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Recent Developments in Asymmetric Transfer Hydrogenation with Hantzsch Esters: A Biomimetic Approach

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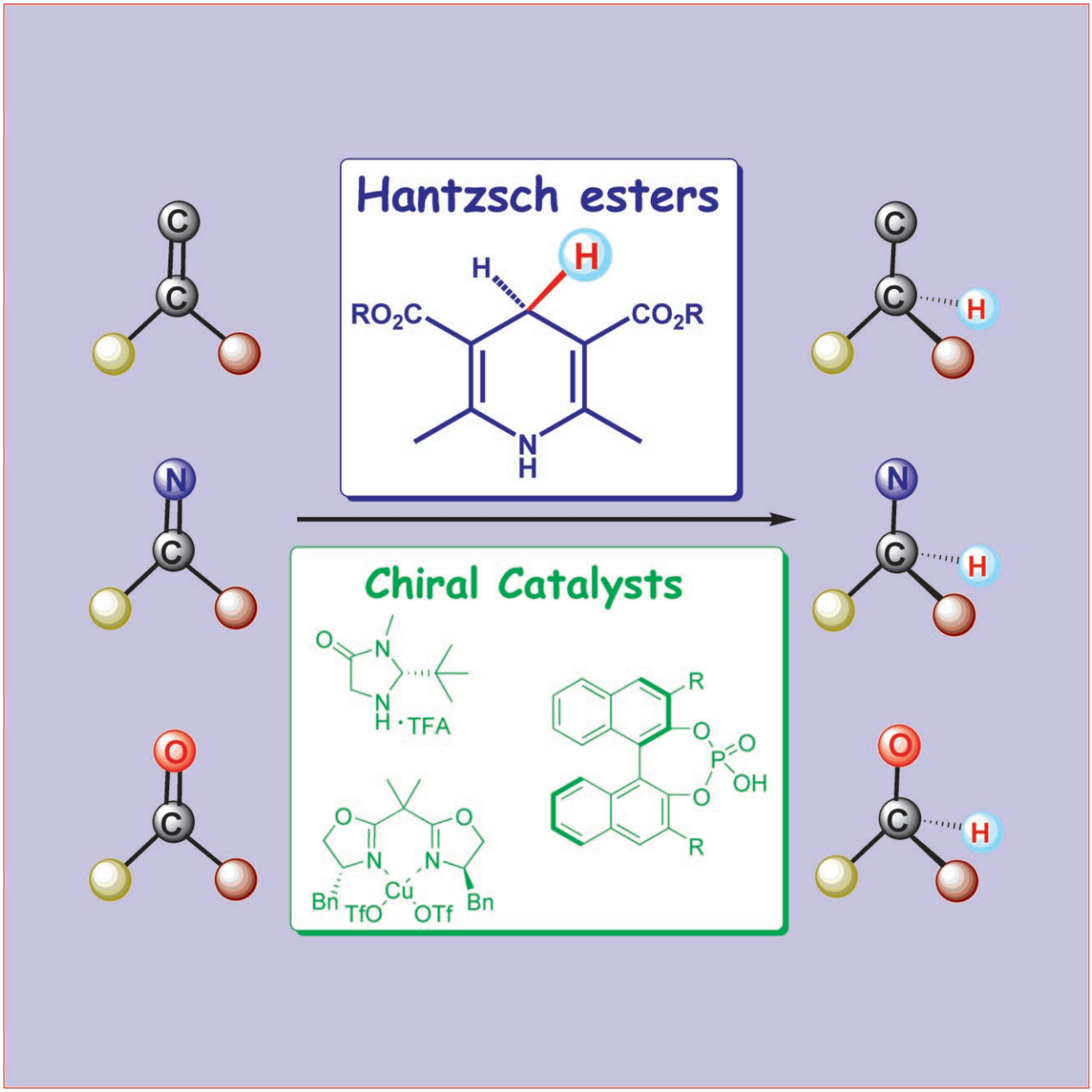

Abstract: By utilizing Hantzsch esters as the hydrogen source, asymmetric transfer hydrogenation of C=C, C=N, and C=O is realized in the presence of an organocatalyst or a metal–ligand complex, thus affording versatile chiral building blocks in high yields with excellent enantioselectivities under mild conditions. A detailed discussion of recent findings and an assessment of this biomimetic approach are presented in this review.

