Binaphthol-derived phosphoric acid as a versatile catalyst for enantioselective carbon–carbon bond forming reactions

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Received (in Cambridge, UK) 6th May 2008, Accepted 4th June 2008
First published as an Advance Article on the web 11th July 2008
DOI: 10.1039/b807577h

Binaphthol-derived monophosphoric acids have been designed as novel chiral Brønsted-acid catalysts. The chiral phosphoric acids thus developed function as efficient enantioselective catalysts for a variety of organic transformations, especially for carbon–carbon bond forming reactions.

1. Introduction

The electrophilic activation of a substrate by means of a Brønsted acid is, undoubtedly, the most straightforward and common approach used to promote a reaction and hence Brønsted acids have been widely utilized as efficient catalysts for numerous organic transformations. The development of novel Brønsted acid catalysts has been continuously studied due to their broad synthetic applicability. The majority of research looks toward the development of highly active Brønsted acids, known as superacids (or magic acids),[1] to generate unstable, and hence highly reactive, cationic (protonated) intermediates (**Sub**-H^+) (Fig. 1(a)). In this context, much attention has been devoted to the design and synthesis of uncoordinatable conjugate bases ($\mathbf{A}^-$) to gain high catalytic activities, in which it is expected that *unfavorable interactions*, such as hydrogen bonding, are suppressed between the conjugate base ($\mathbf{A}^-$) and the protonated intermediate (**Sub**-H^+). In Brønsted acid catalysis, it was previously considered that the Brønsted acid would have to have a "proton-like" character to effectively activate a substrate, and hence the conjugate base ($\mathbf{A}^-$) would not be expected to have any effect in the selective formation of products, such as in stereo- and regioselective transformations, and would only influence catalytic activity. However, in the past decade, innovative research on Brønsted acid catalysis has enabled great progress. Specifically, research has focused on '*chiral Brønsted acid catalysis*', in which enantioenriched products are obtained using a catalytic amount of a chiral organic molecule bearing an acidic functionality.[2] The key to realizing enantioselective catalysis using a chiral Brønsted acid is the *hydrogen bonding* interaction between a protonated substrate (**Sub**-H^+) and the chiral conjugate base ($\mathbf{A}^{*-}$) (Fig. 1(b)). Thus the organic transformations proceed under a chiral environment created by the chiral conjugated base ($\mathbf{A}^{*-}$), which exists in the vicinity of the substrate through hydrogen bonding interactions.

The first example of chiral Brønsted acid catalysis was reported by Jacobsen and co-workers in the enantioselective Strecker reaction catalyzed by peptide-based thiourea derivatives as hydrogen-bond-donor catalysts.[3] Since their landmark report in 1998, enantioselective catalysis by chiral Brønsted acids has become of

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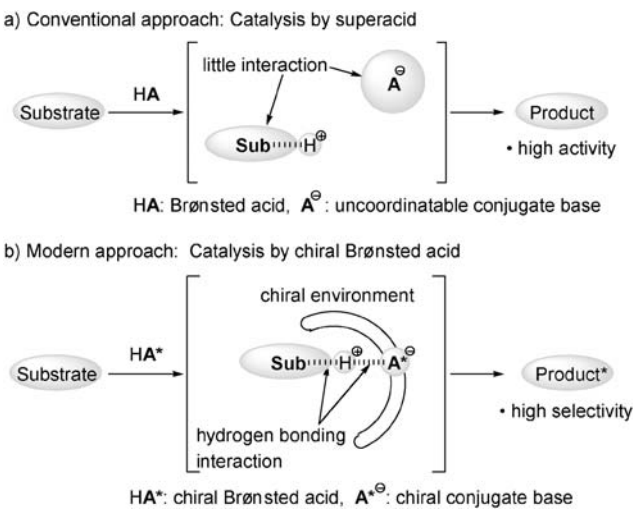


Fig. 1 Brønsted acid catalysis in organic transformations.

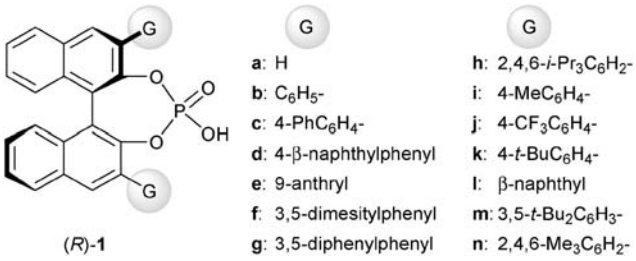


Fig. 2 BINOL-derived monophosphoric acids (**1**) as the chiral Brønsted acid catalyst.

great interest. Their achievement clearly indicated that a chiral Brønsted acid can allow discrimination between enantiotopic faces of an imine substrate *via* hydrogen bonds, and has opened up a new avenue in enantioselective catalysis without the use of chiral metal (Lewis acid) catalysts. Currently, chiral Brønsted acids represent an important and widely applicable class of catalysts for a variety of enantioselective transformations. In this article, we review our recent achievements in developing enantioselective carbon–carbon bond forming reactions using 1,1′-bi-2-naphtohol (BINOL)-derived monophosphoric acids (**1**) as chiral Brønsted acid catalysts (Fig. 2).

2. Design of a chiral Brønsted acid catalyst for enantioselective transformations: structural and chemical features of phosphoric acids

When we started working on chiral Brønsted acid chemistry in 2002, Jacobsen's work was the only report on chiral Brønsted acid catalysis. However, during our investigation, an excellent work on the enantioselective hetero-Diels–Alder reaction was reported by Rawal and coworkers in 2003 using TADDOL (*t*etra*a*ryl-1,3-*d*ioxolane-4,5-*d*imethan*ol*) on its own as a chiral Brønsted acid catalyst.[4] It is well known that TADDOLs were originally developed by Seebach *et al*. as chiral ligands for metal complexes.[5] These milestone achievements have strongly influenced current studies on the development of chiral Brønsted acid catalysts. However the acidity of the thiourea and aliphatic alcohol functionalities is rather weak, with pK_a values ranging from 20 to 28 in DMSO.[6] In contrast to these advanced studies, we envisioned an inventive approach to the development of chiral Brønsted acid catalysts, to enable catalysts which possess strong acidic functionalities. For this purpose, we surveyed a range of common organic acids at the beginning of our research. Representative organic acids are depicted in Fig. 3. Sulfonic acid is one of the most common acid catalysts (Fig. 3(a)), however, it seems likely that sulfonic acid is too strong to maintain hydrogen bonding interactions between a protonated substrate and the conjugated base. Carboxylic acids and sulfinic acids would be good candidates in terms of their appropriate acidity (Fig. 3(b) and (c)). However, the acidic functionality should be introduced to a chiral backbone *via* a single bond, which might make it difficult to provide an efficient chiral environment due to free rotation around the single bond. In addition, introduction of substituents is restricted to the α-position of these acids (Fig. 3(b) and (c)), four atoms away from the proton which functions as the activation site for an electrophilic component.

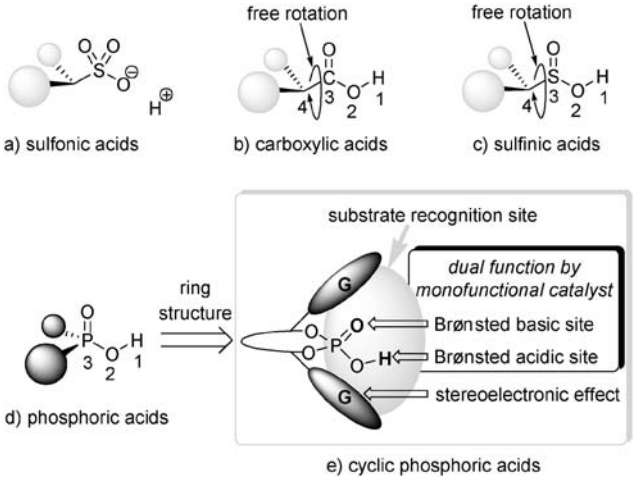


Fig. 3 Organic acids to be developed as a chiral Brønsted acid catalyst.

In contrast, in a phosphoric acid, two substituents can be directly introduced at the phosphorous atom (Fig. 3(d)), albeit three atoms away from the acidic proton. This means that a chiral environment can be created one atom closer to the activation site of the phosphoric acids than that could be achieved using carboxylic and sulfinic acids. Among the various organic Brønsted acids surveyed, phosphoric acids have become the focus of our attention as potential chiral Brønsted acid catalysts because of their unique structural and chemical features (Fig. 3(e)).

The desirable features of phosphoric acids are summarized as follows (Fig. 3(e)):

(1) Phosphoric acids are expected to capture electrophilic components through hydrogen bonding interactions without the formation of loose ion-pairs due to their relatively strong but appropriate acidity.[7]

(2) The phosphoryl oxygen would function as a Brønsted basic site and hence we can anticipate acid/base *dual function* even for *monofunctional* phosphoric acid catalysts. This catalyst design is conceptually similar to the mainstream of designing bifunctional organocatalysts reported to date.[8,9] But, in a strict sense, the phosphoric acid catalysts should be distinguished from most bifunctional organocatalysts, in which rather weak acidic and basic functionalities are introduced individually to the catalyst molecule.

(3) When a ring structure is introduced to the phosphoric acid, an acidic functionality is still available. This ring system prevents free rotation at the α-position of the phosphorus center. This characteristic can not be found in other Brønsted acids such as carboxylic and sulfinic acids, *etc*.

(4) Substituents (G) can be introduced on the ring system to provide a chiral environment for enantioselective transformations.

As mentioned above, it is anticipated that an efficient substrate recognition site could be constructed around the activation site of the phosphoric acid catalyst, namely the acidic proton, as a result of the acid/base dual function and the stereoelectronic influence of the substituents (G).

As shown in Fig. 2, BINOL derivatives were selected as chiral sources to construct the ring structure. BINOL is

well-known as an axially chiral molecule having C_2-symmetry, whose derivatives have been extensively utilized as chiral ligands for metal catalysts.[10] This C_2-symmetry is crucial in our catalytic design because it means that the same catalyst molecule is generated when the acidic proton migrates to the phosphoryl oxygen. In addition, both enantiomers of the binaphthols are commercially available and numerous protocols for introducing substituents have been reported to date, in which the substituent (G) is introduced at the 3,3′-position of the binaphthyl backbone. These stereoelectronically adjustable substituents (G) can be utilized to create an appropriate chiral environment for enantioselective transformations. In 2004, we successfully demonstrated highly enantioselective transformations using BINOL-derived phosphoric acids (**1**)[11] as chiral Brønsted acid catalysts.[12] Akiyama *et al*. also independently reported enantioselective catalysis using similar phosphoric acids.[13]

3. Enantioselective direct Mannich reaction

Enantioselective Mannich reactions are one of the most widely utilized chemical transformations for the construction of optically active β-amino carbonyl compounds, which are versatile synthetic intermediates for biologically active compounds.[14] The development of the direct Mannich reaction, which avoids the need to prepare preformed enolate equivalents such as silyl enol ethers, has been stimulated by both ecological and economical considerations.

