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Reduction of Oximes and Hydrazones: Asymmetric and Diastereoselective Approaches

João L. P. Ribeiro,[1] Cláudia Alves,[1] Ana L. Cardoso, Susana M. M. Lopes, Teresa M. V. D. Pinho e Melo*

University of Coimbra, Coimbra Chemistry Centre and Department of Chemistry, 3004-535 Coimbra

Abstract – The asymmetric reduction of oximes and hydrazones is an attractive and versatile strategy for the synthesis of chiral amines, which are valuable building blocks in organic synthesis. This review summarizes the relevant developments, made in the last decade, on the enantioselective and diastereoselective reduction of oximes and hydrazones involving metal-catalyzed hydrogenation/hydrogenolysis reactions, hydride donor reactions, and electrochemical reactions.

Keywords: Chiral amines, asymmetric reduction, enantioselective reduction, diastereoselective reduction, oximes, chiral hydroxylamines, hydrazones, chiral hydrazines.

1. INTRODUCTION

Chiral compounds have been valuable assets over the past decades, mainly in the pharmaceutical and agrochemical industries, due to their unique properties. In recent years, the research on asymmetric synthetic methodologies has been growing exponentially owing to the increasing demand for enantiomerically pure compounds [1-6]. Among these, enantiopure chiral amines are extremely valuable and versatile building blocks for the synthesis of many small molecule pharmaceuticals, fine chemicals and agrochemicals [7-9]. In fact, it has been estimated that chiral amine precursors have been involved in the synthesis of more than one third of the 200 most prescribed small molecule drugs. Selected examples of chiral amine-based drugs are shown in Figure 1, which have been used in clinical practice [10-15].

In addition, chiral amines have also been widely used as chiral ligands or organocatalysts in asymmetric catalysis [16-18]. The extensive range of applications of these valuable intermediates has led to a growing interest in their asymmetric synthesis, and in the last decades, numerous methods have been developed to prepare chiral amines [8, 19-22]. Within these, an attractive synthetic strategy towards chiral amines involves the asymmetric reduction of oximes or hydrazones, since the initially formed chiral hydroxylamines and hydrazines can be easily transformed into the desired amines while maintaining the optical purity (Figure 2).

[1] These two authors contributed equally to this work.

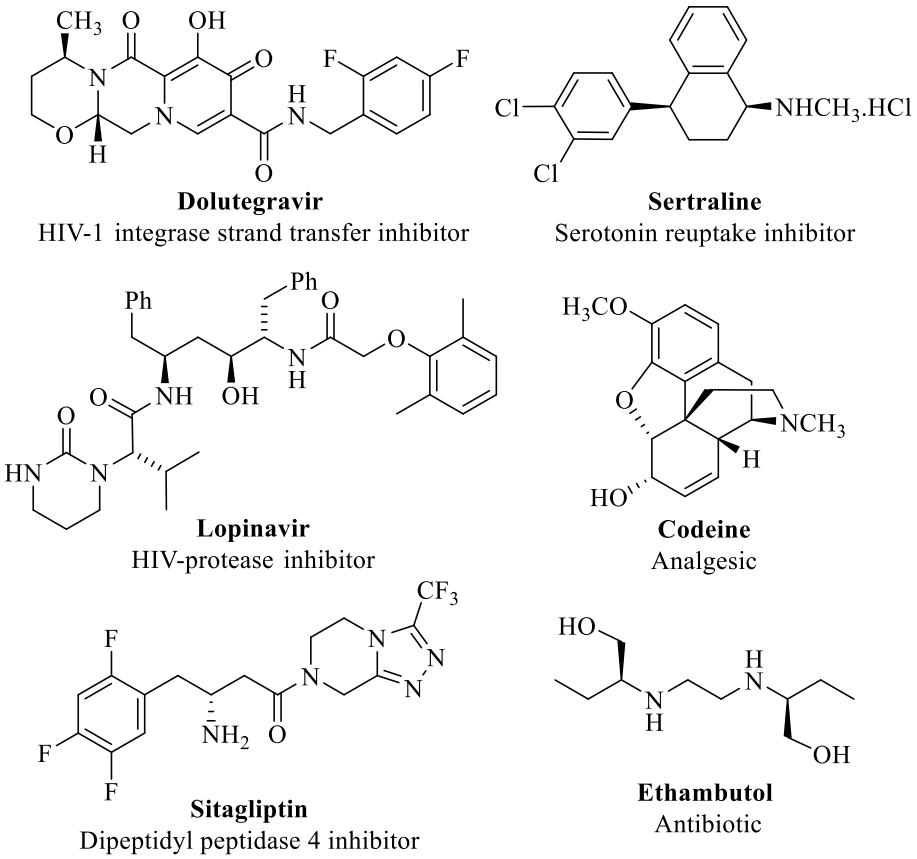


Figure 1. Selected examples of amine-based drugs.

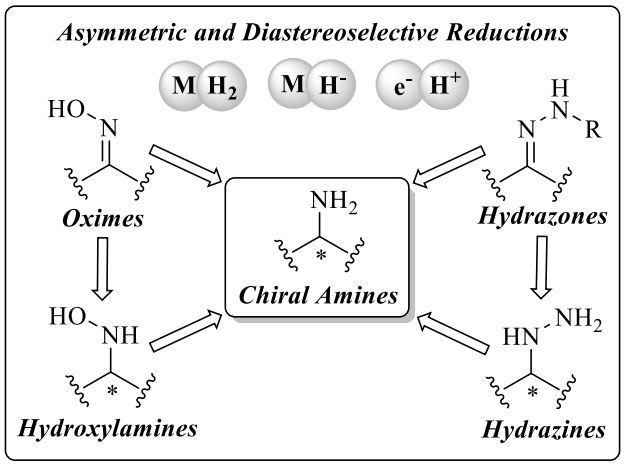


Figure 2. Synthetic strategies towards chiral amines.

The principal aim of this review is to assemble the most recent advances in the asymmetric reduction of oximes and hydrazones, since 2010. Topics related to efficiency, scope and selectivity of these transformations will be addressed, as well as the mechanisms underlying these asymmetric reactions.

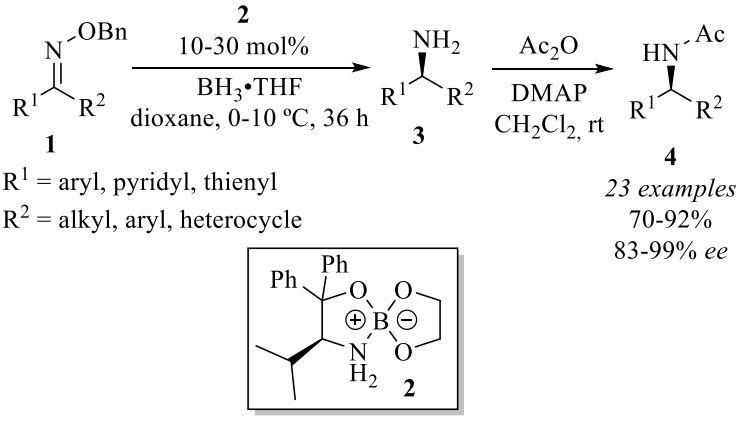
2. ENANTIOSELECTIVE REDUCTION OF OXIMES

The enantioselective reduction of oximes has been studied for over 40 years, due to the importance in obtaining optically pure amines [23]. Since the first report of an enantioselective hydrogenation of a ketoxime, through ruthenium catalysis, described by Botteghi *et al.* in 1975 [24], numerous efforts have been made to further explore these transformations. In addition to the synthesis of chiral amines, the enantioselective reduction of oximes can also produce chiral hydroxylamines. These compounds possess a N-O bond which has been associated with interesting biological properties [25-27] and can act as one-atom nitrogen source for metal-catalyzed cycloaddition reactions [28]. In recent years, several groups studied the enantioselective reduction of oximes taking advantage of the borane-mediated reductions, metal-catalyzed hydrogenation/hydrogenolysis and hydride transfer as described below.

2.1. Borane Reduction Mediated by Chiral Spiroborate Esters or Oxazaborolidines

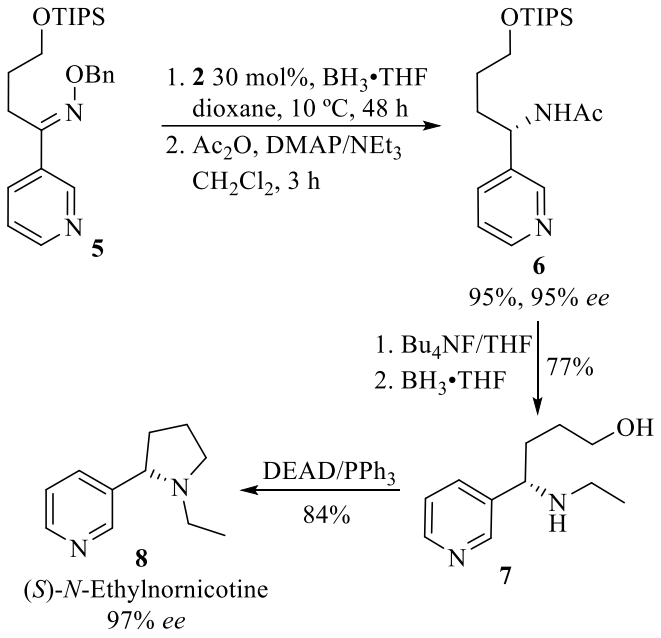
The first report on the enantioselective borane-mediated reduction of ketoximes was published in 1987 by Itsuno and co-workers [29]. The reduction of acetophenone *O*-benzyloxime using 10 mol% of the chiral complex formed *in situ* by the addition of borane to (*S*)-diphenylvalinol, gave (*S*)-1-phenylethanamine with 52% *ee*. Since then, the enantioselective borane-mediated reductions have been widely explored in organic synthesis [30-32].

Ortiz-Marciales and co-workers developed the synthesis of stable enantiopure spiroborate esters [33-35] and explored their application in the borane-mediated enantioselective reduction of *O*-benzyl ketoxime ether derivatives. Spiroborate ester **2** stood out as the best chiral catalyst to carry out these asymmetric reductions (Scheme 1). *O*-Benzyl ketoximes **1** were reduced to the corresponding chiral amines **3** using borane-tetrahydrofuran complex (BH_3•THF) in dioxane in the presence of 10 mol% of the chiral catalyst **2**. The primary amines **3**, isolated as the corresponding acetyl derivatives **4**, were obtained in good yields (70-90%) and excellent enantiomeric excess (83-99% *ee*). A series of pyridyl enantiopure amines **3** with *ee* up to 99%, were also obtained through the reduction of the corresponding *O*-benzyl ketoximes **1** (R^1 = pyridyl), using 30 mol% of catalyst **2** [36-38].



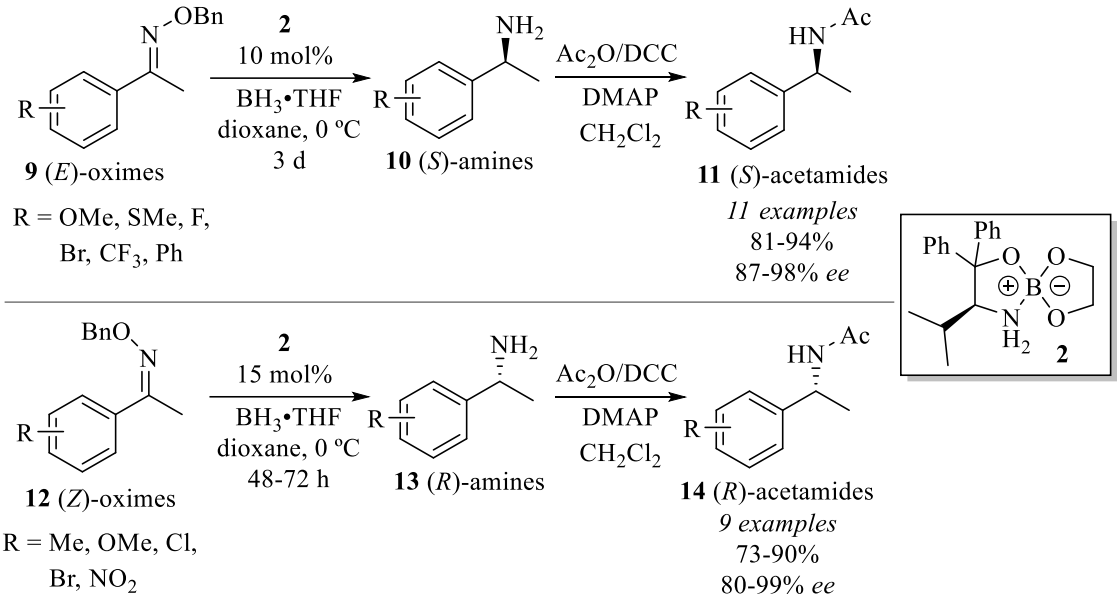
Scheme 1. Borane-mediated reduction of *O*-benzyloximes.

The synthesis of chiral amine **6** is the key step in the preparation of nicotine analogues, such as (*S*)-*N*-ethylnornicotine (**8**) (Scheme 2). Thus, the reduction of the *O*-benzyl ketoxime **5** with BH_3•THF in presence of 30 mol% of chiral catalyst **2**, followed by the treatment with acetic anhydride gave the target chiral amine in 95% yield and 95% *ee*. Deprotection of the hydroxyl group and reduction of the acetyl group gave compound **7** which underwent cyclization to afford (*S*)-*N*-ethylnornicotine (**8**). The asymmetric reduction of ketoximes was also used as a synthetic strategy for the synthesis of mexiletine analogues, used as antiarrhythmic and analgesic drugs [39].



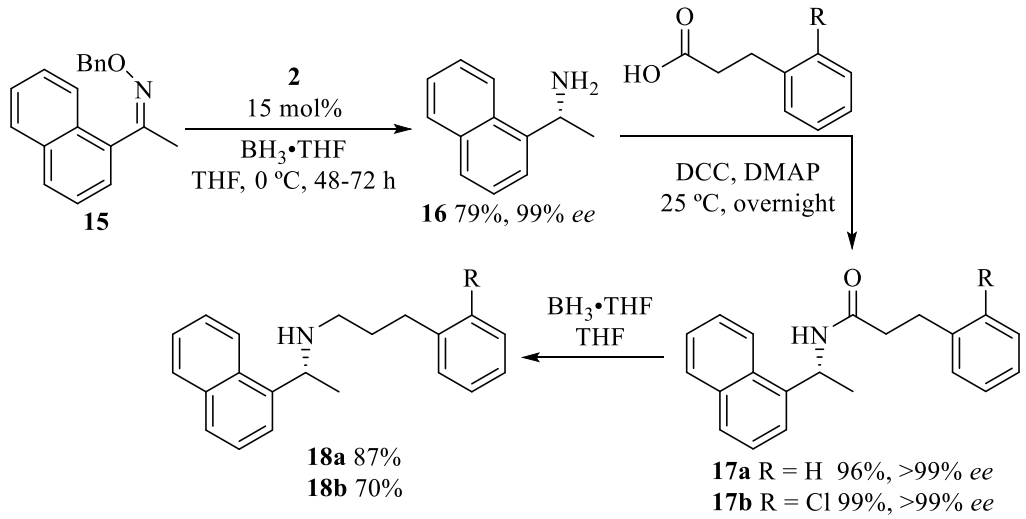
Scheme 2. Synthesis of (*S*)-*N*-ethylnornicotine, a nicotine analogue.

The enantioselectivity of the oxime reduction depends not only on the chiral catalyst but also on the oxime's *E*/*Z* configuration. Ortiz-Marciales and co-workers demonstrated that the borane-mediated reduction of single-isomeric (*E*)- or (*Z*)-*O*-benzyloximes, in presence of the spiroborate **2**, leads to highly enantiopure (1-aryl)- and (1-naphthyl)-1-ethylamines (Scheme 3) [40]. Thus, the asymmetric reduction of single-isomer (*E*)-*O*-benzyloximes ethers **9** with BH_3•THF in presence of 10 mol% of spiroborate ester catalyst **2** gave amines **10** with *S* configuration, which were isolated as the corresponding (*S*)-acetamides **11** in high yields (81-94%) and 87-98% enantiomeric excess. The enantiomeric purities of the (*S*)-amines were not affected by the electron-donating or electron-withdrawing character of the substituents in the aromatic ring. On the other hand, the borane-mediated reduction of the (*Z*)-*O*-benzyloximes **12** afforded (*R*)-amines **13**, which were converted into the corresponding (*R*)-acetamides **14** in good yields and enantiomeric purities up to 99% *ee* (Scheme 3). In this case, higher amount of the chiral catalyst **2** was required (15 mol%) to achieve good enantioselectivities. Additionally, the enantioselectivity was higher carrying out the reaction in tetrahydrofuran than in dioxane. Moreover, the 1-(4-nitrophenyl)ethanamine was obtained with lower enantioselectivity (80% *ee*) than other 1-(4-aryl)ethanamine derivatives [40].



Scheme 3. Asymmetric borane-mediated reduction of (*E*)- and (*Z*)-*O*-benzyloximes.

