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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2011

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Teichert, J. F. (2011). Catalytic asymmetric synthesis of heterocycles Groningen: University of Groningen

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Catalytic Asymmetric Synthesis of Heterocycles

Johannes Florian Teichert

The work described in this thesis was carried out at the Stratingh Institute for Chemistry, Groningen, The Netherlands.

The work was financially supported by the Dutch National Research School Combination Catalysis Controlled by Chemical Design (NRSC-Catalysis).

Printed by: Ipskamp Drukkers, Enschede, The Netherlands

Cover design: Photograph taken by Nopporn Ruangsupapichat. Artwork by Pieter Bos.

RIJKSUNIVERSITEIT GRONINGEN

Catalytic Asymmetric Synthesis of Heterocycles

Proefschrift

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. E. Sterken,
in het openbaar te verdedigen op
vrijdag 25 maart 2011
om 16.15 uur

door

Johannes Florian Teichert

geboren op 7 juli 1980
te Hamburg, Duitsland

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Prof. dr. J. G. Roelfes

ISBN: 978-90-367-4836-0 (print)
978-90-367-4835-3 (digital)

“Scientists are a friendly, atheistic, hard-working, beer-drinking lot whose minds are preoccupied with sex, chess and baseball when they are not preoccupied with science.”

Yann Martel, *Life of Pi*

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Chapter 1

Asymmetric Synthesis of Chiral Heterocycles

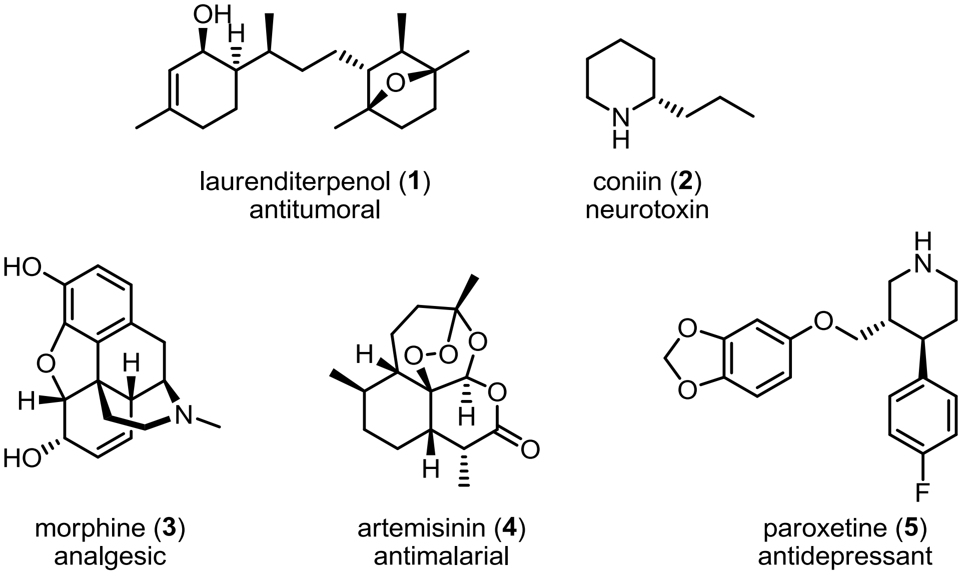
A selection of enantioselective synthetic approaches to chiral heterocycles is presented. The focus lies on catalytic asymmetric transformations with transition metal catalysts. Chiral phosphoramidite ligands serve as the vantage point as they have been applied to a wide variety of asymmetric catalytic reactions.

Parts of this chapter have been published:

Teichert, J.F.; Feringa, B.L. *Angew. Chem. Int. Ed*. **2010**, *49*, 2486 - 2528.

1. Chiral Heterocycles

Many naturally occuring compounds with biological activity posess chiral heterocycles as structural elements. Some illustrative examples are displayed in Figure 1. Laurenditerpenol (**1**), containing a bicyclic tetrahydrofuran moiety, was found to be a small molecule suppressor of tumor growth in human breast tumor cells.[1,2] The substituted chiral piperidine alkaloid[3] coniin (**2**) is a potent neurotoxin which acts by blocking the nicotinic receptor in the post-synaptic membrane.[4] Complex opoid alkaloid morphine (**3**) is used as a potent painkiller.[4] It posesses both a nitrogen- and an oxygen-containing heterocycle. Artemisinin (**4**) bears a rare example of a naturally occuring peroxide, which is key to its anti-malarial activity, even though the exact mode of action is still subject of discussion.[5-9] Finally, synthetic chiral piperidine paroxetine (**5**) is a selective serotonine reuptake inhibitor antidepressant (SSRI), and one of the 100 best selling drugs worldwide.[10,11]


laurenditerpenol (**1**)
antitumoral

coniin (**2**)
neurotoxin

morphine (**3**)
analgesic

artemisinin (**4**)
antimalarial

paroxetine (**5**)
antidepressant

Figure 1 Some biologically active compounds bearing chiral heterocycles

The broad range of biological activites of chiral heterocyclic compounds makes them valuable and interesting targets for organic synthesis, both from the industrial as well as academic perspective. On the one hand, large-scale and cost-effective synthesis is of major interest, whereas on the other hand, method-development or structural confirmation might be the main focus of researchers. This holds true not only for naturally occuring products, but also for synthetic analogues thereof or *de novo* designed biologically active compounds.

2. Synthetic approaches to chiral heterocycles

When the synthesis of a chiral molecule, for example a chiral heterocyclic structure, is envisaged, a variety of approaches can be followed to introduce the stereogenic centers.[12-14] The most common include racemic synthesis followed by separation of enantiomers, synthesis based on the chiral pool or enantioselective synthesis.[15-18] Each of these approaches has its advantages and there is no general gold-standard. Rather, the strategic use and combination of these methods, before the background of cost-effectiveness and synthetic difficulty, seems to be the ideal approach to a particular target.[19-21] In the following, the focus shall be on of the major approaches to enantioselective synthesis, namely asymmetric catalysis.

3. Asymmetric transition metal-catalyzed reactions

The field of asymmetric transition metal-catalysis is wide,[15] and has been recognized by the 2001 chemistry Nobel prize,[22-24] which awarded the development of "*chirally catalyzed*" reactions.[25] The notion of introducing stereogenic centers using metal-catalysts bearing chiral ligands has some advantages: Ideally, a very small amount of chiral catalyst is sufficient for the synthesis of a large quantitiy of a chiral product. In the case where both enantiomers of the chiral catalyst of interest are available, both enantiomers of the desired product can be synthesized selectively. Catalyst optimization by ligand screening opens up the possibility to quickly select, optimize and improve the asymmetric transformation.

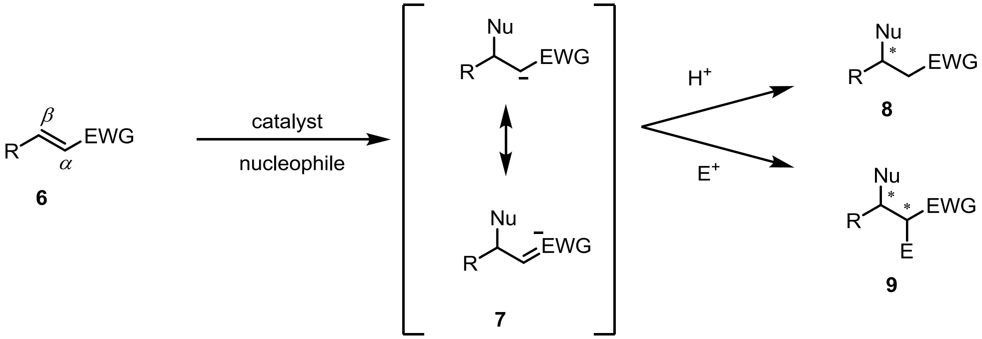
Over the years, some so-called "privileged ligands" have emerged, which can be successfully applied to many different asymmetric transformations.[26] In the following section, asymmetric catalysis with chiral phosphoramidite ligands will be discussed. On the one hand, this showcases the versatility of this class of ligands, which can partly be attributed to their modular setup and the resulting facile diversification. On the other hand, as these types of ligands have been applied to a wide variety of reactions,[27-32] they serve as a good example and overview for the wide applicability and synthetic usefulness of asymmetric transition metal catalysis in general. In the following section, some applications of phosphoramidites in the synthesis of key chiral building blocks for the synthesis of chiral heterocycles will be discussed.

4. Synthesis of chiral heterocycles with phosphoramidite ligands

In this section, a selection of catalytic asymmetric transformations is presented, which are based on phosphoramidite-transition metal complexes as chiral catalysts for the synthesis of chiral heterocycles. This section is subdivided by reaction mechanisms; starting off with the Cu-catalyzed conjugate addition reaction (see section 4.1). This transformation employs organometallic reagents as carbon nucleophiles, therefore it mostly makes use of heterocyclic α,β-unsaturated carbonyl compounds as substrates, when chiral heterocycles are envisaged. A different approach can be taken when the allylic substitution reaction is chosen (see section 4.2): especially the Ir-catalyzed allylic substitution, which accepts a wide variety of heteroatom-based nucleophiles is ideally suited for the construction of chiral heterocycles. Other than the transition metal-catalyzed conjugate addition, which is mainly restricted to the use of carbon nucleophiles, the heteroatom can be introduced directly through this methodology and has led to many examples of syntheses of chiral heterocylces (*vide infra*). Finally, a selection of asymmetric catalytic approaches based on other mechanisms is discussed (section 4.3).

4.1 Cu-catalyzed conjugate addition reactions

The asymmetric conjugate addition reaction ranks among the most studied synthetic transformation in the last decades.[33-37] Especially the development of an effective enantioselective copper-catalyzed conjugate addition of organometallic reagents has for a long time been a major challenge in synthetic chemistry.[27,38-43] In this transformation, the nucleophile is transferred to the β-position of an α,β-unsaturated system **6** (*e.g.* an enone) to yield a stabilized carbanion **7** (Scheme 1). This intermediate can subsequently be protonated, yielding β-chiral product **8** or it can be quenched by addition of another electrophile to provide chiral compounds **9** with vicinal stereocenters.

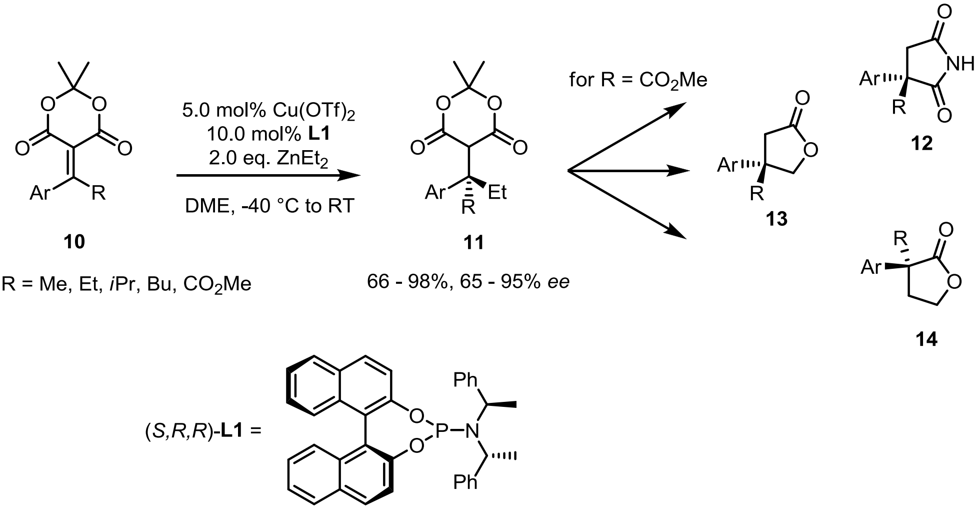


Scheme 1 Conjugate addition

A well-known problem that had to be overcome was the high affinity of organometallic reagents towards the 1,2-addition directly to the electron withdrawing group. This catalytic asymmetric conjugate addition methodology has successfully been developed for a wide variety of substrates (*e.g.* enones, α,β-unsaturated esters, nitroalkenes, etc.) and organometallic nucleophiles (Grignard reagents, organozinc, and -aluminium compounds) and furthermore has been applied to numerous natural product syntheses.[33-40,44] Two representative examples are discussed in the following section.

Asymmetric synthesis of chiral heterocycles bearing quaternary centers

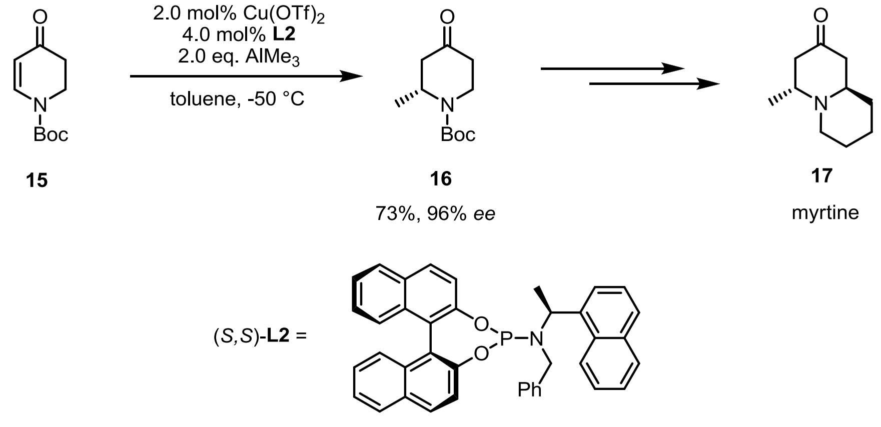
The copper-catalyzed conjugate addition of diethylzinc to enones was applied to derivatives of Meldrum's acid, yielding derivatives of β-substituted carboxylic acids.[45] This transformation was extended to arylalkylidene derivatives of Meldrum's acid **10**, carrying two substituents at the olefin moiety (Scheme 2).[46] With phosphoramidite ligand **L1** the addition products **11** were obtained in excellent yields and *ee* values up to 95%. This reaction furnishes an attractive route for the synthesis of chiral quaternary carbon atoms[47-53] and has recently been applied to the asymmetric synthesis of chiral succinimides **12** and chiral γ-butyrolactones **13** and **14**.[54]


5.0 mol% Cu(OTf)$_2$
10.0 mol% **L1**
2.0 eq. ZnEt$_2$
DME, -40 °C to RT
Ar
R
Et
O
10
11
R = Me, Et, *i*Pr, Bu, CO$_2$Me
66 - 98%, 65 - 95% *ee*
for R = CO$_2$Me
NH
12
13
14
(*S,R,R*)-**L1** =
Ph
P
N

Scheme 2 Conjugate addition to derivatives of Meldrum's acid

Asymmetric synthesis of myrtine

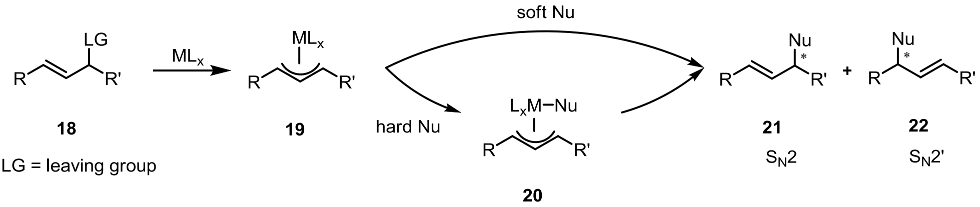
The copper-catalyzed asymmetric conjugate addition reaction with trialkylaluminum reagents to enones[28,55-62] has been applied in the first catalytic asymmetric synthesis of the alkaloid myrtine (**17**),[63] which has been isolated from heather plants[64] (Scheme 3). For the key step, introducing the first stereogenic center, a copper-catalyzed addition of trimethylaluminum to **15** with phosphoramidite ligand **L2** was employed to achieve high yields and stereoselectivites. The conjugate addition product **16** was formed with excellent enantioselectivity.



Scheme 3 Catalytic enantioselective synthesis of myrtine

4.2 Asymmetric allylic substitution reactions

The allylic substitution, especially the methodology based upon palladium catalysis, is a reaction of major significance for the generation of chiral, multifunctional building blocks and ranks among the key transformations for organic synthesis.[65-71] One of the typical features of the palladium-catalyzed reaction is that 'soft' nucleophiles such as malonates are transferred directly to the allyl-complex **19**, whereas 'hard' nucleophiles like organozinc or Grignard reagents are proposed as being transmetalated to palladium to give allyl-palladium complex **20** prior to C-C bond formation (Scheme 4).[70,71] Thus a different outcome for the products **21**/**22** of the substitution reaction occurs for the different types of nucleophiles. Contrary to the conjugate addition reactions (*vide supra*), the phosphoramidite to metal ratio required for the best results in terms of enantioselectivity is 1:1, not depending on which metal is employed as catalyst (Cu, Ir or Pd). It should be noted that the leaving group in the allylic substitutions is different for the various catalytic systems. Whereas the Cu/phosphoramidite catalysts perform best with allylic halides (Cl or Br),[37,72] the related Cu/ferrocenyl-based bisphosphine catalysts[35] strictly require bromides as leaving groups for best performance. Asymmetric allylic substitutions with chiral Cu/NHC complexes employ allylic phosphonates as leaving groups[73]; Pd-catalyzed allylic substitutions generally use allylic acetates, carbonates or benzoates[65,66,68-71] and the Ir/phosphoramidite catalysts give the best results with allylic carbonates.[74] This sensitivity with regard to the leaving group in allylic substitution reactions could stem from the different structural requirements of the catalysts as well as from the different acidities of the various leaving groups.



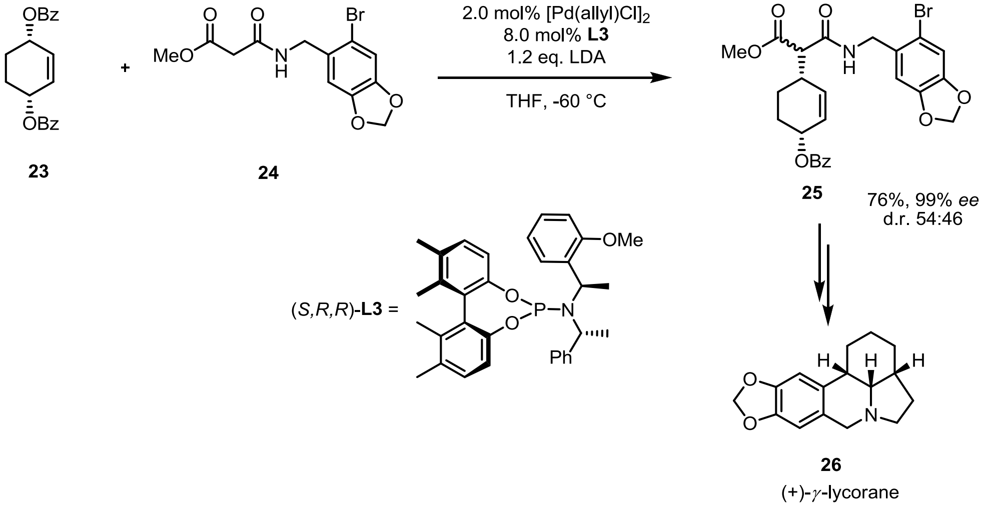
Scheme 4 Allylic substitution

Pd-catalyzed allylic substitutions

The Tsuji-Trost palladium-catalyzed allylic substitution is a well-established transformation to yield important, multifunctional chiral building blocks for organic synthesis and has been the key step in numerous total syntheses.[65,66,68-71] In recent years, phosphoramidite ligands have been applied to these palladium-catalyzed reactions.

Asymmetric total synthesis of γ-lycorane

The highest enantioselectivities so far with the Pd/phosphoramidite catalytic system in allylic substitutions were obtained in the desymmetrization reactions of dibenzoylcyclohexene **23** (Scheme 5).[75] In order to synthesize the naturally occuring alkaloid γ-lycorane **26**, malonate derivative **24** was employed as carbon nucleophile. With phosphoramidite ligand **L3**, excellent *ee* values up to 99% for cyclohexene **25**, a key precursor to **26**, were reached. Unfortunately, the stereogenic center of the malonate moiety could not be installed with high diasteroselectivity due to epimerization.

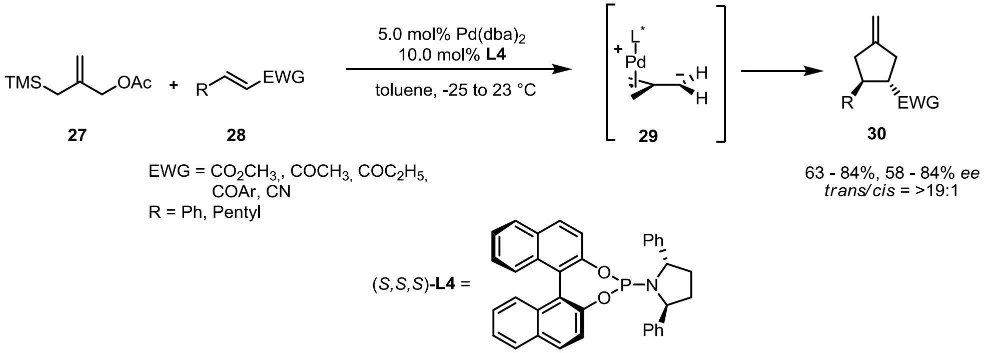


Scheme 5 Desymmetrization based on Pd-catalyzed allylic substitution

Pd-catalyzed [3+2] trimethylenemethane cycloadditons

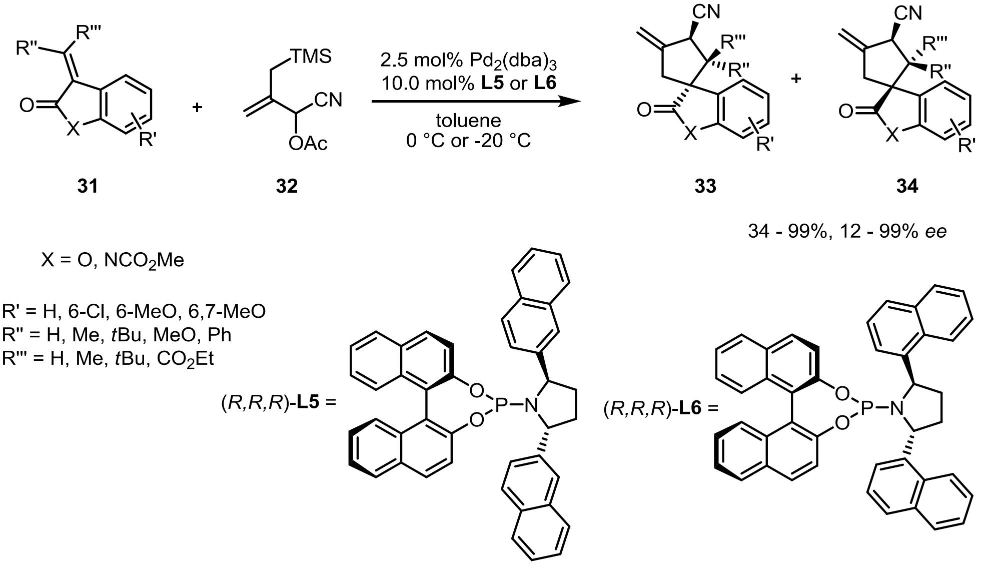
The closely related palladium-catalyzed [3+2] cycloaddition of a trimethylenemethane unit is a marvellous and extremely useful transformation to provide 5-membered cyclic compounds and the development of an asymmetric variant has long been a highly warranted goal.[76]

Recently, an asymmetric Pd-catalyzed [3+2] trimethylenemethane cycloaddition of 3-acetoxy-2-trimethylsilyl-methylpropene **27** to various Michael acceptors **28** in the presence of phosphoramidite ligands was disclosed.[77] The application of phosphoramidites to this particular transformation marks a major breakthrough, as catalysts based on these chiral ligands achieve for the first time high enantioselectivities. The reaction mechanism is noteworthy, as it combines transition-metal chemistry, through metal-allyl species, with the 1,3-dipolar cycloaddtions. The mechanism can be exemplified with the transformation depicted in Scheme 6. Substituted allyl acetate **27** can form a Pd-allyl complex through oxidative addition, the leaving group (in this case the acetate) is reacting further, and attacks the TMS group. The Si-C bond is then cleaved, leaving zwitterionic complex **29** behind. This carbanion, together with the positively charged Pd-allyl moiety, now forms the 1,3-dipolar partner for the subsequent cycloaddition with an olefin (**28**) or another unsaturated substrate. This reaction gave important multi-functionalised, chiral cyclopentanes **30** in good overall yields and enantioselectivities (up to 84%, 84% *ee*). However, further research is needed to improve the enantioselectivities for these transformations. **L4** proved to be the preferred ligand for this transformation (Scheme 6). The choice of ligand proved to be crucial in order to create the steric constraints at the palladium catalyst required for high selectivities (compare also Chapter 2) in the outer-sphere addition[76] distal from the coordinating ligand of the intermediate **29** to the olefin. Equally good results were obtained for the reaction with aryl- and alkylidene tetralones as Michael acceptors as well as with imines.[78]



Scheme 6 Pd-catalyzed [3+2] trimethylenemethane cycloaddition

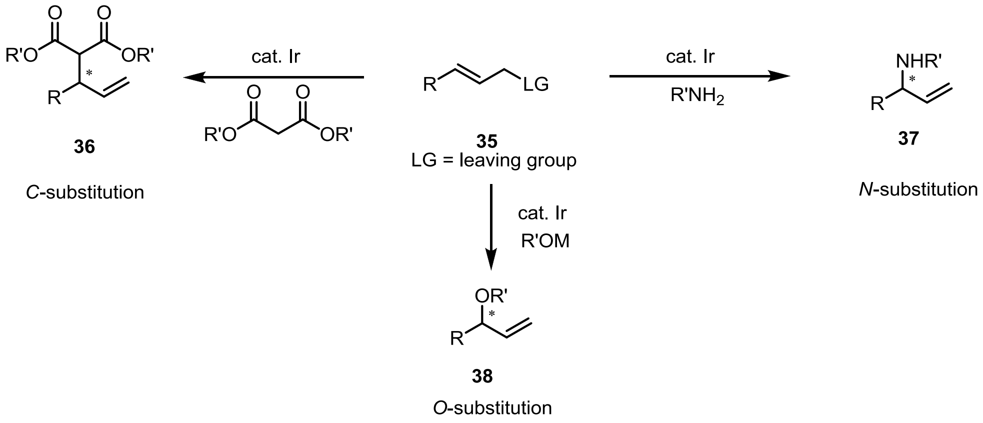
This method was successfully extended to accomplish the synthesis of important intermediates including spirocyclic oxindole cyclopentanes **33** and **34**.[79] Oxindoles **31** were reacted with allylic acetate **32** to yield the spirocyclic compounds **33** and **34** in excellent yields and stereoselectivities (up to 99% *ee*) (Scheme 7). Just as in the aforementioned example, the choice of the phosphoramidite ligand proved to be critical. With 1-naphthyl-pyrrolidine-derived **L6**, compound **33** was the favoured product (reaching diastereoselectivities **33**/**34**: >20:1), whereas with the 2-naphthyl-derived ligand **L5** diastereoisomer **34** (**33**/**34**: 1:6) was obtained. The authors claim that the origin of this selectivity lies in the different steric demands of the two ligands that results in a different approach of **31** to the intermediate palladium-complex either from the *re* or the *si* face.


R''
R'''
O
X
R'
+
TMS
CN
OAc
2.5 mol% $Pd_2(dba)_3$
10.0 mol% **L5** or **L6**
toluene
0 °C or -20 °C
CN
R'''
R''
+
31
32
33
34
34 - 99%, 12 - 99% *ee*
X = O, NCO_2Me
R' = H, 6-Cl, 6-MeO, 6,7-MeO
R'' = H, Me, *t*Bu, MeO, Ph
R''' = H, Me, *t*Bu, CO_2Et
(*R,R,R*)-**L5** =
(*R,R,R*)-**L6** =
O
P
N

Scheme 7 Pd-catalyzed [3+2] cycloaddition with oxindole substrates

Ir-catalyzed allylic substitutions

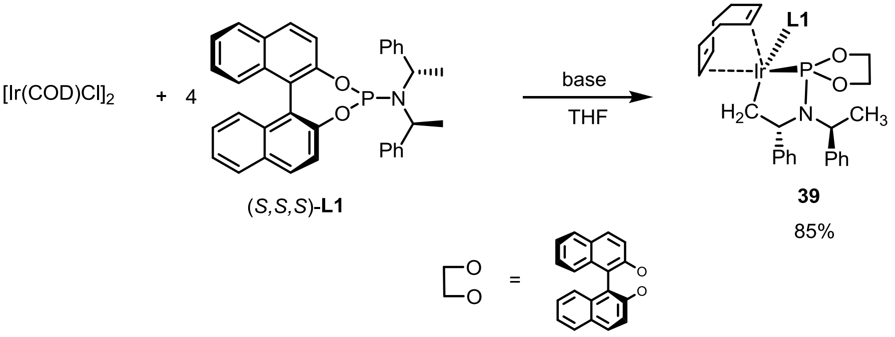
Iridium-catalyzed substitution reactions have gained much attention over the last years.[74,80-83] In fact, next to the copper-catalyzed conjugate addition, the iridium-catalyzed allylic substitution has been one of the most prominent reactions in general for which phosphoramidite ligands were applied. The first appearance of this reaction employing phosphoramidites as chiral ligands was as early as 1999, when the iridium-catalyzed allylic alkylation of allylic acetates **35** (LG = OAc) with sodium malonates to form **36** was reported (Scheme 8).[84] Although, with some exceptions, low enantioselectivities were observed at that time, the transformation set the stage for numerous important iridium-based methods developed in recent years. One important feature of the iridium-catalyzed allylic substitution is that it allows for the application of carbon-, oxygen-, sulfur- as well as nitrogen-based nucleophiles to give **36** to **38** (Scheme 8); even ammonia can be employed as nitrogen-nucleophile.[85-91]



Scheme 8 Ir-catalyzed allylic substitution

Mechanistic studies and identification of the active Ir catalyst

Elaborate studies of this transformation were carried out, focussing on the origin of regio- and stereoselectivity as well as on the influence of different phosphoramidite ligands.[92,93] However, the reaction mechanism and the active species involved remained largely unclear, and the desired optically active products were only obtained when LiCl was employed as an additive. The presence of halide ions ensured fast σ-π isomerization of the intermediate Ir-allyl complex,[94,95] and thus higher control of the stereoselectivity by the chiral phosphoramidite ligand. It was not until 2003 that the non-innocence of the amine moiety of the phosphoramidite ligand **L1** was discovered when studying the related allylic amination and etherification reaction,[96,97] thus paving the way for more sophisticated catalyst design.[98] These investigations showed that, under basic conditions, phosphoramidite ligand (*S*,*S*,*S*)-**L1** forms iridacycle **39** from the iridium(I) precursor via a C-H activation of a methyl group in the amine moiety of the phosphoramidite (Scheme 9). Remarkable is the fact that only the (*S,S,S*)-**L1** diastereoisomer undergoes this activation and can subsequently serve as a good catalyst for the iridium-catalyzed allylic substitution reaction. This is in contrast to the conjugate addition reactions (*vide supra*), where the (*S,R,R*)-**L1** isomer was the preferred ligand.


[Ir(COD)Cl]$_2$
+ 4
Ph
O
P
N
O
Ph
(S,S,S)-L1
base
THF
L1
Ir
P
O
O
H$_2$C
N
CH$_3$
Ph
Ph
39
85%
O
O
=
O
O

Scheme 9 Cyclometalation of L1

Since the allylic substitution furnishes a stereogenic center with a heteroatom and a neighbouring terminal double bond, ideal starting points for further synthesis, the transformation with *O*- or *N*-nucleophiles is perfectly suited to be applied in the synthesis of chiral heterocycles. This has been demonstrated by a variety of total syntheses which rely on the Ir-catalyzed allylic substitution methodology as key steps.[99-105] Some target molecules are depicted in Figure 2, two representative syntheses are discussed in more detail below (see Scheme 10 and Scheme 11).

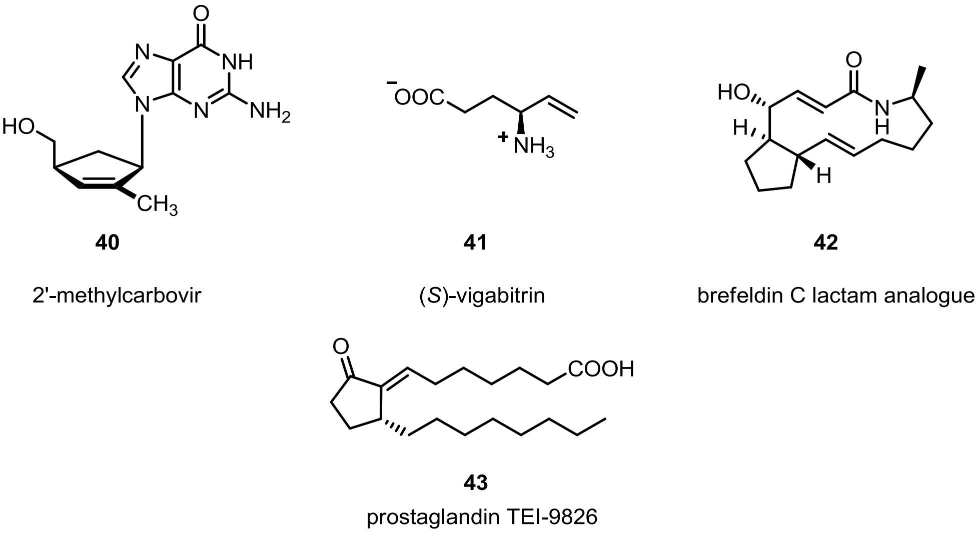
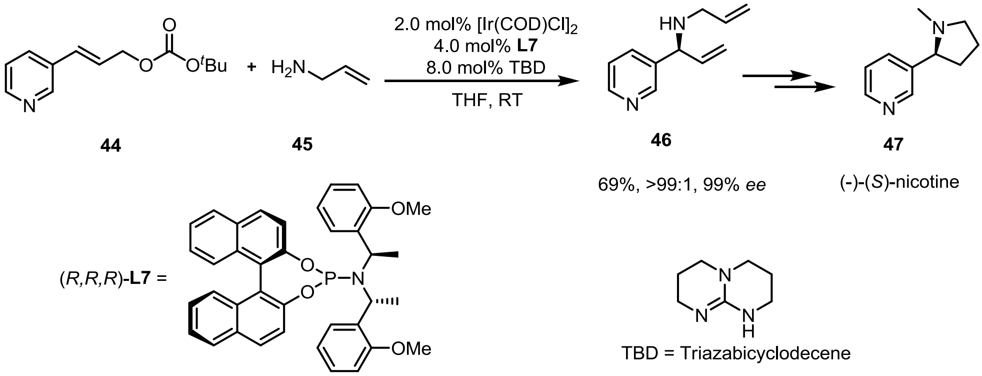

O
N
NH
N
N
NH$_2$
HO
CH$_3$
40
2'-methylcarbovir
$^-$OOC
$^+$NH$_3$
41
(S)-vigabitrin
HO
O
N
H
H
H
42
brefeldin C lactam analogue
O
COOH
43
prostaglandin TEI-9826

Figure 2 Target molecules obtained by routes involving asymmetric Ir-catalyzed allylic substitutions

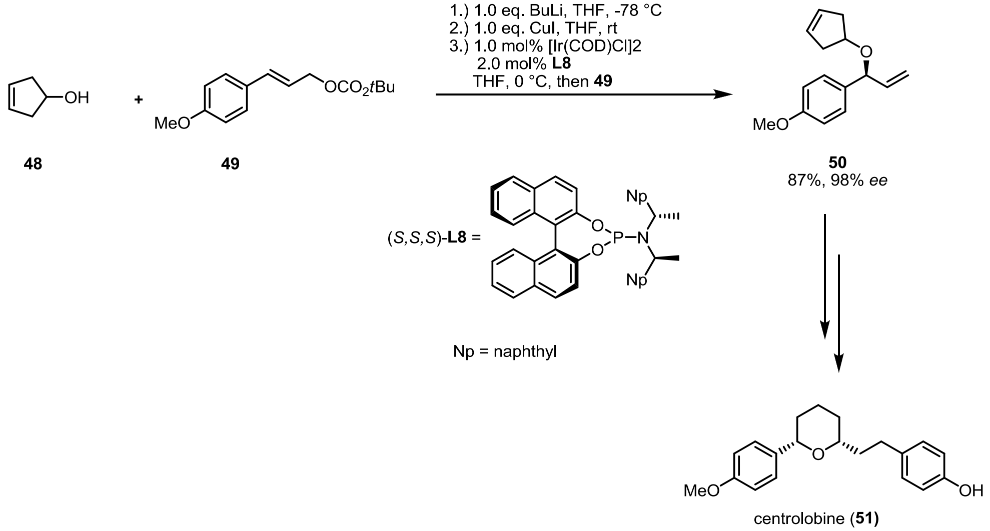
Asymmetric synthesis of nicotine

A total synthesis of nicotine (**47**) was reported based on the allylic amination as the key step to introduce the desired chiral amine (Scheme 10).[106] In this synthetic route, allylic carbonate **44** was reacted with allylamine **45** in the presence of an iridium/phosphoramidite catalytic system to give the corresponding chiral diallylamine **46**. With ligand **L7**[107] allylic amine **46** was formed in moderate yield but with excellent regio- and stereoselectivity. This secondary amine served as the key chiral building block and was transformed into nicotine **47** in a few steps.


O
O
O^tBu
N
+
H2N
2.0 mol% [Ir(COD)Cl]2
4.0 mol% L7
8.0 mol% TBD
THF, RT
HN
N
N
N
44
45
46
47
69%, >99:1, 99% ee
(-)-(S)-nicotine
(R,R,R)-L7 =
O
O
P
N
OMe
OMe
N
N
N
H
TBD = Triazabicyclodecene

Scheme 10 Total synthesis of (-)-(*S*)-nicotine

An iridium/phosphoramidite-catalyzed etherification was used as one of the key steps in a total synthesis of centrolobine (**51**) (Scheme 11).[99] For the total synthesis, the Cu-alkoxide of cyclopentenol **48** was reacted with allyl carbonate **49** in the presence of a Ir/**L8**[108] complex to yield the corresponding branched allylic ether **50** with excellent *ee*. The use of the copper alkoxide had been found to be crucial with regards to the branched/linear selectivity and the enantioselectivity for the reaction of secondary alkoxides.[109] Compound **50** could be transformed into centrolobine **51** in a few steps.



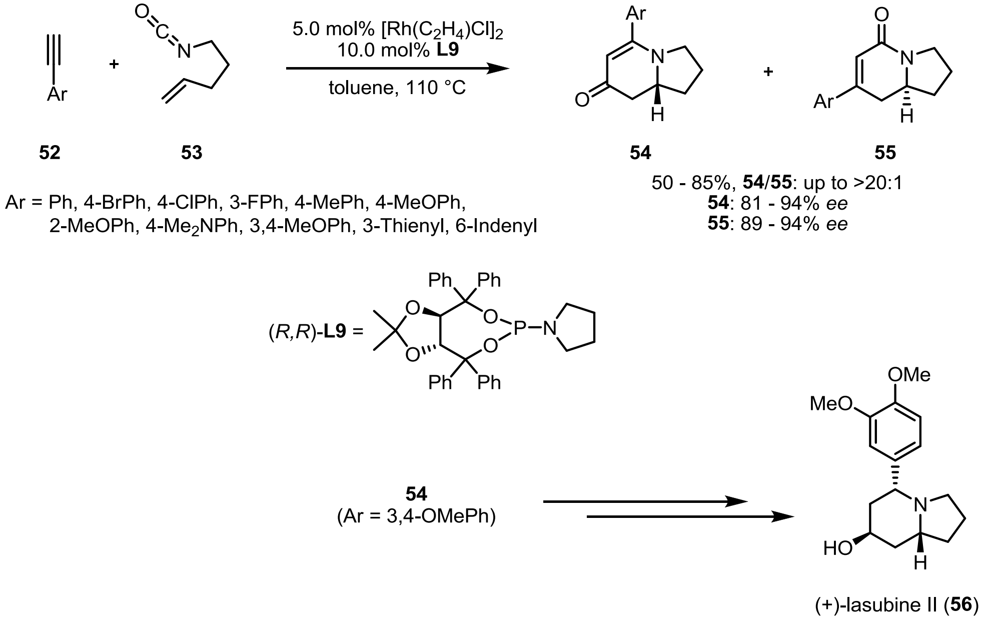
Scheme 11 Asymmetric synthesis of centrolobine

4.3 Miscellaneous reactions

In this section, some reactions leading to chiral heterocycles will be discussed, that do not employ the abovementioned conjugate addition or allylic substitution mechanisms, but nevertheless serve as good examples for the effective construction of chiral heterocycles.

Rh-catalyzed [2+2+2] cycloaddition reactions

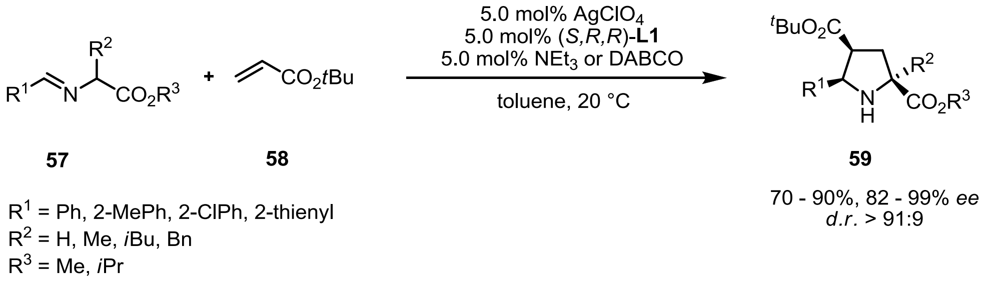
A new intermolecular rhodium-catalyzed [2+2+2] cycloaddition of a variety of aryl acetylenes **53** and alkenyl isocyanates **53** was discovered (Scheme 12).[110,111] Using TADDOL-derived phosphoramidite ligand **L9**, the nitrogen-bridged bicyclic enones **54** and **55** were obtained with *ee*'s up to 94%. The predominant product **54** was obtained exlusively when donor-substituted arylacetylenes **52** were used. Heterocycle **54** could be used as the key chiral building block for the synthesis of lasubine II (**56**), a natural alkaloid found in the tree *Lagerstroemia subcostata.*[112] The Rh-catalyzed asymmetric [2+2+2] cycloaddition has recently been extended to *gem*-disubstituted olefins, rendering this method suitable for the preparation of quaternary stereogenic centers.[113] Further extensions include the use of internal alkynes[114,115] and carbodiimides[116] as substrates, and the expansion to a related [4+2+2] cycloaddition.[117]


52
53
5.0 mol% [Rh(C2H4)Cl]2
10.0 mol% L9
toluene, 110 °C
54
55
Ar = Ph, 4-BrPh, 4-ClPh, 3-FPh, 4-MePh, 4-MeOPh, 2-MeOPh, 4-Me2NPh, 3,4-MeOPh, 3-Thienyl, 6-Indenyl
50 - 85%, 54/55: up to >20:1
54: 81 - 94% ee
55: 89 - 94% ee
(R,R)-L9 =
54
(Ar = 3,4-OMePh)
(+)-lasubine II (56)

Scheme 12 Rh-catalyzed [2+2+2] cycloaddition

Ag-catalyzed 1,3-dipolar cycloaddition reactions

The first successful catalytic application of a phosphoramidite-silver complex was also recently reported.[118] A silver-catalyzed 1,3-dipolar cycloaddition of aryl-substituted iminoglycinates **57** and activated olefins such as *tert*-butyl acrylate **58**[119] furnished proline derivatives **59**. With phosphoramidite **L1** (compare Scheme 2) a variety of pyrrolidines **59** with multiple stereogenic centers were obtained, with generally good yields and excellent stereoselectivities (Scheme 13).


5.0 mol% AgClO4
5.0 mol% (S,R,R)-L1
5.0 mol% NEt3 or DABCO
toluene, 20 °C
57
58
59
R1 = Ph, 2-MePh, 2-ClPh, 2-thienyl
R2 = H, Me, iBu, Bn
R3 = Me, iPr
70 - 90%, 82 - 99% ee
d.r. > 91:9

Scheme 13 Ag-catalyzed 1,3-diploar cycloaddition

5. Aim and outline of this thesis

As chiral heterocyclic compounds are of major importance through their biological activities, selective synthetic routes towards these targets are highly warranted, especially if a possible natural source cannot be exploited in large quantities. Furthermore, many non-natural pharmaceuticals bear chiral heterocycles as key structural elements. Therefore, the development of new synthetic routes towards these structures is of major importance for organic synthesis.

The aim of this thesis was to develop new catalytic asymmetric transformations for the synthesis of chiral heterocycles. Ideally, the corresponding chiral heteroatom-containing building blocks should become available in high yields and stereoselectivities. Furthermore, since our approach is based on chiral metal-complexes, both enantiomers of the desired products should become available.

Our approach was based on catalytic asymmetric methodology developed in our laboratories as well as chiral catalysts known in the literature. Starting from the established methods, also new catalytic asymmetric transformations were developed. In chapter 2, the asymmetric synthesis of 2,5-arylpyrrolidines employing Ir-catalyzed allylic amination with ammonia is described. The extension of this work can be found in chapter 3, where the development of the first asymmetric Ir-catalyzed intramolecular allylic amidation is described. Chiral tetrahydroisoquinolines, important chiral building blocks as well as 5- to 7-membered saturated *N*-heterocycles could be obtained via this new approach. The attempted extension of this to the asymmetric synthesis of chiral β-carboline compounds is described in chapter 4. Related chiral saturated *N*-heterocycles with various ring sizes could be obtained via a complementary route employing a combination of Cu-catalyzed asymmetric allylic alkylation and ring-closing metathesis. This project is described in chapter 5. During the course of this research, also an approach to chiral oxygen-containing heterocycles was developed: the access to chiral coumarin dervatives using Cu-catalyzed conjugate additions of Grignard reagents employing a Cu/bisphosphine catalyst is discussed in chapter 6. The reaction intermediates of these reactions were found to be good starting points for a variety of reactions to give, among others, formal conjugate addition products of α,β-unsaturated amides. Finally, the application of phosphoramidite ligands synthesized from chiral pyrrolidines (compare chapter 2) in asymmetric Ni-catalyzed reductive coupling reactions are described in chapter 7.

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(119) For clarity, only tert-butyl acrylate is shown here.

Chapter 2

Catalytic Asymmetric Synthesis of 2,5-Naphthylpyrrolidine

A novel, straightforward fully catalytic asymmetric synthesis of chiral 2,5-naphthylpyrrolidine based upon an iridium-catalyzed double allylic amination with ammonia has been developed. The products are available in high yields and enantioselectivities.

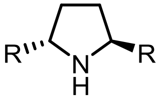
Parts of this chapter have been/will be published:

Teichert, J.F.; Feringa, B.L. *Synthesis*, **2010**, *7*, 1200-1204.

Teichert, J.F.; den Hartog, T.; Hanstein, M.; Smit, C.; ter Horst, B.; Hernández-Olmos, V.; Feringa, B.L., Minnaard, A.J. *ACS Catal.,* accepted for publication.

1. Introduction

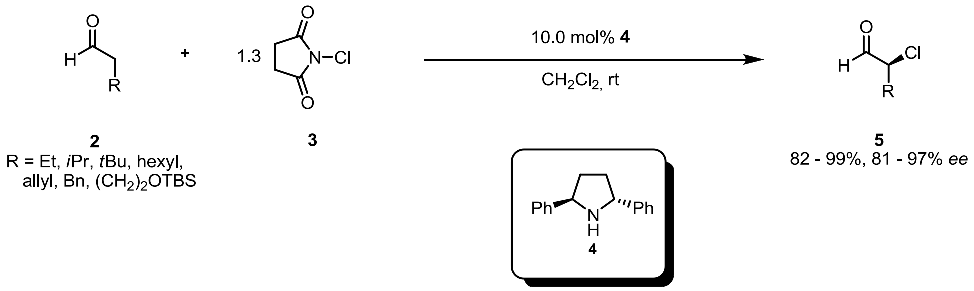
Chiral 2,5-disubstituted pyrrolidines **1** (Figure 1) are versatile chiral compounds that have been used for a large variety of asymmetric transformations. For example, they have been employed as chiral C_2-symmetric auxiliaries[1] for the asymmetric synthesis of α-amino acids through α-alkylation of glycine derivatives[2] or stereoselective iodolactonization.[3] Furthermore, derivatives of 2,5-chiral pyrrolidines have been shown to act as stereodirecting auxiliaries in asymmetric Wittig rearrangements.[4] In catalytic asymmetric transformations, these compounds have been used as chiral ligands for the asymmetric addition of diethylzinc to aldehydes[5] or in palladium-catalyzed allylic alkylation reactions.[6,7]



1

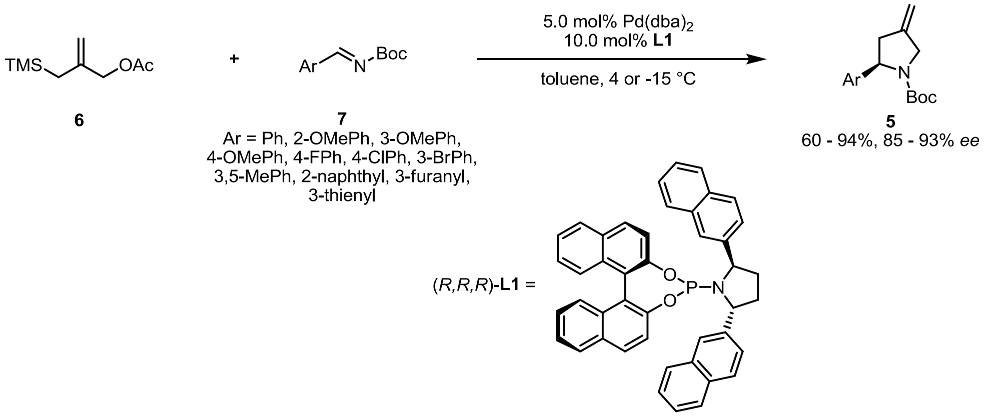
Figure 1 Chiral 2,5-disubstituted pyrrolidines

More recently, chiral 2,5-disubstituted pyrrolidines have been shown to be efficient organocatalysts for a variety of asymmetric transformations such as Michael additions[8] and α-halogenation of aldehydes and ketones.[9-11] As an example, the α-chlorination of aldehydes is depicted in Scheme 1.[10] When aldehydes **2** were reacted with NCS (**3**) as the chlorine source in the presence of catalytic amounts of 2,5-phenylpyrrolidine **4**, the corresponding α-chlorinated aldehydes **5** were isolated in up to excellent yields and enantioselectivities.



Scheme 1 Organocatalytic asymmetric α-chlorination of aldehydes

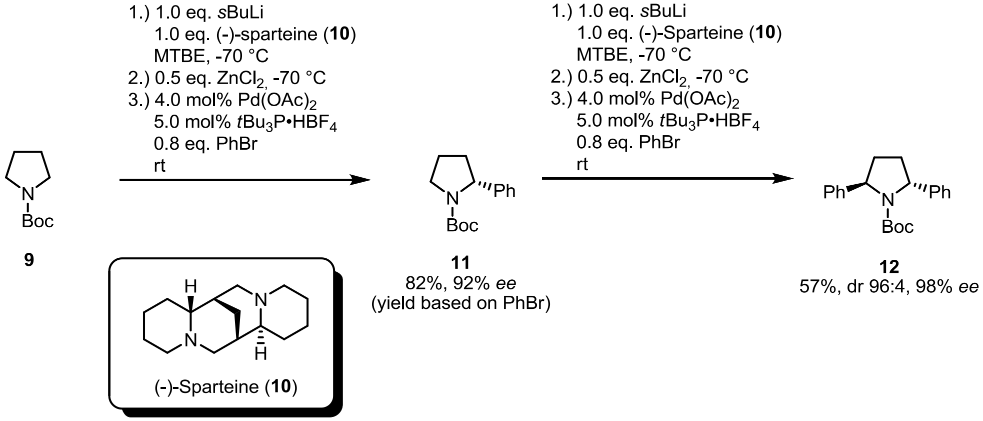
Phosphoramidite ligands[12,13] prepared from chiral 2,5-disubstituted pyrrolidines were reported to give high enantioselectivities in asymmetric palladium-catalyzed [3+2] trimethylenemethane cycloadditions (see also Chapter 1).[14-17] This methodology represents an elegant route towards cyclic compounds, including heterocycles.[16,17] When allyl acetate **6** was reacted with Boc-protected imines **7** in the presence of a Pd/**L1** complex, the corresponding chiral pyrrolidines **8** were accessible in high yields and enantioselectivities (Scheme 2). It was shown that the phosphoramidites derived from chiral 2,5-arylpyrrolidines such as **L1** were key to achieve high enantioselectivities for this transformation. Replacement of the naphthyl substitutents on the pyrrolidine with phenyl groups led to a dramatic drop in enantioselectivity (to 35% *ee* for **5** (Ar = Ph)). Ligand **L1** thus creates a unique chiral environment around the catalytically active metal atom upon coordination.[17]



Scheme 2 Pd-catalyzed asymmetric [3+2] trimethylenemethane addition with imines

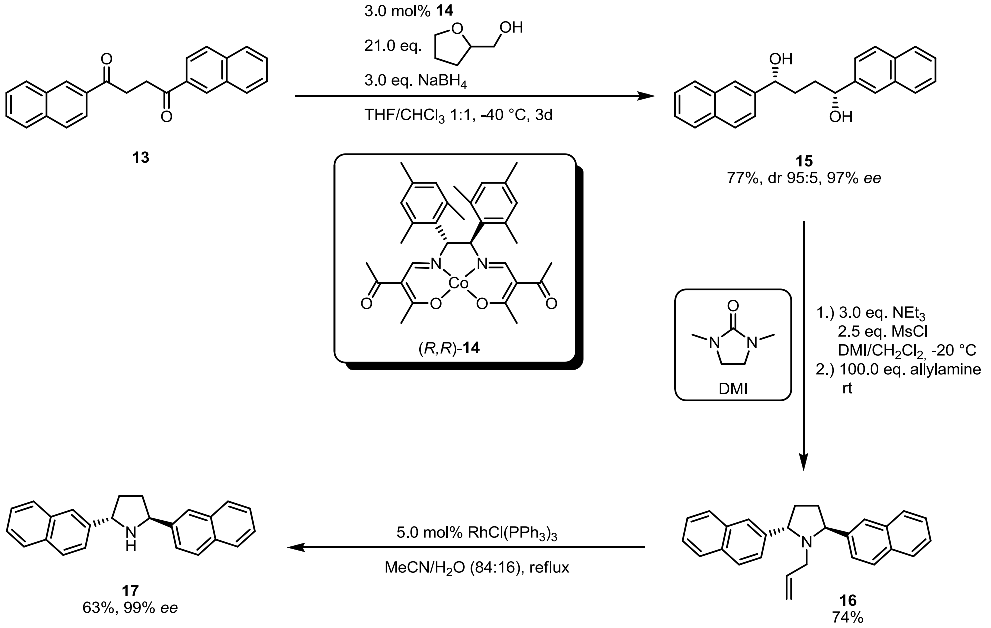
Although a few synthetic routes towards chiral 2,5-arylpyrrolidines are known,[18-22] they do not include the preparation of sterically demanding aryl-substituted pyrrolidines **1**, such as naphthyl-subsituted ones. A report employing asymmetric borane reduction of 1,4-diketones specifically highlights the elusiveness of these substrates in undergoing reduction.[21]

Approaches based upon the enantioselective deprotonation/arylation of Boc-protected pyrrolidines utilizing organolithium reagents and naturally occurring (-)-sparteine have been disclosed.[22-24] One example of a sparteine-mediated asymmetric lithiation of *N*-Boc-pyrrolidine **9** followed by a Negishi coupling in a one-pot protocol has been reported (Scheme 3).[22] When **9** was lithiated in the presence of (-)-sparteine (**10**), then transmetalated to zinc and a subsequent Negishi coupling with phenylbromide was carried out, chiral 2-phenyl-pyrrolidine **11** was isolated in very good yields and enantioselectivity. The same reaction could be carried out on **11** once more to give the corresponding 2,5-diphenyl pyrrolidine **12**. These transformations have been reported to work well with a variety of aromatics, however, the possibility to construct naphthyl-substituents (precursors for **L1**) was not disclosed. The use of an enantiomerically pure stoichiometric reagent such as **10** renders this method not attractive in terms of atom economy. Moreover, since only one enantiomer of sparteine (**10**) is available, only one enantiomer of the products **11** and **12** is accessible through this approach; a drawback when chiral ligands such as **L1** derived from chiral pyrrolidines are employed in the synthesis of complex target molecules where a particular stereoisomer is desirable.


1.) 1.0 eq. *s*BuLi
1.0 eq. (-)-sparteine (**10**)
MTBE, -70 °C
2.) 0.5 eq. $ZnCl_2$, -70 °C
3.) 4.0 mol% $Pd(OAc)_2$
5.0 mol% $tBu_3P•HBF_4$
0.8 eq. PhBr
rt
1.) 1.0 eq. *s*BuLi
1.0 eq. (-)-Sparteine (**10**)
MTBE, -70 °C
2.) 0.5 eq. $ZnCl_2$, -70 °C
3.) 4.0 mol% $Pd(OAc)_2$
5.0 mol% $tBu_3P•HBF_4$
0.8 eq. PhBr
rt
N
Boc
9
N
Ph
Boc
11
82%, 92% *ee*
(yield based on PhBr)
Ph
N
Ph
Boc
12
57%, dr 96:4, 98% *ee*
H
N
N
H
(-)-Sparteine (**10**)

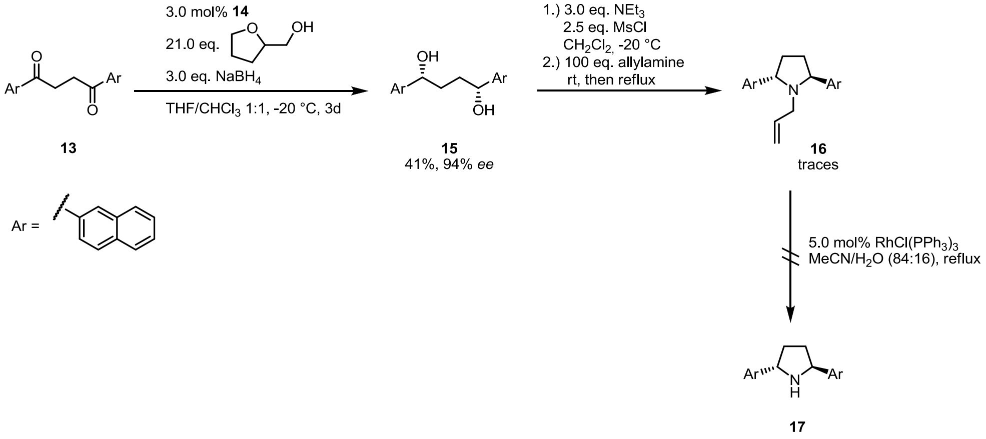
Scheme 3 Asymmetric lithiation/Negishi coupling

A catalytic enantioselective synthesis of chiral 2,5-naphthylpyrrolidines based on the reduction of 1,4-diketones with chiral cobalt-salen complexes was reported.[25] 1,4-Diketone **13**[26] could be selectively reduced to the chiral 1,4-diol **15** in the presence of a chiral Co-salen complex **14**, employing $NaBH_4$ as the reducing agent (Scheme 4). For this reaction to proceed with high yields and enantioselectivities, it is important that tetrahydrofuryl alcohol (THFA) and $NaBH_4$ are premixed, since this will form a $NaBH_x$(THFA) adduct, which ensures high selectivities and reactivities.[27] With diol **15** in hand, it could be transformed to the corresponding *N*-allylpyrrolidine **16** in good yields, followed by a deprotection of the allyl moiety with Wilkinsons's catalyst to give the desired chiral 2,5-dinaphthylpyrrolidine **17** in good yields and excellent enantioselectivity.



Scheme 4 Reported synthesis of 2,5-dinaphthylpyrrolidine

Unfortunately, in our hands, these results were not reproducible or not practicable for the synthesis of naphthyl-substituted pyrrolidine **17** for a variety of reasons. First, the synthesis of the chiral salen ligand of **14** could not be achieved, as the literature procedures[28] turned out to be not reproducible in our hands. The optically active cobalt complex **14** is commercially available, so we could still attempt the asymmetric synthesis of **17** (Scheme 5). The Co-catalyzed asymmetric reduction of **13** could be rendered feasible only if higher temperatures than reported were employed. In our hands, carrying out the synthesis at -40 °C, as reported, led to no conversion of **13**. When we raised the temperature to -20 °C, we could isolate chiral diol **14** in low yields but with enantioselectivities close to the ones previously reported. The following transformation to the *N*-protected pyrrolidine **16** turned out to be not reproducible either: under the reported conditions, no reaction to **16** was observed, in our hands, the best results were found when solvents, reactions times and temperatures were changed to more drastic conditions. However, even then chiral pyrrolidine **16** was only isolated in trace amounts. The following deprotection of the allylamine moiety of **16** to give pyrrolidine **17** did not occur at all under the published conditions and could furthermore not be rendered feasible with a variety of other deprotection conditions. With these disappointing results in hand, we decided to abandon this synthetic route, as it was not a useful one to obtain chiral 2,5-dinaphthylpyrrolidine **17** in reasonable amounts.

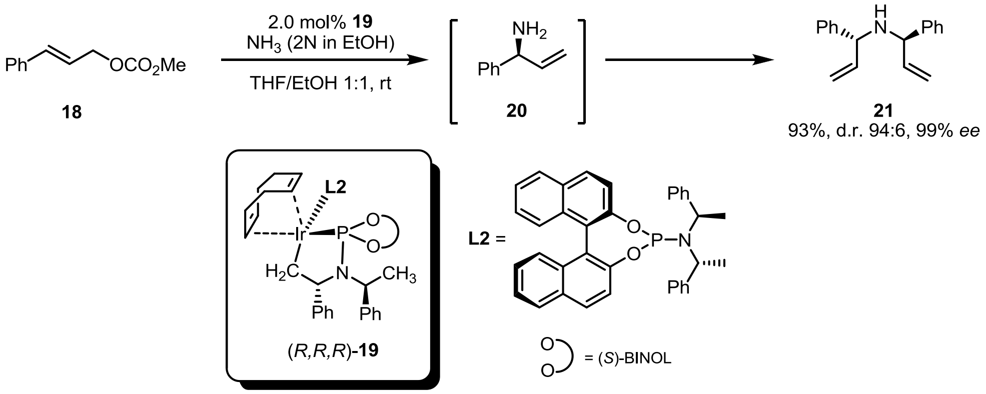

3.0 mol% 14
21.0 eq.
OH
3.0 eq. NaBH4
THF/CHCl3 1:1, -20 °C, 3d
1.) 3.0 eq. NEt3
2.5 eq. MsCl
CH2Cl2, -20 °C
2.) 100 eq. allylamine
rt, then reflux
5.0 mol% RhCl(PPh3)3
MeCN/H2O (84:16), reflux
Ar
O
N
H
Ar =
13
15
41%, 94% ee
16
traces
17

Scheme 5 Attempted synthesis of 17

2. Goal

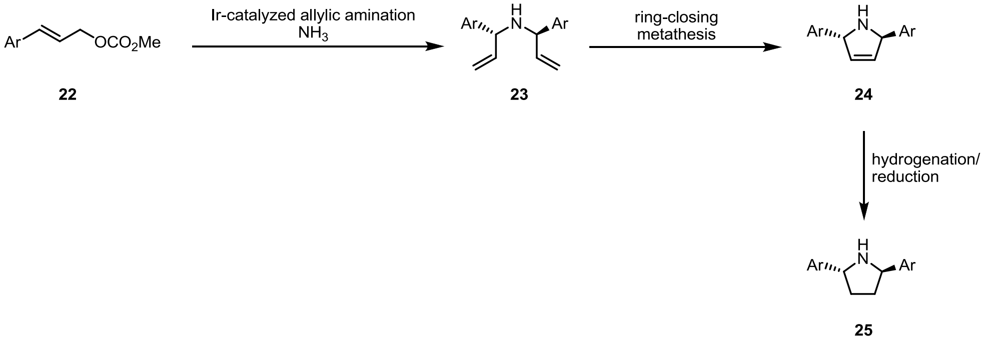
We were interested in the application of sterically very demanding phosphoramidite ligands **L1** for the use in Ni-catalyzed reductive coupling reactions (see Chapter 7), as we expected them to improve the enantioselectivity in those transformations. Therefore, we were interested in a synthetic pathway towards C_2-symmetric chiral pyrrolidines. As the only literature procedure was not reproducible in our hands (see Scheme 4 and Scheme 5), we sought to develop a new synthetic route towards chiral 2,5-diarylpyrrolidines that would provide the products in high optical purity. Ideally this new approach would furnish both enantiomers of the envisaged products. With foresight to possible applications as parts of chiral ligands or as organocatalysts, both enantiomers of the chiral diarylpyrrolidines should be available.

A study regarding the direct allylic amination with ammonia was disclosed,[29] in which the authors found not the anticipated monoamination of cinnamyl carbonate **18** to chiral allylamine **20** in the presence of catalytic amounts of iridacycle **19**, but reaction towards the secondary diallylamine **21** (Scheme 6). This observation stems most probably from the fact that primary amine **20** is a much better nucleophile with regard to Ir-catalyzed allylic amination than ammonia itself. Hence, no traces of the reaction intermediate **20** were observed in the reaction mixture. Nevertheless, the disubstituted product **21** was isolated in excellent yield and stereoselectivities.


2.0 mol% 19
NH3 (2N in EtOH)
THF/EtOH 1:1, rt
18
20
21
93%, d.r. 94:6, 99% ee
(R,R,R)-19
L2 =
= (S)-BINOL

Scheme 6 Ir-catalyzed double allylic amination with ammonia

We decided to make use of this – originally unwanted – diallylation reaction of allylic carbonates **22** with ammonia and use diallylamines **23** as possible starting points for the synthesis of chiral 2,5-diarylpyrrolidines. With chiral compounds **23** in hand, ring-closing metathesis would lead to the corresponding diarylpyrrolines **24**, subsequent reduction of the double bond would furnish the desired diarylpyrrolidines **25** (Scheme 7). Since the two stereogenic centers are constructed early in the synthesis, it is a prerequisite that the subsequent reactions do not compromize the stereochemistry generated at the α-position of the nitrogen atom. This is especially important for the hydrogenation step to give **25**, since many transition metal-based hydrogenation protocols are known to jeopardize stereogenic allylic centers.[30-40]

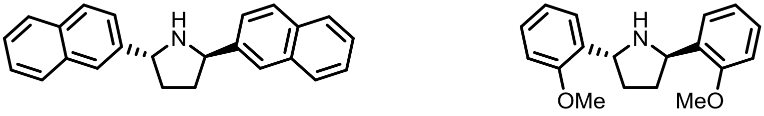

Ir-catalyzed allylic amination
NH3
ring-closing metathesis
hydrogenation/ reduction
22
23
24
25

Scheme 7 Anticipated synthetic route

Since both enantiomers of the phosphoramidite ligand **L2** are readily available, also both enantiomers of **25** should be accessible, which is a major advantage over the previously mentioned synthetic routes (*vide supra*).

3. Results and Discussion

When we started off to probe the viability of the anticipated synthetic route to diarylpyrrolidines, we chose to use the 2-naphthyl-substituted pyrrolidines **26** and **27** as targets to develop and optimize the synthesis (Figure 2). The corresponding phosphoramidite ligand had shown remarkable effects in the asymmetric Pd-catalyzed [3+2] trimethylenemethane addition reaction (*vide supra*).[15,17] Furthermore, *ortho*-methoxyphenyl-derived pyrrolidine **27** should be an interesting chiral building block for phosphoramidite ligands, as *ortho*-methoxy substituents often show remarkable effects in comparison with the corresponding phenyl substituents in chiral phosphoramidite ligands in various catalytic asymmetric transformations.[13]

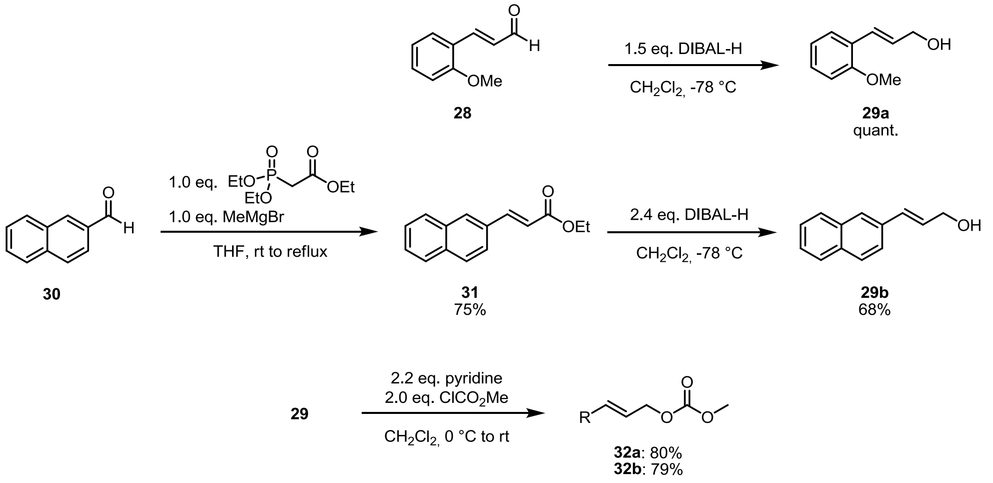


26 **27**

Figure 2 Envisaged target structures

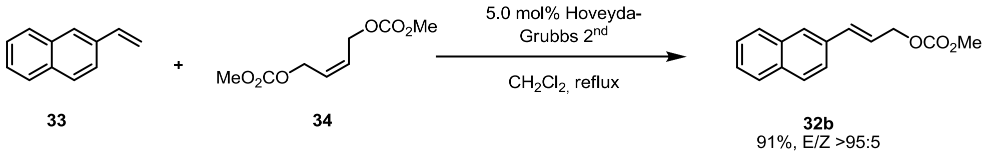
3.1 Synthesis of starting materials

Allylic carbonates **32**, starting materials for the double allylic amination with ammonia, with a 2-naphthyl and a *ortho*-methoxyphenyl moiety were synthesized in a straightforward manner (Scheme 8). Allylic alcohol **29a** was prepared from the corresponding α,β-unsaturated aldehyde **28** by reduction with DIBAL-H. For naphthyl-substituted substrate **32b**, we started with naphthaldehyde **30**, which was converted to the corresponding α,β-unsaturated ester **31** by Horner-Wadsworth-Emmons reaction[41] in good yield (75%). Subsequent reduction of the ester to the allylic alcohol **29b** proceeded in moderate yield. Both allylic alcohols **29** could smoothly be transformed to the corresponding allylic carbonates **32**.


28
1.5 eq. DIBAL-H
CH2Cl2, -78 °C
29a
quant.
30
1.0 eq. EtO-P(O)(OEt)CH2CO2Et
1.0 eq. MeMgBr
THF, rt to reflux
31
75%
2.4 eq. DIBAL-H
CH2Cl2, -78 °C
29b
68%
29
2.2 eq. pyridine
2.0 eq. ClCO2Me
CH2Cl2, 0 °C to rt
32a: 80%
32b: 79%

Scheme 8 Synthesis of allylic carbonates

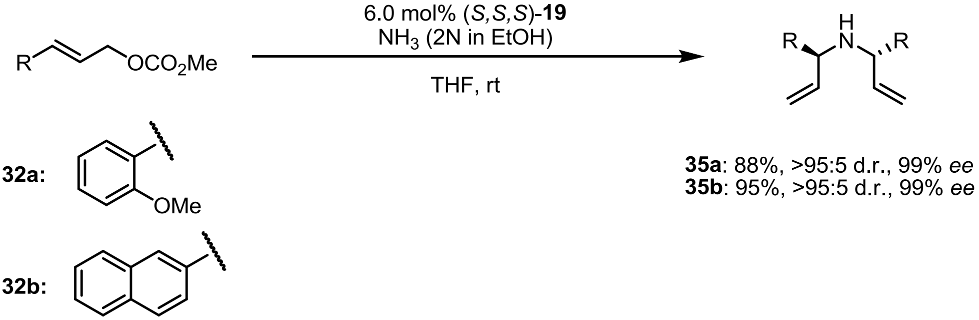
At a later stage of this project, a shorter route to **32b** was developed; commercially available 2-vinylnaphthalene **33** could be transformed to the corresponding allylic carbonate by cross-metathesis with Hoveyda-Grubbs 2nd generation catalyst[42] with dicarbonate **34** in very good yield (Scheme 9). The dicarbonate **34** ensured full conversion to **32b**, since cross metathesis of **33** with the corresponding allyl methyl carbonate under similar reaction conditions led to low conversion to **32b** and dicarbonate **34** was isolated as the major product.[43]


33
34
5.0 mol% Hoveyda-Grubbs 2nd
CH2Cl2, reflux
32b
91%, E/Z >95:5

Scheme 9 Alternative synthesis of allylic carbonate 32b

3.2 Ir-catalyzed double allylic amination

When the allylic amination of allylic carbonates was studied with (*S,S,S*)-**19** as catalyst, we were delighted to find that **32a** and **32b** were converted smoothly to the corresponding amines **35** (Scheme 10). **35b** was isolated with excellent stereoselectivities and yields after 16 hours, whereas diallylamine **35a** was formed in slightly lower yields, however, with the same results in terms of stereoselectivity.


R
OCO$_2$Me
6.0 mol% (*S,S,S*)-**19**
NH$_3$ (2N in EtOH)
THF, rt
H
N
R
R
32a:
OMe
32b:
35a: 88%, >95:5 d.r., 99% *ee*
35b: 95%, >95:5 d.r., 99% *ee*

Scheme 10 Ir-catalyzed allylic amination

A few factors have been found to be influential on the outcome of this transformation, which has been optimized with the transformation of substrate **32b**:

Catalyst loading

It was found that with 2.0 mol% of (*S,S,S*)-**19** the reaction proceeded with the same outcome with regards to stereoselectivity, but with considerably lower conversion of **32b** (~40% conversion, as judged by ^{1}H NMR). Adding the catalyst in four batches of 0.5 mol% over a period of 4 hours did not improve the conversion, indicating that the catalyst stays active in the reaction mixture.

Temperature

The reaction was also run at elevated temperature (50 °C), and did show faster conversion to the desired product **35b** with equally good enantioselectivities, however, still 6.0 mol% of (*S,S,S*)-**19** were necessary to ensure full consumption of allylic carbonate **32b**. For practical reasons, the reactions were run at ambient temperature in the following.

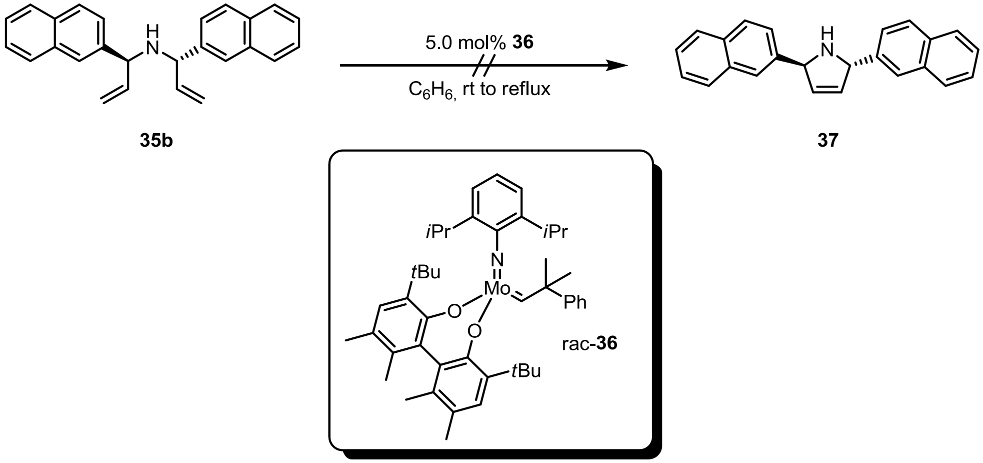
Concentration

The amounts of solvents proved to be influential on the conversion of **32** as well. In a typical experiment, a NH$_3$ solution in EtOH was added to the allylic carbonate to give a ~0.7 molar suspension. Carbonates **32** do not dissolve well in the ammonia solution, so THF was added until all carbonate was dissolved (typically at a ratio EtOH/THF 2:1) and the reaction mixture stirred overnight, which ensured full conversion of **32**. If more THF was added (exceeding ratios EtOH/THF 1:1), the reaction would still take place with the same stereoselectivities, however, with considerably lower conversion. From this observation, it can be concluded that a too low concentration of the nucleophile (NH$_3$) is detrimental in terms of conversion. It is improbable that the catalyst loses its activity because of the higher ratio of THF, as this is the solvent of choice for most of the Ir/phoshoramidite-catalyzed allylic substitutions.[13]

It should be noted that the enantioselectivity of **35** was determined by comparison of both enantiomers of **35** by chiral HPLC, since a direct racemic allylic amination was not available. (*i.e.* no non-chiral phosphoramidite-based iridacycle has been synthesized) At the same time, this served as an example that both enantiomers of **35** are available through this allylic amination protocol. The absolute configuration of **35b** was later assigned by comparison of the NMR data and optical rotation of phosphoramidite **L1**, synthesized from chiral pyrrolidine **26** (*vide infra*) with literature.[17] The absolute configuration of **35a** was then assigned in analogy to **35b**.

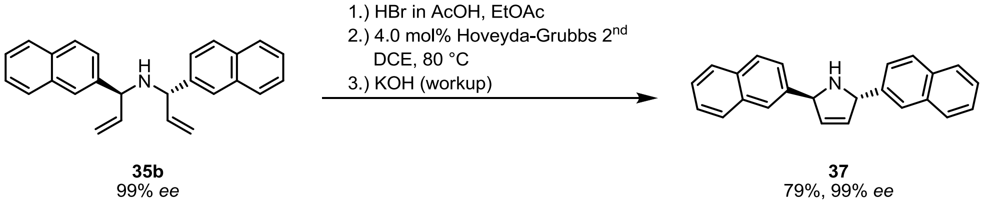
3.3 Ring-closing metathesis to give chiral pyrrolines

With chiral diallylamines **35** in hand, we went on to investigate the following ring-closing metathesis towards the corresponding chiral pyrrolines **37**. Ring-closing metathesis of **35b** was initially examined with Mo-based catalysts, since they were reported to exert catalytic activity with unprotected secondary amines (Scheme 11).[44] In our case however, employing catalytic amounts of the Schrock-Hoveyda catalyst **36**, no turnover of **35b** was observed, which we attribute to the steric constraints of **35b**.



Scheme 11 Attempted ring-closing metathesis with Mo-based catalyst

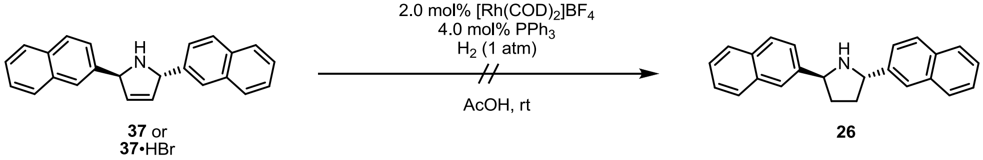
Ring-closing metathesis of **35** based upon ruthenium catalysts is hampered by the potential donor abilities of the nitrogen in **35**, so we decided to convert **35b** to the corresponding HBr salt to conceal this functionality. This approach had been employed successfully in the literature.[45-47] We then probed the ring-closing metathesis of **35b**•HBr with Hoveyda-Grubbs 2nd generation catalyst, which had been reported to be the catalyst of choice for the formation of pyrrolines.[42,45,47,48] Employing elevated temperatures (1,2-dichloroethane at reflux) and 4.0 mol% Hoveyda-Grubbs 2nd generation catalyst, chiral pyrroline **37** was obtained in 79% yield (Scheme 12). Importantly, **37** was formed without loss of *ee*. Noteworthy is the fact that the corresponding HCl salt of **35b** led to decomposition of the starting material under reaction conditions. This particular behaviour had been observed in previous studies,[45] and the origin of this effect is unclear. With other Grubbs or Hoveyda-Grubbs (1st or 2nd generation) catalysts **37** was obtained in lower yields. Several factors are influencing the positive outcome of this reaction: The HBr salt of **35b** has to be thoroughly dried, so that no traces of acetic acid are present (HBr was employed as a solution in acetic acid). Secondly, the catalyst has to be added in two batches of 2.0 mol% each, since rapid catalyst deactivation was observed. Furthermore, to achieve high isolated yields, a two step procedure has to be followed: After cooling down, the first batch of the product can just be filtered off and washed with acetone. Like this, analytically pure HBr salt of **37** is obtained (~60%). However, it turned out that not all **37**•HBr was precipitated as after workup of the reaction mixture, a second part of the product was obtained after deprotection of the salt and purification by column chromatography. It is important that the column is run not too slow, since decomposition of **37** during chromatography is observed. The combined batches after filtration and column chromatography amount for the reported 79% yield. As will be seen in the following section, the reduction of the double bond is carried out with an excess of base, so that deprotection of the HBr salt of **37** poses no problems.



Scheme 12 Ring-closing metathesis with Ru-based catalyst

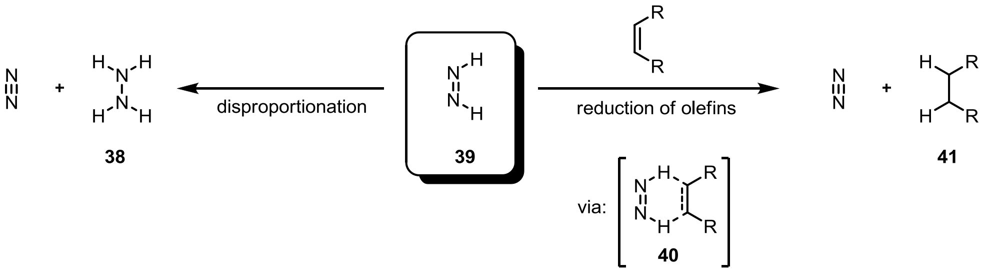
3.4 Reduction of the double bond

The subsequent reduction of the olefin in pyrroline **37** was first attempted by homogenous Rh-catalysed hydrogenation[49] (Scheme 13), but here also, the unprotected amine suppressed any conversion. The hydrogenation of the corresponding HBr salt of **37** under the same conditions turned out to be unfruitful as well.



