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Recent advances in the stereoselective synthesis of *trans*-3,4-disubstituted-piperidines: applications to (−)-paroxetine

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Abstract—Piperidine ring systems are the key structural elements in a vast array of natural products as well as in a large class of biologically active natural products, being also often embedded within scaffolds recognized as privileged structures by medicinal chemists. Accordingly, new stereoselective routes to substituted piperidines are of widespread interest. An overview of the asymmetric synthetic routes to *trans*-3,4-disubstituted piperidines, featuring the substitution pattern of (−)-paroxetine [(3*S*,4*R*)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine], a well-known selective serotonin reuptake inhibitor (SSRI) used worldwide as an antidepressant in humans, is presented. This review is mainly focused on the enantioselective routes to (−)-paroxetine, which has become a very popular synthetic target to test the efficiency of new methodologies. Some recent stereoselective approaches to the racemic compound are also included.

Contents

1. Introduction

A vast array of piperidine containing compounds, both natural and synthetic, is of biological and medicinal interest and this has led to the development of many synthetic approaches to these heterocyclic scaffolds.[1,2] Nevertheless, the variety of functionality and substitution patterns found in piperidine targets and the widely accepted concept that the biological properties of piperidines are highly dependent on the type and location of substituents on the heterocyclic ring continue to drive the search for new methodologies. Accordingly, great attention has been paid to the construction of functionalized piperidine compounds and the development of methods for the synthesis of optically active substituted piperidines has been the subject of considerable synthetic efforts.[3–5]

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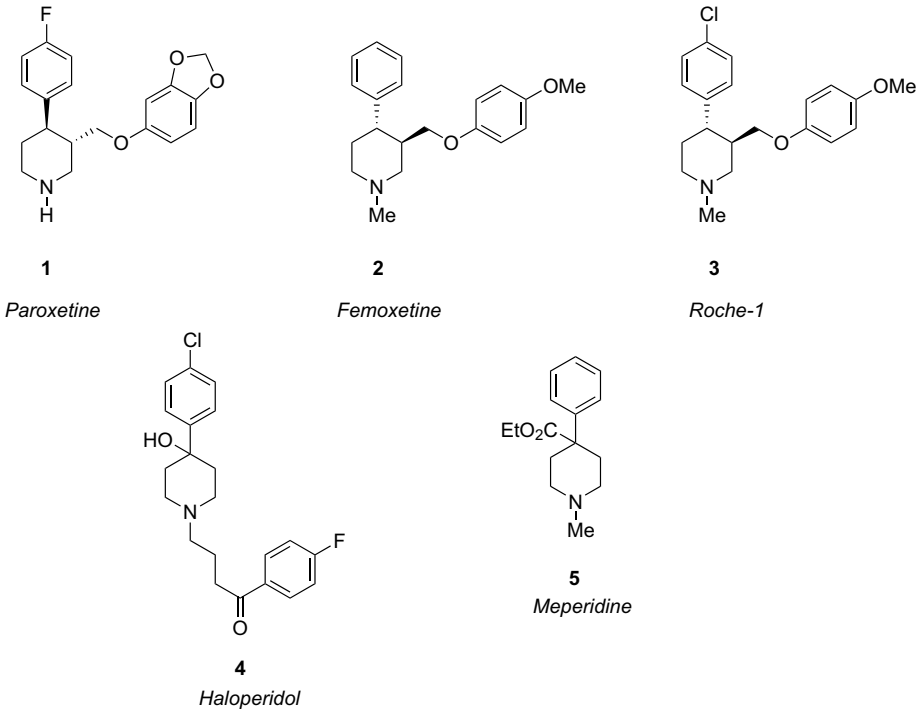


Figure 1.

The absolute configurations at the C-3 and C-4 positions of the piperidine ring are critical for the activity of these compounds and it is noteworthy that 4-arylpiperidine is an important structural motif in many biologically active compounds,[6,7] including paroxetine **1**, femoxetine **2**, Roche-1 **3**, haloperidol **4**, and meperidine **5** (Fig. 1).

Interestingly, most of these compounds feature a benzylic carbon stereocenter, a recurring stereochemical motif given a 'privileged' status in medicinal chemistry.[8]

Nevertheless, methods providing substitutions at C-3 and C-4 of the piperidine ring system are quite limited in comparison to the number of strategies focusing on carbon substitution at C-2, C-6 positions.

The therapeutic success of (−)-**1** (Paxil®, Seroxat®), a selective serotonin (5-hydroxy-tryptamine, 5-HT) reuptake inhibitor used for the treatment of depression, anxiety, and panic disorder,[9] has inspired continuous synthetic efforts that have led to the development of a number of new strategies for its stereo- and enantioselective synthesis.

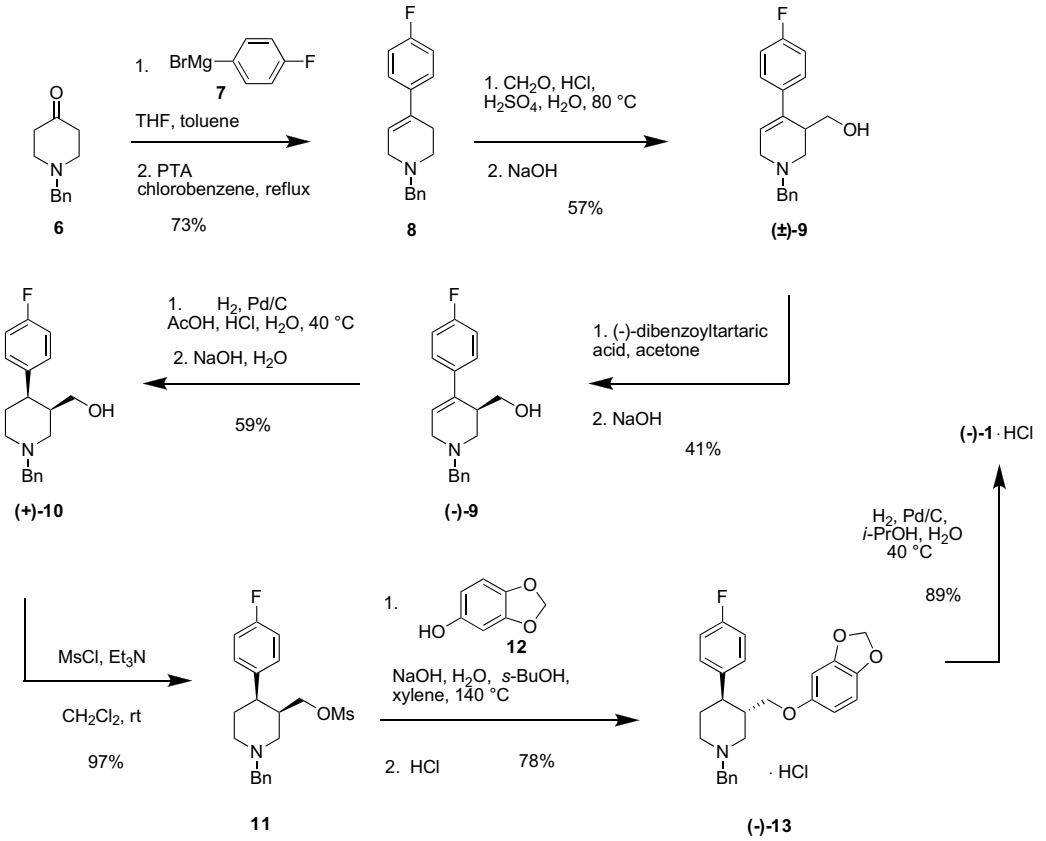
It has been known that the enantiomers and diastereomers of (−)-**1** and (+)-**2** exhibit different activities toward 5-HT uptake inhibition. Therefore, it is quite important to establish a synthetic route for all of the diastereomers of 3,4-disubstituted piperidines in pure form.

This review concentrates on the strategies developed to obtain (−)-**1**, but also includes some recent approaches to the racemic molecule which has become a very popular synthetic target to validate new synthetic methodologies, both in the racemic series and in the enantiopure form.

The asymmetric synthesis routes to 3,4-disubstituted piperidine derivatives en route to **1** have been classified in different sections according to the way the asymmetry has been introduced, following the historical development of the synthetic approaches to (−)-**1**. Thus, syntheses of the target molecule involving classical resolution methods are discussed in Section 2, followed by examples of chiral auxiliary-assisted approaches in Section 3. Synthetic routes entailing on the asymmetric lithiation using chiral bases are covered in Section 4, while Section 5 is dedicated to the use of naturally occurring homochiral starting materials. The subsequent two sections deal with catalytic enantioselective transformations (Section 6) and enzymatic asymmetrizations (Section 7). In the final Section 8 we collected both the most recent entries to paroxetine, although in racemic form, and some recent approaches leading to the stereoselective synthesis of piperidine-based scaffolds as suitable candidates for the preparation of pharmaceutically important drugs, including **1**.

2. Resolution of racemates

Chemical as well as biocatalytic resolutions have been used to obtain (−)-**1**. The still very important physical separation of racemates has been used not only in the early patent literature,[10] but also in an efficient eight-step stereoselective synthesis of (−)-**1**, recently described by a Hungarian group along the pathway depicted in Scheme 1.[11]



Scheme 1.

The readily available 1-benzyl-4-piperidone **6** was used as the starting point. Addition of the required Grignard reagent **7** to the carbonyl group, followed by the *p*-toluensulfonic acid (PTA)-promoted dehydration of the derived tertiary alcohol produced the *N*-benzyl-protected tetrahydropyridine **8**, isolated as the *p*-toluenesulfonate salt in 73% yield.

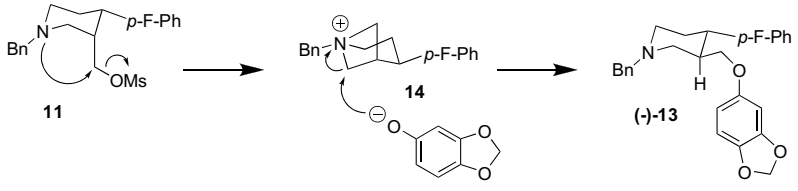
Prins reaction of **8** gave rise to the formation of tetrahydropyridine-3-methanol (±)-**9**, which was partially resolved by means of (−)-L-dibenzoyltartaric acid monohydrate providing (−)-**9** in 41% yield.

Interestingly, the subsequent reduction of (−)-**9** on Pd/C catalyst proceeded stereoselectively with the retention of the *N*-benzyl protective group, leading to the formation of *cis*-piperidine-3-methanol (+)-**10**, the 3,4-*cis* relationship being assigned on the basis of the ^{1}H NMR coupling constants. Alcohol (+)-**10** was converted into mesylate **11** and reacted with sesamol **12** in boiling xylene in the presence of NaOH, allowing for the formation of *trans*-*N*-benzyl paroxetine (−)-**13**, isolated as its hydrochloride in 78% yield.

Hydrogenolytic removal of the nitrogen protective group completed the synthesis of (−)-**1**, isolated as the corresponding hydrochloride in 89% yield with specific rotation value similar to the reported values.

The formation of *trans*-(−)-**13** from *cis*-**11** had been explained through a mechanistic pathway which has been already reported for similar reactions.[12] As shown in Scheme 2, *cis*-**11** reacts via the intermediate 1-azonia-1-methyl-4-phenyl-[3.1.1]bicycloheptane cation **14**, the subsequent nucleophilic attack occurring from the less crowded side, opposite to the 4-aryl group, leading to the 3,4-*trans* configuration.

The synthesis of the optically active amino alcohol (−)-**20**, a paroxetine metabolite, through a route incorporating a late stage resolution of the corresponding racemic mixture,



Scheme 2.

had been previously reported by the Sumika Fine Chemicals Co. group (Scheme 3).[13]

Thus, the addition of methyl cyanoacetate to methyl *p*-fluorocinnamate **16**, in turn prepared by the reaction of *p*-fluorobenzaldehyde **15** with methyl acetate in the presence of NaOMe, produced adduct (±)-**17** in 79% yield. Its hydrogenation in the presence of Raney Ni–cobalt gave rise to the mixture of *cis*-(±)-**18** and *trans*-(±)-**19**, the *cis*-diastereomer (±)-**18** being transformed to the more stable *trans*-derivative (±)-**19** by treatment with NaOMe. Reduction of (±)-**19** with $LiAlH_4$ gave amino alcohol (±)-**20**, which was resolved using L-*o*-chlorotartranilic acid.

Biotransformations are well recognized as an excellent strategy for the preparation of fine chemicals. The wide substrate acceptance coupled with a high regio- and enantioselectivity make lipases (triacylglycerol acylhydrolases, EC 3.1.1.3) the most frequently used enzymes in organic chemistry.[14] Thus, the enzymatic hydrolysis of acetylated alcohols or the enzymatic transesterification reactions of alcohols have been widely investigated for the preparation of a great number of synthons for the synthesis of homochiral drugs. Several intermediates along the synthetic pathways to (−)-**1** are suitable for enzymatic resolution (Fig. 2).

Thus, the enantioselective hydrolysis of the *N*-methyl derivative of imidoester (±)-**21** catalyzed by enzymes[15,16] and microorganisms[16] has been described in the patent literature.

Unsuccessful attempts to resolve (±)-**21** via hydrolysis, transesterification, and aminolysis reactions catalyzed by commercially available lipases prompted Gotor et al.[17–20] to focus on the resolution of (±)-**20**, which could be easily derived from (±)-**21** by $LiAlH_4$ reduction.

Four representative carbamate derivatives (±)-**23**(**a**–**d**) of various sizes were selected in order to investigate the scope of the enzymatic reactions (Scheme 4).

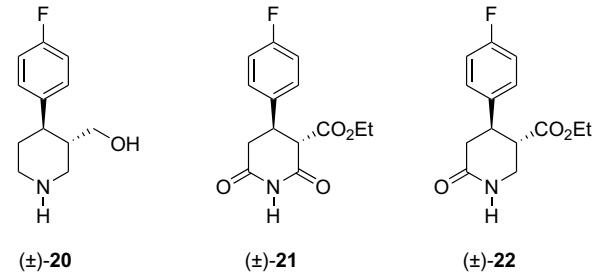


Figure 2.

