Enantioselective copper-catalysed addition of organometallic reagents using phosphoramidite ligands

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ENANTIOSELECTIVE COPPER-CATALYSED ADDITION OF ORGANOMETALLIC REAGENTS USING PHOSPHORAMIDITE LIGANDS

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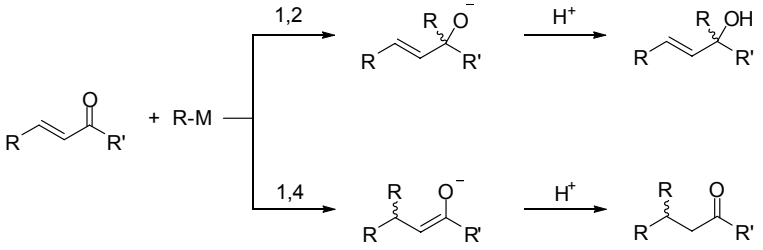
Chapter 1
Introduction

1.1 Conjugate addition reactions

The term conjugate addition refers to a reaction in which a nucleophile reacts with an α,β-unsaturated electrophile at the β-position. The presence of an electron-withdrawing (EWG) group in conjugation with the double bond activates the β-position toward the reaction with the nucleophilic species. The attack of the nucleophile results in the formation of a stabilized carbanion in which the negative charge is delocalized by resonance on the conjugated EWG group. Typical examples of substrates employed in the conjugate addition reaction are α,β-unsaturated ketones, aldehydes, esters, thioesters, nitriles and nitro compounds.[1] Most commonly the unsaturated group at which the addition takes place is a C=C bond, however, recently, examples of 1,4-addition to C=N[2] and N=N[3] double bonds or C≡C triple bonds[4] have been described. As far as the nucleophile is concerned, this can be a carbon species as well as an amine, an alkoxide or a thiolate anion.[1] This thesis will focus on the addition of carbon nucleophiles and in particular of organometallic reagents leading to the formation of C-C bonds. [5]



Scheme 1.1 *C-C bond formation by 1,2- and 1,4-addition of a carbon nucleophile to an α,β-unsaturated system.*

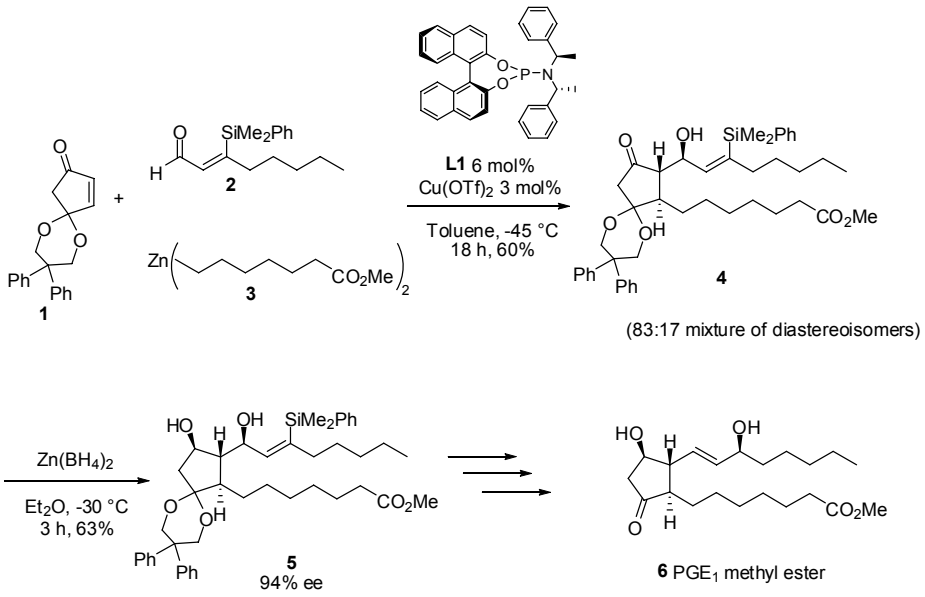
Depending on the polarization of the C-M bond of the organometallic species, the addition reaction can occur preferentially at the 1,2- or 1,4-position (Scheme 1.1). In particular, the regioselectivity shown by hard nucleophiles[6] (high polarization of the C-M bond) lies towards 1,2-addition. In contrast, if a

weakly polarized organometallic reagent is used, the addition reaction occurs preferably in the conjugate manner. These types of nucleophiles can be generated *in situ* by alkylation of a transition metal salt with organolithium, organoboron, organomagnesium, organosilicon, organozinc or organoaluminum reagents. Although several transition metals have been used to carry out this transformation,[7] organocuprates have offered the most widespread application in both stoichiometric and catalytic procedures.[8]

Over the last ten years a tremendous number of catalyzed enantioselective conjugate additions employing chiral copper complexes have been reported.[9] These methodologies have been the topic of several reviews.[10] The goal of this chapter is to offer the reader an understanding of the contribution that these developments have brought to synthetic organic chemistry, as exemplified by the number of synthetic applications of this method. A comprehensive survey of the mechanistic studies that appeared on this topic is also presented. The next section is focused on important synthesis of natural and biologically active products, based on enantioselective copper-catalyzed conjugate additions that have appeared in the literature recently.

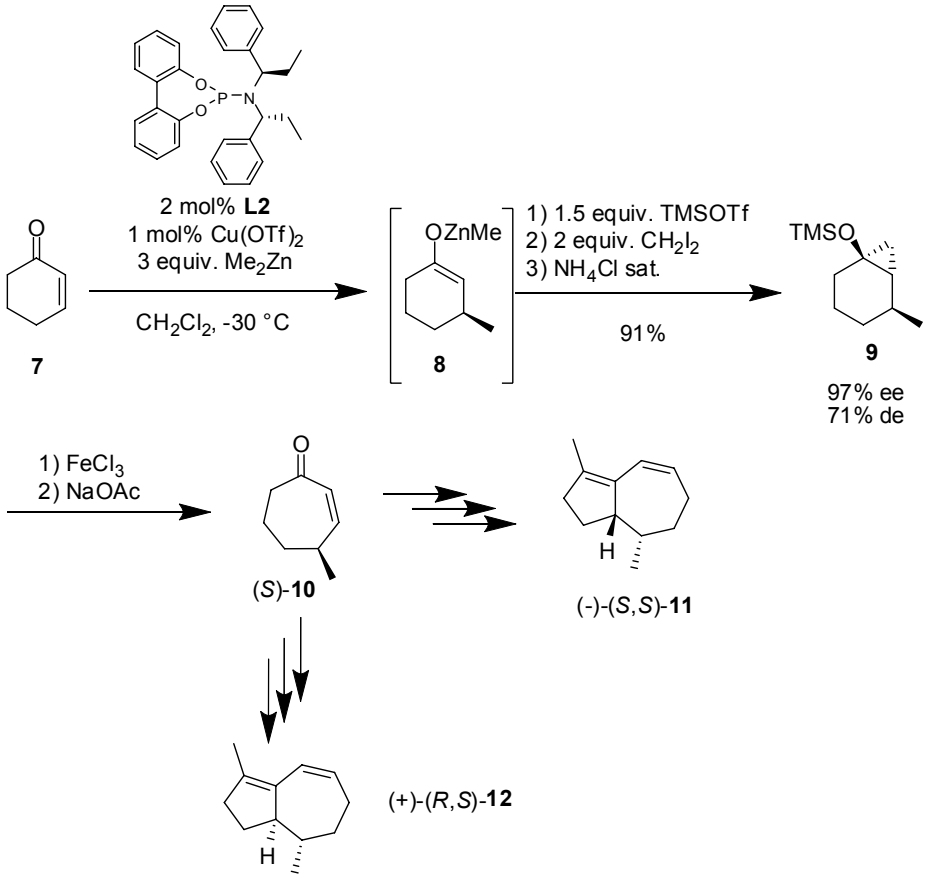
1.2 Synthetic applications

The synthetic utility of the copper-catalyzed 1,4-addition of organometallic reagents has been demonstrated by its application as a key step in numerous syntheses of natural products and biologically active compounds.[5,11] A notable example is the use of a tandem 1,4-addition-enolate-trapping reaction in the synthesis of prostaglandin PGE_1 methyl ester **6** reported by Minnaard, Feringa and co-workers (Scheme 1.2).[12] The synthetic approach followed is reminiscent of the three-component coupling reaction introduced by Noyori.[13] The enantioselective 1,4-addition of zinc reagent **3** to cyclopentene-3,5-dione monoacetal **1** in presence of $Cu(OTf)_2$ and the chiral phosphoramidite **L1** was followed by the trapping of the zinc enolate with aldehyde **2**. This tandem procedure afforded compound **4** in 60% yield as a mixture of diastereoisomers (*trans-threo*/*trans-erythro* ratio 83:17). After reduction of the ketone moiety to the corresponding alcohol, the major diastereoisomer **5**, featuring all structural and stereochemical elements of PGE_1 methyl ester, could be isolated in 63% yield and 94% ee.



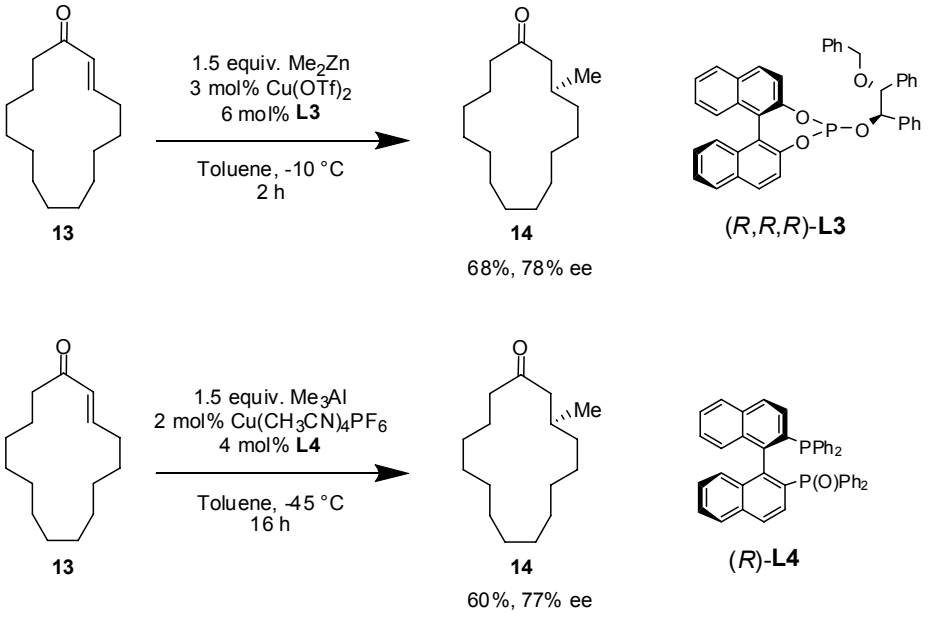
Scheme 1.2 *Synthesis of prostaglandin PGE_1 methyl ester* ***6****.*[12]

A tandem enantioselective conjugate addition-cyclopropanation sequence has been used as a key step in the formal synthesis of the sesquiterpenes (-)-(*S*,*S*)-clavukerin A **11** and (+)-(*R*,*S*)-isoclavukerin **12**.[14] Starting from cyclohexenone **7**, 1,4-addition of Me_2Zn was performed using 1 mol% of $Cu(OTf)_2$ and 2 mol% of **L2** (Scheme 1.3). The zinc enolate **8** was silylated with TMSOTf and the resulting silylenolate was cyclopropanated in the presence of diiodomethane. Compound **9** was obtained in high yield (91%) and enantioselectivity (97%). The π-face selectivity of the cyclopropanation was only modest (71% de), however the disappearance of these stereocentres in the sequential transformation to compound **10** renders the low de value unimportant.



Scheme 1.3 *Synthesis of (-)-(S,S)-clavukerin A **11** and (+)-(R,S)-isoclavukerin **12**.*[14]

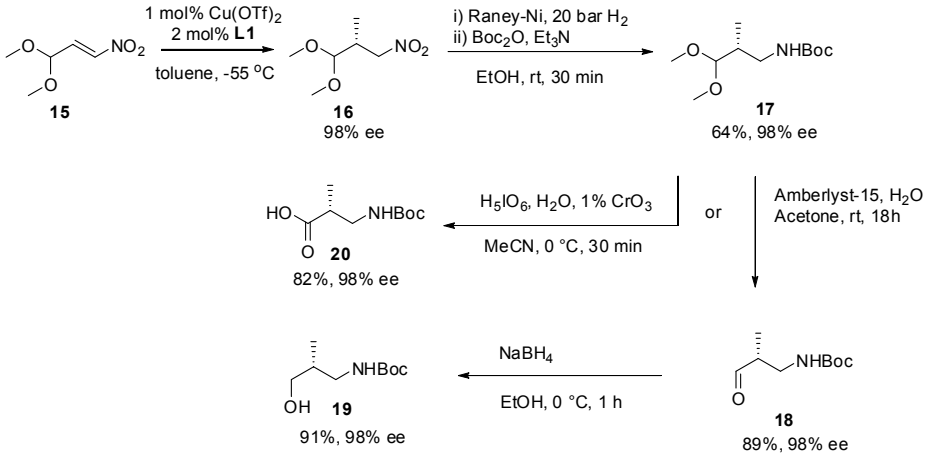
In 2003 a straightforward asymmetric synthesis of (*R*)-(-)-muscone **14**, the key flavour component of musk, was achieved via conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one **13**.[15] The use of phosphite **L3** as chiral ligand in combination with $Cu(OTf)_2$ afforded the desired product in 68% yield and 78% ee after 2 h (Scheme 1.4). The conjugate addition of Me_3Al to **13** in the presence of $Cu(CH_3CN)_4PF_6$ and ligand **L4** affords (*R*)-(-)-muscone **14** in 60% isolated yield and with 77% ee.[16] A recent synthesis of muscone based on the conjugate addition of Me_3Al to a cyclic dienone is discussed in chapter 6.



Scheme 1.4 *Syntheses of (R)-(-)-muscone **14** based on the conjugate addition of Me_2Zn[15] and Me_3Al[16] to **13**.*

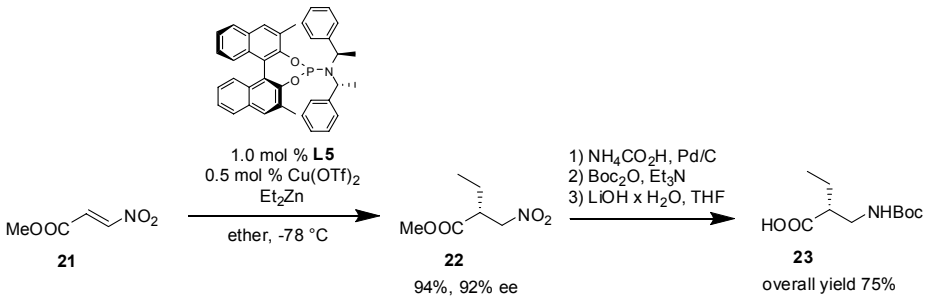
Nitro-olefins represent an important class of acceptors in 1,4-addition reactions due to the versatility of the nitro group in organic synthesis. Enantioselective 1,4-addition to nitroalkenes provides an attractive route to β^2-amino acids and derivatives, which are important building blocks in the synthesis of natural products, β-peptides and pharmaceuticals.[17] The copper-catalyzed addition of organozinc reagents to acetal substituted nitroalkenes was developed in our group.[18] Using 1 mol% of $Cu(OTf)_2$ and 2 mol% of the chiral phosphoramidite **L1**, excellent results were obtained both in terms of yield and enantioselectivity in the conjugate addition of several organozinc reagents to substrate **15**. In particular, product **16** can be converted readily to the protected β-amino aldehydes, alcohols and acids (Scheme 1.5). For example, reduction of **16**, followed by Boc-protection and cleavage of the acetal provides the β-amino aldehyde **18**, a building block in the total synthesis of cyclamenol A.[19] Subsequent reduction of **18** gives the β-amino alcohol **19**, a starting material in the synthesis of β-methyl carbapenem antibiotics.[20] Compound **17** can also be

oxidized to the *N*-Boc-protected β-amino acid **20**, used in the total synthesis of cryptophycins.[21]



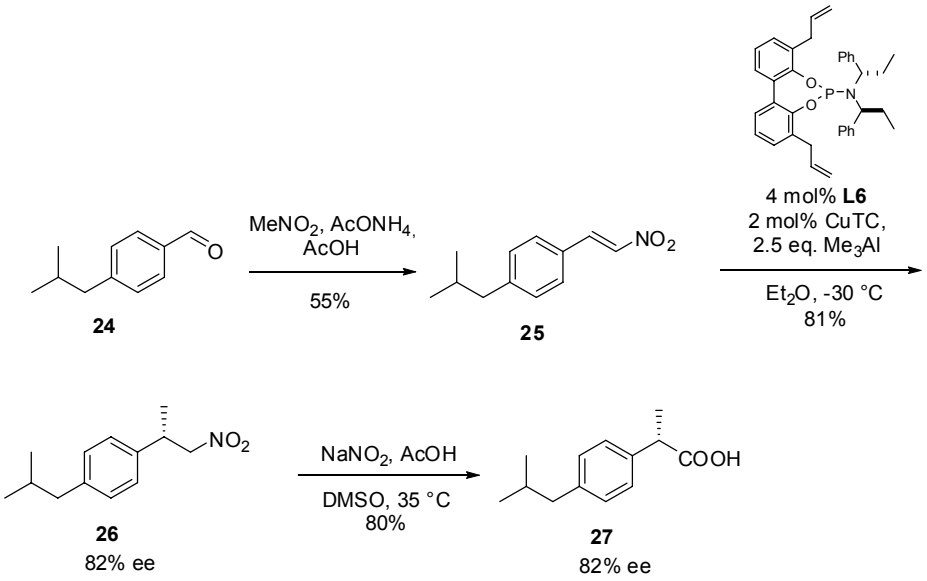
Scheme 1.5

Sewald et al. described the 1,4-addition of Et_2Zn to the activated nitro-olefin methyl 3-nitropropenoate.[22] Ligand **L5** provided the highest level of enantioselectivity, reaching 92% ee in presence of only 0.5 mol% of the catalyst (Scheme 1.6). The β-nitroester **22** can be reduced readily, Boc-protected and subsequently saponified to give the β^2-homoamino acid **23**.



Scheme 1.6

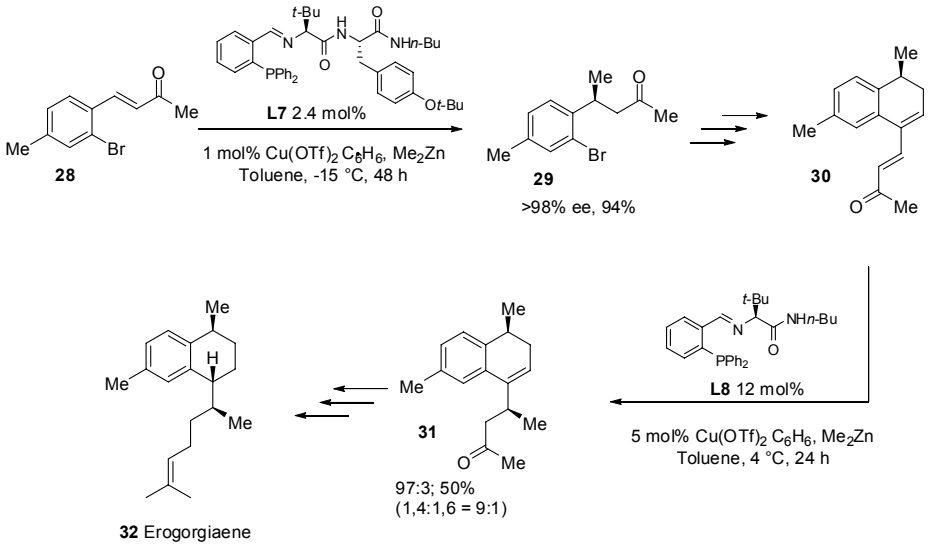
Nitroolefins have proven to be useful as starting materials in the synthesis of molecules belonging to the profen family. In particular, the asymmetric synthesis of (+)-ibuprofen, based on asymmetric conjugate addition has been described by Polet and Alexakis.[23] The introduction of the methyl substituent was achieved using Me_3Al instead of the less reactive Me_2Zn (Scheme 1.7). The α,β-unsaturated substrate is obtained via Henry condensation from compound **24**; conjugate addition in the presence of 2 mol% of copper thiophene carboxylate (CuTC) and 4 mol% of **L6** on nitroalkene **25** affords the β-methylated product **26** in good yield and 82% ee. Further functional group modification, according to literature procedures, yields (+)-ibuprofen **27**.



Scheme 1.7 *Synthesis of (+)-ibuprofen **27**.*[23]

In 2004 Hoveyda et al. applied the asymmetric Cu-catalyzed conjugate addition of Me_2Zn to acyclic enones in the total synthesis of the antimycobacterial agent erogorgiaene **32** (Scheme 1.8).[24] First, the α,β-unsaturated enone **28** underwent addition of Me_2Zn, on a multigram scale, in the presence of 1.0 mol% of $[(CuOTf)_2 \cdot C_6H_6]$ and 2.4 mol% of chiral phosphine **L7**, to deliver β-methyl ketone **29** in 94% isolated yield and more than 98% ee. This result is, at first glance, in contrast to the low reactivity shown in general by β-aryl-substituted acyclic enones in this type of reaction.[25] However, detailed studies

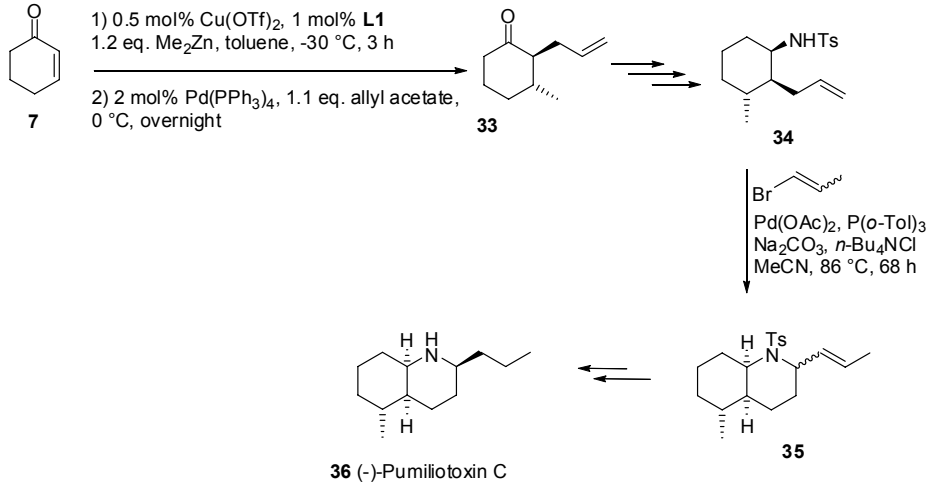
proved that the presence of a substituent at the *ortho* position of the phenyl ring, regardless of its electronic properties, was beneficial for the rate of the reaction. A second diastereoselective copper-catalyzed conjugate addition was performed on enone **30**; in this case the best results both in terms of diastereo- and regioselectivity were obtained using the chiral phosphine **L8** and increasing the catalyst loading to 5 mol%. A three-step conversion to **32** included a diastereoselective reduction which allowed for the introduction of the third stereocentre.



Scheme 1.8 *Synthesis of erogorgiaene **32**.*[24]

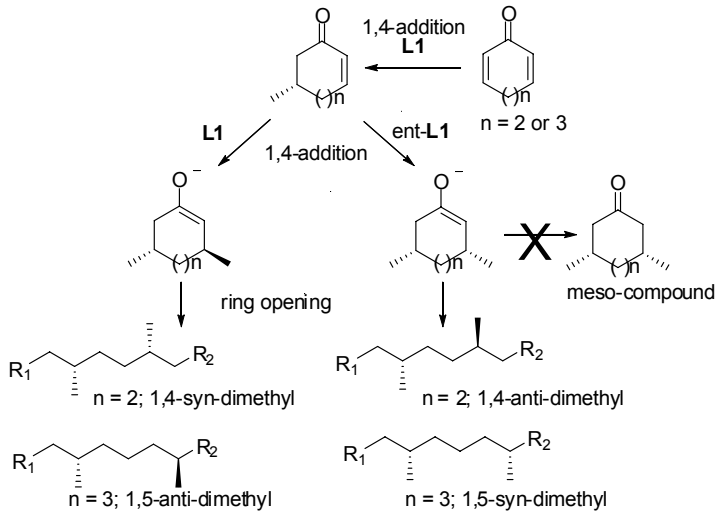
In the same year, Feringa and co-workers reported the asymmetric synthesis of (-)-pumiliotoxin C (**36**) based on two tandem catalytic reactions.[26] A first tandem asymmetric conjugate addition-allylic substitution reaction, carried out on 2-cyclohexenone, allowed for the introduction of two stereocentres providing **33** as a mixture of *trans*/*cis* isomers (ratio 8:1) in 84% yield and 96% ee (Scheme 1.9). Conversion of the carbonyl group into an *N*-tosylamine gave compound **34** which can undergo a tandem Heck-allylic substitution reaction[27] to create the perhydroquinoline skeleton with both the natural and unnatural

configuration at the C2 stereocentre (**35**). Two additional steps afforded the desired compound **36.**



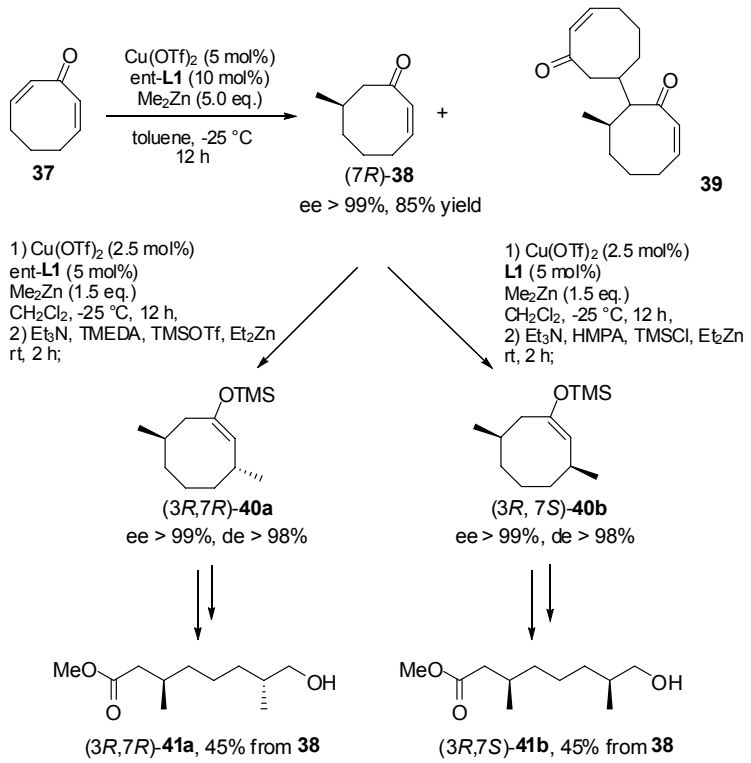
Scheme 1.9 *Synthesis of pumilotoxin C* ***36****.*[26]

Recently, Feringa, Minnaard and co-workers described the first catalytic procedure capable of preparing all 4 diastereoisomers of a versatile saturated isoprenoid building block.[28] This method is based on the iterative enantioselective conjugate addition of Me_2Zn to cyclic dienones which, after oxidative ring opening, allows to obtain enantiopure *syn*- and *anti*-dimethyl arrays in 1,4- or 1,5-relationship, according to the size of the ring (Scheme 1.10). As depicted in Scheme 1.10, the conjugate addition of Me_2Zn to the dienone in the presence of ligand **L1** allows to introduce a methyl substituent with complete enantiocontrol. In the sequential conjugate addition, the use of the same chiral ligand **L1** or its enantiomer *ent*-**L1** will result in a *trans* or a *cis* relationship of the two methyl substituents, respectively. In the case of the *cis*-adduct, quenching of the zinc enolate with a proton source generates a meso compound that, after ring opening, provided a racemic product. In order to avoid this loss of chiral information the enolate can be trapped *in situ* as a silyl enol ether before the ring opening.



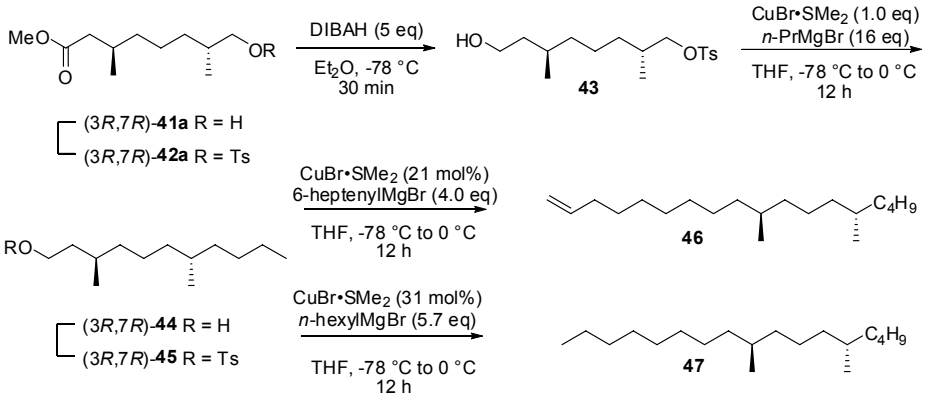
Scheme 1.10 *Synthesis of syn- and anti-dimethyl arrays.*

Scheme 1.11 gives an illustrative example of this method. Cycloocta-2,7-dienone **37** was subjected to conjugate addition of Me_2Zn to give compound **38** with complete enantiocontrol. A catalyst loading of 5 mol%, slow addition of the substrate as well as an excess of organozinc reagent (5.0 eq.) are necessary to minimize the formation of side product **39**, due to Michael addition of the zinc enolate to the starting material (Scheme 1.11). Compound **38** can be subjected to a second conjugate addition of Me_2Zn. In this case the side reaction is not observed, allowing for a lower amount of catalyst (2.5 mol%) and Me_2Zn (1.5 eq.) to be used. In the case of the *trans* adduct, the silyl enol ether **40a** can be obtained by trapping the zinc enolate with TMSOTf in the presence of TMEDA and Et_3N. In the case of the *cis* adduct, partial racemization was observed using this trapping procedure. The use of TMSCl in the presence of HMPA and Et_3N, instead afforded compound **40b** enantiomerically pure and with high de (>98%). Ring opening via ozonolysis followed by reduction of the aldehyde to an alcohol and esterification of the free carboxylic acid gives the isoprenoid building block **41**.



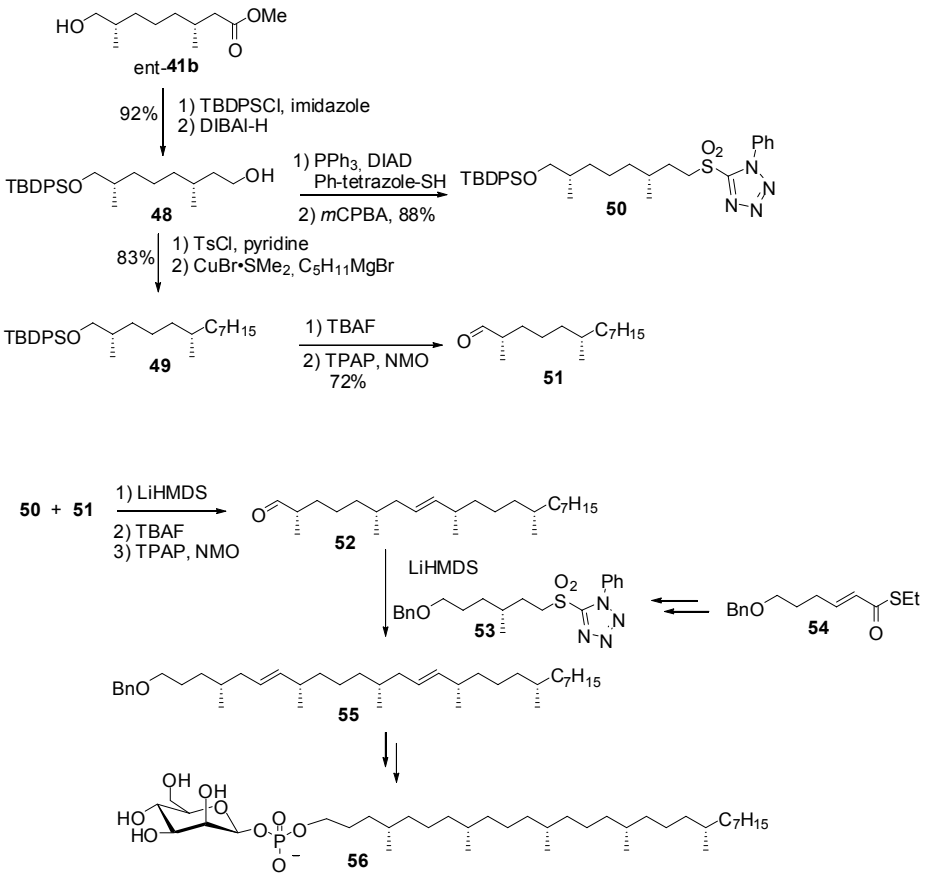
Scheme 1.11 *Synthesis of the isoprenoid building blocks **41a** and **41b**.*[28]

A demonstration of the synthetic versatility of this catalyzed system is seen in the total synthesis of two pheromones **46** and **47** produced by the female of the apple leafminer featuring an anti-1,5-array of methyl groups. Starting from compound **41a**, reduction of the ester moiety followed by chain elongations on both sides of the isoprenoid building block gives **46** and **47** in five steps (Scheme 1.12).



Scheme 1.12 *Synthesis of the apple leafminer pheromones **46** and **47**.*[28]

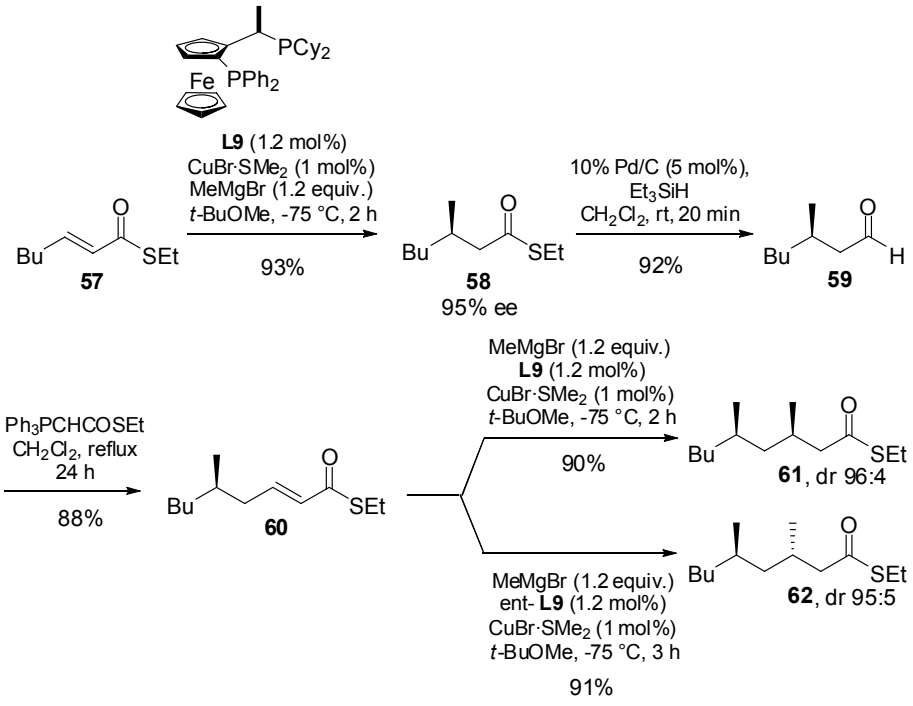
The synthetic versatility of isoprenoid building block **41** was demonstrated further in the total synthesis of β-mannosyl phosphomycoketide **56**, a potent mycobacterial antigen for T cells, isolated from *Mycobacterium tuberculosis*.[29] This natural product has a challenging array of 5 methyl groups in a 1,5-all-*syn* relationship. The synthetic scheme (Scheme 1.13) indicates that it is possible to build an acyclic structure with an array of four methyl groups (**52**), via connection of the chiral building blocks **50** and **51**, which can be constructed starting from the same isoprenoid building block ent-**41b**. The Julia-Kocienski coupling of **52** and fragment **53** allows to introduce the fifth methyl group with a *syn*-relationship. Interestingly, fragment **53** can be obtained through an enantioselective Cu-catalyzed 1,4-addition of MeMgBr to the linear α,β-unsaturated thioester **54**.[30] The development and applications of this method will be discussed further on.



Scheme 1.13 *Synthesis of β-mannosyl phosphomycoketide (MPM)* ***56****.*[29]

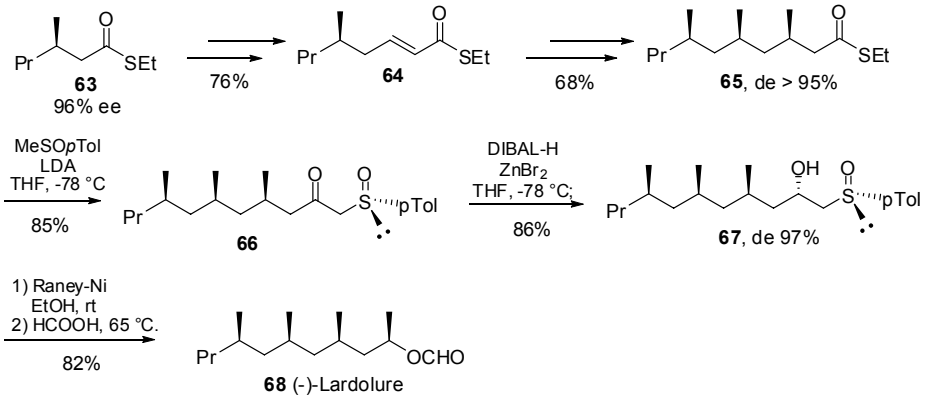
The construction of deoxypropionates and acyclic synthons in general with 1,3-arrays of methyl substitution, with *syn* or *anti* stereochemistry, poses another major challenge to catalytic conjugate addition.[31] The Cu-catalyzed addition of Grignard reagents to α,β-unsaturated thioesters in the presence of Josiphos type ligands has been developed recently by Minnaard, Feringa and co-workers[30]. As depicted in Scheme 1.14, the conjugate addition of MeMgBr to thioester **57**, in the presence of a 1 mol% of catalyst derived from $CuBr{\cdot}SMe_2$ and Josiphos **L9**, provides the β-methyl substituted compound **58** in excellent yield (93%) and enantioselectivity (95% ee). Fukuyama reduction[32] of the thioester moiety to the corresponding aldehyde followed by a Wittig reaction

affords the new Michael acceptor **60** again featuring an α,β-unsaturated thioester.



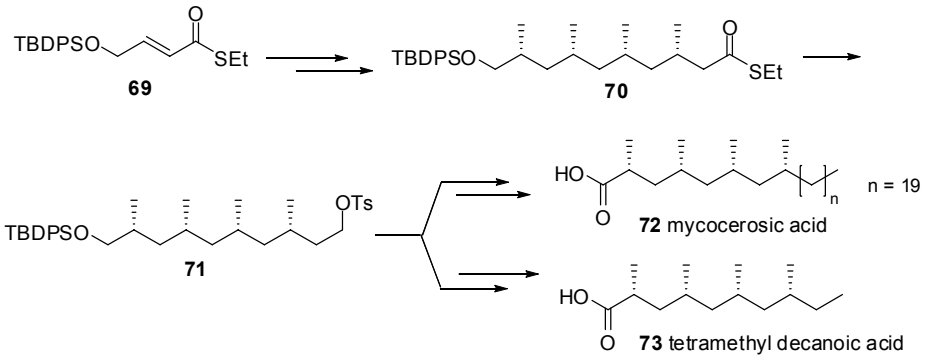
Scheme 1.14

A second catalyzed conjugate addition reaction using **L9** or its enantiomer ent-**L9** afforded with excellent yield (90%) and selectivity (dr 96:4) the *syn*- and *anti*-1,3-dimethyl derivatives **61** and **62**, respectively. The synthetic utility of this iterative process has been demonstrated in the asymmetric total synthesis of (—)-lardolure **68**, a pheromone of the acarid mite *Lardoglyphus konoi* (Scheme 1.15).[30] The iterative sequence allows for the formation of compound **65**, in which three methyl groups have been introduced by catalyzed conjugate addition with *syn* stereochemistry and de > 95%. Modification of the thioester functional group afforded the target compound **68** in four additional steps.



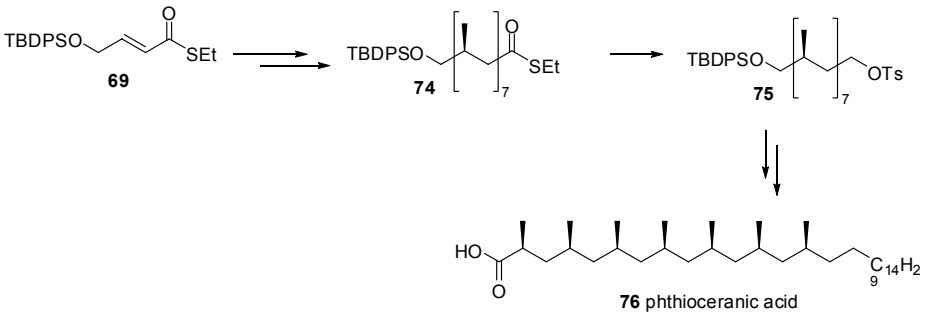
Scheme 1.15 *Synthesis of (-)-lardolure **68**.*[30]

The same iterative sequence for the formation of 1,3-dimethyl arrays has been applied in the asymmetric syntheses of mycocerosic acid **72**, one of the many methyl-branched fatty acids from *Mycobacterium tuberculosis* and the related tetramethyl-substituted fatty acid **73**, found in the preen-gland wax of the graylag goose *Anser anser* (Scheme 1.16).[33] The reaction protocol was applied four times in an iterative manner to arrive at the tetramethyl substituted compound **71** in ten steps with excellent selectivity and an overall yield of 21% from **70**. Two-fold reduction of thioester **70** with DIBALH and reaction of the obtained alcohol with TsCl gave silyl ether **71**, a common intermediate in the synthesis of the fatty acids **72** and **73**.



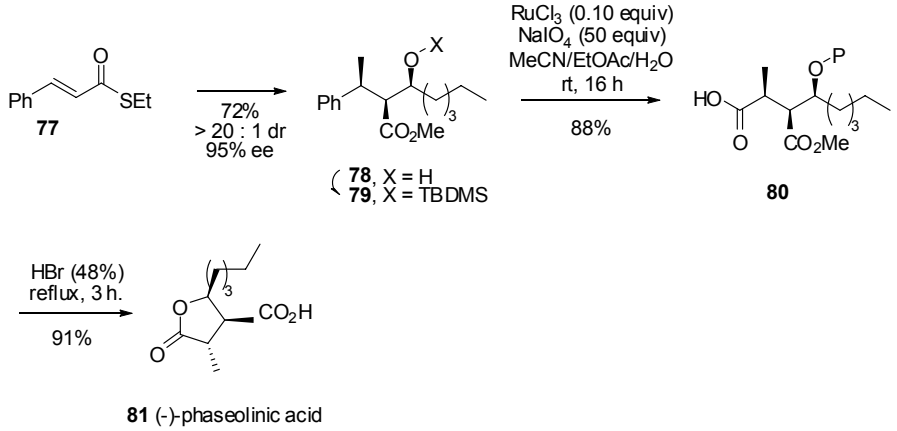
Scheme 1.16 *Synthesis of mycocerosic acid **72** and its analogue **73**.*[33]

Continued iteration, starting with unsaturated thioester **69**, allows for the introduction of seven methyl groups to yield compound **74**, which can be used as a building block in the synthesis of phthioceranic acid **76**, a fatty acid from the virulence factor Sulfolipid-I (2), found in *Mycobacterium tuberculosis*.[34] The same route to the tosylated derivative **75** was followed. Elongation of the aliphatic chain and introduction of the carboxylic acid moiety afforded the target compound **76** in 4% yield over 24 steps (Scheme 1.17).



Scheme 1.17 *Synthesis of phthioceranic acid **76**.*[34]

The synthetic versatility of the thioester moiety was also demonstrated in the synthesis of (-)-phaseolinic acid **81** from the paraconic acid family, representing an important class of biologically active compounds. The 1,4-addition-aldol method affords the target compound **81** in only four steps (Scheme 1.18).[35] The 1,4-addition of MeMgBr to thioester **77** proceed with high enantioselectivity (95%) and after trapping of the magnesium enolate with hexanal, the tandem product **78** can be obtained with remarkable stereocontrol as a single diastereoisomer in 72% yield. Protection of the free alcohol and oxidation of the aromatic ring afford compound **80**, which can be transformed in to (-)-phaseolinic acid by treatment with HBr (48%).



Scheme 1.18 *Synthesis of (-)-phaseolinic acid **81**.*[35]

The high *syn*-selectivity of the aldol product can be rationalized in terms of a chair-like transition state in which the large phenyl substituent on the aldehyde assumes a pseudoequatorial position to minimize unfavourable diaxial interactions (Figure 1.1a). In the resulting transition state, minimization of the *syn*-pentane interaction between the phenyl substituent on the aldehyde and the chiral enolate, would favour a *Si*-facial attack, resulting in the preponderant formation of the *syn*,*syn* diastereomer (Figure 1.1b).

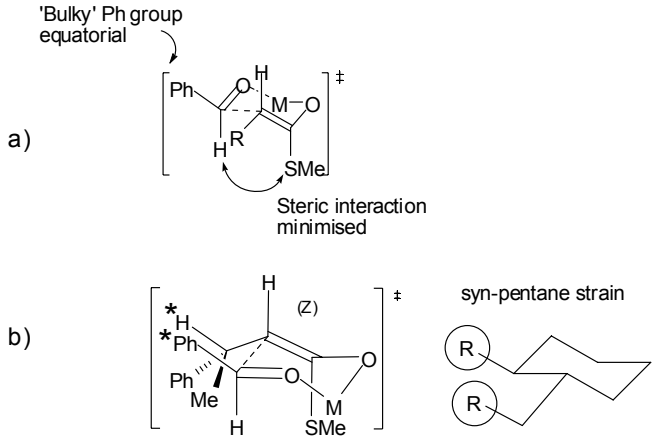


Figure 1.1 *Models to rationalize the syn,syn selectivity.*[35]

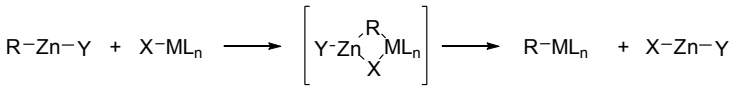
1.3 Mechanistic studies

The challenge of developing a general enantioselective catalyst for this useful class of reactions has led, over the last two decades, to a widespread screening of chiral ligands. Excellent results have been obtained in particular using organozinc reagents, organomagnesium reagents and, more recently, organoaluminium compounds. Although there is a wealth of earlier structural and mechanistic information in organocuprate chemistry,[36] much less effort has been directed to the elucidation of the mechanism of this asymmetric transformation, as well as the structure of the actual catalytically active species, despite the help such information can offer in the systematic study of ligand optimization. In this section we present an overview of studies of organometallic reagents in the copper-catalyzed asymmetric conjugate addition reactions, which provides insight into the reaction mechanisms involved.

1.3.1 Dialkylzinc

1.3.1.1 Phosphorus ligands

Over the past decade, enantioselective carbon-carbon bond formation using organozinc reagents has gained a prominent role in the area of 1,2-[37] and conjugate additions.[5,38] Although dialkylzinc reagents show low reactivity with enones, effective catalysis has been achieved by several ligands and transition metal complexes. The catalytic effect can be explained either by changes in geometry and bond energy of the zinc reagent upon coordination with an appropriate ligand or by alkyl transfer to another metal (Scheme 1.19).



R = alkyl
Y = R, halide
M = Ti, Pd, Ni, Cu
X = halide, OTf
L = ligand

Scheme 1.19

Despite the large number of ligands described, little is known about the structure of the precatalytic complex that forms upon mixing of the copper salt (Cu(II) or Cu(I)) and the chiral ligand. To date only two crystal structures of copper(I) complexes with less selective phosphoramidites have been reported.[39] The first example was reported in 1996: a copper-complex formed from CuI and monophos was recrystallized from benzene affording a stable, albeit catalytically inactive monomeric complex in which three ligands are coordinated to the copper atom (Figure 1.2a).[40]

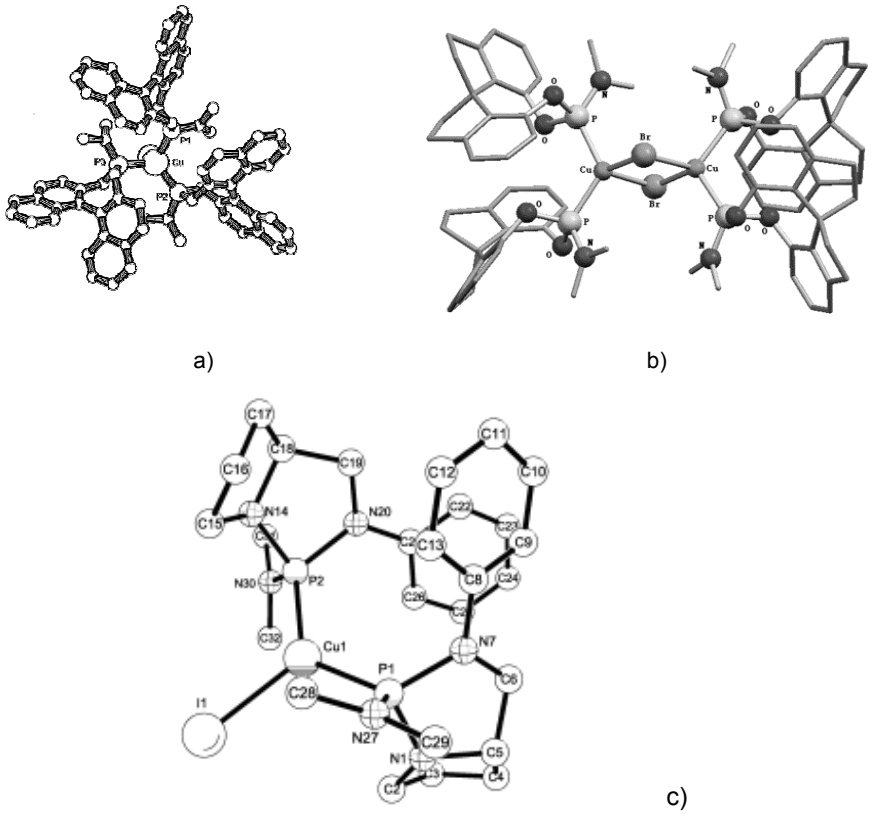
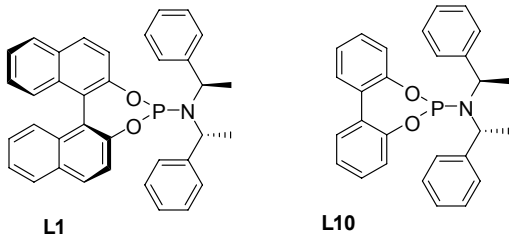


Figure 1.2 *Crystal structures of copper phosphoramidite complexes reported to date.*

In the case of the complex studied by Shi et al. the X-ray analysis showed the existence of a C2-symmetric dimer connected by bromide bridges.[41] Moreover each copper atom is coordinated to two molecules of the spiro phosphoramidite (Figure 1.2b). A crystal structure clearly showing a ligand/copper ratio of 2:1 and a trigonal planar arrangement around Cu was obtained in 2004 by Schrader et al.[42] The addition of a large excess of diethylzinc and cyclohexenone to this precatalyst, formed from CuI and a phosphorus triamide ligand, started the conjugate addition proving the activity of the complex (Figure 1.2c). Recently, the first study on the precatalytic copper complex with phosphoramidite ligands in solution has appeared.[43] Zhang and Gschwind investigated the structures of the complexes formed from CuCl and the phosphoramidite ligands **L1** and **L10**, (Figure 1.3) in $CDCl_3$. A ratio of 2:1 between copper and ligand was chosen, in accordance with the optimal ratio based on synthetic procedures.[40,44]



L1 **L10**

Figure 1.3

$CDCl_3$ was the solvent of choice because, in this solvent, only a single copper species could be detected. This experimental evidence is in agreement with the strong solvent effect observed in catalysis.[44b,38,,45] By combining information from ^{31}P-NMR spectroscopy, mass spectrometry and elemental analysis, a mixed trigonal/tetrahedral configuration of the precatalytic complex of general formula $[L_3Cu_2Cl_2]$ was proposed (Figure 1.4). Such a stoichiometry can explain why ratios of ligand to copper lower than 1.5:1 were leading to reduced ee values.[38b] The presence of three equiv. of ligand can account for the negative nonlinear effect observed,[44a] assuming that the copper complex formed from different enantiomers of the ligand may lead to an active catalyst

which generate racemic product. Moreover the aggregation level of the complex and the presence of bridging anions may account, respectively, for the influence of the solvent and the dependence on the copper salt used.

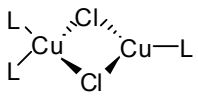
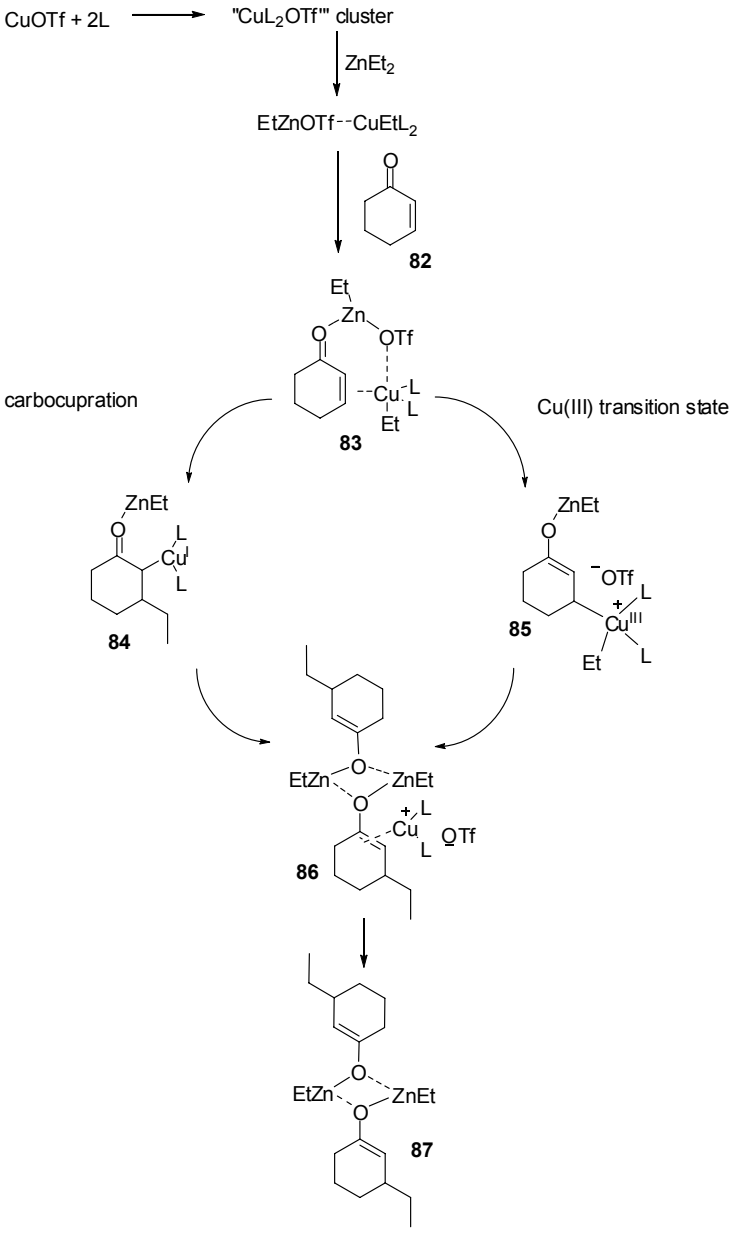


Figure 1.4 *Precatalytic complex in $CDCl_3$ (L = **L1** or **L10**).*[43]

Several copper salts have been tested in the 1,4-addition of diorganozincs to α,β-unsaturated systems.[38b,40,47] Optimal results have been obtained with $Cu(OTf)_2$[38c] as well as CuTC,[46] $Cu(OAc)_2 \cdot H_2O$ and Cu naphthenate.[44b] It has been shown that both Cu(I) and Cu(II) salts can be used with comparable results: for example CuOTf and $Cu(OTf)_2$ show the same activity but $Cu(OTf)_2$ has a better solubility in organic solvents and is more convenient to handle.[38c] *In situ* reduction of Cu(II) to Cu(I) by R_2Zn is presumed to occur.[38c,47,48] A first experimental proof of this assumption has been reported in 1999 by Chan[49] who has shown by ^{31}P-NMR that a new phosphorus species appears upon addition of diethylzinc to a $Cu(OTf)_2$/diphosphite solution. This was proposed to be the LCuEt species. More recently both Schrader[42] and Piarulli[50] observed, using EPR spectroscopy, in the reaction of $Cu(OTf)_2$ with an excess of Et_2Zn complete conversion of paramagnetic Cu(II) to the diamagnetic Cu(I).

By analogy with organocuprate[36] and zincate chemistry,[51] Feringa et al. postulated for the first time in 1997 a similar mechanism for the copper-catalyzed organozinc addition.[44a,47] First alkyl transfer[51b,52] from the organozinc reagent to the copper centre is assumed (Scheme 1.20). Coordination of the zinc to the carbonyl function (hard/hard) and π-complexation of the copper to the double bond of the enone **82** (soft/soft) results in complex **83**.


CuOTf + 2L
"CuL2OTf" cluster
ZnEt2
EtZnOTf--CuEtL2
82
carbocupration
Cu(III) transition state
83
84
85
86
87

Scheme 1.20

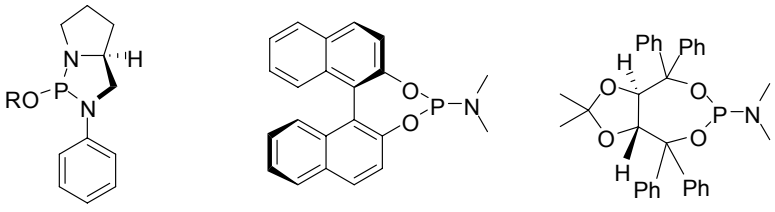
Considering the high levels of enantioselectivity reached in this reaction, it is possible that species **83** is a bridged bimetallic complex in which the conformation of the enone is fixed. Both Alexakis and Noyori have proposed that, before the alkyl transfer, complex **83** reacts with a molecule of diethyl zinc to generate a highly reactive Cu/Zn cluster (not shown). [44b,53a]

At this point two reaction pathways are possible: the carbocupration mechanism involving **84** in which the alkyl transfer occurs by means of a 1,2-migratory insertion or an oxidative addition/reductive elimination mechanism in which a 3-cuprio(III) enolate **85** is formed. [54]

In the first case the stereochemistry of the product should be established in the formation of the α-cuprio(I) ketone **84** by alkyl transfer to the favorable π-face of complex **83**. For the Cu(III) intermediate pathway the formation of two diastereomeric enolates **85** is assumed: a selective reductive elimination, in which the alkyl transfer occurs faster for one of the two diastereomers, should determine the enrichment in one of the two enantiomers.[54]

Regardless of the mechanism both reaction pathways generate, in the end, the copper-bound enolate **86** as an intermediate which releases the zinc enolate **87** in its thermodynamically stable dimeric form.[53]

Unfortunately, to date experimental evidence to discriminate between the two mechanisms has not been reported. Kinetic studies carried out by Schrader[42] support both a carbocupration and a rate-limiting reductive elimination. Investigations on ligand acceleration were performed with various classes of trivalent phosphorus ligands (Figure 1.5) having different electronic and steric properties.[42]



L11a: R = methyl
L11b: R = α-naphthyl

L12

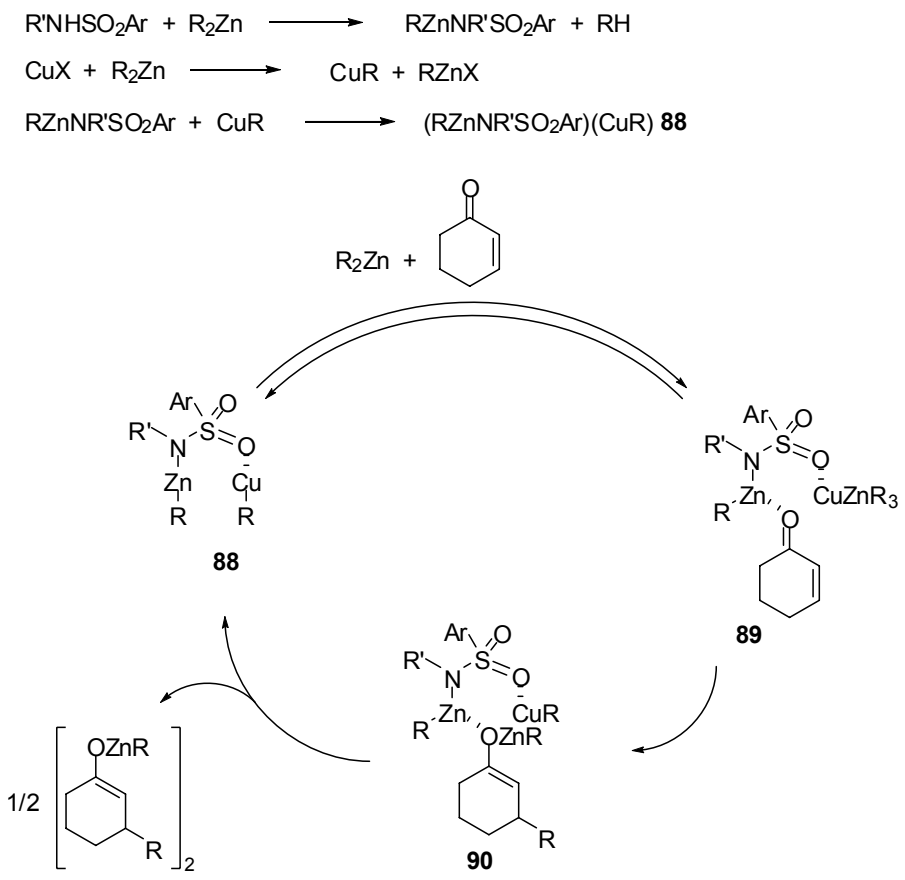
L13

Figure 1.5

In the $Cu(OTf)_2$-catalyzed addition of diethylzinc to cyclohexenone both ligands **L12** and **L13** proved to provide much faster reactions than the phosphorus acid diamide monoester **L11a/b**. This result is in agreement with a rate-limiting reductive elimination step in which electron donation to the Cu(III) centre is required and, hence, electron-withdrawing P(III) ligands facilitate this process. By contrast, electron-donating ligands improve the nucleophilicity of the alkyl-Cu species, and should accelerate the rate of the oxidative addition step. Furthermore, for all the ligands examined, first order kinetics in substrate, Et_2Zn and catalyst were observed in accordance with the assumption that the three components form a ternary 1:1:1 π-complex in which the alkyl transfer takes place.[42]

1.3.1.2 Non-phosphorus ligands

Different results were observed with the use of sulfonamides,[50,53a,55] bis(oxazolines)[56] and phosphoramides.[57] In 2000 Noyori et al.[53a] proposed a catalytic cycle (Scheme 1.21) in which a bimetallic complex **88** is formed upon reaction of Et_2Zn, *N*-monosubstituted sulfonamide and the alkyl-Cu complex generated *in situ* by transmetalation. In species **88** the sulfonamide ligand serves as a three atom-spacer bridging between the Zn and Cu atoms. The ethyl group on the copper atom in **88**, however, is not reactive enough to undergo nucleophilic attack to the cyclohexenone. Species **88** acts as a bifunctional catalyst in the reaction between Et_2Zn and cyclohexenone by coordinating both the reactants. In particular, the Lewis acidic zinc atom can coordinate the carbonyl group of cyclohexanone while the cuprate moiety can interact with a molecule of Et_2Zn to form a Cu/Zn cluster **89** (species **89** is a schematic representation of the actual species that would constitute a more complex cluster).