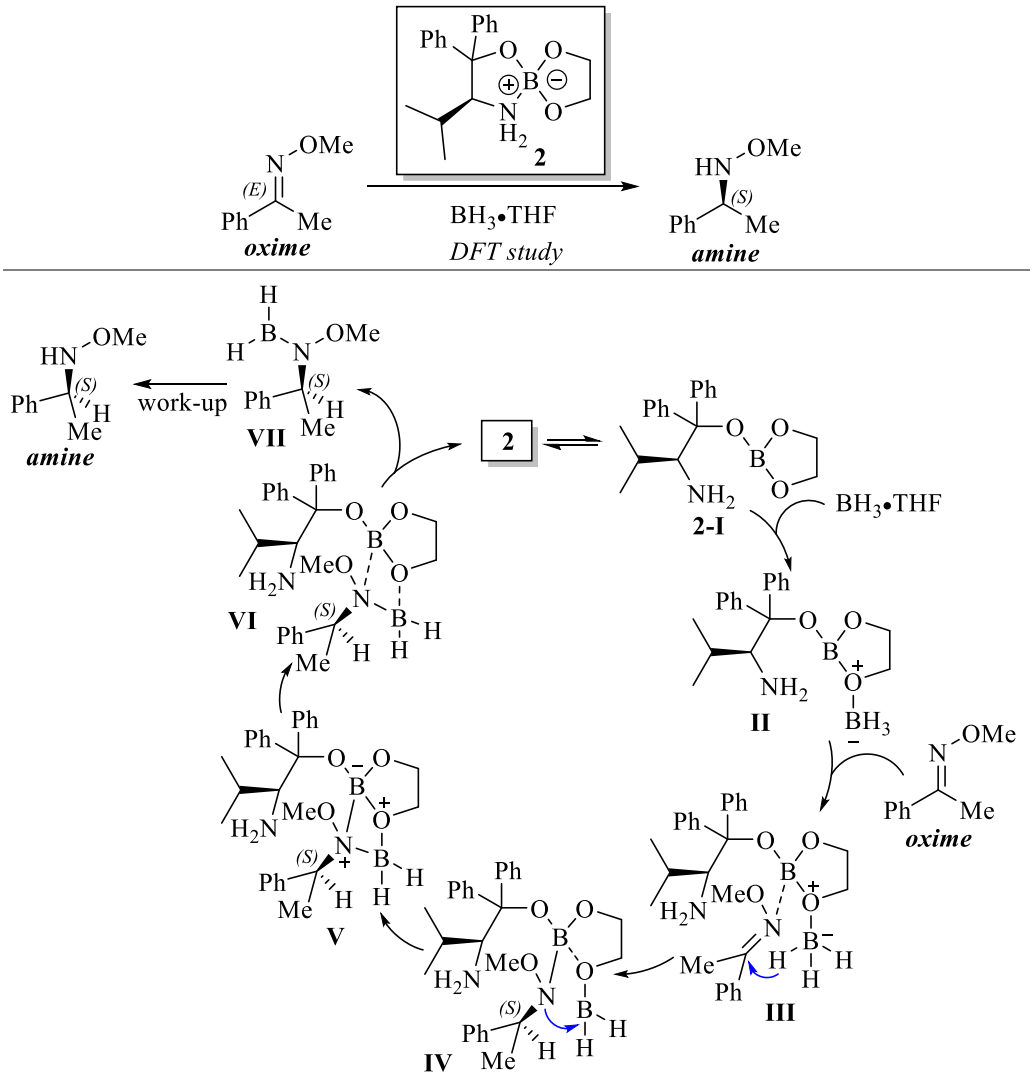
Calcimimetic analogues **18** were synthesized through the asymmetric reduction of the (*Z*)-1-naphthylethyl-(*O*)-benzyloxime (**15**) with BH_3•THF in presence of 15 mol% of the chiral catalyst **2** (Scheme 4). The (*R*)-(1-naphthalen-1-yl)ethylamine (**16**) was obtained with excellent enantiomeric purity (99% *ee*) and in good yield (79%). Ethylamine **16** reacted with 3-arylpropionic acids at room temperature to give amides **17**, without loss of chirality. Finally, the reduction of amide functionality of **17** into the corresponding secondary amine gave calcimimetic analogues **18** in modest to good yields [40].



Scheme 4. Synthesis of calcimimetic analogues via asymmetric reduction of oximes.

The mechanism of the asymmetric borane-mediated reduction of (*E*)-acetophenone *O*-methyloxime using chiral spiroborate ester **2** was proposed and supported by chemical calculations at the DFT level [41]. Two possible pathways were considered in this study

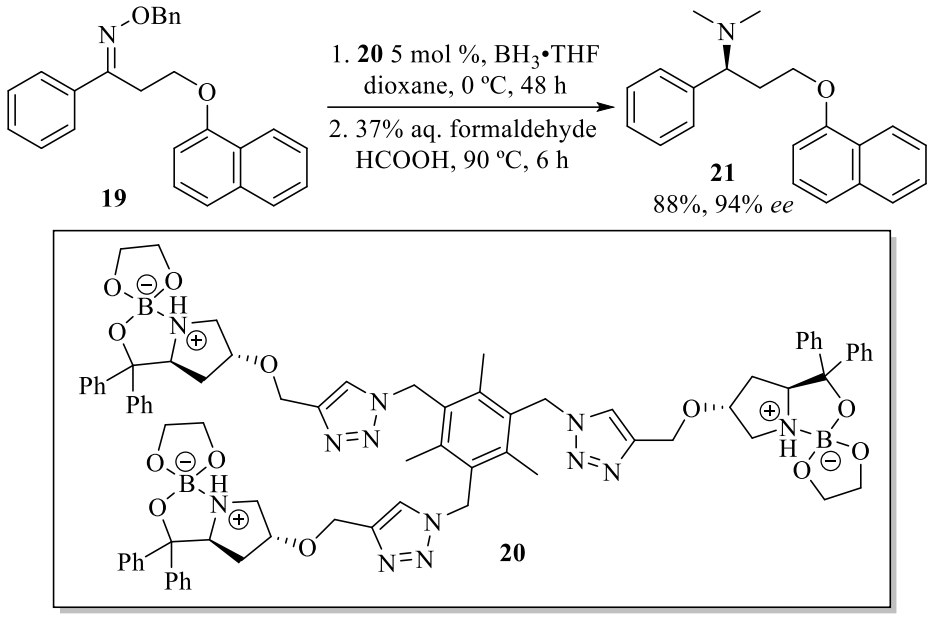
and the more energetically favourable is outlined in Scheme 5. Spiroborate ester **2** is in equilibrium with **2-I**, the effective catalyst, which by addition of BH_3•THF is converted into complex **II**. The first step of the reduction involves the interaction of the oxime's *N* lone pair with complex **II** to give intermediate **III**. At this stage, a hydride is transferred to the prochiral center of C=N double bond by the *Si* face, determining the observed stereoselectivity. Intermediate **IV** undergoes a [2+2] cycloaddition reaction to form the four-membered ring present in **V**. A sequential two bond cleavage releases the catalyst and **VII,** which gives the chiral amine after work-up [41].



Scheme 5. Mechanism of borane reduction of oximes catalyzed by spiroborate ester **2**.

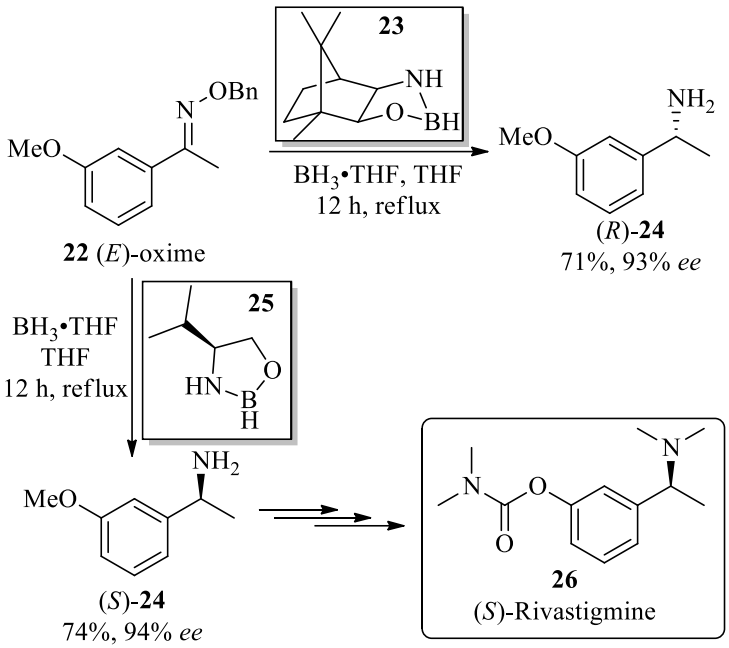
Inspired by the success of spiroborate esters in the asymmetric reduction of oximes, Anandhan and co-workers described the synthesis of triazole-based dendrimers supported spiroborate esters and explored their behaviour in the asymmetric reduction of (*E*)-*O*-benzyloximes. Thus, the borane-mediated reduction of *O*-benzyloxime **19** in the presence of chiral catalyst **20**, followed by the reaction with formaldehyde in formic acid gave the antidepressant drug (*S*)-dapoxetine (**21**) in good yield (88%) and high *ee* (94%) (Scheme

6). Chiral catalyst **20** could be recovered from the reaction media and reused without loss of activity [42].



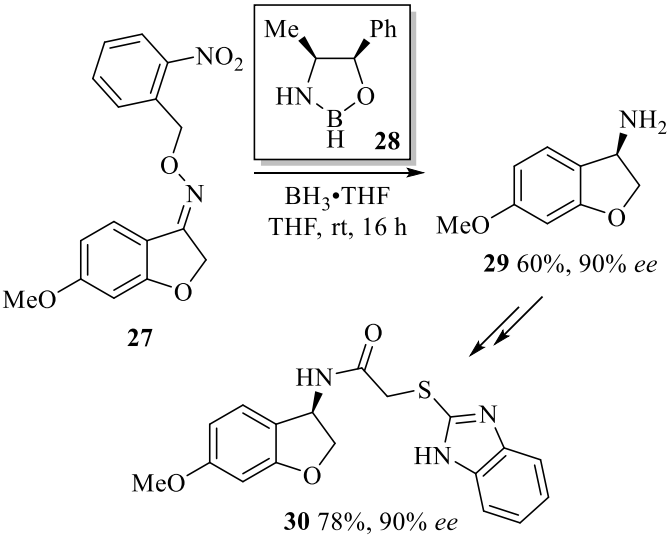
Scheme 6. Synthesis of (*S*)-dapoxetine.

Pakulski *et al.*, reported the asymmetric reduction of a series of alkyl-aryl *O*-benzyloximes in the presence of terpene oxazaborolidines (*e.g.* **23**) and oxazaborolidines derived from amino acids or amino alcohols (*e.g.* **25**) as chiral transfer agents (Scheme 7). The configuration of the amine obtained from (*E*)-benzyloximes was determined by the choice of the chiral transfer agent. Thus, reduction of the (*E*)-*O*-benzyloxime **22** with borane in presence of terpene oxazaborolidine **23** gave the corresponding amine **24** with *R* configuration in 93% enantiomeric excess and in good yield (71%). On the other hand, the reduction in the presence of oxazaborolidine **25**, prepared from (*S*)-valinol, gave amine **24** with *S* configuration in 74% yield and 94% *ee*. (*S*)-1-(3-Methoxyphenyl)ethanamine ((*S*)-**24**) is an important precursor of the synthesis of (*S*)-rivastigmine, a drug used in the treatment of Alzheimer's and Parkinson's disease [43].



Scheme 7. Borane reduction of (*E*)-1-(3-methoxyphenyl)ethanone *O*-benzyloxime mediated by different catalysts.

Łączkowski described the successful asymmetric reduction of the (*Z*)-6-methoxy-2,3-dihydrobenzofuran3-one-2-nitrobenzyloxime ether (**27**) into the corresponding chiral (*R*)-amine **29**, in 69% yield and 90% *ee*, using (1*R*,2*S*)-(-)-norephedrineoxazaborolidine **28** as chiral transfer agent (Scheme 8). Acetamide **30** was prepared from the *R*-amine **29** in good yield without loss of stereochemical integrity [44].



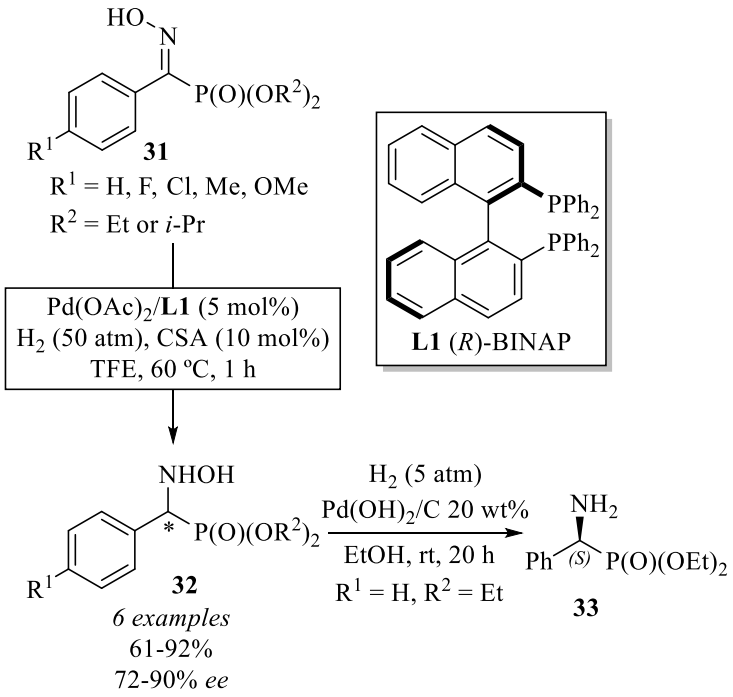
Scheme 8. Reduction of (*Z*)-6-methoxy-2,3-dihydrobenzofuran3-one-2-nitrobenzyloxime ether (**27**) with borane using (1*R*,2*S*)-(-)-norephedrine as catalyst.

2.2. Metal-catalyzed Hydrogenation/Hydrogenolysis

One of the most efficient methods to obtain single chiral molecules is the asymmetric hydrogenation of prochiral bonds using molecular hydrogen and chiral transition metal complexes [20, 45, 46]. The enantioselective hydrogenation/hydrogenolysis of oximes is no exception and several methodologies have been described.

2.2.1 Palladium-based Catalysis

In 2012, Goulioukina described the successful asymmetric hydrogenation of phosphonate oximes, in the presence of a palladium catalyst. The authors found an optimum hydrogenation system using $Pd(OAc)_2$/**L1** (5 mol%) as catalyst and (1*S*)-(+)-10-camphor-sulfonic acid (10 mol%) as activator, in trifluoroethanol. The enantioselective reduction of (*E*)-oximes **31** using the optimum conditions led to the isolation of *N*-hydroxy-α-amino phosphonates **32** in good yields and enantioselectivities up to 90% (Scheme 9). Furthermore, the transformations of one *N*-hydroxy-α-amino phosphonate into the corresponding amine **33**, showed that the major enantiomers made available by the reported methodology had *S* configuration (*e.g.* **32**) [47].

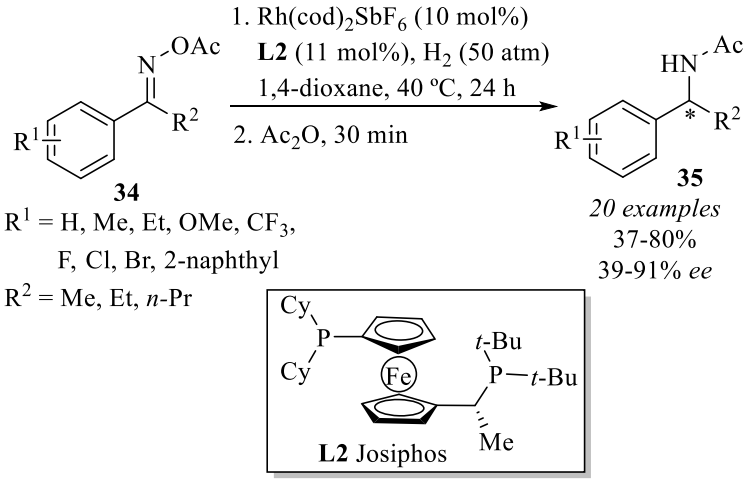


Scheme 9. Pd-catalyzed asymmetric hydrogenation/hydrogenolysis of phosphonate oximes.

2.2.2. Rhodium-based Catalysis

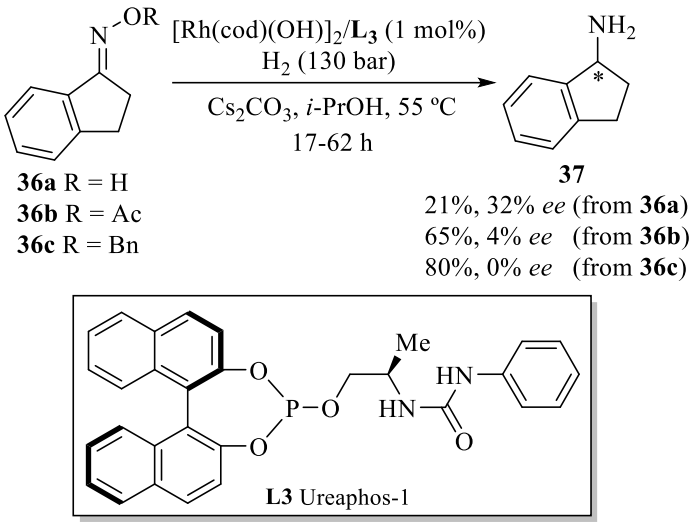
Huang *et al.*, described for the first time the Rh-catalyzed asymmetric hydrogenation/hydrogenolysis of a series of *O*-acetyloximes using $Rh(cod)_2SbF_6$ as the Rh source and **L2** Josiphos as the chiral ligand (Scheme 10) [48]. The reduction of *O*-acetyloximes **34** was carried out using 10 mol% of $Rh(cod)_2SbF_6$ in the presence of **L2** (11 mol%) in 1,4-dioxane giving chiral amines, which were converted, without loss of

chirality, into acetamides **35**. These reaction conditions were generally suitable for the majority of the *O*-acetyloximes with enantioselectivities up to 91% *ee*. However, the efficiency and enantioselectivity of the reduction reactions was strongly influenced by the position and nature of substituents at the oxime's aryl group. In fact, a methoxy group at *para*-position and substituents at *ortho*-position of the aromatic ring led to a drastic decrease in yield (37-52% yield) and enantioselectivity (39-47% *ee*). The loss of enantioselectivity was also observed for the asymmetric reduction of a *E*/*Z* mixture of oximes and when R^2 was Et or *n*-Pr. Substituents at *meta*-position were well tolerated without significant changes in the enantiopurity of the formed amines [48].



Scheme 10. Rh-catalyzed enantioselective hydrogenolysis of *O*-acetyloximes.

