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Organocatalysis in the Asymmetric Synthesis of Nitrogen-Containing Compounds: How and Why

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Abstract: Various types of polyfunctionalised stereodefined organic molecules appear to be highly serviceable as organocatalysts in the asymmetric synthesis of nitrogen-containing compounds. Beyond name reactions such as the aza-Henry, the Friedel-Crafts, and the Strecker other representative transformations like the hydrophosphonylation can be easily approached by using the suitable organocatalytic species and are herein reported with a special emphasis placed on the reaction and stereochemical outcomes and on the mechanistic insights.

Keywords: Asymmetric organocatalysis · Aza-Henry · Friedel-Crafts · Hydrophosphonylation · Strecker

1. Introduction

Enantioselective organocatalysis has become a field of central importance for the asymmetric synthesis of chiral molecules. In the last ten years, this field has grown at an extraordinary level disclosing novel general concepts, atypical reactivities and widely applicable reactions.[1] Moreover, novel modes of substrate activation have been achieved using organic catalysts that can deliver complementary selectivities in comparison to a number of established metal-catalysed transformations. On the other hand the high importance of chiral nonracemic nitrogen-containing compounds in biological systems, as pharmaceuticals and in industrially relevant basic and fine chemicals, has led during the last decades to significant research efforts for their efficient synthesis.[2] The application of the organocatalytic concepts to this goal outlines an important breakthrough in asymmetric synthesis which would as well meet important issues in the development of sustainable chemical transformations.

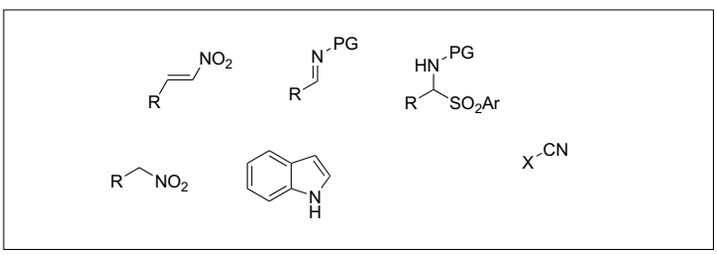

Fig. 1. Nitrogen-containing substrates for organocatalytic asymmetric synthesis

The aim of the present report is not to furnish a comprehensive collection of the literature concerning the use of organocatalytic methodologies for the synthesis of nitrogen-containing compounds, which can be found elsewhere.[1] This article consists instead of a critical perspective on how the involvement of simple nitrogen-containing building blocks in organocatalytic processes can disclose novel routes towards the target-oriented synthesis of more complex molecular systems. Several representative examples are treated in detail, wherein a nitrogen moiety is present in the nucleophilic as well as in the electrophilic reaction partner. In particular very common substrates like nitroalkenes, nitroalkanes, imines, indoles, α-amido sulfones and cyanides (Fig. 1) are taken into consideration and their role as sources of nucleophilic and electrophilic species and the modes of interaction with the organocatalysts are discussed.

Following a general outline, an easy access and a bifunctional mode of action (Fig. 2) are usually the common requirements to be pursued in the choice of the organocatalytic species. Paralleling enzymatic processes, in many cases only the possibility of placing both electrophilic and nucleophilic species in close proximity in the chiral pocket of the catalyst allows the achievement of high levels of stereocontrol in the chemical transformation.

2. Results and Discussion

2.1. *Aza-Henry Reaction*

The aza-Henry reaction, the nucleophilic addition of nitroalkanes to imines to give β-nitroamine derivatives, is a useful carbon–carbon bond-forming process in organic chemistry.[3] The diversity of the transformations of β-nitroamines, such as the reduction to 1,2-diamines and Nef re-

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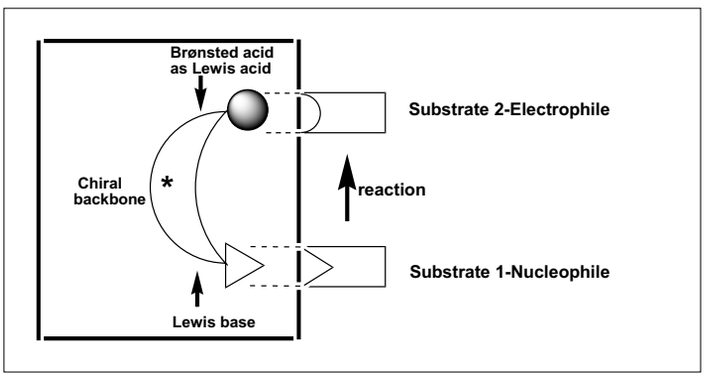


Fig. 2. Typical mode of action of a chiral bifunctional catalyst

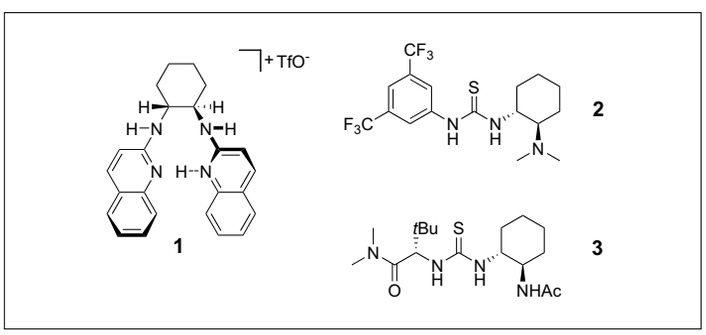


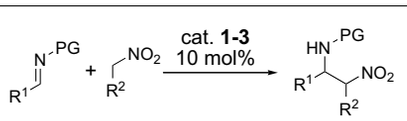
Fig. 3. Three types of organocatalysts with different action in the aza-Henry reaction

action to α-aminoacids, provides numerous applications of this process.[4] The production of both families of target molecules in non-racemic forms bears considerable interest. The enantioselective version of this reaction, until recently, has been nearly unexplored. Before 2004, only few groups reported on catalytic asymmetric aza-Henry reactions and all of the reactions reported were metal-catalysed.[5]

Beyond these metal-catalysed variants, several reports of enantioselective organocatalytic aza-Henry reactions have appeared recently. Mainly three types of organocatalysts, each of them based on a completely different approach, have proved to be highly serviceable for a smooth and very effective occurrence of the reaction between preformed imines and nitroalkanes (**1**–**3**) (Fig. 3).

Based on the concept that the proton H^+ is the most common Lewis acid found in Nature the use of the polar ionic hydrogen bond has been demonstrated to be highly efficient both for activating (function) and for controlling (structure) the absolute and relative stereochemistry.[6] An enzyme-mimicking 'chiral proton-catalysed' reaction based on the bench-stable Brønsted acid salt **1** of the bisamidine ligand, furnished the aza-Henry adducts in up to 69% yield and 95% *ee* (Scheme 1).[7] Speculation about the exact nature of the stereochemical-determining catalyst-substrate complex has not been yet disclosed by these authors. The key role played by the proton in both substrate activation and orientation leading to asymmetric induction is supported by the fact that the chiral ligand alone furnished a result comparable to the uncatalysed reaction.

