Thieme Chemistry Journal Awardees – Where Are They Now? Asymmetric Brønsted Acid Catalyzed Transfer Hydrogenations

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Received 12 November 2009

Abstract: Asymmetric hydrogenations are of great importance in the synthesis of optically active amines. This account highlights the development of the first metal-free transfer hydrogenation that is both highly enantioselective and inspired by nature's dehydrogenase. Further focus is given to the extension of this bioinspired process to provide a variety of valuable, biologically active products and natural products under mild reaction conditions.

Key words: binol phosphate, Brønsted acid, Hantzsch ester, transfer hydrogenation, organocatalysis, asymmetric reduction

1 Introduction

Compounds with hydrogen as part of the stereocenter are frequently found in various biologically active compounds and natural products. Asymmetric hydrogenation of unsaturated compounds, including olefins, carbonyls and imines represents the most important and convenient route to the corresponding optically active products. So far, most of these enantioselective reductions rely on different transition-metal-catalyzed high-pressure hydrogenations, hydrosilylations and transfer hydrogenations. While almost all of these metal-catalyzed processes show high reactivities and selectivities most of these protocols suffer from significant drawbacks including a limited substrate scope and difficulties encountered with catalyst separation and recycling. Given the above limitations an alternative approach to chiral amines would be of great value. In this account we would like to disclose our studies towards the development of the first highly enantioselective metal-free transfer hydrogenation using nature's dehydrogenase as a role model and we like to highlight our attempts for the development and generalization of this hydrogenation protocol.

SYNLETT 2010, No. 6, pp 0852–0865
Advanced online publication: 18.02.2010
DOI: 10.1055/s-0029-1219528; Art ID: S12909ST

2 Nature's Reductions: Dehydrogenases as a Role Model

Nicotinamide adenine dinucleotide (NADH) is an important co-factor in nature, which serves as a hydride source for a broad variety of reductions, including reductive aminations. One very important example represents the glutamate dehydrogenase catalyzed reductive amination of 2-ketoglutarate to provide the amino acid glutamate (Equation 1). The reaction is reversible although the equilibrium favors glutamate formation.

By means of detailed kinetic studies and crystallographic structure analysis a mechanism for the action of glutamate

Equation 1 Reductive amination of 2-ketoglutarate to glutamate catalyzed by glutamate dehydrogenase

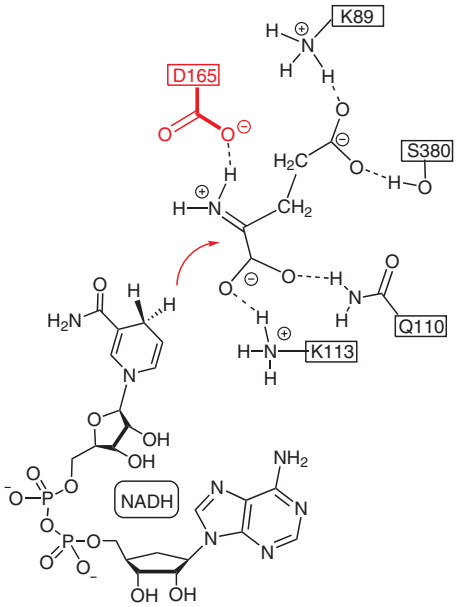


Figure 1 Proposed activation mechanism: α-imino glutarate is activated through a catalytic protonation by aspartate D165 which enables a hydride transfer from the NADH to provide the amino acid glutamate

dehydrogenase was proposed by Stillman and co-workers (Figure 1).[1]

The enzyme consists of different amino acids in the catalytic active pocket yet it was proposed that the aspartate D165 is crucial for the reductive amination as it protonates the α-imino glutarate which is formed from ammonia and 2-ketoglutarate to give a highly reactive iminium ion. The subsequent hydride transfer from NADH leads to the formation of the amino acid glutamate. This proposed mechanism was later supported by site-directed mutagenesis studies in which the putative catalytic aspartyl residue was replaced by other amino acids. Although the modified enzymes still appeared to be correctly folded the high catalytic activity was lost.[2] This clearly indicated the crucial role that aspartate plays in the transfer hydrogenation and underlines the protonation step as key step for the reductive amination.

3 Brønsted Acid Catalyzed Transfer Hydrogenation of Ketimines

Based on the above activation mechanism and analogous to nature's dehydrogenases we wondered whether it would be possible to accomplish the transfer hydrogenation of imines with a combination of NADH as a hydride source and catalytic amounts of a Brønsted acid. The activation of the imine would be achieved by catalytic protonation which would result in the formation of an iminium ion. This would enable the subsequent hydride transfer to yield the corresponding amine in a bioinspired fashion, mimicking the mechanism of glutamate dehydrogenase (Scheme 1).

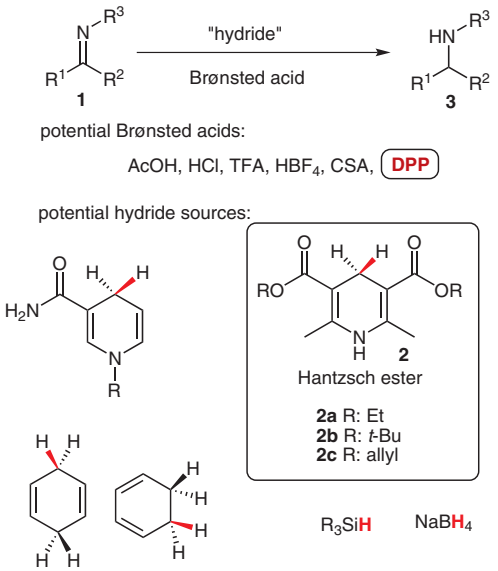
1,4-Dihydropyridines, also known as Hantzsch esters (HEH),[3] are commonly known as synthetic analogues of NADH. In 1955 Mauzerall and Westheimer[4] showed for

Biographical Sketches

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-professorship, the Degussa Endowed Professorship of Synthetic Organic Chemistry, at the Goethe-University Frankfurt. After four years in Frankfurt he received several offers of academic positions and decided to accept 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

Erli Sugiono graduated from the Johannes Gutenberg University of Mainz and obtained her Ph.D. under the direction of PD Dr. Heiner Detert within the research group of Prof. Dr. Herbert Meier. She then moved to the Max Planck Institute of Polymer Research (Mainz) as a postdoctoral fellow in the group of Prof. Dr. Hans Wolfgang Spiess working with PD Dr. Ingo Schnell investigating the orientation of phospholipid bilayers within polymer matrices in magnetic fields. After a two and half years stay at the Max Planck Institute she joined Prof. Rueping's group in 2005 and was appointed to the position of senior scientist in 2009. Her work centers on the development of new methodologies for asymmetric catalytic transformations, catalytic flow reactions and the synthesis of biologically active compounds.

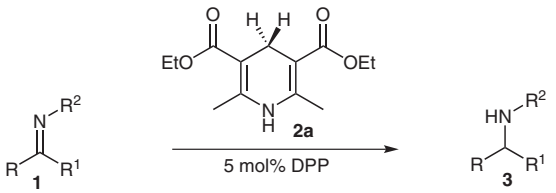
Fenja R. Schoepke was born in Dortmund, Germany in 1982. She graduated with distinction from the Goethe University in Frankfurt 2007 and was awarded a stipend from the German Fonds der Chemischen Industrie for her postgraduate studies. She started her Ph.D. in the group of Prof. Rueping at the Goethe University and transferred with his group to the RWTH Aachen University in 2009. She is currently working on organocatalytic transfer hydrogenations and the immobilization of organocatalysts.