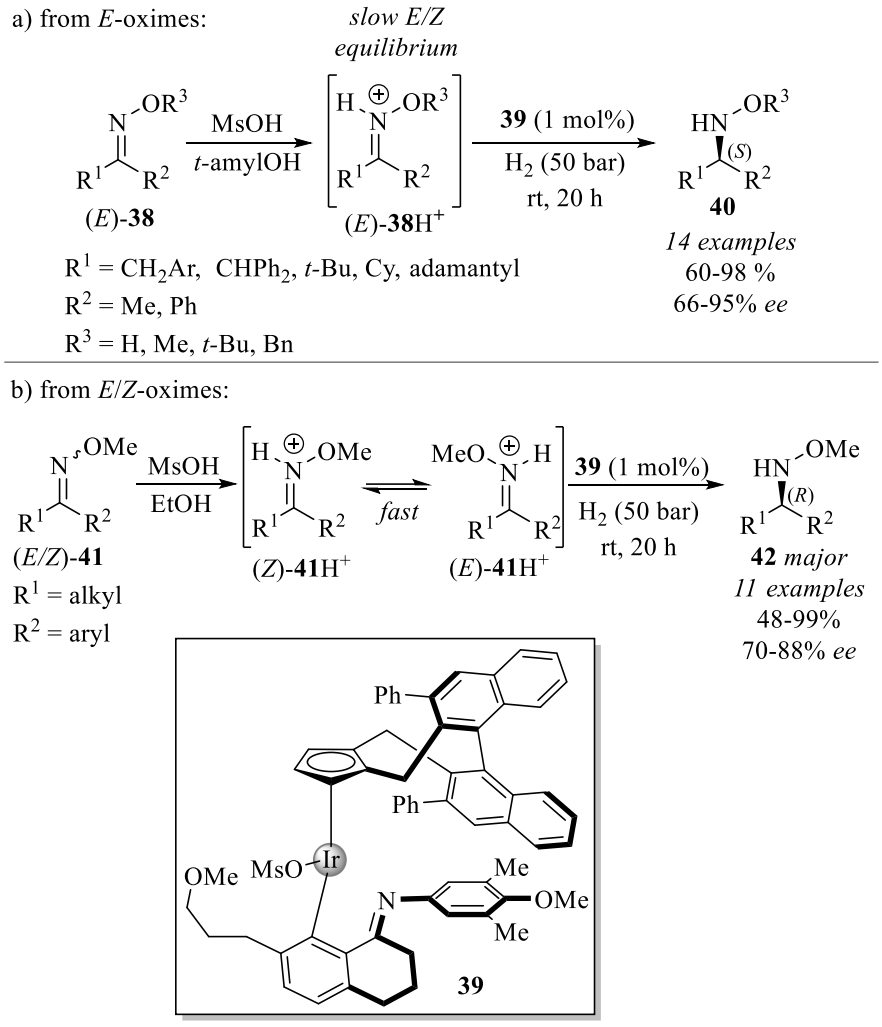
Maj and co-workers described the Rh-catalyzed enantioselective hydrogenolysis of 2,3-dihydro-1*H*-inden-1-one oximes **36** into the corresponding amine **37**, a synthetic precursor of Rasagiline, a drug used in the treatment of early symptoms of Parkinson's disease [49]. The optimized asymmetric hydrogenolysis of (*E*)-2,3-dihydro-1*H*-indenone oxime (**36a**) using the $[Rh(cod)OH]_2$/**L3** (1 mol%) as the catalytic system, led to the desired amine **37** in low yield (21%) and selectivity (32% *ee*). Amine **37** was obtained in high yields, 65% and 80%, when the reduction conditions were applied to the acetyl (**36b**) or benzyl (**36c**) oxime derivatives, respectively, however, racemic mixtures were obtained (Scheme 11).



Scheme 11. Rh-catalyzed enantioselective hydrogenolysis of cyclic indanone oximes.

2.2.3. Iridium-based Catalysis

The selective synthesis of chiral hydroxylamines via asymmetric reduction of oximes is a challenge, since the cleavage of the weak nitrogen-oxygen bond must be avoided. Recently, Cramer and co-workers described the acid-mediated asymmetric hydrogenation of oximes to the corresponding chiral hydroxylamines using iridium complex **39** as catalyst (Scheme 12) [50, 51]. The methodology was first applied in the reduction of (*E*)-oximes **38** giving chiral hydroxylamines **40** with *S* configuration in good yields (60-98%) and 66% to 95% *ee* (Scheme 29a). Initially, the nitrogen of the oxime group underwent protonation by methanesulfonic acid (MsOH) giving intermediate (*E*)-**38**H^+, which exists in a slow equilibrium with its *Z* form. Hydrogenation of this intermediate in presence of iridium catalyst **39** afforded the final hydroxylamines **40**. When (*Z*)-oximes were used instead of (*E*)-oximes, hydroxylamines with the *R* configuration were obtained. The scope of the reaction using *E*/*Z* mixtures of oximes under the same reaction conditions was also evaluated (Scheme 29b). Thus, the *N*-protonation of the *E*/*Z*-oximes **41** gave the intermediates (*Z*)-**41**H^+ and (*E*)-**41**H^+, which are in a fast equilibrium. The subsequent hydrogenation in presence of the catalyst **39** occurs faster with intermediate (*Z*)-**41**H^+ than with its isomer (*E*)-**41**H^+ leading to hydroxylamines **42** mostly with *R* configuration.



Scheme 12. Ir-catalyzed enantioselective hydrogenation of oximes.

3. DIASTEREOSELECTIVE REDUCTION OF OXIMES

The oxime reduction of compounds containing another chiral center is an important research topic since this process gives access to diastereoisomeric pure amines. In 1987, Chiba *et al.* reported the synthesis of 3,4-*cis*-azetidinones through the reduction of β-hydroxyiminoesteres with sodium cyanoborohydride in acidic conditions, followed by hydrogenation with Raney-Ni [52]. The process was highly stereoselective but racemic mixtures of *cis* isomers were obtained. Since then, a wide range of methods have been developed to carry out the diastereoselective reduction of oximes employing, among others, metal-catalyzed hydrogenation/hydrogenolysis, the use of hydride donor reagents and electrochemical reductions, with satisfying results regarding both reaction yields and diastereoisomeric ratios.

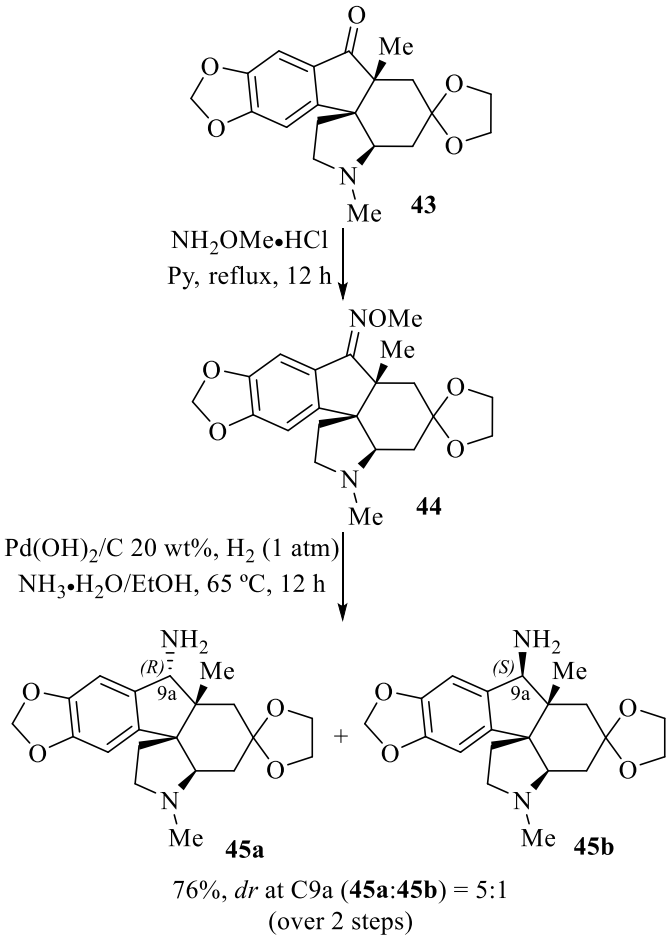
3.1. Metal-catalyzed Hydrogenation/Hydrogenolysis

Metal-based catalysts often ensure reductions to occur with high stereoselectivity, generally providing the desired isomers with excellent diastereoisomeric ratios and in moderate to excellent yields, being widely used in the preparation of optically active primary amines from oximes [53]. In the last decade, several groups reported the diastereoselective reduction of oximes taking advantage of palladium-, zinc-, platinum- and iron-based catalysis.

3.1.1. Palladium-based Catalysis

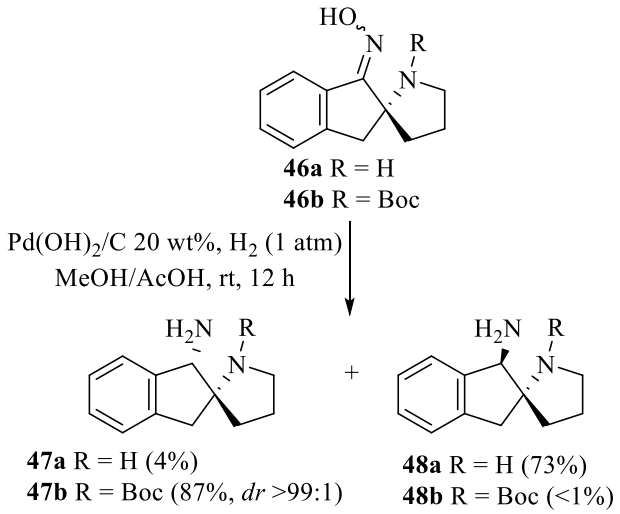
Palladium-based catalytic hydrogenations have been the most widely used methodology to synthesize chiral amines from oximes, accounting for over 60% of the reported oxime metal-based reductions, in the last decade.

The total synthesis of Gracilamine, a pentacyclic alkaloid extracted from the *Amaryllidaceae* plants, was achieved by a multi-step approach [54]. One of the steps involves the synthesis and reduction of *O*-methyloxime **44** (Scheme 13). Primary amines **45** were obtained in 76% yield (over 2 steps) and diastereoselective 5:1 ratio, through the hydrogenolysis of oxime **44**, in the presence of $Pd(OH)_2/C$ 20 wt% (Pearlman's catalyst) and ammonium hydroxide in ethanol. The two diastereoisomers could be separated by column chromatography allowing the isolation of the isomer with *R* configuration at C9a in pure form in 64% yield [54].



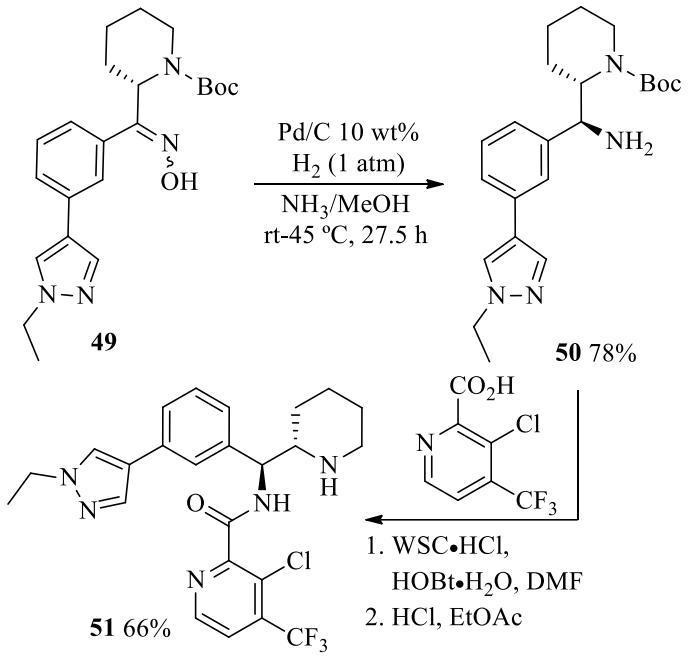
Scheme 13. Synthesis and diastereoisomeric reduction of *O*-methyloxime **44**.

In an effort to prepare several diamine ligands, suitable for asymmetric Henry reactions, Ćwiek *et al.* explored the asymmetric reduction of oximes. Oximes **46**, having a spiroindane-2,2'-pyrrolidine backbone, were obtained from the reaction of the corresponding aminoketones with hydroxylamine and reduced using the Pearlman's catalyst ($Pd(OH)_2$/C 20 wt%) and acetic acid in methanol under hydrogen atmosphere (Scheme 14). Firstly, the reduction of oxime **46a** was carried out giving a mixture of diamines **47a** and **48a**, with *trans*-isomer **48a** as the major isolated product (73% yield) [55]. In order to obtain *cis*-diamines, the reduction of oxime **46b**, in which the pyrrolidine nitrogen was protected by a Boc group, was carried out. This amine protection favours the hydrogen addition through the *Re*-face, by shielding the *Si*-face, as previously demonstrated by Crooks [56]. This strategy was successful allowing the isolation of *cis*-isomer **47b** in 87% yield and *dr* >99:1 [55].



Scheme 14. Diastereoselective reduction of spiroindane-2,2'-pyrrolidine oximes.

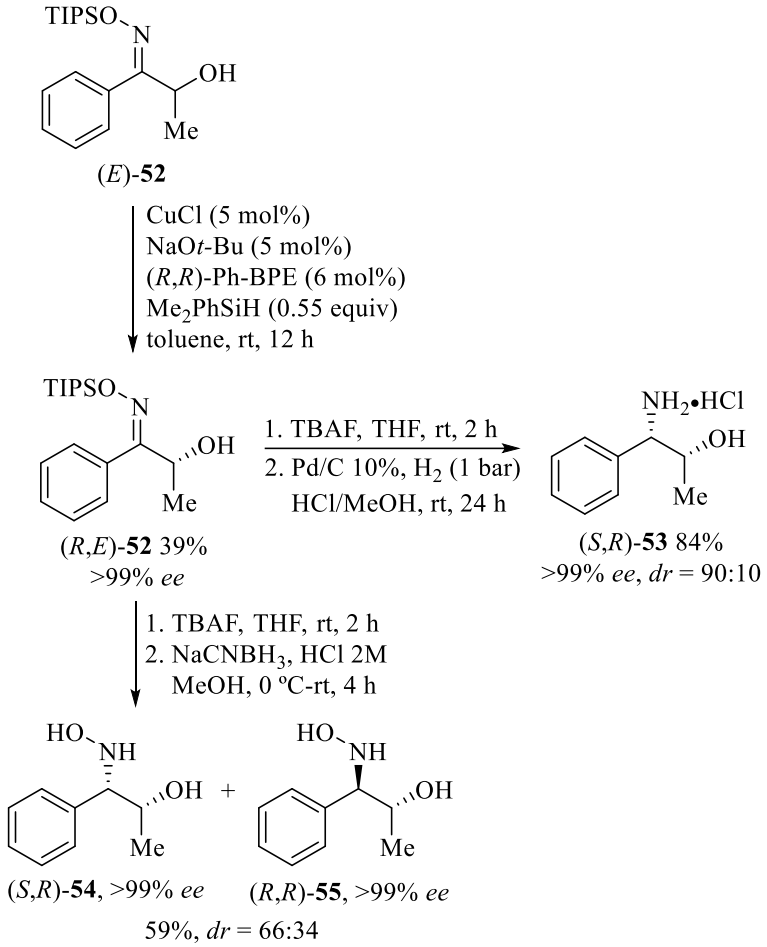
The palladium-catalyzed diastereoselective hydrogenolysis of oxime **49** was one of the methods used by Yamamoto *et al.*, in order to improve the synthesis of compound **51**, which is a potent glycine transporter 1 inhibitor (Scheme 15). Thus, the reduction of oxime **49** was achieved using Pd/C (10 wt%) as catalyst and ammonia in methanol under hydrogen atmosphere, affording chiral amine **50** in good yield (78%) without racemization [57].



Scheme 15. Diastereoisomeric catalytic hydrogenolysis of a chiral piperidine-derived oxime.

Oestreich and co-workers developed a highly enantioselective protocol for the kinetic resolution of α-hydroxy-substituted oxime ethers by dehydrogenative Si-O coupling under copper catalysis, using a combination of simple hydrosilanes (*e.g.* Me_2PhSiH) and (*R,R*)-Ph-BPE as ligand. This strategy gave access to enantioenriched α-hydroxyoxime ethers (*e.g.* (*R,E*)-**52**) which are important scaffolds for the synthesis of other valuable

compounds (Scheme 16). The Pd/C-catalyzed hydrogenolysis of (*R*,*E*)-**52** in acidic methanol allowed the preparation of β-amino alcohol (*S*,*R*)-**53** in good diastereoselectivity (90:10) while maintaining the stereochemical integrity of the oxime's α-carbon. On the other hand, deprotection of the oxime group followed by reduction with sodium cyanoborohydride under acidic conditions gave β-hydroxy-hydroxylamines **54** and **55** with poor diastereoselectivity (66:34) [58].

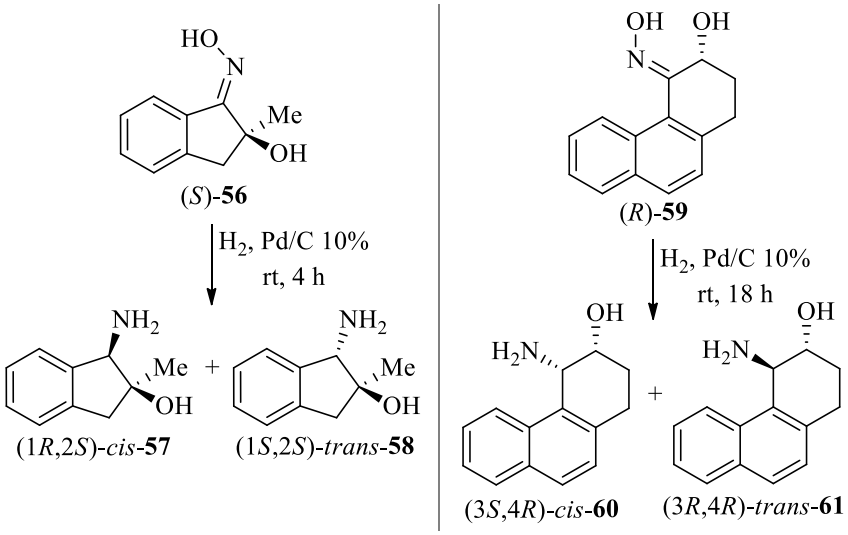


Scheme 16. Reduction of a α-hydroxy-substituted oxime ether under different reaction conditions.

The synthesis of two sterically hindered amino alcohols was explored by Owsianik and co-workers. Chiral 1,2-amino alcohols **57-58** and **60-61**, were synthesized through the Pd/C-catalyzed hydrogenolysis of oximes (*S*)-*anti*-**56** and (*R*)-**59**, respectively (Table 1) [59]. In this study, it was observed that using methanol as solvent, oxime (*S*)-*anti*-**56** was converted into the corresponding amines in 73% yield with 75:25 diastereoselective ratio (entry 1). However, with the addition of hydrobromidric acid to the reaction medium the yield was improved to 85% and the mixture was enriched in the *cis*-**57** isomer (*dr* = 34:66) (entry 2). Nevertheless, the best diastereoselective ratio was achieved when a mixture of methanol/water (10:1) was used as solvent giving the target 1,2-amino alcohols in 98% yield (*dr* = 3:97) (entry 3). The same study was performed for the transformation of oxime (*R*)-**59** into chiral amines *cis*-**60** and *trans*-**61**. In this case, the addition of HBr to the reaction medium improved the stereoselectivity for the *cis*-**60**

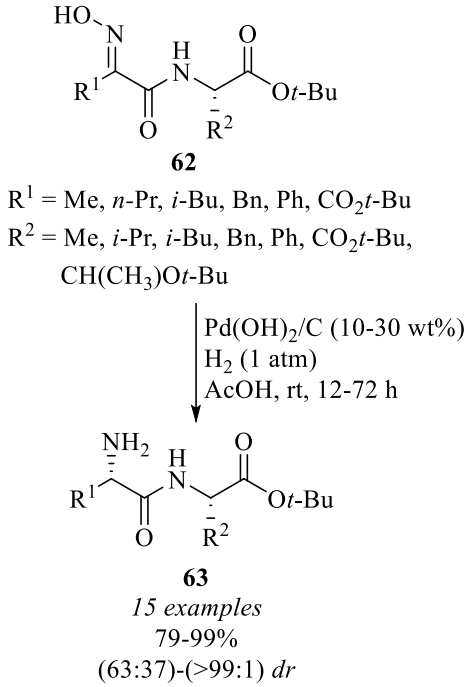
isomer 60:40 (entries 1 and 2), while using MeOH/H_2O (10:1) as solvent (entry 3), a 50:50 diastereoselective ratio was obtained [59].

