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New Concepts for Catalysis

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Abstract

Organocatalysis, the catalysis with low-molecular weight catalysts where a metal is not part of the catalytic principle, can be as efficient and selective as metal- or biocatalysis. Important discoveries in this area include novel Lewis base-catalyzed enantioselective processes and, more recently, simple Brønsted acid organocatalysts that rival the efficiency of traditional metal-based asymmetric Lewis acid-catalysts. Contributions to organocatalysis from our laboratories include several new and broadly useful concepts such as enamine catalysis and asymmetric counteranion directed catalysis. Our lab has discovered the proline-catalyzed direct asymmetric intermolecular aldol reaction and introduced several other organocatalytic reactions.

Introduction: Organocatalysis

When chemists make chiral compounds – molecules that behave like object and mirror image, such as amino acids, sugars, drugs, or nucleic acids – they like to use asymmetric catalysis, in which a chiral catalyst selectively accelerates the reaction that leads to one mirror-image isomer, also called enantiomer. For decades, the generally accepted view has been that there are two classes of efficient asymmetric catalysts: enzymes and synthetic metal complexes [1]. However, this view is currently being challenged, with purely organic catalysts emerging as a third class of powerful asymmetric catalysts (Figure 1).

Most biological molecules are chiral and are synthesized in living cells by enzymes using asymmetric catalysis. Chemists also use enzymes or even whole cells to synthesize chiral compounds and for a long time, the perfect enantioselectivities observed in enzymatic reactions were considered beyond reach for non-biological catalysts. Such biological catalysis is increasingly used on an industrial scale and is particularly favoured for hydrolytic reactions. However, it became evident that high levels of enantioselectivity can also be achieved using synthetic metal complexes as catalysts. Transition metal catalysts are particularly useful for asymmetric hydrogenations, but may leave possibly toxic traces of heavy metals in the product.

In contrast, in organocatalysis, a purely organic and metal-free small molecule is used to catalyze a chemical reaction. In addition to enriching chemistry with another useful strategy for catalysis, this approach has some important advantages. Small organic molecule catalysts are generally stable and fairly easy to design and synthesize. They are often based on nontoxic compounds, such as sugars, peptides, or even amino acids, and can easily be linked to a solid support, making them useful for industrial applications. However, the property of organocatalysts most attractive to organic chemists may be the simple fact that they are organic molecules. The interest in this field has increased spectacularly in the last few years [2].

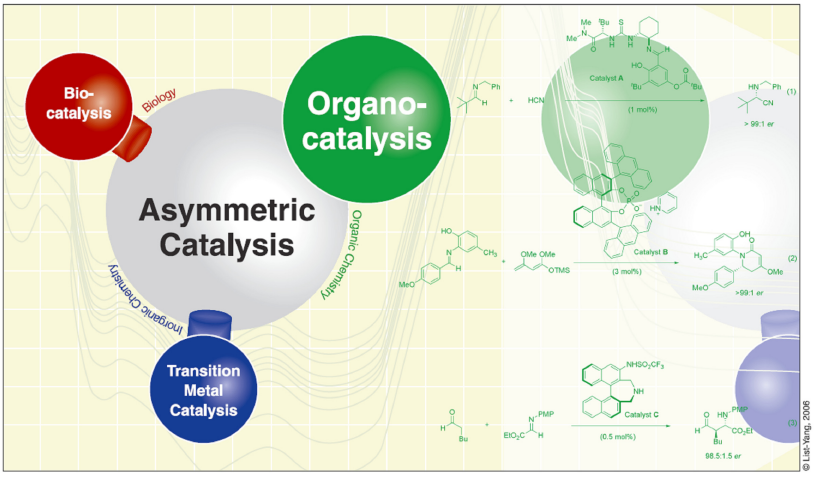
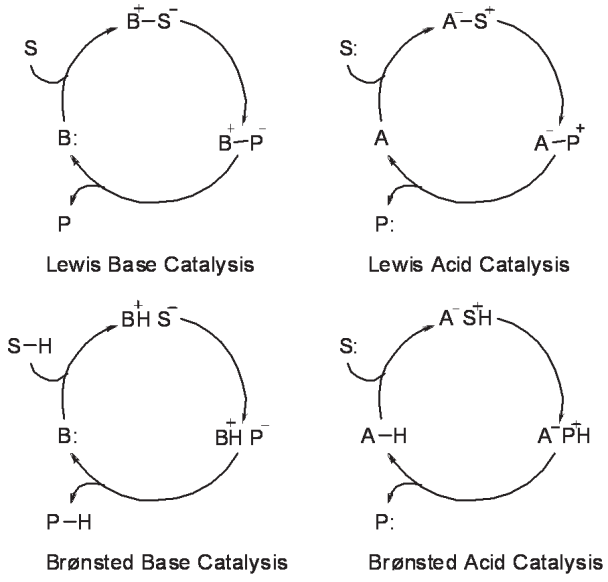


Figure 1. The three pillars of asymmetric catalysis: Biocatalyis, Metal Catalysis and Organocatalysis

Organocatalysts can be broadly classified as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids [3]. The corresponding (simplified) catalytic cycles are shown in Scheme 1. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the

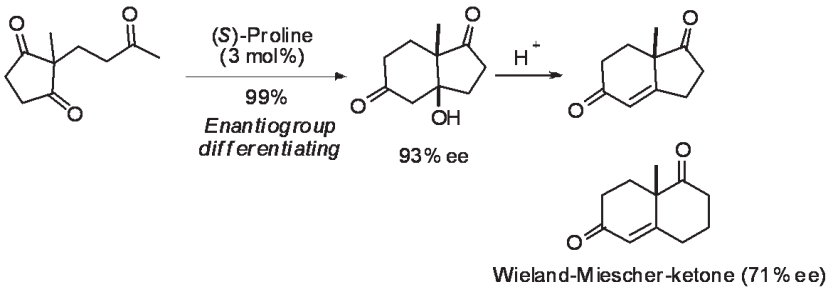
product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.



Scheme 1. Organocatalytic cycles.

Enamine Catalysis

Enamine catalysis involves a catalytically generated enamine intermediate that is formed via deprotonation of an iminium ion and that reacts with various electrophiles or undergoes pericyclic reactions. The first example of asymmetric enamine catalysis is the Hajos-Parrish-Eder-Sauer-Wiechert reaction [4] (Scheme 2), an intramolecular aldol reaction catalyzed by proline. Despite its use in natural product and steroid synthesis, the scope of the the Hajos-Parrish-Eder-Sauer-Wiechert reaction had not been explored, its mechanism was poorly understood, and its use was limited to a narrow context. Inspired by the development of elegant biocatalytic and transition metal complex-catalyzed direct asymmetric aldolizations [5], a revival of this chemistry was initiated with the discovery of the proline-catalyzed direct asymmetric intermolecular aldol reaction about thirty years later [6]. Since then proline-catalyzed enantioselective intermolecular aldol reactions [7], Mannich reactions [8] and Michael additions [9] have been developed [10].



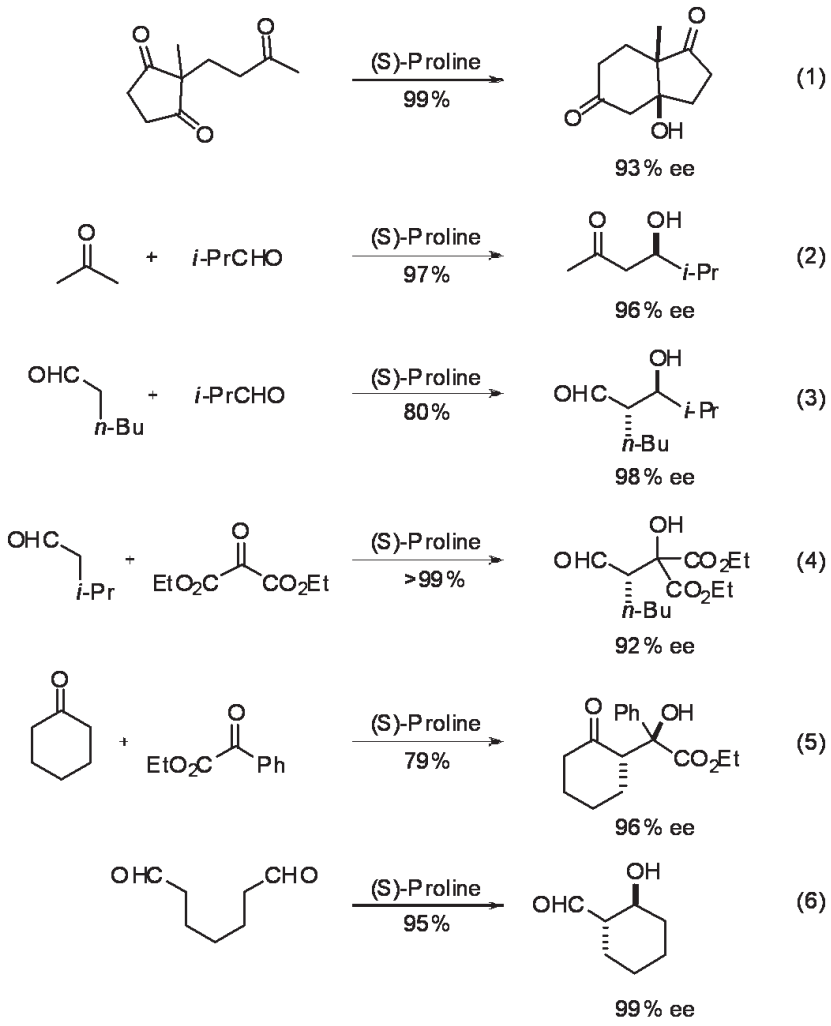
Scheme 2. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

This concept has also been extended to highly enantioselective α-functionalizations of aldehydes and ketones such as aminations [11], hydroxylations [12], alkylations [13], chlorination [14], fluorination [15], bromination [16], sulfenylation [17] and an intramolecular Michael reaction [18] using proline, as well as other chiral secondary amines and chiral imidazolidinones as the catalysts.

