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VERSATILE ENANTIOSELECTIVE APPROACHES TO CHIRAL AMINE SYNTHESIS-A REVIEW

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Abstract – In this review the importance of chirality in nature is highlighted considering the synthesis of enantiomerically pure compounds in the form of entioenriched amines which have immense pharmaceutical importance, Different strategies are considered here such as enantioselective reduction of imines, chiral pool approach, imine and enamide synthesis, stereoselective conversion of prochiral substrates to enantiopure compounds, enantioselective reduction of enamides, enantioselective imine reduction using organocatalyts and chiral auxiliary approach. Reductive amination is found to be an important strategy to synthesize chiral primary amines. The pros and cons of each strategies are discussed in this review in details. This will be helpful to researchers working in this field to design and plan their future activities which will benefit the society as a whole.

Key words*: enantiomeric excess, chiral auxiliary, asymmetric synthesis, α-chiral amine, reductive amination*

1. INTRODUCTION

The importance of α-chiral amines in pharmaceutical drugs, natural products, fine chemicals and agrochemicals have inspired scientists to develop a variety of methodologies to synthesize them in high enantioselectivity and yield. The literature is replete with strategies to synthesize α-chiral amines. Different strategies are discussed in this review in details with critical analysis of their importance and limitations. In one such methodologies enantioselective imine reduction of C-N bond is an important organic transformation using different chiral catalysts containing Ru, Rh, Ir and Ti transition metals which has shown amazing reactivity and selectivity. In another strategy enantioselective transfer hydrogenation reactions for transforming imines to amines have been examined by Noyori's group [124]. In another methodology the presence of chiral auxiliary influences diastereoselectivity by facilitating the attack on the substrate concerned from

a preferred direction in which the auxiliary is removed from the product to obtain the necessary chiral compound. Reductive amination methodology is the direct conversion of prochiral ketones or aldehydes to chiral amines in one or two steps using different reduction methods, which include, hydride reduction, transfer hydrogenation and hydrogenation. This reductive amination was found to be one of the better strategies among many to be pursued further.

2. VERSATILE STRATEGIES TO CHIRAL AMINE SYNTHESIS

Chirality is ubiquitous in nature, it is one of the key factors influencing biological processes. The history of chirality however dates back to the year 1817 when the French physicist Jean-Baptiste Biot discovered the phenomenon of optical activity.[1] It was his student Louis Pasteur who introduced the concept of chirality (Greek word *cheir* meaning hand) in 1848.[2] He proposed the concept that the observed property of optical activity in organic substances is due to their molecular asymmetry and manifests itself as pairs of enantiomers (Greek word: *enantio* meaning opposite) which are defined as non-superimposable mirror-image structures e.g. enantiomers of lactic acid (Figure 1). It was in 1874 that van't Hoff and Le Bell independently solved the reasons behind molecular asymmetry as proposed by Pasteur. According to van't Hoff [3] the carbon compounds that are optically active possess an asymmetric carbon centre which was generalized by Le Bell [4] when he supported the argument that asymmetry is due to the whole molecule and not restricted to an individual

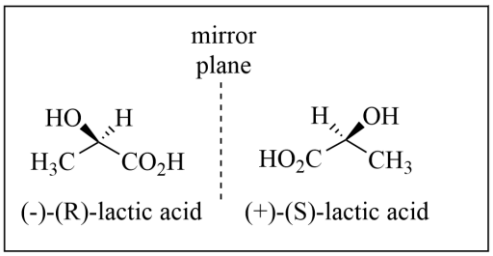


Figure 1: Enantiomers of Lactic acid.

carbon centre.A chiral molecule is not superimposable with its mirror-image while an achiral is superimposable with its mirror-image. This can be explained by using the analogy of a right and left hand as an example.[5] The most common chiral molecules contain a tetrahedral carbon centre with four different groups or atoms attached to it. Such molecules have identical chemical properties in an achiral environment.

The optical purity of a sample is determined by the formula: Optical purity = $[\alpha]/[\alpha]_0$; where $[\alpha]$ refers to the specific rotation of an enantiomeric mixture and $[\alpha]_0$ refers to that by a pure sample. Another important expression which will be mentioned repeatedly is *enantiomeric excess* (*ee*) which defines the preferential formation of one enantiomer over the other. The formula is as below:

enantiomeric excess (*ee*) = [(R-S)/(R+S)] x 100; R and S refers to the quantities of the two enantiomers present in a given solution.

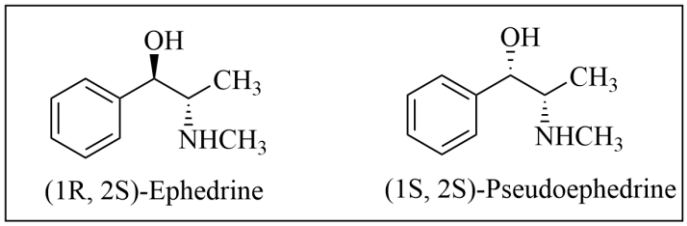


Figure 2. Ephedrine and Pseudoephedrine diastereomers

When a compound has more than one stereogenic center then more than one stereoisomers is possible in which some of the stereoisomers may not bear mirror-image relationship with each other, they are called diastereomers. Unlike enantiomers the diastereomers differ in physical and chemical properties for example the drugs ephedrine and pseudoephidrine (Figure 2). The preferential formation of one diastereomer over the other is referred to as *diastereomeric excess* (*de*) as shown below:

diastereomeric excess (*de*) = $[(X_1-X_2)/(X_1+X_2)]$ x 100; X_1 and X_2 refers to the quantities of the two diastereomers present in a given solution.

A. Importance of chirality in Nature [6]

The phenomenon of selectivity in biological processes is universal. This phenomenon is largely inherent in all bioactive substances such as drugs, insecticides, pesticides, herbicides, flavors and fragrances. Pasteur was the first one to observe a close relationship between biological catalysis and bioactivity. Emil Fischer [7] in 1894 introduced the concept of "Lock and Key" based on his observation that the enzyme emulsin catalyzes the hydrolysis of β-methyl-D-glycoside and it is the enzyme maltase instead that hydrolyzes α-methyl-D-glycoside. He went on to conclude that the enzyme and the glycoside must fit like a lock to a key for the chemical transformation to occur. Another important postulation by Easson and Stedman [8] in

1933 is noteworthy, which is known as a three-point contact model which explains the enantioselectivity in drug-receptor interactions. They proved that due to geometrical features the more active enantiomer of the drug binds tightly with the receptor while the inactive enantiomer does not. This also points to similar concept that the right configuration of the drug is essential to interact with the receptor, which can well be explained by the glove-hand example.

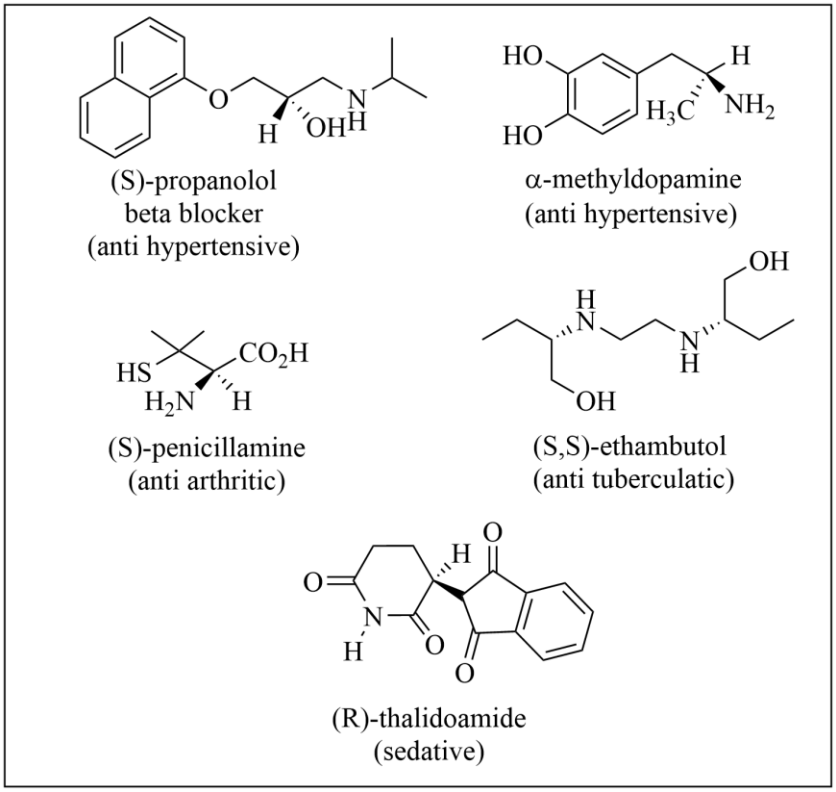


Figure 3. Drugs sold as a single enantiomer and its pharmaceutical value.

There are various examples in which drugs can be administered as racemates or as pure enantiomers. (S)-Propanolol, a *beta*-blocker that produce an anti-hypertensive effect, for example is sold as a racemate (Figure 3). The (S) enantiomer is more active while the (R) isomer is totally inactive. α-Methyldopa was the first drug developed as a single enantiomer.[9] There are examples, in which one enantiomer can exhibit undesirable side effects and so recommended to be administered only as pure enantiomer. A few examples of these drugs are anti-arthritis agent penicillamine and anti-tubercular agent ethambutol (Figure 3). In the former the (S) enantiomer is the active agent while the (R)-penicillamine is extremely toxic.[10] In case of ethambutol the (S,S)-enantiomer is active while (R,R)-causes optical neuritis that can result in blindness. The well known example of the serious side effect of an enantiomer was demonstrated

by thalidomide (Figure 3) in 1960 which was sold as a racemate. It was later discovered that the (R)-isomer was the sedative agent while the (S)-isomer is highly teratogenic and caused fatal abnormalities in children born to mothers who have consumed them.[11] Similar to drug design in pharmaceutical industries agrochemical industries also produce herbicides, pesticides and fungicides as single enantiomers.

Flavors and fragrances of different foods are also influenced by chirality. A stereospecific interaction by the flavor and fragrance substances with the olfactory receptor of the nose determine the perception of different odor and taste. These can be explained by some examples, (S)-limonene has a lemon odor while its (R) counterpart has an orange odor or (S,S)-aspartame has sweet taste as compared to (R,R)- aspartame, which has bitter taste (Figure 4).

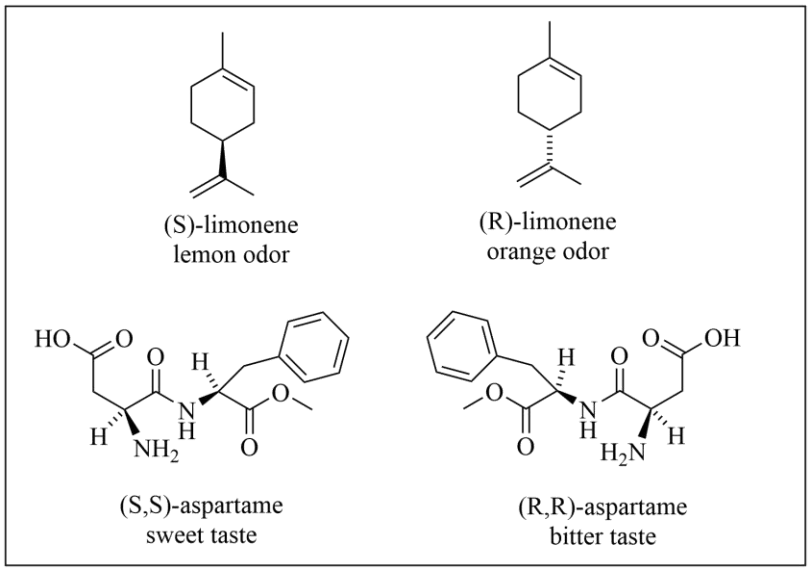


Figure 4. Enantioselectivity-an effect in odour and taste perception

B. Synthesis of enantiomerically pure compounds

The importance of chirality and strong need for enantiomerically pure substances has encouraged scientists to develop versatile methodologies to meet this objective. There are three main processes as shown in Figure 5: Resolution of racemates; Chiral pool approach; and Stereoselective conversion of prochiral substrates to enantiopure compounds (asymmetric synthesis via catalytic or stoichiometric process).

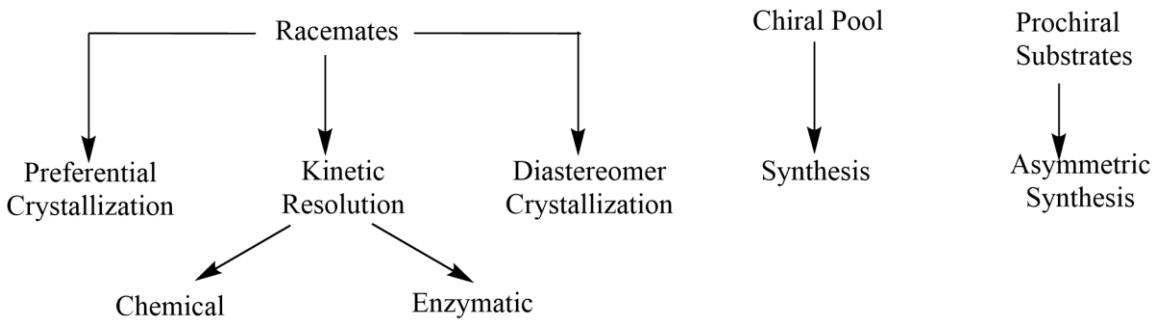


Figure 5. Processes for the synthesis of chiral non-racemic compounds

Resolution

The resolution technique in the most classical route to form enantiopure compounds. Although it has been overtaken by asymmetric synthesis, this method is still persisted in numerous examples till the present day. There are three main techniques of resolution as shown in Figure 5.

Resolution via preferential crystallization

Preferential crystallization is possible for racemates which form conglomerates. A conglomerate is a mixture of crystals of individual enantiomers that can, in principle, be separated mechanically. Generally only 5-10% of racemates form conglomerates.[6] Success of this method depends on the fact that for a conglomerate the racemic mixture is more soluble than either of the enantiomers. The industrial resolution of α-methyl-L-dopa by taking advantage of this property.

