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TUTORIAL REVIEW

Advances in catalytic metal-free reductions: from bio-inspired concepts to applications in the organocatalytic synthesis of pharmaceuticals and natural products

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This review focuses on recent advances in catalytic metal-free transfer hydrogenations. In recent years dihydropyridines have been widely used as reducing agents in organocatalytic reductions. Analogous to nature's co-factor nicotinamide adenine dinucleotide (NADH), Hantzsch esters serve as efficient hydride donors. In combination with chiral organocatalysts, including chiral secondary amines, hydrogen bond donors or Brønsted acids, efficient catalytic asymmetric reductions have been developed which provide a diverse set of biologically active compounds, synthetic building blocks and natural products. These recent advances in developing green and sustainable reductions employing organocatalytic strategies are promising and important alternatives to conventional metal- and bio-catalyzed reductions.

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Introduction

Enantioselective hydrogenations are an ubiquitous tool to access a broad range of biological active compounds, which often consist of a hydrogen as part of the stereocenters. While

Magnus Rueping

Magnus Rueping studied at the Technical University of Berlin, Trinity College Dublin and ETH Zürich, where he completed his diploma thesis under the direction of Professor Dieter Seebach. He stayed in the Seebach group and obtained his Ph.D. from the ETH in 2002 working on the synthesis and structural and biological aspects of oligo(hydroxybutanoates) and of β- and γ-peptides. Magnus then moved to Harvard University to work with Professor David A. Evans on enantioselective transition-metal catalysis. In August 2004 he was directly appointed to a C3 associate professorship, the Degussa Endowed Professorship of Synthetic Organic Chemistry, at the Goethe-University Frankfurt. After four years in Frankfurt he accepted a Chair and Full Professorship of Organic Chemistry at RWTH Aachen University. His group's research activities are directed toward the development and simplification of synthetic catalytic methodology and technology, and their application in the rapid synthesis of diverse functional natural and unnatural molecules, not only to address chemical, biological and physical problems but also to generate new molecules with potentially interesting properties.

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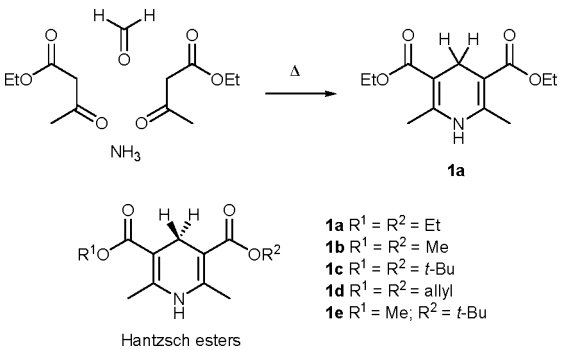
enantioselective organometallic reductions have been known for a long time, asymmetric metal-free hydrogenations have only arisen over the past few years and an impressive number of organocatalytic reductions have been reported. In contrast to metal-catalyzed hydrogenations, which often apply elementary hydrogen as reducing agent, organocatalytic transfer hydrogenations are based on a biomimetic approach, using for instance Hantzsch esters (HEH) as the hydrogen source. This review summarises the impressive developments of metal-free transfer hydrogenations mediated by organic hydride sources.

Hantzsch esters

1,4-Dihydropyridines, also known as Hantzsch esters (HEH), were first synthesized by Arthur Hantzsch in 1882.[1] Ethyl-derived Hantzsch ester **1a** was formed when two equivalents of ethyl acetoacetate was reacted with formaldehyde and ammonia (Scheme 1).[2]



Scheme 1 Synthesis of Hantzsch ester.

Driven by the aromatization energy dihydropyridines can be easily oxidized to the corresponding pyridines **2** (Scheme 2). As a hydride is being abstracted in this aromatization process, Hantzsch esters can serve as very mild reducing agents.

In 1939, Mumm and Diederichsen utilized a Hantzsch ester for the first time as a reducing agent in the reduction of

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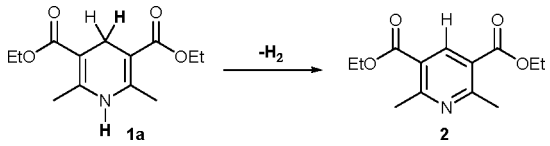
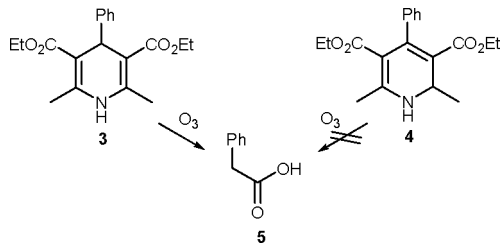


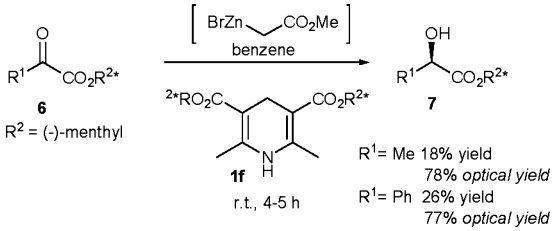
Scheme 2 Hantzsch ester as a mild hydride source.

maleic anhydride to succinic anhydride.[3] Although they realized that a hydride is transferred from the dihydropyridine, they proposed the wrong structure for the Hantzsch ester as they assumed that the reduction could only be accomplished by a 1,2-dihydropyridine rather than by a 1,4-dihydropyridine. In 1955, Berson and Brown resolved the structure of a Hantzsch ester from its chemical properties and ultraviolet absorption and assigned it as a 1,4-dihydropyridine.[4] Kuss and Karrer substantiated these results in 1957 by degrading Hantzsch ester **3** with ozone (Scheme 3).[5] The 1,4-dihydropyridine structure of the Hantzsch ester was confirmed as they obtained phenylacetic acid **5** after degradation.



Scheme 3 Ozonolytic degradation for the elucidation of the structure of Hantzsch ester.

In 1955, Mauzerall and Westheimer studied the mechanism of hydrogen transfer by 1,4-benzyldihydronicotinamide in order to find which hydrogen was transferred.[6] By isotopic labelling experiments, they showed that deuterium was transferred to the substrate in case of the 1-benzyl-4-deutero-dihydronicotinamide but not with the 2- or 6-deutero-substituted derivatives. In 1958, Abeles and Westheimer extended these experiments to the Hantzsch ester and demonstrated that a direct hydrogen transfer took place from the Hantzsch ester to the substrate. In case of deuterated solvent no incorporation into the reduced product could be detected.[7] The group of Westheimer then concentrated its studies on the reduction of various olefinic double bonds and carbonyl compounds by using Hantzsch ester or its nicotinamide analogues.[8] In 1960, Linstead and co-workers reported for the first time Hantzsch ester-mediated transfer hydrogenations of various nitrogen-containing heterocycles.[9] In contrast to previous results which only reported traces of reduced product, the group of Linstead achieved moderate to good yields for the transfer hydrogenation. In 1976, Inouye and co-workers finally employed a mono-ionized zinc-species to accelerate the reduction.[10] While no product was obtained in the transfer hydrogenation of methyl benzoylformate with Hantzsch ester, 56% yield was isolated by applying a zinc-species, which was preformed in a Reformatsky reaction. When they additionally treated the reaction mixture with *p-tert*-butylcatechol, they improved yield to 79%. Shortly afterwards, they extended this methodology to the asymmetric reduction of pyruvates and benzoylformates by applying a chiral (–)-menthyl-substituted



Scheme 4 Transfer hydrogenation of α-ketoesters by a chiral Hantzsch ester associated with zinc species.

Hantzsch ester **1f** (Scheme 4).[11] By double asymmetric induction in combination with a chiral substrate **6**, they achieved optical yields up to 78%.

Since then, a large number of transfer hydrogenations mediated by Hantzsch esters associated with various additives and Lewis acids has been reported. However, these applications will not be described in detail in this review.[12] Instead, recent advances in the metal-free, organocatalytic reductions will be highlighted.

Hantzsch esters as biomimetic hydrogen sources

In nature, transfer hydrogenation processes are typically mediated by a co-factor associated with an enzyme. Hantzsch esters are synthetic analogues of nature's fundamental reduction co-factors such as NADH (nicotinamide adenine dinucleotide) or its phosphate, NADPH (Fig. 1).[13]

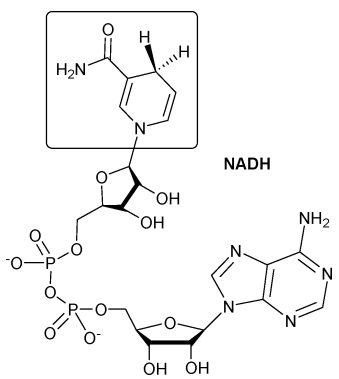
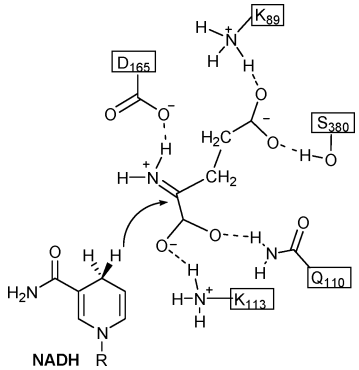


Fig. 1 Structure of NADH.

Among the numerous reductions in which NADH is involved, the glutamate dehydrogenase-catalyzed reductive amination of 2-ketoglutarate is a good example for understanding the mechanism of nature's hydrogenations. The group of Stillman proposed a mechanism supported by kinetic studies and X-ray analyses explaining the role of the enzyme glutamate dehydrogenase in the reductive amination. The catalytic active site of the enzyme contains different amino acids (Scheme 5) and aspartate D165 was proposed to be critical in the reduction process. α-Iminoglutarate, formed from ammonia and 2-ketoglutarate, is activated by catalytic protonation through aspartate D165 which allows a hydride transfer from NADH, thus yielding the amino acid glutamate.

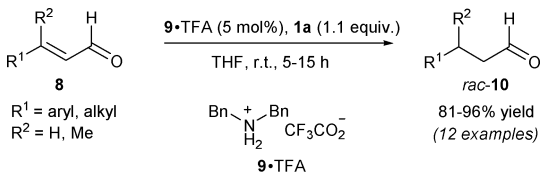
One year later, site-directed mutagenesis studies agreed with the above mechanism. The replacement of the aspartate residue (D165) with different amino acids resulted in the loss of catalytic activity of the enzyme. These results prove the fundamental role of the aspartate in nature's transfer hydrogenation as well as the importance of imine activation by protonation.



Scheme 5 Proposed mechanism for the reductive amination of 2-ketoglutarate to glutamate by NADH.

Catalytic asymmetric transfer hydrogenation of C═C bonds

Although Hantzsch esters have been established as mild reducing agents, reaction conditions and outcomes could still be improved. In 2004, List and co-workers reported for the first time a catalytic metal-free reduction of α,β-unsaturated aldehydes **8** to the corresponding saturated aldehydes **10** (Scheme 6).[14]

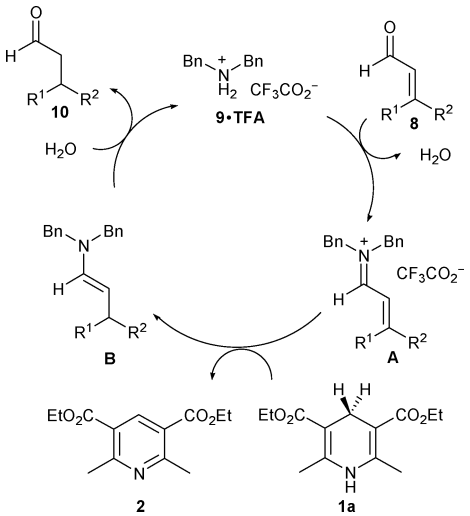


Scheme 6 Catalytic metal-free reduction of α,β-unsaturated aldehydes.

In contrast to previous Hantzsch ester-mediated reductions, this process proceeded without additional metallic species.[15] The ammonium trifluoroacetate salt **9**·TFA was applied to activate the aldehyde by *in situ* formation of the corresponding iminium-ion. This concept of metal-free activation had previously been described by MacMillan.[16] By reversible formation of an iminium-ion, the LUMO of the aldehyde is lowered in energy, thereby activating it toward a nucleophilic attack. Accordingly, List and co-workers proposed a mechanism starting with the formation of an iminium-ion **A**. This activated species then undergoes a conjugated hydride addition from Hantzsch ester **1a** while pyridine **2** is produced (Scheme 7).

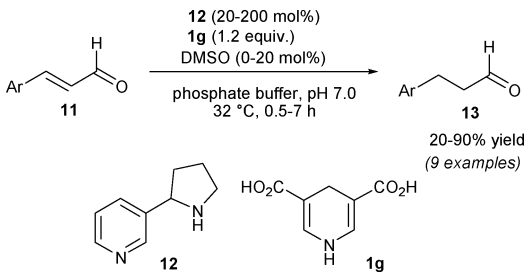
Terminal hydrolysis of enamine **B** affords the saturated aldehyde **10** while releasing the catalyst **9**·TFA. By employing this organocatalytic strategy, List *et al.* were able to reduce a broad range of α,β-unsaturated aldehydes (Scheme 6). Interestingly, the reduction proceeds highly chemoselective, without affecting nitro-, cyano-, benzyloxy- or alkenyl groups, which are usually reduced in regular hydrogenation reactions.