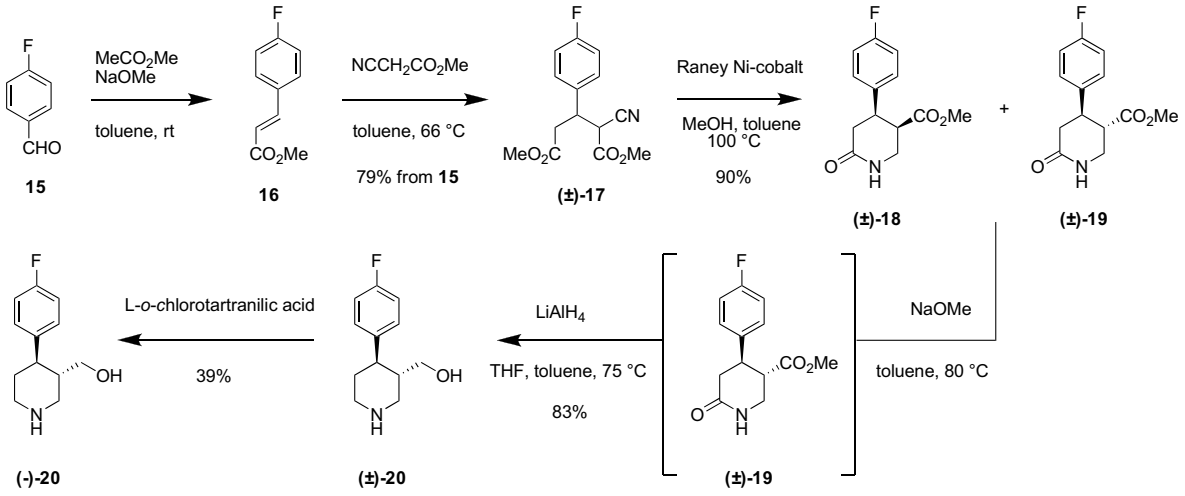
The resolution of compound (±)-**20** was carried out both through the enzymatic hydrolysis of acylated compound *trans*-(±)-**24a** and through the lipase-catalyzed acylation of derivatives *trans*-(±)-**23**(**a**–**d**) (Scheme 5).[17,18]

Moreover, the application of lipases for the resolution of (±)-**23a** *via* enzymatic alkoxycarbonylation processes has been also investigated by the same research group.[19]

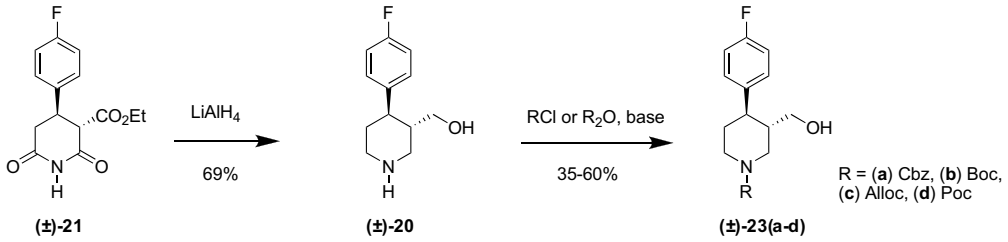
Despite the availability, the low cost, and the low environmental impact of these lipase-catalyzed reactions, the need for a chromatographic separation of the obtained products represented a major drawback, thus preventing the large-scale production of (−)-**1**.

On the contrary, a lipase-catalyzed esterification with cyclic anhydrides was especially advantageous, leading to the formation of a monoester of a diacid that was easily separated from the unreacted alcohol by extraction with a base.[20] Very good yields and enantioselectivities were achieved when carbamate (±)-**23d** was treated with glutaric anhydride **26** in the presence of *Candida antarctica* lipase B (CAL-B) in toluene at 30 °C (Scheme 6).

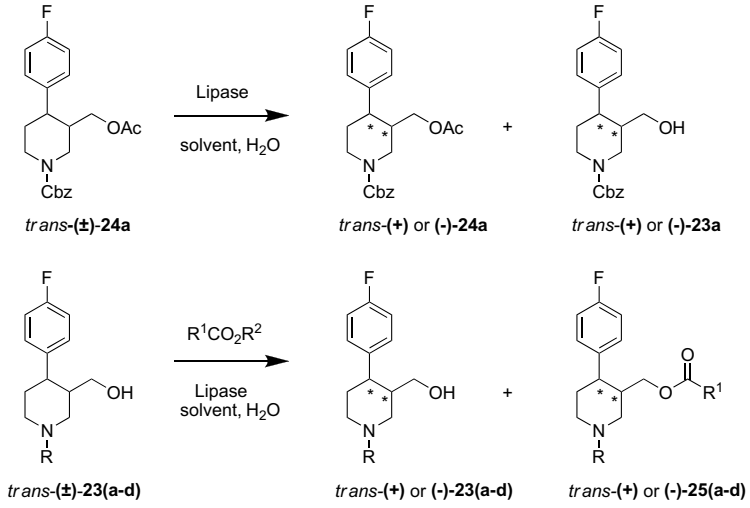
Similar results were obtained when using succinic anhydride, while no reaction was observed with other anhydrides, such as maleic and phthalic. Meldrum's acid was used as a synthetic equivalent of the malonic anhydride,



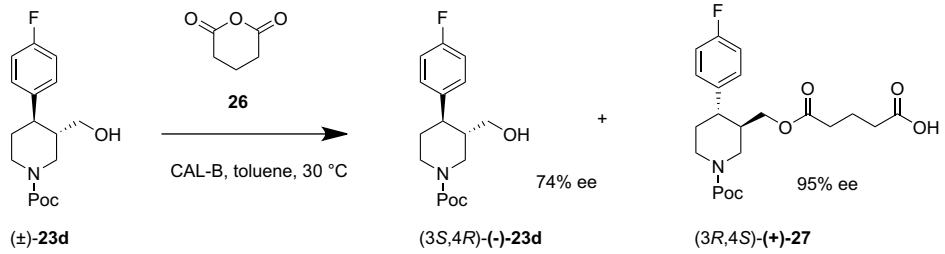
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

moderate to good conversions being achieved only in toluene at 50 °C, or in solvents such as *t*-BuOMe or *i*-Pr_2O, but enantioselectivities were too low.

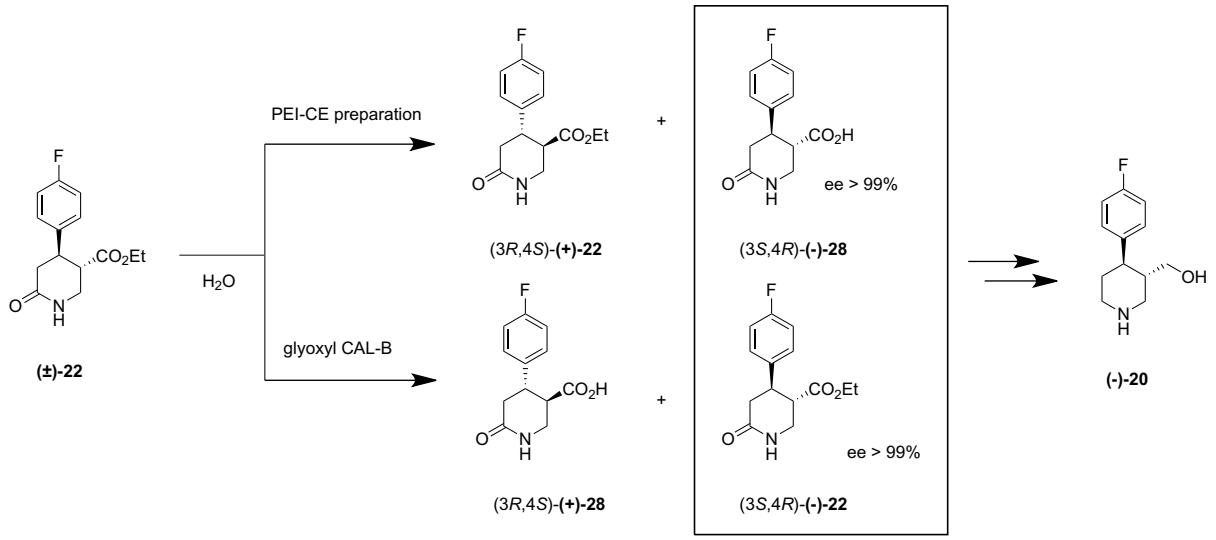
Another research group utilized four different microbial lipases for the enantioselective hydrolysis of (±)-**22**, a poor substrate for most lipases, except for *C. antarctica B* (CAL-B).[21] This enzyme was purified via adsorption on hydrophobic supports and immobilized using different protocols. The enzyme immobilized on octadecyl-Sepabeads was not enantioselective at all, while glyoxyl-CAL-B preparation gave unreacted (3*S*,4*R*)-(−)-**22** in enantiomerically pure form (ee >99%) at 50% conversion (Scheme 7). No decrease in the enzyme activity, or alteration in the enantioselectivity was detected, even after ten reaction cycles.

Shortly after,[22] the same research group was able to resolve (±)-**22** using an immobilized contaminant esterase contained in the commercial *C. antarctica* A (CAL-A) preparation (PEI-CE preparation), when CAL-A showed almost no activity with this compound. Compound (3*S*,4*R*)-(−)-**28** was thus obtained with ee >99% at 50% conversion (Scheme 7).

Derivatives (−)-**22** and (−)-**28** possess the correct configuration to allow the synthesis of (−)-**20**, an immediate precursor of (−)-**1**.

3. Chiral auxiliary-assisted approaches

Use of chiral non-racemic amino alcohol-derived bicyclic lactams as a highly useful and practical strategy for the asymmetric synthesis of functionalized carbocycles and nitrogen heterocycles has been pioneered by Meyers et al.[23]



Scheme 7.

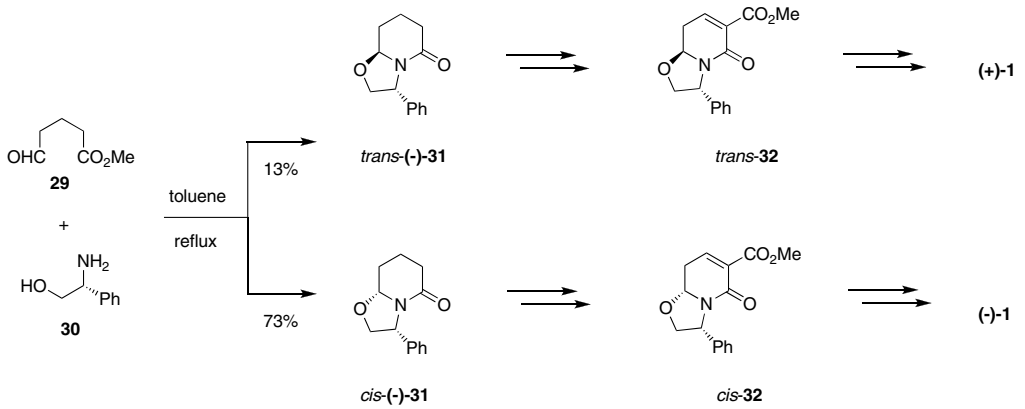
Thus, chiral non-racemic bicyclic lactams derived from homochiral β-amino alcohols are commonly considered useful starting materials for the enantioselective synthesis of polysubstituted piperidines. In these syntheses, the bicyclic ring system is usually generated by the cyclocondensation of δ-oxoacid derivatives with suitable β-amino alcohols.

In particular, phenylglycinol-derived oxazolopiperidone lactams are exceptionally versatile building blocks for the enantioselective construction of structurally diverse piperidine-containing natural products and bioactive compounds. These lactams are readily available in both enantiomeric series by the cyclocondensation of the chiral amino alcohol with a δ-oxo acid derivative and allow the substituents to be introduced at different ring positions in a regio- and stereocontrolled manner, providing access to enantiopure polysubstituted piperidines bearing virtually any type of substitution pattern, and also quinolizidines, indolizidines, perhydroquinolines, hydroisoquinolines, as well as complex indole alkaloids.[24]

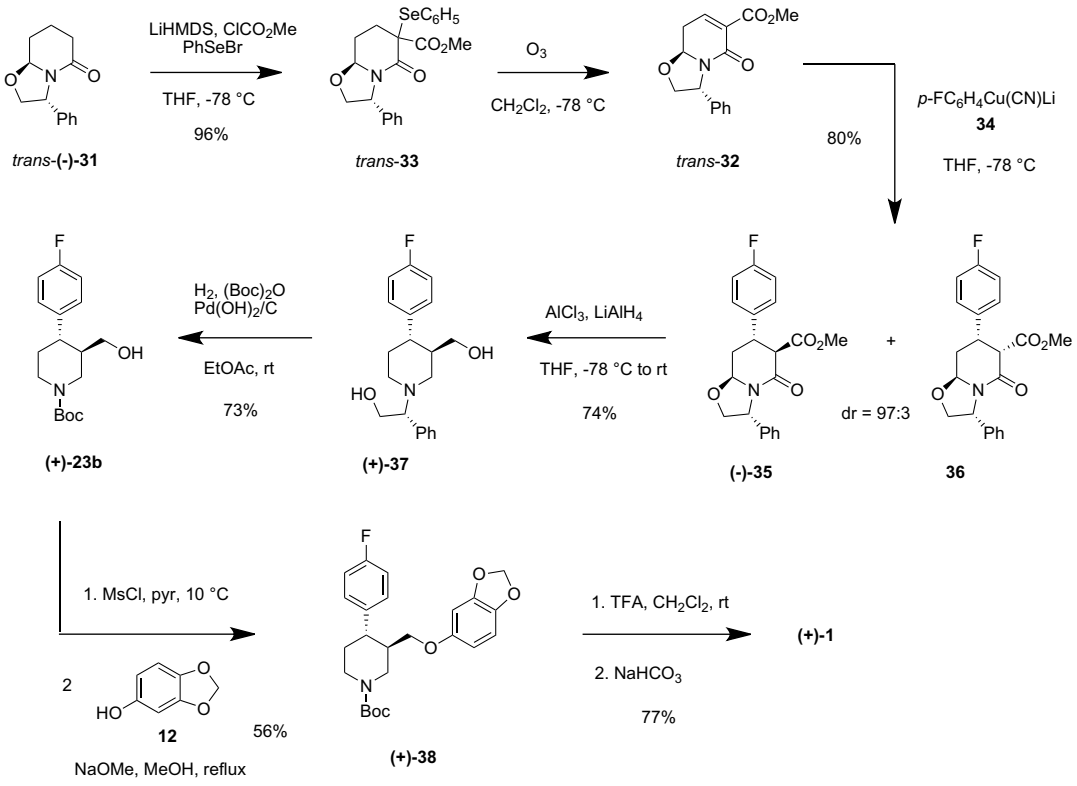
An enantiodivergent synthesis of (+)- and (−)-**1** commenced with the cyclodehydration of methyl 5-oxopentanoate **29** and (*R*)-phenylglycinol **30** by heating a toluene solution at reflux for 36 h under neutral conditions, with the azeotropic removal of water, affording a chromatographically separable 85:15 mixture of bicyclic lactams (−)-*cis*- and (−)-*trans*-**31**, respectively, in 86% overall yield. (Scheme 8).[25]

Lactams (−)-*cis*- and (−)-*trans*-**31** were converted into the corresponding α,β-unsaturated lactams *cis*- and *trans*-**32** to accomplish the introduction of the aryl substituent at the piperidine 4-position through a conjugate addition reaction. The additional electron-withdrawing moiety on the α position has been used in order to enhance the reactivity of the conjugated system, since it is well known that simple α,β-unsaturated lactams are poor Michael acceptors.

Lactam *trans*-**32** has been easily prepared in excellent overall yield by the sequential treatment of *trans*-(−)-**31** with lithium hexamethyldisilazide (LiHMDS, 2.2 equiv), methyl chloroformate (1.0 equiv), and phenylselenyl bromide (1.4 equiv), followed by the ozonolysis of the resulting diastereomeric selenides *trans*-**33** under neutral conditions (Scheme 9).



Scheme 8.



Scheme 9.

Interestingly, the crude unsaturated lactam *trans*-**32** undergoes conjugate addition of lithium (*p*-fluorophenyl)cyanocuprate **34** affording products (−)-**35** and **36** in high yield (80%) and stereoselectivity (dr = 97:3).

