilibration reactions affording a single isomer are synthetically very useful. Thus, the observed iodide-catalyzed equilibration reaction represents a cheap and environmentally benign alternative to Ibukas protocol, avoiding the use of costly and toxic palladium.

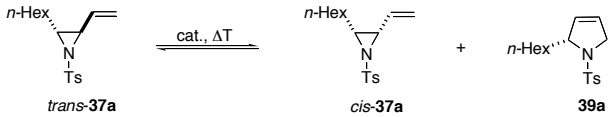
2.3.3. Optimization

To optimize the conditions for the rearrangement, we performed a series of experiments, varying the solvent, catalyst and temperature of the reaction (Table 1). Typical catalysts for the mechanistically related Baylis-Hillman reaction[74] such as DABCO and triphenylphosphine proved to be much less efficient than NaI. With nucleophilic solvents as MeOH and DMSO, the

[73] Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999.
[74] Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

vinylaziridine underwent ring-opening or oxidation, respectively, and none of the desired products was formed (entries 7 and 8). DMF led to the best conversion but also gave considerable amounts of unidentified products (entry 6). The best solvent proved to be MeCN since no formation of by-products was observed (entry 5).

***Table 1**. Optimization of the rearrangement of trans-**37a**.*



trans-**37a** *cis*-**37a** **39a**

entry	cat (equiv.)	solvent	*T* (°C)	*t* (h)	ratio *trans*-**37a**: *cis*-**37a**:**39a**[a]
1	NaI (8)	acetone	reflux	48	4:88:8
2	NaI (8)	acetone	100[b]	4	8:82:10
3	DABCO (1)	tol	180[b]	1	3:95:2
4	PPh_3 (1)	acetone	reflux	20	96:4:0
5	NaI (8)	MeCN	100[b]	15	8:83:9
6	NaI (8)	DMF	100[b]	15	11:65:24
7	NaI (8)	MeOH	100[b]	15	-
8	NaI (8)	DMSO	100[b]	15	-
9	NaI (2)	MeCN	160[c]	0.17	17:71:12
10	NaI (2)	MeCN	200[c]	0.33	0:0:100
11	LiI (2)	MeCN	200[c]	0.33	0:0:100

[a] Determined by ^{1}H NMR of the crude reaction product. [b] The reaction was performed in a sealed tube. [c]The Reaction was performed under microwave irradiation.

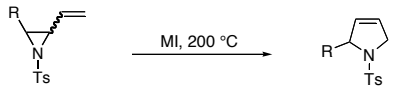
Since these results were not satisfactory, we decided to perform the reaction under microwave irradiation, which often leads to strongly enhanced reaction rates.[75] Pleasingly, when *trans*-**37a** was treated with NaI or LiI in MeCN under microwave irradiation (20 min, 200 °C), full conversion was achieved (entries 10 and 11) and the desired product **39a** could be obtained in 90% yield (Table 2, entry 1). Without a catalyst, no reaction could be observed under the same conditions, proving that the observed rearrangement is not occurring thermally.

[75] For a recent review, see: Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

2.3.4. Screening of different substituents

To verify the generality of the reaction, 2-vinylaziridines **37a-f** were tested under the optimized reaction conditions and successfully transformed into 3-pyrrolines **39** (Table 2). All reactions were found to proceed smoothly in good to excellent yields. The only exception, both in reaction time and yield, was **37f** (entry 8). The phenyl substituent seems to increase the reactivity and to decrease the selectivity of the reaction, affording a lot of unidentified byproducts. Compound **37c** gave only moderate yields with NaI, whereas with LiI as catalyst, **39c** was obtained in good yields (entries 4 and 5).

***Table 2**. Microwave assisted rearrangement of 2-vinylaziridines to 3-pyrrolines.*[a]



37a-f **39a-f**

entry	**37**	R	*cis*:*trans*[b]	MI	*t* (min)	yield (%)[c]
1	**a**	*n*-Hexyl	0:100	NaI	20	90
2	**a**	*n*-Hexyl	100:0	NaI	20	86
3	**b**	$BnOCH_2$	0:100	NaI	10	94
4	**c**	Cy	31:69	NaI	30	54
5	**c**	Cy	31:69	LiI	30	82
6	**d**	$Ph(CH_2)_2$	28:72	LiI	15	92
7	**e**	*t*-Bu	18:82	LiI	30	95
8	**f**	Ph	30:70	LiI	1	41

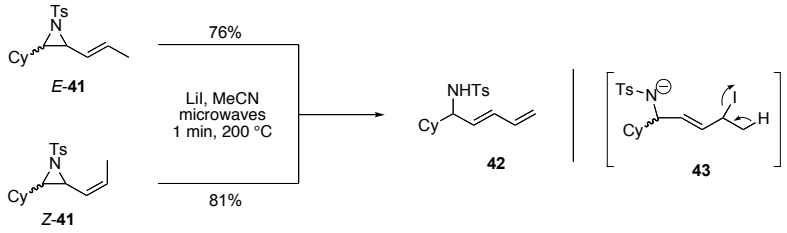
[a] Conditions: 2 equiv. MI, MeCN, microwave heating, 200 °C. [b] Isomeric ratios of **37** determined by ^{1}H NMR. [c] Isolated yield.

2.3.5. Substituted vinylaziridines

With working conditions in hand, we became interested in investigating the reaction of 2-crotylaziridines (*E*)-**41** and (*Z*)-**41**. Since the ring-expansion of these substrates would result in the formation of a new stereocenter, we were especially interested in exploring the effect of the configuration of the double bond. Disappointingly, when **41** was employed under standard conditions for only 1 min, diene **42** was exclusively formed in both cases, probably caused by a 1,2-elimination of the intermediate allylic iodide (**43**, Scheme 10). Attempts to suppress this undesired process by lowering the reaction temperature or using different catalysts met with no success. Since the formation of diene **42**

requires a substituent bearing an α-proton, it can be assumed that elimination could be prevented by use of substituents such as phenyl or *t*-butyl. However, due to the limited substrate scope of such a process, no efforts were made to further explore this reaction.

Scheme 10. Elimination to diene **42**.

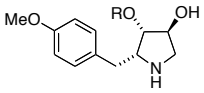


2.4. Formal total synthesis of (–)-anisomycin

2.4.1. Introduction

To demonstrate the utility of the developed ring expansion reaction in natural product synthesis, we set out to apply this protocol in a formal total synthesis of the antibiotic (–)-anisomycin **44** (Figure 9).

Figure 9. *Structure of (–)-anisomycin (**44**) and (–)-deacetylanisomycin (**45**).*



44: R = Ac
45: R = H

(–)-Anisomycin (**44**) was first isolated in 1954 by Sobin and Tanner from fermentation broths of *streptomyces griseolus* and *streptomyces roseochromogenes*.[76] The relative and absolute configurations were established by spectroscopy,[77] and finally by chemical correlation with L-tyrosine, respectively.[78] **44** has clinically been used with success for the treatment of both amoebic dysentery[79] and vaginitis due to *trichomonas vaginilis*,[80] and has

[76] Sobin, B. A.; Tanner, F. W. *J. Am. Chem. Soc.* **1954**, *76*, 4053.
[77] Schaefer, J. P.; Wheatley, P. J., *J. Org. Chem.* **1968**, *33*, 166.
[78] Wong, C. M. *Can. J. Chem.* **1968**, *46*, 1101.
[79] Santander, V. M.; Cue, A.B.; Diaz, J. G. H.; Balmis, F. J.; Miranda, G.; Urbina, E.; Portilla, J.; Plata, A. A.; Zapata, H. B.; Munoz, V. A.; Abreu, L. M. *Rev. Invest. Biol. Univ. Guadalajara* **1961**, *1*, 94.

also been employed as a fungicide to eradicate bean mildew and other fungal plant infections.[81] Recently, anisomycin has received attention as a potent *in vitro* antitumor agent with IC_{50} values in the nanomolar range.[82] In eukaryotes, anisomycin exerts its cytotoxic effects through the inhibition of peptidyl transferase in the 60S ribosomal subunit. Studies have shown that the pyrrolidine ring is crucial for the translational inhibitory activity; *N*-acetylation or deacetylation at the 3'-position inhibits this activity.[83]

(–)-Anisomycin has also been used as an extremely potent activator of kinase cascades in mammalian cells, especially the stress-activated mitogen-activated protein (MAP) kinase subtypes. Recently, the immunomodulating properties of anisomycin have been reported: Su et al. have shown that a quite low dose of **44** was sufficient to block proliferation of T-cells.[84] In addition to these interesting biological activities, the methylene-linked five-six ring system of anisomycin is a common molecular framework for known drugs.[85]

2.4.2. Previous syntheses of anisomycin

Due to its various bioactive properties, much effort has been devoted to the development of an efficient synthesis of anisomycin and its biosynthetic precursor deacetylanisomycin (**45**) within the last 40 years, and more than 25 different routes have been reported to date.[86] In 1968, the first total synthesis of **45** was accomplished by Wong and coworkers,[87] followed by the synthesis of **44** one year later by the same group.[88] Like Wong's synthesis, most of the syntheses being reported in the literature rely on chiral pool starting materials, such as D-glucose, L-tartaric acid, D-mannitol, and D-tyrosine.

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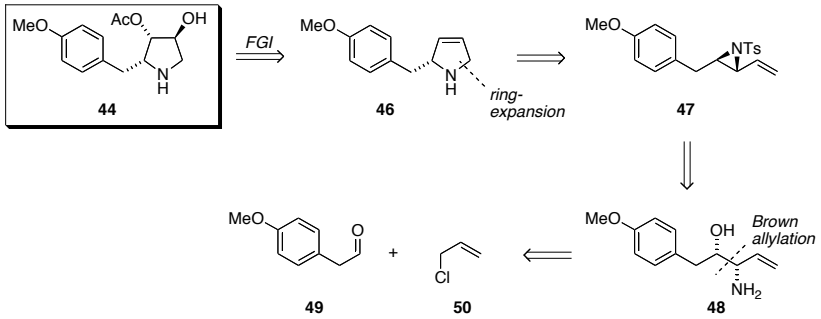
[80] Frye, W. W.; Mule, J. G.; Swartzwelder, C. *Antibiol. Ann.* **1955**, 820.
[81] Windholz, M., Ed. *The Merck Index*, 10th ed.: Merck: Rahway, NJ, 1983; p 98.
[82] Hosoya, Y.; Kameyama, T.; Naganawa, H.; Okami, Y.; Takeuchi, T. *J. Antibiot.* **1993**, *46*, 1300.
[83] Jimènez, A.; Vázquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer-Verlag: Berlin, 1979; pp 1-19.
[84] Xing, F. Y.; Yu, Z.; Liu, J.; Di, J. F.; Zeng, S.; Chen, D.; Chen, L.; Fang, Z. Y.; Guo, Z. F.; Pan, S.; Wang, J. K.; Li, Y. T.; Hao, W. T.; Fan, Z. H.; Teng, Z. P.; Chen, G. L.; Chen, Z. C.; Mao, C. Q.; Long, Y. T.; Liu, N. *Journal of Immunotherapy* **2008**, *31*, 858.
[85] Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887.
[86] For recent examples, see: (a) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Tian, Y. S.; Ham, W. H. *Org. Lett.* **2007**, *9*, 3627. (b)Kim, J. H.; Crutis-Long, M. J.; Seo, W. D.; Ryu, Y. B.; Yang, M. S.; Park, K. H. *J. Org. Chem.* **2005**, *70*, 4082. (c) Ono, M.; Tanikawa, S.; Suzuki, K.; Akita, H. *Tetrahedron* **2004**, *60*, 10187. (d) Hulme, A. N.; Rosser, E. M. *Org. Lett.* **2002**, *4*, 265. (e) Hutin, P.; Haddad, M.; Larcheveque, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2547. (f) Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383.
[87] Wong, C. M.; Buccini, J. Raa, J. T. *Can. J. Chem.* **1968**, *46*, 3091.
[88] Wong, C. M.; Buccini, J.; Chang, I.; Te Raa, J.; Schwenk, R. *Can. J. Chem.* **1969**, *47*, 2421.

2.4.3. Retrosynthetic analysis

Retrosynthetically, we set out to install the pyrrolidine functionality with the correct C2-stereochemistry by ring-expansion of the corresponding vinylaziridine **47**. This compound should be available from *syn*-amino alcohol **48**, which in turn is readily prepared from aldehyde **49** and allyl chloride (**50**), using a modified Brown allylation reaction. The realization of this strategy yields a short synthesis of **44**, as shown in Scheme 11.

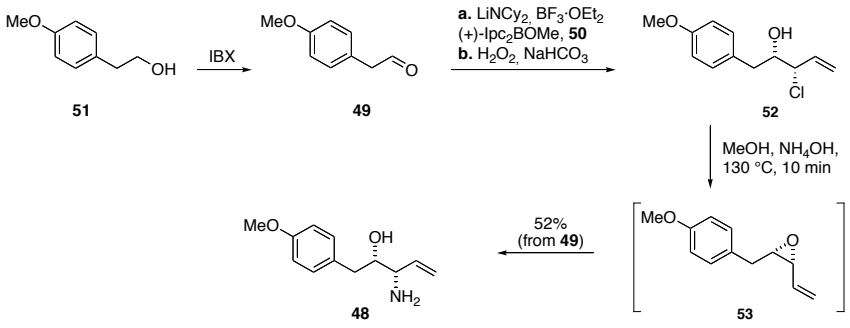
Scheme 11. *Retrosynthetic analysis of (–)-anisomycin.*



2.4.4. Synthesis of (–)-anisomycin

Asymmetric α-chloroallylboration[89] of aldehyde **49**, obtained by IBX-oxidation[90] of commercially available alcohol **51**, yielded the corresponding *syn*-chlorohydrine **52** in excellent enantioselectivity (*ee* > 95%).

