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# Asymmetric syntheses of enantioenriched 2,5-disubstituted pyrrolidines

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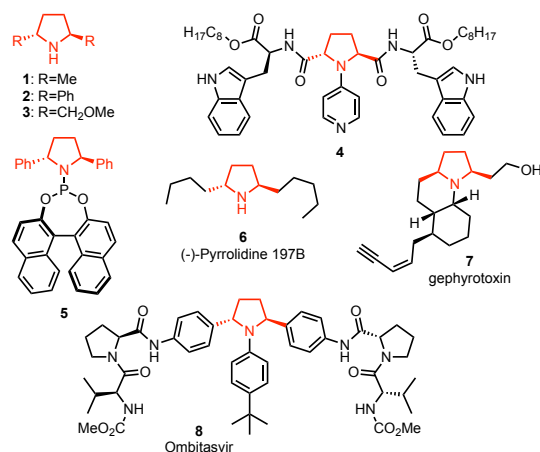
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**ABSTRACT:**  $C_2$ -Symmetrical scaffolds are privileged ligands in metal catalysis and are also widely used in organocatalysis. Among these, 2,5-disubstituted pyrrolidines hold a paramount importance especially since they also find application in medicinal chemistry. This review highlights the stereoselective syntheses of these  $C_2$ -symmetrical nitrogen heterocycles. It includes the 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 fifth position among the most predominant nitrogen heterocycles for U.S. FDA approved pharmaceuticals.<sup>1</sup> 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.<sup>2</sup> Among pyrrolidines, 2,5-disubstituted ones are particularly important (Figure 1). Indeed,  $C_2$ -symmetrical pyrrolidines **1-3** were broadly used as chiral auxiliaries for a variety of transformations.<sup>3-7</sup> Pyrrolidine **2** was also among the very first aminocatalysts enabling high enantioselectivities<sup>8</sup> as well as a key motif in the design of important chiral phosphoramidite ligands such as **5**.<sup>9</sup> Moreover, chiral Lewis base **4** is an efficient organocatalyst for chemoselective acylations of polyhydroxylated substrates.<sup>10,11</sup> On the other hand, 2,5-disubstituted pyrrolidines are frequently encountered in natural products, notably in the venoms of amphibians<sup>12</sup> and ants<sup>13</sup> 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.<sup>14</sup>

**Figure 1. Important 2,5-disubstituted pyrrolidines.**



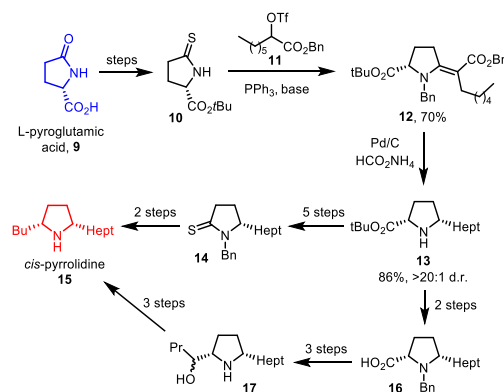
Initially, enantioenriched 2,5-disubstituted pyrrolidines were obtained by resolution of racemates with chiral acids.<sup>4,5</sup> Because of their importance, many research groups then designed stereoselective strategies to access them. In this review, we will first discuss about early asymmetric syntheses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

## 2. ASYMMETRIC STRATEGIES FROM THE CHIRAL POOL

### 2.1. Syntheses starting from amino acids.

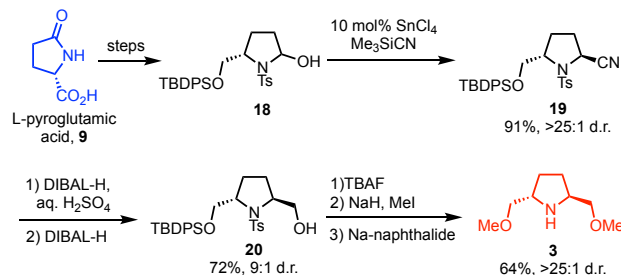
To the best of our knowledge, the first stereoselective strategy toward the synthesis of enantiopure 2,5-disubstituted pyrrolidines was developed by Rapoport in the context of the total synthesis of naturally-occurring alkaloids (Scheme 1).<sup>15</sup> They started from L-pyroglutamic acid **9** that 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 vinylogous 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.