Scheme 1.21

Based on kinetic studies, the formation of a catalyst/Et_2Zn/substrate cluster **89** is assumed. The first order kinetics in both [Et_2Zn] and $[substrate]_{t=0}$ suggests the alkyl transfer as the rate determining step, rather than the product release step.[50,53a] The formation of a bimetallic complex in which one molecule of ligand provides a bridge between the two metals was also proposed for bis(oxazoline) and binaphthyl-thiophosphoramide type of ligands (Figure 1.6).

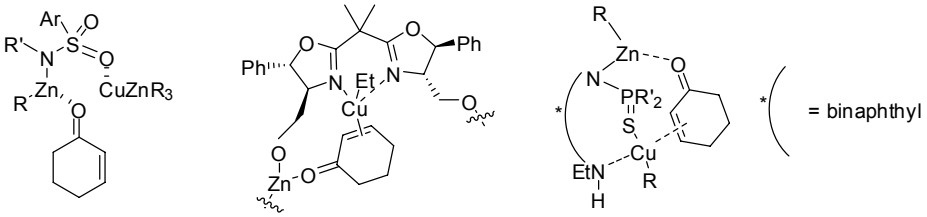


Figure 1.6

A major difference in mechanistic interpretation compared to those based on the catalytic cycles proposed for the Cu-phosphorous ligands system discussed so far, arises from the analysis of the $^{12}C/^{13}C$ isotope effect which suggests a concerted mechanism for the alkyl transfer (Figure 1.7).[55]

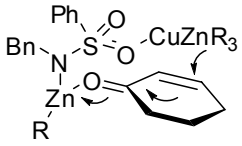
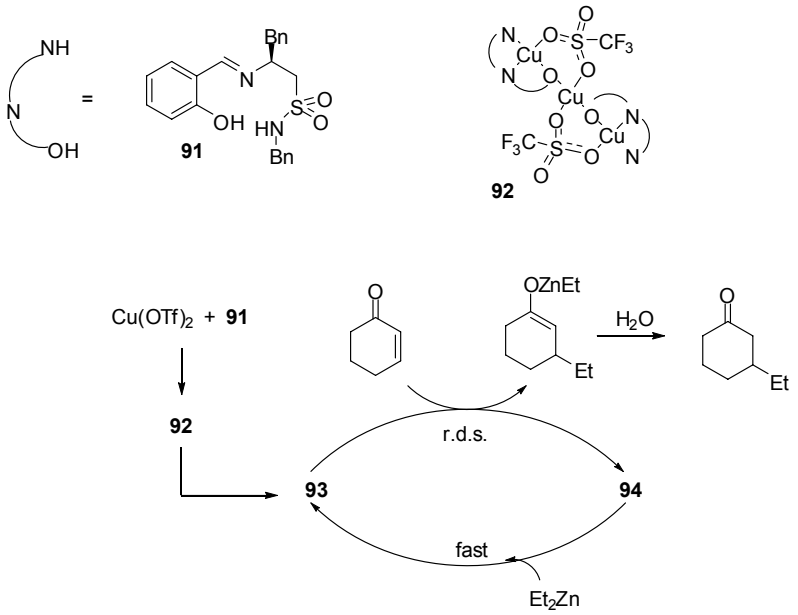


Figure 1.7

In 2004 Gennari and Piarulli[50] studied the 1,4-addition of Et_2Zn to cyclohexenone catalyzed by $Cu(OTf)_2$ and ligand **91** (Scheme 1.22). The authors proposed structure **92** for the complex formed upon reaction of $Cu(OTf)_2$ and the Schiff base **91**. Reaction of **92** with an excess of Et_2Zn yields the catalytically active species **93**, which can transfer the ethyl group to the β-position of the cyclohexenone following first-order kinetics. The resulting copper species **94** can then react with Et_2Zn to regenerate the active catalyst **93**.

The lack of a general mechanistic insight into the asymmetric conjugate addition of organometallic reagents can partly be attributed to the sensitivity of the reaction itself to almost any variation in the reaction parameters.[38]



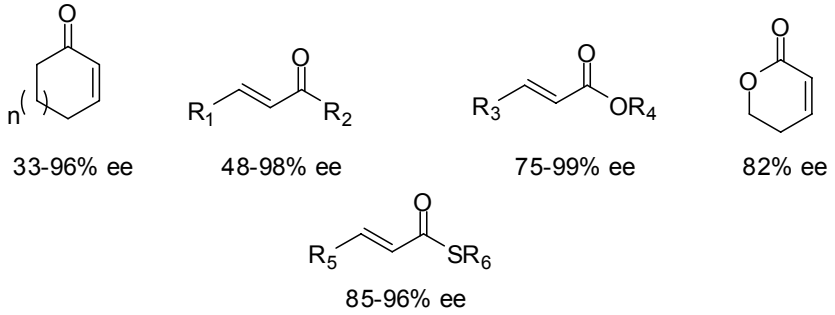
Scheme 1.22

1.3.2 Grignard reagents

The higher reactivity of Grignard reagents in comparison with organozinc reagents has hampered for a long time the development of highly efficient copper-catalyzed enantioselective methods for the conjugate addition to α,β-unsaturated compounds. Competition between 1,2- and 1,4-addition is often responsible for lower selectivity while the presence of a fast uncatalyzed reaction or catalysis by free copper salts decreases the level of enantiocontrol. Moreover, the existence of different competing organometallic complexes in solution, as usually observed in cuprate chemistry, renders the design of efficient catalytic systems more difficult.

Recently, Feringa *et al.* developed the first highly enantioselective method for the conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds based on the use of catalytic amounts of Cu(I) salts and chiral ferrocenyl diphosphine ligands, such as Josiphos (**L14**) and Taniaphos. This

method proved to be extremely efficient for a broad range of substrates including cyclic and acyclic enones, enoates and thioenoates (Scheme 1.23).[30,58]



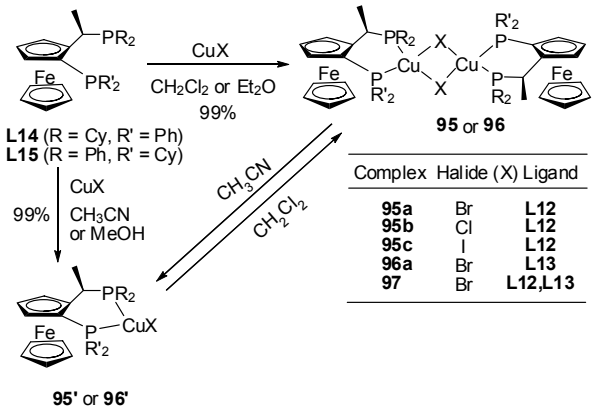
33-96% ee | 48-98% ee | 75-99% ee | 82% ee

85-96% ee

Scheme 1.23

Inspired by this excellent result, a detailed mechanistic study of the copper-catalyzed conjugate addition of Grignard reagents was undertaken.[59]

The air stable complexes **95** and **96** were prepared by addition of equimolar amounts of copper(I) salt and the chiral ligands **L14** and **L15**, respectively, in the appropriate solvent (Scheme 1.24).



Complex	Halide (X)	Ligand
95a	Br	**L12**
95b	Cl	**L12**
95c	I	**L12**
96a	Br	**L13**
97	Br	**L12,L13**

Scheme 1.24

Interestingly, a solvent-dependent equilibrium between dinuclear (**95** or **96**) and mononuclear (**95'** or **96'**) species was established in solution.[58c] The crystal

structure of the dinuclear complex **96a**, prepared from $CuBr{\cdot}SMe_2$ and **L15**, was obtained:[60] the asymmetric unit consists of one moiety of a dinuclear copper complex, which is bridged by two Br atoms resulting in a C_2-symmetric unit. A molecule of water is also present in the cell (Figure 1.8).

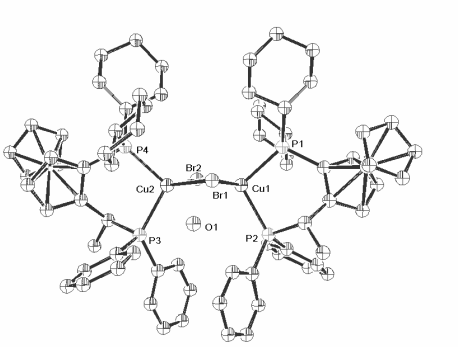


Figure 1.8 *X-ray structure of (S,R)-**96a** (hydrogen atoms are omitted for clarity).*[60]

The X-ray structure of the mononuclear complex **95a'** (Figure 1.9) and of the heterocomplex **97** (Figure 1.10), prepared from (*R,S*)-**L14**, (*S,R*)-**L15** and $CuBr{\cdot}SMe_2$ in the ratio 1:1:2 (see Scheme 1.24), were obtained also.

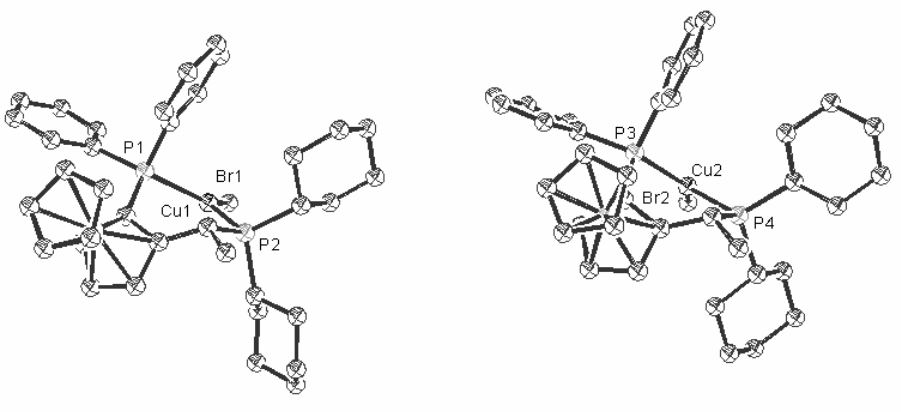


Figure 1.9 *X-ray structure of **95a'** (hydrogen atoms are omitted for clarity).*

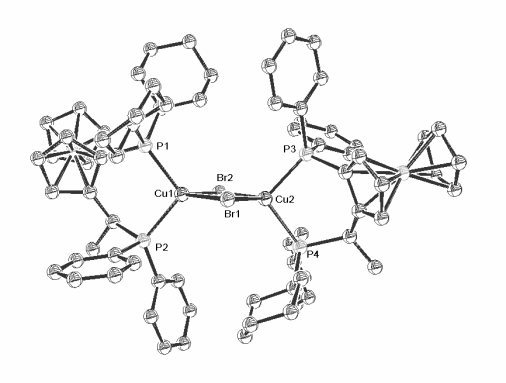
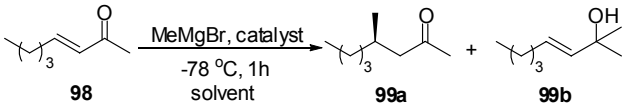


Figure 1.10 *X-ray structure of (R,S,S,R)-**97** (hydrogen atoms are omitted for clarity).*

Electrochemical studies were performed in order to study the different electronic properties of the copper(I) complexes **95** and **96** and the effect of ligand and halide variation. The copper complexes **95a-c**, formed from CuBr, CuCl and CuI, respectively, gave almost identical electrochemistry while significant differences were observed in the redox properties of the copper(I) centres upon ligand variation. The copper complex **96a**, for example, undergoes oxidation more easily than complex **95a** because it is more electron rich. This finding suggests that the difference in reactivity may be explained in terms of the energy match between substrate and catalyst. Next, the influence of the solvent and the halide was investigated for the addition of MeMgBr to octenone under three different sets of conditions (Scheme 1.25): (1) in the absence of catalyst, (2) using 5 mol% of $CuBr{\cdot}SMe_2$, (3) in the presence of 5 mol% of chiral complexes **95a-c**. Good results both in terms of regio- and enantioselectivity were obtained in CH_2Cl_2, toluene, Et_2O and tBuOMe. The use of THF afforded mainly the 1,2-addition product **99b** while the 1,4-adduct **99a** was obtained in racemic form. The solvent dependence is probably determined primarily by the Schlenk equilibrium,[61] which favours the solvent-coordinated monoalkylmagnesium species $EtMgBr{\cdot}Et_2O$ in Et_2O and the species R_2Mg and $MgBr_2$ in THF.

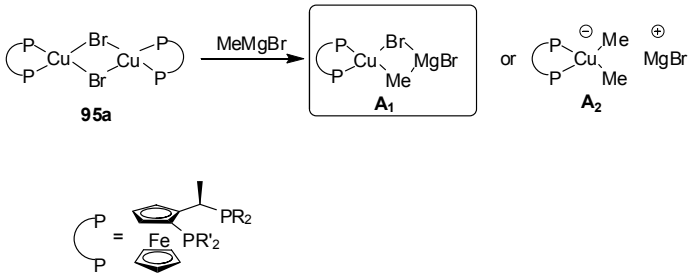


Conditions:

(1) Uncatalyzed reaction: MeMgBr (1.5 equiv)
(2) Racemic series: CuBr·SMe$_2$, (5 mol%), MeMgBr (1.5 equiv)
(3) Enantioselective series: **95a-c** (5 mol%), MeMgBr (1.1 equiv)

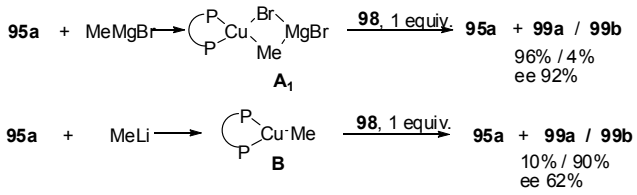
Scheme 1.25 *Addition of MeMgBr to octenone **98**[59] (see text).*

The nature of the halide used has a remarkable effect on the outcome of the reaction. The presence of bromide either in the Grignard reagent or in the Cu(I) salt appears to be essential to achieve of high regio- and enantioselectivity. This points to a bridging role for the bromide in the anticipated dinuclear complex (vide infra) with precise geometrical constraints. By analogy to non-catalytic cuprate chemistry,[36] it is proposed that the copper complexes **95a** and **96a** undergo transmetalation upon addition of the organometallic reagent. ^{31}P-NMR studies, performed at -60 ˚C, reveal that upon addition of MeMgBr to **95a** the formation of a new species **A** takes place. This result is compatible with the large ^{31}P-NMR upfield shift assigned by Chan and coworkers to a (L)nCuEt species, generated from Et_2Zn, $Cu(OTf)_2$ and a phosphine ligand.[49] On the base of kinetic measurements as well as the linear relationship between the product and the catalyst enantiomeric purity, two different structures are proposed for **A** (Scheme 1.26). The 1:1 ratio between Cu and Me revealed by ^{1}H-NMR, excludes $\mathbf{A_2}$ and confirm that the active form of the catalyst is the copper complex $\mathbf{A_1}$.



Scheme 1.26 *Structure proposed for species **A**.*

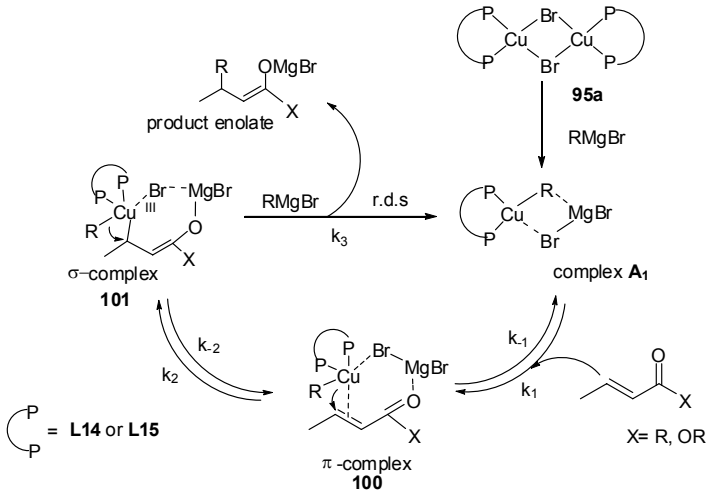
Addition of MeMgBr to **95a** gives the Cu-complex $\mathbf{A_1}$ as the major product also in Et_2O and in toluene. On the other hand, in THF the formation of a different species **B** is observed by ^{31}P-NMR spectroscopy (Scheme 1.27). The role played by species $\mathbf{A_1}$ and **B** in the catalyzed conjugate addition was investigated via ^{1}H- and ^{31}P-NMR spectroscopic studies conducted after stoichiometric addition of octenone **98** to their solutions at -78 °C. Addition of an equimolar amount of **98** to $\mathbf{A_1}$ provided the 1,4-adduct **99a** with a regioselectivity of 96% and 92% ee while the same addition to species **B** gave mainly the 1,2-addition product and only 10% of the 1,4-product with 62% ee (Scheme 1.27). This result is in agreement with the experiments, which show a high regio- and enantioselectivity in toluene and poor selectivity in THF, indicating that the formation of complex $\mathbf{A_1}$ is essential for the successful outcome of the reaction.



Scheme 1.27

In the proposed catalytic cycle (Scheme 1.28) the unsaturated carbonyl compound approaches the alkylcopper complex $\mathbf{A_1}$ from the least hindered side forming, in a reversible way, a π-complex **100** between the alkene moiety of the substrate and the copper atom; further stabilization of the π-complex **100** is provided by the complexation through Mg^{2+} and the carbonyl oxygen. The reversible formation of such π-complex is supported by the ability of the catalytic system to effect *cis-trans* isomerization of the enone.[59,62] The π-complex is probably in fast equilibrium with to a Cu(III) intermediate **101**, formed via an intramolecular rearrangement, where the copper atom is bound to the β-carbon of the substrate. Kinetic studies suggest that the formation of the Cu(III) intermediate **101** is followed by the rate-limiting reductive elimination step in which both the substrate and Grignard reagent are involved, as suggested by the dependence of the reaction rate on their concentrations. In

the case of the Grignard reagents such a dependence suggests that it acts to displace the product from the Cu(III) intermediate **101** and reform the catalytically active complex $\mathbf{A_1}$.

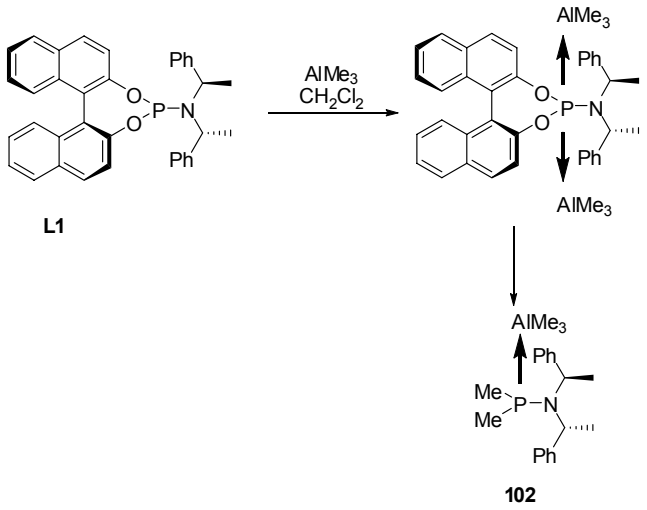


Scheme 1.28 *Proposed catalytic cycle for the CA addition of Grignard reagents to α,β-unsaturated carbonyl compounds.*

1.3.3 Trialkylaluminium

In recent years, in particular due to efforts in the Woodward group, it has been shown that trialkylaluminium reagents, i.e. Me_3Al, can be employed successfully in copper-catalyzed conjugate additions.[63,64,65] Despite the high selectivities obtained, no mechanistic studies to elucidate the nature of the catalytically active species have been reported thus far. Only one example of ^{31}P-NMR spectroscopic analysis has been described, although in that study the catalyst is used to perform asymmetric ring opening of meso bicyclic hydrazines.[66] The authors propose, based on ^{31}P-NMR spectroscopic data, that the catalytic system $Cu(OTf)_2$/**L1** can undergo *in situ* replacement of the Binol moiety of **L1** with methyl groups, triggered by Me_3Al (Scheme 1.29). This results in the formation of a potentially active species **102**. The same behavior is observed in toluene while no modification of the phosphoramidite could be observed in THF or diethyl ether.

Further investigations are needed to clarify the actual mechanism of the 1,4-addition in presence of trialkylaluminium reagents as nucleophiles.



L1 **102**

Scheme 1.29

1.4 Aim and outline of this thesis

The work described in this thesis is focused on broadening the scope of the enantioselective copper-catalyzed addition of organometallic reagents, in particular organozinc reagents and trimethylaluminum, to the synthesis of several versatile chiral synthons. Particular attention is dedicated to the enantioselective synthesis of *N*-heterocycles and to their sequential functionalization to form natural products and to the enantioselective synthesis of acyclic α-chiral amines, versatile building blocks for the synthesis of biologically active compounds. Different approaches will be discussed and investigated with particular focus on the use of copper complexes in combination with chiral phosphoramidite ligands.

In Chapter 2 the synthesis of optically active α-substituted piperidones is reported, using the conjugate addition of organozinc reagents and trimethylaluminum to the corresponding 2,3-dehydro-4-piperidones. The

interest in these compounds derives from the possibility of employing them as precursor in the synthesis of several alkaloid natural products. The recurrence in nature of substitution at both the α-positions of the piperidine ring prompted us to develop a stereoselective protocol for such transformations, as will be discussed in Chapter 3. An example of the synthetic application of this method will be presented via the total synthesis of the alkaloid (+)-myrtine.

In Chapter 4 a new procedure for the catalytic enantioselective synthesis of α-chiral amides is shown. The α,β-unsaturated systems, at which the addition reaction is performed, consist of *N*-formylimines, generated *in situ* starting from stable amido sulfone precursors. Interestingly, modification of the phosphoramidite ligand is observed under the reaction conditions. An investigation of the causes and the effects of such transformations on the outcome of the addition reaction is provided.

In Chapter 5 the first catalyzed enantioselective addition of Et_2Zn to *in situ* generated *N*-acyloxyiminium ions, focusing on the synthesis of chiral-substituted tetrahydroisoquinolines, is introduced. A thorough optimization of the reaction conditions allows to obtain the desired product in modest enantioselectivity, opening the way to the development of more efficient catalysts for this reaction.

Chapter 6 deals with the broadening of the scope of the copper catalyzed 1,4-addition to the challenging acyclic dienone substrates. A survey of the recent progress made in this area is given. The enantioselective copper/phosphoramidite-catalyzed 1,4-addition of dialkylzinc reagents and trimethylaluminum to acyclic dienones is described. The products of this reaction, obtained with enantioselectivities of up to 95%, can be further functionalized by a second conjugate addition, or employed in an enolate trapping, ring-closing metathesis protocol to yield optically active cyclopentenones.

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Chapter 2

Catalytic enantioselective conjugate addition to 2,3-dehydro-4-piperidones

The first, highly enantioselective, copper/phosphoramidite-catalyzed conjugate addition of dialkylzinc reagents and trimethylaluminum to N-substituted 2,3-dehydro-4-piperidones is described.

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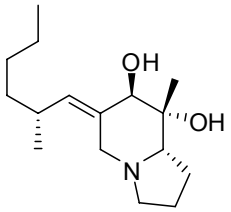
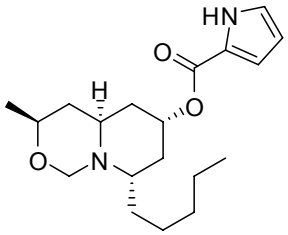
2.1 Introduction

The piperidine ring motif is ubiquitous by appearing in the structure of many alkaloid natural products and drugs. The synthetic importance of substituted piperidines has led to a wide area of research devoted to the preparation of these systems.[1] In particular the interest with regard to biologically active target molecules has driven tremendous efforts toward the development of diastereo- and enantioselective syntheses of piperidines.[2]

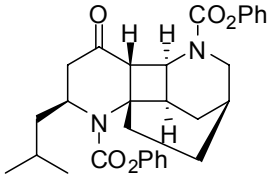
Amongst piperidine derivatives, optically active α-substituted 4-piperidones play a key role as versatile building blocks for the synthesis of alkaloids (Scheme 2.1).



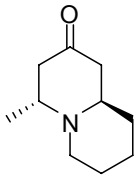
(+)-Allopumiliotoxin 267A



(+)-Hyperaspine



intermediate in the synthesis of Spirolucidine

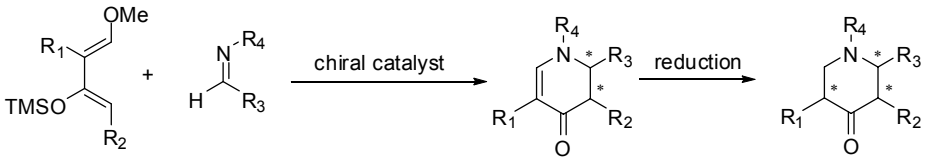


(+)-myrtine

Scheme 2.1

The development of stereoselective methods based on the use of catalytic amounts of a chiral source for the synthesis of these compounds, however, is still considered a challenge. Only a few catalytic enantioselective procedures for the preparation of optically active α-substituted piperidones have been reported in the literature. Furthermore, most of these methods are based on the catalytic enantioselective aza-Diels-Alder reaction, which in fact affords

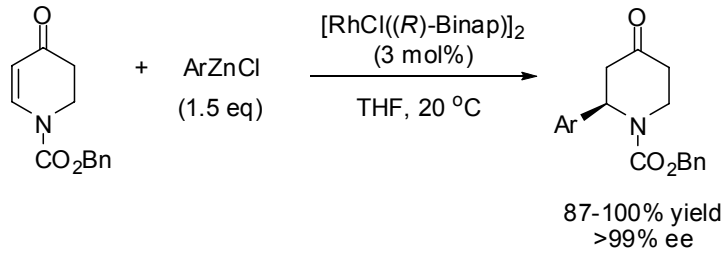
chiral α-substituted 2,3-dehydropiperidones.[3] Reduction of the olefin moiety is required to yield the desired product.[4]



Scheme 2.2 *An aza-Diels-Alder reaction followed by reduction of the double bond.*

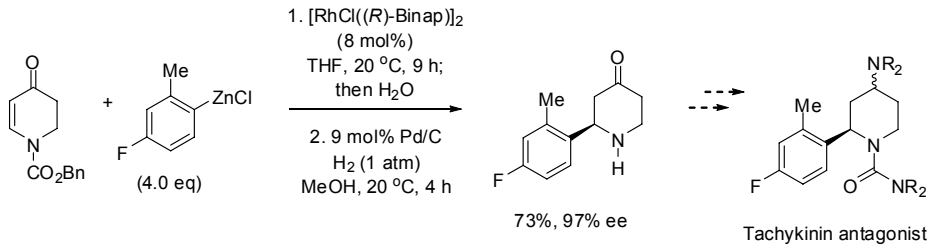
A powerful tool in the synthesis of α-substituted 4-piperidones consists of the conjugate addition of organometallic reagents to *N*-protected-2,3-dehydro-4-piperidones, however, only two examples of the catalytic enantioselective version of this reaction have been described thus far.[5,6]

In 2004 Hayashi and coworkers[5] described the highly enantioselective rhodium-catalyzed addition of arylzinc reagents to *N*-acyl-2,3-dehydro-4-piperidones (Scheme 2.3).



Scheme 2.3 *The conjugate addition of ArZnCl to dehydropiperidones.*[5]

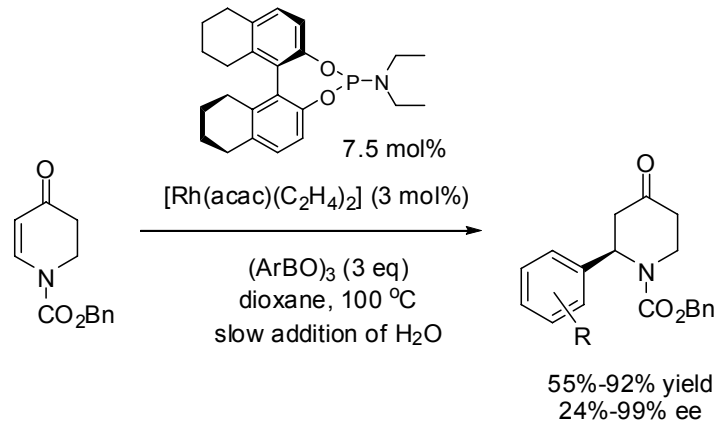
Using a rhodium catalyst containing (*R*)-Binap as the chiral ligand, 2-aryl-4-piperidones were obtained in high yield and with complete stereocontrol. The method described has been applied to the preparation of an intermediate in the synthesis of a Tachykinin antagonist employed in the treatment of depressive states and anxiety (Scheme 2.4).



Scheme 2.4 *Synthesis of a Tachykinin antagonist intermediate.*

The use of other organometallic reagents, such as organoboron or organotitanium reagents, as nucleophiles was investigated also. However, using Binap as the chiral ligand, full conversion was not observed despite the addition products being obtained with high enantioselectivity.

Organoboron reagents proved to be highly effective in the rhodium/phosphoramidite catalyzed 1,4-addition to *N*-Cbz-2,3-dehydro-4-piperidones developed by Minnaard et al.[6] in 2005 (Scheme 2.5).



Scheme 2.5 *The conjugate addition of organoboron reagents to dehydropiperidones.*[6]

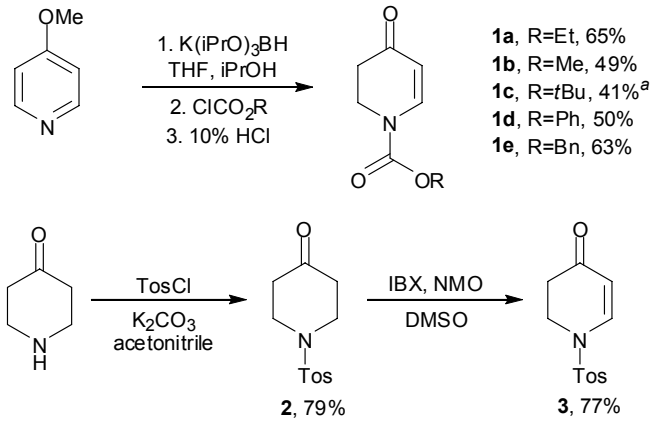
In this procedure the arylboronic acid is gradually generated *in situ* by slow hydrolysis of the corresponding arylboroxine. The use of three equivalents of the arylboroxine is required to reach full conversion.

Both these procedures allow the introduction, in high yield and with high enantioselectivity, of several aryl substituents. The presence of an alkyl substituent at the 2-position of the piperidone moiety is a recurrent structural feature in alkaloids also (Scheme 2.1), therefore it was envisioned that the conjugate addition of dialkylzinc reagents would offer a complementary route for the asymmetric synthesis of 2-alkyl-4-piperidones.

2.2 Copper/phosphoramidite catalyzed addition of dialkylzinc reagents to N-protected-2,3-dehydro-4-piperidones

2.2.1 Results and discussion

N-substituted-2,3-dehydro-4-piperidones **1a**-**e**, bearing carbamate protecting groups, were synthesized from 4-methoxypyridine in one step using the procedure of Comins et al.[7] Tosyl-protected 2,3-dehydro-4-piperidone **3** was prepared in two steps from 4-piperidone, via IBX-promoted oxidation[8] of piperidone **2**[9] (Scheme 2.6).



[a] In case of R = *t*-Bu, Boc_2O was used together with citric acid workup.

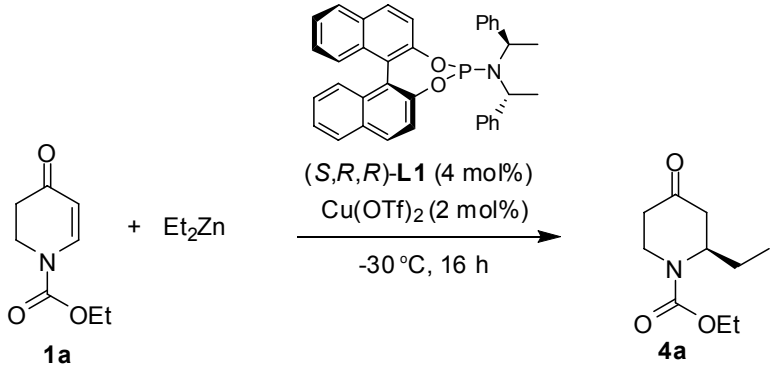
Scheme 2.6 *Synthesis of the precursors used in this chapter.*

The starting compounds obtained were subjected to the copper catalyzed conjugate addition of dialkylzinc reagents in the presence of a copper catalyst

generated *in situ* from one equiv of $Cu(OTf)_2$ and two equiv of the chiral phosphoramidite ligand (*S*,*R*,*R*)-**L1**.

Copper complexes based on homochiral BINOL-based phosphoramidites proved to be excellent catalysts in the conjugate addition of dialkylzinc reagents to enones.[10] In the case of 2-cyclohexenone,[11] for example, full conversion of the starting material was observed after 3 h, using 2 mol% of the copper catalyst formed from ligand (*S*,*R*,*R*)-**L1**. The addition product was obtained in 94% isolated yield and with >98% ee. Under the same experimental conditions, it was not possible to achieve full conversion of the *N*-acyl-2,3-dehydropiperidones that were examined (Scheme 2.6). Because of the lower reactivity shown by these compounds compared to other enones the reaction time was extended to 16 h.

Table 2.1 *Screening of solvents used in the CA reaction.*

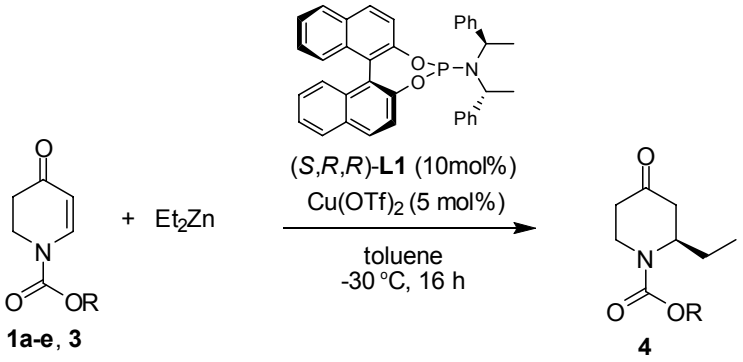


1a **4a**

Entry	Solvent	Conv. (%)	ee (%)
1	toluene	87	92
2	*n*-hexane	20	66
3	Et_2O	25	55
4	CH_2Cl_2	36	13
5	THF	10	2

The Et_2Zn addition in toluene, at -30 °C to the model substrate **1a** yielded product **4a** with 92% ee (Table 2.1, entry 1). Lower enantioselectivities were observed in all the other solvents examined. Prompted by this promising result, a further optimization of the reaction conditions was undertaken. It was found that it was necessary to increase the catalyst loading to 5 mol% in order to achieve good to full conversions in toluene.

Table 2.2 *Variation of the nitrogen protecting group.*

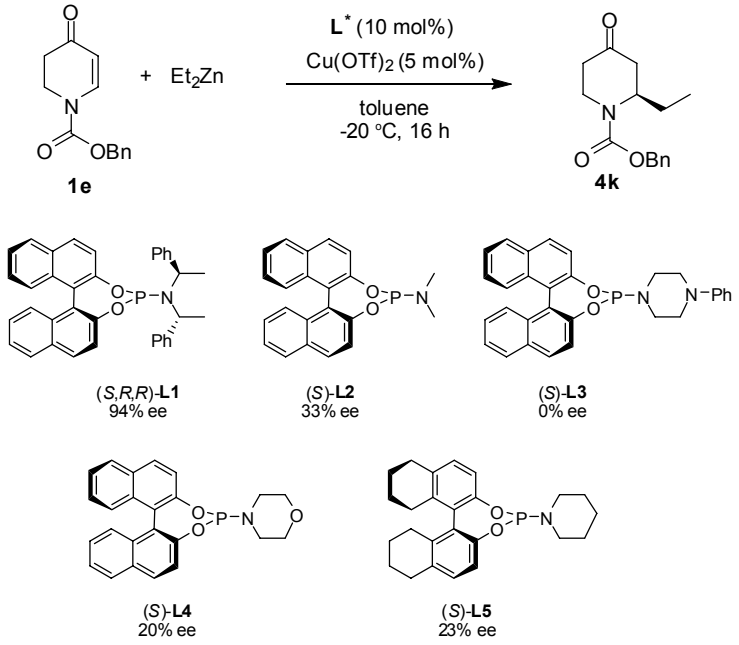


Entry	Substrate	R	Time (h)	Temp. (°C)	Product	Yield (%)	ee (%)
1	**1a**	Et	16	-25	**4a**	35	94
2	**1a**	Et	16	-25	**4a**	50[a]	92
3	**1b**	Me	40	-25	**4d**	20	87
4	**1c**	*t*-Bu	24	-20	**4f**	58	91
5	**1d**	Ph	16	-25	**4g**	87	94
6	**1e**	Bn	8	0	**4k**	69	91
7	**1e**	Bn	28	-20	**4k**	70	94
8	**3**	Tos[b]	24	-20	**4o**	50	81

[a] 2 mol% of catalyst loading and 1 equiv of $[Zn(OTf)_2]$. [b] The nitrogen is protected with a *p*-tosyl group.

The type of carbamate protecting group used was found to influence the isolated yields of the addition products (Table 2.2). Compounds **4a** and **4d** were obtained in 35% and 20% yield, respectively (entries 1 and 3). The addition of 1 equiv of $Zn(OTf)_2$ improved the yield of **4a** to 50%, using only 2 mol% of catalyst. The enantioselectivity was unaffected. Better results were obtained with substrate **1c** (entry 4). Substrates **1d** and **1e** protected, respectively, with a phenoxy or benzyloxy carbamate afforded the corresponding addition products **4g** and **4k** in good to high yield and with 94% enantioselectivity (entries 5-7). Protection of the nitrogen with a *p*-tosyl group (**3**) gave product **4o** with 91% ee but with lower yield (50%).

Variation in the chiral ligand employed resulted in a dramatic decrease in the stereocontrol observed indicating that the combined effect of the chiral C_2-symmetric and sterically demanding amine and the BINOL moieties is important (Scheme 2.7).



Scheme 2.7 *Structure of the phosphoramidite ligands tested in the catalyzed CA of Et_2Zn.*

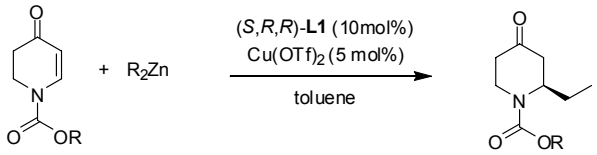
2.2.2 Scope of the reaction

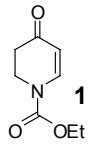
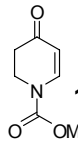
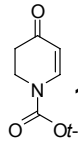
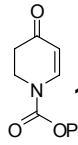
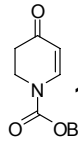
Using the copper catalyst formed from 5 mol% of $Cu(OTf)_2$ and 10 mol% of the chiral phosphoramidite ligand (*S*,*R*,*R*)-**L1** in toluene, the scope of the reaction regarding the use of other dialkylzinc reagents was investigated (Table 2.3).

Full conversion was observed for the conjugate addition of *i*-Pr_2Zn to all the substrates tested. The α-substituted piperidones **4b**,**e**,**i**,**m** were obtained in good to high yields (68%-84%) and with enantioselectivities ranging between 94% and 97% (Table 2.3, entries 2, 5, 9, 13). The addition of *n*-Bu_2Zn was performed on the dehydropiperidones **1a**, **1d** and **1e**; modest to good enantioselectivity (59%-82% ee) was achieved, albeit with low yields for the addition products in all the cases (entries 3, 10, 14). An increase of the temperature from 0 ˚C to room temperature was necessary for the addition to substrate **1e** to proceed (entry 14).

As for the *n*-butyl substitution, the introduction of a methyl group using Me_2Zn was problematic, also. Because of the lower reactivity of Me_2Zn in comparison to Et_2Zn and *i*-Pr_2Zn, no conversion was detected for reactions performed below 0 °C. The addition was slow even at room temperature affording product **4h** in 25% yield (entry 8) and product **4l** in 44% yield (entry 12) after, respectively, 48 and 24 h. Product **4l** was isolated with high enantioselectivity (96%). Because of the low yield and the formation of by-products that makes purification difficult, this method for the formation of α-methyl-substituted piperidones can be considered far from optimal, however. Further studies were, therefore, undertaken to develop a successful procedure for methyl substitution.

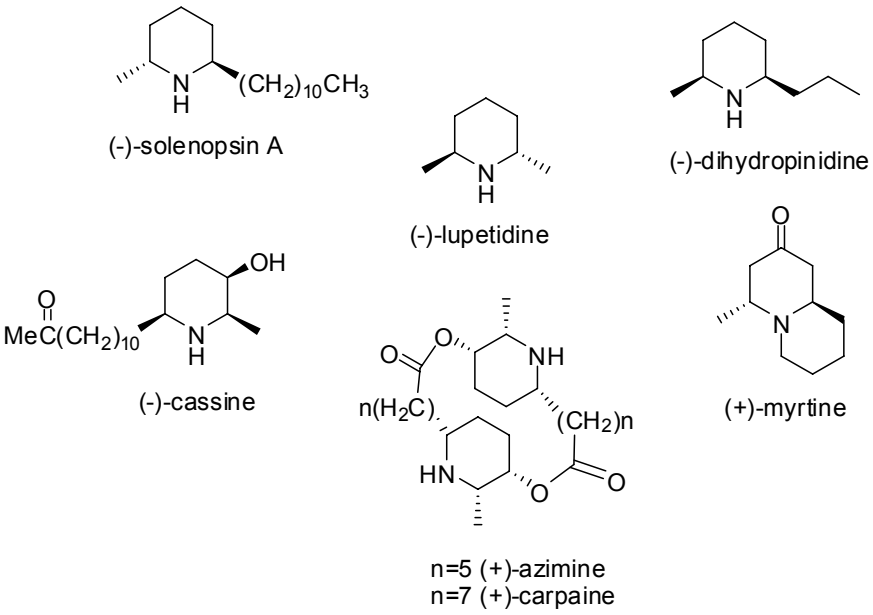
Table 2.3 *Scope of the reaction.*



Entry	Substrate	R_2Zn	Time (h)	T (°C)	Product	Yield (%)	ee (%)
1	 **1a**	Et_2Zn	16	-25	**4a**	35	94
2		*i*-Pr_2Zn	16	-25	**4b**	80	96
3		*n*-Bu_2Zn	16	-25	**4c**	16	74
4	 **1b**	Et_2Zn	40	-25	**4d**	20	97
5		*i*-Pr_2Zn	16	-25	**4e**	79	94
6	 **1c**	Et_2Zn	24	-20	**4f**	58	91
7	 **1d**	Et_2Zn	16	-25	**4g**	87	94
8		Me_2Zn	48	rt	**4h**	25	48
9		*i*-Pr_2Zn	16	-25	**4i**	84	97
10		*n*-Bu_2Zn	16	-25	**4j**	22	82
11	 **1e**	Et_2Zn	28	-20	**4k**	70	94
12		Me_2Zn	24	0 - rt	**4l**	44	96
13		*i*-Pr_2Zn	24	-20	**4m**	68	95
14		*n*-Bu_2Zn	48	0 - rt	**4n**	12	59

2.3 Copper/phosphoramidite catalyzed addition of Me_3Al to *N*-protected-2,3-dehydro-4-piperidones

The research efforts directed towards a method that provides α-methyl-4-piperidones in high yield and with high enantioselectivity are justified by the frequent recurrence of this structural motif in piperidine based natural products and alkaloids of biological importance (Scheme 2.8). Solenopsine A, for example, is one of the several alkaloids present in the venom of the red fire ant, *Solenopsis invicta*. The fire ant alkaloids exhibit hemolytic, insecticidal and antibiotic activity.[12] (-)-Cassine has antimicrobial activity against Staphylococcus aureus.[13] Azimine[14] and carpaine,[15] isolated, respectively, from *Azima tetracantha L.* and *Carica papaya L.*, are a novel class of macrocyclic dilactones containing a 2,3,6-trisubstituted piperidine skeleton, and carpaine is reported to exhibit a wide range of biological properties including antitumor activity at low concentrations.

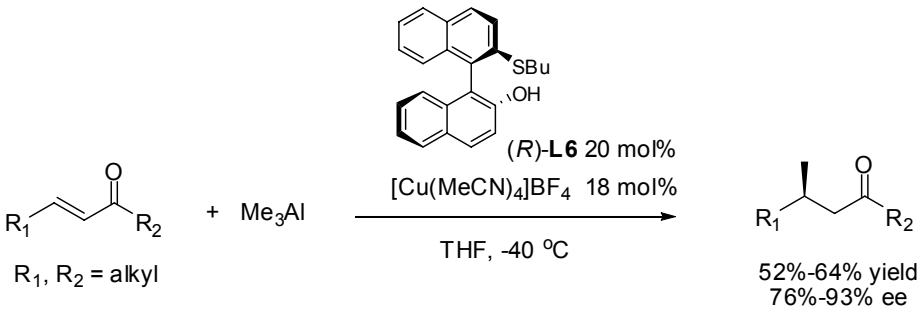


Scheme 2.8 *α-Methyl motif in alkaloid structures.*

We decided to investigate the use of the reactive species Me_3Al as a methyl source in the copper-catalyzed conjugate addition to *N*-acyl-2,3-dehydro-4-piperidones. The development of synthetic procedures based on the use of trialkylaluminum reagents is interesting due to their low toxicity and high chemoselectivity.[16]

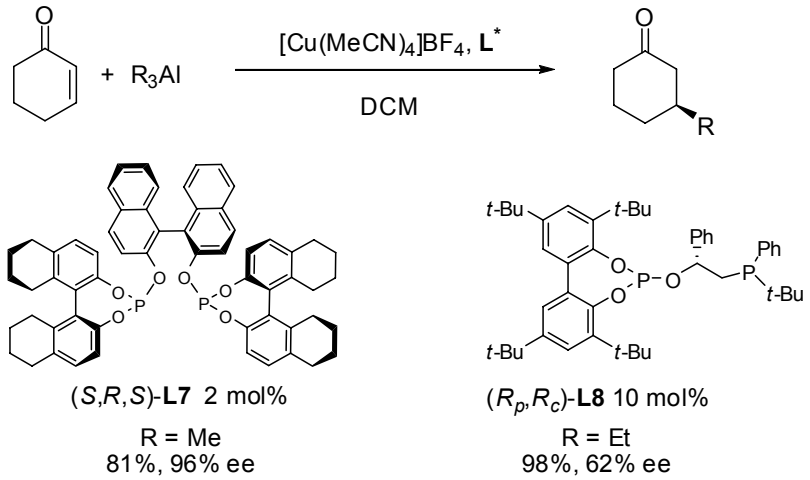
2.3.1 Literature precedents

A number of procedures have been reported for the asymmetric conjugate addition of R_3Al reagents to enones. Woodward *et al.*[17] studied the asymmetric copper catalyzed addition of Me_3Al to linear aliphatic enones, in the presence of chiral thioether and thiouretane ligands. Noteworthy, with the chiral 2-hydroxy-2'-alkylthio-1,1'-binaphthyl ligand (*R*)-**L6** depicted in Scheme 2.9 enantioselectivities of up to 93% were reached.



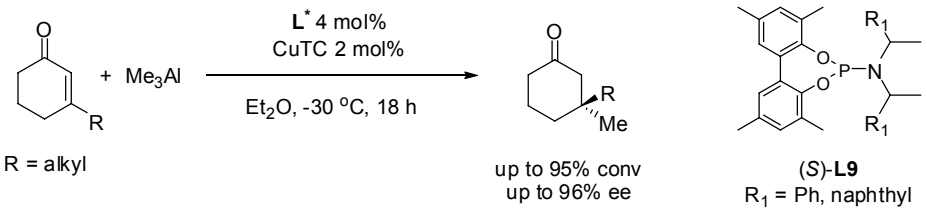
Scheme 2.9 *Me_3Al addition to linear aliphatic enones.*

High enantioselectivity (96%) in the conjugate addition of Me_3Al to 2-cyclohexenone was reported first by Chan and coworkers[18] using a catalytic amount of $[Cu(MeCN)_4]BF_4$ and the BINOL-based diphosphite ligand (*S*,*R*,*S*)-**L7** (Scheme 2.10). Lower enantioselectivity (68%) was achieved in the addition of Et_3Al to cyclohexen-2-one in the presence of the chiral phosphine-phosphite ligand (R_p,R_c)-**L8**.[19] The related addition of Et_3Al to cyclopenten-2-one,[20] using the same class of ligands, was described also.



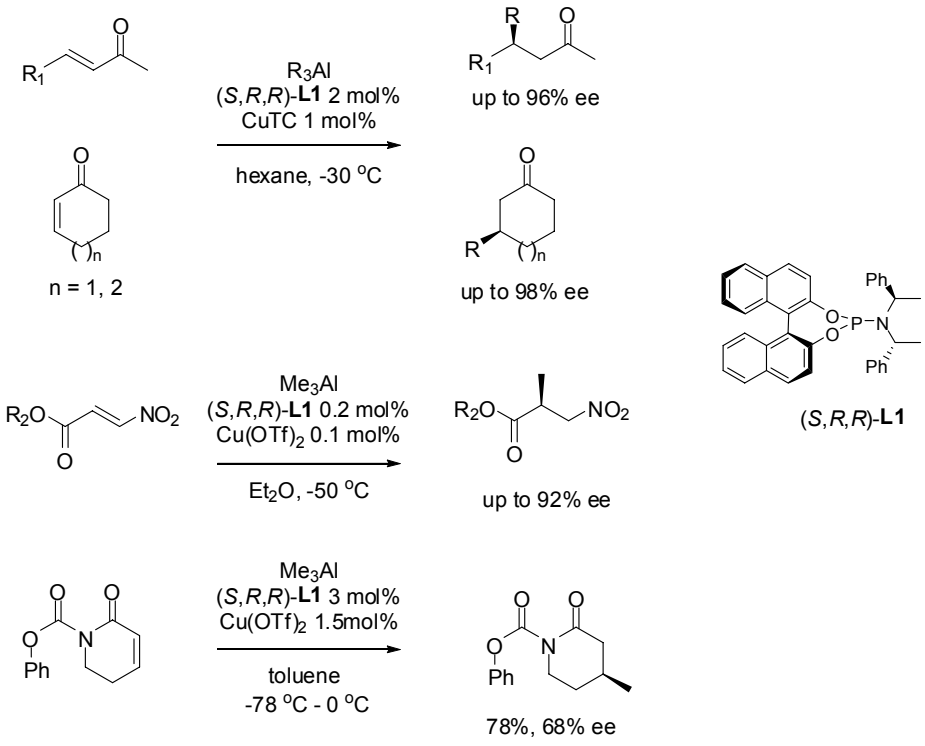
Scheme 2.10 *R_3Al addition to 2-cyclohexenone.*

Chiral phosphoramidites proved to be a competitive alternative to phosphite ligands. Remarkably, the addition of Me_3Al to β-trisubstituted enones allows for the formation of quaternary stereocenters (Scheme 2.11).[21]



Scheme 2.11 *Formation of quaternary stereocenters.*

Interestingly, the BINOL-based phosphoramidite **L1** has been shown to induce high levels of stereocontrol in the organoaluminum addition (Me_3Al, Et_3Al) to a variety of substrates such as cyclic and acyclic enones,[22] nitroalkenes[23] and α,β-unsaturated lactams (Scheme 2.12).[24]



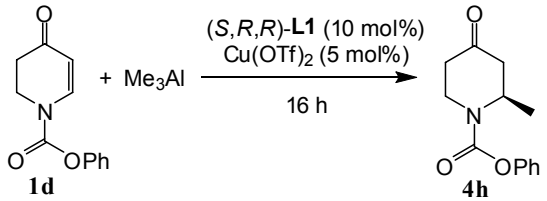
Scheme 2.12 *Cu/**L1**-catalyzed conjugate additions of R_3Al.*

2.3.2 Results and discussion

The chiral phosphoramidite ligand (*S*,*R*,*R*)-**L1** was tested in the $Cu(OTf)_2$ catalyzed addition of Me_3Al to *N*-protected-2,3-dehydro-4-piperidones. Compound **1d** was chosen as a model substrate in the optimization of reaction conditions. The catalyst was prepared freshly prior to the reaction and its loading was set to 5 mol%. The reactions were carried out in several solvents at -50 °C. Low conversion to product **4h** was observed in *t*-BuOMe and THF (Table 2.4, entries 1 and 2), while complete consumption of the starting material was detected in CH_2Cl_2 and in toluene (entries 3 and 4). However, the formation of a mixture of products in the first case made the isolation of **4h** inconvenient. The reaction in toluene, on the other hand, proceeded smoothly to give the methyl-substituted product **4h** in 87% yield and with 90% ee. Good

results were also obtained in Et_2O (76%, 92% ee), even though after reaction overnight some starting material was still present (entry 5).

Table 2.4 *Solvent and temperature effects in the Me_3Al addition to **1d**.*



Entry	Solvent	T (°C)	conv.(%)	Yield (%)	ee (%)	Remarks
1	*t*-BuOMe	-50	14	n.d.	0	
2	THF	-50	29	n.d.	n.d.	by-products
3	CH_2Cl_2	-50	full	n.d.	n.d.	by-products
4	toluene	-50	full	87	90	
5	Et_2O	-50	85	76	92	
6	Et_2O	-78	50	22	93	
7	toluene	-78		no reaction		
8	toluene	-60		no reaction		

A decrease in the temperature to -78 °C resulted in lower conversion of **1d** when the reaction was carried out in Et_2O and no conversion in toluene. Further investigations showed that, in toluene, the addition of Me_3Al to **1d** does not occur if the temperature is brought even a few degrees below -50 °C. The reason for this can be attributed to the different aggregation level of the Me_3Al in the different solvents. In hydrocarbon solvents, such as toluene, the coordination of the solvent to the Me_3Al may be weak, therefore self-association of Me_3Al molecules is possible. ^{1}H-NMR spectroscopy studies[25] conducted in toluene indicate that at -55 °C almost all of the Me_3Al is in its dimeric form (Figure 2.1). At that temperature, in fact, the ratio between bridged and terminal methyl group was found to be 1:2. By increasing the

temperature, the signals of the two types of methyl groups merge into one peak due to rapid exchange. At higher temperatures the existence of monomeric Me_3Al can be expected. In a coordinating solvent such as Et_2O, on the other hand, the interaction between the oxygen atom in the solvent molecules and the aluminum atom may prevent the self-association of the organometallic molecules.

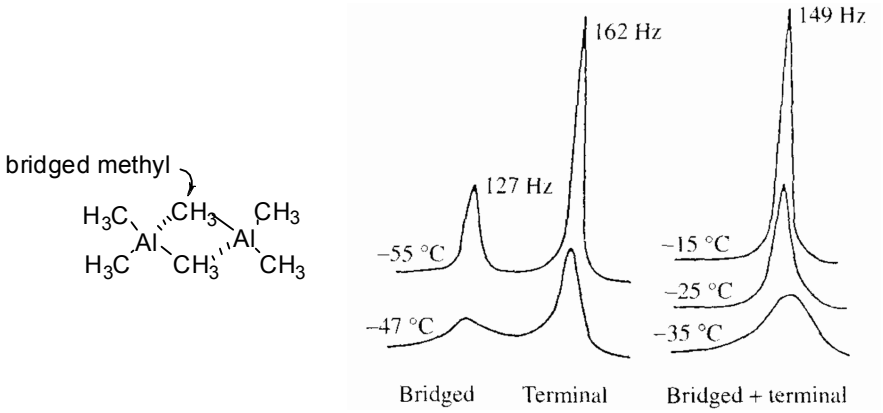
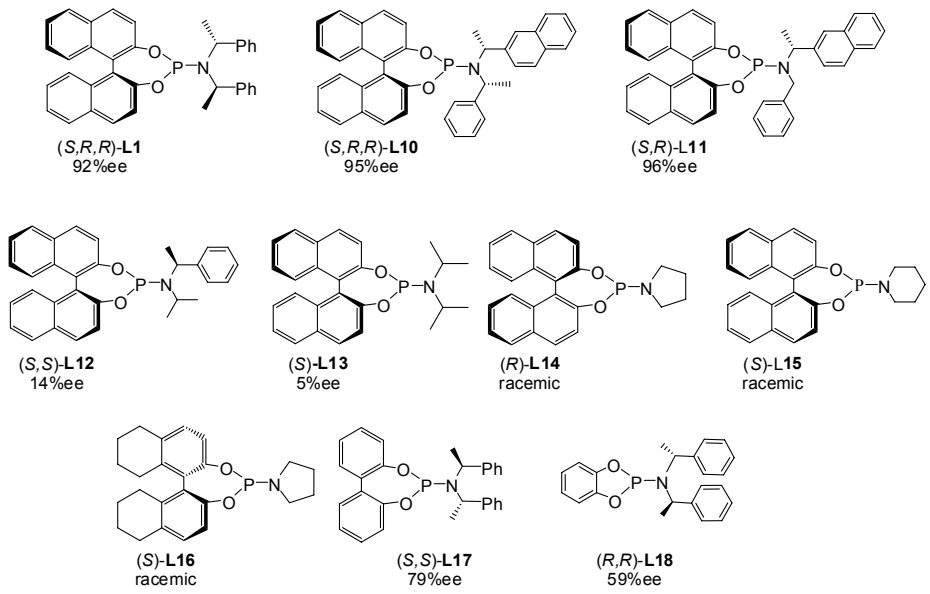


Figure 2.1 *^{1}H-NMR spectrum of trimethylaluminum in toluene.*[25]

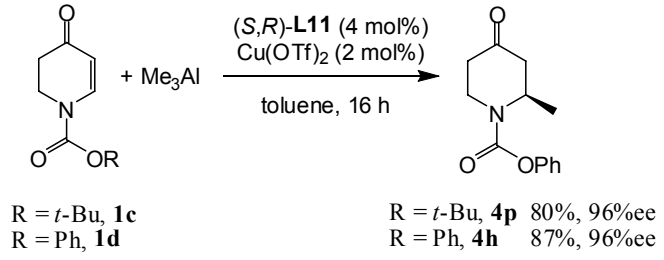
It is possible that when the Me_3Al is present in dimeric form, the methyl transfer is hampered due to the stability of the dimer. Furthermore, in the addition reaction the aluminium reagent can act as a Lewis acid, activating the enone moiety toward the nucleophilic addition. In the bridged structure the aluminum atom might be unavailable for such interaction with the substrate.

The use of other, structurally related, phosphoramidite ligands was investigated. The substitution of one of the phenyl groups of the amine moiety in (*S*,*R*,*R*)-**L1** with a naphthyl substituent resulted in an increase in enantioselectivity (Scheme 2.13, (*S*,*R*,*R*)-**L10** and (*S*,*R*)-**L11**). Removal of the aromatic groups of the amine part turned out to decrease the ee obtained. Modification of the BINOL moiety led to a decrease in stereocontrol also.



Scheme 2.13 *Phosphoramidite ligands tested in the copper catalyzed CA of Me_3Al.*

The chiral phosphoramidite (*S*,*R*)-**L11** was selected as ligand of choice. High yield and 96% enantioselectivity were obtained in the Me_3Al addition to **1c** and **1d** under optimized conditions. The catalyst loading was reduced to 2 mol% without affecting the isolated yield or the enantioselectivity (Scheme 2.14).



Scheme 2.14 *Me_3Al addition under optimized conditions.*

2.3.3 Co-solvent effect

The addition reaction of Me_3Al to the *N*-acyl-2,3-dehydro-4-piperidones catalyzed by the complex formed from $Cu(OTf)_2$ and (*S*,*R*)-**L11** was found to be difficult to reproduce. For the addition reaction of Me_3Al to compound **1c**, conversions ranging between 43% and 95% were observed in combination with enantioselectivities between 46% and 96%.

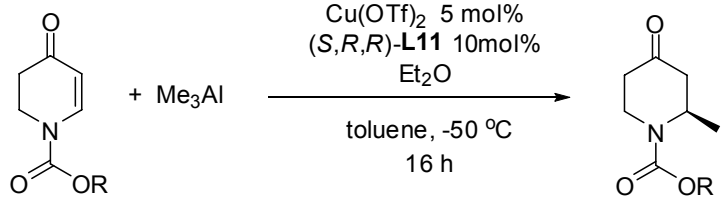
A possible explanation can be found in the formation of a heterogeneous system upon addition of the organometallic species to the reaction mixture in which the copper complex and the starting material are present already. The formation of insoluble aggregates might inhibit the reaction and makes mixing inefficient. Dissolution of the suspension is achieved by increasing the temperature from -50 °C to -40 °C, in which case the addition product **4p** can be obtained in 75% yield and with a reproducible but lower 88% ee.

Further investigations revealed that the addition of a small amount of an appropriate co-solvent was crucial to the reproducibility of the results. The addition of 5 to 25 mol% of dry Et_2O, with respect to the substrate, to the reaction mixture guaranteed high conversion and a reproducible high ee (Table 4.5, entries 1-4, 7). Interestingly, if the reaction is carried out in Et_2O using (*S*,*R*)-**L11** as chiral ligand, the addition product is obtained in racemic form (entries 6 and 8). The presence of a coordinating species might break up, at least partially, the existing aggregates facilitating the reaction. Over the course of the reaction, a gradual disappearance of the turbidity was observed. At 50% conversion, a clear solution was observed.

Furthermore, the coordinating properties of the co-solvent might affect the aggregation level of the Me_3Al, favoring the monomeric reactive species (vide supra).

A similar effect was observed upon addition of a small amount of other solvents, such as THF, EtOAc and CH_2Cl_2. The use of Et_2O, however, provides the highest enantioselectivity of 96% and 73% isolated yield.