Our study of chiral phosphoric acid catalysis commenced with the development of an enantioselective direct Mannich reaction of imine (**2**) with acetylacetone (**3**),[12] because it was anticipated that the dual function of the phosphoric acid moiety would allow the reaction to accelerate smoothly (Fig. 4). In general, acetylacetone (**3**) tautomerizes to the corresponding enol in considerable quantities even in a less polar organic solvent. The enol proton and the O–H proton of **1** function as the acidic sites, while the nitrogen atom of the imine (**2**) and the phosphoryl oxygen function as the basic sites. Fig. 4(a) highlights the acidic and basic sites of the reactants and the catalyst (**1**) as hollow and dashed circles, respectively. In the direct Mannich reaction of **2** with **3**, it is considered that **1** enables assembly of the transient structure through a hydrogen bonding network that connects the acidic and basic sites with each other (Fig. 4(b)). Thus, the phosphoric acid catalyst (**1**) electrophilically activates **2** through the acidic proton, and the Brønsted basic phosphoryl oxygen interacts with the O–H proton of the enol form of **3**. Subsequent bond recombination results in formation of the Mannich product and regeneration of the catalyst (**1**) (Fig. 4(b) to (c)). From this mechanistic assumption, it would seem likely that the phosphoric acid catalysts would accelerate the reaction smoothly. More importantly, it is anticipated that the reaction would proceed under a chiral environment created by the chiral conjugate base of **1**.

Preliminary studies showed that the chiral phosphoric acid (**1a**) exhibited extremely high catalytic activity for the direct Mannich reaction of *N*-Boc-protected imine (**2a**) with acetylacetone (**3**). Fortunately, the resulting β-aminoketone (**4a**) was obtained in an optically active form (12% ee) (Scheme 1).

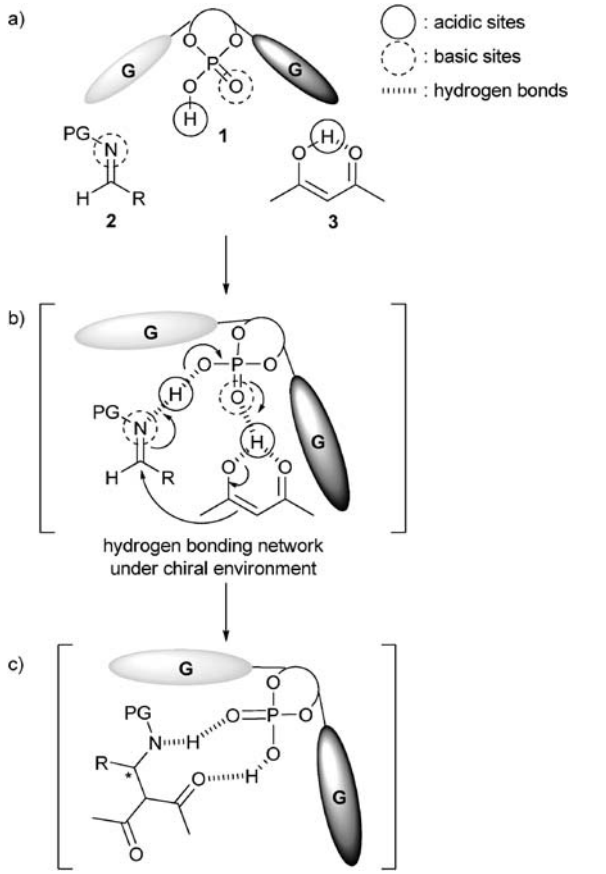
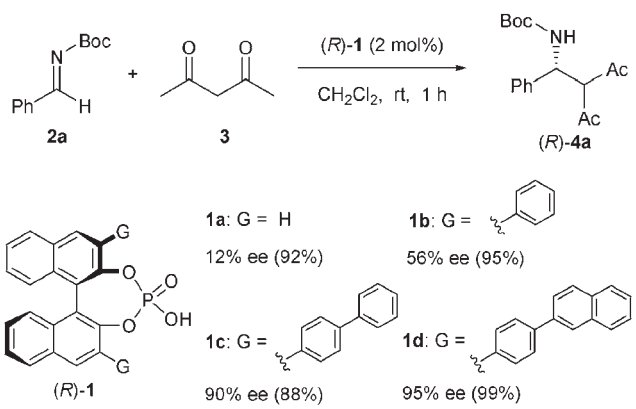
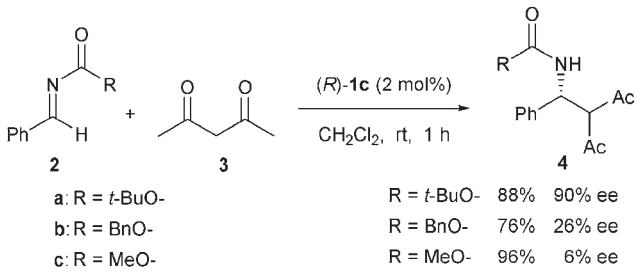


Fig. 4 Assumed mechanism of enantioselective direct Mannich reaction catalyzed by chiral phosphoric acid.

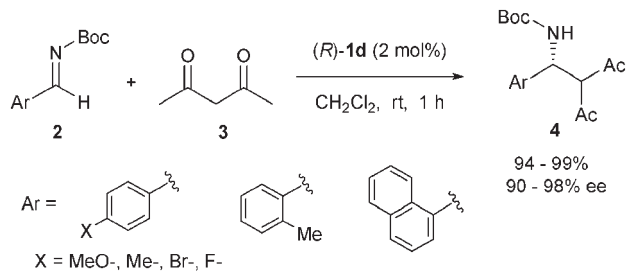
The result obviously indicates that **1a** can provide a chiral environment for the transient assembly in the Mannich reaction. The beneficial effects of the diaryl substituents at the 3,3′-position of the binaphthyl backbone are noteworthy in regards to the enantioselectivity. For instance, performing the direct Mannich reaction using the 3,3′-phenyl-substituted phosphoric acid (**1b**) furnished **4a** in 56% ee. Interestingly, the simple extension of aromatic substitution to the para position improved the enantioselectivity dramatically. Use of **1d** as a catalyst further increased the enantioselectivity to 95% ee giving **4a** in nearly quantitative yield.



Scheme 1 Enantioselective direct Mannich reaction catalyzed by **1**.



Scheme 2 Effect of *N*-protective group on enantioselectivities.



Scheme 3 Enantioselective direct Mannich reaction of various imines (**2**).

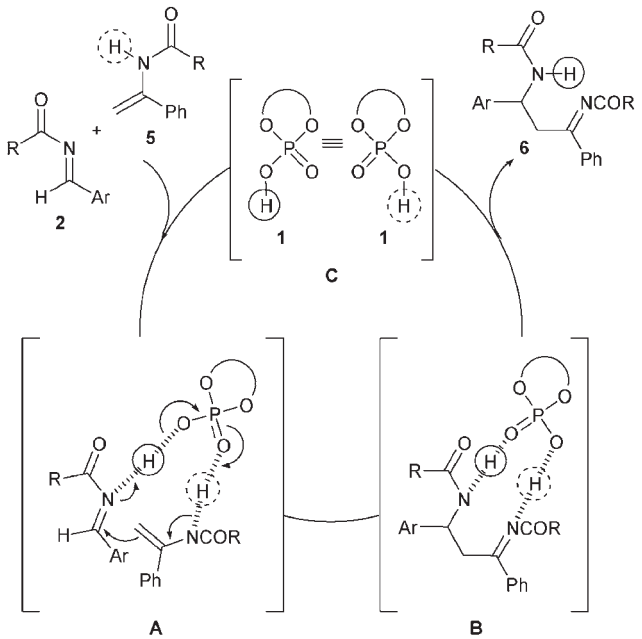


Fig. 5 Mechanistic assumption of aza-ene type reaction catalyzed by **1**.

The protective group on the imine is also crucial to achieving a high enantioselectivity (Scheme 2).[15] When the steric demand of the protective group was decreased, the enantioselectivities were enormously reduced. In Mannich reaction catalyzed by **1c**, the ee of the product dropped dramatically when benzyloxycarbonyl protected imine **2b** was employed, and the reaction became much less stereoselective with imine **2c**, which has the less sterically demanding methoxycarbonyl moiety as the protective group.

The present catalytic reaction could be applied to *ortho*-, *meta*- and *para*-substituted *N*-Boc-protected arylimines and the corresponding products (**4**) were obtained in excellent chemical yields with high enantioselectivities (Scheme 3). This reaction was carried out on a scale as large as 1 g without any detrimental effects on either the yield or the enantioselectivity, and a single recrystallization gave the pure enantiomer. It is noteworthy that only 1 mol% catalyst was sufficient for completion of the reaction within 2 h to give **4a** in 94% ee, and **1d** was recovered in over 80%.

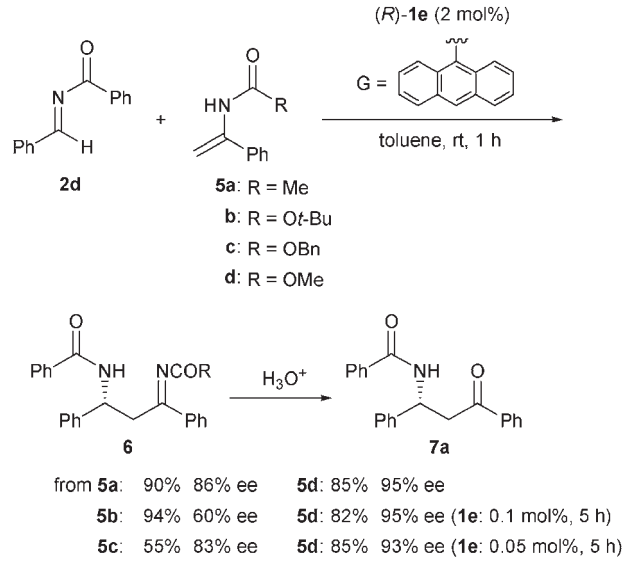
4. Aza-ene type reaction of imines with enecarbamates

4.1 Low loading of the chiral phosphoric acid catalyst

The enantioselective catalysis of organic reactions involving small organic molecules, known as organocatalysis, has become a rapidly growing area of research as it offers operational simplicity, mild reaction conditions, and is environmentally benign.[9] Although organocatalysis has proven to be beneficial in many respects, one critical drawback inherent in the methodologies to date is the inadequate catalytic efficiency.[16] Most organocatalytic reactions are performed at catalyst loadings of 10 mol% or more to achieve sufficient chemical yields and to avoid loss of enantioselectivity. To ensure a high efficiency, one of the greatest challenges in practical organocatalysis is to decrease the catalyst loading.

