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Asymmetric Tandem Lithium Amide Conjugate Addition/Radical Reactions and Their
Application in the Total Synthesis of Natural Products

Asymetrická tandemová konjugovaná adice lithného amidu/radikálové reakce a jejich
aplikace v totální syntéze přírodních látek

Ph.D. Thesis

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Prohlášení:

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.....
Denisa Hidasová

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Abstract

This thesis deals with single-electron transfer (SET) radical processes mediated by ferrocenium hexafluorophosphate and TEMPO and their application in the total synthesis of natural products. Asymmetric aminooxygenation methodology for the synthesis of *anti*- β -amino- α -hydroxy acid derivatives has been developed by utilizing a highly diastereoselective aza-Michael addition of chiral lithium amides to various α,β -unsaturated esters or amides/SET oxidation/radical α -oxygenation. The potential of this methodology was demonstrated in short total syntheses of the *anti*- β -amino- α -hydroxy acid fragments of the macrocyclic (depsi)peptides perthamide C and largamide H, and (–)-cytoxazone, which is a selective modulator of T_H2 cytokine secretion.

The SET-catalyzed asymmetric tandem lithium amide conjugate addition/5-*exo* radical cyclization/oxygenation reactions were applied in the synthesis of highly substituted pyrrolidines, azabicyclo[n.3.0]alkanes and spiropyrrolidines.

An enantioselective total synthesis of the pyrrolidine alkaloid (–)- α -kainic acid was accomplished by employing the SET-catalyzed 5-*exo* radical cyclization/oxygenation.

Abstrakt

Tato práce se zabývá radikálovými procesy s jednoelektronovým přenosem (SET), které jsou zprostředkovány ferrocenium hexafluorofosfátem a TEMPO radikálem, a jejich aplikací v totální syntéze přírodních látek. Byla vyvinuta asymetrická aminooxygenační metodika pro syntézu derivátů *anti*- β -amino- α -hydroxy kyselin s využitím vysoce diastereoselektivní aza-Michaelovy adice chirálních lithných amidů na různé α,β -nenasycené estery nebo amidy/SET oxidace/radikálové α -oxygenace. Potenciál této metodiky byl prokázán v krátkých totálních syntézách *anti*- β -amino- α -hydroxykyselinových fragmentů makrocyclických (depsi)peptidů perthamidu C a largamidu H, a (–)-cytoxazonu, který je selektivním modulátorem sekrece cytokinů T_H2.

SET-katalyzovaná asymetrická tandemová konjugovaná adice lithného amidu/5-*exo* radikálová cyklizace/oxygenační reakce byly použity při syntéze vysoce substituovaných pyrrolidinů, azabicyklo[n.3.0]alkanů a spiropyrrolidinů.

Byla provedena enantioselektivní totální syntéza pyrrolidinového alkaloidu, (–)- α -kainové kyseliny, za použití SET-katalyzované 5-*exo* radikálové cyklizace/oxygenace.

List of abbreviations

AAA	asymmetric allylic amination
Å	Ångström
Ac	acetyl
APT	attached proton test
ATR	attenuated total reflectance
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
br	broad
CAN	ceric ammonium nitrate
cat.	catalytic
CI	chemical ionization
COSY	¹ H- ¹ H correlation spectroscopy
CSA	camphorsulfonic acid
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMEAD	di-2-methoxyethyl azodicarboxylate
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DYKAT	dynamic kinetic asymmetric transformation
EI	electron ionization
equiv	equivalent(s)
ESI	electrospray ionization
EWG	electron withdrawing group
FHFP	ferrocenium hexafluorophosphate
HATU	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5 <i>b</i>]pyridinium 3-oxid hexafluorophosphate
HMBC	heteronuclear multiple-bond correlation
HPLC	high-performance liquid chromatography

HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IR	infrared spectroscopy
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
m.p.	melting point
MS	mass spectrometry
MW	microwave
<i>n</i> BuLi	<i>n</i> -butyllithium
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Pg	protecting group
PRE	persistent radical effect
ROESY	rotating frame nuclear Overhauser effect spectroscopy
R _f	retention factor
r.t.	room temperature
SET	single-electron transfer
TBAF	tetrabutylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMP	2,2,6,6-tetramethylpiperidin-1-yl

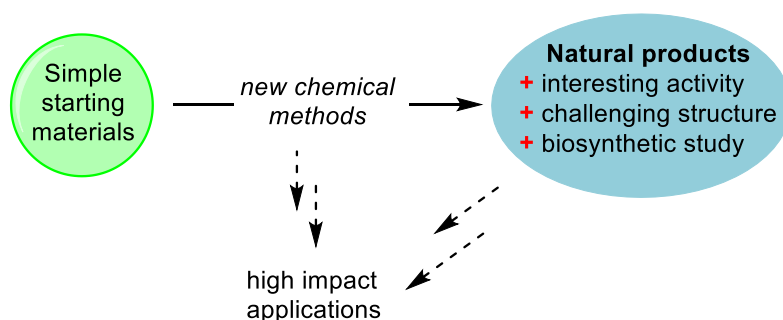
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1. Introduction

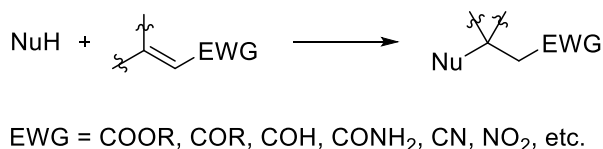
For many years, organic synthesis has been at the heart of chemistry. It contributes to the technological progress of our society by allowing the discovery, supply and exploitation of natural and nonnatural compounds that form the foundation of our survival and comfort. Despite the complexity of natural products, total synthesis is clearly standing at the forefront of synthetic organic chemistry. However, such complex synthetic targets have repeatedly shown the limitations of the best available chemical methodologies and have thus inspired the invention of new strategies (Scheme 1.1).



Scheme 1.1 Total synthesis of natural products as an inspiration for new methodologies.

The increasing growth of methodologies involving tandem reactions is predominately due to its advantages.^[1] Tandem approaches allow to build complex molecules with high stereoselectivity in one step. They are often more atom economic, less expensive because of fewer purification and separation steps, and also more environmentally friendly.

The Michael reaction is the addition of carbanions or heteroatom-centred nucleophiles to α,β -unsaturated carbonyl compounds (Scheme 1.2). It is an efficient reaction, which uses cheap and easily available starting materials. It is a very popular and fundamental method for the construction of C-C or C-X (X = N, O, S, Se, P) bonds in organic synthesis.^[2]

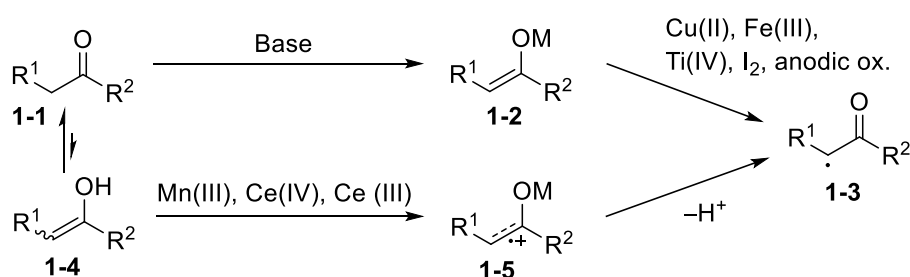


Scheme 1.2 Michael addition reaction.

The aza-Michael reaction has gained large attention.^[3] Asymmetric versions of aza-Michael reactions have also been reported.^[4] Lithium amides bearing a homochiral *N*-(1-phenyl)ethyl group were in detail studied by Davies as Michael donors in highly diastereoselective aza-Michael additions.^[4b,d,f] In principle, this reaction is the shortest route to β -amino acids and their derivatives,^[5] and to β -aminocarbonyl derivatives,^[6] which are valuable starting materials for the synthesis of various nitrogen-containing bioactive natural products and drugs. In addition, the aza-Michael reaction often initiates tandem transformations resulting in the formation of polyfunctional compounds, including heterocycles and analogues of natural products.^[7]

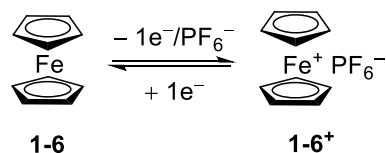
Radical reactions have been extensively used in organic synthesis.^[8] Radicals can be generated in a number of ways, which include the applications of chemical,^[9] electrochemical^[10] and photochemical methods.^[11] The potential of radical reactions is very high due to the mild conditions under which radicals can be generated. These mild reaction conditions tolerate a wide range of functionality in the substrates allowing the preparation of complex molecules; enantioselective radical reactions have also been developed.^[12,9f]

Oxidative SET can generate α -carbonyl radicals from corresponding carbonyl compounds by enolate (A) or neutral pathways (B) (Scheme 1.3). In pathway A, the carbonyl compound **1-1** is deprotonated by base to form metal enolate **1-2**. SET oxidation of the enolate by Cu(II),^[8b,13] Ti(IV),^[14] I₂^[14e,f,g] or Fe(III)^[14f,15] salts furnishes the α -carbonyl radical **1-3**. Pathway B starts with neutral carbonyl compounds **1-4**; SET oxidation of the corresponding enol form generates a radical cation **1-5** that deprotonates to give the α -carbonyl radical **1-3**. Mn(OAc)₃,^[16] CAN^[15e,17] and Ce(III)^[18] salts have been used for such transformation. Electrochemical oxidation of enolates is also possible.^[19] Both pathways A and B are suited for α -functionalization.



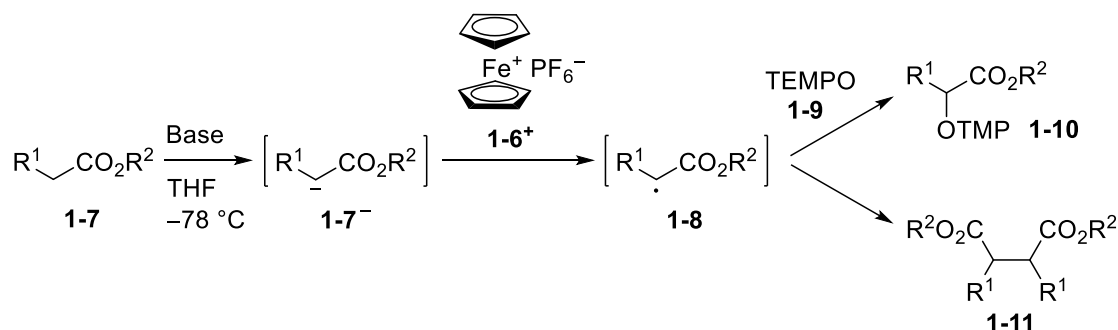
Scheme 1.3 Oxidative SET generates the α -carbonyl radical.

Among Fe(III)-based SET oxidants, ferrocenium hexafluorophosphate (FHFP) **1-6⁺** was established as an appropriate SET oxidant for the generation of α -carbonyl radicals from enolates, which is functional group tolerant and its reduced form **1-6** is recyclable (Scheme 1.4).^[20] The redox potential of ferrocenium salts can be tuned by the choice of substituents at the cyclopentadienyl ligands.^[21]



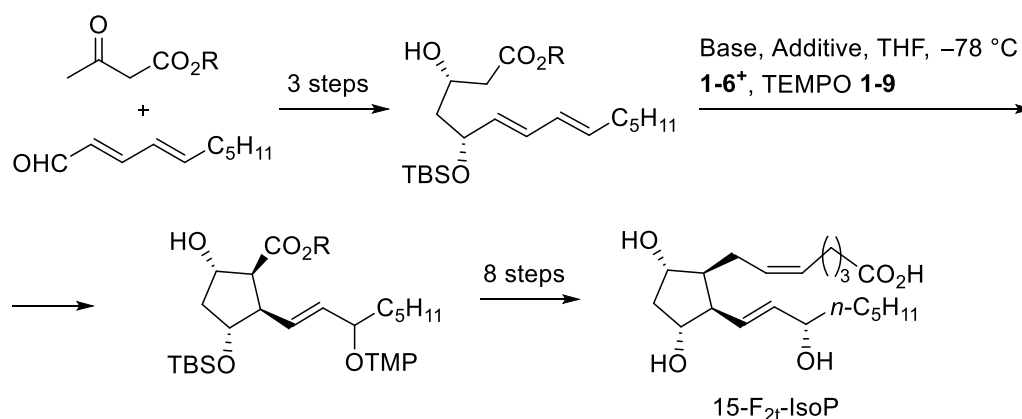
Scheme 1.4 Ferrocene/ferrocenium couple.

SET-mediated polar-radical crossover reactions between enolates and corresponding α -carbonyl radicals have been studied by the Jahn group over the years. One example of such transformations is SET-oxidation of malonate enolates^[20a,c] or ester enolates^[20b] **1-7** to α -carbonyl radicals **1-8** that were effectively trapped by TEMPO **1-9** to form α -(aminoxyl) esters **1-10** or by dimerization to form **1-11** (Scheme 1.5).



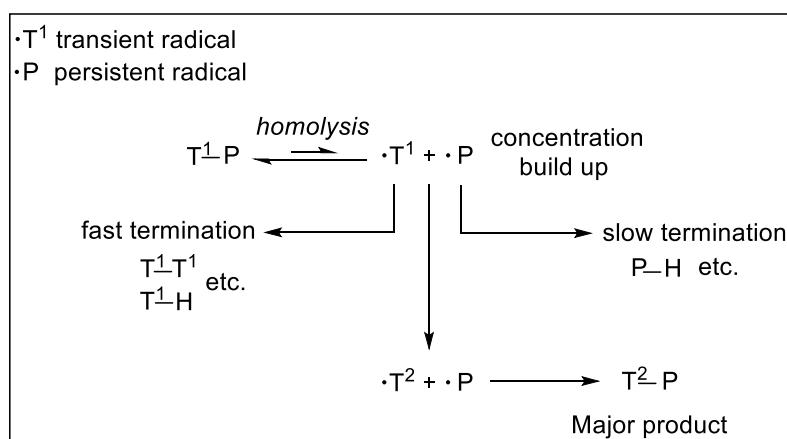
Scheme 1.5 SET oxidation of ester enolates with **1-6⁺**.

FHFP **1-6⁺** has been used in oxidative tandem sequences for the construction of polysubstituted pyrrolidines,^[22] cyclopentanes^[23] and tetrahydrofurans.^[24] The Jahn group reported applications of FHFP in isoprostane^[25] and terpene total syntheses.^[26] In the total synthesis of 15-F_{2t}-isoprostane the key SET oxidative radical cyclization/oxygenation sequence allows to prepare the cyclopentane core of isoprostanes (Scheme 1.6).



Scheme 1.6 Application of SET-mediated 5-*exo* radical cyclization/TEMPO trapping reactions as a key step in total synthesis of 15-F_{2t}-IsoP.

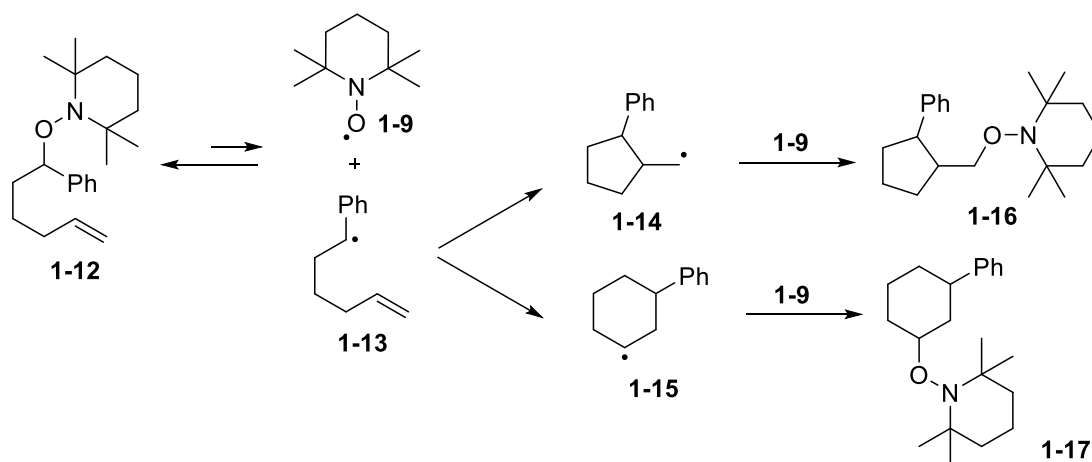
The persistent radical effect (PRE) explains the highly selective cross-coupling between a persistent (long-lived) and a transient (short-lived) radical when both species are formed at equal rates (Scheme 1.7).^[27] At the start, homolysis of a C-O bond gives transient ($\cdot T^1$) and persistent ($\cdot P$) radicals that are generated in equal concentration. Whereas the transient radical ($\cdot T^1$) disappears from the reaction mixture by the fast termination (e.g. dimerization), this does not happen to ($\cdot P$) and leads to a concentration build-up of the persistent radical. This concentration imbalance leads to a fast and selective cross-coupling between a persistent and a transient radical either by back reaction or by trapping of a product radical ($\cdot T^2$) without further self-termination of transient radicals.



Scheme 1.7 Principle of the persistent radical effect (PRE).

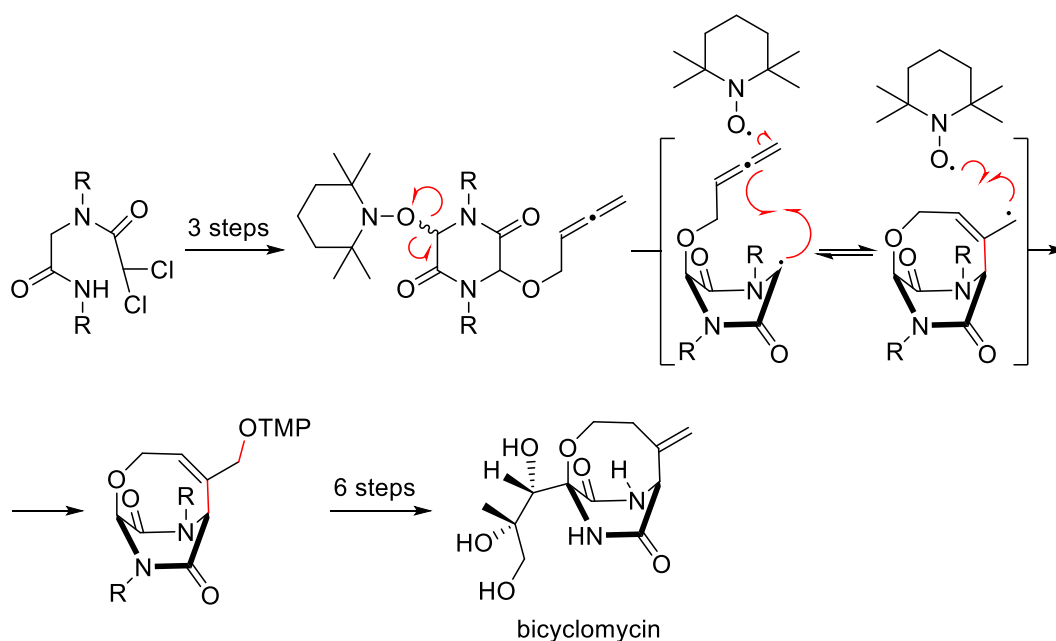
Persistent radical TEMPO was used in PRE-mediated processes. The weak C-O bond in alkoxyamines **1-12** was homolytically cleaved by heating to form a transient C-radical **1-13**

and the persistent radical **1-9** in equal concentration (Scheme 1.8).^[28] Transient radical **1-13** underwent 5-*exo* or 6-*endo* cyclization in competition to back reaction to form transient radicals **1-14** and **1-15** that were irreversibly trapped by **1-9** to form **1-16** and **1-17**.



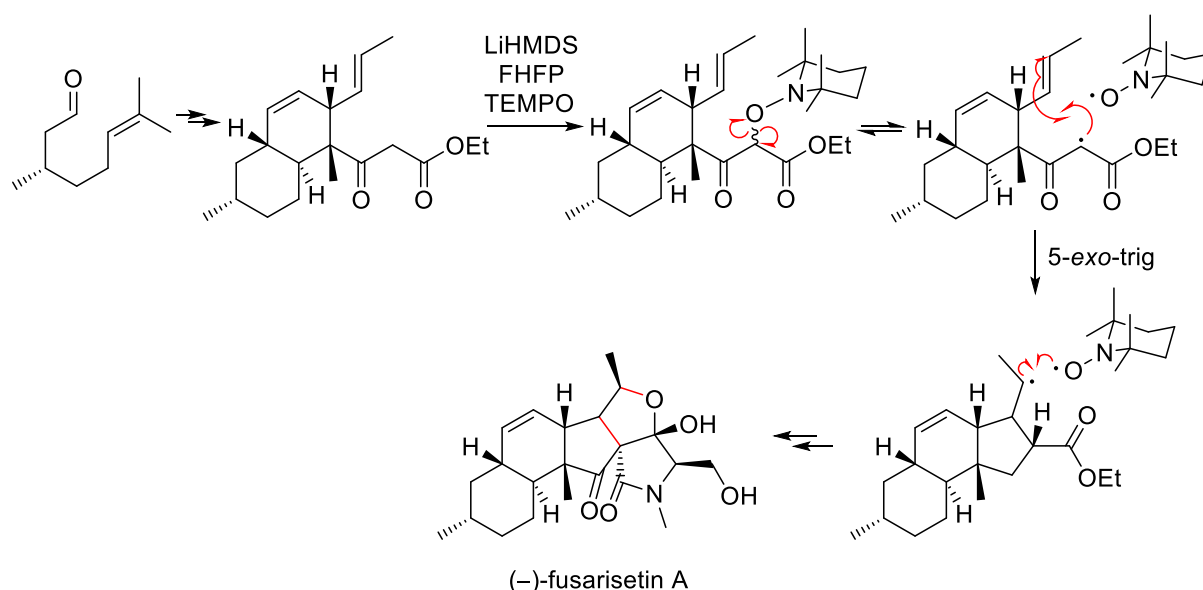
Scheme 1.8 Radical cyclizations using the PRE.

TEMPO-derived alkoxyamines have been applied in the total synthesis of natural products.^[29] The Jahn group synthesized diverse bridged diketopiperazines by cyclization of amino acid-derived alkoxyamines using the PRE and the potential of the methodology was demonstrated in a formal total synthesis of the antibiotic bicyclomycin (Scheme 1.9).^[30]



Scheme 1.9 PRE as a key step in a formal total synthesis of bicyclomycin.

The Theodorakis group reported the persistent radical effect in their total synthesis of (–)-fusarisetin A (Scheme 1.10).^[31]



Scheme 1.10 Total synthesis of (–)-fusarisetin A using the PRE.

1.1 β -Amino- α -hydroxy acids and their asymmetric synthesis

β -Amino- α -hydroxy acid derivatives are important constituents of a large variety of bioactive natural products and drugs.^[32] The *syn*- β -amino- α -hydroxy acid motif is found in peptides, such as bestatin,^[33] microginin,^[34] valinoctin A^[35] and in the side chain of Taxol[®],^[36] whereas the *anti*-diastereomers occur in macrocyclic peptides, e.g. perthamide C^[37] and largamide H,^[38] natural products such as cytoxazone,^[39] or the synthetic kynostatins as HIV-1 protease inhibitors (Figure 1.1).^[40] Asymmetric syntheses of β -amino- α -hydroxy acid derivatives have been reported in the literature using diverse synthetic strategies.^[41]

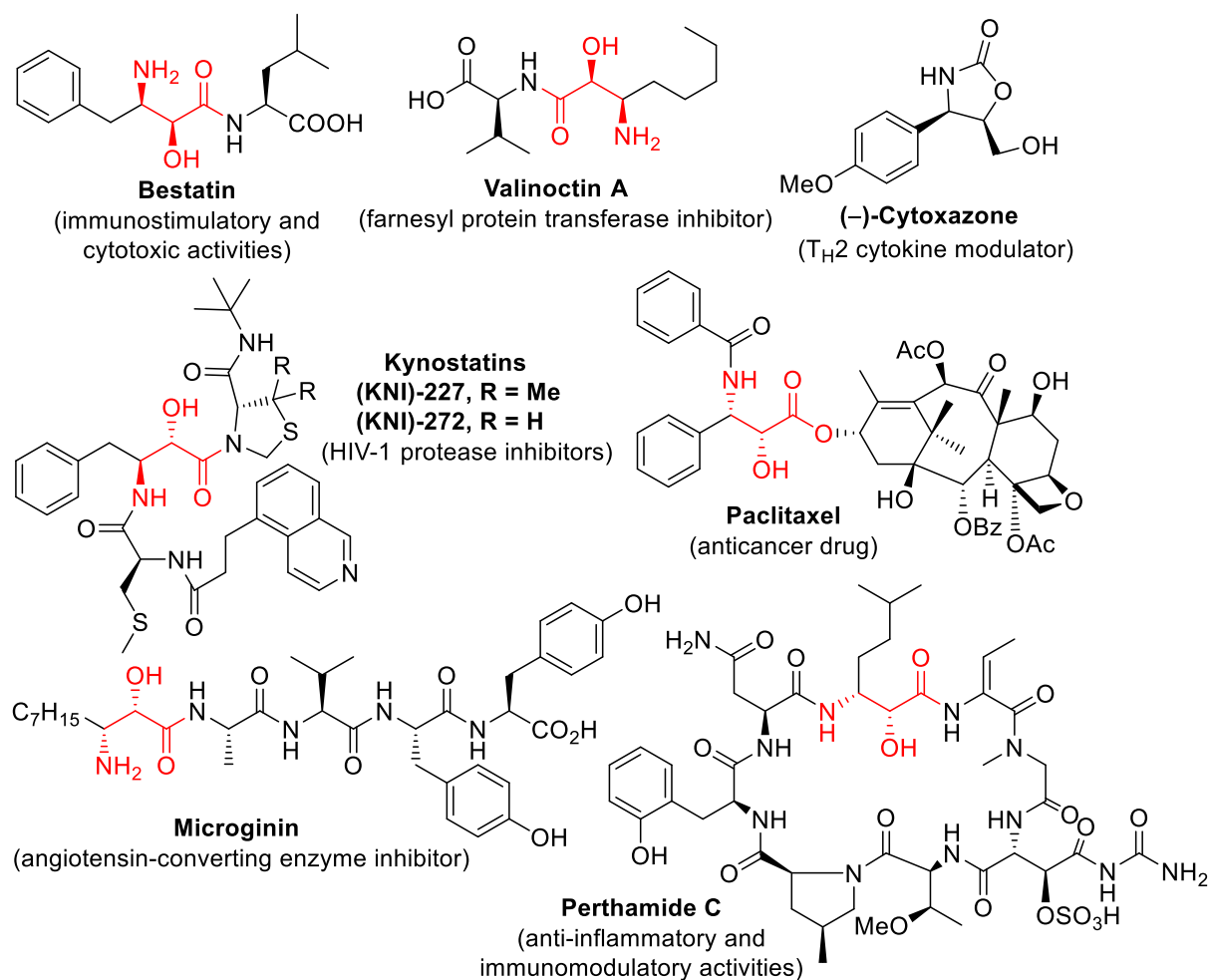
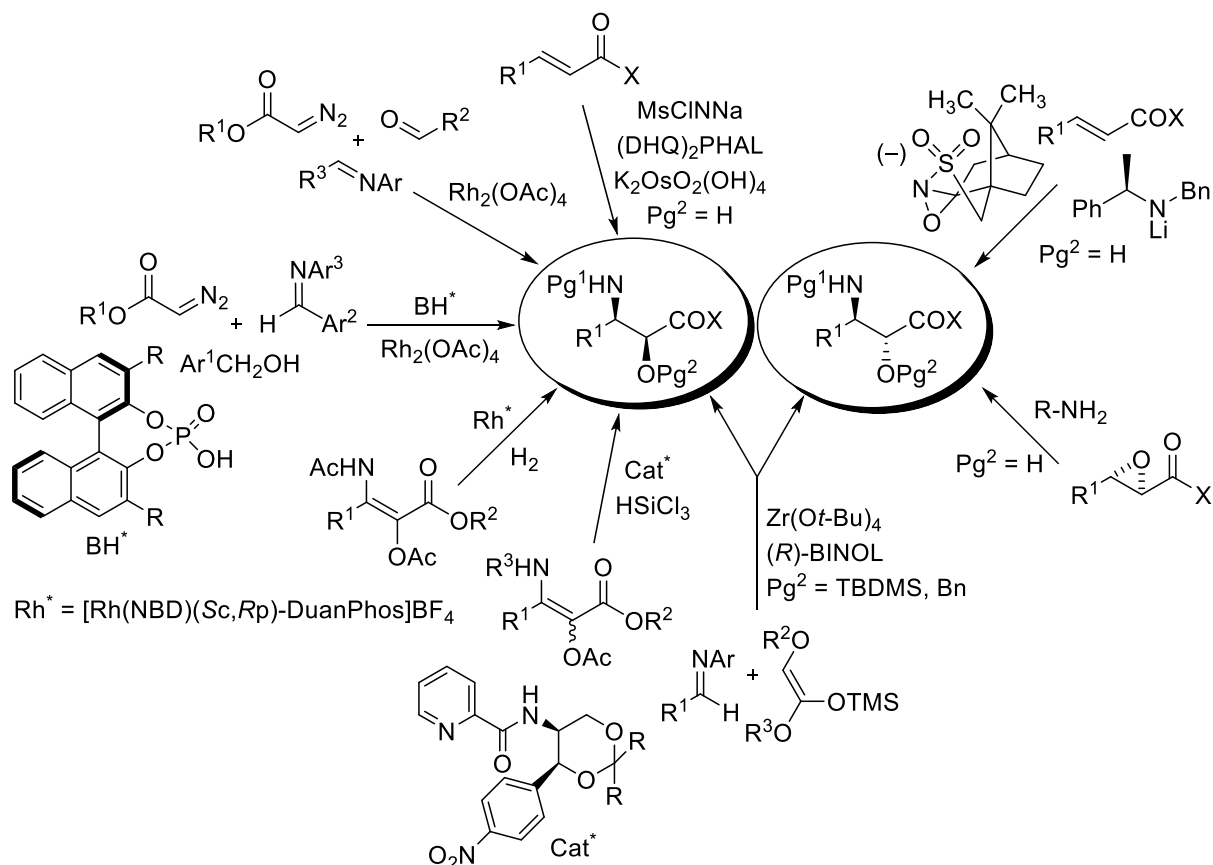


Figure 1.1 Examples of bioactive natural products with β -amino- α -hydroxy acid moiety.

Common single-step approaches to optically active *syn*- β -amino- α -hydroxy acid derivatives include the Sharpless asymmetric aminohydroxylation,^[42] rhodium-catalyzed carbonyl ylide 1,3-dipolar cycloadditions,^[43] three-component reactions,^[44] as well as asymmetric hydrogenation^[45] or hydrosilylation^[46] reactions (Scheme 1.11). The *anti*- β -amino- α -hydroxy esters can be prepared by nucleophilic ring opening of chiral epoxides by nitrogen nucleophiles^[47] or Davies' tandem conjugate addition of homochiral secondary lithium amides derived from α -methylbenzylamine, followed by polar enolate oxygenation with (camphorsulfonyl)oxaziridine (CSO).^[4b,d,f] These approaches introduce a free alcohol functionality and separate protection steps are later required for total synthesis of complex natural products.^[47,48]

Concerning one-step approaches to *O*-protected derivatives, only a few examples of organocatalytic,^[49a,b] Zr-^[49c] as well as Cu-catalyzed,^[49d] or auxiliary-based Mannich reactions of α -alkoxy carbonyl compounds are known.^[49e] However, these methods are largely limited

to arylimines, affording predominately *syn*- α -alkoxy- β -aryl- β -arylamino carboxylic acid derivatives, which are difficult to deprotect at nitrogen. In the Zr-catalyzed methodology, both *syn*- (for $\text{Pg}^2 = \text{TBDMS}$) or *anti*-isomers (for $\text{Pg}^2 = \text{Bn}$) can be formed with high diastereoselectivity.^[49]



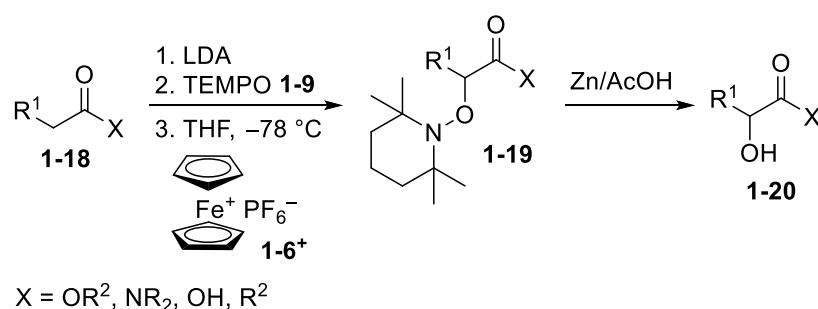
Scheme 1.11 Common single-step approaches to optically active β -amino- α -hydroxy acid derivatives.

1.2 Radical α -oxygenation of carbonyl compounds by TEMPO

TEMPO **1-9**, which is sufficiently inexpensive for use on a laboratory scale, is one of the most common radical scavengers. Trapping of carbon-centered radicals with TEMPO is a fast process; the rate constant ranges between $5 \times 10^7 - 2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.^[50] It has been used as a convenient reagent to introduce oxygen into organic molecules. The first method for α -oxygenation of esters with TEMPO was developed simultaneously by Jahn and Braslau.^[20b,51] This method is based on the generation of enolate followed by SET-oxidation

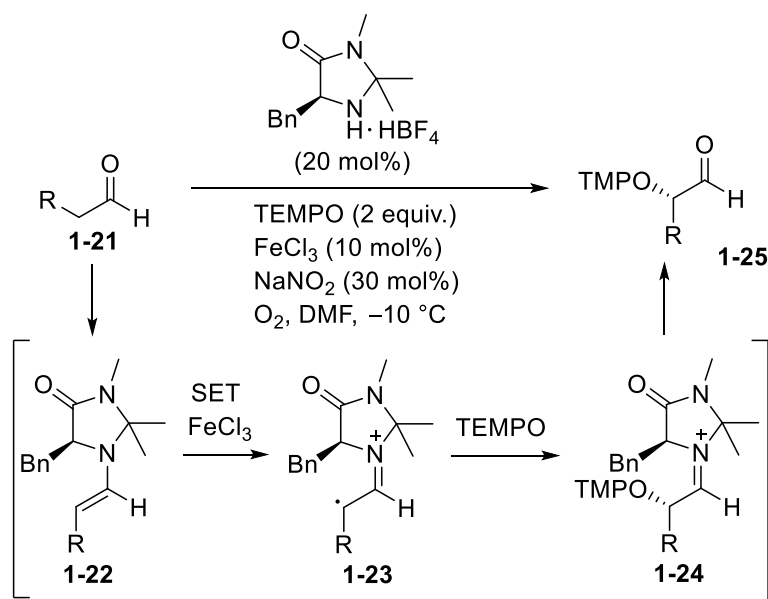
by FHFP^[20b] or by CuCl₂^[51] to the corresponding α -carbonyl radical, which couples with TEMPO.

The Jahn group developed a general α -oxygenation method for almost all carbonyl compounds **1-18** by SET oxidation of their enolates mediated by **1-6**⁺.^[52] TEMPO served as the oxygenating reagent for radicals furnishing racemic oxygenated carbonyl compounds **1-19** in high yields (Scheme 1.12). Deprotection of α -aminoxy carbonyl compounds **1-19** with excess zinc powder in acetic acid gives α -hydroxy carbonyl compounds **1-20** mostly in good yields. The tetramethylpiperidinyl protecting group can be removed chemoselectively for most compounds except for those having a reduction potential lower than that of the N-O bond. Renaud and Studer developed α -oxygenation reactions of enol borates with TEMPO that similarly provide racemic α -aminoxy ketones.^[53]



Scheme 1.12 α -Oxygenation of carbonyl compounds with TEMPO.

Asymmetric α -oxygenations by radical heterocoupling using TEMPO are rare. The first example of enantioselective organocatalytic α -oxyamination of aldehydes **1-21** was achieved by Sibi using MacMillan's imidazolidinone catalyst and TEMPO (Scheme 1.13).^[54] Here, the initially formed enamine **1-22** is oxidized by FeCl₃ *via* SET to give a radical cation intermediate **1-23** that is trapped by TEMPO in a stereoselective manner, because the top face is sterically shielded by the benzyl group. Aldehyde **1-25** is obtained by hydrolysis of iminium ion **1-24**, thus releasing the catalyst. Following this achievement another variants of enantioselective organocatalytic α -oxygenation reactions using TEMPO have been developed.^[55]



Scheme 1.13 Sibi's first enantioselective α -oxyamination of aldehydes with TEMPO.

A mild method for asymmetric α -oxygenation of *N*-acyl oxazolidinones by radical addition of TEMPO to titanium enolates was developed by Zakarian.^[56] The above mentioned methods for the asymmetric α -oxygenations with TEMPO are largely limited to substrates, such as aldehydes^[54,55] or *N*-acyl oxazolidinones.^[56]

1.3 Polysubstituted pyrrolidines and their synthesis *via* SET-induced aza-Michael addition/5-exo radical cyclization/oxygenation with TEMPO reactions

Enantioselective synthesis of polysubstituted pyrrolidines is highly needed because the pyrrolidine core is found in a variety of natural and unnatural bioactive products.^[57] Important examples are the neuroexcitatory compounds (–)- α -kainic acid and (+)- α -allokainic acid,^[58] the DNA polymerase inhibitor plakoridine A,^[59] the *anti*-inflammatory compounds codonopsine,^[60] (+)-erysotrine,^[61] (–)-martinellic acid,^[62] the *anti*-cancer (–)-cephalotaxine and its esters (–)-harrigtonine and (–)-homoharrigtonine,^[63] and the antitussic and anthelmintic compound neostenine coming from the *Stemona* alkaloids (Figure 1.2).^[64] The pyrrolidine motif has gained interest in medicinal chemistry,^[65a] enantiomerically pure pyrrolidines are also useful chiral auxiliaries and ligands in asymmetric synthesis.^[65b-f]

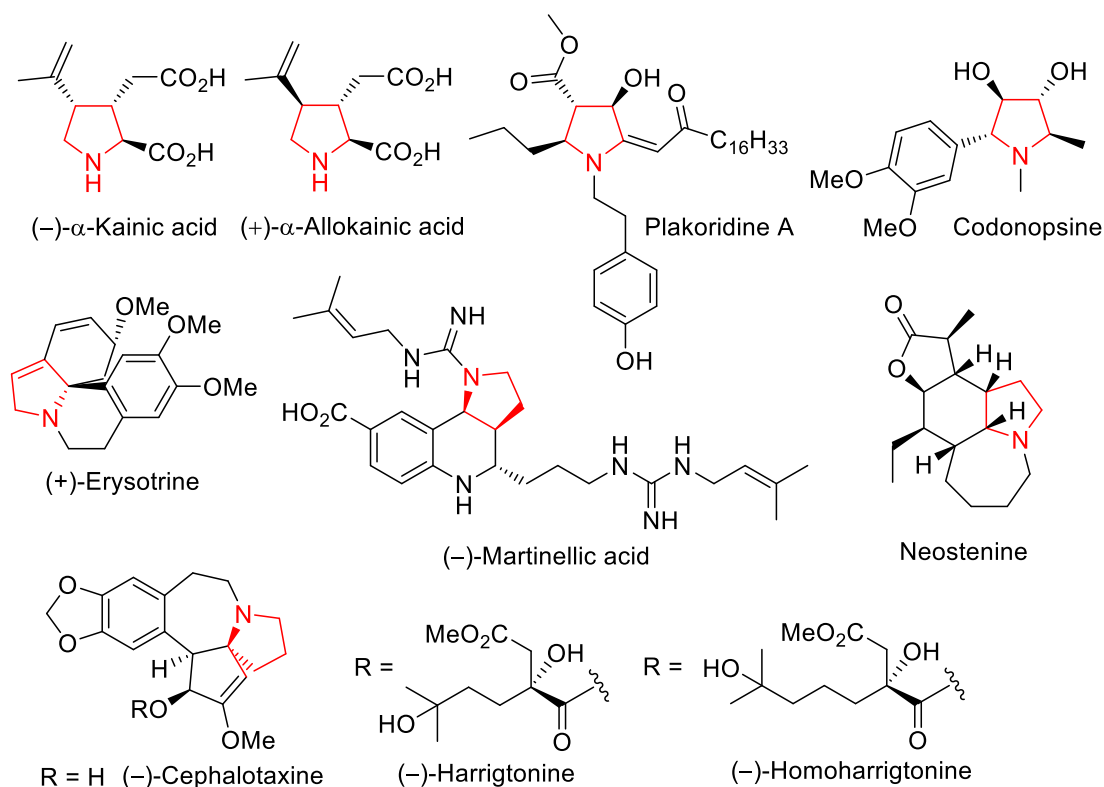
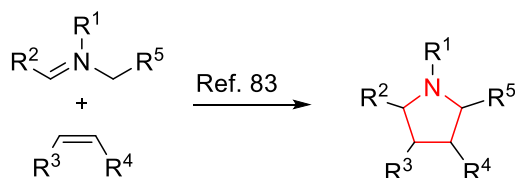


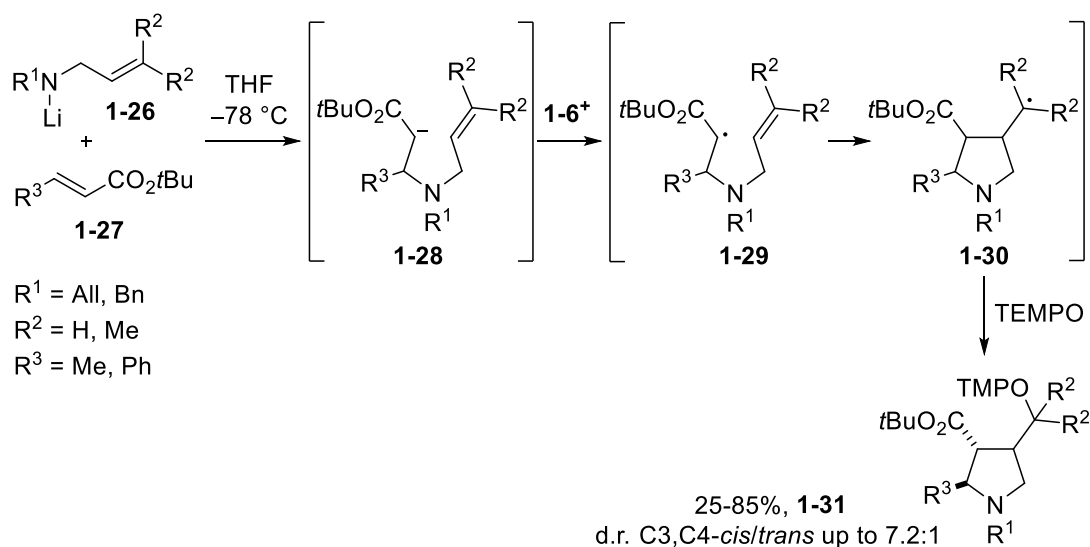
Figure 1.2 Examples of bioactive pyrrolidines.

Over the last decades, a plethora of synthetic strategies have been developed for the synthesis of pyrrolidines. The synthetic routes to pyrrolidines involve two general categories: a) Functionalization reactions of the existing pyrrolidine ring,^[66] and b) Construction of the pyrrolidine scaffold from various acyclic precursors. The second category includes number of traditional methods, such as [3+2] annulation,^[67] intramolecular hydroamination,^[68] alkenylative cyclization,^[69] intramolecular aza-Michael addition,^[70] double-Michael reaction,^[71] *N*-heterocyclization of primary amines,^[72] polar iodine atom transfer cyclization,^[73] iodo-aldol cyclization,^[74] cycloisomerization of dienes,^[75] aza-Payne rearrangement,^[76] reductive cyclization of acetylenic aldehydes,^[77] annulation reaction of 1,1-cyclopropanediester,^[78] reduction of substituted pyrroles,^[79] and cyclization of γ -(*N*-substituted) alkenes with aryl bromides.^[80] Beyond these traditional methods, I_2 ^[81] or $Hg(OAc)_2$ ^[82] activated intramolecular cyclization of a nitrogen nucleophile onto a pendant olefin provides the pyrrolidine ring. The most common method for rapid construction of highly substituted pyrrolidines is the [3+2] cycloaddition of azomethine ylides with substituted olefins (Scheme 1.13).^[83]



Scheme 1.13 [3+2] cycloaddition of azomethine ylides with substituted olefins.

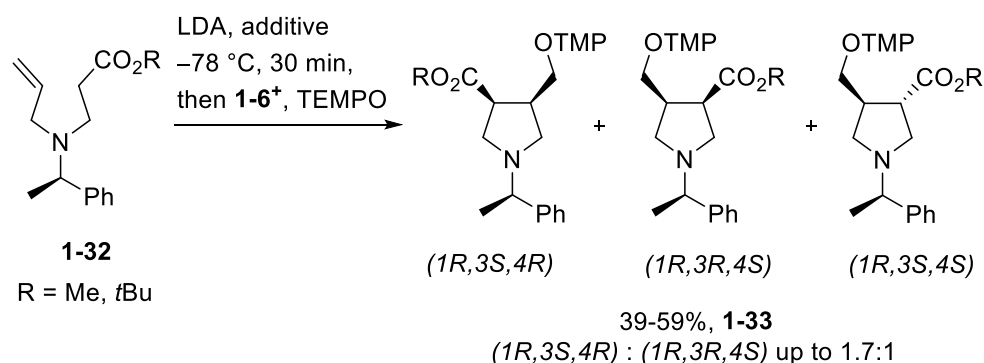
The most effective way for synthesis of pyrrolidines is a one-pot process involving two variable components. In 2000, the Jahn group has reported first tandem lithium amide conjugate addition/5-*exo* radical cyclization/oxygenation reactions for the synthesis of highly functionalized pyrrolidines (Scheme 1.14).^[22a] In this study, simple *N*-allyl amides **1-26** were added to *tert*-butyl enoates **1-27** forming the corresponding β -amino enolates **1-28**. Single-electron oxidation gives radicals **1-29**, which cyclize to radicals **1-30**. For the termination of the radical sequence, free radical TEMPO was added, which reacts slower with α -carbonyl radicals than with alkyl radicals providing oxygenated products in acceptable to very good yields with exclusive C2,C3-*trans* selectivity. The oxygenated products **1-31** are suitable for further transformations. However, this methodology provides racemic products.



Scheme 1.14 Racemic synthesis of functionalized pyrrolidines by SET-mediated tandem anionic-radical processes.

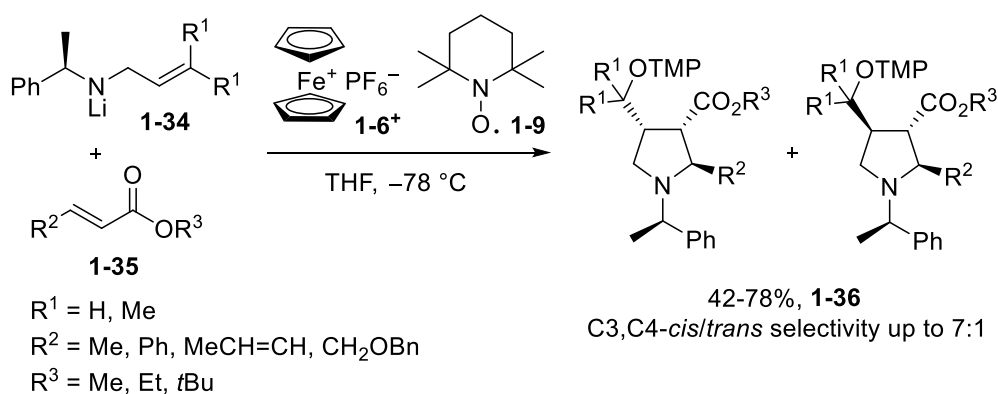
Later in 2009, *N*,3,4-trisubstituted pyrrolidines were synthesized by electron transfer-induced oxidative cyclizations of *N*-allylic β -amino ester enolates.^[22b] By applying *N*-(1-phenylethyl)-substituted β -amino esters **1-32** the asymmetric synthesis of pyrrolidines was

achieved (Scheme 1.15). Firstly, *N*-allylic β -alanine derivatives **1-32** were prepared in high yields by lithium chloride-catalyzed aza-Michael addition of allylic amines to acrylates. In the second step, β -alanine ester was deprotonated with LDA generating the corresponding enolate, which underwent SET oxidation/5-*exo* radical cyclization/oxygenation sequences. *N*-Protected 4-(oxymethyl)pyrrolidine-3-carboxylates **1-33** were synthesized in moderate to acceptable yields. The selective generation of either (*E*)- or (*Z*)-enolates allows controlling and switching the diastereoselectivity from moderate to high C3,C4-*cis* to moderate C3,C4-*trans* diastereoselectivity.



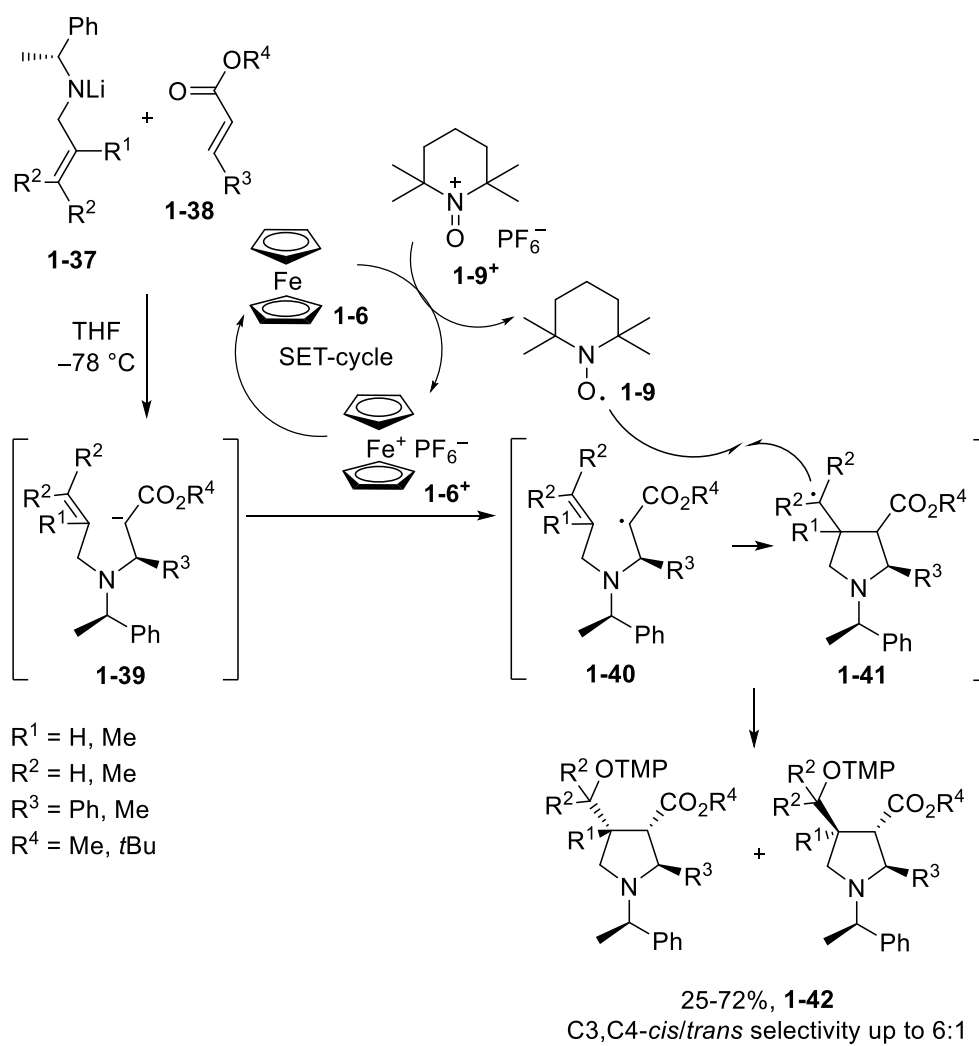
Scheme 1.15 *N*,3,4-trisubstituted pyrrolidines by oxidative cyclizations of chiral *N*-allylic β -amino esters enolates.

Recently, an enantioselective synthesis of *N*,2,3,4-tetrasubstituted pyrrolidines was achieved by asymmetric tandem aza-Michael addition/5-*exo* radical cyclization/oxygenation sequences mediated by ferrocenium hexafluorophosphate **1-6⁺** (Scheme 1.16).^[22c] The asymmetric aza-Michael addition was performed with enantiomerically pure *N*-allylic 1-phenylethylamides **1-34** according to Davies' original conditions, followed by FHFP-mediated 5-*exo* radical cyclization/oxygenation. In this reaction simple substrates give highly functionalized pyrrolidines **1-36** in up to 78% yield with up to 6:1 C3,C4-*cis*/C3,C4-*trans* diastereoselectivity.



Scheme 1.16 Enantioselective synthesis of *N*,2,3,4-tetrasubstituted pyrrolidines by SET-mediated tandem processes.

After SET-induced tandem processes mediated by FHFP **1-6**⁺ and TEMPO stoichiometric amounts of ferrocene **1-6** are always produced as waste. In 2014, the Jahn group published the enantioselective synthesis of *N*,2,3,4-tetrasubstituted pyrrolidines by first SET-catalyzed tandem aza-Michael addition/5-*exo* radical cyclization/oxygenation reactions (Scheme 1.17),^[84] proceeding with catalytic amounts of cheap ferrocene **1-6** and 2,2,6,6-tetramethyl-*N*-oxopiperidinium hexafluorophosphate **1-9**⁺ as the stoichiometric oxidant. The first step, amide conjugate addition of **1-37** to esters **1-38**, generates enolates **1-39**. The catalytic SET oxidation cycle begins with oxidation of ferrocene **1-6** by the stable oxopiperidinium salt **1-9**⁺ leading to **1-6**⁺ that oxidizes enolates **1-39** to α -carbonyl radicals **1-40**. The radical undergoes 5-*exo* cyclization and the reduced species TEMPO **1-9** from the catalytic cycle serves as coupling agent for radicals **1-41**. The oxygenated pyrrolidines **1-42** were prepared in mostly good yields similarly as in the stoichiometric version using **1-6**⁺ and TEMPO (*cf.* Scheme 1.16).

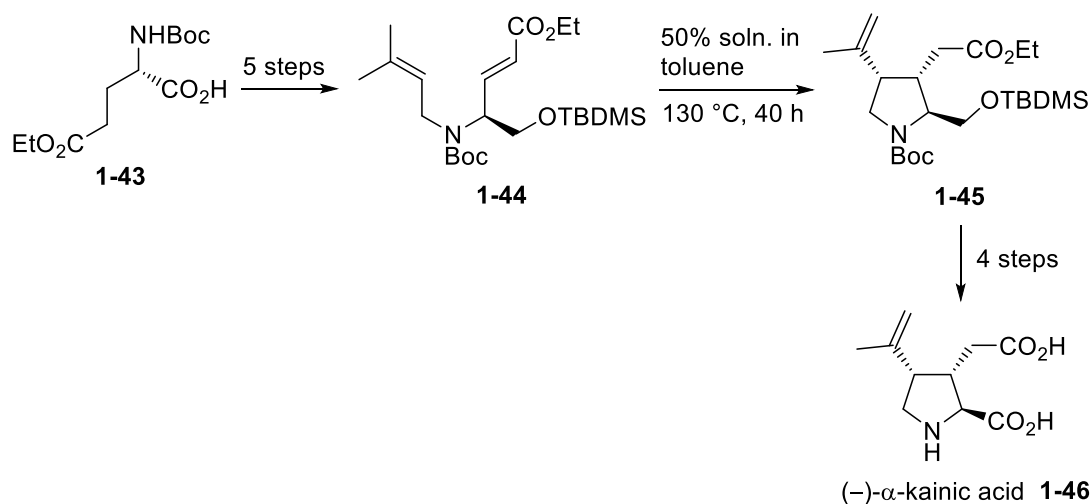


Scheme 1.17 SET-catalyzed tandem asymmetric aza-Michael addition/5-*exo* radical cyclization/oxygenation with TEMPO.

1.4 Total syntheses of (–)- α -kainic acid

(–)- α -Kainic acid has gained considerable attention as a synthetic target from organic chemists because of its important neurobiological activity and the characteristic framework. To date, more than 60 total syntheses of kainic acid have been reported in the literature using different strategies.^[85] These retrosynthetic strategies can be divided into single bond disconnections, multiple bond disconnections and functionalizations of the existing pyrrolidine ring. The first approach included C²-C³, the most common C³-C⁴, C⁴-C⁵ and C-N bond formation pathways. Cycloaddition pathways forming two C-C bonds simultaneously belong to the multiple bond disconnections.

The first enantioselective total synthesis of (–)- α -kainic acid **1-46** was reported by Oppolzer and Thirring in 1982.^[86] The diene **1-44** was prepared from the commercially available (*S*)-glutamic acid **1-43**. Heating a 50% solution of **1-44** in toluene at 130 °C for 40 h furnished the desired trisubstituted pyrrolidine **1-45** (Scheme 1.18). Conversion of **1-45** to **1-46** was achieved in six straightforward steps. The synthesis of **1-46** was accomplished in 10 steps with 5% overall yield.

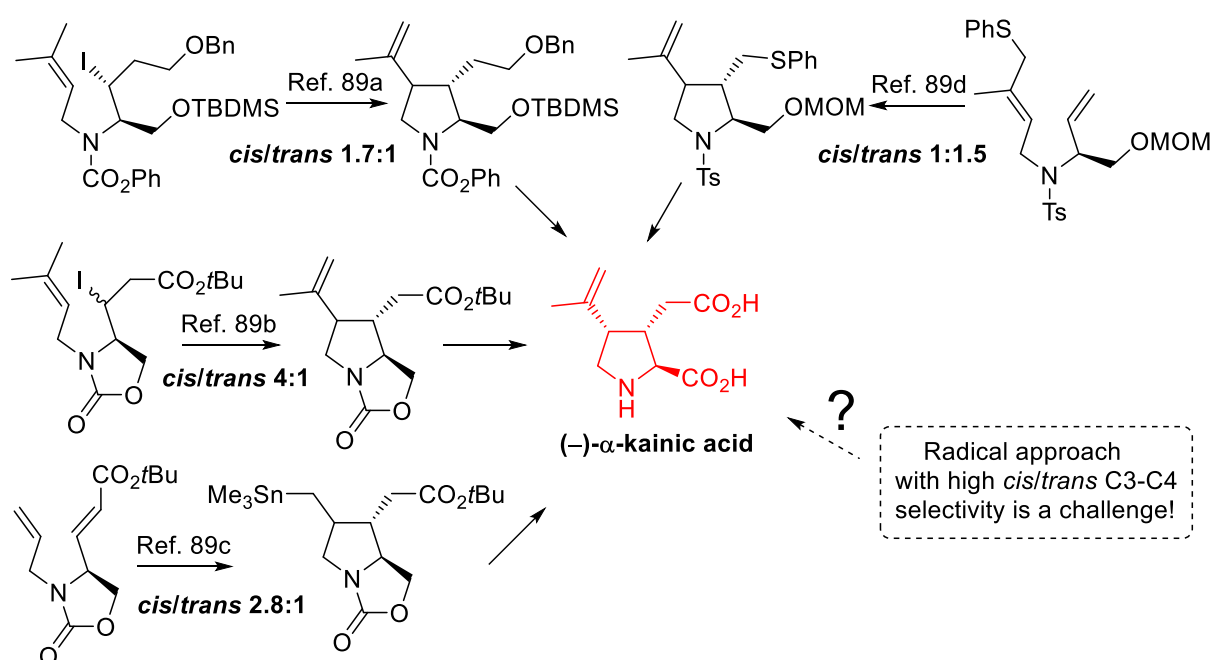


Scheme 1.18 Oppolzer's first enantioselective total synthesis of (–)- α -kainic acid.

A short synthesis with 7 steps and the highest 40% overall yield was achieved by Lin and co-workers in 2012.^[87] In 2015, Ohshima and co-workers reported the shortest total synthesis of (–)- α -kainic acid with 6 steps and 34-37% overall yield.^[88]

1.5 Radical-based total syntheses of (–)- α -kainic acid

The construction of three contiguous stereogenic centers at the pyrrolidine ring, especially the thermodynamically less favorable *cis* C3-C4 configuration, is very difficult. Radical approaches represent an elegant approach to *cis* C3-C4 pyrrolidines by installing two of the three contiguous stereogenic centres in a single step. Only a few radical-based approaches to (–)- α -kainic acid have been reported to date,^[89] however, they suffered from poor selectivity in the cyclization step (Scheme 1.19). The presence of the oxazolidinone ring provides the best, but still moderate 4:1 *cis/trans* C3-C4 selectivity in the radical ring closure.



Scheme 1.19 Radical-based approaches to (–)- α -kainic acid.

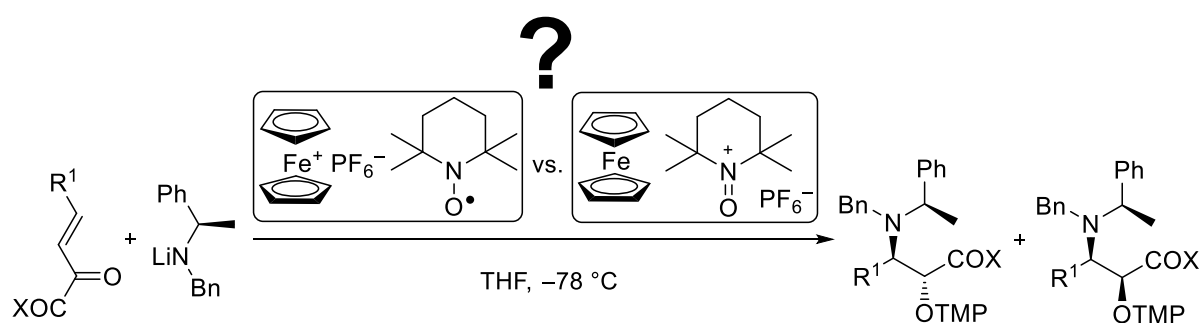
It remains a challenge to develop radical approaches that will generate exclusively *cis*-C3-C4 trisubstituted pyrrolidine rings for the total synthesis of (–)- α -kainic acid. However, Jahn group has previously developed SET-mediated 5-*exo* radical cyclization/oxygenation reactions of chiral β -alaninates for the synthesis of trisubstituted pyrrolidine rings with all stereogenic centers comprising (–)- α -kainic acid.^[90] This approach outlines the synthesis of an advanced intermediate that was however not possible to deprotect at nitrogen and on oxygen without leaving the alkene untouched. Moreover, some synthetic steps suffered from poor chemoselectivity or yields.

2. Aims of the work

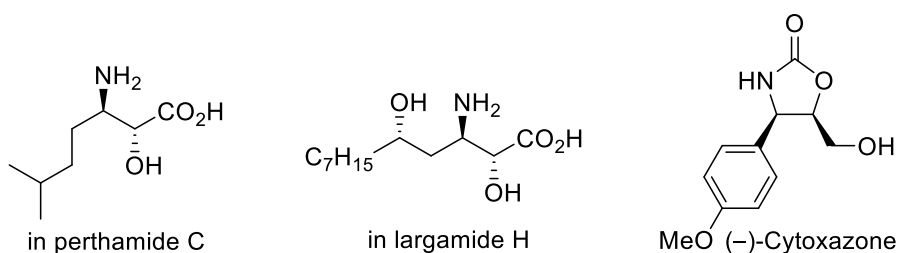
The previously developed methodology in the Jahn group provides many opportunities for further development. Based on the tandem anionic-radical reactions we hypothesized, whether highly diastereoselective aza-Michael reactions together with radical α -oxygenation of carbonyl compounds could be used for asymmetric synthesis of β -amino- α -hydroxy acid derivatives. Furthermore, it is important to significantly broaden the applicability of the SET-catalyzed tandem anionic-radical crossover methodology to more complex and diverse pyrrolidines. Based on the previous unsuccessful approach toward (–)- α -kainic acid it is important to select suitable protecting groups and to reevaluate some synthetic steps to accomplish the total synthesis of this important target.

Specific aims are:

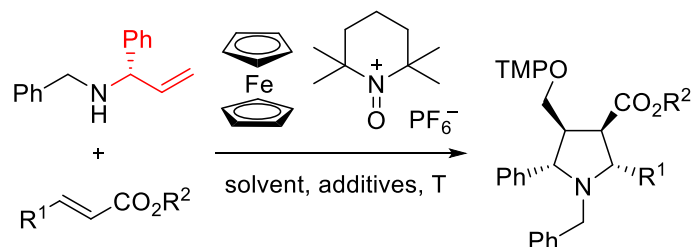
- Study the tandem conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(1-phenylethyl)amide to esters and amides followed by single-electron oxidation/radical α -oxygenation. The optimal reagent system, either ferrocenium hexafluorophosphate/TEMPO or ferrocene/2,2,6,6-tetramethyl-*N*-oxopiperidinium salt, has to be evaluated.



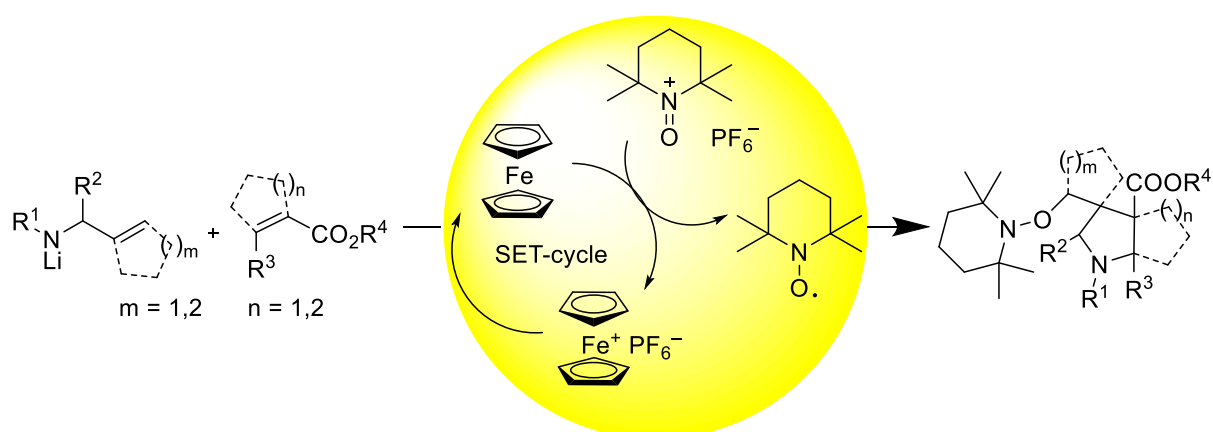
- Apply the asymmetric aminooxygenation methodology in the synthesis of *anti*- β -amino- α -hydroxy acid structures, present in macrocyclic peptides perthamide C, largamide H and in a total synthesis of (–)-cytoxazone.



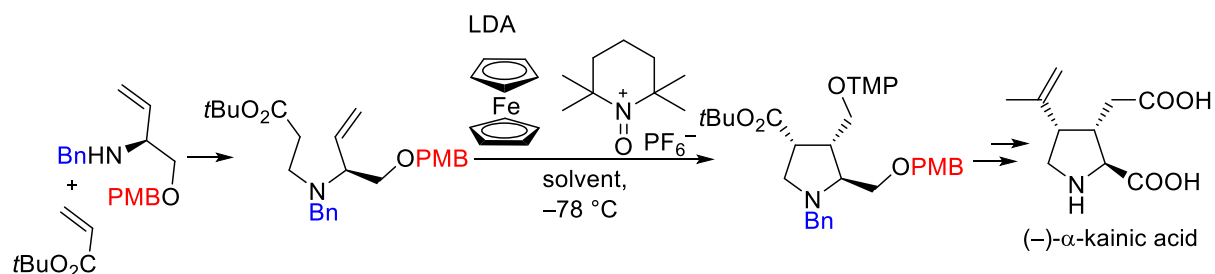
- Study the scope and diastereoselectivity of new lithium amides bearing the chirality in the allylic chain in the SET-catalyzed aza-Michael addition/5-*exo* radical cyclization/oxygenation reactions for the synthesis of *N*,2,3,4,5-pentasubstituted pyrrolidines.



- Apply catalytic traceless tandem lithium amide conjugate addition/5-*exo* radical cyclization/oxygenation reactions to the synthesis of polyfunctional pyrrolidines, azabicyclo[*n*.3.0]alkanes and spiropyrrolidines.



- Choose suitable *N*- and *O*- protecting groups and apply the catalytic oxidative tandem anionic-radical crossover methodology to the total synthesis of (–)- α -kainic acid.

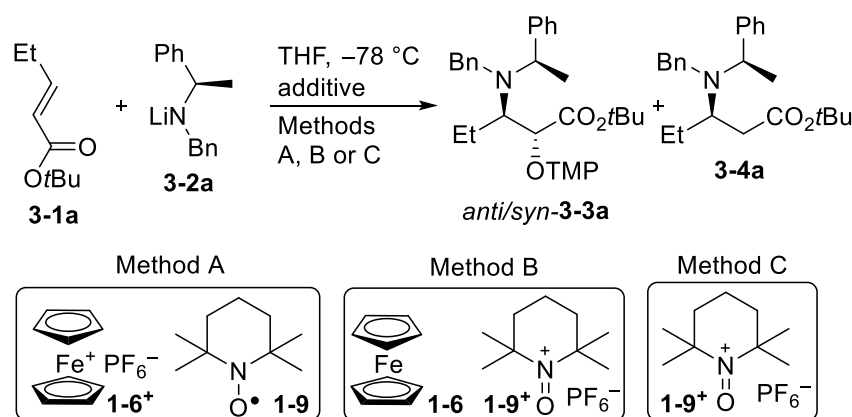


3. Results and discussion

3.1 Asymmetric lithium amide conjugate addition/SET oxidation/radical α -oxygenation reactions for the synthesis of *anti*- β -amino- α -hydroxy carboxylic acid derivatives

3.1.1 Initial results of the asymmetric conjugate addition of lithium (*R*)-*N*-benzyl-*N*- α -methylbenzylamide to *tert*-butyl *trans*-pent-2-enoate followed by SET-induced α -oxygenation

The aza-Michael addition of enantiomerically pure *N*-1-phenylethyl amides to esters proceeds with high enantio- and diastereomeric excess as shown previously by Davies.^[4b,d,f] This methodology was coupled with single-electron transfer (SET) oxidation by ferrocenium hexafluorophosphate **1-6**⁺ and radical heterocoupling with persistent free radical TEMPO (Scheme 3.1.1). The investigation began with finding suitable conditions for SET oxidation/radical α -oxygenation.



Scheme 3.1.1 Tandem aza-Michael reaction/ α -oxygenation reactions of amide **3-2a** with ester **3-1a**.

The initial experiment showed that the addition of lithium amide **3-2a** to *tert*-butyl *trans*-pent-2-enoate **3-1a** followed by SET oxidation using ferrocenium hexafluorophosphate **1-6**⁺ and oxygenation by TEMPO **1-9** provided the oxygenated ester **3-3a** in moderate 44% yield with 10:1 diastereomeric ratio together with aza-Michael adduct **3-4a** as a single diastereomer (Table 3.1.1, entry 1). The use of a catalytic amount of LiCl for the aza-Michael

addition as recently suggested by Collum et al.^[91] and using **1-6**⁺ and **1-9** for oxygenation improved the yield of product **3-3a** considerably without changing the diastereoselectivity of the radical coupling (Table 3.1, entry 2). The catalytic ferrocene-based oxygenation system consisting of 10 mol% **1-6** and *N*-oxoiminium salt **1-9**⁺ (Table 3.1, entry 3) or **1-9**⁺ alone (Table 3.1, entry 4) gave also the ester **3-3a** at –78 °C, but in somewhat lower yields and diastereomeric ratio. Small amounts of aza-Michael adduct **3-4a** were isolated under these conditions.

Table 3.1.1 Results of the initial aminooxygenation reactions of amide **3-2a** with ester **3-1a**.^[a]

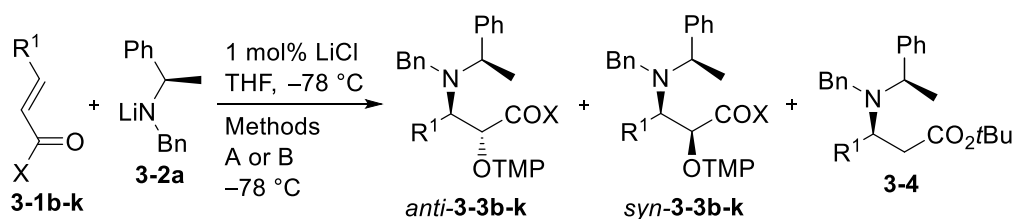
Entry	Additive (mol%)	Oxygenation (Method)	3-3a (%)	<i>anti/syn</i> - 3-3a	3-4a (%)
1	-	1-6 ⁺ , 1-9	44	10:1	16
2	LiCl	1-6 ⁺ , 1-9 (A)	72	10:1	-
3	LiCl	1-6 , 1-9 ⁺ (B)	50	10:1	14
4	LiCl	1-9 ⁺ (C)	66	7:1	5

[a] General conditions: **3-2a** (0.709 mmol), *n*BuLi (0.709 mmol), LiCl (1 mol%), –78 °C, 30 min, then **3-1a** (0.442 mmol), 90 min, followed by addition of **1-6**⁺/**1-9** (Method A), **1-6**/**1-9**⁺ (Method B) or **1-9**⁺ (Method C).

These results can be explained by the fact that with stoichiometric amounts of ferrocenium hexafluorophosphate **1-6**⁺ and TEMPO **1-9** high concentrations of persistent radical TEMPO are always present in the reaction mixture, thus α -coupling of the C-centered radical is more efficient than in the catalytic system **1-6**/**1-9**⁺ where the concentration of TEMPO **1-9** remains low (Table 3.1.1, entry 2 vs. entry 3).

3.1.2 Substrate scope of the asymmetric aminooxygenation methodology

To further examine the aza-Michael addition/radical α -oxygenation methodology a variety of aliphatic, cinnamic and β -heteroaryl α,β -unsaturated carbonyl compounds **3-1b-k** were tested with lithium amide **3-2a** under the optimal conditions (Scheme 3.1.2).



Scheme 3.1.2 Aza-Michael addition/radical α -oxygenation of **3-2a** with a variety of esters and amides **3-1b-k**.

Table 3.1.2 The results of aza-Michael addition/radical α -oxygenation of **3-2a** with **3-1b-k**.^[a]

Entry	3-1	R ¹	X	Oxidation (Method)	3-3 (%)	<i>anti</i> / <i>syn</i> -3-3	3-4 (%)
1	b	Me	O <i>t</i> Bu	A	b 73	11:1	-
2	c	Et	NMe ₂	A	c 75	>20:1	-
3	d	Isopropyl	O <i>t</i> Bu	A	d 47 ^[b]	>20:1	-
4	e	TBDMSOCH ₂	OE <i>t</i>	A	e 52	3:1	18
5	e	TBDMSOCH ₂	OE <i>t</i>	B	e 69	5:1	-
6	f	Bn	O <i>t</i> Bu	A	f 55	10:1	6
7	g	(<i>E</i>)-Propenyl	O <i>t</i> Bu	A	g 67 ^[b]	3:1	-
8	h	2-Furyl	O <i>t</i> Bu	A	h 78	4:1	15
9	i	Ph	O <i>t</i> Bu	A	i 73	3:1	7
10	j	Ph	NMe ₂	A	j 73	4:1	-
11	k	4-MeOC ₆ H ₄	OMe	A	k 71	2:1	-

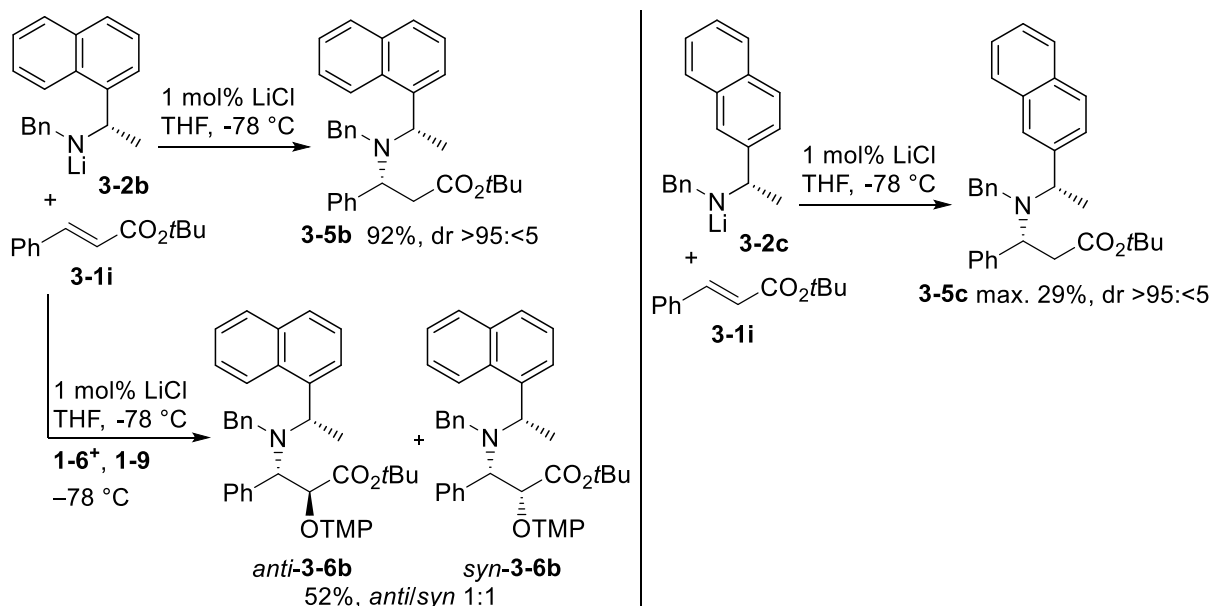
[a] Standard conditions: **3-2a** (1.04 mmol), *n*BuLi (1.04 mmol), LiCl (1 mol%), $-78\text{ }^{\circ}\text{C}$, 30 min, **3-1b-k** (0.650 mmol), 90 min, **1-6**⁺, **1-9** (Method A) or **1-6**, **1-9**⁺ (Method B). [b] LiCl (1.5 equiv) present in the beginning.

Aliphatic α,β -unsaturated carbonyl compounds provided *anti*-**3-3b-e,f** with moderate to good yields and moderate to excellent diastereoselectivities (Table 3.1.2, entries 1-4,6). In case of compound **3-3e** the catalytic method B using **1-6**/**1-9**⁺ turned out to be more efficient with respect to yield and diastereoselectivity (Table 3.1.2, entry 5 vs. 4). The conjugate addition/oxygenation reaction using *t*-butyl sorbate **3-1g** provided product **3-3g** in reasonable yield, but the diastereoselectivity decreased (Table 3.1.2, entry 7). The use of stoichiometric LiCl proved to be better than catalytic amounts in the aminooxygenation reactions of **3-1d** and **3-1g** (Table 3.1.2, entries 3,7).

The aminooxygenation reaction of cinnamic **3-1i-k** and β -heteroaryl- α,β -unsaturated **3-1h** acid derivatives gave good yields, but only moderate 2-4:1 *anti/syn* diastereoselectivities (Table 3.1.2, entries 8-11). Esters and amides provided similar results with respect to yields and diastereoselectivities (Compare Table 3.1.1, entry 2 with Table 3.1.2, entry 2, and Table 3.1.2, entry 9 with entry 10).

The absolute configuration is set in the aza-Michael addition step. The relative configuration of products *anti*-**3-3b** and *anti*-**3-3i** was proved by X-ray crystallography.^[92] The configuration of **3-3a**, **3-3c-h** and **3-3j,k** was assigned by analogy and the similarity of their spectroscopic data.

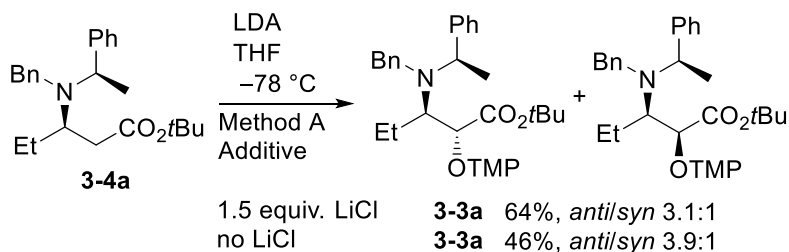
In order to improve the diastereoselectivity of the aminooxygenation reaction different amides as the second variable component were screened. The more sterically hindered reagents such as (*S*)-*N*-benzyl-1-(naphthalen-1-yl)ethan-1-amide **3-2b** and (*S*)-*N*-benzyl-1-(naphthalen-2-yl)ethan-1-amide **3-2c**, which is isomeric to **3-2b**, have been tested in the aminooxygenation reaction (Scheme 3.1.3). Initially, the aza-Michael reaction of **3-2b** to **3-1i** proceeded in 72% yield. However, in the presence of catalytic LiCl the yield was significantly improved to 92% and the β -amino ester **3-5b** was isolated as a single diastereomer. The tandem aza-Michael addition/oxygenation gave product **3-6b** in moderate 52% yield with 1:1 *anti/syn* diastereoselectivity. The corresponding (*S*)-*N*-benzyl-1-(naphthalen-2-yl)ethan-1-amide **3-2c** added only very slowly to **3-1i** and the β -amino ester **3-5c** was isolated in maximal 29% yield. However, the aminooxygenation reaction of **3-2b** with **3-1i** did not provide the oxygenated product.



Scheme 3.1.3 The sterically more congested lithium amides **3-2b** and **3-2c** in the aminooxygenation reactions.

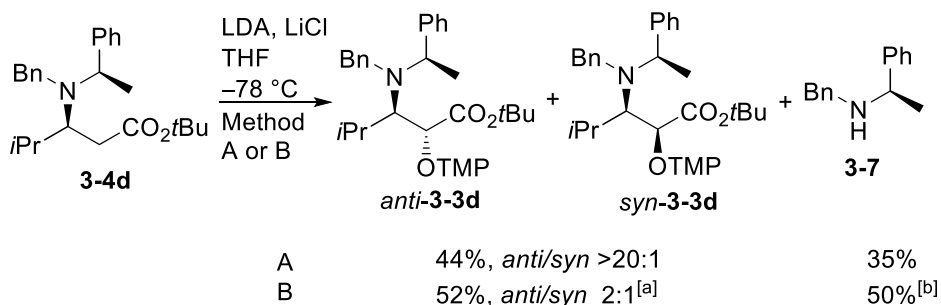
3.1.3 Two-step methodology for the asymmetric synthesis of β -amino- α -hydroxy acid derivatives

The best way to confirm the advantages of the aminooxygenation methodology was to compare the tandem process with a stepwise procedure. Therefore, β -aliphatic and β -aromatic amino esters **3-4a**, **3-4d** and **3-4i** were prepared and isolated individually. Deprotonation of aminoester **3-4a** with LDA followed by SET oxidation with **1-6⁺** and oxygenation with TEMPO **1-9** provided oxygenated ester **3-3a** in 46% yield with significantly reduced 3.9:1 *anti/syn* diastereoselectivity (Scheme 3.1.4, *cf.* Table 3.1.1). The same reaction with 1.5 equivalents of LiCl gave significantly improved 64% yield of **3-3a** with 3.1:1 *anti/syn* diastereoselectivity.



Scheme 3.1.4 Oxygenation of ester **3-4a** by **1-6⁺** and TEMPO **1-9**.

