Enantioselective copper-catalysed addition of organometallic reagents using phosphoramidite ligands

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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.

Part of this chapter has been published:

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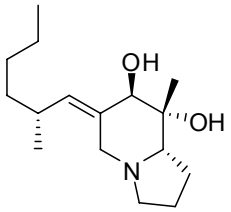
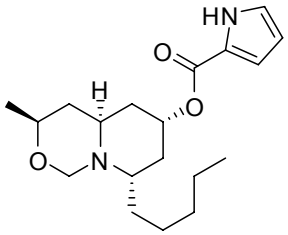
2.1 Introduction

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]

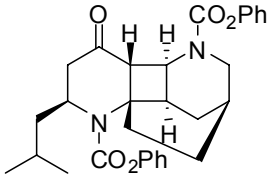
Amongst piperidine derivatives, optically active α-substituted 4-piperidones play a key role as versatile building blocks for the synthesis of alkaloids (Scheme 2.1).



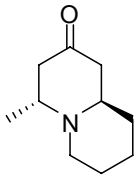
(+)-Allopumiliotoxin 267A



(+)-Hyperaspine



intermediate in the synthesis of Spirolucidine

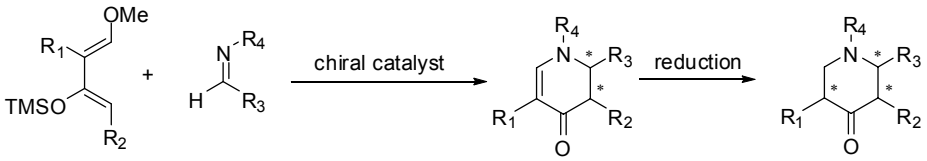


(+)-myrtine

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

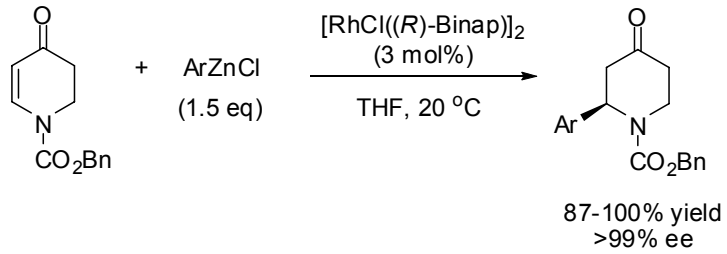
chiral α-substituted 2,3-dehydropiperidones.[3] Reduction of the olefin moiety is required to yield the desired product.[4]



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

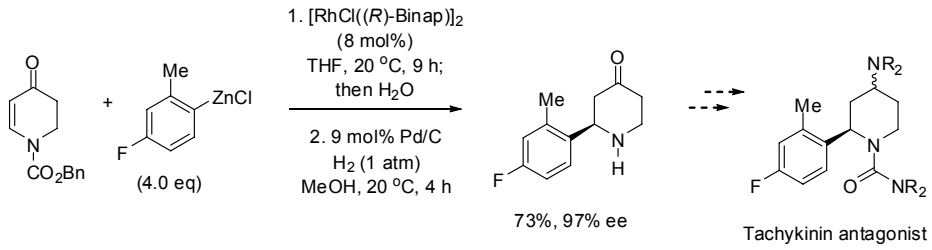
A powerful tool in the synthesis of α-substituted 4-piperidones consists of the conjugate addition of organometallic reagents to *N*-protected-2,3-dehydro-4-piperidones, however, only two examples of the catalytic enantioselective version of this reaction have been described thus far.[5,6]

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]

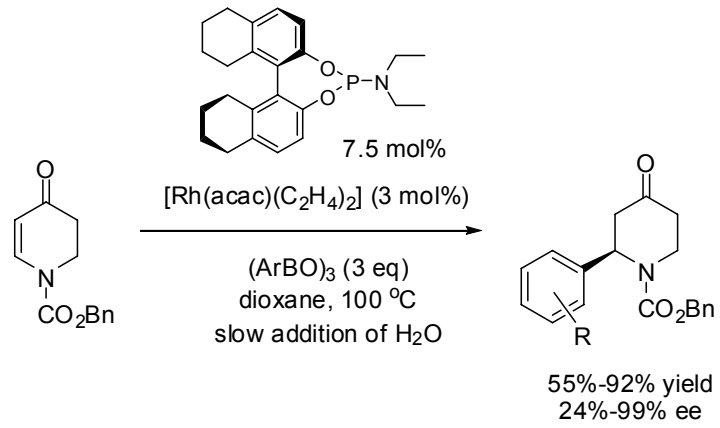
Using a rhodium catalyst containing (*R*)-Binap as the chiral ligand, 2-aryl-4-piperidones were obtained in high yield and with complete stereocontrol. The method described has been applied to the preparation of an intermediate in the synthesis of a Tachykinin antagonist employed in the treatment of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

