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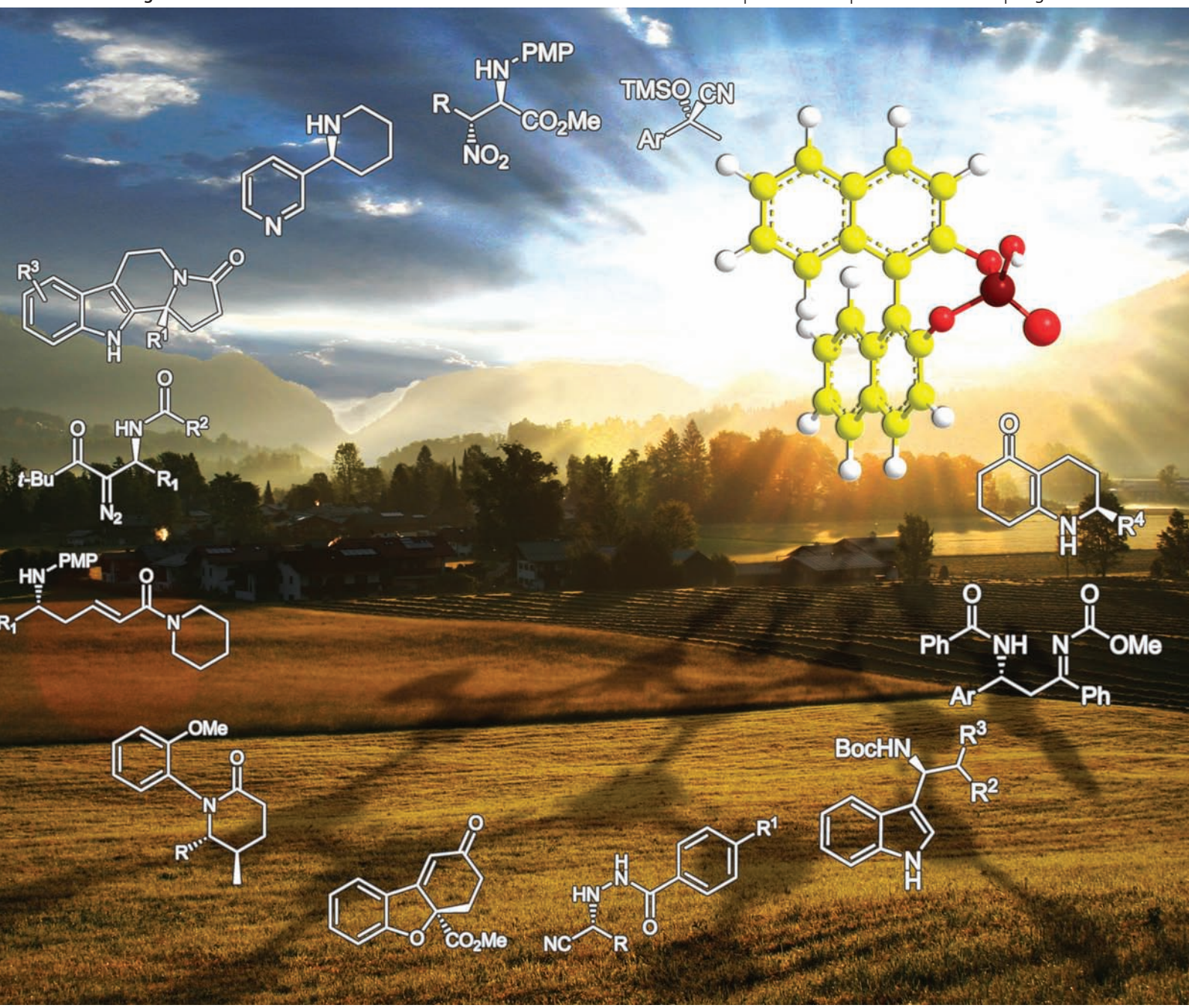

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PERSPECTIVE

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Chiral BINOL-derived phosphoric acids: privileged Brønsted acid organocatalysts for C–C bond formation reactions

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BINOL-derived phosphoric acids have emerged during the last five years as powerful chiral Brønsted acid catalysts in many enantioselective processes. The most successful transformations carried out with chiral BINOL phosphates include C–C bond formation reactions. The recent advances have been reviewed in this article with a focus being placed on hydrocyanations, aldol-type, Mannich, Friedel–Crafts, aza-ene-type, Diels–Alder, as well as cascade and multi-component reactions.

1 Introduction

The development of stereospecific C–C bond-forming reactions is of utmost importance in the field of synthetic organic chemistry. Especially evident in pharmaceutical and natural product synthesis, enantioselective reactions are important for introduction of chiral centers throughout a bioactive compound. There are many proven enantioselective methods utilized in natural product synthesis. In particular, enzymatic processes and transition metal-based catalysis have garnered much attention.

Over the recent years, asymmetric organocatalysis has emerged as a new exciting and environmentally friendly methodology in organic chemistry, complementing bio- and metal-catalysis.[1] Increasing attention has been paid to asymmetric organocatalytic reactions *via* hydrogen bonding activation and/or Brønsted acid activation of carbonyl compounds and imines.[2] In particular, the use of chiral phosphoric acids for the synthesis of optically active compounds has become a new and exciting area of contemporary synthetic organic chemistry.

Since the pioneering studies of the groups of Akiyama[3] and Terada[4] in 2004 on the application of chiral BINOL-derived phosphoric acids as powerful Brønsted acid catalysts in Mannich-type reactions[3,4a] and aza-Friedel–Crafts alkylation,[4b] the development of novel BINOL phosphate-catalyzed reactions has been continuously studied and enabled great progress in recent years.[5] Several research groups reported the application of BINOL phosphates in numerous highly enantioselective transformations. In most cases the key aspect of catalysis is the bifunctional character (Brønsted acid/Lewis base) of the phosphoric acid moiety.[5b]

In this Perspective, we attempt to offer an overview of enantioselective C–C bond formation reactions catalyzed by chiral BINOL-derived phosphoric acids published after 2006 through to the beginning of 2010. Specifically, this article is focused on hydrocyanations, aldol-type, Mannich, Friedel–Crafts, aza-ene-type, Diels–Alder, as well as cascade and multi-component reactions.

2 Hydrocyanations

The addition of hydrogen cyanide to imines and/or ketones constitutes one of the most direct and practical methods for the synthesis of α-amino acids, tertiary cyanohydrins and derivatives.[6]

Rueping and Azap[7] employed the axially chiral phosphoric acid **1** (Fig. 1) for the enantioselective hydrocyanation of imines derived from aromatic aldehydes (Scheme 1a). The authors directly used HCN and isolated the respective amino nitriles in moderate

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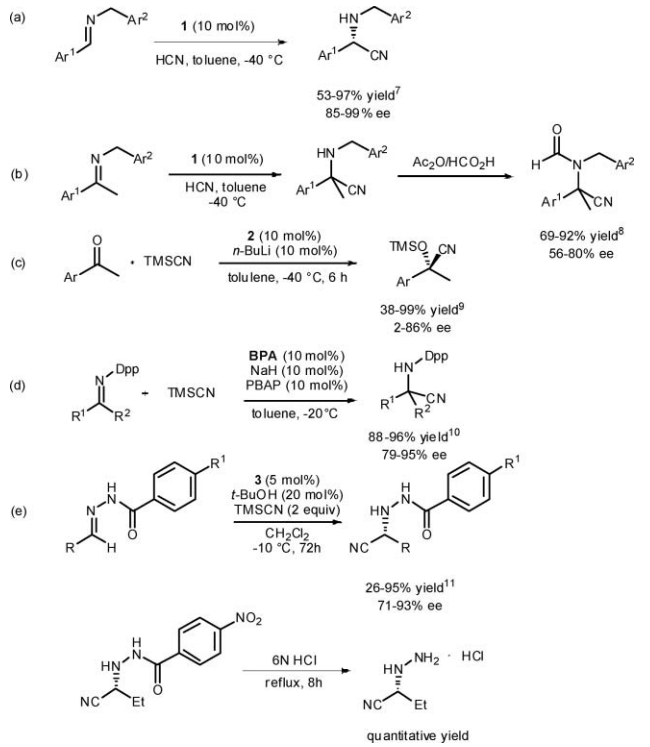
Alexandru Zamfir

Alexandru Zamfir was born in Bucharest, 1982. He studied chemistry at Göttingen University where he finished with a Diploma in 2007. The same year he began his graduate studies at Erlangen-Nürnberg University under the supervision of Prof. Svetlana Tsogoeva. His research includes binaphthyl-derived Brønsted and Lewis acids for diverse organocatalytic reactions.

Sebastian Schenker

Sebastian Schenker was born in Augsburg, in 1984. He received his B.Sc and M.Sc degrees in Molecular Science from the University of Erlangen- Nuremberg. Since 2008 he has been in the Tsogoeva research group, working on DFT and ab initio simulations of organocatalytic C–C-bond formation reactions in collaboration with Prof. Tim Clark.



Scheme 1

to high yields (53–97%) and good to high enantioselectivities (85–99%). Rueping's group[8] further employed catalyst **1** for the enantioselective hydrocyanation of ketimines derived from aryl methyl ketones (Scheme 1b). The products of this reaction were isolated as formamides, which can serve as valuable precursors for amino acids bearing a quaternary stereocenter. Similar to their previous report, the enantioselectivity is steered by the formation of a chiral ion pair between the catalyst and the imine.