Diastereomer crystallization

This method was developed by Pasteur in 1854, [12] in which a racemate interacts with an enantiopure compound to form diastereomeric salt which can be separated by crystallization due to unequal solubility in a given solvent. These enantiopure compounds are called resolving agents and are obtained from the chiral pool, *e.g*. L-tartaric acid, D-camphor sulfonic acid or some alkaloid bases (Figure 6). One example of such a process is the crystallization of the salt of one enantiomer of 1,2 diamino cyclohexane obtained from the interaction of the racemic mixture of the same with enantiopure tartaric acid (Scheme 1).[13]

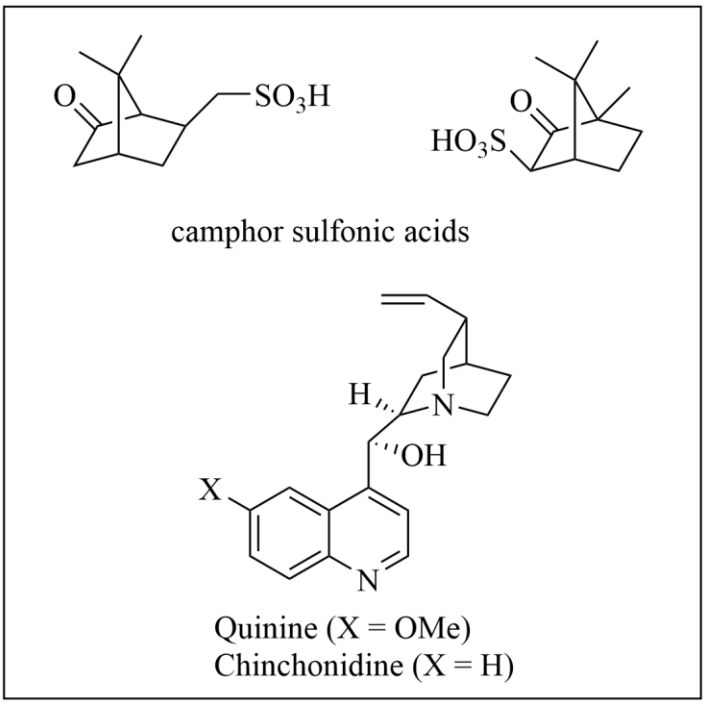
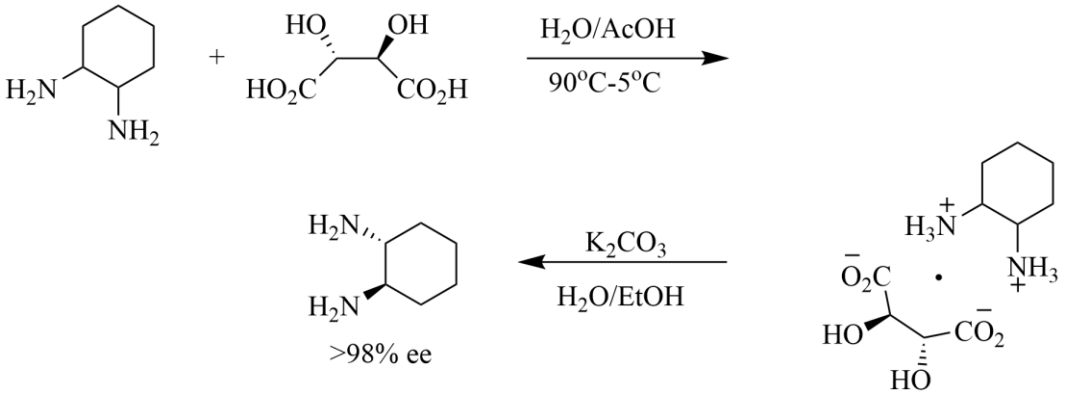


Figure 6. Chiral resolving agents.

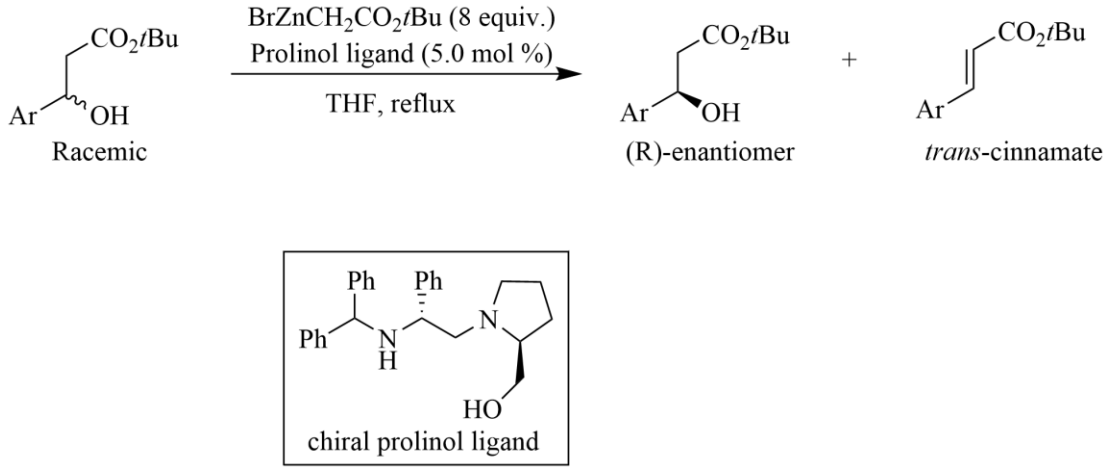


Scheme 1. Resolution of trans-1,2-diaminocyclohexane.

Kinetic resolution [14]

This resolution method depends primarily on the difference in rate of reactivity of the two enantiomers with a chiral entity. This chiral entity should be used in catalytic amount and can be either a biological catalyst (e.g. enzyme) or a chemical catalyst (*e.g.* chiral metal complex or organocatalyst). Generally for kinetic resolution to be successful one enantiomer must react faster than the other. In such a situation theoretically 50% of product from one enantiomer and

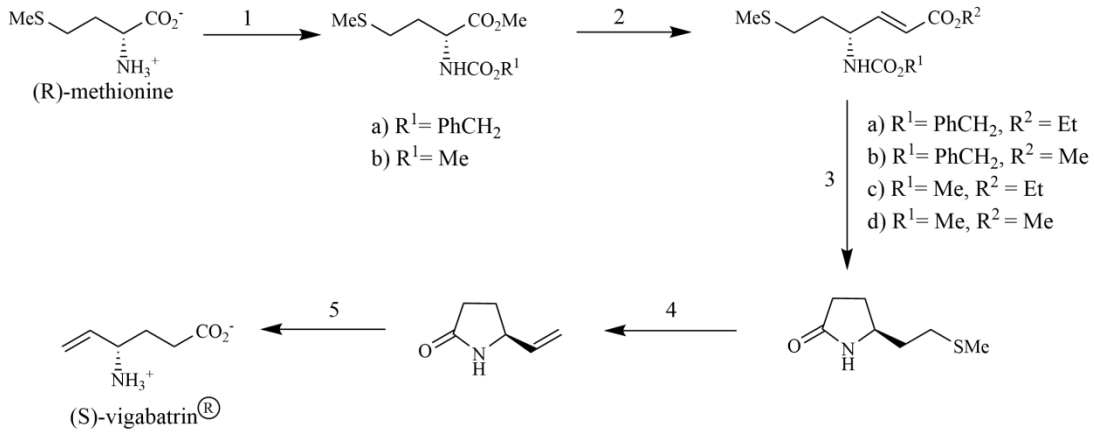
50% of the unreacted enantiomer should be obtained. This can be explained by an example shown below in which racemic β-aryl-β-hydroxy esters with different substitution patterns on the aryl moiety provides preferably the (R)-enantiomer with 93-98% ee and 32-41% isolated yield (Scheme 2).[15] The ratio of the rate constants between the two enantiomers varies between 15-42 in favour of the (S)-isomer.



Scheme 2. Kinetic resolution of racemic β-aryl-β-hydroxy esters.

Chiral pool approach

Chiral pool refers to the chiral compounds available naturally (e.g. carbohydrates, amino acids, lactic acid, etc.), from which the required chiral center can be incorporated into the desired product. These substances are transformed into products by chemical processes, which involve retention of configuration, inversion or chirality transfer. The chiral starting material is called chiral synthon and the chirality transfer can occur from the chiral starting material. Unlike a chiral auxiliary approach (we will discuss this in Section **1.2.3**), in which the chirality is installed into the compound (which is achiral) by the auxiliary and later detached from it. An example of this approach is depicted by the synthesis of (S)-vigabatrin ®, a potent GABA-T inhibitor from (R)-methionine by Knaus and Wei in 96% yield and >98% *ee* as shown below (Scheme 3).[16]



1. i) MeOH/$SOCl_2$, ii) $NaHCO_3$/$ClCO_2R^1$, 82-86% yield; 2. $(R_2O)P(O)CH_2CO_2R^2$/*t*BuLi/DIBAL-H, 62-78% yield; 3. Mg/MeOH, 92-95% yield; 4. i) $NaIO_4$, ii) 190°C, 56% yield; 5) KOH/*i*PrOH/H_2O, 96% yield, >98% *ee*.

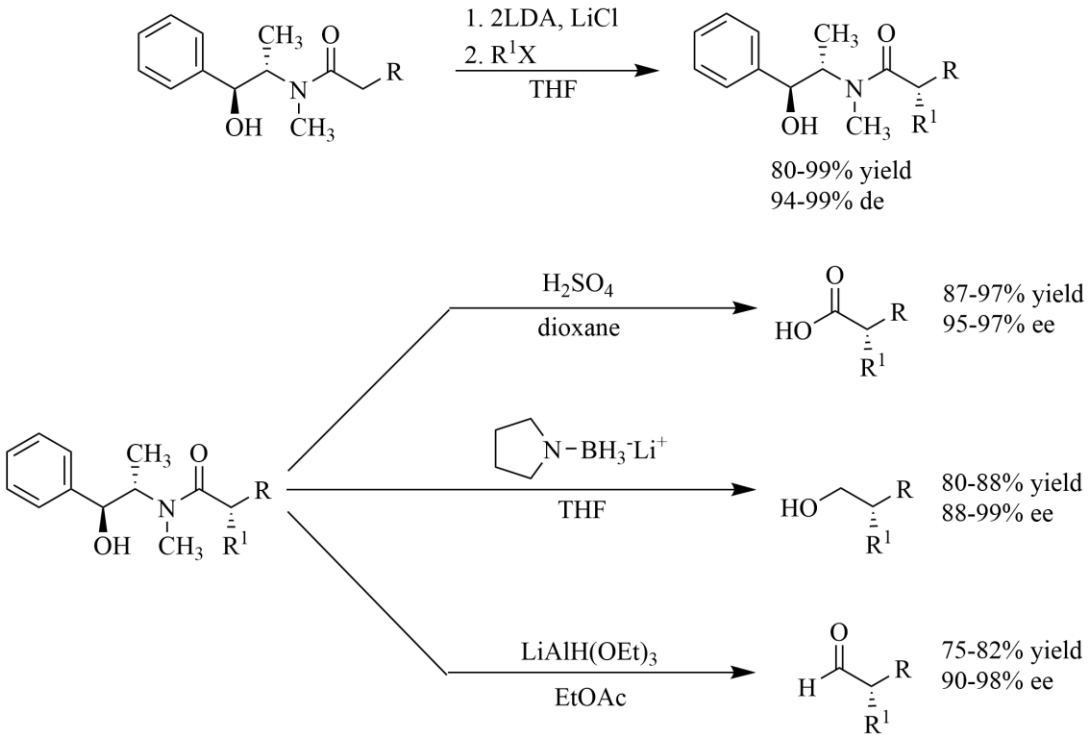
Scheme 3. Synthesis of (S)-vigabatrin ® from (R)-methionine-a chiral pool approach.

C. Stereoselective conversion of prochiral substrates to enantiopure compounds (Asymmetric Synthesis)

In asymmetric synthesis a stereogenic centre is formed under the influence of an external or internal chiral inducing agent. This process can be carried out by three methods: Substrate-controlled method; chiral auxiliary approach; and catalyst-controlled method.

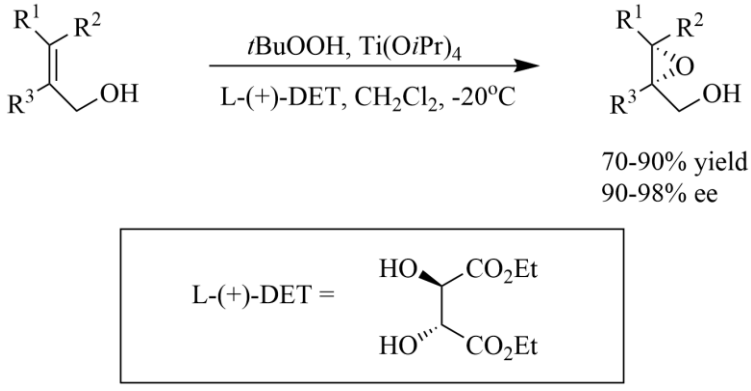
In substrate controlled methods chirality is present internally within the molecule which makes the remaining groups or face diastereotopic. This approach is limited to enantiopure starting materials that are easily available, and reacting centers within close proximity to the auxiliary.

The other two approaches involve the conversion of an achiral to a chiral compound either stoichiometrically as in auxiliary approach or sub-stoichiometrially as in catalyst-controlled methods. In chiral auxiliary approach the chiral information is transferred from the external chiral molecule to the achiral starting material by forming a covalent bond with it initially. This auxiliary is then cleaved from the final product in an additional step. This additional step can sometimes be sensitive to the product chirality which may be destroyed by racemization. One example of this auxiliary approach is shown in Scheme 4, in which (1S,2S)-(+)-pseudoephedrine (structure in Figure 2) is used as the chiral auxiliary to produce diastereomeric alkylated pseudoephedrine amides which can form enantioenriched carboxylic acids (by hydrolysis), alcohols and aldehydes (by reduction). [17]



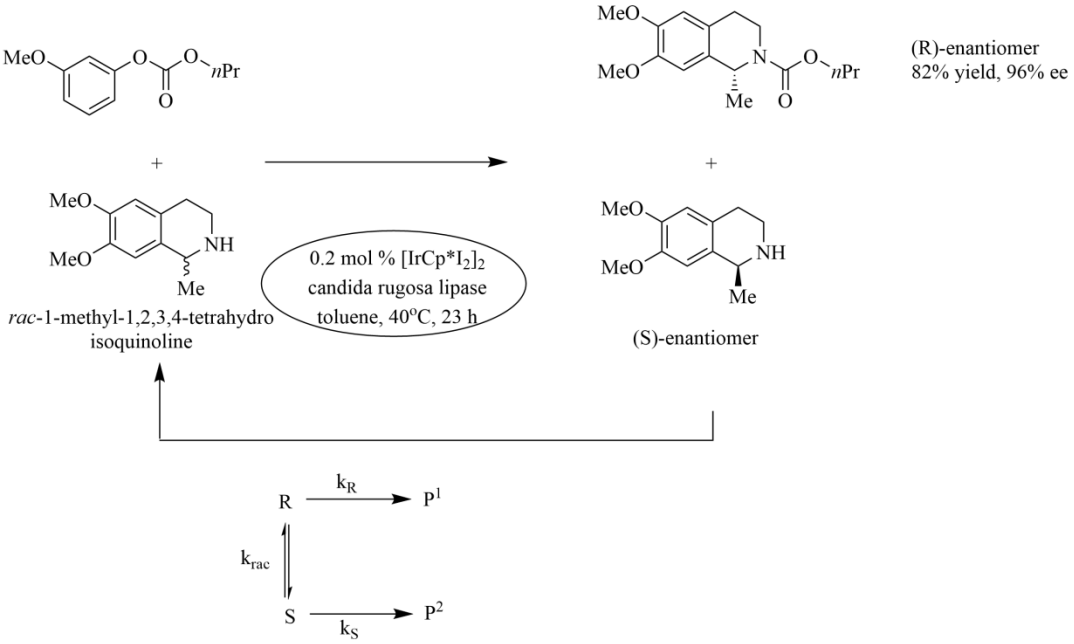
Scheme 4. A chiral auxiliary approach for asymmetric synthesis.