Keywords: asymmetric catalysis · Hantzsch esters · hydrogenation · organocatalysis · reductive amination

1. Introduction

The synthesis of enantiopure products by asymmetric catalysis of organic reactions represents one of the most important areas in modern synthetic chemistry.[1] Among many successful asymmetric reactions, asymmetric hydrogenation has been most extensively studied in academia and most widely applied in industry,[2] as affirmed by the award of the 2001 Nobel Prize in chemistry to two prominent scientists in this field.[3] In the last few decades, significant progress has been made towards the asymmetric hydrogenation of C=C,[4] C=N,[5] and C=O[6] by utilizing transition-metal chiral-ligand complexes.[7]

Most asymmetric hydrogenation processes involve the use of transition metals in conjunction with hydrogen gas[2a–d] and, in the case of transfer hydrogenation,[2e] isopropanol or formic acid. On the other hand, naturally occurring hydrogenation processes rely on a combination of enzymes and hydride-reduction cofactors such as NADH, NADPH, or $FADH_2$ (reduced flavin adenine dinucleotide) (Scheme 1).[8] A biomimetic approach that involves the utilization of Hantzsch esters, which are nicotinamide analogues, was recently developed by List and co-workers,[9] MacMillan and co-workers,[10] Rueping et al.,[11] and Zhao and Córdova[12] to realize the highly enantioselective transfer hydrogenation of C=C, C=N, and C=O in the presence of catalytic amounts of small organic molecules or metal complexes. Two reviews on this topic have been documented; however, both of them summarize only part of the results on asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.[13] In this review, progress in the use of Hantzsch esters as the hydrogen donor in catalytic asymmetric transfer hydrogenation, including recent findings and an assessment of this approach, will be discussed in detail.

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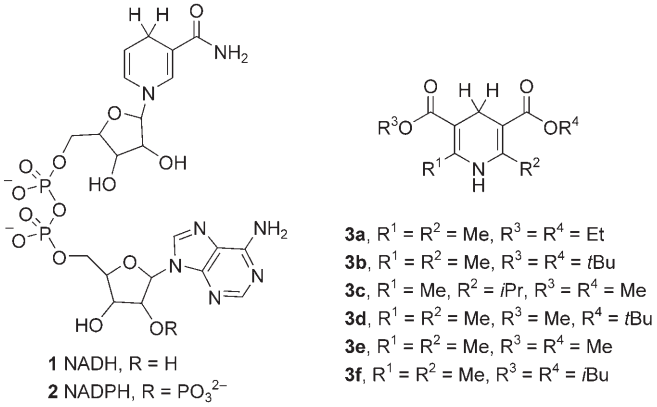
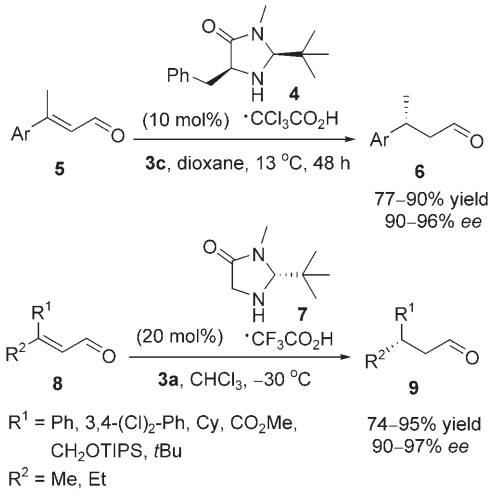
2. Reduction of C=C Bonds

Reduction of the C=C bond of α,β-unsaturated aldehydes represents a fascinating challenge in organic synthesis as reduction of the carbonyl group often occurs as the side reaction. A successful enantioselective reduction of α,β-unsaturated aldehydes would have to overcome the difficulty of chemoselectivity. The activation of the C=C bonds of α,β-unsaturated aldehydes by the iminium catalyst of Lelais and MacMillan has been well-recognized in many catalytic asymmetric processes.[14] By using such imidazolidinone catalysts together with Hantzsch esters, asymmetric transfer hydrogenation of α,β-unsaturated aldehydes was independently developed by List and MacMillan and their co-workers. List and co-workers found that various ammonium salts can cat-



Scheme 1. Naturally occurring hydride-reduction cofactors and Hantzsch esters.

alyze the conjugate reduction of α,β-unsaturated aldehydes to their corresponding saturated aldehydes by using Hantzsch ester **3a** with high chemoselectivity.[9a] An asymmetric variant of this reaction with aryl enals and Hantzsch ester **3c** was also demonstrated successfully.[9b] In the presence of 10 mol% of imidazolidinone salt **4**, treatment of α,β-unsaturated aldehydes **5** with Hantzsch ester **3c** afforded aldehydes **6** in 77–90% yield with 90–96% *ee* (Scheme 2, top). Almost simultaneously, MacMillan and co-workers utilized imidazolidinone salt **7**, developed in their own laboratory, to catalyze the asymmetric transfer hydrogenation of various α,β-unsaturated aldehydes in good yield with excellent *ee* (74–95% yield, 90–97% *ee*; Scheme 2, bottom).[10a]



