Chem Soc Rev

Cite this: *Chem. Soc. Rev.*, 2012, **41**, 2498–2518

www.rsc.org/csr

CRITICAL REVIEW

Transfer hydrogenation with Hantzsch esters and related organic hydride donors

Chao Zheng and Shu-Li You*

Received 27th September 2011
DOI: 10.1039/c1cs15268h

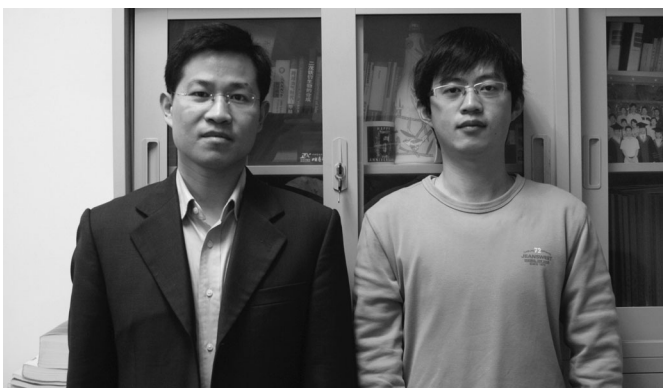
In recent years, Hantzsch esters and their related organic hydride donors have been widely utilized in biomimetic approaches of asymmetric transfer hydrogenation (ATH) reactions. Various compounds containing C═C, C═N and C═O unsaturated functionalities could be reduced in the presence of organocatalysts or transition metal complexes, affording versatile chiral building blocks in high yields and excellent enantioselectivities under mild conditions. In this *critical review*, recent advances in this area are summarized and classified according to unsaturated functional groups being reduced and catalytic systems employed (91 references).

Introduction

Asymmetric catalysis represents one of the most important research areas in modern synthetic chemistry since it provides quick access to various enantiopure compounds with only catalytic amounts of chiral molecules.[1] Among various successful asymmetric reactions, asymmetric hydrogenation has been most extensively studied in academia and widely applied in industry, which was exemplified by the fact that two prominent researchers in this field, Knowles and Noyori, were awarded the Nobel Prize in Chemistry in 2001.[2] In traditional asymmetric hydrogenation processes, hydrogen gas is typically used as the reducing agent with transition metal-based chiral catalysts,[2c–g] while in the case of asymmetric transfer hydrogenation, isopropanol and formic acid are the most frequently employed hydrogen sources.[2f] Although most of these transition metal-catalyzed processes show high reactivity and selectivity, some of them still suffer from considerable drawbacks including limited substrate scope, difficulty in catalyst separation and recycling as well as the danger in handling high pressure of hydrogen gas.

Nature, on the other hand, performs the asymmetric transfer hydrogenations (ATH) in an amazing way in biological systems, taking advantage of enzymes and organic hydride reduction cofactors such as NADH **1a**, NADPH **1b** and $FADH_2$ **2**.[3] Inspired by the manner that nature conducts reduction, chemists have developed a biomimetic ATH approach employing Hantzsch ester **3**[4] and some other heterocyclic compounds as good NADH mimics in the presence of catalytic amount of small organic molecules or metal complexes (Fig. 1). Over the past few years there have been significant developments in this area. Double bonds such as C═C, C═N and C═O can be

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China. E-mail: slyou@sioc.ac.cn; Web: http://shuliyou.sioc.ac.cn/; Fax: (+86) 21-5492-5087; Tel: (+86) 21-5492-5085



Shuli You and Chao Zheng

Chao Zheng was born in 1985 in Hubei province, China and received his BSc degree in Chemistry from Shanghai Jiao Tong University in 2007. Then he joined Professor Shuli You's group at Shanghai Institute of Organic Chemistry as a PhD student. His current work focuses on understanding reaction mechanisms through computational method.

Dr Shu-Li You received his BSc in chemistry from Nankai University in 1996. He obtained his PhD from the Shanghai Institute of Organic Chemistry (SIOC) in 2001 under the supervision of Prof. Li-Xin Dai before doing postdoctoral studies with Prof. Jeffery W. Kelly at The Scripps Research Institute. From 2004, he worked at the Genomics Institute of the Novartis Research Foundation as a Principal Investigator before returning to SIOC in 2006. His research interests include asymmetric catalysis, synthetic methodology, natural product synthesis, as well as medicinal chemistry.

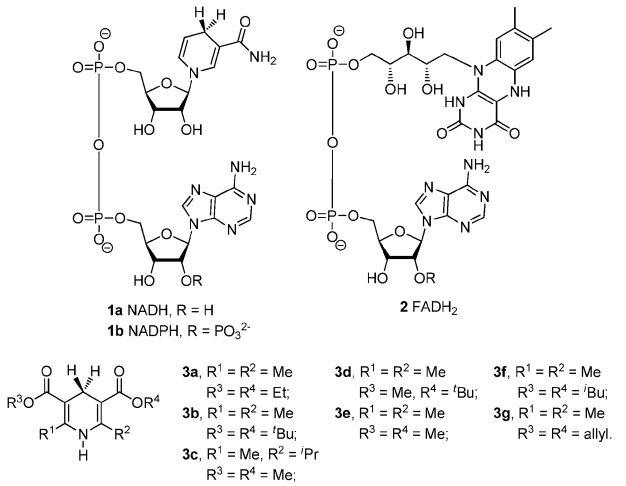


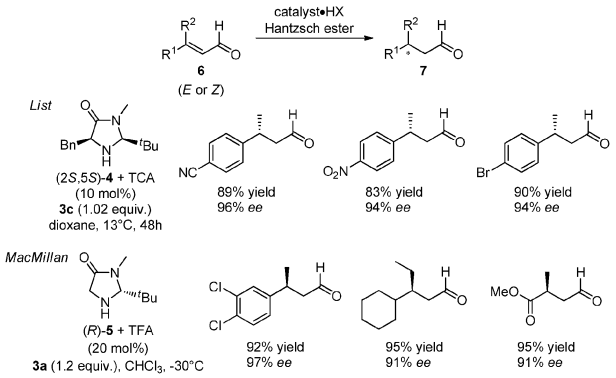
Fig. 1 The structures of naturally occurring hydride-reduction cofactors and Hantzsch esters.

successfully reduced affording versatile chiral building blocks in high yields with typically excellent *ee*s under mild conditions. A great deal of useful methodologies were reported and led to many practical syntheses of complex molecules and natural products.[5]

In this critical review, we will discuss the use of Hantzsch esters and related organic hydride donors in transfer hydrogenation reactions which is classified by the reduced functional groups and catalytic systems, with a focus on the recent advance (mainly after 2004) on *catalytic asymmetric* reactions by organocatalysts or transition metal-catalysts. Theoretical investigations on the origin of the enantioselectivity and some non-enantioselective but intriguing works will also be covered.[6] In addition, we present here a very brief discussion about some recent studies on the understanding of the fundamental thermodynamic properties of organic hydride donors. This aspect was seldom mentioned in previous reviews on Hantzsch ester-mediated ATH reactions.

Catalytic ATH reactions of C=C double bonds

Although the Hantzsch ester-mediated reduction has been established for a long time, it wasn't until 2004 that the first catalytic ATH reaction of activated C=C double bond was reported, owing to the emergence of the concept of iminium activation.[7] By using the chiral secondary amine catalyst (2*S*,5*S*)-**4** in conjunction with trichloroacetic acid (TCA), List and co-workers[8] demonstrated the ATH reaction of α,β-unsaturated aldehydes with Hantzsch ester **3c** as the hydride donor. Electron-poor aromatic substituted substrates typically gave good yields and *ee*s. Almost at the same time, MacMillan *et al.*[9] reported a very similar strategy to accomplish the ATH reaction of α,β-unsaturated aldehydes. Chiral amine catalyst (*R*)-**5** and trifluoroacetic acid (TFA) proved to be the best catalyst combination. The substrate scope here is relatively broader – aromatic and aliphatic substituted and even some functionalized α,β-unsaturated aldehydes can be tolerated (Scheme 1). These reactions demonstrated high chemoselectivity given the fact that the carbonyl group of the α,β-unsaturated aldehydes remain untouched during the reduction process.



Scheme 1 Catalytic ATH reaction of α,β-unsaturated aldehydes by List and MacMillan.

This method was later employed by Paterson and Miller[10] in the total synthesis of marine macrolide (+)-neopeltolide.

Another attractive advantage of these reactions is the *enantioconvergence*, a highly desired yet rare feature of a catalytic asymmetric reaction. The geometry of the double bond in the starting materials has little effect on the enantioselectivity of the final products. It was proposed that the *E*- and *Z*-α,β-unsaturated iminium ion intermediates are in a fast equilibrium *via* a conjugate dienamine species. The subsequent rate-limiting hydride transfer proceeds much easier with the *E*-isomer [$k(E) > k(Z)$], which predominantly affords the (*R*)-product (Fig. 2). This feature permits the use of starting materials with low geometric purity, which undoubtedly enhances the practical utility of this operationally simple asymmetric reduction. Notably, NADH was not a viable reagent for this hydrogenation and the reaction with *N*-benzylnicotinamide was quite selective but in a much lower conversion.[9]

In 2009, Cossy and co-workers[11] extended the substrate scope of the above ATH reaction to β-azole containing α,β-unsaturated aldehydes. Chiral secondary amine (2*R*,5*R*)-**4** or (*R*)-**5** was identified as the optimal catalyst in the presence of TFA. A set of oxazole and thiazole substituted α,β-unsaturated aldehydes **8** could be converted to the corresponding chiral alcohols **9** with up to 84% yield and 94% *ee* after a subsequent sodium borohydride reduction (Scheme 2). This simple process was further applied to the synthesis of the C7–C14 fragment of ulapualide A, a natural product that exhibits promising antitumor activity.

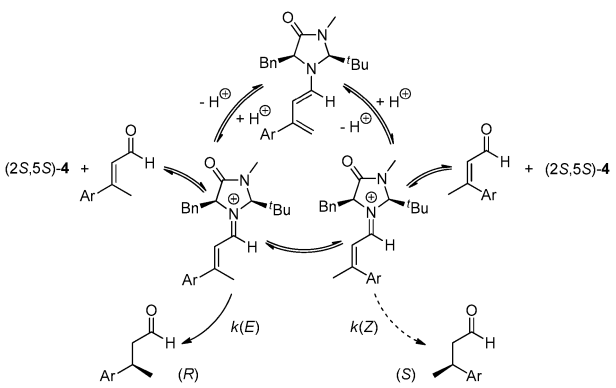
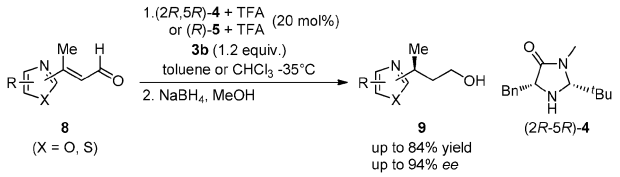


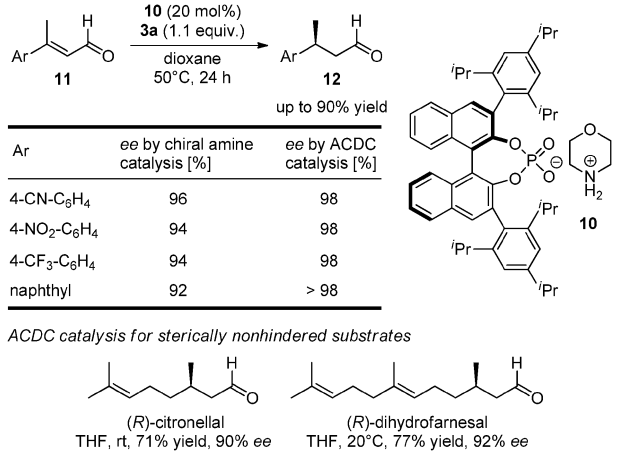
Fig. 2 The proposed mechanism of the ATH reaction catalyzed by chiral secondary amine and the origin of the enantioconvergence.



Scheme 2 Catalytic ATH reaction of β-azole containing α,β-unsaturated aldehydes by Cossy.

Instead of using a chiral secondary amine in conjunction with an achiral acid, Mayer and List[12] developed a different strategy called asymmetric counteranion-directed catalysis (ACDC),[13] expecting that the chiral counteranion could induce the enantioselectivity of the reaction. After screening different combinations of various commercially available primary and secondary amines with BINOL-derived chiral phosphoric acids, they found the sterically demanding TRIP anion (TRIP: 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate) exhibited remarkable asymmetric inducing ability with morpholinium ion **10** in the ATH reaction of α,β-unsaturated aldehydes. As shown in Scheme 3, for a series of aromatic substituted substrates **11**, the ACDC strategy could offer higher *ee*s than the previous chiral secondary amine catalytic system. Additionally, taking advantage of the chiral environment generated by the large counteranion, the ACDC strategy also worked well for sterically *nonhindered* aliphatic substrates. For example, (*R*)-citronellal and (*R*)-dihydrofarnesal could be obtained from the corresponding α,β-unsaturated aldehydes with 90% and 92% *ee*s using this method. Chiral amine catalysts (2*S*,5*S*)-**4** and (*S*)-**5** were less effective. Only 40% *ee* of (*R*)-citronellal was given when either of them was used.

Kudo *et al.*[14] recently disclosed that a resin-supported *N*-terminal prolyl peptide with a β-turn motif and hydrophobic polyleucine tether could effectively catalyze the ATH reaction of α,β-unsaturated aldehydes with Hantzsch esters in aqueous media (THF/H_2O).[15] The yields and *ee*s of the products could be obtained up to 76% and 96%, respectively. The investigation elucidated that the peptide catalyst could form active iminium species with its prolyl segment. The polyleucine chain was able to provide a hydrophobic microenvironment and was essential for both reaction efficiency and enantioselectivity.



Ar	*ee* by chiral amine catalysis [%]	*ee* by ACDC catalysis [%]
4-CN-C_6H_4	96	98
4-NO_2-C_6H_4	94	98
4-CF_3-C_6H_4	94	98
naphthyl	92	> 98

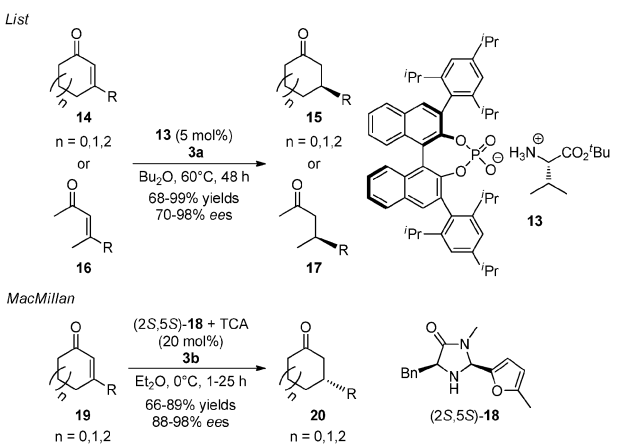
Scheme 3 ACDC strategy in ATH reaction of α,β-unsaturated aldehydes by List.

An obvious question after the success of the ATH reaction of α,β-unsaturated aldehydes with Hantzsch esters was whether these processes could be applied to α,β-unsaturated ketones. Neither the previously reported ACDC strategy nor the chiral imidazolinone catalysts mentioned previously could give satisfying results, mainly due to the fact that ketones are sterically and electronically deactivated toward iminium formation. After a survey of various sterically reduced primary amine catalysts, Martin and List[16] found the salt of chiral valine *t*-butyl ester with TRIP anion **13** was optimal to catalyze the ATH reaction of cyclic α,β-unsaturated ketones with the Hantzsch ester **3a** as the hydride source. Excellent *ee*s could be obtained for five- to seven-membered-ring substrates **14**. Noticeably, acyclic α,β-unsaturated ketones **16** could also be tolerated (Scheme 4, top).

At the same time, MacMillan and co-workers[17] demonstrated a simple protocol of the ATH reaction of α,β-unsaturated ketones by using the furyl-derived imidazolinone catalyst (2*S*,5*S*)-**18** which has previously enabled enantioselective Diels–Alder reactions with cyclic enones.[18] Hantzsch ester **3b** was found to be the best hydride donor. A series of cyclic α,β-unsaturated ketones **19** were suitable substrates, affording the hydrogenated products in high yields and *ee*s (Scheme 4, bottom).

Houk and co-workers[19] conducted theoretical investigations on the ATH reaction of α,β-unsaturated ketones (**19**, n = 0, R = Ph) catalyzed by chiral imidazolinonium salt. DFT calculations at the B3LYP/6-31G(d) level of theory suggested that the *E*-iminium ion should be the favored intermediate when (2*S*,5*S*)-**18** was used as the catalyst. The Hantzsch ester transferred the hydride preferentially from the less hindered *bottom* face of the iminium moiety (opposite from the benzyl and furyl group) in an *anti* way. The calculated energetic barrier of this transition state was 1.1 kcal mol^{-1} lower than its diastereomeric counterpart, which resulted in the experimentally observed enantioselectivity (Fig. 3).

ATH reactions with Hantzsch esters were also found compatible with chiral thiourea catalysis.[20] List *et al.*[21] discovered the ATH reaction of β,β-disubstituted nitroolefins and β-nitroacrylates by utilizing chiral thiourea catalyst **21** and Hantzsch ester **3b** as the hydride source. The reactions showed high reactivity and



Scheme 4 Catalytic ATH reaction of α,β-unsaturated ketones by List and MacMillan.