Scheme 12. *Synthesis of amino alcohol **48**.*



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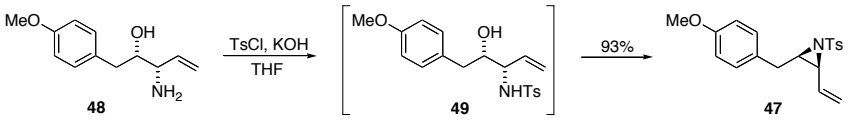
[89] (a) Hu, S.; Jayaraman S.; Oehlschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513. (b) Hertweck, C.; Boland, W. *Tetrahedron* **1997**, *53*, 14651.

[90] Moore, J. D.; Finney, S. N. *Org. Lett.* **2002**, *4*, 3001.

Since the purification of **52** by flash chromatography proved to be tedious, the crude product was dissolved in a mixture of NH_4OH and methanol and heated in a sealed tube for 10 min at 130 °C, yielding the desired *syn*-amino alcohol **48** in 52% overall yield. Notably, the aminolysis of **52** occurs with retention of the configuration, due to the intermediate formation of vinylepoxides **53**.

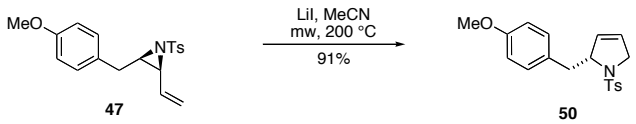
Tosylation of **48** and a subsequent ring-closure to the corresponding vinylaziridine **47** was first achieved by a 2-step procedure, using a Mitsunobu cyclization. However, the yield was not satisfactory and we began to investigate if this transformation could be accomplished by a one-pot procedure, using an excess of TsCl together with a base. Disappointingly, the use of organic bases (DBU, NEt_3) led mainly to decomposition of the starting material. Gratifyingly, when **48** was treated under biphasic conditions with TsCl and KOH in anhydrous THF, the desired *cis*-vinylaziridine **47** was obtained in excellent yields (Scheme 13).

***Scheme 13**. Synthesis of **47** by a one-pot protection/cyclization procedure.*



With an enantioselective synthesis of the desired vinylaziridine in hand, we were pleased to find that the rearrangement of **47** to **50** proceeded in excellent yield with retained stereochemistry under the optimized reaction conditions (Scheme 14).

***Scheme 14**. Rearrangement of 2-vinylaziridine **47**.*



Deprotection of **50** afforded enantiopure secondary amine **46**, which has been converted to *ent*-**44**.[91] Alternatively, iodohydroxylation of pyrroline **50**, followed by basic workup with NaOH afforded epoxide **51**, which was deprotected to **52**, a known intermediate in the synthesis of **44**.[92]

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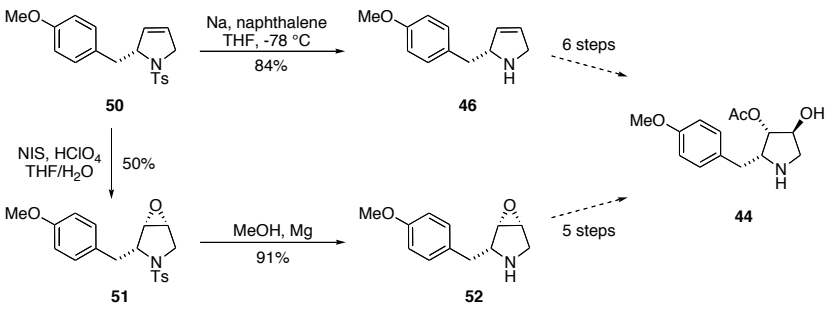
[91] Meyers, A. I.; Dupre, B. *Heterocycles* **1987**, 25, 113.

[92] (a) Buchanan, J. G.; MacLean, K. A.; Wightman, R. H.; Paulsen, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1463. (b) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076. (c) Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1969**, *17*, 1405.

***Scheme 15**. Formal total synthesis of of (–)-anisomycin (**44**).*



2.5. Conclusions

In summary, we have developed a straightforward and high-yielding protocol for the synthesis of synthetically important 3-pyrrolines by a microwave assisted rearrangement of 2-vinylaziridines. The synthetic utility of this ring-expansion reaction has successfully been demonstrated by a short formal total synthesis of the antibiotic (–)-anisomycin.

3. Synthesis of α-Amino Acids via Umpolung of Weinreb Amide Enolates

(Paper II - III)

3.1. Introduction

α-Amino acids are one of the most important families of natural products and have been of great interest in many scientific areas for over 150 years. Beyond their fundamental role as building-blocks of peptides and proteins, α-amino acids are extensively used as food supplements, additives to animal feeds, agrochemicals, and pharmaceuticals. Moreover, they are widely used templates in asymmetric catalysis, versatile building blocks in total synthesis and common subunits in pharmaceuticals and natural products.

Consequently, the development of new methods for the synthesis of α-amino acids has been a field of active research for many years.[93] Especially the synthesis of non-proteinogenic and unnatural α-amino acids has attracted much attention since these compounds provide access to new drug candidates and can act as valuable biological probes.[94] Classical, yet industrially still relevant, methods for the synthesis of α-amino acids include the Strecker synthesis, the amination of α-halo acids, and approaches through hydantoins and oxazolones. During the last decades, a wide range of asymmetric, often catalytic syntheses has been developed, including catalytic asymmetric hydrogenations of dehydro-α-amino acids,[93a] asymmetric modifications of the Strecker reaction,[95] enantioselective alkylations of glycine derivatives under phase-transfer conditions[93b,c] and catalytic asymmetric addition of nucleophiles to α-imino esters.[93d] Despite this great variety of well-tried methods and new asymmetric methodologies for the synthesis of α-amino acids, there is still a need for the development of efficient and technically feasible methods. For example, to date no general and economically viable process for the asymmetric synthesis of α-amino acids has yet emerged.[96]

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[93] For reviews on the synthesis of α-amino acids, see: (a) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (d) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

[94] For examples, see: (a) Hicks, R. P.; Bhonsle, J. B.; Venugopal, D.; Koser, B. W.; Magill, A. J. *J. Med. Chem.* **2007**, *50*, 3026. (b) Wang, J. Y.; Xie, J. M.; Schultz, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 8738. (c) Jain, R.; Chawrai, S. *Mini Rev. Med. Chem.* **2005**, *5*, 469.

[95] For a review, see: (a) Stephen J. Connon, *Angew. Chem. Int. Ed.* **2008**, *47*, 1176.

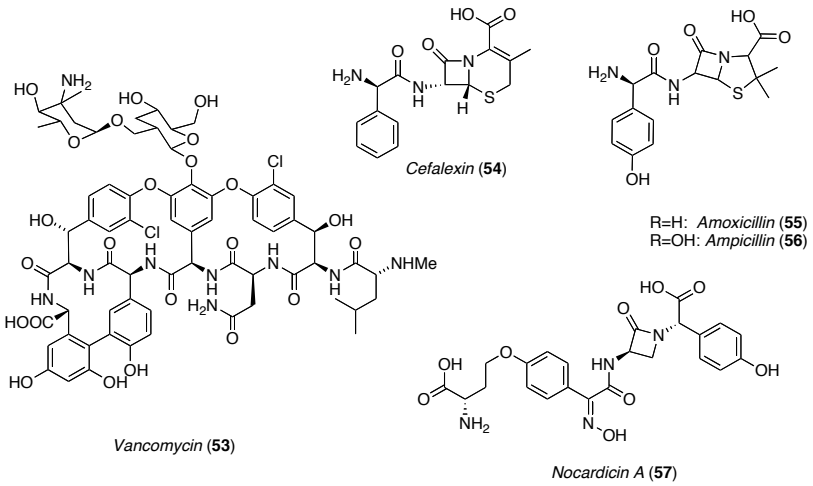
[96] Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788.

3.2. Arylglycines

3.2.1. Introduction

α-Aryl-α-amino acids (arylglycines) are among the most important types of non-proteinogenic α-amino acids, due to their prevalence in many significant bioactive compounds. This includes commercial blockbusters like the antiplatelet agent Plavix™ (**13**, Figure 5),[97] as well as many important glycopeptide- and β-lactam antibiotics (Figure 10).

Figure 10. *Important antibiotics bearing the arylglycine moiety.*



Vancomycin (**53**), the first and most important member of the family of glycopeptide antibiotics, is one of the best-studied and most interesting natural sources of arylglycines.[98] First isolated from cultures of an Indonesian soil sample in 1956,[99] vancomycin exhibits excellent antibacterial activity against Gram-positive organisms by inhibiting cell wall synthesis. Several other glycopeptide antibiotics, such as ristocetin and teicoplanin, contain several structural types of arylglycines, and have been used for the treatment of some of the most serious and potentially lethal infections involving *staphylococci* and *enterococci*.

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97 Coukell, A. J.; Markham, A. *Drugs* **1997**, *54*, 745.

98 For a recent review, see: Nicolaou, K. C.; Chena, J. S.; Dalby, S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290.

99 McCormick, M. H.; Stark, W. M.; Pittenger, G. F.; Pittenger, R. C.; McGuire, G. M. *Antibiot. Annu.* **1955-1956**, 606.

Another important natural source of arylglycines are the nocardicins, a family of monocyclic β-lactam antibiotics isolated from *nocardia uniformis*, the most potent of which is nocardicin A (**57**).[100] Apart from their prevalence in naturally occurring compounds, arylglycines represent important building blocks for synthetic pharmaceuticals. For example, some of the most important β-lactam antibiotics contain D-arylglycines as a side chain moiety, including cefalexin (**54**), amoxicillin (**55**) and ampicillin (**56**). These compounds belong to the most commonly prescribed antibiotics and have been categorized as "essential medicines" by the World Health Organization (WHO).[101] In 2000, **55** and **56** combined accounted for almost half of the 45,000 tons of β-lactam antibiotics produced globally.[102]

Economically, the most important drug bearing the arylglycine moiety is probably the blockbuster drug clopidogrel (**13**, Figure 5), better known under its trade name Plavix™. Clopidogrel is a strong platelet aggregation inhibitor, which is widely administered, often in combination with Aspirin™, to atherosclerotic patients with the risk of a heart attack or stroke caused by blood clots. It had been the 2nd top selling drug in the world for a few years, with worldwide sales of $6.4 billion in 2006.[103]

3.2.2. Synthesis of arylglycines

Despite the apparent simplicity of the arylglycine structure, the synthesis of arylglycines is still a challenging task in organic chemistry. On the one hand, many standard methods for the synthesis of other types of α-amino acids, like the phase-transfer catalyzed alkylation of glycine derivatives or the hydrogenation of enamines are not applicable to the synthesis of arylglycines. On the other hand, their stereoselective synthesis is complicated by the ease of base-catalyzed racemization of the α-methine proton, rendering these substances challenging synthetic targets to obtain in enantiomerically pure form (phenylglycine is 60 times more prone toward racemization than alanine).[104]

Due to the significance of the arylglycine structural feature, numerous approaches to this important class of amino acids have been developed,

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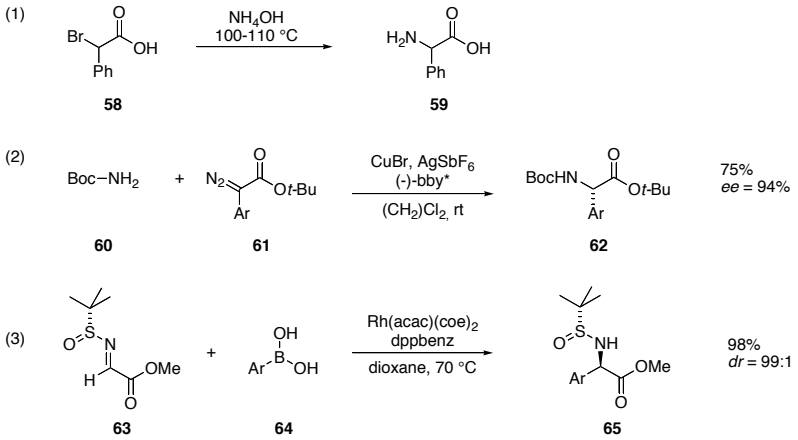
[100] Kelly, W. L.; Townsend, C. A. *J. Am. Chem. Soc.* **2002**, *124*, 8186.
[101] World Health Organization. WHO model list of essential medicines. 15th list. Geneva, Switzerland 2007. http://www.who.int/medicines/publications/EML15.pdf
[102] Elander, R.P. *Appl. Microbiol. Biotechnol.* **2003**, *61*, 385.
[103] Grimley, J. *Chem. Eng. News*, 2006, Dec. 4th, pp. 17-28.
[104] G. G. Smith, T. Sivakua, *J. Org. Chem.* **1983**, *48*, 627.

including methods based on electrophilic amination of chiral enolates,[105] Friedel-Crafts additions to electrophilic glycine templates,[106] the Petasis reaction[107] and aminohydroxylation[108]. The first synthesis of an arylglycine dates back to 1878, when Stöckenius prepared phenylglycine (**59**) by the aminolysis of bromide **58** (Scheme 16, equation 1).[109] Recent developments include the asymmetric insertion of α-diazocarbonyl compounds (**61**) into the N–H bonds of carbamates **60**[110] (equation 2) and the transition-metal catalyzed addition of arylboronic acids (**64**) to iminoesters (**65**) (equation 3).[111]

Scheme 16. *Various strategies towards the synthesis of arylglycines.*



However, due to the lack of generality and functional diversity of most of these methods, the synthesis of arylglycines remains a challenging problem in organic chemistry, and the development of a general, stereoselective, environmental friendly and economically reasonable protocol for their preparation remains elusive.