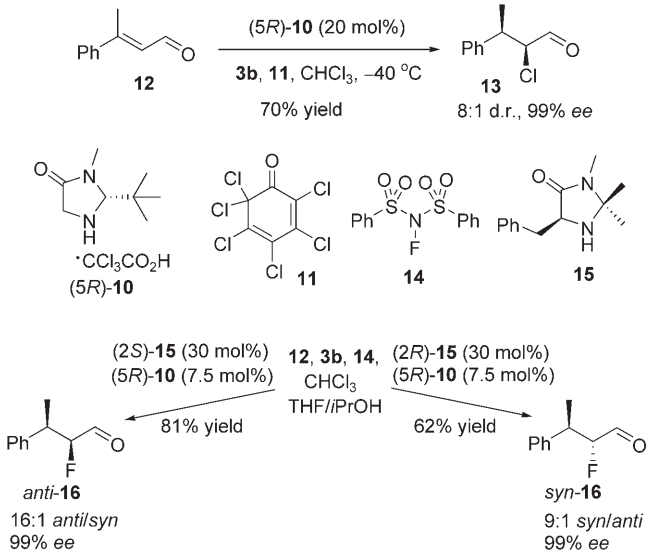
Scheme 2. Asymmetric transfer hydrogenation of α,β-unsaturated aldehydes catalyzed by imidazolidinone salts. Cy = cyclohexyl, TIPS = triisopropylsilyl.

Interestingly, the geometry of the aldehyde olefin was found to have a very limited effect on the enantioselectivity; both conformations lead to the same product enantiomer. The origin of stereoconvergence here arises from catalyst-accelerated *E*–*Z* isomerization prior to selective transfer hydrogenation of the *E*-olefin isomer. Tolerance of the starting material with low geometric purity undoubtedly enhances the utility of this hydrogenation process. Notably, NADH is not a viable reagent for hydrogenation, and reaction with *N*-benzylnicotinamide was quite selective but with a low conversion.[10a]

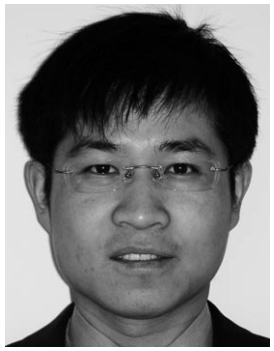
Abstract in Chinese:

Hantzsch酯作为氢源应用在不对称氢转移反应中最近引起化学家的重视并取得了一些很好的结果。利用有机小分子催化剂或金属络合物，通过对碳碳、碳氮、碳氧双键以及喹啉衍生物的不对称氢转移还原，可以得到多种重要手性砌块，反应具有产率优良、对映选择性高、反应条件温和等特点。本文将综述该领域的最新进展及评估该仿生合成方法优缺点。

A distinct difference between this Hantzsch ester hydrogenation process and that with hydrogen gas is the stepwise nucleophilic addition of hydride, which generates a new nucleophile and enables the "cascade catalysis" in the presence of an electrophile. Recently, this concept was realized independently by MacMillan[10b] and List[9c] and their co-workers. MacMillan and co-workers developed enantioselective organocascade catalysis by combining transfer hydrogenation with Hantzsch esters and halogenation with electrophilic sources such as **11** and **14** (Scheme 3).[10b] Treatment of **12** with 20 mol% of (5*R*)-**10** followed by Hantzsch ester **3b** and the electrophile source **11** gave the hydrohalogenated product **13** in 70% yield with 8:1 d.r. and 99% *ee* (Scheme 3).[10b] Remarkably, the authors demonstrated rapid access to complex molecular architecture by using two different amine catalysts that can be easily modified to deliver the required diastereo- and enantioselective outcome. For



Scheme 3. Organocascade catalysis for asymmetric transfer hydrogenation and halogenation of **12**.



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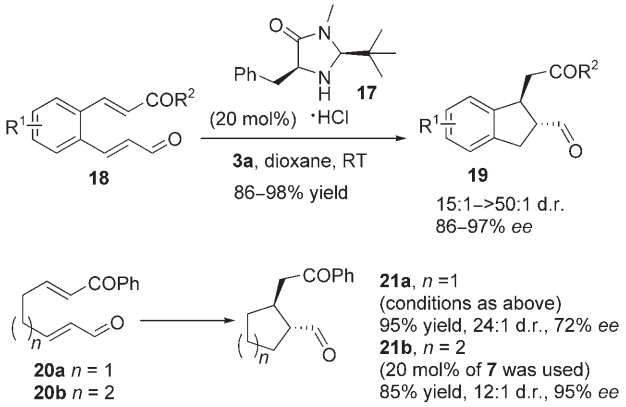
instance, with (2*S*)-**15** (30 mol%) and (5*R*)-**10** (7.5 mol%) as the catalysts, **16** was obtained in 81% yield with 99% *ee* and 16:1 d.r. in favor of the *anti* isomer. The *syn* isomer can be accessed with 9:1 d.r. and 99% *ee* simply by changing (2*S*)-**15** to (2*R*)-**15** in the catalyst combination.