**Scheme 1. Synthesis of 15 from pyroglutamic acid by Rapoport and coworkers.**



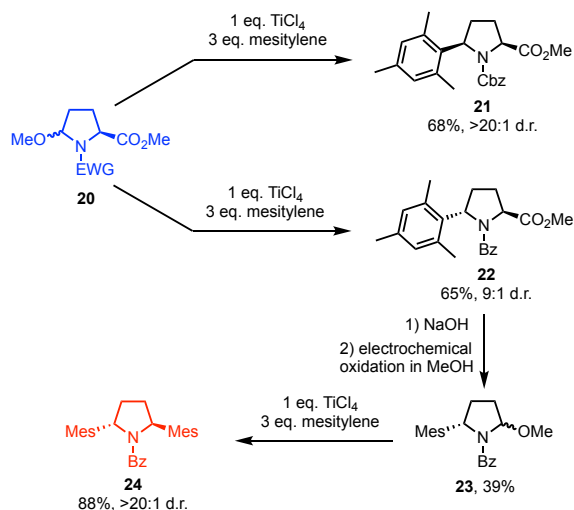
Pyroglutamic acid was also the starting point for other synthetic strategies leading to 2,5-disubstituted pyrrolidines. For example, Somfai reported the synthesis of Katsuki's pyrrolidine **3** according to the following route (Scheme 2).<sup>16</sup> Pyroglutamic acid **9** was transformed into the 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.

**Scheme 2. Synthesis of 3 from pyroglutamic acid by Somfai and Ahman.**



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).<sup>17</sup> 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 an electrochemical decarboxylative methoxylation led to hemiaminal **23** that was further reacted under the previously developed conditions to selectively afford *C*<sub>2</sub>-symmetrical pyrrolidine **24**.

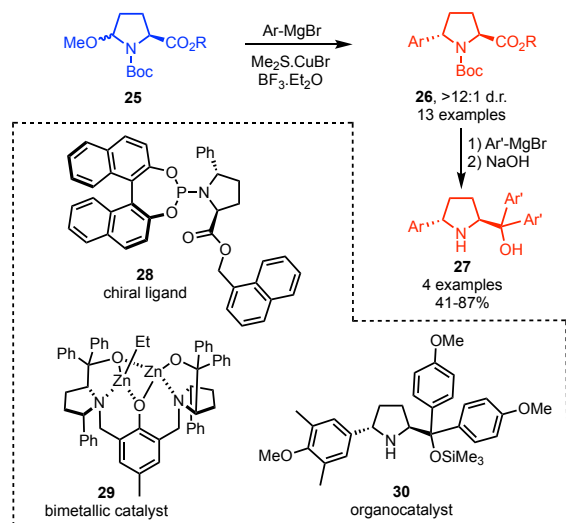
**Scheme 3. Synthesis of 24 from pyroglutamic acid by Onomura and coworkers.**



To illustrate the high diversity provided by this method, hemiaminals **25** were also the starting point for Trost and coworkers to access a variety of *trans*-2,5-disubstituted pyrrolidines required for the synthesis of chiral phosphine ligand

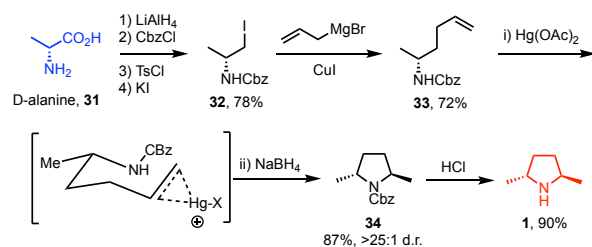
**28**<sup>18</sup> or sterically constrained binuclear zinc-catalyst **29** (Scheme 4).<sup>19</sup> To this purpose, they developed a copper-mediated addition of Grignard reagents to **25** that proceeds with good to excellent diastereoselectivities to afford valuable pyrrolidines **26**. Then, a double Grignard addition to the ester moiety of **26** followed by the removal of the Boc-protecting group yielded prolinols **27**. A similar strategy was later employed by Pikho and coworkers to synthesize a range of prolinol-based organocatalysts such as **30** required for an enantioselective Mukaiyama-Michael addition.<sup>20</sup>

**Scheme 4. Synthesis of 26 and 27 from pyroglutamic acid by Trost and coworkers.**



The importance of *C*<sub>2</sub>-symmetric pyrrolidines **1** and **3** as chiral auxiliaries<sup>3</sup> was 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).<sup>21</sup> 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 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 coworkers.<sup>22</sup> The 5-*exo*-trig-cyclization proceeds with high stereocontrol through a chair-like transition state. The desired *trans*-pyrrolidine **1** was finally obtained after 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.<sup>23</sup>