The catalytic asymmetric transformation is facilitated by a chiral entity, which is generally used in catalytic amounts to enhance the economic viability of the process. The chiral entity can be a chemical catalyst (e.g. chiral acid, bases or chiral metal complexes) or even a biological catalyst. Knowles[18] synthesized L-DOPA (Scheme 5), which was the first industrial asymmetric synthesis popularized by Monsanto. In this process he used Rh(DiPAMP) as a chiral catalyst and obtained L-DOPA in 100% yield and 97.5% *ee*.



Scheme 5. Monsanto L-DOPA process-a catalytic asymmetric synthesis.

Royoji Noyori, [19] published a paper in 1980 about the synthesis of chiral BINAP, which was also applied by him as a ligand in Rh complexes in catalytic quantities to synthesize amino acids. Takasago industries used Noyori's catalysts to build up chiral menthols. Barry Sharpless [20] introduced asymmetric synthesis to oxidation reactions. He used diethyltartarate complex of titanium as a catalyst in the epoxidation of allylic alcohols (Scheme 6). The pioneering works by the above scientists were rewarded with the Noble prize for chemistry in 2001 by the Royal Swedish academy of sciences.

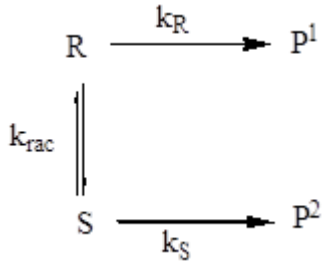


Scheme 6. Sharpless epoxidation of allylic alcohols.

D. Asymmetric synthesis *vs* Kinetic resolution *vs* Chiral pool

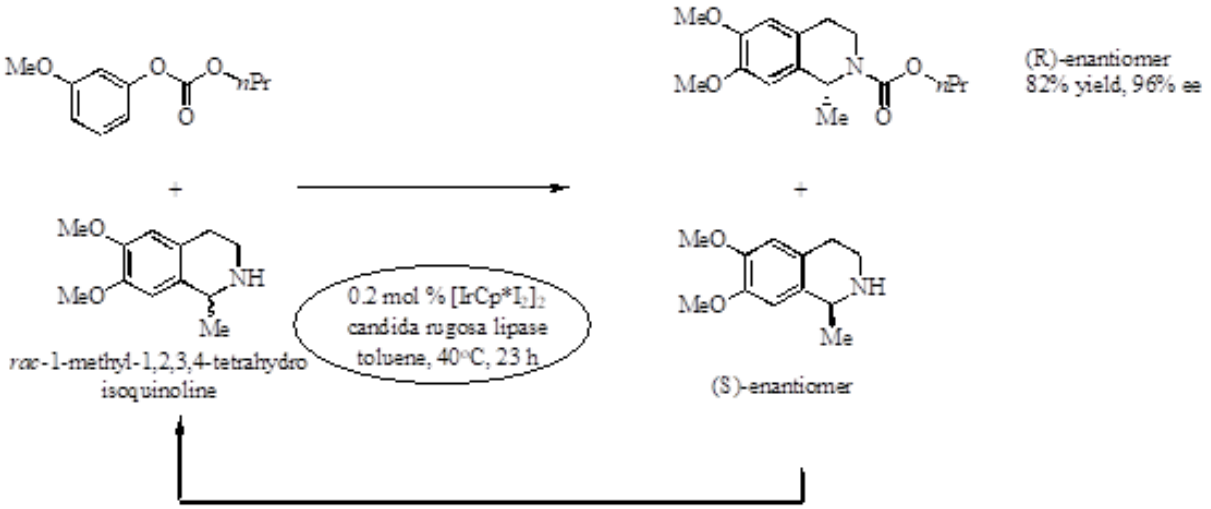
From the above discussions it can be concluded that in resolution processes the main draw back is a yield of only 50% (theoretically) from the racemates that can be obtained where as the maximum expected yield from asymmetric synthesis is 100%. In kinetic resolutions however, the enantioselectivity can be tuned to any desired value simply by manipulating the degree of conversion which is not possible in asymmetric processes. The yield in the kinetic resolutions can be improved by fast conversion of the (S)-enantiomer into the racemic mixture and the (R)-enantiomer reacts preferably to form the desired product in high yield and *ee*. This whole conversion is referred to as dynamic kinetic resolution which can be feasible only if $k_{rac}>k_R>k_S$, that is the rate of racemisation (k_{rac}) is faster compared to rate of reaction (k_R or k_S) (Scheme 7).

This is further explained by an example in which *rac*-1-methyl-1,2,3,4-tetrahydroisoquinoline provides the carbamoylated (R)-enantiomer in 82% yield and 96% *ee* in a chemoenzymatic process (Scheme 8). [21]



Scheme 7. Dynamic kinetic resolution-a schematic representation.

In a chiral pool approach, although the methodology can be cost effective, sometimes we find that production of one enantiomer over the other may not be possible due to their non-availability as most natural products are formed as single enantiomers. This elevates asymmetric synthesis employing the use of enzymes, transition metal catalysts or organocatalyts to the preferable choice.



Scheme 8. Dynamic kinetic resolution of a secondary amine.

D. α-Chiral amines-defining terms

Amino compounds with a stereogenic centre at the position α-to the amino group are called α-chiral amines (Figure 7). These are useful intermediates for alkaloid natural product synthesis, and have been successfully incorporated into billion dollar drugs, e.g. several ACE inhibitors and Flomax. [22] The importance of α-chiral amines can be exemplified by the fact that at least 40% of all optically active pharmaceutical drugs contain this moiety, and 80% of the synthesis still

rely on classical resolution methods. [22a] There is a lack in efficient and simple methods to synthesize them. [23] Especially synthesis of alkyl-alkyl' substituted amines continues to be a challenge and our main objective was to address this need.

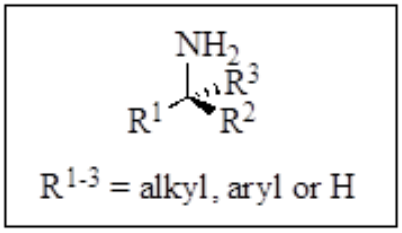


Figure 7. α-Chiral amine-a generic structure.

Enantiomerically pure amines with an α-stereocenter play an important role in organic synthesis. Their applications are innumerable: as chiral resolving agents, [24] as chiral auxiliaries, [25] as ligands in various asymmetric transformations, [26] and as advanced building blocks in pharmaceutical and agrochemical industries. [27-33] They are also useful as chiral ligands in metal-complex catalysis. [34] Figure 8 shows some of the α-chiral amines available commercially.

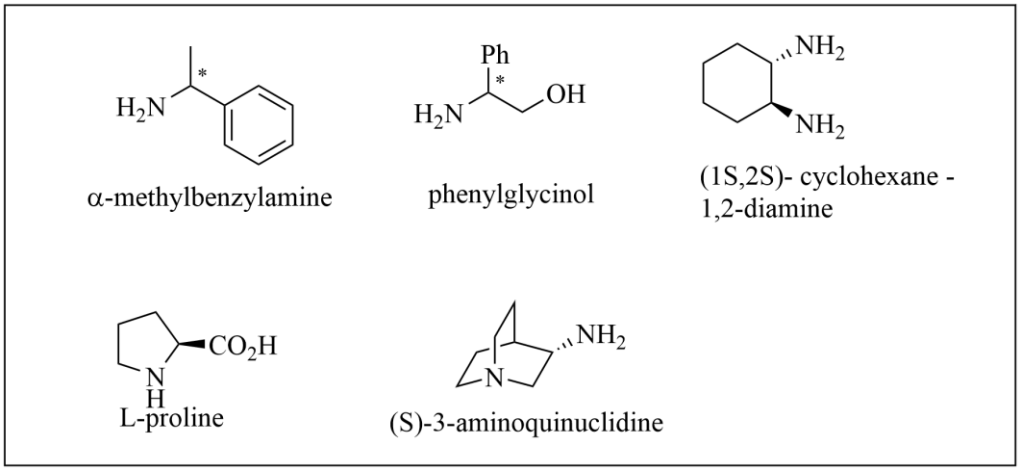


Figure 8. Some representative examples of enantiopure amines commercially available.

Chiral (R)- or (S)- α-methylbenzylamine are often used as chiral auxiliaries [35, 36] and as resolving agents. [37] They have been used in the synthesis of biologically active molecules such as Labetalol (β-blocker) and Tamsulosin (Figure 9). [32] Among α-amino acids proline has a unique value in asymmetric processes, such as, its use as a ligand in transition metal-catalysis,

[38, 39] and in organocatalysis chemistry, for example, Aldol, [40] Mannich [41] and Michael [42] reactions to mention a few.

The quinuclidine family is another class of chiral α-chiral amines, which are used in synthesis of pharmaceutical building blocks. An example of this class includes enantiopure 3-aminoquinuclidine, an important intermediate in the synthesis of 5-HT_3 serotonin ligands, [43, 44] such as zacopride (Figure 9). (1S,2S)-Cyclohexane-1,2-diamine is used as chemotherapeutic agents, [45] also finds application as chiral auxiliary, transition metal-catalysis and oraganocatalysis. [31] These compounds are often used to synthesize pharmaceutical drugs, agrochemicals, and other natural products. [29] Some examples of relevant drugs with α-chiral amines are shown in Figure 9.

E. α-Chiral amine synthesis-different methodologies

The literature is replete with strategies for α-chiral amines synthesis. Some of the methodologies are industrially viable and others are better suited for combinatorial studies or to provide a perspective in the various ongoing trends in this emerging field. For a methodology to be applied on an industrial scale should satisfy certain features e.g. should be cost effective and generate low waste. In this respect several α-chiral amine methods have scale-up potential in relation to the number of steps from the starting material, which is usually an aldehyde or a ketone.

Among the versatile strategies, [46] hydrogenation of enamine esters (diastereo and enatioselective), [47] hydrogenation of α- or β-*N*-acetylenamide esters, [48] 1,4-addition of amines to enones, [49] chemical [50] and enzymatic [51] reductive amination of α- ketoacids, and remote amination via C-H insertion [52] will not be discussed here but are mentioned here to provide a perspective. Another important methodology include the hydroamination of olefins, [53] which are not well examined.

The main focus here is to discuss unfunctionlized starting aldehydes and ketones. The various strategies includes the following: 1) transfer hydrogenation or hydrogenation of imines, 2) reductive amination of ketones, 3) *N*-acetylenamide reduction, 4) carbanion addition to aldimine and ketimine derivatives, and 5) sequential amination-alkylation of aldehydes. The first three methodologies will be discussed in detail with various examples available in literature.

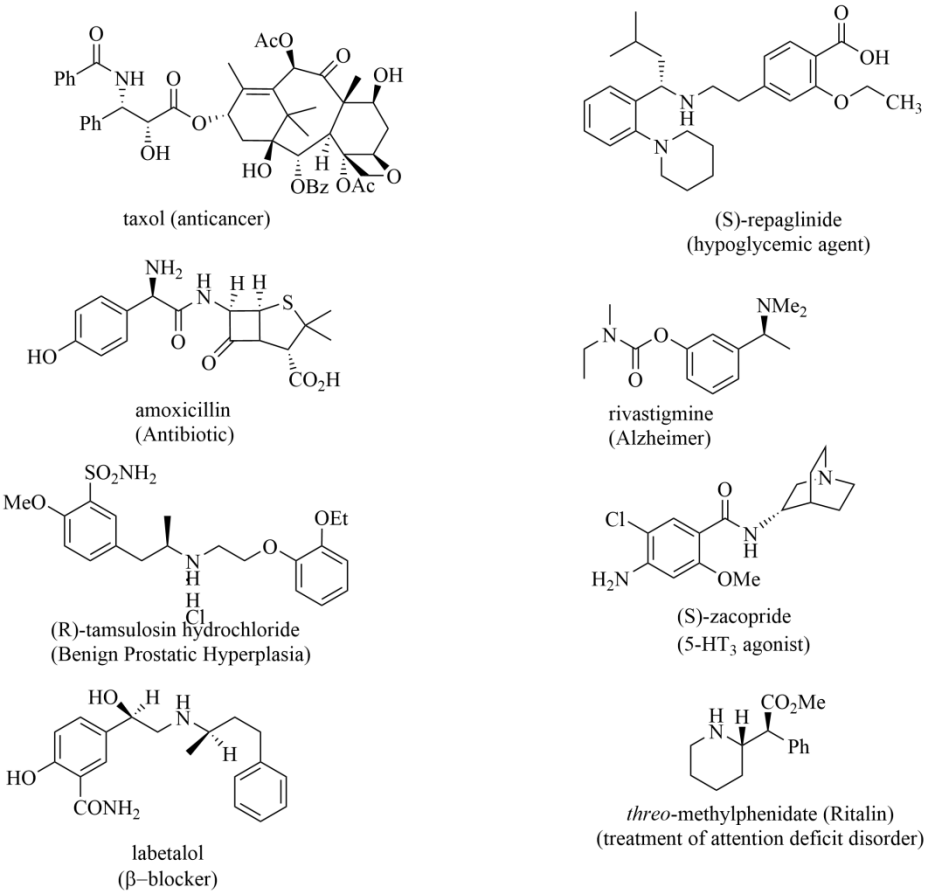


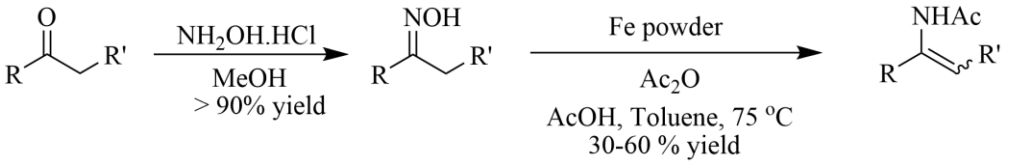
Figure 9. Pharmaceutical drugs with an α-chiral amine moiety.

F. Imine and enamide synthesis-a perspective

A discussion about the preparation of imine and enamide are necessary as most of the examples in scientific journals focus mainly on the manipulation of imines (*N*-phosphinoyl imines) or *N*-acyl enamines as starting materials without a clear picture about their preparations. The overall yield of the chiral amine products is very rarely discussed and therefore a perspective in this regard needs to be established.