Alane reduction of the *p*-fluorophenyl derivative (−)-**35** resulted in the cleavage of the oxazolidine ring and the reduction of the ester and lactam carbonyl groups, affording the *trans*-piperidine (+)-**37**, which was converted into alcohol (+)-**23b** by hydrogenolysis in the presence of di-*tert*-butyl-dicarbonate. Mesylation of (+)-**23b**, followed by reaction with the sodium salt of sesamol **12** gave (+)-**38**, which, on treatment with trifluoroacetic acid (TFA), afforded (+)-**1**.

A parallel synthetic sequence achieved the preparation of (−)-**1**, starting from *cis*-(−)-**31**.

Taking into account that the starting lactams are easily accessible from the same enantiomer of phenylglycinol, this strategy constitutes a nice example of enantiodivergent synthesis of **1**. The observed stereoselectivity of the conjugate addition has been rationalized by considering a stereocontrolled kinetic axial attack of the nucleophile, as depicted in Figure 3.

The synthetic potential of this strategy is further illustrated by the synthesis of the closely related 5-HT reuptake inhibitor (+)-**2**, starting from lactam *trans*-**32** (Scheme 10).[25b]

Introduction of the phenyl substituent, reduction, hydrogenolytic removal of the chiral auxiliary in the presence

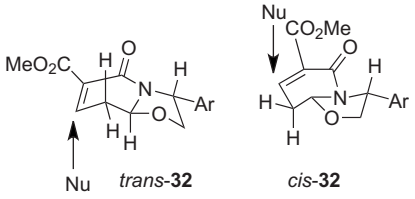
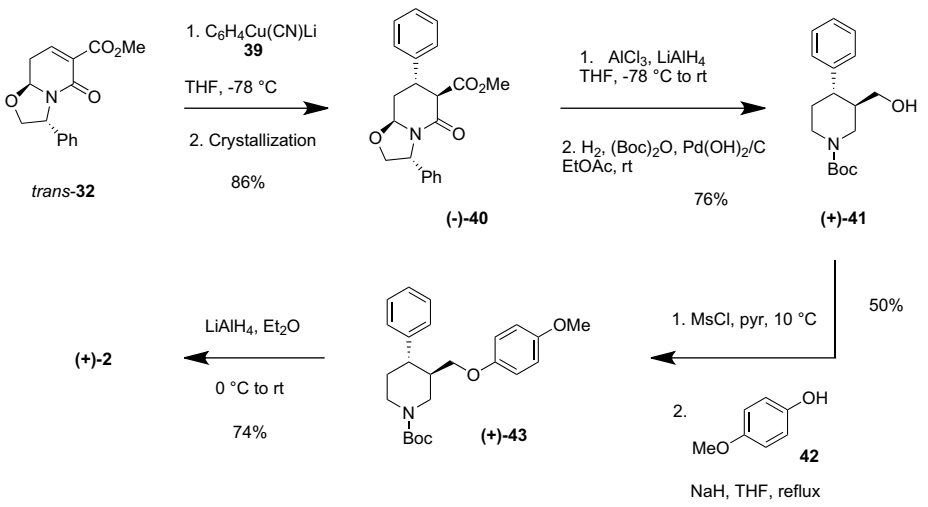


Figure 3.

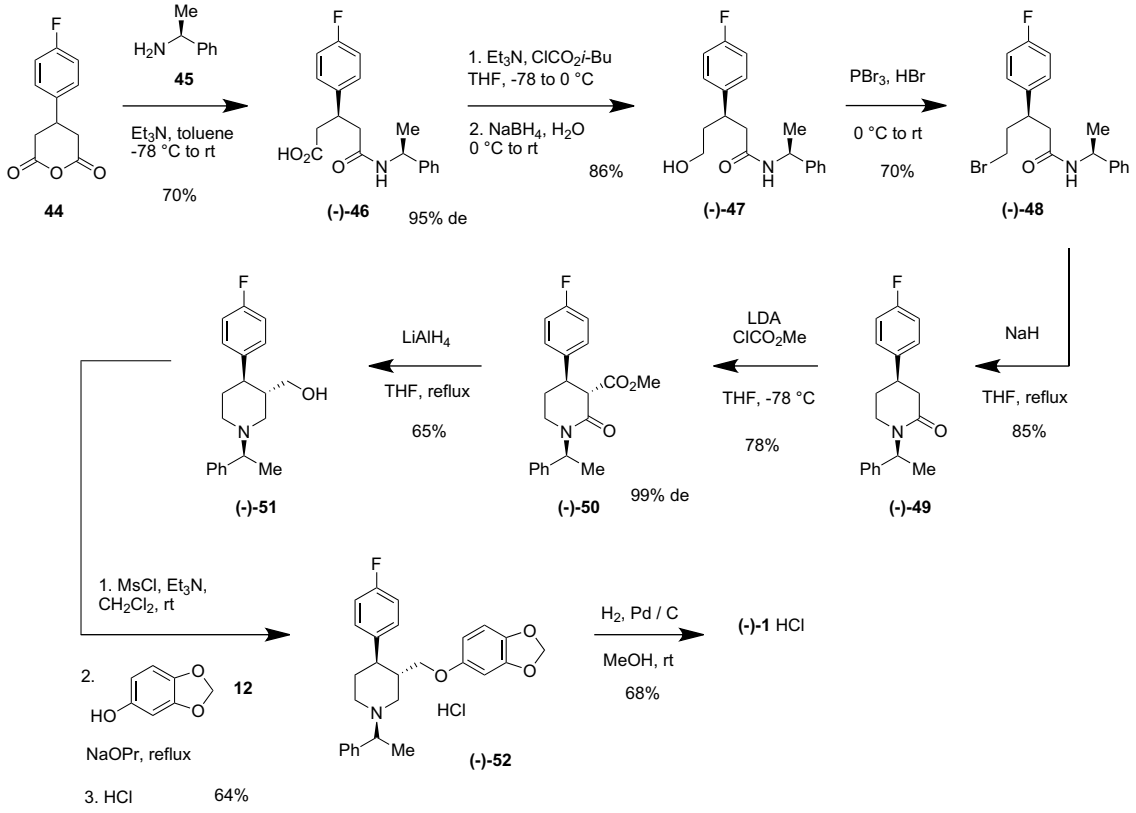
of di-*tert*-butyl-dicarbonate, and etherification with *p*-methoxyphenol **42** provided *N*-Boc piperidine (+)-**43**. Finally, the reduction of the nitrogen protecting group with lithium aluminum hydride gave the target molecule (+)-**2** in 24% overall yield.

A very nice chiral auxiliary-assisted diastereoselective synthesis of chiral 4-substituted and *trans*-3,4-disubstituted 2-piperidinones has been reported by Liu et al.[26] This approach entailed the desymmetrization of *meso*-3-substituted glutaric anhydride **44** with (*S*)-methylbenzylamine **45** in toluene at −78 °C as the starting step (Scheme 11).

The amido acid (−)-**46** was obtained in 70% yield and excellent diastereoselectivity (95% de) after single recrystallization. The carboxyl group was reduced with sodium borohydride via a mixed anhydride to the primary alcohol (−)-**47**, subsequently transformed by the action of phosphorus tribromide and hydrobromic acid into the corresponding bromide (−)-**48**. The latter underwent an intramolecular amide alkylation producing 2-piperidinone



Scheme 10.



Scheme 11.

(−)-**49** in 85% yield after recrystallization, in >99% diastereomeric purity.

Acylation at the α-carbon by treatment with an excess of lithium diisopropylamide (LDA) and 1.5 equiv of methyl chloroformate produced the corresponding 3,4-disubstituted piperidine derivative (−)-**50**, which was reduced with $LiAlH_4$ to 3-hydroxymethyl piperidine (−)-**51**. Finally, mesylation of the primary hydroxyl group of (−)-**51** followed by nucleophilic displacement with the sodium salt of sesamol **12** produced the corresponding aryl ether, which was purified by the crystallization of the hydrochloride salt (−)-**52**. Hydrogenolytic removal of the chiral auxiliary completed the synthesis of (−)-**1** as its hydrochloride (68% yield).

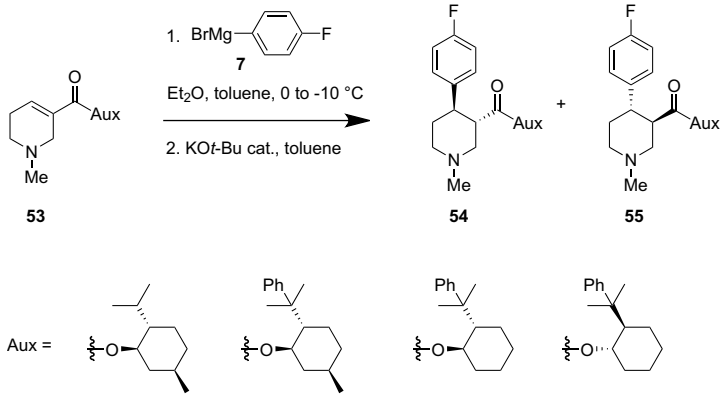
The asymmetric conjugate addition reaction of Grignard reagents to various arecoline-derived chiral α,β-unsaturated esters has been exploited by Murthy and Rey to achieve the enantioselective synthesis of 3-substituted-4-

aryl piperidines which have been used for the preparation of chiral pharmaceutics, including **1**.[27]

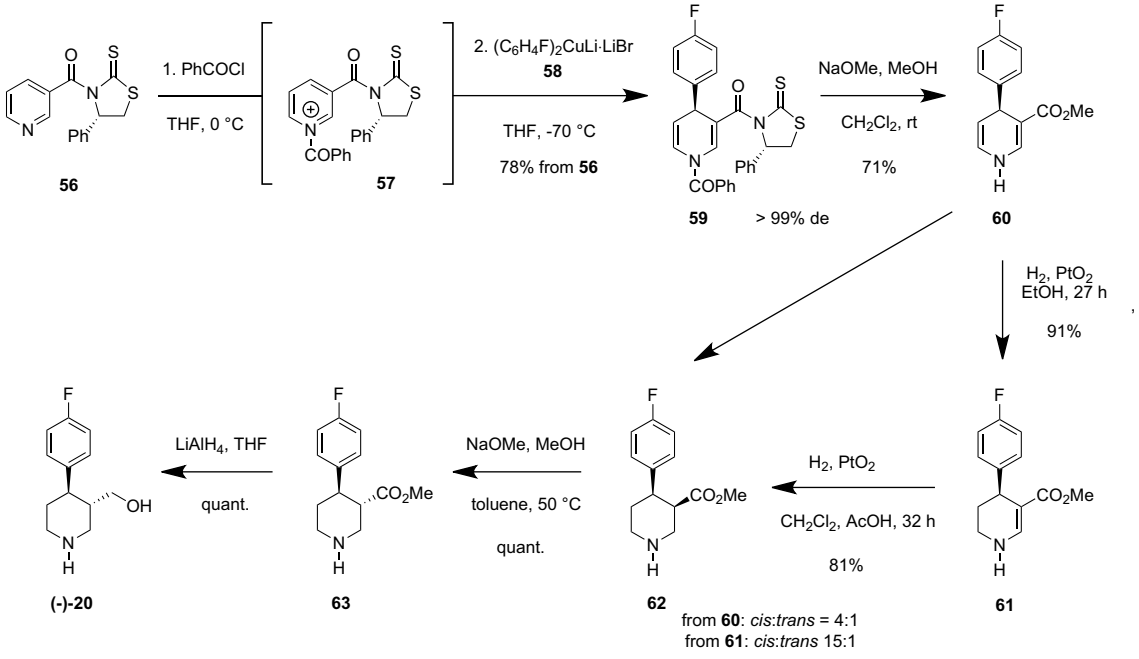
Thus, the reaction of (*p*-fluorophenyl)magnesium bromide **7** with compounds of general structure **53** followed by the basic treatment of the crude reaction mixture gave (3*S*,4*R*)-**54** and (3*R*,4*S*)-**55** which were readily separated by chromatographic techniques (Scheme 12).

Later, a new entry to the formal synthesis of (−)-**1** has been described by Yamada and Jahan.[28] The synthetic approach is based on a general route to 3,4-disubstituted piperidines starting from readily available homochiral 1,4-dihydropyridine derivatives as key intermediates (Scheme 13).

In particular, the reaction of cuprate **58**, generated from (*p*-fluorophenyl)lithium and $CuBr{\cdot}SMe_2$, with the pyridinium salt **57**, in turn obtained from the chiral non-racemic nicotinamide **56** by treatment with benzoyl chloride, allowed the introduction of the 4-fluorophenyl group at the 4-position giving 1,4-adduct **59** in 99% de. Removal of the chiral auxiliary by the treatment of **59** with NaOMe followed by the catalytic hydrogenation of intermediate **60** in EtOH for 27 h gave dihydropyridine **61**, which could be further reduced to provide piperidine **62** as a 15:1 *cis*:*trans* mixture. Prolonged reaction times (EtOH, 6 days) in the reduction of **60** allowed the direct isolation of the same intermediate **62**, but in a different diastereomeric ratio (*cis*:*trans* = 4:1). Compound **62** was isomerized into *trans*-piperidine **63** in quantitative yield by treatment with NaOMe at 50 °C in toluene. Reduction of the ester moiety of **63** provided alcohol (−)-**20**, a well established precursor of (−)-**1**. It is worth noting that the chiral auxiliary can be recovered and reused.



Scheme 12.



Scheme 13.

The good stereoselectivity observed in the conjugate addition reaction has been explained in terms of the addition of the nucleophile from the less hindered side of the intermediary cation–π complex (Fig. 4).[29]

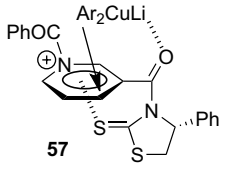


Figure 4.

Interestingly, the same approach was applied to the synthesis of alcohol (+)-**41**, a precursor of (+)-**2** (Scheme 14).

Addition of cuprate **64** to the nicotinic amide *ent*-**56** opened the way to the preparation of amino alcohol **67**, which was eventually protected as the corresponding *tert*-butyl carbamate to yield the target molecule.

4. Asymmetric lithiation using chiral bases

One of the most commonly employed reactions in organic synthesis involves the formation of a reactive carbon nucleophile by a metallation process, an operation that can be accomplished enantioselectively in case chiral non-racemic bases call in.[30]

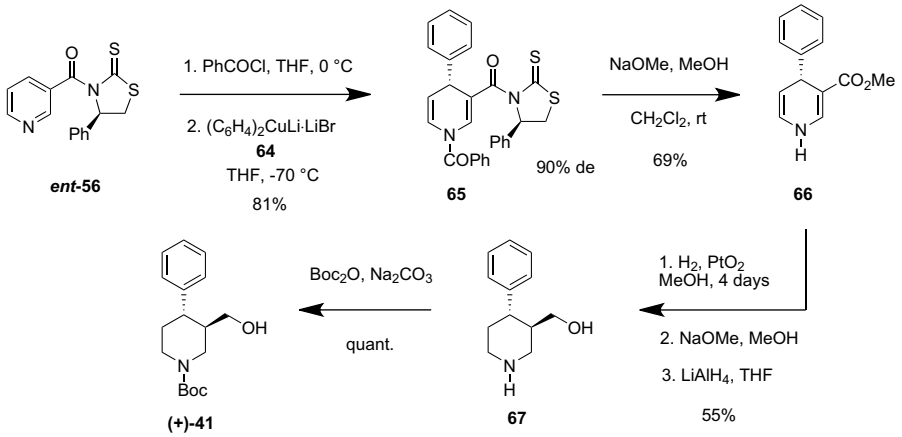
An efficient access to substituted six-membered rings such as piperidones and piperidines based on the asymmetric conjugate addition of lithiated *N*-Boc-*N*-(*p*-methoxyphenyl)-allylamines to nitroalkenes to provide enecarbamate derivatives which can be readily converted to substituted piperidines, has been developed by Beak et al.[31] along the steps shown in the general Scheme 15.