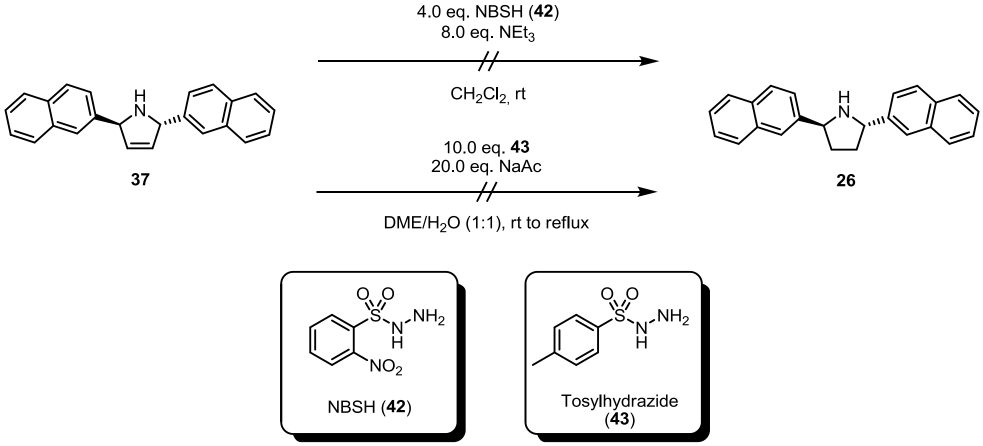
Scheme 13 Attempted hydrogentation of 37

Since heterogeneous hydrogenation with palladium on solid supports is known to racemize allylic amines,[30-40] we refrained from applying this methodology into our synthesis. Instead, we were investigating the use of diimide (**39**) as reducing agent[50] for the double bond of pyrroline **37**. Diimide (or diazene) itself is unstable, as it readily disproportionates to hydrazine **38** and dinitrogen (Scheme 14). However, when formed *in situ*, it can be used as a reducing agent for non-polarized double bonds, diimid itself being oxidized to dinitrogen, leaving the reduced product **41** behind.[50] The most important feature of this reduction protocol is the fact that it is assumed to proceed via a concerted mechanism with a six-membered transition state **40**. This fact makes the use of this methodology inobjectionable for the reduction of double bonds bearing α-stereogenic centers.



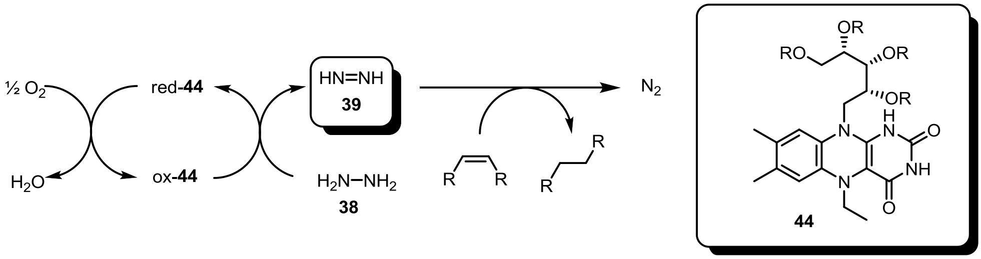
Scheme 14 Reduction with diimide / disproportionation of diimide

It had been reported in the literature that diimide can be generated *in situ* under basic conditions from *ortho*-nitrobenzenesulfonylhydrazide (NBSH, **42**)[51,52] or tosylhydrazine (**43**)[53,54] and directly used as mild reducing agents for olefins. We tried both conditions on chiral pyrroline **37**, but neither of the reactions led to conversion of **37** (Scheme 15), as in both cases, the starting material was isolated unreacted. This is possibly due to the short lifetime of diimide under the given reaction conditions. Effectively, the concentration of diimide **39** has to be higher to ensure reduction of the sterically demanding substrate **37**.


4.0 eq. NBSH (42)
8.0 eq. NEt3
CH2Cl2, rt
10.0 eq. 43
20.0 eq. NaAc
DME/H2O (1:1), rt to reflux
37
26
NBSH (42)
Tosylhydrazide (43)

Scheme 15 Attempted reduction of 37 with diimide

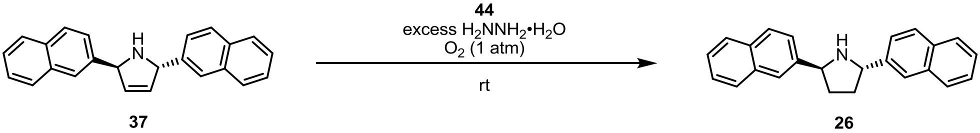
In our institute, a metal-free reduction of olefins based on catalytic formation of diimide **39** from cheap and readily available hydrazine with riboflavin-derived catalyst **44** and molecular oxygen has been developed.[55] In this reaction, **44** oxidizes hydrazine to the actual reducing agent, diimide **39**, and then gets reoxidized by molecular oxygen (Scheme 16). The actual role of the organocatalyst **44** on the double bond reduction is therefore of indirect nature.


½ O2
H2O
red-44
ox-44
HN=NH
39
H2N–NH2
38
N2
R
44

Scheme 16 Organocatalytic reduction of double bonds

Catalyst **44** can be synthesized in a one-step procedure from riboflavine. When we applied the standard reaction conditions[55] to the reduction of **37** (Table 1), no conversion to **26** was observed, most probably due to the insolubility of **37** in ethanol (Table 1, entry 1). When the same reaction was carried out in a mixture of dichloromethane and ethanol to ensure solubility of **37**, we observed that the corresponding pyrrolidine **26** was formed, albeit in very low yields (Table 1, entry 2). Raising the catalyst loading to 50.0 mol% led to a significant increase in conversion of **37** (Table 1, entry 3). It is important to note that even with comparatively high catalyst loading of **44** we can still speak of an efficient catalyst, since **44** is only catalytically converting hydrazine **38** to diimide **39**, which in turn facilitates the double bond reduction. Riboflavine **44** has thus no direct effect on the transformation of **37**. We found that when the catalyst and hydrazine were added slowly (over a period of 10 hours via syringe pump) to the reaction mixture, a remarkable increase in conversion was observed (Table 1, entry 4). Finally, full conversion to **26** was obtained with 1.0 eq. of riboflavine **44** with respect to pyrroline **37** (Table 1, entry 5). As expected, the corresponding pyrrolidine **26** was formed without loss of *ee*. Furthermore, as this transformation is carried out in basic conditions, also the HBr salt of **37**, which was obtained from the previous reaction, could be employed directly.

Table 1 Reduction of 37 with riboflavine organocatalyst 44



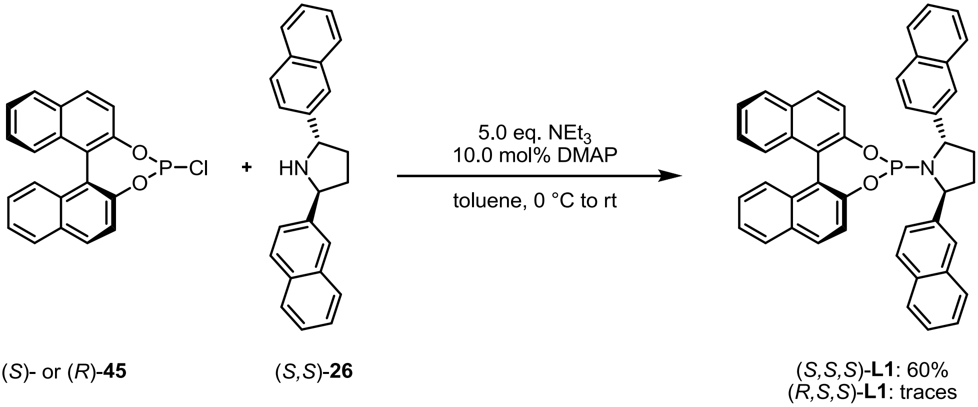
Entry	Solvent	Amount of 44	Conversion[a]
1	EtOH	10	n.d.
2	CH_2Cl_2/EtOH 1:1	10	traces
3	CH_2Cl_2/EtOH 1:1	50[b]	50%
4	CH_2Cl_2/EtOH 1:1	50[c]	80%
5	CH_2Cl_2/EtOH 1:1	100[c]	full[d]

[a]Determined by ^{1}H NMR. [b]**44** and hydrazine hydrate added in 5 min. [c]**44** and hydrazine hydrate added slowly over a period of 10 h. [d]81% isolated yield.

The success of the slow-addition protocol for this demanding substrate with regards to reduction of the double bond can be explained by the fact that the catalyst **44** as well as diimide (**39**) have a limited lifetime under the given reaction conditions. The active concentration of the reducing agent is effectively lowered during the reaction by diimide disproportionation to dinitrogen and hydrazine (see Scheme 14).[56,57] By adding the organocatalyst **44** and hydrazine **38** slowly to the mixture, the active concentration of diimide (**39**) stays constant during the reaction, allowing for higher turnover of the reduction of sterically demanding substrates. This new protocol has also been used successfully in the reduction of other olefins bearing α-stereogenic centers.[58]

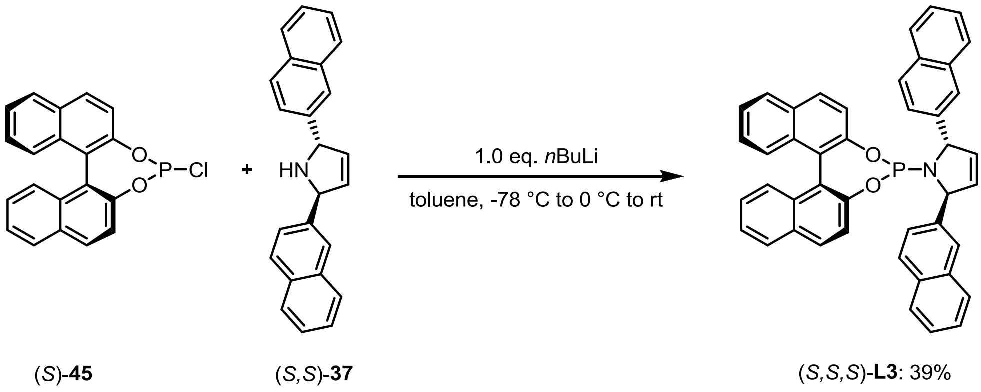
3.5 Synthesis of the corresponding phosphoramidite ligands

With chiral 2,5-naphthylpyrrolidine in hand, we went on to synthesize the corresponding phosphoramidite ligand **L1**. When **26** was reacted in the presence of phosphochloridite **45**,[59] the corresponding phosphoramidite ligand **L1** was obtained in 60% yield (Scheme 17). It is important to note that the triethylamine used has to be freshly distilled over CaH_2 for this transformation to proceed smoothly. Failure to do this resulted in rapid hydrolysis of phosphochloridite **45** and therefore no conversion of pyrrolidine **26**. The analytical data of **L1** served as basis for the determination of the absolute configuration of **26** and thus also its precursors by comparison with literature data.[17] It can be said that the Ir-catalyzed double allylic amination with ammonia employing (*S,S,S*)-**19** as catalyst gives the corresponding (*S,S*)-products **35**, such as displayed in the previous schemes. It is important to note that the attempted synthesis of the (*R,S,S*)-diastereomer of **L1** gave only traces of product via this synthetic route, indicating that the (*S,S,S*)-diastereomer of **L1** is sterically favoured.



Scheme 17 Synthesis of phosphoramidites L1 (only the *S*-diastereomer of BINOL is displayed)

The synthetic intermediate pyrroline **37** could also be transformed to a phosphoramidite ligand. For this reaction to occur, a different synthetic procedure was chosen. First, pyrroline **37** was transformed to the corresponding Li-amide, and then reacted with phosphochloridite **45** to give the phosphoramidite **L3** in moderate yields (Scheme 18). It should be noted that the purification of phosphoramidites **L1** and **L3** is difficult due to their instability on silicagel, which leads to decomposition to the corresponding starting materials, pyrroline **37** or pyrrolidine **26**, respectively, during purification. Therefore, column chromatography has to be carried out quickly with high polarity of the eluent.



Scheme 18 Synthesis of phosphoramidite L3

4. Conclusions

In summary, we have developed a new, concise catalytic asymmetric synthetic route towards chiral 2,5-diarylpyrrolidines. The key step of this synthetic route is a double asymmetric allylic amination with ammonia catalyzed by an iridium/phosphoramidite complex. This is a powerful reaction which creates two stereogenic centers in one transformation in high stereoselectivities, at the same time, it is atom-economic in terms of the nitrogen nucleophile used, namely ammonia. All steps of the pyrrolidine synthesis are high yielding and both enantiomers of the products are available through this novel pathway. The latter is a clear advantage over the existing sparteine-mediated processes. Furthermore, with the exception of salt formation of **35**, the synthesis is protecting group free.

We successfully employed this new synthetic route to prepare the corresponding pyrrolidine- and pyrroline-based phosphoramidite ligands **L1** and **L3**.

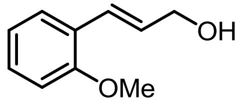
Along the way, we have optimized the protocol for the organocatalytic reduction of double bonds employing a riboflavine catalyst. With the new reaction protocol for the riboflavine-catalyzed reduction of double bonds, also sterically demanding and compounds prone to racemization under hydrogenative conditions can be reduced smoothly without endangering any stereogenic center.

5. Experimental section

General

Starting materials were purchased from Acros, Sigma–Aldrich or Strem and were used as received unless stated otherwise. All solvents were reagent grade and, if necessary, dried and distilled prior to use. Toluene was distilled over Na, THF and diethylether were distilled over Na/benzophenone. Column chromatography was performed on silica gel (Silicycle SiliaFlash P60, 230–400 mesh). TLC was performed on silica gel 60/Kieselguhr F254. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200, a Varian VXR300 (299.97 MHz for ^{1}H, 75.48 MHz for ^{13}C) or a Varian AMX400 (399.93 MHz for ^{1}H, 100.59 MHz for ^{13}C) spectrometer. Chemical shifts are reported in δ values (ppm) relative to literature values of solvents and reference compounds.[60] The following abbreviations are used to indicate multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Mass spectra (HRMS) were performed on a Orbitrap system from Thermo Scientific. HPLC analysis was performed on a Shimadzu HPLC system equipped with two LC-10AD vp solvent delivery systems, a DGU-14 A degasser, a SIL-10AD vp auto injector, an SPD-M10 A vp diode array detector, a CTO-10 A vp column oven and an SCL-10A vp system controller by using the columns indicated for each compound separately. All glassware was flame-dried prior to use unless noted otherwise. Phosphochloridite **45**[59], Iridacycle **19**[29,61] and riboflavin **44**[55] were synthesized according to literature procedures.

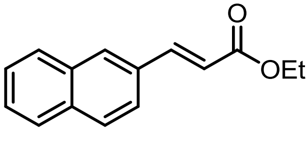
(*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ol 29a



29a

(*E*)-3-(2-methoxyphenyl)acrylaldehyde **28** (1.0 eq., 2.00 g, 12.33 mmol) was dissolved in CH_2Cl_2 (50 ml) and cooled to -78 °C, then 1.50 eq. diisobutylaluminum hydride (18.50 ml, 18.50 mmol) solution (c = 1.0 M in CH_2Cl_2) was added dropwise. The mixture was allowed to warm to ambient temperature and stirred for 16 h. After completion of the reaction, as judged by TLC, 50 mL of a saturated solution of Rochelle's salt (potassium sodium tartrate) was added and the resulting slurry stirred at rt for 2 h. The mixture was then extracted with Et_2O (3x 20 mL) and washed with water (2x 30 mL). The combined organic phases were dried over $MgSO_4$ and all volatiles were removed in vacuo to give (*E*)-3-(2-methoxyphenyl)prop-2-en-1-ol **29a** (2.025 g, 12.33 mmol, quant.) as a colourless oil. The product was used directly in the next reaction without further purification.

(*E*)-Ethyl 3-(naphthalen-2-yl)acrylate 31

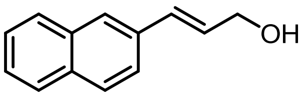


31

According to a literature procedure,[41] 1.0 eq. triethyl phosphonoacetate (3.97 ml, 20.0 mmol) was dissolved in 75 mL dry THF at rt. Then, 1.0 eq methylmagnesium bromide (6.67 ml, 20.0 mmol) solution (c = 3.0 M) was added dropwise via syringe. The solution was stirred at r.t. for 15 min. Then, a solution of 1.1 eq. naphthaldehyde **30** (3.44 g, 22.0 mmol) in 25 mL dry THF was added slowly through a syringe. The resulting yellow mixture was heated at reflux for 16 h. After cooling to rt, the reaction was quenched by addition of sat. aq. NH_4Cl solution (50 ml). The mixture was extracted with diethyl ether (3x

25 mL), dried over $MgSO_4$, and subsequently, all volatiles were removed *in vacuo* to yield a yellow solid. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 800:15, R_f = 0.2 in pentane/EtOAc 100:1) to yield 3.39 g (15.0 mmol, 75%) of the desired product **31** as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.90 – 7.80 (m, 4H), 7.67 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.56 – 7.47 (m, 2H), 6.55 (d, *J* = 16.0 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.39 – 1.33 (t, J = 7.4 Hz, 3H). HRMS-ESI$^+$: *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}NO_2$: 227.1067; found: 227.1065

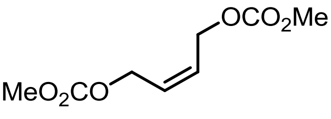
(*E*)-3-(Naphthalen-2-yl)prop-2-en-1-ol 29b



29b

(*E*)-Ethyl 3-(naphthalen-2-yl)acrylate **31** (1.0 eq., 9.866 g, 43.6 mmol) was dissolved in CH_2Cl_2 (50 ml) and cooled to -78 °C. To this solution, 2.4 eq. diisobutylaluminum hydride (105 ml, 105 mmol) solution (c = 1.0 in CH_2Cl_2) was added dropwise. The reaction mixture was stirred for 1 h at the same temperature. When TLC analysis showed complete dissappearence of the starting material, the reaction mixture was warmed to rt and a 100 mL sat. solution of Rochelle's salt was added carefully to quench the reaction. This mixture was stirred vigorously at rt for 3 h. This mixture was extracted with CH_2Cl_2 (3x 50 mL). The combined organic phases were dried over $MgSO_4$ and all volatiles were removed *in vacuo* to yield (*E*)-3-(naphthalen-2-yl)prop-2-en-1-ol **29b** (5.46 g, 29.6 mmol, 68 %) as a white powder. This was used without further purification. (R_f = 0.25 in Pentane / EtOAc 40:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (ddd, *J* = 13.5, 8.2, 3.7 Hz, 3H), 7.74 (s, 1H), 7.61 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.52 – 7.41 (m, 2H), 6.79 (d, *J* = 15.9 Hz, 1H), 6.50 (dt, *J* = 15.9, 5.7 Hz, 1H), 4.39 (td, *J* = 5.8, 1.4 Hz, 2H), 1.49 (t, *J* = 5.9 Hz, 1H). HRMS-ESI$^+$: *m/z* $[M+H^+-H_2O]$ calcd for $C_{13}H_{11}$: 167.0855; found: 167.0852.

(*Z*)-But-2-ene-1,4-diyl dimethyl dicarbonate 34[62]



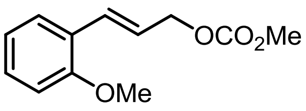
34

(*Z*)-But-2-ene-1,4-diol (1.0 eq., 5.0 ml, 60.7 mmol), 2.0 eq. pyridine (9.82 ml, 121 mmol) were dissolved in CH_2Cl_2 (50 ml) at 0 °C, then 2.2 eq. chloro methylformiate (10.32 ml, 134 mmol) were added dropwise and the mixture was allowed to warm to room temperature. After TLC showed full conversion (~1 h), the mixture was extracted 3x with aq. HCl (2N) and the resulting organic phases were dried over Na_2SO_4. After removal of all volatiles *in vacuo*, (*Z*)-but-2-ene-1,4-diyl dimethyl dicarbonate **34** (11.91 g, 58.3 mmol, 96 %) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 – 5.67 (m, 2H), 4.69 – 4.63 (m, 4H), 3.70 – 3.65 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.28, 127.74, 62.90, 54.61. HRMS-ESI$^+$: *m/z* $[M+Na^+]$ calcd for $C_{18}H_{12}O_6Na$: 227.0526; found: 227.0535.

General procedure for the synthesis of allylic carbonates 32:

To a solution of allyl alcohol **29** (1.0 eq.) and pyridine (2.2 eq.) in CH_2Cl_2 (20 mL/mmol) methyl chloroformate (2.0 eq.) was added dropwise at 0 °C. After 5 min. the solution was warmed to room temperature and was stirred for 1 h. Then, it was washed with aq. HCl (2N) (3x 5 mL/mmol) and dried over Na_2SO_4. The corresponding products **32** were obtained as a white solid after evaporation of the solvent.

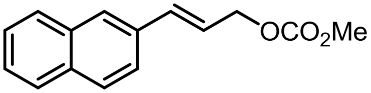
(*E*)-3-(2-Methoxyphenyl)allyl methyl carbonate 32a



32a

According to the general procedure, 1.00 eq. (*E*)-3-(2-methoxyphenyl)prop-2-en-1-ol **29a** (2.025 g, 12.33 mmol) was transformed to (*E*)-3-(2-methoxyphenyl)allyl methyl carbonate **32a** (2.20 g, 9.90 mmol, 80 %) as a white powder. ^{1}H NMR (201 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.32 – 7.15 (m, 1H), 6.97 (d, *J* = 4.2 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 2H), 6.49 – 6.18 (m, 1H), 4.89 – 4.71 (m, 2H), 3.84 (s, 3H), 3.80 (s, 3H). HRMS-ESI$^+$: *m/z* [M-OCO_2Me] calcd for $C_{11}H_{10}O$: 147.0810; found: 147.0804.

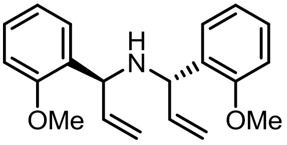
(*E*)-Methyl 3-(naphthalen-2-yl)allyl carbonate 32b[63]



32b

2-Vinylnaphthalene **33** (1.00 eq., 0.154 g, 1.00 mmol) was dissolved in 10 mL CH_2Cl_2 at room temperature and butenedimethylcarbonate **34** (2.00 eq., 0.409 g, 2.00 mmol) were added. Then, a solution of 5 mol% Hoveyda-Grubbs 2nd generation catalyst (0.031 g, 0.05 mmol) in 0.5 mL CH_2Cl_2 was added and the reaction mixture was heated at reflux for 16 h. After cooling, all volatiles were removed *in vacuo* to give a brown-green solid. This was purified by column chromatography (SiO_2, pentane/EtOAc 20:1, R_f = 0.8 in pentane/EtOAc 10:1) to give **32b** as a white powder (0.218 g, 0.9 mmol, 90%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.90 – 7.72 (m, 4H), 7.60 (m, 1H), 7.48 (m, 2H), 6.86 (d, *J* = 15.9 Hz, 1H), 6.43 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.86 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.85 – 3.82 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.66, 134.85, 133.44, 133.42, 133.20, 128.28, 128.05, 127.64, 127.01, 126.33, 126.15, 123.41, 122.70, 68.46, 54.85. HRMS-ESI$^+$: *m/z* [M-OCO_2Me]$^+$ calcd for $C_{13}H_{11}$: 167.0861; found: 167.0853.

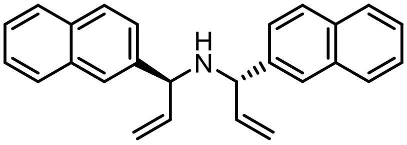
(*S*)-Bis((S)-1-(2-methoxyphenyl)allyl)amine 35a



35a

(*E*)-3-(2-Methoxyphenyl)allyl methyl carbonate **32a** (1.0 eq., 0.027 g, 0.121 mmol) and 0.06 eq. (*S,S,S*)-**19** (0.010 g, 7.25 µmol) were mixed in a dried Schlenk tube and 1 mL ammonia in EtOH (c = 2.0 M) was added. THF was added until all starting materials were dissolved (~0.7 mL). The reaction was stirred for 16 h at rt. The conversion was checked by TLC analysis. After full conversion was reached, all volatiles were removed *in vacuo* to yield the crude product, which was further purified by column chromatography (SiO_2, Pet-ether 40-60/EtOAc 20:1 + 1% NEt_3, R_f = 0.45 in Pet-ether 40-60/ EtOAc 10:1) to yield (*S*)-bis((*S*)-1-(2-methoxyphenyl)allyl)amine **35a** as a white solid (0.033 g, 0.106 mmol, 88 %, 99% *ee*). ^1H NMR (201 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.4 Hz, 2H), 7.29 – 7.14 (m, 2H), 7.06 – 6.78 (m, 4H), 6.23 – 5.81 (m, 2H), 5.26 – 4.94 (m, 4H), 4.53 (t, *J* = 6.9 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 2.14 (s (br), 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.16, 140.33, 128.39, 127.82, 120.71, 114.64, 110.69, 104.99, 57.29, 55.29. HRMS-ESI$^+$: *m/z* [M+H$^+$] calcd for $C_{20}H_{24}NO_2$: 310.1802; found: 310.1800. HPLC analysis: The *ee* was determined by HPLC analysis, Chiralpak AD (*n*-heptane/*i*-PrOH 99:1, 200 nm, flow rate 0.5 mL/min), retention times (min.) *S,S*-enantiomer: 4.49, *R,R*-enantiomer: 5.03. The enantiomeric excess was obtained by comparison of both the pure enantiomers as well as a mixture of both enantiomers of **35a**.

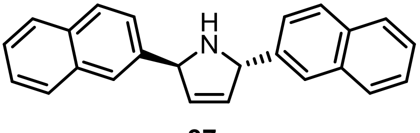
(*S*)-Bis((*S*)-1-(naphthalen-2-yl)allyl)amine 35b



35b

In a glovebox, (*E*)-methyl (3-(naphthalen-2-yl)allyl) carbonate **32b** (1.00 eq., 0.242 g, 1.00 mmol) and 6.00 mol% **19** (0.083 g, 0.060 mmol) were introduced into a flame-dried Schlenk tube. After sealing, the tube was taken out of the glovebox, flushed with nitrogen and 1.5 mL of a 2.0 M solution of ammonia in ethanol was added. Then, dry THF was added dropwise until all of the starting material was dissolved (~0.8 mL). The yellow mixture was stirred at room temperature for 16 h. After full conversion was reached, as checked by TLC, all volatiles were removed *in vacuo* and the resulting yellow oil was purified by flash chromatography (SiO_2, pentane/EtOAc 40:1 + 1% NEt_3, R_f = 0.85 in pentane/EtOAc 10:1) to yield (*S*)-bis((*S*)-1-(naphthalen-2-yl)allyl)amine **35b** (0.166 g, 0.475 mmol, 95 % yield) as a colourless oil. $[\alpha]_D^{20}$ = -104.6 (c = 1.02, $CHCl_3$) ^1H NMR (200 MHz, $CDCl_3$): δ = 7.97 – 7.81 (m, 6H), 7.77 (s, 2H), 7.62 – 7.40 (m, 6H), 6.26 – 5.90 (m, 2H), 5.33 (t, *J* = 1.4 Hz, 1H), 5.28 – 5.21 (m, 2H), 5.20 – 5.15 (m, 1H), 4.41 (d, *J* = 6.6 Hz, 2H), 3.86 (s (br), 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.80, 140.01, 133.45, 132.85, 128.29, 127.81, 127.63, 126.13, 125.98, 125.64, 125.61, 115.23, 62.28. HRMS-ESI$^+$: *m/z* [M+H]$^+$ calcd for $C_{26}H_{24}N$: 350.1909; found: 350.1901. HPLC analysis: *ee* was determined by HPLC analysis, Chiralpak AD (*n*-heptane/*i*-PrOH 95:5, 215 nm, flow rate 0.5 mL/min), retention times (min.) *S,S*-enantiomer: 4.05, *R,R*-enantiomer: 4.67. The enantiomeric excess was obtained by comparison of both the pure enantiomers as well as a mixture of both enantiomers of **35b**.

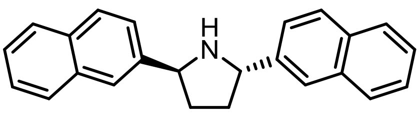
(2*S*,5*S*)-2,5-Di(naphthalen-2-yl)-2,5-dihydro-*1H*-pyrrole 37



37

(*S*)-Bis((*S*)-1-(naphthalen-2-yl)allyl)amine **35b** (1.00 eq., 0.330 g, 0.944 mmol) was dissolved in 10 mL EtOAc at r.t. and 5 mL hydrogen bromide solution (32% in AcOH) was added. After stirring for 5 min, all volatiles were removed *in vacuo* and the yellow oil was dried under vacuum for 16 h to yield a pale yellow solid. This was dissolved in degassed DCE (5.00 mL) and subsequently 2.0 mol% Hoveyda-Grubbs 2nd generation catalyst (0.024 g, 0.038 mmol) in 1 mL of DCE (5.00 mL) were added. This mixture was heated to reflux for 6 h. Then, 2.0 mol% of catalyst were added and the reaction mixture was heated at reflux for 16 hours. The conversion of the reaction was checked by ^{1}H NMR (Samples were washed with 2N aq. KOH and extracted with CH_2Cl_2). After cooling, the mixture was filtered and the resulting brown solid was washed several times with acetone to yield the HBr salt of the desired product **37** as an off-white solid after drying. The resulting organic phase was washed with 2N aq. KOH solution (3x 10 mL). After re-extraction of the aqueous layers with 10 mL CH_2Cl_2, the combined organic phases were dried over Na_2SO_4 and all volatiles were removed *in vacuo* to yield a dark green solid. This was purified by column chromatography (SiO_2, Pentane/EtOAc 20:1 + 1% NEt_3, $R_f = 0.5$ in Pentane/EtOAc 10:1) to yield (2*S*,5*S*)-2,5-di(naphthalen-2-yl)-2,5-dihydro-*1H*-pyrrole **37** (0.240 g, 0.746 mmol, 79 % yield) as a white powder. (Combined yield from column chromatography and filtration). $[\alpha]_D^{20} = -521.25$ (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 – 7.80 (m, 8H), 7.54 (m, 2H), 7.52 – 7.42 (m, 4H), 6.11 (m, 2H), 5.56 (m, 2H), 2.44 (s (br), 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.72, 133.49, 132.91, 132.49, 128.55, 128.36, 127.83, 127.65, 126.64, 126.08, 125.67, 125.32, 125.11, 69.57. HRMS-ESI$^+$: *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}N$: 322.1596; found: 322.1591. HPLC analysis: *ee* was determined by HPLC analysis, Chiralcel OD-H (*n*-heptane/*i*-PrOH 95.5:0.5, 210 nm, flow rate 0.5 mL/min), retention times (min.) *S,S*-enantiomer: 9.47, *R,R*-enantiomer: 10.29. The enantiomeric excess was obtained by comparison of both the pure enantiomers as well as a mixture of both enantiomers of **37**.

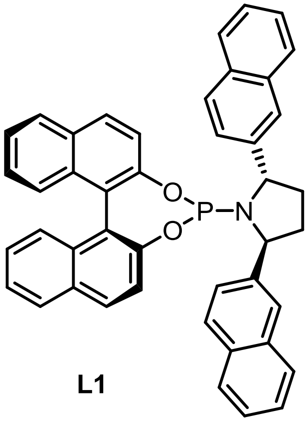
(2*S*,5*S*)-2,5-Di(naphthalen-2-yl)pyrrolidine 26[25]



26

(2*S*,5*S*)-2,5-Di(naphthalen-2-yl)-2,5-dihydro-*1H*-pyrrole **37** (1.00 eq., 0.142 g, 0.442 mmol) (or the corresponding HBr salt) was dissolved in 10 mL CH_2Cl_2 at r.t., an oxygen atmosphere was applied (1 atm) and the reaction mixture was stirred extremely vigourously. Then, via syringe pump, a solution of riboflavin catalyst **44** (0.180 g) in 10 mL ethanol and an excess hydrazine hydrate (4.30 ml, 88.00 mmol) were added over a period of 10 h. The reaction mixture was stirred at rt for 16 h and the progress of the reaction was checked by ^{1}H NMR. (Samples were washed with H_2O and extracted with CH_2Cl_2.) The mixture was washed with water (3x 10 mL), the aqueous layers were reextracted with CH_2Cl_2 (10 mL) and the organic layers combined. After drying over Na_2SO_4, all volatiles were removed *in vacuo* to yield a pale yellow solid. This was purified by column chromatography (SiO_2, pentane/EtOAc 20:1 + 1% NEt_3, R_f = 0.3 in pentane/EtOAc 10:1) to yield (2*S*,5*S*)-2,5-di(naphthalen-2-yl)pyrrolidine **26** (0.116 g, 0.358 mmol, 81 % yield) as a white powder. $[\alpha]_D^{20}$ = -127.9 (c = 0.91, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 – 7.82 (m, 8H), 7.61 (dd, *J* = 8.5, 1.7 Hz, 2H), 7.55 – 7.42 (m, 4H), 4.82 (t, *J* = 6.8 Hz, 2H), 2.66 – 2.46 (m, 2H), 2.39 (s (br), 1H), 2.07 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.16, 133.41, 132.63, 128.29, 127.76, 127.60, 126.03, 125.47, 124.99, 124.50, 62.47, 35.53. HRMS-ESI$^+$: *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}N$: 324.1752; found: 324.1745. HPLC analysis: *ee* was determined by HPLC analysis, Chiralpak AD (*n*-heptane/*i*-PrOH 95:5, 225 nm, flow rate 0.5 mL/min), retention times (min.) *R,R*-enantiomer: 12.33, *S,S*-enantiomer: 15.03. The enantiomeric excess was obtained by comparison of both the pure enantiomers as well as a mixture of both enantiomers of **26**.

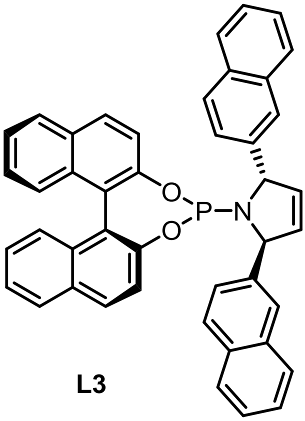
(*S,S,S*)-Phosphoramidite ligand L1[17]



L1

(2*S*,5*S*)-2,5-di(naphthalen-2-yl)pyrrolidine **26** (1.00 eq., 0.085 g, 0.263 mmol), triethylamine (5.00 eq., 0.183 ml, 1.314 mmol) and DMAP (0.01 eq., 3.2 mg, 0.027 mmol) were dissolved in 5 mL toluene and cooled to 0 °C. To this, a 0.5 molar solution of (*S*)-phosphochloridite **45** (1.20 eq., 0.631 ml, 0.315 mmol) was added dropwise. The reaction was allowed to warm up to room temperature and stirred for 16 h. Then, all volatiles were removed *in vacuo* and the residual off-white solid was purified by column chromatography. (SiO_2, Pentate / EtOAc 10:1 + 1% NEt_3, R_f = 0.9 in pentane / EtOAc 10:1) to yield phosphoramidite **L1** (0.100 g, 0.157 mmol, 60% yield) as a white powder. $[\alpha]_D^{20}$ = -6.2 (c = 0.86, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.79 (m, 10H), 7.56 (m, 5H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.29 (m, 3H), 7.25 – 7.15 (m, 2H), 7.11 (m, 2H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.87 (d, *J* = 8.0 Hz, 1H), 5.39 (d, *J* = 6.6 Hz, 2H), 2.54 (m, 2H), 1.81 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.48, 149.04, 143.39, 143.29, 133.43, 132.75, 131.25, 130.19, 129.89, 128.26, 127.99, 127.70, 127.06, 126.94, 126.24, 125.70, 125.41, 125.22, 124.58, 123.98, 121.91, 120.84, 62.86, 33.23. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = 145.98. HRMS-APCI$^+$: *m/z* $[M+H]^+$ calcd for $C_{44}H_{33}NO_2P$: 638.2249; found: 638.2245.

(*S,S,S*)-Phosphoramidite ligand L3



L3

(2*S*,5*S*)-2,5-Di(naphthalen-2-yl)-2,5-dihydro-1H-pyrrole **37** (1.0 eq. 0.065 g, 0.202 mmol) was dissolved in toluene (2 ml) and cooled to -78 °C. Then, 1.0 eq. *n*BuLi (0.126 ml, 0.202 mmol) solution (c = 1.6 M) was added slowly. The reaction mixture was stirred at –78 ° for 2 h, then the lithium amide solution was added to a solution of (S)-phosphorchloridite **45** (0.485 ml, 0.243 mmol) in toluene (10 mL), which was cooled to 0 °C. The mixture was stirred overnight and was allowed to warm up to rt. Subsequently, the reaction mixture was filtered through celite and all volatiles were removed *in vacuo* to yield the crude product as a yellow solid. This was purified by column chromatography (SiO_2, pentane / EtOAc 20:1 + 1% NEt_3, R_f = 0.9 in pentane / EtOAc 10:1) to yield **L3** (0.050 g, 0.079 mmol, 39%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.78 (dd, *J* = 8.7, 5.5 Hz, 4H), 7.61 – 7.42 (m, 12H), 7.32 – 7.17 (m, 6H), 6.21 (d, *J* = 8.8 Hz, 1H), 6.04 (s, 2H), 5.99 (d, *J* = 8.7 Hz, 1H), 5.86 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.29, 133.52, 133.09, 132.00, 131.24, 131.05, 130.08, 128.69, 128.46, 128.12, 127.93, 127.66, 127.62, 127.14, 126.63, 126.49, 126.21, 126.10, 125.76, 125.70, 125.56, 125.14, 124.56, 123.68, 123.14, 121.87, 120.98, 69.98. ^{31}P NMR (162 MHz, $CDCl_3$) δ 145.22. $[\alpha]_D^{20}$ = -12.4 (c = 0.77 in $CHCl_3$). HRMS-ESI$^+$: *m/z* $[M+H]^+$ calcd for $C_{44}H_{31}NO_2P$: 636.2105; found: 636.2105.

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Chapter 3

Iridium-catalyzed Allylic Amidation - Asymmetric Synthesis of Tetrahydroisoquinolines and Saturated *N*-Heterocycles

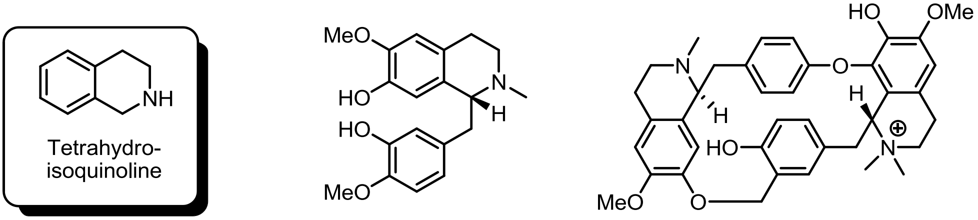
The first intramolecular asymmetric Ir-catalyzed allylic amidation has been developed. Using this transformation, the asymmetric synthesis of chiral nitrogen-containing heterocycles, especially tetrahydroisoquinolines is achieved in excellent yields and enantioselectivities. The products are important chiral building blocks for the synthesis of biologically active products, in particular alkaloids.

Parts of this chapter have been published: Teichert, J.F.; Fañanás-Mastral, M.; Feringa, B.L. *Angew. Chem. Int. Ed.* **2011**, *123*, 714 - 717.

1 Introduction

1.1 Tetrahydroisoquinolines

Naturally occuring or synthetic compounds based on the bicyclic tetrahydroisoquinoline core are a large class of compounds which often show interesting biological activities.[1,2] As examples, Reticuline (**1**) and Tubocurarine (**2**) are depicted (Figure 1). Reticuline is an alkaloid found in the latex of opium poppy; it has recently been suggested that it is one of the intermediates for the *in vivo* biosynthesis of morphine, indicating that it is an important compound related to intercellular signalling.[3,4] Tubocurarine (**2**) is found in the plant extracts of the climbing plant *Chondrodendron tomentosum* which has been used by South American natives as arrow poison.[1] It has been used since the 1970s as anaesthetic and **2** and derivatives thereof are in use today as highly active[5] neuromuscular blocking muscle relaxants.[6,7]

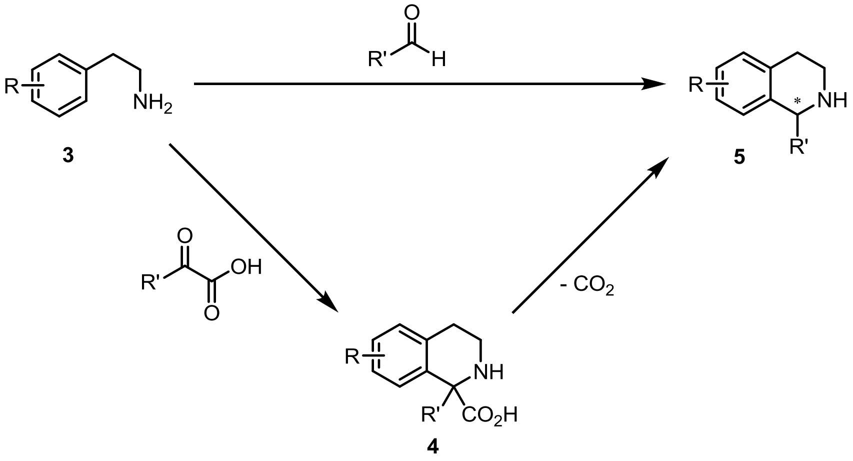


Reticuline (**1**)
Opiate

Tubocurarine (**2**)
Muscle relaxant and
anaesthetic

Figure 1 Examples of biologically active chiral tetrahydroisoquinolines

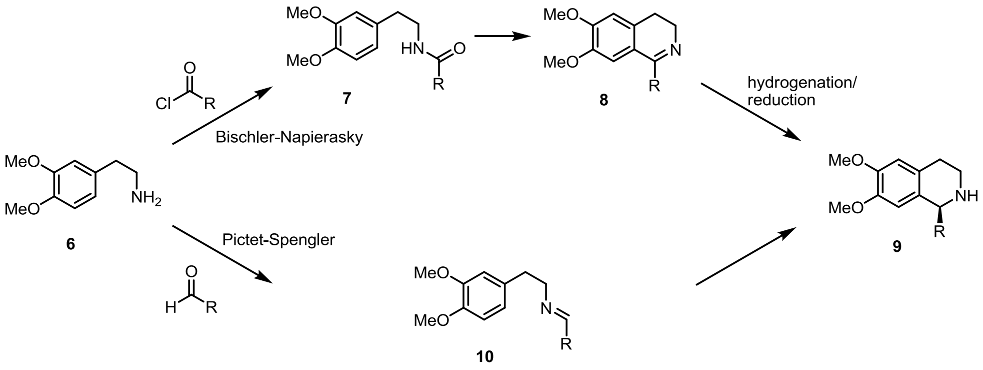
In living organisms, the tetrahydroisoquinoline core is constructed via two closely related pathways, employing a Mannich-type or Pictet-Spengler-type reaction (Scheme 1):[1] Phenylethylamine precursors **3**, derived from tyrosine, are transformed to tetrahydroisoquinolines **5** either by direct condensation with an aldehyde to form **5** directly, or via the second pathway employing α-ketoacids, that runs via amino acid intermediates **4** followed by decarboxylation to yield **5**. Both pathways have been found in nature, and generally more sophisticated substitutents (R') like aryl groups are introduced as the corresponding aldehydes, whereas simpler substituents like H or Me are usually incorporated to the target structures **5** via the ketoacids.



Scheme 1 Biosynthesis of tetrahydroisoquinolines

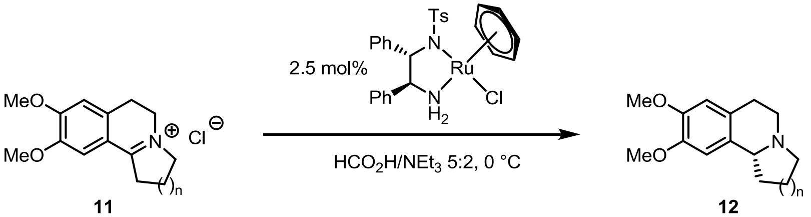
1.2 Synthetic approaches to chiral tetrahydroisoquinolines

Tetrahydroisoquinoline compounds represent important targets for synthesis, and therefore much effort has been directed towards the development of efficient enantioselective routes to prepare these important chiral structures.[8-13] Generally, the approaches taken from the phenylethylamine **6** follow two distinct routes, mimicking nature's approach to the same compounds.[8] The first is via Bischler-Napieralsky cyclization of amides **7** followed by hydrogenation/reduction of the resulting iminium ion **8** to **9** and the second is by Pictet-Spengler condensation reactions of **6** with aldehydes to give **9** (Scheme 2). It should be noted that the Pictet-Spengler reaction gives better results when electron-rich aromatic compounds are employed. The Bischler-Napieralksy reaction, on the other hand, has a broader scope in this regard. Although a variety of enantioselective methods using the former approach are known, a general asymmetric Pictet-Spengler reaction to generate tetrahydroisoquinolines with high yields and enantioselectivities is not known so far.[8]



Scheme 2 General synthetic approaches to tetrahydroisoquinolines

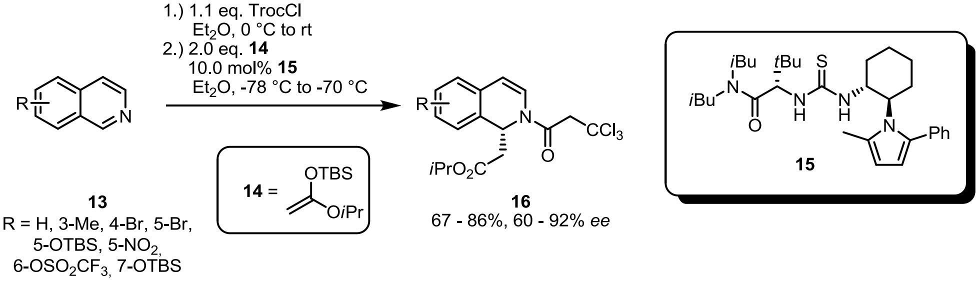
Some of the reported strategies will be discussed briefly. One approach to chiral tetrahydroisoquinolines is based on an asymmetric Ru-catalyzed transfer hydrogenation of cyclic iminium ions – products of the Bischler-Napieralsky reaction - giving tetrahydroisoquinolines **12** bearing unfunctionalized 5- or 6-membered rings.[14,15] In this case, iminium ion **11** can be converted to the corresponding chiral isoquinoline **12** (n = 1, Crispine A – vide infra) in very good yields and enantioselectivities (Scheme 3). For the asymmetric transfer hydrogenation, a Ru catalyst based on a chiral diamine was employed.



n = 1: 91%, 92% *ee*
n = 2, 97%, 87% *ee*

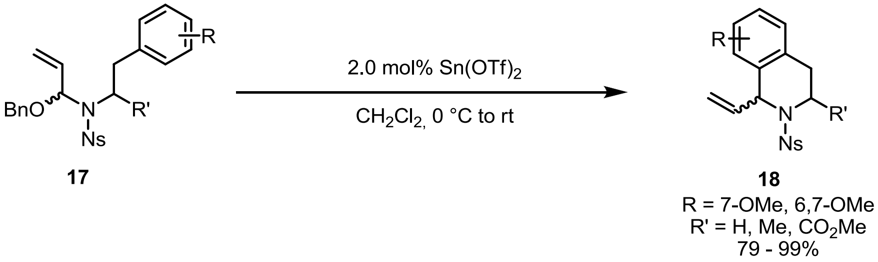
Scheme 3 Asymmetric transfer hydrogenation

An acyl-Mannich reaction to construct the related chiral dihydroisoquinolines **16** has recently been described.[16] With chiral thiourea **15** in 10 mol% loading, the conversion of quinolines **13** with silyl enolether **14** to the desired chiral products **16** proceeds with generally very good yields and enantioselectivities. It has to be noted, though, that the temperature plays a critical role in this transformation and has to be carefully controlled to achieve the reported results, certainly a downside in terms of applicability. To reach the envisaged tetrahydroisoquinolines, one further reduction/hydrogenation step has to be carried out.


1.) 1.1 eq. TrocCl
Et$_2$O, 0 °C to rt
2.) 2.0 eq. **14**
10.0 mol% **15**
Et$_2$O, -78 °C to -70 °C
R
N
13
R = H, 3-Me, 4-Br, 5-Br,
5-OTBS, 5-NO$_2$,
6-OSO$_2$CF$_3$, 7-OTBS
14 =
OTBS
O*i*Pr
R
N
CCl$_3$
O
*i*PrO$_2$C
16
67 - 86%, 60 - 92% *ee*
*i*Bu
*t*Bu
S
N
*i*Bu
O
N
H
N
H
N
Ph
15

Scheme 4 Asymmetric acyl-Mannich reaction

A Lewis acid-catalyzed aromatic cyclization of allylamines **17** was reported.[17] This transformation gives rise to the corresponding *N*-protected tetrahydroisoquinolines **18** with a terminal double bond as substituent in up to excellent yields. These compounds are valuable building blocks with a variety of possibilities for further functionalization. The substituent R' in the α-position to the nitrogen atom was found to have little influence on the diastereoselectivity. It is important to note that for this transformation, only electron-rich aromatic compounds **17** are converted to the desired products **18**. If R = Me, no turnover was found under a number of cyclization conditions. This marks an important downside of this method and the related Pictet-Spengler reaction[8] which requires activated aromatic compounds for the ring-closing to occur.


R
BnO
N
R'
Ns
17
2.0 mol% Sn(OTf)$_2$
CH$_2$Cl$_2$, 0 °C to rt
R
N
R'
Ns
18
R = 7-OMe, 6,7-OMe
R' = H, Me, CO$_2$Me
79 - 99%

Scheme 5 Lewis-acid catalyzed aromatic cyclizations

2 Goal

The aim of this research was to develop a transition-metal based catalytic asymmetric approach to chiral tetrahydroisoquinolines. It should be general in terms of substrate scope and thus independent of the electronic parameters of the aromatic system. In this manner, problems associated with the widely-used Pictet-Spengler reaction should be overcome. Ideally, this approach to chiral nitrogen-containing heterocycles should be general and not be limited to tetrahydroisoquinolines alone or 6-membered *N*-heterocycles. Needless to say, the formation of both enantiomers should be feasible with high selectivity. We envisaged that an allylic substitution protocol should be able to fulfill all of the above prerequisites. Furthermore, it would furnish a stereogenic center bearing a terminal double bond, which is an ideal starting point for further synthesis. As the last requirement, if an *N*-protecting group had to be employed, it should be easily removable.

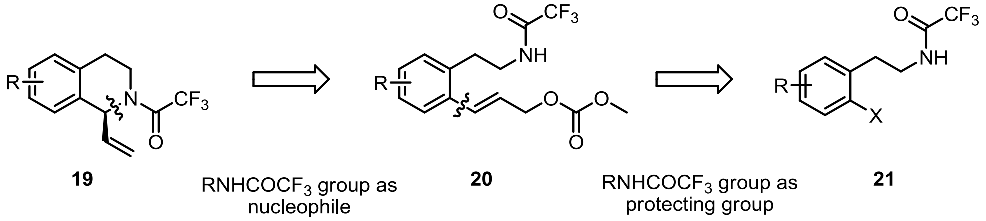
3 Results and Discussion

From related studies on β-carboline compounds (see Chapter 4), it was clear that the direct allylic amination approach was not viable, *i.e.* making use of an unprotected ethylamine moiety and employing it as nucleophile for the intramolecular allylic amination. We instead chose to employ a nitrogen-based functional group that could act both as the nucleophile for the allylic substitution as well as acting as a protecting group during the preparation of the desired starting material. As a third requirement, the protecting group should be easily removed after installation of the tetrahydroisoquinoline structure. We therefore chose the (trifluoro)acetamide as a nucleophile/protecting group for our approach.

The Ir-catalyzed asymmetric allylic substitution[18-23] with phosphoramidites[24-28] as chiral ligands represents powerful synthetic methodology which has found application in many natural product syntheses.[18,24] One major advantage of the asymmetric iridium-catalyzed allylic substitution is its tolerance towards a large variety of nucleophiles, including ammonia.[29-33] Amides as nucleophiles for these transformations have only been reported in the case of potassium trifluoroacetamide as ammonia surrogate[29] or in allylic amidation reactions via decarboxylative pathways.[34,35] Apart from the aforementioned literature precedents, a general, highly selective allylic amidation had not been developed, therefore we chose to investigate the Ir-catalyzed allylic amidation for the synthesis of tetrahydroisoquinolines. Employing iridium catalysts would enable us to work at ambient temperatures with a well-understood, but still tunable catalyst system.

3.1 Synthetic approach

To synthesize the envisaged starting materials **20** for the allylic amidation, *i.e.* phenylethylamines bearing an *ortho*-allylic carbonate substituent, the approach taken was to make use of a Pd-catalyzed cross-coupling reaction to install the allylic alcohol moiety (Scheme 6). For this, 2-iodo or 2-bromo phenylethylamine derivatives **21** had to be prepared, which could subsequently be cross-coupled to an appropriate organometallic compound. It turned out that the preparation of the 2-halophenylethylamines **21** represented the bottleneck of the synthesis, since selective *ortho*-halogenation with both electron-rich and –deficient aromatics cannot be achieved via a single methodology. Thus, one of the limitations of the scope for the preparation of tetrahydroisoquinolines via Ir-catalyzed allylic amidation as described in this chapter turned out to be the preparation of the corresponding halogenated starting materials (*vide infra*).


R
N
CF3
O
19
RNHCOCF3 group as nucleophile
O
CF3
NH
R
O
O
O
20
RNHCOCF3 group as protecting group
O
CF3
NH
R
X
21

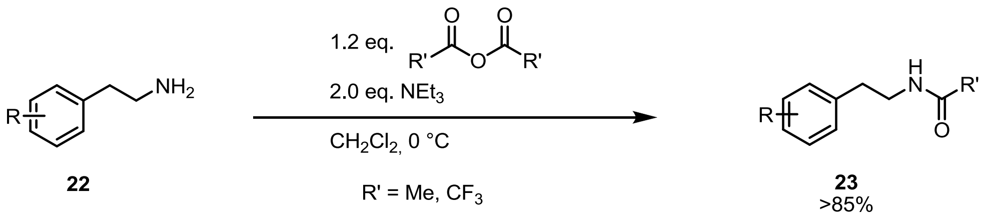
Scheme 6 Retrosynthetic approach

As mentioned before, the usefulness of the trifluoroacetamide group in the selected synthetic approach is twofold. First it serves as protecting group during the synthesis of the allylic carbonates **20**, whose key step relies on a Pd-catalyzed cross-coupling reaction to introduce the allylic moiety (Scheme 6). Here, unprotected amines are generally not accepted. Second, amide **20** serves as the actual nucleophile of the Ir-catalyzed allylic substitution, which furnishes the tetrahydroisoquinoline core **19**. An important property of the trifluoroacetamide group is that the secondary amine moiety could easily be deprotected without jeopardizing the adjacent sensitive allylic-benzylic stereocentre. This is a major advantage over *N*-protecting groups which have to be removed by hydrogenolysis,[36,37] or other harsh conditions that could endanger racemization-sensitive stereocenters.[38-48]

3.2 Synthesis of starting materials

Synthesis of the 2-halophenylethylamine derivatives

First, the commercially unavailable *ortho*-halophenylethylamine derivatives had to be synthesized. The protection of the primary amines **22** to the corresponding (trifluoro)acetamides **23** with the appropriate anhydrides was carried out (Scheme 7).

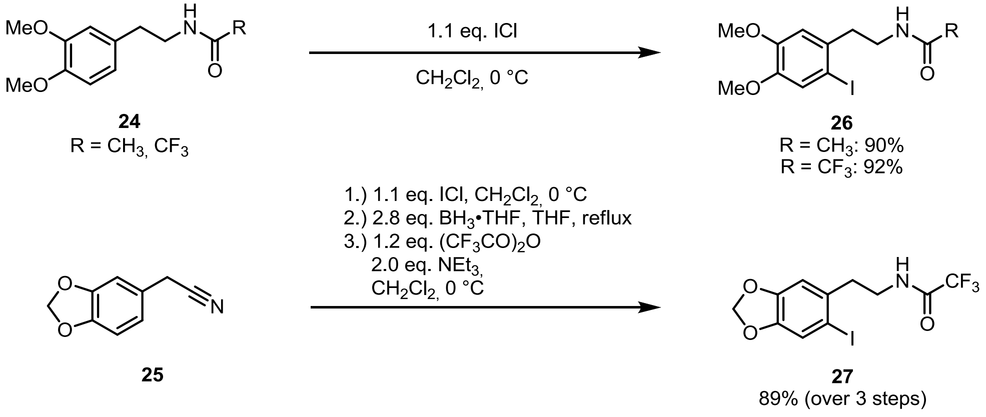


22

23
>85%

Scheme 7 Preparation of (trifluoro)acetamides 23

The choice of the appropriate iodination method was crucial with for a high yielding and regioselective transformation. With electron-rich (trifluoro)acetamides **24** , simple iodination with the electrophilic reagent ICl could be achieved according to literature procedures[49] yielding the desired *ortho*-iodophenylethylamides **26** with high yields and complete regioselectivity (Scheme 8). The preparation of **27** was carried out according to a literature procedure,[50] starting from the commercially available nitrile **25**, which was converted to **27** through a iodination/reduction/protection protocol in good yield.


MeO
MeO
H
N
R
O
1.1 eq. ICl
CH$_2$Cl$_2$, 0 °C
I
1.) 1.1 eq. ICl, CH$_2$Cl$_2$, 0 °C
2.) 2.8 eq. BH$_3$•THF, THF, reflux
3.) 1.2 eq. (CF$_3$CO)$_2$O
2.0 eq. NEt$_3$,
CH$_2$Cl$_2$, 0 °C
N
CF$_3$

24
R = CH$_3$, CF$_3$

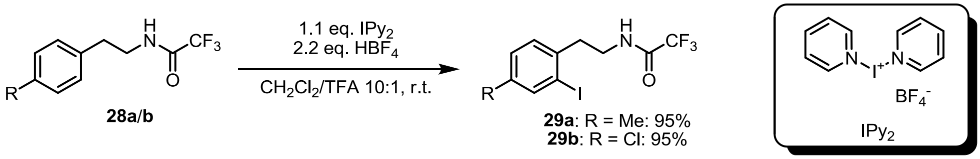
26
R = CH$_3$: 90%
R = CF$_3$: 92%

25

27
89% (over 3 steps)

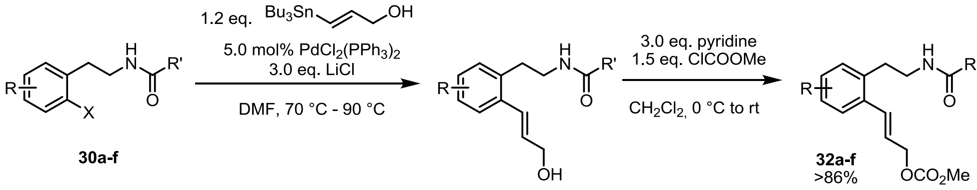
Scheme 8 Iodination of electron-rich phenylethylamines[49,50]

However, iodination of *para*-tolylphenylethyltrifluoroacetamide **28a** could not be carried out in a selective fashion according to the same approach due to lack of regioselectivity of the aromatic substitution, which can be attributed to the lower electron density of the aromatic ring. The same holds true for the *para*-chloro derivative **28b**. For the selective *ortho*-iodination of those two compounds, an iodination protocol employing bis(pyridine)iodonium tetrafluoroborate (IPy$_2$)[51] was employed (Scheme 9).[52] The corresponding iodides **29** were obtained with excellent yields and regioselectivities. Finally, for the unsubstituted phenylethylamine derivative **30f** (see Scheme 10), the trifluoroacetamide-derivative of the commercially available bromide was used for the subsequent cross-coupling reaction.



Scheme 9 Selective Iodination with IPy$_2$

To prepare the corresponding allylic alcohols **31**, a Stille coupling reaction[53] with *E*-tributylstannylpropenol[54] with 5.0 mol% Pd catalyst was carried out at 70 °C (Scheme 10). This coupling method was found to be the highest yielding and most reliable coupling protocol, as established in preliminary studies (see also chapter 4). Iodides **30** were smoothly converted to the allylic alcohols **31** in high yields, an exception being the electron poor *para*-chloro compound **31e**, with 51% isolated yield. In the case of the bromo-phenylethyltrifluoroacetamide with no further substituents on the aromatic ring, a slightly elevated temperature of 90 °C had to be used to achieve full conversion to the desired product. Already at this stage the detrimental performance of the acetamide protection group in comparison to the trifluoroacetamide group was visible, since the acetamide-protected allylic alcohol **31f** was isolated in substantially lower yield, due to the (unexpected) considerably higher polarity and subsequent difficult purification. This general trend is visible through the following transformations, further supporting the choice of trifluoroacetamide as the protecting group. Conversion of the allylic alcohols **31** to the corresponding carbonates **32** with methyl chloroformate proceeded in high yields.

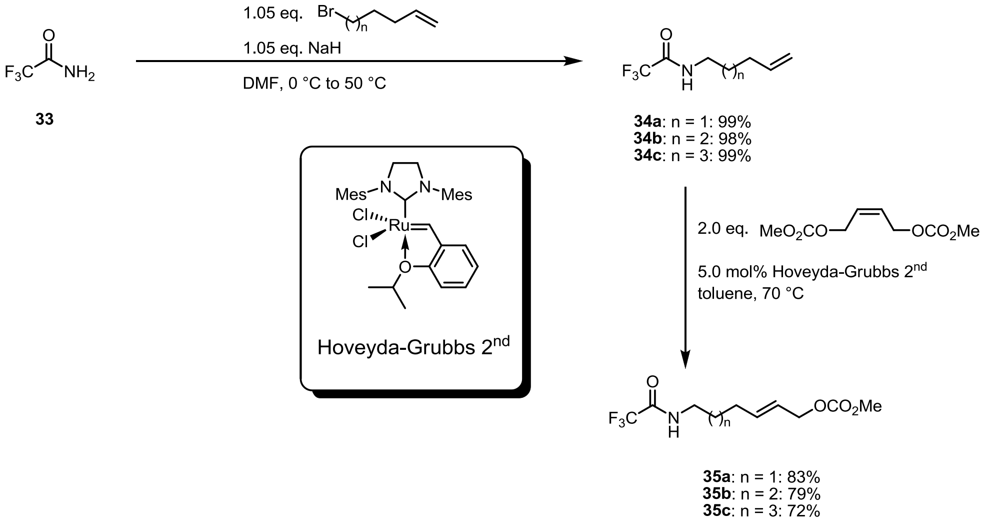


31a: R = 4,5-OMe, R' = CF$_3$: 83%
31b: R = 4,5-OCH$_2$O-, R' = CF$_3$: 78%
31c: R = 4-Me, R' = CF$_3$: 72%
31d: R = H, R' = CF$_3$: 79% (X = Br)
31e: R = 4-Cl, R' = CF$_3$: 51%
31f: R = 4,5-OMe, R' = CH$_3$: 30%

Scheme 10 Stille coupling and transformation to allylic carbonates

Synthesis of the linear allylic carbonates

The synthesis of the linear allylic carbonates for the allylic amidation to give saturated *N*-heterocycles is straightforward (Scheme 11). Trifluoroacetamide (**33**) was alkylated with bromoalkenes of varying chain lengths to give the corresponding terminal alkenes **34** in excellent yields. Alkenes **34** were subsequently transformed to the allylic carbonates **35** by cross-metathesis with Z-butenediyl methyl carbonate in good yields,[31] employing Hoveyda-Grubbs 2nd generation catalyst (Scheme 11).[55] It is important to note that for the latter reaction to occur in high yields, elevated temperatures of 70 °C were necessary. Reactions in refluxing CH_2Cl_2 gave low conversions to the corresponding carbonates **35**.


1.05 eq. Br
n
1.05 eq. NaH
DMF, 0 °C to 50 °C
F3C NH2
O
33
F3C N H
n
34a: n = 1: 99%
34b: n = 2: 98%
34c: n = 3: 99%
2.0 eq. MeO2CO OCO2Me
5.0 mol% Hoveyda-Grubbs 2nd
toluene, 70 °C
Mes N N Mes
Cl Ru
Cl
O
Hoveyda-Grubbs 2nd
OCO2Me
35a: n = 1: 83%
35b: n = 2: 79%
35c: n = 3: 72%

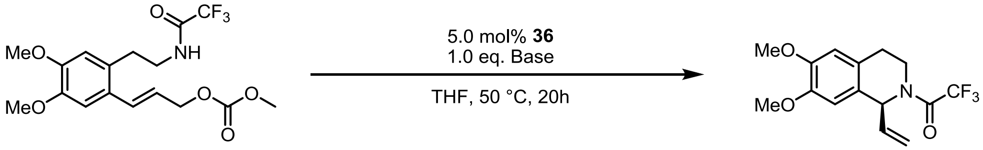
Scheme 11 Preparation of linear allylic carbonates

3.3 Catalyst optimization

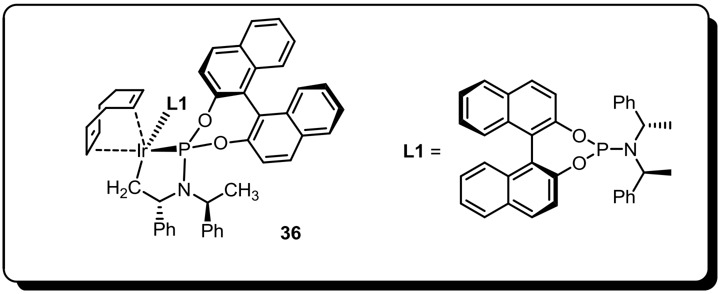
Base screening

One of the most influential components of the Ir-catalyzed allylic amidation turned out to be the base. Not only were substantial changes in the conversion of the benchmark substrate **32a** observed, but the base proved to be highly influential in terms of enantioselectivity. Compound **32a** was chosen as the starting point of the investigation since the 4,5-dimethoxy substitution of **37a** is very common in naturally occuring tetrahydroisoquinoline alkaloids, but also it served as a point of comparison to the related Pd-based catalytic systems.[13,49] We set off to investigate the influence of various bases on the catalytic system, which was comprised of preformed iridacycle **36** in THF at 50 °C (Table 1).[20] In **36**, two phosphoramidite ligands are bound to the Ir, one in a κ[1] fashion via the P atom and one in a κ[2] fashion, where both a P and a C atom coordinate to Ir to form a five-membered iridacycle. DBU gave 70% conversion and 81% *ee* (Table 1, entry 1). With catalytic amounts of DBU the same enantioselectivity was found, however the reactions did not achieve full conversion to **37a**. Other related organic bases such as TBD and DABCO (see Table 1), which had been reported earlier in combination with Ir catalysts for allylic substitutions[56,57] led to significantly lower or no conversion and low enantioselectivities (Table 1, entries 2,5). In the case of TBD, the starting material was recovered (Table 1, entry 2). Inorganic bases such as K_3PO_4 and Cs_2CO_3 (Table 1, entries 3,4) performed similarly disappointing with regard to conversion and enantioselectivities.

Table 1 Base Screening[a]



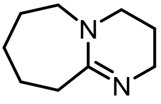
32a **37a**



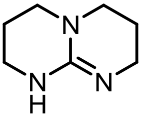
Entry	Base	Conversion[b]	*ee*[c]
1	DBU[d]	70%	81%
2	TBD[e]	n.d.	n.d.
3	K_3PO_4	10%	19%
4	Cs_2CO_3	15%	22%

Entry	**Base**	**Conversion**[b]	***ee***[c]
5	DABCO[f]	10%	31%

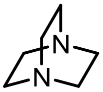
[a] Reaction conditions: 1.0 eq. **32a** (16.9 mg, 0.05 mmol), 5.0 mol% **36** (3.45 mg, 0.0025 mmol) and 1.0 eq. base (0.05 mmol) were dissolved in 1 mL THF and stirred under a N_2 atmosphere at 50 °C for 20 h. [b]Determined by HPLC. [c]Determined by chiral HPLC, see experimental section. [d]1,8-Diazabicyclo[5.4.0]undec-7-ene. [e]1,5,7-Triazabicyclo[4.4.0]dec-5-ene. [f]1,4-Diazabicyclo[2.2.2]octane**.**



DBU



TBD



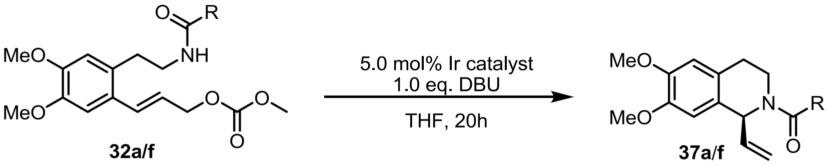
DABCO

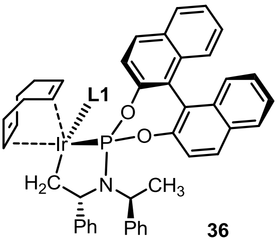
From these results it became clear that the base plays a crucial role for the performance of the catalyst with regard to both turnover as well as stereodiscrimination. This seems to be in contrast with some of the previously reported allylic amination protocols which work well without a base (apart from the catalytic amounts of base necessary for the activation of the catalyst).[20,23,57] In those cases, the alkoxide leaving group acts as an additional base to neutralize the protons of the nucleophile. One could speculate that the positively charged counterion that is formed by protonation of the base could have an influence on the allylic substitution, possibly due to a coordinating and thus activating effect of the leaving group or the nucleophile. Additional studies are clearly needed to elucidate the role of the base in allylic substitutions with iridacycles as catalysts.

Catalyst optimization

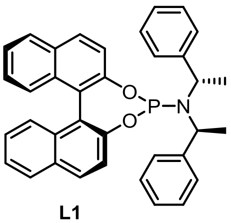
Further investigations to improve the catalytic allylic amidation were carried out. With preformed iridacycle **36** at elevated temperatures (50 °C) the reaction did not reach full conversion overnight, and the desired tetrahydroisoquinoline **37a** could be isolated in only 33% yield (Table 2, entry 1). However, we were delighted to find that an *in situ* formed iridacycle, prepared from catalytic amounts of phosphoramidite ligand **L1** and $[Ir(COD)Cl]_2$, showed a higher activity and led to full conversion (73% yield) under the same conditions (Table 2, entry 2) with similar enantioselectivities (83% *ee*). This effect could be explained by the fact that in preformed catalyst **36**, the κ^1-phosphoramidite has to decoordinate to liberate a coordination site for the intermediate Ir-allyl species[22,58,59] to form. In the case of the *in situ* prepared iridacycle, only one equivalent of phosphoramidite ligand **L1** with respect to the iridium is present, so that the last coordination site of the catalyst is most probably occupied by a solvent molecule, in our case THF. This is expected to dissociate more quickly, giving rise to a much more active catalyst. One would hypothesize that the enantioselectivity should remain the same for both catalysts, since the ligand staying on the Ir atom stays the same, which is in accordance to our observations (Table 2, entries 1,2). It has been established earlier that it is the stereogenic center of the iridacycle that governs the stereodiscrimination of the transformation.[60] Lowering the temperature (RT) did not affect the enantioselectivity but again resulted in incomplete conversion (Table 2, entry 3). Turning to the related, methoxy-substituted phosphoramidite **L2**,[61] we found the product of the intramolecular asymmetric allylic amidation in excellent enantioselectivities (95% *ee*), with an even higher yield observed at room temperature (Table 2, entries 4,5). The *ortho*-methoxy substitution of **L2** clearly has a remarkable effect on the transformation. However, it is not established whether this effect has its origin in a possible additional coordination, changes in the electronic properties or steric effects of ligand **L2**. Particularly noteworthy is the fact that when the corresponding acetamide was subjected to the optimized reaction conditions, no allylic amidation occurred even at elevated temperatures (Table 2, entry 6), indicating that trifluoroacetamides possess ideal electronic and/or acidic requirements for the asymmetric transformation envisaged.

Table 2 Catalyst optimization[a]

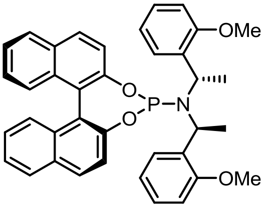




36



L1



L2

Entry	R	Catalyst	Temp.	Yield[b]	*ee*[c]
1	CF_3 (**32a**)	**36**	50 °C	33%[e]	81%
2	CF_3 (**32a**)	Ir/**L1**[d]	50 °C	73%	83%

3	CF_3 (**32a**)	Ir/**L1**[d]	RT	55%[e]	80%
4	CF_3 (**32a**)	Ir/**L2**[d]	50 °C	82%	94%
5	CF_3 (**32a**)	Ir/**L2**[d]	**RT**	**90%**	**95%**
6	CH_3 (**32f**)	Ir/**L2**[d]	50 °C	n.d.	n.d.

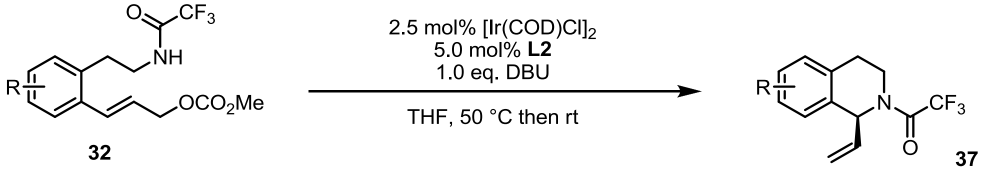
[a]Reaction conditions: 1.0 eq. **32a** or **32f** (0.05 mmol), 5.0 mol% Ir catalyst (0.0025 mmol) and 1.0 eq. DBU (8 µL, 0.05 mmol) were dissolved in 1 mL THF and stirred under a N_2 atmosphere at the indicated temperature until TLC showed full conversion. [b]Isolated yields. [c]Determined by HPLC, see experimental section. [d]See Experimental section. [e]Reaction did not reach full conversion.

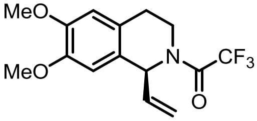
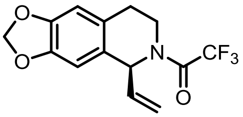
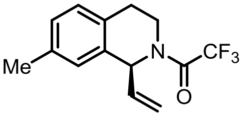
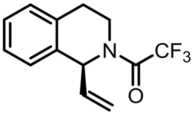
3.4 Substrate scope

Tetrahydroisoquinolines

To probe the substrate scope of the catalytic system, a collection of chiral tetrahydroisoquinolines were prepared, posessing the most common substitution patterns of natural products (Table 3).[1,2] Tetrahydroisoquinolines with donor substituents, such as methoxy-, dioxo- as well as methyl groups **37a-c** (Table 3, entries 1-3) were all obtained in very good yields and with excellent enantiomeric excesses ranging from 91 - 95%. Furthermore, the unsubstituted tetrahydroisoquinoline **37d** (Table 3, entry 4) could be isolated with similarly good results (78%, 94% *ee*). The reactions could be scaled up to 1 mmol scale with the same results in terms of yields and enantioselectivities. The absolute configuration of the products was established by comparison of the sign of the optical rotation of **37a** to earlier studies.[13] The absolute configurations of the other products **37** were assigned accordingly.

Table 3 Substrate Scope Tetrahydroisoquinolines[a]

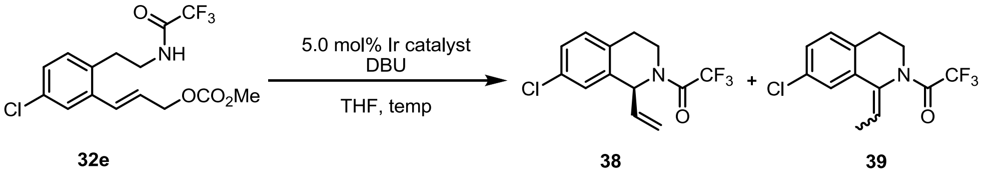


Entry	Product		Temp.	Yield[b]	*ee*[c]
1		**37a**	rt	97%	95%
2		**37b**	rt	89%	94%
3		**37c**	rt	92%	91%
4		**37d**	rt	78%	94%

[a] See experimental section. [b] Isolated yields. [c] Determined by HPLC, see experimental section.

With chloro-substituted substrate **32e**, unexpected results were obtained when the Ir-catalyzed allylic amidation was attempted (Table 4). Under optimized reaction conditions (Table 4, entry 1), full conversion was observed overnight, but as the sole product the isomerized enamide **39** was isolated as a mixture of E and Z double bond isomers. The same outcome was found with a catalyst prepared from the related phosphoramidite ligand **L1** (Table 4, entry 2), albeit with slightly lower conversion, reflecting the same trends in terms of activity as found earlier. To probe whether the base had an influence on the double-bond isomerization, the reaction was carried out at ambient temperature with only catalytic amounts of DBU, which had led to lower conversion in the previously studied cases. In the case of substrate **32e**, however, full conversion to the unwanted enamide **39** was observed (Table 4, entry 3). Preformed iridacycle **36** led to no conversion of the allylic carbonate **32e**, independent of the presence of base (Table 4, entries 4,5). In previous studies of Ir-catalyzed asymmetric allylic etherifications, a similar effect of double bond isomerization had been observed.[62] In that case, the addition of catalytic amounts of phenylpropyne to the catalyst had been shown to prevent the unwanted isomerization from occuring. When we carried out the allylic amidation in the presence of catalytic amounts of phenylpropyne (Table 4, entry 6), still the same complete isomerization to enamide **39** was observed. It can be speculated that the electronic parameters of the substrate enabled the unwanted isomerization to take place, this would then represent a limitation of this catalytic transformation.

Table 4 Ir-catalyzed allylic amidation of 32e

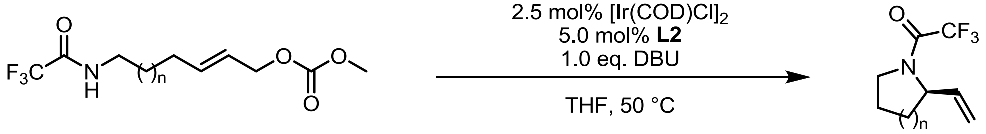


Entry	Conditions	38/39	Conversion	*ee*
1	2.5 mol% $[Ir(COD)Cl]_2$ 5.0 mol% **L2**, 2.0 eq. DBU, 50 °C	0/100	Full (63% yield)	n.d.
2	2.5 mol% $[Ir(COD)Cl]_2$ 5.0 mol% **L1**, 2.0 eq. DBU, 50 °C	0/100	80% (32% yield)	n.d.
3	2.5 mol% $[Ir(COD)Cl]_2$ 5.0 mol% **L2**, 10 mol% DBU, rt	0/100	full	n.d.
4	5.0 mol% **36** (preformed), 50 °C	-	none	n.d.
5	5.0 mol% **36** (preformed) 2.0 eq. DBU, 50 °C	-	none	n.d.
6	2.5 mol% $[Ir(COD)Cl]_2$ 5.0 mol% **L2** 20 mol% phenylpropyne 2.0 eq. DBU, 50 °C	0/100	Full	n.d.

Saturated N-heterocycles

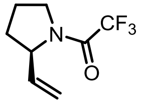
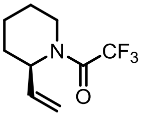
The methodology of the asymmetric intramolecular allylic amidation could be extended to the synthesis of other chiral nitrogen-containing heterocycles. This shows the generality of this transformation, which is not limited to substrates bearing aromatic rings in the backbone. Along these lines, 5-, 6- and 7-membered chiral heterocycles **40a-c** could be synthesized (Table 5, entries 1 – 3). For these reactions to proceed smoothly, elevated temperatures of 50 °C were required to ensure full conversion. At room temperature, the reactions proceeded with the same outcome in terms of enantioselectivity, but with about 50% conversion. The reason that in the earlier case of the tetrahydroisoquinolines a lower temperature was sufficient for full conversion could be explained by the *ortho*-substitution of both the nucleophile as well as the allyl carbonate on the phenyl ring. In this case, the two reaction partners are spatially already closer to each other and less energy is necessary for the molecule to adopt a conformation that is beneficial for the allylic amidation to take place. This phenomenon is known in literature under the name “steric compression”.[63] In all cases of the saturated heterocycles, however, very good to excellent enantioselectivities (up to 96% *ee*) were found, demonstrating the versatility of our new catalytic transformation. The actual yields of the products **40a** and **40b** are low due to their volatilty, however, full conversion to the desired heterocycles **40** could be established by ^{1}H NMR analysis of the crude reaction mixture.

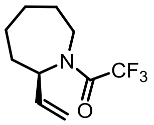
Table 5 Substrate scope saturated *N*-heterocycles[a]



35a-c
n = 1-3

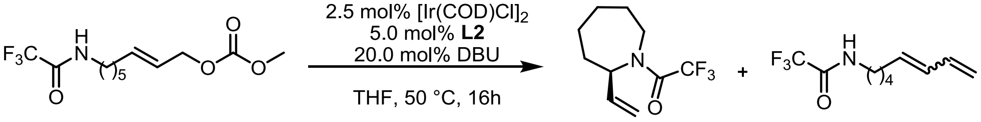
40a-c

Entry	Product		Yield[b]	*ee*[c]
1		**40a**	56%[d, e]	96%
2		**40b**	68%[d, e]	88%

Entry	Product		Yield[b]	*ee*[c]
3[f]		**40c**	25%[d, e]	92%

[a]See experimental section. [b]Isolated yields. [c]Determined by HPLC, see experimental section. [d]Products are volatile. [e]100% conversion, determined by ^{1}H NMR. [f]A side reaction was observed, see Scheme 12.

Noteworthy is the fact that when the synthesis of chiral azepane **40c** was investigated (Table 5, entry 3), an unexpected side reaction occurred. When allylic carbonate **35c** was reacted under allylic amidation conditions at 50 °C, chiral azepane **40c** was found along with linear diene **42** as the major product (Scheme 12). The product distribution seemed to be independent of temperature (*i.e.* the same outcome was observed at room temperature) and amount of DBU employed. This side reaction was only observed for **40c** and not in the synthesis of piperidine **40b** or pyrrolidine **40a**, indicating that the mechanism of the formation of the 7-membered ring requires special spatial constraints. Therefore, the formation of the azepane is slower and the intermediate Ir-allyl species can react further in via other pathways. In the absence of the Ir-catalyst, no reaction was observed, indicating that the Ir catalyst is essential for this transformation to take place.



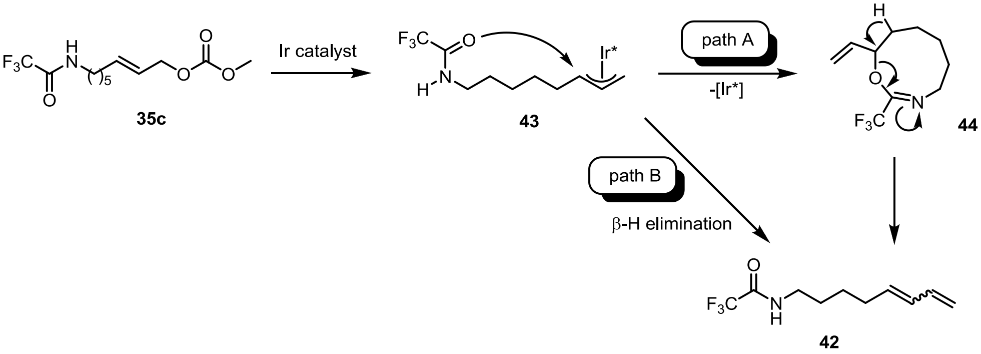
35c

40c
25%

42
68%

Scheme 12 Observed side reaction / formation of azepane

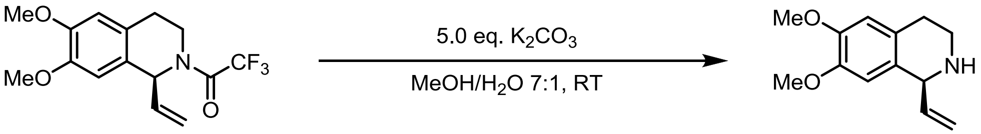
There are two possible mechanisms for the formation of the linear diene **42**. Since it was observed that the formation of **42** only takes place in the presence of the Ir catalyst, it can be assumed that the first step involves the formation of the Ir-allyl complex. This had previously been isolated and postulated as one of the key steps of Ir-catalyzed allylic substitution.[22,58,59] After formation of the allyl-Ir-complex from allylic carbonate **35c**, the oxygen atom of the trifluoroacetate could act as a nucleophile for the allylic substitution (Scheme 13, path A); a reaction related to recent observations made in the Ir-catalyzed asymmetric allylic substitution with thiocarbamates,[64] resulting in a 9-membered heterocycle **44**, which can subsequently undergo elimination to form the linear diene **42**. Alternatively, Ir-complex **43** could undergo β-hydride elimination to form **42** directly (Scheme 13, path B). This decomposition reaction would hint towards a relatively long-lived intermediate **43**, which could be explained by the sterically unfavoured formation of the envisaged product **44** containing a seven-membered ring. This would also explain why similar side-reactions were not observed in the synthesis of pyrrolidine **40a** and piperidine **40b**.