The bifunctionality concept clearly emerges considering the thiourea-based catalyst **2**, where H-bond donors and Lewis base functionalities are bound through a chiral cyclohexyl scaffold.[8] Takemoto and co-workers reported aza-Henry reactions performed with both N-phosphinoyl and N-Boc imines. The corresponding β-nitroamines were obtained in good to excellent



Catalyst **1**: R^1= Ar, PG= Boc; R^2= H,Me: 50-69% Yield, 59-95% *ee*. Ref. [7]
Catalyst **2**: R^1= Ar, PG= Boc,P(O)Ph_2; R^2= H,Alk: 57-99% Yield, 63-98% *ee*. Ref. [8b,c]
Catalyst **3**: R^1= Ar, PG= Boc; R^2= H,Alk: 79-99% Yield; 92-97% *ee*. Ref. [10]

Scheme 1. Asymmetric aza-Henry reaction catalysed by **1**–**3**

chemical yields and enantiomeric excesses (Scheme 1).[8b,c] A number of different mechanistic scenarios may be considered in the case of the aza-Henry reaction performed by organocatalyst **2**. The mechanism suggested by the authors is shown in Fig. 4: the N-Boc imine is activated by the thiourea moiety while the nitronate is bound in a tight ionic couple with the ammonium counterpart. Unfortunately no suggestions were given regarding the inversion of the stereoselectivity depending on the protecting group of the imine.[8c]

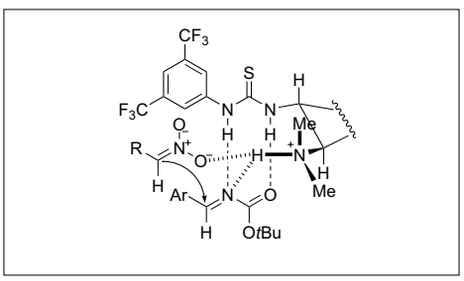
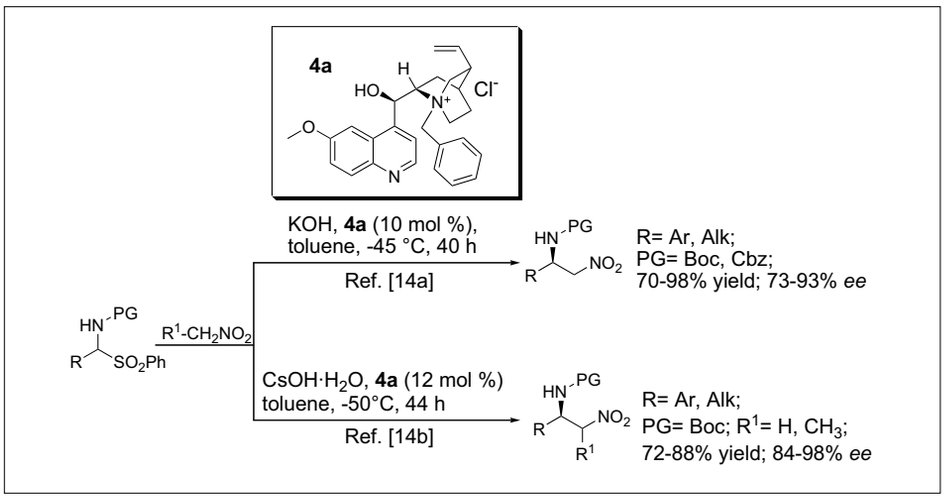


Fig. 4. Takemoto's proposed transition state model

Besides two other reports using a catalytic system based on a very similar bifunctional concept,[9] also catalyst **3**, introduced by Jacobsen and co-workers, showed an excellent activity with N-Boc imines in the aza-Henry reaction (Scheme 1).[10] This catalyst does not have a basic moiety, therefore it is necessary to add an external base (Et_3N or Hünig's base) to promote the reaction. The possible mechanism of action was not described, although the authors reported an analogy with a related catalyst used successfully in a Strecker reaction, wherein the imine is strongly activated by the catalyst through H-bonding with the thiourea moiety.[11] However, simple binding of the deprotonated nitroalkane or even a double activation cannot be ruled out. A comparison between these three organocatalytic reactions, regarding the chemical efficiency, the stereochemical outcome and the reaction scope is shown in Scheme 1.

However, in spite of these satisfactory results, a limitation to the generality of the application of this reaction lies in the fact that the preformed N-protected imines derived from aliphatic enolizable aldehydes readily tautomerise to the corresponding enecarbamate, thus precluding their use in the catalytic reaction.[12] A possible way to overcome these drawbacks and to extend the scope of the reaction has been envisaged with the *in situ* generation of the imine through the use of suitable imine precursors with a good leaving group at the carbon α to the nitrogen atom. Among these, α-amido sulfones are particularly attractive being bench-stable and easily obtainable solids.[13] Two papers appeared recently almost contemporaneously describing



Scheme 2. Asymmetric aza-Henry reaction under PTC conditions

a new catalytic, highly enantioselective aza-Henry methodology.[14] They both use phase-transfer catalysis (PTC) conditions and employ readily available aromatic as well as aliphatic α-amido sulfones and the commercially available quinine-based quaternary ammonium salt **4a** as the organocatalyst (Scheme 2).

As shown in Scheme 2 both procedures appear highly effective in the conversion of aromatic and aliphatic α-amido sulfones into N-protected β-nitroamines through the intermediate *in situ* formation of the electrophilic azomethine precursors. Beyond the high yields, the generally excellent *ee*s, and the wide scope, the easy availability of the organocatalyst and the operational simplicity are good assets of these reactions.

Regarding the possible mechanistic pathways involved, the chiral phase-transfer catalyst acts in a dual fashion, first promoting the formation of the imine under mild conditions [15] and then facilitating the asymmetric nucleophilic addition of nitronate to the imines. Concerning the mechanism of the asymmetric addition, the authors did not offer any suggestions. A speculation about the possible transition state is shown in Fig. 5 in which hydrogen bonds may be eventually formed between the hydroxy group of the catalyst and the imine as well as the nitronate, activating the electrophile for the addition and the nucleophile.

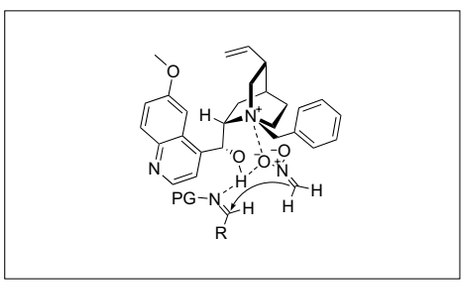


Fig. 5. Proposed transition state model for the PTC aza-Henry reaction

2.2. *Friedel-Crafts Alkylation*

The addition of electron-rich aromatic or heteroaromatic substrates to electron-deficient alkenes or carbonyl compounds, which in many respects may be considered Friedel-Crafts type alkylations, are key reactions in synthetic organic chemistry for the formation of new C–C bonds.[16] Catalytic enantioselective versions of these reactions have been reported, which use metal-based chiral complexes as catalysts, or an imidazolidinone organocatalyst.[17] Classical Lewis acid/Lewis base interaction and formation of an intermediate iminium ion, account respectively for the activation of the carbonyl moieties in these reactions. In sharp contrast with these remarkable achievements, until recently there have not been reports in which nitrogen-containing electrophiles have been engaged in organocatalysed Friedel-Crafts type alkylations.