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[105] (a) Evans, D. A,; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395. (b) Evans, D. A,; Britton,T. C. *J. Am. Chem.* Soc. **1987**, *109*, 6881.

[106] (a) Schollkopf, U.; Gruttner, S.; Anderskewitz, R.; Egert, E.; Dyrbusch, M. *Angew. Chem. Int. Ed.* **1987**, *26*, 683. (b) Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891.

[107] Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.

[108] Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207.

[109] Stöckenius, O. *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 2002.

[110] E. C. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 12066.

[111] (a) H. Dai, M. Yang, X. Lu, *Adv. Synth. Catal.* **2008**, *350*, 249. (b) M. A. Beenen, D. J. Weix, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 6304.

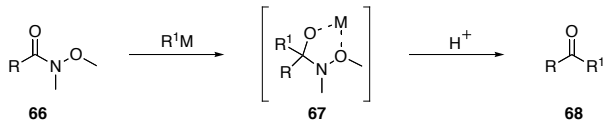
3.3. Weinreb amides in organic synthesis

3.3.1. Introduction

Since the initial report of Nahm and Weinreb in 1981,[112] *N*-methoxy-*N*-methyl amides (Weinreb amides) have become important and widely used intermediates for a variety of synthetic transformations. In particular, the reaction of Weinreb amides with organolithium or Grignard reagents to form ketones, and the selective reduction of this moiety to aldehydes are common transformations in modern organic synthesis.[113]

The unique reactivity of Weinreb amides is due to the putatively stable tetrahedral intermediate **67**, formed upon addition of the first equivalent of the organometallic species (Scheme 17). This stability precludes the collapse to a ketone under the reaction conditions and thus prevents the formation of tertiary alcohols even with a large excess of organometallic compound.[114]

Scheme 17. *Synthesis of ketones via a tetrahedral intermediate.*



66 **67** **68**

3.3.2. Demethoxylation of Weinreb amides

One of the most common side reactions of Weinreb amides with organometallic reagents and strong bases arises from reductive cleavage of the N-O bond, resulting in demethoxylation of the Weinreb amide. For example, when Weinreb amide **69** was treated with LDA at -78 °C, amide **70** was obtained as the major product (73%). Similar results were observed with Grignard[115] and organolithium reagents[116]. Mechanistically, the reaction was believed to take place through an E2 elimination as depicted in Scheme 18.[117]

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[112] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815.

[113] For reviews on Weinreb amides, see: (a) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707. (b) Sibi, M. P. *Org. Prep. Proced. Int*. **1993**, *25*, 15.

[114] For a detailed discussion of the mechanism, see: (a) Qu, B.; Collum D. B. *J. Org. Chem*. **2006**, *71*, 7117. (b) Adler, M.; Adler, S.; Boche, G. *J. Phys. Org. Chem*. **2005**, *18*, 193.

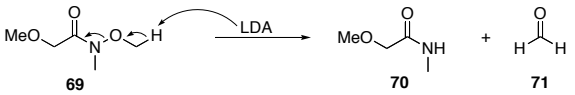
[115] Sibi, M. P.; Marvin, M.; Sharma, R. *J. Org. Chem*. **1995**, *60*, 5016.

[116] For recent examples, see: (a) Williams, I.; Reeves, K.; Kariuki, B. M.; Cox, L. R. *Org. Biomol*. Chem. **2007**, 5, 3325 (b) Shi, B.; Tang, P.; Hu, X.; Liu, J. O.; Yu, B. *J. Org. Chem*. **2005**, *70*, 10354.

[117] Graham, S. L.; Scholz, T. H. *Tetrahedron Lett*. **1990**, *31*, 6269.

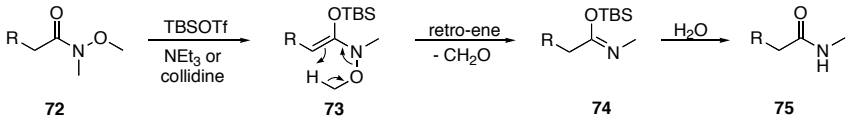
An alternative mechanism, involving initial formation of an enolate, was considered but dismissed as inconsistent with the experimental evidence.

Scheme 18. *Demethoxylation along an E2-mechanism*



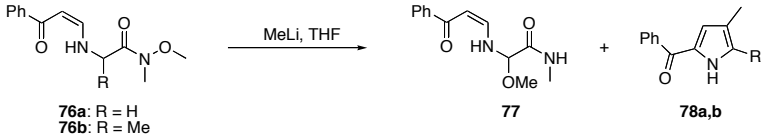
However, such a scenario was provided by Keck and coworkers for the reaction of Weinreb amide **72** with Et_3N and TBS triflate (Scheme 19).[118] It was suggested, that initial enolization leads to a retro-ene reaction to give imidate **74**, which affords the demethoxylated product **75** upon aqueous workup. A similar mechanism based on the formation of an imidate was also reported by Sardina and co-workers.[119]

Scheme 19. *Demethoxylation by a retro-ene fragmentation.*



A completely different type of demethoxylation was reported by Ortega and coworkers.[120] During their attempts to prepare pyrrole **78a** from Weinreb amide **76a** by addition of MeLi, migration of the *N*-methoxy substituent occurred and *N,O*-acetal **77** was isolated as the main product (61%). It was highlighted that no rearrangement is observed with α-substituted amide **76b** under the same reaction conditions (Scheme 20). However, no mechanism for the formation of **77** was given (a more detailed discussion about this type of rearrangement will be presented in chapter 4 of this thesis).

Scheme 20. *Intramolecular N→C-migration*

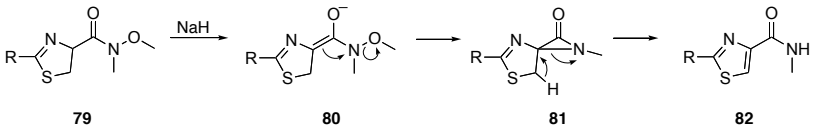


[118] Keck G. E.; McHardy S. F.; Murry J. A. *Tetrahedron Lett*. **1993**, *34*, 6215.
[119] Paleo, M. R.; Calaza, M. I.; Graña, P.; Sardina, F. J. *Org. Lett*. **2004**, *6*, 1061.
[120] Alberola, A.; Ortega, A. G.; Sadaba, M. L.; Sanudo, C. *Tetrahedron* **1999**, *55*, 6555.

3.3.3. Generation of α-lactams from Weinreb amides

Recently, Mislin and coworkers reported on a new type of demethoxylation[121] which involved the intermediate formation of α-lactams from Weinreb amides (Scheme 21).[122] During a synthesis of pyochelin analogues, it was observed that upon treatment with a base, thiazoline **79** was surprisingly converted to thiazole **82**. Mechanistically, the reaction was suggested to proceed via the deprotonation of **79** to enolate **80**, followed by cyclization to give α-lactam **81**. Aromatization and cleavage of the α-lactam moiety then yields **82**.

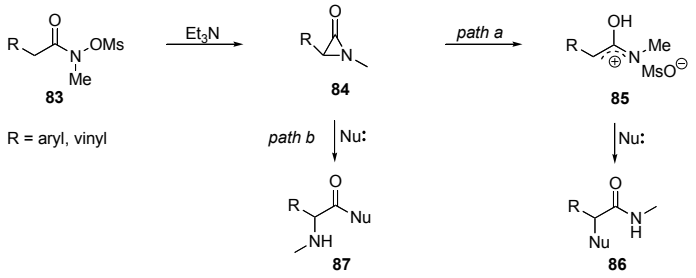
Scheme 21. *Intermediate formation of α-lactams from Weinreb amides.*



79 **80** **81** **82**

While the generation of α-lactams from Weinreb amides is very unusual and unexplored, other hydroxamic acid derivatives are known to easily form α-lactams upon treatment with a base. A well-studied example is the formation of α-lactam **84** from *N*-mesyloxy amides **83** (Scheme 22).[123] When **83** is reacted with weak nucleophiles such as hindered amines, chloride[123b] or azide,[123c] the lactam is regioselectively opened to give α-substituted amides **86**, the reaction most likely proceeding through an azaoxallyl cation intermediate **85** (path a). Stronger nucleophiles directly add to the carbonyl group and give rearranged α-amino amides **87** (path b).

Scheme 22. *Intermediate formation of α-lactams from N-mesyloxy amides.*



83 **84** **85** **87** **86**

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[121] Mislin, G. L.; Burger, A.; Abdallah, M. A. *Tetrahedron* **2004**, *60*, 12139.

[122] For a review, see: Lengyel, I.; Sheehan, J. C. *Angew. Chem. Int. Ed.* **1968**, *7*, 25.

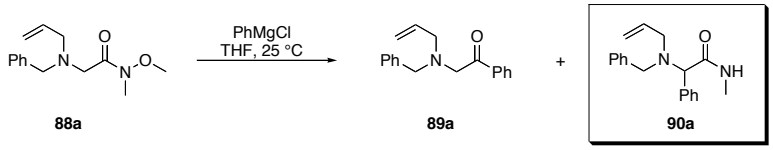
[123] (a) Hoffman, R. V.; Nayyar, N. K.; Klinekole, B. W. *J. Am. Chem. Soc.* **1992**, *114*, 6262. (b) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1992**, *57*, 5700. (c) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Am. Chem. Soc.*, **1993**, *115*, 5031. (d) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1993**, *58*, 2355. (e) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1995**, *60*, 4121.

3.4. Synthesis of α-amino acids from Weinreb amides

3.4.1. Introduction

During previous studies in our group, it was observed that the reaction of Weinreb amide **88a** with PhMgCl afforded secondary amide **90a** as the main product, as well as the desired ketone **89a** (Scheme 23).[124]

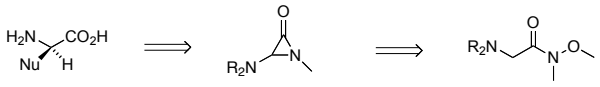
Scheme 23. *Weinreb amides derived from α-lactams.*



88a **89a** **90a**

Intrigued by the very surprising reaction outcome and, in particular, the synthetic value of the α-arylated product **90a**, we decided to further investigate this reaction. Speculating that the observed α-arylation reaction involves the intermediate generation of an α-lactam, we envisioned that this intermediate could serve as a new type of electrophilic glycine equivalent, representing a novel entry to α-amino acids (Figure 11).

Figure 11. *Weinreb amides as a new type of electrophilic glycine synthons.*



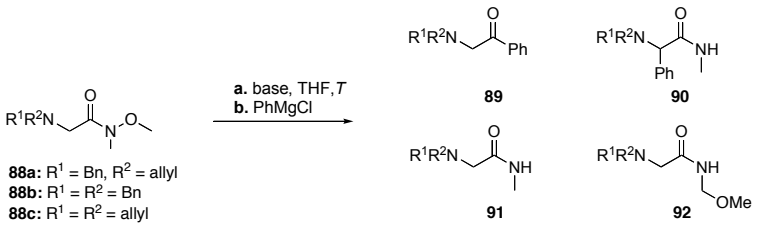
3.4.2. Screening of bases

Initial focus was directed towards identifying the optimal base and reaction conditions for generating the desired α-lactam. Our investigations commenced with amide **88b**, which was selected for initial screening due to its easy preparation and relatively simple ^{1}H NMR spectrum.[125] Deprotonation of **88b** with NaH under similar reaction conditions to those reported by Mislin (Scheme 21), followed by addition of PhMgCl, yielded the desired product **90b**, albeit in low yield (Table 3, entry 1). A similar result was obtained when the Grignard reagent itself was used as base and added at 0 °C to the reaction mixture (entry 2). It was speculated that the sterically demanding NBn_2 moiety in **88b** prevented a facile deprotonation at the α-carbon and to test this, compounds **88a**, **c**, having smaller *N*-protecting groups, were subjected to the

[124] Panknin, O.; Somfai, P. *unpublished results*.
[125] For the preparation of Weinreb amides **88a-c**, see paper IV.

reaction conditions (entries 3 and 4). Indeed, this resulted in an improved yield of the desired α-arylated products **90b**, **c** and lower amounts of the corresponding ketones. To suppress the formation of ketone **89** it is necessary that amide **88** is completely converted into the corresponding enolate prior to the addition of the nucleophile. However, deprotonation of **88b** with stronger bases such as LHMDS and *n*-BuLi gave only traces of the desired product (entries 5, 6). When LDA was used as base, formation of the acylation product **89a** could be completely prevented but the desired product **90b** was isolated in only 12% yield (entry 7). Instead, the main product from this reaction was demethoxylated amide **91a** and *N*,*O*-acetal **92a**.