The group of Ishihara used the same strategy for the cyanation of ketones,[9] leading to synthetically valuable tertiary cyanohydrins. Salts of phosphoric acid **2** were used, showing best results for Li^+ as a counterion (up to 99% yield and 86% ee, Scheme 1c).

The sodium salt of unsubstituted binaphthyl phosphoric acid (BPA), has been successfully employed by the group of Feng[10] for the cyanation of ketimines. High yields and selectivities were obtained in the presence of *para* butyl-*ortho*-adamantyl phenol (PBAP) as an additive. The reaction is remarkable, because available binaphthyl phosphate is used to generate quaternary carbon centers (Scheme 1d).

Very recently, our group reported the first organocatalytic enantioselective route for the conversion of readily prepared and air stable aliphatic hydrazones to synthetically valuable α-hydrazinonitriles (Scheme 1e).[11] The BINOL phosphate **3**-catalyzed Strecker-type reaction provided a new practical and direct route to α-hydrazino acids of synthetic and biological importance. The actually active catalyst is proposed to be an *in situ* formed *O*-silylated BINOL-phosphate, thus shifting the nature of catalysis from Brønsted acid to Lewis acid organocatalysis. This rare example of a cyanation of C=N bonds catalyzed by a Lewis acid, generated *in situ* from a Brønsted acid, has been conducted in up to 95% yield and up to 93% ee.

3 Aldol-type and related reactions

The aldol-type reactions, as well as nitroaldol, aza-nitroaldol and Robinson annulation reactions, are among the most commonly applied C–C bond forming reactions.[12] The versatility of these reactions stem from their utility in constructing chiral building blocks for the synthesis of structurally complex molecules, namely natural products or pharmaceuticals.

For a synthetic pathway to α,β-diamino carboxylic acids, Rueping and coworkers[13] developed the axially chiral phosphoric acid **4** as organocatalyst for the addition of nitroalkanes to the

Matthias Freund

Matthias Freund was born in Deggendorf, Germany, in 1978. In 2004, he received his diploma degree in Chemistry from the Regensburg University, Germany. Until 2006, he worked in the group of Professor Buschauer at the same university, to synthesize ligands for the Neuropetide Y receptor. In 2007 he joined the group of Professor Tsogoeva at the University of Erlangen-Nürnberg, Germany. His research mainly focuses on asymmetric organocatalysis mediated by small molecules, especially peptides in aqueous systems.

Svetlana B. Tsogoeva

Svetlana B. Tsogoeva has been a professor of organic chemistry at the Friedrich-Alexander-University of Erlangen-Nuremberg, *since February 2007. She was born in 1973, studied chemistry at* St. Petersburg State University, *where she completed her doctoral thesis in 1998. Then, she moved to the* Johann Wolfgang Goethe-University Frankfurt am Main, *for a postdoctoral project. In July 2000 she joined the* Degussa AG *Fine Chemicals Division as a research scientist. In January 2002 she was appointed a first junior professor in Germany at the* Georg-August-University of Göttingen. *Her research is currently focused on asymmetric organocatalysis, organo-autocatalysis, asymmetric oxidations with non-heme iron complexes, as well as synthesis of natural product hybrids for medicinal chemistry.*

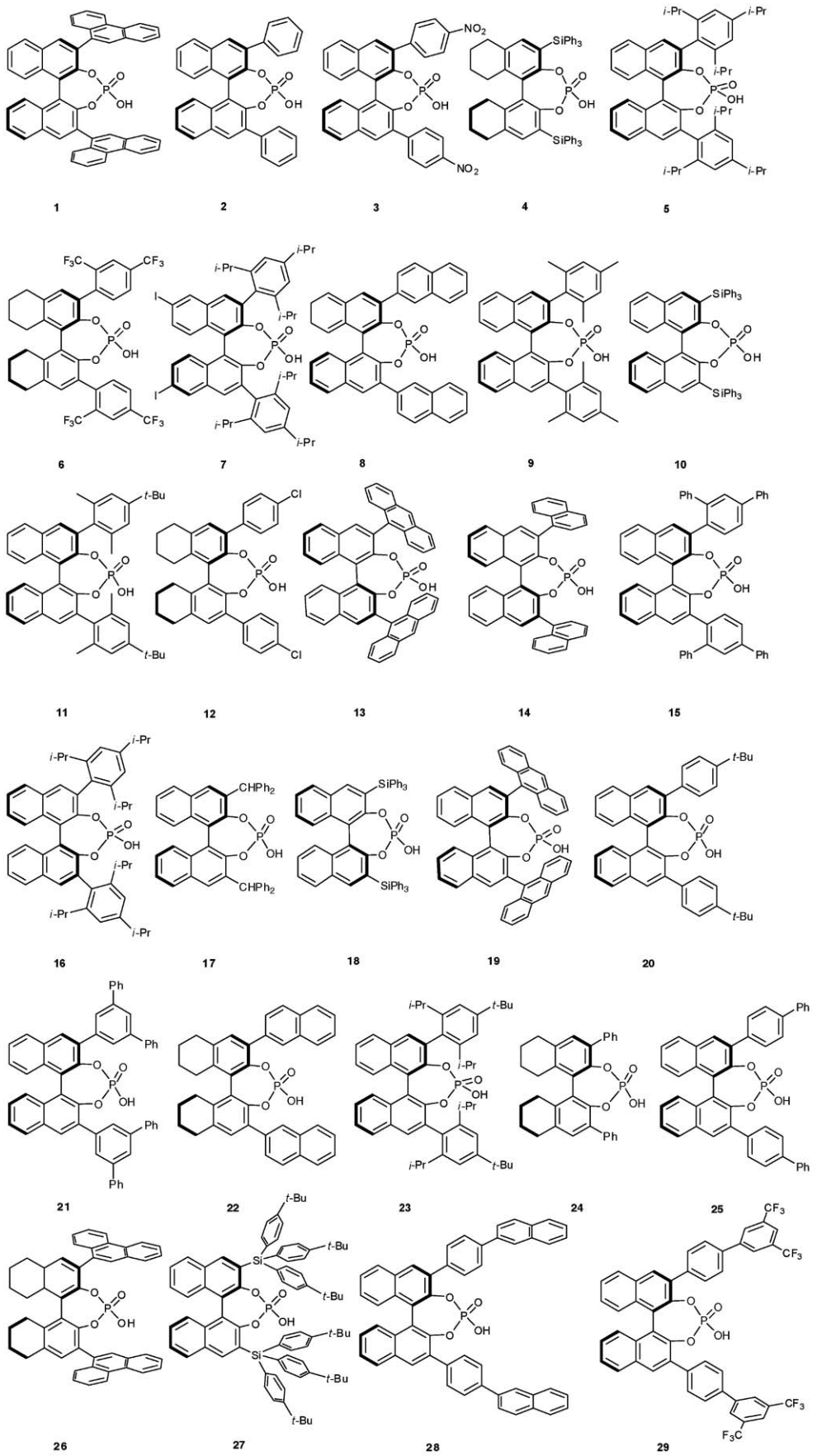
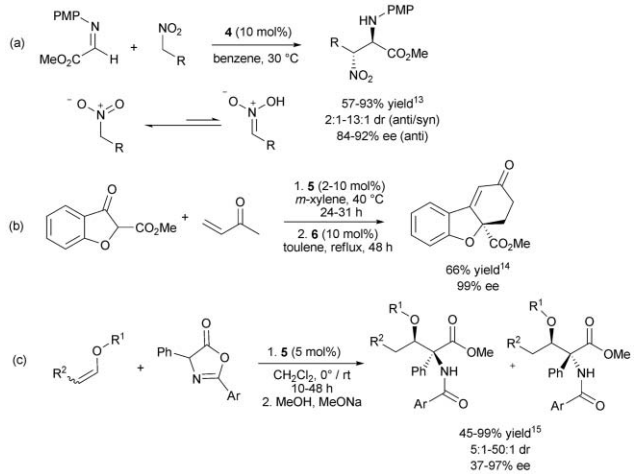


Fig. 1

N-PMP α-iminoester. In the presence of the catalyst, the imine might be protonated and therefore is activated for the addition, in a chiral environment. Similarly, the nitroalkane–nitronate equilibrium, which is in favor of the former, is shifted towards the nitronate, the actual reactive species (Scheme 2a).



Scheme 2

Akiyama *et al.* reported the Robinson annulation-type reaction of 3-buten-2-one with diverse substituted indanone derivatives, catalyzed by two chiral phosphoric acids **5** and **6** at only 2–10 mol% loading (Scheme 2b).[14] The first step, the Michael addition reaction, showed yields up to 99% and ee values of up to 83%. In combination with the second reaction, yield decreases, but enantioselectivities increase. For the complete reaction yields up to 66% and ee values of up to 99% were observed.

Terada *et al.* developed the direct aldol-type reaction of azlactones with an oxocarbenium ion[15] *via* protonation of a vinyl ether by a chiral phosphoric acid catalyst **5**, which provides β-hydroxy-α-amino acid derivatives having a quaternary stereogenic center at the α-carbon atom in a highly enantio- and diastereoselective manner (Scheme 2c). The reaction shows remarkable *syn* selectivity (up to 50 : 1 dr) and, for the most cases, very good enantioselectivity (up to 97%).

