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New Perspectives in Asymmetric Organolithium Chemistry: Weinreb Amides Acylations en route to Chiral α-Substituted Ketones

verfasst von / submitted by

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Praise the Lord for every single step you make!

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1 Introduction

1.1 General principles of organolithium chemistry

The element lithium was discovered somewhat over 200 years ago, while the first organolithium compounds have been synthesized by Wilchelm Schlenk over 100 years ago.[1, 2] For this period of time one has become clear—organolithium chemistry is a fundamental and very perspective branch of chemical science. The facts speak for themselves—new synthetic pathways utilizing lithiated species find place in the most respected chemical journals and are defined by their chemo-, regio-, enantio- or diastereoselectivity.[3] Furthermore, more than 95% of natural product syntheses involve lithium chemistry[4], lithium-containing compounds are implemented as reagents, reactants or intermediates in the development and production of novel active pharmaceutical ingredients[1], while the most commonly used organolithium compounds are commercially available in high purity.[5] All these fields of interest make organolithiums the most widely applicable organometallic species in chemistry.[6]

The three major strategies to generate lithiated species are: reductive lithiations, transmetallation reactions and lithium-hydrogen exchange (deprotonation).[5]

One of the most distinctive features of organolithium compounds is their nucleophilicity. Because carbon is more electronegative than lithium, the former carries a negative formal charge, hence can subsequently attack species with a positive formal charge termed electrophiles in a process named nucleophilic substitution.[7] A sequence of lithiating the starting material, followed by a nucleophilic substitution (often referred to in literature as “lithiation-trapping”[8]) is mostly applied in organic chemistry to form new carbon-carbon bonds or carbon-heteroatom bonds.[7]

1.2 Milestones in the lithiation-trapping of *N*-Boc-pyrrolidine

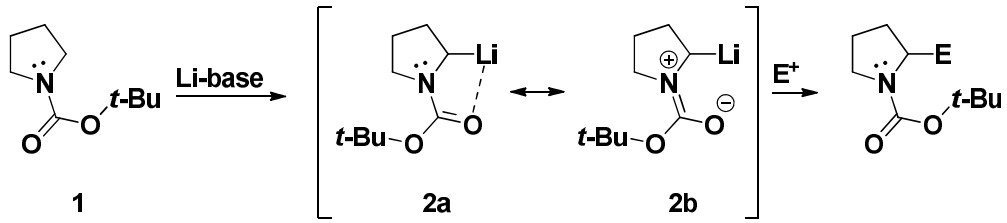
1.2.1 Generation of dipole-stabilized organolithium.

Lithium-hydrogen exchange is in its essence an acid-base reaction, *i.e.* a proton exchange between a proton acceptor (a lithium-containing base) and a proton donor.

The discovery that the methylene proton in α-position to nitrogen of *N*-Boc-pyrrolidine **1** is acidic enough to be lithiated by deprotonation and the metallated intermediate **2** can be subsequently trapped by electrophiles was made by Beak and Lee in 1989.[9] The reason making this lithiation-substitution sequence possible is the increased CH-acidity (also termed "activation") of the α-position induced by the stabilizing effects of the *tert*-butoxycarbonyl (Boc) group on the metallated transition state **2** (Scheme 1).[10]

Generally, the Boc group is electron-withdrawing and stabilizes the intermediate **2** by complexation of lithium **2a** and by dipole stabilization **2b**.[10]

Dipole stabilization **2b** is quantitatively the most important factor for the stability of **2**.[9] In this case the activating Boc group converts by electron withdrawal the nitrogen into the positive end of a dipole **2b**, which stabilizes the lithiated intermediate **2**.[11] Organolithium species, which can be stabilized by an adjacent partial positive charge induced by electron withdrawal from an activating group are termed dipole-stabilized carbanions **2b**.[10, 11]

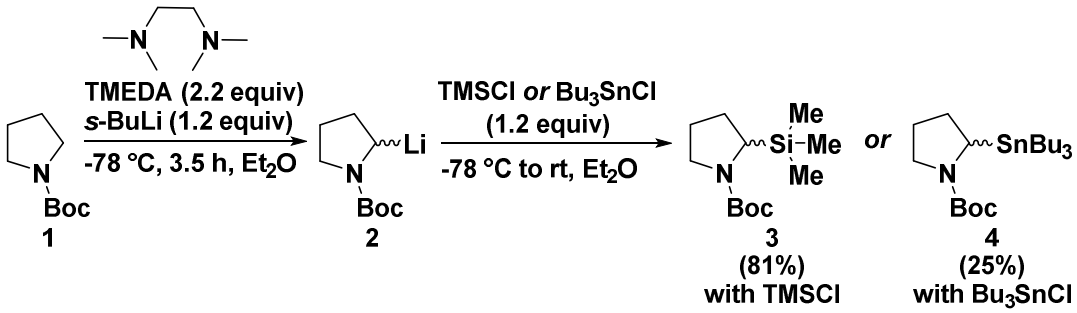


Scheme 1. Activation of the α-position to nitrogen in *N*-Boc-pyrrolidine.

Another advantage of the electron withdrawing Boc group is that the lone pair of nitrogen is not available for a nucleophilic attack, so there could be no interference with the electrophile and formation of undesired *N*-substituted pyrrolidines.[10] Due to the sterical hindrance of the *tert*-butyl residue the carbamate carbonyl is protected from nucleophilic attacks. Further essential criteria for activating groups which the Boc functionality fulfils are lack of acidic protons in the group itself, stability towards basic reagents, straightforward introduction in the beginning and convenient removal (if necessary) at the very end of the reaction sequence.[10]

1.2.2 Lithiation-trapping of *N*-Boc-pyrrolidine

The complete initial protocol for lithiation-trapping of *N*-Boc-pyrrolidine **1** is depicted in the following Scheme 2.[9] The deprotonation was carried out at -78 °C in diethyl ether (Et_2O) in presence of *N*,*N*,*N*',*N*'-Tetramethylethylenediamine (TMEDA) for 3.5 hours. The very first electrophiles for the trapping were chlorotrimethylsilane (TMSCl) and tributyltin chloride (Bu_3SnCl) and the reactions gave yields of 81% and 25% respectively.



Scheme 2. Racemic lithiation-trapping of *N*-Boc-pyrrolidine.

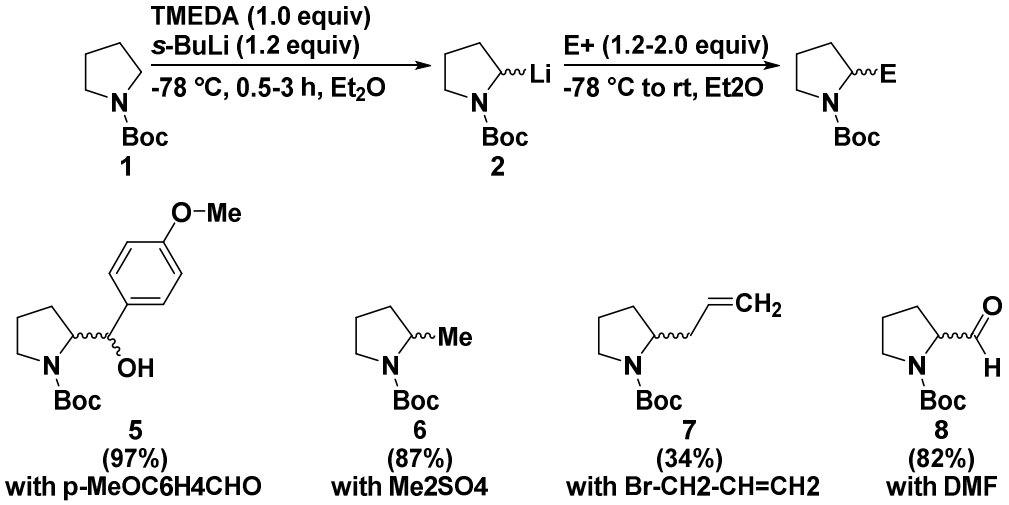
The utilized metallating agent is the combination of *sec*-Butyllithium (*s*-BuLi) and TMEDA. The choice of Et_2O as solvent and lithiation temperature of -78 °C, represent standard conditions for this protocol.[8, 9]

s-BuLi is a strong organometallic base, which is responsible for the actual lithium-hydrogen exchange.[12] Lithiations employing *s*-BuLi are most often performed in electron-donating ethereal type solvents such as Et_2O or tetrahydrofuran (THF) which facilitate "depolymerization of higher order organolithium aggregates (tetramers) into smaller units (dimers and monomers)" by complex formation with lithium, enhancing the activity of the organolithium reagent.[12] *s*-BuLi is usually added to the reaction mixture at low temperatures (usually -78 °C). At elevated temperatures, the organolithium could react with the solvent giving undesired byproducts.[12]

During the metalation process, the generated lithiated species benefits from stabilizing effects offered by TMEDA.[12] TMEDA belongs to the diamine class of compounds and it is used in organic chemistry as a bidentate ligand with high affinity to lithium-ions which stabilizes and activates organolithium reagents and affords higher product yields.[13] It is believed that TMEDA also works by producing lower aggregates of the organolithium.[14]

In a communication from 1993, a broadened scope of the reaction was reported (Scheme 3).[15] *N*-Boc-2-lithiopyrrolidine **2**, generated at -78 °C in Et_2O by *s*-BuLi/TMEDA, was trapped with

electrophiles such as *p*-anisaldehyde, dimethyl sulfate, allyl bromide, *N,N*-Dimethylformamide (DMF) to afford a series of α-elaborated *N*-Boc-pyrrolidine derivatives (**5-8**) in yields from 34 to 97%.



Scheme 3. Utility of the racemic lithiation-trapping of *N*-Boc-pyrrolidine.

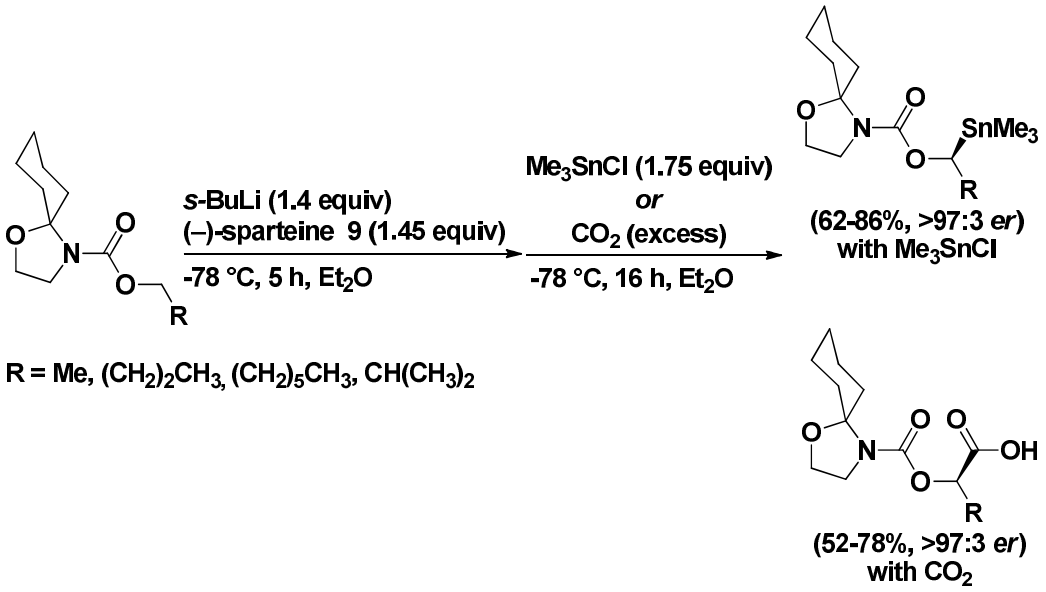
The α-elaboration of *N*-Boc-pyrrolidine **1** was a synthetic breakthrough, but there were some points that still required further optimization.

Since the starting material *N*-Boc-pyrrolidine **1** is prochiral, deprotonation with TMEDA resulted not in a stereoselective approach.[9] In fact, it yielded only racemic products.

Moreover, the reaction is characterized by an inconveniently long lithiation time (>3 hours) and the conditions are not complying with several principles of Green Chemistry.[16] Lithiation time over 3 hours is related to a large energy consumption[17], which is against the 6th principle "Design for Energy Efficiency". The use of Et_2O, a well-known unsustainable solvent, contradicts the 5th principle "Safer Solvents and Auxiliaries".

1.2.3 (–)-sparteine and (+)-sparteine in enantioselective deprotonation

A potential solution to the stereoselectivity problem was published in 1990 when Dieter Hoppe *et al.* reported the utilization of the pair *s*-BuLi/(–)-sparteine **9** instead of *s*-BuLi/TMEDA for the enantioselective deprotonation of weakly CH-acidic prochiral *O*-alkyl carbamate (Scheme 4).[18] Lithiation with *s*-BuLi/(–)-sparteine **9** at -78 °C for 5 hours in Et_2O afforded α-oxygen dipole stabilized carbanions. After trapping with trimethyltin chloride (Me_3SnCl) and carbon dioxide (CO_2), yields in the range 52-86% with excellent > 97:3 *er* were reported. Hoppe's group disclosed that sparteine mediated enantioselective deprotonation was the key mechanism for achieving enantioselectivity in the lithiation-trapping sequence of *O*-alkyl carbamates.



Scheme 4. Enantioselective lithiation-trapping of Hoppe alkyl carbamates.

(–)-sparteine **9** is a naturally occurring alkaloid, biosynthesized by members of the *Fabaceae* plant family.[19] The chemical features of (–)-sparteine **9** include a tetracyclic ring system with a bispidine core, four chiral centers, two tertiary amino groups and the existance of two conformations (Fig. 1).[20] Being "equipped with an attractive metal chelating conformation"[21] (**9A**, Fig. 1) (–)-sparteine **9** serves in deprotonation-substitution sequences in combination with organolithium compounds as a chirality inducing bidentate ligand.[22]

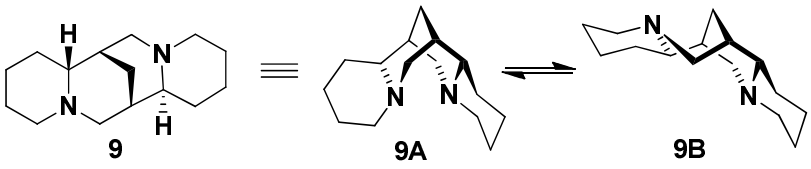
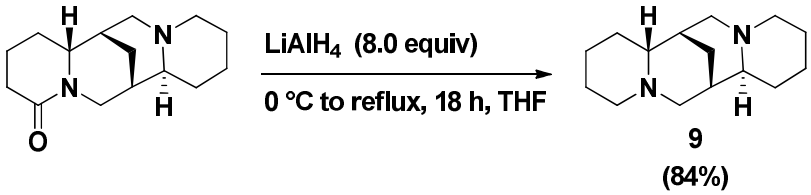


Fig. 1. Structural formula and conformations of (–)-sparteine.

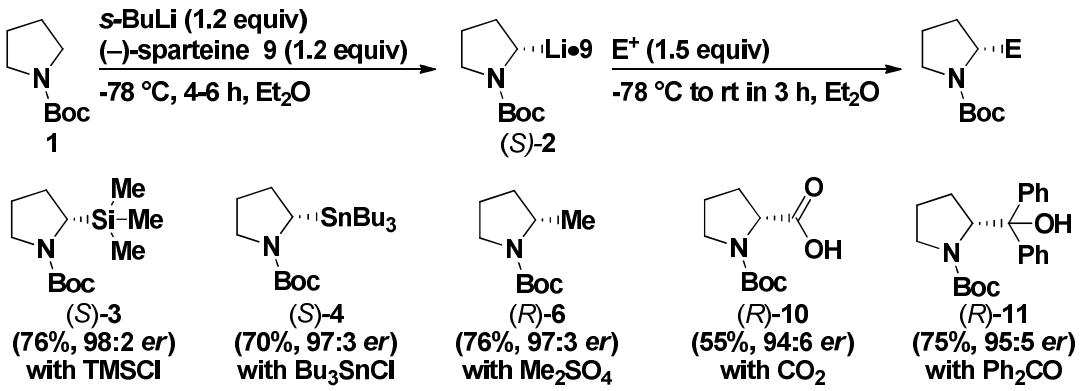
(–)-sparteine **9** belongs to the bisquinolizidine class of alkaloids[23] and was first isolated in 1851 from seeds of Scotch broom (*Cytisus scoparius* (L.) Link*).*[20] Other genera, where this molecule can be found are *Lupinus* and *Spartium.*[19]

The main route for obtaining enantiopure (–)-sparteine **9** is isolation from branches of Scotch broom.[24] This process is also possible on a big scale and is industrially used.[21] Another method for affording substancial amounts of this compound is partial chemical synthesis from (+)-lupanine (Scheme 5).[20, 23]



Scheme 5. Semisynthesis of (–)-sparteine from (+)-lupanine.

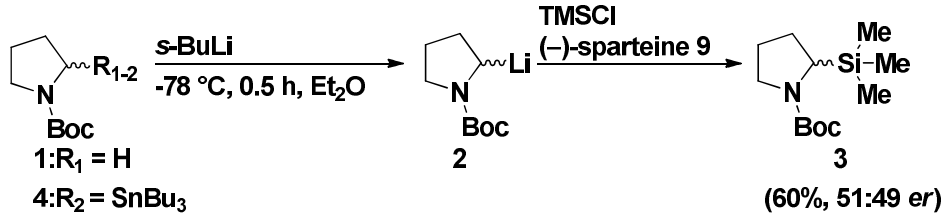
Led by the progress in the field of stereoselectivity achieved by D. Hoppe, the Beak group applied (–)-sparteine **9** to the carbamate *N*-Boc-pyrrolidine **1** (Scheme 6).[25] **1** was metallated with equimolar amounts of *s*-BuLi/(–)-sparteine **9** at -78 °C for 4-6 hours in Et_2O, then the dipole-stabilized lithiated intermediate was trapped with a range of electrophiles. The scope of the stereoselective lithiation-substitution sequence included stannylation, carboxylation, silylation, methylation and benzophenone-trapping with overall yields ranging from 55-76% with *er* up to 98:2. Despite the longer lithiation time with *s*-BuLi/(–)-sparteine **9** than *s*-BuLi/TMEDA (4-6 vs 3.5 hours) this protocol allows achieving full stereocontrol over the sequence of lithiation-nucleophilic substitution involving *N*-Boc-pyrrolidine **1**.



Scheme 6. Asymmetric lithiation-trapping of *N*-Boc-pyrrolidine.

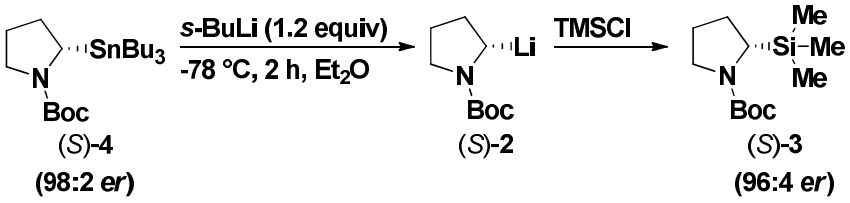
Two possible mechanisms of enantioinduction in the lithiation-trapping sequence of *N*-Boc-pyrrolidine **1** are worth considering—either the pair *s*-BuLi/(–)-sparteine enantioselectively deprotonates **1** leading to a configurationally stable enantioenriched intermediate (*S*)-**2**, which reacts stereoselectively with the electrophile or an enantioenriched product is formed from the complex between racemic lithiated intermediate **2** and (–)-sparteine during the nucleophilic substitution.[25]

In order to prove if the key to enantioinduction is enantioselective deprotonation or the enantioenriched products are formed during the nucleophilic substitution, experiments have been designed to test the effect of (–)-sparteine **9** selectively over the substitution pathway (Scheme 7).[6, 25] Adding TMSCl and (–)-sparteine **9** to *rac*-*N*-Boc-2-lithio-pyrrolidine **2** generated by deprotonation of *N*-Boc-pyrrolidine **1** or from **4** by tin-lithium exchange gave essentially racemic products, which undoubtedly proves that (–)-sparteine **9** exerts no enantioinducing influence over the nucleophilic substitution pathway.[6]



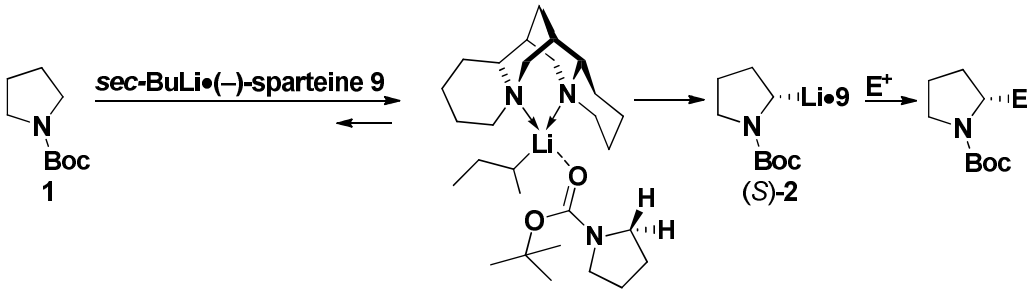
Scheme 7. Role of (–)-sparteine in the substitution pathway.

Moreover, lithiated intermediate (*S*)-**2** was formed from enantioenriched stannylpyrrolidine (*S*)-**4** (98:2 *er*) *via* tin-lithium exchange (Scheme 8).[6, 26] After trapping with TMSCl, (*S*)-**3** was synthesized in 96:4 *er*. This proves that (2*S*)-*N*-Boc-2-lithiopyrrolidine (*S*)-**2** is configurationally stable at -78 °C and that exclusively asymmetric deprotonation is the enantiodetermining step.



Scheme 8. Lithiation by tin-lithium exchange.

Having found that the deprotonation of *N*-Boc-pyrrolidine **1** by the pair *s*-BuLi/(–)-sparteine **9** is the vital step for enantiocontrol, its mechanism was revealed (Scheme 9).[27, 28] The chelate between *s*-BuLi and (–)-sparteine **9**, which serves as a chiral base, binds reversibly to the carbonyl oxygen of *N*-Boc-pyrrolidine **1** to form rapidly a prelithiation complex. Next, the actual lithiation takes place—the chiral base detaches selectively the *pro*-(*S*) hydrogen by recognizing enantiotopic faces[20], so the configurationally stable (2*S*)-*N*-Boc-2-lithio-pyrrolidine (*S*)-**2** originates. The deprotonation is a slower process than the precomplex formation, hence is rate determining. After trapping with electrophiles, the configuration of the chiral center is retained.[25]

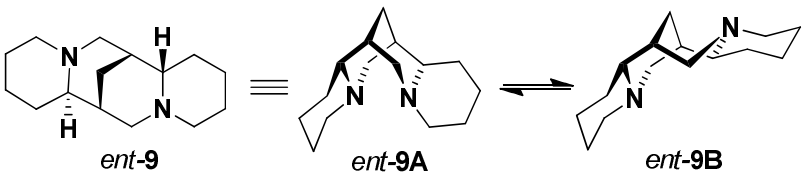


Scheme 9. Mechanism of the asymmetric lithiation of *N*-Boc-pyrrolidine.

It is well known, that (–)-sparteine **9** cannot unveil its enantioinducing potential in coordinating solvents such as THF, *i.e.* the products are racemic.[29] This phenomenon is explained either by lack of chelation between *s*-BuLi and (–)-sparteine **9** or by a faster deprotonation of *N*-Boc-pyrrolidine **1** by the complex *s*-BuLi/THF than *s*-BuLi/(–)-sparteine **9**.[8] Hence, noncoordinating solvents must be employed for highly enantioselective deprotonation processes using *s*-BuLi/(–)-sparteine **9**.[29] This justified the use of Et_2O in all enantioenriched syntheses, involving lithiation-trapping of *N*-Boc-pyrrolidine **1**.