Table 3. *Screening of base.*



entry	**88**	base (equiv)	*T* (°C)	products	product ratio[b]	yield **90** (%)[c]
1	**b**	NaH (1.2)	25	**90b**, **89b**	1:6	10
2	**b**	-	0	**90b**, **89b**	1:7	12[d]
3	**a**	-	0	**90a**, **89a**	1:1	44[d]
4	**c**	-	0	**90c**, **89c**	1:1	38[d]
5	**a**	LHMDS (1.5)	-78	n/d	n/d	n/d
6	**a**	BuLi (1.5)	-78	n/d	n/d	n/d
7	**a**	LDA (1.5)	-78	**90a**, **91a, 92a**	n/d	12

[a] Conditions: **88** (1.0 equiv), base and PhMgCl (2.0 equiv) in THF. [b] Ratio determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yield. [d] No base and 3.0 equiv PhMgCl were used.

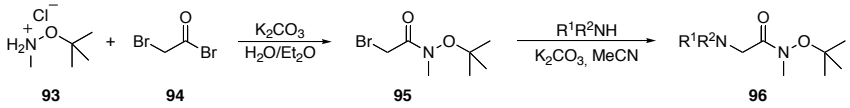
3.4.3. Use of N-tert-butoxy Weinreb amides

To minimize the formation of demethoxylated product **91**, the *N*-methoxy substituent in **88** was replaced by a *N-tert*-butoxy moiety. Thus modified Weinreb amides have recently been introduced by Genêt and coworkers in order to avoid demethoxylation along an E2 pathway (Scheme 18).[126]

[126] Labeeuw, O.; Phansavath, P.; Genêt, J.-P. *Tetrahedron Lett*. **2004**, *45*, 7107.

Substrates **96a-c** were synthesiszed from the corresponding secondary amines and bromide **95**, which can be obtained in good yield from hydrochloride **93**[126] and bromoacetyl bromide (**94**) (Scheme 24).

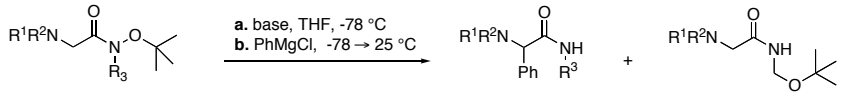
Scheme 24. *Synthesis of modified Weinreb amides* ***96****.*



93 **94** **95** **96**

To our delight, when subjecting amide **96a** to LDA and PhMgCl at -78 °C, the desired product **90a** was isolated in 77% yield (Table 4, entry 1). Simply decreasing the amount of base used resulted in an increased yield, allowing for 86% of **90a** (entry 2). Excellent yields were also obtained for bisallyl derivative **96c** (entry 3), while the use of amide **96b** (entry 4) resulted in the formation of considerable amounts of *N*,*O*-acetal **97b**. Thus, it seems that increased steric bulk at the α-amino moiety in **90** significantly slows down the enolization and allows for competing reaction pathways. In order to avoid the formation of **97**, the *N*-methyl substituent in **90b** was replaced by a phenyl group to give amide **98**. However, this compound gave the desired arylated product **99** only in moderate yields (entry 5).

Table 4. *Initial screening for optimal reaction conditions.*



96a: R^1 = Bn, R^2 = allyl, R^3 = Me
96b: R^1 = R^2 = Bn, R^3 = Me
96c: R^1 = R^2 = allyl, R^3 = Me
96d: R^1 = Bn, R^2 = allyl, R^3 = Ph

90a-c
98

97a-c

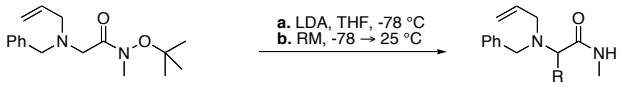
entry	**96**	base (equiv)	product	product ratio[b]	yield **90** (%)[c]
1	**a**	LDA (1.5)	**90a** + **97a**	>20:1	77
2	**a**	LDA (1.0)	**90a** + **97a**	>20:1	86
3	**c**	LDA (1.0)	**90c** + **97c**	>20:1	87
4	**b**	LDA (1.0)	**90b** + **97b**	7:1	72[e]
5	**d**	LDA (1.0)	**98**	n/d	70

[b] Ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yield. [d] No base and 3.0 equiv PhMgCl were used. [e] LDA was added at 0 °C.

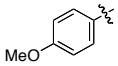
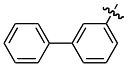
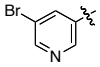
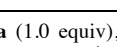
3.4.4. Screening of nucleophiles

With optimized conditions in hand, the reaction of **96a** with various nucleophiles was investigated (Table 5).

Table 5. *Reaction of Weinreb amide* ***96a*** *with nucleophiles.*[a]



96a **90a, e-n**

entry	R	RM	product	yield[b]
1		PhMgCl	**90a**	86
2		PhLi		n/d
3		Ph_2CuLi		n/d
4		PhZnCl		75
5		RMgBr	**90e**	77[c]
6		RMgBr	**90f**	92
7		RMgBr	**90g**	81[d]
8		RMgBr	**90h**	91[c]
9		RMgCl·LiCl	**90i**	77[d]
10		RMgCl·LiCl	**90j**	76[d]
11	Me	MeMgBr	**90k**	82[d]
12		*i*-PrMgCl	**90l**	79[d]
13		RMgBr	**90m**	82[d]
14		RMgCl·LiCl	**90n**	0

[a] Conditions: **96a** (1.0 equiv), LDA (1.0 equiv) and RM (2.0 equiv) in THF. [b] Isolated yield. [c] 1.5 equiv LDA were used. [d] LDA was added at 0 °C.

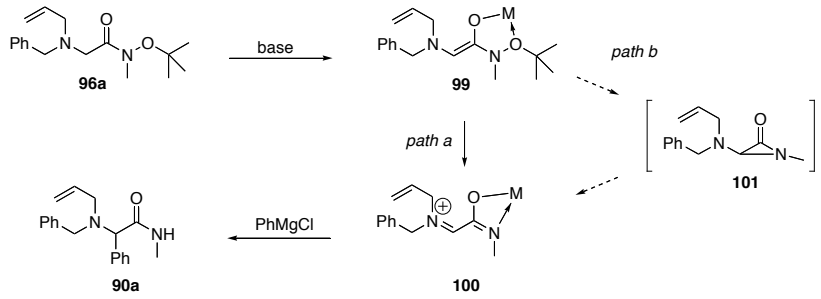
Both PhLi and Ph_2CuLi gave complex reaction mixtures with only trace amounts of **90a** being formed (entries 2, 3). Using PhZnCl gave good yields of **90a**, if the base was added at 0 °C. Both electron poor and electron rich aryl Grignard reagents proved compatible with the conditions and gave good to

excellent yields of the corresponding adduct (entries 5, 6). Similar yields were also obtained with bisphenyl (entry 7), heteroaromatic (entries 8, 9) and functionalized heteroaromatic Grignard reagents (entry 10). Remarkably, also alkyl and alkenyl Grignards can also be employed in the addition to **96a** (entries 11-13) while the use of Grignard reagent derived from (trimethylsilyl)acetylene gave only trace amounts of the desired product after column chromatography (entry 14).

3.4.5. Mechanistic considerations

The proposed mechanism for the formation of compound **90a** from **96a** is depicted in Scheme 25. In the first step, Weinreb amide **96a** is deprotonated to afford enolate **99**. As seen in Table 3, it is important that the base is sufficiently strong to allow for a fast and complete enolization in order to avoid undesired ketone formation by attack on the Weinreb amide. Similarly, if the α-carbon in **96** is sterically hindered, the base will preferentially deprotonate the amide *N*-Me moiety. Subsequent elimination of *t*BuO$^-$ from **99** constitutes the key step and generates iminium ion **100**. Addition of PhMgCl to **100** then gives amide **90a**. For the base-promoted addition of amines and halides to *O*-sulfonylated hydroxamic acid derivatives it has been shown that both α-CH deprotonation and loss of the *N*-OR moiety are occurring at the transition state of the rate-determining step.[123] Application of this scenario to the present reaction suggests the direct formation of iminium ion **100** from enolate **99** (path a), or conversion of **99** into the corresponding α-lactam **101** followed by ring opening to give **100** (path b). The overall result of this elimination is an unusual dipole reversal (umpolung) of the α-carbon in **96**,[127] converting the nucleophilic character of the enolate to an electrophilic one.

Scheme 25. *Proposed mechanism for the α-arylation of Weinreb amides*



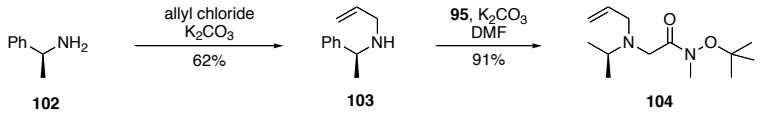
[127] Hase, T. *Umpoled Synthons: A Survey of Sources and Uses in Synthesis*; Wiley: New York, 1987.

3.5. Asymmetric synthesis of arylglycines

3.5.1. Use of (–)-α-methylbenzylamine as chiral auxiliary

With an operationally simple and high yielding procedure at hand, we next set out to develop an auxiliary controlled synthesis of enantiomerically enriched α-amino acids. Our investigations commenced with amide **104**, which was synthesized in two steps from (–)-α-methylbenzylamine (**102**), a simple yet powerful, chiral adjuvant (Scheme 26).[128] Both **102** and its enantiomer are available inexpensively in very high enantiomeric purity, which makes them attractive as stereodifferentiating agents even for large-scale operations.

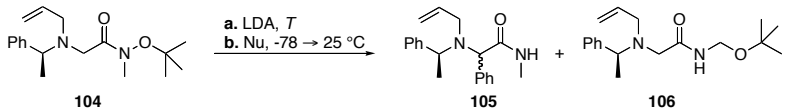
Scheme 26. *Synthesis of chiral Weinreb amide* ***104****.*



102 **103** **104**

With pure amide **104** in hand, we were pleased to find that α-arylation with PhMgCl and LDA afforded the desired product **105** (Table 6, entry 1).

Table 6*. Optimization of α-arylation using chiral amide* ***104***[a]



104 **105** **106**

entry	Nu	solvent	LDA (equiv)	*T* (°C)	**105** : **106**[b]	*dr* **105**[b]
1	PhMgCl	THF	1.4	-78	1.9:1	2.0:1
2	PhMgBr	THF	1.4	-78	2.5:1	1.4:1
3	$PhCeCl_2$	THF	1.4	-78	1.3:1	1.9:1
4	Ph_2Zn	THF	1.4	0	2.2:1	4.7:1
5	PhZnCl	THF	1.4	0	2.5:1	6.3:1
6	PhZnCl	tol	1.4	0	1.8:1	5.7:1
7	PhZnCl	Et_2O	1.4	0	4.0:1	5.5:1
8	PhZnCl	Et_2O	1.05	0	4.4:1	6.9:1[c]

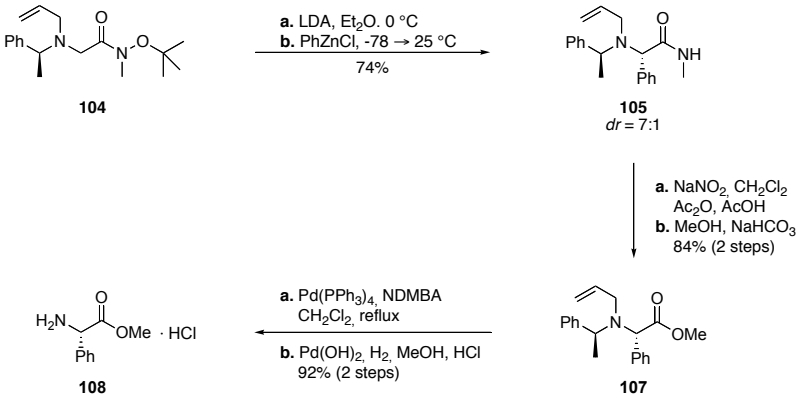
[a] Conditions: **104** (1.0 equiv), PhMgCl (2.0 equiv). [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] 1.2 equiv PhMgCl used.

[128] Juaristi, E., León-Romo, J.L., Reyes, A., Escalante, J. *Tetrahedron Asymmetry* **1999**, *10*, 2441.

However, **105** was formed with low diastereoselectivity and moderate yield (>60%), together with considerable amounts of *N,O*-acetal **106**. Apparently, the increased steric bulk imposed by the α-methylbenzyl moiety retards the desired enolization, making rearrangement to **106** competitive. Screening of less basic nucleophiles showed that zinc reagents gave both higher diastereoselectivities and less rearranged product (entries 3-5). By optimizing the solvent and amount of base, high selectivities were achieved when the reaction was performed in Et_2O with PhZnCl (entries 6-8). These optimized conditions afforded the desired α-arylated product in good yield and selectivity (74%, *dr* = 7:1).