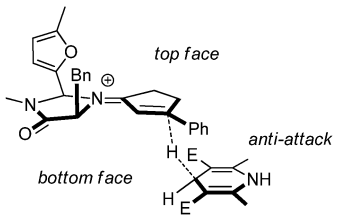
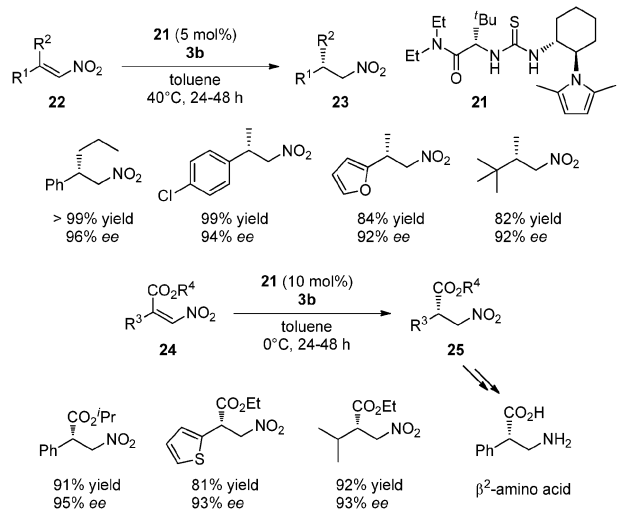


Fig. 3 Schematic structures of the critical transition state for the ATH reactions of cyclic α,β-unsaturated ketone suggested by Houk.



Scheme 5 Catalytic ATH reaction of β,β-disubstituted nitroolefins and β-nitroacrylates by List.

enantioselectivity with a broad substrate scope. Various aromatic and aliphatic nitroolefins **22** and β-nitroacrylates **24** could be reduced to their corresponding hydrogenated products with up to 99% yield and 96% *ee* (Scheme 5). In addition, the obtained β-nitroesters were easily converted into β^2-amino acids, a class of compounds with potentially biological and medicinal applications which are difficult to access with other methods.[22]

In contrast to the stereoconvergence phenomenon observed in the ATH reaction of α,β-unsaturated aldehyde by iminium activation, the absolute configuration of the nitroolefin reduction by thiourea catalysis strongly depends on the geometry of the double bond in the substrates. For instance, reduction of *E*- or *Z*-**26** gave opposite enantiomers of **27** with high enantioselectivity while that of a 1 : 1 mixture resulted in a racemic product. However, by adding a catalytic amount of PPh_3, the stereoconvergence could be observed with (*R*)-**27** as the major product. The authors suggested that the additive creates a rapid equilibrium between *E*- and *Z*-**26** through a conjugate addition/elimination pathway, and the reaction of the *E*-isomer is faster than that of the *Z*-isomer (Fig. 4).

Recently, Paradies and co-workers[23] disclosed that bifunctional thioureas derived from commercially available and readily accessible chiral amino alcohols could be used as new catalysts for the ATH reactions of nitroolefins with Hantzsch esters. After an intensive screening of catalysts, chiral thiourea with a primary alcohol functionality **28** was identified as the optimal one, displaying high activity (up to 99% yield) and moderate

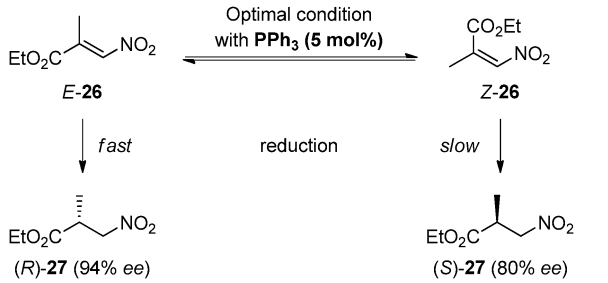
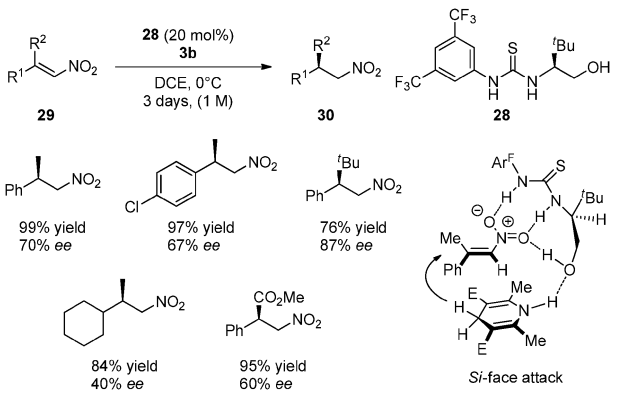


Fig. 4 Effect of the olefin geometry on enantioselectivity in ATH reaction of α,β-nitroacrylates.



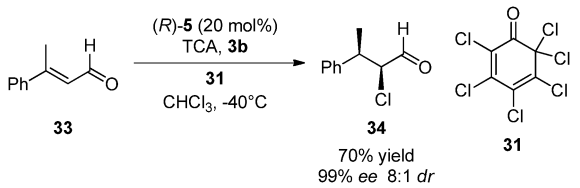
Scheme 6 Catalytic ATH reaction with nitroolefins using bifunctional thiourea by Paradies.

to good enantioselectivity (up to 87% *ee*) with various nitroolefins and nitroacrylates **29**. The hydroxyl group was found to be essential for forming a ternary complex with both the substrate and the hydride donor through H-bonds with nitro group and N–H moiety in the Hantzsch ester (Scheme 6). Reactions with the O–TMS protected catalyst led to lower yield and diminished *ee*. Removal of the hydroxyl group or using N–Me protected Hantzsch esters only gave racemic products with poor yields.

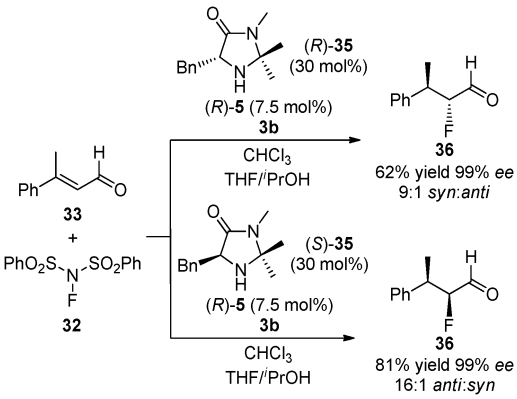
A distinct difference between the ATH reaction of activated C=C double bonds with Hantzsch esters and the traditional transition-metal-catalyzed hydrogenation process is the stepwise nucleophilic addition of hydride, generating a nucleophile *in situ* that could be captured by external electrophilic reagents. This reaction mode provides unique opportunities for quick construction of complex molecules with multi-chiral centers or polycyclic structures through *cascade* reactions. This idea was first realized by MacMillan *et al.* and List *et al.* independently.

MacMillan *et al.*[24] developed an enantioselective organocatalytic cascade by combining the ATH reaction of α,β-unsaturated aldehydes with Hantzsch esters and halogenation with electrophilic chlorine and fluorine source (**31**, **32**), which effectively allowed the formal asymmetric addition of HCl and HF across trisubstituted olefins **33** with excellent enantio- and diastereoselectivity (Schemes 7 and 8). Notably, the superior yields indicate the high chemoselectivity of the reaction sequence, that is, the hydride source should be consumed before the next electrophilic addition took place.

Remarkably, the authors emphasized rapid access to complex molecular architecture by using two different amine



Scheme 7 Organocatalytic cascade for ATH and chlorination reaction of α,β-unsaturated aldehydes by MacMillan.

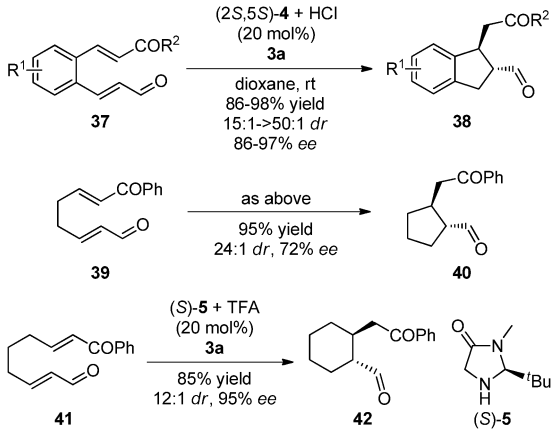


Scheme 8 Organocatalytic cascade for ATH and fluorination reaction of α,β-unsaturated aldehydes by MacMillan.

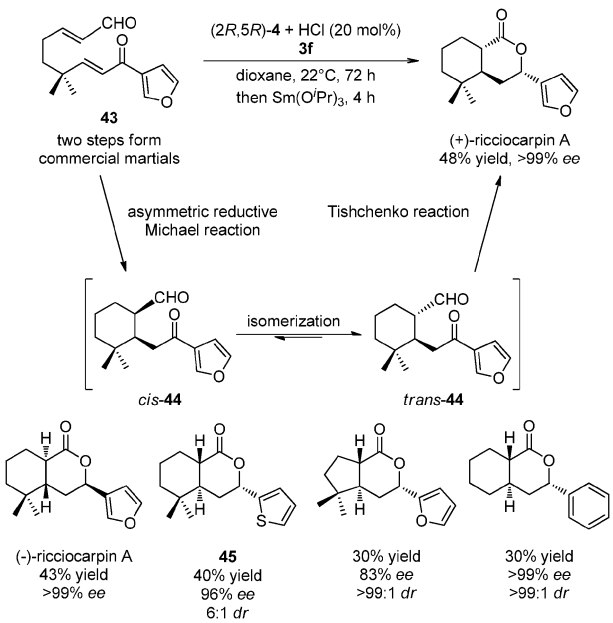
catalysts to deliver the required diastereo- and enantioselective outcomes. The configurations of the two chiral centers generated in these two distinct catalytic cycles were fully controlled by different catalysts. For instance, with (*S*)-**35** (30 mol%) and (*R*)-**5** (7.5 mol%) as the catalysts, **36** was obtained in 81% yield with 99% *ee* and 16 : 1 *dr* in favor of the *anti* isomer. The *syn* isomer could be accessed with 9 : 1 *dr* and 99% *ee* simply by switching (*S*)-**35** to (*R*)-**35** in the catalyst combination (Scheme 8).

Instead of using electrophilic sources for halogenation, List and co-workers[25] incorporated an intramolecular α,β-unsaturated ketone moiety as the nucleophile acceptor. Since α,β-unsaturated aldehydes generally exhibit higher reactivity in the ATH reaction with Hantzsch esters, the α,β-unsaturated ketone structure was expected to trap the *in situ* generated enamine, accomplishing the asymmetric reductive Michael cyclization. With chiral secondary amine catalyst (2*S*,5*S*)-**4** and Hantzsch ester **3a**, various aromatic enal enone substrates **37** underwent asymmetric reductive Michael cyclization, affording functionalized *trans* disubstituted rings **38** with excellent diastereo- and enantioselectivities. Moreover, aliphatic enals (**39**, **41**) were also viable substrates. The corresponding five- or six-membered ring products (**40**, **42**) could be obtained with high yields in enantio-enriched form when (2*S*,5*S*)-**4** or (*S*)-**5** was used as the catalyst (Scheme 9).

In 2009, Michrowska and List[26] applied the asymmetric reductive Michael addition strategy to the concise synthesis of natural product ricciocarpin A. As shown in Scheme 10, enal substrate **43**, which could be prepared straightforwardly in two steps from commercially available starting materials, was subjected to the asymmetric reductive Michael condition (catalyst (2*R*,5*R*)-**4** and Hantzsch ester **3f**) to generate ketoaldehyde intermediate **44**. Although this intermediate was first obtained as the



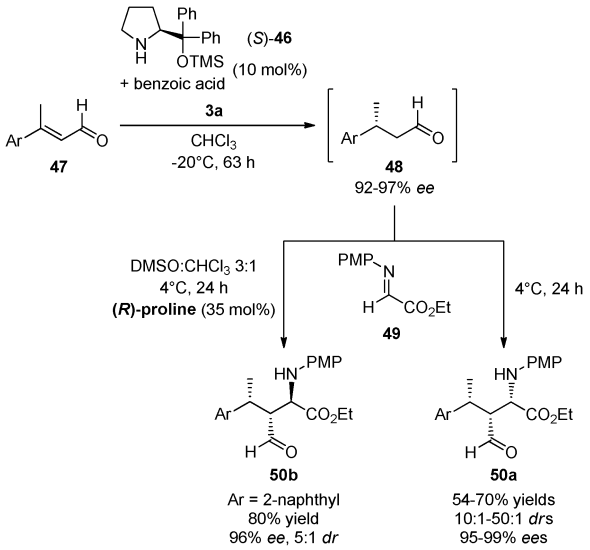
Scheme 9 The catalytic asymmetric reductive Michael cyclization by List.



Scheme 10 Asymmetric reductive Michael–Tishchenko cascade reaction and concise syntheses of ricciocarpin A and its analogs by List.

undesired *cis*-isomer (2 : 1, 79% yield), subsequent treatment with $Sm(O^iPr)_3$ could promote the isomerization to the thermodynamically more stabilized *trans*-isomer following Tishchenko reaction to give (+)-ricciocarpin A as a single diastereomer (>99% *ee*) in 48% yield. With this efficient protocol, several analogs of this natural product were also synthesized, one of which (**45**) exhibited significantly improved molluscicidal activity.

Shortly after MacMillan and List's initial works, Zhao and Córdova[27] reported another elegant example of a cascade reaction by employing α-imino esters as the external electrophiles. Chiral pyrrolidines were found to catalyze the ATH reaction of α,β-unsaturated aldehydes **47** with Hantzsch ester **3a** as the hydride source. The enantioenriched hydrogenated compounds **48** (92–97% *ee*) could react with α-imino ester **49** within the same catalytic system to form the final products **50a**, bearing three contiguous stereocenters with high chemo-, diastereo- and enantioselectivity (10 : 1–50 : 1 *dr*s and 95–99% *ee*s). The other

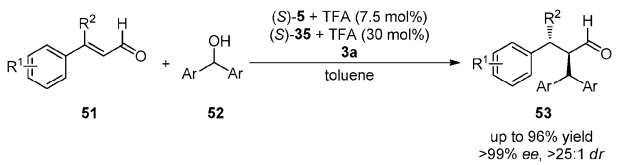


Scheme 11 The catalytic asymmetric reductive Mannich reaction by Córdova.

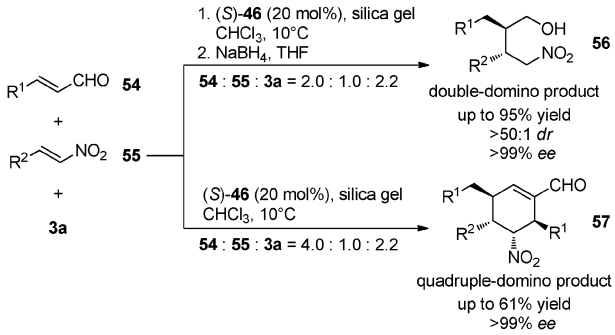
diastereomers **50b** could also be achieved by this reductive Mannich protocol when a catalytic amount of (*R*)-proline was added to the reaction mixture together with the α-imino ester (Scheme 11).

Recently, Jiao *et al.*[28] reported a catalytic cascade of ATH reaction and alkylation of α,β-unsaturated aldehydes. The authors employed secondary amine catalysts (7.5 mol% of (*S*)-**5** + TFA and 30 mol% of (*S*)-**35** + TFA) and Hantzsch ester **3a** as the hydride donor. A series of different α,β-unsaturated aldehydes **51** could be reduced and the *in situ* formed nucleophilic intermediate then reacted with the carbocation species generated from diarylalcohols **52** to give the final alkylated products **53** with good *ee*s and *dr*s (Scheme 12). In this transformation, the chiral ammonium salts played three kinds of catalytic functions including iminium catalysis, enamine catalysis and acid catalysis. Similar to the reports from List and MacMillan, the geometry of the double bonds in the starting materials has limited influence on the absolute configuration of the reduced products.

Another recent contribution to the field of organocatalytic cascades involving ATH reaction of α,β-unsaturated aldehydes was reported by Rueping and co-workers.[29] With chiral pyrrolidine (*S*)-**46** as the catalyst, unsaturated aldehydes **54** could be reduced by Hantzsch ester **3a** in the presence of nitroolefin **55**. Subsequent Michael addition was then promoted by the same catalytic system allowing highly enantioselective construction of nitroaldehydes which are useful synthons for the preparation of biologically relevant and synthetically valuable δ-amino alcohol and γ-amino acid derivatives. Interestingly, by simply increasing



Scheme 12 The catalytic asymmetric reductive alkylation reaction by Jiao.

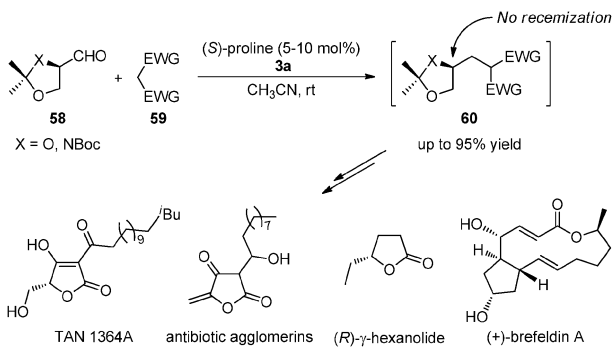


Scheme 13 Organocatalytic double and quadruple-domino reaction by Rueping.