Table 1. Studies on the diastereoselective reduction of α-hydroxy-substituted oximes.



entry	solvent	**57+58** (%)	*dr* (*cis:trans*)	**60+61** (%)	*dr* (*cis:trans*)
1	MeOH	73	75:25	72	50:50
2	MeOH, HBr	85	34:66	66	60:40
3	MeOH/H_2O (10:1), HBr	98	3:97	68	50:50

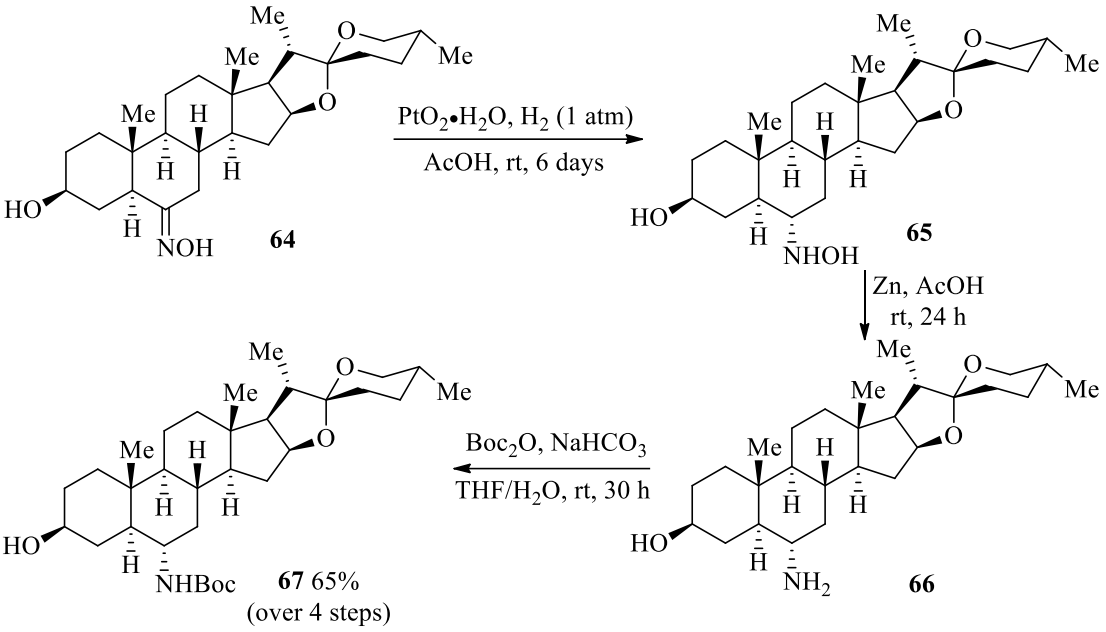
A synthetic methodology for the synthesis of di- and tripeptides with high diastereoselectivities via palladium-catalyzed hydrogenation of oxime esters was described by Muramatsu and co-workers [60]. The hydrogenolysis of oxime esters **62** was performed in presence of Pearlman's catalyst ($Pd(OH_2)$/C) in acetic acid at room temperature, giving the di- and tripeptides **63** with *S* configuration at the new chiral center (Scheme 17). These reaction conditions were generally well tolerated for a wide range of functional groups, including sterically hindered R^1 groups, giving good yields (79-99%) and diastereoselectivities ranging from 63:37 *dr* for R^1 = Bn to >99:1 *dr* for R^1 = *n*-Pr. Moreover, it was possible to obtain highly pure diastereoisomers by recrystallization, chiral derivatization or silica-gel column chromatography, even when the diastereoselectivity was not high [60].



Scheme 17. Diastereoselective hydrogenolysis of dipeptide precursors.

3.1.2. Platinum-based Catalysis

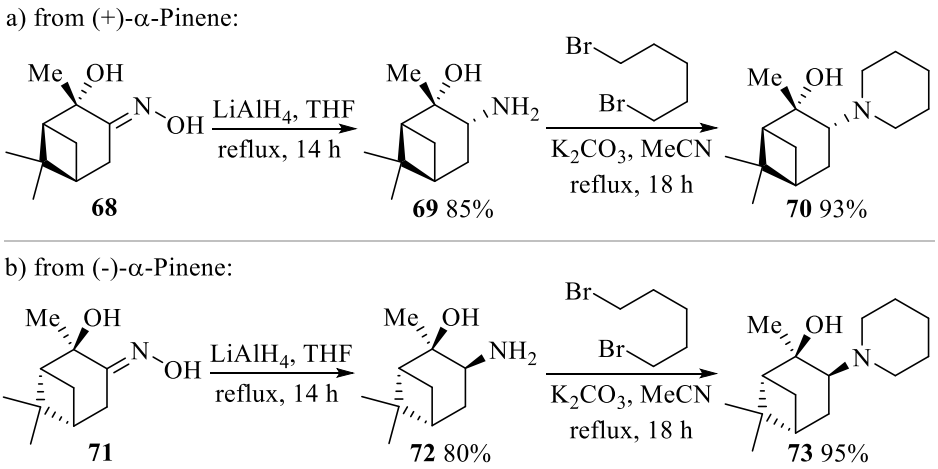
Steroid **67**, containing a *N*-Boc protected amino group at 6-position of the steroid structure, was used in the synthesis of macrocyclic peptide-steroid conjugates. The synthetic strategy to obtain steroid **67** was the platinum-catalyzed hydrogenation of the laxogenin oxime **64**, prepared by oximation of the natural sapogenin laxogenin. Thus, hydroxylamine steroid **65** was obtained stereoselectively using Adam's catalyst (PtO_2) in acetic acid, which was further reduced with Zn/AcOH to amine **66**. *N*-Boc protection of the amino group gave steroid **67** as single diastereoisomer in 65% overall yield (Scheme 18) [61].



Scheme 18. Asymmetric reduction of laxogenin oxime.

3.2. Hydride Donor Reactions

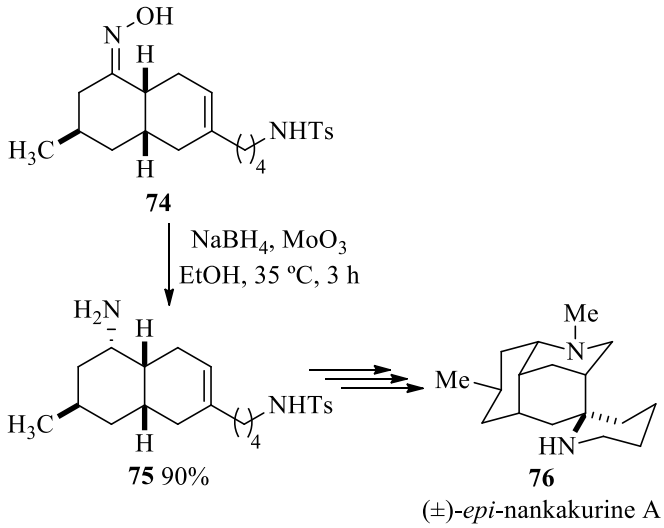
The synthesis of chiral ligands to be used in the enantioselective addition of organozinc compounds to carbonyl compounds is one topic of great importance in asymmetric catalysis. Marques and co-workers developed the synthesis of chiral ligands derived from (+)- and (-)-α-pinene, in which the diastereoselective reduction of oximes **68** and **71** is the crucial step (Scheme 19). Thus, chiral amines **69** and **72** were prepared from the corresponding oximes, in high yields (85% and 80%, respectively) as single diastereoisomers, by the reduction with lithium aluminium hydride in refluxing THF. Chiral ligands **70** and **73** with opposite configurations, prepared from the corresponding chiral amines, were used in the asymmetric addition of diethylzinc to aldehydes, providing secondary alcohols with *R* and *S* configurations, respectively, in good enantioselectivity [62].



Scheme 19. Diastereoselective reduction of oximes derived from (+)- and (-)-α-pinene.

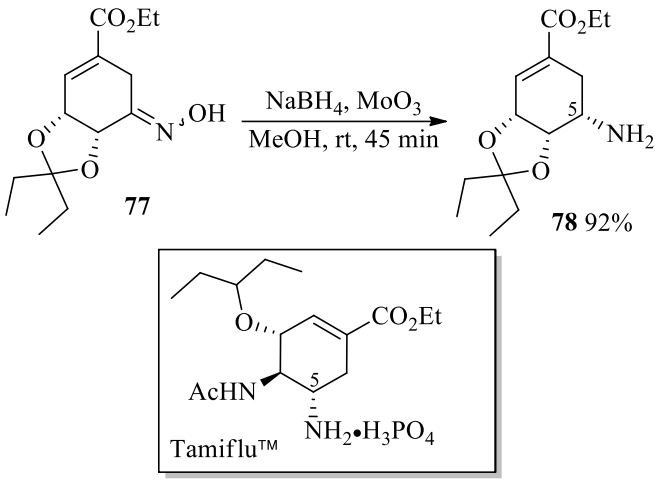
Sodium borohydride is a mild reducing agent making the combination of sodium borohydride with inorganic compounds such as transition metal complexes, iodine or sulfuric acid, sometimes required to reduce certain functional groups. This strategy has been used to reduce α-amino alcohols [63, 64], alkenes [65, 66], nitriles [67], nitro compounds [68, 69], and others [70]. The reduction of 1-hydroxyiminophosphanates was also achieved using sodium borohydride in presence of molybdenum oxide or nickel chloride, giving amino phosphonic acids [71]. In recent years, the diastereoselective reduction of oximes with sodium borohydride metal-catalyzed has been explored by many researchers.

Overman and co-workers described the first total synthesis of nankakurines A and B and (±)-*epi*-nankakurine A, three natural *Lycopidium* alkaloids, with potential neuroprotective properties [72]. The reduction of the *cis*-oxime **74** with $NaBH_4$ catalyzed by MoO_3 in refluxing ethanol gave exclusively the *cis*-octahydronaphthalene amine **75** in good yield (90%). This amine is an important intermediate in the synthesis of (±)-*epi*-nankakurine A (**76**) (Scheme 20).



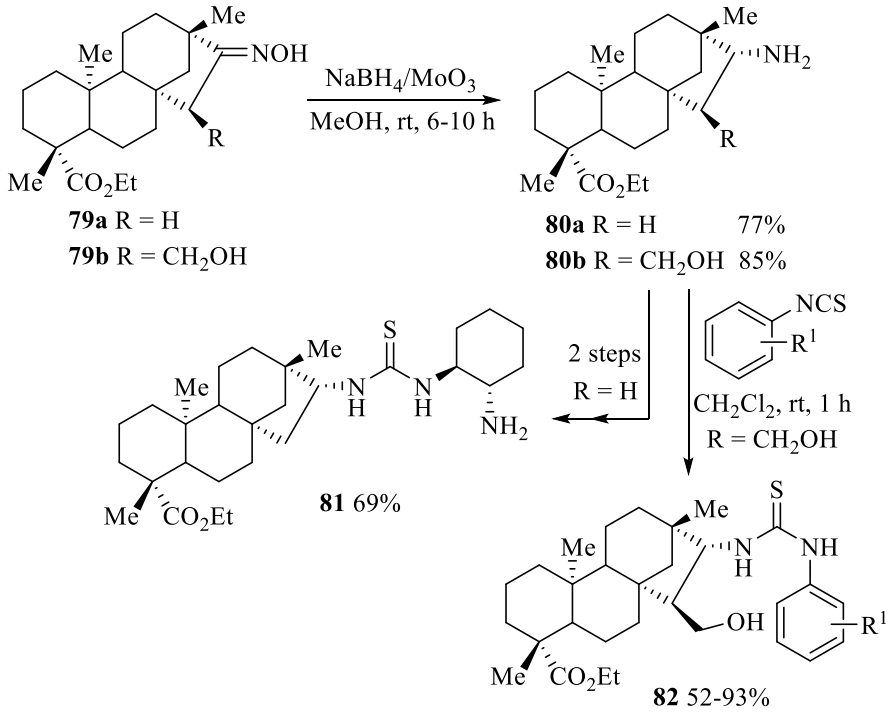
Scheme 20. Diastereoselective reduction of a *cis*-octahydronaphthalene oxime derivative.

This methodology was also used to obtain a key synthetic precursor of Tamiflu™, a neuraminidase inhibitor used in the treatment of infections caused by influenza and H5N1 viruses [73, 74]. The 5α-amino shikimic acid ester **78** was obtained as single diastereoisomer in high yield (92%) by reduction of oxime **77** with $NaBH_4$ in the presence of MoO_3, in methanol at room temperature (Scheme 21). It is noteworthy that the selective creation of the new chiral center (C5) was crucial to ensure the diastereomeric purity of Tamiflu™. Rao and co-workers used the same strategy to synthesize valiolamine analogues, which are aminocyclitols with α-*D*-glucosidase inhibitory activity, from *D*-mannose [75].



Scheme 21. Synthesis of a key synthetic precursor of Tamiflu™.

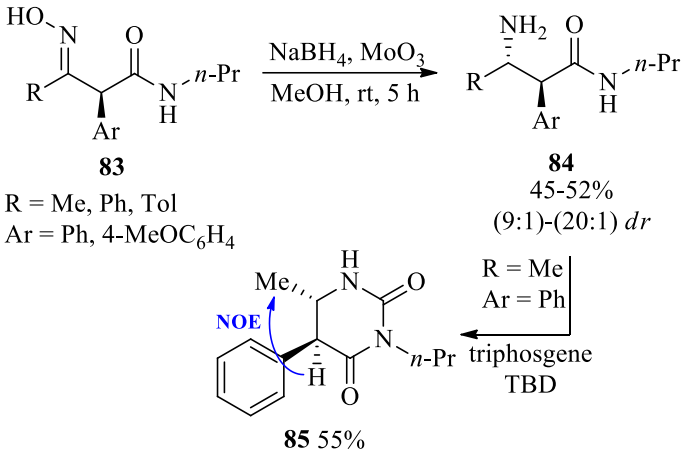
Sodium borohydride diastereoselective molybdenum-catalyzed reductions were also applied in the synthesis of multifunctional thioureas from the natural compound stevioside [76-78]. Oximes **79** were reduced by $NaBH_4/MoO_3$ in methanol at room temperature, to give chiral amines **80** diastereoselectively in yield ranging from 77% to 85% (Scheme 22). Amine **80a** was converted into thiourea-amine **81**, which is an effective catalyst of the asymmetric Michael addition of isobutyraldehyde to maleimides [76, 77]. On the other hand, amino alcohol **80b** reacted with isothiocyanates to give thiourea derivatives **82**, which exhibit notable anticancer activity [78].



Scheme 22. Synthesis of chiral multifunctional thioureas.

More recently, Vishe and Johnston used the same methodology for the diastereoselective synthesis of several *anti*-$\beta^{2,3}$-amino amide derivatives [79]. Thus, the

reduction of β-oximino-amides **83** with $NaBH_4/MoO_3$, gave *anti*-$\beta^{2,3}$-amino amides **84** diastereoselectively in moderate yields (45-52%). *Anti*-$\beta^{2,3}$-amino amide **84** (R = Me, Ar = Ph) was converted into the corresponding dihydropyrimidinone **85**, which stereochemistry assignment was confirmed by NOE experiments (Scheme 23).



83

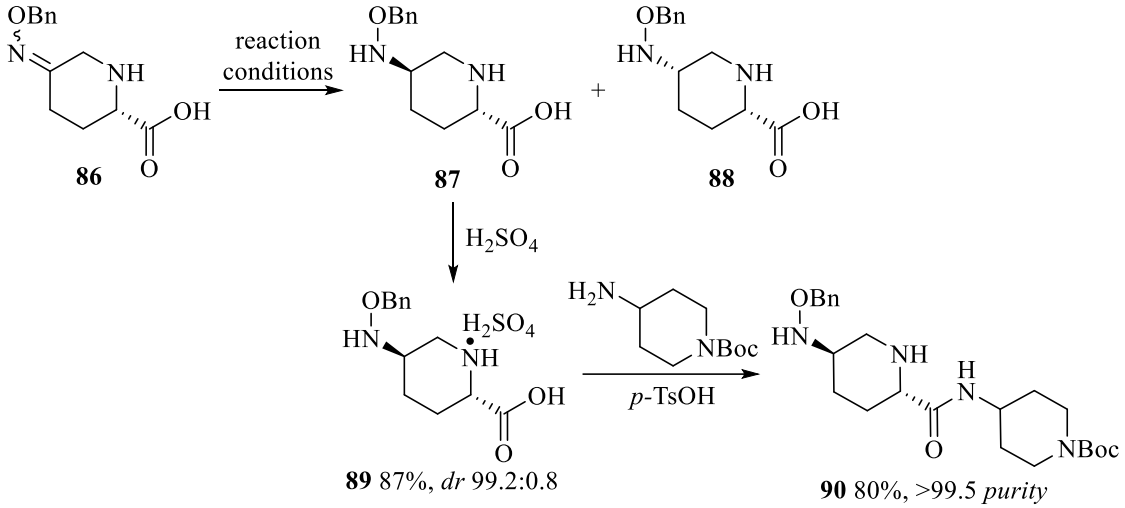
84 45-52% (9:1)-(20:1) *dr*

85 55%

Scheme 23. Synthesis of *anti*-$\beta^{2,3}$-amino amide derivatives.