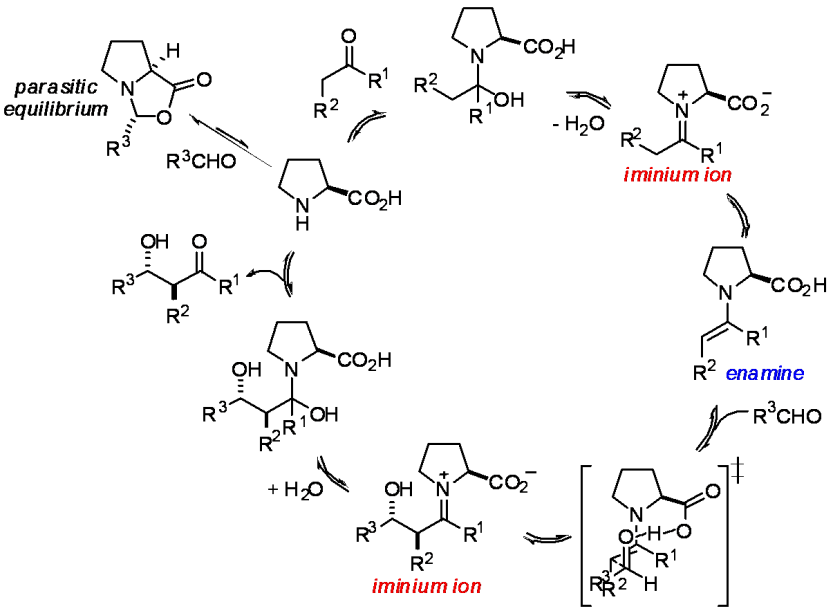
The proline-catalyzed asymmetric aldol reaction: scope, mechanism and consequences

In addition to catalyzing the well-known Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 3, eq. 1), we found in early 2000 that proline also catalyzes intermolecular aldolizations (e. g. eq. 2). Thereafter, our reaction has been extended to other substrate combinations (aldehyde to aldehyde, aldehyde to ketone, and ketone to ketone, eq. 3 – 5) and to enolexo-aldolizations (eq. 6) [7a, 7b, 19]. Proline seems to be a fairly general, efficient, and enantioselective catalyst of the aldol reaction and the substrate scope is still increasing continuously.

Both experimental and theoretical studies have contributed significantly to the elucidation of the reaction mechanism. We found that in contrast to earlier proposals [20], proline catalyzed aldol reactions do not show any non-linear effects in the asymmetric catalysis [21]. These lessons as well as isotope incorporation studies provided experimental support for our previously proposed single proline enamine mechanism and for Houk's similar DFT-model of the transition state of the intramolecular aldol reaction [22]. On the basis of these results we proposed the mechanism shown in Scheme 4. Key intermediates are the iminium ion and the enamine. Iminium ion formation effectively lowers the LUMO energy of the system. As a result, both nucleophilic additions and α-deprotonation become more facile. Deprotonation leads to the generation of the enamine, which is the actual nucleophilic carbanion equivalent. Its reaction with the aldehyde then provides, via transition state **TS** and hydrolysis, the enantiomerically enriched aldol product.

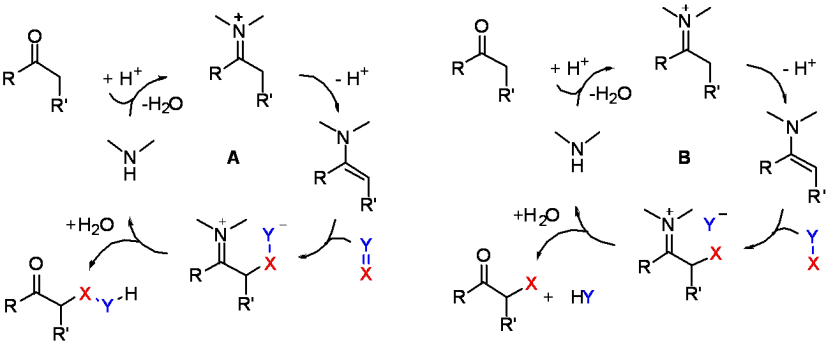


Scheme 3. Proline-catalyzed asymmetric aldol reactions.



Scheme 4. Proposed mechanism and transition state of proline-catalyzed aldolizations.

For us, the intriguing prospect arose, that the catalytic principle of the proline-catalyzed aldol reaction may be far more general than originally thought. We reasoned that simple chiral amines including proline should be able to catalytically generate chiral enamines as carbanion equivalents, which then may undergo reactions with various electrophiles. We termed this catalytic principle *enamine catalysis* (Scheme 5) [23]. Accordingly, the enamine, which is generated from the carbonyl compound via iminium ion formation can react with an electrophile X = Y (or X-Y) via nucleophilic addition (or substitution) to give an α-modified iminium ion and upon hydrolysis the α-modified carbonyl product (and HY).

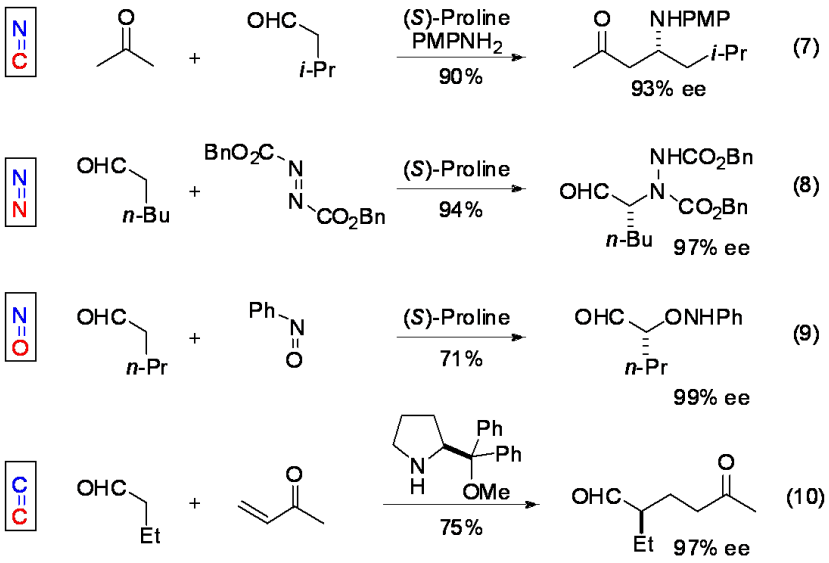


Scheme 5. Enamine catalysis of nucleophilic addition (**A**)- and substitution (**B**) reactions (arrows may be considered equilibria).

Enamine catalysis has developed dramatically in the last few years and it turns out that its scope not only exceeds our most optimistic expectations but also that of the traditional stoichiometric enamine chemistry of Stork and others.

Enamine catalysis of nucleophilic addition reactions

Enamine catalysis using proline or related catalysts has now been applied to both intermolecular and intramolecular nucleophilic addition reactions with a variety of electrophiles. In addition to carbonyl compounds (C = O), these include imines (C = N) in Mannich reactions [8], azodicarboxylates (N = N) [11], nitrosobenzene (O = N) [12], and Michael acceptors (C = C) [18, 24] (see Scheme 6, eq. 7 – 10 for selected examples).