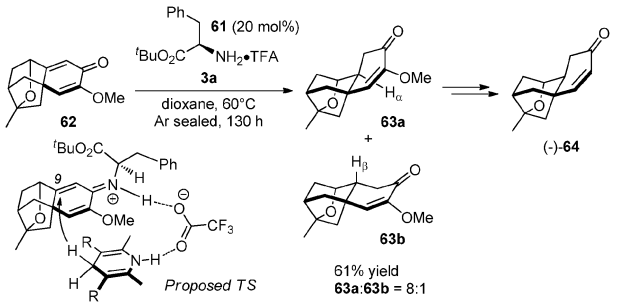
the concentration of aldehyde substrates, a second Michael addition of the nitroaldehyde intermediate to the α,β-unsaturated aldehyde could occur to furnish a quadruple-domino synthesis yielding the cyclic products **57** bearing four consecutive chiral centers with excellent stereoselectivities (Scheme 13).

Ramachary's group[30] systematically studied the catalytic multi-component cascade reactions (Knoevenagel/hydrogenation/alkylation *etc.*) to construct a variety of chiral building blocks. In one of their recent works,[30f] for example, they showed that (*R*)-glyceraldehyde acetonide (**58**, X = O) and (*S*)-Garner aldehyde derivatives (**58**, X = NBoc) are suitable substrates for (*S*)-proline-catalyzed cascade reductive alkylations. Chiral aldehyde **58** was first condensed with various active methylene compounds **59** and then reduced by Hantzsch ester to give valuable building block **60** in high yield without racemization of the α-position to the carbonyl group. The formal synthesis of many natural products and useful target molecules could be achieved based on this methodology (Scheme 14).

Eey and Lear[31] recently applied the chiral amine catalyzed ATH reaction in the synthesis of the key intermediate (−)-**64** of (−)-platensimycin. Although several common hydrogenation methods failed to give satisfactory chemo- and stereoselectivity in the conjugate reduction of the dearomatized substrate, the authors eventually found that the *t*-butyl-ester of (*R*)-phenylalanine **61** together with TFA was the optimal catalyst which promoted the Hantzsch ester **3a** to attack the C9 preferentially from the less hindered bottom face, giving the desired isomer **63a** in a reasonable yield (61%, **63a** : **63b** = 8 : 1) (Scheme 15).



Scheme 14 Organo-catalyzed multi-component reductive alkylation reaction by Ramachary.



Scheme 15 Organocatalyzed ATH reaction in the synthesis of the key intermedeate of (−)-platensimycin by Lear.

Catalytic ATH reactions of C═N double bonds

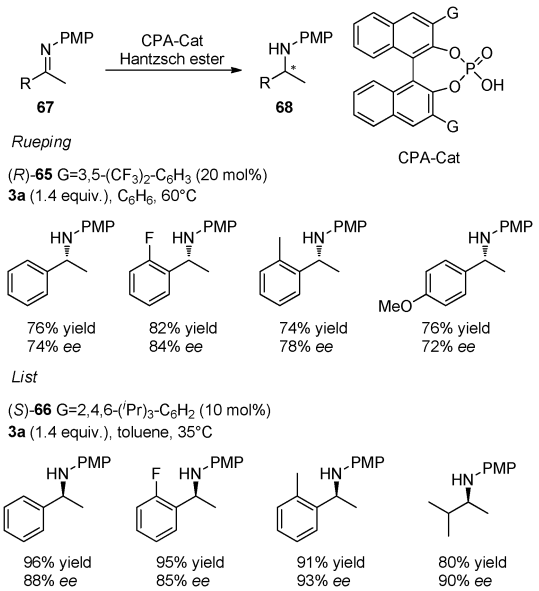
The first report on the catalytic ATH reaction of C═N double bonds with Hantzsch esters could date back to 1989. Singh and Batra[32] used various chiral α-amino acids, camphor sulfonic acid, abietic acid and tartaric acid to catalyze the reduction of prochiral imines using **3a** as the hydride donor. To our knowledge, no related work was reported in the following years before 2005 when chiral phosphoric acids (CPA) emerged and showed high activity in activating the imine group,[33] which led to a boost in the field of catalytic ATH reactions of C═N double bonds.

Rueping *et al.*[34] found that chiral phosphoric acid was an effective catalyst in the ATH reaction of ketimines. With 20 mol% of (*R*)-**65** as the catalyst, various PMP-protected (PMP: *p*-methoxylphenyl) aryl methyl ketimines **67** underwent the transfer hydrogenation reaction with Hantzsch ester **3a** in benzene at 60 °C, affording the desired amine products **68** in good yields (46–91%) and *ee*s (70–84%). Different substituents on the aryl moiety have little effect on the outcome of the reaction. In the parallel studies from List's group,[35] the sterically hindered (*S*)-**66** was identified as the optimal catalyst. Good to excellent yields (80–98%) and *ee*s (80–93%) could be attained for aryl methyl ketimines in the presence of Hantzsch ester **3a** under milder conditions (toluene, 35 °C). Noticeably, the relatively less reactive isopropyl methyl ketimine was also well tolerated (Scheme 16).

Both authors proposed a similar catalytic cycle which is initiated by protonation of the ketimine substrate with the CPA catalysts. The resulting iminium intermediate is chiral and its reaction towards the Hantzsch ester could give the enantioenriched amine and pyridine byproduct, and the catalyst is then regenerated (Fig. 5a).

In order to deeply understand the reaction mechanism and elucidate the origin of the observed enantioselectivity, DFT calculations on chiral phosphoric acid-catalyzed ATH reaction of ketimines have been conducted by Goodman *et al.*[36] and Himo *et al.*[37] All of the studies suggest that chiral phosphoric acid acts as a bifunctional catalyst in which the acidic proton and the P═O moiety of the catalyst form the hydrogen bond with imine and Hantzsch ester, respectively. The well-defined cyclic transition state structure well explains the high level of enantioselectivity of the reaction.

The geometry of the imine is also crucial in understanding the enantioselectivity because the hydride addition on the same face of the *Z*- and *E*-imine will yield opposite enantiomers of



Scheme 16 Catalytic ATH reaction of simple ketimines by Rueping and List.

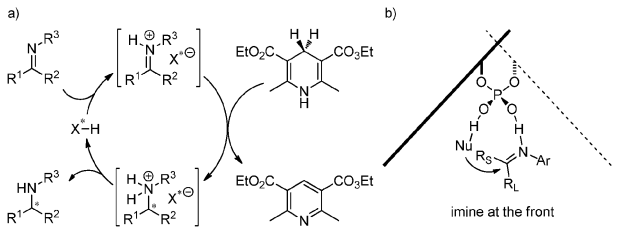
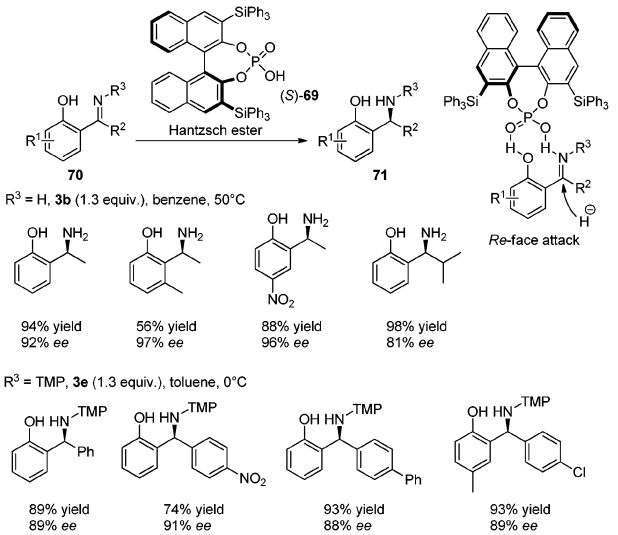


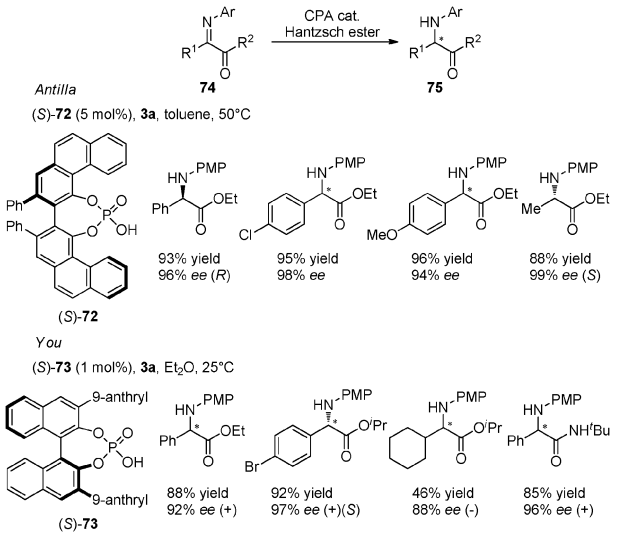
Fig. 5 (a) The proposed catalytic cycle of chiral phosphoric acid-catalyzed ATH reaction of imines. (b) The schematic description of the key transition state for predicting the stereochemistry of the reaction.

the amine product. Although the *E*-imine is generally the more stabilized isomer in the ground state, the transition state with the *Z*-imine is lower in energy according to the calculation study. Meanwhile, this geometric arrangement also reduces the steric congestion between the bulky groups of the catalyst and imine substrate. Based on these results, a simplified working model for predicting the stereochemistry of the chiral phosphoric acid-catalyzed ATH reaction of ketimine has been proposed. The imine substrate reacts with the catalyst in the *Z*-form with the *N*-phenyl and the largest substituent away from the bulky catalyst. The Hantzsch ester then interacts with the other phosphoryl oxygen of the catalyst and delivers the hydride from the corresponding face (Fig. 5b).

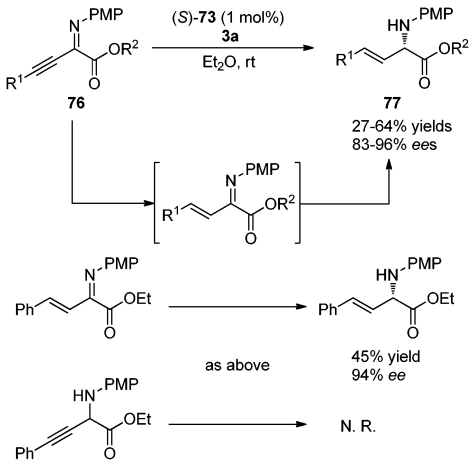
The reaction scope of the chiral phosphoric acid-catalyzed ATH of ketimines has been extended to a series of functionalized imines. In 2010, Wang and co-workers[38] demonstrated chiral phosphoric acid-catalyzed ATH reactions of unprotected *ortho*-hydroxyaryl alkyl N–H ketimines. In the presence of a catalytic amount of (*S*)-**69** and Hantzsch ester **3b** as the hydride source, substrates bearing various functional groups could be converted to the corresponding hydrogenated products with up to 98% yield and 99% *ee*. Different from the previously reported *N*-protected ketimines, ^{1}H NMR experiment indicated the hydroxyl group on the phenyl ring plays an important role



Scheme 17 Catalytic ATH reaction of *ortho*-hydroxyaryl ketimines by Wang.



Scheme 18 Catalytic ATH reaction of α-imino esters by Antilla and You.



Scheme 19 Catalytic ATH reaction of β,γ-alkynyl α-imino esters by You.

in the reaction. The phenolic OH originally could form a strong intramolecular H-bond with the imine nitrogen. However, the catalyst was capable of breaking this intramolecular H-bond by establishing two intermolecular H-bonds with imine and hydroxyl moieties. The cyclic transition state structure may account for the high enantioselectivity of the reaction. Shortly after this success, Wang *et al.*[39] reported another work in which the *N*-TMP protected (TMP: 3,4,5-trimethoxylphenyl) *ortho*-hydroxybenzophenone ketimines could be reduced under very similar ATH conditions (Scheme 17).

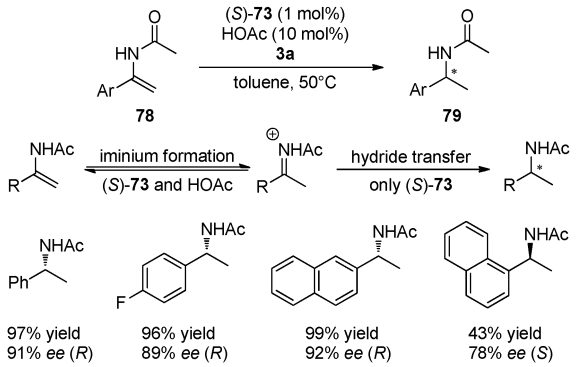
α-Imino esters are attractive substrates for catalytic ATH reactions because they can provide simple and straightforward access to various chiral α-amino acid derivatives. This idea was achieved by Antilla *et al.* and You *et al.* independently. By using VAPOL-derived chiral phosphoric acid (*S*)-**72**, together with Hantzsch ester **3a**, a variety of α-imino esters **74** were converted to the corresponding α-amino esters **75** by Antilla *et al.*[40] with high efficiency (85–98% yields, 94–99% *ee*s). Interestingly, the product with the opposite configuration could be obtained by simply switching the R^1 group from aryl to methyl. In the report by You *et al.*,[41] with chiral phosphoric acid (*S*)-**73** as the optimal catalyst, high yields (up to 95%) and excellent enantioselectivites (up to 98% *ee*) were obtained with various α-imino esters. Notably, *N*-*t*-butyl α-imino amide was also a viable substrate (Scheme 18).

Unprecedented results were observed by You and co-workers[42] when they tried to expand the reaction scope to β,γ-alkynyl α-imino esters **76**. Under the same reduction condition as above, both the alkynyl and imino moiety were reduced affording *trans* β,γ-alkenyl α-amino esters **77** with high enantioselectivity. Preliminary mechanistic studies indicated that the reduction of the C≡C triple bond occurs prior to the imine reduction. In a control experiment, the *trans* β,γ-alkenyl α-imino esters were reduced smoothly under the optimal conditions while the β,γ-alkynyl α-amino esters remained intact (Scheme 19).

In addition to various imines, Li and Antilla[43] found *N*-acyl enamides could also be employed in the ATH reaction catalyzed by a dual chiral–achiral acid system. In their initial screening of the catalysts, several BINOL- and VAPOL-derived chiral phosphoric acids were less effective at giving satisfactory results which led them coming to the assumption that the iminium formation was the rate-determining step. Then, a suitable achiral acid should be able to facilitate the iminium formation while being inactive in the hydrogenatioin step. As expected, when 10 mol% of acetic acid was added as a cocatalyst, a series of aromatic enamides **78** could be reduced to their corresponding enantioenriched secondary amides **79** in up to 99% yield and 95% *ee* (Scheme 20).

Reductive amination reactions are of great importance since they can often reduce the labors of synthesis and separation of imines and allow rapid and general access to stereogenic C–N bonds. In their first publication of the ATH reaction of imines, List and co-workers[35] showed one example that the imine formation, asymmetric reduction and oxidative removal of the PMP group could be performed in one pot with the *ee* conserved.

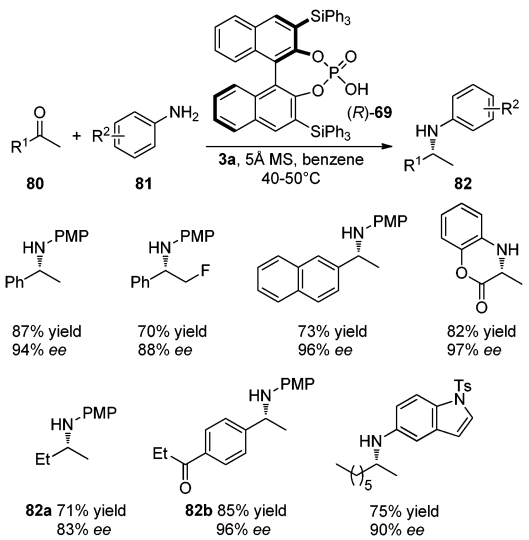
The first general protocol of enantioselective reductive amination with an Hantzsch ester as the reducing agent was reported by MacMillan *et al.*[44] Several chiral H-bonding



Scheme 20 Catalytic ATH reaction of *N*-acyl enamides by Antilla.

catalysts including thiourea and TADDOL did not induce reductive amination while chiral phosphoric acid could provide desired amine products. It was finally discovered that the sterically hindered $SiPh_3$-substituted chiral phosphoric acid (*R*)-**69** exhibited much improved activity and satisfactory asymmetric control. A large array of structurally diverse ketones **80** were converted to amines **82** with superior yields and enantioselectivites, even with the ketone contained dialkyl substituents of similar steric and electronic character **82a**. Besides, the catalytic system showed remarkable chemoselectivity. For example, the diketone substrate underwent reduction to yield monoaminated product **82b** preferentially at the methyl ketone site (18 : 1), with the ethyl ketone moiety remaining untouched. Notably, the water generated in the initial condensation step has a deleterious impact on the reaction. The utilizing of molecular sieves was found to be critical to achieve good results (Scheme 21).

Recently, List and co-workers[45] developed a practical protocol for Hantzsch ester mediated asymmetric reductive amination of ketones by using readily removable benzylamine instead of *p*-anisidine as the reaction component. In addition, the azeotropic removal of water with a Dean–Stark trap under refluxing conditions at reduced pressure (toluene, 57 °C, 167 mbar) was found to be quite effective and practical compared to the use of molecular sieves. The authors also

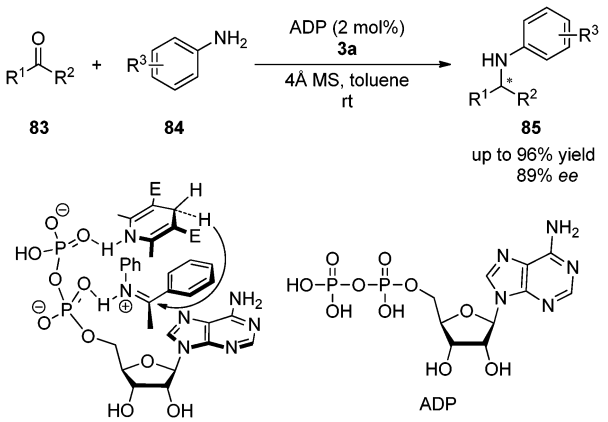


Scheme 21 The enantioselective reductive amination reaction by MacMillan.

