

Asymmetric Syntheses of Enantioenriched 2,5-Disubstituted Pyrrolidines

Yanis Lazib, Junio Guimaraes Naves, Agnès Labande, Philippe Dauban,* and Tanguy Saget*

Cite This: *ACS Org. Inorg. Au* 2023, 3, 120–129

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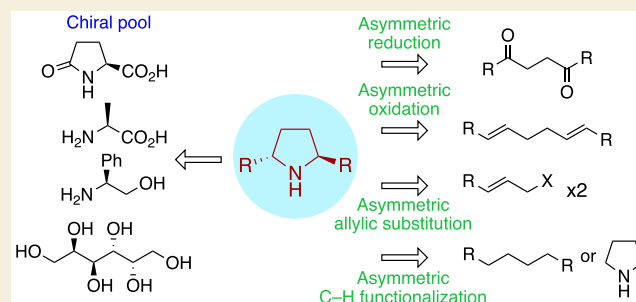
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ABSTRACT: C_2 -Symmetrical scaffolds are privileged ligands in metal catalysis and are also widely used in organocatalysis. Among these, 2,5-disubstituted pyrrolidines hold a paramount importance, especially since they also find application in medicinal chemistry. This review highlights the stereoselective syntheses of these C_2 -symmetrical nitrogen heterocycles. It includes synthetic strategies based on the use of the chiral pool as well as the more recent sequences designed following major achievements in asymmetric catalysis.

KEYWORDS: pyrrolidine, nitrogen heterocycle, natural product, C_2 symmetry, asymmetric synthesis, organometallic catalysis, organocatalysis, biocatalysis



1. INTRODUCTION

Pyrrolidines are ubiquitous in natural products and bioactive compounds as well as privileged motifs in stereoselective synthesis. In this respect, a recent study showed that the pyrrolidine ring is ranking in the fifth position among the most predominant nitrogen heterocycles for U.S. FDA approved pharmaceuticals.¹ In addition, the 2021 Nobel Prize in chemistry was awarded for the advent of organocatalysis, where pyrrolidine-based catalysts hold a key importance, notably in the field of aminocatalysis.² Among pyrrolidines, 2,5-disubstituted ones are particularly important (Figure 1).

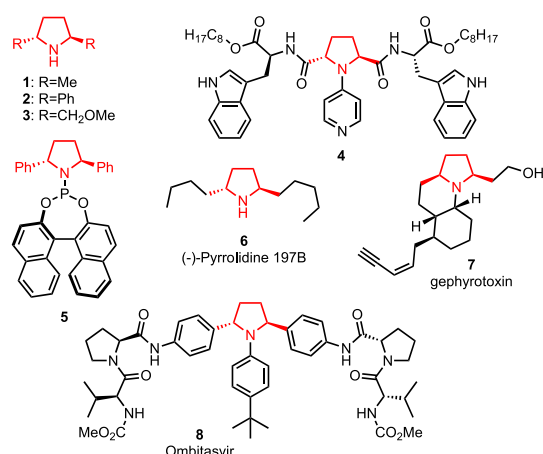


Figure 1. Important 2,5-disubstituted pyrrolidines.

Indeed, C_2 -symmetrical pyrrolidines 1–3 have been broadly used as chiral auxiliaries for a variety of transformations.^{3–7} Pyrrolidine 2 was also among the very first aminocatalysts enabling high enantioselectivities⁸ as well as a key motif in the design of important chiral phosphoramidite ligands such as 5.⁹ Moreover, chiral Lewis base 4 is an efficient organocatalyst for the chemoselective acylation of polyhydroxylated substrates.^{10,11} On the other hand, 2,5-disubstituted pyrrolidines are frequently encountered in natural products, notably in the venoms of amphibians¹² and ants¹³ such as (–)-pyrrolidine 197B (6) and gephyrotoxin 7. Last but not least, this motif is also relevant for the pharmaceutical industry, as exemplified by Ombistavir 8, an antiviral drug recently approved for the treatment of hepatitis C virus.¹⁴

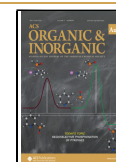
Initially, enantioenriched 2,5-disubstituted pyrrolidines were obtained by resolution of racemates with chiral acids.^{4,5} Because of their importance, many research groups then designed stereoselective strategies to access them. In this review, we will first discuss early asymmetric syntheses starting from the chiral pool and then focus on more recent syntheses involving an enantioselective step or relying on asymmetric catalysis.

Received: November 28, 2022

Revised: February 17, 2023

Accepted: February 22, 2023

Published: March 8, 2023

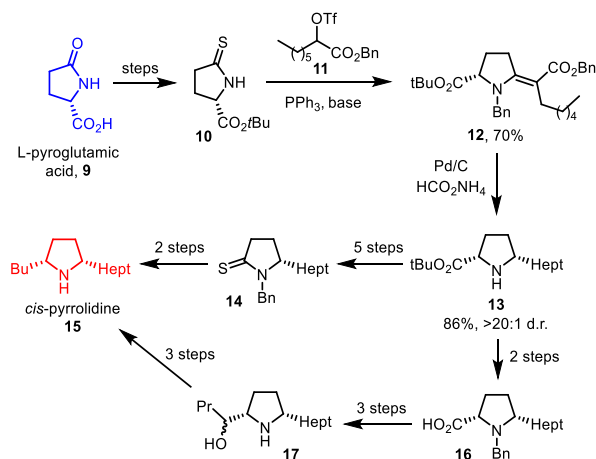


2. ASYMMETRIC STRATEGIES FROM THE CHIRAL POOL

2.1. Syntheses Starting from Amino Acids

To the best of our knowledge, the first stereoselective strategy toward the synthesis of enantiopure 2,5-disubstituted pyrrolidines was developed by Rapoport in the context of the total synthesis of naturally occurring alkaloids (Scheme 1).¹⁵ They

