Asymmetric Hydrogenation of Prochiral Amino Ketones to Amino Alcohols for Pharmaceutical Use

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ABSTRACT

This Account gives an overview of the homogeneously catalyzed asymmetric hydrogenation of prochiral amino ketones. The preparation of enantiopure arylalkanolamines, which are potent and economically very important pharmaceuticals, is described. Classical routes of synthesis are compared with the new asymmetric hydrogenation route for a number of compounds from the viewpoint of an industrial pharmaceutical chemist.

Introduction

Optically active amino alcohols are a very important class of compounds, both in nature and in the pharmaceutical world. A very large number of active pharmaceutical substances contain the amino alcohol moiety and exhibit chirality.

There are many industrially applicable routes by which enantiopure amino alcohols can be obtained. Some are available from a chiral pool via reduction of the corresponding amino acid, while others may be obtained from natural hydroxyacids or, in rare cases, from sugars.

Currently, however, resolution remains the most widely used technology for obtaining enantiomerically pure amino alcohols and, in many cases, it is the most economical.[1,2]

Biotechnology represents another option for the production of optically active amino alcohols, and in recent years, a number of well-established biotechnological methods have been developed for specific targets. These include enzymatic kinetic resolution,[3] asymmetric reductive amination of hydroxyketones[4] and enzymatic reduction of amino ketones.[5]

In addition to biotechnological methods, a wide variety of chemical processes have been developed for the asymmetric reduction of prochiral amino ketones. The hydrogen equivalent can be transferred to the carbonyl group using a number of different methods. Complex metal hydride reagents or boranes modified with chiral ligands have been used extensively in asymmetric reductions.

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Prominent examples include R. Noyori's BINAL-H,[6] a chiral modified aluminum hydride, M. M. Midland's alpine-borane,[7] and H. C. Brown's DIP-chloride,[8] both of which are chiral borane reagents based on α-pinene. Enantiomerically pure amino alcohols are usually obtained indirectly by this methodology, either via amine substitution of enantiopure halohydrins[9] or via the opening of the corresponding epoxide.[10] These technologies require stoichiometric amounts of chiral reducing agent, however, and they are therefore uneconomical from an industrial point of view.

In the Corey–Bakshi–Shibata (CBS) reduction,[11] chiral boranes synthesized from borane and, usually, another enantiopure amino alcohol are used. This technique can be carried out using catalytic amounts of chiral ligands, but again, amino alcohols are obtained only indirectly because of ligand competition with substrate, intermediate, or product. In order to achieve useful productivities on an industrial scale, the ratio of chiral ligand to substrate, the turnover number (TON) is usually in the range of 5–100 (1–20 mol%). Also, the hydrogen source is borane, which is associated with serious hazards and which is relatively expensive compared with the value of the product.

In principle, the most economic source of reduction equivalent is hydrogen itself. Therefore, the most economical way of performing asymmetric reductions of either amino ketones or hydroxyimines leading to amino alcohols is via catalytic hydrogenation.

Although heterogeneous asymmetric hydrogenations,[12] which historically were the first examples of catalytic hydrogenation,[13] are currently undergoing a revival (cf. recent work on the immobilization of metal–phosphine complexes[14]), homogeneous catalytic hydrogenations are the most economical way of performing enantioselective reductions on an industrial scale.[15–17]

The first paper in the special field of enantioselective homogeneously catalyzed hydrogenations of prochiral amino ketones, which is the main topic of this Account, was published by T. Hayashi et al.[18] in 1979. The studies described in this paper employed the rhodium complex of BPPFOH ((*R*)-α-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethanol) as ligand. Subsequent studies carried out by K. Achiwa et al.[19] used BPPM ((2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine), which became the lead structure for an entire class of ligands.[20] These two classical phosphine ligands are very useful for the reduction of many different prochiral substrates and especially for prochiral amino ketones, which lead to the arylalkanolamines.

Enantioselective Homogeneously Catalyzed Hydrogenation of Arylalkanolamines

Arylalkanolamines in general are a very important class of pharmaceuticals and represent a major share of the world drug market. Most continue to be marketed as racemates despite the fact that, in the majority of cases, the D- and L-enantiomers have different pharmacological

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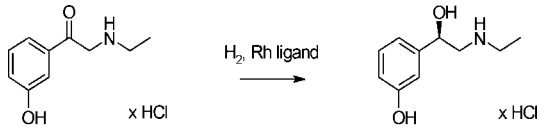
properties.[21] In the case of adrenaline (epinephrine), the comparative effect of the racemate and the two enantiomers on blood pressure was investigated as early as 1908.[22] By the middle of the 20th century, many arylalkanolamines had been resolved, their absolute configurations had been established and their pharmacological properties investigated.[23] A large number of these compounds came onto the market at around this time, and they continue to find application as antiarrhythmics, antihypotonics, antiasthmatics, rhinologics, ophthalmics, and vasoconstrictors.

The early work on the asymmetric synthesis of arylethanolamines of the adrenaline type by Hayashi and Achiwa triggered the development of new industrial processes for these well-established active pharmaceutical ingredients.

Etilefrine

The (*R*)-enantiomer of the sympathomimetic agent etilefrine is about 20 times more pharmacologically active than the (*S*)-enantiomer. In 1984, scientists at Boehringer Ingelheim synthesized both enantiomers via enantioselective hydrogenation.[24] Originally, the rhodium complex of BPPFOH was used as the catalyst, with a low TON, low activity (turnover frequency, TOF), and relatively low enantiomeric excess (ee) (Scheme 1).