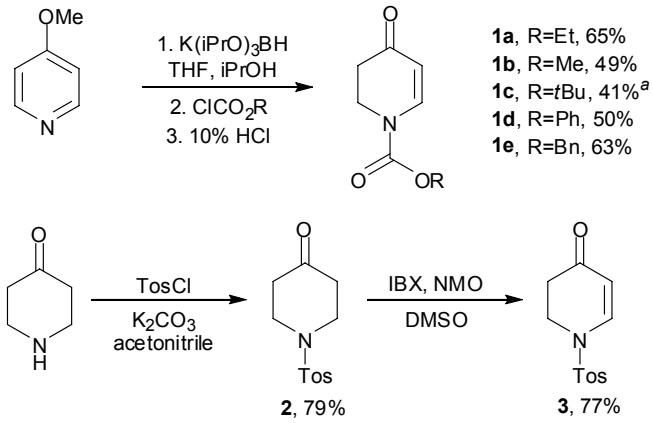
In this procedure the arylboronic acid is gradually generated *in situ* by slow hydrolysis of the corresponding arylboroxine. The use of three equivalents of the arylboroxine is required to reach full conversion.

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.

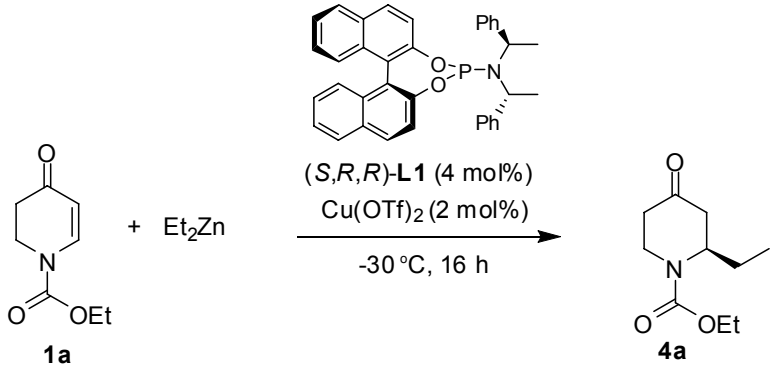
Scheme 2.6 *Synthesis of the precursors used in this chapter.*