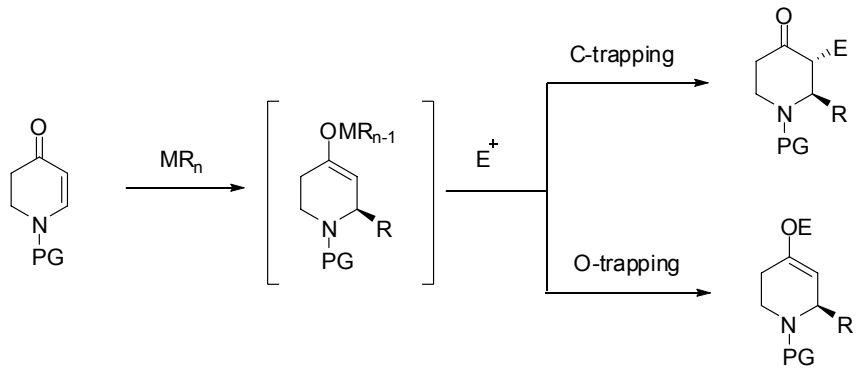
Table 4.5 *Co-solvent effect.*



Entry	Substrate	Et_2O (mol%)	Product	conv. (%)	ee (%)
1	**1c**	5	**4p**	82	95
2	**1c**	10	**4p**	86	96
3	**1c**	15	**4p**	84	96
4	**1c**	25	**4p**	84	94
5	**1c**	200	**4p**	38	44
6	**1c**	solvent	**4p**	24	5
7	**1d**	10	**4h**	> 95	95
8	**1d**	solvent	**4h**	76	0

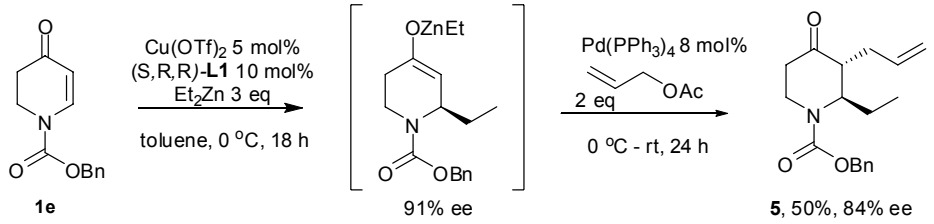
2.4 Further developments

The primary product of a conjugate addition of an organometallic reagent to an α,β-unsaturated system is, indeed, a metal enolate which can be further functionalized in a one-pot procedure.[26,27] Addition of an appropriate electrophile to the enolate formed *in situ* can furnish the α,β-disubstituted product, in case of C-trapping, or an enol ether in the case of O-trapping (Scheme 2.15).



Scheme 2.15 *General scheme for the enolate-trapping reaction with electrophiles.*

The aluminum enolates generated from the *N*-protected-2,3-dehydro-4-piperidones showed to be unreactive towards several electrophiles such as alkyl halides, pivaloyl chloride and benzaldehyde. However, it was possible to trap the enolate formed from **1e** and Et_2Zn in a palladium-catalyzed allylation using 8 mol% of $Pd(PPh_3)_4$ and allyl acetate. The reaction proceeded with complete diastereocontrol affording exclusively the *trans* isomer of the α,β-disubstituted piperidone **5** in 50% yield and with 84% ee (Scheme 2.16).



Scheme 2.16 *Tandem 1,4-addition-allylation.*

In the first step of the reaction, the Et_2Zn addition to **1e** is carried out at 0 ˚C affording the 1,4-addition product **4h** with 91% ee. The tandem product, on the other hand, was isolated with an enantioselectivity of 84%. This unexpected decrease in the optical purity of **5** suggests that the two enantiomers of the zinc enolate react in the allylation reaction with different speed; in particular the minor enantiomer might react faster, leading to a decrease in the enantioselectivity. Such an effect might be explained considering the presence of the chiral phosphoramidite ligand in the reaction mixture. The existence of a

dynamic equilibrium of transmetallation of the chiral ligand (*S*,*R*,*R*)-**L1** from the copper to the palladium complex would result in the formation of a chiral catalyst in the allylation reaction as well. In this case, the formation of two diastereomeric transition states would account for the different reaction rates observed for the two enantiomers of the zinc enolate.

2.5 Conclusions

The first highly efficient copper-catalyzed addition of organozinc reagents and trimethylaluminum to *N*-protected-2,3-dehydro-4-piperidones has been described. This method is a powerful tool to obtain 2-alkyl-4-piperidones, key building blocks in the synthesis of alkaloid natural products. The use of organozinc reagents allows the introduction of Et, *i*-Pr and *n*-Bu groups in good yield and with enantioselectivities of up to 97%, using the phosphoramidite (*S*,*R*,*R*)-**L1** as chiral ligand. The use of Me_3Al represents an useful alternative to Me_2Zn in the synthesis of 2-methyl-4-piperidones. In the latter case, enantioselectivities of up to 96% are obtained using the chiral phosphoramidite (*S*,*R*)-**L11**. The presence of a catalytic amount of a co-solvent proved to be essential for the reproducibility of the results.

The trapping of the zinc enolate formed in the Et_2Zn addition to compound **1e** via palladium catalyzed allylation shows the synthetic versatility of this reaction, affording exclusively the *trans* 2,3-disubstituted-4-piperidones in a one-pot procedure. Moreover, the presence of an allylic moiety makes the system prone to further functionalization that can lead to complex target molecules.

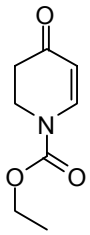
2.6 Experimental Section

General Methods. All reactions were performed in oven or flame dried glassware under inert atmosphere of N_2 or argon and conjugate additions were carried out using standard Schlenk techniques. Toluene, THF and ether were distilled from sodium, *n*-hexane and CH_2Cl_2 from CaH_2. Dialkylzinc reagents: Me_2Zn (2M in toluene), Et_2Zn (1M in *n*-hexane), *i*-Pr_2Zn (1M in toluene) and Me_3Al (1 M in *n*-heptane) were purchased from Aldrich, Bu_2Zn (1M in *n*-heptane) was purchased from Fluka. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 TLC-plates F254 and visualized using UV or phosphomolybdic acid. Flash chromatography was carried out on silica gel (Aldrich, 230 – 400 mesh). ^1H NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ as solvent, ^{13}C NMR spectra were obtained at 50, 75 or 100 MHz in $CDCl_3$ (Varian spectrometers). Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for hydrogen atoms, δ = 77.0 for carbon atoms). Optical rotations were recorded on Schmidt+Haench Polartronic MH8 instrument at 589 nm. Gas chromatography was performed on Hewlett-Packard HP 6890 Series GC System with flame ionization detector on chiral columns and HPLC on Shimadzu LC-10AD VP instrument equipped with six parallel normal phase chiral columns, using a diode array detector. Mass spectra were recorded on an AEI-MS-902 mass spectrometer. Absolute configurations were assigned on the basis of the facial selectivity observed with the same catalysts with enones.[11]

General procedure for preparation of substrates 1a,b,d,e.

4-Methoxypyridine (1.0 mL, 10 mmol) was dissolved in *i*-PrOH (20 mL) and cooled to -20 °C. K(*i*-PrO)$_3$BH[28] (20 mL, 20 mmol, 1M in THF) was added followed by the appropriate chloroformate (11 mmol) in Et_2O (3 mL) over 10 min. The reaction mixture was stirred at -20 °C for 1 h and then it was poured into 1M aq. HCl (30 mL) and stirred for 10 min at r.t. The resulting solution was diluted with Et_2O, the phases separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography or by crystallization.

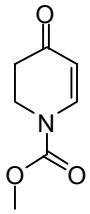
1-Ethoxycarbonyl-2,3-dehydro-4-piperidone (1a).[7]



Following general procedure A pure **1b** was obtained in 65% yield as a colorless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.82 (m, 1H), 5.31 (d, *J*=8.0 Hz, 1H), 4.27 (q, *J*=7.1 Hz, 2H), 4.00 (t, *J*=7.4 Hz, 2H), 2.53 (t, *J*=7.2 Hz, 2H), 1.32 (t, *J*=7.2 Hz, 3H).

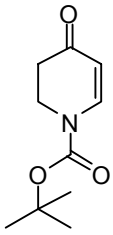
1-Methoxycarbonyl-2,3-dehydro-4-piperidone (1b).[29]



Following general procedure A pure **1a** was obtained in 49% yield as a colorless oil.

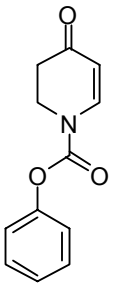
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.78 (m, 1H), 5.29 (d, *J*=8.0 Hz, 1H), 3.98 (t, *J*=7.4 Hz, 2H), 3.82 (s, 3H), 2.51 (t, *J*=7.4 Hz, 2H).

1-*t*-Butoxycarbonyl-2,3-dehydro-4-piperidone (1c).



4-Methoxypyridine (0.50 mL, 5.0 mmol) was dissolved in *i*-PrOH (10 mL) and cooled to -15 °C (ice-methanol). K(*i*-PrO)$_3$BH (10 mL, 10 mmol, 1M in THF) was added to this solution followed by Boc_2O (1.20 g, 5.5 mmol) in Et_2O (3 mL). The resulting mixture was stirred for 1 h at -15 °C and then 10% aq. citric acid (20 mL) was added and the stirring continued for 10 min at r.t. The solution was diluted with Et_2O, phases were separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (*n*-heptane/AcOEt=2:1) to give 409 mg (41%) of **1c** as a white solid. M.p. 53-54°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=5.9 Hz, 1H), 5.29 (d, *J*=8.1 Hz, 1H), 3.96 (t, *J*=7.1 Hz, 2H), 2.53 (t, J=7.1 Hz, 2H), 1.53 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.6, 144.0, 106.72, 83.5, 42.3, 41.2, 35.7, 28.0. Elem. anal. calcd. for $C_{10}H_{15}NO_3$ C 60.90, H 7.67, N 7.10; found C 60.90, H 7.72, N 7.13. HRMS calc. for $C_{10}H_{15}NO_3$ 197.1052, found 197.1058.

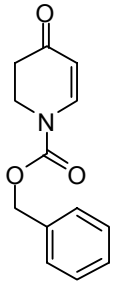
1-Phenoxycarbonyl-2,3-dehydro-4-piperidone (1d).[29]



The crude product obtained by general procedure A was purified by flash chromatography (*n*-pentane/AcOEt=2:1) followed by crystallization from CH_2Cl_2/*n*-hexane to give pure **1d** in 50% yield as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.92 (d, *J*=8.1 Hz, 1H), 7.37 (t, *J*=7.8 Hz, 2H), 7.23 (t, *J*=7.5 Hz, 1H), 7.12 (d, *J*=8.7 Hz, 2H), 5.41 (d, *J*=7.8 Hz, 1H), 4.13 (m, 2H), 2.61 (t, *J*=7.3 Hz, 2H).

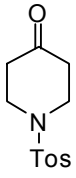
1-Benzyloxycarbonyl-2,3-dehydro-4-piperidone (1e)[5]



The crude product obtained by general procedure A was purified by crystallization from AcOEt/*n*-hexane to give pure **1e** in 63% yield as a white solid.

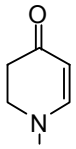
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.39 (m, 5H), 5.36 (m, 1H), 5.26 (s, 2H), 4.05 (t, *J*=7.2 Hz, 2H), 2.56 (t, *J*=7.2 Hz, 2H).

1-(Toluene-4-sulfonyl)-4-piperidone (2).[30]



4-Piperidone hydrochloride hydrate (1.54 g, 10 mmol) and K_2CO_3 (4.84 g, 35 mmol) were suspended in CH_3CN (30 mL) and the mixture cooled in an ice-bath. An acetonitrile (20 mL) solution of *p*-TsCl (2.10 g, 11 mmol) was added at once and the reaction mixture was stirred for 18 h, allowing the temperature to reach r.t. The solution was acidified with 1M aq. HCl until all white solid dissolved and extracted with AcOEt (3x). The combined organic extracts were washed with $NaHCO_3$ and brine, then dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (*n*-heptane/AcOEt=2:1) to give 2.01 g of **2** (79%) as a white solid. ^{1}H NMR (300 MHz, CDCl3) δ 7.68 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=7.3 Hz, 2H), 3.39 (t, *J*=5.9 Hz, 4H), 2.53 (t, *J*=5.9 Hz, 4H), 2.44 (s, 3H).

1-(Toluene-4-sulfonyl)- 2,3-dehydro-4-piperidone (3).

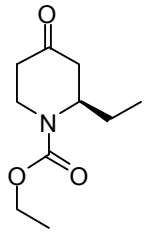


IBX (2.46 g, 8.8 mmol) and NMO (1.03 g, 8.8 mmol) were dissolved in DMSO (8 mL) at r.t. To this solution piperidone **2** (1.01 g, 4.0 mmol) in DMSO (12 mL) was added at once and the resulting clear solution was stirred for 72 h at r.t. in a flask covered with aluminium foil. The reaction mixture was poured into sat. $NaHCO_3$ solution and extracted with Et_2O (3x). The combined organic extracts were extracted with sat. $NaHCO_3$ solution, H_2O and brine, then dried ($MgSO_4$) and concentrated. The resulting crude product was purified by flash chromatography (*n*-heptane/AcOEt=3:1) to yield 0.77 g (77%) of **3** as a white solid. M.p. 108-111°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 3H), 7.33 (d, *J*=7.7 Hz, 2H), 5.32 (d, *J*=8.1 Hz, 1H), 3.67 (t, *J*=7.0 Hz, 2H), 2.47 (t, *J*=7.0 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.5, 145.4, 143.5, 130.3, 127.3, 108.2, 43.9, 35.4, 21.6, 18.4. Elem. anal. calcd. for $C_{12}H_{13}NO_3S$ C 57.35, H 5.21, N 5.57, S 12.76; found C 57.80, H 5.43, N 5.38, S 13.07. HRMS calc. for $C_{12}H_{13}NO_3S$ 251.0616, found 251.0628.

General procedure for the copper-phosphoramidite conjugate addition of dialkylzinc reagents to *N*-protected-2,3-dehydro-4-piperidones.

$Cu(OTf)_2$ (9 mg, 0.025 mmol) and ligand (0.050 mmol) were dissolved in anhydrous toluene (1 mL) and stirred for 40 min at r.t. To this solution was added a solution of substrate (0.50 mmol) in toluene (2 mL) and the mixture was cooled to -25°C. A solution of a R_2Zn (1.50 mmol) was added dropwise and the reaction mixture was stirred at specified temperature, then quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography.

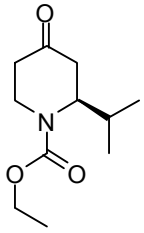
(*R*)-1-Ethoxycarbonyl-2-ethyl-4-piperidone (4a).



The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4c** in 35% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.51 (m, 1H), 4.33 (m, 1H), 4.18-4.11 (m, 2H), 3.14 (dt, *J*=12.8, 3.4 Hz, 1H), 2.60 (dd, *J*=14.8, 7.0 Hz, 1H), 2.48-2.39 (m, 1H), 2.28 (dd, *J*=14.4, 1.4 Hz, 2H), 1.54-1.40 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H), 0.83 (t, *J*=7.6 Hz, 3H). ^{13}C NMR (100 MHz;

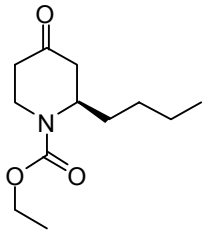
$CDCl_3$) δ 207.9, 155.6, 61.7, 53.5, 45.2, 40.5, 38.1, 25.3, 14.5, 10.0. HRMS calc. for $C_{10}H_{17}NO_3$ 199.1208, found 199.1204 GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100 °C, init. time: 15 min, rate: 10 °C/min, final temp. 150 °C, t_R 23.7 (minor), t_R 24.0 (major). $[\alpha]_D$ = –9.3 (c=0.72, $CHCl_3$), 92% ee.

(*R*)-1-Ethoxycarbonyl-2-isopropyl-4-piperidone (4b).



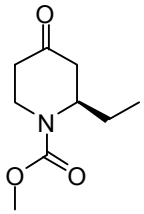
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4d** in 80% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.43 (m, 1H), 4.20-4.16 (m, 3H), 3.12 (t, *J*=6.6 Hz, 1H), 2.54-2.43 (m, 3H), 2.35 (dd, *J*=14.8, 2.0 Hz, 1H), 1.76-1.67 (m, 1H), 1.28 (t, *J*=7.2 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H), 0.86 (d, *J*=6.4 Hz, 3H). ^{13}C NMR (50 MHz; $CDCl_3$) δ 208.0, 155.7, 61.7, 58.5, 43.2, 40.6, 38.7, 29.2, 19.5, 18.7, 14.6. HRMS calc. for $C_{11}H_{19}NO_3$ 213.1365, found 213.1376. GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100 °C, init. time: 15 min, rate: 10 °C/min, final temp. 150 °C, t_R 26.3 (minor), t_R 26.5 (major). $[\alpha]_D$ = –14.6 (c=0.68, $CHCl_3$), ee=94%.

(*R*)-1-Ethoxycarbonyl-2-butyl-4-piperidone (4c).



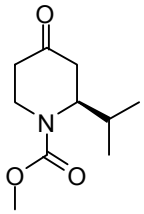
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4e** in 16% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.60 (m, 1H), 4.35 (m, 1H), 4.20-4.10 (m, 2H), 3.16 (dt, *J*=12.1, 3.6 Hz, 1H), 2.61 (dd, *J*=16, 6.6 Hz, 1H), 2.49-2.41 (m, 1H), 2.31-2.25 (m, 2H), 1.54-1.42 (m, 1H), 1.41-1.35 (m, 1H), 1.34-1.14 (m, 4H), 1.26 (t, *J*=7.0 Hz, 3H), 0.85 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (50 MHz; $CDCl_3$) δ 207.9, 155.6, 61.7, 52.1, 45.5, 40.6, 38.3, 31.9, 27.7, 22.2, 14.6, 13.9. HRMS calc. for $C_{12}H_{21}NO_3$ 227.1521, found 227.1528 GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100 °C, init. time: 15 min, rate: 10 °C/min, final temp. 150 °C, t_R 29.4 (minor), t_R 29.8 (major). $[\alpha]_D$ = +19.6 (c=0.73, $CHCl_3$), 74% ee.

(*R*)-1-Methoxycarbonyl-2-ethyl-4-piperidone (4d).



The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4a** in 20% yield as a colorless oil. ^1H NMR (400 MHz; $CDCl_3$) δ 4.49 (m, 1H), 4.32 (m, 1H), 3.71 (s, 3H), 3.15 (dt, *J*=13.0, 3.6 Hz, 1H), 2.59 (dd, *J*=14.4, 6.8 Hz, 1H), 2.48-2.39 (m, 1H), 2.28 (d, *J*=14.8 Hz, 2H), 1.54-1.41 (m, 2H), 0.83 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (50 MHz; $CDCl_3$) δ 207.8, 156.1, 53.6, 52.9, 45.1, 40.5, 38.2, 25.3, 10.0. HRMS calc. for $C_9H_{15}NO_3$ 185.1052, found 185.1059. GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100 °C, init. time: 15 min, rate: 10 °C/min, final temp. 150 °C, t_R 23.9 (minor), t_R 24.3 (major). $[\alpha]_D$ = –16.8 (c=0.58, $CHCl_3$), 88% ee.

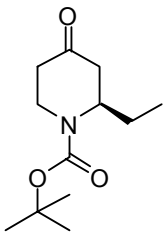
(R)-1-Methoxycarbonyl-2-isopropyl-4-piperidone (4e).



The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4b** in 79% yield as a colorless oil.

^1H NMR (400 MHz; $CDCl_3$) δ 4.51-3.92 (m, 2H), 3.74 (s, 3H), 3.13 (t, *J*=11.4 Hz, 1H), 2.58-2.39 (m, 3H), 2.30 (d, *J*=13.2 Hz, 1H), 1.79-1.66 (m, 1H), 0.96 (d, *J*=6.8 Hz, 3H), 0.86 (d, *J*=6.4 Hz 3H). ^{13}C NMR (50 MHz; $CDCl_3$) δ 207.9, 156.2, 58.7, 52.9, 43.2, 40.6, 38.8, 29.2, 19.5, 18.7. It was not possible to obtain an exact mass because the compound fragmented during HRMS measurement. CI-MS calc. for $C_{10}H_{18}NO_3$ (MH+) 200, found 200. GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100 °C, init. time: 15 min, rate: 10 °C/min, final temp. 150 °C, t_R 23.5 (minor), t_R 23.9 (major). $[\alpha]_D$ = +13.6 (c=0.69, CHCl3), 94% ee

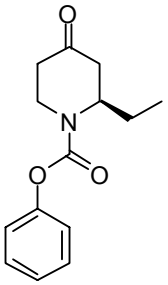
(*R*)-1-*t*-Butoxycarbonyl-2-ethyl-4-piperidone (4f).



The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4f** in 58% yield as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 4.48 (m, 1H), 4.21 (m, 1H), 3.14 (m, 1H), 2.64 (dd, *J*=14.3, 6.6 Hz, 1H), 2.47 (m, 1H), 2.30 (m, 2H), 1.49-1.25 (m, 3H), 1.49 (s, 9H), 0.87 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (50

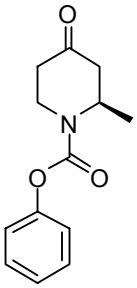
MHz, $CDCl_3$) δ 208.3, 154.0, 80.2, 53.4, 45.3, 40.6, 38.1, 28.4, 25.5, 10.2. HRMS calc. for $C_{12}H_{21}NO_3$ 227.1521, found 227.1337. HPLC on Chiralpack AS column, (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 5.3 (major), t_R 6.4 (minor). $[\alpha]_D$ = –4.8 (c=0.40, $CHCl_3$), 91% ee.

(*R*)-1-Phenoxycarbonyl-2-ethyl-4-piperidone (4g).



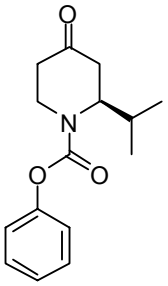
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4g** in 87% yield as a colorless oil. ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.33 (t, *J*=7.9 Hz, 2H), 7.17 (t, *J*=7.2 Hz, 1H), 7.07 (d, *J*=8.1 Hz, 2H), 4.63 (m, 1H), 4.48-4.42 (m, 1H), 3.30 (m, 1H), 2.75-2.68 (m, 1H), 2.61-2.49 (m, 1H), 2.38-2.33 (br d, 2H, *J*=15 Hz), 1.61-1.50 (m, 2H), 0.92 (m, 3H). ^{13}C NMR (50 MHz; $CDCl_3$) δ 207.1, 151.2, 129.3, 125.5, 121.6, 54.2, 45.1, 40.5, 38.8, 29.7, 25.5, 25.3, 10.2. HRMS calc. for $C_{14}H_{17}NO_3$ 247.1208, found 247.1120 HPLC on Chiralpak AS column, (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 15.8 (major), t_R 19.8 (minor). $[\alpha]_D$ = –2.8 (c=0.70, $CHCl_3$), 97% ee.

Phenyl 2-methyl-4-oxopiperidine-1-carboxylate (4h).[4b]



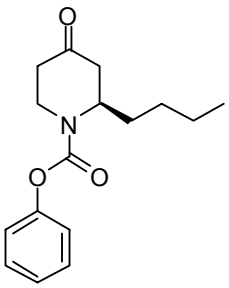
Purification by column chromatography (SiO_2; EtOAc / *n*-pentane / NEt_3 20:79:1) afforded 93 mg of a colorless oil (Yield 80%). HPLC on Chiralpak AS column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 18.3 min (major), Rt = 33.3 min (minor). 89% ee. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.36 (t, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 4.91-4.84 (m, 1H), 4.42-4.38 (m, 1H), 3.52 (t, *J* = 9.0 Hz, 1H), 2.78 (dd, *J* = 14.6 Hz, 6.7 Hz, 1H), 2.64-2.55 (m, 1H), 2.46-2.40 (m, 1H), 2.36-2.31 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 207.2, 253.5, 151.1, 129.3, 125.5, 121.6, 48.6, 46.4, 40.4, 38.9, 19.1 ppm. HRMS calcd. for $C_{13}H_{15}NO_3$: 233.10518, found 233.10520.

(*R*)-1-Phenoxycarbonyl-2-isopropyl-4-piperidone (4i).



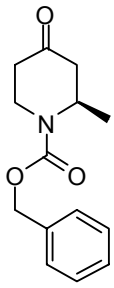
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4h** in 84% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.33 (t, *J*=7.6 Hz, 2H), 7.17 (t, *J*=7.6 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 2H), 4.53-4.48 (m, 1H), 4.29 (m, 1H), 3.23 (m, 1H), 2.60-2.51 (m, 3H), 2.34 (d, *J*=14.8 Hz, 1H), 1.77 (m, 1H), 0.97 (d, *J*=6.4 Hz, 3H), 0.81 (d, *J*=6.4 Hz, 3H). ^{13}C NMR (50 MHz; $CDCl_3$) δ 207.4, 154.1, 151.2, 129.3, 125.5, 121.6, 59.2, 43.2, 40.5, 39.3, 29.4, 19.5, 18.8. HRMS calc. for $C_{15}H_{19}NO_3$ 261.1365, found 261.1362. HPLC on Chiralpak AS column, (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 10.7 (major), t_R 18.0 (minor). $[\alpha]_D$ = +5.5 (c=0.55, $CHCl_3$), 97% ee.

(*R*)-1-Phenoxycarbonyl-2-butyl-4-piperidone (4j).



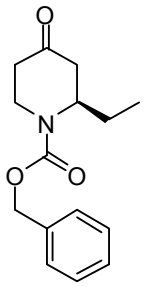
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1 +1% Et_3N) to give pure **4i** in 22% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34 (t, *J*=7.4 Hz, 2H), 7.18 (t, *J*=7.4 Hz, 1H), 7.07 (d, *J*=7.6 Hz, 2H), 4.72 (m, 1H), 4.45 (q, *J*= 6.9 Hz, 1H), 3.34-3.26 (m, 1H), 2.73-2.70 (m, 1H), 2.60-2.51 (m, 1H), 2.39-2.32 (m, 2H), 1.60 (m, 1H), 1.48-1.44 (m, 1H), 1.31-1.24 (m, 4H), 0.86 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (50 MHz; $CDCl_3$) δ 207.3, 153.9, 151.1, 129.3, 125.5, 121.5, 52.7, 45.5, 40.5, 38.8, 32.0, 30.9, 27.7, 22.2, 13.9 HRMS calc. for $C_{16}H_{21}NO_3$ 275.1521, found 275.1534. HPLC on Chiralpak AS column, (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 23.5 (minor), t_R 27.5 (major). $[\alpha]_D$ = –1.2 (c=0.52, $CHCl_3$), 82% ee.

(*R*)-1-Benzyloxycarbonyl-2-methyl-4-piperidone (4k).



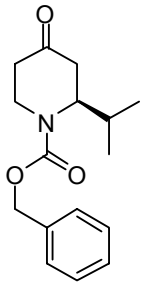
The crude product obtained by general procedure B was purified by flash chromatography (*n*-heptane/AcOEt=4:1) to give pure **4j** in 44% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.18 (s, 2H), 4.80 (m, 1H), 4.31 (m, 1H), 3.40 (m, 1H), 2.70 (dd, *J*=6.6, 14.6 Hz, 1H), 2.50-2.25 (m, 3H), 1.21 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.7, 155.0, 136.4, 128.6, 128.2, 128.0, 67.5, 48.2, 46.5, 40.5, 38.6, 18.9. HRMS calc. for $C_{14}H_{17}NO_3$ 247.1208, found 247. 1220. HPLC on Chiralpack AS column (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 12.1 (major), t_R 15.5 (minor). $[\alpha]_D$ = –6.5 (c=0.37, $CHCl_3$), 96% ee.

(*R*)-1-Benzyloxycarbonyl-2-ethyl-4-piperidone (4l).



The crude product obtained by general procedure B was purified by flash chromatography (*n*-heptane/AcOEt=4:1) to give pure **4k** in 70% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.18 (s, 2H), 4.58 (m, 1H), 4.41 (m, 1H), 3.22 (m, 1H), 2.65 (dd, *J*=14.6, 6.6 Hz, 1H), 2.47 (m, 1H), 2.33 (m, 2H), 1.61-1.46 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.6, 155.5, 136.4, 128.6, 128.2, 127.9, 67.6, 53.8, 45.2, 40.6, 38.4, 25.4, 10.1. HRMS calc. for $C_{15}H_{19}NO_3$ 261. 1365, found 261.1369. HPLC on Chiralpack AS column (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 11.1 (major), t_R 14.8 (minor). $[\alpha]_D$ = –2.3 (c=0.53, $CHCl_3$), 94% ee.

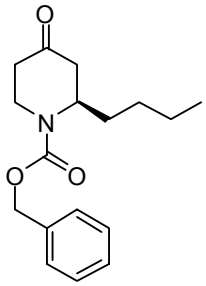
(*R*)-1-Benzyloxycarbonyl-2-(2-propyl)-4-piperidone (4m).



The crude product obtained by general procedure B was purified by flash chromatography (*n*-heptane/AcOEt=4:1) to give pure **4l** in 68% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.19 (s, 2H), 4.43 (m, 1H), 4.26 (m, 1H), 3.16 (m, 1H), 2.56 (m, 3H), 2.32 (m, 1H), 1.74 (m, 1H), 0.97 (d, *J*=5.9 Hz, 3H), 0.87 (d, *J*=6.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.8, 155.5, 136.4, 128.5, 128.2, 127.9, 67.6, 58.7, 43.2, 40.6, 38.9, 29.3, 19.5, 18.8. HRMS calc. for $C_{16}H_{21}NO_3$ 275.1521, found 275.1530. HPLC on Chiralpack AS column (*n*-

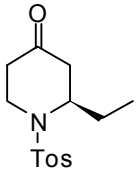
heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 9.7 (major), t_R 13.3 (minor). $[\alpha]_D$ = –7.1 (c=0.56, $CHCl_3$), 95% ee.

(*R*)-1-Benzyloxycarbonyl-2-butyl-4-piperidone (4n).



The crude product obtained by general procedure B was purified by flash chromatography (*n*-heptane/AcOEt=4:1) to give pure **4m** in 12% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 5.18 (AB, *J*=3.7 Hz, 2H), 4.68 (m, 1H), 4.39 (m, 1H), 3.22 (m, 1H), 2.64 (dd, *J*=14.7, 6.6 Hz, 1H), 2.45 (m, 1H), 2.31 (m, 2H), 1.56-1.36 (m, 2H), 1.26 (m, 4H), 0.85 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.7, 136.4, 128.5, 128.4, 128.2, 128.0, 67.6, 52.3, 45.6, 40.6, 38.4, 32.0, 27.8, 22.2, 13.9. HRMS calc. for $C_{17}H_{23}NO_3$ 289.1678, found 289.1679. HPLC on Chiralpack AS column (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 9.0 (major), t_R 10.4 (minor). $[\alpha]_D$ = +1.6 (c=0.32, $CHCl_3$), 59% ee.

(*R*)-1-(Toluene-4-sulfonyl)-2-ethyl-4-piperidone (4o).



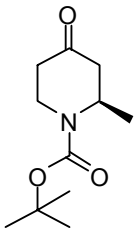
The crude product obtained by general procedure B was purified by flash chromatography (*n*-heptane/AcOEt=4:1) to give pure **4n** in 50% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J*=7.7 Hz, 2H), 7.33 (d, *J*=7.3 Hz, 2H), 4.30 (q, *J*=7.0 Hz, 1H), 4.15 (dd, *J*=14.3, 7.0 Hz, 1H), 3.26 (m, 1H), 2.57-2.34 (m, 2H), 2.44 (s, 3H), 2.23 (m, 2H), 1.44 (m, 2H), 0.83 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.5, 143.8, 137.6, 129.9, 127.0, 56.1, 45.1, 40.3, 39.9, 25.4, 21.5, 10.5. HRMS calc. for $C_{14}H_{19}NO_3S$ 281.1085, found 281.1075. HPLC on Chiralcel OD column (*n*-heptane/isopropanol=90:10, flow = 1.0 mL/min): t_R 10.3 (minor), t_R 11.3 (major). $[\alpha]_D$ = +7.3 (c=0.41, $CHCl_3$), 81% ee.

General procedure for the copper-phosphoramidite conjugate addition of trimethylaluminum to *N*-protected-2,3-dehydro-4-piperidones.

$Cu(OTf)_2$ (180 mg, 0.5 mmol) and ligand (*S*,*R*,*R*)-**L11** (1 mmol) were dissolved in anhydrous toluene (40 mL) and stirred for 40 min at r.t. To this solution 1

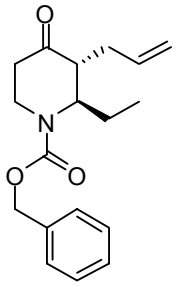
mmol of dry Et_2O was added, followed by a solution of substrate (10 mmol) in toluene (60 mL) and the mixture cooled to -50°C. A solution of Me_3Al (20 mmol) was added dropwise and the reaction mixture was stirred at the specified temperature overnight. The reaction was stopped after 16 h at 80% conversion. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3x). Combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography.

***tert*-Butyl 2-methyl-4-oxopiperidine-1-carboxylate (4p).**



Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 25:75) afforded 1.55 g of a white solid (Yield 73%). Mp = 57.7 °C. GC on CP Chiralsil Dex CB column, 25m × 0.25mm × 0.25 µm, He-flow: 1mL/min, oven temp.: 120 °C, init., time: 10 min, rate: 1 °C/min, finel temp.: 150 °C, t_R = 23.5 min (minor), t_R = 23.9 min (major). $[\alpha]_D$ = -18.6 (c 2.01, $CHCl_3$) for 96% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 4.67-4.65 (m, 1H), 4.21-4.15 (m, 1H), 3.31-3.21 (m, 1H), 2.62 (dd, *J* = 14.4 Hz, 6.7 Hz, 1H), 2.48-2.37 (m, 1H), 2.30-2.17 (m, 2H), 1.43 (s, 9H), 1.12 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 208.4, 154.4, 80.3, 47.9, 46.6, 4.06, 38.3, 28.4, 18.9 ppm. HRMS calcd. for $C_{11}H_{19}NO_3$: 213.13647, found 213.13836.

(2*R*,3*R*)-1-Benzyloxycarbonyl-2-ethyl-3-(2-propenyl)-4-piperidone (5).



$Cu(OTf)_2$ (9 mg, 0.025 mmol) and (*S*,*R*,*R*)-**L1** (27 mg, 0.050 mmol) were dissolved in anhydrous toluene (1 mL) and stirred 40 min at r.t. The substrate **1e** (116 mg, 0.50 mmol) in toluene (2 mL) was added and the resulting solution was cooled to 0 °C. Et_2Zn (1M in *n*-hexanes, 1.50 mL, 1.50 mmol) was added and the reaction mixture was stirred for 18 h at 0 °C. Subsequently a solution of $Pd(PPh_3)_4$ (46 mg, 0.040 mmol) and allyl acetate (0.11 mL, 100 mg, 1.0 mmol) in toluene (2 mL), was added and the mixture was stirred for 24 h allowing the temperature to rise gradually to r.t. The reaction mixture was treated with sat. aqueous NH_4Cl solution and extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The

crude product was purified by flash chromatography (*n*-heptane/AcOEt=4:1) to give 76 mg (50%) of **5** as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.65 (m, 1H), 5.19 (s, 2H), 5.05-4.94 (m, 2H), 4.48-4.34 (m, 2H), 3.14 (m, 1H), 2.55 (m, 1H), 2.30-2.20 (m, 4H), 1.57-1.47 (m, 3H), 0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 134.2, 128.5, 128.2, 128.0, 117.8, 67.6, 57.1, 55.2, 38.2, 37.6, 35.3, 25.0, 10.1. HRMS calc. for $C_{18}H_{23}NO_3$ 301.1678, found 301.1670. HPLC on Chiralpack AS column (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 7.0 (minor), t_R 8.0 (major). $[\alpha]_D$ = –50.8 (c=0.89, $CHCl_3$), 84% ee.

2.7 References

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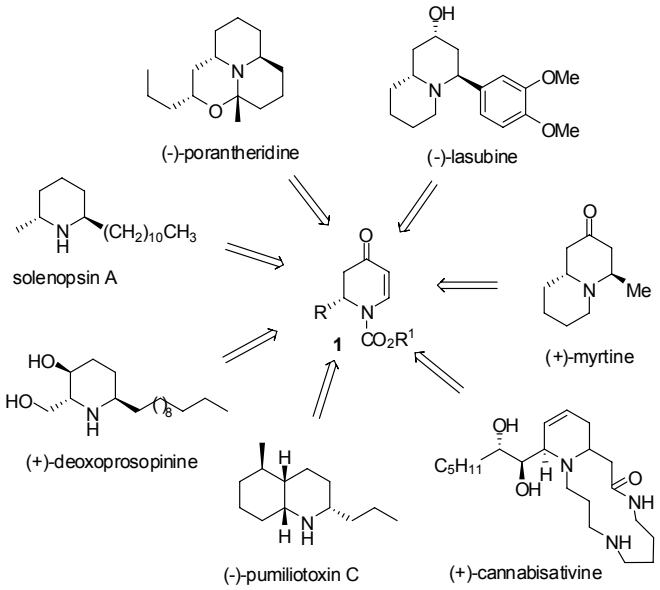
Chapter 3

Preparation of *trans*-2,6-disubstituted-4-piperidones; total synthesis of (+)-myrtine

A new route towards optically active trans-2,6-disubstituted-4-piperidones based on an ACA/lithiation/substitution sequence is described. The potential of this protocol is demonstrated in the total synthesis of the natural alkaloid (+)-myrtine.

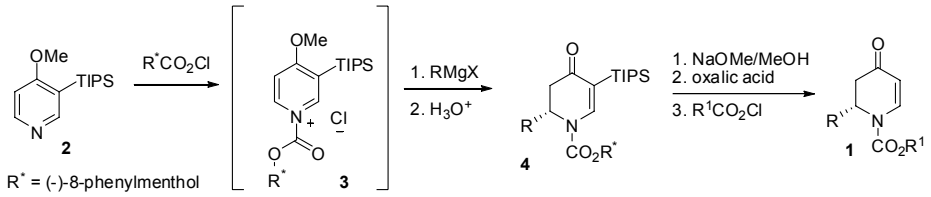
3.1 Introduction

In Chapter 2 the first highly efficient catalytic enantioselective addition of organozinc reagents as well as trimethylaluminium to *N*-protected-2,3-dehydro-4-piperidones was described. This method allows for the synthesis of optically active *N*-protected-2-alkyl-4-piperidones, which represent versatile building blocks in the synthesis of piperidine-based alkaloids.[1] Another important structural motif found frequently in biologically active natural products consists of substitution at both the α-positions of the heterocyclic ring. Simple 2,6-disubstituted piperidine alkaloids isolated from the fire ant venom have been reported to possess different properties such as insecticidal, anti-HIV, antibacterial and antifungal activities.[2] Furthermore, 2,6-disubstituted piperidines can be used as intermediates in the synthesis of more complex indolizidine and quinolizidine ring systems. A wide range of biologically active alkaloids containing the 2,6-disubsituted piperidine ring has been prepared by Comins and coworkers[3] starting from enantiomerically pure *N*-protected-2,3-dehydro-4-piperidones of type **1** (Scheme 3.1).



Scheme 3.1

The optically active *N*-protected-2,3-dehydro-4-piperidones **1** used by Comins *et al.*[4] were obtained by asymmetric addition of a Grignard reagent to a chiral *N*-acylpyridinium salt **3** generated *in situ* from the 3-substituted 4-methoxypyridine **2** and a chiral chloroformate, derived from (-)-8-phenylmenthol (Scheme 3.2). The presence of a bulky triisopropylsilyl group at the C-3 position of **2** hinders Grignard addition at the C-2 position, allowing the nucleophilic attack to occur exclusively at the C-6. The decrease in the number of sites available for the nucleophilic attack results in an increase of the diastereoselectivity.[5] The dehydropiperidone **4** can be obtained diastereomerically pure by chromatography or recrystallization. Removal of the C-3 substituent and recovery of the chiral auxiliary, by replacement with an achiral carbamate, affords optically pure **1** in good overall yield.[6]



Scheme 3.2 *Asymmetric synthesis of N-acyl dehydropiperidones based on a chiral auxiliary approach.*[5]

3.2 Copper-catalyzed conjugate addition to *N*-protected 4-pyridones

The synthetic versatility of compounds of type **1** (Figure 3.1) prompted us to evaluate the application of the highly efficient enantioselective addition protocol, described in the previous chapter, to their syntheses.

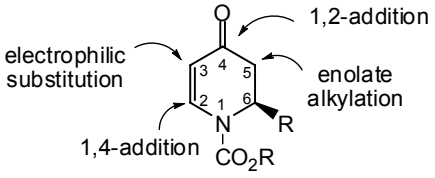
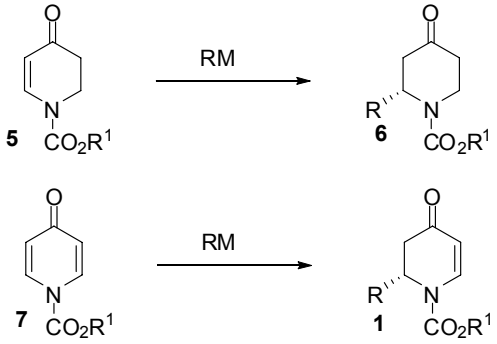


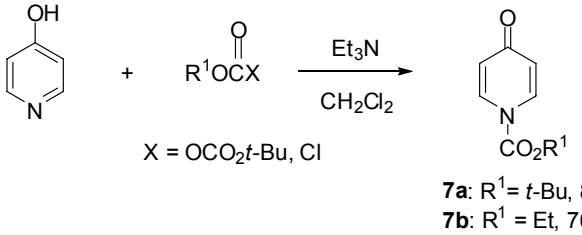
Figure 3.1

As shown in Chapter 2, starting from *N*-protected-2,3-dehydro-4-piperidones **5**, the copper/phosphoramidite-catalyzed addition of organozinc reagents and trimethylaluminium affords 2-substituted-4-piperidones **6** in high yield and with high enantioselectivity. We reasoned that the use of an *N*-protected 4-pyridone **7** as a starting material in the conjugate addition reaction would allow for the formation of enantiomerically enriched 6-substituted-2,3-dehydro-4-piperidones **1** (Scheme 3.3).



Scheme 3.3

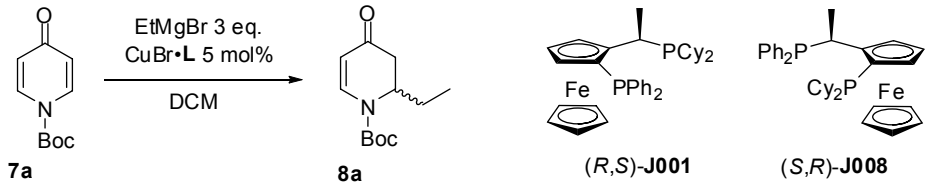
The substrates **7a** and **7b** were synthesized in high yield from 4-hydroxy-pyridine (Scheme 3.4) and tested in the copper-catalyzed addition of Et_2Zn and Me_3Al under optimized conditions.



Scheme 3.4 *Synthesis of N-protected-4-pyridones.*

In order to perform the organometallic addition on compounds **7a** and **7b** in Et_2O and toluene, at several temperatures, 5 mol% of the catalyst formed from $Cu(OTf)_2$ and the chiral phosphoramidite ligand (*S*,*R*,*R*)-**L1** were used. The formation of the desired product was not observed in any of the reactions, however. Full conversion of the starting material occurred to a complex mixture

of products. Only in the conjugate addition of EtMgBr to **7a** using 5 mol% of the catalyst formed from CuBr and a Josiphos type ligand, it was possible to isolate the desired addition product, albeit in low yield (11%) and as a racemate (Scheme 3.5).

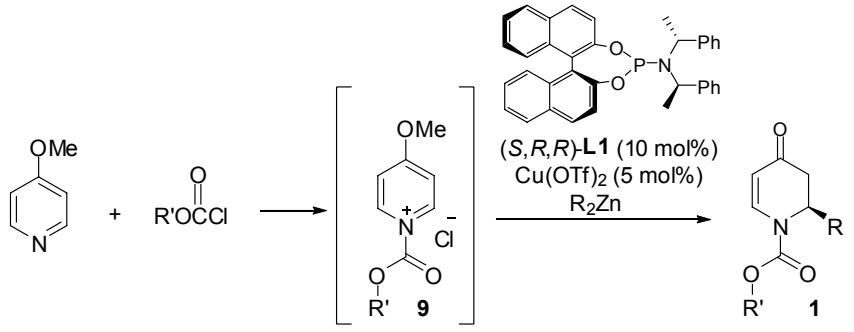


Scheme 3.5 *Conjugate addition of EtMgBr to 4-pyridone* ***7a****.*

The impossibility to isolate the desired product in a decent yield under all the reaction conditions tested led us to a change of strategy for the synthesis of compound **1**.

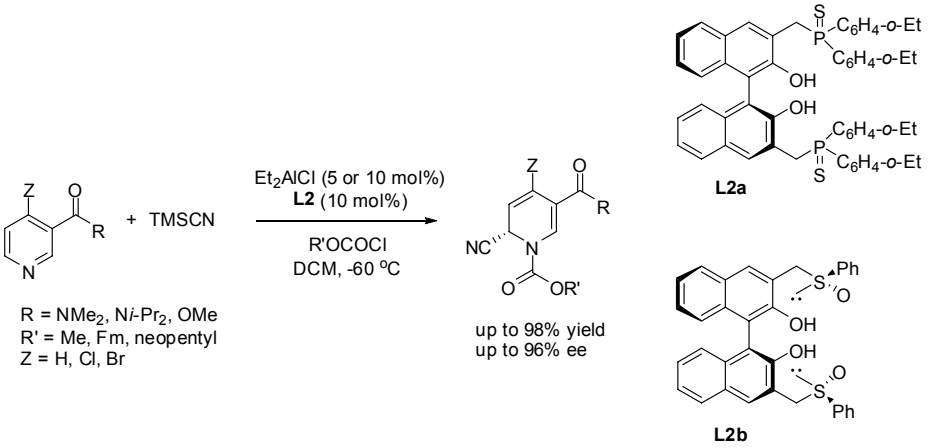
3.3 Catalytic enantioselective addition of diethylzinc to N-acyliminium ions

A second attempt to develop an enantioselective one-pot synthesis of 6-substituted-2,3-dehydro-4-piperidones **1** consisted of the copper-catalyzed conjugate addition of organometallic reagents to *N*-acyliminium ion **9** generated *in situ* from 4-methoxy-pyridine and various chloroformates.



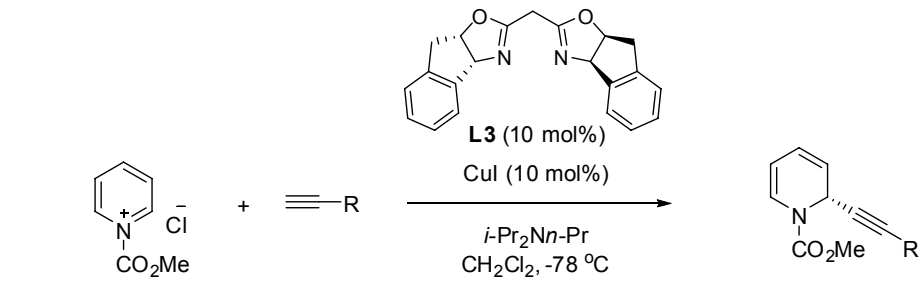
Scheme 3.6 *Conjugate addition to N-acylpyridinium ions generated in situ.*

Only few examples of enantioselective catalytic additions of nucleophiles to *N*-acylpyridinium salts have been reported in the literature.[7] The enantioselective catalytic Reissert reaction of *N*-acyliminium ions derived from nicotinamide derivatives has been described by Shibasaki *et al.*[8] Using a catalyst formed from Et_2AlCl and the chiral ligand **L2**, the addition of TMSCN proceeds with high regio- and enantioselectivity (Scheme 3.7).



Scheme 3.7 *Enantioselective catalytic Reissert reaction.*[8]

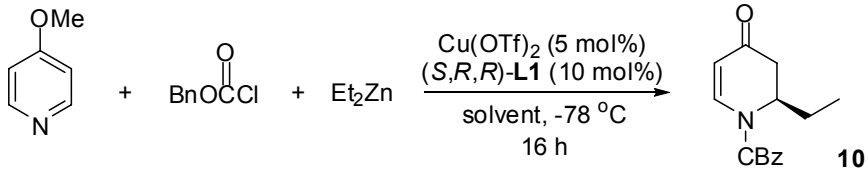
The catalytic enantioselective addition of terminal alkynes to *N*-acylpyridinium salts has been described recently.[9] 10 mol% of a copper-bis(oxazoline) complex catalyzes the addition of 1-alkynes to iminium salts formed from pyridine and a number of chloroformates. The use of a base, such as *i*-Pr_2N*n*-Pr, and of alkynes bearing a carbonyl group in the 3-position was found to be essential in obtaining high enantioselectivity. Furthermore, a five-fold excess of the chloroformate, the alkyne and the base are necessary to isolate the final product in good yield (Scheme 3.8).



Scheme 3.8 *Copper-catalyzed addition of 1-alkynes to N-acylpyridinium salts.*

To the best of our knowledge, a catalytic enantioselective addition of organometallic reagents to these systems has not been reported thus far; therefore the addition of Et_2Zn to *N*-acyliminium salts of 4-methoxy-pyridine was investigated, using the copper complex prepared *in situ* from $Cu(OTf)_2$ and the chiral phosphoramidite ligand (*S*,*R*,*R*)-**L1**, as catalyst.

Table 3.1 *Solvent scope in the addition of Et_2Zn to N-acylpyridinium salts.*

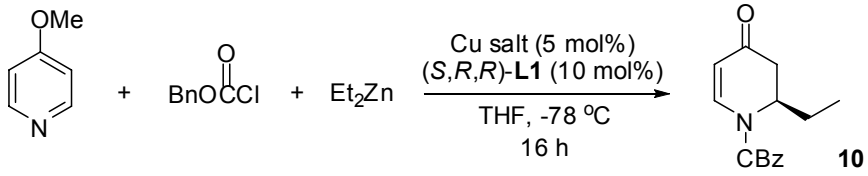


Entry	Solvent	Yield (%)	Ee (%)
1	THF	26	34
2	Toluene	30	8
3	Et_2O	26	5
4	CH_2Cl_2	30	12
5[a]	THF	50	12

[a] The reaction was carried out at -30 °C.

Using a 5 mol% catalyst loading, the addition of Et_2Zn to the *N*-acyliminium ion, generated *in situ* by mixing 4-methoxy-pyridine with an equimolar amount of benzyl chloroformate, was performed in several solvents at -78 °C (Table 3.1). The *N*-protected 6-ethyl-2,3-dehydro-4-piperidone **10** was isolated in low yield (26%-30%), with all the solvents used so far. Almost no enantioselectivity was observed in toluene or Et_2O (Table 3.1, entries 2 and 3) while 34% enantioselectivity was achieved in THF (entry 1). An increase of the temperature from -78 °C to -30 °C resulted in a higher isolated yield (50%) accompanied by a decrease of the ee to 12% (entry 5). The use of an alternative copper source resulted in complete loss of enantiocontrol (Table 3.2).

Table 3.2 *Screening of copper salts in the addition of Et_2Zn to N-acylpyridinium salts.*

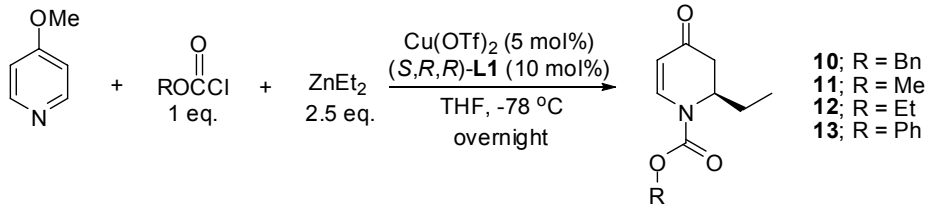


10

Entry	Cu salt	Yield (%)	Ee (%)
1	$Cu(OTf)_2$	26	34
2	CuTC	16	-
3	$Cu(OAc)_2 \cdot H_2O$	8	-
4	$Cu(acac)_2$	9	-
5	CuI	-	-

The influence of different protecting groups was investigated also. *N*-acyliminium ions formed from a range of chloroformates were subjected to the addition of Et_2Zn in THF, at -78 °C (Table 3.3).

Table 3.3 *Screening of protecting groups in the addition of Et_2Zn to N-acylpyridinium salts.*



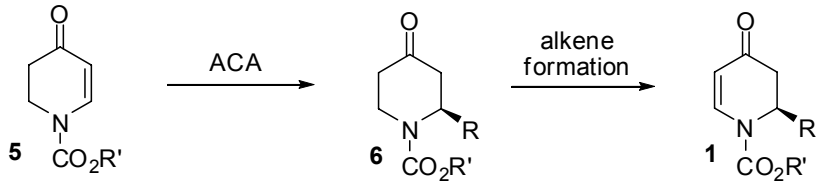
Entry	R	Product	Yield (%)	Ee (%)
1	Bn	**10**	26	34
2	Me	**11**	25	5
3	Et	**12**	18	10
4	Ph	**13**	25	rac

The use of methyl, ethyl or phenyl chloroformate afforded the respective addition product in a yield comparable with **10** but with lower or no enantioselectivity. No addition reaction was detected when Boc anhydride or triflic anhydride were employed in the formation of the *N*-acylpyridinium ion. Using EtMgBr as ethyl source afforded compound **10** in 41% yield as a racemate, when carrying out the reaction in *t*-BuOMe, at -20 °C. In this case the reaction was catalyzed by a complex formed from CuBr and ligand (*R*,*S*)-**J001** in 1:1 ratio.

Considering the fact that the optically active *N*-protected 2,3-dehydro-4-piperidones could not be obtained in useful yield and ee via a catalytic enantioselective addition to either *N*-protected 4-pyridones or *N*-acyliminium ions, alternative approaches were investigated.

3.4 Dehydrogenation of chiral 2-substituted-4-piperidones

A different route toward optically active *N*-protected 2,3-dehydro-4-piperidones (**1)** consists of the introduction of a double bond to the ring of chiral 2-substituted-4-piperidones **6** (Scheme 3.9).

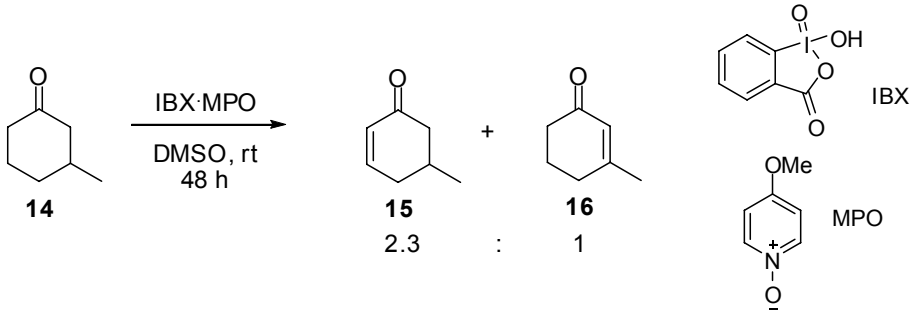


Scheme 3.9

Several procedures were attempted to carry out such a transformation. A survey of the dehydrogenation techniques explored is presented in this paragraph.

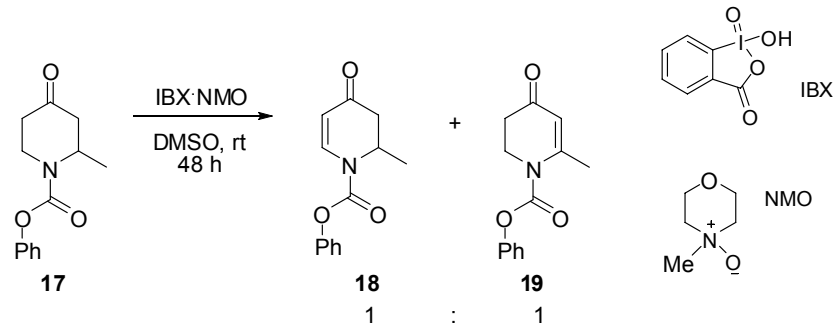
3.4.1 IBX-mediated dehydrogenation

IBX (*o*-iodoxybenzoic acid)[10] has proved to be a useful reagent for the dehydrogenation of aldehydes and ketones to the corresponding α,β-unsaturated compounds at elevated temperatures.[11] In 2002, Nicolaou *et al.*[12] reported that the reactivity of IBX can be modulated by complexation with an appropriate ligand. In particular the complexes of IBX with *N*-oxides appear to be much more active than IBX alone, dehydrogenating carbonyl compounds even at room temperature and in the presence of several functional groups. When IBX·MPO (MPO = 4-methoxy-pyridine *N*-oxide) complex is used to promote the dehydrogenation of 3-methyl-cyclohexanone **14**, a mixture of the two isomers **15** and **16** in ratio 2.3:1 was obtained (Scheme 3.10).



Scheme 3.10 *IBX·MPO-mediated dehydrogenation of **14**.*

When the reaction is performed using an enantiomerically enriched substrate, the formation of isomer **16** will result in a loss of chirality. As the reaction on 3-methyl-cyclohexanone **14** favors the formation of the double bond at the unsubstituted side, we decided to apply this method to the dehydrogenation of the chiral *N*-protected 2-alkyl-4-piperidones, obtained by the ACA of organometallic reagents to **1** (Scheme 3.11).

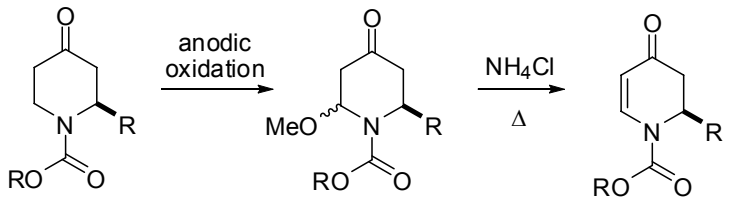


Scheme 3.11 *IBX·NMO-mediated dehydrogenation of **17**.*

Compound **17** was chosen as model substrate and the reaction was carried out using the IBX·NMO (NMO = *N*-methylmorpholine-*N*-oxide) complex, which is known to have comparable activity to the IBX·MPO complex.[12] However, after two days at room temperature, starting material could still be detected; the two unsaturated isomers **18** and **19** were isolated in a 1:1 ratio in 40% total yield. As the reaction did not show any regioselectivity, an optimization was not attempted.

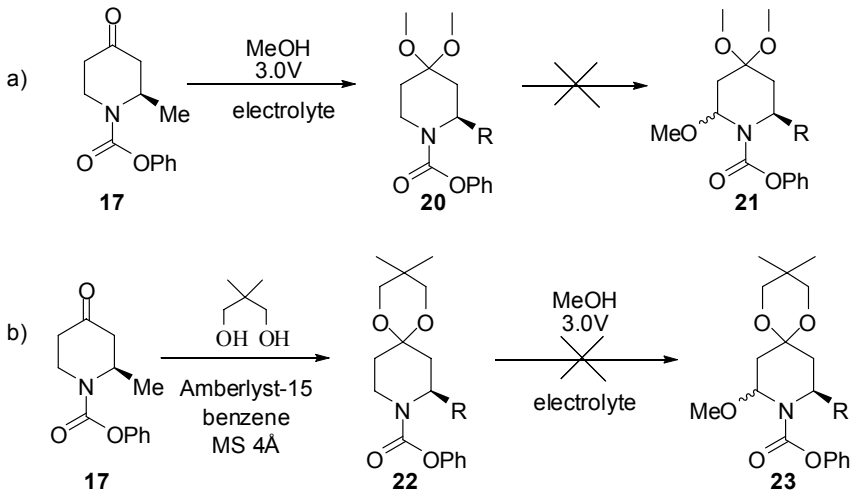
3.4.2 Anodic oxidation of carbamates

The target compound **18** can be considered as an α,β-unsaturated ketone as well as an enecarbamate. The formation of the latter can be achieved via elimination of methanol from α-methoxy carbamates obtained by anodic oxidation (Scheme 3.12).[13] One of the main advantages of this procedure is that the anodic α-methoxylation occurs selectively at the less substituted carbon.



Scheme 3.12 *Preparation of 2-substituted-2,3-dehydropiperidones via anodic oxidation/elimination.*

The anodic α-methoxylation of substrate **17** did not occur under the conditions reported in the literature for piperidine based Boc-carbamates.[14] A constant potential of 3.0 V was applied using C or Pt electrodes, in the presence of $LiClO_4$, Et_4NOTs or $PhSO_3Na$, in MeOH. After 3 h electrolysis, we observed protection of the ketone as its dimethoxy acetal (Scheme 3.13 a).The acetal formation is probably due to traces of acid in the solution, due to the oxidation of MeOH to formic acid. No further transformation was detected running the reaction over longer periods. Moreover, when the carbonyl function of **17** was already protected only the starting material **22** was recovered after 6 h electrolysis (Scheme 3.13 b).



Scheme 3.13 *Attempts towards the anodic methoxylation of **17**.*

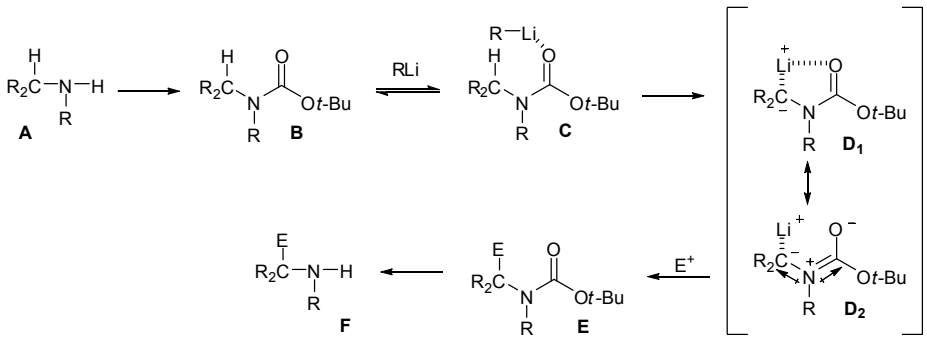
α-Methoxylation of the carbamate was not observed performing the electrolysis experiment under several reaction conditions in which the effect of the supporting electrolyte, nature of the electrode and value of the potential were studied. Once again the use of a different approach was considered.

3.5 α-Lithiation of Boc-protected amines

The lithiation-substitution sequence of secondary amines protected at the nitrogen atom with an activating group represents a powerful tool for the introduction of substituents α to the nitrogen.