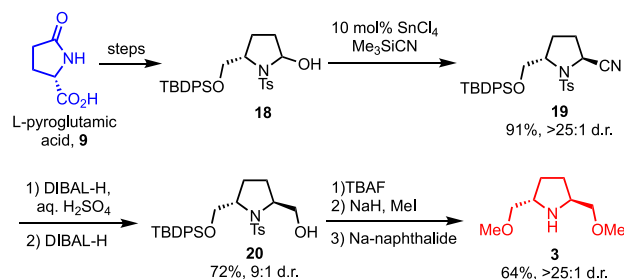
Scheme 1. Synthesis of 15 from Pyroglutamic Acid by Rapoport and Co-workers



started from L-pyroglutamic acid **9** that was transformed into thiolactam **10** after some functional group manipulation. S-Alkylation of **10** with triflate **11**, followed by the addition of triphenylphosphine and a tertiary amine base, led to vinyllogous carbamate **12** which was selectively transformed into *cis*-pyrrolidine **13** by hydrogenolysis and a decarboxylation mediated by palladium on charcoal and ammonium formate. Then intermediate **13** could be elaborated to enantiopure *cis*-2,5-dialkylpyrrolidines **15** via two different synthetic sequences, each of them requiring several steps.

Pyroglutamic acid was also the starting point for other synthetic strategies leading to 2,5-disubstituted pyrrolidines. For example, Somfai reported the synthesis of Katsuki's pyrrolidine **3** according to the following route (Scheme 2).¹⁶

Scheme 2. Synthesis of 3 from Pyroglutamic Acid by Somfai and Ahman

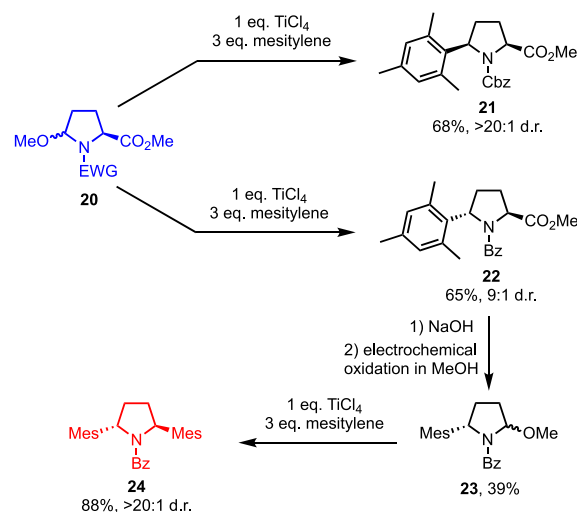


Pyroglutamic acid **9** was transformed into hemiaminal **18**. Lewis acid activation of **18** and *trans*-selective addition of cyanide led to **19** that was then reduced to the corresponding alcohol **20** with partial epimerization. Removal of the silicon protecting group, double Williamson etherification with methyl iodide, and final deprotection of the nitrogen afforded **3** in good overall yield. Importantly, after etherification, the *cis*-

isomer could be easily removed by chromatography, so that the desired *trans*-product was obtained diastereoisomerically pure.

The group of Onomura reported the synthesis of both *cis*- and *trans*-2,5-disubstituted pyrrolidines starting from the pyroglutamic acid-derived hemiaminal **20** (Scheme 3).¹⁷

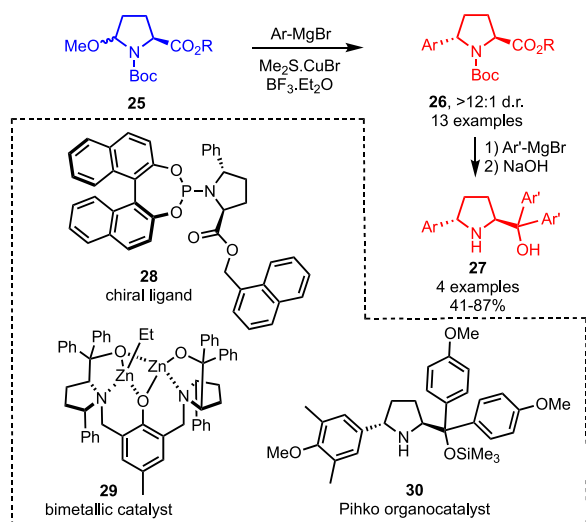
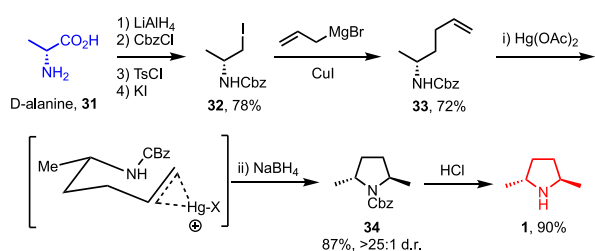
Scheme 3. Synthesis of 24 from Pyroglutamic Acid by Onomura and Co-workers



Under Lewis acidic conditions, the *in situ*-formed iminium can be trapped by an electron rich aromatic, such as mesitylene. The selectivity of the addition could be controlled by varying the protecting group on the nitrogen. Carbamates favor the formation of *cis*-pyrrolidines such as **21** while a benzamide gives the *trans*-pyrrolidine **22** as the major isomer. Saponification of the methyl ester of **22** followed by electrochemical decarboxylative methoxylation led to hemiaminal **23** that was further reacted under the previously developed conditions to selectively afford C₂-symmetrical pyrrolidine **24**.

