Chapter 2
Asymmetric Transfer Hydrogenations Using Hantzsch Esters

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Abstract 1,4-Dihydropyridines are extensively used as reducing agents in asymmetric organocatalytic protocols. In particular, readily available Hantzsch esters are competent hydrogen equivalents for iminium ion-, Brønsted acid- and hydrogen bonding-catalyzed reactions. These methodologies give often unsurpassed degrees of stereocontrol in the reduction of α,β-unsaturated carbonyl compounds, cyclic/acyclic imines and activated olefins. In addition, dihydropyridine-mediated reductions can be easily implemented in asymmetric cascade processes using one or more catalysts. The versatility of these catalytic protocols has been demonstrated by their application to the synthesis of a variety of biologically active compounds.

2.1 Introduction

The stereocontrolled addition of hydrogen to an unsaturated substrate is probably the asymmetric catalytic transformation which has been studied in more detail both in industry and in academia [1]. Countless examples of transition metal-catalyzed enantioselective reductions can be found in the chemical literature, in many cases with virtually perfect degree of stereocontrol. While hydrogen gas remains the most popular reducing agent for asymmetric hydrogenations, the use of small molecules able to formally transfer two atoms of hydrogen to a substrate (transfer hydrogenation) has become a well-established strategy in view of its advantages in terms of safety and operational simplicity [2]. Initially confined to transition metal catalysis (especially ruthenium complexes), asymmetric transfer hydrogenation can nowadays be performed with different substrates classes using chiral organic molecules

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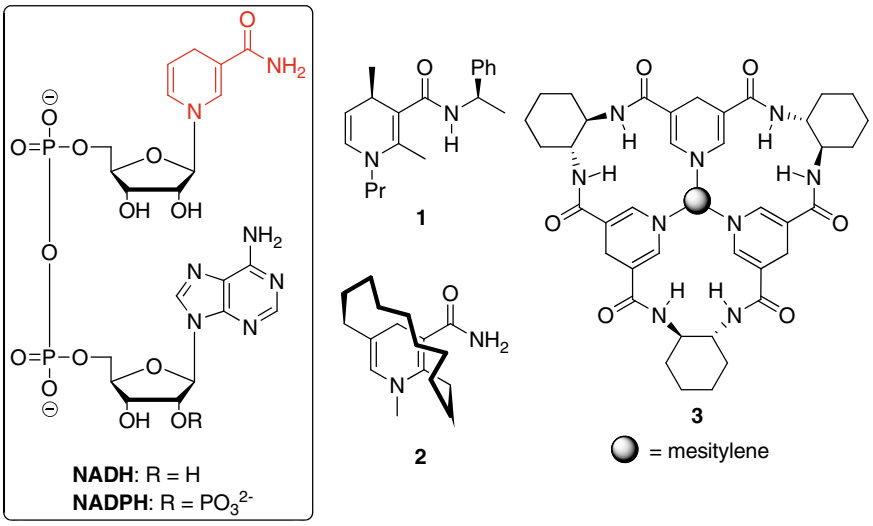


Fig. 2.1 NAD(P)H and chiral N-alkyl nicotinamides

as catalysts. In this respect, nearly the entirety of these protocols makes use of dihydropyridines as hydrogen donors. This Chapter gives an overview of organocatalyzed asymmetric transfer hydrogenations, highlighting their applications to the synthesis of biologically relevant molecules. For the sake of completeness, non-asymmetric catalytic reductions using dihydropyridines are also briefly discussed.

2.1.1 NADH and NADPH Mimics

Nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) are ubiquitous cofactors mediating an impressive variety of redox processes in living organisms (Fig. 2.1) [3]. These compounds owe their unique reactivity to the dihydropyridine core of the nicotinamide subunit which can (formally) lose a hydride at the C_4 position with concomitant aromatization of the heterocycle yielding the oxidized form of the coenzyme, $NAD(P)^+$. Throughout the second half of the twentieth century, considerable efforts have been spent in the development of small-molecule NAD(P)H mimics, mainly to gain insights on mechanistic aspects of redox biological processes [4–6]. In particular, a major controversy addressed using synthetic nicotinamides involved whether the oxidation of NAD(P)H takes place as a single-step hydride transfer or as a sequential electron-proton-electron transfer. In this respect, depending on the type of process examined, there are experimental data in support of both hypotheses [7].

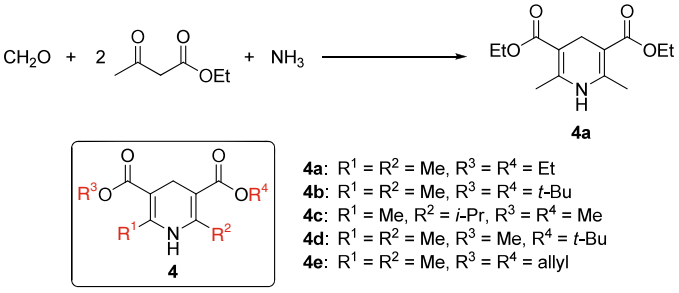
The reactivity of synthetic nicotinamides has been studied with several substrates, often in the presence of Lewis acids. Among the remarkable variety of

NAD(P)H mimics which have been synthesized, various chiral nicotinamides were tested for their ability to deliver a hydride to unsaturated substrates in an enantioselective fashion; representative examples are given in Fig. 2.1.

Compound **1** contains two stereocenters, one of them on the C_4 position which is destroyed upon hydride transfer [8]. Bicyclic amide **2** features an alkyl chain bridging C_2 and C_5 of the dihydropyridine core to mimic the lipophilic region of the active site of L-lactate dehydrogenase [9]. Finally, in trimeric compound **3** the chirality comes from 1,2-*trans*-cyclohexyldiamine, a very popular building block for asymmetric (organo)catalysts [10]. These compounds have all been shown to reduce α-ketoesters in a highly enantioselective fashion in the presence of magnesium perchlorate.

2.1.2 Hantzsch Esters

1,4-Dihydropyridines find important applications in medicine (mainly as calcium channel blockers) and their chemistry has been thoroughly investigated over the last decades [11–14]. The first synthesis of dihydropyridines **4** was reported by Arthur Rudolf Hantzsch over a century ago and involved the condensation between ammonia, an aldehyde and two molecules of a β-ketoester (Scheme 2.1) [15]. Use of a modified procedure allowed synthesis of unsymmetrical dihydropyridines starting from two different β-ketoesters [16]. Compounds **4** are known as Hantzsch esters and have been extensively used as pyridine precursors in the synthesis of heterocyclic compounds.