Janda and co-workers reported a similar reduction of α,β-unsaturated aldehydes in aqueous media.[17] A variety of cinnamaldehyde derivatives **11** were reduced using nornicotine **12** as a catalyst or mediator and HEH analogue **1g** as the hydride



Scheme 7 Mechanism of the iminium-activated transfer hydrogenation.

source in a phosphate buffer solution. Addition of DMSO was required when the starting material was not soluble in water (Scheme 8). Even if the reaction is limited to aromatic α,β-unsaturated aldehydes and gives average yields, it represents an interesting starting point toward the development of further related ecological transformations.

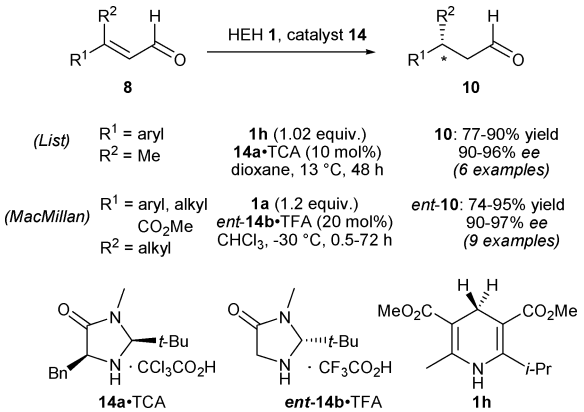


Scheme 8 Metal-free transfer hydrogenation of α,β-unsaturated aldehydes in aqueous media.

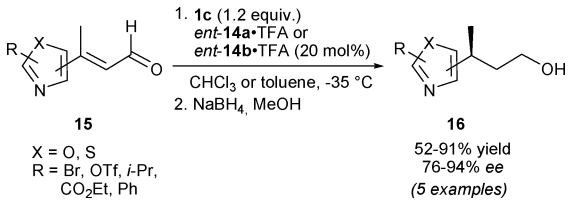
By utilizing the ammonium salts of chiral imidazolidinones **14a** and *ent*-**14b**, the groups of List,[18] and MacMillan[19] could achieve chiral induction and obtained diversely substituted aldehydes **10** and *ent*-**10** in good yields and with excellent enantioselectivities up to 97% *ee* (Scheme 9). Both groups realized that this protocol proceeds enantioconvergent, providing the same enantiomer, regardless of whether the *E*- or *Z*-olefin was used.

This methodology was recently applied by Cossy and co-workers for the enantioselective transfer hydrogenation of enals attached to an azole.[20] A range of oxazoles and thiazoles **15** bearing a α,β-unsaturated aldehyde was subjected to transfer hydrogenation with HEH **1c** and 20 mol% of imidazolidinone catalysts *ent*-**14a**·TFA or *ent*-**14b**·TFA (Scheme 10). Subsequent reduction of the aldehyde function afforded the corresponding enantioenriched alcohols **16** in good yields and with up to 94% *ee*. The process was successfully applied to the synthesis of the C7–C14 fragment of Ulapualide A.[21]

Recently, the group of Kudo reported an additional Hantzsch ester mediated hydrogenation of enals using a polymer-supported catalyst.[22] They showed that the TFA salt of peptide

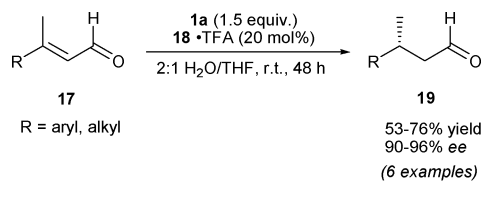


Scheme 9 Asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.



Scheme 10 Asymmetric conjugated reduction of enal-substituted azoles.

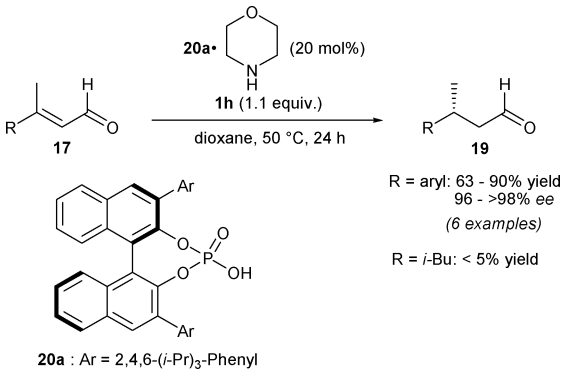
Pro-D-Pro-Aib-$(Try)_2$-$(Leu)_{25.4}$-NH-$(CH_2)_2$-PEG-PS **18**, bearing a proline as active site, could reduce enals **17** with HEH **1a** in an aqueous media (Scheme 11). Saturated aldehydes **19** were obtained in good yields with excellent enantioselectivities.



Scheme 11 Asymmetric conjugate reduction of enals catalyzed by a resin-supported peptide.

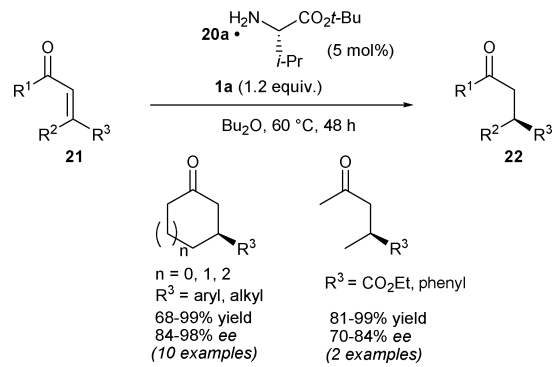
In 2006, List and co-workers reported an improved method for the transfer hydrogenation of α,β-unsaturated aldehydes **17**, (Scheme 12).[23] Instead of using a chiral amine in combination with an achiral counteranion, they utilized chiral phosphates as counteranions together with an achiral amine. This kind of axially chiral Brønsted acid catalyst[24] had been previously developed by both Akiyama[25] and Terada[26] and used in metal-free activation of imines. By applying the morpholine salt of the sterically demanding TRIP-BINOL-phosphate **20a**,[27] which had already been proven to be an excellent metal-free catalyst, the corresponding saturated aldehydes **19** were obtained in good yields and with excellent enantioselectivities (Scheme 12). While non-sterically hindered substrates could be reduced in high yields and enantioselectivities, sterically more demanding substrates like the *tert*-butyl substituted α,β-unsaturated aldehyde could not be hydrogenated.

Extending this methodology, List reduced α,β-unsaturated ketones to the corresponding saturated ketones (Scheme 13).[28]



Scheme 12 Counteranion-directed hydrogenations.

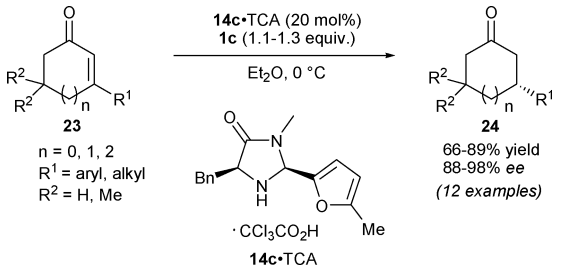
While preliminary studies on the reduction of ketones with the chiral imidazolidinones resulted in low conversions, better results were obtained by applying primary amines. By combining a valine-derivative as a chiral primary amine and TRIP-BINOL-phosphate **20a** as chiral counteranion, various α,β-unsaturated cyclic and acyclic ketones **21** could be hydrogenated to the desired ketones **22** in high yields and enantioselection (Scheme 13).



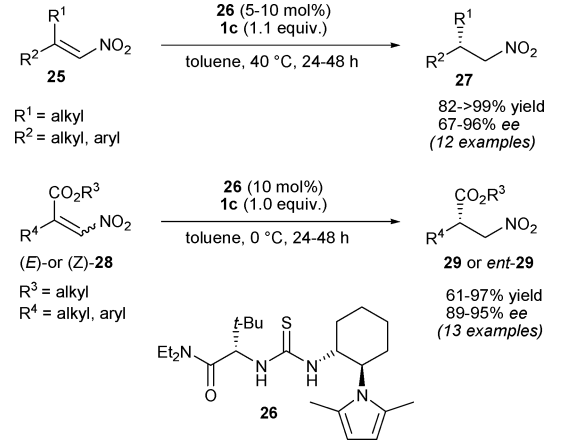
Scheme 13 Enantioselective reduction of enones.

At the same time, the group of MacMillan examined the asymmetric transfer hydrogenation of α,β-unsaturated ketones.[29] In accordance with the observations of List *et al.*, MacMillan and co-workers reported that the imidazolidinone salts only resulted in low conversions, as ketones are sterically and electronically deactivated towards the formation of an iminium ion. However, by applying the furyl imidazolidinone catalyst **14c**, reactivities were considerably higher, although enantioselectivities were only moderate. Higher chiral induction was finally achieved with the sterically more demanding bis(*tert*-butyl)-substituted Hantzsch ester **1c**, affording the transfer hydrogenation of several cyclic enones **23** in high yields and enantioselectivities (Scheme 14).

Schreiner and co-workers reported a first transfer hydrogenation of nitroalkenes catalyzed by thioureas.[30] Shortly thereafter, List and co-workers examined the enantioselective version of this reduction (Scheme 15).[31] While BINOL-phosphates gave only low enantioselectivities, albeit with good yields, various thiourea-derived catalysts resulted in better yields and enantioselectivities. Bis(*tert*-butyl)-substituted Hantzsch ester **1c** not only improved enantioselectivities further, but also increased reactivity was observed. Indeed, nitroalkanes **27** were



Scheme 14 Enantioselective transfer hydrogenation of cyclic enones catalyzed by furanyl imidazolidinone.



Scheme 15 Enantioselective reduction of nitroolefins.

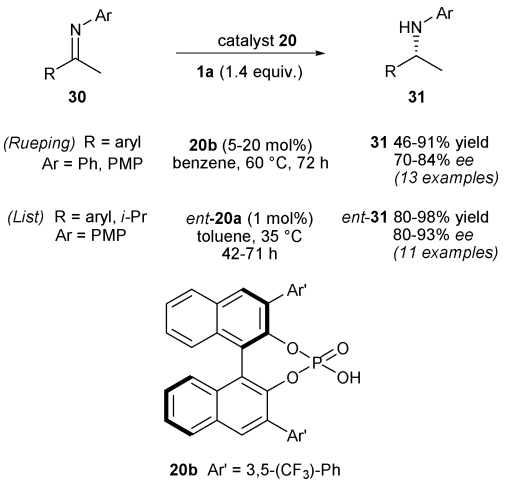
obtained with excellent yields and enantioselectivities up to 96% *ee*.

The same protocol could also be applied to the transfer hydrogenations of β-nitroacrylates **28**, which can be easily obtained by Henry reaction and subsequent dehydratation (Scheme 15).[32] Again, List *et al.* could isolate the corresponding nitroalkanes **29** in high yields and enantioselectivities. Further reduction of the nitro-group led to the corresponding β^2-amino acids which are difficult to access by alternative methods. In contrast to the reduction of α,β-unsaturated aldehydes, which proceeded *enantio*-convergently, the transfer hydrogenation of *E*-nitroolefins resulted in the opposite enantiomer than the corresponding *Z*-nitroolefins. Whereas in case of non-functionalized nitroolefins **25**, only the *E*-isomer resulted in high enantioselectivities, for β-nitroacrylates **28**, both isomers lead to high enantioselectivities. Consequently, a 1 : 1 mixture of both *E*- and *Z*-isomers leads to the racemic product. By addition of catalytic amounts of triphenylphosphine, stereoconvergence could be achieved, due to an equilibration of *E*- and *Z*-isomers.

Catalytic asymmetric transfer hydrogenation of C═N bonds

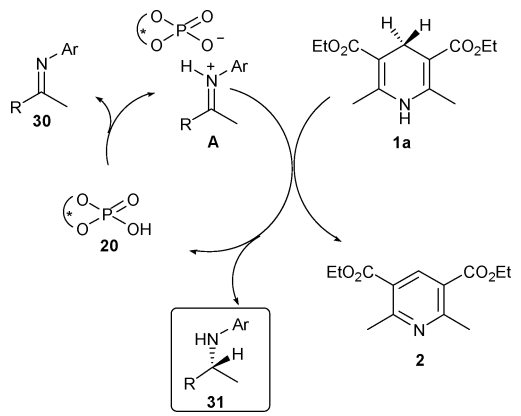
Beside the reduction of alkenes, Hantzsch esters have also been recently used for metal-free asymmetric hydrogenations of imines. The asymmetric hydrogenation of C═N bonds is a highly useful reaction in organic chemistry. Indeed, it gives access to chiral amines, a common structure found in many medicinal compounds and natural products. Historically, Singh and Batra reported the first enantioselective imine reduction

using Hantzsch esters in 1989.[33] Acetophenone-derived imines were reduced in the presence of dihydropyridine **1a** and α-amino acid hydrochlorides such as cysteine. However, the enantioselectivities observed were moderate and not reproducible. In 2005, during a study on protected imine transfer hydrogenation, the group of Rueping showed that this transformation could be performed best with **1a** in the presence of catalytic amounts of diphenylphosphate (DPP).[34] Based on this observation, Rueping investigated the enantioselective version of this reaction using chiral BINOL-derived phosphoric acid catalysts.[35,36] After reaction optimization, chiral phosphoric acid **20b** proved to be most enantioselective catalyst, yielding N-protected-arylmethylamines **31** in good yields and with good enantioselection, 70–84% *ee*. (Scheme 16).