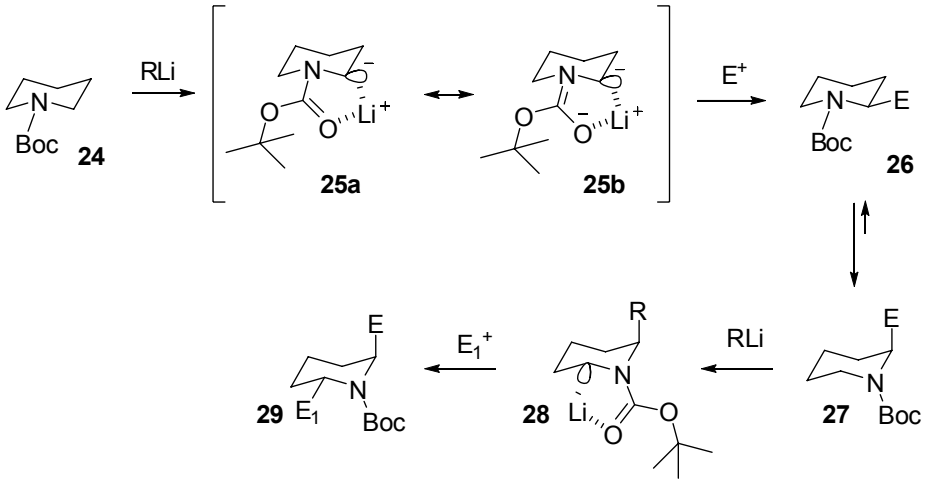
In order to successfully promote the reaction, the nitrogen protecting group needs to fulfill several requirements. The α-protons of amines are not sufficiently acidic to be removed using a strong base except in systems which are additionally activated. Substitution at the nitrogen with an electron withdrawing group , for example, causes an increase in the acidity of the α-protons. In the lithiation-substitution sequence, removal of an α-proton from compound **B** results in the formation of carbanion **D**, which can react with the electrophile to afford the substituted product **E** (Scheme 3.14).[16] Association of the organolithium reagent with the activating group in a preequilibrium complex **C** can bring the reactive groups in proximity for directed deprotonation (Complex Induced Proximity Effect).[15] Another key role played by the *N*-protecting group is the stabilization of the species **D** via complexation with the metal of the base and dipole stabilization.[16] These possible contributions are represented, respectively, by the structures $\mathbf{D_1}$ and $\mathbf{D_2}$ in Scheme 3.14.

Several activating groups are known to promote the electrophilic substitution adjacent to the nitrogen, however amongst the most efficient and probably the most commonly used is the *t*-butyl carbamate group.[17,18] In addition to activating the α protons towards the lithiation and providing stabilization of the intermediate species **C**, the Boc group is inert under strongly basic conditions and does not interfere with the electrophilic substitution. Furthermore it can be attached easily to the nitrogen and removed easily.



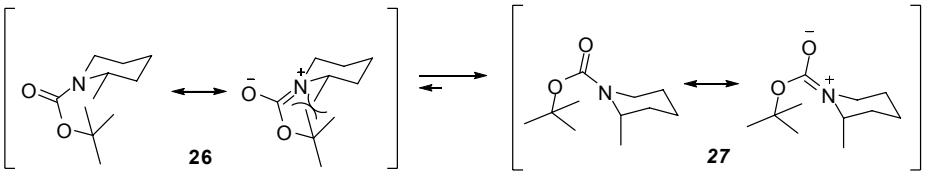
Scheme 3.14 *Lithiation-substitution sequence of a Boc-protected amine.*

Of particular interest in the current study is the stereochemical outcome of the lithiation reactions involving Boc-protected piperidines. The formation of a stabilized carbanion **25** requires abstraction of an equatorial proton from the Boc-piperidine **24** (Scheme 3.15).[18,19] The equatorial lithiation, in fact, allows an effective complexation of the lithium with the carbonyl oxygen and avoids the repulsive interaction between the carbanionic lone pair and the л-system of the amide.[15b] Compound **25** reacts with the electrophile, with retention of configuration,[19,20] to give compound **26**. Equatorially substituted 2-piperidines are known to be less stable than the corresponding axially substituted compounds due to $A^{1,3}$ strain (Scheme 3.16).[21] Therefore compound **26** is likely to undergo "ring flip" to product **27** in which the allylic strain is released. If compound **27** is subjected to a second lithiation-substitution sequence, the final product **29** will have *trans* geometry according to the stereochemical requirements (Scheme 3.15).[18]



Scheme 3.15 *Stereochemistry of the lithiation of Boc-piperidines.*

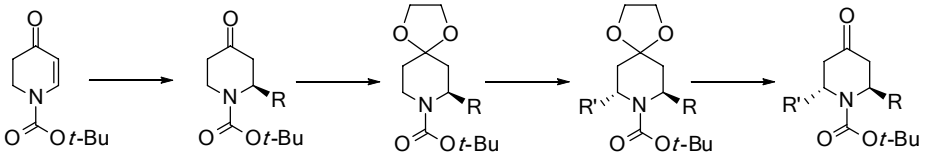
The occurrence of $A^{1,3}$ strain in an equatorially substituted piperidine is apparent when considering the resonance structure for **26**. In this structure the interaction between the equatorial 2-substituent and the alkyl part of the carbamate moiety causes destabilization in comparison with the conformation in which the 2-substituent assumes an axial position as in **27** (Scheme 3.16).



Scheme 3.16 *$A^{1,3}$ strain in equatorially substituted 2-piperidines.*

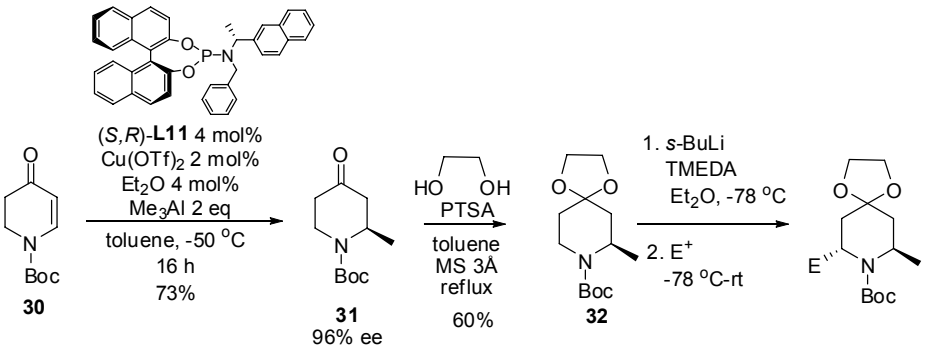
The same factor influences the conformational equilibrium of the enantioenriched 2-substituted piperidones obtained from the asymmetric conjugate addition to *N*-protected 2,3-dehydro-4-piperidones. Therefore, the combination of the asymmetric conjugate addition and the lithiation-substitution

sequence offers a powerful tool for the synthesis of enantioenriched 2,6-disubstituted *trans*-piperidones (Scheme 3.17). Protection of the carbonyl moiety prior to the lithiation reaction is necessary to avoid 1,2-addition of the organometallic reagent.



Scheme 3.17 *ACA-lithiation-substitution sequence.*

In Chapter 2 the addition of trimethylaluminium to the Boc-protected dehydropiperidone **30** afforded the methyl-substituted compound **31** in 73% yield and with 96% ee. The recurrence of the methyl group in many biologically active alkaloids (see Chapter 2) prompted us to investigate the use of compound **31** in a lithiation-substitution sequence (Scheme 3.18).

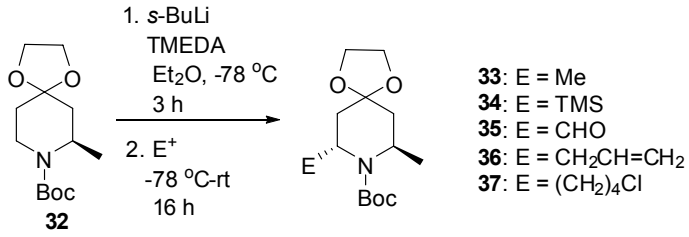


Scheme 3.18

The carbonyl moiety of **31** was protected via acetal formation using ethylene glycol (Scheme 3.18). After 24 h reaction, the protected product was recovered in 60% isolated yield together with the remaining starting material. Compound

32 was subjected to lithiation with *s*-BuLi and TMEDA followed by reaction with a range of electrophiles (Table 3.4).

Table 3.4 *Lithiation-substitution of **32**.*



Entry	E^+	Product	Yield (%)	dr (%)[a]
1	MeI	**33**	71	95:5
2	TMSCl	**34**	74	96:4
3	DMF	**35**	56	55:45
4	Allyl bromide	**36**	-	-
5	$I(CH_2)_4Cl$	**37**	-	-

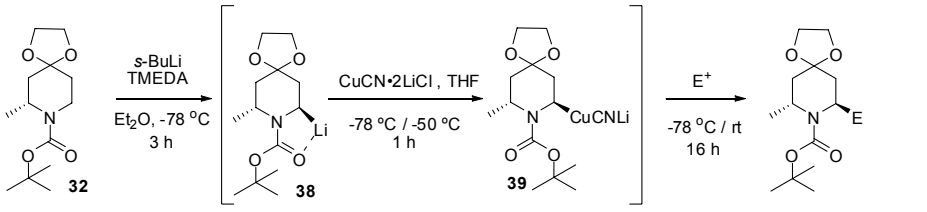
[a] Determined by ^{1}H-NMR and ^{13}C-NMR.

According to literature procedures,[17b,18] formation of a stabilized carbanion was accomplished reacting *s*-BuLi with **32** in the presence of TMEDA, at -78 °C. After 3 h the electrophile was added and the temperature allowed to increase to room temperature slowly. The reactions with MeI and TMSCl as electrophilic species proceeded to give compounds **33** and **34** in good yield and with high diastereomeric ratio (Table 3.4, entries 1 and 2). Comparison of the spectroscopic data recorded for **33** with literature data confirmed the compound is obtained prevalently as the *trans* diastereoisomer.[17]

The addition of DMF afforded a mixture of the *cis* and *trans* isomers of **35** in a ratio close to 1:1 (Table 3.4, entry 3). We attribute this lack of diastereoselectivity to epimerization of the aldehyde under basic conditions.

The use of allyl bromide or 1-chloro-4-iodobutane as electrophiles did not lead to the desired products, however. Formation of compounds **36** and **37** was accomplished following the lithiation\transmetallation procedure developed by Dieter *et al.*[22,23] Addition of a THF solution of CuCN·2LiCl to the lithiated species forms a *N*-Boc-piperidyl-cuprate by lithium\copper exchange.[22] Subsequent addition of the electrophile yielded the products **36** and **37** in, respectively, 64% and 62% yield and with complete diastereoselectivity (Table 3.5).

Table 3.5 *Lithiation-transmetallation of* ***32****.*

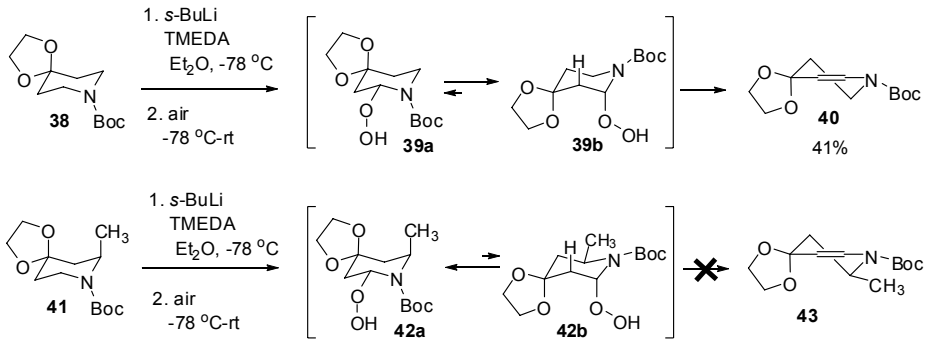


Entry	E^+	Product	Yield (%)	dr (%)[a]
1	allylbromide	**36**	64	>99:1
2	$I(CH_2)_4Cl$	**37**	62	>99:1

[a] Determined by ^{1}H-NMR and ^{13}C-NMR.

An experimental proof that the lithiation of **32** followed by electrophilic substitution gives preferably the *trans* diastereoisomer of the disubstituted product is found upon analyzing the stereochemical properties of the dimethylated compound **33**. A *cis* relationship of the two methyl α-substituents in **33** would result in an achiral *meso* compound. The presence of optical activity detected for **33** excludes the possibility that the product obtained is an achiral molecule, therefore indicating a *trans* relationship of the methyl groups.

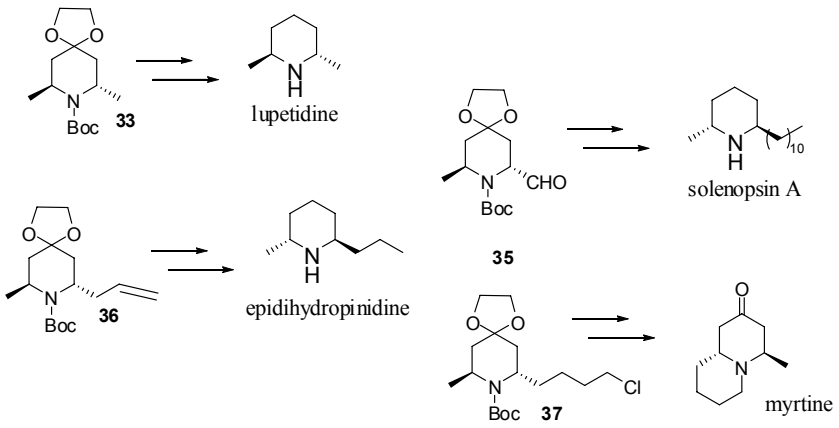
The *trans* selectivity observed for the 2,6-disubstituted-piperidones might account as well for the different outcome of the lithiation reactions performed on the substrates **38** and **41** using oxygen as electrophile (Scheme 3.19).



Scheme 3.19

When the lithiated species formed from **38** is allowed to react with oxygen present in the air, the formation of a peroxide-substituted piperidone **39** can be envisioned. As previously mentioned, the presence of allylic strain between the α-substituent and the Boc group will destabilize the equatorial conformation **39a**. In the axial conformer **39b** the antiperiplanarity between the α-substituent and the β-hydrogen enables the elimination of the peroxide to afford product **40** in 41% isolated yield. On the other hand, when compound **41** is subjected to the same conditions a complex mixture of products is obtained. In this case the *trans* stereochemistry of the two α-substituents of the piperidone **42** requires one of the groups to be in the equatorial position. Of the two possible conformers **42a** and **42b** the one with less steric interactions will be favored. The fact that the formation of the unsaturated product **43** is not detected suggests that the peroxide substituent assumes preferably an equatorial orientation from which the elimination process cannot occur.

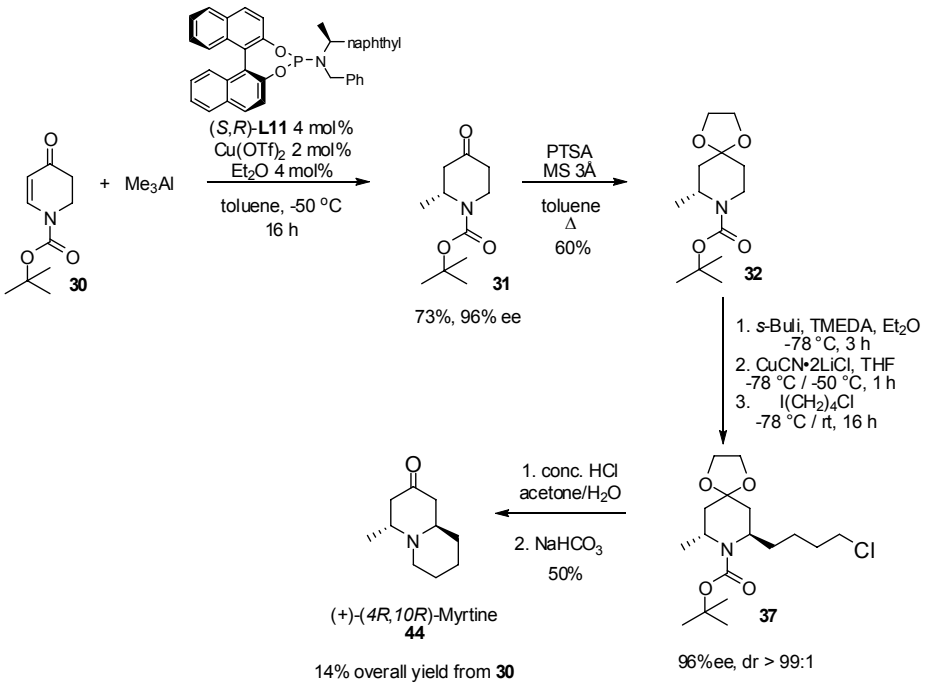
The protocol developed provides 2,6-disubstituted-*trans*-piperidones in good yield and with high enantioselectivities. These compounds can be used as precursors in the synthesis of several alkaloids (Scheme 3.20). The application of this protocol to the synthesis of (+)-myrtine is described in the next section.



Scheme 3.20 *Synthetic applications.*

3.6 Synthesis of (+)-myrtine

Myrtine is a quinolizidine alkaloid isolated from *Vaccinium myrtillus* whose structure and absolute configuration were determined by Slosse and Hootelé [24] in 1978. Although a number of syntheses of myrtine in racemic form have appeared in the literature,[24b,25] only two asymmetric syntheses of (+)-myrtine[26,27] and one asymmetric synthesis of the unnatural isomer (-)-myrtine[28] have been described. The existing asymmetric procedures, however, are based on the use of chiral auxiliaries[26,28] or the use of optically active precursors obtained via enzymatic resolution.[27] In this section a four step catalytic enantioselective synthesis of (+)-myrtine starting from the Boc-protected 2,3-dehydro-4-piperidone **30** is described (Scheme 3.21).



Scheme 3.21 *Total synthesis of (+)-(4R,10S)-myrtine **44**.*

We reported previously (*vide supra*) that the asymmetric conjugate addition of Me_3Al to the dehydropiperidone **30** afforded the 2-methyl-substituted product **31** in 73% isolated yield and with 96% ee. Protection of the carbonyl moiety as a ketal to afford **32** allowed a lithiation-substitution sequence to be performed with 1-chloro-4-iodobutane as the electrophile. Transmetallation of Li to Cu was necessary to promote the reaction and, under the conditions described in the previous section, compound **37** was obtained in 62% isolated yield. A one-pot deprotection-cyclization procedure led to compound **44** in 50% yield. Comparison with the spectroscopic data reported in literature[24,25] confirmed that the diastereoisomer obtained has the *trans* configuration, corresponding to the structure of the alkaloid myrtine. Moreover, comparison of the optical rotation measured with the literature values indicates that the *trans* isomer obtained corresponds to the natural occurring enantiomer (+)-myrtine in which

the absolute configuration of the two stereogenic centers has been established to be (*4R*,*10R*).[24] This finding imposes *R* configuration to the product of the Me_3Al conjugate addition to **30**, using the chiral phosphoramidite (*S*,*R*)-**L11**.

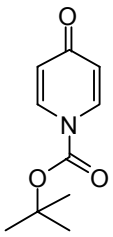
3.7 Conclusions

A new protocol for the synthesis of *trans*-2,6-disubstituted-4-piperidones has been developed. The copper/phosphoramidite catalyzed ACA of organometallic reagents to dehydropiperidones is the key step in which the chirality is introduced into the system. The well-defined stereochemical outcome of the lithiation-substitution reaction allows one of the possible diastereoisomers to be obtained during the formation of the second stereogenic center. Enantiomerically enriched *trans*-2,6-disubstituted-4-piperidones represent versatile building blocks for the synthesis of piperidine, indolizidine and quinolizidine natural products. To show its potential in synthesis, this approach was applied in the synthesis of the natural alkaloid (+)-myrtine in four steps and 14% overall yield from **30**. This represents the first synthesis of myrtine based on a catalytic enantioselective procedure. The comparison with the optical and spectroscopic data reported in the literature allows to assign the absolute configuration of the stereogenic centers formed as (*4R*,*10R*).

3.8 Experimental section

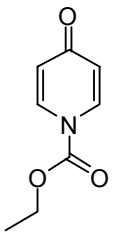
General Methods. For general information see Chapter 2.

***tert*-Butyl 4-oxopyridine-1(4H)-carboxylate (7a).**[29]



4-Hydroxypyridine (0.5 g; 5.3 mmol) was added to a solution of Boc anhydride (1.1 g; 5.5 mmol) in CH_2Cl_2 (20 mL) at room temperature. Et_3N (2.8 mL; 20 mmol) was added and the reaction mixture was stirred for 3 h. The reaction mixture was then diluted with H_2O (15 mL) and the pH was adjusted to pH 7 using aq. HCl (1N). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2; CH_2Cl_2 / MeOH 19:1) afforded 0.87 g of a white solid (Yield 84%). Mp = 79.0 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 8.2 Hz, 2H), 6.27 (d, *J* = 8.2 Hz, 2H), 1.59 (s, 9H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 180.5, 147.8, 134.8, 118.2, 87.2, 27.7 ppm. HRMS calc. for $C_{10}H_{13}NO_3$: 195.08952, found 195.08995.

Ethyl 4-oxopyridine-1(4H)-carboxylate (7b).[30]

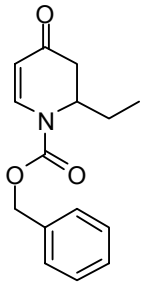


4-Hydroxypyridine (0.5 g; 5.3 mmol) was added to a solution of ethyl chloroformate (0.53 mL; 5.5 mmol) in CH_2Cl_2 (20 mL) at room temperature. Et_3N (2.8 mL; 20 mmol) was then added and the reaction mixture was stirred for 5 h. The reaction mixture was then diluted with H_2O (15 mL) and the pH was adjusted to pH 7 using aq. HCl 1N. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2; CH_2Cl_2 / MeOH 19:1) afforded 0.67 g of a white solid (Yield 76%). Mp = 66.8 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 8.2 Hz, 2H), 6.27 (d, *J* = 8.2 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H) ppm.

General procedure for the copper catalyzed addition of Et_2Zn to *N*-acyl-iminium ions.

A solution of 4-methoxy-pyridine (20.3 µL; 0.2 mmol) in THF (2 mL) was cooled to -78 °C. A solution of chloroformate (0.2 mmol) in THF (1 mL) was added and the reaction mixture stirred at the specified temperature for 30 min. A THF (2 mL) solution of the catalyst freshly prepared from $Cu(OTf)_2$ (3.6 mg; 0.01 mmol) and (*S*,*R*,*R*)-**L1** (10.8 mg; 0.02 mmol) was added, followed by a Et_2Zn solution (1.0 M in *n*-heptane, 0.4 mL; 0.4 mmol). After 16 h the reaction mixture was poured in aqueous HCl 1 M (10 mL) and stirred for 10 min. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

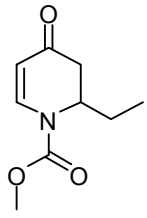
Benzyl 2-ethyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (10).[31]



Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 3:7) afforded 15 mg of a colorless oil (Yield 26%). R_f = 0.5. HPLC on Chiralpak AS column, 4.6 × 250 mm, 10 µm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 21.2 min, Rt = 35.2 min. 34% ee. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 7.4 Hz, 1H), 7.40-7.37 (m, 5H), 5.30 (d, *J* = 7.1 Hz, 1H), 5.26 (s, 2H), 4.53-4.51 (m, 1H), 2.79 (dd, *J* = 16.6 Hz, 6.6 Hz, 1H), 2.47 (d, *J* = 16.6 Hz, 1H), 1.74-1.61 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 193.1, 141.5, 134.9, 128.7, 128.4, 107.1, 69.0, 54.7, 39.3, 23.6, 10.2 ppm. HRMS calcd. for $C_{15}H_{17}NO_3$: 259.1208, found 259.1219.

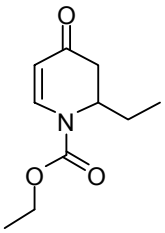
Methyl 2-ethyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (11).

Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 3:7) afforded



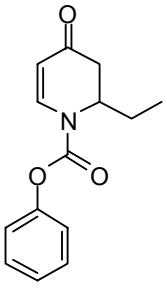
9 mg of a colorless oil (yield 25%). R_f = 0.4. HPLC on Chiralpak AS column, 4.6 × 250 mm, 10 µm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 19.5 min, Rt = 39.5 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 8.1 Hz, 1H), 4.47 (br s, 1H), 3.84 (s, 3H), 2.76 (dd, *J* = 16.6 Hz, 6.6 Hz, 1H), 2.45 (d, *J* = 16.6 Hz, 1H), 1.73-1.57 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 193.1, 153.2, 141.6, 107.0, 54.6, 54.0, 39.1, 23.4, 10.1 ppm. HRMS calcd. for $C_9H_{13}NO_3$: 183.0895, found 183.0902.

Ethyl 2-ethyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (12).



Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 3:7) afforded 7 mg of a colorless oil (Yield 18%). R_f = 0.5. HPLC on Chiralpak AS column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 14.1 min, Rt = 27.4 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 7.2 Hz, 1H), 5.29 (d, *J* = 8.2 Hz, 1H), 4.51-4.47 (m, 1H), 4.33-4.25 (m, 2H), 2.78 (dd, *J* = 16.6 Hz, 6.6 Hz, 1H), 2.46 (d, *J* = 16.6 Hz, 1H), 1.74-1.60 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 193.2, 152.7, 141.7, 106.8, 63.3, 54.4, 39.3, 23.5, 14.3, 10.2 ppm. HRMS calcd. for $C_{10}H_{15}NO_3$: 197.1052, found 197.1061.

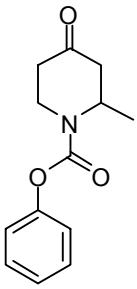
Phenyl 2-ethyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (13).



Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 3:7) afforded 12 mg of a colorless oil (Yield 25%). R_f = 0.5. HPLC on Chiralpak OD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 21.5 min, Rt = 23.6 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 5.40 (d, *J* = 7.9 Hz, 1H), 4.66-4.65 (br s, 1H), 2.90 (dd, *J* = 16.7 Hz, 6.4 Hz, 1H), 2.54 (d, *J* = 16.6 Hz, 1H), 1.87-1.69 (m, 2H), 0.98 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 192.9, 150.4, 141.1, 129.6, 126.3, 121.2, 108.0, 55.1, 39.4, 23.7, 10.3 ppm. HRMS calcd. for $C_{14}H_{15}NO_3$: 245.1052, found 245.1055.

Phenyl 2-methyl-4-oxopiperidine-1-carboxylate (17).[32]

Purification by column chromatography (SiO_2; EtOAc / *n*-pentane / NEt_3 20:79:1) afforded 93 mg of a colorless oil (Yield 80%). HPLC on Chiralpak AS column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 18.3 min (major), Rt = 33.3 min (minor). 89% ee. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.36 (t, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 4.91-4.84 (m, 1H), 4.42-4.38 (m, 1H), 3.52 (t, *J* = 9.0 Hz, 1H), 2.78 (dd, *J* = 14.6 Hz, 6.7 Hz, 1H), 2.64-2.55 (m, 1H), 2.46-2.40 (m, 1H), 2.36-2.31 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 207.2, 253.5, 151.1, 129.3, 125.5,



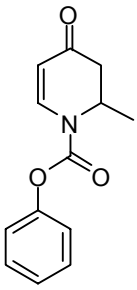
121.6, 48.6, 46.4, 40.4, 38.9, 19.1 ppm. HRMS calcd. for $C_{13}H_{15}NO_3$: 233.10518, found 233.10520.

Procedure for the IBX-mediated oxidation.

IBX (159 mg, 0.57 mmol) and NMO (66.8 mg, 0.57 mmol) were dissolved in DMSO (2 mL) at room temperature To this solution, piperidone **17** (50 mg, 0.21 mmol) in DMSO (0.5 mL) was added at once and the resulting clear solution was stirred for 48 h at room temperature in a flask covered with aluminium foil. The reaction mixture was poured into sat. aq. $NaHCO_3$ solution and extracted with Et_2O (3x). The combined organic extracts were washed with sat. aq. $NaHCO_3$ solution, H_2O and brine, then dried ($MgSO_4$) and concentrated. The resulting crude product was purified by flash chromatography to give 10 mg of **18** and 10 mg of **19**.

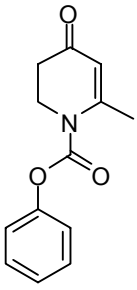
Phenyl 2-methyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (18).[32]

Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 25:75) afforded 10 mg of a white solid (Yield 20%). Mp = 100.1-100.8 °C. HPLC on Chiralcel OD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 97:3, flow = 1.0 mL/min): Rt = 35.1 min, Rt = 39.6 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.31-7.27 (m, 1H), 7.20-7.16 (m ,2H), 5.45 (d, *J* = 9.1 Hz, 1H), 4.88 (br s, 1H), 2.97 (dd, *J* = 19.7 Hz, 6.9 Hz, 1H), 2.40 (dt, *J* = 16.5 Hz, 1.5 Hz, 1H), 1.38 (d, *J* = 6.2 Hz, 3H) ppm. HRMS calcd. for $C_{13}H_{13}NO_3$: 231.08952, found 231.08911.

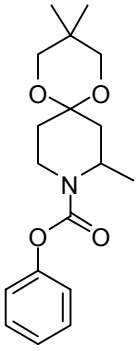


Phenyl 6-methyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (19).

Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 25:75) afforded 10 mg of a colorless oil. (Yield 20%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.37 (t, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.12-7.09 (m, 2H), 5.42 (s, 1H), 4.20 (t, *J* = 6.8 Hz, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 193.8, 156.7, 151.8, 150.3, 129.6, 126.2, 121.3, 113.7, 46.5, 36.7, 23.4 ppm. HRMS calcd. for $C_{13}H_{13}NO_3$: 231.08952, found 231.08890.

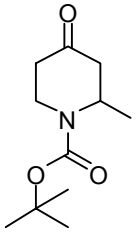


Phenyl 3,3,8-trimethyl-1,5-dioxa-9-azaspiro[5.5]undecane-9-carboxylate (22).



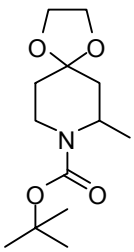
2,2-Dimethylpropane-1,3-diol (96.7 mg; 0.93 mmol) was added to a solution of **17** (180 mg; 0.77 mmol) in toluene (2.5 mL). Amberlyst-15 (1 mg) was added and the reaction mixture was refluxed overnight in the presence of molecular sieves 4Å. After cooling down to room temperature, the molecular sieves and the Amberlyst-15 were removed by filtration. H_2O (4 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 2:8) afforded 235 mg of a white solid (Yield 96%). Mp = 91.1-91.4 °C. HPLC on Chiralcel OD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 97:3, flow = 1.0 mL/min): Rt = 8.7 min, Rt = 11.0 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.27-7.23 (m, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 2H), 4.53-4.47 (m, 1H), 4.04-4.00 (m, 1H), 3.48 (t, *J* = 11.3 Hz, 2H), 3.39-3.36 (m, 2H), 3.17 (t, *J* = 12.9 Hz, 1H), 2.25-2.20 (m, 1H), 2.05-2.01 (m, 1H), 1.64-1.50 (m, 2H), 1.24 (d, *J* = 7.1 Hz, 3H), 0.95 (s, 3H), 0.83 (s, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 153.5, 151.4, 129.2, 128.3, 125.1, 121.7, 96.1, 70.2, 70.0, 47.0, 36.6, 34.3, 34.0, 30.1, 22.8, 22.5, 17.5 ppm. HRMS calcd. for $C_{18}H_{25}NO_4$: 319.17834, found 319.17944.

***tert*-Butyl 2-methyl-4-oxopiperidine-1-carboxylate (31).**



Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 25:75) afforded 85 mg of a white solid (Yield 80%). Mp = 57.7 °C. GC on CP Chiralsil Dex CB column, 25m × 0.25mm × 0.25 μm, He-flow: 1mL/min, oven temp.: 120 °C, init., time: 10 min, rate: 1 °C/min, final temp.: 150 °C, t_R = 23.5 min (minor), t_R = 23.9 min (major). $[\alpha]_D$ = -18.6 (c 2.01, $CHCl_3$) for 96% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 4.67-4.65 (m, 1H), 4.21-4.15 (m, 1H), 3.31-3.21 (m, 1H), 2.62 (dd, *J* = 14.4 Hz, 6.7 Hz, 1H), 2.48-2.37 (m, 1H), 2.30-2.17 (m, 2H), 1.43 (s, 9H), 1.12 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 208.4, 154.4, 80.3, 47.9, 46.6, 4.06, 38.3, 28.4, 18.9 ppm. HRMS calcd. for $C_{11}H_{19}NO_3$: 213.13647, found 213.13836.

***tert*-Butyl 7-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (32).**[17]



Compound **31** (620 mg; 2.9 mmol) was dissolved in toluene (6 mL). Ethylene glycol (0.48 mL; 8.7 mmol) and *p*-toluenesulfonic acid (270 mg; 1.45 mmol) were added and the reaction mixture was refluxed overnight in the presence of molecular sieves (3Å). After cooling down to room temperature, the molecular sieves were removed by filtration and the reaction mixture was poured in a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 10:90) afforded 447 mg of a colorless oil (Yield 60%). $[\alpha]_D$ = -28.5 (c 0.92, $CHCl_3$) for 96% ee. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.44-4.39 (m, 1H), 3.97-3.84 (m, 4H), 3.05-2.98 (m, 1H), 1.81 (dd, *J* = 13.6 Hz, 6.6 Hz, 1H), 1.62-1.52 (m, 4H), 1.40 (s, 9H), 1.17 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 154.6, 107.3, 79.4, 64.6, 63.7, 46.5, 38.3, 36.7, 34.5, 28.4, 17.4 ppm. HRMS calcd. for $C_{13}H_{23}NO_4$: 257.16269, found 257.16335.

General procedure A for the lithiation.[17]

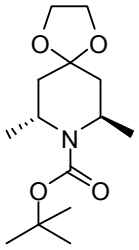
TMEDA (0.090 mL; 0.6 mmol) was added to a solution of compound **32** (64.2 mg; 0.25 mmol) in Et_2O (4 mL). The resulting solution was cooled to -78 °C and a solution of *s*-BuLi (1.3 M in cyclohexane, 0.46 mL; 0.6 mmol) was added. The reaction mixture was stirred at -78 °C. After 3 h a solution of the electrophile (0.6 mmol) in Et_2O (1 mL) was added. The reaction mixture was allowed to slowly warm up to room temperature. After stirring overnight the mixture was poured in H_2O (5 mL). The water layer was extracted with Et_2O (2 × 10 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

General procedure B for the lithiation.[23]

TMEDA (0.18 mL; 1.2 mmol) was added to a solution of compound **32** (128.5 mg; 0.5 mmol) in Et_2O (9 mL). The resulting solution was cooled to -78 °C and a solution of *s*-BuLi (1.3 M in cyclohexane, 0.92 mL; 1.2 mmol) was added. The reaction mixture was stirred at -78 °C. After 3 h a solution in THF (3.5 mL) of the copper complex [CuCN·2LiCl], freshly prepared from CuCN (107 mg; 1.2 mmol) and LiCl (100 mg; 2.4 mmol), were added. The reaction mixture was

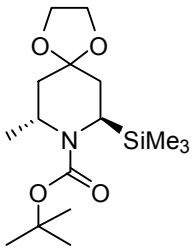
warmed to -50 °C and stirred at this temperature for 30 min. Then, the temperature was brought once again to -78 °C and a solution of the electrophile (1.2 mmol) in Et_2O (1 mL) was added. The reaction mixture was allowed to slowly warm up to room temperature. After overnight the mixture was poured in H_2O (5 mL). The water layer was extracted with Et_2O (2 × 10 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

(7*R*,9*R*)-*tert*-Butyl 7,9-dimethyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (33).[17]



From procedure A. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded 48 mg of a colorless oil (Yield 71%). R_f = 0.3. $[\alpha]_D$ = +4.6 (c 0.57, $CHCl_3$) for 96% ee and dr 95:5. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.10-4.05 (m, 2H), 3.98-3.92 (m, 2H), 3.88-3.82 (m, 2H), 2.20 (dd, *J* = 14.7 Hz, 5.5 Hz, 2H), 1.82 (dd, *J* = 14.7 Hz, 3.0 Hz, 2H), 1.45 (s, 9H), 1.25 (d, *J* = 6.9 Hz, 6H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 154.8, 106.4, 79.1, 63.7, 46.0, 39.2, 28.5, 20.9 ppm. HRMS calcd. for $C_{14}H_{25}NO_4$: 271.1784, found 271.1780.

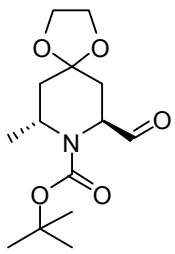
(7*R*,9*R*)-*tert*-Butyl 7-methyl-9-(trimethylsilyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (34).



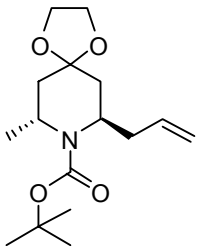
From procedure A. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 5:95) afforded 61 mg of a colorless oil (Yield 74%). Rf = 0.7. $[\alpha]_D$ = -13.2 (c 0.55, $CHCl_3$) for 96% ee and dr 96:4. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.46-4.38 (m, 1H), 3.98-3.87 (m, 4H), 2.64 (dd, *J* = 12.6 Hz, 2.6 Hz, 1H), 1.80-1.75 (m, 1H), 1.64-1.52 (m, 3H), 1.41 (s, 9H), 1.24 (d, *J* = 7.1 Hz, 3H), 0.05 (s, 9H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 155.0, 108.0, 79.1, 64.4, 63.7, 48.1, 39.6, 38.8, 35.8, 28.4, 18.1, -0.5 ppm. MS-CI for $C_{16}H_{31}NO_4Si$: 330 $[M+H]^+$. HRMS calcd. for $C_{15}H_{28}NO_4Si$ $[M-CH_3]$: 314.1788, found 314.1778.

(7*S*,9*R*)-*tert*-Butyl 7-formyl-9-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (35).

From procedure A. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 2:8) afforded 40 mg of a colorless oil (Yield 56%). Rf = 0.5. $[\alpha]_D$ = -19.6 (c 0.58, $CHCl_3$) for 96% ee and dr 1:1. ^{1}H-NMR (400 MHz, $CDCl_3$) mixture of the two diastereoisomers δ = 9.61 (d, *J* = 1.0 Hz, 1H), 9.44 (d, *J* = 2.1 Hz, 1H), 4.65-4.62 (m, 1H), 4.51-4.47 (m, 1H), 4.40-4.36 (m, 1H), 3.97-3.97 (m, 8H), 2.44-2.40 (m, 1H), 1.98-1.91 (m, 2H), 1.80-1.74 (m, 2H), 1.67-1.56 (m, 4H), 1.46 (s, 9H), 1.43 (s, 9H), 1.29-12.7 (m, 6H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 202.3, 196.0, 155.1, 106.5, 106.1, 81.6, 80.6, 64.8, 64.3, 63.9, 63.8, 59.8, 58.7, 48.0, 47.4, 38.8, 37.6, 34.0, 32.3, 28.3, 28.2, 20.7, 18.7 ppm. MS-CI for $C_{14}H_{23}NO_5$: 286 $[M+H]^+$. HRMS calcd. for $C_{13}H_{22}NO_4$ [M-CHO]: 256.1549, found 256.1558.

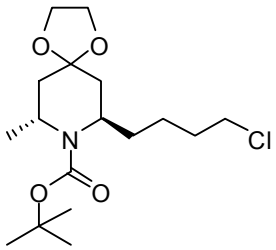


(7*R*,9*R*)-*tert*-Butyl 7-allyl-9-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (36).



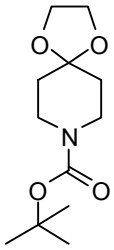
From procedure B. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded 95 mg of a colorless oil (Yield 64%). Rf = 0.6. $[\alpha]_D$ = +27.4 (c 0.50, $CHCl_3$) for 96% ee and dr > 99:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.78-5.68 (m, 1H), 5.09-5.00 (m, 2H), 4.05-4.02 (M, 1H), 3.95-3.77 (m, 5H), 2.45-2.39 (m, 1H), 2.35-2.28 (m, 1H), 2.14 (dd, *J* = 14.7 Hz, 5.4 Hz, 1H), 1.98 (d, *J* = 4.1 Hz, 2H), 1.81 (dd, *J* = 14.7 Hz, 3.3 Hz, 1H), 1.44 (s, 9H), 1.25 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 154.7, 135.5, 117.2, 106.3, 79.2, 63.8, 63.5, 50.6, 46.1, 39.6, 38.6, 34.8, 28.5, 20.8 ppm. MS-CI for $C_{15}H_{24}NO_4$: 298 $[M+H]^+$.

(7*R*,9*R*)-*tert*-Butyl-7-(4-chlorobutyl)-9-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (37).



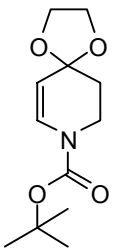
From procedure B. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 1:9) afforded 107 mg of a colorless oil (Yield 62%). Rf = 0.5. $[\alpha]_D$ = +8.2 (c 0.49, $CHCl_3$) for 96% ee and dr 97:3. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.99-3.79 (m, 6H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.10-1.98 (m, 2H), 1.93-1.89 (m, 1H), 1.79-1.71 (m, 3H), 1.70-1.52 (m, 2H), 1.47-1.31 (m, 2H), 1.42 (s, 9H), 1.24 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 154.8, 106.5, 79.2, 63.8, 63.7, 50.5, 46.1, 44.9, 39.5, 35.7, 33.2, 32.3, 28.4, 23.9, 20.8 ppm. HRMS calcd. for $C_{17}H_{30}NO_4Cl$: 347.1863, found 347.1847.

***tert*-Butyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (38).**[17]



The *N*-Boc-protected-4-piperidone (3 g; 15 mmol) was dissolved in ethylene glycol (75 mL). *p*-Toluenesulfonic acid (2.85 g; 15 mmol) was added and the reaction mixture was stiired at room temperature in the presence of molecular sieves (4Å). After 48 h the molecular sieves were removed by filtration and the reaction mixture was poured in a saturated $NaHCO_3$ aqueous solution. The aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 10:90) afforded 2.77g of a colorless oil which slowly solidified (Yield 76%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.90 (s, 4H), 3.43 (t, *J* = 5.7 Hz, 4H), 1.58 (t, *J* = 5.7 Hz, 4H), 1.39 (s, 9H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 154.6, 107.1, 79.5, 64.3, 41.8, 34.9, 28.4 ppm. HRMS calcd. for $C_{12}H_{21}NO_4$: 243.14703, found 243.14805.

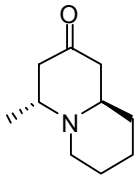
***tert*-Butyl 1,4-dioxa-8-azaspiro[4.5]dec-6-ene-8-carboxylate (40).**



TMEDA (0.075 mL; 0.5 mmol) was added to a solution of compound **38** (64.2 mg; 0.25 mmol) in dry Et_2O (5 mL), under a N_2 atmosphere. The resulting solution was cooled to -78 °C and a solution of *s*-BuLi 1.3M in cyclohexane (0.33 mL; 0.5 mmol) was added. The reaction mixture was stirred at -78 °C. After 2.5 h the N_2 flow was stopped and contact with air was allowed through a

$CaCl_2$ tube. The reaction mixture was slowly warmed up to room temperature. After overnight the mixture was poured in H_2O (5 mL). The water layer was extracted with Et_2O (2 × 10 mL) and the combined organic phases were with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 2:3) afforded 25 mg of a colorless oil (Yield 41%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 5.81 (br s, 1H), 4.26 (d, *J* = 9.6 Hz, 1H), 4.07-3.95 (m, 4H), 3.28-319 (m, 1H), 1.94-1.91 (m, 1H), 1.75-1.70 (m, 2H), 1.46 (s, 9H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 154.5, 107.3, 80.4, 64.8, 64.2, 39.0, 33.8, 28.3 ppm. HRMS calcd. for $C_{12}H_{19}NO_4$: 241.13138, found 241.13237.

(4*R*,9a*R*)-4-Methylhexahydro-1H-quinolizin-2(6H)-one. (+)-Myrtine. (44).



Compound **37** (100 mg, 0.29 mmol) was refluxed in a mixture of acetone (3 mL) and H_2O (0.5 mL) to which conc. HCl (1 mL) had been added. After 16 h the reaction mixture was cooled to 0 °C in a ice bath and the pH was increased by slowly adding $NaHCO_3$. The reaction mixture was stirred at room temperature for an additional 16 h and then poured in H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2; EtOAc / *n*-pentane 2:8) afforded 23 mg of a yellow oil (Yield 50%). Rf = 0.7. $[\alpha]^{20}_D$ = +10.2 (c 1.77, $CHCl_3$) for 96% ee and dr 97:3; (lit.[24b] $[\alpha]^{28}_D$ = +11.3 (c 2.7, $CHCl_3$). Spectroscopic data correspond to the literature.[24b] ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.40-3.33 (m, 1H), 2.83 (dd, *J* = 13.4 Hz, 5.9 Hz, 1H), 2.80-2.75 (m, 1H), 2.67-2.60 (m, 1H), 2.46 (dt, *J* = 11.5 Hz, 2.8 Hz, 1H), 2.27-2.15 (m, 3H), 1.71-1.55 (m, 4H), 1.31-1.18 (m, 2H), 0.95 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 209.5, 57.1, 53.5, 51.4, 48.6, 48.0, 34.2, 25.8, 23.4, 11.0 ppm. MS-CI for $C_{10}H_{17}NO_4$: 168 $[M+H]^+$.

3.9 References

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Chapter 4

Catalytic enantioselective addition of organometallic reagents to *N*–formylimines using copper/phosphoramidite catalysts

The asymmetric synthesis of protected amines via the copper/phosphoramidite-catalyzed addition of organozinc and organoaluminum reagents to N-formylimines, generated in situ from aromatic and aliphatic α-amidosulfones, is reported. High yields of optically active N-formyl protected amines and enantioselectivities of up to 99% were obtained. Under the reaction conditions, partial oxidation of the phosphoramidite ligand to the corresponding phosphoric amide was detected. A preliminary study on the origin of this oxidation and its effect on the catalytic addition reaction is presented.

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4.1 Introduction

Enantiomerically pure chiral amines play a prominent role in the area of fine chemicals and pharmaceuticals comprising resolving agents,[1] chiral auxiliaries[2] and catalysts[3] as well as building blocks for the synthesis of biologically active compounds.[4]

The asymmetric nucleophilic addition to imines and their derivatives is one of the most powerful methods available to synthesize α-chiral amines.[5] As shown in Scheme 4.1, this strategy provides access to a wide range of compounds with different functionalization patterns.

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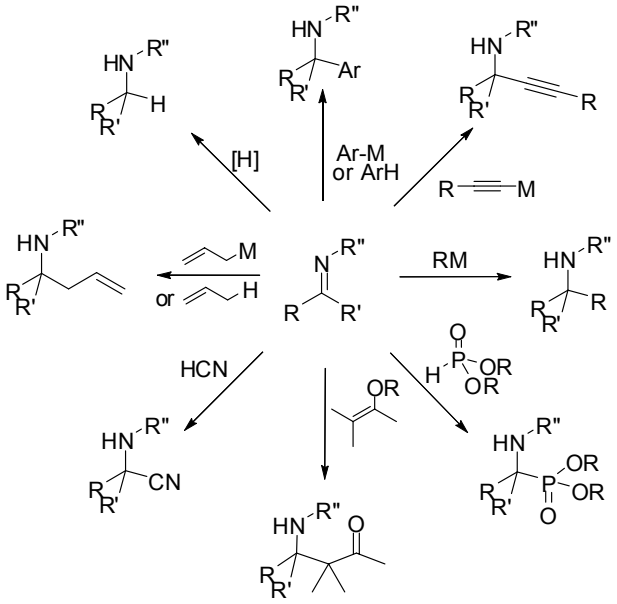
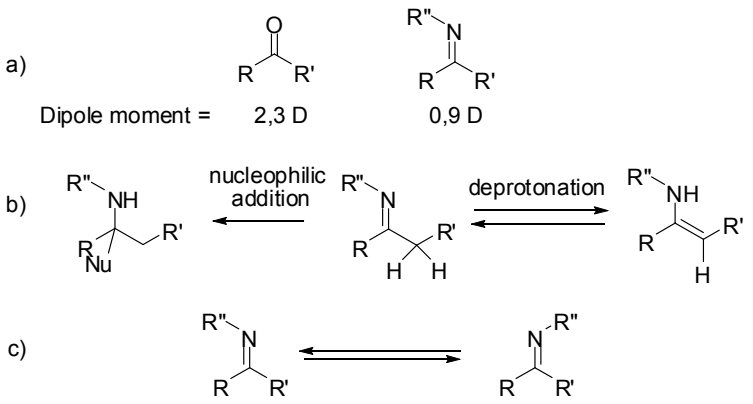


Scheme 4.1 *Nucleophilic addition to the C=N double bond.*

For example, probably the most convenient way to introduce an alkyl substituent at the α-carbon of an amine in an asymmetric fashion consists of the enantioselective addition of organometallic reagents to C=N double bonds.[6] The development of this reaction, however, has been limited in comparison to

the corresponding addition to carbonyl compounds, by several factors associated with the reactivity of imines. The poor electrophilicity of the azomethine carbon, compared to carbonyl compounds, makes imines less reactive toward nucleophilic attack (Scheme 4.2a); furthermore, enolizable imines show a high propensity to undergo deprotonation, rather than addition (Scheme 4.2b). Controlling stereoselectivity in this reaction is difficult due to the existence of *cis-trans* isomers (Scheme 4.2c).[7]



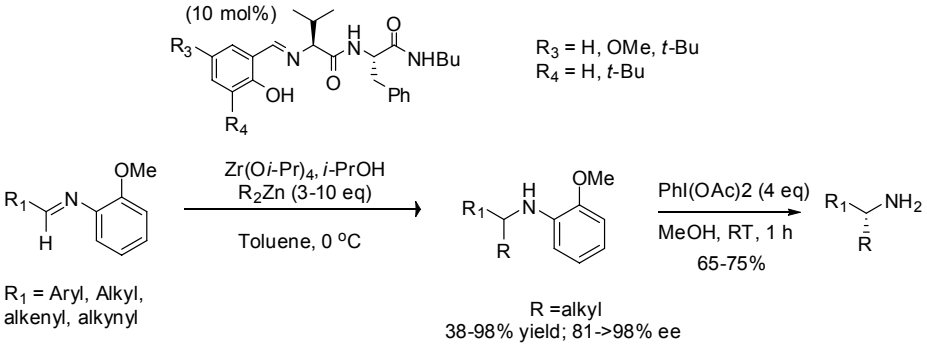
Scheme 4.2 *Some characteristic properties of imines.*

Although many procedures employing chiral auxiliaries[6a-e,8] and stoichiometric chiral ligands[6a-c,e,9] have been described in the literature, the development of catalytic versions of the organometallic addition to the C=N doube bond has been hampered by the ability of the nitrogen atom to bind to the catalyst (for example Lewis acids) strongly, interrupting the catalytic cycle. Only recently, highly enantioselective catalytic methods have appeared in literature.[6e,f,g]

High enantioselectivities for the addition of dialkylzinc reagents have been obtained with imine derivatives protected through *N*-alkylation[10,11] or activated via *N*-sulfonylation,[12,13] *N*-phosphonylation[14,15] or *N*-acylation.[16,17]

4.2 State of the art in the addition of organozinc reagents to imines

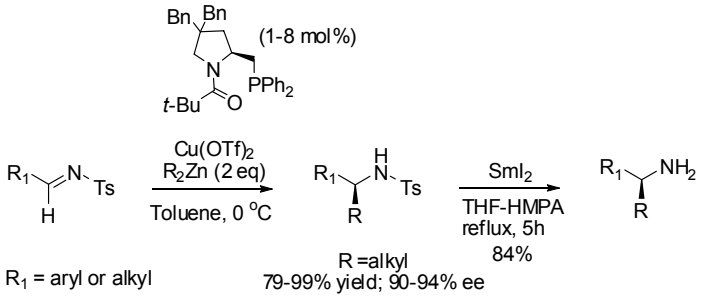
Hoveyda reported the first efficient catalytic method for the enantioselective addition of dialkylzinc reagents to a variety of *N*-*o*-methoxyphenyl alkyl/aryl-aldimines (Scheme 4.3).[10a-c] The aromatic substrates can be isolated whereas the aliphatic substrates are generated more conveniently *in situ* to circumvent formation of enamines and the corresponding homocoupling products (for example, aldol- and Mannich-type additions). The use of chiral Zr-dipeptide complexes as Lewis acid activators of the imino acceptors allows for the preparation of the corresponding *o*-anisidine amines with enantioselectivities exceeding 98%. Oxidative removal of the anisidoyl group affords the enantiomerically enriched amines without loss of enantioselectivity. The low yields observed for the aliphatic substrates were improved by using less Lewis acidic Hf-complexes.[10d]



Scheme 4.3 *Addition of alkylzinc reagents to N-o-anisidine aldimines.*

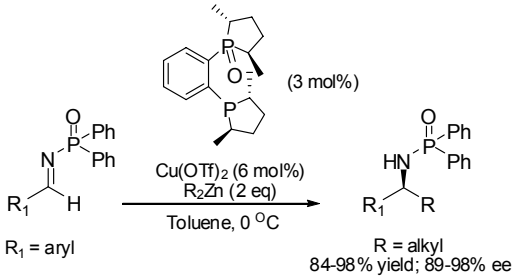
N-Sulfonylimines can undergo diethylzinc addition in high yields and with ee's up to 96% in the presence of $Cu(OTf)_2$ and amidophosphine ligands, under mild conditions, as described by Tomioka *et al*. (Scheme 4.4).[12] The best results in terms of both reactivity and enantioselectivity were obtained with *N*-tosylimines and *N*-mesylimines. Tuning of the steric features of the substituents on the pyrrolidine ring of the chiral ligand played a crucial role in achieving a

high level of enantioselection. Also in this case the procedure can be extended to asymmetric amine synthesis by deprotection of the *N*-sulfonylamide by SmI_2.



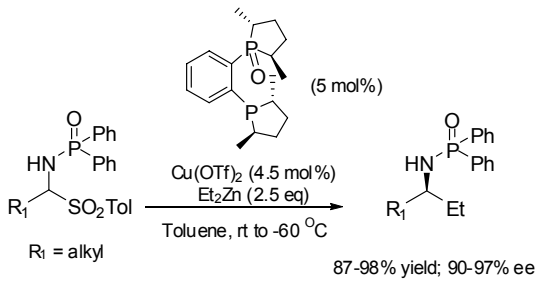
Scheme 4.4 *Addition of alkylzinc reagents to N-sulfonylimines.*

The state of the art for the dialkylzinc addition to *N*-diphenylphosphinoylimines is currently represented by the protocol developed by the Charette group[14] in which the use of a catalytic amount of $Cu(OTf)_2$ in combination with (*R*,*R*)-BozPHOS promotes the alkylation of several aromatic aldimines and ketimines in high yields and with high enantioselectivities (Scheme 4.5).



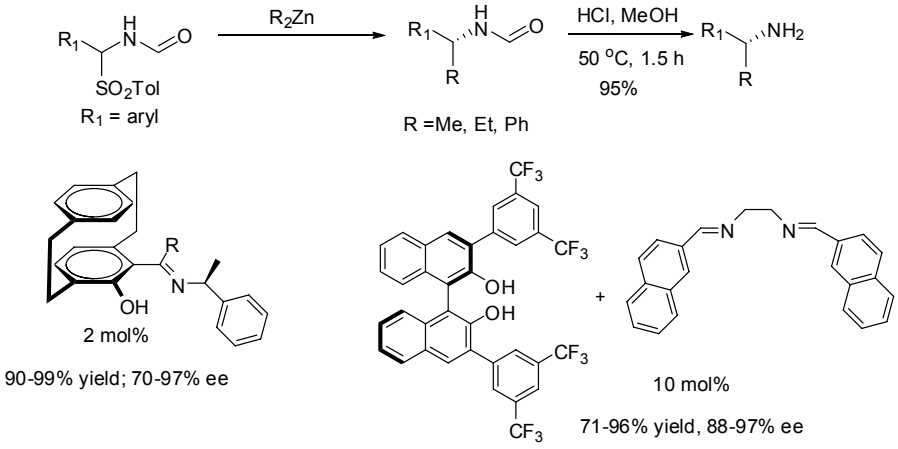
Scheme 4.5 *Addition of alkylzinc reagents to aromatic N-phosphinoylimines.*

Due to extensive decomposition of the *N*-diphenylphosphinoylimines derived from aliphatic aldehydes, bearing enolizable protons, sulfinate adducts of the starting materials were required as masked imines. Reaction of the adduct under standard conditions led to the desired addition product in high yield and with high enantioselectivity (Scheme 4.6).[14f] The use of a larger amount of Et_2Zn was necessary in order to form the imine *in situ*.



Scheme 4.6 *Addition of diethylzinc to alkyl N-phosphinoylimines generated in situ.*

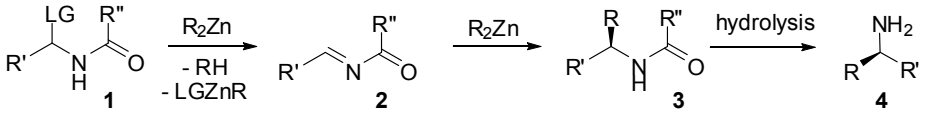
Finally, the scope of the addition of diorganozinc reagents to *N*-formylimines generated *in situ* has been investigated by Bräse[16] and Gong[17] using, respectively, [2,2]paracyclophane-based *N,O*-ligands and 3,3'-substituted optically active BINOLs in combination with racemic and achiral diimines as effective activators (Scheme 4.7).



Scheme 4.7 *Addition of diorganozinc reagents to N-formylimines.*

Although these methods provide access to chiral N-formylamines in high yields and with high enantioselectivities, they are restricted to the use of substrates derived from aryl aldehydes. Furthermore, the laborious synthesis of the chiral ligand or high catalyst loadings are required frequently. The use of N-formylimines as substrates for the synthesis of alkylated chiral amines, however, appears particularly attractive for several reasons. First, the product

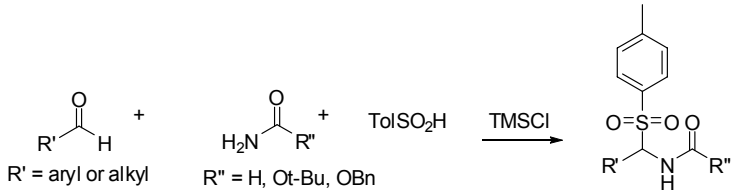
of the reaction is a formamide, which can be deprotected under acidic conditions and without loss of enantioselectivity. In order to circumvent practical problems arising from the inherent instability of acylimines, especially those derived from aliphatic aldehydes, it is possible to generate these substrates in situ from stable precursors. A detailed explanation of this strategy is presented in Scheme 4.8.



R = Me, Et, Ph
R' = aryl, alkyl
R" = H, OR

Scheme 4.8 *Addition of organozinc reagents to in situ generated imines.*

The starting material **1** is an imine adduct substituted at the α-carbon with a leaving group. Elimination of the leaving group under basic conditions generates the imine **2**, which can undergo nucleophilic attack to form the *N*-acylamine **3**. Deprotection of **3** affords the free α-chiral amine **4**. In the addition reaction of R_2Zn, the nucleophile acts as a base also generating the *N*-acylimine together with an equimolar amount of RH and of the adduct LGZnR. It is important that such a species does not inhibit the catalysis. Several leaving groups have been used to form *N*-acylimines, e.g. benzotriazolates,[18] succinimidates[19] and sulfinates.[16,17,20] In the addition reaction of diorganozinc reagents, sulfinate is often the leaving group of choice as its adduct with R_2Zn does not affect the addition reaction[14c] and as the corresponding α-amidosulfones are readily available via a one-pot condensation of the desired aldehyde with *p*-toluenesulfinic acid and an amide or a carbamate (Scheme 4.9).[21]



Scheme 4.9 *Synthesis of the starting material.*

We considered these features highly attractive in order to develop a short and practical catalytic, enantioselective route to chiral amines, starting from aromatic and aliphatic aldehydes, formamide and organometallic reagents, based on the use of readily available chiral phosphoramidite ligands[22] in combination with Cu(II) salts.

4.3 Copper-catalyzed addition of organozinc reagents using phosphoramidite ligands

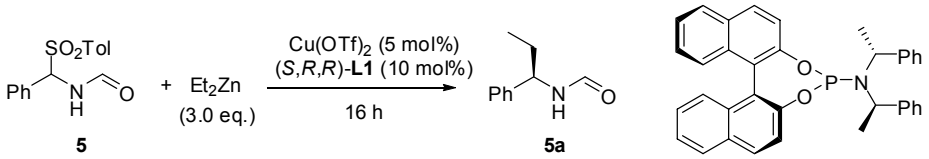
Initially, we investigated the reactivity of the α-amidosulfone **5** (Table 4.1), derived from the condensation of benzaldehyde, *p*-toluenesulfinic acid and formamide, in the copper/phosphoramidite-catalyzed addition of Et_2Zn.

For the optimization of the reaction conditions, 5 mol% of $Cu(OTf)_2$ and 10 mol% of the homochiral monodentate phosphoramidite (*S*,*R*,*R*)-**L1**[22,23] (2.0 equiv. with respect to Cu) were used.

4.3.1 Optimization of the reaction conditions

A preliminary screening, carried out at -30 °C, showed that the reaction proceeds to full conversion and with good enantioselectivity in several solvents (Table 4.1; entries 3-7). In *n*-hexane, because of the poor solubility of the substrate, the reaction proceeds at r.t. only (entry 1). The reaction temperature was decreased in order to obtain higher enantioselectivities. In DCM and THF full conversion was still achieved at -50 °C providing 73% and 96% ee, respectively (entries 11 and 12). A further decrease of the reaction temperature to -78 °C resulted in lower or no conversion.

Table 4.1 *Screening of solvents and temperature.*



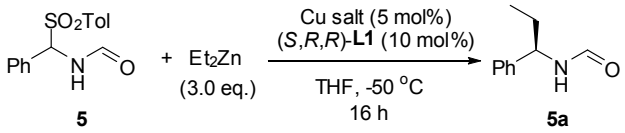
(*S*,*R*,*R*)-**L1**

Entry	T(°C)	solvent	conv(%)	ee(%)	Remarks
1	r.t.	hexane	100	73	36h
2	-30	hexane	-	-	no reaction
3	-30	Et_2O	70	90	
4	-30	toluene	60	90	
5	-30	DCM	100	65	
6	-30	EtOAc	100	90	
7	-30	THF	100	92	
8	-50	Et_2O	-	-	no reaction
9	-50	toluene	-	-	no reaction
10	-50	EtOAc	-	-	no reaction
11	-50	DCM	100	73	
12	-50	THF	100	96	
13	-60	THF	72	96	24h
14	-78	THF	<10	82	24h
15	-78	DCM	-	-	no reaction

The use of THF as the solvent gave the best results affording at -50 °C, product (*R*)-**5a** in quantitative yield and with 96% ee, hence it was used as solvent of choice for further investigations.