Scheme 1



Etilefrine x HCl

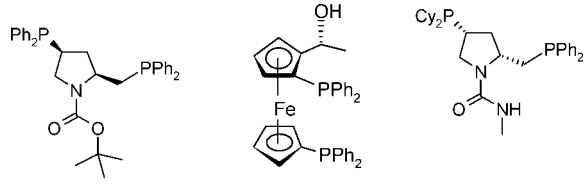
Optical purity was enhanced by recrystallization. Much better reactivity, as well as better enantioselectivity, was achieved with MCCPM than with BPPM or BPPFOH (Table 1, Figure 1). The substrate/catalyst (S/C) ratio in this case was 10 000. Using the corresponding *N*-benzylamino ketone, we obtained 90% ee under the same conditions.

Table 1

ligand	reaction conditions	yield (%)	ee	configuration
(*R*,*S*)-BPPFOH	25 °C, 48 h	84	78	R
(*S*,*S*)-BPPM	25 °C, 24 h	80	68	R
(*R*,*R*)-MCCPM	50 °C, 1 h	80	80	S

Phenylephrine

A structurally similar molecule that has been well established in the pharmaceutical market for many



(S,S)-BPPM (R,S)-BPPFOH (R,R)-MCCPM

FIGURE 1. Structure of ligands described in Table 1.

years is the α-adrenergic agonist phenylephrine (Figure 2)[25].

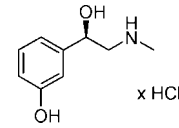
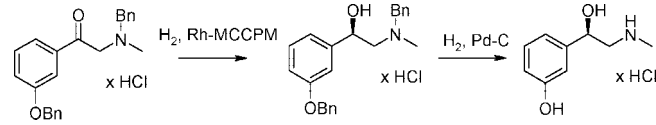


FIGURE 2. Structure of phenylephrine hydrochloride.

Worldwide, there are over 100 trademarked preparations of phenylephrine.[25c] In addition to its main use as a nasal decongestant, it is also a mydriatic, a cardiotonic, and a vasoconstrictor. It was first marketed in 1936 by Boehringer Ingelheim, as the hydrochloride salt, under the name Adrianol. Today, the world market for phenylephrine is over 100 tons per annum. The classical industrial synthetic route was developed in the late 1920s and early 1930s and published in a series of patents by H. Legerlotz.[26] These describe the synthesis of racemic phenylephrine and give details of the resolution procedure using tartaric acid and the Walden inversion by which the undesired isomer is transformed into the desired isomer. This route was subsequently investigated further and refined.[27–29] A number of alternative methods of synthesis, which are not of industrial interest, were subsequently developed,[30] but it was Takeda et al. who published the first asymmetric route to phenylephrine in 1989 (Scheme 2)[31].

Scheme 2



In principle, this route can be used industrially, but it has several disadvantages. More than 50% of the molecular weight of the substrate for the asymmetric hydrogenation consists of protecting groups, which have to be removed in a later step. The TON (ca. 2000) and the TOF (ca. 100 h^{-1}) of the hydrogenation step are relatively low. In addition, the optical purity of the crude product is only 88% ee, and the final product cannot be efficiently purified by recrystallization.

In our studies, we used *N*-benzylphenylephrone, which is an intermediate in the classical industrial synthesis, as the starting material. Surprisingly, this substrate gave much better results in terms of TON, TOF, and enantiomeric excess for the asymmetric hydrogenation (Scheme 3).

A number of bisphosphine ligands (Figure 3) have been tested for this substrate. Some results are given in Table 2.

The classical Noyori ruthenium-BINAP[32] system gave 86% ee but a very low reactivity. The best enantiomeric excess was achieved with the Cy,Cy-oxoProNOP ligand[33] (92% ee), but the reactivity was much lower than with the MCCPM or even the BCPM system.

These results showed that the 2,4-disubstituted pyrrolidine ligands are the most promising candidates for an industrial process. Most importantly, the two phosphorus atoms have two different substituents. When both the

Scheme 3

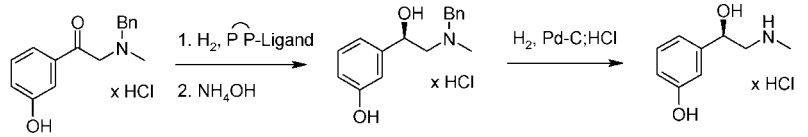


Table 2

ligand	metal	ee (%)	S/C ratio	reaction conditions
BPPFOH	Rh	16	1000	20 bar, 50 °C, 20 h
BINAP	Rh	20	1000	20 bar, 50 °C, 20 h
BINAP	Ru	86	125	100 bar, 25 °C, 24 h
BPPM	Rh	68	1000	20 bar, 50 °C, 14 h
BCPM	Rh	88	10000	20 bar, 50 °C, 10 h
MCCPM	Rh	90	10000	20 bar, 50 °C, 3 h
Duphos	Rh			no reaction
Josiphos	Rh	4	1000	20 bar, 50 °C, 20 h
Cy,Cy-oxoProNOP	Rh	92	10000	20 bar, 50 °C, 32 h
Deguphos	Rh			No reaction

