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Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Carbon–Carbon Bond Forming Reactions

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An inventive approach to the development of chiral Brønsted acid catalysis, to enable catalysts which possess strong acid functionalities, has been accomplished. 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. The desirable features of phosphoric acids as chiral Brønsted acid catalysts are summarized as follows. 1) Phosphoric acids are expected to have relatively strong yet appropriate acidity. 2) The phosphoryl oxygen would function as a Brønsted basic site and hence it is anticipated that it would convey acid/base dual function even to monofunctional phosphoric acid catalysts. 3) An acidic functionality is available even with the introduction of a ring system which effectively restricts the conformational flexibility of the chiral backbone. 4) Substituents can be introduced to the ring system to provide an efficient chiral environment for enantioselective transformations. It is anticipated that an efficient substrate recognition site would be constructed around the activation site due to the acid/base dual function and the steric and electronic influence of the substituents introduced at the ring system. In this context, we developed 1,1′-bi-2-naphthol (BINOL)-derived monophosphoric acids as chiral Brønsted acid catalysts. The chiral phosphoric acids thus developed functioned as efficient enantioselective catalysts for a variety of carbon–carbon bond forming reactions via activation of a series of functionalities, affording enantioenriched products in excellent selectivities. In this article, we review our recent achievements in developing enantioselective reactions using the chiral phosphoric acid catalysts. The contents are arranged according to the type of functionality, including imines, hemiaminal ethers, aldehydes, and electron-rich double bonds, followed by specific reaction types.

1. Introduction

Over the past decade, enantioselective catalysis by a small organic molecule, so-called organocatalysis, has become a rapidly growing area of research as it offers operational simplicity, uses mild reaction conditions, and is environmentally benign.[1] Among the organocatalysts reported to date, research has focused on chiral Brønsted acid catalysis, of which innovative methods have enabled great achievement to afford enantioenriched products using a catalytic amount of a chiral organic molecule bearing an acidic functionality.[2] The first example of chiral Brønsted acid catalysis was reported by Jacobsen and co-workers in an 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 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. Thereafter an excellent work on the enantioselective hetero Diels–Alder reaction was reported by Rawal and co-workers 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] 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.[5] In contrast to these advanced studies, we envisioned an inventive approach to the development of chiral Brønsted acid catalysts, to enable catalysts which possess strongly acidic functionalities. In this context, we developed 1,1′-bi-2-naphthol (BINOL)-derived monophosphoric acids **1** as chiral Brønsted acid catalysts.[6] In this article, we review our recent achievements in developing enantioselective carbon–carbon bond forming reactions using the phosphoric acid catalysts **1** (Figure 1).[7]

2. Design of Chiral Phosphoric Acids as Enantioselective Brønsted Acid Catalysts

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

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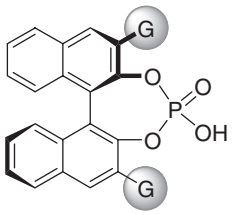


(*R*)-**1**

G G

a: H
b: C_6H_5-
c: 4-PhC_6H_4-
d: 4-β-naphthylphenyl
e: 3,5-dimesitylphenyl
f: α-naphthyl
g: 3,5-diphenylphenyl
h: 9-anthryl
i: (4-*t*-$BuC_6H_4)_3Si$-
j: 2,4,6-*i*-$Pr_3C_6H_2$-
k: 4-*t*-Bu-2,6-*i*-$Pr_2C_6H_2$-
l: 4-$CF_3C_6H_4$-
m: 4-MeC_6H_4-
n: 4-*t*-BuC_6H_4-
o: β-naphthyl
p: 3,5-*t*-$Bu_2C_6H_3$-
q: 2,4,6-$Me_3C_6H_2$-
r: 9-phenanthryl

Figure 1. BINOL-derived monophosphoric acids **1** as chiral Brønsted acid catalysts.

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,[8] to generate unstable, and hence highly reactive, cationic (protonated) intermediates (**Sub**-H^+) (Figure 2a). 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 bonds, are suppressed between the conjugate base ($\mathbf{A}^-$) and the protonated intermediate (**Sub**-H^+). In sharp contrast, to accomplish enantioselective catalysis using a chiral Brønsted acid, interaction between protonated substrate (**Sub**-H^+) and the chiral conjugate base ($\mathbf{A}^{*-}$) is indispensable (Figure 2b). The key to realizing enantioselective catalysis using a chiral Brønsted acid is the hydrogen-bonding interaction. 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.

In order to develop chiral Brønsted acid catalysts with strong acid functionality, we surveyed a range of common organic acids at the beginning of our research. Representative organic acids are depicted in Figure 3. Sulfonic acid is one of the most common acid catalysts (Figure 3a), 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 (Figures 3b and 3c). 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 because of free rotation around the single bond. In addition, introduction of substituents is restricted to the α-position of these acids (Figures 3b and 3c), four atoms away from the proton which functions as the activation site for an electrophilic component. In contrast, in a phosphoric acid, two substituents can be directly introduced at the phosphorous atom (Figure 3d), 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 (Figure 3e).

The desirable features of phosphoric acids as chiral Brønsted acid catalysts are summarized as follows.

1) Phosphoric acids are expected to capture electrophilic components through hydrogen-bonding interactions without

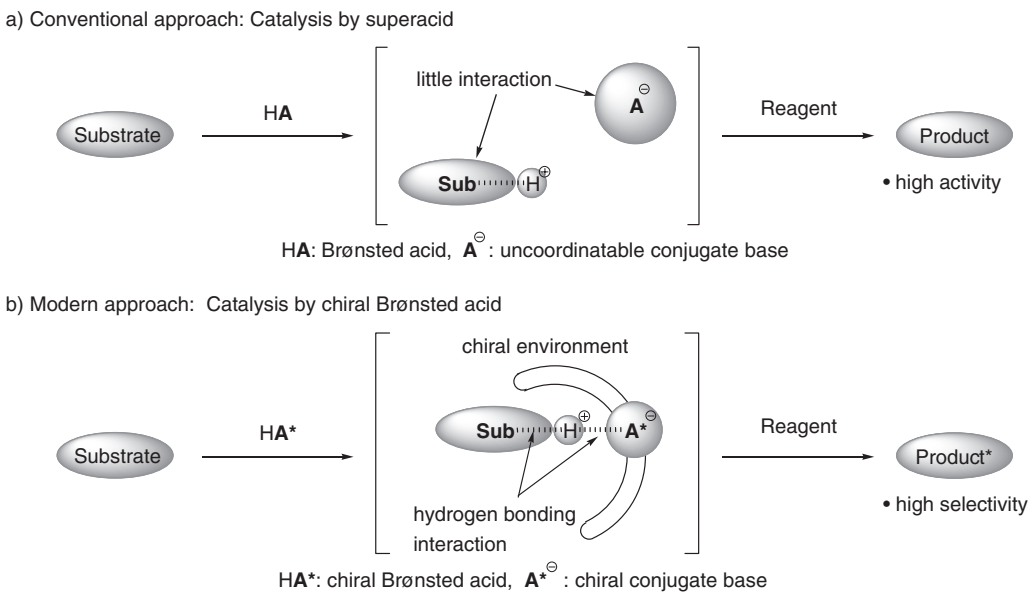


Figure 2. Brønsted acid catalysis in organic transformations.

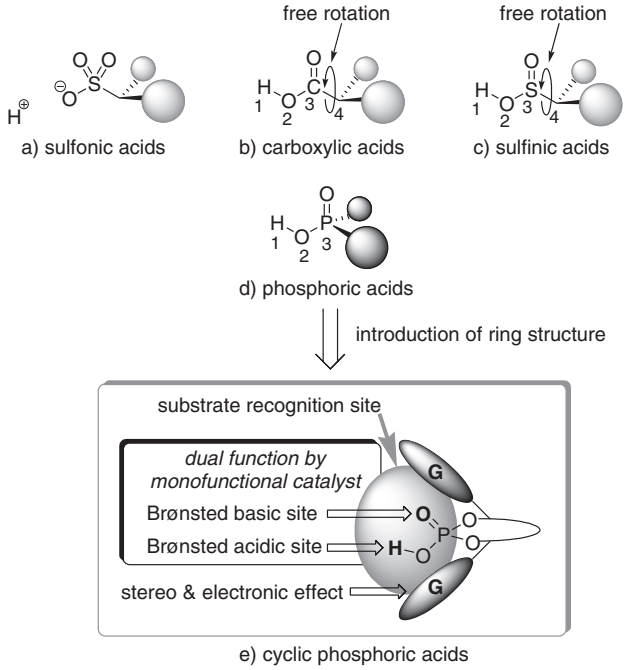


Figure 3. Organic acids to be developed as chiral Brønsted acid catalysts.

forming loose ion pairs due to their relatively strong yet appropriate acidity.[9]

2) The phosphoryl oxygen would function as a Brønsted basic site and hence it is anticipated that it would convey acid/base dual function even to monofunctional phosphoric acid catalysts. This catalyst design is conceptually similar to the mainstream of designing bifunctional organocatalysts reported to date.[1,10] 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) An acidic functionality is available even with the introduction of a ring system. It is likely that this ring system effectively restricts the conformational flexibility of the chiral backbone.

4) Substituents (G in Figure 3e) can be introduced to the ring system to provide a chiral environment for enantioselective transformations.

It is anticipated that an efficient substrate recognition site would be constructed around the activation site, namely the acidic proton of the phosphoric acid catalyst, as a result of the acid/base dual function and the steric and electronic influence of the substituents (G).

As shown in Figure 1, 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 are extensively utilized as chiral ligands for metal catalysts.[11] 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 sterically but also electronically adjustable substituents (G) can be utilized to create an appropriate chiral environment for enantioselective transformations. In 2004, Akiyama[12] and our research group[13] independently demonstrated highly enantioselective transformations using BINOL-derived phosphoric acids **1** as chiral Brønsted acid catalysts.[2a,6,7] Among chiral Brønsted acids reported hitherto, chiral phosphoric acids derived from axially chiral biaryls represent an attractive and widely applicable class of enantioselective organocatalysts for a variety of organic transformations.[2,14]

3. Activation of Imines

Akiyama and co-workers reported enantioselective catalysis in a Mukaiyama type Mannich reaction that used BINOL-derived phosphoric acids **1** as chiral Brønsted acid catalysts.[12] In the same year, our research group independently demonstrated a highly enantioselective direct Mannich reaction using similar phosphoric acids.[13] Since these enantioselective Mannich reactions were successfully developed, chiral phosphoric acids have been widely utilized as efficient enantioselective organocatalysts for numerous organic transformations. Among asymmetric reactions investigated, the electrophilic activation of imines by chiral phosphoric acid has proven to be an attractive and efficient method for constructing nitrogen-substituted stereogenic centers in optically active forms.[15]

3.1 Mannich Reaction. Enantioselective Mannich reactions are widely utilized for the construction of optically active β-amino carbonyl compounds[16] that serve as versatile intermediates for the synthesis of biologically active compounds and drug candidates. Highly enantioselective Mannich reactions have been established using other types of organocatalysts, such as proline and its derivatives, chiral secondary amines.[17]

In 2004, we developed the chiral phosphoric acid **1**-catalyzed enantioselective direct Mannich reaction of imine **2** with acetylacetone.[13] In the present direct Mannich reaction, it is anticipated that the dual function of the phosphoric acid moiety would smoothly accelerate the reaction (Figure 4). The enol proton of the acetylacetone tautomer and the O–H proton of **1** function as acidic sites, while the nitrogen atom of **2** and the phosphoryl oxygen function as basic sites. In the direct Mannich reaction of **2** with acetylacetone, it is considered that **1** would enable the formation of a transient structure through a hydrogen-bonding network that connects the acidic and basic sites with each other (Figure 4b). Thus, phosphoric acid catalyst **1** electrophilically activates **2** through the acidic proton, and Brønsted basic phosphoryl oxygen interacts with the O–H proton of the enol form of acetylacetone. Subsequent bond recombination results in the formation of the Mannich product and the regeneration of catalyst **1** (Figures 4b and 4c). From this mechanistic assumption, it seems 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**.