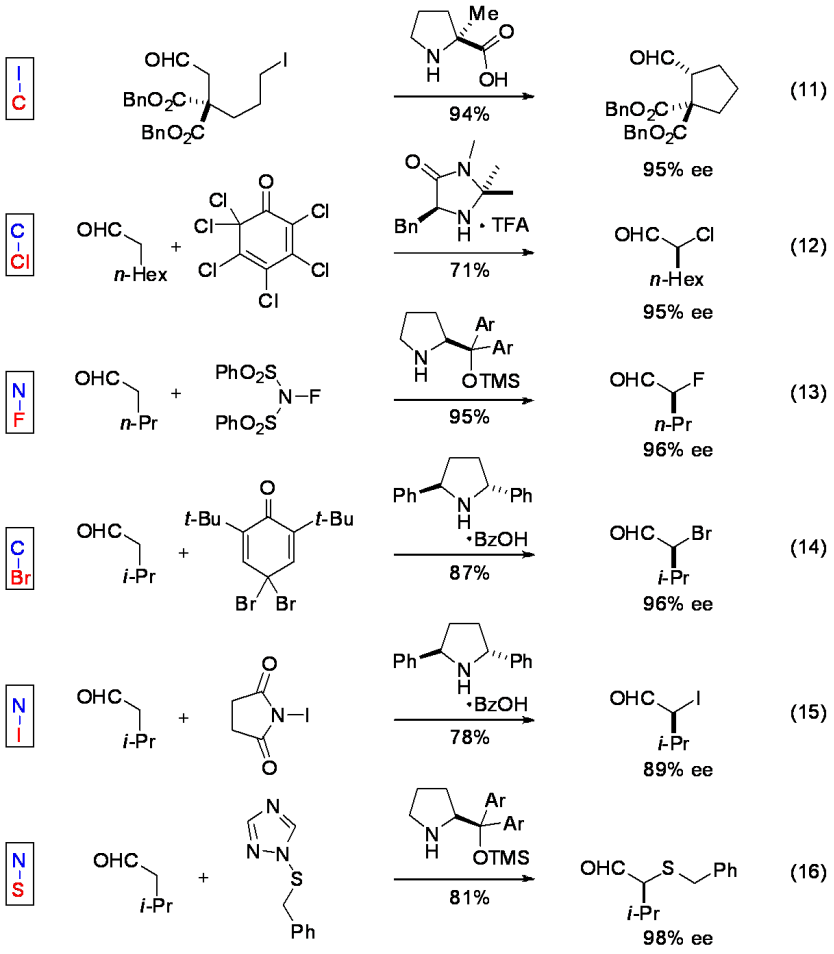
Scheme 6. Enamine catalysis of nucleophilic addition reactions.

Enamine catalysis often delivers valuable chiral compounds such as alcohols, amines, aldehydes, and ketones. Many of these are normally not accessible using established reactions based on transition metal catalysts or on preformed enolates or enamines, illustrating the complimentary nature of organocatalysis and metallocatalysis.

Enamine catalysis of nucleophilic substitution reactions

The first example of an asymmetric enamine catalytic nucleophilic substitution was a reaction that may have been considered impossible only a few years ago. We found that proline and certain derivatives such as α-methyl proline efficiently catalyze the asymmetric α-alkylation of aldehydes [13]. Catalytic α-alkylation reactions of substrates other than glycine

derivatives have been rare and that of aldehydes has been completely unknown before. In our process we could cyclize 6-halo aldehydes to give cyclopentane carbaldehydes in excellent yields and *ee*s (Scheme 7, eq. 11). Other important and remarkably useful enamine catalytic nucleophilic substitution reactions have been developed subsequently and include enantioselective α-chlorinations [14], α-fluorinations [15], α-brominations [16], α-iodinations, and α-sulfenylations [17] (eq. 12 – 16).

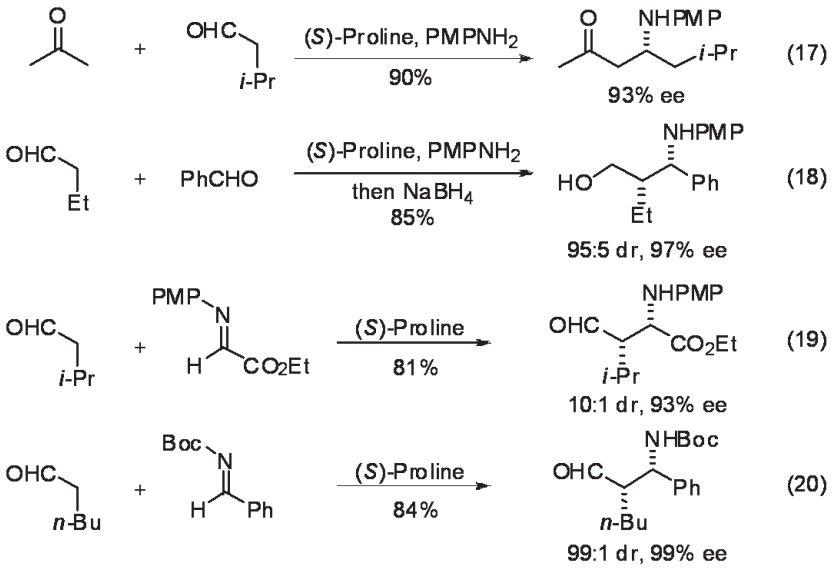


Scheme 7. Enamine catalysis of nucleophilic substitution reactions.

Once again, most of these reactions have never been realized before using preformed enamines or any other methodology but lead to highly valuable products of potential industrial relevance.

The proline-catalyzed asymmetric Mannich reactions

The catalytic asymmetric Mannich reaction is arguably the most useful approach to chiral α-amino carbonyl compounds. In the year 2000, we discovered a proline-catalyzed version of this powerful reaction [8a]. Originally, ketones, aldehydes, and an aniline as the amine component were used in a catalytic asymmetric three-component reaction (Scheme 8, eq 17). After our report, proline catalyzed Mannich reactions with aldehydes as the donor have also been developed [8d, 8e] (eq 18 – 19). Despite its frequent use, both in an academic as well as an industrial context, the main limitation of the proline-catalyzed Mannich reaction has been the requirement to use anilines as the amine component. Although optically enriched *p*-anisidylamines are of potential utility in asymmetric synthesis, facile and efficient removal of the *N*-protecting group to yield the unfunctionalized amine is required. Generally, the removal of the most commonly used *p*-methoxyphenyl (PMP) group from nitrogen requires rather drastic oxidative conditions involving harmful reagents such as ceric ammonium nitrate that are not compatible with all substrates. We have now identified reaction conditions that allow for the use of simple preformed aromatic *N*-Boc-imines in proline-catalyzed Mannich reactions (eq. 20). Remarkably, the reaction provides chiral β-amino aldehydes and ketones as stable, crystalline compounds in generally high diastereo- and enantioselectivities without the requirement for chromatographic purification [25].



Scheme 8. Proline-catalyzed asymmetric Mannich reactions.

A typical experimental procedure is illustrated in Figure 2. Mixing the 2-naphthaldehyde-derived *N*-Boc imine with isovaleraldehyde in the presence of (S)-proline (20 mol%) in acetonitrile at 0 °C resulted in an initially homogenous reaction mixture (Figure 2a). After complete consumption of the starting material (10 h), a large amount of the desired product had precipitated and could easily be collected by filtration (Figure 2b).

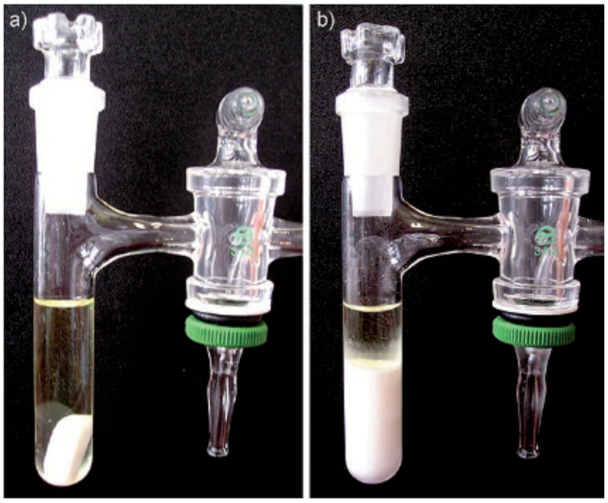
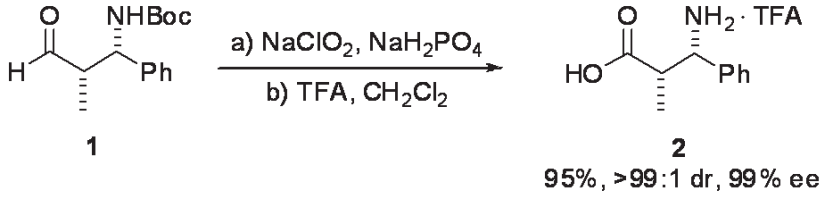


Figure 2. The reaction of isovaleraldehyde with 2-naphthyl *N*-Boc-imine in the presence of (S)-proline (20 mol%) in CH_3CN. (**a**) Homogenous reaction mixture after mixing all components. (**b**) Reaction mixture after completion of the reaction (10 h).