The synthesis of imines from ketones require dehydration to drive the reaction equilibrium forward. There are various processes, by which water can be removed from the reaction vessel, one is by azeotropic distillation technique with benzene or toluene with a Dean-Stark trap with [54] or without [55] catalytic *p*TsOH. Molecular sieves can sometimes also be used as dehydrating agents when high temperature might prove detrimental to the products. [56, 57] When the synthesis of ketimine is difficult to form, which is not so uncommon it can be achieved

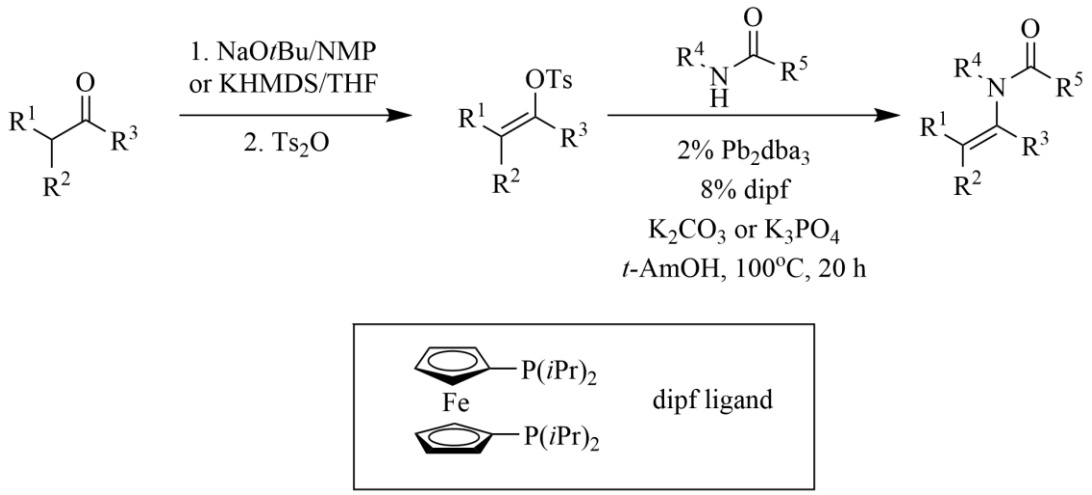
by using the Lewis acid, $TiCl_4$ with triethylmine at temperature range between -35°-0°C. [58, 59] Considering the above methods it can be concluded that imine synthesis are low yielding and tedious, it is therefore desirable to pursue a strategy which avoids the isolation of imines.



Scheme 9. Synthesis of *N*-aceyl enamide from a ketone.

Here we will discuss about two methods of enamide generation. The commonly used method of enamide [60] synthesis is the one in which the desired compound was synthesized from different substituted ketones in two steps as carried out by Burk (Scheme 9). [61] In the first step of this synthesis the ketone is converted to an oxime with hydroxylamine hydrochloride in MeOH, the yield of the ketoxime is generally >90%. The next step is the interaction of the resultant ketoxime with Iron powder and acetic anhydride with AcOH in toluene at a temperature of 75 °C. The yield of the enamide is generally between 30-60% in this step.[61] So, the enamide generation methodology is low yielding overall. Besides possibility of diacetyl formation in the second step is another drawback. The E/Z mixtures obtained with R' as non-hydrogen atom are difficult to separate.

Another method for enamide synthesis was reported recently by Klapars *et al.*, carried out *via* palladium-catalyzed coupling of tosylates and amides (Scheme 10). [62] In this method the tosylates are generated from the ketones with acidic hydrogen by enolate formation by bases such as NaO*t*Bu or KHMDS (for more acidic ketones) which is then converted to a tosylate derivative by *p*-toluenesulfonic anhydride. The amidation is carried out with a palladium complex of chiral dipf ligand (1-4 mol %) with 80-97% yield in *tert*-amyl alcohol as solvent at 100 °C. This is a convenient method for synthesizing tri and tetra substituted enamides. The method is convenient in terms of yield but limited to tosylates bearing aryl substituents or an electron withdrawing group in the double bond.



Scheme 10. Enamine synthesis via Palladium-catalyzed amidation of enol tosylates.

Considering the limitations of the formation of imines and enamides from the examples discussed above it is desirable to avoid their synthesis and thus improve the overall efficiency of the reaction.

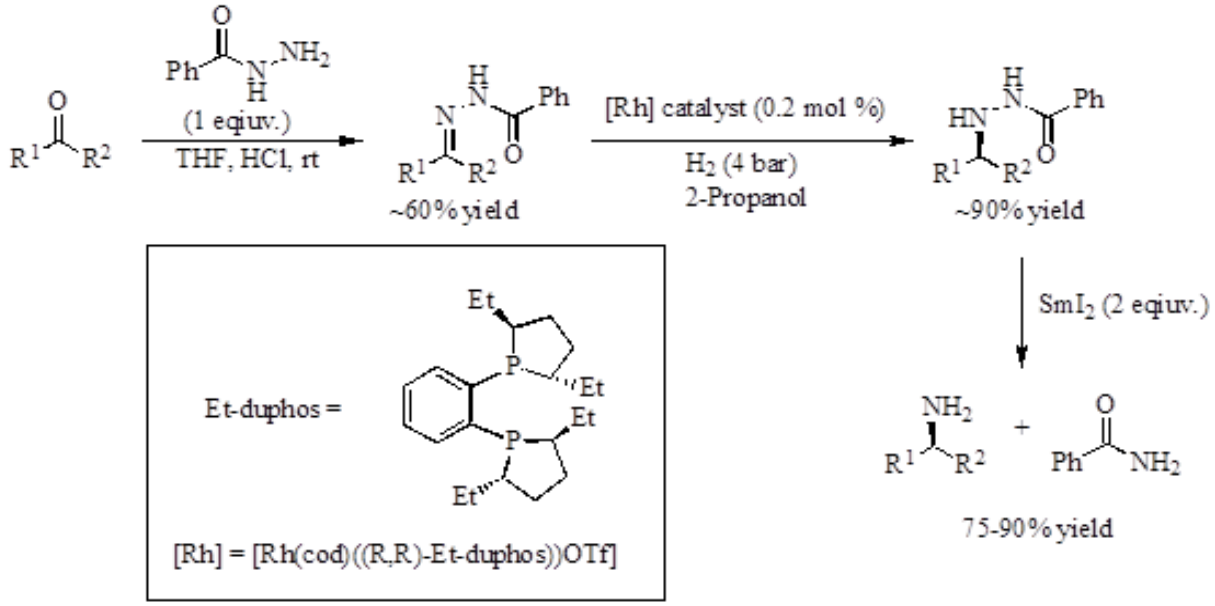
G. Enantioselective reduction of imines

The reduction of unactivated C = N bonds are difficult compared to C = C or C = O reduction due to their lessened reactivity. [63] These bonds are generally sensitive to hydrolysis and the amine product may deactivate metal complexes that act as catalysts. In some examples the Lewis acids are used to activate starting ketones, which may be trapped by imines and/or product amines making the catalytic reactions with these acids difficult to perform.[64] Imines are sometimes used in activated forms in which the nitrogen atom of the imine is linked to groups such as tosyl, [65] sulfinyl, [66] hydroxyl, [67] aryl [68-71] and diphenylphosphinoyl [72] to name a few.

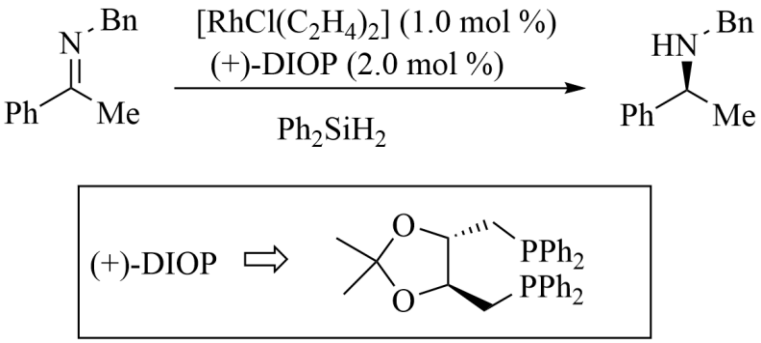
In 1973 Kagan *et al*. reported the first reaction of this kind, in which he achieved a 50% ee by the reduction of *N*-(α-methylbenzylidine)benzylamine with Rh[DIOP] catalyst in 1.0 mol% with diphenylsilylhydride as the hydride donor (Scheme 11). [72] Since this important discovery many other groups have come forth with different solutions to this problem achieving higher enantioselectivity. In the next few paragraphs we discuss some of those methods.

The literature is replete with publications related to enantioselective imine reduction chemistry. This C-N bond formation is an important organic transformation and different chiral catalysts containing ruthenium, [73] rhodium, [74] iridium [75] and titanium [76] transition metals have

shown amazing reactivity and selectivity. However, the substrates chosen as examples are generally limited to aromatic imines. In the case of ketimines, especially enantioselective transfer hydrogenation or hydrogenation of *N*-phosphinoylimines, have shown high enantioselectivity but as recently discussed generally require multi-step synthesis.



Scheme 11. First enantioselective reduction of imines by Kagan [72]

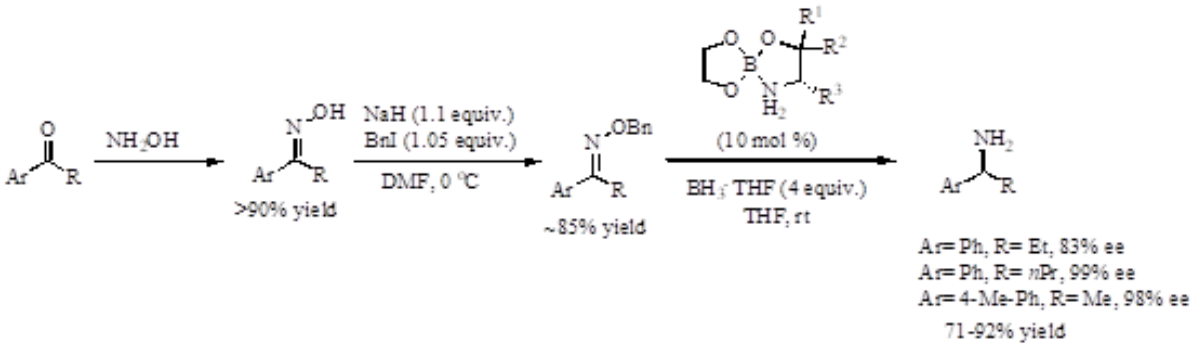


Scheme 12. Burk's catalytic hydrogenation of hydrazones.

Catalytic enantioselective hydrogenation of an activated imine in the form of *N*-benzoyl hydazone derivative has been carried out by Burk *et al.* in presence of of Rh-DuPHOS catalyst (0.2 mol %) and hydrogen (4 bar) (Scheme 12). [77] Aryl-alkyl ketones provided >91% ee with R^1 = *p*-NO_2Ph and R^2 = Me providing the highest ee (97%). The acylhydrazones derived from alkyl-alkyl ketones (such as R^1 = *i*Pr or *t*Bu groups; R^2 = Me) the ees are drastically low (43-

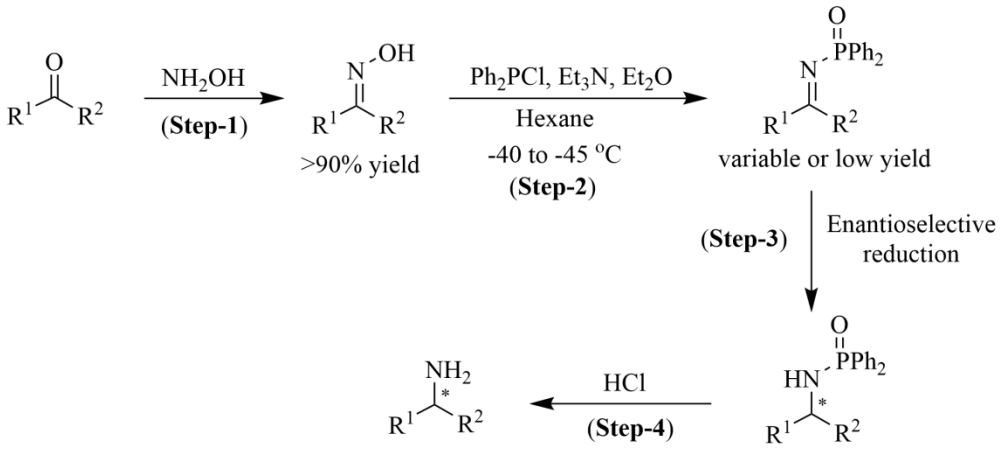
75%). This reaction is carried out in three steps, which involves the formation of the *N*-benzoylhydrazone derivative followed by hydrogenation and cleavage of the nitrogen-nitrogen bond of the benzoylhydrazone moiety. Low overall yield from starting ketones are observed. Obviously, apart from the alkyl-alkyl ketones are not the preferred substrates and also the reactions are marred by long reaction times (36 h).

Recently Oritz-Marciales *et al*.[78] employed their spiroborate esters as catalysts for the borane reduction of O-benzyloxime ethers to primary amines with 10 mol % loading under mild conditions (0 ^{o}C) (Scheme 13). The substrate breadth is limited to acyclic aryl-alkyl ketones (e.g. phenyl ethyl ketone, phenyl-*n*-propyl ketone, etc.) (with 83-99% ee) and cyclic aryl-alkyl ketones (e.g. benzosuberone and 1-indanone) (84-97% ee). These reactions also have the disadvantage of long reaction times (36 h). Besides, high catalyst loadings (10 mol %) and large excess (4 equiv.) of the reducing agent are also some of the limitations.

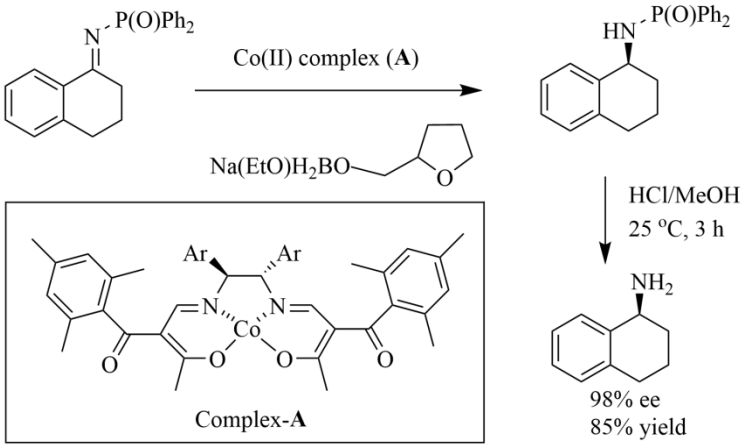


Scheme 13. Enantioselective borane reduction of oxime ethers by spiroborate ester.

Mukaiyama [79] reported the use of chiral cobalt(II) complexes (Complex **A**) (1.0 mol %) in the reduction of *N*-tosyl imines and *N*-diphenylphosphinoyl imines [80] with pre-modified sodium borohydride (Scheme 15). Imines derived from α-tetralone produced the highest ee of 98% under these conditions. The corresponding *N*-tosyl imine derivative provided a low ee (71%). Other aryl-alkyl (cyclic and acyclic) imines with *N*-diphenylphosphinoyl activation provided ees in the range of 90-92%. The method is only limited to aryl-alkyl ketones and also required the synthesis of *N*-phosphinoyl protected imine which reduces the overall yield of the primary amine products derived from them (Scheme 14).