For affording opposite enantiomers chemists can uitilize (+)-sparteine *ent*-**9** with similar outcome (Fig. **2.**).[20] All of the above mentioned mechanistic principles also apply to this alkaloid. Being the enantiomer of (–)-sparteine **9**, (+)-sparteine *ent*-**9** promotes the deprotonation on the opposide side of the pyrrolidine ring plain by selectively detaching the pro-(*R)* hydrogen, hence (2*R*)-*N*-Boc-2-lithio-

pyrrolidine originates. After trapping with electrophiles, the configuration of the chiral centre is retained.[6, 20]

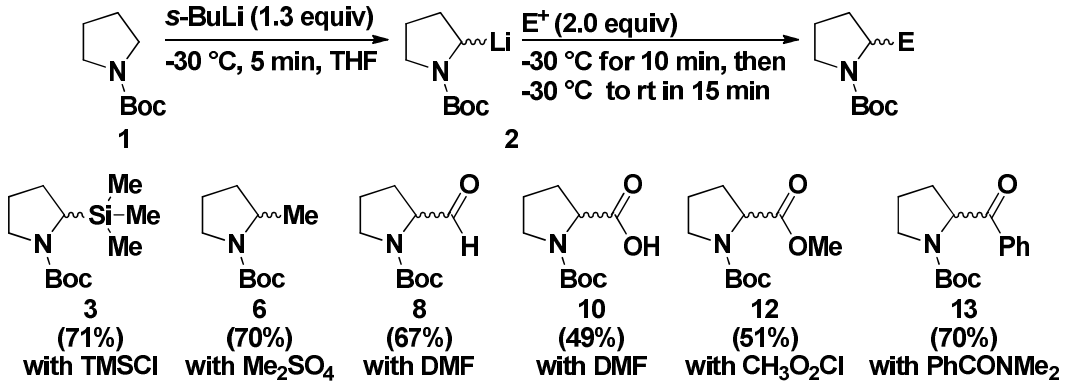


ent-**9** *ent*-**9A** *ent*-**9B**

Fig. 2. Structural formula and conformations of (+)-sparteine.

1.2.4 Diamine-free lithiation-trapping

In a communication from 2010, O´Brien *et al.* disclosed a simple and convenient protocol applicable only for the syntheses of racemic samples, which seems to solve the Green Chemistry related problems of the initial procedure.[8] By switching from Et_2O to the more coordinating solvent THF and by running the reaction at -30 °C instead of -78 °C, it was shown that a diamine-free lithiation of *N*-Boc-pyrrolidine **1** over the time of 5 minutes can be achieved. The lithiated pyrrolidine **1** in absence of TMEDA was then trapped with a range of electrophiles to give products **3, 6, 8, 10, 12, 13** in yields from 49-71% (Scheme 10). Due to the coordinating effects of THF to the organolithium the pair *s*-BuLi/THF serves as a base, making the diamine unnecessary, while elevating the reaction temperature accelerates the lithiation process. In this manner, the atom economy and energy efficiency are improved.[17] 2-Methyltetrahydrofuran (2-MeTHF), which is a "greener" alternative to THF, also can be used as a solvent in this diamine-free protocol, because the complex *s*-BuLi/2-MeTHF is also an effective proton acceptor.[17]

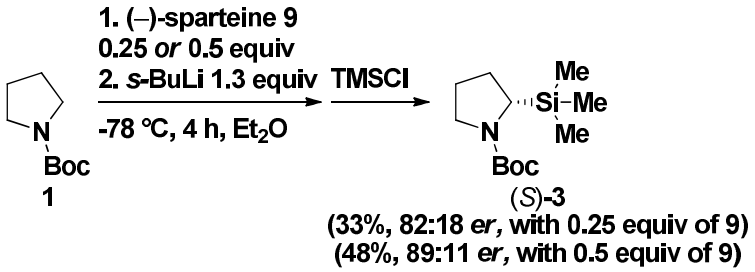


Scheme 10. Racemic lithiation-trapping of *N*-Boc-pyrrolidine.

1.2.5 Stoichiometry and temperature in asymmetric lithiation-trapping

Despite decreasing the atom economy[17], a chiral ligand is an absolute necessity for synthesizing enantioenriched products—*s*-BuLi and (–)- or (+)-sparteine form a chiral base, which induces the enantiodetermining deprotonation.[5, 27, 28]

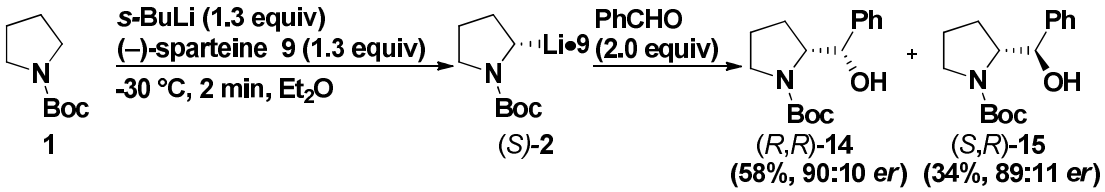
An attempt to determine if (–)-sparteine **9** can be reduced from equimolar to a substoichiometric amount in accordance to the "Catalysis" principle has also been carried out (Scheme 11).[26] Utilizing the standard 1.3 equivalents of *s*-BuLi paired with 0.25 equivalents or 0.5 equivalents of (–)-sparteine **9** for metallating *N*-Boc pyrrolidine **1** at -78 °C for 4 hours in Et_2O eroded the yields as well the *er* after trapping with TMSCl. The reported results were 33% yield, 82:18 *er* for 0.25 equivalents and 48% yield, 89:11 *er* for 0.5 equivalents of (–)-sparteine **9**. This proves that applying this chiral diamine in equimolar to *s*-BuLi amounts is a must in order to achieve high yields and enantioenrichement over 95% in asymmetric deprotonation reactions.[25, 31]



Scheme 11. Catalytic asymmetric deprotonation of *N*-Boc pyrrolidine.

A "greener" and more convenient asymmetric lithiation procedure, distinguished by a significantly shorter duration of asymmetric lithiation, which consumes less energy in accordance to the 6th Green Chemistry principle "Design for Energy Efficiency", has been reported by O´Brien and coworkers (Scheme 12).[30] The main principle is analogous to previous work—elevating the reaction temperature.

After treatment of *N*-Boc-pyrrolidine **1** with the pair *s*-BuLi/(–)-sparteine **9** in Et_2O at -30 °C for 2 minutes and trapping with benzaldehyde (1*R,*2*R*)-**14** and (1*S,*2*R*)-**15** were formed in 92% total yield and respective *er* of 90:10 and 89:11.



Scheme 12. Asymmetric lithiation-trapping protocol at -30 °C.

Higher temperatures accelerate the rate of deprotonation, but bear the risks that the chemical stability of the metallated intermediate (*S*)-**2**, the enantioselectivity of deprotonation and the configurational stability of the lithiated species (*S*)-**2** can be compromised.[30] The latter two factors are the reason why O'Brien's protocol is distinguished by lower enantiopurity of the synthesized samples than originally reported by Beak (~90:10 versus > 95:5 *er*).

1.2.6 Points still open for further optimization

As already mentioned, the vast majority of the successful asymmetric syntheses (*er* ~95:5) involving lithiation-trapping of *N*-Boc-pyrrolidine **1** have taken place in Et_2O. This solvent however is characterized by volatility and low boiling point, formation of explosive peroxides and insufficient recovery after work-up due to solubility in the water phase.[32] These factors make Et_2O an unsustainable solvent, which could lead to environmental pollution and pose a hazard for the operating chemist. This is why it can be stated that one unsolved problem of all reported lithiation-trapping protocols for *N*-Boc-pyrrolidine **1** over the years is finding a "green" solvent.

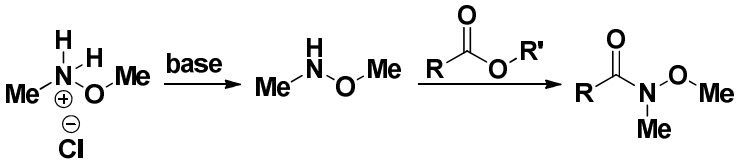
Another point would be finding conditions offering a better balance between duration of asymmetric lithiations and enantiopurity of the final product. Despite being characterized by moderate to high yields (55-76%) and excellent *er* (>95:5), Beak's 1991 reported protocol[25] is inconveniently long for performing metalation of *N*-Boc-pyrrolidine 1, requiring between 4 and 6 hours at -78 °C. O'Brien's stereoselective protocol from 2013[30], on the other hand, is distinguished by a much shorter lithiation time (2 minutes at -30 °C in Et_2O), but also by undesirably lower *er* compared with Beak's results (~90:10 vs >95:5), which means that the strategy to elevate the deprotonation temperature did compromise the enantiopurity of the final product.

1.3 Weinreb Amides—a brief overview

Since their invention in 1981, the *N*-methoxy-*N*-methyl-amides, more commonly known as Weinreb amides[33], have proven to be first line reagents for affording ketones *via* coupling with organolithium or organomagnesium (Grignard) compounds.[34] In this chapter, the most common ways of synthesizing Weinreb amides and selected examples, illustrating the pharmaceutical value of their application will be briefly presented.

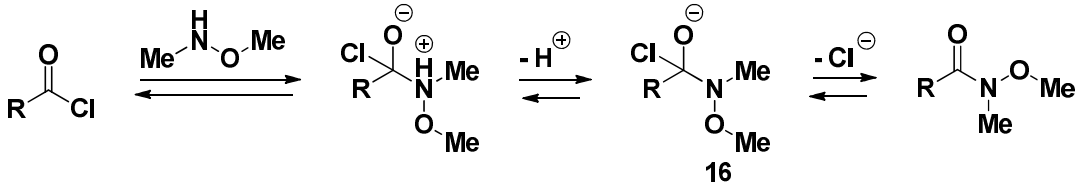
1.3.1 Preparation of Weinreb amides

Generally, the reaction for obtaining a Weinreb amide involves a carboxylic acid derivative and *N,O*-Dimethylhydroxylamine, generated *in situ* by deprotonation from the corresponding *N,O*-Dimethylhydroxylamine hydrochloride (MeONHMe•HCl) (Scheme 13).[35]



Scheme 13. Synthesis of Weinreb amides.

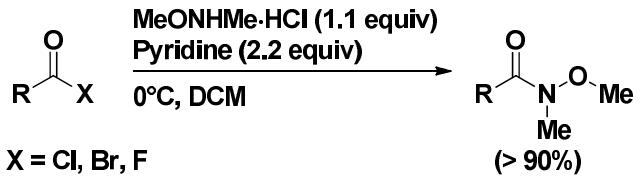
If an acyl halide is available, building a Weinreb amide from it is a relatively straightforward procedure.[36] This reaction is a nucleophilic substitution,[7] in which the nucleophile *N,O*-Dimethylhydroxylamine, liberated by bases, attacks the strongly positively polarized acyl carbon of the halide. After an intramolecular acid-base reaction, the desired *N*-methoxy-*N*-methylamide is formed after collapse of the tetrahedral intermediate **16** under departing of the leaving group Cl^- (Scheme 14).



Scheme 14. Mechanism of Weinreb Amide synthesis starting from acyl chlorides.

A standard procedure for this type of synthesis (Scheme 15), although characterized by high yields (>90%)[33], requires excess of toxic bases such as pyridine or other amines (2.2 equivalents),

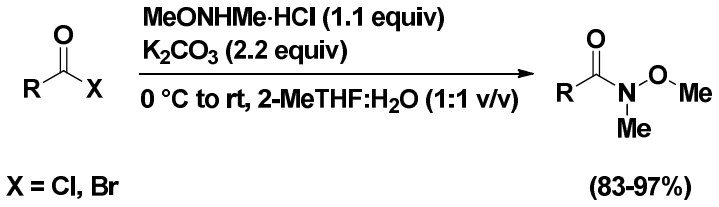
halogenated or ether-type solvents and in some cases purification of the crude product (by chromatography, recrystallization or distillation).[37] These three factors are disadvantages of the method—the health or safety of the organic chemist can be endangered by noxious organic chemicals, while crude purifications make the method more time consuming and lead to excessive use of solvents, related to environmental pollution.[37]



Scheme 15. Weinreb Amide synthesis starting from acid halides.

Recent advances in the preparation of Weinreb amides from acid halides have been made by Pace and coworkers (Scheme 16).[37] The Pace group developed a method distinguished by the use of the anorganic and non-toxic base K_2CO_3, mild reaction conditions in the "green" biphasic solvent medium 2-MeTHF/water, almost quantitative conversion (isolated yields range is 83-97%) and thus no necessity to purify the crude product after work-up which saves time, effort and use of organic solvents.

Being almost effortless and safe for the operating chemist, furthermore environmentally benign[37], this approach to Weinreb amide synthesis starting from acid halides offers very strong advantages compared to the previously reported examples in literature.



Scheme 16. Preparation of Weinreb Amides in 2-MeTHF/H_2O.

However, if an acid chloride is not synthesizable without "damaging" other key molecule functionalities, another option for Weinreb amide formation is the utilisation of carboxylic acids as starting materials.[38] The direct reaction between the free amine *N,O*-Dimethylhydroxylamine and a COOH group would result not in amide bond formation, but in the generation of a stable salt through an acid-base reaction. In order to transform the ionic bond into an amide bond (*i.e.* to condense the

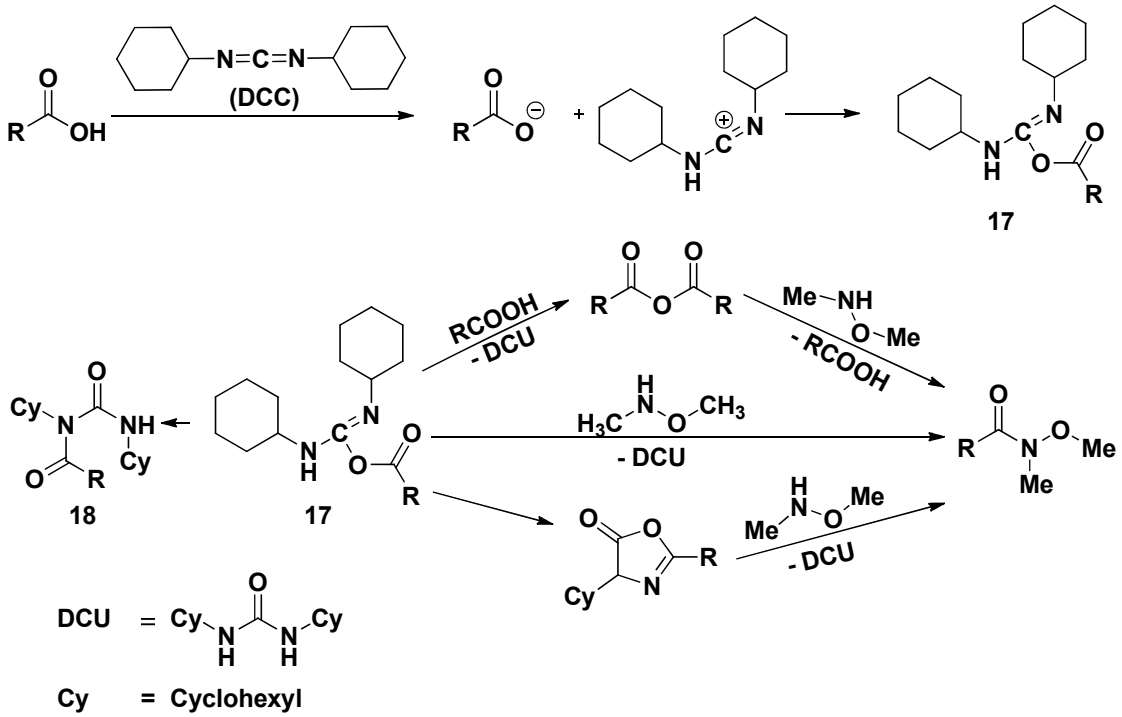
salt) temperatures in the range 160-180 °C are needed, which are inconveniently high and potentially harmful for other molecule functionalities.[39]

However, activating the acid by letting it react with a so called coupling reagent makes a subsequent nucleophilic attack from the amine and an immediate formation of the amide bond possible. The carboxylic acid reacts with the coupling reagent to form a strong acylating reagent, which is then aminolysed to the desired Weinreb amide.[39, 40]

The most common approach used to form Weinreb amides from acids is using dicyclohexylcarbodiimide (DCC) as a coupling reagent.[40] Generally, after the addition of the carboxylic acid to the carbodiimide, an *O*-acylisourea **17** is formed *in situ* as a key acylating intermediate, which is then aminolysed to give the desired amide and dicyclohexylurea (DCU) as a byproduct.[40]

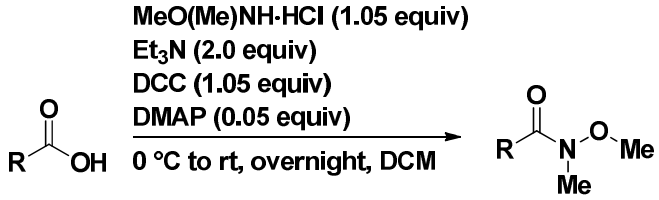
The exact mechanism[40, 41] (Scheme 17) of this transformation consists of the following steps: after an acid-base reaction, the nucleophilic addition of the carboxylate to the carbodiimide takes place, which genererates the key *O*-acylisourea **17**. *O*-acylisourea **17** is a highly reactive acylating agent. There are three possible pathways which lead from *O*-acylisourea **17** to the desired product. First, immediate nucleophilic attack from the amine to the carboxyl atom of generates the Weinreb amide. Second, attack by a second molecule of the carboxylate gives a symmetrical anhydride, which is then aminolysed to give the expected Weinreb amide. Third, *O*-acylisourea **17** cyclizes to an oxazolone, a species also subsequently aminolysed under amide bond formation.

However, *O*-acylisourea **17** is involved in a 4th pathway, which can reduce the overall yield. In an intramolecular rearrangement reaction, *N*-acylurea **18** can be formed.[40] This species is resistant to nucleophilic attacks, so formation of *N*-acylurea **18** is an undesired side reaction.



Scheme 17. Mechanism of Weinreb amide synthesis from carboxylic acid.

A standard reaction set-up for this type of synthesis[42] (Scheme 18) serves two purposes—amide bond formation and suppression of *N*-acylurea **18** formation. The amide bond is formed from the already mentioned *N,O*-Dimethylhydroxylamine hydrochloride, deprotonated by a base such as triethylamine (Et_3N) and a carboxylic acid, activated by DCC. 4-Dimethylaminopyridine (DMAP) and dichloromethane (DCM) are applied in order to suppress the *N*-acylurea **18** formation. DMAP is a nucleophile that attacks *O*-acylisourea **17** faster than the competing intramolecular *N*-acylurea rearrangement and generates an intermediate still active enough to be aminolysed.[39] The *N*-acylurea rearrangement reaction is much slower in the solvent DCM.[40]



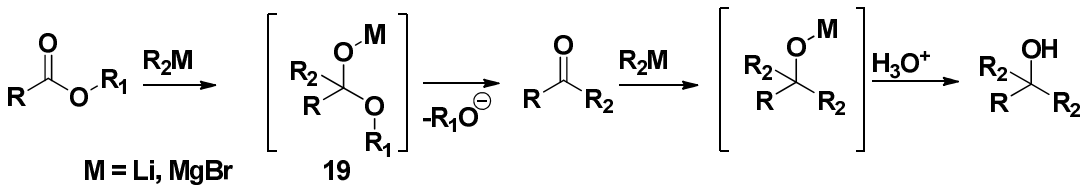
Scheme 18. Weinreb amide synthesis with DCC as a coupling reagent.

The drawbacks of the carboxylic acid activation approach are the pyrophoric or explosive properties of DCC and production of accompanying byproducts (DCU, *N*-acylurea **18**) due to formation of the active intermediate *O*-acylisourea **17**. The latter requires (in some cases complicated and not always successful) chromatographic purifications associated with contaminant solvents.[37]

In conclusion, it can be said that this method is effective regarding the Weinreb amide synthesis[37], but it cannot be termed a "green" approach, since its characteristics do not correspond to the 1st ("Prevention"), 2nd ("Atom Economy"), 3rd ("Less Hazardous Chemical Synthesis") and 5th ("Safer Solvents and Auxiliaries") Green Chemistry principles.

1.3.2 Use of Weinreb amides in ketones synthesis

Activated carboxylic acid derivatives, such as esters, lead to a tertiary alcohol after treatment with organometallics (Scheme 19).[43] Mechanistically, the first step involves the nucleophilic addition of one equivalent of the organometallic reagent to the carbonyl producing a tetrahedral intermediate **19**. Next, under departure of the alcoholate group $R'O^-$ the intermediate **19** collapses, so a ketone is formed. Ketones are much more electrophilic than carboxylic acid derivatives, so the attack of a second molecule of the nucleophile and thus the formation of a tertiary alcohol is inevitable.[44] This is why carboxylic acid derivatives are associated with over-addition of the organometallic reagent.

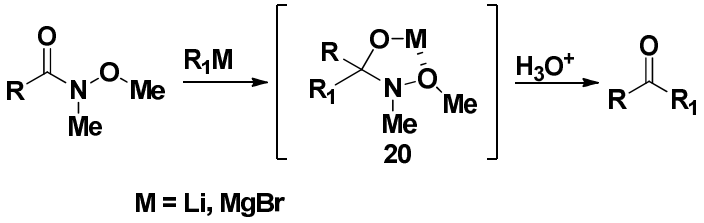


Scheme 19. Reactivity of carboxylic acid derivatives with organometallics.

Weinreb amides, however, produce ketones chemoselectively after reacting with organolithiums or Grignard reagents, which represents the major advantage of these *N*-methoxy-*N*-methyl-substituted amide moieties over other activated carboxylic acid derivatives (Scheme 20).[34, 36, 38]

From a mechanistic point of view, the first step is the same as other carboxylic moieties—the nucleophilic addition of one equivalent of the organometallic reagent to the carbonyl, forming the tetrahedral intermediate **20**. However, unlike **19**, **20** is stabilized by the complex formation between metal cation and methoxy oxygen. This interaction, characteristic exclusively for Weinreb amides, prevents the intermediate **20** from collapsing. Hence, no leaving group is removed and there is no further attack from the organometallic compound.

The stable intermediate **20** is converted by acidic hydrolysis into the corresponding carbonyl compound at the very end of the reaction process.[33]



Scheme 19. Mechanism of ketone synthesis from Weinreb amides.