4 Mannich and Mannich-type reactions

Asymmetric Mannich reactions are among the most powerful tools for preparing β-amino carbonyl compounds, which are useful intermediates for further elaboration to other valuable products.[16] The first application of chiral BINOL phosphate catalysis to an asymmetric Mannich process is dated back to 2004, when Akiyama[3] and Terada[4] independently disclosed the potential of BINOL phosphate catalysis in the Mannich and/or Mannich-type reactions.

Another Mannich-type reaction through chiral BINOL-based organocatalysis has been presented: the reaction proceeds between aldimines and ketene silyl acetals (Scheme 3a).[17] In the best cases, diastereoselectivities of >99 : 1 and enantioselectivities of up to 96% ee and yields of up to 99% can be achieved. The results of this reaction were rationalized by DFT calculations. Akiyama's group could show that the *N*-aryl group plays a crucial role in the formation of the typical double H-bond interaction pattern, which allows phosphoric acid derivatives to catalyze in an enantioselective fashion.

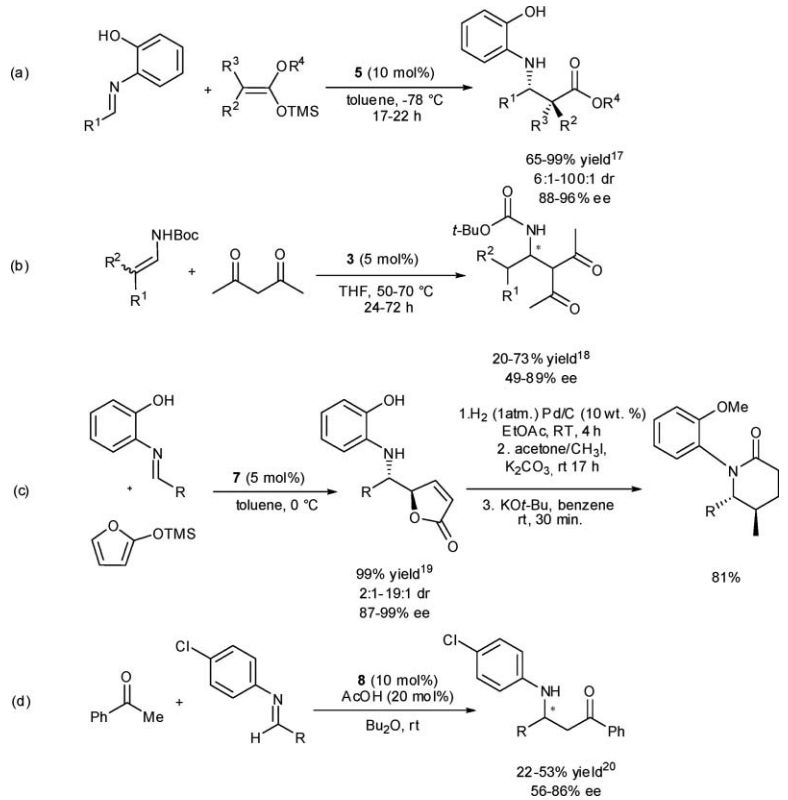
Terada demonstrates the direct Mannich reaction of *N*-Boc enamines with pentane-2,4-dione.[18] The reaction proceeds with moderate to good yields and enantioselectivities (Scheme 3b). The reaction is *R*-selective and allows a broad scope of alkylenamines with one H in α-position. An α-methyl group already leads to reduced yields. In terms of enantioselectivity it plays no role if the *E*- or *Z*-isomer of the enecarbamate is used.

Akiyama *et al.* describe the vinylogous Mannich reaction of aldimines with 2-trimethylsiloxyfuran catalyzed by a BINOL phosphoric acid derivative.[19] They were able to achieve up to quantitative yields and 99% ee with comparably low catalyst loadings of 5%. The best catalyst he found is a BINOL-derivative substituted by iodine in the 6,6′ positions and 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ in the 3,3′ positions (Scheme 3c). Akiyama employed his reaction for the synthesis of γ-butenilide derivatives. *Ab initio* calculations let him assume activation *via* a 9-membered ring interaction pattern between the reactant and the catalyst.

Rueping and coworkers[20] disclosed for the first time an enantioselective Brønsted acid-catalyzed direct Mannich reaction of acetophenone with aldimines (Scheme 3d), in which a chiral and an achiral Brønsted acid assisted synergistically. In the presence of the combination of axially chiral phosphoric acid **8** and acetic acid, acetophenone reacted with different *N*-aryl aldimines to the corresponding Mannich products in low to moderate yields (22–53%) and good ee values (56–86%). However, the authors did not give information about the absolute configuration in the isolated products. Mechanistically it was suggested that the chiral Brønsted acid activates the imine by forming an ion pair in a chiral environment. Acetic acid shifts the keto–enol equilibrium of acetophenone more to the reactive part, the enol. This mechanism is supported by the fact that *no* reaction was observed without acetic acid.

Sickert and Schneider[21] reported the first catalytic, enantioselective vinylogous Mukaiyama–Mannich reactions of acyclic silyl dienolates and imines to furnish highly valuable δ-amino α,β-unsaturated carboxylic esters in high yields (up to 94%), complete regioselectivity and good to very good enantioselectivities (80–90%, Scheme 4a). They employed 3,3′-substituted BINOL phosphoric acid derivatives. The reaction between the TBS-substituted dienolate and PMP-derived aryl aldimines has a high tolerance concerning the aryl group. For most halogen-phenyl, hetero-aryl and alkyl-phenyl-derived substrates, the yield is 80–94%, only for 4-(MeO)C$_6$H$_4$ does the yield significantly drop to 66%. R^1 can also be an alkyl group like *t*-Bu. Remarkably, the reaction can also be carried out in a two step one pot reaction without decrease in yield or enantioselectivity. A catalytic cycle is proposed, where the key step might be an iminium ion–BINOL phosphate complex.

Furthermore, Schneider reported another vinylogous Mannich reaction of vinylketene silyl *N*,*O*-acetals, catalyzed by a BINOL phosphoric acid-derived catalyst.[22] The reaction is carried out in an alcoholic solvent mixture to allow temperatures of −30 °C. The reaction shows good to excellent yields and high enantioselectivities for a number of aryl substituted imines (Scheme 4b). A drawback might be the long reaction times necessary, up to ten days.



Scheme 3

Schneider reported a procedure of a BINOL-phosphoric acid derivative catalyzed Mukayama-Mannich reaction (Scheme 4c–f).[23] The reaction shows excellent yield and enantioselectivities over a wide range of substrates (14 examples with yield >90%; 19 examples with ee >90%). The reaction can be carried out as two-component as well as three-component reaction.

An optimized procedure for the Mukaiyama–Mannich reaction can be employed as key step in the five step total synthesis of (*S*)-anabasine with 92% ee; Schneider's group optimized the reaction conditions to achieve a yield of 96% and 92% ee at a low catalyst loading of 3 mol%. The total yield over five reaction steps was 55%.

A multicomponent enantioselective Mannich reaction has been developed in the group of J. Zhu.[24] The reaction uses enecarbamates as nucleophiles, thus leading to *anti*-1,3-diamines. The reaction shows high yields and excellent enantioselectivities (Scheme 4g). As a catalyst, a H_8-binaphthyl-derivative of the phosphoric acid (catalyst **12**) was used. The authors proposed a mechanism in which the reactive imine is built *in situ* and can be activated by the Brønsted functionality of the catalyst, while the enecarbamate coordinates at the basic site of the catalyst. First an aminoether is built that is reduced without further purification with $NaBH_3CN$.

An intriguing study has been carried out in the group of Ishihara.[25] Being aware that binaphthyl phosphoric acids are readily neutralized to alkali or earth-alkali metal salts even upon purification on silica gel, Ishihara decided to investigate whether such compounds could have catalytic activity in known reactions. Studying the Mannich reaction of aldimines with acetylacetone, he arrived at the surprising finding that calcium salts of catalyst **28** gave similar results to the previously published work[4a] obtained under the same conditions where the involvement of Brønsted acid catalyst **28** itself was implied. Furthermore, when the catalyst **28** was washed with 2 M HCl after purification on silica gel to ensure the absence of salts, poor yields were observed and the opposite enantiomer was obtained in excess. Both the system with chiral phosphoric acid and the system with calcium salts are used for a series of substrates, the results being summarized in Scheme 4h.