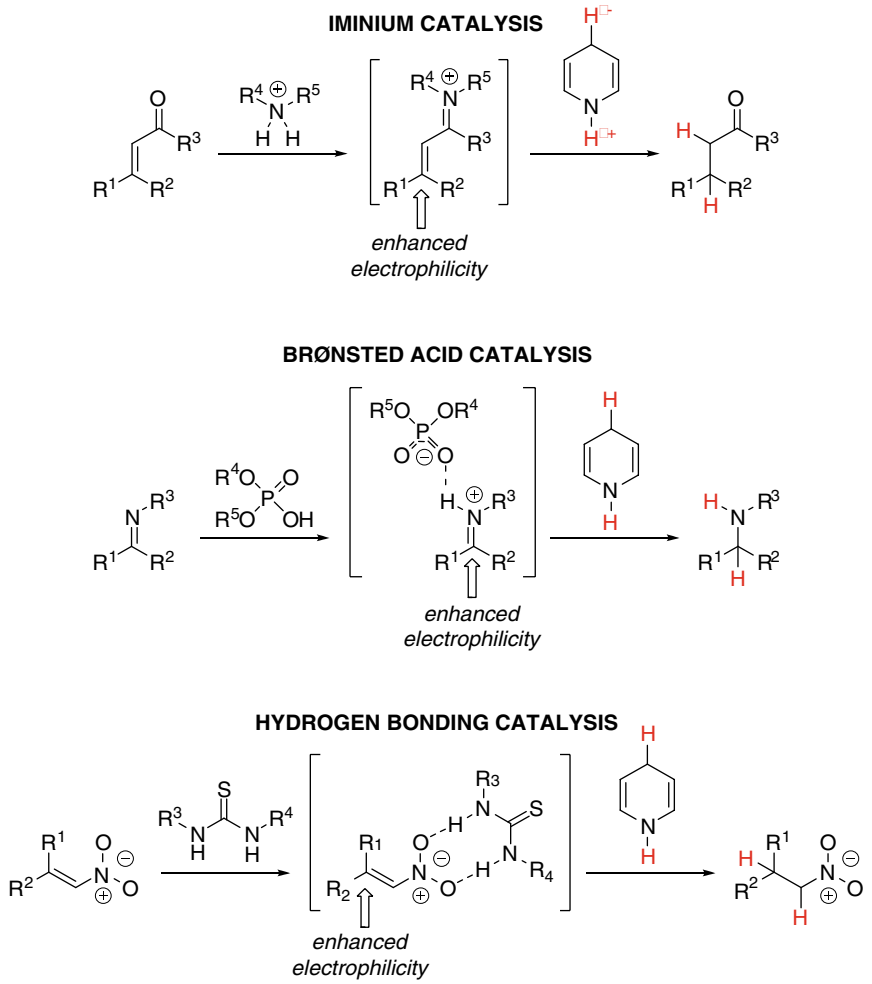


Scheme 2.1 Hantzsch synthesis of dihydropyridines and common Hantzsch esters used in asymmetric organocatalytic transfer hydrogenations

The hydride donor ability of Hantzsch ester **4a** has been experimentally determined to be slightly higher than that of N-benzylnicotinamide, both being comparable to the borane-triethylamine complex [17]. Together with trichlorosilane [18], Hantzsch esters **4** are the reagents of choice to effect asymmetric reductions using chiral organocatalysts.

2.1.3 *Organocatalysis*

Within the recent wave of interest in organocatalysis, several research groups tackled the challenging task of developing transition metal-free asymmetric hydrogenations, mainly using Hantzsch esters as the hydrogen source. In little more than 5 years, an impressive variety of organocatalytic protocols for the asymmetric reduction of different functionalities (such as activated olefins and imines) has been reported [19–21]. In general, three main types of organocatalytic transfer hydrogenation can be identified, depending on the substrate and the type of catalysts (Scheme 2.2).



Scheme 2.2 Classes of organocatalyzed transfer hydrogenations using dihydropyridines

For all these reactions, there is general consensus that the transfer hydrogenation takes place *via* hydride transfer rather than electron/proton/electron donation. These three classes of reactions are very different and are individually discussed in the following sections. Nevertheless, the role of the catalyst is common to all these processes and is namely to increase of electrophilicity of a carbon atom by either: (1) formation of a covalent intermediate with the substrate [22], (2) explicit protonation of an electronegative atom [23], or (3) complexation by hydrogen bonding [24]. In addition to that, catalysts occasionally also interact with the Hantzsch esters, increasing their reactivity and positioning them in a geometric arrangement suitable for the subsequent hydride transfer.

The following pages give an overview of the various types of organocatalytic asymmetric transfer hydrogenations which have been realized so far, mostly yielding valuable chiral building blocks with very high enantioselectivities. In addition to that, the well-known versatility of iminium and Brønsted acid catalysis has been often exploited to couple an enantioselective reduction step with other organocatalytic transformations in cascade processes giving access to highly enantioenriched, drug-like compounds [25]. The examples described below are divided according to the type of mechanism; cascade reactions with more than one catalyst are included in the section corresponding to the mode of substrate activation for the hydride transfer step.

2.2 Iminium Ion Catalysis

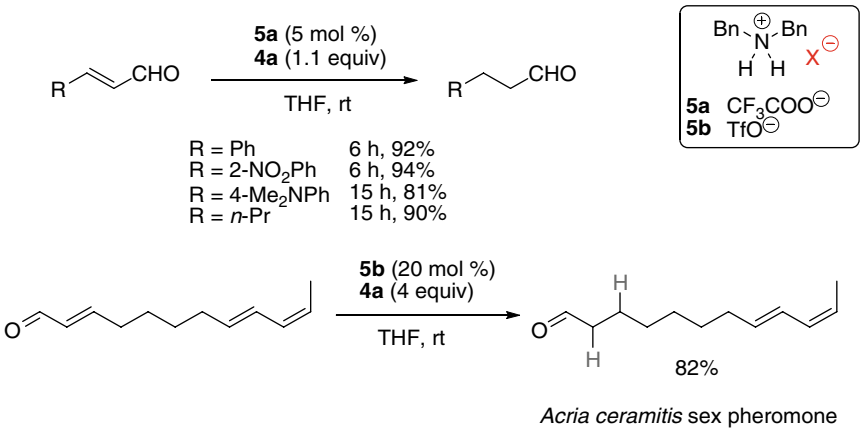
2.2.1 Achiral Catalysts

The capability of dialkylammonium salts to react with α,β-unsaturated aldehydes generating an iminium ion particularly activated towards 1,4-additions was exploited to realize a highly selective conjugate reduction of enals [26]. The optimized conditions for this reaction envision the use of 5 mol% dibenzylammonium trifluoroacetate **5a** in combination with Hantzsch ester **4a**, to yield reduced aldehydes with short reaction times in the case of electron-deficient substrates. The intrinsic regioselectivity of this approach found application in the synthesis of various lepidopteran sex pheromones [27] (Scheme 2.3).

2.2.2 Chiral Catalysts

Several protocols for the asymmetric reduction of α,β-unsaturated carbonyl compounds rely on the use of acid salts of chiral imidazolidinones **6**, a very popular catalyst class for enantioselective conjugate additions [22] (Fig. 2.2).

For instance, the trifluoroacetic (TFA) salt of imidazolidinone **6a** proved very effective for the enantioselective 1,4-reduction of enals [28]. Interestingly, reaction



Scheme 2.3 Organocatalytic conjugate reduction of enals

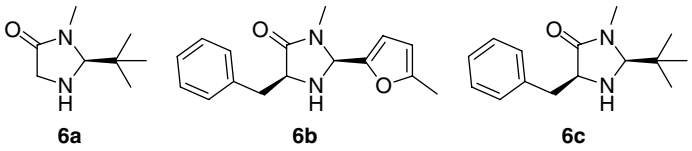
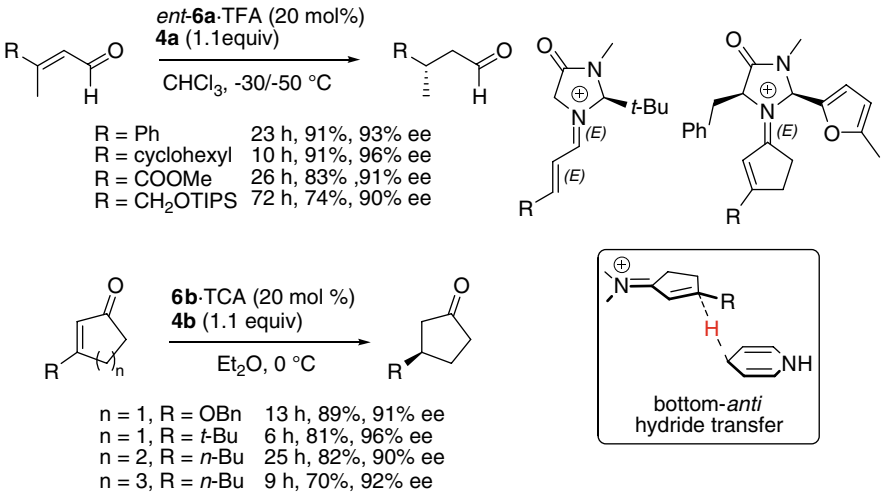