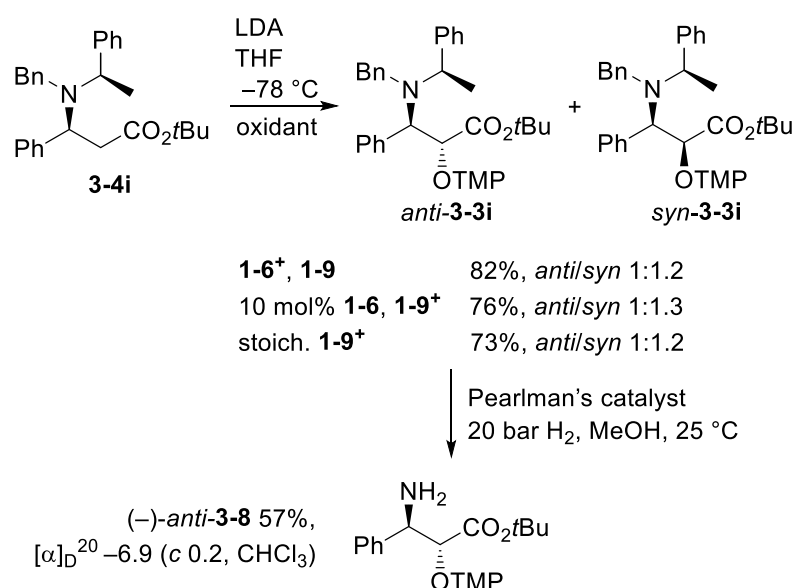
Deprotonation of **3-4d** with LDA in the presence of 1.5 equivalents of LiCl followed by oxygenation using ferrocenium hexafluorophosphate **1-6**⁺ and TEMPO **1-9** provided *anti*-**3-3d** as a single diastereomer in 44% isolated yield (Scheme 3.1.5), which is the same result as the one obtained from the tandem reaction (*cf.* Table 3.1.2). Moreover, 35% of (*R*)-*N*-benzyl-1-phenylethylamine **3-7** was isolated from the reaction mixture. The diastereoselectivity of **3-3d** was in contrast to the one obtained from the oxygenation of **3-4a** (Scheme 3.1.4). Therefore, the oxygenation of **3-4d** was repeated under the catalytic conditions using 5 mol% ferrocene **1-6** and salt **1-9**⁺ thus enabling easier NMR analysis of the crude reaction mixture than with the oxidation system **1-6**⁺/**1-9** containing an excess paramagnetic species. Indeed, ¹H-NMR spectroscopic analysis of the crude reaction mixture confirmed a 2:1 *anti*/*syn* diastereoselectivity ratio for **3-3d** (52% calculated yield) and recovered **3-4d** (14% calculated yield), but without **3-7**. This result is in agreement with the one obtained from oxygenation of **3-4a** and confirmed the decreased diastereoselectivity of the two-step procedure. The *syn*-diastereomer of **3-3d** always decomposed during purification by column chromatography providing chromatographically stable *anti*-**3-3d** as the only purified product and forming significant amounts of amine **3-7**.



Scheme 3.1.5 Oxygenation of β -amino ester **3-4d**. [a] Determined by ¹H NMR spectroscopy of the crude mixture. [b] Contaminated with minor impurities.

Because of the chromatographic lability of *syn*-**3-3d** the tandem aza-Michael addition/oxygenation was repeated to confirm the previously observed excellent diastereoselectivity (*cf.* Table 3.1.2). The tandem reaction was performed with the catalytic condition using 10 mol% ferrocene **1-6** and oxoiminium salt **1-9**⁺. The crude ¹H-NMR analysis of the reaction mixture confirmed that *anti*-**3-3d** formed as the single product in the tandem reaction (*cf.* Table 3.1.2).

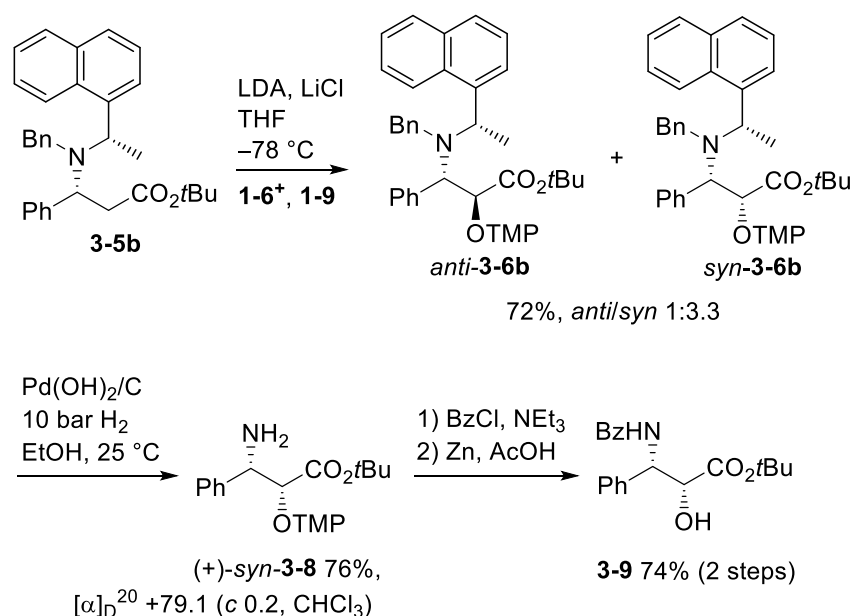
To further explore the diastereoselectivity of the two-step procedure, aromatic β -amino ester **3-4i** was deprotonated with LDA and SET oxidation by **1-6⁺** and oxygenation by **1-9** provided **3-3i** in 82% yield with 1:1.2 *anti/syn* diastereoselectivity (Scheme 3.1.6). The catalytic conditions using **1-6/1-9⁺** or the use of stoichiometric 2,2,6,6-tetramethyl-*N*-oxopiperidinium hexafluorophosphate **1-9⁺** gave the same results. To conclude, all three oxidation systems gave identical results showing that yield and diastereoselectivity of the oxygenation is not influenced by the reagent system. The *N*-benzyl protecting groups in *anti*-**3-3i** were removed by hydrogenolysis with Pearlman's catalyst and the resulting free amino ester (–)-*anti*-**3-8** displays a specific rotation of –6.9°.



Scheme 3.1.6 Oxygenation of β -amino ester **3-4i** using various oxygenation reagents and deprotection of the *N*-benzyl protecting groups from *anti*-**3-3i**.

Deprotonation of aromatic β -amino ester **3-5b** with LDA in the presence of 1.5 equivalents of LiCl followed by oxygenation using **1-6⁺/1-9** gave product **3-6b** in 72% yield with 1:3.3 *anti/syn* diastereoselectivity (Scheme 3.1.7). The relative configuration of *anti*-**3-6b** and *syn*-**3-6b** was assigned by hydrogenolysis of the major isomer of **3-6b**, which gave a diastereomeric product as judged by comparison of its NMR data with those of *anti*-**3-8** and an [α]_D²⁰ +79.1 (c 0.2, CHCl₃), thus the hydrogenolysis product must have *syn* configuration. To confirm the absolute configuration, (+)-*syn*-**3-8** was converted by *N*-benzoylation and reductive deprotection of the tetramethylpiperidynyl protecting group to *syn*-3-benzamido-2-hydroxy ester **3-9**. This compound is the *tert*-butyl ester of the *N*-benzoyl

phenylisoserine side chain of paclitaxel and all analytical data including optical rotation match those of authentic material.^[44a] These results demonstrate that the conditions for enolate generation and the nitrogen protecting groups are crucial for the diastereoselectivity in the oxygenation step.



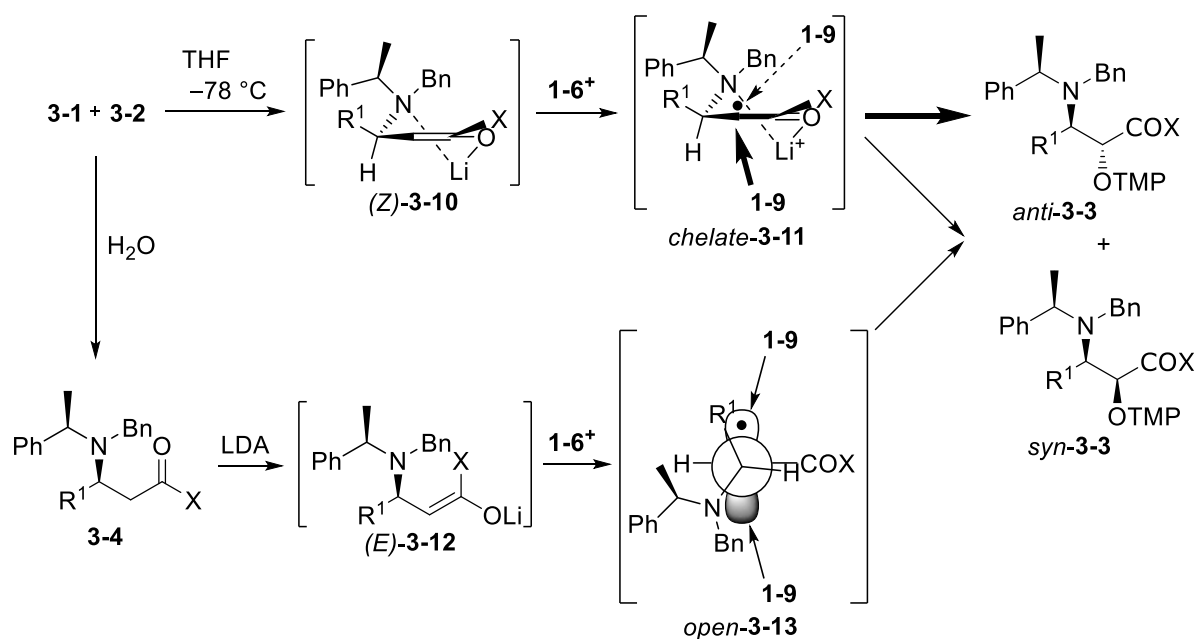
Scheme 3.1.7 Oxygenation of β -amino ester **3-5b** and confirmation of the major *syn*-diastereomer of **3-6b** by synthesis of the *tert*-butyl phenylisoserinate side chain of paclitaxel.

3.1.4 Mechanistic rationalization of the diastereoselectivity of the aminooxygenation reactions

The results from one-step and two-step methodology indicate that several particular factors determine the stereochemical results (Scheme 3.1.8). The conjugate addition of lithium amides **3-2a** or **3-2b** to α,β -unsaturated carbonyl compounds **3-1** proceeds reliably with >95 % *de* according to Davies's results and the stereocenter bearing the amine function is predictively formed. The aza-Michael addition step gives (*Z*)-enolate (*Z*)-**3-10**, which exists in solution as a six-membered chelate.^[93] After SET oxidation of (*Z*)-**3-10** by ferrocenium hexafluorophosphate **1-6⁺** radical *chelate*-**3-11** is formed, which remains stable at low temperature. Persistent radical TEMPO **1-9** is approaching *chelate*-**3-11** from the bottom face because of hindrance steric, thus providing *anti*-**3-3** with good diastereoselectivity if R¹ is an

alkyl group. For the oxygenated compound **3-3e**, possibly alternative chelation modes reduce the observed diastereoselectivity. The significantly lower diastereoselectivity in favor of *anti*-**3-3** is observed if R¹ is vinyl and aromatic. Only steric effects cannot be responsible for these results, and it is expected that the aromatic or vinylic substituent is involved either in π - π interactions with the neighboring benzyl or 1-phenylethyl groups, or in interactions of the α -radical with the π -system of R¹. These interactions may lead to a change in the conformation of the chelate ring, thus also allowing radical coupling with TEMPO from the top face of *chelate*-**3-11**.

The diastereoselectivity in the two-step methodology can be rationalized as follows. Deprotonation of β -amino esters **3-4** with LDA leads to (*E*)-enolates (*E*)-**3-12**, which are also efficiently oxidized but can only form non-chelated radicals *open*-**3-13**. Since radicals with an ester group in the α -position were shown to have a significant rotational barrier,^[94] the configuration of the enolate is translated into that of the radical and the orientation of the substituents in β -position is determined by A^{1,3}-strain.^[95] In this arrangement both the R¹ and amino groups interfere with the approach of TEMPO toward radical *open*-**3-13**, leading to significantly reduced *anti*-diastereoselectivity for R¹ = alkyl substituents. For R¹ = aryl, no face selectivity of radical coupling is observed, whereas the bulkier 1-naphthylethylamino group apparently leads to a change of the reactive conformation, so that the approach of TEMPO **1-9** from the bottom face becomes favored leading to preferred formation of the *syn*-diastereomer of **3-6b** (*cf.* Scheme 3.1.7).

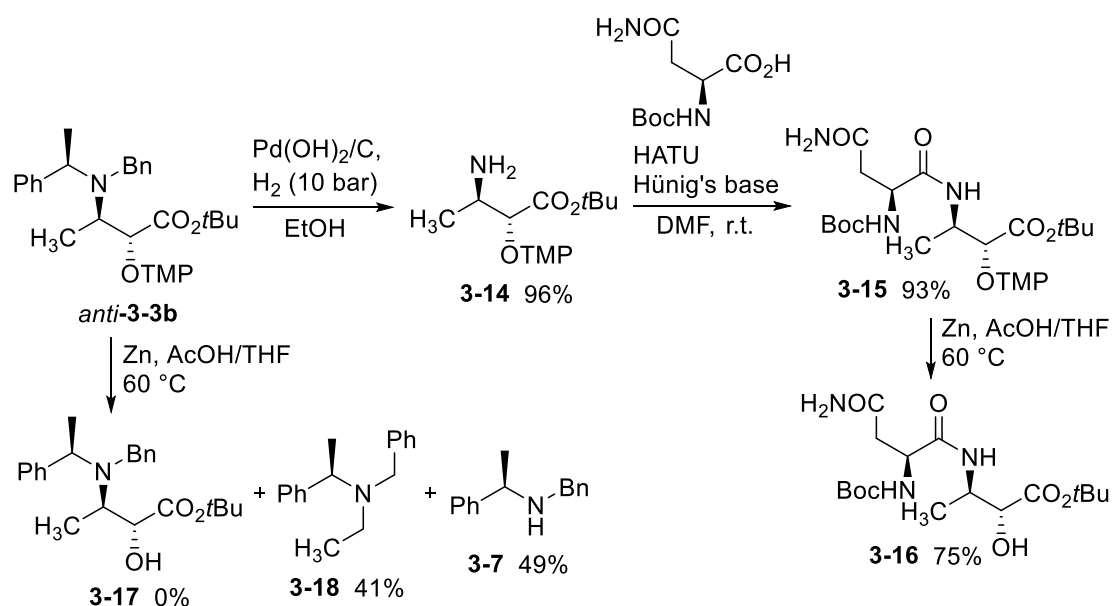


Scheme 3.1.8 Rationalization of the diastereoselectivity of the aminooxygenation reactions.

3.1.5 Selective deprotection of β -amino- α -hydroxy acid derivatives

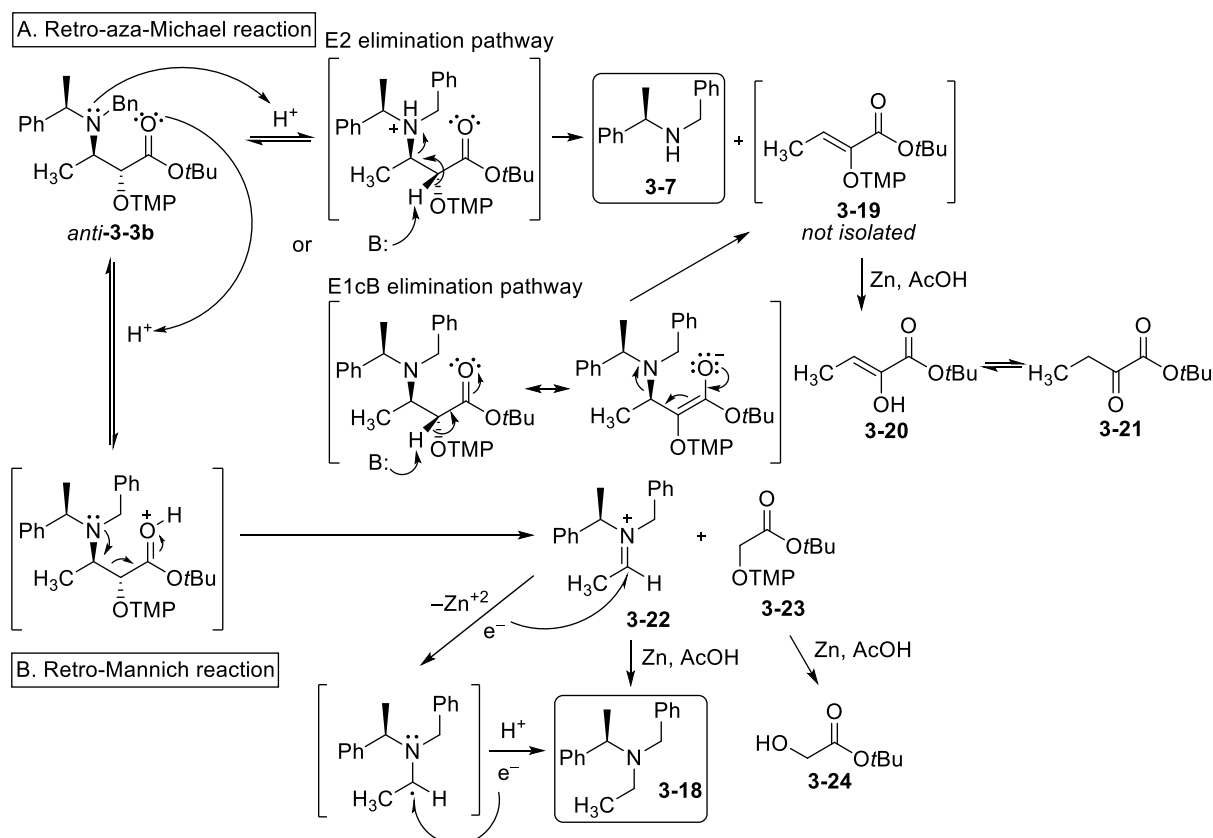
The deprotection steps play an important role for the application of fully protected compounds *anti*-**3-3** in total syntheses of complex naturally occurring *anti*- β -amino- α -hydroxy acid-containing peptides. However, the order of steps played an important role as shown in Scheme 3.1.9.

The *N*-benzyl protecting groups of reverse threonine derivative *anti*-**3-3b** were efficiently removed by hydrogenolysis with Pearlman's catalyst in ethanol. Dipeptide **3-15** was obtained in excellent yield from the reaction of free amino ester **3-14** with *N*-Boc-protected asparagine in HATU-mediated peptide coupling. The *O*-protected dipeptide **3-15** subsequently underwent standard reductive N–O bond cleavage providing free dipeptide **3-16** in 75% yield. Notably, no epimerization occurred under the acidic reaction conditions, and the *tert*-butoxycarbonyl protecting group remained untouched under these conditions.



Scheme 3.1.9 Selective *N*-deprotection, peptide coupling and *O*-deprotection reactions of *anti*-**3-3b**.

In contrast, reductive N–O bond cleavage of compound *anti*-**3-3b** gave the undesired secondary amine **3-7** and tertiary amine **3-18**. However, no product of TMP group deprotection **3-17** was observed. This result shows that a retro-aza-Michael reaction and a retro-Mannich reaction operate here in parallel as shown in Scheme 3.1.10.

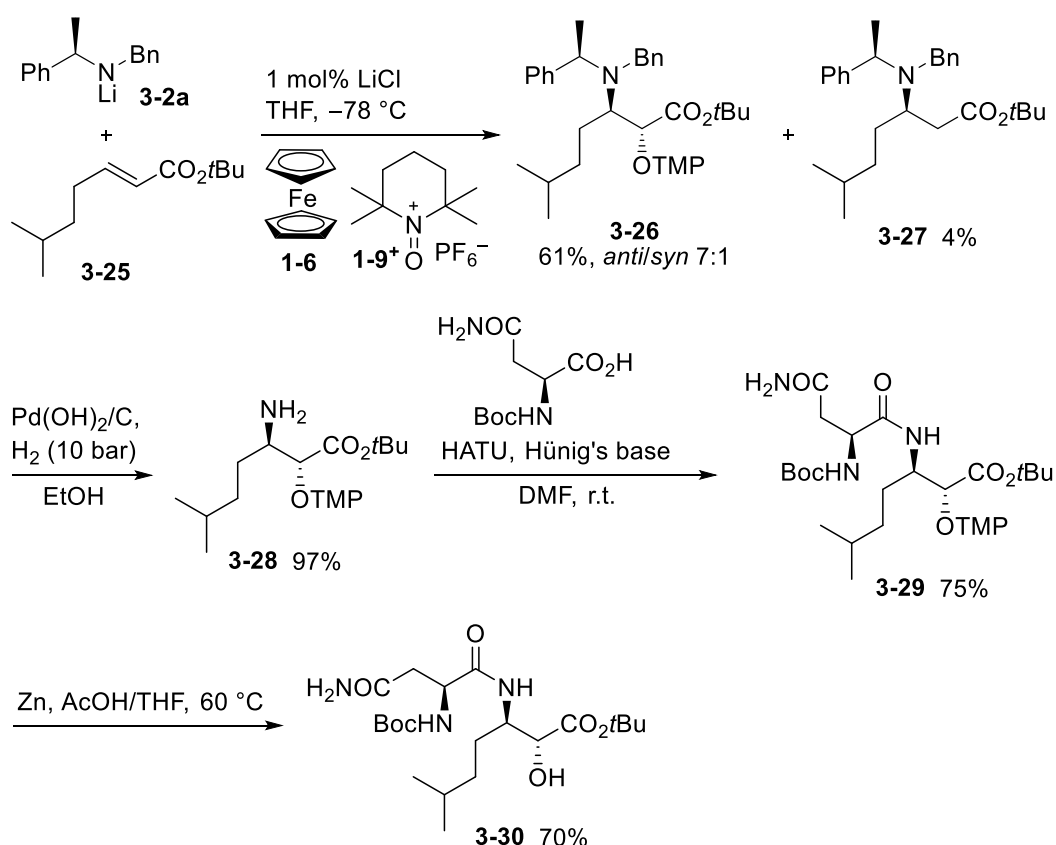


Scheme 3.1.10 Mechanisms of a retro-aza-Michael reaction and a retro-Mannich reaction that operate in reductive N-O bond cleavage of *anti*-**3-3b**.

Secondary amine **3-7** is formed in retro-aza-Michael reaction *via* E2 elimination pathway upon deprotonation of *anti*-**3-3b** with base and the protonated β -amino functionality in *anti*-**3-3b** serves as a good leaving group. Amine **3-7** can also be formed *via* E1cB elimination pathway. However, the second component **3-19** was not isolated; it subsequently undergoes standard reductive N–O bond cleavage providing **3-20**, which tautomerizes to volatile α -keto ester **3-21** (b.p.: 55–60 °C, 6–7 Torr). Furthermore, under the acidic conditions iminium ion **3-22** is formed, which is *in-situ* reduced with zinc to tertiary amine **3-18**. As a second product of this retro-Mannich reaction is α -tempoxy ester **3-23**, which probably undergoes standard reductive N-O bond cleavage to form volatile hydroxy compound **3-24** (b.p.: 56 °C, 12 Torr).

3.1.6 Applications of aminooxygenation reactions in target-oriented synthesis

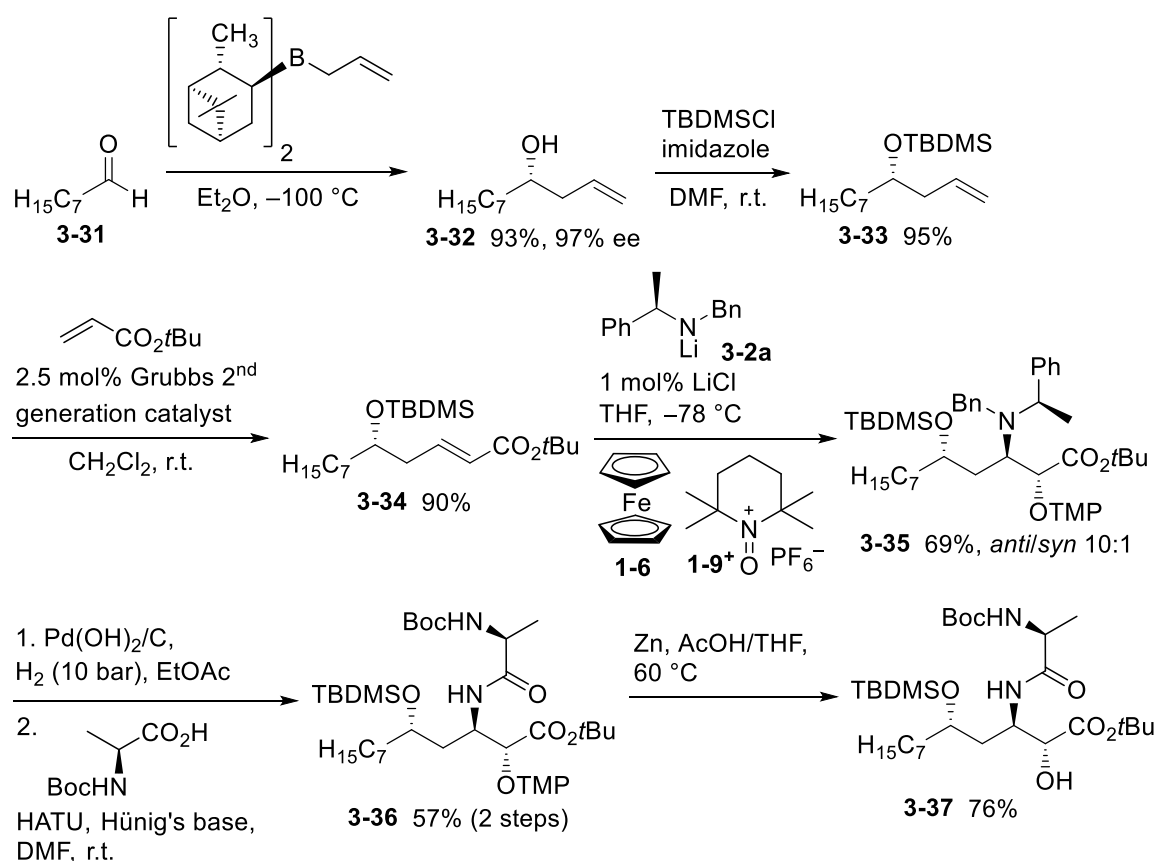
To prove the efficiency and simplicity of the tandem amide conjugate addition/oxygenation methodology short total syntheses were performed. The tandem aza-Michael addition of lithium amide **3-2a** to ester **3-25** followed by oxygenation using catalytic ferrocene **1-6** and tempoxonium salt **1-9⁺** provided fully protected *anti*- β -amino- α -hydroxy unit of perthamide C^[37] **3-26** in good yield and reasonable diastereoselectivity (Scheme 3.1.11). The *N*-benzyl protecting groups in **3-26** were removed by hydrogenolysis using Pearlman's catalyst and the resulting free amino ester **3-28** underwent HATU-mediated peptide coupling with *N*-Boc-protected asparagine in good yield. The final step in the synthesis was *O*-deprotection of the dipeptide **3-29** using standard reductive N–O bond cleavage furnishing dipeptide **3-30** in 70% yield. No epimerization was observed during N–O bond cleavage.



Scheme 3.1.11 Aminooxygenation reaction as a key step in the synthesis of dipeptide fragment **3-30** in perthamide C.

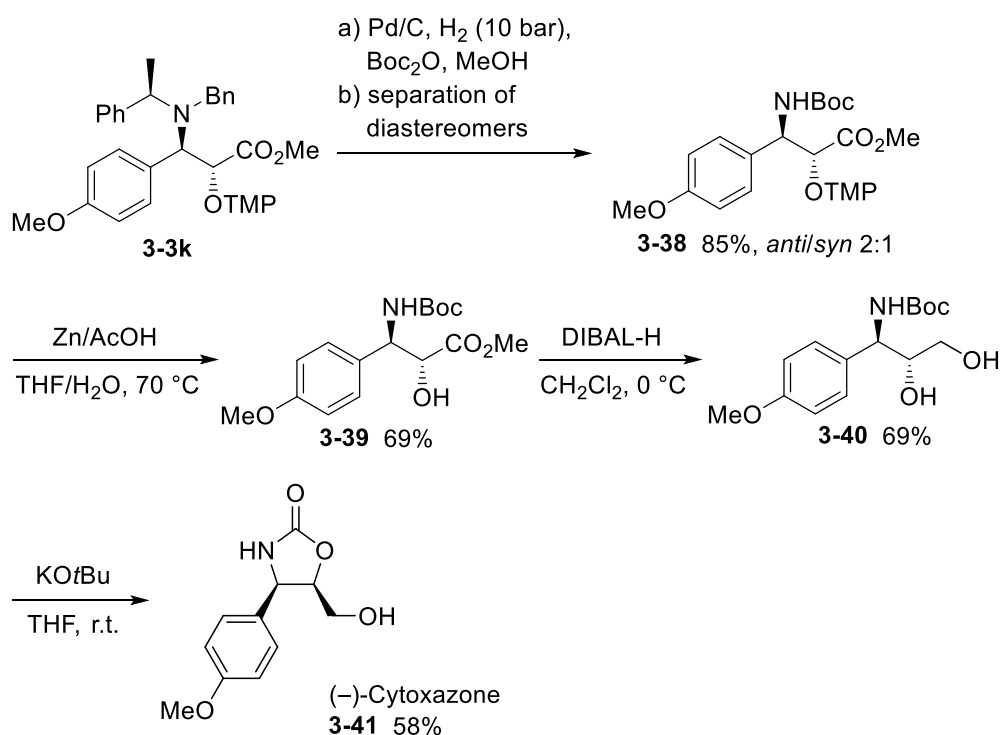
The aza-Michael addition/oxygenation reaction was also applied as a key step in a short total synthesis of the β -amino- α -hydroxy acid fragment of the more complex

macrocyclic peptide largamide H (Scheme 3.1.12).^[96] The synthesis started with Brown's allylboration of octanal **3-31** with *B*-allyldiisopinocampheylborane, providing homoallylic alcohol **3-32** in almost quantitative yield with 97% *ee*.^[97] Protection of alcohol **3-32** with *tert*-butyldimethylsilyl chloride gave silyl ether **3-33**, which subsequently reacted with *tert*-butyl acrylate in a cross-metathesis reaction giving α,β -unsaturated ester **3-34** in 90% yield. The tandem aza-Michael addition of lithium amide **3-2a** with ester **3-34** followed by SET oxidation/radical α -oxygenation using catalytic amounts of ferrocene **1-6** and **1-9⁺** furnished fully protected β -amino- α,δ -dihydroxy ester **3-35** with good yield and diastereoselectivity. Deprotection of the *N*-benzylic protecting groups from **3-35** followed by HATU-mediated peptide coupling with *N*-Boc-protected alanine gave dipeptide **3-36**. Finally, reductive N–O bond cleavage in **3-36** afforded the silyl-protected β -amino- α -hydroxy acid-containing dipeptide **3-37** of largamide H in 76% yield. To summarize, the synthesis was accomplished in 22% yield over 7 steps; the previously published synthesis has ten steps and 24% overall yield.^[96]



Scheme 3.1.12 Aminooxygenation reaction as a key step in the synthesis of dipeptide fragment **3-37** in largamide H.

Furthermore, the asymmetric tandem amide conjugate addition/ α -oxygenation methodology was applied as key step in the total synthesis of (–)-cytoxazone (Scheme 3.1.13). Amino-oxygenation product **3-3k** was subjected to one-pot hydrogenolysis with palladium on charcoal in methanol and subsequent protection of the resulting amine as its *tert*-butyl carbamate derivative **3-38** in 85% yield. At this step, the *anti*- and *syn*-diastereomers of **3-38** were separated by column chromatography. The relative configuration of *anti*-**3-38** was established by X-ray crystallography (Figure 3.1.1). Reductive removal of the tetramethylpiperidinyloxy protecting group provided *anti*-amino hydroxy ester **3-39** in good yield. Reduction of the methyl ester with DIBAL-H gave aminodiol **3-40**, which accomplished (–)-cytoxazone **3-41** by base-promoted cyclization in 11% overall yield over five steps. This approach ranks among the shorter syntheses, in comparison to previously published approaches in 10–71% overall yields over 4–11 steps.^[98]



Scheme 3.1.13 Amino-oxygenation reaction as a key step in a total synthesis of (–)-cytoxazone **3-41**.

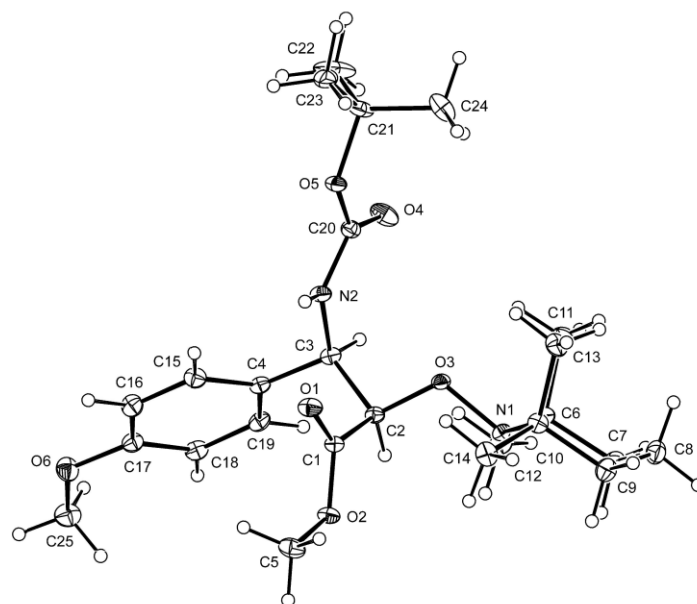
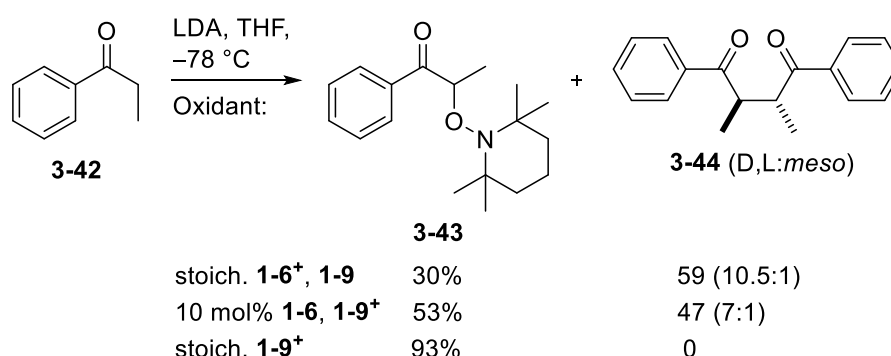


Figure 3.1.1 Structure of *anti*-3-38. Displacement ellipsoids are drawn at the 30 % level.

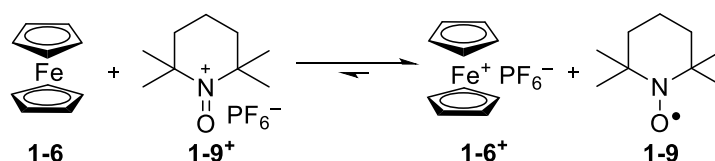
3.2 Asymmetric SET-catalyzed tandem lithium amide conjugate addition/5-*exo* radical cyclization/oxygenation reactions for the synthesis of highly functionalized pyrrolidines, azabicyclo[n.3.0]alkanes and spiropyrrolidines

To demonstrate that the ferrocene-catalyzed tandem reaction proceeds identically to the tandem reactions mediated by stoichiometric amounts of ferrocenium hexafluorophosphate, propiophenone was tested with various oxidant systems (Scheme 3.2.1).



Scheme 3.2.1 Propiophenone **3-42** was tested with various oxidant systems.

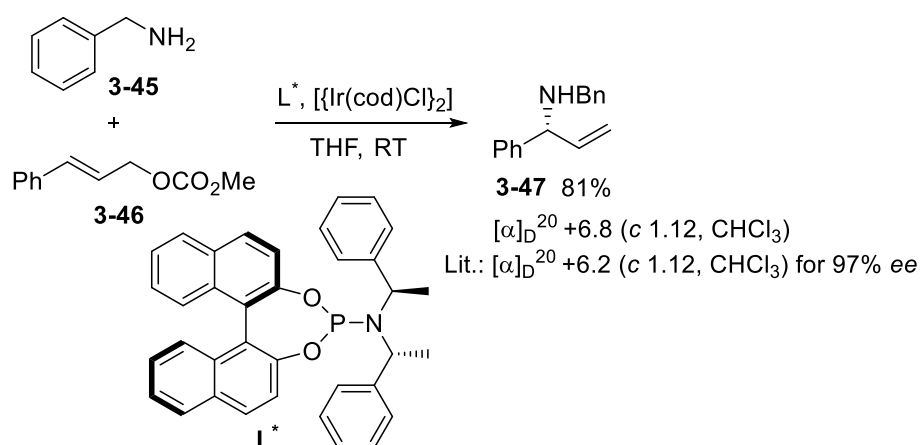
Propiophenone **3-42** provided similar distribution of oxygenation **3-43** and radical dimerization **3-44** products under the stoichiometric conditions **1-6⁺/1-9** and under the catalytic conditions **1-6/1-9⁺**, thus indicating the similarity of the process. 2,2,6,6-Tetramethyl-*N*-oxopiperidinium hexafluorophosphate **1-9⁺** gave only oxygenated product **3-43** without the radical derived product **3-44**. Thus, **1-9⁺** serves as an oxidant and does not act as a mediator for the same transformation. The same product distribution of the stoichiometric and catalytic versions indicates that 2,2,6,6-tetramethyl-*N*-oxopiperidinium hexafluorophosphate **1-9⁺** is capable of oxidizing ferrocene **1-6** to ferrocenium hexafluorophosphate **1-6⁺**, which mediates the SET oxidation, and TEMPO serves as the oxygenation reagent for the C-centered radical (Scheme 3.2.2).^[84,90]



Scheme 3.2.2 2,2,6,6-Tetramethyl-*N*-oxopiperidinium hexafluorophosphate **1-9⁺** is capable of oxidizing ferrocene **1-6** to **1-6⁺**.

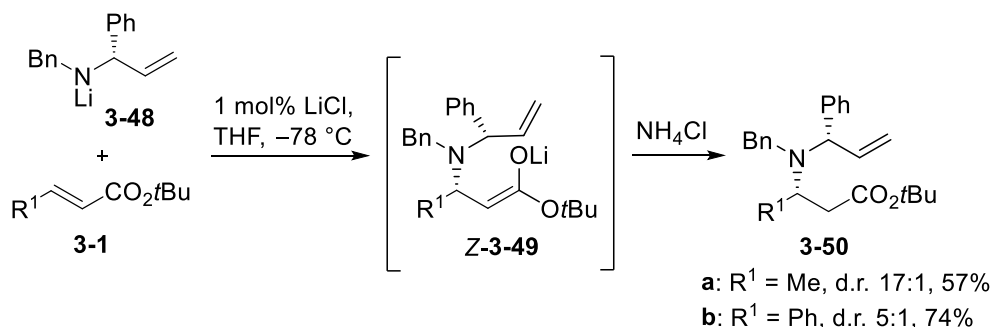
3.2.1 Applying new chiral *N*-allylic *N*-benzylamide in aza-Michael reaction to α,β -unsaturated esters

The most efficient approach for the synthesis of *N*-heterocyclic compounds is ideally a one-step process involving two variable components. In chapter 3.2 the variable components represent differently substituted chiral *N*-allylic amides and α,β -unsaturated esters or amides. *N*-allylic *N*-benzylamine **3-47** having the chirality in the allylic chain was prepared by the iridium-catalyzed Hartwig-Helmchen allylic amination reaction (Scheme 3.2.3). The obtained yield and enantioselectivity were in agreement with the literature.^[99]



Scheme 3.2.3 Allylic amination of achiral allylic carbonate catalyzed by an iridium–phosphoramidite complex.

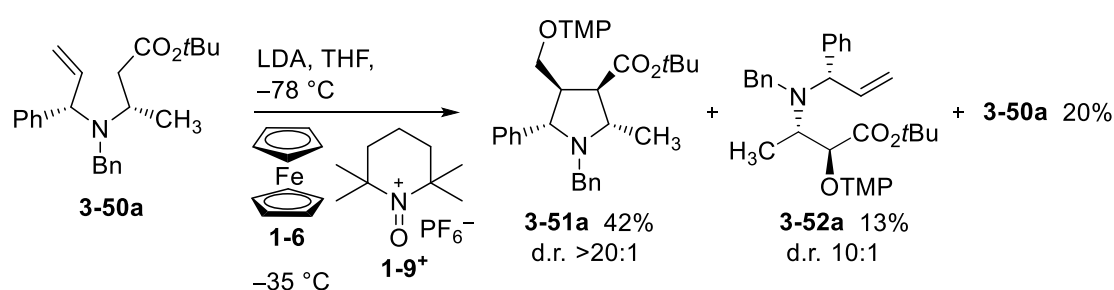
Amide **3-48** was tested in aza-Michael additions to α,β -unsaturated esters **3-1** (Scheme 3.2.4). The addition reactions were carried out in the presence of lithium chloride^[91] at low temperature. β -Amino esters **3-50** were isolated in good yields and excellent diastereoselectivity for **3-50a**; only moderate diastereoselectivity was observed for **3-50b**.



Scheme 3.2.4 Asymmetric aza-Michael addition of amide **3-48** to esters **3-1**.

3.2.2 Traceless catalytic oxidative asymmetric tandem lithium amide conjugate addition/radical cyclization/oxygenation reactions for the synthesis of *N*,2,3,4,5-pentasubstituted pyrrolidines

Initially, oxidative cyclization of β -amino ester **3-50a** was performed by deprotonation with LDA in THF and subsequent SET oxidation/*5-exo* radical cyclization/oxygenation mediated by catalytic amounts of ferrocene **1-6** and 2,2,6,6-tetramethyl-*N*-oxopiperidinium hexafluorophosphate **1-9⁺** (Scheme 3.2.5). *N*,2,3,4,5-pentasubstituted pyrrolidine **3-51a** was synthesized in moderate yield and excellent C3,C4-*cis* diastereoselectivity. α -TEMPO oxygenated product **3-52a** and starting ester **3-50a** were also isolated.



Scheme 3.2.5 Catalytic oxidative cyclization of β -amino ester **3-50a**.

The relative configuration of compound **3-51a** was confirmed by X-ray crystallography (Figure 3.2.1), which showed a *trans*-orientation of the *tert*-butyl carboxylate at C3 and alkyl group at C4.

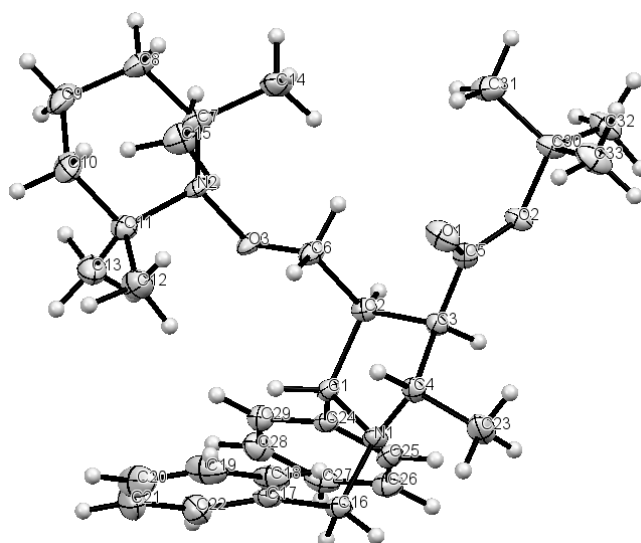
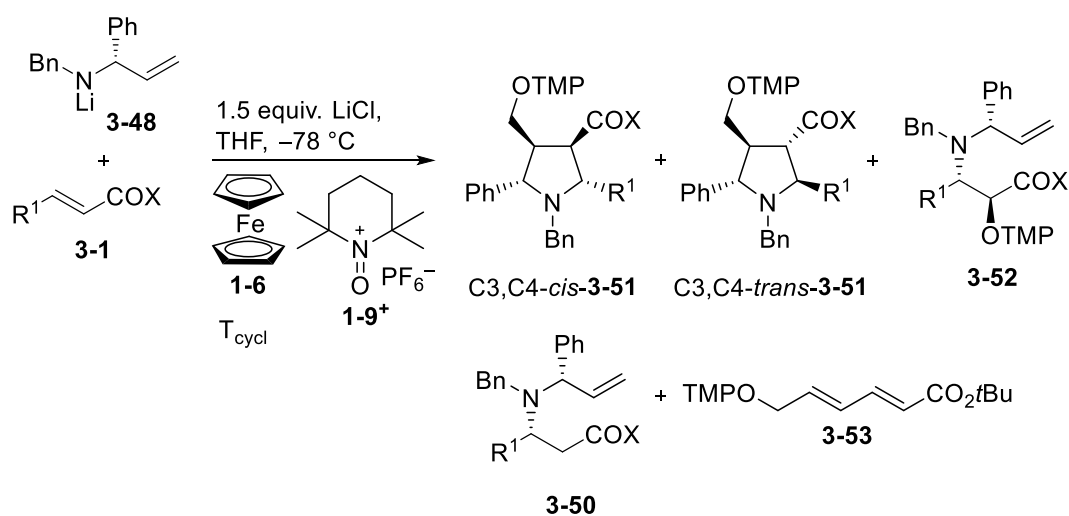


Figure 3.2.1 Structure of **3-51a** in the crystal with atom numbering scheme. Displacement ellipsoids are drawn at 30 % level.

The absolute configuration of **3-52a** is set in the aza-Michael addition step. The relative configuration of major diastereomer *anti*-**3-52a** was assigned by analogy with aminooxygenated product **3-3b** and the similarity of their ¹H NMR coupling constants.

A range of pentasubstituted pyrrolidines **3-51** was prepared by tandem asymmetric conjugate addition of amide **3-48** to esters and amides **3-1** followed by SET oxidation/5-*exo* radical cyclization/TEMPO oxygenation reactions mediated by **1-6** and **1-9⁺** (Scheme 3.2.6).



Scheme 3.2.6 SET-catalyzed tandem aza-Michael addition/5-*exo* radical cyclization/oxygenation reactions.

The use of superstoichiometric LiCl proved to be better than catalytic amounts (Table 3.2.1, entries 1,2 vs. entries 3,4). Aliphatic α,β -unsaturated esters and amide gave pyrrolidines **3-51** in moderate to good yields and excellent C3,C4-*cis* diastereoselectivities (Table 3.2.1, entries 1,5 and 6). Cinnamic and β -heteroaryl derivatives provided **3-51** in good yields and very good diastereoselectivity (Table 3.2.1, entries 2,7). *tert*-Butyl sorbate afforded the cyclized product in moderate yield and very good diastereoselectivity (Table 3.2.1, entry 8). Almost in all cases small amounts of aza-Michael adducts **3-50** were isolated.

Table 3.2.1 Results of tandem aza-Michael addition/radical cyclization/oxygenation reactions of amide **3-48** with α,β -unsaturated carbonyl compounds **3-1**.^[a]

Entry	R ¹	X	T _{cycl}	3-51 (%)	<i>cis</i> -C3-C4: <i>trans</i> - C3-C4 3-51	3-52 (%)	3-50 (%)
1 ^[b]	Me	<i>Ot</i> Bu	−35 °C	a 42	>20:1	3	8
2 ^[b]	Ph	<i>Ot</i> Bu	−35 °C	b 41	6:1	-	25
3	Me	<i>Ot</i> Bu	−20 °C	a 66	>20:1	6	19
4	Ph	<i>Ot</i> Bu	−20 °C	b 53	6:1	-	8
5	Et	<i>Ot</i> Bu	−20 °C	c 61	>20:1	-	9
6	Et	NMe ₂	−20 °C	d 33	>20:1	-	-
7 ^[b]	2-Furyl	<i>Ot</i> Bu	−20 °C	e 62	10:1	-	10
8 ^[b]	(<i>E</i>)-Propenyl	<i>Ot</i> Bu	−20 °C	f 44 ^[c]	11:1	-	11

[a] Standard conditions: **3-47** (0.360 mmol), *n*BuLi (0.360 mmol), LiCl (1.5 equiv.), THF, −78 °C, 30 min, **3-1** (0.277 mmol), 90 min, **1-6**, **1-9**⁺. [b] LiCl (1 mol%) present.

[c] Additionally, 5% of ϵ -deprotonation/oxygenation product isolated **3-53**.

The stereochemistry of minor diastereomer of pyrrolidine **3-51b** was confirmed by ROESY analysis (Figure 3.2.2). There are NOE contacts between the proton on phenyl ring at C2 and the proton at C3, as well as between protons at C3 and methylene protons at C4 (CH₂OTMP), thus suggesting C2,C3- and C3,C4-*trans* stereochemistry on the pyrrolidine ring. No NOE contact between protons at C2 and C5 would speak for minor diastereomer **3-51b**, which comes from the second diastereomer generated in the aza-Michael addition step.

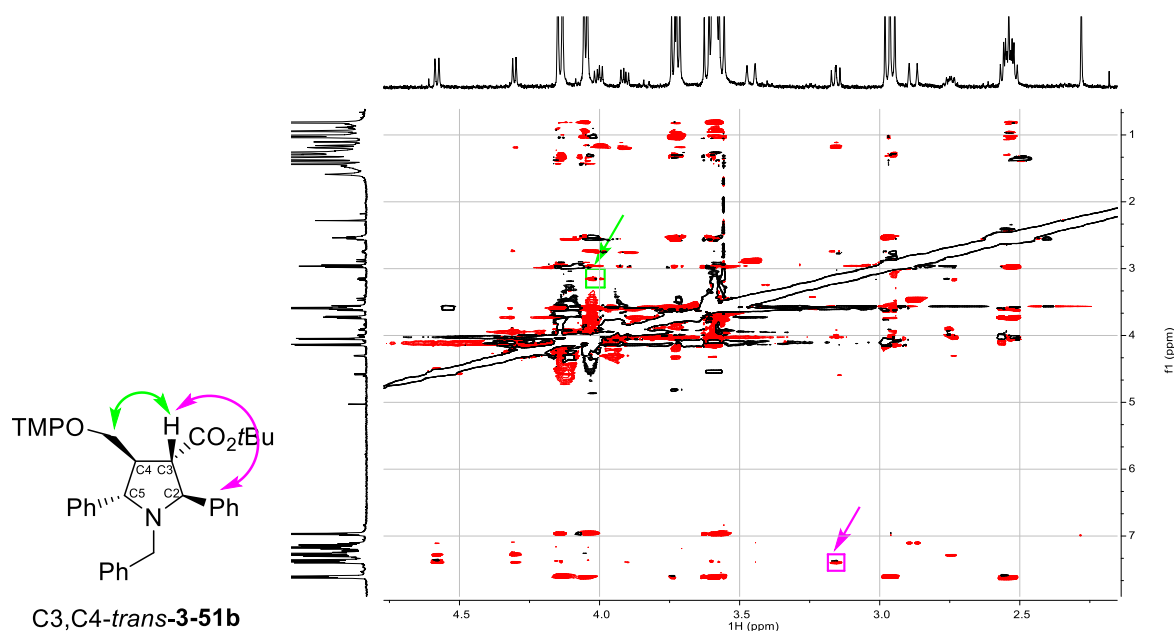
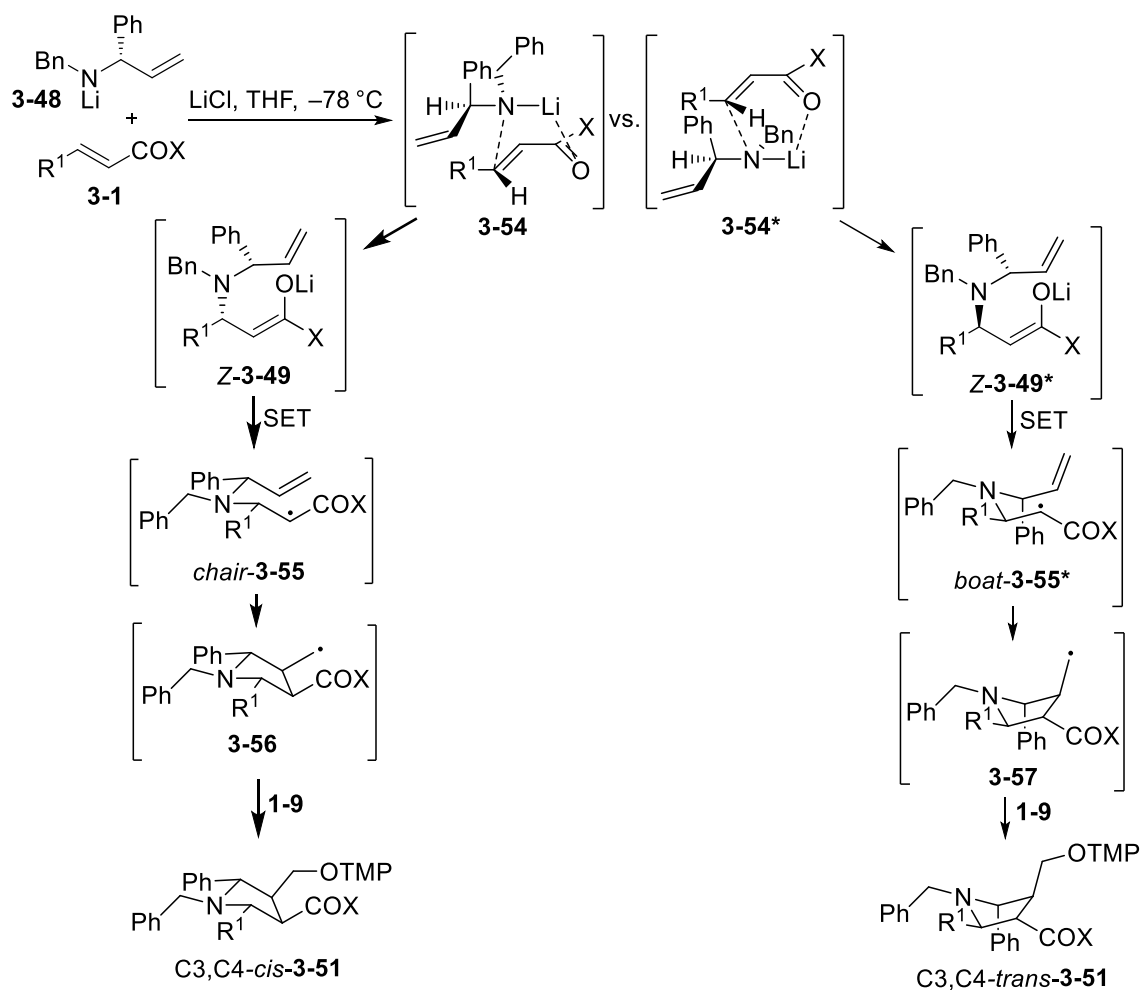


Figure 3.2.2 The observed NOE contacts in minor diastereomer of **3-51b**.

Previously reported enantioselective tandem aza-Michael addition/radical cyclization sequences using *N*-allylic *N*-(1-phenylethyl)amides and α,β -unsaturated esters provided *N*,2,3,4-tetrasubstituted pyrrolidines with exclusive C2,C3-*trans* and moderate C3,C4-*cis* diastereoselectivity, no matter whether the (*Z*)-enolate resulting from aza-Michael addition step or (*E*)-enolate generating from deprotonation of β -amino esters by LDA was used.^[22c] An explanation for the preferential formation of C3,C4-*cis* **3-51** is shown in Scheme 3.2.7. Conjugate addition of lithium amide **3-48** to α,β -unsaturated esters and amides **3-1** forms (*Z*)-enolates (*Z*)-**3-49**,^[22a,93] which after SET oxidation by **1-6** and **1-9**⁺ give α -carbonyl radicals **3-55**. According to the Beckwith-Houk transition state model *chair*-**3-55** transition state explains the formation of C3,C4-*cis* **3-51** as the major product upon 5-*exo* radical cyclization and coupling of the cyclic radical **3-56** by TEMPO. The minor diastereomer C3,C4-*trans* **3-51** comes from SET oxidation of (*Z*)-**3-49**^{*} to α -carbonyl radical **3-55**^{*}, a diastereomeric transition state to **3-55**. α -Carbonyl radical **3-55**^{*} undergoes 5-*exo* cyclization via *boat*-**3-55**^{*} transition state and radical coupling of cyclic radical **3-57** with TEMPO.



Scheme 3.2.7 Rationalization of the diastereoselectivity for the formed pyrrolidines **3-51**.

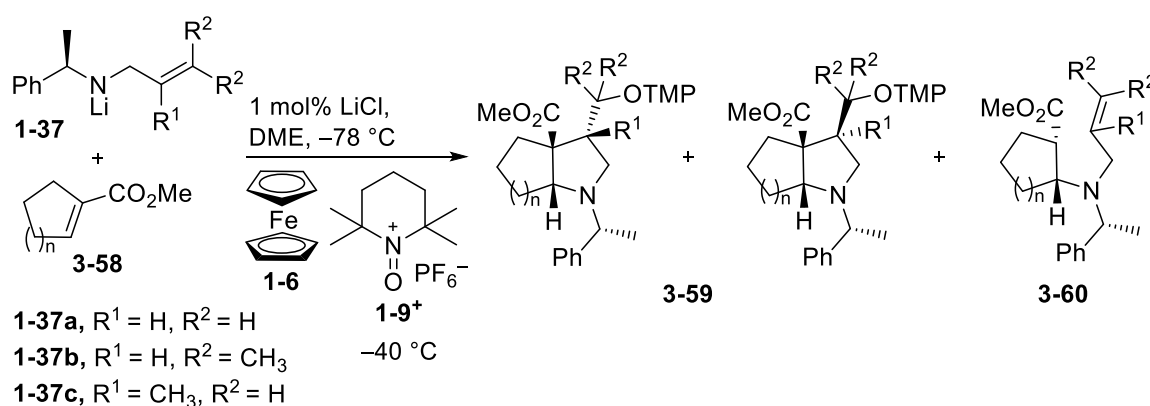
3.2.3 Traceless catalytic oxidative asymmetric tandem lithium amide conjugate addition/radical cyclization/oxygenation reactions for the synthesis of azabicyclo[n.3.0]alkane derivatives

Previously, Davies employed homochiral *N*-benzyl-*N*- α -methylbenzamides in highly stereoselective conjugate additions to *tert*-butyl cyclopent-1-enecarboxylate and *tert*-butyl cyclohex-1-enecarboxylate followed by quenching with 2,6-di-*tert*-butylphenol in order to synthesize the antifungal antibiotic (–)-(1*R*,2*S*)-cispentacin.^[100]

Chiral allylic amides **1-37** and cycloalkenecarboxylates **3-58** were efficiently employed in tandem amide conjugate addition/cyclization/oxygenation sequences mediated by **1-6** and **1-9**⁺ (Scheme 3.2.8). The tandem reaction of amide **1-37a** with ester **3-58a** was

tried in two solvents commonly used for lithium amide conjugate additions, THF and DME, and different cyclization temperatures (Table 3.2.2). Performing the tandem reaction in THF resulted in a low 34% yield (Table 3.2.2, entry 1). The best yields of **3-59a** were achieved in DME as solvent at -40°C cyclization temperature (Table 3.2.2, entry 3).

A range of azabicyclo[n.3.0]alkane derivatives **3-59** was prepared by the catalytic tandem amide conjugate addition/cyclization/oxygenation sequence promoted by **1-6** and **1-9⁺** as the major products in low to good yields with good to excellent diastereoselectivity (Table 3.2.2). The major side products were aza-Michael addition products **3-60**. Protonation of their enolates gave diastereomeric mixtures of conjugate adducts **3-60**; moderate or excellent diastereoselectivity of **3-60** was observed (Table 3.2.2, entries 1-3,6 and 4,7).



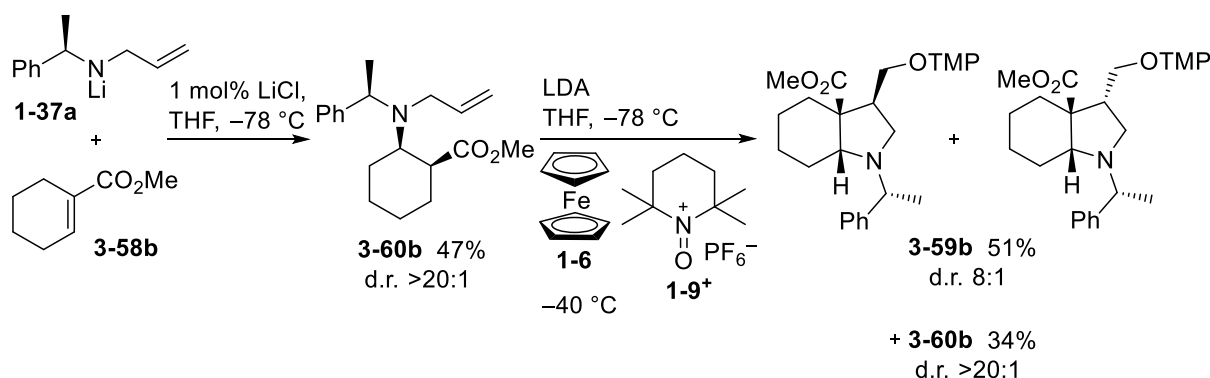
Scheme 3.2.8 Annulation reactions using cyclic α,β -unsaturated esters **3-58**.

Table 3.2.2 Results of annulation reactions of amide **1-37** with ester **3-58**.^[a]

Entry	Amide 1-37	Ester 3-58 (n)	3-59 (%)	3-59 (d.r.)	3-60 (%)	3-60 (d.r.)
1 ^[b]	a	a (1)	a (34)	6:1 ^[c]	a (19)	2.6:1
2 ^[d]	a	a (1)	a (52)	6:1 ^[c]	a (14)	3.6:1
3	a	a (1)	a (63)	6:1 ^[c]	a (17)	3.7:1
4	a	b (2)	b (24)	1:8	b (11)	1:0
5 ^[e]	a	c (3)	c (68)	1:10	-	-
6	b	a (1)	d (52)	20:1 ^[c]	d (12)	7:1
7 ^[e]	c	a (1)	e (29)	15:1 ^[c]	e (17)	1:0

[a] Standard conditions: **1-37** (0.456 mmol), LiCl (1 mol%), DME, -78°C , 30 min, **3-58** (0.351 mmol), 90 min, **1-6**, **1-9⁺**. [b] Reaction in THF. [c] Relative configuration of OTMP bearing stereocenter not assigned. [d] Cyclization at -78°C . [e] LiCl (1.5 equiv) present in the beginning.

In order to increase the yield of **3-59b**, the two-step methodology was tested (Scheme 3.2.9). β -Amino ester **3-60b** was prepared by individual aza-Michael addition in maximal 47% yield. Deprotonation/SET oxidation/oxygenation of **3-60b** mediated by **1-6** and **1-9⁺** gave azabicyclo[4.3.0]alkane **3-59b** in moderate 51% yield. The starting aza-Michael adduct **3-60b** was isolated in 34% yield. To sum up, the overall yield of **3-59b** in the two-step methodology is indeed similar to that of the tandem process.



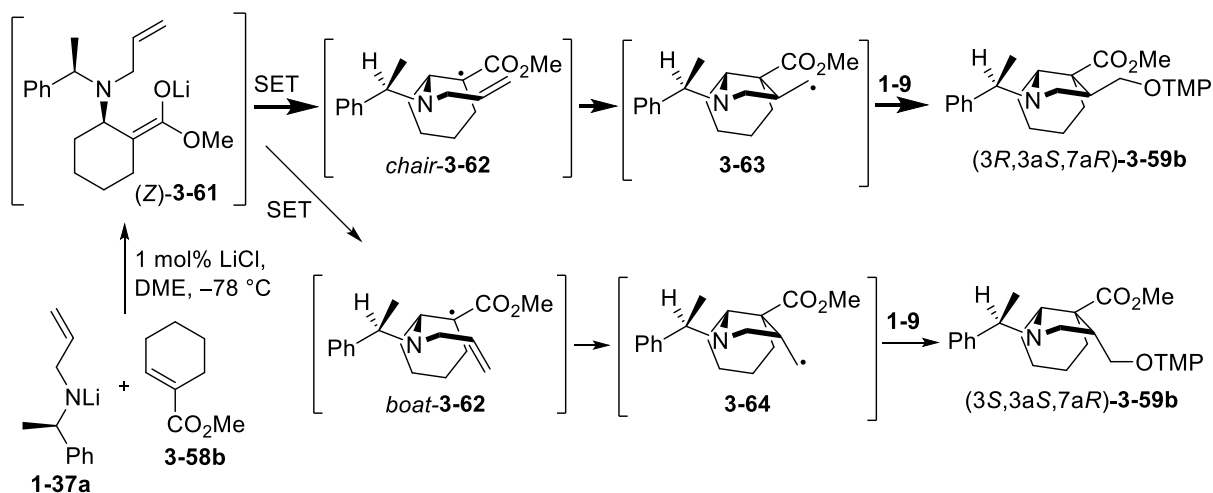
Scheme 3.2.9 Deprotonation/SET oxidation/oxygenation of **3-60b**.

The relative configuration of major bicyclic pyrrolidine **3-59b** was established by forming lactone **3-77b** as the exclusive product in the TMP deprotection reaction (p. 58, Scheme 3.2.17). The configuration of **3-59c** was assigned by analogy because of the similarity of six- and seven-membered rings.

The relative configuration of bicyclic pyrrolidines **3-59a,d,e** could so far not be reliably assigned by NOE measurements. The diastereomeric mixtures could not be crystallized, therefore, it will be necessary to obtain crystalline compounds by derivatization reactions.

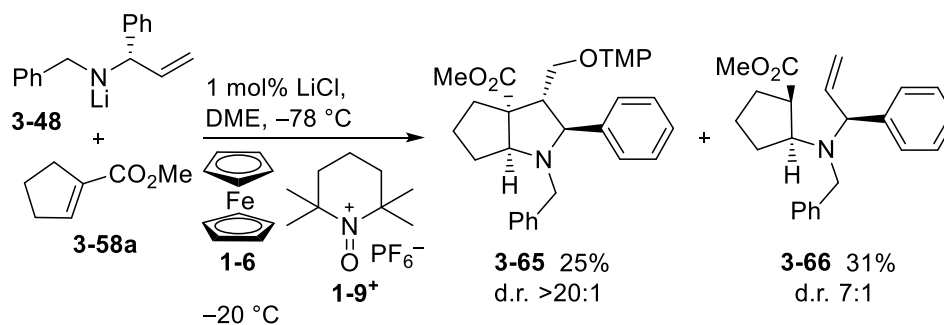
Examples in the literature support the formations of *cis*-fused rings in these radical cyclizations.^[101] 5,5- and smaller fusions proceed exclusively with *cis* selectivity.^[101a,b] The formation of 6,5-^[101c] and even 6,6-fused^[101d] rings typically proceeds with good to excellent *cis* selectivity. A proposal for the preferential formation of (3*R*,3*aS*,7*aR*)-**3-59b** is shown in Scheme 3.2.10. The aza-Michael addition generates (*Z*)-enolate (*Z*)-**3-61**.^[102] SET oxidation forms α -carbonyl radical **3-62**, which undergoes 5-*exo* radical cyclization to the terminal double bond. The cyclization proceeds through transition states **3-62**; *chair*-**3-62** is more populated and leads to cyclic radical **3-63**, which couples with TEMPO to give (3*R*,3*aS*,7*aR*)-

3-59b. The minor diastereomer (*3S,3aS,7aR*)-**3-59b** must result from a cyclization via *boat-3-62* transition state.



Scheme 3.2.10 Rationalization of the diastereoselectivity of annulation reactions of amide **1-37a** with cyclic α,β -unsaturated ester **3-58b**.

The annulation reaction of a cyclic ester **3-58a** and amide **3-48** did not give a good yield in the lithium amide conjugate addition step and bicyclic **3-65** was isolated in 25% yield (Scheme 3.2.11).



Scheme 3.2.11 Annulation attempts using ester **3-58a** and amide **3-48**.

The absolute configuration of compound **3-65** was confirmed by X-ray crystallography (Figure 3.2.3), which showed a *trans*-orientation of the H1 and H2, together with *cis*-orientation of the *tert*-butyl carboxylate at C3 and the CH₂OTMP group at the C2 atom.

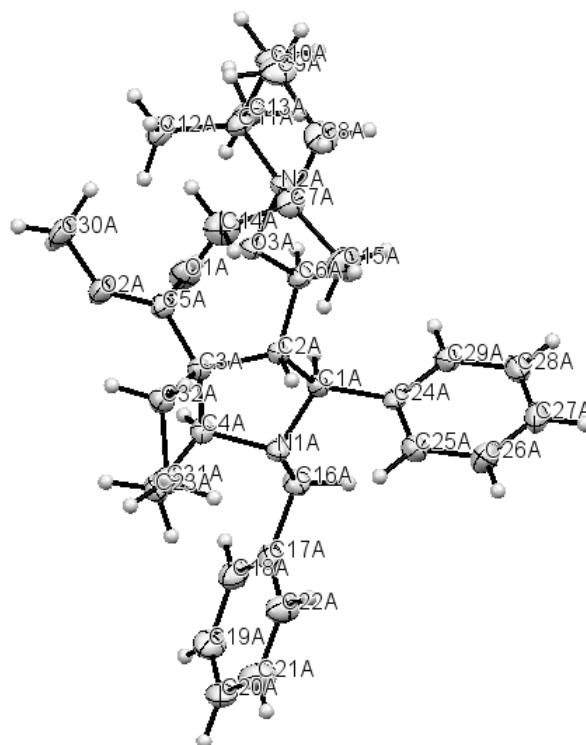
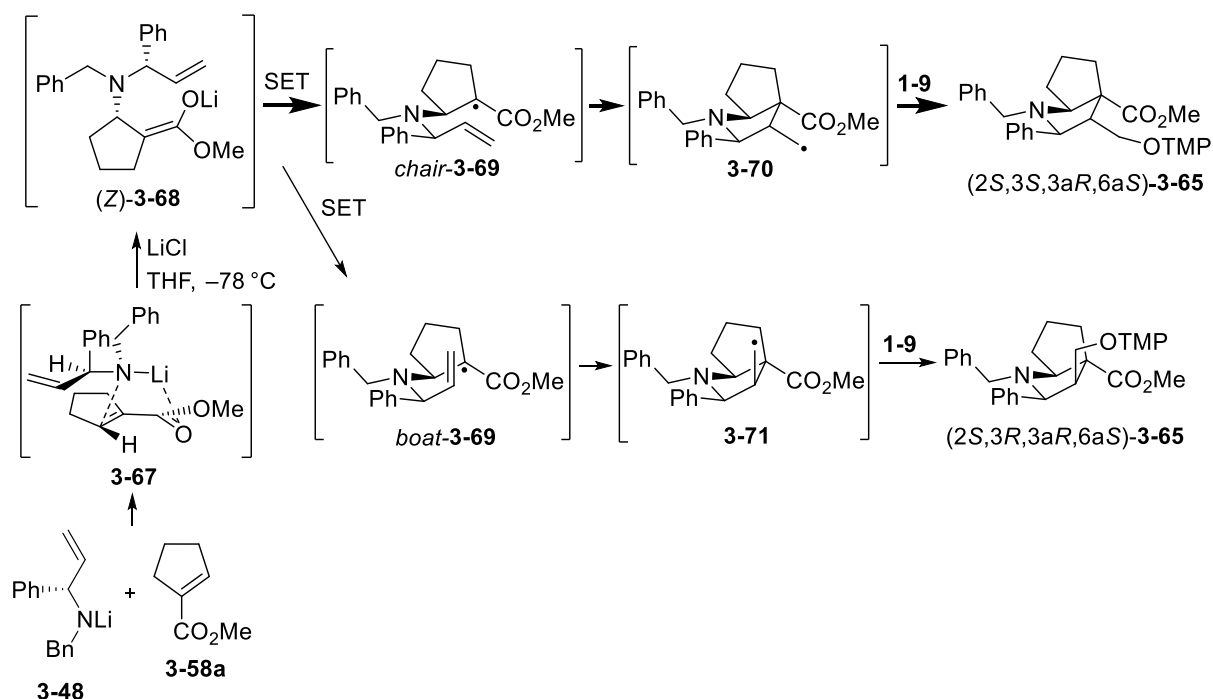


Figure 3.2.3 Structure of **3-65** in the crystal with atom numbering scheme. Displacement ellipsoids are drawn at the 30 % level.

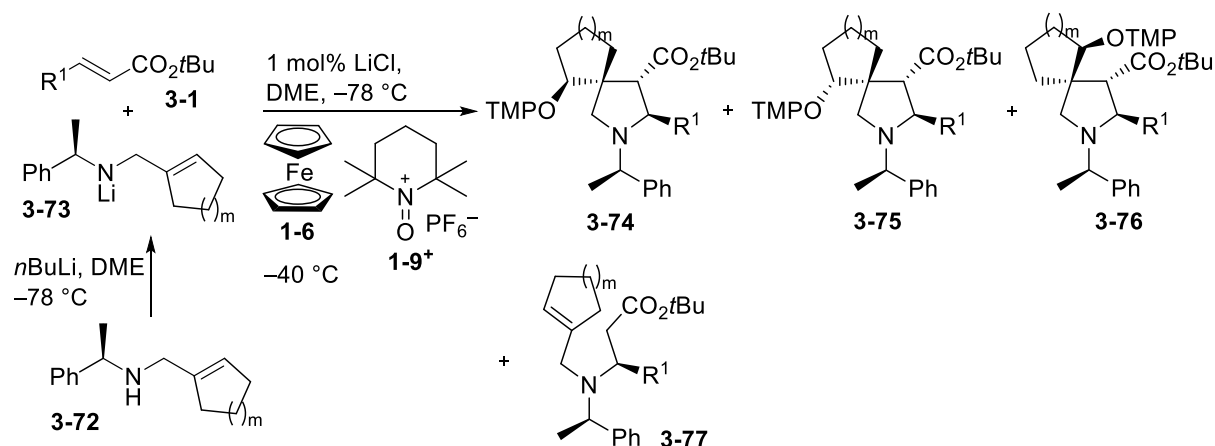
The diastereoselectivity of the radical cyclization forming azabicyclo[3.3.0]alkane **3-65** is shown in Scheme 3.2.12. (*Z*)-Enolate (*Z*)-**3-68** is formed *via* aza-Michael reaction.^[102] On SET oxidation by **1-6**⁺ α -carbonyl radical **3-69** is formed, which undergoes 5-*exo* radical cyclization. The phenyl substituent in the allylic position occupies a pseudoequatorial orientation. The 5-*exo* cyclization proceeds predominately *via* transition state *chair-3-62*, which is more populated than *boat-3-62*, and leads to cyclic radical **3-70** that couples with TEMPO to give single diastereomer of **3-65**.



Scheme 3.2.12 Rationalization of the diastereoselectivity of annulation reaction of amide **1-48** with cyclic α,β -unsaturated ester **3-58a**.

3.2.4 Traceless catalytic oxidative asymmetric tandem lithium amide conjugate addition/radical cyclization/oxygenation reactions for the synthesis of spiropyrrolidines

Chiral amines **3-72** with cycloalkenylmethyl^[103] units were efficiently prepared and employed in the synthesis of spiropyrrolidines (Scheme 3.2.13). Tandem amide conjugate addition/spirocyclizations were performed with lithium amides **3-73** and α,β -unsaturated esters **3-1** (Table 3.2.3). The tandem reaction proceeded with high conjugate addition diastereoselectivity, the cyclization diastereoselectivity **3-74+3-75:3-76** was moderate to very good, but the oxygenation diastereoselectivity **3-74:3-75** and **3-76** was for both cyclization diastereomers high, since the approach of TEMPO to the cyclic radicals is favored only from the face opposite to R^1 and the ester group.



Scheme 3.2.13 Catalytic tandem amide conjugate addition/spirocyclization/oxygenation reactions.

A range of substituted spiropyrrolidines was prepared mostly in moderate yields *via* catalytic tandem amide conjugate addition/spirocyclization/oxygenation reactions. If R¹ was an alkyl substituent (i.e. methyl, Table 3.2.3, entries 1,2), the obtained yields were lower than for aryl groups (i.e. phenyl, 2-furyl, Table 3.2.3, entries 4,5), but the observed cyclization diastereoselectivity was slightly better.

Table 3.2.3 Results of spirocyclization reactions of amides **3-73** with α,β -unsaturated esters **3-1**.^[a]

Entry	R ¹ 3-1	Amide 3-73 (m)	3-74+3-75+3-76 (%)	3-74:3-75:3-76 (d.r.)	3-77 (%)	3-77 (d.r.)
1	Me	a (1)	a (29)	4:0:1	a (28)	1:0
2 ^[b]	Me	a (1)	a (36)	4:0:1	a (41)	1:0
3	Et	a (1)	b (43)	5.7:0:1	b (17)	1:0
4	Ph	a (1)	c (55)	14:1:6	c (18)	1:0
5	2-Fur	a (1)	d (47)	6:1:2	d (17)	1:0
6 ^[b]	Me	b (2)	e (47)	8:0:1	e (25)	1:0
7	Et	b (2)	f (43)	6.7:0:1	f (17)	1:0

[a] Standard conditions: **3-72** (0.456 mmol), *n*BuLi (0.456 mmol), LiCl (1 mol%), -78 °C, DME, 30 min, **3-1** (0.351 mmol), 90 min, **1-6**, **1-9**⁺. [b] LiCl (1.5 equiv) present in the beginning.

The absolute configuration of the major diastereomer **3-74f** was confirmed by X-ray crystallography (Figure 3.2.4). The cyclohexane ring of **3-74f** has a typical chair conformation, while the cyclopentane ring adopts a half chair conformation with the substituents in C3 and C4 positions oriented *trans* to each other. The relative configuration of the major diastereomer **3-74f** was confirmed by ROESY analysis.

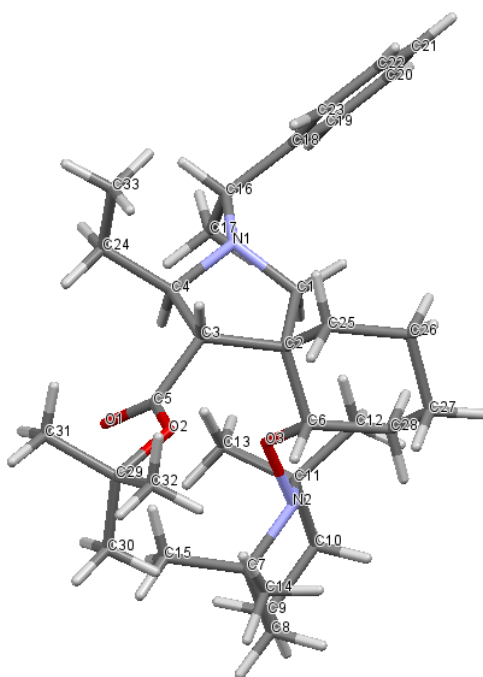


Figure 3.2.4 Structure of **3-74f** in the crystal with atom numbering scheme.

The relative configuration of major isomer **3-74a** was determined by ROESY analysis (Figure 3.2.5). The methyl group at the pyrrolidine ring showed NOE contacts to the protons at C3 and C9, thus showing that the substituents at C2 and C3 atoms are oriented *trans* to each other. The methylene protons at C5 of the pyrrolidine ring showed interactions with the protons at C6 and C9, thus strongly suggesting that CHOTMP group at C4 atom and *tert*-butoxycarbonyl at C3 occupied *cis* orientation and the approach of TEMPO must occur from the face opposite to the ester group.

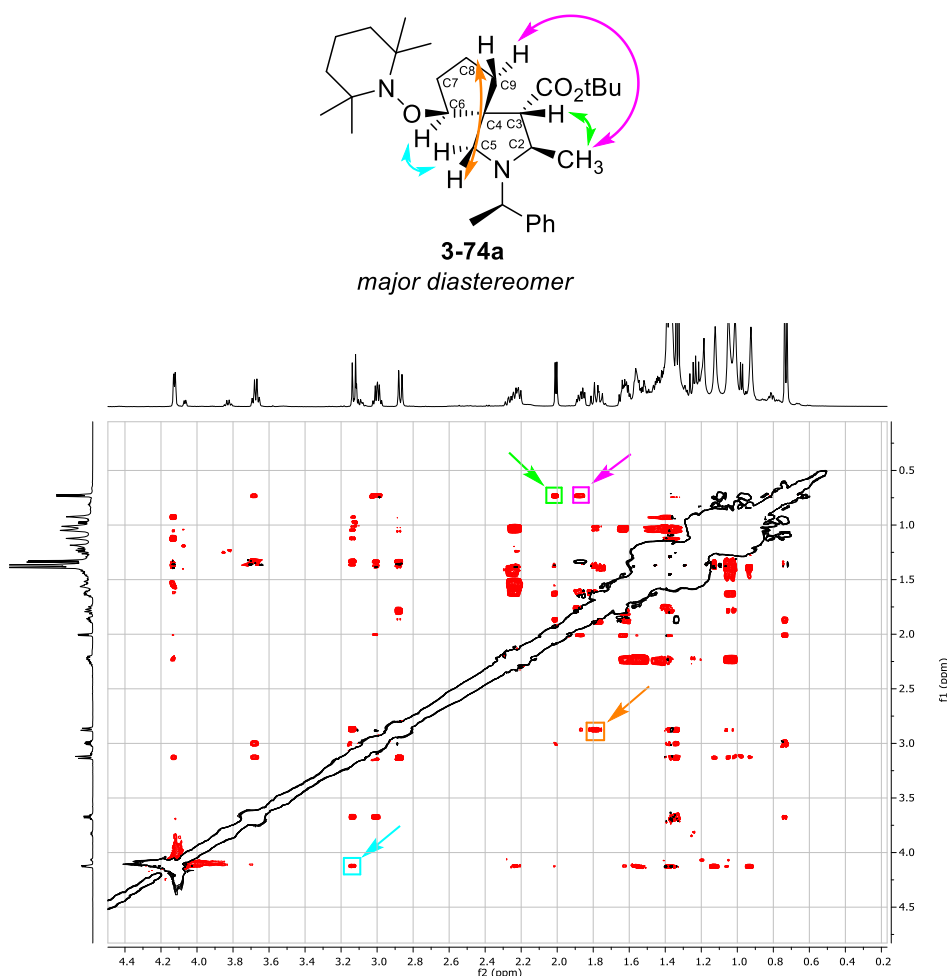


Figure 3.2.5 The observed NOE contacts in **3-74a**.

Moreover, the relative configuration of **3-74d** and **3-76d** was confirmed by ROESY analysis (Figure 3.2.6). The key NOE contact in **3-74d** is between proton at C3 (doublet at 2.55 ppm) and one methylene proton at the five-membered ring. NOE contact in **3-76d** is between proton at C3 (doublet at 3.05 ppm) and CHOTMP proton. The relative configuration of **3-74c** and **3-76c** was assigned by analogy. The relative configuration of the third diastereomer **3-75c** was assigned by the TMP deprotection/oxidation sequence that suggests its structural similarity to major diastereomer **3-74c**, but with opposite configuration at the carbon atom bearing the OTMP group (p. 60, Scheme 3.2.18). The relative configuration of **3-75d** was assigned by analogy to the **3-75c**.