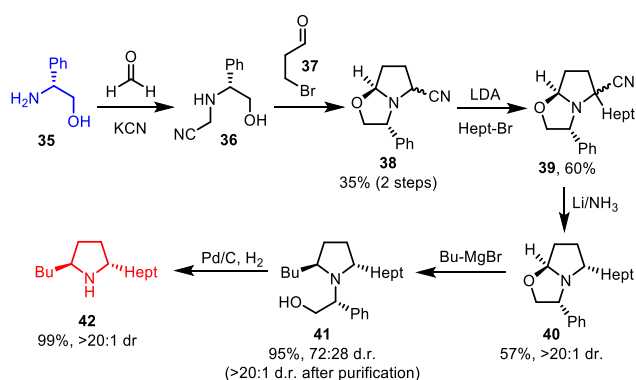
**Scheme 5. Synthesis of 1 from D-alanine by Schlessinger and coworkers.**



## 2.2. Syntheses starting from phenylglycinol.

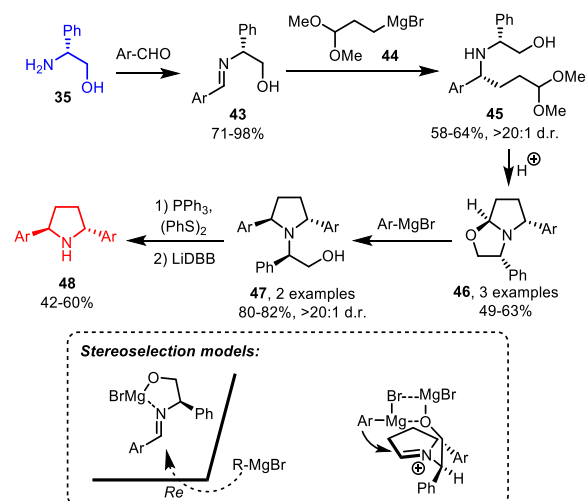
Early on, Husson and coworkers developed a general route to access *trans*-2,5-disubstituted pyrrolidines starting from (*R*)-phenylglycinol **35** (Scheme 6).<sup>24</sup> Condensation with formaldehyde followed by the addition of potassium cyanide gave aminonitrile **36**, which was then reacted with 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/NH<sub>3</sub> occurs with high stereocontrol (d.r. > 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,<sup>25</sup> and conveniently an improved protocol for the synthesis of intermediate **38** was also developed by the same group.<sup>26</sup>

**Scheme 6. Synthesis of *trans*-2,5-dialkylpyrrolidines from (*R*)-phenylglycinol by Husson and coworkers.**



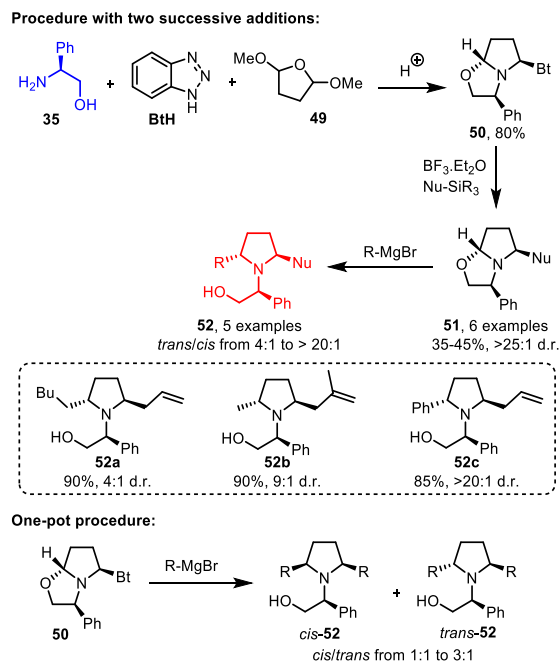
Inspired by the work of Husson *et al.*, Higashiyama and coworkers demonstrated the versatility of the method by extending its scope to the synthesis of *trans*-2,5-bis(aryl) pyrrolidines (Scheme 7).<sup>27</sup> The key steps are two diastereoselective additions of Grignard reagents, first to chiral 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 the chiral (*R*)-benzylamines **45**, which were then converted into **46** with a catalytic amount of methanolic hydrochloric acid. Oxazolidinones **46** were further reacted with another 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 a substitution of the hydroxyl group by a phenyl sulfide followed by a 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 non-symmetrical pyrrolidines as shown later by the group of Katritzky.

