# Enantioselective copper-catalysed addition of organometallic reagents using phosphoramidite ligands

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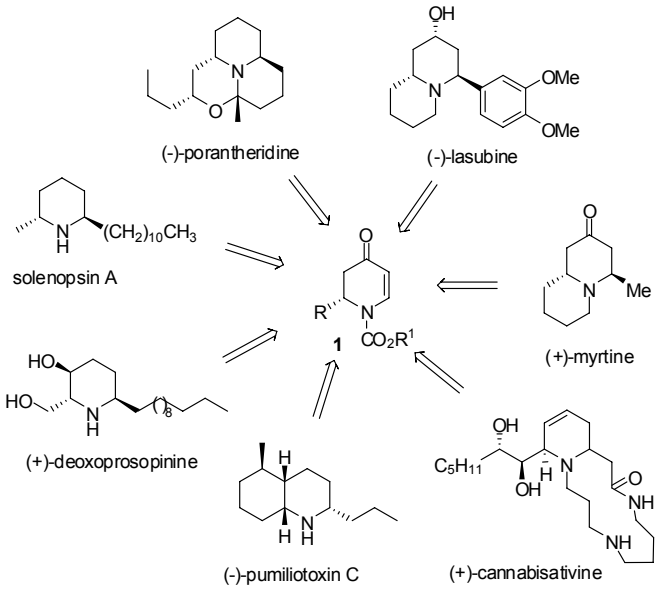
Chapter 3

# 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.*

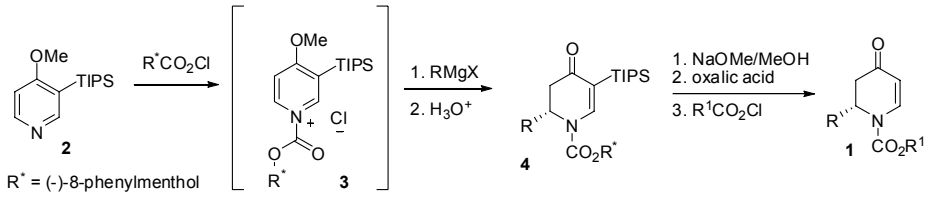
## 3.1 Introduction

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.

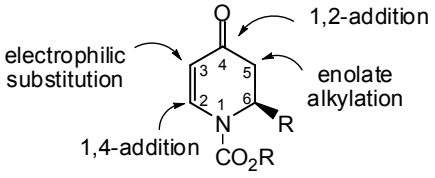
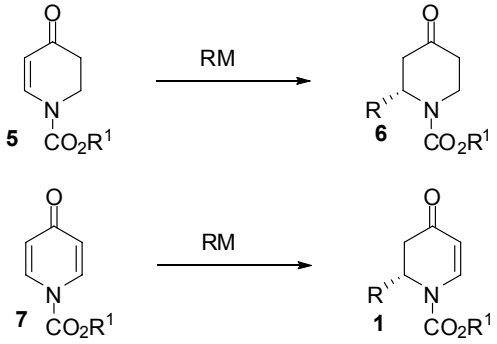


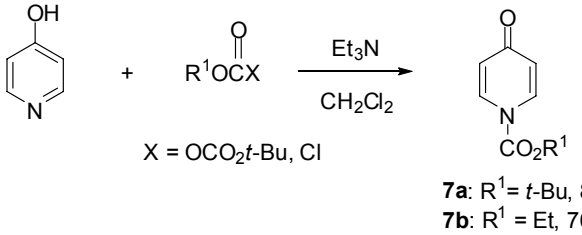

**Figure 3.1**

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**

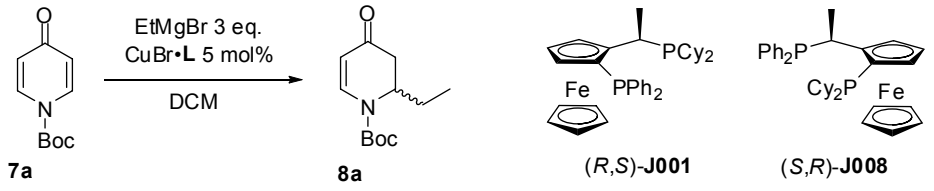
The substrates **7a** and **7b** were synthesized in high yield from 4-hydroxy-pyridine (Scheme 3.4) and tested in the copper-catalyzed addition of $Et_2Zn$ and $Me_3Al$ under optimized conditions.