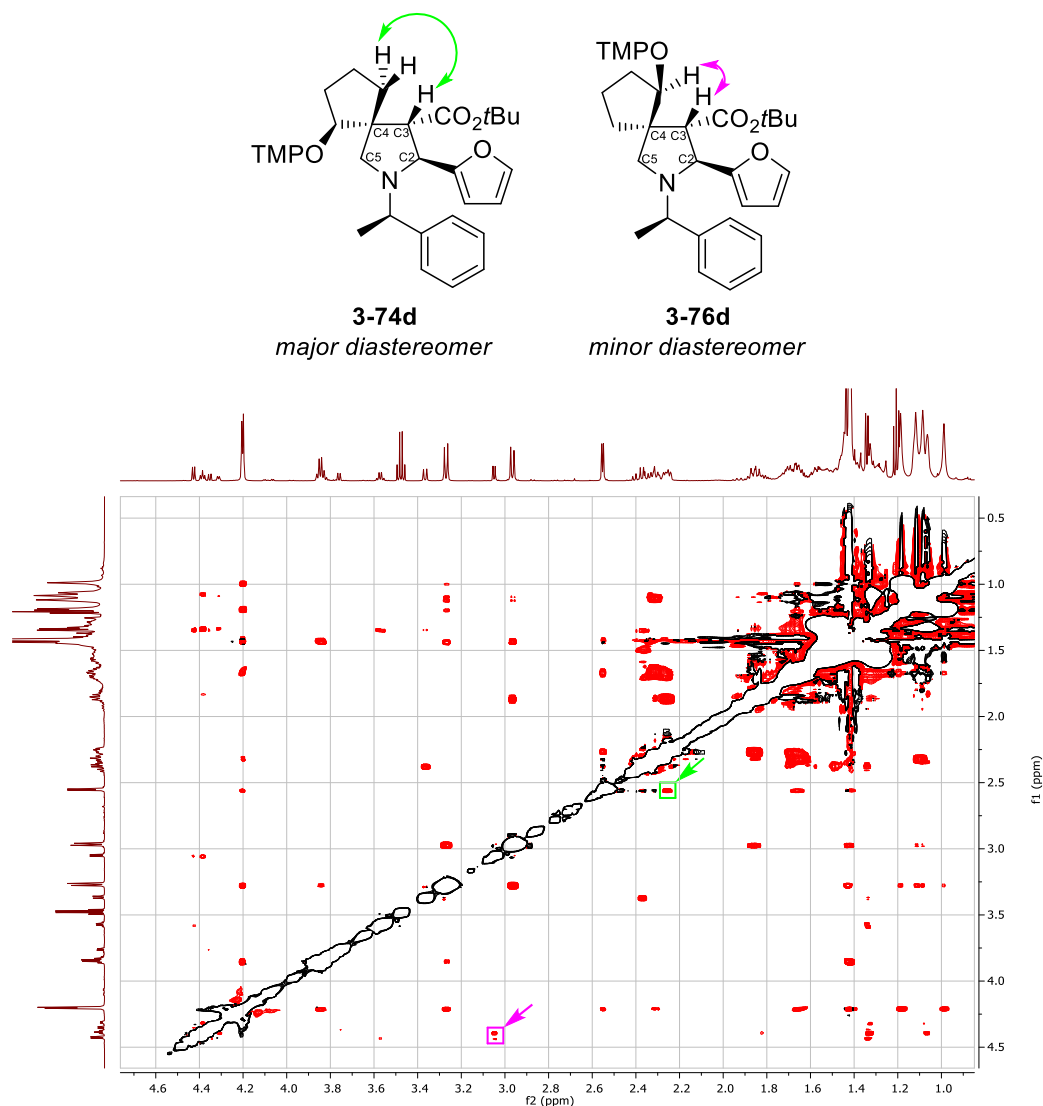
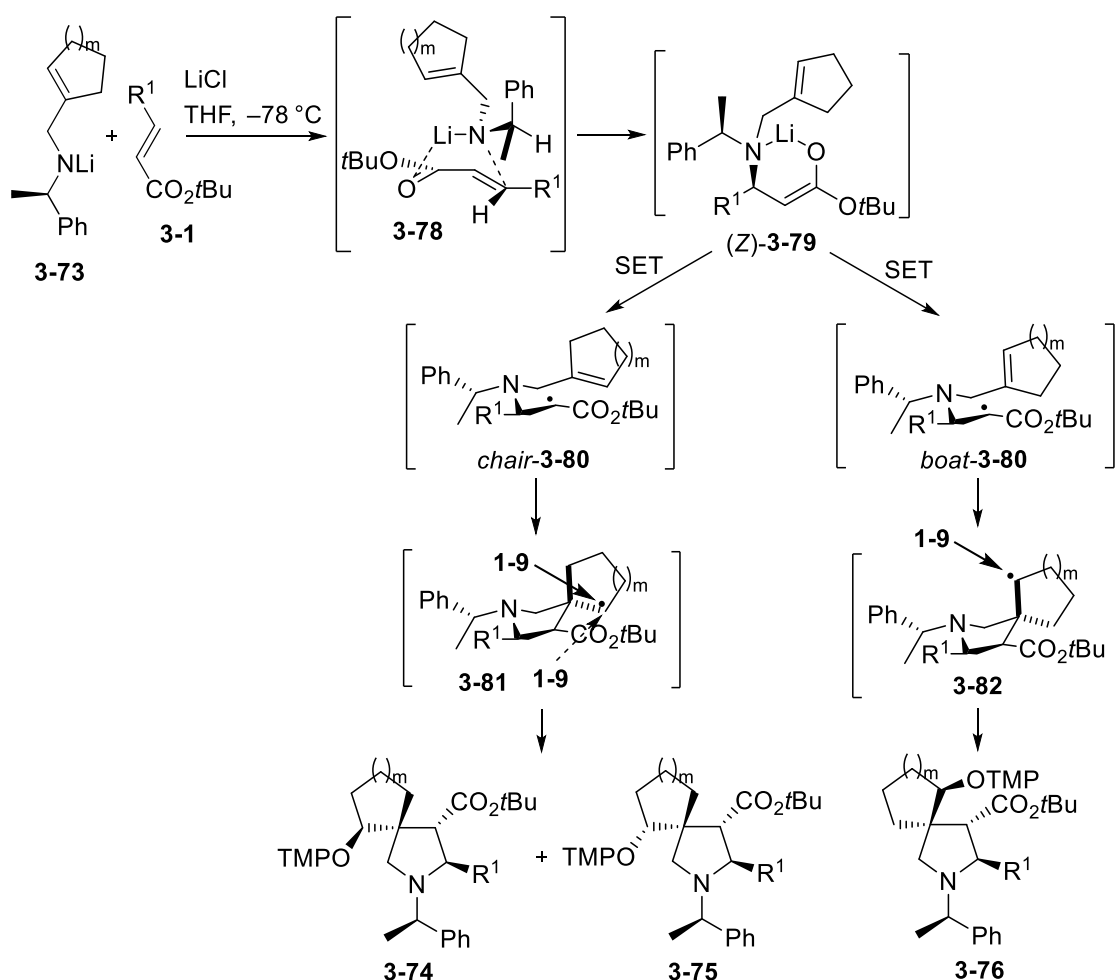


Figure 3.2.6 Observed NOE contacts in major diastereomer **3-74d** and in minor diastereomer **3-76d**.

It was previously shown in the Jahn group that the aza-Michael addition of amides **3-73** to esters **3-1** generates (*Z*)-enolate (*Z*)-**3-79**,^[103] which was subjected to diazo transfer with nonafllyl azide and intramolecular [3+2] dipolar cycloaddition leading to tricyclic pyrazolopyrrolidines.

(*Z*)-Enolate (*Z*)-**3-79** provides after SET oxidation by **1-6**⁺ α -carbonyl radical **3-80**, which undergoes efficient 5-*exo* cyclization to the cycloalkenyl ring forming secondary radicals **3-81** and **3-82** (Scheme 3.2.14). The radical cyclization must be fast, since no formation of another radical derived products was observed. The oxygen functionality is introduced in the final step by radical coupling with persistent radical TEMPO. The preference of *chair*-**3-80** transition state leads after intermolecular radical coupling of the

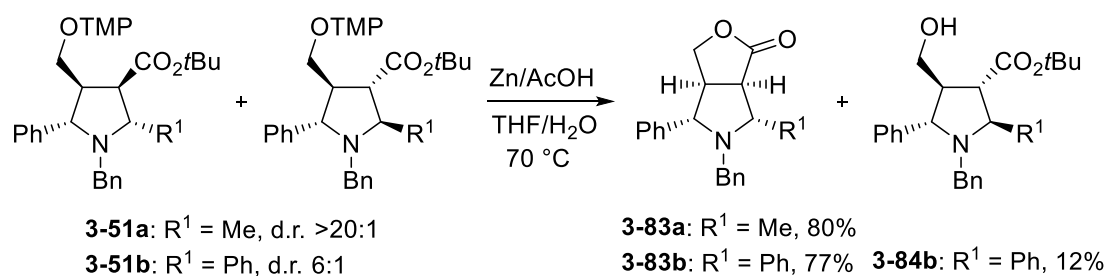
cyclic radical **3-81** with TEMPO to a mixture of spiropyrrolidines **3-74** and **3-75**. The TEMPO oxygenation of **3-81** may occur either from front or back site. However, the sterically hindered *tert*-butyl ester group enforces the attack of TEMPO from the back site leading to **3-74** as the major diastereomer. The minor diastereomer **3-76** results from a cyclization via transition state *boat-3-80* to secondary radical **3-82**, which couples selectively with TEMPO from the back site. Aza-Michael addition products **3-77** were always isolated as the major side products.



Scheme 3.2.14 Rationalization of the tandem amide conjugate addition/spirocyclization diastereoselectivity.

3.2.5 Reductive deprotection of the tetramethylpiperidiny protecting group from pyrrolidines, azabicyclo[n.3.0]alkanes and spiropyrrolidines

The deprotection of the tetramethylpiperidiny unit in pyrrolidines plays an important role for their application in total synthesis of complex natural products or as scaffolds in medicinal chemistry. It also serves as a tool for determining the configuration of the products. The N-O bond of the alkoxyamine function in pyrrolidines can be efficiently cleaved with zinc and acetic acid by heating at 70 °C.^[22a] The reductive cleavage of the N-O bond in compound C3,C4-*cis* **3-51a** gave lactone **3-83a** in very good yield (Scheme 3.2.15). Heating a diastereomeric mixture of pyrrolidines **3-51b** gave bicyclic lactone **3-83b** in 77% yield and free alcohol **3-84b** in 12% yield.



Scheme 3.2.15 Reductive deprotection of the tetramethylpiperidiny protecting group in pyrrolidines **3-51a,b**.

The absolute configuration of lactone **3-83b** was confirmed by X-ray crystallography (Figure 3.2.7). Figure 3.2.7 shows an overlapped picture of crystal structures of **3-83b**, since it contains two independent conformers.

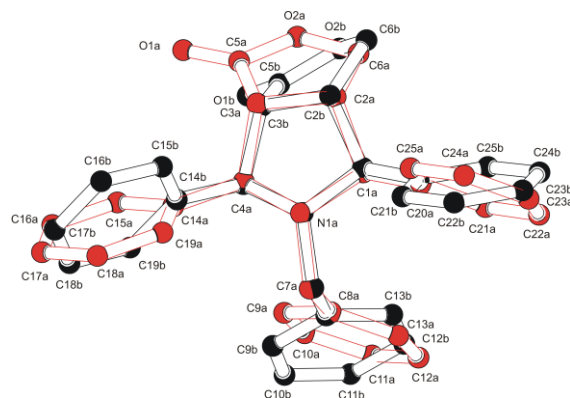
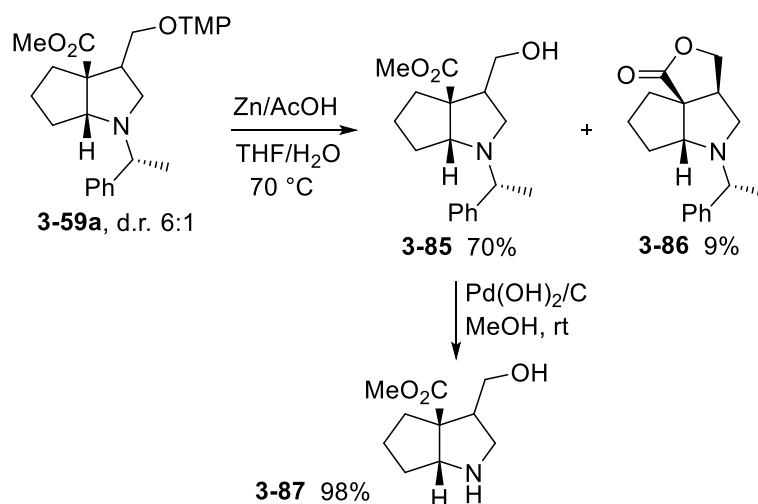


Figure 3.2.7 Image of overlapped crystal structures of **3-83b**.

Reductive deprotection of the tetramethylpiperidinyl unit in bicyclic pyrrolidine **3-59a** gave azabicyclo[3.3.0]alkane with free alcohol functionality **3-85** in good 70% yield and tricyclic lactone **3-86** (Scheme 3.2.16). Here, N-O bond cleavage serves as a tool for resolving diastereomeric mixtures. Further transformation, the hydrogenolytic debenzylation of enantio- and diastereomerically pure **3-85**, leads to cyclic β -amino ester **3-87**, an important scaffold in peptide research and drug design.^[104]



Scheme 3.2.16 Reductive alkoxyamine cleavage in azabicyclo[3.3.0]alkane **3-59a**.

The relative configuration of **3-85** was confirmed by ROESY analysis as shown in Figure 3.2.8. The key NOE contact is between the bridge proton (*CHN*) and the proton at C3. Further the bridge proton (*CHN*) shows NOE contacts between protons H _{β} at C4 and H _{β} at C2. Moreover, the H _{α} proton at C4 shows NOE contacts with methylene protons of the CH₂O group and the H _{α} proton at C2. However, NOE relative configuration establishment of **3-85** is in contrast with compounds **3-58b** and **3-65**, whose absolute configuration was confirmed by X-ray crystallography. I do not have a crystal structure of **3-85**, which will help to define the configuration at C3 stereocenter. Therefore, the configuration at C3 of **3-85** in Scheme 3.2.16 remains undefined.

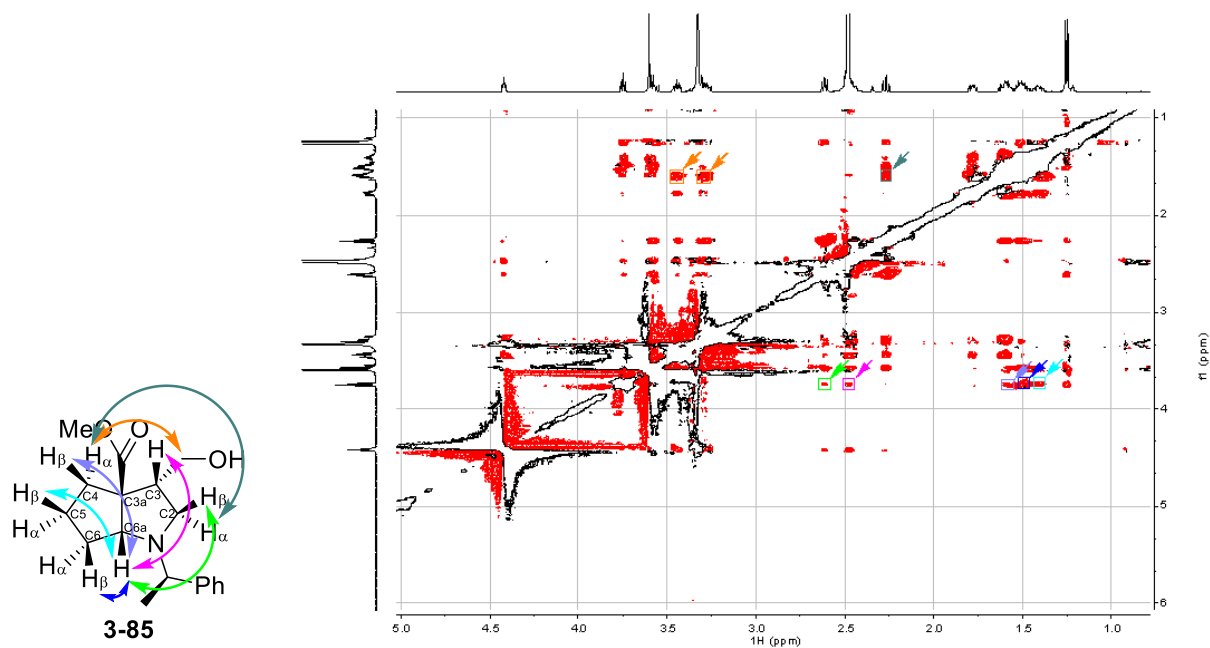
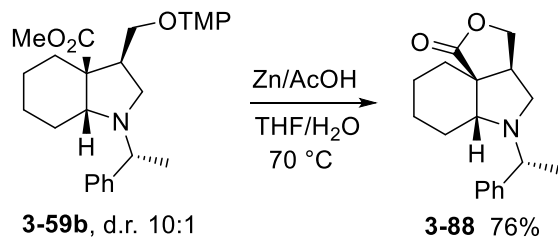


Figure 3.2.8 The observed NOE contacts in **3-85**.

Azabicyclo[4.3.0]alkane **3-59b** gave exclusively tricyclic lactone **3-88** in very good yield (Scheme 3.2.17).



Scheme 3.2.17 Deprotection of the tetramethylpiperidinyl unit from **3-59b**.

The absolute configuration of lactone **3-88** was confirmed by X-ray crystallography (Figure 3.2.9).

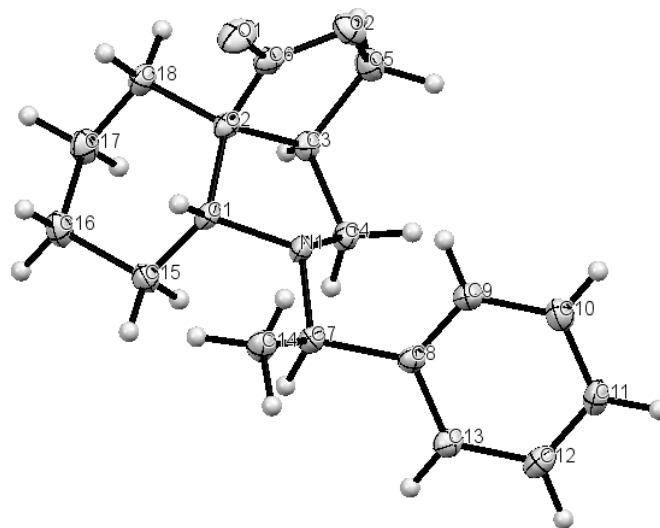
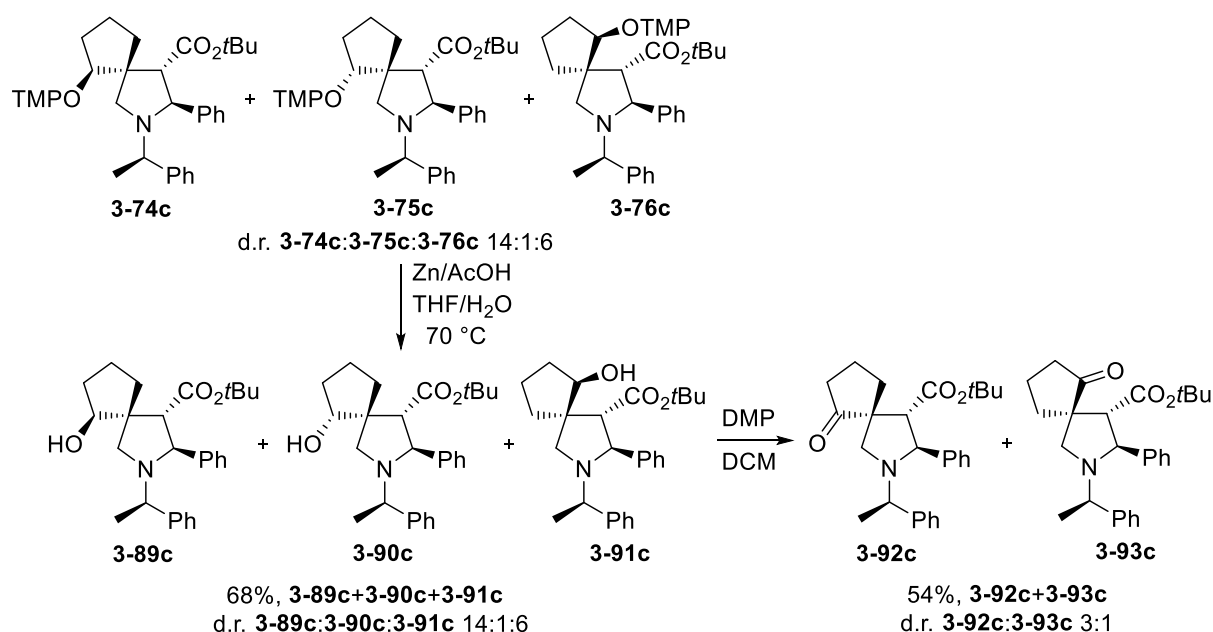


Figure 3.2.9 Structure of **3-88** in the crystal with atom numbering scheme. Displacement ellipsoids are drawn at the 30 % level.

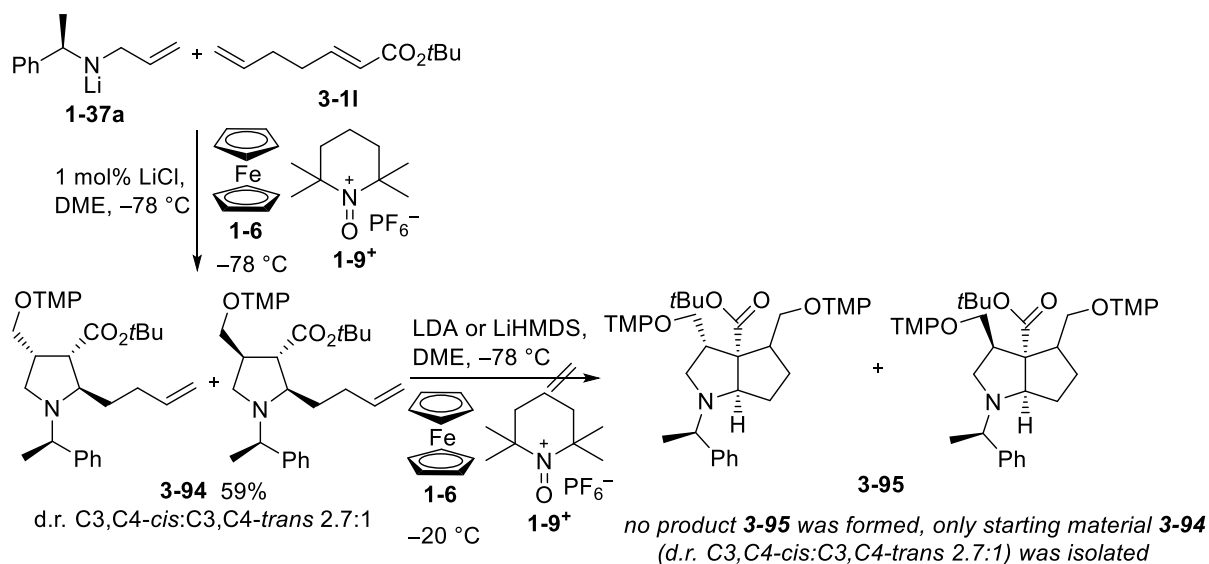
The diastereomeric mixture of spiropyrrolidines **3-74c+3-75c+3-76c** (d.r. 14:1:6) was subjected to deprotection under standard conditions giving an inseparable mixture of spiropyrrolidines **3-89c+3-90c+3-91c** with free alcohol group in a 14:1:6 diastereomeric ratio (Scheme 3.2.18). However, Dess-Martin oxidation of the alcohol mixture **3-89c+3-90c+3-91c** provided two ketones **3-92c+3-93c** as a 3:1 mixture of two diastereomers. These results indeed confirmed the observed diastereoselectivity of the tandem amide conjugate addition/spirocyclization/oxygenation reactions because oxidation of the mixture of **3-89c** and **3-90c** has to give a single diastereomer **3-92c**.



Scheme 3.2.18 TEMPO deprotection/Dess-Martin oxidation reactions for determining product configuration in mixture **3-74c**+**3-75c**+**3-76c**.

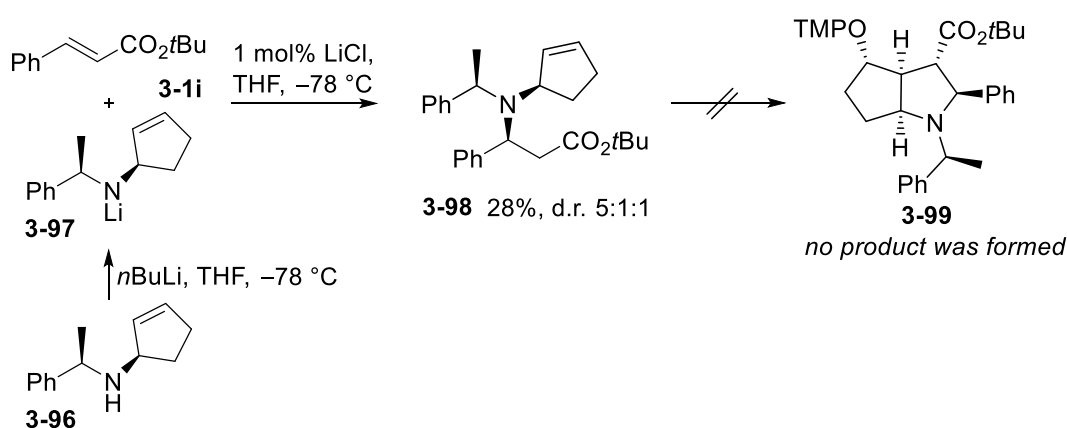
3.2.6 Further aza-Michael addition/radical cyclization attempts for the synthesis of bicyclic pyrrolidines

Double 5-*exo* radical cyclization offers a valuable tool to construct complex bicyclic pyrrolidines. Azabicyclo[3.3.0]alkanes **3-95** can be potentially prepared from pyrrolidines **3-94** by second SET oxidation/5-*exo* radical cyclization. In this regard, pyrrolidine **3-94** was prepared by aza-Michael addition of lithium amide **1-37a** to α,β -unsaturated ester **3-11**/SET oxidation/5-*exo* radical cyclization/oxygenation sequences in good 59% yield as a 2.7:1 diastereomeric mixture (Scheme 3.2.19). *N*,2,3,4-Tetrasubstituted pyrrolidine **3-94** was subsequently subjected to another deprotonation by base and 5-*exo* radical cyclization reactions. LDA or LiHMDS were used for deprotonation of pyrrolidine **3-94**. However, its deprotonation/SET oxidation/radical cyclization/oxygenation reactions did not proceed to **3-95** and only starting material **3-94** was isolated. Since no radical derived product was isolated, SET oxidation in this case did not occur probably due to insufficient deprotonation of pyrrolidines **3-94**.



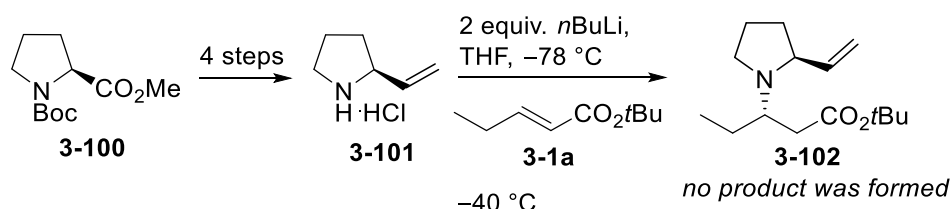
Scheme 3.2.19 Attempt for deprotonation/SET oxidation/radical cyclization/oxygenation reactions of pyrrolidine **3-94**.

N-Substituted cyclopent-2-enyl amines are potentially valuable precursors for fused azaheterocyclic compounds. Therefore, *N*-substituted cyclopent-2-enyl amine **3-96** was prepared according to the reported procedure^[90] in very good 13:1 diastereoselectivity. Its deprotonation generated amide **3-97**, which was added to *tert*-butyl cinnamate **3-1i** and the reaction resulted in formation of aza-Michael adduct **3-98** in poor 28% yield and moderate 5:1:1 diastereoselectivity (Scheme 3.2.20). Due to this poor result the cyclization to bicyclic product **3-99** was abandoned.



Scheme 3.2.20 Annulation attempt using acyclic ester **3-1i** and amide **3-97**.

Cyclic amine **3-101** with a vinyl substituent was prepared from commercially available Boc-L-proline-methyl ester **3-100** according to literature procedures.^[105] Its deprotonation by two equivalents of *n*BuLi followed by addition of ester **3-1a** did not lead to product formation **3-102** (Scheme 3.2.21). This result may be explained by too hygroscopic material **3-101** and insufficient deprotonation.



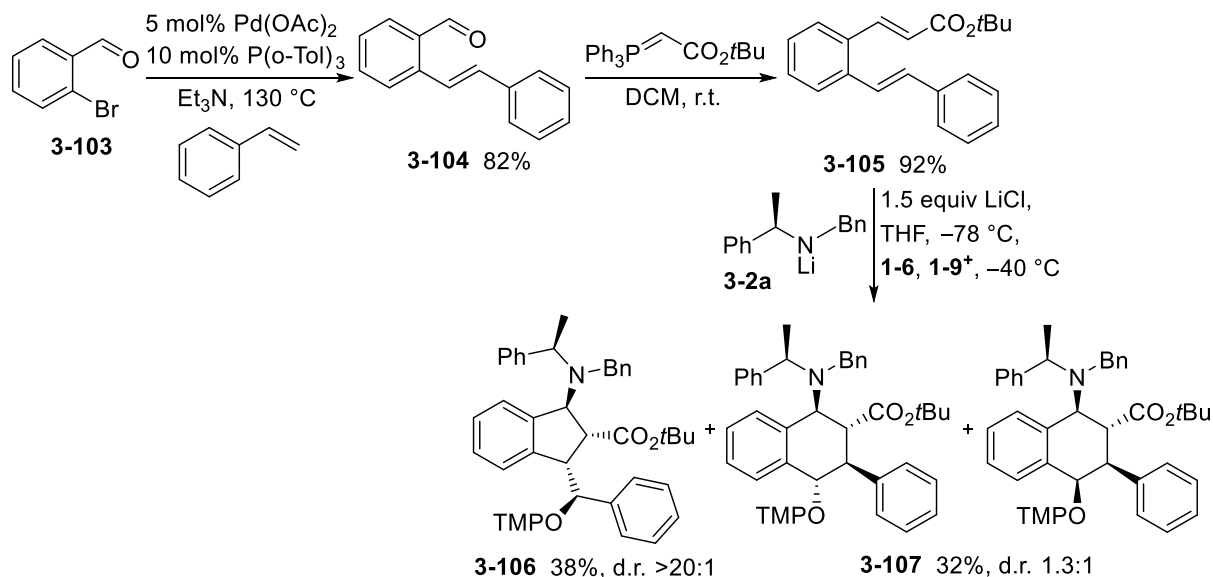
Scheme 3.2.21 Attempt of applying cyclic amine **3-101** in aza-Michael reaction.

3.2.7 Use of aza-Michael addition/5-*exo* radical cyclization/oxygenation reactions for the synthesis of 1,2,3-trisubstituted indanes

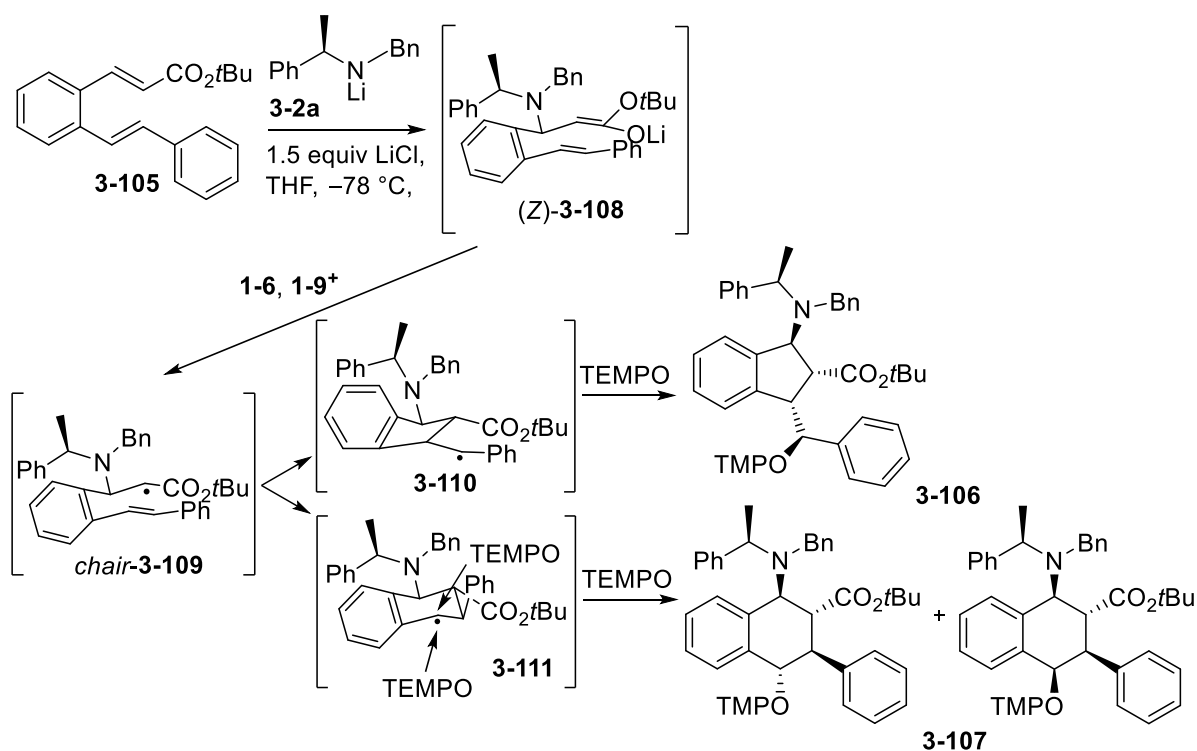
Indanes have found widespread application as key structural units in medicinal chemistry; many natural and synthetic compounds with this skeleton have shown significant biological activities.^[106] Therefore, a new asymmetric synthesis of functionalized indanes based on tandem aza-Michael/SET oxidation/5-*exo* radical cyclization/oxygenation sequences has been developed (Scheme 3.2.22). The key ester **3-105** was prepared over two steps from commercially available 2-bromobenzaldehyde **3-103**. Palladium-catalyzed Heck cross-coupling reaction of **3-103** with styrene gave **3-104**, which subsequently reacted with (*tert*-butoxycarbonylmethylene)triphenylphosphorane in a Wittig reaction to form α,β -unsaturated ester **3-105**. Asymmetric conjugate addition of amide **3-2a** to ester **3-105** followed by SET oxidation/5-*exo* radical cyclization/oxygenation reactions gave the product of 5-*exo* cyclization, 1,2,3-trisubstituted indane **3-106** in 38% yield as a single diastereomer and the product of 6-*endo* cyclization **3-107** in 32% yield as a mixture of two diastereomers in a 1.3:1 ratio.

The diastereoselectivity of products **3-106** and **3-107** can be rationalized as shown in Scheme 3.2.23. The aza-Michael addition generates (*Z*)-enolate (*Z*)-**3-108**,^[93] which after SET oxidation results in α -carbonyl radical *chair*-**3-109**. Two possible cyclization modes operate;

the 5-*exo* cyclization leads to cyclic radical **3-110**, which upon TEMPO oxygenation from the least hindered side gives product **3-106** as a single diastereomer. However, 6-*endo* cyclization results in cyclic radical **3-111**, which is unselectively oxygenated by TEMPO from both faces and thus leading to product **3-107** with a 1.3:1 diastereomeric ratio.



Scheme 3.2.22 The synthesis of 1,2,3-trisubstituted indane **3-106** and 1,2,3,4-tetrahydronaphthalene **3-107** via tandem aza-Michael addition of amide **3-2a** to ester **3-105**/SET oxidation/5-*exo* radical cyclization/oxygenation with TEMPO.



Scheme 3.2.23 Rationalization of the diastereoselectivity in products **3-106** and **3-107**.

The absolute configuration of compound **3-106** was confirmed by X-ray crystallography (Figure 3.2.10). The crystallographic analysis was crucial for determining the absolute configuration at C7, since this stereocentre cannot be assigned using ^1H -NMR NOE techniques.

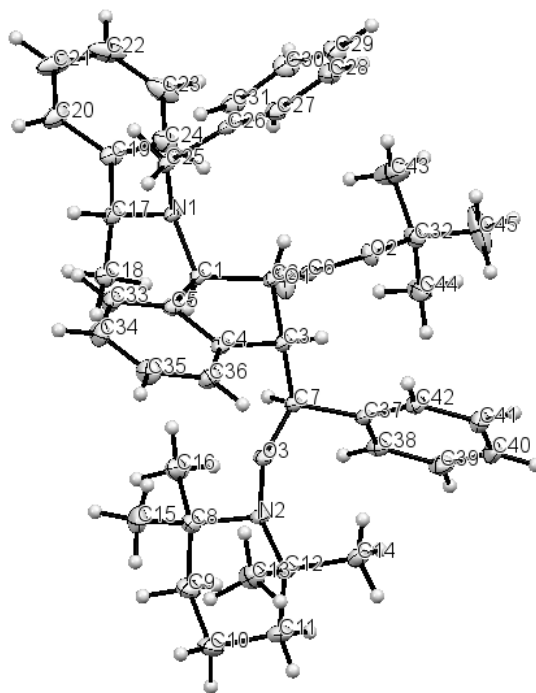
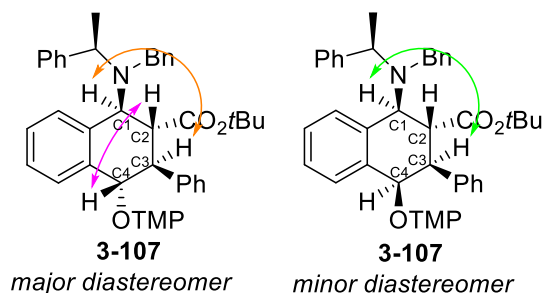


Figure 3.2.10 Structure of **3-106** in the crystal with atom numbering scheme. Displacement ellipsoids are drawn at the 30% level.

NOE analysis of the 1.3:1 diastereomeric mixture **3-107** revealed that the absolute configuration of major and minor diastereomers differs at C4 (Figure 3.2.11). Indeed, strong NOE contacts in major diastereomer **3-107** can be observed between protons at carbons C1-C3 and C2-C4. In the minor diastereomer an NOE contact can be observed between protons at carbons C1 and C3.



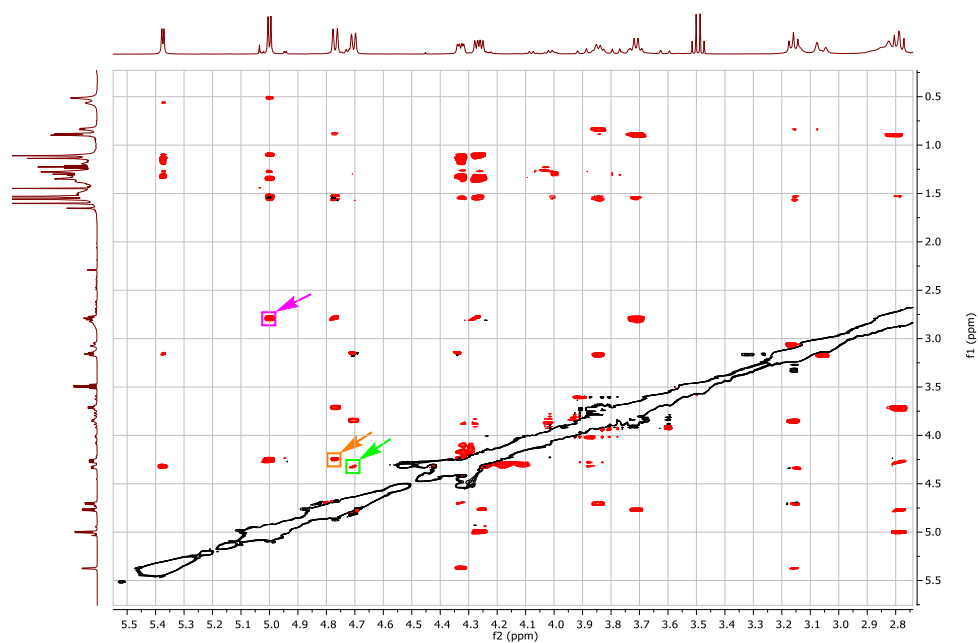
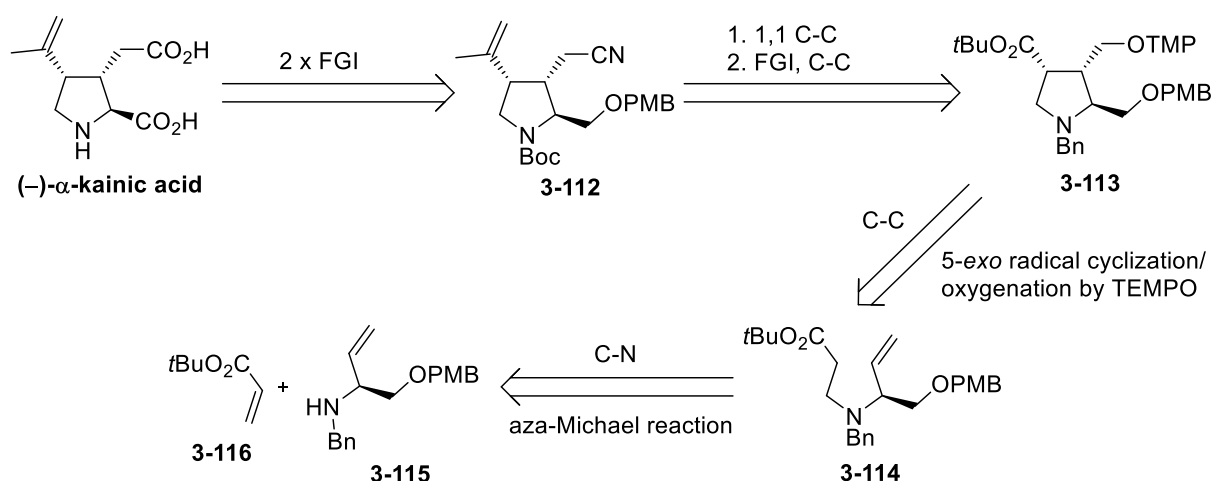


Figure 3.2.11 Observed NOE contacts in major and minor diastereomers **3-107**.

3.3 Enantioselective total synthesis of (–)- α -kainic acid by merging polar aza-Michael reaction and 5-*exo* radical cyclization/oxygenation reactions

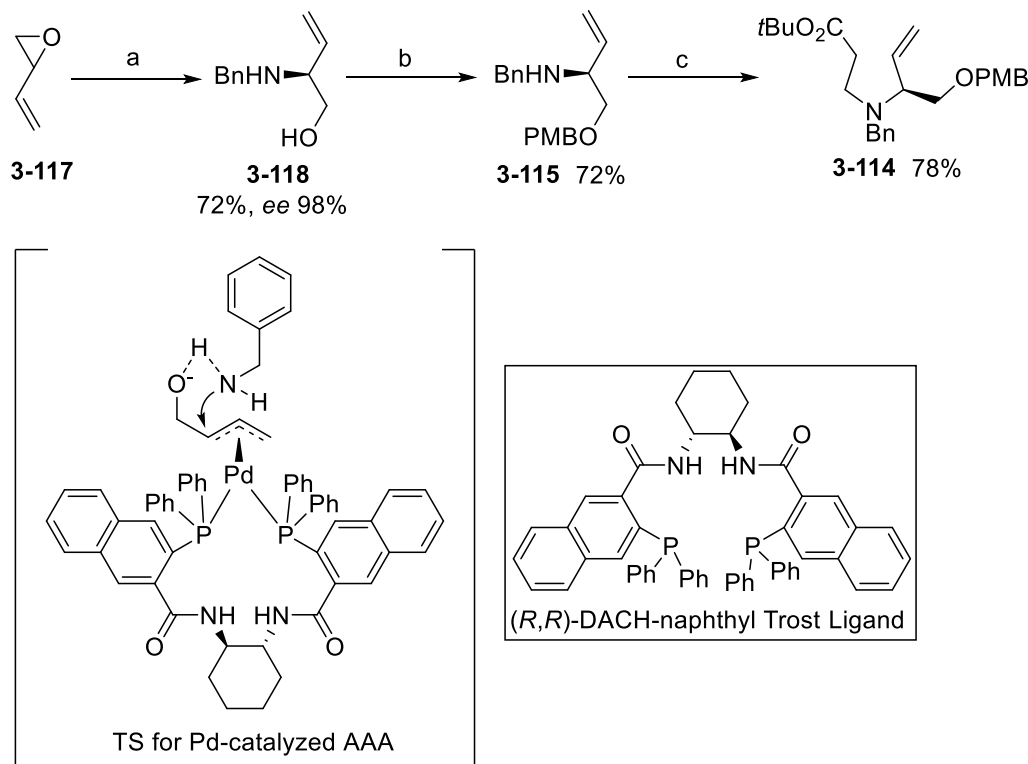
This chapter deals with application of SET-catalyzed 5-*exo* radical cyclization/oxygenation reactions as the key step in a total synthesis of the valuable pyrrolidine target (–)- α -kainic acid.^[58] In terms of synthetic strategy, it is envisioned that the total synthesis of (–)- α -kainic acid could be easily achieved from advanced intermediate **3-112** in four-step transformation (Scheme 3.3.1). The C4 isopropylidene unit of the late-stage intermediate **3-112** would arise from *tert*-butoxycarbonyl group in **3-113** and the cyano group at C3 in **3-112** would be obtained from alkoxyamine by deprotection/Mitsunobu reactions. Pyrrolidine **3-113** with all stereogenic centers comprising that of (–)- α -kainic acid is envisaged to be obtained by oxidative cyclization of chiral β -amino ester **3-114**. The cyclization precursor **3-114** would arise from chiral amine **3-115** and acrylate **3-116** by aza-Michael reaction.



Scheme 3.3.1 Retrosynthetic analysis of (–)- α -kainic acid.

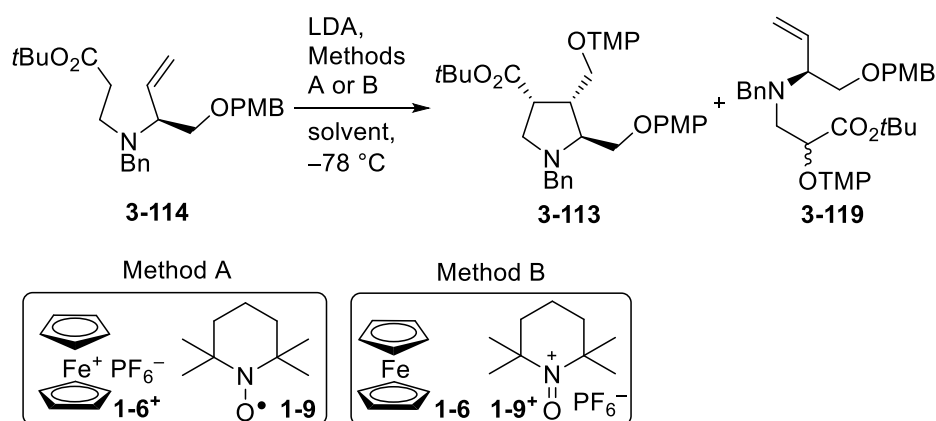
The synthesis of chiral β -alaninate **3-114** started with amination of butadiene monoepoxide **3-117** by a palladium catalyzed DYKAT AAA using C2-symmetric phosphine ligands as developed by Trost and co-workers (Scheme 3.3.2).^[107] It was found that optimal reaction conditions required an excess of benzylamine, minimally 1.5 equivalents, which was added slowly to a solution of catalyst, ligand and butadiene monoepoxide in dichloromethane. The benzyl derivative of vinylglycinol **3-118** was obtained in good yield with 98% *ee*, which was determined by chiral HPLC. The free alcohol function in **3-118** was protected as the *p*-methoxybenzyl ether **3-115** in good 72% yield. The highest yield of **3-115** was obtained

after 25 h and adding *p*-methoxybenzyl bromide slowly into the reaction mixture. The aza-Michael addition of **3-115** to acrylate **3-116** gave product **3-114** in very good 78% yield after heating in methanol.



Scheme 3.3.2 Synthesis of the chiral β -alaninate **3-114**. a) Benzylamine, $[\text{PdCl}(\text{allyl})]_2$ (0.4 mol%), (*R,R*)-DACH-naphthyl Trost ligand (1.2 mol%), DCM, r.t., 24 h; b) PMBBBr, NaH, THF, 0 °C to r.t., 25 h; c) *tert*-Butyl acrylate **3-116**, MeOH, 60 °C, 8 days.

Amino ester **3-114** was deprotonated by LDA at -78 °C followed by SET oxidation/*5-exo* radical cyclization under stoichiometric (Method A) or catalytic conditions (Method B) (Scheme 3.3.3). The reaction in THF provided product **3-113** in poor 32% yield; the same conditions in DME gave only 18% of **3-87** (Table 3.3.1, entry 1 and 2). The best reaction conditions proved to be catalytic **1-6/1-9⁺**, 1.5 equivalents of anhydrous lithium chloride and THF as the solvent (Table 3.3.1, entry 3). The desired cyclized product (*2S,3S,4R*)-**3-113** was isolated in 55% yield and excellent diastereoselectivity (d.r. >20:1) as the major product. The acyclic product of premature TEMPO radical coupling **3-119** was isolated in 40% yield with 1.1:1 diastereomeric ratio.



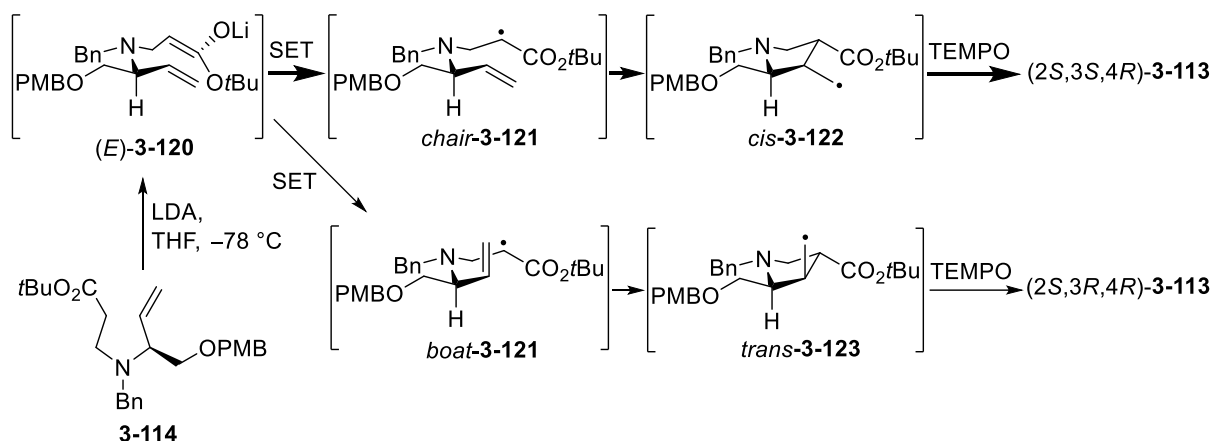
Scheme 3.3.3 Deprotonation/SET oxidation/5-*exo* radical cyclization/oxygenation reactions of **3-114**.

Table 3.3.1 Optimization of 5-*exo* radical cyclization/oxygenation reactions of **3-114**.^[a]

Entry	Solvent	Method	3-113 (%)	3-113 (d.r.)	3-119 (%)	3-119 (d.r.)
1	THF	A	32	>20:1	41	1.1:1
2	DME	A	18	>20:1	33	1.1:1
3 ^[b]	THF	B	55	>20:1	40	1.1:1

[a] Standard conditions: LDA (0.580 mmol), THF, -78°C , 30 min, then **3-114** (0.446 mmol), 90 min, **1-6/1-9⁺** or **1-6⁺/1-9**, -78°C ; [b] Anhydrous LiCl (1.5 equiv) added prior to **3-114** deprotonation.

The preferential formation of the C3,C4 *cis*-isomer (2*S*,3*S*,4*R*)-**3-113** can be rationalized as shown in Scheme 3.3.4. β -Amino ester **3-114** forms (*E*)-enolate (*E*)-**3-120** upon deprotonation with LDA.^[22c] The *p*-methoxybenzyl substituent in the allylic position is in pseudoequatorial orientation. On SET oxidation by **1-6⁺** α -ester radical **3-121** results. The radical cyclization proceeds *via* Beckwith-Houk transition state **3-121**; *chair*-**3-121** is more populated and leads to cyclic radical *cis*-**3-122**, which couples with TEMPO to give (2*S*,3*S*,4*R*)-**3-113**. The minor diastereomer (2*S*,3*R*,4*R*)-**3-113** must result from a cyclization *via boat*-**3-121**.

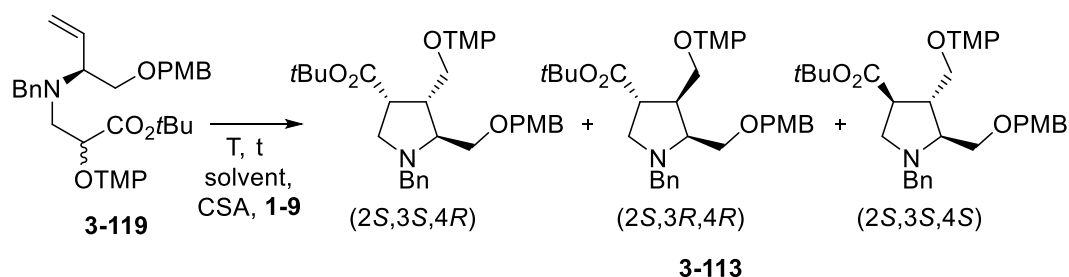


Scheme 3.3.4 Rationalization of the C3,C4-*cis/trans* diastereoselectivity at the pyrrolidine ring.

Acyclic TEMPO adduct **3-119** can undergo a 5-*exo* radical cyclization upon heating by using the PRE (*cf.* Scheme 1.8).^[27c] Upon heating at 150 °C, the C-OTMP bond in **3-119** homolyzes forming transient radical **3-121** and persistent radical **1-9**. Intermediate **3-121** undergoes 5-*exo* cyclization forming cyclic radicals **3-122** or **3-123** (Scheme 3.3.4). Subsequent radical trapping by **1-9** leads to pyrrolidines **3-113**. Thermal cyclizations of **3-119** were efficiently conducted in a microwave reactor, which enables heating the reaction mixture above the solvent boiling point (Scheme 3.3.5). Additives play an important role in the PRE cyclizations.^[108] TEMPO-mediated alkoxyamine isomerizations are accelerated upon addition of CSA, thus a trace amount of (+)-camphor-10-sulfonic acid (CSA) has successfully been used in that regard (Table 3.3.2, entry 1).

To suppress the formation of byproducts, the reaction mixture was degassed and a trace of **1-9** was added prior to heating in *tert*-butanol. Under these conditions, the cyclized product **3-113** was isolated in good 72% yield (Table 3.3.2, entry 1). The cyclization carried out in trifluorotoluene as a solvent gave **3-113** in less satisfactory 58% yield (Table 3.3.2, entry 2).

The diastereoselectivity of the PRE cyclisation was much lower than that of the SET-induced oxidative cyclizations. For convenience the ratio of desired (2*S*,3*S*,4*R*)-**3-113** to the sum of the undesired C3,C4-*trans* diastereomers was determined and it remained fairly constant at 2:1 through all experiments (Table 3.3.2, entries 1,2).



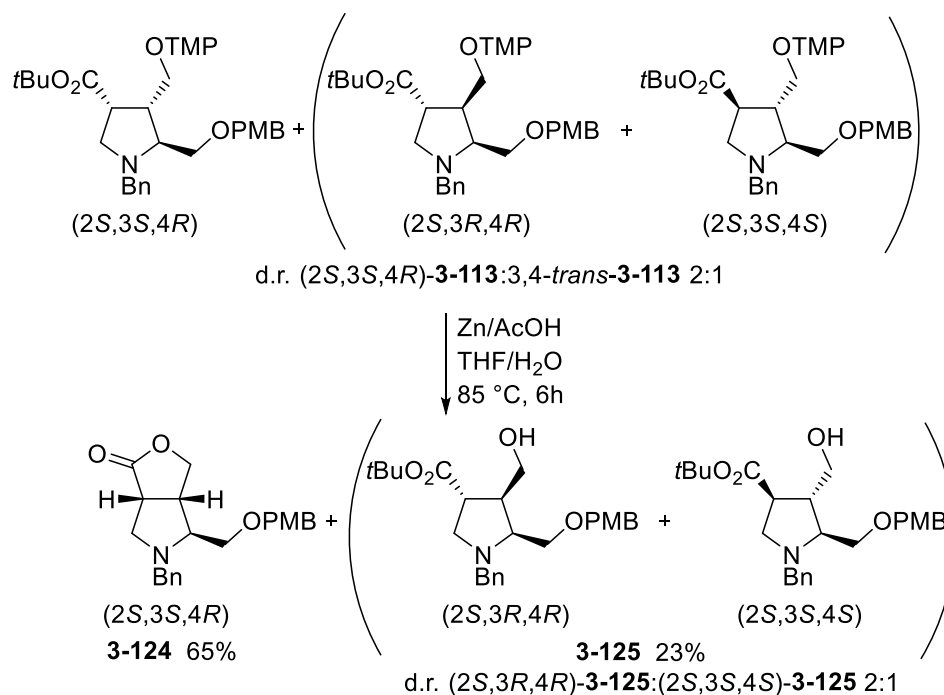
Scheme 3.3.5 PRE cyclizations of TEMPO adducts **3-119** under thermal conditions.

Table 3.3.2 Optimization of PRE cyclizations of **3-119**.

Entry	Solvent	3-119 (mol/l)	Temp. (°C)	Time (min)	3-113 (%)	(2 <i>S</i> ,3 <i>S</i> ,4 <i>R</i>)- 3-113 : 3,4- <i>trans</i> ^[a] - 3-113
1	<i>t</i> BuOH	0.073	150	60	72	2:1
2 ^[b]	C ₆ H ₅ CF ₃	0.073	150	60	58	2:1

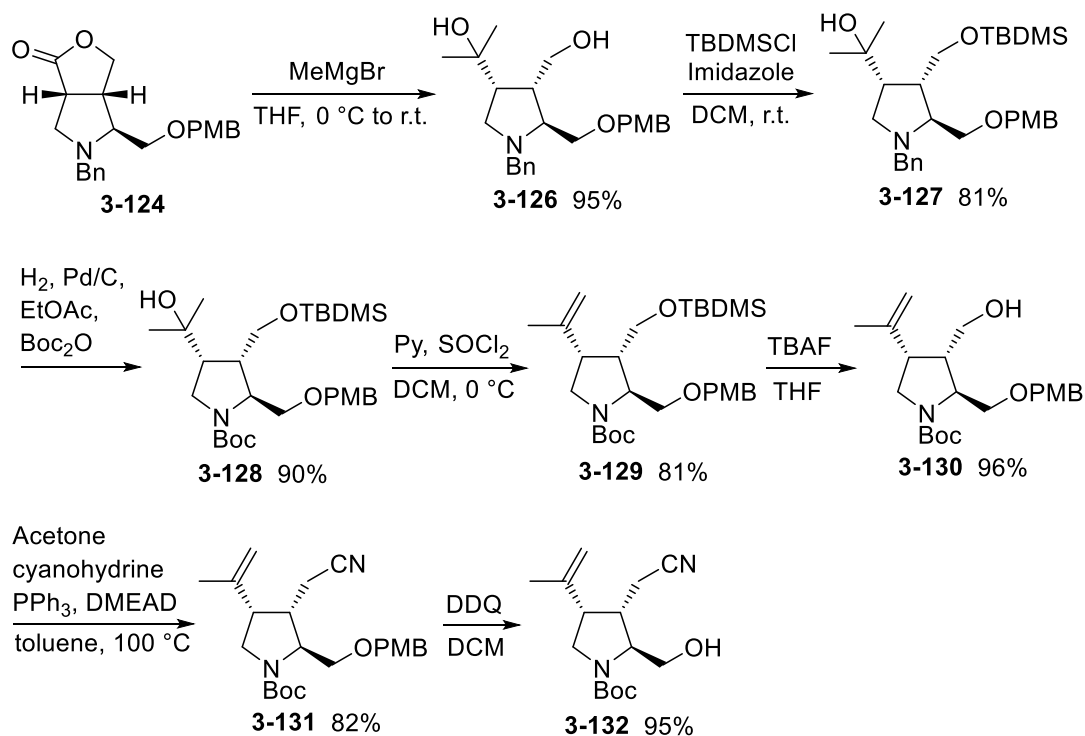
[a] The combined amount of (2*S*,3*R*,4*R*)-**3-87** and (2*S*,3*S*,4*S*)-**3-87**. [b] No CSA was added.

With pyrrolidine **3-113** at hand, the completion of the total synthesis of (–)-kainic acid was straightforward. Reductive removal of the tetramethylpiperidiny group from the C3,C4-*cis* pyrrolidine **3-113** (d.r. >20:1) under the standard zinc powder/acetic acid conditions gave the desired lactone **3-124** in good 61% yield.^[90] The reductive deprotection of the PRE-cyclized mixture of pyrrolidines **3-113** (d.r. C3,C4-*cis*:C3,C4-*trans* 2:1) gave lactone **3-124** as the major product in good 65% yield and a mixture of pyrrolidines with free alcohol group **3-125** (Scheme 3.3.6). Here, the deprotection of the TMP group served as a tool for resolving diastereomeric mixtures.



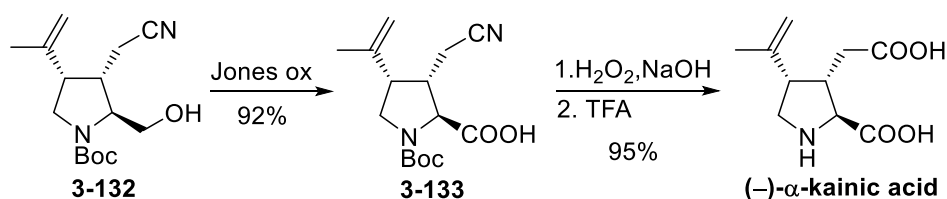
Scheme 3.3.6 Reductive removal of the tetramethylpiperidinyl group from **3-113**.

Tertiary alcohol **3-126** was successfully synthesized by addition of methylmagnesium bromide to lactone **3-124** (Scheme 3.3.7). Due to the fact that two free hydroxy groups in **3-126** may cause difficulties in the next steps, the primary alcohol was protected with TBDMSCl as silyl ether **3-127** in very good 81% yield. Monosilylated product **3-127** was subjected to one-pot hydrogenolysis with palladium on charcoal in ethyl acetate and subsequent Boc protection furnishing **3-128** in 90% yield. Dehydration of the tertiary alcohol in **3-128** with SOCl_2 and pyridine in dichloromethane at $0\text{ }^\circ\text{C}$ provided the desired (propen-2-yl)pyrrolidine **3-129** in very good 81% yield. Compound **3-129** was subjected to TBDMS group deprotection using tetrabutylammonium fluoride (TBAF). Subsequently the formed primary alcohol **3-130** was subjected to a Mitsunobu reaction affording nitrile **3-131** in very good 82% yield.^[109] Finally, deprotection of the nitrile **3-131** with DDQ gave the desired 2-hydroxymethyl pyrrolidine **3-132** in almost quantitative yield.



Scheme 3.3.7 Synthesis of the advanced intermediate **3-132** from pyrrololactone **3-124**.

Primary alcohol **3-132** was subjected to Jones oxidation and carboxylic acid **3-133** was isolated in excellent 92% yield (Scheme 3.3.8). Hydrolysis of the nitrile in **3-133** with H_2O_2 and NaOH by heating at $90\text{ }^\circ\text{C}$ gave the Boc-protected dicarboxylic acid. Finally, removal of the Boc group with TFA afforded (–)- α -kainic acid in 95% yield over two steps. Thus, the total synthesis of (–)- α -kainic acid was accomplished in 15 steps in overall 5% yield. The optical rotation of (–)- α -kainic acid did not match the value from literature possibly because of impurities for which a further purification system has to be established.



Scheme 3.3.8 Completion of the total synthesis of (–)- α -kainic acid.

4. Experimental part

General: All reactions were performed in flame-dried glassware under an argon atmosphere. Solvents and additives were dried prior to use according to standard procedures. TLC plates Silicagel 60 F₂₅₄ (Merck KGaA) were used for monitoring reactions. Flash column chromatographic separations were performed on silica gel 60 (Fluka, 230-400 mesh). IR spectra were taken on a Bruker ALPHA FT-IR spectrometer as neat samples using an ATR device except for compounds **3-8**, **3-14** and **3-28**, which were measured on a Nicolet 6700 spectrometer in CHCl₃ solution. ¹H and ¹³C NMR spectra were recorded, unless otherwise noted, at room temperature on Bruker Avance 600, 500 and 400 spectrometers at 600.1, 499.9 and 400.1 MHz for ¹H NMR or 150.9, 125.7 and 100.6 MHz for ¹³C NMR, respectively. Connectivity was determined by ¹H-¹H COSY and HMBC experiments. Relative configurations of cyclic compounds were determined by NOE or ROESY experiments, comparison of NMR shifts and X-ray crystallography. ¹³C NMR assignments were obtained from APT and HSQC experiments. EI-mass spectra were recorded on a Waters GCT Premier Spectrometer at 70 eV. ESI Mass spectra were obtained on a Thermo Fisher Scientific LCQ Fleet spectrometer, sample concentration approx. 1 µg/mL, spray voltage pos. mode: 3.3 kV. CI and ESI HRMS spectra were measured on a Waters Q-Tof microspectrometer, resolution: 100000. Combustion analyses were performed at the Microanalytical Laboratories of IOCB Prague. Melting points are uncorrected.

Starting materials: 1-Oxo-2,2,6,6-tetramethylpiperidinium hexafluorophosphate (**1-9**⁺),^[110] pent-2-enoic acid dimethylamide (**3-1c**),^[111] (2*E*)-ethyl 4-{[*tert*-butyl(dimethyl)silyl]oxy}but-2-enoate (**3-1e**),^[112] (*E*)-*N,N*-dimethylcinnamide (**3-1j**),^[113] methyl *p*-methoxycinnamate (**3-1k**),^[113] (3*R*)-*tert*-butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]pentanoate (**3-4a**),^[114] (3*S*)-*tert*-butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-4-methylpentanoate (**3-4d**),^[114] (3*S*)-*tert*-butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-3-phenylpropanoate (**3-4i**),^[115] (*S*)-undec-1-en-4-ol (**3-32**),^[97] and ((*S*)-undec-1-en-4-yloxy)(*tert*-butyl)dimethylsilane (**3-33**)^[116] were prepared according to literature procedures. Their spectral and physical data matched those reported.

(2*E*,4*E*)-*tert*-Butyl hexa-2,4-dienoate (**3-1g**)^[117] and (2*E*)-*tert*-butyl pent-2-enoate (**3-1a**)^[118] were prepared according to a literature procedure using the corresponding acid chloride.^[119] The analytical data matched those reported.

(2*E*)-*tert*-Butyl 4-methylpent-2-enoate (**3-1d**),^[120] (2*E*)-*tert*-butyl 4-phenylbut-2-enoate (**3-1f**),^[120] (2*E*)-*tert*-butyl 3-(furan-2-yl)acrylate (**3-1h**),^[121] were prepared from (*tert*-butoxycarbonylmethylene)triphenylphosphorane and the corresponding aldehyde in analogy to a literature procedure.^[122] Their analytical data matched those reported.

(*S*)-*N*-Benzyl-1-(1-naphthyl)ethylamine^[123] and (*S*)-*N*-benzyl-1-(2-naphthyl)ethylamine^[124] were prepared according to a literature procedure using benzyl bromide as the alkylating agent.^[84] Its analytical data matched those reported.

(+)-(*S*)-*N*-Benzyl-1-phenylprop-2-en-1-amine (**3-47**),^[99] (*R*)-*N*-allyl (1-phenylethyl)amines (**1-37a-c**)^[84], methyl cyclohept-1-ene-1-carboxylate (**3-58c**),^[125] (*R*)-*N*-(cycloalkenylmethyl)-*N*-(1-phenylethyl)amines (**3-72a,b**),^[103] (*S*)-2-vinylpyrrolidine hydrochloride (**3-101**)^[105] and (*E*)-2-styrylbenzaldehyde (**3-104**)^[126] were prepared according to literature procedures and their analytical data matched those reported.

4.1 Asymmetric synthesis of β -amino- α -hydroxy acid derivatives

General procedure for tandem lithium amide conjugate addition/oxygenation reactions.

Method A (with 1 mol% LiCl): *n*BuLi (650 μ L, 1.04 mmol, 1.6M in hexanes) was added to a stirred solution of (*R*)-*N*-benzyl-1-phenylethylamine **3-2a** or (*S*)-*N*-benzyl-1-(1-naphthyl)ethylamine **3-2b** (1.04 mmol) in dry THF (6 mL) at -78°C under an argon atmosphere. A LiCl solution (65 μ L, 0.0065 mmol, 0.1M in dry THF) was added using a syringe. After stirring for 25 min, a solution of **3-1** (0.650 mmol) in dry THF (1 mL) was added using a syringe. The mixture was stirred at -78°C for 30-120 min, **1-9** (102 mg, 0.65 mmol) was added and the mixture was stirred for 1-2 min until it dissolved, and **1-6**⁺ was added in portions at -78°C , until the reaction mixture remained blue for 20 min (total 323 mg, 0.975 mmol). The mixture was stirred at -78°C for 40-60 min and quenched with four drops of saturated NH₄Cl solution.

Method A (with 1.5 equiv. LiCl): Anhydrous LiCl (41.3 mg, 0.975 mmol) was flame-dried in high vacuum in a Schlenk flask five times for around 2 min. Dry THF (6 mL) was added followed by (*R*)-*N*-benzyl-1-phenylethylamine **3-2a** (220 mg, 1.04 mmol) under an argon atmosphere. The mixture was cooled to -78°C and *n*BuLi (650 μ L, 1.04 mmol, 1.6M in hexanes) was added. After stirring for 25 min, a solution of **3-1d** or **3-1g** (0.650 mmol) in dry THF (1 mL) was added using a syringe. The mixture was stirred at -78°C for 30-120 min, **1-**

9 (102 mg, 0.65 mmol) was added, the mixture was stirred for 1-2 min until it dissolved, and **1-6⁺** was added in portions at $-78\text{ }^{\circ}\text{C}$, until the reaction mixture remained blue for 20 min (total 323 mg, 0.975 mmol). The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 40-60 min and quenched with four drops of saturated NH_4Cl solution.

Method B: *n*BuLi (650 μL , 1.04 mmol, 1.6M in hexanes) was added to a stirred solution of (*R*)-*N*-benzyl-1-phenylethylamine **3-2a** (1.04 mmol) in dry THF (6 mL) at $-78\text{ }^{\circ}\text{C}$ under an argon atmosphere. A LiCl solution (65 μL , 0.0065 mmol, 0.1M in dry THF) was added using a syringe. After stirring for 25 min, a solution of **3-1** (0.650 mmol) in dry THF (1 mL) was added using a syringe. After stirring for 30-120 min, **1-6** (12 mg, 0.065 mmol) was added in one portion followed by small portions of **1-9⁺** at $-78\text{ }^{\circ}\text{C}$ until the mixture remained green-blue for 20 min (total 254 mg, 0.845 mmol). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 40-60 min and quenched with four drops of saturated NH_4Cl solution.

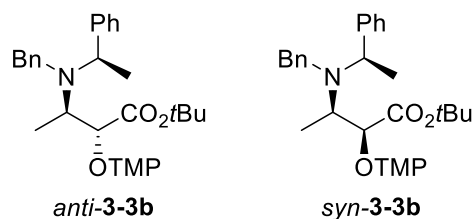
Method C: *n*BuLi (650 μL , 1.04 mmol, 1.6M in hexanes) was added to a stirred solution of (*R*)-*N*-benzyl-1-phenylethylamine **3-2a** (1.04 mmol) in dry THF (6 mL) at $-78\text{ }^{\circ}\text{C}$ under an argon atmosphere. A LiCl solution (65 μL , 0.0065 mmol, 0.1M in dry THF) was added using a syringe. After stirring for 25 min, a solution of **3-1** (0.650 mmol) in dry THF (1 mL) was added using a syringe. After stirring for 30-120 min, **1-9⁺** (254 mg, 0.845 mmol) was added in small portions at $-78\text{ }^{\circ}\text{C}$. Vigorous stirring at $-78\text{ }^{\circ}\text{C}$ was continued for 30 min and the reaction mixture was quenched with four drops of water.

Workup: The reaction mixture was stirred for 5 min, diluted with diethyl ether to the double volume, warmed to room temperature and filtered through a plug of silica gel. The solvent was evaporated and the crude product mixture was purified by column chromatography. The eluents are given at the individual compounds.

General procedure for oxygenation of β -amino ester 3-4i. *n*BuLi (360 μL , 0.568 mmol, 1.6M in hexanes) was added to a stirred solution of diisopropylamine (80 μL , 0.568 mmol) in dry THF (4 mL) at $-78\text{ }^{\circ}\text{C}$ under an argon atmosphere. After stirring for 30 min, a solution of **3-4i** (0.437 mmol) in dry THF (0.5 mL) was added using a syringe. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 50 min, **1-9** (68 mg, 0.568 mmol) was added, the mixture was stirred for 1-2 min until it dissolved, and **1-6⁺** was added in portions at $-78\text{ }^{\circ}\text{C}$ until the reaction mixture remained blue for 20 min (total 217 mg, 0.655 mmol). The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 40-60 min, quenched with four drops of saturated NH_4Cl solution, stirred for 5 min, diluted with diethyl ether to the double volume and filtered through a plug of silica gel. The solvent

(*c* 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 7.48-7.42 (m, 2H, Ph), 7.35-7.17 (m, 8H, Ph), 4.17 (d, *J* = 15.4 Hz, 1H, PhCH₂), 4.08 (d, *J* = 4.3 Hz, 1H, CHOTMP), 3.91 (q, *J* = 7.0 Hz, 1H, PhCHCH₃), 3.66 (d, *J* = 15.5 Hz, 1H, PhCH₂), 3.09 (dt, *J* = 8.5, 4.3 Hz, 1H, CH₃CH₂CHN), 1.92-1.78 (m, 1H, CH₃CH₂), 1.50 (s, 9H, C(CH₃)₃), 1.48-1.17 (m, 7H, NCCH₂CH₂CH₂CN, CH₃CH₂), 1.28 (d, *J* = 7.0 Hz, 3H, PhCHCH₃), 1.08 (s, 3H, NC(CH₃)₂), 1.07 (s, 3H, NC(CH₃)₂), 1.01-0.93 (m, 9H, CH₃CH₂, NC(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 171.4 (C, CO₂), 143.3 (C, *ipso*-Ph), 142.9 (C, *ipso*-Ph), 128.3 (CH, Ph), 128.24 (CH, Ph), 128.15 (CH, Ph), 128.0 (CH, Ph), 126.9 (CH, *p*-Ph), 126.38 (CH, *p*-Ph), 83.5 (CH, CHOTMP), 80.1 (C, C(CH₃)₃), 62.5 (CH, CH₃CH₂CHN), 61.0 (CH, PhCHCH₃), 60.8 (C, NC(CH₃)₂), 59.8 (C, NC(CH₃)₂), 51.3 (CH₂, PhCH₂), 41.0 (CH₂, NCCH₂CH₂CH₂CN), 40.4 (CH₂, NCCH₂CH₂CH₂CN), 34.5 (CH₃, NC(CH₃)₂), 33.8 (CH₃, NC(CH₃)₂), 28.4 (CH₃, C(CH₃)₃), 21.2 (CH₃, PhCHCH₃), 21.0 (CH₃, NC(CH₃)₂), 20.80 (CH₂, CH₃CH₂), 20.77 (CH₃, NC(CH₃)₂), 17.24 (CH₂, NCCH₂CH₂CH₂CN), 13.1 (CH₃, CH₃CH₂); **syn-3-3a** R_f(pentane/Et₂O 10:1) = 0.7; ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 7.55-7.49 (m, 2H, Ph), 7.48-7.41 (m, 2H, Ph), 7.38-7.17 (m, 6H, Ph), 4.29-4.22 (m, 2H, CHOTMP, PhCHCH₃), 3.96 (d, *J* = 15.0 Hz, 1H, PhCH₂), 3.92 (d, *J* = 15.0 Hz, 1H, PhCH₂), 3.10 (ddd, *J* = 9.0, 6.5, 3.8 Hz, 1H, CH₃CH₂CHN), 1.61-1.30 (m, 7H, CH₃CH₂, NCCH₂CH₂CH₂CN), 1.44 (s, 9H, C(CH₃)₃), 1.30-1.23 (m, 1H, NCCH₂CH₂CH₂CN), 1.18 (d, *J* = 6.9 Hz, 3H, PhCHCH₃), 1.12 (s, 3H, NC(CH₃)₂), 1.11 (s, 3H, NC(CH₃)₂), 1.09 (s, 3H, NC(CH₃)₂), 0.95 (t, *J* = 7.3 Hz, 3H, CH₃CH₂), 0.84 (s, 3H, NC(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 171.8 (C, CO₂), 145.9 (C, *ipso*-Ph), 143.8 (C, *ipso*-Ph), 128.20 (CH, Ph), 128.19 (CH, 2 x Ph), 127.9 (CH, Ph), 126.7 (CH, *p*-Ph), 126.35 (CH, *p*-Ph), 86.7 (CH, CHOTMP), 81.0 (C, C(CH₃)₃), 61.8 (CH, CH₃CH₂CHN), 60.8 (CH, PhCHCH₃), 60.3 (C, NC(CH₃)₂), 59.7 (C, NC(CH₃)₂), 51.2 (CH₂, PhCH₂), 40.7 (CH₂, NCCH₂CH₂CH₂CN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 34.1 (CH₃, NC(CH₃)₂), 33.9 (CH₃, NC(CH₃)₂), 28.1 (CH₃, C(CH₃)₃), 21.7 (CH₂, CH₃CH₂), 20.78 (CH₃, NC(CH₃)₂), 20.75 (CH₃, PhCHCH₃, NC(CH₃)₂), 17.23 (CH₂, NCCH₂CH₂CH₂CN), 12.8 (CH₃, CH₃CH₂).

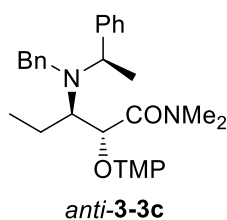
(2*R*,3*R*)- and (2*S*,3*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]butanoate (3-3b**):**



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 50:1 gradient to 5:1) to afford 242 mg (73%) of **3-3b** as a partially separable 11:1 *anti*/*syn*-mixture. IR: 3003, 2932, 1734, 1541, 1456, 1364, 1255, 1215, 1153, 1071, 730, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 531 (10, M+Na⁺), 509 (20, M+H⁺), 353 (10, M+H⁺-TEMPO), 318 (10), 238 (100, M+H⁺-TMPOCH₂CO₂*t*Bu); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₂H₄₉N₂O₃ 509.3736; Found 509.3738; Anal. Calcd for C₃₂H₄₈N₂O₃: C, 75.55; H, 9.51; N, 5.51; Found: C, 75.48; H, 9.55; N, 5.36; *anti*-3-3b Colorless solid. Mp: 69-70 °C; R_f(pentane/Et₂O 10:1) = 0.3; [α]_D²⁰ +60.4 (*c* 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 7.40-7.15 (m, 10H, Ph), 4.00 (q, *J* = 7.0 Hz, 1H, PhCHCH₃), 3.92-3.86 (m, 2H, PhCH₂, CHOTMP), 3.57 (d, *J* = 14.6 Hz, 1H, PhCH₂), 3.49 (dq, *J* = 8.6, 7.0 Hz, 1H, CH₃CHN), 1.55 (s, 9H, C(CH₃)₃), 1.41-1.18 (m, 6H, NCCH₂CH₂CH₂CN), 1.34 (d, *J* = 7.0 Hz, 3H, PhCHCH₃), 1.07 (s, 3H, NC(CH₃)₂), 0.99 (s, 6H, NC(CH₃)₂), 0.95 (d, *J* = 7.0 Hz, 3H, CH₃CHN), 0.85 (s, 3H, NC(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 172.0 (C, CO₂), 143.4 (C, *ipso*-Ph), 142.2 (C, *ipso*-Ph), 129.0 (CH, Ph), 128.10 (CH, Ph), 127.98 (CH, Ph), 127.95 (CH, Ph), 126.9 (CH, *p*-Ph), 126.5 (CH, *p*-Ph), 84.8 (CH, CHOTMP), 80.3 (C, C(CH₃)₃), 63.0 (CH, PhCHCH₃), 60.8 (C, NC(CH₃)₂), 59.44 (C, NC(CH₃)₂), 58.4 (CH, CH₃CHN), 49.0 (CH₂, PhCH₂), 40.8 (CH₂, NCCH₂CH₂CH₂CN), 40.3 (CH₂, NCCH₂CH₂CH₂CN), 34.2 (CH₃, NC(CH₃)₂), 33.8 (CH₃, NC(CH₃)₂), 28.5 (CH₃, C(CH₃)₃), 20.6 (CH₃, NC(CH₃)₂), 20.5 (CH₃, NC(CH₃)₂), 20.37 (CH₃, PhCHCH₃), 17.22 (CH₂, NCCH₂CH₂CH₂CN), 12.87 (CH₃, CH₃CHN); *syn*-3-3b R_f(pentane/Et₂O 10:1) = 0.2; ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 7.59-7.53 (m, 2H, Ph), 7.50-7.45 (m, 2H, Ph), 7.40-7.15 (m, 6H, Ph), 4.04 (d, *J* = 5.8 Hz, 1H, CHOTMP), 4.00 (q, *J* = 6.8 Hz, 1H, PhCHCH₃), 3.83 (d, *J* = 14.7 Hz, 1H, PhCH₂), 3.79 (d, *J* = 14.8 Hz, 1H, PhCH₂), 3.34 (q, *J* = 7.0, 5.8 Hz, 1H, CH₃CHN), 1.42 (s, 9H, C(CH₃)₃), 1.39-1.18 (m, 6H, NCCH₂CH₂CH₂CN), 1.28 (d, *J* = 6.8 Hz, 3H, PhCHCH₃), 1.23 (d, *J* = 7.0 Hz, 3H, CH₃CHN), 1.06 (s, 3H, NC(CH₃)₂), 1.04 (s, 3H, NC(CH₃)₂), 0.97 (s, 3H, NC(CH₃)₂), 0.50 (s, 3H, NC(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 172.0 (C, CO₂), 144.7 (C, *ipso*-Ph), 141.9

(C, *ipso*-Ph), 128.6 (CH, Ph), 128.2 (CH, Ph), 128.12 (CH, Ph), 127.97 (CH, Ph), 126.7 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 87.0 (CH, CHOTMP), 81.3 (C, C(CH₃)₃), 59.9 (C, NC(CH₃)₂), 59.46 (C, NC(CH₃)₂), 57.3 (CH, PhCHCH₃), 53.9 (CH, CH₃CHN), 50.9 (CH₂, PhCH₂), 40.4 (CH₂, NCCH₂CH₂CH₂CN), 34.1 (CH₃, NC(CH₃)₂), 33.2 (CH₃, NC(CH₃)₂), 28.1 (CH₃, C(CH₃)₃), 20.41 (CH₃, NC(CH₃)₂), 20.36 (CH₃, PhCHCH₃), 20.34 (CH₃, NC(CH₃)₂), 17.16 (CH₂, NCCH₂CH₂CH₂CN), 12.85 (CH₃, CH₃CHN).