**Scheme 7. Synthesis of *trans*-2,5-diarylprrrolidines from (*R*)-phenylglycinol by Higashiyama and coworkers.**



Again starting from phenylglycinol as initial source of chirality, the group of Katritzky developed a similar strategy (Scheme 8).<sup>28</sup> The condensation between benzotriazole BtH, (*S*)-phenylglycinol and succindialdehyde equivalent **49** under acidic conditions directly led to oxazolopyrrolidine **50** in 80% yield on a 100 mmol scale. Intermediate **50** could be activated by BF<sub>3</sub>·Et<sub>2</sub>O 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, the *cis*-products being formed predominantly. Conveniently, the two isomers could be easily separated after chromatography.

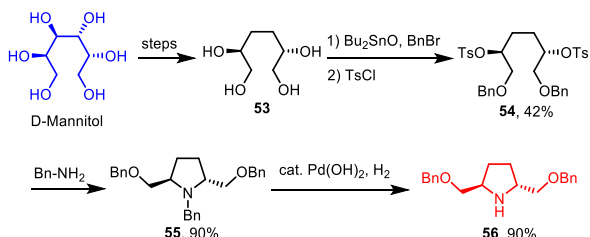
**Scheme 8. Synthesis of 2,5-disubstituted pyrrolidines from (*R*)-phenylglycinol by Katritzky and coworkers.**



### 2.3. Syntheses starting from carbohydrates.

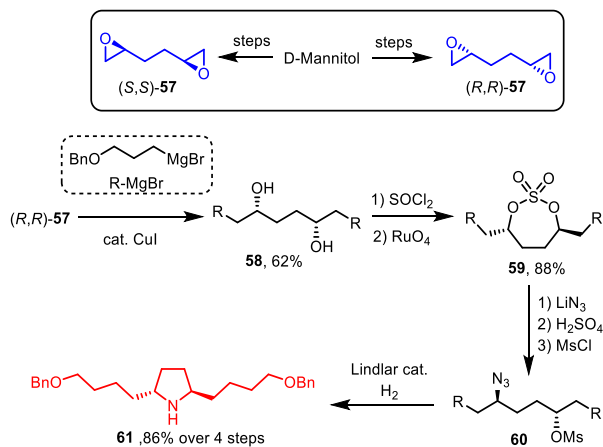
Misiti and Marzi developed a concise stereoselective synthesis of Katsuki's chiral auxiliary **56** starting from **53**, that can be accessed from D-mannitol (Scheme 9).<sup>29</sup> Selective benzylation of the primary alcohols followed by tosylation of the remaining secondary alcohols led to C<sub>2</sub>-symmetrical compound **55**. Then, a double nucleophilic substitution with benzylamine followed by a chemoselective N-debenzylation afforded optically pure (*R*)-**56**.

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



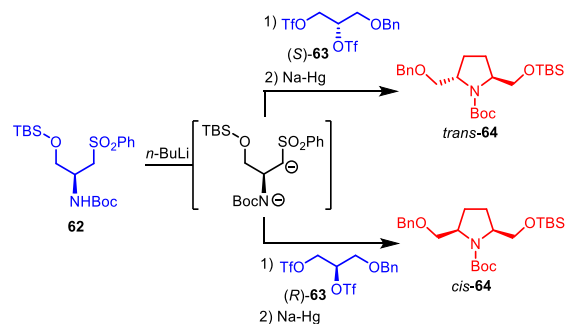
D-mannitol was also used by the group of Kibayashi for the enantiodivergent synthesis of various naturally-occurring *trans*-2,5-dialkylpyrrolidines since it can be readily transformed into bis-epoxides (*S,S*)- and (*R,R*)-**57** in two and four steps respectively (Scheme 10).<sup>30</sup> (*R,R*)-**57** was reacted with two equivalents of an organocuprate to give the corresponding C<sub>2</sub>-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**.

**Scheme 10. Synthesis of **61** from D-mannitol by Kibayashi and coworkers.**



Sasaki *et al.* reported a stereocontrolled synthesis of 2,5-disubstituted pyrrolidines by reacting two chiral starting materials, a glycerol-derived bis-triflate **63** and an aminosulfone **62** (Scheme 11).<sup>31</sup> 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<sub>N</sub>2 displacements including a stereospecific cyclization. Removal of the sulfone under reductive conditions afforded the corresponding pyrrolidine **64**. Since each enantiomer of **63** is readily available, both *cis*- and *trans*-**64** could be accessed *via* this route.