Recently Kobayashi and co-workers successfully demonstrated the first use of enamides and enecarbamates as nucleophiles in enantioselective reactions with either glyoxylates or glyoxylate derived-imines catalyzed by chiral copper complexes.[17] Their mechanistic proposal, in which the reaction proceeds *via* an aza-ene type pathway, inspired us to develop a highly efficient organocatalytic reaction using the phosphoric acid catalyst (**1**) (Fig. 5). In our catalytic reaction, it is considered that **1** is assembled into the transient structure of the aza-ene type reaction of **2** with enamide (or enecarbamate) (**5**) through a hydrogen bonding network (**A**), as proposed in the direct Mannich reactions (Fig. 4(b)). Thus, the key aspect of catalysis is the dual function of the phosphoric acid moiety, which electrophilically activates **2** through the proton (hollow circle) and accepts the N-H proton (dashed circle) of **5** through the Brønsted basic phosphoryl oxygen. Ideally, subsequent bond recombination leading to the aza-ene type product and regeneration of the catalyst (**1**) would take place (**A** to **C** *via* **B**). On the basis of this mechanistic assumption, it is anticipated that the reaction could operate under low catalyst loading.

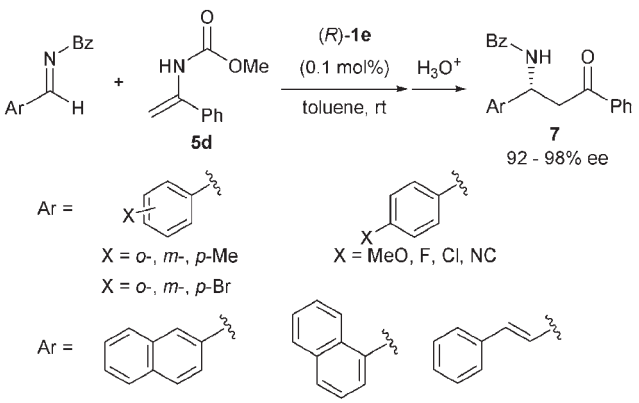
To ascertain the viability of low catalyst loading in the aza-ene type reaction, we first set the catalyst loading to 2 mol% using chiral monophosphoric acid (**1e**).[18] The catalytic efficiency was screened in the reaction of the benzaldehyde-derived *N*-benzoylimine (**2d**) with an enamide or enecarbamate (**5**) in toluene at room temperature (Scheme 4). The yields and enantioselectivities were determined after hydrolysis of imine adducts (**6**) to β-aminoketones (**7a**) under acidic work-up conditions. It is noteworthy that the protective group at the nitrogen atom of **5** is crucial for achieving a high enantioselectivity, and thus the steric bulk of the alkoxy moiety of the enecarbamates (**5**) exhibited a significant effect on the enantioselectivity. That is, the enantioselectivity increased with the



Scheme 4 Enantioselective aza-ene type reaction catalyzed by **1e** under low catalyst loading.

decrease in steric demand of the alkoxy moiety, following the order *t*-BuO (**5b**) < BnO (**5c**) < MeO (**5d**), and reaching 95% ee in the reaction with the less hindered methyl carbamate (**5d**). After observing the successful results for catalytic efficiency in the initial screening, we reduced the catalyst loading to less than 0.1 mol%. Although a prolonged reaction time was required to achieve a comparable level of product formation, the decrease in catalyst loading was clearly still effective; the enantioselectivity and the chemical yield were maintained at an equally high level. It should be emphasized that the reaction can be performed without considerable loss of enantioselectivity even with a decrease in the catalyst loading to as low as 0.05 mol%.

The applicability of the present highly efficient organocatalysis to a series of *N*-benzoylimines derivatives was investigated (Scheme 5). To ensure the catalytic efficiency of **1**, we set the catalyst loading to 0.1 mol%. It was found that *para*- and *meta*-substitution, or the use of a fused ring system, resulted in excellent chemical yields (82–97%) and enantioselectivities (92–98% ee), irrespective of the electronic properties of the substituents. Although *ortho*-substitution led to a reduction in



Scheme 5 Enantioselective aza-ene type reaction of enecarbamate (**5d**) with various *N*-benzoylimines catalyzed by 0.1 mol% of (*R*)-**1e**.

the catalytic efficiency, giving the product in moderate chemical yields (53–61%), the yields were improved in these cases (82–84%) by increasing the catalyst loading to 0.5 mol%. An imine derived from an α,β-unsaturated aldehyde is also applicable to the present reaction, giving the product in good yield (81%) with high enantioselectivity (93% ee). The utility of the low catalyst loading was highlighted by performing a gram-scale experiment. The reaction proceeded smoothly without any detrimental effect even on a gram scale. It is noteworthy that only 3.5 mg of **1e** was sufficient for completion of the reaction to yield 1.7 g (89% isolated yield) of β-aminoimine product (**6d**: R = OMe) in high enantiomeric excess (95% ee).

4.2 Cascade reaction based on tandem aza-ene type reaction

The development of efficient methods to access complex molecules with multiple stereogenic centers continues to be a substantial challenge in both academic research and industrial applications. One approach towards this challenge is the use of catalytic enantioselective cascade reactions,[19] which have emerged as powerful tools to enable a rapid increase in molecular complexity from simple and readily available starting materials, thus producing enantioenriched compounds in a single operation. Cascade reactions catalyzed by chiral Brønsted acids are attractive because such catalytic processes would allow the production of enantioenriched compounds by ecologically and economically favorable methods.

As mentioned previously in section 4.1, we successfully developed a highly efficient and enantioselective aza-ene type reaction of *N*-acyl aldimines (**2**) with di-substituted enecarbamates (**5**: $R^3 \neq H$) catalyzed by chiral monophosphoric acids (**1**),[18] in which the corresponding products (**6**) were obtained in ketimine form. Inspired by the formation of imines, we envisioned a sequential process using mono-substituted enecarbamates (**8**: $R^3 = H$)[17e] instead of the di-substituted versions (**5**) (Fig. 6).[20] The acid-catalyzed reaction of the initial aldimines (**2**) with **8** would generate aza-ene type products of *N*-acyl aldimines (**9**) as reactive intermediates and hence **9** would undergo further aza-ene type reaction leading to the subsequent generation of aldimines (**10**). If intramolecular

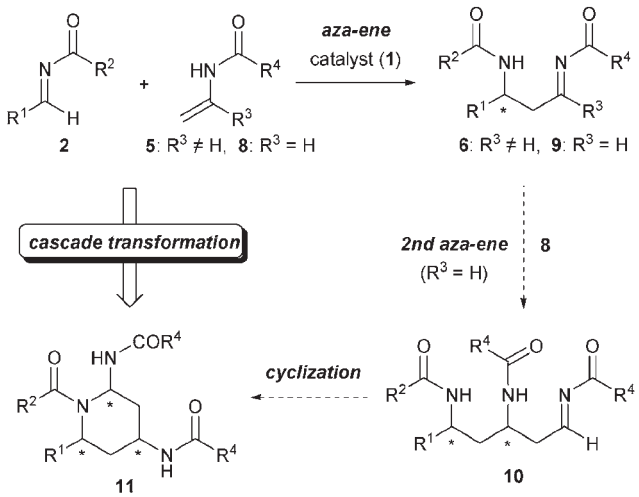
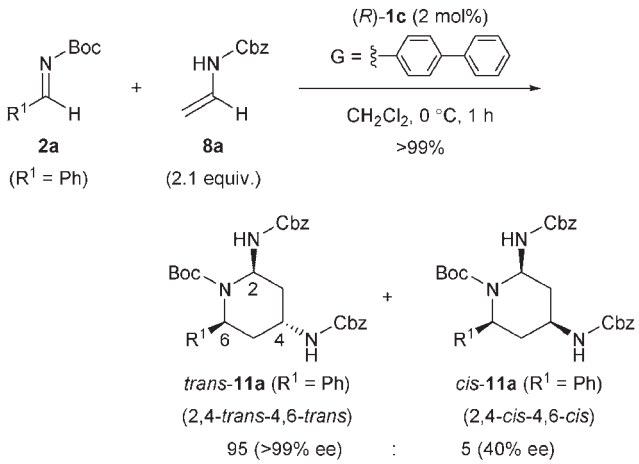


Fig. 6 One-pot entry to piperidine derivatives *via* tandem aza-ene type reaction/cyclization cascade.



Scheme 6 Cascade reaction of **2a** with **8a** catalyzed by (*R*)-**1c** to afford piperidine derivatives (**11a**).

cyclization of **10** could be enacted to terminate the tandem aza-ene type reaction sequence, our synthetic methodology would allow rapid access to piperidine derivatives (**11**) with multiple stereogenic centers, as key structural elements of numerous natural products.

The proposed cascade transformation was performed in the reaction of benzaldehyde-derived *N*-Boc aldimine (**2a**) with *N*-Cbz enecarbamate (**8a**) catalyzed by chiral phosphoric acids (**1**). To our delight, the cascade reaction proceeded smoothly to afford the desired piperidine derivative (**11a**: R^1 = Ph) in good yield (Scheme 6).[20] After screening of chiral phosphoric acid catalysts (**1**) bearing various types of aromatic substituents (G), we were able to attain excellent performance using the chiral catalysts (**1c**) in terms of diastereo- and enantioselectivity and catalytic efficiency. The cascade reaction of **2a** with **8a** was completed within 1 h at 0 °C in the presence of (*R*)-**1c** (2 mol%) to give a mixture of two diastereoisomers of piperidine derivatives (*trans*- and *cis*-**11a**: R^1 = Ph) in nearly enantiopure form. It is noteworthy that only two diastereomers were obtained from among the four diastereomers possible from three stereogenic centers.

To investigate the scope of the present cascade transformations, the reaction of **8a** with a series of aldimines was examined using (*R*)-**1c** (Fig. 7). It should be emphasized that, in most cases, one stereoisomer was formed exclusively from among the eight possible stereoisomers consisting of four pairs of enantiomers. Excellent enantioselectivities along with high diastereoselectivities were attained using aromatic aldimines, regardless of their electronic nature. Heteroaromatic and α,β-unsaturated aldimines were also encouraging, giving the corresponding products (**11d** and **11e**) in acceptable yields. Moreover, the glyoxylate-derived aldimine could be transformed to the highly functionalized piperidine derivative (**11f**) in excellent enantioselectivity. An aliphatic aldimine was also applicable to the present reaction, giving the corresponding product (**11g**) in high stereoselectivity. The high enantio- and diastereoselectivities observed can be attributed to the double asymmetric induction arising from the matched combination between the optically active aldimine intermediates (**9**) and (*R*)-**1c**.