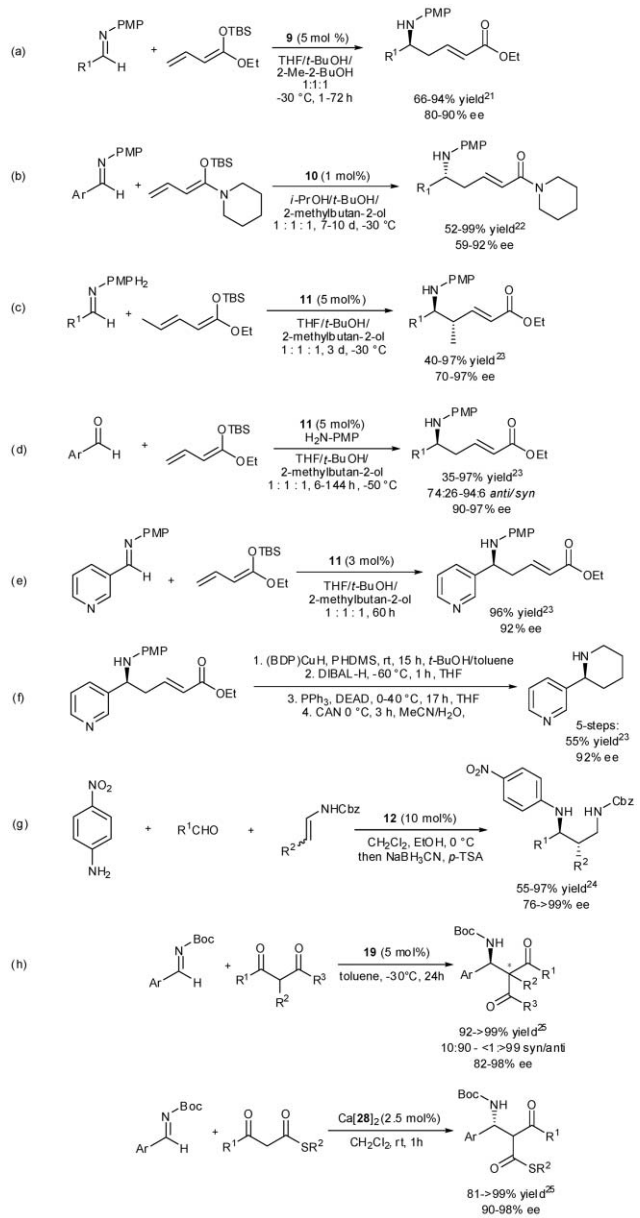
5 Friedel–Crafts-type reactions

The Friedel–Crafts (F–C) alkylation,[26] one of the oldest organic transformations, represents an important C–C bond-forming process for the synthesis of versatile building blocks of biologically active compounds. The field of organocatalysis has recently paved the way to the discovery of new asymmetric F–C reactions.[27]

In 2004, Terada and co-workers first employed a chiral phosphoric acid to promote the F–C alkylation of 2-methoxyfuran with *N*-Boc aldimines, and the products (furan-2-ylamines) were obtained in excellent chemical yields and enantioselectivities.[4b]

The F–C reaction of indoles with imines is investigated by the group of S.-L. You.[28] Using catalyst **14**, excellent enantioselectivities of beyond 99% are observed (Scheme 5a). Also remarkably, the reaction times are mostly kept below 1 h. The yields are high: mostly above 80%.

Zhou and He[29] used a H_8-BINOL-derived catalyst (**12**) for the asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aromatic ketones. While moderate selectivities have

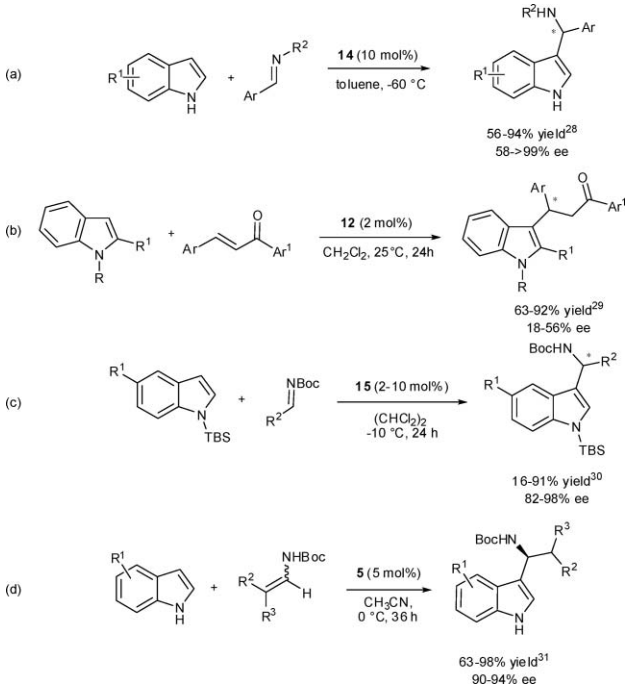


Scheme 4

been obtained, the advantage of the method lies in the use of only 2 mol% organocatalysts (Scheme 5b).

A highly enantioselective 1,2-aza-Friedel–Crafts reaction of indole with aromatic imines using a BINOL-derived monophosphoric acid catalyst is reported.[30] The achieved yields are mostly very good and enantioselectivities are remarkably high for a broad scope of *N*-Boc benzimine derivatives (Scheme 5c). Only a few indole derivatives have been tested and also show high enantioselectivities.

Terada *et al.* demonstrated the enantioselective F–C reaction catalyzed by a BINOL-based chiral monophosphoric acid **5** *via* activation of electron-rich alkenes.[31] The reaction works for a scope of substituted indoles and alkyl- or phenyl-substituted *N*-Boc-enamines. The reaction proceeds throughout with moderate to good yield and remarkably constant high enantioselectivity (Scheme 5d). Whether the enamine is present as single isomer or



Scheme 5

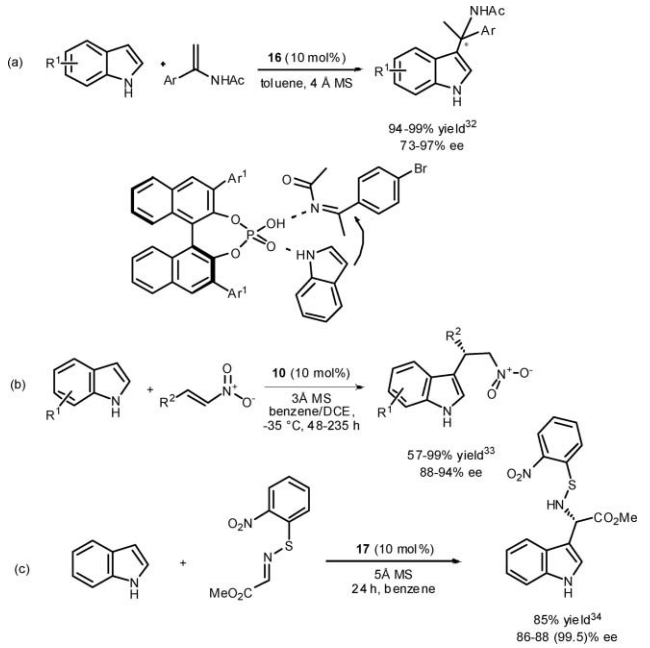
in *E*/*Z*-mixtures does not play a role. Both the *E*- and *Z* isomers yield the same product in a test reaction. Thus, the reaction is proposed to proceed *via* an imine intermediate.

Q.-L. Zhou describes the Brønsted acid-catalyzed enantioselective F–C reaction between indoles and α-aryl enamides.[32] The reaction is synthetically valuable because quarternary carbon centres are being built. After finding the proper reaction conditions, a set of substrates is tested which gave excellent yields and high enantioselectivities. When the reaction with *N*-methylated reactants was tested, no reaction occurred, a sign that the enamine–ketimine equilibrium is part of the mechanism. The key step of the proposed mechanism is depicted in Scheme 6a.

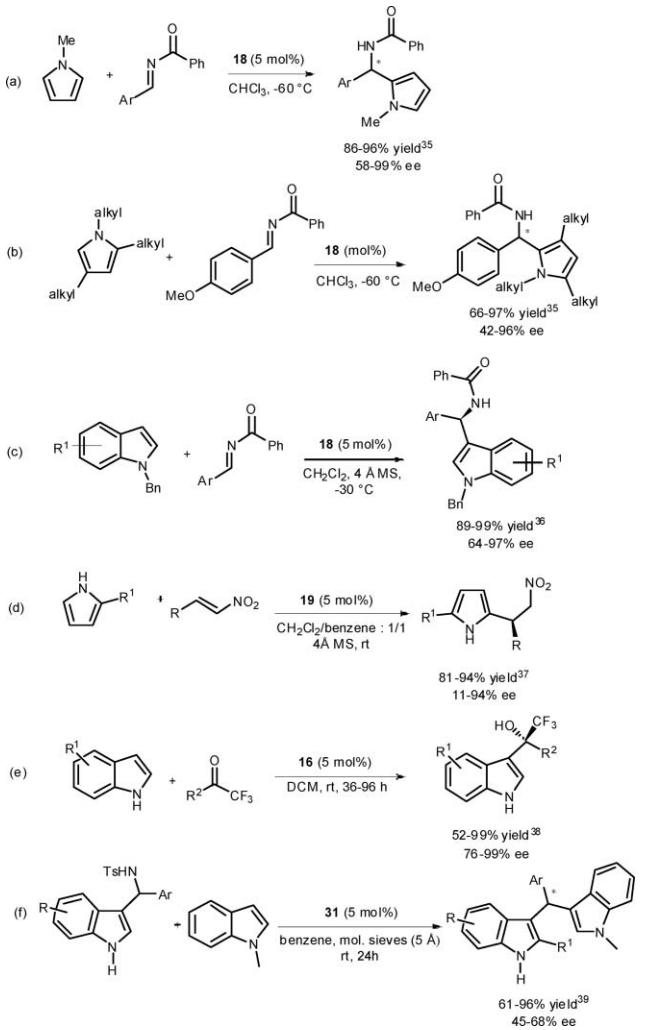
The enantioselective F–C alkylation of substituted indoles with nitrostyrene catalyzed by a chiral BINOL-based phosphoric acid is described.[33] Itoh and Akiyama were able to achieve up to quantitative yield and high enantioselectivities of up to 94% ee (Scheme 6b). It has been reported that a crucial point in the course of the reaction is the choice of the right molecular sieve. The best results are achieved with 3 Å molecular sieves.