**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).

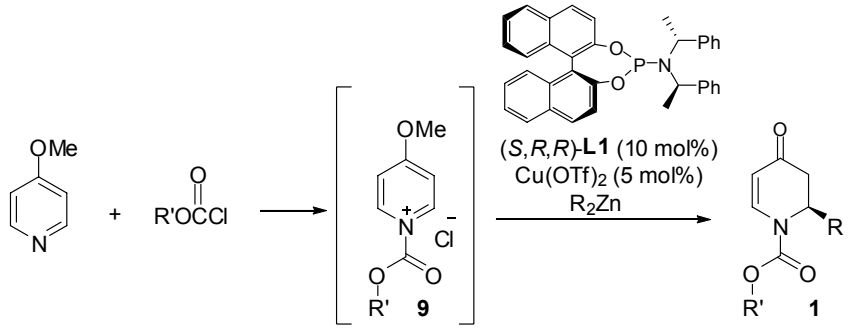



**Scheme 3.5** *Conjugate addition of EtMgBr to 4-pyridone* ***7a****.*

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**.

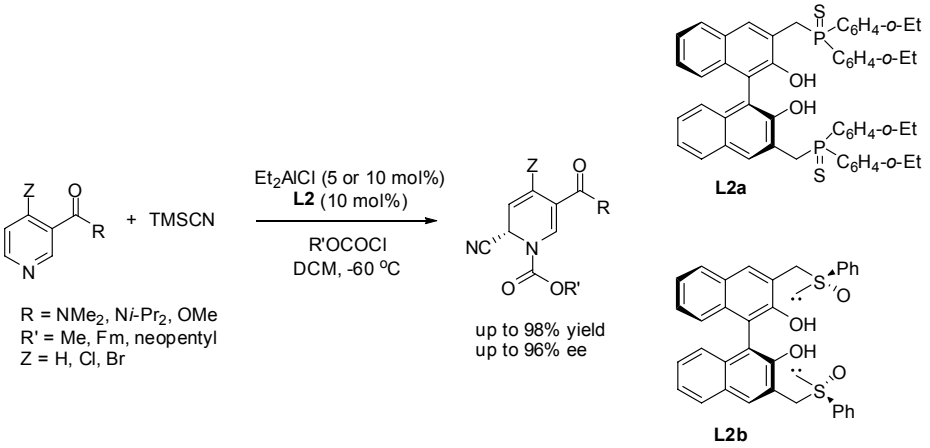
## 3.3 Catalytic enantioselective addition of diethylzinc to N-acyliminium ions

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.



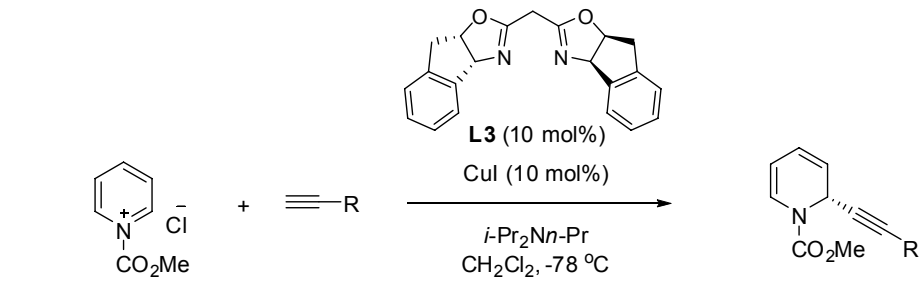

**Scheme 3.6** *Conjugate addition to N-acylpyridinium ions generated in situ.*

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]

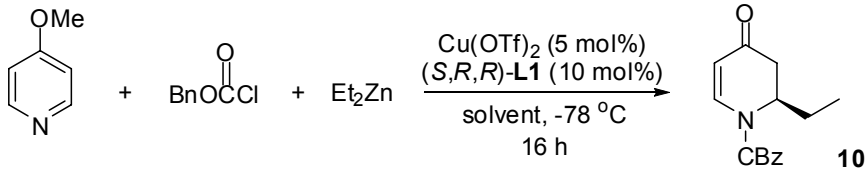
The catalytic enantioselective addition of terminal alkynes to *N*-acylpyridinium salts has been described recently.[9] 10 mol% of a copper-bis(oxazoline) complex catalyzes the addition of 1-alkynes to iminium salts formed from pyridine and a number of chloroformates. The use of a base, such as *i*-$Pr_2N$*n*-Pr, 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.*