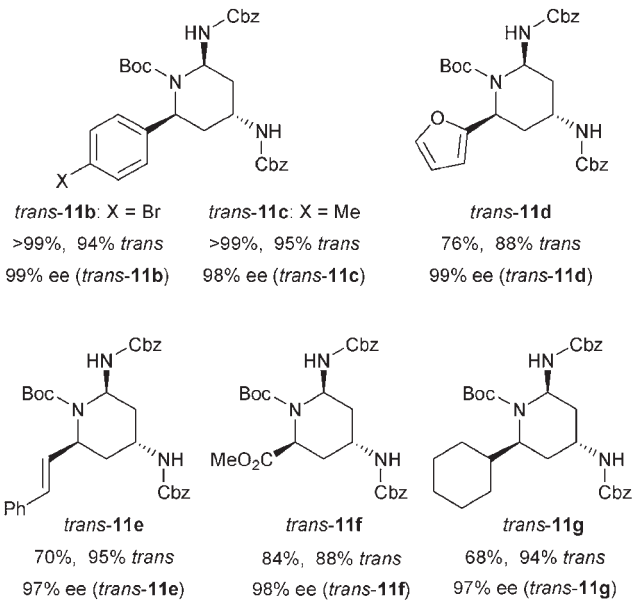


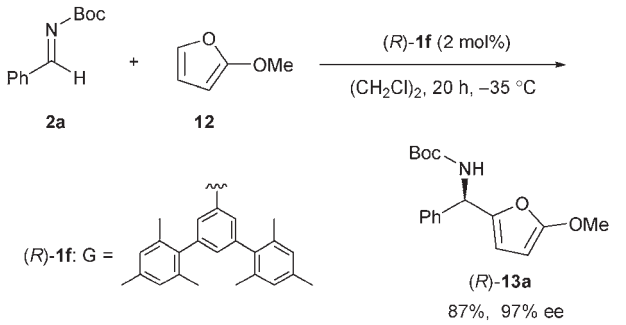
Fig. 7 Scope of the cascade reaction of imines with **8a** catalyzed by (*R*)-**1c**.

5. Friedel–Crafts reaction of imines

5.1 1,2-Aza-Friedel–Crafts reaction of 2-methoxyfuran

Enantioselective Friedel–Crafts (F–C) reaction *via* activation of electron deficient multiple bonds is undoubtedly the most straightforward, atom-economical, and practical approach for the introduction of a chiral side chain to aromatic compounds.[21] Since the 1,4-F–C reaction of α,β-unsaturated carbonyl compounds with pyrrole derivatives promoted by organocatalysts was accomplished by MacMillan and coworkers,[22] the development of organocatalytic F–C reaction has been a challenging topic of continued interest in synthetic organic chemistry. Although several efficient organocatalysts have been reported, an enantioselective 1,2-aza-F–C reaction of aldimines promoted by organocatalysts has yet to be reported as of 2004. Since optically active furan-2-yl amines are highly useful synthetic building blocks, we focused on the development of an enantioselective 1,2-aza-F–C reaction of 2-methoxyfuran (**12**) with *N*-Boc aldimine derivatives (**2**).[23]

The initial study of the 1,2-aza-F–C reaction was performed using commercially available 2-methoxyfuran (**12**) and *N*-Boc aldimine (**2a**). After screening of a series of substituents (G) for the catalysts (**1**), the sterically hindered hexamethylterphenyl (HMT)-substituted catalyst ((*R*)-**1f**) was found to be the best catalyst in terms of enantioselectivity; in the presence of 2 mol% of (*R*)-**1f,** the reaction proceeded smoothly in a highly enantioselective manner (Scheme 7). Further optimization of reaction conditions by screening different solvents and reducing the reaction temperature resulted in an increase in the enantioselectivity to 97% ee. The absolute configuration of the F–C reaction product (**13a**) was determined to be of *R*-configuration by derivatization to the stereochemically known compound. The present F–C reaction and the Mannich reaction,[12] demonstrated previously by us (section 3), gave the products (**13a** and **4a**) in the same *R*-configuration using (*R*)-**1f** and (*R*)-**1d**, respectively. However, particular attention should

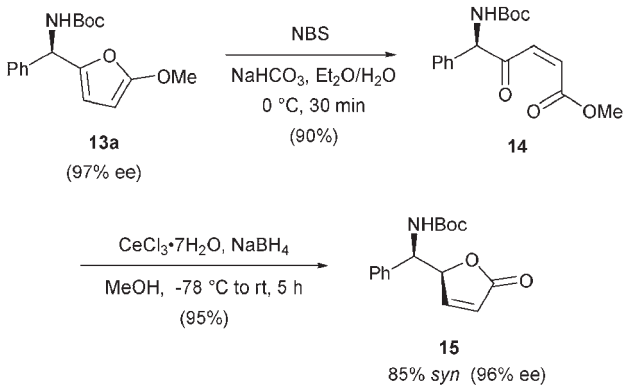


Scheme 7 1,2-Aza-F–C reaction of imine (**2a**) with 2-methoxyfuran (**12**) catalyzed by (*R*)-**1f**.

be given to the enantiofacial selection conferred by these catalysts. That is, each catalyst directs attack to the opposite enantiotopic face of the imine (see section 5.2).

Experiments to probe the scope of the 1,2-aza-F–C reaction were conducted using a series of *N*-Boc aldimine derivatives (Scheme 8). The reaction was relatively less sensitive to the stereoelectronic properties of the aldimine aromatic ring in terms of enantioselectivity and catalytic efficiency. Aldimines substituted by electron donating and withdrawing groups at the para position proved to be suitable substrates in the present F–C reaction, providing the corresponding product in excellent enantioselectivities (96–97% ee). The introduction of an ortho-substituent onto the aldimines was also tolerated for the reaction (91–94% ee). Meta-substituted aromatic rings (94–96% ee) and naphthyl and furyl rings (86–96% ee) were also good reaction partners. Most notably, the reaction can be performed in the presence of as little as 0.5 mol% of (*R*)-**1f** without any detrimental effect even on a gram scale (95% yield, 97% ee). Moreover, (*R*)-**1f** was readily recovered during purification of the product and could be applied to subsequent reactions without any special treatment prior to use.

The synthetic utility of this transformation is highlighted by derivatization of the furyl ring to γ-butenolide (Scheme 9). Since the γ-butenolide architecture is a common building block in the synthesis of various natural products, **13** represents a new entry to synthetic precursors of nitrogen-containing molecules. Indeed, the aza-Achmatowicz reaction of **13a** (97% ee) cleaved the furan ring cleanly to form the 1,4-dicarbonyl compound



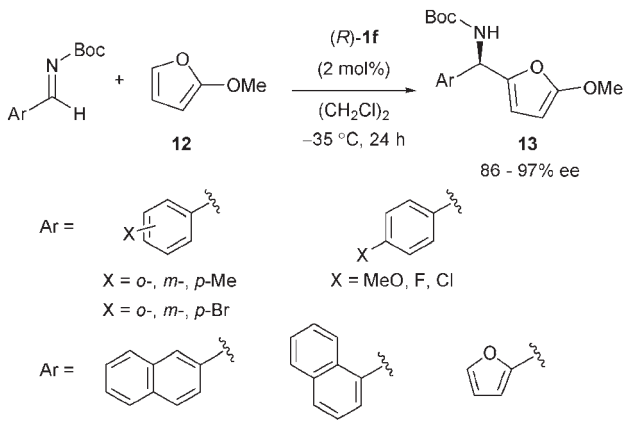
Scheme 9 Synthetic utility of furan-2-yl amine products (**13**).

(**14**) in 96% ee. Subsequent reductive-cyclization of **14** under Luche conditions led to the γ-butenolide (**15**) in 95% yield without significant loss of enantiomeric excess (96% ee).

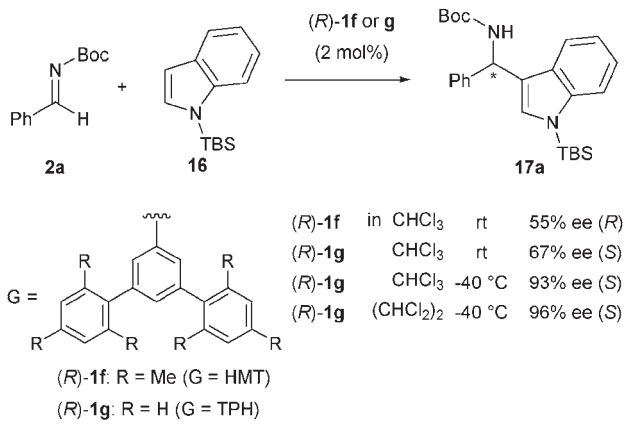
5.2 1,2-Aza-Friedel–Crafts reaction of indoles

Further application of the chiral phosphoric acid-catalyzed 1,2-aza-F–C reaction is highly desirable, as it has the potential to provide a diverse array of optically active aryl methanamine derivatives with high catalytic efficiency and enantioselectivity. In particular, 1,2-aza-F–C reaction of indoles is an attractive transformation towards enantioenriched 3-indolyl methanamine derivatives.[24] These indolyl derivatives are widely identified as ''privileged'' structures among pharmacophores and are represented in thousands of natural isolates and many medicinal agents of versatile therapeutic action.

An initial experiment of the 1,2-aza-F–C reaction was performed using the *N*-*tert*-butyldimethylsilyl (TBS) protected indole (**16**) and *N*-Boc imine (**2a**) under the influence of the sterically hindered HMT-substituted catalyst ((*R*)-**1f**) (Scheme 10),[25] as it was the most enantioselective and efficient catalyst for the 1,2-aza-F–C reaction of 2-methoxyfuran (**12**) with *N*-Boc imines (**2a**), as shown in Scheme 7.[23] The 1,2-aza-F–C reaction was carried out using 2 mol% of (*R*)-**1f**, and an enantioenriched F–C product (**17a**) was obtained in 68% yield (55% ee (*R*)). However, catalysis of the reaction by (*R*)-**1f** was sluggish and the enantioselectivity was not sufficient despite thorough optimization of the



Scheme 8 1,2-Aza-F–C reaction of 2-methoxyfuran (**12**) with various imines catalyzed by (*R*)-**1f**.



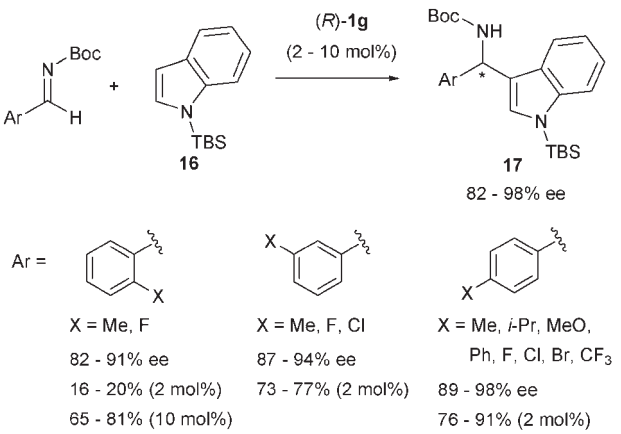
Scheme 10 1,2-Aza-F–C reaction of imine (**2a**) with *N*-TBS indole (**16**) catalyzed by (*R*)-**1**.

reaction conditions. In order to enhance the catalytic activity and enantioselectivity, we screened the catalyst (**1**) by changing the substituent (G) attached at the 3,3′-position of the binaphthyl backbone.