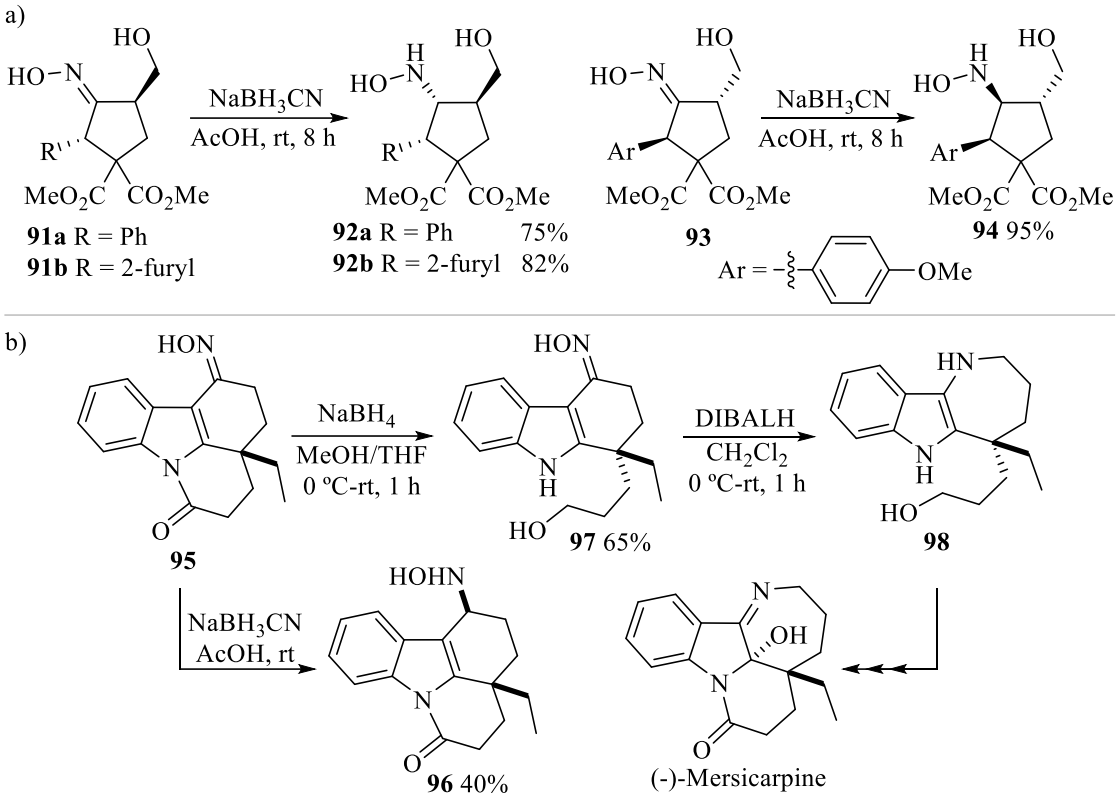
Recently, Chung *et al.* described the synthesis of chiral piperidine **90**, an important intermediate in the synthesis of the β-lactamase inhibitor relebactam, through the diastereoselective reduction of pipecolic acid oxime ether **86** (Table 2) [80]. The reduction of oxime **86** was achieved in excellent diastereoselectivity (100:1) and high yield (92%) using Rh-catalyzed hydrogenation (entry 1). However, the high cost of Rh-catalyst and the high pressure employed (500 psi H_2), led to the search of an alternative approach. Thus, *O*-benzyloxime **86** was reduced by sodium triformyloxyborohydride under acidic conditions affording hydroxylamines **87**/**88** in high yield, but with low diastereoselectivity (83:17) (entry 2) [81]. Nevertheless, they found that the hydroxylamine **87** could be obtained in high yield (98%) and high diastereoselectivity (96:4) by $NaBH_4/FeCl_3$ reduction of oxime **86** (entry 3). During the efforts to carry out the reduction reaction scale-up, better results were obtained when the $NaBH_4$ was added to the reaction media through a triglyme solution. Moreover, the presence of water improved the reaction rate and the diastereoselective ratio. Hydroxylamines **87**/**88** precipitated directly from reaction media by the addition of H_2SO_4 leading to an enhancement of the diastereoselectivity ratio (99.2:0.8). Mechanistic studies were performed to rationalize the high diastereoselectivity [80].

Table 2. Diastereoselective reduction of *O*-benzyloximes with $NaBH_4/FeCl_3$ complex.



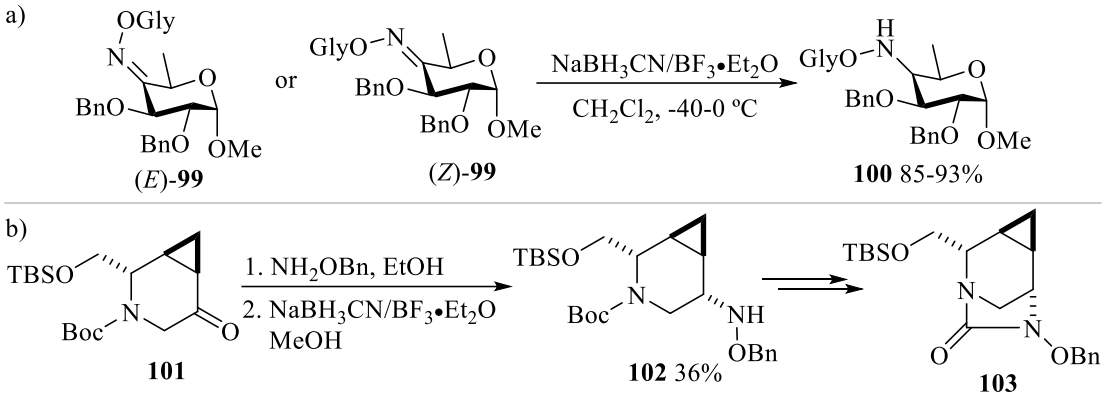
Entry	reaction conditions	yield (%)	*dr* **87**/**88**
1	$(nbd)_2RhBF_4$/dcpf (0.7 mol%), HBF_4 (0.6 mol%) H_2 (500 psi), 10% H_2O/EtOH	92	100:1
2	$NaBH(OCHO)_3$, H_2SO_4, MeCN	94	83:17
3	$NaBH_4$/triglyme, $FeCl_3 \bullet 6H_2O$, EtOH, -30 ºC	98	96:4

Hydroxylamines were also obtained from the reduction of the corresponding oximes using sodium cyanoborohydride as reducing agent. This strategy was used by Rodriguez and co-workers in the diastereoselective synthesis of functionalized cyclopentanes [82]. Thus, the reduction of cyclopentanone (*E*)-oximes **91** was performed with $NaBH_3CN$ in acetic acid at room temperature giving hydroxylamines **92** as single diastereoisomers in good yields (75-82%). Starting from (*E*)-oxime **93**, with the opposite configuration of **91**, under the same reaction conditions, hydroxylamine **94** was obtained diastereoselectively in 95% yield and with the opposite configuration of hydroxylamines **92** (Scheme 24a). This methodology was also applied by Iwama *et al.* in the diastereoselective reduction of tetracyclic oximes (*e.g.* **95**) providing the corresponding hydroxylamines (*e.g.* **96**) as single stereoisomers in moderate yield (Scheme 24b) [83]. Furthermore, it was demonstrated that these cyclic amines were formed as intermediates in the reductive ring-expansion reaction promoted by DIBALH to yield azepinoindoles (*e.g.* **98**), the key precursor of (-)-mersicarpine.



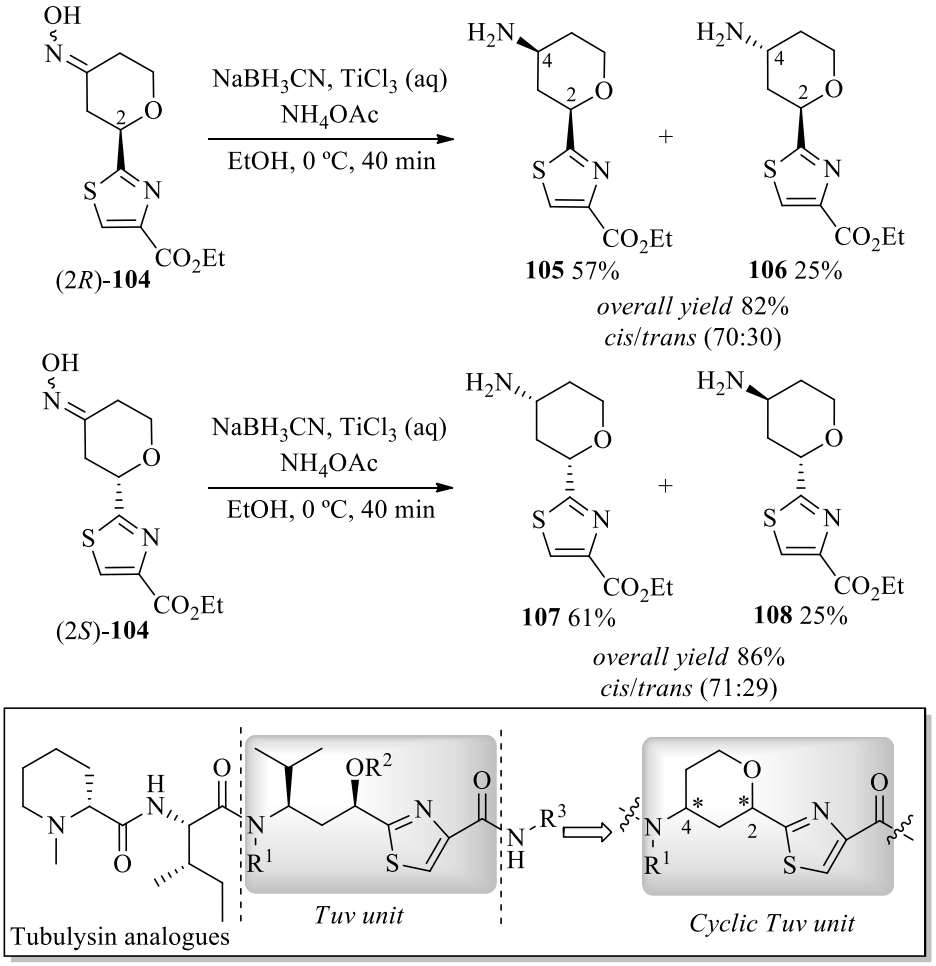
Scheme 24. Diastereoselective $NaBH_3CN$ reduction: a) of cyclopentanone (*E*)-oximes; b) of tetracyclic oximes.

Yu and co-workers used $NaBH_3CN/BF_3{\bullet}Et_2O$ for the reduction of disaccharides containing a methyl 2,3-di-*O*-benzyl-6-deoxy-α-*D*-gluco/galactopyranoside 4-oxime moiety, under mild reduction conditions to avoid the cleavage of the N-O bond (Scheme 25a). In fact, the reduction of oxime disaccharides (*e.g.* **99**) led to N-O linked galactose derivatives (*e.g.* **100**) diastereoselectively and in high yields (85-93%). In the majority of the reductions, the stereochemistry of the product was not dependent on the configuration of the oxime. The same diastereoisomer was obtained starting from the *E* or *Z* isomers separately or when they were used as an isomeric mixture [84]. The same reductive conditions were used in the multi-step synthesis towards tricyclic urea **103** (Scheme 25b) [85]. Thus, ketone **101** was converted *in situ* to the corresponding *O*-benzyloxime, followed by reduction with a large excess of $NaBH_3CN$ and $BF_3{\bullet}Et_2O$, to give selectively hydroxylamine **102** in 36% yield. Contrary to the expectations, the stereoselectivity of the reduction reaction was not affected by the presence of the cyclopropane ring and, instead, the large TBS ether group induced the axial attack of the hydride on the oxime group giving rise to the formation of the undesired *cis* isomer of urea **103**.



Scheme 25. Stereoselective $NaBH_3CN/BF_3•Et_2O$ reduction: a) of oxime disaccharides; b) of cyclic enones.

Tubulysin are natural linear tetrapeptides with potent antimitotic activity and its structural and biological properties led to the development of tubulysin analogues. Ryu and co-workers developed the synthesis of a wide range of cyclic analogues using four stereoisomeric cyclic tubuvaline (Tuv) units. Aminotetrahydropyran derivatives **105-108** were obtained through the diastereoselective reduction of the corresponding tetrahydropyranone oximes **104**, two oximes with opposite configuration at the C2 stereocenter (Scheme 26). Metal-catalyzed hydrogenolysis or reduction using the $NaBH_4/NiCl_2$ complex gave the target products in low yield and diastereoselectivity or even no products. The reduction of tetrahydropyranone oximes (2*R*)- and (2*S*)-**104** was achieved with $NaBH_3CN/TiCl_3$ in the presence of NH_4OAc, allowing the synthesis of aminotetrahydropyran derivatives **105-108** in good overall yields (82-86%) and moderate diastereoselectivity (*cis*/*trans* isomers 70:30). However, the enantiopure stereoisomers could be separated by column chromatography and used in the synthesis of cyclic tubulysin analogues [86].

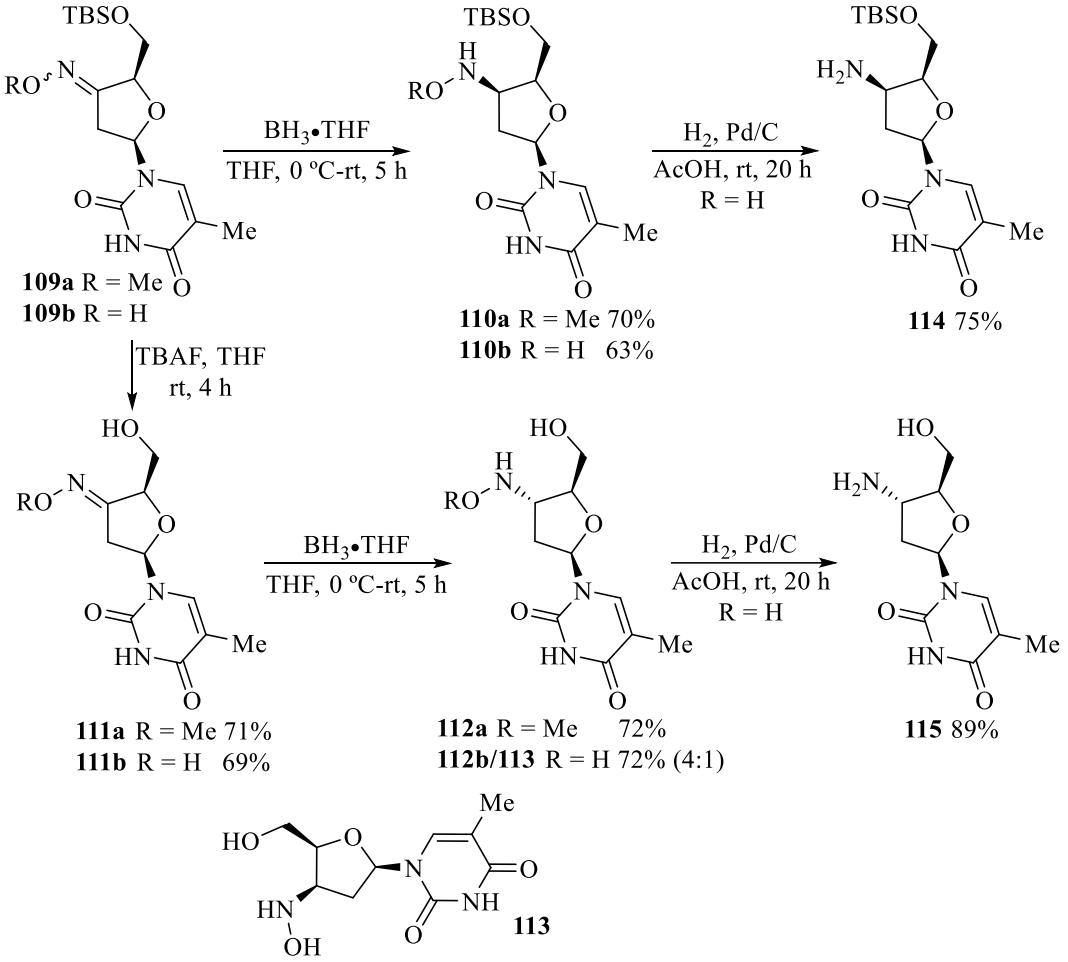


Scheme 26. Diastereoselective synthesis of aminotetrahydropyran derivatives.

Borane-tetrahydrofuran complex is an effective reducing agent for oximes. In fact, numerous authors have been using this reagent in the presence of a chiral catalyst not only for the enantioselective reduction (see section 2.1) but also for the diastereoselective reduction of oximes. Wei and co-workers used this strategy to prepare a chiral amine, during the asymmetric synthesis of the enantiomer of the clinical agent CP-99,994 [87].

Bose and Hodgson explored this approach to carry out the reduction of oximes **109** leading to 3'-methoxy and 3'-hydroxyamino-2',3'-dideoxynucleosides **110** in good yields, exclusively as *cis* isomers (Scheme 27) [88]. When the same reduction conditions were applied to oximes **111**, derived from oximes **109** by cleavage of the TBS protecting group, *trans*-3'-substituted-thymidine derivatives **112** were obtained. The *cis*-3'-hydroxy-thymidine **113** was obtained as minor product from the reduction of oxime **111b** (**112b**/**113** = 4:1, separated by column chromatography). ^{11}B NMR studies of the $B(OMe)_3$ complex with both protected (**109a**) and unprotected (**111a**) oximes were carried out to rationalize the selectivity of hydride transfer. There was evidence that in the reduction of oxime **109a** only B-N complexation via the imine nitrogen occurs allowing the formation of *cis*-isomer, whereas with oxime **111a** the complexation of boron should occur via boron-hydroxyl group and B-N complexes affording the *trans*-isomer. This methodology was extended to other nucleoside derivatives giving a wide range of chiral 3'-hydroxy- and 3'methoxyamino nucleosides which are inaccessible

otherwise. 3'-Hydroxylamine derivatives **110b** and **112b** were further reduced by Pd/C-catalyzed hydrogenolysis in acetic acid affording 3'-amino-thymidine **114** and **115**, respectively, in 75% and 89% yield [88].



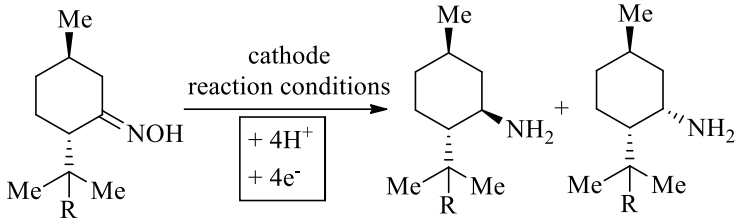
Scheme 27. Synthesis of 3'-amino-thymidine derivatives.

3.3. Electrochemical Reductions

Waldvogel and co-workers have developed a methodology for the asymmetric reduction of (-)-menthone oximes *via* an electrochemical approach. Several cathodes were tested for the diastereoselective reduction of the (-)-menthone oximes **116** and it was found that mercury pool and lead were the ones that gave better results (Table 3). Furthermore, additional studies were conducted in order to evaluate the influence of temperature and additives in the diastereoselectivity. The reduction of oxime **116a** using the mercury pool cathode gave menthylamines **117a** and **118a** in high yield (86%) and moderate diastereoselectivity (2.4:1) (entry 1). On the other hand, when the lead cathode was used to reduce the same oxime an inversion of diastereoselectivity was observed (entry 3) [89]. Later, the same research group extended the study to several 8-substituted (1*R*)-menthone oximes (*e.g.* **116b**) showing that the presence of substituents at the 8-position, greatly increases the stereoselectivity using both cathodes. Moreover, for these

oximes, the lead cathode gave the corresponding menthylamines (*e.g.* **117b** and **118b**) in better yields than the mercury pool cathode, and an improvement in the diastereoisomeric ratio was also observed, from *dr* = 6:1 to *dr* = 8:1 (entries 2 and 4). Furthermore, the combination of the lead cathode with alkylammonium salts as additives, improved the overall yields and diastereoselectivity of the process [90].

Table 3. Electrochemical induced diastereoselective reduction of menthanone oximes.