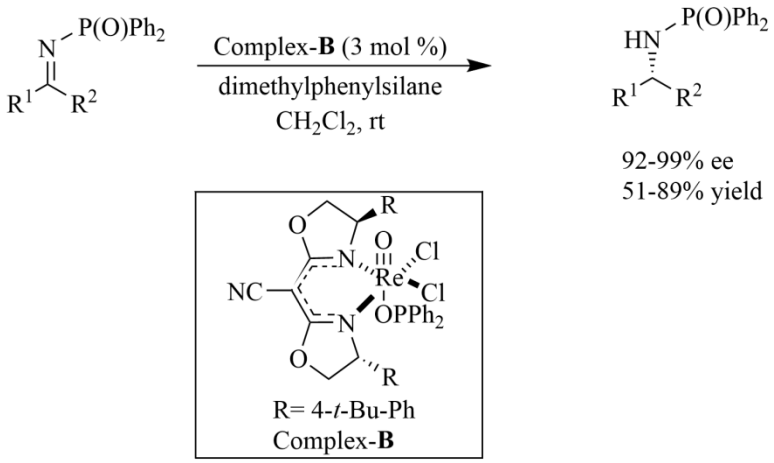


Scheme 14. Four step synthesis of a α-chiral primary amine through *N*-phosphinoylimine.

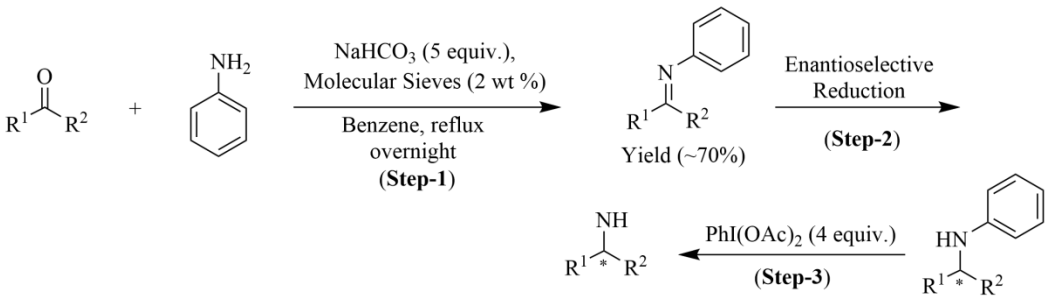


Scheme 15. Mukaiyama's catalytic enantioselective reduction of activated imines.

Toste and coworkers [81] showed the use of a higher oxidation state metal-oxo catalyst (Complex **B**) (3.0 mol %) to enantioselectively reduce *N*-phosphinoylimine substrates (Scheme 16). It is widely observed that low oxidation state transition metal complexes are involved in reduction but use of higher oxidation metal complexes is generally not common for reductions. The Complex-**B** is stable in air and with dimethylphenylsilane as hydride donor provided very high ee (92-99%) for cyclic and acyclic aryl-alkyl ketones. The only demonstrated aliphatic substrate was from cyclopropyl methyl ketone (32% ee). The main advantage of this catalyst is its stability in air which allows the reaction to be performed in an open flask. However, the limited substrate scope, relatively high catalyst loading and stepwise long procedure (as shown in Scheme 14) are the points for future improvement.



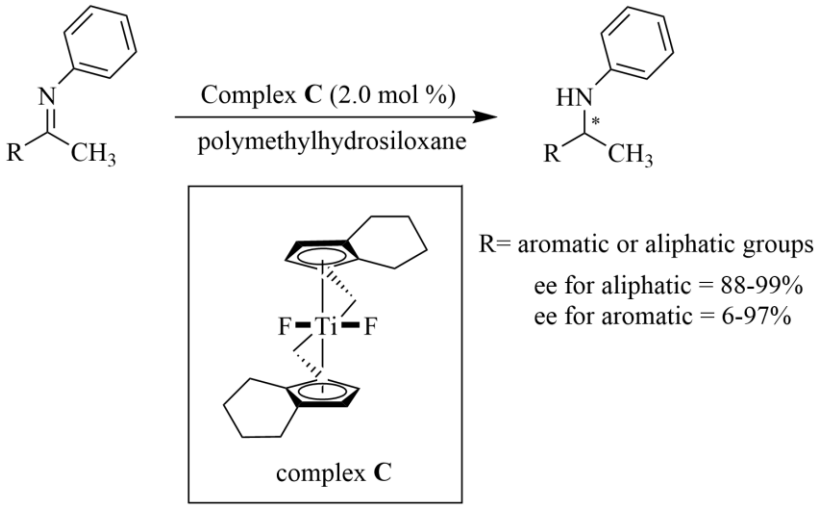
Scheme 16. Chiral Re(V)-Oxo catalyst for imine reduction.



Scheme 17. Three step synthesis of a α-chiral primary amine through *N*-aryl imine.

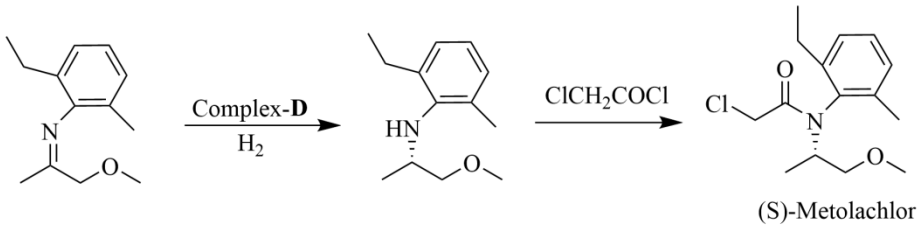
Buchwald and coworkers used ethylene bis (η^5-tetrahydroindenyl) titanium difluoride (Complex **C**) as a precatalyst for the reduction of alkyl-alkyl and aryl-alkyl' substituted *N*-aryl imines (Scheme 18). Polymethylhydrosiloxane was used as the hydride donor and *iso*-butylamine as a promoter. They achieved 88-99% ee for aliphatic R substitutents at 60 ^{o}C. *p*-Methoxy, *m*-methyl substitution on the *N*-aryl moiety provided higher selectivity for alkyl-alkyl imines. Aryl-alkyl imines on the other hand generally provided poor ee except for the imine derived from α-indanone, which gave 97% ee and quantitative yield. [56] Previously, Buchwald also used molecular hydrogen as a reducing agent at 138 bar (2000 psi) using the binaphtholate instead of fluoride analog of the titanocene complex to achieve medium to high ee values (85-98%) for aryl-alkyl substituted *N*-benzyl imines. Imine derived from cyclohexyl methyl ketone provided 76% ee at the above mentioned hydrogen pressure and only 43% ee at 35 bar (500 psi). [55, 82]

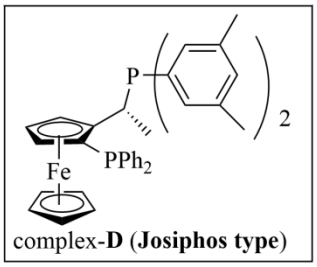
Buchwald used an unparalled substrate breadth of *N*-aryl and *N*-benzyl imines which varies from aryl-alkyl to alkyl-methyl ketones with low catalyst loading (0.1-2.0 mol %) is noteworthy. The yield and ee of the product amines are good to high. However, his methods lack in descriptions regarding imine preparation (Scheme 17) and deprotection of the nitrogen atom (from benzyl and aryl groups) in the final product. Based on literature though it is known that the hydrogenolytic cleavage of the *N*-benzyl amine is facile and high yielding, while the oxidative cleavage of the *N*-aryl products is low yielding. [83]



Scheme 18. Enantioselective reduction of *N*-arylimines with titanocene complexes.

The very long and dedicated work at Solvias enabled the development of ferrocenylphosphine bound Ir complexes as catalysts and achieved 1,000,000 of substrate/catalyst ratio and 80% ee for the reduction of **1**, *N*-aryl imino ether, to produce the (S)-Metolachlor, a potent herbicide (Scheme 19). [84] Splindler and Blaser later modified the Josiphos type ligand (**D**) (in Scheme 19) by introducing cyclohexyl group instead of the phenyl attached to the phosphorus atoms and with *N*-phosphenyl derived imine of acetophenone a 99% ee was achieved at 60 ^{o}C and 70 bar hydrogen pressure. [85]

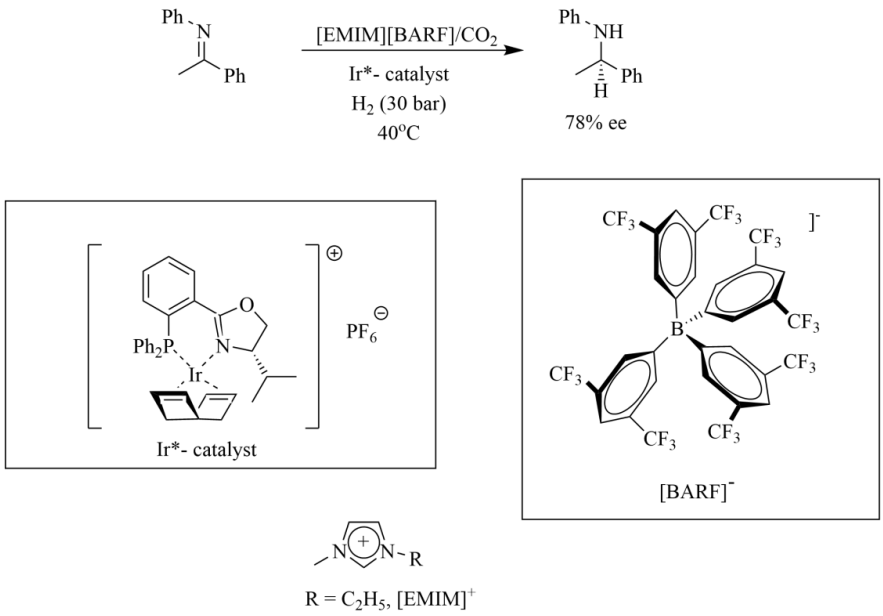




Scheme 19. Synthesis of (S)-Metolachlor at Solvias.

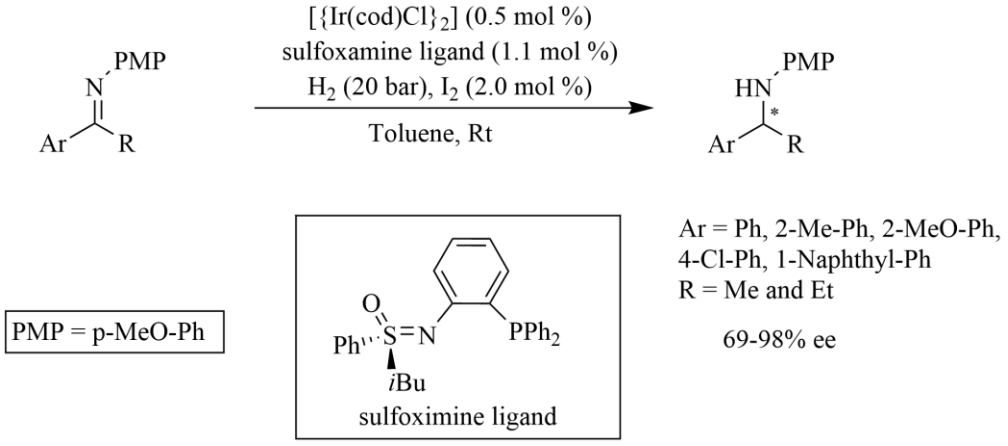
Pfaltz and coworkers have developed phosphine-oxazolidine Ir complexes and used them as catalysts (0.1 mol %) for reduction of *N*-phenylimine derived from acetophenone. He achieved a high ee of 89% and 99% yield. [86] Again this system lacks substrate breadth.

Recently, Pfaltz *et al.* have introduced a new concept in imine hydrogenation utilizing cationic iridium complexes with chiral phosphazoline ligands in ionic liquid (IL)/ supercritical carbon dioxide reaction medium (Scheme 20). He used *N*-(1-phenylethylidene)aniline to give the corresponding amine at 78% ee with [EMIM][BARF] as IL. Here the main focus was to elucidate upon the various advantages of such biphasic systems, they are: 1) the presence of CO_2 can be beneficial or even mandatory for efficient hydrogenation in IL; 2) the precursor catalyst is activated by IL by anion exchange; 3) the anion of IL greatly influence the catalyst selectivity; 4) the product is readily isolated from CO_2 without any contamination by the IL or the catalyst; and 5) the presence of ILs in the system install greater stability to the catalyst. [87]



Scheme 20. Enantioselective hydrogenation of imines in multiphase catalysis.

Bolm and Moessner introduced chiral sulfoximine ligands in enantioselective imine hydrogenation (Scheme 21). The substrates used are generally aryl-methyl or aryl-ethyl substituted *N*-methoxy phenyl imines. He analysed that *ortho*, *meta* and *para* substitution with methyl, methoxy or chloro groups produce high ees (90-98%). However, with imines formed via the reaction of *p*-Cl-acetophenone and 2-naphthyl acetophenone with *ortho*-anisidine provided 75% and 69% ee respectively. The substrate breadth is limited to *N*-aryl imines of aryl-alkyl ketones with no yield reported for their preparations. High hydrogen pressure (20 bar) is another drawback. [69]



Scheme 21. Chiral sulfoximine ligands in imine hydrogenation.