Screening of the substituents (G) revealed that terphenyl (TPH) groups (**1g**) were effective for the present enantioselective F–C reaction, albeit affording only moderate enantioselectivity (67% ee). It is noteworthy that, for enantioselective catalysis by (*R*)-**1g**, the stereochemical outcome of (*S*)-**17a** was opposite to that observed for catalysis by (*R*)-**1f**, where the methyl groups were removed from the HMT substituent without any change to the terphenyl skeleton. To our delight, further optimization of the catalysis by (*R*)-**1g** markedly improved the enantioselectivity from 67 to 96% ee; in the optimum reaction conditions the temperature was set to –40 °C and the solvent was 1,1,2,2-tetrachloroethane. The reaction can be performed using a low loading of the catalyst (2 mol%) and the use of only a slight excess of imines (**2a**) to *N*-TBS indole (**16**). Under these optimized conditions it was possible to afford the corresponding product (**17a**) in good chemical yield without formation of the bisindolyl byproduct.

The scope of the enantioselective 1,2-aza-F–C reaction catalyzed by (*R*)-**1g** is shown in Scheme 11. High enantioselectivities were observed for a series of aromatic imines examined, but the position of the substituent on the aromatic ring exhibited a strong impact on the catalytic activity. For example, the *ortho* substituents retarded the reaction markedly and an increase in catalyst loading to 10 mol% was required to obtain the desired product in an acceptable yield. Although meta substitution resulted in slightly lower enantioselectivities (87–94% ee), **1g** exhibited excellent performance in reaction with *para*-substituted aromatic imines bearing a broad range of substituents irrespective of their stereoelectronic properties (89–98% ee).

In an effort to understand the inversion in the sense of stereochemical outcome observed in the catalysis between (*R*)-**1f** and (*R*)-**1g**, we conducted a computational study of the 3D-structures of the catalysts (**1**) at the B3LYP/6-31G** level of theory.[15,25] The optimized 3D-structures of (*R*)-**1g** and (*R*)-**1f** are shown in Fig. 8. We speculate that the observed inversion of the enantioselectivity would be attributed to the



Scheme 11 1,2-Aza-F–C reaction of *N*-TBS indole (**16**) with various imines catalyzed by (*R*)-**1g**.

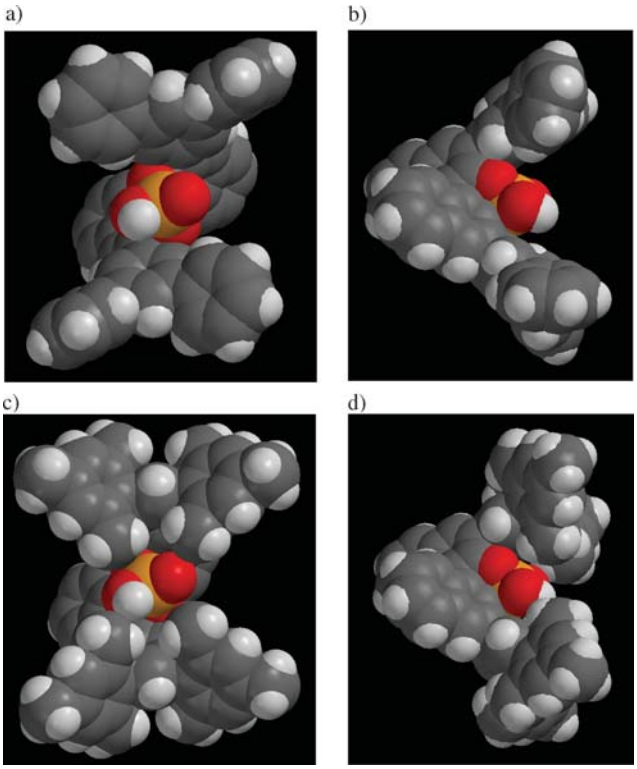


Fig. 8 3D-structures for the optimized geometries of (*R*)-**1**. P tan, O red, C gray, H white. (a) Front view of (*R*)-**1g** (G = TPH). (b) Side view of (*R*)-**1g**. (c) Front view of (*R*)-**1f** (G = HMT). (d) Side view of (*R*)-**1f**.

accessibility of the reactants to the acidic site of the catalyst (**1**). As depicted in Fig. 8(a) and (b), the TPH substituents of (*R*)-**1g** were arranged in a nearly parallel arrangement on the top and bottom sides of the phosphoric acid moiety, forming a reaction pocket in the region which we term the "front" of the acid moiety. It is likely that the catalyst (*R*)-**1g** provides enough space to allow assembly of the transient structure of the F–C reaction in front of the acidic moiety (Fig. 8(a)). In contrast, for the sterically demanding HMT substituents of (*R*)-**1f** (Fig. 8(c) and (d)), the *ortho* methyl substituents force the mesityl ring to be perpendicular to the basal phenyl moiety and thus the "front" side of the acidic moiety is congested. Hence, formation of the transient structure of the F–C reaction would be prevented on the "front" side of the acidic moiety (Fig. 8(c)). As a result, we speculate that the catalytic reaction would proceed in such a manner as to avoid the sterically congested front side of the acidic moiety. The above considerations on the inversion in the sense of the stereochemical outcome would be applicable to the previous case of the direct Mannich reaction (section 3) *vs.* the F–C reaction of furan (section 5.1).

5.3 α-Alkylation reaction of diazoacetate

The catalytic asymmetric electrophilic substitution reaction of an sp^2 C–H bond by carbonyl, imine and α,β-unsaturated carbonyl compounds, such as F–C alkylations, is a powerful yet challenging organic transformation.[21] Mechanistically, these F–C alkylations, known as formal substitution reactions,

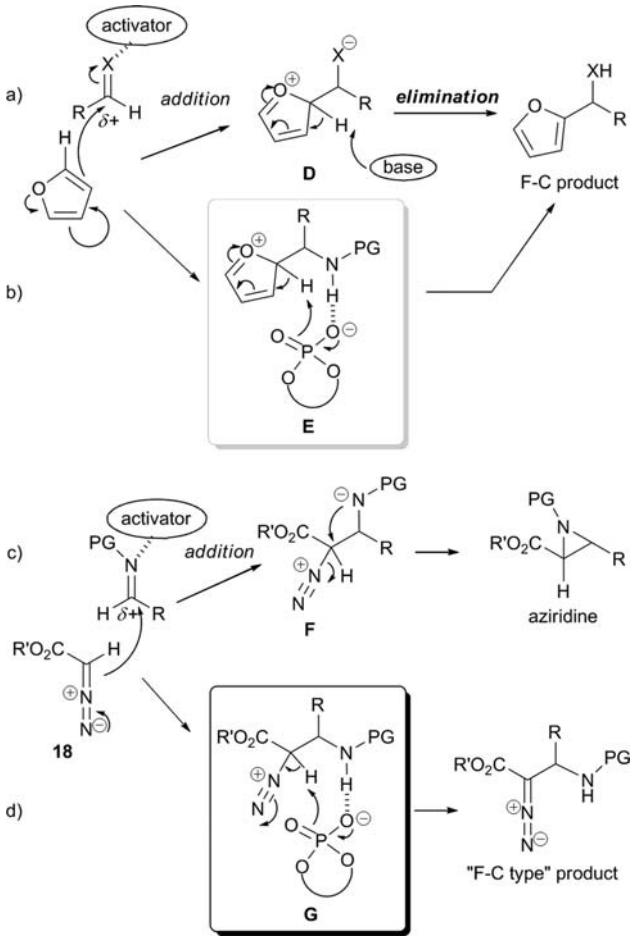


Fig. 9 Mechanistic resemblance between F–C alkylations and α-alkylation reactions of diazoacetate.

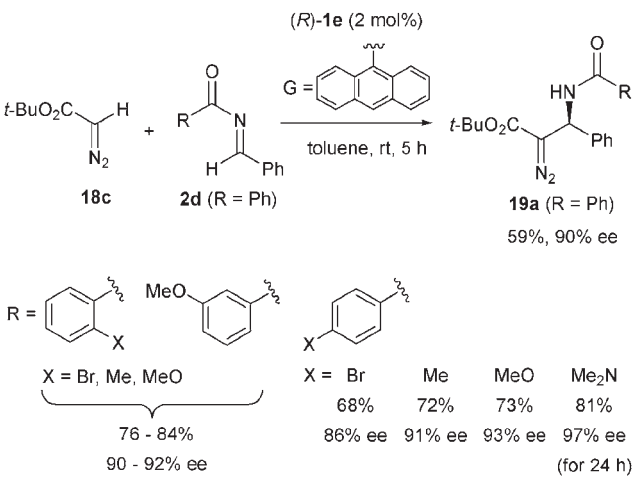
comprise sequential addition–elimination pathways (Fig. 9(a)). For instance, an electron rich aromatic or heteroaromatic compound attacks an activated, thus electron deficient, sp^2-carbon and subsequent deprotonation provides the F–C alkylation product exclusively. As mentioned in sections 5.1 and 5.2, the highly enantioselective 1,2-aza-F–C reactions of 2-methoxyfuran (**12**) and indole (**16**) with *N*-Boc aldimines have been demonstrated using chiral phosphoric acid catalysts (**1**).[23,25] In consideration of the catalytic cycle of these F–C reactions, the phosphoric acid would be expected to promote these addition–elimination pathways as a result of its dual function (Fig. 9(b)). It is expected that the phosphoric acid activates an electrophile and accelerates the addition reaction at the electron deficient carbon, while in the elimination step the phosphate anion would accept a proton, and it is even possible that the phosphoryl oxygen functions as an intracomplex basic site *via* an intermediate **E**.

Diazoacetate, which has an electronically unique sp^2-carbon, is a rather interesting motif from this viewpoint because of the resemblance between the addition intermediates **D** and **F** (Fig. 9(a) and (c)). Although diazoacetate (**18**) is commonly used in aziridine formation reactions (aza-Darzens reaction) under Lewis[26] and Brønsted[27] acidic conditions (Fig. 9(c)), a possible intracomplex deprotonation from intermediate **G** by the phosphoryl oxygen (Fig. 9(d)), as shown in a similar intermediate **E** (Fig. 9(b)), might allow direct alkylation of diazoacetate *via* C–H bond cleavage, giving an α-diazo-β-amino acid ester through an ''F–C type'' reaction pathway (Fig. 9(d)).