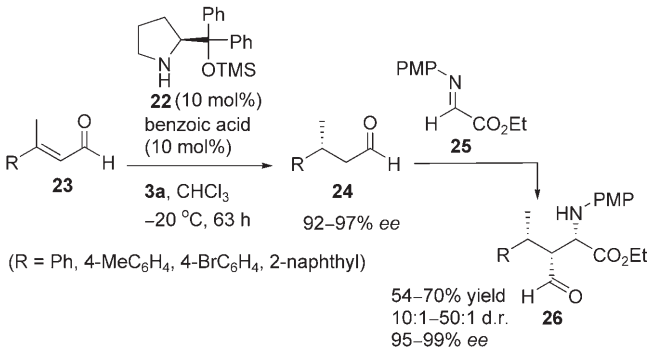
Instead of using electrophilic sources for halogenation, List and co-workers utilized α,β-unsaturated ketones as the nucleophilic acceptor to realize the asymmetric reductive Michael cyclization (Scheme 4).[9c] In the presence of



Scheme 4. Asymmetric reductive Michael cyclization.

20 mol% of **17** and Hantzsch ester **3a**, a variety of enal enones underwent the reductive Michael cyclization to afford functionalized five- and six-membered rings with excellent diastero- and enantioselectivities. The spacers used are not limited to substituted benzene rings; the cyclization of aliphatic enal **20b** in the presence of catalyst **7** provided the product **21b** with 95% *ee* and 12:1 d.r.

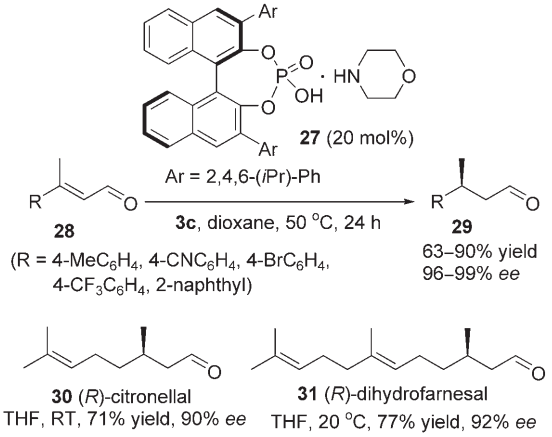
Almost simultaneously, the asymmetric reductive Mannich-type reaction, another excellent example of cascade reactions, was introduced by Zhao and Córdova.[12] Asymmetric transfer hydrogenation of aldehydes **23** with 10 mol% of chiral pyrrolidine **22** and **3a** as the hydrogen source was carried out in 63 h to afford **24** with 92–97% *ee* (Scheme 5). The same catalyst then catalyzed the Mannich reaction of hydrogenated aldehydes **24** with imine **25** to yield **26** with



Scheme 5. Asymmetric reductive Mannich-type reactions. PMP = *para*-methoxyphenyl, TMS = trimethylsilyl.

excellent levels of diastereo- and enantioselectivity (54–70% yield, 10:1–50:1 d.r., 95–99% *ee*).

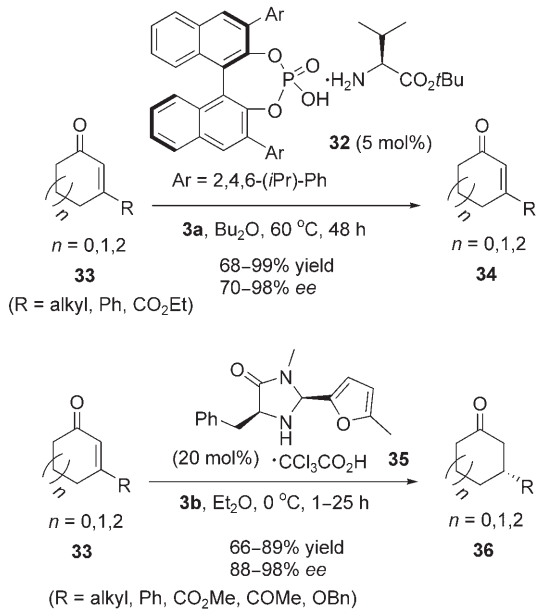
By using an approach other than iminium activation via a chiral amine and an achiral acid salt, Mayer and List[9e] and their co-workers elegantly designed and developed a method that employs an achiral amine and a chiral Brønsted acid catalyst.[15,16] Asymmetric counteranion-directed catalysis (ACDC), named by List and co-workers, is an effective strategy for asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.[9e] Screening of various ammonium phosphates, prepared easily by mixing amines with chiral phosphoric acids, revealed that ammonium phosphate **27** is optimal as catalyst. With 20 mol% of **27**, α,β-unsaturated aldehydes **28** bearing aromatic substituents were reduced to their corresponding saturated aldehydes **29** in moderate to good yields with excellent enantioselectivities (96–99% *ee*; Scheme 6). For less-hindered aliphatic substrates, ammonium phosphate **27** showed superior enantioselectivities than