Imamoto *et al.* have utilized the (S,S)-1,2 bis(tert-butylmethylphosphino)ethane with tetrakis-(3,5-bis(trifluoromethylphenyl)borate as the counter ion (Figure 10) to catalyse the hydrogenation of acylic *N*-arylimines of aryl-alkyl ketones under 1 atm of hydrogen pressure at room temperature. Generally for this system it is observed that any substitution pattern on the *N*-aryl group whether electron-withdrawing or donating resulted in good to high ee (80-99%). The low catalyst loading of 0.5 mol %, mild reaction conditions and high yields of the product amines from imines (91-99%) are the main highlight of this catalyst system. The *N*-arylimines of alkyl-alkyl ketones are not the preferred substrates (e.g. *N*-aryl imine of *tert*-butyl methyl ketone gave no product). [68]

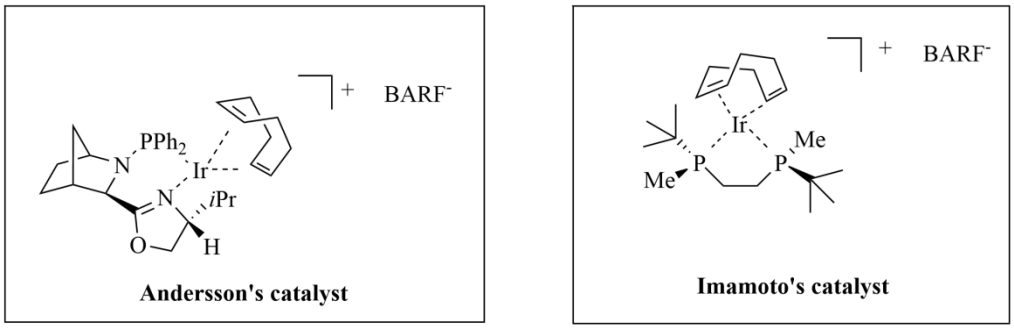
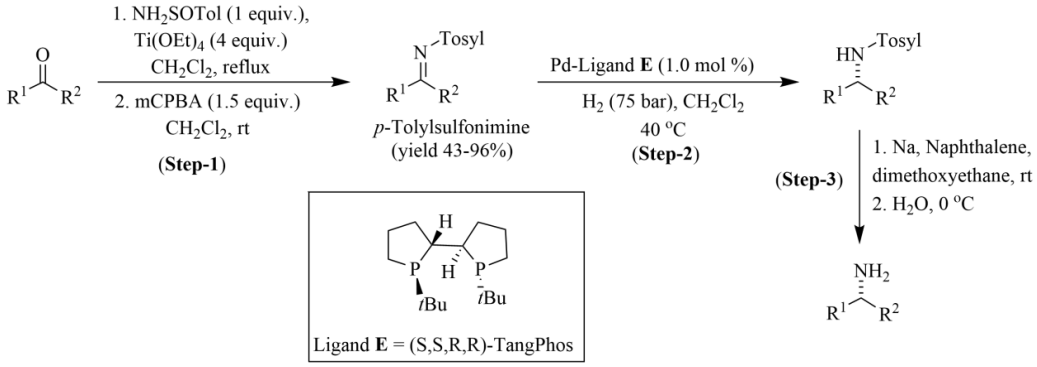


Figure 10. Chiral Iridium catalysts for imine hydrogenation.

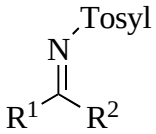
The Andersson group have recently reported the reduction of the acyclic *N*-aryl imines of aryl-methyl ketones with Ir based chiral phosphine-oxazoline complexes (1.0 mol %) (Figure 10). They achieved 83-90% ee on the *ortho* (*e.g.* Me) and *para* (*e.g.* methoxy, chloro and fluoro) substitution patterns on the aryl moiety of these aryl-methyl ketones. The ee decreased to 66% when the *N*-arylimine is replaced by *N*-benzyl imine for one example. Apart from the substrate limitations a high hydrogen pressure (20 bar) and no report on the product yield from imine reduction are the points lacking. [70]



Scheme 22. Three step synthesis of α-chiral primary amines through *N*-tosylimines.

Considering the obstacles faced by different imines like different enantioselectivities for E and Z isomers of acyclic imines, [55, 64, 76a-b] the instability of some imines, and the likely inhibitory effects of some product amines on metal catalysts, Zhang *et al.* chose *N*-tosylimines as substrates (Scheme 22). [88]These imines are relatively stable, highly reactive due to the electron withdrawing nature of the tosyl group and isolated preferably as E isomer. They used $Pd(OCOCF_3)_2$-(S,S,R,R) TangPhos catalyst (1.0 mol %) to perform the hydrogenation on a series of aryl-alkyl and alkyl-alkyl *N*-tosylimines as shown in Table 1. The main highlight of this methodology is the moderate to high ee for imines derived from alkyl-alkyl' ketones (75-98%). Cyclopropyl methyl ketone result (Table 1, entry 4) can be directly compared with Buchwald's method in which a comparable ee was obtained (discussed previously). Cyclic aryl-alkyl *N*-tosylimines derived from α-indanone and α-tetralone provided ees of 98% and 94% respectively. The yield of imine synthesis from these cyclic ketone substrates are moderate (~75%) and so the overall yield of the product amine is relatively higher than other reported methods. A high hydrogen pressure (75 bar) is the major drawback of this methodology.

Table 1. Enantioselective hydrogenation of *N*-tosylimines. [88]

Entry	Imine structure	R^1	R^2	ee (%)
1		Ph	CH_3	99
2		Ph	C_2H_5	93
3		*t*Bu	CH_3	98
4		Cyclopropyl	CH_3	75

Enantioselective transfer hydrogenation reactions for transforming imines to amines have been examined by Noyori's group. [89] They used some chiral ruthenium diamine catalysts with cyclic imines as examples. Formic acid and triethyl amine were used as a hydrogen source and the reaction was carried out under mild conditions with low catalyst loadings (0.1-1.0 mol %). The enantioselectivity varied from 94-97% for these cyclic imines. *N*-benzylimines derived from acetophenone, which is an acyclic imine showed an ee of 77%. One of the imines was reduced even in acetone as solvent showing overwhelming chemoselectivity in favor of imines. The reported yield from this transformation is good (72-82%) to high (90-99%).

Avecia Limited have used CATHy^{TM} (Catalytic Asymmetric Transfer Hydrogenation) catalysts in enantioselective imine reduction of three main substrates as shown in Table 2. [46] This is a four step process (Scheme 14) with industrially acceptable catalyst loadings (0.25-1.0 mol % for Rh catalysts and 1.0 mol % for Ir catatysts) documented in a review. [90] This method was demonstrated to be feasible in an industrial scale. [91]

Table 2. Imine reduction by Avecia Limited method. [90]

Entry	Substrate	Preferred metal[a]	Amine Product ee (%), overall yield (%)
1	1-Acetyl naphthalene	Rh[b]	99, 46
2	Acetophenone	Rh[c]	86, 64
3	2-Octanone	Ir[d]	95, 48

[a] Refers to the enantioselective reduction of phosphinoyl imines, 24 equiv. of Et_3N/ HCO_2H (2:5 ratio), rt.

[b] 0.25 mol% of $[RhCp^*Cl_2]_2$ with 0.5 mol % (R,R)-*N*-tosyl-1,2-diamino-1,2-diphenylethane.

[c] 1.0 mol% of $[RhCp^*Cl_2]_2$ with 2.0 mol % (R,R)-*N*-tosyl-1,2-diamino-1,2-diphenylethane.

[d] 1.0 mol% of $[IrCp^*Cl_2]_2$ with 2.0 mol % (R,R)-*N*-tosyl-1,2-diamino-1,2-diphenylethane.

H. Enantioselective reduction of enamides

It was previously described that *N*-acyl enamide synthesis is a two step process and a further two steps are involved, reduction of the enamides and hydrolysis of the enamide, before the primary amine is obtained in mediocre overall yield (~50%). These enamides generally are obtained as E and Z mixtures, but this does not affect enantioselectivity in the reduction and are obtained in high *ee*. Two general substrates are generally chosen in enamide reduction protocol, pinacolone and aryl-alkyl ketones. [61b, 92] Non *N*-acyl enamines, i.e. enamines, as of yet cannot function as substrates for this methodology. This should not be confused with the successful reduction of some classes of enamines originating from β-keto esters. [47] Here, we mainly focus on enamide methods allowing alkyl-alkyl' and aryl-alkyl substituted α-chiral amine synthesis.

Burk and coworkers [61a-b] have chosen aryl-alkyl or alkyl-alkyl' enamides as substrates and achieved high *ee* (>95%) with Rh[Me-DUPHOS] or Rh[Me-BPE] catalysts (Figure 11). The

substrates chosen are mainly acyclic and benzocyclic aryl-alkyl ketones, and for alkyl-methyl ketone with sterically encumbered group such as *t*Bu (pinacolone) as alkyl substituent. The main point that is lacking in this work is the absence of any definitive yields from the starting ketone to the chiral amine synthesis. The substrate breadth for alkyl-alkyl ketones is also limited.

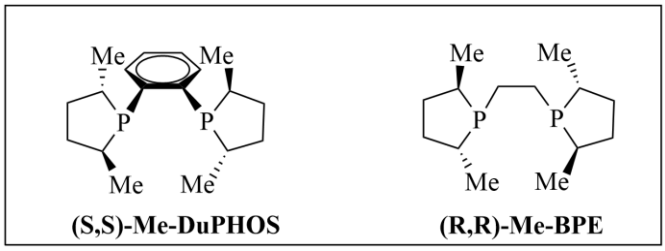
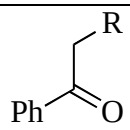


Figure 11. Chiral ligands used by Burk in enamide hydrogenation.

Table 3. Enantioselective *N*-acetyl-α-aryl-enamide reduction by Zhang. [93, 95]

Entry	Ketone (general structure)	R	Chiral catalyst used	ee (%)
1		H	$[Rh(COD)_2]SbF_6$-(R,S,S,R)-DIOP (2.0 mol %)	98
2		CH_3	$[Rh(COD)_2]SbF_6$-(R,S,S,R)-DIOP (2.0 mol %)	97
3		Et	$[Rh(COD)_2]PF_6$-(R,R)-Binaphane (1.0 mol %)	97
4		*i*Pr	$[Rh(COD)_2]SbF_6$-(R,S,S,R)-DIOP (2.0 mol %)	99
5		Bn	$[Rh(COD)_2]SbF_6$-(R,S,S,R)-DIOP (2.0 mol %)	99

Zhang has reported extensively on enantioselective reduction of *N*-acetyl enamides. In Table 3 high *ee* is reported for R substitutions with long reaction times varying between 48-60 h under mild conditions of temperature and hydrogen pressure (10 bar) (applicable for entries 1, 2, 4 and 5). [93] Earlier (R,R)-BICP ligand was used with $[Rh(COD)_2]OTf$ (1.0 mol %) for enamide hydrogenation (2.8 bar H_2) (Figure 12). This catalyst provided high ees ranging from 86-95% for aryl-alkyl ketones with different substitution patterns on the aryl ring (this includes 2-naphthyl). With this catalyst ees in the range of 60-78% are achieved for cyclic enamides.[94] (R,S,R,S)-Me-Pennphos ligand with $[Rh(COD)_2]PF_6$ proved fruitful for the cyclic *N*-acetyl enamides derived from benzocyclic ketones, e.g α-tetralone, α-indanone and α-chromanone. Excellent ees (90-99%) were obtained with different substituents on the aromatic ring. [95] Another chiral catalyst based on (R,R)-binaphane and $[Rh(COD)_2]PF_6$ (1.0 mol %) provided high ees (82-99%) for E/Z

mixture of enamides derived from ketones e.g. acetophenone, ethyl phenyl ketone, propyl phenyl ketone, *iso*-butyl phenyl ketone, benzyl phenyl ketone and 2-naphthyl methyl ketone. [96] Zhang *et al*. synthesized (S)-o-Ph-hexMeO-BIPHEP ligands and carried out the hydrogenation of cyclic enamides with $[Rh(NBD)_2]SbF_6$ and obtained excellent ee (96-98%). The drawback of this catalyst is that substitution at β-position in enamides derived from β-tetralone, α-chromanone or acetophenone, however, showed low enantioselectivity (37-70%). [97] Zhang and Tang designed another new chiral ligand namely 1,2-bisdiphosphane (TangPhos) (Ligand **E** in Scheme 22) and used them in the asymmetric hydrogenation of α-enamides to achieve ee >97% irrespective of different substitution patterns on the phenyl ring. [98] Another problem in this enamide hydrogenation chemistry is the limited progress made in substrates with *ortho* substituted groups in the α-aryl moiety of the *N*-acetyl enamides. Chiral pseudo-C_2 symmetric phosphine-phosphoramidite ligands along with $[Rh(COD)_2]BF_4$ proved fruitful and a high ee (87-99%) was achieved. [99]

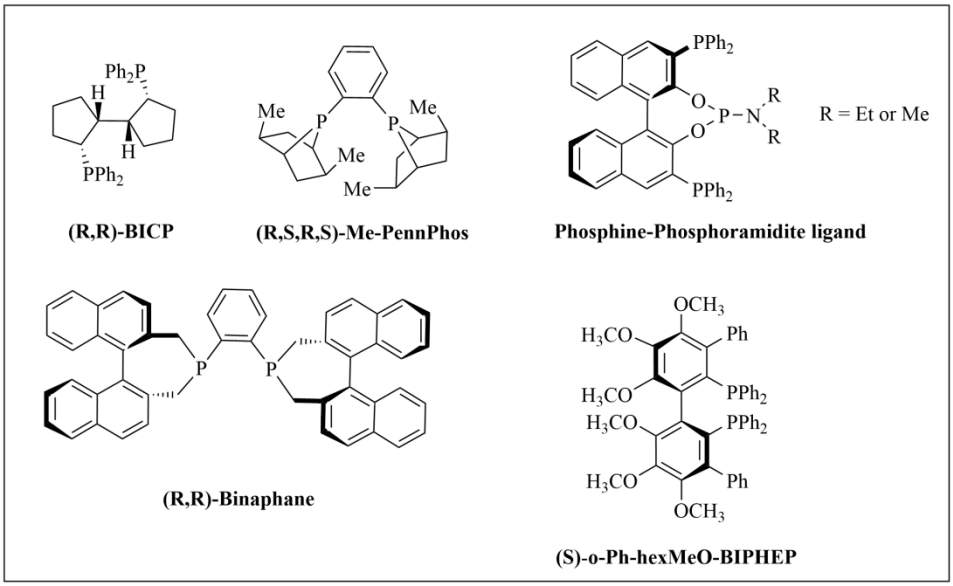
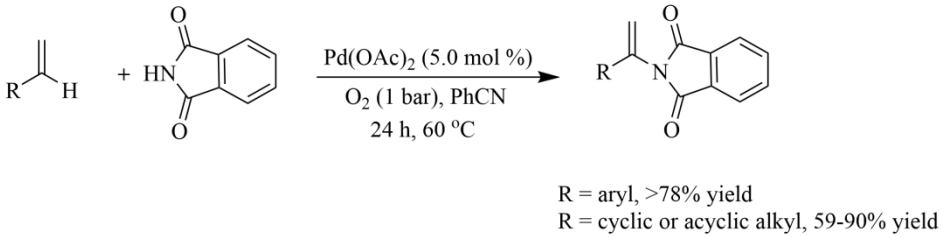


Figure 12. Chiral ligands used by Zhang in enantioselective *N*-acetyl-enamide hydrogenation [93-99]