To illustrate the high diversity provided by this method, hemiaminals **25** were also the starting point for Trost and co-workers to access a variety of *trans*-2,5-disubstituted pyrrolidines required for the synthesis of chiral phosphine ligand **28**¹⁸ or sterically constrained binuclear zinc catalyst **29** (Scheme 4).¹⁹ To this purpose, they developed a copper-mediated addition of Grignard reagents to **25** that proceeds with good to excellent diastereoselectivities to afford valuable pyrrolidines **26**. Then a double Grignard addition to the ester moiety of **26** followed by the removal of the Boc-protecting group yielded prolinol **27**. A similar strategy was later employed by Pihko and co-workers to synthesize a range of prolinol-based organocatalysts such as **30** required for an enantioselective Mukaiyama-Michael addition.²⁰

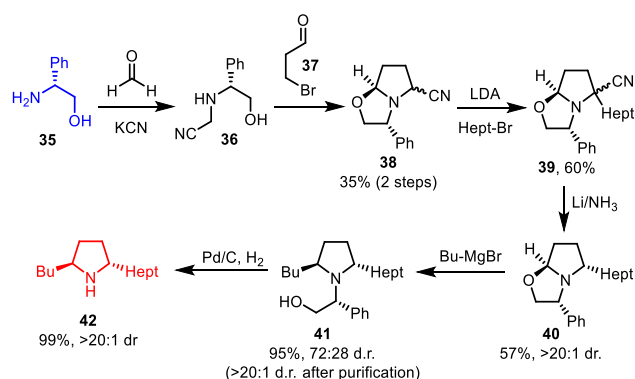
The importance of C₂-symmetric pyrrolidines **1** and **3** as chiral auxiliaries³ has been a considerable driving force for the development of stereoselective strategies to access them. In this respect, the group of Schlessinger developed the first stereoselective synthesis of each enantiomer of *trans*-2,5-dimethylpyrrolidines **1** starting from readily available D- or L-alanine (Scheme 5).²¹ The synthesis begins with the reduction of D-alanine **31** to the corresponding aminoalcohol and the selective protection of the amine with benzyl chloroformate. Then tosylation of the alcohol followed by a Finkelstein reaction with potassium iodide gave **32** which was engaged in a

Scheme 4. Synthesis of **26** and **27** from Pyroglutamic Acid by Trost and Co-workers**Scheme 5.** Synthesis of **1** from D-Alanine by Schlessinger and Co-workers

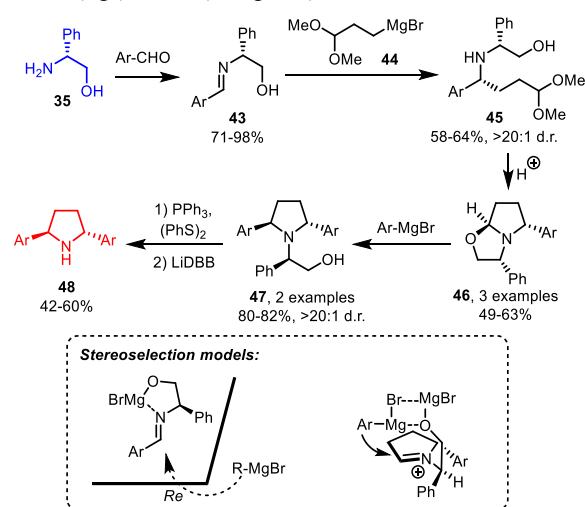
copper-mediated reaction with allyl magnesium bromide to afford **33**. Compound **33** was cyclized by an intramolecular aminomercuration followed by a reduction with sodium borohydride according to a procedure developed by Harding and co-workers.²² The *S*-*exo*-trig cyclization proceeds with high stereocontrol through a chairlike transition state. The desired *trans*-pyrrolidine **1** was finally obtained after the removal of the Cbz group. This route was further optimized by the group of Welch, who developed a more robust cuprate addition to reproducibly access intermediate **33** on a decagram scale.²³

2.2. Syntheses Starting from Phenylglycinol

Early on, Husson and co-workers developed a general route to access *trans*-2,5-disubstituted pyrrolidines starting from (*R*)-phenylglycinol **35** (Scheme 6).²⁴ Condensation with formaldehyde, followed by the addition of potassium cyanide, gave aminonitrile **36**, which was then reacted with bromoaldehyde **37** to afford intermediate **38**. Alkylation of the anion of **38** with heptyl bromide led to **39** as an inconsequential mixture of diastereoisomers since its reduction with Li/NH₃ occurs with high stereocontrol (dr >20:1) to afford **40**. Then the addition of butyl magnesium bromide to **40** gave predominantly the *trans*-2,5-dialkylpyrrolidine **41** from which the chiral auxiliary could be removed by hydrogenolysis to access stereopure pyrrolidine **42**. This strategy was further applied to the synthesis of several *trans*-2,5-dialkylpyrrolidines,²⁵ and conveniently, an improved protocol for the synthesis of intermediate **38** was also developed by the same group.²⁶

Scheme 6. Synthesis of *trans*-2,5-Dialkylpyrrolidines from (*R*)-Phenylglycinol by Husson and Co-workers

Inspired by the work of Husson *et al.*, Higashiyama and co-workers demonstrated the versatility of the method by extending its scope to the synthesis of *trans*-2,5-bis(aryl) pyrrolidines (Scheme 7).²⁷ The key steps are two diaster-

Scheme 7. Synthesis of *trans*-2,5-Diarylpyrrolidines from (*R*)-Phenylglycinol by Higashiyama and Co-workers

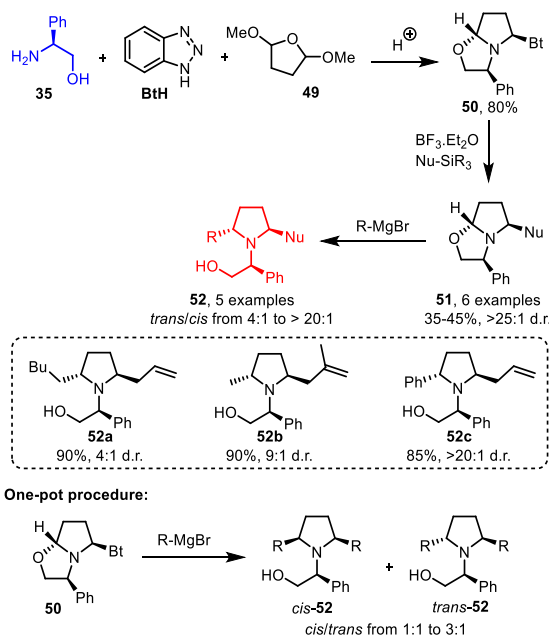
oselective additions of Grignard reagents, first to chiral imines and then to 1,3-oxazolidines. The synthesis starts with the condensation of (*R*)-phenylglycinol **35** with aromatic aldehydes to afford imines **43**. These imines were then reacted with Grignard reagent **44** prepared from bromopropionaldehyde dimethyl acetal. The additions proceed on the *Re* face with complete diastereoselectivity to afford chiral (*R*)-benzylamines **45**, which were then converted into **46** with a catalytic amount of methanolic hydrochloric acid. Oxazolidinones **46** were further reacted with other aryl Grignard reagents to give the stereopure adducts **47**. The addition of the Grignard reagent to the *in situ*-formed iminium is believed to be directed by the alkoxy group of the chiral auxiliary, thus leading to a *trans*-(*R,R*)-disubstituted pyrrolidine. Removal of the chiral auxiliary, however, limits the overall efficiency of the method as it requires a two-step and moderately yielding procedure involving substitution of the hydroxyl group by a phenyl sulfide followed by reductive fragmentation mediated by lithium di-*tert*-butylbiphenylide (LiDBB). Of note, this route afforded so far only symmetrical disubstituted pyrrolidines **48**, but it offers