116a R = H
116b R = Ph

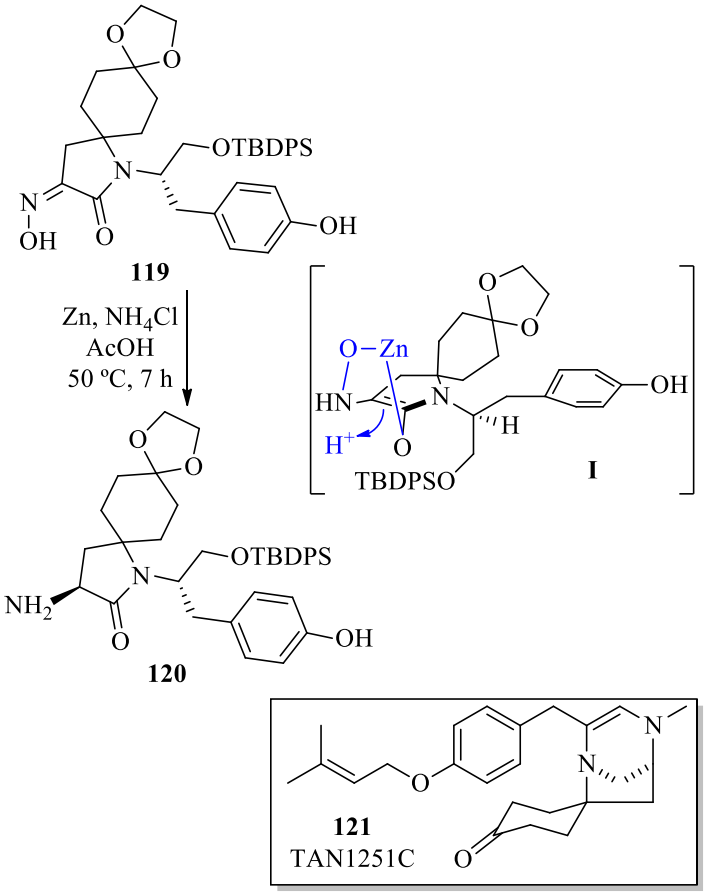
117a R = H
117b R = Ph

118a R = H
118b R = Ph

entry	cathode	reaction conditions	yield (%)	*dr*
1	mercury pool	2% H_2SO_4, DME/H_2O (1:1)	86	**117a**/**118a** = 2.4:1
2		0 ºC, 46 $mAcm^{-2}$, 10 F mol^{-1}	19	**117b**/**118b** = 6:1
3	lead	0.5% MTES, 2% H_2SO_4, MeOH	99	**117a**/**118a** = 0.6:1
4		20 ºC, 12.5 $mAcm^{-2}$, 10 F mol^{-1}	93	**117b**/**118b** = 8:1

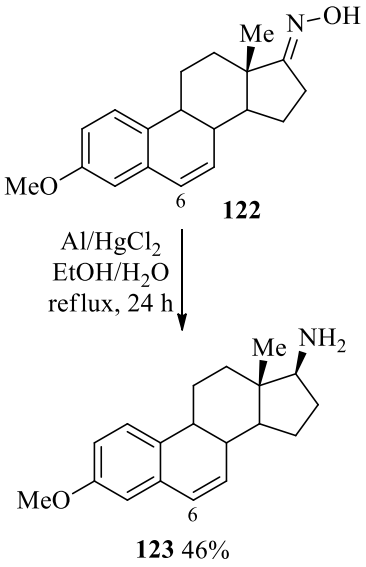
3.4. Other Reduction Reactions

Nagasaka *et al.* described the total synthesis of TAN1251C (**121**), a compound isolated from a culture of *Penicillium thomii*, with antispasmodic and antiulcer potential. One of the critical steps in this synthesis is the diastereoselective reduction of oxime **119**, which was achieved with Zn/NH_4Cl in refluxing acetic acid, affording chiral amine **120** as a single diastereoisomer (Scheme 28). The zinc-mediated reduction of the oxime double bond generates intermediate **I**, in which the Zn atom is located at the less hindered β-side of the spirolactam inducing the subsequent protonation from the α-side, giving product **120** with the desired stereochemistry [91]. This transformation can be regarded as a side-chain-controlled reduction since the α-side steric hindrance is due to the constrained conformation of the rigid spiro skeleton's side chain.



Scheme 28. Diastereoselective Zn-catalyzed reduction of a spiro-γ-lactam derived oxime.

The diastereoselective reduction of steroidal oxime **122** was the key step in the synthesis of several steroidal-hydroxycinnamide conjugates (Scheme 29). Optically active steroidal amine **123** was obtained in moderate yield (46%) as a single diastereoisomer, through the reduction of oxime **122** with aluminium amalgam ($Al/HgCl_2$) in refluxing ethanol/water after 24 h. This methodology was successful in the selective reduction of the oxime while maintaining the double bond at the 6-position. However, due to the poisonous nature of the mercury (II) salts, it is rarely used nowadays [92].



Scheme 29. Diastereoselective reduction of a steroidal oxime using aluminium amalgam.

4. ENANTIOSELECTIVE REDUCTION OF HYDRAZONES

Asymmetric reduction methodologies of hydrazones allow the preparation of enantiomerically enriched hydrazines, which can then be further transformed into the desired chiral amines. Nevertheless, chiral hydrazines themselves are also of great importance in the pharmaceutical and agricultural industries. In fact, several chiral compounds bearing the hydrazine moiety exhibit pharmacological properties such as Atazanavir (**124**), a therapeutic agent against HIV [93]. Additionally, chiral hydrazines are widely used as synthetic intermediates in the preparation of various heterocyclic compounds and natural products such as compound **125**, the key synthetic precursor of alkaloid manzacidin C [94].

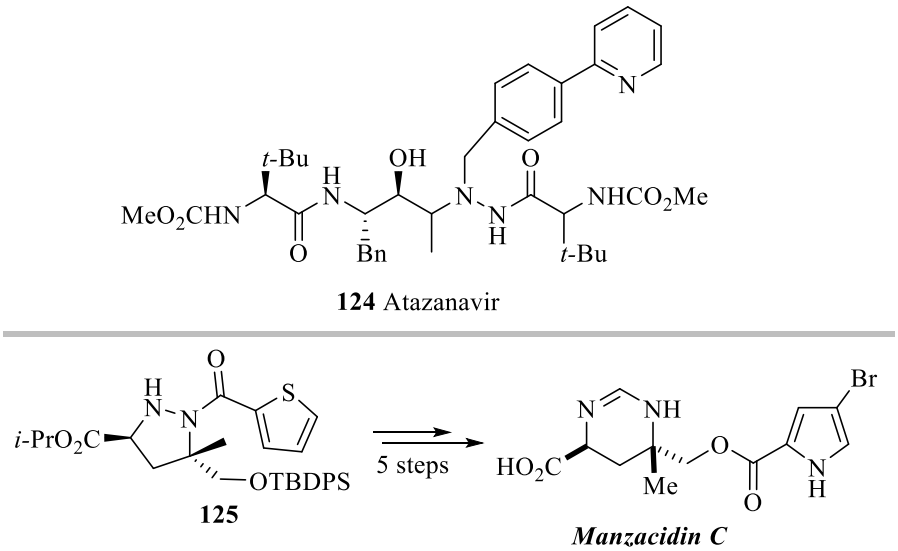


Figure 3. Examples of chiral hydrazine-containing compounds.

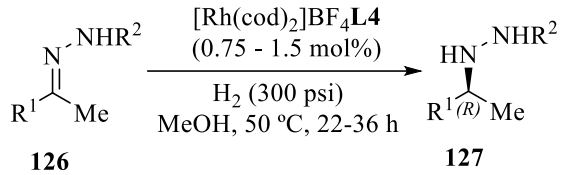
4.1 Metal-catalyzed Hydrogenation/Hydrogenolysis

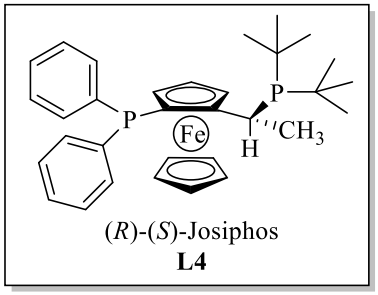
Hydrazones, with their azomethine –NHN=CH group, can be stereoselectively reduced to the desired compounds through asymmetric hydrogenation promoted by organometallic catalysts. Despite the progress achieved in the asymmetric hydrogenation of C=N double bond, the asymmetric reduction of hydrazones is still quite challenging with only a few transition metals and ligands being successfully employed throughout the last years, and with the substrate scope being almost limited to *N*-acylhydrazones. The enantioselectivity and efficiency of these transformations are strongly influenced not only by the metal and ligand complex used, but also by the *E/Z*-configuration of certain substrates. Moreover, the presence of a directing/activating group in the hydrazone substrates is often required to achieve high levels of enantioselectivity [95].

4.1.1. Rhodium-based Catalysis

Rhodium complexes have been one of the elected organometallic catalysts by various research groups for the asymmetric hydrogenation of hydrazones. In 2010, Sheppard and co-workers described the asymmetric hydrogenation of *N*-alkoxycarbonylhydrazones (Table 4) [96]. Initially, the asymmetric hydrogenation reaction of hydrazones **126** in the presence of Rh-EtDuphos catalyst, under the hydrogenation protocol previously described by Burk, was investigated [97]. Thus, the hydrogenation of a Boc-protected hydrazone was performed in isopropyl alcohol using 22 mol% of catalyst and 90 psi H_2 for 20 h. However, the results were unsatisfactory with the desired product being isolated in low yield and 20% *ee*, and a range of other chiral Rh complexes were evaluated. Within the tested catalyst complexes, the $Rh(cod)_2BF_4$/Josiphos complex presented the best results, affording the desired *N*-alkoxycarbonylhydrazines with *R* configuration in moderate to high enantioselectivity and excellent conversion efficiency. Under the optimized reaction conditions, using only 0.75-1.5 mol% catalyst load in methanol at 50 °C and 300 psi H_2 for 22-36 hours, several *N*-alkoxycarbonylhydrazines **127** bearing different protective groups (Boc, methoxycarbonyl and CBz) were isolated with enantiomeric excesses ranging from 44% to 91% (Table 4) [96]. Upon treatment with benzensulfonic acid in ethanol at 60 ºC, *N*-Boc hydrazine bearing an ester group in the phenyl ring (R^1 = 4-(EtO_2C)C_6H_4, R^2 = Boc), was easily converted into the desired unprotected hydrazine in high yield and >99% *ee*, without reduction of the ester group.

Table 4. Rh-catalyzed asymmetric hydrogenation of *N*-alkoxycarbonylhydrazones.

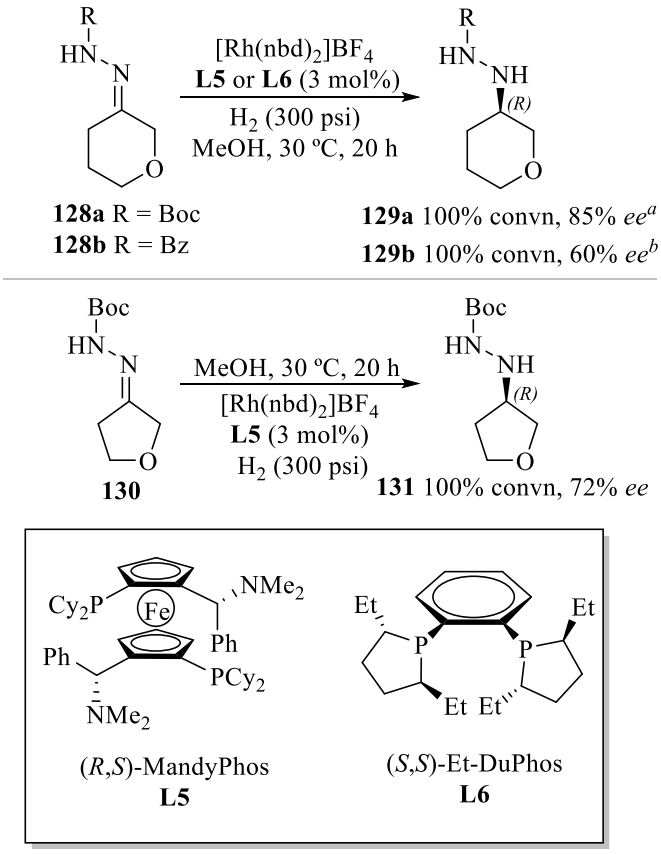




(*R*)-(*S*)-Josiphos
L4

Entry	R^1	R^2	yield (%)	*ee* (%)
1	4-(EtO_2C)C_6H_4	Boc	99	86
2	4-BrC_6H_4	Boc	100	91
3	Ph	Boc	99	86
4	CO_2Me	Boc	97	44
5	4-(EtO_2C)C_6H_4	CO_2Me	99	73
6	4-(EtO_2C)C_6H_4	CBz	100	78

In the following year, Senanayake's group developed an enantioselective hydrogenation methodology for five- and six-membered ring heterocyclic *N*-Boc-hydrazones **128a** and **130** and *N*-benzoylhydrazone **128b**, using $Rh(nbd)_2BF_4$ as catalyst (Scheme 30). Among the several ligands screened in these transformations, the (*R*,*S*)-MandyPhos ligand presented the highest activity for *N*-Boc-hydrazones, providing total conversion of the substrates into the corresponding hydrazines, albeit with moderate to high *ee* (72-85%). A different outcome was observed when applying the same method to *N*-Bz-hydrazone **128b**, where poor conversions and low enantioselectivity (14%) were observed. On the other hand, the use of (*S*,*S*)-Et-DuPhos ligand led to the target hydrazine **129b** in higher conversion percentage (100%) and higher *ee* (60%) (Scheme 31) [98]. The enantiomeric purity could be further improved up to >99% *ee* by crystallization from ethyl acetate. Interestingly, an unexpected inversion of enantioselectivity was observed when performing the hydrogenation of the six-membered heterocyclic hydrazones in non-coordinating solvents such as dichloromethane or 1,2-dichloroethane. According to deuterium labeling and NOE NMR experiments, neither the initial hydrazone configuration nor the hydrazone double bond isomerization played a significant role in the detected reversed enantioselectivity.

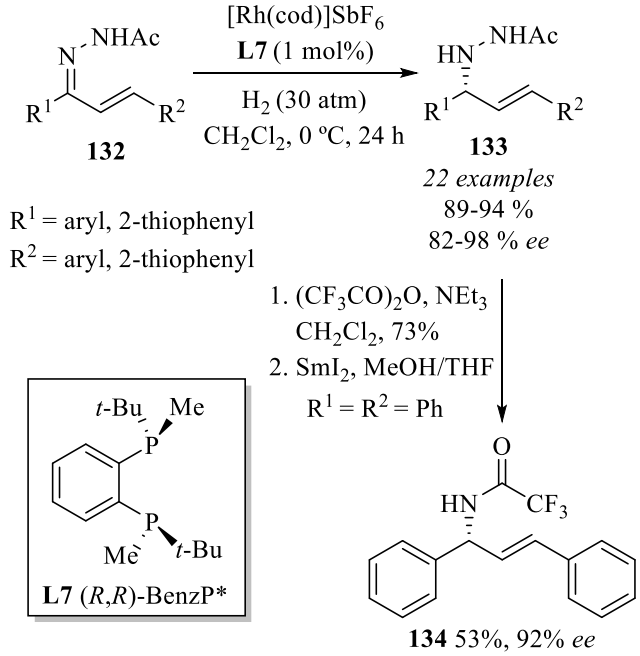


(*a*) Using **L5** as ligand;(*b*) Using **L6** as ligand

Scheme 30. Rh-catalyzed asymmetric hydrogenation of heterocyclic *N*-benzoylhydrazones and *N*-Boc-hydrazones.

The synthesis of chiral allylic amines starting from allylic hydrazone precursors is a very challenging goal since high chemoselectivity is required in the reduction step in order to retain the vinyl group. Following a previous work on the chemoselective and asymmetric hydrogenation of α-vinyl enamides into alkyl-vinyl amines under rhodium catalysis [99], Zhang and co-workers reported an efficient approach towards the synthesis of chiral aryl-vinyl amines. Starting from *N*-amido aryl-vinyl ketimines **132** and carrying out the hydrogenation reaction using rhodium complex (Rh[(*R*,*R*)BenzP*(cod)]SbF_6) as catalyst, assisted by an amido directing group, provided chemo- and enantioselectively the corresponding (*R*)-aryl-vinylhydrazines **133** in high yields and good to excellent enantioselectivities (Scheme 31) [100]. An initial study involving the hydrogenation of several allylic imines bearing different NH-protecting groups was carried out, in order to find the appropriate directing group for the desired selectivity. The presence of NH-Ac as directing group was found to be crucial for the success of the protocol, since the presence of other groups such as NHTs or NHBoc led to no reaction due to their weak coordinating ability. Furthermore, it was observed that the *E*-isomer of the model substrate was more reactive than the *Z*-isomer, giving rise to the exclusive formation of the hydrazine (*R*)-isomer in higher enantioselectivity, whereas the latter afforded the corresponding (*S*)-isomer in lower yield and *ee*. This was rationalized considering different coordinative interactions between the substrate and the metal center caused by steric hindrance. The best results were obtained when the reaction was performed in

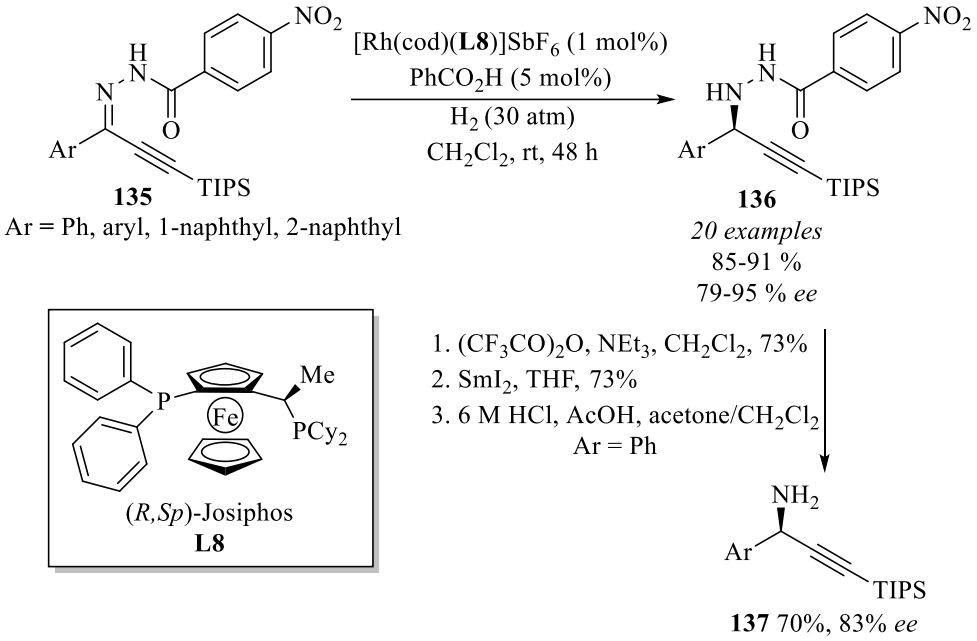
dichloromethane at 0 °C for 24 hours, using 30 atm of H_2 and 1 mol% of Rh[(*R*,*R*)-BenzP*(cod)]SbF_6 as catalyst. Moreover, (*E*)-imines bearing electron-donating or -withdrawing groups at the phenyl rings were suitable substrates for this reaction, as well as those containing the thiophenyl substituent. Additionally, the efficiency of this method was reproducible on a gram scale, allowing further transformations of the chiral hydrazines, namely trifluoracetylation followed by treatment with SmI_2, affording *N*-trifluoroacetyl-substituted allylic amine **134** in 92% *ee* (Scheme 31) [100].