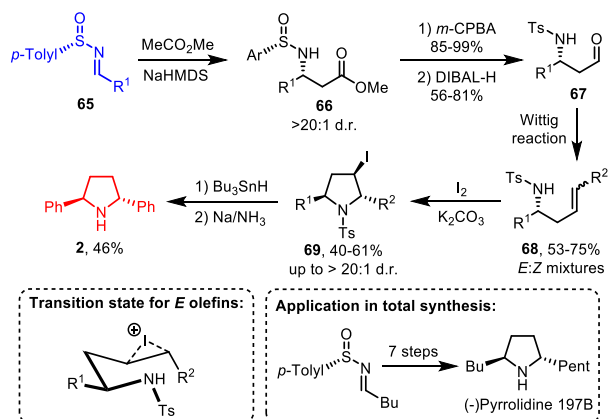
**Scheme 11. Synthesis of *cis*- and *trans*-**64** by Sasaki and coworkers.**



### 2.4. Miscellaneous.

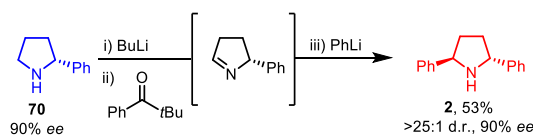
Davis *et al.* developed a conceptually different route to access 2,5-disubstituted pyrrolidines.<sup>32</sup> Their strategy relies on a diastereoselective Mannich reaction and then an iodocyclization to forge the pyrrolidine ring in a stereoselective manner (Scheme 12). First, the addition of the enolate of methyl acetate to chiral sulfinimines **65** gave Mannich products **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 chair-like transition state while the (*E*)-isomers did not react under these conditions because of the unfavourable A<sup>1,3</sup> strain. Removal of the iodide with Bu<sub>3</sub>SnH followed by a reductive cleavage of the sulfonamide protecting group with Na/NH<sub>3</sub> afforded *trans*-2,5-substituted pyrrolidines such as **2**. This strategy is appropriate for the preparation of specific targets as demonstrated by the synthesis of (-)-pyrrolidine 197B,<sup>12,30</sup> 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*.

**Scheme 12. Synthesis of *trans*-2,5-disubstituted pyrrolidines by Davis and coworkers.**



By comparison, more powerful and versatile is the method developed by Seidel and coworkers relying on a one-pot C-H functionalization of unprotected cyclic amines that proceeds selectively  $\alpha$  to the nitrogen.<sup>33</sup> 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 coworkers.



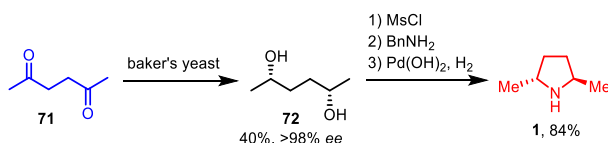
## 3. ENANTIOSELECTIVE AND CATALYTIC ASYMMETRIC STRATEGIES

### 3.1. Reductive strategies from 1,4-ketones.

#### 3.1.1. Enantioselective reduction to 1,4-diols.

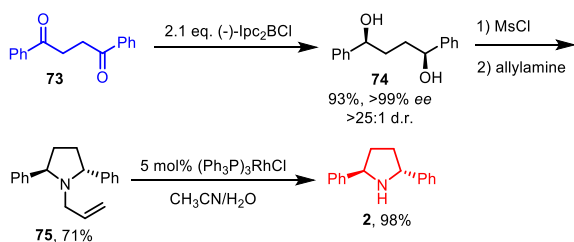
Masamune *et al.* developed a very concise synthesis of chiral auxiliary **1** starting from 2,5-hexanedione **71** that was reduced to diol **72** with excellent stereoselectivities using baker's yeast (Scheme 14).<sup>34</sup> Indeed, a high enantioselectivity was obtained because of the Horeau amplification effect<sup>35,36</sup> and only traces of the corresponding meso-diol were detected. Moreover, a single recrystallization gave the stereopure diol **72** on a multigram scale. The diol was then activated as a bis-methane sulfonate and reacted with benzyl amine to form the pyrrolidine ring *via* two consecutive nucleophilic displacements. Removal of the benzyl protecting group afforded stereopure **1** with a good overall yield.

#### Scheme 14. Catalytic enantioselective synthesis of **1** by Masamune and coworkers.



The strategy of Masamune and coworkers is versatile as it can be applied to the preparation of related C<sub>2</sub>-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<sub>2</sub>BCl) to access diol **74** with excellent stereoselectivities (Scheme 15).<sup>37</sup> The diol was again activated as a bis-mesylate and reacted with allylamine to form the pyrrolidine ring. The allyl group was finally removed by a rhodium(I)-catalyzed olefin isomerization followed by hydrolysis to afford enantiopure free pyrrolidine **2**.