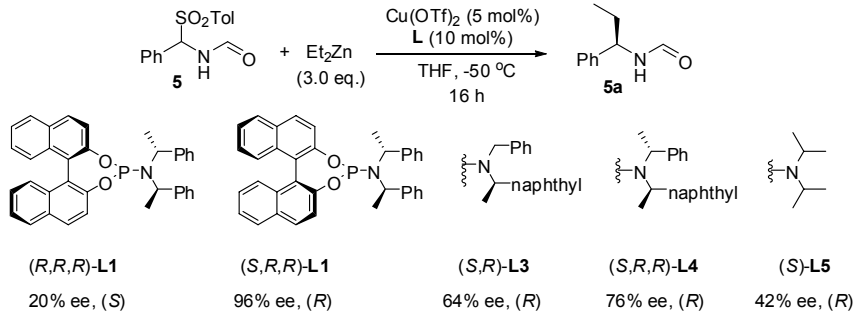
The screening of different copper sources showed no influence of the counter ion on the stereochemical outcome of the reaction. In addition, both Cu(II) and Cu(I) salts proved to be effective in the addition of diethylzinc to the α-amido sulfone **5** (Table 4.2).

Table 4.2 *Screening of copper salts.*



Entry	Cu salt	ee(%)
1	$Cu(OTf)_2$	96
2	$Cu(OAc)\cdot H_2O$	96
3	$Cu(acac)_2$	96
4	$CuBr\cdot SMe_2$	96
5	CuI	94
6	$CuCl_2$	95

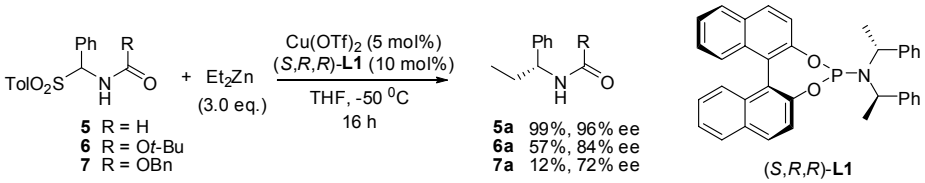
Next a number of chiral phosphoramidite ligands were screened. Phosphoramidite (*R*,*R*,*R*)-**L1**, a diastereoisomer of (*S*,*R*,*R*)-**L1**, afforded **5a** with 20% ee, indicating a mismatch combination of the binaphthol and chiral amine moieties. Moreover, the formation of the opposite enantiomer of **5a**, in this experiment, suggests that the binaphthol part is the dominant feature contributing to the chiral induction. Phosphoramidite ligands **L3**-**L5** gave full conversion of **5** to product **5a** at -50 °C in THF, however, with lower enantioselectivity in comparison to (*S*,*R*,*R*)-**L1** (Scheme 4.10). On the basis of these preliminary studies we concluded that (*S*,*R*,*R*)-**L1** is the ligand of choice.



Scheme 4.10. *Screening of phosphoramidite ligands for the addition of Et_2Zn to **5**.*

Further screening of the reaction conditions showed that it is possible to lower the catalyst loading to 2 mol% and the amount of diethylzinc to 2.5 equiv. without affecting the yield or the enantioselectivity. A decrease of the amount of catalyst to 1 mol% resulted in longer reaction times (full conversion only after 36 h).

Replacing the amide moiety for a carbamate reduced both the isolated yield and the enantioselectivity significantly (Scheme 4.11, substrates **6** and **7**).



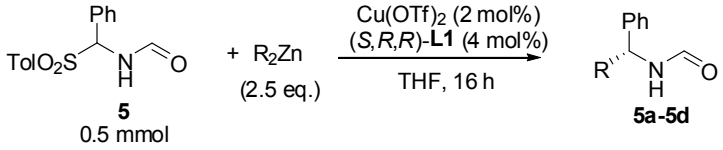
Scheme 4.11 *Screening of protecting groups.*

4.3.2 Organometallic reagent scope

Next the use of other commercially available organozinc reagents in the addition to the *N*-formylimine generated *in situ* from **5** was investigated. Using 2 mol% of the chiral Cu/phosphoramidite catalyst and 2.5 equiv. of the organozinc reagent (Table 4.3), *i*-Pr_2Zn and *n*-Bu_2Zn afforded compound **5b** and **5c** in high yield and 91% and 88% enantioselectivity, respectively (entries 2, 3).

The introduction of a methyl substituent was not possible at -50 °C because of the lower reactivity of Me_2Zn. At -30 °C, two products could be observed by TLC and detected by GS-MS: the expected product **5d** and benzaldehyde.[24]

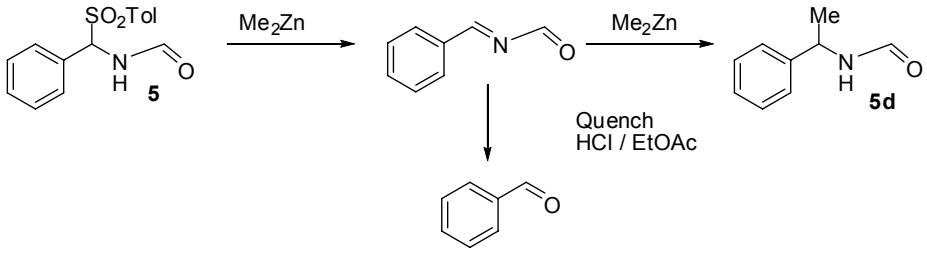
Table 4.3 *Addition of diorganozinc reagents to **5**.*



Entry	R_2Zn	T (°C)	Product	Yield (%)[a]	Ee (%)
1	Et_2Zn	-50	**5a**	99	96-(+)-(*R*)
2	*i*Pr_2Zn	-50	**5b**	97	91-(+)-(*R*)
3	*n*Bu_2Zn	-50	**5c**	92	88-(+)-(*R*)[b]
4	Me_2Zn	-50	**5d**	-	-
5	Me_2Zn	-30	**5d**	n.d.	27-(+)-(*R*)
6	Me_2Zn	-10	**5d**	99	10-(+)-(*R*)

[a] Isolated yield. [b] The absolute configuration of **5c** was tentatively assigned by analogy on the basis of the selectivity observed with the same catalyst (*S*,*R*,*R*)-**L1** in the addition of the other organozinc reagents to **5**.

The latter derives from the hydrolysis of the *in situ* generated imine during the quenching of the reaction mixture (aq. HCl, 1M), indicating that, using Me_2Zn, the rate-determining step is the addition reaction and not the formation of the imine (Scheme 4.12). Product **5d** could be isolated in quantitative yield carrying out the addition reaction at higher temperature (-10 °C), however, the enantioselectivity was low (entry 6).

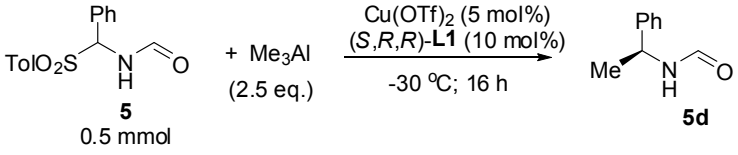


Scheme 4.12 *Addition of Me_2Zn to compound **5** at -30 °C.*

The methyl group is ubiquitous in biologically active compounds. Difficulties are however encountered frequently in the transfer of a methyl group in organometallic addition reactions. Hence, we made considerable efforts to achieve high enantioselectivity in the addition of methyl nucleophiles. Towards this goal, we investigated the use of Me_3Al as methyl source. [25]

The addition reaction of Me_3Al to α-amido sulfone **5** under standard conditions did not proceed at -50 °C. Although full conversion to product **5d** was reached in THF at -30 °C after overnight reaction, the product was obtained in racemic form (Table 4.4, entry 1). No enantioselectivity was observed in toluene either (entry 2), while better results were achieved in ethereal solvents. Thus, **5d** could be obtained with 80% enantioselectivity in *i*-Pr_2O (entry 6).

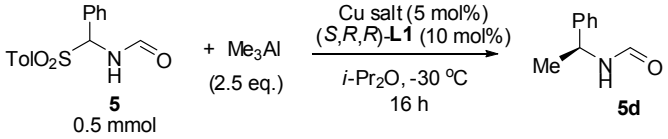
Table 4.4 *Solvent screening for the addition of Me_3Al to **5**.*

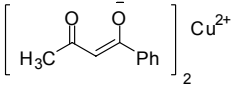
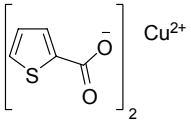
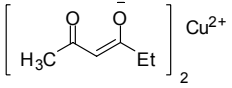
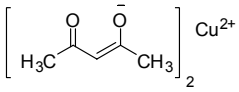
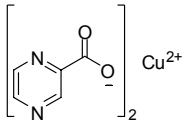
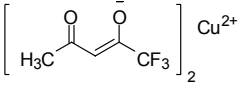
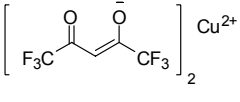


Entry	Solvent	Conv. (%)	ee(%)
1	THF	100	-
2	Toluene	100	-
3	Et_2O	>90	50
4	*n*-Bu_2O	≈50	70
5	*t*-BuOMe	100	65
6	*i*-Pr_2O	100	80

A further improvement was achieved using a different copper source. CuTC (TC = 2-thiophenecarboxylate) gave approximately the same enantioselectivity observed with $Cu(OTf)_2$, (Table 4.5, entry 2).

Table 4.5 *Copper salt screening for the addition of Me_3Al to **5**.*



Entry	Cu salt	ee(%)	Entry	Cu salt	ee(%)
1	$Cu(OTf)_2$	80	8		80
2		81	9		81
3	$CuBr{\cdot}SMe_2$	rac	10	$Cu(BF_4)_2{\cdot}6H_2O$	32
4	$Cu(OAc)_2{\cdot}H_2O$	84	11	CuSPh	rac
5		86	12		rac
6		78	13	$CuSO_4{\cdot}5H_2O$	rac
7		83	14	Cu(*L*-Proline)$_2$	rac

A higher level of stereocontrol (84% ee) was reached with $Cu(OAc)_2{\cdot}H_2O$ (entry 4), however the highest ee (86%) was obtained using $Cu(acac)_2$ (entry 5). The use of copper salts structurally related to $Cu(acac)_2$ did not lead to better results (entries 6-9). The enantioselectivity dropped dramatically using $Cu(BF_4)_2{\cdot}6H_2O$ (entry 10) and racemic product was obtained with $CuBr{\cdot}SMe_2$, CuSPh, Cu(2-piperazinecarboxylate)$_2$ and $CuSO_4{\cdot}5H_2O$ (entries 3, 11-13), confirming the importance of the counter ion for the formation of an efficient

catalyst. $Cu(acac)_2$ turned out to be the best choice leading to the desired product in 70% isolated yield and 86% ee (entry 5). When the catalyst loading was decreased to 2 mol% both lower isolated yield (44%) and lower enantioselectivity (67%) were obtained.

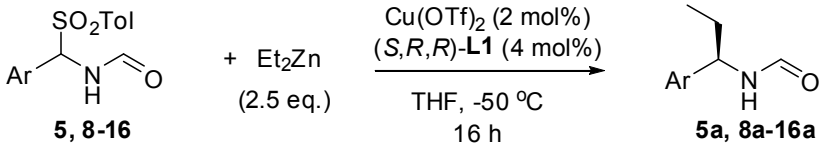
Interestingly, in contrast to the formation of (+)-(*R*)-**5d** using Me_2Zn, the application of Me_3Al resulted in the formation of (-)-(*S*)-**5d** using the same enantiomer of the phosphoramidite ligand (*S*,*R*,*R*)-**L1**. A rationalization for this experimental observation will be provided later in this chapter.

4.3.3 Substrate scope

The scope of *in situ* generated aromatic and aliphatic *N*-formylimines for the copper/phosphoramidite-catalyzed addition of Et_2Zn to aromatic α-amidosulfones was investigated next (Table 4.6). Electronic effects do not seem to play a major role: substitution at the *para* position of the aryl moiety with electron-donating and electron-withdrawing groups does not affect the enantioselectivity and the *N*-formylamines were isolated with ≥96% ee and near quantitative yield (entries 2-5). High enantioselectivities were obtained with *meta*-substituted substrates as well (entries 6 and 7). The introduction of a substituent in the *ortho* position resulted in a dramatic decrease in the ee to less than 50% (entries 8 and 9). We attribute this reduction in stereocontrol to steric effects of the *o*-substituent. Addition to the 2-naphthyl substituted sulfone **16** gave product **16a** in 80% ee.

α-Amidosulfones derived from aliphatic aldehydes showed lower reactivity in the addition reaction than their aromatic counterparts. Compound **17** was chosen as model substrate. No addition reaction was observed in THF, at -50 °C (Table 4.7, entry 1). An increase in temperature to -20 °C was necessary to achieve full conversion of the starting material after overnight reaction and the enantioselectivity observed was modest (entry 2). Further screening of solvents revealed that toluene and Et_2O provide better results compared to THF (entry 4).

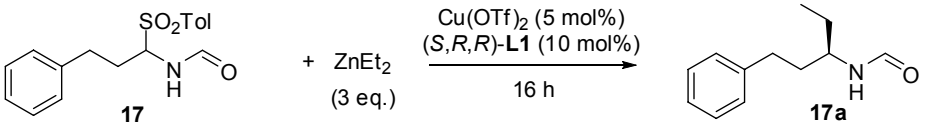
Table 4.6 *Cu-catalyzed addition of Et_2Zn to N-acyl imines generated in situ from aromatic α-amidosulfones.*



5, 8-16 **5a, 8a-16a**

Entry	Compound	Ar	Product	Yield (%)	ee (%)
1	**5**	Ph	**5a**	99	96-(+)-(*R*)
2	**8**	4-Cl-Ph	**8a**	94	97-(+)-(*R*)
3	**9**	4-Br-Ph	**9a**	94	99-(+)-(*R*)
4	**10**	4-MeO-Ph	**10a**	99	97-(+)-(*R*)
5	**11**	4-Me-Ph	**11a**	90	96-(+)-(*R*)
6	**12**	3-Me-Ph	**12a**	99	95-(+)-(*R*)
7	**13**	3-MeO-Ph	**13a**	96	95-(+)
8	**14**	2-MeO-Ph	**14a**	99	47-(-)
9	**15**	2-BnO-Ph	**15a**	99	45-(-)
10	**16**	2-naphthyl	**16a**	94	80-(+)

Table 4.7 *Solvent screening for the addition of Et_2Zn to **17**.*

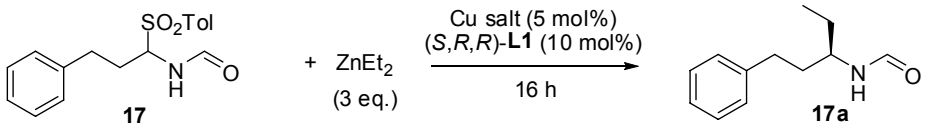


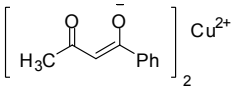
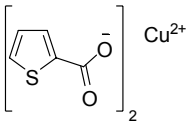
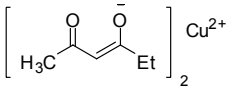
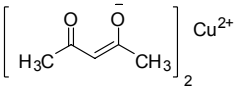
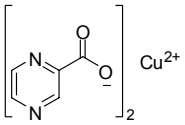
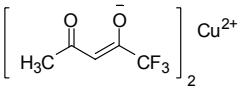
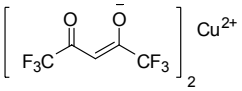
17 **17a**

Entry	Solvent	T(°C)	conv.%)	ee(%)
1	THF	-50	<10	-
2	THF	-20	100	17
3	Toluene	-20	100	37
4	Et_2O	-20	100	38
5	iPr_2O	-30	100	20

Several copper salts were tested in order to improve the enantioselectivity of the reaction. Using $Cu(OAc)_2 \cdot H_2O$, product **17a** was obtained with a strongly increased 66% ee (Table 4.8, entry 3).

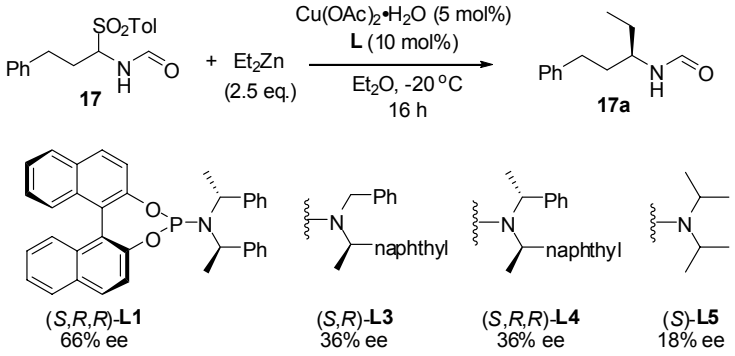
Table 4.8 *Screening of copper salt for the addition of Et_2Zn to **17**.*



Entry	Cu salt	ee(%)	Entry	Cu salt	ee(%)
1	$Cu(OTf)_2$	40	8		54
2		60	9		12
3	$CuBr \cdot SMe_2$	36	10	$Cu(BF_4)_2 \cdot 6H_2O$	54
4	$Cu(OAc)_2 \cdot H_2O$	66	11	CuSPh	rac
5		58	12		rac
6		48	13	$CuSO_4 \cdot 5H_2O$	rac
7		45			

Several phosphoramidite ligands were tested in order to improve the enantioselectivity for the addition of Et_2Zn to **17** also (Scheme 4.13). In this

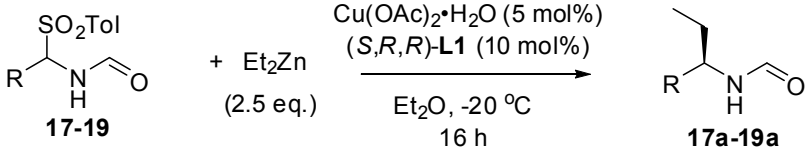
case, however, ligand (*S*,*R*,*R*)-**L1** proved again to be the most selective. Variation of the steric or chiral properties of the amine moiety in ligands **L3**-**L5** resulted, invariably, in a decrease in the enantioselectivity.



Scheme 4.13 *Ligand screening for the Et_2Zn addition to **17**.*

In summary, using (*S*,*R*,*R*)-**L1**, high yields and enantioselectivities varying between 45% and 70% were obtained for the Cu-catalyzed addition of diethylzinc to aliphatic substrates (Table 4.9).

Table 4.9 *Cu-catalyzed addition of Et_2Zn to N-acyl imines generated in situ from aliphatic α-amidosulfones.*



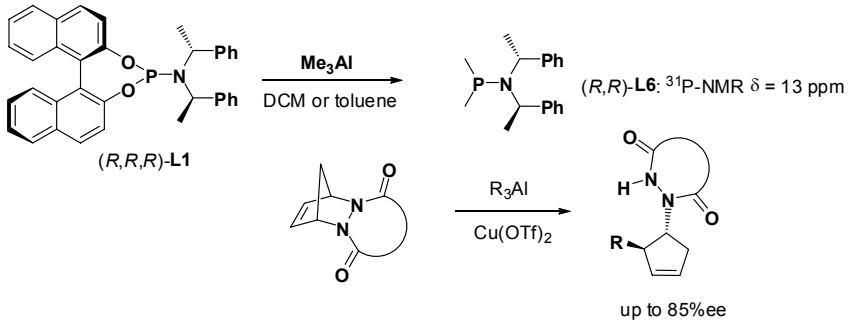
Entry	Compound	R	Product	Yield (%)	ee (%)
1	**17**	$PhCH_2CH_2$	**17a**	81	66-(+)
2	**18**	*c*-hexyl	**18a**	99	45-(+)
3	**19**	*n*-hexyl	**19a**	99	70-(+)

4.4 Studies on *in situ* ligand oxidation

Isolation of (*S*,*R*,*R*)-**L1** after the addition reaction of Et_2Zn to **5** carried out on 1.5 mmol scale in THF, at -50 °C was attempted in order to investigate the efficiency of recovery of the chiral phosphoramidite ligand. Ligand (*S*,*R*,*R*)-**L1** was recovered in 61% yield. It is possible that partial hydrolysis of the phosphoramidite occurs during the quenching of the reaction and during column chromatography over silica gel. Together with (*S*,*R*,*R*)-**L1**, a second compound containing phosphorus was isolated as a white foamy solid. The ^{1}H-NMR spectrum of this species appeared rather similar to that of (*S*,*R*,*R*)-**L1** while the ^{31}P-NMR spectrum showed one single absorption at 12.3 ppm. The spectroscopic data as well as HRMS analysis suggested that this new species was (*S*,*R*,*R*)-**L2** (Figure 4.1a,b).

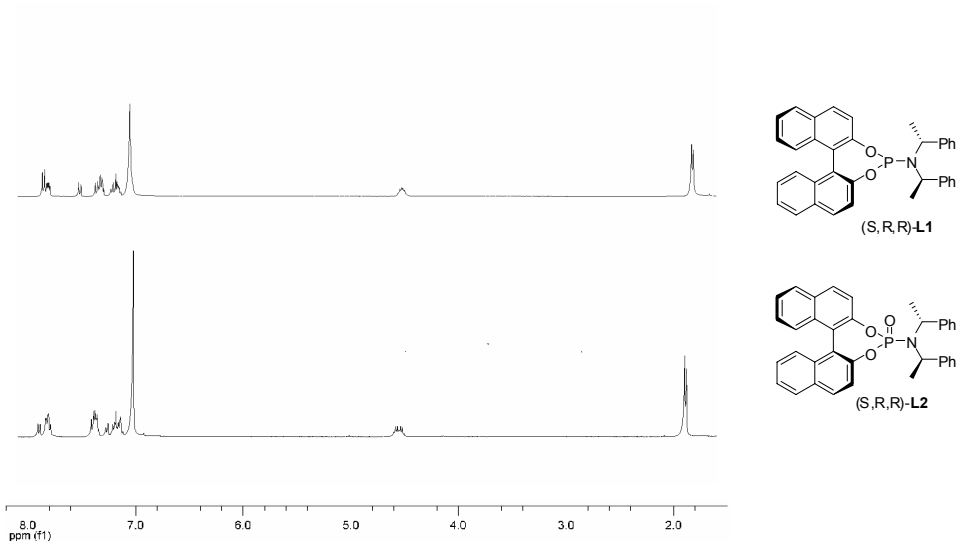
Further investigations revealed that the formation of the species (*S*,*R*,*R*)-**L2** could be detected after performing the addition reaction of both Me_3Al and Et_2Zn to substrate **5** in the solvents THF, Et_2O, *i*-Pr_2O, EtOAc and CH_2Cl_2. By contrast, if the reactions were performed in hexane, at room temperature, or in toluene, at -30 °C, the only phosphorous compound recovered was (*S*,*R*,*R*)-**L1**.

Modification of phosphoramidite ligands[26] during a reaction using organometallic reagents has been reported previously. Recently, Alexakis and Micouin[27] observed that, in the $Cu(OTf)_2$-catalyzed ring opening of meso bicyclic hydrazines, the phosphoramidite (*R*,*R*,*R*)-**L1** reacts with Me_3Al, in dichloromethane and toluene, leading to the corresponding aminophosphine, which is the actual ligand in the reaction (Scheme 4.14).

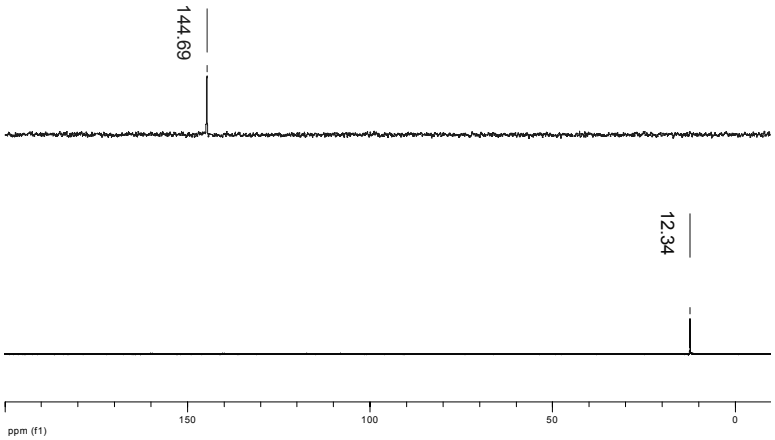


Scheme 4.14 *Phosphoramidite modification reported in the literature.*[27]

Figure 4.1 NMR spectra of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2**.

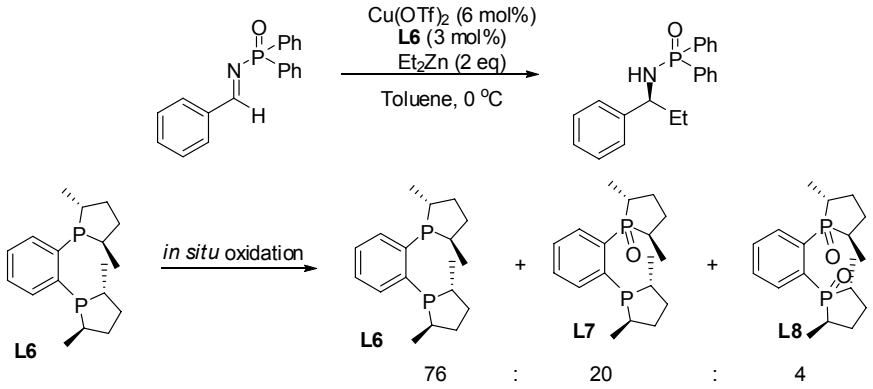


a) ^{1}H-NMR in $CDCl_3$, 400 MHz



b) ^{31}P-NMR in $CDCl_3$, 400 MHz

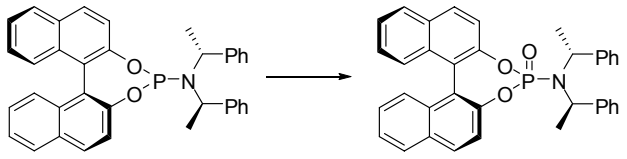
In our case, even though the chemical shift of the newly formed species (*S*,*R*,*R*)-**L2** in the ^{31}P-NMR spectrum would be consistent with the formation of the dimethylaminophosphine, the ^{1}H-NMR spectrum data rules out this possibility. The ^{1}H-NMR spectrum, in fact, clearly shows that the BINOL moiety is still present in (*S*,*R*,*R*)-**L2**. The substitution pattern is similar to (*S*,*R*,*R*)-**L1**: only minor shifts can be observed for the doublet corresponding to the methyl group and for the signal of the benzylic hydrogen; small differences are present in the aromatic region. The work of Charette et al.,[28] provided inspiration for the elucidation of the structure of (*S*,*R*,*R*)-**L2**. They found that, in the Cu-catalyzed addition of diorganozinc reagents to *N*-phosphonoylimines, an *in situ* oxidation of Me-Duphos by Cu(II) salts occurs, to produce the highly effective monoxide ligand (BozPHOS) and, to a lesser extent, the Me-Duphos bisoxide (Scheme 4.15). Furthermore, it was proven that in the bidentate ligand (BozPHOS), the cooperative effect of both donor groups, namely the phosphine and the hemilabile phosphinoxide moieties, is essential to reach high enantioselectivities.[28]



Scheme 4.15 *Ligand oxidation described by Charette.*[28]

Redox processes between phosphorous based ligands and transition metals have been reported previously.[29] Pd(II) salts, for example, can be reduced to Pd(0) in the presence of Ph_3P, producing $Ph_3P{=}O$ as the by-product.[30] Regarding this type of chemistry much less is known for copper. It has been reported that Cu(II) salts are reduced by 1,2-bis(diphenylphosphino)ethane to

produce several phosphine/phosphine oxide ligands,[31] however, to the best of our knowledge, no precedents for the Cu-catalyzed oxidation of phosphoramidite ligands are described in the literature. We decided to investigate the possibility of *in situ* oxidation of the phosphoramidite ligand (*S*,*R*,*R*)-**L1** to the corresponding phosphoric amide (*S*,*R*,*R*)-**L2** under the reaction conditions and its possible role in asymmetric catalysis (Scheme 4.16).



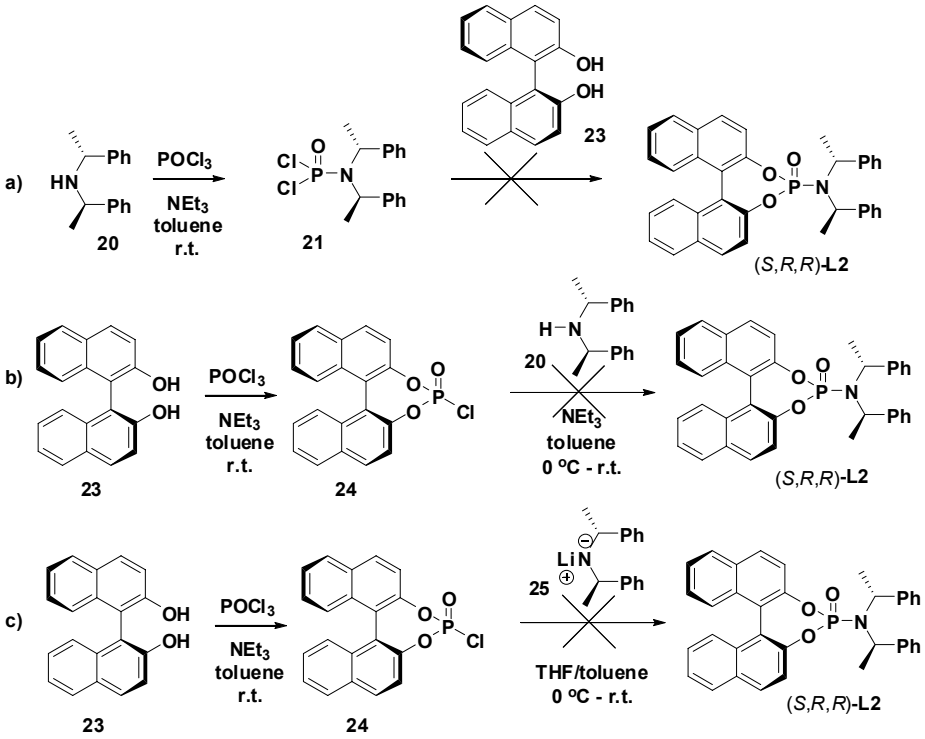
(*S*,*R*,*R*)-**L1** (*S*,*R*,*R*)-**L2**

Scheme 4.16 *In situ ligand oxidation.*

4.4.1 Synthesis of the phosphoric amide (*S*,*R*,*R*)-L2

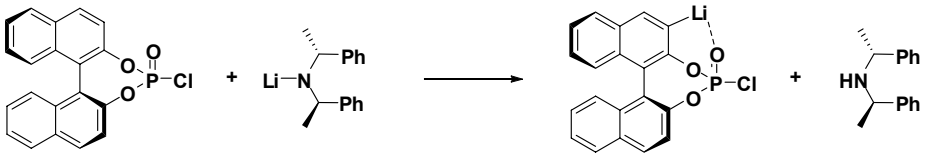
Several approaches for the synthesis of phosphoric amide (*S*,*R*,*R*)-**L2** were tried. At first, the use of procedures based on the synthesis of phosphoramidite (*S*,*R*,*R*)-**L1**[32] were investigated (Scheme 4.17).

The first attempt consisted of the synthesis of the phosphoroyl chloride **21** from $POCl_3$ and the chiral amine **20**, followed by substitution with (*S*)-BINOL **23** (Scheme 4.17a); however, the reaction did not proceed. Next the inverse procedure was used (Scheme 4.17b). The phosphoroyl chloride **24** was formed from $POCl_3$ and (*S*)-BINOL **23**.[33] Compound **24** is rather stable and was isolated and purified by column chromatography. In the second step of the synthesis the phosphoroyl chloride was reacted with the chiral amine **20** in presence of Et_3N. The reaction is known to work with non-sterically hindered secondary amines and cyclic aliphatic secondary amines like pyrrolidine and piperidine,[34] however, under these conditions, the bis(dimethyl-benzyl)amine **20** was recovered.



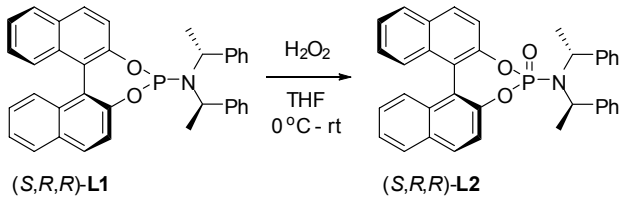
Scheme 4.17 *Attempts in the synthesis of (S,R,R)-**L2**.*

Sterically demanding amines undergo substitution on BINOL-based phosphorus chlorides successfully if the more reactive Li-amide is first formed.[32] In the case of the phosphoroyl chloride, however, this approach did not furnish the desired product either (Scheme 4.17c). It is possible that the formation of a stabilized carbanion, via coordination of the lithium to the P=O bond, promotes the deprotonation on the 3 position of the binaphthol moiety by the Li-amide rather than the substitution of the chloride (Scheme 4.18).



Scheme 4.18 *Reaction of the Li-amide with **24**.*

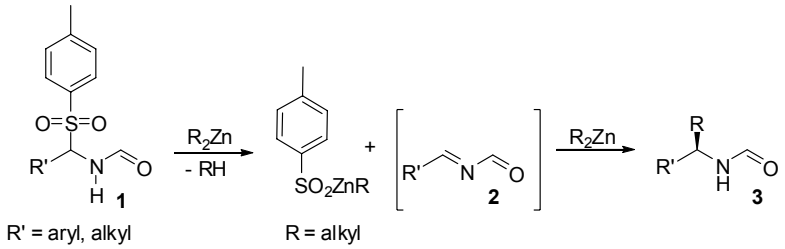
Finally, the phosphoric amide (*S*,*R*,*R*)-**L2** was synthesized, in quantitative yield, upon reaction of (*S*,*R*,*R*)-**L1** with hydrogen peroxide (Scheme 4.19). Characterization by ^{1}H-NMR and ^{31}P-NMR spectroscopy, HRMS and elemental analysis of the phosphoric amide synthesized and the isolated species (*S*,*R*,*R*)-**L2** confirmed that the two compounds are identical.



Scheme 4.19 *Synthesis of (S,R,R)-**L2**.*

4.4.2 Ligand oxidation

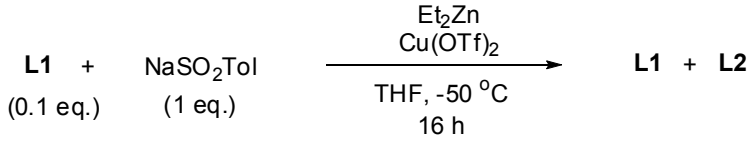
We hypothesized that the ligand oxidation, observed in the Cu-catalyzed addition of diorganozinc and organoaluminium reagents to *N*-formylimines could be due to the substrate itself. The *in situ* formation of the imine, in fact, generates 1 equivalent of the zinc-sulfinate adduct, which could act as an oxidizing agent (Scheme 4.20).



Scheme 4.20 *Formation of the zinc sulfinate adduct.*

To confirm this hypothesis, we investigated the effect that sulfinate, added as the sodium salt, has on ligand (*S*,*R*,*R*)-**L1**, under different conditions (Table 4.10).[35] If no sulfinate was present in the reaction mixture, no oxidation occurred (entry 1); when the sulfinate was added in a copper-free environment, with or without Et_2Zn, a small percentage (< 10%) of (*S*,*R*,*R*)-**L1** was oxidized to (*S*,*R*,*R*)-**L2** (entries 2 and 3). On the other hand, if both the sulfinate and a copper salt were added to the reaction mixture, complete oxidation of (*S*,*R*,*R*)-**L1** to the phosphoric amide was observed after overnight reaction, suggesting that the copper salt acts as a catalyst for the reaction (entry 4).

Table 4.10 *Effect of sulfinate on (S,R,R)-**L1**.*



Entry	$NaSO_2Tol$ (eq.)	Et_2Zn (eq.)	$Cu(OTf)_2$ (eq.)	L1 / L2 [a]
1	0	3	0.05	100 / 0
2	1	3	0	95 / 5
3	1	0	0	94 / 6
4	1	0	0.05	0 / 100

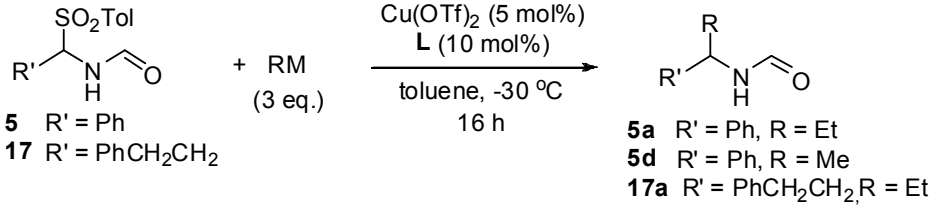
[a] The **L1** / **L2** ratio was determined by ^{31}P-NMR of the crude product after quenching with a saturated aqueous solution of NH_4Cl.

We were interested to see whether the chiral phosphoric amide (*S*,*R*,*R*)-**L2** was merely a by-product in the reaction or actually part of the active catalyst.

We mentioned earlier that no ligand modification was detected when the Me_3Al or Et_2Zn addition to compound **5** was performed in hexane or in toluene. This allowed us to analyze the activity and enantioselectivity of the species (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2**, used separately, from a mixture of the two (that would be formed inevitably *in situ*, when performing the reaction in THF, DCM or ethereal solvents, starting with (*S*,*R*,*R*)-**L1** alone).

The addition of Me_3Al and Et_2Zn to the α-amidosulfone **5** and the addition of Et_2Zn to the aliphatic α-amidosulfone **17** were carried out in toluene, at -30 °C, using 5 mol% of $Cu(OTf)_2$ and 10 mol% of the ligand (*S*,*R*,*R*)-**L1**, (*S*,*R*,*R*)-**L2** or their 1/1 mixture (5 mol% of (*S*,*R*,*R*)-**L1** plus 5 mol% of (*S*,*R*,*R*)-**L2**). The results are presented in Table 4.11. Entries 3, 6 and 9 demonstrate that the phosphoric amide (*S*,*R*,*R*)-**L2** is not an efficient chiral ligand by itself, affording product **5a** in full conversion but in racemic form. Moreover, low conversions of the starting material (< 10%) were observed for the addition of Et_2Zn to compound **17** and the addition of Me_3Al to compound **5**. No significant difference in the enantioselectivity was observed in the addition of diethylzinc to compound **5** in the presence of only (*S*,*R*,*R*)-**L1** or a 1/1 mixture of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** (entries 1, 2). The reaction proceeded to full conversion, overnight, and high ee's of 85% and 86%, respectively, were achieved for the product **5a**. However, the use of a 1/1 mixture of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** led to a slight improvement in the enantioselectivity of the addition of diethylzinc to the aliphatic α-amidosulfone **17** (entries 4 and 5).

Table 4.11 *Study on the effect of (S,R,R)-**L2** in toluene.*



5 R' = Ph
17 R' = $PhCH_2CH_2$

5a R' = Ph, R = Et
5d R' = Ph, R = Me
17a R' = $PhCH_2CH_2$, R = Et

Entry	Comp.	L	RM	Prod.	Conv. (%)	ee(%)
1	5	**L1**	Et_2Zn	**5a**	100	85
2	5	**L1**+**L2** (1/1)	Et_2Zn	**5a**	100	86
3	5	**L2**	Et_2Zn	**5a**	100	-
4	17	**L1**	Et_2Zn	**17a**	100	38
5	17	**L1**+**L2** (1/1)	Et_2Zn	**17a**	100	47
6	17	**L2**	Et_2Zn	**17a**	<10	-
7	5	**L1**	Me_3Al	**5d**	100	-
8	5	**L1**+**L2** (1/1)	Me_3Al	**5d**	100	52
9	5	**L2**	Me_3Al	**5d**	<10	-
10[a]	5	**L1**+**L2** (1/1)	Me_3Al	**5d**	100	60
11[a]	5	**L1**+HMPA (1/1)	Me_3Al	**5d**	100	50

[a] $Cu(acac)_2$ was used as copper source.

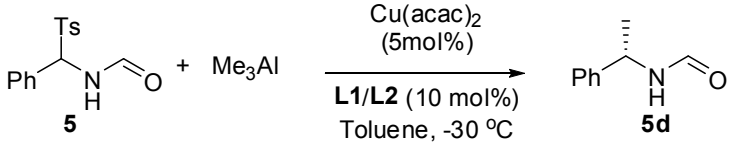
A striking improvement in the enantioselectivity was reached using Me_3Al in the formation of **5d**, that went from 0%, when (*S*,*R*,*R*)-**L1** was used as the only chiral species (entry 7), to 52% when both (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** were present in the reaction mixture (entry 8). These results suggest that the phosphoric amide (*S*,*R*,*R*)-**L2**, indeed, can have an effect on the enantioselectivity of the reaction.

We considered that (*S*,*R*,*R*)-**L2** could act as a chiral analogue of HMPA, whose strong coordinating properties are known to largely affect the regio- and stereochemical outcome of reactions involving organometallic species.[36] The

presence of a metal coordinating species might vary the structure of the actual catalyst, for example in terms of aggregation level, which is known to be strongly dependent on several factors, above all the solvent.[37] This observation prompted us to study the effect of the addition of HMPA in place of (*S*,*R*,*R*)-**L2** (Table 4.11, entry 11). Having observed a major influence of the phosphoric amide (*S*,*R*,*R*)-**L2** in the addition of Me_3Al to compound **5**, we decided to evaluate the effect of HMPA addition in the same reaction. $Cu(acac)_2$ was used instead of $Cu(OTf)_2$ because, from the screening of the copper salts for the Me_3Al addition (Table 4.5), it was proven to be the most effective. As shown in Table 4.11 (entries 10 and 11), HMPA seems to play a similar role compared to (*S*,*R*,*R*)-**L2**. With $Cu(acac)_2$ as copper source, the use of a 1/1 mixture of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** afforded the product **5d** with 60% ee, while the use of a 1/1 mixture of (*S*,*R*,*R*)-**L1** and HMPA gave **5d** with a slightly lower, but significant, 50% ee, suggesting that the effect that (*S*,*R*,*R*)-**L2** has on the enantioselectivity of the Me_3Al addition to **5** might not be due to its chiral properties but rather an additional (HMPA type) co-ligand effect.

We investigated the dependence of the enantioselectivity observed for **5d** as a function of the amount of phosphoric amide (*S*,*R*,*R*)-**L2** present in the reaction mixture. Keeping the total amount of (*S*,*R*,*R*)-**L1** plus (*S*,*R*,*R*)-**L2** fixed to 10 mol%, we varied the relative ratio of the two chiral species. As shown in Table 4.12 the highest ee (72%, entry 2) is obtained when a 75/25 mixture of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** is used. Interestingly, the formation of a similar ratio of (*S*,*R*,*R*)-**L1** to (*S*,*R*,*R*)-**L2** is detected by ^{31}P-NMR spectroscopy after the addition of Me_3Al to **5** in *i*-Pr_2O. Higher loadings of (*S*,*R*,*R*)-**L2** resulted in a decrease of the enantioselectivity (entries 3 and 4). Considering that the total amount of the species (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** is kept constant to 10 mol% (2.0 equiv compared to copper), the reason for this decrease might be attributed to a decrease of the relative ratio between the chiral ligand (*S*,*R*,*R*)-**L1** and the copper salt.

Table 4.12 *Effect of (S,R,R)-**L2** loading.*



Entry	L1/L2	ee (%)
1	100/0	-
2	75/25	72
3	50/50	60
4	25/75	64
5	0/100	0

Further investigations are needed to clarify the exact role of (*S*,*R*,*R*)-**L2** in the Cu-catalyzed addition of organometallic reagents to N-formylimines generated *in situ* from α-amidosulfones.

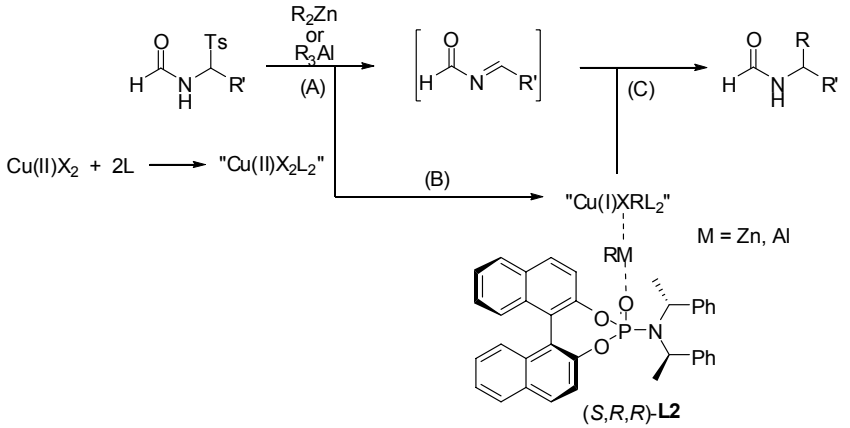
4.5 Conclusions

We showed that the copper/phosphoramidite-catalyzed addition of diorganozinc reagents and trimethylaluminum to *N*-acylimines generated *in situ* from aromatic and aliphatic α-amidosulfones furnishes optically active α-alkylamides in high yield and enantiomeric excess of up to 99%.

Beside providing a convenient method for the synthesis of optically active α-chiral amines, the development of this reaction offered several reflection points based on experimental observations. We mentioned that, in attempting to introduce a methyl substituent (*vide supra*), we observe opposite enantioselection in the formation of product **5d** switching from Me_2Zn to Me_3Al.

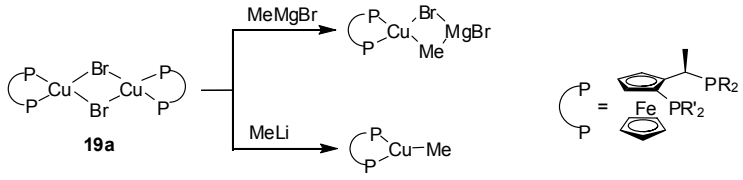
It is known that the organometallic reagent has multiple functions during the catalytic reaction. First of all, it acts as a base in order to generate *in situ* the actual substrate for the nucleophilic addition (Scheme 4.21, path (A)). The organometallic reagent is responsible for the reduction of the precatalytic copper(II) complex to a copper(I) active species[38] in which transmetallation of

the alkyl group “R” has occurred[39] (Scheme 4.21, path (B)). Then, the active catalyst can transfer the alkyl group to the *in situ* generated imine forming the final product (Scheme 4.21, path (C)).



Scheme 4.21 *Copper catalyzed organometallic addition to α-amido sulfones.*

A different stereochemical outcome of the reaction upon changing of the organometallic reagent suggests that the latter is involved in the structure of the active catalytic system, also. We assume that by switching from an organozinc to an organoaluminum reagent two different catalysts are formed, thereby changing the final outcome of the reaction. This assumption is in agreement with what was demonstrated for the copper catalyzed 1,4-addition of Grignard reagents[40] in which the addition of different organometallic species to a same precatalytic system, under the same conditions, leads to the formation of two different copper complexes (Scheme 4.22).



Scheme 4.22

A second striking experimental finding consists of the modification of the chiral ligand *in situ*. In particular, oxidation of the chiral phosphoramidite (*S*,*R*,*R*)-**L1** to the corresponding phosphoric amide (*S*,*R*,*R*)-**L2**, under the reaction conditions, was observed when performing the organometallic addition in THF, Et_2O, *i*Pr_2O, DCM and EtOAc, but not in hexane or toluene. A preliminary investigation into the effect of the chiral phosphoric amide (*S*,*R*,*R*)-**L2** shows that, under certain conditions, the presence of this species in the reaction mixture can improve the level of the enantioselectivity of the reaction. In the addition of Me_3Al to **5** in toluene, in fact, the presence of (*S*,*R*,*R*)-**L2** is essential to achieve enantioselectivity in the reaction, however, the same species does not seem to play a prominent role in the addition of organozinc reagents.

Assuming that the influence of (*S*,*R*,*R*)-**L2** is due to its coordinating properties (*vide supra*), it is plausible that such a coordination occurs to the metal, Zn or Al, of the organometallic species (Scheme 4.21). A stronger interaction with the more oxophilic aluminum atom can account for the marked effect on the stereochemical outcome of the Me_3Al addition reaction when the phosphoric amide is present.

Further mechanistic studies are required to clarify the actual role played by (*S*,*R*,*R*)-**L2**, however the advantage of readily available and stable starting materials as well as the easy deprotection of the α-alkylamides obtained make the new method a useful alternative to existing methods for the formation of optically active α-chiral amines.

4.6 Experimental section

General Methods.

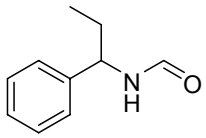
All reactions were performed in oven or flame dried glassware under an inert atmosphere of N_2 or argon and using standard Schlenk techniques. Toluene, THF and ether were distilled from sodium, *n*-hexane and CH_2Cl_2 from CaH_2. Dialkylzinc reagents: Me_2Zn (2 M in toluene), Et_2Zn (1 M in *n*-hexane), *i*-Pr_2Zn (1 M in toluene) and Me_3Al (1 M in *n*-heptane) were purchased from Aldrich, Bu_2Zn (1 M in *n*-heptane) was purchased from Fluka. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 TLC-plates F254 and visualized using UV or phosphomolybdic acid. Flash chromatography was carried out on silica gel (Aldrich, 230 – 400 mesh). ^{1}H NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ or DMSO-d^6 as solvent, ^{13}C NMR spectra were obtained at 50 or 100 MHz in $CDCl_3$ or DMSO-d^6 (Varian spectrometers). Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for hydrogen atoms, δ = 77.0 ppm for carbon atoms; DMSO-d^6, δ = 2.54 ppm for hydrogen atoms, δ = 40.45 ppm for carbon atoms). Optical rotations were recorded on Schmidt+Haench Polartronic MH8 instrument at 589 nm. Gas chromatography was performed on Hewlett-Packard HP 6890 Series GC System with flame ionization detector using chiral columns and HPLC analyses were performed on a Shimadzu LC-10AD VP instrument equipped with 6 parallel normal phase chiral columns, using a Chiralpak AD column (4.6 × 250 mm, 10 μm) and a diode array detector. Mass spectra were recorded on an JEOL JMS·600H mass spectrometer.

General procedure for the copper/phosphoramidite catalyzed addition of dialkylzinc reagents to aromatic α-amidosulfones.

$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and ligand (*S*,*R*,*R*)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous THF (10 mL) and stirred for 30 min at room temperature. The mixture was cooled to -50 °C and the substrate (0.50 mmol) was added. A solution of a R_2Zn (1.25 mmol) in the indicated solvent was added dropwise and the reaction mixture was stirred for 16 h at -50 °C, then

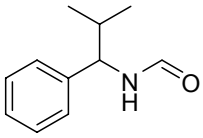
quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography.

(*R*)-(+)-*N*-(1-Phenyl-propyl)-formamide (5a).[16a]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **5a** in 99% isolated yield (Rf = 0.4) as a colorless oil which slowly solidified, m.p. = 56.8-58.8 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt(*S*) = 95.17 min (minor), Rt(*R*) = 95.75 min (major); 96% ee. $[\alpha]_D$ = + 136.1 (c 0.99, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.18 (s, 1H, C*H*O), 7.36-7.22 (m, 5H, H_{Ar}), 6.02 (s, br, 1H, N*H*), 4.96 (q, *J* = 7.8 Hz, 1H, C*H*), 1.92-1.80 (m, 2H, CH_2), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 162.1, 141.0, 128.6, 127.5, 126.6, 54.2, 28.9, 10.6 ppm. Minor rotamer ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 12.0 Hz, 1H, C*H*O), 7.36-7.22 (m, 5H, H_{Ar}), 6.30 (s, br, 1H, N*H*), 4.37 (q, *J* = 7.2 Hz, 1H, C*H*), 1.92-1.80 (m, 2H, CH_2), 0.94 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 165.9, 140.8, 128.9, 127.9, 126.2, 59.1, 30.1, 10.5 ppm. HRMS calcd. for $C_{10}H_{13}NO$ 163.1004, found 163.0997.

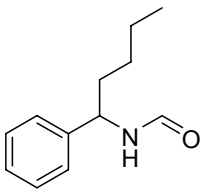
(*R*)-(+)-*N*-(1-Phenyl-2-methyl-propyl)-formamide (5b).[41]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **5b** in 97% isolated yield (Rf = 0.4) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt(*S*) = 97.42 min (minor), Rt(*R*) = 98.49 min (major); 91% ee. $[\alpha]_D$ = + 102.3 (c 1.07, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 3:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.15 (s, 1H, C*H*O), 7.34-7.18 (m, 5H, H_{Ar}), 6.69 (br s, 1H, N*H*), 4.79 (t, *J* = 8.5 Hz, 1H, C*H*), 2.09-1.95 (m, 1H, C*H*), 0.94 (d, *J* = 6.7 Hz, 3H, CH_3), 0.81 (d, *J* = 6.7 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.7, 141.0, 128.3, 127.1, 126.8, 57.8, 33.2, 19.6, 18.6 ppm. Minor rotamer ^{1}H-NMR (400

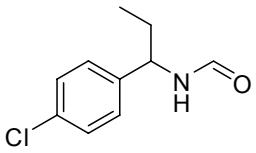
MHz, $CDCl_3$) δ = 8.08 (d, *J* = 11.7 Hz, 1H, C*H*O), 7.34-7.18 (m, 5H, H_{Ar}), 6.69 (s, br, 1H, N*H*), 4.15 (t, *J* = 7.2 Hz, 1H, C*H*), 2.09-1.95 (m, 1H, C*H*), 0.93 (d, *J* = 6.7 Hz, 3H, CH_3), 0.85 (d, *J* = 6.7 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 165.0, 141.0, 128.6, 127.4, 126.5, 62.9, 33. 8, 19.7, 18.2 ppm. HRMS calcd. for $C_{11}H_{15}NO$ 177.1154, found 177.1163.

(*R*)-(+)-*N*-(1-Phenyl-pentyl)-formamide (5c).



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **5c** in 92% isolated yield (Rf = 0.5) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt(*R*) = 108.43 min (major), Rt(*S*) = 106.70 min (minor); 88% ee. $[\alpha]_D$ = + 99.6 (c 1.09, $CHCl_3$).[42] The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09 (s, 1H, C*H*O), 7.35-7.21 (m, 5H, H_{Ar}), 6.57 (br d, *J* = 7.5 Hz, 1H, N*H*), 4.98 (q, *J* = 7.7 Hz, 1H, C*H*), 1.80-1.74 (m, 2H, CH_2), 1.35-1.18 (m, 4H, CH_2), 0.86 (t, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.5, 142.0, 128.5, 127.2, 126.4, 52.1, 35.8, 28.2, 22.3, 13.8 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09-8.06 (m, 1H, C*H*O), 7.35-7.21 (m, 5H, H_{Ar}), 6.76 (br t, *J* = 10.7 Hz, 1H, N*H*), 4.40 (q, *J* = 7.7 Hz, 1H, C*H*), 1.80-1.74 (m, 2H, CH_2), 1.35-1.18 (m, 4H, CH_2), 0.89 (t, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.5, 142.1, 128.7, 127.5, 126.0, 56.7, 36.9, 28.2, 22.2, 13.8 ppm. HRMS calcd. for $C_{12}H_{17}NO$ 191.1310, found 191.1320.

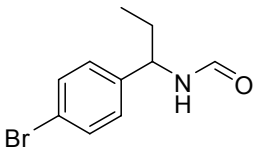
(*R*)-(+)-*N*-[1-(4-Chloro-phenyl)-propyl]-formamide (8a).[16a]



Purification by column chromatography (SiO_2; EtOAc/ *n*-pentane 1:1) afforded compound **8a** in 94% isolated yield (Rf = 0.28) as a colorless oil which slowly solidified, m.p. = 94.0-94.8 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 180 °C; Rt(*S*) = 117.57 min (minor), Rt(*R*) = 118.06 min (major); 97% ee. $[\alpha]_D$ = + 149.5 (c 1.06, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 1H, C*H*O), 7.31-7.25 (m, 2H, H_{Ar}), 7.19-7.15 (m, 2H, H_{Ar}), 6.54 (br d, *J* = 7.2 Hz,

1H, N*H*), 4.86 (q, *J* = 7.6 Hz, 1H, C*H*), 1.84-1.71 (m, 2H, CH_2), 0.92-0.84 (m, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.8, 140.0, 133.1, 128.7, 127.9, 53.3, 28.9, 10.5 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.31-7.25 (m, 2H, H_{Ar}), 7.19-7.15 (m, 2H, H_{Ar}), 7.06 (br t, *J* = 10.0 Hz, 1H, N*H*), 4.31 (q, *J* = 7.6 Hz, 1H, C*H*), 1.84-1.71 (m, 2H, CH_2), 0.92-0.84 (m, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.5, 140.2, 133.5, 129.0, 127.6, 57.7, 30.1, 10.5 ppm. HRMS calcd. for $C_{11}H_{12}ClNO$ 197.0607, found 197.0604. Elem. Anal. calcd. for $C_{11}H_{12}ClNO$: C 60.76%, H 6.12%, N 7.09%, found: C 60.60%, H 6.13, N 6.97%.

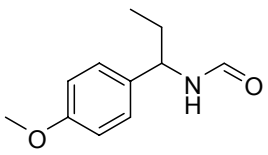
(*R*)-(+)-*N*-[1-(4-Bromo-phenyl)-propyl]-formamide (9a).[17b]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **9a** in 94% isolated yield (Rf = 0.43) as a white solid, m.p. = 100.6-101.7 °C. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 98:2, flow = 1.0 mL/min): Rt(*R*) = 47.21 min (major), Rt(*S*) = 51.64 min (minor); 99% ee. $[\alpha]_D$ = + 133.7 (c 0.92, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.13$ (s, 1H, C*H*O), 7.46-7.41 (m, 2H, H_{Ar}), 7.14-7.09 (m, 2H, H_{Ar}), 6.38 (br s, 1H, N*H*), 4.85 (q, *J* = 7.6 Hz, 1H, C*H*), 1.85-1.71 (m, 2H, CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.6, 140.7, 131.6, 128.2, 121.1, 53.1, 28.9, 10.5 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 11.8 Hz, 1H, C*H*O), 7.46-7.41 (m, 2H, H_{Ar}), 7.14-7.09 (m, 2H, H_{Ar}), 6.72 (br s, 1H, N*H*), 4.30 (q, *J* = 7.6 Hz, 1H, C*H*), 1.85-1.71 (m, 2H, CH_2), 0.91 (t, *J* = 7.3 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.5, 140.8, 131.8, 127.8, 121.4, 57.6, 30.1, 10.5 ppm. MS-EI calcd. for $C_{10}H_{12}BrNO$: 241 (27) $[M]^+$, 212 (100) $[M\text{-}Et]^+$. HRMS calcd. for C_8H_7BrNO [M-Et]: 211.9711, found 211.9708. Elem. Anal. calcd. for $C_{10}H_{12}BrNO_2$: C 49.61%, H 5.00%, N 5.79%, found: C 49.40%, H 5.10%, N 5.62%.

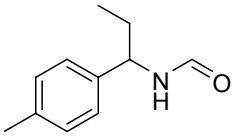
(*R*)-(+)-*N*-[1-(4-Methoxy-phenyl)-propyl]-formamide (10a).[16a]

Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 3:2) afforded compound **10a** in 99% isolated yield (Rf = 0.5) as a colorless oil which slowly solidified, m.p. = 73.0-74.4 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60



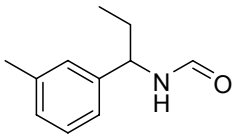
°C, 10 min.-1 °C/min till 180 °C; Rt(*S*) = 118.90 min (minor), Rt(*R*) = 119.23 min (major); 97% ee. $[\alpha]_D$ = + 141.9 (c 1.10, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.12$ (s, 1H, C*H*O), 7.18 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.87-6.82 (m, 2H, H_{Ar}), 6.54 (br s, 1H, N*H*), 4.87 (q, *J* = 7.7 Hz, 1H, C*H*), 3.76 (s, 3H, OCH_3), 1.85-1.71 (m, 2H, CH_2), 0.86 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.4, 158.7, 133.7, 127.6, 113.9, 55.2, 53.0, 28.9, 10.6 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.13 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.87-6.82 (m, 2H, H_{Ar}), 6.54 (br s, 1H, N*H*), 4.23 (q, *J* = 7.6 Hz, 1H, C*H*), 3.77 (s, 3H, OCH_3), 1.85-1.71 (m, 2H, CH_2), 0.90 (t, *J* = 7.3 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.5, 158.8, 133.8, 127.2, 114.0, 57.5, 53.0, 30.2, 10.6 ppm. HRMS calcd. for $C_{11}H_{15}NO_2$ 193.1103, found 193.1102. Elem. Anal. calcd. for $C_{11}H_{15}NO_2$: C 68.37%, H 7.82%, N 7.25%, found: C 68.40%, H 7.90%, N 7.07%.

(*R*)-(+)-*N*-[1-(4-Methyl-phenyl)-propyl]-formamide (11a).[16a]



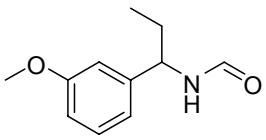
Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **11a** in 90% isolated yield (Rf = 0.43) as a colorless oil which slowly solidified, m.p. = 67.0-68.8 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 180 °C; Rt(*S*) = 110.45 min (minor), Rt(*R*) = 111.13 min (major); 96% ee. $[\alpha]_D$ = + 149.8 (c 1.05, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 3.3:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.16$ (s, 1H, C*H*O), 7.17-7.10 (m, 4H, H_{Ar}), 6.05 (s, br, 1H, N*H*), 4.91 (q, *J* = 7.7 Hz, 1H, C*H*), 2.32 (br s, 3H, CH_3), 1.88-1.74 (m, 2H, CH_2), 0.89 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.4, 138.5, 137.1, 129.3, 126.4, 53.4, 29.0, 21.0, 10.6 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.17-7.10 (m, 4H, H_{Ar}), 6.29 (s, br, 1H, N*H*), 4.31 (q, *J* = 7.5 Hz, 1H, C*H*), 2.33 (br s, 3H, CH_3), 1.88-1.74 (m, 2H, CH_2), 0.92 (t, *J* = 7.3 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.4, 138.7, 137.4, 129.5, 126.0, 57.8, 30.2, 21.0, 10.6 ppm. HRMS calcd. for $C_{11}H_{15}NO$ 177.1154, found 177.1161. Elem. Anal. calcd. for $C_{11}H_{15}NO$: C 74.54%, H 8.53%, N 7.90%, found: C 74.29%, H 8.60%, N 7.75%.

(*R*)-(+)-*N*-[1-(3-Methyl-phenyl)-propyl]-formamide (12a).[16a]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **12a** in 99% isolated yield (Rf = 0.47) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min., 1 °C/min till 180 °C; Rt(*S*) = 99.91 min (minor), Rt(*R*) = 100.77 min (major); 95% ee. $[\alpha]_D$ = + 128.8 (c 0.905, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 3:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H, C*H*O), 7.24-7.17 (m, 1H, H_{Ar}), 7.09-7.01 (m, 3H, H_{Ar}), 6.56 (br s, 1H, N*H*), 4.88 (q, *J* = 7.7 Hz, 1H, C*H*), 2.31 (s, 3H, CH_3), 1.87-1.72 (m, 2H, CH_2), 0.88 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.6, 141.6, 138.0, 128.3, 128.0, 127.3, 123.3, 53.6, 29.0, 21.3, 10.6 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.24-7.17 (m, 1H, H_{Ar}), 7.09-7.01 (m, 3H, H_{Ar}), 6.69 (br s, 1H, N*H*), 4.32-4.26 (m, 1H, C*H*), 2.33 (s, 3H, CH_3), 1.87-1.72 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.6, 141.7, 138.4, 128.6, 128.2, 126.8, 123.0, 58.1, 30.1, 21.3, 10.6 ppm. HRMS calcd. for $C_{11}H_{15}NO$ 177.1154, found 177.1163.