Scheme 16 Asymmetric transfer hydrogenation of N-protected ketimines.

Concerning the mechanism, Rueping *et al.* proposed that the Brønsted acid-catalyzed hydrogenation follows a similar pathway to nature's reductive amination by glutamate dehydrogenase (Scheme 17). Imine **30** is initially protonated by the chiral phosphoric acid **20** resulting in a chiral ion pair **A**, consisting of an iminium ion and a phosphonate counter-anion. Subsequently, Hantzsch ester **1a** transfers a hydride yielding the chiral amine **31** along with pyridine **2** while the catalyst is released. A stereochemical model based on the X-ray crystal



Scheme 17 Proposed catalytic cycle for the phosphoric acid catalyzed transfer hydrogenation of C═N bonds with Hantzsch esters.

structure of the phosphoric acid catalyst was suggested which is in line with the absolute configuration of the amine. In the transition state the ketimine is activated by the Brønsted acid in such a way that the nucleophilic approach is from the less hindered *Si*-face as the *Re*-face is shielded (Fig. 2, left). More detailed theoretical reports by Goodman and Himo[37,38] revealed that the catalyst could also act as a Brønsted acid/Lewis base bifunctional catalyst.

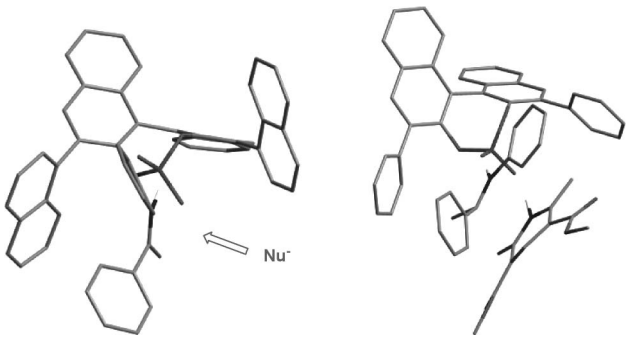


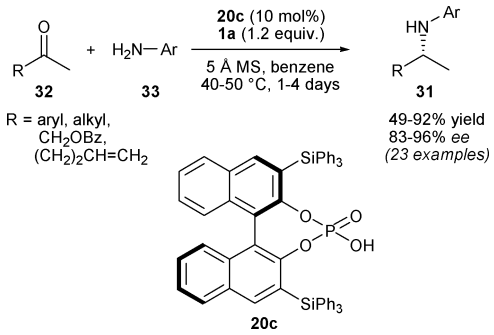
Fig. 2 Stereochemical model of the phosphoric acid-catalyzed activation of imines.

Indeed, the phosphoric acid could be involved in a plausible dual activation in which the imine is protonated and the Hantzsch ester is activated by a hydrogen bond from the Lewis basic oxygen of the phosphoryl group (Fig. 2, right).

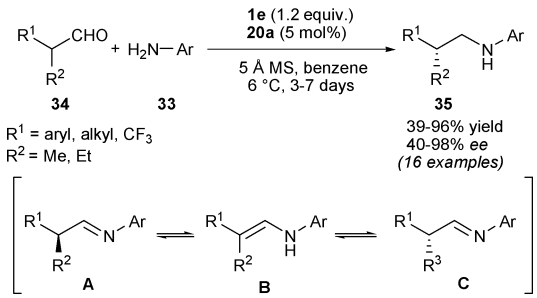
The work of Rueping's group represented the first disclosure in this area and was shortly followed by a similar study by List and co-workers.[39] Employing the more sterically-demanding catalyst TRIP-derived *ent*-**20a**, improved results were reported in terms of enantioselectivity (80–93% *ee*, Scheme 16) and catalyst loading (1 mol% *vs.* 5–20 mol%). List *et al.* also showed that a dialkyl imine substrate could be used in this reaction and reported one example of an *in situ* generation of imine (81% yield, 88% *ee*). Additionally, the group of Schreiner published in 2007 a transfer hydrogenation of aldimines catalyzed by thioureas.[40] After List's report, MacMillan and co-workers published a study of an efficient enantioselective reductive amination using **1a** as transfer hydrogenation reagent.[41] Even though a methylketone is necessary for the process, the scope is broad as the reaction can be performed between aryl, vinyl or alkyl methylketones **32** and a wide range of anilines and heterocyclic amines **33**. The key to the success of this reaction is the use of a triphenylsilyl-subsituted catalyst **20c** in combination with 5 Å molecular sieves. Thus, the corresponding chiral amines **31** were obtained with 83–96% *ee* and, good yields (Scheme 18).

It has to be mentioned that several non-selective reductive aminations, catalyzed by thioureas, have also been reported since early 2006.[42]

Both, the asymmetric transfer hydrogenations of imines and the reductive amination of ketones mentioned above gave access to α-branched chiral amines. Subsequently to these reports, List disclosed an approach to β-branched chiral amines by reductive amination of aldehydes with Hantzsch ester derivatives *via* dynamic kinetic resolution.[43] Racemic α-branched aldehydes **34** together with anilines **33** in the presence of 5 mol% of catalyst **20a** and modified Hantzsch ester **1e** furnished β-branched chiral amines **35** in 39–96% yield and 40–98% *ee* (Scheme 19). In this



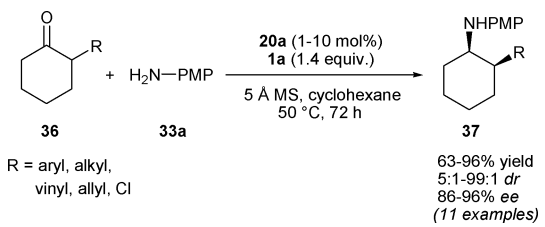
Scheme 18 Enantioselective reductive amination *via* transfer hydrogenation.



Scheme 19 Asymmetric reductive amination of aldehydes by dynamic kinetic resolution.

process, imine enantiomers **A** and **C** were quickly equilibrated by acid catalysis *via* achiral enamine **B**. A subsequent transfer hydrogenation triggered by the chiral catalyst **20a** produced the enantioenriched β-branched amine **35** by *enantio*-differentiating kinetic resolution.

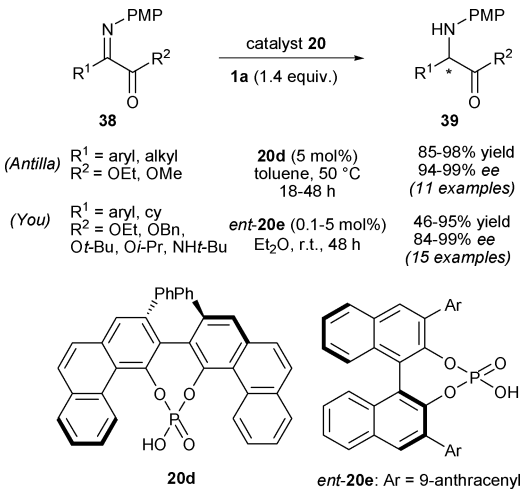
This enantioselective process was very efficient with aldehydes (R^2 = Me, Et) substituted by aromatic groups (R^1 = aryl) (88–98% *ee*). Aliphatic aldehydes were also tolerated although lower enantioselectivities were observed (40–80% *ee*). The main limitation is the exclusive use of aromatic amines. Recently, List *et al.* extended his methodology to the more challenging α-branched cyclic ketones.[44] Racemic α-branched cyclohexanones **36** were reacted with *p*-anisidine **33a**, in the presence of catalytic amounts of catalyst **20a** and Hantzsch ester **1a** to yield 2-substituted amines **37** (Scheme 20). The reaction proved to be diastereoselective (5 : 1 to 99 : 1 *dr*) and highly enantioselective (86–96% *ee*) providing *cis*-2-branched cyclohexylamines, a synthetically valuable motif found in numerous biologically active compounds.[44]



Scheme 20 Asymmetric reductive amination of α-branched ketones by dynamic kinetic resolution.

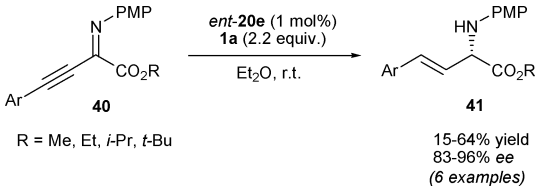
The scope of this reaction was broad, including 2-aryl or heteroaryl cyclohexanones as well as 2-alkyl, -vinyl, -allyl and even chlorinated cyclohexanones. The limitation resided in the use of cyclohexanones or cyclopentanones as substrates. The reductive amination was also applied to the preparation of the core structure of perindopril, a long-acting ACE inhibitor. Interestingly, List *et al.* recently reported an asymmetric reductive amination of ketones with benzylamine.[45] Even though the scope was limited and enantioselectivities were moderate to good, the presence of a benzyl group that can easily be removed was an improvement. They also demonstrated a convenient method of separating the Hantzsch pyridine byproduct by hydrolysis.

In 2007, Antilla and co-workers,[46] shortly followed by You *et al.*,[47] reported another interesting application of enantioselective transfer hydrogenation in the synthesis of N-protected α-amino esters. The group of Antilla used a (*S*)-VAPOL-derived phosphoric acid **20d** to enantioselectively hydrogenate α-imino esters **38** in the presence of **1a** (Scheme 21). Diverse α-amino esters **39** could be obtained with excellent yields and enantioselectivities (94–98% *ee*).



Scheme 21 Enantioselective preparation of α-amino esters.

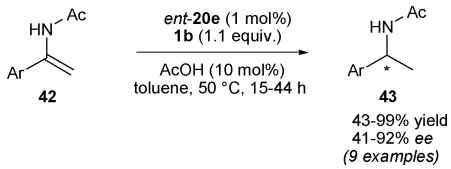
Even more challenging alkyl-substituted substrates, formed *in situ* from the corresponding α-aliphatic ketoesters, were tolerated in the reaction (96–99% *ee*). Independently, You *et al.* published a similar reaction using a BINOL-derived phosphoric acid (Scheme 21). Catalyst *ent*-**20e**, bearing bulky anthracenyl groups, in association with stoichiometric **1a** was found to be most effective for the transfer hydrogenation of N-PMP-α-imino esters **38**. This mild reaction was performed with aromatic or heteroaromatic N-PMP-α-imino esters **38** bearing different esters (78–95%, 84–99% *ee*). Moreover, the catalyst loading could be reduced to 0.1 mol% without significant loss of efficiency or selectivity. Contrary to Antilla's work, the reaction was shown to be less effective with alkyl substituted iminoesters (46% yield, 88% *ee*). However, the scope of this transfer hydrogenation was broadened as α-imino carboxamides were tolerated in the reaction (85% yield, 96% *ee*). In early 2008, You *et al.* extended this methodology to the reduction of both the alkyne and the imine moieties of β,γ-alkynyl α-imino esters **40** (Scheme 22).[48] By using 1 mol% of the catalyst *ent*-**20e**, along with **1a**, a range of aromatic β,γ-alkenyl α-amino esters **41** were synthesized in moderate yield and very good selectivities. The size of the ester group was shown to have an influence on the



Scheme 22 Asymmetric transfer hydrogenation of β,γ-alkynyl α-imino esters.

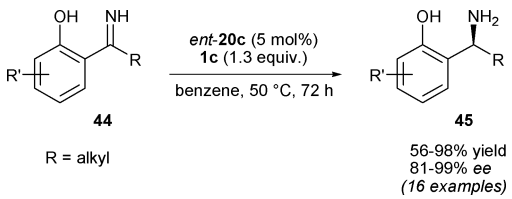
efficiency of the reaction as bulky esters gave better yields than methyl or ethyl esters.

The transfer hydrogenations of C=N bonds presented have been limited to N-aryl protected substrates. To reveal useful enantiopure amines, the deprotection of the corresponding N-aryl amines could require harsh conditions. This limitation was overcome by Antilla in 2009 when he demonstrated a highly enantioselective reduction of N-acyl enamides (Scheme 23).[49] Indeed, the corresponding N-acyl amines are much easier to deprotect than their N-aryl analogues. By using a dual catalytic acid system[50] (chiral acid *ent*-**20e** with achiral acetic acid) with **1b**, aryl enamides **42** were efficiently reduced to the aryl amines **43** with good enantioselectivities. The achiral Brønsted acid was shown to accelerate the reaction by generating a sufficient concentration of the active iminium species by tautomerization of the enamide. The use of 10 mol% of acetic acid allowed use of catalyst quantities as low as 1 mol%.



Scheme 23 Asymmetric transfer hydrogenation of N-acetyl enamides.