Scheme 13 Proposed mechanisms for the formation of diene 42

3.5 Deprotection of the trifluoroacetamide

The ease of deprotection of the products of the intramolecular asymmetric allylic amidation, *i.e.* chiral secondary trifluoroacetamides, was demonstrated with the conversion of **37a** (Scheme 14). The product was simply stirred at ambient temperature in the presence of an excess of K_2CO_3 in MeOH/H_2O to yield the corresponding chiral homoallylic amine **45** in excellent yield, without loss of *ee*. Bearing both a terminal olefin and a secondary amine, **45** is a highly versatile chiral building block for the synthesis of chiral tetrahydroisoquinoline-derived structures.



37a

45
96 %, 96 % *ee*

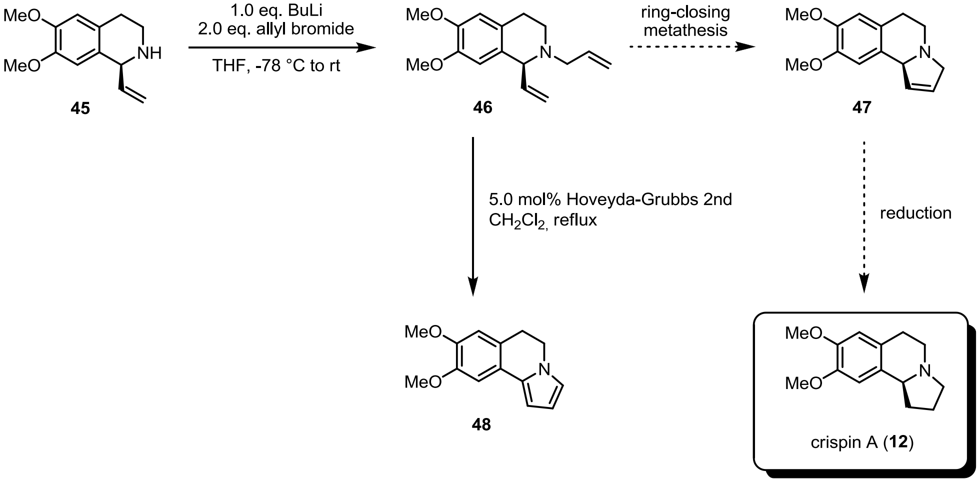
Scheme 14 Deprotection of trifluoroacetamide 30a

3.6 Application of chiral tetrahydroisoquinolines in synthesis

To demonstrate the synthetic utility of the chiral allylic amidation products **37** they were explored in synthetic studies towards natural products and biologically active compounds. In both cases, the following synthetic steps were building upon the highly functional building blocks such as **45**, making use of the secondary amine and the terminal double bond.

Attempted Synthesis of Crispine A

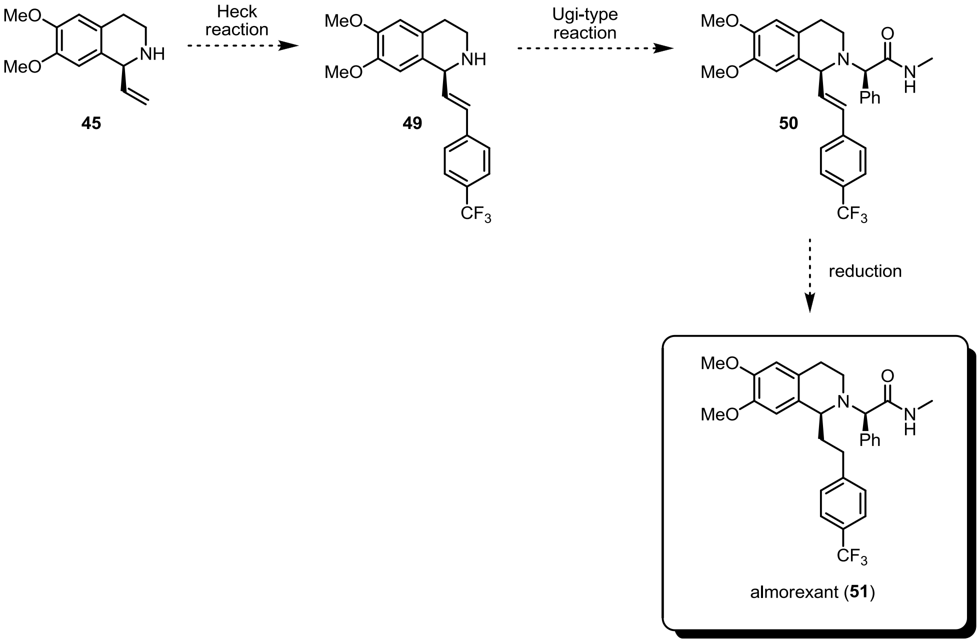
Crispine A (**12**) is an isoquinoline alkaloid isolated from the thistle *Carduus crispus*, from which extracts have been used in traditional Chinese medicine for the treatment of rheumatism.[65] The attempted synthesis was based on chiral tetrahydroisoquinoline **45**, which was *N*-allylated to give **46** in good yields (Scheme 15). The subsequent synthetic route comprised a ring-closing metathesis reaction with Ru-based catalysts,[55] to give the tricyclic precursor to Crispine A **47**. To finish the synthesis, a metal-free reduction of the double bond was intended,[66,67] however, the ring-closed product was oxidized during the metathesis reaction to give pyrroline **48**. The tendency to quickly oxidize had been observed with related compounds earlier,[17] and in our hands could not be prevented by changing the reaction conditions to lower temperatures and/or variation of the metathesis catalyst. The use of Mo-based metathesis catalysts[68] did not show conversion in this case.



Scheme 15 Attempted Synthesis of Crispine A

Attempted Synthesis of Almorexant

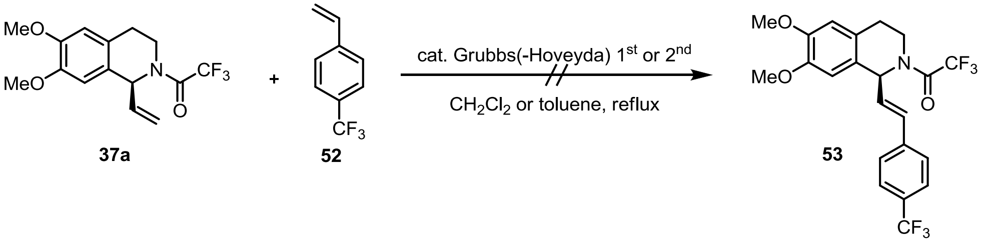
Almorexant (**51**)[69] is a potent inhibitor of the orexin neuropeptide hormones in humans, which have an influence on awakeness (Scheme 16).[70] Therefore, orexin inhibitors are used for the treatment of insomnia. It carries a chiral tetrahydroisoquinoline core next to an α-chiral amide. We chose this molecule as a potential synthetic target to demonstrate the usefulness of the Ir-catalyzed allylic amidation. From the *N*-deprotected compound **45**, a functionalization of the terminal double bond via Pd-catalyzed cross-coupling followed by a Ugi-type reaction[71] should lead to **50**. It needed to be investigated in how far the stereogenic center of **49** could induce steroselectivity for the formation of the second stereocenter in **50**. Finally, reduction of the double bond[66,67] would give rise to Almorexant (**51**).



Scheme 16 Anticipated total synthesis of almorexant (51)

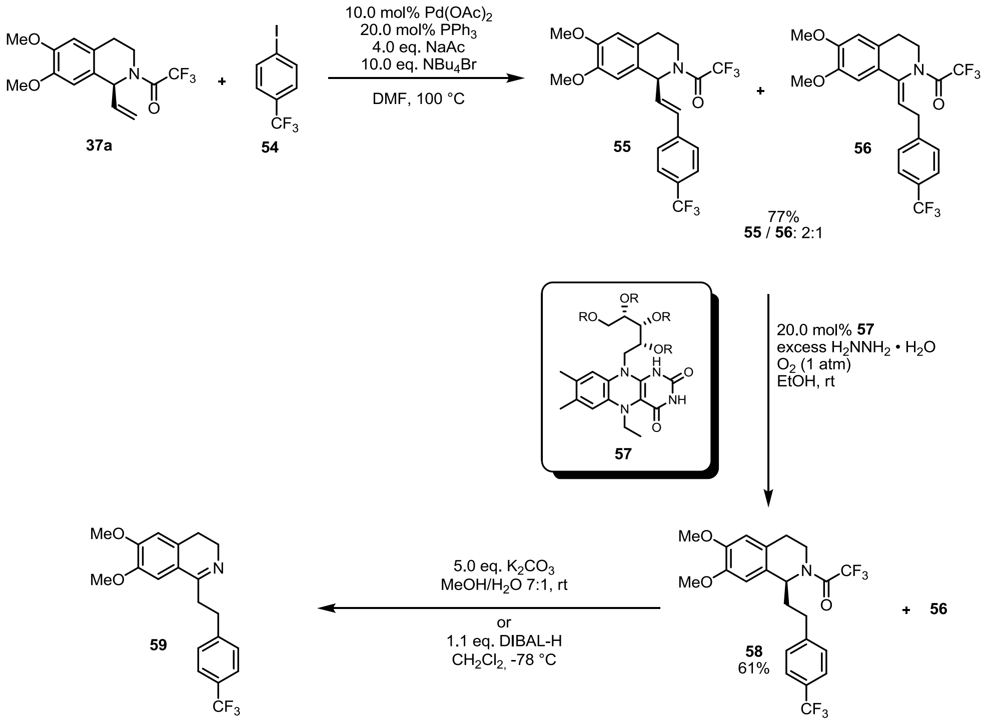
Preliminary synthetic studies revealed the general feasiblity of the envisaged synthesis, however, as in the previous case with Crispine A, partial oxidation of the nitrogen-containing ring of the tetrahydroisoquinoline core presented some synthetic challenge.

We started off by investigating the possibility of directly installing the *para*-trifluorostyrene moiety by cross-metathesis with the *N*-protected tetrahydroisoquinoline **37a**, however, all attempts with Ru-based metathesis catalysts did not lead to conversion of **37a** to **53** (Scheme 17). The fact that mainly the homodimer of **52** was found in the reaction mixture is indicative that the reactivity of the terminal olefin of **37a** is relatively low. The same low reactivity was also found in preliminary attempts to carry out a hydroboration on **37a** which led to no conversion either.



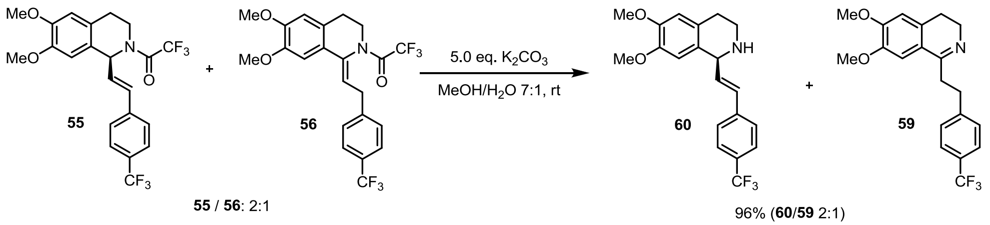
Scheme 17 Attempted cross metathesis

The functionalization of the terminal double bond of **37a** to yield styrene **55** was achieved by employing the Heck reaction. The desired product **55** could be obtained from the reaction of tetrahydroisoquinoline **37a** with iodobenzene **54** in good yield (Scheme 18). However, it should be mentioned that as a side product, the isomerized enamide **56** was found. This preliminary result indicates that some optimization of the Heck reaction conditions is still necessary. The mixture of **55** with **56** was subjected to a reduction of the internal double bond employing a metal-free flavin-catalyzed recuction protocol[66,67] furnishing **58** in moderate yield. Again, **56** was still present in the reaction mixture. The following deprotection of the trifluoroacetamide group went smoothly, however it was accompanied by complete oxidation to the corresponding ketimine **59**. It is expected that side-product **56** also gives **59** after deprotection and isomerization (see also Scheme 19). Even under reductive deprotection conditions employing DIBAL-H, **59** was the only product isolated, indicating a very fast oxidation of the anticipated secondary amine to **59** upon contact with air.


37a
54
10.0 mol% $Pd(OAc)_2$
20.0 mol% PPh_3
4.0 eq. NaAc
10.0 eq. NBu_4Br
DMF, 100 °C
55
56
77%
55 / 56: 2:1
57
20.0 mol% 57
excess $H_2NNH_2 \cdot H_2O$
O_2 (1 atm)
EtOH, rt
58
61%
+ 56
5.0 eq. K_2CO_3
MeOH/H_2O 7:1, rt
or
1.1 eq. DIBAL-H
CH_2Cl_2, -78 °C
59

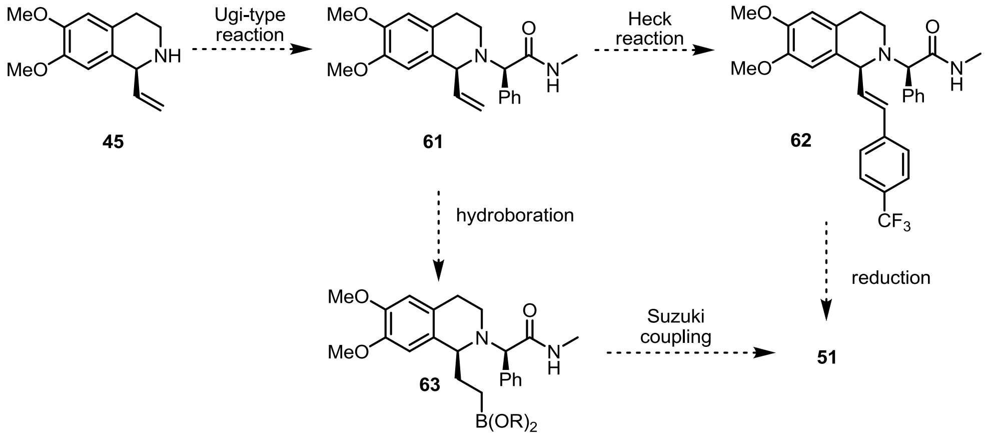
Scheme 18 Attempted synthesis of Almorexant

To avoid oxidation of the products, the synthetic steps of reduction and deprotection were reversed (Scheme 19). When the impure mixture of the Heck reaction, namely trifluoroacetamide **55** and enamide **56**, was deprotected before the internal olefin was reduced, the desired product **60** could be found as the major product. In this case we find it as a mixture with the isomerized product **59**, which we attributed as the product of the deprotection and isomerization of **56**. This result and the outcome of the previous attempt (Scheme 17) show that, in principle, the deprotection of the trifluoroacetamide moiety is possible, however, the presence of the olefin is necessary to prevent oxidation or isomerization to unwanted side products.


55
56
55 / 56: 2:1
5.0 eq. K_2CO_3
MeOH/H_2O 7:1, rt
60
59
96% (60/59 2:1)

Scheme 19 Deprotection of 55

The aforementioned results lead to the conclusion that a revised synthetic route should be followed to prevent any isomerization or oxidation (Scheme 20): Starting off from the deprotected tetrahydroisoquinoline **45**, which has been known to be stable towards oxidation, first the Ugi-type reaction[71] to yield the amide should be carried out. The next step would be functionalization of the terminal olefin to introduce the trifluorotolyl group with subsequent reduction of the double bond. This can be carried out by the Heck reaction, which is to be optimized to prevent the formation of side-products. This route would lead to the target molecule, almorexant (**51**) avoiding oxidation-labile intermediates. As an alternative, the hydroboration of **61** and subsequent Suzuki coupling of **63** would circumvent the need for later reduction of the internal double bond.


45
Ugi-type reaction
61
Heck reaction
62
hydroboration
reduction
63
Suzuki coupling
51

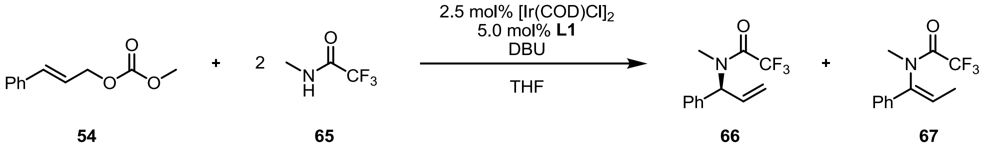
Scheme 20 Suggested revised synthesis of Almorexant (51)

3.7 Intermolecular allylic amidation

It was anticipated that the newly developed catalyst system for the Ir-catalyzed allylic amidation could be extended to an intermolecular variant. This would bear some advantages: It would open up the possibility to introduce amines bearing a short (*i.e.* methyl or ethyl) alkyl group, which are difficult to employ in the allylic amination due to the fact that they are gaseous. Secondly, since the amines would be introduced to the new molecule bearing a trifluoroacetamide group, they would be introduced in a protected fashion. If a longer synthesis is envisaged or the allylic amidation is carried out early in the synthetic route, this could be advantageous.

The reaction of *N*-methyl trifluoroacetamide **65** with cinnamyl methyl carbonate **64** was used as the benchmark reaction to investigate this catalytic transformation (Table 6). With the Ir/**L1** catalyst, full conversion of the starting material was achieved, however, the only product isolated was the isomerized enamide **67** (Table 6, entry 1). The same results were found at ambient temperature and with only catalytic amounts of base (Table 6, entries 2,3). Also the addition of catalytic amounts of phenylpropyne, as mentioned earlier, did not prevent the isomerization from taking place (Table 6, entry 4). Again, as in the case of the *para*-chloro tetrahydroisoquinoline **32** (*vide supra*), it seems that the electronic properties of the substrate govern the product distribution of this transformation. For example, the phenyl substituent could lead to the isomerization, as the double bond in **67** is stabilized through conjugation.

Table 6 Intermolecular allylic amidation



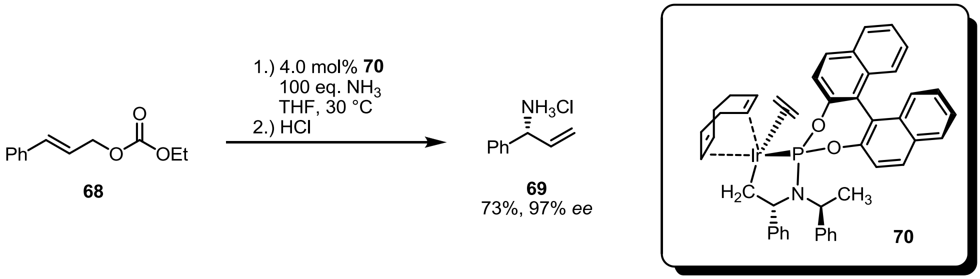
Entry	Conditions	Conversion	**66** / **67**
1	2.0 eq. DBU, 50 °C	full	0/100
2	2.0 eq. DBU, rt	~80%	0/100
3	10.0 mol% DBU, 50 °C	full	0/100
4	2.0 eq. DBU, 50 °C 20.0 mol% phenylpropyne	full	0/100

4 Conclusions and Future prospects

In conclusion, we have developed a new asymmetric synthesis of chiral nitrogen-containing heterocycles, especially tetrahydroisoquinolines, which are important building blocks for the synthesis of biologically active products. Our approach is based on the first intramolecular asymmetric Ir-catalyzed allylic amidation, and the desired products are accessible in excellent yields and enantioselectivities. The trifluoroacetamide group serves two purposes in this approach; initially it is used as a protecting group during the synthesis stage of the starting materials, but further on its enhanced nucleophilicity is exploited for the key asymmetric allylic amidation step. We have also demonstrated that deprotection to the corresponding amine can be readily executed without loss of *ee*.

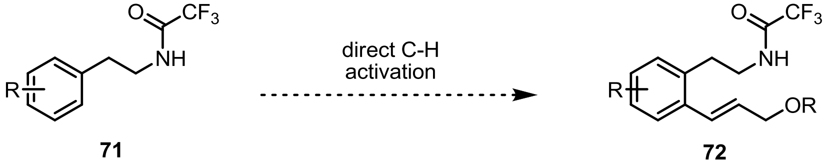
The applicability of the corresponding products has been demonstrated by two attempted synthesis of a naturally occuring and a biologically active product. Both syntheses did reveal the tendency of certain tetrahydroisoquinolines to oxidize. However, for the synthesis of Almorexant, preliminary studies have led to the proposal of a revised synthetic route which should not be hampered by possible oxidation of intermediates.

In the case of the attempted intermolecular allylic amidation and the attempted synthesis of *para*-chlorotetrahydroisoquinoline, where only the isomerized enamides were isolated, albeit in good yield, more work has to be done to overcome the deterioration of the desired products. The above mentioned discovery that the addition of internal alkynes could prevent a similar isomerization for an allylic etherification with Ir catalysts has recently led to the identification of a highly active Ir-ethene complex **70**, which is also capable of selective direct asymmetric amination with ammonia (Scheme 21).[30,72] This more selective catalyst should be employed to reinvestigate the reactions which so far have led to the isomerized enamides.



Scheme 21 Direct asymmetric allylic amination with ammonia

One disadvantage of the present catalytic asymmetric synthesis of tetrahydroisoquinolines is that the substrate scope is effectively limited by the problematic introduction of the halogens for the Stille cross-coupling, which installs the allylic alcohol moiety. Ideally, the allylic alcohol could be introduced without prior halogenation of the aromatic ring. A directed C-H activation with transition metals[73,74] could be envisaged (Scheme 22). Again, the trifluoracetamide group could be employed: it could direct the C-H activation to the *ortho* position of **71**, leading to the desired substitution pattern of the aromatic ring **72**. In this manner, the synthetic route towards tetrahydroisoquinolines would be shortened significantly.



Scheme 22 Proposed C-H activation methodology

5 Experimental Section

General

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60,0.25 mm. Components were visualized by UV and cerium/molybdenum staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on a AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H, ^{19}F and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using TMS or $CFCl_3$ as reference, a Varian VXR300 (300 and 75 MHz, respectively) or a Varian Gemini 200, using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a *Schmidt* + *Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Enantiomeric excesses (*ee* values) were determined by HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector and chiral columns as indicated. *Ee*s were determined by comparison with the corresponding chiral compounds or the mixtures of both R and S enantiomers. All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. CH_2Cl_2 was dried and distilled over calcium hydride, THF and

Et_2O were dried and distilled over Na/benzophenone. Toluene was dried and distilled over Na. $[Ir(COD)Cl]_2$ was purchased from Strem Chemicals, Inc.. Complex **36** was prepared according to literature.[20,29] Ligand **L1** was prepared according to literature.[75] Ligand **L2** was prepared according to literature.[61]

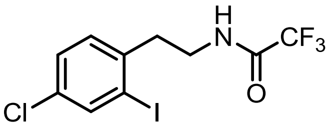
General trifluroacetylation/acetylation protocol:

To a solution of the corresponding amine (1.0 eq.) and NEt_3 (2.0 eq.) in CH_2Cl_2 (2 mL/mmol) was added dropwise trifluoroacetic anhydride (1.2 eq.) (or acetic anhydride in the case of **30f**) at 0 °C. The mixture was stirred at this temperature for 1 h. The reaction was quenched with water (10 ml) and the mixture extracted with CH_2Cl_2 (3 x 5mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to afford the corresponding *N*-trifluoroacetyl or *N*-acetyl compound. The products were used without further purification.

Preparation of halides 30a-e

Substrate **30a** (X = I) was synthesized following literature procedures.[49] Substrate **30b** (X = I) was prepared following the general trifluoroacetylation protocol (see above) from 2-(2-iodo-3,4-methyldioxyphenyl)ethylamine which was made following literature procedures.[50] **30c** (X = I) was synthesized from **30a** using IPy_2BF_4 (which was recrystallized from CH_2Cl_2/Et_2O before use) as iodinating agent following a literature procedure.[52] Substrate **30d** (X = Br) was prepared following the general trifluoroacetylation protocol (see above) from commercial 2-bromophenethylamine. **30f** was synthesized following the same procedure as for **30a**,[49] but with *N*-acetylation instead of *N*-trifluoroacetylation (see general procedure above).

N-(4-chloro-2-iodophenethyl)-2,2,2-trifluoroacetamide (30e)



30e

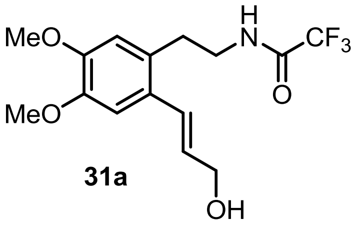
In analogy to a literature procedure,[52] 1.00 eq. *N*-(4-chlorophenethyl)-2,2,2-trifluoroacetamide **29b** (0.126 g, 0.5 mmol) was dissolved in a mixture of CH_2Cl_2 (100 ml) and trifluoracetic acid (10 ml). 4.40 eq. of tetrafluorboric acid in Et_2O (0.295 ml, 2.0 mmol) was added, followed by slow addition of freshly recrystallized 2.20 eq. bispyridineiodonium tetrafluoroborate (0.371 g, 2.0 mmol). The reaction mixture was stirred at room temperature until full conversion was reached as judged by GC/MS (~1h). Then, the reaction was quenched by addition of cold water (50 mL), the mixture was washed with saturated aq. $Na_2S_2O_3$ solution (2x 50 mL). After drying over Na_2SO_4 and removal of all volatiles *N*-(4-chloro-2-iodophenethyl)-2,2,2-trifluoroacetamide **30e** (0.175 g, 0.464 mmol, 93 %) was obtained as a white solid. This material was used without further purification. ^1H

NMR (201 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.1 Hz, 1H), 7.32 – 7.20 (m, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.92 (s (br), 1H), 3.57 (dd, *J* = 13.4, 6.8 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.53 (q, *J* = 36.0 Hz), 138.94, 138.89, 133.33, 130.34, 128.74, 115.69 (q, *J* = 293.2 Hz),100.02, 39.67, 38.66. ^{19}F NMR (189 MHz, $CDCl_3$) δ -75.90. HRMS: (ESI$^+$) calculated for $C_{10}H_9ClF_3INO$ [M+H$^+$]: 377.9364, found: 377.9358.

General procedure for the synthesis of substrates 31 (Stille coupling):

To a mixture of halides **30** (1.0 eq.), *E*-β-tributylstannylpropenol[54] (1.2 eq.) and LiCl (3.0 eq.) in dry DMF (6 mL/mmol), bis(triphenylphosphine)palladium dichloride (5.0 mol%) was added under nitrogen atmosphere. The resulting solution was stirred at 70 °C for 16 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (15 mL/mmol) and washed with water (4 x 10 mL/mmol). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography afforded **31** as white solids.

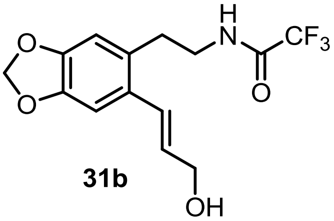
(*E*)-2,2,2-Trifluoro-*N*-(2-(3-hydroxyprop-1-enyl)-4,5-dimethoxyphenethyl)acetamide 31a



31a

Following the general procedure, 274 mg of **31a** (0.83 mmol, 83%) were isolated from the reaction of iodide **30a** (403 mg, 1 mmol) after purification by column chromatography using ethyl acetate/pentane 3:1 as eluent. ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.93 (br s, 1H), 6.80 (dt, *J* = 15.6, 1.4 Hz, 1H), 6.60 (s, 1H), 6.17 (dt, *J* = 15.6, 5.4 Hz, 1H), 4.31 (dd, *J* = 5.4, 1.6 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.48 (q, *J* = 6.7, 2H), 2.89 (t, *J* = 6.7, 2H), 2.52 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (q, *J* = 37.0 Hz), 148.8, 148.1, 129.5, 128.4, 127.7, 127.2, 115.8 (q, *J* = 287.8 Hz), 112.8, 109.3, 63.4, 55.9, 55.9, 40.9, 32.0.

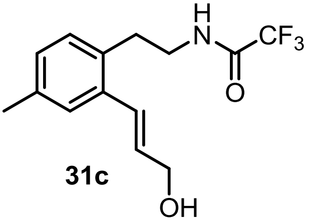
(*E*)-2,2,2-Trifluoro-*N*-(2-(6-(3-hydroxyprop-1-enyl)benzo[d][1,3]dioxol-5-yl)ethyl)acetamide 31b



31b

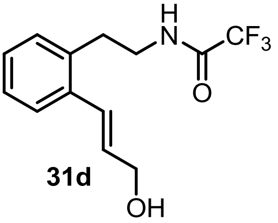
Following the general procedure, 297 mg **31b** (0.94 mmol, 78%) were isolated from the reaction of iodide **30b** (464 mg, 1.2 mmol) after purification by column chromatography using ethyl acetate/pentane 2:1 as eluent. ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.82 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.61 (s, 1H), 6.46 (br s, 1H), 6.16 (dt, *J* = 15.6, 5.3 Hz, 1H), 5.95 (s, 2H), 4.33 (t, *J* = 5.3 Hz, 2H), 3.49 (q, *J* = 7.1 Hz, 2H), 2.89 (t, *J* = 7.1 Hz, 2H), 1.91 (t (br), *J* = 5.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (q, *J* = 37.0 Hz), 147.4, 147.2, 130.1, 130.0, 129.8, 128.7, 127.10, 109.6, 106.4, 101.1, 63.4, 40.9, 32.4. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -75.98. HRMS (ESI+, *m/z*): calculated for $C_{14}H_{14}F_3NO_4Na$ [M+Na$^+$]: 340.07671, found: 340.07650.

(*E*)-2,2,2-Trifluoro-*N*-(2-(3-hydroxyprop-1-enyl)-4-methylphenethyl)acetamide 31c


31c

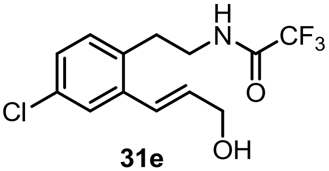
Following the general procedure, 104 mg **31c** (0.36 mmol, 72%) were isolated from the reaction of iodide **30c** (178 mg, 0.5 mmol) after purification by column chromatography using ethyl acetate/pentane 2:1 as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.2 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.88 (dt, *J* = 15.7, 1.2 Hz, 1H), 6.75 (s (br), 1H), 6.26 (dt, *J* = 15.7, 5.2 Hz, 1H), 4.34 (dd, *J* = 5.2, 1.2 Hz, 2H), 3.50 (q, *J* = 7.3 Hz, 2H), 2.92 (t, *J* = 7.3 Hz, 2H), 2.33 (s, 3H), 1.87 (s (br), 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (q, *J* = 36.9 Hz), 137.0, 136.1, 131.9, 131.4, 129.8, 128.7, 127.4, 127.3, 63.4, 40.8, 32.2, 21.0. The CF_3 peaks could not be detected. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -75.99.

(*E*)-2,2,2-trifluoro-*N*-(2-(3-hydroxyprop-1-enyl)phenethyl)acetamide 31d


31d

Following the general procedure, heating the reaction mixture at 90 °C in this case, 108 mg **31d** (0.4 mmol, 79%) were isolated from the reaction of bromide **30d** (148 mg, 0.5 mmol) after purification by column chromatography using ethyl acetate/pentane 2:1 as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.24 – 7.21 (m, 2H), 7.13 (dd, *J* = 6.7, 2.2 Hz, 1H), 6.92 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.90 (s (br), 1H), 6.26 (dt, *J* = 15.7, 5.2 Hz, 1H), 4.34 (dd, *J* = 5.2, 1.6 Hz, 2H), 3.51 (q, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.3 Hz, 2H), 2.61 (s (br), 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5 (q, *J* = 37.1 Hz), 136.3, 134.9, 131.6, 129.9, 127.9, 127.5, 127.3, 126.7, 115.8, (q, *J* = 287.4 Hz), 63.3, 40.6, 32.6. HRMS (ESI+, *m/z*): calculated for $C_{13}H_{14}F_3NO_2Na$ [M+Na$^+$]: 296.0869, found: 296.0867.

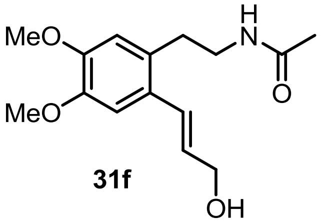
(E)-N-(4-chloro-2-(3-hydroxyprop-1-enyl)phenethyl)-2,2,2-trifluoroacetamide 31e


31e

Following the general procedure, (E)-N-(4-chloro-2(3-hydroxyprop-1-en-1-yl)phenethyl)-2,2,2-trifluoroacetamide **31e** (0.074 g, 0.240 mmol, 52%) was isolated from the reaction of iodide **30e** (175 mg, 0.46 mmol) after purification by column chromatography (SiO_2, pentane/EtOAc 1:1, R_f = 0.60 in pentane/EtOAc 1:1). ^{1}H NMR (201 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.0

Hz, 1H), 7.33 – 7.10 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 15.8 Hz, 1H), 6.35 – 6.14 (m, 1H), 4.33 (dd, *J* = 4.8, 1.4 Hz, 2H), 3.45 (dd, *J* = 14.8, 6.6 Hz, 2H), 3.02 – 2.85 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.98, 133.34, 133.09, 132.78, 131.15, 127.63, 126.44, 125.81, 62.89, 40.45, 32.06. $COCF_3$ signals were not observed. ^{19}F NMR (189 MHz, $CDCl_3$) δ -75.97. HRMS: (ESI$^+$) calculated for $C_{13}H_{13}ClF_3NO_2Na$ [M+Na$^+$]: 330.0479, found: 330.0472.

(*E*)-*N*-(2-(3-hydroxyprop-1-enyl)-4,5-dimethoxyphenethyl)acetamide 31f



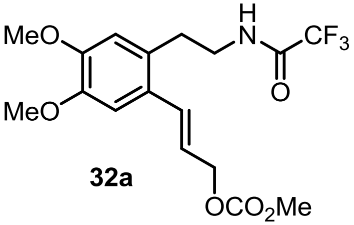
31f

Following the general procedure, heating the reaction mixture at 80 °C in this case, 42 mg **31f** (0.15 mmol, 30%) were isolated from the reaction of iodide **30f** (139 mg, 0.4 mmol) after purification by column chromatography using ethyl acetate/methanol 10:1 as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.88 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.62 (s, 1H), 6.17 (dt, *J* = 15.7, 5.4 Hz, 1H), 5.71 (s (br), 1H), 4.33 (dd, *J* = 5.3, 1.4 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.38 (q, *J* = 7.4 Hz, 2H), 2.83 (t, *J* = 7.4 Hz, 2H), 2.65 (s (br), 1H), 1.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 148.6, 147.8, 129.3, 128.8, 128.6, 127.7, 112.8, 109.1, 63.5, 56.0, 55.9, 40.7, 33.0, 23.3.

General procedure for the synthesis of allylic carbonates 32:

To a solution of allyl alcohol **31** (1 equiv.) and pyridine (3 equiv.) in CH_2Cl_2 (20 mL/mmol) methyl chloroformate (1.5 equiv.) was added dropwise at 0 °C. After 5 min. the solution was warmed to room temperature and was stirred for 1 h. Then, it was washed with aq. HCl (2N) (3 x 5 mL/mmol) and dried over Na_2SO_4. The corresponding products **32** were obtained as a white solid after evaporation of the solvent.

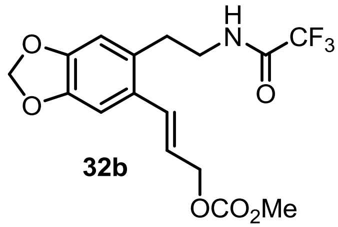
(*E*)-3-(4,5-Dimethoxy-2-(2-(2,2,2-trifluoroacetamido)ethyl)phenyl)allyl methyl carbonate 32a



32a

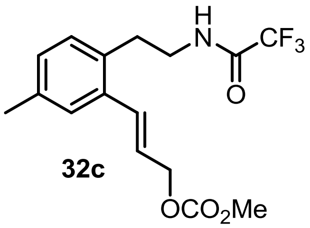
Following the general procedure, 280 mg of **32a** (0.72 mmol, 90%) were isolated as a white solid from the reaction of allyl alcohol **31a** (267 mg, 0.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.89 (dt, *J* = 15.6, 1.0 Hz, 1H), 6.62 (s, 1H), 6.47 (s (br), 1H), 6.11 (dt, *J* = 15.6, 6.6 Hz, 1H), 4.80 (dd, *J* = 6.6, 1.0 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.51 (q, *J* = 6.8 Hz, 2H), 2.92 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (q, *J* = 36.7 Hz), 155.7, 149.3, 148.1, 131.9, 128.3, 127.4, 123.0, 115.8 (q, *J* = 287.8 Hz), 112.7, 109.2, 68.6, 55.9, 55.8, 54.8, 40.8, 31.8.

(*E*)-Methyl 3-(6-(2-(2,2,2-trifluoroacetamido)ethyl)benzo[d][1,3]dioxol-5-yl)allyl carbonate 32b


32b

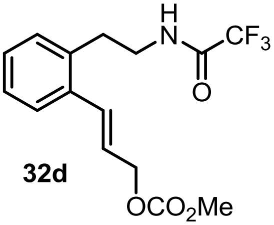
Following the general procedure, 258 mg of **32b** (0.70 mmol, 92%) were isolated from the reaction of allyl alcohol **31b** (240 mg, 0.76 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.87 (dt, *J* = 15.6, 1.2 Hz, 1H), 6.62 (s, 1H), 6.59 (s (br), 1H), 6.05 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.94 (s, 2H), 4.77 (dd, *J* = 6.5, 1.2 Hz, 2H), 3.79 (s, 3H), 3.47 (q, *J* = 7.1 Hz, 2H), 2.88 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (q, *J* = 36.9 Hz), 155.7, 148.0, 147.1, 132.0, 129.6, 128.9, 123.5, 115.8 (q, *J* = 287.7 Hz), 109.7, 106.4, 101.3, 68.5, 54.8, 40.8, 32.2. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -76.01. HRMS (ESI,$^+$, *m/z*): calculated for $C_{16}H_{16}F_3NO_6Na$ [M+Na$^+$]: 398.0822, found: 398.0839.

(E)-Methyl 3-(5-methyl-2-(2-(2,2,2-trifluoroacetamido)ethyl)phenyl)allyl carbonate 32c


32c

Following the general procedure, 114 mg of **32c** (0.33 mmol, 95%) were isolated from the reaction of allyl alcohol **31c** (101 mg, 0.35 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.3 Hz, 1H), 7.12 – 6.98 (m, 2H), 6.93 (dt, *J* = 15.7, 1.3 Hz, 1H), 6.44 (s (br), 1H), 6.18 (dt, *J* = 15.6, 6.4 Hz, 1H), 4.80 (dd, *J* = 6.4, 1.3 Hz, 2H), 3.80 (s, 3H), 3.50 (q, *J* = 7.0 Hz, 2H), 2.93 (t, *J* = 7.0 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (q, *J* = 36.9 Hz), 155.3, 137.0, 135.1, 132.4, 132.2, 129.9, 129.3, 127.4, 125.0, 115.8 (q, *J* = 287.8 Hz), 68.5, 54.8, 40.7, 31.9, 21.0. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -76.02. HRMS (ESI$^+$, *m/z*): calculated for $C_{16}H_{18}F_3NO_4Na$ [M+Na$^+$]: 368.1080, found: 368.1062.

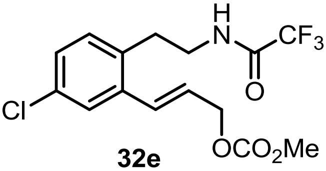
(*E*)-methyl 3-(2-(2-(2,2,2-trifluoroacetamido)ethyl)phenyl)allyl carbonate 32d



32d

Following the general procedure, 126 mg of **32d** (0.38 mmol, 95%) were isolated from the reaction of allyl alcohol **31d** (108 mg, 0.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 5.7, 3.7 Hz, 1H), 7.31 – 7.18 (m, 2H), 7.14 (dd, *J* = 5.6, 3.6 Hz, 1H), 6.97 (dt, *J* = 15.7, 1.2 Hz, 1H), 6.73 (s (br), 1H), 6.18 (dt, *J* = 15.6, 6.4 Hz, 1H), 4.80 (dd, *J* = 6.4, 1.2 Hz, 2H), 3.78 (s, 3H), 3.51 (q, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, (q, *J* = 37.0 Hz), 155.7, 135.4, 135.4, 132.1, 129.9, 128.5, 127.5, 126.8, 125.3, 115.8 (q, *J* = 287.7 Hz), 68.4, 54.8, 40.6, 32.4. HRMS (ESI$^+$, *m/z*): calculated for $C_{15}H_{16}F_3NO_4Na$ [M+Na$^+$]: 354.0924, found: 354.0913.

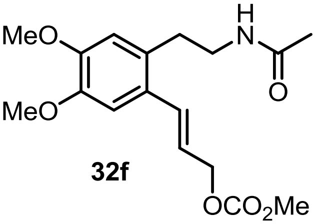
(E)-3-(5-chloro-2-(2-(2,2,2-trifluoroacetamido)ethyl)phenyl)allyl methyl carbonate 32e



32e

Following the general procedure, (E)-3-(5-chloro-(2-(2,2,2-trifluoroacetamido)ethyl)phenyl)allyl methyl carbonate **32e** (0.084 g, 0.230 mmol, 96 %) were isolated as a white solid from the reaction of allyl alcohol **31e** (74 mg, 0.24 mmol). ^{1}H NMR (201 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.1 Hz, 1H), 7.20 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.05 (dd, *J* = 9.6, 5.6 Hz, 1H), 6.89 (d, *J* = 15.7 Hz, 1H), 6.79 (s (br), 1H), 6.17 (dt, *J* = 15.6, 6.2 Hz, 1H), 4.77 (dt, *J* = 10.5, 5.3 Hz, 2H), 3.86 – 3.73 (m, 3H), 3.47 (dd, *J* = 14.1, 6.9 Hz, 2H), 2.92 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.30 (q, *J* = 36.2 Hz), 155.65, 137.06, 133.81, 133.16, 131.23, 130.62, 128.29, 126.61, 126.56, 115.71 (q, *J* = 291.0 Hz), 68.00, 54.86, 40.37, 31.79. ^{19}F NMR (189 MHz, $CDCl_3$) δ -76.00. HRMS: (ESI$^+$) calculated for $C_{13}H_{15}ClF_3NO_4Na$ [M+Na$^+$]: 388.0534, found: 388.0533.

(*E*)-3-(2-(2-acetamidoethyl)-4,5-dimethoxyphenyl)allyl methyl carbonate 32f



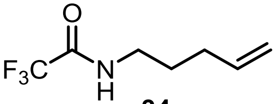
32f

Following the general procedure, 29 mg of **32f** (0.08 mmol, 86%) were isolated from the reaction of allyl alcohol **31f** (28 mg, 0.1 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.90 (d, *J* = 15.6 Hz, 1H), 6.64 (s, 1H), 6.10 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.61 (s (br), 1H), 4.79 (d, *J* = 6.6 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.40 (q, *J* = 6.9 Hz, 2H), 2.84 (t, *J* = 6.9 Hz, 2H), 1.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 155.7, 149.3, 147.9, 132.3, 129.6, 127.3, 122.4, 112.8, 109.0, 68.7, 55.97, 55.9, 54.8, 40.7, 32.5, 23.3.

General Procedure for the alkylation of 2,2,2-trifluoroacetamide to give 34

2,2,2-trifluoroacetamide (**33**) (1.0 eq.) was dissolved in DMF (Volume: 50 ml per 10 mmol) and added to a suspension of 1.05 eq. sodium hydride in DMF (Volume: 20 ml per 10 mmol) at 0 °C. After all gas evolution ceased, 1.05 eq. of the appropriate bromide was added and the reaction mixture was heated to 50 °C for 3 h. After the reaction showed full conversion (by TLC), 50 mL EtOAc was added and the reaction mixture was washed with water (80 mL per 10 mmol) and 2x with brine (2x 80 mL per 10 mmol). After drying over $MgSO_4$, all volatiles were removed under reduced pressure to give the desired alkyltrifluoroacetamides **34**. These products were used without further purification.

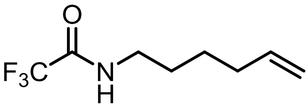
2,2,2-trifluoro-*N*-(pent-4-en-1-yl)acetamide 34a[76]



34a

Following the general procedure for the alkylation of 2,2,2-trifluoroacetamide, 1.442 g of **34a** (7.96 mmol, 99%) were isolated as a pale yellow oil from the reaction of 2,2,2-trifluoroacetamide **33** (0.909 g, 8.04 mmol) with 5-bromopent-1-ene (1.00 ml, 8.44 mmol). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.23 (s (br), 1H), 5.75 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.14 – 4.84 (m, 2H), 3.39 – 3.22 (m, 2H), 2.19 – 1.95 (m, 2H), 1.78 – 1.58 (m, 3H). ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 157.4 (q, *J* = 36.7 Hz), 137.0, 115.8 (q, *J* = 287.2 Hz), 115.5, 39.4, 30.7, 27.7. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -76.21. HRMS (ESI$^+$): calculated for $C_7H_{11}F_3NO$ [M+H$^+$]: 182.0787, found: 182.0784.

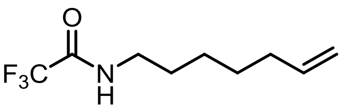
2,2,2-trifluoro-*N*-(hex-5-en-1-yl)acetamide 34b



34b

Following the general procedure for the alkylation of 2,2,2-trifluoroacetamide, 1.352 g **34b** (6,93 mmol, 98%) were isolated as a pale yellow oil from the reaction of 2,2,2-trifluoroacetamide **33** (0.799 g, 7.07 mmol) with 6-bromo-1-hexene (1.00 ml, 7.42 mmol). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.30 (s (br) 1H), 5.83 – 5.59 (m, 1H), 5.11 – 4.70 (m, 2H), 3.34 – 3.22 (m, 2H), 2.09 – 2.00 (m, 2H), 1.63 – 1.48 (m, 2H), 1.47 – 1.31 (m, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ = 157.3 (q, *J* = 36.8 Hz), 137.9, 115.9 (q, *J* = 287.8 Hz), 114.8, 39.7, 33.0, 28.1, 25.8. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -76.10. HRMS (ESI$^+$): calculated for $C_8H_{13}F_3NO$ [M+H$^+$]: 196.0944, found: 196.1103.

2,2,2-trifluoro-*N*-(hept-6-en-1-yl)acetamide 34c



34c

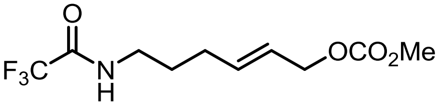
Following the general procedure for the alkylation of 2,2,2-trifluoroacetamide, 1.294 g **34c** (6.19 mmol, 99%) were isolated as a pale yellow oil from the reaction of 2,2,2-trifluoroacetamide **33** (0.706 g, 6.25 mmol) with 7-bromohept-1-ene (1.00 ml, 6.56 mmol). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.68 (s (br), 1H), 5.92 –

5.61 (m, 1H), 5.08 – 4.84 (m, 2H), 3.40 – 3.27 (m, 2H), 2.12 – 1.97 (m, 2H), 1.67 – 1.51 (m, 2H), 1.48 – 1.29 (m, 4H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ = 157.3 (q, *J* = 36.8 Hz), 138.4, 115.9 (q, *J* = 288.3 Hz), 114.6, 39.9, 33.4, 28.7, 28.3, 26.0. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -76.07. HRMS (ESI$^+$): calculated for $C_9H_{15}F_3NO$ [M+H$^+$]: 210.1100, found: 210.2215.

General Procedure for the cross-metathesis of 34 with butendiyl dimethylcarbonate[77] to give allylic carbonates 35

Trifluoroacetamides **34a-c** (1.0 eq.) were dissolved under a N_2 atmosphere in degassed toluene (10 ml per 2 mmol), then 2.00 eq. of (Z)-but-2-ene-1,4-diyl dimethyl dicarbonate were added and finally 5.0 mol% Hoveyda-Grubbs 2nd generation was added. The mixture was heated to 70 °C and stirred until TLC showed full conversion (2-6 h). After cooling to ambient temperature, all volatiles were removed under reduced pressure and crude product was purified by column chromatography (SiO_2, Pentane/EtOAc) to give the pure compounds **35**.

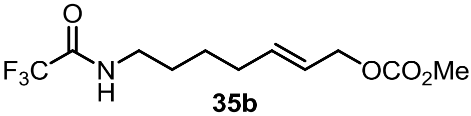
(E)-Methyl (6-(2,2,2-trifluoroacetamido)hex-2-en-1-yl) carbonate 35a



35a

Following the general procedure for the cross-metathesis with butendiyl dimethylcarbonate, 1.00 g **34a** (5.52 mmol) was reacted with 2.254 g butendiyl dimethylcarbonate (11.04 mmol) to give 1.233 g **35a** (4.58 mmol, 83%) after column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.20 in Pentane/EtOAc 10:1). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.75 (s (br), 1H), 5.76 (dd, *J* = 14.4, 7.6 Hz, 1H), 5.67 – 5.54 (m, 1H), 4.54 (d, *J* = 6.3 Hz, 2H), 3.75 (s, 3H), 3.34 (dd, *J* = 13.4, 6.7 Hz, 2H), 2.11 (dd, *J* = 14.2, 7.1 Hz, 2H), 1.77 – 1.57 (m, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ = 157.2 (q, *J* = 36.7 Hz), 155.6, 135.0, 124.6, 115.8 (q, *J* = 289.6 Hz), 68.1, 54.7, 39.3, 29.3, 27.8. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -76.02. HRMS (ESI$^+$): calculated for $C_{10}H_{14}F_3NO_4Na$ [M+Na$^+$]: 292.0767, found: 292.0762.

(E)-Methyl (7-(2,2,2-trifluoroacetamido)hept-2-en-1-yl) carbonate 35b

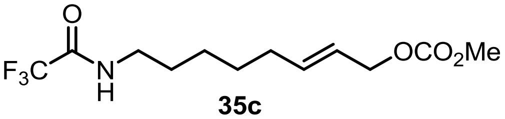


35b

Following the general procedure for the cross-metathesis with butendiyl dimethylcarbonate, 0.500 g **34b** (2.56 mmol) were reacted with 1.046 g butendiyl dimethylcarbonate (5.12 mmol) to give 0.573 g **35b** (2.20 mmol, 79%) after column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.18 in Pentane/EtOAc 10:1). ^{1}H NMR: (201 MHz, $CDCl_3$) δ = 7.22 (s (br), 1H), 5.87 – 5.35 (m, 2H), 4.47 (d, *J* = 6.2 Hz, 2H), 3.77 – 3.57 (m, 3H), 3.25 (dd, *J* = 13.0, 6.6 Hz, 3H), 2.15 – 1.91 (m, 2H), 1.76 – 1.24 (m, 4H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ = 157.2 (q, *J* = 37.1 Hz), 155.4, 136.0, 123.7, 115.8 (q, *J* = 290.2 Hz), 68.2, 54.4, 39.5, 31.4, 28.0, 25.5. ^{19}F NMR: (189 MHz,

$CDCl_3$) δ = -76.15. HRMS (ESI$^+$): calculated for $C_{11}H_{13}F_3NO_4Na$ [M+Na$^+$]: 306.0924, found: 306.0908.

(E)-methyl (8-(2,2,2-trifluoroacetamido)oct-2-en-1-yl) carbonate 35c

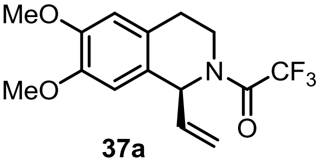

35c

Following the general procedure for the cross-metathesis with butendiyl dimethylcarbonate, 1.00 g **34c** (4.78 mmol) was reacted with 1.952 g butendiyl dimethylcarbonate (9.56 mmol) to give 1.023 g **35c** (3.44 mmol, 72%) after column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.22 in Pentane/EtOAc 10:1). ^{1}H NMR: (201 MHz, $CDCl_3$) δ = 6.73 (s (br), 1H), 5.93 – 5.36 (m, 2H), 4.53 (d, *J* = 6.3 Hz, 2H), 3.74 (s, 3H), 3.31 (dd, *J* = 13.4, 6.7 Hz, 2H), 2.16 – 1.91 (m, 2H), 1.68 – 1.46 (m, 2H), 1.46 – 1.17 (m, 4H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ = 157.2 (q, *J* = 36.4 Hz), 155.6, 136.6, 123.5, 115.9 (q, *J* = 288.5 Hz), 68.5, 54.6, 39.8, 31.9, 28.6, 28.1, 26.0. ^{19}F NMR: (189 MHz, $CDCl_3$) δ = -76.04. HRMS (ESI$^+$): calculated for $C_{12}H_{18}F_3NO_4Na$ [M+Na$^+$]: 320.1080, found: 320.1077.

General Procedure for the Iridium-catalyzed asymmetric allylic amidation

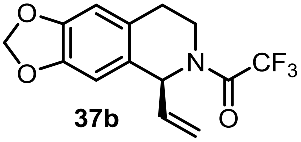
$[Ir(COD)Cl]_2$ (2.5 mol%) and 5.0 mol% **L2** were dissolved in dry THF (1.0 mL per 0.2 mmol) under a N_2 atmosphere. Then, 1.00 eq. DBU was added and the reaction mixture was heated at 50 °C for 30 min. Then, the solution was brought to the appropriate temperature and 1.0 eq. allylic carbonate **32** or **35** was added. The reaction mixture was stirred until TLC showed full conversion. All volatiles were removed under reduced pressure to yield the crude product as an orange oil. This was purified by column chromatography (SiO_2, Pentane/EtOAc) to yield the desired trifluoroacetamide.

(*S*)-1-(6,7-Dimethoxy-1-vinyl-3,4-dihydroisoquinolin-2(*1H*)-yl)-2,2,2-trifluoroethanone 37a


37a

The title compound was prepared from **32a** (117 mg, 0.30 mmol) following the general procedure for the Ir-catalyzed asymmetric allylic amidation at room temperature. Purification by column chromatography (SiO_2, Pentane/EtOAc 3:1) afforded **37a** (92 mg, 0.29 mmol, 95% *ee*, 97%) as a colourless oil as a mixture of two conformers in 3.6:1 ratio (determined by ^{1}H NMR at 20 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 1H, minor), 6.60 (s, 1H, major), 6.58 (s, 1H, major), 6.55 (s, 1H, minor), 6.00 – 5.91 (m, 2H major + 1H minor), 5.44 (d, *J* = 4.0 Hz, 1H minor), 5.30 (dd, *J* = 9.9, 0.8 Hz, 1H major), 5.29 (d, *J* = 10.0 Hz, 1H minor), 5.12 (dd, *J* = 15.5, 0.8 Hz, 1H major), 5.03 (d, *J* = 17.1 Hz, 1H minor), 4.51 – 4.46 (m, 1H minor), 4.03 – 3.98 (m, 1H major), 3.85 (s, 3H, minor), 3.84 (s, 3H, major), 3.84 (s, 3H, minor), 3.83 (s, 3H, major), 3.53 (ddd, *J* = 13.8, 12.1, 3.9 Hz, 1H major), 3.24 (td, *J* = 12.2, 4.2 Hz, 1H minor), 3.00 – 2.90 (m, 1H major + 1H minor), 2.76 – 2.68 (m, 1H major + 1H minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (q, *J* = 35.8 Hz) (major), 148.6 (minor), 148.3 (major), 147.8 (major), 147.7 (minor), 136.5 (minor), 135.6 (major), 126.0 (minor), 125.3 (major), 124.7 (major), 124.4 (minor), 118.6 (major), 118.5 (minor), 116.8 (q, *J* = 287.9 Hz), 111.4 (minor), 111.1 (major), 110.6 (major), 110.3 (minor), 57.9 (minor), 56.0 (minor), 56.0 (major), 55.9 (major), 55.5 (major), 40.0 (major), 37.7 (minor), 28.7 (major), 27.2 (minor). ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -68.7 (minor), -69.4 (major). HRMS (APCI+, *m/z*): calculated for $C_{15}H_{17}F_3NO_3$ [M+H$^+$]: 316.1155, found: 316.1140. $[\alpha]_D^{20}$ = + 168.3 (c = 0.85 in $CHCl_3$) *ee* determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 90:10, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 19.7 min (major), 24.7 min (minor).

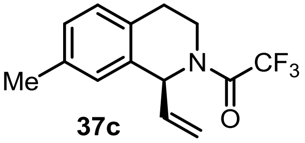
(*S*)-2,2,2-Trifluoro-1-(5-vinyl-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-6(*5H*)-yl)ethanone 37b



37b

The title compound was prepared from **32b** (75 mg, 0.20 mmol) following the general procedure at room temperature. Purification by column chromatography (SiO_2, Pentane/Et_2O 10:1) afforded **37b** (54 mg, 0.18 mmol, 94% *ee*, 89%) as a colourless oil as a mixture of two conformers in 3.5:1 ratio (determined by ^{1}H NMR at 20 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H, minor), 6.58 (s, 2H, major), 6.56 (s, 1H, minor), 6.02 – 5.88 (m, 4H major + 3H minor), 5.40 (d, *J* = 4.2 Hz, 1H minor), 5.30 (dd, *J* = 9.9, 1.0 Hz, 1H major), 5.29 (d, *J* = 10.1 Hz, 1H minor), 5.12 (dd, *J* = 15.5, 1.0 Hz, 1H major), 5.05 (d, *J* = 17.2 Hz, 1H minor), 4.46 – 4.39 (m, 1H minor), 4.02 – 3.94 (m, 1H major), 3.54 (ddd, *J* = 14.0, 11.6, 3.9 Hz, 1H major), 3.24 (td, *J* = 11.5, 4.7 Hz, 1H minor), 2.97 – 2.87 (m, 1H major + 1H minor), 2.75 – 2.68 (m, 1H major + 1H minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (q, *J* = 35.8 Hz) (major), 147.3 (minor), 147.0 (major), 146.5 (major), 146.4 (minor), 136.4 (minor), 135.5 (major), 127.3 (minor), 126.5 (major), 125.8 (major), 125.6 (minor), 118.5 (major), 118.4 (minor), 116.5 (q, *J* = 288.0 Hz) (major), 108.6 (minor), 108.3 (major), 107.8 (major), 107.4 (minor), 101.2 (minor), 101.1 (major), 58.1 (minor), 55.9 (major), 40.0 (major), 37.9 (minor), 29.1 (major), 27.6 (minor). ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -68.7 (minor), -69.4 (major). HRMS (APCI+, *m/z*): calculated for $C_{14}H_{13}F_3NO_3$ [M+H$^+$]: 300.0842, found: 300.0839. $[\alpha]_D^{20}$ = + 153.2 (c = 1.0 in $CHCl_3$) *ee* determination by chiral HPLC (Chiralpak AD-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 23.4 min (minor), 24.7 min (major).

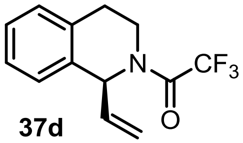
(*S*)-2,2,2-Trifluoro-1-(7-methyl-1-vinyl-3,4-dihydroisoquinolin-2(*1H*)-yl)ethanone 37c



37c

The title compound was prepared from **32c** (34 mg, 0.15 mmol) following the general procedure at room temperature. Purification by column chromatography (SiO_2, Pentane/Et_2O 20:1) afforded **37c** (25 mg, 0.14 mmol, 91% *ee*, 92%) as a colourless oil as a mixture of two conformers in 3.1:1 ratio (determined by ^{1}H NMR at 20 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.2 Hz, 1H major +1H minor), 7.04 (s, 1H, major + 1H minor), 6.95 (d, *J* = 8.2 Hz, 1H major +1H minor), 6.06 – 5.93 (m, 2H major + 1H minor), 5.50 (d, *J* = 4.0 Hz, 1H minor), 5.32 – 5.28 (m, 1H major +1H minor), 5.12 (dd, *J* = 16.3, 0.7 Hz, 1H major), 5.04 (d, *J* = 17.0 Hz, 1H minor), 4.49 – 4.44 (m, 1H minor), 4.05 – 4.00 (m, 1H major), 3.58 (ddd, *J* = 14.0, 11.8, 4.0 Hz, 1H major), 3.24 (td, *J* = 12.4, 4.7 Hz, 1H minor), 3.03 – 2.93 (m, 1H major + 1H minor), 2.84 – 2.76 (m, 1H major + 1H minor), 2.33 (s, 3H minor), 2.33 (s, 3H major). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (q, *J* = 36.0 Hz) (major), 136.6 (minor), 136.3 (major), 136.1 (minor), 135.6 (major), 132.8 (major), 132.6 (minor), 130.1 (major), 130.0 (minor), 128.9 (minor), 128.6 (major), 128.5 (major), 128.2 (major), 128.1 (minor), 118.2 (major), 118.1 (minor), 116.5 (q, *J* = 287.7 Hz) (major), 58.3 (minor), 56.0 (major), 40.3 (major), 38.22 (minor), 28.7 (major), 27.2 (minor), 21.0 (major), 20.99 (minor). ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -68.7 (minor), -69.4 (major). HRMS (ESI+, *m/z*): calculated for $C_{14}H_{15}F_3NO$ [M+H$^+$]: 270.1100, found: 270.1088. $[\alpha]_D^{20}$ = + 152.4 (c = 1.0 in $CHCl_3$) *ee* determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 13.3 min (minor), 15.2 min (major).

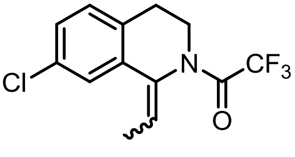
(*S*)-2,2,2-Trifluoro-1-(1-vinyl-3,4-dihydroisoquinolin-2(*1H*)-yl)ethanone 37d



37d

The title compound was prepared from **32d** (33 mg, 0.10 mmol) following the general procedure at room temperature. Purification by column chromatography (SiO_2, Pentane/Et_2O 15:1) afforded **37d** (20 mg, 0.08 mmol, 94% *ee*, 78%) as a colourless oil as a mixture of two conformers in 3.4:1 ratio (determined by ^{1}H NMR at 20 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.11 (m, 4H major + 4H minor), 6.05 – 5.93 (m, 2H major + 1H minor), 5.55 (d, *J* = 3.8 Hz, 1H minor), 5.31 (dd, *J* = 9.8, 1.1 Hz, 1H major), 5.30 (d, *J* = 10.2 Hz, 1H minor), 5.12 (dd, *J* = 16.5, 1.1 Hz, 1H major), 5.05 (d, *J* = 17.1 Hz, 1H minor), 4.51 – 4.45 (m, 1H minor), 4.08 – 4.00 (m, 1H major), 3.60 (td, *J* = 12.0, 4.0 Hz, 1H major), 3.33 (td, *J* = 12.0, 4.5 Hz, 1H minor), 3.08 – 2.98 (m, 1H major + 1H minor), 2.88 – 2.80 (m, 1H major + 1H minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (q, *J* = 36.0 Hz) (major), 136.6 (minor), 135.6 (major), 133.9 (minor), 133.6 (minor), 133.2 (major), 133.0 (major), 129.1 (minor), 128.8 (major), 128.2 (major), 127.7 (minor), 127.7 (minor), 127.3 (major), 126.6 (major), 126.5 (minor), 118.3 (major), 118.3 (minor), 116.5 (q, *J* = 287.9 Hz) (major), 58.2 (minor), 55.9 (major), 40.1 (major), 38.0 (minor), 29.1 (major), 27.6 (minor). ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -68.7 (minor), -69.4 (major). HRMS (ESI+, *m/z*): calculated for $C_{13}H_{13}F_3NO$ [M+H$^+$]: 256.0944, found: 256.0941. $[\alpha]_D^{20}$ = + 186.8 (c = 1.0 in $CHCl_3$) *ee* determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 220 nm, flow rate 0.5 mL/min), retention times: 12.1 min (minor), 14.4 min (major).

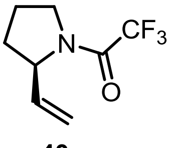
1-(7-Chloro-1-ethylidene-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone 39



39

The title compound was prepared from **32e** (0.020 g, 0.055 mmol) following the general procedure for the Ir-catalyzed asymmetric allylic amidation at 50 °C. Purification by column chromatography (SiO_2, Pentane/EtOAc 20:1, R_f = 0.95 in Pentane/EtOAc 10:1) afforded 1-(7-chloro-1-ethylidene-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone **39** (0.010 g, 0.035 mmol, 63%) as a colourless oil. **39** was isolated as a mixture of 2 isomers (ratio 1:1.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.1 Hz, 1H, major), 7.40 (d, *J* = 2.1 Hz, 1H, minor), 7.25 – 7.14 (m, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.32 (q, *J* = 7.1 Hz, 1H, major), 6.16 (q, *J* = 7.2 Hz, 1H, minor), 5.03 – 4.77 (m, 1H), 3.33 – 3.10 (m, 2H), 2.88 – 2.71 (m, 1H), 1.85 (d, *J* = 7.1 Hz, 3H, minor), 1.70 (d, *J* = 7.1 Hz, 3H, major). ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.43, 130.31, 130.12, 128.18, 127.86, 123.81, 123.39, 121.80, 45.10, 29.62, 27.43. Only major peaks are given. ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.21 (major), -70.20 (minor). HRMS: (ESI$^+$) calculated for $C_{13}H_{12}ClF_3NO$ [M+H$^+$]: 290.0554, found: 290.0547.

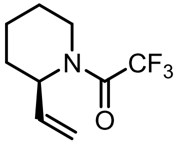
(*R*)-2,2,2-Trifluoro-1-(2-vinylpyrrolidin-1-yl)ethanone 40a



40a

The title compound was prepared from **35a** (0.100 g, 0.371 mmol) following the general procedure for the Ir-catalyzed asymmetric allylic amidation at 50 °C. Purification by column chromatography (SiO_2, Pentane/EtOAc 10:1, R_f = 0.75 in pentane/EtOAc 10:1) afforded **40a** (0.040 g, 0.207 mmol, 96% *ee*, 56%) as a colourless oil. **40a** was isolated as a mixture of 2 conformers. (ratio 1 : 2.5) ^{1}H NMR: (201 MHz, $CDCl_3$) δ = 5.92 – 5.53 (m, 1H), 5.28 – 4.97 (m, 2H), 4.67 (d, *J* = 4.9 Hz, 1H), 3.78 – 3.46 (m, 2H), 2.16 – 1.70 (m, 4H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ = 155.4 (q, *J* = 37.1 Hz), 136.8 (minor), 135.3 (major), 116.3 (q, *J* = 287.9 Hz, major), 116.2 (q, *J* = 286.6 Hz, minor), 115.4 (major), 115.1 (minor), 60.4 (major), 59.8 (minor), 47.3 (minor), 46.6 (major), 32.3 (minor), 29.8 (major), 23.8 (major), 20.1 (minor). ^{19}F NMR: (189 MHz, $CDCl_3$) δ = -70.94 (minor), -72.71 (major). HRMS (ESI$^+$): calculated for $C_8H_{11}F_3NO$ [M+H$^+$]: 194.0787, found: 194.0790. $[\alpha]_D^{20}$ = 44.6 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak AD-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 10.5 min (major enantiomer), 11.5 min (minor enantiomer).

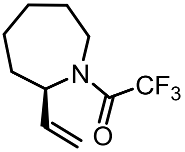
(*R*)-2,2,2-Trifluoro-1-(2-vinylpiperidin-1-yl)ethanone 40b



40b

The title compound was prepared from **35b** (0.060 g, 0.212 mmol) following the general procedure for the Ir-catalyzed asymmetric allylic amidation at 50 °C. Purification by column chromatography (SiO_2, Pentane/EtOAc 20:1, R_f = 0.90 in pentane/EtOAc 10:1) afforded **40b** (0.030 g, 0.144 mmol, 88% *ee*, 68%) as a colourless oil. **40b** was isolated as a mixture of 2 conformers (ratio 1:1.7). ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 5.95 – 5.65 (m, 1H), 5.31 (t, *J* = 11.5 Hz, 1H), 5.26 (s (br), 1H major), 5.15 (t, *J* = 16.4 Hz, 1H), 4.68 (s, 1H, minor), 4.39 (d, *J* = 12.7 Hz, 1H, minor), 3.80 (d, *J* = 13.3 Hz, 1H, major), 3.24 (t, *J* = 13.3 Hz, 1H, major), 2.91 (t, *J* = 13.0 Hz, 1H, minor), 1.90 (d, *J* = 13.2 Hz, 1H), 1.81 – 1.60 (m, 4H), 1.58 – 1.41 (m, 1H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ = 156.8 (q, *J* = 36.6 Hz), 135.2 (minor), 134.6 (major), 117.8 (minor), 117.5 (major), 116.7 (q, *J* = 186.9 Hz), 54.8 (minor), 51.9 (major), 42.0 (minor), 39.2 (major), 29.6 (minor), 28.3 (major), 26.0 (major), 25.3 (minor), 19.3. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -68.75 (minor), -68.79 (major). HRMS (ESI$^+$): calculated for $C_9H_{12}F_3NONa$ [M+Na$^+$]: 230.0763, found: 230.0752. $[\alpha]_D^{20}$ = 55.6 (c = 1.2 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 99.9:0.1, 40 °C isotherm, 230 nm, flow rate 0.5 mL/min), retention times: 13.5 min (minor enantiomer), 15.2 min (major enantiomer).

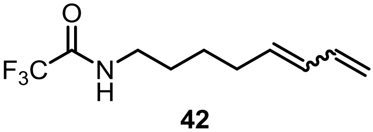
(*R*)-2,2,2-Trifluoro-1-(2-vinylazepan-1-yl)ethanone 40c



40c

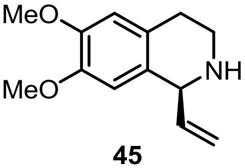
The title compound was prepared from **35c** (0.100 g, 0.336 mmol) following the general procedure for the Ir-catalyzed asymmetric allylic amidation at 50 °C. Purification by column chromatography (SiO_2, Pentane/EtOAc 10:1, R_f = 0.90 in pentane/EtOAc 10:1) afforded **40c** (0.019 g, 0.086 mmol, 92% *ee*, 25%) as a colourless oil. **40c** was isolated as a mixture of 2 conformers. (ratio 2:3) ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 5.87 – 5.64 (m, 1H), 5.13 (dd, *J* = 19.5, 10.6 Hz, 1H), 5.05 (d, *J* = 17.3 Hz, 1H), 4.92 – 4.81 (m, 1H, minor), 4.45 (s (br), 1H, major), 4.06 (d, *J* = 13.6 Hz, 1H, major), 3.81 (d, *J* = 15.0 Hz, 1H, minor), 3.19 – 3.04 (m, 1H, minor), 2.82 (t, *J* = 12.7 Hz, 1H, major), 2.20 (ddd, *J* = 23.2, 15.0, 7.2 Hz, 1H), 1.98 – 1.79 (m, 2H), 1.69 - 1.46 (m, 3H), 1.30 (tt, *J* = 17.3, 8.7 Hz, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ = 136.7 (major), 135.6 (minor), 114.8 (major), 114.6 (minor), 58.3 (minor), 57.9 (major), 43.1 (minor), 42.9 (major), 33.7 (major), 32.3 (minor), 30.7 (minor), 29.6 (major), 28.9 (minor), 26.6 (major), 24.8 (minor), 23.9 (major). The $COCF_3$ peaks could not be detected. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -68.31 (major), -68.72 (minor). HRMS (ESI$^+$): calculated for $C_{10}H_{15}F_3NO$ [M+H$^+$]: 222.1100, found: 222.1103. $[\alpha]_D^{20}$ = 76.8 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak AS-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 220 nm, flow rate 0.5 mL/min), retention times: 9.4 min (minor enantiomer), 10.0 min (major enantiomer).

2,2,2-Trifluoro-*N*-(octa-5,7-dienyl)acetamide 42


42

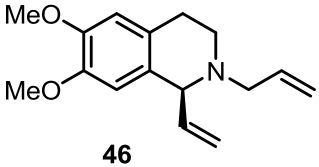
The title compound was prepared from **35c** (0.100 g, 0.336 mmol) following the general procedure for the Ir-catalyzed asymmetric allylic amidation at 50 °C. Purification by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.70 in Pentane/EtOAc 10:1) afforded **42** (0.019 g, 0.086 mmol, 92% *ee*, 25%) as a colourless oil. **42** was isolated as a mixture of 2 isomers. (ratio 3:2) ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.60 (dt, *J* = 16.9, 10.6 Hz, 1H, major), 6.41 (s (br), 1H), 6.36 – 6.23 (m, 1H, minor), 6.13 – 5.97 (m, 1H), 5.78 – 5.59 (m, 1H, minor), 5.50 – 5.34 (m, 1H, major), 5.20 (d, *J* = 16.9 Hz, 1H, major), 5.16 – 5.04 (m, 1H), 4.98 (d, *J* = 10.1 Hz, 1H, minor), 3.36 (dd, *J* = 13.4, 6.7 Hz, 2H), 2.23 (q, *J* = 7.3 Hz, 2H, major), 2.12 (dd, *J* = 14.3, 7.1 Hz, 2H, minor), 1.69 – 1.53 (m, 2H), 1.51 – 1.38 (m, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ = 157.2 (q, *J* = 39.0 Hz), 137.0, 134.0, 131.9, 131.7, 131.4, 123.0, 117.5, 115.8 (q, *J* = 288.0 Hz), 115.3, 39.8, 31.9, 29.7, 28.41, 27.0, 26.5, 26.1. ^{19}F NMR: (376 MHz, $CDCl_3$) δ = -76.00. HRMS (ESI$^+$): calculated for $C_{10}H_{15}F_3NO$ [M+H$^+$]: 222.1103, found: 222.1100.

(*S*)-6,7-Dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 45


45

Trifluoroacetamide **37a** (46 mg, 0.15 mmol) was dissolved in a mixture of MeOH/water (7 mL/1 mL) at room temperature. K_2CO_3 was added to the solution and the resulting mixture was stirred during 16 h. Then, MeOH was removed under vacuum, water was added (10 mL) and the aqueous solution was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed to afford amine **45** as a white solid (32 mg, 96%, 97% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (s, 1H), 6.57 (s, 1H), 5.93 (ddd, *J* = 17.4 Hz, 10.0, 7.8 Hz, 1H), 5.24 (d, *J* = 17.4 Hz, 1H), 5.23 (d, *J* = 10.0 Hz, 1H), 4.40 (d, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.27 – 3.19 (m, 1H), 3.06 – 2.97 (m, 1H), 2.86 – 2.77 (m, 1H), 2.67 (dt, *J* = 16.1, 4.8 Hz, 1H), 2.13 (s (br), 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.3, 140.8, 128.7, 127.1, 117.5, 111.8, 110.5, 60.2, 56.2, 55.9, 41.9, 29.3. HRMS (ESI+, *m/z*): calculated for $C_{13}H_{18}NO_2$ [M+H$^+$]: 220.1332, found: 220.1325. $[\alpha]_D^{20}$ = + 76.0 (c = 0.5, $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 30.4 min (major), 38.7 min (minor).

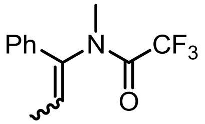
(*S*)-2-Allyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 46



46

(S)-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline **45a** (1.00 eq., 0.020 g, 0.091 mmol) was dissolved in THF (Volume: 10 ml) and cooled to -78 °C. Then 1.00 eq. BuLi solution in hexanes (c = 1.6 M) (0.057 ml, 0.091 mmol) was added dropwise and the reaction was stirred at -78 °C for 1 h. Then, 2.00 eq. allyl bromide (0.016 ml, 0.182 mmol) were added and the mixture was allowed to warm to r.t. and stirred for 16 h. The reaction was quenched by addition of sat. aq. NH_4Cl solution (10 mL). Extraction with Et_2O (2x 30 mL) and subsequent drying of the organic phases over $MgSO_4$, filtration and removal of all volatiles under reduced pressure yielded the crude product. This was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.80 in pentane/EtOAc 8:2) to yield (S)-2-allyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline **46** (0.020 g, 0.077 mmol, 85 %) as a colourless oil. ^1H NMR (201 MHz, $CDCl_3$) δ 6.50 (s, 2H), 6.00 – 5.44 (m, 2H), 5.36 – 5.02 (m, 4H), 3.91 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.52 – 3.30 (m, 1H), 3.17 – 2.88 (m, 2H), 2.86 – 2.62 (m, 2H), 2.47 (ddd, *J* = 12.2, 7.7, 4.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.45, 146.87, 139.33, 135.32, 127.74, 126.53, 118.04, 117.58, 111.07, 110.90, 66.09, 57.39, 55.72, 55.66, 46.15, 28.11. HRMS: (ESI^+) calculated for $C_{16}H_{22}NO_2$ $[M+H^+]$: 260.1645, found: 260.1640. $[\alpha]_D^{20}$ = 55.2 (c = 1.1 in $CHCl_3$).

2,2,2-Trifluoro-N-methyl-N-(1-phenylprop-1-enyl)acetamide 67



67

67 was prepared in the reaction of 1.0 eq. cinnamyl methyl carbonate **64** (0.020 g, 0.104 mmol) and 2.0 eq. 2,2,2-trifluoro-*N*-methylacetamide **65** (0.026 g, 0.208 mmol) following the general procedure for the Ir-catalyzed asymmetric allylic amidation at 50 °C, employing **L1** as ligand. Purification by column chromatography (SiO_2, Pentane/EtOAc 20:1, R_f = 0.60 in Pentane/EtOAc 10:1) afforded 2,2,2-trifluoro-*N*-methyl-N-(1-phenylprop-1-en-1-yl)acetamide **67** (0.016 g, 0.066 mmol, 63%) as a colourless oil. **67** was isolated as two double bond isomers (ratio: 1:5.5) ^1H NMR (201 MHz, $CDCl_3$) δ 7.60 – 7.20 (m, 5H), 6.38 (q, *J* = 7.1 Hz, 1H, major), 6.20 (dd, *J* = 14.0, 7.0 Hz, 1H, minor), 3.23 (s, 3H, minor), 3.18 (s, 3H, major), 1.82 (d, *J* = 7.1 Hz, 3H, major), 1.75 (d, *J* = 7.0 Hz, 3H, minor). ^{13}C NMR (50 MHz, $CDCl_3$) δ 128.86, 128.81, 128.36, 128.31, 124.72, 124.29, 37.10, 13.85. Only major peaks are given, the $COCF_3$ peaks were not observed. ^{19}F NMR (189 MHz, $CDCl_3$) δ -69.86 (minor), -69.97 (major). HRMS: (ESI^+) calculated for $C_{12}H_{13}F_3NO$ $[M+H^+]$: 244.0944, found: 244.0930.

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Chapter 4

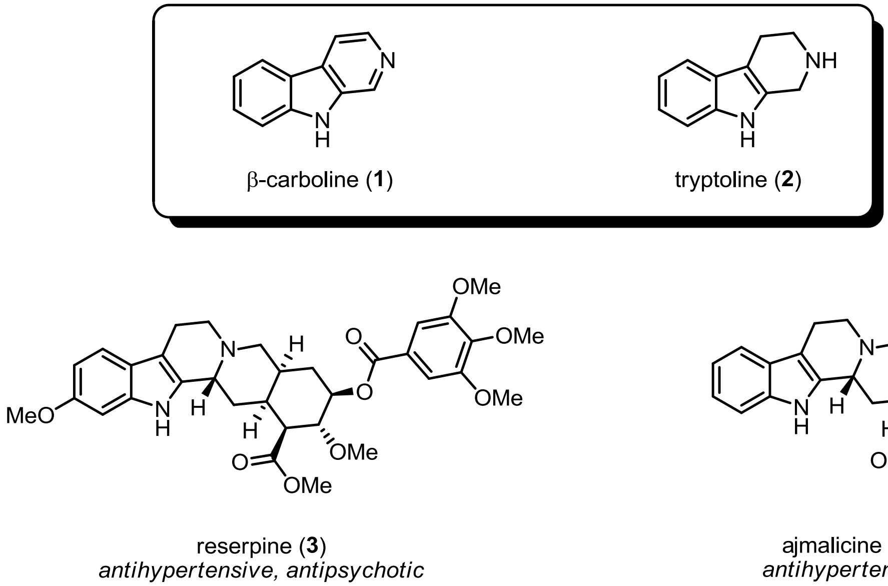
Synthetic Approaches towards β-Carbolines

The catalytic asymmetric synthesis of multifunctional chiral β-carboline compounds was attempted through two Ir-catalyzed allylic substitution protocols. The asymmetric allylic amination as well as the allylic amidation were investigated. Synthetic routes towards the required allylic carbonates were developed, however, those compounds could not be transformed to the desired β-carbolines through Ir-catalyzed allylic substitutions.

Parts of this chapter will be published: Teichert, J.F.; Fañanás-Mastral, M.; Feringa, B.L. *submitted*.

1. Introduction

β-Carboline- or tryptoline-derived alkaloids[1-3] are a large class of naturally occuring compounds which show a wide variety of biological and therapeutic activities (Figure 1).[4-6] As examples of this family[7] of molecules, the two antihypertensives reserpine (**3**) and ajmalicine (**4**) are displayed.[8-10] Both **3** and **4** can be isolated from evergreen trees of the *Rauwolfia* species. Reserpine (**3**) acts through the inhibition of accumulation of biologically active amines, *e.g.* serotonin and catecholamines, in the brain and other body organs.[9] Structurally related ajmalicine (**4**), however, is an inhibitor of α1-andrenergic receptors[11] displaying just a small variety of the biological activities associated with this class of compounds. Many synthetic strategies have been developed to make substituted indoles and tryptamines,[12-14] Pictet-Spengler and Mannich-type condensation reactions being among the most prominent ones.[15-17]


β-carboline (**1**)

tryptoline (**2**)

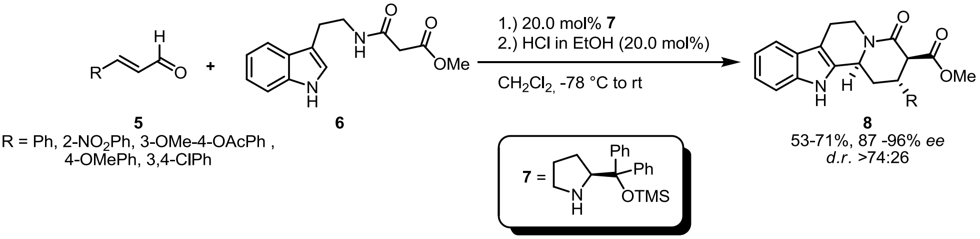
reserpine (**3**)
antihypertensive, antipsychotic

ajmalicine (**4**)
antihypertensive

Figure 1 Examples of β-carboline compounds

Some of the synthetic approaches to chiral β-carbolines are discussed in the following sections.