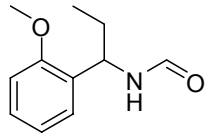
(+)-*N*-[1-(3-Methoxy-phenyl)-propyl]-formamide (13a).[43]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **13a** in 96% isolated yield (Rf = 0.30) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min., 1 °C/min till 180 °C; Rt = 121.75 min (minor), Rt = 122.98 min (major); 95% ee. $[\alpha]_D$ = + 116.1 (c 1.025, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1H, C*H*O), 7.26-7.20 (m, 1H, H_{Ar}), 6.85-6.76 (m, 3H, H_{Ar}), 6.44 (br s, 1H, N*H*), 4.89 (q, *J* = 7.7 Hz, 1H, C*H*), 3.76 (s, 3H, OCH_3), 1.84-1.73 (m, 2H, CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.6, 159.6, 143.2, 129.6, 118.7, 112.4, 112.4, 55.1, 53.6, 29.0, 10.6 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.26-7.20 (m, 1H, H_{Ar}), 6.85-6.76 (m, 3H, H_{Ar}), 6.44 (br s, 1H, N*H*), 4.29 (q, *J* = 7.6 Hz, 1H, C*H*), 3.77 (s, 3H, OCH_3), 1.84-1.73 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-

NMR (100 MHz, $CDCl_3$) δ = 164.6, 159.8, 143.4, 129.8, 118.3, 112.6, 112.0, 58.1, 55.1, 30.1, 10.6 ppm. HRMS calcd. for $C_{11}H_{15}NO_2$ 193.1103, found 193.1102.

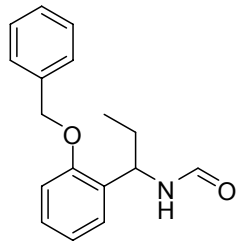
(–)-*N*-[1-(2-Methoxy-phenyl)-propyl]-formamide (14a).



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **14a** in 99% isolated yield (Rf = 0.31) as a white solid. Mp = 122.4-124.2 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 111.15 min (major), Rt = 112.39 min (minor); 47% ee. $[\alpha]_D$ = - 47.8 (c 0.98, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 2.5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.16 (s, 1H, C*H*O), 7.26-7.21 (m, 1H, H_{Ar}), 7.71-7.11 (m, 1H, H_{Ar}), 6.93-6.87 (m, 2H, H_{Ar}), 6.73 (br s, 1H, N*H*), 5.10 (q, *J* = 8.1 Hz, 1H, C*H*), 3.84 (s, 3H, OCH_3), 1.87-1.78 (m, 2H, CH_2), 0.85 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.3, 156.9, 129.0, 128.8, 128.4, 120.7, 110.9, 55.2, 52.0, 28.2, 11.0 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 12.0 Hz, 1H, C*H*O), 7.26-7.21 (m, 1H, H_{Ar}), 7.71-7.11 (m, 1H, H_{Ar}), 6.93-6.87 (m, 2H, H_{Ar}), 6.54 (br s, 1H, N*H*), 4.45 (q, *J* = 8.2 Hz, 1H, C*H*), 3.82 (s, 3H, OCH_3), 1.87-1.78 (m, 2H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.1, 156.4, 129.3, 128.7, 127.5, 120.7, 110.8, 55.7, 52.0, 28.6, 11.0 ppm. HRMS calcd. for $C_{11}H_{15}NO_2$ 193.1103, found 193.1102. Elem. Anal. calcd. for $C_{11}H_{15}NO_2$: C 68.37%, H 7.82%, N 7.25%, found: C 68.45%, H 7.89%, N 7.04%.

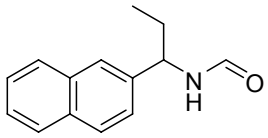
(–)-*N*-[1-(2-Benzyloxy-phenyl)-propyl]-formamide (15a).

Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **15a** in 99% isolated yield (Rf = 0.44) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 122.34 min (major), Rt = 143.18 min (minor); 45% ee. $[\alpha]_D$ = - 11.7 (c 1.07, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 2.5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.10 (br s, 1H, C*H*O), 7.44-7.33 (m, 5H, H_{Ar}), 7.27-7.17



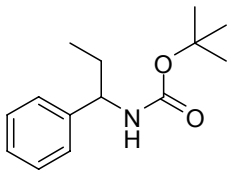
(m, 2H, H_{Ar}), 6.97-6.91 (m, 2H, H_{Ar}), 6.73 (br d, *J* = 9.3 Hz, 1H, N*H*), 5.11 (s, 2H, CH_2), 5.16 (q, *J* = 8.1 Hz, 1H, C*H*), 1.92-1.80 (m, 2H, CH_2), 0.86 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.4, 156.0, 136.5, 129.7, 129.1, 128.6, 128.4, 128.0, 127.3, 127.2, 120.9, 112.1, 70.1, 52.0, 28.2, 11.0 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 12.0 Hz, 1H, C*H*O), 7.44-7.33 (m, 5H, H_{Ar}), 7.27-7.17 (m, 2H, H_{Ar}), 6.97-6.91 (m, 2H, H_{Ar}), 6.78 (br m, 1H, N*H*), 5.09 (s, 2H, CH_2), 4.61-4.55 (m, 1H, C*H*), 1.92-1.80 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.5, 155.5, 136.3, 129.7, 129.1, 128.6, 128.4, 128.0, 127.3, 127.2, 121.0, 112.0, 70.1, 54.7, 28.5, 10.9 ppm. HRMS calcd. for $C_{17}H_{19}NO_2$ 269.1416, found 269.1423.

(+)-*N*-(1-Naphthyl-propyl)-formamide (16a).



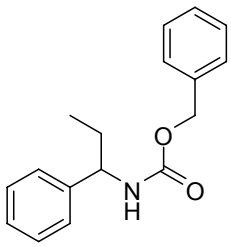
Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **16a** in 94% isolated yield (Rf = 0.29) as a colorless oil which slowly solidified, m.p. = 85.2-86.7 °C. HPLC on Chiralpak AD column (heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): t_R 15.88 min (major), t_R 20.08 min (minor). 80% ee. $[\alpha]_D$ = + 138.4 (c 1.00, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 3:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.19 (s, 1H, C*H*O), 7.83-7.78 (m, 3H, H_{Ar}), 7.72 (s, 1H, H_{Ar}), 7.50-7.44 (m, 2H, H_{Ar}), 7.38 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.28 (br d, *J* = 6.5 Hz, 1H, N*H*), 5.11 (q, *J* = 7.7 Hz, 1H, C*H*), 1.97-1.84 (m, 2H, CH_2), 0.97-0.90 (m, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.6, 138.8, 133.2, 132.7, 128.5, 127.8, 127.5, 126.2, 125.8, 125.3, 124.6, 53.7, 28.9, 10.7 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.83-7.78 (m, 3H, H_{Ar}), 7.67 (s, 1H, H_{Ar}), 7.50-7.44 (m, 2H, H_{Ar}), 7.32 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.65 (br t, *J* = 11.2 Hz, 1H, N*H*), 4.49 (q, *J* = 7.6 Hz, 1H, C*H*), 1.97-1.84 (m, 2H, CH_2), 0.97-0.90 (m, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.7, 139.0, 133.1, 132.7, 128.8, 127.8, 127.6, 126.4, 126.1, 125.0, 124.0, 58.2, 30.0, 10.7 ppm. HRMS calcd. for $C_{14}H_{15}NO$ 213.1154, found 213.1155. Elem. Anal. calcd. for $C_{14}H_{15}NO$: C 78.84%, H 7.09%, N 6.57%, found: C 78.56%, H 7.12%, N 6.51%.

(+)- (1-Phenyl-propyl)-carbamic acid *tert*-butyl ester (6a).[44]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 2:98) afforded compound **6a** in 57% isolated yield (Rf = 0.38) as a colorless oil which slowly solidified. HPLC on Chiralpak AD column, 4.6 × 250 mm, 10 μm, (heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 11.12 min (major), Rt = 12.28 min (minor); 84% ee. $[\alpha]_D$ = + 44.0 (c 0.91, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.34-7.30 (m, 2H, H_{Ar}), 7.26-7.22 (m, 3H, H_{Ar}), 4.84 (br s, 1H, N*H*), 4.53 (br s, 1H, C*H*), 1.78-1.75 (m, 2H, CH_2), 1.42 (s, 9H, C(CH_3)$_3$), 0.89 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 155.3, 142.8, 128.4, 127.0, 126.3, 79.3, 56.31, 29.8, 28.3, 10.6 ppm. HRMS calcd. for $C_{14}H_{21}NO_2$ 235.1572, found 235.1577. Elem. Anal. calcd. for $C_{14}H_{21}NO_2$: C 71.46%, H 8.99%, N 5.95%, found: C 71.32%, H 9.02%, N 5.85%.

(+)- (1-Phenyl-propyl)-carbamic acid benzyl ester (7a).[45]

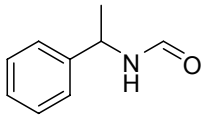


Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:9) afforded compound **7a** in 12% isolated yield (Rf = 0.64) as a colorless oil. HPLC on Chiralpak AD column, 4.6 × 250 mm, 10 μm, (heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 13.27 min (major), Rt = 15.64 min (minor); 49% ee. $[\alpha]_D$ = + 16.4 (c 0.78, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.35-7.26 (m, 10H), 5.13-5.03 (m, 3H), 4.62-4.62 (br m, 1H), 1.83-1.77 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 155.7, 142.3, 136.4, 128.5, 128.5, 128.1, 127.3, 126.4, 66.7, 56.9, 29.6, 10.6 ppm. HRMS calcd. for $C_{17}H_{19}NO_2$ 269.1416, found 269.1407.

Procedure for the copper/phosphoramidite catalyzed addition of trimethylaluminum to 1. $Cu(acac)_2$ (6.6 mg, 0.025 mmol) and ligand **(*S*,*R*,*R*)-L1** (27.0 mg, 0.050 mmol) were dissolved in anhydrous *i*Pr_2O (10 mL) and the mixture stirred for 45 min at room temperature. The mixture was cooled to -30 °C and substrate **5** (0.50 mmol) was added. A 1M solution of Me_3Al in heptane (1.25 mmol) was added dropwise and the reaction mixture was stirred for 16 h at -30 °C, then quenched with 1M aq. HCl (10 mL) and extracted with EtOAc (3

x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography.

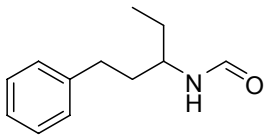
(*S*)-(–)-*N*-(1-Phenyl-ethyl)-formamide (5d).[46]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 3:2) afforded compound **5d** in 70% isolated yield (Rf = 0.37) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 89.32 min (major), Rt = 91.05 min (minor); 85% ee. $[\alpha]_D$ = - 102.3 (c 1.05, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09 (br s, 1H, C*H*O), 7.37-7.23 (m, 5H, H_{Ar}), 6.32 (br s, 1H, N*H*), 5.20-5.13 (m, 1H, C*H*), 1.48 (d, *J* = 6.9 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.3, 142.6, 128.6, 127.4, 126.0, 47.5, 21.7 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.12 (br s, 1H, C*H*O), 7.37-7.23 (m, 5H, H_{Ar}), 6.44 (br s, 1H, N*H*), 4.69-4.61 (m, 1H, C*H*), 1.53 (d, *J* = 6.9 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.2, 142.6, 128.8, 127.6, 125.7, 51.6, 23.5 ppm. HRMS calcd. for $C_9H_{11}NO$ 149.0841, found 149.0847.

General procedure for the copper/phosphoramidite catalyzed addition of diethylzinc to aliphatic α-amido sulfones. $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.010 mmol) and ligand (***S***,***R***,***R***)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous Et_2O (10 mL) and the mixture stirred for 45 min at r.t. The mixture was cooled to -20 °C and the substrate (0.50 mmol) was added. A 1M solution of a Et_2Zn in hexane (1.25 mmol) was added dropwise and the reaction mixture was stirred for 16 h at -20 °C, then quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography.

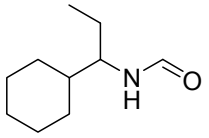
(+)-*N*-(1-Ethyl-3-phenyl-propyl)-formamide (17a).



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 6:4) afforded compound **17a** in 81% isolated yield (Rf = 0.44) as a colorless oil which slowly solidified, m.p. = 46.8-48.1 °C. Chiral GC - CP

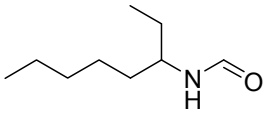
Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 111.79 min (minor), Rt = 112.76 min (major); 66% ee. $[\alpha]_D$ = + 16.5 (c 0.935, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 2.2:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 1H, C*H*O), 7.30-7.25 (m, 2H, H_{Ar}), 7.21-7.14 (m, 3H, H_{Ar}), 5.83 (d, *J* = 7.9 Hz, 1H, N*H*), 4.03-3.94 (m, 1H, C*H*), 2.79-2.54 (m, 2H, CH_2), 1.91-1.79 (m, 1H, CH_2), 1.76-1.54 (m, 2H, CH_2), 1.40-1.38 (m, 1H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 161.0, 141.6, 128.3, 128.2, 125.8, 49.3, 36.4, 32.2, 27.8, 10.0 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.30-7.25 (m, 2H, H_{Ar}), 7.21-7.14 (m, 3H, H_{Ar}), 6.22 (t, *J* = 10.9 Hz, 1H, N*H*), 3.20-3.11 (m, 1H, C*H*), 2.79-2.54 (m, 2H, CH_2), 1.91-1.79 (m, 1H, CH_2), 1.76-1.54 (m, 2H, CH_2), 1.40-1.38 (m, 1H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.5, 140.8, 128.4, 128.3, 126.0, 53.6, 36.8, 31.9, 29.0, 10.2 ppm. HRMS calcd. for $C_{12}H_{17}NO$ 191.1310, found 191.1319. Elem. Anal. calcd. for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32, found: C 74.88, H 8.93, N 7.20.

(+)-*N*-(1-Cyclohexyl-propyl)-formamide (18a).



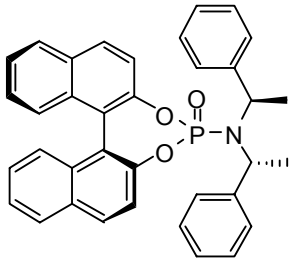
Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **18a** in 99% isolated yield (Rf = 0.38) as a colorless oil which slowly solidified, m.p. = 58.0-58.6 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 91.98 min (minor), Rt = 93.23 min (major); 45% ee. $[\alpha]_D$ = + 13.5 (c 0.90, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 1.6:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 1H, C*H*O), 5.64 (br s, 1H, N*H*), 3.80-3.72 (m, 1H, C*H*), 1.75-1.54 (m, 6H), 1.40-0.93 (m, 7H), 1.01-0.85 (m, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 161.1, 53.8, 41.3, 29.6, 28.2, 26.3, 26.1, 24.6, 10.4 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 11.9 Hz, 1H, C*H*O), 6.01 (br s, 1H, N*H*), 2.96-2.88 (m, 1H, C*H*), 1.75-1.54 (m, 6H), 1.40-0.93 (m, 7H), 1.01-0.85 (m, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.7, 59.5, 42.0, 29.9, 27.8, 26.2, 26.0, 26.0, 25.4, 10.6 ppm. HRMS calcd. for $C_{10}H_{19}NO$ 169.1467, found 169.1471. Elem. Anal. calcd. for $C_{10}H_{19}NO$: C 70.96%, H 11.31%, N 8.28%, found: C 71.04%, H 11.27%, N 8.05%.

(+)-*N*-(1-Ethyl-*n*-hexyl)-formamide (19a).[47]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **19a** in 99% isolated yield (Rf = 0.44) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 72.77 min (minor), Rt = 74.77 min (major); 70% ee. $[\alpha]_D$ = + 7.4 (c 0.96, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 2:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.16 (s, 1H, C*H*O), 5.62 (br s, 1H, N*H*), 3.91-3.84 (m, 1H, C*H*), 1.58-1.19 (m, 10H), 0.91-0.82 (m, 6H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.9, 49.5, 34.5, 31.6, 27.8, 25.4, 22.5, 13.9, 10.1 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 11.9 Hz, 1H, C*H*O), 5.89 (br s, 1H, N*H*), 3.18-3.10 (m, 1H, C*H*), 1.58-1.19 (m, 10H), 0.91-0.82 (m, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.3, 54.5, 35.5, 31.4, 28.9, 25.5, 22.5, 13.9, 10.3 ppm. HRMS calcd. for $C_9H_{19}NO$ 157.1467, found 157.1468.

***O*,*O*'-(*S*)-(1,1'-Dinaphthyl-2,2'diyl)-*N*,*N*-di-(*R*,*R*)-1-phenylethylphosphoricamide (*S*,*R*,*R*)-L2.**

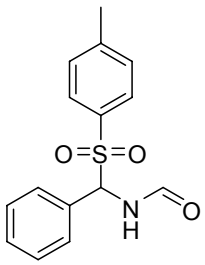


Phosphoramidite (*S*,*R*,*R*)-**L1** (770 mg, 1.43 mmol) was dissolved in 25 mL of THF. The solution was cooled down to 0 °C and 5 mL of a solution of H_2O_2 30% in water were added. Formation of a white precipitate was observed. The reaction mixture was warmed up to r.t. and stirred overnight. The reaction mixture was treated with a saturated aqueous solution of Na_2SO_3 (15 mL) and extracted (2 × 10 mL) with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 788 mg (1.42 mmol) of (*S*,*R*,*R*)-**L2** as a white solid, m.p = 184.8-185.0 °C. Yield 99%. $[\alpha]_D$ = + 384.1 (c 1.01, $CHCl_3$).^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.03-8.00 (m, 1H), 7.95-7.90 (m,3H), 7.53-7.44 (m, 4H), 7.39-7.24 (m, 4H), 7.12 (br s, 10H), 4.65-4.52 (m, 2H), 1.83 (d, *J* = 7.1 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.3, 149.0, 148.9, 146.6, 146.6, 141.2, 141.2, 132.5, 132.3, 131.7, 131.1, 131.0, 130.5, 128.4, 128.1, 128.0, 127.7, 127.4, 127.0, 126.9, 126.4, 126.3, 125.4, 121.7, 121.7, 120.4, 120.3, 54.7, 54.6, 20.3 ppm. ^{31}P-NMR (95 MHz, $CDCl_3$) δ = 12.34

ppm. HRMS calcd. for $C_{36}H_{30}NO_3P$ 555.1963, found 555.1932. Elem. Anal. calcd. for $C_{36}H_{30}NO_3P$: C 77.82%, H 5.44%, N 2.52%, found: C 77.50%, H 5.71%, N 2.55%.

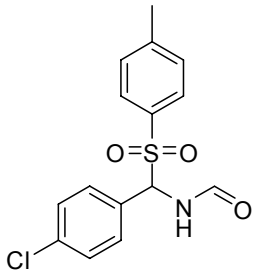
Characterization of the starting materials. All the starting materials were synthesized according to literature procedures.[21]

***N*-[Phenyl(toluene-4-sulfonyl)methyl]formamide (5).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.75 (d, *J* = 10.8 Hz, 1H, N*H*), 7.95 (s, 1H), 7.71- 7.69 (m, 2H), 7.56-7.52 (m, 2H), 7.47-7.34 (m, 5H), 6.37 (d, *J* = 10.4 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 161.0, 145.5, 134.1, 131.0, 130.3, 130.1, 129.8, 129.0, 126.2, 70.9, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.40 (t, *J* = 10.6 Hz, 1H), 7.88 (d, *J* = 10.4 Hz, 1H), 7.71- 7.69 (m, 2H), 7.56-7.52 (m, 2H), 7.47-7.34 (m, 5H), 6.25 (d, *J* = 10.8 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.7, 145.5, 134.1, 131.0, 130.4, 130.1, 130.0, 128.8, 126.2, 76.6, 21.8 ppm. M.p. = 144.9-145.2 °C. MS-EI for $C_{15}H_{15}NO_3S$: 104 (100), 133 (63.3) [M-SO_2Tol], 156 (42.5) [SO_2Tol]; MS-CI: 307 [M+NH_4^+], 290 [M+H^+]. Elem. Anal. calcd. for $C_{15}H_{15}NO_3S$: C 62.26%, H 5.23%, N 4.84%, found: C 62.25%, H 5.22%, N 4.88%.

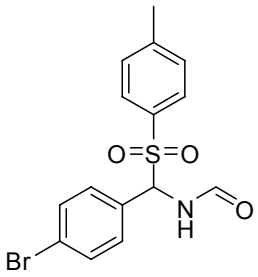
***N*-[4-Chloro-phenyl(toluene-4-sulfonyl)methyl]formamide (8).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9. 76 (d, *J* = 10.0 Hz, 1H), 7.93 (s, 1H), 7.72-7.70 (m, 2H), 7.62-7.51 (m, 2H), 7.57-7.46 (m, 2H), 7.44-7.39 (m, 2H), 6.45 (d, *J* = 10.4 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 160.9, 145.6, 135.1, 133.9, 131.9, 130.3, 130.0, 129.9, 129.0, 70.1, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.44 (t, *J* = 10.6 Hz, 1H), 7.85 (d, *J* = 10.4 Hz, 1H), 7.72-7.70 (m, 2H), 7.62-7.51 (m,

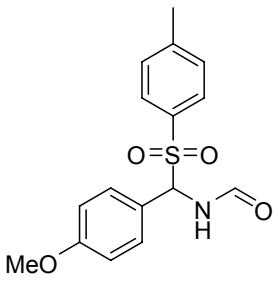
2H), 7.57-7.46 (m, 2H), 7.44-7.39 (m, 2H), 6.31 (d, *J* = 10.4 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.4, 145.9, 135.0, 133.0, 131.7, 130.5, 130.1, 129.9, 129.0, 75.8, 21.8 ppm. M.p. = 122.6-124.9 °C. MS-EI for $C_{15}H_{14}ClNO_3S$: 92 (94.5), 138 (100), 156 (19.7) [SO_2Tol],167 (15.7) [M-SO_2Tol]; MS-CI: 324 [M+H^+], 341[M+NH_4^+]. Elem. Anal. calcd. for $C_{15}H_{14}ClNO_3S$: C 55.64%, H 4.36%, N 4.33%, found: C 55.79%, H 4.39%, N 4.34%.

***N*-[4-Bromo-phenyl(toluene-4-sulfonyl)methyl]formamide (9).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.76 (d, *J* = 10.5 Hz, 1H), 7.94-7.40 (m, 9H), 6.42 (d, *J* = 10.6 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 161.0, 145.7, 133.8, 132.2, 132.0, 130.3, 129.9, 123.8, 70.2, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.43 (t, *J* = 10.5 Hz, 1H), 7.94-7.40 (m, 9H), 6.28 (d, *J* = 10.7 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.5, 145.9, 133.0, 133.0, 132.0, 130.5, 124.9, 123.8, 75.9, 21.8 ppm. M.p. = 124.5-125.6 °C. Elem. Anal. calcd. for $C_{15}H_{14}BrNO_3S$: C 48.92%, H 3.83%, N 3.80%, found: C 49.01%, H 3.88%, N 3.84%.

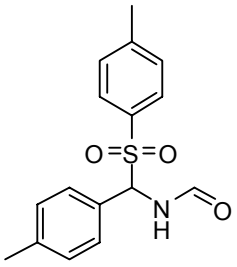
***N*-[4-Methoxy-phenyl(toluene-4-sulfonyl)methyl]formamide (10).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.70 (d, *J* = 10.6 Hz, 1H), 7.92 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.49-7.44 (m, 2H), 7.41-7.37 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.30 (d, *J* = 10.6 Hz, 1H), 3.75 (s, 3H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 160.8, 160.7, 145.4, 134.2, 131.5, 130.3, 129.8, 122.6, 114.4, 70.4, 55.9, 21.82 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.34 (t, *J* = 9.3 Hz, 1H), 7.85 (d, *J* = 10.4 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.49-7.44 (m, 2H), 7.41-7.37 (m, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.17 (d, *J* = 10.7 Hz, 1H), 3.73 (s, 3H), 2.27 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.6, 160.7, 145.5, 133.4,

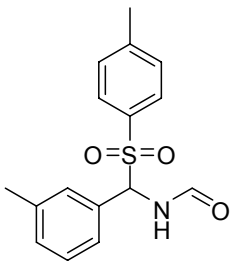
131.3, 130.4, 129.9, 122.8, 114.3, 76.1, 55.9, 21.8 ppm. M.p. = 127.6-128.9 °C. MS-EI for $C_{16}H_{17}NO_4S$: 92 (100), 134 (89.2), 163 (54.8) [M-SO_2Tol], 156 (26.7) [SO_2Tol]; MS-CI: 320 [M+H^+]. Elem. Anal. calcd. for $C_{16}H_{17}NO_4S$: C 60.17%, H 5.37%, N 4.39%, found: C 60.18%, H 5.35%, N 4.37%.

***N*-[4-Methyl-phenyl(toluene-4-sulfonyl)methyl]formamide (11).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.70 (d, *J* = 10.0 Hz, 1H), 7.92 (s, 1H), 7.68 (d, br, *J* = 6.4 Hz, 2H), 7.41-7.39 (m, 4H), 7.20 (d, *J* = 6.8 Hz, 2H), 6.30 (d, *J* = 10.8 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 160.9, 145.4, 139.7, 134.2, 130.3, 130.0, 129.8, 129.5, 127.9, 70.7, 21.8, 21.5 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.33 (t, *J* = 9.8 Hz, 1H), 7.86 (d, *J* = 10.8 Hz, 1H), 7.55 (d, br, *J* = 6.4 Hz, 2H), 7.41-7.39 (m, 2H), 7.33 (d, br, *J* = 6.4 Hz, 2H), 7.14 (d, *J* = 6.8 Hz, 2H), 6.18 (d, *J* = 10.8 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.6, 145.6, 139.6, 133.4, 130.4, 129.9, 129.9, 129.4, 128.0, 76.4, 21.8, 21.5 ppm. M.p. = 143.3-144.0 °C. MS-EI for $C_{16}H_{17}NO_3S$: 91 (100), 118 (91.6), 147 (42.5) [M-SO_2Tol], 156 (27.9) [SO_2Tol]; MS-CI: 321 [M+NH_4^+], 304 [M+H^+]. Elem. Anal. calcd. for $C_{16}H_{17}NO_3S$: C 63.34%, H 5.65%, N 4.62%, found: C 62.98%, H 5.66%, N 4.66%.

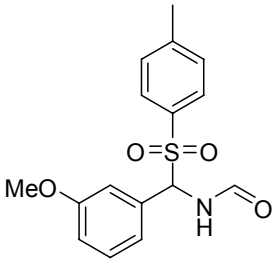
***N*-[3-Methyl-phenyl(toluene-4-sulfonyl)methyl]formamide (12).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.77 (d, *J* = 10.6 Hz, 1H), 7.92 (s, 1H), 7.69 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 2H), 7.48-7.09 (m, 6H), 6.28 (d, *J* = 10.5 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) = 160.9, 145.5, 138.2, 134.1, 130.8, 130.6, 130.3, 129.8, 128.9, 127.3, 126,2, 70.9, 21.8, 21.6 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.34$ (t, *J* = 10.6 Hz, 1H), 7.85 (d, *J* = 10.4 Hz, 1H), 7.56 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 2H), 7.48-7.09 (m, 6H), 6.20 (d, *J* = 10.6 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) = 165.5, 145.6, 138.0, 133.3, 130.9, 130.7, 130.4, 129.9, 128.7,

127.0, 126.2, 76.5, 21.8, 21.6 ppm. M.p. = 114.2-115.1 °C. Elem. Anal. calcd. for $C_{16}H_{17}NO_3S$: C 63.34%, H 5.65%, N 4.62%, found: C 63.23%, H 5.63%, N 4.65%.

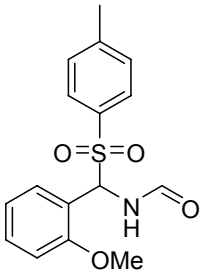
***N*-[3-Methoxy-phenyl(toluene-4-sulfonyl)methyl]formamide (13).**



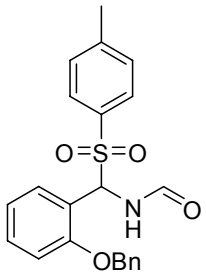
The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.72 (d, *J* = 10.0 Hz, 1H), 7.95 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.12-6.92 (m, 3H), 6.35 (d, *J* = 10.8 Hz, 1H), 3.72 (s, 3H), 2.39 (s, 3H) ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.38$ (t, *J* = 10.6 Hz, 1H), 7.88 (d, *J* = 10.4 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.12-6.92 (m, 3H), 6.21 (d, *J* = 10.8 Hz, 1H), 3.67 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C-NMR major rotamer + minor rotamer (50 MHz, DMSO-*d*^{6}) δ = 165.5, 160.9, 159.7, 159.6, 145.6, 145.5, 134.1, 133.3, 132.4, 130.4, 130.3, 130.0, 129.8, 122.4, 115.8, 115.7, 115.2, 76.6, 70.9, 55.9, 21.8 ppm. M.p. = 116.3-116.9 °C. Elem. Anal. calcd. for $C_{16}H_{17}NO_4S$: C 60.17%, H 5.37%, N 4.39%, found: C 60.08%, H 5.35%, N 4.17%.

***N*-[2-Methoxy-phenyl(toluene-4-sulfonyl)methyl]formamide (14).**

The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 10:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.72 (d, *J* = 9.9 Hz, 1H), 8.06 (br s, 1H), 7.58-7.52 (m, 3H), 7.46-7.36 (m, 3H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 10.7 Hz, 1H), 3.57 (s, 3H), 2.39 (s, 3H) ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.30$ (t, *J* = 10.6 Hz, 1H), 8.14 (d, *J* = 10.4 Hz, 1H), 7.68-7.66 (m, 1H), 7.58-7.52 (m, 2H), 7.46-7.36 (m, 3H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.22 (d, *J* = 10.8 Hz, 1H), 3.44 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C-NMR major rotamer + minor rotamer (50 MHz, DMSO-*d*^{6}) δ = 165.4, 160.4, 156.8, 156.3, 144.7, 144.6, 133.7, 132.9, 131.0, 129.4, 129.2, 129.1, 128.8, 120.3, 118.9, 118.5, 111.0, 110.8, 63.8, 55.5, 55.3, 21.0 ppm. M.p. = 134.6-135.5 °C. Elem. Anal. calcd. for $C_{16}H_{17}NO_4S$: C 60.17%, H 5.37%, N 4.39%, found: C 60.11%, H 5.36%, N 4.21%.

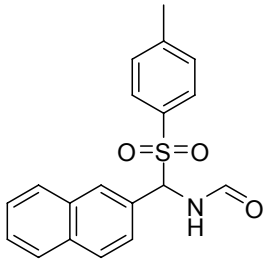


***N*-[2-Benzyloxy-phenyl(toluene-4-sulfonyl)methyl]formamide (15).**



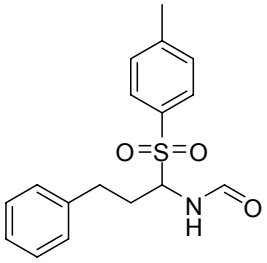
The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 7:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.77 (d, *J* = 10.7 Hz, 1H), 8.00 (br s, 1H), 7.60 (br d, *J* = 7.9 Hz, 1H), 7.54-7.52 (m, 2H), 7.47-7.27 (m, 7H), 7.06 (t, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 10.7 Hz, 1H), 5.10 (d, *J* = 12.1 Hz, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 2.36 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 161.1, 156.9, 145.5, 137.5, 134.6, 131.7, 130.3, 130.0, 129.4, 129.1, 128.6, 127.9, 121.4, 119.8, 113.2, 70.4, 64.2, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.34$ (t, *J* = 10.7 Hz, 1H), 8.00 (br s, 1H), 7.68 (br d, *J* = 7.8 Hz, 1H), 7.54-7.52 (m, 2H), 7.47-7.27 (m, 7H), 7.00 (t, *J* = 7.7 Hz, 2H), 6.25 (d, *J* = 10.8 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.83 (d, *J* = 12.4 Hz, 1H), 2.36 (s, 3H) ppm. M.p. = 131.6-132.0 °C. Elem. Anal. calcd. for $C_{22}H_{21}NO_4S$: C 66.82%, H 5.35%, N 3.54%, found: C 66.78%, H 5.31%, N 3.60%.

***N*-[2-Naphtyl(toluene-4-sulfonyl)methyl]formamide (16).**



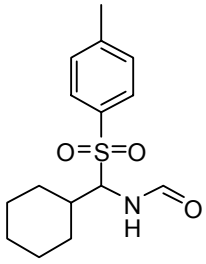
The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.92 (d, *J* = 10.6 Hz, 1H), 8.10-7.83 (m, 5H), 7.76-7.67 (m, 2H), 7.62-6.97 (m, 5H), 6.56 (d, *J* = 10.5 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 161.0, 145.6, 134.1, 133.8, 132.9, 130.4, 129.8, 128.7, 128.5, 128.5, 128.3, 127.8, 127.4, 127.1, 126.2, 125.2, 71.0, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.54$ (d, *J* = 10.6 Hz, 1H), 8.10-7.83 (m, 5H), 7.76-7.67 (m, 2H), 7.62-6.97 (m, 5H), 6.44 (d, *J* = 10.7 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.6, 145.7, 133.7, 133.3, 132.8, 130.5, 130.0, 128.8, 128.6, 128.5, 128.3, 127.8, 127.4, 127.0, 126.2, 125.2, 76.7, 21.5 ppm. M.p. = 135.3-135.7 °C. Elem. Anal. calcd. for $C_{19}H_{17}NO_3S$: C 67.24%, H 5.05%, N 4.13%, found: C 66.82%, H 5.08%, N 4.05%.

***N*-[(3-Phenyl)propyl(toluene-4-sulfonyl)methyl]formamide (17).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.02 (d, *J* = 10.0 Hz, 1H), 7.98 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.28-7.24 (m, 2H), 7.19-7.12 (m, 3H), 5.06 (dt, J_1 = 10.4 Hz, J_2 = 2.6 Hz, 1H), 2.72-2.63 (m, 1H), 2.56-2.51 (m, 1H), 2.37 (s, 3H), 2.31-2.21 (m, 1H), 1.95-1.80 (m, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-*d*^{6}) δ = 161.6, 145.4, 140.8, 134.0, 130.4, 129.8, 129.1, 129.0, 126.9, 67.5, 31.3, 29.0, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 8.64 (t, *J* = 10.2 Hz, 1H), 7.78 (d, *J* = 10.8 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.28-7.24 (m, 2H), 7.19-7.12 (m, 3H), 4.86 (dt, J_1 = 10.4 Hz, J_2 = 2.8 Hz, 1H), 2.72-2.63 (m, 1H), 2.56-2.51 (m, 1H), 2.39 (s, 3H), 2.31-2.21 (m, 1H), 1.95-1.80 (m, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-*d*^{6}) δ = 165.9, 145.7, 140.9, 133.0, 130.7, 130.0, 129.2, 128.9, 126.9, 73.2, 31.5, 29.0, 21.8 ppm. M.p. = 137.1-143.5 °C. Elem. Anal. calcd. for $C_{17}H_{19}NO_3S$: C 64.33%, H 6.03%, N 4.41%, found: C 64.60%, H 6.05%, N 4.37%.

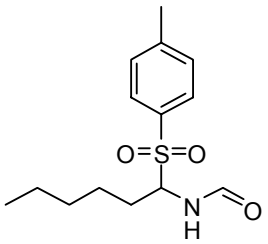
***N*-[Cyclohexyl(toluene-4-sulfonyl)methyl]formamide (18).**



The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 7:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.02 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.36-7.29 (m, 2H), 6.77 (d, *J* = 10.8 Hz, 1H), 5.13 (dd, J_1 = 11.0 Hz, J_2 = 3.7 Hz, 1H), 244-2.40 (m, 4H), 2.13-2.09 (m, 1H), 1.76-1.65 (m, 4H), 1.39-1.06 (m, 5H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.30, 145.1, 134.3, 129.8, 128.7, 70.7, 36.5, 30.5, 27.2, 25.9, 25.6, 25.5, 21.6 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 11.2 Hz, 1H), 7.36-7.29 (m, 2H), 6.55 (t, *J* = 11.1 Hz, 1H), 4.15 (dd, J_1 = 11.3 Hz, J_2 = 3.5 Hz, 1H), 244-2.40 (m, 4H), 2.13-2.09 (m, 1H), 1.76-1.65 (m, 4H), 1.39-1.06 (m, 5H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 163.8, 145.7, 133.2, 130.2, 129.1, 70.7, 36.2, 30.6, 27.0, 25.9, 25.6, 25.5, 21.6 ppm. M.p. = 105.4-105.5 °C. Elem. Anal.

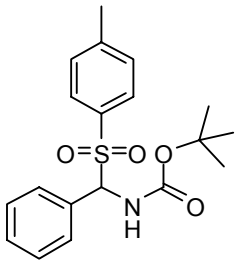
calcd. for $C_{15}H_{21}NO_3S$: C 60.99%, H 7.17%, N 4.74%, found: C 61.36%, H 7.22%, N 4.55%.

***N*-[Hexyl(toluene-4-sulfonyl)methyl]formamide (19).**



The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 7:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.69-7.65 (m, 2H), 7.37 (d, J = 10.4 Hz, 1H), 7.29-7.23 (m, 2H), 5.17 (dt, J_1 = 10.8 Hz, J_2 = 2.9 Hz, 1H), 2.32 (s, 3H), 2.09-2.03 (m, 1H), 1.74-1.60 (m, 1H), 1.36-1.17 (m, 6H), 0.78-0.75 (m, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.8, 145.0, 132.9, 129.5, 128.9, 67.2, 30.7, 26.1, 24.5, 21.9, 21.3, 13.5 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, J = 11.2 Hz, 1H), 7.69-7.65 (m, 2H), 7.29-7.23 (m, 2H), 7.10 (t, J = 10.6 Hz, 1H), 4.40 (dt, J_1 = 10.6 Hz, J_2 = 2.9 Hz, 1H), 2.32 (s, 3H), 2.09-2.03 (m, 1H), 1.74-1.60 (m, 1H), 1.36-1.17 (m, 6H), 0.78-0.75 (m, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.7, 145.5, 131.5, 129.9, 129.2, 73.2, 30.6, 26.5, 24.7, 21.9, 21.3, 13.5 ppm. M.p. = 73.5-74.6 °C. Elem. Anal. calcd. for $C_{14}H_{21}NO_3S$: C 59.34%, H 7.47%, N 4.94%, found: C 59.58%, H 7.52%, N 4.91%.

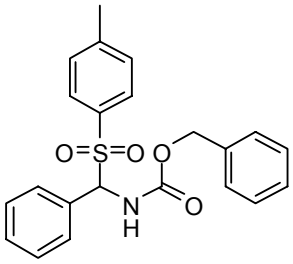
***N*-[Phenyl(toluene-4-sulfonyl)methyl]tert-butoxycarbamate (6).**



^{1}H-NMR (400 MHz, DMSO-d^6) δ = 8.64 (d, J = 10.8 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.62-7.59 (m, 2H), 7.41-7.36 (m, 5H), 5.93 (d, J = 10.8 Hz, 1H), 2.35 (s, 3H), 1.16 (s, 9H) ppm. ^{13}C-NMR (50 MHz, DMSO-d^6) δ = 159.6, 149.9, 139.4, 135.8, 135.3, 134.9, 134.7, 133.5, 84.7, 79.8, 33.2, 26.5 ppm. M.p. = 163.3-164.5 °C. Elem. Anal. calcd. for $C_{19}H_{23}NO_4S$: C 63.13%, H 6.41%, N 3.88%, found: C 63.10%, H 6.42%, N 3.74%.

***N*-[Phenyl(toluene-4-sulfonyl)methyl]benzyloxycarbamate (7).**

^{1}H-NMR (400 MHz, DMSO-d^6) δ = 9.14 (d, J = 10.8 Hz, 1H), 7.67-7.58 (m, 4H), 7.40-7.43 (m, 7H), 7.20-7.09 (m, 3H), 6.01 (d, J = 10.7 Hz, 1H), 4.90 (d, J = 12.6 Hz, 1H), 4.83 (d, J = 10.6 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-d^6) δ = 155.9, 145.3, 137.5, 137.0, 134.4, 131.1, 130.3, 130.2, 130.0, 129.8, 129.0, 128.8, 128.6, 128.3, 125.0, 75.5, 66.7, 21.9 ppm. M.p. = 163.3-164.5 °C.



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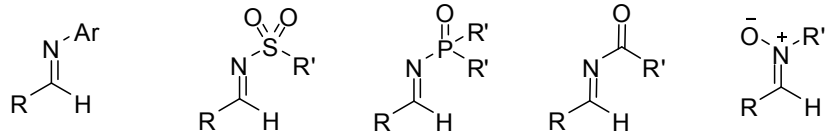
Chapter 5

Catalytic enantioselective addition of organozinc reagents to *N*–acyloxyiminium ions

The first catalytic enantioselective addition of organozinc reagents to in situ generated N-acyloxyiminium ions, using copper/phosphoramidite catalysts, is described.

5.1 Introduction

The asymmetric nucleophilic addition to the C=N double bond is one of the most versatile synthetic tools for the formation of optically active α-chiral amines. In the previous chapter a survey of the most efficient catalytic enantioselective methods for the addition of organozinc reagents to imine derivatives was presented. Several highly efficient enantioselective catalyzed procedures have been developed for the addition to imines protected via *N*-arylation (**1**) or activated via *N*-sulphonylation (**2**), *N*-phosphonylation (**3**) or *N*-acylation (**4**), however, much less synthetic effort has been directed towards the use of *N*-oxides (**5**) (Scheme 5.1).



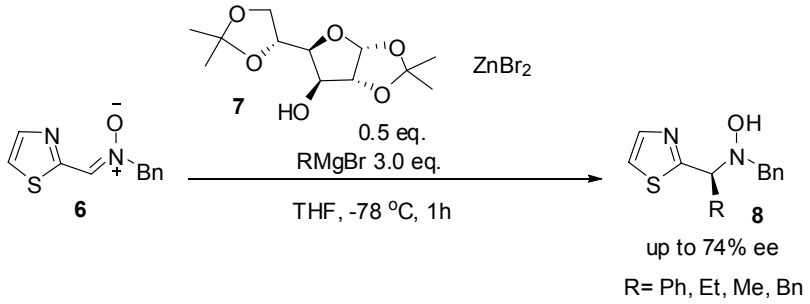
1 **2** **3** **4** **5**

Scheme 5.1

N-oxides (**5**) represent an interesting class of imine derivatives in which the C=N double bond is activated toward nucleophilic attack and the electronegative oxygen atom can coordinate to metal ions. The products of the addition reaction to *N*-oxides are *N*-hydroxylamines, which can be used as building blocks in the synthesis of more complex natural products[1] or converted readily to their respective amines.[2,5,11d] Furthermore, *N*-oxides can be obtained from both acyclic and cyclic amines,[3] which makes it possible to expand the scope of the catalytic enantioselective protocols for the organometallic addition to include addition to C=N double bond in cyclic systems.

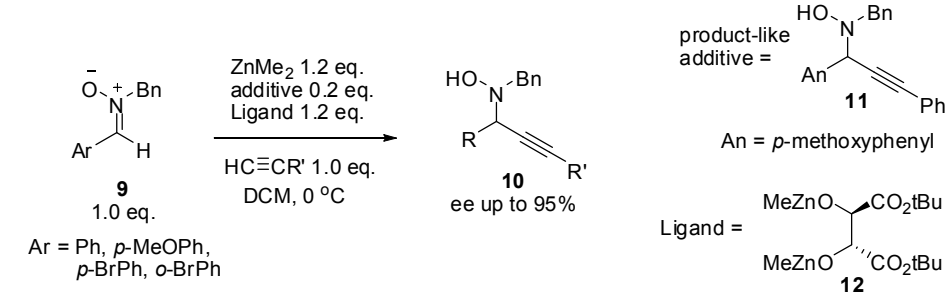
Although numerous diastereoselective additions of organometallic reagents to *N*-oxides have been reported,[4] very few procedures which use a chiral ligand have been described. In 1996 Tejero *et al.*[5] investigated the enantioselective alkylation of *N*-benzyl-α-(2-thiazolyl)nitrone **6** with Grignard reagents, using a substoichiometric amount of D-glucose diacetonide **7** in combination with an equimolar amount of $ZnBr_2$ (Scheme 5.2). Good yields and enantioselectivities of up to 74% were obtained for the resulting α-hydroxylamino-2-alkylthiazoles

8, which can be used as building blocks for alkaloid synthesis[6] or as precursors of α-aminoaldehydes through the thiazol to formyl conversion.[7]



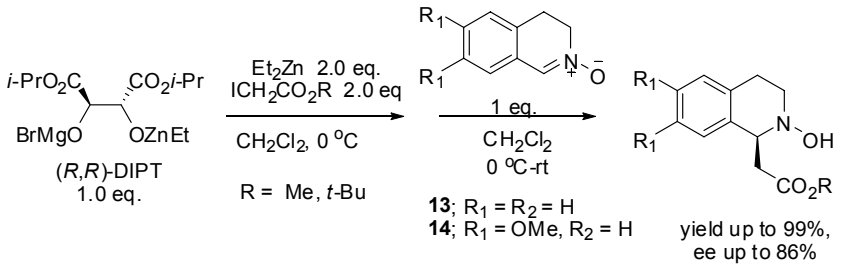
Scheme 5.2 *Enantioselective alkylation of N-benzyl-α-(2-thiazolyl)nitrone **6**.*

Ukaji and coworkers[8] reported the enantioselective synthesis of propargylic hydroxylamines **10** via addition of a zinc acetylide reagent to acyclic nitrones such as **8**. A stoichiometric amount of a zinc salt of the *t*-butyl ester of (*R*,*R*)-tartrate **12** was used as the chiral source. Interestingly, the addition of 0.2 equiv of an additive similar to the product, e.g. **11**, resulted in an increase in the enantioselectivity observed (Scheme 5.3). A catalytic version of this method was reported recently by the same group.[9]



Scheme 5.3 *Enantioselective alkynylation of the acyclic nitrone **9**.*

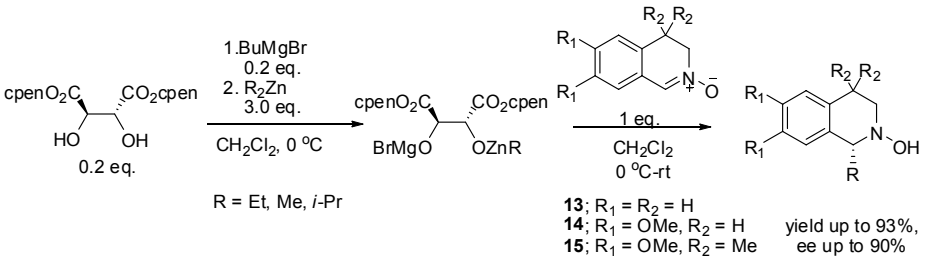
Another example of the enantioselective addition of functionalized organometallic reagents, involving a stoichiometric amount of a chiral ligand, is the addition of Reformatsky-type reagents to 3,4-dihydroisoquinoline *N*-oxides **13**-**14** (Scheme 5.4).[10]



Scheme 5.4 *Asymmetric addition of Reformatsky-type reagents to N-oxides.*

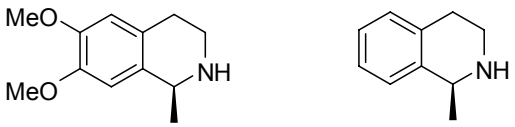
The nucleophile, prepared *in situ* from Et_2Zn and an iodoacetic acid ester, adds to the *N*-oxide, in the presence of 1 equiv of a magnesium zinc salt of (*R*,*R*)-DIPT, to give the corresponding β-hydroxylamino esters with enantioselectivities of up to 86%.

The first catalytic enantioselective addition reaction of organozinc reagents to 3,4-dihydroisoquinoline *N*-oxides **13**-**15** was developed by Ukaji *et al.*[11] (Scheme 5.5).



Scheme 5.5 *Catalytic enantioselective addition of R_2Zn to N-oxides.*

In this procedure 0.2 equiv of a magnesium zinc salt derived from an ester of (*R*,*R*)-tartrate was used to catalyze the reaction. The highest enantioselectivities were reached when the *N*-oxide was added slowly to a mixture of the catalyst prepared *in situ* and an excess of R_2Zn. Good isolated yields and enantioselectivities of up to 90% were obtained after 19 h at room temperature. The products of this reaction can be easily converted into the corresponding 1-alkyl-tetrahydroisoquinolines,[11d,e] immediate precursors of biologically relevant alkaloids (Scheme 5.6).[12]



salsolidine 1MeTIQ

Scheme 5.6 *Some isoquinoline-based alkaloids.*

Salsolidine, for example, is a potent inhibitor of human monoamine oxidases,[13] while 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) is an endogenous substance which provides protection against the development of the Parkinson disease.[14]

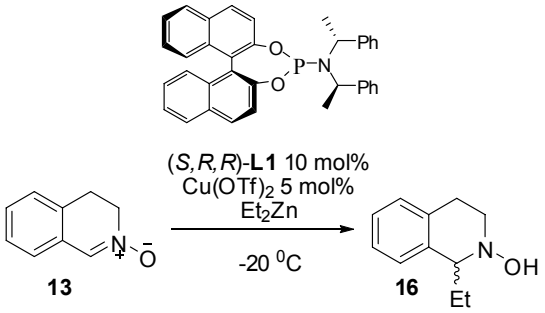
Prompted by the synthetic importance of 1-alkyl-tetrahydroisoquinolines, we decided to investigate the possibility of developing a new approach for their synthesis based on the use of chiral phosphoramidite ligands.

5.2 Results and discussion

5.2.1 From *N*-oxides to *N*-acyloxyiminium ions

Initial attempts involved the addition of diethylzinc to 3,4-dihydroisoquinoline *N*-oxides **13** in the presence of $Cu(OTf)_2$ and the chiral phosphoramidite (*S*,*R*,*R*)-**L1**. It was apparent from these preliminary studies that the combination of this catalyst system and *N*-oxide substrates was ineffective. The addition reaction afforded racemic **16** in all of the solvents used (Table 5.1, entries 1-4). The reason for this may be due to the ability of the oxygen atom of the starting material to coordinate strongly to metal centres, therefore displacing the chiral ligand from the copper complex.

Table 5.1 *Addition of Et_2Zn to 3,4-dihydroisoquinoline N-oxide **13**.*



Entry	Solvent	Additive	Ee(%)
1	THF	-	-
2	Toluene	-	-
3	Et_2O	-	-
4	CH_2Cl_2	-	-
5	THF	TMSCl	-
6	THF	$ZnBr_2$	-
7	THF	$MgBr_2$	-

^{31}P-NMR spectroscopic studies allowed for the formation of the precatalytic copper complex to be followed. When the phosphoramidite was mixed with $Cu(OTf)_2$ in toluene at room temperature, for 30 min, the signal at 146 ppm, corresponding to the free chiral ligand (*S*,*R*,*R*)-**L1** (Figure 5.1a), was replaced by a new signal at 125 ppm (Figure 5.1b). The appearance of this new signal is attributed to the chiral copper complex formed *in situ* in which (*S*,*R*,*R*)-**L1** coordinates the metal via the phosphorous atom. Addition of the *N*-oxide to a toluene solution resulted in a reappearance of the signal of the free phosphoramidite ligand, suggesting that the *N*-oxide had replaced the chiral ligand in the copper complex (Figure 5.1c). The poor resolution of the signals in Figure 5.1b and 5.1c is attributed to the presence of the paramagnetic Cu(II) species.

The use of additives such as TMSCl, $ZnBr_2$ and $MgBr_2$ that might compete for coordination to the oxygen atom of the substrate and therefore prevent the

displacement of the chiral ligand, did not lead to any improvement in enantiocontrol (Table 5.1, entries 5-7).

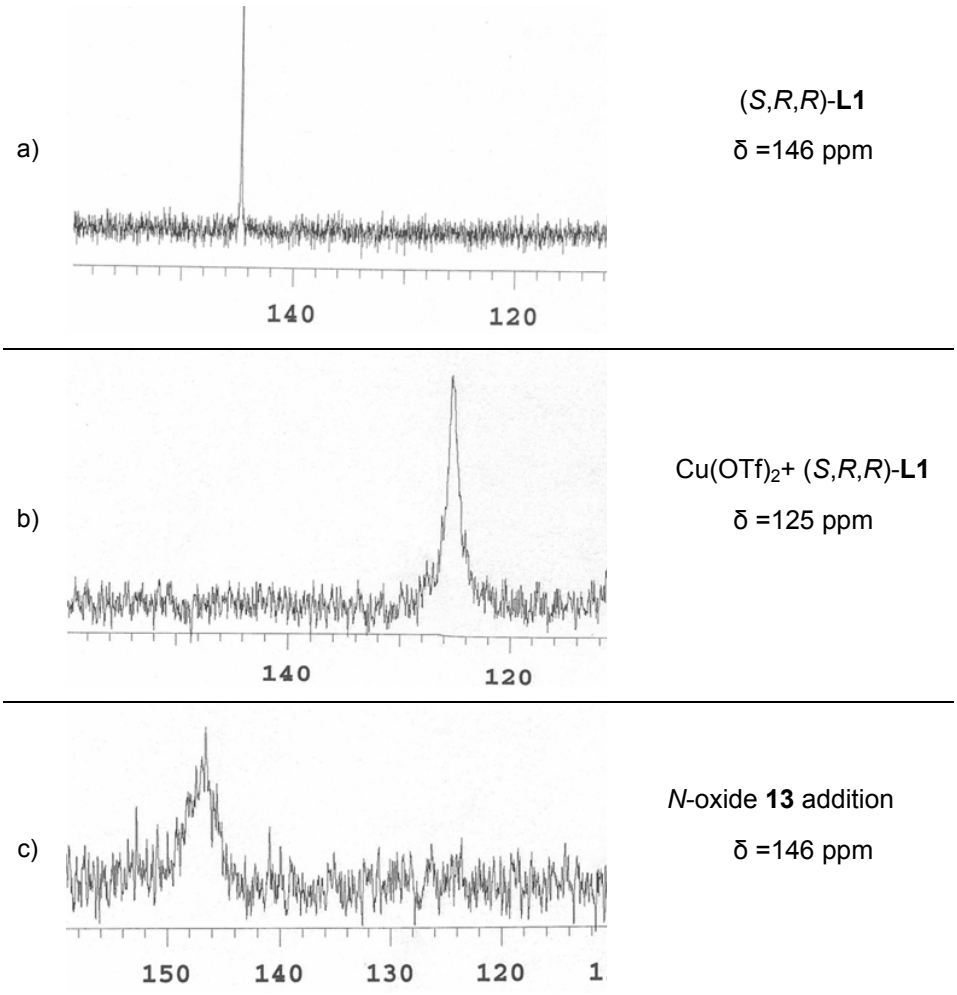
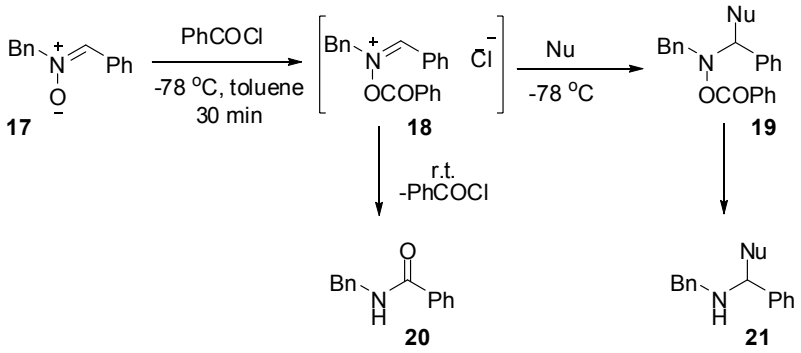


Figure 5.1 *^{31}P-NMR spectra recorded in d^8-toluene at room temperature.*

A second possibility to prevent the displacement of the chiral ligands from the precatalytic copper complex consists of blocking the coordination of the *N*-

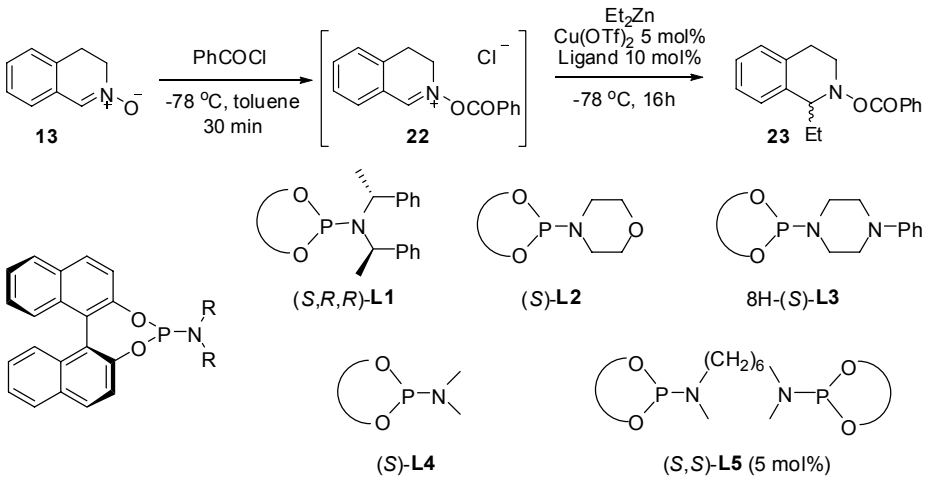
oxide by covalent binding to an appropriate protecting group. It is known that the reaction of a nitrone such as **17** with an acyl halide leads to formation of an *N*-acyloxyiminium species **18**.[15] Such species can, under certain conditions, rearrange to form an amide[16] or an imine[17] or it can be trapped with a nucleophile at low temperatures to form **19**. The latter can then be converted in to the corresponding free amine **21** (Scheme 5.7).[2a] Moreover the formation of a *N*-acyloxyiminium species increases the reactivity of the C=N double bond toward nucleophilic attack.



Scheme 5.7 *Possible reactions of a N-acyloxyiminium species.*[15c]

5.2.2 Enantioselective addition to *N*-oxide via *N*-acyloxyiminium ions

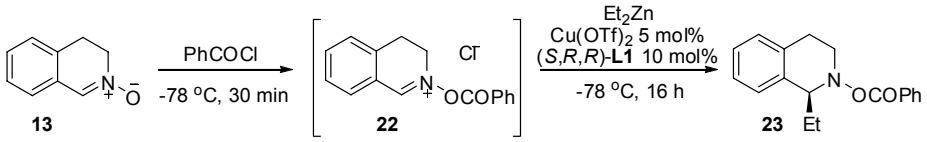
The synthetic potential of the *N*-acyloxyiminium ions led us to explore the catalytic enantioselective addition of diethylzinc to species **22** obtained upon treatment of the *N*-oxide **13** with an acyl halide. A solution of the substrate **13** and benzoyl chloride in toluene was stirred for 30 min, at -78 °C to form the *N*-acyloxyiminium ion **22**. To this solution, the freshly prepared copper complex, formed from $Cu(OTf)_2$ and the chiral ligand (*S*,*R*,*R*)-**L1** was added, followed by an excess of Et_2Zn (Scheme 5.8). However the desired product **21** was isolated in racemic form for all of the phosphoramidite ligands tested.



Scheme 5.8 *Addition of Et_2Zn to **13** via the N-acyloxyiminium species **22**.*

A study of the solvent influence showed that the use of chlorinated solvents is essential to achieve enantiocontrol in the reaction (Table 5.2).

Table 5.2 *Solvent dependence of the addition of Et_2Zn to **22**.*

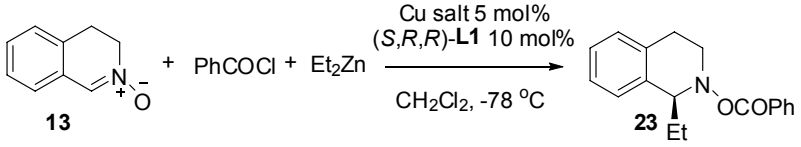


Entry	Solvent	Yield (%)	ee (%)	Remarks
1	toluene	70	rac	
2	THF	65	rac	
3	Et_2O	66	rac	
4	EtOAc	-	-	Starting material
5	CH_2Cl_2	45	37	
6	$CHCl_3$	73	10	-65 ˚C
7	$Cl(CH_2)_2Cl$	56	12	-35 ˚C

With the chiral phosphoramidite (*S*,*R*,*R*)-**L1**, product **23** was isolated in good yield albeit as a racemate, in toluene, THF and Et_2O (Table 5.2, entries 1-3). The reaction did not proceed in EtOAc (entry 4), while in chlorinated solvents modest to good yields of **23** were obtained and enantioselectivities of up to 37% were observed (entries 5-7). The temperature chosen to carry out the additions in $CHCl_3$ and 1,2-dichloroethane was set according to the freezing point of the solvent. Because the highest enantioselectivity for **21** (37%) was reached in CH_2Cl_2, the following investigations were conducted in this solvent.

The use of a copper source other than $Cu(OTf)_2$ did not lead to an improvement of the enantioselectivity observed for **23**, albeit the use of $Cu(acac)_2$ or $Cu(OAc)_2{\cdot}H_2O$ led to a better isolated yield of, respectively, 68% and 82% (Table 5.3, entries 4 and 5).

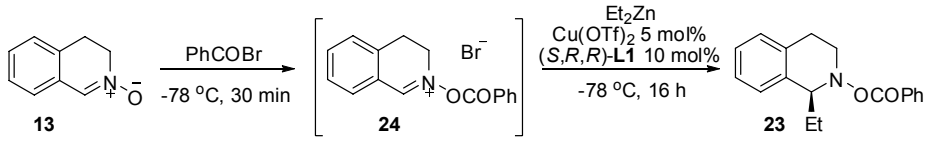
Table 5.3 *Screening of copper salts in the Et_2Zn addition to **20**.*



Entry	Cu salt	Yield (%)	ee (%)
1	$Cu(OTf)_2$	40	37
2	CuCl	43	rac
3	CuTC	39	32
4	$Cu(acac)_2$	68	22
5	$Cu(OAc)_2{\cdot}H_2O$	82	18

The influence of the counter ion of the acyloxyiminium ion was taken into consideration. Use of benzoyl bromide, instead of benzoyl chloride, to generate the *N*-acyloxyiminium species **24**, resulted in a complete loss of enantiocontrol, albeit the final product was obtained in higher yield (75%).