The diastereomers could be separated by flash chromatography and the absolute configuration of the newly formed stereocenter in **105** was determined to be (*S*) via transformation into phenylglycine methyl ester hydrochloride **108** (Scheme 27). *N*-Nitrosation of **105** under standard conditions gave complete conversion to the corresponding nitrosoamide, which was directly subjected to MeOH and saturated $NaHCO_3$ to give ester **107** in 84% yield. Subsequent deallylation[129] and catalytic hydrogenolysis with $Pd(OH)_2$ gave enantiomerically pure **108** in good overall yield. No epimerization of the α-stereocenter could be observed during the ester formation and deallylation steps (Scheme 27) as determined by ^{1}H-NMR spectroscopic analysis of the crude products. For *ee* determination, **108** was converted to the free amine by treatment with $NaHCO_3$ in H_2O, and the *ee* was shown to be >96% by chiral HPLC.

Scheme 27. *Diastereoselective nucleophilic addition to amide* ***104****.*



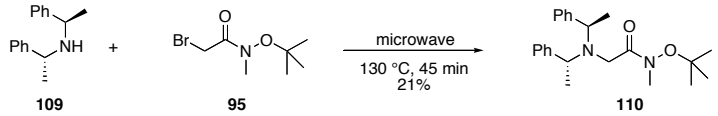
[129] Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109.

3.5.2. Use of (R,R)-α,α'-dimethyldibenzylamine as chiral auxiliary

As an expansion of our studies towards the diastereoselective synthesis of arylglycines, the use of (*R*,*R*)-α,α′-dimethyldibenzylamine (**109**) as an alternative chiral auxiliary was studied. Both **109** and its enantiomer are commercially available and have found wide application in organic synthesis, especially for the enantioselective deprotonation of prochiral ketones ("Simpkins base").[130] We reasoned that the use of this C_2-symmetric auxiliary should result in a strong chiral induction effect, due to the presence of two chiral centers close to the α-carbon.

However, the synthesis of amide **110** from chiral amine **109** and bromide **95** turned out to be a challenging problem. Due to the strong steric hindrance of **109**, no reaction occurred under standard alkylation conditions. Deprotonation of **109** with BuLi prior to the addition of **95** resulted exclusively in decomposition of the starting material. Gratifyingly, when **109** and **95** were heated without any solvent for 45 min under microwave irradiation, the desired product **110** was formed, albeit in low yield (Scheme 28). Even though no deeper investigation was undertaken, further optimization of the applied reaction conditions might result in the development of a straightforward protocol for the alkylation of sterically hindered amines.

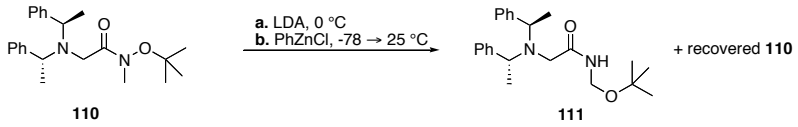
Scheme 28. *Synthesis of chiral Weinreb amide* ***110****.*



109 **95** **110**

With pure **110** in hand, the reaction with LDA and PhZnCl was investigated. Unfortunately, when **110** was treated under optimized reaction conditions, the main product formed was *N*,*O*-acetal **111**, and only traces of the desired arylated product could be isolated. Not surprisingly, the increased steric bulk imposed by the chiral auxiliary retards the desired enolization, making rearrangement to **111** the preferred reaction path.

Scheme 29. *Attempted α-arylation of* ***110****.*



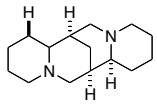
110 **111**

[130] For a review, see: Jaen, J. C. *Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis*; Paquette, L. A., Ed.; Wiley Interscience: New York, 2003; p 252.

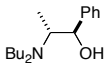
3.5.3. Enantioselective synthesis

Next, the enantioselective addition of PhMgCl to Weinreb amide **90a** was briefly investigated, examining a structurally diverse set of chiral ligands that have proved useful in a number of other enantioselective processes (Figure 12). Our initial focus was directed towards the use of (–)-sparteine (**112**), which previously has been used to achieve asymmetric reactions of organolithium and Grignard reagents.[131]

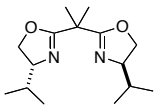
Figure 12. *Ligands used for the enantioselective a-arylation of Weinreb amides.*



112



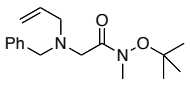
113



114

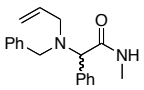
Disappointingly, employing conditions that sucessfully have been used by Fu and coworkers for the enantioselective desymmetrization of anhydrides, only little enantioselectivity was obtained. By using Mg(TMP)Cl as base, better enantioselection was achieved but the desired product was formed in very poor yield (entry 2). Running the reaction with a large excess of sparteine (4 equiv) led to a complete desactivation of the Grignard reagent, and only traces of product were formed (entry 3). Likewise, using amino alcohol **113** and bisoxazoline **114** as chiral ligands, formation of product was almost completely prevented (entries 4, 5).

Table 7. *Enantioselective α-arylation.*[a]



96a

a. base, -78 °C
b. PhMgCl, **L***



90a

entry	**L*** (equiv)	base	*ee* (%)[b]	yield (%)[c]
1	**112** (1.3)	LDA	8	89
2	**112** (1.3)	Mg(TMP)Cl	23	11
3	**112** (4.0)	LDA	n.d	<5
4	**113** (1.3)	LDA	n.d	<5
5	**114** (2.0)	LDA	n.d	<5

[a] Conditions: **96a** (0.5 equiv), PhMgCl (1.0 equiv). [b] Determined by chiral HPLC. [c] Determined by ^{1}H NMR of the crude reaction mixture, using 1-methoxy maphthalene as external standard.

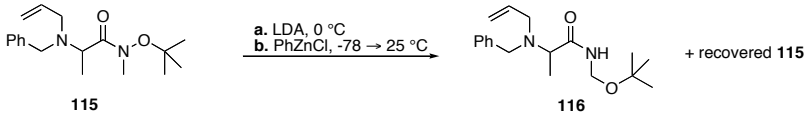
[131] Shintani, R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1057.

3.6. Synthesis of quaternary α-amino acids

Quaternary α-amino acids are an important class of compounds and display a variety of interesting biological properties.[132] For example, derivatives of α-methyl phenylglycine and its analogues have shown promising inhibitory activity toward metabotropic glutamate receptors.[133]

We decided to briefly investigate if the current methodology could be used for preparing such compounds. However, subjecting amide **115** to the standard conditions gave none of the desired product and only recovered starting material and *N*,*O*-acetal **116** were isolated (Scheme 30). In analogy to the attempted α-arylation of amide **110**, the additional steric hindrance at the α-carbon in **115** prevents an efficient enolization and makes the formation of the corresponding *N*,*O*-acetal a more favored process.

Scheme 30. *Attempted α-arylation of Weinreb amide* ***115****.*



3.7. Conclusions

In summary, an efficient and diastereoselective synthesis of α-amino acids from modified Weinreb amides and Grignard reagents has been developed. The key feature of this reaction is an umpolung of a glycine derived enolate, providing an alternative approach for the synthesis of α-amino acids.

[132] For a recent review, see: Vogt, H; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406.
[133] Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *64*, 120

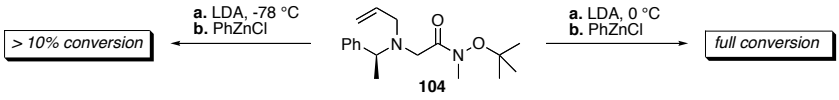
4. Synthesis of α-Amino Amides via *N,O*-Acetals Derived from Weinreb Amides

(Paper IV)

4.1. Introduction

During our studies on the α-arylation of Weinreb amides (see chapter 3), it was observed that for some substrates the conversion was strongly dependent on the temperature at which the base was added to the reaction mixture. For example, in the reaction of amide **104** with PhZnCl, full conversion was achieved when LDA was added at 0 °C. However, when LDA was added at -78 °C, **104** was almost completely recovered (Figure 13). Intrigued by this surprising result, we decided to reinvestigate the reaction mechanism.

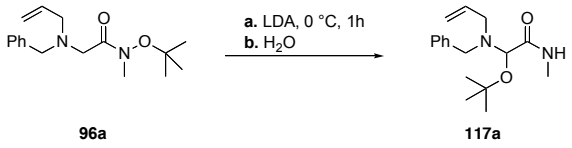
Figure 13. *Temperature dependence of the conversion of amide* ***104****.*



4.2. Rearrangement of Weinreb amides

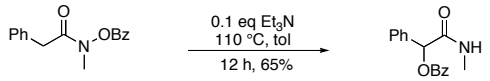
Our investigations commenced with quenching experiments, in which the reaction of Weinreb amide **96a** with LDA was terminated by the addition of water. When LDA was added at -78 °C, followed by quenching at the same temperature, only starting material was recovered. However, when the reaction was carried out at 0 °C and quenched after 1 h, the starting material was completely consumed, and a new compound, *N,O*-acetal **117a**, was formed as the main product (Scheme 31).

Scheme 31. *Base-induced rearrangement of Weinreb amide* ***96a****.*



It is of note that the same type of rearrangement has previously been described by Ortega and coworkers (see chapter 3.2, Scheme 20). Moreover, a related rearrangement of activated *N*-alkyl-*O*-acyl hydroxamic acid derivatives **118** has been reported by Clark and coworkers, showing that these substrates undergo smooth rearrangement to give secondary 2-acyloxyamides **119** upon heating with catalytic organic bases such as Et_3N (Scheme 32).[134]

Scheme 32. *Rearrangement of N-alkyl-O-acyl hydroxamic acid derivatives.*



118 **119**

Although it was initially postulated that the rearrangement of **118** takes place via a [3,3]-sigmatropic rearrangement of the corresponding enol form, cross-over experiments suggest that a free acyloxy anion is most likely to be involved.[134c] More recently, the rearrangement of unactivated substrates was accomplished by using phosphazene bases.[134] Interestingly, strong inorganic bases such as LDA or KHMDS do not yield any rearranged product, suggesting that the presence of a coordinating metal may switch the conformation of **118** to an unreactive one.

4.2.1. Results and discussion

The initial focus was directed towards optimizing the reaction conditions of the discovered rearrangement and examining its scope and limitations. As a first step we had to find a solution to the difficulties in isolating the formed *N,O*-acetal from the crude reaction mixture. However, all attempts to purify **117a** by standard methods failed, probably due to the sensitive nature of the *N,O*-acetal moiety. In order to circumvent purification and to reduce the formation of byproducts, a significantly milder base was employed. Indeed, with LHMDS full conversion was achieved after only 30 min, and quantitative yields of **117a** could be isolated after simple filtration (Table 8, entry 1). Also Weinreb amide **88a** and chiral substrate **104** afforded quantitative yields of the corresponding *N,O*-acetals (entries 2, 3). Notably, for the more bulky substrate **104** a prolonged reaction time (2 h) was necessary in order to achieve full conversion, and the product was obtained as a mixture of diastereomers (*dr* = 1:1.6). To investigate the influence of the hybridization of the *N*-substituents,

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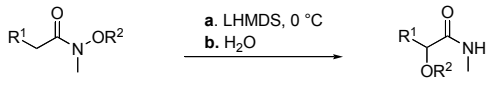
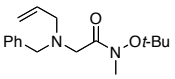
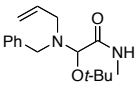
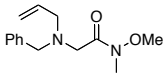
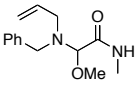
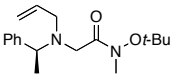
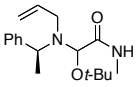
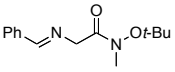
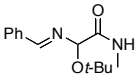
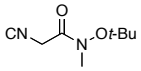
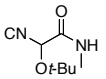
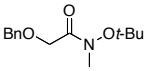
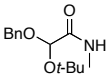
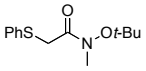
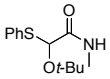
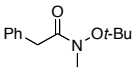
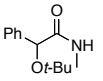
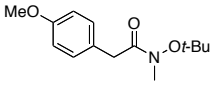
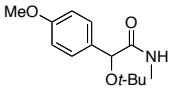
[134] (a) Clark, A. J.; Peacock, J. L. *Tetrahedron Lett*. **1998**, 39, 1265. (b) Al-Faiyz, Y. S. S.; Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Tetrahedron Lett*. **1998**, 39, 1269. (c) Clark, A. J.; Al-Faiyz, Y. S. S.; Broadhurst, M. J.; Patel, D.; Peacock, J. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, *7*, 1117. (d) Clark, A. J.; Al-Faiyz, Y. S. S.; Patel, D.; Broadhurst, M. J. *Tetrahedron Lett*. **2001**, *42*, 2007.

amides **120d, e** bearing an α-imino and α-isonitrilo group, respectively, were synthesized and employed under the same reaction conditions. However, no conversion was observed in either cases, and only starting material was recovered (entries 4, 5).