Scheme 1 Development of a biomimetic transfer hydrogenation of ketimines with NADH analogues

the first time that these dihydropyridines are able to reduce carbonyl compounds by a direct hydrogen transfer to the substrate. Since then a broad range of transfer hydrogenations conducted with HEH in combination with different Lewis acids and additives has been reported.[5,6] Additionally, List and MacMillan and their respective coworkers have reported the highly enantioselective organocatalytic transfer hydrogenations of enones and enals applying chiral imidazolidinone catalysts.[7,8]

We decided to examine a Brønsted acid catalyzed transfer hydrogenation of ketimines **1** with Hantzsch dihydropyridine **2a** as the hydride source to afford the corresponding amines **3** (Scheme 2).[9] Initial investigations started with the identification of a suitable Brønsted acid.[10] From the different acids tested, diphenyl phosphate (DPP) gave the highest efficiency in the reduction of ketimine **1**.



Scheme 2 Brønsted acid catalyzed transfer hydrogenation of ketimines

Further examination of the reaction conditions showed that the transformation proceeded efficiently in nonpolar aromatic or halogenated solvents. With the optimal reaction conditions in hand we extended our studies to evaluate the substrate scope. As shown in Figure 2 the reaction conditions are applicable to differently substituted alkyl and aryl ketimines, including α-imino esters, and the products could be isolated in good to excellent yields.

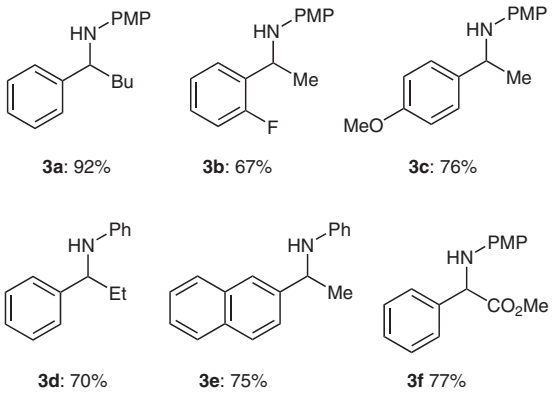
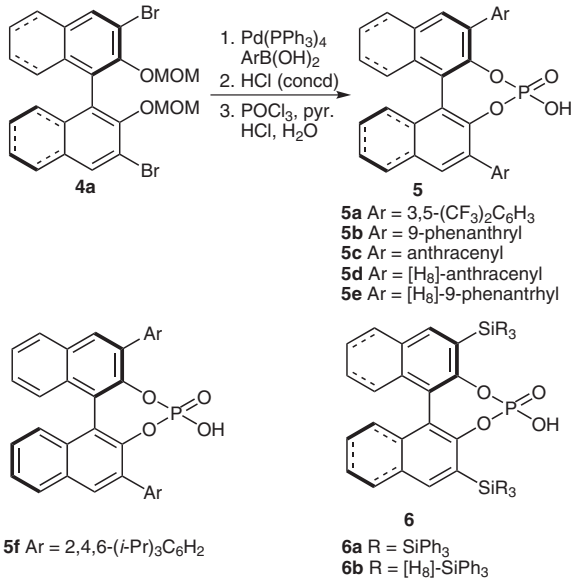


Figure 2 A new Brønsted acid catalyzed transfer hydrogenation

As the reduction of ketimines leads to the formation of a stereocenter it seemed reasonable to apply a chiral proton source as the catalyst.[11] In the aforementioned transfer hydrogenation of ketimines diphenyl phosphate (DPP) performed best in terms of yields. Therefore, we decided to employ chiral phosphoric acids based on the BINOL core structure.[12,13] These had previously been used for the resolution of amines, as ligand in metal catalysis and more recently by Akiyama and Terada in metal-free activation of imines.[14,15]

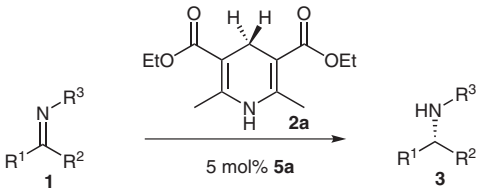
The synthesis of the chiral BINOL phosphates can be accomplished according to the strategy outlined in Scheme 3.[13–16] The protected (*R*)-3,3′-dibromo-1,1′-binaphthyl-2,2′-diol (**4a**) or the octahydro derivative were prepared in two steps from BINOL or H8-BINOL by protection of the hydroxyl groups with methoxymethyl groups, followed by bromination. The Suzuki coupling of **4a** with various aryl boronic acids gave the corresponding 3,3-aryl-substituted BINOL derivatives. Subsequent deprotection and phosphorylation yielded the desired catalysts **5a–e** while catalyst **5f** can be prepared by a protocol



Scheme 3 Synthesis of differently substituted BINOL-phosphoric acids **5** and **6**

established by List and co-workers.[17a] The synthesis of the silylated Brønsted acids **6** was accomplished following a general procedure reported by Yamamoto[18] and MacMillan.[17b] This involved a Brook-type rearrangement of the BINOL-derivative **4b** using *t*-BuLi and subsequent phosphorylation.

After having prepared several chiral BINOL–phosphoric acid derivatives **5a–e**, we started to investigate the utility of these catalysts on the enantioselective transfer hydrogenation of ketimines **1** (Scheme 4).



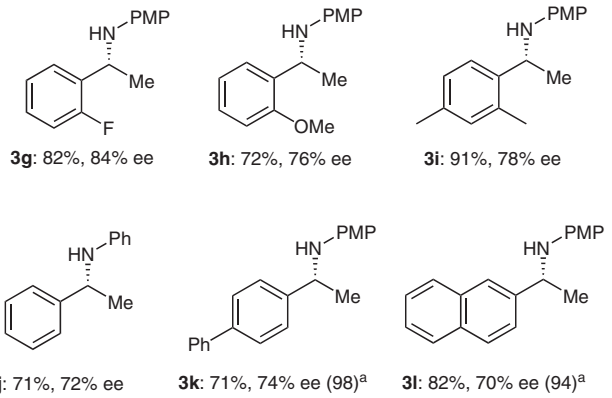
Scheme 4 Organocatalytic asymmetric transfer hydrogenation of ketimines

After reaction optimization, including a survey of different solvents, temperatures, Hantzsch esters and Brønsted acid catalysts, we found that indeed enantioselectivities were observed and our best results were obtained with Brønsted acid catalyst **5a** and dihydropyridine **2a**. Thus a broad range of differently substituted ketimines could be reduced to the corresponding amines in good yields and with good enantioselectivities (Figure 3).[11]

List et al. and MacMillan et al. described catalytic enantioselective reductive aminations employing the same combination of BINOL–phosphoric acid and Hantzsch ester.[17] By using phosphoric acids with sterically more demanding residues in the 3,3-position of the BINOL skeleton (i.e. catalyst **5f** and **6a**) they obtained better enantioselectivities even in a one-pot procedure. Antilla and You subsequently reported an enantioselective transfer hydrogenation of α-imino esters yielding enantioenriched α-amino acids.[19] More recently, the Antilla group succeeded in the use of acetyl-protected imines. This procedure clearly demonstrates a significant improvement over our initial reaction in that the deprotection step is much easier to accomplish.[20]

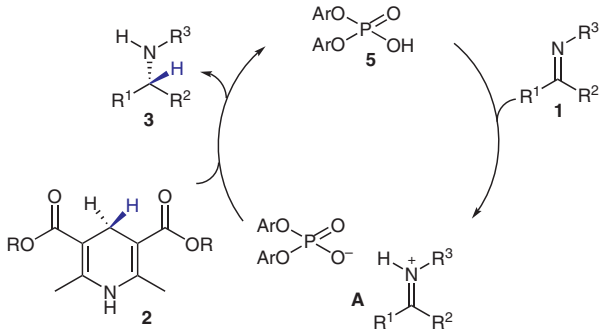
With regard to the mechanism we assume that the Brønsted acid catalyzed transfer hydrogenation proceeds similarly to the reaction of the glutamate dehydrogenase (Scheme 5).[11]