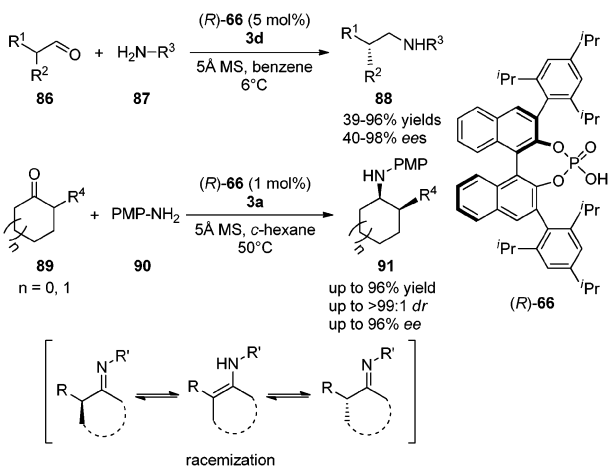
introduced a simple purification method allowing the scale up of the process.

Kumar *et al.*[46] developed a genuine biomimetic reductive amination process which employed a single nucleotide adenosine 5′-diphosphate (ADP) as the catalyst. By using Hantzsch ester **3a** as the reducing reagent, ATH reactions occurred converting several types of ketones **83** to their corresponding secondary amines **85** in up to 96% yield and 89% *ee* under mild conditions. A plausible transition state was also proposed. Both the Schiff base and Hantzsch ester were attached to the phosphate group of the ADP and the transition state might be further stabilized *via* π–π interactions between the Schiff base and adenine. The hydride was then transferred to the imine mainly from the less crowded *Si*-face (Scheme 22).

List and co-workers[47] realized catalytic asymmetric reductive amination of α-branched aldehydes and ketones through dynamic kinetic resolution (DKR). Once again, the TRIP acid was identified as the most powerful catalyst. As shown in Scheme 23, exposed to a catalytic amount of (*R*)-**66** and 5 Å molecular sieves, a series of α-branched aldehydes **86** and cyclic α-branched ketones **89** could be hydrogenated to the corresponding chiral amines (**88** and **91**) under mild conditions with Hantzsch esters **3d** and **3a** as the hydride source, respectively. Good to excellent



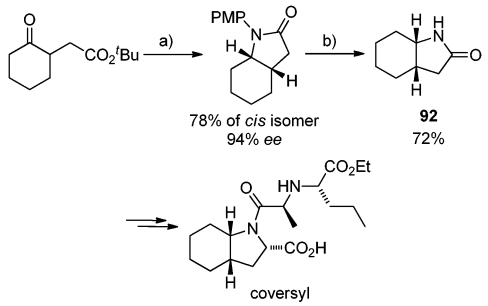
Scheme 22 The enantioselective reductive amination reaction catalyzed using ADP by Kumar.



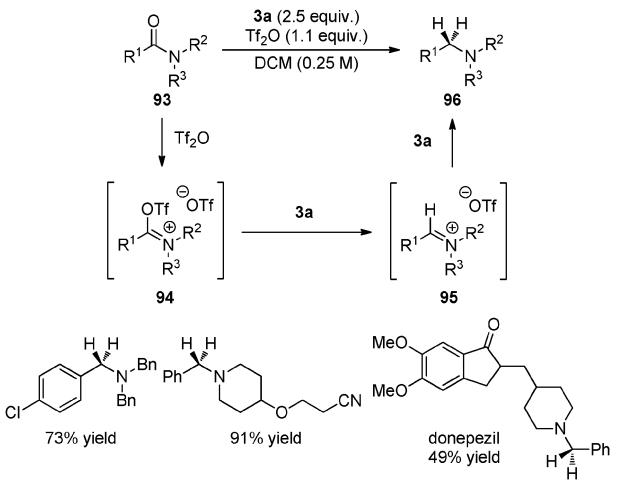
Scheme 23 Catalytic asymmetric reductive amination of α-branched aldehydes and ketones *via* DKR by List.

*ee*s could be obtained typically, owing to the fast racemization of the α-branched carbonyl substrates in the presence of amine and acid catalyst *via* an imine/enamine tautomerization. For the cyclic α-branched ketones, the *syn* disubstituted cyclic amines were afforded preferentially with up to >99 : 1 ratio. Based on this transformation, bicyclic lactam **92**, a key intermediate in the synthesis of coversyl which is a long-acting ACE inhibitor, could be obtained with high efficiency (Scheme 24).

Intriguingly, Charette and co-workers[48] utilized Hantzsch esters in a highly chemoselective metal-free reduction of amides. As depicted in Scheme 25, tertiary amides **93** could be transformed into highly electrophilic iminium derivatives **94** when treated with Tf_2O. The intermediate could subsequently be reduced to the corresponding amines **96** using Hantzsch ester as a mild reducing agent. This reaction exhibited a broad substrate scope. Tertiary amides bearing (α,β-unsaturated) ketone, ester, nitrile, epoxide, alkyne and ether were all well tolerated and could be reduced with up to 91% yield. The authors demonstrated the synthetic potential of this novel methodology by an efficient construction of donepezil, an acetylcholine esterase inhibitor used for the treatment of Alzheimer's disease. The same group[49] also realized a tandem reduction of secondary amides with silane and Hantzsch ester to afford amines in a controlled and chemoselective manner.



Scheme 24 Efficient synthesis of the key intermediate of coversyl by List.

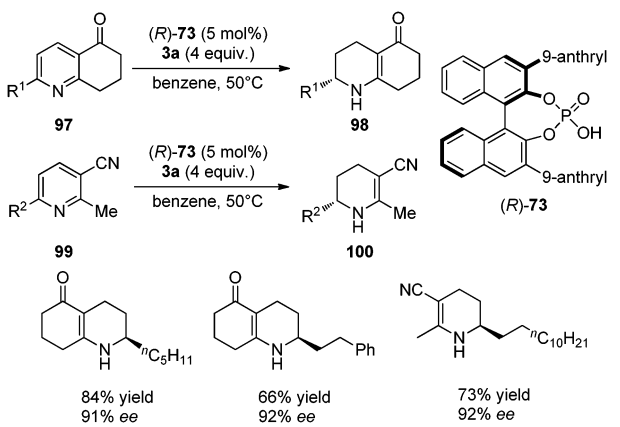


Scheme 25 Highly chemoselective metal-free reduction of tertiary amides with Hantzsch esters by Charrete.

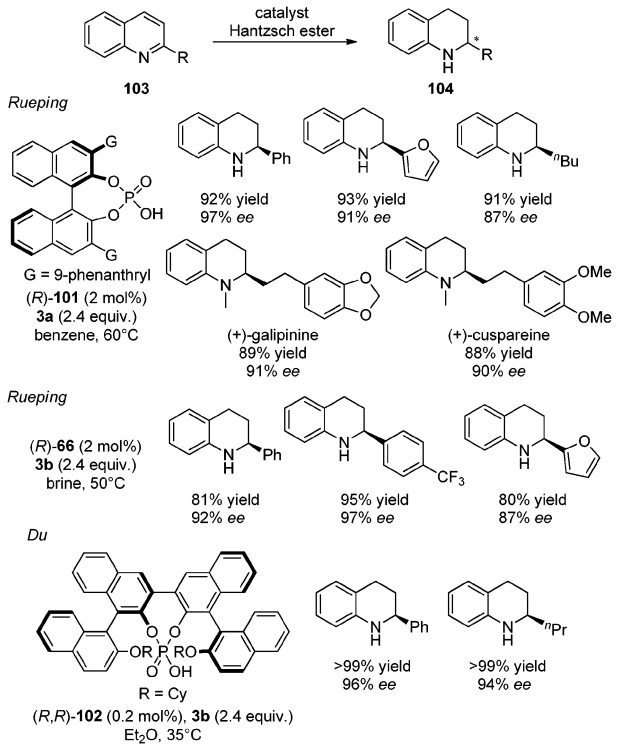
In addition to the *acyclic* imines mentioned above, *N*-heteroaromatic compounds and related cyclic imines constitute another large class of suitable substrates for the ATH reaction with Hantzsch esters. Several groups have dedicated to this area and developed a lot of elegant methods for the construction of chiral *N*-heterocyclic compounds with excellent enantioselectivity.

In 2007, Rueping *et al.*[50] demonstrated that in the presence of chiral phosphoric acid (*R*)-**73** and Hantzsch ester **3a**, a set of trisubstituted pyridine derivatives (**97** and **99**) could be reduced *via* 1,4-hydride addition, isomerization and 1,2-hydride addition, providing the corresponding chiral tetrahydropyridine derivatives (**98** and **100**) with generally high yields and *ee*s (Scheme 26). It is worth noting that an electron-withdrawing group (ketone or cyano) at the 3-position of the pyridine cycle is necessary for the reaction, likely contributing the stabilization of the unreacted double bond in the product. This novel method could also be applied in the formal synthesis of *di-epi*-pumiliotoxin C.

Several groups have reported the ATH reaction of substituted quinolines. Rueping and co-workers[51] showed that by utilizing 2 mol% of chiral phosphoric acid (*R*)-**101** in conjunction with 2.4 equiv. of Hantzsch ester **3a** as the hydride donor, various 2-substituted quinolines could be reduced to tetrahydroquinolines with excellent enantioselectivities (up to >99% *ee*). Several biologically active alkaloids such as (+)-galipinine, (+)-cuspareine and (−)-angustureine could be synthesized efficiently with this methodology (Scheme 27). Recently, they[52] found this reaction could be executed in aqueous solution if a steric much hindered TRIP acid (*R*)-**66** was employed as the catalyst. Hantzsch ester **3b** was the most effective reducing agent. A series of 2-aryl substituted quinolines could be converted to the corresponding tetrahydroquinoline derivatives with up to 95% yield and 97% *ee* in saturated NaCl solution (Scheme 27). Du *et al.*[53] reported the design and synthesis of double axially phosphoric acid (*R*,*R*)-**102**. With this newly developed catalyst, together with Hantzsch ester **3b**, they also demonstrated the ATH reaction of 2-substituted quinolines. Quantitative yields and up to 98% *ee* could be typically achieved. Catalyst loading could be reduced to 0.2 mol% in some cases (Scheme 27). In addition, Metallinos *et al.*[54] realized the ATH reaction of 2- and 2,9-substituted 1,10-phenanthrolines in a range of yields (40–88%) and good to excellent levels of



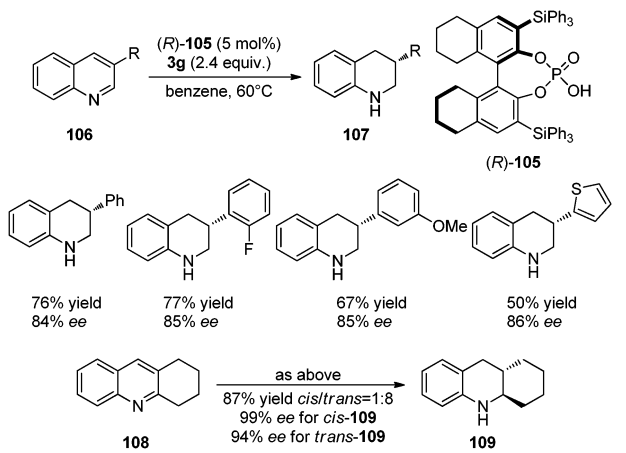
Scheme 26 Catalytic ATH reaction of trisubstituted pyridines by Rueping.



Scheme 27 Catalytic ATH reaction of 2-substituted quinolines by Rueping and Du.

enantiomeric purity (78–99% *ee*), by using a catalytic system similar to that reported by Rueping.

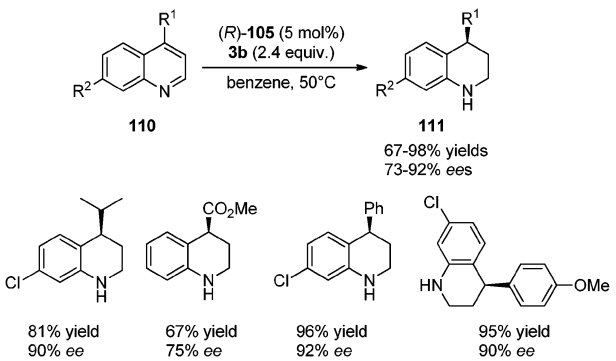
3-Substituted quinolines were also found as suitable substrates for the ATH reaction with Hantzsch ester. By using 5 mol% of [8H]-BINOL-phosphoric acid bearing $SiPh_3$ functionality (*R*)-**105** and 2.4 equiv. of Hantzsch ester **3g**, Rueping and co-workers[55] were able to hydrogenate 3-aryl substituted quinolines **106** with reasonable yields and *ee*s (Scheme 28). The key step of this transformation is the Brønsted acid-catalyzed asymmetric protonation process at the 3-position after the first hydride transfer at the 4-position of the quinoline. When subjected to standard conditions, 2,3-disubstituted quinoline **108** could also be reduced with high stereoselectivity.



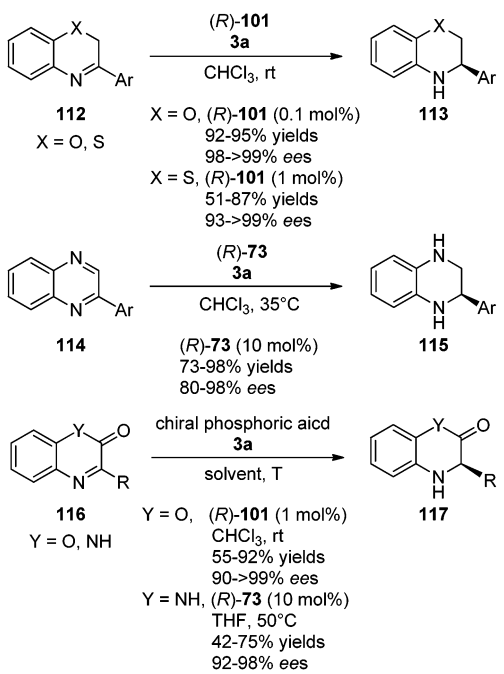
Scheme 28 Catalytic ATH reaction of 3-substituted quinolines by Rueping.

Very recently, Rueping and co-workers[56] demonstrated the first organocatalyzed ATH reaction of 4-substituted quinolines. Since the stereocenter being generated is relatively far away from the protonated nitrogen and the catalytic center with this type of substrate, a catalyst bearing a large steric-demanding group may be necessary. After careful evaluation of different chiral phosphoric acids, the best selectivity was observed with (*R*)-**105**. With Hantzsch ester **3b** as the hydride source, a set of 4-substituted quinolines **110** could be reduced with good yields (67–98%) and enantioselectivity (73–92% *ee*s). Notably, incorporation of a chlorine atom at the 7-position of the quinoline substrates often led to enhanced reaction results (Scheme 29).

Rueping *et al.*[57] investigated the ATH reactions of six-membered cyclic imines bearing two heteroatoms such as benzoxazines (**112**, X = O), benzothiazines (**112**, X = S), quinoxalines **114**, benzoxazinones (**116**, Y = O) and quinoxalinones (**116**, Y = NH). As shown in Scheme 30, all of these substrates could be reduced by Hantzsch ester **3a** when a chiral phosphoric acid ((*R*)-**101** or (*R*)-**73**) was employed as the catalyst.



Scheme 29 Catalytic ATH reaction of 4-substituted quinolines by Rueping.

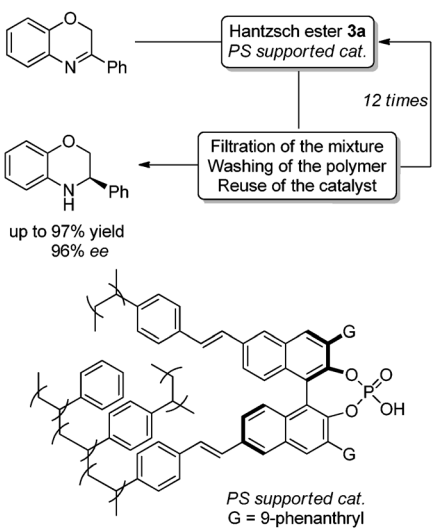


Scheme 30 Catalytic ATH reaction of benzoxazines, benzothiazines, benzoxazinones, quinoxalines and quinoxalinones by Rueping.

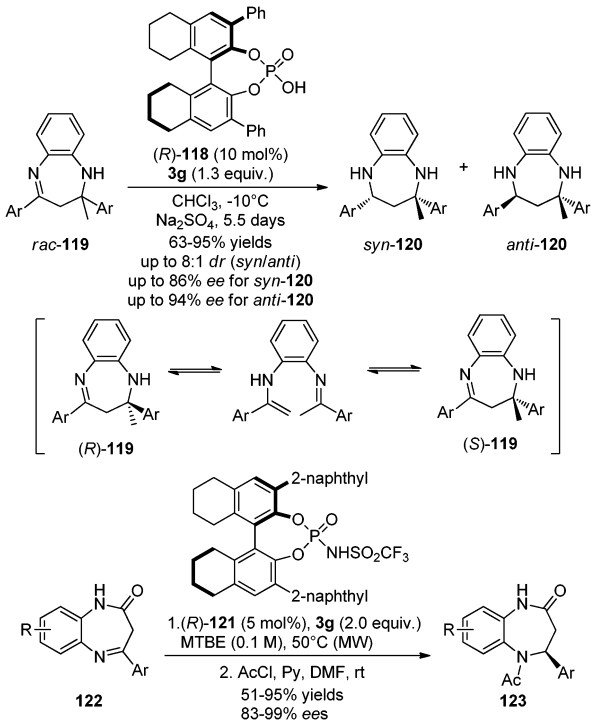
Typically, the corresponding hydrogenated products could be obtained in excellent yields and *ee*s (up to 95% yield and 99% *ee*). Remarkably low catalyst loading (even at 0.01 mol%) could be achieved in some cases. The highly enantioselective hydrogenation of benzothiazines (**112**, X = S) demonstrates the advantage of this organocatalytic approach over the application of most metal catalysts, which are known to be poisoned by sulfur-containing substrates. The ATH reactions were also used by Rueping *et al.*[58] for the construction of fluorinated quinolones, allowing fast and efficient access to the antibiotics (*R*)-flumequine and (*R*)-levofloxacin.