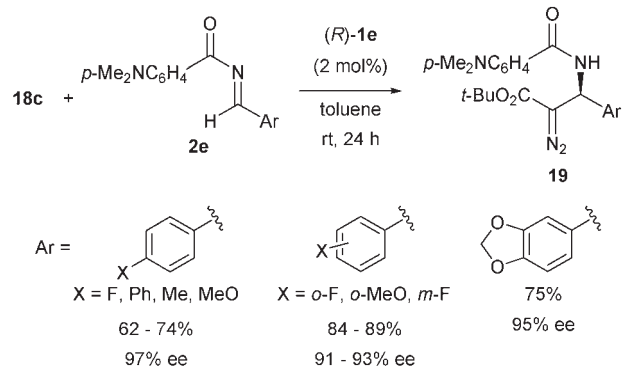
For the first step of the proposed enantioselective direct alkylation, the reaction of ethyl diazoacetate (**18a**) with *N*-benzyl imine (**2d**) was attempted with screening of the phosphoric acid catalysts (**1**). Among the catalysts tested, the catalyst (*R*)-**1e** proved to be the best in terms of enantioselectivity (79% ee),[28] and the expected alkylation product (**19**) was obtained in good yield under the influence of 2 mol% of **1e** in toluene at room temperature. Fortunately, the enantioselectivity was improved by increasing the steric demand of the ester moiety of diazoacetate (**18**), thus following the order: ethyl ester (**18a**), 79% ee < isopropyl ester (**18b**), 84% ee < *tert*-butyl ester (**18c**), 90% ee (Scheme 12). These results obviously indicate that the phosphoric acid catalyst efficiently promotes the direct alkylation of α-diazoesters *via* C–H bond cleavage, although the precise action of the phosphoryl oxygen has not yet been clarified at the deprotonation step.

Interestingly, the electronic properties of the acyl protective group of the imine nitrogen profoundly affected enantioselectivity and reactivity (Scheme 12). Although there was little effect on the selectivity with modification at the *ortho*- or *meta*-position of the acyl aromatic moiety, the *para*-substituents exhibited a marked effect on the enantioselectivity; introduction of electron-donating substituents provided better results. Among the substituents attempted, *para*-dimethylaminobenzoyl aldimine (**2e**) was the best in terms of the enantioselectivity, although there was a marked reduction in the reaction rate. Fortunately, this problem could be circumvented by a prolonged reaction time.

Experiments that probe the scope of this transformation are summarized in Scheme 13. In general, *para*-substituted aromatics showed excellent enantioselectivity irrespective of their electronic properties. *Ortho*- and *meta*-substitution as well as fused-ring systems were also tolerated. The β-amino-α-diazoester products (**19**) thus obtained can be transformed to the common synthetic intermediates β-amino acid derivatives *via* simple reduction or oxidation of the diazo moiety.



Scheme 12 α-Alkylation of diazoacetate (**18c**) with imine (**2d**) catalyzed by (*R*)-**1e**.



Scheme 13 α-Alkylation of diazoacetate (**18c**) with various imines catalyzed by (*R*)-**1e**.

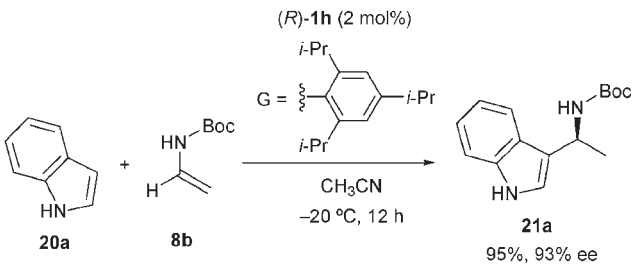
5.4 Friedel–Crafts reaction *via* activation of electron rich alkenes

F–C reaction is one of the most powerful methods for the formation of a new carbon–carbon bond and has been widely utilized from bench-top experiments to industrial processes. Enantioselective variants of this fundamental transformation have also been investigated using metal-based chiral catalysts or chiral organocatalysts.[21–25] These enantioselective catalyses have been accomplished *via* activation of electron deficient multiple bonds, such as C═O, C═NR, and C═C–X (X: electron-withdrawing group) *etc*. Acid-catalyzed F–C reactions of arenes with electron rich alkenes are practical and atom-economical methods for providing alkylated arenes and have been applied to numerous industrial processes. Recently, and for the first time, we successfully demonstrated highly enantioselective F–C reaction initiated by activation of electron rich multiple bonds using a chiral Brønsted acid catalyst.[29] The chiral phosphoric acid (**1h**) exhibited excellent performance for this activation mode, which utilized the catalytic reaction of indoles (**20**) with enecarbamates (**8**) as electron rich alkenes, yielding the desired F–C products (**21**) in high enantioselectivities as exemplified in Scheme 14. The present approach provides efficient access to enantioenriched 3-indolyl methanamines with a variety of aliphatic substituents and effectively complements our previous method that afforded aromatic-group substituted 3-indolyl methanamines *via* activation of aryl aldimines as mentioned in section 5.2.

The proposed enantioselective F–C reaction was first examined using indole (**20a**), *N*-Boc protected enamine (**8b**), and 2 mol% of (*R*)-**1h** at room temperature in various organic solvents. It is noteworthy that not only the catalytic activity but also the asymmetric induction were highly dependent on the solvents employed. The less polar aromatic solvent toluene was useful for chiral phosphoric acid-catalyzed F–C reaction *via* activation of an electron deficient double bond, C═NR,[23,25] but in this activation mode **1h** suffered from a marked retardation in the catalytic activity (26%, 80% ee). While, in the more polar aromatic solvent $PhCF_3$, **1** exhibited high catalytic efficiency, affording the F–C product (**21a**) in high chemical yield without notable loss of enantiomeric excess (91%, 79% ee). The halogenated solvent CH_2Cl_2, possessing a similar polarity to $PhCF_3$, was also tolerated by the reaction (84%, 84% ee). However, either the chemical yields or the enantioselectivities were seriously diminished in highly polar and protophilic solvents[30] such as DMF and DMSO (17–22%, 10–54% ee). Among the solvents tested, the highly polar but protophobic acetonitrile[30] was found to be the best with respect to the catalytic activity and the asymmetric induction (84%, 88% ee). As expected, the enantiomeric excess increased with a decrease in reaction temperature, reaching 93% ee at −20 °C (Scheme 14).

As shown in Fig. 10, the phosphoric acid catalyst **1h** displayed excellent performance for the reaction of various indole derivatives (**20**) with a broad range of substituted enecarbamates (**8**). Uniformly high enantioselectivities and chemical yields were obtained in the reaction of indole (**20a**) with **8** bearing either a linear or branched alkyl group as well as an aromatic substituent. In addition, the sterically hindered disubstituted enecarbamate was also applicable to the present enantioselective F–C reaction. Moreover, the enantioselectivities were maintained at an equally high level for a wide variety of indole derivatives (**20**), irrespective of their electronic properties. It is noteworthy that the present catalytic system allows for the reaction of indoles substituted with electron-withdrawing groups, such as bromo and methoxycarbonyl substituents, affording the F–C products in high yield.

As shown in Fig. 11, the geometric isomers (*E*)- and (*Z*)-**8c** gave the product (**21b**) with the same level of enantioselectivity. These results suggest that both reactions proceeded



Scheme 14 F–C reaction *via* activation of enecarbamate (**8**) by phosphoric acid catalyst (*R*)-**1h**.

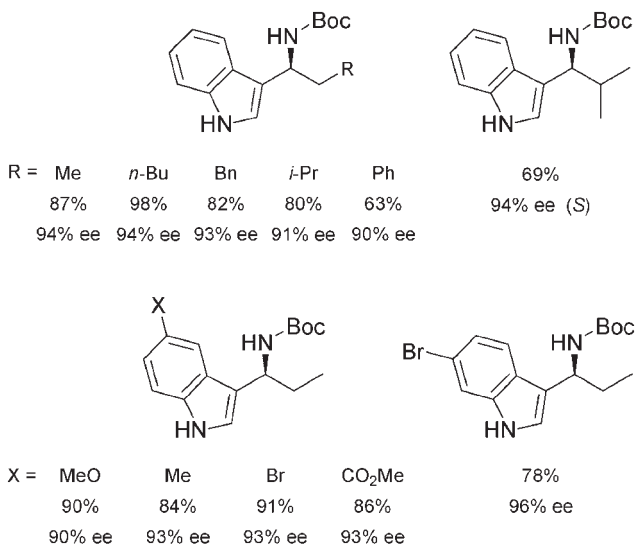


Fig. 10 F–C reaction of indole derivatives (**20**) with substituted enecarbamates (**8**) catalyzed by (*R*)-**1h**.

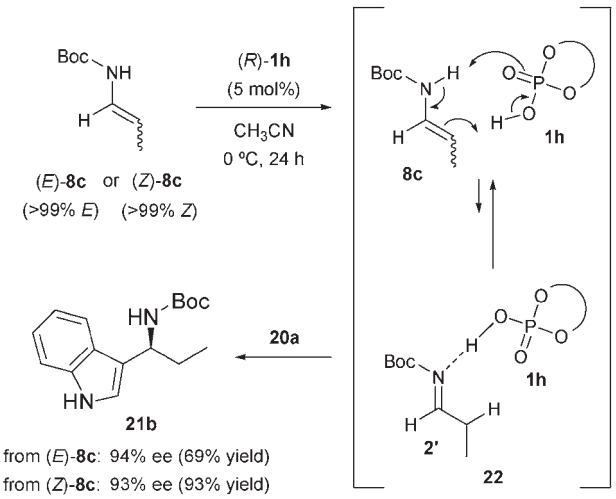
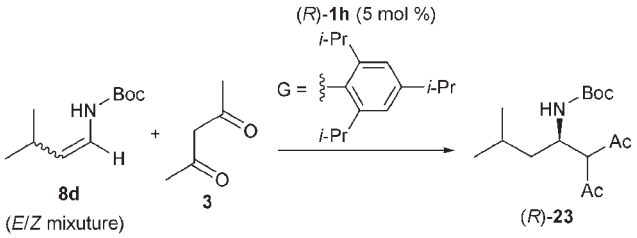


Fig. 11 Mechanistic considerations of the F–C reaction of **8** with indole (**20a**) catalyzed by (*R*)-**1h**.

through the common intermediate (**22**), composed of **1h** and an aliphatic imine (**2′**), as it was generated by the protonation of enecarbamates (**8c**).[24d] Hence the present activation mode is regarded as an efficient method for generating aliphatic imines (**2′**),[31] which are generally labile and difficult to isolate. Furthermore, the reaction rate was dependent on the geometry of the enecarbamate employed; (*Z*)-**8c** showed higher reactivity than (*E*)-**8c**. It can be considered that the protonation of **8** by **1h** *via* ionic transition states would be the rate-determining step. This mechanistic assumption is strongly supported by the solvent effect, in which a high catalytic efficiency was observed in a highly polar but protophobic solvent.