Scheme 6. Asymmetric transfer hydrogenation of α,β-unsaturated aldehydes catalyzed by an ammonium phosphate.

those of previous imidazolidinone catalysts. For instance, with 20 mol% of **27**, (*R*)-citronellal (**30**) and (*R*)-dihydrofarnesal (**31**) were obtained with 90 and 92% *ee*, respectively. The former was formed with only 40% *ee* in the presence of catalyst **4** or **7**.

Hantzsch esters have also been used for asymmetric transfer hydrogenation of α,β-unsaturated ketones in the presence of an ammonium phosphate salt, recently introduced by Martin and List.[9g] During the search for an efficient catalyst, however, both aforementioned ACDC and chiral imidazolidinone catalysts failed to provide satisfying yields or enantioselectivities. Interestingly, ammonium phosphate **32**, derived from a chiral phosphoric acid and a valine *tert*-butyl ester, proved effective for this process. In the presence of 5 mol% of **32**, cyclic α,β-unsaturated ketones were reduced with excellent enantioselectivities (Scheme 7, top). Excellent yields were obtained for six- and seven-membered-ring substrates, and moderate yields were obtained for five-membered-ring substrates even with 10 mol% of catalyst. Notice-



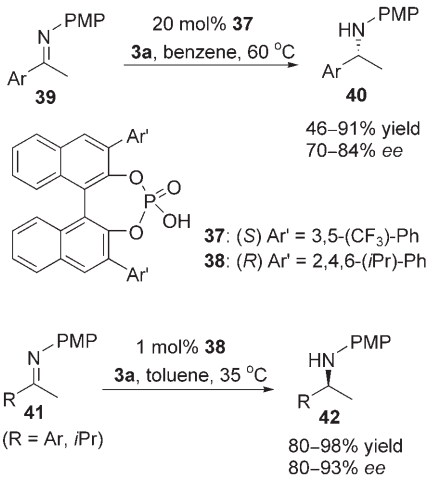
Scheme 7. Asymmetric transfer hydrogenation of α,β-unsaturated ketones.

ably, acyclic α,β-unsaturated ketones were also reduced with good enantioselectivities.

Just before the above work was carried out, MacMillan and co-workers also found that the imidazolidinone catalysts identified earlier for enal hydrogenation were less reactive towards hydrogenation of α,β-unsaturated ketones.[10d] Interestingly, further elaborate examination of the catalysts and reaction conditions revealed that imidazolidinone salt **35** is a good catalyst for this transformation (Scheme 7, bottom).[10d] *tert*-Butyl ester **3b** was found to be optimal for the enantioselectivity after various Hantzsch esters were screened. In the presence of 20 mol% of **35** and 1.1 equivalents of **3b**, a series of cyclic α,β-unsaturated ketones **33** afforded the hydrogenated products **36** in 66–89% yield with 88–98% *ee* (Scheme 7, bottom).

3. Reduction of C=N Bonds (Imines and Quinolines)

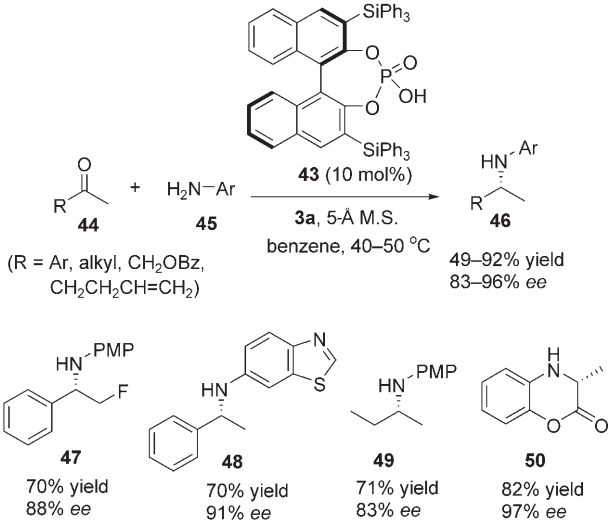
Besides the hydrogenation of C=C bonds, Hantzsch esters were also used to reduce imines to their corresponding amines. The first asymmetric example involving the use of an achiral Hantzsch ester was reported as early as 1989 by Singh and Batra. Prochiral imines were reduced by Hantzsch ester **3a** in the presence of α-amino acid hydrochlorides or chiral acids to afford amines with moderate enantioselectivities (up to 63% *ee*).[17] Recently, Rueping et al. found that a chiral phosphoric acid is an effective catalyst.[11a] In the presence of 20 mol% of **37**, various aryl methyl ketimines underwent transfer hydrogenation with Hantzsch ester **3a** in benzene at 60°C to give the desired amines in 46–91% yield with 70–84% *ee* (Scheme 8, top).