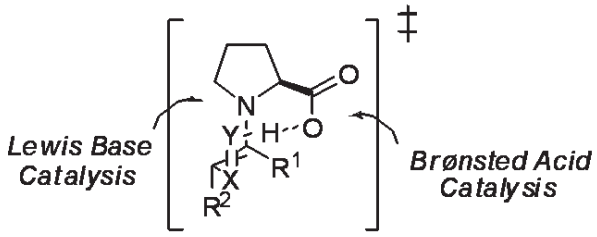
The *N*-Boc-imine-derived Mannich products can readily be converted into the corresponding α,β-branched-β-amino acids ($\beta^{2,3}$-amino acids). For example, oxidation of the product **1** to the carboxylic acid followed by acid-mediated deprotection provided the amino acid salt **2** without loss of stereochemical integrity (Scheme 9, TFA = trifluoroacetic acid). Measuring NMR spectra and optical rotation of the corresponding HCl salt allowed us to confirm the expected absolute and relative configuration of the product.



Scheme 9. Conversion of the Mannich product **1** to the β-amino acid **2.**

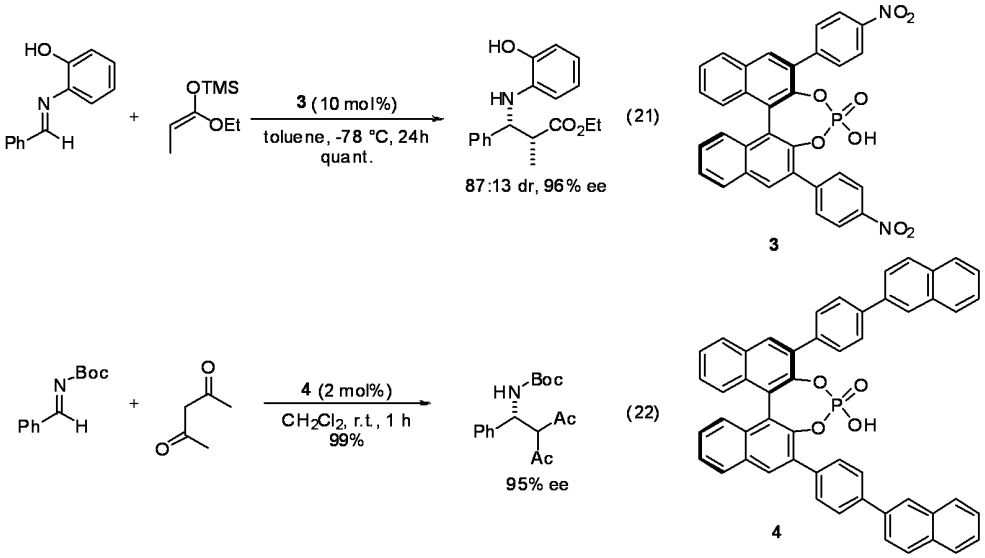
Brønsted Acid Catalysis

In the proline-based enamine catalysis, proline actually plays a dual role. The amino-group of proline acts as a Lewis base, whereas the carboxylic group acts as a Brønsted acid (Scheme 10).



Scheme 10. Proline: a bifunctional catalyst.

The potential of using relatively strong chiral organic Brønsted acids as catalysts (Specific Brønsted acid catalysis) has been essentially ignored over the last decades. Achiral acids such as p-TsOH have been used as catalysts for a variety of reactions since a long time, but applications in asymmetric catalysis have been extremely rare. Only very recently, Akiyama *et al.* [26] and Terada *et al.* [27] in pioneering studies demonstrated that relatively strong chiral binaphthol-derived phosphoric acids are efficient and highly enantioselective catalysts for addition reactions to aldimines (Scheme 11).

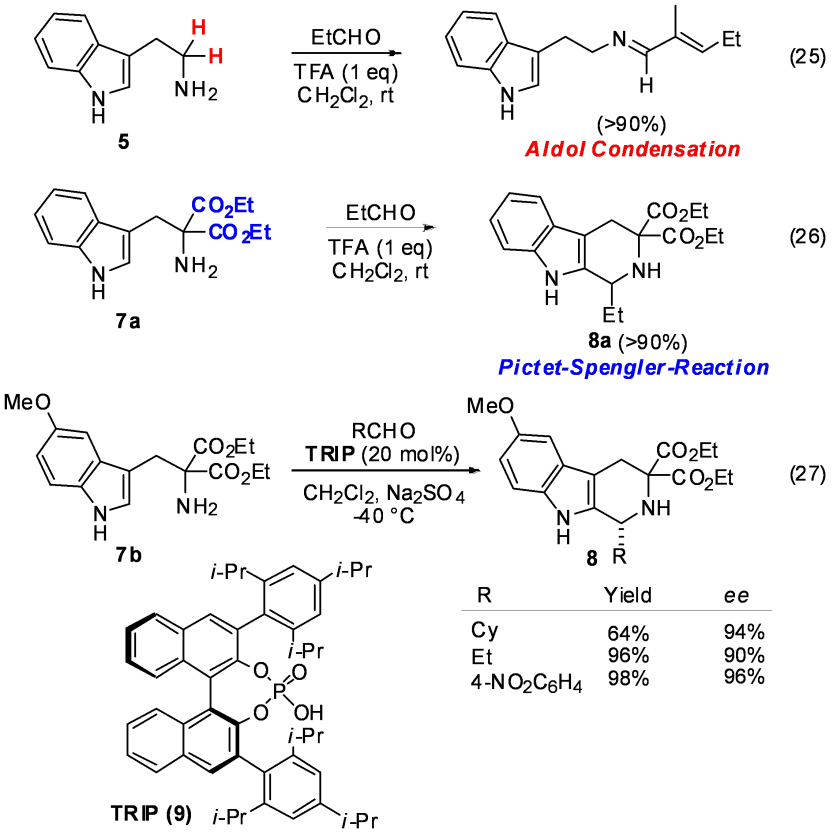


Scheme 11. Phosphoric acid catalysis pioneered by Akiyama and Terada.

Catalytic asymmetric Pictet-Spengler reaction

The Pictet-Spengler reaction [28] is an important acid-catalyzed transformation frequently used in the laboratory as well as by various organisms for the synthesis of tetrahydro-β-carbolines and tetrahydroisoquinolines from carbonyl compounds and 2-phenylethylamines or tryptamines, respectively.

Very recently, Jacobsen *et al.* [29] reported the first truly catalytic version by using an elegant organocatalytic acyl-Pictet-Spengler approach. The direct Pictet-Spengler reaction of aldehydes with 2-arylethylamines however, has been an illusive target for small molecule catalysis. Since the addition reactions to aldimines developed by Akiyama and Terada are assumed to involve chiral iminium phosphate ion pairs, we reasoned that a chiral phosphoric acid-catalyzed approach might be as well applicable to the Pictet-Spengler reaction, which also proceeds via iminium ion intermediates.



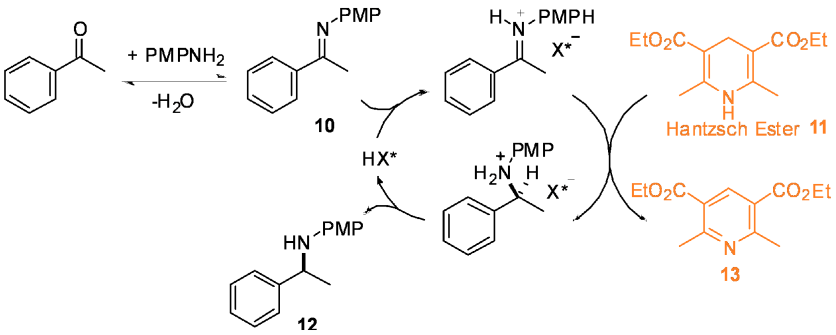
Scheme 12. Brønsted acid-catalyzed Pictet-Spengler reaction.

In line with observations by Jacobsen *et al.* attempts toward Brønsted acid catalysis of the Pictet-Spengler reaction of simple substrates such as unsubstituted tryptamines **5** and 2-phenylethylamines failed due to competing homoaldol condensation followed by imine formation (Scheme 12, eq. 25). A solution to this problem was the use of more reactive substrates such as geminally disubstituted tryptamines **7a** [30] predisposed for cyclization by virtue of a Thorpe-Ingold effect. Treatment of **7a** with TFA cleanly provided the desired Pictet-Spengler product **8a** in > 90% yield (eq. 26). Encouraged by this result we went on to develop an asymmetric version with the use of a chiral Brønsted acid catalyst. In the presence of BINOL phosphate **TRIP** (**9**) bearing bulky 2,4,6-triisopropylphenyl substituents at the 3,3'-positions of the binaphthyl scaffold and Na_2SO_4, tetrahydro-β-carbolines **8** were obtained in high yields along with excellent enantioselectivities (eq. 27) [31]. Remarkably, the reaction tolerates a variety of both aliphatic and aromatic aldehydes with excellent results.