In order to recycle the catalysts, Rueping and co-workers[59] developed a new methodology for the immobilization of chiral phosphoric acids. They tested these polystyrene-based heterogeneous systems in the ATH reaction of quinolines and benzoxazines with Hantzsch esters and found the new catalysts were stable and as effective as their homogeneous counterparts. Based on this tea-bag approach, the solid-supported catalysts could be easily removed from the reaction mixture and reused in multiple consecutive catalytic cycles without loss of reactivity and enantioselectivity (Scheme 31).

The ATH reactions of seven-membered cyclic imines have also been reported. In 2009, Gong and co-workers[60] presented an elegant ATH reaction of dihydrobenzodiazepines through dynamic kinetic resolution (DKR). The two enantiomers of racemic 2,4-diaryl-2,3-dihydrobenzo[*b*][1,4]diazepines **119** could be interconverted *via* retro-Mannich/Mannich reactions catalyzed by chiral phosphoric acid (*R*)-**118**. The (*S*)-**119** underwent a fast transfer hydrogenation with Hantzsch ester **3g**. The hydrogenated products **120** were afforded with up to 95% yield and 8 : 1 *dr* (*syn*/*anti*). The *ee*s of both products were moderate to good (Scheme 32). Shortly after that, Rueping *et al.*[61] reported a highly enantioselective synthesis of benzodiazepinones by ATH reactions. The *N*-triflyl phosphoramide (*R*)-**121** was found as the most effective catalyst. A lot of different 4-substituted-1*H*-[1,5]benzoidazepin-2(3*H*)-ones **122** could be reduced with Hantzsch ester **3g** with excellent *ee*s and broad functional group tolerance. Microwave irradiation



Scheme 31 Polystyrene-based chiral phosphoric acid-catalyzed ATH reaction by Rueping.

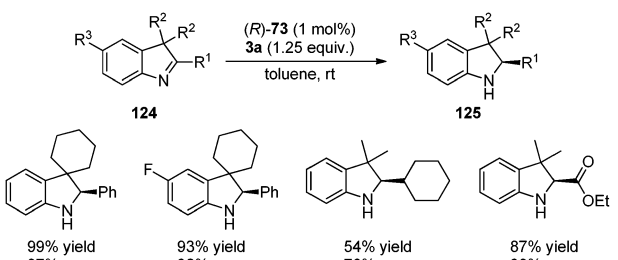


Scheme 32 Catalytic ATH reactions of dihydrobenzodiazepines and benzodiazepinones by Gong and Rueping.

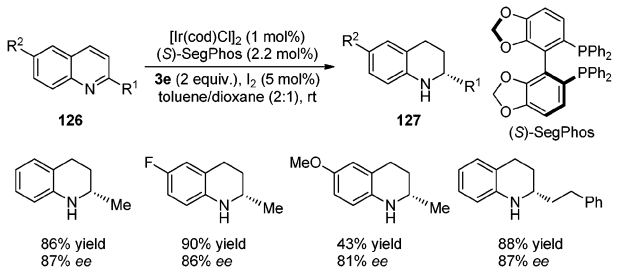
proved to be beneficial to obtain improved yields (Scheme 32). Moreover, a one-pot procedure involving *in situ* generation of the benzodiazepinone substrates before ATH reaction was also developed.

Inspired by the success of the ATH reactions of pyridines, quinolines and other related C=N double bonds, Rueping *et al.*[62] recently investigated the ATH reaction of 3*H*-indoles **124**. With 1 mol% of (*R*)-**73** and 1.25 equiv. of Hantzsch ester **3a**, various 2-aryl-substituted 3*H*-indoles were reduced in typically high yields (84–99%) and excellent enantioselectivities (96–>99% *ee*), while only moderate to high yields (54–71%) and selectivities (70–76% *ee*) could be obtained if 2-alkyl-substituted substrates were subjected to standard conditions (Scheme 33). This transformation constitutes an efficient method for the synthesis of various optically active indoline derivatives.

In addition to the various organocatalytic systems mentioned above, the ATH reactions with Hantzsch esters were also found to be compatible with some transition-metal catalysts. Zhou and co-workers[63] disclosed that the dehydroaromatization reaction of Hantzsch esters could be used to generate hydrogen gas with



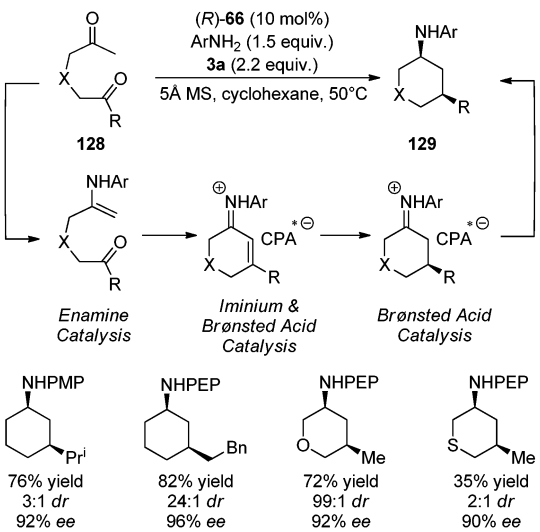
Scheme 33 Catalytic ATH reactions of 3*H*-indoles by Rueping.



Scheme 34 Ir-catalyzed asymmetric hydrogenation of quinolines by Zhou.

a catalytic amount of $[Ir(cod)Cl]_2$/BiPhep and iodine. Fueled by this initial result, they[64] subsequently used Hantzsch esters instead of hydrogen gas in the Ir-catalyzed asymmetric hydrogenation of 2-substituted quinolines **126**. With (*S*)-SegPhos as the optimal ligand, the corresponding tetrahydroquinolines **127** could be obtained with up to 98% yield and 88% *ee* (Scheme 34).

It has become an attractive research area to combine Hantzsch ester-mediated ATH reactions of C=N double bonds with other distinct organic transformations into cascade fashion, especially in the context of fast assembly of complex molecules. As mentioned previously, List's group[12,16] has demonstrated that the combination of a chiral phosphate anion and either achiral or chiral ammonium was a superior catalytic system for the ATH reaction of α,β-unsaturated carbonyl compounds. Based on these results and the well-known ability of amine salts to catalyze aldol reactions,[65] Zhou and List[66] developed a highly enantioselective synthesis of pharmaceutically relevant 3-substituted cyclohexylamines *via* an organocatalytic aldolization/dehydration/conjugate reduction/reductive amination cascade. As shown in Scheme 35, 2,6-diketones **128** could be converted to their corresponding chiral amines **129** by *p*-anisidine and Hantzsch ester **3a** in the presence of (*R*)-**66** and 5 Å MS in high yields (up to 89%) and excellent stereoselectivities (up to 96% *ee* and >20 : 1 *dr*). Further mechanistic studies showed that the initial aldolization was rapid and kinetically controlled. Both aldolization and conjugate addition steps were mediated

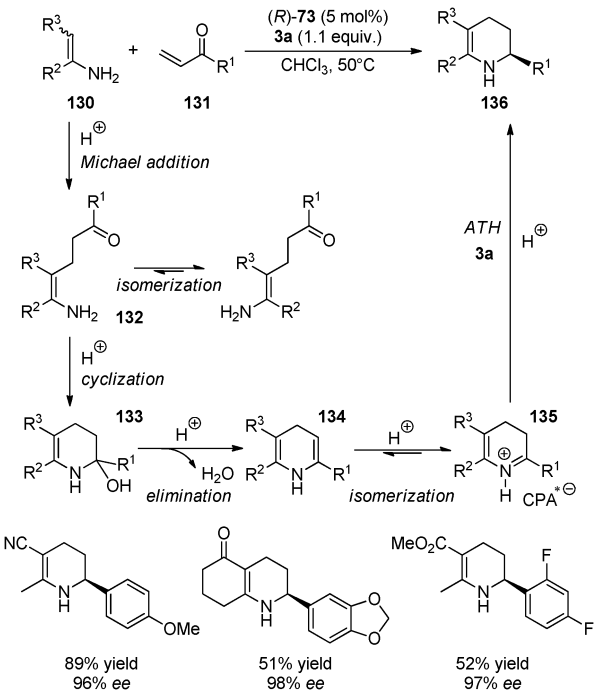


Scheme 35 Organocatalytic aldolization/dehydration/conjugate reduction/reductive amination cascade by List.

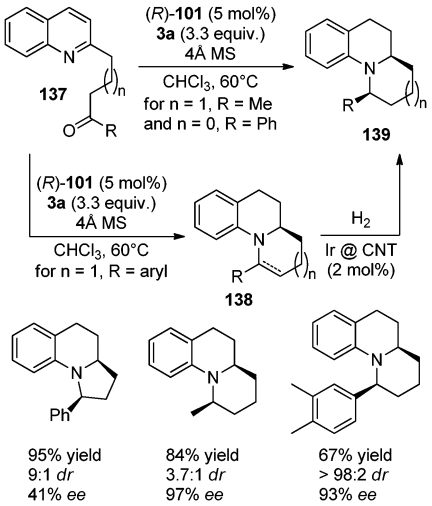
by the acid and the amine. In the final reductive amination, the TRIP catalyst was crucial to achieve the observed *cis*-selectivity while alternative phosphoric acids typically gave the corresponding *trans*-isomer.

Based on their successes of chiral phosphoric acid-catalyzed ATH reactions of *N*-heteroaromatics, Rueping *et al.*[67] proposed an organocatalytic multi-step cascade involving ATH reaction with Hantzsch esters that allows efficient access to valuable tetrahydropyridines and azadecalinones **136** from readily available enamines **130** and α,β-unsaturated ketones **131** (Scheme 36). By utilizing 5 mol% of (*R*)-**73** as the catalyst and 1.1 equiv. of Hantzsch ester **3a** as the hydride donor, this cascade protocol could be accomplished to afford a set of tetrahydropyridine derivatives with reasonable yields (42–89%) and excellent enantioselectivities (up to 99% *ee*). Each step was catalyzed by the chiral phosphoric acid and some key intermediates (**132**, **134** and **135**) were detected by GC-MS analysis of the reaction mixture. The electron-withdrawing group (ketone, ester or cyano) in the enamine substrate might play a critical role, improving the selectivity of the isomerization of **134** as well as stabilizing the double bond in the final products.

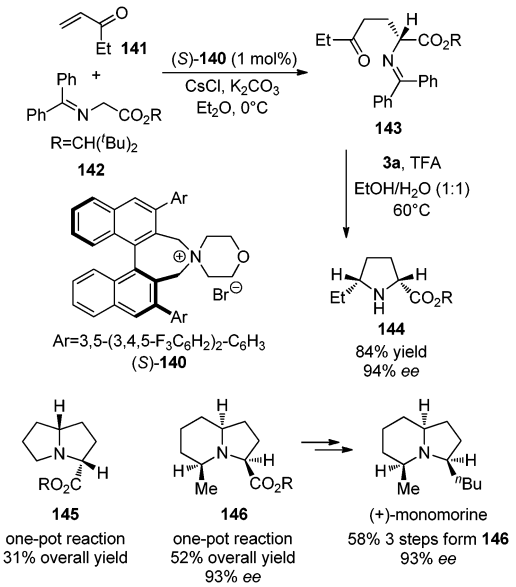
Quinolizidines and indolizidines **139** are common structural motifs of many natural products. Recently, Rueping and Hubener[68] developed an enantioselective synthesis of these *N*-heterocycles through a catalytic asymmetric hydrogenation cascade. With chiral phosphoric acid (*R*)-**101** as the optimal catalyst, the readily accessible 5-(2-quinolinyl)-2-pentanone (**137**, n = 1, R = Me and n = 0, R = Ph) could first undergo ATH reaction of the quinoline ring with Hantzsch ester as the hydride source. The subsequent reductive amination under the same catalytic system produced the desired product with good results. The reduction of aryl-3-quinolinylbutanones (**137**, n = 1 R = aryl) was incomplete, probably due to the higher



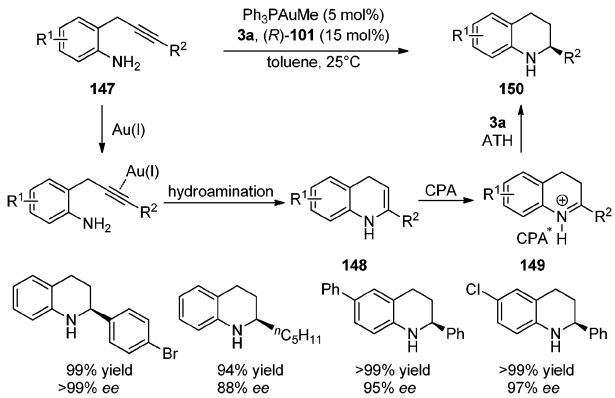
Scheme 36 Organocatalytic cascade for the synthesis of tetrahydropyridine derivatives by Rueping.



Scheme 37 Catalytic asymmetric hydrogenation cascade for the synthesis of quinolizidines and indolizidines by Rueping.



Scheme 38 Organocatalytic one-pot synthesis of pyrrolidine, hexahydropyrrolizine and octahydroindolizine core structures by Maruoka.



Scheme 39 Intramolecular hydroamination/ATH cascade catalyzed by achiral gold(I) complex/chiral phosphoric acid by Gong.

stability of the aromatic enamine intermediates. Fortunately, the enamine–amine mixture **138** could be hydrogenated by a heterogeneous hydrogenation catalyst (iridium nanoparticles reductively deposited on carbon nanotubes, Ir@CNT), affording final products with good yields and high stereoselectivities (Scheme 37).

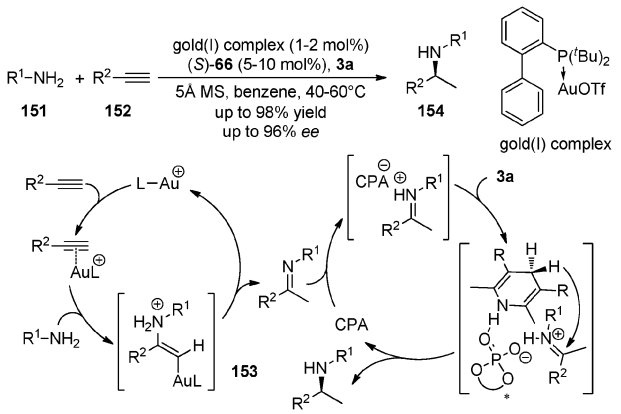
Transfer hydrogenation using Hantzsch esters as the reducing agent has recently been employed in combination with asymmetric conjugated addition catalyzed by chiral phase transfer catalyst. Maruoka and co-workers[69] applied this strategy to realize the enantioselective one-pot synthesis of pyrrolidine **144**, hexahydropyrrolizine **145** and octahydroindolizine **146** core structures. Treatment of readily available α,β-enones **141** and glycine derivative **142** with catalytic amount of spiro-type chiral catalyst (*S*)-**140** led to the formation of key ketone adduct **143** with high enantioselectivities (up to 94% *ee*). This intermediate underwent transfer hydrogenation with Hantzsch ester **3a** and TFA affording the corresponding chiral *N*-heterocyclic motif (Scheme 38). The authors also conducted a short synthesis of physiologically active (+)-monomorine in a highly stereoselective manner taking advantage of this novel methodology.

Combining the transition metal complexes and small organic molecules in cooperative and relay catalysis holds remarkable opportunities for developing efficient enantioselective organic transformations. Elegant work from Gong *et al.*[70] clearly showed that the organocatalytic ATH reaction of C=N double bonds with Hantzsch esters was compatible with gold(I) complex catalyzed hydroamination reactions in a consecutive manner. As shown in Scheme 39, the 2-(2-prorynyl)aniline substrates **147** first underwent an intramolecular hydroamination reaction catalyzed by 5 mol% of Ph_3PAuMe affording 1,4-dihydroquinoline **148** that could be isomerized into 3,4-dihydroquinolinium **149** with a chiral phosphoric acid (*R*)-**101**. The final step of the cascade was constituted of the ATH reaction of this intermediate with the same catalytic system to generate a wide spectrum of desired tetrahydroquinolines **150** with up to quantitative yield and >99% *ee*.