Scheme 8. Asymmetric transfer hydrogenation of imines by chiral phosphoric acids.

Subsequently, List and co-workers looked into the same transformation in more detail.[9d] By utilizing 1 mol% of **38**, a more sterically hindered phosphoric acid, good to excellent yields and enantioselectivities were attained for a variety of aryl methyl ketimines in the presence of Hantzsch ester **3a** in toluene at 35°C (Scheme 8, bottom). Furthermore, 80% yield and 90% *ee* resulted for isopropyl methyl ketimine, an aliphatic ketimine (Scheme 8, bottom). Notably, the *ee* was preserved when imine formation and reduction were performed in situ in the presence of molecular sieves.

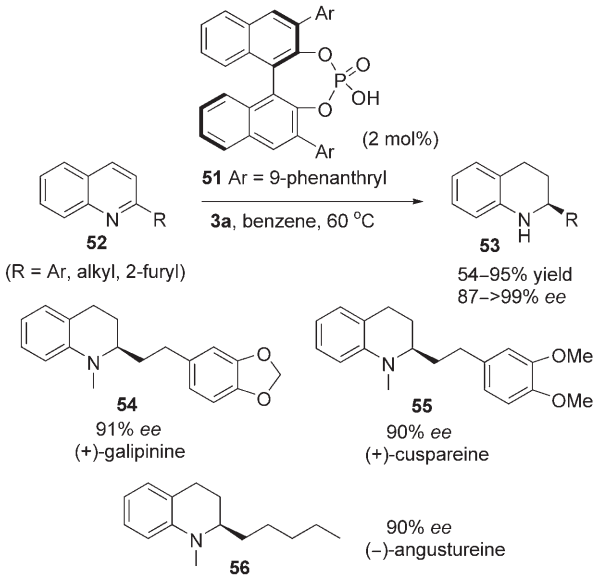
Soon after these results, MacMillan and co-workers reported an effective reductive amination with Hantzsch ester **3a** as the hydrogen source.[10c] The newly designed phosphoric acid **43**, which bears two triphenylsilyl groups on the 3- and 3′-positions of the binaphthyl scaffold, was found to be optimal for the enantioselectivity (Scheme 9). With



Scheme 9. Enantioselective reductive amination by a chiral phosphoric acid. M.S. = molecular sieves.

10 mol% of **43**, a broad spectrum of structurally diverse amines **46** was provided in the presence of 5-Å molecular sieves, and both the yields and enantioselectivities were superior. For instance, fluoromethyl-bearing amine **47** (88% *ee*), heteroaromatic amine **48** (91% *ee*), 2-butylamine **49** (83% *ee*), and cyclic amine **50** (97% *ee*) were all obtained with excellent enantioselectivities (Scheme 8). A single-crystal X-ray structure of **43** bound with an imine substrate was also obtained, which provided direct insight into the origin of the enantiofacial discrimination.

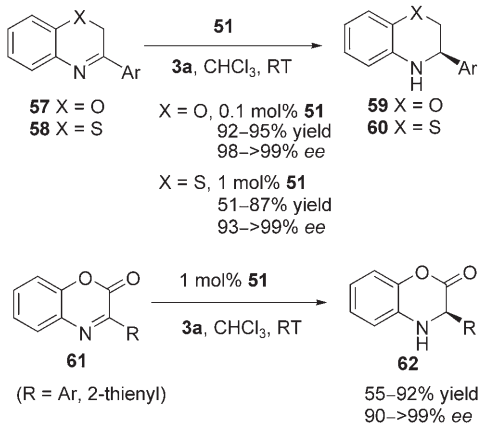
Inspired by the Hantzsch ester mediated hydrogenation of alkenes and imines, Rueping et al. very recently showed that phosphoric acid **51** could catalyze transfer hydrogenation of quinolines, an important class of heteroaromatic compounds.[11b] By using Hantzsch ester **3a** as the hydrogen source, a proposed cascade-hydrogenation process including 1,4-hydride addition, isomerization, and 1,2-hydride addition afforded tetrahydroquinolines **53** with excellent enantioselectivities of up to >99% *ee* in the presence of 2 mol% of **51** (Scheme 10). This methodology has been applied to the