The renewed interest for the asymmetric synthesis of nitrogen-containing compounds, prompted very recently several authors to pursue the development of novel and efficient organocatalytic enantioselective Friedel-Crafts alkylations of heteroaromatic systems using not only very attractive Michael acceptors like nitroalkenes, but also N-protected imines. Representative results regarding this approach are focused especially on the alkylation of indole, one of the 'privileged' structures in pharmaceutical chemistry but also of the electron-rich furan ring system. Mainly three types of organocatalysts (**5**–**7**) have been shown to be effective in promoting these reactions (Fig. 6).

Simple chiral phosphoric acids like **5**, pioneered by Akiyama's and Terada's groups,[18] have been reported to behave as highly efficient organocatalysts for the activation of imines through a H-bond interaction. In this context, the development of optically active furan-2-ylamines, useful synthetic building blocks, has been performed based on the organocatalysed 1,2-aza-Friedel-Crafts reaction of commercially available 2-methoxyfuran with N-Boc aldimines (Scheme 3).[19] The low catalyst loading such as 0.5 mol % outlines another good asset of this reaction.

An extensive investigation regarding the reaction medium and the nature of the group Ar in the organocatalyst **5** outlined the optimised conditions for this Friedel-Crafts alkylation. High yields ranging from 80–96% and excellent *ee*s up to 97% were achieved employing **5a** with a wide range of aromatic N-Boc imines. Some time after this first report, two new catalytic, intermolecular asymmetric Friedel-Crafts

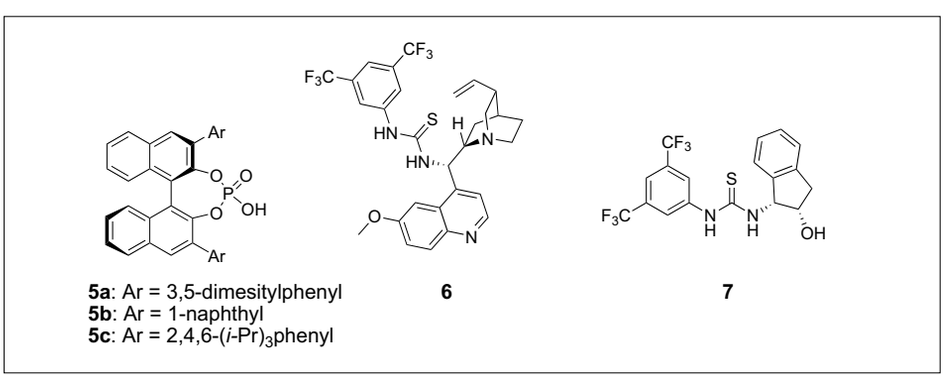
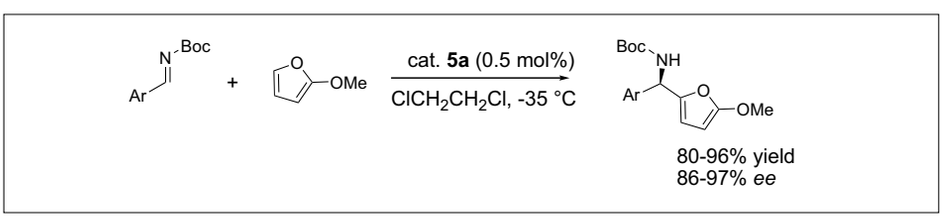
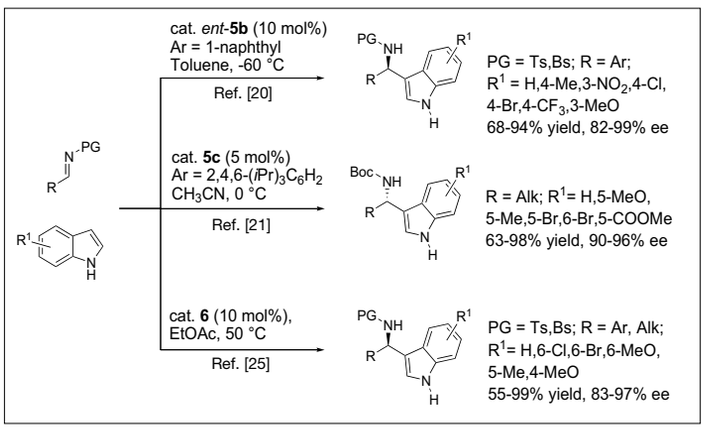


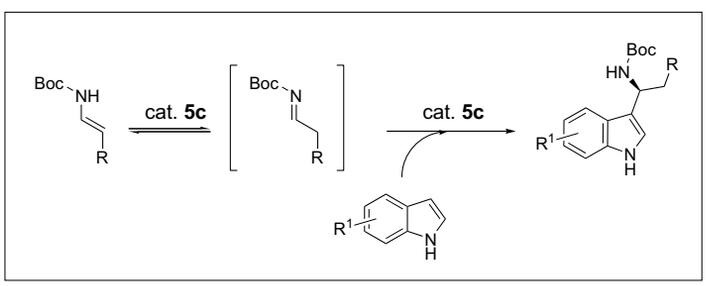
Fig. 6. Organocatalysts used in Friedel-Crafts type alkylations



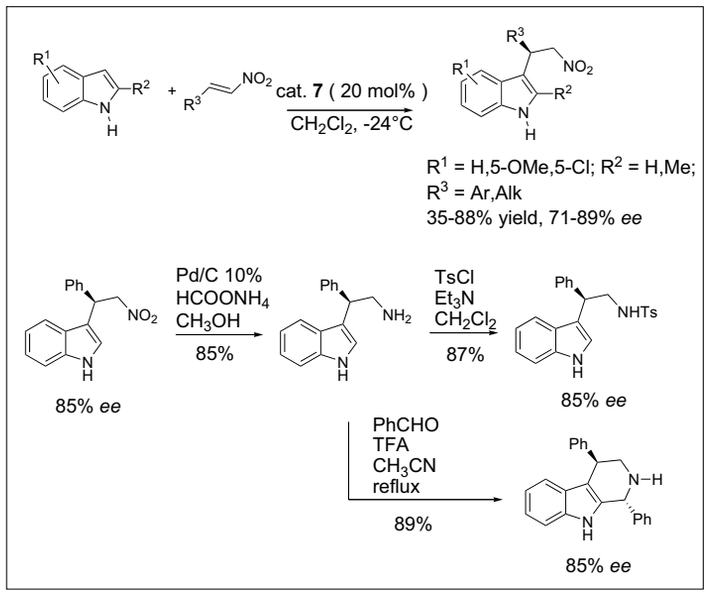
Scheme 3. Organocatalysed asymmetric 1,2-aza-Friedel-Crafts reaction of 2-methoxyfuran with N-Boc aldimines