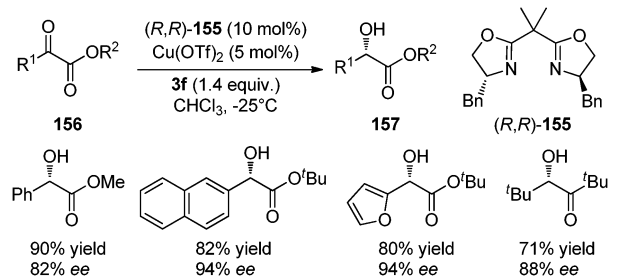
Almost at the same time, Liu and Che[71] reported the intermolecular version of this attractive cascade hydroamination/ATH reaction with a similar gold(I) complex and chiral Brønsted acid protocol. A combination of (^{t}Bu)$_2$(*o*-biphenyl)PAuOTf (1 mol%) and chiral phosphoric acid (*S*)-**66** was identified as the optimal catalytic system. The reaction exhibited a very broad substrate scope to afford chiral amines **154** with diverse substitution patterns in up to 98% yield and 96% *ee* (Scheme 40). Control experiments revealed that the Au-catalyzed hydroamination occurred first in the catalytic sequence and the key intermediate **153** could be detected by the ESI-MS analysis. Thus, a plausible catalytic cycle was proposed although an alternative mechanism involving gold(I) complex cation–chiral counteranion ion pair could not be easily excluded.[13b]

Catalytic ATH reactions of C=O double bonds

Compared to the various examples on the catalytic ATH reaction of C=C and C=N double bonds mediated by Hantzsch esters discussed above, fairly limited work has been reported on the ATH reaction of C=O double bonds. In all these reactions, the carbonyl group was activated by a chiral



Scheme 40 Intermolecular hydroamination/ATH cascade catalyzed by achiral gold(I) complex/chiral phosphoric acid by Che.



Scheme 41 Catalytic ATH reaction of α-ketoesters by List.

Lewis acid. In the 1980s, Zehani and Gelbard[72] found methyl phenylglyoxylate could be converted to methyl mandelate with 55% *ee* by Hantzsch ester **3e** when 10 mol% of chiral shift reagent (+)-Eu(tfc)$_3$ was employed as a Lewis acid ((+)-Eu(tfc)$_3$: Tris-[3-(trifuoromethylhydroxymethylene)-(+)-camphorato]europium).

In 2006, by using C_2-symmetric chiral Cu(II)-bisoxazoline complex as the catalyst, Yang and List[73] developed a general protocol to achieve highly enantioselective transfer hydrogenation of α-ketoesters with 78–94% *ee*s when Hantzsch ester **3f** was utilized as the hydride donor (Scheme 41).

ATH reactions with other related organic hydride donors

Great efforts have also been devoted to modification of Hantzsch esters and developing other organic analogs as the hydride sources for the ATH reactions. In the last several decades, groups across the world have synthesized numerous chiral NADH model compounds.[74] The design of these chiral hydride donors are generally according to three aspects: (i) introducing chiral functional groups or sterically demanding side chain to replace the original substituent of dihydronicotinamide; (ii) directly incorporating a substituent at the reaction center, 4-position of the dihydronicotinamide ring, and (iii) making the compounds in a special conformation to obtain stereoselectivity. Structures of some representative chiral hydride donors[75] are shown in Fig. 6. These NADH mimics were usually tested in the ATH reaction of C=O double bonds like magnesium(II) mediated asymmetric reduction of methyl

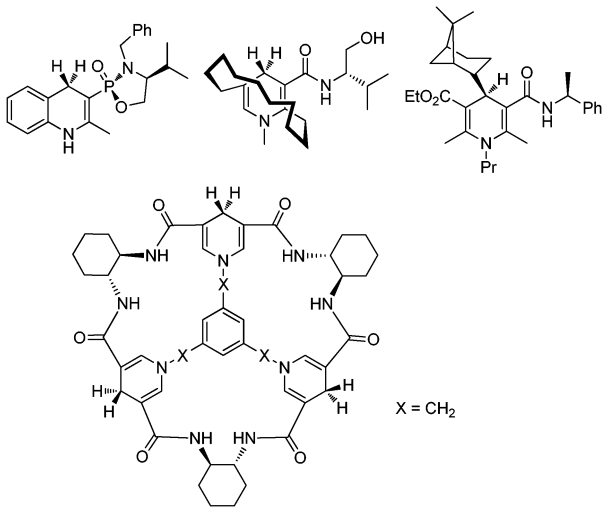
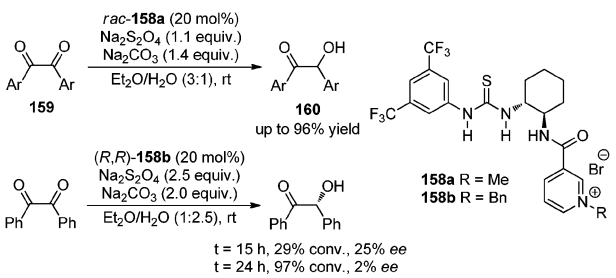


Fig. 6 Representative chiral NADH model compounds.

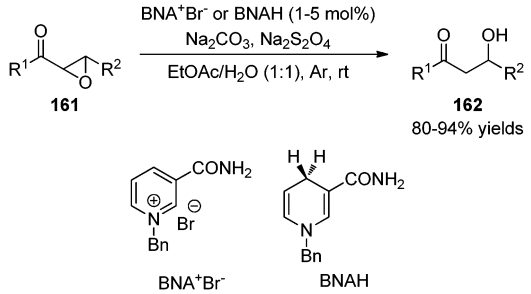
phenylglyoxylate and related substrates, some of which could exhibit high enantioselectivity.

Procuranti and Connon[76] proposed that transfer hydrogenation reactions could be furnished with a substoichiometric amount of organocatalyst incorporating *both* a substrate-activating moiety and an organic hydride donor if this hydrogen source could be generated and recycled *in situ* with an inexpensive co-reductant. Considering that sodium dithionate is known as a standard reductant for the preparation of 1,4-dihydropyridines from alkyl pyridinium salts, they prepared a series of racemic thiourea catalysts bearing an NADH analog-component and used them in catalytic amount together with 1.1 equiv. of sodium dithionate to test their performance in the reduction of 1,2-diketone substrates. Several aromatic 1,2-diketones **159** could be reduced in 65–96% yields under mild conditions with *rac*-**158a** as the optimal catalyst (Scheme 42). Using enantiopure (*R*,*R*)-**158b** could lead to moderate enantioselectivity (29% conv. and 25% *ee* when t = 15 h) but product racemization under the reaction conditions made evaluating the potential of this methodology complicated (97% conv. and 2% *ee* when t = 24 h).

Liu, Wu and their co-workers[77] applied a similar strategy to demonstrate the hydrogenation of α,β-epoxy ketones to their corresponding β-hydroxyl ketones[78] using a catalytic amount of NADH model compound BNAH or BNA$^+$Br$^-$ with sodium dithionate as the ultimate reducing agent. A lot of different α,β-epoxy ketones **161** could be reduced using 1–5 mol% of BNAH or BNA$^+$Br$^-$ with 80–94% yields (Scheme 43). The authors suggested the reaction occurred *via* a radical mechanism.



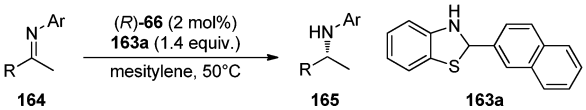
Scheme 42 Transfer hydrogenation of 1,2-diketone using thiourea-based bifunctional organocatalyst by Connon.



Scheme 43 Hydrogenation of α,β-epoxy ketones mediated by BNAH or BNA^+Br^- by Liu and Wu.

Oxygen could suppress the transformation and the irradiation with a 450 W mercury lamp led to an acceleration of the reaction. It was also found that Hantzsch esters could not be used for the catalytic reaction but the *N*-methylated Hantzsch ester, which is analogous to BNAH, could mediate the reaction as efficiently as BNAH.

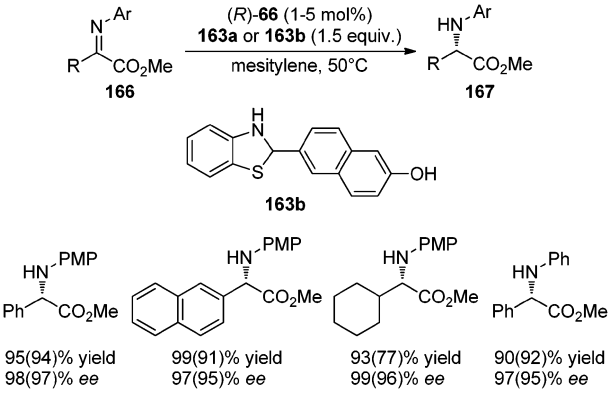
In 2009, Zhu and Akiyama[79] reported benzothiazolines were highly efficient hydride donors for the chiral phosphoric acid-catalyzed ATH reaction of ketimines. Compared to the previous reports[34,35] with Hantzsch ester **3a** as the reducing agent, various aromatic and aliphatic ketimines **164** were converted to the hydrogenated products using benzothiazoline **163a** with uniformly higher enantioselectivety (95–98% *ee*s) (Scheme 44). The catalyst loading could be reduced to 2 mol% and the benzothiozoline could be generated *in situ*. Subsequently, the same group[80] applied this protocol in the chiral phosphoric acid-catalyzed ATH reaction of α-imino esters. With (*R*)-**66** as the optimal catalyst, α-imino esters **166** with diverse substitution patterns could be reduced with excellent levels of stereocontrol (94–99% *ee*s) (Scheme 45). One of the disadvantages of the Hantzsch ester-mediated transfer hydrogenation reaction is the separation of the pyridine byproducts generated during the reduction. The reaction using benzothiazolines **163a** also faced similar isolation problems. Akiyama *et al.* found this difficulty could be overcome by using a hydroxyl group-substituted benzothiazoline **163b** as the hydride source because the benzothiazole byproduct could precipitate in the reaction mixture and be readily removed by filtration. The yields



Ar	R	*ee* with **3a** [%][a]	*ee* with **163a** [%]
PMP	Ph	88	98
PMP	2-naphthyl	84	98
PMP	3,4-$(MeO)_2$-C_6H_3	89	98
PMP	4-NO_2-C_6H_4	80	95
PMP	Cy	/	98
4-Br-C_6H_4	Ph	/	97

[a] Results from List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424-7427.

Scheme 44 Catalytic ATH reactions of ketimines using benzothiazoline as the hydride donor by Akiyama.

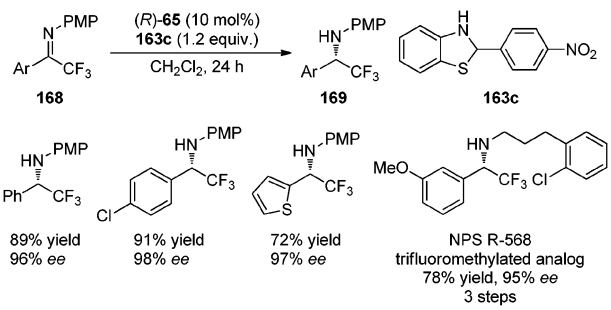


Scheme 45 Catalytic ATH reactions of α-imino esters using benzothiazolines as the hydride donor by Akiyama. Yields and *ee*s in parentheses are obtained using **163b**.

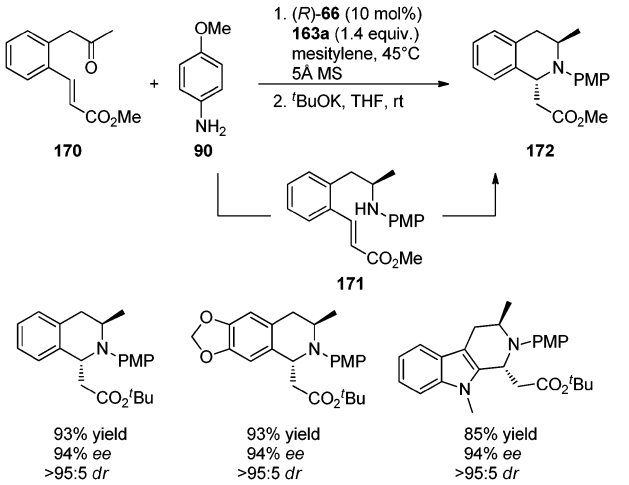
and *ee*s with this improved reductant could be maintained. Very recently, Akiyama *et al.*[81] demonstrated the chiral phosphoric acid-catalyzed ATH reactions of trifluoromethylated ketimines **168**. Good to excellent yields (72–99%) and *ee*s (96–98%) were typically obtained with benzothiazoline **163c** as the most efficient reductant, while using Hantzsch ester **3a** only gave a trace amount of (4%) product with diminished enantioselectivity (45% *ee*). Further investigation showed that the required *N*-PMP-protected ketimines could be generated *in situ* in a direct reductive amination manner. Deuterated experiments strongly supported the hydride transfer mechanism for the benzothiazoline-mediated reduction. They also applied this method in the synthesis of a perfluoroalkylated analog of NPS R-568 (Scheme 46). The same group[82] also reported a Brønsted acid-catalyzed reductive amination of aldehydes using benzothiazoline as a highly efficient hydride donor.

Enders and co-workers[83] used benzothiazoline as the reductant in the construction of *trans*-1,3-disubstituted tetrahedroisoquinolines through an asymmetric reductive amination/aza-Michael sequence. As shown in Scheme 47, substrate **170** was subjected to reductive amination conditions (*p*-anisidine, (*R*)-**66** and reductant) to afford chiral amine structures **171**. The following aza-Michael addition occurred with ^{t}BuOK as the base to give the desired products in high yields and excellent stereoselectivities. In addition, indole-derived acrylates are also viable substrates leading to the formation of the important class of β-carboline derivatives.

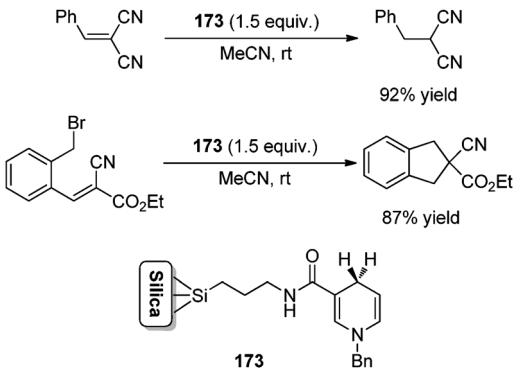
Another attractive technique for practical application of transfer hydrogenation is to immobilize the NADH model



Scheme 46 Catalytic ATH reactions of trifluoromethylated ketimines with benzothiazoline by Akiyama.



Scheme 47 The asymmetric reductive amination/aza-Michael sequence with benzothiazolines by Enders.

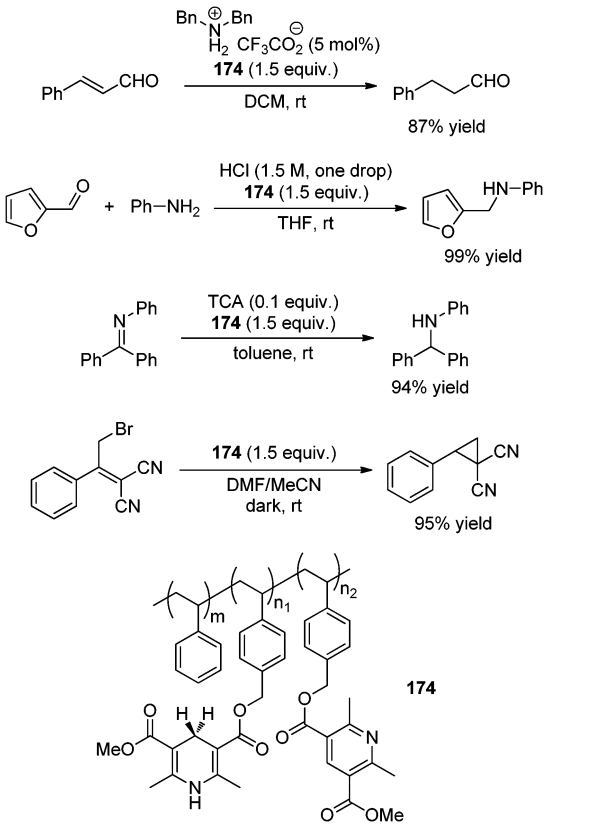


Scheme 48 Transfer hydrogenations of activated olefins using polysiloxane-supported NADH analogs by Zhu and Cheng.

compounds to solid phase supports, because it may make the workup and separation procedure easy to operate.[84] In 2003, Zhu, Cheng and their co-workers[85] reported a polysiloxane-supported 1-benzyl-1,4-dihydronicotinamide **173** and its application in the reduction of some activated olefins (Scheme 48). This novel reductant was very effective at reducing olefins activated by electron-withdrawing groups such as CN and CO_2Et, as well as some allylic and benzylic bromides under mild conditions (dry MeCN, rt) and showed no obvious decrease in reactivity after being reused three times.

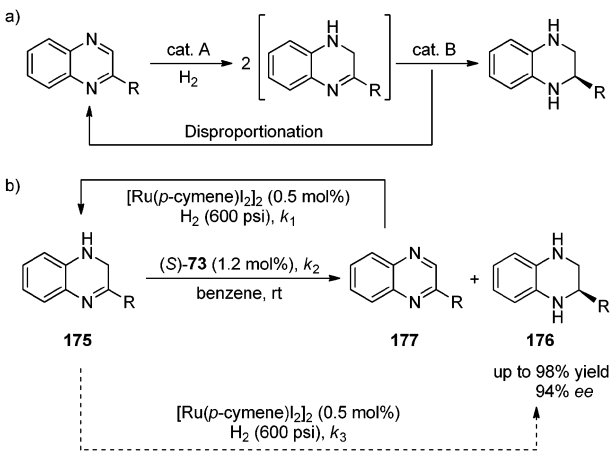
Recently, Lam *et al.*[86] developed soluble polymer-supported Hantzsch ester **174** ($m/(n_1 + n_2) = 4.48$, $n_1/(n_1 + n_2) = 89\%$) as an efficient biomimetic hydride source and succeeded in using it in the reduction of activated alkenes, reductive amination of aldehydes, Brønsted acid-catalyzed reduction of ketimines and reduction of *Z*-α-cyano-β-bromoethylcinnamates (Scheme 49). Typically, these reactions could afford the corresponding products in comparable or even higher yields than employing ordinary Hantzsch esters as the reducing agent.