Fig. 2.2 Imidazolidinones catalysts used in asymmetric transfer hydrogenation (represented as free bases)

of the two isomers of a same olefin gives identical stereochemical outcome, in stark contrast with what observed for many metal-catalyzed hydrogenations. While this catalyst is not able to promote the conjugate reduction of cyclic enones, furyl-substituted catalyst **6b·TCA** (trichloroacetic acid) in combination with Hantzsch ester **4b** was shown to successfully reduce cyclic α,β-unsaturated ketones of different ring sizes (5–7 atoms) with good levels of asymmetric induction [29]. For enals, it has been proposed that the catalyst reacts with the substrate leading to the predominant formation of an *E*,*E*-iminium ion which undergoes hydride attack. Likewise, for cyclic enones the *E* iminium ion leaves the bottom face of the conjugated system unshielded. High-level DFT calculations confirmed this hypothesis reproducing the experimental enantioselectivity [30]. The computational results also indicate that in the energetically most accessible arrangement of the reactants for the hydride transfer step, the Hantzsch ester and the iminium ion lie in an *anti* geometry, hence with the dihydropyridine N-H pointing away from the catalyst (Scheme 2.4).

These protocols for conjugate reductions were exploited in the synthesis of various biologically relevant targets. For instance, it was shown that α,β-unsaturated aldehydes containing either a thiazole or an oxazole as β-substituent are competent substrates for the transfer hydrogenation even though the reduced products are obtained with slightly lower enantiomeric excesses. The resulting chiral heterocyclic



Scheme 2.4 Enantioselective conjugate reduction of α,β-unsaturated carbonyl compounds

derivatives represent a rather common motif in biological compounds and this methodology was applied in the synthesis of the C7–C14 fragment of Ulupualide A [31]. The imidazolidinone-catalyzed conjugate reduction was also employed in a total synthesis of (+)-neopeltolide A, a highly cytotoxic marine macrolide [32]. Enantioselective reduction of a cyclic enone containing an ester group as β-substituent provided a chiral building block which was further elaborated to a spliceosome inhibitor designed starting from an overlay of the structures of FR901464 and pladienolide, two natural bioactive compounds presumably sharing the same mode of action [33] (Fig. 2.3).

In asymmetric counteranion-directed catalysis (ACDC), chiral acids are used to generate the active form of the catalyst (in the abovementioned cases, an imidazolidinonium cation). This strategy, which has been applied to various organocatalytic transformations, proved very successful in the case of conjugate reductions using Hantzsch esters [34]. In particular, salts obtained from bulky chiral phosphoric acids and α-amino esters or achiral secondary amines have been shown to be powerful catalysts for the transfer hydrogenation of problematic substrates (Scheme 2.5). For instance, catalyst **7a** can be used to obtain high degrees of stereocontrol with in the reduction of nonhindered aliphatic enals, whereas imidazolidinone-based catalysts give unsatisfactory results [35]. The levels of enantioselectivities obtained using this catalyst remain high even at elevated temperatures, as demonstrated in the synthesis of the fragrance (*S*)-Florhydral® [36]. Valine-derived catalyst **7b** gave excellent results in the reduction of cyclic enones and, remarkably, promoted the transfer hydrogenation of acyclic α,β-unsaturated ketones, although with somewhat lower enantioselectivities [37].

Highly enantioselective reductions in aqueous media were realized using peptide catalysts covalently attached to polyethylene glycol grafted on polystyrene resin. Catalyst **8** gave the best results among various oligopeptides screened for the

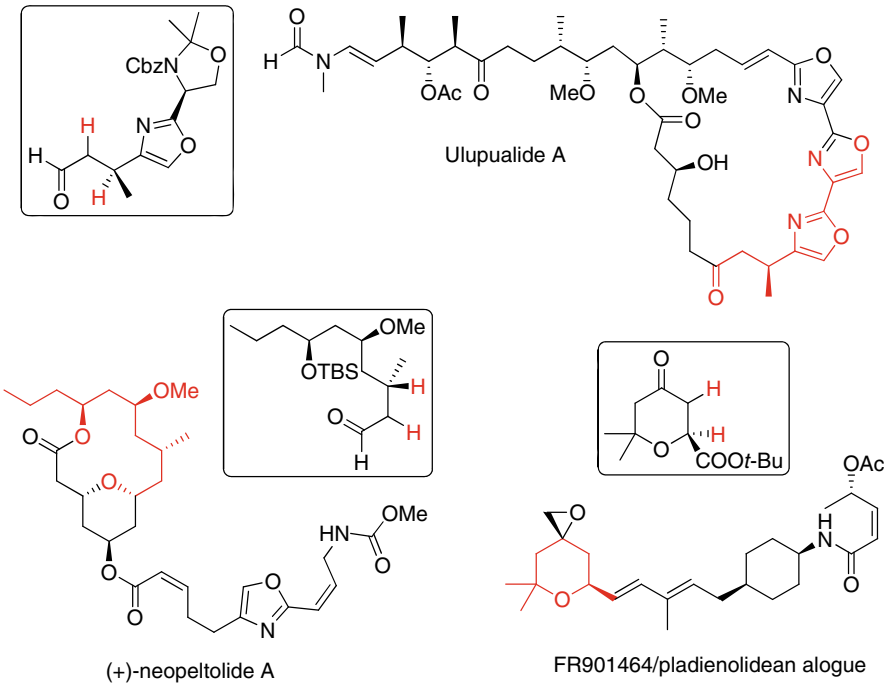
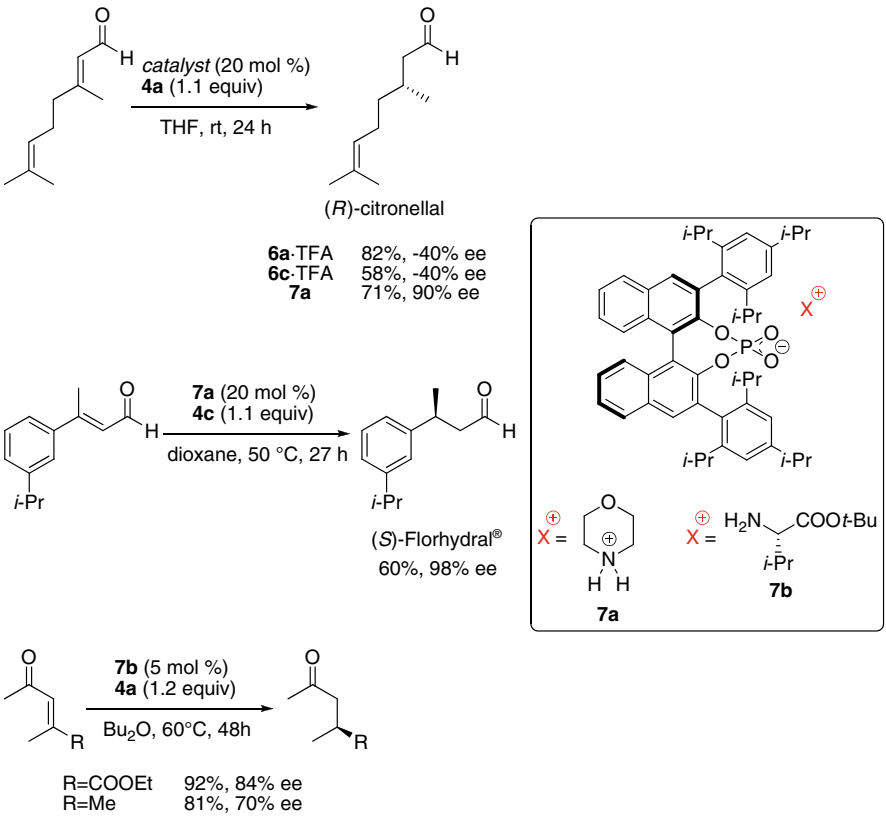