Organocatalytic asymmetric reductive amination

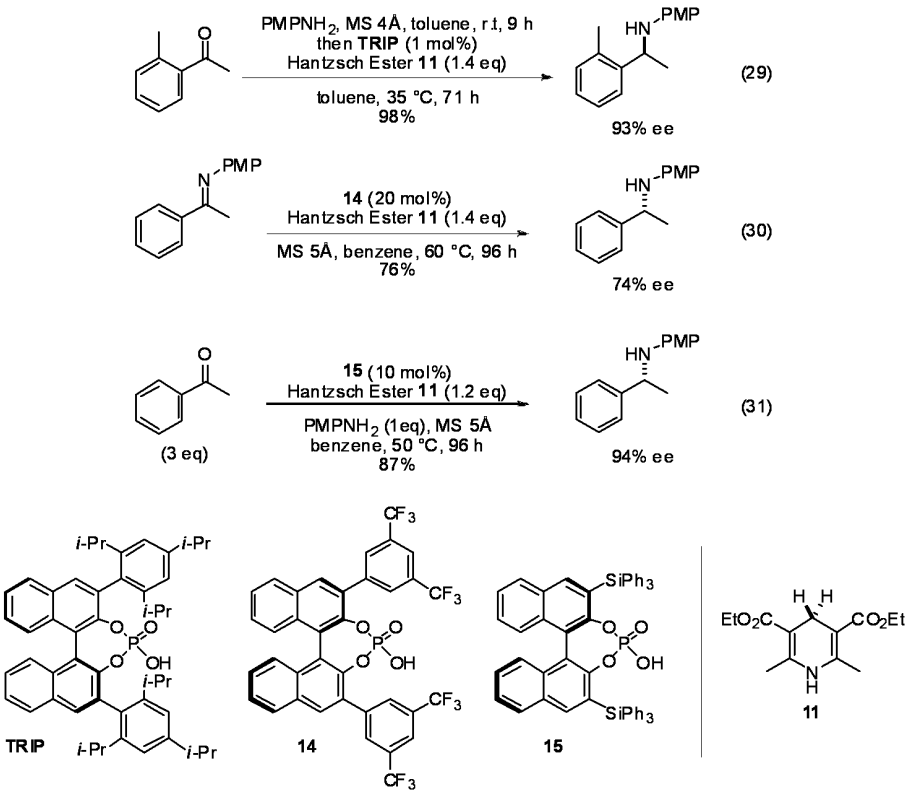
Catalytic asymmetric hydrogenations are among the most important transformations in organic chemistry. Although numerous methods employing olefins or ketones as substrates have been described [32], the corresponding hydrogenations or transfer hydrogenations of imines are less advanced [33]. Living organisms apply cofactors such as nicotinamide adenine dinucleotide (NADH) for enzyme-catalyzed reductions of imines [34].

Inspired by the recent observation that imines are reduced with Hantzsch dihydropyridines as a NADH analogue in the presence of achiral Lewis or Brønsted acid catalysts [35], we envisioned a catalytic cycle for the reductive amination of ketones which is initiated by protonation of the *in situ* generated ketimine **10** by a chiral Brønsted acid catalyst (Scheme 13). The resulting iminium ion pair is chiral and its reaction with the Hantzsch ester **11** could give rise to enantiomerically enriched α-branched amine **12** and pyridine **13.**



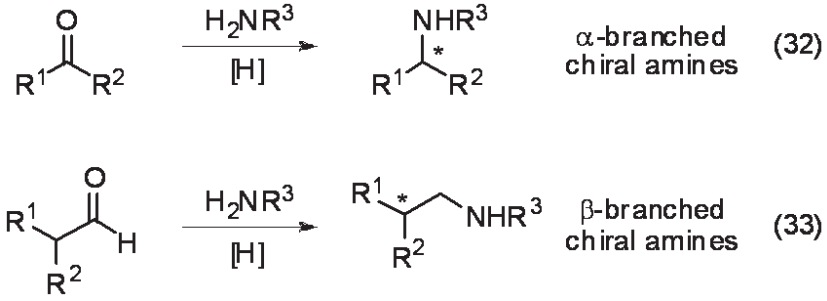
Scheme 13. Chiral Brønsted acid-catalyzed reductive amination.

Among all the phosphoric acids tested as chiral Brønsted acid catalyst in this reaction, TRIP was found to be the best. Only 1 mol% of TRIP was sufficient to give the desired product in an excellent yield of 96% and with 93% ee. (Scheme 14, eq. 29) [36]. A similar study by the Rueping group using Akiyama's phosphoric acid catalyst **14** appeared during the preparation of our manuscript (eq. 30) [37]. MacMillan and co-workers also developed a reductive amination of various ketones catalyzed by BINOL phosphate **15** (eq. 31) [38].

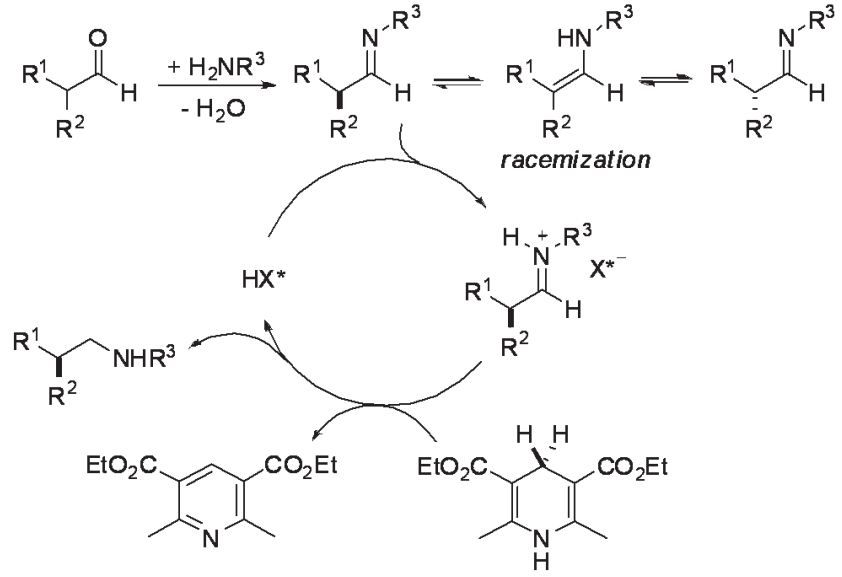


Scheme 14. Chiral phosphoric acid-catalyzed asymmetric reductive amination of ketones.

The previous examples are selected asymmetric reductive aminations of ketones to give chiral, α-branched amines (eq. 32); however, the corresponding reactions of aldehydes are unknown. We reasoned that such a process might be realized if enolizable, α-branched aldehydes are employed. Their asymmetric reductive amination should give β-branched amines via an enantiomer-differentiating kinetic resolution (eq. 33).



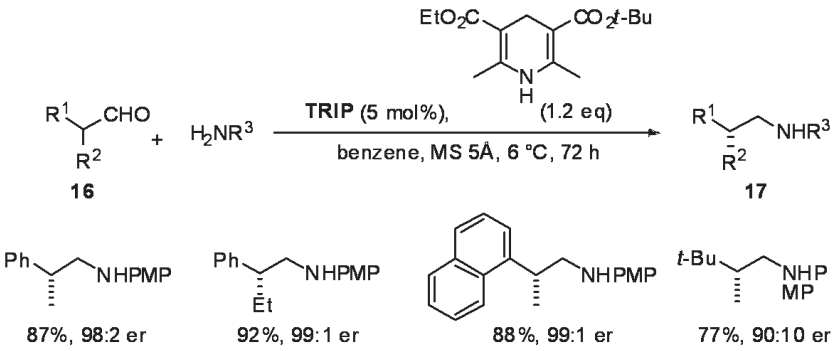
At the onset of this study, we hypothesized that under our reductive amination conditions an α-branched aldehyde substrate would undergo a fast racemization in the presence of the amine and acid catalyst via an imine/enamine tautomerization. The reductive amination of one of the two imine enantiomers would then have to be faster than that of the other, resulting in an enantiomerically enriched product via a dynamic kinetic resolution (Scheme 15) [39].



Scheme 15. Catalytic asymmetric reductive amination of aldehydes.

Indeed, when we studied various phosphoric acid catalysts for the reductive amination of hydratopicaldehyde (**16**) with *p*-anisidine ($PMPNH_2$) in the presence of Hantzsch ester **11** to give amine **17**, the observed enantioselectivities and conversions are consistent with a facile *in situ* racemization of the substrate and a resulting dynamic kinetic resolution (Scheme 16).