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.*

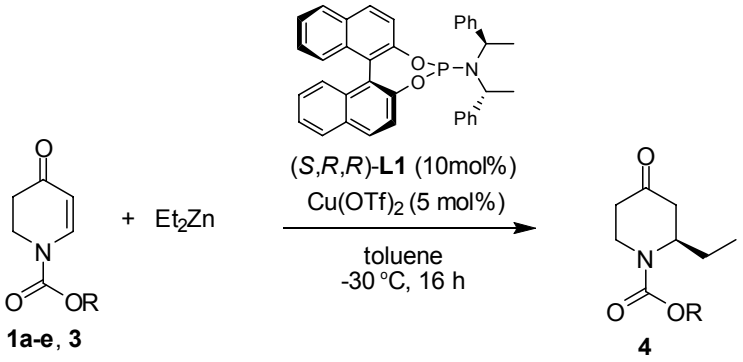


1a **4a**

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.*

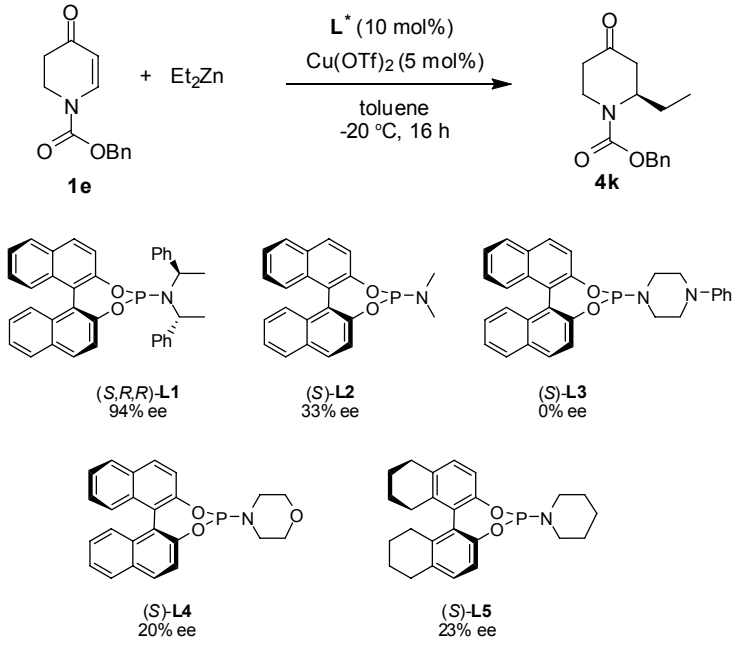


Entry	Substrate	R	Time (h)	Temp. (°C)	Product	Yield (%)	ee (%)
1	**1a**	Et	16	-25	**4a**	35	94
2	**1a**	Et	16	-25	**4a**	50[a]	92
3	**1b**	Me	40	-25	**4d**	20	87
4	**1c**	*t*-Bu	24	-20	**4f**	58	91
5	**1d**	Ph	16	-25	**4g**	87	94
6	**1e**	Bn	8	0	**4k**	69	91
7	**1e**	Bn	28	-20	**4k**	70	94
8	**3**	Tos[b]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

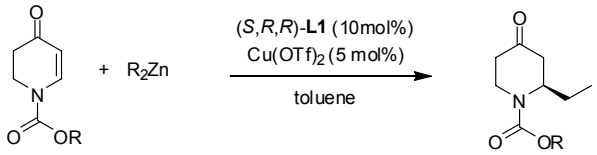
2.2.2 Scope of the reaction

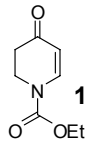
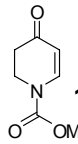
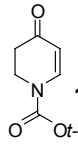
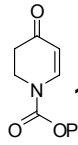
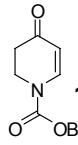
Using the copper catalyst formed from 5 mol% of $Cu(OTf)_2$ and 10 mol% of the chiral phosphoramidite ligand (*S*,*R*,*R*)-**L1** in toluene, the scope of the reaction regarding the use of other dialkylzinc reagents was investigated (Table 2.3).

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.

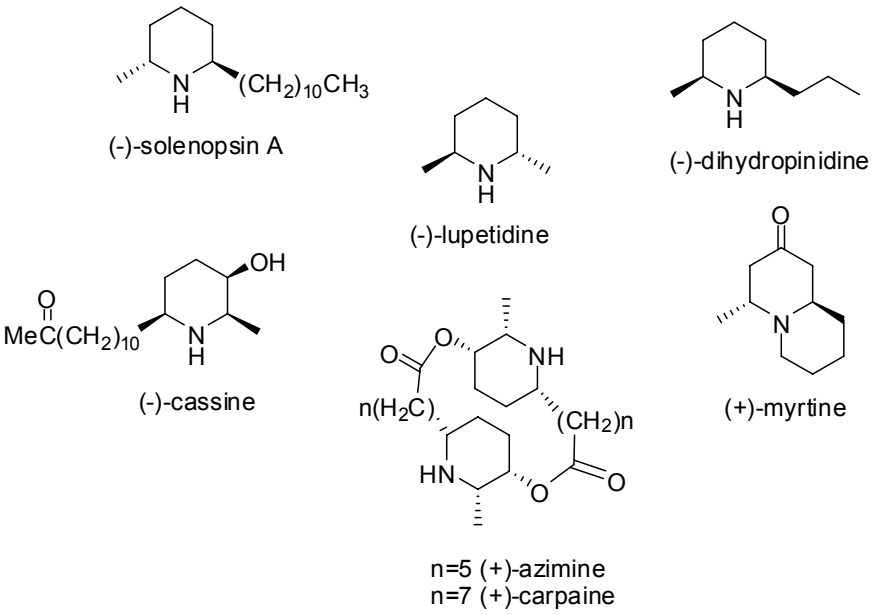
Table 2.3 *Scope of the reaction.*



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.