Scheme 4. Chiral Friedel-Crafts type reactions catalysed by *ent*-**5b**, **5c**, **6**



Scheme 5. *In situ* formation of imines from enecarbamate for the asymmetric Friedel-Crafts type reaction catalysed by **5c**



Scheme 6. Asymmetric organocatalytic Friedel-Crafts type alkylation of indole with nitroalkenes and synthetic utility of the products

reactions based again on the activation of imines with phosphoric acids of type **5** appeared. In both cases, indole was chosen as the nucleophilic reaction partner. In the first report, (Scheme 4, top) activated N-tosyl imines were found to undergo a very efficient reaction with a series of differently substituted indoles, using the phosphoric acid **5b** bearing 1-naphthyl substituent as the Ar group.[20] Impressive results were obtained with several aromatic imines and all the indoles tested, although a fine tuning of the catalyst structure was necessary for some particular substrates, and an imine derived from an aliphatic aldehyde performed poorly in the reaction. Interestingly, a preparative scale reaction was performed using a lower catalyst loading (5 mol%) with similar efficiency.

In the second report, the limitation of using aromatic imines in a Friedel-Crafts reaction with indole was finally overcome, by the use of aliphatic, enolisable imines obtained *in situ* from enecarbamates (Scheme 4, middle).[21] Since starting either from a *Z*- or an *E*-enecarbamate provided the product with very similar enanatioselectivity, the catalyst **5c** was proposed to promote first the enecarbamate-imine tautomerism, through protonation of the double bond, and then to activate the imine for the nucleophilic addition of indoles (Scheme 5). Optimisation of the reaction solvent allowed the preparation of several 1-indolyl-1-alkyl amines in good yields (63–98%) and excellent enantioselectivities (90–96%).

This latter approach, besides providing a new and efficient access to this class of compounds, demonstrates also the possibility of using enecarbamates as imine surrogates[22] in the presence of this class of chiral Brønsted acid catalysts, thus potentially expanding their use to imines derived from aliphatic, enolisable aldehydes bearing easily removable protecting groups at nitrogen such as Boc.

Though not specified, the role played by organocatalysts **5** in the stereodetermining step of the reactions might be that of a bifunctional Brønsted acid bearing both Brønsted acid and Brønsted basic sites (Fig. 7),[23] able to interact eventually with the N-indolyl proton (*vide infra*).

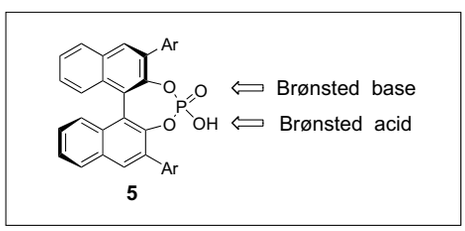


Fig. 7. Assumed bifunctional mode of action for catalyst **5**

Besides phosphoric acids, chiral hydrogen-bond donors such as chiral thioureas have been identified as effective catalysts for the activation of simple imines and nitroalkenes towards various enantioselective nucleophilic additions. On the other hand, chiral hydrogen-bond acceptors such as cinchona alkaloids were shown to be effective for the activation of organic molecules bearing acidic C–H hydrogens. Such traits might render cinchona alkaloid derivatives bearing a thiourea functionality like **6**, firstly synthesized by the groups of Soós and Chen,[24] suitable to address several challenging problems in the development of enantioselective protocols acting as efficient bifunctional catalysts in a number of reactions. Accordingly, the ability of the 9-thiourea cinchona alkaloid **6** to promote the Friedel-Crafts reaction of indole was displayed by using a wide range of N-Ts or N-Bs imines (Scheme 4, bottom).[25] The expected amino indole derivatives were obtained in good yields and most significantly excellent enantioselectivities ranging from 94–96% *ee* could be achieved also with various N-Ts alkyl imines, including those bearing no α-substituent. Remarkably, the enantioselectivity remained very high even at 50 °C, at which temperature the reaction was much faster.

Following previous mechanistic studies on cinchona alkaloids and chiral thioureas one could assume that this kind of bifunctional organic catalysts can promote asymmetric reactions through a network of hydrogen bonding interactions with the reacting nucleophiles and electrophiles.[26] This assumption was substantiated by the enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes as Michael acceptors (Scheme 6, top) catalysed by **7** leading to the expected 2-indolyl-1-nitro derivatives in fairly good yields and with up to 89% *ee*.[27]

These could be easily converted into the corresponding tryptamines and subsequently into a 1,2,3,4-tetrahydro-β-carboline system without any loss in the enantiomeric enrichment of the products (Scheme

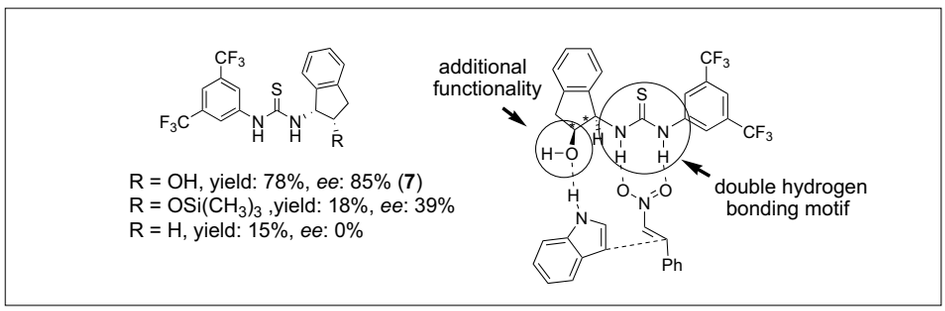


Fig. 8. Variation in the structure and mode of action of the catalyst **7**

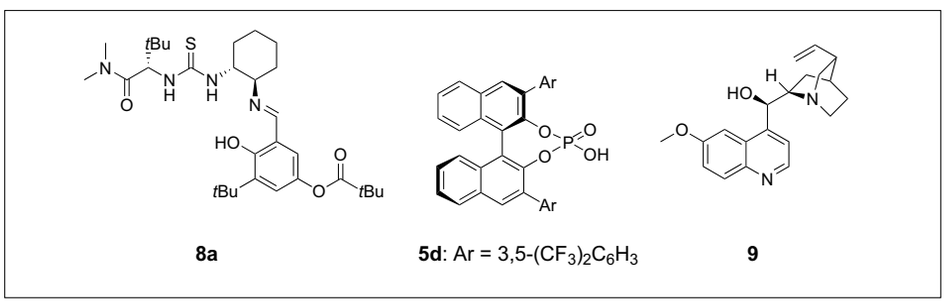


Fig. 9. Organocatalysts used in the hydrophosphonylation of imines

6). Regarding the role of the organocatalyst employed (**7**) this has been disclosed by introducing simple structural variations in its scaffold. With respect to the parent organocatalyst, thiourea derivatives analogous to **7** in which the hydroxy group was protected by silylation or were lacking the alcoholic function, showed poor performances in the reaction between indole and *trans*-β-nitrostyrene not only with regard to the enantioselectivity but also in terms of the catalytic activity (Fig. 8, left).