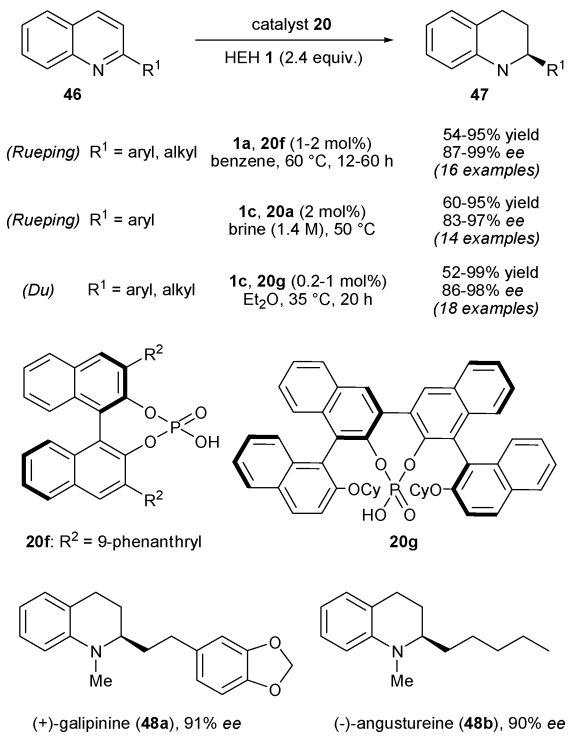
Recently, Wang, Guéritte and co-workers reported a breakthrough in the transfer hydrogenation of imines as unprotected ketimines were for the first time enantioselectively hydrogenated employing phosphoric acid catalysis.[51] *Ortho*-hydroxyaryl alkyl N–H ketimines **44** were reduced to their corresponding primary amines **45** by Hantzsch di-*tert*-butyl ester **1c** and catalyst *ent*-**20c**. Good yields and enantioselectivities were generally obtained (Scheme 24).



Scheme 24 Asymmetric transfer hydrogenation of unprotected *ortho*-hydroxyaryl alkyl N–H ketimines.

The authors suggested a transition state in which both the imine and the hydroxyl groups formed hydrogen bonds to the phosphoric acid catalyst.

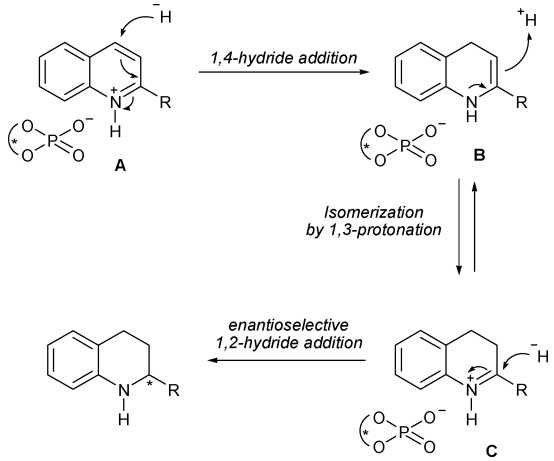
Inspired by the asymmetric transfer hydrogenation of imines, Rueping *et al.* examined the reduction of N-heterocycles by focusing on quinolines. Indeed, the resulting products, tetrahydroquinolines, are an important class of compounds found in many natural and medicinal products and used as synthetic intermediates in pharmacy, agrochemistry or material science. Previous methods used were metal-catalyzed reactions, including hydrogenations, hydroborations or transfer hydrogenations, which had limitations in terms of scope and enantioselectivity.[52] In early 2006, Rueping and co-workers reported the first metal-free Brønsted acid-catalyzed transfer hydrogenation of quinolines.[53] The use of Hantzsch ester as reducing agent and 1 mol% of DPP afforded differently substituted dihydroquinolines. Subsequently, they developed the asymmetric version of this reaction by employing chiral BINOL-derived phosphoric acids.[36,54] It was found that the phenanthryl-substituted phosphoric acid **20f**, associated with Hantzsch ester **1a** was promoting the asymmetric transfer hydrogenation of 2-substituted quinolines **46** with excellent enantioselectivities (Scheme 25). This mild, powerful, low-catalyst loading and metal-free reduction gave access to 2-alkyl, aryl and heteroaromatic-substituted tetrahydroquinolines **47** in high yields with 87–99% *ee*. It was proposed that the process involves a cascade hydrogenation consisting of a 1,4-hydride addition, an enamine-imine isomerization by protonation and a final 1,2-hydride addition (Scheme 26).



Scheme 25 Asymmetric transfer hydrogenation of 2-substituted quinolines - Application towards the synthesis of natural alkaloids.

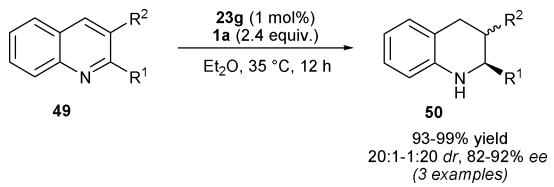
To attest the potential of this methodology, Rueping *et al.* applied it to the synthesis of tetrahydroquinoline alkaloids bearing biological properties, such as (+)-galipinine (**48a**), (+)-cuspareine and (–)-angustureine (**48b**) (Scheme 25).[55] Enantioselective reduction of the corresponding 2-substituted quinolines followed by N-methylation gave the natural products with high enantioselectivities and yields.

Very recently, Rueping and co-workers extended their methodology to an unprecedented and surprising asymmetric



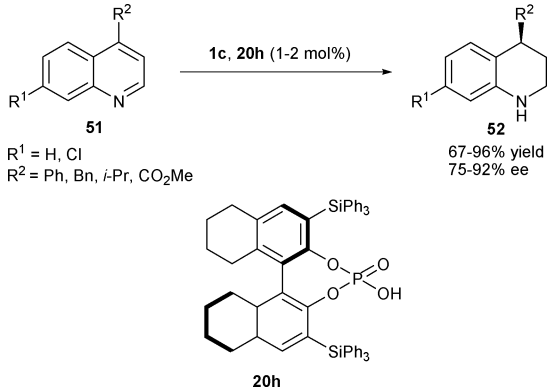
Scheme 26 Proposed mechanism for the enantioselective reduction of quinolines.

Brønsted acid transfer hydrogenation in aqueous media. Aromatic tetrahydroquinolines **47** were efficiently synthesized with good enantioselectivities by reducing the corresponding quinolines in aqueous solution (Scheme 25).[56] This remarkable reaction, made possible by using the principle of hydrophobic hydration, is the first organocatalytic example of a non-covalent chiral induction in pure aqueous medium. This ecological and economical process undoubtedly paves the way for future developments in this attractive area. In 2008, Du *et al.* developed new double axially chiral phosphoric acids to catalyze the reduction of 2-substituted quinolines **46**. The tetrahydroquinolines **47** were prepared in high yields and with similar enantioselectivities (Scheme 25). Interestingly, Du and co-workers also reported a highly diastereoselective and enantioselective hydrogenation of cyclic and acyclic 2,3-substituted quinolines **49** (Scheme 27).[57]



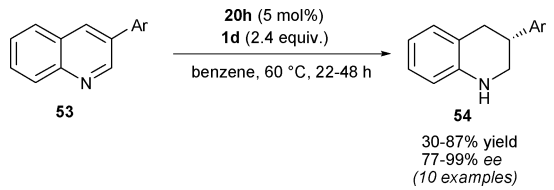
Scheme 27 Asymmetric transfer hydrogenation of 2,3-disubstituted quinolines.

Subsequently, the group of Metallinos extended the transfer hydrogenation to the enantioselective reduction of disubstituted 1,10-phenanthrolines.[58] Additionally, Perumal *et al.* developed recently a racemic one pot synthesis of N-substituted tetrahydroquinolines by reducing quinolines with Hantzsch esters.[59] After dealing with the reduction of 2-substituted quinolines, the group of Rueping examined the preparation of enantiopure 4-substituted tetrahydroquinolines, which are biologically active compounds.[60] However, no direct enantioselective reduction had been reported.[61] Even though the newly formed stereocenter is far from the catalytic center of the phosphoric acid, it was possible to reduce 4-substituted quinolines **51**, employing octahydro-BINOL derived catalyst **20h** and *tert*-butyl Hantzsch ester **1c**, in good yields and with good to excellent enantiomeric excess (Scheme 28).[62]



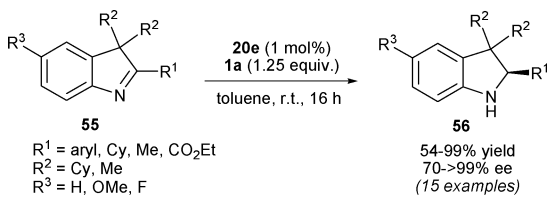
Scheme 28 Asymmetric transfer hydrogenation of 4-substituted quinolines.

Rueping *et al.* also investigated the transfer hydrogenation of 3-aryl substituted quinolines **53** and found that this process was best performed with catalyst **20h** along with the allyl-derived Hantzsch ester **1d** (Scheme 29).[63] 3-Aryl-quinolines **54** were produced in good yields and high selectivity as well as one 2,3-disubstituted quinoline. The enantiodetermining step of this process is a Brønsted acid catalyzed protonation, contrary to the enantioselective hydride transfer in the reduction of 2- or 4-substituted quinolines. This work represents a new organocatalytic protonation but also the first direct enantioselective route to 3-substituted quinolines.



Scheme 29 Enantioselective protonation of 3-substituted quinolines.

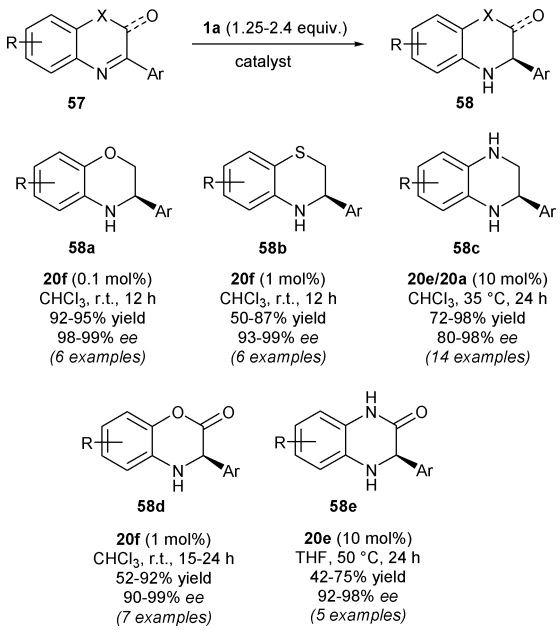
Next, Rueping's group turned its attention to the synthesis of indolines, present in numerous biologically active natural alkaloids, by employing their Brønsted acid catalyzed transfer hydrogenation in the reduction of 2,3,3-trisubstituted-3*H*-indoles **55**. Such a process complemented the only metal-catalyzed enantioselective reduction of 2,3,3-trisubstituted-3*H*-indoles known to date.[64] The feasibility of this reduction was demonstrated by utilizing 1 mol% of chiral phosphoric acid **20e** and HEH **1a** in toluene and a variety of 2,3,3-trisubstituted-indolines **56** were obtained in good yields and with excellent enantioselectivities up to 99% *ee* (Scheme 30).[65]



Scheme 30 Preparation of enantiopure indolines.

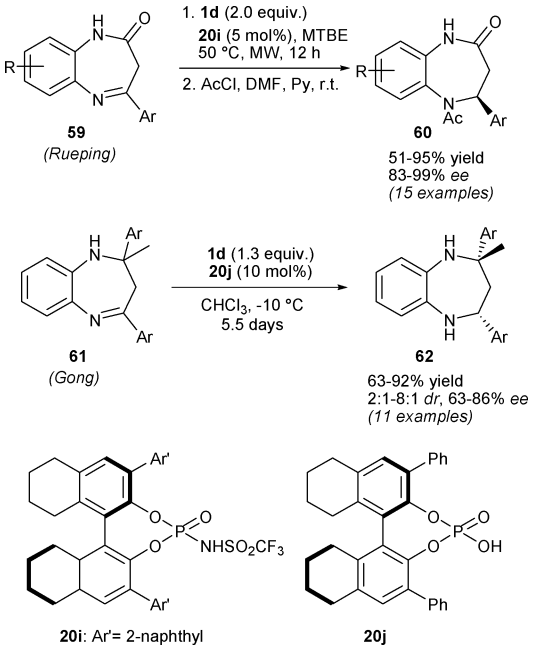
After the successful enantioselective transfer hydrogenation of imines, quinolines and indoles, the group of Rueping focused

on the reduction of various imine-containing heterocycles **57**, including benzoxazines, benzothiazines, benzoxazinones, quinoxalines and quinoxalinones (Scheme 1). Indeed, the desired dihydro-2*H*-compounds **58** constitute the structural skeleton of natural products with interesting biological properties and have been used for the preparation of several pharmaceuticals, such as antidepressants, antimicrobial, antinociceptive, anti-inflammatory and antibacterial agents, non-nucleoside HIV-1 reverse transcriptase inhibitors and calcium antagonists.[66] Although the enantioselective reduction of the imine containing heterocycles is the most straightforward way for preparing these compounds only a few metal-catalyzed hydrogenation have been reported. However, these are typically limited to alkyl-substituted heterocycles.[67] After screening of the reaction conditions, Rueping and co-workers found that the reduction of benzoxazines, benzothiazines and benzoxazinones could be best performed with a low loading of catalyst **20f** (0.1–1 mol%) in $CHCl_3$ or toluene at room temperature (Scheme 31).[68] For the transfer hydrogenation of quinoxalines and quinoxalinones, the catalysts **20e** and **20a** gave the highest selectivities.[69] The mild conditions provided a range of 2-aryl and heteroaromatic dihydro-2*H*-compounds **58a–e** with excellent enantioselectivities and yields. Interestingly, the new organocatalytic reaction showed a high tolerance for various halogenation patterns that could become useful for further functionalization of the dihydro-2*H*-heterocycles. Furthermore, dihydro-2*H*-benzoxazines **58a** were produced using remarkably low catalyst loadings. With a substrate/catalyst ratio of 10 000 : 1, no significant loss in reactivity or enantioselectivity was observed (0.01 mol% of **20f**, 90% yield, 93% *ee vs.* 0.1 mol%, 95% yield, 96% *ee*).