the opportunity to access related nonsymmetrical pyrrolidines as shown later by the group of Katritzky.

Again starting from phenylglycinol as initial source of chirality, the group of Katritzky developed a similar strategy (Scheme 8).²⁸ The condensation between benzotriazole **BtH**,

Scheme 8. Synthesis of 2,5-Disubstituted Pyrrolidines from (*R*)-Phenylglycinol by Katritzky and Co-workers

Procedure with two successive additions:

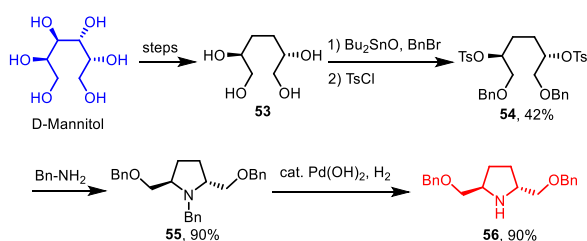


(*S*)-phenylglycinol, and succinaldehyde equivalent **49** under acidic conditions directly led to oxazopyrrolidine **50** in 80% yield on a 100 mmol scale. Intermediate **50** could be activated by BF₃·Et₂O and reacted with a range of nucleophilic partners such as allylsilanes, silyl enol ethers, and triethyl phosphite to selectively afford addition products **51** as single isomers. Then the addition of a Grignard reagent to **51** led to the corresponding pyrrolidines **52** with good to excellent *trans*-diastereoselectivities. However, the direct addition of an excess of Grignard reagents to **50** proved much less selective, as varying mixtures of *cis*- and *trans*-substituted pyrrolidines were obtained, with the *cis*-products being formed predominantly. Conveniently, the two isomers could be easily separated after chromatography.

2.3. Syntheses Starting from Carbohydrates

Misiti and Marzi developed a concise stereoselective synthesis of Katsuki's chiral auxiliary **56** starting from **53**, which can be accessed from D-mannitol (Scheme 9).²⁹ Selective benzoylation

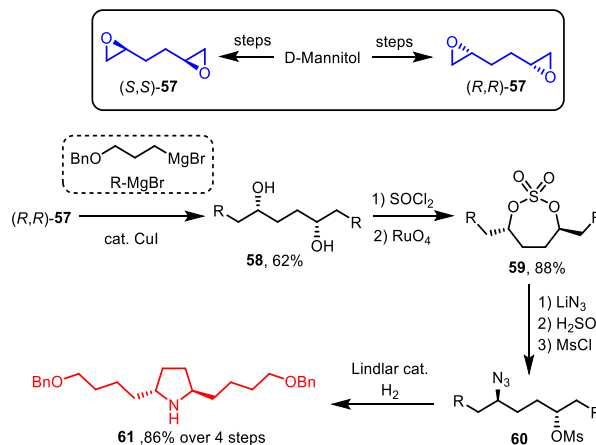
Scheme 9. Synthesis of 56 from D-Mannitol by Misiti and Marzi



of the primary alcohols followed by tosylation of the remaining secondary alcohols led to C₂-symmetrical compound **54**. Then a double nucleophilic substitution with benzylamine followed by a chemoselective N-debenzylation afforded optically pure (*R*)-**56**.

D-Mannitol was also used by the group of Kibayashi for the enantiodivergent synthesis of various naturally occurring *trans*-2,5-dialkylpyrrolidines since it can be readily transformed into bisepoxides (*S,S*)- and (*R,R*)-**57** in two and four steps, respectively (Scheme 10).³⁰ (*R,R*)-**57** was reacted with two

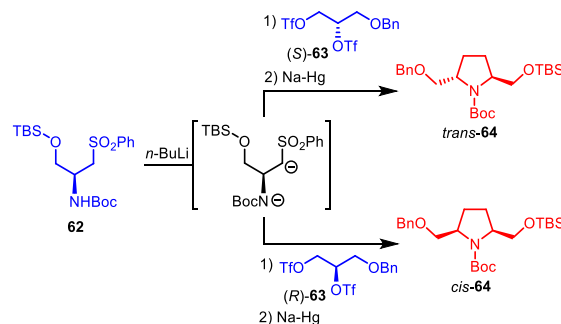
Scheme 10. Synthesis of 61 from D-Mannitol by Kibayashi and Co-workers



equivalents of an organocuprate to give the corresponding C₂-symmetrical 1,4-diol **58**; however, the formation of the targeted pyrrolidines requires several additional steps. After conversion to the cyclic sulfate **59** in two steps, nucleophilic displacement of the sulfate by an azide, followed by the activation of the remaining alcohol as a mesylate, led to **60**. Reduction of the azide to an amine directly triggered a 5-*exo*-tet cyclization to afford enantiopure *trans*-2,5-dialkylpyrrolidine **61**.