In the first step of the transfer hydrogenation the imine is activated by the chiral Brønsted acid catalyst which results in the generation of an iminium ion, a chiral ion pair **A**. Subsequent hydride transfer from the Hantzsch ester **2** results in the desired chiral amine **3** and the catalyst is regenerated. The absolute configuration of the amine can be explained by a stereochemical model based on the X-ray crystal structure of the chiral Brønsted acid catalyst. In the transition state the ketimine is activated by the Brønsted



a After one recrystallization from methanol

Figure 3 Scope of the asymmetric biomimetic transfer hydrogenation of ketimines



Scheme 5 Proposed mechanism of the Brønsted acid catalyzed transfer hydrogenation of ketimines

acid in such a way that the nucleophile then has to approach from the less hindered *si*-face as the *re*-face is effectively shielded (Figure 4, left). More detailed theoretical investigations by Goodman and Himo revealed a plausible bifunctional activation in which the ketimine is protonated, and the dihydropyridine is activated by a hydrogen bond formed from the Lewis basic oxygen of the phosphoryl group (Figure 4, right).[21] The phosphoric acid catalyst thereby acts as a Brønsted acid/Lewis base bifunctional catalyst.

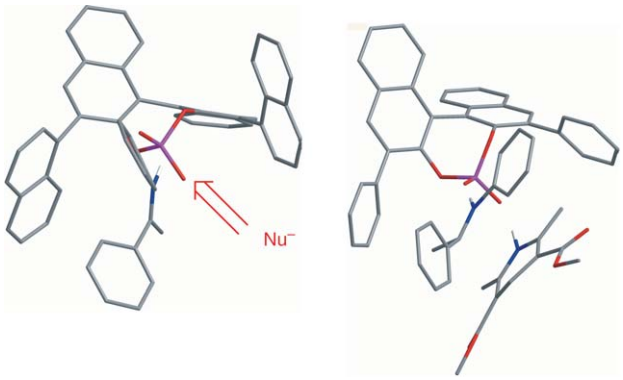


Figure 4 Stereochemical model of the BINOL–phosphoric acid catalyzed activation of ketimines

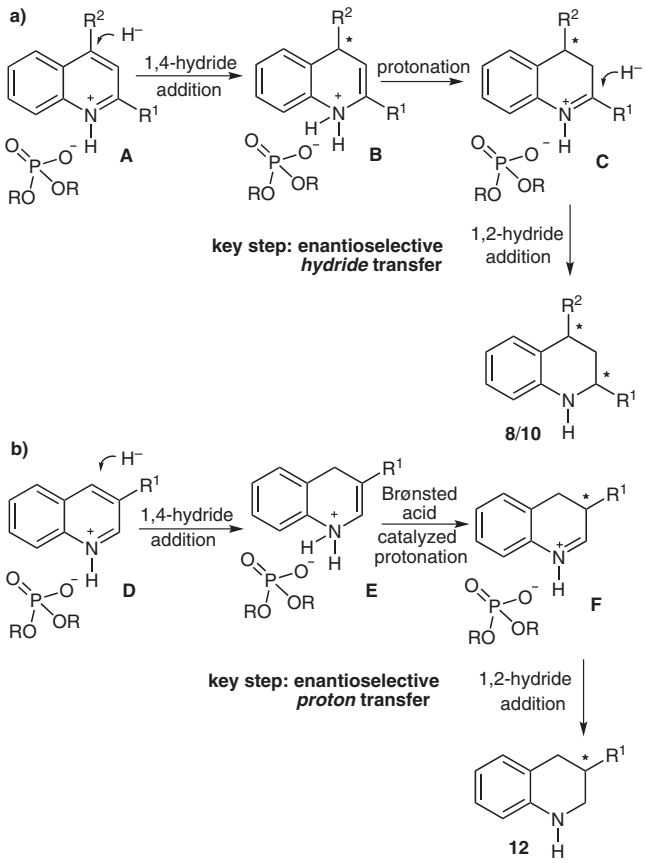
4 Asymmetric Organocatalytic Reduction of Quinolines

Building on this first organocatalytic, enantioselective transfer hydrogenation of ketimines, the reduction of other imines, such as quinolines, seemed feasible. The resulting tetrahydroquinolines are widely distributed in nature. Due to their importance as synthetic intermediates in the preparation of pharmaceuticals, agrochemicals, and in material science, considerable effort has been made to prepare these molecules and numerous synthetic methodologies have been reported. Established methods include homogeneous and heterogeneous metal-catalyzed hydrogenations, hydroborations and transfer hydrogenations.[22] However, all these methods still suffer from a limited substrate scope and examples of efficient asymmetric hydrogenations of aromatic and heteroaromatic compounds are scarce. Thus, the development of a Brønsted acid catalyzed, enantioselective hydrogenation of quinolines would be highly desirable as it provides an efficient and straightforward metal-free access to optically pure tetrahydroquinolines.

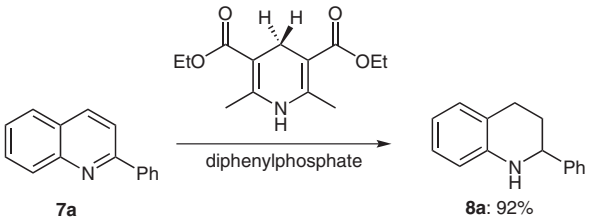
In accordance with our previous studies we presumed that the reduction of quinolines could proceed via a Brønsted acid catalyzed protonation of the quinoline to form an intermediary chiral ion pair **A** or **D** (Scheme 6). The subsequent first hydride transfer would then occur in the 4-position of the quinoline and the enamine **B** or **E** would be formed. The following isomerization should yield the corresponding iminium ion **C** or **F**, and a second hydride transfer would result in the desired tetrahydroquinoline. Depending on the nature of the quinoline and the substitution pattern the stereodetermining step in this hydrogenation cascade has to vary. In the case of 2- and 4-substituted quinolines enantioselectivity will be induced by the hydride transfer (Scheme 6a). However, in the case of 3-substituted quinolines neither the 1,2- nor the 1,4-hydride addition provides a stereocenter and, therefore, the enantiodetermining step has to be an asymmetric Brønsted acid catalyzed protonation (Scheme 6b).

Hence our initial investigations focused on the exploration of appropriate Brønsted acids for the reduction of 2-phenyl-substituted quinoline **7a** with Hantzsch dihydropyridine **2a** as the hydride source. The experiments revealed that several Brønsted acids promote this transformation. The highest activity, however, was achieved with diphenyl phosphate, providing the corresponding 2-substituted 1,2,3,4-tetrahydroquinoline **8a** in excellent yields (Scheme 7).[23]

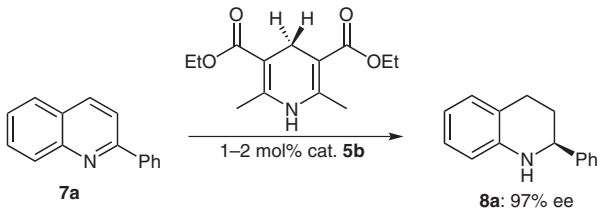
Encouraged by these studies, we turned our attention to extend the procedure to the asymmetric variant by employing chiral BINOL-phosphates.[24] Initial studies on the structural influence of the catalyst revealed that catalyst **5b**, bearing phenanthryl groups in the 3,3′-position of the BINOL scaffold, promoted the enantioselective hydrogenation with an excellent level of asymmetric induction,



Scheme 6 Proposed mechanism of a) enantioselective hydride transfer and b) enantioselective protonation as a function of the substitution pattern of the quinoline



Scheme 7 First metal-free reduction of quinolines



Scheme 8 BINOL–phosphoric acid catalyzed transfer hydrogenation of 2-substituted quinolines

and the desired tetrahydroquinoline **8a** could be isolated with an enantiomeric excess of 97% ee (Scheme 8).