The synthetic utility of the methodology has been clearly demonstrated through an efficient application to (−)-**1** (Scheme 16).[31a] The key step was the formation of the chiral organolithium complex **70**, followed by the asymmetric Michael addition to nitroalkene **71** providing intermediate (+)-**72** as a single diastereomer in good yield.

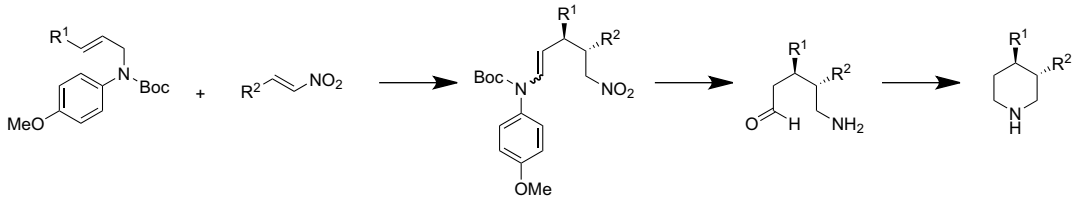
Acid hydrolysis and reduction of enecarbamate (+)-**72** to the nitro alcohol (+)-**73** was followed by the reduction of the nitro group by transfer hydrogenation and subsequent *N*-Boc-protection to give the intermediate (−)-**74** in 84% yield from (+)-**72**. Cyclization through mesylation and base treatment, followed by the deprotection of the silyl ether, afforded the *N*-Boc-piperidine (−)-**23b**, which has been converted to (−)-**1** (72% yield, er >97:3) through a well established protocol.[25b]

The methodology based on the asymmetric conjugate addition of lithiated *N*-Boc-*N*-(*p*-methoxyphenyl)-allylamines to nitroalkenes has also been applied to the synthesis of (+)-**2** (Scheme 17).[31b]

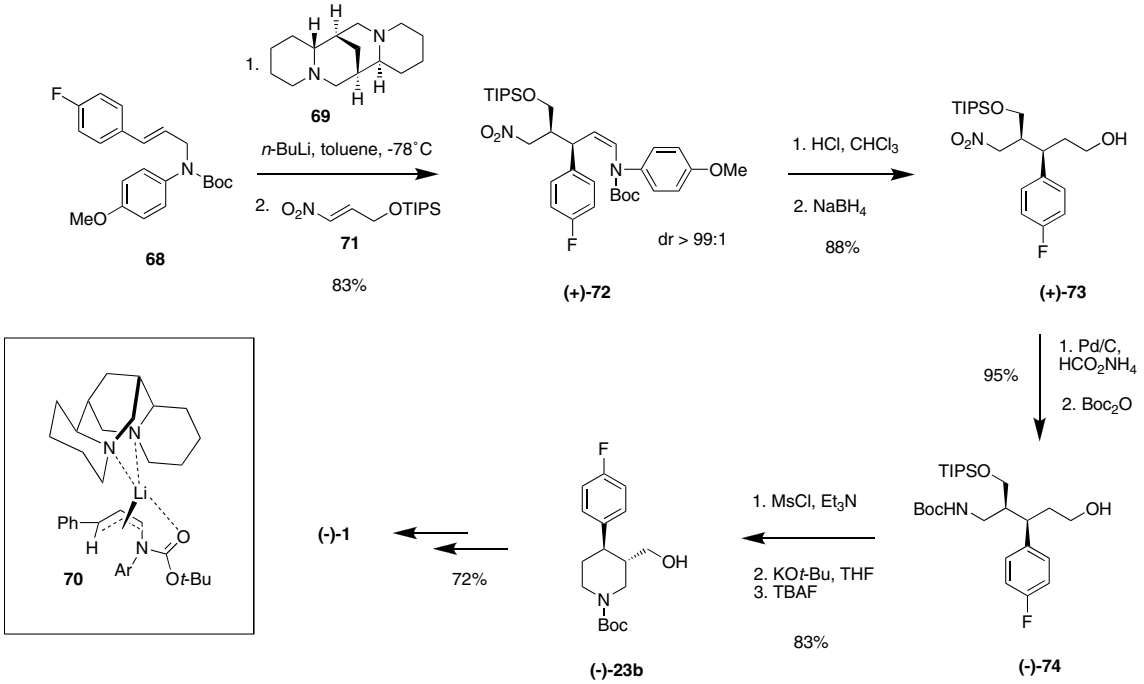
Enecarbamate (+)-**77** was converted to the 4-phenyl-substituted lactam (−)-**79**, which was used in an enolization/substitution sequence. The treatment of (−)-**79** with *t*-BuLi



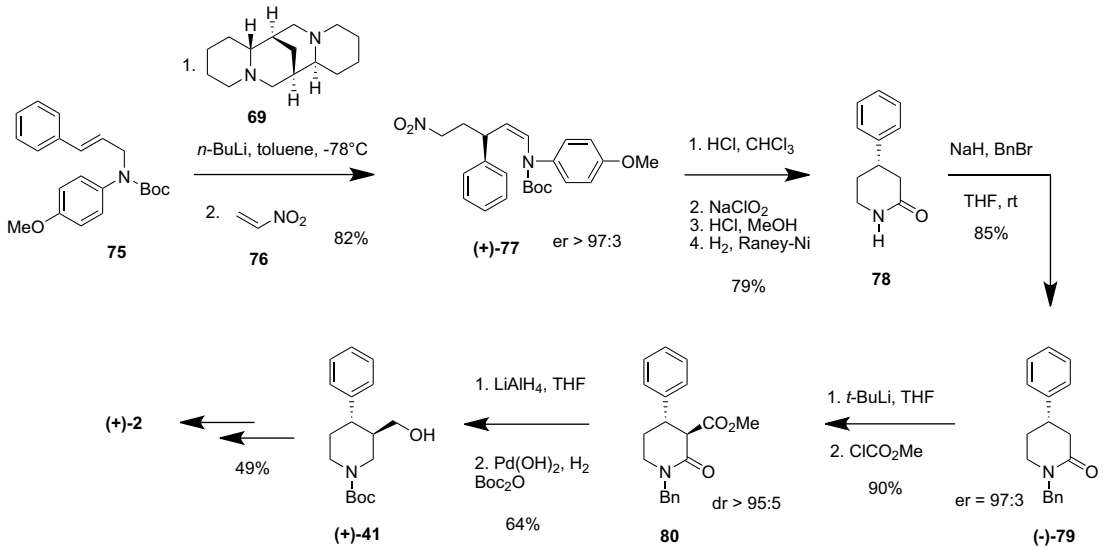
Scheme 14.



Scheme 15.



Scheme 16.



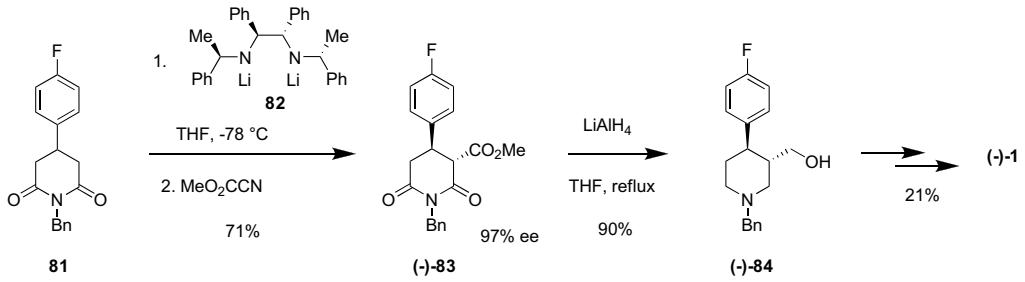
Scheme 17.

and substitution with methyl chloroformate provided **80** in 90% yield and excellent enantioselectivity (dr >95:5). $LiAlH_4$ reduction of both the amide functionality and the ester functionality, followed by the interconversion of the benzyl group with the *t*-butoxycarbonyl group, provided a 64% yield of intermediate (+)-**41**, whose conversion to (+)-**2** has been conveniently achieved in 49% yield through the reported route.[25b]

The asymmetric deprotonation chemistry using chiral lithium amides, which are essentially chiral variants of the commonly used lithium diisopropylamide, constitutes an efficient and versatile tool for asymmetric synthesis. Most of the enantioselective deprotonation reactions of these chiral bases involve discrimination between enantiotopic hydrogens activated by a single common functional group.[30]

The synthetic potential of chiral lithium amides has been extensively studied over the last decade by Simpkins et al.,[32] and a nice application of this chemistry to the synthesis of (−)-**1** has been disclosed.

The desymmetrization of 4-aryl-substituted glutarimide **81** has been accomplished through sequential treatment with the chiral bis-lithium amide base **82** and quenching



Scheme 18.

of the resulting enolate with methyl cyanoformate, giving compound (−)-**83** in 71% yield and 97% ee (Scheme 18).

Reduction of imide (−)-**83** gave piperidine alcohol (−)-**84**, to which the C-3 side-chain was introduced by conventional means, via mesylation and nucleophilic displacement with sesamol. Final removal of the benzyl group gave (−)-**1** in 21% overall yield from (−)-**84**.

5. Asymmetry from the chiral pool

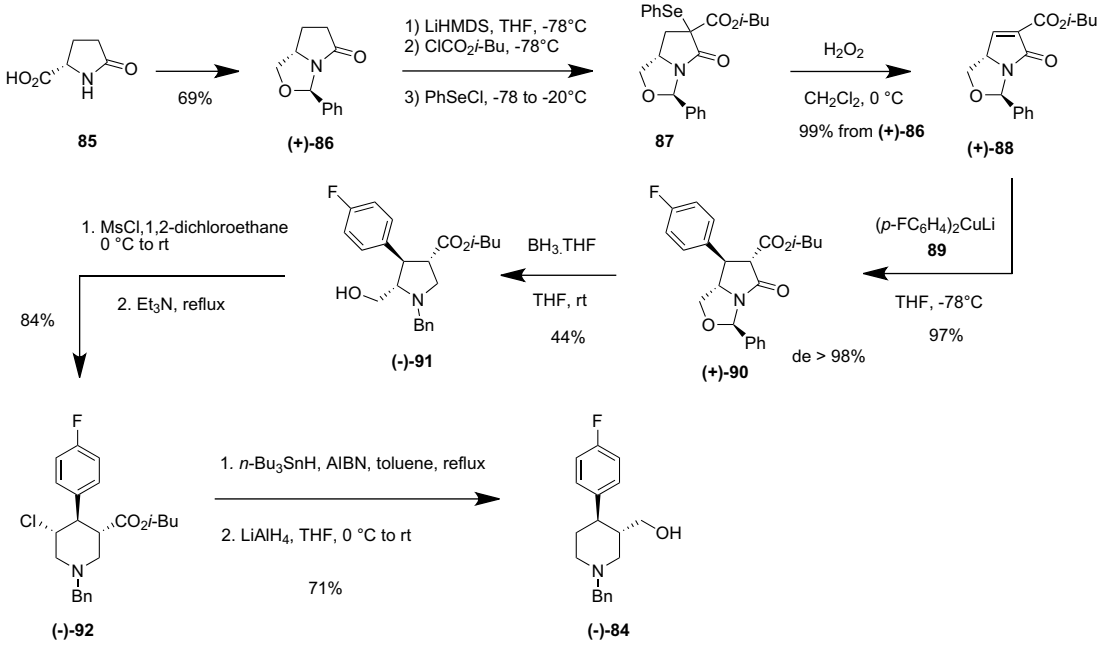
Pyroglutamic acid derivatives are important scaffolds, widely used for the synthesis of natural products and nitrogen heterocycles.[33]

A ring expansion of a prolinol nucleus was the key step for the formal synthesis of (−)-**1**, a radical dehalogenation being an additional featuring step of the complete sequence. Cossy et al.[34] envisaged a ten-step synthesis of precursor (−)-**84**, using L-pyroglutamic acid **85** as the starting material, in an overall yield of 13.9% (Scheme 19).

Thus, **85** was transformed into the enantiomerically pure bicyclic compound (+)-**86**, through a previously reported[35] three-step sequence involving (i) esterification with thionyl chloride in methanol (88% yield), (ii) reduction of the corresponding methyl ester with $NaBH_4$ (EtOH, 0 °C to room temperature, 90% yield), and (iii) protection of the amido-alcohol with benzaldehyde in the presence of a catalytic amount of *p*-toluensulfonic acid.

The enantiomerically pure bicyclic compound (+)-**86** was isolated in 69% yield and was cleanly converted to the unsaturated ester (+)-**88** in order to allow the introduction of the aromatic group present in **1**. This transformation was accomplished in 99% overall yield for the two-step sequence involving the treatment of (+)-**86** with an excess of LiHMDS (2.1 equiv), successive quenching with isobutyl chloroformate (1 equiv, 45 min) and phenylselenenyl chloride (1 equiv, 1.2 h), and oxidation of the crude mixture of diastereomeric selenides **87** with H_2O_2 (5 equiv, 30 min).

The conjugate addition of lithium bis(*p*-fluorophenyl)cuprate **89** to (+)-**88** gave compound (+)-**90** in 97% yield



Scheme 19.

and with a de >98%. The relative *trans* stereochemistry of the substituents at C-3 and C-4 was established from the ^{1}H NMR coupling constant between 3-H and 4-H ($J = 10.7$ Hz).

Reaction of (+)-**90** with BH_3·THF (10 equiv, 1.5 h) furnished prolinol (−)-**91** in 44% yield, through concomitant reduction of the carbonyl lactam group and cleavage of the oxazolidine ring. Treatment of (−)-**91** with mesyl chloride at 0 °C for 50 min and subsequent heating of the reaction mixture in the presence of triethylamine for 36 h promoted a ring expansion process providing the trisubstituted 3-chloropiperidine (−)-**92** as a single diastereomer in 84% yield. The relative *trans* configuration of the chloride and the *p*-F-phenyl groups was determined by ^{1}H NMR analysis. Cleavage of the C–Cl bond and reduction of the ester group of (−)-**92** completed the synthesis of (−)-**84**.

The ring expansion of 3-substituted prolinols into 4-substituted piperidines has been later used by a Taiwanese group as the key step for a formal synthesis of (±)-**1** (see Scheme 37).