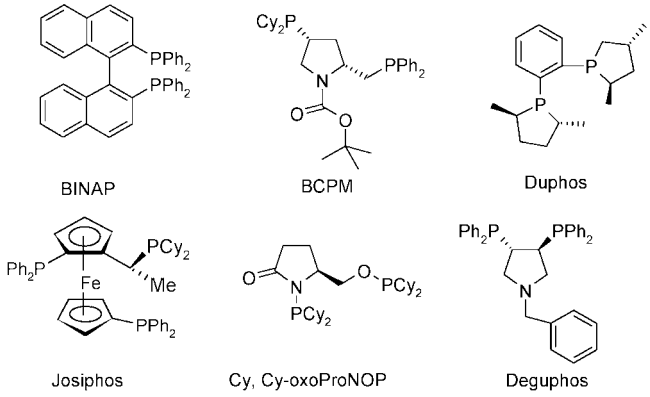


FIGURE 3. Structure of bisphosphine ligands in Table 2 (see also Figure 1).

phosphorus atoms are phenyl-substituted, as is the case with BPPM, reactivity and enantioselectivity are lower.

Catalyst Optimization and Mechanistic Considerations

Because of the very good reactivity and reasonable enantioselectivity of the substitution pattern in BCPM and MCCPM, the easily tunable functionality at the nitrogen in the pyrrolidine ring was modified (Figure 4). Some results are given in Table 3.

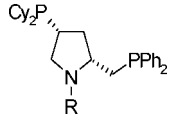


FIGURE 4. General structure of the modified pyrrolidine ligand R-CCPM as in Table 3.

This investigation clearly showed that the best enantioselectivity coupled with the best reactivity was achieved with the alkyl-substituted urea functionalities. There were no major differences between the methyl, ethyl, propyl, or phenyl substituents at the nitrogen. However, the benzyl substitution exhibited lower enantioselectivity and slightly lower reactivity.

The catalysis is obviously most effective when there is a carbonyl group next to the ring nitrogen and when this

Table 3

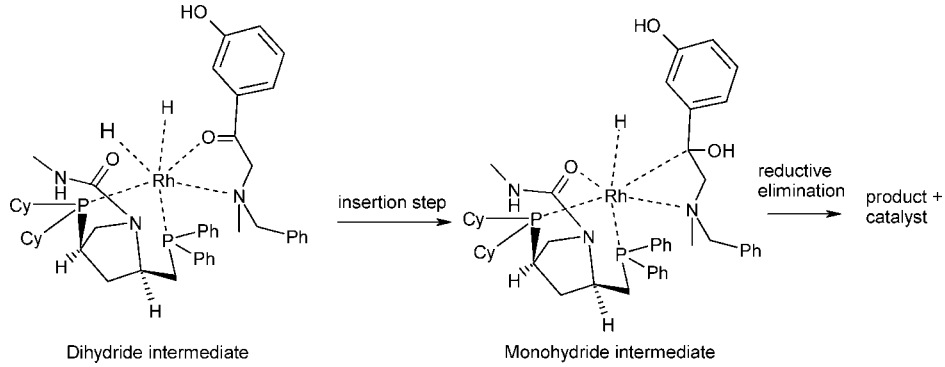
	R	ee (%)	S/C ratio	reaction time (h)[a]
1	H	28	1000	70
2	CHO	78	850	3.5
3	COMe	84	850	3.5
4	$COCF_3$	30	850	24 (50% conversion)
5	COtBu	76	850	3.3
6	COOMe	88	850	3.3
7	COOnPr	87	850	2.3
8	COOiPr	86	850	4
9	COOPh	82	850	2.5
10	COOtBu	88	1000	10
11	COSMe		850	24 (<50% conversion)
12	$POPh_2$	52	1000	3.3
13	$CONMe_2$	66	850	3.5
14	CONHMe	90	1000	<1
15	CONHEt	86	850	2
16	CONHnPr	85	850	2
17	CONHPh	88	1000	2.5
18	CONHBn	82	1000	3

[a] Reaction conditions: solvent MeOH; 20 bar H_2; 50 °C; Et_3N; $(RhCODCl)_2$.

carbonyl group is connected with a relatively electron-rich functionality such as NH-alkyl. Sterically, the residue at the carbonyl function should be small. The results indicate that a small, electron-rich substituent at the urea nitrogen leads to good reactivity and reasonably good enantioselectivity for the substrate investigated. How can the substituents at the ring nitrogen influence the catalysis? Clearly, the electronic influences on the complexing phosphorus atoms are minimal, and the steric effects cannot be the reason for the differences in reactivity and enantioselectivity since both small and large substituents gave low selectivities. The results further suggest that the functionality at the nitrogen somehow participates directly in the catalysis. In both the "unsaturated" and the "dihydride mechanism"[34] pathways, there is an insertion step, the transfer of the first hydrogen atom, followed by a reductive elimination to the catalyst–product complex. After one hydrogen atom has been transferred, the free binding site, which is usually occupied by a solvent molecule, could be coordinated intramolecularly to the carbonyl oxygen of the urea functionality, which acts as a third binding site in the ligand (Scheme 4). A mechanism of this type could explain the strongly enhanced reactivity of this ligand system.