Tritylsulfenyl- and 2-nitrophenylsulfenyl-substituted glyoxyl imines were used in chiral phosphoric acid catalyzed F–C reactions with indole (Scheme 6c).[34] High yields and ee values ranging from 86% for Nps-protected (*S*)-indolylglycine to 88% for Trs-protected (*R*)-indolylglycine were observed. On a preparative scale, a F–C product with 99.5% ee and 71% yield was obtained by crystallization from the reaction mixture. Removal of the Nps protecting group under mild acidic conditions did not affect the stereochemical integrity of the α-carbon atom and (*S*)-indolylglycine was afforded in 98% ee.

Antilla and coworkers[35] developed an organocatalytic version of enantioselective Friedel–Crafts reactions between pyrroles and imines. As the catalyst, the silylated axially chiral phophoric acid



Scheme 6



Scheme 7

18 was employed (Scheme 7a,b). As the authors investigated variations of the acceptor, different aromatic *N*-benzoyl imines were found to be suitable for the reaction with *N*-methyl pyrrole and furnished the corresponding products in very good yields and good to very good ee. With respect to variations of the donor, the authors studied different *N*- and core-substituted pyrroles, which were also more or less suitable in the reaction with the imine, as these furnished the products in moderate to very good yield and ee.

The group of Antilla[36] developed a method for the enantioselective addition of *N*-benzyl indoles to *N*-benzoyl imines derived from aromatic aldehydes. the axially chiral silylated phosphoric acid **18** served as the a catalyst, which furnished the products in good to very good yield and ee (Scheme 7c).

The group of You investigated the Friedel–Crafts alkylation of pyrroles with nitroolefins using binaphthyl-based phosphoric acid **19**.[37] A wide range of substrates has been tested, the reaction showing overall very high yields and high enantioselectivity (Scheme 7d). The authors suggest as an explanation of the reaction mechanism the bifunctional character of the binaphthyl-based phosphoric acid. In this case the acidic function can coordinate the nitro function of the nitroolefin while the Brønsted acidic site can coordinate with the NH of the pyrrole, thus bringing the two molecules in reactivity range.

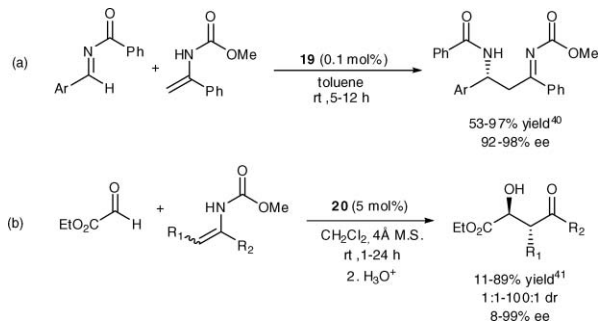
A direct and efficient Brønsted acid-promoted arylation of trifluoromethyl ketones has been developed[38] providing good to excellent enantioselectivities from (76 to 99% ee) for indoles as aromates (Scheme 7e). The yield of this reaction is reported to be 52–99% for the reported substrates. The reaction runs very well with a series of substituted indoles. If substituted pyrroles are employed, the enantioselectivity drops to <70% while the reaction rate increases and the yield remains good.

Instead of trifluoromethyl-aryl ketones, also difluorometyl-aryl ketones and perfluoroethyl-aryl ketones can be employed. The reaction seems to be tolerant concerning the aryl groups of the ketone. DFT calculations have been carried out to investigate the charge distribution in the products. According to these calculations, fluorinated groups are needed to avoid bisalkylation reactions.

A Friedel–Crafts reaction leading to asymmetrical triarylmethanes has been developed in the group of S.-L. You.[39] BINOL phosphate **29** has been used as catalyst with a loading of 5 mol%. While the yields were high, the observed selectivities remained moderate (Scheme 7f).

6 Reactions of enecarbamates: aza-ene-type, self-coupling

In 2006 Terada *et al.* developed a highly efficient enantioselective aza-ene-type reaction of *N*-benzoylimines with enecarbamates.[40] The reaction can be performed at extremely low loading of a chiral BINOL phosphoric acid **19** achieving throughout very good enantioselectivity (Scheme 8a). The reaction was shown to work well for a broad scope of arylaldimines. The present method provides a practical route to useful β-aminoimine derivatives which can be readily transformed to 1,3-diamine derivatives.



Scheme 8

Terada and co-workers further demonstrated a highly enantio- and diastereoselective aza-ene-type reaction of glyoxylate with enecarbamates catalyzed by a chiral BINOL-based phosphoric acid **20** (Scheme 8b).[41] The achievable yield, selectivity and ee was strongly dependant on the substitution pattern of the enecarbamate. (*E*)-Enecarbamates where shown to perform much better—mostly 99% ee and good diastereoselectivities—than the respective (*Z*)-isomers. The same authors carried out hybrid DFT B3LYP/6-31G** calculations on the proposed double H-bond interaction pattern, with which they were able to rationalize the observed selectivity.

The enantioselective construction of quaternary carbon centers, and in particular, those bearing nitrogen or another heteroatom, is still one of the most challenging tasks in organic chemistry. Recently our group[42] reported the enantioselective BINOL phosphate **3**-catalyzed formation of a quaternary carbon center, bearing a N-atom, through the self-coupling reaction of enamides (Scheme 9a). The corresponding products have been isolated in up to >99% ee and their application for the synthesis of versatile synthetic building blocks—β-methyl-β-aminoketones—has been demonstrated (Scheme 9b).

Terada's group[43] reported an enantioselective two-carbon homologation method using enecarbamate derivatives as an acetaldehyde anion equivalent through the activation of hemiaminal ethers by the chiral phosphoric acid catalysts **9** and **21** (Scheme 9c,d). This method is applicable to not only aromatic hemiaminal ethers but also to aliphatic hemiaminal ethers to give the corresponding product in good to high enantioselectivity (up to 97% ee). The method provides access to enantioenriched 1,3-diamine derivatives, which are potentially useful synthetic intermediates.

7 Diels–Alder and related cycloadditions

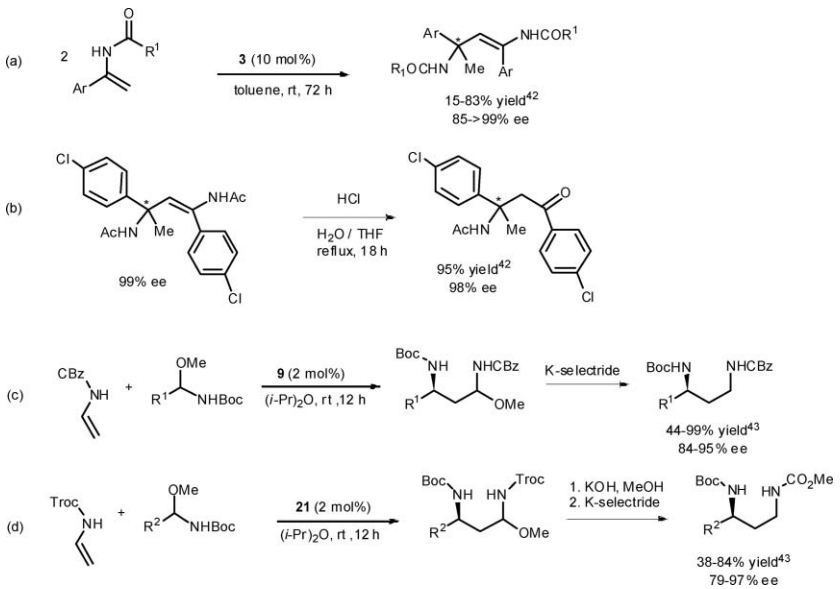
The enantioselective Diels–Alder reaction is one of the most important and powerful reactions for the synthesis of complex molecules. It provides access to chiral carbocyclic compounds in a single step. As a result, extensive research effort has been dedicated to the development of chiral catalysts for highly stereo- and regioselective versions of the transformation.[44]

Asymmetric catalysis in the Diels–Alder reaction has also been realized using chiral Brønsted-acid catalysts.

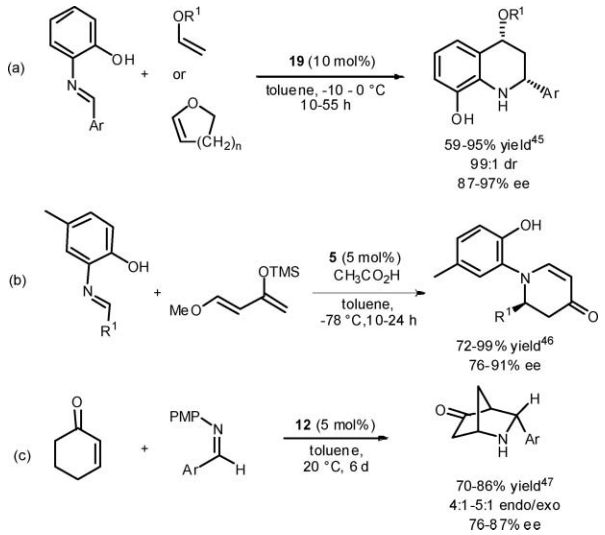
Akiyama *et al.*[45] have developed an inverse electron-demand aza-Diels–Alder reaction of aldimines with electron-rich alkenes (vinyl ethers) to form tetrahydroquinoline derivatives with high to excellent enantioselectivity (up to 97%, Scheme 10a). The reactions catalyzed by chiral phosphoric acid **19** are applicable for linear as well as cyclic vinyl ethers. The presence of the OH moiety on the *N*-aryl group of aldimines was found to be essential for attaining high enantioselectivity, indicating that the phosphoryl oxygen of **19** might form a hydrogen bond with the hydrogen of the imine OH moiety.