On these grounds and also considering the very poor asymmetric induction (6% *ee*) observed in the reaction of N-methyl indole, a possible bifunctional mode of activation of catalyst **7** was envisioned (Fig. 8, right).

2.3. *Hydrophosphonylation of Imines*

Optically active α-amino phosphonic acids serve as bio-isosteric analogues of the corresponding α-amino acids, in which the planar and less bulky carboxylic acid group is replaced by a tetrahedral phosphonic acid functionality. For these reasons, α-amino phosphonic acids and their phosphonate esters are usually incorporated into short peptides. These derivatives display interesting biological and biochemical properties giving rise to antibacterial and antifungal agents, and to excellent inhibitors of a wide range of proteolitic enzymes.[28] Several protocols for efficient catalytic asymmetric synthesis of α-amino phosphonic acid derivatives have emerged in recent years, and have been recently reviewed.[29] The addition of phosphites to imines (hydrophosphonylation) is probably the most general and direct approach to α-amino phosphonates.

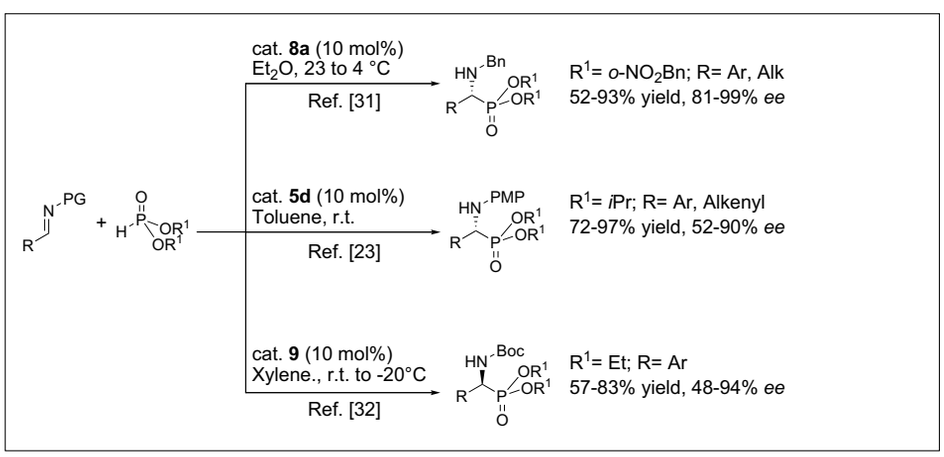
Relevant results were achieved by Shibasaki and co-workers based on the use of heterobimetallic catalysts with the highest selectivities generally restricted to cyclic imines.[30] Recently an important breakthrough appeared in the literature regarding the possibility of performing this reaction using organocatalysis. Though so far only a limited number of reactions have been reported, these can be considered representative of the potential and versatility of the organocatalytic approach. To date the following three organocatalysts have been successfully employed (Fig. 9).

Jacobsen and co-workers described a highly enantioselective hydrophosphonylation of N-benzyl imines promoted by the thiourea catalyst **8a** (Scheme 7, top).[31] The electronic nature of the nucleophilic phosphite was identified as the key parameter with the di-(2-nitrobenzyl) phosphite giving the best results in terms of both yields and enantiomeric excesses. High enantioselectivities (81–99%) and good yields (52–93%) were obtained for a wide range of both branched aliphatic and aromatic imines. Global deprotection under mild hydrogenolytic conditions, afforded enantiomerically enriched α-amino phosphonic acids. Unfortunately any suggestion about the mechanism was not given, even if some analogies might be found with the strong thiourea activation of N-allylimine in the Strecker reaction.[11]

The BINOL-derived phosphoric acid **5d** was also shown to behave as an efficient catalyst for the hydrophosphonylation of aromatic and alkenylic aldimines with diisopropyl phosphite at room temperature (Scheme 7, middle).[23] This process affords α-amino phosphonates in good to high enantioselectivity (52–90% *ee*). An even more operationally simpler and efficient organocatalytic enantioselective hydrophosphonylation of imines has been more recently devised by using an unmodified cinchona alkaloid (Scheme 7, bottom).[32] An initial screening revealed the key role played by the free hydroxy group in the organocatalyst which led to the use under the optimized conditions of quinine **9**. With N-Boc imines using **9** and running the reaction at –20°C, enhanced enantioselectivities (88–94%) were obtained. A quite similar mechanistic proposal has been outlined for the role of the catalysts **5d** and **9** and is shown in Fig. 10.

At the outset of the mechanistic insights it must be assumed that a phosphonate–phosphite tautomerism occurs with the phosphite form acting as the active nucleophilic species and the phosphonate tautomer as the most exclusively favoured, but non-nucleophilic form (Scheme 8).[33]

The shift of the equilibrium towards the phosphite form is likely to be promoted by Brønsted bases such as the phosphoryl oxygen in catalyst **5d** and the quinuclidinic nitrogen in catalyst **9** (Fig. 10). Furthermore interaction of the imine with the catalysts *via* hydrogen bonding might provide at the



Scheme 7. Hydrophosphonylation of imines performed by catalysts **8a**, **5d**, **9**

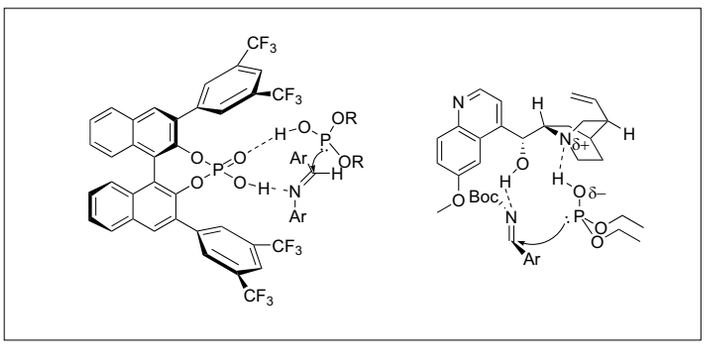
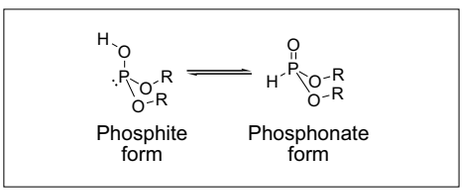


Fig. 10. Proposed model for **5d** and **9** catalysed hydrophopshonylation of imines



Scheme 8. Phosphite-phosphonate tautomerism

same time activation of the electrophilic azomethine carbon and generation of a rigid chiral network which could affect the enantioselectivity of the attack by the nucleophilic phosphite.