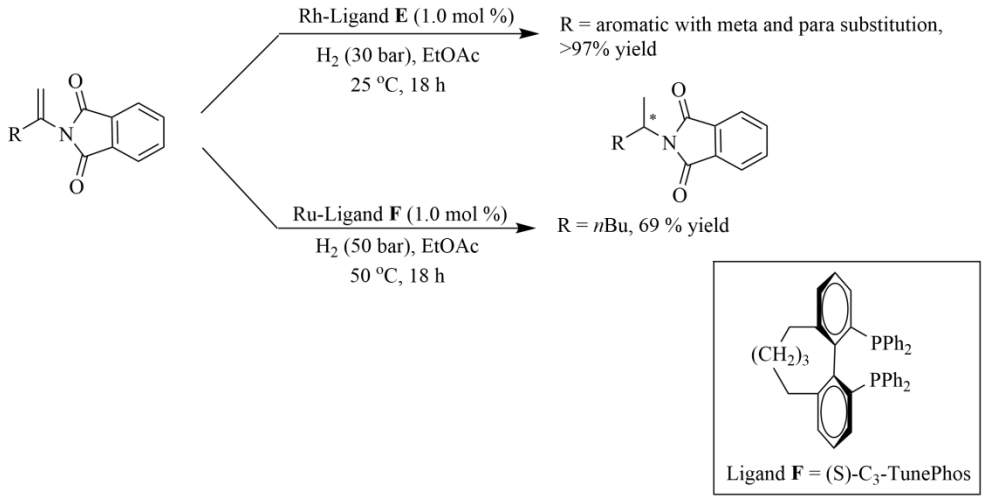
There is one report on the reduction of *N*-phthaloyl enamide by Zhang and coworkers. They have used Stahl's [100] method of oxidative amination of alkenes to synthesize pthalidomide derivative of aryl or alkyl enamides (Scheme 23). [Rh (R_P,S_C)-TangPhos] complexes are found to be effective catalysts for such transformations as shown in Scheme 24. 1.0 mol % of the catalyst loading with a hydrogen pressure of 30 bar at room temperature provided excellent ee (>97%) for *para* substituents on the aromatic moiety with *ortho* substituted phenyl rings

provided poor enantioselectivity (46% for chloro and 28% for methyl). Alkyl enamides with allylic hydrogen was also hydrogenated to provide only 69% ee but under harsh conditions such as 50 atm and 50 ^{o}C using [Ru-(S)-(C_3)-TunaPhos] (Ligand **F** in Scheme 24) catalyst. Clearly again we can find another system not beneficial for aliphatic primary amine synthesis. [101] Again the hydrolysis of the phthalimide, though high yielding (98%), is carried out under harsh condition (EtOH reflux) in presence of hydrazine. [102]



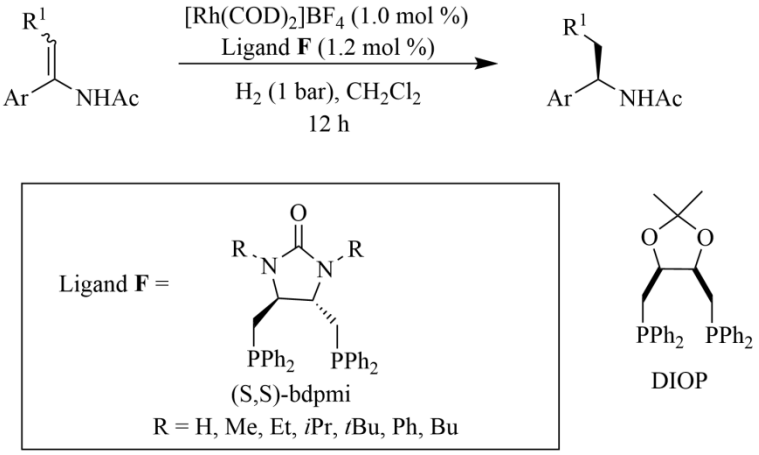
Scheme 23. Aerobic oxidation of unactivated alkenes catalyzed by $Pd(OAc)_2$

Immobilization of homogeneous catalysts on solid supports could solve some problems inherent in the homogeneous systems i.e. catalyst recovery for recycle and metal leaching into the products. Ding *et al.* envisioned some self-assembled metal-organic framework which contain porosity and absorption capacity of organic guest molecules. In order to forsee the utility of this system they used Feringa's Rh/monophos complexes for enantioselective hydrogenation of β-aryl or alkyl substituted dehydro-α-amino acid and enamide derivatives. Examination of dehydo amino acid derivatives showed excellent ee ranging from 94-97% which is comparable to that showed by homogeneous catalysts, and for *N*-acetyl-α-aryl enamides this system proved to be superior (96-97% ee) to homogeneous catalytic processes (88-89% ee). Low catalyst loadings (1.0 mol %) and mild conditions along with the ability to recycle these catalysts (7 times with 5% variation in ee) are the main features of this system. [103]



Scheme 24. Enantioselective hydrogenation of *N*-phthaloyl enamides

Kagan and Dang [72] developed the first C_2 symmetric ligand (DIOP) in the early 1970 and since then many analogs of this ligand have been developed and applied in various asymmetric synthesis but provided poor enantioselectivity. The main reason for this is attributed to the conformationally flexible backbone of these ligands form seven-membered metal-chelate complexes, which results in inefficient chirality transfer through the methylene moeity to the phenyl groups. In order to overcome such shortcomings Lee *et al.* designed a ligand, (S,S)-bdpmi, with gauche interaction with *N*-substituents and the phosphomethyl groups (Scheme 25). According to the authors, this interaction influence the conformational flexibility of the seven-membered chelate with the metal-complex. The simple (S,S)-DIOP ligand provides only 60% *ee* for the enantioselective hydrogenation of enamides while the ligand (S,S)-bdpmi provided an enhanced ee ranging from 86-97%. Varying the R^1 group in the substrate enamide provided higher enantioselectivity with electron-donating groups than with electron-withdrawing groups. E-and Z- mixtures of *N*-acetyl enamides were also hydrogenated with excellent *ee* (>99%).



Scheme 25. 1, 4- Diphosphane ligands with imidazolidin-2-one backbone

Reetz and coworkers [105] used a hetero combinations of (1:1 ratio) monodentate phosphite, phosphonite and phosphine ligands (Figure 13) with Rh as a transition metal to gain a remarkable improvement in enantioselectivity. He used *N*-acetyl-α-aryl enamides e.g. enamides derived from acetophenone and obtained a 97% ee with hetero combination of phosphine (R = benzyl) (**2**) and phosphite ligands (R = *t*Bu) (**3**) (while a homo combinations of the same ligands provided **2** = 91%, and **3** = 13% respectively). With 2-naphthyl methyl ketone derived *N*-acetyl enamides he used the same combination but with R = CH_3 (**4**) on the chiral phosphine ligand and achieved a ee of 97% (while a homo combinations of the same ligands provided **4** = 76%, and **3** = <3% respectively). Though there is no yield and substrate breadth provided by the authors the reaction is a relatively new approach.

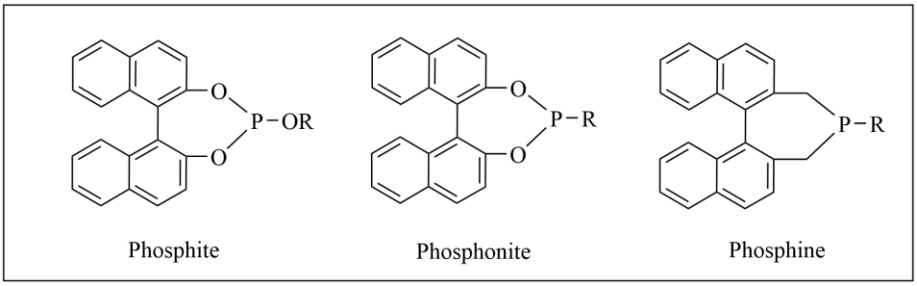
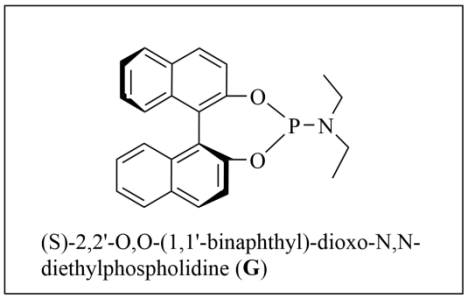


Figure 13. Different monodentate phosphorus containing ligands.

In another example, Chan and coworkers used monodentate phosphoramidite ligand (S)-**G** (Figure 14) along with Rh for enamide hydrogenation and achieved excellent ee (>99%) for *p*-trifluoro methyl substituted α-aryl enamides. Electron-donating or electron withdrawing groups attached to the aryl moiety were used as examples and ee of >93% are obtained and >99% yield.

1-naphthyl methyl ketone derived enamide proved less efficient (ee of 59%) was obtained for this catalyst system. [106]



(S)-2,2'-O,O-(1,1'-binaphthyl)-dioxo-N,N-diethylphospholidine (**G**)

Figure 14. Mondentate Phosphoramidite ligand.

The use of unsymmetric ligands is uncommon in hydrogenation of enamides. Recently, Zhang *et al.* described the importance of the unsymmetrical bidentate ferrocene based phosphine-phosphoramidite ligands (Figure 15). The combination of $Rh(COD)_2BF_4$ and (S_c,R_p,S_a)-**H1** or (S_c,S_p,R_a)-**H3** proved to be the best among these group of ligands for hydrogenation of *N*-acetyl-α-aryl enamides with ee of >98%. The axial chirality of the binaphthyl backbone play a crucial role in reactivity and selectivity. However, the substrate breadth is only limited to acetophenone derived enamides and its p-substituted analogs. The main advantage of this catalyst system is generally its ease in preparation and air stability.

Examining all the various enamide synthesis methodologies especially with *N*-acetyl enamides we find a general lack in reported isolated yields. The ultimate product α-chiral primary amine synthesis is a four step process through this enamide generation strategy and produces a low overall yield. Besides, the last step of amide hydrolysis requires harsh acidic or basic conditions, which can be detrimental to other functionalities present. Nevertheless, these drawbacks does not reduce the efficacy of this procedure and its industrial value due to high *ee*s and high yields in the enantiodifferentiating step.

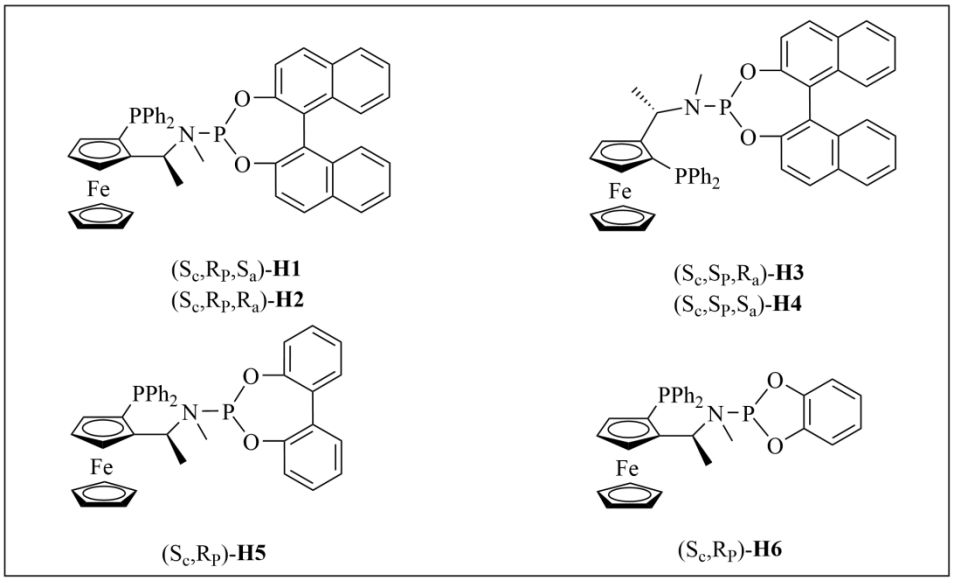
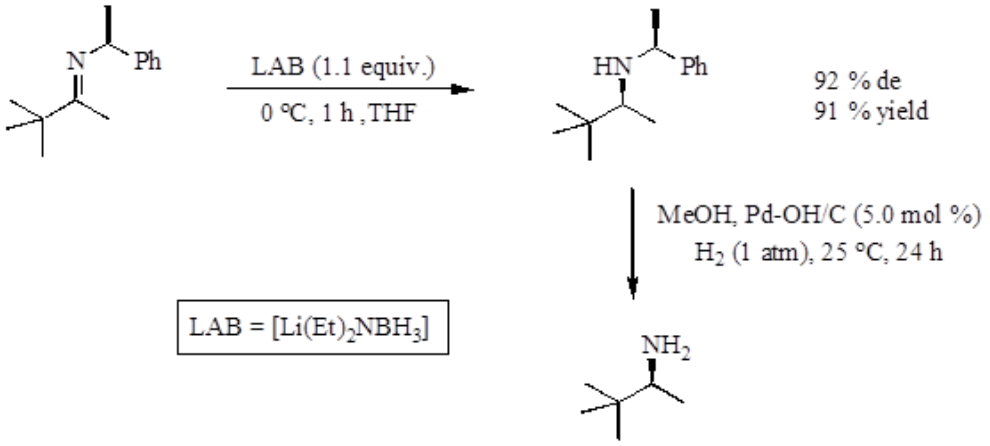


Figure 15. Unsymmetrical bidentate ferrocene-based phosphine-phosphoramidite ligands.

I. Imine to chiral amine-an auxiliary approach

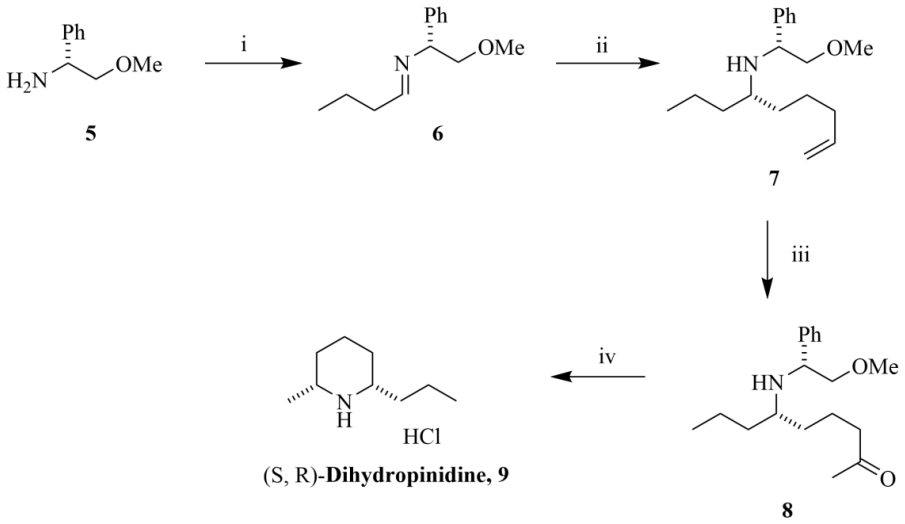
The presence of chiral auxiliary influences diastereoselectivity by facilitating the attack on the substrate concerned from a preferred direction. The auxiliary is then removed from the product to obtain the necessary chiral compound. This reactivity pattern is followed in diastereoselective imine reduction with α-methylabenzylamine (α-MBA) as the chiral auxiliary. The reduction is usually carried out by hydrogen or by hydride donors.