Table 8. *Base-promoted rearrangement of Weinreb amides* ***120****.*[a]



120 **117**

entry	Weinreb amide		*t* (min)	product		yield (%)[b,c]
1		**90a** (**120a**)	30		**117a**	quant
2		**88a** (**120b**)	30		**117b**	99
3		**104a** (**120c**)	120		**117c**	99[d]
4		**120d**	120		**117d**	0[e]
5		**120e**	120		**117e**	0[e]
6		**120f**	30		**117f**	92
7		**120g**	30		**117g**	0[e]
8		**120h**	120		**117h**	0[e]
9		**120i**	360		**117i**	9
10			360			14[f]

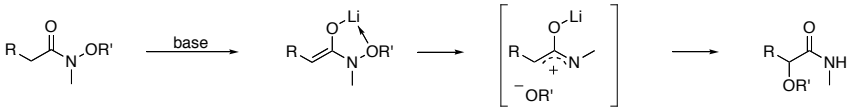
[a] Conditions: **120** (0.20 mmol), base (0.24 mmol), THF (2 mL). [b] Isolated yield. [c] "quant" means: ^{1}H NMR purity of the crude product > 95%; mass balance > 99%. [d] *dr* = 1:1.6, determined by ^{1}H NMR of the crude product. [e] Starting material recovered. [f] LHMDS was added at room temperature.

Remarkably, when the amino moiety was replaced by an α-hydroxy substituent to give amide **120f**, full conversion to the corresponding *O*,*O*-acetal **117f** was achieved, while the use of α-thiophenyl amide **120g** resulted exclusively in recovery of starting material (entries 6, 7). Based on these results, we were intrigued to determine if substrates lacking an α-heteroatom would show similar rearrangement upon treatment with a base, and substrate **120h** with an α-phenyl substituent was tested under the same reaction conditions. However, no rearranged product **117h** was obtained, and only starting material could be recovered (entry 8). In order to increase the reactivity, we next exchanged the phenyl substituent for a 4-methoxyphenyl group, envisioning that any positive charge formed during the elimination of *t*-BuO^- would be stabilized by the strongly electron-donating substituent. Indeed, stirring Weinreb amide **120i** with LHMDS for 6 h at 0 °C afforded the desired product **117i**, albeit in poor yield along with unreacted starting material (entry 9). Increasing the reaction temperature resulted in full conversion, but the yield was only slightly improved, and many unidentified byproducts were formed (entry 10).

4.2.2. Mechanistic considerations

Without further experimental data, the exact mechanism for the rearrangement of Weinreb amides **120** to secondary 2-alkoxy amides **117** can only be speculated. It is believed that the reaction occurs in analogy to the α-arylation of Weinreb amides described in chapter 3, the first step being a deprotonation of amide **120** to afford enolate **121**. Subsequent elimination of the *N*-alkoxy moiety generates then an ion pair **122**, which recombines to give the final rearranged product **117** (Scheme 33).

Scheme 33. *Suggested mechanism for the rearrangement of Weinreb amides* ***120****.*



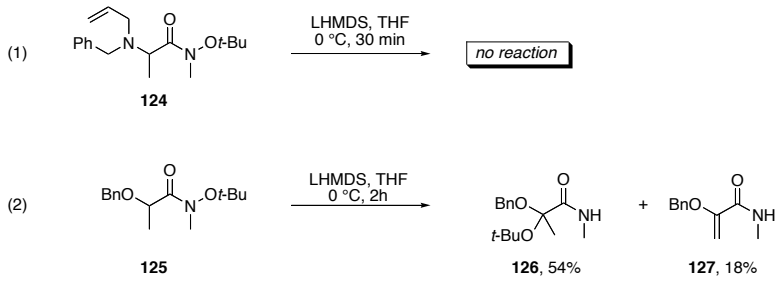
120 **121** **122** **117**

Alternatively, an intramolecular displacement of the *N*-alkoxy group in **121** furnishes an α-lactam, which then ring opens to ion pair **122**. However, as seen in Table 8, for the rearrangement to occur it is crucial that the α-substituent R is capable to stabilize a positive charge by a sufficiently strong mesomeric or inductive effect, indicating that elimination to an ion pair is the rate-determining step. This is in contrast to the related rearrangement of *N*-sulfonyloxy and *N*-acyloxy amides, where enolization of the amide has been shown to be the rate-determining step, and groups that were able to stabilize a negative charge led to increased rates of product formation.

To provide further evidence for the existence or non-existence of an intermediate α-lactam, the effect of an α-substituent was investigated. In this respect, it was reported both by Clark and Hofmann that *N*-sulfonyloxy and *N*-acyloxy amides with an additional substituent at C-2 do not undergo base mediated rearrangements, due to a large steric interaction with the *N*-Me substituent, which prevents the formation of an α-lactam.[123c, 134c]

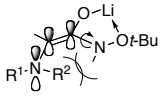
Indeed, employing α-substituted amide **124** under standard conditions, no rearrangement occurred even when a large excess of base (10 equiv) was used, and only starting material could be recovered (Scheme 34, equation 1). However, when α-substituted amide **125** was treated with LHMDS at 0 °C, full conversion was achieved within 2 h, and the desired ketal **126** was formed in 54% yield, along with minor amounts of amide **127** (equation 2).

Scheme 34. *Base mediated rearrangement of α-substituted Weinreb amides.*



Thus, it appears that the rearrangement of amides **120** and **125** most likely proceeds via the direct formation of an ion pair from the corresponding enolate. The different reactivity between α-substituted amides **124** and **125** might be due to their enolate geometry. It is believed that enolates derived from substrates with an additional α-methyl substituent will preferentially have (*E*) geometry, due to $A^{1,3}$ interactions between the α-carbon substituent and the *N*-Me substituent. However, the elimination of *t*-BuO^- requires a conformation in which the N–O bond is anti-periplanar to the π-system to enable overlap with the N–O antibonding orbital. Thus, the missing ability of **124** to undergo rearrangement can be explained as a failure to achieve the requisite N–O bond orientation, due to a large steric interaction between the amino substituents and the *N*-Me moiety (Figure 14).

Figure 14. *Hindered rotation around the C-N bond in the enolate of* ***124****.*



4.3. Synthesis of α-amino amides from *N,O*-acetals

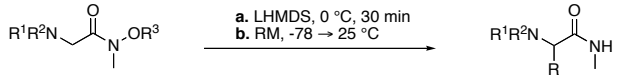
N,O-acetals represent versatile intermediates in organic synthesis and have frequently been used as electrophilic glycine synthons for the synthesis of α-amino acids.[135] Consequently, with an easy and high yielding procedure for the synthesis of *N,O*-acetals **117** in hand, we set out to explore their potential as versatile glycine cation equivalents.[136, 137]

4.3.1. Results and discussion

Due to the delicate nature of *N,O*-acetals **117**, we planned to generate them in situ, prior to the addition of a nucleophile. Thus, when **96a** was treated with LHMDS for 30 min at 0 °C, followed by addition of PhMgCl at -78 °C, complete conversion was achieved and amide **90a** could be isolated in 96% yield (Table 9, entry 1). Somewhat surprisingly, when Weinreb amide **88a** was used instead, the desired product was only isolated in moderate yields (entry 2) together with unreacted *N,O*-acetal **117b**. Also bis(allyl)-protected amide **96c** gave excellent yields whereas in the reaction of the bis(benzyl)-protected substrate **96b** some byproducts were formed (entries 3, 4).

Screening of different Grignard reagents showed that electron rich (entry 5), electron poor (entry 6) and functionalized heteroaromatic arylgrignards (entry 7) gave excellent yields under the selected reaction conditions. In addition, it was found that the use of alkyl- (entries 8, 9), alkenyl- (entry 10) and alkynyl (entry 11) Grignard reagents also afforded the corresponding α-amino amides in quantitative yields. For several products no purification by column chromatography was needed and quantitative amounts of the analytically pure material could be obtained by simple filtration through silica (entry 6, 9-11).

Table 9. *Synthesis of α-amino amides* ***90*** *from in-situ generated N,O-acetals.*[a]

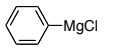
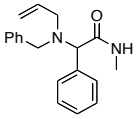
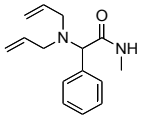
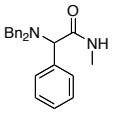
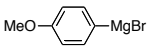
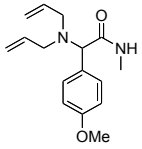
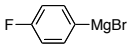
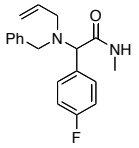
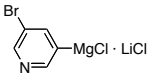
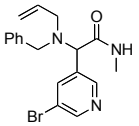
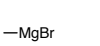
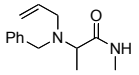
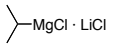
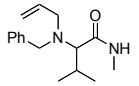
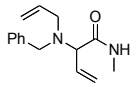
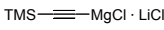
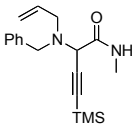


96 **90**

[135] For reviews, see: Meester, W. J. N.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. *Eur. J. Org. Chem.* **2003**, 2519.

[136] For related applications of *N,O*-acetals, see: (a) Sakai, N.; Asano, J.; Shimano, Y.; Onakahara, T. *Tetrahedron* **2008**, *64*, 9208. (b) Bourhis, M.; Bosc, J. J.; Golse, R. *J. Organomet. Chem.* **1983**, *256*, 193. (c) Gloede, J.; Freiberg, J.; Bürger, W.; Ollmann, G.; Groß, H. *Arch. Pharm.* **1969**, *302*, 354. (d) Groß, H.; Gloede, J.; Freiberg, J. *Liebigs Ann. Chem.* **1967**, *702*, 68.

[137] For a review on glycine cation equivalents, see: Bailey, P. D.; Boa, A. N.; Clayson, J. *Contemp. Org. Synth.* **1995**, *2*, 173.

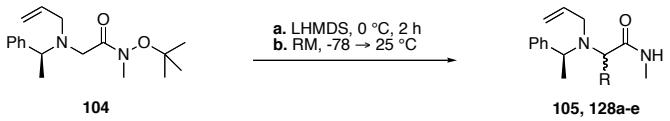
entry	amide	RM	product		yield (%)[b,c]
1	**96a**			**90a**	96
2	**88a**				51
3	**96c**			**90c**	97
4	**96b**			**90b**	82
5	**96c**			**90o**	95[d]
6	**96a**			**90e**	96 (quant)[e]
7	**96a**			**90j**	85
8	**96a**			**90k**	96
9	**96a**			**90l**	quant
10	**96a**			**90m**	quant
11	**96a**			**90n**	quant

[a] Conditions: **88**, **96** (0.1 mmol), LHMDS (0.12 mmol), RM (0.2 mmol), THF (2 mL). [b] Isolated yield. [c] "quant" means: ^{1}H NMR purity of the crude product >95%; mass balance >99%. [d] The reaction was performed on a 0.2 mmol scale. [e] The reaction was performed on a 2.5 mmol scale.

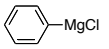
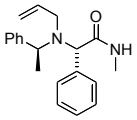
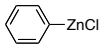
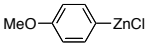
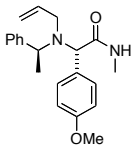
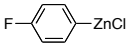
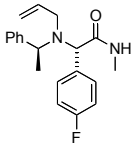
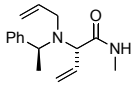
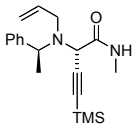
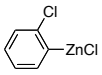
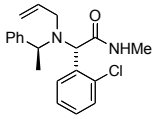
4.3.2. Diastereoselective synthesis

In the next step, the stereoselective synthesis of α-substituted glycine derivatives was investigated. Towards this end, subjecting chiral amide **104** to LHMDS for 2 h at 0 °C, followed by addition of PhMgCl at -78 °C, afforded compound **105** in excellent yield, but in poor *dr* (Table 10, entry 1).

Table 10. *Asymmetric synthesis of α-amino amides*[a]



104 **105, 128a-e**

entry	RM	product		yield (%)[b,c]	*dr*[d]
1			**105**	91	2:1
2				93	8:1
3			**128a**	95	6:1
4			**128b**	90	4:1
5			**128c**	67	2:1
6			**128d**	quant	2:1
7			**128e**	84[e]	7:1

[a] Conditions: **104** (0.2 mmol), LHMDS (0.24 mmol), RM (0.3 mmol), THF (2 mL). [b] Isolated yield. [c] "quant" means: ^{1}H NMR purity of the crude product >95%; mass balance >99%. [d] dr determined by ^{1}H NMR of the crude product. [e] The reaction was performed on a 8.15 mmol scale.

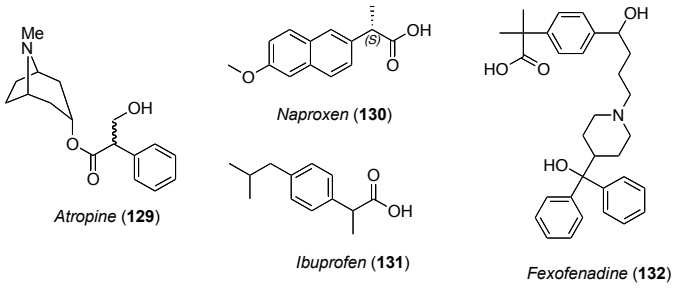
However, when PhZnCl was used instead, the selectivity was significantly enhanced, and amide **105** was obtained in 93% yield as a 8:1 mixture of diastereomers (entry 2). It should be noted that the dr obtained in these reactions do not correspond to the one obtained for the formation of **117c** (Table 8, entry 3), indicating that an iminium ion is formed upon the addition of the nucleophile. Similar yields and selectivities were also obtained for electron rich (entry 3) and electron poor arylzinc reagents (entry 4), whereas only moderate selectivity was obtained with alkenyl- and alkynylzinc reagents (entry 5, 6). Using (2-ClC_6H_4)ZnCl as a nucleophile, amide **128e** could be synthesized in good yield and selectivity on gram scale (entry 7). Based on this intermediate, a straightforward synthesis of clopidogrel (**13**) should be possible, and future work will focus on the realization of this strategy.[138]

4.4. α-Arylation of Weinreb amides

4.4.1. Introduction

As an extension of the methodology discussed in this chapter, we envisioned that Weinreb amides without an α-amino group would likewise represent suitable substrates for the α-arylation with Grignard reagents. The products formed in such a reaction, α-aryl carboxylic acid derivatives, represent highly valuable building blocks in organic synthesis and are prevalent in many important natural products and drugs (Scheme 35), such as atropine (**129**), naproxen (**130**), ibuprofen (**131**) and fexofenadine (**132**). Consequently, the development of efficient methods for the synthesis of α-aryl carboxylic acids is an important area of research in synthetic organic chemistry.