Chiral phosphoric acid **1a** exhibited extremely high catalytic activity for the direct Mannich reaction of *N*-Boc-protected imine **2a** with acetylacetone (Scheme 1). The resulting β-

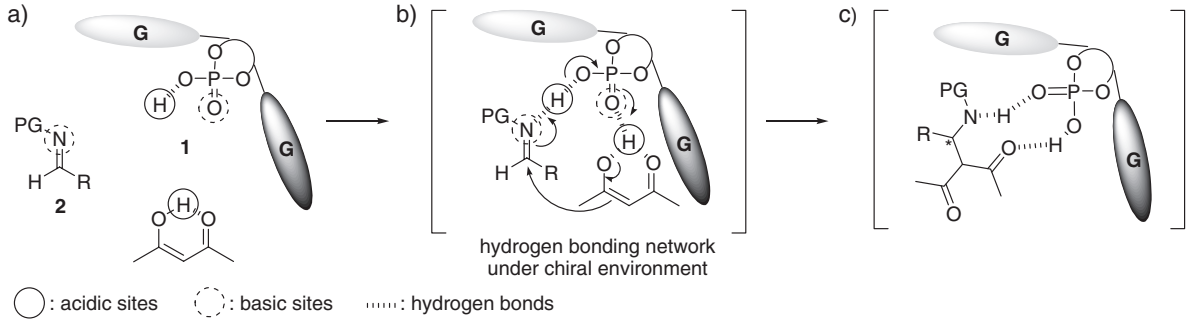
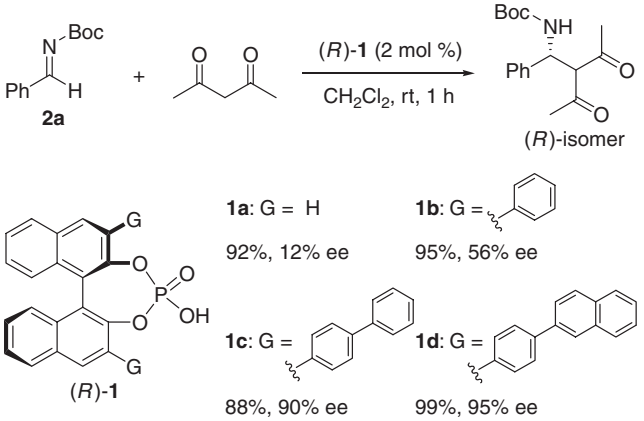
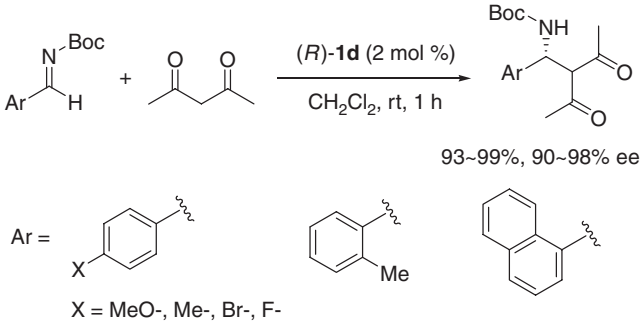


Figure 4. Assumed mechanism of enantioselective direct Mannich reaction catalyzed by chiral phosphoric acid.



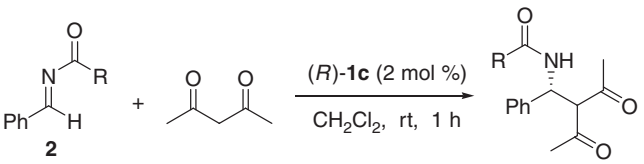
Scheme 1. Enantioselective direct Mannich reaction catalyzed by **1**.



Scheme 3. Enantioselective direct Mannich reaction of various imines.

amino ketone was obtained in an optically active form (12% ee). The beneficial effects of the diaryl substituents at the 3,3′-positions of the binaphthyl backbone are noteworthy in regard to the enantioselectivity. For instance, performing the direct Mannich reaction using 3,3′-phenyl-substituted phosphoric acid **1b** furnished the corresponding product 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 the product in nearly quantitative yield.

The protective group on the imine is also crucial to achieving a high enantioselectivity (Scheme 2).[18] When the steric demand of the protective group was decreased, the enantioselectivities were significantly 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



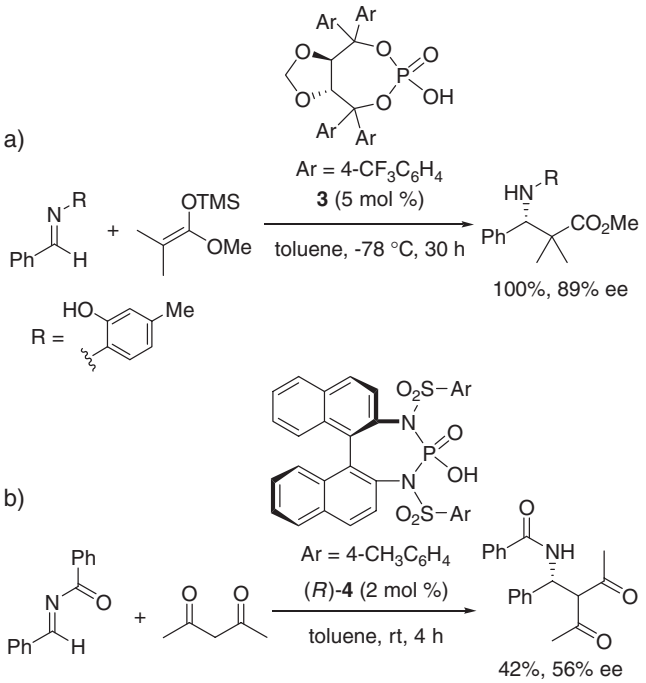
Scheme 2. Effect of *N*-protective group on enantioselectivities.

with imine **2c**, which has the less sterically demanding methoxycarbonyl moiety as the protective group.

The present catalytic reaction was applicable to *ortho*-, *meta*-, and *para*-substituted *N*-Boc-protected arylimines and the corresponding products were obtained in excellent chemical yields with high enantioselectivities (Scheme 3). The reaction proceeded smoothly without any detrimental effects even on a gram scale and the catalyst load could be decreased to 1 mol % while maintaining high yield and enantioselectivity. In addition, more than 80% of catalyst **1d** could be recovered.

The creation of a new structural motif of chiral phosphoric acids is a challenging task to broaden the scope of chiral Brønsted acid catalysis. Akiyama et al. demonstrated that chiral phosphoric acid **3** derived from TADDOL functioned as an efficient enantioselective catalyst for the Mukaiyama type Mannich reaction of imines with ketene silyl acetals (Scheme 4a).[19] We also developed phosphorodiamidic acid **4** for use as an efficient Brønsted acid catalyst in the direct Mannich reaction of *N*-acylimines with 1,3-dicarbonyl compounds (Scheme 4b).[20] Although the asymmetric induction of the Mannich reaction is still moderate, phosphorodiamidic acid **4** is a viable structural motif of chiral Brønsted acid catalysts. Further modification of the chiral diamine backbone or the substituents on the nitrogen atoms of the catalyst could lead to its becoming an efficient enantioselective catalyst.

3.2 Friedel–Crafts Reaction. The Friedel–Crafts (F–C) reaction via activation of electrophiles functionalized by a nitrogen atom, such as imines, is undoubtedly the most practical and atom-economical approach to introduce a nitrogen-substituted side chain to aromatic compounds. The enantioselective version of the F–C reaction of nitrogen-substituted substrates, including imines, with electron-rich

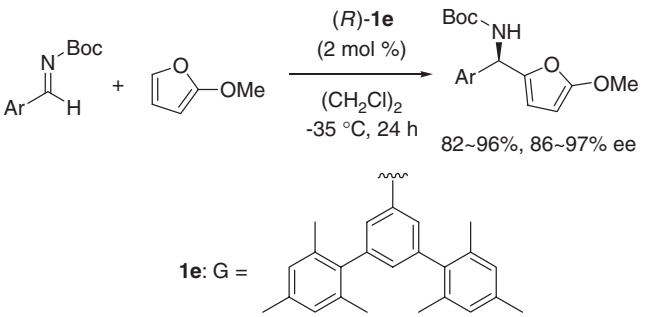


Scheme 4. Novel structural motifs of chiral phosphoric acid catalysts.

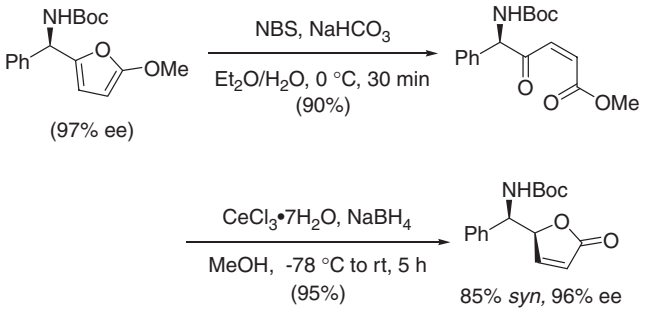
aromatic compounds enables efficient access to enantioenriched aryl methanamine derivatives.[21] Several excellent approaches to highly enantioselective F–C reactions have been established using chiral phosphoric acid catalysts.[22–30]

We successfully demonstrated for the first time an enantioselective 1,2-aza-F–C reaction of 2-methoxyfuran with *N*-Boc aldimines using a catalytic amount of chiral phosphoric acid (Scheme 5).[22] In the presence of 2 mol % **1e** with sterically hindered 3,5-dimesitylphenyl substituents, the corresponding F–C products were obtained in excellent enantioselectivities irrespective of the electronic properties of the aromatic imines employed. Most notable was that the reaction could be performed in the presence of as little as 0.5 mol % **1e** without any detrimental effects even on a gram scale (Ar = Ph: 95%, 97% ee).

The synthetic utility of the present transformation is highlighted by the derivatization of the furyl ring to form γ-butenolide (Scheme 6). As the γ-butenolide architecture is a common building block in the synthesis of various natural products, the F–C reaction product represents a new entry to the



Scheme 5. Enantioselective 1,2-aza-Friedel–Crafts reaction of *N*-Boc imines with 2-methoxyfuran.