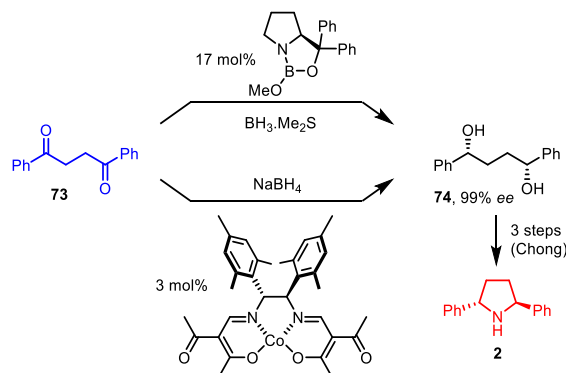
#### Scheme 15. Synthesis of **2** by Chong and coworkers.



The group of Steel later developed a catalytic protocol to access diol **74**<sup>38</sup> relying on the Masui version of the Corey-Bakshi-Shibata reaction (Scheme 16).<sup>39</sup> 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 homol-

ogated diketone to then access the corresponding C<sub>2</sub>-symmetrical piperidine. 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 access the corresponding C<sub>2</sub>-symmetrical azetidines, pyrrolidines and piperidines.<sup>40</sup>

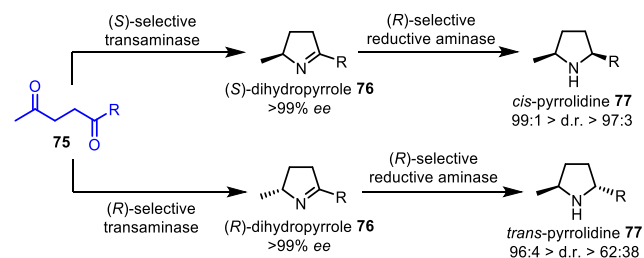
#### Scheme 16. Catalytic enantioselective synthesis of **2** by the groups of Steel and Yamada.



#### 3.1.2. Biocatalyzed transaminations and reductive aminations.

Turner *et al.* developed multi-enzymatic cascade processes involving a transaminase and a reductive aminase that lead to enantiomerically pure 2,5-disubstituted pyrrolidines **77** starting from non-symmetrical 1,4-diketones **75** (Scheme 17).<sup>41</sup> Both a (*R*)- and a (*S*)-selective transaminase were identified for the first step, fully converting 1,4-diketones into enantiopure dihydropyrroles **76**. Then, a (*R*)-selective reductive aminase enabled the 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 enzymes combination.

#### Scheme 17. Biocatalytic synthesis of pyrrolidines by the group of Turner.



## 3.2. Direct C-H Functionalization of pyrrolidines.

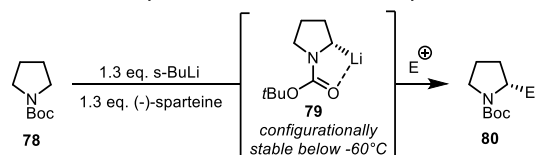
#### 3.2.1. Enantioselective lithiation.

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).<sup>42</sup> 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

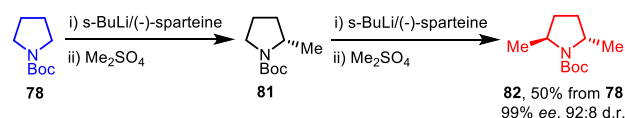
convert **78** into enantiopure **82** in 50% overall yield on a gram-scale.<sup>43</sup>

### Scheme 18. Synthesis of **82** by enantioselective deprotonation by Beak and coworkers.

Enantioselective deprotonation / functionalization sequence:

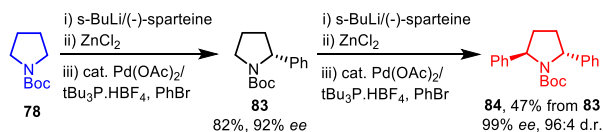


Synthesis of **82** by two consecutive sequences:



Based on the work of Beak, Campos and coworkers later developed an enantioselective palladium-catalyzed arylation of *N*-Boc-pyrrolidine (Scheme 19).<sup>44</sup> To preserve the stereochemical integrity of the lithiated species **79** at higher temperatures, they performed a transmetalation with  $\text{ZnCl}_2$  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 onto 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 coworkers.