The reaction conditions for the asymmetric hydrogenation of benzylphenylephrone were optimized to give an ee value of about 92%.[35] The ee value depends principally on the reaction temperature, the amount of catalyst, and the solvent used; the hydrogen pressure has relatively little influence. The preferred solvent is methanol, among other reasons because of the solubility characteristics of the starting material. The amount of catalyst used, which is a compromise between economic and scientific factors, is

Scheme 4



Dihydride intermediate Monohydride intermediate

usually around a TON of 40 000; however, in this case it can be increased to ca. 100 000 without substantially reducing enantioselectivity. The reaction temperature, which is a compromise between good selectivity and a short reaction time (typically ca. 3 h), is usually between 50 and 60 °C; the geometry of the autoclave and the configuration of the stirrer also play an important role.

Benzylphenylephrine can easily be obtained in enantiopure form by crystallization of the free base. Debenzylation is performed in the usual way by hydrogenation in the presence of a palladium catalyst. This allows phenylephrine to be generated in good yield and in an efficient and industrially applicable manner.

Adrenaline

A substance that is chemically very similar to phenylephrine is adrenaline (epinephrine), which is of considerable value in the treatment of anaphylactic shock and as an adjunct to local anesthetics. It has a well-documented and wide range of activities.[36] Industrially, adrenaline is usually manufactured by nonselective hydrogenation of 3′,4′-dihydroxy-2-*N*-methylaminoacetophenone, or a protected derivative thereof, and subsequent chiral resolution[37] (Scheme 5).

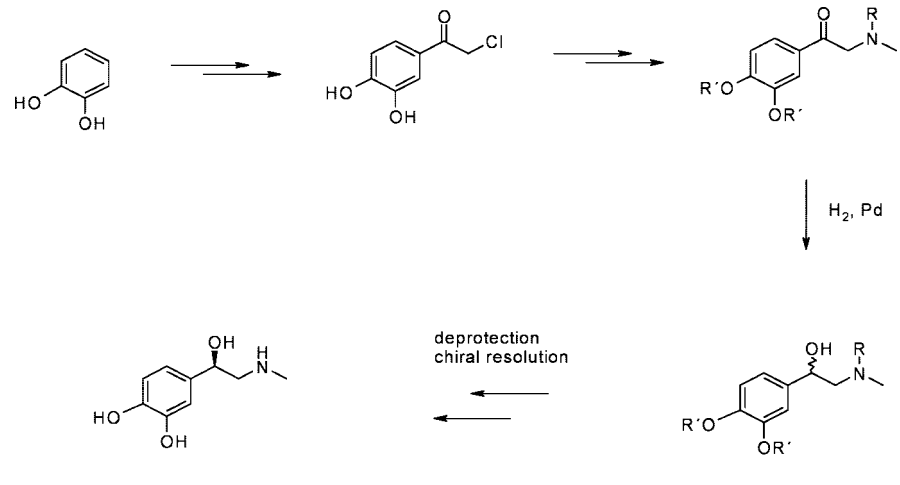
As mentioned previously, the first example of an enantioselective hydrogenation of an amino ketone of this type (R=R′=H) was reported by T. Hayashi et al.[18] The catalyst used was the rhodium complex of BPPFOH, at a S/C molar ratio of 100. The hydrogenation, which was carried out at a hydrogen pressure of ca. 50 bar, was complete in 2–4 days resulting in L-adrenaline of 90% ee.

We used benzyladrenalone hydrochloride as substrate and the rhodium complex of MCCPM as catalyst under conditions similar to those described for phenylephrine. Hydrogenation, which was carried out using a S/C molar ratio of 10 000, a hydrogen pressure of 20 bar, and a temperature of ca. 50 °C, was followed by precipitation with aqueous ammonia. This resulted in benzyladrenaline free base with a very high optical purity (>98% ee).[38]

Adrenaline sulfate, the commercial form of adrenaline, is obtained via debenzylation by hydrogenation in the presence of palladium in diluted sulfuric acid (Scheme 6).

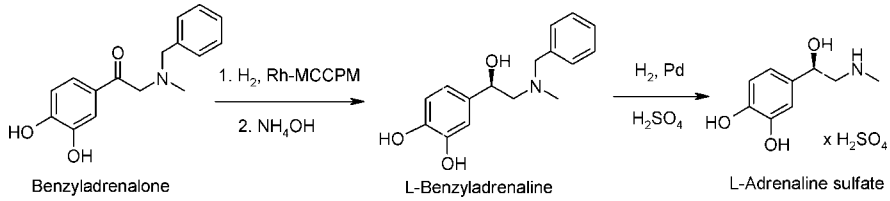
MCCPM and closely related derivatives, which were introduced by K. Achiwa in the mid-1980s,[39] have not commonly been used in asymmetric catalysis except by the originator. However, the rhodium complex of alkyl-CCPM appears to be of particular value in the asymmetric hydrogenation of prochiral amino ketones. A literature review of α-amino arylketones shows that, in comparison with other phosphine ligands, the MCCPM family is the most reactive and selective.[40] In addition to the industrial syntheses of phenylephrine and adrenaline described above, the synthesis of other α-amino ketones has been investigated.