Scheme 31 Asymmetric transfer hydrogenation of various heterocycles.

The synthetic utility of dihydro-2*H*-benzoxazinones **58d** was demonstrated by opening the latter, in the presence of a primary amine, to the corresponding amino acid amides without racemization. The advantage of this enantioselective transfer hydrogenation over metal-based reduction is illustrated by the reduction of sulfur-containing benzothiazines that would poison most metal catalysts. Although the chiral phosphoric acids were very effective for the reduction of the above heterocycles, they were inefficient for the reduction of benzodiazepinones **59**. At this point, BINOL-based *N*-triflylphosphoramides were examined. These catalysts have a lower pK_a due to electron withdrawing triflyl groups and thus are more reactive.[70] To date, they have been used mainly in enantioselective Brønsted acid-catalyzed activations of carbonyl groups such as ene reactions, Nazarov cyclizations, protonations, Diels–Alder reactions or dipolar cycloadditions.[70,71] Only a few recent examples of imine activation with this kind of acid have been reported. These include Mannich-ketalization and Friedel–Crafts reactions.[72] Reduction of benzodiazepinones **59** using catalyst **20i** (5 mol%) and **1d** in MTBE proceeded efficiently by microwave heating. The corresponding dihydrobenzodiazepinones **60** were obtained after acylation with excellent enantioselectivities (Scheme 32).[73] Additionally, Gong and co-workers published a dynamic kinetic reduction of benzodiazepines **61** catalyzed by phosphoric acid **20j**.[74] Dihydrobenzodiazepines **62** were then produced with good yields for both diastereoisomers (*dr* up to 8 : 1) and modest to good enantioselectivities.

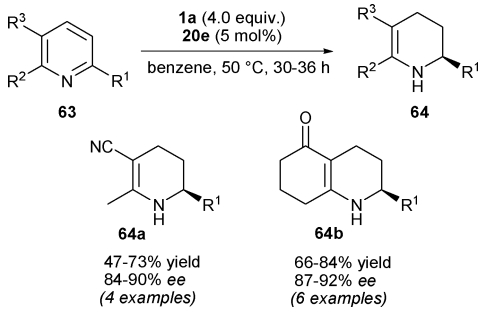


Scheme 32 Asymmetric transfer hydrogenation of benzodiazepinones and benzodiazepines.

So far, the generality of the enantioselective transfer hydrogenation has been demonstrated on a range of imine-containing heterocycles. For most of the N-heterocycles, the reaction conditions are mild and require the Hantzsch ethyl ester **1a** associated with phenantryl-, anthracenyl- or triisopropylphenyl-derived BINOL phosphoric acids to furnish the corresponding alkyl- or aryl substituted products in an efficient and enantioselective way. Continuing these studies, Rueping *et al.* examined the transfer hydrogenation of more challenging pyridine substrates. Indeed, the corresponding chiral piperidines are important as they represent the core structure of many alkaloids and other biologically active compounds. In principle this class of

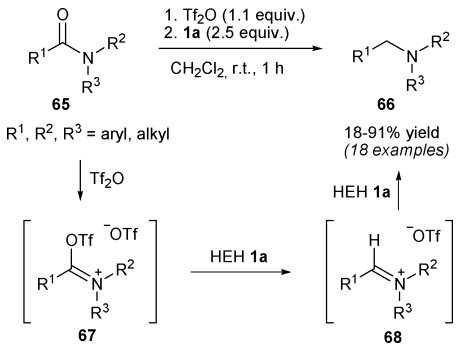
compounds could be readily prepared by asymmetric reduction of pyridines. However, only a few enantioselective metal-catalyzed hydrogenations have been reported.[75] Based on the previous metal-free hydrogenations, Rueping and co-workers were able to extend his methodology and thus developed the first enantioselective reduction of pyridines catalyzed by Brønsted acids.[76]

By using 5 mol% of phosphoric acid **20e** and **1a**, reduction of pyridines **63** proceeded smoothly to afford various tetrahydropyridines **64a** as well as azadecalinones **64b** with excellent enantioselectivities (Scheme 33). The potential of this powerful methodology was illustrated by carrying out a formal synthesis of a natural alkaloid *diepi*-pumiliotoxin C. This work represents a great advance in the field of pyridine reduction as previously reported metal-catalyzed reduction could not provide the important compounds **64** and generally gave lower enantioselectivities.



Scheme 33 Asymmetric transfer hydrogenation of pyridines.

Recently, Charette and co-workers developed an elegant metal-free reduction of tertiary amides.[77] Amides **65** were sequentially treated with trifluoromethanesulfonic acid anhydride and HEH **1a** to afford the corresponding amines **66** with good yields (Scheme 34). This chemoselective and mild reduction probably occurred *via* the formation of an active iminium species **67** which is then reduced with HEH.

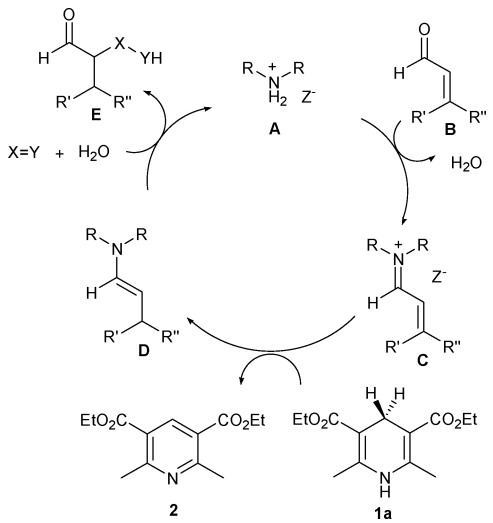


Scheme 34 Hantzsch ester-mediated reduction of tertiary amides.

Recently, they extended this methodology to the chemoselective reduction of secondary amides using a similar activation with trifluoromethanesulfonic acid anhydride followed by addition of triethylsilane and finally Hantzsch ester.[78]

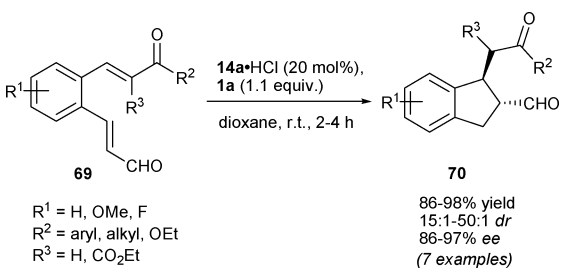
Cascade reactions

Cascade or domino reactions play an increasing role in organic chemistry. They do not only save time and avoid waste, but are highly efficient. While in nature many domino reactions are known, such as the biosynthesis of fatty acids and steroids, in organocatalysis the development of domino reactions has arisen only over the last few years.[79] Notably secondary amine catalysts, such as imidazolidinones or prolinols play a significant role in cascade reactions as they are able to activate the substrate in form of a nucleophile as well as electrophile. In the previously mentioned amine-catalyzed transfer hydrogenation of C=C bonds, an enamine **D** appears as an intermediate, which is usually hydrolysed to yield the corresponding saturated product. However, in the presence of a suitable electrophile (X = Y), this enamine is amenable to reacting further, thereby conducting a domino-sequence to afford product **E** (Scheme 35).



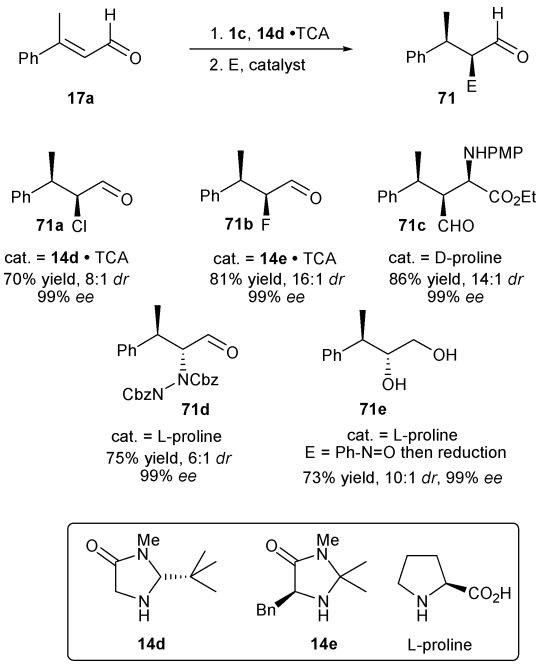
Scheme 35 Mechanism of iminium-enamine catalysis.

This methodology was first utilized independently by the groups of List and MacMillan. List and co-workers developed an imidazolidinone-catalyzed asymmetric reductive Michael cyclization.[80] The latter involved an initial iminium-ion catalyzed conjugate reduction of the α,β-unsaturated aldehyde followed by an intramolecular asymmetric Michael addition at the 4-position of the α,β-unsaturated ketone or diester. Compounds **70** were efficiently obtained from **69** with enantioselectivities up to 97% *ee* by using imidazolidinone **14a**·HCl in combination with Hantzsch ester **1a** (Scheme 36).



Scheme 36 Enantioselective reductive Michael cyclization.

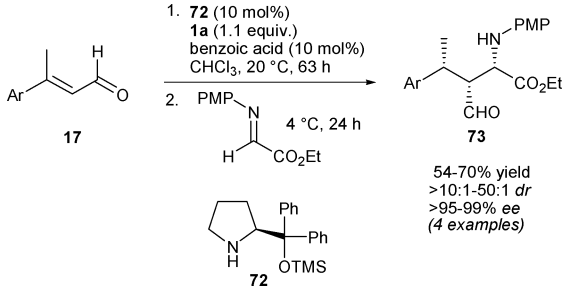
MacMillan and co-workers utilized this strategy and applied a chlorinated quinone as electrophile.[81] Subsequent to imidazolidinone catalyzed transfer hydrogenation of an α,β-unsaturated aldehyde **17a**, the α-chlorination resulted in the formation of aldehyde **71a** (Scheme 37). Similarly, they obtained the α-fluorinated product **71b** by using NFSI as the electrophile. Interestingly, they observed that by employing two distinct catalysts for each cascade cycle, selectivities could be controlled, yielding selectively the *anti*- or *syn*-isomer. To further improve this cycle-specific catalysis, MacMillan investigated L-Proline as enamine catalyst.[82] Due to its bifunctional ability, they suggested a broader applicability of electrophiles, such as dibenzylazodicarboxylate, nitroso-benzene or glyoxylate imine. Indeed, with these electrophiles, asymmetric olefin hydroamination (**71c**), olefin hydro-oxidation (**71e**) and reductive Mannich (**71d**) reaction could be accomplished with high enantio- and diastereoselectivities (Scheme 37).



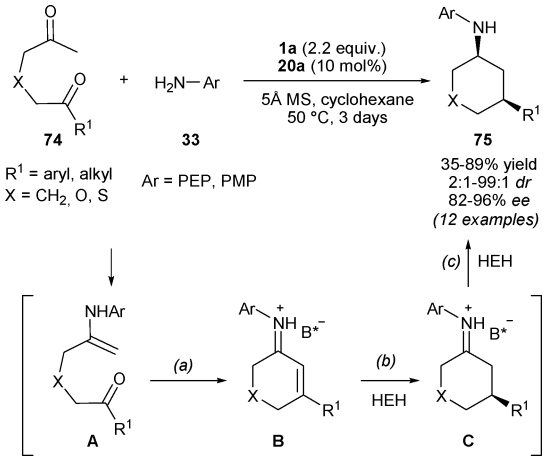
Scheme 37 MacMillan's organocatalytic cascade from α,β-unsaturated aldehyde.

A similar procedure for a reductive Mannich reaction had already been published by the group of Córdova.[83] Instead of the imidazolidinone catalyst, they applied a diphenylprolinol silylether **72**, which had been proven to be more active under the reaction conditions (Scheme 38). By further addition of (*R*)-proline, by analogy to the cycle-specific catalysis of MacMillan, they altered the selectivity and obtained the *syn*- **73** instead of the *anti*-isomer, albeit in lower diastereoselectivity.

An additional cascade reaction developed by List *et al.*, combined enamine, iminium and Brønsted acid catalysis to give access to chiral 3-substituted cyclohexamines **75**.[84] 2,6-Diones **74** were treated with N-arylamines **33**, Hantzsch ester **1a** and TRIP-phosphoric acid **20a** to yield *cis*-3-substituted (hetero)cyclohexamines **75** with moderate to high diastereoselectivities and excellent enantioselectivities (Scheme 39).



Scheme 38 Enantioselective reductive Mannich reaction.

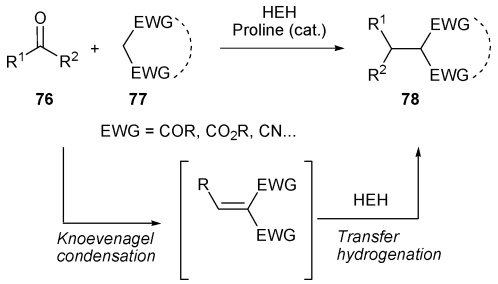


Scheme 39 Brønsted acid-catalyzed enantioselective cascade to substituted cyclohexamines.