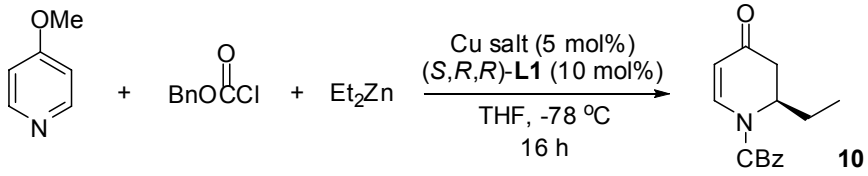



| Entry | Solvent | Yield (%) | Ee (%) |
|---|---|---|---|
| 1 | THF | 26 | 34 |
| 2 | Toluene | 30 | 8 |
| 3 | $Et_2O$ | 26 | 5 |
| 4 | $CH_2Cl_2$ | 30 | 12 |
| 5[a] | THF | 50 | 12 |

[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.*

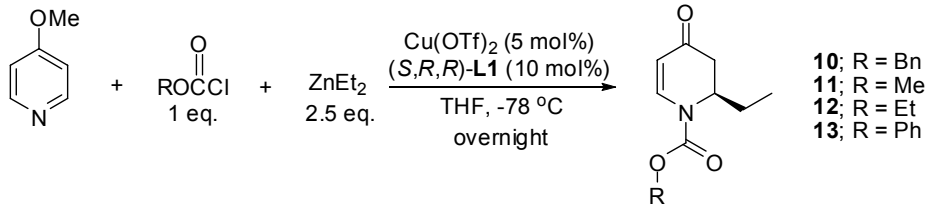



**10**

| 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.*



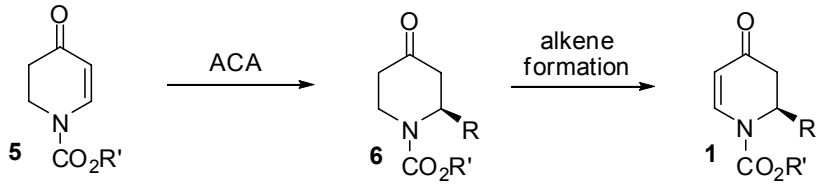

| Entry | R | Product | Yield (%) | Ee (%) |
|---|---|---|---|---|
| 1 | Bn | **10** | 26 | 34 |
| 2 | Me | **11** | 25 | 5 |
| 3 | Et | **12** | 18 | 10 |
| 4 | Ph | **13** | 25 | rac |

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).

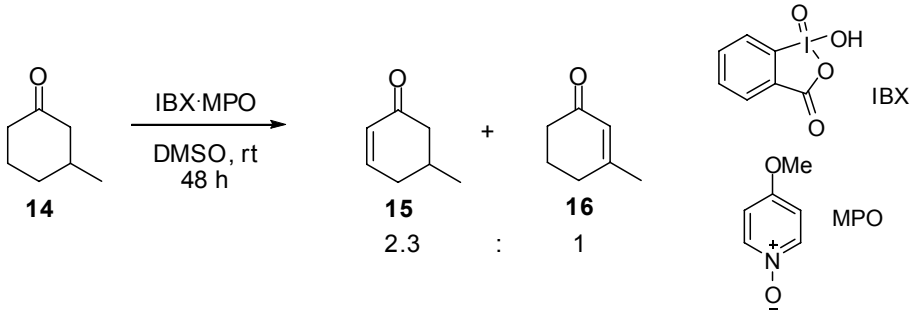



**Scheme 3.9**

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

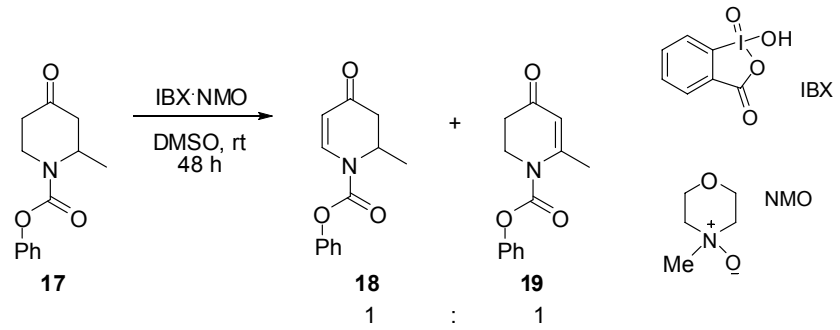
### 3.4.1 IBX-mediated dehydrogenation

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).