6. Catalytic enantioselective transformations

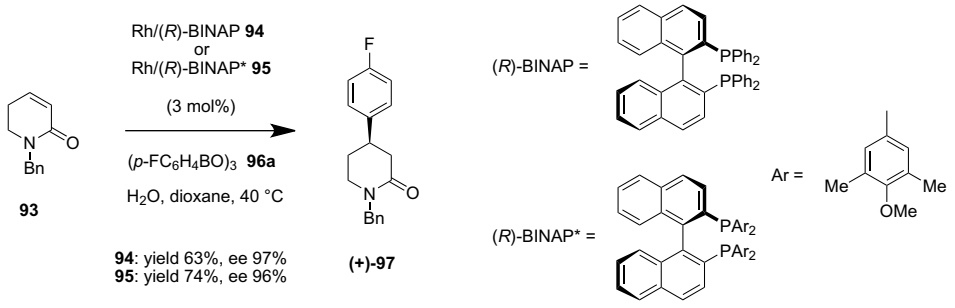
Asymmetric catalysis has and will continue to play an increasing role in synthetic organic chemistry.[36]

The asymmetric 1,4-addition of arylboron reagents to 5,6-dihydro-2(1*H*)-pyridinones in the presence of a chiral bis-phosphine–rhodium catalyst was the innovative step introduced by Hayashi et al. for a new catalytic asymmetric synthesis of 4-aryl-2-piperidinones.[37]

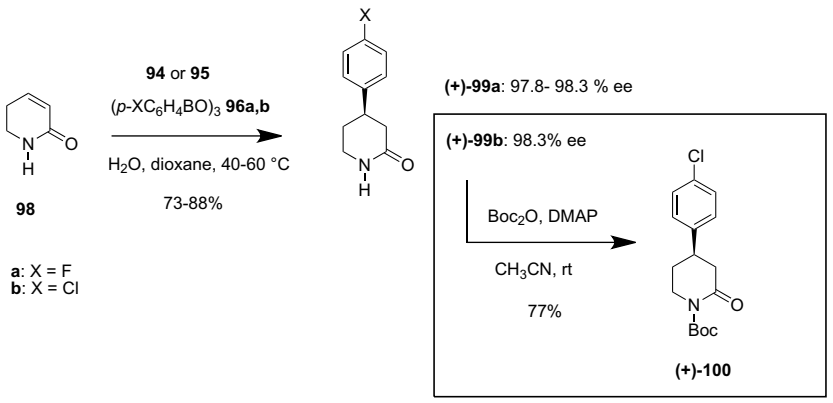
The reaction introducing the 4-fluorophenyl group was accomplished by means of 4-fluorophenylboroxine **96a** and 1 equiv (to boron) of water at 40 °C to obtain the highest yield of the arylation product with high enantioselectivity. A minimum amount of water was necessary to avoid the main side reaction, that is, hydrolysis of the boronic acid giving fluorobenzene. Thus, the reaction of *N*-benzyl-5,6-dihydro-2(1*H*)-pyridinone **93** with 4-fluorophenylboroxine **96a** and water in the presence of a catalytic system Rh/(*R*)-BINAP **94** in dioxane at 40 °C for 12 h gave (+)-**97** in 63% yield and 97% ee (Scheme 20). Further modification by the use of catalyst Rh/(*R*)-BINAP* **95** improved the yield up to 74%, the enantioselectivity being essentially the same (96% ee). In all cases, the catalyst was generated from rhodium complex Rh(acac)$_2$(C_2H_4)$_2$ and (*R*)-BINAP or its analog.

It was observed that 5,6-dihydro-2-(1*H*)-pyridinone **98** reacted with 4-fluorophenylboroxine **96a** and 4-chlorophenylboroxine **96b** more readily than the *N*-benzyl derivative **93**, giving arylation products (+)-**99a** and (+)-**99b** in high yields and around 98% ee (Scheme 21).

The absolute (*R*)-configuration of the arylation products (+)-**99a,b** was established by correlation with the known *N*-Boc-protected piperidinone (*R*)-(+)-**100.**[38] Furthermore, it is also consistent with the absolute configuration which



Scheme 20.



Scheme 21.

can be deduced from an empirical rule previously proposed by the authors.[39]

Highly enantioselective conjugate additions of electron-deficient nitrile derivatives to acyclic α,β-unsaturated imides catalyzed by a chiral (salen)–aluminum complex paved the way to the preparation of enantiomerically enriched piperidines, as exemplified by an expedient asymmetric catalytic synthesis of (−)-**1** (Scheme 22).[40]

Thus, the μ-oxo dimer **102** catalyzes the addition of methyl cyanoacetate to imide **101** with high enantioselectivity and in the absence of Brönsted base. The use of nonpolar solvents led to increased enantioselectivity, and cyclohexane affording optimal results. This improvement was accompanied by decreases in reaction rate; however, useful reactivity could be restored by the addition of *tert*-butyl alcohol. Intermediate **103** was obtained in 96% ee by recrystallization from ethanol (77% recovery) and converted into lactams **18** and **19** (dr = 2:1) through the reduction of the nitrile group and subsequent intramolecular lactamization. Starting from the mixture of **18** and **19**, (−)-**1** has been obtained in a total yield of 47% over seven steps, following the synthetic approach developed at Sumika Fine Chemicals (Scheme 2).[13]

A general methodology for the synthesis of five- and six-membered lactones and lactams possessing a β-stereocenter, through copper-catalyzed enantioselective conjugate reduction of the corresponding α,β-unsaturated precursors, has been described by Buchwald et al.[41] The addition of alcohol additives was found to be crucial for obtaining higher yields of the desired products and for a dramatic increase in the reaction rates.

This protocol paved the way to a brief, catalytic enantioselective approach to (−)-**1**. The starting material **105**, in turn obtained by the reaction of *p*-anisidine with 4-fluoro-3′-chloropropiophenone **104**, was transformed into α,β-unsaturated lactam **106** (Scheme 23). The latter was reduced with polymethylhydrosiloxane (PMHS) using the chiral bisphospine-copper catalyst **107**, generated in situ from (*R*)-*p*-tol-BINAP (0.5 mol %), $CuCl_2$ (2.5 mol %), and *t*-BuONa (5 mol %). This operation provided piperidone (+)-**108** in 90% yield and 90% ee. A two-step sequence allowed for the conversion of (+)-**108** to (−)-**110** in 83% overall yield.

Difficulties encountered in the removal of the PMP functionality for the presence of a second electron-rich aromatic ring suggested a switch to the Boc protecting group, affording known intermediate (−)-**23b** in 75% yield over two steps.

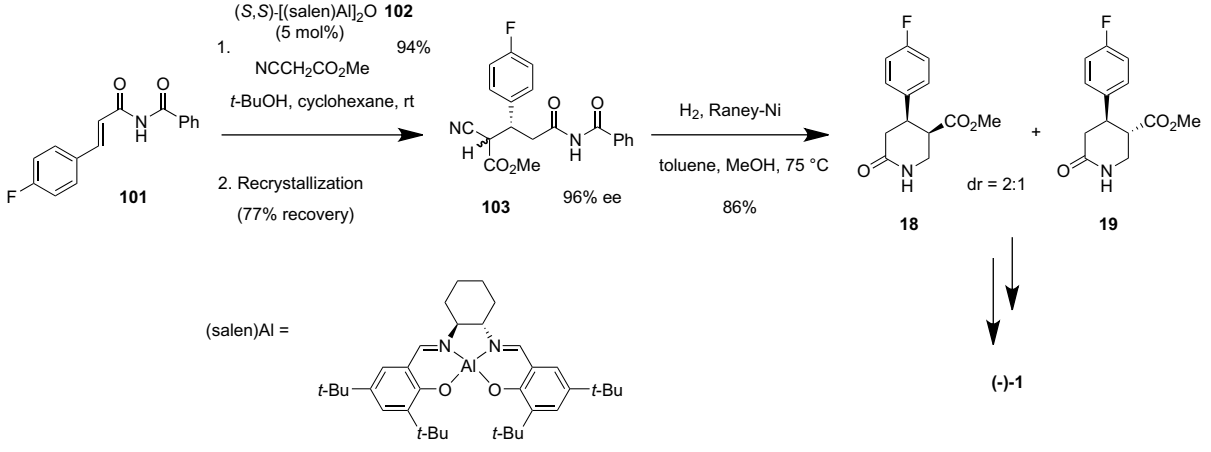
The synthesis of (−)-**1** called for the introduction of the sesamol side chain. This operation has been achieved by the treatment of (−)-**23b** with aryltosylate **111** in the presence of Cs_2CO_3 in refluxing xylene, through a quite unusual transfer of activation. As proposed by the authors, a tosyl transfer between (−)-**23b** and **111** should take place producing a primary tosylate and a phenol. In the basic medium, the phenol displaces the primary tosylate to give the expected coupling product.

Finally, removal of the Boc group provided the target molecule in 52% yield from (−)-**23b**.

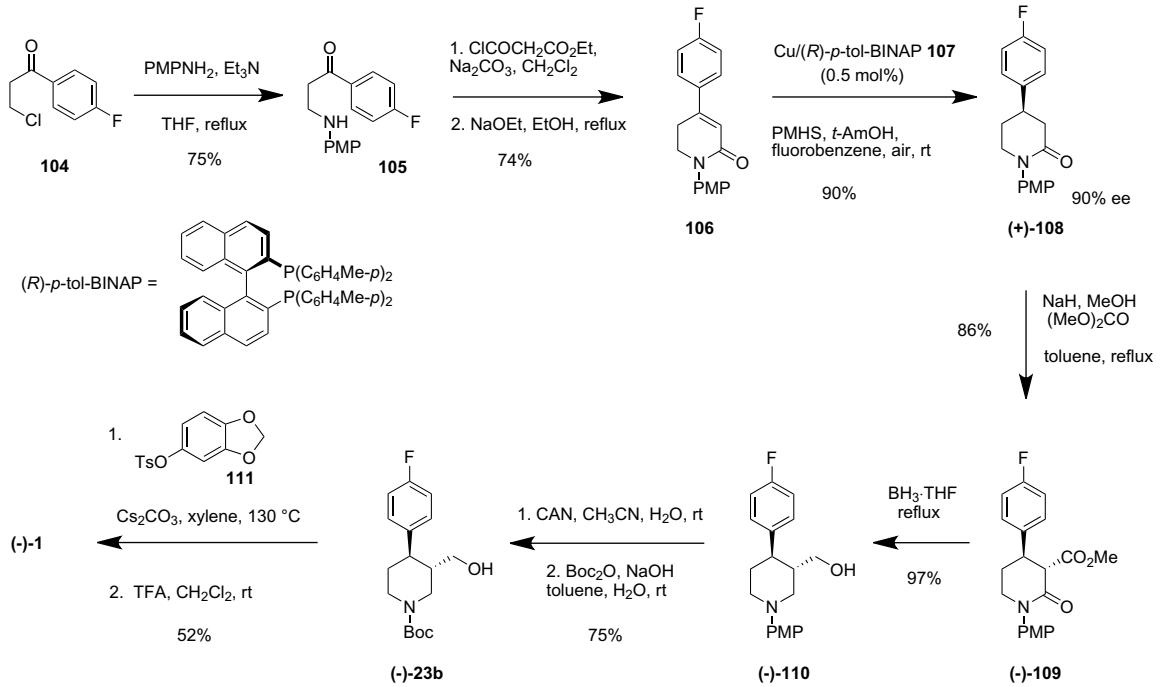
The phosphine-catalyzed α-arylation of *N*-benzyl dihydropyridinone **112** was used strategically in the enantioselective total synthesis of (−)-**1**.[42]

As depicted in Scheme 24, **112** was exposed to (*p*-F-Ph)$_3$$BiCl_2$ **113** in the presence of tributylphosphine (10 mol %) and Hünig's base at ambient temperature in CH_2Cl_2/*t*-BuOH (9:1) providing the α-arylated dihydropyridinone **114**, which was isolated as a single regioisomer, as confirmed by ^{1}H NMR analysis. Catalytic asymmetric 1,2-reduction of the *N*-carbamoyl-protected enone **115** by using oxazaborolidine (−)-**116** as the catalyst gave the allylic alcohol (+)-**117** in 95% yield and 96% ee.

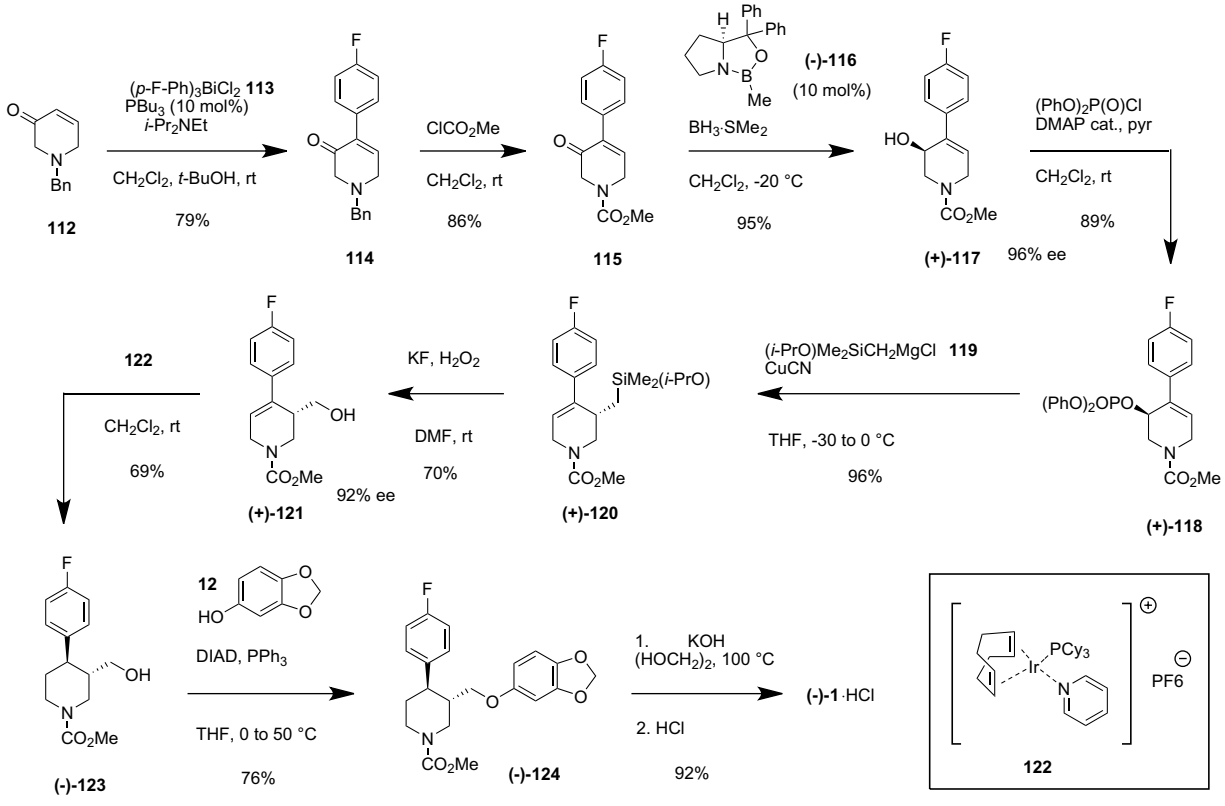
Alcohol (+)-**117** was converted into the corresponding diphenyl phosphate derivative (+)-**118**, which underwent an *anti*-selective copper-mediated S_N2' allylic substitution by reaction with (*i*-PrO)Me_2SiCH_2MgCl **119**, the Grignard reagent acting as a hydroxymethyl anion equivalent. The silylated compound (+)-**120** was then subjected to Tamao



Scheme 22.



Scheme 23.



Scheme 24.

oxidation[43] to provide the homo-allylic alcohol (+)-**121** in 70% yield and 92% ee.

Stereoselective substrate-directed catalytic homogeneous hydrogenation[44] of (+)-**121** was accomplished using Crabtree's catalyst **122**[45] to provide the corresponding saturated alcohol (−)-**123** in 69% yield as a single diastereomer.