2.4. *Strecker Reaction*

The Strecker reaction is one of the most attractive methods for the synthesis of α-amino acids and their derivatives.[34] The wide use of α-amino acid derivatives as building blocks in the synthesis of important complex natural products led to the development of several enantioselective variants of this reaction over the past few years. Most significantly, the first catalytic asymmetric Strecker reaction reported employed an organic molecule as the catalyst, specifically the diketopiperazine **10** (Fig. 11).[35] After this first example, efforts towards the development of a catalytic asymmetric Strecker reaction showed that a broad range of catalysts are suitable for this transformation, covering metal-based catalysts and organocatalysts.[36] A number of organocatalysed enantioselective Strecker reactions have been recently reported, some of them employing chiral imine-containing urea and thiourea-based systems of type **8**,[11,37] the BINOL derived phosphoric acid **5e**,[38] and others based on the very simple C_2 symmetric chiral guanidine **11**,[39] on a cinchona alkaloid derived ammonium salt **12**,[40] or on *in situ* prepared chiral N,N'-dioxides **13** (Fig. 11).[41]

A comparative overview of the chemical and stereochemical outcomes of the Strecker reactions employing these organocatalytic species is shown in Scheme 9.

Good yields and excellent *ees* can be obtained throughout under the optimized conditions set up after a careful screening of the protecting groups at nitrogen, the reaction medium and the temperature. It is worth noting that the organocatalysed enantioselective Strecker protocols employing catalysts **8** and **13** offer also a versatile, attractive and rarely reported solution to a general and practical preparation of optically pure quaternary α-amino acids starting from ketoimines.[37c,41] However, most of these catalytic asymmetric methodologies rely on the use of hydrogen cyanide, either as a anhydrous gas either prepared *in situ* from trimethylsilylcyanide, which poses important problems to be addressed particularly when large-scale applications are considered.

Beyond these reactions performed in monophasic organic media, only in 2006

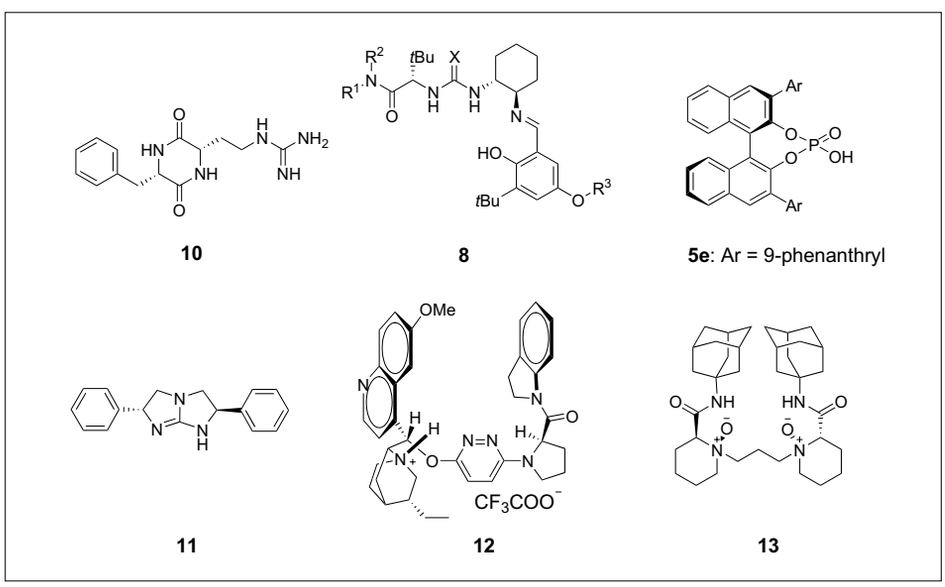
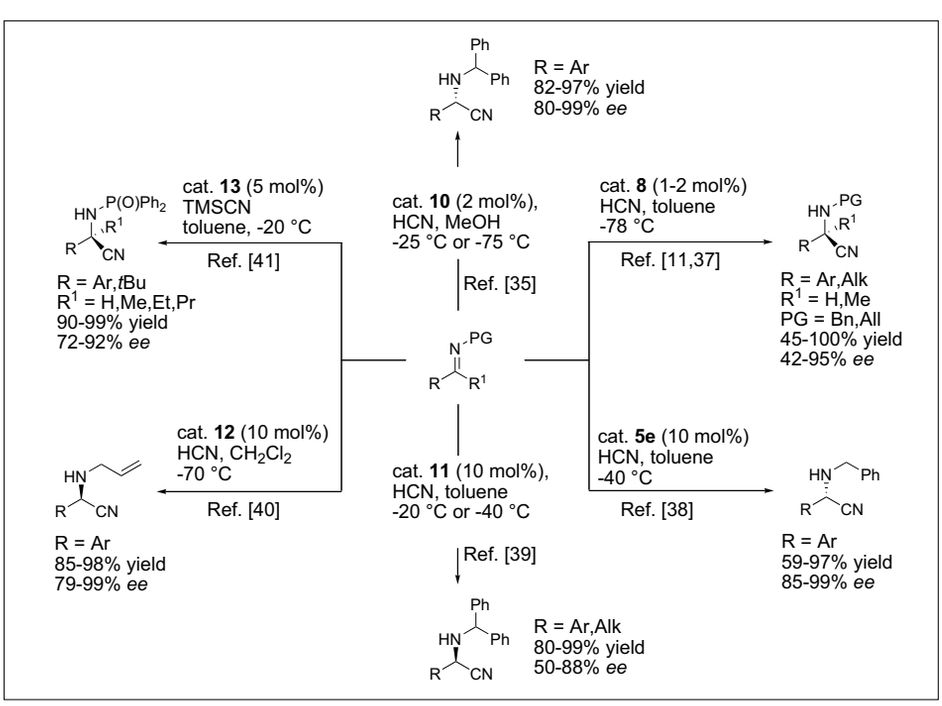
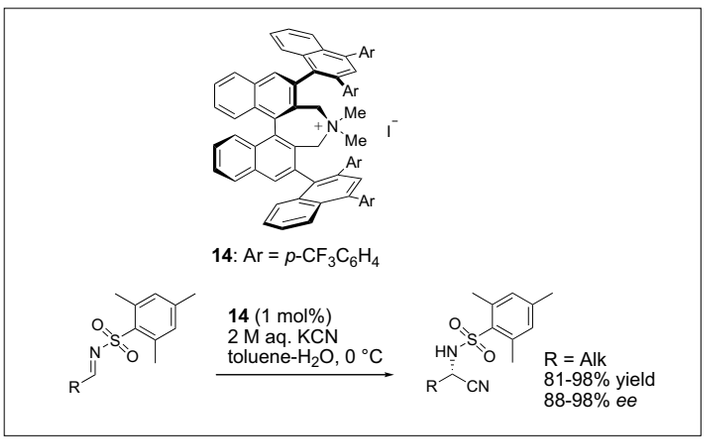


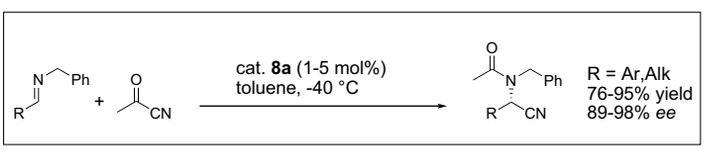
Fig. 11. Common organocatalysts used in the Strecker reaction