An organocatalytic cascade reaction to give the related quinolizidine compounds **8** in straightforward manner was recently reported (Scheme 1).[18] With catalytic amounts of prolinol **7** the desired products **8** were accessible in a one-pot procedure from α,β-unsaturated aldehydes **5** and tryptamine **6**. Compounds **8** were isolated in up to good yields reaching excellent enantioselectivities. Even though the aryl-substituted tetracyclic compounds are not commonly found in nature, this marks an impressive transformation, generating three stereocenters in one reaction.



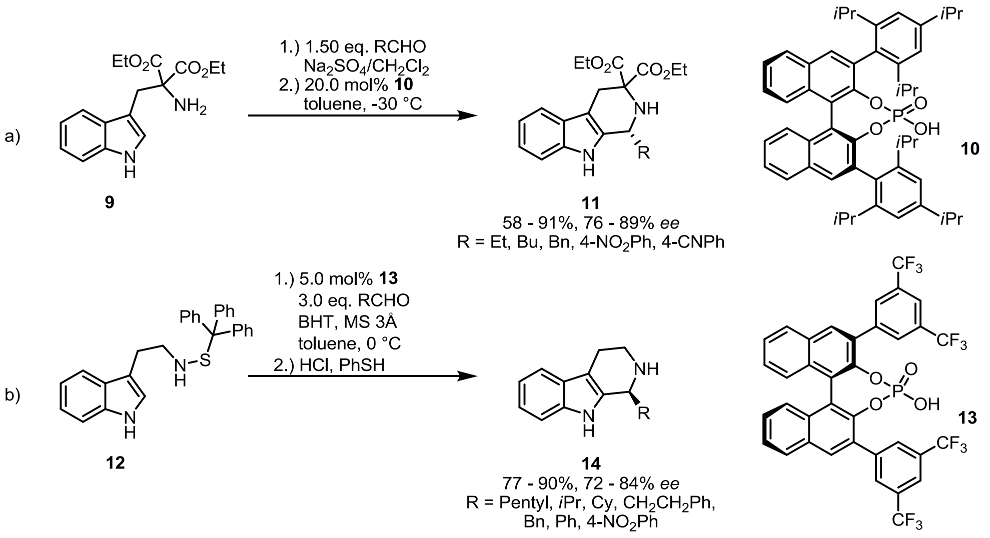
5 R = Ph, 2-NO$_2$Ph, 3-OMe-4-OAcPh, 4-OMePh, 3,4-ClPh

6

8 53-71%, 87 -96% *ee*, *d.r.* >74:26

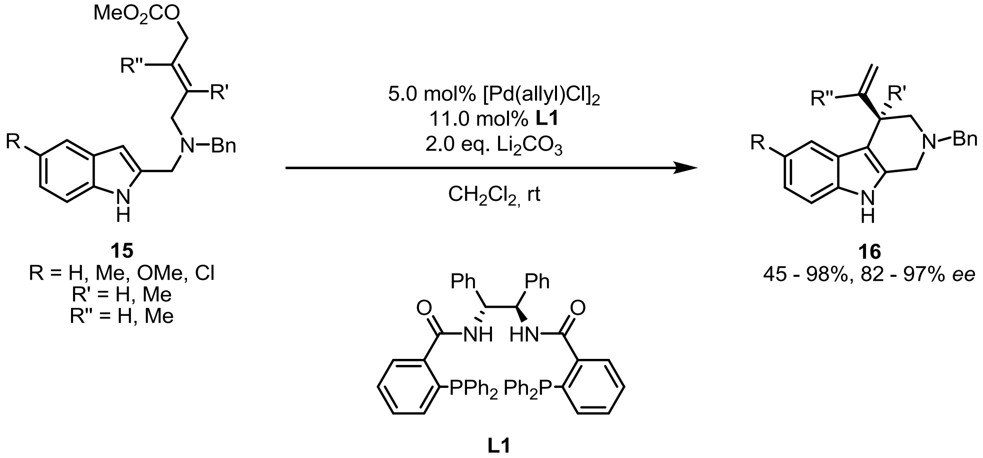
Scheme 1 Organocatalytic cascade reaction

The direct asymmetric Pictet-Spengler reaction with tryptamines and aldehydes to chiral β-carbolines represents a major challenge since after imine formation from the aldehyde and the primary amine fast isomerization to the corresponding enamines and subsequent aldol condensations take place.[19] This problem was overcome in related yet different ways recently (Scheme 2).[19-21] The asymmetric Pictet-Spengler reactions were carried out with catalytic amounts of chiral phosphoric acids[22,23] **10** and **13**. In the first case (Scheme 2a) the aldol condensation reaction could be suppressed by geminal substitution with esters **9**. Via this pathway, the corresponding β-carbolines **11** were isolated in up to very good yields and with good enantioselectivities. In the second case (Scheme 2b), the primary nitrogen was protected as the sulfenylamine **12** preventing the unwanted aldol-condensation from taking place. The sulfenylamine protecting group could be removed *in situ*. Like this, chiral β-carbolines **14** bearing no substituents on the piperidine ring were obtained with up to good selectivities. These two reports mark important breakthroughs for the asymmetric Pictet-Spengler reactions, however, it should be noted that the aldehydes and the corresponding R groups in products **11** and **14** are mostly unfunctionalized and hence prevent easy further application in synthesis, such as annulation to tetracyclic compounds. One notable exception to this is the use of an aldehyde bearing an acetal-protected ketone.[24]


a)
9
1.) 1.50 eq. RCHO
Na2SO4/CH2Cl2
2.) 20.0 mol% 10
toluene, -30 °C
11
58 - 91%, 76 - 89% ee
R = Et, Bu, Bn, 4-NO2Ph, 4-CNPh
10
b)
12
1.) 5.0 mol% 13
3.0 eq. RCHO
BHT, MS 3Å
toluene, 0 °C
2.) HCl, PhSH
14
77 - 90%, 72 - 84% ee
R = Pentyl, iPr, Cy, CH2CH2Ph,
Bn, Ph, 4-NO2Ph
13

Scheme 2 Catalytic asymmetric Pictet-Spengler reactions

Next to the abovementioned examples of organocatalytic approaches to β-carbolines also some transition metal-catalyzed reactions are known. In Scheme 3, an asymmetric Pd-catalyzed intramolecular allylic substitution is depicted.[25] When tryptamines **15** bearing an allylic carbonate moiety were subjected to allylic substitution conditions with catalytic amounts of a Pd/**L1** complex, the corresponding chiral β-carbolines **16** were isolated in up to excellent yields and with very good enantioselectivities. It should be noted, however, that if **16** was employed as a chiral building block in further synthesis, deprotection of the *N*-benzyl group under hydrogenolytic conditions would jeopardize the terminal double bond as well and thus would limit the possible further functionalizations at that position.



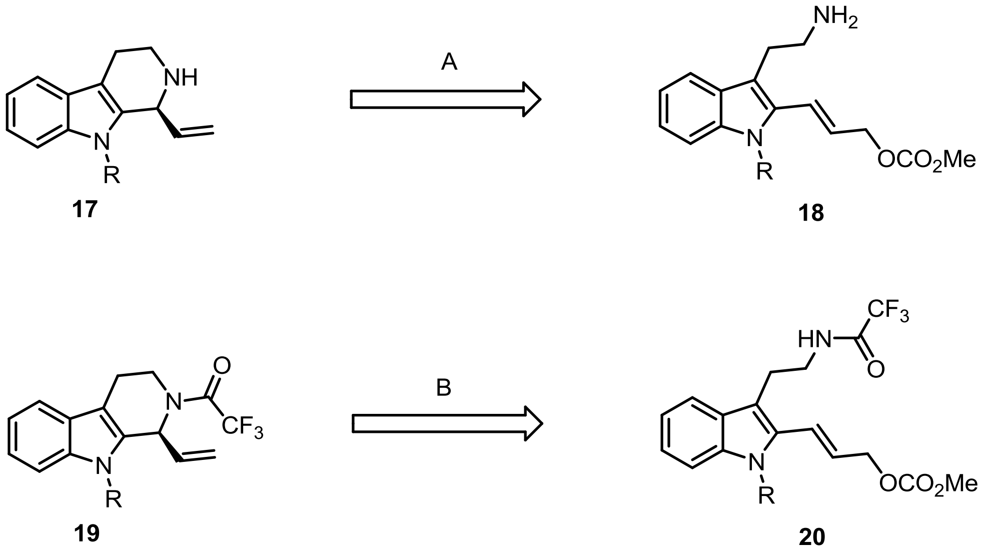
Scheme 3 Pd-catalyzed asymmetric synthesis of β-carbolines

2. Goal

The aim of this project was to develop a catalytic asymmetric synthesis of chiral β-carboline building blocks, in analogy to the asymmetric Ir-catalyzed allylic amidation for the synthesis of chiral tetrahydroisoquinolines (see Chapter 3). β-Carbolines and tetrahydroisoquinolines are related structures, the only difference being the "backbone" of the molecule containing an indole or a phenyl moiety, respectively. We therefore sought to expand the allylic substitution methodology to these structures. In analogy to the previously described catalytic asymmetric methodology, chiral building blocks with a multitude of starting points for further functionalization should be obtained via the envisaged route, furnishing valuable synthetic intermediates for further synthesis.

3. Results and discussion

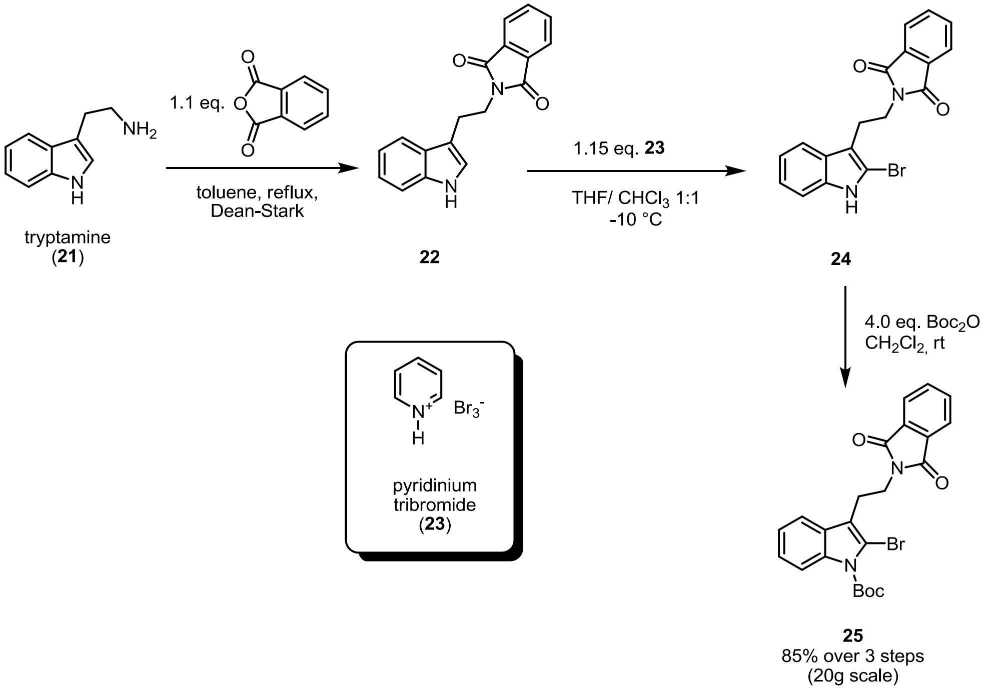
Two synthetic approaches were taken in this project, the first was to employ a direct allylic amination with a primary amine to construct the chiral piperidine of the β-carboline cores **18** with an unprotected primary nitrogen (path A in Scheme 4). This approach proved to be problematic due to the choice of protecting groups necessary for synthesis as well as incompatibility of the synthetic approach to **18** with the required leaving group for the allylic subsititution, the methyl carbonate. The second approach was to attempt the allylic amidation as outlined in Chapter 3, making use of a TFA *N*-protecting group in **20** that can still act as a nucleophile in the Ir-catalyzed allylic substitution (path B in Scheme 4). This approach was synthetically more viable, and the desired starting materials **20** for the construction of the chiral β-carbolines **19** were accessible in this way.



Scheme 4 Retrosynthetic approach to chiral β-carbolines

3.1 The direct allylic amination approach

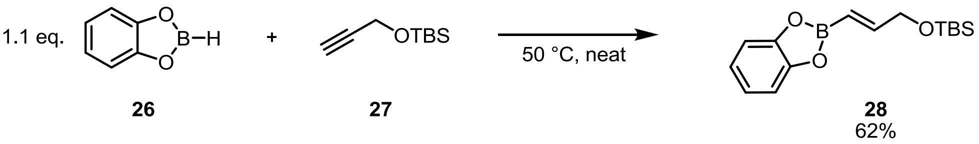
The synthetic approach to primary amine **18** was based upon literature precedents for the preparation of synthetic intermediates **22** to **25**,[26,27] employing a phthalimide protecting group for the primary amine of tryptamine (Scheme 5). We anticipated that the late-stage deprotection of the phthalimide to the primary amine should be compatible with the allylic carbonate moiety. After protection of both nitrogen atoms of **21** with a Boc and a phthalimide group, respectively, tryptamine **24** was converted to bromide **25** with pyridinium tribromide in excellent yields. Compound **25** served as precursor for the first key step in the synthesis of β-carbolines, since the allyl alcohol moiety would be installed via Pd-catalyzed cross coupling methodology.


1.1 eq.
toluene, reflux, Dean-Stark
tryptamine (21)
22
1.15 eq. 23
THF/ CHCl3 1:1
-10 °C
24
4.0 eq. Boc2O
CH2Cl2, rt
pyridinium tribromide (23)
25
85% over 3 steps
(20g scale)

Scheme 5 Synthesis of bromide 25

Suzuki cross coupling

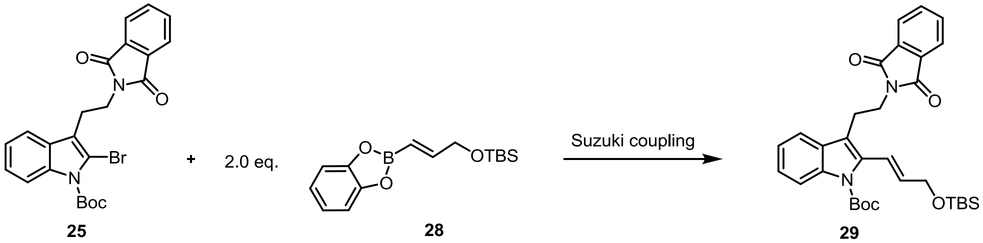
Among the first attempts to install the allyl alcohol moiety in the 2-position of the indoles was the investigation of a Suzuki coupling[28-32] of bromide **25** with boronate **28**,[26] which had been prepared from catecholborane (**26**) and TBS-protected propargylic alcohol **27** (Scheme 6).


1.1 eq.
26
27
50 °C, neat
28
62%

Scheme 6 Preparation of catecholboronate 28

The results of the Suzuki coupling are summarized in Table 1. First, literature conditions[26] were applied for the transformation of **25** (Table 1, entry 1), however, it was observed that only low coversion to the desired coupling product **29** was achieved. Milder conditions (Table 1, entry 2) did not lead to any conversion either. However, when a catalyst comprising of palladium(II) acetate and triphenylphosphine in the presence of aqueous sodium carbonate solution was investigated under different reaction conditions (Table 1, entries 3,4), it was found that both in propanol/water and THF/water mixtures the corresponding protected allylic alcohols **29** could be obtained with good yields after short reaction times. However, it turned out that these reactions were not reproducible, as the conversion was very low in most of the cases. Unfortunately, even after tedious purification of both **25** and **28**, the Suzuki coupling could not be rendered reproducible, so that it was necessary to investigate other cross coupling reactions.

Table 1 Suzuki coupling of bromide 25

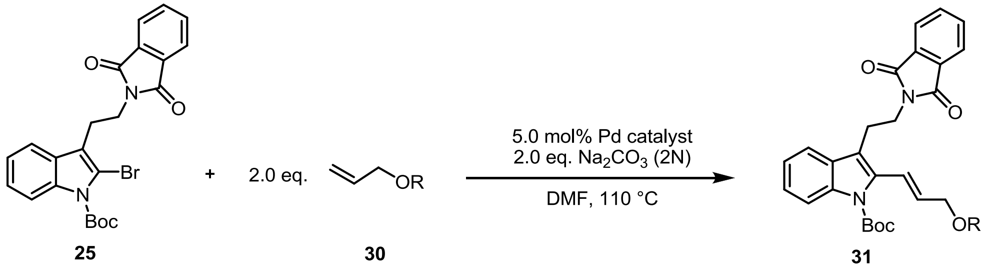


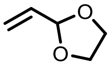
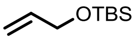
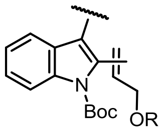
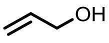
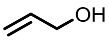
Entry	Conditions	Additive(s)	Comment	Yield of 29
1[26]	5.0 mol% $Pd(PPh_3)_4$ toluene, 100 °C	2N NaOH, 5.0 mol% LiCl	Low conversion	n.d.
2	5.0 mol% $Pd(PPh_3)_4$ 2.0 eq. Na_2CO_3 THF/H_2O 5:1, rt	-	No conversion	-
3	5.0 mol% $Pd(OAc)_2$ 10 mol% PPh_3 2.0 eq. Na_2CO_3 n-propanol/H_2O 5:1, reflux	-	Full conversion in 30 min, reaction is not reproducible	70%
4	5.0 mol% $Pd(OAc)_2$ 10 mol% PPh_3 2.0 eq. Na_2CO_3 THF/H_2O 5:1, reflux	5 drops ethylene glycol	Full conversion in 30 min, reaction is not reproducible	78%

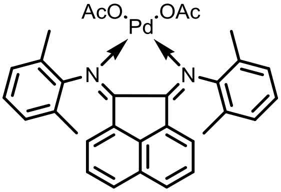
Heck cross coupling

The Heck reaction[31,33,34] of bromide **25** with allyl alcohol or derivatives thereof (**30**) was attempted next. With acetal-protected acrolein (Table 2, entry 1) no turnover was found with the standard catalyst comprising palladium(II) acetate and triphenylphosphine. Under the same conditions, TBS-protected allylic alcohol as well as allylic alcohol itself (Table 2, entries 2,3) were giving full conversion in short reaction times (~1 h), however the desired product **31** was isolated as a mixture with all other double bond isomers (E/Z, terminal/vicinal substitution), which could not be separated, rendering this coupling not useful for the further synthesis. The same result was found when Pd-BIAN[35] complex **32**, which had been successfully used in the related oxidative Heck reaction,[36] was employed for the Heck reaction with allyl alcohol.

Table 2 Heck reaction of bromide 25



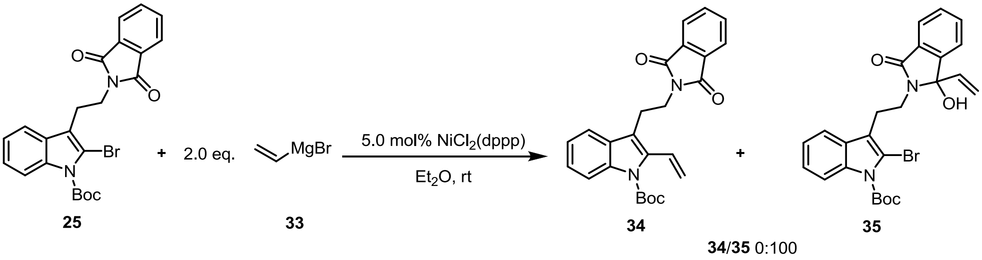
Entry	Catalyst	Allyl alcohol	Comment	
1	5.0 mol% $Pd(OAc)_2$ 10.0 mol% PPh_3		No conversion	
2	5.0 mol% $Pd(OAc)_2$ 10.0 mol% PPh_3		Full conversion, mixture of double bond isomers (65%)	
3	5.0 mol% $Pd(OAc)_2$ 10.0 mol% PPh_3		Full conversion, mixture of double bond isomers	
4	5.0 mol% **32**		Full conversion, mixture of double bond isomers	



32

Kumada cross coupling

The Kumada cross coupling[37] of **25** with vinylmagnesium bromide was also investigated. The corresponding terminal olefin **34** was anticipated to be further transformed to the desired allyl carbonate by cross metathesis (compare Chapters 2 and 3). However, it was found that under the reaction conditions, the phthalimide protecting group was not tolerated, as a fast and selective attack on the imide to give **35**, was observed.

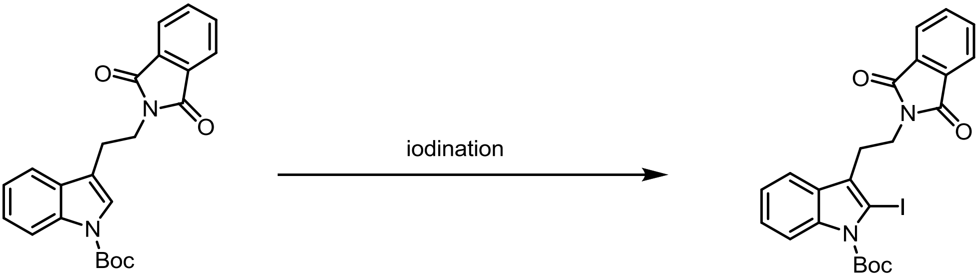


Scheme 7 Attempted Kumada coupling

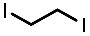
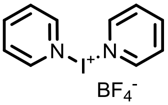
Stille cross coupling

As the last option, we attempted the Stille reaction to install the allylic alcohol moiety in the 2-position of the indole. Since it is known that the Stille reaction works best with unsaturated iodides as coupling partners,[38-40] we set out to synthesize the corresponding iodide, starting off from fully protected tryptamine **36**. As illustrated in Table 3, a variety of conditions were investigated. Most of the entries – with the exception of entry 3 – do give conversion to the desired iodide **37**, however, the products are accompanied by side-products or not-separable impurities. Similar results were found with lithiation and subsequent trapping with iodine or 1,2-diiodoethane[41] (Table 3, entries 1,2). With the strongly electrophilic iodonium monochloride, deprotection of the Boc group was observed (Table 3, entry 3), most probably due to a Lewis acid-promoted elimination of the *tert*-butoxy moiety. Using the highly active bispyridine iodonium tetrafluoroborate (Table 3, entry 4),[42] the desired product **37** was observed in the reaction mixture, but could not be obtained pure. To our delight, a mercury-mediated iodination[43] gave excellent results in terms of yields and selectivities, and **37** could be obtained in up to 2 g scale via this method (Table 3, entry 5).

Table 3 Iodination of tryptamine 36

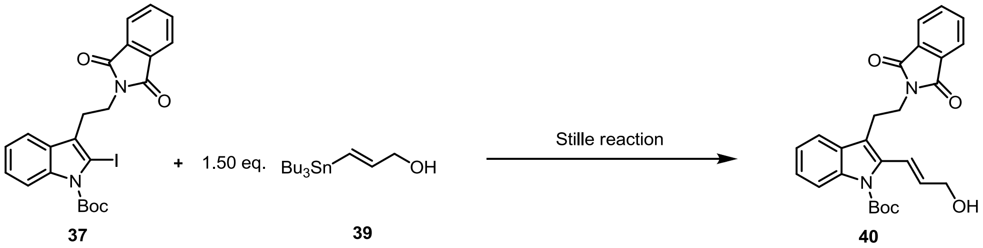


36 **37**

Entry	Conditions	Conversion	Comment
1	2.4 eq. *t*BuLi, 2.6 eq. I_2 THF, -78 °C to rt	Mixture of products	
2	1.1 eq. *t*BuLi, 1.0 eq. **38**[41]	Mixture of products	 **38**
3	1.1 eq. ICl, CH_2Cl_2, rt	Full conversion, deprotection of Boc group	
4[42]	1.1 eq. IPy_2, 2.2 eq. HBF_4, CH_2Cl_2, rt	Mixture of products	 IPy_2
5[43]	1.3 eq. $Hg(OTFA)_2$, CH_2Cl_2, rt 1.5 eq. I_2	Selective reaction, quantitative yield	can be scaled to 2g

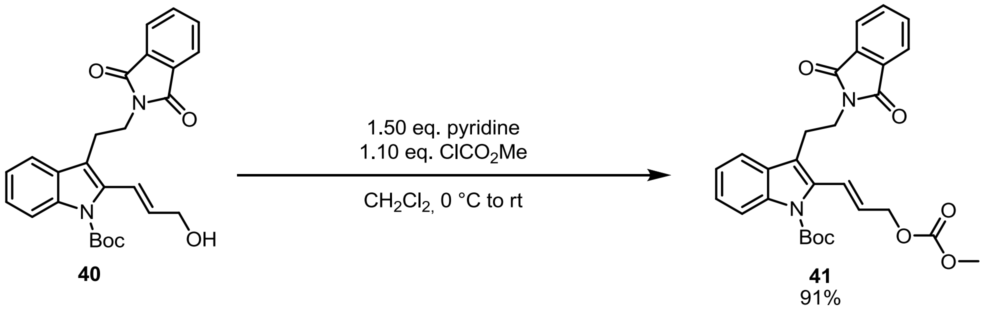
With iodide **37** in hand, we investigated the Stille coupling reaction (Table 4) with stannane **39**, which was obtained in one step from propargyl alcohol.[44] We started off optimizing the reaction conditions, employing $Pd(PPh_3)_4$ as catalyst and LiCl as additive.[38] However, with various solvents tested, little or no conversion to the coupling product **40** was observed (Table 4, entries 1-3). Addition of CsF and catalytic amounts of CuI, which had led to improved results in earlier studies,[45] showed no effect on the envisaged reaction (Table 4, entry 4). However, at elevated temperatures and with a Pd(II) precatalyst, the desired product was obtained in acceptable yield (Table 4, entry 5). Furthermore, this reaction proved to be scalable without compromizing the yields. From the optimization, it is not clear yet whether the temperature or the additive in combination with the Pd precursor was the decisive change for the positive outcome of the reaction.

Table 4 Optimization Stille coupling



Entry	Conditions	Additives	Comment
1	5.0 mol% Pd(PPh$_3$)$_4$, DMF, 50 °C	3.0 eq. LiCl	Low conversion
2	5.0 mol% Pd(PPh$_3$)$_4$, THF, 50 °C	3.0 eq. LiCl	Low conversion
3	5.0 mol% Pd(PPh$_3$)$_4$, toluene, 50 °C	3.0 eq. LiCl	Low conversion
4[45]	5.0 mol% Pd(PPh$_3$)$_4$, DMF, 50 °C	2.0 eq. CsF 10 mol% CuI	Low conversion
5	5.0 mol% PdCl$_2$(PPh$_3$)$_2$, DMF, 75 °C	3.0 eq. LiCl	65% yield

Allylic alcohol **40** could be smoothly transformed to the corresponding methyl carbonate **41** (Scheme 8), which bears the necessary leaving group for the anticipated Ir-catalyzed allylic substitution.

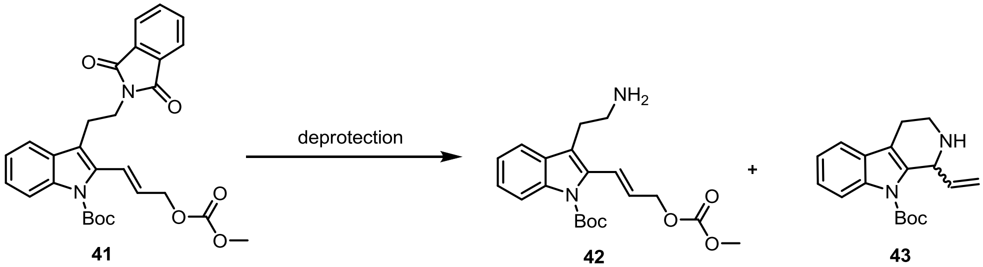


Scheme 8 Synthesis of allylic carbonate 41

With allylic carbonate **41** in hand, we set off to investigate the deprotection of the phthalimide protection group. This was expected to be a difficult transformation, since phthalimides are generally cleaved with nucleophilic reagents. However, the allylic carbonate which is also present in **41** should also be susceptible to nucleophilic attack. The same holds true if a reductive pathway should be chosen. Therefore, judicious choice of deprotection conditions was expected to be necessary. As a third requirement, the Boc protection of the indole moiety in **41** should remain intact, since indoles are known to be *N*-nucleophiles in the Ir-catalyzed allylic amination.[46] Protection of this position ensured supression of a competing intermolecular allylic substitution.

We started off by investigating the deprotection of the phthalimide group with hydrazine hydrate (Table 5).[47] Under standard conditions in ethanol at ambient temperature, it was observed that **41** did not dissolve and with one equivalent of hydrazine, no reaction took place (Table 5, entry 1). When more equivalents of hydrazine were added, little conversion to the desired deprotected primary amine was observed (Table 5, entry 2). However, when the reaction mixture was allowed to stir overnight, full conversion of the primary amine **42** to the ring-closed β-carboline **43** was observed, most probably due to the basicity of hydrazine (Table 5, entry 3). Reactions which employed hydrazine stock solutions in either EtOH or THF led to no conversion (Table 5, entries 4-6), with the exception of the reaction using an excess of hydrazine in THF, which led to equal amounts of the desired **42**, next to the ring-closed **43** and aminoalcohol **44** (Table 5, entry 7). It is known in literature that phthalimides can also be deprotected with primary amines,[47-49] so we investigated this possibility next. Indeed, this manner of deprotection proved to be more fruitful, since we observed full conversion of phthalimide **41** with an excess of methylamine in water (Table 5, entry 8), albeit with complete conversion to β-carboline **43**. When the solvent was changed to ethanol, full conversion to the desired primary amine **42** was achieved, however in this case, diamide **45** and semi-deprotected diamide **46** being inseparable impurities (Table 5, entries 9,10). It was compound **42** from these reactions that was used for further studies. Finally, the deprotection with butylamine was attempted to achieve an easier purification of **42**, but these reaction either led to low conversion to **42** overnight, or to complete deprotection to amino alcohol **44** (Table 5, entries 11,12).

Table 5 Deprotection of phthalimide 41

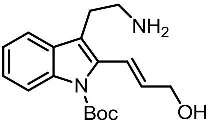


41 **42** **43**

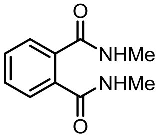
Entry	Conditions	Comment	42/43[a]	
1	1.0 eq. $H_2NNH_2{\bullet}H_2O$, EtOH, rt	After 1h, no conv.	-	**41** does not dissolve
2	3.0 eq. $H_2NNH_2{\bullet}H_2O$, EtOH, rt	After 1h, low conv. (~10%)	100/0	**41** dissolves
3	3.0 eq. $H_2NNH_2{\bullet}H_2O$, EtOH, rt	After 16h, low conv. (~20%)	0/100	**41** dissolves
4	1.0 eq. $H_2NNH_2{\bullet}H_2O$[b], EtOH, rt	No conv. after 16h	-	-
5	5.0 eq. $H_2NNH_2{\bullet}H_2O$[b], EtOH, rt	No conv. after 16h	-	-
6	1.0 eq. $H_2NNH_2{\bullet}H_2O$[c], EtOH, rt	No conv. after 16h	-	-
7	4.0 eq. $H_2NNH_2{\bullet}H_2O$[c], EtOH, rt	2h, (50% conv.)	20/20	**44** as sideproduct
8	5.0 eq. $MeNH_2$ (40% in H_2O), EtOH, rt, 16h	Full conv.	0/100	50% **43**
9	5.0 eq. $MeNH_2$ (33% in EtOH), EtOH, rt, 16h	50% conv.	100/0	Major impurities **45** + **46**

Entry	Conditions	Comment	42/43[a]	
10	10.0 eq. $MeNH_2$ (33% in EtOH), EtOH, rt, 16h	Full conv.	100/0	Major impurities **45** + **46**
11	10.0 eq. $BuNH_2$, EtOH, rt, 16h	20% conv.	100/0	
12	10.0 eq. $BuNH_2$, EtOH, rt, 48h	80% conv.	-	Only **44** found

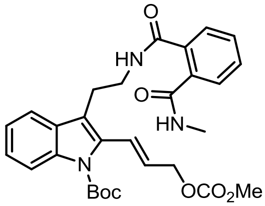
[a]Arbitrary units, ratio measured by ^{1}H NMR. [b]Hydrazine hydrate stock solution in EtOH (1M). [c]H_2NNH_2 solution in THF (1M).



44



45

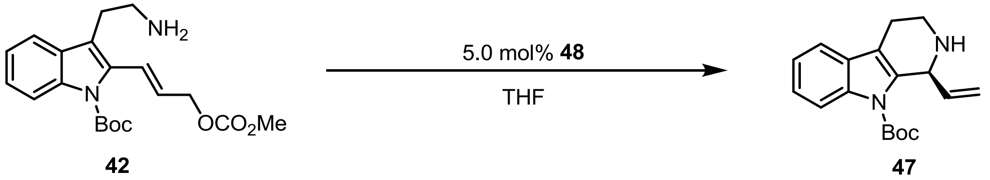


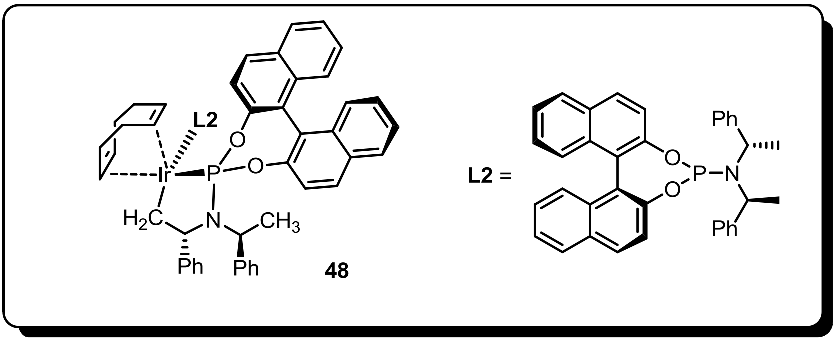
46

From the attempts to deprotect phthalimide **41** selectively, it can be concluded that one the one hand, employing hydrazine the desired selective deprotection could not be achieved due to overreaction to **43**. On the other hand, with methylamine the reaction does work and can be summarized as follows: The first nucleophilic attack on the phthalimide to give diamide **46** is very fast (1 h), the second attack on **46** itself is then much slower, which is accompanied by unwanted side reactions to amino alcohol **44**.

With impure **42** in hand, we attempted the Ir-catalyzed allylic amination with iridacycle **48** (Table 6). Generally, this reaction does not require a base,[50] but under these conditions, no conversion of **42** was found (Table 6, entry 1). With more drastic conditions employing Cs_2CO_3 as a base and elevated temperatures, which had been employed earlier for the allylic substitution with indoles,[51] also no conversion to **47** was found either (Table 6, entry 2).

Table 6 Attempted Ir-catalyzed allylic amination





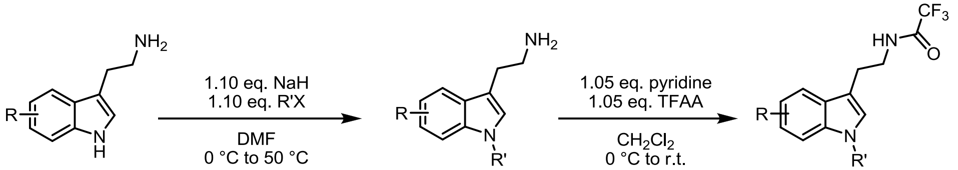
Entry	Conditions	Comment
1	rt, 16h	No conversion
2	2.0 eq. Cs_2CO_3, 50 °C, 16h	No conversion

From these results is was not clear as to why the anticipated reaction did not work as envisaged. It could be that the impurities of **42** played a role, although a possible coordination of the Boc-group to the Ir-catalyst and subsequent deactivation of the catalyst could not be excluded. It is also interesting to note that under basic conditions during the deprotection of the phthalimide with hydrazine (see Table 5) the corresponding β-carboline **43** was observed, but not in the case of the reaction with Cs_2CO_3 with elevated temperatures. Thus, another possibility of deactivation of the catalyst could be the strong interaction of the allylic carbonate **42** with the catalyst that would lead to deactivation by formation of a catalytically inactive Ir complex.

With the results of the unsuccessful allylic amination to give β-carbolines and the problems associated with the deprotection of the phthalimide protecting group in hand, we decided to adapt our synthetic approach. Having established the key synthetic steps to construct the allylic carbonate via Stille coupling of a 2-iodoindole (*vide supra*), we decided to change the protecting group strategy, but keep the same synthetic approach. We envisioned to investigate the use of an *N*-substituent that would serve on the one hand as a protecting group during the Pd-catalyzed cross coupling, and on the other hand act as the nucleophile for an allylic substitution (see also Chapter 3). Furthermore, the protecting group of the indole-nitrogen was varied, so that possible influences of the Boc-group of the previous approach could be investigated.

3.2 The allylic amidation approach

Our synthetic approach started from commercially available tryptamines **21** (Scheme 9). After protection of the indole nitrogen and trifluoroacetylation of the primary amine we obtained the protected tryptamines **48a-c** in very good yields. Furthermore, trifluoroacetamide **47d** without a substituent on the indole nitrogen could be synthesized.



21
R = H, 5-OMe

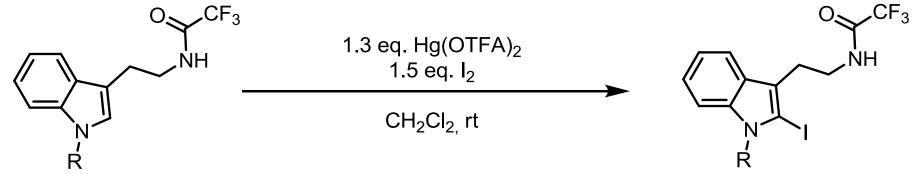
47a: R = H, R' = Me
47b: R = H, R' = Bn
47c: R = 5-OMe, R' = Bn

yield over 2 steps
48a: R = H, R' = Me, 84%
48b: R = H, R' = Bn, 87%
48c: R = 5-OMe, R' = Bn, 81%
47d: R = H, R' = H, 98% (from **21**)

TFAA = Trifluoracetic ahydride

Scheme 9 Synthesis of trifluoroacetamide-protected indoles

We then went on to investigate the possible iodination of **48** in the 2-position of the indole system. The reported Hg-mediated iodination[43], that had been used earlier on Boc-protected indoles **36** (*vide supra*) worked also fine for the trifluoroacetamide **48d** with a Boc protecting group (Scheme 10). However, in the case of indoles **48a-c** with a different substitution than Boc on the indole-nitrogen, this transformation proved to be difficult when scaling up the reactions. This outcome was unexpected, and could be explained by solubility problems of either the indoles **48a-c** or the mercury salt, as very high dilutions have been shown to be necessary for the reaction to proceed smoothly. About a further coordination or a stabilizing role of the previously employed Boc-protecting group can only be speculated at this point.

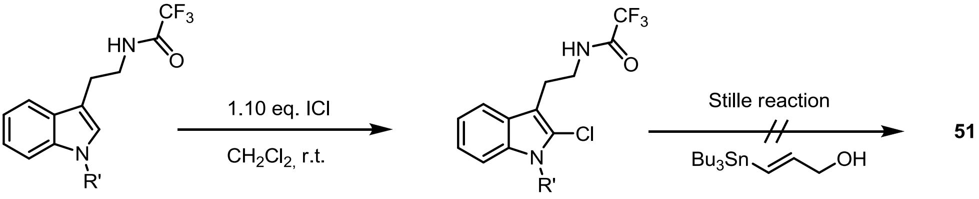


48
R = H, Me, Bn, Boc

49a-c: R = H, Me, Bn: low conversion
49d: R = Boc: 66%

Scheme 10 Hg-mediated iodination of 48

We turned to the use of iodine monochloride as an electrophilic iodination agent for **48**, which we had successfully applied on electron-rich phenylethylamine derivatives (see Chapter 3).[52,53] In the case of tryptamines **48a** and **47d** this showed to be no feasable synthetic pathway, as the corresponding chlorides **50** were isolated (Scheme 11), resulting from a reaction of the indole moiety of **47d**/**48a** in the 2-position with ICl. The following Stille reaction (see also Scheme 12) with stannane **52** showed no turnover with the chlorides **50**.



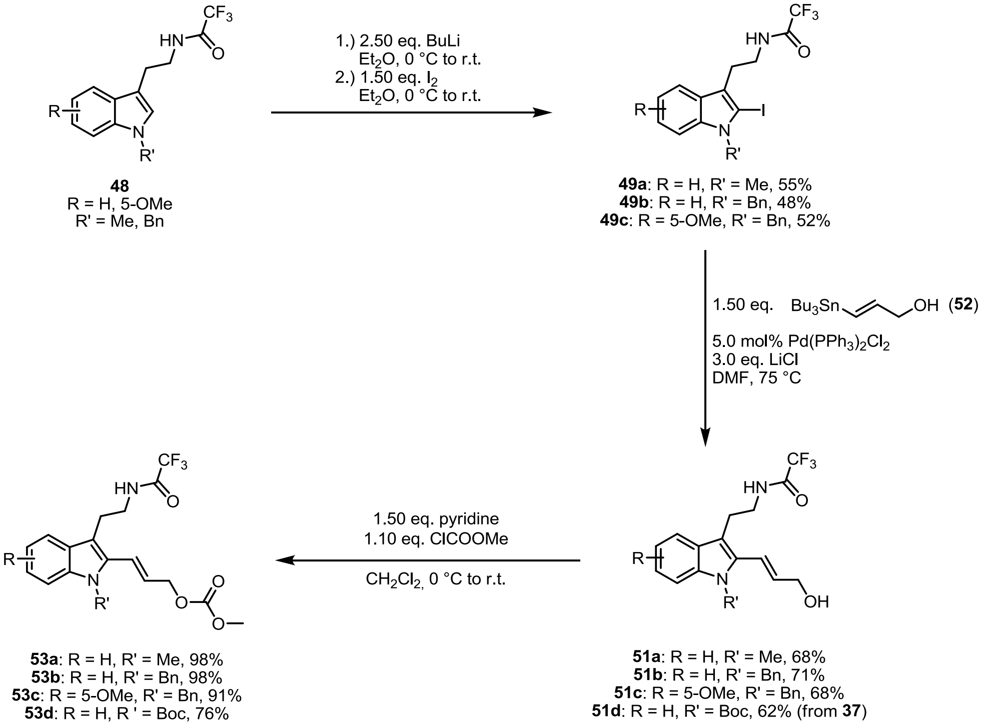
(**52**)

47d: R' = H
48a: R' = Me

50a: R' = H, 80%
50b: R' = Me, 78%

Scheme 11 Attempted Stille reaction with chlorotryptamines

For the synthesis of the desired iodoindoles **49**, suitable reagents for the envisaged Pd-catalyzed carbon-carbon coupling reaction later on in the synthetic route, we refrained to a lithiation-iodination protocol. After metalation of **48** with butyllithium, iodine as electrophile furnishes the desired iodine-substituted indoles **49** in moderate yields. (For the trapping of the lithiated species with another electrophile, see Scheme 16) For the following cross-coupling, the role of the trifluoroacetamide group as a protecting group was exploited. Since Pd-catalyzed couplings only rarely proceed in the presence of primary amines, this feature comes in to our advantage. Subsequently, the allylic alcohol moiety was introduced via Stille coupling with stannane **52**.[44] In the case of the iodides **49**, the coupling proceeded smoothly to the desired allylic alcohols **51** (68 - 71%). These could be transformed to the corresponding methyl carbonates **53** in a straightforward manner (Scheme 12).

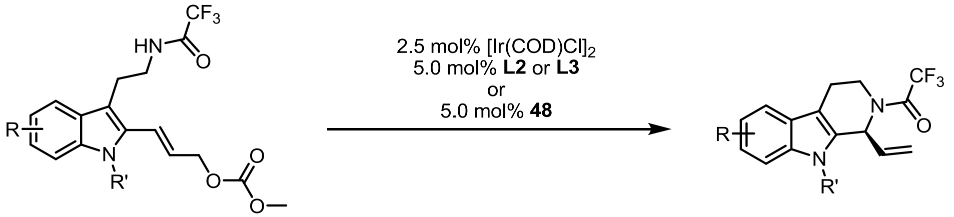

CF3
HN
O
R
N
R'
48
R = H, 5-OMe
R' = Me, Bn
1.) 2.50 eq. BuLi
Et2O, 0 °C to r.t.
2.) 1.50 eq. I2
Et2O, 0 °C to r.t.
I
49a: R = H, R' = Me, 55%
49b: R = H, R' = Bn, 48%
49c: R = 5-OMe, R' = Bn, 52%
1.50 eq. Bu3Sn OH (52)
5.0 mol% Pd(PPh3)2Cl2
3.0 eq. LiCl
DMF, 75 °C
OH
51a: R = H, R' = Me, 68%
51b: R = H, R' = Bn, 71%
51c: R = 5-OMe, R' = Bn, 68%
51d: R = H, R' = Boc, 62% (from 37)
1.50 eq. pyridine
1.10 eq. ClCOOMe
CH2Cl2, 0 °C to r.t.
53a: R = H, R' = Me, 98%
53b: R = H, R' = Bn, 98%
53c: R = 5-OMe, R' = Bn, 91%
53d: R = H, R ' = Boc, 76%

Scheme 12 Synthesis of protected allylic carbonates

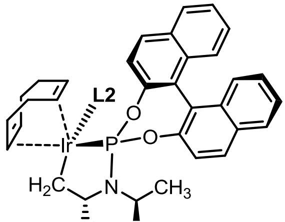
With allylic carbonates **53** in hand, we set off to investigate whether they would serve as precursors to a selection of transition metal-catalyzed allylic amidation reactions, based on Ir or Pd catalysts. Both methodologies had been proven viable for the related phenylethylamine derivatives[53,54] to give tetrahydroisoquinolines, and, in the case of the Ir-catalyzed allylic amidation, also chiral saturated *N*-heterocycles (see Chapter 3).

The results of the attempted Ir-catalyzed allylic amidation are summarized in Table 7. First, the influence of different substitutions on the indole moiety were investigated with a catalyst comprising 2.5 mol% of $[Ir(COD)Cl]_{2,}$ 5.0 mol% phosphoramidite **L2** and two equivalents of DBU (Table 7, entries 2-6). Under these conditions, neither of the allylic carbonates **53** gave any conversion to **54**, supporting the notion that the influence of the Boc-group which was believed to prevent the Ir-catalyzed allylic amination from occuring earlier (Table 6) does not have a major influence on the catalyst. Also, **L3** was employed in one case (Table 7, entry 4) but no improvement was observed. When the temperature was raised to 90 °C, a small amount of the desired product **53** was observed (Table 7, entries 7-10), however, it could be shown that this was the product of a blank reaction independent of the presence of Ir-catalyst and **54** was thus formed in a racemic fashion (Table 7, entry 8). Finally, the influence of a variety of bases was investigated with benzyl-protected indole **53** (Table 7, entries 11-17). Again, it was found that the influence of the base on the envisaged reaction is remarkable, with TBD leading to decomposition of the starting material (Table 7, entry 11) and K_3PO_4 leading to no conversion at all (Table 7, entry 13). However, it could be established that the blank reaction without Ir catalyst proceeded cleanly to the desired products at elevated temperatures in dioxane with Cs_2CO_3 as a base (Table 7, entry 17). The employment of the much stronger base NaH led to decomposition of allylic carbonate **53** to the corresponding allylic alcohol **51** (Table 7, entries 18,19).

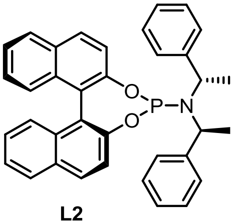
Table 7 Attempted Ir-catalyzed allylic amidation



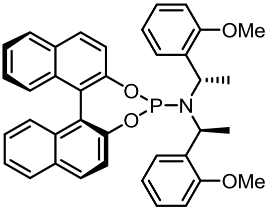
53 **54**



48



L2



L3

Entry	R	R'	Catalyst	Conditions	Comment
1	H	Boc	-	2.0 eq. DBU, THF, 50 °C, 16h	no conversion
2	H	Boc	$[Ir(COD)Cl]_2$/**L2**	2.0 eq. DBU, THF, 50 °C, 16h	no conversion
3	H	Me	$[Ir(COD)Cl]_2$/**L2**	2.0 eq. DBU, THF, 50 °C, 16h	no conversion
4	H	Me	$[Ir(COD)Cl]_2$/**L3**	2.0 eq. DBU, THF, 50 °C, 16h	no conversion
5	H	Bn	$[Ir(COD)Cl]_2$/**L2**	2.0 eq. DBU, THF, 50 °C, 16h	no conversion

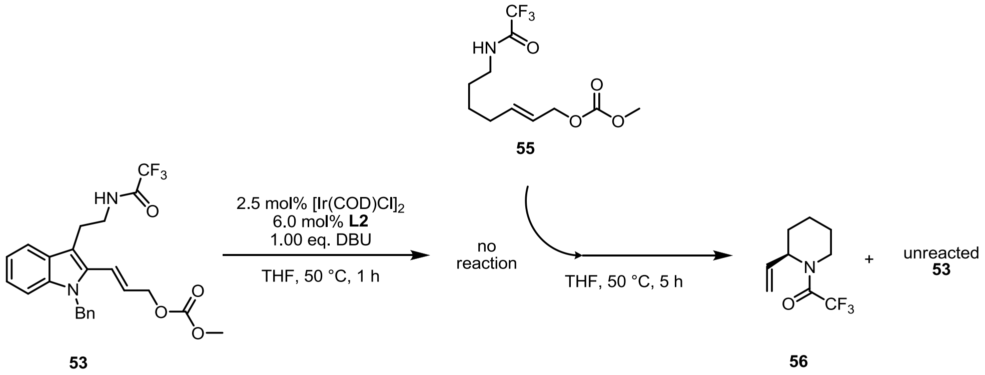
Entry	R	R'	Catalyst	Conditions	Comment
6	OMe	Bn	$[Ir(COD)Cl]_2$/**L2**	2.0 eq. DBU, THF, 50 °C, 16h	no conversion
7[a]	H	Me	**48**	2.0 eq. DBU, THF, 50 °C to 90 °C, 16h	no conversion
8	H	Me	**-**	2.0 eq. DBU, dioxane, 90 °C, 16h	~10% conversion[b]
9	H	Me	**48**	2.0 eq. DBU, dioxane, 90 °C, 16h	~10% conversion[b]
10	H	Me	$[Ir(COD)Cl]_2$/**L3**	2.0 eq. DBU, dioxane, 90 °C, 16h	~10% conversion[b]
11	H	Bn	**48**	2.0 eq. TBD, dioxane, 100 °C, 16h	decomposition of **53**
12	H	Bn	**48**	2.0 eq. DABCO, dioxane, 100 °C, 16h	~50% conversion[b,c]
13	H	Bn	**48**	2.0 eq. K_3PO_4, dioxane, 100 °C, 16h	no conversion
14	H	Bn	**48**	2.0 eq. Cs_2CO_3, dioxane, 100 °C, 16h	~70% conversion[b,c]
15	H	Bn	**48**	2.0 eq. Cs_2CO_3, toluene, 100 °C, 16h	~10% conversion[b,c]
16	H	Bn	**48**	2.0 eq. Cs_2CO_3, dioxane, 100 °C,[d] 16h	Full conversion[b,c]
17	H	Bn	**-**	2.0 eq. Cs_2CO_3, dioxane, 100 °C, 16h	full conversion
18	H	Bn	-	1.0 eq. NaH, THF, rt	full conversion to **51**
19	OMe	Bn	-	1.0 eq. NaH, THF, rt	full conversion to **51**

[a]Reaction was carried out in a sealed tube. [b] Determined by ^{1}H NMR. [c]**53** was isolated as a racemic mixture. [d]Microwave heating (300W, 2h).

From these results it was concluded that the Ir-catalyzed intermolecular allylic amidation to form β-carbolines was not successful. It could be speculated as to why this reaction did not take place, keeping in mind that the related tetrahydroisoquinolines were easily accessible through this synthetic pathway (see Chapter 3). In the case of **54**, the six-membered heterocycles formed is part of a ring system that is annulated to a five membered ring, namely the indole. This is in contrast to the tetrahydroisoquinolines, where a phenyl ring was attached to the piperidine to be formed. This structural change could have lead to steric constraints which prevented the Ir-catalyst to attack, or prevent an intermediate Ir-allyl complex from reacting further to the desired products. Furthermore, it could be speculated that the electronic changes brought about by the indole moiety change the electronic nature of the allylic carbonate in such a way that an allylic substitution is prevented from taking place. A last possibility would be the formation of a catalytically inactive Ir-indole complex which would lower the concentration of active catalyst in the reaction mixture. To probe some of these issues, a variety of test reactions were carried out.

Competition Experiments

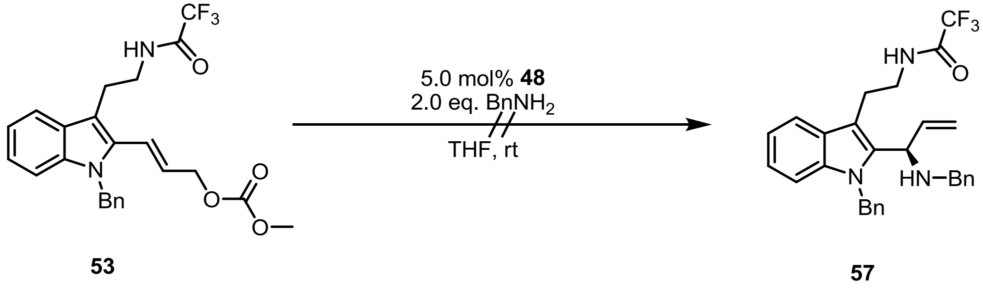
To probe as to why the Ir-catalyzed allylic amidation of **53** would not take place, we conducted a competition experiment (Scheme 13). Carbonate **53** was subjected to the standard asymmetric allylic amidation conditions for 1 h, after which **53** was found to be completely unreacted in the mixture. Then, linear allylic carbonate **55** was added and stirred under the same conditions for 5 more hours. After this time, carbonate **55** had been fully converted to chiral piperidine **56** as previously reported (see Chapter 3), whereas tryptamine-derived carbonate **53** was left unreacted in the mixture. From this experiment it can be concluded that no stable Ir complex with tryptamine **53** is formed, since no deactivation of the catalyst was observed when a second substrate was added. The formation of a catalytically active species of the Ir complex with **53** seemed to be prevented due to the steric and/or electronic parameters of **53**. The competition experiment was also carried out in deuterated THF and followed by ^{31}P NMR spectroscopy, but no catalytically active species was observed, so no clear conclusions could be drawn from this experiment. The observation of an active catalytic species in Ir-catalyzed allylic substitutions has generally been elusive.[55-58]



Scheme 13 Competition experiment

Intermolecular allylic amination

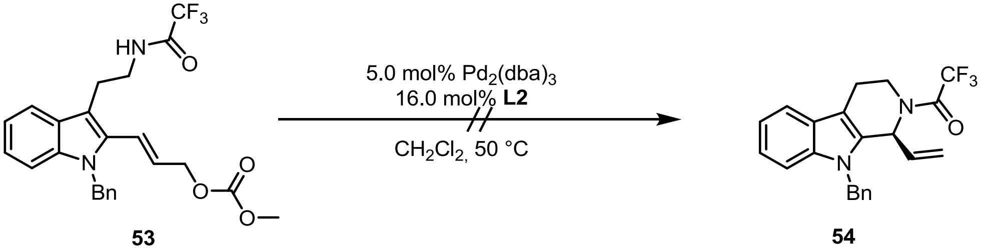
To test whether or not an Ir-allyl complex, which is generally accepted to be the key catalytic intermediate in Ir-catalyzed allylic substitutions[56,58,59] was formed, an intermolecular allylic amination was carried out under previously published reaction conditions (Scheme 14).[55] When allylic carbonate **53** was reacted with an excess of benzylamine in the presence of iridacycle **48** as catalyst, no conversion of the starting material was observed.[60] From this observation it can be concluded that most probably there is no Ir-allyl species formed, which is a prerequisite for the allylic substitution to occur. Therefore, it seems that attack of the Ir catalyst on allylic carbonate **53** is prevented either by steric or electronic factors.



Scheme 14 Attempted intermolecular allylic amination

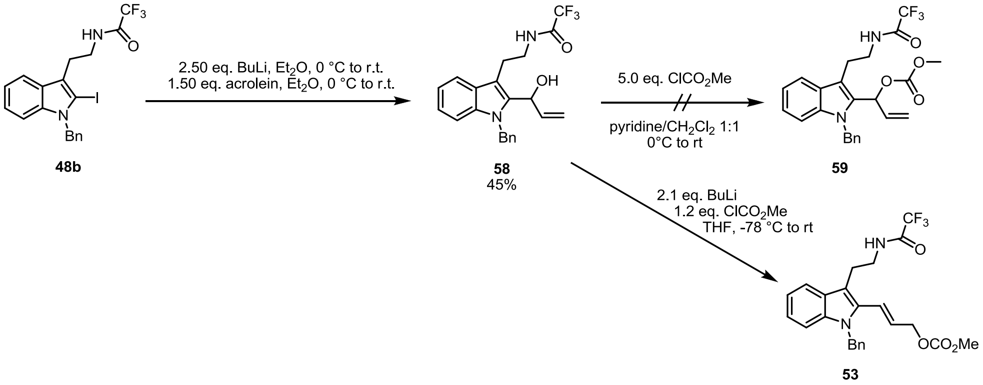
Pd-catalyzed allylic amidation

Finally, an effort was made to examine the allylic amidation with a Pd-phosphoramidite complex as catalyst. This had been published earlier as an efficient catalyst to prepare a chiral tetrahydroisoquinoline from the corresponding allylic carbonates and trifluoroacetamides.[54] However, under these conditions (Scheme 15), no conversion of **53** was observed. This hints at a problem with the reactivity of the starting material, since two transition metal-based catalysts, previously successful for the synthesis of tetrahydroisoquinolines, did not achieve any conversion to the desired product **54**.



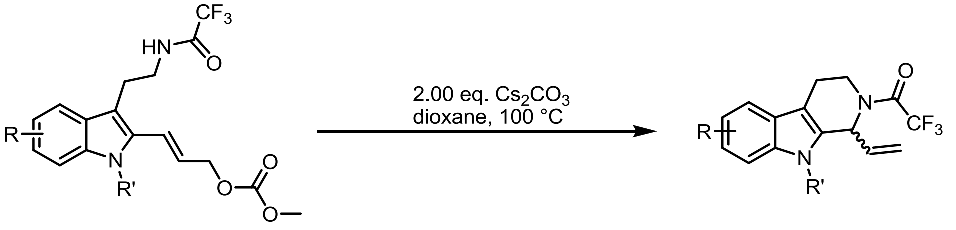
Scheme 15 Attempted Pd-catalyzed allylic amidation

To make the allylic carbonate more accessible for a potential transition metal-based catalyst, we attempted to synthesize an allylic carbonate with a “reversed” allyl moiety, meaning that the corresponding secondary allylic alcohol would be synthesized. These kind of substrates had been shown to undergo allylic amination with Ir-phosphoramidite catalysts as well.[61] When iodoindole **48b** was lithiated as shown previously and then quenched with acrolein as electrophile, secondary allylic alcohol **58** could be obtained. It was then attempted to transform **58** to the desired carbonate **59**, however the standard conditions for the transformation of an alcohol to a carbonate failed to give any conversion (Scheme 16). When the same experiment was carried out with the stronger base BuLi, the rearranged linear allylic carbonate **53** was isolated. This route was not followed further.


2.50 eq. BuLi, Et2O, 0 °C to r.t.
1.50 eq. acrolein, Et2O, 0 °C to r.t.
5.0 eq. ClCO2Me
pyridine/CH2Cl2 1:1
0°C to rt
2.1 eq. BuLi
1.2 eq. ClCO2Me
THF, -78 °C to rt
48b
58
45%
59
53

Scheme 16 Attempted synthesis of an indole carrying a secondary allyl carbonate

In the end, racemic β-carbolines were synthesized via the route that had been discovered during the catalyst screening process (compare Table 7). When allylic carbonates **53a-c** were reacted with Cs_2CO_3 as a base at elevated temperatures, the corresponding β-carbolines **60a-c** were obtained in good yield (Scheme 17).

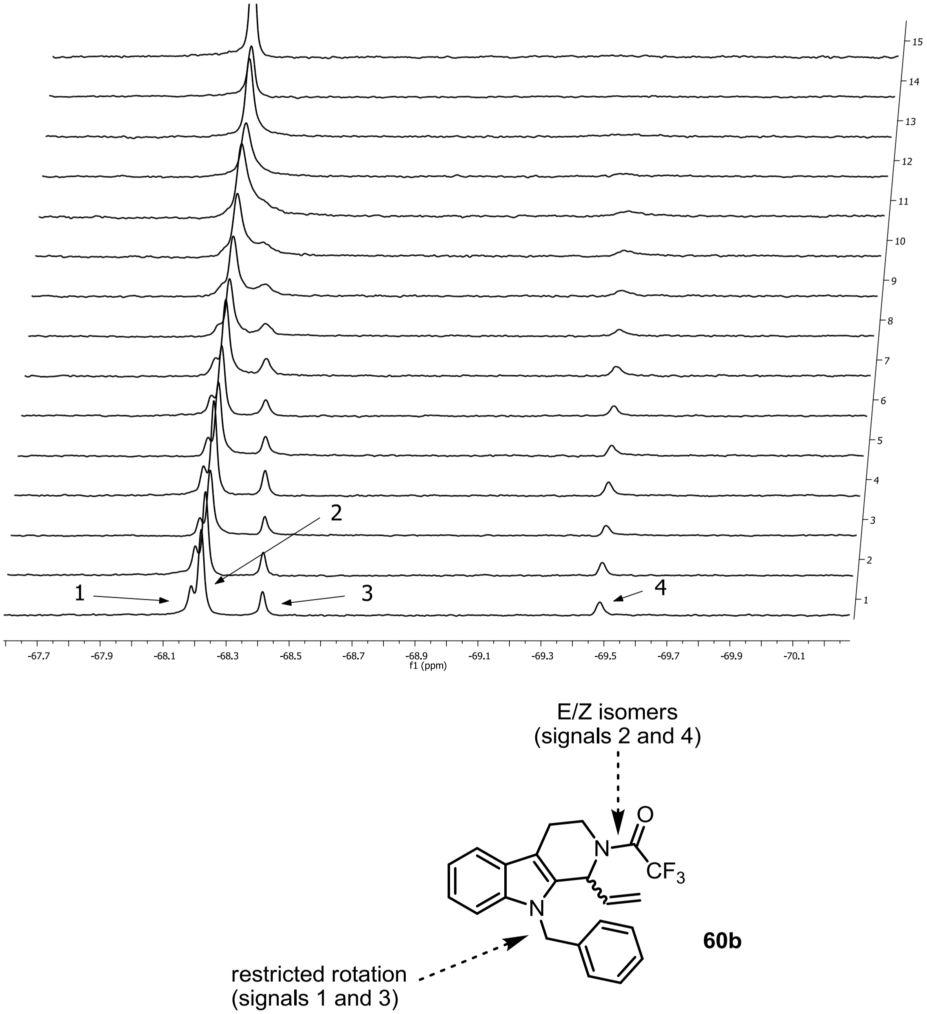

2.00 eq. Cs2CO3
dioxane, 100 °C

53

60a: R = H, R' = Me, 82%
60b: R = H, R' = Bn, 76%
60c: R = 5-OMe, R' = Bn, 82%

Scheme 17 Racemic synthesis of β-carbolines

It is interesting to note that the products **60a-c** were isolated as mixtures of isomers/rotamers. Whereas **60a** shows two distinct signals in ^{19}F NMR, which we attribute to the *E*/*Z* isomers of the trifluoroacetamide, **60b** and **60c** show two additional resonances, giving a set of four signals in ^{19}F NMR. We assigned these extra signals to two rotamers resulting from the hindered rotation of the benzyl protecting group. To probe this hypothesis, we have conducted variable temperature ^{19}F NMR measurements of **60b** in DMSO-d_6 (Figure 2). From the NMR spectra can be seen that 2 signals (1 and 3 in Figure 2) coalesce at 80 °C, as can be expected from rotamers. The fourth resonance (4 in Figure 2) gradually disappears at higher temperatures, a phenomenon that can be attributed to *E*/*Z* isomers of the trifluoroacetamide moiety, since at higher temperature the thermodynamically more stable species (signal 2 in Figure 2) should be prevalent in the mixture.



60b

Figure 2 VT^{19}F NMR of 60b in DMSO-d$_6$, t from 25 °C (= 1) to 95 °C (= 15) in increments of 5 °C

4. Conclusions

It was attempted to develop an Ir-catalyzed intramolecular allylic substitution with nitrogen nucleophiles for the synthesis of chiral β-carboline building blocks. The synthesis of the precursors of the final asymmetric metal-catalyzed step was achieved and is based upon a key Pd-catalyzed cross coupling to introduce the allyl alcohol moiety in the 2-position of the indole. A direct allylic amination was attempted but this could not be realized through difficulties with the selective synthesis of a primary amine in the presence of the allylic carbonate required for the Ir-catalyzed step. A second approach to develop an allylic amidation circumvented this problem, but suffered from the fact that the Ir-based catalysis did not take place. From a number of test experiments it can be concluded that the formation of the key intermediate for the catalysis, the Ir-allyl species, does not form with the indole precursors due to steric and/or electronic reasons. However, the racemic synthesis of the desired products could finally be achieved. It should be noted that also for this transformation to run smoothly, judicious choice of base is necessary (with Cs_2CO_3 being the base of choice in this case).

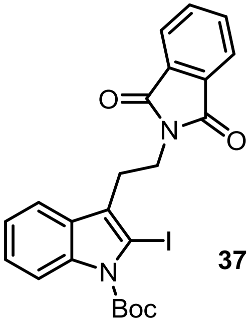
It is not clear with the present results whether the envisaged intramolecular allylic amination or amidation can be rendered feasible with transition metal-based catalysts. However, many methods for catalytic asymmetric allylic substitution are known and it could be investigated in how far they are applicable for the synthesis of β-carboline compounds.

5. Experimental section

General

For general remarks, see chapter 3. Stannane **52** was prepared according to literature.[44] **L3** was prepared according to literature.[62]

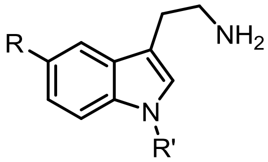
tert-Butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-iodo-1H-indole-1-carboxylate (37)



37

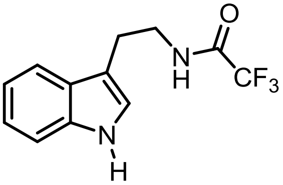
tert-Butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1H-indole-1-carboxylate **36**[63] (1.0 eq., 4.00 g, 10.25 mmol) was dissolved in 200 mL CH_2Cl_2 at 21 °C. Then 1.3 eq. bis(2,2,2-trifluoroacetoxy)mercury (5.68 g, 13.32 mmol) was added and the mixture was stirred for 20 min. Then it was washed with 2M aq. KI solution (2x 100 mL), dried over Na_2SO_4 and filtered. To the filtrate was added 1.5 eq. iodine (3.90 g, 15.37 mmol) and the mixture was stirred for another 3 h at 21 °C. The red precipitate was filtered and the filtrate was washed with saturated solution of $Na_2S_2O_3$ (2x 100 mL), dried over Na_2SO_4 and all volatiles were removed under reduced pressure to give tert-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-iodo-1H-indole-1-carboxylate **37** (3.86 g, 7.48 mmol, 73%) as an off-white solid. ^{1}H NMR (201 MHz, $CDCl_3$) δ 8.17 – 7.98 (m, 1H), 7.97 – 7.74 (m, 2H), 7.74 – 7.55 (m, 3H), 7.39 – 7.07 (m, 2H), 4.12 – 3.75 (m, 2H), 3.32 – 2.97 (m, 2H), 1.70 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.04, 149.20, 137.97, 133.80, 132.05, 129.46, 125.99, 124.36, 123.10, 122.76, 118.02, 115.53, 85.01, 79.15, 36.62, 28.24, 27.34, 27.04. HRMS: (ESI^+) calculated for $C_{23}H_{21}IN_2O_4$ [$M+H^+$]: 516.0541, found: 516.0507.

General procedure for the *N*-protection of tryptamines (Synthesis of 47)


47a-c
R = H, OMe
R' = Me, Bn

1.0 eq. of the appropriate tryptamine was dissolved in DMF (Volume: 50 ml / 20 mmol) at 21 °C and added to a solution of 1.1 eq. sodium hydride in DMF (Volume: 50 ml / 20 mmol) and the solution was stirred for 30 min. Then, it was cooled to 0 °C and 1.1 eq. methyl iodide was added dropwise. After stirring at 21 °C for 1 h, the reaction was quenched with water and the mixture extracted with EtOAc. After drying over $MgSO_4$ and removal of all volatiles under reduced pressure, **47** were isolated as brown solids. These products were used without further purification.

N-(2-(1H-Indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (47d)

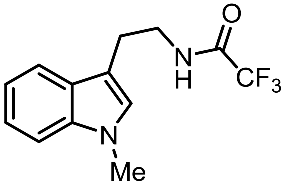

47d

Tryptamine **21** (1.0 eq., 1.00 g, 6.24 mmol) was dissolved in CH_2Cl_2 (Volume: 50 ml) and cooled to 0 °C. Then, 4.0 eq. pyridine (0.530 ml, 6.55 mmol) were added and subsequently, 5.0 eq. trifluoroacetic anhydride (0.926 ml, 6.55 mmol) were added dropwise. The mixture was allowed to warm to room temperature and stirred for 16 h. After completion (as judged by TLC), the mixture was washed with 2N aq. HCl (3x 20 mL) and dried over $MgSO_4$. After filtration and removal of all volatiles under reduced pressure, *N*-(2-(1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **47d** (1.567 g, 6.12 mmol, 98%) was obtained as a brown solid. This was used without further purification. ^{1}H NMR: (201 MHz, $CDCl_3$) δ 8.46 (s (br), 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.20 (m, 3H), 7.17 – 6.97 (m, 2H), 3.70 (q, *J* = 6.6 Hz, 2H), 3.10 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 157.40 (q, *J* = 36.9 Hz), 136.31, 126.85, 122.28, 122.02, 119.31, 118.19, 115.84 (q, *J* = 286.8 Hz), 111.36, 111.29, 40.17, 24.31. ^{19}F NMR: (189 MHz, $CDCl_3$) δ -75.89. HRMS: (ESI^+, m/z) calculated for $C_{12}H_{12}F_3N_2O_1$ [$M+H^+$]: 257.0896, found: 257.0877.

General procedure for the preparation of trifluoroacetamides 48

1.0 eq. **47** was dissolved in CH_2Cl_2 (Volume: 50 ml / 20 mmol) and the solution was cooled to 0 °C. Then, 1.05 eq. pyridine was added and subsequently 1.05 eq. 2,2,2-trifluoroacetic anhydride was added dropwise. The mixture was allowed to warm to room temperature and stirred for 16 h. After completion, the mixture was washed with 2N aq. HCl (3x 50 mL / 20 mmol) and dried over MgSO$_4$. After filtration and removal of all volatiles under reduced pressure, compounds **48** were obtained as brown solids. These products were used without further purification.

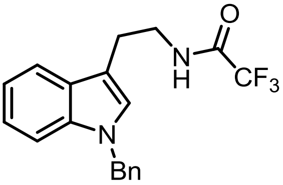
2,2,2-Trifluoro-*N*-(2-(1-methyl-1H-indol-3-yl)ethyl)acetamide (48a)



48a

Following the general procedure, the reaction of 1.0 eq. 2-(1-methyl-1H-indol-3-yl)ethanamine **47a** (3.48 g, 20 mmol) gave to 2,2,2-trifluoro-*N*-(2-(1-methyl-1H-indol-3-yl)ethyl)acetamide **48a** (4.70 g, 17.40 mmol, 87%). ^{1}H NMR: (201 MHz, CDCl$_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.09 (m, 3H), 6.91 (s, 1H), 6.70 – 6.30 (s (br), 1H), 3.76 (s, 3H), 3.68 (dd, *J* = 12.9, 6.5 Hz, 2H), 3.15 – 2.97 (m, 2H). ^{13}C NMR: (50 MHz, CDCl$_3$) δ 137.18, 127.37, 126.91, 121.98, 119.16, 118.50, 110.14, 109.44, 40.28, 32.61, 24.56. COCF$_3$ peaks not observed. ^{19}F NMR: (189 MHz, CDCl$_3$) δ -76.00. HRMS: (ESI$^+$, m/z) calculated for $C_{13}H_{14}F_3N_2O_1$ [M+H$^+$]: 271.1053, found: 271.1035.

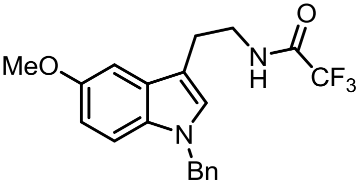
N-(2-(1-Benzyl-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (48b)



48b

Following the general procedure, the reaction of 1.0 eq. 2-(1-benzyl-1H-indol-3-yl)ethanamine **47b** (5.01 g, 20 mmol) gave *N*-(2-(1-benzyl-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **48b** (6.44 g, 18.60 mmol, 93%). ^{1}H NMR: (201 MHz, CDCl$_3$) δ 7.81 – 7.59 (m, 1H), 7.51 – 7.11 (m, 8H), 7.09 – 6.90 (m, 2H), 5.31 (s, 2H), 3.73 (dd, *J* = 13.1, 6.7 Hz, 2H), 3.12 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR: (50 MHz, CDCl$_3$) δ 137.24, 136.68, 128.77, 128.60, 127.58, 127.51, 126.66, 126.13, 122.00, 119.26, 118.59, 110.84, 109.80, 49.68, 40.04, 24.41. COCF$_3$ peaks not observed. ^{19}F NMR: (189 MHz, CDCl$_3$) δ -75.74. HRMS: (APCI, m/z) calculated for $C_{19}H_{18}F_3N_2O_1$ [M+H$^+$]: 347.1366, found: 347.1361.

N-(2-(1-Benzyl-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (48c)



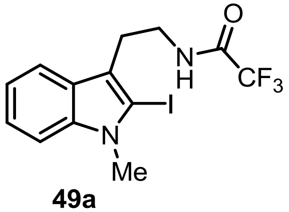
48c

Following the general procedure, the reaction of 1.0 eq. 2-(1-benzyl-5-methoxy-1H-indol-3-yl)ethanamine **47c** (1.475 g, 5.26 mmol) gave *N*-(2-(1 benzyl-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **48c** (1.657 g, 4.40 mmol, 84%). ^{1}H NMR: (400 MHz, CDCl$_3$) δ 7.35 – 7.22 (m, 2H), 7.18 (d, *J* = 8.9 Hz, 1H), 7.10 (d, *J* = 6.5 Hz, 2H), 7.02 (s, 1H), 6.95 (s, 1H), 6.91 – 6.83 (m, 1H), 6.41 (s (br), 1H), 5.25 (s, 2H), 3.86 (s, 3H), 3.68 (dd, *J* = 12.7, 6.4 Hz, 2H), 3.02 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR: (101 MHz, CDCl$_3$) δ 154.13, 137.31, 132.10, 128.77, 127.89, 127.69, 126.85, 126.73, 112.47, 110.83, 110.23, 100.32, 55.85, 50.14, 40.00, 24.64. $COCF_3$ peaks not observed. ^{19}F NMR: (376 MHz, $CDCl_3$) δ -75.97. HRMS: (ESI^+, m/z) calculated for $C_{20}H_{19}F_3N_2O_2Na$ [$M+Na^+$]: 399.1291, found: 399.1277.

General procedure for the iodination of tryptamines 48 (Synthesis of 49)

Trifluoroacetamide **48** (1.0 eq.) was dissolved in Et_2O (Volume: 10 ml / 2 mmol) and the solution cooled to 0 °C. Then, 2.5 eq. BuLi were added dropwise and the reaction was allowed to warm to room temperature. After 2 hours, the reaction mixture was cooled to 0 °C again, and 1.5 eq. iodine was added. After warming to room temperature, the reaction was quenched by addition of a saturated $Na_2S_2O_3$ solution (10 ml / 2 mmol), the mixture was washed with water (3x 10 mL / 2 mmol) and extracted with Et_2O (2x 20 mL / 2 mmol). After drying over $MgSO_4$, all volatiles were removed under reduced pressure. Purification of the crude mixture by column chromatography gave **49**.

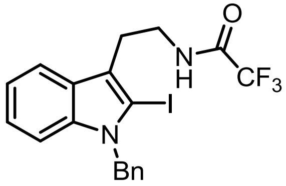
2,2,2-Trifluoro-*N*-(2-(2-iodo-1-methyl-1H-indol-3-yl)ethyl)acetamide (49a)



49a

Following the general procedure, the reaction of 1.0 eq. 2,2,2-trifluoro-*N*-(2-(1-methyl-1H-indol-3-yl)ethyl)acetamide **48a** (0.500 g, 1.850 mmol) gave 2,2,2-trifluoro-*N*-(2-(2-iodo-1-methyl-1H-indol-3-yl)ethyl)acetamide **49a** (0.403 g, 1.018 mmol, 55%) as a white solid after purification by column chromatography (R_f = 0.80 in pentane/EtOAc 8:2, SiO_2, pentane/EtOAc 8:2). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 15.9, 7.9 Hz, 2H), 7.07 (s (br), 1H), 3.75 (s, 3H), 3.65 (q, *J* = 6.7 Hz, 2H), 3.09 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 159.29 (q, *J* = 36.8 Hz), 138.40, 127.36, 122.03, 119.50, 117.49, 116.63, 115.76 (q, *J* = 288.6 Hz), 109.69, 87.84, 39.92, 33.99, 26.61. ^{19}F NMR: (189 MHz, $CDCl_3$) δ -75.67. HRMS: (APCI, m/z) calculated for $C_{13}H_{13}F_3N_2O_1$ [$M+H^+$-I]: 270.0980, found: 269.9763.

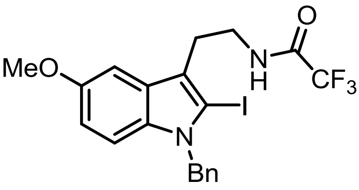
N-(2-(1-Benzyl-2-iodo-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (49b)



49b

Following the general procedure, the reaction of 1.0 eq. *N*-(2-(1-benzyl-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **48b** (2.00 g, 5.77 mmol) gave *N*-(2-(1-benzyl-2-iodo-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **49b** (1.309 g, 2.77 mmol, 48%) as a white solid after purification by column chromatography (R_f = 0.66 in pentane/EtOAc 10:1, SiO_2, pentane/EtOAc 10:1). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.64 – 7.51 (m, 1H), 7.37 – 7.21 (m, 4H), 7.20 – 7.09 (m, 2H), 7.07 – 6.97 (m, 2H), 6.35 (s (br), 1H), 5.44 (s, 2H), 3.69 (q, *J* = 6.4 Hz, 2H), 3.11 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 157.21 (q, *J* = 36.4 Hz), 138.37, 136.87, 128.65, 127.78, 127.44, 126.24, 122.48, 119.99, 117.74, 117.44, 115.75 (q, *J* = 286.8 Hz), 110.34, 87.87, 50.60, 39.87, 26.83. ^{19}F NMR: (376 MHz, $CDCl_3$) δ -75.77. HRMS: (APCI, m/z) calculated for $C_{19}H_{17}F_3N_2O_1$ $[M+H^+-I]$: 346.1293, found: 346.0073.

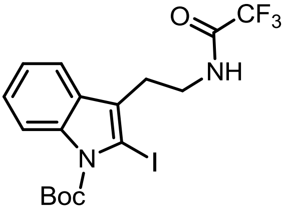
N-(2-(1-Benzyl-2-iodo-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (49c)



49c

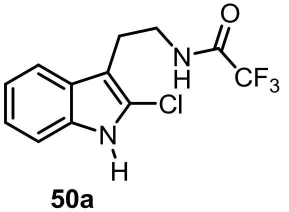
Following the general procedure, the reaction of 1.0 eq. *N*-(2-(1-benzyl-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **48c** (1.657 g, 4.40 mmol) gave *N*-(2-(1-benzyl-2-iodo-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **49c** (1.150 g, 2.289 mmol, 52%) as a white solid after purification by column chromatography (R_f = 0.55 in pentane/EtOAc 10:1, SiO_2, pentane/EtOAc 10:1). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.43 – 7.21 (m, 4H), 7.15 (d, *J* = 8.9 Hz, 1H), 7.01 (dd, *J* = 9.3, 2.5 Hz, 2H), 6.78 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.37 (s (br), 1H), 5.39 (s, 2H), 3.84 (s, 3H), 3.68 (dd, *J* = 12.7, 6.4 Hz, 2H), 3.07 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 154.41, 137.00, 133.78, 128.76, 128.56, 127.55, 126.98, 126.27, 116.70, 112.81, 111.30, 99.36, 55.79, 50.92, 39.88, 26.88. $COCF_3$ peaks not observed. ^{19}F NMR: (189 MHz, $CDCl_3$) δ -75.88. HRMS: (ESI^+, m/z) calculated for $C_{20}H_{18}F_3IN_2O_2Na$ $[M+Na^+]$: 525.0257, found: 525.0236.

tert-Butyl 2-iodo-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate 49d



tert-Butyl 3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate (1.0 eq., 0.278 g, 0.780 mmol) **48**^{64} was dissolved in CH_2Cl_2 (50 ml) at 21 °C. Then 1.3 eq. bis(2,2,2-trifluoroacetoxy)mercury (0.433 g, 1.015 mmol) was added and the mixture was stirred for 20 minutes. Then it was washed with 2M aq. KI solution (2x 30 mL), dried over Na_2SO_4 and filtered. To the filtrate was added 1.5 eq. diiodine (0.297 g, 1.171 mmol) and the mixture was stirred for another 3h at 21 °C. The red precipitate was filtered and the filtrate was washed with saturated aq. solution of $Na_2S_2O_3$ (2x 30 ml), dried over Na_2SO_4 and all volatiles were removed under reduced pressure to give the crude product. This was purified by column chromatography (R_f = 0.85 in pentane / EtOAc 8:2, SiO_2, pentane/EtOAc 10:1) to yield tert-butyl 2-iodo-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate **49d** (0.248 g, 0.515 mmol, 66%) as white solid. ^{1}H NMR (201 MHz, $CDCl_3$) δ 8.18 – 7.99 (m, 1H), 7.48 (ddd, *J* = 10.3, 6.2, 2.8 Hz, 1H), 7.35 – 7.16 (m, 2H), 6.76 (s (br), 1H), 3.62 (q, *J* = 6.7 Hz, 2H), 3.06 (t, *J* = 6.9 Hz, 2H), 1.71 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.15 (q, *J* = 39.9 Hz), 157.03, 149.15, 138.04, 129.33, 125.58, 124.69, 122.94, 117.77, 115.69 (q, *J* = 286.1 Hz), 115.61, 85.37, 39.23, 28.21, 26.95. ^{19}F NMR (189 MHz, $CDCl_3$) δ -75.87.