Scheme 5



L-Adrenaline

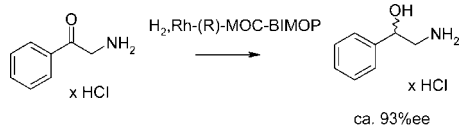
Scheme 6



Asymmetric Hydrogenation of Other α-Amino Ketones

α-Amino acetophenone, a primary amine, has been successfully asymmetrically hydrogenated as its hydrochloride salt (Scheme 7).

Scheme 7



The rhodium complexes of (*S*)-Cy,Cy-oxoProNOP and (*R*)-MOC-BIMOP[41] (Figure 5) gave an ee value of 93%, albeit with a relatively low reactivity.

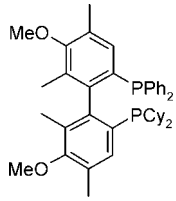
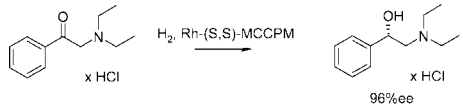


FIGURE 5. Structure of (*R*)-MOC-BIMOP.

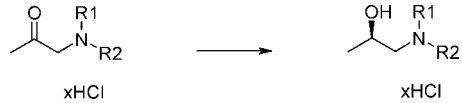
Various N-substituted α-amino acetophenones have been hydrogenated using a number of catalysts. By far the most reactive is the rhodium complex of MCCPM, which can catalyze the hydrogenation of *N*,*N*-diethyl-α-amino acetophenone with a TON of ca. 100 000 to give an ee value of 96% (Scheme 8)[19].

Scheme 8



N,*N*-Dialkyl-substituted aminopropanone-2 was hydrogenated enantioselectively using a variety of catalysts (Scheme 9). When the BINAP-Ru system[42] was used, the *N*,*N*-dimethyl derivative (R_1=R_2=Me) had an ee value of 99%, but reactivity was relatively low (TON ca. 1000) and a high hydrogen pressure (>100 bar) was required.

Scheme 9



When Cy,Cy-oxoProNOP-Rh was used, an ee value of 97% was achieved at a hydrogen pressure of ca. 50 bar and an even lower reactivity (TON ca. 200).[43] The ruthenium-xylyl-BINAP/DAIPEN complex (Figure 6), which was developed by Noyori originally for the asymmetric hydrogenation of unfunctionalized ketones, is also an efficient catalyst for these types of substrates. With a TON of ca. 2000 and under mild reaction conditions (8 atm H_2, 25 °C), an ee value of 92% was achieved.[44] The enantioselectivity achieved with this system is the opposite of the classical Ru-BINAP system, which demonstrates the different mechanisms of hydrogen transfer to the carbonyl group.

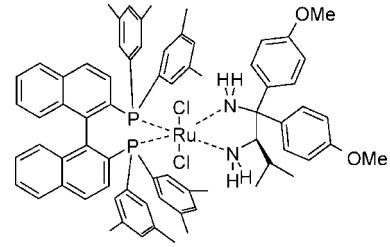


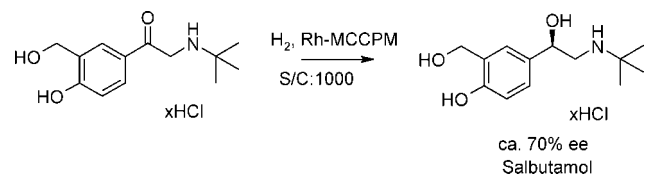
FIGURE 6. *trans*-$RuCl_2$[(*R*)-xylBINAP)][(*R*)-DAIPEN].

N,*N*-Dibenzyl-1-aminopropanone was enantioselectively hydrogenated using Rh-MCCPM as catalyst to give a product with an ee value of 90% (Scheme 10). Optical purity was increased to >98% ee, with high yield, by a single recrystallization of the hydrochloride salt[45].

Scheme 10

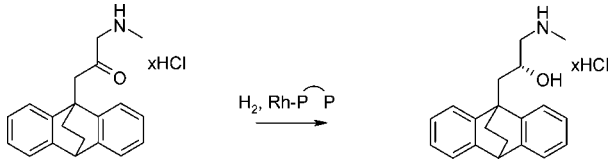
A compound of great commercial interest is the β_2-adrenergic agonist (*R*)-salbutamol, which is used as a bronchodilator. This molecule can be obtained in 70% ee by the asymmetric hydrogenation of salbutamone. The crude product can be purified by recrystallizing the hydrochloride salt and precipitating the free base with aqueous ammonia (Scheme 11)[46].

Scheme 11



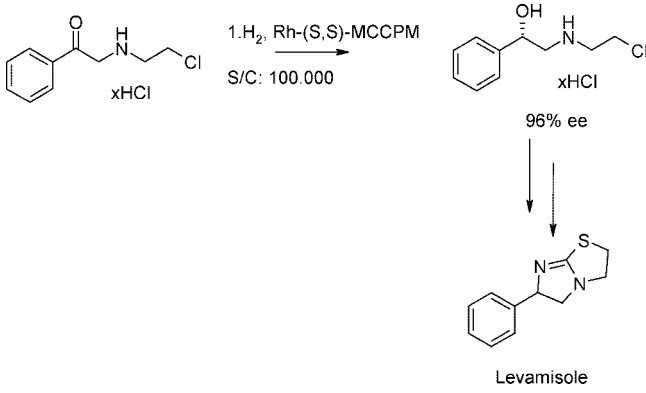
A further secondary α-amino ketone leading to (*R*)-levoprotiline, a noradrenaline uptake inhibitor developed by Novartis for use as an antidepressant, was considered for synthesis by asymmetric hydrogenation.[47] Eight different metal–bisphosphine ligand complexes were studied as potential catalysts (Scheme 12). The BPPFOH ligand gave the best enantioselectivity (98%) but, as with all the other ligands tested, the TONs and TOFs were low. An alternative route of synthesis was eventually chosen.