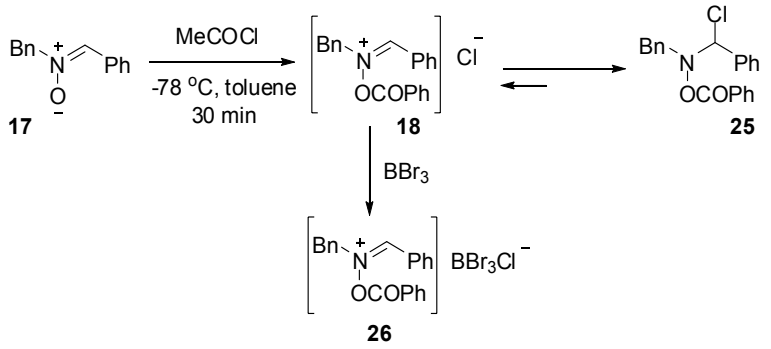
Table 5.4 *Counter ion effect.*



13 24 23

Entry	Solvent	Yield (%)	ee (%)
1	toluene	86	rac
2	CH_2Cl_2	75	rac

This effect can be rationalised in terms of the equilibrium depicted in Figure 5.2. A ^{1}H-NMR spectroscopic study was carried out to characterize the *N*-acyloxyiminium ion **18** generated *in situ* from the *N*-oxide **17** and acetyl chloride.[11d] Acetyl chloride was chosen as the acylating agent, instead of benzoyl chloride, to avoid overlap of the signals in the spectra. After mixing **15** and acetyl chloride in $CDCl_3$, at -78 °C for 30 min, the ^{1}H-NMR spectrum showed two sets of signals corresponding to the iminium ion **18** and the α-chloroamine **25**, derived from the nucleophilic attack of the chloride on **18**. The integration of the NMR signals revealed a ratio 1:11 in favour of **25**. When BBr_3 was added to the mixture to trap the chloride, the *N*-acyloxyiminium ion **26** was the only species present. Exclusive formation of the *N*-acyloxyiminium ion **18** was recorded using acetyl bromide as the acylating agent, also.[11d]



17 18 25 26

Figure 5.2 *Equilibrium between the N-acyloxyiminium ion **18** and the α-chloroamine **25**.*[11d]

By analogy, the existence of an equilibrium between the iminium ion and the α-haloamine upon acylation of the *N*-oxide **13** is possible (Figure 5.3). If the α-chloroamine **27** is formed preferentially when using benzoyl chloride, the reactive species **22** will probably be formed gradually *in situ* during the reaction. As the concentration of the reacting *N*-acyloxyiminium ion in solution is maintained at a constant, low, level, then the relative amount of the catalyst will be considerably higher than 5 mol%. Such an effect might have a positive influence on the enantiocontrol of the addition reaction. By contrast, the absence of the aforementioned equilibrium in the case of the bromide counter ion, might result in a considerable decrease in the enantioselectivity observed.

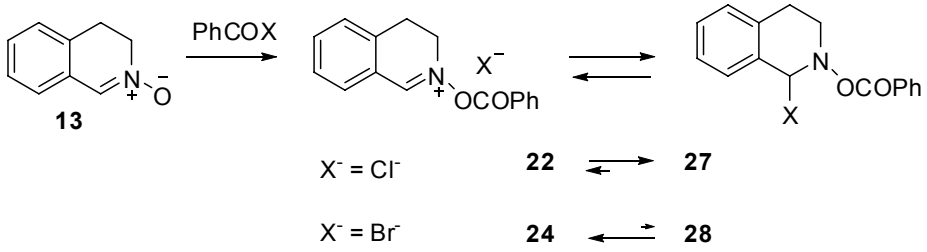
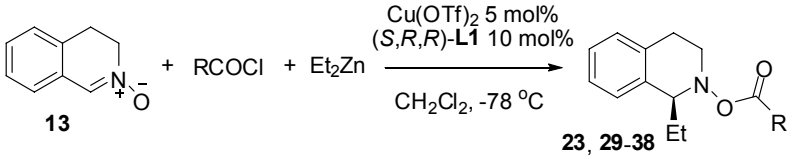


Figure 5.3 *Equilibrium between the N-acyloxyiminium ion and the α-chloroamine formed from **13**.*

Having established the importance of the counter ion to the enantioselectivity of the reaction, the effect of a change in the nature of the acyl chloride was evaluated. Substitution of benzoyl chloride for an aliphatic acyl chloride resulted in a racemic product (Table 5.5, entries 2 and 3). Complete loss of enantioselectivity was observed using the 2-naphthoyl chloride, also (entry 4). All the other aromatic acyl chlorides tested, however, provided a modest enantioselectivity in the corresponding Et_2Zn addition product. The highest ee (50%) and the highest yield (91%) were achieved where 2,4,6-trimethylbenzoyl chloride was employed as the acylating agent (entry 6). A further improvement was not observed upon increasing of the steric interactions of the protecting group (entry 7). Substitution of the aromatic moiety of the acyl chloride with electron-donating groups afforded good yields of the desired product and a modest enantioselectivity of 46% (entry 8) for the 2,4-dimethoxybenzoyl chloride and 32% for the 2,6-dimethoxybenzoyl chloride (entry 9). When acyl chlorides bearing electron-withdrawing groups were employed, only addition products of the Et_2Zn to the acyl group were detected (entries 10 and 11). It is

possible that the higher efficiency of the aromatic acyl chlorides in inducing enantioselectivity is due to presence of л,л-interactions between the protecting group and the aromatic moiety of the tetrahydroisoquinoline, which can shield one side of the molecule from the nucleophilic attack.

Table 5.5 *Effect of protecting groups on the addition of Et_2Zn.*

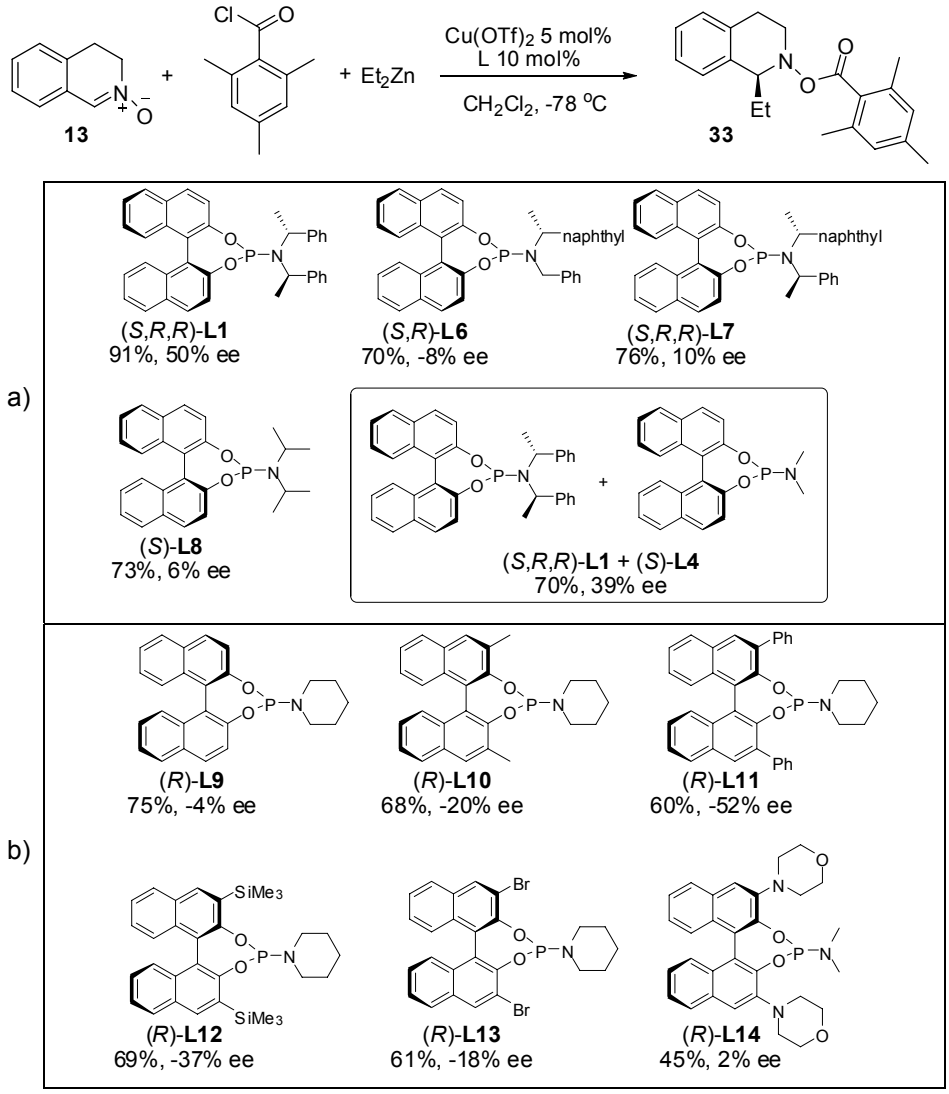


Entry	R	Product	Yield (%)	ee (%)
1	Ph	**23**	40	37
2	Me	**29**	70	rac
3	*t*-Bu	**30**	52	rac
4	2-naphthyl	**31**	53	rac
5	9-anthracenyl	**32**	42	23
6	2,4,6-trimethylbenzoyl	**33**	91	50
7	2,4,6-triisopropylbenzoyl	**34**	66	27
8	2,4-dimethoxybenzoyl	**35**	73	46
9	2,6-dimethoxybenzoyl	**36**	63	32
10	3,5-dinitrobenzoyl	**37**	-	-
11	2,4-dinitrobenzoyl	**38**	-	-

2,4,6-Trimethylbenzoyl chloride, which gave the highest yield and enantioselectivity in the addition of Et_2Zn to the *N*-oxide **13**, was used to generate the corresponding *N*-acyloxyiminium ion in the subsequent studies.

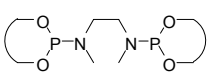
Several monodentate phosphoramidite ligands were tested in the reaction reported in Scheme 5.9. Variation of the amine moiety of (*S*,*R*,*R*)-**L1** resulted in a dramatic decrease of the enantioselectivity observed for **33**. A modest 39% ee was obtained using a combination of (*S*,*R*,*R*)-**L1** and (*S*)-**L4** in 1:1 ratio (Scheme 5.9a). The influence of 3,3'-substitution on the BINOL moiety of the ligand was studied also. A series of substituted ligands derived from (*R*)-**L9**[18] was employed in the addition reaction. The presence of substituents on the

BINOL moiety of the ligands (*R*)-**L10**-(*R*)-**L13** resulted in an improvement of the enantioselectivity compared to the unsubstituted ligand (*R*)-**L9**.

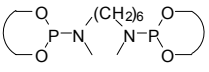


Scheme 5.9 *Monodentate phosphoramidite ligands discussed in the text and yields and ee's obtained in the addition of Et_2Zn to **13**.*

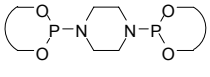
Nearly racemic **33** was isolated using the chiral ligand (*R*)-**L14** (Scheme 5.9b). Bidentate phosphoramidite and phosphine ligands were tested as well, however the product was obtained as a racemate in all cases (Scheme 5.10).



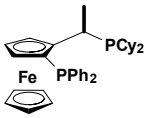
(*S*,*S*)-**L15**
82%, 4% ee



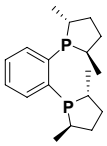
(*S*,*S*)-**L5**
56%, 2% ee



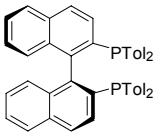
(*S*,*S*)-**L16**
65%, 1% ee



(*R*,*S*)-**J001**
46%, 4% ee



(*R*,*R*)-**Me-duPHOS**
51%, 1% ee



(*S*)-**TolBinap**
46%, 1% ee

Scheme 5.10 *Bidentate ligands.*

In summary, the copper complex formed from $Cu(OTf)_2$ and the chiral phosphoramidite ligand (*S*,*R*,*R*)-**L1** showed the highest efficiency in catalyzing the addition of Et_2Zn to the *N*-acyloxyiminium ion generated *in situ* from the *N*-oxide **13** and 2,4,6-trimethylbenzoyl chloride. The reaction is sensitive to any variation of the reaction conditions. Enantioselectivity is achieved only in chlorinated solvents. The difference in the results obtained in terms of isolated yield and enantioselectivity with different copper salts indicate that the copper counter ion plays a role also. Monodentate phosphoramidite ligands proved to be more efficient in inducing enantiocontrol in the reaction than bidentate ligands, however differences in the chirality and steric properties of the ligand result in a range of enantioselectivities between 2% and 52%. These observations are not surprising considering that the outcome of copper catalyzed conjugate additions is known to be strongly dependent on the salt, the solvent and the structure of the phosphoramidite ligand used (see Chapter 1).[19] These factors have been shown to influence the structure and the aggregation level of the precatalyst system formed in solution.[20] Much less is known about the catalyst in its active form, however if such an influence is transferred to the structure of the latter, the variation of copper salt, solvent and

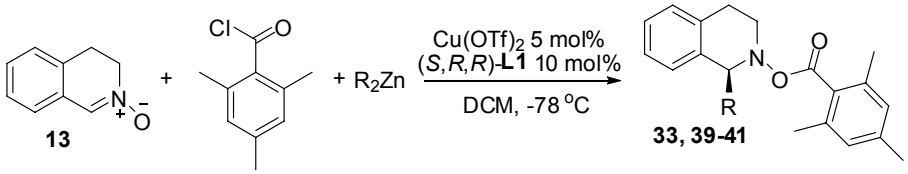
ligand might account for the formation of different species, showing different reactivity and enantioselectivity.

At present, the tools available for the prediction of the optimal combination of copper salt and ligand are still limited. A thorough screening of the reaction conditions remains the most appropriate way to proceed. A detailed mechanistic study of the copper catalyzed conjugate addition of organozinc reagents is necessary to gain further insight in the effects observed upon variation in the reaction parameters.

5.2.3 Scope of organozinc reagents

The addition of other commercially available organozinc reagents to the *N*-acyloxyiminium ion, generated *in situ* from the *N*-oxide **13** and 2,4,6-trimethylbenzoyl chloride, was explored. The results are listed in Table 5.6. The addition of Me_2Zn afforded the methylated product **39** in good yield (80%) but with low enantioselectivity (entry 2). The high reactivity of *i*-Pr_2Zn resulted in the addition of the organometallic species to the acyl chloride, precluding formation of the desired product. *n*-Bu_2Zn afforded compound **41** with 55% ee, albeit in lower yield than employing Et_2Zn (entry 4)

Table 5.6 *Enantioselective addition of organozinc reagents.*



Entry	R	Product	Yield (%)	ee (%)
1	Et	**33**	91	50
2	Me	**39**	80	8
3	*i*-Pr	**40**	-	-
4	*n*-Bu	**41**	57	55

Me_3Al is a potential alternative to Me_2Zn for the introduction of a methyl group, however with this reagent a mixture of addition products derived from the

attack of the reactive Me_3Al to the acyloxy moiety and to the free *N*-oxide were obtained.

5.3 Conclusions

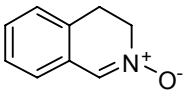
The first catalytic enantioselective addition of organozinc reagents to *N*-acyloxyiminium ions to synthesize chiral-substituted tetrahydroisoquinolines has been reported. The reactive species are generated *in situ* from the corresponding nitrone and an acyl chloride. Optimization of the reaction conditions in terms of acyl halide, copper source, chiral ligand, temperature and solvent provided enantioselectivities of up to 55% using a catalyst formed *in situ* from $Cu(OTf)_2$ and the phosphoramidite ligand (*S*,*R*,*R*)-**L1**. The product of the reaction can be deprotected to the corresponding hydroxylamine and further reduced to the free amine.[2]

The reaction proved to be highly sensitive to variation of the reaction parameters. However, it was established that chlorinated solvents and low temperatures were essential to achieve enantioselectivity; in particular, the best results were obtained with CH_2Cl_2 at -78 °C. Acyl halides are excellent reagents for the *in situ* formation of the *N*-acyloxyiminium species. Other reagents such as Boc anhydride, triflic anhydride, chloroformates and sulfonyl chlorides did not react with the *N*-oxide **13** at low temperature. The nature of the halide plays an important role also (*vide supra*). When bromide was used as the counterion of the *N*-acyloxyiminium species only racemic products were obtained. Several copper salts and chiral ligands were examined and the combination of $Cu(OTf)_2$ and the phosphoramidite (*S*,*R*,*R*)-**L1** was found to be the most efficient, however further investigations, eventually based on the use of libraries of ligands may be necessary to find the optimal catalyst system. Another possibility is to replace the diorganozinc reagents with a different organometallic species. The high reactivity of organomagnesium and organoaluminium compounds makes these systems unsuitable because of the formation of side products derived from the attack on the acyloxy moiety. Less reactive organozinc halides, however, would significantly broaden the scope of the reaction enabling the introduction of both alkyl and aryl groups. Furthermore, the use of Reformatsky-type reagents[10] could open the way to the development of new catalytic enantioselective routes for the asymmetric synthesis of β-amino acids.

5.4 Experimental section

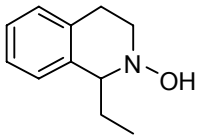
General Methods. For general information see Chapter 2.

3,4-Dihydroisoquinoline 2-oxide (13). [21]



Compound **13** was synthesized according to a literature procedure.[21] ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.26-7.19 (m, 3H), 7.11-7.08 (m, 1H), 4.09 (t, *J* = 7.7 Hz, 2H), 3.16 (t, *J* = 7.7 Hz, 2H) ppm. HRMS calcd. for C_9H_9NO: 147.0684, found: 147.0681.

1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-ol (16).[11b]



$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and ligand (*S*,*R*,*R*)-**L1** (10.8 mg, 0.020 mmol) were dissolved in the solvent indicated (3 mL) and stirred for 30 min at r.t. The mixture was cooled to -20 °C and a solution of the substrate in the same solvent (0.25 mmol, 0.125 M) was added. A solution of a R_2Zn (1.25 mmol) in the solvent indicated was added dropwise and the reaction mixture was stirred for 16 h at -20 °C, then quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (SiO_2; CH_2Cl_2/MeOH 15:1) afforded compound **16** as a colorless oil. HPLC on a Chiralcel OD-H column, 4.6 × 250 mm, 5 μm, (*n*-heptane/propan-2-ol = 99.5:0.5, flow = 0.5 mL/min): Rt = 22.6 min, Rt = 25.0 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.18-7.11 (m, 3H), 7.09-7.07 (m, 1H), 3.96 (t, *J* = 5.3 Hz, 1H), 3.47-3.41 (m, 1H), 3.21-3.15 (m, 1H), 3.02-2.86 (m, 2H), 2.10-2.00 (m, 1H), 1.92-1.81 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 136.6, 133.8, 128.3, 126.9, 126.1, 126.0, 68.0, 51.8, 26.4, 9.8. MS-CI found for $C_{11}H_{15}NO$: 178 [$M+H^+$].

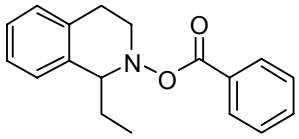
General procedure for the copper/phosphoramidite catalyzed addition of dialkylzinc reagents to *N*-acyloxyiminium ions.

$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and ligand (*S*,*R*,*R*)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous CH_2Cl_2 (3 mL) and stirred for 30 min at r.t. A solution of the acyl halide in anhydrous CH_2Cl_2 (0.25 mmol, 0.25 M) was added dropwise, at -78 °C to a solution of compound **13** in anhydrous CH_2Cl_2 (0.25 mmol, 0.25 M). The mixture was stirred for 30 min at -78 °C. To this mixture a

solution of a R_2Zn (1.25 mmol) in the solvent indicated was added dropwise and the reaction mixture was stirred for 16 h at -78 °C, then quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography.

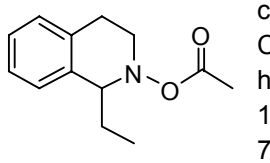
1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl benzoate (23).

Purification by column chromatography (SiO_2; EtOAc/pentane 4:96) afforded compound **23** as a colorless oil (Rf = 0.6). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 97:3, flow = 1.0 mL/min): Rt = 7.2 min (major), Rt = 12.3 min (minor). 37% ee. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.21-7.14 (m, 4H), 4.30 (t, *J* = 5.9 Hz, 1H), 3.71-3.65 (m, 1H), 3.54-3.47 (m, 1H), 3.04 (t, *J* = 6.1 Hz, 2H), 2.00-1.88 (m, 2H), 1.09 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.9, 136.2, 133.4, 132.9, 129.4, 129.3, 128.5, 128.3, 126. 8, 126.3, 126.1, 66.4, 49.6, 27.5, 25.5, 10.3 ppm. MS-CI calcd. for $C_{18}H_{19}NO_2$: 282 $[M+H]^+$. HRMS calcd. for $C_{16}H_{14}NO_2$ [M-Et]: 252.1025, found 252.1032.



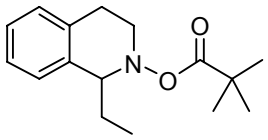
1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl acetate (29).

Purification by column chromatography (SiO_2; EtOAc/pentane 5:95) afforded compound **29** as a colorless oil (Rf = 0.5). HPLC on a Chiralcel OB-H column, 4.6 × 250 mm, 5 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 0.5 mL/min): Rt = 13.1 min, Rt = 15.4 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.20-7.09 (m, 4H), 4.10 (t, *J* = 5.8 Hz, 1H), 3.55-3.49 (m, 1H), 3.38-3.32 (m, 1H), 2.94 (t, *J* = 5.8 Hz, 2H), 2.03 (s, 3H), 1.89-1.81 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 169.6, 136.1, 133.3, 128.4, 126.8, 126.3, 126.0, 66.2, 49.3, 27.5, 25.3, 19.7, 10.3 ppm. HRMS calcd. for $C_{13}H_{17}NO_2$: 219.1259, found 219.1258.



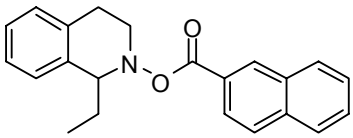
1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl pivalate (30).

Purification by column chromatography (SiO_2; EtOAc/pentane 5:95) afforded compound **30** as a colorless oil (Rf = 0.6). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 4.7 min, Rt = 5.5 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ =



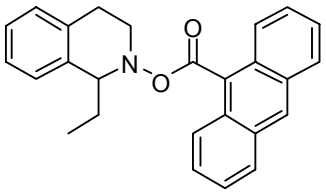
7.17-7.08 (m, 4H), 4.10 (t, *J* = 5.9 Hz, 1H), 3.56-3.49 (m, 1H), 3.35-3.29 (m, 1H), 2.96-2.92 (m, 2H), 1.89-1.81 (m, 2H), 1.17 (s, 9H), 1.03 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 176.2, 136.3, 133.4, 128.4, 126.7, 126.2, 126.0, 109.9, 66.1, 49.3, 38.6, 27.1, 25.5, 10.2 ppm. HRMS calcd. for $C_{14}H_{18}NO_2$: 232.1337, found 232.1346.

1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl 2-naphthoate (31).



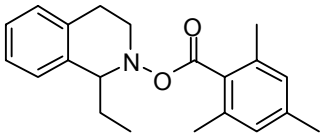
Purification by column chromatography (SiO_2; EtOAc/pentane 5:95) afforded compound **31** as a colorless oil (R_f = 0.6). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 98:2, flow = 1.0 mL/min): Rt = 14.3 min, Rt = 31.5 min. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.52 (s, 1H), 7.98-7.91 (m, 2H), 7.87-7.83 (m, 2H), 7.60-7.51 (m, 2H), 7.23-7.16 (m, 2H), 4.36 (t, *J* = 5.8 Hz, 1H), 3.74-3.70 (m, 1H), 3.58-3.52 (m, 1H), 3.08 (t, *J* = 6.1 Hz, 2H), 2.02-1.91 (m, 2H), 1.11 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 165.1, 136.3, 135.4, 133.5, 132.3, 130.8, 129.3, 128.5, 128.2, 128.1, 127.7, 126.8, 126.6, 126.3, 126.1, 125.0, 66.5, 49.8, 27.5, 25.7, 10.4 ppm. HRMS calcd. for $C_{20}H_{16}NO_2$: 302.1181, found 302.1190.

1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl anthracene-9-carboxylate (32).



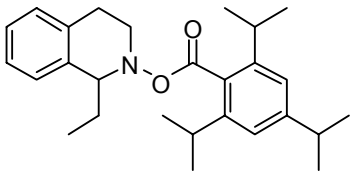
Purification by column chromatography (SiO_2; EtOAc/pentane 5:95) afforded compound **32** as a yellow solid (R_f = 0.5). Mp. = 92.1-92.5 ºC. HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 11.5 min (major), Rt = 31.3 min (minor). 23% ee. $[\alpha]_D$ = + 7.5 (c 0.97, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.48 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.52-7.44 (m, 4H), 7.18-7.12 (m, 3H), 7.09-7.07 (m, 1H), 4.42 (t, *J* = 5.8 Hz, 1H), 3.96-3.89 (m, 1H), 3.74-3.68 (m, 1H), 3.06 (t, *J* = 6.2 Hz, 2H), 2.05-1.95 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 168.2, 136.0, 133.2, 130.8, 130.6, 129.3, 128.6, 128.5, 127.7, 126.9, 126.8, 126.6, 126.4, 126.1, 125.6, 125.4, 124.6, 124.5, 66.6, 49.7, 27.7, 25.5, 10.4 ppm. HRMS calcd. for $C_{26}H_{23}NO_2$: 381.1729, found 381.1737. Elem. Anal. calcd. for $C_{26}H_{23}NO_2$: C 81.86%, H 6.08%, N 3.67%, found C 81.43%, H 6.04%, N 3.64%.

1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl 2,4,6-trimethylbenzoate (33).



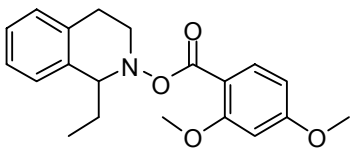
Purification by column chromatography (SiO_2; EtOAc/pentane 5:95) afforded compound **33** as a colorless oil which slowly solidified (R_f = 0.6). Mp = 81.5-81.8 ºC. HPLC on Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 9.1 min (major), Rt = 15.1 min (minor); 60% ee. $[\alpha]_D$ = + 4.6 (c 0.87, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.09-7.08 (m, 4H), 6.82 (s, 2H), 4.24 (t, *J* = 5.8 Hz, 1H), 3.74-3.68 (m, 1H), 3.54-3.48 (m, 1H), 3.02-2.99 (m, 2H), 2.28 (s, 6H), 2.26 (s, 3H), 1.97-1.90 (m, 2H), 1.11 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 168.5, 139.4, 136.1, 135.0, 133.2, 129.8, 128.5, 128.2, 126.8, 126.3, 126.0, 66.4, 49.4, 27.6, 25.5, 21.1, 19.5, 10.3 ppm. HRMS calcd. for $C_{21}H_{25}NO_2$: 323.1885, found 323.1890. Elem. Anal. calcd for $C_{21}H_{25}NO_2$: C 77.98%, H 7.79%, N 4.33%, found C 77.91%, H 7.80%, N 4.33%.

1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl 2,4,6-triisopropylbenzoate (34).



Purification by column chromatography (SiO_2; EtOAc/pentane 2:98) afforded compound **34** as a colorless oil (R_f = 0.4). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 6.9 min (major), Rt = 7.7 min (minor). 27% ee. $[\alpha]_D$ = - 3.2 (c 0.37, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.18-7.06 (m, 4H), 6.98 (s, 2H), 4.26 (t, *J* = 6.0 Hz, 1H), 3.76-3.69 (m, 1H), 3.58-3.52 (m, 1H), 3.08-3.00 (m, 1H), 2.96-2.84 (m, 4H), 1.98-1.86 (m, 2H), 1.24 (t, *J* = 6.6 Hz, 12H), 1.17-1.12 (m, 9H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 168.9, 150.4, 145.2, 136.2, 133.0, 128.8, 128.5, 127.0, 126.4, 125.9, 120.8, 66.4, 48.7, 34.4, 31.4, 28.1, 25.1, 24.2, 24.1, 23.9, 10.6 ppm. MS-CI calcd. for $C_{27}H_{37}NO_2$: 408 $[M+H]^+$.

1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl 2,4-dimethoxybenzoate (35).

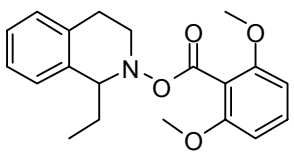


Purification by column chromatography (SiO_2; EtOAc/pentane 25:75) afforded compound **35** as a colorless oil (R_f = 0.4). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 19.6 min (major), Rt = 32.0 min (minor). 46% ee. $[\alpha]_D$ = + 7.0 (c

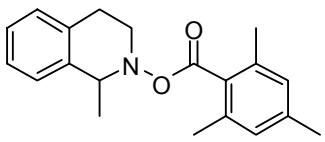
0.87, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 8.6 Hz, 1H), 7.18-7.10 (m, 4H), 6.46-6.41 (m, 2H), 4.24 (t, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.69-3.71 (m, 1H), 3.51-3.45 (m, 1H), 3.08-2.92 (m, 2H), 1.99-1.83 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.7, 164.1, 161.0, 136.7, 133.7, 137.4, 128.4, 126.9, 126.1, 125.9, 112.0, 104.5, 99.0, 66.2, 55.7, 55.4, 49.1, 27.7, 25.4, 10.5 ppm. MS-CI calcd. for $C_{20}H_{23}NO_4$: 341 $[M+H]^+$. HRMS calcd. for $C_{18}H_{18}NO_4$ [M-Et]: 312.1236, found 312.1249.

1-Ethyl-3,4-dihydroisoquinolin-2(1*H*)-yl 2,6-dimethoxybenzoate (36).

Purification by column chromatography (SiO_2; EtOAc/pentane 2:8) afforded compound **36** as a yellow solid (R_f = 0.4). Mp = 96.1-97.9 ºC. HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 12.6 min (major), Rt = 19.1 min (minor). 32% ee. $[\alpha]_D$ = + 12.9 (c 0.52, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.28-7.23 (m, 1H), 7.15-7.08 (m, 4H), 6.51 (d, *J* = 8.4 Hz, 2H), 4.22 (t, *J* = 5.5 Hz, 1H), 3.78 (s, 6H), 3.75-3.66 (m, 1H), 3.46-3.39 (m, 1H), 3.11-3.03 (m, 1H), 2.98-2.92 (m, 1H), 2.12-2.02 (m, 1H), 1.96-1.85 (m, 1H), 1.06 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 165.2, 157.5, 136.5, 133.8, 131.1, 128.4, 126.6, 126.1, 125.9, 112.1, 103.8, 66.3, 55.8, 50.2, 26.4, 25.8, 10.0 ppm. MS-CI calcd. for $C_{20}H_{23}NO_4$: 341 $[M+H]^+$. HRMS calcd. for $C_{18}H_{18}NO_4$ [M-Et]: 312.1236, found 312.1237. Elem. Anal. for $C_{20}H_{23}NO_4$: C 70.36%, H 6.79%, N 4.10%, found C 70.45%, H 6.82%, N 4.06%.



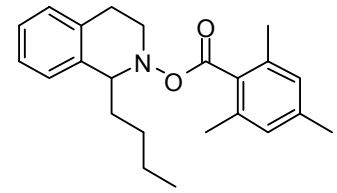
1-Methyl-3,4-dihydroisoquinolin-2(1*H*)-yl 2,4,6-trimethylbenzoate (39).



Purification by column chromatography (SiO_2; EtOAc/pentane 1:9) afforded compound **39** as a colorless oil (R_f = 0.6). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 13.7 min (major), Rt = 20.6 min (minor); 8% ee. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.18-7.07 (m, 4H), 6.83 (s, 2H), 4.42 (br s, 1H), 3.78-3.72 (m, 1H), 3.50-3.44 (m, 1H), 3.12-2.98 (m, 2H), 2.31 (s, 6H), 2.27 (s, 3H), 1.60 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 168.7, 139.5, 137.4, 135.0, 132.5, 129.6, 128.4, 128.2, 126.5, 126.4, 126.2, 60.9, 49.8, 26.1, 21.1, 19.6 ppm. HRMS calcd. for $C_{20}H_{23}NO_2$: 309.1729, found 309.1736.

1-*n*-Butyl-3,4-dihydroisoquinolin-2(1*H*)-yl 2,4,6-trimethylbenzoate (41).

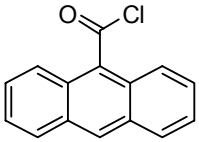
Purification by column chromatography (SiO_2; EtOAc/pentane 5:95) afforded



compound **41** as a colorless oil which slowly solidified (R_f = 0.5). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 8.4 min (major), Rt = 12.3 min (minor); 55% ee. $[\alpha]_D$ = -11.6 (c 0.51, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.17-7.07 (m, 4H), 6.81 (s, 2H), 4.29 (t, *J* = 6.0 Hz, 1H), 3.73-3.66 (m, 1H), 3.58-3.52 (m, 1H), 3.07-2.99 (m, 1H), 2.96-2.89 (m, 1H), 2.27 (s, 6H), 2.25 (s, 3H), 1.92-1.79 (m, 2H), 1.69-1.52 (m, 2H), 1.44-1.32 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 168.5, 139.4, 136.6, 135.1, 133.0, 129.8, 128.5, 128.2, 126.9, 126.3, 126.0, 65.2, 48.8, 35.1, 28.1, 25.0, 22.8, 21.1, 19.5, 14.0 ppm. HRMS calcd. for $C_{23}H_{29}NO_2$: 351.2198, found 351.2181.

Anthracene-9-carbonyl chloride.[22]

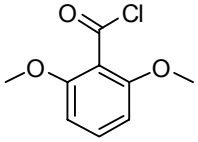
Quantitative yield; yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.59 (s, 1H),



8.12 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.66-7.61 (m, 2H), 7.57-7.53 (m, 2H) ppm.

2,6-Dimethoxybenzoyl chloride.[22]

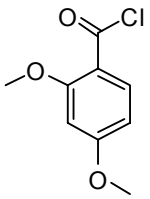
Quantitative yield; light yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.35 (t, *J* =



8.5 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 2H), 3.87 (s, 6H) ppm.

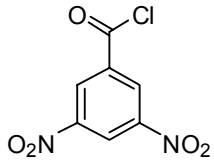
2,4-Dimethoxybenzoyl chloride.[22]

Quantitative yield; light yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.16 (d, J = 9.0 Hz, 1H), 6.55 (dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 1H), 6.46 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H) ppm.



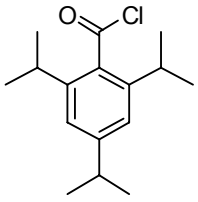
3,5-Dinitrobenzoyl chloride.[22]

Quantitative yield; light yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.35-9.33 (m, 1H), 9.25-9.24 (m, 2H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 165.1, 146.9, 136.4, 130.3, 124.1 ppm.

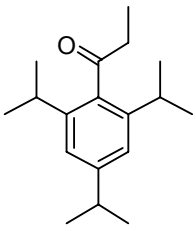


2,4,6-Triisopropylbenzoyl chloride.[22]

Quantitative yield; white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.04 (s, 2H), 3.11-3.01 (m, 2H), 2.95-2.88 (m, 2H), 1.29 (d, J = 6.8 Hz, 12H), 1.26 (d, J = 6.9 Hz, 6H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 171.1, 151.1, 143.0, 153.2, 121.3, 34.4, 31.4, 23.9, 23.8 ppm.



1-(2,4,6-Triisopropylphenyl)propan-1-one.[23]



Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.99 (s, 2H), 2.92-2.85 (m, 1H), 2.72 (q, J = 7.2 Hz, 2H), 2.65-2.58 (m, 2H), 1.27-1.18 (m, 21H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 211.9, 149.3, 143.4, 138.2, 121.0, 39.5, 34.3, 31.1, 24.2, 24.0, 7.7 ppm. HRMS calcd. for $C_{18}H_{28}O$: 260.2140, found 260.2132.

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Chapter 6

Copper-catalyzed enantioselective conjugate addition of organometallic reagents to acyclic dienones

The enantioselective copper/phosphoramidite-catalyzed 1,4-addition of dialkylzinc reagents and trimethylaluminum to acyclic dienones is described. The products of this reaction, obtained with enantioselectivities of up to 95%, can be further functionalized by a second conjugate addition, or employed in an enolate trapping, ring-closing metathesis protocol.

Part of this chapter has been published:

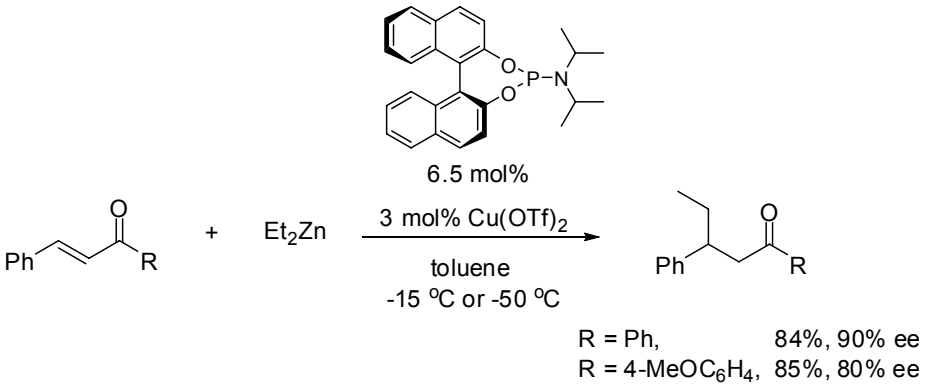
Šebesta, R.; Pizzuti, M.G.; Minnaard, A.J.; Feringa, B.L. *Adv. Synth. Catal.* **2007**, *349*, 1931-1937.

6.1 Introduction

The conjugate addition of organometallic reagents to α,β-unsaturated systems is an important transformation in synthetic organic chemistry.[1] Considerable effort has been devoted over the past decade to the development of enantioselective copper-catalyzed conjugate addition reactions.[2] Copper complexes based on chiral phosphoramidite ligands are established versatile catalysts for the enantioselective 1,4-addition of dialkylzinc reagents to a range of enones.[3] Although more recently a variety of other chiral ligands has been introduced for this C-C bond forming reaction,[2,4] acyclic α,β-unsaturated systems constitute a considerable challenge as it has proven to be much more dificult to obtain high enantioselectivity with these types of substrates. Recently several structurally diverse chiral ligands were reported to be suitable for a number of important acyclic substrates. [3b,4b,5] A short survey, with focus on the most efficient methods available, is presented in the next paragraph.

6.1.1 Enantioselective copper-catalyzed conjugate addition of organozinc reagents to acyclic substrates

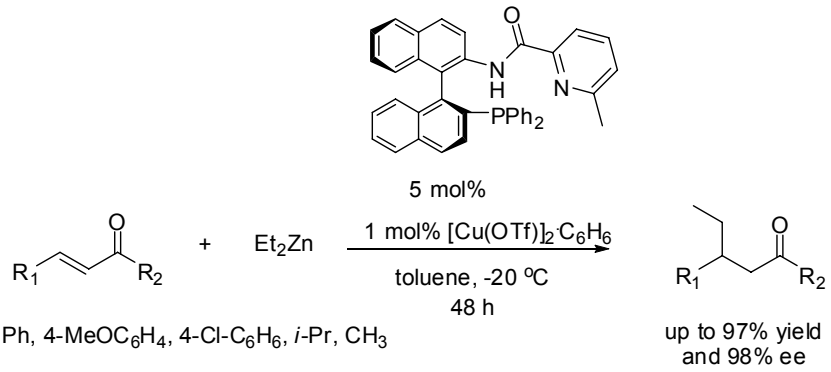
BINOL-based phosphoramidites were the first class of chiral ligands reported to achieve high enantioselectivities in the copper catalyzed conjugate addition of organozinc reagents to acyclic substrates.[3b]



Scheme 6.1

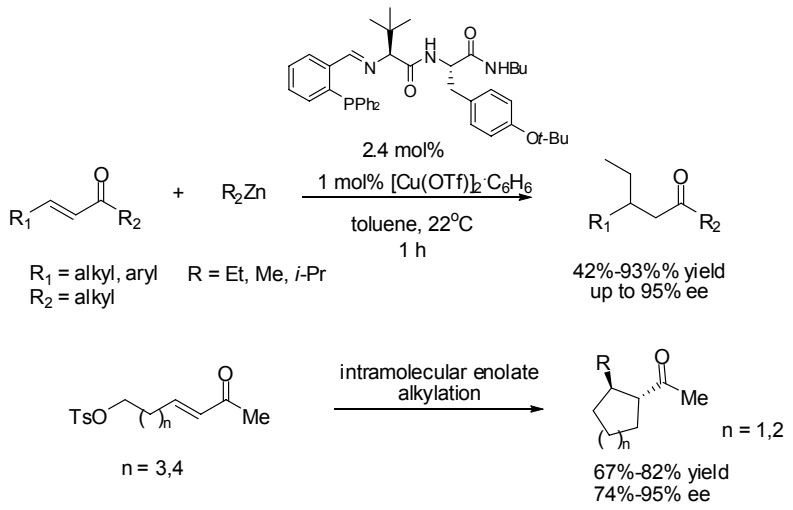
The addition of Et_2Zn to chalcone in the presence of $Cu(OTf)_2$ and a chiral ligand in a ratio of 1:2 afforded the desired product in 84% yield and with 90% ee (Scheme 6.1).

A further improvement in the enantioselective addition of Et_2Zn to chalcone and its derivatives was achieved using the P,N chiral ligand depicted in Scheme 6.2, in combination with $[Cu(OTf)]_2 \cdot C_6H_6$.[4b] However, long reaction times (48 h) are required.



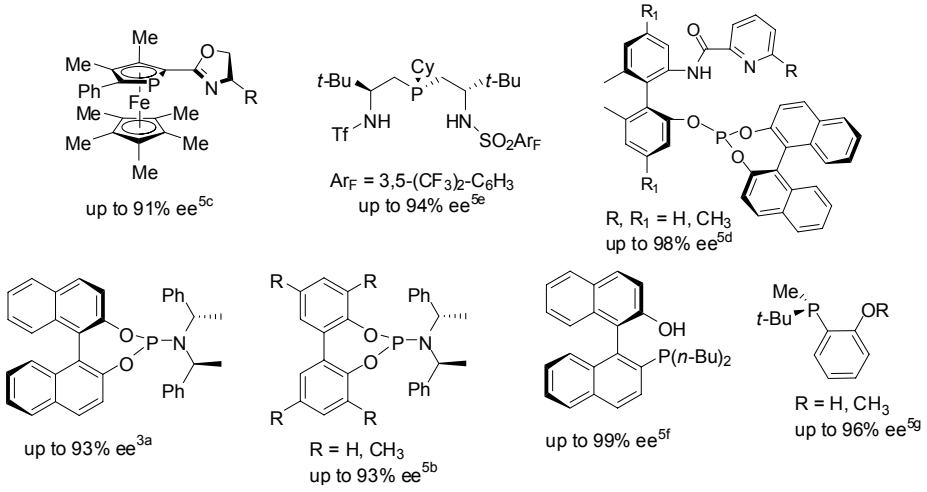
Scheme 6.2

Employing a new class of chiral diphenyl phosphine ligands, Hoveyda and coworkers[5a] extended in 2002 the scope of the copper-catalyzed conjugate addition to linear α,β-unsaturated ketones to a wide range of dialkylzinc reagents. The copper complex of the chiral dipeptide phosphine ligand afforded the 1,4-products in moderate to high yields (42%-93%) and high enantioselectivities (up to 95%) (Scheme 6.3). The possibility of inter- and intramolecular enolate alkylation was investigated as well. In the latter case substituted cyclopentyl and cyclohexyl ketones were obtained in good yield and enantioselectivities of up to 95%. This catalytic reaction was applied in the total synthesis of *erogorgiaene*,[6] in which the asymmetric conjugate addition of Me_2Zn to an acyclic α,β-unsaturated ketone is the key step (see Chapter 1).



Scheme 6.3

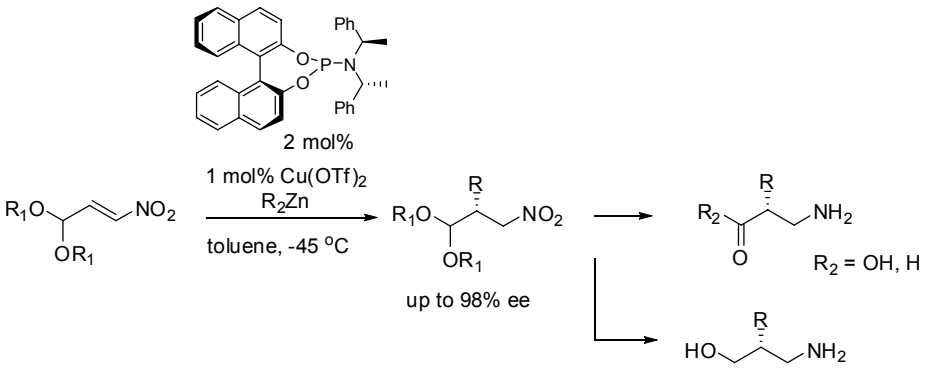
Since this report, several other chiral ligands for the copper catalyzed conjugate addition of dialkylzinc reagents to α,β-unsaturated ketones have been described.[3a,5b-g] Amongst the most efficient are those depicted in Scheme 6.4.



Scheme 6.4

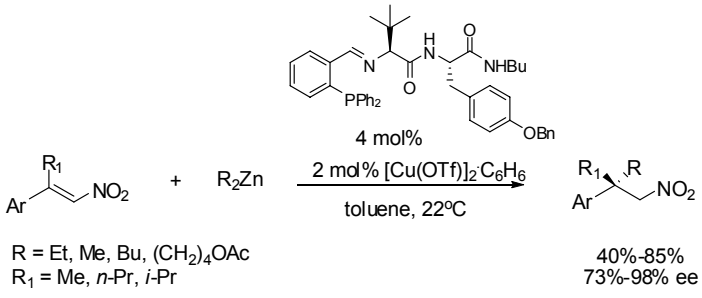
With regard to substrate scope, phosphoramidite ligands stand out with respect to efficiency. Full conversion and enantioselectivities of up to 99% were observed in the addition to aromatic acyclic nitroalkenes using chiral BINOL- or biphenyl-based phosphoramidites in combination with $Cu(OTf)_2$.[7a,d]

In particular, the use of functionalized substrates such as 3-nitropropanoates[7b] or acetal substituted nitroalkenes[7a] provides a catalytic enantioselective route to β[2]-amino aldehydes, acids and aminoalcohols (Scheme 6.5).



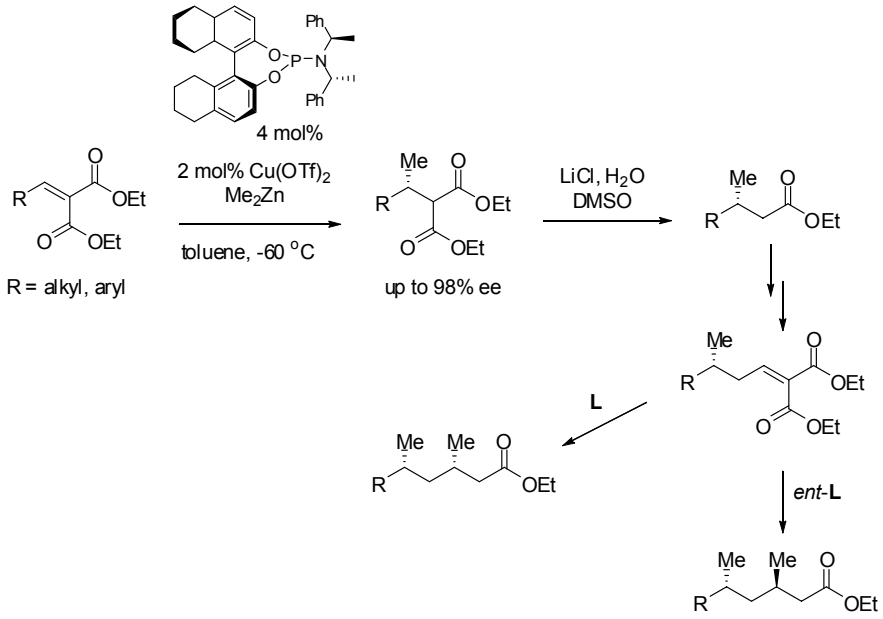
Scheme 6.5

A particular achievement is the addition of dialkylzinc reagents to β-substituted nitroalkenes described by Hoveyda and coworkers for the formation of quaternary stereogenic centers.[7f] The β-disubstituted nitroalkanes were obtained in moderate to good yields and with enantioselectivities of up to 98% using chiral dipeptide phosphine ligands in combination with $[Cu(OTf)]_2{\cdot}C_6H_6$ (Scheme 6.6).



Scheme 6.6

High enantioselectivities were observed for the addition of dimethylzinc to acyclic esters, also. Acyclic malonates are the substrates of choice since simple α,β-unsaturated esters are unreactive toward the conjugate addition of dialkylzinc reagents. It is possible to convert the 1,4-addition product to a mono-ester via decarboxylation (Scheme 6.7). This method can be extended to an iterative procedure to yield either *syn*- or *anti*-3,5-dimethyl carbonyl compounds.



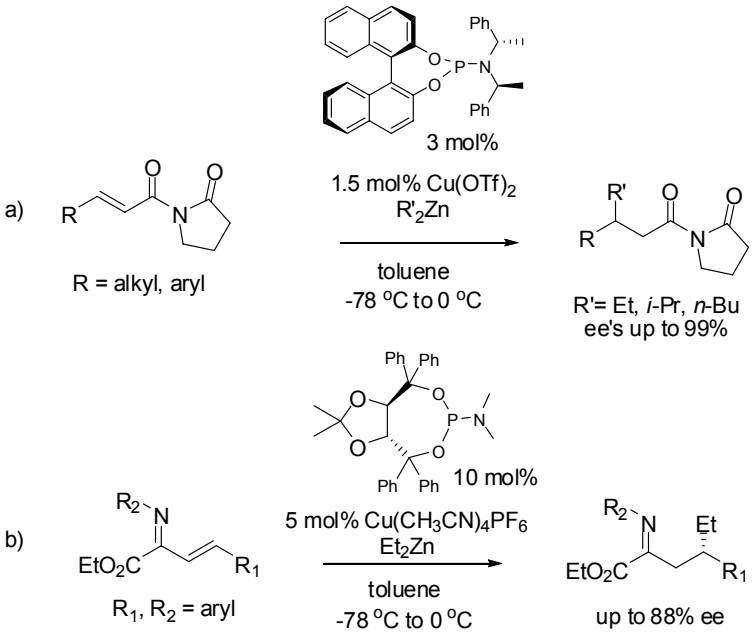
Scheme 6.7

TADDOL- and BINOL-based phosphoramidite ligands were also employed successfully in the copper-catalyzed addition of diorganozinc reagents to α,β-unsaturated imides and imines, respectively.[8]

N-acyl-pyrrolidinones have been used for the first time as α,β-unsaturated carboxylic acids derivatives (Scheme 6.8a).[8a] Good conversion and typically high ee are achieved in the addition of different dialkylzinc reagents (Et_2Zn, *i*-Pr_2Zn, *n*-Bu_2Zn). The β-substituted-*N*-acylpyrrolidones can be converted to the

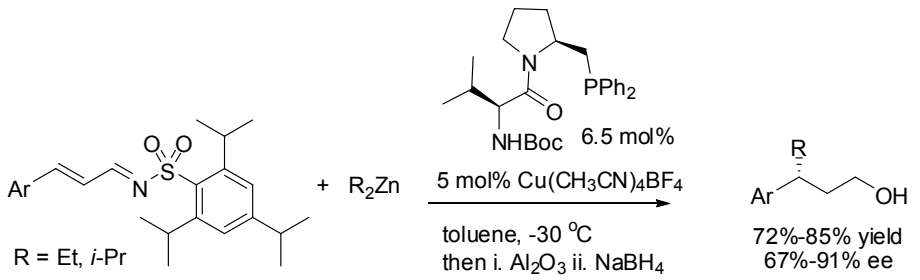
corresponding esters, using a catalytic amount of $[Er(OTf)_3]$ in EtOH, or by hydrolysis to the carboxylic acid.

In the second case α-iminoesters bearing a stereogenic center in the γ-position were obtained in good yield and with enantioselectivities of up to 88%.[8b] $[Cu(CH_3CN)_4]PF_6$ provided better results compared to the more commonly used $Cu(OTf)_2$. High regioselectivities in favor of the 1,4-adduct were observed (Scheme 6.8b).



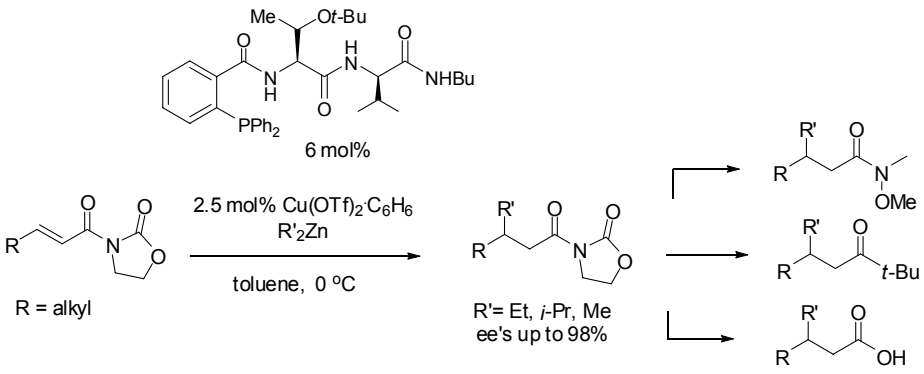
Scheme 6.8

Unsaturated sulfonylaldimines have been shown to undergo conjugate addition of dialkylzinc reagents to afford the 1,4-adducts with high regio- and enantioselectivity in presence of copper complexes with chiral amidophosphane ligands (Scheme 6.9).[9] Deprotection of the imine after the conjugate addition and reduction of the corresponding aldehyde yields the corresponding β-alkylated alkanols with up to 91% ee.



Scheme 6.9

A further broadening of the substrate scope for the copper-catalyzed addition of diorganozinc reagents to acyclic α,β-unsaturated systems was achieved through the use of *N*-acyloxazolidinones, whose masked functionality can be used to give a wide range of carbonyl derivatives such as ketones, Weinreb amides and carboxylic acids[10] (Scheme 6.10).



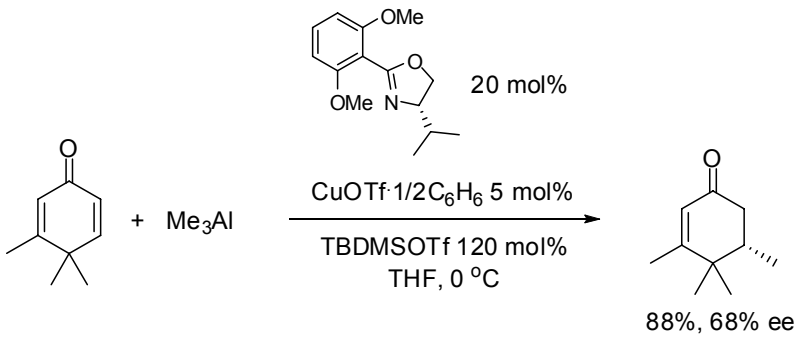
Scheme 6.10

6.1.2 Enantioselective copper catalyzed conjugate addition of organozinc and organoaluminum reagents to cyclic dienones

Much less effort has been devoted to dienones, although these compounds offer considerable potential for further functionalization after the conjugate addition through the second enone moiety. Thus far, only enantioselective

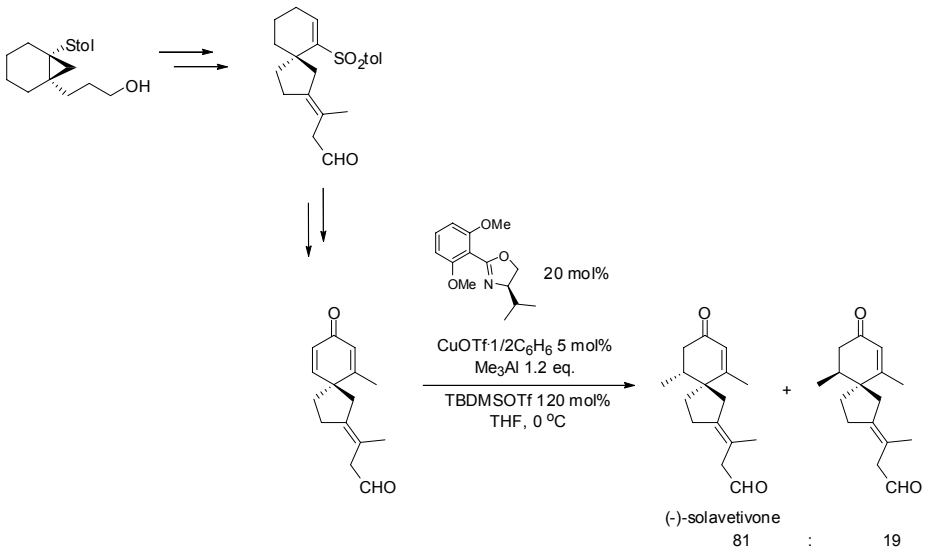
catalytic additions of organozinc reagents and trimethylaluminum to cyclic dienones have been reported and shown to provide versatile chiral synthons for natural product synthesis.

The first example of a copper-catalyzed conjugate addition to a dienone, in the presence of an external chiral ligand, concerns the addition of trimethylaluminum to a substituted cyclohexa-2,5-dienone.[11] 5 mol% of [CuOTf·1/2C_6H_6] in combination with 20 mol% of a chiral 2-aryloxazoline were used to catalyze the addition of Me_3Al to 3,4,4-trimethylcyclohexane-2,5-dienone in 88% isolated yield and 68% ee. The addition of 120 mol% of TBDMSOTf was found to be crucial in achieving high enantioselectivity (Scheme 6.11).



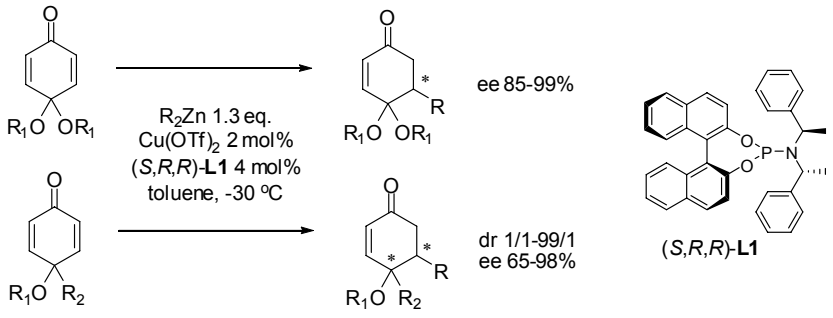
Scheme 6.11

This reaction was used by the same group as a key step in the enantioselective synthesis of (-)-solavetivone,[12] a phytoalexin[13] isolated from potato tubers infected with the blight fungus *Phytophthora infestans* or air cured tobacco leaves. The reaction afforded two diastereoisomers in a 81:19 ratio in favor of the desired product. Separation by HPLC chromatography provided enantiomerically pure (-)-solavetivone in 72% yield (Scheme 6.12).



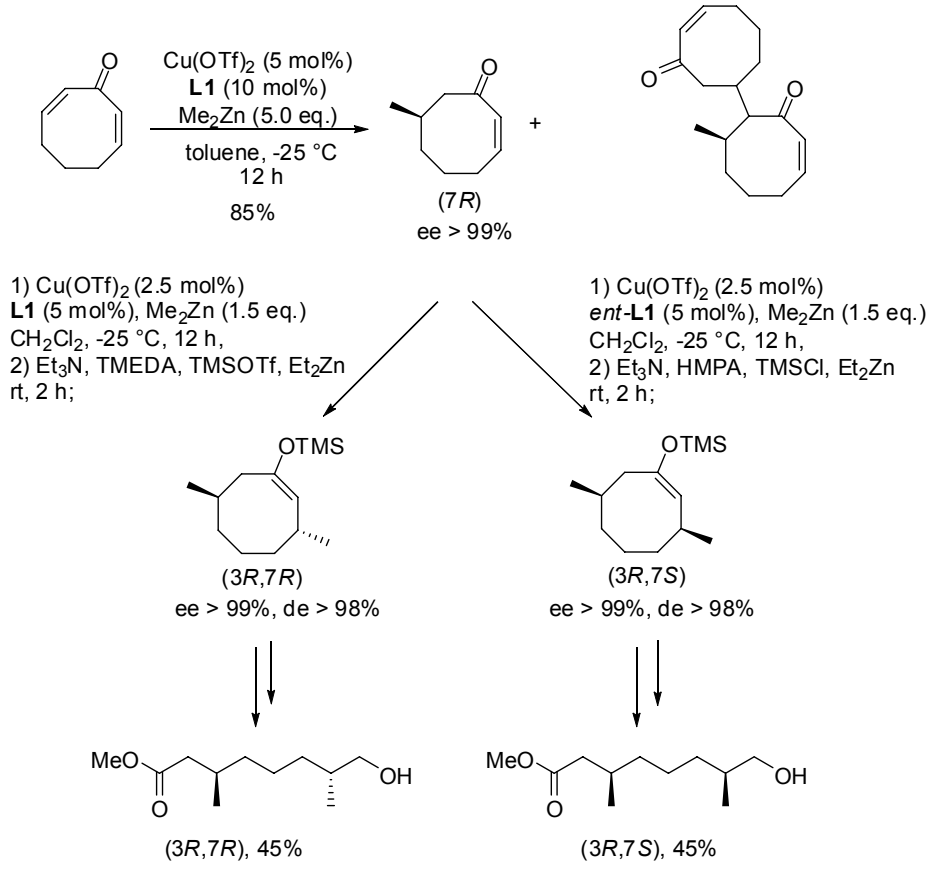
Scheme 6.12

The use of the phosphoramidite ligand (*S*,*R*,*R*)-**L1** allowed high stereoselectivity in the copper-catalyzed addition of organozinc reagents to 4,4-disubstituted cyclohexadienones.[14] In particular, an enantioselectivity of up to 97% was obtained in the desymmetrization of prochiral dienones bearing equal substituents at the 4 position. For substrates substituted with two different groups, two stereogenic centers are formed at the same time during the reaction. Diastereomeric ratio's ranging between 1/1 and 99/1 and moderate to high ee's of the isomers were observed (Scheme 6.13).



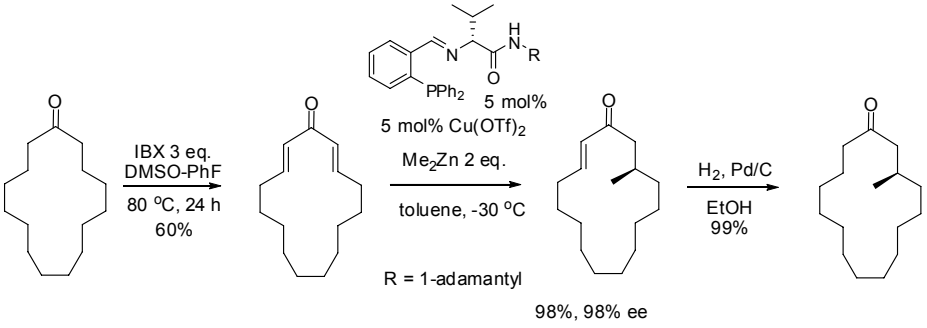
Scheme 6.13

A further example of the synthetic possibilities afforded by the products of the conjugate addition of organozinc reagents to dienones is represented by the procedure, developed in our group, for the addition of Me_2Zn to cycloocta-2,7-dienone (Scheme 6.14).[15] This catalytic procedure allows for the preparation of all four diastereoisomers of a versatile isoprenoid derivative which has been employed as building block in the synthesis of apple leafminer pheromones and of the *β*-mannosyl phosphomycoketide, a potent mycobacterial antigen for T-cells, isolated from *Mycobacterium tuberculosis*[16] (see Chapter 1 for a detailed description).