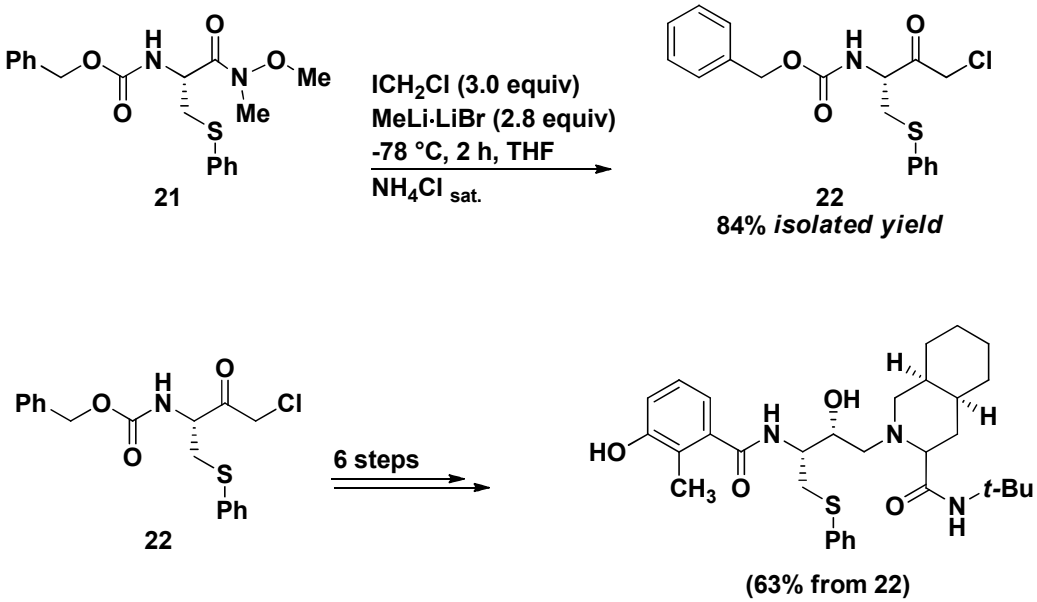
Chemoselective ketone synthesis is the most important utilization of the *N*-methoxy-*N*-methyl amide motif in organic chemistry.[34, 36, 38] Besides being a one-pot reaction, Weinreb's ketone synthesis is characterized by good to excellent yields under mild conditions. It is carried out at -78 or 0 °C, and involves ethereal type solvents such as THF, Et_2O or 1,2-dimethoxy ethane (DME).[34]

1.3.3 Applications of Weinreb in medicinal chemistry

Weinreb's ketone synthesis has turned into a fundamental synthetic pathway in organic chemistry. The formed carbonyl species usually serve as building blocks (synthons) in multistep reaction sequences, focused *inter alia* on obtaining complex natural products[45, 46] or pharmaceuticals[47].

Since there are a vast number of reported examples, one recent example from the category drug synthesis will be presented in this chapter.

The densely substituted Weinreb amide **21**, along with its corresponding α-chloromethyl ketone **22** are key synthons for the stepwise formation of a chiral substituted 1,3-diamino-butan-2-ol, the pharmacophore structure of the HIV-protease inhibitor Nelfinavir, as reported by Pace *et al.* (Scheme 21).[47] The Weinreb amide **21** was homologated to the ketone **22** by treatment with $LiCH_2Cl$, generated *in situ* from excess of chloroiodomethane (ICH_2Cl) and methyllithium-lithium bromide at -78 °C for 2 hours in THF. The α-chloromethyl ketone **22** was obtained in 84% isolated yield. Nelfinavir mesylate was obtained from **22** in 63% yield in 6 steps.



Scheme 21. Pace's Nelfinavir synthesis.

1.4 CPME—a perspective "green" solvent

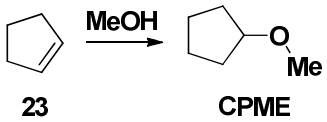
Cyclopentyl methyl ether (CPME) belongs to the class of ethereal type solvents, along with Et_2O, THF, 1,4-dioxane, DME and methyl *tert*-butyl ether (MTBE).[32]

Despite being commercially available just since 2005, CPME is rapidly gaining popularity in the field of organic synthesis and is considered to be a highly perspective "green" solvent.[32] The advantageous features that make CPME a "green" solvent are:

- high hydrophobicity, which is a prerequisite for efficient recovery of the solvent from the water phase after aqueous work-up[32, 48]
- low peroxide formation and a narrow explosion range, making the solvent safe to store and handle[32, 48]
- low acute or subchronic toxicity and negative genotoxicity and mutagenicity.[48]

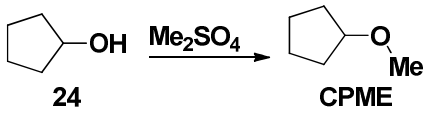
1.4.1 Preparation of CPME

Synthesizing CPME by the addition of methanol (MeOH) to cyclohexane is a perfect illustration of a "green" chemical reaction (Scheme 22).[32, 48] Since in this case the two reagents form together only one product, no organic byproducts (*i.e*. no waste) is generated and the mass of all starting materials is completely incorporated in the final product. These two facts are in absolute accordance to the 1st and 2nd Green Chemistry principle, termed "Prevention" and "Atom Economy" respectively.[16]



Scheme 22. Preparation of CPME from cyclopentene.

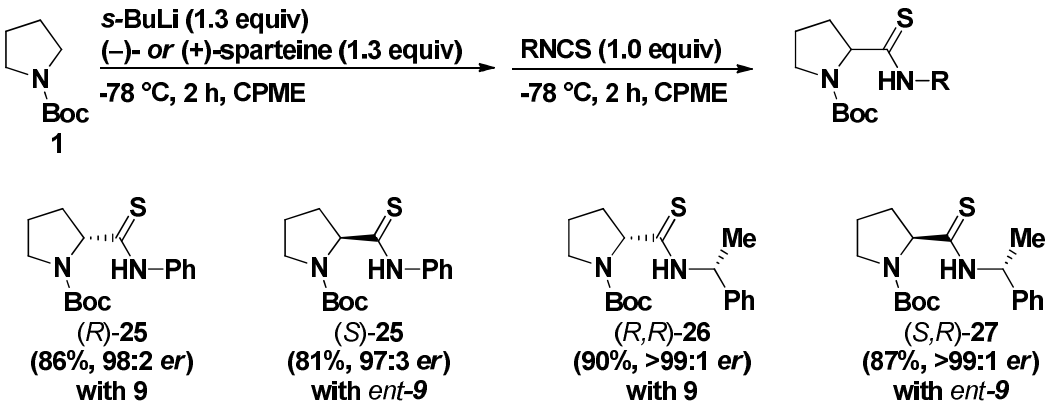
CPME can also be obtained by reacting cyclopentanol **24** with dimethyl sulfate Me_2SO_4 in a nucleophilic substitution process (Scheme 23).[32] This synthetic approach, however, has the drawback that byproducts are formed, which contradicts to the 1st and 2nd principle of Green Chemistry.[16] Furthermore, $(CH_3)_2SO_4$ is a highly toxic alkylating reagent,[49] which is opposed to the 3rd Anastas' principle "Less Hazardous Chemical Synthesis".[16]



Scheme 23. Preparation of CPME from cyclopentanol.

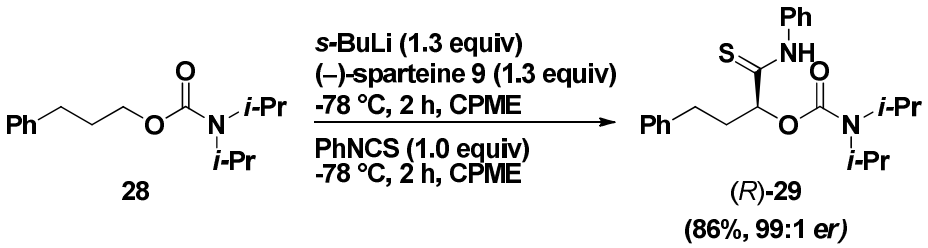
1.4.2 CPME in enantioselective lithiations

Two factors make CPME a suitable solvent for organometallic reactions. Distinguished by high hydrophobicity, CPME is very easy to dry, hence suitable for reactions involving water-sensitive compounds such as organolithiums.[32, 48] Furthermore, being chemically inert towards nucleophiles and strong bases,[32, 48] CPME can successfully be utilized as a solvent for lithiation-trapping sequences. Recent work of Pace *et al.* can be referenced as a noteworthy example for deprotonative enantioselective lithiations in CPME.[50] Lithiating *N*-Boc-pyrrolidine **1** by excess of the pair *s*-BuLi/(–)-sparteine **9** for 2 hours at -78 °C in CPME; followed by trapping with achiral or optically pure isothiocyanates for 2 hours at -78 °C resulted in obtaining enantio- or diastereopure thioamides in high yields from 81% to 90% and excellent *er* up to > 99:1 (Scheme 24).



Scheme 24. First asymmetric lithiation-trapping of *N*-Boc-pyrrolidine in CPME.

The portfolio of dipole stabilized carbanions generated by asymmetric lithiation in CPME was broadened by the lithiation of Hoppe's carbamate **28**.[50] Deprotonating by excess of *s*-BuLi and (–)-sparteine **9**, followed by trapping with phenyl isothiocyanate under the above described conditions led to affording enantioenriched thioamide (*R*)-**29** in 86% yield and >99:1 *er* (Scheme 25).



Scheme 25. Asymmetric lithiation-trapping of Hoppe's carbamate in CPME.

2 Own contribution

As we have learned in Chapter 1, the initial procedure for lithiation-trapping of *N*-Boc-pyrrolidine **1** has been dramatically improved over the years. First, stereoselective syntheses with excellent enantiopurity (>95:5 *er*) of 2-substituted *N*-Boc-pyrrolidine derivatives are now possible by applying (–)-sparteine **9** and (+)-sparteine *ent*-**9** instead of TMEDA. Second, a much more convenient procedure for racemic lithiation-trapping has been reported—the lithiation times for racemic products have been shortened from 3.5 hours to just 10 minutes by substituting the original solvent Et_2O by the more coordinating THF and elevating the reaction temperature from -78 °C to -30 °C.

However, if we take asymmetric lithiations into account, there are two issues that need to be addressed—a "green" solvent, as well as conditions offering a balance between lithiation duration and enantiopurity of the final product still need to be found. Beak's 1991 reported protocol[25] is characterized by moderate to high yields (55-76%) and excellent *er* (>95:5), but the procedure is rather inconveniently long (4-6 hours at -78 °C) and utilizes Et_2O, an unsustainable solvent. O'Brien's stereoselective protocol from 2013[30], on the other hand, is distinguished by a much shorter lithiation time than Beak reported (2 minutes at -30 °C in Et_2O), but also by undesirably lower *er* than Beak's results (~90:10).

In this context, this thesis reports an asymmetric lithiation protocol for *N*-Boc-pyrrolidine **1** at -78 °C for 30 minutes utilizing the solvent CPME, which has two beneficial features. First, CPME is a "green" solvent, which makes the reaction set-up more adherent to the requirements and trends of Green Chemistry.[16] Second, by utilizing CPME as a solvent instead of Et_2O the stereoselective deprotonation procedure of *N*-Boc-pyrrolidine **1** is characterized by a much shorter duration at -78 °C than originally reported[25] (30 minutes instead of 4 to 6 hours) but equally good yields and enantioselectivity (75-88% yield, *er* ranges from 95:5 to >99:1). Hence, a protocol that offers an optimal balance between lithiation time, lithiation temperature, yields and *er* has been developed.

This thesis also broadens the scope of the asymmetric lithiation-trapping of *N*-Boc-pyrrolidine **1**—for the very first time Weinreb amides have been employed as electrophiles in the trapping step. Herein the syntheses of 11 enantioenriched acylpyrrolidines are reported (75-88% yield, up to >99:1 *er*).

2.1 Results and discussion

2.1.1 Reaction conditions

The starting point of the project was to find the best lithiation time for *N*-Boc-pyrrolidine **1** in the new solvent CPME. The temperature was kept at -78 °C throughout the whole sequence for several reasons—this is a standard temperature for reactions with lithium containing compounds, which reduces the risk of undesired byproducts' formation[12] and bears minimal risk of compromising the enantiopurity of the product.[30] Since we speculated that the solvent would not influence the duration of nucleophilic substitution, trapping time was kept constant at 3 hours with the electrophile

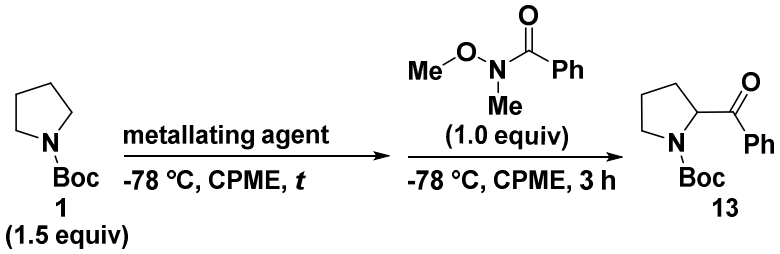
N-methoxy-*N*-methyl-benzamide. In fact, the lithiation time was the only variable to be examined.

In order to find suitable conditions for the syntheses of racemic samples which would serve for determining the enantiomeric ratio (*er*) as a reference, a few reactions utilizing the deprotonating agent

s-BuLi/TMEDA in CPME were performed (Table 1, entries 1-4). The initial attempt involved a two-hour metallation (Table 1, entry 1). However, since NMR-control showed that almost no conversion of the starting material had occurred, it was clear that after two hours there was very little amount of the lithiated species available for a nucleophilic attack, so we decided to shorten the deprotonation times. More notable results were obtained after 15 and 5 minutes (59% vs 65% yield; Table 1, entries 3 and 4). Hence, 5 minutes lithiation time was selected for performing the syntheses of racemic compounds.

The suitable conditions for asymmetric lithiations in CPME, which are the main goal of this project, were found after only one lithiation attempt. Deprotonation of **1** by the pair *s*-BuLi/(–)-sparteine **9** for

30 minutes at -78 °C in CPME, followed by trapping with *N*-methoxy-*N*-methyl-benzamide gave product **13** in pleasing 85% yield. (Table 1, entry 5). Therefore, a lithiation time of 30 minutes was accepted as the "gold standard" for chiral lithiations.



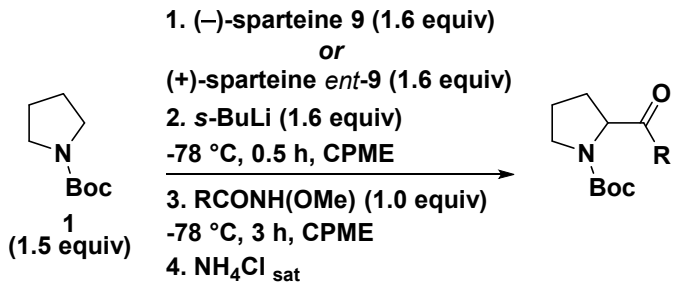
Entry	Metallating agent	Lithiation time (min)	Yield (%)
1	*s*-BuLi/TMEDA	120	-
2	*s*-BuLi/TMEDA	60	-
3	*s*-BuLi/TMEDA	15	59
4	*s*-BuLi/TMEDA	5	65
5	*s*-BuLi/(–)-sparteine **9**	30	85

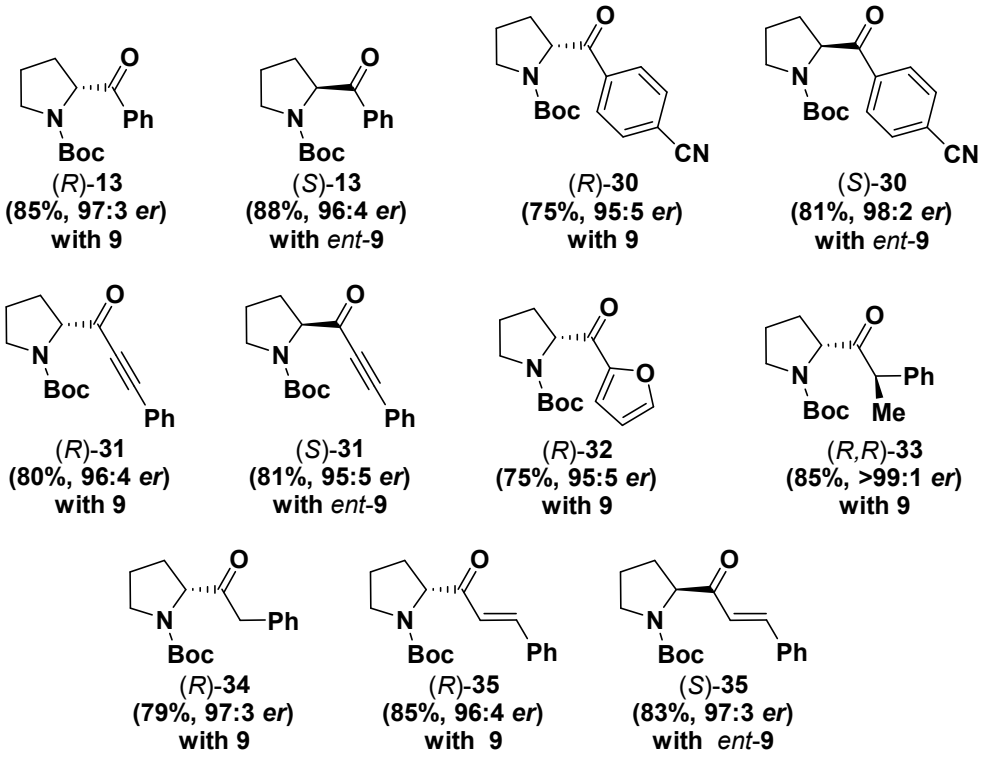
Table 1. Optimization of the reaction.

2.1.2 Own syntheses

Ultimately, we selected 30 minutes at -78 °C in CPME for the asymmetric lithiation of *N*-Boc-pyrrolidine **1** and trapped with a range of electrophiles, focusing exclusively on ketone synthesis with Weinreb amides as acyl precursors. Two ligands are the key to stereocontrol–the (*R*)-series of ketones was synthesized by utilizing (–)-sparteine **9**, while for the opposite enantiomers we resorted to (+)-sparteine *ent*-**9** to afford analogous excellent enantiopurity. The results are presented in Scheme 26.

Benzoylation proceeded smoothly to give (*R*)-**13**[51] (85%, 97:3 *er*) and (*S*)-**13**[52] (88%, 96:4 *er*), while *p*-cyanobenzoylation was characterized by lower yields but equally good stereoselectivity—(*R*)-**30** (75%, 95:5 *er*) and (*S*)-**30** (81%, 98:2 *er*). We successfully introduced allyloxo (*R*)-**35**[53] (85%, 96:4 *er*) and (*S*)-**35**[53] (83%, 97:3 *er*), as well as propargyloxo types of functionalities (*R*)-**31** (80%, 96:4 *er*) and (*S*)-**31**[54] (81%, 95:5 *er*) *via* reactions with the corresponding Weinreb amides. We have also obtained (*R*)-**32** (75%, 95:5 *er*) through furoylation and (*R*)-**34** (79%, 97:3 *er*) through phenylacetylation in very good yields. Finally, the reaction between the generated chiral organolithium and an optically active Weinreb amide proceeded with an excellent diastereoselectivity to afford (*R,R*)-**33** (85%, >99:1 *er*). The absolute configuration of the chiral centers of (*R*)-**13** and (*R,R*)-**33** was determined *via* X-ray analysis.



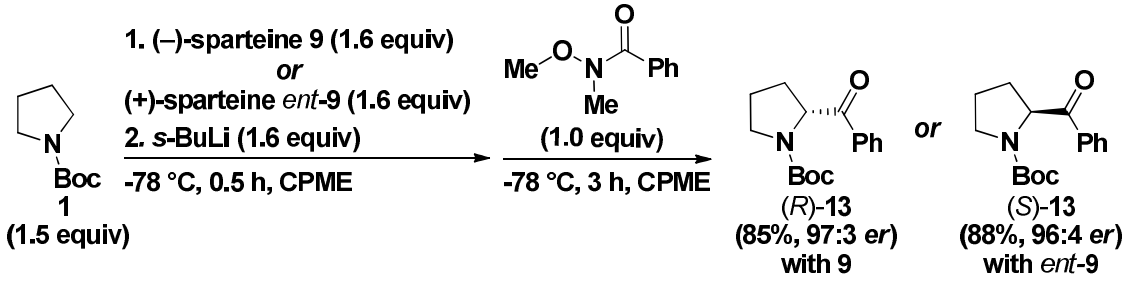


Scheme 26. Scope of the reaction.

The very first pair of synthesized optical antipodes in the project were two known benzoylated *N*-Boc-pyrrolidine derivatives (Scheme 27). (*R*)-**13**[51] was synthesized after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (–)-sparteine **9** for 30 minutes at -78 °C in CPME, followed by trapping with *N*-methoxy-*N*-methyl-benzamide for 3 hours at -78 °C and isolated in sufficient purity from the respective crude product after column chromatography in 85% yield. The absolute configuration of the chiral center was determined *via* X-ray analysis.

Compound (*S*)-**13**[52] was formed after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (+)-sparteine *ent*-**9** for 30 minutes at -78 °C in CPME, followed by trapping with *N*-methoxy-*N*-methyl-benzamide for 3 hours at -78 °C and extracted from the crude product by column chromatography in 88% yield.

The enantiopurity of the products, expressed as *er,* was determined in both cases using High Performance Liquid Chromatography (HPLC) and was 97:3 for (*R*)-**13** and 96:4 for (*S*)-**13**.

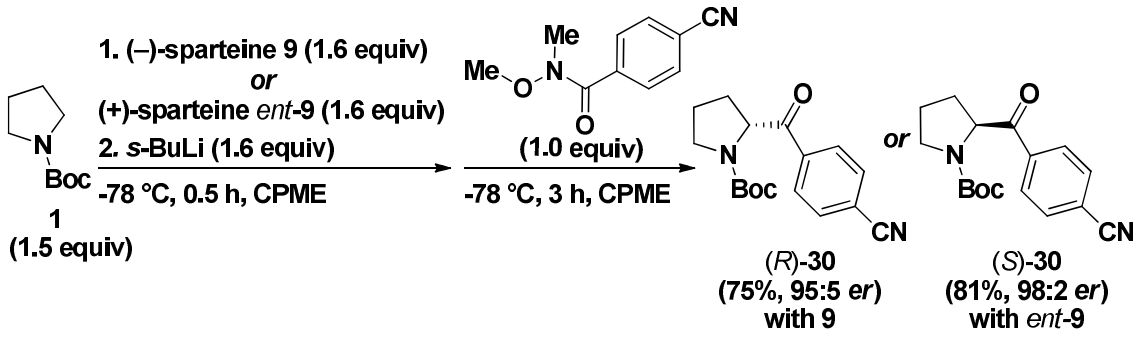


Scheme 27. Synthesis of (*R*)-**13** and (*S*)-**13**.

The product portfolio was broadened by introducing a *p*-cyanophenyl residue to our series of asymmetric *N*-Boc-pyrrolidinyl ketones (Scheme 28). (*R*)-**30** was synthesized after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (–)-sparteine **9** for 30 minutes at -78 °C in CPME and subsequent trapping with 4-cyano-*N*-methoxy-*N*-methyl-benzamide for 3 hours at -78 °C. The pure product (*R*)-**30** was obtained after comlumn chromatography in 75% overall yield.

Utilizing *s*-BuLi and (+)-sparteine *ent*-**9** for the deprotonation of *N*-Boc-pyrrolidine **1** for 30 minutes at -78 °C in CPME and trapping with 4-cyano-*N*-methoxy-*N*-methyl-benzamide for 3 hours at -78 °C afforded (*S*)-**30**, isolated by column chromatography in 81% yield.

The *er* was determined by HPLC as follows: 95:5 for (*R*)-**30** and 98:2 for (*S*)-**30**.