Further examinations concentrated on the substrate scope of this first Brønsted acid catalyzed cascade transfer hydrogenation of 2-substituted quinolines. The results are summarized in Figure 5. In general, 2-substituted quinolines with aromatic and heteroaromatic residues as well as

aliphatic substituents were tolerated in this enantioselective transfer hydrogenation and the corresponding tetrahydroquinolines could be isolated in good yields and with excellent enantioselectivities. Interestingly, halogenated aromatic and aliphatic residues were also tolerated in this metal-free hydrogenation.

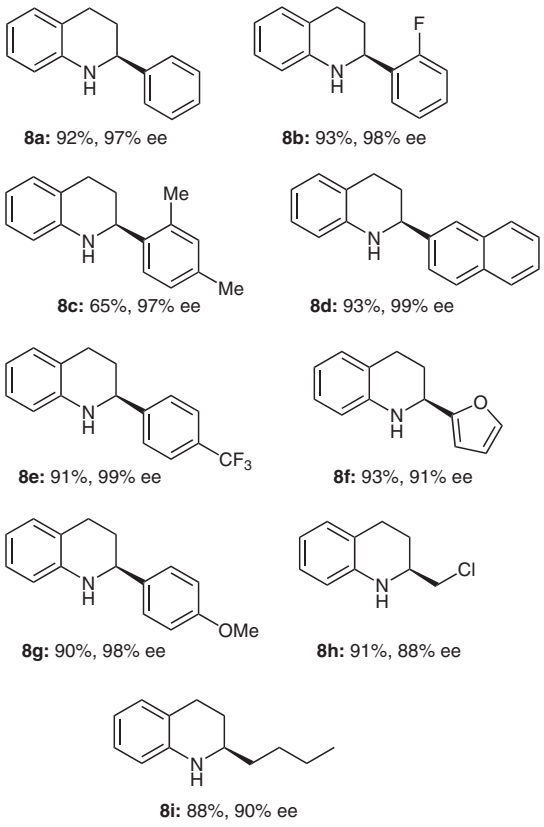
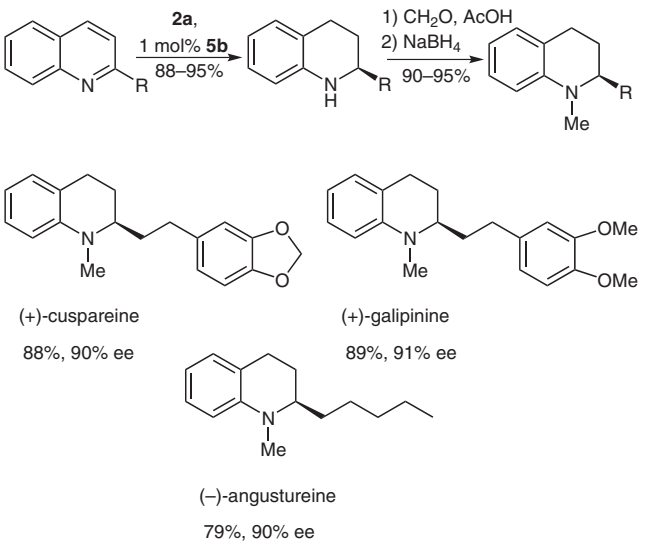


Figure 5 Substrate scope of the transfer hydrogenation of 2-substituted quinolines **7**

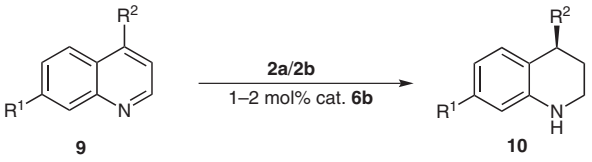
The synthetic potential of this highly enantioselective cascade transfer hydrogenation was demonstrated in the synthesis of biologically active tetrahydroquinoline natural products, such as galipinine, cuspareine and angustureine.[25] Thus, the organocatalytic hydrogenation of readily available 2-substituted quinolines, which were prepared by simple alkylation of 2-methylquinoline, generated the tetrahydroquinoline derivatives with excellent enantioselectivities. The enantioenriched products were subsequently N-methylated to give the desired natural products in good overall yields (Scheme 9).

Mirroring our Brønsted acid catalyzed transfer hydrogenation, Du and co-workers reported the use of double axially chiral phosphoric acids in the reduction of 2-substituted quinolines giving rise to the corresponding tetrahydroquinolines with comparable enantioselectivities.[26] Additionally, Metallinos et al. reported a Brønsted acid catalyzed enantioselective reduction of the structurally related disubstituted 1,10-phenanthrolines.[27]

In addition to the transfer hydrogenation of 2-substituted quinolines we also examined the reduction of 4-substituted derivatives **9**. To date, no direct enantioselective approach to 4-substituted tetrahydroquinolines **10** has been described. So far, multistep reactions have been employed to obtain these valuable chiral 4-substituted tetrahydroquinolines,[28] which have been shown to have biological activity in vivo.[29] Therefore, the development of the first catalytic asymmetric route to these products would be a substantial improvement (Scheme 10).



Scheme 9 Synthesis of natural product alkaloids applying the enantioselective Brønsted acid catalyzed transfer hydrogenation of 2-substituted quinolines



Scheme 10 Asymmetric Brønsted catalyzed transfer hydrogenation of 4-substituted quinolines

Given that the stereocenter is further away from both the protonated nitrogen and the catalytic center of the phosphoric acid catalyst, a larger residue in the 3,3-position of the BINOL skeleton would be necessary. Following optimization of the reaction parameter, the best results so far, with regard to both reactivity and selectivity, have been obtained with a combination of catalyst **6b** and *tert*-butyl Hantzsch ester **2b**. A preliminary substrate scope is shown in Figure 6, demonstrating that several 4-substituted tetrahydroquinolines can be prepared in good yields and with good to excellent enantioselectivities.[30]

To conclude our investigations of the transfer hydrogenation of quinolines, we examined the reduction of 3-substituted quinolines **11**. This reaction proceeds via an enantioselective Brønsted acid catalyzed protonation (Scheme 6b) and represents the first direct access to optically active 3-substituted tetrahydroquinolines **12** (Scheme 11). Similar to the 4-substituted quinolines, application of Brønsted acid catalyst **6b** gave the best chiral

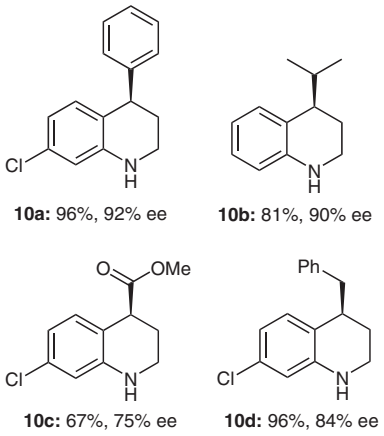
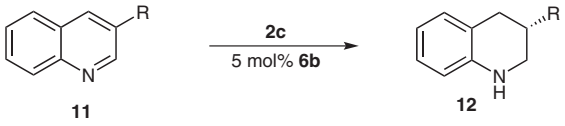


Figure 6 Scope of the Brønsted acid catalyzed transfer hydrogenation of 4-substituted quinolines



Scheme 11 Reduction of 3-substituted quinolines to the optically active 3-substituted tetrahydroquinolines

induction. Evaluation of various Hantzsch esters revealed the allyl ester **2c** to be a superior hydride source resulting in slightly better enantioselectivities than the ethyl derivative **2a**.