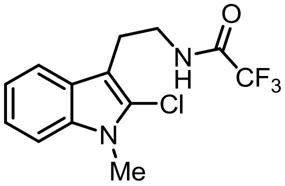
N-(2-(2-Chloro-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (50a)



50a

1.0 eq. *N*-(2-(1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **47d** (2.00 g, 7.81 mmol) was dissolved in CH_2Cl_2 (Volume: 60 ml) at 21 °C. Then, a solution of 1.1 eq. iodine monochloride in CH_2Cl_2 (1N) (11.71 ml, 11.71 mmol) was added dropwise. The reaction mixture was stirred at this temperature, and the progress of the reaction was followed by TLC. After full conversion, the mixture was washed with water and brine and the organic phases were dried over $MgSO_4$. After removal of all volatiles, the crude product was purified by column chromatography (R_f = 0.75 in pentane/EtOAc 8:2, SiO_2, pentane/EtOAc 10:1) to yield *N*-(2-(2-chloro-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **50a** (1.807 g, 6.22 mmol, 80%) as a light brown solid. ^{1}H NMR: (201 MHz, $CDCl_3$) δ 8.43 (s (br), 1H), 7.56 – 7.43 (m, 1H), 7.38 – 7.06 (m, 3H), 6.60 (s (br), 1H), 3.64 (q, *J* = 6.5 Hz, 2H), 3.03 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 134.49, 127.08, 122.64, 121.71, 120.46, 117.68, 110.75, 107.79, 39.77, 23.15. $COCF_3$ peaks not observed. ^{19}F NMR: 189 MHz, $CDCl_3$) δ -76.06. HRMS: (APCI, m/z) calculated for $C_{12}H_{10}F_3N_2O_1$ [M-Cl$^-$]: 255.0745, found: 255.0737.

N-(2-(2-chloro-1-methyl-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (50b)



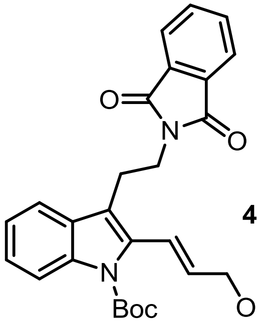
50b

1.0 eq. 2,2,2-trifluoro-*N*-(2-(1-methyl-1H-indol-3-yl)ethyl)acetamide **48a** (1.920 g, 7.10 mmol) was dissolved in CH_2Cl_2 (Volume: 50 ml) at 21 °C. Then, a solution of 1.1 eq. iodine monochloride (1M in CH_2Cl_2) (7.81 ml, 7.81 mmol) was added dropwise. The reaction mixture was stirred at this temperature, and the progress of the reaction was followed by TLC. After full conversion, the mixture was washed with water and brine and the organic phases were dried over $MgSO_4$. After removal of all volatiles, the crude product was purified by column chromatography (R_f = 0.80 in pentane/EtOAc 8:2, SiO_2, pentane/EtOAc 10:1) to yield *N*-(2-(2-chloro-1-methyl-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **50b** (1.688 g, 5.54 mmol, 78%) as a yellow solid. ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.24 – 7.08 (m, 1H), 6.48 (s (br), 1H), 3.74 (d, *J* = 2.5 Hz, 3H), 3.64 (q, *J* = 6.4 Hz, 2H), 3.06 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 135.82, 126.20, 124.50, 122.22, 120.19, 117.70, 109.30, 106.86, 39.87, 29.89, 23.58. $COCF_3$ peaks not observed. ^{19}F NMR: (189 MHz, $CDCl_3$) δ -76.06. HRMS: (APCI, m/z) calculated for $C_{13}H_{12}F_3N_2O_1$ [M-Cl$^-$]: 269.0902, found: 269.0894.

General procedure for the Stille coupling of iodides 37/49 (Synthesis of 40/51)

1.0 eq. of iodide **49**, 1.5 eq. of (*E*)-3-(tributylstannyl)prop-2-en-1-ol **52**, 5.0 mol% bis(triphenylphosphine)palladium(II) chloride and 3.0 eq. of lithium chloride were dissolved in DMF (Volume: 20 ml / mmol) and the mixture was heated to 75 °C. The reaction mixture was stirred at this temp for 16 h. The reaction was quenched by addition of water (20 ml / mmol), EtOAc (50 ml / mmol) was added and the organic phases were washed with brine (2x 50 mL / mmol). After drying over $MgSO_4$ and removal of all volatiles the crude mixture was purified by column chromatography to give **51**.

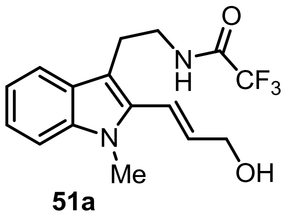
(*E*)-*tert*-Butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-hydroxyprop-1-enyl)-1H-indole-1-carboxylate (40)



40

Following the general procedure, 0.304 g (*E*)-*tert*-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-hydroxyprop-1-en-1-yl)-1H-indole-1-carboxylate **40** (0.681 mmol, 65%) were isolated from the reaction of *tert*-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-iodo-1H-indole-1-carboxylate **37** (0.541 g, 1.048 mmol) after purification by column chromatography using EtOAc/pentane 1:1 as eluent. (R_f = 0.85 in pentane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 7.97 (m, 1H), 7.89 – 7.77 (m, 2H), 7.75 – 7.58 (m, 3H), 7.37 – 7.19 (m, 2H), 6.78 (d, *J* = 16.1 Hz, 1H), 6.25 (ddd, *J* = 16.1, 5.7, 4.1 Hz, 1H), 4.42 (d, *J* = 5.0 Hz, 2H), 3.95 – 3.77 (m, 2H), 3.24 – 2.98 (m, 2H), 1.65 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.13, 150.22, 135.33, 134.85, 133.89, 132.89, 131.90, 129.58, 124.48, 123.13, 122.80, 122.36, 118.48, 115.76, 115.44, 83.87, 63.51, 37.71, 28.11, 23.75. HRMS: (ESI$^+$) calculated for $C_{26}H_{25}N_2O_5$ [M+H$^+$]: 445.1758, found: 445.1761.

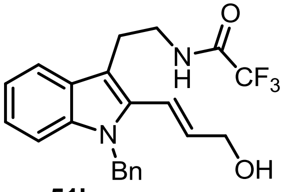
(*E*)-2,2,2-Trifluoro-*N*-(2-(2-(3-hydroxyprop-1-enyl)-1-methyl-1H-indol-3-yl)ethyl)acetamide (51a)



51a

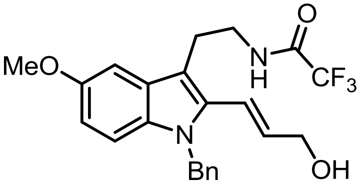
Following the general procedure, the reaction of 1.0 eq. 2,2,2-trifluoro-*N*-(2-(2-iodo-1-methyl-1H-indol-3-yl)ethyl)acetamide **49a** (0.300 g, 0.757 mmol) gave (*E*)-2,2,2-trifluoro-*N*-(2-(2-(3-hydroxyprop-1-en-1-yl)-1-methyl-1H-indol-3-yl)ethyl)acetamide **51a** (0.167 g, 0.512 mmol, 68%) as an orange solid after purification by column chromatography (R_f = 0.30 in Pentane / EtOAc 1:1, SiO_2, pentane/EtOAc 1:1). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.44 – 7.22 (m, 3H), 7.20 – 7.07 (m, 1H), 6.69 (d, *J* = 16.3 Hz, 1H), 6.29 (dd, *J* = 13.4, 8.1 Hz, 1H), 4.40 (d, *J* = 5.3 Hz, 2H), 3.69 (s, 3H), 3.59 (dd, *J* = 13.7, 6.8 Hz, 2H), 3.14 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 157.44 (q, *J* = 37.3 Hz), 137.16, 134.46, 133.84, 127.26, 122.17, 119.43, 118.92, 118.09, 115.78 (q, *J* = 287.9 Hz), 109.19, 109.09, 63.31, 40.45, 30.42, 23.92. ^{19}F NMR: (189 MHz, $CDCl_3$) δ -75.88. HRMS: (APCI, m/z) calculated for $C_{16}H_{18}F_3N_2O_2$ [M+H$^+$]: 327.1320, found: 325.1147.

(*E*)-*N*-(2-(1-Benzyl-2-(3-hydroxyprop-1-enyl)-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (51b)


51b

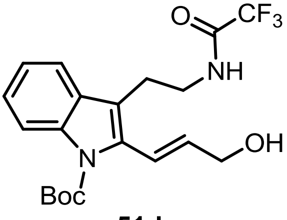
Following the general procedure, the reaction of 1.0 eq. *N*-(2-(1-benzyl-2-iodo-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **49b** (0.285 g, 0.604 mmol) gave (*E*)-*N*-(2-(1-benzyl-2-(3-hydroxyprop-1-en-1-yl)-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **51b** (0.172 g, 0.427 mmol, 71%) as a white solid after purification by column chromatography (R_f = 0.50 in pentane/EtOAc 1:1, SiO_2, pentane/EtOAc 1:1). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.33 – 7.10 (m, 6H), 7.00 (d, *J* = 7.0 Hz, 2H), 6.71 – 6.54 (m, 2H), 6.18 (dt, *J* = 16.1, 5.3 Hz, 1H), 5.37 (s, 2H), 4.28 (d, *J* = 5.2 Hz, 2H), 3.65 (dd, *J* = 13.4, 6.8 Hz, 2H), 3.19 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 137.61, 137.15, 134.73, 134.59, 128.80, 127.56, 127.37, 125.87, 122.68, 119.98, 118.80, 118.33, 109.88, 109.60, 63.47, 47.31, 40.42, 24.04. $COCF_3$ peaks not observed. ^{19}F NMR: (376 MHz, $CDCl_3$) δ -76.00. HRMS: (ESI+, m/z) calculated for $C_{22}H_{21}F_3N_2O_2Na$ [M+Na$^+$]: 425.1447, found: 425.1432.

(*E*)-*N*-(2-(1-Benzyl-2-(3-hydroxyprop-1-en-1-yl)-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (51c)


51c

Following the general procedure, the reaction of *N*-(2-(1-benzyl-2-iodo-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **49c** (0.270 g, 0.538 mmol) gave (*E*)-*N*-(2-(1-benzyl-2-(3-hydroxyprop-1-en-1-yl)-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **51c** (0.158 g, 0.366 mmol, 68%) as a white solid after purification by column chromatography (R_f = 0.5 in pentane/EtOAc 1:1, SiO_2, pentane/EtOAc 1:1). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 6.7 Hz, 3H), 7.08 (d, *J* = 8.6 Hz, 1H), 7.03 (s, 1H), 6.98 (d, *J* = 6.0 Hz, 2H), 6.91 (s (br), 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.58 (d, *J* = 16.2 Hz, 1H), 6.15 (d, *J* = 15.8 Hz, 1H), 5.31 (s, 2H), 4.25 (s, 2H), 3.85 (s, 3H), 3.62 (d, *J* = 5.6 Hz, 2H), 3.14 (s (br), 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 157.38 (q, *J* = 37.6 Hz), 154.40, 137.70, 135.12, 134.11, 132.39, 128.75, 127.92, 127.30, 125.80, 118.89, 115.83 (q, *J* = 287.4 Hz), 112.75, 110.70, 109.22, 100.08, 63.40, 55.83, 47.34, 40.29, 24.06. ^{19}F NMR: (376 MHz, $CDCl_3$) δ -75.94. HRMS: (ESI$^+$, m/z) calculated for $C_{23}H_{23}F_3N_2O_3Na$ [M+Na$^+$]: 455.1553, found: 455.1539.

(*E*)-*tert*-Butyl 2-(3-hydroxyprop-1-enyl)-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate 51d



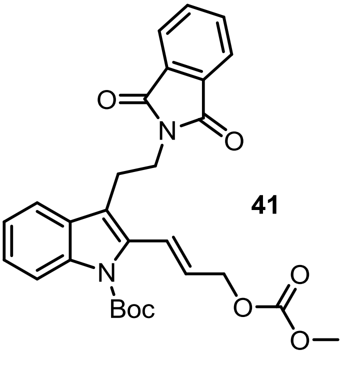
51d

Following the general procedure, the reaction of 1.0 eq. *tert*-butyl 2-iodo-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate **49d** (0.240 g, 0.498 mmol) gave (*E*)-*tert*-butyl 2-(3-hydroxyprop-1-en-1-yl)-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate **51d** (0.129 g, 0.314 mmol, 63%) as a white solid after purification by column chromatography (R_f = 0.5 in pentane/EtOAc 1:1, SiO_2, pentane/EtOAc 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 8.54 (m, 1H), 8.14 (dd, *J* = 15.1, 7.4 Hz, 2H), 8.01 – 7.70 (m, 2H), 7.51 – 7.24 (m, 1H), 6.82 – 6.50 (m, 1H), 4.93 (dd, *J* = 14.8, 8.7 Hz, 2H), 4.11 (d, *J* = 5.9 Hz, 2H), 3.66 (dd, *J* = 23.4, 14.9 Hz, 2H), 2.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.61 (q, *J* = 36.0 Hz), 150.40, 135.36, 134.87, 132.45, 129.52, 124.70, 122.96, 122.90, 118.41, 115.89, 115.83 (q, *J* = 291.0 Hz), 115.58, 84.25, 63.24, 40.06, 28.13, 23.87.

General procedure for the synthesis of allylic carbonates 41/53:

To a solution of allyl alcohol **40** or **51** (1 eq.) and pyridine (3 eq.) in CH_2Cl_2 (20 mL / mmol) methyl chloroformate (1.5 eq.) was added dropwise at 0 °C. After 5 min. The solution was warmed to room temperature and stirred for 1 h. Then, it was washed with aq. HCl (2N) (3 x 5 mL/mmol) and dried over Na_2SO_4. The corresponding products **41**/**53** were obtained as white solids after evaporation of the solvent.

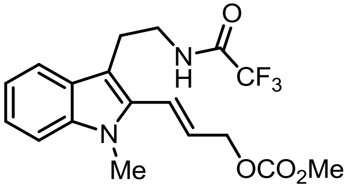
(*E*)-*tert*-Butyl-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-(methoxycarbonyloxy)prop-1-enyl)-1H-indole-1-carboxylate (41)



41

Following the general procedure, 0.428 g (*E*)-*tert*-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-((methoxycarbonyl)oxy)prop-1-en-1-yl)-1H-indole-1-carboxylate **41** (0.848 mmol, 91%) were isolated from the reaction of (E)-tert-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-hydroxyprop-1-en-1-yl)-1H-indole-1-carboxylate **40** (0.415 g, 0.929 mmol) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, *J* = 13.4 Hz, 1H), 7.82 (dt, *J* = 6.9, 3.5 Hz, 2H), 7.76 – 7.64 (m, 3H), 7.37 – 7.21 (m, 2H), 6.87 (t, *J* = 21.8 Hz, 1H), 6.33 – 6.07 (m, 1H), 4.89 (dt, *J* = 24.2, 12.1 Hz, 2H), 3.97 – 3.86 (m, 2H), 3.82 (s, 3H), 3.07 (dt, *J* = 32.4, 14.9 Hz, 2H), 1.65 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.90, 155.52, 150.12, 135.57, 133.86, 133.78, 132.00, 129.50, 126.26, 125.20, 124.73, 123.06, 122.84, 118.70, 116.55, 115.46, 83.97, 67.93, 54.73, 37.74, 28.08, 24.01. HRMS: (ESI$^+$) calculated for $C_{28}H_{28}N_2O_7Na$ [M+Na$^+$]: 527.1789, found: 527.1782.

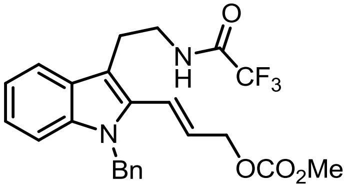
(*E*)-Methyl 3-(1-methyl-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl carbonate (53a)



53a

Following the general procedure, the reaction 1.0 eq. (*E*)-2,2,2-trifluoro-*N*-(2-(2-(3-hydroxyprop-1-en-1-yl)-1-methyl-1H-indol-3-yl)ethyl)acetamide **51a** (0.160 g, 0.490 mmol) gave (*E*)-methyl (3-(1-methyl-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl) carbonate **53a** (0.185 g, 0.481 mmol, 98%) as a yellow foam. ^{1}H NMR: (400 MHz, CDCl$_3$) δ 7.62 – 7.55 (m, 1H), 7.32 – 7.25 (m, *J* = 8.3, 7.8, 0.9 Hz, 2H), 7.17 – 7.10 (m, *J* = 8.0, 6.6, 1.4 Hz, 1H), 6.84 – 6.72 (m, *J* = 16.2, 1.3 Hz, 2H), 6.19 (dt, *J* = 16.2, 6.2 Hz, 1H), 4.85 (dd, *J* = 6.2, 1.4 Hz, 2H), 3.83 – 3.82 (s, 2H), 3.73 (s, 3H), 3.60 (q, *J* = 6.8 Hz, 2H), 3.13 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR: (101 MHz, CDCl$_3$) δ 157.14 (q, *J* = 36.5 Hz), 155.47, 137.51, 133.42, 127.18, 126.88, 122.84, 122.70, 119.66, 118.37, 115.73 (q, *J* = 288.2 Hz), 110.40, 109.30, 68.29, 54.78, 40.41, 30.70, 23.96. ^{19}F NMR: (376 MHz, CDCl$_3$) δ -75.98. HRMS: (APCI, m/z) calculated for $C_{16}H_{16}F_3N_2O_1$ [M-OCO$_2$Me]: 309.1215, found: 309.1199.

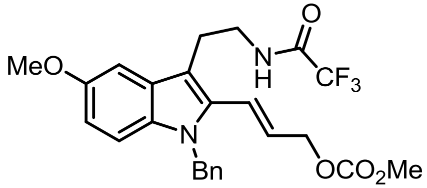
(*E*)-3-(1-Benzyl-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl methyl carbonate (13b)



53b

Following the general procedure, the reaction 1.0 eq. (E)-*N*-(2-(1-benzyl-2-(3-hydroxyprop-1-en-1-yl)-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **51b** (0.230 g, 0.572 mmol) gave (*E*)-3-(1-benzyl-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl methyl carbonate **53b** (0.257 g, 0.558 mmol, 98%) as a yellow foam. ^{1}H NMR: (201 MHz, CDCl$_3$) δ 7.65 (d, *J* = 6.9 Hz, 1H), 7.41 – 7.10 (m, 6H), 7.09 – 6.98 (m, 2H), 7.10 – 6.95 (m, 2H), 6.12 (dt, *J* = 16.2, 6.1 Hz, 1H), 5.38 (s, 2H), 4.76 (d, *J* = 6.1 Hz, 2H), 3.79 (s, 3H), 3.66 (dd, *J* = 13.2, 6.7 Hz, 2H), 3.19 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR: (50 MHz, CDCl$_3$) δ 155.39, 137.39, 137.36, 133.54, 128.74, 127.53, 127.47, 127.34, 125.82, 123.01, 122.57, 120.03, 118.55, 110.79, 109.83, 68.12, 54.76, 47.29, 40.33, 24.10. COCF$_3$ peaks not observed. ^{19}F NMR: (189 MHz, CDCl$_3$) δ -75.95. HRMS: (APCI, m/z) calculated for $C_{22}H_{20}F_3N_2O_1$ [M-OCO$_2$Me]: 385.1528, found: 385.1507.

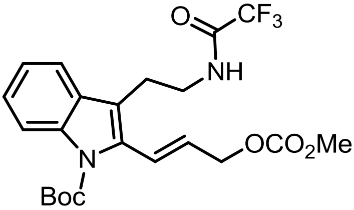
(*E*)-3-(1-Benzyl-5-methoxy-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl methyl carbonate (53c)



53c

Following the general procedure, the reaction 1.0 eq. (*E*)-*N*-(2-(1-benzyl-2-(3-hydroxyprop-1-en-1-yl)-5-methoxy-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **51c** (0.137 g, 0.317 mmol) gave (*E*)-3-(1-benzyl-5-methoxy-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl methyl carbonate **53c** (0.142 g, 0.290 mmol, 91%) as a yellow foam. ^{1}H NMR: (201 MHz, CDCl$_3$) δ 7.35 – 7.20 (m, 3H), 7.11 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 7.03 – 6.96 (m, 2H), 6.85 (dd, J = 8.9, 2.4 Hz, 1H), 6.79 – 66.0 (m, 2H), 6.07 (dt, J = 16.2, 6.1 Hz, 1H), 5.33 (s, 2H), 4.74 (dd, J = 6.1, 1.2 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.65 (dd, J = 13.2, 6.7 Hz, 2H), 3.14 (t, J = 7.0 Hz, 2H). ^{13}C NMR: (50 MHz, CDCl$_3$) δ 157.15 (q, J = 37.0 Hz), 155.41, 154.49, 137.48, 133.95, 132.65, 128.75, 127.82, 127.34, 127.08, 125.79, 122.74, 115.76 (q, J = 287.2 Hz), 113.38, 110.74, 110.39, 100.00, 68.18, 55.70, 54.78, 47.41, 40.24, 24.14. ^{19}F NMR: (189 MHz, CDCl$_3$) δ -75.93. HRMS: (ESI$^+$, m/z) calculated for $C_{25}H_{25}F_3N_2O_5Na$ [M+Na$^+$]: 513.1608, found: 513.1585.

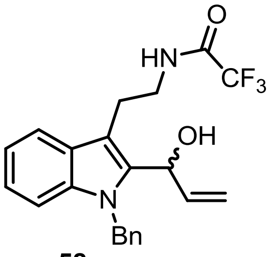
(*E*)-*tert*-Butyl 2-(3-(methoxycarbonyloxy)prop-1-enyl)-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate 53d



53d

Following the general procedure, (*E*)-*tert*-butyl 2-(3-((methoxycarbonyl)oxy)prop-1-en-1-yl)-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate **53d** (0.108 g, 0.230 mmol, 76%) were isolated from the reaction of (*E*)-*tert*-butyl 2-(3-hydroxyprop-1-en-1-yl)-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indole-1-carboxylate **51d** (0.125 g, 0.303 mmol) as a white solid. ^{1}H NMR (201 MHz, CDCl$_3$) δ 8.12 (d, J = 8.2 Hz, 1H), 7.67 – 7.49 (m, 1H), 7.42 – 7.18 (m, 2H), 6.92 (d, J = 16.1 Hz, 1H), 6.81 (s (br), 1H), 5.98 (dt, J = 16.1, 6.1 Hz, 1H), 4.84 (d, J = 6.1 Hz, 2H), 3.80 (s, 3H), 3.59 (dd, J = 13.9, 6.9 Hz, 2H), 3.02 (dd, J = 17.3, 10.3 Hz, 2H), 1.66 (s, 9H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 157.28 (q, J = 36.9 Hz), 155.65, 150.13, 135.63, 133.99, 129.34, 126.46, 125.90, 125.04, 122.98, 118.53, 116.41, 115.78 (q, J = 288.8 Hz), 115.64, 84.32, 67.92, 54.83, 40.10, 28.13, 23.98. ^{19}F NMR (189 MHz, CDCl$_3$) δ -75.96.

N-(2-(1-Benzyl-2-(1-hydroxyallyl)-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (58)



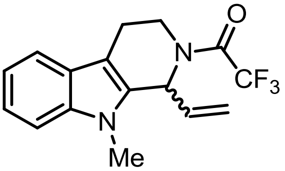
58

N-(2-(1-benzyl-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **48b** (1.0 eq., 1.00 g, 2.89 mmol) was dissolved in Et_2O (Volume: 10 ml) and cooled to 0 °C. Then, 2.5 eq. BuLi (3.97 ml, 6.35 mmol) were added dropwise and the reaction mixture was allowed to warm to room temperature. After 2 hours, the reaction mixture was cooled to 0 °C again, and 1.5 eq. acrylaldehyde (0.212 ml, 3.18 mmol) were added. After warming to room temperature, the reaction was quenched by addition of 10ml saturated $Na_2S_2O_3$ solution, washed with water (3x 20ml) and extracted with Et_2O (3x 30 ml). After drying over $MgSO_4$, all volatiles were removed under reduced pressure to give the crude product, which was purified by column chromatography (R_f = 0.90 in pentane/EtOAc 8:2, SiO_2, pentane/EtOAc 7:3) to yield *N*-(2-(1-benzyl-2-(1-hydroxyallyl)-1H-indol-3-yl)ethyl)-2,2,2-trifluoroacetamide **58** (0.523 g, 1.299 mmol, 45%) as a yellow solid. ^1H NMR: (400 MHz, $CDCl_3$) δ 8.14 (s (br), 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.10 (m, 6H), 6.97 (d, *J* = 6.6 Hz, 2H), 6.04 (ddd, *J* = 17.0, 10.4, 5.0 Hz, 1H), 5.56 (d, *J* = 5.0 Hz, 1H), 5.44 (d, *J* = 4.6 Hz, 2H), 5.33 – 5.11 (m, 2H), 3.64 (dd, *J* = 11.9, 5.0 Hz, 3H), 3.37 – 3.08 (m, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 157.52 (q, *J* = 37.6 Hz), 137.81, 137.69, 136.81, 135.86, 128.63, 127.27, 127.24, 125.66, 122.47, 119.71, 118.37, 115.84 (q, *J* = 288.4 Hz), 115.52, 109.84, 109.69, 67.47, 46.83, 40.60, 22.47. ^{19}F NMR: (376 MHz, $CDCl_3$) δ -75.67. HRMS: (ESI$^+$, m/z) calculated for $C_{22}H_{21}F_3N_2O_2Na$ [M+Na$^+$]: 425.1447, found: 425.1456.

General Procedure for the racemic synthesis of β-carbolines 60 from carbonates 53

1.0 eq. allyl carbonate **53** was dissolved in dioxane (5 ml / 0.1 mmol) and 2.0 eq. Cs_2CO_3 was added. The reaction mixture was allowed to stir for 16 hours at 100 °C. After cooling, water (5 ml / 0.1 mmol) was added and the mixture was extracted with Et_2O (2x 10 ml / 0.1 mmol) . After drying over $MgSO_4$ and removal of all volatiles under reduced pressure, the crude products were purified by column chromatography to yield **60**.

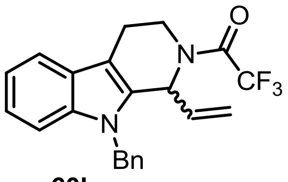
2,2,2-Trifluoro-1-(9-methyl-1-vinyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)ethanone (60a)



60a

Following the general procedure, the reaction of 1.0 eq. (*E*)-methyl (3-(1-methyl-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl) carbonate **53a** (0.020 g, 0.052 mmol) gave 2,2,2-trifluoro-1-(9-methyl-1-vinyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)ethanone **60a** (0.013 g, 0.043 mmol, 82%) as a white solid after purification by column chromatography (R_f = 0.95 in pentane/EtOAc 10:1, SiO_2, pentane/EtOAc 10:1). The product was isolated as a mixture of two rotamers (ratio 1:7) ^{1}H NMR: Only signals of the major isomer are given. (201 MHz, $CDCl_3$) δ 7.57 – 7.45 (m, 1H), 7.38 – 7.23 (m, 2H), 7.23 – 7.06 (m, 1H), 6.23 (d (br), *J* = 5.2 Hz, 1H), 6.17 – 5.95 (m, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 5.09 (d, *J* = 17.0 Hz, 1H), 4.17 (d (br), *J* = 14.1 Hz, 1H), 3.71 – 3.47 (m, 4H), 3.12 – 2.74 (m, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 133.05, 130.56, 129.98, 125.93, 122.02, 121.22, 119.47, 118.26, 109.07, 107.83, 51.60, 39.91, 29.86, 22.15. $COCF_3$ peaks not observed. ^{19}F NMR: (189 MHz, $CDCl_3$) δ -68.55 (minor), -68.99 (major). HRMS: (APCI, m/z) calculated for $C_{16}H_{16}F_3N_2O_1$ [M+H$^+$]: 309.1209, found: 309.1220.

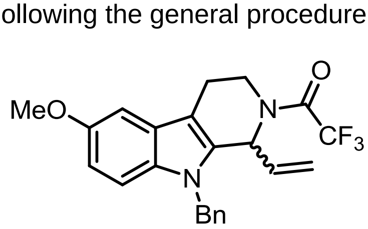
1-(9-Benzyl-1-vinyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone (60b)



60b

Following the general procedure, the reaction of 1.0 eq. (*E*)-3-(1-benzyl-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl methyl carbonate **53b** (0.037 g, 0.080 mmol) gave 1-(9-benzyl-1-vinyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone **60b** (0.023 g, 0.061 mmol, 76%) as a white solid after purification by column chromatography (R_f = 0.85 in pentane/EtOAc 10:1, SiO_2, pentane/EtOAc 10:1). The product was isolated as a mixture of four isomers ratio 1.5 : 5 : 1.5 : 1. Only signals for the major isomer are given. ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.53 – 7.41 (m, 1H), 7.31 – 7.00 (m, 7H), 6.95 – 6.83 (m, 1H), 6.10 – 1.03 (m, 1H), 6.01 – 5.81 (m, 1H), 5.45 – 5.25 (m, 2H), 5.18 (d, *J* = 10.3 Hz, 1H), 5.13 – 4.87 (m, 1H), 4.20 – 4.00 (m, 1H), 3.63 – 3.42 (m, 1H), 3.08 – 2.72 (m, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 137.19, 136.86, 132.94, 128.99, 128.84, 127.54, 126.08, 125.78, 122.34, 121.24, 120.29, 119.74, 118.34, 109.96, 47.01, 29.70, 22.18. $COCF_3$ peaks not observed. ^{19}F NMR: (189 MHz, $CDCl_3$) δ -68.91 (1.5), -68.97 (5), -69.04 (1.5), -70.17 (1). HRMS: (ESI$^+$, m/z) calculated for $C_{22}H_{20}F_3N_2O_1$ [M+H$^+$]: 385.1522, found: 385.1511.

1-(9-Benzyl-6-methoxy-1-vinyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone (60c)



60c

Following the general procedure, the reaction of 1.0 eq. (*E*)-3-(1-benzyl-5-methoxy-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1H-indol-2-yl)allyl methyl carbonate **53c** (0.025 g, 0.051 mmol) gave 1-(9-benzyl-6-methoxy-1-vinyl-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone **60c** (0.017 g, 0.042 mmol, 82%) as a white solid after purification by column chromatography (R_f = 0.65 in pentane/EtOAc 10:1, SiO_2, pentane/EtOAc 10:1). The product was isolated as four isomers (ratio 2:6:2:1). ^{1}H NMR: Only major resonances are reported. (400 MHz, $CDCl_3$) δ 7.44 – 6.77 (m, 8H), 6.11 (d, *J* = 5.4 Hz, 1H), 6.07 – 5.93 (m, 1H), 5.50 – 4.98 (m, 4H), 4.25 – 4.12 (m, 1H), 3.85 (s, 3H), 3.67 – 3.54 (m, 1H), 3.11 – 2.94 (m, 1H), 2.93 – 2.78 (m, 1H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 155.97 (q, *J* = 35.2 Hz), 154.29, 136.96, 132.96, 131.19, 128.98, 128.83, 127.52, 126.06, 125.95, 121.13, 116.52 (q, *J* = 287.7 Hz), 112.17, 110.77, 108.02, 100.46, 55.90, 51.76, 47.14, 39.92, 22.23 ^{19}F NMR: (376 MHz, $CDCl_3$) δ -68.91 (2), -68.96 (6), -69.02 (2), -70.18 (1). HRMS: (ESI^+, m/z) calculated for $C_{23}H_{22}F_3N_2O_2$ $[M+H^+]$: 415.1628, found: 415.1631.

6. References

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Chapter 5

Asymmetric Allylic Alkylation in Combination with Ring-Closing Metathesis for the Preparation of chiral *N*-Heterocycles

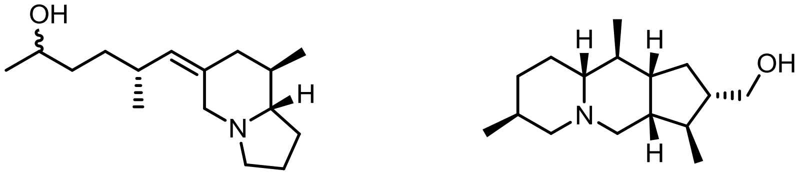
Asymmetric copper-catalyzed allylic substitution with methylmagnesium bromide is employed in combination with ring-closing olefin metathesis or ene-yne metathesis to achieve the synthesis of chiral, unsaturated nitrogen heterocycles. The resulting six- to eight-membered chiral heterocycles are accessible in high yields and with excellent enantioselectivities. Preliminary studies to extend this concept to the synthesis of chiral lactams have been conducted.

Parts of this chapter have been published:

Teichert, J.F.; Zhang, S.; van Zijl, A.W., Slaa, J.W.; Minnaard, A.J.; Feringa, B.L. *Org. Lett.* **2010**, *12*, 4658 – 4660.

1. Introduction

Nitrogen-containing heterocycles are ubiquitous in naturally occurring compounds, in particular alkaloids, and they are also key structural features in many biologically active products.[1-4] Among these, nitrogen heterocycles with various ring sizes bearing stereogenic centers are frequently observed.[5-10] For example, poison dart frogs (*Dendrobatidae*) produce a wide variety of biologically active alkaloids in their secretions and thus on their skin. Many of these compounds are poisonous and are part of the frog's defense mechanism. Among these alkaloids, chiral piperidines featuring methyl substituents at the stereogenic centers are often found.[11,12] As examples for this class of structures, bicyclic deoxypumiliotoxin 251H (**1**)[13] and tricyclic indolizidine 251F (**2**)[14] are shown in Figure 1.



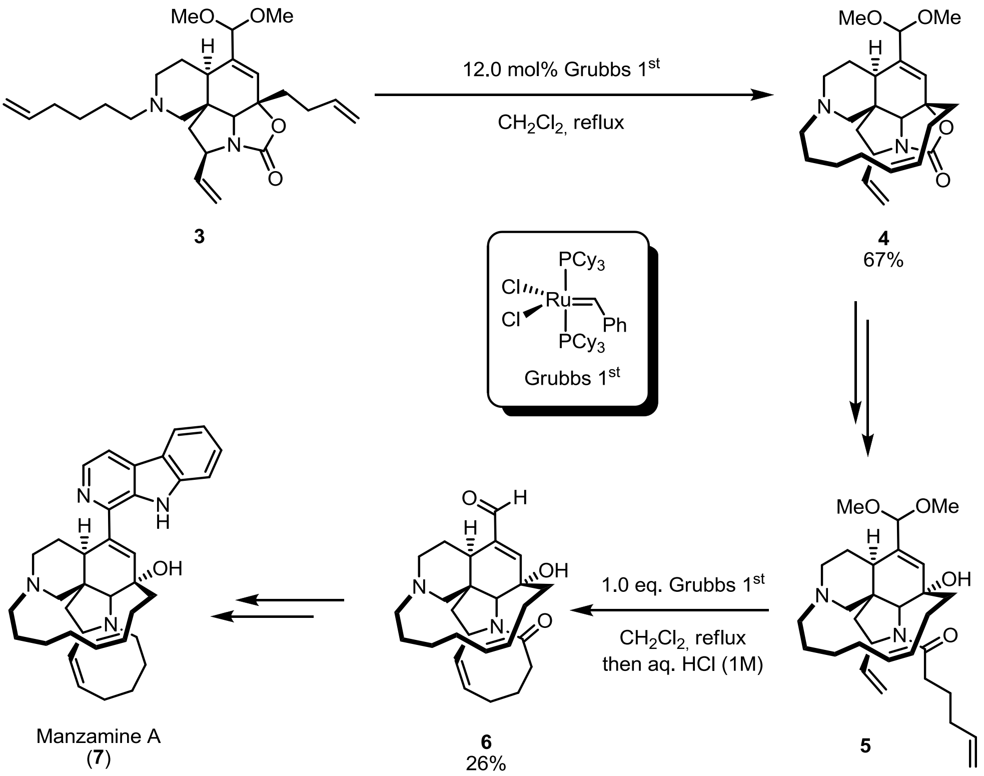
Deoxypumiliotoxin 251H
(**1**)

Indolizidine 251 F
(**2**)

Figure 1 Alkaloids from poison dart frogs

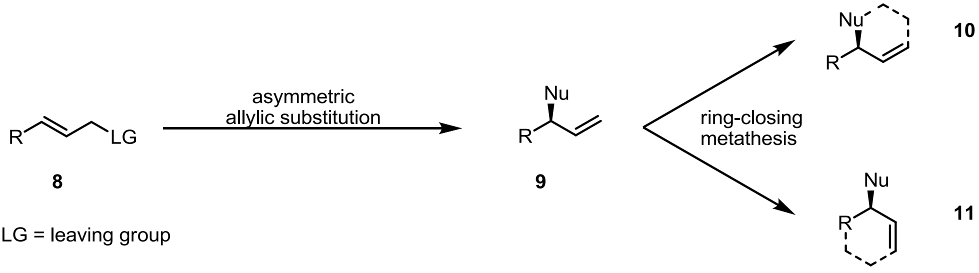
Chiral nitrogen-containing heterocycles represent interesting targets for synthesis,[15-18] imposing particular challenges with regard to the construction of the stereogenic centers with high selectivity. One approach that has been frequently exploited is the use of ring-closing metathesis for the construction of *N*-heterocycles.[16,19-22]

In the synthesis of marine alkaloid manzamine A (**7**), which shows some antitumor activity,[23] two ring-closing metathesis reactions with Ru-based catalysts[24] have been used to construct the two large nitrogen-containing heterocycles,[25] showcasing the potential of this transformation (Scheme 1). Starting with tetracyclic precursor **3** the 13-membered heterocycle was constructed with catalytic amounts of Grubbs 1st generation catalyst to give **4** in 67% yield. At a later stage of the synthesis, the eight-membered heterocycle was constructed from **5** using the same catalyst. However, in the latter case, very low conversion to the desired product **6**, which contained the pentacyclic core of manzamine A, was observed even with equimolar amounts of the ruthenium catalyst.


MeO
OMe
H
N
O
N
O
3
12.0 mol% Grubbs 1st
CH2Cl2, reflux
4
67%
PCy3
Cl
Ru
Ph
PCy3
Grubbs 1st
1.0 eq. Grubbs 1st
CH2Cl2, reflux
then aq. HCl (1M)
OH
5
O
H
6
26%
N
H
Manzamine A
(7)

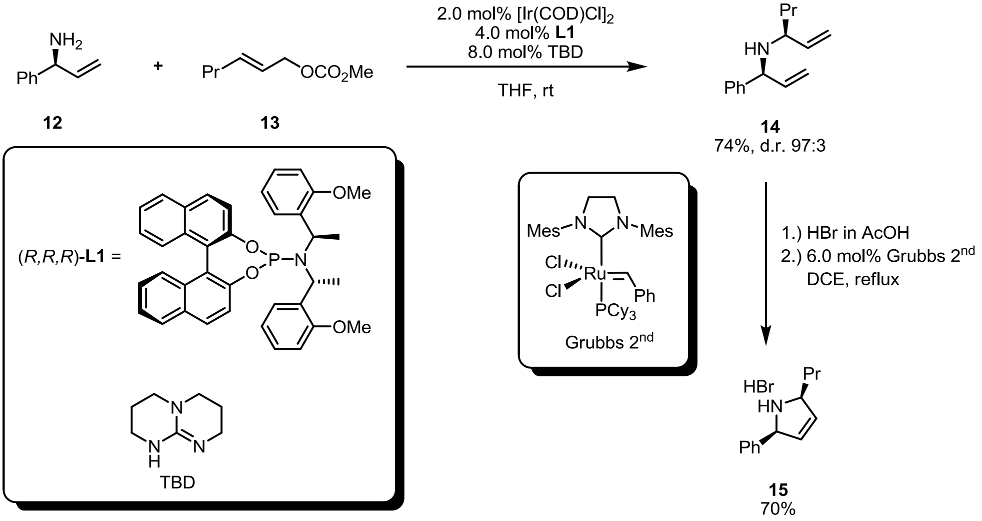
Scheme 1 Ring-closing metathesis in the synthesis of manzamine A

The combination of asymmetric allylic substitution reactions with ring-closing metathesis is a powerful synthetic pathway to chiral hetero- or carbocycles (Scheme 2). The allylic substitution furnishes a chiral compound with a terminal double bond **9**. Compound **9** is an ideal starting point for further functionalization by metathesis. If either the backbone R of allylic compound **8** or the backbone of the nucleophile carries an olefin (or an alkyne), then different ring structures **10** or **11** are available by ring-closing metathesis (or ene-yne metathesis, respectively). This approach has been applied in a variety of cases (see also Chapter 2), some of which are presented in the following.


R
LG
8
LG = leaving group
asymmetric
allylic substitution
Nu
R
9
ring-closing
metathesis
Nu
R
10
Nu
R
11

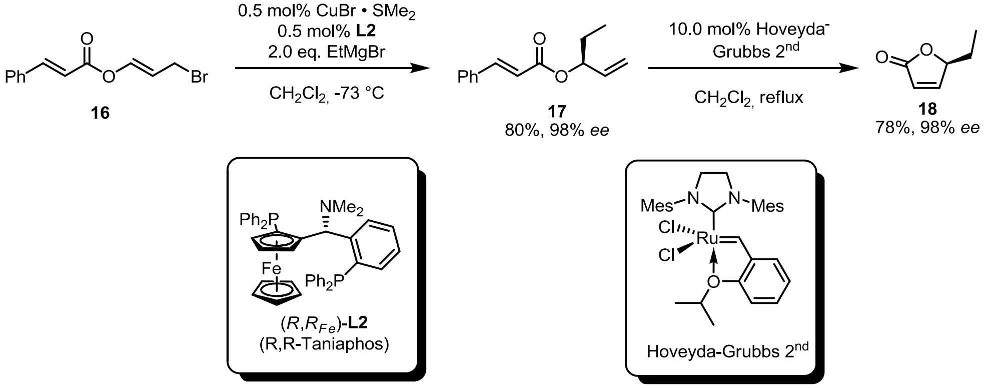
Scheme 2 Combination of asymmetric allylic substitution and ring-closing metathesis

The combination of Ir-catalyzed allylic amination and ring-closing metathesis for the synthesis of chiral pyrrolines **15** was reported.[26] When chiral primary allylic amine **12** (also a product of an Ir-catalyzed allylic amination) was reacted with allylic carbonate **13** in the presence of catalytic amounts of an Ir/**L1** complex, the corresponding diallylamine **14** was obtained in good yields and excellent diastereoselectivity (Scheme 3). This compound could, after protection as the HBr salt, be transformed to chiral pyrroline **15** with catalytic amounts of Grubbs 2nd generation catalyst. The choice of salt proved to be crucial for the latter transformation, as the corresponding HCl salt of **14** led to partial decomposition of **14**. It is important to note that the other diastereomer of **14** (and hence also of **15**) is available in high stereoselectivity via this synthetic route as well, simply by employing the opposite enantiomer of phosphoramidite ligand **L1**.


NH2
Ph
12
+
Pr
OCO2Me
13
2.0 mol% [Ir(COD)Cl]2
4.0 mol% L1
8.0 mol% TBD
THF, rt
Pr
HN
Ph
14
74%, d.r. 97:3
(R,R,R)-L1 =
O
P
N
O
OMe
OMe
N
N
N
H
TBD
Mes
N
N
Mes
Cl
Ru
Cl
Ph
PCy3
Grubbs 2nd
1.) HBr in AcOH
2.) 6.0 mol% Grubbs 2nd
DCE, reflux
HBr
HN
Pr
Ph
15
70%

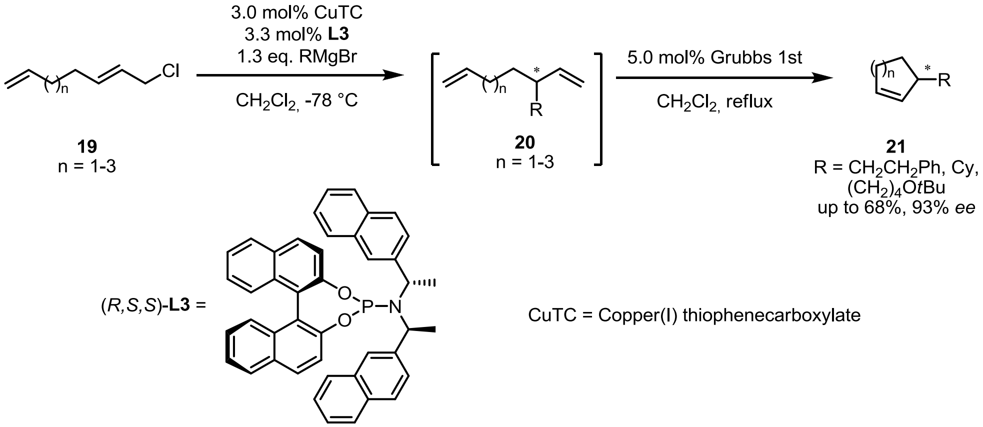
Scheme 3 Ir-catalyzed allylic amination in combination with ring-closing metathesis

An example of an asymmetric allylic substitution in combination with ring-closing metathesis was developed in our laboratories.[27] When α,β-unsaturated ester **16** posessing an allylic bromide moiety was subjected to Cu-catalyzed allylic alkylation conditions with ethylmagnesium bromide, the corresponding chiral ester **17** was obtained in good yield and excellent enantioselectivity (Scheme 4). Compound **17** could subsequently be transformed to chiral lactone **18** without loss of *ee* and in good yields employing Hoveyda-Grubbs 2nd generation catalyst. In this case, styrene is produced as a by-product.


Ph
O
O
Br
16
0.5 mol% CuBr • SMe2
0.5 mol% L2
2.0 eq. EtMgBr
CH2Cl2, -73 °C
Ph
O
O
17
80%, 98% ee
10.0 mol% Hoveyda-
Grubbs 2nd
CH2Cl2, reflux
O
O
18
78%, 98% ee
Ph2P
NMe2
Fe
Ph2P
(R,RFe)-L2
(R,R-Taniaphos)
Mes
N
N
Mes
Cl
Ru
Cl
O
Hoveyda-Grubbs 2nd

Scheme 4 Cu-catalyzed allylic alkylation in combination with ring-closing metathesis

A final example of the abovementioned strategy to synthesise chiral cyclic structures is a combination of Cu-catalyzed allylic alkylation with Grignard reagents to furnish chiral carbocycles (Scheme 5).[28] Allylic chlorides (**19**) bearing terminal olefins (**19**) were transformed to the corresponding chiral compounds **20** with a Cu-phosphoramidite complex as catalyst. It was shown that these intermediates **20** could be transformed to chiral carbocycles **21** in a one-pot protocol employing catalytic amounts of Grubbs 1st generation catalyst. The products **21** are available in very good enantioselectivities.

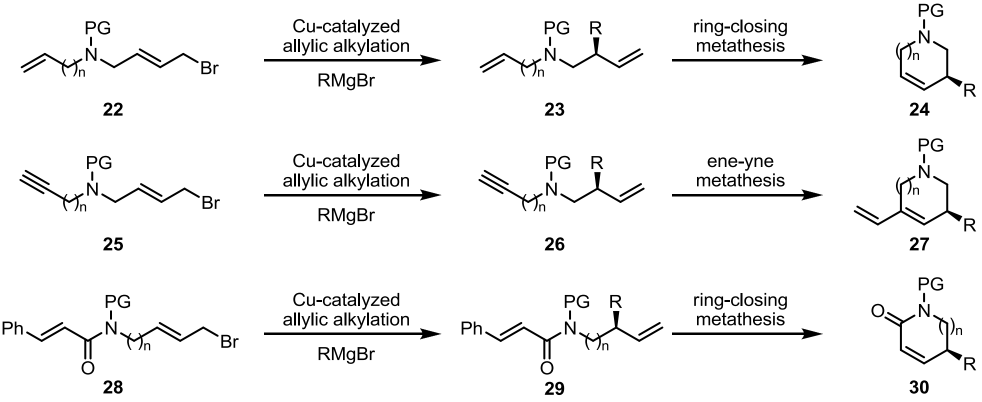

3.0 mol% CuTC
3.3 mol% **L3**
1.3 eq. RMgBr
CH_2Cl_2, -78 °C
5.0 mol% Grubbs 1st
CH_2Cl_2, reflux
Cl
n
R
*
19
n = 1-3
20
n = 1-3
21
R = CH_2CH_2Ph, Cy, $(CH_2)_4OtBu$
up to 68%, 93% *ee*
(*R,S,S*)-**L3** =
O
P
N
CuTC = Copper(I) thiophenecarboxylate

Scheme 5 Cu-catalyzed allylic alkylation in combination with ring-closing metathesis

2. Goal

The aim of this research was to develop a synthetic route to chiral nitrogen-containing heterocycles with various ring sizes. The proposed approach is to comprise two transition metal-based catalytic transformations: First, the Cu-catalyzed allylic alkylation with Grignard reagents, and second, a ring-closing metathesis employing Ru-based catalysts (Scheme 6).

Allylic bromides with terminal alkenes or alkynes **22** and **25** at the protected nitrogen (PG = protecting group) should undergo transformation to chiral amines **23** and **26** in a straightforward manner. These chiral building blocks bear two terminal olefins (**23**) or an olefin/alkyne substitution (**26**) that are suitable for a subsequent ring-closing or ene-yne metathesis, respectively. This should give rise to the chiral *N*-heterocycles **24** and **27** with various ring sizes. Furthermore, a similar approach can be taken to synthesize chiral lactams **30**, when starting off from the corresponding α,β,-unsaturated amides **28**.



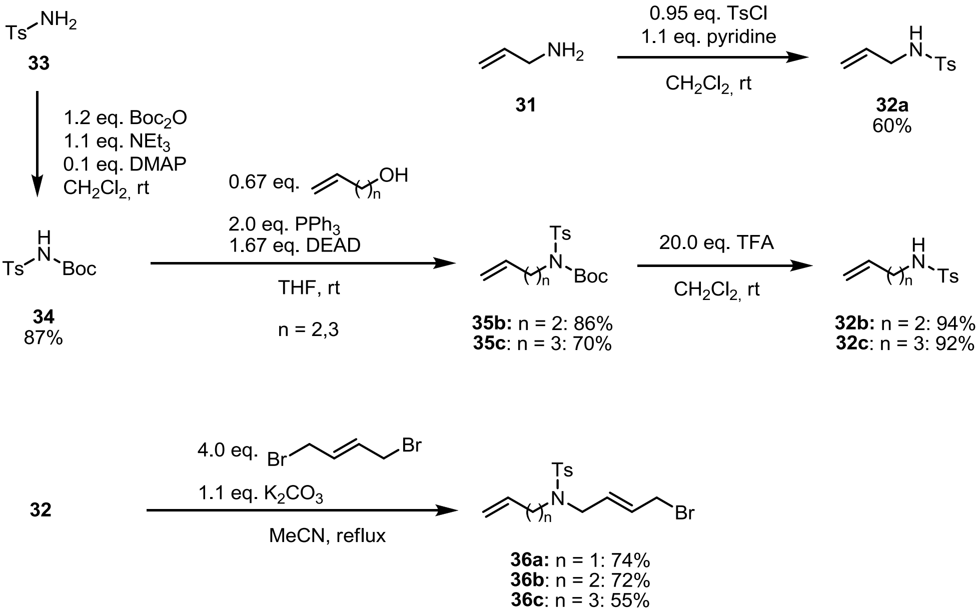
Scheme 6 Envisaged synthetic approaches to chiral N-heterocycles

The envisaged approach has several advantages; it is short and the substituents on the stereogenic center stem from the Grignard reagents, which allow for easy variation at this position. Furthermore, different ring sizes should be accessible with the same approach, making this synthetic route very versatile.

3. Results and Discussion

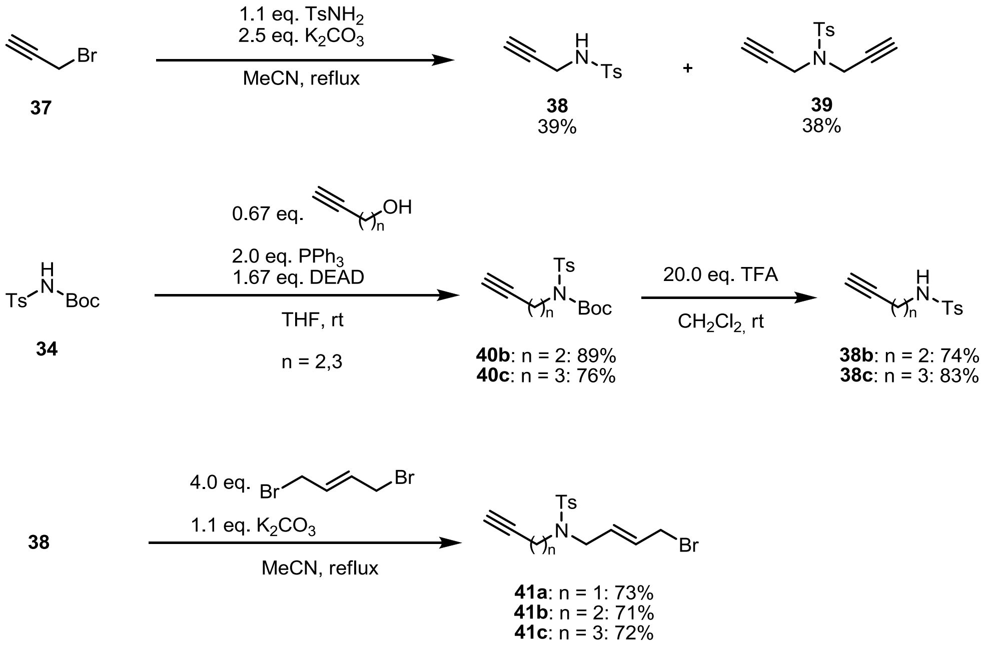
3.1 Synthesis of starting materials

The tosyl-protected allylic bromides **36** bearing olefin substituents with different chain lengths for the allylic alkylation were synthesized as depicted in Scheme 7. Tosyl-allylamine **32a** (n = 1) was prepared from allylamine **31** directly, whereas the longer chains (**32b** and **c**, n = 2,3) were introduced via a Mitsunobu reaction[29] from the corresponding commercially available alcohols and *N*-Boc-tosylamine (**34**) to give double protected amines **35b**,**c** in good yields. The Boc group was subsequently removed to give tosylamides **32b** and **32c**, which were transformed to the allyl bromides **36** with dibromobutene in good yields. The double protection route to amines **32** (via **35**) was chosen because of the higher yields of the Mitsunobu reaction, even though two extra synthetic steps (protection of **33** with a Boc group, deprotection of the Boc group to give **32**) are necessary. These transformations, however, run smoothly with high yields.


33
1.2 eq. Boc$_2$O
1.1 eq. NEt$_3$
0.1 eq. DMAP
CH$_2$Cl$_2$, rt
34
87%
31
0.95 eq. TsCl
1.1 eq. pyridine
CH$_2$Cl$_2$, rt
32a
60%
0.67 eq.
2.0 eq. PPh$_3$
1.67 eq. DEAD
THF, rt
n = 2,3
35b: n = 2: 86%
35c: n = 3: 70%
20.0 eq. TFA
CH$_2$Cl$_2$, rt
32b: n = 2: 94%
32c: n = 3: 92%
32
4.0 eq.
1.1 eq. K$_2$CO$_3$
MeCN, reflux
36a: n = 1: 74%
36b: n = 2: 72%
36c: n = 3: 55%

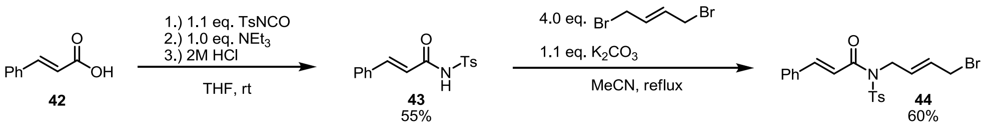
Scheme 7 Synthesis of starting materials for allylic alkylation

For the preparation of allyl bromides **41** posessing a terminal alkyne substituent a similar approach was taken (Scheme 8). The amine (**38a**) with the shortest chain length could be prepared directly from commercially available propargyl bromide **37** with tosylamide to give **38a**, albeit in low yields due to the formation of the double substituted tosylamide **39**. For substrates bearing longer chains, the Mitsunobu approach from the corresponding alcohols with Tosyl-Boc-amine **34** (see Scheme 7) was followed. The Mitsunobu reaction to give **40b**,**c** followed by subsequent deprotection of the Boc group gave the desired products **38b** and **38c** in good yields. Subsequent substitution with dibromobutene gave the allylic bromides with alkyne substituents **41** in good yields.


1.1 eq. TsNH2
2.5 eq. K2CO3
MeCN, reflux
Br
37
H
N
Ts
38
39%
+
Ts
N
39
38%
0.67 eq.
OH
n
2.0 eq. PPh3
1.67 eq. DEAD
THF, rt
n = 2,3
H
N
Ts
Boc
34
Ts
N
Boc
n
40b: n = 2: 89%
40c: n = 3: 76%
20.0 eq. TFA
CH2Cl2, rt
H
N
Ts
n
38b: n = 2: 74%
38c: n = 3: 83%
38
4.0 eq.
Br
Br
1.1 eq. K2CO3
MeCN, reflux
Ts
N
n
Br
41a: n = 1: 73%
41b: n = 2: 71%
41c: n = 3: 72%

Scheme 8 Synthesis of starting materials for allylic alkylation II

The synthesis of allyl bromide **44** with an α,β-unsaturated amide substituent was carried out in a straightforward manner based on a decarboxylative amidation protocol developed in our group (Scheme 9).[30] Cinnamic acid **42** was reacted with tosylisocyanate to give tosylamide **43**. Compound **43** was then transformed to the corresponding allyl bromide **44** by substitution with dibromobutene in moderate yield.

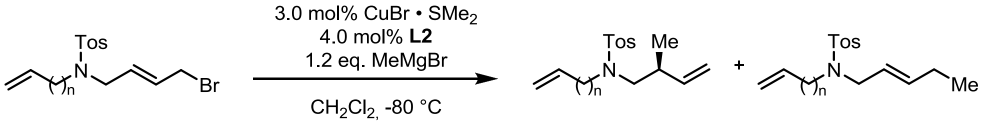

Ph
O
OH
42
1.) 1.1 eq. TsNCO
2.) 1.0 eq. NEt3
3.) 2M HCl
THF, rt
Ph
O
N
H
Ts
43
55%
4.0 eq.
Br
Br
1.1 eq. K2CO3
MeCN, reflux
Ph
O
N
Ts
Br
44
60%

Scheme 9 Synthesis of starting material for allylic alkylation III

3.2 Cu-catalyzed allylic alkylation of allyl bromides bearing terminal olefins substituents

The conditions for the allylic alkylation of allyl bromide **36a** had been described in earlier studies,[31] and were similar to those reported earlier.[32-34] During further investigations, we found that lower temperatures of -80 °C (instead of -78 °C)[31] were necessary to ensure full regioselectivity. When allyl bromides **36** with terminal olefin substituents were subjected to allylic alkylation conditions (3.0 mol% CuBr • SMe_2, 4.0 mol% **L2** (Taniaphos[35-37]), 1.2 eq. MeMgBr in CH_2Cl_2 at -80 °C), the desired chiral products **45** were obtained in good yields and up to excellent enantioselectivities (reaching 99% *ee*, Table 1, entry 1). Furthermore, at this temperature, the product distribution of branched (**45**) to linear (**46**) was very good, exceeding 92:8 favoring the branched products **45**. To reach full conversion of **36c** (n = 3) (Table 1, entry 3), a higher catalyst loading of 6.0 mol% CuBr • SMe_2 and 8.0 mol% **L2** was required. One could speculate that with this particular chain length the coordination of the substrate or the corresponding product to the catalyst is much stronger, due to the possible coordination of **36c** or **45c** to the Cu catalyst through the terminal olefin moiety. Therefore, a higher catalyst loading was necessary to overcome catalyst deactivation. It is remarkable that **45a** and **45c** are formed with excellent enantioselectivity, whereas **45b** with an intermediate chain length is formed with significantly lower *ee*. This, hints towards a secondary coordination or steric effect of **36b** to the catalyst, which interferes with the stereodiscriminating step of the transformation.

Table 1 Asymmetric allylic alkylation of allylic bromides 36



36a-c **45a-c** **46a-c**

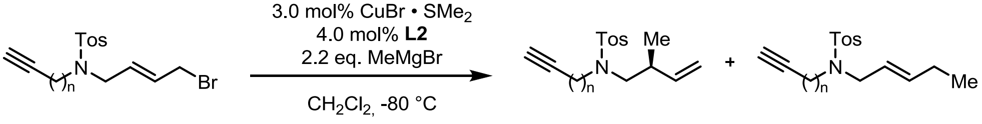
Entry	n	Branched (45)/linear (46)	Isolated yield (for 45)	*ee*
1	1 (**36a**)	95:5	62% (**45a**)	99%
2	2 (**36b**)	98:2	84% (**45b**)	90%
3	3[a] (**36c**)	92:8	72% (**45c**)	98%

[a] 6.0 mol% CuBr • SMe_2 and 8.0 mol% **L2** were used.

3.3 Cu-catalyzed allylic alkylation of allyl bromides bearing terminal alkyne substituents

For the synthesis of chiral *N*-heterocycles carrying a diene motif (**27**), the synthesis started from allylic bromides **41** bearing terminal alkyne substituents of various chain lengths. Under standard allylic substitution conditions, the desired chiral products **47** were isolated in good yields (Table 2). In all cases, excellent regio- and enantioselectivities were achieved (**47**/**48** >95:5, 99% *ee*). Since the terminal alkyne protons of **41** are acidic and have to be deprotonated first, 2.2 equivalents of methylmagnesium bromide were necessary for this transformation to achieve full conversion of bromides **41**. One exception in this particular series of transformations is the reaction of the alkyne **41b**, which only went to 75% conversion. Remarkably, the reaction to the desired chiral homoallylic tosylamides **47** still proceeds in the presence of the Mg-acetylidene moiety, in spite of the fact that Cu-acetylide complexes are known to be very stable.[38,39] In this case, the stability of the Cu-bisphosphine complex seems to be high enough for the reaction to proceed with acceptable yields providing excellent enantioselectivities. As in the case of the olefinic substrates **36** (Table 1), the longest spacer length (**41c**, n = 3) required a slightly higher catalyst loading to achieve full conversion to **47c** (Table 2, entry 3).

Table 2 Asymmetric allylic alkylation of allylic bromides 41



41a-c **47a-c** **48a-c**

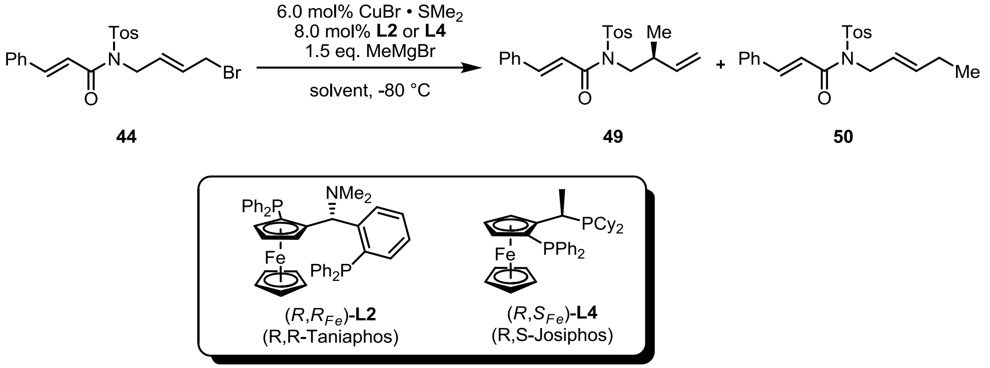
Entry	n	Branched (47)/linear (48)	Isolated yield for 47	*ee*
1	1 (**41a**)	95:5	77% (**47a**)	99%
2	2 (**41b**)	96:4	53% (**47b**)[a]	99%
3	3[b] (**41c**)	95:5	82% (**47c**)	99%

[a]Reaction reaches 75% conversion of **41b**, no side products were observed. [b]6.0 mol% CuBr • SMe_2 and 8.0 mol% **L2** were used.

3.4 Cu-catalyzed allylic alkylation of cinnamide 44

The allylic alkylation of cinnamide **44** was investigated next, which required a more thorough optimization of the reaction conditions. At first, the transformation of **44** to the corresponding addition products **49** and **50** with a catalyst comprising 6.0 mol% CuBr • SMe_2 and 8.0 mol% bisphosphine ligand at -80 °C was investigated (Table 3). From earlier studies, it was known that ferrocenyl-based ligands **L2** and **L4** are generally the best-performing in terms of enantioselectivities and yields for allylic alkylations,[31,33,34] and thus they were tested in a variety of solvents (Table 3). Dichloromethane outperforms MTBE and Et_2O in terms of regio- and enantioselectivities (Table 3, entries 1,4; regioselectivity **49**/**50**: >95:5). The low conversion in Et_2O could be explained by the fact that cinnamide **44** does not fully dissolve in this solvent under the reaction conditions. It is also apparent that the Taniaphos ligand **L2** outperforms Josiphos **L4** with regard to enantioselectivity (97% (**L2**) *vs.* 67% *ee* (**L4**)), however, at the expense of conversion (27% (**L2**) *vs.* full conversion (**L4**)). It is important to note that this reaction, just as in the case of the conjugate addition to coumarins (see Chapter 6), had to be quenched with a HCl solution in Et_2O. This was necessary to prevent the desired product **49** from decomposing during workup. When the reaction was quenched with MeOH, quick and complete esterification to methyl cinnamate was observed.

Table 3 Cu-catalyzed allylic alkylation of 44[a]

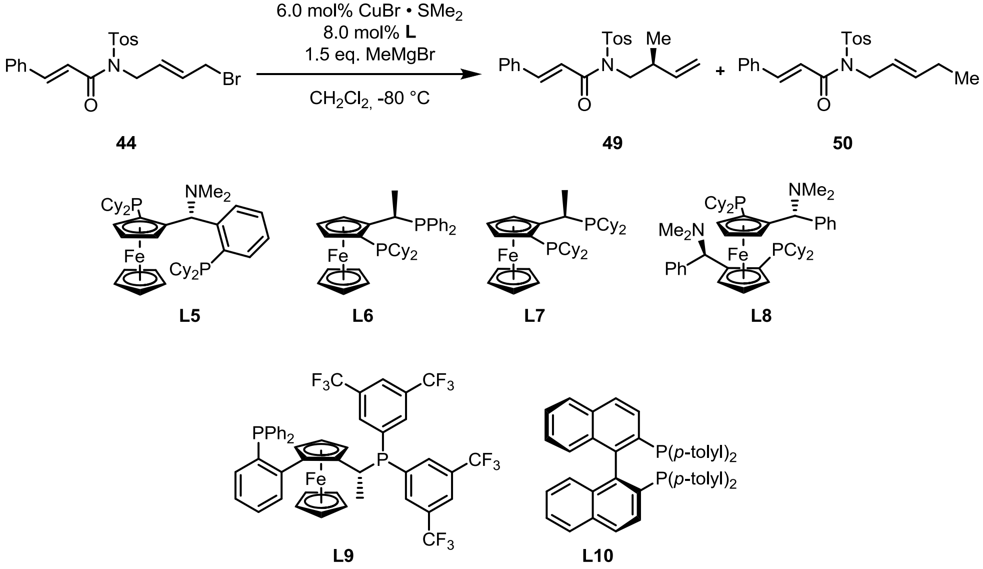


Entry	L	Solvent	Conversion[b]	49:50[b]	*ee*[c]
1	**L2**	CH_2Cl_2	27%	>95:5	97%
2	**L2**	MTBE	16%	83:17	56%
3	**L2**	Et_2O	7%	57:43	87%
4	**L4**	CH_2Cl_2	full	>95:5	67%
5	**L4**	MTBE	85%	71:29	11%
6	**L4**	Et_2O	80%	76:24	5%

[a] Reaction conditions: MeMgBr (1.5 eq.), **44** (1.0 eq., added slowly (~1h) after all the other reagents), $CuBr•SMe_2$ (6.0 mol%) and **L** (8.0 mol%), -80 °C, 17h, reaction quenched with HCl (3M in Et_2O). [b] Determined by ^1H NMR. [c] Determined by chiral HPLC.

To further improve the allylic alkylation of **44** in terms of enantioselectivity and conversion, some structurally related ferrocenyl-based ligands were tested under the optimized reaction conditions (compare Table 3). As can be seen from Table 4, none of the ligands could outperform the two orginally tested ones Taniaphos **L2** and Josiphos **L4** in terms of enantioselectivity and conversion (Table 4, entries 1,3). The structurally related ligands **L5** – **L7** (Table 4, entries 2,4,5) gave much lower conversion, and, with the exception of **L6**, lower enantioselectivity as well. This shows that even small structural and/or electronic changes of the ligands, especially of the aryl-substituents on the phosphorus atoms, have a large impact on the outcome of the reaction. Other ligand classes, like the Mandyphos (**L8**) and the Walphos (**L9**) class as well as the CuI/tolBINAP (**L10**) catalyst[40] (Table 4, entries 6-8) could not compete with the previous chiral ligands, again emphasizing the special spatial requirements of the allylic alkylation catalyst for this particular transformation.

Table 4 Ligand screening for allylic alkylation of cinnamide 44[a]



Entry	L	Conversion[b]	49:50[b]	*ee*[c]
1	**L2**	**27%**	**>95:5**	**95%**
2	**L5**	52%	34:66	7%
3	**L4**	**full**	**>95:5**	**67%**
4	**L6**	full	>95:5	64%

Entry	L	Conversion[b]	49:50[b]	*ee*[c]
5	**L7**	66%	69:31	30%
6	**L8**	30%	70:30	0%
7	**L9**	15%	47:53	23%
8[d]	**L10**	95%	70:30	21%

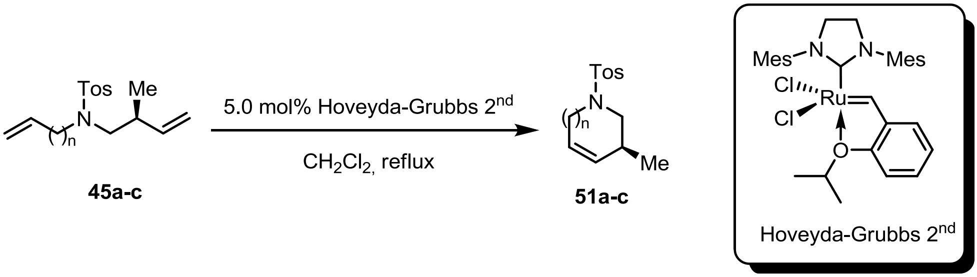
[a]Reaction conditions: MeMgBr (1.5 eq.), **44** (1.0 eq., added slowly (~2h) after all the other reagents), CuBr•SMe$_2$ (6.0 mol%) and **L** (8.0 mol%), -80 °C, 17h, reaction quenched with HCl (3M in Et$_2$O). [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC. [d] 6.0 mol% of CuI was used.

Summarizing the attempts to develop an efficient allylic alkylation of cinnamide **44**, it can be said that the results display a dilemma: The desired product **49** is either available in very good enantioselectivity, but with low yield, employing **L2**, or with moderate enantioselectivity and high yields, using **L4**. The regioselectivity in both cases is very good, favouring the branched product. Attempts to improve the conversion with **L2** by employing higher amounts of Grignard reagent or by changing the order of addition of substrates and Grignard reagent did not lead to better results. Furthermore, it was established that chiral amide **49** is stable under the reaction conditions, so that *in situ* deterioration of the desired product can be excluded.

3.5 Ring-closing metathesis of chiral diolefins

Chiral diolefins **45** could subsequently be transformed to the corresponding *N*-heterocycles **51** by ring-closing metathesis (Table 5). With 5.0 mol% Hoveyda-Grubbs 2nd generation catalyst,[24] the six- to eight-membered rings were obtained in moderate to good yields. The best result was found for the eight-membered unsaturated azocane **51c** (77%, Table 5, entry 3). It is important to note that the *ee* of the desired products **51** was not compromized during the reaction.

Table 5 Ring-closing metathesis of chiral diolefins



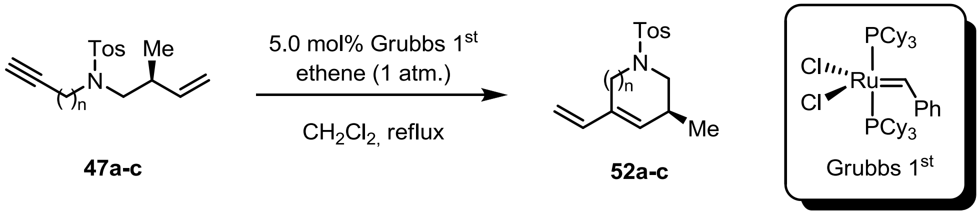
Entry	n	Yield	*ee*
1	1 (**45a**)	54% (**51a**)	99%
2	2 (**45b**)	46% (**51b**)	90%
3	3 (**45c**)	77% (**51c**)	98%

The yield of chiral piperidine **51a** (Table 5, entry 1) is comparatively low, even though the reaction reaches full conversion. In the crude reaction mixture, one unidentified side product is present. It is known from studies of ring-closing metathesis of related lactams[41] that the concentration of the starting materials has an influence on the reaction since theoretically, also the homodimer of **45a** could be obtained. In general, higher concentrations (40 mM) of the starting materials yield homodimers, whereas lower concentrations (1 mM) of the starting materials in the reaction mixture afford the desired ring-closed products. The ring-closing metathesis reactions in Table 5 were run at a concentration of 5 mM and therefore the formation of homodimers (and polymers) of **45a** could not be excluded, but it was unlikely. From the crude ^{1}H NMR, no such products were observed, an thus the side-products observed must arise from another reaction pathway.

3.6 Ring-closing ene-yne metathesis of chiral terminal alkynes

For the ene-yne metathesis of compounds **47** to reach full conversion, 5.0 mol% Grubbs 1st generation catalyst under an ethene atmosphere was employed.[31] The addition of ethene was found to be essential for the reaction to proceed to **52**, as in its absence, no conversion was observed (see section 3.7).[42] The resulting six- and seven-membered nitrogen-containing rings with diene motifs **52a,b** were isolated in good yields (Table 6). Again, no loss of *ee* was observed in this transformation, making this a viable pathway for the construction of chiral nitrogen-containing heterocycles with various ring sizes.

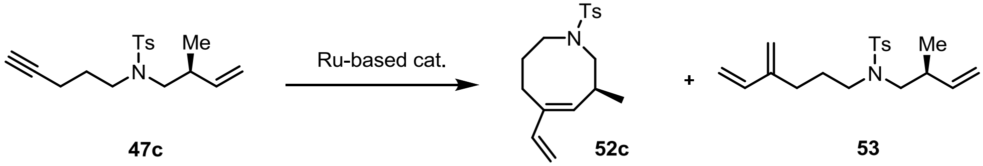
Table 6 Ene-yne metathesis of chiral terminal alkynes



Entry	n	Yield	*ee*
1	1 (**47a**)	77% (**52a**)	99%
2	2 (**47b**)	65% (**52b**)	99%
3	3 (**47c**)	N/A	N/A

The reaction of **47c** under the given conditions did not produce the desired eight-membered ring **52c**. The ene-yne metathesis proceeded to the linear product **53** in moderate yields (Table 7, entries 1,2), where the alkyne moiety of **52c** reacted in an intermolecular fashion with ethene instead of intramolecularly with the terminal olefin. Product **53** did not react any further to the desired ring system under the reaction conditions. Furthermore, this reaction could not be improved in terms of conversion to **53**, as other Ru-based metathesis catalysts under a variety of conditions[43] did not give any conversion to neither **52c** nor **53** (Table 7). It is known in literature that the synthesis of eight-membered rings via cross-metathesis is difficult, due to steric restraints of the products as well as the kinetics of the ring-closing reactions.[44] This can lead to unwanted side-reactions such as polymerization of the starting materials and/or products.

Table 7 Ene-yne metathesis of 47c

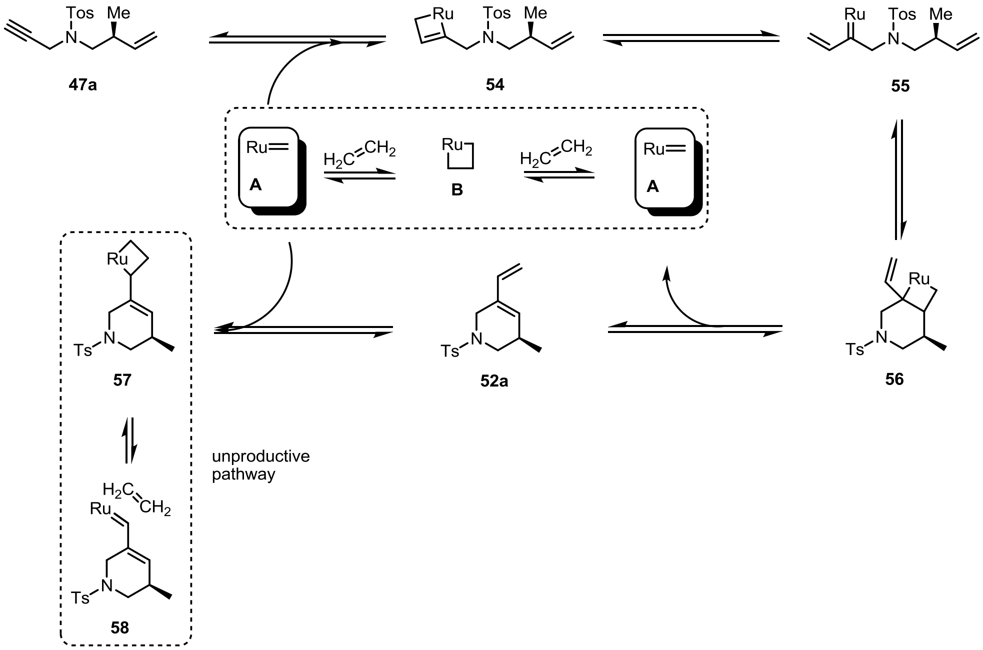


Entry	Catalyst (mol%)	Solvent	Atm.	Temp.	Yield (53)
1	Grubbs 1st (5.0)	CH_2Cl_2	ethene	40 °C	9%[a,b]
2	**Grubbs 1st (10.0)**	**CH_2Cl_2**	**ethene**	**40 °C**	**35%**[a,b]
3	Grubbs 1st (5.0)	CH_2Cl_2	-	40 °C	n.d.[a]
4	Grubbs 1st (5.0)	toluene	ethene	70 °C	n.d.[a]
5	Grubbs 1st (5.0)	toluene	-	70 °C	n.d.[a]
6	Hoveyda-Grubbs 2nd (5.0)	CH_2Cl_2	ethene	40 °C	n.d.[a]
7	Hoveyda-Grubbs 2nd (5.0)	toluene	ethene	70 °C	n.d.[a]
8	Grubbs 2nd (5.0)	CH_2Cl_2	ethene	40 °C	n.d.[a]

[a] Low conversion. [b] Complex mixture of products.

3.7 Role of the ethene atmosphere for the ene-yne metathesis

It was found that an ethene atmosphere was crucial for the ene-yne metathesis of terminal alkynes **47** to cyclic dienes **52**, an observation that had been made in earlier studies of ene-yne metathesis reactions.[42] The necessity for the ethene atmosphere can be explained with the various equilibria present in an ene-yne metathesis reaction (Scheme 10). The Ru-alkylidene catalyst **A** reacts, due to the higher electron density, first with the terminal alkyne of **47a** to yield a ruthenacyclobutene **54**. This undergoes cycloreversion to yield Ru-alkylidene **55**. The intramolecular olefin metathesis leads to diene **52a** via ruthenacyclobutane **56**. The driving force of this reaction pathway is the thermodynamic stability of the diene **52a**. However, the Ru-catalyst **A** can enter a non-productive olefin cross metathesis with the terminal diene of **52a** leading to ruthenacycle **57**, and finally to Ru-alkylidene **58** and ethene. This last equilibrium is affected by an ethene atmosphere, as it should lie on the side of **57**, and therefore also further on the side of the desired product, and free alkylidene **A**. Through the unproductive pathway, the effective amount of active catalyst in the reaction mixture is lowered. If an ethene atmosphere is present, any ruthenacycle **57** formed is quickly reacted back to the free Ru-alkylidene catalyst **A** (and possibly onward to ruthenacycle **B**) and the desired product **52a**, and thus removed from the unproductive pathway.

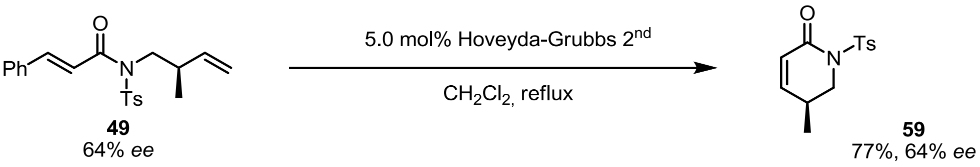


Tos
Me
47a
Ru
54
55
Ru=
A
$H_2C{=}CH_2$
B
Ru
57
52a
56
unproductive pathway
Ts
N
58

Scheme 10 Ene-yne metathesis in the presence of ethene atmosphere

3.8 Ring-closing metathesis for the synthesis of a chiral lactam

Enantioenriched amide **49**, from the reaction with ligand **L4** (*vide supra*), was subjected to ring-closing metathesis conditions to probe whether the anticipated pathway to synthesize chiral lactams was viable. When **49** was reacted in the presence of catalytic amounts of Hoveyda-Grubbs 2^{nd} generation catalyst, the corresponding chiral lactam **59** was isolated in good yields without compromizing the *ee* (Scheme 11). This shows that the general approach to chiral lactams is indeed feasible as anticipated.



Ph
O
N
Ts
49
64% ee
5.0 mol% Hoveyda-Grubbs 2nd
CH_2Cl_2, reflux
59
77%, 64% ee

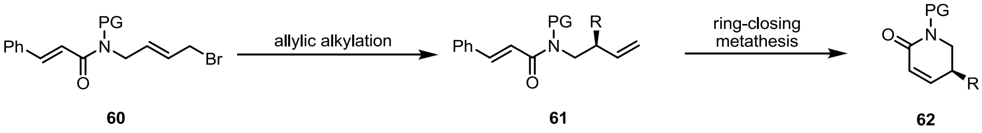
Scheme 11 Ring-closing metathesis for the synthesis of chiral lactam

4. Conclusions and future prospects

In summary, we have demonstrated that chiral unsaturated heterocycles are available in excellent enantiomeric excess and good yields via a combination of Cu-catalyzed allylic substitution and Ru-catalyzed ring-closing metathesis. Six- to eight-membered chiral nitrogen-containing rings are easily available through this short synthetic pathway in high enantioselectivity. By employing terminal olefins, singly unsaturated rings are accessible, while terminal alkynes were transformed to the corresponding dienes in good yields and 99% *ee*. The obtained compounds are ideal chiral building blocks for further functionalization through the olefinic bonds. It should be noted that the synthesis of an eight-membered diene was not achieved via this synthetic route, since a side reaction to a linear diene moiety was found.

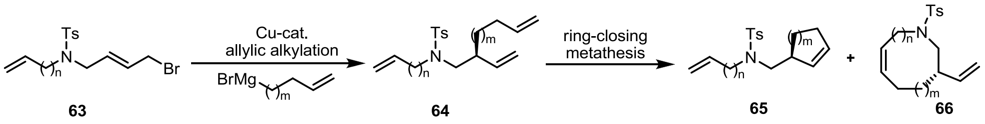
It has been demonstrated that the same pathway can be employed for the synthesis of chiral lactams, when allylic bromides with amide substituents are used. The allylic substitution has yet to be optimized, since either high enantioselectivity accompanied by low yields, or high yields accompanied with moderate enantioselectivities are obtained with the tested catalysts. However, it has been shown that the subsequent ring-closing metathesis proceeds without endangering the chiral information.