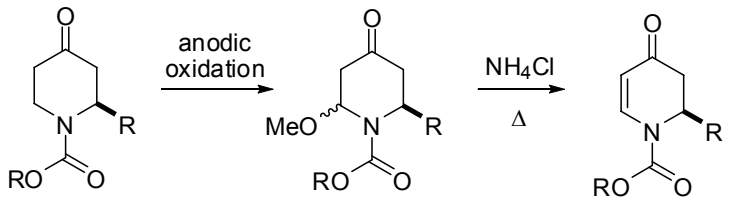



**Scheme 3.11** *IBX·NMO-mediated dehydrogenation of **17**.*

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.

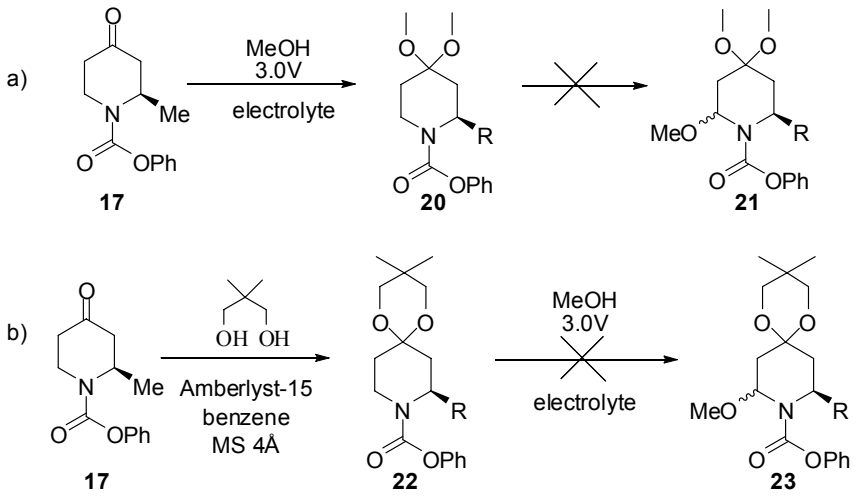
### 3.4.2 Anodic oxidation of carbamates

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**.*

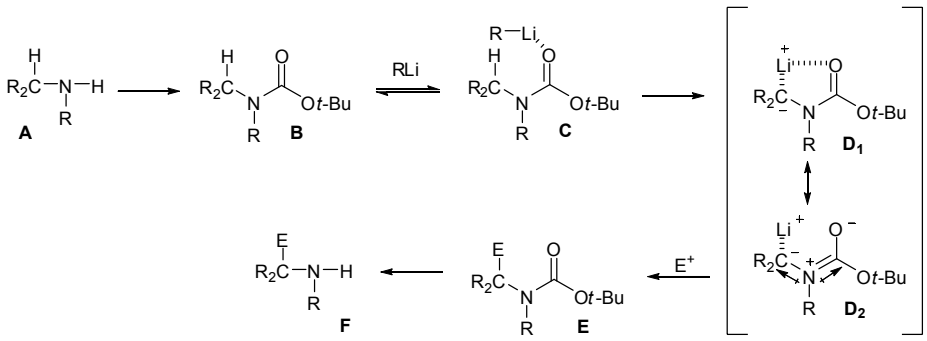
α-Methoxylation of the carbamate was not observed performing the electrolysis experiment under several reaction conditions in which the effect of the supporting electrolyte, nature of the electrode and value of the potential were studied. Once again the use of a different approach was considered.

## 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.

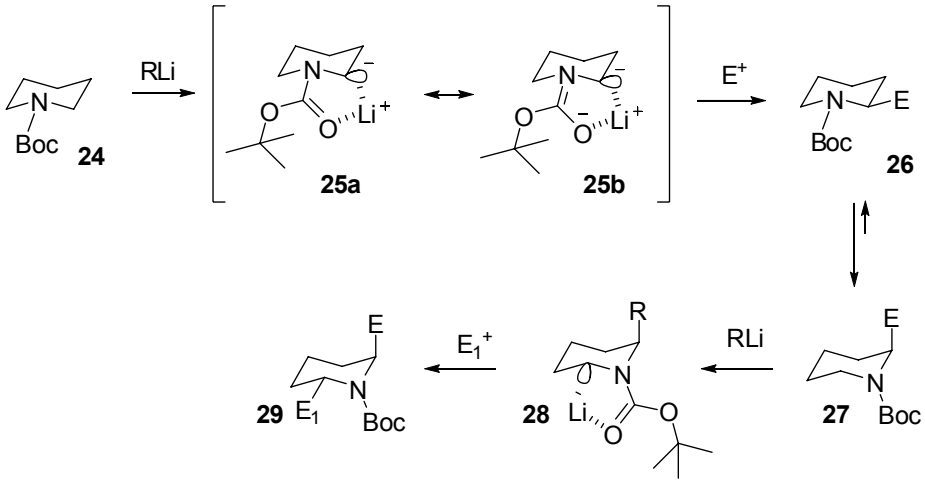
In order to successfully promote the reaction, the nitrogen protecting group needs to fulfill several requirements. The α-protons of amines are not sufficiently acidic to be removed using a strong base except in systems which are additionally activated. Substitution at the nitrogen with an electron withdrawing 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.