TRIP (**9**) once again turned out to be the most effective and enantioselective catalyst for this transformation and provided the chiral amine products with different α-branched aldehydes and amines in high enantioselectivities [40].

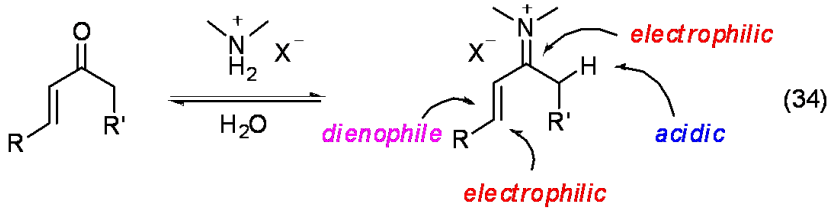


Scheme 16. Catalytic asymmetric reductive amination of aldehydes using **TRIP.**

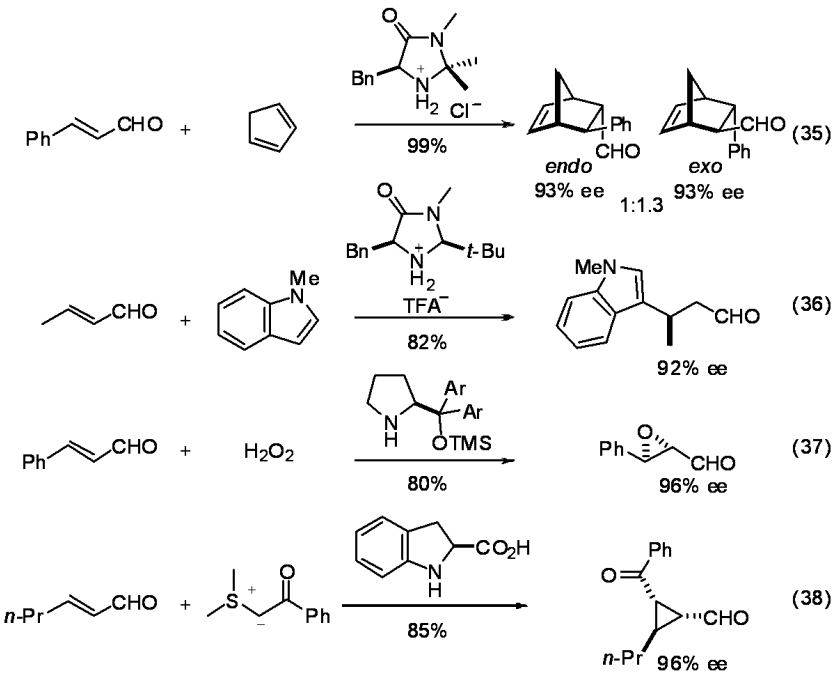
We later developed an analogous enantioselective hydrogenation of aldehydes to the corresponding β-branched alcohols using [$RuCl_2$(xylyl-BINAP)(DPEN or DACH)] as the catalyst [41].

Iminium Catalysis

The *in situ* generation of an iminium ion from a carbonyl compound lowers the LUMO energy of the system. *Iminium catalysis* is comparable to Brønsted- or Lewis acid activation of carbonyl compounds. The LUMO energy is lowered, the α-CH-acidity increases, and nucleophilic additions including conjugate additions as well as pericyclic reactions are facilitated (eq. 34).



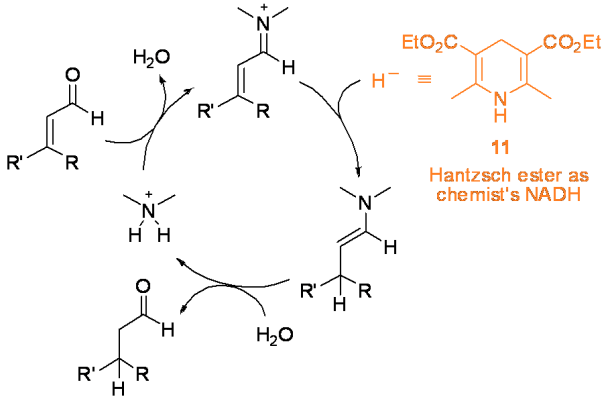
The first highly enantioselective examples of this catalysis strategy were reported by MacMillan *et al.* in 2000 [42], shortly after our first report on the proline-catalyzed intermolecular aldol reaction had appeared. The MacMillan group has quickly established that Diels-Alder reactions, 1,3-dipolar cycloadditions [43], and conjugate additions of electron rich aromatic and heteroaromatic compounds can be catalyzed using chiral amino acid derived imidazolidinones as catalysts (Scheme 17, eq. 35 – 38) [44]. In addition, highly enantioselective epoxidations [45] and cyclopropanations [46] have recently been developed.



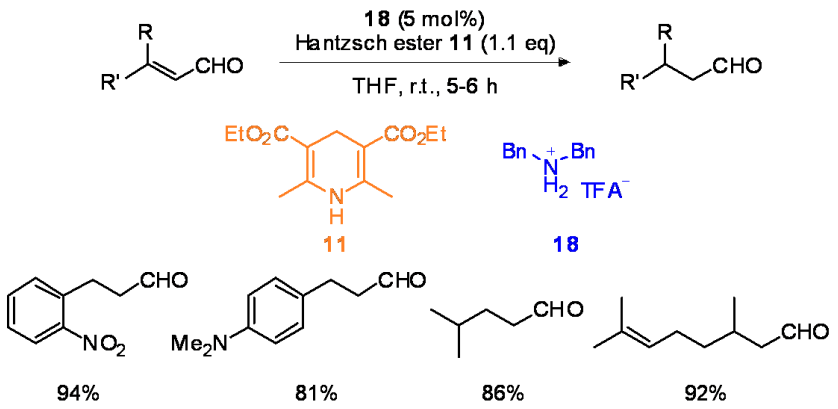
Scheme 17. Iminium catalytic asymmetric transformations.

Organocatalytic conjugate reduction of α,β*-unsaturated aldehydes*

In 2001, we reasoned that this catalysis strategy might be applicable to the conjugate reduction of α,β-unsaturated carbonyl compounds if a suitable hydride-donor could be identified. Hantzsch ester **11** was chosen as the hydride source for this reaction (Scheme 18).



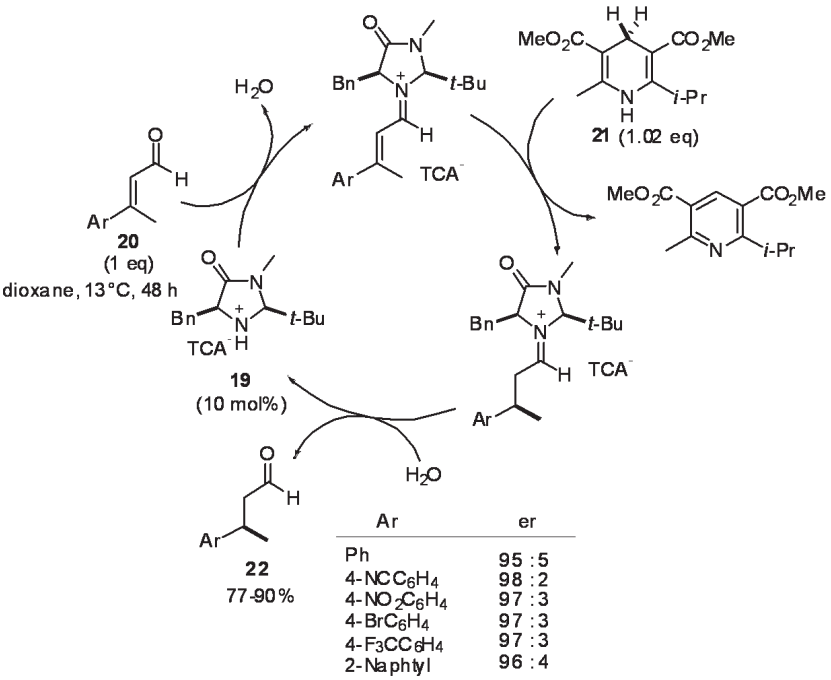
Scheme 18. Iminium catalytic transfer hydrogenation of α,β-unsaturated aldehydes.



Scheme 19. Organocatalytic transfer hydrogenation of enals.

This process was published in 2004 and constitutes the first metal-free organocatalytic transfer hydrogenation of α,β-unsaturated aldehydes [47a]. Dibenzylammonium trifluoroacetate **18**, was found to be an efficient catalyst for this reaction. The reduction worked extremely well with a diverse set of unsaturated aldehydes, including substituted aromatic and aliphatic ones and the yields exceed 90% in almost all cases (Scheme 19). A variety of functional groups that are sensitive to standard hydrogenation condition (nitro, nitrile, benzyloxy, and alkene functional groups) were tolerated in the process.