For further extension of this project, some follow-up studies could be envisaged. To improve the results of the allylic alkylation of amides different *N*-protecting groups (like Boc) or no *N*-protecting group of **60** could be tested in the enantioselective reaction to give **61**. It is possible that the tosyl group used in this study is interfering with the catalyst and therefore reducing the catalytic activity. Further transformation to chiral lactam **62** (Scheme 12) has been shown to work well and it is not expected to encounter problems with different *N*-protecting groups.



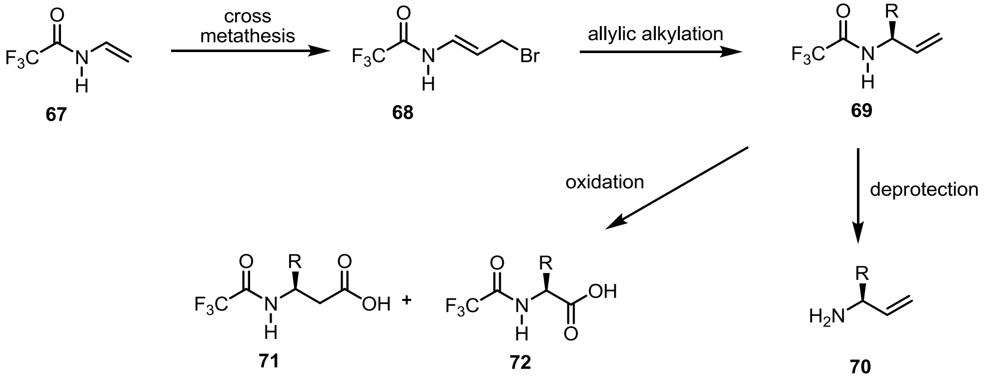
Scheme 12 Change of protecting group for the synthesis of chiral lactams

Secondly, the newly developed allylic alkylation-ring-closing metathesis protocol could be extended to the use of functionalized Grignard reagents, ideally ones bearing terminal olefins (Scheme 13). Through this approach, a multifunctional chiral building block **64** would be accessible. Posessing three terminal double bonds, a variety of chiral carbo- or heterocycles **65** and **66** would be accessible, and it would be interesting to probe whether the ring-closing metathesis step could be rendered selective towards one of the products.


Ts
N
n
Br
63
Cu-cat.
allylic alkylation
BrMg
m
64
ring-closing
metathesis
65
+
66

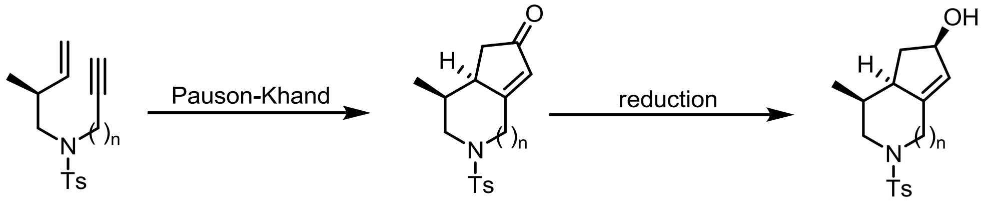
Scheme 13 Allylic alkylation with functionalized Grignard reagents

One of the most interesting future prospects of this work would be to examine the asymmetric alkylation to enamides **68** (Scheme 14). The trifluoroacetamide **67** is accessible,[45] and conversion to the corresponding allyl bromide **68** could be envisaged. If the asymmetric allylic alkylation of enamides could be accomplished, it would not only be the aza-version of the already reported work with esters,[27] but **69** itself is an important multifunctional building block. By deprotection of the trifluoroacetamide,[46] chiral primary allylic amines **70** would be accessible. Secondly, **69** could be used to prepare chiral aminoacids **71** and **72** by oxidation of the double bond either by a hydroboration-oxidation sequence or by ozonolysis with oxidative workup.


O
F_3C
N
H
67
cross
metathesis
Br
68
allylic alkylation
R
69
oxidation
deprotection
OH
+
71
72
H_2N
70

Scheme 14 Synthesis of chiral nitrogen-containing building blocks

As a last possible extension of this project, one could envisage the use of the chiral building blocks **73**, products of the asymmetric allylic alkylation to substrates bearing terminal alkynes, in new transformations such as for example the Pauson-Khand reaction,[47] which would furnish chiral bicyclic systems **74** (Scheme 15). Reduction of the α,β,-unsaturated ketone[48] would furnish bicyclic compound **75** with three stereocenters.



73 **74** **75**

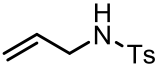
Scheme 15 Possible further reactions of 73

5. Experimental Section

General remarks:

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian AMX400 (400 and 100 MHz, respectively), a Varian VXR300 (300 and 75 MHz, respectively), or a Varian VXR200 NMR spectrometer (200 MHz and 75 MHz, respectively) with $CDCl_3$ as solvent. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for ^{1}H NMR, δ = 77.0 ppm for ^{13}C NMR). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; qi, quintet; m, multiplet; br, broad, app, apparent. Enantiomeric excesses were determined by chiral HPLC using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector, in comparison with racemic products or, in some cases, mixtures of both enantiomers. Racemic products were obtained by the same procedure as the enantioselective allylic alkylation only using $CuBr \cdot SMe_2$ (10 mol%), PPh_3 (20 mol%) and MeMgBr (1.15 eq.) at -40 °C in CH_2Cl_2. The opposite enantiomer of a product is obtained by using the enantiomer of **L2**, following the general procedure **D**. Regioselectivities were determined by ^{1}H NMR. Optical rotations were measured on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL) at 20 °C. Thin-layer chromatography (TLC) was performed on Merck TLC Silica gel 60 Kieselguhr $F_{254.}$ Flash chromatography was performed on silica gel Merck Type 9385 230-400 mesh. Mass spectra were recorded on a AEI-MS-902 mass spectrometer (EI$^+$) or a LTQ Orbitrap XL (ESI$^+$).

N-Allyl-4-methylbenzenesulfonamide (32a)[1]

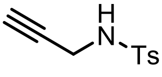


32a

p-Toluenesulfonyl chloride (37.9 mmol, 7.23 g, 0.95 eq.) and pyridine (44 mmol, 3.5 g, 1.1 eq.) were added to a solution of allylamine (40 mmol, 2.28 g, 1.0 eq.) in dry CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 16 h and washed with aqueous 0.5 M HCl (3 x 5 mL). The combined aqueous phases were extracted with CH_2Cl_2 (10 mL) and the organic layer was dried and concentrated under reduced pressure to afford product **32a** (75% yield, 6.3 g, R_f (1:5 EtOAc/heptane) = 0.51) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* =

8.1 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.76-5.63 (m, 1H), 5.10 (dd, *J* = 24.9 Hz, 13.7 Hz, 2H), 4.92 (br, 1H), 3.55 (t, *J* = 5.9 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.81, 143.51, 128.66, 127.49, 126.37, 113.35, 43.44, 21.00. HRMS calcd. for $C_{10}H_{14}NO_2S$ [M+H$^+$]: 212.0745, found 212.0740.

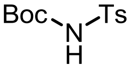
4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (38a)[2]



38a

A mixture of *p*-toluenesulfonamide (22 mmol, 3.77 g, 1.1 eq.) and K_2CO_3 (50 mmol, 6.9 g, 2.5 eq.) in MeCN (500 mL) was stirred at room temperature. To this mixture a solution of propargyl bromide (20 mmol, 2.38 g, 1.0 eq.) in MeCN (20 mL) was added dropwise. The mixture was heated to reflux for 16 h, cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (SiO_2, 1:7 EtOAc/heptane, R_f (1:5 EtOAc/heptane) = 0.37) to yield the product (39% yield, 1.64 g) as a colorless oil. The disubstituted side product **38a** (38%, 1.63 g, R_f (1:5 EtOAc/heptane) = 0.45) was obtained as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.53 (br, 1H), 3.83 (dd, *J* = 6.1 Hz, 2.5 Hz, 2H), 2.44 (s, 3H), 2.11 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.83, 139.31, 129.93, 126.68, 98.20, 74.22, 36.39, 21.73. HRMS calcd. for $C_{10}H_{12}NO_2S$ [M+H$^+$]: 210.0589, found 210.0583.

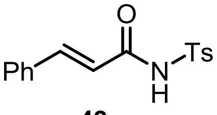
tert-Butyl tosylcarbamate (34)[3]



34

p-Toluenesulfonamide (30 mmol, 5.14 g, 1.0 eq.) was suspended in CH_2Cl_2 (25 mL) containing Et_3N (33 mmol, 3.34 g, 1.1 eq.) and DMAP (3 mmol, 0.37 g, 0.1 eq.). A solution of di-(*t*-butyl) dicarbonate (36 mmol, 7.86 g, 1.2 eq.) in CH_2Cl_2 (40 mL) was added dropwise with stirring over 8 min. After 2 h, the solution was concentrated under reduced pressure and the residue treated with EtOAc (100 mL) and 2 M aq. HCl (60 mL). The organic phase was washed successively with water and brine, dried and concentrated under reduced pressure to afford a solid. Heating in pentane (30 mL), cooling to room temperature and filtration provided the product as a white solid (87% yield, 7.06 g, R_f (1:5 EtOAc/heptane) = 0.57). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.19, 144.97, 136.15, 129.71, 128.46, 84.28, 28.09, 21.88. HRMS calcd. For $C_{12}H_{18}NO_4S$ [M+H$^+$]: 272.0957, found 272.0951.

N-Tosylcinnamamide (43)[4]



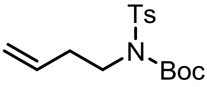
43

E-Cinnamic acid (6.8 mmol, 1.0 g, 1.0 eq.) was dissolved in dry THF (20 mL) under nitrogen and tosyl isocyanate (7.4 mmol, 1.46 g, 1.1 eq.) was added to the solution. After stirring at room temperature for 10 min the inert atmosphere was disconnected and triethylamine (7.4 mmol, 0.75 g, 1.1 eq.) was added drop-wise to the open flask, allowing the release of the formed CO_2. After stirring for 1h at room temperature the solution was diluted with 20 mL of EtOAc and washed with 2M aq. HCl and brine. After drying and filtration the organic phase was concentrated *in vacuo* and the product was precipitated by addition of pentane to a saturated ether solution followed by decantation and washing with pentane. Compound **43** was obtained as a pale yellow solid (71% yield, 1.4 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 15.7 Hz, 2H), 7.49 – 7.32 (m, 7H), 6.44 (d, *J* = 15.7 Hz, 2H), 2.42 (d, *J* = 4.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.65, 145.94, 145.10, 135.64, 133.69, 130.82, 129.62, 128.88, 128.40, 128.36, 117.51, 21.61. HRMS calcd. for $C_{16}H_{15}NO_3SNa$ [M+Na$^+$]: 324.0665, found 324.0659.

General procedure A: Preparation of olefinic and propargylic *N*-Boc protected sulfonamides[5] (35b,c and 40b,c)

N-Boc *p*-toluenesulfonamide **34** (7.37 mmol, 2.0 g, 1.5 eq.) was dissolved in dry THF (3 mL) and triphenylphosphine (14.7 mmol, 3.87 g, 3.0 eq.) was added. The solution was stirred under nitrogen atmosphere and the olefinic or propargylic alcohol (4.9 mmol, 1.0 eq.) was added followed by diethyl azodicarboxylate (12.2 mmol, 2.12 g, 2.5 eq.). The mixture was stirred at room temperature for 3h, concentrated under reduced pressure and the product was purified by flash chromatography (SiO_2).

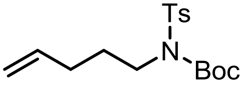
(*N*-*tert*-Butoxycarbonyl)(but-3-enyl)tosylamide (35b)[6]



35b

The title compound was prepared from 3-buten-1-ol (5.5 mmol, 0.40 g) following general procedure **A**. Purification by column chromatography (SiO_2, 1:8 EtOAc/heptane, R_f (1:5 EtOAc/heptane) = 0.54) afforded product **35b** as a yellow oil (86% yield, 1.54 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.91 – 5.71 (m, 1H), 5.20 – 5.02 (m, 2H), 3.92 – 3.85 (m, 2H), 2.58 – 2.46 (m, 2H), 2.44 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.14, 144.26, 137.74, 134.62, 129.42, 128.08, 117.64, 84.34, 46.60, 34.80, 28.09, 21.81. HRMS calcd. for $C_{16}H_{23}NO_4SNa$ [M+Na$^+$]: 348.1245, found 348.1240.

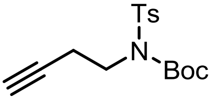
(*N-tert*-Butoxycarbonyl)(but-3-ynyl)tosylamide (35c):



35c

The title compound was prepared from 4-penten-1-ol (0.81 mmol, 70 mg) following general procedure **A**. Purification by column chromatography (SiO_2, 1:8 EtOAc/pentane, R_f (1:6 EtOAc/pentane) = 0.44) afforded product **35c** as a colorless oil (97% yield, 266 mg). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.81 (ddt, *J* = 16.7 Hz, 10.2 Hz, 6.5 Hz, 1H), 5.11 – 4.91 (m, 2H), 3.85 – 3.73 (m, 2H), 2.40 (s, 3H), 2.16 – 2.05 (m, 2H), 1.91 – 1.80 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.91, 144.02, 137.47, 137.41, 129.19, 127.72, 115.17, 84.04, 46.71, 30.82, 29.18, 27.83, 21.54. HRMS calcd. for $C_{17}H_{26}NO_4S[M+H^+]$: 340.1583, found 340.1577.

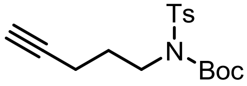
(*N-tert*-Butoxycarbonyl)(but-3-ynyl)tosylamide (40b)[7]



40b

The title compound was prepared from 3-butyn-1-ol (1.4 mmol, 95 mg) following general procedure **A**. Purification by column chromatography (SiO_2, 5:1 heptane/EtOAc, R_f = 0.24) afforded product **40b** as an opaque oil (89% yield, 391 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.03 – 3.98 (m, 2H), 2.69 – 2.63 (m, 2H), 2.44 (s, 3H), 2.03 – 2.01 (m, 1H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.93, 144.46, 137.45, 129.47, 128.11, 84.74, 80.65, 70.60, 45.42, 28.06, 21.82, 20.21. HRMS calcd. for $C_{16}H_{21}NO_4SNa$ [M+Na$^+$]: 346.1089, found 346.1084.

(*N-tert*-Butoxycarbonyl)(pent-4-ynyl)tosylamide (40c)



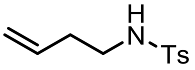
40c

The title compound was prepared from 4-pentyn-1-ol (0.64 mmol, 54 mg) following general procedure **A**. Purification by column chromatography (SiO_2, 5:1 heptane/EtOAc, R_f = 0.27) afforded product **40c** as an opaque oil (76% yield, 165 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 3.90 (t, *J* = 8.0 Hz, 2H), 2.41 (s, 3H), 2.26 (td, *J* = 7.1 Hz, 2.4 Hz, 2H), 1.97 (m, 3H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.07, 144.36, 137.53, 129.46, 128.00, 84.42, 83.24, 69.23, 46.48, 29.10, 28.05, 21.75, 16.20. HRMS calcd. for $C_{12}H_{16}NO_2S$ [M-Boc+H$^+$]: 238.0896, found 238.0889.

General procedure B: Preparation of olefinic and propargylic tosylamides (32b,c and 38b,c)[8]

To a solution of the *N*-Boc olefinic or propargylic tosylamide **35** or **40** (0.62 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (12.4 mmol, 1.41 g, 20 eq.) at 0 °C, and the mixture was stirred at rt for 3 h. The mixture was diluted with EtOAc, and the organic layer was washed with saturated aq. $NaHCO_3$ solution and saturated aq. NaCl solution, dried and concentrated to afford the products as colorless oils.

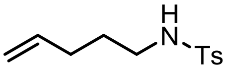
N-3-Buten-1-yl-4-methyl-benzenesulfonamide (32b)[9]



32b

The title compound was prepared from **35b** (4.74 mmol, 1.54 g) following general procedure **B** (70% yield, 744 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.69 – 5.55 (m, 1H), 5.07 – 4.98 (m, 2H), 4.66 (t, *J* = 5.7 Hz, 1H), 3.00 (app q, *J* = 6.6 Hz, 2H), 2.42 (s, 3H), 2.19 (app q, *J* = 6.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.63, 137.21, 134.39, 129.92, 127.34, 118.31, 42.31, 33.83, 21.73. HRMS calcd. for $C_{11}H_{16}NO_2S$ [M+H$^+$]: 226.0902, found 226.0896.

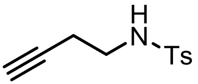
N-4-Penten-1-yl-4-methyl-benzenesulfonamide (32c)[9]



32c

The title compound was prepared from **35c** (0.77 mmol, 260 mg) following general procedure **B** (86% yield, 157 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.68 (ddt, *J* = 16.9 Hz, 10.2 Hz, 6.7 Hz, 1H), 5.01 (t, *J* = 6.1 Hz, 1H), 4.97 – 4.89 (m, 2H), 2.91 (dd, *J* = 13.5 Hz, 6.8 Hz, 2H), 2.41 (s, 3H), 2.02 (app q, *J* = 7.2 Hz, 2H), 1.54 (app qi, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.29, 137.25, 136.95, 129.66, 127.06, 115.44, 42.58, 30.60, 28.63, 21.48. HRMS calcd. for $C_{12}H_{17}NO_2SNa$ [M+Na$^+$]: 262.0878, found 262.0872.

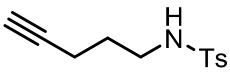
N-3-Butyn-1-yl-4-methyl-benzenesulfonamide (38b)[10]



38b

The title compound was prepared from **40b** (0.62 mmol, 200 mg) following general procedure **B** (74% yield, 103 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.13 (t, *J* = 6.2 Hz, 1H), 3.08 (app q, *J* = 6.6 Hz, 2H), 2.41 (s, 3H), 2.32 (td, *J* = 6.7 Hz, 2.6 Hz, 2H), 1.98 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.81, 137.13, 130.00, 127.29, 80.61, 71.02, 41.89, 21.74, 20.00. HRMS calcd. for $C_{11}H_{14}NO_2S$[M+H$^+$]: 224.0745, found 224.0740.

N-4-Pentyn-1-yl-4-methyl-benzenesulfonamide (38c)[11]



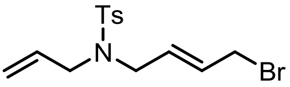
38c

The title compound was prepared from **40c** (0.50 mmol, 170 mg) following general procedure **B** (83% yield, 99 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.54 (br, 1H), 3.08 (app q, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 2.22 (td, *J* = 6.8 Hz, 2.5 Hz, 2H), 1.95 (s, 1H), 1.69 (qi, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.42, 136.86, 129.71, 127.07, 82.89, 69.39, 42.11, 28.12, 21.50, 15.69. HRMS calcd. for $C_{12}H_{16}NO_2S$ [M+H$^+$]: 238.0902, found 238.0896.

General procedure C: Preparation of allylic bromide substrates (36a-c, 41a-c)

To a suspension of olefinic or propargylic tosylamide **32** or **38** (19.2 mmol, 1.0 eq.) and K_2CO_3 (28.8 mmol, 3.98 g, 1.1 eq.) in 20 mL MeCN was added 1,4-dibromobut-2-ene (77.0 mmol, 16.5 g, 4.0 eq.) and the mixture was heated to reflux for 24 h. The mixture was then concentrated under reduced pressure and water (10 mL) and Et_2O (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2) yielded desired products.

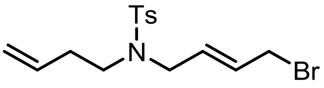
(*E*)-*N*-(4-Bromo-2-buten-1-yl)-4-methyl-N-2-propen-1-yl-benzenesulfonamide (36a)[12]



36a

The title compound was prepared from **32a** (19.2 mmol, 4.06 g) following general procedure **C**. Purification by column chromatography (SiO_2, 1:5 EtOAc/Pentane, R_f = 0.38) afforded **36a** (70% yield, 4.63 g) as an opaque oil. ^{1}H NMR (200 MHz, CDCl $_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.85 – 5.68 (m, 1H), 5.66 – 5.43 (m, 2H), 5.20 – 5.08 (m, 2H), 3.85 (d, *J* = 7.3 Hz, 2H), 3.78 (d, *J* = 6.2 Hz, 4H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.63, 137.36, 132.73, 130.71, 129.99, 129.84, 127.38, 119.57, 49.94, 47.94, 31.67, 21.75. HRMS calcd. for $C_{14}H_{19}BrNO_2S$ [M+H$^+$]: 344.0320, found 344.0314.

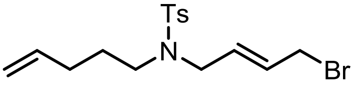
(*E*)-*N*-(4-Bromo-2-buten-1-yl)-4-methyl-N-3-buten-1-yl-benzenesulfonamide (36b)



36b

The title compound was prepared from **32b** (2.87 mmol, 734 mg) following general procedure **C**. Purification by column chromatography (SiO_2, 1:5 EtOAc/Pentane, R_f = 0.23) afforded **36b** (74% yield, 762 mg) as an opaque oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.87 – 5.76 (m, 1H), 5.74 – 5.54 (m, 2H), 5.11 – 4.98 (m, 2H), 3.87 (d, *J* = 7.4 Hz, 2H), 3.81 (d, *J* = 6.3 Hz, 2H), 3.17 (t, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 2.27 (app q, *J* = 6.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.56, 137.15, 134.77, 130.42, 130.37, 129.94, 127.39, 117.41, 49.37, 47.32, 33.22, 31.51, 21.73. HRMS calcd. for $C_{15}H_{21}BrNO_2S$ [M+H$^+$]: 358.0476, found 358.0471.

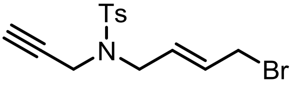
(*E*)-*N*-(4-Bromo-2-buten-1-yl)-4-methyl-N-4-penten-1-yl-benzenesulfonamide (36c)



36c

The title compound was prepared from **32c** (0.648 mmol, 155 mg) following general procedure **C**. Purification by column chromatography (SiO_2, 1:7 Et_2O/Pentane, R_f (1:6 Et_2O/Pentane) = 0.23) afforded **36c** (47% yield, 116 mg) as an opaque oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.87 – 5.69 (m, 2H), 5.65 – 5.55 (m, 1H), 5.04 – 4.92 (m, 2H), 3.86 (d, *J* = 7.4 Hz, 2H), 3.78 (d, *J* = 6.5 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 2.02 (dd, *J* = 14.2 Hz, 7.2 Hz, 2H), 1.64 – 1.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.28, 137.42, 136.83, 130.24, 130.09, 129.70, 127.13, 115.27, 49.10, 47.25, 31.33, 30.66, 27.49, 21.49. HRMS calcd. for $C_{16}H_{23}BrNO_2S$ [M+H$^+$]: 372.0633, found 372.0627.

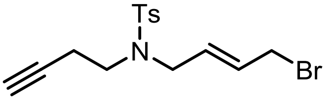
(*E*)-*N*-(4-Bromo-2-buten-1-yl)-4-methyl-N-2-propyn-1-yl-benzenesulfonamide (41a)[13]



41a

The title compound was prepared from **38a** (1.20 mmol, 250 mg) following general procedure **C**. Purification by column chromatography (SiO_2, 1:15 EtOAc/Heptane, R_f (1:9 EtOAc/Heptane) = 0.25) afforded **41a** (73% yield, 299 mg) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.98-5.90 (m, 1H), 5.75 – 5.64 (m, 1H), 4.09 (d, *J* = 2.4 Hz, 2H), 3.92 (d, *J* = 7.5 Hz, 2H), 3.85 (d, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.03 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.73, 135.75, 131.46, 129.55, 128.71, 127.72, 76.31, 74.01, 47.39, 36.03, 31.15, 21.57. HRMS calcd. for $C_{14}H_{16}BrNO_2SNa$ [M+Na$^+$]: 363.9983, found 363.9977.

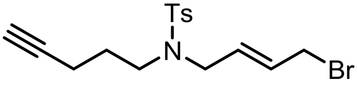
(*E*)-*N*-(4-Bromo-2-buten-1-yl)-4-methyl-N-3-butyn-1-yl-benzenesulfonamide (41b)



41b

The title compound was prepared from **38b** (0.34 mmol, 76 mg) following general procedure **C**. Purification by column chromatography (SiO_2, 1:7 EtOAc/Heptane, R_f (1:5 EtOAc/Heptane) = 0.22) afforded **41b** (71% yield, 85 mg) as an opaque oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.84 (dt, *J* = 14.8 Hz, 7.4 Hz, 1H), 5.69 – 5.55 (m, 1H), 3.93 – 3.81 (m, 4H), 3.28 (t, *J* = 7.4 Hz, 2H), 2.46 (m, 2H), 2.43 (s, 3H), 1.97 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.79, 136.93, 130.76, 130.11, 130.03, 127.40, 81.13, 70.51, 49.92, 46.53, 31.32, 21.74, 19.66. HRMS calcd. for $C_{15}H_{19}BrNO_2S$ [M+H$^+$]: 356.0320, found 356.0314.

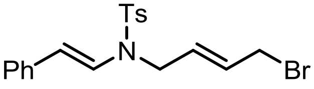
(*E*)-*N*-(4-Bromo-2-buten-1-yl)-4-methyl-N-4-pentyn-1-yl-benzenesulfonamide (41c)



41c

The title compound was prepared from **38c** (0.12 mmol, 28 mg) following general procedure **C**. Purification by column chromatography (SiO_2, 1:8 EtOAc/Heptane, R_f (1:5 EtOAc/Heptane) = 0.29) afforded **41c** (72% yield, 78 mg) as an opaque oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.83 (dt, *J* = 15.0 Hz, 7.5 Hz, 1H), 5.66 – 5.55 (m, 1H), 3.87 (d, *J* = 7.5 Hz, 2H), 3.80 (d, *J* = 6.5 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.20 (dt, *J* = 7.0 Hz, 2.6 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.75 (app qi, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.41, 136.60, 130.44, 129.96, 129.75, 127.18, 83.13, 69.11, 49.49, 46.65, 31.25, 27.38, 21.51, 15.73. HRMS calcd. for $C_{16}H_{20}BrNO_2SNa$ [M+Na$^+$]: 392.0296, found 392.0290.

N-((*E*)-4-Bromobut-2-en-1-yl)-*N*-tosylcinnamamide (44)



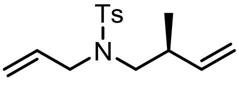
44

The title compound was prepared from **43** (6.2 mmol, 1.86 g) following general procedure **C**. Purification by column chromatography (SiO_2, 1:5 EtOAc/heptane, R_f (1:3 EtOAc/heptane) = 0.48) afforded **44** (75% yield, 2.02 g) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 15.4 Hz, 1H), 7.51 – 7.49 (m, 2H), 7.43 – 7.37 (m, 3H), 7.34 – 7.28 (m, 3H), 6.05 – 5.96 (m, 1H), 5.93 – 5.84 (m, 1H), 4.56 (d, *J* = 5.5 Hz, 2H), 3.95 (d, *J* = 8.0 Hz, 2H), 2.42 (d, *J* = 7.8 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 165.62, 146.11, 144.90, 136.70, 134.30, 130.59, 130.27, 129.78, 128.87, 128.26, 127.65, 126.59, 117.83, 46.94, 31.38, 21.53. HRMS calcd. for $C_{20}H_{21}BrNO_3S$ [M+H$^+$]: 434.0426, found 434.0420.

General procedure D: Enantioselective Cu-catalyzed allylic alkylation with methylmagnesium bromide (45a-c, 47a-c)

In a dry Schlenk tube equipped with septum and stirring bar, CuBr·SMe_2 (15 μmol, 3.1 mg, 1.0 mol%) and **L2** (18 μmol, 12.4 mg, 1.2 mol%) were dissolved in CH_2Cl_2 (2.0 mL) and stirred under nitrogen atmosphere at room temperature for 10 min. The mixture was cooled to -80 °C and a solution of methylmagnesium bromide (1.73 mmol, 3M solution in Et_2O, 1.15 eq.) in 1.0 mL CH_2Cl_2 was added dropwise over 20 min via syringe pump. Subsequently, a solution of allylic bromide **36** or **41** (1.5 mmol) in 1.0 mL CH_2Cl_2 was added dropwise over 30 min via syringe pump. Once the addition was complete, the resulting mixture was stirred at -80 °C for 16h. The reaction was quenched by addition of MeOH (2.0 mL) and was allowed to warm up to rt. Aqueous NH_4Cl solution (1M, 10 mL) was added and the organic phase separated. The aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude product which was purified by flash chromatography SiO_2.

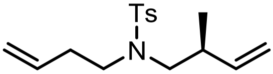
(*S*)-*N*-Allyl-4-methyl-*N*-(2-methylbut-3-en-1-yl)benzenesulfonamide (45a)



45a

The title compound was prepared from **36a** (1.50 mmol, 516 mg) following general procedure **D**. Purification by column chromatography (SiO_2, EtOAc/pentane 1:9, R_f = 0.44) afforded **45a** (74% yield, 277 mg, ratio **45a:46a** = 95:5, 99% *ee*, $[\alpha]_D$ = -1.1 (*c* 17.4, $CHCl_3$)) as a yellow oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak AD (99% *n*-heptane/1% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 16.1 (major) and 17.4 (minor). ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.75 – 5.41 (m, 2H), 5.13– 4.92 (m, 4H), 3.76 (d, *J* = 6.4 Hz, 2H), 3.10 – 2.86 (m, 2H), 2.51 – 2.42 (m, 1H), 2.36 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.38, 141.27, 137.31, 133.25, 129.85, 127.38, 119.11, 115.01, 52.92, 51.32, 36.71, 21.67, 17.62. HRMS calcd. for $C_{15}H_{22}NO_2S$ $[M+H^+]$: 280.1371, found 280.1366.

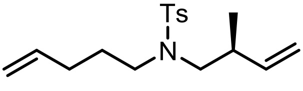
(S)-*N*-(But-3-en-1-yl)-4-methyl-*N*-(2-methylbut-3-en-1-yl)benzenesulfonamide (45b)



45b

The title compound was prepared from **36b** (0.017 mmol, 3.4 mg) following general procedure **D**. Purification by column chromatography (SiO_2, EtOAc/Pentane 1:7, R_f (EtOAc/pentane 1:5) = 0.64) afforded **45b** (84% yield, 69 mg, ratio **45b:47b** = 98:2, 90% *ee*, $[\alpha]_D$ = +1.2 (*c* 0.5, $CHCl_3$)) as a yellow oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel OJ (99% *n*-heptane/1% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 9.3 (major) and 11.6 (minor). ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.76 – 5.59 (m, 2H), 5.07 – 4.95 (m, 4H), 3.15 (m, 2H), 3.09 – 2.93 (m, 2H), 2.54 – 2.44 (m, 1H), 2.41 (s, 3H), 2.32 – 2.17 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.30, 141.21, 137.20, 134.94, 129.79, 127.44, 117.14, 115.13, 54.26, 48.47, 37.06, 33.16, 21.69, 17.70. HRMS calcd. for $C_{16}H_{24}NO_2S$ $[M+H^+]$: 294.1528, found 294.1522.

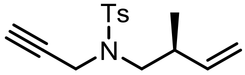
(*S*)-4-Methyl-*N*-(2-methylbut-3-en-1-yl)-*N*-(pent-4-en-1-yl)benzenesulfonamide (45c)



45c

The title compound was prepared from **36c** (0.11 mmol, 42 mg) following general procedure **D**. Purification by column chromatography (SiO_2, Et_2O/pentane 1:8, R_f = 0.39) afforded **45c** (72% yield, 25 mg, ratio **45c:46c** = 92:8, 98% *ee*, $[\alpha]_D$ = +0.7 (*c* 0.8, $CHCl_3$)) as a yellow oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak OD-H (99.5% *n*-heptane/0.05% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 45.4 (minor) and 47.9 (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.80 – 5.63 (m, 2H), 5.06 – 4.94 (m, 4H), 3.11 – 3.05 (m, 2H), 3.05 – 2.94 (m, 2H), 2.53 – 2.43 (m, 1H), 2.42 (s, 3H), 2.00 (dd, *J* = 14.2 Hz, 7.4 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.22, 141.27, 137.67, 137.14, 129.76, 127.45, 115.47, 115.08, 54.35, 48.71, 37.17, 31.13, 27.75, 21.69, 17.72. HRMS calcd. for $C_{17}H_{25}NO_2SNa$ [M+Na$^+$]: 330.1504, found 330.1498.

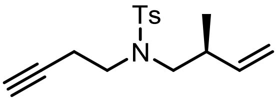
(*S*)-4-Methyl-*N*-(2-methylbut-3-en-1-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (47a)



47a

The title compound was prepared from **41a** (22 mmol, 75 mg) following general procedure **D**. Purification by column chromatography (SiO_2, EtOAc/petroleum ether 40-60 1:9, R_f = 0.59) afforded **47a** (77% yield, 47 mg, 99% *ee*, $[\alpha]_D$ = -4.9 (*c* 1.4, $CHCl_3$)) as a colorless oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak AD (99% *n*-heptane/1% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 17.6 (major) and 19.1 (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.72 (ddd, *J* = 17.5 Hz, 10.3 Hz, 7.5 Hz, 1H), 5.11 – 5.01 (m, 2H), 4.20 – 4.06 (m, 2H), 3.14 – 3.02 (m, 2H), 2.57 – 2.44 (m, 1H), 2.41 (s, 3H), 1.99 (t, *J* = 2.5 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.63, 141.04, 136.21, 129.62, 127.95, 115.28, 76.68, 73.99, 51.74, 36.92, 36.35, 21.73, 17.71. HRMS calcd. for $C_{15}H_{20}NO_2S$ [M+H$^+$]: 278.1215, found 278.1209.

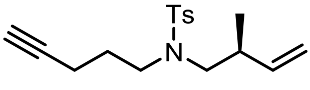
(*S*)-*N*-(But-3-yn-1-yl)-4-methyl-*N*-(2-methylbut-3-en-1-yl)benzenesulfonamide (47b)



47b

The title compound was prepared from **41b** (84 μmol, 30 mg) following general procedure **D**. Purification by column chromatography (SiO_2, 1:7 Et_2O/ petroleum ether 40-60, R_f (1:5 Et_2O/ petroleum ether 40-60) = 0.43) afforded **47b** (53% yield, 13 mg, 99% *ee*, $[\alpha]_D$ = -1.4 (*c* 1.0, $CHCl_3$)) as an opaque oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak AD (95% *n*-heptane/5% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 8.1 (major) and 9.6 (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.74 – 5.59 (m, 1H), 5.08 – 4.93 (m, 2H), 3.33 – 3.20 (m, 2H), 3.12 – 2.99 (m, 2H), 2.54 – 2.47 (m, 1H), 2.47 – 2.43 (m, 2H), 2.41 (s, 3H), 1.99 – 1.92 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.58, 141.03, 136.78, 129.91, 127.45, 115.39, 81.22, 70.44, 54.82, 47.94, 37.17, 21.73, 19.47, 17.73. HRMS calcd. for $C_{16}H_{22}NO_2S$ [M+H$^+$]: 292.1371, found 292.1366.

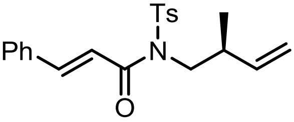
(*S*)-4-Methyl-*N*-(2-methylbut-3-en-1-yl)-*N*-(pent-4-yn-1-yl)benzenesulfonamide (47c)



47c

The title compound was prepared from **41c** (0.26 mmol, 80 mg) following general procedure **D**. Purification by column chromatography (SiO_2, 1:7 EtOAc/heptane, R_f (1:6 EtOAc/heptane) = 0.45) afforded **47c** (82% yield, 66 mg, 99% *ee*, $[\alpha]_D$ = -3.2 (*c* 1.1, $CHCl_3$)) as an opaque oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralcel OJ (97% *n*-heptane/3% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 11.7 (major) and 13.7 (minor). ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.69 (ddd, *J* = 17.5 Hz, 10.3 Hz, 7.4 Hz, 1H), 5.10 – 4.95 (m, 2H), 3.25 – 3.13 (m, 2H), 3.12 – 2.91 (m, 2H), 2.61 – 2.45 (m, 1H), 2.42 (s, 3H), 2.18 (td, *J* = 6.9 Hz, 2.6 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.85 – 1.67 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.13, 140.97, 136.60, 129.59, 127.25, 115.00, 69.03, 54.52, 48.02, 44.41, 36.91, 27.35, 21.47, 17.55, 15.92. HRMS calcd. for $C_{17}H_{23}BrNO_2SNa$ [M+Na$^+$]: 328.1347, found 328.1342.

(*S*)-*N*-(2-Methylbut-3-en-1-yl)-*N*-tosylcinnamamide (49)



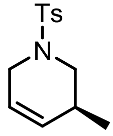
49

The title compound was prepared from **44** (0.114 mmol, 50 mg) following general procedure **D**, except that the reaction was quenched with 3.0 M HCl solution in Et_2O (1 mL). Purification by column chromatography (SiO_2, Et_2O/Pentane 1:9, R_f (Et_2O/Pentane 1:7) = 0.43) afforded **49** (71% yield, 30 mg, ratio **49:50** = 95:5, 67% *ee*, $[\alpha]_D$ = +20.5 (*c* 0.7, $CHCl_3$)) as a colorless oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak OJ-H (99% *n*-heptane/1% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 17.3 (major) and 19.1 (minor). ^1H NMR (200 MHz, $CDCl_3$) δ 7.80 – 7.24 (m, 11H), 5.85 – 5.62 (m, 1H), 5.15 – 4.95 (m, 2H), 3.96 – 3.70 (m, 2H), 2.80 – 2.65 (m, 1H), 2.39 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.32, 145.57, 144.68, 140.56, 137.22, 134.53, 130.51, 129.78, 128.91, 128.29, 127.30, 118.70, 115.53, 51.39, 38.50, 21.58, 17.53. HRMS calcd. for $C_{21}H_{23}NO_3SNa$ [M+Na$^+$]: 392.1291, found 392.1275.

General procedure E: Ru-catalyzed olefin ring-closing metathesis (51a-c)

Substrate (**45a-c**) was dissolved in degassed CH_2Cl_2 (5 mL) and Hoveyda-Grubbs 2nd generation catalyst (5.0 mol%) was added to the solution under a N_2 atmosphere. The mixture was stirred at rt until full conversion (3h) was achieved, as judged by TLC. The mixture was concentrated under reduced pressure and purified by column chromatography to yield the desired product **51a-c** as colorless oils.

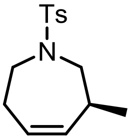
(*S*)-3-Methyl-1-tosyl-1,2,3,6-tetrahydropyridine (51a)



51a

The title compound was prepared from **45a** (0.80 mmol, 223 mg) following general procedure **E**. Purification by column chromatography (SiO_2, 1:9 EtOAc/heptane, R_f (1:5 EtOAc/heptane) = 0.45) afforded **51a** (54% yield, 80 mg, 99% *ee*, $[\alpha]_D$ = -0.4 (*c* 5.2, $CHCl_3$)) as a colorless oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak AS-H (95% *n*-heptane/5% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 17.1 (minor) and 17.8 (major). ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.1 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 5.63 – 5.54 (m, 2H), 3.68 (d, *J* = 16.4 Hz, 1H), 3.45 – 3.33 (m, 1H), 2.55 – 2.45 (m, 2H), 2.42 (s, 3H), 0.99 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.68, 133.56, 131.63, 129.84, 127.85, 121.84, 49.60, 44.94, 30.49, 21.72, 18.49. HRMS calcd. for $C_{13}H_{18}NO_2S$ [M+H$^+$]: 252.1058, found 252.1053.

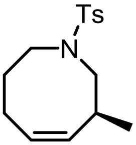
(*S*)-3-Methyl-1-tosyl-2,3,6,7-tetrahydro-1H-azepine (51b)



51b

The title compound was prepared from **45b** (0.14 mmol, 34 mg) following general procedure **E**. Purification by column chromatography (SiO_2, 1:9 EtOAc/heptane, R_f = 0.34) afforded **51b** (61% yield, 19 mg, 90% *ee*, $[\alpha]_D$ = -1.8 (*c* 1.0, $CHCl_3$)) as a colorless oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak OJ-H (99% *n*-heptane/1% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 40.9 (minor) and 42.2 (major). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.30 – 7.28 (m, 2H), 5.69 – 5.62 (m, 1H), 5.55 – 5.49 (m, 1H), 3.55 – 3.45 (m, 2H), 2.97 (ddd, *J* = 13.1 Hz, 7.4 Hz, 4.0 Hz, 1H), 2.76 (dd, *J* = 13.0 Hz, 9.1 Hz, 1H), 2.57 (br, 1H), 2.42 (s, 3H), 2.35 – 2.25 (m, 2H), 1.05 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.24, 137.29, 129.86, 128.40, 127.23, 77.42, 54.58, 48.63, 35.63, 29.98, 21.69, 19.47. HRMS calcd. for $C_{14}H_{20}NO_2S$ [M+H$^+$]: 266.1215, found 266.1209.

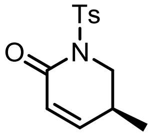
(S)-7-Methyl-1-tosyl-1,2,3,4,7,8-hexahydroazocine (51c)



51c

The title compound was prepared from **45c** (34 µmol, 10.5 mg) following general procedure **E**. Purification by column chromatography (SiO_2, 1:8 Et_2O/pentane, R_f (1:7 Et_2O/pentane) = 0.37) afforded **51c** (77% yield, 7.0 mg, 98% *ee*, $[\alpha]_D$ = +5.7 (*c* 0.7, $CHCl_3$)) as a colorless oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak OD-H (98% *n*-heptane/2% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 26.2 (major) and 27.6 (minor). ^1H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 9.1 Hz, 2H), 5.70 – 5.54 (m, 1H), 5.40 – 5.30 (m, 1H), 3.54 – 3.43 (m, 1H), 3.36 (dt, *J* = 14.8, 4.1 Hz, 1H), 2.87 (ddd, *J* = 14.8, 10.7, 4.1 Hz, 1H), 2.75 – 2.63 (m, 1H), 2.47 – 2.34 (m, 2H), 2.47 – 2.31 (m, 5H), 2.10 – 1.99 (m, 2H), 1.52 – 1.39 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.85, 135.46, 129.57, 129.55, 126.84, 57.39, 48.42, 33.21, 29.84, 29.68, 24.09, 21.46, 18.80. HRMS calcd. for $C_{15}H_{21}NO_2SNa$ [M+Na$^+$]: 302.1202, found 302.1181.

(*R*)-5-Methyl-1-tosyl-5,6-dihydropyridin-2(1H)-one (59)



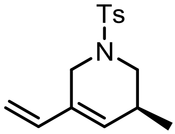
59

The title compound was prepared from **49** (43 mmol, 16 mg) following general procedure **E**. Purification by column chromatography (SiO_2, 1:30 MeOH/toluene, R_f (1:25 MeOH/toluene) = 0.53) afforded **59** (65% yield, 7.5 mg, % *ee*, $[\alpha]_D$ = +36.0 (*c* 1.2, $CHCl_3$)) as a colorless oil. Enantiomeric excess could not be determined by chiral HPLC analysis or chiral GC analysis. ^1H NMR (200 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.65 (dd, *J* = 9.7, 3.6 Hz, 1H), 5.77 (dd, *J* = 9.8, 1.9 Hz, 1H), 4.16 (dd, *J* = 12.2, 5.1 Hz, 1H), 3.65 (dd, *J* = 12.2, 8.2 Hz, 1H), 2.83 – 2.71 (m, 1H), 2.42 (s, 3H), 1.18 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.98, 150.46, 144.94, 136.13, 129.57, 128.77, 124.00, 50.39, 30.69, 21.86, 17.08. HRMS calcd. for $C_{13}H_{16}NO_3S$ [M+H$^+$]: 266.0845, found 266.0842.

General procedure F: Ru-catalyzed ene-yne metathesis (52a-b)

Substrate (**47a-b**) was dissolved in degassed CH_2Cl_2 (5 mL) and Grubbs 1st generation catalyst (1.0 mol% per hour during 5 h) was added to the solution. The mixture was refluxed under an ethylene atmosphere (1 atm, balloon) until full conversion was reached, as judged by TLC. The mixture was concentrated under reduced pressure and purified by column chromatography to yield the desired products **52a-b** as a colorless oils.

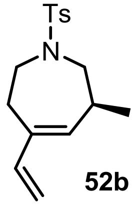
(*S*)-3-Methyl-1-tosyl-5-vinyl-1,2,3,6-tetrahydropyridine (52a)



52a

The title compound was prepared from **47a** (0.15 mmol, 42 mg) following general procedure **F**. Purification by column chromatography (SiO_2, 1:9 Et_2O/petroleum ether 40-60, R_f (5:95 Et_2O/ petroleum ether 40-60) = 0.15) afforded **52a** (77% yield, 31 mg, 99% *ee*, $[\alpha]_D$ = +33.6 (*c* 0.6, $CHCl_3$)) as a colorless oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak AS-H (99% *n*-heptane/1% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 29.6 (minor) and 31.3 (major). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.24 (dd, *J* = 17.8 Hz, 11.0 Hz, 1H), 5.63 (s, 1H), 5.11 – 4.93 (m, 2H), 3.88 (d, *J* = 15.4 Hz, 1H), 3.51 – 3.46 (m, 2H), 2.52 – 2.46 (m, 2H), 2.43 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.71, 136.57, 132.97, 131.59, 129.89, 127.85, 118.71, 111.91, 49.65, 44.26, 30.79, 21.71, 18.36. HRMS calcd. for $C_{15}H_{20}NNaO_2S$ [M+Na$^+$]: 300.1046, found 300.1026

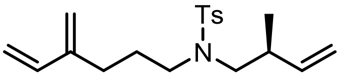
(*S*)-3-Methyl-1-tosyl-5-vinyl-2,3,6,7-tetrahydro-1H-azepine (52b)



52b

The title compound was prepared from **47b** (38 µmol, 11 mg) following general procedure **F**. Purification by column chromatography (SiO_2, 1:6 Et_2O/ petroleum ether 40-60, R_f (1:4 Et_2O/ petroleum ether 40-60) = 0.38) afforded **52b** (65% yield, 7 mg, 99% *ee*, $[\alpha]_D$ = -8.4 (*c* 1.0, $CHCl_3$)) as a colorless oil. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak OJ-H (95% *n*-heptane/5% *i*-PrOH, flow rate 0.5 mL/min), 40 °C, retention times (min) 22.5 (minor) and 25.4 (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.24 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.55 (d, *J* = 3.4 Hz, 1H), 5.07 – 4.93 (m, 2H), 3.67 (ddd, *J* = 13.1, 8.0, 2.3 Hz, 1H), 3.60 – 3.53 (m, 1H), 2.89 (ddd, *J* = 13.0, 8.9, 1.9 Hz, 1H), 2.71 – 2.66 (m, 2H), 2.59 – 2.50 (m, 1H), 2.41 (s, 3H), 1.08 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.38, 140.37, 139.20, 138.82, 136.13, 129.90, 127.31, 111.41, 53.80, 47.10, 34.37, 27.55, 21.73, 19.98. HRMS calcd. for $C_{16}H_{22}NO_2S$ $[M+H^+]$: 292.1371, found 292.1366.

(*S*)-4-Methyl-*N*-(2-methylbut-3-en-1-yl)-*N*-(4-methylenehex-5-en-1-yl) benzenesulfonamide (53)



53

The title compound was prepared from **47c** (43 µmol, 13 mg) following general procedure **F** with the following modification: Grubbs 1st generation catalyst was added to the reaction mixture (2.0 mol%) and the same amount again after 8 h and the reaction was heated to reflux for 7 days. Purification by column chromatography (SiO_2, 1:7 Et_2O/ petroleum ether 40-60, R_f = 0.42) afforded **53** (35% yield, 5 mg, $[\alpha]_D$ = +4.0 (*c* 0.3, $CHCl_3$)) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.6 Hz, 2H), 7.27 (dd, *J* = 9.9, 4.7 Hz, 2H), 6.34 (dd, *J* = 17.0, 10.1 Hz, 1H), 5.67 (dd, *J* = 17.2, 7.4 Hz, 1H), 5.14 (d, *J* = 17.7 Hz, 1H), 5.09 – 4.88 (m, 5H), 3.10 (t, *J* = 10.3 Hz, 2H), 3.05 – 2.89 (m, 2H), 2.53 – 2.43 (m, 1H), 2.41 (s, 3H), 2.14 (t, *J* = 7.7 Hz, 2H), 1.70 (dd, *J* = 14.8, 6.9 Hz, 2H), 1.01 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.09, 143.00, 141.05, 138.59, 136.98, 129.56, 127.23, 116.00, 114.88, 113.39, 54.00, 48.63, 36.92, 28.50, 26.45, 21.46, 17.52. HRMS calcd. for $C_{19}H_{28}NaNO_2S$ $[M+Na^+]$: 370.1823, found 370.1801.

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Chapter 6

Catalytic Asymmetric Conjugate Addition of Grignard Reagents to Coumarins – Synthesis of Versatile Chiral Building Blocks

A new protocol for the Cu-catalysed asymmetric conjugate addition of Grignard reagents to coumarins has been developed. The corresponding products are formed in high yields and enantioselectivites. Through a sequential protocol involving conjugate addtion followed by nucleophilic ring opening of the chiral enolate, chiral esters and amides are readliy accessible.

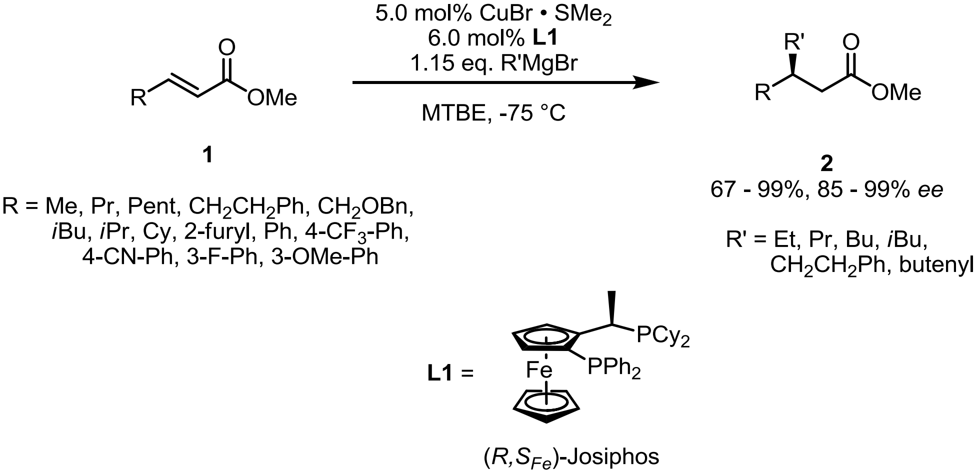
Parts of this chapter will be published: Teichert, J.F.; Feringa, B.L. *Chem. Commun.* **2011**, DOI: 10.1039/C0CC05160H.

1 Introduction

1.1 Cu-catalyzed conjugate addition of organometallic reagents

The Cu-catalyzed asymmetric conjugate addition of organometallic reagents, such as diorganozinc, triorganoaluminum and organomagnesium compounds, to unsaturated carbonyl compounds is a well-established synthetic methodology that has been studied extensively and reviewed thoroughly.[1-8] A wide variety of chiral copper catalysts, based on various ligands has been reported. Notable are the catalysts based on *N*-heterocyclic carbene,[9-13] phosphoramidite,[5,14-18] peptide-derived,[14,15,19] BINAP-derived[20] and ferrocenyl-based[21-24] ligands.

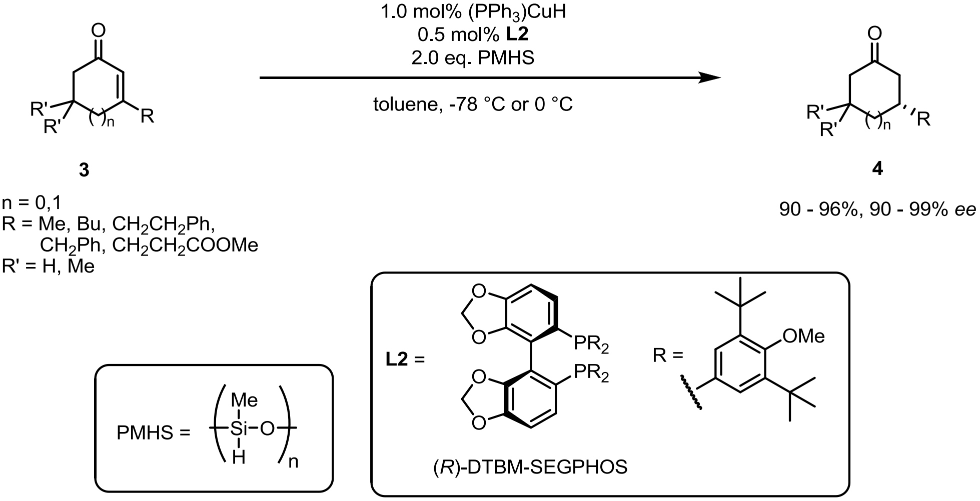
As a representative example, the asymmetric Cu-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated esters based on a chiral Cu-Josiphos complex is depicted in Scheme 1.[21] This reaction is especially suited for the transformation of alkyl Grignard reagents, leading to the corresponding chiral conjugate addition products in high yields and with excellent enantiomeric excesses. A wide variety of alkyl- as well as aryl-substituted esters **1** are transformed to β-chiral esters.


5.0 mol% CuBr • SMe2
6.0 mol% L1
1.15 eq. R'MgBr
MTBE, -75 °C
O
R
OMe
1
R' O
R
OMe
2
67 - 99%, 85 - 99% ee
R = Me, Pr, Pent, CH2CH2Ph, CH2OBn, iBu, iPr, Cy, 2-furyl, Ph, 4-CF3-Ph, 4-CN-Ph, 3-F-Ph, 3-OMe-Ph
R' = Et, Pr, Bu, iBu, CH2CH2Ph, butenyl
L1 =
PCy2
Fe
PPh2
(R,SFe)-Josiphos

Scheme 1 Cu-catalyzed asymmetric 1,4-addition of Grignard reagents with Josiphos

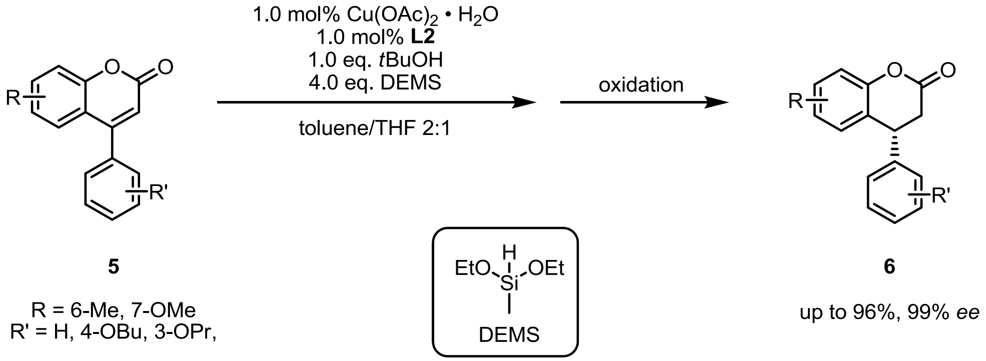
1.2 Asymmetric Cu-catalyzed conjugate reduction reactions

A related synthetic methodolgy is the conjugate reduction of α,β-unsaturated carbonyl compounds based on copper hydride complexes.[25] This marks an extension of the previously reported asymmetric catalytic reduction of ketones with the same catalysts.[26,27] If a stoichiometric external reducing agent, for example a silane,[28] is employed, the conjugate reduction of α,β,-unsaturated carbonyl compounds can be conducted with catalytic amounts of Cu-H complexes.[29,30] Furthermore, if the α,β,-unsaturated substrate bears substituents either in the α- or the β-position, this transformation can be rendered enantioselective. As an example, the Cu-catalyzed asymmetric conjugate reduction of cyclopentenones and cyclohexenones **3** is depicted (Scheme 2).[29] When **3** is subjected to conjugate reduction conditions with a catalyst comprising of $[(PPh_3)CuH]_6$ ("Stryker's reagent")[31] and SEGPHOS ligand **L2**, the resulting chiral ketones **4** are available in excellent yields and enantioselectivities. In this case, polymethylhydrosiloxane (PMHS) is employed as a stoichiometric reducing agent.



Scheme 2 Cu-catalyzed asymmetric conjugate reduction

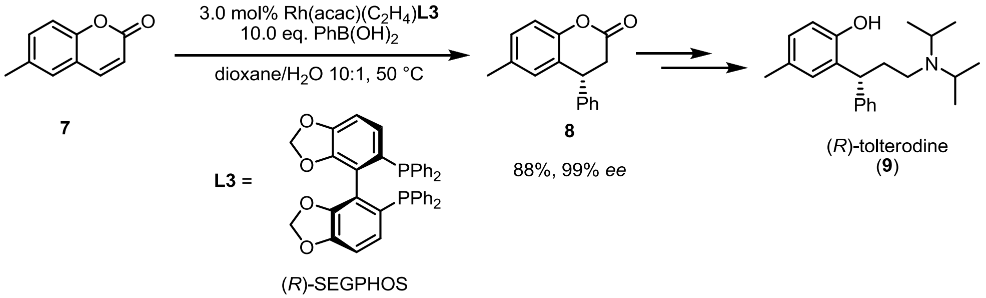
This methodology has recently been applied to the asymmetric conjugate reductions of coumarin derivatives.[32] A variety of 3-aryl coumarins **5** could be reduced with the abovementioned catalyst. However, overreduction to the corresponding lactols could not be suppressed, so that an additional oxidation step was necessary to obtain the desired chiral lactones **6** reaching excellent yields and enantioselectivities (Scheme 3). In this transformation, diethoxymethylsiloxane (DEMS) was used as the stoichiometric reducing agent. The products **6** were shown to be valuable chiral building blocks for the synthesis of a variety of biologically active compounds. In this study, the reactivity of the chiral lactones **6** and the corresponding lactols was exploited in various ways *e.g.* ring-opening, demonstrating the synthetic utility of those structures.


1.0 mol% Cu(OAc)2 • H2O
1.0 mol% L2
1.0 eq. tBuOH
4.0 eq. DEMS
toluene/THF 2:1
oxidation
R
R'
H
EtO
OEt
Si
DEMS
5
R = 6-Me, 7-OMe
R' = H, 4-OBu, 3-OPr,
6
up to 96%, 99% ee

Scheme 3 Cu-catalyzed conjugate reduction of coumarins

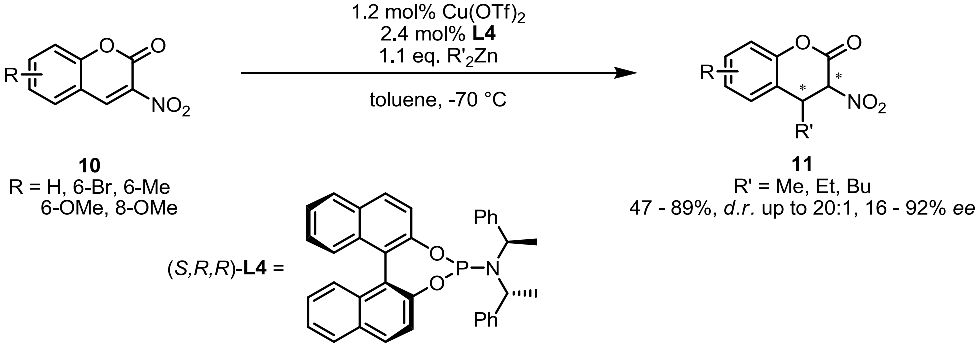
1.3 Rh-catalyzed asymmetric conjugate addition of boronic acids to coumarins

The Rh-catalyzed conjugate addition is a well-established synthetic methodology to construct chiral β-aryl carbonyl compounds, which is especially well suited for cyclic enones and arylboronic acids as substrates.[33,34] This transformation has also been applied in the asymmetric conjugate addition to coumarins, employing chiral Rh complexes with diene and phosphine ligands.[35,36] The application of this methodology for the synthesis of (*R*)-Tolterodine (**9**), a drug against incontinence, was recently disclosed.[36] When 6-methyl coumarin **7** was reacted with a large excess of phenylboronic acid in the presence of a chiral rhodium catalyst, the corresponding lactone **8**, a synthetic intermediate for the synthesis of (R)-Tolterodine, was isolated with excellent enantioselectivities (Scheme 4).


3.0 mol% Rh(acac)(C2H4)L3
10.0 eq. PhB(OH)2
dioxane/H2O 10:1, 50 °C
7
8
88%, 99% ee
Ph
OH
N
(R)-tolterodine
(9)
L3 =
PPh2
PPh2
(R)-SEGPHOS

Scheme 4 Rh-catalyzed asymmetric conjugate addition of phenylboronic acid/synthesis of (*R*)-tolterodine

Other asymmetric approaches to chiral coumarin derivatives include asymmetric electrochemical reduction,[37,38] or asymmetric sparteine-mediated lithiation of amides followed by ring-closing[39] or Cu-catalyzed asymmetric conjugate addition to α-nitrocoumarins **10**.[40] The latter reaction is depicted in Scheme 5. When 3-nitrocoumarins **10** were subjected to conjugate addition with dialkylzinc reagents using a Cu/**L4** complex, the corresponding addition products **11** were accessible in good yields and stereoselectivities (up to 20:1 d.r. and 92% *ee*). The presence of the nitro group is crucial for this reaction to occur, as most likely a conjugate addition to the nitroolefin moiety[5] takes place. When we studied this particular catalytic system with the unsubstituted coumarin (see Table 1 below), no reaction took place.



Scheme 5 Cu-catalyzed conjugate additions to 3-nitrocoumarins

2 Goal

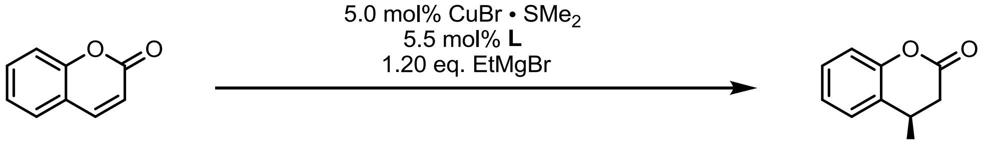
The aim of this research project was to develop an asymmetric conjugate addition protocol of Grignard reagents to coumarins. It has been shown that the corresponding chiral lactones are versatile chiral building blocks in synthesis. By employing the asymmetric Cu-catalyzed conjugate addition, it would be possible to introduce alkyl chains at the sterogenic center of the coumarin derivatives. These products are not accessible via Rh-catalyzed conjugate addtions of boronic acids, since this methodology is limited to arylboronic acids. Furthermore, this new approach would offer a substantial advantage over the related conjugate reduction, since it would be much more modular and thus circumvent the necessity to introduce the substituents at the stereogenic center in earluer stages of the synthesis.

3 Results and Discussion

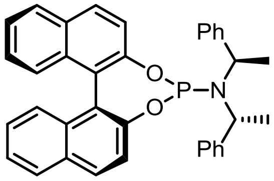
3.1 Catalyst screening and optimization

The low reactivity of coumarin (**12**) made it necessary to develop a new catalyst system. Our investigation started with the conjugate addition of dialkylzinc reagents to **12** employing phosphoramidite ligands.[5,17] This catalytic system did not prove to be reactive enough and did not result in any turnover (Table 1, entry 1). When we turned our attention to the conjugate addition reaction with the more reactive Grignard reagents[2,3] employing Josiphos ligand **L1** (compare Scheme 1), full conversion to the desired 1,4-adduct **13a** with 82% *ee* was observed,[41] when **12** was reacted with ethylmagnesium bromide (Table 1, entry 3). Ligand **L6**, which had been previously employed in the related 1,6-conjugate addition,[42] proved to be the ligand of choice to reach high levels of enantiocontrol. At -78 °C, the conjugate addition product **13a** was formed with 96% *ee*, albeit in a low yield (Table 1, entry 4). Neither Taniaphos (**L7**) nor the Cu-tolBINAP (**L5**) catalyst, which had previously been reported for conjugate addition reactions with Grignard reagents,[20] could compete with our findings in terms of conversion or enantioselectivity (Table 1, entries 2,8). It appeared that fine-tuning of the electronic properties of the ligand was necessary to obtain the conjugate addition product with high enantioselectivity. To achieve full conversion with **L6**, higher amounts of Grignard reagent were necessary along with a slightly higher reaction temperature of -72 °C (Table 1, entry 7).[43] Furthermore, the catalyst loading could be lowered to 2.5 mol% of Cu without compromising the yield or the enantioselectivity. The absolute configuration of the conjugate addition product **13a** was established by comparison of the sign of the optical rotation values to literature sources.[44,45] All other absolute configurations were assigned in accordance to this compound.

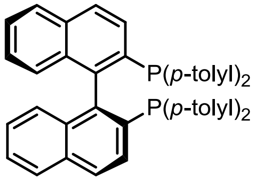
Table 1 Ligand Screening / Optimization[a]



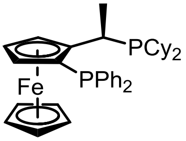
12 **13a**



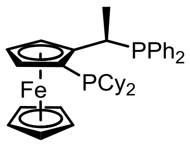
(*S,R,R*)-**L4**



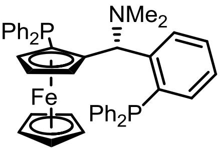
(*S*)-**L5**



(*R*,S_{Fe})-**L1**
(R,S-Josiphos)



(*R*,S_{Fe})-**L6**
(R,S-reversed-Josiphos)



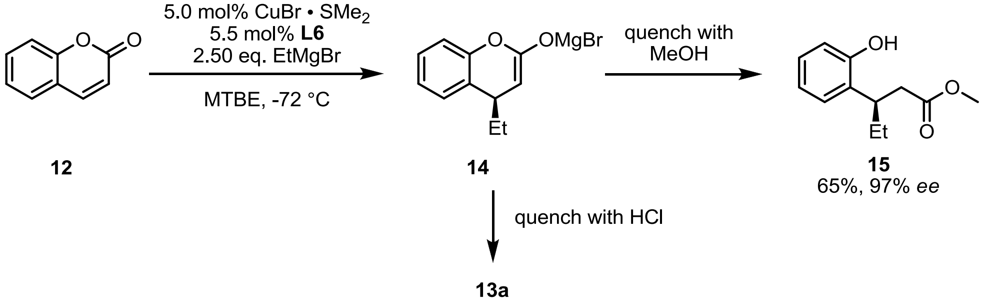
(*R*,R_{Fe})-**L7**
(R,R-Taniaphos)

Entry	Ligand	Solvent	Temperature	Conversion (yield)	*ee*[b]
1[c]	**L4**	toluene	-40 °C	-	-
2[d]	**L5**	MTBE	-40 °C	Full (55%)	21% (*R*)
3	**L1**	MTBE	-78 °C	Full (57%)	82% (*R*)
4	**L6**	MTBE	-78 °C	50% (26%)	96% (*R*)
5	**L6**	CH_2Cl_2	-78 °C	40% (25%)	81% (*R*)
6[e]	**L6**	MTBE	-78 °C	80% (62%)	95% (*R*)
7[e]	**L6**	**MTBE**	**-72 °C**	**Full (92%)**	**95% (*R*)**
8	**L7**	MTBE	-78 °C	Traces (-)	-

[a] Reaction conditions: CuBr • SMe_2 (0.01 mmol, 5.0 mol%, 2.1 mg) and 5.5 mol% (0.0105 mmol) of the appropriate ligand were dissolved in 5 mL solvent and stirred at RT for 15 min. After cooling to the appropriate temperature, 1.2 eq. of EtMgBr solution (c = 3.0M in Et_2O, 0.24 mmol, 0.08 mL) were added dropwise over 10 min. Then, 1.0 eq. of a coumarin solution (0.20 mmol, 0.029 g) in 2.5 mL solvent was

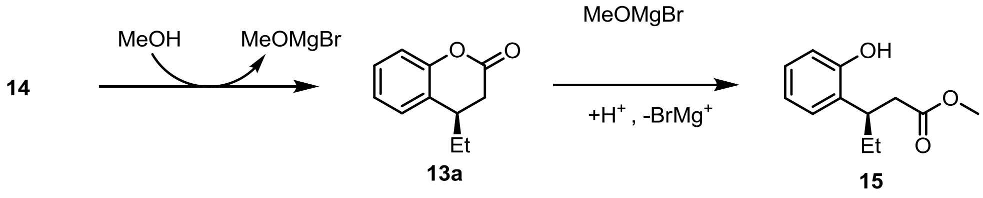
added dropwise over a period of 1 h. Quenching with 2.0 mL of HCl in Et_2O (2M). [b] Determined by chiral HPLC. [c] 11.0 mol% of ligand, and 5.0 mol% of $Cu(OTf)_2$ and 2.0 eq. $ZnEt_2$ were used. [d] 5.0 mol% CuI were used. [e] 2.5 eq. EtMgBr were used.

During the catalyst optimization experiments, it was observed that, in contrast to the high conversion, the isolated yields of the desired addition product **13a** was low. It was found that the cause of this problem was the quenching method employed, which led to the unwanted transformation of the intermediate magnesium enolate to a side product. The standard quenching protocol, by adding methanol at low temperatures (usually -78 °C) followed by warming to room temperature and washing with saturated aq. NH_4Cl solution, led to the formation of considerable amounts of side products, one of which was identified to be ester **15** (Scheme 6). Under those conditions, varying amounts of the ring-opened ester **15** were isolated next to the desired product **13a**. To overcome this problem, a different procedure for quenching the reaction had to be devised. When the reaction was quenched with methanol and stirred at room temperature longer than 1 hour before the wash/extraction with NH_4Cl was carried out, full conversion to ester **15** was found. However, the enantiomeric excess of the product remained the same (97% *ee*).



Scheme 6 Nucleophilic ring opening of enolate 14 during quenching

This reaction can be explained as follows: The intermediate magnesium enolate **14** and/or the excess of Grignard reagent in solution leads to deprotonation of methanol to form methoxide, which acts as a nucleophile to faciliate the ring opening of lactone **13a** to give ester **15** (Scheme 7). To prevent the subsequent ring-opening during workup, the reaction could simply been quenched by addition of HCl solution (2M) in Et_2O at low temperatures followed by the usual extraction/workup protocol. However, it was found that this side reaction could be exploited to develop a sequential conjugate addition/nucleophilic ring opening for the synthesis of chiral esters and amides (*vide infra*).

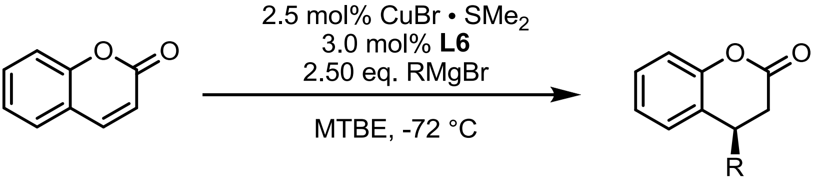


Scheme 7 Plausible mechanism for the formation of ester 15

3.2 Scope of Grignard reagents

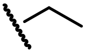
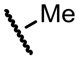
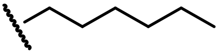
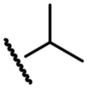
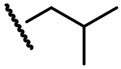
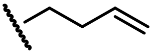
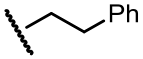
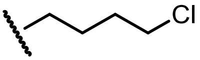
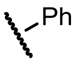
With the optimised conditions in hand, we set off to investigate the scope of the reaction. A variety of alkyl Grignard reagents are compatible with this transformation (Table 2). Similar trends in reactivity to our previously reported conditions with ferrocenyl-based ligands were observed,[21-23] which implied high catalyst control of the envisaged transformation. There is a preference for linear unfunctionalized alkyl Grignard reagents, which could be transformed to chiral lactones **13** in high yields and enantioselectivites reaching 99% *ee* (Table 2, entries 1,3,5-8). Use of the relatively unreactive methylmagnesium bromide gave no conjugate addition product. As previously observed, α-branched reagents such as isopropylmagnesium bromide gave low enantioselectivity for **13d**, whereas the β-branched reagent was smoothly incorporated into the desired chiral products **13e** with high *ee* (Table 2, entries 4,5). One key feature of the catalyst is the fact that it tolerates functionalized Grignard reagents; an important advantage with foresight to possible synthetic applications of this method. However, slightly higher catalyst loadings were necessary to achieve acceptable results in terms of yields. Butenyl-substituted **13f** as well as halogenated products **13h** were accessible with excellent enantioselectivities when a higher catalyst loading was employed (Table 2, entries 6,8). The attempt to employ aryl Grignard reagents such as phenylmagnesium bromide gave only trace amounts of the desired product (Table 2, entry 9).

Table 2 Scope of Grignard reagents[a]



12

13a-i

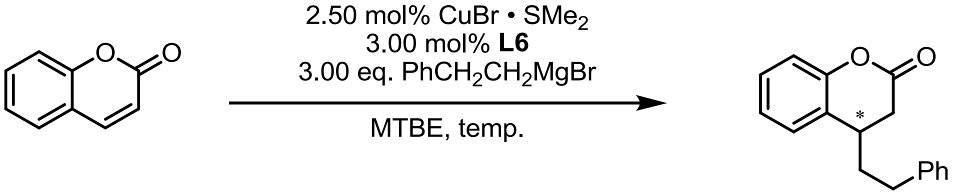
Entry	R		Yield[b]	ee[c]
1		**13a**	96%	95%
2		**13b**	-	-
3		**13c**	95%	99%
4		**13d**	95%	63%
5		**13e**	72%	93%
6[d]		**13f**	66%	93%
7[d]		**13g**	73%	94%
8[d,e]		**13h**	46%	98%
9		**13i**	traces	-

[a] For reaction conditions, see experimental section. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 5.0 mol% CuBr • SMe$_2$ and 5.5 mol% **L6** were used. [e] The product was isolated as a mixture with traces of the dehalogenated product.

From Table 2 can be seen that higher catalyst loadings were necessary to achieve acceptable yields with functionalized Grignard reagents (Table 2, entries 6-8). To probe whether the conversion and thus the isolated yield could be improved by raising the temperature, a series of experiments with varying temperatures were carried out (Table 3). Coumarin (**12**) was reacted under optimized catalyst loading and amount of Grignard reagent with phenylethylmagnesium bromide. At -78 °C,

13g was formed with 94% *ee*, however turnover was low (Table 3, entry 1). When the temperature was raised slightly to -72 °C, a remarkable improvement in conversion was observed, and **13g** was isolated in 73% yield with the same *ee* (Table 3, entry 2). Raising the temperature even further led to full conversion to **13g** but this improvement in yield was accompanied by a decrease of enantioselectivity (Table 3, entry 3), thus all reactions with various Grignard reagents were carried out at -72 °C, which seemed to be acceptable in terms of enantioselectivity and yield.

Table 3 Temperature dependence of conjugate addition



10

11g

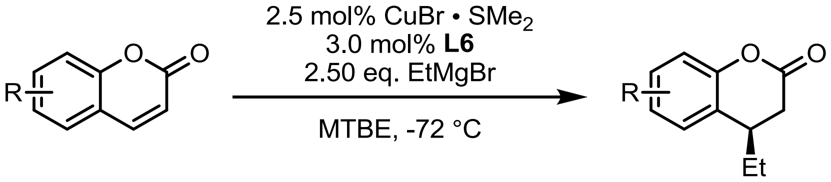
Entry	Temp	Conversion	*ee*
1	-78 °C	~ 40% (TLC)	94%
2	-72 °C	~ 90% (TLC)[a]	94%
3	-60 °C	Full	80%

[a] 73% isolated yield.

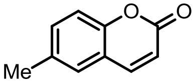
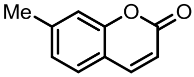
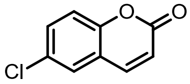
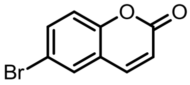
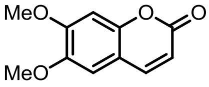
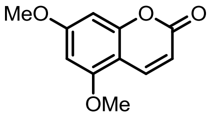
3.3 Coumarin Scope

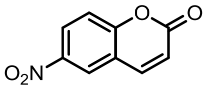
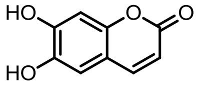
Subsequently, the scope of our new catalytic transformation with regard to substituted coumarins **16** was investigated (Table 4). Methyl substituents in positions 6 and 7 were readily tolerated as the desired conjugate addition products could be isolated with very good yields and enantioselectivities (Table 4, entries 1,2). Furthermore, halogen substituents are tolerated and give addition products **17c** and **17d** with similarly good results (Table 4, entries 3,4). Dimethoxycoumarins **16e** and **16f** could also be converted to the corresponding conjugate addition products, albeit with lower yield and enantioselectivity (Table 4, entries 5,6). This marks a limitation of this transformation. Two electron-donating groups on the aromatic ring result in a lower reactivity to conjugate addition reactions compared to coumarin itself. The lower enantioselectivity of **17f** compared to **17e** could be explained by the fact that the methoxy-substituent in the 5-position of **16f** interferes with the Cu-catalyst. To overcome this problem the conjugate addition was attempted with 6,7-dihydroxy coumarin **16h**. A higher amount of Grignard reagent was employed, but the reaction did not yield the desired product (Table 4, entry 8), possibly due to strong coordination of the dioxycoumarin dianion to the Cu catalyst through a chelating effect, and subsequent deactivation of the catalyst. This problem could be overcome in the future by preparing the corresponding coumarin boronate,[46] followed by the conjugate addition, as the conjugate addition reaction is known to tolerate boron-based functional groups.[47] The strongly electron-withdrawing nitro-group of **16g** (Table 4, entry 7) is not tolerated due to fast decomposition of the starting material under the reaction conditions.

Table 4 Scope of coumarins[a]



16a-h **17a-h**

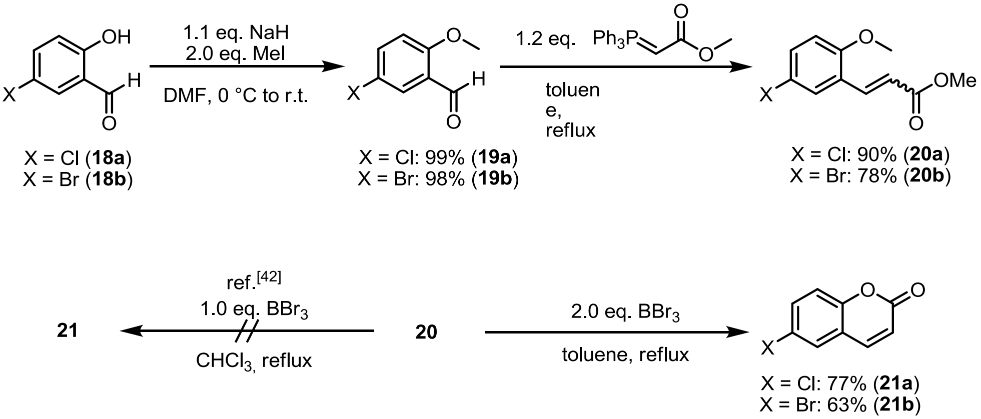
Entry	Coumarin 3	Product	Yield[b]	ee[c]
1		**17a**	92%	94%
2		**17b**	93%	97%
3		**17c**	80%	95%
4		**17d**	86%	96%
5[d]		**17e**	55%	64%
6[d]		**17f**	66%	48%

Entry	Coumarin 3	Product	Yield[b]	ee[c]
7[d]		**17g**	traces	-
8[e]		**17h**	-	-

[a] For reaction conditions, see experimental section. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 5.0 mol% CuBr • SMe_2 and 5.5 mol% **L6** were used. [e] 5.0 eq. of EtMgBr were used.

3.4 Synthesis of coumarins

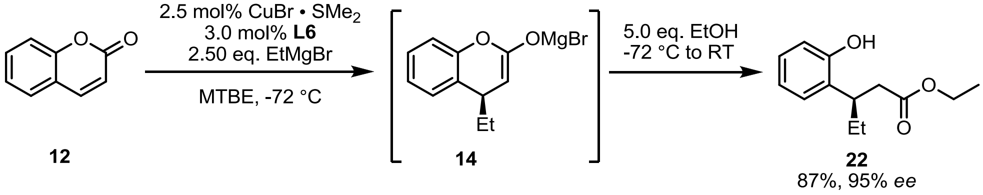
The two 6-halosubstituted coumarins **16c** and **16d** were not commercially available, and were therefore synthesized. The synthesis was carried out according to a modified literature procedure for a tandem phenol ether deprotection/lactonization reaction (Scheme 8).[48] Starting from the commercially available salicylaldehydes **18**, *O*-methylation with MeI and a subsequent Witttig reaction yielded α,β-unsaturated esters **20** in very good yields. It was reported[48] that one equivalent of BBr_3 and refluxing $CHCl_3$ was sufficient to facilitate the lactone formation, however, in our hands, the reaction proceeded smoothly only with 2.0 equivalents of BBr_3 in refluxing toluene to give the desired halocoumarins **21** in good yields.


OH
X
H
O
1.1 eq. NaH
2.0 eq. MeI
DMF, 0 °C to r.t.
X = Cl (18a)
X = Br (18b)
O
X
H
O
X = Cl: 99% (19a)
X = Br: 98% (19b)
1.2 eq. Ph3P
O
O
toluen
e,
reflux
O
OMe
X
O
X = Cl: 90% (20a)
X = Br: 78% (20b)
21
ref.[42]
1.0 eq. BBr3
CHCl3, reflux
20
2.0 eq. BBr3
toluene, reflux
O
O
X
X = Cl: 77% (21a)
X = Br: 63% (21b)

Scheme 8 Synthesis of 6-halocoumarins

3.5 Trapping of intermediates / nucleophilic ring opening

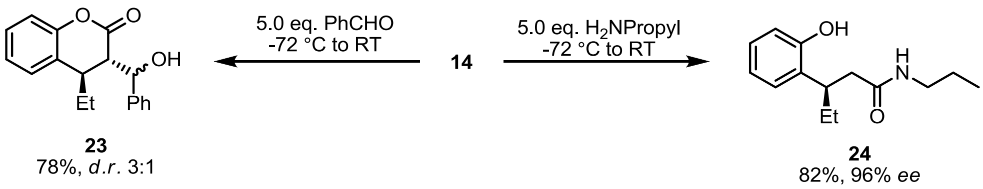
One of the major advantages of the conjugate addition reaction to coumarins was discovered during the course of this study: The intermediate chiral magnesium enolate **14** is a highly versatile chiral building block and can be converted *in situ* to a variety of important chiral products. The absence of a fully conjugated enone results in a higher reactivity of intermediate **14**, which can be exploited by reactions with nucleophiles to invoke a ring-opening, as well as electrophiles to trap the enolate. When **14** was quenched with ethanol at -72 °C and then warmed up to room temperature, the resulting chiral ester **22** was isolated in very good yields without compromising the stereogenic center (Scheme 9). It is important to note that *ortho*-phenol esters like **22** were previously not accessible via the conjugate addition methodology,[2-4,21-23] rendering this transformation a valuable addition to the present conjugate addition protocols.