Fig. 2.3 Applications of the asymmetric conjugate reduction to the synthesis of bioactive compounds

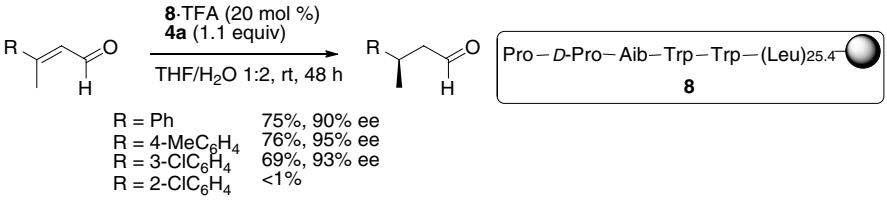
reduction of β-methyl cinnamaldehydes (Scheme 2.6) [38]. Key elements in the catalyst design included the presence of a 2-aminoisobutyrric acid / D-proline (Aib−d-Pro) motif, which is known to induce a β-turn in organic solvents, and a rather long hydrophobic polyleucine chain (25.4 residues on average). This catalyst gave good results with several α,β-unsaturated aldehydes although it failed in promoting the reaction of sterically hindered substrates. IR studies on the solution structure of the catalyst indicated that the polyleucine chain folds to a stable α helix and confirmed the presence of a β-turn [39].

2.2.3 Cascade Processes

Upon addition of a hydride to the α,β-unsaturated iminium intermediate, the resulting nucleophilic enamine can be trapped with a suitable electrophile present in the reaction mixture (tandem iminium-enamine catalysis) [40]. While in the abovementioned cases the enamine intermediate is quenched with a proton, some methodologies exploit the reactivity of enamines to couple conjugate reduction to the formation of a new C-C bond. For instance, α,β-unsaturated aldehydes containing a second Michael acceptor in their structure undergo reductive cyclization processes resulting in the formation of a cyclopentane ring with two contiguous stereocenters



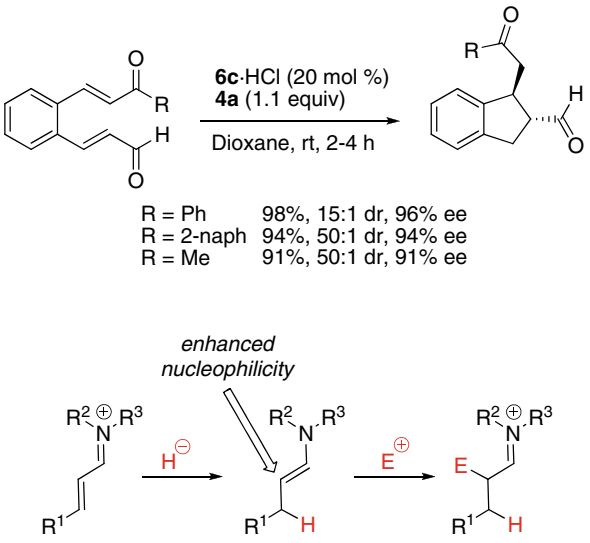
Scheme 2.5 Counteranion-directed enantioselective conjugate reduction of α,β-unsaturated carbonyl compounds



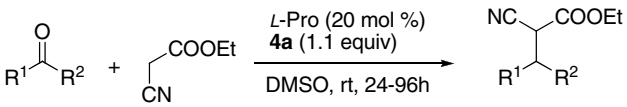
Scheme 2.6 Oligopeptide-catalyzed enantioselective reduction of enals

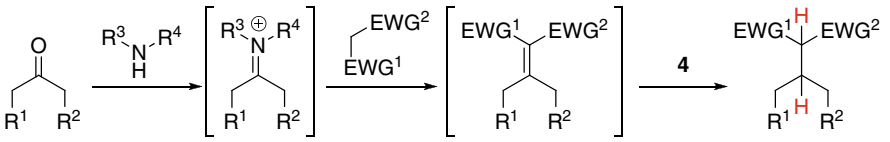
(Scheme 2.7) [41]. The same concept has also been applied to intermolecular reactions such as a reductive Mannich reaction between enals and α-imino esters using Hantzsch esters as the hydrogen source [42]. In this case, however, the electrophile (α-imino ester) is added after the reduction of the starting material is complete and both reaction medium and temperature are adjusted to optimize yield and diastereoselectivity in the Mannich step.

Scheme 2.7 Asymmetric reductive Michael cyclization and schematic representation of the tandem iminium-enamine catalysis mechanism



Hanztsch esters have also been used as hydrogen donors for organocatalytic cascade reductive alkylations of carbonyl compounds. In this approach, a Knoevenagel condensation between a ketone and an activated methylene compound is followed by a transfer hydrogenation [43, 44]. While these reactions are catalyzed by protonated cyclic secondary amines (such as proline and derivatives), from a mechanistical point of view they share little resemblance to the previously discussed examples. In more detail, the role of the catalyst is to promote the alkylation step and the resulting intermediate is activated enough to undergo spontaneous hydride transfer (Scheme 2.8). Although in most cases the enantiomeric excess of the products was not determined, this mechanistic hypothesis implies the substantial absence of stereocontrol in the hydride transfer step. Nevertheless, this tandem





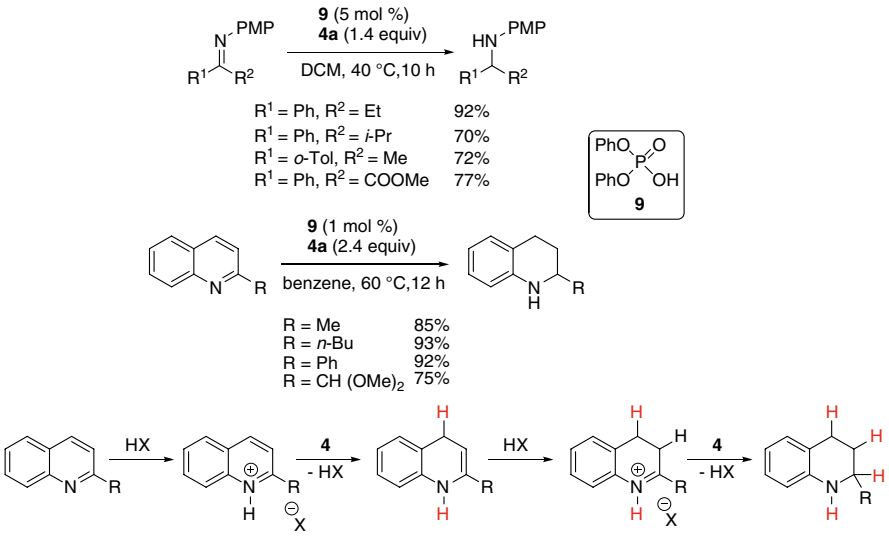
Scheme 2.8 Tandem Knoevenagel/transfer hydrogenation and proposed mechanism

Knoevenagel / transfer hydrogenation has been coupled to other organocatalytic reactions (often in one-pot procedures) to synthesize libraries of enantioenriched chiral compounds, either by means of chiral starting materials [45] or by using well-developed enantioselective reactions before or after the reductive alkylation step [46, 47].

2.3 Brønsted Acid Catalysis

2.3.1 Achiral Catalysts

Early reports on the use of Hantzsch esters as reducing agents for carbon-nitrogen double bonds described the screening of a variety of Brønsted acids as catalysts. Interestingly, several of them were found to promote the transfer hydrogenation of N-*para*-methoxyphenyl (PMP) ketimines [48] and quinolines [49]. In both cases, however, the best results were obtained using diphenyl phosphate **9** as catalyst (Scheme 2.9). Quinolines react with two equivalents of Hantzsch ester yielding tetrahydroquinolines at remarkably low catalyst loadings. This reaction is presumed to proceed via an initial conjugate reduction followed by isomerization to the 3,4-dihydropyridine and subsequent 1,2-reduction. In alternative to this catalytic approach, a methodology making use of acyl chlorides in stoichiometric amount for quinoline activation (hence yielding N-acyl derivatives) has also been developed [50].