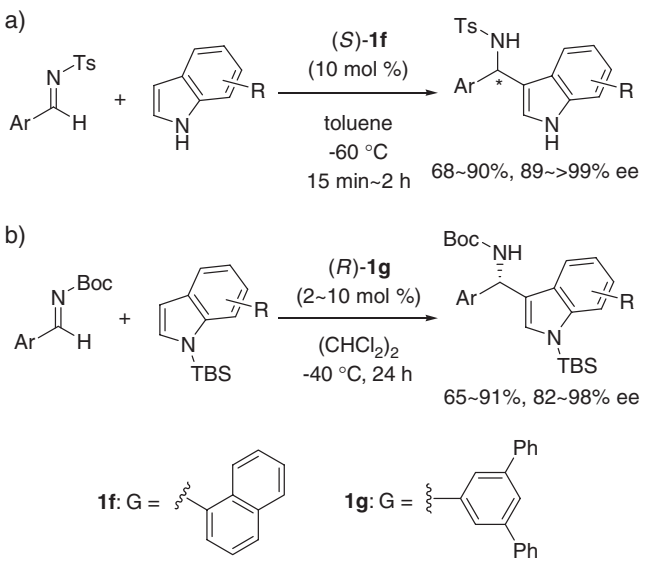


Scheme 6. Synthetic utility of 2-furylamine products.

synthetic precursors of nitrogen-containing molecules. The aza-Achmatowicz reaction,[31] followed by reductive cyclization of the 1,4-dicarbonyl intermediate under Luche conditions, produced the γ-butenolide in good yield.

Further application of the chiral phosphoric acid catalyzed 1,2-aza-F–C reaction was investigated by several research groups and the developed methods afforded a diverse array of optically active arylmethaneamine derivatives with high enantioselectivities. In particular, the 1,2-aza-F–C reaction of indoles was intensively investigated because the enantioenriched products, namely, (3-indolylmethyl)amine derivatives, are widely known as valuable structures among pharmacophores and are present in thousands of natural products and many medicinal agents possessing versatile therapeutic effects.[32] You and co-workers (Scheme 7a),[23] Antilla and co-workers,[24] and our group (Scheme 7b)[25] independently developed the highly enantioselective F–C reaction of indoles with aromatic imines. The reaction of α-imino esters as an electrophilic component was also reported by You and co-workers[26] and Hiemstra and co-workers.[27] The enantioselective F–C reactions catalyzed by chiral phosphoric acids were further applied to such electron-rich aromatic compounds as pyrroles[28,29] and 4,7-dihydroindoles.[30]

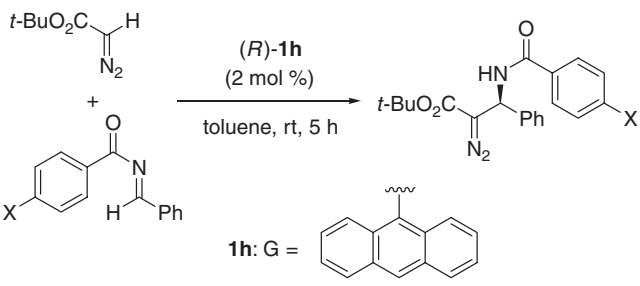
3.3 α-Alkylation Reaction of Diazoacetate. α-Diazocarbonyl compounds have been extensively studied and their



Scheme 7. Enantioselective 1,2-aza-Friedel–Crafts reaction of indoles with various imines.

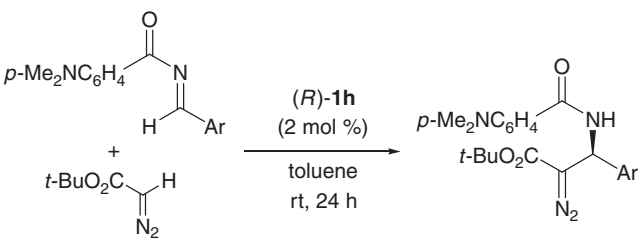
most important application is for the generation of metal carbene species. α-Diazocarbonyl compounds have an electronically unique sp^2-carbon to which the diazo group is attached. Thus, these compounds have a partially negative charge and function as nucleophiles. In the reactions of imines, α-diazocarbonyl compounds are commonly used in aziridine formation reactions (aza-Darzens reaction) under Lewis[33] and Brønsted[34] acidic conditions. Meanwhile, we reported enantioselective direct substitution at the α-position of diazoacetate using a chiral phosphoric acid catalyst.[35] Phosphoric acid catalyst **1h** efficiently promoted the substitution reaction of α-diazoacetates with *N*-acylimines to give Mannich type products, β-amino esters bearing a diazo substituent at the α-position, in optically active forms (Scheme 8). Interestingly, the electronic properties of the acyl protective group of the imine nitrogen profoundly affected the enantioselectivity. The *para*-substituents of the *N*-acyl aromatic moiety had a marked effect on the enantioselectivity; the introduction of an electron-donating dimethylamino moiety gave the best results.

A series of aromatic imines are applicable to the present substitution reactions (Scheme 9). *Para*-substituted aromatics showed excellent enantioselectivities irrespective of their



X =	Br	H	Me	MeO	Me_2N
	68%	59%	72%	73%	81%
	86% ee	90% ee	91% ee	93% ee	97% ee (for 24 h)

Scheme 8. Enantioselective α-substitution reaction of diazoacetate with imine.



62~74%	84~89%	75%
97% ee	91~93% ee	95% ee

Scheme 9. α-Substitution reaction of diazoacetate with various imines.

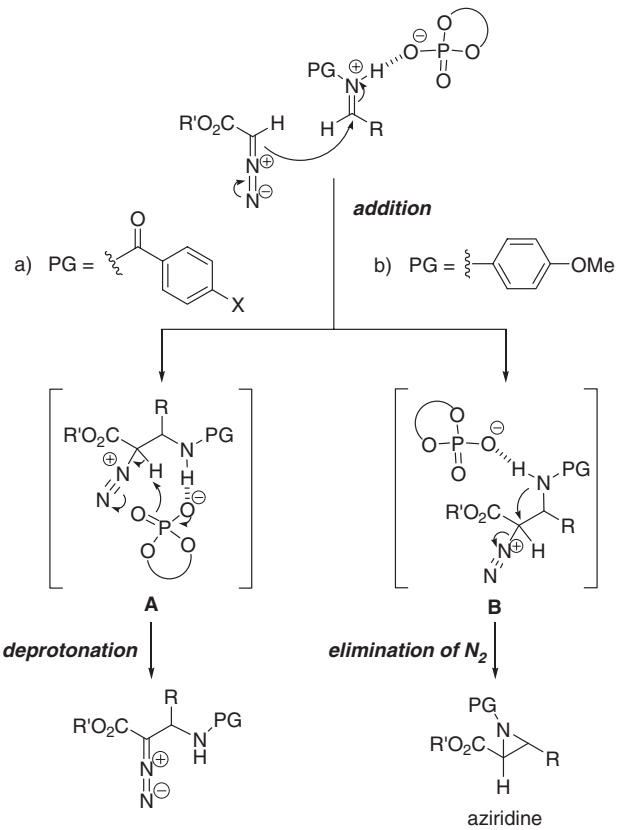
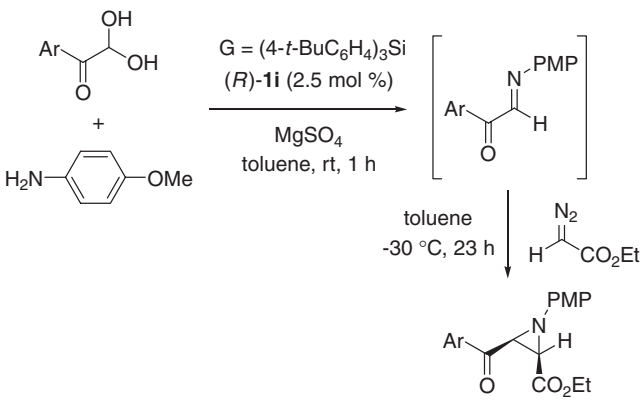


Figure 5. Mechanistic proposal for diazoacetate reactions.

electronic properties. *Ortho*- and *meta*-substitutions as well as fused-ring systems were also applicable. Thus obtained β-amino-α-diazoester products could be transformed into common synthetic intermediates, i.e., β-amino acid derivatives, via simple reduction or oxidation of the diazo moiety.

The phosphoric acid is expected to promote the substitution reaction as a result of its dual function (Figure 5a). Intracomplex deprotonation from **A** by the basic phosphoryl oxygen would allow the direct substitution of diazoacetate, giving a Mannich type product without the formation of aziridine products.[36]



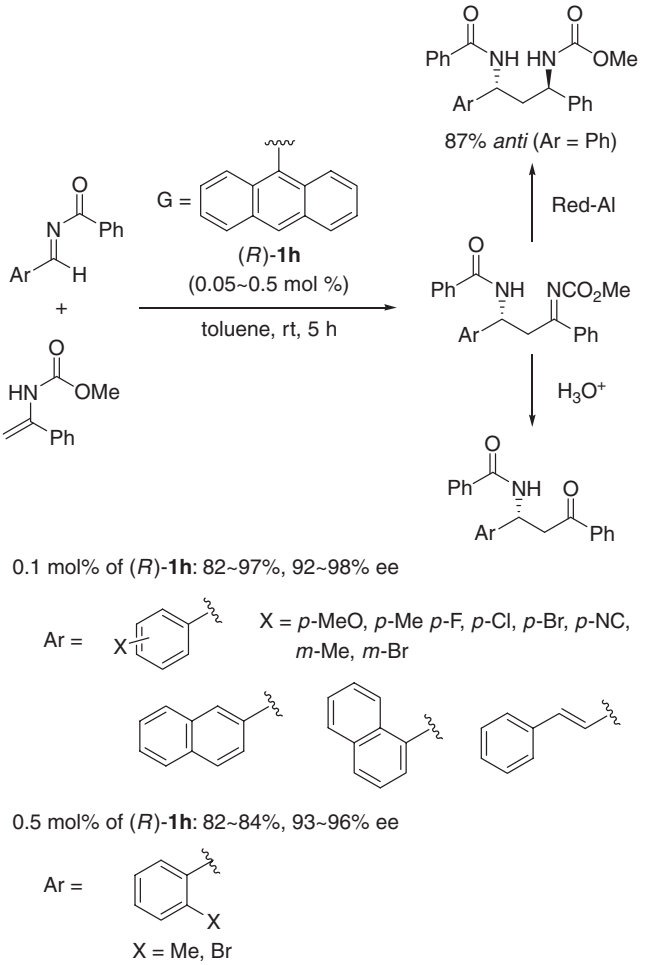
Scheme 10. Enantioselective aza-Darzens reaction.

Meanwhile, Akiyama et al. reported the aziridine formation reaction (aza-Darzens reaction) using PMP (*p*-methoxyphenyl)-protected imines and α-diazoacetate (Scheme 10).[37] Chiral phosphoric acid catalyst **1i** gave the corresponding aziridine products with high enantioselectivities. The PMP protective group would preserve the nucleophilicity of the nitrogen atom and hence the intramolecular substitution by the nitrogen atom would proceed exclusively via intermediate **B** (Figure 5b). This contrasts the reaction of *N*-benzoylimines where Mannich type products were obtained in high yields. The electron-withdrawing property of the *N*-benzoyl protective group significantly decreased the electron density of the nitrogen atom, effectively suppressing nucleophilic substitution by the nitrogen atom.

3.4 Aza-Ene Type Reaction. Kobayashi and co-workers pioneered the use of enamides or enecarbamates as nucleophiles in enantioselective reactions with either glyoxylates or glyoxylate-derived imines catalyzed by chiral copper complexes.[38] The reaction using enamides or enecarbamates as nucleophilic components, namely, the aza-ene reaction, with imines provides β-amino imines that can be readily transformed into 1,3-diamine derivatives via nucleophilic addition to the imine moiety of the corresponding products.