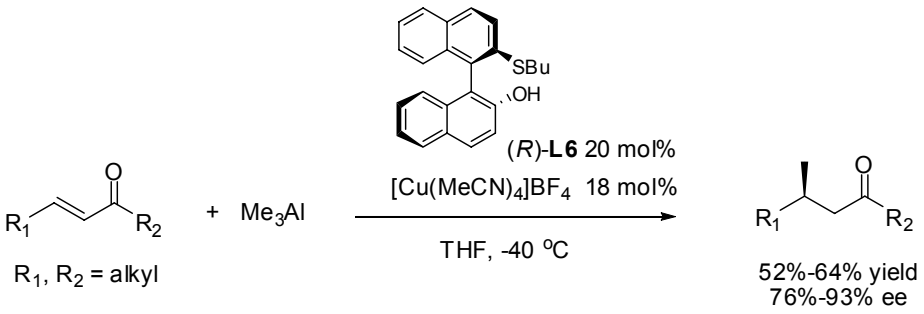


Scheme 2.8 *α-Methyl motif in alkaloid structures.*

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]

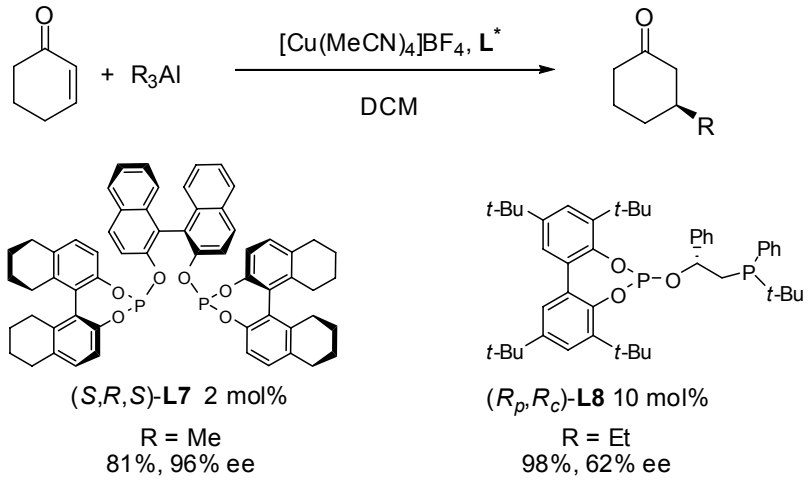
2.3.1 Literature precedents

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.



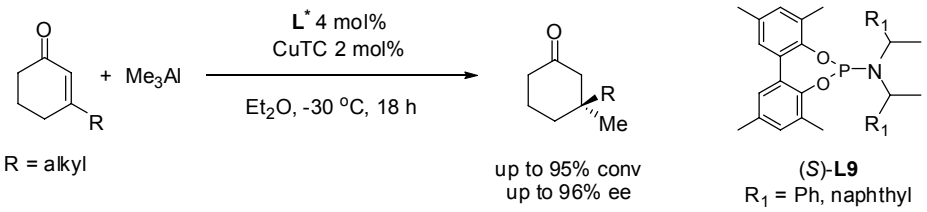
Scheme 2.9 *Me_3Al addition to linear aliphatic enones.*

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.



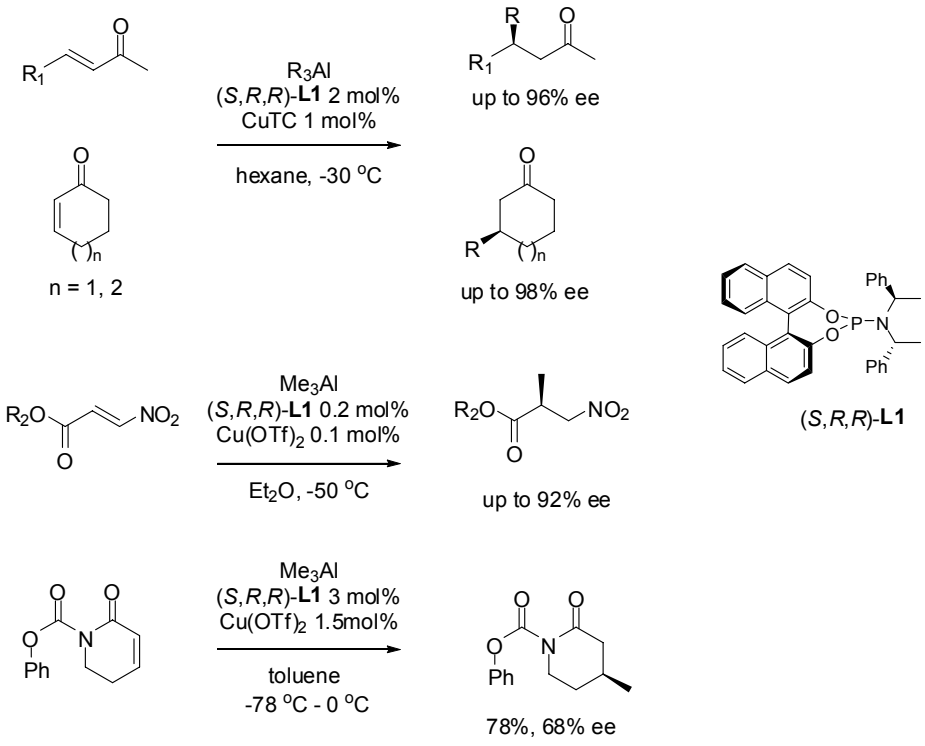
Scheme 2.10 *R_3Al addition to 2-cyclohexenone.*