Scheme 2.9 Brønsted acid-catalyzed reduction of N-aryl ketimines and 2-substituted quinolines. PMP = *p*-methoxyphenyl

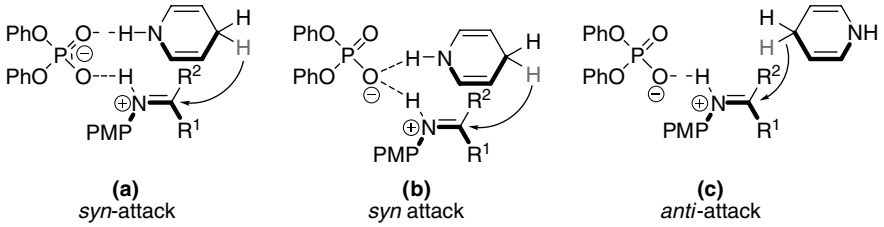


Fig. 2.4 Mechanistic possibilities for the phosphoric acid-catalyzed hydrogenation of N-PMP imines

Computational studies on the mechanism of the transfer hydrogenation of N-aryl imines using an achiral phosphoric acid catalyst identified different possible modes of substrate(s) activation [51, 52] (Fig. 2.4). In more detail, upon protonation of the imine, the phosphate group can (a) engage in two hydrogen bonds with the substrate and the Hantzsch ester using both oxygens; (b) interact with the iminium and the dihydropyridine N-H with the same oxygen; (c) interact exclusively with the N-aryl iminium ion. The calculations indicate that mode (a) is by far preferred over the other two which are not energetically accessible. Moreover, calculations on the reaction of *E*- and *Z*-iminium ions showed that both isomers have similar energy once they are complexed by the phosphate anion and they are equally competent substrates for hydride transfer.

2.3.2 Chiral Catalysts

The advent of axially chiral phosphoric acids as powerful organocatalysts for nucleophilic additions to C=N bonds [53] prompted several research groups to investigate the feasibility of enantioselective transfer hydrogenations of imines (and related compounds) using Hantzsch esters. In general, bulky 2,2′-disubstituted BINOL-derived phosphoric acids **10** gave excellent results with many substrates combinations. In some cases, partially hydrogenated BINOL derivatives or C_2-symmetric catalysts based on other scaffolds gave advantages in terms of reactivity and selectivity (Fig. 2.5).

The enantioselective reduction of N-PMP ketimines using BINOL-derived catalysts **10** has been investigated by different research groups [54–56]. These studies showed that consistently high levels of chiral induction can be obtained in this reaction for structurally different imines, including challenging substrates such as 2-butanone PMP imine. Moreover, the imines can be efficiently generated *in situ* starting from the corresponding ketones and *p*-anisidine without altering the reaction outcome (Scheme 2.10). The origin of enantioselectivity for this type of reactions was investigated using different computational techniques. The calculations indicate that the bulky substituents in the 2 and 2′ positions of the catalyst control the binding geometry of substrate and Hantzsch ester. As a result, hydride transfer to the Z-iminium ion becomes energetically favoured and governs the stereochemical outcome of the reaction [51, 52].

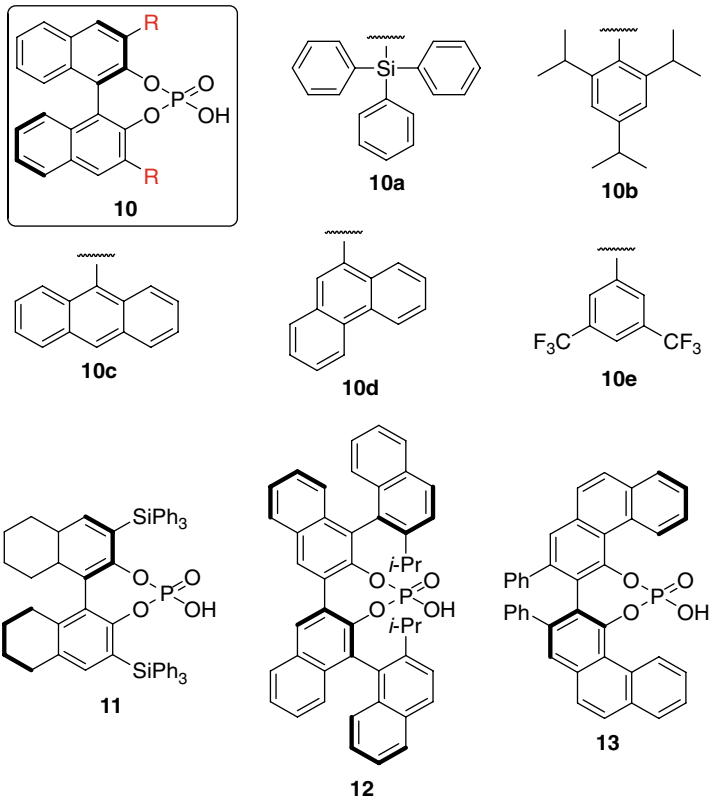
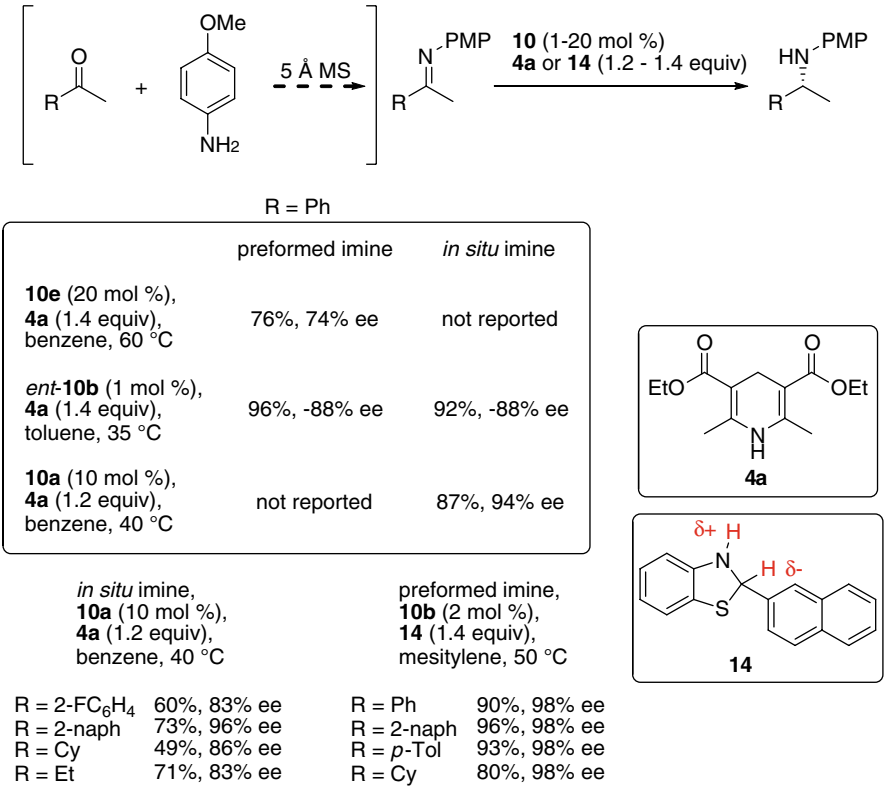


Fig. 2.5 C_2-symmetric phosphoric acid catalysts used for transfer hydrogenations