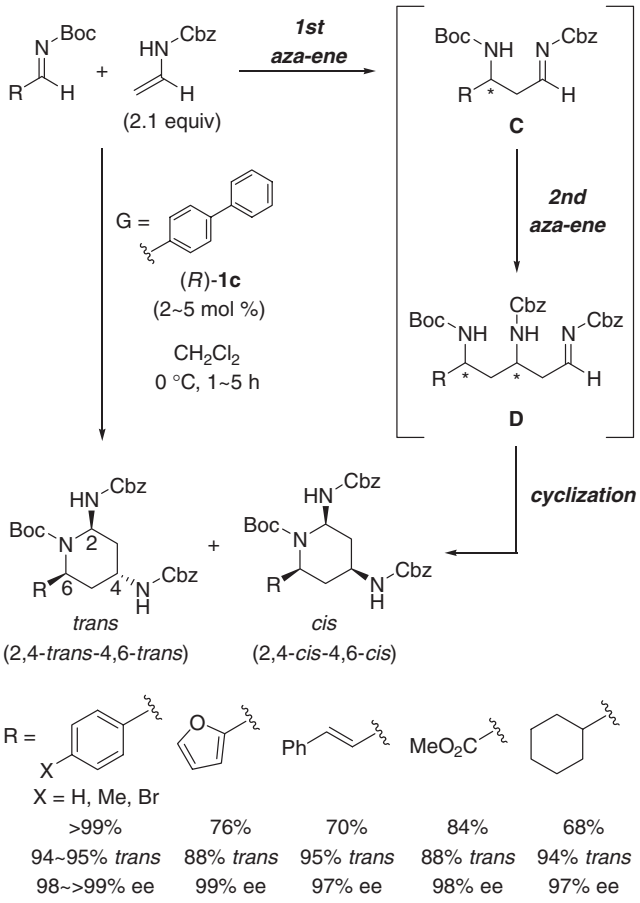
3.4.1 Low Loading of Chiral Phosphoric Acid Catalyst: Organocatalysis has been proven to be beneficial in many respects. However, one critical drawback inherent to the methodologies reported to date is the inadequate catalytic efficiency. Most organocatalytic reactions are performed at catalyst loads of 10 mol % or more to achieve sufficient chemical yields and to avoid loss of enantioselectivity. To ensure high efficiency, one of the greatest challenges in practical organocatalysis is to decrease the catalyst load.[3c,39] We demonstrated a highly efficient organocatalytic reaction that uses phosphoric acid with a significantly low catalyst load in the aza-ene type reaction (Scheme 11).[40] The reaction of aromatic imines with enecarbamates can be accomplished in the presence of 0.1 mol % phosphoric acid catalyst **1h**. *Para*- and *meta*-substitution to aromatic imines, or substitution to fused aromatic and α,β-unsaturated ones, resulted in excellent chemical yields and enantioselectivities, irrespective of the electronic properties of the substituents. Although *ortho*-substitution reduced the catalytic efficiency, giving products in moderate chemical yields, the yields were improved in these cases by increasing the catalyst load to 0.5 mol %. It is noteworthy that the reaction can be performed without considerable loss of enantioselectivity even with a decrease in the catalyst load to as low as 0.05 mol %. The synthetic applicability of the present highly efficient organocatalysis was demonstrated by the reduction of the imine moiety by Red-Al, giving *anti*-1,3-diamine derivatives predominantly.

3.4.2 Cascade Transformations Based on Tandem Aza-Ene Type Reaction: The development of efficient methods to access complex molecules with multiple stereogenic centers continues to be a formidable challenge in both academe and industry. One approach is the use of catalytic enantioselective cascade reactions[41] that have emerged as powerful tools to rapidly increase molecular complexity from simple and readily available starting materials, thus producing enantioenriched compounds in a single operation.



Scheme 11. Enantioselective aza-ene type reaction under low catalyst load.

We successfully applied the aza-ene type reaction to the cascade transformation by taking advantage of the formation of imine products (Scheme 12).[42] We employed mono-substituted enecarbamates,[38e] instead of the di-substituted versions, and as a result, piperidine derivatives with multiple stereogenic centers were obtained in high stereoselectivities. The acid-catalyzed aza-ene type reaction of the initial aldimines with mono-substituted enecarbamates afforded aza-ene type products of *N*-acyl aldimines (=*N*-acylalkylideneamines) **C** as reactive intermediates and **C** underwent further aza-ene type reaction leading to the subsequent generation of aldimines **D**. The intramolecular cyclization of intermediate **D** was conducted to terminate the tandem aza-ene type reaction sequence. It is noteworthy that one stereoisomer was formed exclusively from among the eight possible stereoisomers consisting of four pairs of enantiomers under the influence of phosphoric acid catalyst **1c**. Not only aromatic but also aliphatic aldimines could be used in the present cascade reaction. Moreover, the glyoxylate-derived aldimine could be transformed into the highly functionalized piperidine derivative with excellent enantioselectivity. This cascade methodology allows rapid access to piperidine derivatives with multiple stereogenic centers, as key structural elements of numerous natural products.



Scheme 12. One-pot entry to piperidine derivatives via tandem aza-ene type reaction/cyclization cascade.

4. Activation of Hemiaminal Ethers

Although a number of excellent approaches to the enantioselective reactions of imines catalyzed by either chiral metal complexes or organic molecules have been reported to date, most imines employed are derived from aromatic aldehydes or glyoxylate. Aliphatic imines possessing hydrogen atoms at the α-position have rarely been explored due to their lability in isomerization to the corresponding enamine form. The development of the reaction using aliphatic imines is a challenging issue to be addressed. To overcome this intrinsic problem, in situ generation of aliphatic imines has been investigated.[43] We recently developed an efficient method for in situ generation of aliphatic imines from hemiaminal ethers (=(1-alkoxyalkyl)-amines) **5** using chiral phosphoric acid catalysts (Figure 6). This protocol has the distinct advantage of in situ generation of unstable aliphatic imines from storable, and hence easily handled, hemiaminal ethers **5**.

4.1 Two-Carbon Homologation. The homologation of a carbon unit is an important and fundamental methodology in the construction of carbon frameworks in synthetic organic chemistry. Much attention has been devoted to the development of two-carbon homologation using acetaldehyde anion equivalents, as these can be directly utilized in further transformations. From a synthetic viewpoint, mono-substituted enecarbamates are attractive as acetaldehyde anion equivalents for the two-carbon homologation reaction because they are readily available and can provide aldimine products.[38e,44] These aldimines can be directly transformed into 1,3-diamine derivatives, when two-carbon homologation reactions are conducted with imines as the substrate.

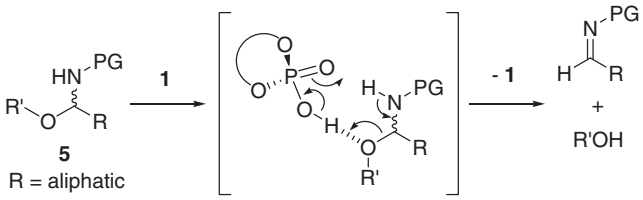
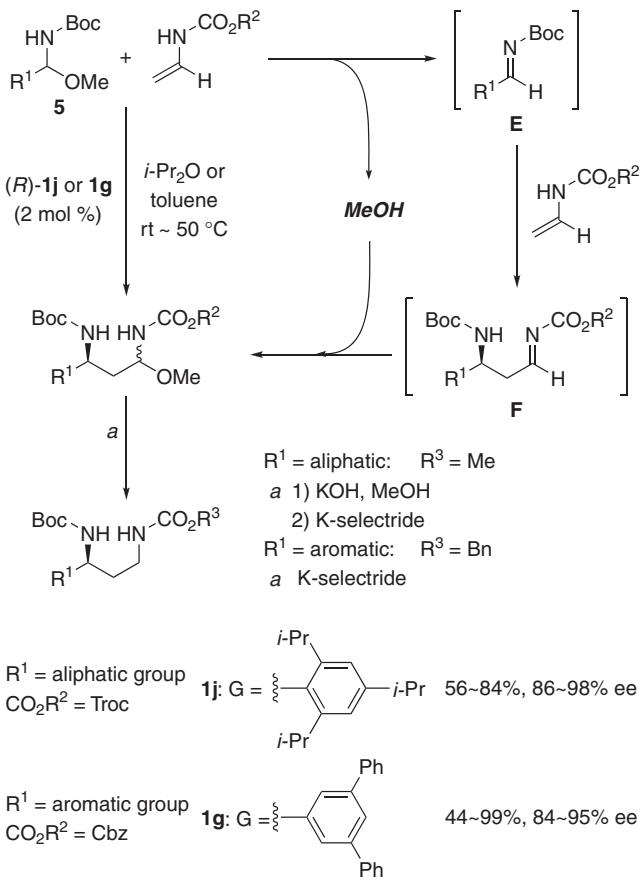
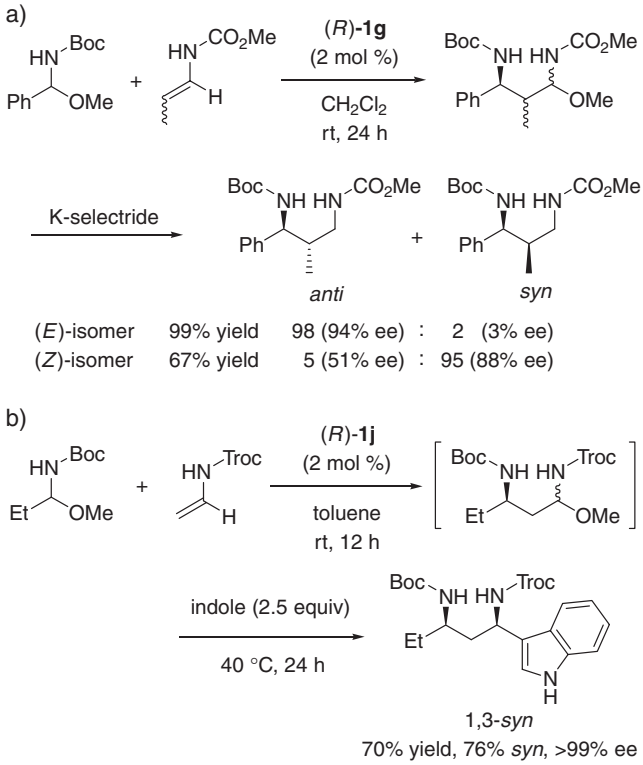


Figure 6. In situ generation of aliphatic imines from hemiaminal ethers **5**.

Although the high reactivity of aldimine products (**F**) hindered the development of the two-carbon homologation reaction due to overreaction, we demonstrated two-carbon homologation using enecarbamates and hemiaminal ethers **5** instead of imines (**E**) as the substrate (Scheme 13).[45] In the acid-catalyzed reaction of hemiaminal methyl ethers, intermediary and reactive aldimine (**F**) was entrapped by methanol that was generated during the course of imine (**E**) formation. A series of aliphatic hemiaminal ethers were employable for the present homologation reaction in the presence of phosphoric acid catalyst **1j**, giving hemiaminal products with high enantioselectivities, although in this case, the more electron-



Scheme 13. Two-carbon homologation of aliphatic and aromatic hemiaminal ethers by enecarbamate.