Alcohol (−)-**123** was subsequently converted into the phenolic ether (−)-**124** in 76% yield through reaction with

sesamol under Mitsunobu's conditions. The final deprotection of methyl carbamate was achieved under basic conditions, and the free amine was treated with anhydrous HCl to provide (−)-**1** as the hydrochloride salt in 92% yield.

Sodium borohydride in combination with catalytic amounts of $CoCl_2$ has been conveniently used as an excellent catalytic system in the reductive cyclizations of azido- and cyano-substituted α,β-unsaturated esters to afford γ- and δ-lactams in high yields.[46]

The efficiency of the process has been demonstrated through the enantioselective synthesis of (*R*)-4-fluorophenylpiperidinone (+)-**99a**, a potential precursor for (−)-**1** (Scheme 25).

The synthesis of (+)-**99a** started with the Pd-catalyzed arylation of ethyl crotonate with aryl boronic acid **125** to afford the α,β-unsaturated ester **126** in 80% yield. Allylic bromination and subsequent displacement of bromide with cyanide allowed for the isolation of cyano ester **128** in 68% yield over the two steps. Co-catalyzed asymmetric reduction of the latter with $NaBH_4$-bisoxazoline **129** system gave (+)-**99a** in 99% yield and 86% ee.

During their efforts devoted to the development of transition-metal/NH bifunctional molecular catalysts including Cp^*Ru(II) complexes bearing protic amine ligands, Ikariya el al.[47] found that the chiral catalyst $Cp^*RuCl[(S)\text{-}Ph_2P(CH_2)_3NH\text{-}k^2\text{-}P,N]$ **130** effected an efficient desymmetrization of prochiral *N*-protected 4-(4-fluorophenyl)glutarimides through a highly enantioselective hydrogenation reaction, the best selectivities being obtained when the nitrogen atom was substituted with an aryl group.

These results opened the way to chiral piperidone (+)-**99a** starting from imide **132**, in turn easily prepared from 3-(4-fluorophenyl)glutaric anhydride **44** through condensation with the required amine **131** (Scheme 26).

Enantioselective hydrogenation of **132** in the presence of **130** (1 mol %) and KO*t*-Bu in 2-propanol at 60 °C produced amide (−)-**133** in essentially quantitative yield and 99% ee. The latter was converted to the corresponding amido bromide, which was directly subjected to NaH-induced cyclization, affording (+)-**134** in 35% unoptimized yield over the two steps. Ceric ammonium nitrate (CAN)-mediated dearylation of (+)-**134** completed the synthesis of (+)-**99a**, which represented an important synthetic intermediate for the preparation of (−)-**1**.

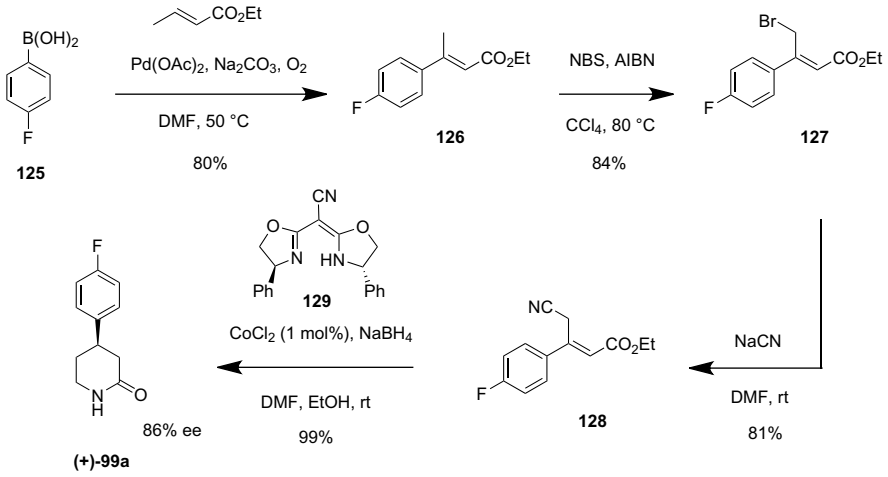
A general methodology for the Ir-catalyzed asymmetric allylic alkylation of terminal allylic carbonates using chiral diaminophosphine oxides (DIAPHOXs) has been recently developed by the Hamada group.[48] Best conditions were found to involve mixing the Ir catalyst (5 mol %), the DIAPHOX (5 mol %), $NaPF_6$ (10 mol %), and LiOAc (10 mol %) in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 3 equiv). The corresponding branched products were obtained in excellent yield and high enantioselectivity (up to 95%).

The Ir–DIAPHOX–$NaPF_6$ catalyst system has been conveniently applied to the formal enantioselective synthesis of (−)-**1** (Scheme 27). Thus, the allylic alkylation of **135** with dimethyl malonate using (R,S_P)-**136** and chloro(1,5-cyclooctadiene)iridium(I) dimer ($[Ir(cod)Cl]_2$) **137** provided (*R*)-**138** in 90% yield with 92% ee.

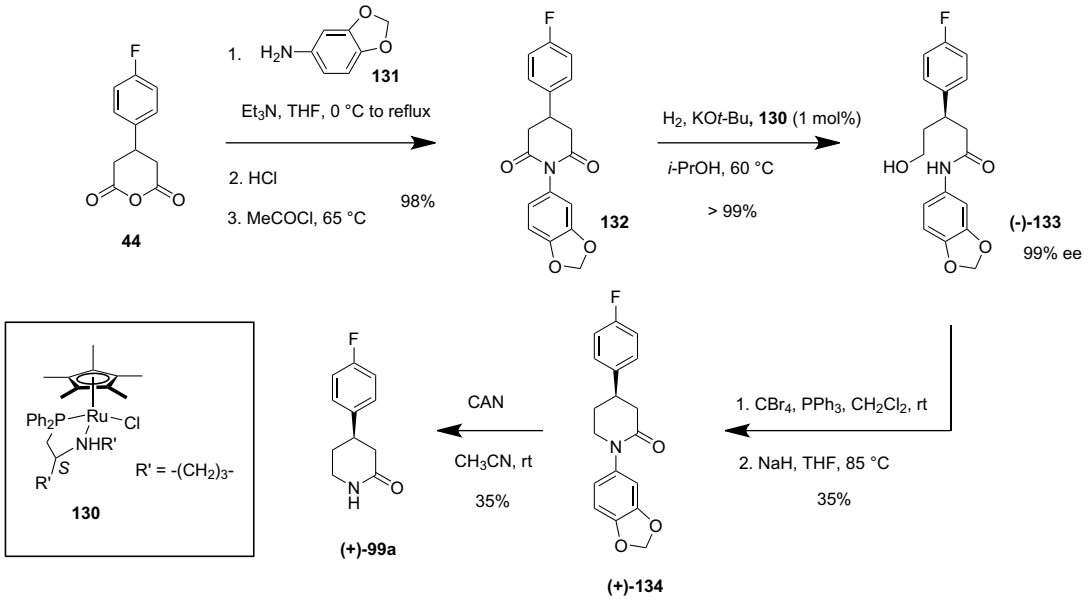
Hydroboration in the presence of Wilkinson's catalyst **139**,[49] followed by work-up with hydrogen peroxide, gave primary alcohol **140**, which was smoothly converted into azide **141**. Its catalytic reduction proceeded with concomitant cyclization of the intermediate primary amine, providing *trans*-lactam **142** as a single diastereomer (dr >99:1). Finally, the reduction of **142** with BH_3·THF complex allowed for the isolation of the paroxetine precursor (−)-**20**.

Stereospecific cleavage of C-3 substituted 1,3-cyclic sulfamidates[50] with a stabilized enolate provided an easy entry to a concise, asymmetric synthesis of (−)-**1**.[51]

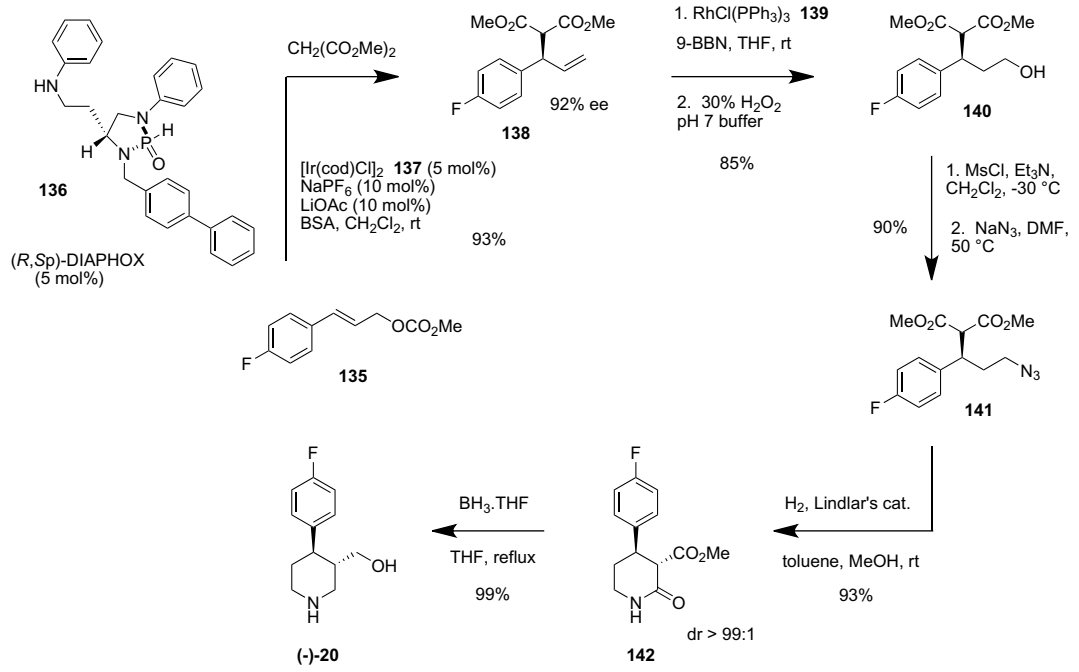
The synthetic approach to the target molecule started from the commercially available β-keto ester **143**, which



Scheme 25.



Scheme 26.

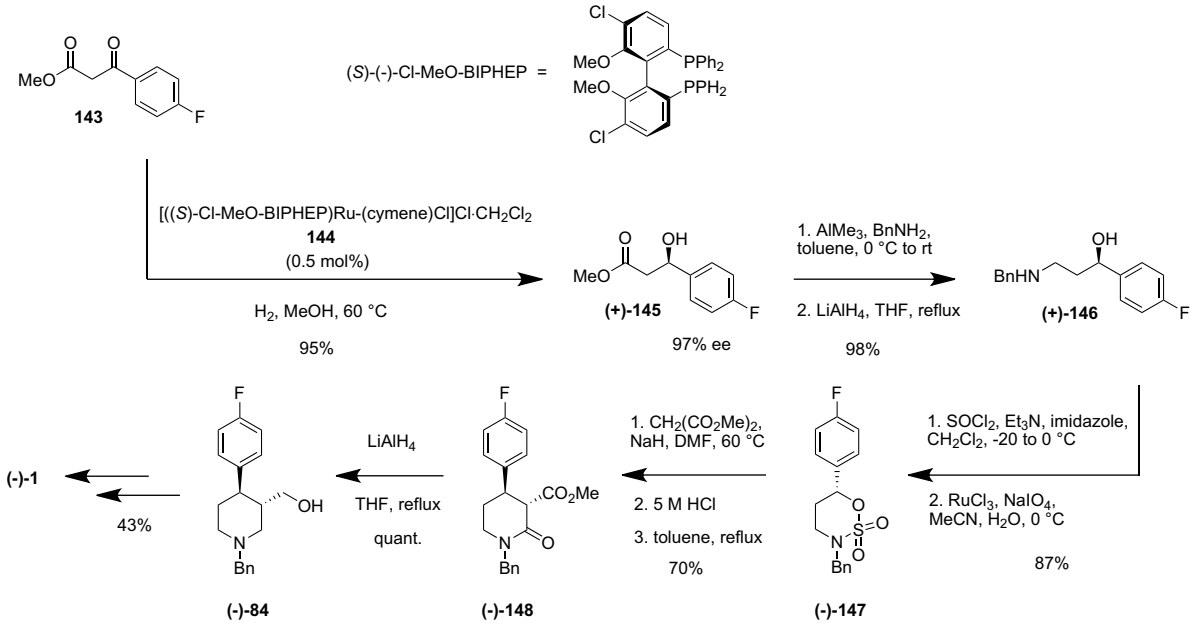


Scheme 27.

was reduced to β-hydroxy ester (+)-**145** in 95% yield and 97% ee, using the [Ru][Cl-MeO-BIPHEP] catalyst system **144** (Scheme 28). Sequential aluminum-mediated amidation and $LiAlH_4$ reduction provided amino alcohol (+)-**146** in 98% yield. Subsequent cyclization with thionyl chloride in the presence of triethylamine and imidazole, followed by the oxidation of the intermediate sulfamidite gave access to the sulfamidate (−)-**147** in 83% yield.

After the initial nucleophilic displacement with the sodium enolate of dimethyl malonate, acidic hydrolysis of the intermediate *N*-sulfate was followed by neutralization and thermolysis to achieve lactamization. This three-step sequence provided *N*-benzyl piperidone (−)-**148** in 70% yield as a single diastereomer, as determined from ^1H NMR spectrum of the crude product (dr >95:5). To complete the synthesis of (−)-**1**, (−)-**148** was reduced to amino alcohol (−)-**84**, which has been eventually taken to the target molecule through standard chemistry.[32] The overall sequence from **143** proceeded in 24% overall yield over 10 synthetic operations.

Enantioselective organocatalysis has emerged as a powerful synthetic tool that is complementary to the metal-cata-



Scheme 28.

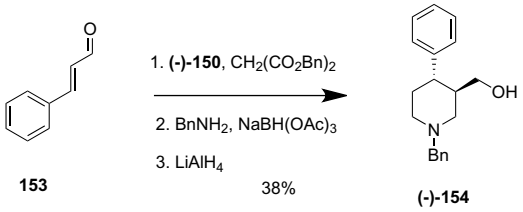
lyzed transformations. Of crucial importance is that it offers a mild, practical and, generally, simple method of making small, functionalized molecules with high enantiopurity and, therefore, has great potential in discovery chemistry.

Enantioselective organocatalytic processes have been developed as new methods to make optically active **1**.

In this context, Jørgensen et al.[52] reported a short, simple method for producing chiral lactam intermediates based on an organocatalytic enantioselective conjugate addition of malonates to aromatic α,β-unsaturated aldehydes. The addition products have been used to obtain convenient precursors for (−)-**1** and (+)-**2**, thus establishing their asymmetric formal synthesis.

The addition of dibenzyl malonate to *trans*-(4-fluoro)-cinnamaldehyde **149** in the presence of homochiral proline-based catalyst (+)-**150** promoted the formation of adduct (−)-**151** in 72% yield and 86% ee (Scheme 29). A three-step tandem procedure involving imine formation, reduction and lactamization provided the *trans*-lactam **152** as the major isomer (*cis*:*trans* = 1:13). Finally, reduction of the latter with $LiAlH_4$ gave piperidine alcohol (−)-**84**.