Sasaki *et al.* reported a stereocontrolled synthesis of 2,5-disubstituted pyrrolidines by reacting two chiral starting materials, a glycerol-derived bistriflate **63** and an aminosulfone **62** (Scheme 11).³¹ Multiple deprotonation of **62** by an excess of *n*-BuLi followed by the addition of **63** led to the corresponding pyrrolidine via two sequential S_N2 displacements, including a stereospecific cyclization. Removal of the sulfone under reductive conditions afforded the corresponding

Scheme 11. Synthesis of *cis*- and *trans*-64 by Sasaki and Co-workers

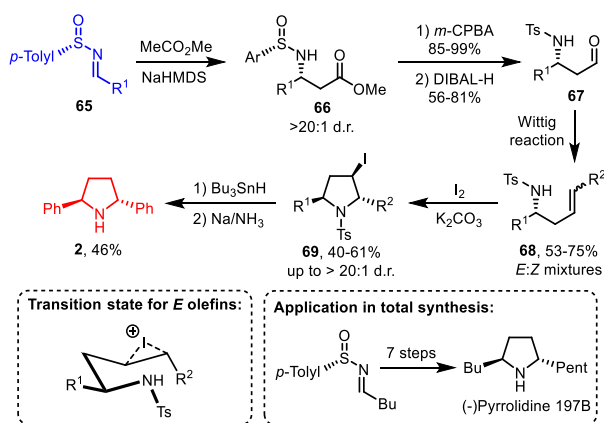


pyrrolidine **64**. Since each enantiomer of **63** is readily available, both *cis*- and *trans*-**64** could be accessed *via* this route.

2.4. Miscellaneous

Davis *et al.* developed a conceptually different route to access 2,5-disubstituted pyrrolidines.³² Their strategy relies on a diastereoselective Mannich reaction and then an iodocyclization to forge the pyrrolidine ring in a stereoselective manner (Scheme 12). First, the addition of the enolate of methyl

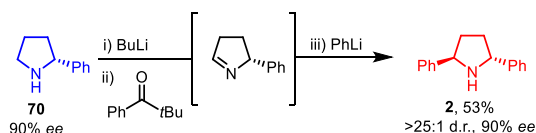
Scheme 12. Synthesis of *trans*-2,5-Disubstituted Pyrrolidines by Davis and Co-workers



acetate to chiral sulfinimine **65** gave Mannich product **66**. Oxidation of the sulfinyl moiety led to sulfonamides, and the ester group was then reduced with DIBAL-H to afford aldehydes **67**, which were reacted with phosphonium ylides to give **68** as mixtures of olefin isomers. In the presence of iodine and base, the *Z*-isomers could undergo a diastereoselective iodocyclization through a chairlike transition state, while the *E*-isomers did not react under these conditions because of the unfavorable $A^{1,3}$ strain. Removal of the iodide with Bu_3SnH followed by reductive cleavage of the sulfonamide protecting group with Na/NH_3 afforded *trans*-2,5-disubstituted pyrrolidines, such as **2**. This strategy is appropriate for the preparation of specific targets, as demonstrated by the synthesis of (–)-pyrrolidine 197B,^{12,30} an alkaloid present in poison frogs of the family *Dendrobates histrionicus* and in the venom of fire ants of the genus *Solenopsis* and *Monomorium latinode*.

By comparison, more powerful and versatile is the method developed by Seidel and co-workers relying on a one-pot C–H functionalization of unprotected cyclic amines that proceeds selectively α to the nitrogen.³³ Their operationally simple procedure involves an intermolecular hydride transfer to generate an imine, which is then reacted *in situ* with an organolithium reagent. Interestingly, their method was tested on enantioenriched pyrrolidine **70** to directly access **2** as the single *trans*-isomer without any erosion of the enantiopurity (Scheme 13).

Scheme 13. Synthesis of 2 by Seidel and Co-workers

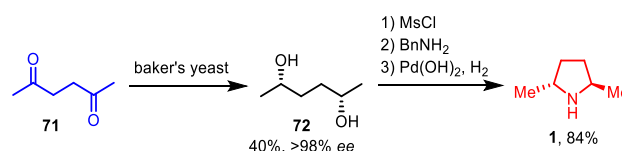


3. ENANTIOSELECTIVE AND CATALYTIC ASYMMETRIC STRATEGIES

3.1. Reductive Strategies from 1,4-Ketones

3.1.1. Enantioselective Reduction to 1,4-Diols. Masamune *et al.* developed a very concise synthesis of chiral auxiliary **1** starting from 2,5-hexanedione **71** that was reduced to diol **72** with excellent stereoselectivities using baker's yeast (Scheme 14).³⁴ Indeed, a high enantioselectivity was obtained

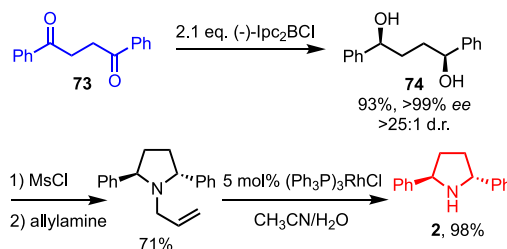
Scheme 14. Catalytic Enantioselective Synthesis of 1 by Masamune and Co-workers



because of the Horeau amplification effect,^{35,36} and only traces of the corresponding *meso*-diol were detected. Moreover, a single recrystallization gave stereopure diol **72** on a multigram scale. The diol was then activated as a bismethanesulfonate and reacted with benzyl amine to form the pyrrolidine ring *via* two consecutive nucleophilic displacements. Removal of the benzyl protecting group afforded stereopure **1** in good overall yield.