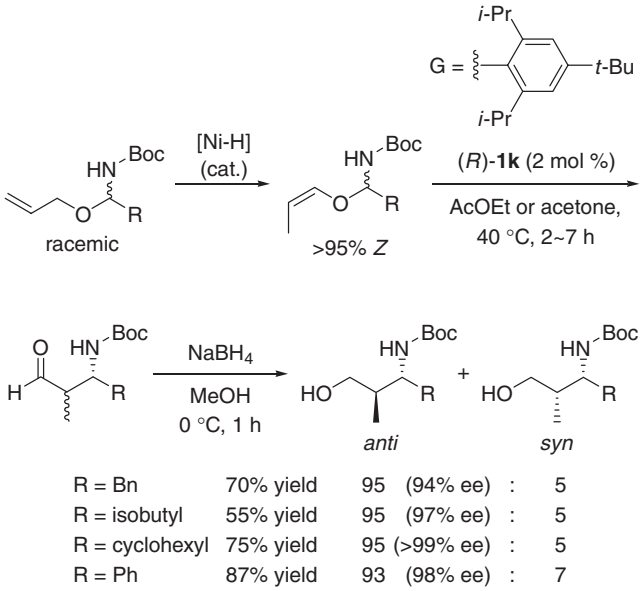


Scheme 14. Application of two-carbon homologation reaction.

withdrawing trichloroethoxycarbonyl (Troc) group was required for the protection of enecarbamate at the nitrogen atom to suppress the formation of by-products. Aromatic hemiaminal ethers were also applicable to the present homologation in the presence of phosphoric acid catalyst **1g**. The reactivity of the aromatic hemiaminal ethers was considerably dependent on the electronic properties of the substituents on the aromatic ring.

The present homologation reaction can be applied to a substituted enecarbamate (Scheme 14a). Either the *anti*- or *syn*-product could be obtained in a highly diastereoselective manner from the respective geometric isomers of the enecarbamates, and each of the major diastereomers exhibited good to high enantioselectivity. The synthetic utility of the present homologation reaction is highlighted by the sequential transformation of homologation/F–C reaction in one pot (Scheme 14b). Catalyst **1j** also accelerated the F–C reaction of hemiaminal ether with indole to afford the desired 1,3-diamine derivatives in good yields and nearly optically pure forms, albeit moderate *syn*-diastereoselectivities. The method enables facile access to highly enantioenriched 1,3-diamine derivatives as pharmaceutically and biologically intriguing molecules.

4.2 Aza-Petasis–Ferrier Rearrangement. Organocatalysis in the direct Mannich reactions of aldehydes with aldimines using chiral secondary amine catalysts has emerged as a powerful tool to provide β-amino aldehydes with high diastereo- and enantioselectivities.[17,43i,46] However, one critical drawback inherent to the methodologies reported to date is that aromatic or glyoxylate-derived aldimines are employed as adaptive substrates in most cases. The enantioselective direct Mannich reaction of aliphatic aldimines has largely been unexploited.[46c] We developed an alternative strategy to furnish optically active β-amino aldehydes having an aliphatic substituent (R) at the β-position by combining two catalytic reactions (Scheme 15).[47] The sequence involves initial metal-catalyzed (*Z*)-selective isomerization of a double bond, followed by chiral phosphoric acid catalyzed aza-Petasis–Ferrier rearrangement,[48] using readily available hemiaminal allyl ethers as the substrate. The aza-Petasis–Ferrier rearrangement of hemiaminal vinyl ethers proceeded via C–O bond cleavage of the ether moiety by acid catalyst **1k**, generating a reactive iminium intermediate and an enol form of the aldehyde (Figure 7). Subsequent recombination with C–C bond formation resulted in rearranged products, thus providing β-amino aldehydes with not only aliphatic but also aromatic substituents at the β-position in high *anti*- and enantioselectivities.



Scheme 15. Double bond isomerization/aza-Petasis–Ferrier rearrangement sequence for preparing β-amino aldehydes.

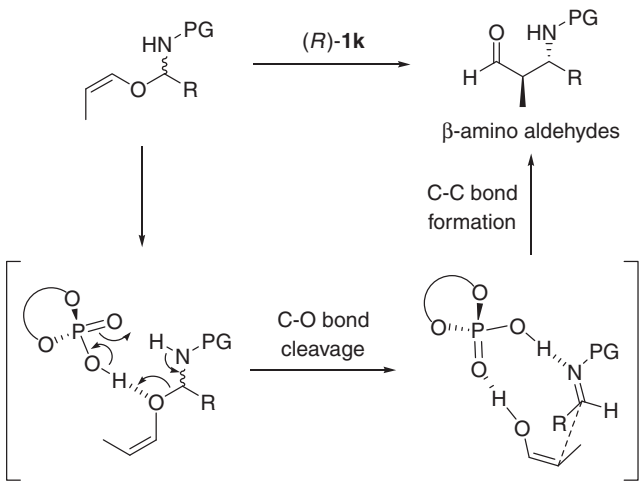


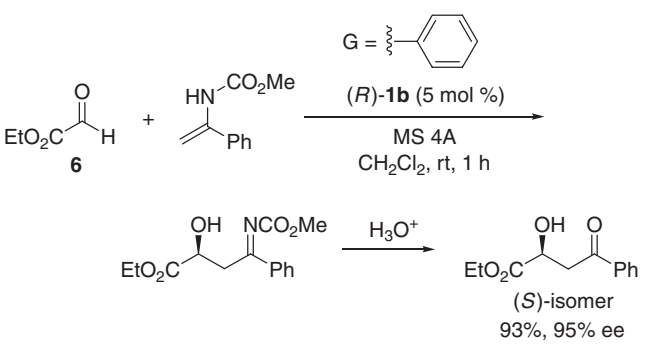
Figure 7. Aza-Petasis–Ferrier rearrangement catalyzed by chiral phosphoric acid **1k**.

5. 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.[49] 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.[50,51] 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.

5.1 Aza-Ene Type Reaction of Aldehydes. Recently, we successfully demonstrated the first example of enantioselective activation of aldehydes using a chiral phosphoric acid catalyst,[52] in which aza-ene type reaction of glyoxylate **6** as a reactive aldehyde with enecarbamate afforded the corresponding products with excellent enantioselectivity (Scheme 16).[38c–38e] The catalyst **1b** efficiently accelerated the aza-ene type reaction of glyoxylate **6** in the presence of molecular sieves (MS) 4A, which were employed as scavengers of acidic impurities.[53] After hydrolysis of the corresponding product to β-hydroxy ketone, 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 achieve 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 Figure 8, there was a marked relationship between the substituent pattern on the phenyl ring and the catalytic performance in terms of both activity and enantioselectivity.



Scheme 16. Aza-ene type reaction of glyoxylate **6** with enecarbamate catalyzed by (*R*)-**1b**.

Excellent performance was maintained when the substituents were introduced to the *para*-position of the phenyl ring, irrespective of their steric and electronic properties (Figure 8a). 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 (Figure 8b), then the catalytic activity and enantioselectivity was compromised.

These substituent effects are well rationalized by complexation modes of glyoxylate and the phosphoric acids **1** (Figure 9). As illustrated in Figure 9a, the key feature of the complexation modes is the double hydrogen bond.[54] The additional hydrogen bond that exists between the formyl hydrogen atom and the phosphoryl oxygen atom forces a coplanar orientation of the formyl group and the phosphoric acid subunit.[55] The 3D structures optimized by DFT computational analysis of methyl glyoxylate (**6′**) and the phosphoric acids **1b** and **1q** are shown in Figures 9b and 9c. In the 3D-structure of the double hydrogen-bonded pairs of **1b** with **6′** (Figure 9b), 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 Figure 9b), 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 (Figure 8a). In contrast, the mesityl rings of (*R*)-**1q** 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 (Figure 9c). 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 **1q**. Similar conformational restrictions would occur in the other catalysts having bulky substituents (G) (Figure 8b).

The aza-ene type reaction of glyoxylate is applicable to a series of substituted enecarbamates, which demonstrate the stereochemical issue of enantio- and diastereoselection (Table 1). Among the catalysts **1** examined (Figure 8), **1n** exhibited excellent performance in terms of both catalytic activity and enantioselectivity (Entry 1) and hence was employed as a promising catalyst for subsequent reactions.

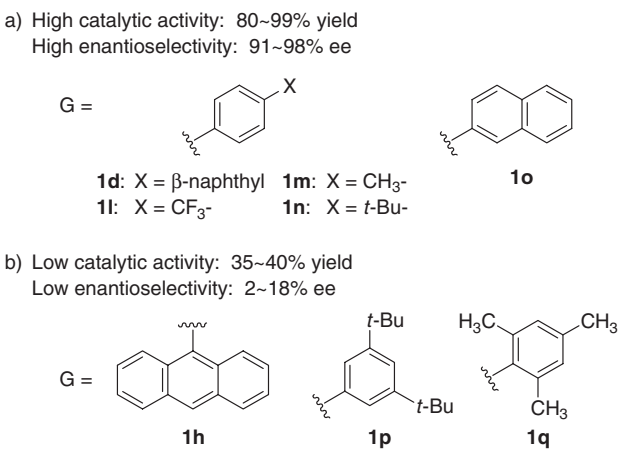


Figure 8. Aza-ene type reaction of glyoxylate **6** with enecarbamate catalyzed by a series of (*R*)-**1**.

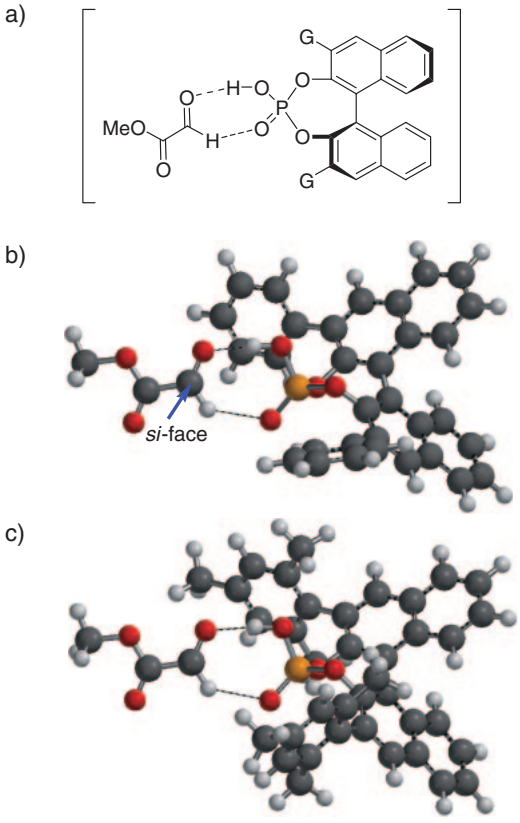
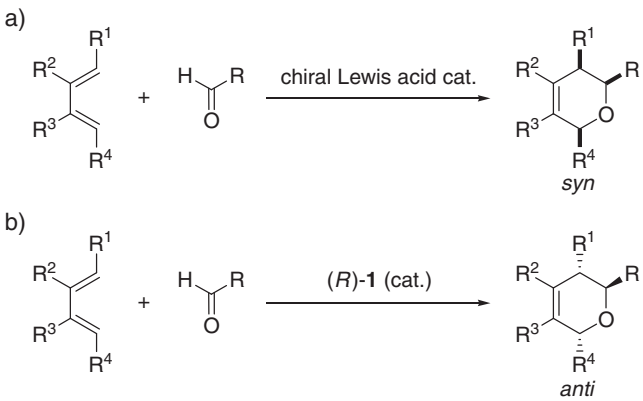


Figure 9. Structure of double hydrogen-bonded complexes formed between (*R*)-**1** and **6′**. a) Illustration of double hydrogen-bonding model; b) Three-dimensional structure of (*R*)-**1b**/**6′**; c) Three-dimensional structure of (*R*)-**1q**/**6′**. P tan, O red, C gray, H white.