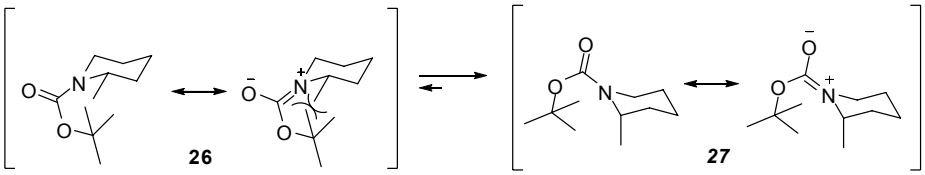
**Scheme 3.14** *Lithiation-substitution sequence of a Boc-protected amine.*

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.*

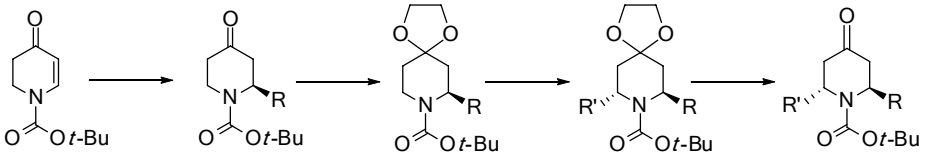
The occurrence of $A^{1,3}$ strain in an equatorially substituted piperidine is apparent when considering the resonance structure for **26**. In this structure the interaction between the equatorial 2-substituent and the alkyl part of the carbamate moiety causes destabilization in comparison with the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

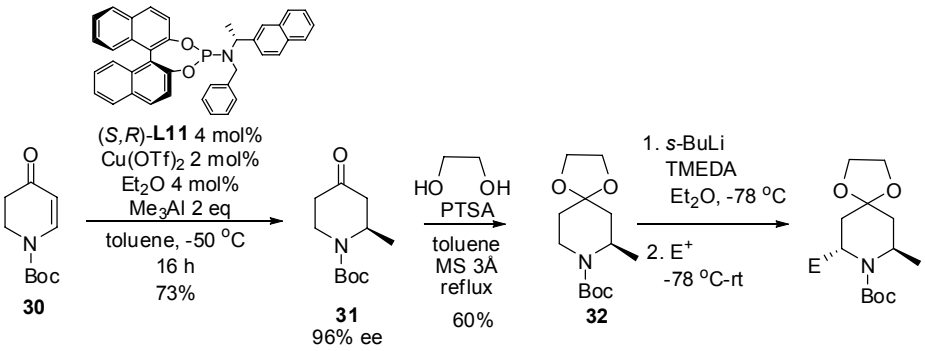
The same factor influences the conformational equilibrium of the enantioenriched 2-substituted piperidones obtained from the asymmetric conjugate addition to *N*-protected 2,3-dehydro-4-piperidones. Therefore, the combination of the asymmetric conjugate addition and the lithiation-substitution

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).

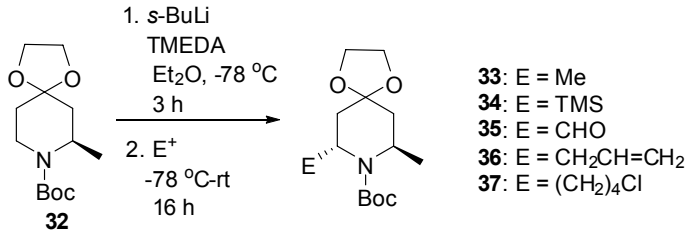



**Scheme 3.18**

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** | - | - |

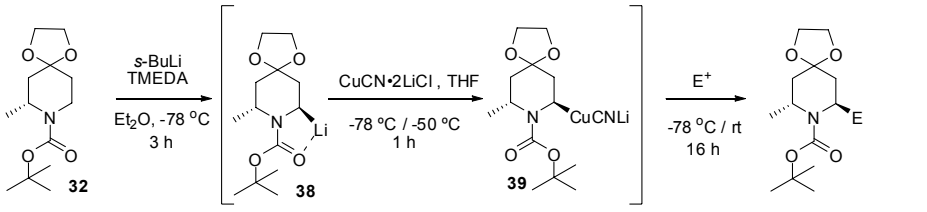
[a] Determined by $^1$H-NMR and $^{13}$C-NMR.