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]



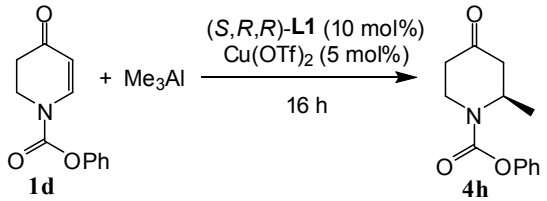
Scheme 2.12 *Cu/**L1**-catalyzed conjugate additions of R_3Al.*

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.

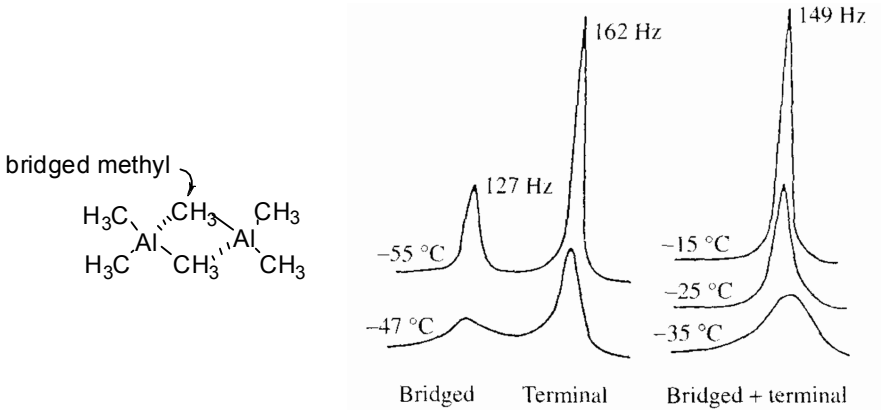
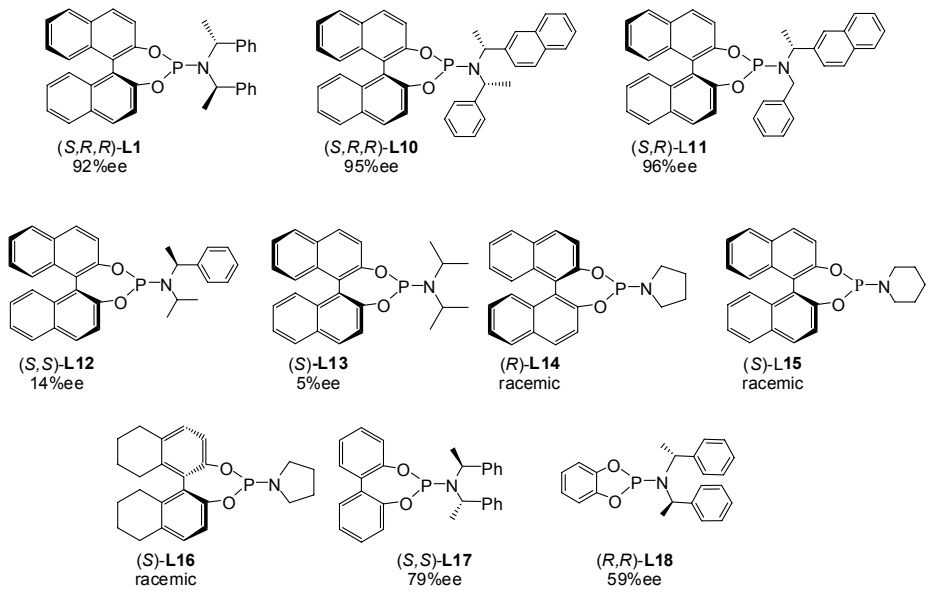