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). The exclusive formation of *anti*-products from the (*E*)-isomers could be attributed to the well-defined *exo*-transition state.[38c]

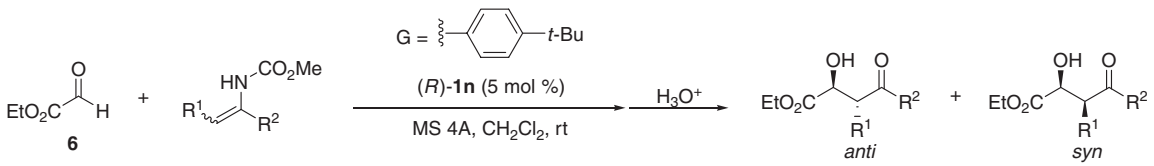
5.2 Hetero Diels–Alder Reaction. Hetero Diels–Alder (D–A) reactions of dienes with aldehydes have been an efficient entry to provide dihydropyran derivatives.[56] The development of catalytic enantio- and diastereoselective variants is an area of considerable importance.[57] Extensive studies have been previously made by the use of chiral Lewis acid catalysts to control high levels of stereoselectivity (Scheme 17a).[58] It is noteworthy that vicinal substituents of the dihydropyran were controlled exclusively in *syn* selective manner, where the diene approaches the aldehyde with an *endo*-orientation presumably due to secondary π-orbital interactions and more importantly to avoid the steric repulsion between the incoming diene and the sterically demanding Lewis acid catalyst.[59] In contrast, alternative *exo*-oriented enantioselective processes, affording *anti*-isomers, have yet to be fully established.[60] We recently developed unprecedented *anti*- and enantioselective hetero D–A reaction of siloxy- or methoxydienes with glyoxylate using chiral phosphoric acid catalyst **1** (Scheme 17b).[61]

The catalyst **1b** bearing unmodified phenyl groups (G = Ph) also exhibited excellent performance in the hetero D–A reaction of glyoxylate **6** with (2*Z*,4*E*)-3-*t*-butyldimethylsiloxy-2,4-hexadiene, giving the corresponding product in high yield with extremely high stereoselectivity (Scheme 18). It is noteworthy that chiral phosphoric acid **1b** is uniquely efficient in affording



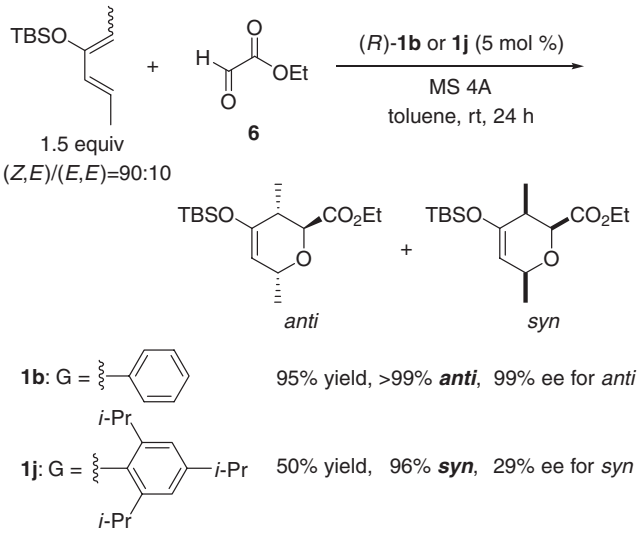
Scheme 17. Hetero Diels–Alder reaction of siloxy- or methoxydiene with glyoxylate.

Table 1. Aza-Ene Type Reaction of Various Enecarbamates with Glyoxylate **6** Catalyzed by (*R*)-**1n**[a)]



Entry	Enecarbamate	Time/h	Yield/%	*anti*:*syn*	ee/% of *anti*	ee/% of *syn*
1	R^1 = H, R^2 = Ph	1	99	—	98[b)]	—
2	R^1 = Me, R^2 = Ph (>99% *E*)	2	73	>99:<1	>99	53
3	R^1 = Me, R^2 = Et (>99% *E*)	2	73	96:4	99	56
4[c)]	R^1 = Et, R^2 = Ph (>99% *E*)	4	75	99:1	99	74
5	R^1, R^2 = –$(CH_2)_4$–	1	89	89:11	99	98
6	R^1 = Me, R^2 = Ph (>99% *Z*)	24	11	72:28	26	88
7	R^1 = Me, R^2 = Et (>99% *Z*)	2	74	50:50	28	69
8[c)]	R^1 = Et, R^2 = Ph (>99% *Z*)	24	67	92:8	8	74

a) 1.7 equiv of freshly distilled **6**. b) Enantiomeric excess of the product (R^1 = H, R^2 = Ph). c) 3.0 equiv of freshly distilled **6**.



Scheme 18. Hetero Diels–Alder reaction of siloxydiene with glyoxylate catalyzed by (*R*)-**1b** and (*R*)-**1j**.

anti-adduct as the single diastereomer in nearly optically pure form, although chiral Lewis acids have typically provided the *syn*-adduct. In sharp contrast, the chiral phosphoric acid **1j** with a bulkier aryl group at the 3,3′-position yielded the *syn*-isomer as the major product. The dramatic reverse in the diastereoselectivity observed between **1b** and **1j** suggests that the substituents at the 3,3′-position of the chiral phosphoric acid function as an important element in controlling stereochemical outcomes in the transition state.

The observed reverse in diastereoselectivities can be rationalized by transition-state models (TSs) of a concerted [4 + 2] cycloaddition (Figure 10).[62] For the **1j**-catalyzed reaction, the *endo*-orientation (**TS1**) of the diene to the aldehyde is preferred over the *exo*-orientation (**TS2**) due to the steric congestion around the activation site of **1j**, where steric repulsion between the diene substituents and the bulky aryl substituents (G = 2,4,6-*i*-$Pr_3C_6H_2$–) of **1j** would be a dominant factor rather than the secondary π-orbital interaction. For the **1b**-catalyzed reaction, the much smaller phenyl group at the 3,3′-position of **1b** allows the diene to occupy an *exo*-position (**TS4**), giving the *anti*-isomer exclusively. The *endo*-orientation (**TS3**) is not favorable because of the steric repulsion between the diene and glyoxylate **6**. This unprecedented *anti*-selective hetero D–A reaction can be ascribed to the fact that the Brønsted acid, thus proton, is the smallest acid catalyst.

The present *anti*- and enantioselective hetero D–A reaction catalyzed by **1b** can be applicable to a series of 2-siloxydienes, giving the corresponding products in good yield with excellent stereoselectivities (Scheme 19a). Although the alkenyl-substituted siloxydiene resulted in a decrease in reactivity, the high stereoselectivity was maintained at an equally high level. Furthermore, methoxydienes were also well tolerated, providing the corresponding *anti*-dihydropyrans predominantly with excellent enantioselectivities (Scheme 19b).

6. Activation of Electron-Rich Double Bonds

Activation of an electron-rich double bond by Brønsted acid is a fundamental method to generate reactive carbocation species. Our catalyst molecules, chiral phosphoric acids **1**, are undoubtedly Brønsted acid possessing relatively strong acidity and hence it can be utilized as a protonating agent of electron-rich double bonds to generate cationic species for further elaboration. The approach opens a new avenue for utilization of chiral phosphoric acids toward advanced enantioselective catalysis.

6.1 Friedel–Crafts Reaction via Activation of Enecarbamates. Enantioselective F–C reactions have been intensively investigated using metal-based chiral catalysts or chiral organocatalysts.[21] These enantioselective catalyses have been accomplished via the activation of electron-deficient multiple

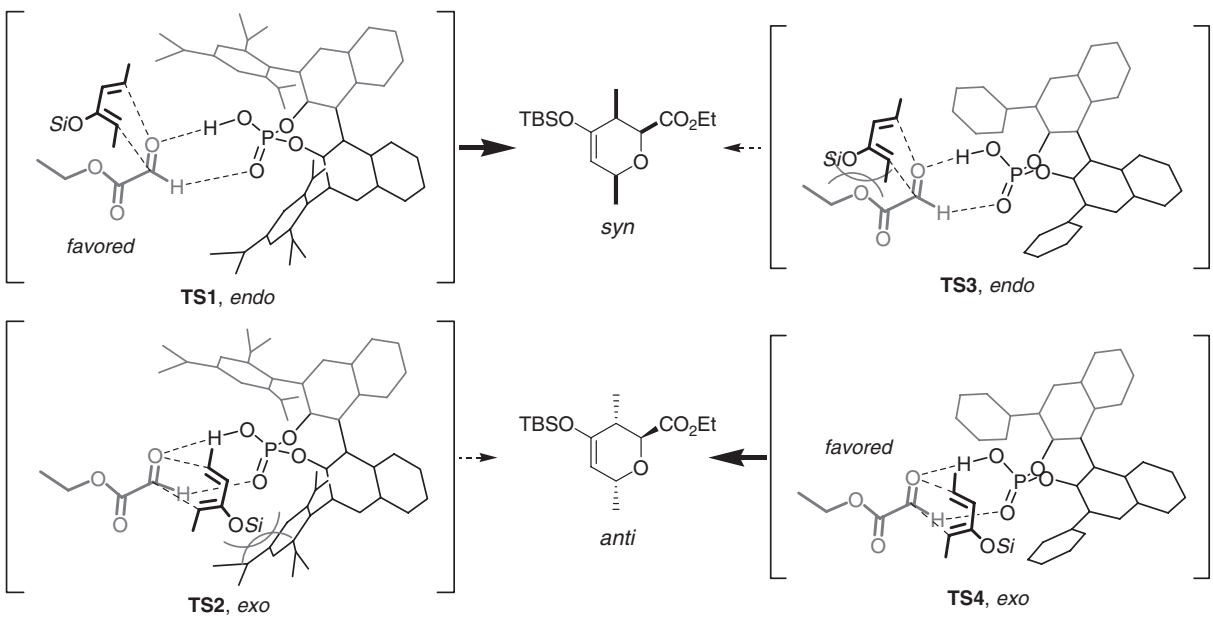
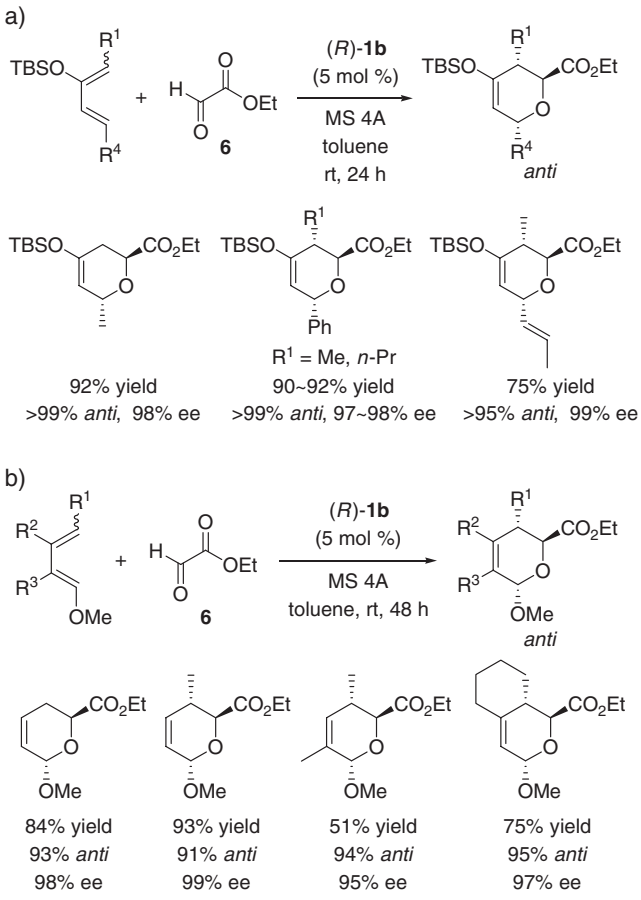