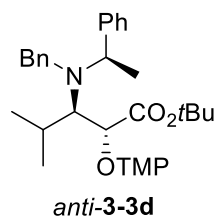
(2*R*,3*R*)-3-[*N*-Benzyl-*N*-((*R*)-1-phenylethyl)amino]-*N*',*N*'-dimethyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]pentanamide (3-3c):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 50:1 gradient to 2:1) to afford 241 mg (75%) of *anti*-3-3c as a single diastereomer as a pale yellow oil. R_f (hexane/EtOAc 7:1) = 0.3; $[\alpha]_D^{20} +58.8$ (c 0.5, CHCl₃); IR: 3070, 2978, 2881, 1649, 1458, 1261, 1179, 1153, 957, 911, 730, 701 cm⁻¹; MS (+ESI) m/z , (%): 1009 (20, 2M+Na⁺), 516 (100, M+Na⁺), 494 (28, M+H⁺), 359 (11, M+Na⁺-TEMPOH), 269 (10, M+Na⁺-TEMPO-PhCH₂), 252 (12, M+H⁺-TMPOCH₂CONMe₂); HRMS (+ESI) m/z : [M+Na⁺] Calcd for C₃₁H₄₇N₃O₂Na 516.3561; Found 516.3561; Anal. Calcd for C₃₁H₄₇N₃O₂: C, 75.41; H, 9.60; N, 8.51; Found: C, 75.15; H, 9.58; N, 8.33; ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.15 (m, 10H, Ph), 4.26 (d, J = 9.4 Hz, 1H, CHOTMP), 4.10 (q, J = 7.1 Hz, 1H, PhCHCH₃), 3.95 (d, J = 15.1 Hz, 1H, PhCH₂), 3.74-3.68 (m, 1H, CH₃CH₂CHN), 3.68 (d, J = 15.2 Hz, 1H, PhCH₂), 2.94 (s, 3H, NCH₃), 2.86 (s, 3H, NCH₃), 2.01-1.88 (m, 1H, CH₂CH₃), 1.68-1.48 (m, 1H, CH₂CH₃), 1.44 (d, J = 7.0 Hz, 3H, PhCHCH₃), 1.42-1.20 (m, 6H, NCCH₂CH₂CH₂CN), 1.12 (s, 3H, NC(CH₃)₂), 1.04 (s, 3H, NC(CH₃)₂), 0.99 (s, 3H, NC(CH₃)₂), 0.91 (s, 3H, NC(CH₃)₂), 0.89 (t, J = 7.4 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 172.9 (C, CO), 145.2 (C, *ipso*-Ph), 142.7 (C, *ipso*-Ph), 128.9 (CH, Ph), 128.1 (CH, 2 x Ph), 127.9 (CH, Ph), 126.7 (CH, *p*-Ph), 126.5 (CH, *p*-Ph), 80.0 (CH, CHOTMP), 63.4 (CH, CH₃CH₂CHN), 62.6 (CH, PhCHCH₃), 61.1 (C, NC(CH₃)₂), 59.6 (C, NC(CH₃)₂), 49.8 (CH₂, PhCH₂), 41.1 (CH₂, NCCH₂CH₂CH₂CN), 40.9 (CH₂, NCCH₂CH₂CH₂CN), 38.6 (CH₃, NCH₃), 36.2 (CH₃, NCH₃), 33.3 (CH₃, NC(CH₃)₂), 32.6 (CH₃, NC(CH₃)₂), 21.5 (CH₂,

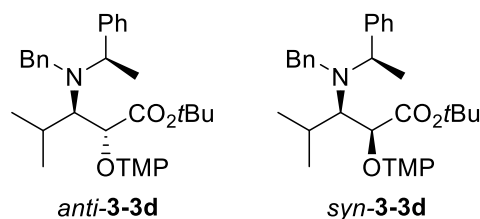
CH₂CH₃), 21.0 (CH₃, NC(CH₃)₂), 20.8 (CH₃, PhCHCH₃), 20.6 (CH₃, NC(CH₃)₂), 17.1 (CH₂, NCCH₂CH₂CH₂CN), 13.4 (CH₃, CH₂CH₃).

(2*R*,3*R*)-tert-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-4-methylpentanoate (3-3d):



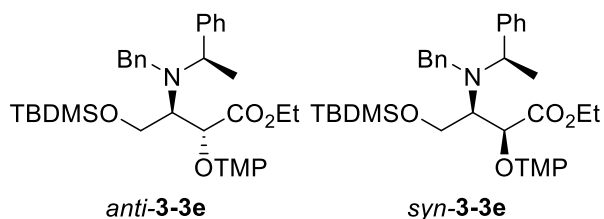
Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 10:1) to afford 164 mg (47%) of *anti*-**3-3d** as a single diastereomer as a colorless solid. Mp: 108-109 °C; R_f(pentane/Et₂O 50:1) = 0.4; [α]_D²⁰ -41.3 (*c* 0.5, CHCl₃); IR: 2984, 2940, 1747, 1461, 1370, 1154, 703 cm⁻¹; MS (+ESI) *m/z*, (%): 559 (37, M+Na⁺), 537 (40, M+H⁺), 266 (100, M+H⁺-TMPOCH₂CO₂tBu); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₃₄H₅₂N₂O₃Na 559.3870; Found 559.3871; Anal. Calcd for C₃₄H₅₂N₂O₃: C, 76.08; H, 9.76; N, 5.22; Found: C, 75.80; H, 9.49; N, 4.92; ¹H NMR (400 MHz, CDCl₃): δ 7.60-7.14 (m, 10H, Ph), 4.76 (d, *J* = 8.8 Hz, 1H, CHOTMP), 4.50 (q, *J* = 7.1 Hz, 1H, PhCHCH₃), 4.27 (d, *J* = 16.6 Hz, 1H, PhCH₂), 4.08 (d, *J* = 16.6 Hz, 1H, PhCH₂), 3.09 (dd, *J* = 8.5, 4.8 Hz, 1H, (CH₃)₂CHCHN), 1.54-1.32 (m, 7H, NCCH₂CH₂CH₂CN, CH(CH₃)₂), 1.46 (s, 9H, C(CH₃)₃), 1.37 (s, 3H, NC(CH₃)₂), 1.35 (s, 3H, NC(CH₃)₂), 1.28 (s, 3H, NC(CH₃)₂), 1.23 (s, 3H, NC(CH₃)₂), 1.11 (d, *J* = 7.0 Hz, 3H, PhCHCH₃), 0.82 (d, *J* = 6.9 Hz, 3H, CH(CH₃)₂), 0.73 (d, *J* = 6.7 Hz, 3H, CH(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 171.2 (C, CO₂), 147.1 (C, *ipso*-Ph), 145.1 (C, *ipso*-Ph), 128.8 (CH, Ph), 128.2 (CH, Ph), 128.1 (CH, Ph), 127.5 (CH, Ph), 126.7 (CH, *p*-Ph), 126.1 (CH, *p*-Ph), 86.5 (CH, CHOTMP), 80.6 (C, C(CH₃)₃), 65.6 (CH, (CH₃)₂CHCHN), 64.9 (CH, PhCHCH₃), 61.2 (C, NC(CH₃)₂), 60.2 (C, NC(CH₃)₂), 53.1 (CH₂, PhCH₂), 41.3 (CH₂, NCCH₂CH₂CH₂CN), 40.8 (CH₂, NCCH₂CH₂CH₂CN), 34.7 (CH₃, NC(CH₃)₂), 34.2 (CH₃, NC(CH₃)₂), 30.6 (CH, CH(CH₃)₂), 28.2 (CH₃, C(CH₃)₃), 22.9 (CH₃, PhCHCH₃), 21.6 (CH₃, NC(CH₃)₂), 21.43 (CH₃, NC(CH₃)₂), 21.38 (CH₃, CH(CH₃)₂), 19.2 (CH₃, CH(CH₃)₂), 17.4 (CH₂, NCCH₂CH₂CH₂CN).

(2*R*,3*R*)- and (2*S*,3*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-4-methylpentanoate (3-3d):



Deprotonation of amino ester **3-4d** by LDA, followed by oxygenation with **1-6/1-9⁺** provided a crude mixture containing 52% of a 2:1 *anti/syn*-mixture of **3-3d** and 14% recovered **3-4d**, that was not purified, because the *syn*-isomer decomposed on purification by column chromatography. ¹H NMR (400 MHz, (CD₃)₂CO): δ 7.67-7.13 (m, 20H, Ph, Ph*), 4.84 (d, *J* = 8.9 Hz, 1H, CHOTMP), 4.59 (q, *J* = 7.0 Hz, 1H, PhCHCH₃), 4.38 (d, *J* = 6.3 Hz, 1H, CHOTMP*), 4.34 (d, *J* = 16.7 Hz, 1H, PhCH₂), 4.15 (d, *J* = 16.7 Hz, 1H, PhCH₂), 4.10 (m, 1H, PhCH₂*), 4.00 (q, *J* = 7.0 Hz, 1H, PhCHCH₃*), 3.91 (d, *J* = 15.8 Hz, 1H, PhCH₂*), 3.34 (dd, *J* = 6.3, 2.1 Hz, 1H, (CH₃)₂CHCHN*), 3.13 (dd, *J* = 8.9, 4.9 Hz, 1H, (CH₃)₂CHCHN), 2.24-2.15 (m, 1H, CH(CH₃)₂*), 1.60-1.00 (m, 67H, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*, CH(CH₃)₂, C(CH₃)₃, C(CH₃)₃*, NC(CH₃)₂, NC(CH₃)₂*, PhCHCH₃, PhCHCH₃*, CH(CH₃)₂*), 0.84 (d, *J* = 7.0 Hz, 3H, CH(CH₃)₂), 0.76 (d, *J* = 6.8 Hz, 3H, CH(CH₃)₂); ¹³C NMR (100 MHz, (CD₃)₂CO) δ 171.4 (C, CO₂), 171.2 (C, CO₂*), 147.9 (C, *ipso*-Ph), 145.6 (C, *ipso*-Ph), 144.4 (C, *ipso*-Ph*), 143.2 (C, *ipso*-Ph*), 129.5 (CH, Ph), 128.96 (CH, Ph), 128.94 (CH, Ph*), 128.89 (CH, Ph*), 128.84 (CH, Ph*), 128.77 (CH, Ph), 128.7 (CH, Ph*), 128.1 (CH, Ph), 127.6 (CH, *p*-Ph*), 127.5 (CH, *p*-Ph), 127.1 (CH, *p*-Ph*), 126.9 (CH, *p*-Ph), 87.1 (CH, CHOTMP), 85.4 (CH, CHOTMP*), 80.9 (C, C(CH₃)₃), 80.1 (C, C(CH₃)₃*), 66.1 (CH, (CH₃)₂CHCHN), 65.9 (CH, (CH₃)₂CHCHN*), 65.6 (CH, PhCHCH₃), 62.6 (CH, PhCHCH₃*), 61.8 (C, NC(CH₃)₂, NC(CH₃)₂*), 60.8 (C, NC(CH₃)₂, NC(CH₃)₂*), 53.9 (CH₂, PhCH₂), 52.8 (CH₂, PhCH₂*), 41.9 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 41.4 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 35.0 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 34.7 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 33.4 (CH, CH(CH₃)₂*), 31.2 (CH, CH(CH₃)₂), 28.7 (CH₃, C(CH₃)₃*), 28.3 (CH₃, C(CH₃)₃), 23.5 (CH₃, PhCHCH₃), 22.4 (CH₃, PhCHCH₃*), 21.9 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 21.8 (CH₃, CH(CH₃)₂), 21.7 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 19.43 (CH₃, CH(CH₃)₂, CH(CH₃)₂*), 19.38 (CH₃, CH(CH₃)₂*), 17.9 (CH₂, NCCH₂CH₂CH₂CN), 16.7 (CH₂, NCCH₂CH₂CH₂CN*). Resonances marked by * correspond to the minor diastereomer.

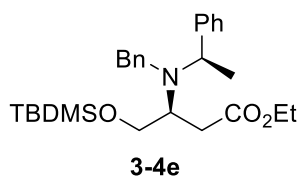
(2*R*,3*R*)- and (2*S*,3*R*)-Ethyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-4-[[*tert*-butyl(dimethyl)silyl]oxy]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]butanoate (3-3e):



Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 50:1 gradient to 10:1) to afford 274 mg (69%) of **3-3e** as an inseparable 5:1 *anti/syn*-mixture as a colorless oil. R_f (hexane/EtOAc 30:1) = 0.2; IR: 2938, 2865, 1743, 1458, 1378, 1367, 1256, 1186, 1138, 1076, 1033, 838, 777, 757, 700 cm^{-1} ; MS (+ESI) m/z , (%): 633 (8, $\text{M}+\text{Na}^+$), 611 (35, $\text{M}+\text{H}^+$), 456 (10, $\text{M}+\text{H}^+-\text{TMP}-\text{CH}_3$), 368 (100, $\text{M}+\text{H}^+-\text{TMPOCH}_2\text{CO}_2\text{Et}$); HRMS (+ESI) m/z : [$\text{M}+\text{Na}^+$] Calcd for $\text{C}_{36}\text{H}_{58}\text{N}_2\text{O}_4\text{SiNa}$ 633.4058; Found 633.4056; Anal. Calcd for $\text{C}_{36}\text{H}_{58}\text{N}_2\text{O}_4\text{Si}$: C, 70.77; H, 9.57; N, 4.59; Found: C, 70.80; H, 9.40; N, 4.40; ^1H NMR (600 MHz, CDCl_3 , 5 $^\circ\text{C}$): δ 7.48-7.44 (m, 4H, Ph*), 7.34-6.10 (m, 16H, Ph, Ph*), 4.20-4.01 (m, 8H, CHOTMP, PhCHCH₃, OCH₂CH₃, CH₂OSi, CH₂OSi*), 4.00-3.89 (m, 6H, CHOTMP*, PhCH₂*, PhCHCH₃*, OCH₂CH₃*), 3.86 (d, J = 14.6 Hz, 1H, PhCH₂), 3.82 (d, J = 14.5 Hz, 1H, PhCH₂), 3.82-3.77 (m, 1H, CH₂CHN), 3.37 (ddd, J = 9.5, 6.2, 3.1 Hz, 1H, CH₂CHN*), 1.51-1.16 (m, 12H, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 1.44 (d, J = 6.9 Hz, 3H, PhCHCH₃), 1.35 (d, J = 6.8 Hz, 3H, PhCHCH₃*), 1.30 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.26 (t, J = 7.2 Hz, 3H, OCH₂CH₃*), 1.04 (s, 3H, NC(CH₃)₂), 1.01 (s, 3H, NC(CH₃)₂), 0.98 (s, 18H, Si(CH₃)₃, Si(CH₃)₃*), 0.97 (s, 3H, NC(CH₃)₂), 0.94 (s, 3H, NC(CH₃)₂*), 0.92 (s, 3H, NC(CH₃)₂*), 0.89 (s, 3H, NC(CH₃)₂), 0.87 (s, 3H, NC(CH₃)₂*), 0.40 (s, 3H, NC(CH₃)₂*), 0.14 (s, 3H, SiCH₃), 0.12 (s, 6H, SiCH₃, SiCH₃*), 0.11 (s, 3H, SiCH₃*); ^{13}C NMR (150 MHz, CDCl_3 , 5 $^\circ\text{C}$) δ 173.2 (C, CO₂*), 172.2 (C, CO₂), 146.4 (C, *ipso*-Ph), 144.3 (C, *ipso*-Ph*), 141.7 (C, *ipso*-Ph*), 141.3 (C, *ipso*-Ph), 129.2 (CH, Ph), 128.8 (CH, Ph*), 128.4 (CH, Ph*), 128.3 (CH, Ph*), 127.96 (CH, Ph*), 127.94 (CH, Ph), 127.86 (CH, Ph), 127.8 (CH, Ph), 126.7 (CH, *p*-Ph*), 126.6 (CH, *p*-Ph*), 126.5 (CH, 2 x *p*-Ph), 85.4 (CH, CHOTMP*), 83.7 (CH, CHOTMP), 61.9 (CH₂, CH₂OSi), 60.8 (CH₂, CH₂OSi*), 60.62 (CH, OCH₂CHN), 60.56 (CH₂, OCH₂CH₃*), 60.3 (CH₂, OCH₂CH₃), 60.1 (CH, OCH₂CHN*), 59.8 (C, NC(CH₃)₃), 59.5 (C, NC(CH₃)₃, NC(CH₃)₃*), 59.2 (C, NC(CH₃)₃*), 55.6 (CH, PhCHCH₃), 55.3 (CH, PhCHCH₃*), 52.6 (CH₂, PhCH₂), 51.1 (CH₂, PhCH₂*), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 40.4 (CH₂, NCCH₂CH₂CH₂CN), 40.2 (CH₂, NCCH₂CH₂CH₂CN*), 40.0 (CH₂, NCCH₂CH₂CH₂CN*),

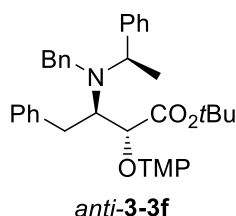
NCCH₂CH₂CH₂CN*), 34.2 (CH₃, NC(CH₃)₂), 33.0 (CH₃, NC(CH₃)₂*), 32.9 (CH₃, NC(CH₃)₂), 32.6 (CH₃, NC(CH₃)₂*), 26.15 (CH₃, SiC(CH₃)₃*), 26.13 (CH₃, SiC(CH₃)₃), 20.7 (CH₃, PhCHCH₃), 20.6 (CH₃, PhCHCH₃*), 20.5 (CH₃, NC(CH₃)₂), 20.3 (CH₃, NC(CH₃)₂), 20.2 (CH₃, NC(CH₃)₂*), 20.1 (CH₃, NC(CH₃)₂*), 18.4 (C, SiC(CH₃)₃*), 18.3 (C, SiC(CH₃)₃), 17.10 (CH₂, NCCH₂CH₂CH₂CN*), 17.06 (CH₂, NCCH₂CH₂CH₂CN), 14.2 (CH₃, OCH₂CH₃), 14.0 (CH₃, OCH₂CH₃*), -5.26 (CH₃, Si(CH₃)₂*), -5.28 (CH₃, Si(CH₃)₂*), -5.36 (CH₃, Si(CH₃)₂), -5.37 (CH₃, Si(CH₃)₂). Resonances marked by * correspond to the minor diastereomer.

(S)-Ethyl 3-[N-benzyl-N-((R)-1-phenylethyl)amino]-4-{{tert-butyl(dimethyl)silyl}oxy}butanoate (3-4e):



The analytical data are in agreement with those reported in the literature.^[112]

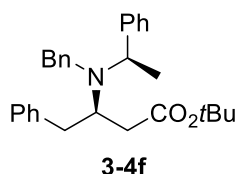
(2R,3R)-tert-Butyl 3-[N-benzyl-N-((R)-1-phenylethyl)amino]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-4-phenylbutanoate (3-3f):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 10:1) to afford 209 mg (55%) of **3-3f** as an inseparable 16:1 *anti/syn*-mixture (dr of the crude product 10:1 as determined by ¹H NMR spectroscopy) as a colorless solid, and 16.8 mg (6%) of **3-4f** as a colorless oil. Mp: 103-104 °C; R_f(hexane/EtOAc 20:1) = 0.5; [α]_D²⁰ +52.7 (c 0.5, CHCl₃); IR: 3036, 2984, 1737, 1498, 1458, 1369, 1158, 911, 733, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 585 (10, M+H⁺), 314 (100, M+H⁺-TMPOCH₂CO₂tBu); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₈H₅₃N₂O₃ 585.4051; Found 585.4052; Anal. Calcd for C₃₈H₅₂N₂O₃: C, 78.04; H, 8.96; N, 4.79; Found: C, 77.99; H, 8.94; N, 5.04; ¹H NMR (400 MHz, CDCl₃): δ 7.43-6.99 (m, 15H, Ph), 4.39 (d, *J* = 15.8 Hz, 1H, PhCH₂), 4.20 (d, *J* = 2.6 Hz, 1H, CHOTMP), 3.83 (d, *J* = 15.8

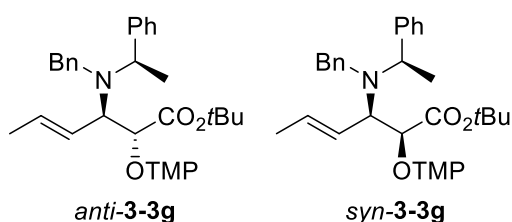
Hz, 1H, PhCH₂), 3.78 (q, *J* = 6.9 Hz, 1H, PhCHCH₃), 3.58 (ddd, *J* = 9.4, 3.7, 2.5 Hz, 1H, PhCH₂CHN), 3.39 (dd, *J* = 14.3, 3.7 Hz, 1H, PhCH₂CHN), 2.80 (dd, *J* = 14.2, 9.5 Hz, 1H, PhCH₂CHN), 1.51 (s, 9H, C(CH₃)₃), 1.43-1.24 (m, 6H, NCCH₂CH₂CH₂CN), 1.11 (s, 6H, NC(CH₃)₂), 0.98 (s, 6H, NC(CH₃)₂), 0.94 (d, *J* = 6.9 Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.1 (C, CO₂), 143.1 (C, *ipso*-Ph), 142.4 (C, *ipso*-Ph), 141.8 (C, *ipso*-Ph), 129.9 (CH, Ph), 128.23 (CH, Ph), 128.18 (CH, Ph), 128.1 (CH, Ph), 127.9 (CH, 2 x Ph), 126.7 (CH, *p*-Ph), 126.4 (CH, *p*-Ph), 125.6 (CH, *p*-Ph), 82.8 (CH, CHOTMP), 80.3 (C, C(CH₃)₃), 62.2 (CH, PhCH₂CHN), 60.9 (C, NC(CH₃)₂), 60.1 (C, NC(CH₃)₂), 59.7 (CH, PhCHCH₃), 52.3 (CH₂, PhCH₂), 41.1 (CH₂, NCCH₂CH₂CH₂CN), 40.6 (CH₂, NCCH₂CH₂CH₂CN), 34.5 (CH₂, PhCH₂CHN), 34.0 (CH₃, NC(CH₃)₂), 33.9 (CH₃, NC(CH₃)₂), 28.4 (CH₃, C(CH₃)₃), 21.1 (CH₃, NC(CH₃)₂), 20.8 (CH₃, NC(CH₃)₂), 20.6 (CH₃, PhCHCH₃), 17.3 (CH₂, NCCH₂CH₂CH₂CN).

(*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-4-phenylbutanoate (3-4f):



The analytical data are in agreement with those reported in the literature.^[127]

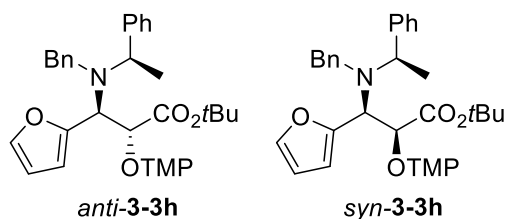
(2*R*,3*R*)- and (2*S*,3*R*)-*tert*-Butyl (4*E*)-3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]hex-4-enoate (3-3g):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 10:1) to afford 233 mg (67%) of **3-3g** as an inseparable 3:1 *anti/syn*-mixture as a colorless solid. *R*_f(hexane/EtOAc 20:1) = 0.4; IR: 2984, 2940, 1740, 1457, 1369, 1246, 1211, 1156, 1081, 972, 913, 734, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 557 (100, M+Na⁺), 535 (87, M+H⁺), 380 (28, M+H⁺-TMP-CH₃), 264 (80, M+H⁺-TMPOCH₂CO₂tBu); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₃₄H₅₀N₂O₃Na 557.3714; Found 557.3714; Anal. Calcd for C₃₄H₅₀N₂O₃: C, 76.36; H,

9.42; N, 5.24; Found: C, 76.27; H, 9.35; N, 5.10; ^1H NMR (400 MHz, CDCl_3): δ 7.53-7.42 (m, 4H, Ph*), 7.33-7.09 (m, 16H, Ph, Ph*), 5.66-5.43 (m, 3H, $=\text{CHCH}$, $\text{CH}_3\text{CH}=\text{*}$, $=\text{CHCH}^*$), 5.37 (dq, $J = 15.2, 6.3$ Hz, 1H, $\text{CH}_3\text{CH}=\text{*}$), 4.34 (d, $J = 7.2$ Hz, 1H, CHOTMP^*), 4.19 (q, $J = 6.8$ Hz, 1H, PhCHCH_3^*), 4.16 (d, $J = 9.0$ Hz, 1H, CHOTMP), 4.03 (q, $J = 6.9$ Hz, 1H, PhCHCH_3), 3.85 (t, $J = 9.1$ Hz, 1H, $=\text{CHCHN}$), 3.80 (d, $J = 15.0$ Hz, 1H, PhCH_2^*), 3.75 (d, $J = 15.0$ Hz, 1H, PhCH_2^*), 3.74 (d, $J = 15.0$ Hz, 1H, PhCH_2), 3.69-3.64 (m, 1H, $=\text{CHCHN}^*$), 3.67 (d, $J = 15.0$ Hz, 1H, PhCH_2), 1.67 (dd, $J = 6.3, 1.5$ Hz, 6H, $\text{CH}_3\text{CH}=\text{*}$, $\text{CH}_3\text{CH}=\text{*}$), 1.54 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.41 (s, 9H, $\text{C}(\text{CH}_3)_3^*$), 1.39 (d, $J = 6.9$ Hz, 3H, PhCHCH_3), 1.33 (d, $J = 6.9$ Hz, 3H, PhCHCH_3^*), 1.44-1.24 (m, 12H, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^*$), 1.10-0.99 (m, 15H, $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 0.97 (s, 6H, $\text{NC}(\text{CH}_3)_2$), 0.88 (s, 3H, $\text{NC}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.7 (C, CO_2), 171.1 (C, CO_2^*), 144.7 (C, *ipso*-Ph*), 144.2 (C, *ipso*-Ph), 142.0 (C, *ipso*-Ph*), 141.6 (C, *ipso*-Ph), 129.70 (CH, $\text{CH}_3\text{CH}=\text{*}$, Ph), 129.2 (CH, $\text{CH}_3\text{CH}=\text{*}$), 128.7 (CH, Ph*), 128.4 (CH, Ph), 128.2 (CH, Ph*), 128.12 (CH, Ph*), 128.06 (CH, Ph*), 127.81 (CH, 2 x Ph), 127.80 (CH, $=\text{CH}$), 127.7 (CH, $=\text{CH}^*$), 126.7 (CH, *p*-Ph), 126.6 (CH, *p*-Ph*), 126.5 (CH, *p*-Ph*), 126.4 (CH, *p*-Ph), 85.7 (CH, CHOTMP^*), 84.4 (CH, CHOTMP), 80.9 (C, $\text{C}(\text{CH}_3)_3^*$), 80.6 (C, $\text{C}(\text{CH}_3)_3$), 64.7 (CH, $=\text{CHCHN}$), 62.7 (CH, $=\text{CHCHN}^*$), 61.1 (CH, PhCHCH_3), 60.9 (C, $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 59.6 (C, $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 57.3 (CH, PhCHCH_3^*), 51.3 (CH_2 , PhCH_2), 51.1 (CH_2 , PhCH_2^*), 40.9 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^*$), 40.5 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^*$), 34.4 (CH_3 , $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 34.0 (CH_3 , $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 28.5 (CH_3 , $\text{C}(\text{CH}_3)_3$), 28.2 (CH_3 , $\text{C}(\text{CH}_3)_3^*$), 20.5 (CH_3 , $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 20.4 (CH_3 , $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 19.9 (CH_3 , PhCHCH_3), 18.30 (CH_3 , $\text{CH}_3\text{CH}=\text{*}$), 18.28 (CH_3 , $\text{CH}_3\text{CH}=\text{*}$), 17.33 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^*$), 17.26 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 16.8 (CH_3 , PhCHCH_3^*). Resonances marked by * belong to the minor diastereomer.

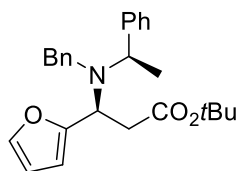
(2*R*,3*S*)- and (2*S*,3*S*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-3-(furan-2-yl)-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (3-3h**):**



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 10:1) to afford 285 mg (78%) of **3-3h** as a partially separable 4:1 *anti*/*syn*-mixture and 33.6 mg (15%) of **3-4h** as a colorless oil. IR: 2984, 2940, 1746, 1459, 1369, 1260, 1217, 1153, 960, 858, 805, 732, 699 cm^{-1} ; MS (+ESI) m/z , (%): 583 (100, $\text{M}+\text{Na}^+$), 561 (11, $\text{M}+\text{H}^+$), 426 (10, $\text{M}+\text{Na}^+-\text{TEMPOH}$), 290 (40, $\text{M}+\text{H}^+-\text{TMPOCH}_2\text{CO}_2t\text{Bu}$); HRMS (+ESI) m/z : [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{35}\text{H}_{49}\text{N}_2\text{O}_4$ 561.3687; Found 561.3689; Anal. Calcd for $\text{C}_{35}\text{H}_{48}\text{N}_2\text{O}_4$: C, 74.96; H, 8.63; N, 5.00; Found: C, 74.73; H, 8.65; N, 4.99; *anti*-3-3h Colorless solid. Mp: 95-97 $^{\circ}\text{C}$; R_f (hexane/EtOAc 20:1) = 0.4; $[\alpha]_D^{20} +24.3$ (c 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.40 (dd, J = 1.8, 0.8 Hz, 1H, Fur), 7.36-7.14 (m, 10H, Ph), 6.35 (dd, J = 3.2, 1.8 Hz, 1H, Fur), 6.07 (d, J = 2.8 Hz, 1H, Fur), 4.74 (d, J = 10.0 Hz, 1H, CHOTMP), 4.50 (d, J = 9.9 Hz, 1H, FurCHN), 4.07 (q, J = 6.9 Hz, 1H, PhCHCH_3), 3.76 (d, J = 14.6 Hz, 1H, PhCH_2), 3.64 (d, J = 14.4 Hz, 1H, PhCH_2), 1.56 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.48-1.25 (m, 6H, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 1.20 (d, J = 6.9 Hz, 3H, PhCHCH_3), 1.18 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 1.01 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 0.80 (s, 6H, $\text{NC}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 170.2 (C, CO_2), 153.3 (C, *ipso*-Fur), 144.3 (C, *ipso*-Ph), 141.09 (CH, Fur), 140.9 (C, *ipso*-Ph), 129.3 (CH, Ph), 128.4 (CH, Ph), 127.9 (CH, Ph), 127.8 (CH, Ph), 126.8 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 110.2 (CH, Fur), 109.4 (CH, Fur), 82.3 (CH, CHOTMP), 80.6 (C, $\text{C}(\text{CH}_3)_3$), 61.1 (C, $\text{NC}(\text{CH}_3)_2$), 60.2 (CH, PhCHCH_3), 59.8 (C, $\text{NC}(\text{CH}_3)_2$), 58.1 (CH, FurCHN), 52.2 (CH_2 , PhCH_2), 41.0 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 40.3 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 34.3 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 33.9 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 28.6 (CH_3 , $\text{C}(\text{CH}_3)_3$), 20.4 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 20.2 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 17.6 (CH_3 , PhCHCH_3), 17.3 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$); *syn*-3-3h R_f (hexane/EtOAc 20:1) = 0.3; ^1H NMR (400 MHz, CDCl_3): δ 7.64-7.60 (m, 2H, Ph), 7.52-7.48 (m, 2H, Ph), 7.37 (dd, J = 1.8, 0.8 Hz, 1H, Fur), 7.36-7.14 (m, 6H, Ph), 6.31 (dd, J = 3.2, 1.8 Hz, 1H, Fur), 6.18 (d, J = 3.0 Hz, 1H, Fur), 4.87 (d, J = 9.5 Hz, 1H, CHOTMP), 4.43 (d, J = 9.5 Hz, 1H, FurCHN), 4.32 (q, J = 6.6 Hz, 1H, PhCHCH_3), 3.93 (d, J = 14.5 Hz, 1H, PhCH_2), 3.80 (d, J = 14.5 Hz, 1H, PhCH_2), 1.48-1.25 (m, 6H, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 1.27 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.17 (s, 12H, $\text{NC}(\text{CH}_3)_2$), 1.04 (d, J = 6.8 Hz,

3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.6 (C, CO₂), 152.6 (C, *ipso*-Fur), 145.0 (C, *ipso*-Ph), 141.12 (CH, Fur), 140.9 (C, *ipso*-Ph), 128.8 (CH, Ph), 128.3 (CH, Ph), 128.2 (CH, Ph), 128.1 (CH, Ph), 126.7 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 110.3 (CH, Fur), 108.9 (CH, Fur), 83.4 (CH, CHOTMP), 80.6 (C, C(CH₃)₃), 61.1 (C, NC(CH₃)₂), 59.8 (C, NC(CH₃)₂), 57.2 (CH, FurCHN), 56.8 (CH, PhCHCH₃), 51.2 (CH₂, PhCH₂), 40.9 (CH₂, NCCH₂CH₂CH₂CN), 40.4 (CH₂, NCCH₂CH₂CH₂CN), 34.1 (CH₃, NC(CH₃)₂), 33.6 (CH₃, NC(CH₃)₂), 28.0 (CH₃, C(CH₃)₃), 21.4 (CH₃, NC(CH₃)₂), 17.4 (CH₂, NCCH₂CH₂CH₂CN), 15.6 (CH₃, PhCHCH₃).

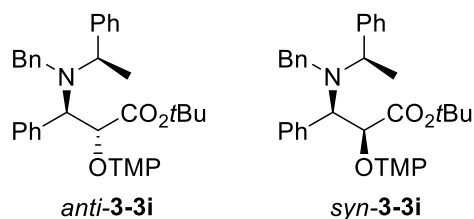
(3*S*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-3-(furan-2-yl)propanoate (3-4h):



3-4h

R_f(hexane/EtOAc 20:1) = 0.2; [α]_D²⁰ −52.2 (*c* 0.5, CHCl₃); IR: 3072, 3037, 2985, 2940, 1733, 1458, 1294, 1260, 1149, 1081, 960, 851, 735, 699 cm^{−1}; MS (+ESI) *m/z*, (%): 428 (100, M+Na⁺), 406 (65, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₂₆H₃₂NO₃ 406.2377; Found 406.2378; Anal. Calcd for C₂₆H₃₁NO₃: C, 77.01; H, 7.71; N, 3.45; Found: C, 77.22; H, 7.69; N, 3.21; ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.37 (m, 3H, Ph, Fur), 7.34-7.13 (m, 8H, Ph), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H, Fur), 6.15 (d, *J* = 3.2 Hz, 1H, Fur), 4.45 (dd, *J* = 8.7, 6.5 Hz, 1H, CHNCH₂CO), 4.04 (q, *J* = 6.8 Hz, 1H, PhCHCH₃), 3.68 (d, *J* = 17.0 Hz, 1H, PhCH₂), 3.63 (d, *J* = 17.0 Hz, 1H, PhCH₂), 2.65 (dd, *J* = 14.9, 8.7 Hz, 1H, CH₂CO₂), 2.58 (dd, *J* = 14.9, 6.5 Hz, 1H, CH₂CO₂), 1.31 (s, 9H, C(CH₃)₃), 1.15 (d, *J* = 6.7 Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.6 (C, CO₂), 156.2 (C, *ipso*-Fur), 144.6 (C, *ipso*-Ph), 141.5 (CH, Fur), 140.9 (C, *ipso*-Ph), 128.7 (CH, Ph), 128.2 (CH, Ph), 128.1 (CH, Ph), 128.0 (CH, Ph), 126.80 (CH, *p*-Ph), 126.75 (CH, *p*-Ph), 110.2 (CH, Fur), 107.4 (CH, Fur), 80.4 (C, C(CH₃)₃), 57.0 (CH, PhCHCH₃), 52.3 (CH, CHNCH₂), 51.1 (CH₂, PhCH₂), 38.4 (CH₂, CH₂CO), 28.1 (CH₃, C(CH₃)₃), 16.5 (CH₃, PhCHCH₃).

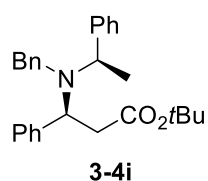
(2*R*,3*R*)- and (2*S*,3*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-3-phenyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (3-3i**):**



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 50:1 gradient to 10:1) to afford 272 mg (73%) of **3-3i** as a partially separable 3:1 *anti*/*syn*-mixture and 19 mg (7%) of **3-4i** as a colorless oil. Deprotonation/oxygenation of **3-4i** furnished 205 mg (82%) of **3-3i** as a 1:1.2 *anti*/*syn*-mixture. IR: 2975, 2928, 1726, 1601, 1493, 1453, 1367, 1301, 1257, 1151, 1083, 1028, 963, 913, 843, 749, 699 cm⁻¹; MS (+ESI) *m/z*, (%): 593 (20, M+Na⁺), 436 (15, M+Na⁺-TEMPOH), 300 (100, M+H⁺-TMPOCH₂CO₂tBu); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₇H₅₁N₂O₃ 571.3894; Found 571.3893; Anal. Calcd for C₃₇H₅₀N₂O₃: C, 77.85; H, 8.83; N, 4.91; Found: C, 77.45; H, 9.00; N, 4.66; *anti*-3-3i Colorless solid. Mp: 43-44 °C; R_f(pentane/Et₂O 10:1) = 0.7; [α]_D²⁰ +26.4 (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.02 (m, 15H, Ph), 4.75 (d, *J* = 9.7 Hz, 1H, CHOTMP), 4.58 (d, *J* = 9.7 Hz, 1H, PhCHN), 4.15 (q, *J* = 6.7 Hz, 1H, PhCHCH₃), 3.68 (d, *J* = 14.8 Hz, 1H, PhCH₂), 3.61 (d, *J* = 14.8 Hz, 1H, PhCH₂), 1.63 (s, 9H, C(CH₃)₃), 1.44-1.16 (m, 6H, NCCH₂CH₂CH₂CN), 1.28 (d, *J* = 6.9 Hz, 3H, PhCHCH₃), 1.13 (s, 3H, NC(CH₃)₂), 1.01 (s, 3H, NC(CH₃)₂), 0.79 (s, 3H, NC(CH₃)₂), 0.62 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 170.4 (C, CO₂), 144.9 (C, *ipso*-Ph), 141.7 (C, *ipso*-Ph), 137.9 (C, *ipso*-Ph), 130.4 (CH, Ph), 129.0 (CH, Ph), 128.3 (CH, Ph), 128.0 (CH, Ph), 127.8 (CH, Ph), 127.4 (CH, Ph), 126.9 (CH, *p*-Ph), 126.8 (CH, *p*-Ph), 126.4 (CH, *p*-Ph), 82.9 (CH, CHOTMP), 80.6 (C, C(CH₃)₃), 65.2 (CH, PhCHN), 61.1 (C, NC(CH₃)₂), 60.0 (CH, PhCHCH₃), 59.9 (C, NC(CH₃)₂), 51.1 (CH₂, PhCH₂), 40.9 (CH₂, NCCH₂CH₂CH₂CN), 40.2 (CH₂, NCCH₂CH₂CH₂CN), 34.3 (CH₃, NC(CH₃)₂), 33.7 (CH₃, NC(CH₃)₂), 28.6 (CH₃, C(CH₃)₃), 21.1 (CH₃, NC(CH₃)₂), 20.6 (CH₃, NC(CH₃)₂), 19.5 (CH₃, PhCHCH₃), 17.3 (CH₂, NCCH₂CH₂CH₂CN); *syn*-3-3i R_f(pentane/Et₂O 10:1) = 0.6; ¹H NMR (400 MHz, CDCl₃): δ 7.60-7.52 (m, 2H, Ph), 7.46-7.37 (m, 2H, Ph), 7.37-7.12 (m, 9H, Ph), 7.12-7.04 (m, 2H, Ph), 5.13 (d, *J* = 10.2 Hz, 1H, CHOTMP), 4.51 (q, *J* = 6.9 Hz, 1H, PhCHCH₃), 4.33 (d, *J* = 10.2 Hz, 1H, PhCHN), 4.05 (d, *J* = 15.0 Hz, 1H, PhCH₂), 3.99 (d, *J* = 14.9 Hz, 1H, PhCH₂), 1.59-1.35 (m, 6H, NCCH₂CH₂CH₂CN), 1.35 (s, 3H, NC(CH₃)₂), 1.29 (s, 3H, NC(CH₃)₂), 1.24 (s, 3H, NC(CH₃)₂), 1.10 (s, 3H, NC(CH₃)₂), 1.05 (s, 9H, C(CH₃)₃),

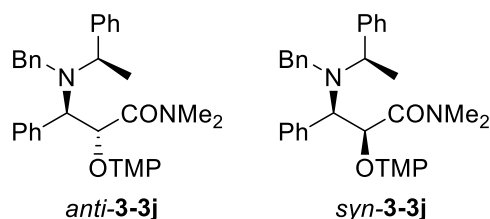
1.02 (d, $J = 6.9$ Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.5 (C, CO₂), 145.8 (C, *ipso*-Ph), 142.1 (C, *ipso*-Ph), 138.9 (C, *ipso*-Ph), 129.5 (CH, Ph), 128.4 (CH, Ph), 128.24 (CH, Ph), 128.20 (CH, Ph), 128.17 (CH, Ph), 127.9 (CH, Ph), 127.2 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 126.5 (CH, *p*-Ph), 84.4 (CH, CHOTMP), 80.3 (C, C(CH₃)₃), 64.0 (CH, PhCHN), 61.3 (C, NC(CH₃)₂), 60.2 (C, NC(CH₃)₂), 58.8 (CH, PhCHCH₃), 50.6 (CH₂, PhCH₂), 41.1 (CH₂, NCCH₂CH₂CH₂CN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 34.6 (CH₃, NC(CH₃)₂), 33.7 (CH₃, NC(CH₃)₂), 27.7 (CH₃, C(CH₃)₃), 21.61 (CH₃, NC(CH₃)₂), 21.56 (CH₃, NC(CH₃)₂), 18.6 (CH₃, PhCHCH₃), 17.5 (CH₂, NCCH₂CH₂CH₂CN).

(3*S*)-tert-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-3-phenylpropanoate (3-4i):



The analytical data are in agreement with those reported in the literature.^[115]

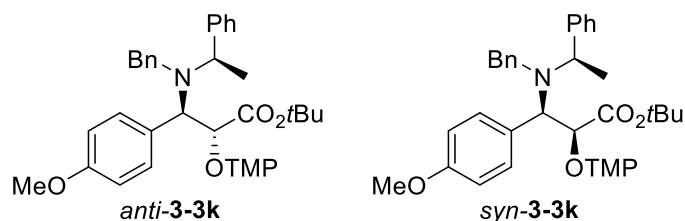
(2*R*,3*R*)- and (2*S*,3*R*)-3-[*N*-Benzyl-*N*-((*R*)-1-phenylethyl)amino]-*N*',*N*'-dimethyl-3-phenyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanamide (3-3j):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 3:1) to afford 256 mg (73%) of **3-3j** as a separable 4:1 *anti*/*syn*-mixture. IR: 3036, 3014, 1659, 1498, 1457, 1137, 1031, 735, 702 cm⁻¹; MS (+ESI) m/z , (%): 542 (100, M+H⁺), 300 (15, M+H⁺-TMPOCH₂CONMe₂); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₃₅H₄₈N₃O₂ 542.3741; Found 542.3742; Anal. Calcd for C₃₅H₄₇N₃O₂: C, 77.59; H, 8.74; N, 7.76; Found: C, 77.38; H, 8.66; N, 7.57; *anti*-**3-3j** Colorless solid. Mp: 140-142 °C (dec. without melting); R_f(hexane/EtOAc 3:1) = 0.3; [α]_D²⁰ +96.8 (*c* 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.51-7.45 (m, 2H, Ph), 7.36-7.20 (m, 7H, Ph), 7.19-7.06 (m, 6H, Ph), 4.97 (d, $J = 9.8$ Hz, 1H, CHOTMP), 4.72 (d, $J = 9.8$ Hz, 1H, PhCHN), 4.20 (d, $J = 15.6$ Hz, 1H, PhCH₂), 4.08-3.96 (m, 2H, PhCH₂, PhCHCH₃), 2.92 (s, 3H, N(CH₃)₂), 2.84 (s, 3H, N(CH₃)₂), 1.40-1.06 (m, 9H,

NCCH₂CH₂CH₂CN, PhCHCH₃), 0.96 (s, 3H, NC(CH₃)₂), 0.90 (s, 3H, NC(CH₃)₂), 0.87 (s, 3H, NC(CH₃)₂), 0.21 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 171.4 (C, CO), 143.3 (C, *ipso*-Ph), 142.0 (C, *ipso*-Ph), 141.8 (C, *ipso*-Ph), 130.4 (CH, Ph), 128.7 (CH, Ph), 128.0 (CH, Ph), 127.9 (CH, Ph), 127.7 (CH, Ph), 127.6 (CH, Ph), 126.9 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 126.4 (CH, *p*-Ph), 77.9 (CH, CHOTMP), 65.6 (CH, PhCHN), 61.1 (C, NC(CH₃)₂), 59.8 (CH, PhCHCH₃), 59.6 (C, NC(CH₃)₂), 52.2 (CH₂, PhCH₂), 41.10 (CH₂, NCCH₂CH₂CH₂CN), 41.07 (CH₂, NCCH₂CH₂CH₂CN), 38.0 (CH₃, N(CH₃)₂), 36.3 (CH₃, N(CH₃)₂), 33.0 (CH₃, NC(CH₃)₂), 32.9 (CH₃, NC(CH₃)₂), 20.3 (CH₃, NC(CH₃)₂), 19.4 (CH₃, NC(CH₃)₂), 17.1 (CH₃, PhCHCH₃), 17.0 (CH₂, NCCH₂CH₂CH₂CN); ***syn*-3-3j** Colorless solid. Mp: 59-61 °C; R_f(hexane/EtOAc 3:1) = 0.4; [α]_D²⁰ -78.8 (c 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃, 0 °C): δ 7.68-7.15 (m, 15H, Ph), 4.86 (d, *J* = 9.1 Hz, 1H, CHOTMP), 4.58 (d, *J* = 9.0 Hz, 1H, PhCHN), 4.38 (q, *J* = 6.8 Hz, 1H, PhCHCH₃), 4.22 (d, *J* = 14.6 Hz, 1H, PhCH₂), 3.68 (d, *J* = 14.5 Hz, 1H, PhCH₂), 3.18 (s, 3H, N(CH₃)₂), 2.68 (s, 3H, N(CH₃)₂), 1.53-1.16 (m, 6H, NCCH₂CH₂CH₂CN), 1.03 (d, *J* = 6.9 Hz, 3H, PhCHCH₃), 0.96-0.85 (m, 12H, NC(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 0 °C) δ 171.8 (C, CO), 145.4 (C, *ipso*-Ph), 141.8 (C, *ipso*-Ph), 138.5 (C, *ipso*-Ph), 131.1 (CH, Ph), 128.6 (CH, Ph), 128.2 (CH, Ph), 128.1 (CH, 2 x Ph), 127.5 (CH, Ph), 126.7 (CH, *p*-Ph), 126.54 (CH, *p*-Ph), 126.47 (CH, *p*-Ph), 79.3 (CH, CHOTMP), 63.5 (CH, PhCHN), 60.9 (C, NC(CH₃)₂), 59.4 (C, NC(CH₃)₂), 57.2 (CH, PhCHCH₃), 52.3 (CH₂, PhCH₂), 40.7 (CH₂, NCCH₂CH₂CH₂CN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 38.7 (CH₃, N(CH₃)₂), 36.0 (CH₃, N(CH₃)₂), 32.8 (CH₃, NC(CH₃)₂), 32.6 (CH₃, NC(CH₃)₂), 20.6 (CH₃, NC(CH₃)₂), 20.5 (CH₃, NC(CH₃)₂), 17.1 (CH₂, NCCH₂CH₂CH₂CN), 16.3 (CH₃, PhCHCH₃).

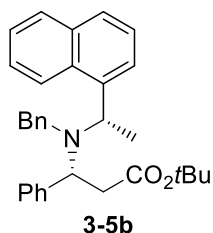
(2*R*,3*R*)- and (2*S*,3*R*)-Methyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-3-(*p*-methoxyphenyl)-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (3-3k):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 25:1 gradient to 10:1) to afford 258 mg (71%) of **3-3k** as a partially separable 2:1 *anti/syn*-mixture. IR: 2939, 1743, 1613, 1516, 1498, 1367, 1254, 1181, 1034, 749, 699 cm⁻¹; MS (+ESI) *m/z*, (%): 581 (15, M+Na⁺), 559 (5, M+H⁺), 424 (15, M+Na⁺-TEMPOH), 402 (20, M⁺-TEMPO), 330 (100,

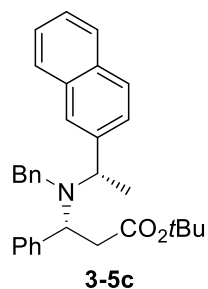
M+H⁺–TMPOCH₂CO₂Me), 226 (45, M+H⁺–TMPOCH₂CO₂Me–PhCH=CH₂); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₃₅H₄₆N₂O₄Na 581.3350; Found 581.3351; Anal. Calcd for C₃₅H₄₆N₂O₄: C, 75.23; H, 8.30; N, 5.01; Found: C, 75.19; H, 8.44; N, 4.79; **anti-3-3k** Colorless solid. Mp: 49-51 °C; R_f(pentane/Et₂O 5:1) = 0.5; [α]_D²⁰ +24.9 (*c* 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 7.36-7.17 (m, 12H, Ar), 6.92-6.86 (m, 2H, *m*-Ar), 4.86 (d, *J* = 10.1 Hz, 1H, CHOTMP), 4.24 (d, *J* = 10.1 Hz, 1H, ArCHN), 4.16 (d, *J* = 13.6 Hz, 1H, PhCH₂), 3.98 (q, *J* = 6.9 Hz, 1H, PhCHCH₃), 3.93 (d, *J* = 13.6 Hz, 1H, PhCH₂), 3.84 (s, 3H, ArOCH₃), 3.52 (s, 3H, CO₂CH₃), 1.40-1.09 (m, 6H, NCCH₂CH₂CH₂CN), 1.02 (s, 3H, NC(CH₃)₂), 1.00 (d, *J* = 7.0 Hz, 3H, PhCHCH₃), 0.89 (s, 3H, NC(CH₃)₂), 0.78 (s, 3H, NC(CH₃)₂), 0.44 (s, 3H, NC(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 171.93 (C, CO₂), 158.6 (C, C_{Ar}OMe), 143.3 (C, *ipso*-Ph), 140.5 (C, *ipso*-Ph), 132.5 (C, *ipso*-Ar), 131.0 (CH, *o*-Ar), 129.1 (CH, Ph), 128.6 (CH, Ph), 128.21 (CH, Ph), 127.8 (CH, Ph), 126.9 (CH, *p*-Ph), 126.7 (CH, *p*-Ph), 113.1 (CH, *m*-Ar), 84.1 (CH, CHOTMP), 62.3 (CH, ArCHN), 60.93 (C, NC(CH₃)₂), 59.5 (C, NC(CH₃)₂), 57.3 (CH, PhCHCH₃), 55.4 (CH₃, ArOCH₃), 52.2 (CH₂, PhCH₂), 51.3 (CH₃, CO₂CH₃), 40.7 (CH₂, NCCH₂CH₂CH₂CN), 40.34 (CH₂, NCCH₂CH₂CH₂CN), 34.4 (CH₃, NC(CH₃)₂), 33.1 (CH₃, NC(CH₃)₂), 20.2 (CH₃, NC(CH₃)₂), 19.7 (CH₃, NC(CH₃)₂), 17.0 (CH₂, NCCH₂CH₂CH₂CN), 14.7 (CH₃, PhCHCH₃); **syn-3-3k** R_f(pentane/Et₂O 5:1) = 0.4; ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 7.54-7.49 (m, 2H, Ar), 7.44-7.39 (m, 2H, Ar), 7.38-7.17 (m, 8H, Ar), 6.82-6.75 (m, 2H, *m*-Ar), 4.85 (d, *J* = 9.4 Hz, 1H, CHOTMP), 4.41-4.35 (m, 2H, ArCHN, PhCHCH₃), 4.03 (d, *J* = 14.8 Hz, 1H, PhCH₂), 3.82 (d, *J* = 15.0 Hz, 1H, PhCH₂), 3.79 (s, 3H, ArOCH₃), 3.38 (s, 3H, CO₂CH₃), 1.57-1.12 (m, 6H, NCCH₂CH₂CH₂CN), 1.10 (s, 3H, NC(CH₃)₂), 1.07-0.94 (m, 12H, PhCHCH₃, NC(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 171.88 (C, CO₂), 158.4 (C, C_{Ar}OMe), 145.2 (C, *ipso*-Ph), 141.7 (C, *ipso*-Ph), 131.1 (CH, *o*-Ar), 130.3 (C, *ipso*-Ar), 128.34 (CH, Ph), 128.30 (CH, Ph), 128.17 (CH, Ph), 128.0 (CH, Ph), 126.63 (CH, *p*-Ph), 126.59 (CH, *p*-Ph), 113.0 (CH, *m*-Ar), 84.9 (CH, CHOTMP), 62.7 (CH, ArCHN), 60.94 (C, NC(CH₃)₂), 59.7 (C, NC(CH₃)₂), 57.8 (CH, PhCHCH₃), 55.2 (CH₃, ArOCH₃), 51.20 (CH₃, CO₂CH₃), 51.17 (CH₂, PhCH₂), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 40.31 (CH₂, NCCH₂CH₂CH₂CN), 33.9 (CH₃, NC(CH₃)₂), 33.3 (CH₃, NC(CH₃)₂), 20.91 (CH₃, NC(CH₃)₂), 20.85 (CH₃, NC(CH₃)₂), 17.4 (CH₂, NCCH₂CH₂CH₂CN), 14.7 (CH₃, PhCHCH₃).

(3*R*)-tert-Butyl 3-{*N*-benzyl-*N*-[(*S*)-1-(naphthalen-1-yl)ethyl]amino}-3-phenylpropanoate (3-5b):



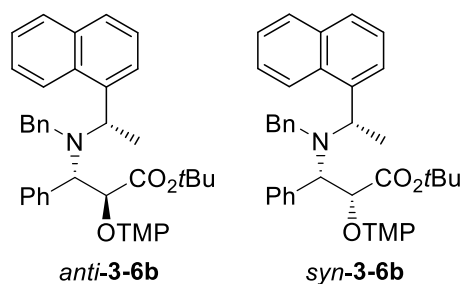
*n*BuLi (650 μ L, 1.04 mmol, 1.6M in hexanes) was added to a stirred solution of **3-2b** (272 mg, 1.04 mmol) in dry THF (6 mL) at -78 $^{\circ}$ C under an argon atmosphere. A LiCl solution (65 μ L, 0.0065 mmol, 0.1M in dry THF) was added using a syringe. After stirring for 25 min, a solution of **3-1i** (133 mg, 0.65 mmol) in dry THF (1 mL) was added using a syringe. The mixture was stirred at -78 $^{\circ}$ C for 120 min, quenched with four drops of saturated NH_4Cl solution, stirred for 5 min, diluted with diethyl ether to the double volume and filtered through a plug of silica gel. The solvent was evaporated and the crude product was purified by flash chromatography (hexane/EtOAc 50:1 gradient to 10:1) to afford 303 mg (92%) of **3-5b** as a colorless oil. R_f (hexane/EtOAc 10:1) = 0.4; $[\alpha]_D^{20} +46.2$ (c 0.5, CHCl_3); IR: 2984, 2941, 1727, 1604, 1499, 1458, 1371, 1260, 1146, 1079, 963, 802, 781, 755, 734, 700 cm^{-1} ; MS (+ESI) m/z , (%): 488 (14, $\text{M}+\text{Na}^+$), 466 (100, $\text{M}+\text{H}^+$), 312 (5, $\text{M}+\text{H}^+-\text{NapCH}=\text{CH}_2$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{32}\text{H}_{36}\text{NO}_2$ 466.2741; Found 466.2741; Anal. Calcd for $\text{C}_{32}\text{H}_{35}\text{NO}_2$: C, 82.54; H, 7.58; N, 3.01; Found: C, 82.28; H, 7.72; N, 2.75; ^1H NMR (400 MHz, CDCl_3): δ 8.17-8.09 (m, 1H, Ar), 7.84-7.77 (m, 1H, Ar), 7.74-7.62 (m, 2H, Ar), 7.47-7.08 (m, 13H, Ar), 4.71 (q, J = 6.7 Hz, 1H, NapCHCH_3), 4.47 (dd, J = 10.2, 5.1 Hz, 1H, CHNCH_2CO), 3.84 (d, J = 15.2 Hz, 1H, PhCH_2), 3.74 (d, J = 15.1 Hz, 1H, PhCH_2), 2.59 (dd, J = 14.6, 5.1 Hz, 1H, CH_2CO_2), 2.51 (dd, J = 14.6, 10.2 Hz, 1H, CH_2CO_2), 1.46 (d, J = 6.8 Hz, 3H, NapCHCH_3), 1.11 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2 (C, CO_2), 142.2 (C, *ipso*-Ar), 141.4 (C, *ipso*-Ar), 140.3 (C, *ipso*-Ar), 134.1 (C, Ar), 132.0 (C, Ar), 128.8 (CH, Ar), 128.7 (CH, Ar), 128.14 (CH, Ar), 128.10 (CH, Ar), 128.0 (CH, Ar), 127.8 (CH, Ar), 127.4 (CH, Ar), 126.4 (CH, Ar), 125.42 (CH, Ar), 125.35 (CH, Ar), 125.33 (CH, Ar), 125.32 (CH, Ar), 124.8 (CH, Ar), 80.2 (C, $\text{C}(\text{CH}_3)_3$), 60.5 (CH, CHNCH_2CO), 55.7 (CH, NapCHCH_3), 51.8 (CH_2 , PhCH_2), 38.1 (CH_2 , CH_2CO), 27.8 (CH_3 , $\text{C}(\text{CH}_3)_3$), 17.9 (CH_3 , NapCHCH_3).

(3*R*)-tert-Butyl 3-{*N*-benzyl-*N*-[(*S*)-1-(naphthalen-2-yl)ethyl]amino}-3-phenylpropanoate (3-5c):



Prepared according to the same procedure as **3-5b** by using amide **3-2c**. The solvent was evaporated and the crude product was purified by flash chromatography (hexane/EtOAc 50:1 gradient to 10:1) to afford 96 mg (29%) of **3-5c** as a colorless oil. R_f (hexane/EtOAc 5:1) = 0.5; $[\alpha]_D^{20}$ -39.9 (c 0.3, CHCl_3); IR: 3059, 3028, 2974, 2930, 1721, 1494, 1454, 1366, 1298, 1256, 1149, 1078, 1028, 961, 857, 842, 819, 749, 698 cm^{-1} ; MS (+ESI) m/z , (%): 488 (100, $\text{M}+\text{Na}^+$), 466 (50, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{32}\text{H}_{35}\text{NO}_2\text{Na}$ 488.2560; Found 488.2560; Anal. Calcd for $\text{C}_{32}\text{H}_{35}\text{NO}_2$: C, 82.54; H, 7.58; N, 3.01; Found: C, 82.28; H, 7.72; N, 2.75; ^1H NMR (400 MHz, CDCl_3): δ 7.85-7.61 (m, 5H, Ar), 7.48-7.10 (m, 12H, Ar), 4.44 (dd, J = 10.2, 5.0 Hz, 1H, CHNCH_2CO), 4.15 (q, J = 6.8 Hz, 1H, NapCHCH_3), 3.75 (d, J = 14.9 Hz, 1H, PhCH_2), 3.67 (d, J = 14.9 Hz, 1H, PhCH_2), 2.61 (dd, J = 14.5, 5.0 Hz, 1H, CH_2CO_2), 2.51 (dd, J = 14.4, 10.3 Hz, 1H, CH_2CO_2), 1.35 (d, J = 6.8 Hz, 3H, NapCHCH_3), 1.17 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2 (C, CO_2), 141.95 (C, *ipso*-Ar), 141.88 (C, *ipso*-Ar), 141.87 (C, *ipso*-Ar), 133.4 (C, Ar), 132.7 (C, Ar), 128.5 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 128.1 (CH, Ar), 128.0 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, Ar), 127.3 (CH, Ar), 127.2 (CH, Ar), 126.6 (CH, Ar), 125.94 (CH, Ar), 125.88 (CH, Ar), 125.6 (CH, Ar), 80.3 (C, $\text{C}(\text{CH}_3)_3$), 60.4 (CH, CHNCH_2CO), 57.3 (CH, NapCHCH_3), 51.1 (CH_2 , PhCH_2), 39.3 (CH_2 , CH_2CO), 27.9 (CH_3 , $\text{C}(\text{CH}_3)_3$), 15.9 (CH_3 , NapCHCH_3).

(2*S*,3*S*)- and (2*R*,3*S*)-*tert*-Butyl 3-{*N*-benzyl-*N*-[(*S*)-1-(naphthalen-1-yl)ethyl]amino}-3-phenyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (3-6b**):**



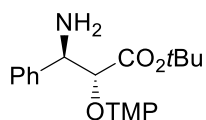
Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 50:1 gradient to 10:1) to afford 210 mg (52%) of **3-6b** as a separable 1:1 *anti*/*syn*-mixture. Deprotonation/oxygenation of **3-5b** furnished 195 mg (72%) of **3-6b** as a 1:3 *anti*/*syn*-mixture. IR: 2984, 2939, 1744, 1604, 1458, 1370, 1258, 1156, 911, 801, 747, 734, 702 cm⁻¹; MS (+ESI) *m/z*, (%): 643 (95, M+Na⁺), 621 (58, M+H⁺), 350 (100, M⁺-TMPOCH₂CO₂*t*Bu); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₄₁H₅₂N₂O₃Na 643.3870; Found 643.3873; Anal. Calcd for C₄₁H₅₂N₂O₃: C, 79.32; H, 8.44; N, 4.51; Found: C, 79.04; H, 8.41; N, 4.30; *anti*-**3-6b** Colorless solid. Mp: 68-70 °C; R_f(hexane/EtOAc 10:1) = 0.6; [α]_D²⁰ -16.7 (*c* 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 8.06 (d, *J* = 8.3 Hz, 1H, Ar), 7.80-7.71 (m, 1H, Ar), 7.68-7.60 (m, 1H, Ar), 7.57-7.50 (m, 1H, Ar), 7.42-7.21 (m, 6H, Ar), 7.21-7.00 (m, 7H, Ar), 4.91 (q, *J* = 6.6 Hz, 1H, NapCHCH₃), 4.84 (d, *J* = 9.5 Hz, 1H, PhCHN), 4.72 (d, *J* = 9.5 Hz, 1H, CHOTMP), 3.76 (d, *J* = 14.8 Hz, 1H, PhCH₂), 3.60 (d, *J* = 14.8 Hz, 1H, PhCH₂), 1.59 (d, *J* = 6.9 Hz, 3H, NapCHCH₃), 1.57 (s, 9H, C(CH₃)₃), 1.42-1.13 (m, 6H, NCCH₂CH₂CH₂CN), 1.04 (s, 6H, NC(CH₃)₂), 0.71 (s, 3H, NC(CH₃)₂), 0.63 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 170.7 (C, CO₂), 141.7 (C, *ipso*-Ar), 141.3 (C, *ipso*-Ar), 137.6 (C, *ipso*-Ar), 134.0 (C, Ar), 132.0 (C, Ar), 130.5 (CH, Ar), 128.9 (CH, Ar), 128.7 (CH, Ar), 127.6 (CH, Ar), 127.5 (CH, Ar), 127.34 (CH, Ar), 126.9 (CH, Ar), 126.3 (CH, Ar), 125.6 (CH, 2 x Ar), 125.21 (CH, Ar), 125.15 (CH, Ar), 124.2 (CH, Ar), 83.0 (CH, CHOTMP), 80.7 (C, C(CH₃)₃), 64.6 (CH, PhCHN), 61.07 (C, NC(CH₃)₂), 59.9 (C, NC(CH₃)₂), 57.1 (CH, NapCHCH₃), 52.4 (CH₂, PhCH₂), 40.8 (CH₂, NCCH₂CH₂CH₂CN), 40.1 (CH₂, NCCH₂CH₂CH₂CN), 34.2 (CH₃, NC(CH₃)₂), 33.70 (CH₃, NC(CH₃)₂), 28.6 (CH₃, C(CH₃)₃), 20.94 (CH₃, NC(CH₃)₂), 20.89 (CH₃, NapCHCH₃), 20.7 (CH₃, NC(CH₃)₂), 17.3 (CH₂, NCCH₂CH₂CH₂CN); *syn*-**3-6b** Colorless solid. Mp: 68-70 °C; R_f(hexane/EtOAc 10:1) = 0.5; [α]_D²⁰ +33.5 (*c* 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 8.23-8.14 (m, 1H, Ar), 7.85-7.77 (m, 1H, Ar), 7.75-7.65 (m, 2H, Ar), 7.48-7.34 (m, 5H, Ar), 7.33-7.16 (m, 6H, Ar), 7.16-7.06 (m, 2H, Ar), 5.28 (q, *J* = 6.9 Hz, 1H, NapCHCH₃), 5.07 (d, *J* = 10.0 Hz, 1H,

CHOTMP), 4.38 (d, $J = 10.0$ Hz, 1H, PhCHN), 4.29 (d, $J = 15.3$ Hz, 1H, PhCH₂), 4.16 (d, $J = 15.3$ Hz, 1H, PhCH₂), 1.44-1.18 (m, 6H, NCCH₂CH₂CH₂CN), 1.29 (d, $J = 6.9$ Hz, 3H, NapCHCH₃), 1.13 (s, 3H, NC(CH₃)₂), 1.11 (s, 3H, NC(CH₃)₂), 1.04 (s, 12H, C(CH₃)₃, NC(CH₃)₂), 1.02 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 169.6 (C, CO₂), 142.2 (C, *ipso*-Ar), 142.0 (C, *ipso*-Ar), 138.6 (C, *ipso*-Ar), 134.2 (C, Ar), 131.7 (C, Ar), 129.7 (CH, Ar), 128.8 (CH, Ar), 128.6 (CH, Ar), 128.2 (CH, Ar), 127.9 (CH, Ar), 127.29 (CH, 2 x Ar), 126.6 (CH, Ar), 125.51 (CH, Ar), 125.46 (CH, Ar), 125.43 (CH, Ar), 125.17 (CH, Ar), 124.4 (CH, Ar), 84.8 (CH, CHOTMP), 80.3 (C, C(CH₃)₃), 65.2 (CH, PhCHN), 61.13 (C, NC(CH₃)₂), 60.1 (C, NC(CH₃)₂), 57.0 (CH, NapCHCH₃), 51.9 (CH₂, PhCH₂), 41.0 (CH₂, NCCH₂CH₂CH₂CN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 34.3 (CH₃, NC(CH₃)₂), 33.72 (CH₃, NC(CH₃)₂), 27.7 (CH₃, C(CH₃)₃), 21.3 (CH₃, NC(CH₃)₂), 21.1 (CH₃, NC(CH₃)₂), 20.2 (CH₃, NapCHCH₃), 17.4 (CH₂, NCCH₂CH₂CH₂CN).

(2*R*,3*R*)-tert-Butyl

3-amino-3-phenyl-2-[(2,2,6,6-tetramethylpiperidin-1-

yl)oxy]propanoate (*anti*-3-8):

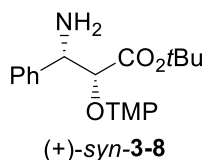


(-)-*anti*-3-8

Pearlman's catalyst (12.4 mg) was added to a solution of *anti*-3-3i (35.4 mg, 0.0621 mmol) in MeOH (0.8 mL) and the mixture was stirred vigorously under 20 bar of H₂ gas at 25 °C for 48 h. The reaction mixture was filtered through Celite[®] with MeOH and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (hexane/EtOAc 10:1 gradient to 100% EtOAc) to afford 13 mg (57%) of *anti*-3-8 as a colorless solid. Mp: 106-108 °C; R_f(hexane/EtOAc 2:1) = 0.2; [α]_D²⁰ -6.9 (c 0.2, CHCl₃); IR: 3373, 3311, 3091, 3066, 2976, 2933, 2873, 2849, 1720, 1605, 1497, 1482, 1467, 1456, 1393, 1376, 1368, 1302, 1261, 1156, 920, 699 cm⁻¹; MS (+ESI) m/z , (%): 753 (5, 2M+H⁺), 399 (10, M+Na⁺), 377 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₂₂H₃₇N₂O₃ 377.2799; Found 377.2799; ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.20 (m, 5H, Ph), 4.64 (d, $J = 4.9$ Hz, 1H, PhCHN), 4.43 (d, $J = 5.0$ Hz, 1H, CHOTMP), 1.80 (br s, 2H, NH₂), 1.63-1.12 (m, 18H, NCCH₂CH₂CH₂CN, NC(CH₃)₂), 1.11 (s, 9H, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 170.4 (C, CO₂), 139.6 (C, *ipso*-Ph), 128.1 (CH, Ph), 127.0 (CH, *p*-Ph), 126.8 (CH, Ph), 88.2 (CH, CHOTMP), 81.1 (C, C(CH₃)₃), 60.3 (C, NC(CH₃)₂), 59.8 (C, NC(CH₃)₂), 56.6 (CH, PhCHN), 40.32 (CH₂, NCCH₂CH₂CH₂CN), 40.26 (CH₂, NCCH₂CH₂CH₂CN), 34.1 (CH₃, NC(CH₃)₂), 33.6 (CH₃,

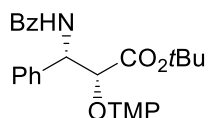
NC(CH₃)₂), 27.6 (CH₃, C(CH₃)₃), 20.4 (CH₃, NC(CH₃)₂), 20.3 (CH₃, NC(CH₃)₂), 17.2 (CH₂, NCCH₂CH₂CH₂CN).

(2*R*,3*S*)-tert-Butyl 3-amino-3-phenyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (*syn*-3-8):



Pearlman's catalyst (22 mg) was added to a solution of *syn*-3-6b (73 mg, 0.119 mmol) in EtOH (1.8 mL) and the mixture was stirred vigorously under 10 bar of H₂ gas at 25 °C for 17 h. The reaction mixture was filtered through Celite[®] with EtOH and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (hexane/EtOAc 10:1 gradient to 100% EtOAc) to afford 34 mg (76%) of *syn*-3-8 as a colorless oil. R_f(hexane/EtOAc 2:1) = 0.2; [α]_D²⁰ +79.1 (*c* 0.2, CHCl₃); IR: 3406, 3379, 3316, 3088, 3065, 3035, 2978, 2933, 2873, 2852, 1727, 1604, 1585, 1494, 1477, 1467, 1456, 1393, 1377, 1368, 1308, 1275, 1196, 1155, 1048, 909, 843, 701 cm⁻¹; MS (+ESI) *m/z*, (%): 775 (75, 2M+Na⁺), 399 (88, M+Na⁺), 377 (100, M+H⁺), 321 (10, M+H⁺-(CH₃)₂C=CH₂); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₂₂H₃₆N₂O₃Na 399.2618; Found 399.2613; ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.35 (m, 2H, Ph), 7.31-7.20 (m, 3H, Ph), 4.47 (d, *J* = 8.6 Hz, 1H, CHOTMP), 4.28 (d, *J* = 8.5 Hz, 1H, PhCHN), 1.78 (s, 2H, NH₂), 1.67-1.11 (m, 18H, NCCH₂CH₂CH₂CN, NC(CH₃)₂), 1.09 (s, 9H, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 170.8 (C, CO₂), 140.3 (C, *ipso*-Ph), 128.6 (CH, Ph), 128.3 (CH, Ph), 127.9 (CH, *p*-Ph), 89.0 (CH, CHOTMP), 80.9 (C, C(CH₃)₃), 61.2 (C, NC(CH₃)₂), 59.6 (C, NC(CH₃)₂), 58.8 (CH, PhCHN), 40.9 (CH₂, NCCH₂CH₂CH₂CN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 34.2 (CH₃, NC(CH₃)₂), 33.9 (CH₃, NC(CH₃)₂), 27.6 (CH₃, C(CH₃)₃), 20.5 (CH₃, NC(CH₃)₂), 20.3 (CH₃, NC(CH₃)₂), 17.1 (CH₂, NCCH₂CH₂CH₂CN).

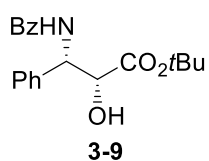
(2*R*,3*S*)-tert-Butyl 3-benzamido-3-phenyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate:



Ester *syn*-3-8 (33.9 mg, 0.09 mmol) was dissolved in CH₂Cl₂ (2 mL), NEt₃ (27.3 mg, 0.27 mmol) was added dropwise and the mixture was stirred at room temperature for 15 min.

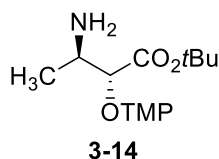
Benzoyl chloride (12.7 mg, 0.09 mmol) was added dropwise at room temperature and stirring was continued for 2 h. The solution was diluted with CH₂Cl₂ (5 mL) and water was added. The organic layer was separated and aqueous extracted with CH₂Cl₂ (2 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (hexane/EtOAc 10:1 gradient to 2:1) afforded 40.5 mg (94%) of the *N*-benzoylated ester as a colorless solid. Mp: 50-52 °C; *R*_f(hexane/EtOAc 2:1) = 0.8; [α]_D²⁰ -35.8 (*c* 0.5, CHCl₃); IR: 3418, 3063, 2975, 2931, 2872, 1737, 1717, 1700, 1653, 1602, 1579, 1509, 1484, 1457, 1393, 1366, 1332, 1289, 1258, 1210, 1155, 1095, 1077, 1056, 1030, 993, 958, 911, 877, 843, 799, 732 cm⁻¹; MS (+ESI) *m/z*, (%): 983 (30, 2M+Na⁺), 503 (100, M+Na⁺); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₂₉H₄₀N₂O₄Na 503.2880; Found 503.2875; ¹H NMR (500 MHz, CDCl₃, 5°C): 7.94-7.88 (m, 2H, Ph), 7.57-7.45 (m, 6H, Ph), 7.34-7.23 (m, 3H, Ph, NH), 6.03 (dd, *J* = 8.8, 3.7 Hz, 1H, PhCHN), 4.70 (d, *J* = 3.8 Hz, CHOTMP), 1.64-1.40 (m, 6H, NCCH₂CH₂CH₂CN), 1.31 (s, 3H, NC(CH₃)₂), 1.26 (s, 9H, C(CH₃)₃), 1.24 (s, 3H, NC(CH₃)₂), 1.17 (s, 6H, NC(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5°C) δ 171.1 (C, CO₂), 166.2 (C, CO), 138.2 (C, *ipso*-Ph), 134.2 (C, *ipso*-Ph), 131.8 (CH, Ph), 128.8 (CH, Ph), 128.3 (CH, Ph), 127.5 (CH, Ph), 127.2 (CH, Ph), 126.9 (CH, Ph), 87.9 (CH, CHOTMP), 82.5 (C, C(CH₃)₃), 60.9 (C, NC(CH₃)₂), 60.3 (C, NC(CH₃)₂), 53.2 (CH, PhCHN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 40.4 (CH₂, NCCH₂CH₂CH₂CN), 34.6 (CH₃, NC(CH₃)₂), 33.4 (CH₃, NC(CH₃)₂), 27.8 (CH₃, C(CH₃)₃), 20.8 (CH₃, NC(CH₃)₂), 20.3 (CH₃, NC(CH₃)₂), 17.1 (CH₂, NCCH₂CH₂CH₂CN).

(2*R*,3*S*)-tert-Butyl 3-benzamido-2-hydroxy-3-phenylpropanoate (3-9):



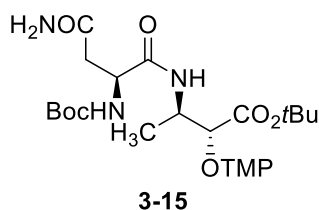
N-Benzoyl ester (39.6 mg, 0.0824 mmol) was heated with zinc dust (269 mg, 4.12 mmol) in AcOH/THF (1.5/0.5 mL) at 60 °C for 2 h. The reaction mixture was diluted with CH₂Cl₂ (5 mL) and filtered through Celite[®]. The filtrate was washed with saturated K₂CO₃ solution (pH = 10) and twice with H₂O, dried over MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc 2:1) to afford 22.1 mg (79%) of **3-9** as a colorless solid. Mp: 105-106 °C; [α]_D²⁰ -24.1 (*c* 1.0, CH₂Cl₂), Ref.^[44a] [α]_D²⁰ -21.3 (*c* 1.0, CH₂Cl₂); The NMR data correspond to those reported in the literature.^[44a]

(2R,3R)-tert-Butyl 3-amino-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]butanoate (3-14):



Pearlman's catalyst (26 mg) was added to a solution of *anti*-**3-3b** (75 mg, 0.147 mmol) in EtOH (1 mL) and the mixture was stirred vigorously under 10 bar of H₂ gas at 25 °C for 24 h. The reaction mixture was diluted with EtOH, filtered through Celite[®] (eluent EtOH) and concentrated *in vacuo* to afford 45 mg (96%) of **3-14** as a pale yellow oil. R_f (EtOAc) = 0.4; $[\alpha]_D^{20} +39.9$ (c 0.5, CHCl₃); IR: 3371, 3306, 2976, 2936, 2873, 2851, 1724, 1598, 1472, 1465, 1457, 1393, 1381, 1376, 1368, 1363, 1256, 1156, 1059, 914 cm⁻¹; MS (+ESI) m/z , (%): 337 (18, M+Na⁺), 315 (100, M+H⁺); HRMS (+ESI) m/z : [M+Na⁺] Calcd for C₁₇H₃₄N₂O₃Na 337.2462; Found 337.2462; Anal. Calcd for C₁₇H₃₄N₂O₃: C, 64.93; H, 10.90; N, 8.91; Found: C, 64.75; H, 10.89; N, 8.66; ¹H NMR (400 MHz, CDCl₃): δ 4.05 (d, J = 4.4 Hz, 1H, CHOTMP), 3.54-3.43 (m, 1H, CH₃CHN), 1.72 (s, 2H, NH₂), 1.48 (s, 9H, C(CH₃)₃), 1.47-1.23 (m, 6H, NCCH₂CH₂CH₂CN), 1.21-1.09 (m, 12H, NC(CH₃)₂), 1.06 (d, J = 6.9 Hz, 3H, CH₃CHN); ¹³C NMR (100 MHz, CDCl₃) δ 170.8 (C, CO₂), 88.7 (CH, CHOTMP), 81.5 (C, C(CH₃)₃), 60.2 (C, NC(CH₃)₂), 59.8 (C, NC(CH₃)₂), 49.0 (CH, CH₃CHN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 34.0 (CH₃, NC(CH₃)₂), 33.7 (CH₃, NC(CH₃)₂), 28.3 (CH₃, C(CH₃)₃), 20.5 (CH₃, NC(CH₃)₂), 20.3 (CH₃, NC(CH₃)₂), 19.1 (CH₃, CH₃CHN), 17.3 (CH₂, NCCH₂CH₂CH₂CN).

(2R,3R)-tert-Butyl 3-{N-[N-(tert-butoxycarbonyl)-(S)-asparaginy]amino}-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]butanoate (3-15):



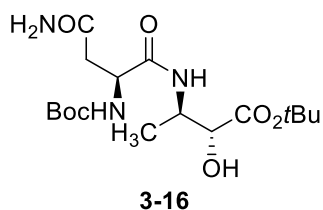
A mixture of **3-14** (45 mg, 0.143 mmol), *N*-Boc-L-asparagine (40 mg, 0.172 mmol) and HATU (71 mg, 0.186 mmol) in dry *N,N*-dimethylformamide (2 mL) was cooled to 0 °C and *N,N*-diisopropylethylamine (90 μ L, 0.515 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and poured into water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with 10% NaHCO₃ solution and brine, dried over MgSO₄, and concentrated *in vacuo*. Purification of the crude

product by flash chromatography (EtOAc) afforded 70 mg (93%) of **3-15** as a colorless solid. Mp: 50-52 °C; R_f (EtOAc) = 0.7; $[\alpha]_D^{20} +31.4$ (c 0.5, $(CH_3)_2CO$); IR: 3403, 2986, 2943, 1724, 1675, 1529, 1461, 1372, 1326, 1257, 1165, 1054, 1028, 962, 915, 848, 737 cm^{-1} ; MS (+ESI) m/z , (%): 551 (66, $M+Na^+$), 529 (100, $M+H^+$); HRMS (+ESI) m/z : $[M+H^+]$ Calcd for $C_{26}H_{49}N_4O_7$ 529.3596; Found 529.3597; ^1H NMR (400 MHz, CD_3CN): δ 7.38 (d, J = 8.3 Hz, 1H, NH), 6.48 (br s, 1H, NH_2), 6.19 (d, J = 4.9 Hz, 1H, $NHBoc$), 5.99 (br s, 1H, NH_2), 4.66-4.53 (m, 1H, CH_3CHN), 4.50-4.37 (m, 1H, CH_2CHN), 4.22 (d, J = 4.8 Hz, 1H, $CHOTMP$), 2.71 (dd, J = 15.6, 5.7 Hz, 1H, CH_2CO), 2.67 (dd, J = 15.8, 6.8 Hz, 1H, CH_2CO), 1.59 (s, 9H, $C(CH_3)_3$), 1.56-1.33 (m, 6H, $NCCH_2CH_2CH_2CN$), 1.54 (s, 9H, $C(CH_3)_3$), 1.30-1.16 (br m, 12H, $NC(CH_3)_2$), 1.13 (d, J = 6.9 Hz, 3H, CH_3CHN); ^{13}C NMR (100 MHz, CD_3CN) δ 173.6 (C, CO), 172.1 (C, CO), 171.8 (C, CO), 156.4 (s, NCO_2), 86.7 (CH, $CHOTMP$), 83.3 (C, $C(CH_3)_3$), 80.4 (C, $C(CH_3)_3$), 61.2 (C, $NC(CH_3)_2$), 60.4 (C, $NC(CH_3)_2$), 52.8 (CH, CH_2CHN), 47.4 (CH, CH_3CHN), 41.0 (CH_2 , $NCCH_2CH_2CH_2CN$), 37.6 (CH_2 , CH_2CO), 34.3 (CH_3 , $NC(CH_3)_2$), 34.1 (CH_3 , $NC(CH_3)_2$), 28.6 (CH_3 , $C(CH_3)_3$), 28.3 (CH_3 , $C(CH_3)_3$), 20.6 (CH_3 , $NC(CH_3)_2$), 20.3 (CH_3 , $NC(CH_3)_2$), 17.8 (CH_2 , $NCCH_2CH_2CH_2CN$), 17.5 (CH_3 , CH_3CHN).