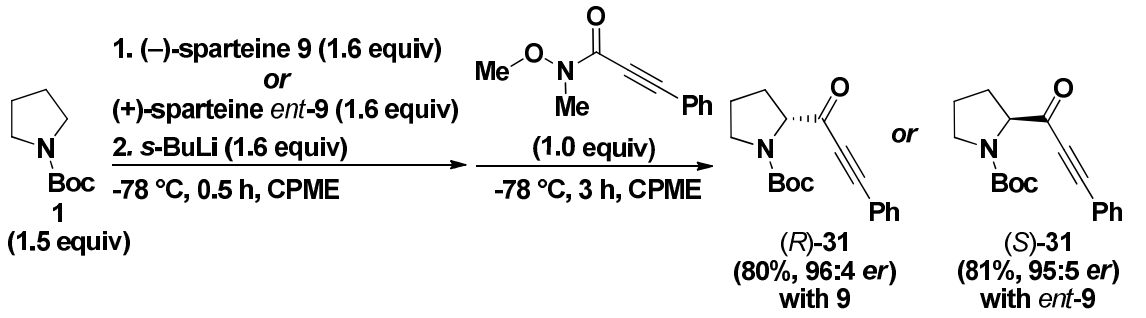


Scheme 28. Synthesis of (*R*)-**30** and (*S*)-**30**.

Next, propargyloxo types of functionalities were introduced (Scheme 29). Compound (*R*)-**31** was formed after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (–)-sparteine **9** for 30 minutes at -78 °C in CPME, followed by trapping with *N*-methoxy-*N*-methyl-3-phenyl-2-propynamide for 3 hours at -78 °C and isolated in sufficient purity from the respective crude product after column chromatography in 80% total yield.

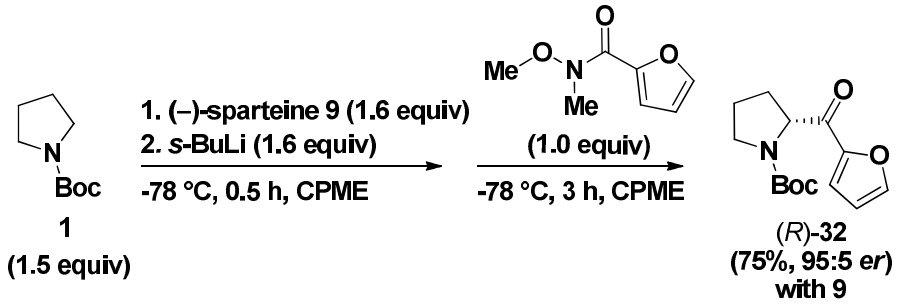
After lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (+)-sparteine *ent*-**9** for 30 minutes at -78 °C in CPME, followed by trapping with *N*-methoxy-*N*-methyl-3-phenyl-2-propynamide for 3 hours at -78 °C, compound (*S*)-**31**[54] was extracted from the crude product by column chromatography in 81% yield.

The enantiopurity of the products, expressed as *er,* was revealed by HPLC and was 96:4 for (*R*)-**31** and 95:5 for (*S*)-**31**.



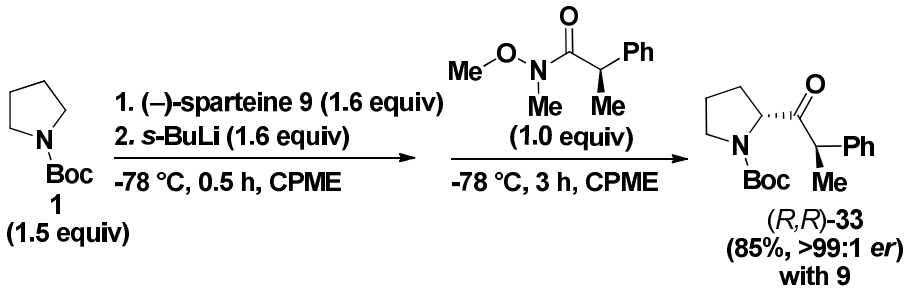
Scheme 29. Synthesis of (R)-**31** and (S)-**31**.

A heteroaromatic product completed our series of aromatic ketones (Scheme 30). *2*-methyl-2-propanyl (*2R)*-2-(2-furylcarbonyl)-1-pyrrolidinecarboxylate (*R*)-**32** was synthesized after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (–)-sparteine **9** for 30 minutes at -78 °C in CPME, followed by trapping with *N*-methoxy-*N*-methylfuran-2-carboxamide for 3 hours at -78 °C and isolated by column chromatography in 75% yield. The enantiopurity of the product, expressed as *er,* was revealed by HPLC analysis and was 95:5 in favour of the *R*-configurated stereoisomer (*R*)-**32**.



Scheme 30. Synthesis of (*R*)-**32**.

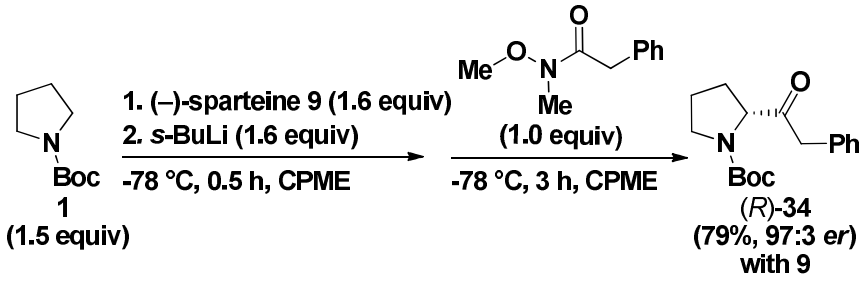
In a further procedure the chiral pool of Weinreb amides and the diastereoselectivity of the reaction protocol were exploited (Scheme 31). (*R,R*)-**33** was synthesized after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (–)-sparteine **9** for 30 minutes at -78 °C in CPME, followed by trapping with (2*R*)-*N*-methoxy-*N*-methyl-2-phenylpropanamide for 3 hours at -78 °C and isolated in sufficient purity from the crude product after column chromatography in 85% yield. The absolute configuration of the chiral center was determined *via* X-ray analysis. The reaction proceeded with an excellent diastereoselectivity (>99:1 *er*) quantified by HPLC.



Scheme 31. Synthesis of (*R,R*)-**33**.

Next, a phenylacetylation reaction was performed (Scheme 32). (*R*)-**34** was synthesized after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (–)-sparteine **9** for 30 minutes at -78 °C in CPME, followed by trapping with *N*-methoxy-*N*-methyl-2-phenylacetamide for 3 hours at -78 °C and isolated in sufficient purity from the crude product after column chromatography in 65% yield.

HPLC analysis confirmed 97:3 *er* in favour of the desired *R*-configurated stereoisomer (*R*)-**34**.

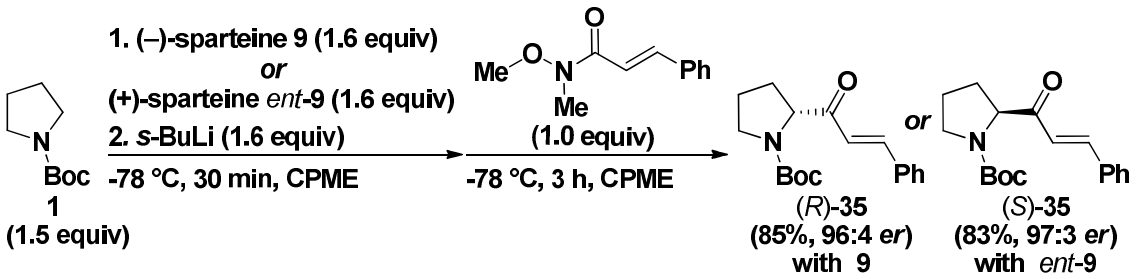


Scheme 32. Synthesis of (*R*)-**34**.

Finally, the product portfolio was completed by indroducing an allyloxo moiety (Scheme 33). (*R*)-**35**[53] was synthesized after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (–)-sparteine **9** for 30 minutes at -78 °C in CPME, followed by trapping with (2*E)*-*N*-methoxy-*N*-methyl-3-phenyl-2-propenamide for 3 hours at -78 °C and isolated in sufficient purity from the respective crude product after column chromatography in 85% yield.

Compound (*S*)-**35**[53] was formed after lithiation of *N*-Boc-pyrrolidine **1** with *s*-BuLi and (+)-sparteine *ent*-**9** for 30 minutes at -78 °C in CPME, followed by trapping with (2*E)*-*N*-methoxy-*N*-methyl-3-phenyl-2-propenamide for 3 hours at -78 °C and extracted from the crude product by column chromatography in 83% yield.

The enantiopurity of the products, expressed as *er,* was determined in both cases using High Performance Liquid Chromatography (HPLC) and was 96:4 for (*R*)-**35** and 97:3 for (*S*)-**35**.



Scheme 33. Synthesis of (*R*)-**35** and (*S*)-**35**.

2.2 Conclusion

It has been showcased on 11 examples, that the asymmetric lithiation of *N*-Boc-pyrrolidine **1** for 30 minutes at -78 °C in CPME proceeds with a high enantioselectivity (*up to* 99:1 *er*) over a short period of time. Furthermore, Weinreb amides make excellent acylating electrophiles for the trapping step. After 3 hours at -78 °C in CPME a series of 2-Acyl-*N*-Boc-pyrrolidinyl ketones was obtained in 75-88% yield and 95:5-99:1 *er.*

3 Experimental Data

3.1 General Methods

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Bruker maXis 4G instrument (ESI-TOF, HRMS). ^{1}H and ^{13}C, NMR spectra were recorded with a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) at 297 K using a directly detecting broadband observe (BBFO) probe. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in CDCl3) and δ 77.0 ppm (^{13}C in CDCl3). Spin-spin coupling constants (*J*) are given in Hz. In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, COSY and NOESY experiments.

CPME was distilled over Na/benzophenone. Chemicals were purchased from SigmaAldrich, Alfa Aesar Acros, Fluorochem and TCI Europe. Weinreb Amides were prepared as previously reported.[42] Solutions were evaporated under reduced pressure with a rotary evaporator. TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merchery-Nagel, Merk); the spots were visualised under UV light (λ = 254 nm) and/or molybdophosphoric acid (solution in ethanol) was used as revealing system.

3.2 General Procedures

General Procedure 1

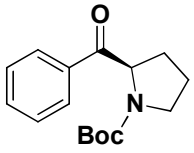
To a cooled (-78 °C) solution 0.2 M of *N*-Boc-pyrrolidine **1** (1.5 equiv) and (–)-sparteine **9** (1.6 equiv) under Argon in dry CPME was added dropwise a solution of *s*-BuLi (1.6 equiv) and the reaction mixture was stirred for 30 min, then Weinreb Amide (1.0 equiv), in CPME was added slowly. The reaction mixture was quenched after 3 hours with sat. NH_4Cl solution (5 mL) and stirred 1-2 min before diethyl ether was added and the phases separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (hexane/AcOEt) to obtain the pure product**.**

General Procedure 2

To a cooled (-78 °C) solution 0.2 M of *N*-Boc-pyrrolidine **1** (1.5 equiv) and (+)-sparteine *ent*-**9** (1.6 equiv) under Argon in dry CPME was added dropwise a solution of *s*-BuLi (1.6 equiv) and the reaction mixture was stirred for 30 min, then Weinreb Amide (1.0 equiv), in CPME was added slowly. The reaction mixture was quenched after 3 hours with sat. NH_4Cl solution (5 mL) and stirred 1-2 min before diethyl ether was added and the phases separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (hexane/AcOEt) to obtain the pure product**.**

3.3 Characterization and Spectral Data of the compounds

2-methyl-2-propanyl (2*R*)-2-benzoyl-1-pyrrolidinecarboxylate (*R*)-**13**[51]



(*R*)-**13**

By following the General Procedure **1** to a solution of *N*-Boc-pyrrolidine **1** (77.8 mg, 0.45 mmol, 1.5 equiv) and (–)-sparteine **9** (112.5 mg, 0.48 mmol, 1.6 equiv) under Argon in dry CPME (2.25 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.37 ml, 0.48 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then *N*-methoxy-*N*-methyl-benzamide (50.0 mg, 0.3 mmol, 1.0 equiv) in CPME was added slowly; compound (*R*)-**13** was obtained by purification on silica gel (80:20 v/v, *n*-hexane/ethyl acetate) in 85% yield (70.2 mg) as a pale yellow solid; mp 64-70 °C
The corresponding racemic sample[55] has been prepared by using TMEDA instead of (–)-sparteine **9** and the spectroscopic data are identical with the ones reported below.

rotamers ratio = 60:40

^{1}H NMR (400 MHz, $CDCl_3$) major rotamer 7.95 (m, 2H, Ph H-2,6), 7.58 (m, 1H, Ph H-4), 7.48 (m, 2H, Ph H-3,5), 5.19 (dd, *J* = 8.9, 4.0 Hz, 1H, Pyr H-2), 3.72-3.43 (m, 2H, Pyr H-5), 2.32 (m, 1H, Pyr H-3), 1.99-1.87 (m, 2H, Pyr H-4), 1.92 (m, 1H, Pyr H-3), 1.25 (s, 9H, $(CH_3)_3$)

^{13}C NMR (100 MHz, $CDCl_3$) major rotamer 198.9 (C=O), 153.8 (N-C(=O)-O), 135.3 (Ph C-1), 133.2 (Ph C-4), 128.7 (Ph C-3,5), 128.2 (Ph C-2,6), 79.8 ($(CH_3)_3\underline{C}O$), 61.3 (Pyr C-2), 46.6 (Pyr C-5), 30.8 (Pyr C-3), 28.2 ($(CH_3)_3$), 23.5 (Pyr C-4)

^{1}H NMR (400 MHz, $CDCl_3$) minor rotamer 7.98 (m, 2H, Ph H-2,6), 7.55 (m, 1H, Ph H-4), 7.44 (m, 2H, Ph H-3,5), 5.33 (m, 1H, Pyr H-2), 3.71-3.44 (m, 2H, Pyr H-5), 2.28 (m, 1H, Pyr H-3), 1.99-1.87 (m, 2H, Pyr H-4), 1.91 (m, 1H, Pyr H-3), 1.46 (s, 9H, $(CH_3)_3$)

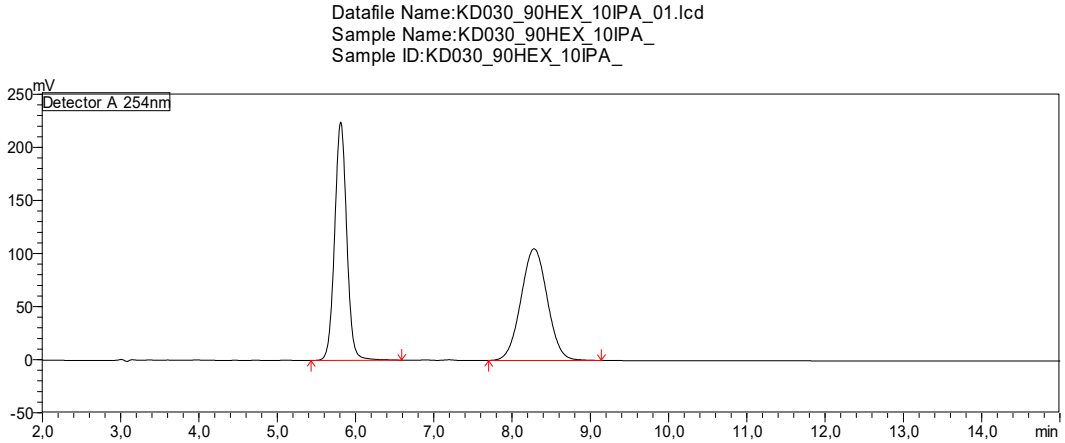
^{13}C NMR (100 MHz, $CDCl_3$) minor rotamer 198.4 (C=O), 154.4 (N-C(=O)-O), 135.1 (Ph C-1), 133.1 (Ph C-4), 128.6 (Ph C-3,5), 128.5 (Ph C-2,6), 79.6 ($(CH_3)_3\underline{C}O$), 61.1 (Pyr C-2), 46.8 (Pyr C-5), 29.8 (Pyr C-3), 28.5 ($(CH_3)_3$), 24.1 (Pyr C-4)

HRMS (ESI), *m/z*: calcd. for $C_{16}H_{21}NNaO_3$: 298.1414 $[M+Na]^+$; found: 298.1415

$[\alpha]_D$=+26.50 (*c* 0.5, $CHCl_3$) (lit[51].+28.10)

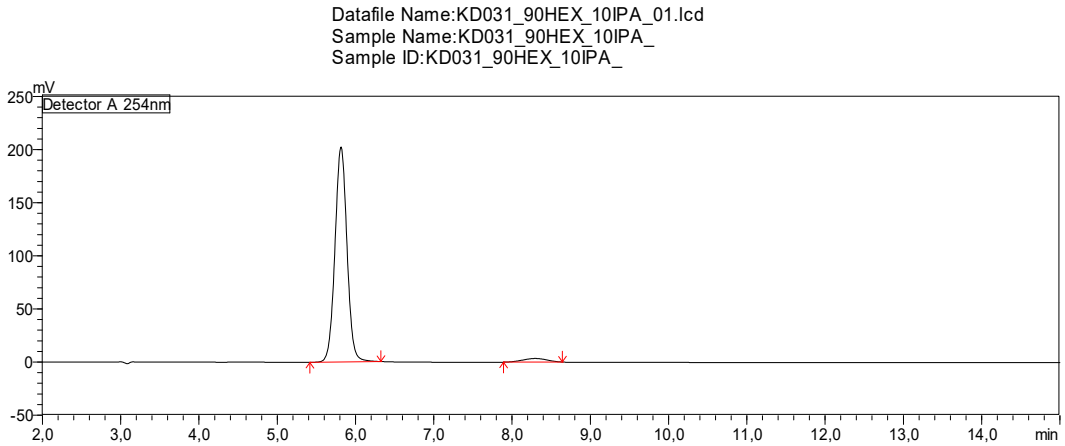
HPLC analysis: Chiralpak IA Column, λ 254 nm, eluent: *n*-hexane / *i*-propanol 90/10. Flow: 1 mL/min

Racemate



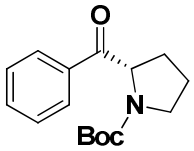
Peaks	Ret.T	Area	Area%
1	5,810	2410041	49,432
2	8,282	2465392	50,568
total		4875433	100,000

Enantioenriched (–)-sparteine



Peaks	Ret.T	Area	Area%
1	5,814	2158925	96,697
2	8,295	73753	3,303
total		2232678	100,000

2-methyl-2-propanyl (2*S*)-2-benzoyl-1-pyrrolidinecarboxylate (*S*)-**13**[52]



(*S*)-**13**

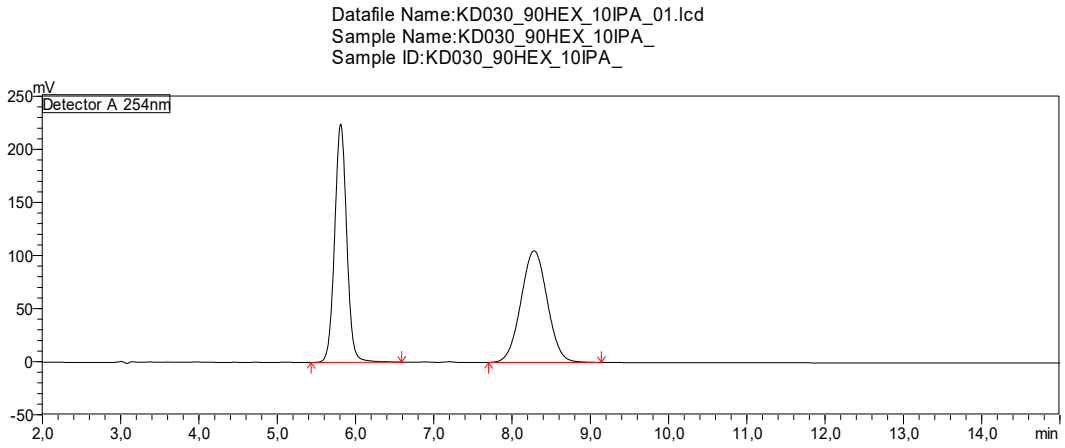
By following the General Procedure **2** to a solution of *N*-Boc-pyrrolidine **1** (77.8 mg, 0.45 mmol, 1.5 equiv) and (+)-sparteine *ent*-**9** (112.5 mg, 0.48 mmol, 1.6 equiv) under Argon in dry CPME (2.25 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.37 ml, 0.48 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then *N*-methoxy-*N*-methyl-benzamide (50.0 mg, 0.3 mmol, 1.0 equiv) in CPME was added slowly; compound (*S*)-**13** was obtained by purification on silica gel (80:20 v/v, *n*-hexane/ethyl acetate) in 88% yield (72.7 mg) as a pale yellow solid; mp 64-70 °C.

The spectroscopic data and physicochemical properties for (*S*)-**13** match the reported values for the optical antipode.

$[\alpha]_D$ = -34.90 (*c* 0.5, $CHCl_3$) (lit.[52] -36.8)

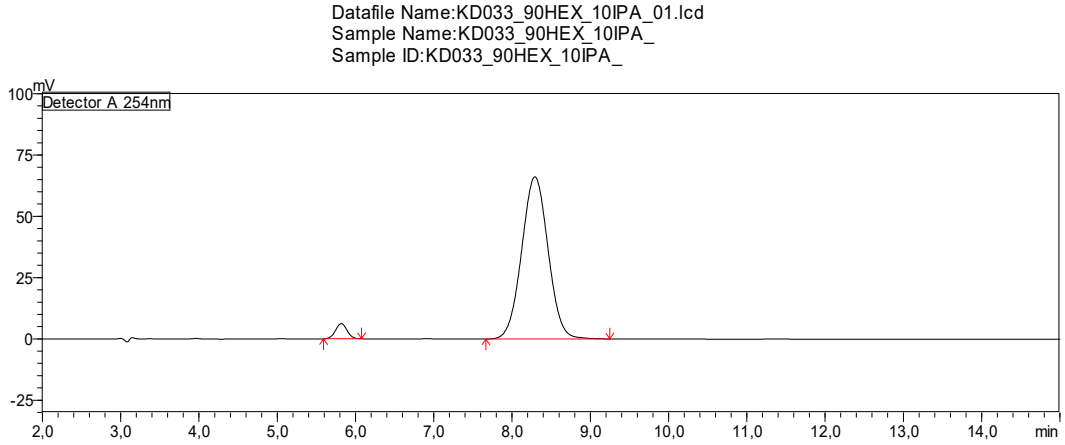
HPLC analysis: Chiralpak IA Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 90/10. Flow: 1 mL/min

Racemate



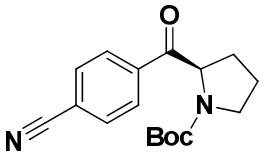
Peaks	*Ret.T*	*Area*	*Area%*
1	*5,810*	*2410041*	*49,432*
2	*8,282*	*2465392*	*50,568*
total		*4875433*	*100,000*

Enantioenriched (+)-sparteine



Peaks	Ret.T	Area	Area%
1	5,818	63844	3,948
2	8,292	1553393	96,052
total		1617236	100,000

2-methyl-2-propanyl (2*R*)-2-(4-cyanobenzoyl)-1-pyrrolidinecarboxylate (*R*)-**30**



(*R*)-**30**

By following the General Procedure **1** to a solution of *N*-Boc-pyrrolidine **1** (66.8 mg, 0.39 mmol, 1.5 equiv) and (–)-sparteine **9** (98.4 mg, 0.42 mmol, 1.6 equiv) under Argon in dry CPME (1.95 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.32 ml, 0.42 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then 4-cyano-*N*-methoxy-*N*-methyl-benzamide (50.0 mg, 0.26 mmol, 1.0 equiv) in CPME was added slowly; compound (*R*)-**30** was obtained by purification on silica gel (75:25 v/v, *n*-hexane/ethyl acetate) in 75% yield (58.5 mg) as a yellowish solid, mp 64-67 °C.