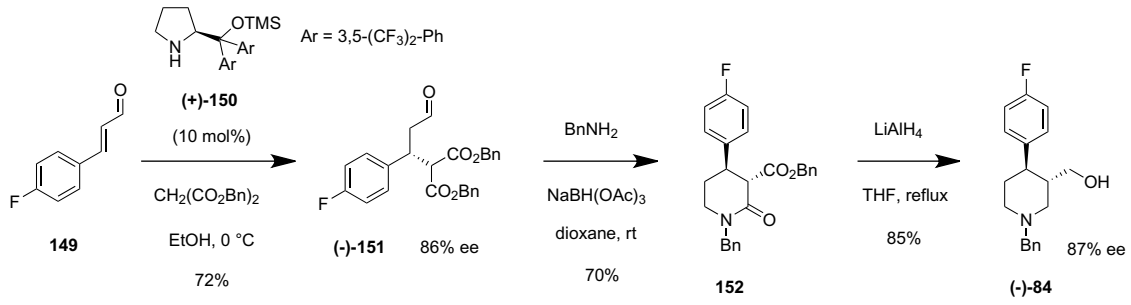
A parallel synthetic scheme gave access to (−)-**154**, a suitable precursor of (+)-**2** (Scheme 30).



Scheme 30.

7. Enzymatic asymmetrization

Asymmetrization of prochiral substrates by means of lipases is a very useful synthetic strategy because the maximum feasible yield upon lipase-catalyzed transformation is not limited to 50% as happens when resolving racemates.[53] Consequently, lipases are frequently used biocatalysts because they accept a broad range of substrates and are usually stable in organic solvents.[14]



Scheme 29.

A porcine liver esterase (PLE)-mediated asymmetric desymmetrization, which would be amenable to large-scale synthesis, has been used by a group of process chemists as the key step in the asymmetric synthesis of (+)- and (−)-**1**.[54]

The synthetic approaches began with the reaction of 4-fluorobenzaldehyde **15** with ethyl acetoacetate, followed by saponification and esterification to give **155** (Scheme 31). Hydrolysis with pig liver esterase afforded optically active acid ester **156** in 86% yield and 95% ee. The absolute stereochemistry of **156** was initially not determined. However, either the acid or the ester groups could be selectively reduced using borane or $LiBH_4$. Therefore, regardless of the absolute stereochemical outcome of the hydrolytic step, both enantiomers of paroxetine could, in principle, be obtained and the required stereochemistry easily determined by the comparison of the specific rotation of the material produced with an authentic sample.

Initially, **156** was reduced with borane to the corresponding primary alcohol **157** that has been converted to (+)-**1** through standard chemistry.

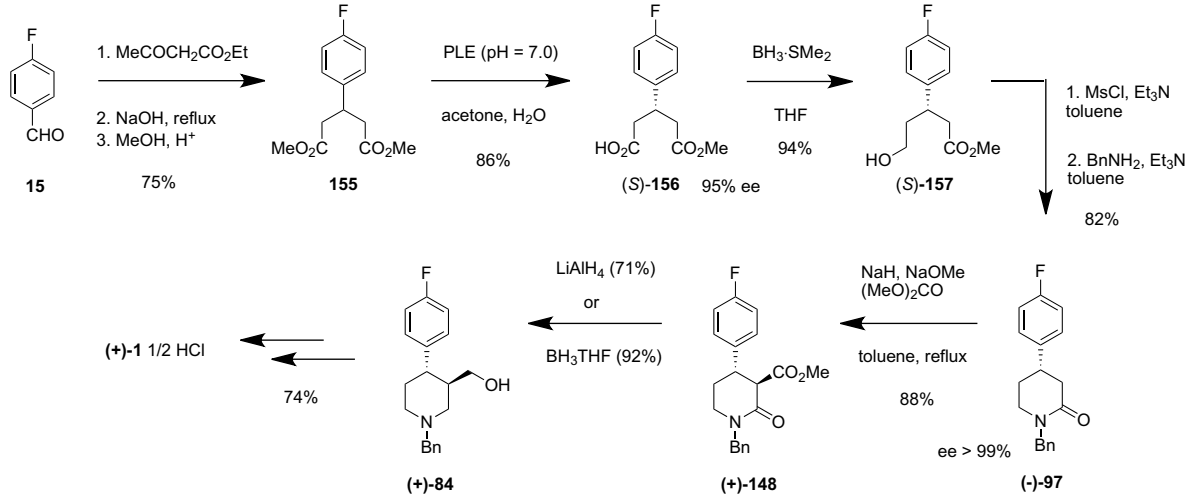
This result established that the desymmetrization step provided acid ester **156** having the (*S*)-configuration at C-3.

In detail, reduction of the acid moiety of (*S*)-**156** with borane furnished alcohol (*S*)-**157** in 94% yield. Its mesylation followed by a treatment with benzylamine provided lactam (−)-**97**, which was acylated to give (+)-**148**, the *trans* relative stereochemistry of the aryl group and the C-3 substituent being established on the basis of ^1H NMR coupling constant between H-3 and H-4 protons ($J = 11.0$ Hz). Finally, reduction of (+)-**148** gave aminoalcohol (+)-**84**, easily taken to (+)-**1** in 74% yield through the conventional three-step sequence involving mesylation, etherification with sesamol, and hydrogenolysis of the benzyl group.

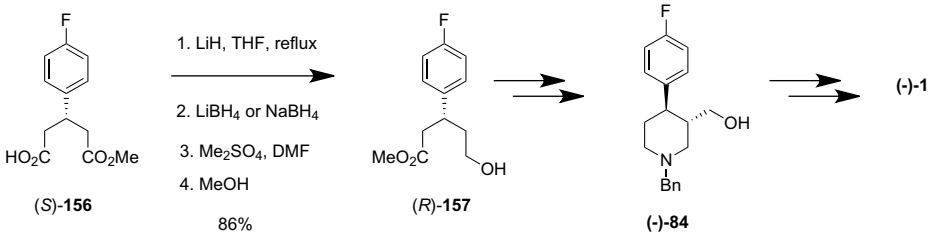
Furthermore, compound (*S*)-**156** was used to obtain (−)-**1**, an inversion of configuration at C-3 by the reduction of the ester being the required step to ensure the proper absolute stereochemistry. A unique one-pot deprotonation–reduction–alkylation procedure was then developed to provide entry to the precursor (−)-**84**.

To this end, the acid ester (*S*)-**156** was converted to an intermediate boronate through LiH-mediated deprotonation followed by the selective reduction of the ester moiety with $LiBH_4$ or $NaBH_4$. Subsequent treatment with dimethyl sulfate and quenching with MeOH afforded δ-hydroxy ester (*R*)-**157** in 86% yield (Scheme 32). The overall result is the net inversion of the C-3 stereocenter, thus achieving the synthesis of the desired alcohol (−)-**84**, and hence (−)-**1**, by the same route as described in Scheme 31.

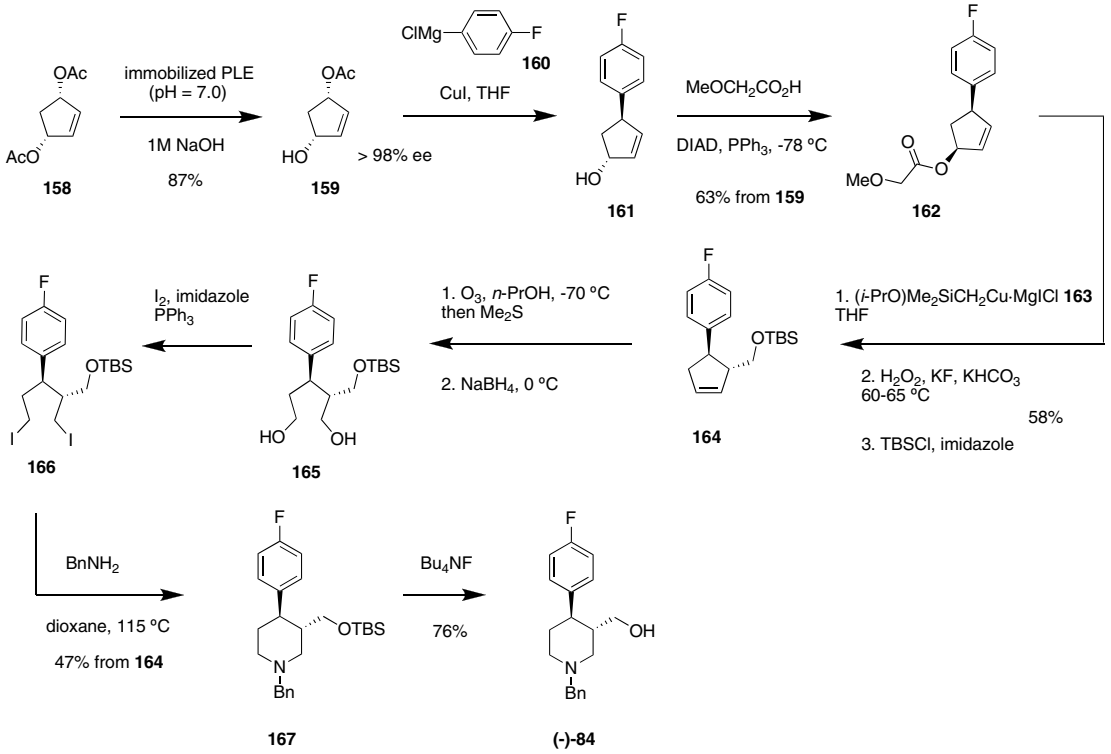
The readily available 4-cyclopentene-1,3-diol monoacetate **159** has become an attractive starting compound in organic



Scheme 31.



Scheme 32.



Scheme 33.

synthesis. Access to both *trans*- and *cis*-3,4-disubstituted piperidines has been opened by Kobayashi et al.[55] through anti S_N2' allylation of 4-substituted 2-cyclopentenyl esters with reagents based on RMgX and CuX.

An elegant and efficient application to the synthesis of the paroxetine intermediate (−)-**84** was envisioned to establish the efficiency of the methodology (Scheme 33). Reaction of **159** with (*p*-fluorophenyl)magnesiumchloride **160** (3 equiv) in the presence of CuI (30 mol %) and subsequent Mitsunobu inversion with $MeOCH_2CO_2H$ gave **162** in 63% yield.

Treatment of **162** with the organometallic compound **163**, followed by Tamao oxidation[43] and TBS protection, provided intermediate **164**. Ozonolysis in *n*-PrOH and reductive work up with $NaBH_4$ afforded diol **165**, which was subsequently converted to the corresponding iodide **166**. Reaction of the latter with benzylamine at 115 °C for 2 h in dioxane produced *trans*-piperidine **167** in 47% overall yield from **164**. Interestingly, the corresponding tosylate derived from diol **165** was less reactive than iodide **166** for the piperidine ring formation. The final deprotection of **167** furnished (−)-**84** in 76% yield.

8. Miscellaneous

In this section we consider several recent approaches to racemic paroxetine which have not been covered in previous reviews and represent new general entry to substituted piperidines.

A well-known methodology for assembling structurally complex organic molecules, namely the diastereoselective conjugate addition of an organocopper reagent to chiral racemic cyclic olefinic amido esters, has been conveniently used by Cossy et al.[56] for the preparation of 3,4-disubstituted piperidines such as **1**. Outstanding results were obtained in this area by Helmchen and Wegner[57] on the conjugate additions of organocopper reagents to enoates of camphor-derived chiral auxiliaries **168** or **169** (Fig. 5), which generally proceed with high diastereoselectivity and in good yields.

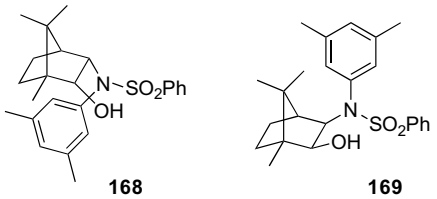
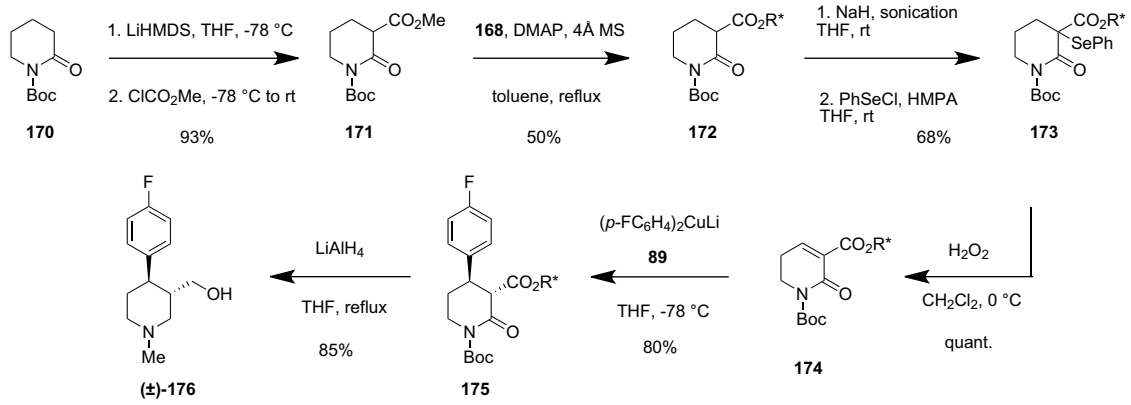


Figure 5.

A formal total synthesis of (±)-**1** has been successfully achieved using the chiral racemic olefinic amido carboxylate **172** as the key intermediate and *N*-Boc δ-valerolactam **170** as the convenient precursor (Scheme 34).

Thus, the treatment of **170** with LiHMDS (1.3 equiv) in THF at −78 °C followed by the addition of methyl chloroformate afforded the corresponding methyl amidocarboxylate **171**, which underwent a 4-dimethylaminopyridine



Scheme 34.

(DMAP)-mediated transesterification reaction with the chiral racemic alcohol **168** to afford **172** as a 65:35 diastereomeric mixture in 50% yield. Subsequent phenylselenation of **172** gave an inseparable 75:25 mixture of diastereomeric selenides **173**, which was directly oxidized with an excess of H_2O_2 to furnish the α,β-unsaturated ester **174** in quantitative yield.

The addition of lithium di(*p*-fluorophenyl)cuprate **89** (4 equiv, THF, −78 °C) to **174** led to the *trans*-piperidone **175** as the sole product, in 80% yield. Compound **175** was reduced by $LiAlH_4$ in boiling THF to produce the known amino alcohol (±)-**176**, which had been already converted to **1**.[6,27]

Chen et al. reported a formal synthesis of (±)-**1** entailing on a general route to substituted δ-lactams via regioselective reduction of *N*-alkyl-3-sulfonyl glutarimides (Scheme 35).[58]

Thus, formal [3+3] cycloaddition between *N*-benzyl-α-sulfonyl-acetamide **177** and ethyl *p*-fluorocinnamate **178** afforded glutarimide (±)-**179**. Regioselective reduction of C-6 carbonyl group to produce the δ-lactam (±)-**180** was efficiently achieved under a quite unusual protocol, which involved the treatment of a THF solution of (±)-**179** with Et_3N (1.2 equiv) at room temperature for 30 min followed by the addition of $LiAlH_4$ (5 equiv), the resulting mixture being further refluxed for 3 h. Finally, reductive desulfonylation of (±)-**180** with sodium amalgam in methanol provided piperidone (±)-**97**.