Scheme 12



A secondary α-amino ketone substituted with a chloroethyl group at the nitrogen, a precursor for the immunoregulating drug levamisole, has been asymmetrically hydrogenated using the Rh-MCCPM system, yielding an impressive ee value and TON (Scheme 13)[48].

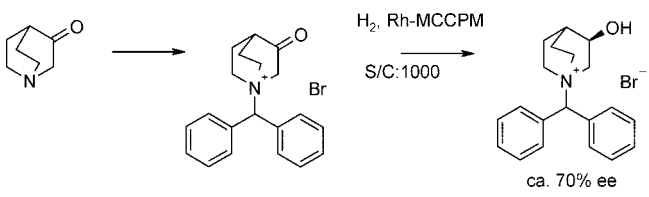
Scheme 13



A scientifically interesting reaction is the asymmetric hydrogenation of quinuclidinone. The two "sides" of the carbonyl group are relatively similar, so the enantiodifferentiation in a catalytic hydrogenation is expected to be low.

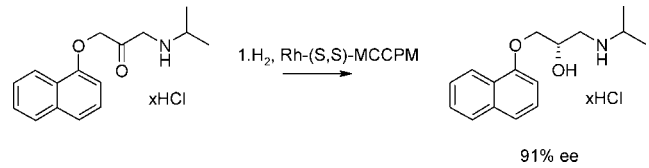
Indeed, with many of the ligands tested, the enantioselectivity was below 5% ee. Interestingly, however, ee values of ca. 50% were achieved using (*R,R*)-MCCPM. Differentiation of the two enantiotopic faces through quaternization at the nitrogen with the diphenyl methyl group increased the enantiomeric excess to 70% (Scheme 14),[49] and this value was increased further by crystallization. An ee value of 60% was reported for the same substrate when the Josiphos ligand was used[50].

Scheme 14



The rhodium–MCCPM system is not only suitable for the asymmetric hydrogenation of arylamino ketones; it has also been used for the enantioselective hydrogenation of aryloxyamino ketones, which are compounds used in the synthesis of β-adrenergic blocking drugs (Scheme 15)[51].

Scheme 15



The amino ketone structure used as the substrate for the asymmetric hydrogenation can obviously be varied in many different ways. R1 can be an alkyl, aryl, or aryloxy substituent (Figure 7). In addition, the amino functional group can be primary, secondary, or tertiary, and the distance between the keto and amino groups can be varied.

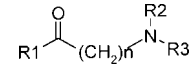


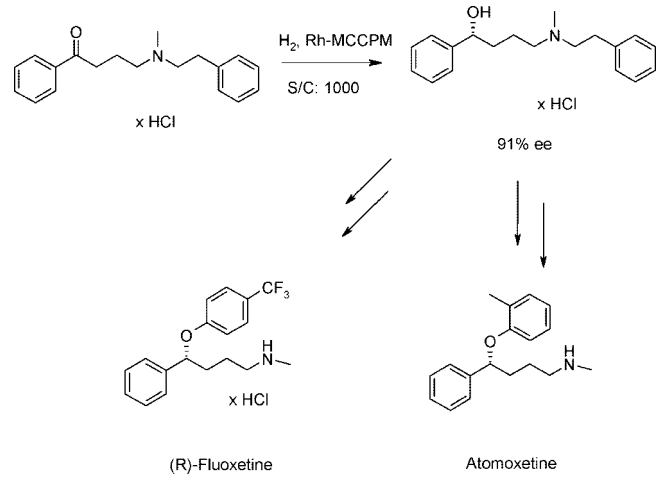
FIGURE 7. General structure of prochiral amino ketones.

Asymmetric Hydrogenation of β- and Higher Amino Ketones

The asymmetric hydrogenation of β- and higher amino ketones has not featured so widely in the literature as that of the α-amino ketones. In principle, however, the same catalysts are active, and there have been numerous reports of their successful use. Reactivity and enantioselectivity are in general slightly lower for the more flexible β- and higher amino ketones.

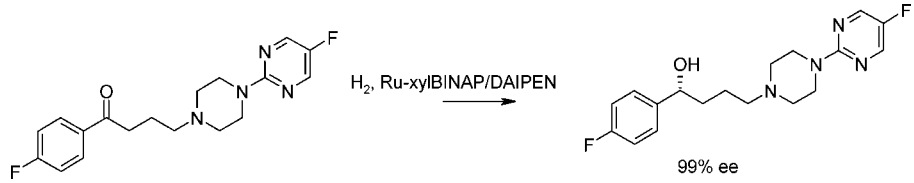
Using the same reaction conditions as for the α-amino ketones, the benzylmethyl amino ketone of Scheme 16 has been hydrogenated with high enantioselectivity using rhodium-MCCPM[52].