The corresponding racemic sample[55] has been prepared by using TMEDA instead of (–)-sparteine **9** and the spectroscopic data are identical with the ones reported below.

rotamers ratio = 51:49

^{1}H NMR (400 MHz, $CDCl_3$) 8.07-8.02 (m, 2H, Ph H-2,6), 7.80-7.74 (m, 2H, Ph H-3,5), 5.25 (dd, *J* = 9.1, 3.8 Hz, 0.49H, Pyr H-2), 5.13 (dd, *J* = 9.3, 4.5 Hz, 0.51H, Pyr H-2), 3.70-3.44 (m, 2H, Pyr H-5), 2.34-2.28 (m, 1H, Pyr H-3), 2.00-1.87 (m, 2H, Pyr H-4), 1.90-1.86 (m, 1H, Pyr H-3), 1.44 (s, 4.5H, $(CH_3)_3$), 1.24 (s, 4.5H, $(CH_3)_3$)

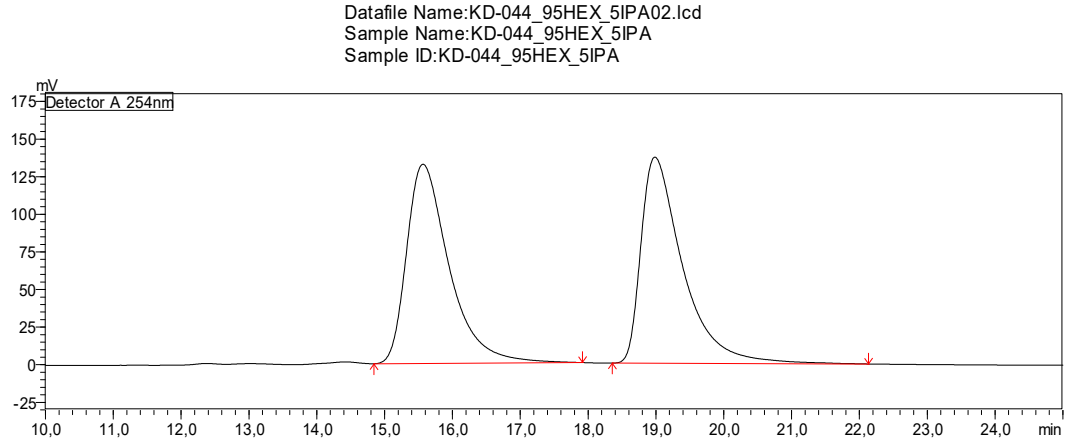
^{13}C NMR (100 MHz, $CDCl_3$) 197.79 (C=O), 197.76 (C=O), 154.4 (NC=O), 153.4 (NC=O), 138.4 (Ph C-1), 138.3 (Ph C-1), 132.6 (Ph C-3,5), 132.4 (Ph C-3,5), 128.8 (Ph C-2,6), 128.5 (Ph C-2,6), 117.9 (C≡N), 117.7 (C≡N), 116.5 (Ph C-4), 116.3 (Ph C-4), 80.1 ($(CH_3)_3\underline{C}O$), 80.0 ($(CH_3)_3\underline{C}O$), 61.5 (Pyr C-2), 61.1 (Pyr C-2), 46.7 (Pyr C-5), 46.6 (Pyr C-5), 30.6 (Pyr C-3), 29.5 (Pyr C-3), 28.4 ($(CH_3)_3$), 28.1 ($(CH_3)_3$), 24.3 (Pyr C-4), 23.5 (Pyr C-4)

HRMS (ESI), *m/z*: calcd. for $C_{17}H_{20}N_2NaO_3$: 323.1366 $[M+Na]^+$; found: 323.1368

$[\alpha]_D$ = +8.00 (*c* 0.5, $CHCl_3$)

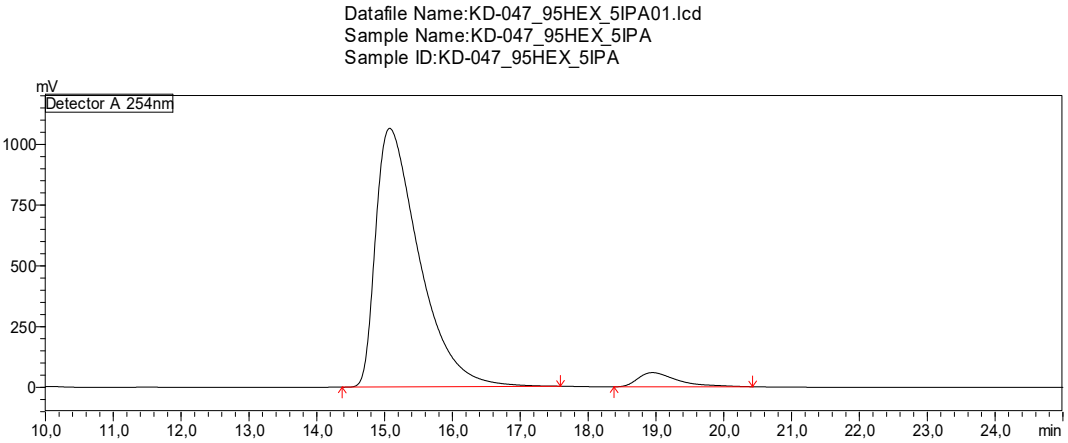
HPLC analysis: Chiralpak IB Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 95/05. Flow: 1 mL/min

Racemate



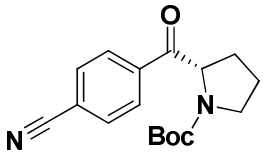
Peaks	Ret.T	Area	Area%
1	15,566	5774381	49,599
2	18,985	5867752	50,401
total		11642134	100,000

Enantioenriched (–)-sparteine



Peaks	Ret.T	Area	Area%
1	15,075	47467160	95,234
2	18,947	2375422	4,766
total		49842581	100,000

2-methyl-2-propanyl (2*S*)-2-(4-cyanobenzoyl)-1-pyrrolidinecarboxylate (*S*)-**30**



(*S*)-**30**

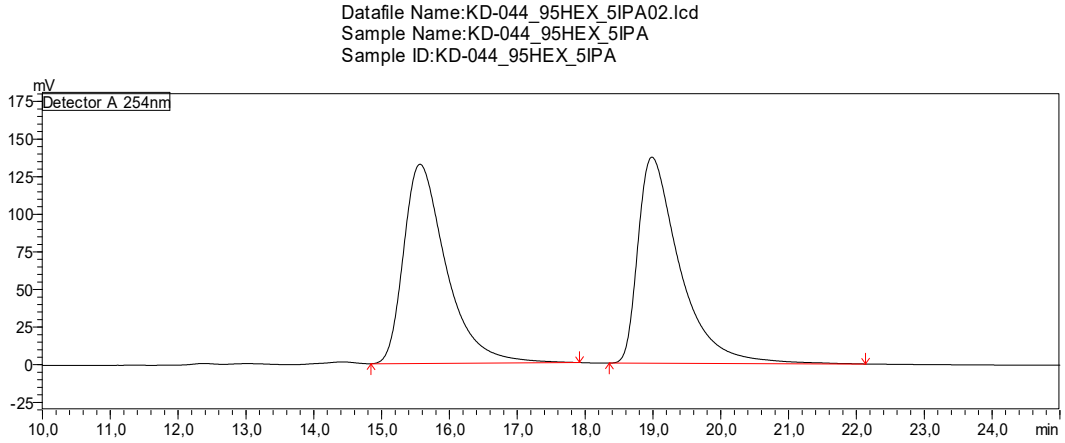
By following the General Procedure **2** to a solution of *N*-Boc-pyrrolidine **1** (66.8 mg, 0.39 mmol, 1.5 equiv) and (+)-sparteine *ent*-**9** (98.4 mg, 0.42 mmol, 1.6 equiv) under Argon in dry CPME (1.95 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.32 ml, 0.42 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then 4-cyano-*N*-methoxy-*N*-methyl-benzamide (50.0 mg, 0.26 mmol, 1.0 equiv) in CPME was added slowly; compound (*S*)-**30** was obtained by purification on silica gel (75:25 v/v, *n*-hexane/ethyl acetate) in 81% yield (63.2 mg).

The spectroscopic data and physicochemical properties for (*S*)-**30** match the reported values for the optical antipode.

$[\alpha]_D$ = -18.66 (*c* 0.5, $CHCl_3$)

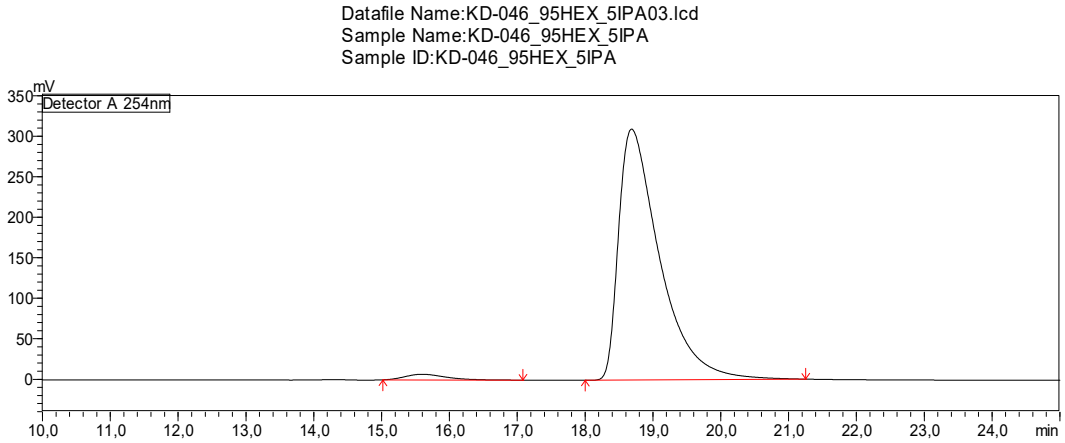
HPLC analysis: Chiralpak IB Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 95/05. Flow: 1 mL/min

Racemate



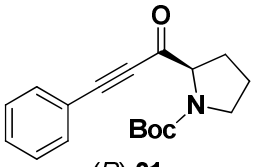
Peaks	*Ret.T*	*Area*	*Area%*
1	*15,566*	*5774381*	*49,599*
2	*18,985*	*5867752*	*50,401*
total		*11642134*	*100,000*

Enantioenriched (+)-sparteine



Peaks	Ret.T	Area	Area%
1	15,601	293721	2,206
2	18,686	13020658	97,794
total		13314379	100,000

2-methyl-2-propanyl (2*R*)-2-(3-phenyl-2-propynoyl)-1-pyrrolidinecarboxylate (*R*)-**31**



(*R*)-**31**

By following the General Procedure **1** to a solution of *N*-Boc-pyrrolidine **1** (66.8 mg, 0.39 mmol, 1.5 equiv) and (–)-sparteine **9** (98.4 mg, 0.42 mmol, 1.6 equiv)under Argon in dry CPME (2.0 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.32 ml, 0.42 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then *N*-methoxy-*N*-methyl-3-phenyl-2-propynamide (49 mg, 0.26 mmol, 1.0 equiv) in CPME was added slowly; compound (*R*)-**31** was obtained by purification on silica gel (85:15 v/v, *n*-hexane/ethyl acetate) in 80% yield (62.3 mg) as a yellowish solid, mp 74-75 °C.
The corresponding racemic sample has been prepared by using TMEDA instead of (–)-sparteine **9** and the spectroscopic data are identical with the ones reported below.

Rotamers ratio = 74:26

^{1}H NMR (400 MHz, $CDCl_3$) major isomer 7.58-7.52 (m, 2H, Ph H-2,6), 7.48-7.41 (m, 1H, Ph H-4), 7.39-7.33 (m, 2H, Ph H-3,5), 4.30 (dd, *J* = 8.5, 5.3 Hz, 1H, Pyr H-2), 3.60 (m, 2H, Pyr H-5), 2.28 (m, 1H, Pyr H-3), 2.07 (m, 1H, Pyr H-3), 2.02-1.84 (m, 2H, Pyr H-4), 1.40 (s, 9H, $(CH_3)_3$)

^{13}C NMR (100 MHz, $CDCl_3$) major isomer 188.6 (C=O), 153.7 (N-C(=O)-O), 133.3 (Ph C-2,6), 130.9 (Ph C-4), 128.6 (Ph C-3,5), 119.6 (Ph C-1), 93.5 (C≡CPh), 85.6 (C≡CPh), 80.4 ($(CH_3)_3CO$), 66.7 (Pyr C-2), 46.6 (Pyr C-5), 30.7 (Pyr C-3), 28.1 ($(CH_3)_3$), 23.7 (Pyr C-4)

^{1}H NMR (400 MHz, $CDCl_3$) minor isomer 7.58-7.52 (m, 2H, Ph H-2,6), 7.48-7.41 (m, 1H, Ph H-4), 7.39-7.33 (m, 2H, Ph H-3,5), 4.49 (dd, *J* = 8.7, 4.4 Hz, 1H, Pyr H-2), 3.47 (m, 2H, Pyr H-5), 2.22 (m, 1H, Pyr H-3), 2.09 (m, 1H, Pyr H-3), 2.02-1.84 (m, 2H, Pyr H-4), 1.44 (s, 9H, $(CH_3)_3$)

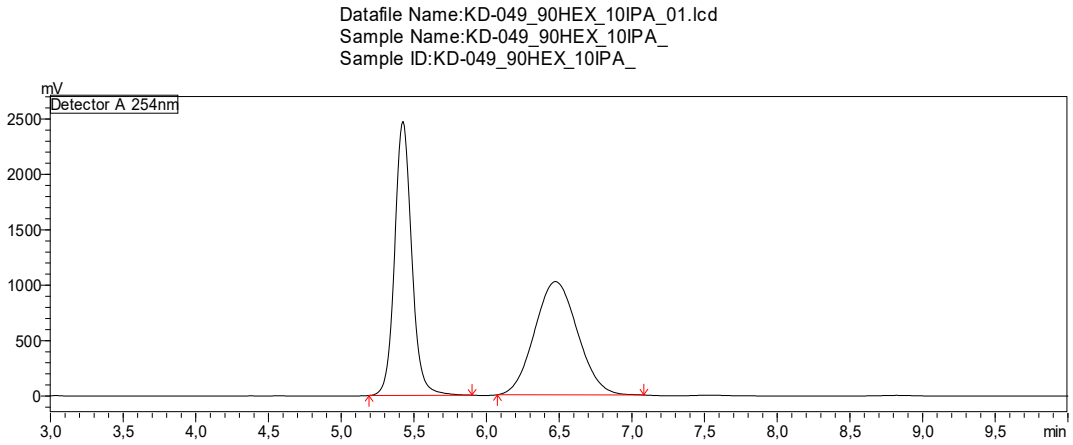
^{13}C NMR (100 MHz, $CDCl_3$) minor isomer 187.8 (C=O), 154.5 (NC(=O)), 133.0 (Ph C-2,6), 130.7 (Ph C-4), 128.5 (Ph C-3,5), 119.9 (Ph C-1), 92.9 (C≡CPh), 86.1 (C≡CPh), 79.9 ($(CH_3)_3CO$), 66.5 (Pyr C-2), 46.8 (Pyr C-5), 29.2 (Pyr C-3), 28.4 ($(CH_3)_3$), 24.3 (Pyr C-4)

HRMS (ESI), *m/z*: calcd. for $C_{18}H_{21}NNaO_3^+$: 322.1414 $[M+Na]^+$; found: 322.1415

$[\alpha]_D$ = +116.25 (*c* 0.5, $CHCl_3$)

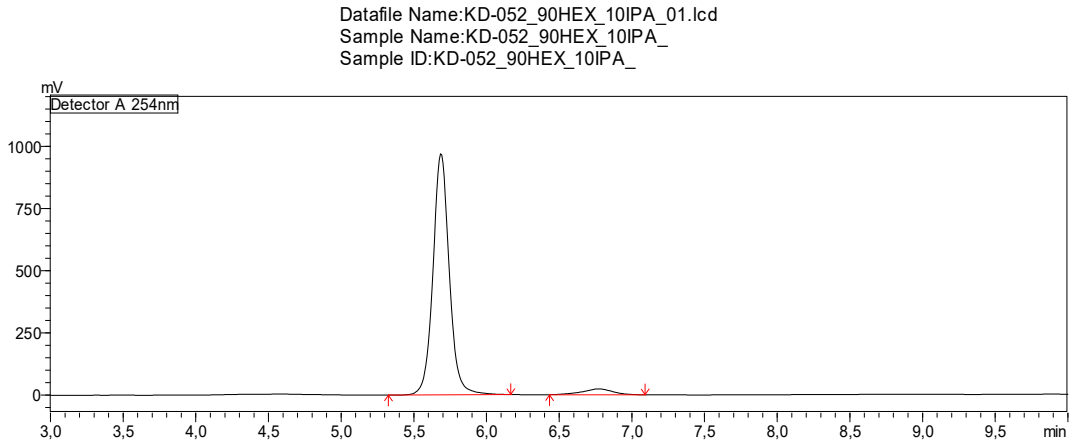
HPLC analysis: Chiralpak IA Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 95/05. Flow: 1 mL/min

Racemate



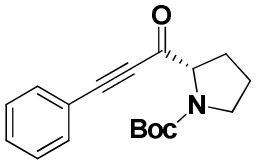
Peaks	Ret.T	Area	Area%
1	5,424	20217455	49,028
2	6,474	21018735	50,972
total		41236189	100,000

Enantioenriched (–)-sparteine



Peaks	Ret.T	Area	Area%
1	5,686	7572598	95,668
2	6,773	342926	4,332
total		7915524	100,000

2-methyl-2-propanyl (2*S*)-2-(3-phenyl-2-propynoyl)-1-pyrrolidinecarboxylate (*S*)-**31**[54]



(*S*)-**31**

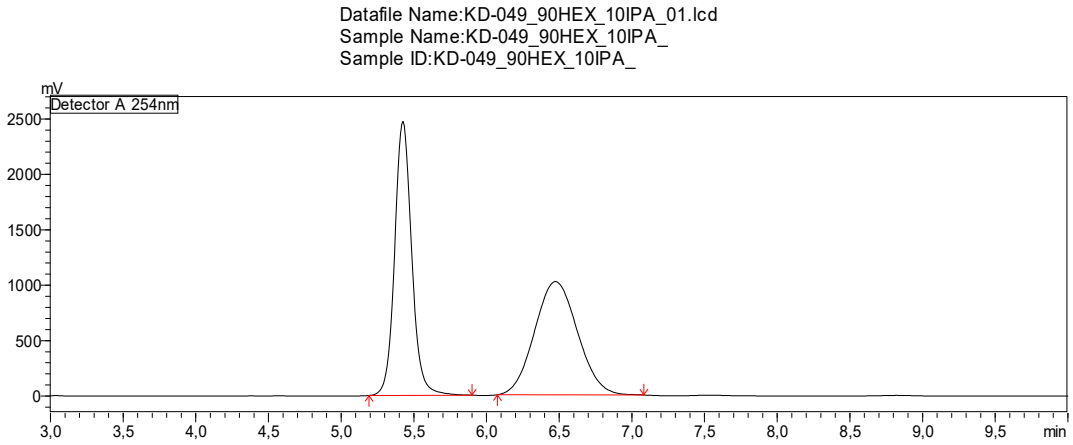
By following the General Procedure **2** to a solution of *N*-Boc-pyrrolidine **1** (66.8 mg, 0.39 mmol, 1.5 equiv) and (+)-sparteine *ent*-**9** (98.4 mg, 0.42 mmol, 1.6 equiv) under Argon in dry CPME (2.0 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.32 ml, 0.42 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then *N*-methoxy-*N*-methyl-3-phenyl-2-propynamide (50.0 mg, 0.26 mmol, 1.0 equiv) in CPME was added slowly; compound (*S*)-**31** was obtained by purification on silica gel (85:15 v/v, *n*-hexane/ethyl acetate) in 81% yield (63.0 mg)

The spectroscopic data and physicochemical properties for (*S*)-**31** match the reported values for the optical antipode.

$[\alpha]_D$ = -118.65 (*c* 0.5, $CHCl_3$)

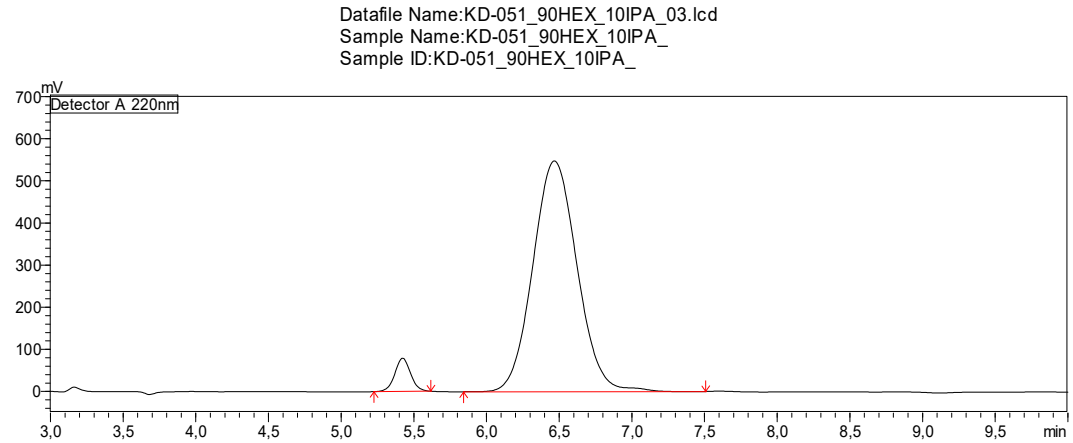
HPLC analysis: Chiralpak IA Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 95/05. Flow: 1 mL/min

Racemate



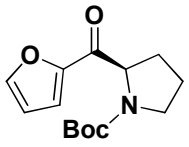
Peaks	*Ret.T*	*Area*	*Area%*
1	*5,424*	*20217455*	*49,028*
2	*6,474*	*21018735*	*50,972*
total		*41236189*	*100,000*

Enantioenriched (+)-sparteine



Peaks	Ret.T	Area	Area%
1	5,423	596986	4,899
2	6,467	342926	95,101
total		12187016	100,000

***2*-methyl-2-propanyl (*2R)*-2-(2-furylcarbonyl)-1-pyrrolidinecarboxylate** (*R*)-**32**



(*R*)-**32**

By following the General Procedure **1** to a solution of *N*-Boc-pyrrolidine **1** (82.8 mg, 0.48 mmol, 1.5 equiv) and (–)-sparteine **9** (119.5 mg, 0.51 mmol, 1.6 equiv) under Argon in dry CPME (2.4 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.39 ml, 0.51 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then *N*-methoxy-*N*-methylfuran-2-carboxamide (50.0 mg, 0.32 mmol, 1.0 equiv) in CPME was added slowly; compound (*R*)-**32** was obtained by purification on silica gel (80:20 v/v, *n*-hexane/ethyl acetate) in 75% yield (63.7 mg) as a brownish solid, mp 68 °C.
The corresponding racemic sample has been prepared by using TMEDA instead of (–)-sparteine **9** and the spectroscopic data are identical with the ones reported below.