This optimized reaction protocol can be applied to the reduction of various 3- and 2,3-substituted quinolines to provide the corresponding tetrahydroquinolines or octahydroacridines in good yields and with high enantioselectivities (Figure 7).[31] In contrast to our previously developed asymmetric transfer hydrogenations of 2- and 4-substituted quinolines which proceed through an enantioselective hydride transfer as a key step, this latest reaction cascade involves a new enantioselective Brønsted acid catalyzed proton transfer as the enantiodifferentiating step. This is not only the first example of an organocatalytic protonation in a cascade reaction but it can also be applied in the preparation of new molecular scaffolds with up to three new stereocenters in a mild and efficient one-pot reaction sequence.

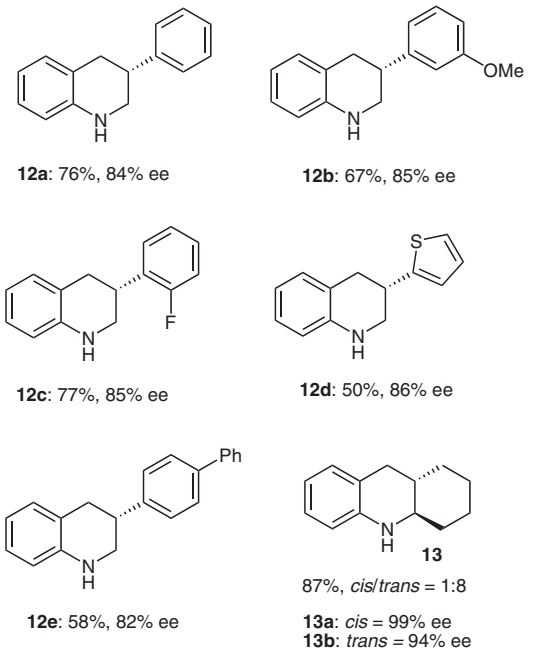


Figure 7 Substrate scope of the Brønsted acid catalyzed enantioselective protonation of 3-substituted quinolines.

5 Asymmetric Organocatalytic Reduction of N-Heterocycles

5.1 Asymmetric Brønsted Acid Catalyzed Hydrogenation of Indoles

Indolines **15** represent a substantial core structure of many natural alkaloids which possess widespread biological and pharmaceutical activity. To date only the metal-catalyzed reduction of trimethyl-3*H*-indole has been reported in order to obtain 2,3,3-trimethylindoline with high enantioselectivities.[32] Given the comparable structural features of indoles and quinolines, the application of our Brønsted acid catalyzed transfer hydrogenation to the reduction of indoles **14** seemed reasonable (Scheme 12).

Scheme 12 Brønsted acid catalyzed transfer hydrogenation of indoles

Indeed, with Brønsted acid **5e** and Hantzsch ester **2a** we were able to isolate a broad range of differently substituted 2,3,3-indolines **15** in high yields and with excellent enantioselectivities up to 99% ee (Figure 8).[33]

5.2 Asymmetric Brønsted Acid Catalyzed Hydrogenation of Benzoxazines, Benzthiazines, Benzoxazinones, Quinoxalines, Quinoxalinones and Benzodiazepinones

Dihydro-2*H*-benzoxazines **20**, dihydro-2*H*-benzthiazines **21**, dihydro-2*H*-quinoxalines **22** as well as dihydro-2*H*-benzoxazinones **23**, diyhdro-2*H*-quinoxalinones **24** and dihydro-2*H*-benzdiazepinones **25** are common structural motifs in a large number of natural products and are reported to have various interesting biological activities (Figure 9). They have also been employed as important chiral building blocks in the synthesis of many pharmaceuticals, such as promising antidepressants, calcium antagonists as well as anti-inflammatory, antinociceptive, antibacterial, antimicrobial agents and non-nucleoside HIV-1 reverse transcriptase inhibitors.[34]

Furthermore, the reduction of benzoxazinones leads to cyclic aryl-substituted amino acid derivatives, which can be

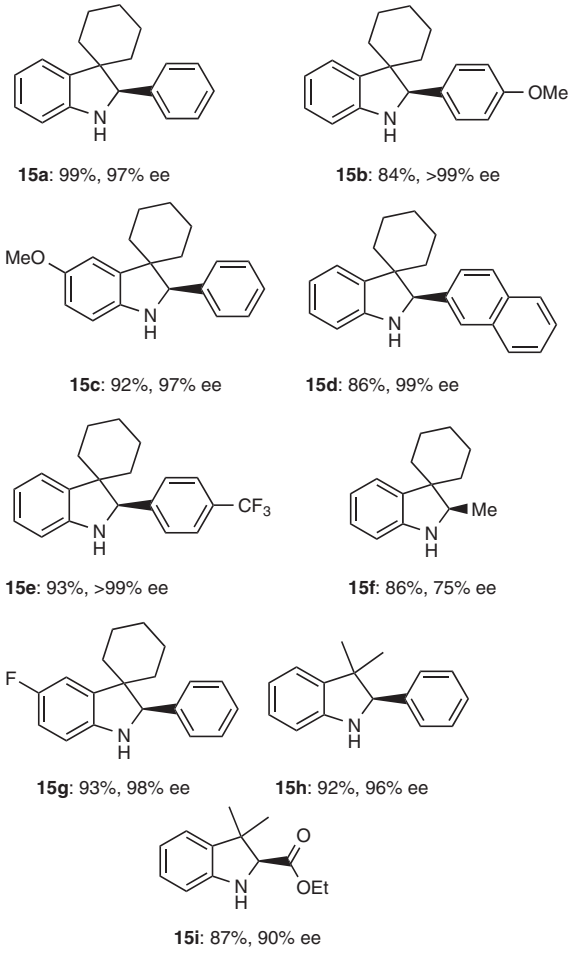


Figure 8 Substrate scope of the first metal-free transfer hydrogenation of 2,3,3-substituted indoles

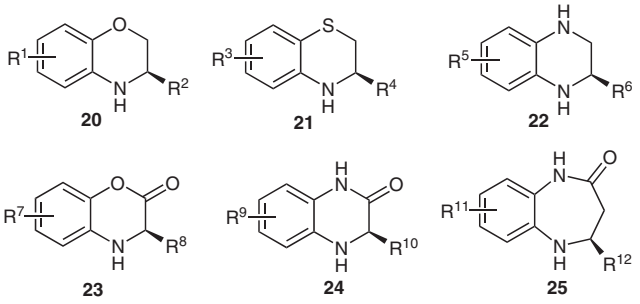
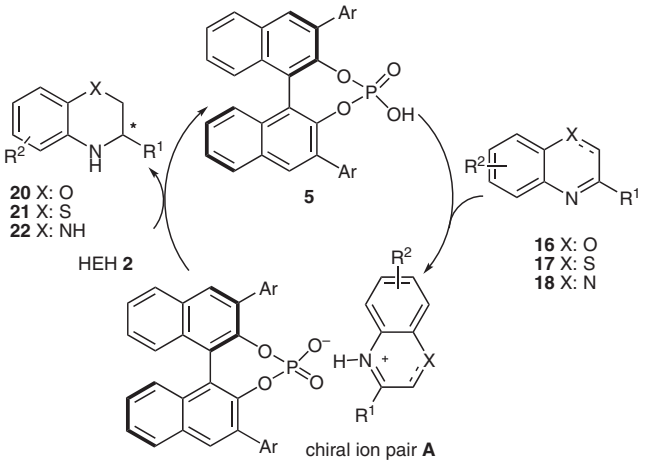


Figure 9 Further desired amine-containing heterocycles

further transformed to the open-chain amino acids. The catalytic enantioselective reduction of imine-containing heterocycles is a direct and most efficient approach to these important compounds. Surprisingly, so far only few catalysts have been reported that catalyze the reduction of these cyclic imines and typically they are restricted to alkyl-substituted derivates, particularly methyl and ethyl derivatives.[35]

Encouraged by the successful organocatalytic enantioselective transfer hydrogenation of imines,[11] quinolines[24] and indoles[33] we became interested in extending our bioinspired strategy to the transfer hydrogenation of the whole set of imine-containing heterocycles (Figure 9). Similar to our previously reported procedure, it was anticipated that the chiral Brønsted acid would activate the substrates through catalytic protonation thereby enabling the hydride transfer from the dihydropyridine to occur (Scheme 13). However, in the case of the quinoxalines a double 1,2-hydride addition has to take place in order to isolate the desired dihydro-2*H*-quinoxalines **22**.