The proposed mechanism is as follow: (a) intramolecular aldol reaction *via* enamine catalysis to give **B**; (b) enantioselective conjugate transfer hydrogenation *via* iminium and Brønsted acid catalysis involving **B**; (c) final asymmetric reduction of **C** *via* Brønsted acid catalysis affording **75**. The TRIP group proved to be essential in the last transfer hydrogenation step for the observed *cis*-selectivity, as other phosphoric acids lead to *trans*-compounds. Interestingly, an achiral version of this cascade catalysed by PTSA was reported to yield *trans*-substituted cyclohexylamines.[85] Recently, List and co-workers confirmed the proposed reaction sequence by detecting and characterizing the main intermediates of the catalytic cycle with mass spectroscopy studies.[86]

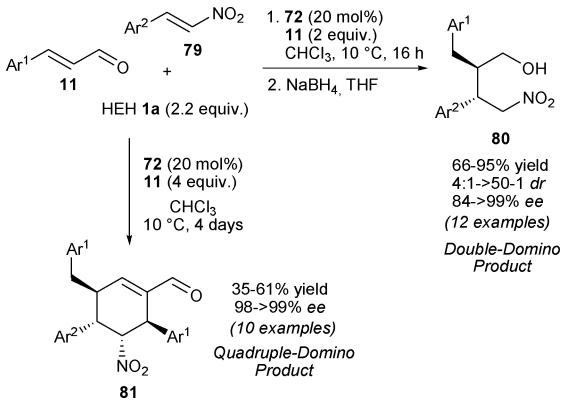
Since 2006, the group of Ramachary developed a range of organocatalytic cascades based on a common concept.[87] In the presence of catalytic proline, a ketone or an aldehyde **76** underwent a Knoevenagel condensation with **77** to produce an electron-deficient olefin which was then reduced *in situ* by a Hantzsch ester (Scheme 40). The reduced compound **78** has been used in several multiple-reaction cascades, including hydrolysis, esterifications, alkylations, Robinson annulations or oxy-Michael reactions. Moreover, the reaction had been applied to the synthesis of drug intermediates and other biologically relevant molecules.

A very impressive example of an organocatalytic cascade-reaction employing a Hantzsch ester is a quadruple domino-reaction, developed by Rueping and co-workers.[88] Starting from very simple starting materials, namely α,β-unsaturated aldehydes **11** and nitroolefins **79**, a six-membered carbocycle **81**



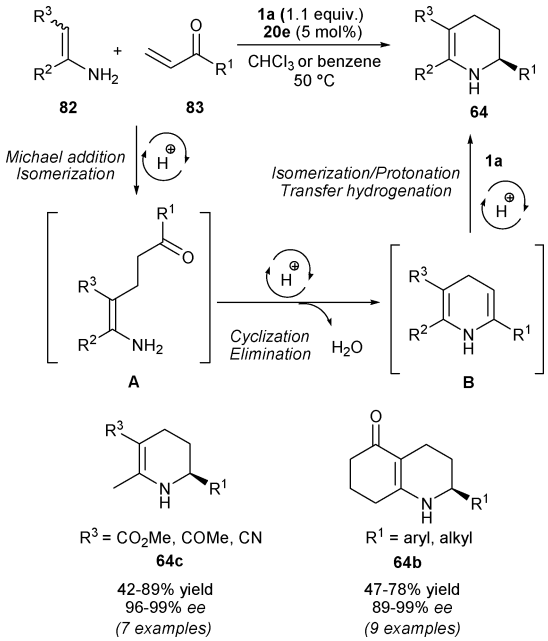
Scheme 40 Knoevenagel condensation/transfer hydrogenation cascade.

with four stereogenic centers is built with high enantioselectivity (Scheme 41). After an initial transfer hydrogenation of the α,β-unsaturated aldehyde, a prolinol (**72**)-catalyzed Michael-type addition of the saturated aldehyde to the nitroolefin takes place. The corresponding double-domino product can further react with a second equivalent of an α,β-unsaturated aldehyde **11**, which finally undergoes an intramolecular aldol-condensation to furnish the desired product **81**.[89]



Scheme 41 Double and quadruple domino reactions involving an enantioselective transfer hydrogenation step.

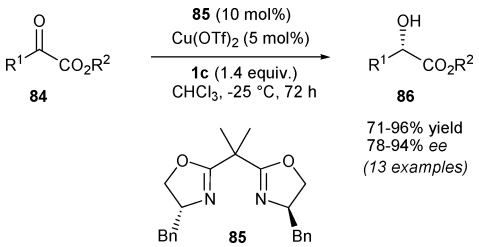
Interestingly, this highly efficient domino reaction could be controlled by a minimal change in the concentration of the substrates. This leads exclusively to either the double-domino product **80** (after reduction of the aldehyde to the alcohol) or the quadruple-domino product **81**. Both reaction pathways were performed with various aromatic substrates in good to very good yields and excellent enantioselectivities (Scheme 41). Finally, Rueping *et al.* developed a novel highly enantioselective Brønsted acid-catalyzed cascade involving a transfer hydrogenation step.[90] Enamines **82** and enones **83** were exposed to Hantzsch ester **1a** and catalytic amounts of chiral BINOL phosphate **20e** to afford a variety of tetrahydropyridines **64c** and azadecalinones **64b** in good yields and with excellent enantioselectivities (Scheme 42). This new organocatalytic cascade sequence comprises six steps and each of them is catalyzed by the same chiral Brønsted acid. The reaction is initiated by a Michael addition between **82** and **83** followed by a geometric isomerization to give adduct **A**. Subsequent cyclization afford a hemiaminal which results in dihydropyridine **B** upon water elimination. Isomerization and protonation by chiral phosphoric acid lead to an iminium ion which undergoes the enantioselective transfer hydrogenation to yield the desired product **64**.



Scheme 42 Three-component enantioselective cascade leading to tetrahydropyridines and azadecalinones.

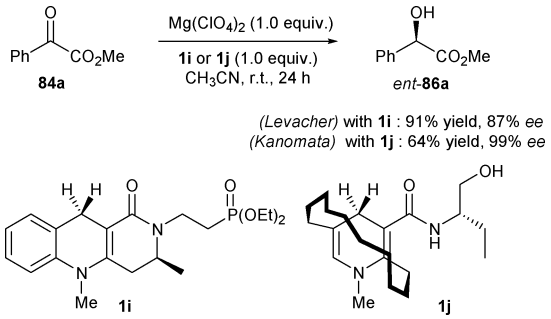
Transfer hydrogenation processes mediated by Hantzsch esters associated with metallic species

Hantzsch esters have been combined with metals in several transfer hydrogenation reactions. In 1985, Gelbard and co-workers reported an enantioselective reduction with Hantzsch ester in the presence of a chiral metal complex.[91] Methyl phenylglyoxylate was hydrogenated with catalytic amount of a chiral europium β-diketonate complex to give the methyl mandelate in 28% yield and with moderate enantioselectivity (55% *ee*). In 2006, List *et al.* described an asymmetric reduction of α-ketoesters by a chiral Cu(II)-bisoxazoline complex.[92] α-Hydroxyesters **86** were produced using a catalyst generated *in situ* from bisoxazoline **85** and $Cu(OTf)_2$ in good yields and up to 94% *ee* (Scheme 43).



Scheme 43 Copper(II) bisoxazoline-catalyzed enantioselective transfer hydrogenation of α-ketoesters.

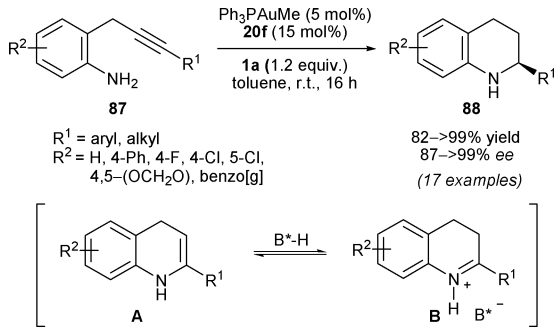
Since 1982, Bourguigon and Quéguiner have studied biomimetic reductions, employing newly designed achiral and chiral Hantzsch ester analogues combined with metallic salts, especially magnesium salts.[93] This method has been lately applied by Levacher to the asymmetric reduction of methyl benzoylformate **84a**.[94] The use of chiral Hantzsch ester derivative **1i** with magnesium perchlorate allowed the synthesis of methyl mandelate *ent*-**86a** in 91% yield and with 87% *ee* (Scheme 44). Additionally, these chiral hydrogen sources have been



Scheme 44 Enantioselective reduction of methyl benzoylformate by a combination of chiral Hantzsch ester analogue and magnesium salt.

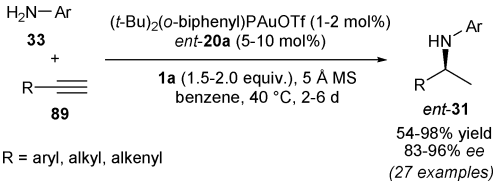
immobilized on Merrifield resin.[95] Kanomata and Nakata also worked on this methodology[96] and obtained 99% *ee* in the reduction of methyl benzoylformate **84a** using a bridged chiral Hantzsch ester analogue **1j** (Scheme 44).[97]

Recently, Liu *et al.* reported a Pd/C-catalyzed hydrogenation of unactivated olefins and α,β-unsaturated ketones using Hantzsch esters as the hydrogen source.[98] In addition to these examples, Hantzsch esters have been used in enantioselective cascade reactions combining both organic catalysts and transition-metal catalysts especially gold catalysts.[99] The group of Gong developed a consecutive gold-catalyzed hydroamination/asymmetric Brønsted acid-catalyzed transfer hydrogenation.[100] A variety of *o*-propargyl anilines **87** were transformed into optically active tetrahydroquinolines **88** with Hantzsch ester **1a** under the dual catalysis of an achiral gold complex and a chiral phosphoric acid **20f** (Scheme 45).



Scheme 45 Intramolecular hydroamination/asymmetric transfer hydrogenation cascade to chiral tetrahydroquinolines.

This highly efficient and enantioselective process involves a hydroamination of alkyne to 1,4-dihydroquinoline **A**, followed by an isomerization with Brønsted acid to chiral iminium complex **B** and a final asymmetric transfer hydrogenation step to the desired product **88**.[53,54] It should be mentioned that a control experiment with a chiral gold phosphate gave lower enantioselectivities and yields. Indeed, it confirmed that the process was mainly catalyzed by a dual system and not the gold phosphate complex. Shortly after this report, Che *et al.* accomplished an intermolecular version of this dual-catalyzed cascade.[101] Anilines **33**, terminal alkynes **89** and Hantzsch ester **1a** were reacted together with a gold complex catalyst and phosphoric acid *ent*-**20a** to afford chiral amines *ent*-**31** in good yields and with high enantioselectivities (Scheme 46). In this reaction, a ketimine intermediate, formed *in situ* by gold-



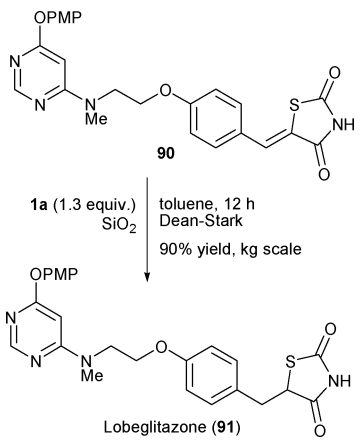
Scheme 46 Intermolecular hydroamination/enantioselective transfer hydrogenation cascade to chiral amines.

catalyzed intermolecular hydroamination is hydrogenated with Brønsted acid catalysis. This relay catalysis proved to be slow but quite general as nearly 30 examples were reported.

Applications of metal-free hydrogenation for the total synthesis of natural products and biologically relevant compounds

Previous paragraphs of this review demonstrated to which extraordinary extent the transfer hydrogenation with Hantzsch esters has grown in the past few years. This metal-free methodology, inspired by nature's dehydrogenase, can be applied to the organocatalytic enantioselective reduction of C=C bonds as well as C=N bonds. This process that generally uses mild conditions has proven to be competitive to metal-catalyzed reductions in terms of functional group tolerance, substrate flexibility, efficiency and selectivity. Since 2007, reductions by Hantzsch esters have found several applications in total syntheses of natural products and other biologically relevant molecules. These applications in either non-selective or asymmetric transfer hydrogenation will be discussed in the following paragraphs.

An important example was reported in 2007 by Lee *et al.* for the last step of the synthesis of Lobeglitazone **91**, a promising antidiabetes drug candidate discovered by Chong Kun Dang Pharmaceutical.[102] Reduction of thiazolidinone **90** was performed using Hantzsch ester **1a** and silica to afford the corresponding hydrogenated Lobeglitazone with an excellent yield (Scheme 47).



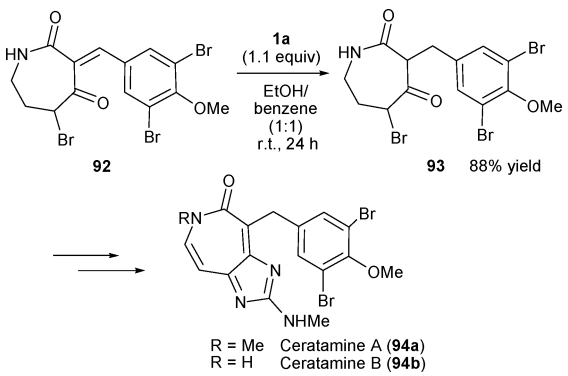
Scheme 47 Kilogram scale preparation of Lobeglitazone by transfer hydrogenation.