A very impressive example from Zhou, Fan and their co-workers[87] presented the potential opportunity of utilizing hydrogen gas as the ultimate reducing agent in the ATH reactions mediated with organic hydride donors. Generally, a disproportionation reaction is not atom-economical because



Scheme 49 Transfer hydrogenation reactions using polymer-supported Hantzsch esters by Lam.

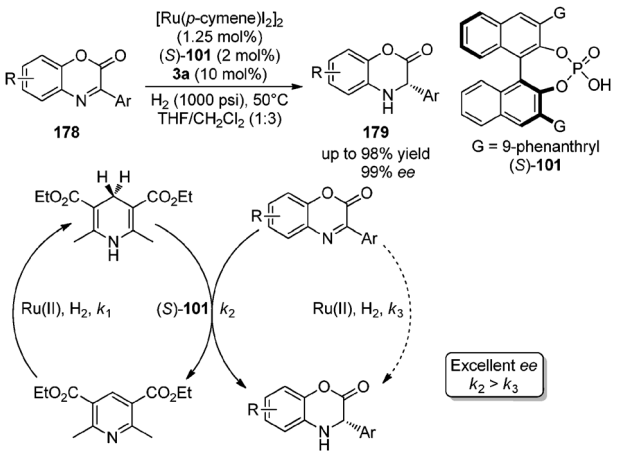
the reaction simultaneously gives both an oxidation product and a reduction product. But the reaction efficiency would be largely improved when the starting material could be regenerated from the oxidation product with an external reductant (Scheme 50a). Unexpectedly, they found dihydroquinoxaline **175** could undergo self-transfer hydrogenation with chiral phosphoric acid (*S*)-**73** as the catalyst, yielding chiral tetrahydroquinoxaline **176** with 93% *ee*. On the other hand, quinoxaline derivatives **177** generated by the disproportionation process could be reduced to dihydroquinoxaline with an achiral metal complex under an H_2 atmosphere. Thus, the authors



Scheme 50 Convergent asymmetric disproportionation of quinoxalines by metal/Brønsted acid relay catalysis by Zhou and Fan.

envisaged that a convergent asymmetric disproportionation reaction of dihydroquinoxaline could be furnished if the rate of chiral phosphoric acid-catalyzed self-transfer hydrogenation was much greater than that of the background hydrogenation of dihydroquinoxaline to tetrahydroquinoxaline ($k_2 > k_3$). After screening reaction parameters, [Ru(*p*-cymene)I_2]$_2$ was identified as the optimal metal catalyst. With 0.5 mol% of this complex together with 1.2 mol% of (*S*)-**73**, the convergent asymmetric disproportionation reaction could be achieved under 600 psi H_2 at room temperature, with up to 98% yield and 94% *ee* (Scheme 50b). Further investigations showed that the N–H moiety in the dihydroquinoxaline was very crucial in this novel transformation since *N*-methyl-3,4-dihydroquinoxaline only gave poor *ee* (7%) and low conversion (24%) under standard conditions. Interestingly, the absolute configuration of the tetrahydroquinoxaline generated in this convergent asymmetric disproportionation reaction was opposite to that obtained in the pure organocatalytic ATH reaction reported by Rueping *et al.*[57b] DFT calculation at B3LYP/6-31G(d,p) level of theory validated that this enantioreversal likely originated from the different steric demands of the 1,2-hydride transfer pathway in the disproportionation of dihydroquinoxaline and the 1,4-hydride transfer pathway using a Hantzsch ester.

Based on the above mentioned success, Zhou *et al.*[88] very recently achieved the ATH reaction with only a catalytic amount of Hantzsch ester. The pyridine byproduct could be reduced when hydrogen gas was employed as the final reductant. The key point to achieve this idea was the efficiency and selectivity for the *in situ* regeneration of the Hantzsch ester. After screening several commercially available Ru(II) complexes, [Ru(*p*-cymene)I_2]$_2$ once again gave the best results. Benzoxazolinone **178** was chosen as a suitable substrate because of its inactivity under hydrogen gas without the addition of Hantzsch pyridine. By utilizing 2 mol% of (*S*)-**101** as the chiral catalyst, in conjunction with 1.25 mol% of the metal complex, various benzoxazolines were hydrogenated under H_2 atmosphere (1000 psi) at a slightly elevated temperature (50 °C) (Scheme 51). Only 10 mol% of Hantzch ester **3a** was enough to mediate the reaction with up to 98% yield and 99% *ee*, indicating the background reduction promoted by the achiral Ru(II) catalyst was totally inhibited ($k_2 > k_3$).



Scheme 51 Catalytic ATH reaction of benzoxazolinones using a catalytic amount of Hantzsch ester by Zhou.

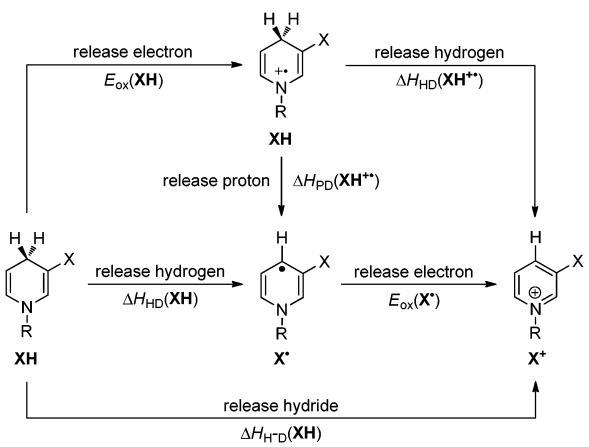
This report exhibits the exciting possibility of making the Hantzsch ester-mediated ATH reaction an ideal atom economic process.

Thermodynamic diagnosis of the properties and mechanism of organic hydride sources

Although plenty of work has emerged on the Hantzsch ester-mediated transfer hydrogenation reactions in the literature, the fundamental aspects of thermodynamic properties of Hantzsch esters and related organic hydride donors, especially the thermodynamic driving forces of these compounds to release hydride anions, hydrogen atoms and protons, as well as the electron transfer abilities, have attracted relatively little attention. However, this type of knowledge will undoubtedly promote the fast development in the field of ATH reactions with organic hydride donors.

Zhu's group[89] has long been devoted to measuring and determining the thermodynamic parameters of various organic hydride donors and their reaction intermediates by using titration calorimetry and electrochemical methods (cyclic voltammetry, CV and Osteryoung square wave voltammetry, OSWV). As shown in Scheme 52, they envisaged that an organic hydride donor could be oxidized (**XH** → $\mathbf{X}^+$) *via* either a concerted pathway (direct hydride transfer) or multistep mechanisms such as e^-–H^+–e^-, e^-–$H^\bullet$ and $H^\bullet$–e^-. The standard state enthalpy change (for example, ΔH_{H-D}(**XH**) means the standard state enthalpy change for **XH** to release a hydride to generate X^+) or standard oxidation potential values (for example, E_{ox}(**XH**) means the standard oxidation potential values for **XH** to release an electron to generate $\mathbf{XH}^{+\bullet}$) of each step with a series of five-membered heterocyclic compounds and dihydropyridine-type compounds were determined experimentally.[90] With these valuable data, one can construct a library of the thermodynamic characteristic graphs (TCGs) of various organic hydride donors, which can be used as "Molecule ID Cards"[91] to quantitatively diagnose the characteristic chemical properties of these compounds and their reaction intermediates in organic redox reactions.

Particularly, the hydride-donating abilities of various organic hydride sources have been measured using their ΔH_{H-D}(**XH**)



Scheme 52 Possible reaction pathways for various organic hydride donors to be oxidized.

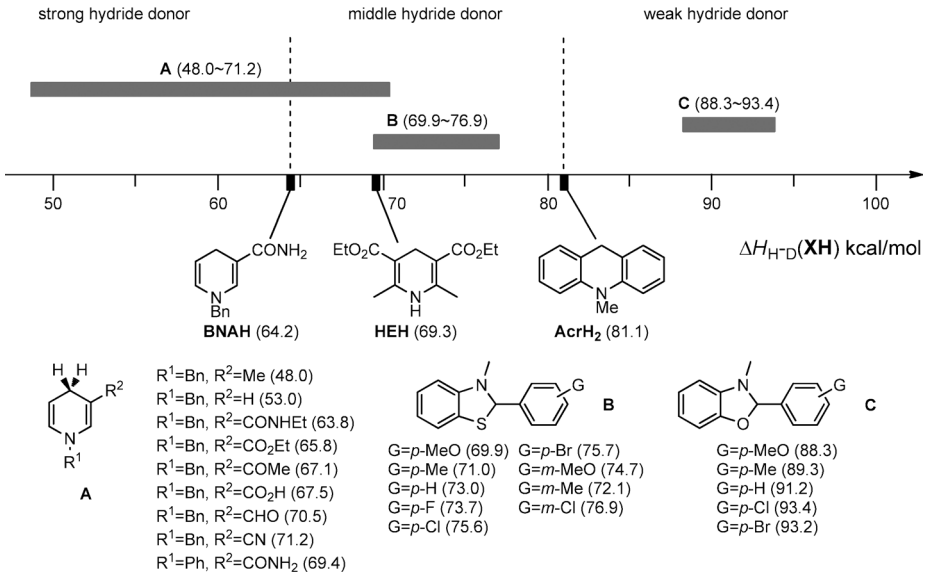


Fig. 7 The thermodynamic driving force of various organic hydride donors to release hydride.

values as criteria. As shown in Fig. 7, most of the *N*-protected dihydropyridine derivatives (BNAH analogs) belong to *strong* hydride donors with the $\Delta H_{H\text{-}D}$(**XH**) values less than 64.2 kcal mol^{-1}. The widely used Hantzsch ester **3a** and *N*-methyl-benzothiazolines are *mid-strength* hydride donors. The ΔH_{H-D}(**XH**) values are in the range of 69.3 to 76.9 kcal mol^{-1}. *N*-Methyl-benzoxazolines generally have larger ΔH_{H-D}(**XH**) values (88.3 to 93.4 kcal mol^{-1}) and therefore are classified as *weak* hydride donors. Zhu and his co-workers[89b] also proved that the kinetics (log k_2) of the hydride transfer reaction have a linear relationship to the thermodynamic driving force for hydride releasing (ΔH_{H-D}(**XH**)) within a series of hydride donors having similar fundamental structures. It is quite conceivable that the rank of hydride-donating abilities of various organic hydride sources can act as an important clue for synthetic chemists to choose the proper reducing agent in combination of certain catalytic system when developing new catalytic ATH reactions.

Summary and outlook

Over the past few years, significant developments within the area of transfer hydrogenation reaction with Hantzsch esters and related organic hydride donors have been achieved. A great deal of new methods have been developed for the asymmetric transformation of C=C, C=N and C=O bonds to the corresponding saturated compounds in an enantio-enriched manner, which acts as an important supplementary to the traditional asymmetric hydrogenation and transfer hydrogenation reactions based on chiral transition metal complexes. Most of these reactions take advantage of the recently emerged organocatalytic systems *e.g.* chiral secondary amines, chiral thioureas and chiral phosphoric acids. On the basis of the nature of stepwise addition of hydride, Hantzsch ester-mediated ATH reactions are often employed in the reaction cascades in conjunction with other highly enantio-selective organic transformations, even including some transition metal-catalyzed reactions, and found wide applications in the rapid construction of molecules of structural complexity and targets possessing various biological activities. The reduction processes with Hantzsch esters are usually performed under mild conditions (at ambient temperature or slightly heating or cooling). The experimental operation is simple and easy to handle because no special apparatus or techniques for high pressure process or air-free conditions are needed, which is typically regarded as a superiority compared to most transition metal-catalyzed hydrogenations. All these points make this biomimetic reductive process very attractive in modern organic synthesis. On the other hand, problems still remain with the current approaches involving Hantzsch esters, such as poor atom economical nature since only two protons are used per molecule and a stoichiometric amount of Hantzsch ester is needed. In addition, difficulties in removing pyridine byproducts may retard its applications in industrial scale synthesis. However, recent advances clearly demonstrated that chemists have already focused on overcoming these obstacles. A cheap and convenient hydrogen source may be employed as the final reductant, making *in situ* regeneration of organic hydride compounds possible. New organic hydride donors, including some polymer-based ones, have been synthesized and exhibited potential for easy-separation and recyclization. The findings discussed in this critical review will hopefully stimulate further development within this field. By overcoming the current drawbacks, it is reasonable to believe that the practical application of this biomimetic asymmetric transfer hydrogenation will arrive soon.

Acknowledgements

We thank the National Basic Research Program of China (973 Program 2010CB833300) and the NSFC (21025209) for generous financial support.

Notes and references

1 For selected reviews, see: (*a*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; (*b*) I. Ojima, *Catalytic Asymmetric Synthesis*, Wiley-VCH, Weinheim, 1999; (*c*) E. N. Jacobsen, A. Pfaltz and H. Yamamoto, *Comprehensive Asymmetric Catalysis*,

Springer, Berlin, 1999, vol. 1; (*d*) G.-Q. Lin, Y.-M. Li and A. S. C. Chan, *Principles and Applications of Asymmetric Synthesis*, Wiley & Sons, New York, 2001.

2 For selected reviews, see: (*a*) W. S. Knowles, *Angew. Chem., Int. Ed.*, 2002, **41**, 1998–2007; (*b*) R. Noyori, *Angew. Chem., Int. Ed.*, 2002, **41**, 2008–2022; (*c*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029–3070; (*d*) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, *Adv. Synth. Catal.*, 2003, **345**, 103–151; (*e*) X. Cui and K. Burgess, *Chem. Rev.*, 2005, **105**, 3272–3296; (*f*) C. Jäkel and R. Paciello, *Chem. Rev.*, 2006, **106**, 2912–2942; (*g*) S. Gladiali and E. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226–236.

3 (*a*) B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts and J. D. Watson, *Molecular Biology of the Cell*, Garland, New York & London, 3rd edn, 2002; (*b*) J. M. Berg, J. L. Tymoczko and J. L. L. Stryer, *Biochemistry*, W. H. Freeman & Company, New York, 5th edn, 2002.

4 (*a*) A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1881, **14**, 1637–1638; (*b*) A. Hantzsch, *Justus Liebigs Ann. Chem.*, 1882, **215**, 1–82.

5 For reviews on transfer hydrogenation reactions with Hantzsch esters, see: (*a*) H. Adolfsson, *Angew. Chem., Int. Ed.*, 2005, **44**, 3340–3342; (*b*) J. Rosen, *Chemtracts*, 2005, **18**, 65–71; (*c*) S.-L. You, *Chem.–Asian J.*, 2007, **2**, 820–827; (*d*) S. G. Ouellet, A. M. Walji and D. W. C. MacMillan, *Acc. Chem. Res.*, 2007, **40**, 1327–1339; (*e*) S. J. Connon, *Org. Biomol. Chem.*, 2007, **5**, 3407–3417; (*f*) C. Wang, X. Wu and J. Xiao, *Chem.–Asian J.*, 2008, **3**, 1750–1770; (*g*) M. Rueping, E. Sugiono and F. R. Schoepke, *Synlett*, 2010, 852–865; (*h*) M. Rueping, J. Dufour and F. R. Schoepke, *Green Chem.*, 2011, **13**, 1084–1105.

6 For selected examples of racemic transfer hydrogenation with Hantzsch esters, see: (*a*) J. B. Steevens and U. K. Pandit, *Tetrahedron*, 1983, **39**, 1395–1400; (*b*) M. Fujii, T. Aida, M. Yoshihara and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 3845–3847; (*c*) T. Itoh, K. Nagata, A. Kurihara, M. Miyazaki and A. Ohsawa, *Tetrahedron Lett.*, 2002, **43**, 3105–3108; (*d*) Z. Zhang, J. Gao, J.-J. Xia and G.-W. Wang, *Org. Biomol. Chem.*, 2005, **3**, 1617–1619; (*e*) D. Menche, J. Hassfeld, J. Li, G. Menche, A. Ritter and S. Rudolph, *Org. Lett.*, 2006, **8**, 741–744; (*f*) Z. Liu, Q. Liu, W. Zhang, R. Mu, L. Yang, Z.-L. Liu and W. Yu, *Synthesis*, 2006, 771–774; (*g*) D. Menche and F. Arikan, *Synlett*, 2006, 841–844; (*h*) M. Rueping, T. Theissmann and A. P. Antonchick, *Synlett*, 2006, 1071–1074; (*i*) D. Menche, S. Böhm, J. Li, S. Rudolph and W. Zander, *Tetrahedron Lett.*, 2007, **48**, 365–369; (*j*) Z. Zhang and P. R. Schreiner, *Synthesis*, 2007, 2559–2564; (*k*) Z. Zhang and P. R. Schreiner, *Synlett*, 2007, 1455–1457; (*l*) J. Zhou and B. List, *Synlett*, 2007, 2037–2040; (*m*) A. Bruckmann, M. A. Pena and C. Bolm, *Synlett*, 2008, 900–902; (*n*) J. Che and Y. Lam, *Synlett*, 2010, 2415–2420; (*o*) M. Zhang, H. Yang, Y. Zhang, C. Zhu, W. Li, Y. Cheng and H. Hu, *Chem. Commun.*, 2011, **47**, 6605–6607.

7 For selected reviews, see: (*a*) B. List, *Tetrahedron*, 2002, **58**, 5573–5590; (*b*) G. Lelais and D. W. C. MacMillan, *Adrichimica Acta*, 2006, **39**, 79–87; (*c*) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discovery Today*, 2007, **12**, 8–27; (*d*) A. Erkkila, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416–5470; (*e*) A. Mielgo and C. Palomo, *Chem.–Asian J.*, 2008, **3**, 922–948; (*f*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138–6171; (*g*) J. B. Brazier and N. C. O. Tomkinson, *Top. Curr. Chem.*, 2010, **291**, 281–347.