(2R,3R)-tert-Butyl

3- $\{[N-(tert-butoxycarbonyl)-(S)$ -asparaginyl]amino-2-

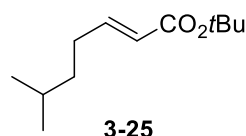
hydroxybutanoate (3-16):



Dipeptide **3-15** (68 mg, 0.129 mmol) was heated with zinc dust (422 mg, 6.45 mmol) in AcOH/THF (1.8/0.6 mL) at 60 °C for 5 h. The reaction mixture was diluted with EtOAc, filtered through a short pad of K_2CO_3 and concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc) to afford 38 mg (75%) of **3-16** as a colorless solid. Mp: 109-110 °C; R_f (EtOAc) = 0.2; $[\alpha]_D^{20} +2.8$ (c 0.2, DMSO); IR: 3346, 2989, 2943, 1735, 1666 (br), 1526, 1459, 1397, 1372, 1255, 1161, 1132, 1055, 1023, 968, 915, 849, 806, 733 cm^{-1} ; MS (+ESI) m/z , (%): 801 (3, $2M+Na^+$), 412 (100, $M+Na^+$); HRMS (+ESI) m/z : $[M+Na^+]$ Calcd for $C_{17}H_{31}N_3O_7Na$ 412.2054; Found 412.2055; ^1H NMR (400 MHz, $(CD_3)_2CO$): δ 7.24 (d, J = 8.6 Hz, 1H, NH), 7.05 (br s, 1H, NH_2), 6.48 (br s, 1H, NH_2), 6.36 (d, J = 7.9 Hz, 1H, $NHBoc$), 4.44-4.34 (m, 1H, $CHNBoc$), 4.32-4.24 (m, 2H, CH_3CHN , $CHOH$), 4.16-4.09 (m, 1H, $CHOH$), 2.80-2.70 (m, 1H, CH_2), 2.63 (dd, J = 15.7, 6.2 Hz, 1H,

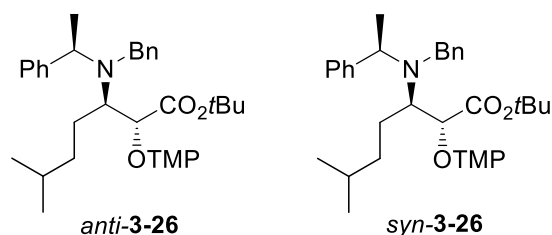
CH₂), 1.48 (s, 9H, C(CH₃)₃), 1.42 (s, 9H, C(CH₃)₃), 1.02 (d, *J* = 6.8 Hz, 3H, CH₃CH); ¹³C NMR (100 MHz, (CD₃)₂CO) δ 173.6 (C, CO), 172.3 (C, CO), 171.4 (C, CO), 156.2 (C, NCO₂), 82.3 (C, C(CH₃)₃), 79.7 (C, C(CH₃)₃), 73.6 (CH, CHOH), 52.2 (CH, CH₂CHN), 48.4 (CH, CH₃CHN), 38.0 (CH₂, CH₂CO), 28.5 (CH₃, C(CH₃)₃), 28.2 (CH₃, C(CH₃)₃), 14.5 (CH₃, CH₃CHN).

(*E*)-*tert*-Butyl 6-methylhept-2-enoate (3-25):^[128]



Prepared according to the literature procedure using 5-methylhex-1-ene.^[117] The analytical data matched those reported.

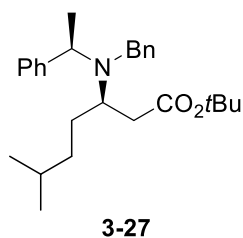
(2*R*,3*R*)- and (2*S*,3*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-6-methyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]heptanoate (3-26):



Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 10:1) to afford 224 mg (61%) of **3-26** as a partially separable 7:1 *anti/syn*-mixture as a colorless oil, and 10.6 mg (4%) of **3-27** as a colorless oil. IR: 3073, 2939, 2879, 1740, 1459, 1369, 1157, 1135, 701 cm⁻¹; MS (+ESI) *m/z*, (%): 603 (18, M+K⁺), 587 (100, M+Na⁺), 430 (50, M+Na⁺-TEMPOH), 340 (8, M+Na⁺-TEMPO-PhCH₂), 316 (42, M+Na⁺-TMPOCH₂CO₂tBu), 294 (97, M+H⁺-TMPOCH₂CO₂tBu), 190 (8, M+H⁺-TMPOCH₂CO₂tBu-PhCH=CH₂); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₃₆H₅₆N₂O₃Na 587.4183; Found 587.4183; Anal. Calcd for C₃₆H₅₆N₂O₃: C, 76.55; H, 9.99; N, 4.96; Found: C, 76.83; H, 9.89; N, 4.87; ***anti*-3-26** R_f(pentane/Et₂O 20:1) = 0.6; [α]_D²⁰ +66.3 (*c* 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 7.46-7.42 (m, 2H, Ph), 7.34-7.18 (m, 8H, Ph), 4.14 (d, *J* = 15.4 Hz, 1H, PhCH₂), 4.10 (d, *J* = 5.1 Hz, 1H, CHOTMP), 3.90 (q, *J* = 7.0 Hz, 1H, PhCHCH₃), 3.65 (d, *J* = 15.4 Hz, 1H, PhCH₂), 3.14 (dt, *J* = 4.8, 7.6 Hz, 1H, CH₂CHN), 1.78-1.68 (m, 1H, CH₂CHN), 1.51 (s, 9H, C(CH₃)₃), 1.46-1.19 (m, 10H,

CH₂CHN, (CH₃)₂CHCH₂, CH(CH₃)₂, NCCH₂CH₂CH₂CN), 1.27 (d, *J* = 7.0 Hz, 3H, PhCHCH₃), 1.09 (s, 3H, NC(CH₃)₂), 1.06 (s, 3H, NC(CH₃)₂), 1.00 (s, 3H, NC(CH₃)₂), 0.99 (s, 3H, NC(CH₃)₂), 0.83 (d, *J* = 6.6 Hz, 3H, CH(CH₃)₂), 0.81 (d, *J* = 6.6 Hz, 3H, CH(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 171.4 (C, CO₂), 143.5 (C, *ipso*-Ph), 143.0 (C, *ipso*-Ph), 128.4 (CH, Ph), 128.2 (CH, Ph), 128.1 (CH, Ph), 128.0 (CH, Ph), 126.9 (CH, *p*-Ph), 126.4 (CH, *p*-Ph), 83.8 (CH, CHOTMP), 80.1 (C, C(CH₃)₃), 61.6 (CH, CH₂CHN), 61.5 (CH, PhCHCH₃), 60.8 (C, NC(CH₃)₂), 59.80 (C, NC(CH₃)₂), 51.08 (CH₂, PhCH₂), 41.0 (CH₂, NCCH₂CH₂CH₂CN), 40.45 (CH₂, NCCH₂CH₂CH₂CN), 37.5 (CH₂, CH₂CH(CH₃)₂), 34.6 (CH₃, NC(CH₃)₂), 33.8 (CH₃, NC(CH₃)₂), 28.6 (CH, CH(CH₃)₂), 28.4 (CH₃, C(CH₃)₃), 25.9 (CH₂, CH₂CHN), 23.1 (CH₃, CH(CH₃)₂), 22.6 (CH₃, CH(CH₃)₂), 21.2 (CH₃, PhCHCH₃), 21.0 (CH₃, NC(CH₃)₂), 20.80 (CH₃, NC(CH₃)₂), 17.28 (CH₂, NCCH₂CH₂CH₂CN); ***syn*-3-26** R_f(pentane/Et₂O 20:1) = 0.5; ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 7.54-7.48 (m, 2H, Ph), 7.47-7.40 (m, 2H, Ph), 7.39-7.16 (m, 6H, Ph), 4.36-4.25 (m, 2H, CHOTMP, PhCHCH₃), 3.98 (d, *J* = 15.0 Hz, 1H, PhCH₂), 3.94 (d, *J* = 15.0 Hz, 1H, PhCH₂), 3.16-3.07 (m, 1H, CH₂CHN), 1.45 (s, 9H, C(CH₃)₃), 1.42-1.20 (m, 10H, CH₂CH(CH₃)₂, CH₂CHN, NCCH₂CH₂CH₂CN, CH(CH₃)₂), 1.19-1.10 (m, 13H, PhCHCH₃, NC(CH₃)₃, CH₂CH(CH₃)₂), 0.95 (s, 3H, NC(CH₃)₃), 0.78 (d, *J* = 6.5 Hz, 3H, CH(CH₃)₂), 0.77 (d, *J* = 6.5 Hz, 3H, CH(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 171.7 (C, CO₂), 146.2 (C, *ipso*-Ph), 144.2 (C, *ipso*-Ph), 128.2 (CH, 3 x Ph), 127.8 (CH, Ph), 126.7 (CH, *p*-Ph), 126.3 (CH, *p*-Ph), 86.7 (CH, CHOTMP), 80.9 (C, C(CH₃)₃), 61.4 (CH, PhCHCH₃), 60.5 (C, NC(CH₃)₂), 60.3 (CH, CH₂CHN), 59.75 (C, NC(CH₃)₂), 51.10 (CH₂, PhCH₂), 40.8 (CH₂, NCCH₂CH₂CH₂CN), 40.48 (CH₂, NCCH₂CH₂CH₂CN), 36.7 (CH₂, (CH₃)₂CHCH₂), 34.1 (CH₃, NC(CH₃)₂), 28.2 (CH₃, C(CH₃)₃), 28.0 (CH, CH(CH₃)₂), 26.6 (CH₂, CH₂CHN), 23.0 (CH₃, CH(CH₃)₂), 22.5 (CH₃, CH(CH₃)₂), 21.3 (CH₃, PhCHCH₃), 20.9 (CH₃, NC(CH₃)₂), 20.83 (CH₃, NC(CH₃)₂), 17.25 (CH₂, NCCH₂CH₂CH₂CN).

(3*R*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-6-methylheptanoate (3-27):

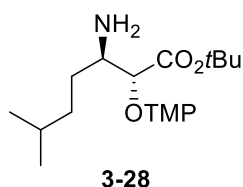


R_f(hexane/EtOAc 50:1) = 0.2; [α]_D²⁰ +8.8 (*c* 1.0, CHCl₃); IR: 3071, 3036, 2964, 2939, 2878, 1728, 1458, 1371, 1147, 747, 701 cm⁻¹; MS (+ESI) *m/z*, (%): 432 (100, M+Na⁺), 410 (59,

M+H⁺), 376 (70, M+Na⁺-CH=C(CH₃)₂), 354 (55, M+H⁺-CH=C(CH₃)₂), 304 (15, M⁺-PhCHCH₃), 250 (65, M+H⁺-CH=C(CH₃)₂-PhCH=CH₂); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₂₉H₄₇N₂O₃ 410.3054; Found 410.3055; Anal. Calcd for C₂₉H₄₆N₂O₃: C, 79.17; H, 9.60; N, 3.42; Found: C, 79.04; H, 9.57; N, 3.29; ¹H NMR (400 MHz, CDCl₃): δ 7.43-7.07 (m, 10H, Ph), 3.73 (q, *J* = 7.0 Hz, 1H, PhCHCH₃), 3.71 (d, *J* = 14.8 Hz, 1H, PhCH₂), 3.40 (d, *J* = 15.0 Hz, 1H, PhCH₂), 3.20 (m, 1H, CH₂CHN), 1.85 (dd, *J* = 15.3, 4.8 Hz, 1H, CH₂CO), 1.79 (dd, *J* = 15.2, 9.6 Hz, 1H, CH₂CO), 1.44-1.34 (m, 3H, CH₂CHN, CH(CH₃)₂, CH₂CH(CH₃)₂), 1.32 (s, 9H, C(CH₃)₃), 1.28 (d, *J* = 7.0 Hz, 3H, PhCHCH₃), 1.23-1.12 (m, 2H, CH₂CHN, CH₂CH(CH₃)₂), 0.80 (d, *J* = 6.0 Hz, 3H, CH(CH₃)₂), 0.78 (d, *J* = 5.8 Hz, 3H, CH(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 172.4 (C, CO₂), 143.2 (C, *ipso*-Ph), 142.1 (C, *ipso*-Ph), 128.33 (CH, Ph), 128.30 (CH, Ph), 128.2 (CH, Ph), 128.1 (CH, Ph), 127.0 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 80.0 (C, C(CH₃)₃), 58.4 (CH, PhCHCH₃), 54.4 (CH, CH₂CHN), 50.2 (CH₂, PhCH₂), 38.1 (CH₂, CH₂CO), 36.4 (CH₂, CH₂CH(CH₃)₂), 31.3 (CH₂, CH₂CHN), 28.2 (CH₃, C(CH₃)₃), 28.1 (CH, CH(CH₃)₂), 23.1 (CH₃, CH(CH₃)₂), 22.6 (CH₃, CH(CH₃)₂), 20.5 (CH₃, PhCHCH₃).

(2*R*,3*R*)-*tert*-Butyl

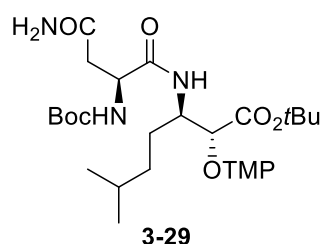
3-amino-6-methyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]heptanoate (3-28):



Pearlman's catalyst (19 mg) was added to a solution of *anti*-**3-26** (63 mg, 0.111 mmol) in EtOH (1 mL) and the mixture was stirred vigorously under 10 bar of H₂ gas at 25 °C for 26 h. The reaction mixture was diluted with EtOH, filtered through Celite[®] (eluent EtOH) and concentrated *in vacuo* to afford 40 mg (97%) of **3-28** as a pale yellow oil. R_f(EtOAc) = 0.2; [α]_D²⁰ +15.0 (*c* 0.5, CHCl₃); IR: 3370, 3308, 2982, 2959, 2871, 1723, 1467, 1457, 1393, 1376, 1368, 1155, 1054, 992, 914, 879 cm⁻¹; MS (+ESI) *m/z*, (%): 763 (22, 2M+Na⁺), 393 (31, M+Na⁺), 371 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₂₁H₄₃N₂O₃ 371.3268; Found 371.3270; Anal. Calcd for C₂₁H₄₂N₂O₃: C, 68.06; H, 11.42; N, 7.56; Found: C, 67.97; H, 11.27; N, 7.35; ¹H NMR (400 MHz, CDCl₃): δ 4.09 (d, *J* = 4.2 Hz, 1H, CHOTMP), 3.32-3.22 (m, 1H, CH₂CHN), 1.83 (br s, 2H, NH₂), 1.50-1.46 (m, 10H, CH(CH₃)₂, C(CH₃)₃), 1.65-1.10 (m, 6H, NCCH₂CH₂CH₂CN), 1.33-1.27 (m, 4H, CH₂CH₂), 1.15 (br s, 3H, NC(CH₃)₂), 1.11 (br s, 9H, NC(CH₃)₂), 0.88 (d, *J* = 6.6 Hz, 3H, CH(CH₃)₂), 0.87 (d, *J* = 6.6 Hz, 3H, CH(CH₃)₂).

CH(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 170.8 (C, CO₂), 87.4 (CH, CHOTMP), 81.5 (C, C(CH₃)₃), 60.2 (C, NC(CH₃)₂), 59.8 (C, NC(CH₃)₂), 54.3 (CH, CH₂CHN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 35.8 (CH₂, CH₂CH(CH₃)₂), 34.0 (CH₃, NC(CH₃)₂), 33.7 (CH₃, NC(CH₃)₂), 31.6 (CH₂, CH₂CHN), 28.5 (CH, CH(CH₃)₂), 28.3 (CH₃, C(CH₃)₃), 22.8 (CH₃, CH(CH₃)₂), 22.6 (CH₃, CH(CH₃)₂), 20.4 (CH₃, NC(CH₃)₂), 20.3 (CH₃, NC(CH₃)₂), 17.3 (CH₂, NCCH₂CH₂CH₂CN).

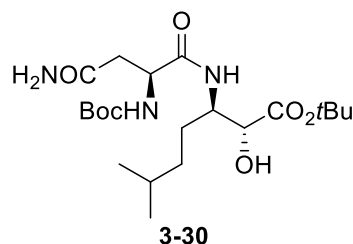
(2*R*,3*R*)-tert-Butyl 3-{[*N*-(tert-butoxycarbonyl)-(*S*)-asparaginy]amino}-6-methyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]heptanoate (3-29):



A mixture of **3-28** (40 mg, 0.107 mmol), *N*-Boc-L-asparagine (30 mg, 0.128 mmol) and HATU (45 mg, 0.118 mmol) in *N,N*-dimethylformamide (1.5 mL) was cooled to 0 °C and *N,N*-diisopropylethylamine (56 µL, 0.321 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and poured into water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with 10% NaHCO₃ solution and brine, dried over MgSO₄, and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) afforded 47 mg (75%) of **3-29** as a colorless solid. Mp: 59-61 °C; *R*_f(EtOAc) = 0.7; [α]_D²⁰ +29.5 (*c* 0.5, (CH₃)₂CO); IR: 3383, 2956, 2931, 2871, 1720, 1666, 1523, 1487, 1392, 1366, 1253, 1216, 1154, 1050, 1023, 912, 845, 795, 732 cm⁻¹; MS (+ESI) *m/z*, (%): 607 (100, M+Na⁺), 585 (55, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₀H₅₇N₄O₇ 585.4222; Found 585.4224; Anal. Calcd for C₃₀H₅₆N₄O₇: C, 61.62; H, 9.65; N, 9.58; Found: C, 61.33; H, 9.43; N, 9.42; ¹H NMR (400 MHz, CD₃CN): δ 7.14 (d, *J* = 8.9 Hz, 1H, CH₂CHNH), 6.31 (br s, 1H, NH₂), 6.09 (br s, 1H, NHBoc), 5.78 (br s, 1H, NH₂), 4.48-4.36 (m, 1H, CH₂CHN), 4.35-4.24 (m, 1H, CHNBoc), 4.14 (d, *J* = 4.6 Hz, 1H, CHOTMP), 2.63-2.49 (m, 2H, CH₂CONH₂), 1.55-1.00 (m, 23H, NCCH₂CH₂CH₂CN, CH₂CH(CH₃)₂, CH₂CHN, NC(CH₃)₂), 1.48 (s, 9H, C(CH₃)₃), 1.42 (s, 9H, C(CH₃)₃), 0.85 (d, *J* = 6.6 Hz, 3H, CH(CH₃)₂), 0.84 (d, *J* = 6.6 Hz, 3H, CH(CH₃)₂); ¹³C NMR (100 MHz, CD₃CN) δ 173.4 (C, CO), 172.3 (C, CO), 171.9 (C, CO), 156.3 (C, NCO₂), 85.8 (CH, CHOTMP), 83.2 (C, C(CH₃)₃), 80.2 (C, C(CH₃)₃), 61.3 (C, NC(CH₃)₂), 60.2 (C, NC(CH₃)₂), 53.0 (CH, CHNCHOTMP), 51.7 (CH, CHNBoc), 41.0 (CH₂, NCCH₂CH₂CH₂CN), 37.6 (CH₂,

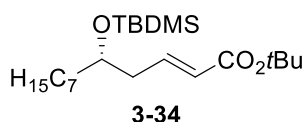
CH₂CONH₂), 35.6 (CH₂, CH₂CH(CH₃)₂), 34.3 (CH₃, NC(CH₃)₂), 34.0 (CH₃, NC(CH₃)₂), 30.8 (CH₂, CH₂CHN), 28.7 (CH, CH(CH₃)₂), 28.6 (CH₃, C(CH₃)₃), 28.3 (CH₃, C(CH₃)₃), 22.8 (CH₃, CH(CH₃)₂), 22.7 (CH₃, CH(CH₃)₂), 20.6 (CH₃, NC(CH₃)₂), 20.3 (CH₃, NC(CH₃)₂), 17.8 (CH₂, NCCH₂CH₂CH₂CN).

(2R,3R)-tert-Butyl 3-([N-(tert-butoxycarbonyl)-(S)-asparaginy]amino)-2-hydroxy-6-methylheptanoate (3-30):



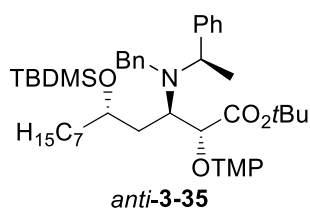
Dipeptide **3-29** (38 mg, 0.0658 mmol) was heated with zinc dust (215 mg, 3.29 mmol) in AcOH/THF (1.2/0.4 mL) at 60 °C for 3.5 h. The reaction mixture was diluted with EtOAc, filtered through short pad of K₂CO₃ and concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc) to afford 22 mg (75%) of **3-30** as a colorless solid. Mp: 128-130 °C; R_f(EtOAc) = 0.3; [α]_D²⁰ +12.5 (*c* 0.5, (CH₃)₂CO); IR: 3353, 2967, 2942, 2880, 1729, 1670 (br), 1527, 1460, 1398, 1372, 1278, 1254, 1165, 1056, 1028, 970, 915, 849, 733 cm⁻¹; MS (+ESI) *m/z*, (%): 915 (16, 2M+Na⁺), 468 (100, M+Na⁺); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₂₁H₃₉N₃O₇Na 468.2680; Found 468.2681; ¹H NMR (400 MHz, (CD₃)₂CO): δ 7.15 (d, *J* = 9.3 Hz, 1H, CH₂CHNH), 7.06 (br s, 1H, NH₂), 6.47 (br s, 1H, NH₂), 6.31 (d, *J* = 6.5 Hz, 1H, NHBoc), 4.40 (q, *J* = 6.3 Hz, 1H, CH₂CHNHBoc), 4.27-4.16 (m, 1H, CHNCHOH), 4.20 (d, *J* = 6.6 Hz, 1H, CHOH), 4.11 (dd, *J* = 6.6, 3.6 Hz, 1H, CHOH), 2.79 (dd, *J* = 16.0, 5.7 Hz, 1H, CH₂CONH₂), 2.65 (dd, *J* = 15.9, 6.4 Hz, 1H, CH₂CONH₂), 1.61-1.36 (m, 2H, CH₂CHN), 1.50 (s, 9H, C(CH₃)₃), 1.44 (s, 9H, C(CH₃)₃), 1.36-1.14 (m, 3H, CH₂CH(CH₃)₂), 0.87 (d, *J* = 6.6 Hz, 6H, CHCH₃); ¹³C NMR (100 MHz, (CD₃)₂CO) δ 173.5 (C, CO), 172.4 (C, CO), 171.8 (C, CO), 156.1 (C, NCO₂), 82.2 (C, C(CH₃)₃), 79.7 (C, C(CH₃)₃), 74.0 (CH, CHOH), 52.7 (CH, CHNCHOH), 52.2 (CH, CHNBoc), 38.2 (CH₂, CH₂CONH₂), 35.8 (CH₂, CH₂CH(CH₃)₂), 28.5 (CH₃, C(CH₃)₃), 28.4 (CH, CH(CH₃)₂), 28.2 (CH₃, C(CH₃)₃), 27.6 (CH₂, CH₂CHN), 23.1 (CH₃, CH(CH₃)₂), 22.5 (CH₃, CH(CH₃)₂).

(2*E*,5*S*)-*tert*-Butyl 5-[(*tert*-butyldimethylsilyl)oxy]dodecan-2-enoate (3-34**):**



Prepared according to a literature procedure^[117] using ((*S*)-undec-1-en-4-yloxy)(*tert*-butyl)dimethylsilane **3-33**. Yield 183 mg (90%) as a colorless oil. R_f (pentane/Et₂O 50:1) = 0.4; $[\alpha]_D^{20}$ -3.6 (*c* 0.5, CHCl₃); IR: 2965, 2938, 2866, 1721, 1660, 1497, 1395, 1371, 1329, 1289, 1258, 1156, 1078, 1008, 986, 941, 837, 810, 776, 725, 665 cm⁻¹; MS (+ESI) *m/z*, (%): 791 (8, 2M+Na⁺), 407 (100, M+Na⁺); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₂₂H₄₄O₃NaSi 407.2952; Found 407.2953; Anal. Calcd for C₂₂H₄₄O₃Si: C, 68.69; H, 11.53; Found: C, 68.94; H, 11.71; ¹H NMR (400 MHz, CDCl₃): δ 6.84 (dt, *J* = 7.5, 15.4 Hz, 1H, CH₂CH=), 5.74 (dt, *J* = 1.3, 15.6 Hz, 1H, =CHCO), 3.81-3.66 (m, 1H, CHOSi), 2.40-2.19 (m, 2H, CH₂CH=), 1.47 (s, 9H, OC(CH₃)₃), 1.39-1.15 (m, 12H, CH₂), 0.96-0.80 (m, 12H, SiC(CH₃)₃, CH₂CH₃), 0.04 (s, 6H, Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃): δ 166.0 (C, CO₂), 145.0 (CH, CH₂CH=), 125.1 (CH, =CHCO₂), 80.1 (C, C(CH₃)₃), 71.6 (CH, CHOSi), 40.2 (CH₂, CH₂CH=), 37.5 (CH₂), 32.0 (CH₂), 29.8 (CH₂), 29.4 (CH₂), 28.3 (CH₃, C(CH₃)₃), 26.0 (CH₃, SiC(CH₃)₃), 25.4 (CH₂), 22.8 (CH₂), 18.3 (C, SiC(CH₃)₃), 14.3 (CH₃, CH₂CH₃), -4.34 (CH₃, Si(CH₃)₂), -4.35 (CH₃, Si(CH₃)₂).

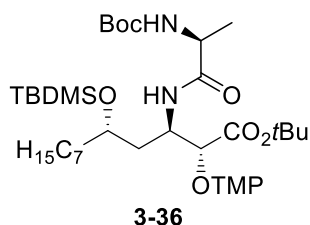
(2*R*,3*R*,5*S*)-*tert*-Butyl 3-[*N*-benzyl-*N*-((*R*)-1-phenylethyl)amino]-5-[(*tert*-butyl(dimethyl)silyl)oxy]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]dodecanoate (3-35**):**



Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 10:1) to afford 337 mg (69%) of **3-35** as a separable 10:1 *anti/syn*-mixture as a colorless oil. *anti*-**3-35** R_f (hexane/EtOAc 50:1) = 0.2; $[\alpha]_D^{20}$ +8.8 (*c* 1.0, CHCl₃); IR: 2937, 2864, 1744, 1460, 1369, 1257, 1154, 1130, 1057, 1032, 995, 837, 775, 702 cm⁻¹; MS (+ESI) *m/z*, (%): 773 (50, M+Na⁺), 751 (38, M+H⁺), 480 (100, M+H⁺-TMPOCH₂CO₂*t*Bu); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₄₆H₇₈N₂O₄NaSi 773.5623; Found 773.5625; Anal. Calcd for C₄₆H₇₈N₂O₄Si: C, 79.17; H, 9.60; N, 3.42; Found: C, 79.04; H, 9.57; N, 3.29; ¹H NMR (500 MHz, CDCl₃, 0 °C): δ 7.28-7.08 (m, 10H, Ph), 4.07-3.99 (m, 1H, CHOSi), 3.94 (d, *J* = 15.1

Hz, 1H, PhCH₂), 3.90 (d, *J* = 5.2 Hz, 1H, CHOTMP), 3.84 (q, *J* = 6.9 Hz, 1H, PhCHCH₃), 3.63 (d, *J* = 15.2 Hz, 1H, PhCH₂), 3.47-3.41 (m, 1H, CH₂CHN), 2.04-1.95 (m, 1H, CH₂CHN), 1.47 (s, 9H, C(CH₃)₃), 1.37-1.12 (m, 19H, CH₂CHN, CH₂, NCCH₂CH₂CH₂CN), 1.30 (d, *J* = 7.0 Hz, 3H, PhCHCH₃), 1.03 (s, 3H, NC(CH₃)₂), 0.98 (s, 3H, NC(CH₃)₂), 0.91 (s, 3H, NC(CH₃)₂), 0.84 (s, 9H, SiC(CH₃)₃), 0.83-0.79 (m, 3H, CH₂CH₃), 0.77 (s, 3H, NC(CH₃)₂), 0.00 (s, 6H, Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃, 0 °C) δ 170.7 (C, CO₂), 143.1 (C, *ipso*-Ph), 142.3 (C, *ipso*-Ph), 128.5 (CH, Ph), 128.21 (CH, Ph), 128.15 (CH, Ph), 128.1 (CH, Ph), 126.9 (CH, *p*-Ph), 126.4 (CH, *p*-Ph), 84.7 (CH, CHOTMP), 80.0 (C, C(CH₃)₃), 71.0 (CH, CHOSi), 60.7 (C, NC(CH₃)₂), 60.2 (CH, PhCHCH₃), 59.9 (C, NC(CH₃)₂), 56.6 (CH, CH₂CHN), 51.6 (CH₂, PhCH₂), 41.0 (CH₂, NCCH₂CH₂CH₂CN), 40.4 (CH₂, NCCH₂CH₂CH₂CN), 37.4 (CH₂), 36.4 (CH₂), 34.2 (CH₃, NC(CH₃)₂), 33.9 (CH₃, NC(CH₃)₂), 32.0 (CH₂), 30.1 (CH₂), 29.5 (CH₂), 28.5 (CH₃, C(CH₃)₃), 26.3 (CH₃, SiC(CH₃)₃), 25.3 (CH₂), 22.9 (CH₂), 21.4 (CH₃, NC(CH₃)₂), 21.1 (CH₃, PhCHCH₃, NC(CH₃)₂), 18.4 (C, SiC(CH₃)₃), 17.3 (CH₂, NCCH₂CH₂CH₂CN), 14.4 (CH₃, CH₂CH₃), -3.4 (CH₃, SiCH₃), -4.0 (CH₃, SiCH₃).

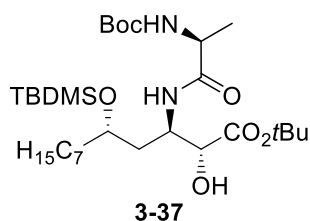
(2*R*,3*R*,5*S*)-*tert*-Butyl 3-{{(*S*)-2-[(*tert*-butoxycarbonyl)amino]propanamido}-5-[(*tert*-butyldimethylsilyl)oxy]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]dodecanoate (3-36):



Pearlman's catalyst (20 mg) was added to a solution of *anti*-**3-35** (61 mg, 0.0813 mmol) in EtOAc (1 mL) and the mixture was stirred vigorously under 20 bar of H₂ gas at 25 °C for 48 h. The reaction mixture was diluted with EtOAc, filtered through Celite[®] (eluent EtOAc) and concentrated *in vacuo* to afford a pale yellow oil that was dissolved in dry *N,N*-dimethylformamide (1.5 mL). *N*-Boc-L-alanine (19 mg, 0.100 mmol) and HATU (34 mg, 0.0894 mmol) were added, the mixture was cooled to 0 °C and *N,N*-diisopropylethylamine (43 μL, 0.244 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and poured into water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were washed with 10% NaHCO₃ solution and brine, dried over MgSO₄, and concentrated *in vacuo*. Purification of the crude product by flash chromatography (hexane/EtOAc 20:1 gradient to 5:1) afforded 34 mg (57% over two steps) of

3-36 as a colorless oil. R_f (hexane/EtOAc 5:1) = 0.3; $[\alpha]_D^{20} +31.6$ (c 0.5, CHCl_3); IR: 3400, 3314, 2928, 2855, 1721, 1684, 1516, 1458, 1366, 1154, 1055, 836, 776 cm^{-1} ; MS (+ESI) m/z , (%): 750 (100, $\text{M}+\text{Na}^+$), 728 (55, $\text{M}+\text{H}^+$), 617 (21, $\text{M}+\text{Na}^+-\text{H}_2\text{NCO}_2t\text{Bu}-\text{CH}_3$); HRMS (+ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for $\text{C}_{39}\text{H}_{77}\text{N}_3\text{O}_7\text{NaSi}$ 750.5423; Found 750.5425; Anal. Calcd for $\text{C}_{39}\text{H}_{77}\text{N}_3\text{O}_7\text{Si}$: C, 64.33; H, 10.66; N, 5.77; Found: C, 64.33; H, 10.50; N, 5.45; ^1H NMR (500 MHz, CDCl_3 , 0 °C): δ 6.74 (d, J = 9.6 Hz, 1H, CH_2CHNH), 5.08 (d, J = 6.8 Hz, 1H, CH_3CHNH), 4.75 (tdd, J = 9.8, 4.6, 2.8 Hz, 1H, CH_2CHN), 4.20-4.12 (m, 1H, CH_3CHN), 4.11 (d, J = 4.6 Hz, 1H, CHOTMP), 3.74-3.60 (m, 1H, CHOSi), 1.47 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.46-1.34 (m, 18H, $\text{C}(\text{CH}_3)_3$, CH_3CHN , CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 1.31-1.12 (m, 17H, CH_2 , CH_2CHN , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$, $\text{NC}(\text{CH}_3)_2$), 1.05 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 1.02 (s, 6H, $\text{NC}(\text{CH}_3)_2$), 0.89-0.82 (m, 12H, CH_2CH_3 , $\text{SiC}(\text{CH}_3)_3$), 0.12 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3); ^{13}C NMR (125 MHz, CDCl_3 , 0 °C) δ 172.4 (C, CO), 172.1 (C, CO), 155.1 (C, NCO_2), 85.5 (CH, CHOTMP), 82.3 (C, $\text{C}(\text{CH}_3)_3$), 79.7 (C, $\text{C}(\text{CH}_3)_3$), 69.0 (CH, CHOSi), 60.7 (C, $\text{NC}(\text{CH}_3)_2$), 59.4 (C, $\text{NC}(\text{CH}_3)_2$), 50.7 (CH, CH_3CHN), 47.8 (CH, CH_2CHN), 40.2 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 39.6 (CH_2), 38.0 (CH_2), 33.8 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 33.4 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 31.9 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 28.4 (CH_3 , $\text{C}(\text{CH}_3)_3$), 28.1 (CH_3 , $\text{C}(\text{CH}_3)_3$), 26.1 (CH_3 , $\text{SiC}(\text{CH}_3)_3$), 24.5 (CH_2), 22.8 (CH_2), 20.3 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 19.6 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 19.1 (CH_3 , CH_3CHN), 18.1 (C, $\text{SiC}(\text{CH}_3)_3$), 17.1 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 14.3 (CH_3 , CH_2CH_3), -4.3 (CH_3 , SiCH_3), -4.5 (CH_3 , SiCH_3).

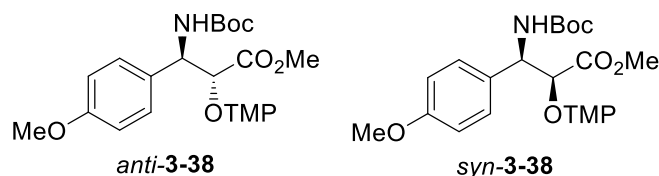
(2*R*,3*R*,5*S*)-tert-Butyl 3-{(S)-2-[(tert-butoxycarbonyl)amino]propanamido}-5-[(tert-butylidimethylsilyl)oxy]-2-hydroxydodecanoate (3-37):



Dipeptide **3-36** (14 mg, 0.02 mmol) was heated with zinc dust (65 mg, 1 mmol) in AcOH/THF (0.6/0.2 mL) at 60 °C for 2.5 h. The reaction mixture was diluted with EtOAc, filtered through a short pad of K_2CO_3 and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane/EtOAc 2:1) to afford 9 mg (76%) of **3-37** as a colorless solid. Mp: 96-98 °C; R_f (hexane/EtOAc 2:1) = 0.3; $[\alpha]_D^{20} +4.3$ (c 0.4, EtOAc); IR: 3309 (br), 2956, 2928, 2856, 1721, 1670, 1527, 1498, 1472, 1458, 1391, 1368, 1250, 1164, 1118, 1071, 1027, 808, 776, 731 cm^{-1} ; MS (+ESI) m/z , (%): 611 (100, $\text{M}+\text{Na}^+$), 555 (8,

M+Na⁺–CH=C(CH₃)₂); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₃₀H₆₀N₂O₇NaSi 611.4062; Found 611.4064; ¹H NMR (500 MHz, CDCl₃, 5 °C): δ 6.49 (d, *J* = 7.9 Hz, 1H, CH₂CHNH), 5.16 (d, *J* = 7.2 Hz, 1H, CH₃CHNH), 4.36 (ddt, *J* = 11.8, 7.9, 2.7 Hz, 1H, CH₂CHN), 4.31 (br s, 1H, CHOH), 4.17-4.08 (m, 1H, CH₃CHN), 3.73-3.67 (m, 1H, CHOSi), 3.46 (br s, 1H, CHOH), 1.68 (ddd, *J* = 14.2, 11.9, 2.0 Hz, 1H, CH₂CHN), 1.48 (s, 9H, C(CH₃)₃), 1.44-1.39 (m, 11H, C(CH₃)₃, CH₂CHOSi), 1.36 (d, *J* = 7.0 Hz, 3H, CH₃CHN), 1.30-1.18 (m, 11H, CH₂, CH₂CHN), 0.89 (s, 9H, SiC(CH₃)₃), 0.86 (t, *J* = 7.0 Hz, 3H, CH₂CH₃), 0.07 (s, 3H, SiCH₃), 0.03 (s, 3H, SiCH₃); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 172.8 (C, CO), 172.1 (C, CO), 155.3 (C, NCO₂), 83.3 (C, C(CH₃)₃), 80.0 (C, C(CH₃)₃), 72.6 (CH, CHOH), 69.0 (CH, CHOSi), 50.2 (CH, CH₃CHN), 49.8 (CH, CH₂CHN), 37.4 (CH₂, CH₂CHOSi), 34.4 (CH₂, CH₂CHN), 31.9 (CH₂), 29.9 (CH₂), 29.4 (CH₂), 28.4 (CH₃, C(CH₃)₃), 28.1 (CH₃, C(CH₃)₃), 26.1 (CH₃, SiC(CH₃)₃), 24.9 (CH₂), 22.8 (CH₂), 19.0 (CH₃, CH₃CHN), 18.2 (C, SiC(CH₃)₃), 14.3 (CH₃, CH₂CH₃), –4.4 (CH₃, SiCH₃), –4.8 (CH₃, SiCH₃).

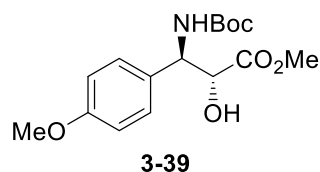
(2*R*,3*R*)- and (2*S*,3*R*)-Methyl 3-[*N*-(*tert*-butoxycarbonyl)amino]-3-(*p*-methoxyphenyl)-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (3-38).



Aminoxy ester **3-3k** (356 mg, 0.637 mmol, *anti/syn* 2:1) was dissolved in anhydrous MeOH (4 mL); Pd on carbon (180 mg, 50% w/w) and di-*tert*-butyl dicarbonate (167 mg, 0.764 mmol) were subsequently added. The mixture was hydrogenated at 5 bar of H₂ at 25 °C for 5 h, filtered through Celite[®] with MeOH and concentrated *in vacuo* to afford a colorless oil. Purification by flash chromatography on silica gel (pentane/Et₂O 10:1 gradient to 2:1) gave 251 mg (85%) of **3-38** as a separable 2:1 *anti/syn*-mixture. IR: 3436, 2984, 2941, 2880, 1725, 1618, 1503, 1462, 1369, 1249, 1168, 1031, 923, 837, 816, 770 cm^{–1}; MS (+ESI) *m/z*, (%): 487 (100, M+Na⁺), 465 (40, M+H⁺), 331 (12, M+Na⁺–TEMPO); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₂₅H₄₀N₂O₆Na 487.2779; Found 487.2780; Anal. Calcd for C₂₅H₄₀N₂O₆: C, 64.63; H, 8.68; N, 6.03; Found: C, 64.97; H, 8.64; N, 5.78; ***anti*-3-38** Colorless solid. Mp: 69-70 °C; R_f(pentane/Et₂O 2:1) = 0.4; [α]_D²⁰ +35.8 (*c* 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.09 (d, *J* = 8.7 Hz, 2H, *o*-Ar), 6.80 (d, *J* = 8.7 Hz, 2H, *m*-Ar), 6.14 (d, *J* = 8.5 Hz, 1H, NH), 5.41 (dd, *J* = 8.6, 5.0 Hz, 1H, CHN), 4.45 (d, *J* = 5.0 Hz, 1H, CHOTMP), 3.75 (s, 3H, ArOCH₃), 3.38 (s, 3H, CO₂CH₃), 1.51-1.20 (m, 6H, NCCCH₂CH₂CH₂CN), 1.44 (s, 9H, C(CH₃)₃), 1.31 (s,

3H, NC(CH₃)₂), 1.15 (s, 3H, NC(CH₃)₂), 1.10 (s, 3H, NC(CH₃)₂), 0.95 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 172.4 (C, CO₂Me), 159.0 (C, C_{Ar}OMe), 156.0 (C, NCO₂), 130.0 (C, *ipso*-Ar), 127.4 (CH, *o*-Ar), 113.9 (CH, *m*-Ar), 86.0 (CH, CHOTMP), 79.3 (C, C(CH₃)₃), 60.92 (C, NC(CH₃)₂), 59.8 (C, NC(CH₃)₂), 55.27 (CH, ArCHN), 55.1 (CH₃, ArOCH₃), 51.3 (CH₃, CO₂CH₃), 40.3 (CH₂, NCCH₂CH₂CH₂CN), 33.6 (CH₃, NC(CH₃)₂), 32.9 (CH₃, NC(CH₃)₂), 28.48 (CH₃, C(CH₃)₃), 20.2 (CH₃, NC(CH₃)₂), 19.9 (CH₃, NC(CH₃)₂), 17.14 (CH₂, NCCH₂CH₂CH₂CN); ***syn*-3-38** Colorless solid. Mp: 118-120 °C; R_f(pentane/Et₂O 2:1) = 0.3; [α]_D²⁰ -32.7 (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.23 (d, *J* = 8.7 Hz, 2H, *o*-Ar), 6.82 (d, *J* = 8.7 Hz, 2H, *m*-Ar), 5.34 (d, *J* = 8.7 Hz, 1H, NH), 5.23-5.11 (br s, 1H, ArCHN), 4.63 (d, *J* = 6.1 Hz, 1H, CHOTMP), 3.77 (s, 3H, ArOCH₃), 3.51 (s, 3H, CO₂CH₃), 1.58-1.33 (m, 6H, NCCH₂CH₂CH₂CN), 1.41 (s, 9H, C(CH₃)₃), 1.22 (s, 3H, NC(CH₃)₂), 1.13 (s, 6H, NC(CH₃)₂), 1.04 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 171.6 (C, CO₂Me), 159.1 (C, C_{Ar}OMe), 155.1 (C, NCO₂), 130.8 (C, *ipso*-Ar), 128.4 (CH, *o*-Ar), 113.8 (CH, *m*-Ar), 87.1 (CH, CHOTMP), 79.7 (C, C(CH₃)₃), 60.85 (C, NC(CH₃)₂), 60.3 (C, NC(CH₃)₂), 55.34/55.31 (CH₃, rotameric ArOCH₃), 55.28/55.26 (CH, rotameric ArCHN), 51.55/51.53 (CH₃, rotameric CO₂CH₃), 40.7 (CH₂, NCCH₂CH₂CH₂CN), 34.3 (CH₃, NC(CH₃)₂), 33.1 (CH₃, NC(CH₃)₂), 28.49 (CH₃, C(CH₃)₃), 20.6 (CH₃, NC(CH₃)₂), 20.4 (CH₃, NC(CH₃)₂), 17.11 (CH₂, NCCH₂CH₂CH₂CN).

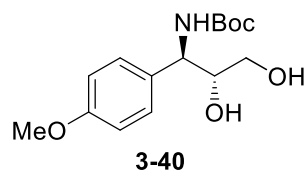
(2*R*,3*R*)-Methyl 3-[*N*-(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-(*p*-methoxyphenyl)propanoate (3-39):



Aminoxy ester *anti*-**3-38** (129 mg, 0.278 mmol) was dissolved in H₂O/AcOH (0.7 mL/2 mL), THF (2 mL) was added, followed by Zn dust (910 mg, 13.9 mmol) with vigorous stirring. The reaction mixture was heated at 70 °C for 4 h, cooled to room temperature, diluted with CH₂Cl₂ (20 mL) and filtered through Celite®. The filtrate was subsequently washed with saturated K₂CO₃ solution (pH = 10) and twice with water, dried over MgSO₄ and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (CH₂Cl₂ gradient to CH₂Cl₂/MeOH 100:1) to afford 62 mg (69%) of **3-39** as a colorless solid. Mp: 149-151 °C; [α]_D²⁰ -28.3 (c 0.5, CHCl₃), Ref.^[129] [α]_D²³ -1.8 (c 0.5, CHCl₃). The optical rotation value is not in agreement with that in the literature, but must be correct here, since the

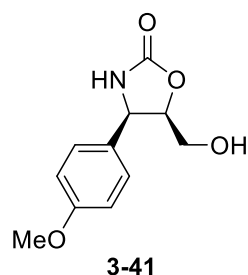
value of the subsequent compound corresponds (see below). The NMR data corresponded to those reported in the literature.^[129]

(1*R*,2*R*)-tert-Butyl 2,3-dihydroxy-1-(*p*-methoxyphenyl)propylcarbamate (3-40):



Ester **3-39** (61 mg, 0.187 mmol) in CH₂Cl₂ (2 mL) was cooled to 0 °C under an argon atmosphere and a solution of DIBAL-H (937 μL, 8.4 mmol, 1M in CH₂Cl₂) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, treated with methanol (0.3 mL) and diluted with 15% w/v aqueous NaOH (0.6 mL). The resulting slurry was warmed to ambient temperature and the layers were separated after 30 min. The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL), the combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH₂Cl₂/MeOH 100:1 gradient to 20:1) to afford 38 mg (69%) of **3-40** as a colorless solid. Mp: 116-118 °C; [α]_D²⁰ –50.9 (*c* 0.5, CHCl₃), Ref.^[129] [α]_D²³ –50.2 (*c* 0.5, CHCl₃); The NMR data corresponded to those reported in the literature.^[129]

(4*R*,5*R*)-5-(Hydroxymethyl)-4-(*p*-methoxyphenyl)oxazolidin-2-one, (–)-Cytosaxone (3-41).



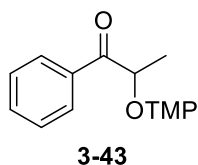
Amino diol **3-40** (29 mg, 0.0968 mmol) was dissolved in dry THF (1.5 mL) and *t*BuOK (14 mg, 0.126 mmol) was added. The mixture was stirred at room temperature for 4 h. THF was evaporated and EtOAc (10 mL) was added. The solution was washed with saturated NH₄Cl solution and brine, dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (CH₂Cl₂/MeOH 20:1 gradient to 4:1) provided 13 mg (58%) of **3-41** as a colorless solid. [α]_D²⁰ –70.9 (*c* 0.4, MeOH), Ref.^[130] [α]_D²¹ –70.0 (*c* 0.1, MeOH); The NMR data correspond to those reported in the literature.^[130]

4.2 Asymmetric SET-catalyzed tandem lithium amide conjugate addition/5-*exo* radical cyclization/oxygenation reactions for the synthesis of highly functionalized pyrrolidines, azabicyclo[n.3.0]alkane derivatives and spiropyrrolidines

Reaction of 1-phenylpropan-1-one (3-42) with 2,2,6,6-tetramethyl-1-oxopiperidinium hexafluorophosphate (1-9⁺) and a catalytic amount of ferrocene (1-6). *n*BuLi (305 μ L, 0.49 mmol, 1.6M in hexanes) was added to a solution of *i*Pr₂NH (69 μ L, 0.49 mmol) in dry THF (4 mL) at -78°C under an argon atmosphere. After stirring for 30 min, a solution of **3-42** (50 mg, 0.38 mmol) in dry THF (0.3 mL) was added by using a syringe. The reaction mixture was stirred at -78°C for 20 min. Ferrocene **1-6** (7 mg, 0.038 mmol) was added in one portion followed by small portions of salt **1-9⁺** (147 mg, 0.49 mmol). Vigorous stirring at -78°C was continued for 20 min. The reaction mixture was quenched with four drops of water, diluted with diethyl ether (7 mL), warmed to room temperature and filtered through a plug of silica gel. The solvent was evaporated and the inhomogeneous mixture was preadsorbed on silica gel and purified by column chromatography (silica gel, pentane/Et₂O 25:1 gradient to 5:1) to give 58 mg (53%) of **3-43** followed by 24 mg (47%) of *D,L*-/*meso*-**3-44** in a 7:1 ratio.

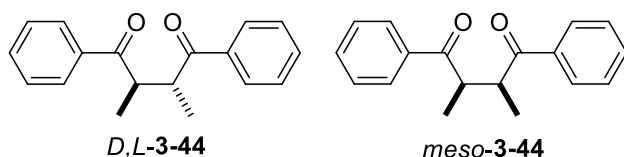
Reaction of 1-phenylpropan-1-one (3-42) with 2,2,6,6-tetramethyl-1-oxopiperidinium hexafluorophosphate (1-9⁺). *n*BuLi (460 μ L, 0.73 mmol, 1.6M in hexanes) was added to a solution of *i*Pr₂NH (103 μ L, 0.73 mmol) in dry THF (6 mL) at -78°C under an argon atmosphere. After stirring for 30 min, a solution of **1-9⁺** (76 mg, 0.56 mmol) in dry THF (0.5 mL) was added by using a syringe. The reaction mixture was stirred at -78°C for 20 min and salt **1-9⁺** (221 mg, 0.73 mmol) was added in small portions at -78°C . Vigorous stirring at -78°C was continued for 20 min. The reaction mixture was quenched with four drops of water, diluted with diethyl ether (10 mL), warmed to room temperature and filtered through a plug of silica gel. The solvent was evaporated and the inhomogeneous residue was preadsorbed on silica gel and purified by column chromatography (silica gel, pentane/Et₂O 25:1) to give 152 mg (93%) of **3-43**.

1-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propan-1-one (3-43):



Colorless solid. Mp: 69-70 °C; (lit.: 69-70 °C).^[53a] The analytical data of **3-43** are in agreement with those reported in the literature.^[53a]

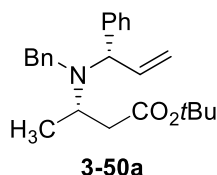
***D,L*- and *meso*-2,3-Dimethyl-1,4-diphenylbutan-1,4-diones (3-44):**



Colorless solid. The analytical data of **3-44** are in agreement with those reported in the literature.^[52a]

General procedure for aza-Michael addition of amides 3-48 to esters 3-1. *n*BuLi (225 µL, 0.360 mmol, 1.6M in hexanes) was added to a stirred solution of **3-48** (80 mg, 0.360 mmol) in dry THF (3 mL) at –78 °C under an argon atmosphere. A LiCl solution (28 µL, 0.0028 mmol, 0.1M in dry THF) was added using a syringe. After stirring for 25 min, a solution of **3-1** (0.277 mmol) in dry THF (0.5 mL) was added using a syringe. The mixture was stirred at –78 °C for 120 min, quenched with four drops of saturated NH₄Cl solution, stirred for 5 min, diluted with diethyl ether to the double volume and filtered through a plug of silica gel. The solvent was evaporated and the crude product was purified by flash chromatography.

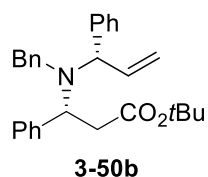
***tert*-Butyl (*S*)-3-[benzyl(*S*)-1-phenylallyl]amino]butanoate (3-50a):**



Prepared according to the general procedure. The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 50:1 gradient to 10:1) to afford 58 mg (57%) of **3-50a** as an inseparable 17:1 diastereomeric mixture as a colorless oil.

$R_f(\text{pentane/Et}_2\text{O } 25:1) = 0.3$; $[\alpha]_D^{20} +32.8$ (c 0.3, CH_2Cl_2); IR: 3072, 3037, 2985, 2941, 1728, 1498, 1458, 1371, 1302, 1260, 1148, 1077, 1063, 1032, 1019, 959, 922, 845, 762, 740, 699 cm^{-1} ; MS (+ESI) m/z , (%): 388 (18, $\text{M}+\text{Na}^+$), 366 (45, $\text{M}+\text{H}^+$), 310 (100, $\text{M}+\text{H}^+-\text{CH}_2=\text{C}(\text{CH}_3)_2$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{24}\text{H}_{32}\text{NO}_2$ 366.2428; Found 366.2428; Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_2$: C, 78.86; H, 8.55; N, 3.83; Found: C, 78.99; H, 8.57; N, 3.68; ^1H NMR (400 MHz, CDCl_3): δ 7.40-7.16 (m, 10H, Ph), 6.00 (ddd, $J = 8.6, 10.1, 17.0$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.20-5.13 (m, 2H, $\text{CH}=\text{CH}_2$), 4.24 (d, $J = 8.5$ Hz, 1H, CHPh), 3.72 (d, $J = 14.9$ Hz, 1H, PhCH_2), 3.67 (d, $J = 14.9$ Hz, 1H, PhCH_2), 3.51-3.41 (m, 1H, CH_3CHN), 2.39 (dd, $J = 5.1, 14.2$ Hz, 1H, CH_2CO_2), 2.11 (dd, $J = 8.9, 14.2$ Hz, 1H, CH_2CO_2), 1.40 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.11 (d, $J = 6.7$ Hz, 3H, CH_3CHN); ^{13}C NMR (100 MHz, CDCl_3) δ 172.0 (C, CO_2), 142.6 (C, *ipso*-Ph), 141.8 (C, *ipso*-Ph), 139.3 (CH, $\text{CH}=\text{CH}_2$), 128.6 (CH, Ph), 128.4 (CH, Ph), 128.33 (CH, Ph), 128.26 (CH, Ph), 127.1 (CH, *p*-Ph), 126.7 (CH, *p*-Ph), 116.8 (CH_2 , $\text{CH}=\text{CH}_2$), 80.2 (C, $\text{C}(\text{CH}_3)_3$), 68.5 (CH, CHPh), 50.8 (CH, CH_3CHN), 50.3 (CH_2 , PhCH_2), 41.2 (CH_2 , CH_2CO_2), 28.3 (CH_3 , $\text{C}(\text{CH}_3)_3$), 17.9 (CH_3 , CH_3CHN).

***tert*-Butyl (*R*)-3-[benzyl(*S*)-1-phenylallyl]amino]-3-phenylpropanoate (**3-50b**):**

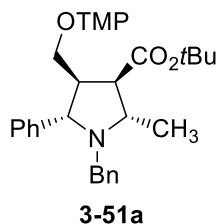


Prepared according to the general procedure. The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/ Et_2O 50:1 gradient to 10:1) to afford 115 mg (74%) of **3-50b** as an inseparable 5:1 diastereomeric mixture as a colorless oil. $R_f(\text{pentane/Et}_2\text{O } 25:1) = 0.3$; IR: 3071, 3038, 2985, 2939, 1728, 1497, 1457, 1370, 1301, 1260, 1149, 1076, 1031, 1002, 959, 920, 873, 846, 794, 752, 699 cm^{-1} ; MS (+ESI) m/z , (%): 450 (75, $\text{M}+\text{Na}^+$), 428 (100, $\text{M}+\text{H}^+$), 372 (75, $\text{M}+\text{H}^+-\text{CH}_2=\text{C}(\text{CH}_3)_2$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{29}\text{H}_{34}\text{NO}_2$ 428.2584; Found 428.2581; Anal. Calcd for $\text{C}_{29}\text{H}_{33}\text{NO}_2$: C, 81.46; H, 7.78; N, 3.28; Found: C, 81.57; H, 7.91; N, 3.02; ^1H NMR (400 MHz, CDCl_3): δ 7.47-7.10 (m, 30H, Ph, Ph^*), 6.11-6.01 (m, 1H, $\text{CH}=\text{CH}_2^*$), 5.98 (ddd, $J = 9.0, 10.1, 17.1$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.20 (dd, $J = 1.6, 10.2$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.14-5.07 (m, 2H, $\text{CH}=\text{CH}_2^*$), 5.08 (dd, $J = 0.9, 17.2$ Hz, 1H, $\text{CH}=\text{CH}_2$), 4.43 (dd, $J = 5.5, 9.9$ Hz, 1H, PhCHN), 4.42-4.37 (m, 1H, PhCHN^*), 4.29 (d, $J = 9.0$ Hz, 1H, CHPh), 4.26 (d, $J = 10.0$ Hz, 1H, CHPh^*), 3.84 (d, $J = 14.8$ Hz, 1H, PhCH_2^*), 3.80 (d, $J = 15.0$ Hz, 1H, PhCH_2), 3.69 (d, $J = 14.8$ Hz, 1H, PhCH_2^*), 3.61 (d, $J = 15.0$ Hz, 1H, PhCH_2), 2.86 (dd, $J = 5.0, 14.7$ Hz, 1H, CH_2CO_2^*), 2.78

(dd, $J = 10.2, 14.7$ Hz, 1H, CH_2CO_2^*), 2.67 (dd, $J = 5.5, 14.3$ Hz, 1H, CH_2CO_2), 2.42 (dd, $J = 9.9, 14.3$ Hz, 1H, CH_2CO_2), 1.22 (s, 18H, $\text{C}(\text{CH}_3)_3$, $\text{C}(\text{CH}_3)_3^*$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.3 (C, CO_2^*), 171.2 (C, CO_2), 142.8 (C, *ipso*-Ph), 142.6 (C, *ipso*-Ph *), 141.9 (C, *ipso*-Ph), 141.6 (C, *ipso*-Ph *), 141.53 (C, *ipso*-Ph *), 141.48 (C, *ipso*-Ph), 138.9 (CH, $\text{CH}=\text{CH}_2^*$), 137.5 (CH, $\text{CH}=\text{CH}_2$), 128.7 (CH, Ph, Ph *), 128.5 (CH, Ph *), 128.4 (CH, Ph, Ph *), 128.28 (CH, Ph), 128.25 (CH, Ph *), 128.22 (CH, Ph), 128.18 (CH, Ph, Ph *), 128.16 (CH, Ph), 128.1 (CH, Ph *), 127.3 (CH, *p*-Ph), 127.20 (CH, *p*-Ph *), 127.17 (CH, *p*-Ph, *p*-Ph *), 126.7 (CH, *p*-Ph *), 126.5 (CH, *p*-Ph), 118.2 (CH_2 , $\text{CH}=\text{CH}_2$), 117.3 (CH_2 , $\text{CH}=\text{CH}_2^*$), 80.4 (C, $\text{C}(\text{CH}_3)_3^*$), 80.3 (C, $\text{C}(\text{CH}_3)_3$), 68.1 (CH, CHPh), 67.7 (CH, CHPh^*), 60.9 (CH, PhCHN), 59.1 (CH, PhCHN^*), 51.8 (CH_2 , PhCH_2^*), 50.8 (CH_2 , PhCH_2), 39.8 (CH_2 , CH_2CO_2), 38.1 (CH_2 , CH_2CO_2^*), 28.0 (CH_3 , $\text{C}(\text{CH}_3)_3$, $\text{C}(\text{CH}_3)_3^*$). Resonances marked by * belong to the minor diastereomer.

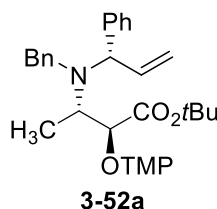
General procedure for deprotonation/SET oxidation/5-*exo* radical cyclization/oxygenation of β -amino ester **3-50a.** *n*BuLi (190 μL , 0.307 mmol, 1.6M in hexanes) was added to a solution of diisopropylamine (43 μL , 0.307 mmol) in THF (3 mL) at -78 $^\circ\text{C}$ under a nitrogen atmosphere. After stirring for 30 min, a solution of **3-50a** (80 mg, 0.219 mmol) in dry THF (0.5 mL) was added by using a syringe. After stirring for 30 min, **1-6** (4.1 mg, 0.0219 mmol) was added in one portion followed by small portions of **1-9 $^+$** (92.4 mg, 0.307 mmol) at -35 $^\circ\text{C}$. Salt **1-9 $^+$** was consumed quickly, and the orange solution was treated subsequently with further portions of **1-9 $^+$** until the mixture remained green-blue. The reaction mixture was quenched with 4 drops of a saturated NH_4Cl solution, stirred for 5 min, diluted with diethyl ether to the double volume and filtered through a plug of silica gel. The solvent was evaporated and the crude product mixture was purified by flash column chromatography (pentane/ Et_2O 50:1 gradient to 20:1) to afford 48.2 mg (42%) of **3-51a** as a single diastereomer as a colorless solid, and 15 mg (13%) of **3-52a** as an inseparable 10:1 *anti/syn*-mixture as a colorless oil.

(2*S*,3*R*,4*S*,5*S*)-tert-Butyl 1-benzyl-2-methyl-4-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl]-5-phenylpyrrolidine-3-carboxylate (3-51a):



Mp: 87-88 °C; R_f (pentane/Et₂O 30:1) = 0.2; $[\alpha]_D^{20}$ -11.1 (*c* 0.5, CHCl₃); IR: 2974, 2933, 2861, 1727, 1457, 1370, 1149, 754, 699 cm⁻¹; MS (+ESI) *m/z*, (%): 521 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₃H₄₉N₂O₃ 521.3738; Found 521.3738; Anal. Calcd for C₃₃H₄₈N₂O₃: C, 76.11; H, 9.29; N, 5.38; Found: C, 76.25; H, 9.33; N, 5.17; ¹H NMR (400 MHz, CDCl₃): δ 7.50-7.43 (m, 2H, Ph), 7.34-7.10 (m, 8H, Ph), 3.91 (d, *J* = 6.5 Hz, 1H, CHPh), 3.84 (d, *J* = 13.9 Hz, 1H, CH₂Ph), 3.76 (dd, *J* = 8.9, 6.2 Hz, 1H, CH₂OTMP), 3.60-3.53 (m, 1H, CH₂OTMP), 3.56 (d, *J* = 13.7 Hz, 1H, CH₂Ph), 3.14 (dq, *J* = 7.4, 6.0 Hz, 1H, CH₃CHN), 2.67 (dd, *J* = 8.5, 7.4 Hz, 1H, CHCO₂), 2.49-2.38 (m, 1H, CHCH₂OTMP), 1.43 (s, 9H, C(CH₃)₃), 1.40-1.18 (m, 6H, NCCH₂CH₂CH₂CN), 1.11 (d, *J* = 6.0 Hz, 3H, CHCH₃), 1.04 (s, 3H, NC(CH₃)₂), 1.01 (s, 3H, NC(CH₃)₂), 0.95 (s, 3H, NC(CH₃)₂), 0.84 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 172.6 (C, CO₂), 144.2 (C, *ipso*-Ph), 138.8 (C, *ipso*-Ph), 129.6 (CH, Ph), 128.2 (CH, Ph), 128.04 (CH, Ph), 127.97 (CH, Ph), 126.9 (CH, *p*-Ph), 126.8 (CH, *p*-Ph), 80.6 (C, C(CH₃)₃), 75.9 (CH₂, CH₂OTMP), 70.5 (CH, CHPh), 60.7 (CH, CHCH₃), 59.7 (C, NC(CH₃)₂), 55.6 (CH₂, CH₂Ph), 53.3 (CH, CHCO₂), 48.2 (CH, CHCH₂OTMP), 39.7 (CH₂, NCCH₂CH₂CH₂CN), 33.1 (CH₃, NC(CH₃)₂), 28.4 (CH₃, C(CH₃)₃), 21.0 (CH₃, CH₃CHN), 20.4 (CH₃, NC(CH₃)₂), 20.1 (CH₃, NC(CH₃)₂), 17.2 (CH₂, NCCH₂CH₂CH₂CN).

(2*S*,3*S*)-tert-Butyl 3-[benzyl((*S*)-1-phenylallyl)amino]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]butanoate (3-52a):



R_f (pentane/Et₂O 30:1) = 0.3; $[\alpha]_D^{20}$ -9.0 (*c* 0.3, CHCl₃); IR: 3026, 3004, 2976, 2930, 2871, 1736, 1494, 1454, 1390, 1365, 1257, 1213, 1152, 1066, 1029, 1010, 973, 958, 919, 735, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 543 (70, M+Na⁺), 521 (70, M+H⁺), 250 (100,

M+H⁺–TMPOCH₂CO₂tBu); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₃H₄₈N₂O₃ 543.3557; Found 543.3556; ¹H NMR (400 MHz, CDCl₃): δ 7.34–7.09 (m, 10H, Ph), 6.08 (ddd, *J* = 17.1, 10.2, 7.7 Hz, 1H, CH=CH₂), 5.12 (ddd, *J* = 10.3, 1.6, 1.0 Hz, 1H, =CH₂), 5.09–5.02 (m, 1H, =CH₂), 4.31 (d, *J* = 7.7 Hz, 1H, PhCH), 4.08 (d, *J* = 8.2 Hz, 1H, CHOTMP), 3.76 (br s, 2H, PhCH₂), 3.60–3.50 (m, 1H, CH₃CHN), 1.54 (s, 9H, C(CH₃)₃), 1.42–1.27 (m, 6H, NCCH₂CH₂CH₂CN), 1.09 (d, *J* = 6.9 Hz, 3H, CH₃CHN), 1.08–0.92 (m, 12H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 171.7 (C, CO₂), 142.1 (C, *ipso*-Ph), 141.6 (C, *ipso*-Ph), 140.2 (CH, CH=CH₂), 129.2 (CH, Ph), 128.7 (CH, Ph), 128.2 (CH, Ph), 127.9 (CH, Ph), 127.0 (CH, *p*-Ph), 126.4 (CH, *p*-Ph), 116.4 (CH₂, CH=CH₂), 85.1 (CH, CHOTMP), 80.3 (C, C(CH₃)₃), 71.3 (CH, PhCH), 56.7 (CH, CH₃CHN), 51.5 (CH₂, PhCH₂), 28.5 (CH₃, C(CH₃)₃), 17.3 (CH₂, NCCH₂CH₂CH₂CN), 12.0 (CH₃, CH₃CHN).

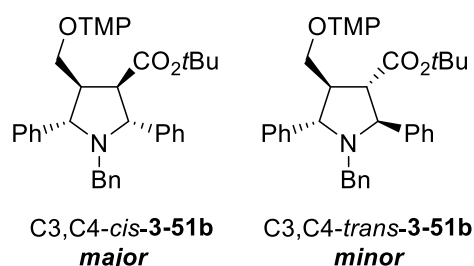
A. Synthesis of *N*,2,3,4,5-substituted pyrrolidines, azabicyclo[n.3.0]alkane derivatives and spiropyrrolidines with 1 mol% LiCl. *n*BuLi (225 μL, 0.360 mmol, 1.6M in hexanes) was added to a stirred solution of **3-48** (80 mg, 0.360 mmol) in dry THF (3 mL) at –78 °C under an argon atmosphere. A LiCl solution (28 μL, 0.0028 mmol, 0.1M in dry THF) was added using a syringe. After stirring for 25 min, a solution of **3-1** (0.277 mmol) in dry THF (0.5 mL) was added using a syringe. The mixture was stirred at –78 °C for 30–120 min, **1-6** (5.2 mg, 0.0277 mmol) was added in one portion followed by small portions of **1-9**⁺ (108.4 mg, 0.360 mmol) at –20 or –40 °C. Salt **1-9**⁺ was consumed quickly, and the orange solution was treated subsequently with further portions of **1-9**⁺ until the mixture remained green-blue. The reaction mixture was quenched with 4 drops of a saturated NH₄Cl solution.

B. Synthesis of *N*,2,3,4,5-substituted pyrrolidines, azabicyclo[n.3.0]alkane derivatives and spiropyrrolidines with 1.5 equiv. LiCl. Anhydrous LiCl (17.6 mg, 0.416 mmol) was flame-dried under high vacuum in a Schlenk flask five times for around 2 min. Dry THF (3 mL) was added followed by **3-48** (80 mg, 0.360 mmol) under an argon atmosphere. The mixture was cooled to –78 °C and *n*BuLi (225 μL, 0.360 mmol, 1.6M in hexanes) was added. After stirring for 25 min, a solution of **3-1** (0.277 mmol) in dry THF (0.5 mL) was added using a syringe. The mixture was stirred at –78 °C for 30–120 min, **1-6** (5.2 mg, 0.0277 mmol) was added in one portion followed by small portions of **1-9**⁺ (108.4 mg, 0.360 mmol) at –20 or –40 °C. Salt **1-9**⁺ was consumed quickly, and the orange solution was treated subsequently with further portions of **1-9**⁺ until the mixture remained green-blue. The reaction mixture was quenched with 4 drops of a saturated NH₄Cl solution.

Scale of reaction for azabicyclo[n.3.0]alkane derivatives: Amide **1-37** (0.456 mmol), ester **3-58** (0.351 mmol), DME (4 mL). For spiropyrrolidines: Amide **3-72** (0.456 mmol), ester **3-1** (0.351 mmol), DME (4 mL).

Workup: The reaction mixture was stirred for 5 min, diluted with diethyl ether to the double volume, warmed to room temperature and filtered through a plug of silica gel, and the solvent was evaporated. The eluents are given at the individual compounds.

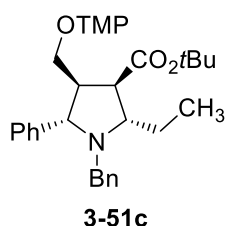
(2*R*,3*R*,4*S*,5*S*)- and (2*S*,3*S*,4*S*,5*S*)-tert-Butyl 1-benzyl-2,5-diphenyl-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-carboxylate (3-51b**):**



Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 10:1) to afford 86 mg (53%) of **3-51b** as an inseparable 6:1 mixture of two diastereomers and 9 mg (8%) of **3-50b** as a colorless oil. *R_f*(pentane/Et₂O 20:1) = 0.3; IR: 3072, 3039, 2984, 2939, 1731, 1459, 1371, 1150, 912, 758, 734, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 605 (21, M+Na⁺), 583 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₈H₅₁N₂O₃ 583.3894; Found 583.3894; Anal. Calcd for C₃₈H₅₀N₂O₃: C, 78.31; H, 8.65; N, 4.81; Found: C, 78.31; H, 8.77; N, 4.52; ¹H NMR (400 MHz, CDCl₃): δ 7.57 (m, 4H, Ph), 7.39-7.04 (m, 24H, Ph, Ph*), 6.98-6.87 (m, 2H, Ph), 4.54 (d, *J* = 7.0 Hz, 1H, CHPh*), 4.26 (d, *J* = 6.0 Hz, 1H, CHPh*), 4.10 (d, *J* = 8.3 Hz, 1H, CHPh), 4.00 (d, *J* = 5.8 Hz, 1H, CHPh), 3.96 (dd, *J* = 8.6, 5.4 Hz, 1H, CH₂OTMP*), 3.87 (dd, *J* = 8.8, 4.9 Hz, 1H, CH₂OTMP*), 3.69 (dd, *J* = 8.9, 6.0 Hz, 1H, CH₂OTMP), 3.60-3.49 (m, 3H, CH₂OTMP, CH₂Ph, CH₂Ph*), 3.42 (d, *J* = 14.3 Hz, 1H, CH₂Ph*), 3.11 (dd, *J* = 8.3, 7.1 Hz, 1H, CHCO₂*), 2.92 (t, *J* = 8.7 Hz, 1H, CHCO₂), 2.76-2.66 (m, 1H, CHCH₂OTMP*), 2.56-2.43 (m, 1H, CHCH₂OTMP), 1.53-1.08 (m, 12H, NCCH₂CH₂CH₂CN*, NCCH₂CH₂CH₂CN), 1.35 (s, 9H, C(CH₃)₃*), 1.26 (s, 9H, C(CH₃)₃), 1.17 (s, 3H, NC(CH₃)₂*), 1.15 (s, 3H, NC(CH₃)₂*), 1.14 (s, 3H, NC(CH₃)₂*), 1.11 (s, 3H, NC(CH₃)₂*), 0.99 (s, 3H, NC(CH₃)₂), 0.97 (s, 3H, NC(CH₃)₂), 0.90 (s, 3H, NC(CH₃)₂), 0.78 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 173.6 (C, CO₂*), 171.5 (C, CO₂), 144.1 (C, *ipso*-Ph), 142.5 (C, *ipso*-Ph), 142.3 (C, *ipso*-Ph*), 142.2 (C, *ipso*-Ph*), 139.6 (C, *ipso*-

Ph*), 135.8 (C, *ipso*-Ph), 130.4 (CH, Ph), 129.3 (CH, Ph*), 128.7 (CH, Ph*), 128.6 (CH, Ph), 128.5 (CH, Ph, Ph*), 128.30 (CH, Ph*), 128.27 (CH, Ph*), 128.2 (CH, Ph), 128.07 (CH, Ph*), 128.04 (CH, Ph), 128.02 (CH, Ph), 127.6 (CH, *p*-Ph*), 127.5 (CH, *p*-Ph), 127.4 (CH, *p*-Ph*), 127.1 (CH, *p*-Ph), 127.0 (CH, *p*-Ph), 126.5 (CH, *p*-Ph*), 80.8 (C, C(CH₃)₃), 80.7 (C, C(CH₃)₃*), 76.6 (CH₂, CH₂OTMP*), 76.1 (CH₂, CH₂OTMP), 68.7 (CH, CHPh*), 67.6 (CH, CHPh), 67.4 (CH, CHPh), 66.1 (CH, CHPh*), 59.7 (C, NC(CH₃)₂, NC(CH₃)₂*), 55.5 (CH, CHCO₂*), 54.8 (CH, CHCO₂), 52.6 (CH₂, CH₂Ph), 51.1 (CH, CHCH₂OTMP*), 50.6 (CH₂, CH₂Ph*), 48.4 (CH, CHCH₂OTMP), 40.0 (CH₂, NCCH₂CH₂CH₂CN*), 39.9 (CH₂, NCCH₂CH₂CH₂CN), 39.8 (CH₂, NCCH₂CH₂CH₂CN), 33.6 (CH₃, NC(CH₃)₂*), 33.3 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 33.1 (CH₃, NC(CH₃)₂), 28.3 (CH₃, C(CH₃)₃), 27.8 (CH₃, C(CH₃)₃*), 20.6 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 20.2 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 17.3 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*). Resonances marked by * belong to the minor diastereomer.

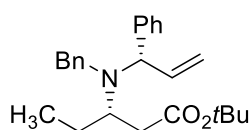
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 1-benzyl-2-ethyl-5-phenyl-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-carboxylate (3-51c**):**



Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 10:1) to afford 90 mg (61%) of **3-51c** as a single diastereomer and 9 mg (9%) of **3-50c** as a colorless oil. R_f (hexane/EtOAc 10:1) = 0.4; $[\alpha]_D^{20}$ -3.8 (*c* 0.5, CHCl₃); IR: 3063, 3028, 2973, 2930, 2873, 1723, 1493, 1454, 1367, 1244, 1208, 1146, 1071, 1029, 994, 957, 924, 844, 790, 753, 698 cm⁻¹; MS (+ESI) *m/z*, (%): 535 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₄H₅₁N₂O₃ 535.3894; Found 535.3887; Anal. Calcd for C₃₄H₅₁N₂O₃: C, 76.36; H, 9.42; N, 5.24; Found: C, 76.60; H, 9.26; N, 4.91; ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.41 (m, 2H, Ph), 7.33-7.10 (m, 8H, Ph), 3.93-3.85 (m, 2H, CH₂OTMP, CHPh), 3.80 (d, *J* = 13.7 Hz, 1H, CH₂Ph), 3.57-3.49 (m, 2H, CH₂OTMP, CH₂Ph), 3.01 (ddd, *J* = 8.1, 4.7, 3.4 Hz, 1H, CHCH₂CH₃), 2.77 (dd, *J* = 8.3, 4.7 Hz, 1H, CHCO₂), 2.48-2.36 (m, 1H, CHCH₂OTMP), 1.45-1.41 (m, 11H, CH₂CH₃, C(CH₃)₃), 1.39-1.28 (m, 6H, NCCH₂CH₂CH₂CN), 1.06 (s, 3H, NC(CH₃)₂), 0.93 (s, 3H, NC(CH₃)₂), 0.91 (s, 3H, NC(CH₃)₂), 0.86 (t, *J* = 7.4 Hz, 3H,

CH₂CH₃), 0.78 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 173.7 (C, CO₂), 144.5 (C, *ipso*-Ph), 139.2 (C, *ipso*-Ph), 129.5 (CH, Ph), 128.19 (CH, Ph), 128.17 (CH, Ph), 128.0 (CH, Ph), 127.1 (CH, *p*-Ph), 126.8 (CH, *p*-Ph), 80.4 (C, C(CH₃)₃), 75.3 (CH₂, CH₂OTMP), 70.9 (CH, CHPh), 67.8 (CH, CHCH₂CH₃), 59.63 (C, NC(CH₃)₂), 59.57 (C, NC(CH₃)₂), 56.6 (CH₂, CH₂Ph), 50.7 (CH, CHCO₂), 48.7 (CH, CHCH₂OTMP), 39.6 (CH₂, NCCH₂CH₂CH₂CN), 33.3 (CH₃, NC(CH₃)₂), 32.8 (CH₃, NC(CH₃)₂), 28.31 (CH₃, C(CH₃)₃), 28.27 (CH₂, CH₂CH₃), 20.2 (CH₃, NC(CH₃)₂), 20.0 (CH₃, NC(CH₃)₂), 17.2 (CH₂, NCCH₂CH₂CH₂CN), 9.8 (CH₃, CH₂CH₃).

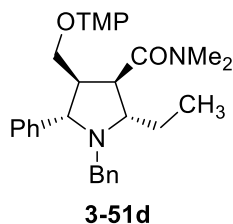
***tert*-Butyl (*S*)-3-[benzyl(*S*)-1-phenylallyl]amino]pentanoate (3-50c):**



3-50c

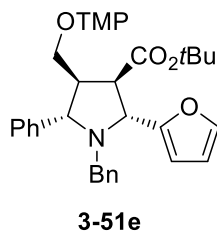
R_f(pentane/Et₂O 10:1) = 0.7; [α]_D²⁰ +38.5 (*c* 0.5, CHCl₃); IR: 3062, 3027, 2974, 2931, 2874, 1723, 1493, 1453, 1391, 1366, 1288, 1253, 1203, 1147, 1084, 1042, 1027, 992, 957, 918, 844, 758, 735, 698 cm⁻¹; MS (+ESI) *m/z*, (%): 380 (100, M+H⁺), 324 (65, M+H⁺-CH₂=C(CH₃)₂); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₂₅H₃₄NO₂ 380.2584; Found 380.2578; ¹H NMR (400 MHz, CDCl₃): δ 7.44-7.13 (m, 10H, Ph), 5.98 (ddd, *J* = 17.1, 10.1, 8.0 Hz, 1H, CH=CH₂), 5.15-5.06 (m, 1H, CH=CH₂), 5.06-4.98 (m, 1H, CH=CH₂), 4.26 (d, *J* = 8.0 Hz, 1H, NCHPh), 3.73 (d, *J* = 14.8 Hz, 1H, PhCH₂), 3.60 (d, *J* = 14.9 Hz, 1H, PhCH₂), 3.25-3.08 (m, 1H, CHNCH₂CO₂), 2.32 (dd, *J* = 14.5, 4.6 Hz, 1H, CH₂CO₂), 2.05 (dd, *J* = 14.5, 8.3 Hz, 1H, CH₂CO₂), 1.63-1.49 (m, 2H, CH₃CH₂), 1.40 (s, 9H, C(CH₃)₃), 0.91 (t, *J* = 7.3 Hz, 3H, CH₃CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 172.4 (C, CO₂), 142.4 (C, *ipso*-Ph), 141.9 (C, *ipso*-Ph), 140.6 (CH, CH=CH₂), 128.7 (CH, Ph), 128.6 (CH, Ph), 128.4 (CH, Ph), 128.2 (CH, Ph), 127.2 (CH, *p*-Ph), 126.5 (CH, *p*-Ph), 116.2 (CH₂, CH=CH₂), 80.1 (C, C(CH₃)₃), 69.2 (CH, CHPh), 57.5 (CH, CH₃CH₂CHN), 50.8 (CH₂, PhCH₂), 37.9 (CH₂, CH₂CO₂), 28.2 (CH₃, C(CH₃)₃), 26.1 (CH₃, CH₃CH₂), 12.0 (CH₃, CH₃CH₂).

(2*S*,3*R*,4*S*,5*S*)-1-benzyl-2-ethyl-*N,N*-dimethyl-5-phenyl-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-amide (3-51d**):**



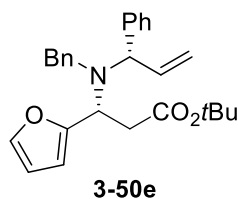
Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 10:1) to afford 46 mg (33%) of **3-51d** as a single diastereomer as a colorless solid. R_f (hexane/EtOAc 1:1) = 0.6; $[\alpha]_D^{20}$ -1.8 (c 0.4, CHCl_3); IR: 3062, 2966, 2929, 2871, 1639, 1493, 1454, 1415, 1398, 1374, 1358, 1262, 1244, 1208, 1133, 1028, 993, 956, 923, 874, 844, 750, 699 cm^{-1} ; MS (+ESI) m/z , (%): 1033 (15, $2\text{M}+\text{Na}^+$), 528 (56, $\text{M}+\text{Na}^+$), 506 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{32}\text{H}_{48}\text{N}_3\text{O}_2$ 506.3741; Found 506.3734; ^1H NMR (400 MHz, CDCl_3): δ 7.45-7.40 (m, 2H, Ph), 7.31-7.09 (m, 8H, Ph), 3.84 (t, J = 9.4 Hz, 1H, CH_2OTMP), 3.78 (d, J = 13.8 Hz, 1H, CH_2Ph), 3.67 (d, J = 9.3 Hz, 1H, CHPh), 3.53 (d, J = 13.8 Hz, 1H, CH_2Ph), 3.41 (dd, J = 9.7, 4.5 Hz, 1H, CH_2OTMP), 3.20-3.14 (m, 2H, CHCH_2CH_3 , CHCONMe_2), 3.13 (s, 3H, $\text{N}(\text{CH}_3)_2$), 2.99 (s, 3H, $\text{N}(\text{CH}_3)_2$), 2.49-2.38 (m, 1H, CHCH_2OTMP), 1.40-1.20 (m, 8H, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$, CH_2CH_3), 1.05 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 0.96 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 0.93 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 0.81 (t, J = 7.4 Hz, 3H, CH_2CH_3), 0.63 (s, 3H, $\text{NC}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 173.9 (C, CONMe_2), 143.4 (C, *ipso*-Ph), 139.7 (C, *ipso*-Ph), 129.3 (CH, Ph), 128.3 (CH, Ph), 128.2 (CH, Ph), 127.9 (CH, Ph), 127.1 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 75.7 (CH_2 , CH_2OTMP), 71.5 (CH, CHPh), 69.0 (CH, CHCH_2CH_3), 59.5 (s, $\text{NC}(\text{CH}_3)_2$), 59.4 (s, $\text{NC}(\text{CH}_3)_2$), 56.6 (CH_2 , CH_2Ph), 49.4 (CH, CHCH_2OTMP), 46.0 (CH, CHCONMe_2), 39.7 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 39.5 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 38.0 (CH_3 , $\text{N}(\text{CH}_3)_2$), 36.0 (CH_3 , $\text{N}(\text{CH}_3)_2$), 33.0 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 32.2 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 27.4 (CH_2 , CH_2CH_3), 20.4 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 20.1 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 17.2 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 9.6 (CH_3 , CH_2CH_3).

(2*R*,3*R*,4*S*,5*S*)-tert-Butyl 1-benzyl-2-(2-furyl)-5-phenyl-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-carboxylate (3-51e):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 10:1) to afford 116 mg (62%) of **3-51e** as an inseparable mixture of two diastereomers in 10:1 ratio and 14 mg (10%) of **3-50e** as a yellow oil. *R*_f(pentane/Et₂O 50:1) = 0.2; [α]_D²⁰ +6.5 (*c* 0.5, EtOAc); IR: 3072, 3037, 2984, 2940, 1731, 1607, 1498, 1475, 1459, 1372, 1248, 1210, 1150, 1072, 1046, 1013, 958, 918, 850, 734, 701 cm⁻¹; MS (+ESI) *m/z*, (%): 573 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₆H₄₉N₂O₄ 573.3687; Found 573.3680; ¹H NMR (400 MHz, CDCl₃): δ 7.59-6.99 (m, 11H, Ph, Fur), 6.31-6.15 (m, 2H, Fur), 4.25 (d, *J* = 7.0 Hz, 1H, CH_{Fur}), 4.01 (d, *J* = 6.4 Hz, 1H, CH_{Ph}), 3.84-3.69 (m, 2H, PhCH₂, CH₂OTMP), 3.68-3.54 (m, 2H, PhCH₂, CH₂OTMP), 3.24 (t, *J* = 7.7 Hz, 1H, CHCO₂), 2.68-2.53 (m, 1H, CHCH₂OTMP), 1.37 (s, 9H, C(CH₃)₃), 1.36-1.07 (m, 6H, NCCH₂CH₂CH₂CN), 1.04 (s, 3H, NC(CH₃)₂), 0.99 (s, 3H, NC(CH₃)₂), 0.94 (s, 3H, NC(CH₃)₂), 0.82 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 170.6 (C, CO₂), 154.5 (C, *ipso*-Fur), 142.7 (C, *ipso*-Ph), 140.9 (CH, Fur), 136.1 (C, *ipso*-Ph), 128.8 (CH, Ph), 127.3 (CH, Ph), 127.0 (CH, 2 x Ph), 126.1 (CH, *p*-Ph), 125.8 (CH, *p*-Ph), 109.2 (CH, Fur), 106.4 (CH, Fur), 79.9 (C, C(CH₃)₃), 74.6 (CH₂, CH₂OTMP), 67.6 (CH, CH_{Ph}), 61.0 (CH, CH_{Fur}), 58.7 (C, NC(CH₃)₂), 53.6 (CH₂, PhCH₂), 50.3 (CH, CHCO₂), 47.5 (CH, CHCH₂OTMP), 38.7 (CH₂, NCCH₂CH₂CH₂CN), 32.1 (CH₃, NC(CH₃)₂), 27.3 (CH₃, C(CH₃)₃), 19.4 (CH₃, NC(CH₃)₂), 19.1 (CH₃, NC(CH₃)₂), 16.2 (CH₂, NCCH₂CH₂CH₂CN).