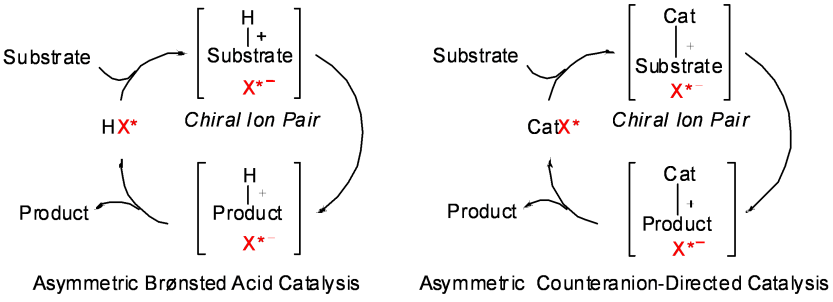
The first example of an asymmetric catalytic version was also presented in our first publication [47a]. This protocol was subsequently optimized and we developed a highly enantioselective variant using the trichloroacetate salt of MacMillan's second generation imidazolidinone (**19**) as the catalyst [47b]. We found that upon treating aromatic, trisubstituted α,β-unsaturated aldehydes **20** with a slight excess of dihydropyridine **21** and a catalytic amount of **19** at 13 °C in dioxane, the corresponding saturated aldehydes **22** were obtained in high yields and enantioselectivities (Scheme 20).



Scheme 20. Organocatalytic asymmetric transfer hydrogenation of enals.

Asymmetric Counteranion-directed Catalysis (ACDC)

Most chemical reactions proceed via charged intermediates or transition states. In asymmetric Brønsted acid catalysis the substrate is protonated by the catalyst and a chiral H-bond-assisted ion pair is generated. We reasoned that in principle any reaction that proceed via cationic intermediates can be conducted highly enantioselectively if a chiral counteranion is introduced into the catalyst, as a result of the generation of a chiral ion pair. We termed this new strategy as *Asymmetric Counteranion-Directed Catalysis* (ACDC) (Scheme 21).

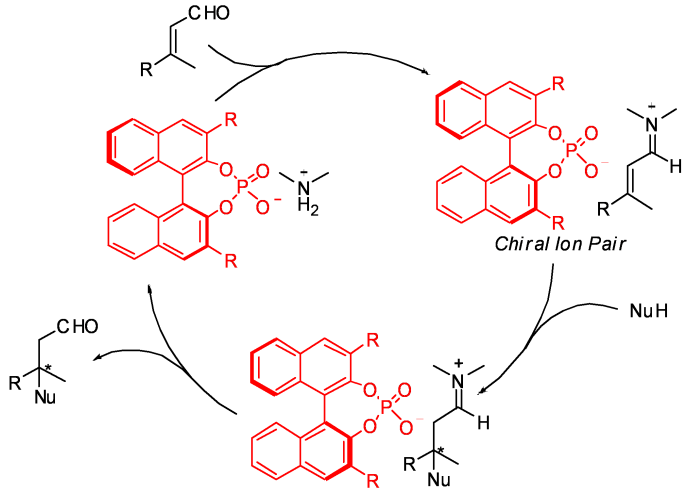


Scheme 21. Asymmetric counteranion-directed catalysis (ACDC).

Although efficient asymmetric catalytic transformations involving anionic intermediates with chiral, cationic catalysts have been realized [48], analogous versions of inverted polarity with reasonable enantioselectivity, despite attempts, have been illusive [49].

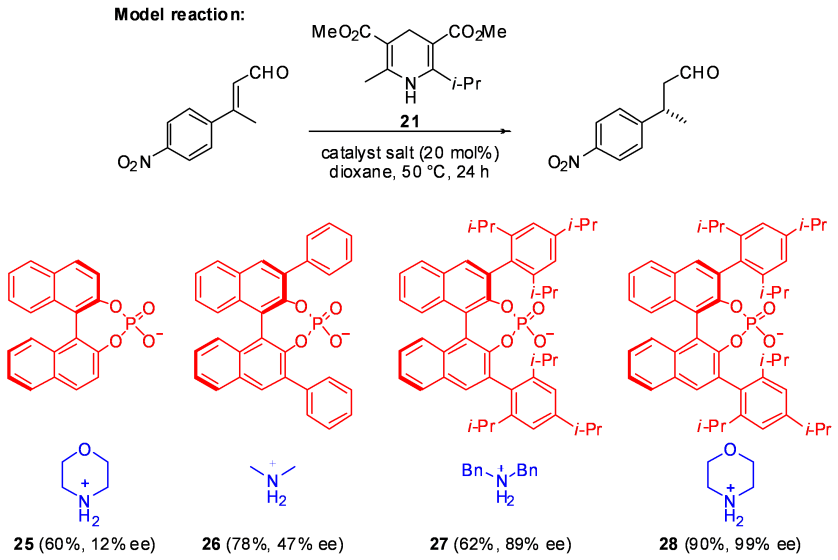
Asymmetric counteranion-directed catalysis: application to iminium catalysis

In iminium catalysis, both we and the group of MacMillan had observed a strong counteranion effect on the yield and enantioselectivity of the reactions. Inspired by recent use of chiral phosphoric acid derivatives as asymmetric catalysts, we hypothesized that catalytic salts of achiral amines and chiral phosphoric acids could induce asymmetry in these processes (Scheme 22).



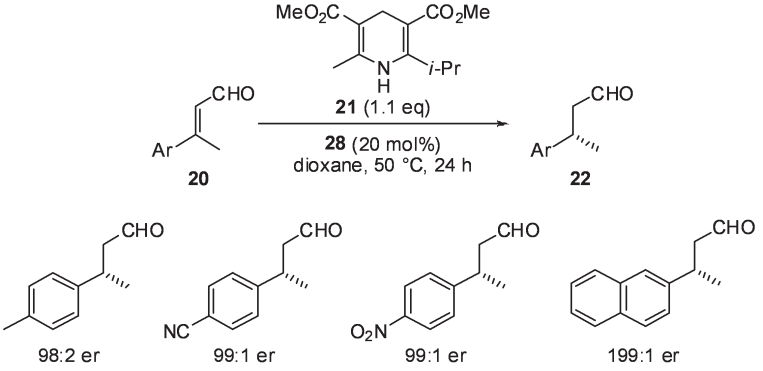
Scheme 22. Asymmetric counteranion-directed catalysis: application to iminium catalysis.

We thought to start with the metal-free biomimetic transfer hydrogenation of α,β-unsaturated aldehydes as a model reaction which has been earlier discovered in our laboratory and independently in that of MacMillan *et al.* (Scheme 23). We have prepared a large number of ammonium salts as crystalline solids by mixing different primary and secondary amines with a chiral phosphoric acid. In particular, the ammonium salts of sterically hindered chiral phosphoric acids could catalyze the reaction with significant enantiomeric excess (ee) values (Scheme 23). After a thorough screening of various amines we identified morpholine salt **28** as a highly enantioselective catalyst [50].



Scheme 23. ACDC: Screening studies.

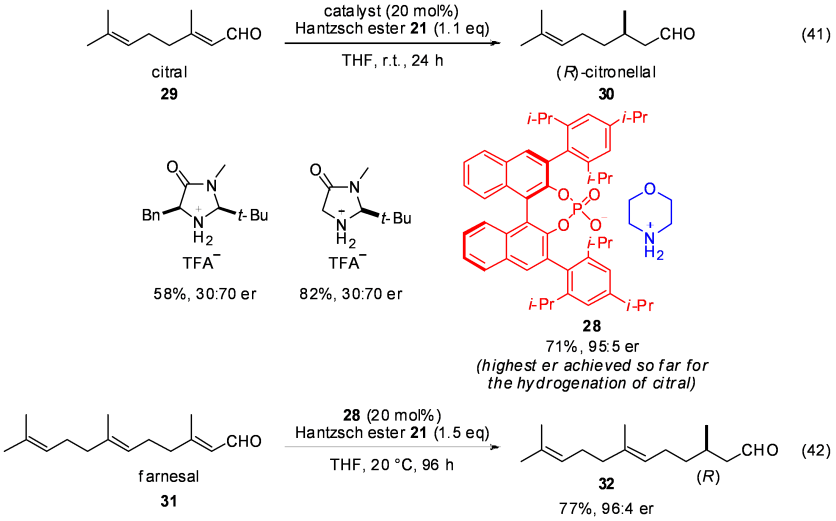
Treating aromatic, trisubstituted α,β-unsaturated aldehydes **20** with a slight excess of dihydropyridine **21** and a catalytic amount of salt **28** at 50 °C in dioxane for 24 h, the corresponding saturated aldehydes **22** were obtained in high yields and in enantioselectivities of 96 – 99% ee (Scheme 24).