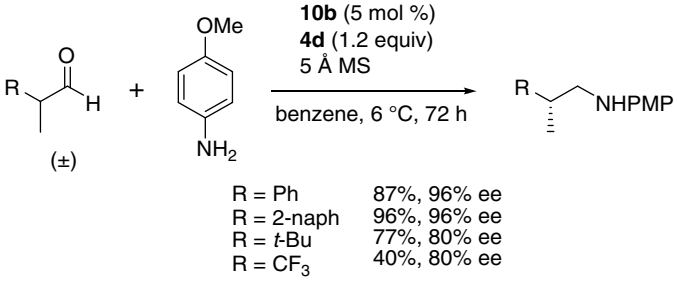
These results prompted other research groups to investigate the use of different catalysts and hydrogen donors for this type of transfer hydrogenation. A survey of different nucleotides containing Brønsted acid moieties revealed that adenosine 5′-diphosphate (ADP) can promote the reductive amination of ketones with *p*-anisidine, although with lower enantioselectivities compared to catalysts **10** [57]. Recent studies showed that benzothiazolines (such as **14**) can efficiently replace Hantzsch esters as hydrogen donors in this reaction under very similar conditions [58]. These compounds, which can be conveniently generated *in situ* from commercially available precursors, lead to occasionally higher enantiomeric excesses in the transfer hydrogenation of N-PMP ketimines. They have been recently exploited in a two-step reductive amination/aza-Michael asymmetric synthesis of tetrahydroisoquinolines and β-carbolines [59].

The ease of racemization of α-branched N-aryl aldimines in the presence of a Brønsted acid was exploited in a dynamic kinetic resolution *via* asymmetric transfer hydrogenation [60]. In this reaction, imines are formed *in situ* and hydride addition does not generate a new chiral center but takes place preferentially with one enantiomer of the substrate. As a result, (nearly) full conversion of an aldehyde to an



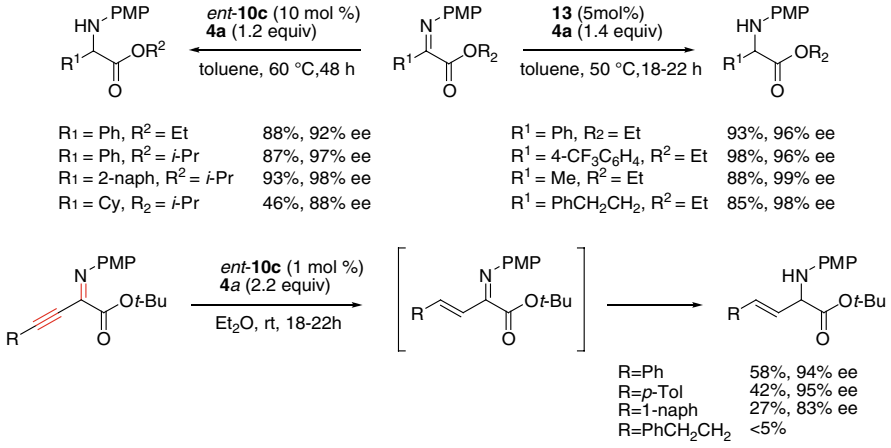
Scheme 2.10 Enantioselective reduction of N-PMP imines

enantiomerically enriched β-branched amine can be achieved using chiral phosphoric acid catalysis (Scheme 2.11). DFT calculations showed that, in this case, the presence of an α-substituent renders hydride transfer to the *E*-iminium energetically favored and the stereoselectivity of the hydride addition is governed by interactions between the catalyst's bulky substituents and the PMP group of the iminium ion [61].



Scheme 2.11 Dynamic kinetic resolution of aldehydes *via* organocatalytic transfer hydrogenation

α-Imino esters were also shown to be competent substrates for the enantioselective reduction using Hantzsch esters and phosphoric acid catalysts. In this reaction, giving access to valuable α-amino acids derivatives, VAPOL-derived catalyst **13** [62] performs somewhat better than BINOL derivatives **10** with respect to both activity and stereocontrol [63] (Scheme 2.12). Interestingly, the sense of stereoinduction for the hydride transfer was found to depend on the nature of the imine substituent, with alanine and phenylglycine derivatives precursors yielding opposite enantiomers. With respect to the nature of the hydrogen donor, benzothiazoline **14** also affords the reduction products with excellent enantiomeric excesses, sometimes higher than those obtained with Hantzsch ester **4a** [64].

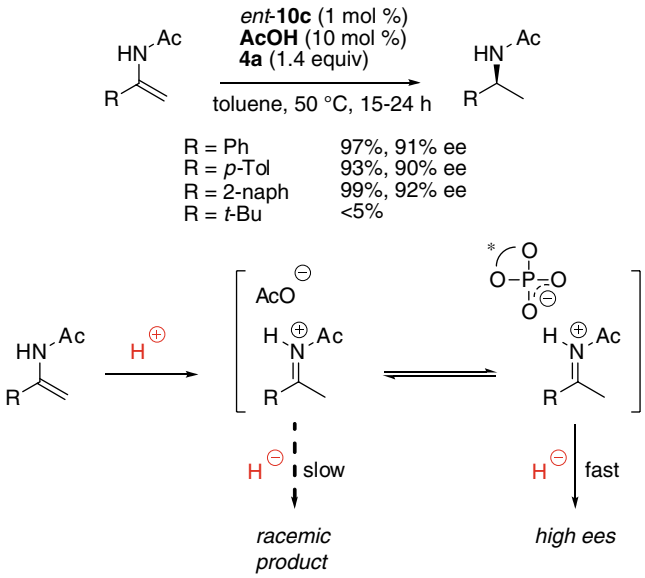


Scheme 2.12 Asymmetric reduction of α-imino esters

The scope of this reaction was expanded with the development of the asymmetric transfer hydrogenation of β-γ-alkynyl α-imino esters. In this reaction, both imine and alkyne undergo reduction to yield synthetically challenging *trans*-alkenyl amino acid derivatives [65]. It was shown that conjugate hydride transfer to the alkyne takes place first, as propargyl α-amino esters failed to undergo reduction under the reaction conditions.

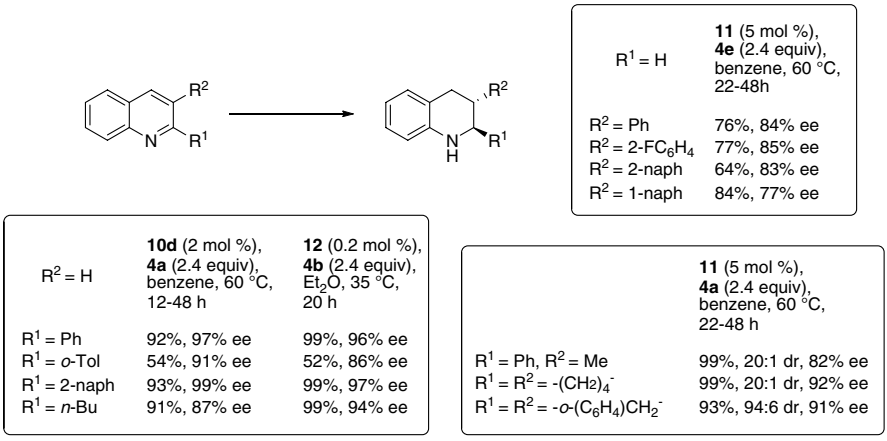
Enamides were explored as substrates for Brønsted acid organocatalytic reductions. While this reaction formally involves hydrogenation of a C=C bond, substrate protonation yields an iminium ion which is subsequently reduced by Hantzsch ester **4a** [66] (Scheme 2.13). Optimization of the reaction conditions revealed that the loading of phosphoric acid catalyst could be dramatically decreased while retaining high degrees of stereocontrol by using acetic acid as cocatalyst to increase the concentration of iminium ion in the reaction mixture.