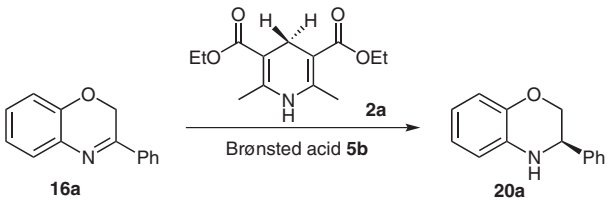
Scheme 13 Mechanism of the transfer hydrogenation of various imine-containing heterocycles

The subsequent reaction optimization showed that highest enantioselectivities were obtained if catalyst **5b** was applied in the reduction of benzoxazines, benzthiazines and benzoxazinones,[36] while the Brønsted acid **5c** gave superior results in the reduction of quinoxalines and quinoxalinones.[37]

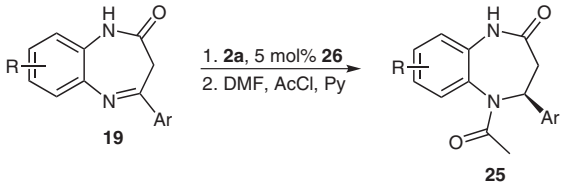
More detailed investigation of the catalyst's activity enabled us to decrease the catalyst loading from 10 mol% to 0.01 mol% (substrate/catalyst ratio = 10000:1). We were pleased to observe that the reduction of benzoxazines with only 0.01 mol% of catalyst, proceeded without considerable loss in reactivity and selectivity and that the corresponding 2*H*-dihydrobenzoxazine **20a** could be isolated in remarkable 90% yield and 93% ee. This corresponds to a TON of 9000 and a TOF of 500 h^{-1} (Table 1). To date this is the lowest catalyst loading reported for an organocatalytic enantioselective transformation. The remarkable, low catalyst loadings and the excellent enantioselectivities of our metal-free transformation render this approach a competitive process compared to enantioselective metal-catalyzed reductions.[36]

Unfortunately, the reduction of the benzodiazepinones **19** proceeded with very low conversion. To circumvent the lack of catalyst reactivity we tested BINOL-based *N*-triflylphosphoramides which, due to the strongly electron-withdrawing triflyl groups, have a considerably lower pK_a and, hence, a higher reactivity (Scheme 14).[38a] So far these catalyst have mainly been employed in asymmetric Brønsted acid catalyzed carbonyl activations, including

Table 1 Catalyst Loading of the Brønsted Acid Catalyzed Transfer Hydrogenation of Benzoxazines



Entry	Loading of **5b** (%)	Yield (%)	ee (%)
1	10	91	96
2	5	95	96
3	2	93	96
4	1	94	96
5	0.1	95	96
6	0.01	90	93



Scheme 14 *N*-Triflylphosphoramide-catalyzed transfer hydrogenation of benzodiazepinones

Diels–Alder reactions, dipolar cycloadditions, ene reactions, protonations or Nazarov cyclizations.[38]

Indeed, with the application of 5 mol% of the *N*-triflylphosphoramide **26** we were able to isolate the dihydrobenzodiazepinones **25** in good yields and with excellent enantioselectivities.[39] Thus, we were able to develop a general protocol for the transfer hydrogenation of a whole set of different N-heterocycles. Typically both, the best reactivities and the best selectivities were achieved with the Hantzsch ethyl ester in combination with phenantryl-, anthracenyl- or triisopropylphenyl-substituted BINOL–phosphoric acid catalysts (Figure 10). In general, the reductions proceeded smoothly under mild reaction conditions and provided differently substituted alkyl- and aryl-substituted products in good yields and with excellent enantioselectivities throughout (Figure 11).

6 Asymmetric Organocatalytic Reduction of Pyridines

Piperidine alkaloids and derivates belong to another very important class of N-heterocycles. Numerous natural products with wide biological and pharmaceutical properties contain this significant structural core. From a synthetic point of view the most convenient and efficient access to these compounds is the catalytic asymmetric hydrogenation of pyridines. However, the enantioselective

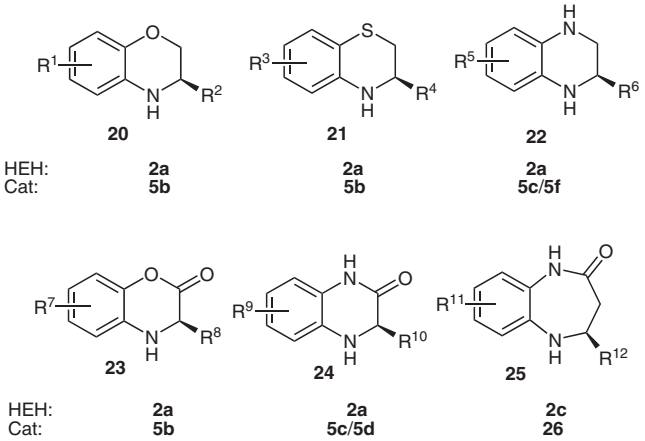
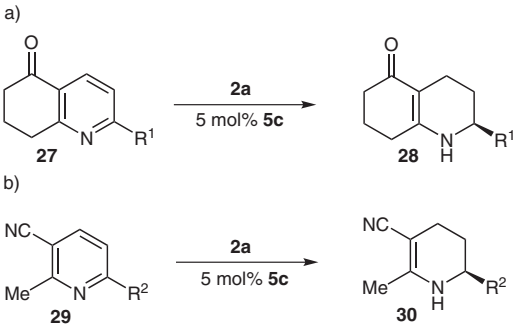


Figure 10 Reaction parameter for the transfer hydrogenation of various imines

reduction of substituted pyridines is still a great challenge and only a few metal-catalyzed reductions are known.[40]



Scheme 15 Transfer hydrogenation of pyridines to the corresponding piperidines

Due to the extensive biological activity, as well as the lack of catalytic asymmetric methods for the preparation of these products, we considered it important to examine an organocatalytic Brønsted acid catalyzed pyridine reduction. Based on our previously developed protocols, we devised a metal-free BINOL–phosphoric acid catalyzed reduction of pyridine derivatives **27** and **29** to obtain the corresponding piperidine derivatives (Scheme 15).[41] With 5 mol% of Brønsted acid **5c** and dihydropyridine **2a** as the hydrogen source we were able to isolate a broad range of different azadecalinones **28** as well as tetrahydropyridines **30** in good yields and with excellent enantioselectivities (Figure 11). Furthermore, we were able to demonstrate that the transfer hydrogenation of pyridine **27c** leads to the corresponding hexahydroquinolinone **28c** which can easily be converted to the alkaloid *diepi*-pumiliotoxin C (Scheme 16).