The use of silica gel to catalyze the transfer hydrogenation of C=C bonds was developed by Ohno.[103] Most importantly, this metal-free reduction requires simple reaction conditions and the convenient work up and purification can be performed

on a kilogram scale. Therefore, the Hantzsch ester mediated reduction, preferred over other hydride reductions, was essential for the GMP-scalable synthesis of Lobeglitazone Sulfate (CKD-501), a product needed in large amount for biological and toxicological preclinical studies. This promising molecule is now in phase III clinical trials for the treatment of type 3 diabetes.

Additionally, other dihydropyridine-mediated reductions of unsaturated thiazolidinones have been reported by pharmaceutical companies in the course of syntheses of biologically relevant compounds: ADAMTS-5 inhibitors for the treatment of osteoporosis (Wyeth)[104] and (–)-LY213829 for the treatment of inflammatory bowel disease (Eli Lilly).[105]

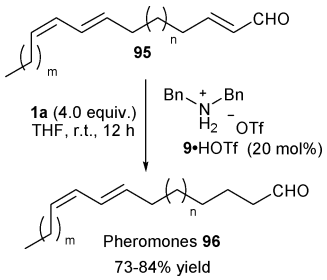
In 2009, Coleman described efficient total syntheses of tubulin-binding agents, ceratamines A (**94a**) and B (**94b**)[106] (Scheme 48) that utilizes a transfer hydrogenation step.[107] The conjugated double bond of compound **92** was efficiently reduced with Hantzsch ester **1a** at room temperature in a mixture of benzene and ethanol, providing a common precursor **93** of ceratamines A and B (Scheme 48).



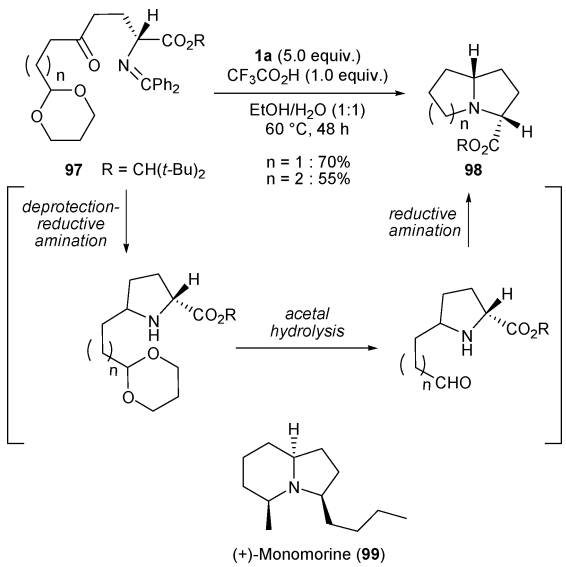
Scheme 48 Transfer hydrogenation step for the synthesis of ceratamines.

Importantly, this example illustrates the tolerance of such a reduction towards functional groups. Indeed, the mild conditions of Hantzsch ester transfer hydrogenation allows the presence of a bromide without over-reduction. An additional relevant example for the reduction of conjugated C=C bonds with Hantzsch ester was published by Christmann and co-workers for the synthesis of lepidopteran sex pheromones.[108] Diverse enals **95** were subjected to the conjugate reduction with dihydropyridine **1a** and a catalytic amount of dibenzylammonium trifluoroacetate **9**·HOTf in THF at room temperature (Scheme 49). A range of pheromones **96** were thus obtained with good yields and excellent regioselectivities as other double bonds remained untouched thanks to imminium activation.

Recently, Maruoka *et al.* designed an original route to pyrrolidine, hexahydropyrrolizine and octahydroindolizine core structures **98** by acid-catalyzed reductive aminations with Hantzsch ester.[109] Enantiomerically pure adducts **97**, readily obtained by asymmetric conjugate addition, were reacted with **1a** in aqueous ethanol in the presence of trifluoroacetic acid to provide the hexahydropyrrolizine or octahydroindolizine **98** in good yields (Scheme 50). This remarkable reaction proceeds *via* a sequence of four steps: amine deprotection, first intramolecular reductive amination, acetal hydrolysis, and second intramolecular reductive amination. This strategy led to an efficient total synthesis of a natural alkaloid, (+)-monomorine (**99**).



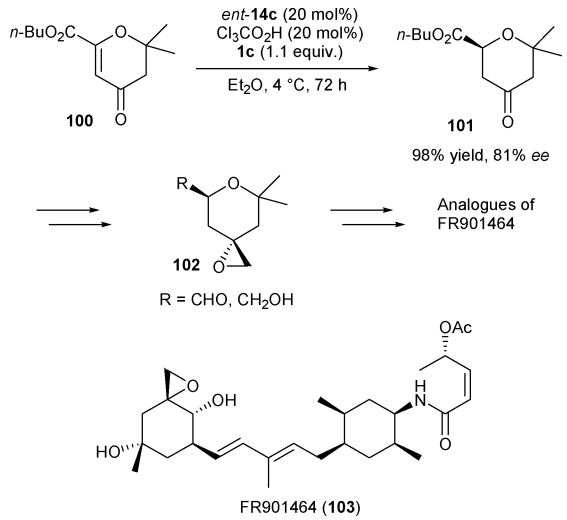
Scheme 49 Preparation of pheromones by reduction of unsaturated aldehydes.



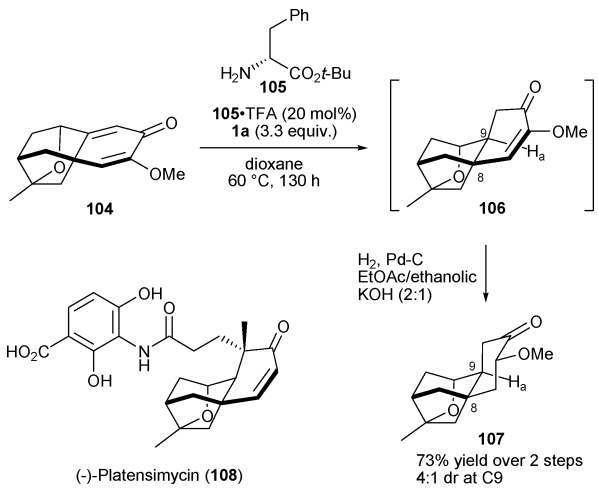
Scheme 50 Synthesis of hexahydropyrrolizines and octahydroindolizines by Hantzsch ester transfer hydrogenation.

In addition to the previous applications of non-selective transfer hydrogenations with Hantzsch esters in the total syntheses of biologically relevant molecules, some related asymmetric reductions have been exploited in the course of total syntheses of natural products. In 2008, the enantioselective conjugate reduction of cyclic enones, developed by MacMillan *et al.*,[29] was applied in the preparation of analogues of a natural product FR901464,[110] a potent antitumor compound (Scheme 51). Enone **100** was reduced with *t*-butyl-derived Hantzsch ester **1c** in the presence of 20 mol% of catalyst *ent*-**14c** and trichloroacetic acid to afford the corresponding saturated cyclic ketone **101** in good yield and with good enantioselectivity. Later **101** was utilized to prepare key building blocks **102** leading to the synthesis of analogues of FR901464 (**103**) with potent antitumor activities.

More recently, the group of Lear described a synthetic approach to (–)-platensimycin (**108**),[111] a natural product with potent antibiotic activity.[112] One of the key steps involved a transfer hydrogenation of cyclic dienone **104** (Scheme 52). Reduction of the latter using the TFA salt of D-phenylalanine derivative **105** along with **1a** yielded **106** as a mixture of C9-epimers. A sequential Pd-catalyzed hydrogenation afforded **107** in 73% overall yield and in a 4 : 1 diastereoisomeric ratio at C9.



Scheme 51 Synthesis of FR901464 analogues by an enantioselective conjugate reduction of enone.

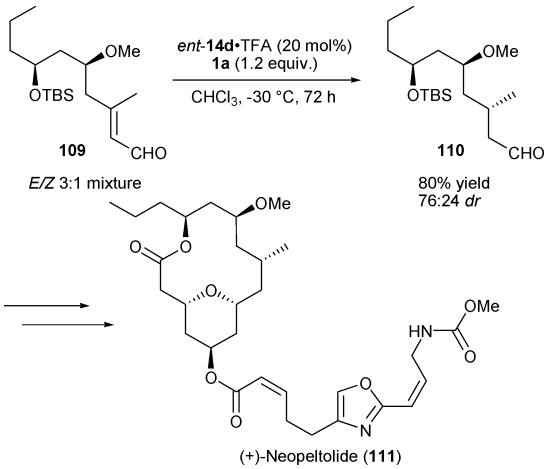


Scheme 52 Diastereoselective conjugate transfer hydrogenation of dienone for the synthesis of the tetracyclic core of (–)-platensimycin.

An important application of the conjugated transfer hydrogenation of enals[19] was reported by Paterson *et al.* in the total synthesis of (+)-neopeltolide (**111**),[113] a marine macrolide with promising antitumoral properties.[114] In a key step of the synthesis a 3 : 1 *E*/*Z* mixture of enal **109** was hydrogenated using Hantzsch ester **1a** and catalytic amount of catalyst *ent*-**14d**·TFA providing the corresponding aldehyde **110** in good yield and with moderate diastereoselectivity (Scheme 53).

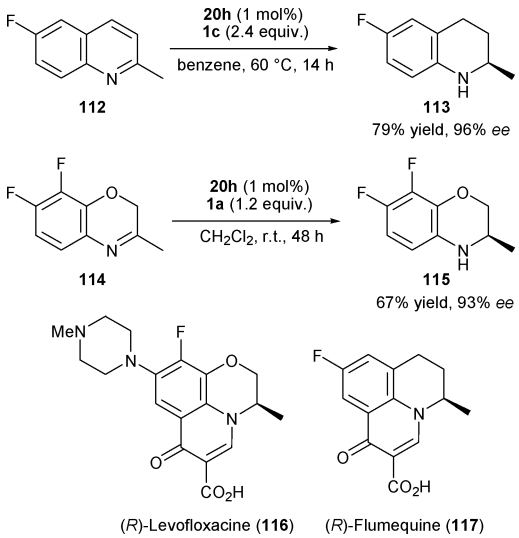
Variations of the reaction conditions and using pure (*E*)-**109** gave the same diastereoselective ratio indicating that the *E* and *Z* isomers lead to the same stereoisomer. The moderate but acceptable diastereoselectivity could be explained by the presence of two other stereogenic centers. Aldehyde **110** was then successfully utilized to complete the total synthesis of (+)-neopeltolide (**111**).

In addition to the above applications of asymmetric conjugated C=C bond reduction, Rueping and co-workers reported very recently an enantioselective C=N transfer hydrogenation applied to the preparation of fluoroquinolones.[115] Importantly, tricyclic fluoroquinolones such as (*R*)-flumequine (**117**) or (*R*)-



Scheme 53 Asymmetric conjugate reduction of enal for the total synthesis of (+)-neopeltolide.

levofloxacin (**116**) display antibacterial activity towards a broad spectrum of bacteria.[116] To synthesize these compounds, readily available fluorinated quinoline **112** and benzoxazine **114** were reduced using their own methodology in the presence of **1a** or **1c** with only 1 mol% of chiral phosphoric acid **20h** (Scheme 54). The corresponding hydrogenated compounds **113** and **115** were obtained with excellent enantioselectivity. These valuable optically pure building blocks have been utilized to complete the syntheses of antibacterial agents (*R*)-levofloxacine and (*R*)-flumequine.

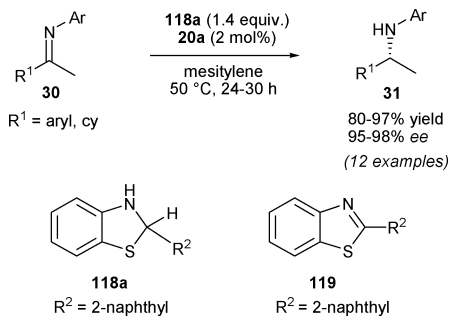


Scheme 54 Enantioselective transfer hydrogenation for the preparation of tricyclic fluoroquinolone antibacterial agents.

Non-metallic organocatalytic transfer hydrogenation with Hantzsch ester is a novel methodology that has already found interesting applications in the synthesis of biologically active compounds in diverse fields of chemistry including process chemistry, medicinal chemistry and total synthesis of natural products. The above examples demonstrate that this reaction represents a powerful tool in enantioselective synthesis, and more developments and applications are likely to arise in the near future.

Alternative hydrogen sources for metal-free transfer hydrogenations

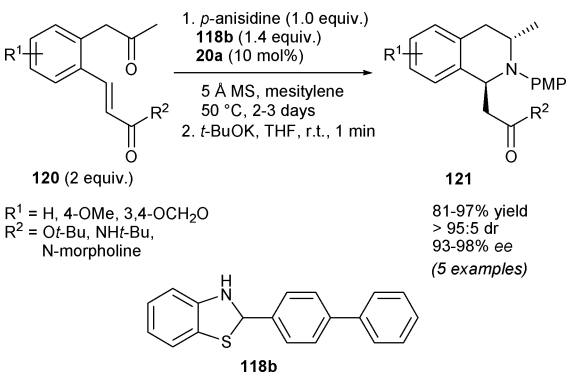
Beside Hantzsch dihydropyridines, several reagents have been shown to be effective hydrogen sources in metal-free transfer hydrogenation reactions. In 2009, Akiyama *et al.* demonstrated that benzothiazolines could serve as hydrogen donors for the enantioselective reduction of ketimines catalyzed by chiral Brønsted acids.[117] Although benzothiazolines had already been used to reduce α,β-unsaturated carbonyl compounds[118] and activated halides or sulfonium salts,[119] the work is the first example of the use of benzothiazolines in asymmetric reduction. Other metal-free reductions of electron-deficient olefins, which have been previously reported, were mediated by benzoimidazolines generated *in situ*.[120] Aryl- and cyclohexyl-substituted ketimines **30** were best hydrogenated with 2 mol% of sterically demanding phosphoric acid **20a** along with stoichiometric benzothiazoline **118a** in mesitylene at 50 °C (Scheme 55). Diverse amines **31** were produced with excellent yields and enantioselectivities. In this reaction, benzothiazolines **118a** are converted into the corresponding aromatic benzothiazoles **119** after releasing a hydride. Interestingly, Akiyama *et al.* also reported a highly enantioselective one pot reaction where the benzothiazoline **118a** is generated *in situ* from the corresponding aldehyde and 2-aminothiophenol.