The previously described double hydrogenation of quinolines to tetrahydroquinolines was also investigated with axially chiral phosphoric acid catalysts. 2-Substituted quinolines were readily reduced in high enantioselectivities using



Scheme 2.13 Enantioselective reduction of enamides using an achiral Brønsted acid cocatalyst

either BINOL-derived catalyst **10d** [67] or bulky phosphoric acid **12** [68] (Scheme 2.14). In the latter case, the catalyst loading could be substantially reduced while maintaining excellent levels of asymmetric induction. This methodology provides easy access to a variety of tetrahydroquinoline alkaloids with an alkyl



Scheme 2.14 Asymmetric transfer hydrogenation of quinolines

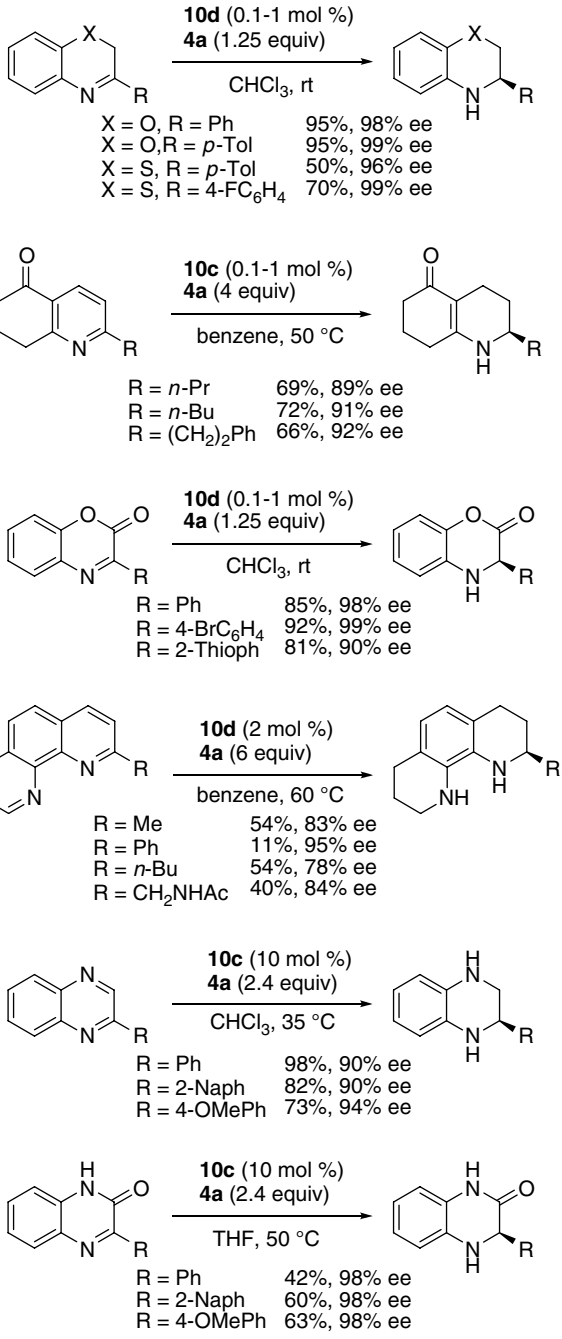
substituent at the 2-position. Asymmetric hydrogenation of 3-substituted quinolines was also successfully accomplished [69]. In this case, it is worth pointing out that the stereochemistry is determined by protonation of the 1,4-dihydroquinoline intermediate rather than by hydride transfer (see Scheme 2.9). Finally, 2,3-disubstituted quinolines were also shown to be competent substrates for this reaction, yielding products with two adjacent stereogenic centers in a *trans* relative arrangement [68].

This approach was later extended to the enantioselective transfer hydrogenation of other nitrogen heterocycles. Benzoxazines, benzothiazines and benzoxazinones were all reduced using remarkably low catalyst loadings with consistently high levels of asymmetric induction [70] (Scheme 2.15). 2-Substituted pyridines containing an electron-withdrawing group on C_3 could be reduced twice yielding chiral tetrahydropyridines with mostly high enantioselectivities [71]. 1,10-Phenanthrolines were also subjected to transfer hydrogenation using BINOL-derived phosphoric acid catalysts [72]. In this case, yields were generally less satisfactory. Finally, quinoxalines and quinoxalinones were shown to be competent substrates for organocatalytic transfer hydrogenation. However, significantly higher catalyst loadings were required to achieve full conversion in an acceptable reaction time [73].

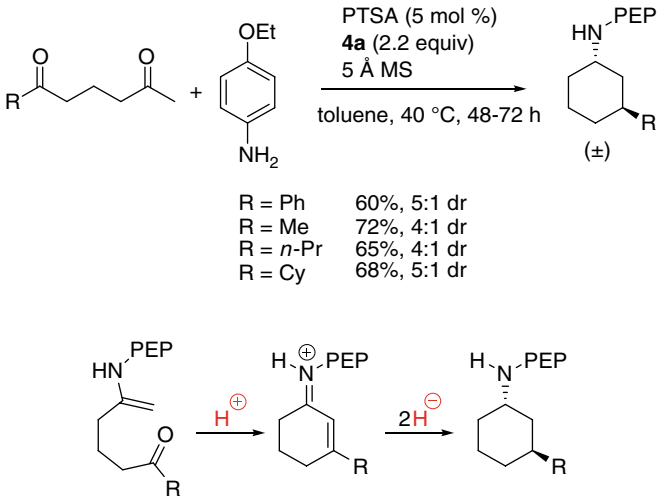
2.3.3 Cascade Processes

In addition to the example discussed in section 1.2.3, the complementary character of iminium and enamine mechanisms was also exploited for the transfer hydrogenation of C=N bonds. Reaction of δ-diketones with aromatic amines in the presence of a Hantzsch ester and an acid catalyst yields prevalently *trans*-disubstitued cyclohexylamines [74] (Scheme 2.16). In this transformation, the initially formed enamine undergoes cyclization yielding an α,β-unsaturated iminium ion which in turn reacts with two molecules of Hantzsch ester to liberate the final product. The acid catalyst is crucial to maintain a high concentration of the iminium ion in the reaction mixture.

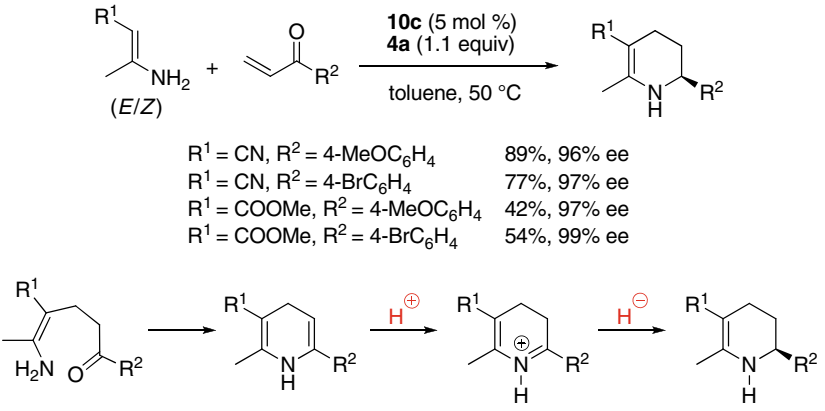
The previously described asymmetric hydrogenation of pyridines [71] was modified and implemented in a cascade sequence beginning with the reaction of an enamine with an α,β-unsaturated ketone [75]. Upon exposure to a Brønsted acid catalyst, these two reaction partners undergo a tandem Michael addition / cyclization yielding a 1,4-dihydropyridine derivative. Protonation of this intermediate provides the cationic substrate for the hydride transfer. A similar approach was used in the cascade synthesis of tetrahydroquinolines. In this case, however, generation of the substrate for transfer hydrogenation was accomplished using gold(I) catalysis. In short, propinyl-substituted anilines were cyclized to 1,4-dihydroquinolines and subsequently reduced by Hantzsch ester **4a** using catalyst **10d** [76]. The optical purities of the resulting adducts are comparable with those obtained in the Brønsted-acid catalyzed transfer hydrogenation [67] (Scheme 2.14).