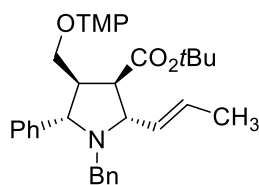
(*R*)-tert-Butyl 3-[*N*-benzyl-*N*-((*S*)-1-phenylallyl)amino]-3-(2-furyl)propanoate (3-50e):



*R*_f(pentane/Et₂O 50:1) = 0.3; [α]_D²⁰ -11.4 (*c* 0.5, CHCl₃); IR: 3072, 3037, 2986, 2940, 1732, 1607, 1498, 1458, 1371, 1298, 1259, 1222, 1151, 1075, 1046, 1014, 981, 919, 848, 809, 736,

699 cm^{-1} ; MS (+ESI) m/z , (%): 418 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{27}\text{H}_{32}\text{NO}_3$ 418.2377; Found 418.2377; ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.13 (m, 11H, Ph, Fur), 6.31 (dd, $J = 3.2, 1.8$ Hz, 1H, Fur), 6.14 (dt, $J = 3.2, 0.8$ Hz, 1H, Fur), 6.03-5.91 (m, 1H, =CH), 5.16-5.09 (m, 2H, =CH₂), 4.62 (t, $J = 7.6$ Hz, 1H, CHN), 4.34 (d, $J = 8.7$ Hz, 1H, PhCH), 3.70 (d, $J = 14.7$ Hz, 1H, PhCH₂), 3.59 (d, $J = 14.6$ Hz, 1H, PhCH₂), 2.59 (d, $J = 7.4$ Hz, 2H, CH₂CO₂), 1.35 (s, 9H, C(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3) δ 170.6 (C, CO₂), 155.2 (C, *ipso*-Fur), 142.5 (CH, Fur), 141.5 (C, *ipso*-Ph), 141.1 (C, *ipso*-Ph), 138.4 (CH, =CH), 128.6 (CH, Ph), 128.4 (CH, Ph), 128.3 (CH, Ph), 128.1 (CH, Ph), 127.2 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 117.3 (CH₂, =CH₂), 110.0 (CH, Fur), 107.8 (CH, Fur), 80.4 (C, C(CH₃)₃), 68.6 (CH, PhCH), 52.9 (CH, CHN), 51.9 (CH₂, PhCH₂), 38.7 (CH₂, CH₂CO₂), 28.1 (CH₃, C(CH₃)₃).

(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 1-benzyl-5-phenyl-2-((*E*)-prop-1-enyl)-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-carboxylate (3-51f**):**

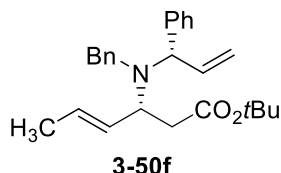


3-51f

Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 10:1) to afford 99 mg (44%) of **3-51f** as an inseparable 11:1 mixture of two diastereomers and 18 mg (11%) of **3-50f** as a yellow oil. R_f (hexane/EtOAc 20:1) = 0.3; $[\alpha]_D^{20}$ -6.2 (c 0.5, CHCl_3); IR: 3072, 3037, 2984, 2939, 1732, 1458, 1370, 1250, 1211, 1149, 1073, 1036, 998, 968, 927, 850, 795, 754, 701 cm^{-1} ; MS (+ESI) m/z , (%): 547 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{35}\text{H}_{50}\text{N}_2\text{O}_3$ 547.3894; Found 547.3896; ^1H NMR (400 MHz, CDCl_3): δ 7.57-6.93 (m, 10H, Ph), 5.76-5.64 (m, 1H, CH₃CH=), 5.43-5.32 (m, 1H, =CH), 3.87 (d, $J = 5.5$ Hz, 1H, CHPh), 3.79 (d, $J = 14.0$ Hz, 1H, CH₂Ph), 3.70 (dd, $J = 9.0, 5.9$ Hz, 1H, CH₂OTMP), 3.59-3.49 (m, 3H, CH₂Ph, CH₂OTMP, CHCH=), 2.79 (t, $J = 8.7$ Hz, 1H, CHCO₂), 2.48-2.35 (m, 1H, CHCH₂OTMP), 1.66 (dd, $J = 6.5, 1.7$ Hz, 3H, =CHCH₃), 1.38 (s, 9H, C(CH₃)₃), 1.41-1.06 (m, 6H, NCCH₂CH₂CH₂CN), 1.02 (s, 3H, NC(CH₃)₂), 1.01 (s, 3H, NC(CH₃)₂), 0.94 (s, 3H, NC(CH₃)₂), 0.82 (s, 3H, NC(CH₃)₂); ^{13}C NMR (100 MHz, CDCl_3) δ 171.6 (C, CO₂), 144.2 (C, *ipso*-Ph), 137.3 (C, *ipso*-Ph), 133.0 (CH, =CH), 130.0 (CH, Ph), 128.3 (CH, =CH), 128.2 (CH, Ph), 127.84 (CH, Ph), 127.80 (CH, Ph), 126.8 (CH, *p*-Ph), 126.7 (CH, *p*-Ph), 80.5

(C, C(CH₃)₃), 76.1 (CH₂, CH₂OTMP), 68.3 (CH, CHPh), 66.8 (CH, CHCH=), 60.1 (C, NC(CH₃)₂), 60.0 (C, NC(CH₃)₂), 53.6 (CH₂, CH₂Ph), 51.7 (CH, CHCO₂), 48.2 (CH, CHCH₂OTMP), 39.7 (CH₂, NCCH₂CH₂CH₂CN), 39.6 (CH₂, NCCH₂CH₂CH₂CN), 33.2 (CH₃, NC(CH₃)₂), 33.0 (CH₃, NC(CH₃)₂), 28.3 (CH₃, C(CH₃)₃), 20.5 (CH₃, NC(CH₃)₂), 20.0 (CH₃, NC(CH₃)₂), 17.9 (CH₃, =CHCH₃), 17.2 (CH₂, NCCH₂CH₂CH₂CN).

***tert*-Butyl (*R,E*)-3-[benzyl(*S*)-1-phenylallyl]amino]hex-4-enoate (3-50f):**

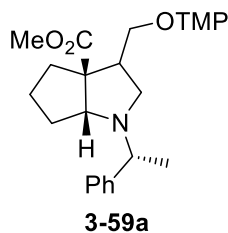


R_f (hexane/EtOAc 20:1) = 0.4; $[\alpha]_D^{20} +9.4$ (c 0.5, CHCl₃); IR: 3063, 3027, 2976, 2930, 2854, 1726, 1493, 1452, 1391, 1366, 1287, 1254, 1154, 1070, 1028, 997, 970, 919, 844, 748, 698 cm⁻¹; MS (+ESI) m/z , (%): 392 (100, M+H⁺), 336 (21, M+H⁺-CH₂=C(CH₃)₂); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₂₆H₃₄NO₂ 392.2584; Found 392.2586; ¹H NMR (400 MHz, CDCl₃): δ 7.43-7.09 (m, 10H, Ph), 6.17-6.02 (m, 1H, CH=CH₂), 5.62-5.41 (m, 2H, CH₃CH=CH), 5.19 (ddd, J = 10.1, 1.8, 0.7 Hz, 1H, =CH₂), 5.13 (ddd, J = 17.1, 1.9, 0.9 Hz, 1H, =CH₂), 4.31 (d, J = 8.7 Hz, 1H, PhCH), 3.84 (ddd, J = 8.9, 6.9, 5.4 Hz, 1H, CHN), 3.74 (d, J = 14.6 Hz, 1H, PhCH₂), 3.61 (d, J = 14.6 Hz, 1H, PhCH₂), 2.42 (dd, J = 14.1, 5.9 Hz, 2H, CH₂CO₂), 2.24 (dd, J = 14.1, 8.9 Hz, 2H, CH₂CO₂), 1.68 (d, J = 5.6 Hz, 3H, CH₃CH=), 1.37 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.3 (C, CO₂), 142.6 (C, *ipso*-Ph), 141.5 (C, *ipso*-Ph), 138.8 (CH, CH=CH₂), 130.7 (CH, CH₃CH=CH), 128.5 (CH, Ph), 128.4 (CH, Ph), 128.2 (CH, Ph), 128.1 (CH, Ph), 127.6 (CH, CH₃CH=CH), 127.0 (CH, *p*-Ph), 126.5 (CH, *p*-Ph), 117.1 (CH₂, CH=CH₂), 80.2 (C, C(CH₃)₃), 67.8 (CH, PhCH), 57.5 (CH, CHN), 51.0 (CH₂, PhCH₂), 40.2 (CH₂, CH₂CO₂), 28.2 (CH₃, C(CH₃)₃), 18.1 (CH₃, CH₃CH=).

(3a*S*,6a*R*)-Methyl

3-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]-1-((*R*)-1-

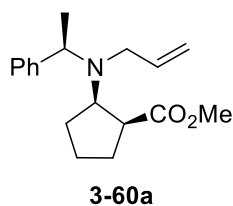
phenylethyl)hexahydrocyclopenta[b]pyrrole-3a(1*H*)-carboxylate (**3-59a**):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 10:1) to afford 98 mg (63%) of **3-59a** as an inseparable 6:1 mixture of two diastereomers as a yellow oil and 17 mg (17%) of **3-60a** as a yellow oil. R_f (pentane/Et₂O 2:1) = 0.5; IR: 2980, 2940, 2880, 1734, 1457, 1377, 1363, 1213, 1168, 1136, 1033, 925, 765, 736, 702 cm⁻¹; MS (+ESI) m/z , (%): 465 (7, M+Na⁺), 443 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₂₇H₄₃N₂O₃ 443.3268; Found 443.3267; Anal. Calcd for C₂₇H₄₂N₂O₃: C, 73.26; H, 9.56; N, 6.33; Found: C, 73.17; H, 9.71; N, 6.01; ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.13 (m, 10H, Ph, Ph*), 3.82-3.53 (m, 7H, PhCHCH₃*, PhCHCH₃, CHN, CHCH₂OTMP, CHCH₂OTMP*), 3.65 (s, 3H, OCH₃), 3.61 (s, 3H, OCH₃*), 3.34 (dd, J = 7.0, 2.6 Hz, 1H, CHN*), 3.17 (dd, J = 8.6, 5.9 Hz, 1H, CH₂N*), 2.91-2.73 (m, 2H, CHCH₂OTMP, CH₂N), 2.60 (dd, J = 11.5, 8.6 Hz, 1H, CH₂N*), 2.42 (t, J = 9.6 Hz, 1H, CH₂N), 2.36-2.26 (m, 1H, CHCH₂OTMP*), 2.09-1.99 (m, 1H, CH₂), 1.93-1.82 (m, 1H, CH₂*), 1.72-1.20 (m, 25H, CH₂, NCCH₂CH₂CH₂CN, CH₂*, NCCH₂CH₂CH₂CN*, PhCHCH₃*), 1.31 (d, J = 6.5 Hz, 3H, PhCHCH₃), 1.12-0.90 (m, 12H, NC(CH₃)₂*), 1.09 (s, 3H, NC(CH₃)₂), 1.06 (s, 3H, NC(CH₃)₂), 1.01 (s, 3H, NC(CH₃)₂), 0.95 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 178.1 (C, CO₂), 176.5 (C, CO₂*), 146.2 (C, *ipso*-Ph), 145.3 (C, *ipso*-Ph*), 128.3 (CH, Ph), 128.2 (CH, Ph*), 128.1 (CH, Ph*), 127.5 (CH, Ph), 127.0 (CH, *p*-Ph*), 126.8 (CH, *p*-Ph), 75.9 (CH₂, CH₂OTMP*), 75.5 (CH₂, CH₂OTMP), 73.8 (CH, CHN*), 73.0 (CH, CHN), 63.5 (CH₃, PhCHCH₃*), 61.8 (C, CCO₂), 61.2 (C, CCO₂*), 59.9 (CH₃, PhCHCH₃), 59.8 (C, NC(CH₃)₂, NC(CH₃)₂*), 55.5 (CH₂, CH₂N*), 52.1 (CH, OCH₃), 51.71 (CH, OCH₃*), 51.67 (CH₂, CH₂N), 47.5 (CH, CHCH₂OTMP*), 44.0 (CH, CHCH₂OTMP), 39.8 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 39.7 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 35.4 (CH₂, CH₂*), 34.7 (CH₂, CH₂*), 33.23 (CH₃, NC(CH₃)₂), 33.15 (CH₃, NC(CH₃)₂*), 33.05 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 30.7 (CH₂, CH₂), 30.5 (CH₂, CH₂), 26.30 (CH₂, CH₂), 24.9 (CH₂, CH₂*), 21.2 (CH₃, PhCHCH₃, PhCHCH₃*), 20.1 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 20.00 (CH₃, NC(CH₃)₂), 19.96 (CH₃, NC(CH₃)₂*), 17.2 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*).

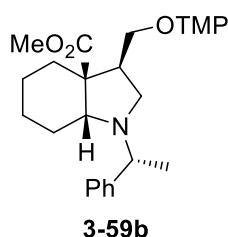
Resonances marked by * belong to the minor diastereomer.

(1*S*,2*R*)-Methyl 2-[allyl((*R*)-1-phenylethyl)amino]cyclopentane-1-carboxylate (3-60a):



R_f (pentane/Et₂O 25:1) = 0.2; IR: 3071, 2958, 2881, 2820, 1735, 1498, 1452, 1439, 1372, 1200, 1164, 916, 770, 736, 700 cm⁻¹; MS (+ESI) m/z , (%): 310 (50, M+Na⁺), 288 (75, M+H⁺), 184 (100, M+H⁺-PhCH=CH₂); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₁₈H₂₆NO₂ 288.1958; Found 288.1959; ¹H NMR (400 MHz, CDCl₃): δ 7.39-7.14 (m, 5H, Ph), 5.75 (dddd, J = 5.5, 6.8, 10.1, 17.1 Hz, 1H, CH₂CH=CH₂), 5.08 (ddd, J = 1.7, 3.4, 17.2 Hz, 1H, CH₂CH=CH₂), 4.96 (ddd, J = 1.5, 3.2, 10.1 Hz, 1H, CH₂CH=CH₂), 4.08 (q, J = 6.8 Hz, 1H, PhCHCH₃), 3.63 (s, 3H, OCH₃), 3.23 (ddd, J = 7.0, 8.5, 10.1 Hz, 1H, CHN), 3.19-3.13 (m, 2H, CH₂CH=CH₂), 2.78 (td, J = 5.0, 8.1 Hz, 1H, CHCO₂), 1.97-1.78 (m, 3H, CH₂), 1.72-1.60 (m, 2H, CH₂), 1.48-1.31 (m, 1H, CH₂), 1.28 (d, J = 6.8 Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 176.0 (C, CO₂), 144.3 (C, *ipso*-Ph), 139.3 (CH, CH=CH₂), 128.1 (CH, Ph), 127.9 (CH, Ph), 126.6 (CH, *p*-Ph), 115.6 (CH₂, CH=CH₂), 63.5 (CH, CHN), 57.0 (CH, PhCHCH₃), 51.3 (CH₃, OCH₃), 50.9 (CH₂, CH₂CH=CH₂), 48.0 (CH, CHCO₂), 28.6 (CH₂, CH₂), 27.6 (CH₂, CH₂), 23.3 (CH₂, CH₂), 14.5 (CH₃, PhCHCH₃).

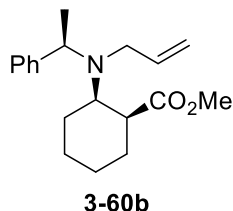
(3*R*,3*aS*,7*aR*)-Methyl 3-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]-1-[(*R*)-1-phenylethyl]octahydro-3*aH*-indole-3*a*-carboxylate (3-59b):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 10:1) to afford 38 mg (24%) of **3-59b** as an inseparable 8:1 mixture of two diastereomers as a colorless oil and 12 mg (11%) of **3-60b** as a yellow oil. R_f (pentane/Et₂O 2:1) = 0.4; $[\alpha]_D^{20}$ -10.2 (*c* 0.5, CHCl₃); IR: 2970, 2929, 2867, 1729, 1493, 1447, 1373, 1358, 1330, 1299, 1260, 1235, 1198, 1173, 1132, 1104, 1061, 1030, 1010, 994, 971, 957, 925, 782, 763, 743, 724

cm⁻¹; MS (+ESI) *m/z*, (%): 457 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₂₈H₄₅N₂O₃ 457.3425; Found 457.3424; ¹H NMR (400 MHz, CDCl₃): δ 7.36 (d, *J* = 7.5 Hz, 2H, *o*-Ph), 7.26 (t, *J* = 7.5 Hz, 2H, *m*-Ph), 7.16 (t, *J* = 7.2 Hz, 1H, *p*-Ph), 3.98 (q, *J* = 6.7 Hz, 1H, PhCHCH₃), 3.65 (s, 3H, OCH₃), 3.57 (dd, *J* = 8.7, 5.4 Hz, 1H, CH₂OTMP), 3.47 (t, *J* = 9.0 Hz, 1H, CH₂OTMP), 3.21 (t, *J* = 3.8 Hz, 1H, CHN), 2.77 (dd, *J* = 9.7, 7.7 Hz, 1H, CH₂N), 2.39 (dd, *J* = 9.8, 5.6 Hz, 1H, CH₂N), 2.13-2.03 (m, 1H, CHCH₂OTMP), 1.93 (dt, *J* = 13.0, 4.0 Hz, 1H, CH₂), 1.72 (td, *J* = 12.9, 3.5 Hz, 1H, CH₂), 1.66-1.06 (m, 12H, CH₂CHN, CH₂, NCCH₂CH₂CH₂CN), 1.25 (d, *J* = 6.6 Hz, 3H, PhCHCH₃), 1.05 (s, 3H, NC(CH₃)₂), 1.02 (s, 3H, NC(CH₃)₂), 0.96 (s, 6H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 175.3 (C, CO₂), 145.1 (C, *ipso*-Ph), 128.1 (CH, Ph), 127.6 (CH, Ph), 126.5 (CH, *p*-Ph), 77.4 (CH₂, CH₂OTMP), 59.8 (C, NC(CH₃)₂), 59.7 (CH, CHN), 54.8 (CH, PhCHCH₃), 53.7 (C, CCO₂), 51.7 (CH₃, OCH₃), 48.4 (CH₂, CH₂N), 44.7 (CH, CHCH₂OTMP), 39.7 (CH₂, NCCH₂CH₂CH₂CN), 33.3 (CH₃, NC(CH₃)₂), 33.0 (CH₃, NC(CH₃)₂), 32.0 (CH₂, CH₂), 24.7 (CH₂, CH₂), 23.2 (CH₂, CH₂), 20.2 (CH₂, CH₂), 20.1 (CH₃, NC(CH₃)₂), 17.2 (CH₂, NCCH₂CH₂CH₂CN), 12.1 (CH₃, PhCHCH₃).

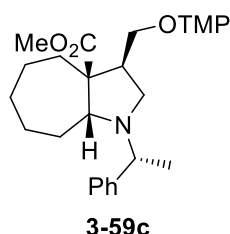
(1*S*,2*R*)-Methyl 2-[allyl((*R*)-1-phenylethyl)amino]cyclohexane-1-carboxylate (3-60b):



R_f(pentane/Et₂O 25:1) = 0.2; [α]_D²⁰ +102.8 (*c* 0.5, EtOAc); IR: 3072, 3035, 2941, 2864, 1733, 1452, 1439, 1374, 1249, 1195, 1158, 1090, 916, 776, 737, 701 cm⁻¹; MS (+ESI) *m/z*, (%): 324 (25, M+Na⁺), 302 (75, M+H⁺), 198 (100, M+H⁺-PhCH=CH₂); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₁₉H₂₈NO₂ 302.2115; Found 302.2115; ¹H NMR (400 MHz, CDCl₃): δ 7.43-7.36 (m, 2H, Ph), 7.30-7.23 (m, 2H, Ph), 7.20-7.12 (m, 1H, Ph), 5.78 (dddd, *J* = 17.4, 10.1, 7.4, 4.8 Hz, 1H, CH=CH₂), 5.11 (dtd, *J* = 17.2, 1.9, 1.2 Hz, 1H, CH=CH₂), 4.98 (dtd, *J* = 10.1, 1.8, 1.1 Hz, 1H, CH=CH₂), 4.10 (q, *J* = 6.7 Hz, 1H, PhCHCH₃), 3.57 (s, 3H, OCH₃), 3.29 (ddt, *J* = 15.3, 4.8, 1.9 Hz, 1H, CH₂CH=CH₂), 3.13 (ddt, *J* = 15.3, 7.4, 1.2 Hz, 1H, CH₂CH=CH₂), 2.63 (ddd, *J* = 12.4, 5.0, 3.8 Hz, 1H, CHN), 2.53-2.45 (m, 1H, CHCO₂), 2.13-1.99 (m, 1H, CH₂), 1.84-1.73 (m, 1H, CH₂), 1.70-1.49 (m, 3H, CH₂CH₂), 1.28 (d, *J* = 6.8 Hz, 3H, PhCHCH₃), 1.26-1.07 (m, 3H, CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 176.1 (C, CO₂), 145.1 (C, *ipso*-Ph), 139.9 (CH, CH=CH₂), 127.9 (CH, Ph), 127.9 (CH, Ph), 126.4 (CH, *p*-Ph), 115.4 (CH₂,

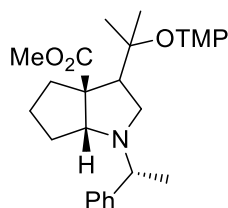
CH=CH₂), 58.2 (CH, CHN), 56.2 (CH, PhCHCH₃), 51.1 (CH₃, OCH₃), 49.9 (CH₂, CH₂CH=CH₂), 44.80 (CH, CHCO₂), 28.8 (CH₂, CH₂), 26.4 (CH₂, CH₂), 26.3 (CH₂, CH₂), 21.1 (CH₂, CH₂), 14.4 (CH₃, PhCHCH₃).

(3*R*,3*aS*,8*aR*)-Methyl decahydro-3-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]cyclohepta[b]pyrrole-3*a*-carboxylate (3-59c):



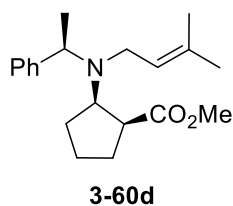
Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 50:1 gradient to 10:1) to afford 112 mg (68%) of **3-59b** as an inseparable 10:1 mixture of two diastereomers as a colorless oil. R_f (hexane/EtOAc 1:1) = 0.5; $[\alpha]_D^{20} +29.5$ (c 0.4, CHCl₃); IR: 2973, 2927, 2852, 1723, 1493, 1454, 1373, 1359, 1242, 1209, 1192, 1166, 1132, 1101, 1082, 1061, 1045, 1032, 995, 970, 958, 924, 877, 847, 814, 782, 765, 748, 719, 701 cm⁻¹; MS (+ESI) m/z , (%): 471 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₂₉H₄₇N₂O₃ 471.3581; Found 471.3576; ¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, J = 7.0 Hz, 2H, *o*-Ph), 7.31 (t, J = 7.4 Hz, 2H, *m*-Ph), 7.23 (t, J = 7.2 Hz, 1H, *p*-Ph), 3.95 (q, J = 6.6 Hz, 1H, PhCHCH₃), 3.82 (dd, J = 9.0, 4.5 Hz, 1H, CH₂OTMP), 3.73 (s, 3H, OCH₃), 3.49 (t, J = 8.5 Hz, 1H, CH₂OTMP), 3.42 (dd, J = 11.4, 2.3 Hz, 1H, CHN), 3.31 (dd, J = 8.0, 5.1 Hz, 1H, CH₂N), 2.52-2.35 (m, 3H, CH₂N, CHCH₂OTMP, CH₂), 1.74-1.60 (m, 1H, CH₂), 1.60-1.15 (m, 17H, CH₂, NCCH₂CH₂CH₂CN, PhCHCH₃), 1.13 (s, 3H, NC(CH₃)₂), 1.09 (s, 3H, NC(CH₃)₂), 1.07 (s, 3H, NC(CH₃)₂), 1.04 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 176.8 (C, CO₂), 144.4 (C, *ipso*-Ph), 128.3 (CH, Ph), 128.2 (CH, Ph), 127.1 (CH, *p*-Ph), 75.9 (CH₂, CH₂OTMP), 70.8 (CH, CHN), 62.3 (CH, PhCHCH₃), 59.8 (C, NC(CH₃)₂), 59.7 (C, NC(CH₃)₂), 58.9 (C, CCO₂), 53.5 (CH₂, CH₂N), 51.9 (CH₃, OCH₃), 47.5 (CH, CHCH₂OTMP), 39.6 (CH₂, NCCH₂CH₂CH₂CN), 33.3 (CH₂, CH₂), 33.2 (CH₂, CH₂), 33.1 (CH₃, NC(CH₃)₂), 33.0 (CH₃, NC(CH₃)₂), 30.3 (CH₂, CH₂), 27.0 (CH₂, CH₂), 25.9 (CH₂, CH₂), 20.1 (CH₃, NC(CH₃)₂), 18.5 (CH₃, PhCHCH₃), 17.1 (CH₂, NCCH₂CH₂CH₂CN).

(3a*S*,6a*R*)-Methyl 1-benzyl-3-{2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]prop-2-yl}hexahydrocyclopenta[b]pyrrole-3a(1*H*)-carboxylate (3-59d):



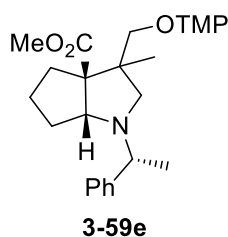
Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 50:1 gradient to 10:1) to afford 86 mg (52%) of **3-59d** as an inseparable 20:1 mixture of two diastereomers as a pale yellow oil and 13 mg (12%) of **3-60d** as an inseparable mixture of two diastereomers in 7:1 ratio as a yellow oil. R_f (hexane/EtOAc 5:1) = 0.2; $[\alpha]_D^{20}$ +20.8 (c 0.4, CHCl_3); IR: 2980, 2941, 2880, 1732, 1457, 1379, 1260, 1224, 1154, 1137, 1087, 1030, 1007, 980, 912, 879, 808, 764, 738, 702 cm^{-1} ; MS (+ESI) m/z , (%): 471 (10, $\text{M}+\text{H}^+$), 315 (100, $\text{M}+\text{H}^+-\text{TEMPO}$), 300 (60, $\text{M}+\text{H}^+-\text{TEMPO}-\text{CH}_3$), 210 (25, $\text{M}^+-\text{TEMPOH}-\text{PhCH}=\text{CH}_2$), 189 (37, $\text{PhCHCH}_3\text{NHCH}_2\text{CH}=\text{C}(\text{CH}_3)_2$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{29}\text{H}_{47}\text{N}_2\text{O}_3$ 471.3581; Found 471.3580; ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.17 (m, 5H, Ph), 3.87 (q, J = 6.5 Hz, 1H, PhCHCH_3), 3.65 (s, 3H, OCH_3), 3.54 (t, J = 6.8 Hz, 1H, CHN), 3.23 (dd, J = 6.3, 10.8 Hz, 1H, $\text{CHC}(\text{CH}_3)_2\text{OTMP}$), 3.16 (dd, J = 6.3, 10.7 Hz, 1H, CH_2N), 2.81 (t, J = 10.7 Hz, 1H, CH_2N), 2.23 (m, 1H, CH_2), 1.92 (m, 1H, CH_2), 1.76-1.38 (m, 10H, CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 1.36 (d, J = 6.6 Hz, 3H, PhCHCH_3), 1.25 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.14 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 1.09 (s, 6H, $\text{NC}(\text{CH}_3)_2$), 1.03 (s, 3H, $\text{NC}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 178.7 (C, CO_2), 146.4 (C, *ipso*-Ph), 128.3 (CH, Ph), 127.6 (CH, Ph), 126.7 (CH, *p*-Ph), 80.5 (C, $\text{C}(\text{CH}_3)_2\text{OTMP}$), 75.4 (CH, CHN), 61.6 (C, CCO_2), 60.0 (CH, PhCHCH_3), 59.6 (C, $\text{NC}(\text{CH}_3)_2$), 59.4 (C, $\text{NC}(\text{CH}_3)_2$), 55.9 (CH, $\text{CHC}(\text{CH}_3)_2\text{OTMP}$), 51.9 (CH₃, OCH_3), 49.8 (CH₂, CH_2N), 41.5 (CH₂, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 41.4 (CH₂, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 35.7 (CH₃, $\text{NC}(\text{CH}_3)_2$), 35.5 (CH₃, $\text{NC}(\text{CH}_3)_2$), 31.7 (CH₂, CH_2), 30.6 (CH₂, CH_2), 28.0 (CH₃, $\text{C}(\text{CH}_3)_2\text{OTMP}$), 26.2 (CH₂, CH_2), 25.4 (CH₃, $\text{C}(\text{CH}_3)_2\text{OTMP}$), 21.5 (CH₃, PhCHCH_3), 21.2 (CH₃, $\text{NC}(\text{CH}_3)_2$), 21.0 (CH₃, $\text{NC}(\text{CH}_3)_2$), 17.2 (CH₂, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$).

(1*S*,2*R*)-Methyl 2-[(3-methylbut-2-en-1-yl)((*R*)-1-phenylethyl)amino]cyclopentane-1-carboxylate (3-60d):



R_f (pentane/Et₂O 5:1) = 0.6; $[\alpha]_D^{20}$ +68.3 (*c* 0.5, CHCl₃); IR: 2975, 2881, 1736, 1451, 1439, 1372, 1200, 1159, 757, 737, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 338 (55, M+Na⁺), 316 (100, M+H⁺), 248 (42, M⁺-CH₂=C(CH₃)-CH=CH₂), 212 (32, M+H⁺-PhCH=CH₂); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₂₀H₃₀NO₂ 316.2271; Found 316.2270; ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.14 (m, 5H, Ph), 5.17-5.02 (m, 1H, CH=), 4.06 (q, *J* = 6.8 Hz, 1H, PhCHCH₃), 3.67 (s, 3H, OCH₃), 3.31-3.20 (m, 2H, CHN, CH₂CH=), 3.12-3.01 (m, 1H, CH₂CH=), 2.83-2.73 (m, 1H, CHCO₂), 2.03-1.81 (m, 3H, CH₂), 1.78-1.60 (m, 3H, CH₂), 1.65 (s, 3H, CCH₃), 1.58 (s, 3H, CCH₃), 1.31 (d, *J* = 6.9 Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 176.1 (C, CO₂), 144.8 (C, *ipso*-Ph), 132.4 (C, CH=C(CH₃)₂), 128.1 (CH, Ph), 127.8 (CH, Ph), 126.4 (CH, *p*-Ph), 125.2 (CH, CH=C(CH₃)₂), 63.4 (CH, CHN), 56.8 (CH, PhCHCH₃), 51.3 (CH₃, OCH₃), 48.2 (CH, CHCO₂), 45.4 (CH₂, CH₂CH=), 28.4 (CH₂, CH₂CHN), 27.7 (CH₂, CH₂CHCO₂), 26.1 (CH₃, =C(CH₃)₂), 23.4 (CH₂, CH₂), 18.0 (CH₃, =C(CH₃)₂), 14.0 (CH₃, PhCHCH₃).

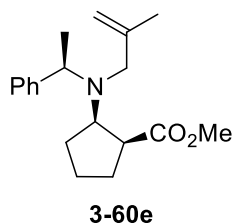
(3*aS*,6*aR*)-Methyl 3-methyl-1-((*R*)-1-phenylethyl)-3-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl}hexahydrocyclopenta[*b*]pyrrole-3*a*(1*H*)-carboxylate (3-59e):



Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 50:1 gradient to 10:1) to afford 47 mg (29%) of **3-59e** as an inseparable 15:1 mixture of two diastereomers as a pale yellow oil and 18 mg (17%) of **3-60e** as a single diastereomer as a yellow oil. R_f (pentane/Et₂O 2:1) = 0.5; $[\alpha]_D^{20}$ -14.7 (*c* 0.5, CHCl₃); IR: 2970, 2932, 2870, 1725, 1492, 1452, 1433, 1373, 1359, 1301, 1282, 1246, 1208, 1164, 1132, 1084, 1042, 993, 968, 956, 924, 875, 846, 797,

764, 700 cm^{-1} ; MS (+CI) m/z , (%): 457 (100, $\text{M}+\text{H}^+$), 441 (10, M^+-CH_3); HRMS (+CI) m/z : [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{28}\text{H}_{45}\text{N}_2\text{O}_3$ 457.3430; Found 457.3434; ^1H NMR (400 MHz, CDCl_3): δ 7.34-7.17 (m, 5H, Ph), 3.89 (d, $J = 7.8$ Hz, 1H, CH_2OTMP), 3.87-3.82 (m, 1H, CHN), 3.69-3.58 (m, 5H, OCH_3 , CH_2OTMP , PhCHCH_3), 3.11 (d, $J = 9.3$ Hz, 1H, CH_2N), 2.48 (d, $J = 9.3$ Hz, 1H, CH_2N), 1.97-1.90 (m, 1H, CH_2), 1.79-1.22 (m, 14H, CH_2 , PhCHCH_3 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 1.20 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 1.15 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 1.09 (s, 3H, $\text{NC}(\text{CH}_3)_2$), 1.06 (s, 3H, CCH_3), 1.03 (s, 3H, $\text{NC}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.5 (C, CO_2), 146.2 (C, *ipso*-Ph), 128.1 (CH, Ph), 127.7 (CH, Ph), 126.7 (CH, *p*-Ph), 79.3 (CH_2 , CH_2OTMP), 70.9 (CH, CHN), 67.2 (C, CCO_2), 61.3 (CH, PhCHCH_3), 60.1 (C, $\text{NC}(\text{CH}_3)_2$), 59.5 (CH_2 , CH_2N), 51.6 (CH_3 , OCH_3), 45.3 (C, CCH_2OTMP), 39.93 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 39.88 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 33.2 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 33.1 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 31.7 (CH_2 , CH_2), 30.7 (CH_2 , CH_2), 26.7 (CH_2 , CH_2), 20.9 (CH_3 , CCH_3), 20.40 (CH_3 , $\text{NC}(\text{CH}_3)_2$), 20.38 (CH_3 , PhCHCH_3 , $\text{NC}(\text{CH}_3)_2$), 17.2 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$).

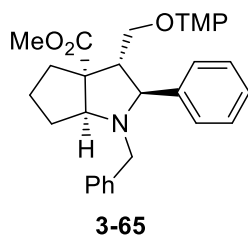
(1*S*,2*R*)-Methyl 2-[(2-methylallyl)((*R*)-1-phenylethyl)amino]cyclopentane-1-carboxylate (3-60e):



R_f (pentane/ Et_2O 5:1) = 0.6; $[\alpha]_{\text{D}}^{20} +68.3$ (c 0.3, CHCl_3); IR: 3063, 3026, 2968, 2949, 2871, 2833, 1729, 1493, 1447, 1434, 1370, 1295, 1244, 1196, 1159, 1130, 1083, 1046, 1026, 983, 953, 892, 839, 767, 749, 735, 699 cm^{-1} ; MS (+CI) m/z , (%): 302 (54, $\text{M}+\text{H}^+$), 301 (55, M^+), 286 (M^+-CH_3), 198 (100, $\text{M}+\text{H}^+-\text{PhCH}=\text{CH}_2$), 105 (19, PhCHCH_3^+); HRMS (+CI) m/z : [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_2$ 302.2122; Found 302.2120; ^1H NMR (400 MHz, CDCl_3): δ 7.44-7.20 (m, 5H, Ph), 4.96 (s, 1H, $=\text{CH}_2$), 4.79 (s, 1H, $=\text{CH}_2$), 4.14 (q, $J = 6.9$ Hz, 1H, PhCHCH_3), 3.67 (s, 3H, OCH_3), 3.24 (d, $J = 15.0$ Hz, $\text{CH}_2\text{C}=\text{}$), 3.19 (ddd, $J = 10.7, 8.2, 6.9$ Hz, 1H, CHN), 2.98 (d, $J = 15.0$ Hz, $\text{CH}_2\text{C}=\text{}$), 2.85 (td, $J = 8.1, 4.6$ Hz, 1H, CHCO_2), 2.03-1.78 (m, 3H, CH_2), 1.72 (s, 3H, CH_3), 1.69-1.58 (m, 2H, CH_2), 1.48-1.33 (m, 1H, CH_2), 1.30 (d, $J = 6.9$ Hz, 3H, PhCHCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 176.2 (C, CO_2), 145.8 (C, $=\text{CCH}_3$), 143.6 (C, *ipso*-Ph), 128.2 (CH, Ph), 128.0 (CH, Ph), 126.7 (CH, Ph), 111.6 (CH_2 , $=\text{CH}_2$), 64.4 (CH, CHN), 57.3 (CH, PhCHCH_3), 54.0 (CH_2 , $\text{NCH}_2\text{C}=\text{}$), 51.4 (CH_3 , OCH_3),

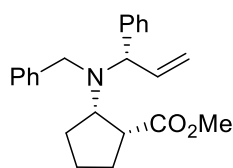
47.4 (CH, CHCO₂), 28.2 (CH₂, CH₂CHN), 27.6 (CH₂, CH₂CHCO₂), 22.9 (CH₂, CH₂), 20.7 (CH₃, =CCH₃), 15.3 (CH₃, PhCHCH₃).

(2*S*,3*S*,3*aR*,6*aS*)-Methyl 1-benzyl-2-phenyl-3-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl}hexahydrocyclopenta[*b*]pyrrole-3*a*(1*H*)-carboxylate (3-65):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 5:1) to afford 44 mg (25%) of **3-65** as a single diastereomer as a colorless solid and 38 mg (31%) of **3-66** as a single diastereomer as a yellow oil. Mp: 89-90 °C; *R*_f(hexane/EtOAc 5:1) = 0.6; [α]_D²⁰ -16.2 (*c* 0.5, CHCl₃); IR: 3037, 2940, 2878, 1737, 1458, 1363, 1271, 1206, 1165, 1135, 1032, 916, 755, 736, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 527 (20, M+Na⁺), 505 (100, M+H⁺), 364 (25, M+H⁺-TMPH), 348 (10, M+H⁺-TEMPOH); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₂H₄₄N₂O₃ 505.3425; Found 505.3419; ¹H NMR (400 MHz, CDCl₃): δ 7.50-7.11 (m, 10H, Ph), 3.83 (t, *J* = 9.2 Hz, 1H, CH₂OTMP), 3.76 (d, *J* = 13.0 Hz, 1H, CH₂Ph), 3.71 (d, *J* = 10.7 Hz, 1H, CHPh), 3.67 (s, 3H, OCH₃), 3.47-3.39 (m, 2H, CH₂OTMP, CHN), 3.33 (d, *J* = 13.1 Hz, 1H, CH₂Ph), 2.22 (ddd, *J* = 10.6, 9.0, 4.9 Hz, 1H, CHCH₂OTMP), 2.13-1.99 (m, 1H, CH₂CCO₂), 1.92-1.74 (m, 2H, CH₂CCO₂, CH₂), 1.65-1.53 (m, 2H, CH₂), 1.45 (m, 1H, CH₂), 1.40-1.12 (m, 6H, NCCH₂CH₂CH₂CN), 1.03 (s, 3H, NC(CH₃)₂), 0.94 (s, 3H, NC(CH₃)₂), 0.86 (s, 3H, NC(CH₃)₂), 0.67 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 176.7 (C, CO₂Me), 142.1 (C, *ipso*-Ph), 139.3 (C, *ipso*-Ph), 129.6 (CH, Ph), 128.4 (CH, Ph), 128.2 (CH, Ph), 128.0 (CH, Ph), 127.6 (CH, Ph), 126.8 (CH, Ph), 75.1 (CH₂, CH₂OTMP), 74.4 (CH, CHN), 72.3 (CH, CHPh), 61.7 (C, CCO₂), 59.63 (C, NC(CH₃)₂), 59.59 (C, NC(CH₃)₂), 57.4 (CH₂, CH₂Ph), 56.7 (CH, CHCH₂OTMP), 51.8 (CH₃, OCH₃), 39.6 (CH₂, NCCH₂CH₂CH₂CN), 39.5 (CH₂, NCCH₂CH₂CH₂CN), 35.5 (CH₂, CH₂), 34.4 (CH₂, CH₂), 33.0 (CH₃, NC(CH₃)₂), 32.2 (CH₃, NC(CH₃)₂), 24.9 (CH₂, CH₂), 19.98 (CH₃, NC(CH₃)₂), 19.96 (CH₃, NC(CH₃)₂), 17.1 (CH₂, NCCH₂CH₂CH₂CN).

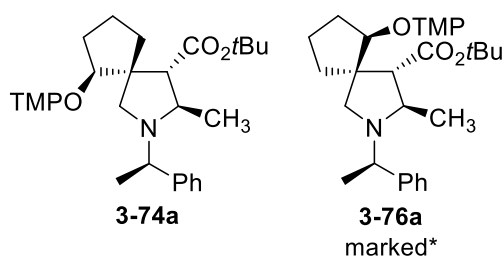
(1*R*,2*S*)-Methyl 2-[benzyl((*S*)-1-phenylallyl)amino]cyclopentane-1-carboxylate (3-66):



3-66

R_f (hexane/EtOAc 25:1) = 0.2; $[\alpha]_D^{20}$ -117.6 (c 0.5, CHCl_3); IR: 3071, 3036, 2958, 2881, 1732, 1498, 1453, 1439, 1366, 1199, 1162, 925, 739, 700 cm^{-1} ; MS (+ESI) m/z , (%): 350 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_2$ 350.2115; Found 350.2115; ^1H NMR (400 MHz, CDCl_3): δ 7.54-7.09 (m, 10H, Ph), 5.87 (ddd, J = 9.1, 10.1, 17.1 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.33 (dd, J = 1.7, 10.1 Hz, 1H, $\text{CH}=\text{CH}_2$), 4.98 (dd, J = 1.2, 17.1 Hz, 1H, $\text{CH}=\text{CH}_2$), 4.21 (d, J = 9.1 Hz, 1H, CHPh), 3.85 (d, J = 14.5 Hz, 1H, CH_2Ph), 3.69 (d, J = 14.5 Hz, 1H, CH_2Ph), 3.65 (s, 3H, OCH_3), 3.39-3.30 (m, 1H, CHN), 2.83 (td, J = 5.4, 8.3 Hz, 1H, CHCO_2), 2.58-2.40 (m, 1H, CH_2), 1.99-1.74 (m, 3H, CH_2CH_2), 1.68-1.53 (m, 1H, CH_2), 1.43-1.28 (m, 1H, CH_2); ^{13}C NMR (100 MHz, CDCl_3) δ 176.1 (C, CO_2), 142.1 (C, *ipso*-Ph), 141.2 (C, *ipso*-Ph), 135.8 (CH, $\text{CH}=\text{CH}_2$), 128.34 (CH, Ph), 128.32 (CH, Ph), 128.22 (CH, Ph), 128.20 (CH, Ph), 127.0 (CH, Ph), 126.7 (CH, Ph), 119.2 (CH_2 , $\text{CH}=\text{CH}_2$), 66.5 (CH, CHPh), 63.4 (CH, CHN), 52.2 (CH_2 , CH_2Ph), 51.7 (CH, OCH_3), 47.9 (CH, CHCO_2), 28.4 (CH_2 , CH_2), 27.8 (CH_2 , CH_2), 23.4 (CH_2 , CH_2).

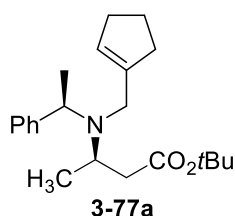
(3*R*,4*S*,5*R*,6*S*)- and (3*R*,4*S*,5*S*,6*R*)-*tert*-Butyl 3-methyl-2-((*R*)-1-phenylethyl)-6-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-2-azaspiro[4.4]nonane-4-carboxylate (3-74a and 3-76a):



Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 5:1) to afford 63 mg (36%) of **3-74a:3-76a** as a 4:1 mixture of diastereomers as a colorless oil and 49 mg (41%) of **3-77a** as a single diastereomer as a pale yellow oil. R_f (pentane/Et₂O 5:1) = 0.3; IR: 2981, 2939, 2881, 1727, 1458, 1370, 1314, 1279, 1258, 1210, 1147, 1086, 1047, 978, 960, 921, 852, 782, 765, 745, 702 cm^{-1} ; MS (+ESI) m/z , (%): 499 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{31}\text{H}_{51}\text{N}_2\text{O}_3$ 499.3894; Found 499.3895; ^1H NMR (400 MHz, CDCl_3):

δ 7.53-7.09 (m, 10H, Ph, Ph*), 4.19 (d, $J = 4.4$ Hz, 1H, CHOTMP), 4.14 (d, $J = 3.5$ Hz, 1H, CHOTMP*), 3.90 (q, $J = 6.9$ Hz, 1H, PhCHCH₃*), 3.74 (q, $J = 6.7$ Hz, 1H, PhCHCH₃), 3.23-3.12 (m, 2H, CHCH₃*, CHCO₂*), 3.20 (d, $J = 9.2$ Hz, 1H, CH₂N), 3.07 (qd, $J = 6.4, 4.7$ Hz, 1H, CHCH₃), 2.94 (d, $J = 9.1$ Hz, 1H, CH₂N), 2.38-2.25 (m, 6H, CH₂N*, CH₂CHOTMP, CH₂CHOTMP*), 2.08 (d, $J = 4.8$ Hz, 1H, CHCO₂), 1.99-1.78 (m, 4H, CCH₂, CCH₂*), 1.75-1.22 (m, 31H, CH₂, CH₂*, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*, NC(CH₃)₂*, PhCHCH₃*), 1.46 (s, 9H, C(CH₃)₃*), 1.44 (s, 9H, C(CH₃)₃), 1.40 (d, $J = 6.7$ Hz, 3H, PhCHCH₃), 1.19 (s, 3H, NC(CH₃)₂), 1.12 (s, 3H, NC(CH₃)₂), 1.08 (s, 3H, NC(CH₃)₂), 1.05 (d, $J = 5.8$ Hz, 3H, CHCH₃*), 0.99 (s, 3H, NC(CH₃)₂), 0.80 (d, $J = 6.4$ Hz, 3H, CHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.8 (C, CO₂*), 174.6 (C, CO₂), 146.5 (C, *ipso*-Ph), 145.9 (C, *ipso*-Ph*), 128.1 (CH, Ph), 128.0 (CH, Ph*), 127.8 (CH, Ph), 127.4 (CH, Ph*), 126.6 (CH, Ph), 126.4 (CH, Ph*), 87.8 (CH, CHOTMP*), 87.2 (CH, CHOTMP), 80.6 (C, C(CH₃)₃), 80.1 (C, C(CH₃)₃*), 62.9 (CH, CHCH₃), 61.1 (CH, CHCO₂, PhCHCH₃), 61.0 (C, NC(CH₃)₂, NC(CH₃)₂*), 60.7 (CH, CHCO₂*), 59.1 (C, NC(CH₃)₂, NC(CH₃)₂*), 58.3 (CH₂, CH₂N*), 57.6 (CH₂, CH₂N), 57.3 (C, C), 56.0 (CH, PhCHCH₃*), 55.6 (C, C*), 54.8 (CH, CHCH₃*), 40.8 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 40.5 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 38.7 (CH₂, CCH₂), 35.6 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 33.9 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 32.2 (CH₂, CCH₂*), 28.4 (CH₃, C(CH₃)₃*), 28.3 (CH₃, C(CH₃)₃), 28.2 (CH₂, CH₂CHO), 27.4 (CH₂, CH₂CHO*), 22.9 (CH₃, CHCH₃), 21.2 (CH₂, CH₂*), 20.9 (CH₂, CH₂), 20.8 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 19.8 (CH₃, CHCH₃*), 18.7 (CH₃, PhCHCH₃), 17.40 (CH₂, NCCH₂CH₂CH₂CN*), 17.35 (CH₂, NCCH₂CH₂CH₂CN), 13.9 (CH₃, PhCHCH₃*).

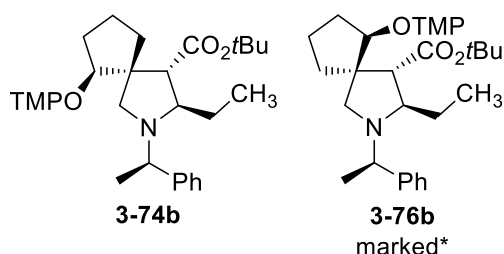
tert-Butyl (R)-3-[(cyclopent-1-en-1-ylmethyl)((R)-1-phenylethyl)amino]butanoate (3-77a):



R_f(pentane/Et₂O 10:1) = 0.2; [α]_D²⁰ -11.8 (*c* 0.8, CHCl₃); IR: 2973, 2931, 2846, 1723, 1493, 1453, 1391, 1366, 1301, 1257, 1208, 1148, 1083, 1044, 1026, 992, 957, 915, 845, 765, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 344 (100, M+H⁺), 288 (40, M+H⁺-C₄H₈); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₂₂H₃₄NO₂ 344.2590; Found 344.2593; ¹H NMR (400 MHz, CDCl₃): δ

7.45-7.11 (m, 5H, Ph), 5.57-5.51 (m, 1H, C=CH), 3.89 (q, $J = 6.8$ Hz, 1H, PhCHCH₃), 3.44-3.32 (m, 1H, CHN), 3.19 (d, $J = 14.9$ Hz, 1H, NCH₂C=), 3.07 (d, $J = 15.0$ Hz, 1H, NCH₂C=), 2.35-2.16 (m, 5H, CH₂, CH₂CO₂), 2.02 (dd, $J = 14.2, 8.9$ Hz, 1H, CH₂CO₂), 1.89-1.78 (m, 2H, CH₂), 1.39 (s, 9H, C(CH₃)₃), 1.36 (d, $J = 6.9$ Hz, 3H, PhCHCH₃), 0.93 (d, $J = 6.6$ Hz, 3H, CHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 172.3 (C, CO₂), 145.1 (C, *ipso*-Ph), 145.0 (C, C=CH), 128.1 (CH, Ph), 127.8 (CH, Ph), 126.6 (CH, C=CH), 126.4 (CH, *p*-Ph), 80.0 (C, C(CH₃)₃), 58.0 (CH, PhCHCH₃), 50.3 (CH, CHN), 46.2 (CH₂, NCH₂C=), 41.1 (CH₂, CH₂CO₂), 33.7 (CH₂, CH₂), 32.5 (CH₂, CH₂), 28.2 (CH₃, C(CH₃)₃), 23.6 (CH₂, CH₂), 18.8 (CH₃, PhCHCH₃), 17.7 (CH₃, CHCH₃).

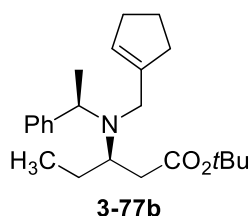
(3*R*,4*S*,5*R*,6*S*)- and (3*R*,4*S*,5*S*,6*R*)-tert-Butyl 3-ethyl-2-[(*R*)-1-phenylethyl]-6-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-2-azaspiro[4.4]nonane-4-carboxylate (3-74b and 3-76b):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 5:1) to afford 77 mg (43%) of **3-74b:3-76b** as a 5.7:1 mixture of two diastereomers as a colorless solid and 21 mg (17%) of **3-77b** as a single diastereomer as a colorless oil. R_f (pentane/Et₂O 10:1) = 0.2; IR: 2978, 2940, 2882, 1727, 1458, 1370, 1254, 1210, 1146, 1087, 1048, 963, 918, 869, 849, 767, 744, 701 cm⁻¹; MS (+ESI) m/z , (%): 513 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₃₂H₅₃N₂O₃ 513.4051; Found 513.4052; ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.14 (m, 10H, Ph, Ph*), 4.19 (d, $J = 4.2$ Hz, 1H, CHOTMP), 4.13 (d, $J = 5.2$ Hz, 1H, CHOTMP*), 3.98 (q, $J = 6.7$ Hz, 1H, PhCHCH₃*), 3.80 (q, $J = 6.7$ Hz, 1H, PhCHCH₃), 3.34 (d, $J = 6.5$ Hz, 1H, CHCO₂*), 3.19 (d, $J = 9.0$ Hz, 1H, CH₂N), 3.12-3.05 (m, 1H, CHCH₂CH₃), 2.92 (dt, $J = 10.0, 3.7$ Hz, 1H, CHCH₂CH₃), 2.86 (d, $J = 8.9$ Hz, 1H, CH₂N), 2.84 (d, $J = 6.5$ Hz, 1H, CH₂N*), 2.41-2.22 (m, 4H, CH₂CHOTMP, CH₂CHOTMP*, CH₂N*), 2.15 (d, $J = 4.3$ Hz, 1H, CHCO₂), 1.98-1.57 (m, 9H, CH₂, CH₂*, CH₂CHOTMP), 1.50-1.15 (m, 43H, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*, CH₂CH₃, CH₂CH₃*, PhCHCH₃, PhCHCH₃*, C(CH₃)₃*, NC(CH₃)₂*), 1.44 (s, 9H, C(CH₃)₃), 1.18 (s, 3H, NC(CH₃)₂), 1.09 (s, 3H, NC(CH₃)₂), 1.08 (s, 3H, NC(CH₃)₂), 0.97 (s, 3H, NC(CH₃)₂), 0.89 (t, $J = 7.5$ Hz, 3H,

CH₂CH₃*), 0.68 (t, $J = 7.4$ Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 175.3 (C, CO₂*), 175.1 (C, CO₂), 146.5 (C, *ipso*-Ph), 145.8 (C, *ipso*-Ph*), 128.04 (CH, Ph), 127.97 (CH, Ph*), 127.6 (CH, Ph), 127.3 (CH, Ph*), 126.5 (CH, *p*-Ph), 126.3 (CH, *p*-Ph*), 87.4 (CH, CHOTMP), 86.7 (CH, CHOTMP*), 80.4 (C, C(CH₃)₃), 79.9 (C, C(CH₃)₃*), 69.4 (CH, CHCH₂CH₃), 66.3 (CH, CHCH₂CH₃*), 61.0 (C, NC(CH₃)₂, NC(CH₃)₂*), 59.8 (CH, PhCHCH₃), 59.1 (C, NC(CH₃)₂, NC(CH₃)₂*), 58.0 (CH, CHCO₂), 57.6 (C, C, C*), 57.1 (CH₂, CH₂N*), 56.5 (CH₂, CH₂N), 54.9 (CH, PhCHCH₃*), 51.4 (CH, CHCO₂*), 41.14 (CH₂, NCCH₂CH₂CH₂CN*), 40.96 (CH₂, NCCH₂CH₂CH₂CN*), 40.8 (CH₂, NCCH₂CH₂CH₂CN), 40.5 (CH₂, NCCH₂CH₂CH₂CN), 38.4 (CH₂, CCH₂), 36.7 (CH₂, CCH₂*), 35.6 (CH₃, NC(CH₃)₂), 35.0 (CH₃, NC(CH₃)₂*), 33.8 (CH₃, NC(CH₃)₂), 33.6 (CH₃, NC(CH₃)₂*), 28.9 (CH₂, CH₂), 28.33 (CH₃, C(CH₃)₃*), 28.29 (CH₂, CH₂CHO), 28.26 (CH₃, C(CH₃)₃), 27.2 (CH₂, CH₂), 26.3 (CH₂, CH₂), 21.3 (CH₂, CHCH₂CH₃*), 20.8 (CH₂, CHCH₂CH₃), 20.7 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 17.40 (CH₂, NCCH₂CH₂CH₂CN*), 17.35 (CH₂, NCCH₂CH₂CH₂CN), 17.1 (CH₃, PhCHCH₃), 15.4 (CH₃, PhCHCH₃*), 10.6 (CH₃, CHCH₂CH₃), 10.1 (CH₃, CHCH₂CH₃*).

(R)-tert-Butyl 3-[(cyclopent-1-en-1-ylmethyl)((R)-1-phenylethyl)amino]pentanoate (3-77b):



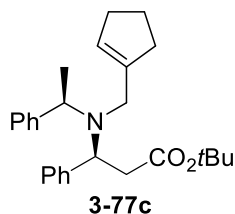
R_f(pentane/Et₂O 10:1) = 0.6; $[\alpha]_D^{20} +10.1$ (c 0.8, CHCl₃); IR: 3028, 2972, 2931, 2871, 2846, 2819, 1725, 1493, 1453, 1390, 1366, 1327, 1291, 1255, 1204, 1143, 1092, 1062, 1028, 991, 966, 920, 849, 763, 701 cm⁻¹; MS (+ESI) m/z , (%): 358 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₂₃H₃₆NO₂ 358.2741; Found 358.2737; ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.16 (m, 5H, Ph), 5.65-5.59 (m, 1H, C=CH), 3.85 (q, $J = 7.0$ Hz, 1H, PhCHCH₃), 3.22-3.12 (m, 1H, CHN), 3.11-3.02 (m, 2H, NCH₂C=), 2.44-2.27 (m, 3H, CH₂), 2.26-2.14 (m, 1H, CH₂), 1.92-1.84 (m, 2H, CH₂), 1.84-1.74 (m, 2H, CH₂CO₂), 1.40-1.36 (m, 12H, PhCHCH₃, C(CH₃)₃), 1.36-1.21 (m, 2H, CH₂CH₃), 0.93 (t, $J = 7.3$ Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 172.6 (C, CO₂), 144.9 (C, *ipso*-Ph), 143.5 (C, C=CH), 128.1 (CH, Ph), 128.0 (CH, Ph), 126.8 (CH, Ph), 126.6 (CH, C=CH), 79.9 (C, C(CH₃)₃), 57.6 (CH, PhCHCH₃), 55.4 (CH, CHN), 46.3 (CH₂, NCH₂C=), 37.9 (CH₂, CH₂CO₂), 33.9 (CH₂, CH₂), 32.6 (CH₂, CH₂),

CHOTMP**), 87.0 (CH, CHOTMP*), 86.9 (CH, CHOTMP), 80.8 (C, C(CH₃)₃), 80.7 (C, C(CH₃)₃*), 80.3 (C, C(CH₃)₃**), 70.0 (CH, CHPh), 69.4 (CH, CHPh**), 68.4 (CH, CHPh*), 62.9 (CH, CHCO₂), 61.1 (C, NC(CH₃)₂*, NC(CH₃)₂**), 61.02 (C, NC(CH₃)₂**), 60.96 (C, NC(CH₃)₂*), 60.9 (CH, CHCO₂*), 59.1 (C, NC(CH₃)₂), 57.8 (C, C), 56.2 (CH, CHCO₂**), 56.1 (C, C*), 56.0 (C, C**), 55.5 (CH, PhCHCH₃), 54.4 (CH, PhCHCH₃*), 54.1 (CH₂, CH₂N**), 53.8 (CH₂, CH₂N), 53.0 (CH, PhCHCH₃**), 51.8 (CH₂, CH₂N*), 40.9 (CH₂, NCCH₂CH₂CH₂CN*), 40.8 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN**), 40.6 (CH₂, NCCH₂CH₂CH₂CN*), 40.5 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN**), 39.6 (CH₂, CH₂), 35.5 (CH₃, NC(CH₃)₂), 35.2 (CH₃, NC(CH₃)₂**), 34.8 (CH₃, NC(CH₃)₂*), 34.5 (CH₃, NC(CH₃)₂*), 33.9 (CH₃, NC(CH₃)₂), 33.6 (CH₃, NC(CH₃)₂**), 32.7 (CH₂, CH₂*), 32.4 (CH₂, CH₂**), 28.6 (CH₂, CH₂*), 28.4 (CH₂, CH₂), 28.2 (CH₃, C(CH₃)₃, C(CH₃)₃*, C(CH₃)₃**), 27.2 (CH₂, CH₂**), 21.2 (CH₂, CH₂**), 20.8 (CH₂, CH₂), 20.71 (CH₃, NC(CH₃)₂, NC(CH₃)₂*, NC(CH₃)₂**), 20.65 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 19.5 (CH₂, CH₂*), 17.4 (CH₂, NCCH₂CH₂CH₂CN*), 17.3 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN**), 12.2 (CH₃, PhCHCH₃), 9.9 (CH₃, PhCHCH₃*), 9.5 (CH₃, PhCHCH₃**).

(*S*)-*tert*-Butyl

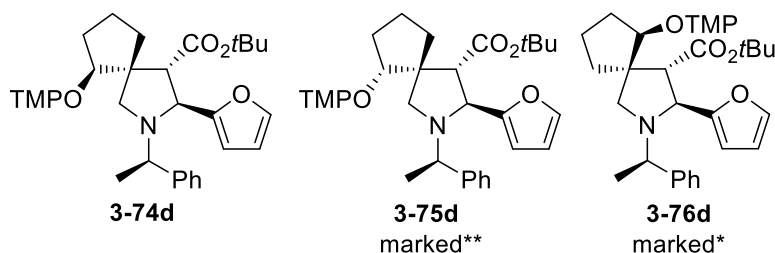
3-[(cyclopent-1-en-1-ylmethyl)((*R*)-1-phenylethyl)amino]-3-

phenylpropanoate (3-77c):



R_f(hexane/EtOAc 50:1) = 0.3; ¹H NMR (400 MHz, CDCl₃): δ 7.33-7.11 (m, 10H, Ph), 5.56 (t, *J* = 2.0 Hz, 1H, C=CH), 4.39 (dd, *J* = 8.9, 6.0 Hz, 1H, PhCHN), 3.98 (q, *J* = 6.8 Hz, 1H, PhCHCH₃), 3.15 (d, *J* = 14.8 Hz, 1H, NCH₂C=), 3.10 (d, *J* = 14.9 Hz, 1H, NCH₂C=), 2.64-2.59 (m, 1H, CH₂CO₂), 2.59-2.52 (m, 1H, CH₂CO₂), 2.35-2.03 (m, 4H, CH₂), 1.85-1.74 (m, 2H, CH₂), 1.26 (s, 9H, C(CH₃)₃), 1.19 (d, *J* = 6.8 Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.5 (C, CO₂), 144.8 (C, *ipso*-Ph), 144.6 (C, C=CH), 142.1 (C, *ipso*-Ph), 128.3 (CH, Ph), 128.06 (CH, Ph), 128.05 (CH, Ph), 127.8 (CH, Ph), 127.0 (CH, *p*-Ph), 126.7 (CH, *p*-Ph), 126.6 (CH, C=CH), 80.2 (C, C(CH₃)₃), 59.2 (CH, PhCHN), 56.4 (CH, PhCHCH₃), 47.4 (CH₂, NCH₂C=CH), 38.8 (CH₂, CH₂CO₂), 33.8 (CH₂, CH₂), 32.5 (CH₂, CH₂), 28.0 (CH₃, C(CH₃)₃), 23.5 (CH₂, CH₂), 16.1 (CH₃, PhCHCH₃).

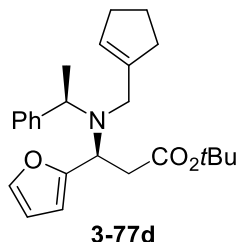
(3*S*,4*S*,5*R*,6*S*)-, (3*S*,4*S*,5*R*,6*R*)- and (3*S*,4*S*,5*S*,6*R*)-*tert*-Butyl 3-(furan-2-yl)-2-((*R*)-1-phenylethyl)-6-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-2-azaspiro[4.4]nonane (3-74d+3-75d+3-76d):



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 5:1) to afford 91 mg (47%) of **3-74d+3-75d+3-76d** as a 6:1:2 mixture of three diastereomers as a colorless oil and 24 mg (17%) of **3-77d** as a single diastereomer as a pale yellow oil. R_f (hexane/EtOAc 30:1) = 0.4; IR: 2972, 2931, 2873, 1720, 1493, 1477, 1453, 1391, 1366, 1305, 1273, 1244, 1208, 1150, 1140, 1075, 1045, 1030, 1010, 959, 944, 915, 877, 850, 806, 778, 762, 731, 699 cm^{-1} ; MS (+ESI) m/z , (%): 551 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{34}\text{H}_{51}\text{N}_2\text{O}_4$ 551.3843; Found 551.3844; ^1H NMR (400 MHz, CDCl_3): δ 7.39-7.05 (m, 18H, Ph, Fur, Ph*, Fur*, Ph**, Fur**), 6.21 (dd, $J = 3.2, 1.8$ Hz, 1H, Fur**), 6.18-6.14 (m, 2H, Fur**, Fur*), 6.08 (dd, $J = 3.2, 1.8$ Hz, 1H, Fur), 6.01 (dd, $J = 3.2, 0.8$ Hz, 1H, Fur*), 5.86 (d, $J = 3.1$ Hz, 1H, Fur), 4.45-4.29 (m, 4H, CHN^* , CHOTMP^* , CHN^{**} , CHOTMP^{**}), 4.20 (d, $J = 4.6$ Hz, 2H, CHN , CHOTMP), 3.85 (q, $J = 6.7$ Hz, 2H, PhCHCH_3 , PhCHCH_3^{**}), 3.76 (d, $J = 6.8$ Hz, 1H, CH_2N^{**}), 3.57 (q, $J = 6.6$ Hz, 1H, PhCHCH_3^*), 3.37 (d, $J = 8.9$ Hz, 1H, CH_2N^*), 3.27 (d, $J = 9.1$ Hz, 1H, CH_2N), 3.05 (d, $J = 6.1$ Hz, 1H, CHCO_2^*), 2.97 (d, $J = 9.1$ Hz, 1H, CH_2N), 2.55 (d, $J = 4.7$ Hz, 1H, CHCO_2), 2.45-2.20 (m, 5H, CH_2 , CH_2N^* , CH_2N^{**} , CHCO_2^{**}), 1.99-0.81 (m, 106H, CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$, $\text{C}(\text{CH}_3)_3$, PhCHCH_3 , $\text{NC}(\text{CH}_3)_2$, CH_2^* , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^*$, $\text{C}(\text{CH}_3)_3^*$, PhCHCH_3^* , $\text{NC}(\text{CH}_3)_2^*$, CH_2^{**} , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^{**}$, $\text{C}(\text{CH}_3)_3^{**}$, PhCHCH_3^{**} , $\text{NC}(\text{CH}_3)_2^{**}$); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0 (C, CO_2^{**}), 173.8 (C, CO_2), 172.7 (C, CO_2^*), 156.6 (C, *ipso*-Fur), 156.3 (C, *ipso*-Fur*), 155.4 (C, *ipso*-Fur**), 145.4 (C, *ipso*-Ph*), 145.1 (C, *ipso*-Ph), 144.8 (C, *ipso*-Ph**), 141.8 (CH, Fur**), 141.3 (CH, Fur, Fur*), 128.0 (CH, Ph*), 127.8 (CH, Ph**), 127.8 (CH, Ph), 127.43 (CH, Ph*), 127.36 (CH, Ph), 127.1 (CH, Ph**), 126.4 (CH, Ph*), 126.3 (CH, Ph, Ph**), 110.1 (CH, Fur), 110.0 (CH, Fur*, Fur**), 107.4 (CH, Fur**), 107.2 (CH, Fur*), 106.5 (CH, Fur), 87.2 (CH, CHOTMP), 87.0 (CH, CHOTMP^{**}), 85.9 (CH, CHOTMP^*), 81.0 (C, $\text{C}(\text{CH}_3)_3$, $\text{C}(\text{CH}_3)_3^*$), 80.5 (C, $\text{C}(\text{CH}_3)_3^{**}$), 64.0 (CH, CHN), 62.6 (CH, CHN^{**}),

61.6 (CH, CHN*), 61.2 (C, NC(CH₃)₂*), 61.1 (C, NC(CH₃)₂**), 61.0 (C, NC(CH₃)₂), 59.7 (CH, PhCHCH₃), 59.5 (CH, PhCHCH₃*), 59.2 (C, NC(CH₃)₂, NC(CH₃)₂*, NC(CH₃)₂**), 58.6 (CH, CHCO₂), 58.1 (C, C), 57.2 (CH, CHCO₂*), 56.6 (C, C*), 56.4 (C, C**), 55.7 (CH₂, CH₂N), 55.22 (CH, PhCHCH₃**), 55.17 (CH₂, CH₂N**), 53.9 (CH₂, CH₂N*), 52.1 (CH, CHCO₂**), 41.1 (CH₂, NCCH₂CH₂CH₂CN**), 40.9 (CH₂, NCCH₂CH₂CH₂CN**), 40.7 (CH₂, NCCH₂CH₂CH₂CN), 40.6 (CH₂, NCCH₂CH₂CH₂CN*), 40.5 (CH₂, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 37.9 (CH₂, CH₂), 35.6 (CH₃, NC(CH₃)₂), 34.8 (CH₃, NC(CH₃)₂*), 34.5 (CH₃, NC(CH₃)₂*), 33.8 (CH₃, NC(CH₃)₂, NC(CH₃)₂**), 33.6 (CH₃, NC(CH₃)₂**), 32.0 (CH₂, CH₂**), 31.6 (CH₂, CH₂*), 28.32 (CH₃, C(CH₃)₃**), 28.27 (CH₃, C(CH₃)₃, C(CH₃)₃*), 28.8 (CH₂, CH₂*), 28.23 (CH₂, CH₂), 27.0 (CH₂, CH₂**), 21.2 (CH₂, CH₂**), 20.9 (CH₂, CH₂), 20.8 (CH₃, NC(CH₃)₂, NC(CH₃)₂*, NC(CH₃)₂**), 19.9 (CH₂, CH₂*), 18.2 (CH₃, PhCHCH₃*), 17.42 (CH₂, NCCH₂CH₂CH₂CN*), 17.39 (CH₂, NCCH₂CH₂CH₂CN**), 17.3 (CH₂, NCCH₂CH₂CH₂CN), 16.8 (CH₃, PhCHCH₃), 12.5 (CH₃, PhCHCH₃**).

(S)-tert-Butyl 3-[(cyclopent-1-en-1-ylmethyl)((R)-1-phenylethyl)amino]-3-(furan-2-yl)propanoate (3-77d):

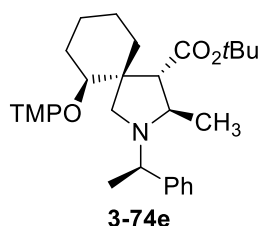


R_f(hexane/EtOAc 5:1) = 0.6; [α]_D²⁰ −1.6 (*c* 0.2, CHCl₃); IR: 2926, 2852, 1729, 1494, 1454, 1391, 1366, 1302, 1281, 1258, 1208, 1143, 1081, 1032, 1011, 977, 957, 928, 910, 884, 852, 805, 731, 699 cm^{−1}; MS (+ESI) *m/z*, (%): 396 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₂₅H₃₄NO₃ 396.2533; Found 396.2531; ¹H NMR (400 MHz, CDCl₃): δ 7.43-7.38 (m, 2H, Ph), 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H, Fur), 7.32-7.26 (m, 2H, Ph), 7.23-7.16 (m, 1H, Ph), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H, Fur), 6.13 (dt, *J* = 3.3, 0.7 Hz, 1H, Fur), 5.55 (t, *J* = 1.8 Hz, 1H, C=CH), 4.48 (dd, *J* = 8.3, 6.9 Hz, 1H, CHN), 4.03 (q, *J* = 6.9 Hz, 1H, PhCHCH₃), 3.22 (d, *J* = 14.0 Hz, 1H, NCH₂C=), 3.02 (d, *J* = 14.0 Hz, 1H, NCH₂C=), 2.70 (dd, *J* = 15.4, 8.0 Hz, 1H, CH₂CO₂), 2.64 (dd, *J* = 15.0, 6.8 Hz, 1H, CH₂CO₂), 2.37-2.19 (m, 3H, CH₂), 2.16-2.02 (m, 1H, CH₂), 1.91-1.74 (m, 2H, CH₂), 1.36 (s, 9H, C(CH₃)₃), 1.07 (d, *J* = 6.8 Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.9 (C, CO₂), 155.2 (C, *ipso*-Fur), 145.4 (C,

C=CH), 143.9 (C, *ipso*-Ph), 141.3 (CH, Fur), 127.9 (CH, Ph), 127.7 (CH, Ph), 127.4 (CH, C=CH), 126.5 (CH, *p*-Ph), 110.2 (CH, Fur), 107.3 (CH, Fur), 80.4 (C, C(CH₃)₃), 56.3 (CH, PhCHCH₃), 52.0 (CH, FurCHN), 47.5 (CH₂, NCH₂C=CH), 38.6 (CH₂, CH₂CO₂), 33.7 (CH₂, CH₂), 32.5 (CH₂, CH₂), 28.1 (CH₃, C(CH₃)₃), 23.6 (CH₂, CH₂), 16.2 (CH₃, PhCHCH₃).

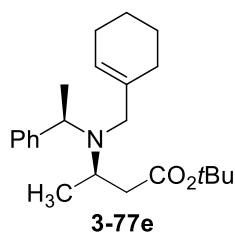
(3*R*,4*S*,5*R*,6*S*)-*tert*-Butyl

3-methyl-2-((*R*)-1-phenylethyl)-6-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-2-azaspiro[4.5]decane-4-carboxylate (3-74e):



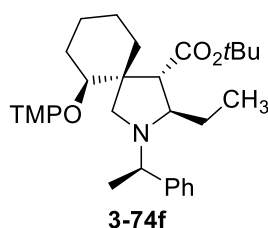
Prepared according to the general procedure (Method B). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 80:1 gradient to 5:1) to afford 76 mg (42%) of **3-74e** as a 8:1 mixture of two diastereomers as a pale yellow oil and 40 mg (32%) of **3-77e** as a single diastereomer as a pale yellow oil. R_f (hexane/EtOAc 5:1) = 0.2; IR: 2972, 2929, 2870, 1730, 1453, 1391, 1367, 1338, 1301, 1276, 1256, 1242, 1208, 1146, 1131, 1087, 1062, 1042, 975, 954, 907, 877, 850, 786, 762, 742, 699 cm⁻¹; MS (+ESI) m/z , (%): 513 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₃₂H₅₃N₂O₃ 513.4051; Found 513.4051; ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.15 (m, 5H, Ph), 4.06-3.92 (m, 2H, CHO, PhCHCH₃), 3.15 (dq, J = 9.2, 5.9 Hz, 1H, CHCHCH₃), 3.07 (d, J = 8.9 Hz, 1H, CH₂N), 2.52 (d, J = 8.8 Hz, 1H, CH₂N), 2.17 (d, J = 9.2 Hz, 1H, CHCO₂), 1.87-1.75 (m, 1H, CH₂), 1.67-1.24 (m, 13H, CH₂, NCCH₂CH₂CH₂CN), 1.47 (s, 9H, C(CH₃)₃), 1.37 (d, J = 6.8 Hz, 3H, PhCHCH₃), 1.17 (s, 6H, NC(CH₃)₂), 1.15 (s, 6H, NC(CH₃)₂), 0.97 (d, J = 5.9 Hz, 3H, CHCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 172.9 (C, CO₂), 145.6 (C, *ipso*-Ph), 128.0 (CH, Ph), 127.6 (CH, Ph), 126.4 (CH, Ph), 82.2 (CH, CHOTMP), 80.7 (C, C(CH₃)₃), 63.5 (CH, CHCO₂), 59.2 (CH, CHCHCH₃), 56.3 (CH, PhCHCH₃), 52.6 (C, C), 48.4 (CH₂, CH₂N), 41.4 (CH₂, NCCH₂CH₂CH₂CN), 38.4 (CH₂, CCH₂), 28.6 (CH₃, C(CH₃)₃), 27.0 (CH₂, CH₂), 23.6 (CH₂, CH₂), 23.5 (CH₂, CH₂), 19.7 (CH₃, CHCHCH₃), 17.2 (CH₂, NCCH₂CH₂CH₂CN), 14.3 (CH₃, PhCHCH₃).

***tert*-Butyl (*R*)-3-[(cyclohex-1-en-1-ylmethyl)((*R*)-1-phenylethyl)amino]butanoate (**3-77e**):**



R_f (hexane/EtOAc 5:1) = 0.6; $[\alpha]_D^{20}$ -19.0 (c 0.5, CHCl_3); IR: 2972, 2928, 2835, 1725, 1493, 1452, 1390, 1366, 1298, 1256, 1207, 1147, 1081, 1037, 993, 957, 918, 844, 783, 763, 738, 699 cm^{-1} ; MS (+ESI) m/z , (%): 358 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{23}\text{H}_{36}\text{NO}_2$ 358.2741; Found 358.2739; ^1H NMR (400 MHz, CDCl_3): δ 7.46-7.13 (m, 5H, Ph), 5.62-5.58 (m, 1H, $\text{C}=\text{CH}$), 3.90 (q, J = 6.8 Hz, 1H, PhCHCH_3), 3.44-3.34 (m, 1H, CHN), 2.99 (d, J = 13.7 Hz, 1H, NCH_2), 2.83 (d, J = 14.1 Hz, 1H, NCH_2), 2.18 (dd, J = 14.3, 5.1 Hz, 1H, CH_2CO_2), 2.04-1.85 (m, 4H, CH_2CO_2 , CH_2), 1.64-1.48 (m, 5H, CH_2), 1.39 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.36 (d, J = 6.9 Hz, 3H, PhCHCH_3), 1.02 (d, J = 6.7 Hz, 3H, CH_2CHCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 172.3 (C, CO_2), 145.0 (C, *ipso*-Ph), 137.5 (C, $\text{C}=\text{CH}$), 128.0 (CH, Ph), 127.9 (CH, Ph), 126.5 (CH, *p*-Ph), 123.8 (CH, $\text{C}=\text{CH}$), 79.9 (C, $\text{C}(\text{CH}_3)_3$), 57.5 (CH, PhCHCH_3), 52.7 (CH_2 , CH_2N), 49.9 (CH, CHN), 41.4 (CH_2 , CH_2CO_2), 28.2 (CH_3 , $\text{C}(\text{CH}_3)_3$), 26.7 (CH_2 , CH_2), 25.5 (CH_2 , CH_2), 23.1 (CH_2 , CH_2), 22.9 (CH_2 , CH_2), 18.3 (CH_3 , PhCHCH_3), 17.8 (CH_3 , CH_2CHCH_3).

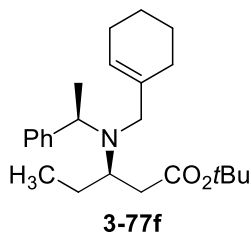
(3*R*,4*S*,5*R*,6*S*)-*tert*-Butyl 3-ethyl-2-((*R*)-1-phenylethyl)-6-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-2-azaspiro[4.5]decane-4-carboxylate (3-74f** + **3-76f**):**



Prepared according to the general procedure (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 80:1 gradient to 5:1) to afford 80 mg (43%) of **3-74f:3-76f** as a 6.7:1 mixture of two diastereomers as a colorless solid and 22 mg (17%) of **3-77f** as a single diastereomer as a colorless oil. Mp: 88-90 °C; R_f (pentane/Et₂O 10:1) = 0.2; IR: 2970, 2929, 2872, 1720, 1453, 1366, 1318, 1256, 1207, 1134, 1016, 974, 908, 877, 864, 850, 782, 765, 733, 699 cm^{-1} ; MS (+ESI) m/z , (%): 527 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{33}\text{H}_{55}\text{N}_2\text{O}_3$ 527.4207; Found 527.4208; ^1H

NMR (400 MHz, CDCl₃): δ 7.48-7.36 (m, 2H, Ph), 7.34-7.13 (m, 3H, Ph), 3.99 (t, J = 4.5 Hz, 1H, CHOTMP), 3.93 (q, J = 6.5 Hz, 1H, PhCHCH₃), 3.10 (d, J = 8.8 Hz, 1H, CH₂N), 3.03 (td, J = 7.0, 2.8 Hz, 1H, CHCH₂CH₃), 2.58 (d, J = 8.7 Hz, 1H, CH₂N), 2.46 (d, J = 6.9 Hz, 1H, CHCO₂), 1.91-1.22 (m, 16H, CH₂, NCCH₂CH₂CH₂CN, CHCH₂CH₃), 1.47 (s, 9H, C(CH₃)₃), 1.38 (d, J = 6.8 Hz, 3H, PhCHCH₃), 1.16 (s, 12H, NC(CH₃)₃), 0.75 (t, J = 7.4 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.3 (C, CO₂), 145.9 (C, *ipso*-Ph), 128.0 (CH, Ph), 127.5 (CH, Ph), 126.4 (CH, Ph), 80.7 (CH, CHOTMP), 80.5 (C, C(CH₃)₃), 65.6 (CH, CHCH₂CH₃), 60.1 (C, C), 59.2 (C, NC(CH₃)₂), 59.1 (C, NC(CH₃)₂), 57.0 (CH, PhCHCH₃, CHCO₂), 54.8 (CH₂, CH₂N), 41.6 (CH₂, NCCH₂CH₂CH₂CN), 40.6 (CH₂, NCCH₂CH₂CH₂CN), 35.7 (CH₂, CCH₂), 34.9 (CH₃, NC(CH₃)₂), 34.2 (CH₃, NC(CH₃)₂), 28.5 (CH₃, C(CH₃)₃), 26.2 (CH₂, CH₂CHO, CH₂), 22.5 (CH₂, CH₂), 22.4 (CH₂, CHCH₂CH₃), 21.0 (CH₃, NC(CH₃)₂), 20.8 (CH₃, NC(CH₃)₂), 17.2 (CH₂, NCCH₂CH₂CH₂CN), 14.5 (CH₃, PhCHCH₃), 9.2 (CH₃, CH₂CH₃).

tert-Butyl (R)-3-[(cyclohex-1-en-1-ylmethyl)((R)-1-phenylethyl)amino]pentanoate (3-77f):

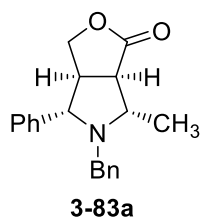


R_f(pentane/Et₂O 10:1) = 0.6; [α]_D²⁰ +13.2 (c 0.5, CHCl₃); IR: 2972, 2928, 2872, 2835, 1725, 1492, 1453, 1390, 1366, 1329, 1289, 1254, 1203, 1143, 1093, 1061, 1028, 992, 957, 919 cm⁻¹; MS (+ESI) m/z , (%): 527 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₃₃H₅₅N₂O₃ 527.4207; Found 527.4208; ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.12 (m, 5H, Ph), 5.67 (s, 1H, C=CH), 3.87 (q, J = 7.0 Hz, 1H, PhCHCH₃), 3.23-3.12 (m, 1H, CHN), 2.99 (d, J = 13.2 Hz, 1H, NCH₂), 2.83 (d, J = 13.8 Hz, 1H, NCH₂), 2.15-1.83 (m, 4H, CH₂), 1.79 (dd, J = 14.9, 9.0 Hz, 1H, CH₂CO₂), 1.72 (dd, J = 14.9, 4.0 Hz, 1H, CH₂CO₂), 1.66-1.02 (m, 6H, CH₂, CH₂CH₃), 1.38 (s, 9H, C(CH₃)₃), 0.94 (t, J = 7.3 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 172.5 (C, CO₂), 143.3 (C, *ipso*-Ph), 137.3 (C, C=CH), 128.0 (CH, Ph), 127.9 (CH, Ph), 126.6 (CH, Ph), 124.0 (CH, C=CH), 79.7 (C, C(CH₃)₃), 56.7 (CH, PhCHCH₃), 55.0 (CH, CHN), 52.7 (CH₂, CH₂N), 37.9 (CH₂, CH₂CO₂), 28.1 (CH₃, C(CH₃)₃), 26.8 (CH₂, CH₂), 25.9 (CH₂, CH₂), 25.4 (CH₂, CH₂), 23.0 (CH₂, CH₂), 22.8 (CH₂, CH₂), 19.7 (CH₃, PhCHCH₃), 12.0 (CH₃, CH₂CH₃).