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****.*

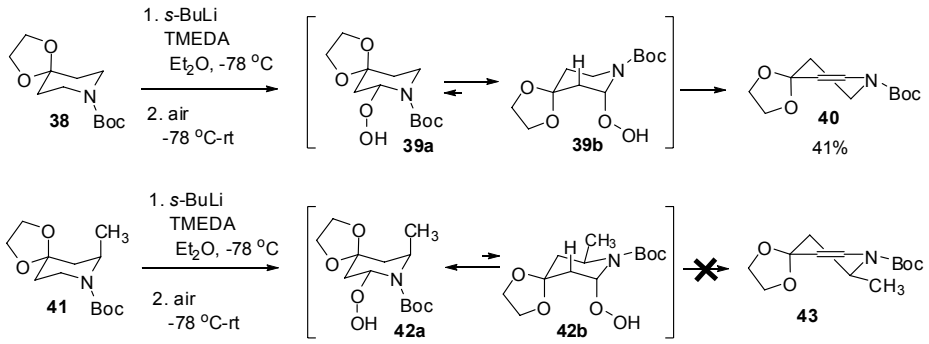



| Entry | $E^+$ | Product | Yield (%) | dr (%)[a] |
|---|---|---|---|---|
| 1 | allylbromide | **36** | 64 | >99:1 |
| 2 | $I(CH_2)_4Cl$ | **37** | 62 | >99:1 |

[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.

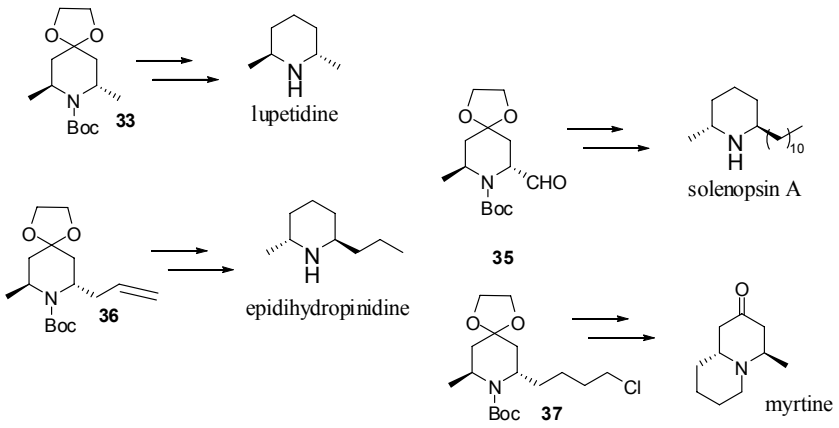
The *trans* selectivity observed for the 2,6-disubstituted-piperidones might account as well for the different outcome of the lithiation reactions performed on the substrates **38** and **41** using oxygen as electrophile (Scheme 3.19).