Rotamers ratio = 61:39

^{1}H NMR (400 MHz, $CDCl_3$) 7.61-7.58 (m, 1H, Fur H-5), 7.26-7.22 (m, 1H, Fur H-3), 6.56-6.52 (m, 1H, Fur H-4), 5.08 (dd, *J* = 8.6, 3.1 Hz, 0.39H, Pyr H-2), 4.90 (dd, *J* = 8.6, 4.6 Hz, 0.61H, Pyr H-2), 3.67-3.42 (m, 2H, Pyr H-5), 2.33-2.23 (m, 1H, Pyr H-3), 2.01-1.88 (m, 3H, Pyr H-3, H-4) 1.45 (s, 3.5H, $(CH_3)_3$), 1.26 (s, 5.5H, $(CH_3)_3$)

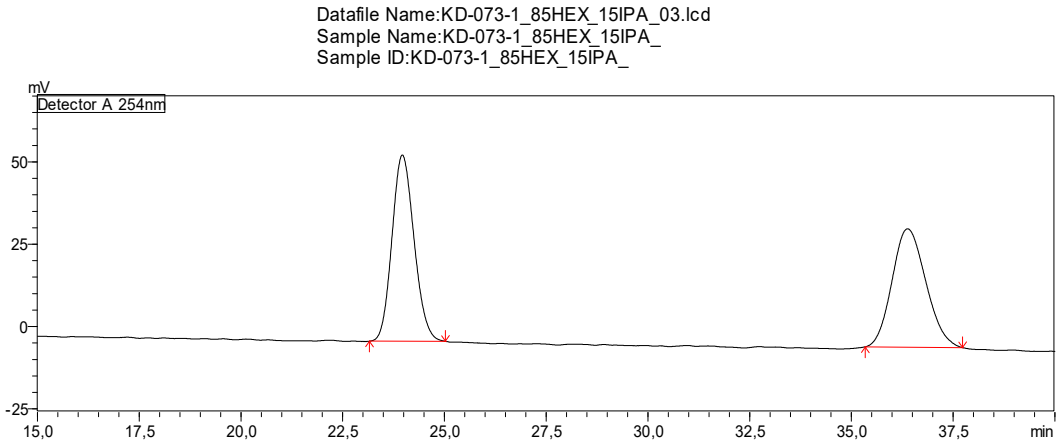
^{13}C NMR (100 MHz, $CDCl_3$) 188.5 (C=O), 187.8 (C=O), 154.4 (NC=O), 153.7 (NC=O), 151.2 (Fur C-2), 146.5 (Fur C-5), 117.9 (Fur C-3), 117.5 (Fur C-3), 112.2 (Fur C-4), 79.9 ($(CH_3)_3\underline{C}O$), 79.7 ($(CH_3)_3\underline{C}O$), 61.8 (Pyr C-2), 61.3 (Pyr C-2), 46.9 (Pyr C-5), 46.7 (Pyr C-5), 30.9 (Pyr C-3), 29.8 (Pyr C-3), 28.4 ($(CH_3)_3$), 28.1 ($(CH_3)_3$), 24.2 (Pyr C-4), 23.7 (Pyr C-4)

HRMS (ESI), *m/z*: calcd. for $C_{14}H_{19}NNaO_4^+$: 288.1206 $[M+Na]^+$; found: 288.1210

$[\alpha]_D$ = +50.30 (*c* 0.5, $CHCl_3$)

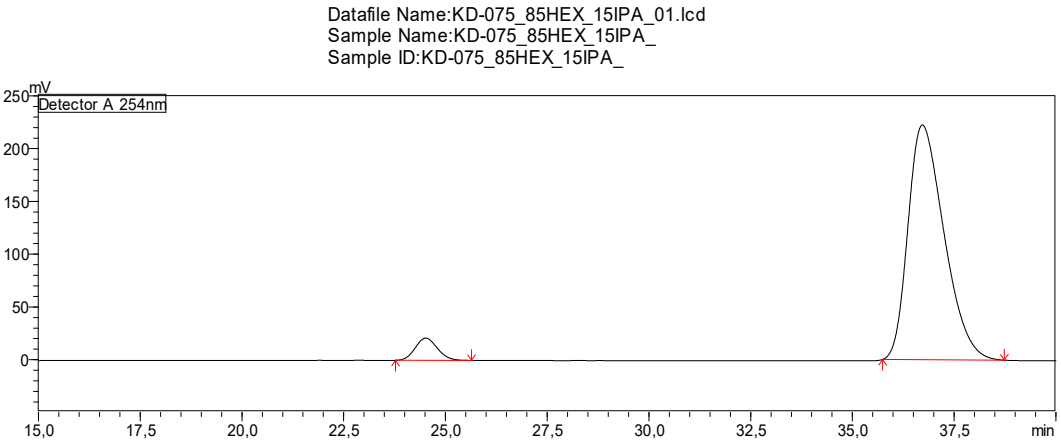
HPLC analysis: Chiralpak IC Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 85/15. Flow: 1 mL/min

Racemate



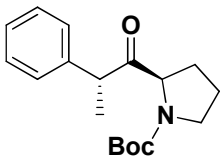
Peaks	Ret.T	Area	Area%
1	23,965	2135782	50,697
2	36,383	2077028	49,303
total		4212810	100,000

Enantioenriched (–)-sparteine



Peaks	Ret.T	Area	Area%
1	24,516	799349	5,509
2	36,719	13709425	94,491
total		14508774	100,000

2-methyl-2-propanyl (*2R)*-2-[(*2R)*-2-phenylpropanoyl]-1-pyrrolidinecarboxylate (*R*,*R*)-**33**



(*R*,*R*)-**33**

By following the General Procedure **1** to a solution of *N*-Boc-pyrrolidine **1** (133.5 mg, 0.78 mmol, 1.5 equiv) and (–)-sparteine **9** (196.8 mg, 0.84 mmol, 1.6 equiv) under Argon in dry CPME (3.9 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.64 ml, 0.84 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then (2*R*)-*N*-methoxy-*N*-methyl-2-phenylpropanamide (100.0 mg, 0.52 mmol, 1.0 equiv) in CPME was added slowly; compound (*R*,*R*)-**33** was obtained by purification on silica gel (90:10 v/v, *n*-hexane/ethyl acetate) in 85% yield (134.1 mg) as a white solid, mp 95-97 °C.

The racemic reference has been synthesized starting from *rac*-*N*-methoxy-*N*-methyl-2-phenylpropanamide, using TMEDA instead of (–)-sparteine **9** and comprises a mixture of 4 stereoisomers.

Rotamers ratio = 65:35

^{1}H NMR (400 MHz, $CDCl_3$) 7.32-7.19 (m, 5H, Ph), 4.36 (dd, *J* = 8.8, 4.1 Hz, 0.39H, Pyr H-2), 4.32 (dd, *J* = 9.2, 4.5 Hz, 0.61H, Pyr H-2), 4.07 (q, *J* = 7.2 Hz, 0.39H, CH), 4.01 (q, *J* = 7.1 Hz, 0.61H, CH), 3.46-3.40 (m, 0.61H, Pyr), 3.32-3.19 (m, 1H, Pyr), 2.91-2.85 (m, 0.39H, Pyr), 2.14-2.05 (m, 0.61H, Pyr), 1.91-1.59 (m, 3H, Pyr) 1.50 (s, 3H, $(CH_3)_3$), 1.42-1.40 (m, 3H, CH_3), 1.31 (s, 6H, $(CH_3)_3$)

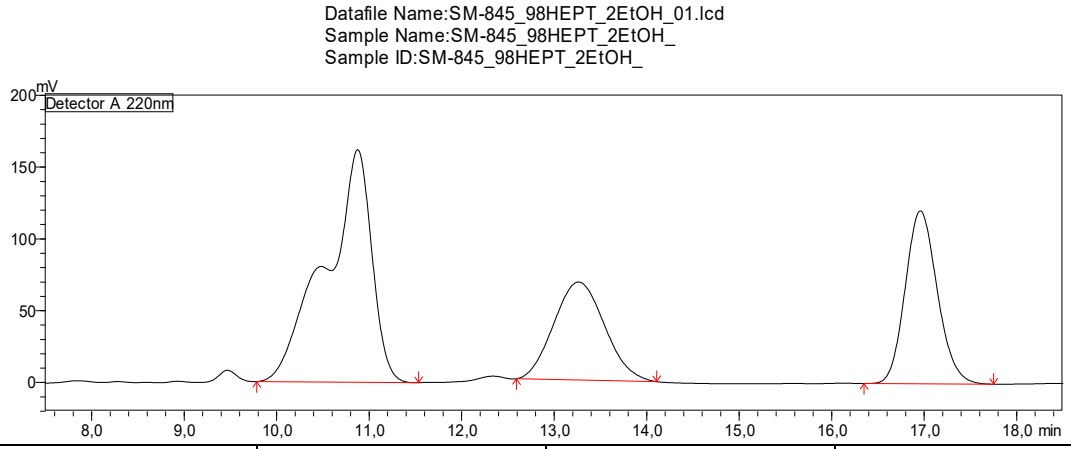
^{13}C NMR (100 MHz, $CDCl_3$) 211.1 (C=O), 210.0 (C=O), 154.2 (NC=O), 140.2 (Ph C-1), 139.9 (Ph C-1), 128.9 (Ph), 128.6 (Ph), 128.1 (Ph), 128.1 (Ph), 127.2 (Ph), 126.9 (Ph), 80.0 ($(CH_3)_3\underline{C}O$), 79.7 ($(CH_3)_3\underline{C}O$), 65.3 (Pyr C-2), 65.1 (Pyr C-2), 49.0 (CH), 48.0 (CH), 46.7 (Pyr), 46.6 (Pyr), 29.7 (Pyr), 29.3 (Pyr C-3), 28.5 ($(CH_3)_3$), 28.2 ($(CH_3)_3$), 24.0 (Pyr), 23.1 (Pyr), 18.7 (CH_3), 18.7 (CH_3)

HRMS (ESI), *m/z*: calcd. for $C_{18}H_{25}NNaO_3^+$: 326.1727 $[M+Na]^+$; found: 326.1732

$[\alpha]_D$ = -72.45 (*c* 0.5, $CHCl_3$)

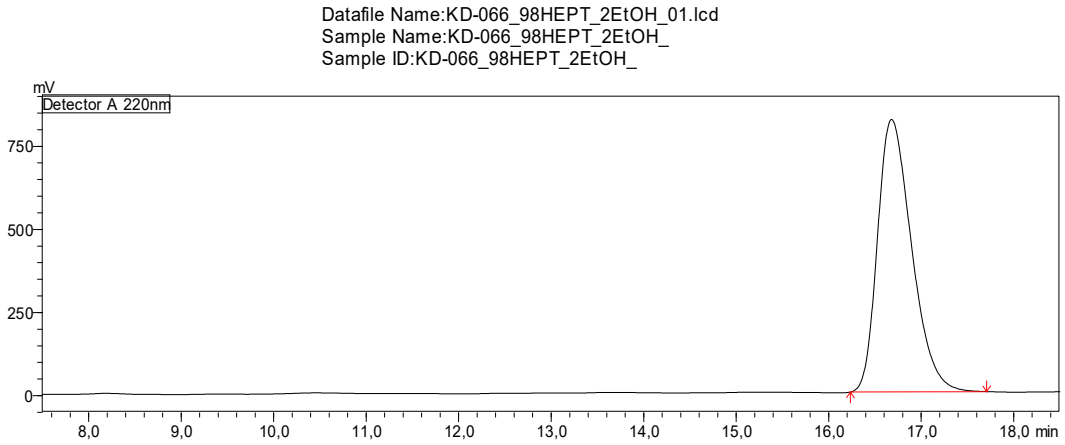
HPLC analysis: Chiralpak IC Column, λ 220 nm, eluent: *n*-heptane / ethanol 98/02. Flow: 1 mL/min

Mixture of stereoisomers



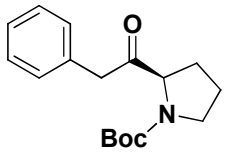
Peaks	Ret.T	Area	Area%
1 + 2	10,467 + 10,875	5644174	50,589
3	13,263	2605175	23,350
4	16,959	2907573	26,061
total		11156922	100,000

One stereoisomer (–)-sparteine



Peaks	Ret.T	Area	Area%
1	16,680	21001961	100
total		21001961	100,000

2-methyl-2-propanyl (*2R)*-2-(phenylacetyl)-1-pyrrolidinecarboxylate (*R*)-**34**



(*R*)-**34**

By following the General Procedure **1** to a solution of *N*-Boc-pyrrolidine **1** (71.9 mg, 0.42 mmol, 1.5 equiv) and (–)-sparteine **9** (105.4 mg, 0.45 mmol, 1.6 equiv) under Argon in dry CPME (2.1 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.35 ml, 0.45 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then *N*-methoxy-*N*-methyl-2-phenylacetamide (50.0 mg, 0.28 mmol, 1.0 equiv) in CPME was added slowly; compound (*R*)-**34** was obtained by purification on silica gel (80:20 v/v, *n*-hexane/ethyl acetate) in 79% yield (64.0 mg) as a light brown solid, mp 54 °C.
The corresponding racemic sample has been prepared by using TMEDA instead of (–)-sparteine **9** and the spectroscopic data are identical with the ones reported below.

Rotamers ratio = 59:41

^{1}H NMR (400 MHz, $CDCl_3$) 7.32-7.21 (m, 5H, Ph), 4.44 (dd, *J* = 8.0, 3.6 Hz, 0.41H, Pyr H-2), 4.36-4.33 (m, 0.59H, Pyr H-2), 3.83 (s, 0.82H, CH_2), 3.75 (s, 1.16H, CH_2), 3.56-3.38 (m, 2H, Pyr), 2.14-2.07 (m, 0.59H, Pyr), 1.99-1.92 (m, 0.41H, Pyr), 1.81-1.74 (m, 3H, Pyr) 1.48 (s, 3.6H, $(CH_3)_3$), 1.39 (s, 5.4H, $(CH_3)_3$)

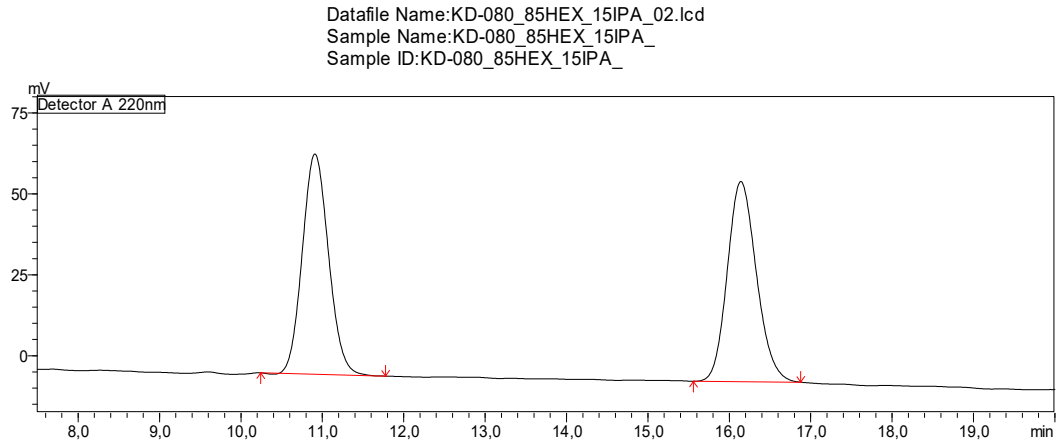
^{13}C NMR (100 MHz, $CDCl_3$) 207.7 (C=O), 207.2 (C=O), 153.9 (NC=O), 133.9 (Ph C-1), 133.5 (Ph C-1), 129.7 (Ph), 129.6 (Ph), 128.6 (Ph), 128.5 (Ph), 127.0 (Ph), 126.8 (Ph), 80.2 ($(CH_3)_3\underline{C}O$), 79.8 ($(CH_3)_3\underline{C}O$), 65.1 (Pyr C-2), 64.5 (Pyr C-2), 46.9 (Pyr), 46.8 (Pyr), 46.7 ($Ph\underline{C}H_2C=O$). 45.8 ($Ph\underline{C}H_2C=O$), 30.2 (Pyr), 29.2 (Pyr), 28.5 ($(CH_3)_3$), 28.3 ($(CH_3)_3$), 24.4 (Pyr), 23.6 (Pyr)

HRMS (ESI), *m/z*: calcd. for $C_{17}H_{23}NNaO_3^+$: 312.1570 $[M+Na]^+$; found: 312.1577

$[\alpha]_D$ = +24.80 (*c* 0.5, $CHCl_3$)

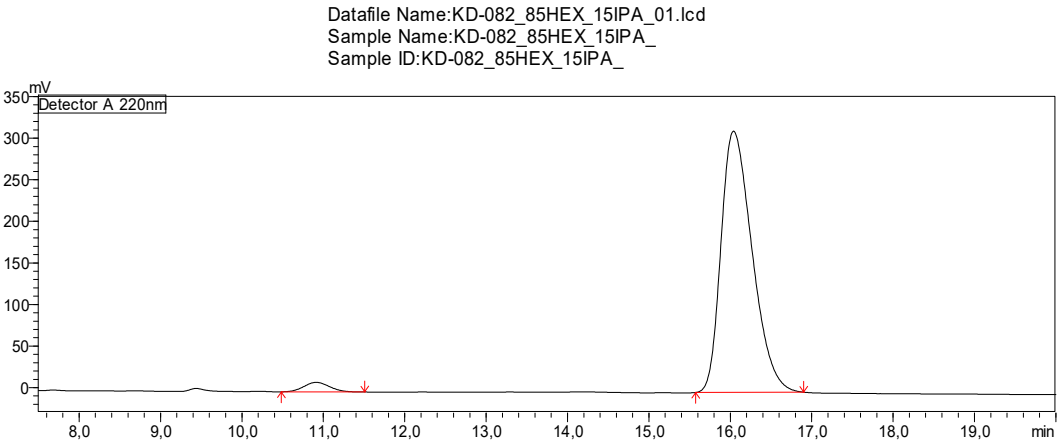
HPLC analysis: Chiralpak IC Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 85/15. Flow: 1 mL/min

Racemate



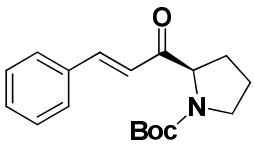
Peaks	Ret.T	Area	Area%
1	10,909	1521977	49,697
2	16,142	1540530	50,303
total		3062507	100,000

Enantioenriched (–)-sparteine



Peaks	Ret.T	Area	Area%
1	10,914	252948	2,939
2	16,040	8354130	97,061
total		8607078	100,000

2-methyl-2-propanyl (*2R*)-2-[(2*E*)-3-phenyl-prop-2-enoyl]-1-pyrrolidinecarboxylate (*R*)-**35**[53]



(*R*)-**35**

By following the General Procedure **1** to a solution of *N*-Boc-pyrrolidine **1** (66.7 mg, 0.39 mmol, 1.5 equiv) and (–)-sparteine **9** (98.4 mg, 0.42 mmol, 1.6 equiv), under Argon in dry CPME (1.95 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.32 ml, 0.42 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then (2*E)-N*-methoxy-*N*-methyl-3-phenyl-2-propenamide (50.0 mg, 0.26 mmol, 1.0 equiv) in CPME was added slowly; compound (*R*)-**35** was obtained by purification on silica gel (80:20 v/v, *n*-hexane/ethyl acetate) in 85% yield (66.6 mg) as a yellow solid, mp 91-93 °C.
The corresponding racemic sample has been prepared by using TMEDA instead of (–)-sparteine **9** and the spectroscopic data are identical with the ones reported below.

Rotamers ratio = 66:34

^{1}H NMR (400 MHz, $CDCl_3$) □: 7.72-7.65 (m, 1H, PhC<u>H</u>=CH), 7.56-7.54 (m, 2H, Ph H-2,6), 7.40-7.37 (m, 3H, Ph H-3,4,5), 6.85 (d, *J* = 16.0 Hz, 1H, PhCH=C<u>H</u>), 4.68-4.66 (m, 0.34H, Pyr H-2), 4.47 (dd, d, *J* = 8.2, 5.2 Hz, 0.66H, Pyr H-2), 3.61-3.45 (m, 2H, Pyr), 2.29-2.18 (m, 1H, Pyr), 1.94-1.87 (m, 3H, Pyr) 1.48 (s, 3.0H, $(CH_3)_3$), 1.39 (s, 6H, $(CH_3)_3$)

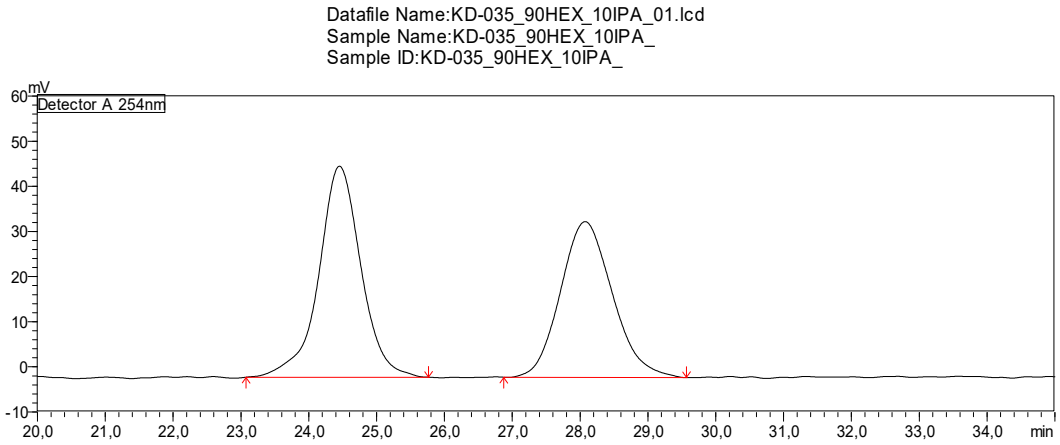
^{13}C NMR (100 MHz, $CDCl_3$) □□ 199.1 (C=O), 198.5 (C=O), 154.5 (NC=O), 154.0 (NC=O), 143.7 (Ph-<u>C</u>=C), 134.6 (Ph C-1), 134.4 (Ph C-1), 130.6 (Ph), 130.4 (Ph), 128.9 (Ph), 128.8 (Ph), 128.3 (PhC=<u>C</u>), 80.1 ($(CH_3)_3\underline{C}O$), 79.7 ($(CH_3)_3\underline{C}O$), 64.8 (Pyr C-2), 63.8 (Pyr C-2), 46.9 (Pyr), 46.8 (Pyr), 30.5 (Pyr C-4), 29.2 (Pyr), 28.4 ($(CH_3)_3$), 28.1 ($(CH_3)_3$), 24.3 (Pyr), 23.8 (Pyr)

HRMS (ESI), *m/z*: calcd. for $C_{18}H_{23}NNaO_3^+$: 324.1570 $[M+Na]^+$; found: 324.1574

$[\alpha]_D$ = +75.10 (*c* 0.5, $CHCl_3$)

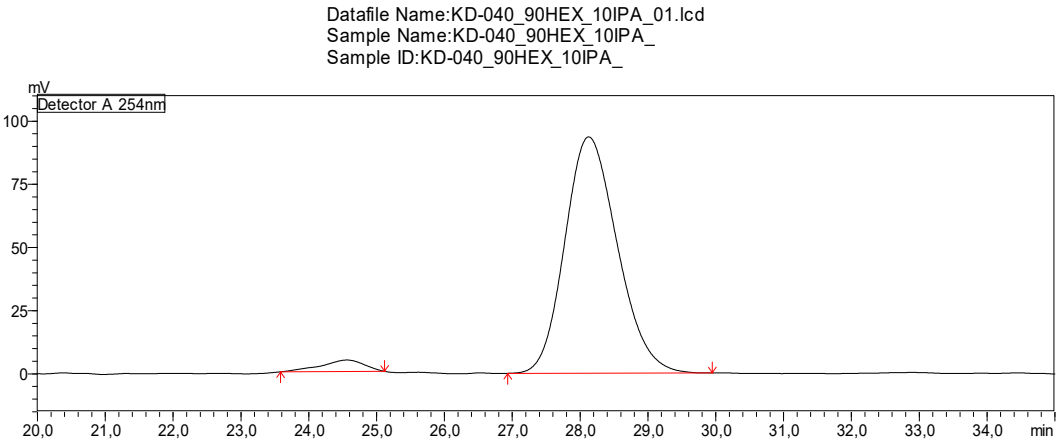
HPLC analysis: Chiralpak IC Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 95/05. Flow: 1 mL/min