Figure 2.1 *^{1}H-NMR spectrum of trimethylaluminum in toluene.*[25]

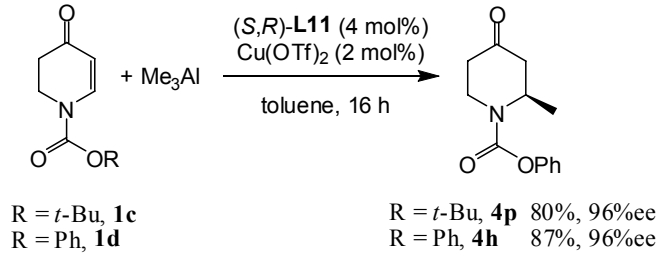
It is possible that when the Me_3Al is present in dimeric form, the methyl transfer is hampered due to the stability of the dimer. Furthermore, in the addition reaction the aluminium reagent can act as a Lewis acid, activating the enone moiety toward the nucleophilic addition. In the bridged structure 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%.

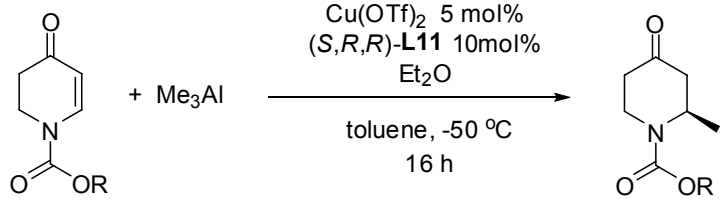
A possible explanation can be found in the formation of a heterogeneous system upon addition of the organometallic species to the reaction mixture in which the copper complex and the starting material are present already. The formation of insoluble aggregates might inhibit the reaction and makes mixing 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.

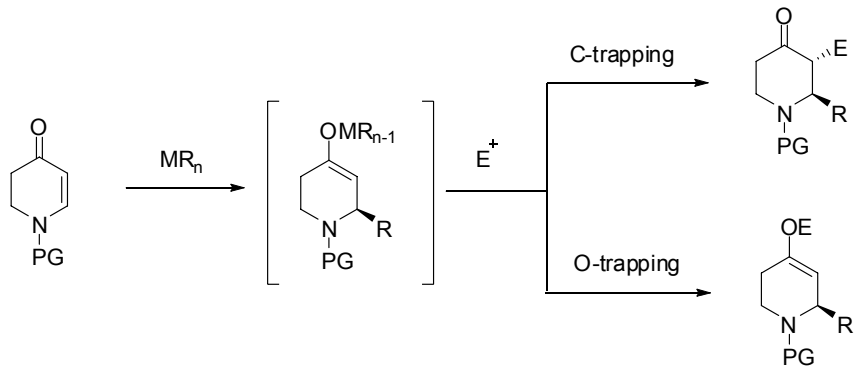
Table 4.5 *Co-solvent effect.*



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

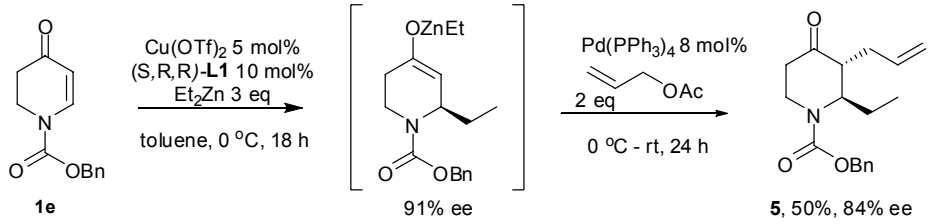
2.4 Further developments

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.

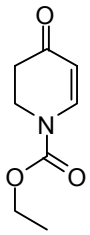
2.6 Experimental Section

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.

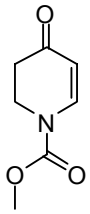
1-Ethoxycarbonyl-2,3-dehydro-4-piperidone (1a).[7]



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).