Singaram *et al.* reported the synthesis of chiral alkyl-alkyl' and aryl-alkyl primary amines by the reduction of their corresponding imines derived from α-MBA with lithium disopropylaminoborohydride [Li(*i*Pr)$_2$NBH$_3$] or lithium diethylaminoborohydride [Li(Et)$_2$NBH$_3$] as hydride donors. In one example, the imine derived from pinacolone and reduced with [Li(Et)$_2$NBH$_3$] gave a 92% de and 91% yield (Scheme 26). The diastereoselectivity for long chain aliphatic ketones are generally low (e.g. 34% for 2-octanone) and for aromatic ketones showed moderate de (51-66%). The product chiral primary amine was obtained by hydrogenolysis using Pd(OH)-C (1.0 mol %) under mild conditions of temperature and pressure. Here, again there is a lack in reported data regarding imine formation.



Scheme 26. Diastereoselective imine reduction with LAB reagents.

Reagents (with yields): i) *n*-butanal, 3 Å MS, CH_2Cl_2; ii) CH_2=$CH(CH_2)_3Br$, Mg, $CeCl_3$, THF (85%); iii) $PdCl_2(MeCN)_2$, $CuCl_2$, O_2, MeOH (74%); iv) H_2/Pd-C, HCl, MeOH (73%).



Scheme 27. Asymmetric synthesis of (S,R)-dihydropinidine using (R)-phenylglycinol-O-methyl ether

Chiral auxiliary approach is an important strategy for natural product synthesis. Here is an example for the synthesis of *cis*-dihydropinidine, a piperidine alkaloid, distributed in *Pinaceae* with (R)-phenylglycine derivative as the auxiliary (Scheme 27). The interesting feature of this method is the presence of less bulky O-methyl substituent of the chiral imine derivative (**6**), which affected the diastereoselectivity in the reaction with organocerium reagents. O-methyl glycinol derivative (**5**) reacted with *n*-butanal to the desired chiral imine (**6**) as a single diastereomer with E configuration. The required organocerium reagent was prepared from the corresponding Grignard reagent and $CeCl_3$ *in situ* and when reacted with the imine **6** resulted in

the product **7**. This secondary chiral amine **7** can be oxidized by Wacker oxidation of terminal olefins method using a reagent combination of $PdCl_2(MeCN)_2$, $CuCl_2$ in presence of molecular O_2 to obtain **8** in 74% yield. The desired final chiral alkaloid **9** was then obtained from **8** by heterocyclization, stereoselective reduction and clevage of the auxiliary by hydrogenolysis using 10% Pd-C and hydrogen (1 bar) in 73% yield. [109]

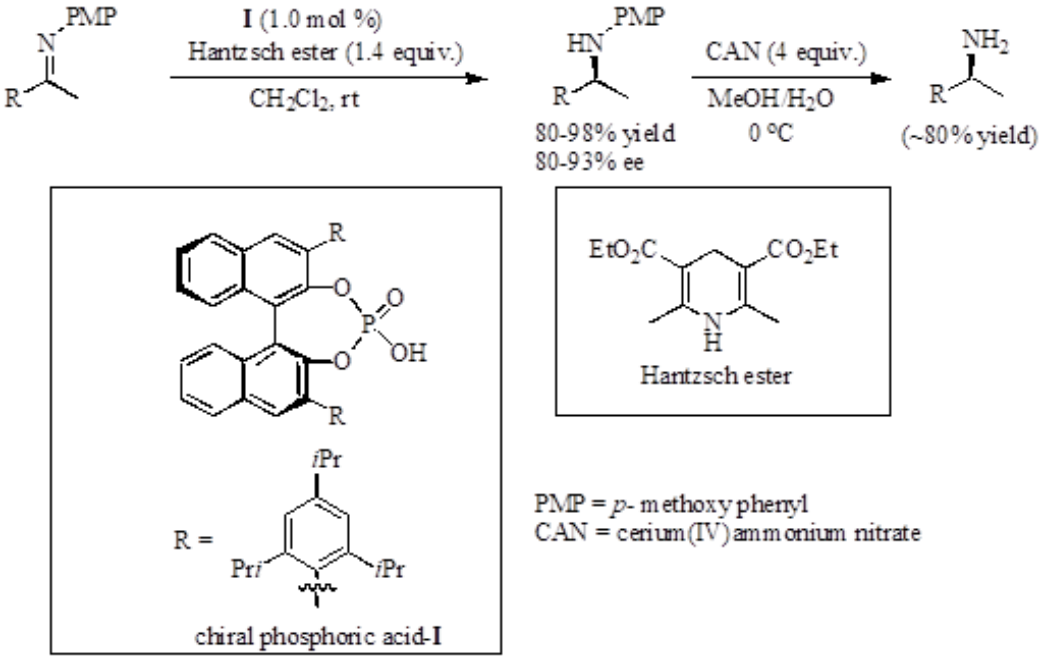
Gutman and coworkers have synthesized primary amines from various benzocyclic ketones such as α-indanone, α-tetralone and benzosuberone with α-MBA as the chiral auxiliary. The imines were synthesized first in presence of catalytic amount of trifluoroacetic acid in toluene with azeotropic removal of water. In the next step these imines were reduced with $NaBH_4$ at low temperatures (-20 ^{o} to -30 ^{o}C). The secondary amines were then hydrogenolysed in presence of AcOH with Pd-C and hydrogen (4 bar) to obtain the desired primary amines. There are two benzylic carbon centers attached to the nitrogen atom and hence possibility of cleavage of both C-N bonds are possible. The ratio is described numerically below in favor of the benzocyclic primary amine formation *vs* α-MBA formation: a) α-indanone, 2.2:1; b) α-tetralone, 3.5:1 and c) benzosuberone, 45.5:1. The main disadvantages of this methodology are tedious synthesis of imines, low product yield and requirement of low temperature for imine reduction. [110]

In another methodology $Zn(BH_4)_2$ was used as a reducing agent and α-MBA as the auxiliary by Cimarelli and Palmieri at 0 ^{o}C. They have reduced a wide range of substrates with different substitution patterns for aromatic to aliphatic ketones. They have achieved the highest de of 95% with 2-phenanthryl derivative. Electron donating groups on the aryl ring of aromatic ketones provided high de as compared to electron withdrawing groups. Aliphatic ketones (e.g. ethyl methyl ketone, *iso*-propyl methyl ketone, tert-butyl methyl ketone, *iso*-pentyl methyl ketone and phenylethyl methyl ketone) provided low to moderate de (43-72%) and yield (51-78%), increasing with steric bulk of the alkyl substituted ketones. [111]

J. Enantioselective imine reduction-organocatalytic approach

Literature is replete with examples of transition metal catalyzed enantioselective reduction of imines but only a few reports have appeared using organocatalysts. Transition metal catalyzed reactions require difficult multi-step synthesis to prepare the chiral ligands, expensive reagents and contamination of the products with toxic metals. This encouraged scientists to develop metal free catalyst systems. Compared to olefin or ketone hydrogenation reactions with

organocatalysts, imine reduction have only been studied recently. List [112] and Rueping [113] have utilized Hantzsch esters as hydride donors for imine reductions taking advantage of the chiral Brønsted acid catalysts developed by Akiyama [114] and Terada. [115] The living organisms use dihydropyridine cofactors such as nicotinamide adenine dinucliotide (NADH) with enzyme catalysts for imine reduction. In the example discussed here List *et al.* used Hantzsch ester (as biomimetic hydrogen source) for *in vitro* imine reduction (Scheme 28).



Scheme 28. Imine reduction with a chiral organocatalyst.

List *et al.* utilized chiral phosphoric acid **I** (1.0 mol %) for the reduction of chiral imines with Hantzsch ester (1.4 equiv) as hydride donor. A series of different substitution patterns at the aromatic group (R) such as electron withdrawing (-NO_2, CN) and electron donating (OMe, Me) showed high ee (80-93%). Even alkyl-alkyl' imines derived from iso-propyl methyl ketone showed high ee (90%). Although the low catalyst loadings of these organocatalysts is an advantage but long reaction times (42-71 h) is the major limitation of this procedure. The synthesis of primary amines from ketones by this methodology is a three step process with the last step involving the deprotection of the imine by oxidative cleavage of the PMP group (*p*-methoxy phenyl) with CAN (cerium(IV)ammonium nitrate). [112]

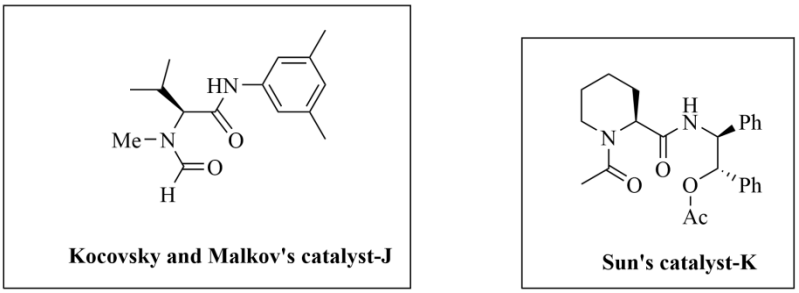


Figure 16. Lewis basic organocatalyst for imine reduction.

Kocovsky and coworkers designed a Lewis basic organocatalyst **J** (figure 14) derived from O-methyl-L-valine encouraged by Matsumura's L-proline derived formamides. [115] All the different functionality present in the catalyst framework are important and contribute to the overall reactivity and enantioselectivity of N-aryl ketimines with trichlorosilane as the hydride donor. The non-covalent interactions such as hydrogen bonding and π-π stacking with the hydride donor and the aryl group of the ketimine respectively are the driving forces behind this whole catalytic activity. This catalyst failed to impose greater enantioselectivity on aliphatic substrates and only limited to aryl groups. Recently, another organocatalyst (**K**) was derived from L-pipecolinic acid (Figure 16) by Sun *et al.* and used in the imine reduction with trichlorosilane. This catalyst is easy to synthesize and provided ee ranging from 87-96% under mild conditions, but with high catalyst loading (10 mol %). The substrate breadth of the catalyst is noteworthy as it includes alkyl-alkyl' imines as well with high ee (>87%) and yield (75-86%).

K. Reductive amination-an important strategy to synthesize chiral primary amines

Considering the above mentioned strategies of imine and enamide reduction the main drawback is the preparation of the starting materials (here imine and enamides) (generally low yielding and lengthy) and protection-deprotection sequences to ultimately produce the chiral amine. Reductive amination is the direct conversion of prochiral ketones or aldehydes to chiral amines in one or two steps using different reduction methods, which include, hydride reduction, transfer hydrogenation and hydrogenation. The main highlight of this strategy is to avoid conversion of the starting carbonyl substrates to intermediates thus saving time and cost of producing them making this process industrially attractive.

The industrial group of Riermeier (Degussa AG) [118, 119] and the academic group of Börner [119] have independently and also in combination made the most important breakthrough till

date in this methodology. They have reported the reductive amination of acetophenone (and its different substitution patterns), acetylnaphthalenes, and phenyl ethyl ketone in high yield and ee (Table 3). In this one-step synthesis of aryl-alkyl substituted chiral primary amines transfer hydrogenation condition of Leuckart-Wallach type, excess NH_3/ $HCOONH_4$ (80 ^oC, ~20 h) have been used. (R)- or (S)-BINAP (or derivatives thereof) have used as the chiral ligand along with $RuCl_2$ complex as a catalyst with a loading varying from 0.5 to 1.0 mol %. In the reaction along with the primary amine a formyl derivative (RHNC(O)H) is produced and in order to improve the yield the crude product is treated with HCl ($EtOH/H_2O$) at reflux to obtain the desired amine in good to excellent yield.

This methodology is not free from disadvantages, the main drawback is the low yield and ee for other aromatic substrates, e.g. 1-indanone (6% yield, no reported ee, chiral Ru catalyst) [119] and aliphatic ketones, e.g. 2-octanone (44% yield, 24% ee, using chiral Ru catalyst) [118]. The authors have recently made a publication on the use of aromatic substrates and hydrogen in reductive amination. [120] The scope now remains on the conversion of aliphatic ketones to chiral amines by enantioselective reductive amination.

The history of reductive amination defines it as a combination of Brønsted acid, a ketone and a reductant to produce the amine, [121] this Brønsted acid strategy was replaced by mild titanium(IV) alkoxides by Mattson *et al.* in 1990 by some modification from the titanium amide chemistry. [122] $Ti(OiPr)_4$ was used as the mild Lewis acid, prestirred with a ketone and amine, $NaBH_3CN$ was the hydride reduction source. Considering the importance of atom economy in chemical reactions hydrogen was developed as a reduction source in asymmetric reductive amination. Reductive amination of enantiopure quinuclidinone by $Ti(OiPr)_4$/Pt-C/H_2 to produce an efficient synthesis of quinuclidine was the starting point for this hydrogenation strategy. [123]

This was then extensively used by our group to synthesize α-chiral primary amines with chiral auxiliary approach (enantiopure (R)- or (S)-α-methylbenzylamine) and a variety of substitution a patterns e.g. alkyl-alkyl' and aryl-alkyl with both aromatic and aliphatic ketones. In this process the nitrogen atom and a new stereogenic center is incorporated simultaneously into the carbonyl carbon of the prochiral ketone avoiding the normal stepwise long procedures with this chiral auxiliary procedures as discussed previously with imines. The use of mild conditions makes the process more advantages for substrates bearing sensitive functionalities such as acetonides, ethers, silyl ethers, bulky esters, secondary amides, tertiary urethanes, etc. There are some

shortcomings for this system as well with non-branched 2-alkanones providing low diastereoselectivity (<75%) and 3-alkanones providing negligible diastereoselection (<5%).

Table 3. Reductive amination by transfer hydrogenation. [118, 119]

Substrate	Yield of the primary amine (%)	ee (%)
Acetophenone	92	95
Phenyl ethyl ketone	89	95
3'-Methylacetophenone	74	89
4'-Methylacetophenone	93	93
4'-Methoxyacetophenone	83	95
4'-Chloroacetophenone	93	92
4'-Bromoacetophenone	56	91
4'-Nitroacetophenone	92	95
1-Acetylnaphthalene	69	86
2-Acetylnaphthalene	91	95
2-Octanone	44	24
2-Methylcyclohexanone	63 (64 *cis*, 36 *trans*)	17 *cis*, 64 *trans*

3. CONCLUSION

Considering the various methodologies discussed above it can be concluded that no general trend can be definitely stated, but the transfer hydrogenation and molecular hydrogen reduction are excellent in differentiating dissimilar α-, α- substitution (adjacent to nitrogen) producing chiral primary amines in high *ee*. The general substrate breadth can be expressed as $R_SC(O)CH_3$, $R_MC(O)CH_3$, $R_LC(O)CH_3$ and $R_SC(O)R_L$ (R_S = ethyl, *n*Pr, *n*Bu; R_M= 2-phenylethyl, *i*Bu; R_L = *i*Pr, Ph). Carbanion chemistry provide high *ee* for two similar substitution patterns on either side of the nitrogen atom. This can be achieved by a carbanion source (R_S or R_M) with aldehydes of the general structure: $R_SC(O)H$ or $R_MC(O)H$ or $R_LC(O)H$, with high ee. Under the present stage of developmental cycle, it can be stated that the two main strategies ('carbanion' addition vs 'hydrogen' addition) complement each other. When the two methods are directly compared the 'hydrogen' based methods are more cost effective.

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