General procedure for reductive N-O bond cleavage of mono- and bicyclic, and spirocyclic pyrrolidines: A (mono- or bicyclic, or spirocyclic) pyrrolidine (amounts at individual compounds) was dissolved in acetic acid (typically 6 mL/mmol of substrate). Then, water (2 mL/mmol of substrate) was added. THF was added dropwise to the resulting turbid solution until the solution became clear. Zinc dust (10 μ m, 50 equivalents) was added portionwise with vigorous stirring and the resulting mixture was heated at 70 °C until the starting material was consumed as indicated by TLC. The reaction mixture was cooled to room temperature, diluted with DCM to the triple volume and filtered. The filtrate was neutralized with saturated K₂CO₃ solution until a pH of ca. 10 was reached. The layers were separated and the organic was washed twice with water, dried over MgSO₄ and evaporated to furnish the crude product, which was purified by flash chromatography.

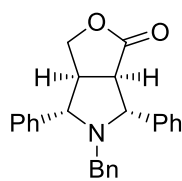
(3a*S*,4*S*,6*S*,6a*R*)-5-Benzyl-6-methyl-4-phenylhexahydro-1*H*-furo[3,4-*c*]pyrrol-1-one

(3-83a):



Prepared according to the general procedure for reductive N-O bond cleavage using **3-51a** (92 mg, 0.176 mmol, d.r. >20:1). Purification by flash column chromatography (hexane/EtOAc 5:1) afforded 44 mg (80%) of **3-83a** as a colorless oil. R_f (hexane/EtAc 5:1) = 0.2; $[\alpha]_D^{20}$ -17.7 (c 0.5, CHCl₃); IR: 3062, 3028, 2969, 2927, 2806, 1764, 1493, 1454, 1370, 1333, 1301, 1276, 1242, 1150, 1096, 1068, 1047, 1028, 990, 944, 842, 755, 739, 699 cm⁻¹; MS (+CI) m/z , (%): 308 (100, M+H⁺), 292 (25, M+H⁺-CH₄), 216 (20, M+H⁺-PhCH₃), 91 (15, PhCH₂⁺); HRMS (+CI) m/z : [M+H⁺] Calcd for C₂₀H₂₂NO₂ 308.1651; Found 308.1650; ¹H NMR (400 MHz, CDCl₃): δ 7.48-7.42 (m, 2H, Ph), 7.41-7.16 (m, 6H, Ph), 7.12-7.06 (m, 2H, Ph), 4.24-4.16 (m, 2H, CH₂O), 3.78 (d, J = 14.3 Hz, 1H, CH₂Ph), 3.38 (d, J = 14.3 Hz, 1H, CH₂Ph), 3.35 (d, J = 8.9 Hz, 1H, CHPh), 3.01-2.97 (m, 1H, CHCHCH₃), 2.87 (dddd, J = 9.7, 8.6, 6.1, 2.3 Hz, 1H, CHCH₂O), 2.75 (dd, J = 9.7, 5.4 Hz, 1H, CHCO), 1.25 (d, J = 6.1 Hz, 3H, CHCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 179.1 (C, CO), 140.4 (C, *ipso*-Ph), 137.1 (C, *ipso*-Ph), 129.4 (CH, Ph), 129.1 (CH, Ph), 128.3 (CH, *p*-Ph), 128.2 (CH, Ph), 128.0 (CH, Ph), 127.2 (CH, *p*-Ph), 74.0 (CH, CHPh), 69.5 (CH₂, CH₂O), 62.0 (CH, CHCHCH₃), 54.0 (CH₂, CH₂Ph), 50.3 (CH, CHCO), 48.1 (CH, CHCH₂O), 21.6 (CH₃, CHCHCH₃).

(3*aS*,4*S*,6*R*,6*aR*)-5-Benzyl-4,6-diphenylhexahydro-1*H*-furo[3,4-*c*]pyrrol-1-one (3-83b):



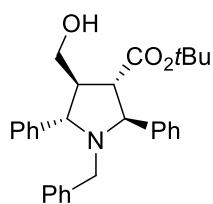
3-83b

Prepared according to the general procedure for reductive N-O bond cleavage using **3-51b** (76 mg, 0.130 mmol, d.r. 6:1). Purification by flash column chromatography (hexane/EtOAc 5:1) afforded 31 mg (77%) of **3-83b** as a colorless solid and 9 mg (12%) of **3-84b** as a colorless oil. Mp: 120-121 °C; R_f (hexane/EtOAc 5:1) = 0.3; $[\alpha]_D^{20} +38.8$ (c 0.5, CHCl₃); IR: 3062, 3029, 2973, 2925, 2853, 2804, 1771, 1492, 1455, 1370, 1271, 1200, 1149, 1113, 1069, 1044, 1028, 989, 755, 699 cm⁻¹; MS (+ESI) m/z , (%): 392 (25, M+Na⁺), 370 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₂₅H₂₄NO₂ 370.1802; Found 370.1797; ¹H NMR (400 MHz, CDCl₃): δ 7.64-7.09 (m, 13H, Ph), 6.87-6.80 (m, 2H, Ph), 4.20-4.17 (m, 2H, CH₂O), 4.02 (d, J = 4.2 Hz, 1H, CHPh), 3.59 (d, J = 14.3 Hz, 1H, CH₂Ph), 3.54 (d, J = 14.3 Hz, 1H, CH₂Ph), 3.47 (d, J = 7.9 Hz, 1H, CHPh), 3.01-2.91 (m, 2H, CHCH₂O, CHCO); ¹³C NMR (100 MHz, CDCl₃) δ 178.4 (C, CO), 142.4 (C, *ipso*-Ph), 140.0 (C, *ipso*-Ph), 134.0 (C, *ipso*-Ph), 130.3 (CH, Ph), 129.2 (CH, Ph), 128.9 (CH, Ph), 128.4 (CH, *p*-Ph), 128.1 (CH, Ph), 128.0 (CH, Ph), 127.8 (CH, *p*-Ph), 127.7 (CH, Ph), 127.3 (CH, *p*-Ph), 70.8 (CH, CHPh), 69.1 (CH₂, CH₂O), 67.4 (CH, CHPh), 51.5 (CH, CHCO), 51.3 (CH₂, CH₂Ph), 48.7 (CH, CHCH₂O).

(2*S*,3*S*,4*S*,5*S*)-*tert*-Butyl

1-benzyl-4-(hydroxymethyl)-2,5-diphenylpyrrolidine-3-

carboxylate



3-84b

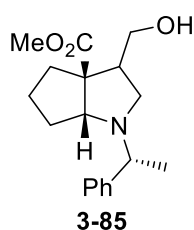
R_f (hexane/EtOAc 5:1) = 0.2; $[\alpha]_D^{20} -29.0$ (c 0.4, CHCl₃); IR: 3394 (br), 3062, 3029, 2976, 2926, 2872, 2853, 2815, 1720, 1493, 1454, 1391, 1367, 1257, 1209, 1149, 1069, 1028, 971, 912, 842, 754, 698 cm⁻¹; MS (+ESI) m/z , (%): 444 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₂₉H₃₄NO₃ 444.2533; Found 444.2536; ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.14 (m, 13H, Ph), 7.08-7.03 (m, 2H, Ph), 4.57 (d, J = 7.7 Hz, 1H, CHPh), 4.12 (d, J = 5.3 Hz, 1H, CHPh), 3.83 (dd, J = 5.7, 2.6 Hz, 2H, CH₂OH), 3.48 (d, J = 14.0 Hz, 1H, CH₂Ph), 3.03 (t, J =

7.8 Hz, CHCO_2), 2.92 (d, $J = 14.3$ Hz, 1H, CH_2Ph), 2.82-2.71 (m, 1H, CHCH_2O), 1.58 (br s, 1H, CH_2OH), 1.42 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 173.3 (C, CO_2), 141.7 (C, *ipso*-Ph), 141.2 (C, *ipso*-Ph), 139.3 (C, *ipso*-Ph), 129.1 (CH, Ph), 128.53 (CH, Ph), 128.49 (CH, Ph), 128.4 (CH, Ph), 128.22 (CH, Ph), 128.15 (CH, Ph), 127.7 (CH, *p*-Ph), 127.6 (CH, *p*-Ph), 126.6 (CH, *p*-Ph), 81.5 (CH_3 , $\text{C}(\text{CH}_3)_3$), 68.6 (CH, CHPh), 67.6 (CH, CHPh), 65.5 (CH_2 , CH_2OH), 56.6 (CH, CHCO_2), 52.4 (CH, CHCH_2OH), 50.5 (CH_2 , CH_2Ph), 28.2 (CH_3 , $\text{C}(\text{CH}_3)_3$).

(3*S*,3*aS*,6*aR*)-Methyl

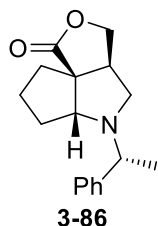
3-(hydroxymethyl)-1-((*R*)-1-

phenylethyl)hexahydrocyclopenta[*b*]pyrrole-3*a*(1*H*)-carboxylate (3-85):



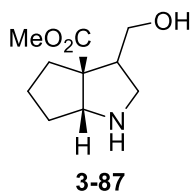
Prepared according to the general procedure for reductive N-O bond cleavage using **3-59a** (220 mg, 0.5 mmol, d.r. 6:1). Purification by flash column chromatography (hexane/EtOAc 5:1) afforded 106 mg (70%) of **3-85** as a colorless oil and 12 mg (9%) of **3-86** as a colorless solid. R_f (hexane/EtOAc 1:1) = 0.2; $[\alpha]_D^{20}$ -6.1 (c 0.5, CHCl_3); IR: 3419 (br), 3037, 2961, 2880, 1729, 1497, 1458, 1439, 1377, 1307, 1266, 1230, 1168, 1086, 1025, 979, 916, 862, 766, 734, 703 cm^{-1} ; MS (+ESI) m/z , (%): 304 (100, $\text{M}+\text{H}^+$), 200 (73, $\text{M}+\text{H}^+ - \text{PhC}=\text{CH}_2$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_3$ 304.1907; Found 304.1906; ^1H NMR (400 MHz, CDCl_3): δ 7.35-7.20 (m, 5H, Ph), 3.80-3.63 (m, 6H, OCH_3 , CHN , CH_2OH), 3.56 (q, $J = 6.6$ Hz, 1H, PhCHCH_3), 3.31 (br s, 1H, CH_2OH), 2.83 (dd, $J = 9.5, 6.2$ Hz, 1H, CH_2N), 2.80-2.69 (m, 1H, CH_2N), 2.65-2.55 (m, 1H, CHCH_2OH), 1.98-1.83 (m, 2H, CH_2CCO_2), 1.81-1.70 (m, 1H, CH_2), 1.66-1.50 (m, 1H, CH_2), 1.45-1.35 (m, 2H, CH_2CHN), 1.40 (d, $J = 6.5$ Hz, 3H, PhCHCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 178.7 (C, CO_2), 144.6 (C, *ipso*-Ph), 128.3 (CH, Ph), 127.5 (CH, Ph), 127.2 (CH, *p*-Ph), 72.7 (CH, CHN), 62.5 (CH_2 , CH_2OH), 61.8 (CH, PhCHCH_3), 61.6 (C, CCO_2), 55.0 (CH_2 , CH_2N), 52.4 (CH_3 , OCH_3), 44.6 (CH, CHCH_2OH), 31.3 (CH_2 , CH_2CCO_2), 30.7 (CH_2 , CH_2CHN), 27.5 (CH_2 , CH_2), 20.7 (CH_3 , PhCHCH_3).

(3a*R*,5a*R*,8a*S*)-5-((*R*)-1-phenylethyl)octahydro-1*H*-cyclopenta[*b*]furo[3,4-*c*]pyrrol-1-one (3-86):



Mp: 92-93 °C; R_f (hexane/EtOAc 1:1) = 0.5; $[\alpha]_D^{20}$ -54.5 (*c* 0.2, CHCl₃); IR: 3027, 2956, 2866, 2798, 1760, 1492, 1453, 1378, 1334, 1304, 1279, 1254, 1225, 1210, 1191, 1160, 1140, 1114, 1061, 1042, 1030, 1006, 985, 965, 942, 917, 760, 731, 702, 680 cm⁻¹; MS (+EI) *m/z*, (%): 271 (7, M⁺), 256 (100, M-CH₃⁺), 105 (22, PhCHCH₃⁺); HRMS (+EI) *m/z*: [M⁺] Calcd for C₁₇H₂₁NO₂ 271.1572; Found 271.1570; ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.18 (m, 5H, Ph), 4.35 (dd, *J* = 9.0, 8.2 Hz, 1H, CH₂O), 4.00 (dd, *J* = 9.0, 4.3 Hz, 1H, CH₂O), 3.83 (dd, *J* = 7.2, 3.4 Hz, 1H, CHN), 3.57 (q, *J* = 6.6 Hz, 1H, PhCHCH₃), 2.82 (dd, *J* = 9.6, 6.0 Hz, 1H, CH₂N), 2.55 (ddt, *J* = 8.4, 6.0, 4.4 Hz, 1H, CHCH₂O), 2.36 (dd, *J* = 9.6, 4.6 Hz, 1H, CH₂N), 2.09-1.97 (m, 1H, CH₂CCO₂), 1.89-1.60 (m, 4H, CH₂CHN, CH₂CCO, CH₂), 1.59-1.46 (m, 1H, CH₂CHN), 1.36 (d, *J* = 6.6 Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 182.8 (C, CO), 145.3 (C, *ipso*-Ph), 128.5 (CH, Ph), 127.3 (CH, Ph), 127.2 (CH, *p*-Ph), 72.8 (CH, CHN), 71.0 (CH₂, CH₂O), 60.4 (CH, PhCHCH₃), 60.1 (C, CCO), 55.5 (CH₂, CH₂N), 45.8 (CH, CHCH₂O), 36.5 (CH₂, CH₂CCO), 28.2 (CH₂, CH₂CHN), 26.9 (CH₂, CH₂), 20.8 (CH₃, PhCHCH₃).

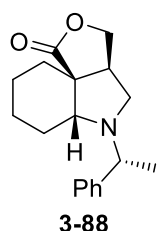
(3*S*,3a*S*,6a*R*)-Methyl 3-(hydroxymethyl)hexahydrocyclopenta[*b*]pyrrole-3a(1*H*)-carboxylate (3-87):



Pearlman's catalyst (12 mg) was added to a solution of **3-85** (40 mg, 0.132 mmol) in MeOH (1 mL) and the mixture was stirred vigorously under 10 bar of H₂ gas at 25 °C for 24 h. The reaction mixture was diluted with MeOH, filtered through Celite[®] (eluent MeOH) and concentrated *in vacuo* to afford 26 mg (98%) of **3-87** as a pale yellow oil. R_f (EtOAc/MeOH 1:1) = 0.2; $[\alpha]_D^{20}$ -6.5 (*c* 0.5, CHCl₃); IR: 3280 (br), 2951, 2871, 1720, 1578, 1434, 1340, 1269, 1208, 1163, 1124, 1086, 1025, 921, 893, 856, 777, 702 cm⁻¹; MS (+ESI) *m/z*, (%): 200

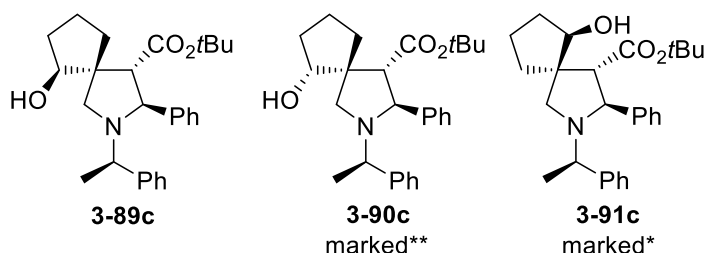
(100, $M+H^+$); HRMS (+ESI) m/z : $[M+H^+]$ Calcd for $C_{10}H_{18}NO_3$ 200.1281; Found 200.1278; ^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (dd, $J = 7.7, 5.6$ Hz, 1H, CHN), 3.81-3.60 (m, 5H, CH_2OH , OCH_3), 3.29-3.16 (m, 1H, CH_2N), 2.76-2.56 (m, 2H, $CHCH_2O$, CH_2N), 2.14-1.95 (m, 2H, CH_2CHN , CH_2CCO_2), 1.82-1.40 (m, 4H, CH_2CHN , CH_2CCO_2 , CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C, CO_2), 70.0 (CH, CHN), 61.8 (C, CCO_2), 61.0 (CH_2 , CH_2OH), 52.6 (CH_3 , OCH_3), 50.6 (CH, $CHCH_2OH$), 49.6 (CH_2 , CH_2N), 34.2 (CH_2 , CH_2CCO_2), 30.6 (CH_2 , CH_2CHN), 26.4 (CH_2 , CH_2).

(3aR,5aR,9aS)-5-((R)-1-phenylethyl)octahydro-1H,3H-furo[3,4-c]indol-1-one (3-88):



Prepared according to the general procedure for reductive N-O bond cleavage using **3-59b** (55 mg, 0.120 mmol, d.r. 8:1). Purification by flash column chromatography (hexane/EtOAc 1:1) afforded 26 mg (76%) of **3-88** as a colorless solid. Mp: 151 °C (dec. without melting); R_f (hexane/EtOAc 1:1) = 0.5; $[\alpha]_D^{20}$ -31.0 (c 0.5, $CHCl_3$); IR: 3028, 2974, 2928, 2856, 2806, 1761, 1491, 1475, 1452, 1377, 1358, 1310, 1277, 1216, 1187, 1170, 1154, 1102, 1070, 1048, 1040, 1027, 1008, 989, 966, 902, 861, 773, 722, 705 cm^{-1} ; MS (+EI) m/z , (%): 285 (17, M^+), 270 (100, $M-CH_3^+$), 208 (20, $M-C_6H_5^+$), 105 (45, $PhCHCH_3^+$); HRMS (+EI) m/z : $[M^+]$ Calcd for $C_{18}H_{23}NO_2$ 285.1729; Found 285.1731; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30-7.18 (m, 5H, Ph), 4.27 (ddd, $J = 9.3, 6.0, 0.9$ Hz, 1H, CH_2O), 4.06 (d, $J = 9.3$ Hz, 1H, CH_2O), 3.63-3.55 (m, 1H, CHN), 3.49 (q, $J = 6.4$ Hz, 1H, $PhCHCH_3$), 2.75 (t, $J = 9.5$ Hz, 1H, CH_2N), 2.63 (ddd, $J = 8.7, 5.9, 2.0$ Hz, 1H, $CHCH_2O$), 2.48 (dd, $J = 10.1, 2.1$ Hz, 1H, CH_2N), 1.91-1.70 (m, 5H, CH_2), 1.32 (d, $J = 6.4$ Hz, 3H, $PhCHCH_3$), 1.30-1.15 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8 (C, CO), 145.8 (C, *ipso*-Ph), 128.5 (CH, Ph), 127.02 (CH, *p*-Ph), 126.97 (CH, Ph), 73.0 (CH_2 , CH_2O), 61.1 (CH, CHN), 58.9 (CH, $PhCHCH_3$), 56.6 (CH_2 , CH_2N), 55.1 (C, CCO), 40.3 (CH, $CHCH_2O$), 28.4 (CH_2 , CH_2), 23.1 (CH_3 , $PhCHCH_3$), 22.9 (CH_2 , CH_2), 22.5 (CH_2 , CH_2), 20.0 (CH_2 , CH_2).

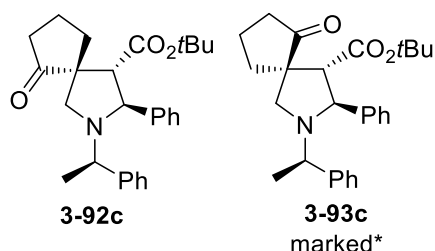
(3*S*,4*S*,5*R*,6*S*)-, (3*S*,4*S*,5*R*,6*R*)- and (3*S*,4*S*,5*S*,6*R*)-*tert*-Butyl 6-hydroxy-3-phenyl-2-((*R*)-1-phenylethyl)-2-azaspiro[4.4]nonane-4-carboxylate (**3-89c**+**3-90c**+**3-91c**):



Prepared according to the general procedure for reductive N-O bond cleavage using **3-74c**+**3-75c**+**3-76c** (108 mg, 0.192 mmol, d.r. 14:1:6). Purification by flash column chromatography (hexane/EtOAc 5:1) afforded 55 mg (68%) of **3-89c**+**3-90c**+**3-91c** as a 14:1:6 mixture of three diastereomers as a colorless solid. R_f (pentane/Et₂O 5:1) = 0.3; IR: 3437, 3061, 3029, 2969, 2874, 1720, 1494, 1454, 1392, 1367, 1287, 1257, 1206, 1148, 1084, 1029, 974, 914, 868, 842, 782, 760, 700 cm⁻¹; MS (+EI) m/z , (%): 421 (5, M⁺), 406 (30, M⁺-CH₃), 364 (25, M⁺-C(CH₃)₃), 316 (75, M⁺-PhCHCH₃), 260 (100, M⁺-PhCHCH₃-CH₂=C(CH₃)₂), 216 (11, M⁺-PhCHCH₂COOtBu), 105 (68, PhCHCH₃⁺); HRMS (+EI) m/z : [M⁺] Calcd for C₂₇H₃₅NO₃ 421.2617; Found 421.2618; ¹H NMR (400 MHz, CDCl₃): δ 7.50-7.15 (m, 30H, Ph, Ph*, Ph**), 4.24 (d, J = 8.4 Hz, 1H, CHPh**), 4.21 (d, J = 7.4 Hz, 1H, CHPh*), 4.09 (d, J = 8.9 Hz, 1H, CHPh), 3.98-3.90 (m, 3H, CHOH, CHOH*, CHOH**), 3.88-3.79 (m, 3H, PhCHCH₃, PhCHCH₃*, PhCHCH₃**), 3.48-3.17 (br s, 2H, OH, OH*), 3.14 (d, J = 8.9 Hz, 1H, CH₂N), 3.10 (d, J = 8.4 Hz, 1H, CHCO₂**), 3.08-3.00 (br s, 1H, OH**), 2.90 (d, J = 9.1 Hz, 1H, CH₂N*), 2.83 (d, J = 7.3 Hz, 1H, CHCO₂*), 2.68 (d, J = 8.8 Hz, 1H, CHCO₂), 2.66 (d, J = 7.9 Hz, 1H, CH₂N**), 2.55 (d, J = 9.2 Hz, 1H, CH₂N*), 2.47 (d, J = 9.0 Hz, 1H, CH₂N**), 2.37 (d, J = 8.9 Hz, 1H, CH₂N), 2.02-1.85 (m, 3H, CH₂CHOH, CH₂, CH₂*), 1.75-1.24 (m, 15H, CH₂CHOH, CH₂, CH₂*, CH₂CHOH*, CH₂**, CH₂CHOH**), 1.41 (s, 9H, C(CH₃)₃*), 1.40 (s, 9H, C(CH₃)₃**), 1.37 (s, 9H, C(CH₃)₃), 1.35-1.29 (m, 9H, PhCHCH₃, PhCHCH₃*, PhCHCH₃**); ¹³C NMR (100 MHz, CDCl₃) δ 174.7 (C, CO₂), 173.2 (C, CO₂**), 173.1 (C, CO₂*), 144.3 (C, *ipso*-Ph), 143.8 (C, *ipso*-Ph**), 143.0 (C, *ipso*-Ph*), 141.7 (C, *ipso*-Ph), 141.4 (C, *ipso*-Ph*), 141.2 (C, *ipso*-Ph**), 128.9 (CH, Ph*), 128.7 (CH, Ph**), 128.6 (CH, Ph), 128.4 (CH, Ph*), 128.3 (CH, Ph**), 128.1 (CH, Ph), 128.0 (CH, Ph**), 127.9 (CH, Ph*), 127.8 (CH, Ph**), 127.7 (CH, Ph), 127.6 (CH, Ph), 127.4 (CH, Ph, Ph*), 127.3 (CH, Ph*), 127.2 (CH, Ph*), 127.0 (CH, Ph**), 126.7 (CH, Ph**), 126.5 (CH, Ph), 82.7 (CH, CHOH), 81.7 (C, C(CH₃)₃), 81.5 (CH, CHOH*, CHOH**), 81.4 (C, C(CH₃)₃*), 81.2 (C, C(CH₃)₃**), 70.1 (CH, CHCHPh), 69.3 (CH, CHCHPh*), 68.6 (CH, CHCHPh**), 63.0 (CH, CHCO₂),

62.0 (CH, CHCO₂*), 56.8 (CH, CHCO₂**), 56.4 (CH₂, CH₂N**), 53.8 (CH, PhCHCH₃), 53.7 (CH, PhCHCH₃*), 53.5 (CH, PhCHCH₃**), 53.1 (C, C), 52.9 (C, C**), 52.6 (C, C*), 49.5 (CH₂, CH₂N, CH₂N*), 38.2 (CH₂, CH₂CHOH, CH₂CHOH*, CH₂CHOH**), 32.2 (CH₂, CH₂*), 31.6 (CH₂, CH₂**), 31.0 (CH₂, CH₂), 28.3 (CH₃, C(CH₃)₃*), 28.20 (CH₃, C(CH₃)₃), 28.17 (CH₃, C(CH₃)₃**), 20.6 (CH₂, CH₂*), 20.2 (CH₂, CH₂**), 18.7 (CH₂, CH₂), 10.0 (CH₃, PhCHCH₃), 9.6 (CH₃, PhCHCH₃*), 9.1 (CH₃, PhCHCH₃**).

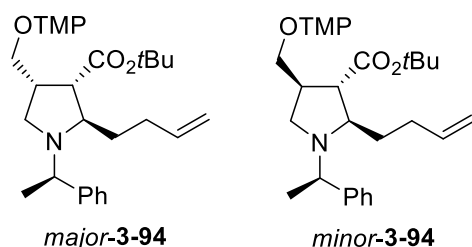
(3*S*,4*S*,5*R*)- and (3*S*,4*S*,5*S*)-*tert*-Butyl 6-oxo-3-phenyl-2-((*R*)-1-phenylethyl)-2-azaspiro[4.4]nonane-4-carboxylate (3-92c+3-93c):



The diastereomeric mixture of alcohol **3-89c+3-90c+3-91c** (29 mg, 0.0685 mmol, d.r. 14:1:6) was dissolved in dry CH₂Cl₂ (1 mL) and drop of water was added. Dess-Martin periodinane (44 mg, 0.103 mmol) was added and the mixture was stirred for two hours. Excess oxidant was destroyed by addition of a solution of sodium bicarbonate (100 mg) and sodium thiosulfate (100 mg) in water (1.5 mL). After 5 min of vigorous stirring the mixture was diluted with CH₂Cl₂ (1.5 mL), organic layer was separated, washed with brine, dried with magnesium sulfate and the solvent was evaporated. The crude product was purified by flash chromatography to afford 16 mg (54%) of **3-92c+3-93c** as a 3:1 mixture of two diastereomers as a colorless solid. *R*_f(pentane/Et₂O 2:1) = 0.6; IR: 3040, 2980, 2941, 1742, 1458, 1372, 1151, 761, 700 cm⁻¹; MS (+EI) *m/z*, (%): 419 (3, M⁺), 404 (15, M⁺-CH₃), 362 (17, M⁺-C(CH₃)₃), 348 (82, M⁺-CH₃-CH₂=C(CH₃)₂), 314 (92, M⁺-PhCHCH₃), 258 (100, M⁺-PhCHCH₃-CH₂=C(CH₃)₂), 214 (80, M⁺-PhCHCH₂COOtBu), 105 (95, PhCHCH₃⁺); HRMS (+EI) *m/z*: [M⁺] Calcd for C₂₇H₃₃NO₃ 419.2460; Found 419.2458; ¹H NMR (400 MHz, CDCl₃): δ 7.62-7.57 (m, 2H, Ph*), 7.56-7.50 (m, 2H, Ph), 7.40-7.13 (m, 16H, Ph, Ph*), 4.36 (d, *J* = 9.2 Hz, 1H, CHPh), 4.26 (d, *J* = 9.1 Hz, 1H, CHPh*), 3.79 (q, *J* = 6.8 Hz, 1H, PhCHCH₃, PhCHCH₃*), 3.30 (d, *J* = 9.1 Hz, 1H, CHCO₂*), 2.84 (d, *J* = 9.5 Hz, 1H, CH₂N*), 2.81 (d, *J* = 9.2 Hz, 1H, CH₂N), 2.79 (d, *J* = 9.3 Hz, 1H, CHCO₂), 2.53 (d, *J* = 9.6 Hz, 1H, CH₂N*), 2.50 (d, *J* = 9.0 Hz, 1H, CH₂N), 2.38-1.86 (m, 10H, CH₂, CH₂*), 1.79-1.62 (m, 2H, CH₂, CH₂*), 1.35 (s, 9H, C(CH₃)₃*), 1.32 (s, 9H, C(CH₃)₃), 1.30 (d, *J* = 6.8 Hz, 3H,

PhCHCH₃), 1.29 (d, *J* = 6.1 Hz, 3H, PhCHCH₃*); ¹³C NMR (100 MHz, CDCl₃) δ 217.6 (C, CO, CO*), 171.3 (C, CO₂*), 170.3 (C, CO₂), 144.0 (C, *ipso*-Ph), 143.6 (C, *ipso*-Ph*), 141.7 (C, *ipso*-Ph), 141.4 (C, *ipso*-Ph*), 128.53 (CH, Ph*), 128.51 (CH, Ph), 128.45 (CH, Ph), 128.2 (CH, Ph*), 128.1 (CH, Ph), 127.6 (CH, Ph*), 127.4 (CH, Ph), 127.2 (CH, Ph*), 126.6 (CH, Ph, Ph*), 81.4 (C, C(CH₃)₃), 81.2 (C, C(CH₃)₃*), 68.0 (CH, CHCHPh*), 67.2 (CH, CHCHPh), 62.9 (CH, CHCO₂), 58.4 (CH, CHCO₂*), 56.3 (C, C), 56.0 (C, C*), 55.6 (CH₂, CH₂N*), 55.0 (CH₂, CH₂N), 53.3 (CH, PhCHCH₃), 52.8 (CH, PhCHCH₃*), 39.8 (CH₂, CH₂), 39.0 (CH₂, CH₂), 36.1 (CH₂, CH₂*), 33.3 (CH₂, CH₂*), 28.3 (CH₃, C(CH₃)₃*), 28.1 (CH₃, C(CH₃)₃), 20.4 (CH₂, CH₂), 19.2 (CH₂, CH₂*), 9.8 (CH₃, PhCHCH₃*), 9.3 (CH₃, PhCHCH₃).

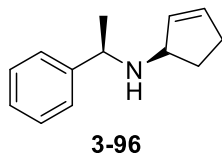
(2*R*,3*S*,4*R*)- and (2*R*,3*S*,4*S*)-*tert*-Butyl 2-(but-3-enyl)-1-((*R*)-1-phenylethyl)-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-carboxylate (3-94):



Prepared according to the general procedure for the synthesis of pyrrolidines (Method A). The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 50:1 gradient to 10:1) to afford 103 mg (59%) of **3-94** as an inseparable 2.7:1 mixture of two diastereomers as a yellow oil. *R*_f(hexane/EtOAc 5:1) = 0.4; IR: 2984, 2938, 1729, 1458, 1372, 1149, 1051, 912, 702 cm⁻¹; MS (+ESI) *m/z*, (%): 499 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₁H₅₁N₂O₃ 499.3894; Found 499.3893; ¹H NMR (400 MHz, CDCl₃): δ 7.41-7.16 (m, 10H, Ph, Ph*), 5.83-5.67 (m, 1H, CH=CH₂*), 5.49-5.31 (m, 1H, CH=CH₂), 5.00-4.87 (m, 2H, CH=CH₂*), 4.87-4.75 (m, 2H, CH=CH₂), 3.97-3.87 (m, 3H, CH₂OTMP, CH₂OTMP*, PhCHCH₃*), 3.77 (q, *J* = 6.7 Hz, 1H, PhCHCH₃), 3.74-3.65 (m, 2H, CH₂OTMP, CH₂OTMP*), 3.19 (dd, *J* = 5.6, 8.0 Hz, 1H, CH₂N), 3.12-3.05 (m, 1H, CHN*), 3.00-2.92 (m, 1H, CHN), 2.78 (dd, *J* = 7.4, 9.8 Hz, 1H, CH₂N*), 2.69 (dd, *J* = 8.1, 11.1 Hz, 1H, CH₂N), 2.66-2.58 (m, 1H, CHCH₂OTMP), 2.58-2.55 (m, 1H, CH₂N*), 2.53 (dd, *J* = 2.5, 7.8 Hz, 1H, CHCO₂), 2.50-2.43 (m, 1H, CHCH₂OTMP*), 2.40 (t, *J* = 6.2 Hz, 1H, CHCO₂*), 2.15-1.99 (m, 2H, CH₂CH=*), 1.99-1.87 (m, 1H, CH₂CH=), 1.78-1.66 (m, 1H, CH₂CH=), 1.64-1.23 (m, 16H, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*, NCHCH₂, NCHCH₂*), 1.47 (s, 9H, C(CH₃)₃), 1.45 (s, 9H, C(CH₃)₃*), 1.41 (d, *J* = 6.6 Hz, 3H,

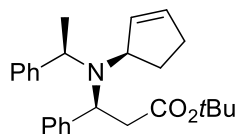
PhCHCH₃), 1.33 (d, J = 6.7 Hz, 3H, PhCHCH₃*), 1.19-0.97 (m, 24H, NC(CH₃)₂, NC(CH₃)₂*); ¹³C NMR (100 MHz, CDCl₃) δ 174.7 (C, CO₂*), 173.8 (C, CO₂), 145.4 (C, *ipso*-Ph), 145.3 (C, *ipso*-Ph*), 138.9 (CH, CH=CH₂*), 138.5 (CH, CH=CH₂), 128.20 (CH, Ph), 128.16 (CH, Ph, Ph*), 127.0 (CH, Ph), 127.6 (CH, Ph*), 126.6 (CH, Ph*), 114.5 (CH₂, CH=CH₂), 114.4 (CH₂, CH=CH₂*), 80.6 (C, C(CH₃)₃), 80.3 (C, C(CH₃)₃*), 78.1 (CH₂, CH₂OTMP*), 76.2 (CH₂, CH₂OTMP), 66.7 (CH, CHN), 63.9 (CH, CHN*), 62.4 (CH, PhCHCH₃), 60.0 (C, NC(CH₃)₂*), 59.8 (C, NC(CH₃)₂), 56.6 (CH, PhCHCH₃*), 54.1 (CH₂, CH₂N), 52.7 (CH, CHCO₂*), 51.6 (CH, CHCO₂), 49.3 (CH₂, CH₂N*), 40.9 (CH, CHCH₂OTMP*), 39.8 (CH₂, NCCH₂CH₂CH₂CN*), 39.71 (CH₂, NCCH₂CH₂CH₂CN), 39.69 (CH, CHCH₂OTMP), 35.8 (CH₂, CH₂), 33.4 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 33.3 (CH₃, NC(CH₃)₂, NC(CH₃)₂*), 32.0 (CH₂, CH₂*), 30.6 (CH₂, CH₂), 29.4 (CH₂, CH₂*), 28.4 (CH₃, C(CH₃)₃), 28.2 (CH₃, C(CH₃)₃*), 20.3 (CH₃, NC(CH₃)₂*), 20.2 (CH₃, NC(CH₃)₂*), 20.1 (CH₃, NC(CH₃)₂), 19.2 (CH₃, PhCHCH₃), 17.3 (CH₂, NCCH₂CH₂CH₂CN), 17.2 (CH₂, NCCH₂CH₂CH₂CN*), 14.7 (CH₃, PhCHCH₃*). Resonances marked by * belong to the minor diastereomer.

(S)-N-[(R)-1-phenylethyl]cyclopent-2-en-1-amine (3-96):



Prepared according to a reported procedure^[90] using cyclopent-2-en-1-yl acetate (133 mg, 1.05 mmol). Yield 127 mg (64%) as a colorless oil. R_f (hexane/EtOAc 1:1) = 0.1; IR: 3067, 2969, 2934, 2860, 1497, 1456, 1363, 1211, 1170, 1131 1104, 1080, 1030, 915, 763, 726, 700 cm⁻¹; MS (+ESI) m/z , (%): 187 (15, M+H⁺), 172 (80, M+H⁺-CH₃), 106 (100, M+H⁺-C₅H₇N); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₁₃H₁₈N 187.1361; Found 187.1360; ¹H NMR (400 MHz, CDCl₃): δ 7.39-7.13 (m, 5H, Ph), 5.89-5.83 (m, 1H, CH=CHCH₂), 5.81-5.76 (m, 1H, CH=CHCH₂), 3.89 (q, J = 6.6 Hz, 1H, PhCHCH₃), 3.70-3.57 (m, 1H, NHCH), 2.40-2.27 (m, 1H, CH=CHCH₂), 2.19-1.97 (m, 2H, CH₂), 1.57-1.45 (br s, 1H, NH), 1.45-1.34 (m, 1H, CH₂), 1.31 (d, J = 6.6 Hz, 3H, PhCHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 146.1 (C, *ipso*-Ph), 133.2 (CH, CH=CHCH₂), 132.7 (CH, CH=CHCH₂), 128.6 (CH, Ph), 127.1 (CH, Ph), 127.0 (CH, Ph), 62.2 (CH, NHCH), 56.6 (CH, PhCHCH₃), 31.9 (CH₂, CH=CHCH₂), 31.2 (CH₂, CH₂), 24.7 (CH₃, PhCHCH₃).

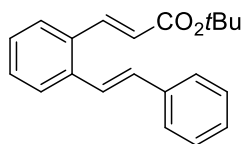
(S)-tert-Butyl 3-(((R)-cyclopent-2-en-1-yl)((R)-1-phenylethyl)amino)-3-phenylpropanoate (3-98):



3-98

Prepared according to general procedure for aza-Michael addition using amine **3-96** (105 mg, 0.560 mmol) and ester **3-1i** (104 mg, 0.508 mmol). The crude product was preadsorbed on silica gel and purified by flash chromatography (pentane/Et₂O 25:1 gradient to 5:1) to afford 61 mg (28%) of **3-98** as an inseparable 5:1:1 diastereomeric mixture as a colorless oil. R_f (pentane/Et₂O 25:1) = 0.3; IR: 3068, 3038, 2983, 2940, 2859, 1730, 1497, 1456, 1394, 1371, 1295, 1259, 1135, 1086, 1032, 964, 915, 846, 755, 700 cm⁻¹; MS (+ESI) m/z , (%): 414 (38, M+Na⁺), 392 (58, M+H⁺), 326 (100, M+H⁺– C₅H₆), 270 (100, M+H⁺– C₅H₆–CH₂=C(CH₃)₂), 166 (19, M+H⁺–C₅H₆–CH₂=C(CH₃)₂–PhCH=CH₂); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₂₆H₃₄NO₂ 392.2584; Found 392.2585; ¹H NMR (400 MHz, CDCl₃): δ 7.52-7.04 (m, 10H, Ph), 5.75-5.71 (m, 1H, CH=CH), 5.64-5.59 (m, 1H, CH=CH), 4.52-4.40 (t, J = 7.5 Hz, 1H, PhCHN), 4.12 (q, J = 6.8 Hz, 1H, PhCHCH₃), 4.05-3.93 (m, 1H, CHCH=CH), 2.62-2.56 (m, 2H, CH₂), 2.48-2.36 (m, 1H, CH₂), 2.23-2.08 (m, 1H, CH₂), 1.20 (d, J = 6.9 Hz, 3H, PhCHCH₃), 1.19 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.2 (C, CO₂), 146.2 (C, *ipso*-Ph), 143.4 (C, *ipso*-Ph), 135.4 (CH, =CH), 131.5 (CH, =CH), 128.4 (CH, Ph), 128.2 (CH, 2 x Ph), 127.6 (CH, Ph), 126.9 (CH, *p*-Ph), 126.4 (CH, *p*-Ph), 80.1 (C, C(CH₃)₃), 63.7 (CH, CHCH=CH), 57.5 (CH, PhCHN), 54.6 (CH, PhCHCH₃), 41.3 (CH₂, CH₂CO₂), 31.5 (CH₂, CH₂), 28.4 (CH₂, CH₂), 28.0 (CH, C(CH₃)₃), 19.1 (CH₃, PhCHCH₃).

tert-Butyl (E)-3-[2-((E)-styryl)phenyl]acrylate (3-105):

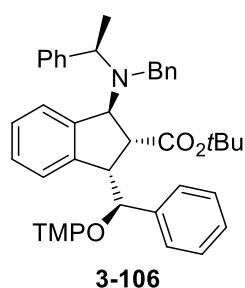


3-105

Prepared according to a literature procedure^[131] using (*E*)-2-styrylbenzaldehyde **3-104**. Yield 183 mg (92%) as a colorless oil. R_f (pentane/Et₂O 5:1) = 0.3; IR: 3060, 3024, 3005, 2976, 2930, 1703, 1631, 1494, 1477, 1447, 1391, 1366, 1318, 1281, 1256, 1204, 1143, 1029, 977, 918, 871, 839, 757, 692 cm⁻¹; MS (+ESI) m/z , (%): 329 (100, M+Na⁺); HRMS (+ESI) m/z : [M+Na⁺] Calcd for C₂₁H₂₂O₂Na 329.1512; Found 329.1512; ¹H NMR (400 MHz, CDCl₃): δ

8.05 (d, $J = 15.8$ Hz, 1H, $\text{CH}=\text{CHCO}_2$), 7.64-7.50 (m, 4H, Ar), 7.44 (d, $J = 16.1$ Hz, 1H, $\text{CH}=\text{CHPh}$), 7.41-7.23 (m, 5H, Ar), 6.99 (d, $J = 16.0$ Hz, 1H, $\text{CH}=\text{CHPh}$), 6.32 (d, $J = 15.8$ Hz, 1H, $\text{CH}=\text{CHCO}_2$), 1.54 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 166.4 (C, CO_2), 141.3 (CH, $\text{CH}=\text{CHCO}_2$), 137.6 (C, Ar), 137.3 (C, *ipso*-Ph), 133.1 (C, Ar), 132.6 (CH, $\text{CH}=\text{CHPh}$), 130.0 (CH, Ph), 128.9 (CH, Ph), 128.2 (CH, Ph), 127.8 (CH, Ph), 127.3 (CH, Ph), 127.0 (CH, Ph), 126.9 (CH, Ph), 125.7 (CH, $\text{CH}=\text{CHPh}$), 122.3 ($\text{CH}=\text{CHCO}_2$), 80.7 (C, $\text{C}(\text{CH}_3)_3$), 28.4 (CH_3 , $\text{C}(\text{CH}_3)_3$).

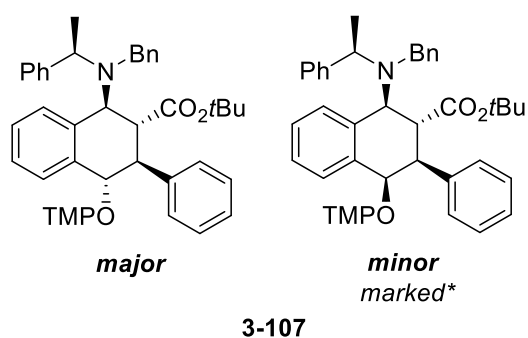
(1*S*,2*R*,3*S*)-tert-Butyl 1-[benzyl((*R*)-1-phenylethyl)amino]-3-[(*S*)-phenyl[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl]-2,3-dihydro-1*H*-indene-2-carboxylate (3-106):



Anhydrous LiCl (17.6 mg, 0.416 mmol) was flame-dried under high vacuum in a Schlenk flask five times for around 2 min. Dry THF (3 mL) was added followed by **3-2a** (90 mg, 0.418 mmol) under an argon atmosphere. The mixture was cooled to -78 °C and *n*BuLi (260 μL , 0.418 mmol, 1.6M in hexanes) was added. After stirring for 25 min, a solution of **3-105** (80 mg, 0.261 mmol) in dry THF (0.5 mL) was added using a syringe. The mixture was stirred at -40 °C for 90 min, **1-6** (4.9 mg, 0.0261 mmol) was added in one portion followed by small portions of **1-9⁺** (102.2 mg, 0.339 mmol) at -40 °C. Salt **1-9⁺** was consumed quickly, and the orange solution was treated subsequently with further portions of **1-9⁺** until the mixture remained green-blue. The reaction mixture was quenched with 4 drops of a saturated NH_4Cl solution, stirred for 5 min, diluted with diethyl ether to the double volume, warmed to room temperature and filtered through a plug of silica gel. The solvent was evaporated and the crude product mixture was purified by column chromatography. The crude product was preadsorbed on silica gel and purified by flash chromatography (hexane/EtOAc 100:1 gradient to 10:1) to afford 66 mg (38%) of **3-106** as a single diastereomer as a colorless solid and 56 mg (32%) of **3-107** as an inseparable 1.3:1 diastereomeric mixture as a colorless solid. Mp: 67-68 °C; R_f (hexane/EtOAc 10:1) = 0.5; $[\alpha]_{\text{D}}^{20}$ -100.2 (*c* 0.5, CHCl_3); IR: 3063, 3029, 2974, 2929, 2870, 1721, 1493, 1454, 1391, 1365, 1279, 1240, 1208, 1145, 1081, 1045, 1026, 975, 955, 910, 875, 845, 785, 759, 750, 734, 696 cm^{-1} ; MS (+ESI) *m/z*, (%): 695 (25,

M+Na⁺), 673 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₄₅H₅₇N₂O₃ 673.4364; Found 673.4370; Anal. Calcd for C₄₅H₅₆N₂O₃: C, 80.32; H, 8.39; N, 4.16; Found: C, 80.42; H, 8.33; N, 4.02; ¹H NMR (400 MHz, CDCl₃): δ 7.71 (d, *J* = 7.5 Hz, 1H, Ph), 7.40-7.07 (m, 17H, Ph), 6.86 (d, *J* = 7.5 Hz, 1H, Ph), 5.15 (d, *J* = 9.6 Hz, 1H, CHOTMP), 4.83 (d, *J* = 6.6 Hz, 1H, CHN), 4.15-4.05 (m, 2H, PhCHCH₃, CHCHOTMP), 3.85 (d, *J* = 15.3 Hz, 1H, PhCH₂), 3.61 (d, *J* = 15.4 Hz, 1H, PhCH₂), 3.08 (dd, *J* = 8.0, 6.6 Hz, 1H, CHCO₂), 1.50-0.75 (m, 18H, NCCH₂CH₂CH₂CN, NC(CH₃)₂), 1.26 (d, *J* = 7.0 Hz, PhCHCH₃), 1.05 (s, 9H, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 172.1 (C, CO₂), 145.2 (C, *ipso*-Ph), 143.5 (C, Ar), 143.1 (C, Ar), 142.5 (C, *ipso*-Ph), 139.7 (C, *ipso*-Ph), 131.6 (CH, Ph), 128.3 (CH, Ph), 127.9 (CH, Ph), 127.7 (CH, 2 x Ph), 127.6 (CH, Ph), 127.03 (CH, 2 x Ph), 126.96 (CH, Ph), 126.9 (CH, Ph), 126.7 (CH, Ph), 126.2 (CH, Ph), 124.8 (CH, Ph), 80.0 (C, C(CH₃)₃), 69.7 (CH, CHN), 62.6 (CH, PhCHCH₃), 60.7 (C, NC(CH₃)₂), 58.7 (C, NC(CH₃)₂), 52.7 (CH, CHCO₂), 50.2 (CH₂, PhCH₂), 47.8 (CH, CHCHOTMP), 40.9 (CH₂, NCCH₂CH₂CH₂CN), 40.1 (CH₂, NCCH₂CH₂CH₂CN), 34.7 (CH₃, NC(CH₃)₂), 32.7 (CH₃, NC(CH₃)₂), 27.6 (CH₃, C(CH₃)₃), 22.7 (CH, PhCHCH₃), 21.4 (CH₃, NC(CH₃)₂), 21.2 (CH₃, NC(CH₃)₂), 17.2 (CH₂, NCCH₂CH₂CH₂CN).

(1*S*,2*R*,3*S*,4*S*)- and (1*S*,2*R*,3*S*,4*R*)-*tert*-Butyl 1-[benzyl(*R*)-1-phenylethyl]amino]-3-phenyl-4-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]-1,2,3,4-tetrahydronaphthalene-2-carboxylate (3-107):

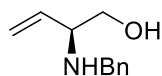


R_f(hexane/EtOAc 10:1) = 0.4; IR: 3062, 3028, 2975, 2932, 2872, 1738, 1493, 1453, 1391, 1369, 1300, 1238, 1142, 1082, 1045, 1027, 985, 957, 913, 878, 845, 782, 749, 698 cm⁻¹; MS (+ESI) *m/z*, (%): 695 (20, M+Na⁺), 673 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₄₅H₅₇N₂O₃ 673.4364; Found 673.4370; ¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, *J* = 7.3 Hz, 1H, Ph), 7.66-6.90 (m, 37H, Ph, Ph*), 5.35 (d, *J* = 3.6 Hz, 1H, CHOTMP*), 4.98 (d, *J* = 5.1 Hz, 1H, CHOTMP), 4.76 (d, *J* = 7.5 Hz, 1H, CHN), 4.70 (d, *J* = 7.6 Hz, 1H, CHN*), 4.31 (dd, *J* = 8.2, 3.4 Hz, 1H, CHPh*), 4.25 (dd, *J* = 9.2, 4.9 Hz, 1H, CHPh), 3.83 (q, *J* = 7.2 Hz,

^1H , PhCHCH_3^*), 3.70 (q, $J = 7.2$ Hz, 1H, PhCHCH_3), 3.20-3.01 (m, 3H, PhCH_2^* , CHCO_2^*), 2.92-2.74 (m, 3H, PhCH_2 , CHCO_2), 1.66-0.95 (m, 36H, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^*$, $\text{NC}(\text{CH}_3)_2^*$, $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$, $\text{NC}(\text{CH}_3)_2$), 1.54 (s, 9H, $\text{C}(\text{CH}_3)_3^*$), 1.52 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.89 (d, $J = 6.8$ Hz, 3H, PhCHCH_3), 0.83 (d, $J = 6.8$ Hz, 3H, PhCHCH_3^*); ^{13}C NMR (100 MHz, CDCl_3) δ 175.5 (C, CO_2^*), 174.7 (C, CO_2), 146.23 (C, *ipso*- Ph^*), 146.18 (C, *ipso*-Ph), 144.7 (C, *ipso*-Ph), 144.0 (C, *ipso*- Ph^*), 143.0 (C, Ar *), 142.7 (C, Ar *), 141.1 (C, *ipso*- Ph^*), 140.43 (C, Ar), 140.37 (C, Ar), 140.1 (C, *ipso*-Ph), 129.9 (CH, Ph), 129.0 (CH, Ph^*), 128.6 (CH, Ph^*), 128.21 (CH, Ph), 128.15 (CH, Ph), 128.1 (CH, Ph^*), 128.0 (CH, Ph^*), 127.8 (CH, Ph), 127.7 (CH, Ph), 127.5 (CH, Ph), 127.41 (CH, Ph), 127.38 (CH, Ph), 127.37 (CH, Ph), 127.34 (CH, Ph), 127.18 (CH, Ph^*), 127.15 (CH, Ph^*), 127.0 (CH, Ph^*), 126.9 (CH, Ph^*), 126.7 (CH, Ph^*), 126.6 (CH, Ph^*), 126.5 (CH, Ph^*), 126.0 (CH, Ph^*), 125.9 (CH, Ph^*), 124.90 (CH, Ph), 124.88 (CH, Ph), 124.8 (CH, Ph), 90.10 (CH, *CHOTMP*), 90.08 (CH, *CHOTMP* *), 80.6 (C, $\text{C}(\text{CH}_3)_3$), 80.3 (C, $\text{C}(\text{CH}_3)_3^*$), 70.4 (CH, *CHN* *), 68.2 (CH, *CHN*), 61.8 (CH, PhCHCH_3), 61.6 (CH, PhCHCH_3^*), 52.8 (CH, *CHCHPh* *), 52.3 (CH, *CHCHPh*), 51.7 (CH_2 , PhCH_2^*), 51.2 (CH_2 , PhCH_2), 48.8 (CH, CHCO_2), 48.7 (CH, CHCO_2^*), 41.0 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^*$), 40.6 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 34.8 (CH_3 , $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 34.5 (CH_3 , $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 28.3 (CH_3 , $\text{C}(\text{CH}_3)_3^*$), 28.2 (CH_3 , $\text{C}(\text{CH}_3)_3$), 23.8 (CH, PhCHCH_3), 23.4 (CH, PhCHCH_3^*), 20.7 (CH_3 , $\text{NC}(\text{CH}_3)_2$, $\text{NC}(\text{CH}_3)_2^*$), 17.2 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}$), 17.1 (CH_2 , $\text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN}^*$).

4.3 Enantioselective total synthesis of (-)- α -kainic acid

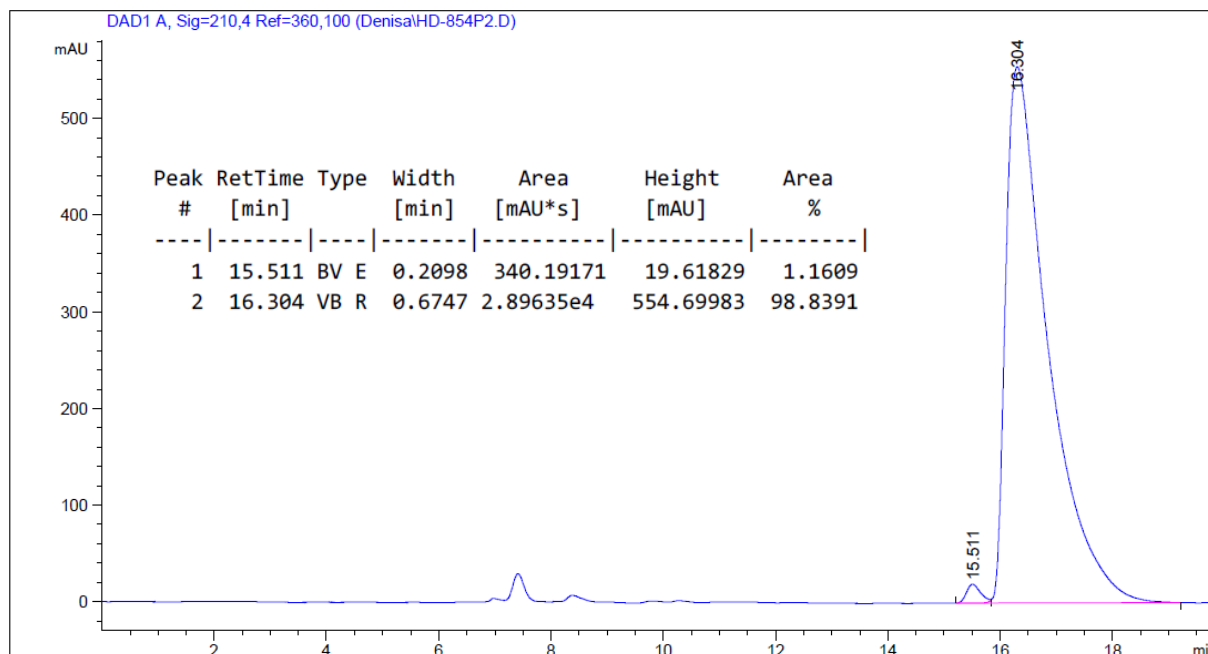
(S)-2-(Benzylamino)but-3-en-1-ol (**3-118**):



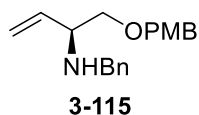
3-118

[Pd(η^3 -C₃H₅)Cl]₂ (6.8 mg, 0.018 mmol) and the (*R,R*)-DACH naphthyl ligand (42.8 mg, 0.054 mmol) were placed in a Schlenk flask and purged by three vacuum-argon cycles. Dry CH₂Cl₂ (8 mL) and butadiene monoepoxide (317 mg, 4.53 mmol) were subsequently added. Benzylamine (966 mg, 9.1 mmol) was added dropwise over 10 min and the resulting mixture was stirred at r.t. overnight. The solvent was removed *in vacuo* and the thick yellow oil was purified by flash chromatography (hexane/EtOAc 1:1 to 100% EtOAc) affording **3-118** as a colorless solid (574 mg, 72%). The analytical data are identical to those in the literature.^[132] Mp: 56-57 °C; [α]_D²⁰ +22.2 (*c* 0.980, CHCl₃, 98% *ee*), Lit. [α]_D²⁰ +18.1 (*c* 0.980, CHCl₃, 93% *ee*).

HPLC [Daicel Chiralcel OD, 250 × 4.6 mm, 5 μ m, with guard cartridge 10 × 4 mm, 5 μ m, *n*-hexane/*i*-PrOH, 85:15, flow = 0.5 mL min⁻¹, r.t., 210 nm]: *t*_R = 15.5 [(-)-(*R*)-**3-118**], 16.3 [(+)-(*S*)-**3-118**].

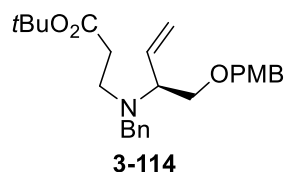


(S)-N-Benzyl-1-[(4-methoxybenzyl)oxy]but-3-en-2-ylamine (3-115):



A solution of **3-118** (172 mg, 0.965 mmol) in dry THF (1 mL) was dropwise added to a suspension of sodium hydride (27.8 mg, 1.16 mmol, 60% dispersion mineral oil washed with pentane and dried *in vacuo* prior to use) in dry THF (9 mL) at 0 °C. The resulting mixture was stirred for 10 min, warmed to r.t. and stirred for another 30 min. The reaction mixture was cooled to 0 °C and a solution of *p*-methoxybenzyl bromide (233.2 mg, 1.16 mmol) in dry THF (1.5 mL) was added dropwise over a 15 min period. The reaction mixture was stirred at 0 °C for 20 min, warmed to r.t. and stirred for 25 h. The reaction was carefully quenched with saturated NaHCO₃ solution (10 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography (hexane/EtOAc 5:1 to 1:1) to furnish 205.9 mg (72%) of **3-115** as a pale yellow oil. *R*_f (hexane/EtOAc 2:1) = 0.2; [α]_D²⁰ +13.5 (*c* 0.509, CHCl₃); IR: 3340, 3074, 3038, 3012, 2911, 2864, 2845, 1617, 1591, 1517, 1460, 1305, 1249, 1177, 1085, 1036, 998, 927, 820, 738, 700 cm⁻¹; MS (+ESI) *m/z*, (%): 298 (100, M+H⁺); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₁₉H₂₄NO₂ 298.1802; Found 298.1802; Anal. Calcd for C₁₉H₂₃NO₂: C, 76.73; H, 7.80; N, 4.71; Found: C, 76.41; H, 7.52; N, 4.36; ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.18 (m, 7H, Ph, *o*-Ar), 6.91-6.83 (m, 2H, *m*-Ar), 5.69 (ddd, *J* = 17.4, 10.3, 7.5 Hz, 1H, CH=CH₂), 5.26 (ddd, *J* = 17.3, 1.8, 0.9 Hz, 1H, CH=CH₂), 5.20 (ddd, *J* = 10.2, 1.8, 0.7 Hz, 1H, CH=CH₂), 4.42 (s, 2H, OCH₂Ar), 3.85 (d, *J* = 13.2 Hz, 1H, PhCH₂), 3.80 (s, 3H, ArOCH₃), 3.64 (d, *J* = 13.2 Hz, 1H, PhCH₂), 3.50-3.32 (m, 3H, OCH₂CH, CHCH=), 2.13 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ 159.3 (C, C_{Ar}OMe), 140.5 (C, *ipso*-Ph), 137.8 (CH, CH=CH₂), 130.3 (C, *ipso*-Ar), 129.5 (CH, *o*-Ar), 128.5 (CH, Ph), 128.4 (CH, Ph), 127.0 (CH, Ph), 118.1 (CH₂, =CH₂), 113.9 (CH, *m*-Ar), 73.1 (CH₂, CH₂OPMB), 73.0 (CH₂, OCH₂Ar), 60.7 (CH, CHCH=), 55.4 (CH₃, ArOCH₃), 51.2 (CH₂, CH₂Ph).

***tert*-Butyl (S)-3-*N*-(benzyl-*N*-[1-(4-methoxybenzyloxy)but-3-en-2-yl]amino]propanoate (3-114):**

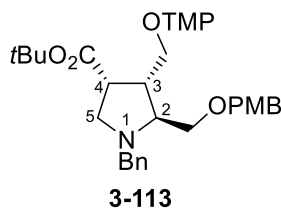


A solution of **3-115** (190.5 mg, 0.641 mmol) and *tert*-butyl acrylate (282 μL , 1.92 mmol) in dry MeOH (1 mL) was stirred at 60 °C for 8 days. After completion as indicated by TLC the reaction mixture was diluted by diethyl ether and filtered through a pad of silica gel. Evaporation of the filtrate afforded a colorless residue, which was purified by flash chromatography (hexane/EtOAc 10:1 to 1:1) to obtain 203.7 mg (75%) of **3-114** as a colorless oil. R_f (hexane/EtOAc 2:1) = 0.5; $[\alpha]_{\text{D}}^{20}$ -9.0 (c 0.5, CHCl_3); IR: 3074, 2986, 2939, 2855, 1730, 1617, 1517, 1459, 1370, 1249, 1177, 1156, 1100, 1037, 953, 925, 849, 822, 739, 701 cm^{-1} ; MS (+ESI) m/z , (%): 448 (5, $\text{M}+\text{Na}^+$), 426 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{26}\text{H}_{36}\text{NO}_4$ 426.2639; Found 426.2640; Anal. Calcd for $\text{C}_{26}\text{H}_{35}\text{NO}_4$: C, 73.38; H, 8.29; N, 3.29; Found: C, 73.68; H, 8.44; N, 3.17; ^1H NMR (400 MHz, CDCl_3): δ 7.39-7.14 (m, 7H, Ph, *o*-Ar), 6.91-6.79 (m, 2H, *m*-Ar), 5.89-5.76 (m, 1H, $\text{CH}=\text{CH}_2$), 5.26 (dd, J = 10.5, 1.0 Hz, 1H, $\text{CH}=\text{CH}_2$), 5.17 (dd, J = 17.2, 1.2 Hz, 1H, $\text{CH}=\text{CH}_2$), 4.40 (s, 2H, OCH_2Ar), 3.80 (s, 3H, ArOCH_3), 3.75 (d, J = 14.2 Hz, 1H, PhCH_2), 3.64-3.48 (m, 3H, OCH_2CH , PhCH_2), 3.40-3.31 (m, 1H, $\text{CHCH}=\text{}$), 2.93 (dt, J = 13.1, 7.5 Hz, 1H, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.73 (dt, J = 13.3, 6.7 Hz, 1H, $\text{CH}_2\text{CH}_2\text{CO}_2$), 2.37-2.30 (m, 2H, CH_2CO_2), 1.42 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 172.2 (C, CO_2), 159.2 (C, $\text{C}_{\text{Ar}}\text{OMe}$), 140.5 (C, *ipso*-Ph), 135.4 (CH, $\text{CH}=\text{CH}_2$), 130.7 (C, *ipso*-Ar), 129.3 (CH, *o*-Ar), 128.7 (CH, Ph), 128.3 (CH, Ph), 126.8 (CH, Ph), 118.3 (CH_2 , $=\text{CH}_2$), 113.8 (CH, *m*-Ar), 80.3 (C, $\text{C}(\text{CH}_3)_3$), 72.8 (CH_2 , OCH_2Ar), 71.3 (CH_2 , CH_2OPMB), 61.8 (CH, $\text{CHCH}=\text{}$), 55.4 (CH_3 , ArOCH_3), 55.2 (CH_2 , CH_2Ph), 46.9 (CH_2 , NCH_2CH_2), 35.6 (CH_2 , CH_2CO_2), 28.3 (CH_3 , $\text{C}(\text{CH}_3)_3$).

(2*S*,3*S*,4*R*)-*tert*-Butyl

1-benzyl-2-(4-methoxybenzyloxymethyl)-3-{{(2,2,6,6-

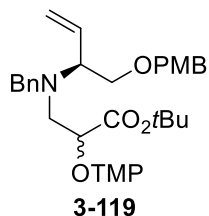
tetramethylpiperidin-1-yl)oxy)methyl}pyrrolidine-4-carboxylate (**3-113**):



Anhydrous LiCl (28.4 mg, 0.669 mmol) was dried under high vacuum in a Schlenk flask five times for around 2 min. Dry THF (5 mL) was added followed by diisopropylamine (81 μ L, 0.580 mmol) under an argon atmosphere. The mixture was cooled to -78 $^{\circ}$ C and *n*BuLi (362 μ L, 0.580 mmol, 1.6M in hexanes) was added. After 30 min, a solution of **3-114** (190 mg, 0.446 mmol) in dry THF (1 mL) was added dropwise. After stirring for 90 min, **1-6** (8.3 mg, 0.0446 mmol) was added in one portion followed by small portions of **1-9⁺** at -78 $^{\circ}$ C until the mixture remained green-blue for 20 min (total 175 mg, 0.580 mmol). The reaction mixture was stirred at -78 $^{\circ}$ C for 60 min, quenched with 4 drops of saturated NH₄Cl solution, stirred for 5 min, diluted with diethyl ether to the double volume and filtered through a plug of silica gel. The solvent was evaporated and the crude product mixture was purified by column chromatography (hexane/EtOAc 50:1 to 1:1) to obtain 142 mg (55%) of **3-113** as a colorless oil and 104 mg (40%) of **3-119** as a 1.1:1 diastereomeric mixture as a colorless oil. R_f (hexane/EtOAc 2:1) = 0.5; $[\alpha]_D^{20}$ -21.0 (c 0.5, CHCl₃); IR: 2983, 2939, 1730, 1618, 1518, 1459, 1395, 1371, 1249, 1150, 1095, 1040, 998, 850, 823, 740, 701 cm^{-1} ; MS (+ESI) m/z , (%): 581 (100, M+H⁺); HRMS (+ESI) m/z : [M+H⁺] Calcd for C₃₅H₅₃N₂O₅ 581.3948; Found 581.3949; Anal. Calcd for C₃₅H₅₂N₂O₅: C, 72.38; H, 9.02; N, 4.82; Found: C, 72.62; H, 8.98; N, 4.38; ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.17 (m, 7H, Ar), 6.89-6.78 (m, 2H, Ar), 4.49 (s, 2H, OCH₂Ar), 4.19 (d, J = 13.1 Hz, 1H, CH₂Ph) 3.84-3.69 (m, 5H, ArOCH₃, CH₂OTMP), 3.61 (dd, J = 9.8, 4.1 Hz, 1H, CH₂OPMB), 3.55-3.42 (m, 2H, CH₂Ph, CH₂OPMB), 3.07-2.93 (m, 3H, H₂, H₄, H₅), 2.64-2.56 (m, 1H, H₅), 2.54-2.45 (m, 1H, H₃), 1.49-1.34 (m, 6H, NCCH₂CH₂CH₂CN), 1.42 (s, 9H, C(CH₃)₃), 1.13 (s, 3H, NC(CH₃)₂), 1.12 (s, 3H, NC(CH₃)₂), 1.07 (s, 3H, NC(CH₃)₂), 1.05 (s, 3H, NC(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 172.0 (C, CO₂), 159.1 (C, C_{Ar}OMe), 139.7 (C, *ipso*-Ph), 131.0 (C, *ipso*-Ar), 129.3 (CH, *o*-Ar), 129.1 (CH, Ph), 128.3 (CH, Ph), 126.9 (CH, *p*-Ph), 113.8 (CH, *m*-Ar), 80.7 (C, C(CH₃)₃), 76.6 (CH, CH₂OTMP), 73.0 (CH₂, CH₂OPMB, OCH₂Ar), 67.1 (CH, C₂), 59.9 (C, NC(CH₃)₂), 59.8 (C, NC(CH₃)₂), 59.7 (CH₂, CH₂Ph), 55.4 (CH₃, ArOCH₃), 55.3 (CH₂, C₅), 45.1 (CH, C₄), 42.2 (CH, C₃), 39.8 (CH₂, NCCH₂CH₂CH₂CN), 39.7 (CH₂, NCCH₂CH₂CH₂CN), 33.6 (CH₃,

NC(CH₃)₂), 33.2 (CH₃, NC(CH₃)₂), 28.3 (CH₃, C(CH₃)₃), 20.5 (CH₃, NC(CH₃)₂), 20.2 (CH₃, NC(CH₃)₂), 17.2 (CH₂, NCCH₂CH₂CH₂CN).

tert-Butyl 3-[N-benzyl-N-((S)-1-(4-methoxybenzyloxy)but-3-en-2-yl)amino]-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (3-119):



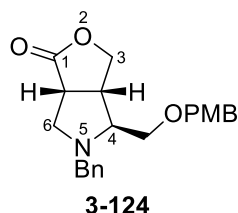
R_f(hexane/EtOAc 2:1) = 0.5; IR: 3074, 2984, 2941, 2878, 1739, 1618, 1518, 1460, 1368, 1250, 1155, 1039, 924, 848, 745, 702 cm⁻¹; MS (+ESI) *m/z*, (%): 603 (57, M+Na⁺), 581 (100, M+H⁺), 310 (53, M+H⁺-TMPOCH₂CO₂tBu); HRMS (+ESI) *m/z*: [M+H⁺] Calcd for C₃₅H₅₂N₂O₅Na 603.3768; Found 603.3770; Anal. Calcd for C₃₅H₅₂N₂O₅: C, 72.38; H, 9.02; N, 4.82; Found: C, 72.45; H, 9.10; N, 4.60; ¹H NMR (600 MHz, CDCl₃, 5 °C): δ 7.36-7.30 (m, 4H, Ph), 7.30-7.19 (m, 8H, Ph, *o*-Ar*), 7.18-7.12 (m, 2H, *o*-Ar), 6.89-6.84 (m, 2H, *m*-Ar*), 6.84-6.79 (m, 2H, *m*-Ar), 5.86-5.72 (m, 2H, CH=CH₂, CH=CH₂*), 5.38 (dd, *J* = 10.3, 1.9 Hz, 1H, CH=CH₂), 5.23-5.04 (m, 3H, CH=CH₂, CH=CH₂*), 4.42-4.35 (m, 3H, OCH₂Ar, OCH₂Ar*), 4.31 (d, *J* = 11.7 Hz, 1H, OCH₂Ar*), 4.25-4.18 (m, 2H, CHOTMP, CHOTMP*), 3.85 (d, *J* = 13.8 Hz, 1H, PhCH₂*), 3.81 (s, 3H, ArOCH₃*), 3.79 (s, 3H, ArOCH₃), 3.75-3.65 (m, 2H, PhCH₂*, PhCH₂), 3.60 (dd, *J* = 9.6, 5.5 Hz, 1H, CHNCH₂O*), 3.51-3.33 (m, 3H, PhCH₂, NCHCH₂O*, NCHCH₂O), 3.42-3.33 (m, 2H, NCHCH=*, NCHCH₂O), 3.16 (td, *J* = 9.0, 4.5 Hz, 1H, NCHCH=), 3.06-2.96 (m, 3H, CH₂CHOTMP*, CH₂CHOTMP), 2.75 (dd, *J* = 12.3, 4.2 Hz, 1H, CH₂CHOTMP), 1.59-1.22 (m, 12H, NCCH₂CH₂CH₂CN, NCCH₂CH₂CH₂CN*), 1.48 (s, 9H, C(CH₃)₃*), 1.47 (s, 9H, C(CH₃)₃), 1.17-1.03 (m, 24H, NC(CH₃)₂, NC(CH₃)₂*); ¹³C NMR (150 MHz, CDCl₃, 5 °C) δ 173.0 (C, CO₂), 172.5 (C, CO₂*), 158.9 (C, C_{Ar}OMe*), 158.8 (C, C_{Ar}OMe), 139.8 (C, *ipso*-Ph*), 139.3 (C, *ipso*-Ph), 136.0 (CH, CH=CH₂*), 133.7 (CH, CH=CH₂), 130.3 (C, *ipso*-Ar, *ipso*-Ar*), 129.23 (CH, *o*-Ar*), 129.19 (CH, *o*-Ar), 129.1 (CH, Ph), 129.0 (CH, Ph*), 128.0 (CH, Ph), 127.9 (CH, Ph*), 126.9 (CH, Ph), 126.7 (CH, Ph*), 120.0 (CH₂, =CH₂*), 117.5 (CH₂, =CH₂), 113.6 (CH, *m*-Ar*), 113.5 (CH, *m*-Ar), 85.1 (CH, CHOTMP*), 84.4 (CH, CHOTMP), 81.2 (C, C(CH₃)₃), 81.0 (C, C(CH₃)₃*), 72.6 (CH₂, OCH₂Ar*), 72.5 (CH₂, OCH₂Ar), 71.4 (CH₂, CH₂OPMB), 69.9 (CH₂, CH₂OPMB*), 60.9 (CH, NCHCH=), 60.7 (CH, NCHCH=*), 60.4 (C, NC(CH₃)₂), 60.2 (C, NC(CH₃)₂*), 59.2 (C, NC(CH₃)₂*), 59.1 (C, NC(CH₃)₂), 55.82 (CH₂, CH₂Ph*), 55.78

(CH₂, CH₂Ph), 55.24 (CH₃, ArOCH₃^{*}), 55.23 (CH₃, ArOCH₃), 52.8 (CH₂, CH₂CHOTMP^{*}), 52.4 (CH₂, CH₂CHOTMP), 40.19 (CH₂, NCCH₂CH₂CH₂CN^{*}), 40.15 (CH₂, NCCH₂CH₂CH₂CN^{*}), 40.07 (CH₂, NCCH₂CH₂CH₂CN), 33.8 (CH₃, NC(CH₃)₂), 33.6 (CH₃, NC(CH₃)₂^{*}), 33.5 (CH₃, NC(CH₃)₂^{*}), 33.3 (CH₃, NC(CH₃)₂), 28.1 (CH₃, C(CH₃)₃, C(CH₃)₃^{*}), 20.1 (CH₃, NC(CH₃)₂, NC(CH₃)₂^{*}), 20.0 (CH₃, NC(CH₃)₂^{*}), 19.9 (CH₃, NC(CH₃)₂), 17.00 (CH₂, NCCH₂CH₂CH₂CN^{*}), 16.99 (CH₂, NCCH₂CH₂CH₂CN).

Procedure for the thermal PRE cyclisation of TEMPO-adduct (3-119)

Alkoxyamine **3-119** (41.9 mg, 0.0721 mmol), a few crystals of TEMPO and (+)-camphor-10-sulfonic acid, respectively, were dissolved in *tert*-butanol (1 mL) in a 10 mL reaction tube. Argon was vigorously bubbled through the solution for 10 min. The reaction vessel was sealed, placed into a microwave reactor and heated at 150 °C for 120 min using 70 W power input. After cooling to room temperature, the reaction mixture was diluted with diethyl ether, evaporated *in vacuo* and purified by flash chromatography (hexane/EtOAc 20/1 to 3/1) to furnish 29.9 mg (72%) of pyrrolidines (2*S*,3*S*,4*R*)-**3-113** and (2*S*,3*R*,4*R*)-**3-113**+(2*S*,3*S*,4*S*)-**3-113** as a 2:1 diastereomeric mixture.

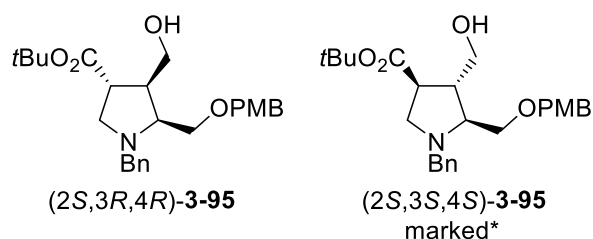
(3*aS*,4*S*,6*aR*)-5-Benzyl-4-[(4-methoxybenzyloxy)methyl]hexahydro-1*H*-furo[3,4-*c*]pyrrol-1-one (**3-124**):



Pyrrolidine (2*S*,3*S*,4*R*)-**3-113** (198.1 mg, 0.341 mmol) from the oxidative cyclization was dissolved in acetic acid (2.4 mL). Water (0.8 mL) was added. To the resulting turbid solution THF (0.8 mL) was added dropwise until the solution became clear. Zinc dust (1.49 g, 22.8 mmol) was added with vigorous stirring and the resulting mixture was heated at 85 °C until the starting material was consumed as indicated by TLC. The reaction mixture was cooled to r.t., diluted with CH₂Cl₂ to the triple volume and filtered. The filtrate was neutralized with saturated K₂CO₃ solution until a pH of ca. 10. The layers were separated and the organic was washed twice with water, dried over MgSO₄ and evaporated to furnish the crude product, which was purified by flash chromatography to obtain 76.5 mg (61%) of **3-124** as a colorless oil. R_f(hexane/EtOAc 1:1) = 0.2; [α]_D²⁰ −6.8 (*c* 0.5, CHCl₃); IR: 3029, 2908, 2836, 1763,

1611, 1585, 1512, 1495, 1454, 1374, 1301, 1245, 1208, 1171, 1091, 1029, 981, 818, 743 cm^{-1} ; MS (+ESI) m/z , (%): 390 (30, $\text{M}+\text{Na}^+$), 368 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_4$ 368.1856; Found 368.1858; ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.18 (m, 7H, Ph, Ar), 6.92-6.84 (m, 2H, Ar), 4.47-4.39 (m, 3H, OCH_2Ar , H3), 4.24 (dd, $J = 9.5$, 3.1 Hz, 1H, H3), 3.92 (d, $J = 13.2$ Hz, 1H, NCH_2Ph), 3.81 (s, 3H, OCH_3), 3.61 (dd, $J = 9.5$, 4.0 Hz, 1H, CH_2OPMB), 3.52-3.45 (m, 2H, NCH_2Ph , CH_2OPMB), 3.27 (t, $J = 9.3$ Hz, 1H, H6), 3.09 (td, $J = 9.4$, 4.7 Hz, 1H, H6a), 2.97 (dddd, $J = 9.5$, 7.6, 5.8, 3.1 Hz, 1H, H3a), 2.79 (td, $J = 5.9$, 4.2 Hz, 1H, H4), 2.74 (dd, $J = 9.7$, 4.7 Hz, 1H, H6); ^{13}C NMR (100 MHz, CDCl_3) δ 179.6 (C, CO), 159.5 (C, $\text{C}_{\text{Ar}}\text{OMe}$), 138.4 (C, *ipso*-Ph), 130.1 (C, *ipso*-Ar), 129.4 (CH, *o*-Ar), 128.7 (CH, Ph), 128.5 (CH, Ph), 127.3 (CH, *p*-Ph), 114.0 (CH, *m*-Ar), 73.3 (CH_2 , OCH_2Ar), 72.0 (CH_2 , C3), 70.0 (CH_2 , CH_2OPMB), 68.3 (CH, C4), 56.7 (CH_2 , NCH_2Ph), 56.0 (CH_2 , C6), 55.4 (CH_3 , ArOCH_3), 44.0 (CH, C3a), 42.6 (CH, C6a).

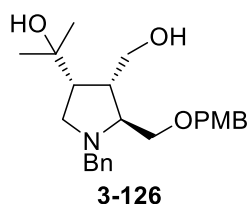
(2*S*,3*R*,4*R*)- and (2*S*,3*S*,4*S*)-*tert*-Butyl 1-benzyl-2-[(4-methoxybenzyl)oxy]methyl}-3-(hydroxymethyl)pyrrolidine-4-carboxylate (3-125):



The inseparable diastereomeric mixture of pyrrolidines (2*S*,3*S*,4*R*)-, (2*S*,3*R*,4*R*)- and (2*S*,3*S*,4*S*)-**3-113** (102.5 mg, 0.177 mmol) from the PRE cyclization was dissolved in acetic acid (1.5 mL). Water (0.5 mL) was added. To the resulting turbid solution THF (0.5 mL) was added dropwise until the solution became clear. Zinc dust (773 mg, 11.9 mmol) was added with vigorous stirring and the resulting mixture was heated at 85 °C until the starting material was consumed after ca. 6 h as indicated by TLC. The reaction mixture was cooled to r.t., diluted with CH_2Cl_2 to the triple volume and filtered. The filtrate was neutralized with saturated K_2CO_3 solution until a pH of ca. 10. The layers were separated and the organic was washed twice with water, dried over MgSO_4 and evaporated to furnish the crude product, which was purified by flash chromatography to obtain 28.2 mg (65%) of **3-124** as a colorless oil. The analytical data correspond to **3-124** obtained from the oxidative cyclization. Additionally, 17.4 mg (23%) of an inseparable mixture of *trans*-alcohols (2*S*,3*R*,4*R*)- and (2*S*,3*S*,4*S*)-**3-125** was isolated in 2:1 diastereomeric ratio. R_f (hexane/EtOAc 1:1) = 0.3; IR: 3421 (br), 2975, 2931, 2862, 2836, 1722, 1612, 1513, 1454, 1391, 1367, 1301, 1245, 1149,

1075, 1031, 911, 846, 819, 735, 699 cm^{-1} ; MS (+ESI) m/z , (%): 464 (25, $\text{M}+\text{Na}^+$), 442 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : $[\text{M}+\text{H}^+]$ Calcd for $\text{C}_{26}\text{H}_{36}\text{NO}_5$ 442.2588; Found 442.2581; ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.18 (m, 16H, Ph, Ar), 6.90-6.83 (m, 2H, Ar), 4.51 (d, $J = 11.4$ Hz, 1H, OCH_2Ar), 4.46 (d, $J = 11.4$ Hz, 1H, OCH_2Ar), 4.47-4.40 (m, 2H, OCH_2Ar^*), 4.00 (d, $J = 13.6$ Hz, 1H, CH_2Ph^*), 3.99 (d, $J = 13.6$ Hz, 1H, CH_2Ph), 3.80 (s, 6H, OCH_3 , OCH_3^*), 3.78-3.48 (m, 8H, CH_2OPMB , CH_2OH , CH_2OPMB^* , CH_2OH^* , CH_2Ph^*), 3.44 (dd, $J = 9.0, 7.7$ Hz, 1H, CH_2OH), 3.37 (d, $J = 13.5$ Hz, 1H, CH_2Ph), 3.18 (dd, $J = 9.2, 2.8$ Hz, 1H, H5), 3.15-3.01 (m, H2, H2*), 2.78-2.68 (m, 1H, H3*), 2.66-2.37 (m, 6H, H5, H4, H3, H4*, H5*), 1.41 (s, 18H, $\text{C}(\text{CH}_3)_3$, $\text{C}(\text{CH}_3)_3^*$); ^{13}C NMR (100 MHz, CDCl_3) δ 173.4 (C, CO_2 , CO_2^*), 159.6 (C, $\text{C}_{\text{Ar}}\text{OMe}^*$), 159.5 (C, $\text{C}_{\text{Ar}}\text{OMe}$), 139.2 (C, *ipso*-Ph), 138.9 (C, *ipso*-Ph*), 129.8 (CH, Ar*), 129.7 (CH, Ar), 129.6 (C, *ipso*-Ar), 129.5 (C, *ipso*-Ar*), 129.74 (CH, Ar*), 129.66 (CH, Ar), 128.8 (CH, Ar*), 128.5 (CH, Ar, Ar*), 128.4 (CH, Ar), 127.2 (CH, *p*-Ph*), 127.1 (CH, *p*-Ph), 114.1 (CH, *m*-Ar, CH, *m*-Ar*), 81.0 (C, $\text{C}(\text{CH}_3)_3^*$), 80.9 (C, $\text{C}(\text{CH}_3)_3$), 73.5 (CH_2 , OCH_2Ar), 72.3 (CH_2 , OCH_2Ar^*), 69.2 (CH_2 , CH_2OPMB^*), 68.1 (CH_2 , CH_2OPMB), 65.6 (CH, C2), 64.7 (CH, C2*), 62.6 (CH_2 , CH_2OH , CH_2OH^*), 59.0 (CH_2 , NCH_2Ph^*), 58.6 (CH_2 , NCH_2Ph), 56.0 (CH_2 , C5, C5*), 55.5 (CH_3 , ArOCH_3^*), 55.4 (CH_3 , ArOCH_3), 50.3 (CH, C4), 46.8 (CH, C4*), 45.8 (CH, C3), 45.4 (CH, C3*), 28.19 (CH_3 , $\text{C}(\text{CH}_3)_3^*$), 28.16 (CH_3 , $\text{C}(\text{CH}_3)_3$).