8 (*a*) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 6660–6662; (*b*) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 108–110.

9 S. G. Ouellet, J. B. Tuttle and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 32–33.

10 I. Paterson and N. A. Miller, *Chem. Commun.*, 2008, 4708–4710.

11 T. J. Hoffman, J. Dash, J. H. Rigby, S. Arseniyadis and J. Cossy, *Org. Lett.*, 2009, **11**, 2756–2759.

12 S. Mayer and B. List, *Angew. Chem., Int. Ed.*, 2006, **45**, 4193–4195.

13 Selected example of ACDC strategy used in other reactions with a chiral phosphate ion providing the chiral environment, see: (*a*) V. Komanduri and M. J. Krische, *J. Am. Chem. Soc.*, 2006, **128**, 16448–16449; (*b*) G. L. Hamilton, E. J. Kang, M. Mba and F. D. Toste, *Science*, 2007, **317**, 496–499; (*c*) S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336–11337; (*d*) X. Wang and B. List, *Angew. Chem.,Int. Ed.*, 2008, **47**, 1119–1122; (*e*) G. L. Hamilton, T. Kanai and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 14984–14985; (*f*) R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner and F. D. Toste, *Angew. Chem. Int. Ed.*, 2010, **49**, 598–601; (*g*) S. Liao and B. List, *Angew. Chem., Int. Ed.*, 2010, **49**, 628–631; (*h*) M. Hatano, K. Moriyama, T. Maki and K. Ishihara, *Angew. Chem., Int. Ed.*, 2010, **49**, 3823–3826; (*i*) Z. Zhang, W. Zheng and J. C. Antilla, *Angew. Chem., Int. Ed.*, 2011, **50**, 1135–1138; (*j*) W. Zheng, Z. Zhang, M. J. Kaplan and J. C. Antilla, *J. Am. Chem. Soc.*, 2011, **133**, 3339–3341; (*k*) V. Rauniyar, Z. J. Wang, H. E. Burks and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 8486–8489; (*l*) G. Jiang, R. Halder, Y. Fang and B. List, *Angew. Chem., Int. Ed.*, 2011, **50**, 9752–9755.

14 (*a*) K. Akagawa, H. Akabane, S. Sakamoto and K. Kudo, *Org. Lett.*, 2008, **10**, 2035–2037; (*b*) K. Akagawa, H. Akabane, S. Sakamoto and K. Kudo, *Tetrahedron: Asymmetry*, 2009, **20**, 461–466.

15 For a nornicotine-catalyzed transfer hydrogenation of α,β-unsaturated aldehydes using 1,4-dihydropyridine-3,5-dicarboxylic acid in aqueous solution, see: A. P. Brogan, T. J. Dickerson and K. D. Janda, *Chem. Commun.*, 2007, 4952–4954.

16 N. J. A. Martin and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13368–13369.

17 J. B. Tuttle, S. G. Ouellet and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 12662–12663.

18 A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 2458–2460.

19 O. Gutierrez, R. G. Iafe and K. N. Houk, *Org. Lett.*, 2009, **11**, 4298–4301.

20 For selected reviews, see: (*a*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289–296; (*b*) T. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299–4306; (*c*) S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418–5427; (*d*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520–1543; (*e*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713–5743; (*f*) Z. G. Zhang and P. R. Schreiner, *Chem. Soc. Rev.*, 2009, **38**, 1187–1198; (*g*) P. M. Pihko, *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH, Weinheim, 2009.

21 (*a*) N. J. A. Martin, L. Ozores and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 8976–8977; (*b*) N. J. A. Martin, X. Cheng and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 13862–13863.

22 Slightly prior to List's work, Stewart *et al.* reported an enzyme-catalyzed ATH reaction of β-nitroacrylates with NADPH as the reducing agent: M. A. Swiderska and J. D. Stewart, *Org. Lett.*, 2006, **8**, 6131–6133.

23 J. F. Schneider, M. B. Lauber, V. Muhr, D. Kratzer and J. Paradies, *Org. Biomol. Chem.*, 2011, **9**, 4323–4327.

24 Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051–15053.

25 J. W. Yang, M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036–15037.

26 A. Michrowska and B. List, *Nat. Chem.*, 2009, **1**, 225–228.

27 G.-L. Zhao and A. Córdova, *Tetrahedron Lett.*, 2006, **47**, 7417–7421.

28 S.-K. Xiang, B. Zhang, L.-H. Zhang, Y. Cui and N. Jiao, *Chem. Commun.*, 2011, **47**, 5007–5009.

29 M. Rueping, K. L. Haack, W. Ieawsuwan, H. Sundén, M. Blanco and F. J. R. Schoepke, *Chem. Commun.*, 2011, **47**, 3828–3830.

30 (*a*) D. B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.*, 2006, **47**, 651–656; (*b*) D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056–5068; (*c*) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2008, **6**, 2488–2492; (*d*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4176–4187; (*e*) D. B. Ramachary, M. Kishor and Y. V. Reddy, *Eur. J. Org. Chem.*, 2008, 975–993; (*f*) D. B. Ramachary and Y. V. Reddy, *J. Org. Chem.*, 2010, **75**, 74–85; (*g*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2010, **8**, 2859–2867; (*h*) D. B. Ramachary and M. S. Prasad, *Tetrahedron Lett.*, 2010, **51**, 5246–5251.

31 S. T.-C. Eey and M. J. Lear, *Org. Lett.*, 2010, **12**, 5510–5513.

32 S. Singh and U. K. Batra, *Indian J. Chem.*, 1989, **28B**, 1–2. Unfortunately, the enantioselectivities reported in this paper could not be reproduced, see ref. 47*b*.

33 For selected reviews, see: (*a*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744–5758; (*b*) M. Terada, *Chem. Commun.*, 2008, 4097–4112; (*c*) M. Terada, *Synthesis*, 2010, 1929–1982; (*d*) M. Terada, *Bull. Chem. Soc. Jpn.*, 2010, 101–119; (*e*) A. Zamfir, S. Schenker, M. Freund and S. B. Tsogoeva, *Org. Biomol. Chem.*, 2010, **8**,

5262–5276; (*f*) M. Rueping, A. Kuenkel and I. Atodiresei, *Chem. Soc. Rev.*, 2011, **40**, 4539–4549; (*g*) M. Rueping, B. J. Nachtsheim, W. Ieawsuwan and I. Atodiresei, *Angew. Chem., Int. Ed.*, 2011, **50**, 6706–6720.
34 M. Rueping, E. Sugiono, C. Azap, T. Theissmann and M. Bolte, *Org. Lett.*, 2005, **7**, 3781–3783.
35 S. Hoffmann, A. M. Seayad and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 7424–7427.
36 L. Simón and J. M. Goodman, *J. Am. Chem. Soc.*, 2008, **130**, 8741–8747.
37 (*a*) T. Marcelli, P. Hammar and F. Himo, *Chem.–Eur. J.*, 2008, **14**, 8562–8571; (*b*) T. Marcelli, P. Hammar and F. Himo, *Adv. Synth. Catal.*, 2009, **351**, 525–529.
38 T. B. Nguyen, H. Bousserouel, Q. Wang and F. Guéritte, *Org. Lett.*, 2010, **12**, 4705–4707.
39 T. B. Nguyen, H. Bousserouel, Q. Wang and F. Guéritte, *Adv. Synth. Catal.*, 2011, **353**, 257–262.
40 G. Li, Y. Liang and J. C. Antilla, *J. Am. Chem. Soc.*, 2007, **129**, 5830–5831.
41 Q. Kang, Z.-A. Zhao and S.-L. You, *Adv. Synth. Catal.*, 2007, **349**, 1657–1660, Corrigendum: *Adv. Synth. Catal.* 2007, **349**, 2075.
42 Q. Kang, Z.-A. Zhao and S.-L. You, *Org. Lett.*, 2008, **10**, 2031–2034.
43 G. Li and J. C. Antilla, *Org. Lett.*, 2009, **11**, 1075–1078.
44 R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84–86.
45 V. N. Wakchaure, M. Nicoletti, L. Ratjen and B. List, *Synlett*, 2010, 2708–2710.
46 A. Kumar, S. Sharma and R. A. Maurya, *Adv. Synth. Catal.*, 2010, **352**, 2227–2232.
47 (*a*) S. Hoffmann, M. Nicoletti and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13074–13075; (*b*) V. N. Wakchaure, J. Zhou, S. Hoffmann and B. List, *Angew. Chem., Int. Ed.*, 2010, **49**, 4612–4614.
48 G. Barbe and A. B. Charette, *J. Am. Chem. Soc.*, 2008, **130**, 18–19.
49 G. Pelletier, W. S. Bechara and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 12817–12819.
50 M. Rueping and A. P. Antonchick, *Angew. Chem., Int. Ed.*, 2007, **46**, 4562–4565.
51 M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 3683–3686.
52 M. Rueping and T. Theissmann, *Chem. Sci.*, 2010, **1**, 473–476.
53 Q.-S. Guo, D.-M. Du and J. Xu, *Angew. Chem., Int. Ed.*, 2008, **47**, 759–762.
54 C. Metallinos, F. B. Barrett and S. Xu, *Synlett*, 2008, 720–724.
55 M. Rueping, T. Theissmann, S. Raja and J. W. Bats, *Adv. Synth. Catal.*, 2008, **350**, 1001–1006.
56 M. Rueping, T. Theissmann, M. Stoeckel and A. P. Antochick, *Org. Biomol. Chem.*, 2011, **9**, 6844–6850.
57 (*a*) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 6751–6755; (*b*) M. Rueping, F. Tato and F. R. Schoepke, *Chem.–Eur. J.*, 2010, **16**, 2688–2691.
58 M. Rueping, M. Stoeckel, E. Sugiono and T. Theissmann, *Tetrahedron*, 2010, **66**, 6565–6568.
59 M. Rueping, E. Sugiono, A. Steck and T. Theissmann, *Adv. Synth. Catal.*, 2010, **352**, 281–287.
60 Z.-Y. Han, H. Xiao and L.-Z. Gong, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3729–3732.
61 M. Rueping, E. Merino and R. M. Koenigs, *Adv. Synth. Catal.*, 2010, **352**, 2629–2634.
62 M. Rueping, C. Brinkmann, A. P. Antonchick and I. Atodiresei, *Org. Lett.*, 2010, **12**, 4604–4607.
63 S.-M. Lu, Y.-Q. Wang, X.-W. Han and Y.-G. Zhou, *Chin. J. Catal.*, 2005, **26**, 287–290.
64 D.-W. Wang, W. Zeng and Y.-G. Zhou, *Tetrahedron: Asymmetry*, 2007, **18**, 1103–1107.
65 For a review, see: B. List, *Amine-catalyzed Aldol Reactions*, in *Modern Aldol Reactions*, ed. R. Mahrwald, Wiley-VCH, Weinheim, Germany, 2004, vol. 1, ch. 4, pp. 161–200.
66 J. Zhou and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 7498–7499.
67 M. Rueping and A. P. Antonchick, *Angew. Chem., Int. Ed.*, 2008, **47**, 5836–5838.
68 M. Rueping and L. Hubener, *Synlett*, 2011, 1243–1246.
69 Y.-G. Wang, T. Kumano, T. Kano and K. Maruoka, *Org. Lett.*, 2009, **11**, 2027–2029.
70 Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 9182–9183.
71 X.-Y. Liu and C.-M. Che, *Org. Lett.*, 2009, **11**, 4204–4207.
72 S. Zehani and G. Gelbard, *J. Chem. Soc., Chem. Commun.*, 1985, 1162–1163.
73 J. W. Yang and B. List, *Org. Lett.*, 2006, **8**, 5653–5655.
74 For reviews, see: (*a*) V. A. Burgess, S. G. Davies and R. T. Skerlj, *Tetrahedron: Asymmetry*, 1991, **2**, 299–328; (*b*) N.-X. Wang and J. Zhao, *Synlett*, 2007, 2785–2791.
75 (*a*) J.-L. Vasse, S. Goumain, V. Levacher, G. Dupas, G. Quéguiner and J. Bourguignon, *Tetrahedron Lett.*, 2001, **42**, 1871–1873; (*b*) N. Kanomata and T. Nakata, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1207–1211; (*c*) N. Kanomata and T. Nakata, *J. Am. Chem. Soc.*, 2000, **122**, 4563–4568; (*d*) X. Li and D. D. Tanner, *Tetrahedron Lett.*, 1996, **37**, 3275–3278; (*e*) N.-X. Wang and J. Zhao, *Adv. Synth. Catal.*, 2009, **351**, 3045–3050.
76 B. Procuranti and S. J. Connon, *Chem. Commun.*, 2007, 1421–1423.
77 H.-J. Xu, Y.-C. Liu, Y. Fu and Y.-D. Wu, *Org. Lett.*, 2006, **8**, 3449–3451.
78 For a non-enantioselective Hantzsch ester-mediated reduction of α,β-epoxy ketones, see: J. Zhang, M.-Z. Jin, W. Zhang, L. Yang and Z.-L. Liu, *Tetrahedron Lett.*, 2002, **43**, 9687–9689.
79 C. Zhu and T. Akiyama, *Org. Lett.*, 2009, **11**, 4180–4183.
80 C. Zhu and T. Akiyama, *Adv. Synth. Catal.*, 2010, **352**, 1846–4850.
81 A. Henseler, M. Kato, K. Mori and T. Akiyama, *Angew. Chem., Int. Ed.*, 2011, **50**, 8180–8183.
82 C. Zhu and T. Akiyama, *Synlett*, 2011, 1251–1254.
83 D. Enders, J. X. Liebich and G. Raabe, *Chem.–Eur. J.*, 2010, **16**, 9763–9766.
84 For selected previous examples for the immobilization of NADH analogs, see: (*a*) R. Mathis, G. Dupas, A. Decormeille and G. Quéguiner, *Tetrahedron Lett.*, 1981, **22**, 59–60; (*b*) G. Dupas, J. Bourguignon, C. Ruffin and G. Quéguiner, *Tetrahedron Lett.*, 1982, **23**, 5141–5144; (*c*) C. Vitry, J.-L. Vasse, G. Dupas, V. Levacher, G. Quéguiner and J. Bourguignon, *Tetrahedron*, 2001, **57**, 3087–3098; (*d*) D. Georges, T. Patrick, T. Thierry, C. Jacques, L. Denis, B. Jean and Q. Guy, *New. J. Chem.*, 1989, **13**, 255–258; (*e*) B. Jean, T. Patrick, T. Thierry, L. Denis, D. Georges and Q. Guy, *Bull. Soc. Chim. Fr.*, 1989, **2**, 264–266.
85 B. Zhang, X.-Q. Zhu, J.-Y. Lu, J. He, P. G. Wang and J.-P. Cheng, *J. Org. Chem.*, 2003, **68**, 3295–3298.
86 (*a*) R. He, P. H. Toy and Y. Lam, *Adv. Synth. Catal.*, 2008, **350**, 54–60; (*b*) J. Che and Y. Lam, *Adv. Synth. Catal.*, 2010, **352**, 1752–1758.
87 Q.-A. Chen, D.-S. Wang, Y.-G. Zhou, Y. Duan, H.-J. Fan, Y. Yang and Z. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 6126–6129.
88 Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432–16435.
89 (*a*) X.-Q. Zhu, M.-T. Zhang, A. Yu, C.-H. Wang and J.-P. Cheng, *J. Am. Chem. Soc.*, 2008, **130**, 2501–2516; (*b*) X.-Q. Zhu, Y. Tan and C.-T. Cao, *J. Phys. Chem. B*, 2010, **114**, 2058–2075.
90 (*a*) X.-Q. Zhu and Y. C. Liu, *J. Org. Chem.*, 1998, **63**, 2786–2787; (*b*) J.-P. Cheng, Y. Lu, X. Zhu and L. Mu, *J. Org. Chem.*, 1998, **63**, 6108–6114; (*c*) X.-Q. Zhu, Y.-C. Liu and J.-P. Cheng, *J. Org. Chem.*, 1999, **64**, 8980–8981; (*d*) X.-Q. Zhu, Y.-C. Liu, H.-Y. Wang and W. Wang, *J. Org. Chem.*, 1999, **64**, 8982–8983; (*e*) J.-P. Cheng, Y. Lu, X.-Q. Zhu, Y. Sun, F. Bi and J. He, *J. Org. Chem.*, 2000, **65**, 3853–3857; (*f*) X.-Q. Zhu, Y. Liu, B.-J. Zhao and J.-P. Cheng, *J. Org. Chem.*, 2001, **66**, 370–375; (*g*) X.-Q. Zhu, H.-R. Li, Q. Li, T. Ai, J.-Y. Lu, Y. Yang and J.-P. Cheng, *Chem.–Eur. J.*, 2003, **9**, 871–880; (*h*) X.-Q. Zhu, L. Cao, Y. Liu, Y. Yang, J.-Y. Lu, J.-S. Wang and J.-P. Cheng, *Chem.–Eur. J.*, 2003, **9**, 3937–3945; (*i*) X.-Q. Zhu, Z. Dai, A. Yu, S. Wu and J.-P. Cheng, *J. Phys. Chem. B*, 2008, **112**, 11694–11707.
91 This idea has been applied in the diagnoses of the characteristic chemical properties of imines and their reaction intermediates by Zhu and his co-workers, see: X.-Q. Zhu, Q.-Y. Liu, Q. Chen and L.-R. Mei, *J. Org. Chem.*, 2010, **75**, 789–808.