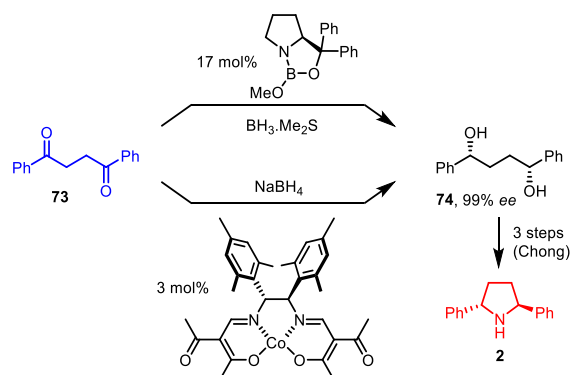
The strategy of Masamune and co-workers is versatile as it can be applied to the preparation of related C_2 -symmetrical pyrrolidines, in particular, pyrrolidines substituted with bulkier aromatic rings. Along this line, the group of Chong reported the asymmetric reduction of diketone **73** with (–)-diisopinocampheylchloroborane (Ipc_2BCl) to access diol **74** with excellent stereoselectivities (Scheme 15).³⁷ The diol was

Scheme 15. Synthesis of 2 by Chong and Co-workers



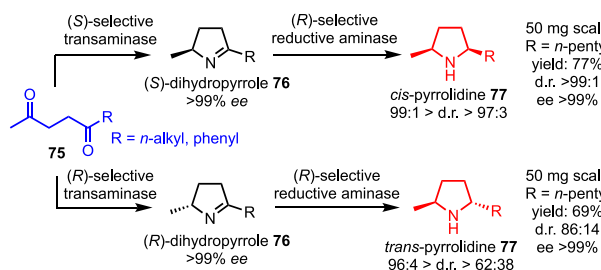
again activated as a bismesylate and reacted with allylamine to form a pyrrolidine ring. The allyl group was finally removed by a rhodium(I)-catalyzed olefin isomerization followed by hydrolysis to afford enantiopure free pyrrolidine **2**.

The group of Steel later developed a catalytic protocol to access diol **74**³⁸ relying on the Masui version of the Corey–Bakshi–Shibata reaction (Scheme 16).³⁹ Then they successfully repeated the synthetic sequence developed by the group of Chong to obtain pyrrolidine **2**. Interestingly, they could also apply this protocol for the asymmetric reduction of the homologated diketone to access the corresponding C_2 -symmetrical piperidine. This strategy was further applied by the group of Pihko to the synthesis of symmetrical and nonsymmetrical 2,5-diarylpyrrolidine organocatalysts.^{40,41} Later, the group of Yamada reported a complementary catalytic system based on a chiral β -ketoiminato cobalt(II) complex for the reduction of several diketones (Scheme 16) to

Scheme 16. Catalytic Enantioselective Synthesis of 2 by the Groups of Steel and Yamada

access the corresponding C_2 -symmetrical azetidines, pyrrolidines, and piperidines.⁴²

3.1.2. Biocatalyzed Transaminations and Reductive Aminations. Turner *et al.* developed multienzymatic cascade processes involving a transaminase and a reductive aminase that led to enantiomerically pure 2,5-disubstituted pyrrolidines 77 starting from nonsymmetrical 1,4-diketones 75 (Scheme 17).⁴³ Both *R*- and *S*-selective transaminases were identified for

Scheme 17. Biocatalytic Synthesis of Pyrrolidines by the Group of Turner

the first step, fully converting 1,4-diketones into enantiopure dihydropyrroles 76. Then a *R*-selective reductive aminase enabled stereoselective reduction of the obtained dihydropyrroles to the corresponding pyrrolidines in the same pot. Interestingly, this enzyme operates more or less independently of the existing stereogenic center, thus giving access to both *cis*-(2*S*,5*R*)- and *trans*-(2*R*,5*R*)-pyrrolidines 77 depending on the selected enzyme combination.

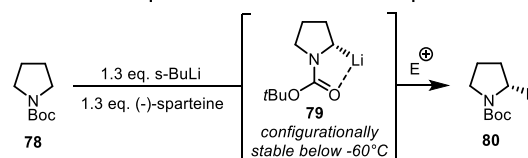
3.2. Direct C–H Functionalization of Pyrrolidines

3.2.1. Enantioselective Lithiation. The group of Beak pioneered a versatile strategy to access enantioenriched pyrrolidines through the asymmetric lithiation of *N*-Boc-pyrrolidine 78 followed by a reaction with an electrophilic partner (Scheme 18).⁴⁴ Indeed, the complexation of *s*-BuLi by (–)-sparteine enables an enantioselective deprotonation of 78 and the corresponding lithiated species 79 is configurationally stable at low temperature. It can then be reacted with a range of electrophiles to afford enantioenriched pyrrolidines 80 with good selectivities. By performing two consecutive asymmetric lithiation/methylation sequences, they could convert 78 into enantiopure 82 in 50% overall yield on a gram scale.⁴⁵

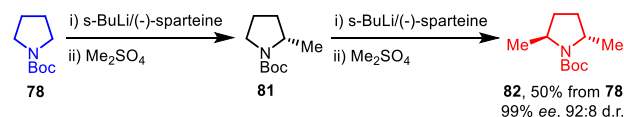
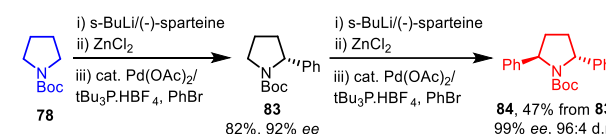
Based on the work of Beak, Campos and co-workers later developed an enantioselective palladium-catalyzed arylation of *N*-Boc-pyrrolidine (Scheme 19).⁴⁶ To preserve the stereo-

Scheme 18. Synthesis of 82 by Enantioselective Deprotonation by Beak and Co-workers

Enantioselective deprotonation / functionalization sequence:



Synthesis of 82 by two consecutive sequences:

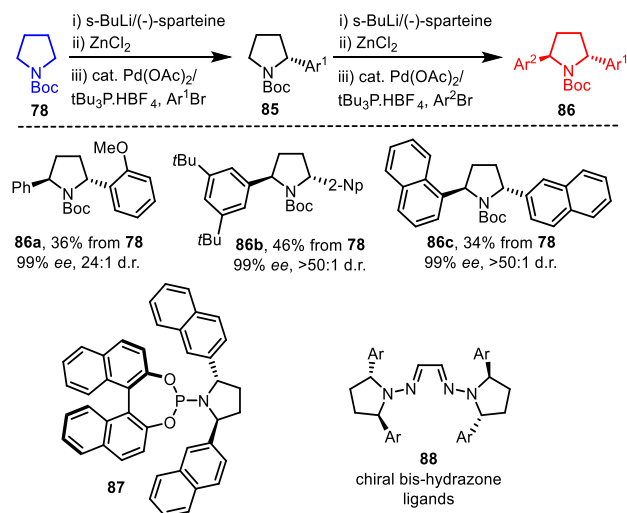
**Scheme 19. Synthesis of 84 by Enantioselective Deprotonation by Campos and Co-workers**

chemical integrity of the lithiated species 79 at higher temperatures, they performed a transmetalation with $ZnCl_2$ at low temperature, and the corresponding organozinc reagent proved to be configurationally stable at room temperature. Pleasingly, this organozinc reagent could also undergo stereoretentive transmetalations with organopalladium species generated from the oxidative addition to a range of aryl bromides to afford the corresponding cross-coupling products consistently with 92% ee. Having developed an enantioselective direct arylation of *N*-Boc-pyrrolidine, the authors also performed two sequential arylations to access the protected chiral auxiliary 84 in an analogous fashion to Beak and co-workers.

The sequential bisarylation of readily available *N*-Boc-pyrrolidine developed by Campos and co-workers is highly efficient and modular as it allows the rapid synthesis of a range of symmetrical and unsymmetrical 2,5-diarylpiperidines 86 with consistently high selectivities, independently of the nature of the aryl substituents. This straightforward strategy was exploited by the group of Trost (Scheme 20) to access a variety of phosphoramidite ligands incorporating a chiral pyrrolidine unit for the development of enantioselective trimethylenemethane [3 + 2] cycloadditions.⁴⁷ Along this line, they synthesized several 2,5-diarylpiperidines to finally obtain chiral ligand 87, which proved to be very efficient for the targeted cycloadditions. This methodology was further applied by the group of Denmark to synthesize chiral bishydrazones 88 for palladium-catalyzed atroposelective cross-coupling reactions with aryldimethylsilanolates.⁴⁸ Overall, this double arylation strategy is powerful to synthesize stereopure 2,5-diarylpiperidines; however, the fact that only one enantiomer can be accessed as (+)-sparteine is not available from nature stands as a limitation especially since the use of chiral sparteine surrogates has proven to be still less efficient so far.

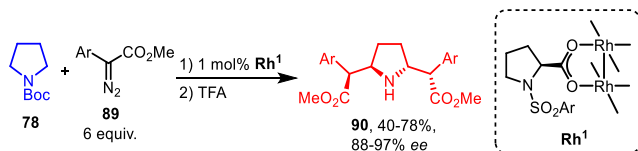
3.2.2. Catalytic Asymmetric C–H Insertion of Carbenes. As highlighted with previously described enantioselective lithiations, the direct difunctionalization of a pyrrolidine moiety is a powerful strategy to access 2,5-disubstituted

Scheme 20. Synthesis of *trans*-2,5-Diarylpyrrolidines by Trost and Co-workers



analogs. Davies *et al.* developed a catalytic version for this strategy enabled by two consecutive rhodium(II)-catalyzed C–H insertions (Scheme 21).⁴⁹ The use of Rh^I as a catalyst and donor–acceptor diazo precursors **89** led to C₂-symmetrical pyrrolidines **90** with high enantio- and diastereocontrol.

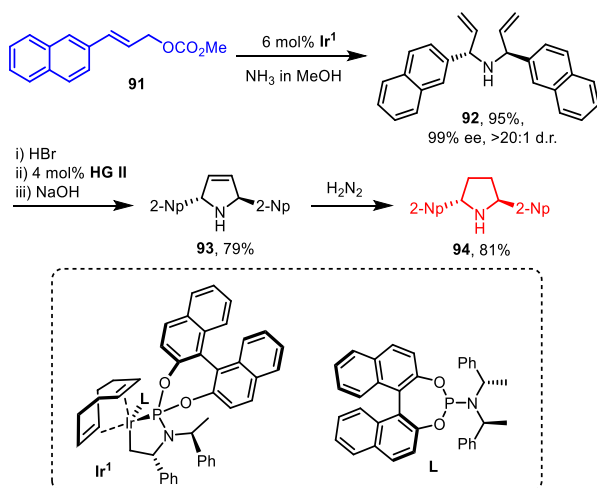
Scheme 21. Synthesis of **90** by Stereoselective C–H Insertions by Davies and Co-workers



3.3. Catalytic Enantioselective Allylic Substitution

Given the importance of chiral ligand **87**,^{47,50,51} an elegant catalytic strategy was developed by the group of Feringa to access both enantiomers of pyrrolidine **94** precursor of **87** (Scheme 22).⁵² To this purpose, they performed a double

Scheme 22. Synthesis of **94** by Enantioselective Allylic Substitutions by Feringa and Co-workers

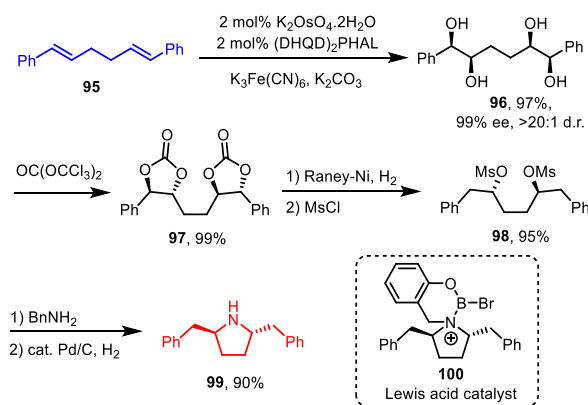


iridium-catalyzed branched-selective allylic substitution with carbonate **91** and ammonia as the nucleophilic partner. The use of chiral iridacycle Ir^I as a catalyst led to high yields and selectivities.⁵³ Importantly, contrary to the strategy involving the enantioselective deprotonation with sparteine, both enantiomers of Ir^I are readily available, so each enantiomer of **92** can be accessed. Stoichiometric protonation of the amine followed by a ring-closing metathesis with a Hoveyda-Grubbs second generation catalyst enabled the formation of dihydropyrrole **93** that was then hydrogenated with diimide to afford the desired pyrrolidine **94**.