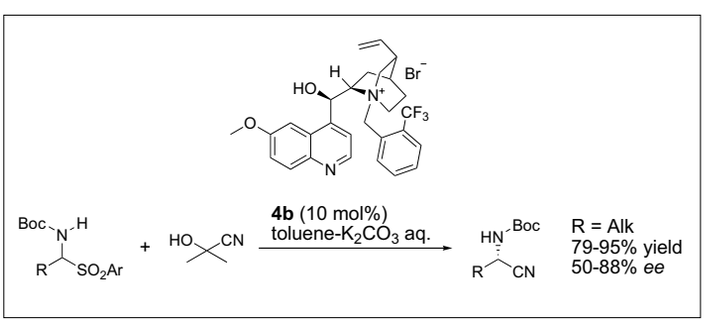
Scheme 9. Asymmetric Strecker reaction performed with various organocatalysts



Scheme 10. Strecker reaction performed with potassium cyanide under PTC conditions



Scheme 11. Chiral Strecker reaction performed with acetyl cyanide



Scheme 12. Asymmetric Strecker reaction with acetone cyanohydrine under PTC conditions

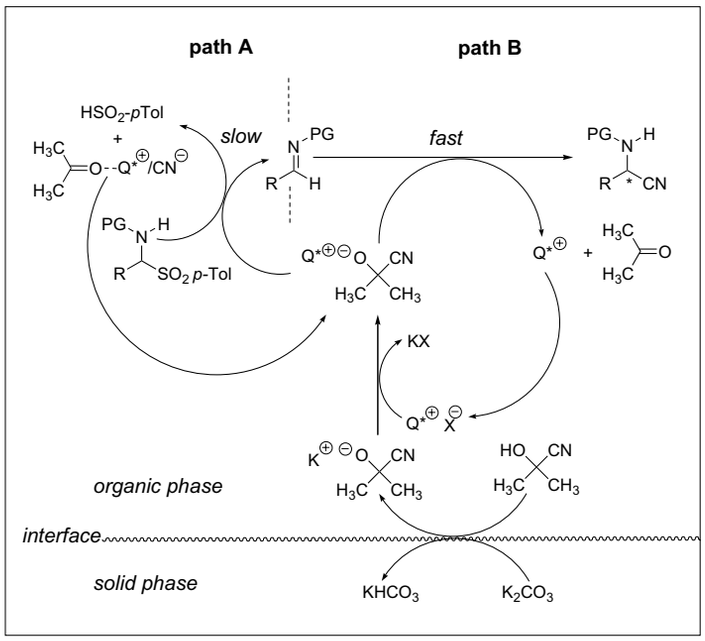


Fig. 12. Assumed mode of action of catalyst **4b** in the Strecker reaction

the first example of a highly enantioselective Strecker reaction of aldimines using a different source of nucleophilic cyanide was disclosed. The chiral phase transfer catalyst **14**, based on a quaternary ammonium salt with a tetra-naphthyl backbone allowed the use of aqueous KCN in a biphasic reaction medium (Scheme 10).[42]

Key to success of this study was the design of a chiral quaternary ammonium salt with the ability to accomplish a facile extraction of the nucleophilic cyanide ion from the aqueous phase to the organic layer, wherein the Strecker reaction occurs with a precise enantiofacial discrimination in the addition to the prochiral imine, dictated by the catalyst. The effectiveness of this new asymmetric Strecker protocol which also opens a route to the search for a safer and more easily scalable cyanide ion source, is demonstrated by the fact that this system accommodates a variety of aliphatic aldimines including pivalaldimine which enables a facile synthesis of enantiomerically enriched *tert*-leucine. Moreover, the procedure has been recently considerably improved from a practical point of view, using N-arylsulfonyl α-amido sulfones as imine surrogates, giving also superior results when primary or secondary aliphatic imines were used.[43]

Shortly after, two different and more convenient cyanide sources based on simple organic molecules such as acetyl cyanide and acetone cyanohydrin were disclosed. Surprisingly, only in 2007 acetyl cyanide has been used for the first time in an organocatalytic asymmetric Strecker reaction,[44] in combination with the chiral thiourea derivative **8a** (see Fig. 9) similar to the catalysts introduced by Jacobsen and co-workers for their Strecker reaction using HCN and the asymmetric hydrophosphonylation of imines.[31,37] Optimisation of the reaction conditions allowed the obtainment of the desired products (as N-acetyl protected and therefore more easily handled) in an essentially pure form with different aromatic, heteroaromatic and aliphatic-branched and un-branched imines (Scheme 11).

Consistent with the hypothesis that type-**8** catalysts are enzyme-like and that all the structural components are vital for both reactivity and enantioselectivity, mechanistic similarities and possibly a similar transition-state structures with respect to the Strecker reaction described by Vachal and Jacobsen[11] have been envisaged by the authors.

The unprecedented use of a chiral phase-transfer catalysis in conjunction with acetone cyanohydrin to effect the enantioselective formation of α-amino nitriles from α-amido sulfones in excellent yields and good *ee*s, has also been recently described.[15b] A range of aliphatic α-amido sulfones were successfully used as imine surrogates outlining the scope of the reaction, which provided α-amino nitriles bearing versatile and easily removable protecting groups such as Boc for the first time (Scheme 12).

The key element for the success of the reaction was the use of the easily available quinine-derived catalyst **4b** bearing an electron-withdrawing group such as a trifluoromethyl at the *ortho* position of the N-benzyl substituent. Also the free hydroxy group plays a significant role both for substrate activation and enantioselectivity. Ancillary experiments carried out using more conventional cyanide ion sources like KCN and TMSCN revealed that in all cases enantiomeric excesses were substantially lower. A mechanism for this PTC reaction, which accounts for the experimental data, was also proposed by the authors, as shown in Fig. 12.

According to this mechanism, the cyanide will play the sequential role of catalytic base and stoichiometric nucleophile through the intermediate formation of a chiral ion pair between the conjugated base of the cyanohydrin and the chiral catalyst. The formation of a chiral ion pair between the catalyst and the acetone cyanohydrin was supported by the strong influence of the structure of the cyanohydrin used on the enantioselectivity of the reaction, as

cyanohydrins derived from benzophenone or fluorenone exhibited significantly lower enantioselectivity.

3. Conclusion

In conclusion, a selection of the great achievements recently made in the organocatalytic asymmetric reactions with simple nitrogen-containing molecules playing the role of electrophilic or nucleophilic species has been reviewed. Enantiomerically enriched molecules often with two nitrogen-based functionalities can be easily approached through the use of the suitable organocatalyst. The variety of organocatalytic species employed indicates the high synthetic value of this approach and its potential for further successful applications addressed towards target-oriented syntheses.

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[1] a) P. I. Dalko, L. Moisan, *Angew. Chem., Int. Ed.* **2001**, *40*, 3726; b) P. I. Dalko, L. Moisan, *Angew Chem., Int. Ed.* **2004**, *43*, 5138; c) H. Berkessel, H. Gröger, 'Asymmetric Organocatalysis', Wiley-VCH, Weinheim, **2005**; d) Special issue on organocatalysis; Eds. K. N. Houk, B. List, *Acc. Chem. Res.* **2004**, *37*, 487.