The same group reported the aza-Diels–Alder reaction between arylimines and Danishefsky's diene using **5** as a catalyst (Scheme 10b).[46] The reaction can be significantly improved through the addition of an achiral Brønsted acid additive. The best additive tested was acetic acid concerning the enhancement of ee.

Gong and co-workers described the first chiral Brønsted acid-catalyzed asymmetric direct aza-hetero-Diels–Alder reaction, catalyzed by H_8-BINOL derivative **12** (Scheme 10c).[47] Good



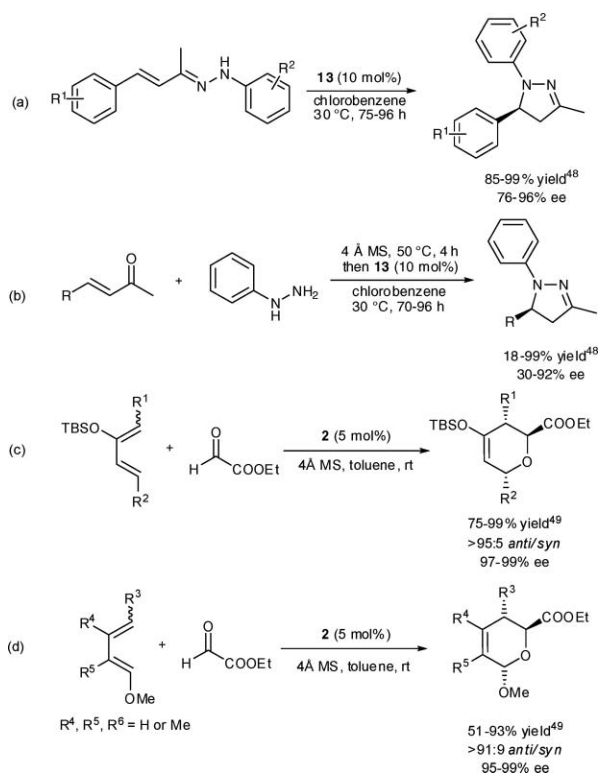
Scheme 9



Scheme 10

enantioselectivities (up to 87%) and yields (up to 86%) have been reported for the reaction of aromatic aldimines with cyclohexenone, yet only a relatively small scope of halogen, methyl and CN-substituted phenylimines has been studied.

The group of List investigated the activity of catalyst **13** on an intramolecular electrocyclization of α,β-unsaturated aryl hydrazones.[48] This reaction leads to synthetically valuable 2-pyrazolines (Scheme 11a). After obtaining high yields and selectivities, a second variant of the reaction was tested in which the hydrazone has been built and used without the need of purification from the appropriate hydrazine and ketone (Scheme 11b). Also



Scheme 11

here, the yields and selectivities were high, except for when long linear alkyl groups were used (R = *n*-C_5H_{11}).

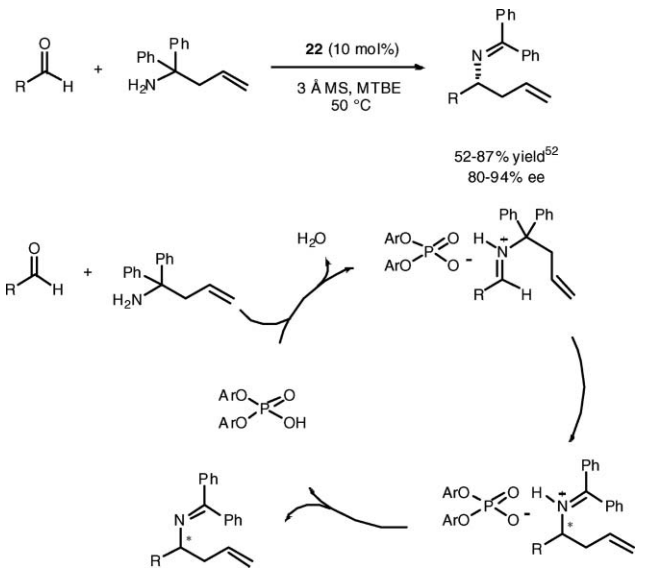
Terada *et al.* developed the first enantio- and *anti*-selective dihydropyran synthesis, catalyzed by BINOL-derived catalyst **2**.[49] Dihydropyrans are achieved by a hetero-Diels–Alder reaction between glyoxylate and 2-*tert*-butyl dimethylsiloxy or 1-methoxy butadienes (Scheme 11c,d). The reaction was found to proceed with excellent enantioselectivities (up to 99%) and mostly good yields and excellent diastereoselectivities (up to 95 : 5 *anti*/*syn*) over the whole substrate scope.

8 Rearrangements

Rearrangements involving carbon–carbon or carbon–heteroatom migrations performed in an enantioselective manner are important reactions because they lead to optically active compounds with molecular frameworks not easily accessible by other approaches.[50]

Within the recent years various enantioselective rearrangement reactions by asymmetric organocatalysis have been reported.[51] In particular, application of chiral BINOL phosphates to this type of transformation opened up a promising new frontier in organic synthesis.

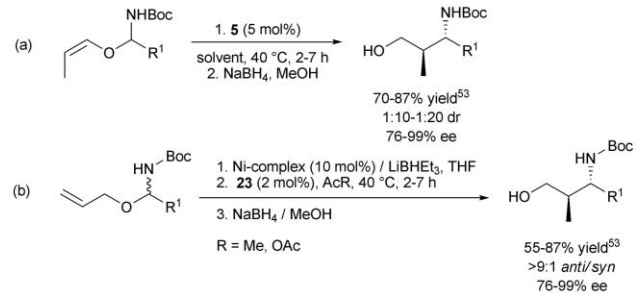
Recently, Rueping and co-workers[52] reported an interesting method for the organocatalytic enantioselective aminoallylation of aldehydes, catalyzed by the axially chiral Brønsted acid **22** (Scheme 12). Various aromatic and one conjugated aldehyde were suitable in the reaction with the homoallylic amine. The corresponding products were isolated in moderate to good yield (up to 87%) and in good to high ees (up to 94% ee). In detail, the authors suggest two key steps in the mechanism. The first one is the formation of an iminium salt with a chiral anion. The second step is an aza-Cope rearrangement in a chiral environment. The release of steric strain (two phenyl substituents) is the driving force here.



Scheme 12

Terada *et al.* reported a highly *anti*- and enantioselective synthesis of β-amino alcohols through the aza-Petasis–Ferrier rearrangement reaction, catalyzed by the chiral phosphoric acid

5 (Scheme 13a).[53] The reaction works with alkyl-, benzyl- and phenyl-substituted hemiaminal ethers. Subsequently, the same research group has reported the organocatalytic enantioselective aza-Petasis–Ferrier reaction of hemiamial vinyl ethers. The reaction is carried out as sequence starting from racemic hemiaminal allyl ethers which are isomerized to the vinyl ethers by Ni-catalysis (Scheme 13b). The reaction has been reported for several alkyl-substituted as well as benzyl- and phenyl-substituted hemiaminal ethers. Throughout the substrate spectrum mostly excellent ees (up to 99%) and good yields (up to 87%) have been observed.



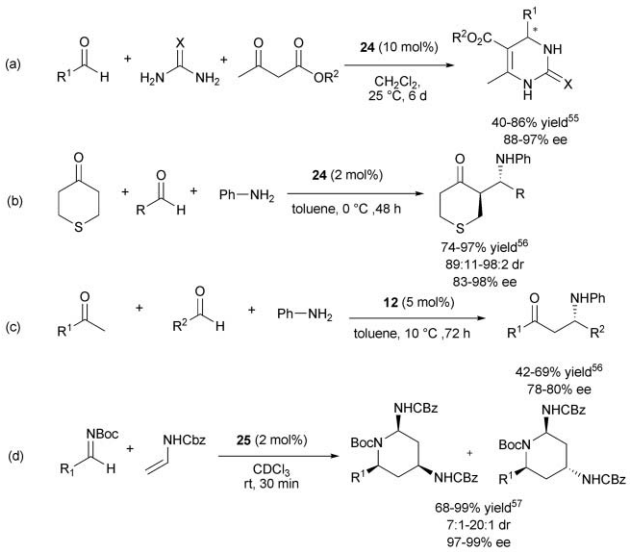
Scheme 13

9 Cascade and multi-component reactions

Since recently, asymmetric organocatalytic cascade reactions (also known as domino or tandem reactions) have become the eminent new strategy in contemporary organic synthesis,[54] allowing increasingly rapid access to structural complexity from simple starting materials and catalysts, while achieving high levels of enantiocontrol. Also, enantioselective one-pot multicomponent reactions, which allow easy access to complex molecules from readily available precursors, are very promising protocols for synthesis.