Figure 15. *Important pharmaceuticals derived from α-aryl carboxylic acids.*

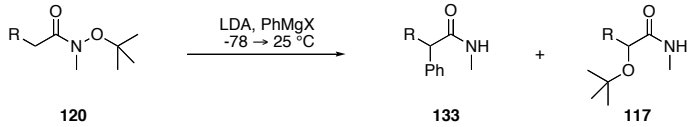


[138] For a recent synthesis of clopidogrel, see: (b) Wang, L. X.; Shen, J. F.; Tang, Y.; Chen, Y.; Wang, W.; Cai, Z. G.; Du, Z. J. *Org. Process Res. Dev.* **2007**, *11*, 487.

4.4.2. Results and discussion

We started our investigations with amide **120i**, speculating that the electron-rich 4-methoxyphenyl substituent not only activates the substrate to migration of the *N*-alkoxy group, but also would facilitate α-arylation. Thus, when **120i** was treated with LDA and PhMgCl at -78 °C and warmed to room temperature, full conversion was achieved within 30 min, and the desired product **133i** was isolated in 42% yield along with equimolar amounts of the migration product **117i** (Table 11, entry 1). Notably, the same reaction gives only traces of **117i** when no Grignard reagent is added. This indicates that PhMgCl not only acts as a nucleophile but also strongly enhances the reactivity of the Weinreb amide. In order to suppress the undesired formation of **117i**, the reaction conditions were optimized: switching from THF to toluene and using an excess of concentrated PhMgBr increased both the yield and selectivity, and **133i** was isolated in 67% yield (entry 2).

Table 11. *α-Arylation of Weinreb amides.*



120 **133** **117**

entry	**120**	R	solvent	PhMgX (equiv)	**133**:**117** [b]	yield **133** (%)[c]
1	**i**	4-MeOC_6H_4	THF	PhMgCl (2)	1:1	42
2	**i**	4-MeOC_6H_4	tol	PhMgBr (7.5)	4:1	67
3	**h**	Ph	tol	PhMgBr (7.5)	n.d.	40
4	**j**	Me	tol	PhMgBr (7.5)	n.d.	56
5	**f**	BnO	tol	PhMgBr (7.5)	1:2	34
6	**g**	PhS	tol	PhMgBr (7.5)	1:3	29

[a] Reaction conditions: **120** (0.20 mmol), LDA (0.24 mmol), THF (2 mL). [b] ratio determined by ^{1}H NMR of the crude product. [c] Isolated yield.

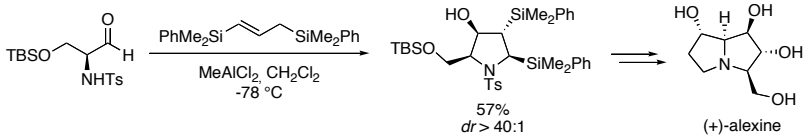
Using these optimized conditions, a selection of Weinreb amides was next screened. Gratifyingly, both substrates bearing non-activated aryl (entry 3) and alkyl (entry 4) groups gave the desired arylated product in moderate yield and without detectable migration of the *tert*-butoxy group. However, with α-heteroatom-substituted Weinreb amides **120f** and **120g**, only minor amounts of the arylated amides were formed, the main product being the corresponding *O,O*- and *S,O*-acetal, respectively (entry 5 and 6).

4.5. Synthesis of α-amino-γ-lactones

4.5.1. Introduction

Allylsilanes are versatile and widely used building blocks in organic chemistry.[139] Due to the efficient σ→p hyperconjugative stabilization of β-silyl carbocations by adjacent C–Si bonds, they can function as synthetic equivalents of 1,2- and 1,3-dipoles in [3+2]-annulation reactions to aldehydes,[140] imines[141] and chlorosulfonyl isocyanates,[142] providing efficient entry to a variety of heterocycles. A recent example is the synthesis of functionalized pyrrolidines by a highly stereoselective [3+2]-annulation reaction of 1,3-bis(silyl)propenes and *N*-Ts-α-amino aldehydes by Restorp et al.,[143] which successfully has been applied in the total synthesis of the pyrrolizidine alkaloid (+)-alexine (Scheme 35).[144]

***Scheme 35**. [3+2]-annulation reaction of 1,3-bis(silyl)propenes.*



4.5.2. Synthesis of α-amino-γ-lactones

Functionalized α-amino-γ-lactones (homoserine lactones) are the structural feature of a number of natural products and have also found application as versatile building blocks in natural product synthesis.[145] For example, lactone **134** has been applied as a key intermediate in the total synthesis of clavalanine (**135**), an antibiotic from *streptomyces clavuligerus* (Scheme 36).[146]

---

[139] For recent reviews, see: (a) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*, Wiley: New York; 2000. (b) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173.

[140] (a) G. C. Micalizio, W. R. Roush, Org. Lett. **2000**, 2, 461. (b) J. S. Panek, M. Yang, *J. Am. Chem. Soc.* **1991**, *113*, 9868. (c) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **2002**, *124*, 3608.

[141] J. S. Panek, N. F. Jain, *J. Org. Chem.* **1994**, *59*, 2674.

[142] (a) A. Romero, K. A. Woerpel, *Org. Lett.* **2006**, *8*, 2127. (b) Roberson, C.W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434.

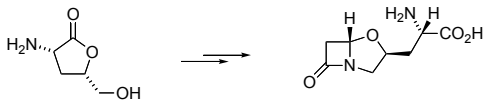
[143] (a) Restorp, P.; Fischer, A.; Somfai, P. *J. Am. Chem. Soc.* **2006**, *128*, 12646. (b) Restorp, P.; Dressel, M.; Somfai, P. *Synthesis* **2007**, 1576.

[144] Dressel, M.; Restorp, P.; Somfai, P. *Chem. Eur. J.* **2008**, *14*, 3072.

[145] Smith, A. B., III; Liu, H.; Hirschmann, R. *Org. Lett.* **2000**, *2*, 2041.

[146] De Bernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50,* 3457.

Scheme 36. *Example for the use of α-amino-γ-lactones in natural product synthesis.*

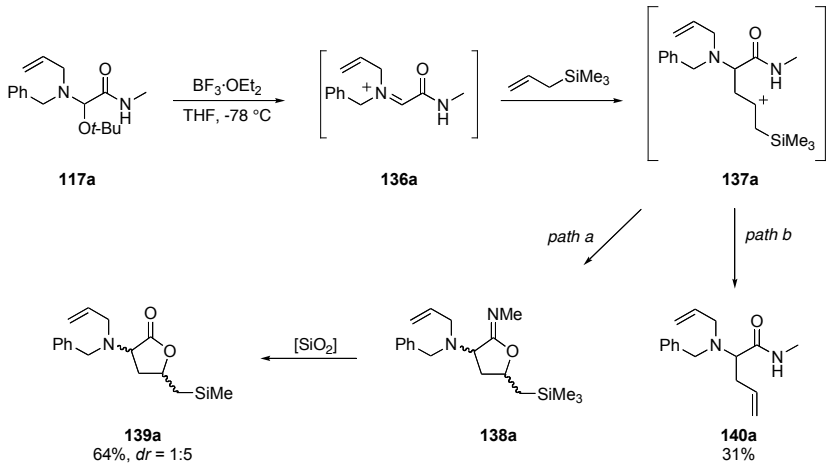


134 *Clavalanine* (**135**)

Only few methods for the preparation of α-amino-γ-lactones have been reported, including $InCl_3$-mediated tandem cyclization of alkenes with glyoxylates and amines,[147] and cycloaddition of nitrenes with alkenes.[148]

It was envisioned that γ-lactones could be prepared from *N,O*-acetals **117** and allylsilanes by a [3+2] annulation reaction. To our delight, when *N,O*-acetal **117a** was treated with allyltrimethylsilane (5 equiv) and $BF_3{\cdot}OEt_2$ (2 equiv) at -78 °C, γ-lactone **139a** was obtained in good yield as a mixture of diastereomers (64%, *dr* = 5:1), along with 31% of amide **140a** (Scheme 37). It is of note, that the initial product formed in the annulation reaction is imino lactone **138a**, which during purification by flash chromatography is hydrolyzed to the final product. The reaction is suggested to commence with the nucleophilic attack of allyltrimethylsilane to the initially formed iminium ion **136a**, furnishing the β-Si-stabilized carbocation **137a**. This is then followed by an intramolecular cyclization to give imino lactone **138a** (path a), or by an elimination of the silyl group to afford amide **140a** (path b).

Scheme 37. *Suggested mechanism for the formation of γ-lactone **139a**.*



117a **136a** **137a**

path a *path b*

139a
64%, *dr* = 1:5

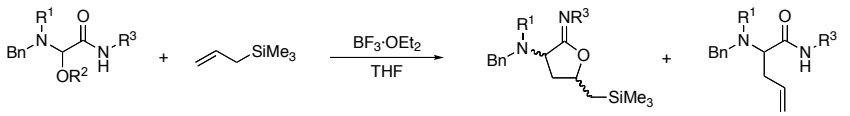
138a

140a
31%

147 Huang, T.; Li, C.-J. *Tetrahedron Lett*. **2000**, *41*, 9747.
148 Baldwin, S. W.; Long, A. *Org. Lett*. **2004**, *6*, 1653.

Next, different reaction conditions were screened to minimize the undesired formation of allylation product **140**, albeit without success (Table 12). Surprisingly, the use of *N,O*-acetal **117b** resulted in a decrease in the formation of cyclized product (entry 2), while variation of the *N*-protective group had little influence on the selectivity (entry 3). Not unexpected, increase of the reaction temperature lead to a strong increase in formation of **140** (entry 4). Finally, replacing the *N*-Me moiety by a phenyl substituent completely suppressed the desired cyclization reaction (entry 5).

Table 12. *[3+2] annulation of N,O-acetals **117** with allyltrimethylsilane.*



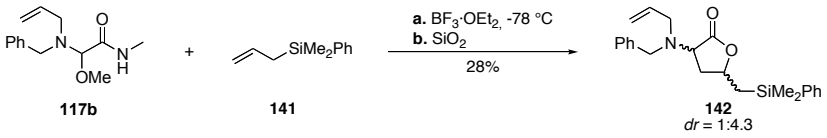
117a, b, j, k **138** **140**

entry	**117**	R^1	R^2	R^3	*T* (°C)	**138**:**140**[a]
1	**a**	allyl	*t*-Bu	Me	-78	71:29
2	**b**	allyl	Me	Me	-78	63:37
3	**j**	Bn	Me	Me	-78	61:39
4	**j**	Bn	Me	Me	-20	39:67
5	**k**	allyl	*t*-Bu	Ph	-78	0:100

[a] Ratio determined by ^{1}H NMR of the crude product.

The synthetic utility of γ-lactone **140** would significantly be increased if the silyl moiety could be converted to a hydroxyl group.[149] In contrast to alkylsilane moieties, which generally cannot be oxidized to a hydroxyl group, the dimethylphenylsilyl group is known as a hydroxyl group equivalent. However, treating *N,O*-acetal **117b** with silane **141** and $BF_3{\cdot}OEt_2$ at -78 °C afforded the desired γ-lactone **142** in poor yield (Scheme 38). Disappointingly, attempts to optimize the reaction by screening a survey of different Lewis acids, solvents and reaction temperatures did not meet with success.[150]

Scheme 38. *[3+2] annulation using N,O-acetal **117b** and silane **141**.*

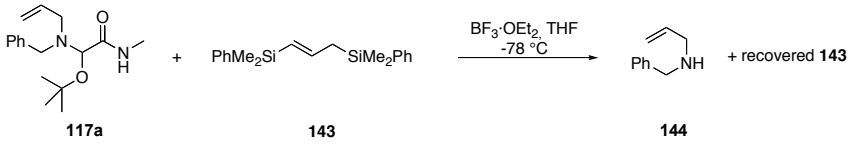


117b **141** **142**
dr = 1:4.3

[149] Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.
[150] Screened Lewis-acids: $TiCl_4$, MgOTf, $(Ph_3C)BF_4$; screened solvents: DCM, toluene.