[2] a) A. Viso, R. Fernández de la Pradilla, A. Garcia, A. Flores, *Chem. Rev.* **2005**, *105*, 3167; b) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem., Int. Ed.* **1998**, *37*, 2580; c) 'Enantioselective Synthesis of β-Amino Acids', Ed. E. Juaristi, Wiley-VCH, New York, **1997**; d) T. Hintermann, D. Seebach, *Chimia* **1997**, *50*, 244; e) J.-A. Ma, *Angew. Chem., Int. Ed.* **2003**, *42*, 4290; f) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069.

[3] a) H. H. Baer, L. Urbas in 'The Chemistry of Nitro and Nitroso Groups', Ed. S. Patai, Interscience, New York, **1970**, Part. 2, p. 117; b) N. Ono, 'The Nitro Group in Organic Synthesis', Wiley, New York, **2001**; c) B. Westermann, *Angew. Chem., Int. Ed.* **2003**, *42*, 151; d) J. C. Anderson, A. Blake, G. P. Howell, C. Wilson, *J. Org. Chem.* **2005**, *70*, 549.

[4] a) D. N. Sarma, R. P. Sharma, *Tetrahedron Lett.* **1985**, *26*, 371; b) D. H. Lloyd, D. E. Nichols, *J. Org. Chem.* **1986**, *51*, 4294; c) A. G. M. Barrett, C. D. Spilling, *Tetrahedron Lett.* **1988**, *29*, 5733; d) A. S. Kende, J. S. Mendoza, *Tetrahedron Lett.* **1991**, *32*, 1699; e) M. A. Sturgess, D. J. Yarberry, *Tetrahedron Lett.* **1993**, *34*, 4743; f) H. Adams, J. C. Anderson, S. Peace, A. M. K. Pennell, *J. Org. Chem.* **1998**, *63*, 9932; g) H. W. Pinnick, *Org. React.* **1990**, *38*, 655; h) C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234; i) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017.

[5] a) K. Yamada, S. J. Harwood, H. Gröger, M. Shibasaki, *Angew. Chem., Int. Ed.* **1999**, *38*, 3504; b) K. Yamada, G. Moll, M. Shibasaki, *Synlett* **2001**, 980; c) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843; d) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2001**, *40*, 2992.

[6] J. A. Pesti, R. DiCosimo, *Curr. Opin. Drug. Discuss. Dev.* **2003**, *6*, 884.

[7] B. M. Nugent, R. A. Yoder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418.

[8] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625; c) X. Xu, T. Furukawa, T. Okino, H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2006**, *12*, 466.

[9] a) L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani, *Tetrahedron* **2006**, *62*, 375; b) C. M. Bode, A. Ting, S. E. Schaus, *Tetrahedron* **2006**, *62*, 11499.

[10] T. P. Yoon, E. N. Jacobsen, *Angew. Chem., Int. Ed.* **2005**, *44*, 466.

[11] P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012.

[12] T. Mecozzi, M. Petrini, *Synlett* **2000**, 73.

[13] M. Petrini, *Chem. Rev.* **2005**, *105*, 3949.

[14] a) F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernardi, A. Ricci, *Angew. Chem., Int. Ed.* **2005**, *44*, 7975; b) C. Palomo, M. Oiarbide, A. Laso, R. Lopez, *J. Am. Chem. Soc.* **2005**, *127*, 17622.

[15] a) V. Banphavichit, S. Chaleawlertumpon, W. Bhanthumnavin, T. Vilaivan, *Synth. Commun.* **2004**, *34*, 3147; b) R. P. Herrera, V. Sgarzani, L. Bernardi, F. Fini, D. Pettersen, A. Ricci, *J. Org. Chem.* **2006**, *71*, 9869.

[16] G. A. Olah, R. Krishnamurty, in 'Comprehensive Organic Chemistry', Eds. B. M. Trost, I. Fleming, 1st ed., Pergamon, Oxford, **1991**, Vol. III, p. 293.

[17] a) K. A. Jørgensen, *Synthesis* **2003**, 1117; b) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem., Int. Ed.* **2004**, *43*, 550; c) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79.

[18] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem., Int. Ed.* **2004**, *43*, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356.

[19] D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804.

[20] Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484.

[21] M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292.

[22] S. Kobayashi, T. Gustafsson, Y. Shimizu, H. Kiyohara, R. Matsubara, *Org. Lett.* **2006**, *8*, 4923.

[23] T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, *Org. Lett.* **2005**, *7*, 2583.

[24] a) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967; b) B. Li, L. Jiang, M. Liu, Y. Chen, L. Ding, Y. Wu, *Synlett* **2005**, 603.

[25] Y.-Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156.

[26] a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem., Int. Ed.* **2006**, *45*, 1520; b) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; c) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289.

[27] a) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem., Int. Ed.* **2005**, *44*, 6576; see also: b) W. Zhuang, R. G. Hazell, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 2566; c) E. M. Fleming, T. McCabe, S. J. Connon, *Tetrahedron Lett.* **2006**, *47*, 7037.

[28] 'Aminophosphonic and Aminophosphinic Acids', Eds. V. P. Kukhar, H. R. Hudson, John Wiley & Sons, New York, **2000**.

[29] J.-A. Ma, *Chem. Soc. Rev.* **2006**, *35*, 630.

[30] a) H. Sasai, S. Arai, Y. Tahara, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 6656; b) H. Gröger, Y. Saida, H. Sasai, K. Yamaguchi, J. Martens, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 3089; c) I. Schlemninger, Y. Said, H. Gröger, W. Maison, N. Durot, H. Sasai, M. Shibasaki, J. Martens, *J. Org. Chem.* **2000**, *65*, 4818.

[31] G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102.

[32] D. Pettersen, M. Marcolini, L. Bernardi, F. Fini, R. P. Herrera, V. Sgarzani, A. Ricci, *J. Org. Chem.* **2006**, *71*, 6269.

[33] T. A. Mastrykukova, I. M. Aladzheva, I. V. Lemont'eva, P. V. Petrovski, E. I. Fedin, M. I. Kabachnik, *Pure Appl. Chem.* **1980**, *52*, 945.

[34] A. Strecker, *Ann. Chem. Pharm.* **1850**, *75*, 27.

[35] M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910.

[36] H. Gröger, *Chem Rev*. **2003**, *103*, 2795.

[37] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; b) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem., Int. Ed.* **2000**, *39*, 1279; c) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867.

[38] M. Rueping, E. Sugiono, C. Azap, *Angew. Chem., Int. Ed.* **2006**, *45*, 2617.

[39] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157.

[40] J. Huang, E. J. Corey, *Org. Lett.* **2004**, *6*, 5027.

[41] J. Huang, X. Liu, Y. Wen, B. Qin, X. Feng, *J. Org. Chem.* **2007**, *72*, 204.

[42] T. Ooi, Y. Uematsu, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2548.

[43] T. Ooi, Y. Uematsu, J. Fujimoto, K. Fukumoto, K. Maruoka, *Tetrahedron Lett.* **2007**, *48*, 1337.

[44] S. C. Pan, J. Zhou, B. List, *Angew. Chem., Int. Ed.* **2007**, *46*, 612.