Scheme 31. Rh-catalyzed enantioselective hydrogenation of allylic hydrazones.

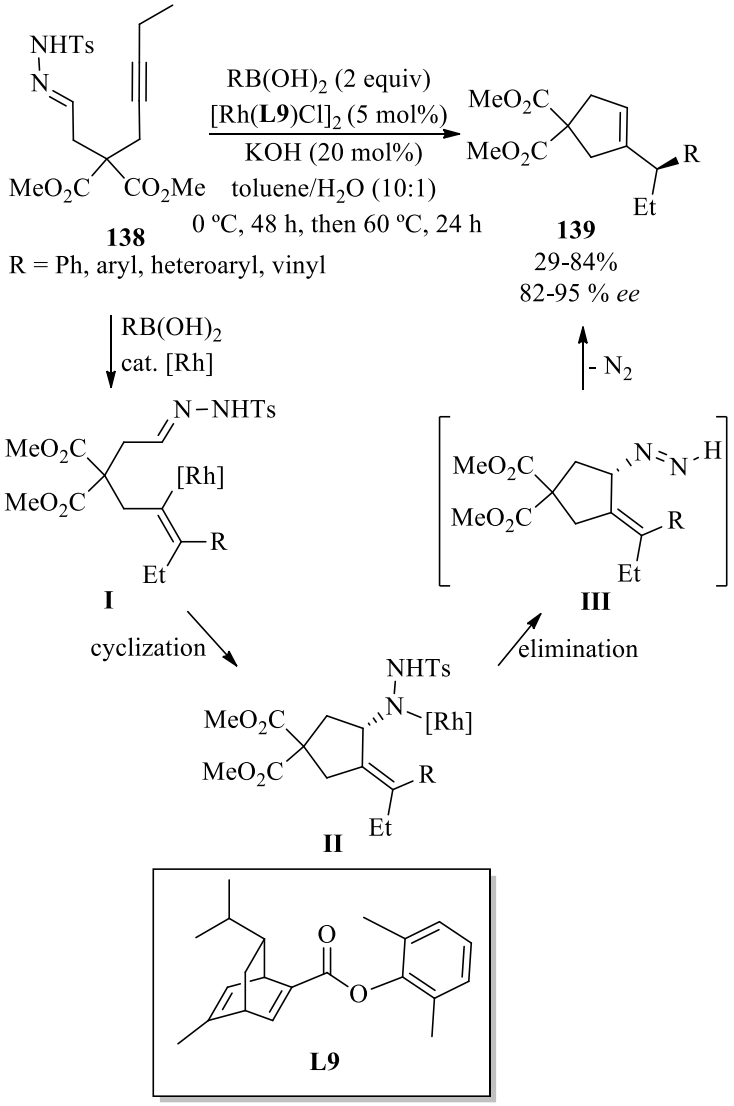
A route to chiral propargylamines based on a highly chemo- and enantioselective hydrogenation method of alkynyl-arylhydrazones, employing rhodium complex [Rh((*R*,*Sp*)-Josiphos)(cod)]SbF_6 as catalyst and benzoic acid as additive, was disclosed (Scheme 32) [101]. Enantiomerically pure propargylamines are very important and valuable substrates in the pharma industry since they are versatile building blocks in organic synthesis [102]. In this protocol, higher chemo- and enantioselectivity was achieved using the planarly chiral (*R*,*Sp*)-Josiphos as ligand and *N*-NH(4-NO_2Bz) as the directing group. Using this highly efficient rhodium complex/$PhCO_2H$ catalytic system, a series of alkynyl-aryl (*Z*)-hydrazones **135**, containing the triisopropylsilyl ether group (TIPS) and different substituents at the phenyl ring, underwent hydrogenation in dichloromethane at room temperature for 48 hours, to give the corresponding (*R*)-propargylhydrazines **136** in good yields, excellent chemoselectivity and enantiomeric excesses ranging from 79% to 95%. It was observed that substrates with electron-donating groups (*e.g.* OMe) or bulky alkyl groups (*e.g. t*-Bu) afforded the desired hydrazines in higher enantioselectivity. As previously observed with chiral allylic hydrazines, (*R*)-propargylhydrazines **136** underwent trifluoroacetylation and N-N bond cleavage with SmI_2 to give the corresponding *N*-trifluoroacetyl-substituted

propargylamine, which upon acidic hydrolysis yields the desired free chiral propargylamine **137**.



Scheme 32. Rh-catalyzed asymmetric hydrogenation of alkynyl-arylhydrazones.

In the same year, Lee and co-workers developed an innovative enantioselective synthetic approach to substituted cyclopentenes involving a rhodium-promoted tandem addition-cyclization-rearrangement of alkynylhydrazones (*e.g.* **138**) with organoboronic acids (Scheme 33) [103]. The catalytic protocol involves the addition of the organoboronic acid and the catalyst to give hydrazone **I**, which upon cyclization of the alkenyl-rhodium moiety to the C=N bond affords allylic carbazate **II**. This intermediate undergoes an elimination reaction to give allylic diazene **III**, followed by a retro-ene reaction to yield the desired chiral cyclopentenes **139** in variable yields (29-84%) and moderate to high enantioselectivities (82-95%). Interestingly, the hydrazone acts not only as directing group but also as π-acceptor. Chiral ligand **L9** containing a diene moiety was found to be the best ligand to perform these cascade reactions. Additionally, several organoboronic acids were successfully explored, with substituted phenylboronic acids bearing both electron-donating and -withdrawing groups leading to higher enantioselectivity than the heteroaryl or alkenyl boronic acids. Furthermore, the reaction temperature control was crucial for the success of the procedure, since it prevents premature sulfinic acid elimination which enables the reaction to proceed through the desirable pathway.



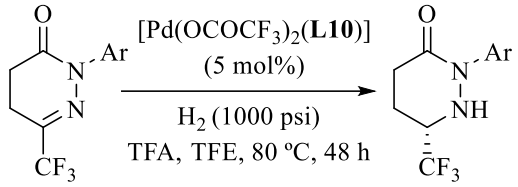
Scheme 33. Rh-catalyzed asymmetric addition-cyclization-rearrangement of alkynylhydrazones with organoboronic acids.

4.1.2. Palladium-based Catalysis

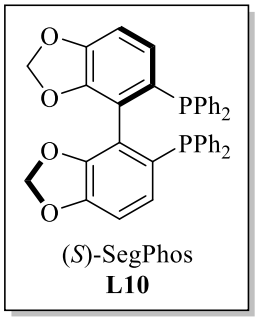
Palladium complexes have also been used successfully as organometallic catalysts in several enantioselective transformations, including the catalyzed asymmetric hydrogenation of hydrazones. However, in general, higher temperatures and H_2 pressures are required than those used under rhodium catalysis to attain high conversions and enantioselectivity. In 2015, Zhou *et al* developed an efficient palladium-catalyzed method towards the synthesis of chiral α-trifluoromethylated hydrazines employing chiral bisphosphine (*S*)-SegPhos **L10** as ligand (Table 5) [104]. Under this catalytic system, a range of cyclic *N*-arylhydrazones **140**, in the presence of trifluoroacetic acid and trifluoroethane at 80 ºC for 48 h, were converted into the corresponding chiral hydrazines in high yields and up to 97% *ee*. The efficiency of the method was not greatly affected by the nature of the aryl substituents, with hydrazone **140** bearing a 4-chlorophenyl group leading to the corresponding hydrazine **141** in the highest enantioselectivity (97%) (Table

5, entry 2). This methodology was further applied to a series of acyclic arylated hydrazones **142**, including β-naphthylhydrazones, furnishing the desired products in high yields (87-94%) and *ee* ranging from 91% to 93% (Scheme 34).

Table 5. Pd-catalyzed hydrogenation of cyclic *N*-substituted hydrazones.

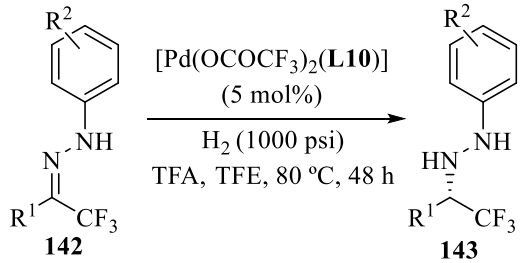


140 **141**



(*S*)-SegPhos
L10

entry	Ar	yield (%)	*ee* (%)
1	Ph	94	95
2	4-ClC_6H_4	93	97 (*S*)
3	2-FC_6H_4	82	92
4	4-FC_6H_4	92	96
5	3,4-$Me_2C_6H_3$	86	95
6	3,5-$Me_2C_6H_3$	97	96



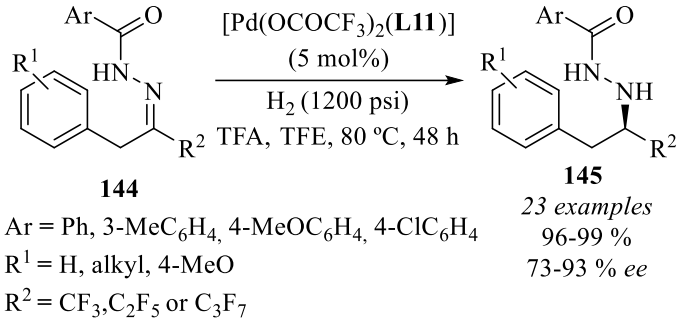
142 **143**

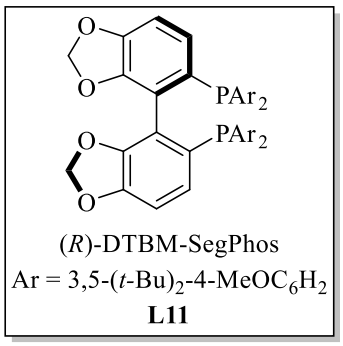
10 examples
87-94 %
91-93% *ee*

Scheme 34. Enantioselective synthesis of acyclic trifluoromethyl-substituted hydrazines.

Aiming to extend the methodologies available for the preparation of optically active fluorine-containing hydrazines, the same group investigated the Pd-catalyzed asymmetric hydrogenation of α-alkyl-substituted trifluoromethylated hydrazones (Scheme 35). The presence of the α-alkyl chain substituents in the hydrazones poses an extra challenge since these substrates are known to be less reactive towards asymmetric catalyzed hydrogenation reactions and afford the corresponding products with poorer

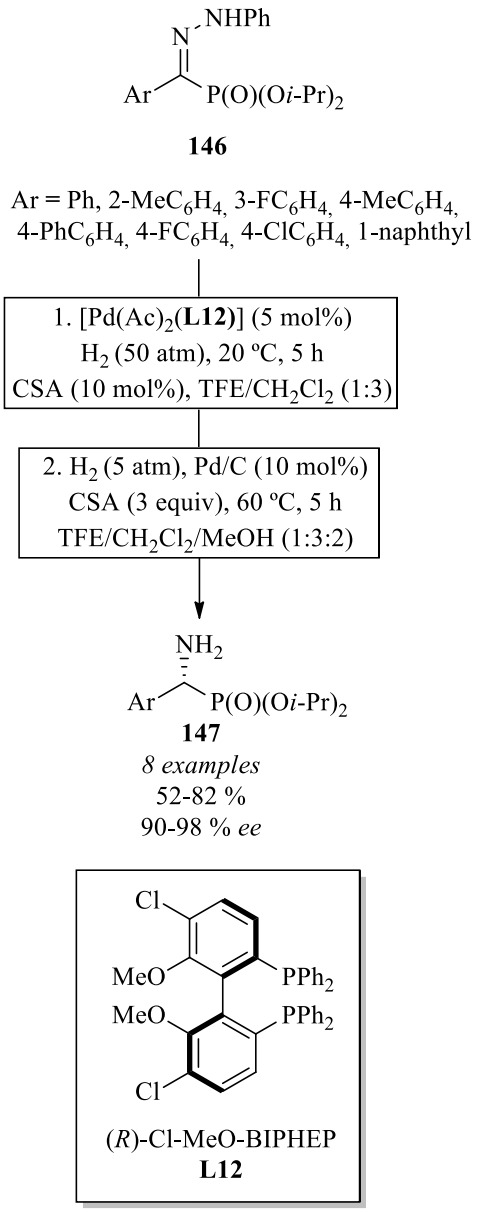
enantioselectivity. Nevertheless, under the optimized reaction conditions using (*R*)-DTBM-SegPhos (**L11**) as ligand, a broad scope of *N*-acylhydrazones **144**, including β-aryl, γ-aryl, and alkyl-chain-substituted, were smoothly converted into the corresponding hydrazines **145** in excellent yields and high enantioselectivity [105]. Hydrazones bearing variable alkyl chain length substituents and branched alkyl groups were suitable substrates as well as the ones containing longer perfluoroalkyl chains. Curiously, the lowest enantiomeric excess was observed with α-benzylhydrazones (73-74% *ee*).





Scheme 35. Enantioselective synthesis of fluorinated *N*-acylhydrazines.

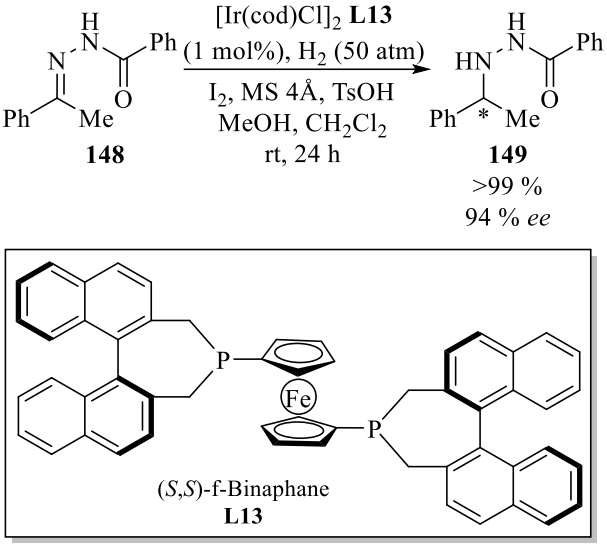
An innovative one-pot two-step catalytic protocol towards enantiomerically enriched α-amino phosphonates, using *Z*-isomers of α-phenylhydrazono phosphonates **146** as prochiral precursors, was developed by Beletskaya and co-workers (Scheme 36) [106]. The procedure involves the palladium-catalyzed hydrogenation of hydrazones **146** using (*R*)-Cl-MeO-BIPHEP (**L12**) as ligand and (1*S*)-(+)-10-camphorsulphonic acid as activator, followed by hydrogenolysis over Pd/C of the *in situ* formed hydrazines to afford the target chiral products **147**, thus combining the advantages of both homogeneous and heterogeneous palladium catalysis. However, the enantioselectivity of this methodology was strongly dependent on the configuration of the C=N double bond with *E*-substrates leading to (*S*)-products via *Re*-face coordination with the palladium complexes, while *Si*-face coordination of *Z*-substrates affords (*S*)-products. The (*R*)-enantiomers were obtained selectively in 52-82% yield and enantiomeric excesses ranging from 90% to 98%, with better results being attained for *para*-phenylsubstituted α-amino phosphonates. In addition, the hydrazones' *N*-substituent plays an important role in the success of these transformations since all attempts to reduce (*Z*)-*N*-benzoylated α-hydrazonophosphonate under the palladium catalysis conditions failed.



Scheme 36. One-pot two-step synthesis of chiral α-amino phosphonates.

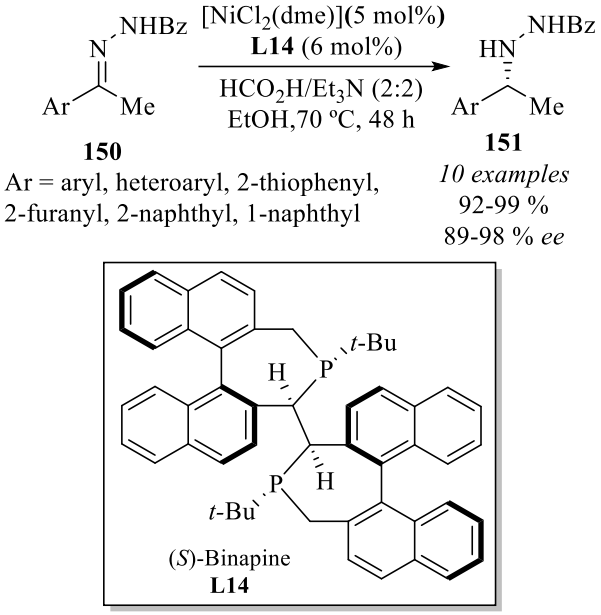
4.1.3. Other Transition Metal-catalysis

Besides rhodium and palladium, other transition metal complexes have been successfully explored as catalysts in the asymmetric reduction of hydrazones. In this context, the enantioselective hydrogenation of *N*-benzoylhydrazone **148** using an iridium-(*S*,*S*)-f-binaphane complex as catalyst, has been described by Zhang and co-workers (Scheme 37) [107]. However, as in other catalytic systems, the efficiency of the hydrogenation was optimized by the addition of additives. Thus, an enhancement from 18% to >99% in the reaction yield was observed by carrying the reaction in the presence of molecular iodine, *p*-toluenesulphonic acid and molecular sieves leading to the corresponding hydrazine **149** in 94% *ee* [107].



Scheme 37. Asymmetric catalytic hydrogenation of *N*-benzoylhydrazones.