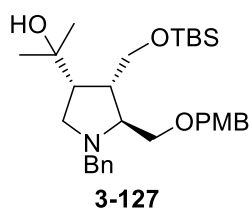
(2*S*,3*S*,4*R*)-1-Benzyl-2-(4-methoxybenzyloxy)methyl-3-hydroxymethyl-4-(2-hydroxyprop-2-yl)pyrrolidine (3-126):



Methylmagnesium bromide (280 μL , 0.832 mmol, 3*M* solution in Et_2O) was dropwise added to a stirred solution of **3-124** (76.5 mg, 0.208 mmol) in dry THF (1 mL) at 0 $^\circ\text{C}$. The reaction mixture was slowly warmed to r.t. and stirred for 2 h. The reaction was quenched with saturated NH_4Cl solution, the aqueous layer was separated and extracted with EtOAc . The combined organic extracts were washed with brine, dried over MgSO_4 and evaporated *in vacuo*. The residue was purified by flash chromatography (100% EtOAc) to afford 79 mg (95%) of **3-126** as a colorless oil. R_f (100% EtOAc) = 0.3; $[\alpha]_{\text{D}}^{20}$ -41.8 (c 0.5, CHCl_3); IR: 3288, 2923, 2854, 1612, 1586, 1512, 1454, 1365, 1301, 1244, 1172, 1083, 1032, 946, 820,

752, 700 cm^{-1} ; MS (+ESI) m/z , (%): 400 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{24}\text{H}_{34}\text{NO}_4$ 400.2482; Found 400.2478; ^1H NMR (400 MHz, CDCl_3): δ 7.34-7.18 (m, 7H, Ph, *o*-Ar), 6.91-6.82 (m, 2H, *m*-Ar), 4.43 (s, 2H, OCH_2Ar), 3.90 (d, $J = 12.9$ Hz, 1H, NCH_2Ph), 3.80 (s, 3H, ArOCH_3), 3.77 (dd, $J = 11.4, 3.3$ Hz, 1H, CH_2OH), 3.69 (dd, $J = 11.4, 5.8$ Hz, 1H, CH_2OH), 3.59 (d, $J = 12.9$ Hz, 1H, NCH_2Ph), 3.40 (dd, $J = 9.5, 4.8$ Hz, 1H, CH_2OPMB), 3.31 (dd, $J = 9.4, 7.3$ Hz, 1H, CH_2OPMB), 3.16 (br s, 2H, OH), 2.90-2.83 (m, 1H, H5), 2.82-2.75 (m, 1H, H2), 2.64-2.54 (m, 1H, H5), 2.31-2.19 (m, 2H, H3, H4), 1.35 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.19 (s, 3H, $\text{C}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 159.3 (C, $\text{C}_{\text{Ar}}\text{OMe}$), 139.5 (C, *ipso*-Ph), 130.6 (C, *ipso*-Ar), 129.3 (CH, *o*-Ar), 129.0 (CH, Ph), 128.4 (CH, Ph), 127.1 (CH, Ph), 113.9 (CH, *m*-Ar), 73.1 (CH_2 , OCH_2Ar), 72.5 (CH_2 , CH_2OPMB), 71.0 (C, $\text{C}(\text{CH}_3)_2$), 67.6 (CH, C2) 63.8 (CH_2 , CH_2OH), 59.8 (CH_2 , NCH_2Ph), 55.4 (CH_3 , ArOCH_3), 53.6 (CH_2 , C5), 50.0 (CH, C4), 45.0 (CH, C3), 31.1 (CH_3 , $\text{C}(\text{CH}_3)_2$), 29.9 (CH_3 , $\text{C}(\text{CH}_3)_2$).

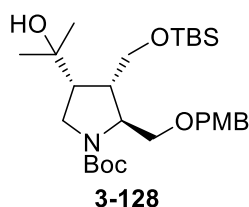
(2*S*,3*S*,4*R*)-1-Benzyl-3-[[*tert*-butyldimethylsilyl]oxy]methyl]-4-(2-hydroxyprop-2-yl)-2-[(4-methoxybenzyloxy)methyl]pyrrolidine (3-127):



Diol **3-126** (74.7 mg, 0.187 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and imidazole (25.5 mg, 0.374 mmol) was added. A solution of TBSCl (32.4 mg, 0.215 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise at r.t. The reaction mixture was stirred for 22 h, quenched by saturated NH_4Cl solution and EtOAc was added. The aqueous layer was separated and washed three times with EtOAc. The combined organic extracts were washed with brine, dried over MgSO_4 , filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography (EtOAc) to afford 77.5 mg (81%) of **3-127** as a pale yellow oil. R_f (hexane/EtOAc 1:1) = 0.5; $[\alpha]_{\text{D}}^{20} -31.2$ (c 0.4, CHCl_3); IR: 3454, 2963, 2864, 1618, 1518, 1469, 1367, 1251, 1075, 1041, 838, 780, 754, 702 cm^{-1} ; MS (+ESI) m/z , (%): 448 (5, $\text{M}+\text{Na}^+$), 426 (100, $\text{M}+\text{H}^+$); HRMS (+ESI) m/z : [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{26}\text{H}_{36}\text{NO}_4$ 426.2639; Found 426.2640; Anal. Calcd for $\text{C}_{26}\text{H}_{35}\text{NO}_4$: C, 70.13; H, 9.22; N, 2.73; Found: C, 70.51; H, 9.17; N, 2.27; ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.16 (m, 7H, Ph, *o*-Ar), 6.87-6.79 (m, 2H, *m*-Ar), 4.53 (br s, 1H, OH), 4.40 (s, 2H, OCH_2Ar), 3.86 (d, $J = 12.8$ Hz, 1H, NCH_2Ph), 3.78 (s, 3H, ArOCH_3), 3.73 (dd, $J = 10.8, 9.5$ Hz, 1H, CH_2OSi), 3.56 (dd, $J = 10.8, 3.6$ Hz, 1H,

CH_2OSi), 3.48 (d, $J = 12.8$ Hz, 1H, NCH_2Ph), 3.33 (dd, $J = 9.3, 4.8$ Hz, 1H, CH_2OPMB), 3.25 (dd, $J = 9.3, 7.8$ Hz, 1H, CH_2OPMB), 2.86 (dd, $J = 8.7, 5.5$ Hz, 1H, H5), 2.48 (dd, $J = 12.0, 8.7$ Hz, 1H, H5), 2.45-2.38 (m, 1H, H2), 2.31-2.16 (m, 2H, H3, H4), 1.28 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.13 (s, 3H, $\text{C}(\text{CH}_3)_2$), 0.89 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.08 (s, 6H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 159.2 (C, $\text{C}_{\text{Ar}}\text{OMe}$), 139.4 (C, *ipso*-Ph), 130.7 (C, *ipso*-Ar), 129.3 (CH, *o*-Ar), 129.2 (CH, Ph), 128.4 (CH, Ph), 127.1 (CH, Ph), 113.9 (CH, *m*-Ar), 73.6 (CH_2 , CH_2OPMB), 73.0 (CH_2 , OCH_2Ar), 69.8 (C, $\text{C}(\text{CH}_3)_2$), 67.0 (CH, C2), 64.1 (CH_2 , CH_2OSi), 60.8 (CH_2 , CH_2Ph), 55.8 (CH_3 , ArOCH_3), 53.5 (CH_2 , C5), 50.9 (CH, C4), 45.5 (CH, C3), 30.7 (CH_3 , $\text{C}(\text{CH}_3)_2$), 29.5 (CH_3 , $\text{C}(\text{CH}_3)_2$), 26.0 (C, $\text{SiC}(\text{CH}_3)_3$), 18.4 (CH_3 , $\text{SiC}(\text{CH}_3)_3$), -5.3 (CH_3 , SiCH_3), -5.4 (CH_3 , SiCH_3).

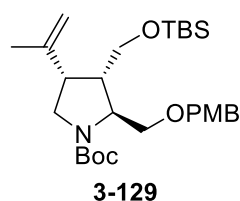
(2*S*,3*S*,4*R*)-1-*tert*-Butoxycarbonyl-3-[(*tert*-butyldimethylsilyl)oxy]methyl}-4-(2-hydroxyprop-2-yl)-2-[(4-methoxybenzyloxy)methyl]pyrrolidine (3-128):



A mixture of **3-127** (56.6 mg, 0.110 mmol), 10% Pd on activated charcoal (17 mg) and di-*tert*-butyl dicarbonate (36.1 mg, 0.165 mmol) in EtOAc (1.5 mL) was stirred at room temperature in an autoclave under a hydrogen atmosphere (4 bar) for 6 h. The reaction mixture was filtered through a pad of Celite[®] and evaporated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc 5:1 to 2:1) affording 52.1 mg (90%) of **3-128** as a colorless oil. R_f (hexane/EtOAc 2:1) = 0.4; $[\alpha]_D^{20}$ -19.8 (c 0.5, CHCl_3); IR: 3360, 2963, 2939, 2865, 1697, 1673, 1618, 1518, 1397, 1370, 1250, 1175, 1136, 1086, 1037, 952, 877, 833, 773 cm^{-1} ; MS (+ESI) m/z , (%): 546 (11, $\text{M}+\text{Na}^+$), 448 (10, $\text{M}^+-\text{C}(\text{CH}_3)_3-\text{H}_2\text{O}$), 432 (100, $\text{M}+\text{Na}^+-\text{Si}(\text{CH}_3)_2-\text{C}_4\text{H}_8$), 310 (11, $\text{M}+\text{Na}^+-\text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3-\text{CH}_2\text{C}_6\text{H}_4\text{OCH}_3$); HRMS (+ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for $\text{C}_{28}\text{H}_{49}\text{NO}_6\text{SiNa}$ 546.3221; Found 546.3221; Anal. Calcd for $\text{C}_{26}\text{H}_{35}\text{NO}_4$: C, 73.38; H, 8.29; N, 3.29; Found: C, 73.83; H, 8.62; N, 3.17; ^1H NMR (400 MHz, CDCl_3): δ 7.29-7.19 (m, 2H, *o*-Ar), 6.92-6.81 (m, 2H, *m*-Ar), 4.57-4.38 (m, 3H, OCH_2Ar , OH), 3.89-3.74 (m, 4H, OCH_3 , CH_2OSi), 3.74-3.50 (m, 3H, H2, CH_2OSi , CH_2OPMB), 3.48-3.20 (m, 3H, H5, CH_2OPMB), 2.51-2.43 (m, 1H, H3), 2.42-2.26 (m, 1H, H4), 1.45 & 1.42 (s, 9H, $\text{OC}(\text{CH}_3)_3$), 1.36 & 1.34 (s, 3H, $\text{C}(\text{CH}_3)_2$), 1.19 (s, 3H, $\text{C}(\text{CH}_3)_2$), 0.91 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.11 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz,

CDCl₃) δ 159.4 & 159.3 (C, C_{Ar}OMe), 154.9 & 154.4 (C, CO₂), 130.7 & 130.4 (C, *ipso*-Ar), 129.2 (CH, *o*-Ar), 113.9 (CH, *m*-Ar), 79.61 & 79.56 (C, C(CH₃)₃), 72.8 (CH₂, OCH₂Ar), 70.3 & 69.8 (CH₂, CH₂OPMB), 69.44 & 69.35 (C, C(CH₃)₂), 64.4 & 64.1 (CH₂, CH₂OSi), 61.2 (CH, C2), 55.44 & 55.37 (CH₃, ArOCH₃), 49.4 & 48.5 (CH, C4), 45.6 (CH₂, C5), 44.1 & 43.0 (CH, C3), 29.9 (CH₃, C(CH₃)₂), 28.6 (CH₃, C(CH₃)₃), 27.5 (CH₃, C(CH₃)₂), 25.99 & 25.96 (SiC(CH₃)₃), 18.3 (CH₃, SiC(CH₃)₃), -5.3 (CH₃, SiCH₃), -5.5 (CH₃, SiCH₃).

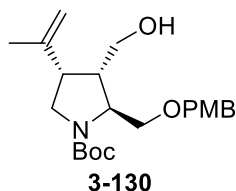
(2*S*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-{[(*tert*-butyldimethylsilyl)oxy]methyl}-2-{[(4-methoxybenzyl)oxy]methyl}-4-(prop-1-en-2-yl)pyrrolidine (3-129):



Pyridine (0.030 mL, 0.356 mmol) and SOCl₂ (0.016 mL, 0.214 mmol) were added at 0 °C to a solution of **3-128** (37.3 mg, 0.0712 mmol) in CH₂Cl₂ (2 mL). The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated NaHCO₃ solution (2 mL). The mixture was extracted with CH₂Cl₂ (3 x 10 mL); the combined organic extracts were washed with brine, dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 10:1 to 2:1) to give 29.1 mg (81%) of alkene **3-129** as a pale yellow oil. *R*_f(hexane/EtOAc 2:1) = 0.7; [α]_D²⁰ -31.8 (*c* 0.5, CHCl₃); IR: 2953, 2929, 2856, 1694, 1613, 1513, 1463, 1391, 1365, 1247, 1174, 1088, 1036, 835, 774 cm⁻¹; MS (+ESI) *m/z*, (%): 528 (100, M+Na⁺); HRMS (+ESI) *m/z*: [M+Na⁺] Calcd for C₂₈H₄₇NO₅SiNa 528.3116; Found 528.3112; ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.15 (m, 2H, *o*-Ar), 6.92-6.80 (m, 2H, *m*-Ar), 4.86 (s, 1H, =CH₂), 4.68 (s, 1H, =CH₂), 4.54-4.39 (m, 2H, OCH₂Ar), 3.80 (s, 3H, OCH₃), 3.70-3.22 (m, 7H, H2, H5, CH₂OSi, CH₂OPMB), 3.04-2.87 (m, 1H, H4), 2.53-2.35 (m, 1H, H3), 1.76 (s, 3H, =CCH₃), 1.43 (s, 9H, C(CH₃)₃), 0.87 & 0.86 (s, 9H, Si(CH₃)₃), 0.02 (s, 3H, SiCH₃), 0.00 (s, 3H, SiCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 159.3 & 159.2 (C, C_{Ar}OMe), 154.8 & 154.6 (C, CO₂), 142.3 & 141.7 (C, C=CH₂), 130.9 & 130.7 (C, *ipso*-Ar), 129.2 & 129.0 (CH, *o*-Ar), 113.9 & 113.8 (CH, *m*-Ar), 111.4 & 111.2 (CH₂, =CH₂), 79.45 & 79.41 (C, C(CH₃)₃), 72.8 & 72.6 (CH₂, OCH₂Ar), 70.7 & 70.6 (CH₂, CH₂OPMB), 63.6 (CH, C2), 62.0 & 61.5 (CH₂, CH₂OSi), 55.4 (CH₃, ArOCH₃), 48.7 & 48.0 (CH₂, C5), 47.5 & 46.8 (CH, C3), 44.8 & 43.9 (CH, C4), 28.7 & 28.6 (CH₃, C(CH₃)₃), 26.11

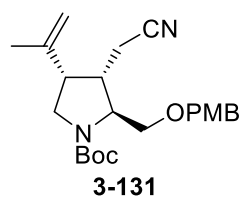
& 26.07 (SiC(CH₃)₃), 23.2 (CH₃, =CCH₃), 18.38 & 18.35 (C, SiC(CH₃)₃), -5.3 (CH₃, SiCH₃), -5.4 (CH₃, SiCH₃).

(2*S*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-(hydroxymethyl)-2-[(4-methoxybenzyloxy)methyl]-4-(prop-1-en-2-yl)pyrrolidine (3-130):



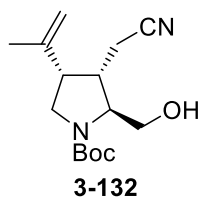
Tetrabutylammonium fluoride (96 μ L, 0.096 mmol, 1M solution in THF) was added at 0 °C to a solution of **3-129** (21.1 mg, 0.0417 mmol) in THF (1 mL), the mixture was gradually warmed to r.t. and stirred for 2 hours. Saturated aqueous NH₄Cl solution was added at r.t. and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over anhydrous MgSO₄ and evaporated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 5:1 to 1:1) gave 15.7 mg (96%) of alcohol **3-130** as a colorless oil. R_f (hexane/EtOAc 2:1) = 0.3; $[\alpha]_D^{20}$ -54.0 (c 0.3, CHCl₃); IR: 3446, 2973, 2934, 2865, 1690, 1671, 1613, 1477, 1401, 1366, 1302, 1247, 1173, 1136, 1115, 1097, 821, 771 cm⁻¹; MS (+ESI) m/z , (%): 805 (35, 2M+Na⁺), 414 (100, M+Na⁺); HRMS (+ESI) m/z : [M+Na⁺] Calcd for C₂₂H₃₃NO₅Na 414.2251; Found 414.2251; ¹H NMR (500 MHz, CDCl₃): δ 7.29-7.20 (m, 2H, *o*-Ar), 6.91-6.83 (m, 2H, *m*-Ar), 4.84 (s, 1H, =CH₂), 4.71 (s, 1H, =CH₂), 4.57-4.41 (m, 2H, OCH₂Ar), 3.91-3.84 (m, 1H, CH₂OPMB), 3.80 (s, 3H, OCH₃), 3.73-3.63 (m, 1H, CH₂OPMB), 3.64-3.31 (m, 5H, H₂, H₅, CH₂OH), 2.96-2.87 (m, 1H, H₄), 2.52-2.41 (m, 1H, H₃), 1.87 (br s, 1H, OH), 1.73 (s, 3H, CCH₃), 1.44 (s, 9H, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ 159.3 & 159.2 (C, C_{Ar}OMe), 154.6 & 154.5 (C, CO₂), 143.2 & 142.7 (C, C=CH₂), 130.1 & 129.9 (C, *ipso*-Ar), 129.4 & 129.1 (CH, *o*-Ar), 113.9 & 113.8 (CH, *m*-Ar), 112.2 (CH₂, =CH₂), 79.8 & 79.7 (C, C(CH₃)₃), 73.0 & 72.9 (CH₂, OCH₂Ar), 70.7 & 70.5 (CH₂, CH₂OPMB), 62.1 & 62.0 (CH₂, CH₂OH), 60.1 & 59.9 (CH, C2), 55.3 (CH₃, ArOCH₃), 49.1 & 48.3 (CH₂, C5), 47.1 & 46.9 (CH, C3), 45.7 & 44.6 (CH, C4), 28.52 & 28.46 (CH₃, C(CH₃)₃), 22.3 & 22.2 (CH₃, CH₃).

(2*S*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-(cyanomethyl)-2-[(4-methoxybenzyloxy)methyl]-4-(prop-1-en-2-yl)pyrrolidine (3-131):



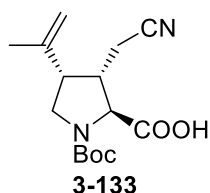
Alcohol **3-130** (9 mg, 0.023 mmol) was dissolved in toluene (1 mL), acetone cyanohydrine (8.4 μ L, 0.092 mmol), PPh_3 (25.3 mg, 0.0966 mmol) and DMEAD (14.5 mg, 0.0621 mmol) were added. The reaction mixture was stirred at 100 $^{\circ}\text{C}$ for 5 h and subsequently at r.t. for 15 h. The organic layer was extracted with water and the combined organic extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/EtOAc 5:1 to 1:1) gave 6.4 mg (70%) of nitrile **3-131** as a colorless oil. R_f (hexane/EtOAc 2:1) = 0.5; $[\alpha]_{\text{D}}^{20}$ -49.1 (c 0.163, CHCl_3); IR: 2972, 2929, 2857, 2246, 1693, 1613, 1513, 1456, 1394, 1366, 1329, 1302, 1247, 1173, 1132, 1088, 1034, 890, 821, 772 cm^{-1} ; MS (+ESI) m/z , (%): 423 (100, $\text{M}+\text{Na}^+$), 367 (26, $\text{M}+\text{Na}^+-\text{CH}_2=\text{C}(\text{CH}_3)_2$); HRMS (+ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for $\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_4\text{Na}$ 423.2254; Found 423.2250; ^1H NMR (500 MHz, CDCl_3): δ 7.29-7.21 (m, 2H, *o*-Ar), 6.91-6.85 (m, 2H, *m*-Ar), 4.98 (s, 1H, $=\text{CH}_2$), 4.77 (s, 1H, $=\text{CH}_2$), 4.58-4.39 (m, 2H, OCH_2Ar), 3.81 (s, 3H, OCH_3), 3.67-3.60 (m, 1H, CH_2OPMB), 3.59-3.51 (m, 1H, CH_2OPMB), 3.50-3.40 (m, 3H, H2, H5), 3.07-2.98 (m, 1H, H4), 2.73-2.65 (m, 1H, H3), 2.28-2.11 (m, 2H, CH_2CN), 1.75 (s, 3H, $=\text{CCH}_3$), 1.47 & 1.43 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (125 MHz, CDCl_3) δ 159.4 & 159.3 (C, $\text{C}_{\text{Ar}}\text{OMe}$), 154.5 & 154.4 (C, CO_2), 140.9 & 140.5 (C, $\text{C}=\text{CH}_2$), 130.4 & 130.1 (C, *ipso*-Ar), 129.4 (CH, *o*-Ar), 119.2 & 119.0 (C, CN), 114.0 & 113.9 (CH, *m*-Ar), 113.7 (CH_2 , $=\text{CH}_2$), 80.4 & 80.1 (C, $\text{C}(\text{CH}_3)_3$), 73.0 & 72.9 (CH_2 , OCH_2Ar), 69.9 & 69.8 (CH_2 , CH_2OPMB), 61.6 (CH, C2), 55.4 (CH_3 , ArOCH_3), 47.6 & 46.7 (CH_2 , C5), 45.6 & 44.6 (CH, C4), 40.5 & 39.9 (CH, C3), 28.61 & 28.55 (CH_3 , $\text{C}(\text{CH}_3)_3$), 22.8 (CH_3 , $=\text{CCH}_3$), 17.8 & 17.7 (CH_2 , CH_2CN).

(2*S*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-(cyanomethyl)-2-(hydroxymethyl)-4-(prop-1-en-2-yl)pyrrolidine (3-132):



DDQ (5.4 mg, 0.024 mmol) was added at r.t. to a stirred solution of **3-131** (8.1 mg, 0.020 mmol) in CH₂Cl₂ (0.5 ml) and water (0.028 ml). After 2.5 h, precipitated DDQH was removed by decantation and washed with a small amount of CH₂Cl₂. The combined CH₂Cl₂ layers were washed with saturated NaHCO₃ solution, brine and dried over MgSO₄. Evaporation of the solvent *in vacuo* gave an oil, which was purified by column chromatography on a silica gel (hexane/EtOAc 1:1) to give **3-132** (5.4 mg, 95%) as a colorless oil. *R*_f(hexane/EtOAc 1:1) = 0.3; [α]_D²⁰ -46.1 (*c* 0.193, CHCl₃); IR: 3442 (br), 2975, 2928, 2248, 1691, 1404, 1367, 1256, 1173, 1134, 1100, 1049, 960, 892, 859, 773 cm⁻¹; MS (+CI) *m/z*, (%): 281 (5, M+H⁺), 249 (20, M⁺-CH₂OH), 225 (100, M+H⁺-C₄H₈), 207 (25, M+H⁺-C₄H₈ -H₂O), 193 (15, M⁺-C₄H₈-CH₂OH), 181 (40, M+H⁺-CO₂-C₄H₈), 149 (32, M⁺-CO₂-C₄H₈-CH₂OH); HRMS (+CI) *m/z*: [M+H⁺] Calcd for C₁₅H₂₅N₂O₃ 281.1865; Found 281.1866; ¹H NMR (400 MHz, CDCl₃): δ 5.01 (s, 1H, =CH₂), 4.80 (s, 1H, =CH₂), 3.94-3.65 (m, 3H, H₂, CH₂O), 3.57-3.42 (m, 2H, H₅), 3.09-2.91 (m, 1H, H₄), 2.69 (br s, 1H, CH₂OH), 2.53-2.37 (m, 1H, H₃), 2.37-2.20 (m, 2H, CH₂CN), 1.75 (s, 3H, CH₃), 1.48 (s, 9H, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃, 5 °C) δ 156.4 & 154.6 (C, CO₂), 140.4 & 140.2 (C, C=CH₂), 119.2 & 118.7 (C, CN), 114.4 & 113.9 (CH₂, C=CH₂), 81.2 & 80.9 (C, C(CH₃)₃), 66.1 (CH₂, CH₂O), 64.3 (CH, C₂), 48.1 & 47.0 (CH₂, C₅), 45.7 & 44.7 (CH, C₄), 40.1 & 39.9 (CH, C₃), 28.5 (CH₃, C(CH₃)₃), 22.9 & 22.6 (CH₃, =CCH₃), 17.70 & 17.65 (CH₂, CH₂CN).

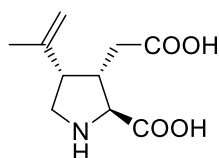
(2*S*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-(cyanomethyl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylic acid (3-133):



Freshly prepared Jones reagent (2.5 M in H₂O, 20 μ L, 0.075 mmol) was added dropwise to a stirred solution of alcohol **3-132** (6.9 mg, 0.025 mmol) in acetone (0.3 mL) at 0 °C. The

mixture was stirred at 0 °C for 1 h, quenched with 2-propanol, and filtered through a plug of Celite. Water (0.5 mL) was added to the filtrate and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to give the carboxylic acid **3-133** (6.6 mg, 92%) as a colorless solid. Mp: 125-126 °C; *R*_f(hexane/EtOAc 1:2) = 0.3; [α]_D²⁰ -26.8 (*c* 0.3, CHCl₃); IR: 3087 (br), 2956, 2925, 2855, 2250, 1700, 1654, 1400, 1368, 1258, 1138, 904, 857, 797, 773 cm⁻¹; MS (-ESI) *m/z*, (%): 294 (15, M⁺), 293 (100, M-H⁺); HRMS (-ESI) *m/z*: [M-H⁺] Calcd for C₁₅H₂₁N₂O₄ 293.1507; Found 293.1502; ¹H NMR (400 MHz, CDCl₃): δ 5.07 (s, 1H, =CH₂), 4.84 (s, 1H, =CH₂), 4.38 & 4.30 (br s, 1H, CHCO₂), 3.88-3.65 (m, 2H, H₅), 3.19-2.98 (m, 2H, H₃, H₄), 2.39 (dd, *J* = 17.0, 6.0 Hz, 1H, CH₂CN), 2.31 (dd, *J* = 17.1, 8.4 Hz, 1H, CH₂CN), 1.81 & 1.78 (s, 3H, CH₃), 1.53 & 1.47 (s, 9H, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ 171.4 (C, CO₂H), 157.1 (C, CO₂), 139.6 & 139.5 (C, C=CH₂), 118.1 & 118.0 (C, CN), 114.6 & 114.3 (CH₂, C=CH₂), 83.1 (C, C(CH₃)₃), 63.7 (CH, C₂), 47.4 (CH₂, C₅), 46.0 (CH, C₄), 39.2 (CH, C₃), 28.35 & 28.25 (CH₃, C(CH₃)₃), 22.65 & 22.58 (CH₃, =CCH₃), 16.8 (CH₂, CH₂CN).

(2*S*,3*S*,4*S*)-3-(Carboxymethyl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylic acid, (-)- α -Kainic acid



(-)- α -kainic acid

Nitrile **3-103** (3.5 mg, 0.0119 mmol) was dissolved in a mixture of ethanol (0.4 mL) and H₂O (0.2 mL), followed by addition of aqueous hydrogen peroxide (35%, 25 μ L) and sodium hydroxide (5 mg, 0.119 mmol) at 0 °C. After stirring at r.t. for 2 h, the solution was heated to reflux for 15 h and cooled to r.t. Ethanol was removed under reduced pressure, the residue was diluted with H₂O, acidified to pH = 2 with HCl (1 mL, 1M) at 0 °C, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to afford 3.5 mg of dicarboxylic acid as a colorless solid. The NMR data correspond to those reported in the literature.^[89b]

TFA (0.1 mL) was added to a solution of the crude dicarboxylic acid in CH₂Cl₂ (0.2 mL) at room temperature. The mixture was stirred for 2 h and concentrated *in vacuo* to give crude kainic acid. The residue was purified using Dowex-50 H⁺ (100–200 wet mesh) column chromatography (elution with 3.8% NH₃) to give (-)- α -kainic acid (2.4 mg, 95%) as

a colorless solid. $[\alpha]_{\text{D}}^{20} -3.6$ (c 0.055, H₂O), Ref.^[85g] $[\alpha]_{\text{D}}^{20} -14.2$ (c 0.2, H₂O); The NMR data correspond to those reported in the literature.^[85g]

4.4 X-Ray crystallography

Crystallographic data for **3-51a** and **3-65** were collected on a Nonius KappaCCD diffractometer equipped with a Bruker APEX-II CCD detector by monochromatized MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) at a temperature 145 K for **3-51a** or at 150 K for **3-65**. Crystallographic data for **3-74f**, **3-83b**, **3-88**, **3-106** were collected on a Bruker diffractometer D8 VENTURE Kappa Duo with PHOTON 100 CMOS detector by I μ S micro-source with Cu radiation ($\lambda = 1.54178 \text{ \AA}$) at a temperature 120 K.

The structures were solved by direct methods (SHELXT2014/5)^[133] and refined by full-matrix least squares based on F^2 (SHELXT2018/3).^[134] The hydrogen atoms on carbon atoms were found on difference Fourier map and recalculated into idealised positions (riding model) and refined with assigned temperature factors $H_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{pivot atom})$ or $1.5 U_{\text{eq}}$ for methyl moiety. The enantiomers of samples **3-51a** and **3-65** have been assigned by reference to an unchanging chiral centre in the synthetic procedure, since it cannot be established by anomalous-dispersion effects.

However absolute configuration of crystals **3-74f**, **3-83b**, **3-88** and **3-106** was established by anomalous-dispersion effects in diffraction pattern. The resulting enantiomers agree well with the expectation based on known chirality of carbon atom.

Table 4.4.1 X-Ray crystallographic data for **3-51a**, **3-65**, **3-74f**.

Compound	3-51a	3-65	3-74f
Formula	C ₃₃ H ₄₈ N ₂ O ₃	C ₃₂ H ₄₄ N ₂ O ₃	C ₃₃ H ₅₄ N ₂ O ₃
M.w.	520.73	504.39	526.78
Crystal system	Tetragonal	Triclinic	Monoclinic
Space group [No.]	<i>P</i> 4 ₃ 2 ₁ 2 (No 96)	<i>P</i> 1 (No 1)	<i>P</i> 2 ₁ (No 4)
<i>a</i> [Å]	12.1263 (6)	10.8489 (3)	9.6656 (4)
<i>b</i> [Å]		13.9936 (4)	10.5332 (4)
<i>c</i> [Å]	41.594 (2)	20.6758 (7)	15.3115 (6)
α [°]		93.046 (1)	
β [°]		104.954 (1)	94.041 (1)
γ [°]		107.138 (2)	
<i>Z</i>	8	4	2
<i>V</i> [Å ³]	6116.3 (7)	2869.43 (15)	1554.98 (11)
<i>D_x</i> [g cm ⁻³]	1.131	1.168	1.125
Crystal size [mm]	0.55 × 0.53 × 0.33	0.57 × 0.38 × 0.24	0.37 × 0.31 × 0.28
Crystal shape	Prism	Prism	Prism
μ [mm ⁻¹]	0.07	0.07	0.55
θ_{max} [°]	26.0	26.1	72.3
Range of <i>h</i> ; <i>k</i> ; <i>l</i>	-14,9; -14,10; -51,48	-9,13; -17,17; -25,25	-10,11; -13,13; -18,18
Measured reflections	27574	27035	29685
Independent diffractions (<i>R_{int}</i> ^a)	5977 (0.036)	18354 (0.020)	6081 (0.031)
Observed diffract. [<i>I</i> > 2σ(<i>I</i>)]	5338	15671	5997
<i>T_{min}</i> , <i>T_{max}</i>	0.962, 0.977	0.959, 0.983	0.70, 0.86
No. of parameters	351	1353	352
<i>w₁</i> , <i>w₂</i> ^b	0.0401, 1.5144	0.0434, 0.0758	0.0353, 0.2708
Absolut. structure param. (Flack)	0.7 (4)	-0.3 (4)	0.02 (4)
<i>R^c</i> [<i>F</i> ² > 2σ(<i>F</i> ²)]	0.041	0.040	0.027
<i>wR</i> (<i>F</i> ²) for all data	0.094	0.092	0.070
GOF ^d	1.06	1.06	1.03
Residual electron density [e/Å ³]	0.16, -0.17	0.16, -0.19	0.19, -0.15

^a $R_{int} = \sum |F_o^2 - F_{o,mean}^2| / \sum F_o^2$, ^b Weighting scheme: $w = [\sigma^2(F_o^2) + (w_1P)^2 + w_2P]^{-1}$,
where $P = [\max(F_o^2, 0) + 2F_c^2]/3$. ^c $R(F) = \sum ||F_o| - |F_c|| / \sum |F_o|$,
 $wR(F^2) = [\sum (w(F_o^2 - F_c^2)^2) / (\sum w(F_o^2)^2)]^{1/2}$. ^d GOF = $[\sum (w(F_o^2 - F_c^2)^2) / (N_{diffs} - N_{params})]^{1/2}$.

Table 4.4.2 X-Ray crystallographic data for **3-83b**, **3-88**, **3-106**.

Compound	3-83b	3-88	3-106
Formula	C ₂₅ H ₂₃ NO ₂	C ₁₈ H ₂₃ NO ₂	C ₄₅ H ₅₆ N ₂ O ₃
M.w.	369.44	285.37	672.91
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group [No.]	C2 (No 5)	<i>P</i> 2 ₁ (No 4)	<i>P</i> 2 ₁ (No 4)
<i>a</i> [Å]	36.613 (2)	8.4766 (6)	9.5896 (4)
<i>b</i> [Å]	7.5438 (4)	10.3113 (8)	20.0219 (7)
<i>c</i> [Å]	13.6433 (7)	9.8045 (7)	10.2776 (4)
α [°]			
β [°]	96.549 (2)	115.379 (1)	105.646 (1)
γ [°]			
<i>Z</i>	8	2	2
<i>V</i> [Å ³]	3743.7 (3)	774.26 (10)	1900.20 (13)
<i>D_x</i> [g cm ⁻³]	1.311	1.224	1.176
Crystal size [mm]	0.49 × 0.25 × 0.09	0.31 × 0.29 × 0.19	0.34 × 0.30 × 0.23
Crystal shape	Prism	Prism	Prism
μ [mm ⁻¹]	0.65	0.62	0.56
θ_{max} [°]	72.2	70.1	79.6
Range of <i>h</i> ; <i>k</i> ; <i>l</i>	-43,44; -9,9; -16,16	-10,10; -12,12; -11,11	-12,11;-25,25; -13,13
Measured reflections	25954	12440	42783
Independent diffractions (<i>R_{int}</i> ^a)	7274 (0.021)	2893 (0.022)	8107 (0.023)
Observed diffract. [<i>I</i> > 2σ(<i>I</i>)]	7201	2883	8059
<i>T_{min}</i> , <i>T_{max}</i>	0.83, 0.94	0.79, 0.89	0.82, 0.88
No. of parameters	506	192	459
<i>w₁</i> , <i>w₂</i> ^b	0.0462, 1.5862	0.0262, 0.1775	0.0405, 0.3552
Absolut. structure param. (Flack)	0.04 (12)	-0.04 (7)	0.01 (4)
<i>R^c</i> [<i>F</i> ² > 2σ(<i>F</i> ²)]	0.030	0.027	0.028
w <i>R</i> (<i>F</i> ²) for all data	0.079	0.066	0.073
GOF ^d	1.04	1.06	1.03
Residual electron density [e/Å ³]	0.24, -0.15	0.22, -0.13	0.22, -0.23

^a $R_{int} = \sum |F_o^2 - F_{o,mean}^2| / \sum F_o^2$, ^b Weighting scheme: $w = [\sigma^2(F_o^2) + (w_1P)^2 + w_2P]^{-1}$,
where $P = [\max(F_o^2, 0) + 2F_c^2]/3$. ^c $R(F) = \sum ||F_o| - |F_c|| / \sum |F_o|$,
 $wR(F^2) = [\sum (w(F_o^2 - F_c^2)^2) / (\sum w(F_o^2)^2)]^{1/2}$. ^d GOF = $[\sum (w(F_o^2 - F_c^2)^2) / (N_{diffs} - N_{params})]^{1/2}$.

5. Conclusions and outlook

This thesis illustrates that merging polar asymmetric aza-Michael addition reactions with radical reactions is a useful synthetic tool for assembling β -amino- α -hydroxy acid scaffolds and *N*-containing heterocyclic compounds.

Diastereoselective radical α -oxygenation of carbonyl compounds with TEMPO was accomplished by a tandem lithium (*R*)-*N*-benzyl-*N*-(1-phenylethyl)amide conjugate addition to α,β -unsaturated carbonyl compounds/SET oxidation/radical α -oxygenation process mediated by ferrocenium hexafluorophosphate. A diverse range of enantiomerically pure β -amino- α -(aminoxy) carboxylic acid derivatives was prepared mostly in good yields with good to excellent *anti*-diastereoselectivity for aliphatic α,β -unsaturated carbonyl compounds and only moderate diastereoselectivity was observed for β -aryl and β -heteroaryl derivatives. Both the amino and the hydroxy group in the aminooxygenated products can be deprotected chemoselectively. The reductive cleavage of the N–O bond to free α -hydroxy compounds proceeded without epimerization at the residing stereocenters and in the presence of acid-labile groups, such as Boc or TBDMS. Although the diastereoselectivity was not excellent for all the compounds, the aminooxygenation methodology represents a new one-step approach to optically active *O*-protected *anti*- β -amino- α -hydroxy acid derivatives, which was indeed applied in total syntheses to the *anti*- β -amino- α -hydroxy acid fragments of the macrocyclic (depsipeptides) perthamide C and largamide H and a total synthesis of (–)-cytoxazone. The total synthesis of the latter ranks among the shorter total syntheses, but is not so efficient in terms of overall yield in comparison to previously published approaches. Preliminary results show that the radical coupling selectivity can be reversed by applying 1-naphthylethylamide in the aza-Michael addition step, thus providing an access to *syn*- β -amino- α -(aminoxy) carboxylic acid derivatives.

SET induced tandem processes mediated by ferrocene and 2,2,6,6-tetramethyl-*N*-oxopiperidinium hexafluorophosphate were applied in the synthesis of complex pyrrolidines *via* different cyclization modes. Previous approaches to enantioselective syntheses of *N*,2,3,4-tetrasubstituted pyrrolidines used the chirality from the (*R*)-1-(phenyl)ethyl group, which served as an external auxiliary introducing three contiguous stereocenters on the pyrrolidine ring. However, only moderate C3,C4-*cis* diastereoselectivity was achieved. *N*-allylic *N*-benzylamide having the chirality in the allylic chain served as a useful internal auxiliary, thus providing pyrrolidines with even more increased functionality. Despite slower 5-*exo*

cyclization and moderate yields, *N*,2,3,4,5-pentasubstituted pyrrolidines were always formed with good to excellent C3,C4-*cis* diastereoselectivities. Therefore, using chiral allylic amides, which bear the chiral center in the allylic fragment will not only lead to highly diastereoselective synthesis of pyrrolidines, but also the chiral auxiliary group is efficiently incorporated into the pyrrolidine core. The absolute configuration of pyrrolidine **3-51a** was confirmed by X-ray crystallography.

The SET-catalyzed tandem amide conjugate addition/5-*exo* cyclization/oxygenation sequence of allylic lithium amides derived from (*R*)-phenylthylamine to cycloalkene carboxylates provided azabicyclo[n.3.0]alkane derivatives mostly in moderate yields with good to excellent diastereoselectivities. Only *cis*-fused rings were formed. Although annulation attempt using allylic amide having the chirality in the allylic chain and cyclopentene carboxylate did not give good yield in tandem reaction, bicyclic pyrrolidine was isolated as a single diastereomer. Its structure was proved by X-ray crystallography.

It was also shown that the formation of stereogenic quaternary C centers is also possible. A range of substituted spiropyrrolidines was prepared mostly in good yields by SET-catalyzed tandem amide conjugate addition/spirocyclization reactions with chiral lithium amides derived from cycloalkenylmethylamines and acyclic α,β -unsaturated esters. The absolute configuration of spiropyrrolidine **3-74f** was confirmed by X-ray crystallography. The tandem reactions proceeded with high conjugate addition diastereoselectivity, the cyclization diastereoselectivity was moderate to very good, but the oxygenation diastereoselectivity was high. Diastereomeric mixtures of pentasubstituted pyrrolidines, azabicyclo[n.3.0]alkanes and spiropyrrolidines were resolved into pure lactones and *trans*-hydroxyalkyl pyrrolidines by reductive deprotection of the tetramethylpiperidinyl protecting group and their absolute configuration was determined by X-ray crystallography.

SET-catalyzed 5-*exo* radical cyclization/oxygenation reactions provided a simple access to a trisubstituted pyrrolidine ring with all stereogenic centers comprising that of (–)- α -kainic acid. As a result, an asymmetric total synthesis of (–)- α -kainic acid was accomplished in 15 steps in overall 5% yield from commercially available racemic butadiene monoxide. Although the total synthesis is rather long, it is the first radical-based approach forming exclusively the C3,C4-*cis* trisubstituted pyrrolidine ring.

The methodology developed in this thesis has many implications for further investigations. For example, steering the stereochemistry of aminooxygenation reactions toward *syn*-isomer should be studied in more detail. The potential use of more hindered nitroxyl radicals in the

aminoxygenation reactions should be explored. Furthermore, a diverse range of amides having the chirality in the allylic chain should be studied in tandem aza-Michael addition/5-*exo* radical cyclization/oxygenation reactions. Overall, highly diastereoselective annulation reactions may be applied in the total synthesis of bioactive Daphniphyllum alkaloids.

6. References

- [1] a) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.*, **1996**, *96*, 195-206; b) S. Gejalakshmi, P. Valentina, A. Maheshwaran, *Int. J. Pharm. Sci. Rev. Res.*, **2017**, *45*, 165-169.
- [2] G. Huang, X. Li, *Curr. Org. Synth.*, **2017**, *14*, 568-571.
- [3] A. Y. Rulev, *Russ. Chem. Rev.*, **2011**, *80*, 197-218.
- [4] a) J. L. Vicario, D. Badía, L. Carrillo, J. Etxebarria, E. Reyes, N. Ruiz, *Org. Prep. Proced. Int.*, **2005**, *6*, 513-538; b) S. G. Davies, A. D. Smith, P. D. Price, *Tetrahedron: Asymmetry*, **2005**, *16*, 2833-2891; c) D. Enders, Ch. Wang, J. X. Liebich, *Chem. Eur. J.*, **2009**, *15*, 11058-11076; d) S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Tetrahedron: Asymmetry*, **2012**, *23*, 1111-1153; e) K. M. Byrd, *Beilstein J. Org. Chem.*, **2015**, *11*, 530-562; f) S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Tetrahedron: Asymmetry*, **2017**, *28*, 1842-1868.
- [5] a) M. Liu, M. P. Sibi, *Tetrahedron*, **2002**, *58*, 7991-8035; b) J. Etxebarria, J. L. Vicario, D. Badia, L. Carrillo, *J. Org. Chem.*, **2004**, *69*, 2588-2590; c) J. Magano, D. Bowles, B. Conway, T. N. Nanninga, D. D. Winkle, *Tetrahedron Lett.*, **2009**, *50*, 6325-6328.
- [6] a) L.-W. Xu, Ch.-G. Xia, *Eur. J. Org. Chem.*, **2005**, 633-639; b) Ch. Huang, Y. Yin, J. Guo, J. Wang, B. Fan, L. Yang, *RSC Adv.*, **2014**, *4*, 10188-10195.
- [7] a) E. V. Gorobets, M. S. Miftakhov, F. A. Valeev, *Russ. Chem. Rev.*, **2000**, *69*, 1001-1019; b) M. Gormen, R. Le Goff, A. M. Lawson, A. Daich, S. Comesse, *Tetrahedron Lett.*, **2013**, *54*, 2174-2176; c) H. Lakhdari, O. Talhi, R. Hassaine, N. Taibi, R. F. Mendes, F. A. Almeida Paz, N. Bennamane, B. Nedjar-Kolli, K. Bachari, A. M. S. Silva, *Synlett*, **2018**, *29*, 1437-1440.
- [8] a) E. Suarez, M. S. Rodriguez, in *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), John Wiley & Sons, Ltd, **2001**; b) G. J. Rowlands, *Tetrahedron*, **2009**, *65*, 8603-8655; c) G. J. Rowlands, *Tetrahedron*, **2010**, *66*, 1593-1636; c) A. Deepthi, V. Sathi, V. Nair, *Tetrahedron Lett.*, **2018**, *59*, 2767-2777.
- [9] a) A. L. J. Beckwith, *Chem. Soc. Rev.*, **1993**, 143-151; b) A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.*, **2016**, *55*, 58-102; c) Q. Liu, X. Dong, J. Li, J. Xiao, Y. Dong, H. Liu, *ACS Catal.*, **2015**, *5*, 6111-6137; d) A. Gualandi, L. Mengozzi, P. G. Cozzi, *Asian J. Org. Chem.*, **2017**, *6*, 1160-1179; e) G. Fang, X. Cong, G. Zanoni, Q. Liu, X. Bi, *Adv. Synth. Catal.*, **2017**, *359*, 1422-1502; f) K. Wang, W. Kong, *Chin. J. Chem.*, **2018**, *36*, 247-256.

- [10] a) L. Becking, H. J. Schäfer, *Tetrahedron Lett.*, **1988**, 29, 2801-2802; b) K. J. Romero, M. S. Galliher, M. A. R. Raycroft, J.-P. R. Chauvin, I. Bosque, D. A. Pratt, C. R. J. Stephenson, *Angew. Chem. Int. Ed.*, **2018**, 57, 17125-17129.
- [11] a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.*, **2013**, 113, 5322-5363; b) J.-P. Goddard, C. Ollivier, L. Fensterbank, *Acc. Chem. Res.*, **2016**, 49, 1924-1936; c) D. Staveness, I. Bosque, Corey R. J. Stephenson, *Acc. Chem. Res.*, **2016**, 49, 2295-2306; d) B.L. Tóth, O. Tischler, Z. Novák, *Tetrahedron Lett.*, **2016**, 57, 4505-4513; e) I. Ghosh, L. Marzo, A. Das, R. Shaikh, B. König, *Acc. Chem. Res.*, **2016**, 49, 1566-1577; f) B. König, *Eur. J. Org. Chem.*, **2017**, 1979-1981; g) K. Jia, Y. Chen, *Chem. Commun.*, **2018**, 54, 6105-6112.
- [12] a) Y.-H. Yang, M. P. Sibi, in *Encyclopedia of Radicals in Chemistry, Biology and Materials* (Eds.: Ch. Chatgililoglu, A. Studer), **2012**, 2, 655-691; b) F. Wang, P. Chen, G. Liu, *Acc. Chem. Res.*, **2018**, 51, 2036-2046.
- [13] U. Jahn, *Top. Curr. Chem.*, **2012**, 320, 323-451.
- [14] a) S.-i. Inaba, I. Ojima, *Tetrahedron Lett.*, **1977**, 18, 2009-2012; b) I. Ojima, S. M. Brandstadter, R. J. Donovan, *Chem. Lett.*, **1992**, 21, 1591-1594; c) Y. Matsumura, M. Nishimura, H. Hiu, M. Watanabe, N. Kise, *J. Org. Chem.*, **1996**, 61, 2809-2812; d) N. Kise, K. Kumada, Y. Terao, N. Ueda, *Tetrahedron*, **1998**, 54, 2697-2708; e) N. Kise, T. Ueda, K. Kumada, Y. Terao, N. Ueda, *J. Org. Chem.*, **2000**, 65, 464-468; f) A. G. Csaky, J. Plumet, *Chem. Soc. Rev.*, **2001**, 30, 313-320; g) K. M. Arason, S. C. Bergmeier, *Org. Prep. Proced. Int.*, **2002**, 34, 337-366.
- [15] a) M. Schmittel, A. Haeuseler, *J. Organomet. Chem.*, **2002**, 661, 169-179; b) P. S. Baran, N. B. Ambhaikar, C. A. Guerrero, B. D. Hafensteiner, D. W. Lin, J. M. Richter, *ARKIVOC*, **2006**, 7, 310-325; c) M. P. Demartino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.*, **2008**, 130, 11546-11560; d) A. A. O. Sarhan, C. Bolm, *Chem. Soc. Rev.*, **2009**, 38, 2730-2744; e) F. Guo, M. D. Clift, R. J. Thomson, *Eur. J. Org. Chem.*, **2012**, 4881-4896; f) U. Jahn, *Top. Curr. Chem.* **2012**, 320, 192-223; g) H.-R. Wu, L. Cheng, D.-L. Kong, H.-Y. Huang, C.-L. Gu, L. Liu, D. Wang, C.-J. Li, *Org. Lett.*, **2016**, 18, 1382-1385.
- [16] a) B. B. Snider, *Chem. Rev.*, **1996**, 96, 339-364; b) T. Linker, *J. Organomet. Chem.*, **2002**, 661, 159-167; c) A.S. Demir, M. Emrullahoglu, *Curr. Org. Synth.*, **2007**, 4, 321-351; d) B. B. Snider, *Tetrahedron*, **2009**, 65, 10738-10744; e) S. B. Herzon, *Synlett*, **2011**, 2105-2114; f) J. W. Burton, in *Encyclopedia of Radicals in Chemistry, Biology and Materials* (Eds.: C. Chatgililoglu, A. Studer), John Wiley & Sons, Ltd, **2012**; g) Y.-C. Wong, T.-T. Kao, J.-K. Huang, Y.-W. Jhang, M.-C. Chou, K.-S. Shia, *Adv. Synth. Catal.*, **2014**, 356, 3025-

3038; h) T. Amatov, M. Gebauer, R. Pohl, I. Císařová, U. Jahn, *Free Radic. Res.*, **2016**, *50*, 6-17.

[17] a) V. Nair, L. Balagopal, R. Rajan, J. Mathew, *Acc. Chem. Res.*, **2004**, *37*, 21-30; b) V. Nair, A. Deepthi, *Chem. Rev.*, **2007**, *107*, 1862-1891; c) V. Nair, A. Deepthi, *Tetrahedron*, **2009**, *65*, 10745-10755.

[18] a) J. Christoffers, T. Werner, M. Rössle, *Catal. Today*, **2007**, *121*, 22-26; b) M. Rössle, J. Christoffers, *Tetrahedron*, **2009**, *65*, 10941-10944.

[19] a) N. L. Weinberg, H. R. Weinberg, *Chem. Rev.*, **1968**, *48*, 449-523; b) G. Pampaloni, P. Zanello, in *The Chemistry of Metal Enolates* (Ed. J. Zabicky), Wiley, Chichester, UK, **2009**, Part 1, 461-550; c) M. Schmitt, M. Lal, R. Lal, M. Röck, A. Langels, Z. Rappoport, A. Basheer, J. Schlirf, H.-J. Deiseroth, U. Flörke, G. Gescheidt, *Tetrahedron*, **2009**, *65*, 10842-10855.

[20] a) U. Jahn, P. Hartmann, *Chem. Commun.*, **1998**, 209-210; b) U. Jahn, *J. Org. Chem.*, **1998**, *63*, 7130-7131; c) U. Jahn, P. Hartmann, I. Dix, P. G. Jones, *Eur. J. Org. Chem.*, **2001**, 3333-3355.

[21] D. A. Khobragade, S. G. Mahamulkar, L. Pospíšil, I. Císařová, L. Rulíšek, U. Jahn, *Chem. -Eur. J.*, **2012**, *18*, 12267-12277.

[22] a) U. Jahn, M. Müller, S. Aussieker, *J. Am. Chem. Soc.*, **2000**, *122*, 5212-5213; b) U. Jahn, F. Kafka, R. Pohl, P. G. Jones, *Tetrahedron*, **2009**, *65*, 10917-10929; c) F. Kafka, R. Pohl, I. Císařová, R. Mackman, G. Bahador, U. Jahn, *Eur. J. Org. Chem.*, **2016**, 3862-3871.

[23] a) U. Jahn, *Chem. Commun.*, **2001**, 1600-1601; b) U. Jahn, P. Hartmann, I. Dix, P. G. Jones, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2277-2282; c) P. R. Jagtap, L. Ford, E. Deister, R. Pohl, I. Císařová, J. Hodek, J. Weber, R. Mackman, G. Bahador, U. Jahn, *Chem. -Eur. J.*, **2014**, *20*, 10298-10304; d) M. Holan, R. Pohl, I. Císařová, B. Klepetářová, P. G. Jones, U. Jahn, *Chem. -Eur. J.*, **2015**, *21*, 9877-9888.

[24] a) U. Jahn, D. Rudakov, *Synlett*, **2004**, 1207-1210; b) U. Jahn, D. Rudakov, *Org. Lett.*, **2006**, *8*, 4481-4484; c) J. -P. Goddard, C. Gomez, F. Brebion, S. Beauviere, L. Fensterbank, M. Malacria, *Chem. Commun.*, **2007**, 2929-2931; d) U. Jahn, D. Rudakov, P. G. Jones, *Tetrahedron*, **2012**, *68*, 1521-1539; e) P. R. Jagtap, I. Císařová, U. Jahn, *Org. Biomol. Chem.*, **2018**, *16*, 750-755.

[25] a) U. Jahn, P. Hartmann, I. Dix, P. G. Jones, *Eur. J. Org. Chem.*, **2002**, 718-735; b) U. Jahn, E. Dinca, *Chem. -Eur. J.*, **2009**, *15*, 58-62; c) U. Jahn, E. Dinca, *J. Org. Chem.*, **2010**, *75*, 4480-4491.

- [26] a) U. Jahn, P. Hartmann, E. Kaasalainen, *Org. Lett.*, **2004**, 6, 257-260; b) L. Řehová, M. Dračinský, U. Jahn, *Org. Biomol. Chem.*, **2016**, 14, 9612-9621.
- [27] a) A. Studer, *Chem. -Eur. J.*, **2001**, 7, 1159-1164; b) H. Fischer, *Chem. Rev.*, **2001**, 101, 3581-3610; c) A. Studer, *Chem. Soc. Rev.*, **2004**, 33, 267-273; d) K. -S. Focsaneanu, J. C. Scaiano, *Helv. Chim. Acta*, **2006**, 89, 2473-2482.
- [28] a) A. Studer, *Angew. Chem. Int. Ed.*, **2000**, 39, 1108-1111; b) G. Audran, P. Brémond, S. R. A. Marque, *Chem. Commun.*, **2014**, 50, 7921-7928.
- [29] K. J. Romero, M. S. Galliher, D. A. Pratt, C. R. J. Stephenson, *Chem. Soc. Rev.*, **2018**, 47, 7851-7866.
- [30] T. Amatov, R. Pohl, I. Císařová, U. Jahn, *Angew. Chem. Int. Ed.*, **2015**, 54, 12153-12157.
- [31] J. Xu, E. J. E. Caro-Diaz, M. H. Lacoske, C.-I. Hung, C. Jamora, E. A. Theodorakis, *Chem. Sci.*, **2012**, 18, 12267-12277.
- [32] a) H. Suda, T. Takita, T. Aoyagi, H. Umezawa, *J. Antibiot.*, **1976**, 29, 100-101; b) I. Saiki, J. Murata, K. Watanabe, H. Fujii, F. Abe, I. Azuma, *Jpn. J. Cancer Res.*, **1989**, 80, 873-878; c) Y. Etoh, M. Miyazaki, H. Saitoh, N. Toda, *Jpn. J. Pharmacol.*, **1993**, 63, 109-119; d) K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem. Int. Ed.*, **1994**, 33, 15-44; e) I. Ojima, M. Das, *J. Nat. Prod.*, **2009**, 72, 554-565.
- [33] a) H. Umezawa, T. Aoyagi, H. Suda, M. Hamada, T. Takeuchi, *J. Antibiot.*, **1976**, 29, 97-99; b) H. Nakamura, H. Suda, T. Takita, T. Aoyagi, H. Umezawa, *J. Antibiot.*, **1976**, 29, 102-103.
- [34] T. Okino, H. Matsuda, M. Murakami, K. Yamaguchi, *Tetrahedron Lett.*, **1993**, 34, 501-504.
- [35] R. Sekizawa, H. Iinuma, Y. Muraoka, H. Naganawa, N. Kinoshita, H. Nakamura, M. Hamada, T. Takeuchi, K. Umezawa, *J. Nat. Prod.*, **1996**, 59, 232-236.
- [36] a) M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.*, **1971**, 93, 2325-2327; b) P. B. Schiff, J. Fant, S. B. Horwitz, *Nature*, **1979**, 277, 665-667.
- [37] V. Sepe, M. V. D'Auria, G. Bifulco, R. Ummarino, A. Zampella, *Tetrahedron*, **2010**, 66, 7520-7526.
- [38] A. Plaza, C. A. Bewley, *J. Org. Chem.*, **2006**, 71, 6898-6907.
- [39] H. Kakeya, M. Morishita, H. Koshino, T.-i. Morita, K. Kobayashi, H. Osada, *J. Org. Chem.*, **1999**, 64, 1052-1053.
- [40] G. Cardillo, C. Tomasini, *Chem. Soc. Rev.*, **1996**, 25, 117-127.

- [41] a) I. Ojima, S. Lin, T. Wang, *Curr. Med. Chem.*, **1999**, *6*, 927-954; b) S. C. Bergmeier, *Tetrahedron*, **2000**, *56*, 2561-2576.
- [42] a) G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 451-454; b) A. E. Rubin, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 2637-2640; c) P. O'Brien, *Angew. Chem. Int. Ed.*, **1999**, *38*, 326-329; d) N. S. Barta, D. R. Sidler, K. B. Somerville, S. A. Weissman, R. D. Larsen, P. J. Reider, *Org. Lett.*, **2000**, *2*, 2821-2824; e) S. H. K. Reddy, S. Lee, A. Datta, G. I. Georg, *J. Org. Chem.*, **2001**, *66*, 8211-8214; f) S. Montiel-Smith, V. Cervantes-Mejía, J. Dubois, D. Guénard, F. Guéritte, J. Sandoval-Ramírez, *Eur. J. Org. Chem.*, **2002**, 2260-2264; g) S. Milicevic, R. Matovic, R. N. Saicic, *Tetrahedron Lett.*, **2004**, *45*, 955-957.
- [43] a) S. Torssell, M. Kienle, P. Somfai, *Angew. Chem. Int. Ed.*, **2005**, *44*, 3096-3099; b) S. Torssell, P. Somfai, *Adv. Synth. Catal.*, **2006**, *348*, 2421-2430.
- [44] a) Y. Qian, X. Xu, L. Jiang, D. Prajapati, W. Hu, *J. Org. Chem.*, **2010**, *75*, 7483-7486; b) M. Zimuwandeyi, F. Kola, A. Lemmerer, D. Brady, A. L. Rousseau, M. L. Bode, *Tetrahedron*, **2018**, *74*, 2925-2941.
- [45] Q. Wang, W. Huang, H. Yuan, Q. Cai, L. Chen, H. Lv, X. Zhang, *J. Am. Chem. Soc.*, **2014**, *136*, 16120-16123.
- [46] Y. Jiang, X. Chen, Y. Zheng, Z. Xue, C. Shu, W. Yuan, X. Zhang, *Angew. Chem. Int. Ed.*, **2011**, *50*, 7304-7307.
- [47] a) J. N. Denis, A. E. Greene, A. A. Serra, M. J. Luche, *J. Org. Chem.*, **1986**, *51*, 46-50; b) J. N. Denis, A. Correa, A. E. Greene, *J. Org. Chem.*, **1990**, *55*, 1957-1959; c) L. Deng, E. N. Jacobsen, *J. Org. Chem.*, **1992**, *57*, 4320-4323; d) D.-M. Gou, Y.-C. Liu, C.-S. Chen, *J. Org. Chem.*, **1993**, *58*, 1287-1289; e) M. Pastó, P. Castejón, A. Moyano, M. A. Pericàs, A. J. Riera, *J. Org. Chem.*, **1996**, *61*, 6033-6037; f) S.-Y. Tosaki, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.*, **2005**, *127*, 2147-2155; g) R. Tak, M. Kumar, T. Menapara, M. K. Choudhary, R. I. Kureshy, N.-U. H. Khan, *ChemCatChem*, **2017**, *9*, 322-328.
- [48] a) E. Abraham, S. G. Davies, N. L. Millican, R. L. Nicholson, P. M. Roberts, A. D. Smith, *Org. Biomol. Chem.*, **2008**, *6*, 1655-1664; b) E. Abraham, E. A. Brock, J. I. Candela-Lena, S. G. Davies, M. Georgiou, R. L. Nicholson, J. H. Perkins, P. M. Roberts, A. J. Russell, E. M. Sánchez-Fernández, P. M. Scott, A. D. Smith, J. E. Thomson, *Org. Biomol. Chem.*, **2008**, *6*, 1665-1673; c) S. G. Davies, J. A. Lee, P. M. Roberts, J. E. Thomson, C. J. West, *Tetrahedron Lett.*, **2011**, *52*, 6477-6480; d) E. A. Brock, S. G. Davies, J. A. Lee, P. M. Roberts, J. E. Thomson, *Org. Biomol. Chem.*, **2013**, *11*, 3187-3202; e) S. G. Davies, A. L. A.

Figuccia, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *J. Org. Chem.*, **2016**, *81*, 6481-6495; f) K. Csatayová, S. G. Davies, A. M. Fletcher, T. R. Fowler, M. S. Kennedy, P. M. Roberts, J. E. Thomson, *J. Org. Chem.*, **2017**, *82*, 12447-12466; g) S. G. Davies, A. M. Fletcher, A. R. Hanby, P. M. Roberts, J. E. Thomson, *Tetrahedron: Asymmetry*, **2017**, *28*, 1756-1764.

[49] a) P. Dziedzic, J. Vesely, A. Córdova, *Tetrahedron Lett.*, **2008**, *49*, 6631-6634; b) P. Dziedzic, P. Schyman, M. Kullberg, A. Córdova, *Chem. Eur. J.*, **2009**, *15*, 4044-4048; c) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.*, **1998**, *120*, 431-432; d) B. Sun, R. Pluta, N. Kumagai, M. Shibasaki, *Org. Lett.*, **2018**, *20*, 526-529; e) F. Gassa, A. Contini, G. Fontana, S. Pellegrino, M. L. Gelmi, *J. Org. Chem.*, **2010**, *75*, 7099-7106.

[50] a) A. L. J. Beckwith, V. W. Bowry, K. U. Ingold, *J. Am. Chem. Soc.*, **1992**, *114*, 4983-4992; b) V. W. Bowry, K. U. Ingold, *J. Am. Chem. Soc.*, **1992**, *114*, 4992-4996.

[51] R. Braslau, L. C. Burrill II, M. Siano, N. Naik, R. K. Howden, L. K. Mahal, *Macromolecules*, **1997**, *30*, 6445-6450; b) R. Braslau, N. Naik, H. Zipse, *J. Am. Chem. Soc.* **2000**, *122*, 8421-8434.

[52] a) E. Dinca, P. Hartmann, J. Smrček, I. Dix, P. G. Jones, U. Jahn, *Eur. J. Org. Chem.*, **2012**, 4461-4482; b) E. Jahn, J. Smrček, R. Pohl, I. Císařová, P. G. Jones, U. Jahn, *Eur. J. Org. Chem.*, **2015**, 7785-7798.

[53] a) M. Pouliot, P. Renaud, K. Schenk, A. Studer, T. Vogler, *Angew. Chem. Int. Ed.*, **2009**, *48*, 6037-6040; b) Y. Li, M. Pouliot, T. Vogler, P. Renaud, A. Studer, *Org. Lett.*, **2012**, *14*, 4474-4477.

[54] M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.*, **2007**, *129*, 4124-4125.

[55] a) S. Bertelsen, M. Nielsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.*, **2007**, *46*, 7356-7359; b) N.-N. Bui, X.-H. Ho, S.-i. Mho, H.-Y. Jang, *Eur. J. Org. Chem.*, **2009**, 5309-5312; c) J. F. Van Humbeck, S. P. Simonovich, R. R. Knowles, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2010**, *132*, 10012-10014; d) S. P. Simonovich, J. F. Van Humbeck, D. W. C. MacMillan, *Chem. Sci.*, **2012**, *3*, 58-61.

[56] a) P. J. Mabe, A. Zakarian, *Org. Lett.*, **2014**, *16*, 516-519; b) A. Gomez-Palomino, M. Pellicena, J. M. Romo, R. Sola, P. Romea, F. Urpi, M. Font-Bardia, *Chem. -Eur. J.*, **2014**, *20*, 10153-10159.

[57] a) J. W. Daly, H. M. Garraffo, T. F. Spende, in *Alkaloids: Chemical and Biological Perspectives* (Ed.: S. W. Pelletier), Vol. 13, Pergamon; New York: **1999**, Chapter 1; b) D. O'Hagan, *Nat. Prod. Rep.*, **2000**, *17*, 435-446; c) S. Leclercq, J. C. Braekman, D. Daloze, J.

- M. Pasteels, *Prog. Chem. Org. Nat. Prod.*, **2000**, 79, 115-229; d) J. W. Daly, T. F. Spande, H. M. Garraffo, *J. Nat. Prod.*, **2005**, 68, 1556-1575.
- [58] a) S. Murakami, T. Takemoto, Z. Shimizu, *J. Pharm. Soc. Jpn.*, **1953**, 73, 1026-1028; b) M. G. Moloney, *Nat. Prod. Rep.*, **1999**, 16, 485-498.
- [59] S. Takeuchi, M. Ishibashi, J. Kobayashi, *J. Org. Chem.*, **1994**, 59, 3712-3713.
- [60] C. L. J. Wang, J. C. Calabrese, *J. Org. Chem.*, **1991**, 56, 4341-4343.
- [61] Y. Tsuda, S. Hosoi, N. Katagiri, C. Kaneko, T. Sano, *Chem. Pharm. Bull.*, **1993**, 41, 2087-2095.
- [62] K. M. Witherup, R. W. Ransom, A. C. Graham, A. M. Bernard, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenberger, S. L. Varga, *J. Am. Chem. Soc.* **1995**, 117, 6682-6685.
- [63] R. G. Powell, D. Weisleder, C. R. Smith Jr., *J. Pharm. Sci.*, **1972**, 61, 1227-1230.
- [64] a) H.-S. Chung, P.-M. Hon, G. Lin, P. P.-H. But, H. Dong, *Planta Med.*, **2003**, 69, 914-920; b) P. H. H. Leung, L. Zhang, Z. Zuo, G. Lin, *Planta Med.*, **2006**, 72, 211-216.
- [65] a) X. Li, J. Li, *Mini-Rev. Med. Chem.*, **2010**, 10, 794-805; b) J. K. Whitesell, *Chem. Rev.*, **1989**, 89, 1581-1590; c) J. A. Sweet, J. M. Cavallari, W. A. Price, J. W. Ziller, D. V. McGrath, *Tetrahedron: Asymmetry*, **1997**, 8, 207-211; d) F. Fache, E. Schultz, M. L. Tomasino, M. Lemaire, *Chem. Rev.*, **2000**, 100, 2159-2232; e) M. Nyerges, D. Bendell, A. Arany, D. E. Hibbs, S. J. Coles, M. D. Hursthouse, P. W. Groundwater, O. Meth-Cohn, *Synlett*, **2003**, 947-950; f) B. H. Kim, H. B. Lee, J. K. Hwang, Y. G. Kim, *Tetrahedron: Asymmetry*, **2005**, 16, 1215-1220.
- [66] G. Sunilkumar, N. Dendukuri, N. P. Argade, K. N. Ganesh, *Synthesis*, **2003**, 15, 2304-2306.
- [67] P. Restorp, A. Fischer, P. Somfai, *J. Am. Chem. Soc.*, **2006**, 128, 12646-12647.
- [68] a) C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.*, **2005**, 127, 1070-1071; b) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.*, **2006**, 128, 9066-9073; c) K. Komeyama, T. Morimoto, K. Takaki, *Angew. Chem. Int. Ed.*, **2006**, 45, 2938-2941; d) X. Han, R. A. Widenhoefer, *Angew. Chem. Int. Ed.*, **2006**, 45, 1747-1749; e) F. E. Michael, B. M. Cochran, *J. Am. Chem. Soc.*, **2006**, 128, 4246-4247; f) C. F. Bender, R. A. Widenhoefer, *Org. Lett.*, **2006**, 8, 5303-5305; g) M. Shi, L.-P. Liu, J. Tang, *Org. Lett.*, **2006**, 8, 4043-4046; h) J. Zhang, C.-G. Yang, C. He, *J. Am. Chem. Soc.*, **2006**, 128, 1798-1799; i) R. L. LaLonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.*, **2007**, 129, 2452-2453.

- [69] a) M. Mori, N. Saito, D. Tanaka, M. Takimoto, Y. Sato, *J. Am. Chem. Soc.*, **2003**, *125*, 5606-5607; b) N. Hayashi, I. Shibata, A. Baba, *Org. Lett.*, **2004**, *6*, 4981-4983; c) T. Shibata, N. Toshida, M. Yamasaki, S. Maekawaa, K. Takagi, *Tetrahedron*, **2005**, *61*, 9974-9979; d) L. Zhao, X. Lu, J. Xu, *J. Org. Chem.*, **2005**, *70*, 4059-4063.
- [70] S. Fustero, D. Jiménez, M. Sánchez-Roselló, C. del Pozo, *J. Am. Chem. Soc.*, **2007**, *129*, 6700-6701.
- [71] V. Sriramurthy, G. A. Barcan, O. Kwon, *J. Am. Chem. Soc.*, **2007**, *129*, 12928-12929.
- [72] a) Y. Tsuji, Y. Yokoyama, K.-T. Huh, Y. Watanabe, *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 3456-3458; b) K. Manna, W. C. Everett, G. Schoendorff, A. Ellern, T. L. Windus, A. D. Sadow, *J. Am. Chem. Soc.*, **2013**, *135*, 7235-7250; c) X. Zhou, B. Wei, X.-Li Sun, Y. Tang, Z. Xie, *Chem. Commun.*, **2015**, *51*, 5751-5753.
- [73] M. Satoshi, K. Daisuke, O. Yoji, K. Mitsuo, *Org. Lett.*, **2002**, *4*, 2097-2099.
- [74] F. Douelle, A. S. Capes, M. F. Greaney, *Org. Lett.*, **2007**, *9*, 1931-1934.
- [75] Y. Terada, M. Arisawa, A. Nishida, *Angew. Chem. Int. Ed.*, **2004**, *43*, 4063-4067.
- [76] J. M. Schomaker, S. Bhattacharjee, J. Yan, B. Borhan, *J. Am. Chem. Soc.*, **2007**, *129*, 1996-2003.
- [77] J. U. Rhee, M. J. Krische, *J. Am. Chem. Soc.*, **2006**, *128*, 10674-10675.
- [78] a) C. A. Carson, M. A. Kerr, *J. Org. Chem.*, **2005**, *70*, 8242-8244; b) Y.-B. Kang, Y. Tang, X.-L. Sun, *Org. Biomol. Chem.*, **2006**, *4*, 299-301.
- [79] a) H.-P. Kaiser; J. M. Muchowski, *J. Org. Chem.*, **1984**, *49*, 4203-4209; b) B. S. Gourlay, J. H. Ryan, J. A. Smith, *Beilstein J. Org. Chem.*, **2008**, *4*, No. 3.
- [80] a) J. E. Ney, J. P. Wolfe, *Angew. Chem. Int. Ed.*, **2004**, *43*, 3605-3608; b) M. B. Bertrand, J. P. Wolfe, *Tetrahedron*, **2005**, *61*, 6447-6459; c) M. B. Bertrand, J. D. Neukom, J. P. Wolfe, *J. Org. Chem.*, **2008**, *73*, 8851-8860.
- [81] a) D. R. Williams, M. H. Osterhout, J. M. McGill, *Tetrahedron Lett.*, **1989**, *30*, 1327-1330; b) S. Takano, M. Moriya, Y. Iwabuchi, K. Ogasawara, *Tetrahedron Lett.*, **1989**, *30*, 3805-3806; c) S. G. Davies, R. L. Nicholson, P. D. Price, P. M. Roberts, A. D. Smith, *Synlett*, **2004**, *5*, 901-903; d) S. G. Davies, R. L. Nicholson, P. D. Price, P. M. Roberts, A. J. Russell, E. D. Savory, A. D. Smith, J. E. Thomson, *Tetrahedron: Asymmetry*, **2009**, *20*, 758-772; e) A. Feula, L. Male, J. S. Fossey, *Org. Lett.*, **2010**, *12*, 5044-5047; f) M. A. Hama Salih, L. Male, N. Spencer, J. S. Fossey, *Org. Chem. Front.*, **2015**, *2*, 1445-1449.

- [82] E. P. Pecanha, H. Verli, C. R. Rodrigues, E. J. Barreiro, C. A. M. Fraga, *Tetrahedron Lett.*, **2002**, 43 1607-1611.
- [83] a) C. Najera, J. M. Sansano, *Angew. Chem. Int. Ed.*, **2005**, 44, 6272-6276; b) J. Adrio, J. C. Carretero, *Chem. Commun.*, **2014**, 50, 12434-12446; c) J. Otero-Fraga, M. Montesinos-Magraner, A. Mendoza, *Synthesis*, **2017**, 49, 802-809.
- [84] F. Kafka, M. Holan, D. Hidasová, R. Pohl, I. Čísařová, B. Klepetářová, U. Jahn, *Angew. Chem., Int. Ed.*, **2014**, 53, 9944-9948.
- [85] a) A. F. Parsons, *Tetrahedron*, **1996**, 52, 4149-4174; b) C. I. Stathakis, E. G. Yioti, J. K. Gallos, *Eur. J. Org. Chem.*, **2012**, 4661-4673; c) M. S. Majik, V. K. Mandrekar, *Curr. Org. Chem.*, **2016**, 20, 939-951; d) H. W. Shi, J. L. Li, Y. M. Liu, Z. L. Du, Z. Y. Huang, N. Zhao, N. Li, J. Yang, *Tetrahedron*, **2016**, 72, 5502-5506; e) J. Suzuki, N. Miyano, S. Yashiro, T. Umezawa, F. Matsuda, *Org. Biomol. Chem.*, **2017**, 15, 6557-6560; f) Z. Tian, F. Menard, *J. Org. Chem.*, **2018**, 83, 6162-6170; g) H. Lei, S. Xin, Y. Qiu, X. Zhang, *Chem. Commun.*, **2018**, 54, 727-730.
- [86] W. Oppolzer, K. Thirring, *J. Am. Chem. Soc.*, **1982**, 104, 4978-4979.
- [87] H.-J. Yu, C. Shao, Z. Cui., C.-G. Feng, G.-Q. Lin, *Chem. -Eur. J.*, **2012**, 18, 13274-13278.
- [88] M. Zhang, K. Watanabe, M. Tsukamoto, R. Shibuya, H. Murimoto, T. Ohshima, *Chem. -Eur. J.*, **2015**, 21, 3937-3941.
- [89] a) J. E. Baldwin, C-S. Li, *J. Chem. Soc. Chem. Commun.*, **1987**, 166-168; b) J. E. Baldwin, M. G. Moloney, A. F. Parsons, *Tetrahedron*, **1990**, 46, 7263-7282; c) S. Hanessian, S. Ninkovic, *J. Org. Chem.*, **1996**, 61, 5418-5424; d) O. Miyata, Y. Ozawa, I. Ninomiya, T. Naito, *Synlett*, **1997**, 275-276.
- [90] F. Kafka, in *Dissertation thesis*, UCT Prague, **2015**.
- [91] Y. Ma, A. C. Hoepker, L. Gupta, M. F. Faggin, D. B. Collum, *J. Am. Chem. Soc.*, **2010**, 132, 15610-15623.
- [92] M. Janák, in *Master thesis*, UCT Prague, **2012**.
- [93] S. G. Davies, I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1129-1139.
- [94] W. Lung-min, H. Fischer, *Helv. Chim. Acta*, **1983**, 66, 138-147.
- [95] D. P. Curran, N. A. Porter, B. Giese, in: *Stereochemistry of Radical Reactions*, VCH, Weinheim, **1996**, pp. 147-177.
- [96] S. Liang, Z. Xu, T. Ye, *Chem. Commun.*, **2010**, 46, 153-155.
- [97] A. Salmon, B. Carboni, *J. Organomet. Chem.*, **1998**, 567, 31-37.

- [98] a) I. L. Miranda, Í. K. B. Lopes, M. A. N. Diaz, G. Diaz, *Molecules*, **2016**, *21*, 1176;
 b) M. Lingamurthy, G. R. Nalliboina, M. V. Rao, B. V. Rao, B. S. Reddy, H. M. S. Kumar, *Tetrahedron*, **2017**, *73*, 1473-1481.
- [99] D. Polet, A. Alexakis, K. Tissot-Croset, C. Corminboeuf, K. Ditrich, *Chem. -Eur. J.*, **2006**, *12*, 3596-3609.
- [100] S. G. Davies, O. Ichihara, I. Lenoir, I. A. S. Walters, *J. Chem. Soc., Perkin Trans. I*, **1994**, 1411-1415.
- [101] a) F. E. Ziegler, A. K. Petersen, *J. Org. Chem.*, **1994**, *59*, 2707-2714; b) C. E. McDonald, R. W. Dugger, *Tetrahedron Lett.*, **1988**, *29*, 2413-2415; c) G. Stork, R. Mook Jr., S. A. Biller, S. D. Rychnovsky, *J. Am. Chem. Soc.*, **1983**, *105*, 3741-3742; d) G. E. Keck, S. F. McHardy, J. A. Murry, *J. Am. Chem. Soc.*, **1995**, *117*, 7289-7290.
- [102] M. E. Bunnage, S. G. Davies, P. M. Roberts, A. D. Smith, J. M. Withey, *Org. Biomol. Chem.*, **2004**, *2*, 2763-2776.
- [103] D. Just, D. Hernandez-Guerra, S. Kritsch, R. Pohl, I. Císařová, P. G. Jones, R. Mackman, G. Bahador, U. Jahn, *Eur. J. Org. Chem.*, **2018**, *37*, 5213-5221.
- [104] L. Kiss, I. M. Mándity, F. Fülöp, *Amino Acids*, **2017**, *49*, 1441-1455.
- [105] M. Arisawa, E. Takezawa, A. Nishida, M. Mori, M. Nakagawa, *Synlett*, **1997**, *10*, 1179-1180.
- [106] N. Ahmed, *Studies in Natural Products Chemistry*, **2016**, *51*, 383-434.
- [107] B. M. Trost, R. C. Bunt, R. C. Lemoine, T. L. Calkins, *J. Am. Chem. Soc.*, **2000**, *122*, 5968-5976.
- [108] T. Vogler, A. Studer, *Synthesis*, **2006**, 4257-4265.
- [109] T. Higashi, Y. Isobe, H. Ouchi, H. Suzuki, Y. Okazaki, T. Asakawa, T. Furuta, T. Wakimoto, T. Kan, *Org. Lett.*, **2011**, *13*, 1089-1091.
- [110] M. Shibuya, M. Tomizawa, Y. Iwabuchi, *J. Org. Chem.*, **2008**, *73*, 4750-4752.
- [111] G. E. Keck, M. D. McLaws, T. T. Wager, *Tetrahedron*, **2000**, *56*, 9875-9883.
- [112] E. Abraham, J. W. B. Cooke, S. G. Davies, A. Naylor, R. L. Nicholson, P. D. Price, A. D. Smith, *Tetrahedron*, **2007**, *63*, 5855-5872.
- [113] J. Li, Y. Sha, *Molecules*, **2008**, *13*, 1111-1119.
- [114] S. G. Davies, N. M. Garrido, D. Kruchinin, O. Ichihara, L. J. Kotchie, P. D. Price, A. J. Price Mortimer, A. J. Russell, A. D. Smith, *Tetrahedron: Asymmetry*, **2006**, *17*, 1793-1811.
- [115] S. G. Davies, D. J. Dixon, *J. Chem. Soc., Perkin Trans. I*, **1998**, 2635-2643.

- [116] H. Nemoto, W. Zhong, T. Kawamura, M. Kamiya, Y. Nakano, K. Sakamoto, *Synlett*, **2007**, 2343-2346.
- [117] S. G. Davies, A. M. Fletcher, P. M. Roberts, A. D. Smith, *Tetrahedron*, **2009**, *65*, 10192-10213.
- [118] S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.*, **2005**, *127*, 3774-3789.
- [119] K. Oe, Y. Ohfuné, T. Shinada, *Org. Lett.*, **2014**, *16*, 2550-2553.
- [120] T. D. W. Claridge, S. G. Davies, J. A. Lee, R. L. Nicholson, P. M. Roberts, A. J. Russell, A. D. Smith, S. M. Toms, *Org. Lett.*, **2008**, *10*, 5437-5440.
- [121] R. M. Archer, M. Hutchby, C. L. Winn, J. S. Fossey, S. D. Bull, *Tetrahedron*, **2015**, *71*, 8838-8847.
- [122] H. H. Wasserman, A. K. Petersen, *J. Org. Chem.*, **1997**, *62*, 8972-8973.
- [123] Y. Liu, R. Melgar-Fernández, E. Juaristi, *J. Org. Chem.*, **2007**, *72*, 1522-1525.
- [124] M. R. Adams, C.-H. Tien, R. McDonald, A. W. H. Speed, *Angew. Chem. Int. Ed.*, **2017**, *56*, 16660-16663.
- [125] J. L. Pawlak, G. A. Berchtold, *J. Org. Chem.*, **1988**, *53*, 4063-4069.
- [126] A. R. Jagdale, S. W. Youn, *Eur. J. Org. Chem.*, **2011**, 3904-3910.
- [127] M. E. Bunnage, S. G. Davies, C. J. Goodwin, O. Ichihara, *Tetrahedron*, **1994**, *50*, 3975-3986.
- [128] H. H. Wasserman, A. K. Petersen, M. Xia, *Tetrahedron*, **2003**, *59*, 6771-6784.
- [129] R. K. Mishra, C. M. Coates, K. D. Revell, E. Turos, *Org. Lett.*, **2007**, *9*, 575-578.
- [130] M. Liu, X.-W. Sun, M.-H. Xu, G.-Q. Lin, *Chem. Eur. J.*, **2009**, *15*, 10217-10224.
- [131] S. G. Davies, A. M. Fletcher, C. J. Greenaway, M. S. Kennedy, C. Mayer, P. M. Roberts, J. E. Thomson, *Tetrahedron*, **2018**, *74*, 5049-5061.
- [132] C. Gnam, G. Franck, N. Miller, T. Stork, K. Broedner, G. Helmchen, *Synthesis*, **2008**, *20*, 3331-3350.
- [133] G. M. Sheldrick, *Acta Cryst.*, **2015**, *A71*, 3-8.
- [134] G. M. Sheldrick, *Acta Cryst.*, **2015**, *C71*, 3-8.