Scheme 2.15 Enantioselective reduction of different nitrogen heterocycles



Scheme 2.16 Cascade enamine/iminium synthesis of cyclohexylamines. PEP = *p*-ethoxyphenyl; PTSA = *p*-toluenesulfonic acid



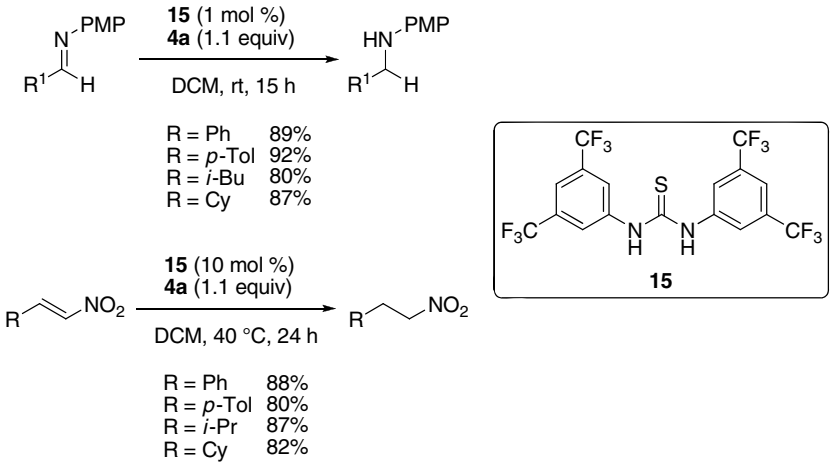
Scheme 2.17 Cascade synthesis of chiral dihydropyridines

2.4 Hydrogen Bonding Catalysis

2.4.1 Achiral Catalysts

The organocatalytic activation of electrophiles through (double) hydrogen bonding has been exploited in the transfer hydrogenation of imines and nitroolefins using Hanztsch esters. Unsubstituted thiourea was reported as efficient catalyst for the one-pot reductive amination of both aldehydes [77] and ketones [78] with various

aromatic amines. However, these results were heavily questioned by another research group who failed to reproduce them in their entirety. Instead, electron-poor thiourea **15** was described as an efficient promoter for the transfer hydrogenation of preformed N-PMP aldimines [79] (Scheme 2.18). The same catalyst was also successfully applied to the conjugate reduction of nitroalkenes [80]. Other substrates, such as chalcones, cyclic enones and acrolein derivatives failed to react under similar conditions.

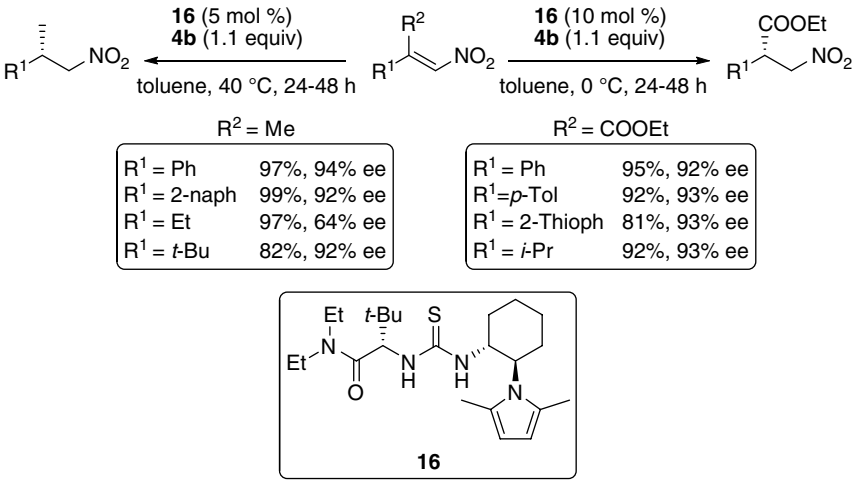


Scheme 2.18 Transfer hydrogenations using thiourea catalyst **15**

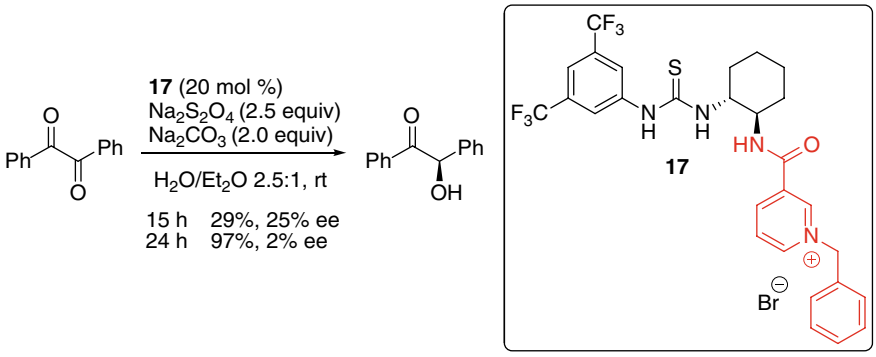
2.4.2 Chiral Catalysts

A highly enantioselective variant of the transfer hydrogenation of nitroolefins has been developed replacing thiourea **15** with chiral catalyst **16** [81, 82]. Using this protocol, β,β-disubstituted nitroalkenes can be reduced with high degrees of stereocontrol. Unlike in the case of α,β-unsaturated carbonyl compounds, the olefin geometry plays a key role in the stereochemical outcome of the reaction, as substrates in a 1:1 *E*/*Z* ratio yield substantially racemic product. Olefins containing an ester group as one of the β-substituents can be efficiently reduced to chiral β-nitroesters, valuable precursors for the synthesis of enantiomerically enriched β-amino acids (Scheme 2.19).

A chiral reductase mimic containing an electron-poor thiourea and an N-benzyl nicotinamide group was tested in the reduction of diketones (Scheme 2.20) [83]. So far, this compound (**17**) constitutes the only example of an organocatalyst incorporating a dihydropyridine group which can mediate the transfer hydrogenation of a substrate and be regenerated by a stoichiometric reducing agent (sodium dithionate). While the *in situ* regeneration of the dihydropyridine moiety was successfully demonstrated, the application of this catalyst to asymmetric reductions gave disappointing results, in that the products were found to undergo fast racemization under the reaction conditions.



Scheme 2.19 Enantioselective conjugate reduction of nitroolefins



Scheme 2.20 Transfer hydrogenation using a thiourea reductase mimic

2.5 Conclusions

The examples described in this chapter unambiguously show that asymmetric organocatalytic reductions using Hantzsch esters have quickly become a powerful tool for the synthesis of chiral compounds. The typical mildness of the reaction conditions coupled with the high chemoselectivity characterizing organocatalytic reactions render some of these protocols very attractive choices for an asymmetric reduction step at a late stage of a synthesis. On the other hand, the combination of these transfer hydrogenations with other catalytic reactions, which has been successfully demonstrated in some remarkable cascade processes, offers a variety of possibilities which still have to be fully explored. It is worth noting how metal-catalyzed

and organocatalyzed transfer hydrogenations are often complementary in scope and they should be regarded as two sides of the same coin. On the other hand, the atom economy of organocatalytic reductions using Hantzsch esters is poor, compound **4a** having a molecular weight of 253. For this reason, recycling of the pyridine byproduct or *in situ* regeneration of active reducing species should be further investigated in the coming years to render this approach attractive for preparative purposes. Considering the pace at which innovative discoveries in asymmetric organocatalysis are reported, it is reasonable to expect several new reductive processes exploiting the peculiar reactivity of dihydropyridines in the near future as well as greener methodologies for transfer hydrogenation making use of these intriguing compounds.

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