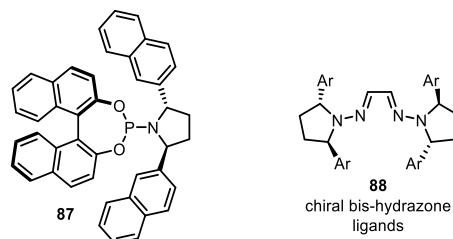
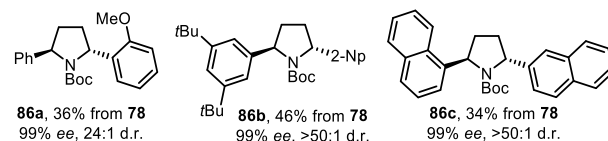
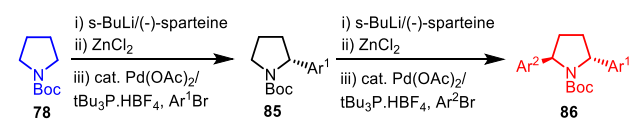
### Scheme 19. Synthesis of **84** by enantioselective deprotonation by Campos and coworkers.



The sequential bis-arylation of readily available *N*-Boc-pyrrolidine developed by Campos and coworkers is highly efficient and modular as it allows the rapid synthesis of a range of symmetrical and unsymmetrical 2,5-diaryl pyrrolidines **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.<sup>45</sup> Along this line, they synthesized several 2,5-diaryl pyrrolidines to finally obtain chiral ligand **87**, which proved very efficient for the targeted cycloadditions. This methodology was further applied by the group of Denmark to synthesize chiral bis-hydrazone ligands **88** for palladium-catalyzed atroposelective cross-coupling reactions with aryldimethylsilylanolates.<sup>46</sup> Overall, this double arylation strategy is powerful to synthesize stereopure 2,5-diaryl pyrrolidines, 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 have proven to be still less efficient so far.

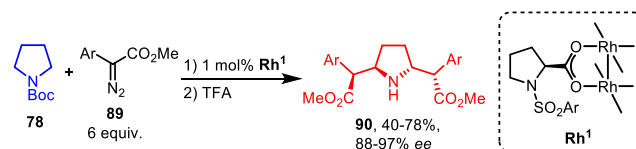
### Scheme 20. Synthesis of *trans*-2,5-diarylpyrrolidines by Trost and coworkers.



### 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 analogs. Davies *et al.* developed a catalytic version for this strategy enabled by two consecutive rhodium(II)-catalyzed C-H insertions (Scheme 21).<sup>47</sup> The use of  $\text{Rh}^{\text{I}}$  as catalyst and donor-acceptor diazo precursors **79** led to  $C_2$ -symmetrical pyrrolidines **90** with high enantio- and diastereocontrol.

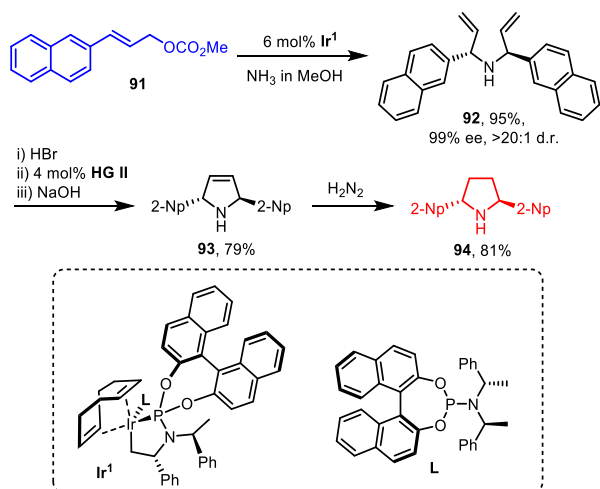
### Scheme 21. Synthesis of **90** by stereoselective C-H insertions by Davies and coworkers.



### 3.3. Catalytic enantioselective allylic substitution.

Given the importance of chiral ligand **87**,<sup>45,48,49</sup> an elegant catalytic strategy was developed by the group of Feringa to access both enantiomers of pyrrolidine **94** precursor of **87** (Scheme 22).<sup>50</sup> To this purpose, they performed a double iridium-catalyzed branched-selective allylic substitution with carbonate **91** and ammonia as nucleophilic partner. The use of chiral iridacycle  $\text{Ir}^{\text{I}}$  as a catalyst led to high yields and selectivities.<sup>51</sup> Importantly, contrary to the strategy involving the enantioselective deprotonation with sparteine, both enantiomers of  $\text{Ir}^{\text{I}}$  are readily available so each enantiomer of **92** can be accessed. Stoichiometric protonation of the amine followed by a ring-closing metathesis with Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst enabled the formation of dihydropyrrole **93** that was then hydrogenated with diimide to afford the desired pyrrolidine **94**.