Scheme 10. Asymmetric transfer hydrogenation of quinolines by a chiral phosphoric acid.

synthesis of several biologically active tetrahydroquinoline alkaloids such as (+)-galipinine (**54**; 91% *ee*), (+)-cuspareine (**55**; 90% *ee*), and (−)-angustureine (**56**; 90% *ee*). The mild reaction conditions, operational simplicity, and relatively low catalyst loading make this organocatalytic approach very attractive for the synthesis of enantio-enriched tetrahydroquinolines.

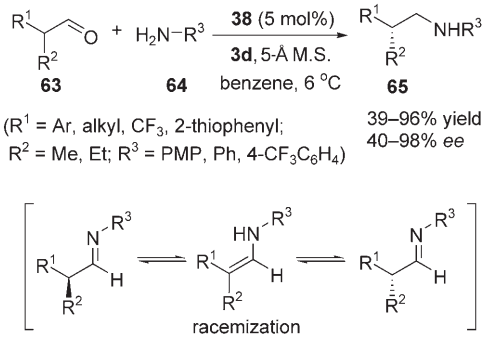
The development of highly efficient organocatalysts for low catalyst loading remains one of the biggest challenges in practical organocatalysis. With the success of highly enantioselective Brønsted acid catalyzed transfer hydrogenation of ketimines and quinolines, Rueping et al. recently extended this approach to the reduction of benzoxazines, benzothiazines, and benzoxazinones.[11c] With a remarkably low catalyst loading (especially for organocatalysis) of 0.1 mol% (even 0.01 mol%) of **51**, benzoxazines were reduced in excellent yields and with excellent enantioselectivities (92–95% yield, 98–>99% *ee*; Scheme 11, top). Benzothiazines



Scheme 11. Asymmetric transfer hydrogenation of benzoxazines, benzothiazines, and benzoxazinones by a chiral phosphoric acid.

and benzoxazinones **61** also underwent transfer hydrogenation with Hantzsch ester **3a** to afford their corresponding hydrogenated products with excellent enantioselectivities (up to >99% *ee*; Scheme 11, bottom). Highly enantioselective hydrogenation of benzothiazines demonstrates the advantage of this organocatalytic approach over the application of most metal catalysts, which are known to be poisoned by sulphur-containing substrates.[11c]

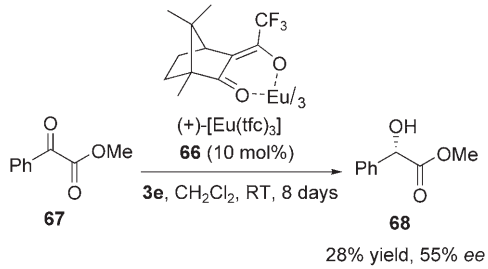
Besides the synthesis of α-branched chiral amines through asymmetric reduction of ketimines or reductive amination from ketones, β-branched chiral amines may be delivered through reductive amination of α-branched aldehydes through dynamic kinetic resolution (DKR; Scheme 12). Recently, List and co-workers successfully realized this concept.[9f] By utilizing 5 mol% of **38**, a series of α-branched aldehydes together with different anilines were hydrogenated in the presence of Hantzsch ester **3d** and 5-Å molecular sieves. In general, the desired β-branched chiral amines were obtained in 39–96% yield and with 40–98% *ee* through DKR. The fast equilibration between imine and enamine is the key to this highly efficient DKR process.



Scheme 12. Asymmetric reductive amination of aldehydes by DKR.

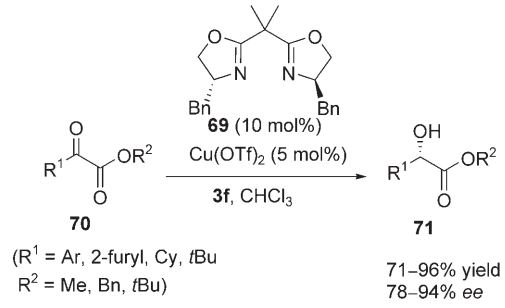
4. Reduction of C=O Bonds with Chiral Metal Complexes

Hantzsch esters are not only amenable to the transfer-hydrogenation process in the presence of an organocatalyst, they are also capable of reducing the carbonyl functionality by utilizing a chiral metal complex. More than two decades ago, Zehani and Gelbard found that lanthanide β-diketonates catalyze the reduction of methyl phenylglyoxylate **67** to methyl mandelate **68** in the presence of Hantzsch esters (Scheme 13).[18] In the presence of 10 mol% of (+)-[Eu(tfc)$_3$] (**66**), a chiral shift reagent, methyl mandelate **68** was obtained with moderate enantioselectivity (55% *ee*).