Scheme 16



The resulting amino alcohol is a precursor for the antidepressant (*R*)-fluoxetine (Prozac) and for atomoxetine, the first drug approved for the treatment of attention

Scheme 17



deficit hyperactivity disorder (ADHD). The corresponding *N*,*N*-dimethyl compound has been asymmetrically hydrogenated with (*S*)-xylBINAP/(*S*)-DAIPEN-ruthenium with an ee value of 97.5% ee and a S/C ratio of 10 000.[44] It has also been converted to (*R*)-fluoxetine.

The same ruthenium catalyst has also been used for hydrogenation of the γ-amino ketone shown in Scheme 17, leading to the production of the antipsychotic compound BMS 181100.

In this case, the catalyst was used in an S/C ratio of 2000 and gave an impressive 99% ee.

A number of precursors for the antidepressant duloxetine, which contains a thiophene ring, have been asymmetrically hydrogenated (Scheme 18).

Scheme 18

The rhodium-duanphos (Figure 8) system gave the highest yield (93%) and turnover (ca. 4500) with an excellent ee value (Table 4).[55] In their paper, Liu et al. report the enantioselective hydrogenation of a series of β-secondary amino ketones, which they call the unsolved class of substrates in asymmetric hydrogenation. In considering these substrates, a distinction must be made between primary, secondary, and tertiary amines. The rhodium-duanphos system functions best for the secondary amines. However, the efficiency of the catalysis is probably highly dependent on the substitution pattern around the amino ketone unit.

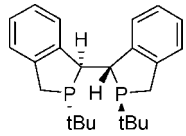


FIGURE 8. Structure of (SC,RP)-duanphos.

Table 4

R_1	R_2	catalyst	ee (%)	ref
Me	Me	Ru-(*R*)-xylBINAP/(*R*)-DAIPEN	92	44
Me	Bn	Rh-MCCPM	95	53
Me	H	Rh-ketalphos	99	54
Me	H	Rh-duanphos	99	55

With the Rh-MCCPM system, however we experienced no general scheme for enantioselectivity and reactivity depending on the substituents at the amino group.

Lobeline

An enantiopure amino alcohol that is of considerable commercial interest is the natural product (–)-lobeline. It is one of the alkaloids of *Lobelia inflata* (Indian tobacco), which is native to the U.S.A. and Canada.

Lobeline is the main alkaloid of the 20 or so known lobelia alkaloids. It is a respiratory analeptic used to treat asthma, collapse, and anesthetic accidents.[56] It has also been developed clinically as a sustained-release antismoking agent,[57] for the treatment of eating disorders,[58] and for the treatment of central nervous system diseases.[59] Since isolation from plants is laborious and time-consuming and therefore uneconomical, many different routes of synthesis have been considered. A phenomenon that complicates the situation is the fact that lobeline exhibits mutarotation.[60] It epimerizes to a mixture of *cis*- and *trans*-lobeline in solution (Scheme 19), especially in hydrophilic solvents, and this epimerization occurs relatively fast in the presence of a base. On the other hand, the crystalline free base is configurationally stable, and the hydrochloride and sulfuric acid salts are also stable in solution.

The fundamental work done by H. Wieland, who elucidated the chemical structure of (–)-lobeline[61] and who, together with C. Schöpf, laid down the basis for the first industrially useful synthesis,[62] was the starting point for extensive research activities. This research has recently been the subject of a comprehensive review.[63] The classical industrial process, developed in the early 1950s at Boehringer Ingelheim, is shown in Scheme 20.[64]

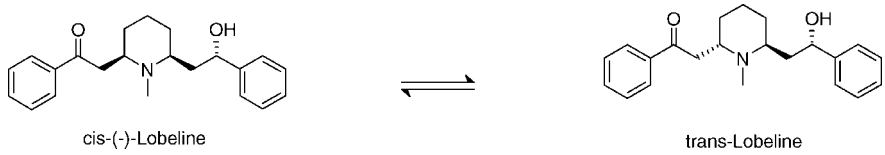
The first step, a Robinson–Schöpf condensation, produces lobelanine under "physiological conditions" in citrate buffer (pH 4) at room temperature in relatively high yield (ca. 80%). Lobelanine is the ideal starting material for a lobeline synthesis. However, on an industrial scale, lobelanine could not be selectively reduced to *rac*-lobeline by a direct route. It first had to be completely reduced to lobelanidine, then selectively oxidized with activated manganese oxide to *rac*-lobeline, and finally resolved with dibenzoyltartaric acid to (–)-lobeline.

All other known syntheses are much longer and are only of academic interest.