A very nice and concise route to functionalized piperidine ring systems took advantage of an intermolecular aza-double Michael reaction starting from simple materials. The method entailed on the coupling between α,β-unsaturated amides and α,β-unsaturated esters for the construction of functionalized piperidin-2-ones, as demonstrated by the synthesis of many interesting targets including **1**.[59]

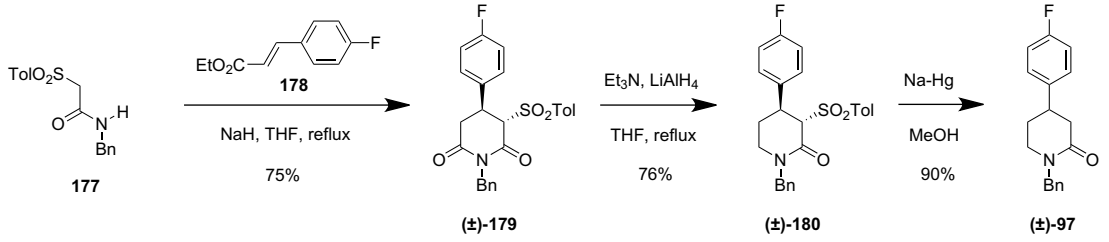
The synthetic potential of this methodology has been demonstrated through the synthesis of intermediate **84** in racemic form, thus establishing a formal synthesis of (±)-**1**.

As summarized in the Scheme 36, the sequence started with the reaction of the unsaturated amide **181** with methyl acrylate in the presence of *tert*-butyldimethylsilyltriflate (TBSOTf, 1.2 equiv), Et_3N (0.7 equiv), and *t*-BuOH (0.25 equiv) to produce the crude mixture of piperidones *cis*-(±)-**182** and *trans*-(±)-**183**, the latter being the sole product after basic epimerization. Final reduction of (±)-**183** with $LiAlH_4$ quantitatively gave amino alcohol (±)-**84**.

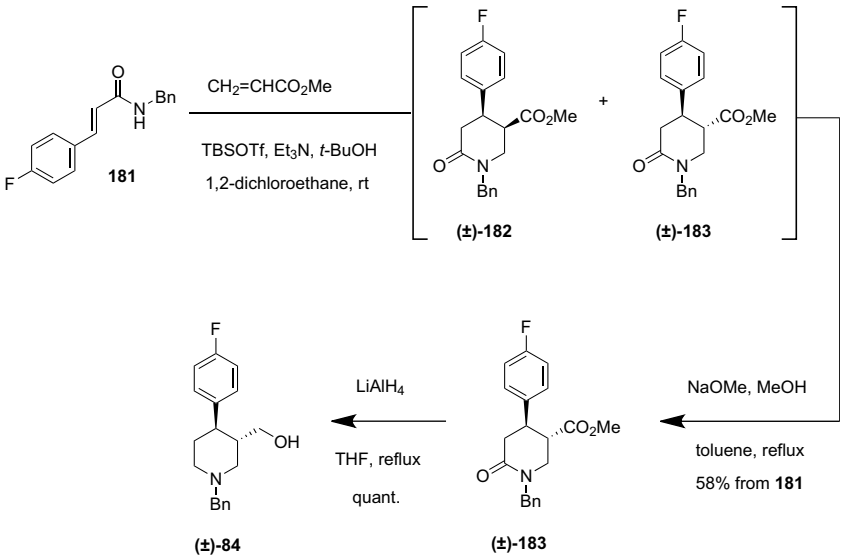
A ring expansion of 3-substituted prolinols into 4-substituted piperidines has been used by a Taiwanese group as the key step of a formal synthesis of (±)-**1** (Scheme 37).[60]

The synthetic scheme entailed the preparation of 3-(*p*-fluorophenyl) prolinol (±)-**186** through reduction and desulfonation of pyroglutamate (±)-**185**, in turn obtained by the base-induced coupling/cyclization reaction of α-sulfonyl-acetamide **177** with 2-bromo-2-propenoate **184**.

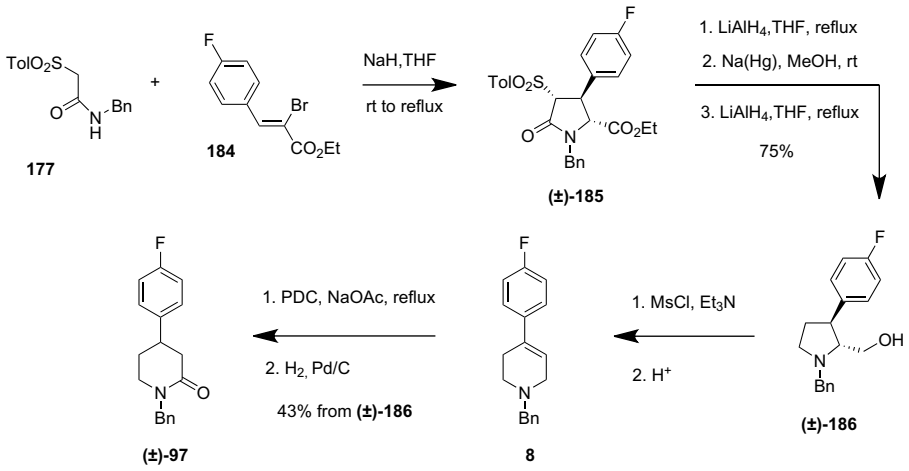
Ring expansion of (±)-**186** according to the reported protocol[34] afforded piperidine **8**, already taken to (−)-**1**.[11] Moreover, allylic oxidation of **8** followed by hydrogenation of the resulting enone yielded piperidone (±)-**97**, which represents a further intermediate toward **1**.



Scheme 35.



Scheme 36.



Scheme 37.

Palladium-catalyzed C–C coupling reactions constitute an important tool in organic synthesis, and the Heck reaction holds a prominent position due to its exceptional versatility. Thus, the Heck arylation of unsubstituted acrylates employing aryl halides, aryl triflates, or even arenediazonium salts is a well-established process,[61] the arenediazonium salts being probably the least explored ones, although they offer considerable advantages over traditional electrophiles.

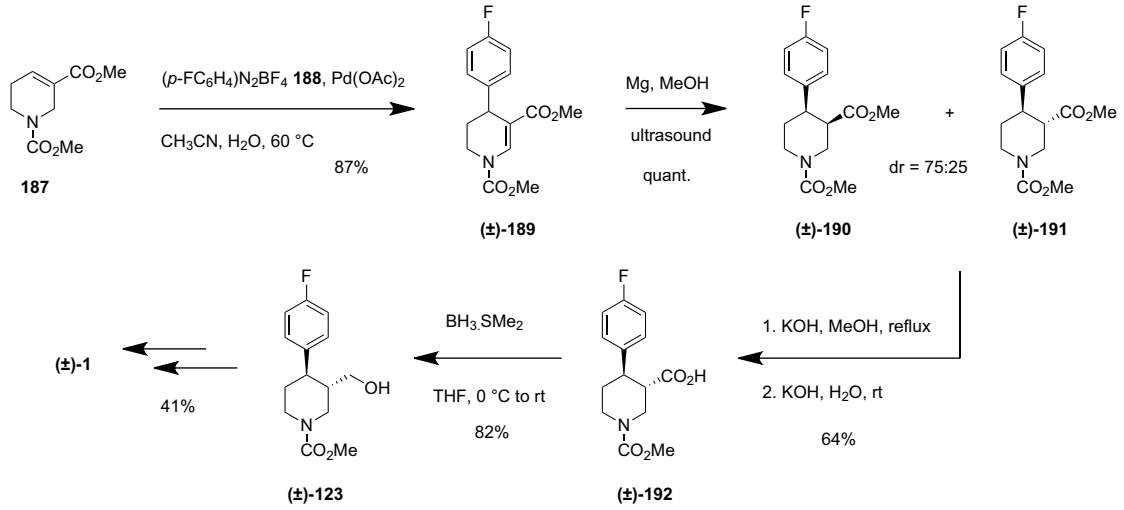
Despite several available methods for preparing the arylpiperidine motif, there are no reports of the Heck arylation to prepare the 4-arylpiperidine system displayed by **1** and related compounds.

Recently, a Brazilian group reported an application of the Heck reaction involving arylation of the aza-endocyclic acrylate derivative **187** with the arenediazonium tetrafluoroborate **188** providing the desired Heck adduct (±)-**189** in good yield as a single product (Scheme 38).[62]

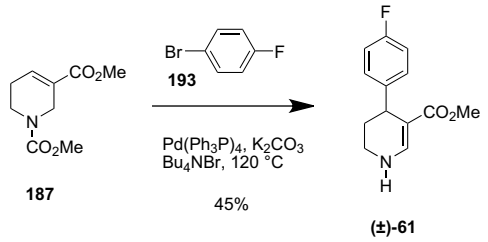
The exclusive formation of the monoaryl Heck adduct (±)-**189** paved the way for a new total synthesis of (±)-**1**, which required the non-trivial reduction of the enamino-ester functionality with Mg (20 equiv) in methanol to give a diastereomeric mixture of 4-(4-fluorophenyl)-piperidine-1,3-dicarboxylic acid dimethyl esters *cis*-(±)-**190** and *trans*-(±)-**191** in quantitative yield (dr = **75**:25).

Basic equilibration to the *trans* isomer, hydrolysis to the *trans*-carboxylic acid (±)-**192** and its reduction with diborane completed the synthesis of primary alcohol (±)-**123**, eventually converted to the target molecule through the well-established protocol.

Interestingly, almost contemporaneously, a further application of the palladium-catalyzed Heck reaction using arenediazonium tetrafluoroborate salts instead of conventional arylhalides/triflates for coupling Baylis–Hillman adducts in the presence of $Pd(OAc)_2$ as catalyst has been described in the literature.[63]



Scheme 38.



Scheme 39.

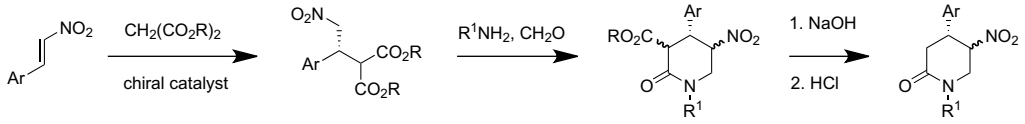
A formal synthesis of (±)-**1** entailing on a solvent-free Heck reaction between olefin **187** and commercially available *p*-fluoro bromobenzene **193** has been recently published by an Indian group (Scheme 39).[64]

The coupling was accompanied by the unmasking of carbamate protection to release amine (±)-**61**, which has been described in enantiomerically pure form by Yamada and Jahan along their route to paroxetine precursor (−)-**84**.[28]

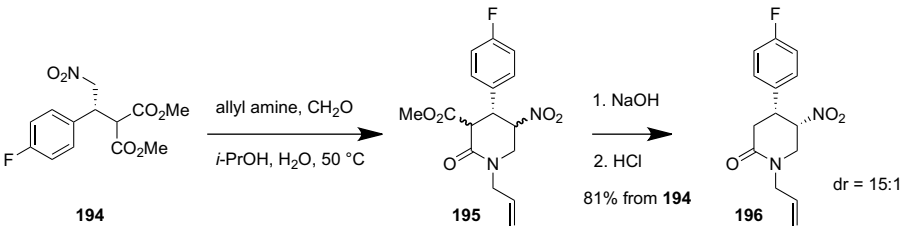
To complete this section, we report recently published emerging methods for the stereoselective construction of piperidine-based scaffolds. Though these compounds have not been used to obtain **1**, they could represent useful intermediates for the preparation of pharmaceutically important drugs including **1**.

A highly diastereoselective one-pot synthesis of 3,4-disubstituted piperidinones has been developed by Xu et al.[65] The Authors envisioned a general access to these compounds, starting from a primary amine, formaldehyde, and an enantiomerically pure nitroalkane, in turn obtained through enantioselective Michael addition of malonates to nitrostyrenes. (Scheme 40).

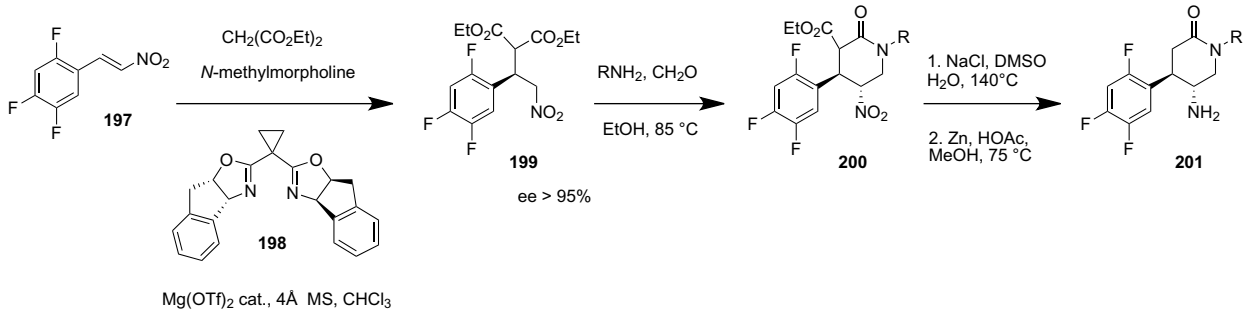
As an application of the general strategy, the nitro derivative **194** was reacted with allyl amine (1.3 equiv) and aqueous formaldehyde (1.05 equiv) in *i*-PrOH at 50 °C providing the corresponding piperidinone **195** as a mixture of isomers (Scheme 41). Basic treatment of the crude product followed by decarboxylation upon acidification gave-*cis*-**196** as the major product.



Scheme 40.



Scheme 41.



Scheme 42.

Asymmetric Michael addition of the malonate anion to nitrostyrene **197** catalyzed by the complex of magnesium triflate with the C_2-symmetric bisoxazoline ligand **198** opened the way to the synthesis of enantiomerically pure piperidinone-constrained phenetylamines **201** (Scheme 42).[66]

Thus, 1,3-diester **199** (ee >95%) took part in a three-component cyclization reaction with paraformaldehyde and amines, providing lactams **200**. Finally, decarboxylation under neutral conditions at 140 °C and subsequent reduction of the nitro group provided amines **201**.

9. Conclusive remarks

Piperidines are widely distributed throughout Nature and represent very important scaffolds for drug discovery, featuring as the core of many pharmaceuticals. Therefore, interest in the development of new, attractive routes toward substituted piperidines continues unabated. Furthermore, the bioactivity of the enantiomerically enriched *trans*-3,4-disubstituted piperidine Paroxetine, a GlaxoSmithKline product marketed as Paxil/Seroxat, has played a major role in stimulating the design of new synthetic methods in this area, evoking a surprisingly diverse array of strategies for its asymmetric synthesis. Thus, the synthetic efforts toward this stimulating target encompassed the physical resolution of racemates, enzyme-catalyzed asymmetric transformations, chiral auxiliary-based approaches, asymmetric deprotonation using chiral bases, catalytic enantioselective transformations, as well as the use of naturally occurring homochiral starting materials.

The strong demand for catalytic enantioselective transformations to access diastereo- and enantiomerically pure 3,4-disubstituted piperidines in high yields has received many positive answers. Chiral auxiliaries and stoichiometric chiral reagents have long been used to control selectivity in the generation of new stereocenters, but asymmetric catalytic methods for accomplishing this same goal are becoming increasingly attractive.

Procedures using either chiral auxiliary or chiral pool starting materials or enzymatic asymmetrization are of course still widely used. Chromatography for purification reduces the viability of large-scale processes.

Acknowledgment

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