It is worth noting that this first enantioselective Brønsted acid catalyzed cascade reduction of pyridines not only gives the corresponding products in good yields and with excellent enantioselectivities but also provides a simple and straightforward route to decahydroquinoline or piperidine alkaloid natural products.[43,44] As previously only metal-catalyzed hydrogenations of pyridines have been

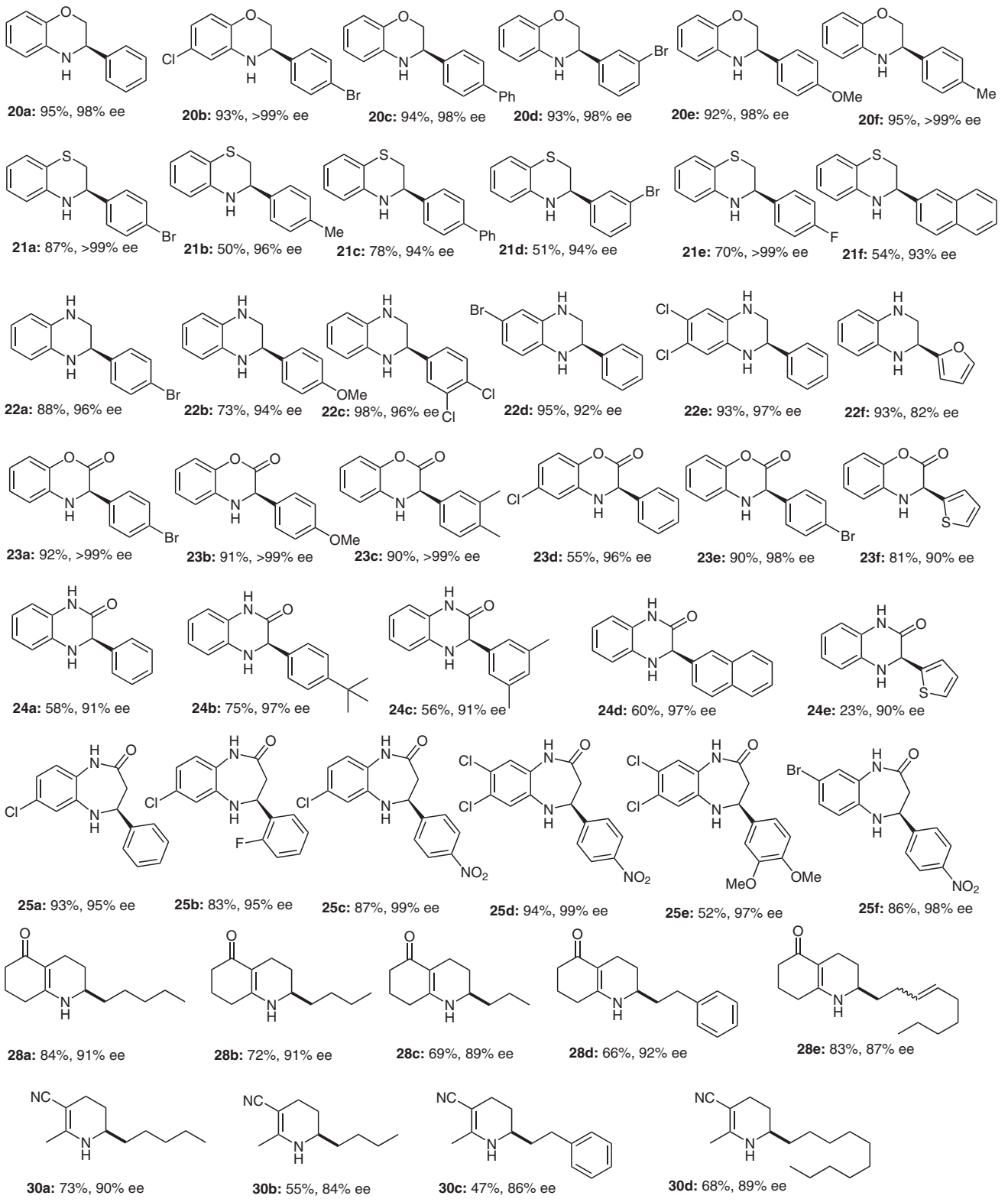
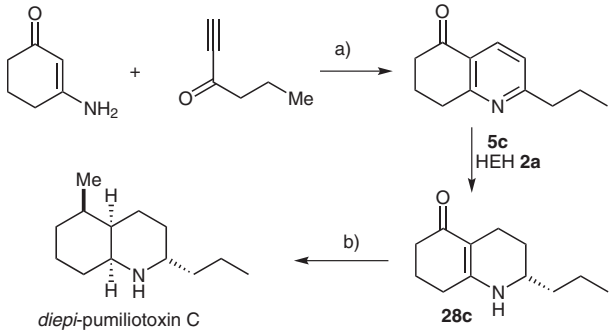


Figure 11 Substrate scope of the transfer hydrogenation of an array of various imine-containing heterocycles

described which did not result in these valuable products and gave typically lower enantioselectivities, our newly developed metal-free Brønsted acid catalyzed procedure represents an important contribution to the enantioselective reduction of pyridines.

7 Asymmetric Organocatalytic Reductions in Cascade Sequences

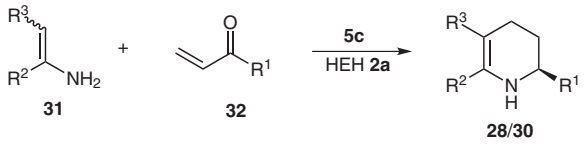
We were able to mimic nature's reduction by replacing the dehydrogenase and NADH system with the simple combination of a readily available Brønsted acid and a di-



Scheme 16 Synthesis of *diepi*-pumiliotoxin C. *Reagents and conditions*: (a) EtOH, 50 °C, 12 h, then 140 °C, 2 h;[42] (b) Ref. 43e.

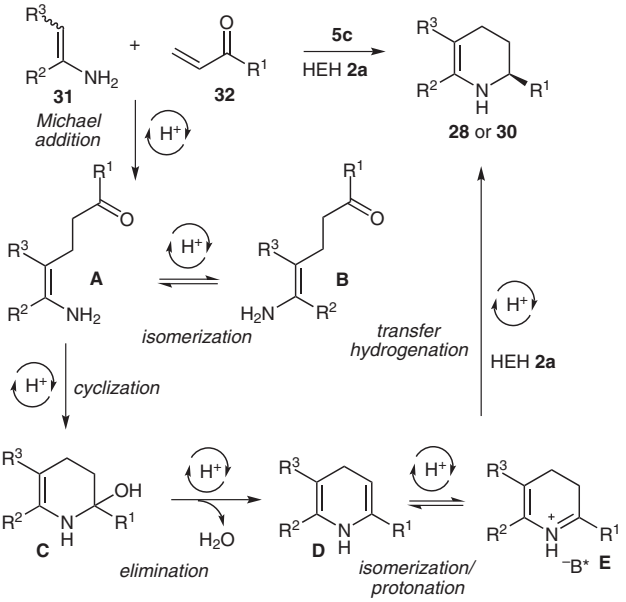
hydropyridine. However, enzyme-catalyzed reactions not only proceed with excellent yields and enantioselectivities they also typically build up very complex structures starting from simple compounds in a minimum number of steps. These enzymatic multistep sequences are often realized in domino and multicomponent reactions and, thus, are blueprints for organic synthesis. Over the past few years the development of organocatalytic domino reactions has become a highly dynamic and topical research area in catalysis.[45,46]

As part of our studies we have developed a new asymmetric organocatalytic cascade reaction in which multiple steps are catalyzed by a chiral Brønsted acid catalyst and which provides valuable tetrahydropyridines and azadecalinones with high enantioselectivities. Based on our original biomimetic strategy and our experience in chiral ion-pair catalysis, we envisioned a new organocatalytic multiple reaction cascade comprising a one-pot Michael addition–isomerization–cyclization–elimination–isomerization–transfer hydrogenation sequence in which each single step is catalyzed by the same chiral Brønsted acid (Scheme 17).