Scheme 9 Synthesis of chiral *ortho*-phenolic ester 22

By intercepting the chiral magnesium enolate **14** with an excess of propylamine, amide **24** could be obtained in good yield (Scheme 10). This result marks the first formal catalytic asymmetric conjugate addition to amides, a reaction pathway that was previously elusive, since α,β-unsaturated amides are not known to be susceptible to catalytic asymmetric conjugate additions with Cu-catalysts.

It is known in literature that the enolates of conjugate addition reactions can be trapped with a variety of electrophiles.[5,18,49,50] Along those lines, enolate **14** could be trapped with benzaldehyde to give the corresponding aldol product **23** with three contiguous stereocenters in good yields. Two diastereomers of **23** could be detected, (in a ratio 3:1) which were attributed to an incomplete stereoinduction at the exocyclic stereocenter formed, *i.e.* the benzylic alcohol. For the relative configuration of the first two stereocenters formed, it is expected with inference to related reactions in literature[17,18,49,51-53] that those will be formed with *trans* configuration.

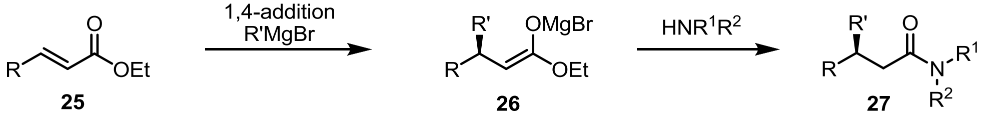


Scheme 10 Trapping / ring opening reactions of enolate 14

4 Conclusion and Future Prospects

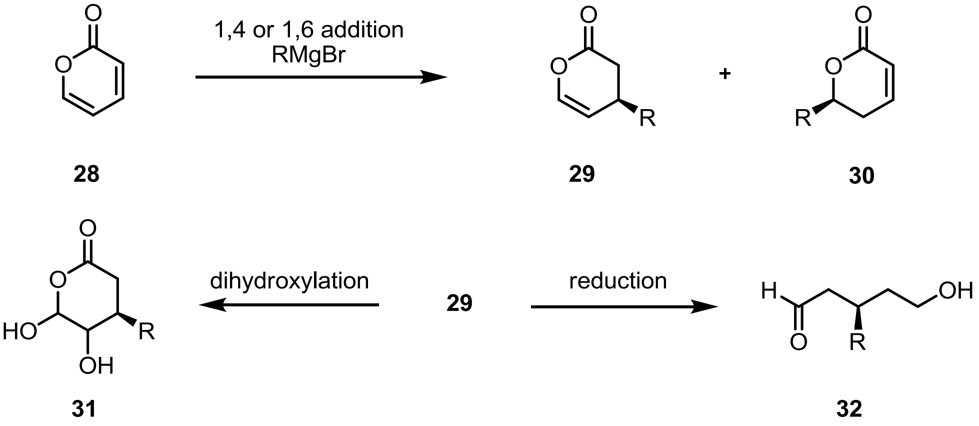
To conclude, we have developed a new, highly selective Cu-catalyzed conjugate addition of Grignard reagents to coumarins. The corresponding chiral products are available with up to excellent enantioselectivities. Furthermore, we have demonstrated that the corresponding enolate is a highly versatile starting point for the synthesis of a variety of chiral products such as esters and amides which were previously not readily available.

The presented findings on the asymmetric conjugate additions to coumarins could lead to some further research: first of all, the generality of the sequential conjugate addItion/amide formation could be investigated. Since an asymmetric conjugate addition protocol to amides is elusive, this could be a viable pathway towards β-chiral amides (Scheme 11). Esters **25** could be converted to amides **27** in a one-pot procedure via their corresponding enolates **26**.



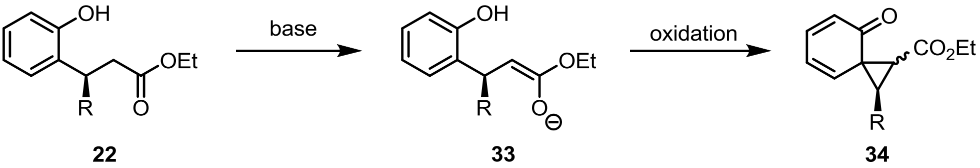
Scheme 11 Proposed synthesis of chiral amides

Secondly, the conjugate addition to 2H-pyranone **28** could be studied. This would be the extension of the conjugate addition reaction to coumarins, except that the aromatic ring of coumarin would be replaced by just a double bond. This could open a variety of interesting routes towards chiral products **31** and **32** among others, since pyranone adduct **29** could be transformed in various ways to give chiral multifunctional building blocks (Scheme 12). Another interesting question would arise if both regio- and enantioselective 1,4- and 1,6-conjugate additions are possible on pyranone to give **29** or **30**. Both the new 1,4 conjugate addition to coumarin as well as the known 1,6 addition to enoates[42] use the same catalytic system, namely reverse Josiphos (**L6**), so it would be interesting to see whether there would be a selectivity towards either one of the products. Furthermore, this experiment could give important insight to the mechanism of the conjugate addition reaction, since 1,6-addition reactions to cyclic systems have not yet been investigated and it would be interesting to determine if the catalyst can compete with such a variety of possible coordinating groups in the vicinity of the catalyst.



Scheme 12 Suggested conjugate addition to pyranone

Finally, it could be investigated if the ring-opened esters such as **22** could undergo oxidative ring closing after conversion to their corresponding ester-enolates **33**, a reaction that has been developed in our group (Scheme 13).[54] This would yield ketones with an α-cyclopropyl moiety **34**.



Scheme 13 Suggested synthesis of α-cyclopropyl ketones

5 Experimental section

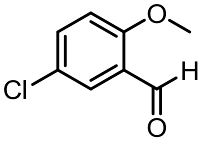
General

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60,0.25 mm. Components were visualized by UV and cerium/molybdenum staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on a AEI-MS-902 mass spectrometer (EI$^+$) or a LTQ Orbitrap XL (ESI$^+$). ^{1}H, ^{19}F and ^{13}C NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively), a Varian VXR300 (300 and 75 MHz, respectively) or a Varian Gemini 200, using CDCl3 as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Enantiomeric excesses (*ee* values) were determined by HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector and chiral columns as indicated. *Ee*s were determined by comparison of the racemic mixture with the corresponding chiral compounds or the mixtures of both R and S enantiomers. All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. CH_2Cl_2 was dried and distilled over calcium hydride, THF and Et_2O were dried and distilled over Na/benzophenone. Toluene was dried and distilled over Na. MTBE was dried and distilled over CaH_2. CuBr•SMe_2 was purchased from Sigma-Aldrich, and used without further purification. Grignard reagents were purchased from Sigma-Aldrich (MeMgBr, EtMgBr, *n*-HexMgBr, *i*-BuMgBr), all other Grignard reagents were prepared from the corresponding bromides with Mg in Et_2O. All Grignard reagents were titrated using *s*-BuOH and catalytic amounts of 1,10-phenanthroline before use. **L4** was prepared according to literature,[55] **L5**-**L7** were purchased from Sigma-Aldrich.

General procedure for the methylation of salicylic aldehydes

Salicylic aldehyde (1.0 eq.) was dissolved in DMF (Volume: 100 mL/10 mmol) and the solution was cooled to 0 °C. Then, 1.0 eq. sodium hydride (as 60% suspension in mineral oil) was added slowly and the reaction was stirred for 15 min at 0 °C (or until gas evolution ceased). Then, 2.0 eq. methyl iodide was added dropwise, and the reaction mixture was allowed to warm to 21 °C. When TLC showed full consumption of the starting material, the reaction was quenched by addition of water (100 mL/10 mmol). The mixture was washed with water and brine (50 mL / 10 mmol each), extracted with EtOAc (2x 50 mL / 10 mmol) and dried over $MgSO_4$. Removal of all volatiles under reduced pressure yielded the crude product, which was used without further purification.

5-Chloro-2-methoxybenzaldehyde (19a)

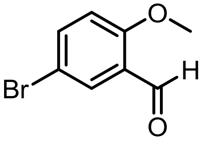


19a

Following the general procedure for methylation of salicylic aldehydes, 2.167 g 5-chloro-2-methoxybenzaldehyde **19a** (12.70 mmol, 99 % yield) was isolated as a pale yellow solid from the reaction of 5-chloro-2-hydroxybenzaldehyde (2.00 g, 12.77 mmol) with methyl iodide (1.597 ml, 25.5 mmol). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.64 (s, 1H), 7.46 – 7.34 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 188.12, 160.07, 135.16, 127.53, 126.00, 125.37, 113.18, 55.79. HRMS: (ESI$^+$) calculated for $C_8H_8ClO_2$ [M+H$^+$]: 171.0207, found: 171.0204.

5-Bromo-2-methoxybenzaldehyde (19b)

Following the general procedure for methylation of salicylic aldehydes, 2.097 g 5-bromo-2-methoxybenzaldehyde **19b** (9,75 mmol, 98 % yield) was isolated as a pale yellow solid from the reaction of 5-bromo-2-hydroxybenzaldehyde (2.00 g, 9.95 mmol) with methyl iodide (1.244 ml, 19.90 mmol). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.83 (d, *J* = 2.6 Hz, 1H), 7.56 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 188.13, 160.57, 138.12, 130.70, 125.83, 113.63, 113.19, 55.82. HRMS: (ESI^+) calculated for $C_8H_8BrO_2$ [M+H$^+$]: 214.9702, found: 214.9696.



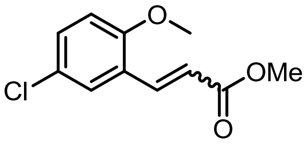
19b

General procedure for the Wittig reaction of methyl 2-(triphenylphosphoranylidene)acetate with salicylic aldehydes

Salicylic aldehyde **19** (1.0 eq.) was dissolved in toluene (Volume: 50 mL/ 10 mmol), and 1.2 eq. methyl 2-(triphenylphosphoranylidene)acetate was added to the mixture. This was heated to 110 °C until TLC showed full conversion of the starting material. After cooling, diethylether (50 mL/10 mmol) was added to precipitate any triphenylphosphine oxide, which was subsequently filtered off. All volatiles were removed under reduced pressure to give the crude product **20**, which was purified by column chromatography (SiO_2, pentane/EtOAc 8:2) to yield the desired products as a mixture of E/Z isomers.

Methyl 3-(5-chloro-2-methoxyphenyl)acrylate (20a)

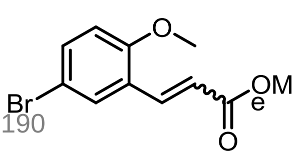
Following the general procedure for the Wittig reaction with salicylic aldehydes, 2.384 g methyl 3-(5-chloro-2-methoxyphenyl)acrylate **20a** (10.52 mmol, 90 % yield) was isolated as a white solid from the reaction of 5-chloro-2-methoxybenzaldehyde **19a** (2.00 g, 11.72 mmol) with methyl 2-(triphenylphosphoranylidene)acetate (4.70 g, 14.07 mmol). (R_f = 0.80 in pentane/EtOAc 8:2). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 16.2 Hz, 1H), 7.41 (d, *J* = 2.6 Hz, 1H), 7.23 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.45 (d, *J* = 16.2 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 167.25, 156.61, 138.50, 130.70, 129.68, 127.97, 125.57, 124.64, 119.30, 112.28, 55.62, 51.50. HRMS: (ESI^+) calculated for $C_{11}H_{12}ClO_3$ [M+H$^+$]: 227.0470, found: 227.0465.



20a

Methyl 3-(5-bromo-2-methoxyphenyl)acrylate (20b)

Following the general procedure for the Wittig reaction with salicylic aldehydes, 1.977 g methyl 3-(5-bromo-2-methoxyphenyl)acrylate **20b** (7.29 mmol, 78 % yield)



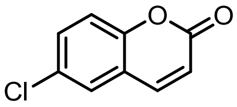
20b

was isolated as a white solid from the reaction of 5-bromo-2-methoxybenzaldehyde **19b** (2.00 g, 9.30 mmol) with methyl 2-(triphenylphosphoranylidene)acetate (3.73 g, 11.16 mmol). (R_f = 0.65 in pentane/EtOAc 8:2). ^{1}H NMR: (201 MHz, CDCl$_3$) δ 7.87 (d, J = 16.2 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.39 (dd, J = 8.8, 2.5 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 16.2 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H). ^{13}C NMR: (50 MHz, CDCl$_3$) δ 167.32, 157.14, 138.52, 138.49, 133.68, 130.99, 125.20, 119.39, 112.85, 112.78, 55.66, 51.61. HRMS: (ESI$^+$) calculated for C$_{11}$H$_{12}$BrO$_3$ [M+H$^+$]: 270.9964, found: 270.9969.

General procedure for the synthesis of coumarin derivatives 21 from methyl acrylates 20

According to a modified literature procedure,[48] 1.0 eq. methyl acrylate **20** was dissolved in toluene (Volume: 50 mL/ 5 mmol) and cooled to 0 °C. Then, 2.0 eq. boron tribromide was added dropwise. The reaction was heated to 110 °C for 4h. After cooling to room temperature, water (50 mL / 5 mmol) was added and the aqueous layer was extracted twice with CHCl$_3$ (30 mL / 5 mmol). After drying over MgSO$_4$ and removal of all volatiles under reduced pressure, the crude mixture was purified by column chromatography (SiO$_2$, pentane/EtOAc 8:2) to yield the desired coumarin **21**.

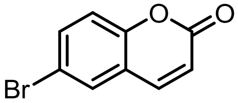
6-Chloro-2H-chromen-2-one (21a)



21a

Following the general procedure for the synthesis of coumarin derivatives from esters, 0.613 g 6-chloro-2H-chromen-2-one **21a** (3.40 mmol, 77 % yield) was isolated as a pale yellow solid from the reaction of methyl 3-(5-chloro-2-methoxyphenyl)acrylate **20a** (1.00 g, 4.41 mmol) with boron tribromide (0.834 ml, 8.82 mmol). (R_f = 0.75 in pentane/EtOAc 8:2). ^{1}H NMR: (201 MHz, CDCl$_3$) δ 7.63 (d, J = 9.6 Hz, 1H), 7.44 (dt, J = 4.9, 2.3 Hz, 2H), 7.30 – 7.18 (m, 1H), 6.44 (d, J = 9.6 Hz, 1H). ^{13}C NMR: (50 MHz, CDCl$_3$) δ 159.94, 152.32, 142.15, 131.65, 129.58, 127.05, 119.72, 118.20, 117.74. HRMS: (ESI$^+$) calculated for C$_9$H$_6$ClO$_2$ [M+H$^+$]: 181.0051, found: 181.0051.

6-Bromo-2H-chromen-2-one (21b)



21b

Following the general procedure for the synthesis of coumarin derivatives from esters, 0.522 g 6-bromo-2H-chromen-2-one **21b** (2.32 mmol, 63 % yield) was isolated as an orange solid from the reaction of methyl 3-(5-bromo-2-methoxyphenyl)acrylate **20b** (1.00 g, 3.69 mmol) with boron tribromide (0.697 ml, 7.38 mmol). (R_f = 0.90 in pentane/EtOAc 8:2). ^{1}H NMR: (201 MHz, CDCl$_3$) δ 7.68 – 7.55 (m, 3H), 7.29 – 7.15 (m, 1H), 6.45 (d, J = 9.6 Hz, 1H). ^{13}C NMR: (50 MHz, CDCl$_3$) δ 164.90, 159.88, 142.04, 134.54, 130.13, 120.28, 118.60, 117.83, 116.94. HRMS: (ESI$^+$) calculated for C$_9$H$_6$BrO$_2$ [M+H$^+$]: 224.9546, found: 224.9548.

General procedure for the asymmetric Cu-catalyzed conjugate addition of Grignard reagents to coumarins

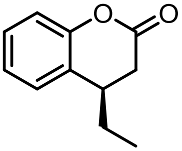
5.0 mol % Copper bromide dimethyl sulfide complex and 5.5 mol % (*R*,S_{Fe})-reverse Josiphos were dissolved in MTBE (Volume: 15 mL / 1 mmol substrate) and the mixture was stirred at room temperature for 15 min. The mixture was then cooled to -72 °C and subsequently 2.5 eq. of the appropriate Grignard reagent were added. The mixture was stirred for an additional 10 min at -72 °C. A solution of 1.0 eq. of the appropriate coumarin in MTBE (Volume: 5 mL / 1 mmol) was added dropwise over a period of 1 h. The reaction mixture was stirred until TLC showed full conversion. The reaction was quenched by adding HCl solution in Et_2O (2.0 mL / 1 mmol substrate) at -72 °C. Saturated aqueous NH_4Cl solution (20 mL / 1 mmol) was added at low temperature and the reaction mixture was allowed to warm to room temperature. The mixture was diluted with Et_2O (30 mL / 1 mmol). After washing two times with aqueous saturated NH_4Cl solution (2x 50 mL / 1 mmol) and reextraction of the aqueous layer with Et_2O (20 mL / 1 mmol), the combined organic layers were dried over $MgSO_4$. All volatiles were removed under reduced pressure to give the crude product, which was purified by column chromatography (SiO_2, EtOAc/Pentane) to yield the desired compounds.

General procedure for the synthesis of racemic products of the Cu-catalyzed conjugate addition to coumarins

The appropriate coumarin (1.0 eq., 0.485 mmol) and 30.0 mol % Copper bromide dimethyl sulfide complex (0.030 g, 0.145 mmol) and 60.0 mol % triphenylphosphine (0.076 g, 0.291 mmol) were dissolved in MTBE (Volume: 15 ml), cooled to -40 °C and the mixture was stirred for 10 min. The appropriate Grignard reagent (2.5 eq., 1.212 mmol) was added dropwise. The reaction mixture was stirred overnight at -40 °C. The reaction was quenched by addition of 2.0 mL HCl in Et_2O (2N), before 20 mL saturated aqueous NH_4Cl solution was added at low temperature and the reaction mixture was allowed to warm to room temperature. The mixture was diluted with Et_2O (30 mL). After washing two times with aqueous saturated NH_4Cl solution (2x 50 mL) and reextraction of the aqueous layer with Et_2O (20 mL), the combined organic layers were dried over $MgSO_4$. All volatiles were removed under reduced pressure to give the crude product, which was purified by column chromatography (SiO_2, EtOAc/Pentane) to yield the desired compounds.

(*R*)-4-Ethylchroman-2-one (13a)

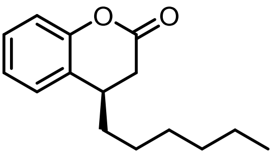
Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.135 g (*R*)-4-ethylchroman-2-one **13a** (0.768 mmol, 96% yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) with ethylmagnesium bromide solution (3.0 molar in Et_2O) (0.67 ml, 2.00 mmol). The



13a

product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.68 in pentane/EtOAc 10:1, 95% *ee*). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1H), 7.21 – 7.15 (m, 1H), 7.11 (dd, *J* = 10.7, 4.2 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.78 (qd, *J* = 15.8, 4.9 Hz, 2H), 1.64 (tdd, *J* = 14.0, 11.3, 6.2 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.48, 151.22, 128.17, 127.84, 126.42, 124.20, 117.00, 36.52, 34.35, 27.50, 11.11. HRMS: (ESI^+) calculated for $C_{11}H_{12}O_2Na$ [M+Na$^+$]: 199.0730, found: 199.0730. $[\alpha]_D^{20}$ = 53.6 (c = 1.0 in $CHCl_3$), $[\alpha]_D^{20}$ = 114.6 (c = 1.0 in PhH). The two $[\alpha]_D^{20}$ values have been used for determination of the absolute configuration by comparison with literature.[44,45] *ee* determination by chiral HPLC (Chiralpak AD: n-heptane/2-propanol 95:5, 40 °C isotherm, 220 nm, flow rate 0.5 mL/min), retention times: 8.3 min (major), 8.9 min (minor).

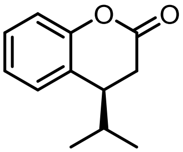
(*R*)-4-Hexylchroman-2-one (13c)



13c

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.177 g (*R*)-4-hexylchroman-2-one **13c** (0.760 mmol, 95 % yield) was isolated as a pale yellow solid from the reaction of 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) with hexylmagnesium bromide solution (2.0 molar in Et_2O) (1.00 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.78 in pentane/EtOAc 10:1, 99% *ee*). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.30 – 6.95 (m, 4H), 3.04 – 2.87 (m, 1H), 2.81 – 2.61 (m, 2H), 1.66 – 1.45 (m, 2H), 1.44 – 1.02 (m, 8H), 0.84 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.26, 151.09, 127.99, 127.65, 126.72, 124.10, 116.85, 34.94, 34.54, 34.47, 31.47, 28.94, 26.44, 22.41, 13.88. HRMS: (ESI^+) calculated for $C_{15}H_{20}O_2Na$ [M+Na$^+$]: 255.1356, found: 255.1356. $[\alpha]_D^{20}$ = 47.6 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 10.5 min (minor), 12.4 min (major).

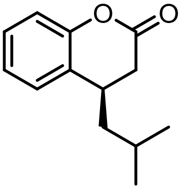
(*S*)-4-Isopropylchroman-2-one (13d)



13d

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.145 g (*S*)-4-isopropylchroman-2-one **13d** (0.760 mmol, 95 % yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) with isopropylmagnesium bromide solution (1.5 molar in Et_2O) (1.33 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.90 in pentane/EtOAc 10:1, 63% *ee*). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 1H), 7.14 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.11 – 7.04 (m, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 2.85 (dd, *J* = 10.7, 8.9 Hz, 1H), 2.78 – 2.63 (m, 2H), 1.82 (dd, *J* = 13.5, 6.7 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.65, 151.46, 128.84, 128.09, 125.30, 123.87, 116.81, 41.61, 32.05, 31.96, 20.00, 19.00. HRMS: (ESI^+) calculated for $C_{12}H_{15}O_2$ [M+H$^+$]: 191.1067, found: 191.1066. $[\alpha]_D^{20}$ = 21.6 (c = 1.0 in $CHCl_3$) *ee* determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 15.5 min (major), 17.2 min (minor).

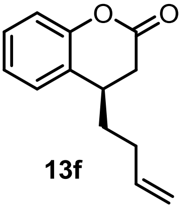
(*R*)-4-Isobutylchroman-2-one (13e)



13e

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.118 g (*R*)-4-isobutylchroman-2-one **13e** (0.576 mmol, 72 % yield) was isolated as a pale yellow solid from the reaction of 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) with isobutylmagnesium bromide solution (2.0 molar in Et_2O) (1.00 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.78 in pentane/EtOAc 10:1, 93% *ee*). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 1H), 7.20 – 7.15 (m, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 3.07 (dd, *J* = 5.3, 3.9 Hz, 1H), 2.76 (ddd, *J* = 19.5, 15.8, 4.7 Hz, 2H), 1.63 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.42 (dtd, *J* = 21.2, 13.9, 7.5 Hz, 2H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.34, 151.20, 128.12, 127.48, 127.17, 124.25, 117.09, 43.62, 34.69, 32.76, 24.84, 22.59, 22.22. HRMS: (ESI$^+$) calculated for $C_{13}H_{17}O_2$ [M+H$^+$]: 205.1223, found: 205.1223. $[\alpha]_D^{20}$ = 72.0 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 13.8 min (major), 15.4 min (minor).

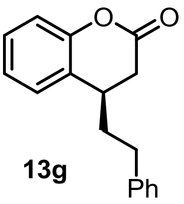
(*R*)-4-(But-3-enyl)chroman-2-one (13f)



13f

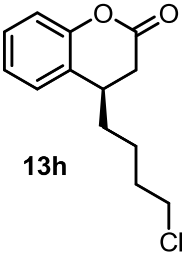
Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.106 g (*R*)-4-(but-3-en-1-yl)-3,4-dihydronaphthalen-2(1H)-one **13f** (0.528 mmol, 66 % yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) with butenylmagnesium bromide solution (2.4 molar in Et_2O) (0.84 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.85 in pentane/EtOAc 10:1, 93% *ee*). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.38 – 6.93 (m, 4H), 5.93 – 5.62 (m, 1H), 5.24 – 4.83 (m, 2H), 3.10 – 2.93 (m, 1H), 2.91 – 2.61 (m, 2H), 2.25 – 1.95 (m, 2H), 1.79 – 1.55 (m, 2H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.20, 151.23, 137.18, 128.27, 127.76, 126.42, 124.26, 117.09, 115.61, 34.57, 34.28, 33.51, 30.54. HRMS: (ESI$^+$) calculated for $C_{13}H_{14}O_2Na$ [M+Na$^+$]: 225.0886, found: 225.0884. $[\alpha]_D^{20}$ = 72.6 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OD-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 20.4 min (minor), 21.6 min (major).

(*R*)-4-Phenethylchroman-2-one (13g)


13g

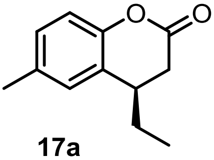
Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.126 g (*R*)-4-phenethylchroman-2-one **13g** (0.499 mmol, 73% yield) was isolated as an orange solid from the reaction of 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) with phenylethylmagnesium bromide solution (1.50 molar in Et_2O) (1.14 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.65 in pentane/EtOAc 10:1, 94% *ee*). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 3H), 7.25 – 7.04 (m, 6H), 3.11 – 2.98 (m, 1H), 2.90 – 2.80 (m, 2H), 2.79 – 2.58 (m, 2H), 2.04 – 1.85 (m, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.06, 151.17, 140.68, 128.39, 128.25, 128.14, 127.68, 126.30, 126.01, 124.23, 117.02, 35.86, 34.48, 34.35, 32.56. HRMS: (ESI^+) calculated for $C_{17}H_{16}O_2Na$ [$M+Na^+$]: 275.1043, found: 275.1042. $[\alpha]_D^{20}$ = 57.0 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak AD: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 8.3 min (minor), 9.0 min (major).

(*R*)-4-(4-Chlorobutyl)chroman-2-one (13h)


13h

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.075 g (*R*)-4-(4-chlorobutyl)chroman-2-one **13h** (0.315 mmol, 46 % yield) was isolated as a yellow oil from the reaction of 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) with (4-chlorobutyl)magnesium bromide solution (2.3 molar in Et_2O) (0.744 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.65 in pentane/EtOAc 10:1, 98% *ee*). The product contains traces of dehalogenated product. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 1H), 7.18 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.11 (td, *J* = 7.4, 1.1 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 3.52 (dt, *J* = 6.5, 5.1 Hz, 2H), 2.99 (dd, *J* = 5.8, 3.8 Hz, 1H), 2.80 (ddd, *J* = 19.7, 15.9, 4.8 Hz, 2H), 1.77 (ddd, *J* = 7.7, 6.1, 3.7 Hz, 2H), 1.68 – 1.52 (m, 4H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.20, 151.21, 128.39, 127.79, 126.33, 124.35, 117.18, 44.58, 35.10, 34.75, 33.87, 32.25, 24.05. HRMS: (ESI^+) calculated for $C_{13}H_{16}O_2$ [$M+H^+$]: 239.0833, found: 239.0842. $[\alpha]_D^{20}$ = 84.6 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OD-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 26.0 min (major), 27.0 min (minor).

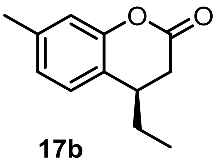
(*R*)-4-Ethyl-6-methylchroman-2-one (17a)


17a

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.140 g (*R*)-4-ethyl-6-methylchroman-2-one **17a** (0.736 mmol, 92 % yield) was isolated as a pale yellow oil from the reaction of 6-methyl-2H-chromen-2-one **16a** (0.128 g, 0.80 mmol) with ethylmagnesium bromide solution (3.0 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column

chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.85 in pentane/EtOAc 10:1, 94% *ee*). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.09 – 6.85 (m, 3H), 2.90 – 2.78 (m, 1H), 2.77 – 2.61 (m, 2H), 2.30 (s, 3H), 1.70 – 1.44 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.51, 149.05, 133.63, 128.50, 128.15, 126.03, 116.53, 36.42, 34.26, 27.43, 20.59, 11.00. HRMS: (ESI^+) calculated for $C_{12}H_{15}O_2$ [$M+H^+$]: 191.1067, found: 191.1067. $[\alpha]_D^{20}$ = 19.0 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 15.8 min (major), 17.3 min (minor).

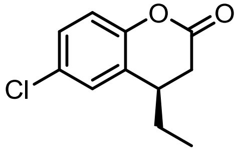
(*R*)-4-Ethyl-7-methylchroman-2-one (17b)



17b

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.141 g (*R*)-4-ethyl-7-methylchroman-2-one **17b** (0.741 mmol, 93 % yield) was isolated as a pale yellow oil from the reaction of 7-methyl-2H-chromen-2-one **16b** (0.128 g, 0.80 mmol) with ethylmagnesium bromide solution (3.0 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.70 in pentane/EtOAc 10:1, 97% *ee*). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 7.7 Hz, 1H), 6.90 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.84 (s, 1H), 2.89 – 2.81 (m, 1H), 2.74 (qd, *J* = 15.7, 4.9 Hz, 2H), 2.31 (s, 3H), 1.59 (qt, *J* = 13.9, 7.2 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 168.54, 151.05, 138.28, 127.47, 124.84, 123.22, 117.30, 36.09, 34.45, 27.50, 20.89, 11.00. HRMS: (ESI^+) calculated for $C_{12}H_{15}O_2$ [$M+H^+$]: 191.1067, found: 191.1062. $[\alpha]_D^{20}$ = 37.0 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 16.9 min (major), 18.2 min (minor).

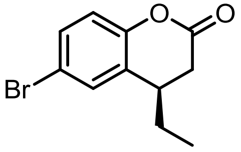
(*R*)-6-Chloro-4-ethylchroman-2-one (17c)



17c

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.135 g (*R*)-6-chloro-4-ethylchroman-2-one **17c** (0.641 mmol, 80 % yield) was isolated as an orange oil from the reaction of 6-chloro-2H-chromen-2-one **16c** (0.144 g, 0.80 mmol), which was added as a solution in 7 mL MTBE/CH_2Cl_2 (5:2), with ethylmagnesium bromide solution (3.0 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.55 in pentane/EtOAc 10:1, 95% *ee*). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 2H), 6.95 (d, *J* = 8.5 Hz, 1H), 2.93 – 2.83 (m, 1H), 2.82 – 2.66 (m, 2H), 1.73 – 1.47 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: (75 MHz, $CDCl_3$) δ 167.55, 149.73, 129.16, 128.09, 127.57, 118.27, 97.86, 36.36, 33.81, 27.23, 10.91. HRMS: (ESI^+) calculated for $C_{11}H_{12}ClO_2$ [$M+H^+$]: 211.0520, found: 211.0517. $[\alpha]_D^{20}$ = 16.8 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 27.0 min (major), 33.1 min (minor).

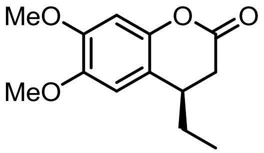
(*R*)-6-Bromo-4-ethylchroman-2-one (17d)



17d

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.175 g (*R*)-6-bromo-4-ethylchroman-2-one **17d** (0.686 mmol, 86 % yield) was isolated as a yellow oil from the reaction of 6-bromo-2H-chromen-2-one **16d** (0.180 g, 0.80 mmol), which was added as a solution in 8 mL MTBE/CH_2Cl_2 (5:3), with ethylmagnesium bromide solution (3.0 molar in Et_2O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.55 in pentane/EtOAc 10:1, 96% *ee*). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.41 – 7.23 (m, 2H), 6.90 (d, *J* = 8.5 Hz, 1H), 2.94 – 2.81 (m, 1H), 2.81 – 2.61 (m, 2H), 1.60 (td, *J* = 14.5, 7.0 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 167.44, 150.25, 131.04, 130.48, 128.54, 118.67, 116.68, 36.31, 33.80, 27.26, 10.93. HRMS: (ESI^+) calculated for $C_{11}H_{12}BrO_2$ [$M+H^+$]: 255.0015, found: 255.0010. $[\alpha]_D^{20}$ = 5.40 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 24.1 min (major), 28.4 min (minor).

(*R*)-4-Ethyl-6,7-dimethoxychroman-2-one (17e)

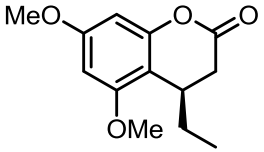


17e

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.063 g (*R*)-4-ethyl-6,7-dimethoxychroman-2-one **17e** (0.267 mmol, 55 % yield) was isolated as a brown oil from the reaction of 6,7-dimethoxy-2H-chromen-2-one **16e** (0.100 g, 0.485 mmol), which was added as a solution in 5.0 mL MTBE/CH_2Cl_2 (1:1), with ethylmagnesium bromide solution (3.0 molar in Et_2O) (0.404 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 8:2, R_f = 0.50 in pentane/EtOAc 8:2, 64% *ee*). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.60 (s, 1H), 3.85 (d, *J* = 3.3 Hz, 6H), 2.88 – 2.63 (m, 3H), 1.60 (dd, *J* = 13.2, 6.6 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.56, 148.72, 145.46, 145.00, 117.27, 110.41, 101.28, 56.41, 56.07, 36.34, 34.49, 27.80, 11.12. HRMS: (ESI^+) calculated for $C_{13}H_{17}O_4$ [$M+H^+$]: 237.1121, found: 237.1118. $[\alpha]_D^{20}$ = 20.8 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak AD-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 32.0 min (major), 44.1 min (minor).

(*R*)-4-Ethyl-5,7-dimethoxychroman-2-one (17f)

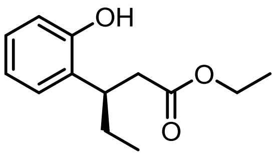
Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.125 g (*R*)-4-ethyl-5,7-dimethoxychroman-2-one **17f** (0.528 mmol, 66 % yield) was isolated as a pale yellow solid from the reaction of 5,7-dimethoxy-2H-chromen-2-one **16f** (0.165 g, 0.80 mmol), which was added as a solution in 5.0 mL



17f

MTBE/CH_2Cl_2 (1:1), with ethylmagnesium bromide solution (3.0 M in Et_2O) (0.667 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO_2, pentane/EtOAc 8:2, R_f = 0.75 in pentane/EtOAc 8:2, 48% *ee*). ^{1}H NMR: (201 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 7.8, 2.3 Hz, 2H), 3.78 (d, *J* = 6.2 Hz, 6H), 3.30 – 3.08 (m, 1H), 2.71 (qd, *J* = 15.9, 4.1 Hz, 2H), 1.66 – 1.33 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 168.64, 159.96, 157.28, 152.52, 107.63, 94.69, 93.82, 55.53, 55.42, 33.82, 30.22, 27.30, 11.03. HRMS: (ESI$^+$) calculated for $C_{13}H_{17}O_4$ [M+H$^+$]: 237.1121, found: 237.1121. $[\alpha]_D^{20}$ = 10.6 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 24.0 min (major), 27.4 min (minor).

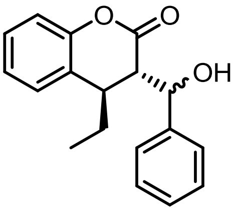
(*R*)-Ethyl 3-(2-hydroxyphenyl)pentanoate (22)



22

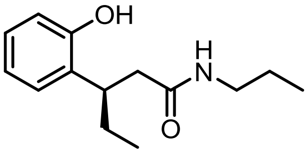
In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.02 mmol) and 3.0 mol% reverse Josiphos (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and stirred at room temperature for 15 min. Then, the mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 M in Et_2O, 0.80 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. Then, a solution of 1.0 eq. 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.0 eq. ethanol (0.234 ml, 4.00 mmol) were added and the reaction mixture was warmed to room temperature and stirred at that temperature for 5 h. Then, the reaction was quenched by adding saturated aq. NH_4Cl solution (50 mL) and the reaction mixture was diluted with Et_2O (50 mL). After separation of the organic phase it was dried over $MgSO_4$ and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO_2, pentane/EtOAc 10:1, R_f = 0.55 in pentane/EtOAc 10:1, 95% *ee*) to yield (*R*)-ethyl-3-(2-hydroxyphenyl)pentanoate **22** (0.154 g, 0.693 mmol, 87 %) as a colourless oil. ^{1}H NMR: (201 MHz, $CDCl_3$) δ 7.19 – 6.98 (m, 3H), 6.96 – 6.82 (m, 2H), 4.30 – 3.91 (m, 2H), 3.36 (dtd, *J* = 13.1, 7.6, 5.3 Hz, 1H), 2.70 (qd, *J* = 16.4, 7.3 Hz, 2H), 1.89 – 1.59 (m, 2H), 1.18 (t, *J* = 7.22 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 174.74, 154.14, 130.49, 127.22, 120.78, 117.03, 60.86, 40.90, 35.98, 27.77, 13.92, 12.02. HRMS: (ESI$^+$) calculated for $C_{13}H_{18}O_3Na$ [M+Na$^+$]: 245.1148, found: 245.1149. $[\alpha]_D^{20}$ = -2.0 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak AD-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 76.2 min (minor), 80.0 min (major).

(3*S*,4*R*)-4-Ethyl-3-(hydroxy(phenyl)methyl)chroman-2-one (23)


23

In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.02 mmol) and 3.0 mol% reverse Josiphos (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and stirred at room temperature for 15 min. Then, the mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 M in Et$_2$O, 0.80 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. Then, a solution of 1.0 eq. 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.0 eq. benzaldehyde (0.405 ml, 4.00 mmol) were added and the reaction mixture was warmed to room temperature and stirred at that temperature for 4 h. Next, the reaction was quenched by adding saturated aq. NH$_4$Cl solution (50 mL) and the reaction mixture was diluted with Et$_2$O (50 mL). After separation of the organic phase it was dried over MgSO$_4$ and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO$_2$, toluene/MeOH 30:1, R_f = 0.45 (major), 0.35 (minor) in toluene/MeOH 30:1) to yield (3*S*,4*R*)-4-ethyl-3-(hydroxy(phenyl)methyl)chroman-2-one **23** (0.176 g, 0.624 mmol, 78 %) as a colourless oil. Compound **23** was isolated as a mixture of 2 diastereomers (ratio 3:1), signals are assigned where resolved. ^{1}H NMR: (201 MHz, CDCl$_3$) δ 7.48 – 6.92 (m, 9H, major + minor), 4.59 (d, *J* = 9.4 Hz, 1H, major), 4.43 (d, *J* = 10.0 Hz, 1H, minor), 3.27 – 3.03 (m, 2H, major + minor), 2.73 (s (br), 1H, major + minor), 2.24 (t, *J* = 7.3 Hz, 1H, minor), 1.49 (qd, *J* = 14.4, 7.3 Hz, 2H, major + minor), 0.90 (t, *J* = 7.3 Hz, 3H, major), 0.77 (t, *J* = 7.3 Hz, 3H, minor). ^{13}C NMR: (50 MHz, CDCl$_3$) δ 168.46 (minor), 167.92 (major), 150.48 (minor), 150.45 (major), 140.77 (major), 140.47 (minor), 129.22, 128.87 (minor), 128.83 (major), 128.61 (major), 128.55 (minor), 128.36, 128.31 (minor), 128.26 (major), 128.09, 127.38, 126.80, 126.34, 125.89, 124.87, 124.32 (minor), 124.26 (major), 116.64 (minor), 116.34 (major), 72.58 (major), 64.91 (minor), 53.93 (major), 53.29 (minor), 39.70 (minor), 39.07 (major), 28.59 (major), 28.18 (minor), 11.07 (major), 10.87 (minor). HRMS: (ESI$^+$) calculated for C$_{18}$H$_{18}$O$_3$Na [M+Na$^+$]: 305.1148, found: 305.1149. [α]$_D^{20}$ = 72.4 (c = 1.0 in CHCl$_3$).

(*R*)-3-(2-Hydroxyphenyl)-*N*-propylpentanamide (24)


24

In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.02 mmol) and 3.0 mol% reverse Josiphos (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and stirred at room temperature for 15 min. Then, the mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 m in

Et_2O, 0.80 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. Then, a solution of 1.0 eq. 2H-chromen-2-one **12** (0.117 g, 0.80 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.0 eq. propan-1-amine (0.33 ml, 4.00 mmol) were added and the reaction mixture was warmed to room temperature and stirred at that temperature for 16 h. Then, the reaction was quenched by adding saturated aq. NH_4Cl solution (50 mL) and the reaction mixture was diluted with Et_2O (50 mL). After separation of the organic phase it was dried over $MgSO_4$ and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO_2, pentane/EtOAc 1:1, R_f = 0.60 in pentane/EtOAc 1:1, 96% *ee*) to yield (*R*)-3-(2-hydroxyphenyl)-*N*-propylpentanamide **24** (0.154 g, 0.656 mmol, 82 %) as a colourless oil. ^1H NMR: (400 MHz, $CDCl_3$) δ 8.71 (s (br), 1H), 7.12 – 7.02 (m, 2H), 6.94 – 6.83 (m, 2H), 6.26 (s (br), 1H), 3.34 (dd, *J* = 11.5, 7.3 Hz, 1H), 3.07 (dd, *J* = 13.3, 6.7 Hz, 2H), 2.65 (dd, *J* = 15.3, 4.3 Hz, 1H), 2.45 (dd, *J* = 15.3, 10.2 Hz, 1H), 1.72 (td, *J* = 14.2, 6.5 Hz, 2H), 1.48 – 1.28 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.75 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 173.76, 154.50, 130.74, 127.19, 127.01, 120.50, 117.24, 43.32, 41.32, 36.21, 27.77, 22.33, 12.15, 11.03. HRMS: (ESI$^+$) calculated for $C_{14}H_{22}NO_2$ [M+H$^+$]: 236.1645, found: 236.1644. $[\alpha]_D^{20}$ = -38.4 (c = 1.0 in $CHCl_3$). *ee* determination by chiral HPLC (Chiralpak AB-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm, flow rate 0.5 mL/min), retention times: 25.9 min (minor), 32.4 min (major).

6 References

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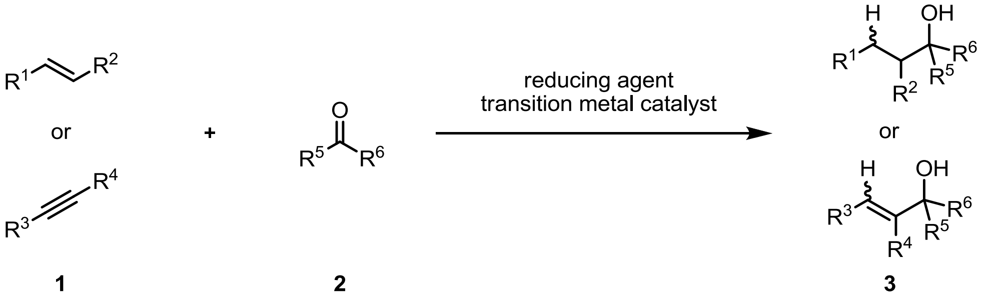
Chapter 7

Ni-catalyzed Reductive Coupling Reactions – Application of Phosphoramidite Ligands bearing chiral *N*-Heterocycles

A new asymmetric nickel-catalyzed reductive coupling of isoprene and benzaldehyde has been developed. The corresponding products bear 1,3-stereogenic centers and are available with excellent diastereoselectivity, albeit with moderate enantioselectivity. An extensive ligand screening has been carried out to identify leading ligand structures. Furthermore, mechanistic studies based on ^{31}P *and* ^{1}H *NMR experiments give evidence to support the proposed mechanism.*

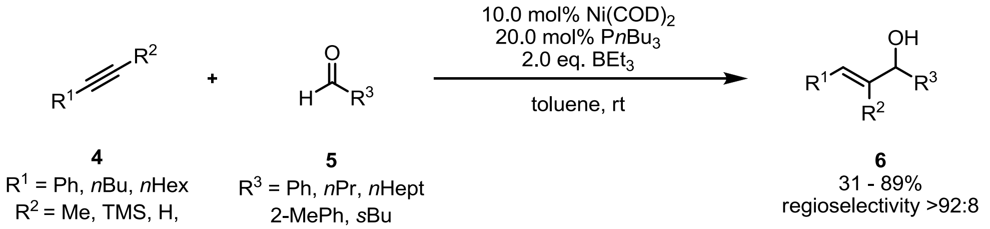
1. Introduction

Transition metal-catalyzed reductive carbon-carbon bond formations represent an emerging field of organic synthesis and catalysis. Next to hydrogenative coupling catalyzed by rhodium and iridium catalysts,[1-3] nickel-[4-8] and cobalt-catalyzed[4,9,10] reductive coupling reactions are among the most prominent. One of the most important advantages of these reaction is the fact that they do not require an organometallic reagent as carbon nucleophile to faciliate the C-C bond formation, what considerably reduces the waste generated during those transformations. (It should be noted, though, that some of the reactions employ organometallic reagents as reducing agents. See below.) The general approach can be summarized as follows: a compound bearing an unsaturated C-C bond such as an alkene or alkyne **1** is coupled to a suitable electrophile, in this case an aldehyde or a ketone **2** (Scheme 1). For this reaction to occur, a reducing agent is necessary to deliver an β-H atom to the alkene/alkyne. The obtained products **3** are highly functionalized and bear at least one stereogenic center adjacent to the alcohol. Furthermore, through judicious choice of the catalyst, different stereoisomers (*cis/trans* and *E/Z*) are available through this methodology.



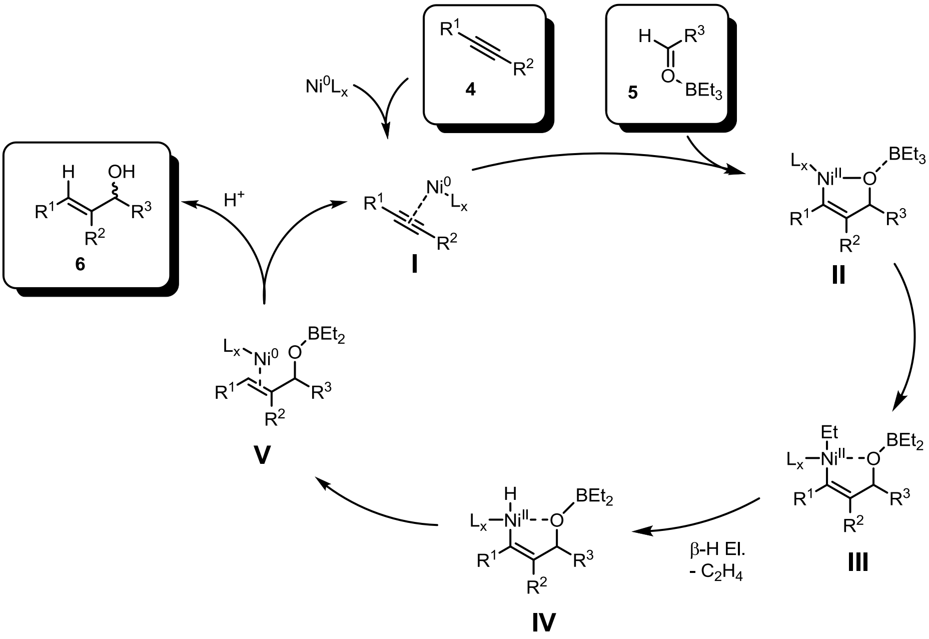
Scheme 1 Reductive coupling reactions

One example of this transformation is depicted in Scheme 2. When internal or terminal alkynes **4** were reacted with aldehydes **5** in the presence of catalytic amounts of a Ni/phosphine complex employing triethylborane as the reducing agent, the corresponding allylic alcohols **6** were obtained reaching very good yields, albeit with relatively high catalyst loadings.[11]


10.0 mol% Ni(COD)2
20.0 mol% PnBu3
2.0 eq. BEt3
toluene, rt
4
R1 = Ph, nBu, nHex
R2 = Me, TMS, H,
5
R3 = Ph, nPr, nHept
2-MePh, sBu
6
31 - 89%
regioselectivity >92:8

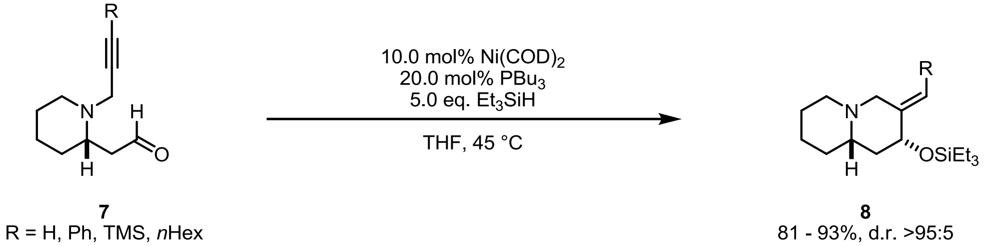
Scheme 2 Ni-catalyzed reductive coupling of alkynes with aldehydes

The proposed catalytic cycle for these transformations[6] is depicted in Scheme 3. The alkyne (**4**) first coordinates to Ni(0) to give intermediate **I**. Then Ni can add to the alkyne in an oxidative fashion, triggering the nucleophilic attack on the activated aldehyde (**5**) to give nickelacycle **II**. It is important to note that here BEt_3 serves as a Lewis acid to activate the aldehyde, whereas it will serve as the reducing agent later on, so the role of BEt_3 is twofold. In the following step, one alkyl group of the boron reagent is transmetallated to nickel to give intermediate **III**. Then, a β-hydride elimination can occur, yielding a nickel-hydride complex (**IV**). Subsequent reductive elimination furnishes the desired product as the boroxide complex **V**. Ni(0) can be liberated from intermediate **V** to enter a new catalytic cycle. During workup, the boroxide is protonated to yield the desired product **6**.


4
5
Ni0Lx
6
H+
I
II
III
IV
V
β-H El.
- C2H4

Scheme 3 Proposed catalytic cycle for the formation of allyl alcohol 6

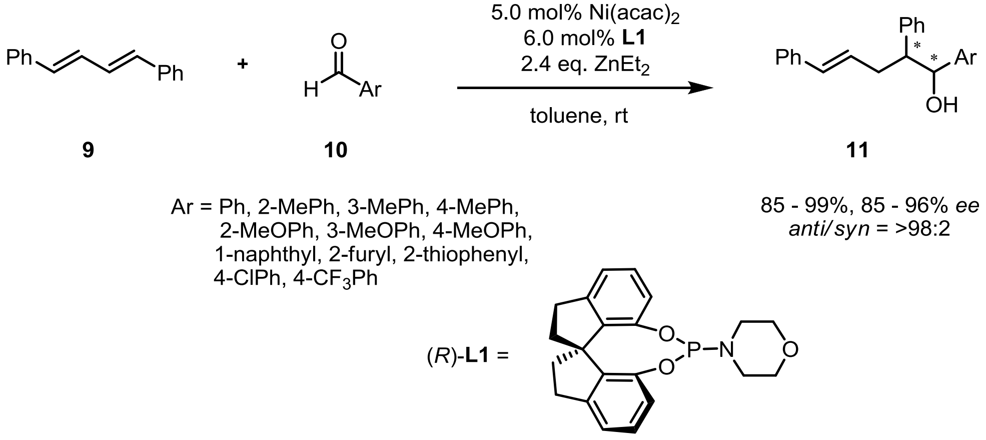
A wide variety of related reactions has been developed,[6] including an intramolecular Ni-catalyzed coupling reaction of alkynes with aldehydes leading to nitrogen-containing bicyclic compounds **8** (Scheme 4).[12,13] In this case triethylsilane is employed as the reducing agent, which leads to *in situ* TMS protection of the corresponding alcohols **8**. When piperidines **7** were reacted in the presence of a Ni catalyst, the corresponding bicyclic TMS-protected alcohols **8** were obtained in very good yields and diastereoselectivities (Scheme 4).



R
N
H
O
H
10.0 mol% Ni(COD)$_2$
20.0 mol% PBu$_3$
5.0 eq. Et$_3$SiH
THF, 45 °C
R
N
H
OSiEt$_3$
7
R = H, Ph, TMS, *n*Hex
8
81 - 93%, d.r. >95:5

Scheme 4 Intramolecular Ni-catalyzed coupling reaction

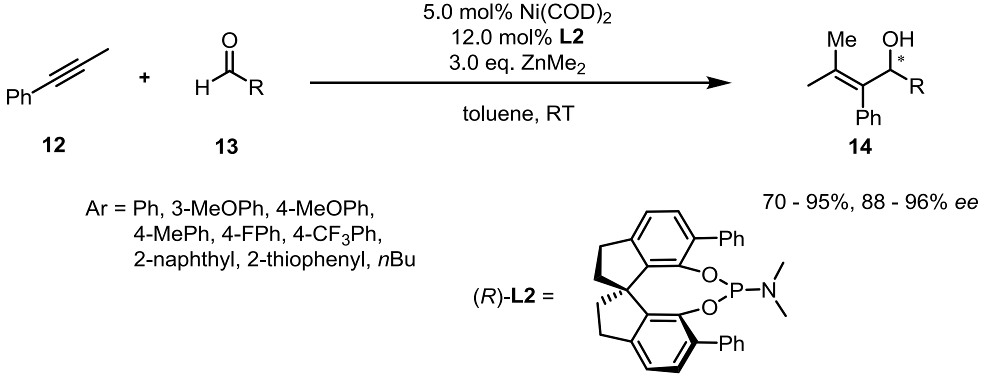
Some enantioselective variants of the Ni-catalyzed reductive coupling reactions are known, employing chiral phosphine[14,15] or *N*-heterocyclic carbene[16] ligands. While this research project was in progress, the application of spiro-phosphoramidites **L1** in a nickel-catalyzed reductive coupling of dienes to aldehydes (Scheme 5) was reported.[17] Using diethylzinc as the reducing agent, 1,4-diphenyl-butadiene **9** was coupled to aromatic aldehydes **10** to yield the products **11** in excellent yields and *ee*. In all cases, the 1,2-*anti*-products **11** were obtained.



Ph
Ph
+
O
H
Ar
5.0 mol% Ni(acac)$_2$
6.0 mol% **L1**
2.4 eq. ZnEt$_2$
toluene, rt
Ph
Ph
*
*
Ar
OH
9
10
11
Ar = Ph, 2-MePh, 3-MePh, 4-MePh, 2-MeOPh, 3-MeOPh, 4-MeOPh, 1-naphthyl, 2-furyl, 2-thiophenyl, 4-ClPh, 4-CF$_3$Ph
85 - 99%, 85 - 96% *ee*
anti/*syn* = >98:2
(*R*)-**L1** =
O
O
P
N
O

Scheme 5 Ni-catalyzed reductive coupling reactions

This methodology was extended to a 3-component coupling reaction[18] of dimethylzinc, phenylpropyne **12** and aldehydes **13** to yield chiral allylic alcohols **14** bearing a tetrasubstituted olefin with excellent enantioselectivities (Scheme 6).[19] In this case, $ZnMe_2$ does not furnish a reducing equivalent in the form of a Ni-H complex, since no β-hydrogens are available in $ZnMe_2$. Instead, the methyl group is incorporated into the corresponding products **14** and thus serves the role of a reducing agent (compare Scheme 3). Again, a phosphoramidite ligand (**L2**) with a spirobiindane backbone gave the best results.

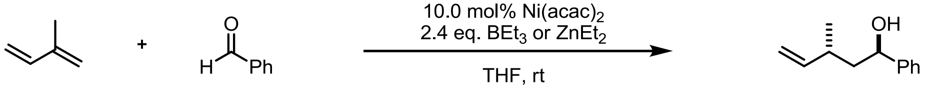


Scheme 6 Ni-catalyzed reductive coupling of alkynes and aldehydes

2. Goal

Background

The aim of this research project was to develop an asymmetric nickel-catalyzed reductive coupling reaction. We became interested in the reductive coupling reaction of 1,3-dienes, especially of isoprene, with aldehydes. This reaction had been reported in a non-stereoselective fashion earlier.[20,21] When an excess of isoprene (**15**) was reacted with benzaldehyde **16** in the presence of $Ni(acac)_2$ as catalyst (acac = acetylacetonato), the corresponding homoallylic alcohol **17** could be isolated with very good diastereoselectivitiy favoring the *anti* isomer (Scheme 7). Both BEt_3 and $ZnEt_2$ were examined as reducing agents and were shown to give the same product, however, BEt_3 as the reducing agent was giving **17** in a considerably higher yield. The diastereoselectivity appeared to be unaffected by the reducing agent.

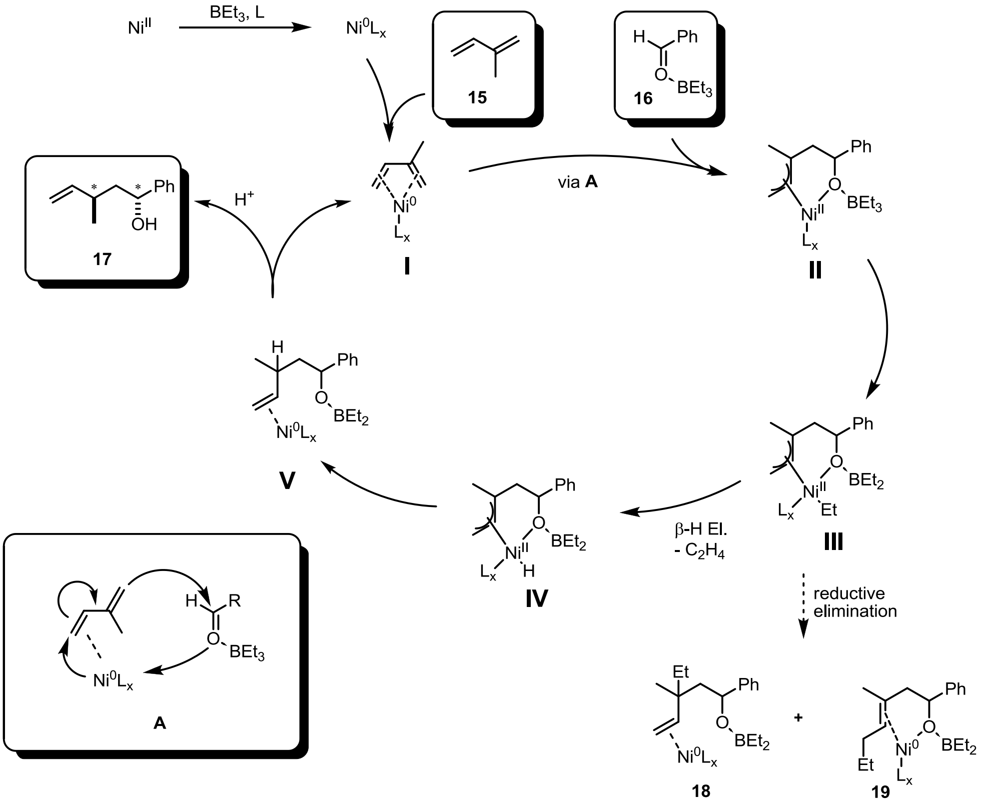


15 **16** **17**

with BEt_3: 90%, *syn/anti* 1:15
with $ZnEt_2$: 63%, *syn/anti* 1:15

Scheme 7 Ni-catalyzed reductive coupling of isoprene with benzaldehyde

The proposed mechanism[7] of this reaction has close analogy to the previously described one (compare Scheme 3), and can generally be described as the vinylogous variant thereof. In this reaction, BEt_3 (or $ZnEt_2$) serves three purposes: first it reduces the Ni(II) precursor to Ni(0), second it activates the aldehyde and finally it acts as the reducing agent for the whole transformation. Isoprene (**15**) can coordinate to nickel(0) and subsequently can undergo an oxidative insertion/cyclization reaction (A in Scheme 8) with the activated aldehyde **16** to give oxallylnickel(II) intermediate **II**. This reaction represents already the key C-C bond forming step and should therefore govern the stereoselectivity at the benzylic position. It can be represented as an oxidative insertion of Ni(0) to the terminal, sterically less demanding, double bond of isoprene, which will subsequently attack the electrophile (**16**) (A in Scheme 8). The resulting alkoxide can then coordinate to Ni(II) to form the neutral cyclic intermediate **II**. In analogy to the mechanism discussed earlier, a transmetallation of one of the alkyl substituents of BEt_3 to nickel can take place, giving intermediate **III**. β-Hydride elimination furnishes a nickel-hydride complex (**IV**), which can undergo reductive elimination to form boroxide adduct **V** of the desired product **17**. Ni(0) can subsequently enter a new catalytic cycle. During the reductive elimination step both the regioselectivity of the double bond position as well as the stereoselectivity of the second stereogenic center formed at the allylic position are determined. Alternatively, intermediate **III** can be the starting point for a reductive elimination reaction to give the three-component coupling products **18** and **19**.[5]



Scheme 8 Proposed catalytic cycle for the formation of 17

Goal

This Ni-catalyzed reductive coupling reaction is interesting for a variety of reasons. First, it uses cheap and readily available starting materials and takes place at ambient temperatures. Second, the products like **17** are highly functional building blocks posessing a terminal olefin moiety, a secondary alcohol and an aromatic ring. Third, this reaction creates two stereocenters in a 1,3-relationship in only one synthetic step. No asymmetric variant of this transformation was known in literature, therefore we decided to explore this possible extension. We envisaged to start off our study with the investigation of Ni/phosphoramidite complexes as chiral catalysts for the reductive coupling of isoprene with aldehydes, since phosphoramidite ligands are, due to their modular design, ideally suited for fine-tuning of their electronic and steric parameters.[22,23] As already mentioned, during the course of this research project, it was demonstrated that those complexes were indeed suitable to induce enantioselectivity in related reactions (see Scheme 5 and Scheme 6). It was to be investigated in how far different ligands and/or reducing agents would affect the diastereo- as well as the enantioselectivity of the reductive coupling of isoprene with aldehydes. Ideally, chiral bishomoallylic alcohols **17** would be available in high enantiomeric excess and accessible selectively as either the *syn* or the *anti* diastereomer.

3. Results and Discussion

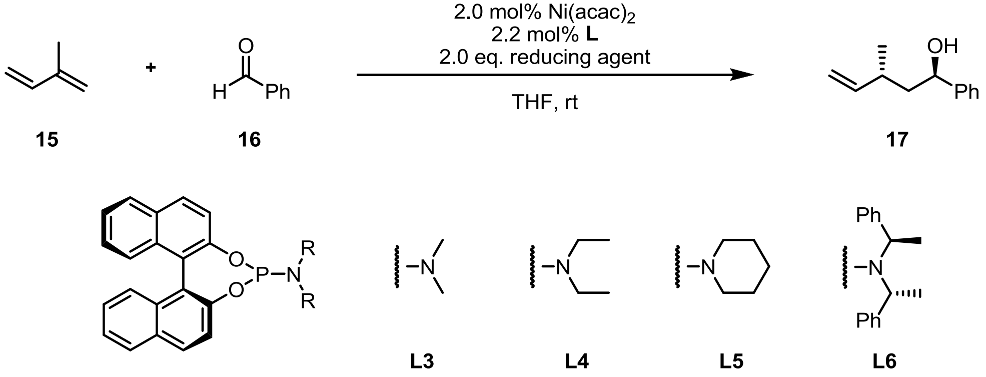
3.1 Initial screening results

Preliminary screening experiments of the envisaged reductive coupling of isoprene (**15**) with benzaldehyde (**16**) in the presence of Ni/phosphoramidite complexes as catalysts revealed several important aspects of this transformation (for selected experiments, see Table 1). First of all, we were delighted to observe that the envisaged coupling reaction took place with catalysts comprising Ni/phosphoramidite complexes with chiral BINOL backbones (Table 1, entries 3-6). Even though comparable results in terms of diastereoselectivity with the previously published work[20,21] were found, no stereoinduction was observed with simple phosphoramidites **L3**-**L5**. With bidentate phosphine ligands, such as BINAP or ferrocenyl-based ligands (Josiphos, Taniaphos) no reaction was observed. These findings indicated that monodentate ligands are required for the Ni-catalyzed reductive coupling to occur.

A second observation made in preliminary experiments was that dialkylzinc reagents had to be employed as reducing agents. When trialkylborane compounds were used as reducing agents, no conversion to the desired coupling product **17** was found (Table 1, entry 3). This is a remarkable observation, since in the original reports employing Ni(acac)$_2$ as catalyst, BEt$_3$ had been employed as the reducing agent for this particular reaction (also compare Table 1, entry 1).[20,21] This result shows that the electronic properties of the nickel/phosphoramidite complexes differ significantly from the properties of their precursors, Ni(acac)$_2$ and Ni(COD)$_2$. Also, in terms of yields and enantioselectivity for **17**, using a nickel(II) precursor (namely Ni(acac)$_2$) or a nickel(0) precursor (Ni(COD)$_2$) did not give different results. This suggests a reduction of the Ni(II) precatalyst to Ni(0) by the dialkylzinc reagent prior to the actual catalytic cycle, which is consistent with the proposed mechanism (see also Scheme 8).[7,20,21] In the following experiments, Ni(acac)$_2$ was employed due to its higher air-stability.

To achieve enantioselectivity in the formation of the desired product **17**, phosphoramidites bearing chiral amine moieties had to be used. Therefore we chose bisphenylethylamine-derived phosphoramidite **L6**, which had been successfully employed in a variety of reactions[23] as the benchmark ligand (Table 1, entry 7). With **L6** and diethylzinc as the reducing agent, **17** was formed in 56% yield and 15% *ee*. It should be noted that in all cases employing $ZnEt_2$ as the reducing agent, full conversion of isoprene (**15**) was observed. Along with the desired product **17**, a variety of side products were observed (**20** – **22**, see Table 2), including 1-phenylpropanol (**22**) resulting from nucleophilic attack of $ZnEt_2$ on benzaldehyde (**16**).

Table 1 Initial screening of ligands and reducing agents[a]



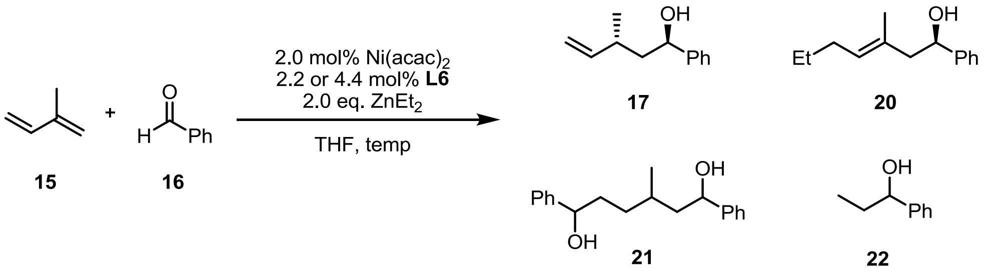
Entry	Ligand	Reducing agent	Yield of 17	d.r.[b] /*ee*[c]
1	-	BEt_3	92%	20:1 / -
2	-	$ZnEt_2$	55%	20:1 / -
3	**L4**	BEt_3	-	- / -
4	**L4**	$ZnEt_2$	71%	10:1 / 0%
5	**L3**	$ZnEt_2$	45%	18:1 / 0%
6	**L5**	$ZnEt_2$	61%	18:1 / 0%
7	**L6**	$ZnEt_2$	56%	19:1 / 15%

[a] Reaction conditions: 0.50 mmol isoprene (**15**), 0.60 mmol benzaldehyde (**16**), 0.01 mmol $Ni(acac)_2$ and 0.011 mmol **L** were dissolved in 2.5 mL THF at rt. Then, 1.0 mmol of $ZnEt_2$ solution (c = 1.0 M in THF) was added dropwise and the reaction mixture was stirred until TLC showed full conversion of **15** (~ 2h).

The reaction was quenched with sat. aq. NH_4Cl solution, and the product obtained by extraction with Et_2O. [b]Determined by GC. The *syn* diastereomer is the major one. [c]Determined by chiral GC or HPLC.

We found that the nickel to ligand ratio needs to be close to 1:1 for the coupling reaction to proceed smoothly to **17**, with compounds **20** to **22** observed as side-products (Table 2, entry 1). **22** is the product of the direct addition of $ZnEt_2$ to benzaldehyde (**16**), the formation of **21** could be explained by the double reaction of isoprene with two equivalents of benzaldehyde. When a Ni/L ratio of 1:2 was employed (Table 2, entry 2), the envisaged coupling reaction still took place, but the desired coupling product **17** was accompanied by equal amounts of sideproducts **20** to **22**. Compound **20** results from the three-component coupling (compare intermediate **III** in Scheme 8). Importantly, **20** is also formed with 15% *ee*, suggesting that **17** and **20** are formed from the same catalytic intermediate in which the stereoinformation at the benzylic position is already fixed (intermediate **II** in Scheme 8).

Table 2 Influence of the Ni/L ratio



Entry	Ni/L6	Temperature	17/20/21/22[a]
1	1 : 1	rt	60 : 20 : 5 : 10
2	1 : 2	rt	20 : 25 : 30 : 20
3	1 : 1	0 °C	0 : 70 : 0 : 30

[a]Determined by both, ^1H NMR and GC/MS. Arbitrary units.

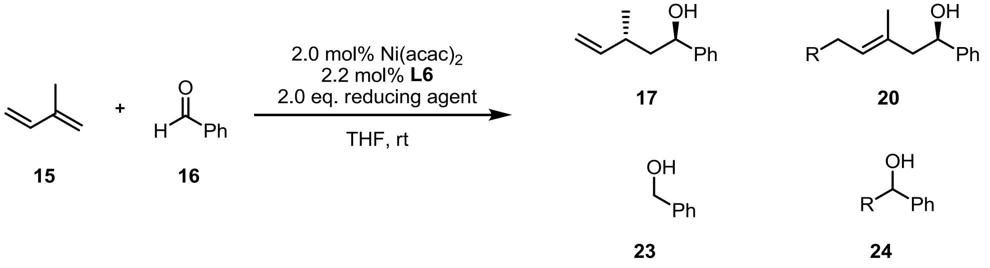
The abovementioned results suggest that several nickel/**L6** complexes with different catalytic behaviour are present in solution. Most probably there are equilibria present between the various species, since even with a 1:2 Ni/**L6** ratio, compound **17** is still formed. A 1:1 ratio of metal and ligand favours the formation of the desired product **17**, a 1:2 ratio leads to the conversion of **15** and **16** to several by-products in an unselective manner. This behaviour could be supported by the proposed mechanism presented in Scheme 8, in which the three Ni(II) intermediates **II** to **IV** leave only one further coordination site to be occupied by a ligand to give rise to a 16 electron complex. The data presented in Table 2 suggest that a Ni/L_2 complex could be catalytically inactive and/or enter different catalytic pathways (for mechanistic investigations, see also section 3.6).

An important finding is reported in Table 2, entry 3. When the reaction was carried out at 0 °C with a Ni/**L6** ration of 1:1, no formation of **17** was observed, however, **20** was formed as the major product. This gives important insight to the proposed mechanism, as the crucial β-hydride elimination seems to be prevented at lower temperatures.[24] This observation can be explained by the fact that eliminations are generally favoured at higher temperatures due to the increase in entropy.

3.3 Screening of reducing agents

Other reducing agents were investigated in the following studies (Table 3). We found that in terms of selectivity, similar results as with $ZnEt_2$ could be observed with $AlEt_3$ (Table 3, entry 2). Remarkably, Zn*i*Pr_2 gave a much more selective reaction towards **17** accompanied by a slightly higher *ee* (Table 3, entry 3). These two examples hint towards the fact that the enantiodiscriminating step does depend on the metal reagent employed, and sterics of the organic substitutents of the organometallic reagent. The related *iso*-propylzinc bromide (Table 3, entry 4), showed similar results in terms of product distribution. However, in this case, the *syn/anti* ratio of **17** was found to be 1:1, and the *ee* dropped to 17%. These two results (Table 3, entries 3,4) demonstrate that with secondary organozinc reagents much more selective reactions can be carried out. This could stem from the higher steric bulk that the *iso*-propyl substituents create around the Ni(II)-center. As expected, the corresponding Grignard reagent led to only 1,2-addition product (Table 3, entry 5). The reactions employing aluminum hydrides or lithium triethylborohydride (Table 3, entries 6-8) led to reduction of benzaldehyde (**16**) to benzylalcohol **23**. The use of borane gave traces of the desired product **17** along with its double bond isomer **20** (R = H), but also in this case, benzylalcohol **23** was the major product (Table 3, entry 9). The use of sodium borohydride and sodium cyanoborohydride did not lead to any conversion (Table 3, entries 10, 11). Attempts to use poly(methylhydrosiloxane (PMHS) as reductant,[25] as well as the attempt to carry out a hydrogenative coupling did not lead to conversion to **17** (Table 3, entries 12, 13). Since the reaction with Zn*i*Pr_2 led to higher *ee* along with a considerably higher selectivity for **17** (Table 3, entry 3), we continued to optimize the asymmetric Ni-catalyzed reductive coupling reaction employing this reducing agent.

Table 3 Screening of reducing agents


15
16
2.0 mol% Ni(acac)2
2.2 mol% L6
2.0 eq. reducing agent
THF, rt
17
20
23
24
OH
Ph
R
H
O

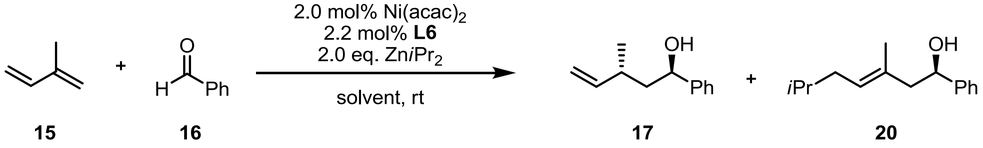
Entry	Reducing agent	17/20/23/24[a]	Comment
1	$ZnEt_2$	60 : 20 : 0 : 10	-
2	$AlEt_3$	60 : 20 : 0 : 10	**17**: 14% *ee*
3	Zn*i*Pr_2	80 : 10 : 0 : 0	**17**: 23% *ee*
4	Zn*i*PrBr	80 : 10 : 0 : 0[b]	**17**: 17% *ee*
5	*i*PrMgCl	0 : 0 : 0 : 100	-
6	DIBAL-H	0 : 0 : 100 : 0	-
7	$LiAlH_4$	0 : 0 : 100 : 0	-
8	$LiHBEt_3$	0 : 0 : 100 : 0	-
9	BH_3	10 : 10 : 30	**23** = **24**
10	$NaBH_4$	-	no reaction
11	$NaCNBH_3$	-	no reaction
12	PMHS[c]	-	no reaction
13	H_2[d]	-	no reaction

[a] Determined by both, ^1H NMR and GC/MS. Arbitrary units. [b] Syn/anti of **17**: 1:1. [c] PMHS = Poly(methylhydrosiloxane). [d] $Ni(COD)_2$ was used as Ni precursor.

3.4 Screening of solvents

With the optimized results for the reducing agents in hand, we went on to investigate the influence of the solvent (Table 4). It was found that the envisaged transformation is relatively robust with respect to the choice of solvent, as conversion to the desired product **17** was found under most conditions tested. The majority of the solvents gave the *anti* diastereomer of **17** as the main product (Table 4, entries 1,2 and 4-6), with toluene giving the highest *ee* for *anti*-**17** (35%). Similar results in terms of enantioselectivity were only found with MeCN as solvent (Table 4, entry 3), however, in this case accompanied by a reversed diastereoselectivity to give the *syn* diastereomer of **17** as the major one. This could be explained by the ability of MeCN to act as a ligand for the Ni catalyst, leading to a catalyst with different spatial constraints. It is remarkable, though, that the opposite effect is observed employing THF as the solvent, which one could also expect to act as a ligand for Ni (Table 4, entry 2).

Table 4 Solvent screening[a]



Entry	Solvent	Conversion[b]	*anti/syn*[b]	*ee* of 17	Comment
1	toluene	full	19 : 1	35%	95% yield
2	THF	full	20 : 1	23%	
3	MeCN	65%	1 : 2	37%	
4	CH_2Cl_2	full	14 : 1	25%	10% **20**
5	TBME	full	8 : 1	30%	traces **20**
6	EtOAc	80%	10 : 1	26%	

[a] Reaction conditions: 0.50 mmol isoprene (**15**), 0.60 mmol benzaldehyde (**16**), 0.01 mmol $Ni(acac)_2$ and 0.011 mmol **L6** were dissolved in 2.5 mL THF at rt. Then, 1.0 mmol of a $ZniPr_2$ solution (c = 1.0 M in THF) was added dropwise and the reaction mixture was stirred until TLC showed full conversion (~ 2h). The reaction was quenched with sat. aq. NH_4Cl solution, and the product obtained by extraction with Et_2O. [b] Determined by both, ^1H NMR and GC/MS.

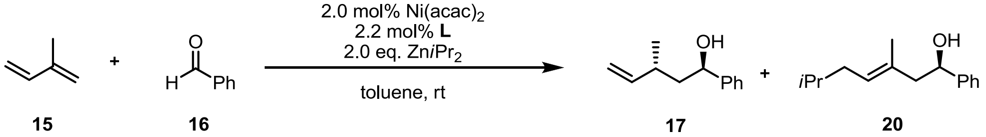
3.5 Ligand screening

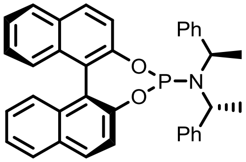
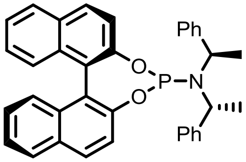
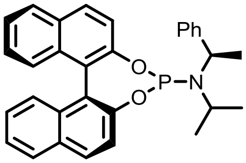
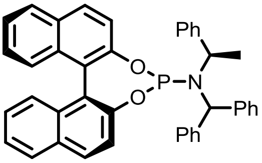
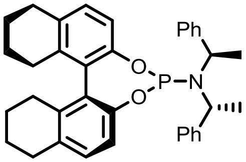
One of the major advantages of phosphoramidite ligands is because of their modularity they can be easily varied and screened for activity and stereoselectivity in catalysis.[23,26-28] With the optimized conditions, we set off to investigate the influence of a variety of phosphoramidite ligands, some of which are reported in Table 5. Starting off from the benchmark ligand (*S,R,R*)-**L6**, we first investigated the influence of its diastereomer, (*R,R,R*)-**L6**, which gave significantly worse results in terms of conversion and stereoselectivity (Table 5, entry 2). This clearly shows a matched/mismatched relationship of the two diastereomers of **L6** for the envisaged reaction. Replacement of one phenylethyl substituent with an isopropyl group led to slightly higher enantioselectivity (Table 5, entry 3), the Ph-substituted derivative gave the three-component coupling product **20** as the major one (Table 5, entry 4). The octahydroBINOL-backbone of **L9** as well as 3,3'-substitution as in **L10** led to lower enantioselectivity (Table 5, entries 5,6). As observed before (see Table 1), phosphoramidites with non-chiral amines **L11** and **L12** gave no enantioselectivity (Table 5, entries 7,8). Ligands bearing (*S*)-prolinate as the amine substituent (Table 5, entries 9,14), posessing an ester moiety which could act as a second coordination unit, were favouring the three-component coupling product **20**. Both **17** and **20** were formed in a racemic fashion. Higher enantioselectivities were observed employing smaller or more flexible diol backbones, as in the case of biphenol-derived **L14** (43% *ee*, Table 5, entry 10) and catechol-derived **L16** (46% *ee*, Table 5, entry 12). However, structural variatons of these two ligands **L15** and **L17** led to lower enantioselectivities (Table 5, entries 11,13). The same holds for TADDOL-derived **L19** (Table 5, entry 15). It is remarkable, though, that some of the ligands investigated gave exceptional levels of diastereoselectivity, as in the case of **L15** and azepine-derived ligand **L20** (Table 5, entries 11,16). It has been reported in the literature that the olefin moiety in **L20** can have a remarkable effect on catalysis, most probably due to a flexible, or labile coordination to the metal.[29] A similar trend was observed when comparing the two 2,5-dinaphthylpyrrolidine-derived[30] ligands **L21** and **L22** (see also Chapter 2, Table 5, entries 17, 18). Whereas both give excellent diastereoselectivities, it can be seen that **L22**, bearing the unsaturated pyrroline moiety gives higher enantioselectivity (40% *ee* vs 33% *ee*), which could be attributed to an additional hemi-labile coordination of the olefin moiety to the Ni.

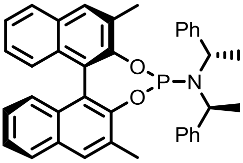
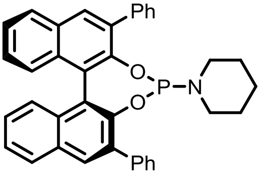
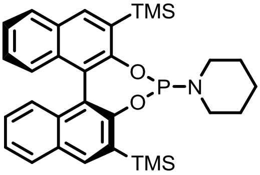
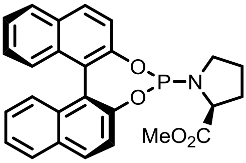
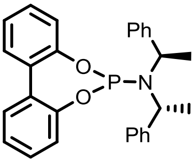
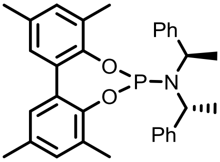
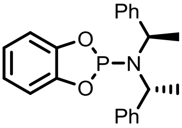
In summary, it can be concluded that the screening of phosphoramidite ligands led to some insights with respect to preferred and less preferred structural features of the ligands, but the *ee* reached remained rather low (46%, **L16**, Table 5, entry 12).

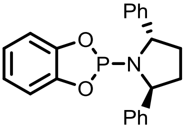
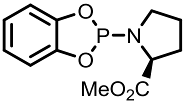
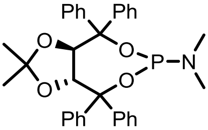
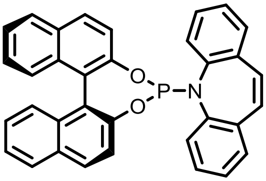
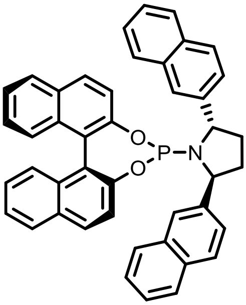
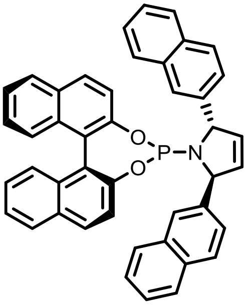
Further structural elaboration of these ligands did not lead to improvements in terms of enantioselectivity. It should be noted though, that some of the reactions achieved outstanding diastereoselectivity favouring the *anti*-product **17**.