Racemate



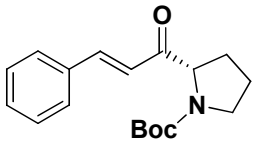
Peaks	Ret.T	Area	Area%
1	24,452	2021480	52,378
2	28,075	1837906	47,622
total		3859386	100,000

Enantioenriched (–)-sparteine



Peaks	Ret.T	Area	Area%
1	24,561	201734	3,857
2	28,126	5028918	96,143
total		5230653	100,000

2-methyl-2-propanyl (*2S)*-2-[(2E)-3-phenyl-prop-2-enoyl]-1-pyrrolidinecarboxylate (*S*)-**35**[53]



(*S*)-**35**

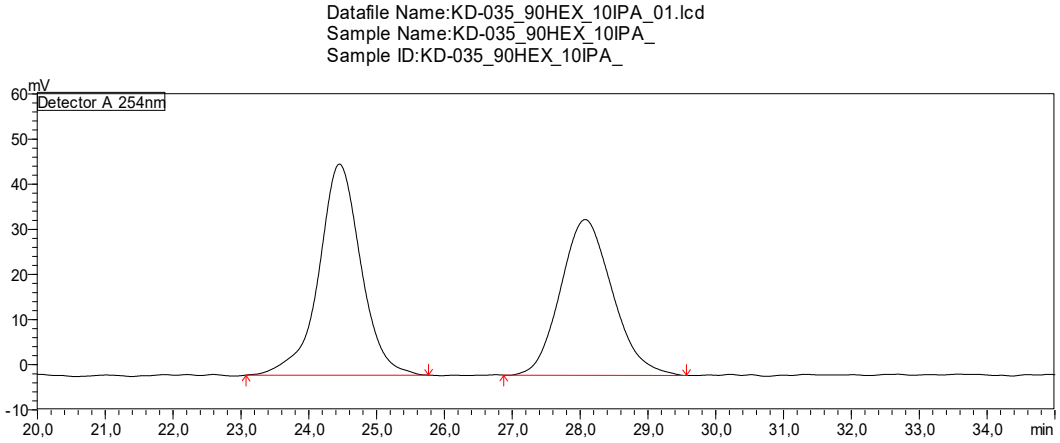
By following the General Procedure **2** to a solution of *N*-Boc-pyrrolidine **1** (66.8 mg, 0.39 mmol, 1.5 equiv) and (+)-sparteine *ent*-**9** (98.4 mg, 0.42 mmol, 1.6 equiv) under Argon in dry CPME (1.95 mL) at -78 °C, *s*-BuLi (1.3 M in cyclohexane, 0.32 ml, 0.42 mmol, 1.6 equiv) was added slowly; the reaction mixture was stirred for 30 min, then *N*-methoxy-*N*-methyl-3-phenyl-2-propenamide (50.0 mg, 0.26 mmol, 1.0 equiv.) in CPME was added slowly; compound (*S*)-**35** was obtained by purification on silica gel (80:20 v/v, *n*-hexane/ethyl acetate) in 83% yield (65.0 mg).

The spectroscopic data and physicochemical properties for (*S*)-**35** match the reported values for the optical antipode.

$[\alpha]_D$ = -53.35 (*c* 0.5, $CHCl_3$)

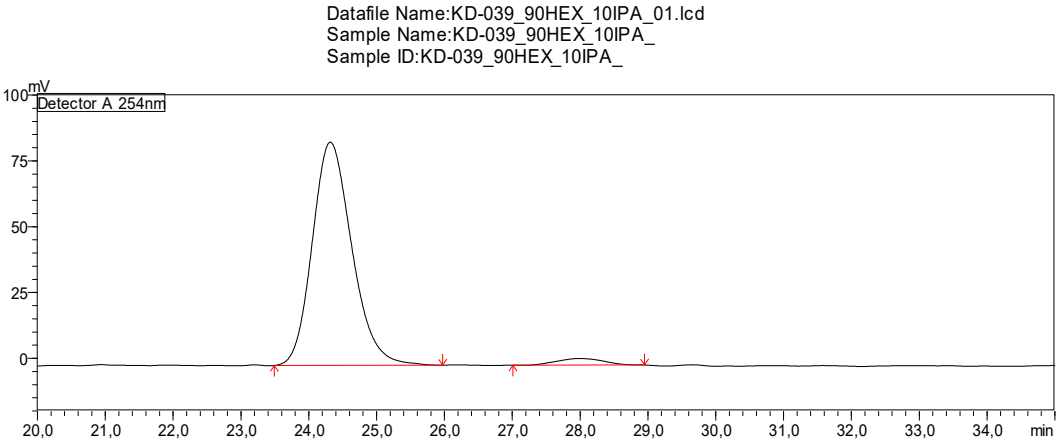
HPLC analysis: Chiralpak IC Column, λ 250 nm, eluent: *n*-hexane / *i*-propanol 95/05. Flow: 1 mL/min

Racemate



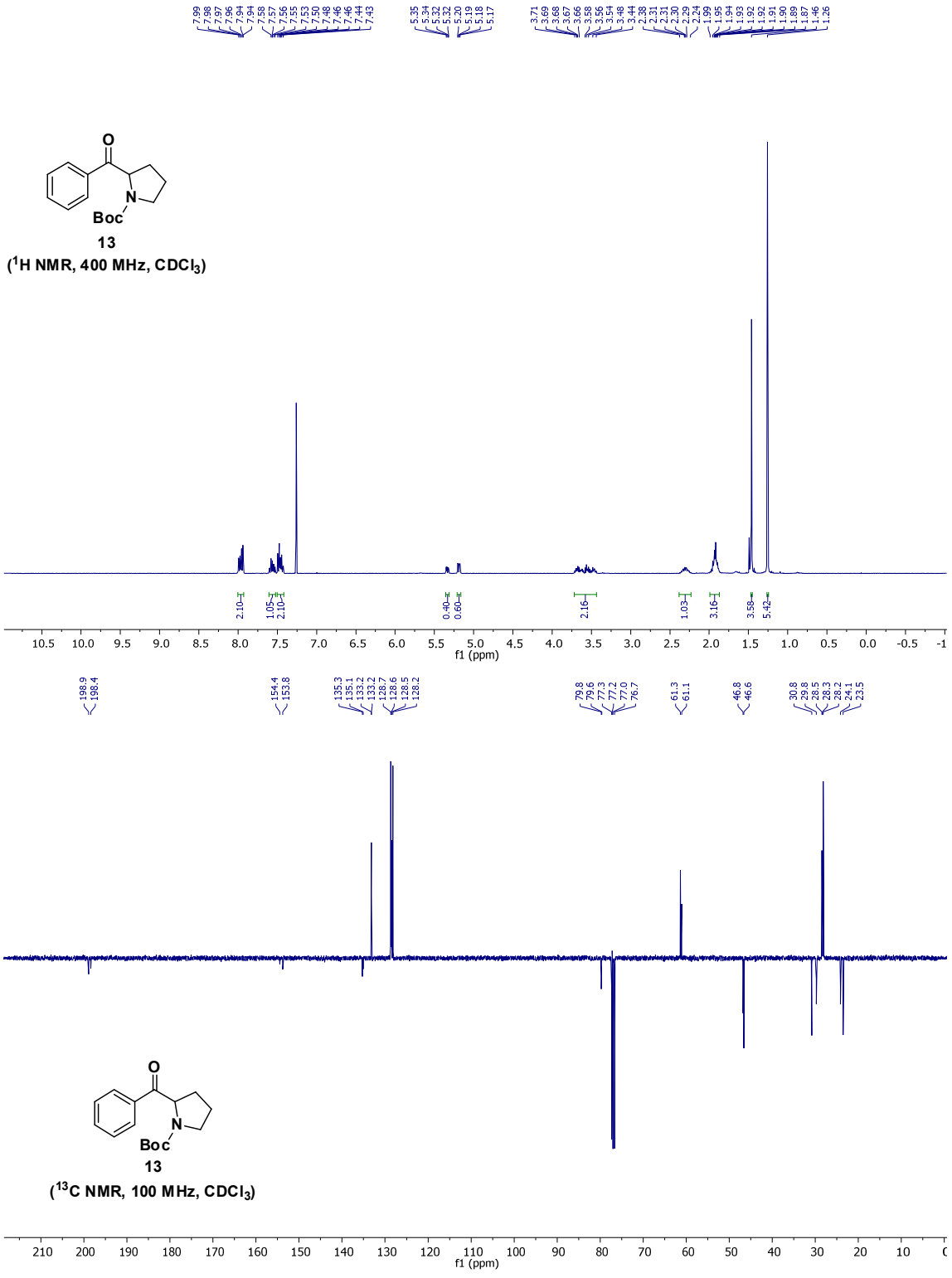
Peaks	*Ret.T*	*Area*	*Area%*
1	*24,452*	*2021480*	*52,378*
2	*28,075*	*1837906*	*47,622*
total		*3859386*	*100,000*

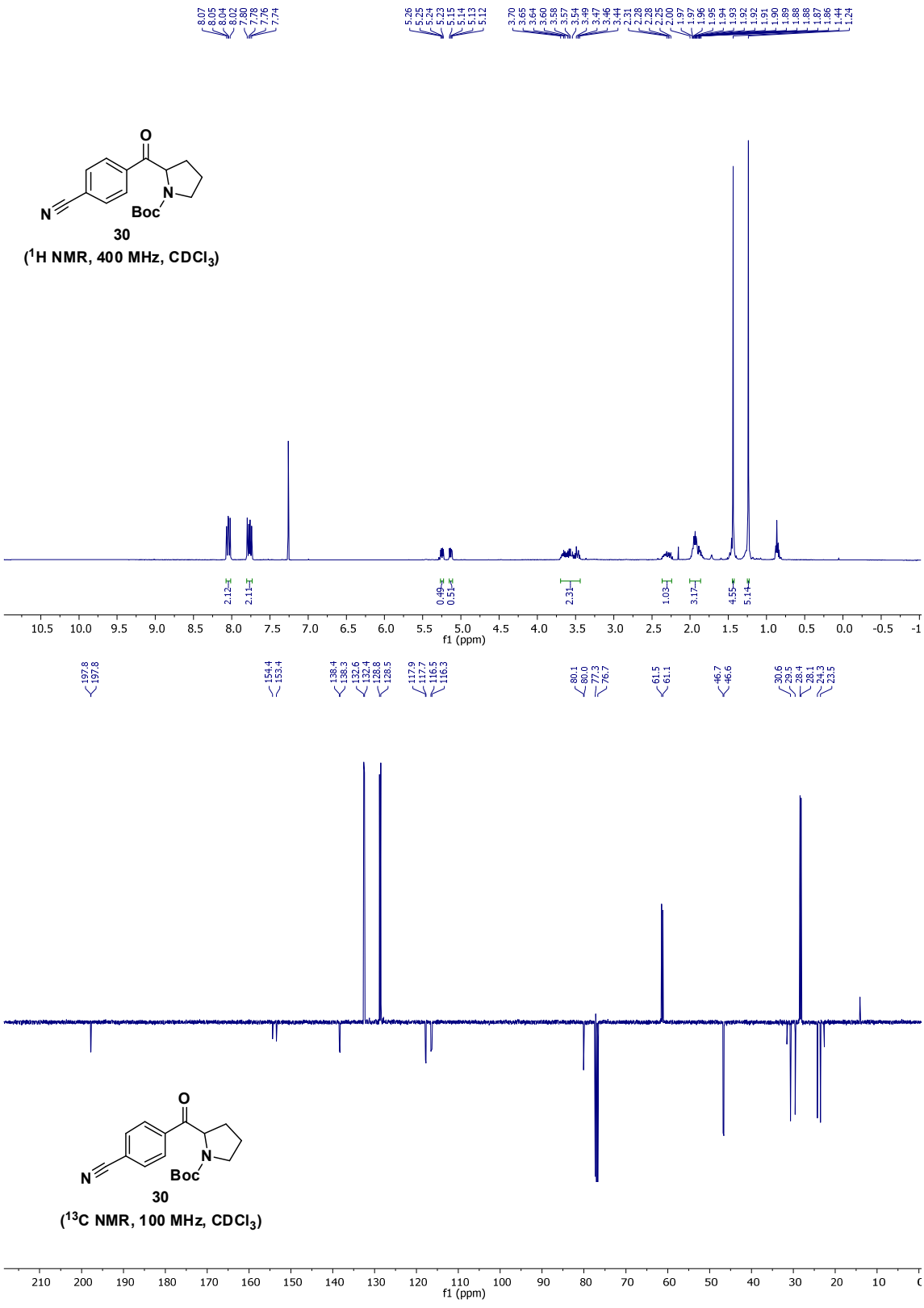
Enantioenriched (+)-sparteine

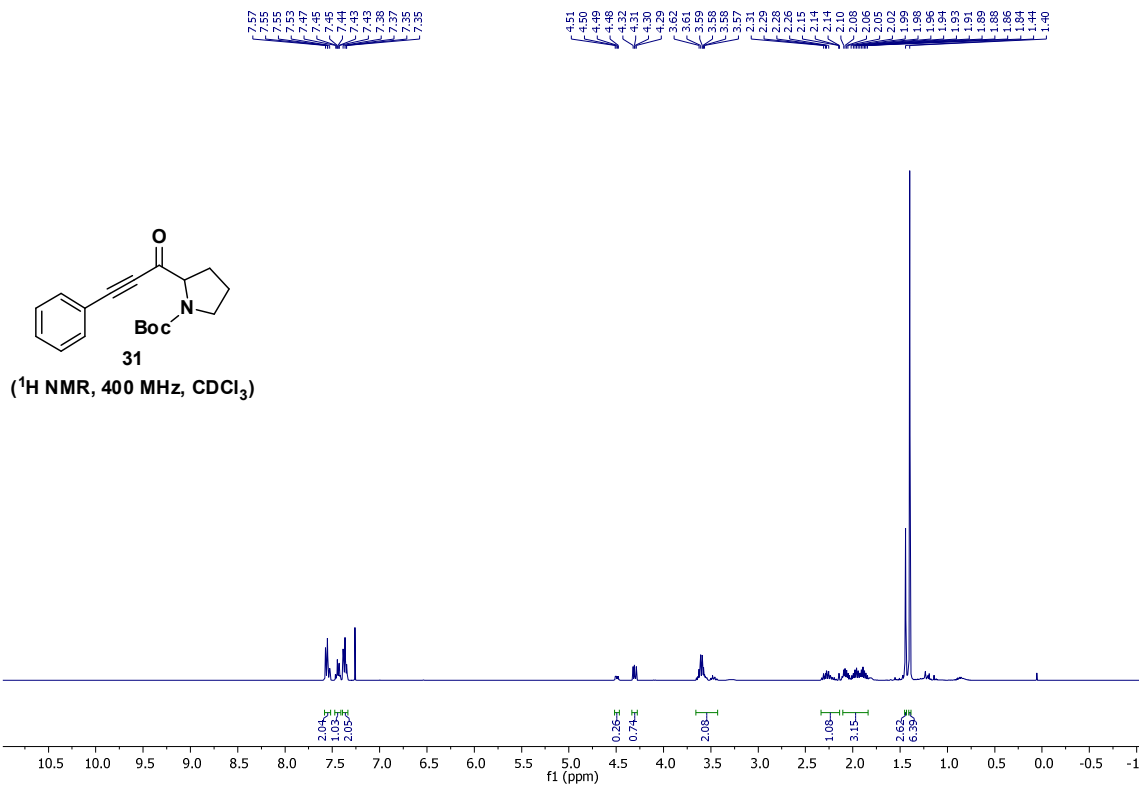


Peaks	Ret.T	Area	Area%
1	24,317	3441466	96,748
2	27,993	115676	3,252
total		3557143	100,000

3.4 Copies of ^{1}H- and ^{13}C-NMR spectra

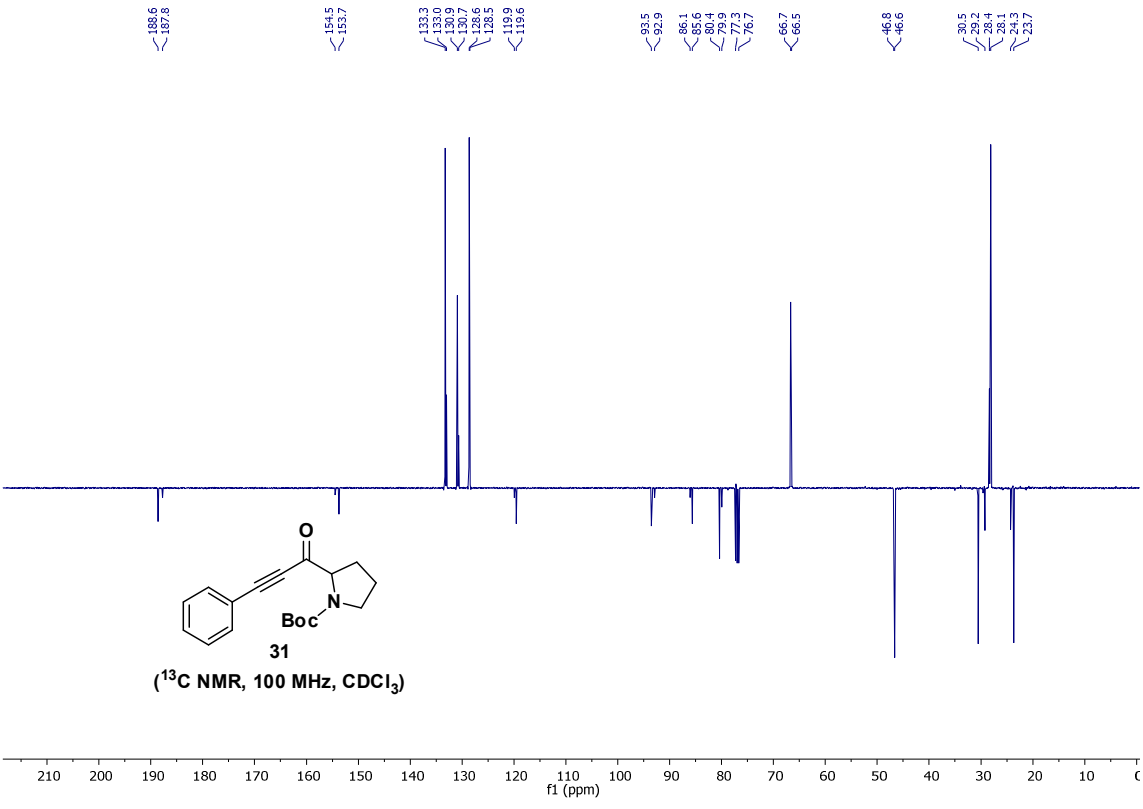



8.07
8.05
8.04
8.02
7.80
7.78
7.76
7.74
5.26
5.25
5.24
5.23
5.15
5.14
5.13
5.12
3.70
3.65
3.64
3.60
3.58
3.57
3.54
3.49
3.47
3.46
3.44
2.31
2.28
2.28
2.25
2.00
1.97
1.97
1.96
1.95
1.94
1.93
1.92
1.92
1.91
1.90
1.89
1.88
1.88
1.87
1.86
1.44
1.24
O
N
Boc
30
(1H NMR, 400 MHz, CDCl3)
2.12
2.11
0.49
0.51
2.31
1.03
3.17
4.55
5.14
f1 (ppm)
197.8
197.8
154.4
153.4
138.4
138.3
132.6
132.4
128.8
128.5
117.9
117.7
116.5
116.3
80.1
80.0
77.3
76.7
61.5
61.1
46.7
46.6
30.6
29.5
28.4
28.1
24.3
23.5
O
N
Boc
30
(13C NMR, 100 MHz, CDCl3)
f1 (ppm)



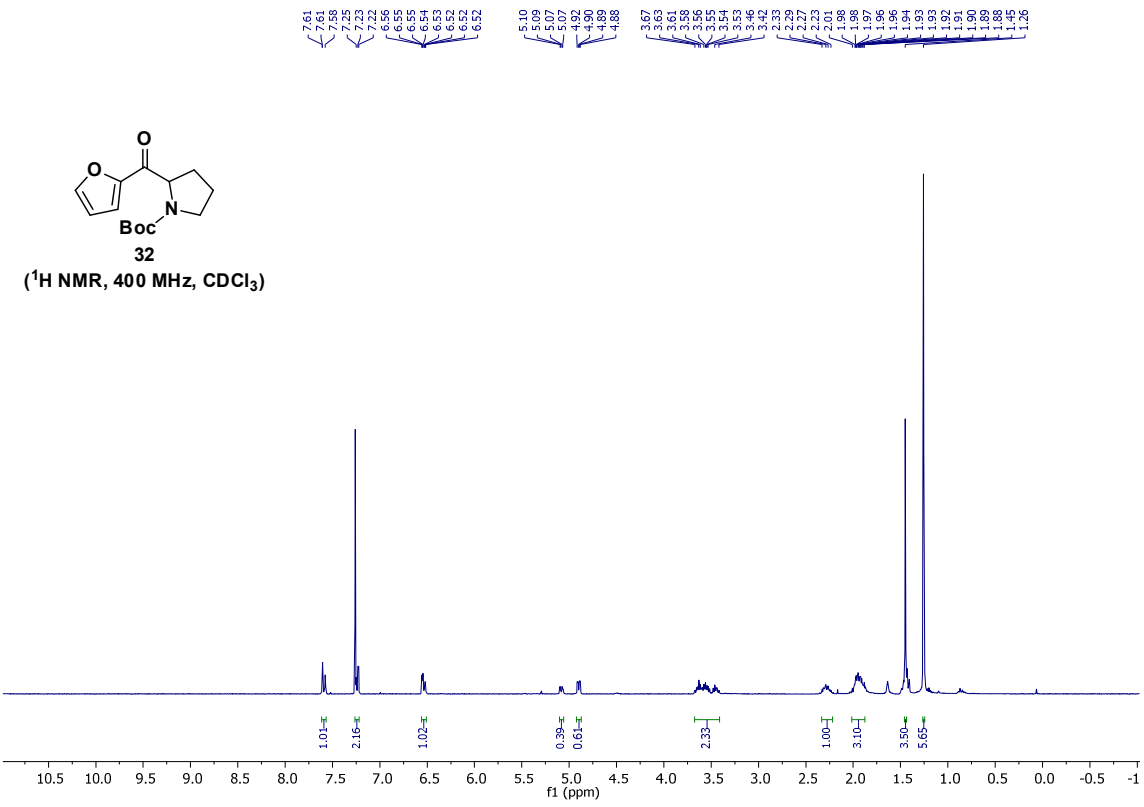
31

(^{1}H NMR, 400 MHz, $CDCl_3$)