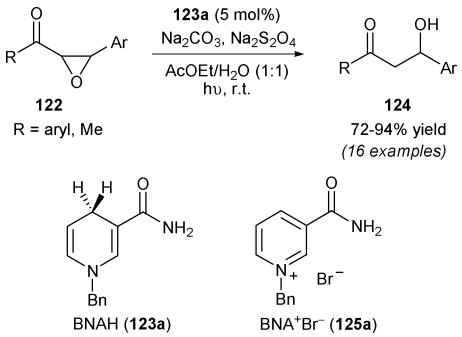
Scheme 55 Asymmetric transfer hydrogenation of ketimines with benzothiazolines.

Another application of benzothiazoline as reducing agent was developed recently by the group of Enders in a cascade reaction involving a reductive amination and an aza-Michael reaction to produce tetrahydroisoquinolines.[121] Methyl ketones **120** were reacted with *p*-anisidine, benzothiazoline **118b** and phosphoric acid **20a**, to afford, after the addition of *t*-BuOK, *trans*-1,3-disubstituted tetrahydroisoquinolines **121** in a highly efficient and enantioselective manner (Scheme 56). Although the reaction was limited to methyl ketones, the reaction was successfully applied to an indole acrylate to form an interesting β-carboline derivative.

Other hydrogen sources utilized are Hantzsch ester analogues based on nature's NADH. In 2006, Liu and Wu examined the use of 1-benzyl-1,4-dihydronicotinamide **123a** (BNAH) for catalytic hydrogenation of α,β-epoxyketones **122** (Scheme 57).[122] This transformation had been previously reported with Hantzsch esters but not in a catalytic fashion.[123] The substrates **122** reacted with 5 mol% of BNABr **125a** in an ethyl acetate–water mixture along with excess sodium dithionite under irradiation. After the completion of the reaction, the corresponding β-hydroxyketones



Scheme 56 Enantioselective reductive amination/aza-Michael cascade with benzothiazoline as reducing agent.

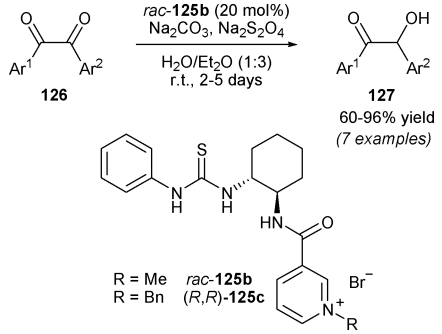


Scheme 57 Catalytic transfer hydrogenation of α,β-epoxyketones with BNAH.

124 were isolated in very good yields. Methyl-substituted ketones gave slightly less yield as compared to the aryl-substituted ones.

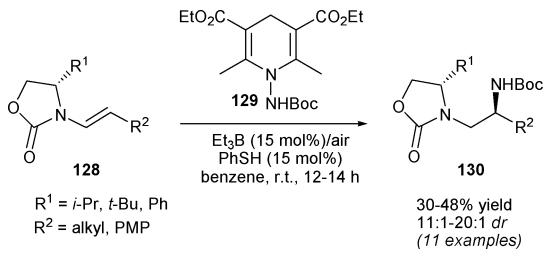
The hydrogen source BNAH is initially formed *in situ* and recycled by the reduction of BNABr with excess sodium dithionite.[124] A radical mechanism was proposed for this transformation, which is in accordance with a faster reaction under irradiation and with no reaction in the presence of oxygen. Most importantly, this reaction is a great illustration of catalytic transfer hydrogenation based on a NADH reduction model. Shortly afterwards, Connon and co-workers reported the use of other NADH analogue catalysts for the reduction of 1,2-diaryldiketones.[125] Novel bifunctional catalysts were designed, bearing a thiourea unit that can activate carbonyl groups and a BNA^+ moiety that can be transformed into a hydrogen source after reduction (Scheme 58). Racemic catalyst *rac*-**125b** proved to be very efficient for the reduction of diketones **126**, when used in a catalytic amount with excess of sodium thionite in a water–diethyl ether mixture. The corresponding benzoins **127** with various electron-rich or -poor aryl groups were obtained with 60–96% yield.

The bifunctional activation was supported by BNAH giving low conversion in this reaction which could be improved by the addition of diverse thioureas. Interestingly, the use of chiral catalyst (*R*,*R*)-**125c** in the reduction of **126** gave induction with 25% *ee* at 29% conversion after 15 h of reaction (Scheme 58). Unfortunately, when the conversion reached 97%, enantiomeric excess dropped to 2% because of product racemization under the basic reaction conditions. Nevertheless, this reaction remains of high importance as enantioselectivity is induced by a chiral hydrogen source and not by an external catalyst.



Scheme 58 NADH analogue-thiourea catalyst for the reduction of 1,2-diketones.

A final example of a Hantzsch ester derived hydrogen source has been described by Studer *et al.* in 2008 in a radical transfer hydroamination of olefins.[126] Reaction conditions were first optimized for the hydroboration of norborene, using Hantzsch-based reagent **129** that was easily prepared from ethyl acetate, formaldehyde and N-Boc-protected hydrazine. They applied the best conditions to the transfer hydroamination of various olefins and developed subsequently a diastereoselective version with olefins **128** bearing a chiral oxazolidinone (Scheme 59).

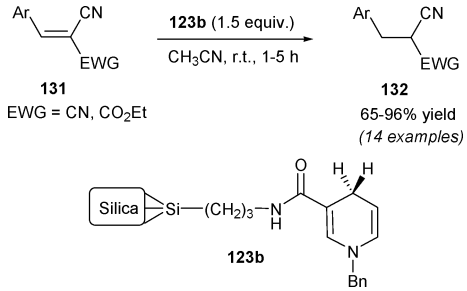


Scheme 59 Diastereoselective transfer hydroamination of olefins with N-Boc dihydropyridines.

Reaction of olefins **128** with **129**, in the presence of triethyl borane under air atmosphere as the initiator and with thiophenol as the propagation reagent, provided protected vicinal diamines **130** with moderate yields and good diastereoselectivities. This radical anti-Markovnikov hydroamination is the first example where a Hantzsch ester derived reagent is used as a hydrogen source in a radical chain reaction.

Immobilized dihydropyridines

Transfer hydrogenations with Hantzsch esters have an advantage over metal catalyzed reductions since the metallic by-products can not always be easily separated from the product. Indeed, this is especially important with regard to pharmaceutical compounds which need to be of highest purity. However, a limitation of the use of Hantzsch esters in reductions is that one equivalent of Hantzsch pyridine is formed. Although purification by recrystallisation is reported, removal of the pyridine by-product typically requires chromatography. To address this problem, Zhu and co-workers reported the preparation of a polysiloxane-supported Hantzsch ester analogue **123b**, bearing a 1-benzyl-1,4-dihydronicotinamide moiety (Scheme 60).[127] The latter was successfully applied to the transfer hydrogenation of activated olefins **131**, producing the corresponding saturated



Scheme 60 Reduction of active olefins by a polysiloxane-supported Hantzsch ester analogue.

compounds **132** in high yields. This reagent has some advantages over other hydrogen sources as the work-up and isolation of the products are easier. Moreover, Zhu *et al.* demonstrated that the reagent can be recycled.

In 2008, the group of Lam published the preparation of a polymer-supported Hantzsch ester for C=C and C=N bond reductions.[128] They synthesized a soluble polymer **1k** by using styrene as monomer with an approximate 5 : 1 styrene z/(dihydropyridine y_2 + pyridine y_1) ratio, corresponding to a loading of 1.6 mmol g^{-1}. Importantly, polymer **1k** contained mainly dihydropyridine y_2 moiety (89%) along with some residual pyridine y_1 (Fig. 3).

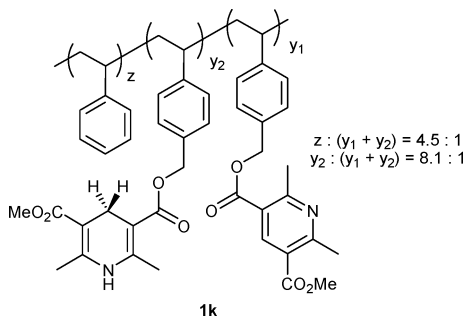
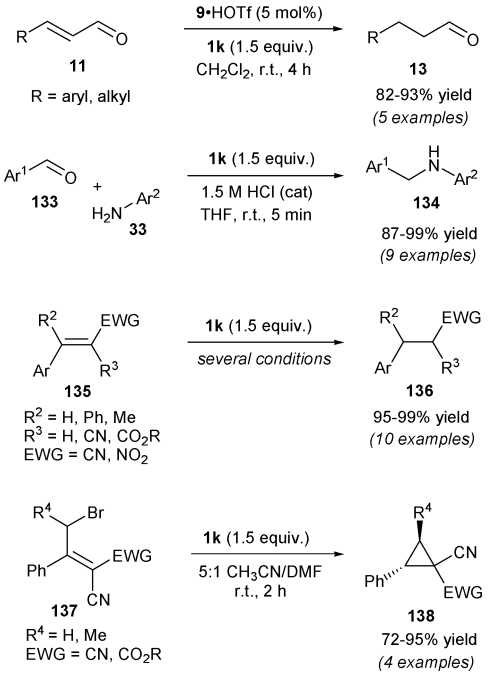


Fig. 3 Polymer-supported Hantzsch ester.

The utility of this polymer-supported Hantzsch ester **1k** was examined in several transfer hydrogenation reactions. The polymer was first utilized for the reduction of unsaturated aldehydes **11** following methodology developed by List.[14] The corresponding reduced aldehydes **13** were obtained in excellent yields by using a combination of polymer **1k** and 5 mol% of benzylammonium trifluoroacetate **9**·HOTf as catalyst in dichloromethane (Scheme 61). Moreover, polymer **1k** showed a great activity in the reductive amination of aromatic aldehydes **133** employing various anilines **33**. Amines **134** were isolated very efficiently within a few minutes by using polymer **1k** and catalytic amount of aqueous hydrochloric acid. Very recently, Lam *et al.* extended this method to the reduction of ketimines and alkenes.[129] 2-Methylenemalonitrile, 2-cyano acrylate analogues and nitroethene compounds **135** were transformed in excellent yield (Scheme 61). Moreover, (*Z*)-α-cyano-β-bromomethyl-cinnamates and analogues **137** were successfully reduced and cyclized to the corresponding cyclopropanes **138**.

These examples clearly demonstrate the synthetic utility of the polymer-supported reagent. The major side product of these



Scheme 61 Application of polymer-supported Hantzsch ester in transfer hydrogenation reactions.

reactions, the Hantzsch pyridine, is linked to the polymer and can be simply removed by filtration.

Conclusion

Although dihydropyridine-mediated reductions have been discovered a long time ago, the field of catalytic enantioselective metal-free transfer hydrogenations has emerged in 2004. Over the past six years, this area has grown rapidly as witnessed by the amount of publications reported. The biomimetic organocatalyzed process, inspired by nature's dehydrogenase, has been successfully applied to the asymmetric reduction of various imines and activated olefins by using Hantzsch esters as the hydride source. The corresponding products have thus been isolated in excellent yields and impressive enantioselectivities. In order to achieve such good selectivities, different organocatalytic activation modes have been utilized, including H-bonding activation or iminium ion activation. As described in this review, asymmetric metal-free transfer hydrogenations have found widespread applications in the preparation of various medicinally relevant amines or nitrogen-containing heterocycles as well as in the total synthesis of natural and bioactive products. In contrast to most metal-catalyzed hydrogenations, the reaction conditions are mild and reactions can typically be carried out in the presence of air and moisture. Furthermore, the operational practicability and safety are also advantageous as no high-pressure is required. Additionally, transfer hydrogenations with Hantzsch esters gave the desired products free of metallic by-products which are often difficult to remove. Importantly, this mild and tolerant process is compatible with various functional groups and different organocatalysts and has therefore been implemented in multi-step cascade or domino-reactions allowing the formation of complex chiral molecules in one pot operations. However, the main drawback of this methodology is still the use of stoichiometric dihydropyridine. In order to reach perfect efficiency and practicability the major challenge which needs addressing is the recycling of the hydride source. Encouraging developments have already been made by either using immobilized hydride donors or by employing catalytic amounts of nicotinamide. However, these examples are so far quite limited. We are confident that further progress in this direction will be made in the years to come. Nevertheless, the metal-free reductions have already provided a range of important biologically compounds and will undoubtedly continue to find broad applications in organic chemistry.

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