The phosphoric acid (**1**) functions as an efficient catalyst for a dual transformation in which there is *in situ* generation of an imine (**2′**) and an enantioselective carbon–carbon bond forming step with indoles as the nucleophilic components. This protocol has the distinct advantage of *in situ* generation of unstable aliphatic imines (**2′**) from storable, and thus easily handled, enecarbamates (**8**) and hence is applicable to other organic transformations. With this in mind, we then attempted utilization of the present method to a direct Mannich reaction, giving rise to β-alkyl-β-aminocarbonyl derivatives in an optically active form.[32] Mannich reactions of aliphatic imines possessing hydrogen atoms at the α-position have rarely been explored to date,[14g,q] although there have been a number of excellent approaches to the enantioselective direct Mannich reaction, in which most imines employed are derived from aromatic aldehydes.[14]

An initial experiment was performed using *N*-Boc protected enecarbamate (**8d**), 10 equivalents of acetylacetone (**3**), and 5 mol% of (*R*)-**1h** at room temperature in acetonitrile (Scheme 15). However, despite using the same catalyst molecule, **1h**, and following similar reaction conditions to those used in the enantioselective Friedel–Crafts reaction of indoles (**20**) as mentioned above, the enantioselectivity was reduced considerably. We further investigated the solvent effect to improve the enantioselectivity, as it was previously found to have a marked influence on catalytic activity and enantioselectivity.[29] Indeed, the activity and selectivity are profoundly dependent on the

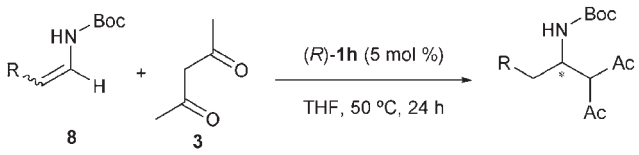


Scheme 15 Direct Mannich reaction *via* activation of enecarbamate (**8**) by (*R*)-**1h**.

solvent employed. After screening of either polar or less-polar organic solvents, ethereal solvents were found to exhibit higher enantioselectivities than those obtained in the less-polar organic solvents which are commonly employed in acid-catalyzed reactions. Among the ethereal solvents tested, THF proved to be the optimal medium in terms of obtaining the highest enantioselectivity, even though an elevated temperature was required to obtain the corresponding product (**23**) in an acceptable yield. Fortunately, the chemical yield was improved by reducing the amount of **3**, albeit with a prolonged reaction time.

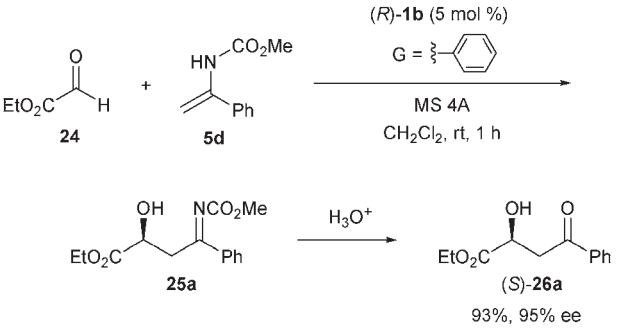
The absolute configuration of the Mannich product (**23**) was determined to be an *R*-configuration after derivatization to the stereochemically known compound.[32] Interestingly, the absolute stereochemistry of **23** was opposite to that observed in the Friedel–Crafts reaction *via* activation of enecarbamates by the exactly same catalyst, (*R*)-**1h** (Fig. 10). The precise mechanism of the enantiofacial selection has not yet been clarified, but it is considered that the stereochemical outcome that results upon addition of the chiral monophosphoric acid catalyst (**1**) is highly dependent not only on the hydrogen bonding interactions between the aliphatic imine (**2′**) and the phosphoric acid (**1**) but also on the transient assembly of a ternary system including a nucleophilic component. This intriguing observation, inversion in the sense of the stereochemical outcome, would be ascribed to the intrinsic flexibility of the hydrogen bond formed between the nitrogen atom of the imine (**2′**) and the oxygen atom of the chiral phosphoric acid (**1h**) in the intermediate (**22**) (Fig. 11).

In order to further characterize the present direct Mannich reaction, we next investigated the substituent effect of enecarbamates (**8**) with varying steric demand of the alkyl moieties (R) introduced at the C2 position under optimized reaction conditions (Scheme 16). The enantioselectivity observed is susceptible to the stereoelectronic properties of the alkyl substituents. The enantioselectivity was enhanced with increasing steric demand of the alkyl group, thus following the order: Me (49% ee) < *n*-Bu (75% ee) < *i*-Pr (86% ee) < *c*-Hex (89% ee), and reaching 89% ee in the reaction with the most sterically hindered *c*-Hex substituted enecarbamate. Introduction of an aromatic substituent into the enecarbamate resulted in detrimental effects on enantioselectivity. These remarkable substituent effects are in contrast to the previous Friedel–Crafts reaction we investigated using this catalyst,[29] in



R =	Me [(*E*)-**8c**]	Me [(*Z*)-**8c**]	*n*-Bu	*c*-Hex	Bn	Ph
	49%	63%	73%	67%	56%	43%
	49% ee	49% ee	75% ee	89% ee	61% ee	51% ee
						(70 °C, 72 h)

Scheme 16 Direct Mannich reaction *via* activation of various enecarbamates (**8**).



Scheme 17 Aza-ene type reaction of glyoxylate (**24**) with enecarbamate (**5d**) catalyzed by (*R*)-**1b**.

which uniformly high enantioselectivity was observed, irrespective of the alkyl substituents.

As shown in Scheme 16, the geometric isomers (*E*)- and (*Z*)-**8c** gave the corresponding product with the same level of enantioselectivity. In addition, (*Z*)-**8c** showed higher reactivity than (*E*)-**8c**. These results suggest that both reactions proceeded through a common intermediate **22**, as illustrated in Fig. 11, and that the protonation of **8** by **1h** would be the rate-determining step, as previously discussed in the Friedel–Crafts reaction.

6. Enantioselective activation of aldehydes

Carbonyl compounds play a central role in a diverse array of organic reactions. In particular, activation of aldehydes represents the most fundamental transformation available to synthetic chemists, and has developed into a broad reaction class that occupies a privileged place in synthetic organic chemistry. Activation of aldehydes using a chiral Brønsted acid was first reported by Rawal and co-workers, who performed a hetero-Diels–Alder reaction in the presence of a catalytic amount of TADDOL.[4a] Since this milestone achievement, chiral Brønsted acid catalysis *via* activation of aldehydes has attracted considerable attention in organic chemistry.[33] Although BINOL-derived phosphoric acid has been shown to be a versatile catalyst in enantioselective transformations, in most of these transformations, imines have been employed as the electrophilic component.[2d,34] Enantioselective activation of aldehydes using a chiral phosphoric acid has yet to be reported in the literature. Hence activation of aldehydes remains a substantial challenge and could be another opportunity for the use of chiral phosphoric acids in catalysis. Recently, we successfully demonstrated the first example of enantioselective activation of aldehydes using a chiral phosphoric acid catalyst,[35] in which aza-ene type reaction of glyoxylate (**24**) as a reactive aldehyde with enecarbamate (**5d**) afforded the corresponding products with excellent enantioselectivity (Scheme 17).[17c]

The catalyst (**1b**) efficiently accelerated the aza-ene type reaction of glyoxylate (**24**). The corresponding product (**25a**) was obtained in high yield within 1 h in the presence of 5 mol% of phosphoric acid catalyst (*R*)-**1b** and molecular sieves (MS) 4A, which were employed as scavengers of acidic impurities.[36] After hydrolysis of **25a** to β-hydroxyl ketone (**26a**), the enantioselectivity was determined. As a result, excellent enantioselectivities were observed even when using the catalyst (**1b**) bearing unmodified phenyl groups (G = Ph). The fact that the simple phenyl-substituted catalyst provides excellent enantioselectivity is noteworthy, since in experiments on the activation of imines it was found that catalysts (**1**) required modified phenyl substituents, in general bulky ones, to obtain high enantioselectivities.

To gain mechanistic insight into the high enantioselectivity observed in catalysis by **1b**, we further investigated a series of catalysts (**1**) bearing substituted phenyl rings. As shown in Fig. 12, there was a marked relationship between the substituent pattern on the phenyl ring and the catalytic performance in terms of both activity and enantioselectivity. Excellent performance was maintained when the substituents were introduced to the *para*-position of the phenyl ring, irrespective of their stereoelectronic properties (Fig. 12(a)). In sharp contrast, if the phenyl ring was substituted either by bulky groups at the 3,5-positions or even by small substituents at the 2,6-positions (Fig. 12(b)), then the catalytic activity and enantioselectivity was compromised.

In an effort to understand the high enantioselectivity observed even for catalyst (*R*)-**1b**, having simple phenyl substituents, we conducted DFT computational studies looking into hydrogen bonding pairs formed between methyl glyoxylate (**24′**) and the phosphoric acids (**1b** and **1n**). As illustrated in Fig 13(a), the key feature of the complexation modes is the double hydrogen bond. The additional hydrogen bond that exists between the formyl hydrogen atom and the phosphoryl

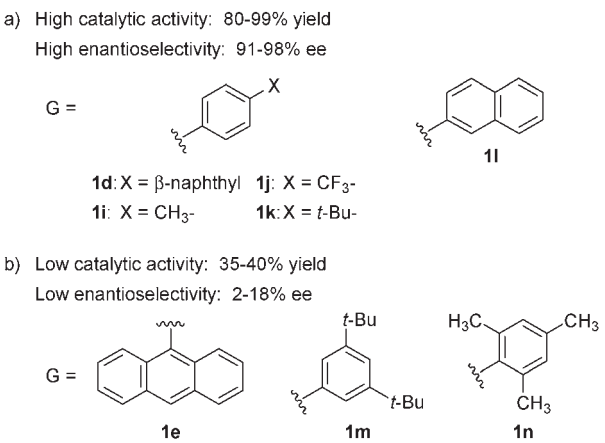


Fig. 12 Aza-ene type reaction of glyoxylate (**24**) with enecarbamate (**5d**) catalyzed by a series of (*R*)-**1**.