Inspired by the work of Somfai and Restorp,[143] the reaction of **117** with 1,3-bis(silyl)propenes was investigated in a last step. Reacting *N,O*-acetal **117a** with silane **143** and $BF_3{\cdot}OEt_2$ at -78 °C resulted in complete decomposition of the *N,O*-acetal (Scheme 39) and no product was formed. However, this result is not unexpected due to the low nucleophilicity of 1,3-bis(silyl)propenes.

Scheme 39. *Attempted [3+2] annulation using silane **143**.*



117a **143** **144**

4.6. Conclusions

In summary, we have demonstrated that Weinreb amides easily can undergo a base-promoted rearrangement, effecting migration of the *N*-alkoxy group to the α-carbon. Based on this reaction we have developed a simple and high yielding synthesis of α-amino amides from readily available starting materials. As an extension of this procedure, we have also shown that modified Weinreb amides without an α-amino group can undergo α-arylation with Grignard reagents. Furthermore, a new approach for the synthesis of functionalized α-amino-γ-lactones by a [3+2]-annulation of *N,O*-acetals and allylsilanes has been developed.

5.
Concluding Remarks

This thesis deals with the development of new methodology in organic synthesis for the stereoselective construction of carbon-carbon bonds.

Specifically, the ring-expansion of 2-vinylaziridines has been studied. This investigation resulted in the development of a straightforward and high-yielding protocol for the synthesis of 3-pyrrolines, an important class of *N*-heterocycles. Furthermore, this approach was successfully implemented as a key step in the formal total synthesis of the antibiotic (–)-anisomycin.

In addition, a general and high yielding protocol for the synthesis of α-amino amides from Weinreb amides and Grignard reagents has been developed. An asymmetric version has also been realized by employing a chiral auxiliary, which easily can be removed to afford the corresponding enantiopure α-amino acid.

To conclude, the development of new methodology in organic chemistry is indispensable to serve the increasing demand for new organic compounds. In particular, future work has to meet the challenges posed by the need for efficient, selective and environmentally benign transformations. To date, only a tiny fraction of the enormous diversity of organic molecules has been explored by synthetic chemists, and further exploration will result in great benefits to mankind.

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Fünf wunderbare Jahre in Stockholm gehen zu Ende, und herzlich sei an dieser Stelle allen gedankt, die das Zustandekommen dieser Dissertation ermöglicht haben.

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Antje und *Sophie* dafür, dass es euch gibt!

Appendix A

The following is a description of my contribution to Publications **I** to **IV**, as requested by KTH.

Paper I: I contributed to the formulation of the research problems, performed the experimental work and wrote the manuscript.

Paper II: I contributed to the formulation of the research problems, performed the experimental work, supervised diploma worker Magnus Edefuhr and wrote the manuscript.

Paper III: I contributed to the formulation of the research problems, performed the majority of the experimental work and supervised Erasmus student Donata K. Kirchner, who prepared and reacted substrate **96d** and **98**. I wrote the manuscript.

Paper IV: I contributed to the formulation of the research problems, performed the experimental work and wrote the manuscript.

Appendix B

This appendix contains spectroscopic data for compounds mentioned in this thesis but not reported in publications I-IV.

Compound **34**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (d, *J* = 12.5 Hz, 1H), 3.66-3.57 (m, 1H), 2.98-2.89 (m, 2H), 1.84-1.78(m, 1H), 1.60-1.22 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.3, 77.0, 76.6, 61.6, 58.4, 55.9, 31.7, 31.5, 29.0, 25.8, 22.5, 14.0 ppm.

Compound **35**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.58 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H,), 5.45 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.25 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.09 (dd, *J* = 7.5, 2.1 Hz, 1H), 2.82 (dt, *J* = 5.6, 2.1 Hz, 1H), 1.60-1.22 (m, 10H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 118.8, 60.4, 58.7, 31.9, 31.7, 29.0, 25.8, 22.5, 14.0 ppm.

Compound **36**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (m, 2H), 7.28 (m, 2H), 5.62 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H), 5.11-5.01 (m, 2H), 5.18 (d, *J* = 8.3 Hz, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 2.41 (s, 3H), 1.90 (d, *J* = 4.8 Hz, 1H), 1.43-1.16 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 137.7, 132.4, 129.5, 127.1, 118.8, 73.6, 60.3, 33.3, 31.6, 29.0, 25.5, 22.5, 21.5, 14.0 ppm.

Compound *trans*-**37a**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (m, 2H), 7.30 (m, 2H), 6.04 (ddd, *J* = 17.0, 10.2, 9.3 Hz, 1H), 5.47 (dd, *J* = 17.0, 0.7 Hz, 1H), 5.33 (dd, *J* = 10.2, 0.7 Hz, 1H), 3.09 (dd, *J* = 9.3, 4.4 Hz, 1H), 2.92 (ddd, *J* = 6.9, 6.0, 4.4 Hz, 1H), 2.42 (s, 3H), 1.28-1.10 (m, 12H), 0.84 (t, *J* = 7.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 137.1, 132.0, 129.3, 127.4, 121.4, 51.8, 48.7, 31.5, 30.5, 28.6, 26.8, 22.3, 21.5, 13.9 ppm.

Compound *cis*-**37a**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (m, 2H), 7.32 (m, 2H), 5.60 (m, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.3 Hz, 1H), 3.36 (t, *J* = 7.2 Hz, 1H), 2.87 (q, *J* = 6.8 Hz, 1H), 1.48-1.37 (m, 2H), 1.30-1.10 (m, 8H), 0.85 (t, *J* = 6.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 135.3, 129.9, 129.5, 127.8, 121.1, 45.6, 45.6, 31.5, 28.7, 26.8, 26.8, 22.4, 21.6, 14.0 ppm.

Compound **37c**
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.69 (m, 2H), 7.28 (m, 2H), 5.58 (m, 2H), 4.36 (m, 1H), 4.12-3.98 (m, 2H), 2.41 (s, 3H), 1.87 (m, 1H), 1.79-1.63 (m, 5H), 1.34-0.84 (m, 5H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.1, 134.9, 129.5, 127.6, 127.3, 125.3, 72.2, 55.9, 43.2, 29.6, 26.9, 26.5, 26.3, 25.8, 21.4 ppm.

Compound **39a**
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (m, 2H), 7.28 (m, 2H), 5.61-5.55 (m, 2H), 4.49-4.44 (m, 1H), 4.12-4.09 (m, 2H), 2.41(s, 3H), 1.83-1.67 (m, 2H), 1.35-1.20 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.2, 134.9, 129.8, 129.5, 127.3, 124.5, 67.3, 55.5, 36.1, 31.7, 29.2, 24.4, 22.5, 21.4, 14.0 ppm.

Compound **42**
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (m, 2H), 7.23 (m, 2H), 6.04 (m, 1H), 5.70 (ddd, *J* = 15.3, 10.4, 0.7 Hz, 1H), 5.25 (dd, *J* = 15.3, 7.9 Hz, 1H), 4.98 (m, 1H), 4.95 (m, 1H), 4.75 (d, *J* = 8.5 Hz, 1H), 3.57 (dt, *J* = 8.0, 5.6 Hz, 1H), 2.38 (s, 3H), 1.76-1.52 (m, 5H), 1.36 (m, 1H), 1.21-0.83 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.0, 138.0, 135.8, 132.7, 131.2, 129.3, 127.2, 117.2, 60.7, 42.7, 28.8, 26.1, 25.9, 21.4 ppm.

Compound **47**
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68 (m, 2H), 7.21 (m, 2H), 6.95 (m, 2H), 6.69 (m, 2H), 5.75 (ddd, *J* = 17.2, 10.4, 6.9 Hz, 1H), 5.50 (d, *J* = 17.2 Hz, 1H), 3.78 (s, 3H), 5.38 (d, *J* = 10.4 Hz, 1H), 3.45 (t, *J* = 7.1 Hz, 1H), 3.08 (q, *J* = 7.0 Hz, 1H), 2.68 (m, 2H), 2.43 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 158.2, 144.1, 135.0, 129.7, 129.5, 129.4, 129.3, 127.7, 121.5, 113.8, 55.1, 46.8, 44.9, 32.2, 21.5 ppm.

Compound **48**
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.16 (m, 2H), 6.84 (m, 2H), 5.88 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.3 Hz, 1H), 3.79 (s, 3H), 3.55 (ddd, *J* = 8.4, 6.6, 4.0 Hz, 1H), 3.20 (t, *J* = 6.6 Hz, 1H), 2.86 (dd, *J* = 14.0, 3.7 Hz, 1H), 2.61 (dd, *J* = 14.0, 8.5 Hz, 1H), 1.75 (br, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 158.1, 140.0, 130.5, 130.3, 115.9, 113.8, 74.9, 58.3, 55.2, 39.1 ppm.

Compound **50**
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.73 (m, 2H), 7.30 (m, 2H), 7.14 (m, 2H), 6.82 (m, 2H), 5.49 (m, 2H), 4.60 (m, 1H), 4.03 (ddd, *J* = 15.1, 4.1, 2.1 Hz, 1H), 3.92 (tdd, *J* = 15.1, 5.6, 1.8 Hz, 1H), 3.79 (s, 3H), 3.19 (dd, *J* = 13.4, 3.5 Hz, 1H), 2.91 (dd, *J* = 13.4, 8.4 Hz, 1H), 2.41 (s, 3H) ppm; ^{13}C NMR (126 MHz,

$CDCl_3$) δ = 158.2, 143.3, 134.7, 130.8, 129.7, 129.2, 129.2, 127.3, 125.0, 113.5, 77.0, 68.5, 55.7, 55.2, 42.1, 21.5 ppm.

Compound **52**
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 (m, 2H), 6.86 (m, 2H), 6.01 (ddd, *J* = 17.2, 9.9, 8.6 Hz, 1H), 5.37 (d, *J* = 17.0, 1H), 5.28 (d, *J* = 10.2, 1H), 4.35 (dd, *J* = 8.2, 4.6 Hz, 1H), 3.89 (m, 1H), 3.80 (s, 3H), 2.91 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.76 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.18 (d, *J* = 5.6 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 158.3, 135.2, 130.3, 129.2, 118.9, 113.9, 75.1, 66.9, 39.3, 55.2 ppm.

Compound **110**
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46-7.38 (m, 4H), 7.34-7.14(m, 6H), 4.20 (q, *J* = 6.8 Hz, 2H), 3.62 (d, *J* = 17.6 Hz, 1H), 3.41 (d, *J* = 17.6 Hz, 1H), 3.10 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 6H), 1.16 (s, 9H) ppm;

Compound **120d**
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.30 (s, 1H), 7.83-7.74 (m, 2H), 7.45-7.36 (m, 3H), 4.58 (s, 2H), 3.31 (s, 3H), 1.37 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 192.3, 165.4, 135.9, 130.9, 128.5, 128.4, 82.9, 60.8, 39.5, 27.7 ppm.

Compound **120e**
^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.41 (s, 2H), 3.26 (s, 3H), 1.28 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.4, 160.2, 83.6, 44.1, 39.7, 27.5 ppm.

Compound **125**
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.40-7.23 (m, 5H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.53 (m, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 3.28 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.23 (s, 9H) ppm.

Compound **126**
^{1}H NMR (500 MHz, $CDCl_3$) δ =7.26-7.08 (m, 5H), 6.82 (s, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 2.70 (d, *J* = 5.0 Hz, 3H), 1.52 (s, 3H), 1.22 (s, 9H) ppm.

Compound **139a**
^{1}H NMR (4:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$) δ = 7.41-7.22 (m, 5H), 5.86 (m, 1H), 5.27 (m, 1H), 5.26 (m, 1H), 4.66 (ddd, *J* = 15.2, 8.1, 3.9 Hz, 1H). 4.38 (m, 1H), 3.90 (d, *J* = 13.7 Hz, 1H), 3.89-3.81 (m, 1H), 3.69 (d, *J* = 13.7 Hz, 1H), 3.89-3.81 (m, 1H), 3.37 (m, 1H), 3.18 (m, 1H), 2.37* (m, 1H), 2.33 (ddd, *J* = 13.0, 8.3, 5.1 Hz, 1H), 1.96* (ddd, *J* = 13.2, 9.5, 3.8 Hz, 1H), 1.79 (m, 1H), 1.25 (dd, *J* = 6.2, 14.1 Hz, 1H), 1.12* (dd, *J* = 14.3, 6.9 Hz, 1H), 0.94 (dd, *J* = 14.1, 8.6 Hz, 1H), 0.88* (dd, *J* = 14.3, 8.4 Hz, 1H), 0.07 (s, 9H), 0.06* (s, 9H) ppm; ^{13}C NMR (126 MHz,

$CDCl_3$) δ = 175.9*, 175.7, 139.2, 139.0*, 136.1, 135.8*, 128.7, 128.3, 127.1, 117.9*, 117.7, 77.1*, 76.3, 60.6, 58.1*, 54.8*, 54.7, 54.1*, 54.0, 34.7, 33.0*, 25.5*, 24.9, -1.0, -1.1* ppm.

Compound **140a**
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36-7.29 (m, 5H), 6.93 (s, 1H), 5.98 (m, 1H), 5.81 (m, 1H), 5.26-5.00 (m, 4H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.61 (d, *J* = 13.7 Hz, 1H), 3.35 (m, 1H), 3.18 (m, 2H), 2.80 (d, *J* = 5.0 Hz, 3H), 2.71 (m, 1H), 2.45 (m, 1H) ppm.