**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.

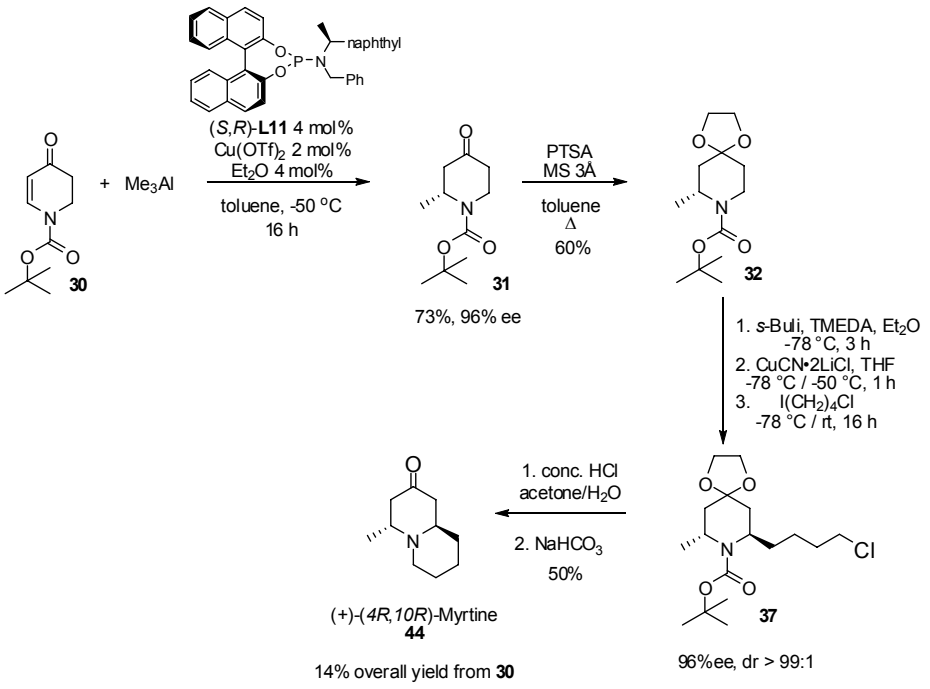
The protocol developed provides 2,6-disubstituted-*trans*-piperidones in good yield and with high enantioselectivities. These compounds can be used as precursors in the synthesis of several alkaloids (Scheme 3.20). The application of this protocol to the synthesis of (+)-myrtine is described in the next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

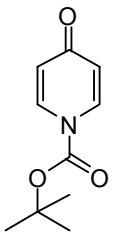
## 3.7 Conclusions

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

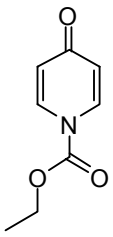
**General Methods.** For general information see Chapter 2.

***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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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]

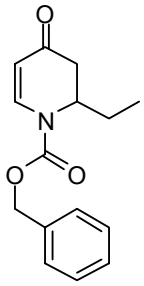


4-Hydroxypyridine (0.5 g; 5.3 mmol) was added to a solution of ethyl chloroformate (0.53 mL; 5.5 mmol) in $CH_2Cl_2$ (20 mL) at room temperature. $Et_3N$ (2.8 mL; 20 mmol) was then added and the reaction mixture was stirred for 5 h. The reaction mixture was then diluted with $H_2O$ (15 mL) and the pH 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, $CDCl_3$) $\delta$ = 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*.

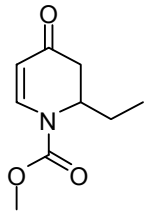
**Benzyl 2-ethyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (10).[31]**



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.

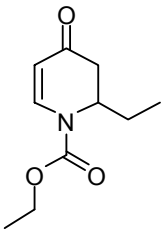
**Methyl 2-ethyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (11).**

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



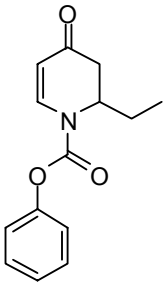
9 mg of a colorless oil (yield 25%). $R_f$ = 0.4. HPLC on Chiralpak AS column, 4.6 × 250 mm, 10 µm, (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 19.5 min, Rt = 39.5 min. $^1$H-NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 8.1 Hz, 1H), 4.47 (br s, 1H), 3.84 (s, 3H), 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.

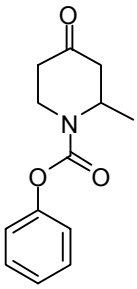
**Phenyl 2-ethyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (13).**



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,



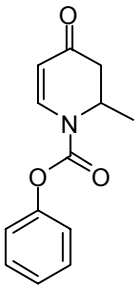
121.6, 48.6, 46.4, 40.4, 38.9, 19.1 ppm. HRMS calcd. for $C_{13}H_{15}NO_3$: 233.10518, found 233.10520.

**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**.

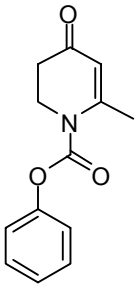
**Phenyl 2-methyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (18).[32]**

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, $CDCl_3$) $\delta$ = 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.

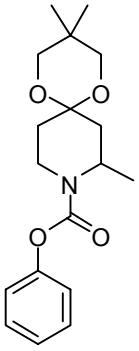


**Phenyl 6-methyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (19).**

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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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.