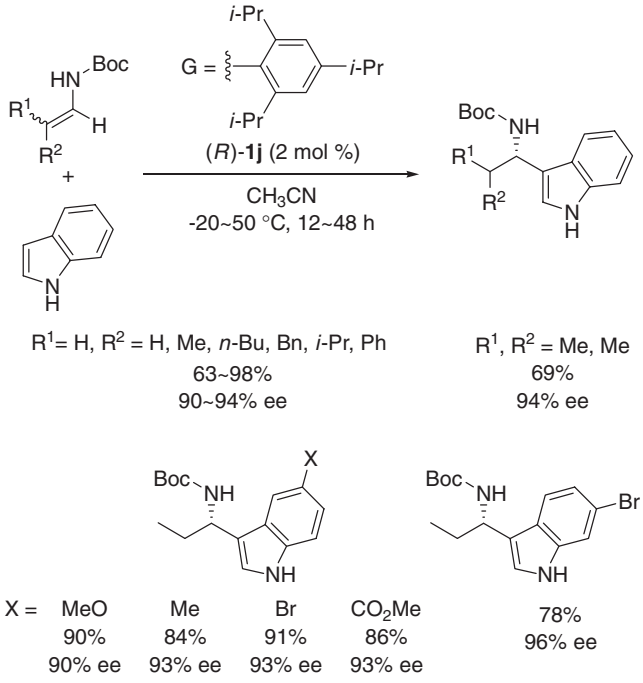
Figure 10. Plausible transition-state models of hetero Diels–Alder reaction catalyzed by chiral phosphoric acids **1**. **1j** (G = 2,4,6-*i*-$Pr_3C_6H_2$–): **TS1** and **TS2**, **1b** (G = Ph): **TS3** and **TS4**.



Scheme 19. Hetero Diels–Alder reaction of siloxy- or methoxydienes with glyoxylate catalyzed by (*R*)-**1b**.

bonds, such as C=O, C=NR, and C=C–X (X: electron-withdrawing group). The acid-catalyzed F–C reactions of arenes with electron-rich alkenes are practical and atom-economical methods for the production of alkylated arenes and have been applied to numerous industrial processes. However, there are no previous reports of the enantioselective catalysis of the F–C reaction initiated by the activation of electron-rich multiple bonds, even using chiral metal catalysts. Recently, we successfully developed a highly enantioselective F–C reaction initiated by the activation of electron-rich multiple bonds using a chiral Brønsted acid catalyst. Chiral phosphoric acid **1j** exhibited excellent performance for the activation, utilizing the catalytic reaction of indoles with enecarbamates as electron-rich alkenes (Scheme 20).[63] Uniformly high enantioselectivities and chemical yields were achieved in the reaction of indole with enecarbamates bearing either a linear or branched alkyl group as well as an aromatic substituent. In addition, the enantioselectivities were maintained at an equally high level for a wide variety of indole derivatives, irrespective of their electronic properties. The present approach provides efficient access to enantioenriched (3-indolylmethyl)amines with a variety of aliphatic substituents and effectively complements previous methods that afforded aromatic group-substituted (3-indolylmethyl)amines via the activation of aromatic imines (Scheme 7).[23–25]

The present F–C reaction proceeded through the in situ



Scheme 20. Friedel–Crafts reaction via activation of enecarbamates by phosphoric acid catalyst.

generation of aliphatic imines that were delivered via the protonation of the enecarbamates by the phosphoric acid catalyst (Figure 11). Phosphoric acid functioned as an efficient catalyst for the dual transformation that involved the in situ generation of imine and the enantioselective carbon–carbon bond formation with indole via the active intermediate (**G**). This protocol provides easy access to generating unstable aliphatic imines in situ from readily available and storable enecarbamates.

Shortly thereafter, Zhou and co-workers independently reported the enantioselective F–C reaction of indoles with α-aryl-substituted enamides catalyzed by chiral phosphoric acid catalyst **1j** (Scheme 21),[64] in which the quaternary stereogenic center bearing the nitrogen atom was constructed in a highly enantioselective manner.

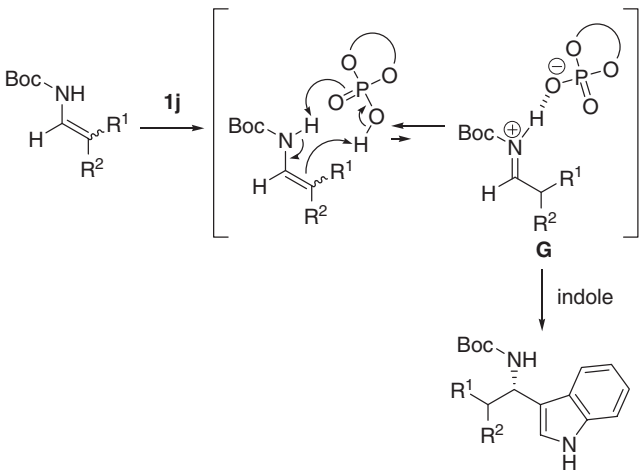
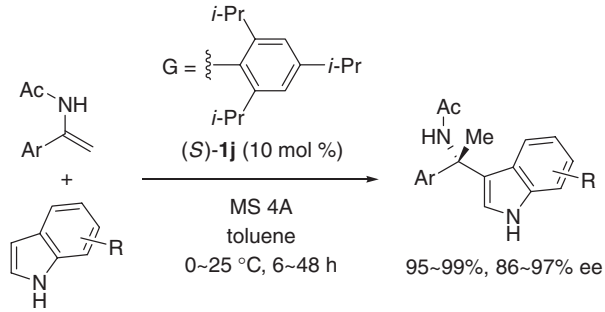


Figure 11. Mechanistic considerations of the Friedel–Crafts reaction of enecarbamates with indole.

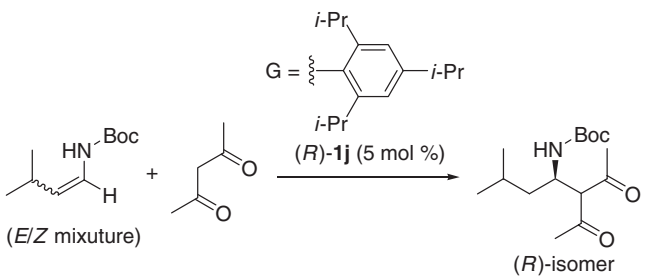


Ar: except *ortho*-substituents

Scheme 21. Enantioselective formation of a quaternary stereogenic center bearing a nitrogen atom in the Friedel–Crafts reaction.

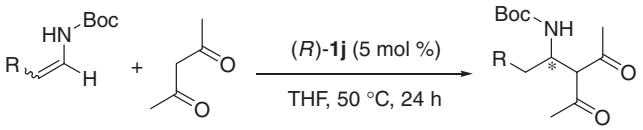
6.2 Mannich Reaction via Activation of Enecarbamates. The present method, in situ generation of aliphatic imines via protonation of enecarbamate, is applicable to other organic transformations. We then attempted utilization of the present method to a direct Mannich reaction, giving rise to β-alkyl-β-aminocarbonyl derivatives in an optically active form. Mannich reactions of aliphatic imines possessing hydrogen atoms at the α-position have rarely been explored to date,[43] 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 or glyoxylates.[17]

The reaction of *N*-Boc-protected enecarbamate with 10 equivalents of acetylacetone using (*R*)-**1j** in acetonitrile exhibited moderate enantioselectivity (Scheme 22),[65] despite using the same catalyst molecule, **1j**, and following similar reaction conditions to those used in the enantioselective F–C reaction of indoles (Scheme 20).[63] The activity and selectivity are profoundly dependent on the solvent employed and ethereal solvents were found to exhibit higher enantioselectivities than those obtained in the less-polar organic solvents. Among the organic 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 in an acceptable yield. Fortunately, the chemical yield was improved by reducing the amount of acetylacetone, albeit with a prolonged reaction time.



CH_3CN	10 equiv of acac	rt, 24 h	77%	69% ee
THF	10 equiv of acac	50 °C, 12 h	58%	85% ee
THF	5 equiv of acac	50 °C, 24 h	73%	86% ee

Scheme 22. Direct Mannich reaction via activation of enecarbamate by (*R*)-**1j**.



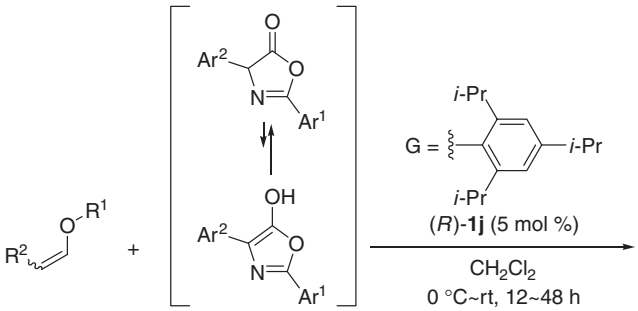
R =	Me (*E*)-isomer	Me (*Z*)-isomer	*n*-Bu	cyclohexyl	Bn
	49%	63%	73%	67%	56%
	49% ee	49% ee	75% ee	89% ee	61% ee

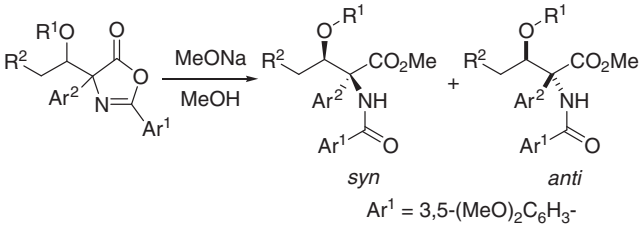
Scheme 23. Direct Mannich reaction via activation of various enecarbamates.

Interestingly, the absolute stereochemistry of the Mannich product was opposite to that observed in the F–C reaction via activation of enecarbamates by exactly the same catalyst, (*R*)-**1j** (Scheme 20). 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 phosphoric acid catalyst **1** is highly dependent not only on the hydrogen-bonding interactions between the aliphatic imine 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 and the oxygen atom of the chiral phosphoric acid **1j** in the active intermediate (**G**) (Figure 11).