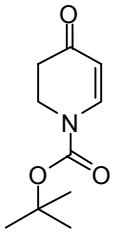
1-Methoxycarbonyl-2,3-dehydro-4-piperidone (1b).[29]



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

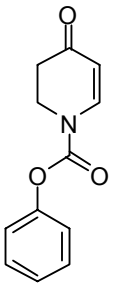
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.78 (m, 1H), 5.29 (d, *J*=8.0 Hz, 1H), 3.98 (t, *J*=7.4 Hz, 2H), 3.82 (s, 3H), 2.51 (t, *J*=7.4 Hz, 2H).

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.

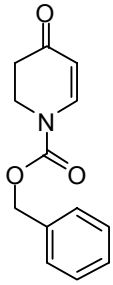
1-Phenoxycarbonyl-2,3-dehydro-4-piperidone (1d).[29]



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).

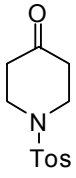
1-Benzyloxycarbonyl-2,3-dehydro-4-piperidone (1e)[5]



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.

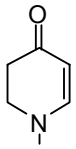
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.39 (m, 5H), 5.36 (m, 1H), 5.26 (s, 2H), 4.05 (t, *J*=7.2 Hz, 2H), 2.56 (t, *J*=7.2 Hz, 2H).

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).

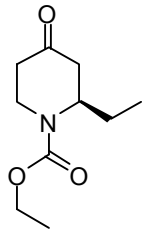


IBX (2.46 g, 8.8 mmol) and NMO (1.03 g, 8.8 mmol) were dissolved in DMSO (8 mL) at r.t. To this solution piperidone **2** (1.01 g, 4.0 mmol) in DMSO (12 mL) was added at once and the resulting clear solution was stirred for 72 h at r.t. in a flask covered with aluminium foil. The reaction mixture was 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.

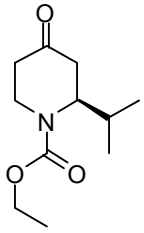
(*R*)-1-Ethoxycarbonyl-2-ethyl-4-piperidone (4a).



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;

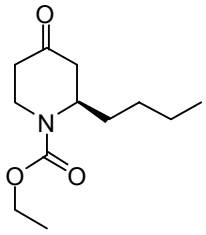
$CDCl_3$) δ 207.9, 155.6, 61.7, 53.5, 45.2, 40.5, 38.1, 25.3, 14.5, 10.0. HRMS calc. for $C_{10}H_{17}NO_3$ 199.1208, found 199.1204 GC on Chiraldex G-TA column, 30m × 0.25mm, He-flow: 1mL/min, oven temp.:100 °C, init. time: 15 min, rate: 10 °C/min, final temp. 150 °C, t_R 23.7 (minor), t_R 24.0 (major).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

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



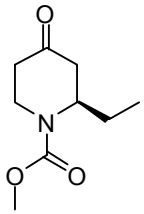
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4d** in 80% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.43 (m, 1H), 4.20-4.16 (m, 3H), 3.12 (t, *J*=6.6 Hz, 1H), 2.54-2.43 (m, 3H), 2.35 (dd, *J*=14.8, 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).



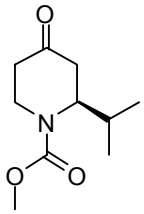
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4e** in 16% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.60 (m, 1H), 4.35 (m, 1H), 4.20-4.10 (m, 2H), 3.16 (dt, *J*=12.1, 3.6 Hz, 1H), 2.61 (dd, *J*=16, 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.

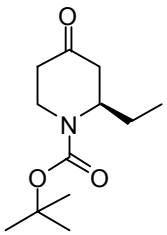
(R)-1-Methoxycarbonyl-2-isopropyl-4-piperidone (4e).



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

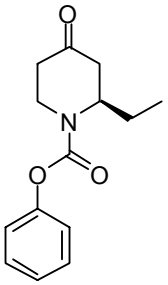
(*R*)-1-*t*-Butoxycarbonyl-2-ethyl-4-piperidone (4f).



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

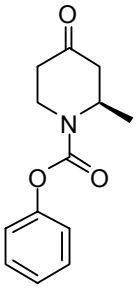
MHz, $CDCl_3$) δ 208.3, 154.0, 80.2, 53.4, 45.3, 40.6, 38.1, 28.4, 25.5, 10.2. HRMS calc. for $C_{12}H_{21}NO_3$ 227.1521, found 227.1337. HPLC on Chiralpack AS column, (*n*-heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 5.3 (major), t_R 6.4 (minor). $[\alpha]_D$ = –4.8 (c=0.40, $CHCl_3$), 91% ee.