3.4. Catalytic Enantioselective Dihydroxylation

Corey and Sprott specifically targeted pyrrolidine **99** as a valuable C₂-symmetrical unit for the design of novel cationic Lewis acid catalysts such as **100** (Scheme 23).⁵⁴ Their

Scheme 23. Synthesis of **99** by Enantioselective Bisdihydroxylation by Corey and Sprott

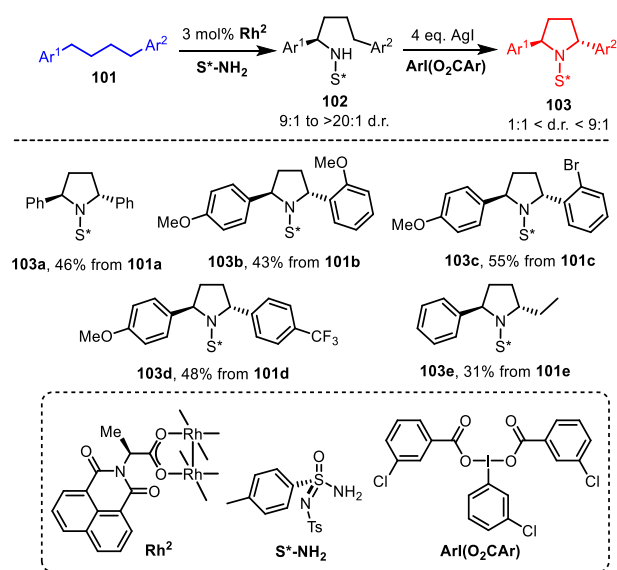


synthesis started from 1,4-diene **95**, easily obtained by a reductive dimerization of cinnamyl bromide, which was engaged in a double Sharpless dihydroxylation to afford **96** as a single stereoisomer. The tetraol **96** was then converted into the bicyclic carbonate **97**. Hydrogenolysis with Raney nickel and mesylation of the resulting diol led to **98** that was reacted with benzylamine. Finally, the removal of the benzyl group afforded pyrrolidine **99**. This strategy should theoretically give access to various 2,5-dibenzylpyrrolidines, but, as a limitation, the diversity is strictly linked to the choice of the starting material.

3.5. Catalytic Stereoselective C(sp³)–H Amination

Recently, Saget, Darses, Dauban, and co-workers envisaged the synthesis of 2,5-disubstituted pyrrolidines through a *de novo* strategy from simple hydrocarbons involving two consecutive C(sp³)–H amination reactions (Scheme 24).⁵⁵ A rhodium(II)-catalyzed asymmetric nitrene C–H insertion with chiral rhodium catalyst Rh² and sulfonimidamide S*-NH₂ enabled the first intermolecular C–H amination on benzylic positions of substrates **101**.⁵⁶ The amination proceeds with high regioselectivities on the most electron-rich benzylic position of 1,4-diarylbutane substrates and diastereoselectivities from 9:1 to >20:1 were consistently obtained for **102**. Then a second intramolecular amination *via* a 1,5-HAT inspired by recent studies on hypoiodite mediated Hofmann–Löffler–Freitag reactions⁵⁷ led to the desired symmetrical and nonsymmetrical pyrrolidines **103** with moderate to good *trans*-diastereoselectivities. Interestingly, the cyclization was not restricted to benzylic positions, as shown with pyrrolidine

Scheme 24. Synthesis of *trans*-2,5-Disubstituted Pyrrolidines 103 by Two Consecutive C(sp³)-H Aminations by Saget, Darses, Dauban, and Co-workers



103e. Of note, this sequence was also applied to alkanes, therefore making these broadly available compounds useful building blocks for the synthesis of heterocycles. Conveniently, stereopure pyrrolidines could be isolated after chromatography and the chiral auxiliary could be removed under reductive conditions to afford the corresponding free pyrrolidines.

4. CONCLUSION

In conclusion, the asymmetric synthesis of enantioenriched 2,5-disubstituted pyrrolidines was the purpose of several studies over the past few decades. Many disconnections have been successfully achieved, involving each of the five bonds present in the pyrrolidine ring. Interestingly, with the advent of catalytic C–H functionalization reactions, new streamlined strategies have been uncovered from readily available pyrrolidines thereby offering the opportunity to access new pseudo C₂-symmetrical scaffolds of potential application as ligands in catalysis. On the other hand, application of C–H functionalization reactions leads to design synthetic schemes for the preparation of substituted pyrrolidines from alkanes. Finally, we notice that strategies involving radical intermediates are still to be reported. But according to the recent achievements in photoredox catalysis and electrochemistry, new methods involving radical intermediates are expected to appear in the near future.⁵⁸

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article.

■ AUTHOR INFORMATION

Corresponding Authors

Tanguy Saget – Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France; Email: tanguy.saget@cnrs.fr

Philippe Dauban – Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette,

France; orcid.org/0000-0002-1048-5529;

Email: philippe.dauban@cnrs.fr

Authors

Yanis Lazib – Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France

Junio Guimaraes Naves – Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, 91198 Gif-sur-Yvette, France

Agnès Labande – LCC-CNRS, Université de Toulouse, 31077 Toulouse, France; orcid.org/0000-0003-0192-2499

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acsorginorgau.2c00061>

Author Contributions

All authors have given approval to the final version of the manuscript. CRediT: **Yanis Lazib** data curation (equal), methodology (equal), writing-original draft (equal); **Junio Guimaraes Naves** data curation (equal), methodology (equal), writing-original draft (equal); **Agnès Labande** project administration (lead), writing-review & editing (supporting); **Philippe Dauban** conceptualization (lead), funding acquisition (lead), project administration (lead), writing-review & editing (lead); **Tanguy Saget** conceptualization (lead), writing-review & editing (lead).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We wish to thank the French National Research Agency (program no. ANR-19-CE07-0043-02; fellowship to J.G.), the COMUE Université Paris-Saclay (program IDEX Paris/Saclay CDE-2018-002093; fellowship to Y.L.), and the ICSN for their support.

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