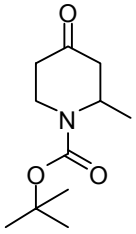


**Phenyl 3,3,8-trimethyl-1,5-dioxa-9-azaspiro[5.5]undecane-9-carboxylate (22).**



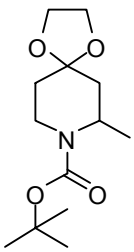
2,2-Dimethylpropane-1,3-diol (96.7 mg; 0.93 mmol) was added to a solution of **17** (180 mg; 0.77 mmol) in toluene (2.5 mL). Amberlyst-15 (1 mg) was added and the reaction mixture was refluxed overnight in the presence of molecular sieves 4Å. After cooling down to room temperature, the molecular sieves 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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]

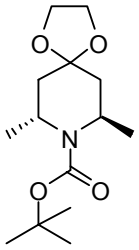
TMEDA (0.090 mL; 0.6 mmol) was added to a solution of compound **32** (64.2 mg; 0.25 mmol) in $Et_2O$ (4 mL). The resulting solution was cooled to -78 °C and a solution of *s*-BuLi (1.3 M in cyclohexane, 0.46 mL; 0.6 mmol) was added. The reaction mixture was stirred at -78 °C. After 3 h a solution of 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

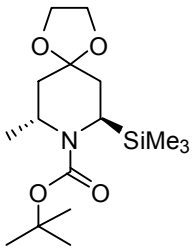
warmed to -50 °C and stirred at this temperature for 30 min. Then, the temperature was brought once again to -78 °C and a solution of the electrophile (1.2 mmol) in $Et_2O$ (1 mL) was added. The reaction mixture was allowed to slowly warm up to room temperature. After overnight the mixture was poured 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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.

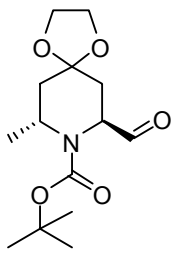
**(7*R*,9*R*)-*tert*-Butyl 7-methyl-9-(trimethylsilyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (34).**



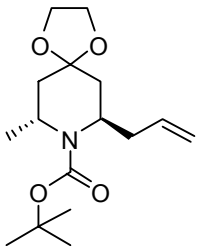
From procedure A. Purification by column chromatography ($SiO_2$; EtOAc / *n*-pentane 5:95) afforded 61 mg of a colorless oil (Yield 74%). Rf = 0.7. $[\alpha]_D$ = -13.2 (c 0.55, $CHCl_3$) for 96% ee and dr 96:4. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ = 4.46-4.38 (m, 1H), 3.98-3.87 (m, 4H), 2.64 (dd, *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, $CDCl_3$) $\delta$ = 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 $\delta$ = 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, $CDCl_3$) $\delta$ = 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.

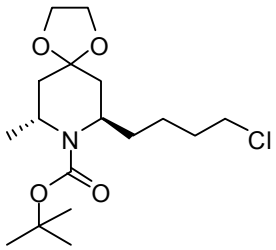


**(7*R*,9*R*)-*tert*-Butyl 7-allyl-9-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (36).**



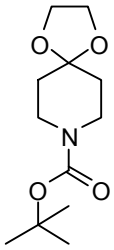
From procedure B. Purification by column chromatography ($SiO_2$; EtOAc / *n*-pentane 1:9) afforded 95 mg of a colorless oil (Yield 64%). Rf = 0.6. $[\alpha]_D$ = +27.4 (c 0.50, $CHCl_3$) for 96% ee and dr > 99:1. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ = 5.78-5.68 (m, 1H), 5.09-5.00 (m, 2H), 4.05-4.02 (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, $CDCl_3$) $\delta$ = 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).**



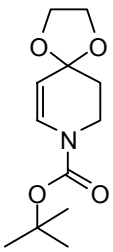
From procedure B. Purification by column chromatography ($SiO_2$; EtOAc / *n*-pentane 1:9) afforded 107 mg of a colorless oil (Yield 62%). Rf = 0.5. $[\alpha]_D$ = +8.2 (c 0.49, $CHCl_3$) for 96% ee and dr 97:3. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ = 3.99-3.79 (m, 6H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.10-1.98 (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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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.

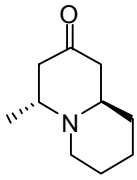
***tert*-Butyl 1,4-dioxa-8-azaspiro[4.5]dec-6-ene-8-carboxylate (40).**



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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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, $CDCl_3$) $\delta$ = 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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[6] As mentioned in Chapter 2, only a few asymmetric syntheses of 2,3-dehydro-4-piperidones, based on an enantioselective aza-Diels-Alder reaction, have been reported.

[7] For examples of nucleophilic addition to chiral *N*-acylpyridinium ions see: a) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc.* **1996**, *118*, 12248. b) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651.

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