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



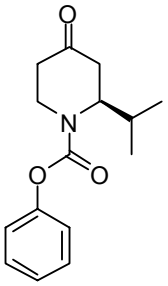
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4g** in 87% yield as a colorless oil. ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.33 (t, *J*=7.9 Hz, 2H), 7.17 (t, *J*=7.2 Hz, 1H), 7.07 (d, *J*=8.1 Hz, 2H), 4.63 (m, 1H), 4.48-4.42 (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]



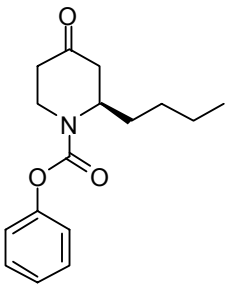
Purification by column chromatography (SiO_2; EtOAc / *n*-pentane / NEt_3 20:79:1) afforded 93 mg of a colorless oil (Yield 80%). HPLC on Chiralpak AS column, 4.6 × 250 mm, 10 μm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 18.3 min (major), Rt = 33.3 min (minor). 89% ee. ^{1}H-NMR (400 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).



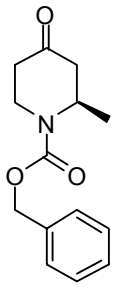
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1+1% Et_3N) to give pure **4h** in 84% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.33 (t, *J*=7.6 Hz, 2H), 7.17 (t, *J*=7.6 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 2H), 4.53-4.48 (m, 1H), 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).



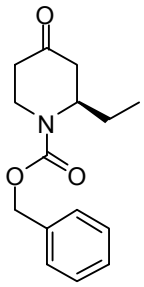
The crude product obtained by general procedure B was purified by flash chromatography (*n*-pentane/AcOEt=4:1 +1% Et_3N) to give pure **4i** in 22% yield as a colorless oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34 (t, *J*=7.4 Hz, 2H), 7.18 (t, *J*=7.4 Hz, 1H), 7.07 (d, *J*=7.6 Hz, 2H), 4.72 (m, 1H), 4.45 (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).



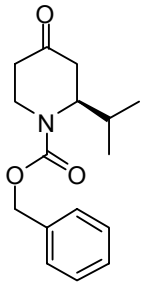
The crude product obtained by general procedure B was purified by flash chromatography (*n*-heptane/AcOEt=4:1) to give pure **4j** in 44% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.18 (s, 2H), 4.80 (m, 1H), 4.31 (m, 1H), 3.40 (m, 1H), 2.70 (dd, *J*=6.6, 14.6 Hz, 1H), 2.50-2.25 (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.

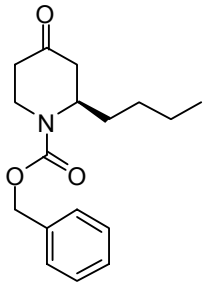
(*R*)-1-Benzyloxycarbonyl-2-(2-propyl)-4-piperidone (4m).



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*-

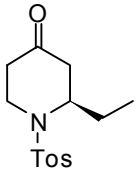
heptane/isopropanol=95:5, flow = 1.0 mL/min): t_R 9.7 (major), t_R 13.3 (minor). $[\alpha]_D$ = –7.1 (c=0.56, $CHCl_3$), 95% ee.

(*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).



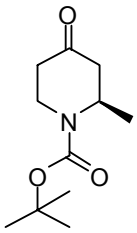
The crude product obtained by general procedure B was purified by flash chromatography (*n*-heptane/AcOEt=4:1) to give pure **4n** in 50% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J*=7.7 Hz, 2H), 7.33 (d, *J*=7.3 Hz, 2H), 4.30 (q, *J*=7.0 Hz, 1H), 4.15 (dd, *J*=14.3, 7.0 Hz, 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

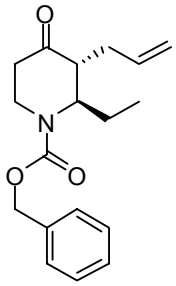
mmol of dry Et_2O was added, followed by a solution of substrate (10 mmol) in toluene (60 mL) and the mixture cooled to -50°C. A solution of Me_3Al (20 mmol) was added dropwise and the reaction mixture was stirred at the specified temperature overnight. The reaction was stopped after 16 h at 80% conversion. 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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