Recently, Gong and coworkers[55] reported different methods to carry out the Biginelli reaction (known as a three-component condensation reaction between an aldehyde, a urea or thiourea, and an easily enolizable carbonyl compound). One of them is the chiral phosphoric acid-catalyzed version (Scheme 14a). The reaction proceeds with moderate to good yields (up to 86%) and mostly very good enantioselectivities (88–97%) in the presence of catalyst **24**. A broad scope of aryl-aldehydes can be used as reactants. The reaction can be carried out with urea and thiourea and several acetoacetic acid esters. The same group developed the chiral Brønsted acid-catalyzed three-component direct Mannich reaction,[56] which performs well with both cyclic and acyclic ketones. For cyclic ketones, yields of 74–97% and enantioselectivities of up to 98% were reported with catalyst **24** (Scheme 14b). Acyclic ketones perform slightly worse with yields of 42–69% and enantioselectivities of 78–80% ee (Scheme 14c).

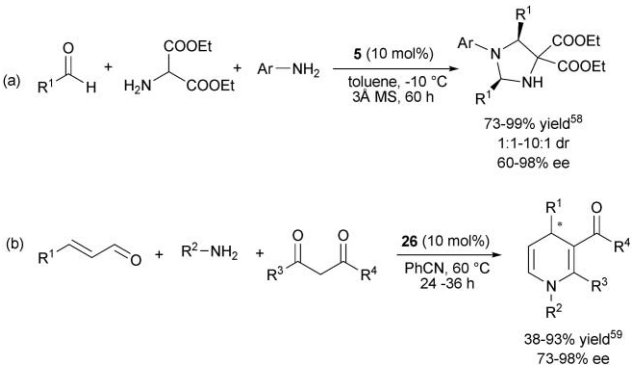
Terada and co-workers[57] have developed an efficient and highly diastereo- and enantioselective tandem aza-ene-type/cyclization cascade reaction (Scheme 14d), featuring a chiral monophosphoric acid catalyst **25**, for a one-pot entry to piperidine derivatives. The reaction allows the formation and control over three stereogenic centres at the same time. Enantioselectivities are remarkably high (up to 99% ee) throughout a broad substrate scope of *N*-Boc-



Scheme 14

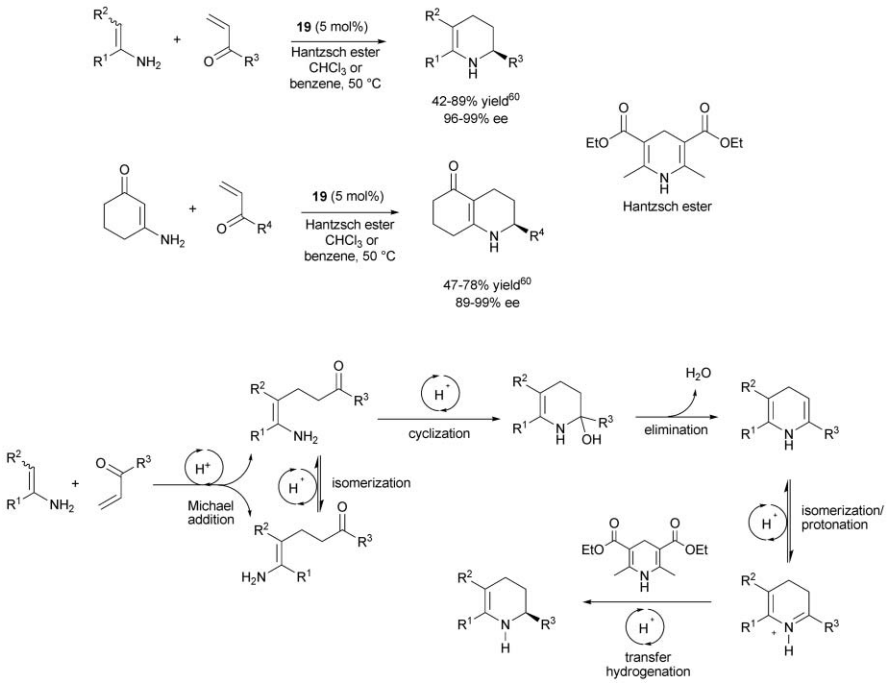
aldimines. Diastereoselectivities where also shown to be very good (up to 20 : 1 dr).

Gong *et al.*[58] reported a catalytic asymmetric 1,3-dipolar cycloaddition that directly assembles aldehydes, amino esters and anilines into chiral imidazolidines with high levels of enantioselectivity (up to 98% ee, Scheme 15a). The reaction can be carried out with a broad scope of arylaldehydes. The same authors also tested cyclopropanecarbaldehyde leading to a decrease in yield and ee (63%; 30% ee) but an increase in diastereoselectivity to >100 : 1. In mechanistic studies, a nonlinear effect between the ee of the catalyst and the product is observed, leading to the conclusion that the reactants are activated by two molecules of the catalyst.



Scheme 15

Furthermore, an asymmetric catalytic three-component cyclization reaction between a cinnamaldehyde, an aromatic primary amine and a 1,3-dicarbonyl compound,[59] that enables the straightforward synthesis of enantiomerically enriched 4-arylsubstituted 1,4-dihydropyridines with high enantioselectivity has been reported (Scheme 15b). The performance of the reaction is remarkably constant over a large range of examples. While the yield varies from moderate to high, the enantioselectivity is mostly >80% ee.



Scheme 16

In an attempt to exploit biomimetic principles, Rueping and coworkers[60] developed an organocatalyzed cascade reaction of preformed enamines and α,β-unsaturated ketones to tetrahydropyridines and azadecalinones, which employs the axially chiral phosphoric acid **19** and the Hantzsch ester (Scheme 16). Various enamines were suitable for the reaction with α,β-unsaturated ketones, as the corresponding products were formed in moderate to very good yields (up to 89%) and in high enantioselectivities (up to 99%). In detail, this cascade of reactions (Scheme 16) includes the following Brønsted acid-catalyzed steps: at first, both building blocks are linked together in a Michael addition. The resulting adduct isomerizes and subsequently forms the cyclic core with concomitant elimination of water. After a further isomerization to a more stable conjugated diene and protonation, an enantioselective transfer hydrogenation with the Hantzsch ester forms the product.

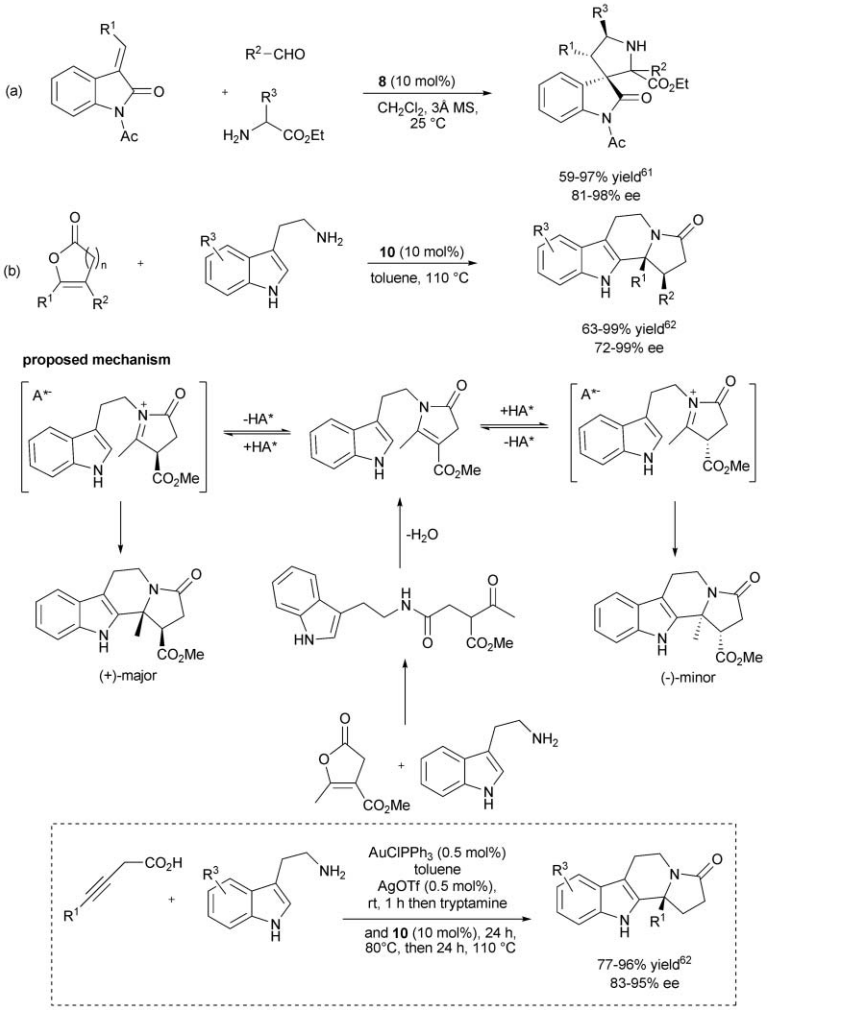
Gong and co-workers reported an unprecedented asymmetric catalytic three-component 1,3-dipolar cycloaddition.[61] The authors have investigated a broad range of substrates and find high to very high yields and selectivities (Scheme 17a). The compounds obtained, namely *spiro*[pyrrolidin-3,3′oxindole] derivatives, may find application in medicinal chemistry. DFT calculations have been also conducted in order to find clues about the reaction mechanism. It seems that π–π stacking interactions between the oxo-indole ring and the formed conjugated ester may play a major role in stabilizing the transition states.