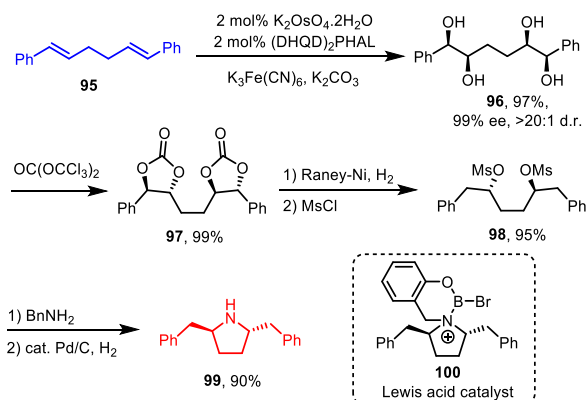
**Scheme 22. Synthesis of 94 by enantioselective allylic substitutions by Feringa and coworkers.**



**3.4. Catalytic enantioselective dihydroxylation.**

Corey and Sprott specifically targeted pyrrolidine **99** as a valuable  $C_2$ -symmetrical unit for the design of novel cationic Lewis acid catalysts such as **100** (Scheme 23).<sup>52</sup> Their 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 bis cyclic carbonate **97**. Hydrogenolysis with Raney nickel and mesylation of the resulting diol led to **98** that was reacted with benzylamine. Finally, removal of the benzyl group afforded pyrrolidine **99**. This strategy should theoretically give access to various 2,5-disubstituted pyrrolidines but, as a limitation, the diversity is strictly linked to the choice of the starting material.

**Scheme 23. Synthesis of 99 by enantioselective bis-dihydroxylation by Corey and Sprott.**

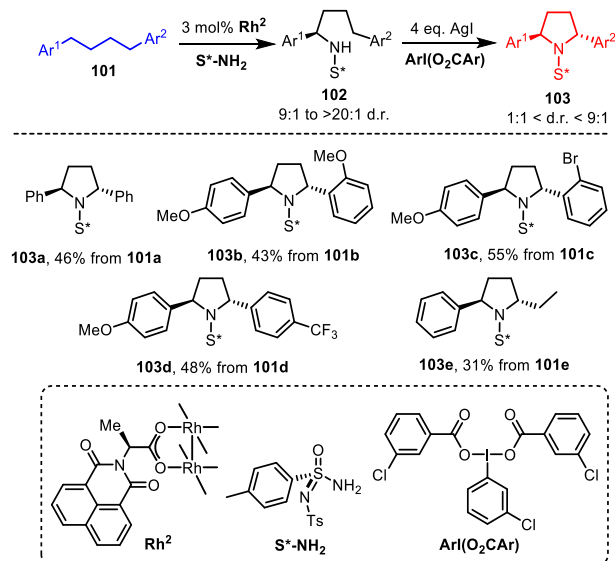


**3.5. Catalytic stereoselective C(sp<sup>3</sup>)-H amination.**

Recently, Saget, Darses, Dauban and coworkers envisaged the synthesis of 2,5-disubstituted pyrrolidines through a *de novo* strategy from simple hydrocarbons involving two con-

secutive C(sp<sup>3</sup>)-H amination reactions (Scheme 24).<sup>53</sup> A rhodium(II)-catalyzed asymmetric nitrene C-H insertion with chiral rhodium catalyst **Rh<sup>2</sup>** and sulfonimidamide **S<sup>\*</sup>-NH<sub>2</sub>** enabled the first intermolecular C-H amination on benzylic positions of substrates **101**.<sup>54</sup> 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 hypiodite mediated Hofmann-Löffler-Freytag reactions<sup>55</sup> led to the desired symmetrical and non-symmetrical pyrrolidines **103** with moderate to good *trans*-diastereoselectivities. Interestingly, the cyclization was not restricted to benzylic positions as shown with pyrrolidine **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 pyrrolidine.

**Scheme 24. Synthesis of *trans*-2,5-disubstituted pyrrolidines 103 by two consecutive C(sp<sup>3</sup>)-H aminations by Saget, Darses, Dauban and coworkers.**



**CONCLUSION**

In conclusion, the asymmetric synthesis of enantioenriched 2,5-disubstituted pyrrolidines was the purpose of several studies over the past 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  $C_2$ -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.<sup>56</sup>



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

### Author Contributions

All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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