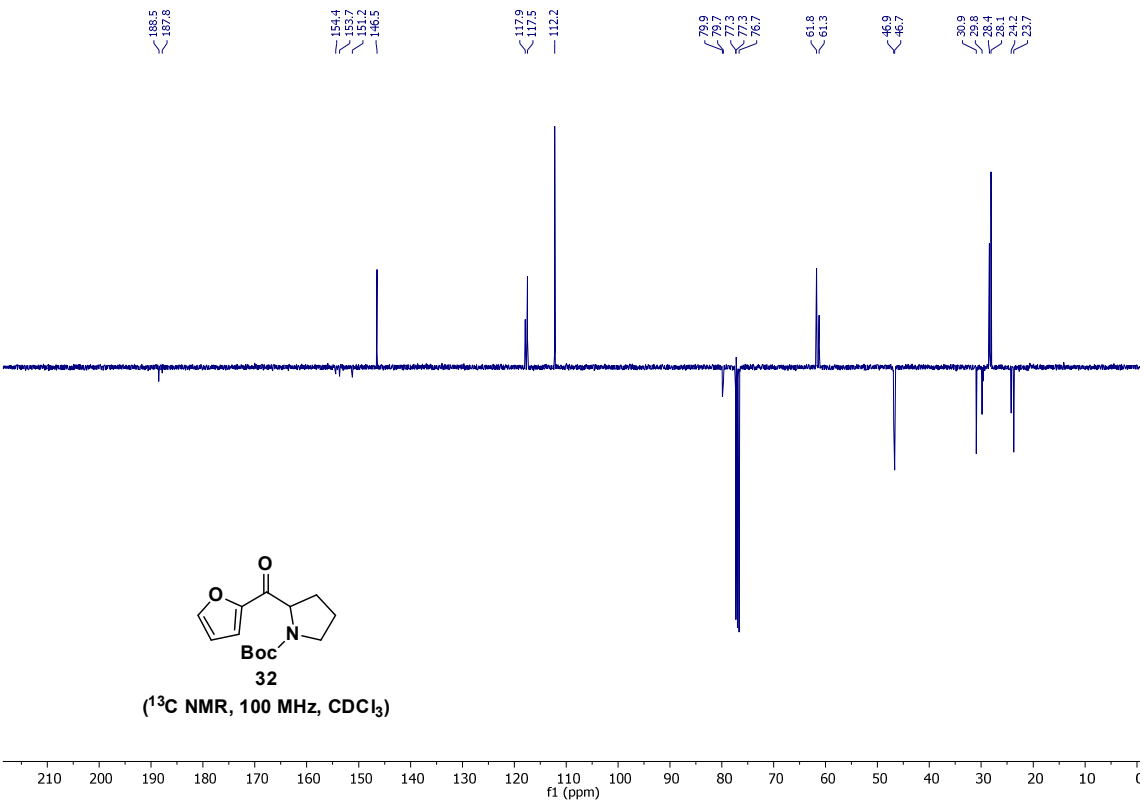
31

(^{13}C NMR, 100 MHz, $CDCl_3$)



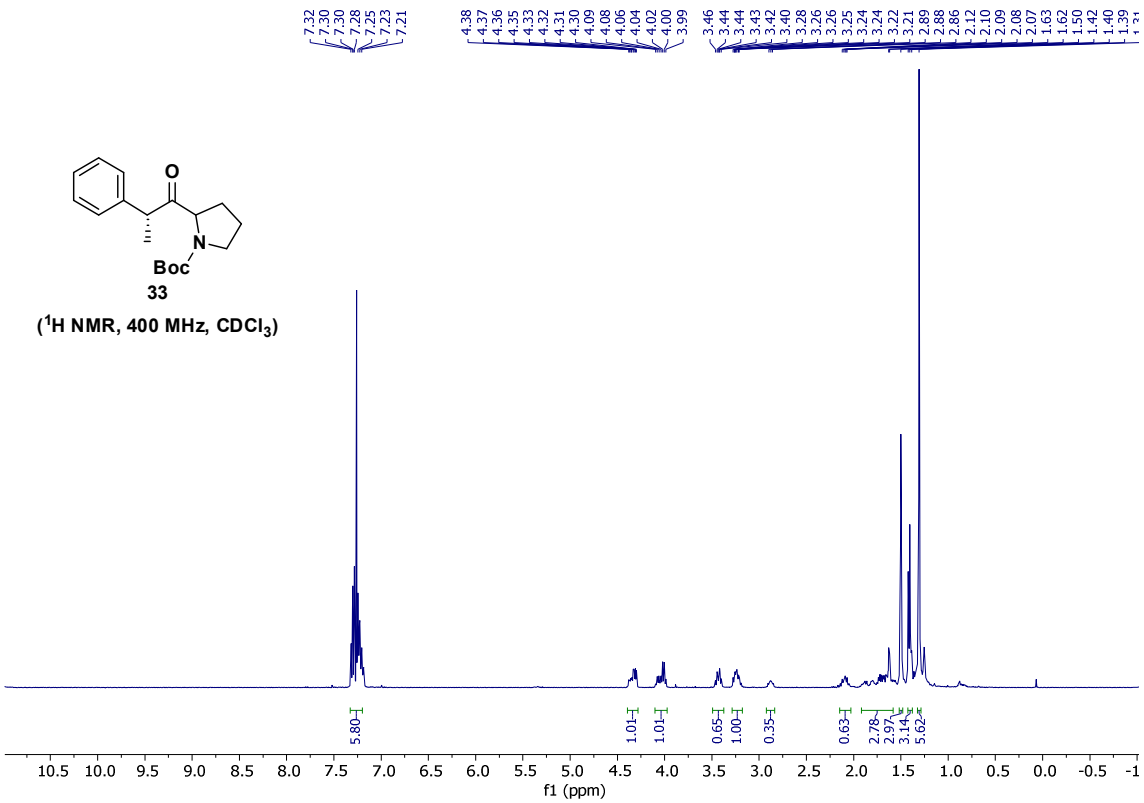
32

(^{1}H NMR, 400 MHz, $CDCl_3$)



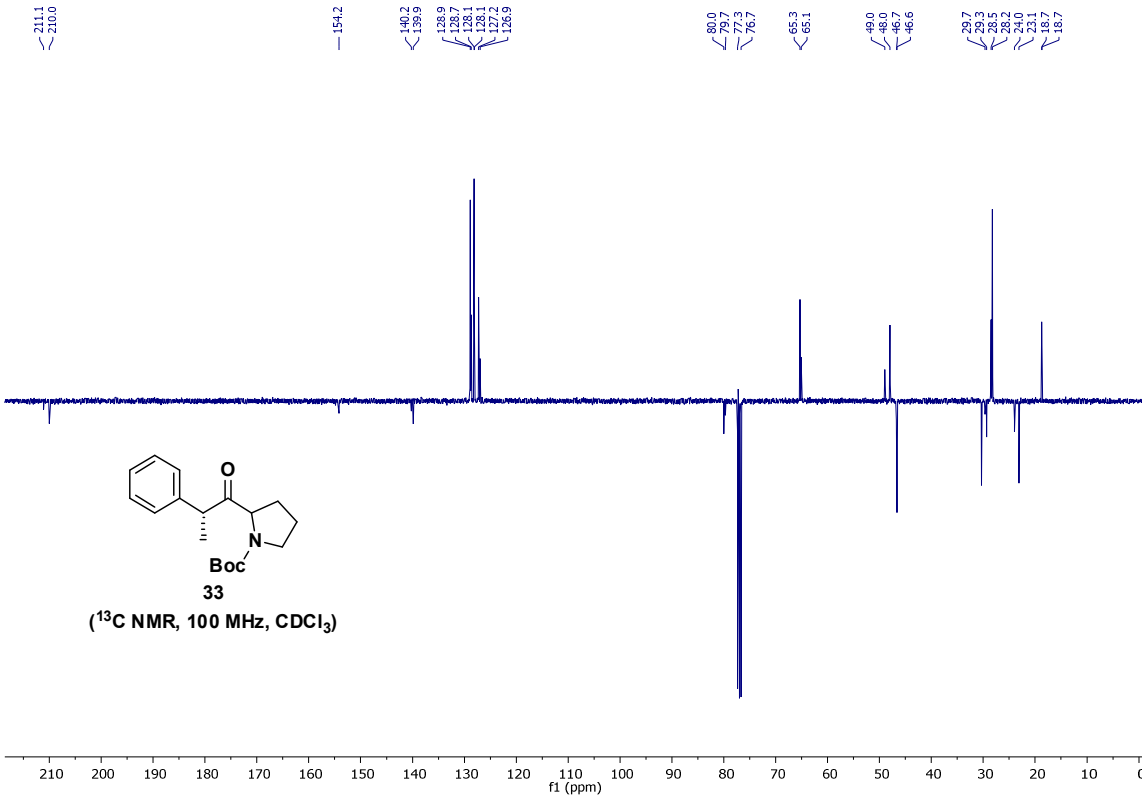
32

(^{13}C NMR, 100 MHz, $CDCl_3$)



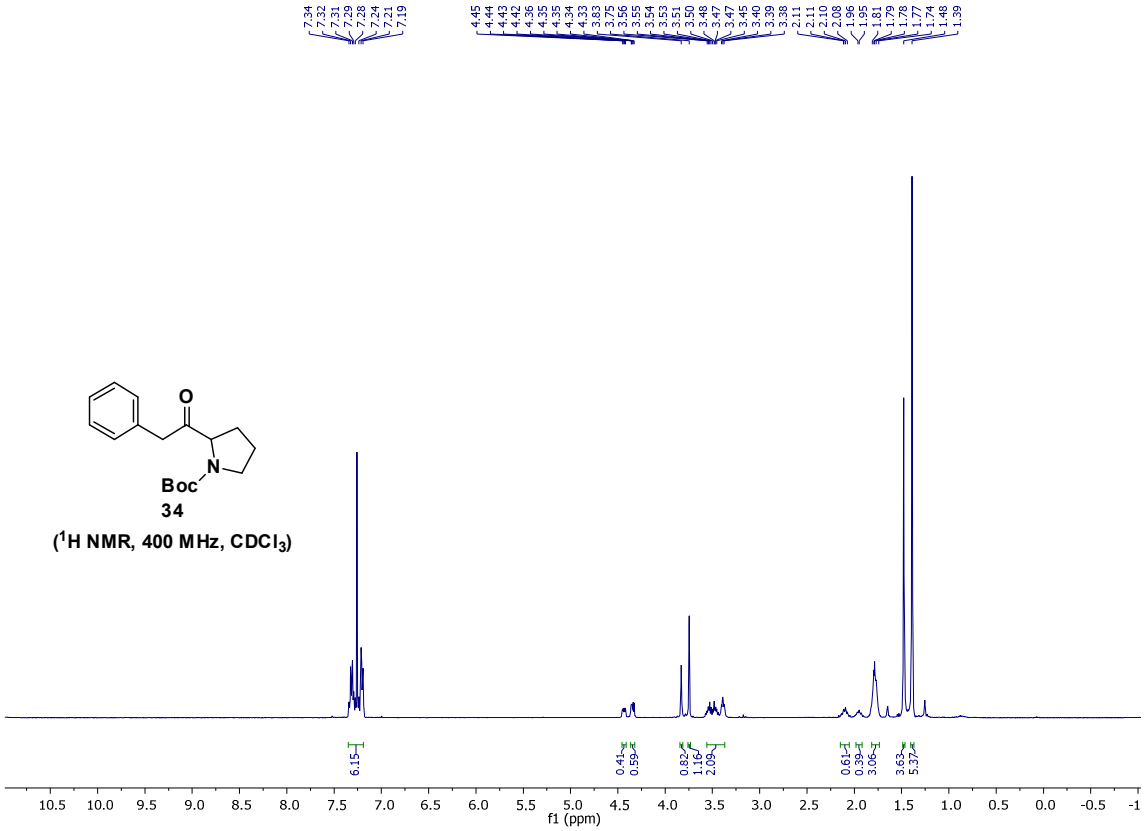
33

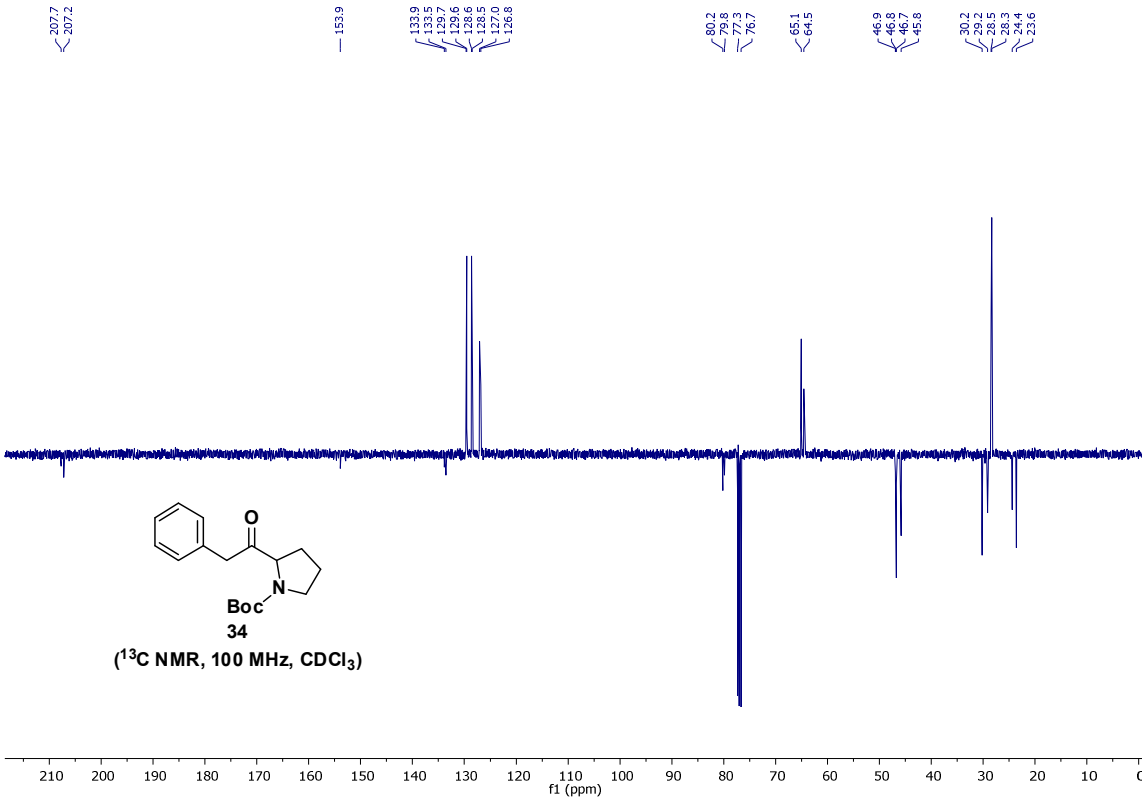
(^{1}H NMR, 400 MHz, $CDCl_3$)

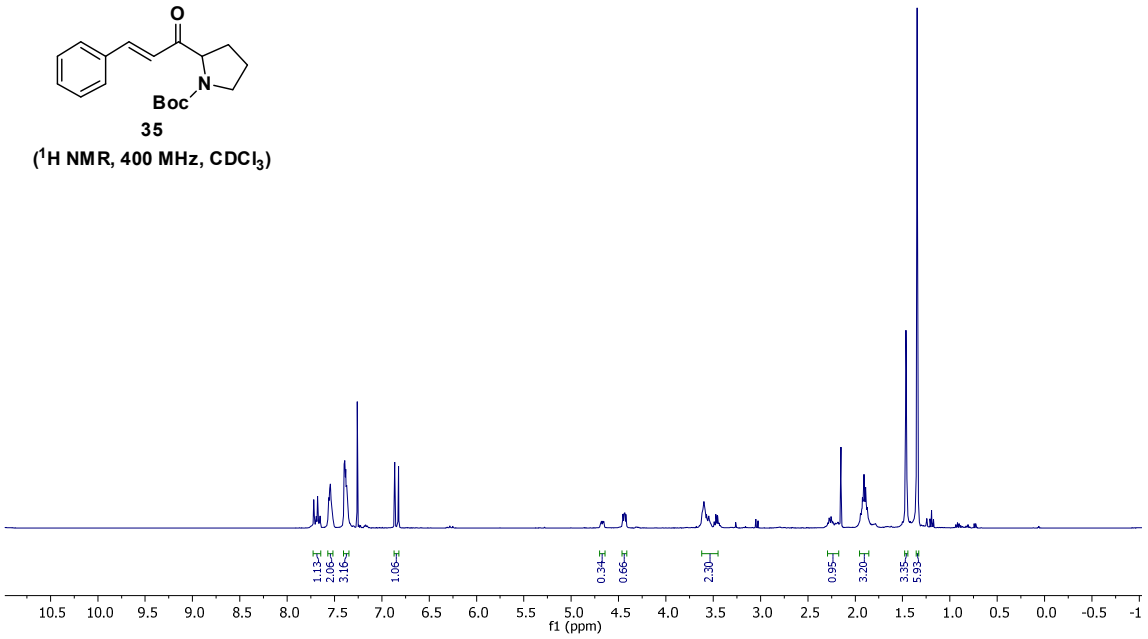


33

(^{13}C NMR, 100 MHz, $CDCl_3$)

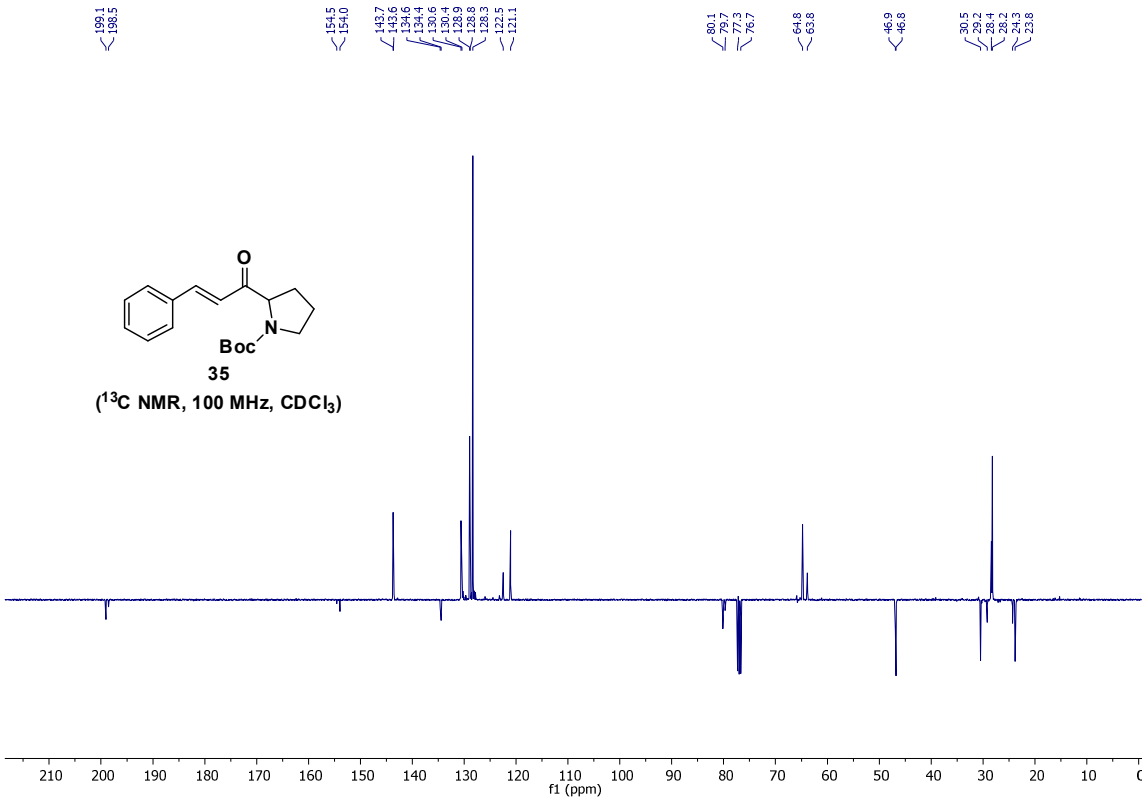

7.34
7.32
7.31
7.29
7.28
7.24
7.21
7.19
4.45
4.44
4.43
4.42
4.36
4.35
4.34
4.33
3.83
3.75
3.56
3.55
3.54
3.53
3.51
3.50
3.48
3.47
3.47
3.45
3.40
3.39
3.38
2.11
2.11
2.10
2.08
1.96
1.95
1.81
1.79
1.78
1.77
1.74
1.48
1.39
O
N
Boc
34
(1H NMR, 400 MHz, CDCl3)
6.15
0.41
0.59
0.82
1.16
2.09
0.61
0.39
3.06
3.63
5.37
f1 (ppm)


207.7
207.2
153.9
133.9
133.5
129.7
129.6
128.6
128.5
127.0
126.8
80.2
79.8
77.3
76.7
65.1
64.5
46.9
46.8
46.7
45.8
30.2
29.2
28.5
28.3
24.4
23.6
O
N
Boc
34
(13C NMR, 100 MHz, CDCl3)
f1 (ppm)



35

(^{1}H NMR, 400 MHz, $CDCl_3$)



35

(^{13}C NMR, 100 MHz, $CDCl_3$)

4 Abstract / Zusammenfassung

This diploma thesis reports an asymmetric lithiation protocol for *N*-Boc-pyrrolidine **1** at -78 °C for 30 minutes utilizing the solvent CPME, which has two beneficial features. First, CPME is a "green" solvent, which makes the reaction set-up more adherent to the requirements and trends of Green Chemistry. Second, by utilizing CPME as a solvent instead of Et_2O the stereoselective deprotonation procedure of *N*-Boc-pyrrolidine **1** is characterized by a much shorter duration at -78 °C than originally reported (30 minutes instead of 4 to 6 hours) but equally good yields and enantioselectivity (75-88% yield, *er* ranges from 95:5 to >99:1). Hence, a protocol that offers an optimal balance between lithiation duration, lithiation temperature, yields and *er* has been developed.

This thesis also broadens the scope of the asymmetric lithiation-trapping of *N*-Boc-pyrrolidine **1**—for the very first time Weinreb amides have been deployed as electrophiles in the trapping step. Herein the syntheses of 11 enantioenriched acylpyrrolidines are reported (75-88% yield, up to >99:1 *er*).

Diese Diplomarbeit berichtet von einem Protokoll zur asymmetrishen Lithiierung von *N*-Boc-Pyrrolidin **1** bei -78 °C für 30 Minuten unter Verwendung des Lösungsmittels CPME, das zwei vorteilhafte Merkmale hat. Erstens, zählt CPME zur Gruppe der grünen Lösungsmittel, was die Reaktionszusammensetzung an den Prinzipien von Grüne Chemie festhaltend macht. Zweitens, unter Verwendung von CPME, die asymmetrische Deprotonierung *N*-Boc-Pyrrolidin **1** ist gekennzeichnet durch eine viel kürzere Dauer bei -78 °C als ursprünglich berichtet (30 Minuten statt 4 bis 6 Stunden), aber durch eine gleich gute Ausbeute und Enantioselektivität (75-88%, 95:5 bis >99:1 *er*). Daher ist ein Reaktionsprotokoll entwickelt worden, das ein optimales Gleichgewicht zwischen Dauer der Lithiierung, Temperatur der Lithiierung, Ausbeute und *er* ermöglicht.

Diese Diplomarbeit erweitert außerdem den Umfang der Abfolge asymmetrische Lithiierung-nukleophile Substitution von *N*-Boc-Pyrrolidin **1**—zum allerersten Mal sind Weinreb Amide als Elektrophile in der Substitutionsstufe verwendet worden. Hiermit wird von den Synthesen von 11 enantiomerenreinen Acylpyrrolidinen berichtet (75-88%, bis >99:1 *er*).

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