Scheme 17 Brønsted acid catalyzed reaction sequence

In our reaction design (Scheme 18) we assumed that exposure of a mixture of enamine **31** and vinyl ketone **32** to catalytic amounts of Brønsted acid should lead to the formation of the corresponding 1,4-addition products **A** and **B**. Subsequent Brønsted acid catalyzed cyclization of **A**, which is in an acid-catalyzed equilibrium with **B**, would give the hemiaminal **C** which upon rapid water elimination results in the formation the dihydropyridine **D**, an intermediate also observed in the asymmetric pyridine reduction. The following Brønsted acid catalyzed protonation should effect the generation of an iminium ion, a chiral ion pair **E** which is activated for an enantioselective hydride transfer to give the desired product **28** or **30**. Central to the utility of this new multiple reaction cascade in asymmetric synthesis is the requirement that the last Brønsted acid catalyzed activation step in this sequence proceeds with high enantiocontrol.



Scheme 18 Mechanism of the Brønsted acid catalyzed domino reaction sequence

Indeed we were able to develop such a transformation by applying the ideal combination of Brønsted acid **5c** and dihydropyridine **2a**.[47] In this new three-component reaction each step of the six-step sequence is catalyzed by the same chiral Brønsted acid allowing rapid, direct and efficient access to valuable tetrahydropyridines and azadecalinones from simple readily available starting materials with the highest levels of enantiocontrol (Figure 12). Thus, we were additionally able to demonstrate that our organocatalytic hydrogenation protocol is amenable to complex molecular cascading.

An additional cascade reaction involving a Brønsted acid catalyzed transfer hydrogenation was developed by List and co-workers.[48] In contrast to their previously developed chiral salt catalyzed transfer hydrogenation of enones[8d] (Scheme 19) this reaction sequence started from linear diketones and afforded substituted cyclohexylamines with high diastereo- and enantioselectivities (Scheme 20).

The reaction proceeds via an intramolecular aldol condensation followed by a double transfer hydrogenation sequence. The proposed catalytic cycle was recently verified by mass spectrometry in which all crucial intermediates were detected.[49] Additionally, this study showed that mass spectroscopy is a well-suited technique for the determination of reaction pathways in Brønsted acid catalysis and is certain to be applied in the future for mechanistic investigations.

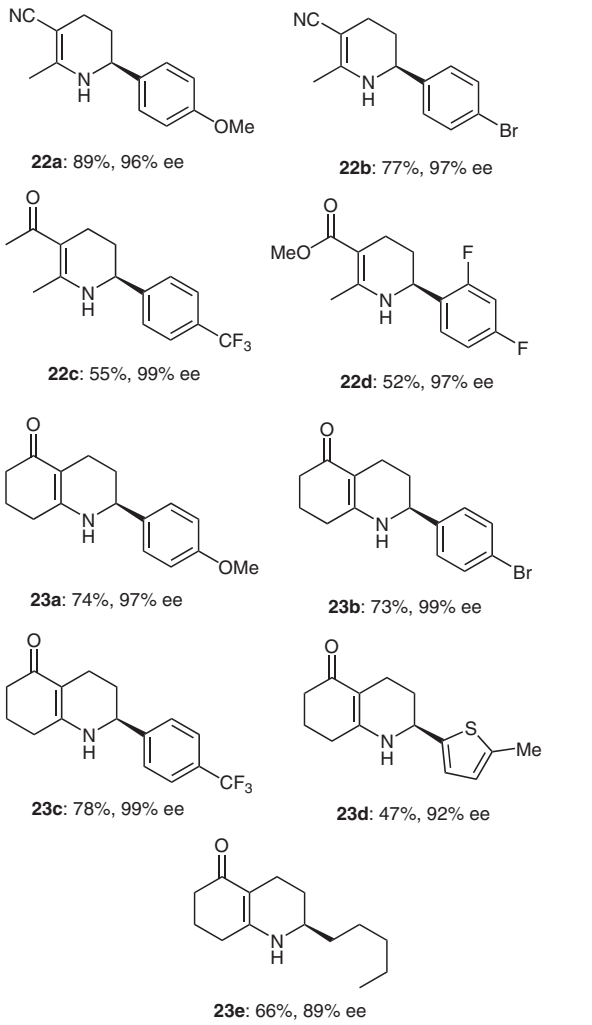
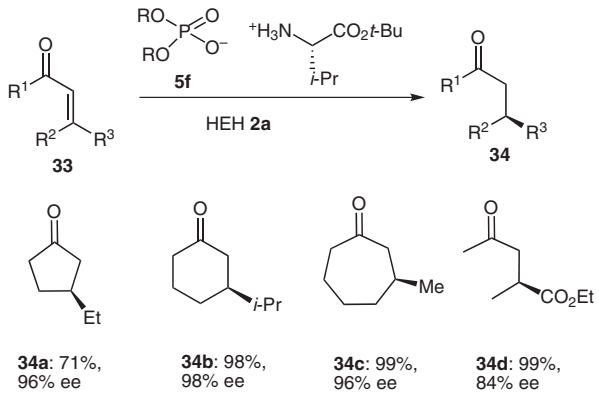


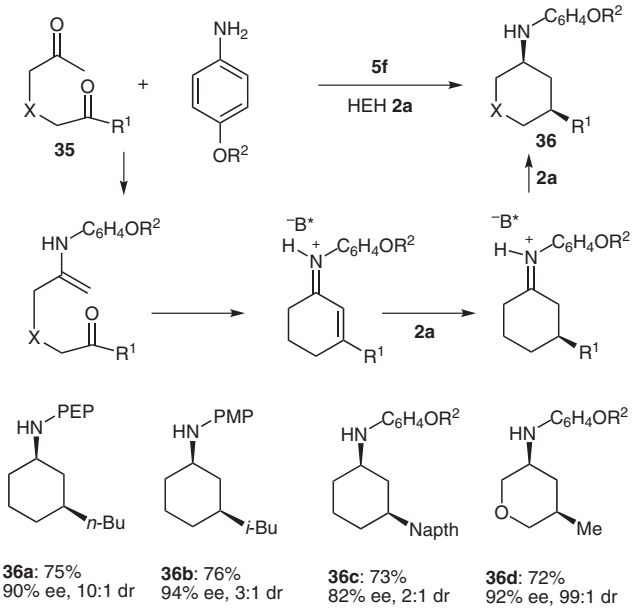
Figure 12 Substrate scope of the Brønsted acid catalyzed cascade



Scheme 19 Brønsted acid catalyzed transfer hydrogenation of enones

8 Conclusion

In the five years since we reported the highly enantioselective Brønsted acid catalyzed transfer hydrogenation which was inspired by nature's dehydrogenase, this field has grown at an extraordinary pace. As seen in this account the initially developed bioinspired transfer hydrogenation of imines represented a key starting point for the development of many powerful reductions. The generality of this BINOL–phosphate–dihydropyridine combination is particularly noteworthy when compared to nature's dehydrogenase–NADH system. Thus, a broad range of diverse cyclic and acyclic amines as well as heterocycles can be readily obtained with impressive enantioselectivities by applying this convenient method which is striking due to its almost optimal reaction conditions and the operational simplicity and practicability. Similar to nature's multicomponent domino reactions it was possible to implement the catalytic asymmetric Brønsted acid catalyzed transfer hydrogenation in efficient multistep reaction sequences showing that this protocol is amenable to be applied in complex molecular cascades. Although we have been able to achieve a broader substrate scope and similarly high reactivities and selectivities compared to our natural role model, dehydrogenase, we are far from being as efficient. Therefore, the future goal is to improve the reaction in such a way that, similar to nature's NADH, our hydride source dihydropyridine can be recycled or employed in catalytic amounts. We are confident that this organocatalytic hydrogenation procedure which provides a series of valuable biologically active products with remarkable levels of selectivity will find widespread application in organic synthesis.



Scheme 20 Brønsted acid catalyzed cascade sequence to substituted cyclohexylamines

Acknowledgment

Financial support by the Evonik Degussa, the DFG (Priority Programme Organocatalysis) and the FCI (Fonds der Chemischen Industrie) is gratefully acknowledged.

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