Scheme 13. Asymmetric transfer hydrogenation of α-ketoesters by a chiral shift reagent. tfc = 3-(trifuoromethylhydroxymethylene)-(+)-camphor.

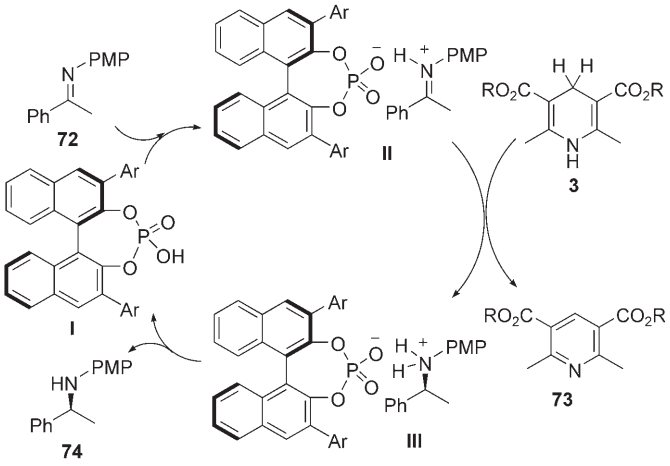
Recently, Yang and List reported an enantioselective reduction of α-ketoesters by a chiral copper(II) bisoxazoline.[9h] As shown in Scheme 14, the copper(II) catalyst generated in situ from 5 mol% of Cu(OTf)$_2$ and 10 mol% of bisoxazoline **69** catalyzed the transfer hydrogenation of α-ketoesters in the presence of **3f** to yield the optically active α-hydroxy esters with 78–94% *ee*.



Scheme 14. Asymmetric transfer hydrogenation of α-ketoesters by a chiral copper(II) bisoxazoline.

5. General Mechanism

Asymmetric transfer hydrogenation catalyzed by a chiral phosphoric acid was used to illustrate the general mechanism for the Hantzsch ester mediated reduction process. As shown in Scheme 15, chiral phosphoric acid **I** protonates imine **72** to form the tight ion pair **II**. The protonated iminium is activated toward nucleophilic attack by the hydrogen atom of Hantzsch ester **3**, for which the major driving force is the formation of an aromatic structure, pyridine **73**. Enantiofacial discrimination occurs during this step as the chiral phosphate creates an asymmetric environment for the iminium moiety. The reduced salt **III** then undergoes dissociation to give amine **74** and releases the chiral phosphoric acid for the next catalytic cycle.



Scheme 15. Catalytic cycle for the phosphoric acid catalyzed transfer hydrogenation of imines with Hantzsch esters.

6. Summary and Outlook

Hantzsch esters, which are analogues of nicotinamide, have been used as the hydrogen source for enantioselective reduction of C=C, C=N, and C=O functionalities. In the presence of catalytic amounts of an organocatalyst or a metal–ligand complex, several enantioselective processes have been developed to provide versatile enantio-enriched organic compounds.

Compared with the traditional method in which hydrogen gas and metal hydrides are used as the hydrogen source, Hantzsch ester mediated reductive processes have the following advantages: 1) mild reaction conditions, as most of the reactions can be carried out at room temperature (or with slight heating and cooling) in conventional solvents; 2) operational simplicity, as there is no requirement either for special high-pressure apparatus, commonly needed for the hydrogen-gas process, or for air-free conditions, which is mostly necessary for the process involving metal hydrides; 3) ready availability of Hantzsch esters; 4) safe handling; 5) compatibility with organocatalysts; 6) suitability for hydrocascade catalysis. All these points make this biomimetic reductive process very attractive in organic synthesis. On the other hand, problems remain with the current approach, such as: 1) poor atom economy, as only two protons are used per molecule and stoichiometric amounts of Hantzsch esters are needed; 2) problematic removal of the pyridine by-product for industrial-scale synthesis; 3) low efficiency for some of the current catalytic systems. Thus, efforts towards the easy separation and recycling of Hantzsch esters will be highly desirable and likely to address some of these remaining issues.[19] The recent significant findings discussed

above will undoubtedly stimulate further development of new hydrogenation reactions with Hantzsch esters. By overcoming the formidable drawbacks, it is reasonable to believe that the practical application of this biomimetic asymmetric hydrogenation will soon arrive.

Acknowledgements

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