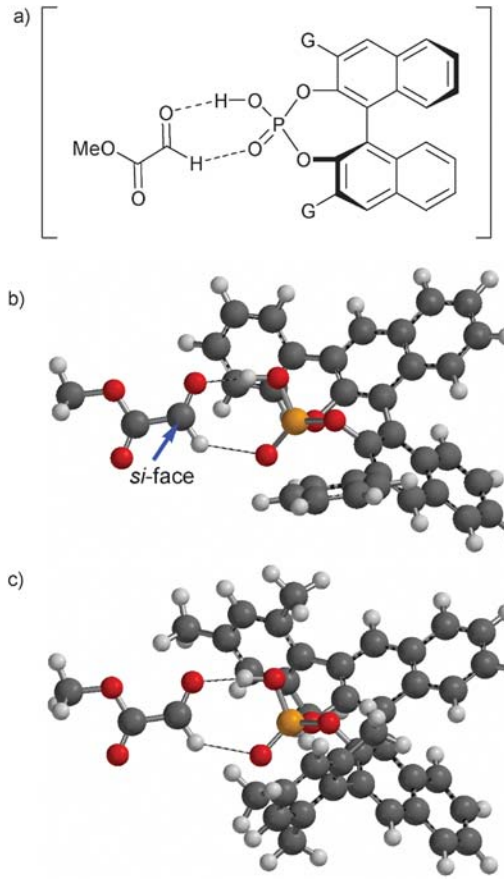
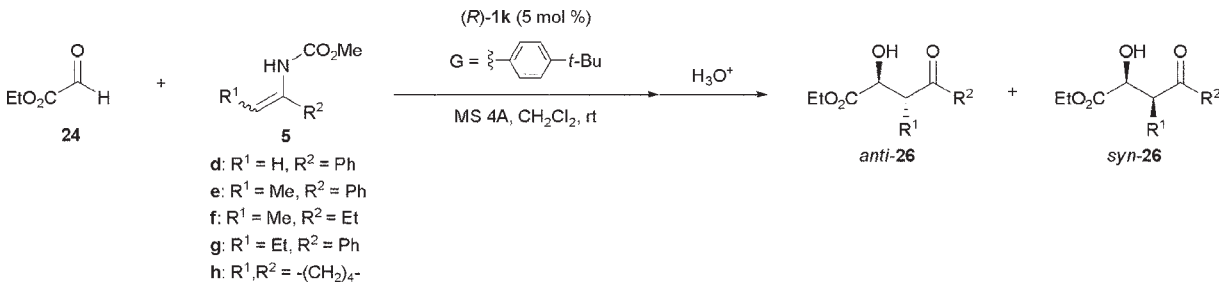


Fig. 13 Structure of double hydrogen-bonded complexes formed between (*R*)-**1** and **24′**. (a) Illustration of double hydrogen-bonding model; (b) three-dimensional structure of (*R*)-**1b**/**24′**; (c) three-dimensional structure of (*R*)-**1n**/**24′**. P tan, O red, C gray, H white.

oxygen atom forces a coplanar orientation of the formyl group and the phosphoric acid subunit.[37] The optimized structures of (*R*)-**1b**/**24′** and (*R*)-**1n**/**24′** are shown in Fig. 13(b) and (c), respectively. The experimental results are well rationalized by these double hydrogen-bonding models.[38] In the 3D-structure of the double hydrogen-bonded pairs of **1b** with **24′** (Fig. 13(b)), one enantiotopic face (*re*-face) of the aldehyde is effectively shielded by one of the phenyl rings. In contrast, the other face (*si*-face) is fully accessible, and hence the enecarbamate attacks from the front side (blue arrow indicated in Fig. 13(b)), affording the (*S*)-product, which is the absolute configuration observed experimentally. Such a conformational arrangement of the phenyl rings would be applicable to the *para*-substituted catalysts (Fig. 12(a)). In contrast, the mesityl rings of (*R*)-**1n** are forced into a perpendicular arrangement with respect to the basal naphthyl moiety due to the two *ortho* methyl substituents, and hence overlapping with the aldehyde occurs (Fig. 13(c)). Both enantiotopic faces are well shielded by the substituents (G) and as a result there is a significant decrease in catalytic activity and enantioselectivity in catalysis by **1n**. Similar conformational restrictions would occur in the other catalysts having bulky substituents (G) (Fig. 12(b)).

The aza-ene type reaction of glyoxylate is applicable to a series of substituted enecarbamates (**5**), which demonstrate the stereochemical issue of enantio- and diastereoselection (Table 1). Among the catalysts (**1**) examined (Fig. 12), **1k** exhibited excellent performance in terms of both catalytic activity and enantioselectivity (entry 1) and hence was employed as a promising catalyst for subsequent reactions. The (*Z*)-enecarbamate retarded the reaction markedly and low enantioselectivity was observed in the major *anti*-isomers (entries 6–8). However, extremely high enantio- and *anti*-selectivities were observed in the reactions of the (*E*)-isomers (entries 2–5). It seems likely that the reaction proceeds *via* cyclic transition states because of the significant difference in both reactivity and enantioselectivity observed between each geometric isomer. The enormous retardation observed for the

Table 1 Aza-ene type reaction of various enecarbamates (**5**) with glyoxylate (**24**) catalyzed by (*R*)-**1k**[a]



Entry	**5**	*t*/h	Yield[b] (%)	*Anti* : *syn*	*Anti*: ee[c] (%)	*Syn*: ee[c] (%)
1	(*E*)-**5d**	1	99	—	98[d]	—
2	(*E*)-**5e**	2	73	>99 : <1	>99	53
3	(*E*)-**5f**	2	73	96 : 4	99	56
4[e]	(*E*)-**5g**	4	75	99 : 1	99	74
5	**5h**	1	89	89 : 11	99	98
6	(*Z*)-**5e**	24	11	72 : 28	26	88
7	(*Z*)-**5f**	2	74	50 : 50	28	69
8[e]	(*Z*)-**5g**	24	67	92 : 8	8	74

[a] Unless otherwise noted, all reactions were carried out using (*R*)-**1k** (5 mol%), 1.7 equiv. of freshly distilled **24**, and enecarbamate **5** in CH_2Cl_2 in the presence of powdered MS 4A. [b] Isolated yield of **26**. [c] Determined by chiral HPLC analysis of **26**. [d] Enantiomeric excess of **26a**. [e] 3.0 equiv. of freshly distilled **3**.

(*Z*)-enecarbamates would be caused by unfavourable interaction between the enecarbamate (**5**) and the double hydrogen-bonding pairs of **1k** with **24**. Whereas the exclusive formation of *anti*-products from the (*E*)-isomers could be attributed to the well-defined *exo*-transition state.[17c]

7. Chiral phosphorodiamidic acids as feasible enantioselective catalysts

In the development of novel chiral Brønsted acid catalysts, the design of new structural motifs that can be modified to construct an efficient chiral environment is a challenging task. In this context, we were interested in phosphorodiamidic acids (**27**) as an attractive candidate for a chiral Brønsted acid catalyst. As shown in Fig. 14, phosphorodiamidic acids (**27**) possess unique structural features. A cyclic structure can be introduced by using diamine as the framework and substituents (G′) can be attached to the nitrogen atoms of the diamine. The stereoelectronic effect of the substituents (G′) can be utilized for controlling not only the acidity, and hence the catalytic activity, but also the steric demand around the activation site. In addition, the cyclic phosphorodiamidic acids can be prepared in a short step from chiral diamines, such as C_2 symmetric diamines, which are readily available. If we introduce a C_2 symmetric diamine, it would be anticipated that the chiral environment of the diamine is transferred to the substituents (G′) on the nitrogen atoms, forcing the substituents (G′) to occupy opposite sides of the diazaphosphacycle plane. In addition, the substituents would be located in the proximity of the activation site, where asymmetric induction is expected at the bond forming step.

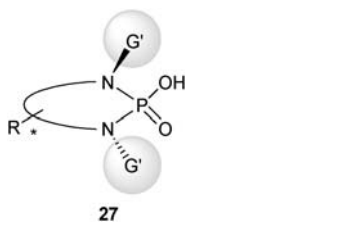


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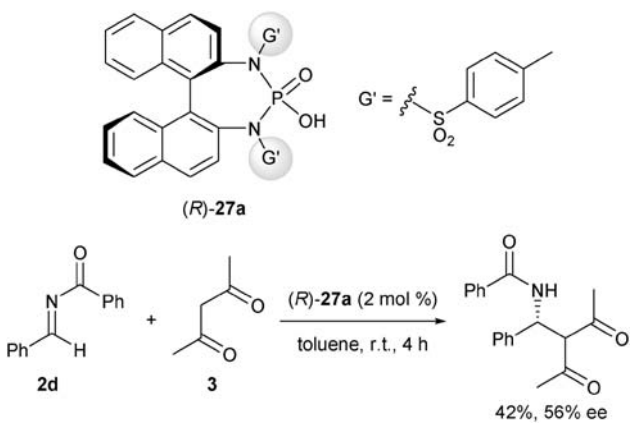
Fig. 14 Phosphorodiamidic acids (**27**) as a novel structural motif for chiral Brønsted acid catalysts.



Scheme 18 Direct Mannich reaction of **2d** with **3** catalyzed by chiral phosphorodiamidic acids (**27a**).

In an effort to develop chiral phosphorodiamidic acid catalyst (**27**), we employed binaphthyl diamine as the C_2 symmetric diamine and introduced arylsulfonyl moieties as the electron-withdrawing group on the nitrogen atoms to secure appropriate acidity.[39] The potential of the chiral phosphorodiamidic acid (**27**) as the chiral Brønsted acid catalyst was proven in the direct Mannich reaction of imines (**2**) with acetylacetone (**3**). After screening of the substituents (G′) introduced to the chiral catalyst (**27**) and the *N*-acyl protective group of the imine (**2**), moderate enantioselectivity was observed in the reaction of *N*-benzoyl imine (**2d**) with **3** catalyzed by (*R*)-**27a** having *p*-toluenesulfonyl moieties as the substituents (G′) (Scheme 18). Although the chemical yield and enantiomeric excess are not currently sufficient, phosphorodiamidic acids (**27**) would be potentially useful as enantioselective catalysts because of the tunability of the chiral diamine framework and the substituents (G′) on the nitrogen atoms of the diamine.

8. Conclusion

This article focused on recent advances in the chemistry of chiral Brønsted acid catalysis using BINOL-derived phosphoric acids for enantioselective transformations, especially for carbon–carbon bond forming reactions. Recently, significant progress has been made in the development of chiral Brønsted acid catalysts. In particular, chiral phosphoric acids have been extensively studied and applied to numerous organic transformations, including not only carbon–carbon bond formations[34b,c,e,f,40] but also carbon-hetero atom bond formations[34d,41] as well as reductions[42] and oxidations.[43] The initial chiral phosphoric acid catalysts were developed by introducing a binaphthyl backbone as the chiral source, but other types of chiral frameworks, such as diols, diamines and amino alcohols, originally developed as chiral ligands for metal complexes, could also be applied to the design of new types of chiral phosphoric acid catalysts. Indeed, novel chiral phosphoric acids bearing a variety of chiral frameworks have been reported by several research groups.[34a,44] Further development of such catalysts will broaden the scope of catalysis by chiral phosphoric acids.

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