Table 5 Ligand Screening[a]


2.0 mol% Ni(acac)2
2.2 mol% L
2.0 eq. ZniPr2
toluene, rt
O
H
Ph
OH
Ph
iPr
OH
Ph
15
16
17
20

Entry	Ligand		Comment	*anti/syn*[b]	*ee*[b]
1		**L6**	Full conversion	19 : 1	+35%
2		**L6**	~40% conversion	3 : 1	rac.
3		**L7**	-	19 : 1	+39%
4	 Ph O P N O Ph Ph	**L8**	Mostly **20**	n.d.	+6%
5		**L9**	-	16 : 1	+29%

Entry	Ligand		Comment	*anti/syn*[b]	*ee*[b]
6		**L10**	-	14 : 1	-22%
7		**L11**	-	15 : 1	rac.
8		**L12**	-	15 : 1	rac.
9		**L13**	**17** / **20** 1:2	n.d.	rac.
10		**L14**	-	18 : 1	+43%
11		**L15**	-	>99 : 1	+22%
12		**L16**	-	19 : 1	+46%

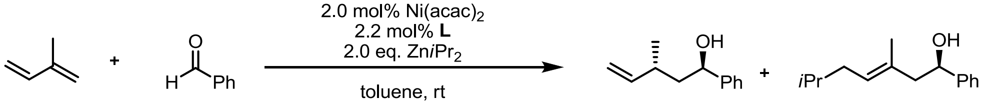
Entry	Ligand		Comment	*anti/syn*[b]	*ee*[b]
13		**L17**	-	16 : 1	-24%
14		**L18**	**17** / **20** 1:1	n.d.	rac.
15		**L19**	-	23 : 1	+18%
16		**L20**	-	>99 : 1	+17%
17		**L21**	-	>99 : 1	+33%
18		**L22**	-	>99 : 1	+40%

[a] Reaction conditions: 0.50 mmol isoprene (**15**), 0.60 mmol benzaldehyde (**16**), 0.01 mmol Ni(acac)$_2$ and 0.011 mmol ligand were dissolved in 2.5 mL THF at rt. Then, 1.0 mmol of Zn*i*Pr$_2$ solution (c = 0.5 M in toluene) was added dropwise and the reaction mixture was stirred until TLC showed full conversion (~

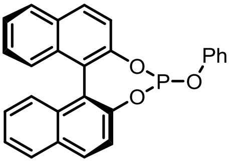
2h). The reaction was quenched with sat. aq. NH_4Cl solution, and the product isolated by extraction with Et_2O. [b]Determined by both, ^1H NMR and GC/MS.

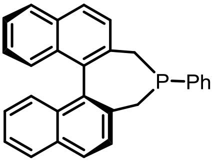
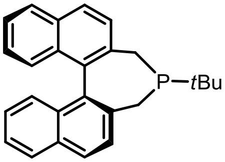
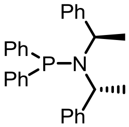
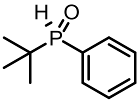
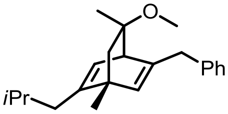
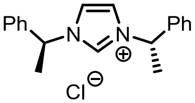
Besides investigating the influence of various phosphoramidite ligands on the Ni-catalyzed reductive coupling reaction, we also studied other types of chiral ligands. The results are summarized in Table 6. The related BINOL-derived phosphite **L23** gave **20** as the major product (Table 6, entry 1), whereas chiral phosphines **L24** and **L25** led to low conversion to **17** and low or no enantioselectivity (Table 6, entries 2,3). Remarkably, aminophosphine **L26**, coined SimplePhos,[31] led to **17** with 23% *ee* and excellent diastereoselectivity favouring the *anti* isomer of **17** (Table 6, entry 4). Secondary phosphine oxide **L27**[32] gave only compound **20** (Table 6, entry 5). An interesting result is shown in entry 6, as chiral diene **L28**[33] also led to some stereoinduction, albeit low (15% *ee*). To the best of our knowledge this marks the first example of an catalytic asymmetric transformation with Ni catalysts bearing a chiral diene ligand.[34] Furthermore, this example demonstrates that a coordination of olefins can have an important influence on the catalyst, as has been seen in the case of some phosphoramidite ligands bearing olefins as additional coordination sites (*vide supra*). Finally, it was shown that *N*-heterocyclic carbene (NHC) ligands can be successfully applied to this kind of transformation, as the reaction employing **L29**[35] gave **17** in 15% *ee* and with excellent diastereoselectivity (Table 6, entry 7). It has to be noted, though, that in the case of NHC ligands, $Ni(COD)_2$ has to be employed. Using $Ni(acac)_2$ as the Ni precursor in those cases lead to considerably lower conversion.

Table 6 Ligand screening II[a]



15 **16** **17** **20**

Entry	Ligand	Comment	***anti/syn***[b]	***ee***[b]
1	 **L23**	80% **20**	n.d.	**17:** rac.

Entry	**Ligand**		**Comment**	***anti/syn*[b]**	***ee*[b]**
2		**L24**	Slow reaction (2d)	18 : 1	+6%
3		**L25**	Low conversion, only **20**	-	-
4		**L26**	-	>99 : 1	+23%
5		**L27**	only **20**	-	-
6		**L28**	-	15 : 1	-15%
7[c]		**L29**	-	>99 : 1	+15%

[a] Reaction conditions: 0.50 mmol isoprene (**15**), 0.60 mmol benzaldehyde (**16**), 0.01 mmol Ni(acac)$_2$ and 0.011 mmol ligand were dissolved in 2.5 mL THF at rt. Then, 1.0 mmol of Zn*i*Pr$_2$ solution (c = 0.5 M in toluene) was added dropwise and the reaction mixture was stirred until TLC showed full conversion (~ 2h). The reaction was quenched with sat. aq. NH$_4$Cl solution, and the product isolated by extraction with Et$_2$O. [b] Determined by both, ^{1}H NMR and GC/MS. [c] Ni(COD)$_2$ was used instead of Ni(acac)$_2$.

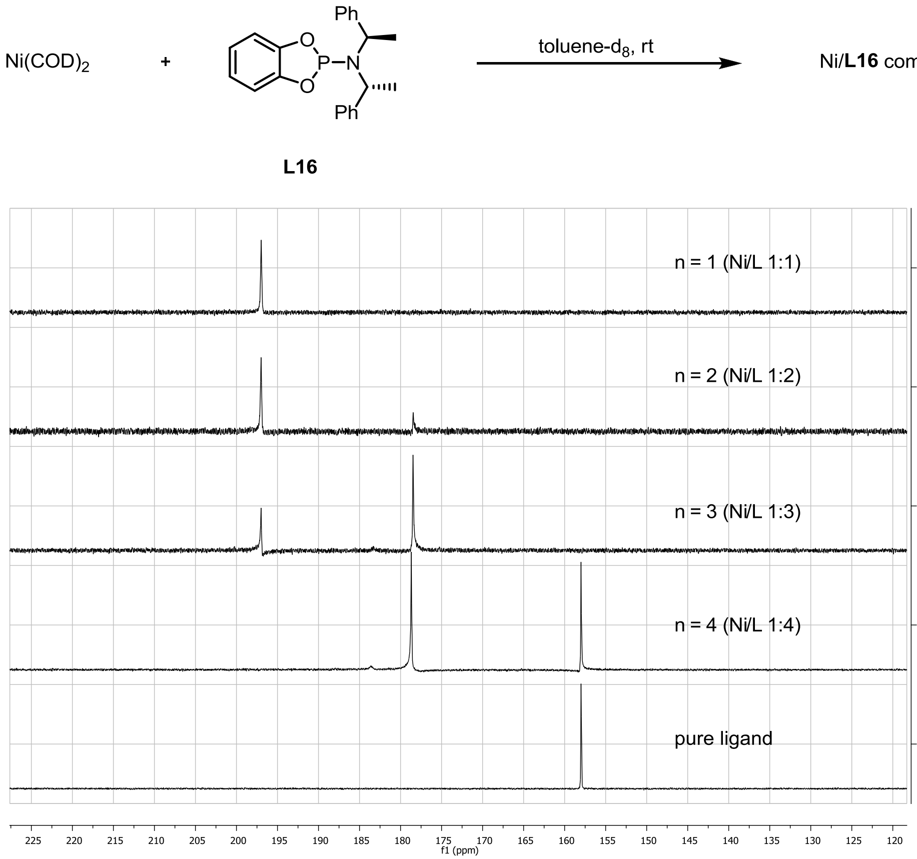
Summarizing the results of the ligand screening, we were able to demonstrate that a variety of chiral monodentate ligands as well as a chiral diene ligand can be successfully employed in the Ni-catalyzed reductive coupling reaction of isoprene with benzaldehyde. With some ligands excellent diastereoselectivities have been achieved, however, the *ee* of this transformation could not be improved to more than 46%.

3.6 Mechanistic studies

Since we found that generally in the Ni-catalyzed reductive coupling of isoprene with benzaldehyde only the use of monodentate ligands led to conversion to the desired coupling product, we decided to study the mechanism of this reaction using Ni/phosphoramidite complexes as a probe for NMR spectroscopy. We anticipated that we could employ ^{31}P NMR spectroscopy to study the reaction in more detail, which might give some support to the proposed mechanism (see Scheme 8).

We started off by carrying out a titration experiment, where various equivalents of catechol-based phosphoramidite **L16** were added to Ni(COD)$_2$ (Figure 1). We observed a fast coordination of **L16** to Ni(0) which was accompanied by a change of colour from bright yellow to orange. We observed that with Ni/L ratios of 1:1 and 1:2 a signal at 197 ppm in the ^{31}P NMR could be observed. When more equivalents of **L16** were added, a second peak at 179 ppm appeared. With an even larger excess of **L16**, the peak at 197 ppm disappeared and a new one became visible at 158 ppm. This can be attributed to the free ligand **L16**. We conclude from these results that more than one Ni/**L16** complex is formed, most probably with a different stoichiometry. The complex with the signal at 197 ppm should have a higher Ni/L ratio in comparison to the one having a signal at 179 ppm, since the latter appears at higher concentrations of **L16** and seems to have a higher number of ligands coordinated to Ni, as with higher concentrations of **L16** the uncoordinated ligand (at 158 ppm) starts to appear. This behaviour is similar to Ni/PPh$_3$ complexes.[36] It is important to note that the complex with a lower Ni/L ratio (at 179 ppm) seems to be symmetric with respect to the coordinating ligands, as only a singlet is observed. If the ligands would be inequivalent, one would expect a P-P coupling between the ligands,[37,38] which had been observed with other Ni/phosphoramidite complexes (*vide infra*).

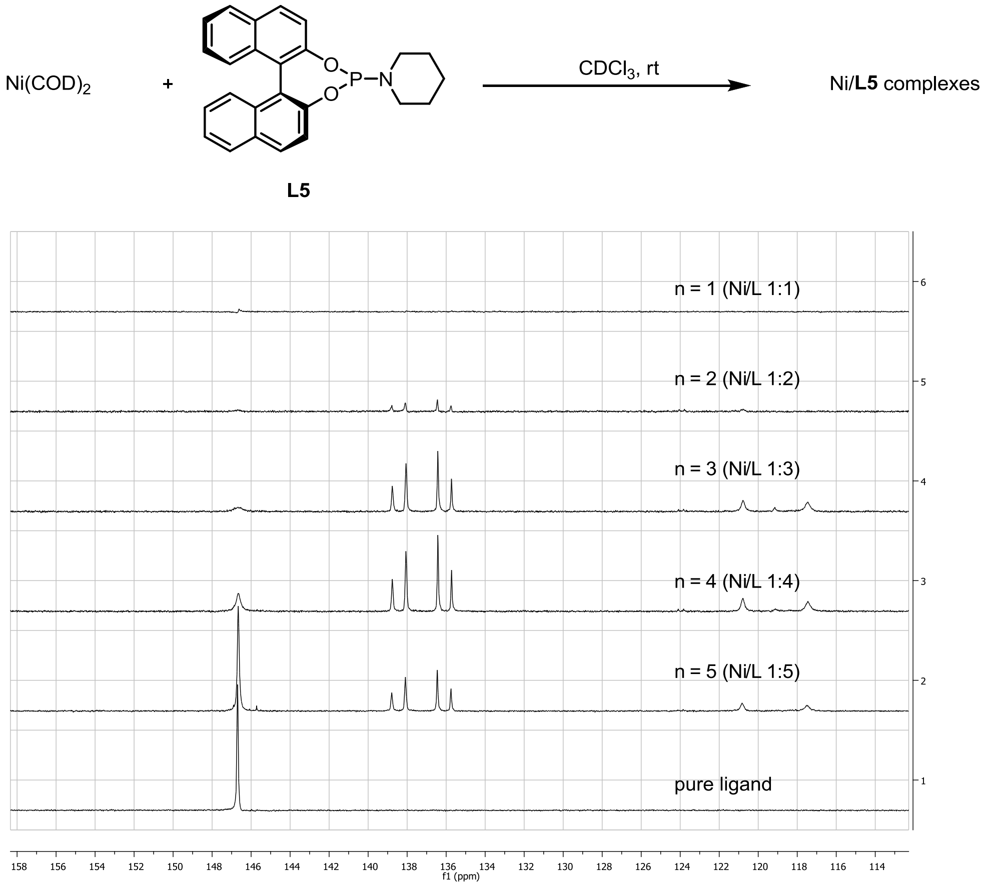
Figure 1 ^{31}P NMR of Ni/L6 complexes[a]



[a]Reaction conditions: 0.02 mmol Ni(COD)$_2$ and n eq. **L16** were dissolved in toluene-d$_8$ at rt and the solution stirred for 5 min. At every stage, samples were taken and analyzed by ^{31}P NMR.

When the complexation of Ni(COD)$_2$ with different equivalents of BINOL-derived **L5** in CDCl$_3$ was followed by ^{31}P NMR, different results were obtained (Figure 2). It should be noted that these experiments were carried out in CDCl$_3$ and therefore a different chemical shift in the ^{31}P NMR is observed. With 1 and 2 equivalents of **L5** with respect to Ni, the corresponding complexes seemed to have a low stability, as quick deposition of elementary Ni on the wall of the NMR tube was observed. When we went to higher equivalents of **L5**, the complexes seemed more stable, and could be detected by ^{31}P NMR. Two doublets with a roof effect (J = 115 Hz) were observed at 137 ppm, which can be interpreted as a Ni/L$_x$ complex with x ≥ 2, in which the ligands are not equivalent and therefore couple to each other. This is an often observed feature with phosphorus-chelating ligands and transition metals.[37-41] Again, when more **L5** was added, the signal of the free ligand (146 ppm) started to increase. When the spectra of Figure 1 and Figure 2 are compared, it can be seen that the structure of the phosphoramidite ligand has a remarkable effect on the symmetry of the corresponding complexes. This could be due to the fact that the BINOL backbone of **L5** is both, sterically more demanding and axially chiral, when compared to the catechol backbone of **L6**.

Figure 2 ^{31}P NMR of Ni/L5 complexes^{a}

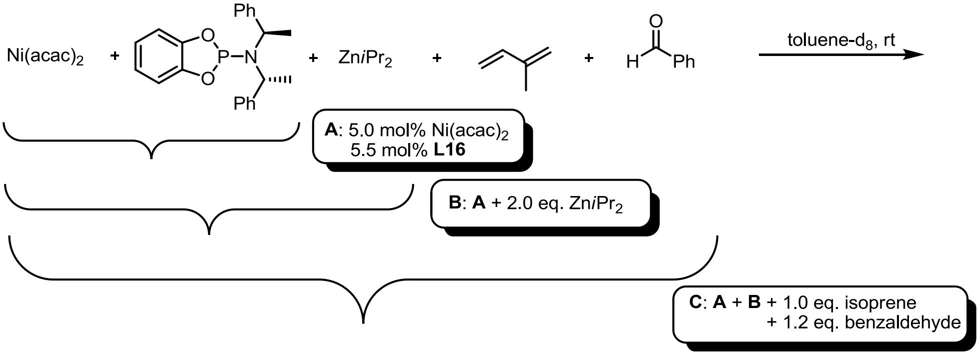


^{a}Reaction conditions: 0.05 mmol $Ni(COD)_2$ and n eq. 0.05 mmol **L5** were dissolved in $CDCl_3$ at rt and the solution stirred for 5 min. At every stage, samples were taken and analyzed by ^{31}P NMR.

Next, we turned our attention to following the Ni-catalyzed reductive coupling reaction of **15** with **16** under the optimized reaction conditions by ^{31}P NMR (Figure 3). The only change compared to the benchtop reaction that was made was the change of solvent to toluene-d_8. As expected, when the Ni(II) precursor, $Ni(acac)_2$, and **L16** were mixed we only observed the signal of the free ligand **L16** (158 ppm), and no Ni/**L16** coordination took place (A in Figure 3). When the reducing agent Zn*i*Pr$_2$ was added, two new species could be observed, at 179 and 177 ppm (B in Figure 3) with full consumption of uncoordinated **L16**. When finally the reagents were added and the reaction was run in the NMR tube, two resonances, at 179 and 158 ppm were observed (C in Figure 3). The latter can be attributed to the uncoordinated ligand. This result is somewhat surprising, as we have found a Ni/**L16** complex at 179 ppm with most probably more than one **L16** coordinated to Ni in previous experiments as well (compare Figure 1). From the optimization of the reaction, we know that a Ni/**L16** ratio of close to 1:1 is ideal for good selectivity towards the desired coupling product. One could speculate on the basis of these results that during the reaction a resting state exists in which the Ni is coordinated by more than one ligand **L16**.

Furthermore, we carried out the same experiment with Ni(COD)$_2$ as the Ni precursor (Figure 4), which had been shown to give the same results in terms of selectivity towards the coupling product (*vide supra*). In this case, we found the same results, except that already during the mixing of **L16** and Ni(COD)$_2$, two complexes with signals at 197 and 179 ppm were formed (A in Figure 4), which is consistent with our previous findings (see Figure 1). Interestingly, when both the reducing agent and the substrates were added (C in Figure 4), the same resting state at 179 ppm as in the case of Ni(acac)$_2$ was observed. This leads to the conclusion that both reactions have the same catalytic cycle with the same resting states, independent of the Ni precursor used. This has also been shown during the optimization of the reaction, as the same results in terms of product distribution and selectivity were found with both Ni(0) and Ni(II) precursors (see section 3.1). Therefore, the ligands of the Ni precursor (acac or COD) seem not to play a role during the reaction.

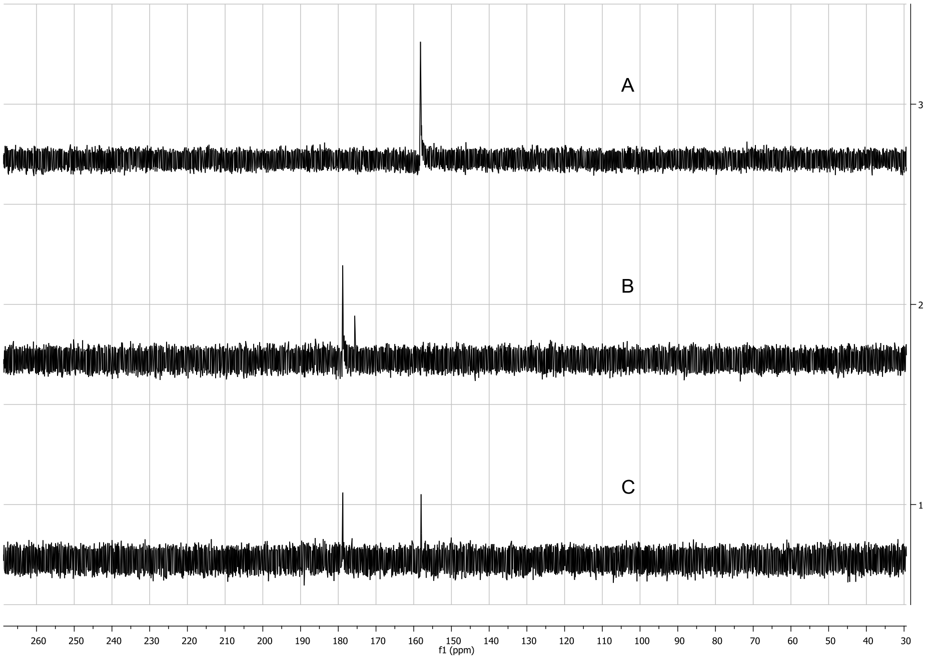
Figure 3 ^{31}P NMR of Ni-catalyzed reductive coupling reaction with L16[a]



A: 5.0 mol% Ni(acac)$_2$
5.5 mol% **L16**

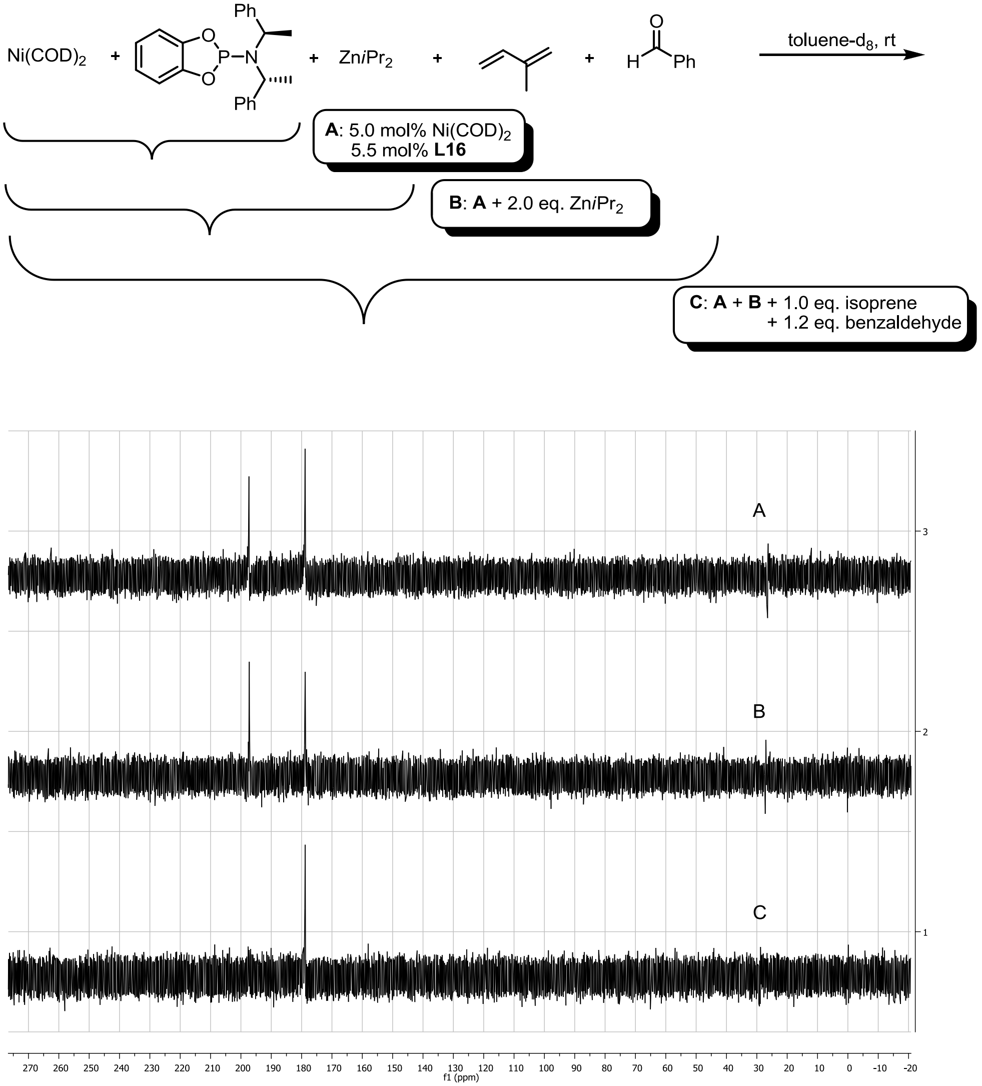
B: **A** + 2.0 eq. Zn*i*Pr$_2$

C: **A** + **B** + 1.0 eq. isoprene
+ 1.2 eq. benzaldehyde



[a] Reaction conditions: 0.01 mmol Ni(acac)$_2$ and 0.011 mmol **L16** were dissolved in toluene-d$_8$ at rt and the solution stirred for 5 min. (= **A**). Then, 2.0 eq. Zn*i*Pr$_2$ (0.40 mmol) was added (= **B**). 1.0 eq. isoprene (0.20 mmol) and 1.2 eq. benzaldehyde (0.24 mmol) were added (= **C**). At every stage, samples were taken and analyzed by ^{31}P NMR.

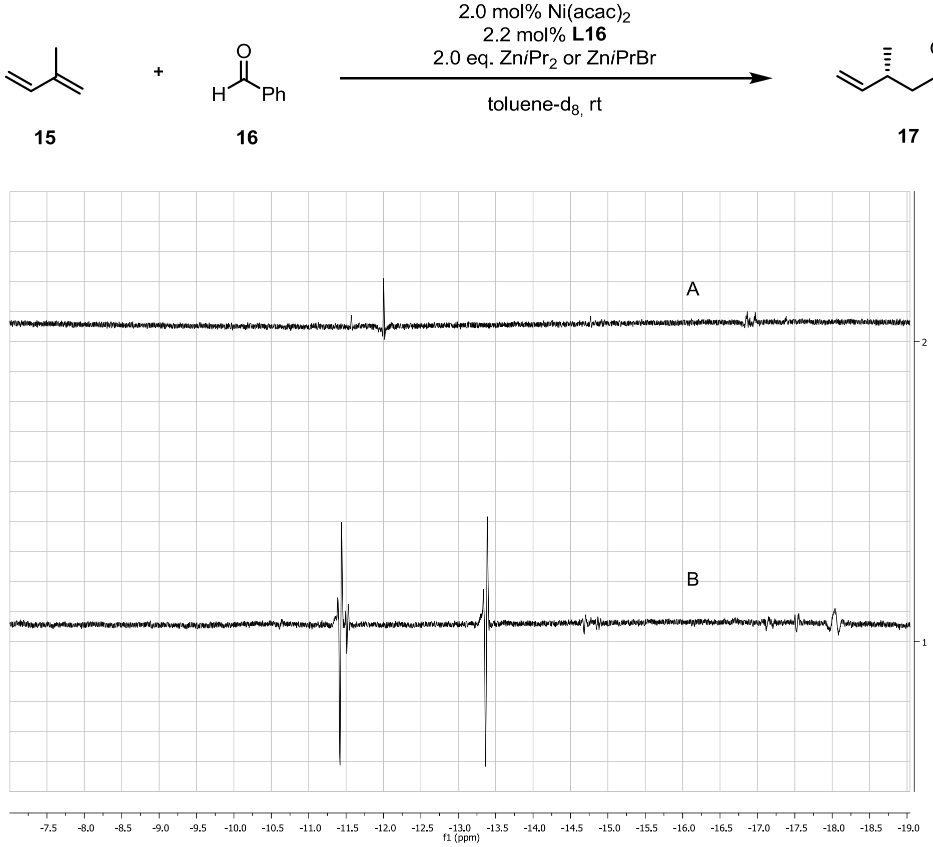
Figure 4 ^{31}P NMR of Ni-catalyzed reductive coupling reaction with L16[a]



[a]Reaction conditions: 0.01 mmol Ni(COD)$_2$ and 0.011 mmol **L16** were dissolved in toluene-d$_8$ at rt and the mixture stirred for 5 min. (= **A**). Then, 2.0 eq. Zn*i*Pr$_2$ (0.40 mmol) was added (= **B**). Subsequently, 1.0 eq. isoprene (0.20 mmol) and 1.2 eq. benzaldehyde (0.24 mmol) were added (= **C**). At every stage, samples were taken and analyzed by ^{31}P NMR.

Besides following the reaction with ^{31}P NMR, we also used ^{1}H NMR for the investigation of the Ni-catalyzed reductive coupling. As in the proposed mechanism for this reaction (Scheme 8), nickel-hydride intermediates were postulated, we were interested in observing those by ^{1}H NMR (Figure 5). Indeed, we were able to observe resonances at around -12 ppm, which is typical for Ni-hydrides.[42-44] Employing Zn*i*Pr$_2$ as the reducing agent, a resonance was observed at -12.0 ppm (A in Figure 5), whereas two signals at -11.5 and -13.5 ppm were found employing Zn*i*PrBr as the reducing agent (B in Figure 5). In the benchtop experiment, it was found that Zn*i*PrBr gave both *syn* and *anti* diastereomers of the product in a 1:1 ratio, whereas Zn*i*Pr$_2$ gave the *anti* coupling product in about 20:1 selectivity (compare Table 1). Therefore, we assign the two signals in B to two diastereomeric Ni-H complexes leading to *syn*-**17** and *anti*-**17**, and the signal in A to an intermediate Ni-H complex leading to *anti*-**17**.

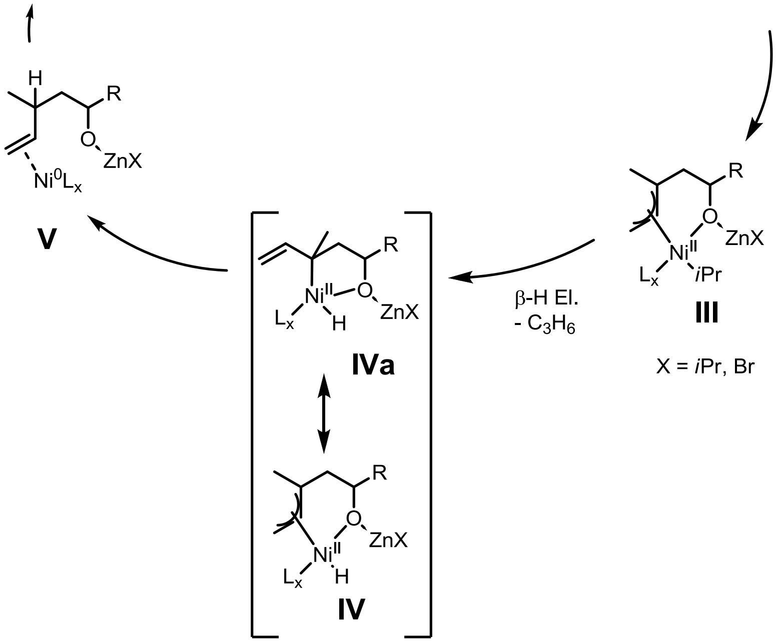
Figure 5 ^{1}H NMR of Ni-catalyzed reductive coupling reaction with L16 ^{a}



15 **16** **17**

^{a}Reaction conditions: 0.01 mmol Ni(acac)$_2$ and 0.011 mmol **L16** were dissolved in toluene-d$_8$ at rt and the mixture stirred for 5 min. Then, 2.0 eq. Zn*i*Pr$_2$ (= **A**) or Zn*i*PrBr (= **B**) (0.40 mmol) was added. Subsequently, 1.0 eq. isoprene (0.20 mmol) and 1.2 eq. benzaldehyde (0.24 mmol) were added.

The observation of nickel-hydride complexes as reaction intermediates in the Ni-catalyzed reductive coupling reaction gives some evidence for the proposed mechanism (Scheme 9). To the best of our knowledge, no further study has been carried out so far to support this mechanism. Based on our detection of intermediate nickel-hydride complexes, we suggest that the mechanism does go via a nickel-hydride intermediate (such as **IV** in Scheme 9). However, since we observed two diastereomeric Ni-H complexes with Zn*i*PrBr, and only one with Zn*i*Pr_2 as the reducing agent, we suggest to adapt the scheme providing the reaction intermediates: since previously drawn intermediate **IV** shows a π-Ni-oxallyl compound that has no specified stereochemistry at the second stereocenter, **IV** should be replaced by the σ-Ni-oxallyl complex **IVa**. Complex **IVa** represents a resonance structure of **IV**, but displays the stereogenic center bearing the methyl group. Therefore, the *syn* and *anti* diastereomers of **IVa** should posess different chemical shifts in ^{1}H NMR.



Scheme 9 Some intermediates from the proposed mechanism

To further gain some insight in the catalytic intermediates of the Ni-catalyzed reductive coupling of isoprene and benzaldehyde, we carried out high resolution mass spectrometry (ESI-TOF) of the reaction mixture. However, no conclusive data could be obtained. We attribute this to the fact that the reaction intermediates as shown in Scheme 3 and Scheme 9 are not charged particles and therefore need to be ionized first. Most probably the intermediate Ni-complexes fragment during ionization and therefore cannot give any further evidence with regards to the catalytic cycle.

4. Conclusions and Future Prospects

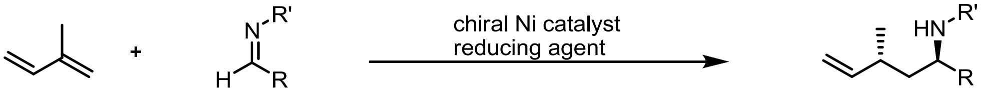
In conclusion, we have developed a new asymmetric Ni-catalyzed reductive coupling reaction of isoprene and benzaldehyde. We were able to demonstrate that a variety of chiral Ni complexes could catalyze this transformation, and that monodentate phosphorus-based ligands were beneficial for conversion to the desired products. In an extensive screening of phosphoramidite ligands we were able to identify some leading ligand structures, however, the maximal enantioselectivity in the envisaged reaction remained at 46% *ee* with **L16**. It should be noted though that unprecedented levels of diastereoselectivity favouring the *anti* product were achieved with some ligands, including *N*-heterocyclic carbene (NHC) ligands. Furthermore, the use of phosphoramidite and NHC ligands allowed for lowering the catalyst loading to 2 mol%.

Furthermore, it was shown that phosphoramidites bearing a second labile coordination moiety generally showed good results with regards to stereoselectivity. Along the same lines, it was shown that chiral diene ligands lead to effective Ni catalysts for the envisaged reductive coupling reaction. These findings could serve as a starting point for a more sophisticated ligand design. The nature of the reducing agent was also shown to be highly influencial on the outcome of the reaction, as the employment of dialkylzinc reagents was found to be beneficial in terms of product selectivity and stereoselectivity.

Based on Ni/phosphoramidite complexes, mechanistic studies showed that the reactions with different Ni precursors run via the same reaction intermediates or resting states, an observation consistent with our experimental findings. Second, ^{1}H NMR analysis of the reactions gave evidence for the presence of Ni-hydride species that had previously been postulated. We were able to produce evidence for a postulated nickel-hydride catalytic intermediate by means of ^{1}H NMR spectroscopy.

A good starting point for future research would be the investigation of chiral NHC ligands for the Ni-catalyzed reductive coupling reaction. It was demonstrated that these ligands lead to some *ee* in the coupling product in our case. Many applications of chiral NHC complexes have been reported in the literature,[45-49] leaving much room for further investigation and optimization of the Ni-catalyzed reductive coupling reactions with these chiral complexes.

As for the reaction itself, a further extension could be the study of the reductive coupling reaction of isoprene (**15**) to imines **25** or related structures (Scheme 10). Since it is expected that the intermediate amines would coordinate well to the Ni-catalyst during the reaction, this could lead to higher enantioselectivity. The non-enantioselective variant has been reported in the literature, demonstrating that in principle Ni catalysts are able to catalyze these transformations.[50] Chiral secondary amines **26** with a 1,3-chiral motif could be valuable chiral building blocks for further functionalization.



15 **25** **26**

Scheme 10 Suggested reductive coupling of isoprene with imines

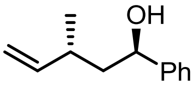
5. Experimental Section

For general remarks, see Chapter 3. Ligands were prepared according to the literature procedures: **L3**[51], **L4**[52], **L5**[53], **L6**[54], **L7**[55], **L8**[55], **L9**[55], **L10**[56], **L11**[56], **L12**[57], **L13**[53], **L14**[26], **L15**[58], **L16**[59], **L17**[59], **L18**[53], **L19**[60], **L20**[29], **L21**[30], **L22**[30], **L23**[61], **L26**[31], **L27**[32], **L29**[35]. **L28** was purchased from Sigma-Aldrich. **L24** and **L25** were kindly donated by DSM.

Ni-catalyzed reductive coupling reaction of isoprene and benzaldehyde

In a flame-dried Schlenck tube, 2.0 mol% Ni(acac)$_2$ (2.59 mg, 10.0 µmol) and 2.1 mol% **L16** (3.82 mg, 10.5 µmol) were dissolved in 2.5 mL dry toluene. Then, 1.00 eq. isoprene (**15**) (0.050 ml, 0.50 mmol) and benzaldehyde (**16**) (0.061 ml, 0.600 mmol) were added. Subsequently, 2.00 eq. diisopropylzinc solution (c = 0.5 M in toluene) (1.0 ml, 1.0 mmol) was added slowly. The colour changed from pale green via yellow to orange/red. The reaction mixture was stirred at room temperature for 2h (or until TLC and/or GC/MS showed full conversion). The reaction mixture was quenched with a sat. aq. solution of NH$_4$Cl (5 mL) and extracted with EtOAc (3x 10 mL). The combined organic phases were dried over MgSO$_4$ and all volatiles were removed *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO$_2$, pentane / EtOAc 40:1, R_f = 0.60 in Pentane / EtOAc 10:1) to yield **17** (0.085 g, 0.480 mmol, 96%) as a colorless oil. The ligand screening described in Table 5 was carried out with half of the amounts given using stock solutions for $Ni(acac)_2$, Isoprene and Benzaldehyde in toluene.

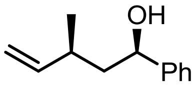
***Anti*-3-methyl-1-phenylpent-4-en-1-ol (17)**



***anti*-17**

^{1}H NMR (201 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 5H), 5.79 (ddd, *J* = 17.8, 10.2, 7.8 Hz, 1H), 5.09 – 4.91 (m, 2H), 4.73 (t, *J* = 6.8 Hz, 1H), 2.23 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.97 (s (br), 1H), 1.95 – 1.77 (m, 1H), 1.67 (dt, *J* = 13.4, 4.8 Hz, 2H), 1.04 (d, *J* = 6.7, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.67, 144.54, 128.46, 127.58, 126.01, 113.24, 73.04, 45.92, 35.18, 20.46. The enantiomeric excess was determined by chiral GC or chiral HPLC. GC: CP-Chiralsil-Dex-CB (25m x 0.25 mm), 95 °C isotherm. Retention times 61.5 min and 62.8 min. HPLC: (Chiralpak OD-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 200 nm), retention times: 30.8 min, 34.6 min. GC/MS: 158 (17%), 143 (80%), 128 (73%), 120 (33%), 115 (33%), 107 (100%), 91 (23%), 79 (60%).

***Syn*-3-methyl-1-phenylpent-4-en-1-ol (17)**



syn-17

Isolated from the reaction with Zn*i*PrBr as reducing agent (0.031 g, 0.175 mmol, 35%) as a colorless oil. Purification by column chromatography (SiO_2, pentane / EtOAc 40:1, Rf = 0.65 in pentane / EtOAc 10:1) gave **17** as a colorless oil. ^{1}H NMR (201 MHz, $CDCl_3$) δ 7.47 – 7.19 (m, 5H), 5.93 – 5.61 (m, 1H), 5.21 – 4.94 (m, 2H), 4.72 (dd, *J* = 9.2, 3.9 Hz, 1H), 2.55 – 2.28 (m, 1H), 1.87 (s (br), 1H), 1.86 – 1.71 (m, 1H), 1.60 (ddd, *J* = 13.7, 9.5, 4.0 Hz, 2H), 1.05 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.11, 143.84, 128.45, 127.42, 125.70, 113.70, 72.32, 46.03, 34.87, 20.93. The enantiomeric excess was determined by chiral GC: CP-Chiralsil-Dex-CB (25m x 0.25 mm), 95 °C isotherm. Retention times 57.6 min and 61.6 min. GC/MS: 158 (19%), 143 (80%), 128 (82%), 120 (45%), 115 (41%), 107 (100%), 91 (24%), 79 (72%).

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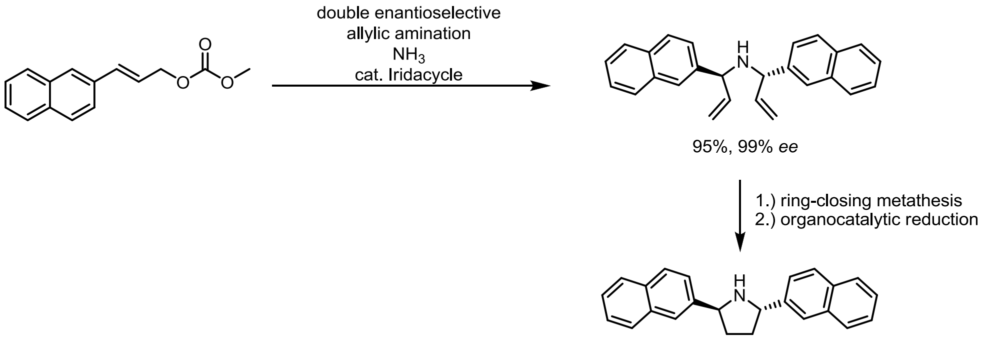
English Summary

Heterocycles are ubiquitous structural features of naturally occurring and/or biologically active chemical compounds. Among these, nitrogen- and oxygen-containing heterocycles with various ring sizes bearing stereogenic centers are frequently observed. The selective construction of these stereogenic centers imposes a particular challenge for chemists.

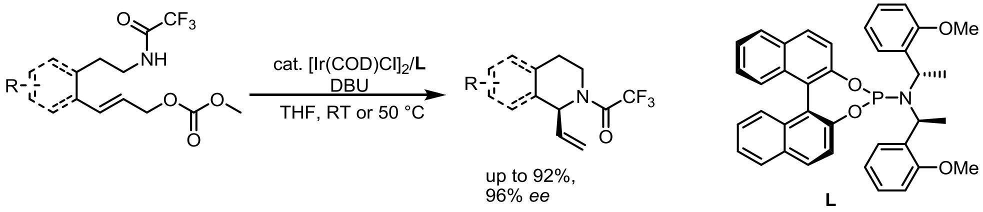
In this work, a variety of synthetic approaches towards nitrogen- and oxygen-containing heterocycles have been developed. All methods developed rely on asymmetric transition metal catalysis. These methodologies bear the advantage that both enantiomers of an envisaged product are accessible, since - in most cases - both enantiomers of the chiral catalysts are available. Literature-known asymmetric transformations have been applied to new targets to open up new routes to chiral heterocyclic compounds, but also new methodologies have been developed. In general, the approaches investigated during this work fall into three different categories:

1) The installation of the stereocenter of interest on a linear substrate followed by the construction of the ring through a later transformation (*e.g.* ring-closing metathesis). (see Chapters 2, 5)
2) An asymmetric ring-closing reaction is carried out, which furnishes both the stereocenter and the ring structure in the same transformation. (see Chapters 3, 4)
3) A catalytic asymmetric reaction on a prochiral heterocyclic structure is carried out. (see Chapter 6)

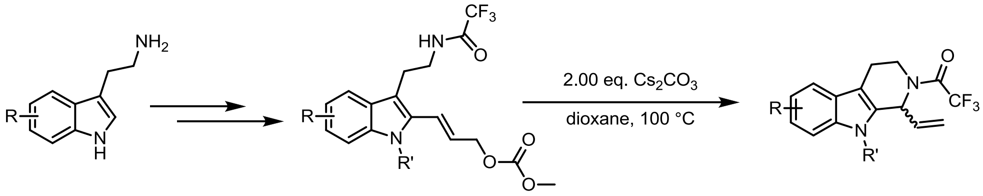
In Chapter 2, the application of iridium-catalyzed allylic amination of allylic carbonates with ammonia has been used to construct 2,5-arylpyrrolidines. These products are used as chiral auxiliaries, organocatalysts and as key structural motifs of phosphoramidite ligands. Ammonia as nitrogen source is a cheap, atom-economic nucleophile. In the course of the reaction, a double allylic amination takes place, as the first addition product, a primary amine, is much more reactive than ammonia and directly undergoes a subsequent reaction with another allylic carbonate molecule. This particular reaction pathway is exploited, as the resulting chiral secondary amine - available in excellent yields and stereoselectivities - can be further transformed to a pyrroline by ring-closing metathesis. The desired products are obtained by a mild and selective organocatalytic reduction with a flavin-derived catalyst. During the course of this research, the latter catalytic transformation has been optimized and a new reaction protocol was developed.


double enantioselective
allylic amination
NH3
cat. Iridacycle
95%, 99% ee
1.) ring-closing metathesis
2.) organocatalytic reduction

Chapter 3 marks one of the highlights of the present work. It describes the development of the first intramolecular asymmetric Ir-catalyzed allylic amidation. This methodology employs chiral Ir/phosphoramidite complexes and exploits the use of the trifluoroacetamide group both as a protecting group in the preparation of the allylic carbonates as well as nucleophiles for the key asymmetric Ir-catalyzed reaction. This transformation furnishes chiral tetrahydroisoquinolines and saturated nitrogen heterocyclic compounds in a highly stereoselective fashion. The products are useful building blocks, as they can easily be modified through the terminal olefin, which has been demonstrated in two attempted syntheses of a naturally occurring compound, Crispine A, as well as a biologically active compound, Almorexant.

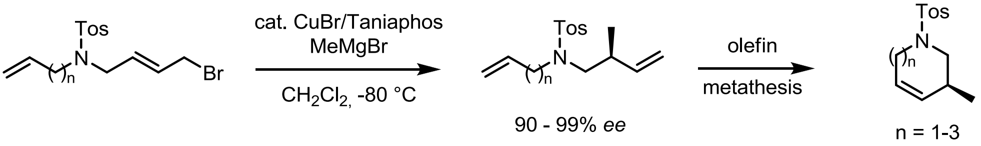

cat. [Ir(COD)Cl]2/L
DBU
THF, RT or 50 °C
up to 92%,
96% ee
L

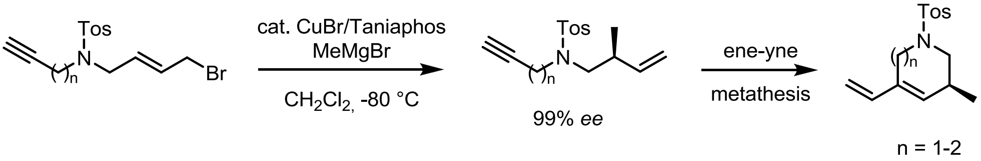
The attempted extension of allylic amidation methodology to the preparation of chiral β-carboline compounds is described in chapter 4. Even though ultimately the desired transformation could not be rendered feasible, a number of synthetic approaches to substituted indole compounds are presented. These investigations gave important insights that influenced the development of the asymmetric allylic amidation presented in chapter 3. Finally, the desired products could be prepared in a racemic fashion via a non-catalyzed pathway.


2.00 eq. Cs2CO3
dioxane, 100 °C

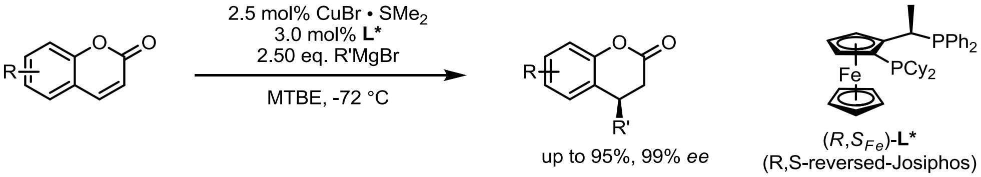
In Chapter 5, the development of a new entry to nitrogen heterocycles with various ring sizes is presented. Here, a similar approach to the one in chapter 2 is followed.

An allylic substitution reaction furnishes a stereogenic center and a terminal double bond of which the latter is subsequently employed for the construction of a heterocycle through a metathesis reaction. By combining copper-catalyzed allylic substitution reactions with Grignard reagents with a subsequent olefin or ene-yne ring-closing metathesis the corresponding chiral products are available in excellent stereoselectivities. One advantage of this variable approach is that six- to eight-membered heterocycles become available. The products from the ene-yne metathesis bear a diene motif, which is perfectly suited for further modifications. It has been demonstrated that his methodology can been extended to the construction of chiral lactams, however, some more investigations are needed to improve yields and enantioselectivities.

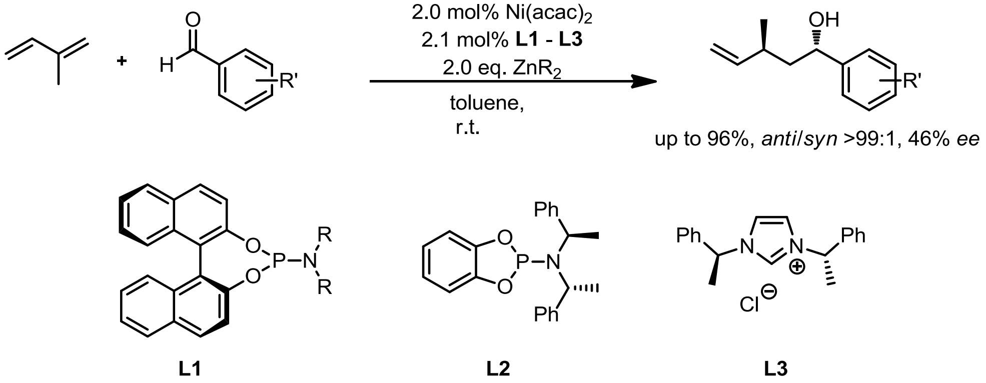

Tos
N
n
Br
cat. CuBr/Taniaphos
MeMgBr
CH2Cl2, -80 °C
Tos
N
n
90 - 99% ee
olefin
metathesis
Tos
N
n
n = 1-3


Tos
N
n
Br
cat. CuBr/Taniaphos
MeMgBr
CH2Cl2, -80 °C
Tos
N
n
99% ee
ene-yne
metathesis
Tos
N
n
n = 1-2

In Chapter 6, another approach to chiral heterocycles is taken, as in this case the starting materials already possess a heterocycle: the development of an asymmetric copper-catalyzed conjugate addition reaction of Grignard reagents to coumarins is presented. These substrates had been elusive for this particular catalytic transformation, since they are relatively unreactive towards Michael addition. However, through judicious choice of ligands, the corresponding chiral lactones are accessible in excellent stereoselectivities. One important feature of this transformation was discovered in the course of the investigations: the intermediate chiral magnesium enolates can be trapped with amines or alcohols to give the ring-opened phenol-derived chiral esters and amides. On the one hand, these particular chiral esters were previously not accessible, on the other hand, this marks the development of a new formal asymmetric conjugate addition to amides.


R
O
O
2.5 mol% CuBr • SMe2
3.0 mol% L*
2.50 eq. R'MgBr
MTBE, -72 °C
R
O
O
R'
up to 95%, 99% ee
PPh2
PCy2
Fe
(R,SFe)-L*
(R,S-reversed-Josiphos)

The research described in chapter 7 was directed towards the development of an asymmetric nickel-catalyzed reductive coupling of dienes with aldehydes yielding chiral bis-homoallylic alcohols. One of the major advantages of this reaction is that it generates two stereocenters in one catalytic transformation. The chiral products are highly functional and perfectly suited for further modification through their terminal olefin, the alcohol and the aromatic group. It was found that chiral nickel complexes with monodentate phosphoramidite or *N*-heterocyclic carbene ligands lead to the desired products in unprecedented diastereoselectivity, but with only moderate enantioselectivity. ^{1}H NMR and ^{31}P NMR studies were carried out to provide some evidence for the postulated reaction mechanism via nickel-hydride complexes.


O
H
R'
+
2.0 mol% Ni(acac)$_2$
2.1 mol% **L1** - **L3**
2.0 eq. ZnR$_2$
toluene,
r.t.
OH
R'
up to 96%, *anti*/*syn* >99:1, 46% *ee*
O
P
N
R
R
Ph
Ph
Cl
L1
L2
L3

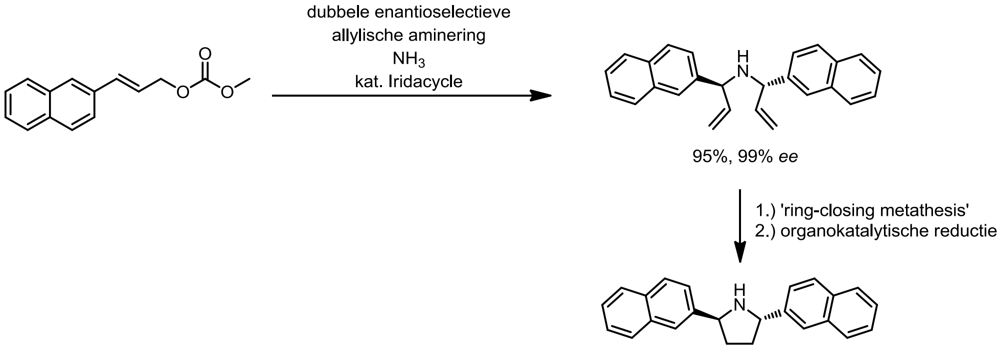
Nederlandse Samenvatting

Heterocyclische substructuren zijn in een groot aantal in de natuur voorkomende en/of biologisch actieve chemische stoffen te vinden. In de natuur komt men vaak stik- en zuurstof bevattende heterocycli van verschillende ring groottes tegen die een stereocentrum in de ring hebben. Vooral het selectief maken van deze stereocentra in heterocycli is een grote uitdaging voor chemici.

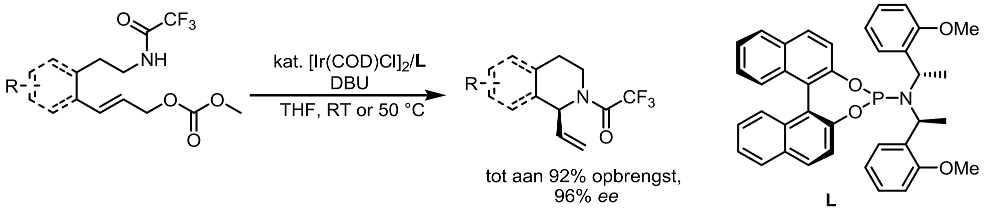
In dit proefschrift wordt de ontwikkeling van een verscheidenheid aan synthetische methoden beschreven die het mogelijk maken stik- en zuurstof bevattende heterocycli te synthetiseren. Asymmetrische katalyse, gebruik makend van overgangsmetalen, wordt in de hier beschreven methoden gebruikt voor het vormen van het gewenste stereocentrum. Een attractief aspect van de nieuw ontwikkelde methoden is dat via deze nieuwe methoden beide enantiomeren van het product gesynthetiseerd kunnen worden, aangezien -in de meeste gevallen- beide enantiomeren van de chirale katalysatoren beschikbaar zijn. Naast het toepassen van in de literatuur bekende asymmetrische transformaties op nieuwe uitgangsstoffen, om op deze manier nieuwe routes te ontwikkelen voor de synthese van chirale heterocyclische stoffen, zijn in dit proefschrift ook nieuwe methoden ontwikkeld voor het synthetiseren van deze klasse van verbindingen. De beschreven methoden kunnen worden onderverdeeld in drie categoriën:

1) Eerst wordt een stereocentrum in een lineair substraat geintroduceerd, waarna in een opvolgende reactie de ring gevormd wordt (bijvoorbeeld via ‘ring-closing metathesis’). (Zie hoofdstukken 2 en 5)
2) Een asymmetrische ring-sluitende reactie wordt uitgevoerd om én het stereocentrum én de ring structuur te vormen in een enkele transformatie. (Zie hoofdstukken 3 en 4)
3) Een katalytische asymmetrische reactie wordt uitgevoerd op een prochiraal heterocyclisch substraat. (Zie hoofdstuk 6)

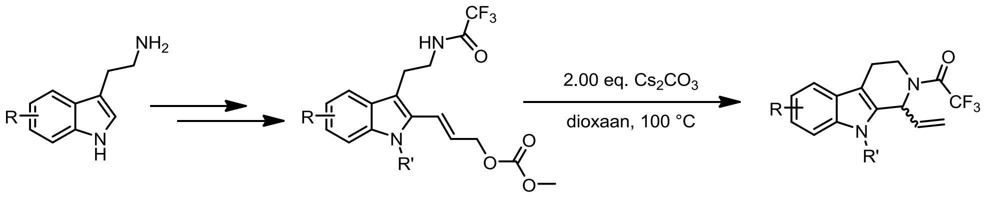
In hoofdstuk 2 wordt iridium-gekatalyseerde allylische aminering van allylische carbonaten met ammonium als nucleofiel gebruikt om 2,5-arylpyrrolidines te synthetiseren. De gevormde producten worden gebruikt als chirale ‘auxiliaries’, als organokatalysatoren en als de belangrijkste structuureenheid van verscheidene fosforamidiet liganden. Het gebruik van ammonium als stikstof nucleofiel is én kostenefficiënt én atoom efficiënt. Tijdens de reactie vindt een dubbele aminering plaats waarbij als eerste additieproduct een primair amine gevormd wordt. Dit primaire amine is veel reactiever dan ammonium en voert direct de volgende additie uit aan een ander allylisch carbonaat molecuul. Deze specifieke manier van synthese wordt gebruikt omdat het aldus gevormde chirale secondaire amine -dat wordt verkregen met excellente opbrengst en selectiviteit- via een ‘ring-closing metathesis’ kan worden omgezet naar het pyrroline. Het gewenste eindproduct wordt vervolgens verkregen door het gebruik van een milde en selectieve organocatalytische reductie met een katalysator wiens structuur gebaseerd is op flavine. Tijdens het hier beschreven onderzoek werd de laatstgenoemde gekatalyseerde transformatie geoptimaliseerd en werd er voor deze omzetting een nieuw reactieprotocol ontwikkeld.


dubbele enantioselectieve
allylische aminering
NH3
kat. Iridacycle
95%, 99% ee
1.) 'ring-closing metathesis'
2.) organokatalytische reductie

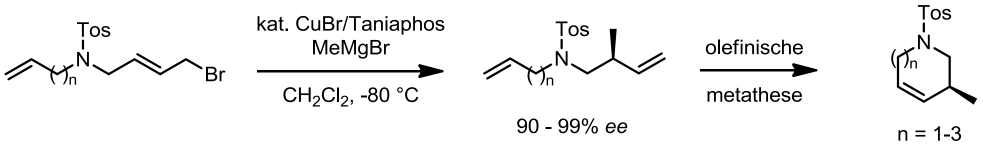
Hoofdstuk 3 is een van de hoogtepunten van het hier beschreven werk. In dit hoofdstuk wordt de ontwikkeling van de eerste intramoleculaire asymmetrische Ir-gekatalyseerde allylische amidering beschreven. Voor deze transformatie worden chirale Ir/fosforamidiet complexen gebruikt als katalysator. Verder wordt de trifluoroacetamide groep gebruikt als beschermgroep én als nucleofiel voor de asymmetrische Ir-gekatalyseerde reactie. De ontwikkelde transformatie vormt chirale tetrahydroisoquinolines en verzadigde stikstof-bevattende heterocyclische verbindingen met uitstekende stereoselectiviteit. De producten zijn bruikbare chemische bouwstenen en kunnen bovendien makkelijk verder worden gefunctionaliseerd door het omzetten van het eindstandige olefine. De vele mogelijkheden voor het gebruik van deze producten wordt geillustreerd door twee, ondernomen maar niet voltooide, syntheseroutes van een in de natuur voorkomende stof, crispine A, en de synthese van een biologisch actieve stof, Almorexant.

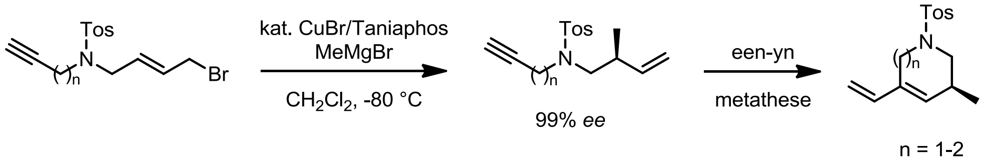


Pogingen tot het gebruik van de ontwikkelde allylische amiderings methodologie voor de vorming van β-carboline verbindingen worden beschreven in hoofdstuk 4. Ondanks dat het uiteindelijke doel, een asymmetrische formatie van de gewenste verbindingen, niet haalbaar bleek, worden toch een aantal syntheseroutes voor het vormen van indol verbindingen beschreven. De studies naar de asymmetrische transformatie hebben ook tot belangrijke inzichten geleid die het mogelijk maakten om de asymmetrische allylische amidering te ontwikkelen die is beschreven in hoofdstuk 3. Uiteindelijk is het ook gelukt om de gewenste produkten racemisch te synthetiseren via een niet-gekatalyseerde route.



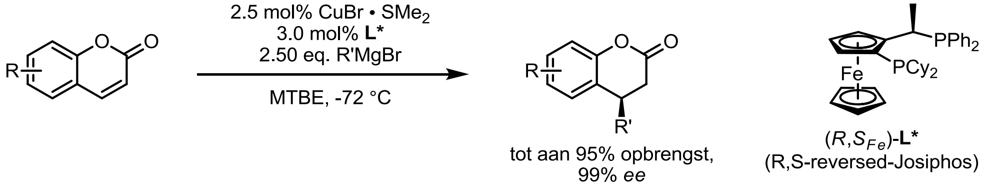
In hoofdstuk 5 wordt een nieuwe route voor het synthetiseren van stikstof heterocycli gepresenteerd. Voor deze nieuwe route wordt een aanpak gebruikt die erg lijkt op de aanpak beschreven in hoofdstuk 2. Een allylische substitutie reactie geeft een stereogeen centrum én een eindstandige dubbele binding, waarna het gevormde olefine wordt gebruikt om een heterocyclisch product te vormen door middel van een metathese reactie. Door de koper-gekatalyseerde allylische substitutie reactie met Grignard reagentia te combineren met een opeenvolgende olefinische of een-yn ‘ring-closing metathesis’ worden de overeenkomstige chirale producten verkregen met excellente stereoselectiviteit. Een voordeel van de modulaire aanpak is dat heterocycli met een grootte van zes tot acht atomen gevormd kunnen worden. Verder kunnen de gevormde producten van de een-yn metatheses, die een dieen functionele groep bezitten, makkelijk verder worden gefunctionaliseerd. Ook wordt gedemonstreerd dat deze methodologie kan worden gebruikt om chirale lactamen te vormen, wel moet door verder onderzoek de opbrengsten en selectiviteiten van de laatst genoemde reacties worden verbeterd.



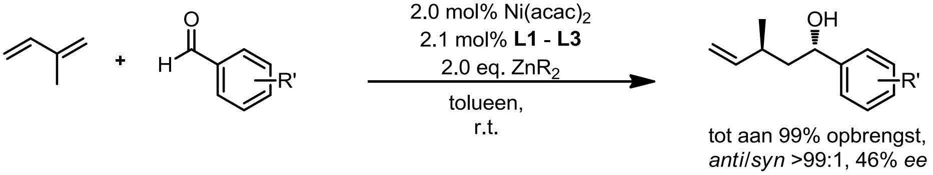


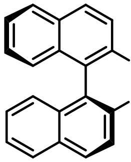
In hoofdstuk 6 wordt gebruik gemaakt van een andere aanpak om chirale heterocycli te vormen. In dit hoofdstuk wordt beschreven hoe door middel van een koper-gekatalyseerde asymmetrische geconjugeerde additie reactie van Grignard reagentia aan coumarines, waarbij het substraat dus al een heterocyclus is, chirale heterocycli gevormd worden. De gekozen substraten werden nog niet gebruikt voor dit soort katalytische transformaties aangezien de coumarines een relatief lage reactiviteit als Michael acceptor hebben. Door het kiezen van de juiste katalysator kunnen de overeenkomstige chirale lactonen worden verkegen met excellente stereoselectiviteit. Een belangrijke eigenschap van deze transformatie werd ontdekt tijdens dit onderzoek: het chirale magnesium enolaat, dat gevormd wordt als intermediair, kan in-situ verder reageren met alcoholen of amines tot ring geopende chirale phenol esters en amides. Voor deze specifieke ring geopende chirale esters bestond nog geen syntheseroute voordat dit onderzoek plaatsvond.

Verder betekend de ring-opening door amines de eerste in literatuur beschreven formele asymmetrische geconjugeerde additie aan amides.

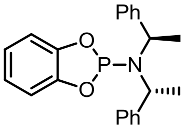

2.5 mol% CuBr • SMe2
3.0 mol% L*
2.50 eq. R'MgBr
MTBE, -72 °C
R
O
O
R'
tot aan 95% opbrengst, 99% ee
PPh2
PCy2
Fe
(R,SFe)-L*
(R,S-reversed-Josiphos)

Het onderzoek dat beschreven wordt in hoofdstuk 7 was gericht op het ontwikkelen van een asymmetrische nikkel-gekatalyseerde reductieve koppeling van diënen met aldehyden dat zou moeten leiden tot chirale bis-homoallylische alcoholen. Een van de grote voordelen van deze reactie is dat twee stereocentra in één gekatalyseerde transformatie gevormd worden. De chirale producten zijn verscheidende malen gefunctionaliseerd en uitstekend geschikt voor verdere modificatie via het eindstandige olefine, het alcohol en de aromatische groep. Het werd ontdekt dat de chirale nikkel complexen met monodentaat fosforamidiet of *N*-heterocyclische carbeen liganden leiden tot het gewenste product met een nog nooit vertoonde hoge diastereoselectiveit, maar met slechts middelmatige enantioselectiveit. ^{1}H NMR en ^{31}P NMR studies werden uitgevoerd om bewijs voor het gepostuleerde mechanisme via nikkel-hydride complexen te verkrijgen.

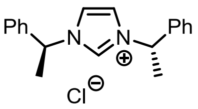

+
O
H
R'
2.0 mol% Ni(acac)2
2.1 mol% L1 - L3
2.0 eq. ZnR2
tolueen,
r.t.
OH
R'
tot aan 99% opbrengst,
anti/syn >99:1, 46% ee



L1



L2



L3

Deutsche Zusammenfassung

Heterozyklische Strukturelemente sind in einer großen Anzahl in natürlich vorkommenden und/oder biologisch aktiven Substanzen zu finden. Darunter finden sich häufig stickstoff- oder sauerstoffhaltige Ringsysteme variabler Größe mit Stereozentren. Der selektive Aufbau letzterer stellt eine Herausforderung für die organische Synthese dar.

In der vorliegenden Arbeit ist die Entwicklung synthetischer Routen zur Konstruktion stickstoff- und sauerstoffhaltiger chiraler Heterozyklen beschrieben. Alle angewandten Synthesestrategien greifen auf die asymmetrische Katalyse mit Übergangsmetallen zurück. Dies ermöglicht den selektiven Aufbau beider Enantiomere des gewünschten Stereozentrums, da in den hier diskutierten Fällen beide Enantiomere des jeweils verwendeten chiralen Liganden erhältlich sind. Dies stellt einen deutlichen Vorteil gegenüber anderen asymmetrischen Synthesemethoden, wie z.B. des Rückgriffs auf den “chiral pool” dar. In dieser Arbeit wurden sowohl literaturbekannte Synthesemethoden auf neue Substrate angewendet als auch neue Methoden für die Synthese von heterozyklischen Verbindungen entwickelt. Die Synthesewege lassen sich in drei Kategorien klassifizieren:

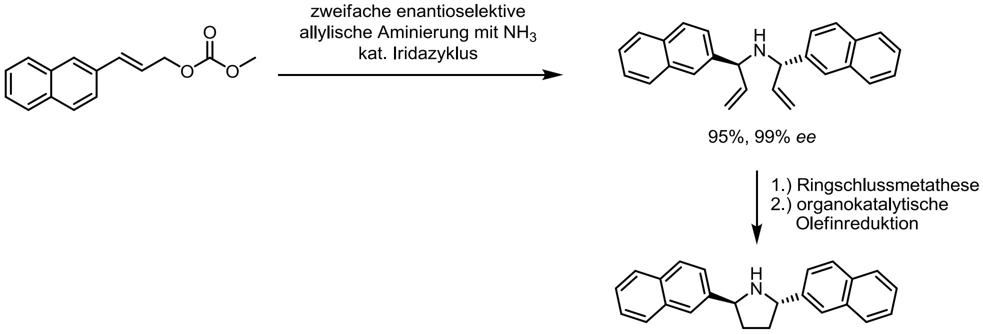
1) Die Konstruktion des gewünschten Stereozentrums an einem linearen Substrat, welches in der Folge durch Ringschlussreaktionen (wie z.B. der Ringschlussmetathese) zu einem Heterozyklus umgesetzt wurde (siehe Kapitel 2 und 5).

2) Sowohl das Stereozentrum als auch der Heterozyklus werden in einer einzigen Reaktion aufgebaut (siehe Kapitel 3 und 4).

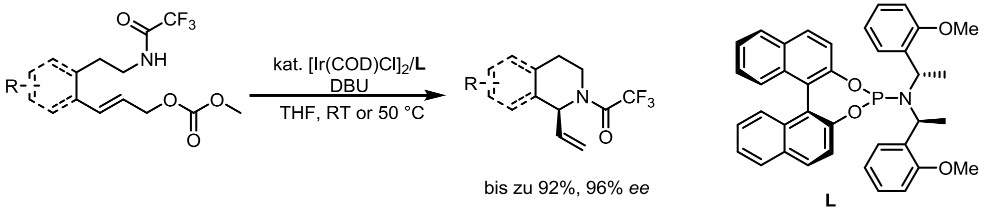
3) Eine katalytisch asymmetrische Transformation an einem prochiralen Heterozyklus wird durchgeführt (siehe Kapitel 6).

In Kapitel 2 wird die Synthese von 2,5-Diraylpyrrolidinen mittels asymmetrischer iridium-katalysierter allylischer Aminierung von Allylcarbonaten mit Ammoniak beschrieben. Die so zugänglichen Produkte finden als chirale Auxiliare, Organokatalysatoren sowie Schlüsselbestandteile von chiralen Phosphoramiditliganden Anwendung in der organischen Chemie. Die Verwendung von Ammoniak als Stickstoffnukleophil ist vorteilhaft, da es günstig und atomökonomisch ist. Im Verlauf der Reaktion kommt es zu einer zweifachen allylischen Aminierung, da das intermediär auftretende primäre Amin ein deutlich besseres Nukleophil als Ammoniak ist und sofort mit einem weiteren Äquivalent Allylcarbonat abreagiert. In unserem Fall ist dieser Reaktionsweg erwünscht, da das resultierende chirale sekundäre Amin – zugänglich in exzellenten Stereoselektivitäten und sehr guter Ausbeute – mittels Ringschlussmetathese zu einem chiralen Pyrrolidin umgesetzt werden kann. Die Synthese der gewünschten chiralen Pyrrolidine wird durch eine organokatalytische Olefinreduktion mit einem

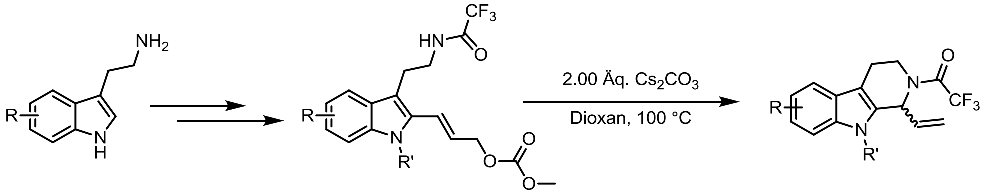
Flavinderivat abgeschlossen. Letztere Reaktion wurde anhand der vorliegenden Reaktion optimiert und daraus ein neues Reaktionsprotokoll entwickelt.


zweifache enantioselektive
allylische Aminierung mit NH_3
kat. Iridazyklus
95%, 99% *ee*
1.) Ringschlussmetathese
2.) organokatalytische Olefinreduktion
O
O
O
H
N

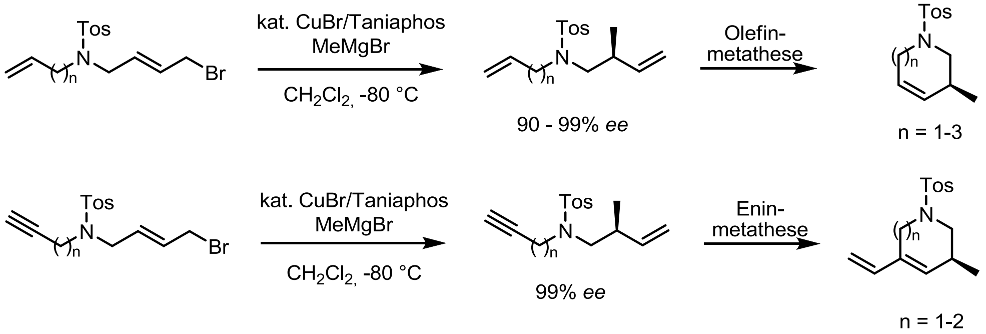
Ein Höhepunkt der vorliegenden Arbeit ist in Kapitel 3 beschrieben. Dort wird die Entwicklung der ersten asymmetrischen intramolekularen iridiumkatalysierten allylischen Amidierung vorgestellt. Diese neue Methode basiert auf der Verwendung von chiralen Iridium-phosphoramiditkomplexen sowie der Ausnutzung der Reaktivität der Trifluoracetamidgruppe als Schutzgruppe zum einen und als Nukleophil in der allylischen Amidierung zum anderen. Die Zielmoleküle dieser Umsetzung, chirale Tetrahydroisoquinoline und gesättigte Stickstoffheterozyklen, sind mit sehr guter Stereoselektivität zugänglich. Beide Produktklassen stellen nützliche Synthesebausteine dar, da sie durch die terminalen Olefine leicht zu modifizieren sind. Die Vielseitigkeit dieser Moleküle wurde in zwei versuchten Synthesen eines natürlich vorkommenden Alkaloid, Crispine A, sowie eines Arzneistoffs, Almorexant, demonstriert.


kat. $[Ir(COD)Cl]_2$/**L**
DBU
THF, RT or 50 °C
bis zu 92%, 96% *ee*
R
NH
CF_3
N
OMe
P
L

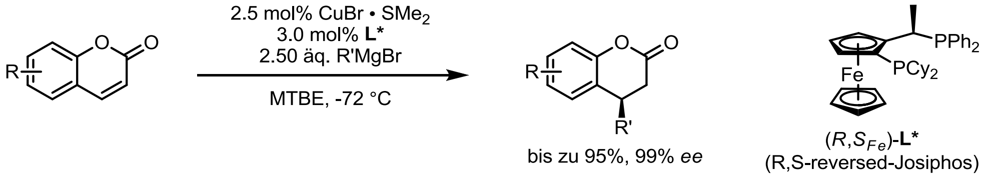
Die angestrebte Erweiterung dieser Methode auf die Synthese von chiralen β-Carbolinverbindungen ist in Kapitel 4 beschrieben. Auch wenn letztendlich die gewünschte Umsetzung nicht erreicht wurde, stellt dieses Kapitel einige mögliche Ansätze für die Synthese von substituierten Indolverbindungen vor. Diese Untersuchungen ergaben wichtige Erkenntnisse, die sich auch für die Entwicklung der in Kapitel 3 vorgestellten Tetrahydroisoquinolinsynthese wertvoll erwiesen haben. Die angestrebten β-Carbolinverbindungen konnten letztendlich auf einem nicht-katalysierten Syntheseweg in racemischer Form hergestellt werden.



In Kapitel 5 wird die Entwicklung einer neuen Synthese von chiralen Stickstoffheterozyklen variaber Ringgröße diskutiert. Ähnlich der in Kapitel 2 vorgestellten Syntheseroute wird hier zunächst ein Stereozentrum an einem linearen Substrat mittels asymmetrischer allylischer Substitution eingeführt, wonach das Ringsystem per Metathese aufgebaut wird. Diese wird durch die terminale Doppelbindung, das Produkt der allylischen Substitution, ermöglicht. Die Kombination von asymmetrischer kupferkatalysierter allylischer Alkylierung mit Ringschlussmetathese liefert die gewünschten sechs- bis achtgliedrigen Heterozyklen in exzellenten Stereoselektivitäten. Diese Variabilität der Syntheseroute stellt einen großen Vorteil dar. Falls eine Enin-metathese verwendet wird, entstehen Heterozyklen mit einem Dienmotiv, welches sich gut für die spätere Funktionalisierung, z.B. durch eine Diels-Alder-Reaktion, eignet. Es konnte gezeigt werden, dass sich diese Methode auch auf die Synthese von chiralen Laktonen erweitern lässt. Allerdings sind weitere Untersuchungen notwendig, um die Ausbeuten und Stereoselektivitäten dieser Umsetzung zu verbessern.



Kapitel 6 beschreibt die Entwicklung einer asymmetrischen kupferkatalysierten konjugierten Additionsreaktion von Grignardreagenzien an Coumarinderivate. Coumarine konnten bisher nicht mit diesem Reaktionstyp umgesetzt werden, da sie verhältnismäßig reaktionsträge sind. Durch die richtige Ligandenwahl sind die Additionsprodukte jedoch in guten Stereoselektivitäten und Ausbeuten erhältlich. Während der Untersuchung dieser Reaktion wurde eine weitere Eigenschaft dieser Substratklasse entdeckt: Die intermediären chiralen Magnesiumenolate lassen sich mit Aminen oder Alkoholen per Ringöffnungsreaktion zu den entsprechenden *ortho*-Phenolestern oder –amiden umsetzen. Zum einen waren diese Ester mit der bisher bekannten Methode nicht herstellbar und zum anderen stellt dies eine neue formale konjugierte Additionsreaktion an α,β-ungesättigte Amide dar.



bis zu 95%, 99% *ee*

(*R*,*S*$_{Fe}$)-**L***
(R,S-reversed-Josiphos)

Im letzten Abschnitt dieser Arbeit (Kapitel 7) werden die Untersuchungen zur Entwicklung einer neuen nickelkatalysierten reduktiven Kupplungsreaktion von Dienen mit Aldehyden zur Herstellung von chiralen Bishomoallylalkoholen vorgestellt. Ein großer Vorteil dieser Reaktion ist die Tatsache, dass in dieser katalytischen Umsetzung zwei Stereozentren zugleich aufgebaut werden können. Die chiralen Produkte sind durch das terminale Olefin, den sekundären Alkohol sowie durch den Aromaten hochfunktional und damit wertvolle chirale Synthesebausteine. Chirale Nickelkomplexe mit Phosphoramidit- oder *N*-heterozyklischen Carbenliganden konnten als sinnvolle Katalysatoren zur Herstellung der gewünschten Produkte identifiziert werden. Diese konnten mit exzellenter Diastereoselektivität, jedoch mit nur mäßiger Enantioselektivität isoliert werden. ^{1}H NMR- und ^{31}P NMR-Studien der Reaktion konnten wichtige Messdaten zur Unterstützung des vorgeschlagenen Reaktionsmechanismus via Nickelhydridkomplexe liefern.

Acknowledgements

The work summarized in this book would not have been possible without the help and input of a lot of people. Furthermore, my personal development would not have been the way it has been without them.

First of all, I would like to thank my supervisor Ben Feringa, for giving me the opportunity to work under his guidance and in the research surrounding that he creates. Ben, your enthusiasm about science has taught me a lot, and without it many days in the last four and a half years would have been less enjoyable. Also, the support not only in difficult times was crucial. The way you bring people together and encourage scientific discussions is unique, and I certainly have and will profit from it.

I would also like to thank Adri Minnaard, who I feel has been like a second promotor to me. It was always possible to approach you with questions and discuss scientific problems. Many of the findings in this book came together with your help, and I am very grateful for all the things you have taught me.

I acknowledge the members of my reading committee, Prof. Günter Helmchen, Prof. Adri Minnaard and Prof. Gerard Roelfes for their quick corrections and their suggestions for the manuscript.

A number of people have been very special to me during my time in Groningen, either in a personal or scientific way, in most cases both, and I would like to say thank you for the time we spent together to: Mike, Steve, Koen, Jérôme, Tati and Bjorn.

I would like to thank my friends and members of the workweek committee 2009, Lachlan and Pieter, for holding out with the organization of the “worstweek”. I think we put together a great program and I enjoyed it a lot, especially the organization dinners. I am very happy about the workweek and I appreciate our friendship deeply.

I have had the pleasure to work in the most infamous of all labrooms: Vyscom! All past and present inhabitants I would like to acknowledge here for creating the best possible working atmosphere, including all those things that bring about that special feeling of Vyscom. Tieme (also for teaching me the first dutch sentence), Qian, Jeroen, Gabriella (it took me a while to accept electronic music – but I think I am cured now), Chris, Maria, Manuel, Peter, Miro, Felix, Dorus, Simon and Cati. Especially I would like to thank those three gentlemen, with whom I have spent the most time in the lab: Thomas, thank you for the time together, and for everything you have taught me about organometallic chemistry and reaggae music. Bas, thanks a lot for so many things, including how to give the right introductory speech to students in the practical courses and teaching me what it means to be Sheriff of Vyscom (“You can take a man out of Vyscom, but you can never take Vyscom out of a man.”). Ashoka, through your presence I have learned many things about you, but certainly many things about myself as well. It was a pleasure working alongside all of you.

A big thank you to all the people in the other labs, and I am sure I forgot a few here. You guys have been special to me and made the time in the lab and the office most enjoyable: Aditya, Danny, Miriam, Jeffrey B. (2x), Eva, Francesca (2x), Davide, David and Karelle, Nataša, Pieter, Bjorn, Nicolas, Jérôme, Martín, Stella, Céline, Bin, Wiktor, Valentin, Alena, Anne, Annick, Bea, Tati, Toon, Jack, Wim, Massimo, Lachlan, Pieter, Núria, Tim (also for the big help you have been with all the things in Zürich and the moving), Tiziana, Lorina, Fiora, Steve, Hella, Barbara, Chris, Nop, Jochem, Jurica, Johan, Arjen, Jos, Hans, Robert (also for for joining me to the choir), Wesley, Manolo, Petra, Tibor, Nathalie, Jetsuda, Arnaud, Jort, Mike, Steve, and Koen. To all the members of the asymmetric catalysis subgroup thank you for your endless help and all the useful discussions, both of which I have both highly depended upon.

With most of the research work I was helped by other members of the lab. Thomas, Martín and Jose, thank you for collaborating with me. I especially thank Stella, whom I had the honour of guiding through her master thesis. You have done an excellent job and your work came out to be one of the chapters in this book. I wish you all the best with your future and your career, which I have no doubts will be successful.

Lachlan, Alena, Martín and Wiktor I would like to acknowledge for the proofreading of the manuscript and all the useful suggestions. Pieter and Nop, thanks for all your help with the design of the cover of this book. Tim and Pieter, many thanks for the last-minute dutch translations.

During my time I had the pleasure to supervise three HBO students with their master research: Martin, Simon, and Dorus. Thank you all for the time in the lab and the patience with my corrections. I wish you all the best for your future.

A great pleasure for me were the Tuesday evenings with the FC Venus 69, formerly known as the football subgroup, which has grown to be an institution in the lab. Thank you guys, especially to the manager, Danny. Somehow, it is still difficult for me to score goals…

No Wednesday night would be complete without the pubquiz team of Pimpmaster Fred & the magic sticks around it’s leader Jochem. Thanks a lot for all the fun we had together and (with the earlier teammates) teaching me dutch. That the nights normally did not end at the Toeter is partly due to Jochem, and I have enjoyed the late night discussions with you a lot.

All the members of the choir “A Capelli” I would like to thank for the great joy of making music together with you, and for being patient while teaching me dutch. You guys are one of the things I will miss the most when I leave Groningen.

I would like to thank Aditya and Ashoka for putting together an extremely eventful and enjoyable trip to India. It was wonderful travelling with you through your home country. Thanks a lot for all your efforts.

Ein großer Dank geht an meine Familie, ohne eure Unterstützung wäre diese Arbeit so nicht möglich gewesen. Vielen Dank für eure Großzügigkeit in so vielerlei Hinsicht.

Am Schluss, Danke Judit. Es fällt mir schwer, an dieser Stelle die richtigen Worte zu finden. Vielen Dank für die tolle gemeinsame Zeit bisher. Die letzen viereinhalb Jahre sind nicht immer leicht gewesen, aber deine stete Zuneigung und Unterstützung haben mich durch die schwierigen Tage getragen. Ich möchte die Zeit mit dir nicht missen wollen und freue mich, dass wir endlich zusammen am gleichen Ort wohnen können. *Without you it’s a waste of time...*

The book is finished:

I especially enjoyed this one, let’s see what’s next…

Johannes