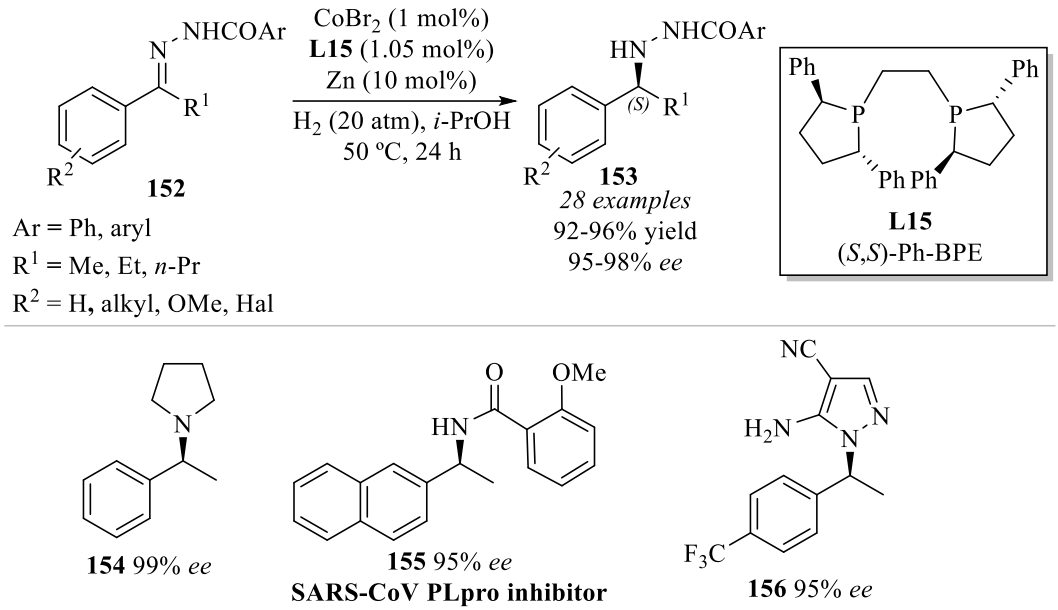
Chiral hydrazines have also been efficiently prepared through the nickel-catalyzed transfer hydrogenation of hydrazones [108]. The catalytic method employs a mixture of formic acid and triethylamine as hydrogen source and strong electron rich and bulky bisphosphines as ligands. Among these, (*S*)-Binapine (**L14**) afforded the highest enantioselectivity providing the desired hydrazines (*e.g.* **151**) with *ee* up to 98% (Scheme 38). A series of α-substituted hydrazones **150** were suitable substrates for this reaction, bearing either electron-donating and -withdrawing groups on the phenyl ring, as well as thiophenyl, furanyl, pyridyl, and a variety of alkyl groups. Nevertheless, the reaction with α-alkyl-substituted hydrazones required the use of a Josiphos ligand, CyPF-Cy, to attain high conversions and *ee*. Additionally, the replacement of the *N*-benzoyl group in the hydrazones by a phenyl group resulted in lower enantioselectivity. Mechanistic studies involving deuterium labeling experiments suggest that the formyl hydrogen atom of formic acid was donated as a hydride via decarboxylation at the nickel center and that prior to hydride donation, an equilibrium between the imine and enamine tautomers of the hydrazone exists. DFT calculations were also carried to rationalize the observed stereoselectivity and, interestingly, revealed that the catalyst complex uses shape complementary and weak attractive interactions to induce asymmetry, as observed in enzymatic catalysis, rather than the conventional steric repulsions.



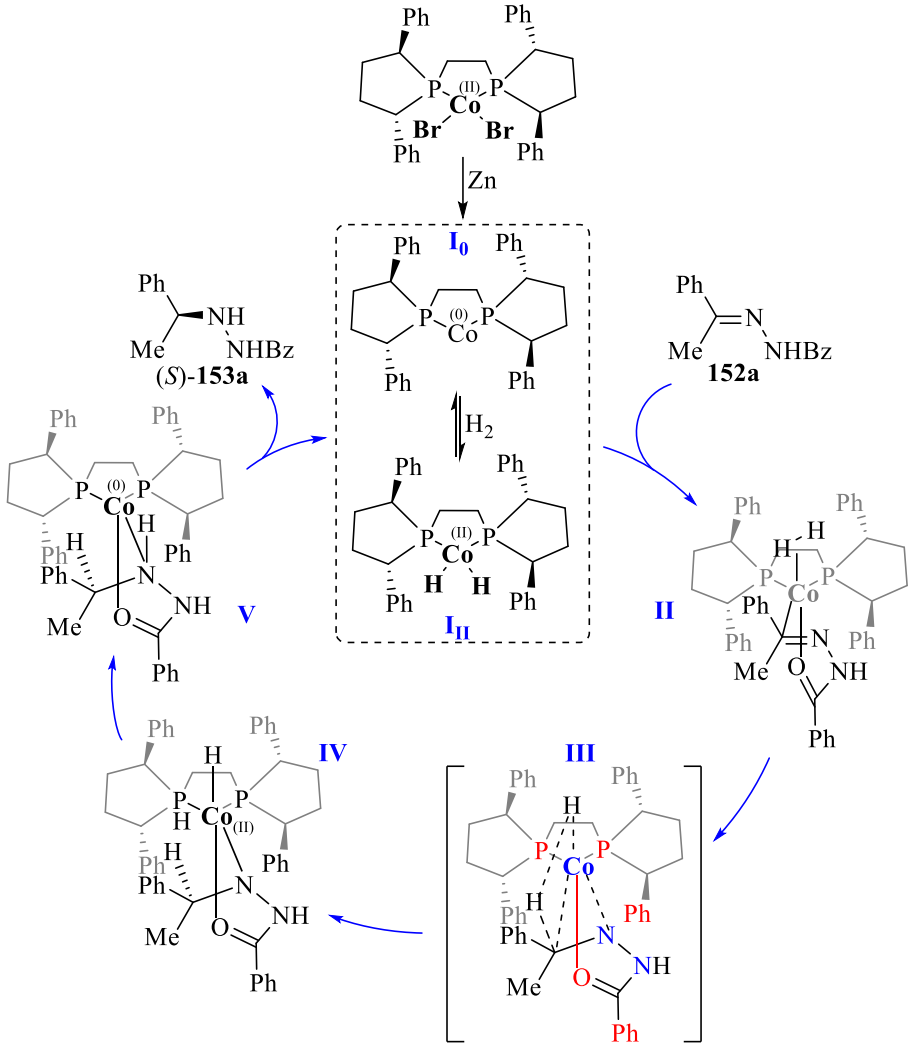
Scheme 38. Ni-catalyzed asymmetric transfer hydrogenation of hydrazones.

Due to its inexpensiveness, stable coordination with both chiral *N*- and *P*-donor ligands and redox properties which enable different catalytic cycles, cobalt has been used as catalyst in several enantioselective transformations such as C-H functionalization or [2+2+2] cycloaddition reactions [109]. However, reports on the cobalt-catalyzed asymmetric hydrogenation of hydrazones remain scarce. Recently, Zhang and co-workers developed a very broad and highly stereoselective method towards (*S*)-*N*-benzoylhydrazines (*e.g.* **153**) using (*S*,*S*)-Ph-BPE/$CoBr_2$/Zn catalytic system (Scheme 39) [110]. The presence of the *N*-NHBz group in the hydrazones is crucial for the success of the reaction since an assisted coordination between the carbonyl group and the cobalt atom occurs, as previously observed in rhodium and iridium catalysis. Thus, the hydrogenation reaction of hydrazones **152**, in the presence of only 1 mol% of cobalt/(*S*,*S*)-Ph-BPE complex (**L15**) and a catalytic amount of zinc (10 mol%) at 50 ºC, gave access to a range of (*S*)-hydrazines **153** in high yields (92-96%) and excellent enantioselectivities (95-98%), with 24 h of reaction time. The reaction has a wide substrate scope, proceeding smoothly to the target products regardless of the electronic nature of the substituent at the phenyl ring. The only exception was observed with 2-naphthyl-substituted hydrazone which required higher temperature (70 ºC) to attain good conversion and high enantiomeric excess (95% yield, 96% *ee*). Notably, the hydrazine products could be further reduced with SmI_2 into the free amines which underwent subsequent transformations to yield chiral amine **154**, chiral amide **155** and chiral pyrazole **156**, retaining the stereochemical integrity. Deuterium labeling experiments demonstrated that the hydrogenation proceeds via the imine state and no equilibrium between the imine and enamine tautomers occurred. Furthermore, it also confirmed that the hydrogen source was the H_2 and not the solvent. Mechanistic studies supported by DFT calculations corroborate the role of NHBz group as directing/activating group and, based on these studies, the Co^0/Co^{II} redox mechanism illustrated in Scheme 40 was proposed for the formation of the major products, the (*S*)-**153**. Initial dibromo-Co^{II} complex reduction with

zinc gives $\mathbf{I_0}$, which upon oxidative addition is converted into $\mathbf{I_{II}}$. The coordination of the substrate with the dihydride-Co^{II} complex originates intermediate **II**, which after an insertion step via transition state **III** generates intermediate **IV**. Subsequent reductive elimination gives rise to intermediate **V** that leads to the formation of (*S*)-hydrazines **153** and catalyst precursor $\mathbf{I_0}$.



Scheme 39. Co-assisted asymmetric hydrogenation of hydrazones.

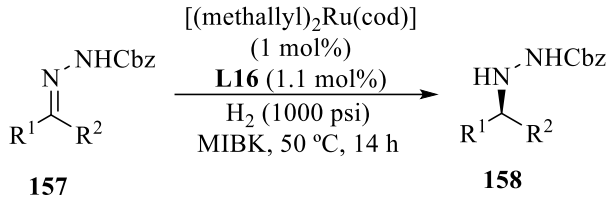


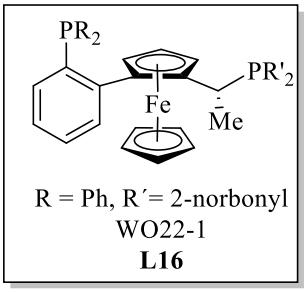
Scheme 40. Proposed mechanism for the Co-assisted asymmetric hydrogenation of hydrazones.

Recently, the first enantioselective ruthenium-catalyzed hydrogenation of hydrazones was disclosed by Shuster *et al.* [111]. Using a combination of chiral phosphine Walphos derivative W022-1 and [(methallyl)$_2$Ru(cod)] as catalyst, a series of *N*-Cbz-protected hydrazones (*e.g.* **157**) bearing different functional groups were hydrogenated under mild reaction conditions, yielding the corresponding chiral hydrazines (*e.g.* **158**) in moderate to excellent yields with up to 99% *ee* (Table 6). The catalytic protocol tolerates a broad substrate scope including both electron-donating and -withdrawing substituents on the phenyl group (entries 2 and 3), heteroaryl groups (entries 5 and 6), cyclohexyl and ethyl groups, as well as cyclic hydrazones. Albeit, the presence of two alkyl groups or a trifluoromethyl group on the hydrazone led to a significant decrease in the selectivity and efficiency of the reaction (entry 4). The effect of the hydrazone protecting group on the selectivity of the reaction was also investigated revealing that the presence of carbamate protecting groups (Cbz and Boc) leads to the desired products in higher enantioselectivity. In fact, in contrast to the majority of enantioselective hydrazone reductions which require *N*-benzoyl protecting groups on the substrates to achieve high levels of enantioselectivity, the ruthenium-promoted hydrogenation of *N*-benzoylhydrazone afforded the corresponding hydrazine in 96%

yield with a surprising 55% *ee*. Similar enantioselectivities were obtained with hydrazones bearing more electron-rich or electron-poor benzoyl groups, thus confirming the carbonate-based protecting groups as the ideal to perform these reductions. Furthermore, subsequent cleavage of the carbonate-protecting group can be easily carried out under Pd/C hydrogenation providing access to hydrazine salts while maintaining optical purity.

Table 6. Ru-catalyzed hydrogenation of hydrazones.





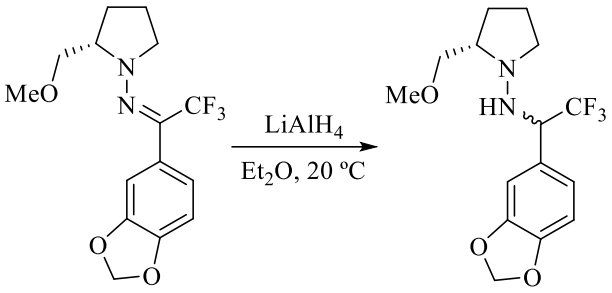
R = Ph, R´= 2-norbonyl
WO22-1
L16

entry	R^1	R^2	yield (%)	*ee* (%)
1	Ph	Me	95	97
2	4-$CF_3C_6H_4$	Me	98	95
3	4-$MeOC_6H_4$	Me	89	96
4	Ph	CF_3	18	43
5	furan-2-yl	Me	94	96
6	thiophen-2-yl	Me	96	96

5. DIASTEREOSELECTIVE REDUCTION OF HYDRAZONES

The use of chiral auxiliaries to induce asymmetry in various transformations has been an efficient methodology for achieving high levels of diastereoselectivity [112, 113]. Among the several chiral auxiliaries available, the (*S*)-proline derivatives have been extensively used with remarkable success in numerous diastereoselective reactions such as diastereoselective α-alkylations of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazones [114, 115].

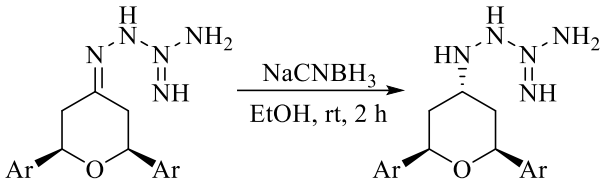
A similar approach has been used by Baudin and co-workers to highlight the application of trifluoromethylated hydrazones (*e.g.* **159**), available through the copper-catalyzed trifluoromethylation of aryl and heteroaryl *N*,*N*-dialkylhydrazones [116]. The reduction of hydrazone **159** bearing SAMP chiral auxiliary with lithium aluminium hydride, in diethyl ether at room temperature, afforded the corresponding hydrazine **160** in 80% yield with a diastereoisomeric ratio of 78:22 (Scheme 41).



159 **160** 80%
dr 78:22

Scheme 41. Diastereoselective reduction of a SAMP-hydrazone.

Another successful example of a chiral auxiliary inducing asymmetry in hydrazones reduction reactions was accomplished by Vasconcellos and co-workers in the synthesis of optically active aminoguanidine tetrahydropyran derivatives (Scheme 42) [117]. A four-step synthetic route, involving enantiopure 4-hydroxy-2,6-diaryltetrahydropyrans as intermediates, gave access to guanylhydrazones **161** in high yields. These underwent reduction reaction over sodium cyanoborohydride, under very mild reaction conditions, to afford the corresponding aminoguanidines **162** as single diastereoisomers, in excellent yields (94-100%). Notably, both hydrazone and aminoguanidine derivatives showed promising biological properties as anticancer agents.



161
Ar = Ph, 4-FC_6H_4, 1-naphthyl

162
3 examples
94-100%

Scheme 42. Stereocontrolled reduction of guanylhydrazones.

6. CONCLUSION

In this review, the synthetic methodologies for the preparation of chiral amines via asymmetric reduction of oximes were highlighted. These highly desirable targets in organic chemistry can be accessed directly from the enantioselective or diastereoselective reduction of oximes through borane-mediated reactions, transition metal assisted hydrogenation/hydrogenolysis reactions, hydride donor reactions, and electrochemical reactions. Chiral hydroxylamines were also obtained from the asymmetric reduction of oximes and can be further reduced to give the corresponding chiral amines.

On the other hand, the enantioselective or diastereoselective reduction of hydrazones via metal-catalyzed hydrogenation or hydride donor reactions, furnishes chiral hydrazines which can be efficiently transformed into chiral amines without significant loss of optical purity.

Despite the recent progress on this topic, the development of more efficient and stereoselective methodologies, suitable for a wider range of substrates, is required. Furthermore, more eco-friendly and sustainable enantioselective synthetic approaches are needed and, hopefully, the fast-growing green chemistry research area can inspire successful developments.

LIST OF ABBREVIATIONS

Ac	=	acetyl
aq	=	aqueous
Ar	=	aryl
(*R*,*R*)-BenzP*	=	(*R*,*R*)-(+)-1,2-bis(*tert*-butyl(methyl)phosphino)benzene
(*R*)-BINAP	=	(*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
(*S*,*S*)-f-Binaphane	=	1,1′-bis[(*S*)-4,5-dihydro-3*H*-binaphtho[2,1-c:1′,2′-e]phosphepino]ferrocene
(*S*)-Binapine	=	(3*S*,3'*S*,4*S*,4'*S*,11b*S*,11'b*S*)-(+)-4,4'-Di-*tert*-butyl-4,4',5,5'-tetrahydro-3,3'-bi-3*H*-dinaphtho[2,1-c:1',2'-e]phosphepin
BIPHEP	=	bis(diphenylphosphino)biphenyl
Bn	=	benzyl
Boc	=	*tert*-butyloxycarbonyl
Bt	=	benzotriazole
Bu	=	butyl
Bz	=	benzoyl
CBz	=	benzyloxycarbonyl
cod	=	1,5-cyclooctadiene
CSA	=	10-camphorsulfonic acid
Cy	=	cyclohexyl
CyPF-Cy	=	(*S*)-1-[(R_P)-2-(dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine
DCC	=	*N*,*N*′-dicyclohexylcarbodiimide
dcpf	=	1,1′-bis(dicyclohexylphosphino)ferrocene
de	=	diastereoselective excess
DEAD	=	diethyl azodicarboxylate

DFT	=	density-functional theory
DIBALH	=	diisobutylaluminium hydride
DMAP	=	4-(dimethylamino)pyridine
DME or dme	=	dimethoxyethane
DMF	=	dimethylformamide
(*R*)-DTBM-SegPhos	=	(*R*)-(−)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
dr	=	diastereoselective ratio
ee	=	enantiomeric excess
Et	=	ethyl
EtDuphos	=	(−)-1,2-bis[(2*R*,5*R*)-2,5-diethylphospholano]benzene
Gly	=	glycine
Hal	=	halogen
HIV	=	human immunodeficiency virus
Josiphos	=	diphosphine-ferrocenyl chiral ligand
(*R*,*S*)-MandyPhos	=	(R_P,R'_P)-1,1′-bis[(*S*)-α-(dimethylamino)benzyl]-2,2′-bis(diphenylphosphino)ferrocene
Me	=	methyl
MIBK	=	methyl isobutyl ketone
Ms	=	mesyl
MS	=	molecular sieves
nbd	=	norbornadiene
NMR	=	nuclear magnetic resonance
NOE	=	nuclear overhauser effect
Ph	=	phenyl
(*S*,*S*)-Ph-BPE	=	(+)-1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane
(*R*,*R*)-Ph-BPE	=	1,2-bis((2*R*,5*R*)-2,5-diphenylphospholan-1-yl)ethane
Pr	=	propyl
Py	=	pyridine
rt	=	room temperature
SAMP	=	(*S*)-1-amino-2-methoxymethylpyrrolidine

SARS-CoV PLpro	=	severe acute respiratory syndrome-coronavirus papain-like protease
TBAF	=	tetra-*n*-butylammonium fluoride
TBD	=	triazabicyclodecene
TBDPS	=	*tert*-butyldiphenylsilyl
TBS	=	*tert*-butyl dimethylsilyl
TFA	=	trifluoroacetic acid
TFE	=	trifluoroethanol
THF	=	tetrahydrofuran
TIPS	=	triisopropysilyl
Tol	=	*p*-methylphenyl
Ts	=	*p*-toluenesulfonyl
Tuv	=	tubuvaline
Ureaphos	=	urea-phosphate chiral ligand
Walphos	=	biferrocene-based diphosphine ligands
WSC•HCl	=	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride

CONSENT FOR PUBLICATION

Not applicable

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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