Scheme 6.14

Recently, Pfaltz et al. reported an enantioselective route to (-)-(*R*)-muscone based on the copper-catalyzed addition of Me_2Zn to cyclopentadecane-2,14-dienone.[17] The starting material can be obtained from commercially available cyclopentadecanone via double IBX dehydrogenation. The introduction of a methyl group, catalyzed by 5 mol% of $Cu(OTf)_2$ and a valine-derived phosphine ligand, proceeds in nearly quantitative yield and 98% ee. Hydrogenation of the remaining double bond over Pd/C gives the (-)-(*R*)-muscone (Scheme 6.15).



Scheme 6.15

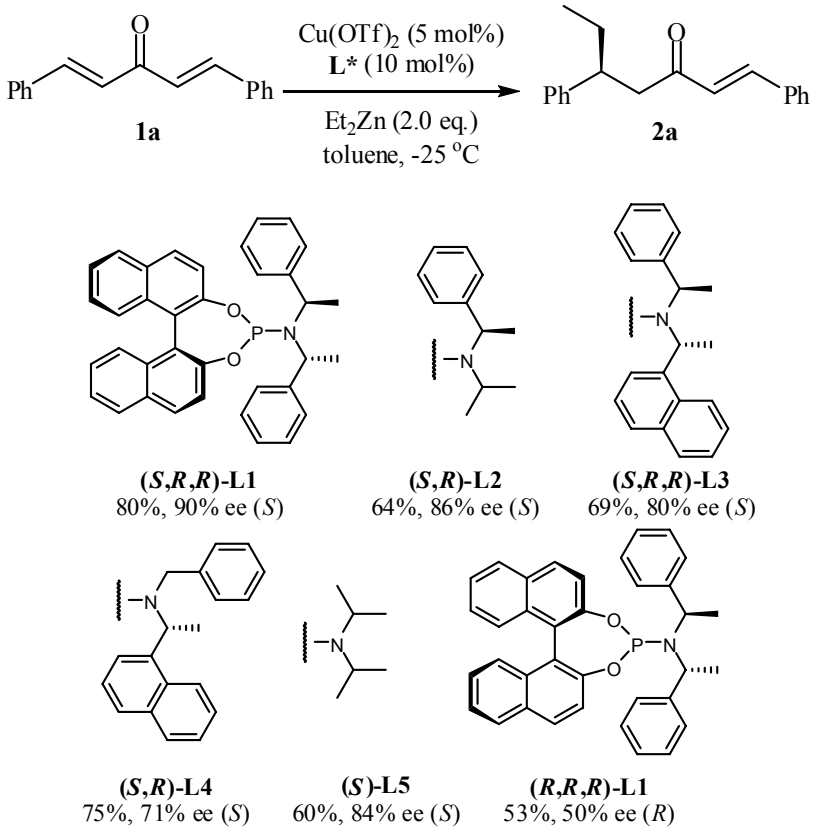
6.2 Copper-catalyzed enantioselective conjugate addition of organozinc reagents and trimethylaluminum to acyclic dienones

Encouraged by the promising results obtained using phosphoramidite ligands for the organozinc addition to acyclic substrates[3b,5b,18] and the high enantioselectivities observed with cyclic dienones,[14,15] we decided to test the catalytic system developed in our group in the enantioselective addition of diethylzinc to α,β-unsaturated acyclic dienones. The possibility of performing double 1,4-addition as well as the introduction of new functionalities in the molecule via trapping of the intermediate enolate are considered.

trans,trans-Dibenzylideneacetone **1a** was used as a model substrate for preliminary investigation. The addition of diethylzinc was performed using 5 mol% of a copper complex prepared *in situ* from $Cu(OTf)_2$ and the phosphoramidite ligand (*S*,*R*,*R*)-**L1** in a ratio of 1:2. Two equivalents of Et_2Zn

were employed. The ethyl substituted product **2a** was obtained, after overnight reaction, in 80% isolated yield and with 90% enantioselectivity (Scheme 6.16).

In order to achieve an improvement in enantiocontrol, several structurally related ligands **L1**–**L5**[3b,5b,19] were tested. (Scheme 6.16).



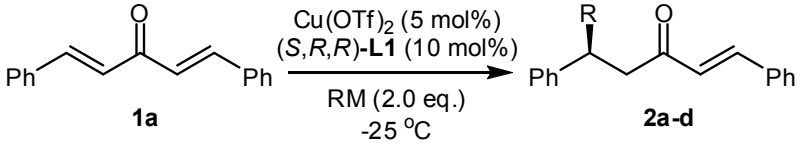
Scheme 6.16 *Screening of phosphoramidite ligands.*

Under the same reaction conditions a slightly lower ee of 86% was achieved using (*S*,*R*)-**L2** in which the steric hindrance of the amine moiety has been reduced and a stereogenic center was removed. Ligand (*S*,*R*,*R*)-**L3**, where a phenyl ring has been replaced by a naphthyl substituent, afforded the product

with 80% ee. In comparison with (*S*,*R*,*R*)-**L3**, the removal of a methyl group in ligand (*S*,*R*)-**L4** resulted in a further decrease in enantioselecivity to 71%. Better results (84% ee) were achieved using ligand (*S*)-**L5** where the chirality is present only in the binaphthol part and the amine moiety is derived from diisopropylamine. The isolated yields of product **2a** using the ligands **L2**-**L5** range between 60% and 75%. The use of the diastereoisomer (*R*,*R*,*R*)-**L1** afforded the product **2a** in low yield (53%) and enantioselectivity (50%) indicating a mismatch combination of the binaphthol and amine chiral moieties. Moreover, the formation of the opposite enantiomer of **2a** indicates that the binaphthol part determines the sign of the chiral induction.

The phosphoramidite ligand (*S*,*R*,*R*)-**L1** proved to be the most efficient, therefore it was used as ligand of choice for further investigations.

Table 6.1 *Addition of organometallic reagents to **1a** catalyzed by $Cu(OTf)_2$ and (S,R,R)-**L1**.*



1a **2a-d**

Entry	RM	Solvent	Product	Yield (%)	ee (%)
1	Et_2Zn	toluene	**2a**	73	92(*S*)
2	Me_2Zn	toluene	**2b**	12	95(*S*)
3	Me_3Al	toluene	**2b**	8	92(*R*)
4	Me_3Al[a]	THF	**2b**	8	92(*R*)
5	Me_3Al[a]	Et_2O	**2b**	16	96(*R*)
6	MeMgBr[b]	*t*-BuOMe	**2b**	50	88(*S*)
7	*i*-Pr_2Zn	toluene	**2c**	60	73(*S*)
8	Bu_2Zn	toluene	**2d**	61	89(*S*)

[a] -50 °C; [b] $CuBr{\cdot}SMe_2$ (5 mol%), (*R*,*S*)-Josiphos (6 mol%), MeMgBr (1.5 eq.), -75 °C.

The introduction of several other alkyl groups using commercially available organozinc reagents was investigated (Table 6.1). The addition of *i*-Pr_2Zn and *n*-Bu_2Zn afforded the corresponding products **2c** and **2d** in 60% isolated yield and with 73% and 89% enantioselectivity, respectively (entries 7 and 8).

The reaction with Me_2Zn afforded the addition product **2b** with 95% ee but in only 12% isolated yield. Furthermore, the formation of several by-products was detected, probably due to the occurrence of addition reactions between the enolate formed and the starting material. Attempts were made to obtain the methyl substituted product **2b** in higher yield. Me_3Al was used instead of the less reactive Me_2Zn. Full conversion was observed after reaction in toluene overnight, at -50 °C. The desired product **2b** was isolated with high enantioselectivity (92%) but in only 8% yield (entry 3). Also in this case the low yield can be ascribed to the presence of side products. A significant improvement was not observed upon changing the solvent to THF or Et_2O where **2b** was obtained in 8% and 16% yield and with 92% and 96% ee, respectively (entries 5 and 6). The introduction of a methyl substituent was achieved in higher yield (50%) and with good enantioselectivity (88%) via the copper-catalyzed addition of MeMgBr using Josiphos as chiral ligand.[20]

Interestingly, the addition reaction of Me_3Al to **1a** afforded the methyl substituted product **2b** with opposite absolute configuration compared to Me_2Zn under the same reaction conditions. The same situation had been observed previously in the copper/phosphoramidite addition of organometallic reagents to *N*-formylimines (see Chapter 4). A possible rationalization of this observation is given in section 4.5.

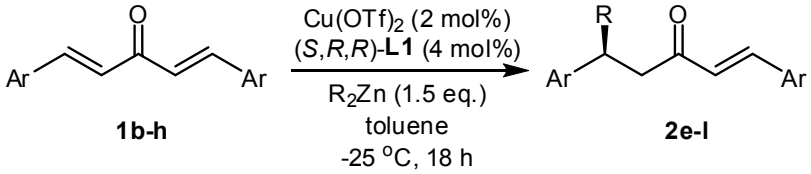
It was possible to decrease the catalyst loading to 2 mol% and the amount of the organozinc reagent to 1.5 equiv without affecting the enantioselectivity of the reaction, although a modest decrease of the isolated yield (to 73%) was observed (Table 6.2, entry 1). Similar results were obtained when the reaction was performed on a larger scale (Table 6.2, entry 2).

The scope of the reaction was explored further by performing the Et_2Zn addition on a series of substituted dienones **1b**–**h** (Table 6.2). The corresponding products **2e** and **2g**–**l** were obtained in good yield and with high enantiomeric excess.

The reaction of dienone **1b** with Et_2Zn affords product **2e** with a lower enantioselectivity of 77% (entry 3), indicating sensitivity to steric bulk near the β-carbon atom. The 34% ee obtained in the addition of *i*-Pr_2Zn to substrate **1b** is in agreement with these results.

Comparison of entries 5-6 and 7-8, where the dienones are substituted at the *meta* and *para* position with electron-withdrawing and electron-donating groups respectively, indicates that electronic effects do not play a major role. Slightly higher enantioselectivities were obtained with *para*-substituted substrates. Good enantioselectivities were obtained with the dienones **1g** and **1h** (entries 9 and 10), although the corresponding products **2k** and **2l** were isolated in lower yields.

Table 6.2 *Addition of organozinc reagents to dienones **1b-h**.*



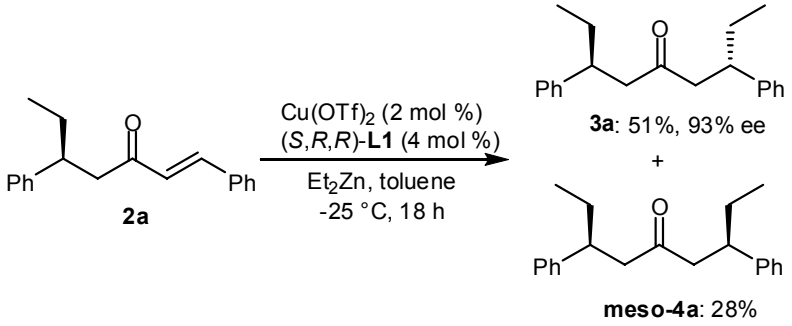
1b-h **2e-l**

Entry	Dienone	Ar	R_2Zn	Product	Yield (%)	ee (%)
1	**1a**	C_6H_5	Et_2Zn	**2a**	73	92(*S*)
2	**1a**[a]	C_6H_5	Et_2Zn	**2a**	75	92(*S*)
3	**1b**	2-Cl-C_6H_4	Et_2Zn	**2e**	79	77(*S*)
4	**1b**	2-Cl-C_6H_4	iPr_2Zn	**2f**	53	34(*S*)
5	**1c**	3-Br-C_6H_4	Et_2Zn	**2g**	66	90(*S*)
6	**1d**	3-Me-C_6H_4	Et_2Zn	**2h**	69	88(*S*)
7	**1e**	4-Cl-C_6H_4	Et_2Zn	**2i**	71	95(*S*)
8	**1f**	4-MeO-C_6H_4	Et_2Zn	**2j**	59	94(*S*)
9	**1g**	2-thienyl	Et_2Zn	**2k**	48	87(*S*)
10	**1h**	1-naphthyl	Et_2Zn	**2l**	53	93(*S*)

[a] Reaction carried out on 4.27 mmol scale of dienone.

6.2.1 Sequential conjugate addition

Conjugate addition to dienone **1a** yielded, again, an α,β-unsaturated system as the final product that can undergo a second conjugate addition reaction (Scheme 6.17).



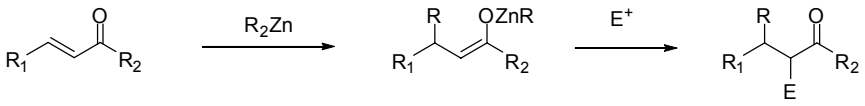
Scheme 6.17 *Sequential conjugate addition.*

Enone **2a** (92% ee) was subjected to Et_2Zn addition under standard conditions. When the introduction of the second ethyl substituent occurs in *trans*-fashion, the chiral C2-symmetric ketone **3a** is obtained. On the other hand if the two ethyl groups have *cis*-relationship, compound **4a** has a meso configuration, in which the enantioselectivity of the first conjugate addition step is lost. The diastereoselectivity observed for the sequential conjugate addition of Et_2Zn to **2a** was in favor of the *trans*-product affording **3a** in 51% yield and with 93% ee together with product **4a** in 28% yield.

6.2.2 Tandem conjugate addition

The actual product of the addition of organozinc reagents to an α,β-unsaturated ketone is, in fact, a zinc enolate which, after acidic hydrolysis, affords the desired β-substituted compound. In the acidic quenching, H_3O^+ is the electrophiilic species that reacts with the zinc enolate generating the saturated ketone. It is possible to use a different electrophile in order to obtain, in a one-pot reaction, an α,β-disubstituted product (Scheme 6.18).

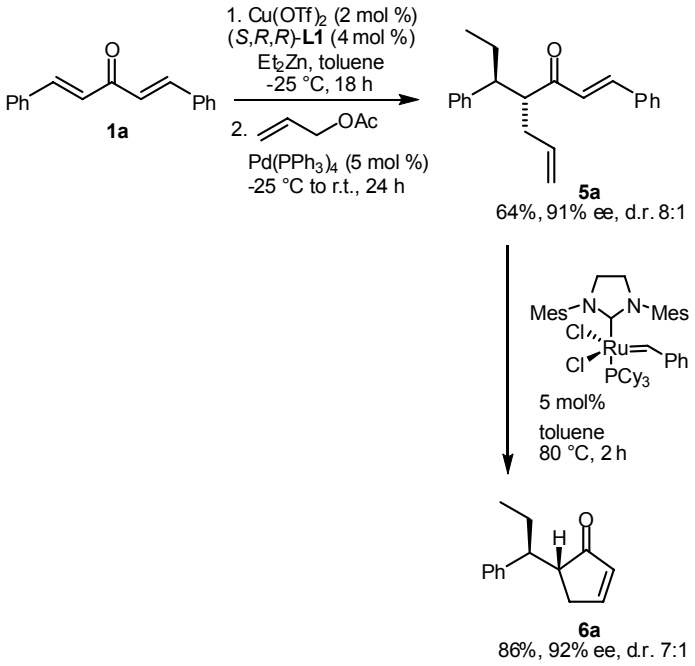
Several examples of the use of this tandem procedure have appeared in the literature.[21] In a number of cases the tandem products have been used in the synthesis of natural products.[22]



Scheme 6.18 *Tandem conjugate addition.*

Considering that the product of the Et_2Zn addition to the acyclic dienone **1a** contains a second double bond, the introduction of an allylic substituent in the α-position would provide an interesting substrate for further functionalization (Scheme 6.19). For example, a substituted cyclopentenone can be obtained by performing a ring-closing metathesis.

Accordingly, the enolate formed from Et_2Zn and dienone **1a** was trapped in a diastereoselective Pd-catalyzed allylation.[22b,c,23] The resulting product **5a** was obtained with 91% ee and 8:1 de in favor of the *trans*-compound (Scheme 6.19).



Scheme 6.19 *Tandem conjugate addition/ring-closing metathesis.*

Ring-closing metathesis (RCM) using 5 mol% of the second generation Grubbs catalyst[24] in toluene, at 80 °C, afforded the 5-substituted cyclopentenone **6a** in 86% yield and with a 7:1 diastereomeric ratio (Scheme 6.19).

6.3 Conclusions

The first enantioselective catalytic addition of organometallic reagents to acyclic dienones is reported. The catalytic system formed using $Cu(OTf)_2$ and the phosphoramidite ligand (*S*,*R*,*R*)-**L1** can be used to introduce alkyl groups such as Et, *i*-Pr and *n*-Bu in good yield and with high enantioselectivity. The introduction of a methyl substituent, a key motif in the structure of several natural products, has been accomplished via the $CuBr{\cdot}SMe_2$-catalyzed addition of MeMgBr using Josiphos as chiral ligand. The co-existence of two enone moieties in the same molecule makes these substrates prone to undergo a sequential conjugate addition, even though the diastereoselectivity observed is modest. The potential of this class of substrates in conjugate additions was demonstrated with the combination of three sequential catalytic steps comprising of a tandem conjugate addition-allylation-RCM resulting in optically active cyclopentenones. This catalytic asymmetric C-C bond formation provides alternative methods to a efficient route to cyclopentenoid natural products.

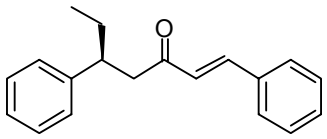
6.4 Experimental

General Methods. For general information see Chapter 2. Absolute configurations were assigned on the basis of the facial selectivity observed using the same catalysts (*S*,*R*,*R*)-**L1** with chalcone.[18]

General procedure for the copper/phosphoramidite catalyzed conjugate addition of dialkylzinc reagents to dienones.

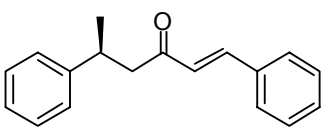
$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and ligand (*S*,*R*,*R*)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous toluene (3 mL) and stirred for 40 min at r.t. The substrate (0.50 mmol) was added to this solution and the mixture was cooled to -25 °C. A solution of a R_2Zn (0.75 mmol) was added dropwise and the reaction mixture was stirred for 18 h at -25 °C, then quenched with sat. aq. NH_4Cl and extracted with AcOEt (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography.

(*S*)-*E*-1,5-Diphenyl-hept-1-en-3-one (2a).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2a** in 73% yield as a white solid, m.p. = 78-79 °C (lit.[25] m.p. = 87 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.81 (t, *J*=7.3 Hz, 3H), 1.58-1.77 (m, 2H); 2.95 (m, 2H), 3.14 (m, 1H); 6.65 (d, *J*=16.5 Hz, 1H), 7.16-7.50 (m, 11H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 12.0, 29.2, 43.3, 48.0, 126.3, 126.5, 127.6, 128.2, 128.4, 128.9, 130.4, 134.5, 142.5, 144.5, 199.3. HRMS calc. for $C_{19}H_{20}O$ 264.1514, found 264.1516. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 7.56 min (minor), t_R 8.62 min (major). $[\alpha]_D$ = +34.0 (c 0.50, $CHCl_3$), 90% ee. Anal. calcd for $C_{19}H_{20}O$: C 86.32, H 7.63 found C 86.30, H 7.62.

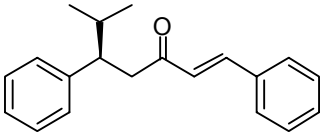
(*S*)-*E*-1,5-Diphenyl-hex-1-en-3-one (2b).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2b** as a white solid, m.p. = 66-68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.33 (d, *J*=7.0 Hz,

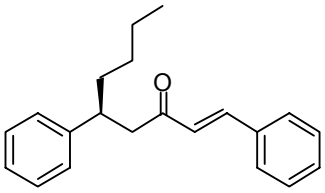
3H), 2.85-3.03 (m, 2H), 3.43 (q, *J*=7.3 Hz, 1H), 6.69 (d, *J*=16.1 Hz, 1H), 7.18-7.53 (m, 11H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 21.8, 35.8, 49.3, 126.3, 126.4, 126.8, 128.2, 128.5, 128.9, 130.4, 134.5, 142.6, 146.4, 199.1. HRMS calc. for $C_{18}H_{18}O$ 250.1358, found 250.1368. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 7.52 min (minor), t_R 8.37 min (major). $[\alpha]_D$ = +20.5 (c 0.20, $CHCl_3$), 95% ee.

(*S*)-*E*-1,5-Diphenyl-6-methyl-hept-1-en-3-one (2c).



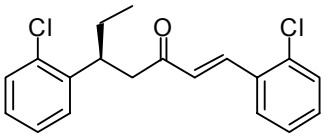
The crude product, obtained by the general procedure, was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2c** in 60% yield as a white solid, m.p. = 97-98 °C (lit.[26] m.p. = 95 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (d, *J*=6.6 Hz, 3H), 1.00 (d, *J*=6.6 Hz, 3H), 1.93 (m, 1H), 3.07 (m, 3H); 6.64 (d, *J*=16.1 Hz, 1H), 7.16-7.50 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.3, 20.9, 33.3, 45.1, 48.2, 126.2, 126.3, 128.1, 128.2, 128.3, 128.9, 130.3, 134.5, 142.2, 143.4, 226.3. HRMS calc. for $C_{20}H_{22}O$ 278.1671, found 278.1673. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 7.76 min (minor), t_R 8.66 min (major). $[\alpha]_D$ = +13.2 (c 0.50, $CHCl_3$), 73% ee.

(*S*)-*E*-1,5-Diphenyl-non-1-en-3-one (2d).



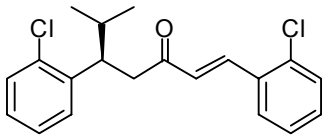
The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2d** in 61% yield as a white solid, m.p. = 89-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.83 (t, *J*=7.0 Hz, 3H), 1.10-1.31 (m, 4H), 1.62-1.71 (m, 2H), 2.94 (dd, *J*=7.0, 2.9 Hz, 2H), 3.23 (m, 1H), 6.64 (d, *J*=16.1 Hz, 1H), 7.18-7.50 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.0, 22.6, 29.7, 36.0, 41.6, 48.4, 126.3, 126.5, 127.6, 128.2, 128.4, 128.9, 130.4, 134.5, 142.5, 144.8, 199.3. Elem. anal. calcd. for $C_{21}H_{24}O$ C 86.26, H 8.27; found C 85.90, H 8.30. HRMS calc. for $C_{21}H_{24}O$ 292.1827, found 292.1819. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 6.88 min (minor), t_R 7.55 min (major). $[\alpha]_D$ = +15.7 (c 0.37, $CHCl_3$), 89% ee. Anal. calcd for $C_{21}H_{24}O$: C 86.26, H 8.27 found C 85.90, H 8.30.

(*S*)-*E*-1,5-Bis-(2-chlorophenyl)-hept-1-en-3-one (2e).



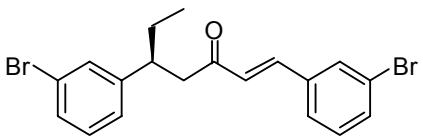
The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2e** in 76% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.84 (t, *J*=7.3 Hz, 3H), 1.77 (m, 2H), 3.00 (m, 2H),. 3.80 (m, 1H), 6.66 (d, *J*=16.1 Hz, 1H), 7.10-7.43 (m, 7H), 7.58 (m, 1H), 7.93 (d, *J*=16.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.8, 28.0, 39.0, 46.5, 127.0, 127.1, 127.4, 127.5, 127.9, 128.6, 129.7, 130.2, 131.1, 132.8, 134.3, 135.2, 138.4, 141.4, 198.6. MS (EI) calc. for $C_{19}H_{18}Cl_2O$ 332, found 332 (It was not possible to obtain an exact mass). HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 97:3, flow = 1.0 mL/min): t_R 7.22 min (minor), t_R 7.78 min (major). $[\alpha]_D$ = +35.5 (c 0.80, $CHCl_3$), 78% ee.

(*S*)-*E*-1,5-Bis-(2chlorophenyl)-6-methyl-hept-1-en-3-one (2f).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2f** in 53% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.84 (d, *J*=6.6 Hz, 3H), 1.03 (d, *J*=6.6 Hz, 3H), 2.00 (m, 1H), 3.04 (m, 2H), 3.68 (m, 1H), 6.61 (d, *J*=16.1 Hz, 1H), 7.07-7.57 (m, 8H), 7.87 (d, *J*=16.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 20.2, 20.7, 33.2, 43.9, 126.7, 127.0, 127.3, 127.5, 128.3, 128.6, 129.7, 130.1, 131.1, 132.8, 135.2, 138.2, 141.1, 198.9. MS (CI) calc. for $C_{20}H_{21}Cl_2O$ (MH^+) 347, found 347; ($M+NH4^+$) calc. 364, found 364. (It was not possible to obtain an exact mass). HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 6.59 min (minor), t_R 6.99 min (major). $[\alpha]_D$ = -6.2 (c 0.50, $CHCl_3$), 34% ee.

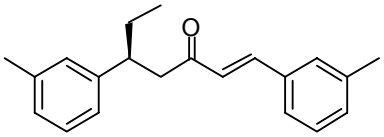
(*S*)-*E*-1,5-Bis-(3-bromophenyl)-hept-1-en-3-one (2g).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3→95:5) to give pure **2g** in 66% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.81 (t, *J*=7.3 Hz, 3H), 1.60-1.74 (m, 2H), 2.93 (d, *J*=7.0 Hz, 2H), 3.11 (m, 1H), 6.63 (d, *J*=16.1 Hz, 1H), 7.15-7.64 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.0, 29.1, 42.8, 47.9,

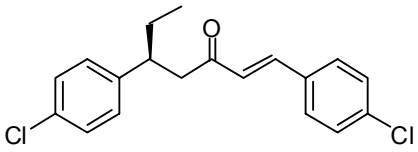
123.0, 126.5, 126.9, 127.3, 127.9, 129.5, 130.0, 130.4, 130.5, 130.8, 133.2, 136.5, 140.8, 146.9, 198.2. HRMS calc. for $C_{19}H_{18}Br_2O$ 419.9724, found 419.9755. HPLC on Chiralcel OD column (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): t_R 23.0 min (minor), t_R 26.0 min (major). $[\alpha]_D$ = +3.1 (c 0.32, $CHCl_3$), 90% ee.

(*S*)-*E*-1,5-Bis-(3-methylphenyl)-hept-1-en-3-one (2h).



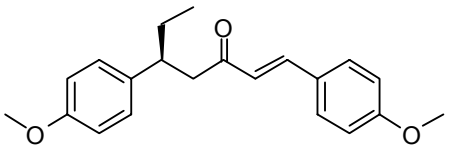
The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3→95:5) to give pure **2h** in 69% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (t, *J*=7.3 Hz, 3H), 1.59-1.77 (m, 2H), 2.33 (s, 3H), 2.36 (s, 3H), 2.93 (d, *J*=7.0 Hz, 2H), 3.11 (m, 1H), 6.64 (d, *J*=16.5 Hz, 1H), 6.99-7.30 (m, 8H), 7.44 (d, *J*=16.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.1, 21.3, 21.5, 29.1, 43.2, 48.0, 124.6, 125.4, 126.3, 127.0, 128.2, 128.4, 128.7, 128.8, 131.2, 134.4, 137.8, 138.5, 142.6, 144.5, 199.4. HRMS calc. for $C_{21}H_{24}O$ 292.1827, found 292.1823. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 98:2, flow = 1.0 mL/min): t_R 7.50 min (minor), t_R 7.98 min (major). $[\alpha]_D$ = +31.3 (c 0.61, $CHCl_3$), 88% ee.

(*S*)-*E*-1,5-Bis-(4-chlorophenyl)-hept-1-en-3-one (2i).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2i** in 71% yield as a white solid, m.p. = 76-77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (t, *J*=7.3 Hz, 3H), 1.54-1.77 (m, 2H), 2.92 (d, *J*=7.3 Hz, 2H), 3.13 (m, 1H), 6.60 (d, *J*=16.1 Hz, 1H), 7.14 (d, *J*=8.1 Hz, 2H), 7.24-7.43 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 12.0, 29.2, 42.5, 48.0, 126.6, 128.5, 129.0, 129.2, 129.4, 131.9, 132.9, 136.4, 141.1, 142.9, 198.5. Elem. anal. calcd. for $C_{19}H_{18}Cl_2O$ C 68.48, H 5.44; found C 68.40, H 5.52. HRMS calc. for $C_{19}H_{18}Cl_2O$ 332.0735, found 332.0729. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): t_R 9.94 min (minor), t_R 13.71 min (major). $[\alpha]_D$ = +33.9 (c 0.75, $CHCl_3$), 95% ee. Anal. calcd for $C_{19}H_{18}Cl_2O$: C 68.48, H 5.44 found C 68.40, H 5.51.

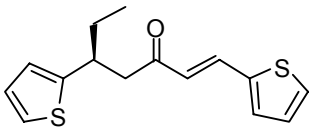
(*S*)-*E*-1,5-Bis-(4-methoxyphenyl)-hept-1-en-3-one (2j).



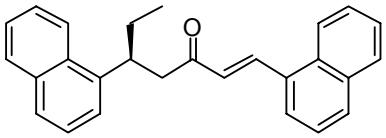
The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 95:5→80:20) to give pure **2j** in 59% yield as a white solid, m.p. = 84-86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.79 (t, *J*=7.3 Hz, 3H), 1.56-1.76 (m, 2H), 2.89 (d, *J*=7.0 Hz, 2H), 3.09 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 6.53 (d, *J*=16.1 Hz, 1H), 6.83 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 7.13 (d, *J*=8.4 Hz, 2H), 7.42 (d, *J*=16.5 Hz, 1H), 7.44 (d, *J*=8.8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 12.0, 29.3, 42.6, 48.1, 55.1, 55.3, 113.7, 114.3, 124.3, 127.1, 128.5, 129.9, 136.6, 142.2, 157.9, 161.5, 199.4. HRMS calc. for $C_{21}H_{24}O_3$ 324.1725, found 324.1724. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 92:8, flow = 1.0 mL/min): t_R 12.26 min (minor), t_R 16.46 min (major). $[\alpha]_D$ = +17.6 (c 0.50, $CHCl_3$), 94% ee. Anal. calcd for $C_{21}H_{24}O_3$: C 77.75, H 7.46 found C 77.44, H 7.43.

(*S*)-*E*-1,5-Dithiophene-2-yl-hept-1-en-3-one (2k).

The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3→95:5) to give pure **2k** in 48% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (t, *J*=7.3 Hz, 3H), 1.62-1.82 (m, 2H), 2.94 (m, 2H), 3.51 (m, 1H), 6.49 (d, *J*=15.7 Hz, 1H), 6.83-7.07 (m, 3H), 7.13 (d, *J*=5.1 Hz, 1H), 7.27 (m, 1H), 7.39 (d, *J*=4.8 Hz, 1H), 7.62 (d, *J*=15.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 11.9, 30.3, 38.5, 48.7, 122.9, 124.1, 125.0, 126.5, 128.2, 128.8, 131.7, 135.1, 139.8, 148.4, 198.1. HRMS calc. for $C_{15}H_{16}OS_2$ 276.0643, found 276.0659. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 8.16 min (minor), t_R 9.32 min (major). $[\alpha]_D$ = +5.6 (c 0.61, $CHCl_3$), 87% ee.

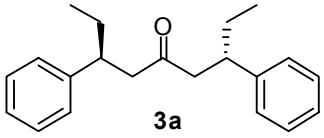


(*S*)-*E*-1,5-Dinaphthalene-1-yl-hept-1-en-3-one (2l).

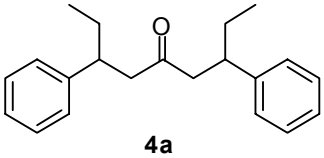


The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3→95:5) to give pure **2l** in 53% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.90 (t, *J*=7.3 Hz, 3H), 1.97 (m, 2H), 3.18 (d, *J*=6.6 Hz, 2H), 4.23 (m, 1H), 6.77 (d, *J*=15.8 Hz, 1H), 7.43-8.34 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.0, 28.7, 48.0, 123.2, 123.3, 125.0, 125.35, 125.41, 126.0, 126.2, 126.75, 126.8, 128.7, 128.8, 128.9, 130.6, 131.5, 131.8, 132.0, 133.6, 134.0, 139.3, 140.7, 199.1. HRMS calc. for $C_{27}H_{24}O$ 364.1827, found 364.1831. HPLC on Chiralcel OD column (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): t_R 23.19 min (minor), t_R 26.30 min (major). $[\alpha]_D$ = +90.6 (c 0.88, $CHCl_3$), 93% ee.

(*S*,*S*)-3,7-Diphenyl-nonan-5-one (3a/4a).



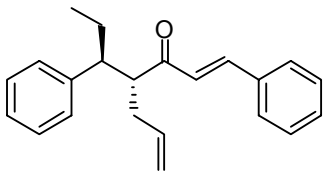
3a



4a

The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 98:2) to give pure **3** (the diastereoisomers could not be separated) in 51% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (signals for the *meso* compound **4a** are in italic) δ = 0.71 (t, *J*=7.3 Hz, 6H), *0.73* (t, *J*=7.3 Hz), 1.45-1.57 (m, 4H), 2.48-2.66 (m, 4H), 2.97 (m, 2H), 7.09-7.30 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.9, *11.91*, 29.1, *42.55*, 42.6, *50.2*, 50.4, 126.2, *127.46*, 127.5, 128.3, 144.4, 209.0. HRMS calc. for $C_{21}H_{26}O$ 294.1984, found 294.1987. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): t_R 6.01 min (minor), t_R 6.72 min (meso), 8.53 min (major). $[\alpha]_D$ = -40.1 (c 0.85, $CHCl_3$), 93% ee, **3a**/**4a** = 72:28.

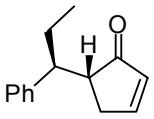
(*4R*,*5S*)-1-Phenyl-4-(1-phenylpropyl)-*n*-heptane-1,6-dien-3-one (5a).



$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and (*S*,*R*,*R*)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous toluene (3 mL) and stirred 40 min at r.t. Dibenzylideneacetone (117 mg, 0.50 mmol)

was added and the resulting yellow solution was cooled to -25 °C. Et_2Zn (1.1M in toluene, 0.68 mL, 0.75 mmol) was added and the reaction mixture was stirred for 18 h at -25°C. Subsequently a solution of $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) and allyl acetate (0.16 mL, 150 mg, 1.5 mmol) in toluene (3 mL), was added and the mixture was stirred for 24 h allowing the temperature to rise gradually to r.t. The reaction mixture was treated with sat. aq. NH_4Cl solution and extracted with AcOEt (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (*n*-heptane/AcOEt=98:2) to give pure **5a** in 64% yield as a slightly yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 0.65 (t, *J*=7.3 Hz, 3H), 1.52-1.69 (m, 2H), 2.00 (m, 1H), 2.21 (m, 1H), 2.82 (dt, *J*=10.6, 3.7 Hz, 1H), 3.17 (dt, *J*=10.3, 4.0 Hz, 1H), 4.85 (m, 2H), 5.58 (m, 1H), 6.85 (d, *J*=16.1 Hz, 1H), 7.12-7.65 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.2, 27.4, 35.7, 50.1, 56.2, 116.6, 126.5, 126.6, 128.2, 128.4, 128.7, 128.9, 130.5, 134.6, 135.3, 142.3, 142.7, 203.3. HRMS calc. for $C_{22}H_{24}O$ 304.1827, found 304.1833. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 98:2, flow = 1.0 mL/min): t_R 7.37 min (major), t_R 8.03 min (minor), 8.80 min (minor diastereoisomer). $[\alpha]_D$ = +24.7 (c 0.76, $CHCl_3$), 91% ee, d.r. 8:1.

(*5R,1'S*)-5-(1-Phenylpropyl)-cyclopent-2-enone (6a).

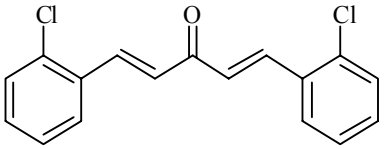


Grubbs 2nd gen. catalyst[24] (17 mg, 0.020 mmol) was dissolved in toluene (5 mL) and to this solution the diene **5a** (122 mg, 0.40 mmol) in toluene (5 mL) was added. The resulting red-brown solution was stirred for 2 h at 80 °C. After cooling, the solvent was evaporated and the residue was purified by flash chromatography (*n*-heptane/AcOEt = 95:5) to afford 69 mg (86%) of pure **6a** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) (signals for the minor diastereoisomer are in italic) δ = *0.79* (t, *J*=7.3 Hz), 0.85 (t, *J*=7.3 Hz, 3H), 1.81 (m, 1H), 2.02 (m, 1H), 2.39 (m, 1H), 2.63 (m, 2H), 3.05 (m, 1H), *3.15* (m), 6.00 (m, 1H), *6.17* (m), 7.12-7.28 (m, 5H), 7.46 (m, 1H), *7.64* (m). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.1, *12.4*, *22.7*, 26.1, *32.1*, 32.5, 47.4, 49.3, *50.9*, 126.4, 128.0, 128.1, *128.4*, 128.6, 134.1, *134.6*, *141.2*, 163.6, *163.9*, 211.6. HRMS calc. for $C_{14}H_{16}O$ 200.1201, found 200.1210. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 99.5:0.5, flow = 1.0 mL/min): t_R 11.25 min (minor), t_R 13.90 min (major), 16.61 min (minor diastereoisomer). $[\alpha]_D$ = -127.7 (c 0.73, $CHCl_3$), 92% ee, d.r. 7:1.

Synthesis of the starting materials 1b-h

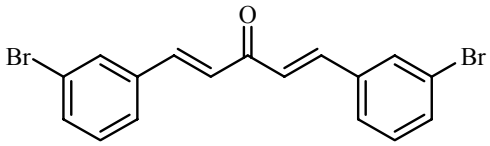
Dienone substrates were prepared by condensation of 2 moles of aldehyde with 1 mole of acetone in an aq. NaOH/EtOH solution according to known procedures.[27] The resulting products were recrystallized from AcOEt to obtain pure *trans,trans*-dienones.

1,5-Bis-(2-chlorophenyl)-pentane-1,4-dien-3-one (1b)[28]



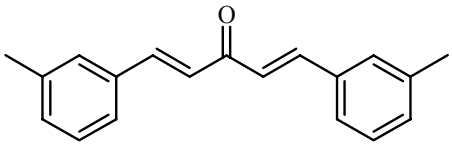
M.p. = 117-118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J*=16.1 Hz, 2H), 7.30-7.47 (m, 6H), 7.73 (m, 2H), 8.15 (d, *J*=15.7 Hz, 2H).

1,5-Bis-(3-bromophenyl)-pentane-1,4-dien-3-one (1c)[29]



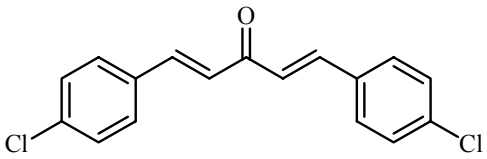
M.p. = 133-134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J*=16.1 Hz, 2H), 7.30 (m, 2H), 7.53 (m, 4H), 7.65 (d, *J*=16.0 Hz, 2H), 7.77 (m, 2H).

1,5-Bis-(3-methylphenyl)-pentane-1,4-dien-3-one (1d)[30]



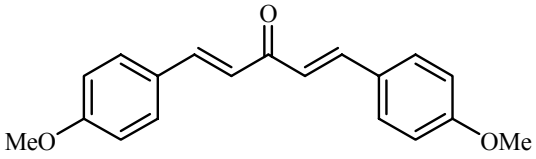
M.p. = 75-76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 6H), 7.08 (d, *J*=15.8 Hz, 2H), 7.27 (m, 4H), 7.43 (m, 4H), 7.72 (d, J=16.1 Hz, 2H).

1,5-Bis-(4-chlorophenyl)-pentane-1,4-dien-3-one (1e)[31]



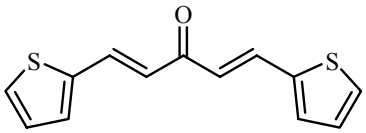
M.p. = 192-193 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J*=16.1 Hz, 2H), 7.39 (d, *J*=7.0 Hz, 4H), 7.55 (d, *J*=7.0 Hz, 4H), 7.68 (d, *J*=15.7 Hz, 2H).

1,5-Bis-(4-methoxyphenyl)-pentane-1,4-dien-3-one (1f)[27a]



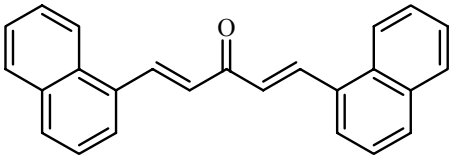
M.p. = 128-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 6H), 6.93 (d, J=8.8 Hz, 4H), 6.96 (d, J=15.7 Hz, 2H), 7.57 (d, J=8.4 Hz, 4H), 7.70 (d, J=15.7 Hz, 2H).

1,5-Bis-(2-thienyl)-pentane-1,4-dien-3-one (1g)[27a]



M.p. = 119-120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J*=15.4 Hz, 2H), 7.08 (m, 2H), 7.34 (m, 2H), 7.42 (m, 2H), 7.85 (d, *J*=15.4 Hz, 2H).

1,5-Bis-(1-naphthyl)-pentane-1,4-dien-3-one (1h)[32]



M.p. = 134-135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J*=15.8 Hz, 2H), 7.57 (m, 6H), 7.92 (m, 6H), 8.29 (m, 2H), 8.66 (d, *J*=15.4 Hz, 2H).

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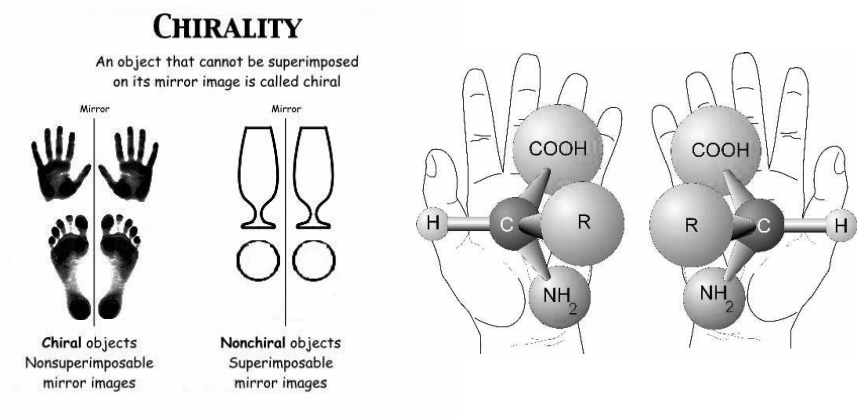
Samenvatting

Chiraliteit is een eigenschap van een object dat op geen enkele manier door draaien omgezet kan worden in zijn spiegelbeeldvorm. De term chiraliteit komt van het Griekse woord $\chi\varepsilon\iota\rho$ (cheir), dat hand betekent. Handen zijn waarschijnlijk het meest algemene voorbeeld van een chiraal object. De linkerhand en de rechtshand zijn spiegelbeelden van elkaar maar ze kunnen niet gedraaid worden dat ze samenvallen. Dit wordt verduidelijkt als een linker handschoen aan de rechter hand wordt geprobeerd te dragen en vice versa. Een chiraal object en zijn spiegelbeeld worden enantiomorphs genoemd of enantiomeren, als het moleculen betreft.



Chirale systemen omringen ons in het alledaagse leven. Schoenen, oren, voeten, schelpen, schroeven, wenteltrappen etc. maar ook moleculen zoals DNA, enzymen, aminozuren en suikers. Het is wel bekend, bij voorbeeld, dat levende wezens aminozuren en suikers nodig hebben om te groeien en leven. Misschien minder bekend is dat alleen een van de enantiomere vormen van deze voedingsstoffen gemetaboliseerd kan worden door het menselijk lichaam. Normaal gesproken, speelt de chiraliteit van een bepaald molecuul een belangrijke rol in biologische systemen. De tegenoverstaande enantiomeren kunnen op een totaal verschillende manier interacties aangaan met enzymen en chirale receptoren zodat ze een verschillende biologische uitwerking hebben. De werkingen die velen chirale geneesmiddelen uitoefenen zijn afhankelijk van de enantiomeer die gebruikt wordt. *Thalidomide* is een geneesmiddel dat eind jaren vijftig als slaapmiddel en als middel tegen ochtendmisselijkheid op de markt werd gebracht. *Thalidomide* werd verkocht

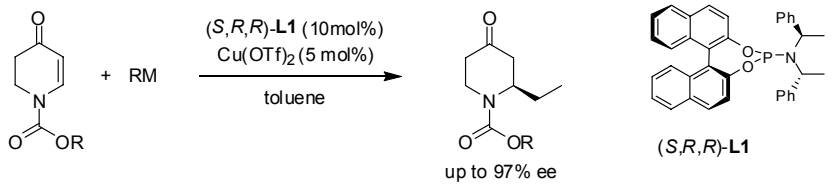
als racemische mengsel (1:1 mengsel van beide enantiomeren). Na een aantal jaren bleek dat het bij baby's ernstige aangeboren afwijkingen veroorzaakte als de moeder het gedurende een bepaalde periode van de zwangerschap had gebruikt. Het is aangenomen dat terwijl één enantiomeer de gewenste werking heeft, het andere een teratogeen effect vertoonde. Ongeveer 12000 baby's werden geboren met schade veroorzaakt door thalidomide. Slechts 5000 van deze baby's bereikten de puberteit. Andere voorbeelden zijn het *ethambutol*, waarbij één enantiomeer gebruikt wordt tegen tuberculose terwijl het andere blindheid veroorzaakt en *naproxen*, waarbij één enantiomeer artritische pijn kan verhelpen en de andere verantwoordelijk is voor lever vergiftiging. Het komt uit deze voorbeelden voort dat het controleren van stereochemie een belangrijk punt is voor farmaceutische en voedings industrie. De noodzaak om producten als één bepaalde enantiomeer te verkrijgen heeft een groeiend belang aan de asymmetrische synthese van chirale moleculen teweeggebracht. In dit proefschrift wordt de synthese van chirale moleculen door asymmetrische katalyse beschreven. In deze methode wordt een chirale katalysator gebruikt om één enantiomeer selectief te produceren. In het algemeen is een katalysator een stof die kan meereageren in een bepaalde reactie om de activerings energie, die nodig is om de reagentia in de producten te transformeren, omlaag te brengen. Aan het eind van de reactie, komt de katalysator weer terug in zijn oorspronkelijke vorm en kan opnieuw een reactie aangaan. Een lagere activerings energie betekent een snellere reactie in vergelijking met de situatie waarin de katalysator niet gebruikt wordt. Een chirale katalysator kan de snelheid van de productie van enantiomeren op verschillende manieren beïnvloeden. Als dit verschil in de snelheid substantieel is, zou een bepaald enantiomer selectief gevormd worden.

Het voornaamste doel van het onderzoek beschreven in dit proefschrift is de ontwikkeling van nieuwe strategieën voor de asymmetrische synthese van veelzijdige verbindingen door het gebruik van katalysatoren gebaseerd op koper en chirale fosforamidiet liganden. Met name, draait dit onderzoek om de enantioselectieve vorming van C-C bindingen door de additie van organometallische reagentia zoals organozink en trimethylaluminium.

Hoofdstuk 1: De meest belangrijke toepassingen van de koper-gekatalyseerde asymmetrische geconjugeerde additie in synthese in de laatste

jaren werden gepresenteerd. Het resultaat van mechanistische onderzoeken over dit onderwerp werd ook beschreven.

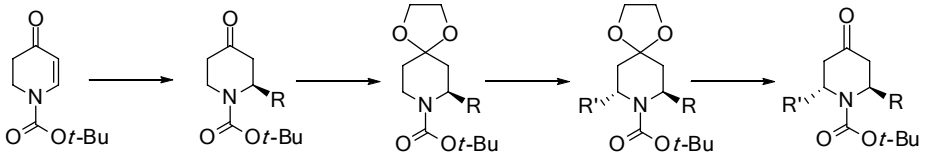
Hoofdstuk 2: De eerste zeer efficiënte katalytische enantioselectieve additie van organozink reagentia en trimethylaluminium aan *N*-beschermde-2,3-dehydro-4-piperidonen werd beschreven. Met deze methode kunnen optisch actieve *N*-beschermde-2-alkyl-4-piperidonen gemaakt worden. Deze producten zijn belangrijke bouwstenen voor de synthese van piperidine alkaloïden.



Schema 1 *Koper-gekatalyseerde geconjugeerde additie van organometallische reagentia aan N-beschermde-2,3-dehydro-4-piperidonen met chirale fosforamidiet liganden.*

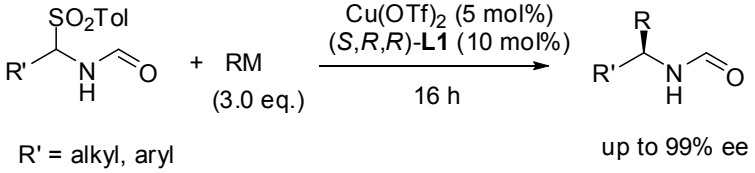
Het directe product van de additie van Et_2Zn aan het substraat is een zink enolaat dat met een “one-pot” palladium-gekatalyseerde allylatie gevangen kan worden om *trans* 2,3-gesubstitueerde-4-piperidonen selectief te vormen.

Hoofdstuk 3: Verschillende methoden voor de synthese van 2,6-gesubstitueerde-piperidonen worden bestudeerd. De geconjugeerde additie van organometallische reagentia aan *N*-beschermde-pyridonen en *N*-acyliminium ionen wordt beschreven. Het gebruik van methoden gebaseerd op α-methoxylatie of IBX oxidatie wordt ook behandeld. De beste methode voor de synthese van *trans* 2,6-gesubstitueerde-piperidonen bleek de lithiatie/substitutie reactie. Dit protocol werd gebruikt om de alkaloïde (+)-myrtine te synthetiseren.



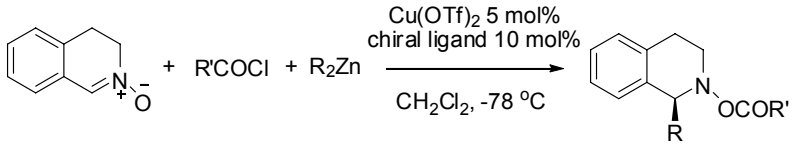
Schema 2 *Asymmetrische geconjugeerde additie / lithiatie / substitutie sequentie.*

Hoofdstuk 4: De koper/fosforamidieten gekatalyseerde additie van organozink reagentia en trimethylaluminium aan *N*-acylimines, *in situ* gevormd uit aromatische en alifatische α-amidosulfonen, levert de gewenste α-alkylamides in hoge opbrengst en een enantioselectiviteit tot 99%. Het chirale fosforamidiet ligand bleek tijdens de reactie gemodificeerd te worden. De oorzaak en het mogelijke gevolg van deze transformatie werden bestudeerd.



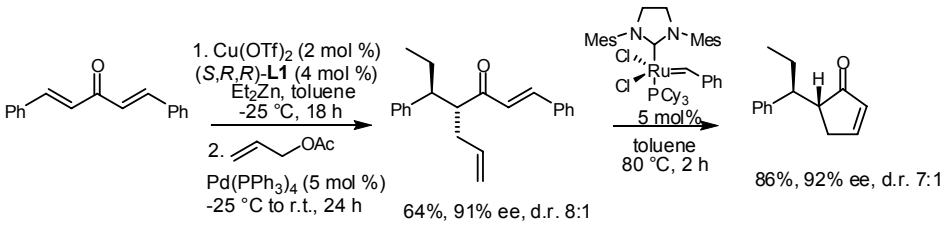
Schema 3 *Koper-gekatalyseerde geconjugeerde additie van organometallische reagentia aan α-amidosulfonen met chirale fosforamidiet liganden.*

Hoofdstuk 5: De eerste gekatalyseerde additie van Et_2Zn aan *N*-acyloxyiminium ionen, *in situ* gevormd uit de overeenkomstige *N*-oxides met een acyl chloride, is beschreven. De invloed op de opbrengst en de enantioselectiviteit van de producten door variatie van de reactie parameters werden in detail geanalyseerd. Door optimalisering van de reactie condities werden enantioselectiviteiten tot 55% verkregen.



Schema 4 *Asymmetrische additie van organozink reagentia aan N-acyloxyiminium ionen, in situ gevormd uit 3,4-dihydroisoquinoline N-oxide.*

Hoofdstuk 6: De enantioselectieve koper/fosforamidieten gekatalyseerde additie van organozink reagentia en trimethylaluminium aan acyclische dienonen is behandeld. De katalysator gevormd uit $Cu(OTf)_2$ en het chirale fosforamidiet ligand (*S*,*R*,*R*)-**L1** kan gebruikt worden om alkyl groepen zoals Et, *i*-Pr en *n*-Bu te introduceren in hoge opbrengst en met een enantioselectiviteit tot 95%.

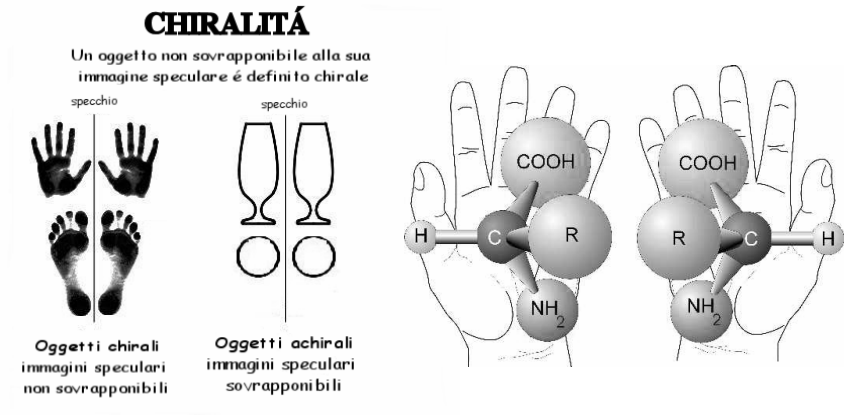


Schema 5 *Tandem geconjugeerde additie / ring-sluitende metathese.*

De mogelijkheden die deze substraten bieden worden gedemonstreerd door de combinatie van drie sequentiële katalytische reacties: geconjugeerde additie, allylatie en ring-sluitende methatese. Optische actieve cyclopentenonen zijn op deze manier verkregen.

Discussione generale

Il termine chiralità indica quella proprietà per cui un oggetto e la sua immagine speculare non sono sovrapponibili. L'etimologia della parola fornisce una piú chiara esemplificazione del suo significato. Di derivazione greca ($\chi\varepsilon\iota\rho$, cheir), il termine chiralità vuol dire "proprio della mano", forse il più comune esempio di oggetto chirale. Guardando le proprie mani ci si rende immediatamente conto che esse sono in relazione speculare l'una con l'altra. Non è possibile, tuttavia, disporle in alcun modo in cui esse si sovrappongano. Questo concetto diviene estremamente chiaro quando si prova ad infilare la mano destra in un guanto sinistro e viceversa. Un matematico definirebbe la chiralità come una proprietà pseudoscalare che resta invariata con un'operazione di simmetria del primo ordine e cambia segno con un'operazione di simmetria del secondo ordine. Un oggetto e la sua immagine speculare non sovrapponibile vengono chiamati enantiomorfi. Quando ci si riferisce a molecole chirali, si parla di enantiomeri.



Sistemi chirali fanno parte della vita di ogni giorno. Basti pensare non solo alle mani e ai guanti ma anche ai piedi, alle scarpe, alle orecchie, alle viti, a certe conchiglie, persino alle scale a chiocciola. A livello molecolare, esempi di sistemi chirali sono il DNA, gli enzimi, gli amminoacidi, gli zuccheri. È comunemente noto che la crescita e la sopravvivenza degli organismi viventi di origine animale sono garantite dall'assunzione di amminoacidi (i costituenti di base delle proteine) e zuccheri attraverso la dieta. Meno noto è che tali organismi sono in grado di metabolizzare esclusivamente uno degli enantiomeri. Non a caso, in natura sia gli amminoacidi che gli zuccheri esistono in una sola forma enantiomerica. Il motivo per cui la natura abbia

scelto di creare i costituenti base della vita sulla Terra in una sola forma enantiomerica e il modo in cui tale *homochiralità* si sia sviluppata sono tuttora fonte di dibattito. Sono state proposte diverse teorie accomunate dalla necessità di chiarificare il meccanismo primordiale in grado di discriminare tra le entità molecolari e le rispettive immagini speculari. La fonte di tale asimmetria potrebbe essere ricondotta a fonti extraterrestri di *homochiralità* (luce polarizzata circolarmente proveniente da stelle) o alla cosiddetta *forza nucleare debole*, l'unica delle quattro interazioni fondamentali della natura a violare la simmetria di parità e di carica. Un filosofo potrebbe forse speculare sull'idea di un *Dio* chirale.

Ciò che è noto a livello fenomenologico è che nei sistemi viventi le proprietà chirali di una molecola giocano un ruolo di fondamentale importanza. I possibili enantiomeri di una stessa molecola possono interagire in modo diverso con gli enzimi e i recettori presenti, ad esempio, nel corpo umano determinando una risposta totalmente differente. Un esempio tristemente noto è rappresentato dalla *talidomide*, il principio attivo di un rimedio somministrato a donne incinte contro la nausea mattutina, dal 1957 al 1961, in 40 diverse nazioni. La *talidomide* può esistere in due forme enantiomeriche, di cui la prima agisce contro i sintomi della nausea mentre la seconda ha effetto teratogeno (sostanza in grado di modificare o alterare il normale sviluppo del feto). A causa della somministrazione del principio attivo come miscela dei due enantiomeri, si calcola che un numero di bambini compreso tra 8000 e 12000 siano nati con gravi malformazioni. Di questi circa 5000 sono sopravvissuti oltre l'infanzia. Altri esempi importanti sono rappresentati dall'*etambutolo*, in cui un enantiomero è usato nel trattamento della tubercolosi mentre l'altro causa cecità e dal *naproxen*, in cui una forma enantiomerica ha effetto analgesico e la sua immagine speculare presenta tossicità epatica. Risulta chiaro, da quanto detto, che il controllo della *stereochimica* di molecole chirali è un punto di centrale importanza per le industrie alimentari e farmaceutiche. La necessità di ottenere prodotti *enantio-puri* ha determinato un crescente interesse scientifico verso la sintesi asimmetrica. Tra i metodi a disposizione, particolare attenzione è stata rivolta alla catalisi asimmetrica, in cui un catalizzatore chirale è usato per ottenere preferibilmente solo uno dei possibili enantiomeri del prodotto finale. In generale, un catalizzatore è definito come una sostanza in grado di interagire con i reagenti di una reazione in modo tale da abbassare l'energia di attivazione necessaria perché tali reagenti evolvano nel prodotto finale. Una

minore energia di attivazione risulta in una maggiore velocità del processo catalizzato rispetto alla stessa trasformazione eseguita in assenza del catalizzatore. Introducendo una fonte di chiralità nel catalizzatore, tale sostanza è in grado di influenzare in modo diverso la velocità dei processi che portano alla formazione dei diversi enantiomeri. Quando la differenza nella velocità di tali processi è sufficientemente elevata, la formazione di un enantiomero (processo più veloce) sarà favorita rispetto all'altro (processo più lento).

Il tema intorno al quale il presente lavoro di tesi è incentrato riguarda lo studio e lo sviluppo di nuove procedure di catalisi asimmetrica basate sull'utilizzo di un catalizzatore chirale formato da un opportuno sale di rame coordinato a dei leganti chirali. La struttura del legante chirale dimostratosi più efficace nel corso di questa ricerca è delucidata in Fig. 1.

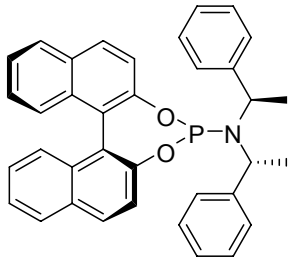


Figura 1 *Phosphoramidita chirale utilizzato come legante in complessi di rame.*

Acknowledgment

It's been four years since the day that, frightened and excited at the same time, I took a plane with destination Holland. I took that plane together with my brother Augusto and my mum. They helped me to carry around 40 Kg of suitcases filled with the warmest pieces of clothing, especially bought to survive to the cold northern climate. Well, it's true. The weather in this country can be very cold, but it is nothing compared to the warmth that I found in the people I have met here in Groningen. By chance, the first person I have met was an other Italian lady. France, you welcomed me in the nicest way offering me your friendship and your spacious room for my dinners. At least you were always invited. I really enjoyed to live in the house of Nieuwe Blekerstraat with you and Marco. I also want to thank you, Marco, for letting me take care of Bengiamino, the only green thing I could ever keep alive. Of course I have not met only Italians in Holland but a lot of people coming from everywhere in the world. Meeting so many new friends and getting to know their cultures opened my mind and enriched me so much. Of course, all of this would not have been possible if my promoters, Ben Feringa and Adri Minnaard, had not welcomed me in this amazing group. I am honored I had the possibility to work with you and to learn from you. You have been great and inspiring mentors. In the same way I would like to thank Prof. Rosini, supervisor of my undergraduate research and member of the reading committee, for the guidance and the support to undertake this career. I would also like to acknowledge Prof. Engberts and Prof. de Vries, members of the reading committee as well, for the careful examination of the manuscript.

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A special thought goes to two special girls: Syuzi and Natalie. I would like to find a fancy way to tell you how much I care, but it is difficult without it sounding forced. Therefore, I will keep it as simple and real as possible. I very much love you and I hope we will keep on being friends even now that we live in different countries.

Toon, going through these four years has been amazing, having the possibility to spend them with you has made it perfect. Ik wou ook graag jouw familie bedanken, Rosa, Ida, Wouter, Marleen, Anne en Toon, omdat ze me zo warm hebben ontvangen.

A questo punto è certo arrivato il momento di scrivere nella mia lingua. Tutto questo lavoro non sarebbe completo senza donare il pensiero più speciale alla mia famiglia che, sicuramente, è al primo posto nel mio cuore.

Alla mia mamma e al mio babbo vorrei dire che anche se la lontananza ci separa voi siete sempre con me; ed il motivo è che siete parte di quello che sono e di ogni mia reale decisione. Spero di rendervi sempre orgogliosi come io lo sono di voi.

Augusto, la tua approvazione mi da la forza di affrontare tutto il resto del mondo. Sei la persona migliore che conosca e, per sempre, il mio fratellone.

Un ultimo pensiero va su in cielo, cercando di raggiungere un’anima dolce che la più pura semplicità, in vita, mi ha mostrato. Ciao, nonna.