An impressive cascade reaction catalyzed by a binaphthyl Brønsted acid was developed by the group of Dixon and coworkers.[62] The first step of the reaction depicted in Scheme 17b is the ring-opening of enol-lactone by tryptamine. Then a cyclization follows under enantioinduction from the binaphthyl-based phosphoric acid **10**. The one-pot reaction afforded high yields and selectivities between 72 and 99%. Furthermore, to this cascade, the initial step of the lactone synthesis catalyzed by a gold compound is added and the true elegance of the reaction is revealed in producing such complex molecules. In the complete process again high yields (up to 96%) and enantioselectivities (83–95%) were observed.

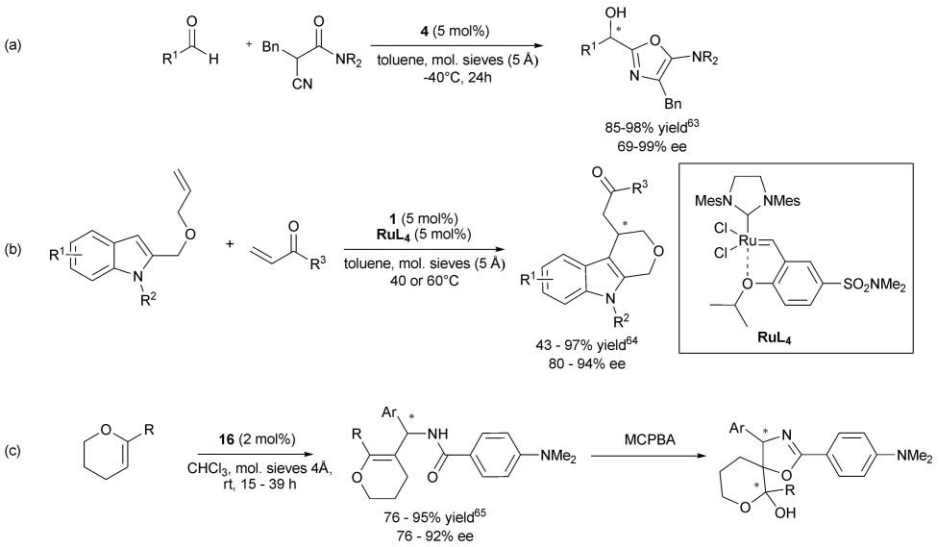
The group of Zhong[63] utilized **4** to catalyze the addition of aliphatic aldehydes to α-isocyanoacetamides and their cyclization to form 5-amino oxazoles with a chiral alcohol residue. The reaction is carried out in dry toluene and exhibits excellent yield and enantioselectivity. The reaction shows a good tolerance for a large number of aliphatic aldehydes. Considering the amine functionality, morpholine- and piperidine-derived tertiary amines have proven to be beneficial here (Scheme 18a).

Ruthenium-catalyzed cross metathesis is combined with a Friedel–Crafts alkylation reaction in a one-pot reaction by the group of You.[64] Following this approach, indoles can be efficiently extended to tetrahydropyrano[3,4-*b*]indoles and tetrahydro-β-carbolines under complete stereocontrol. The initial cross methathesis is catalyzed by 5 mol% of a ruthenium catalyst while the Friedel–Crafts reaction is catalyzed by **1** (Scheme 18b). Optimized conditions found by You and coworkers for both reactions involve toluene as the solvent in the presence of molecular sieves (4 Å).

The group of Antilla developed the addition reaction of hydroxypyrans to *N*-acyl imines.[65] The preferred catalyst was found to be **16**. The respective products can be oxidatively coupled, using MCPBA, to form a spirocyclic compound while completely retaining enantioselectivity. The reaction proceeds in the presence of only 2 mol% catalyst. For (*R*)-**16**, the respective *S*-products were obtained. The reaction was successfully tested for a number of halogenated methylated and methoxylated arylimines and a set of 2-alkyl-hyroxypyrans (Scheme 18c).



Scheme 17

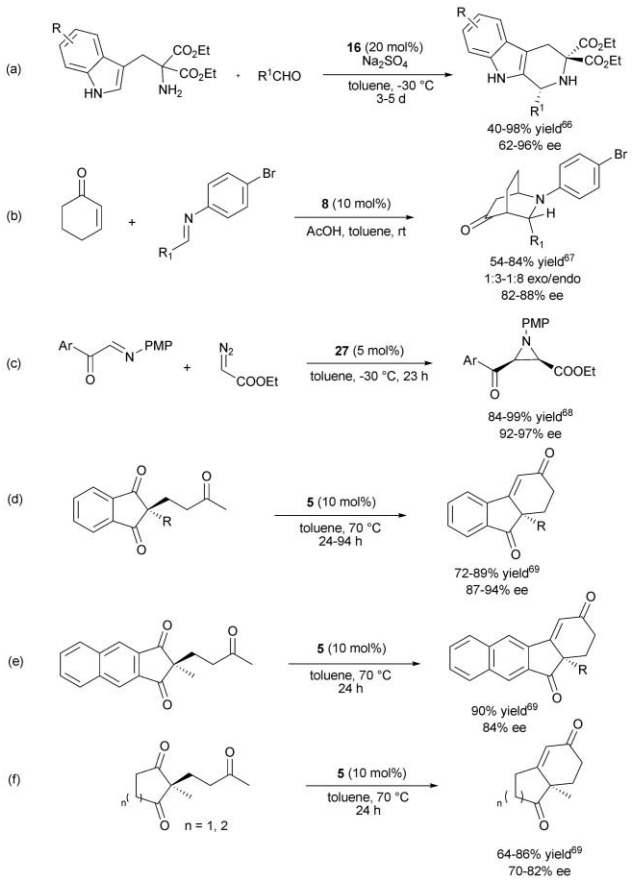


Scheme 18

10 Miscellaneous cyclizations

Chiral BINOL phosphates have also been studied and applied to several cyclization reactions.

The asymmetric Pictet–Spengler reaction remains poorly investigated although it has high synthetical value, leading to tetrahydro-β-carbolines or tetrahydroisoquinolines. Catalyst **16** was found to promote the asymmetric Pictet–Spengler reaction of disubstituted tryptamines (Scheme 19a),[66] giving the corresponding products in moderate to high yields and enantioselectivities (up to 98% yields and up to 96% ee).



Scheme 19

Rueping and Azap[67] disclosed an organocatalytic method for the enantioselective preparation of isoquinuclidines from imines derived from aromatic aldehydes and cyclohex-2-enone (Scheme 19b). The catalytic system involves the synergistic cooperation of an axially chiral phosphoric acid and acetic acid. While the former activates the imine in a chiral environment, by forming a chiral ion pair, the latter activates the donor by shifting the keto–enol tautomerism of the cyclohex-2-enone towards the enol as the reactive intermediate. With respect to the chiral phosphoric acid, two catalyst structures (**8** and **25**) were reported to be suitable, as both generated the products in moderate to good yield and *endo*-selectivity, with a good ee of the corresponding *endo*-products.

Akiyama *et al.* reported the aza-Darzens reaction of α-carbonyl-aldimines with diazo acetate catalyzed by chiral phosphoric acids,[68] and the optimization of the reaction conditions. The optimized reaction is carried out in toluene at a temperature of −30 °C. The highest yield for the reaction was 78% and the best ee 94%. When the imine was generated *in situ*, it was possible to raise the yield up to 97% (Scheme 19c). The same authors reported the synthesis of Hajos–Parrisch and Wieland–Miescher ketone analogues catalyzed by a chiral BINOL phosphoric acid derivative **5**.[69] The reaction is applicable for a series of substituents at the asymmetric carbon center and allows high yields and good enantioselectivities of 70–94% for the investigated substrate spectrum (Scheme 19d–f). The whole reaction can be carried out in a one-pot fashion. The observed selectivities were rationalized using QM/QM (ONIOM: B3LYP/HF) calculations, according to which the catalyst and substrate interact *via* a double hydrogen bonding interaction pattern.

11 Conclusions and outlook

Undoubtedly, one of the important features of organocatalysis is that the same catalyst may be able to catalyze various reactions with high conversions and enantioselectivities. Over the past years, a remarkable number of new enantioselective reactions subject to BINOL-derived Brønsted acid catalysis have been identified, providing solutions to challenging transformations of importance and for a wide range of substrates. In a short time, these BINOL phosphates have qualified themselves as "privileged" organocatalysts and this Brønsted acid catalysis has been established as one of the key catalytic concepts in organocatalysis.

Recent developments in the BINOL phosphate-catalyzed C–C bond formation reactions have been summarized in this review article. Despite the notable achievements already accomplished, the knowledge about the underlying mechanistic details is fairly limited and there are certainly several reactions still waiting to be discovered using this highly versatile methodology. Without question, to realize the full potential of BINOL-derived phosphoric acid catalysis and to pave the way to new organic transformations, a more detailed mechanistic understanding of these powerful Brønsted acid catalysts is needed.

Acknowledgements

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