Scheme 24. ACDC: Transfer hydrogenation of enals.

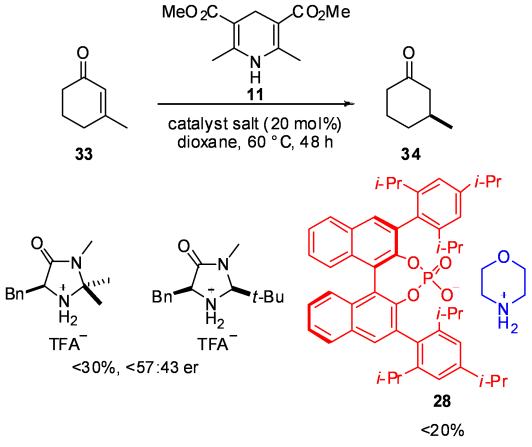
Significantly, the previously developed chiral amine based catalysts that we and MacMillan and co-workers have studied have not been of use for sterically nonhindered aliphatic substrates. For example, citral (**29**), of which the hydrogenation product citronellal (**30**) is an intermediate in the industrial synthesis of menthol and used as a perfume ingredient, could not readily be used (Scheme 25, eq. 41). We could not achieve high enantioselectivity for this particular substrate with either our previous system [47b] or with that of MacMillan and coworkers [47c]. However, with our novel chiral counteranion catalyst **28**, citral is

converted into (R)-citronellal (**30**) with an e.r. value of 95:5. This has been the highest enantioselectivity reported for a catalytic asymmetric (transfer) hydrogenation of citral [51]. Similarly, farnesal (**31**) gave (R)-dihydrofarnesal (**32**) in 77% yield and 96:4 er (Scheme 25, eq. 42).



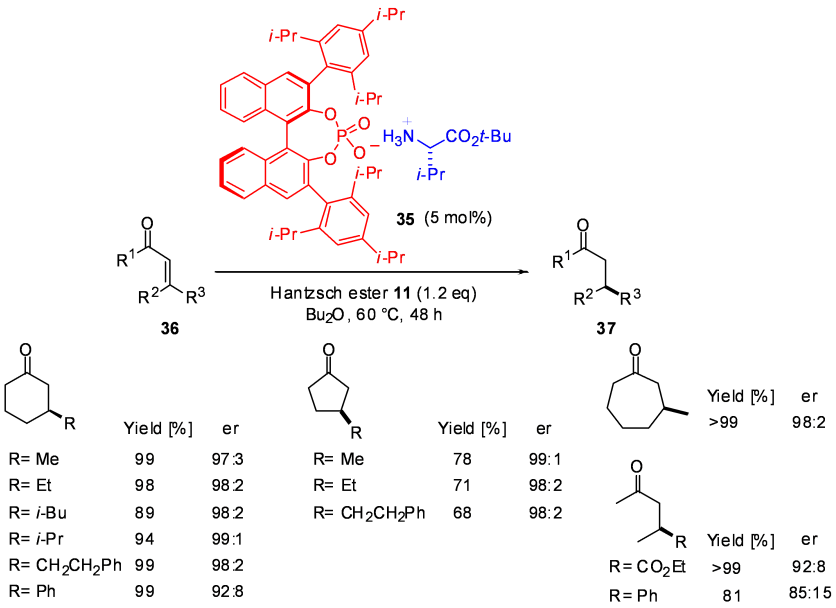
Scheme 25. ACDC: Transfer hydrogenation of citral and farnesal.

Next, we sought to extend this methodology to the conjugate reduction of α,β-unsaturated ketones. However, neither these ACDC-catalysts, nor the commonly used chiral imidazolidinone-catalysts gave satisfying yields or enantioselectivities in the conjugate reduction of 3-methyl cyclohexenone **33** (Scheme 26).



Scheme 26. ACDC: Transfer hydrogenation of 3-methyl cyclohexenone: first attempts.

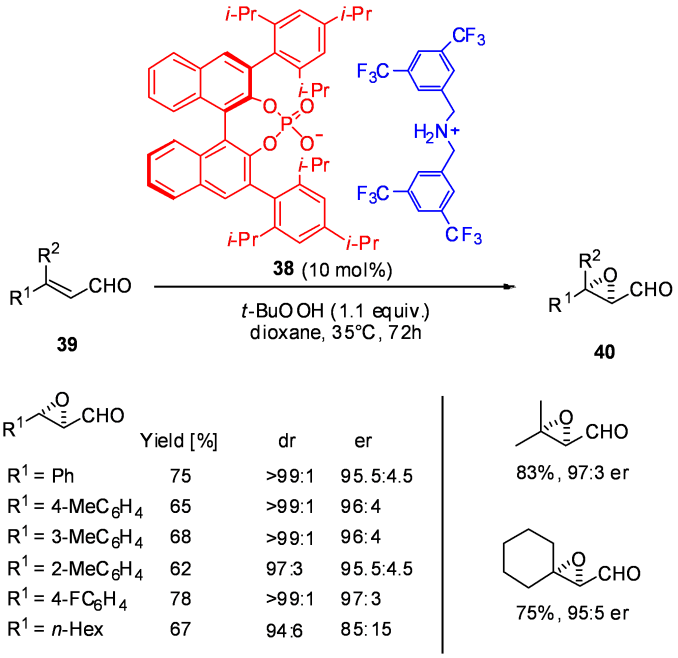
Hypothesizing that primary amine salt catalysts might be suitable for the activation of ketones due to their reduced steric requirements we studied various salts of α-amino acid esters [52]. We have developed a new class of catalytic salts, in which both the cation and the anion are chiral. In particular, valine ester phosphate salt **35** proved to be an active catalyst for the transfer hydrogenation of a variety of α,β-unsaturated ketones **36** with commercially available Hantzsch ester **11** to give saturated ketones **37** in excellent enantioselectivities (Scheme 27) [53].



Scheme 27. ACDC: Transfer hydrogenation of enones.

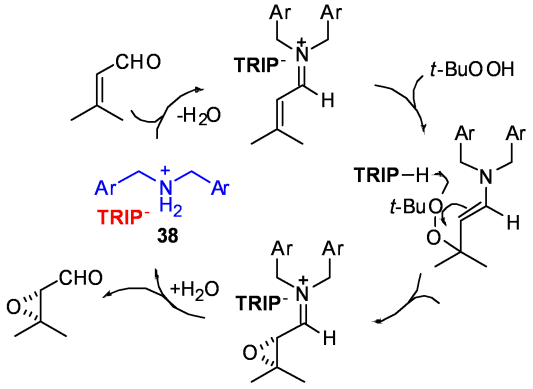
Independently, MacMillan *et al.* developed an efficient catalyst system based on a chiral secondary amine for the transfer hydrogenation of cyclic enones [54].

Furthermore, the ACDC concept was successfully applied to the asymmetric epoxidation of enals (Scheme 28) [55]. Among all the combinations tested the catalyst salt **38** comprising an achiral dibenzylamine derivative together with a chiral binol phosphate counteranion proved to be the catalyst of choice furnishing the desired epoxides in good yields along with high enantioselectivities. Remarkably, also β,β-disubstituted α,β-unsaturated aldehydes gave the corresponding epoxides with excellent enantioselectivities in presence of the ACDC catalyst **38.** This is in sharp contrast to the results obtained when using the system described by Jørgensen and co-workers, where this substrate class could be converted into the corresponding epoxides only with moderate enantioselectivities [45].



Scheme 28. ACDC: Epoxidation of enals.

The high enantioselectivity observed with these trisubstituted substrates raises interesting mechanistic questions. Since the initial addition product is achiral, the stereogenic center is created in the subsequent cyclization. Consequently, the chiral phosphate must be involved in this C-O bond-forming event and we propose the enantioselectivity to result from a **TRIP**-assisted cyclization of the achiral enamine intermediate (Scheme 29).



Scheme 29. ACDC: Proposed mechanism for the enal epoxidation.

Conclusions

Selected recent developments in the area of asymmetric organocatalysis in our laboratory have been briefly summarized. Enamine catalysis, Brønsted acid catalysis, and iminium catalysis turn out to be powerful new strategies for organic synthesis. Using Hantzsch ester as the hydride source, highly enantioselective transfer hydrogenantion reactions have been developed. We have also developed an additional new concept in asymmetric catalysis namely *Asymmetric Counteranion-Directed Catalysis* (ACDC) and successfully applied it to asymmetric iminium catalysis. Asymmetric induction presumably occurs in the cationic iminium ion transition state of the reaction by virtue of a sterochemical communication with the chiral phosphate counteranion, possibly via hydrogen bonding interaction. Our discovery may be of general applicability to other reactions that proceed via cationic intermediates. Despite its long roots, asymmetric organocatalysis is a relatively new and explosively growing field that, without doubt, will continue to yield amazing results for some time to come.

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