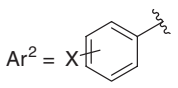
The substituent effect of enecarbamates with varying steric demand of the alkyl moieties (R) introduced at the C2 position showed that the enantioselectivity observed is susceptible to the steric demand of the alkyl substituents (Scheme 23). The enantioselectivity was enhanced with increasing steric congestion of the alkyl group, thus following the order: Me (49% ee) < *n*-Bu (75% ee) < *i*-Pr (86% ee) < cyclohexyl (89% ee), and reaching 89% ee in the reaction with the most sterically hindered cyclohexyl-substituted enecarbamate. These remarkable substituent effects are in contrast to the previous F–C reaction we investigated using this catalyst,[63] in which uniformly high enantioselectivity was observed, irrespective of the alkyl substituents.

6.3 Aldol Type Reaction via Activation of Vinyl Ethers. The activation of vinyl ethers by a Brønsted acid catalyst is an extensively utilized and fundamental method in synthetic organic chemistry, and is employed in the protection of alcohols and the formation of carbon–carbon bonds, among other processes. In this activation mode, the use of chiral phosphoric acids gives rise to ion pairs of a chiral conjugate base and an oxocarbenium ion via protonation of the vinyl ether. We envisioned the development of chiral conjugate base controlled enantioselective transformations[66] involving the oxocarbenium ion as the reactive intermediate.[67] For this purpose, we utilized the intermediary oxocarbenium to a direct aldol type reaction of azlactones[68] via their oxazole tautomer and successfully developed the proposed enantioselective transformation, giving the corresponding products in excellent enantio- and diastereoselectivities (Scheme 24).[69] The method enables efficient access to biologically and pharmaceutically intriguing β-hydroxy-α-amino acid derivatives having a quaternary stereogenic center at the α-carbon atom.





Ar^2 = Ph					
R^1 =	*t*-Bu	*n*-Bu	Bn	*t*-Bu	*t*-Bu
R^2 =	H	H	H	Me	*n*-Pr
	99%	94%	62%	99%	66%
	98% *syn*	82% *syn*	80% *syn*	96% *syn*	88% *syn*
	98% ee	96% ee	93% ee	97% ee	94% ee



R^1 = *t*-Bu, R^2 = H

X = *p*-MeO, *p*-Me, *p*-CF_3, *p*-Br, *m*-Me	X = *o*-F
67~99%	45%
94~98% *syn*	70% *syn*
91~97% ee	37% ee

Scheme 24. Aldol type reaction of azlactones via protonation of vinyl ethers.

The electronic manipulation of Ar^1 substituents introduced at the C2 position of azlactone had a significant impact not only on the reactivity of azlactones but also on the stereochemical outcome in terms of both enantio- and diastereoselectivities. When electron-donating methoxy substituents were introduced to the 3,5-positions of the phenyl ring, the corresponding products were obtained in excellent enantio- and diastereoselectivities. The substituent effect of vinyl ethers showed that the sterically demanding *tert*-butyl ether is important to achieve the high diastereoselectivity. Vinyl ethers with an alkyl group substituted at the terminal position were also applicable, affording the desired products with high enantioselectivities. Azlactones having a series of aromatic groups (Ar^2) revealed uniformly high enantio- and diastereoselectivities for *para*- and *meta*-substituted aromatic rings, irrespective of their electronic properties. However, *ortho*-substitution led to a marked reduction of selectivity and chemical yield. We proposed that the interaction, namely, C–H···O hydrogen-bond formation, between the chiral conjugate base and the oxocarbenium ion would allow the reaction to proceed under a chiral environment regulated by the chiral conjugate base (Figure 12), and hence high stereoselectivities were achieved in the present transformation.

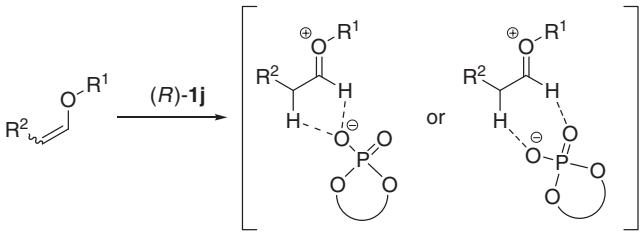


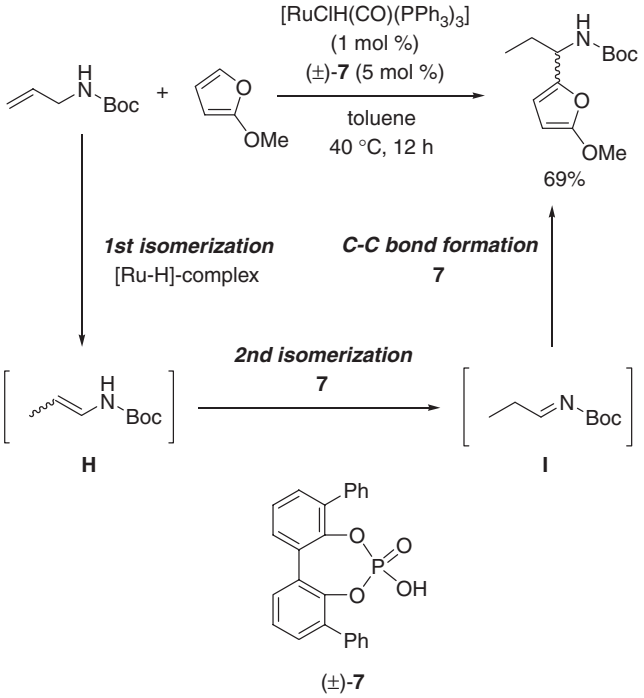
Figure 12. Plausible C–H···O hydrogen-bonding model of chiral conjugate base and oxocarbenium ion.

7. Cooperative Catalysis by Metal Complexes/Brønsted Acids Binary System

In the past decade, tremendous progress has been made in catalysis using small organic molecules, namely, organocatalysis.[1] Meanwhile, catalysis by transition-metal complexes has continuously been applied to a broad range of organic transformations and occupies a privileged position in synthetic organic chemistry. Much of the research on catalysis has centered on the use of metal complexes to activate a variety of chemical bonds. In recent years, armed with the idea of taking advantage of both of these catalytic processes, researchers have combined metal complexes and organic molecules in cooperative catalysis, and this has attracted much attention as it could potentially realize unprecedented transformations. Recently, a couple of excellent approaches were established with the chiral phosphoric acid/metal complex binary catalytic system.[70]

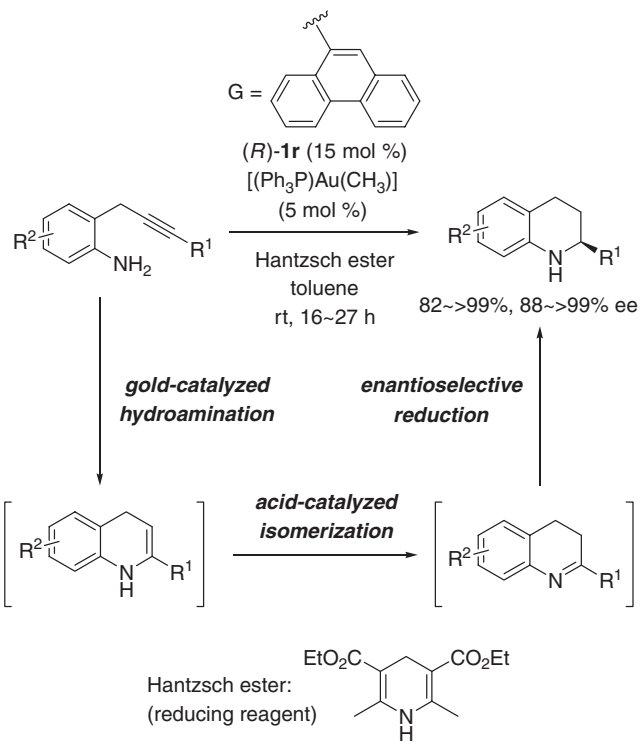
7.1 Metal Complex/Phosphoric Acid Relay Catalysis. In the previous studies,[70] each reactant was activated by one type of catalyst simultaneously; thus, the metal complex activates nucleophiles while the phosphoric acid activates imines as the electrophilic component. We reported an unprecedented consecutive transformation using a binary catalytic system, that is, relay catalysis for tandem isomerization/carbon–carbon bond formation sequence promoted by a binary catalyst consisting of a ruthenium hydride complex and a phosphoric acid **7** (Scheme 25).[71] The reaction of *N*-Boc-protected allylamine with 2-methoxyfuran proceeded smoothly to give a product having a nitrogen functionality at the stereogenic center in good yield. Control experiments revealed that both catalysts, the ruthenium complex and phosphoric acid **7**, are indispensable to the sequential processes.

The present sequential transformation involves a three-step relay catalysis where: (i) isomerization of allylcarbamate to enecarbamate (**H**) is catalyzed by the ruthenium hydride complex; (ii) subsequent isomerization of **H** to intermediary imine (**I**) is relayed by acid catalyst **7**; and (iii) the catalytic sequence is terminated by a carbon–carbon bond forming reaction of **I** with the electron-rich aromatic compounds as a nucleophilic component under the influence of **7**. The advantage of the present relay catalysis is that the method enables the generation of reactive imines **I** from readily available allylcarbamates in a one-pot reaction via tandem isomerization. Although the racemic acid catalyst was employed in this case, an enantioselective version would be applicable to the present relay catalysis, considering recent progress in enantioselective F–C reaction of enecarbamates using chiral phosphoric acid catalyst (Scheme 20).[63]



Scheme 25. Relay catalysis by ruthenium complex/Brønsted acid binary system.

Recently the enantioselective version of the relay transformation by organic and metallic catalyses was successfully demonstrated by Gong and co-workers (Scheme 26).[72] They accomplished the direct transformation of *o*-2-propynylaniline derivatives into tetrahydroquinolines in a highly enantioselective manner through the hydroamination of alkynes/isomerization/enantioselective transfer hydrogenation[73] sequence under the relay catalysis of an achiral Au complex/chiral phosphoric acid binary system.



Scheme 26. Enantioselective relay catalysis by gold complex/chiral phosphoric acid binary system.

8. Conclusion

This article focused on recent advances in the chemistry of chiral Brønsted acid catalysis using BINOL-derived phosphoric acids for enantioselective carbon–carbon bond forming reactions. In initial studies, the chiral phosphoric acids were utilized for activation of imines in most cases. While recently, tremendous progress has been made in the development of chiral phosphoric acid catalysis and broadened the scope of functionalities which can be activated by chiral phosphoric acid catalysts and their derivatives. Today, catalyses by these phosphoric acids have been extensively applied to a variety of functionalities, such as ketones,[50] aziridines,[51a,51b] nitrones,[51c] nitroalkenes,[51d–51f] azomethine ylides,[51g–51i] and alcohols.[51j,51k] In this regard, numerous enantioselective transformations, including not only carbon–carbon bond formations but also carbon–hetero atom bond formations[74] as well as reductions[73] and oxidations,[66b,75] are going to be developed in a highly stereoselective manner. However, the enantioselective versions of many reactions still remain to be developed using chiral phosphoric acids or other types of chiral Brønsted acids.[36,37c,76] Further elaboration of novel chiral Brønsted acids derived not only from other types of chiral backbones,[19,20,51g,73j,74c,77] such as diols, diamines, and amino alcohols, but also from stronger acid functionalities[50c] could allow the discovery of more selective and efficient methods for a wide variety of enantioselective organic transformations.

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