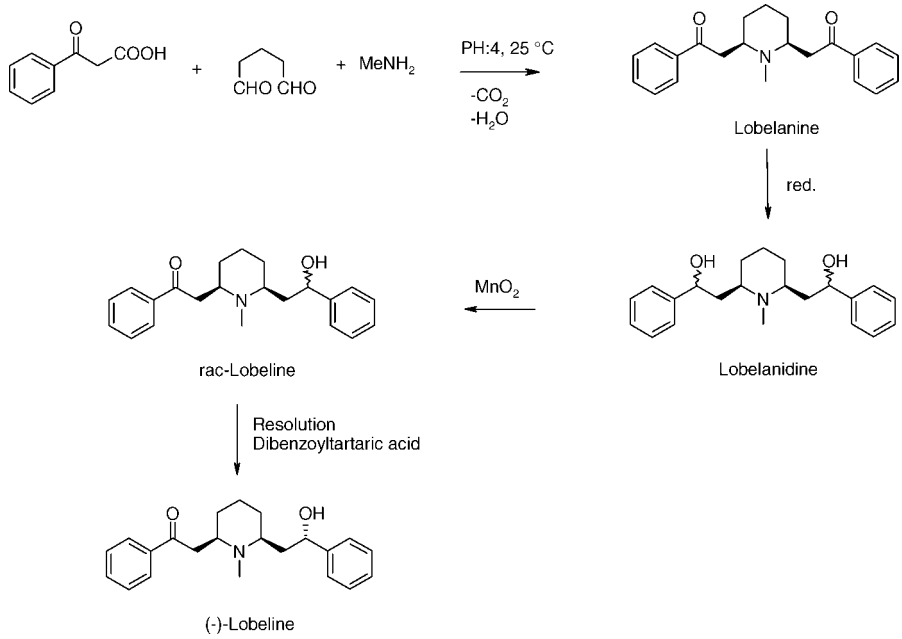
Having developed the asymmetric hydrogenation of structurally similar prochiral amino ketones, we were able to identify conditions under which we could enantioselectively hydrogenate just one of the two keto groups in lobelanine (Scheme 21).[65]

Again, the rhodium complex of (*R*,*R*)-MCCPM was the most reactive and selective catalyst for this asymmetric hydrogenation. Lobelanine hydrochloride is hydrogenated in methanol at ca. 50 °C and 20 bar hydrogen pressure in the presence of Rh-MCCPM. The S/C ratio can be varied and is usually 10 000 on the technical scale. Following hydrogen uptake of 100% of theory and simple workup,

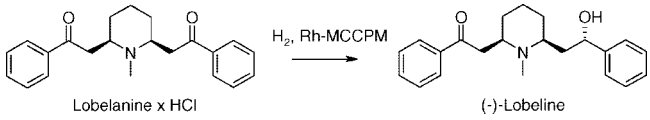
Scheme 19



Scheme 20



Scheme 21



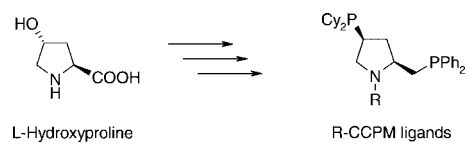
crystalline (–)-lobeline is isolated in chemically (>99%) and optically (>99% ee) pure form in 35–45% yield. Considering the yields obtained with the old technical process and the other methods of synthesis reported in the literature, this is a respectable and technically useful result.

Availability of R-CCPM Ligands

As described above, the different substitution patterns of the two phosphorus atoms in the R-CCPM ligands are very important for the reactivity of rhodium complexes in the asymmetric hydrogenation of amino ketones. These types of ligands are available from chiral pool.

The starting material is the natural amino acid L-hydroxyproline, which can be transformed into the (*S*,*S*)- as well as the (*R*,*R*)-R-CCPM ligands (Scheme 22)[66].

Scheme 22



This relatively lengthy synthesis could be simplified considerably by changing the protecting group strategy and combining steps. The high reactivity and selectivity for many different prochiral amino ketones of the industrially very useful R-CCPM ligands justify a longer synthesis.

Conclusion and General Aspects

Currently, there are relatively few industrially useful catalytic systems for the asymmetric hydrogenation of prochiral amino ketones to amino alcohols. This is probably because amino ketones and amino alcohols themselves are strong binding ligands that interfere in the equilibria of the different intermediates of the catalytic cycle.

Two factors that are very important for the industrial relevance of a catalytic system are enantioselectivity (ee) and reactivity (TON, TOF). Personal experience suggests that reactivity is the most important factor, because the technical parameters that influence the reactivity of a catalyst can usually only be varied within a relatively narrow range. The range of the reaction temperature is limited by the solubility of substrates and products and the physical properties of the chosen solvent and is usually somewhere in the range 20–80 °C. The choice of hydrogen pressure is highly dependent on the equipment available; investment costs and safety considerations are the predominant factors determining the range for this parameter.

Another important factor is the cost of the catalyst, which includes costs for the ligand and the metal precur-

sor and, sometimes, license fees. If the reactivity of a catalyst is very high (TON > 10 000; TOF > 5000 h^{-1}), its cost usually plays a minor role. Another advantage of a highly reactive catalyst is that there is no need to worry about the heavy metal content of the product, which is an important point in the pharmaceutical industry.

Considering all of these factors, the pyrrolidine ligands currently remain the best ligands for the asymmetric hydrogenation of amino ketones.

The oft-heard argument that pyrrolidine ligands of the R-CCPM type are too complicated to synthesize, making them too expensive for technical use, is in my opinion incorrect because these systems are highly reactive for certain substrates, which more than compensates for the relatively high production costs. Furthermore, these systems are "tunable", both at the substituents of the phosphorus atoms and at the ring nitrogen of the pyrrolidine ring.

Industrially speaking, homogeneously catalyzed asymmetric hydrogenation is still in the early stages of development. As always in chemistry (mirroring life itself), there are no general solutions; in other words, there is no universal catalyst that is suitable for every problem. Every single substrate needs a process development and an optimization of its own.

In general, homogeneously catalyzed asymmetric hydrogenation is a very versatile and useful tool for producing enantiopure amino alcohols from amino ketones, and it should always be considered by chemists when they are developing new processes.

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