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Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations

Masahiro Terada*

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan
Fax +81(22)7956602; E-mail: mterada@mail.tains.tohoku.ac.jp

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Abstract: Chiral phosphoric acids derived from axially chiral biaryls and related chiral Brønsted acids have emerged as an attractive and widely applicable class of enantioselective organocatalysts for a variety of organic transformations. This review focuses on recent achievements in the development of enantioselective transformations using these axially chiral phosphoric acids and their analogues as chiral Brønsted acid catalysts. The contents are arranged according to the specific types of carbon–carbon bond-forming reactions, followed by carbon–heteroatom bond-forming reactions and functional group transformations, including reduction and oxidation. Further applications to combined phosphoric acid and metal complex catalytic systems and new aspects in the development of chiral Brønsted acid catalysts are also highlighted.

Key words: asymmetric catalysis, diastereoselectivity, electrophilic addition, enantioselectivity, multicomponent reaction

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 procedures for organocatalysis reported to date, researchers have focused on '*chiral Brønsted acid catalysis*', the innovative methods of which have afforded 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 the enantioselective Strecker reaction catalyzed by peptide-based thiourea derivatives acting as hydrogen-bond donor catalysts.[3] Their landmark report in 1998 has fueled great interest in the enantioselective catalysis by chiral Brønsted acids. Their achievement has clearly indicated that a chiral Brønsted acid enables discrimination between the 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, excellent work on the enantioselective hetero-Diels–Alder reaction was reported by Rawal and co-workers in 2003 using TADDOL (tetraaryl-1,3-dioxolane-4,5-dimethanol) as the chiral Brønsted acid catalyst.[4] These milestones 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.[5,6] In contrast to these advanced studies, an innovative approach to the development of chiral Brønsted acid catalysts that possess strongly acidic functionalities was independently accomplished by Akiyama and co-workers[7] and Terada and co-workers[8] in 2004. Highly enantioselective transformations using 1,1′-bi-2-naphthol (BINOL)-derived monophosphoric acids **1** as chiral Brønsted acid catalysts were demonstrated by these two research groups (Figure 1).[2a,c,9] Among the chiral Brønsted acids reported hitherto,[2] chiral phosphoric acids derived from axially chiral biaryls represent an attractive and widely applicable class of enantioselective organocatalysts for a variety of organic transformations. The present review focuses on recent achievements in the development of enantioselective transformations using axially chiral phosphoric acid catalysts **1** and related chiral Brønsted acids.

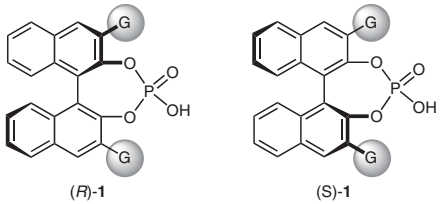

Figure 1 BINOL-derived monophosphoric acids **1** as chiral Brønsted acid catalysts

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2 Chiral Phosphoric Acids as Enantioselective Brønsted Acid Catalysts

The desirable features of phosphoric acids as chiral Brønsted acid catalysts are summarized as follows (Figure 2):

1) Phosphoric acids are expected to capture electrophilic components through hydrogen-bonding interactions without forming loose ion pairs, owing to their relatively strong yet appropriate acidity.[10]

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 bifunctional organocatalyst design reported to date.[1,11] However, in a strict sense, the phosphoric acid catalysts should be distinguished from most bifunctional organocatalysts, in which rather weakly 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 2) 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).

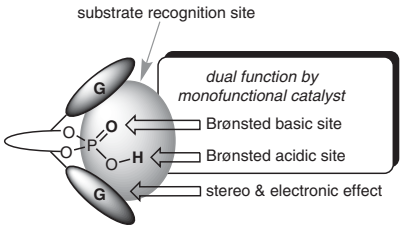


Figure 2 Phosphoric acids to be developed as chiral Brønsted acid catalysts

As shown in Figure 1, axially chiral biaryls, especially BINOL derivatives, were mainly employed as chiral sources for the construction of the ring structure. BINOL is well known as an axially chiral molecule having C_2-symmetry. Its derivatives have been utilized extensively as chiral ligands for metal catalysts.[12] This C_2-symmetry is crucial because it means that the same catalyst molecule is generated when the acidic proton migrates to the phosphoryl oxygen. In addition, both enantiomers of BINOLs are commercially available and numerous protocols for the modification of BINOLs have been reported to date, in which a variety of substituents (G) can be introduced to the 3,3′-positions of the binaphthyl backbone. These sterically but also electronically adjustable substituents (G) can be utilized to create an appropriate chiral environment for enantioselective transformations.[13]

3 Mannich and Related Reactions

Akiyama et al. reported enantioselective catalysis in the Mukaiyama type Mannich reaction that used BINOL-derived phosphoric acids **1** as chiral Brønsted acid catalysts.[7] In the same year, Terada and Uraguchi independently demonstrated a highly enantioselective direct Mannich reaction using similar phosphoric acids.[8] As these enantioselective Mannich reactions were successfully developed, chiral phosphoric acids have been widely utilized as efficient enantioselective organocatalysts for numerous organic transformations. Among the asymmetric reactions investigated, the electrophilic activation of imines by chiral phosphoric acid has been proven to be an attractive and efficient method for the construction of nitrogen-substituted stereogenic centers in optically active forms.[14]

3.1 Mannich Reaction

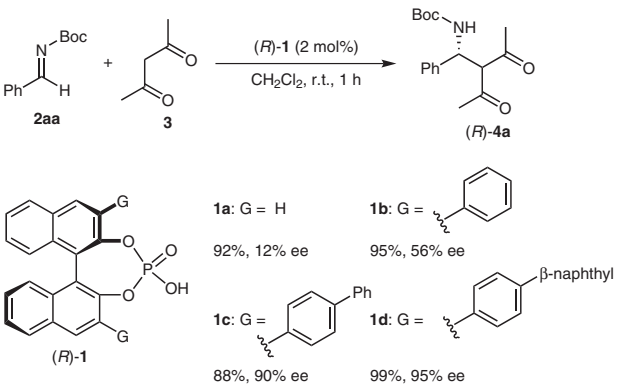
Enantioselective Mannich reactions are widely utilized for the construction of optically active β-amino carbonyl compounds[15] that serve as versatile intermediates for the synthesis of biologically active compounds and drug candidates. Highly enantioselective Mannich reactions have

Biographical Sketch

Masahiro Terada was born in 1964 in Tokyo, Japan. He graduated in 1986 and received his PhD in 1993 from Tokyo Institute of Technology. He was appointed as an Assistant Professor in Professor Mikami's Laboratory at Tokyo Institute of Technology in 1989. He worked as a postdoctoral fellow with Professor M. D. Shair at Harvard University in 1999–2000 and moved to Tohoku University as an Associate Professor in 2001. He has been a Professor of Chemistry at the Graduate School of Science, Tohoku University (Japan) since 2006. He is the recipient of the Incentive Award in Synthetic Organic Chemistry, Japan (2003), The Chemical Society of Japan Award for Creative Work (2008), and the Mukaiyama Award (2010). His current research interests are focused on the development of new and useful synthetic methodologies based on the design of novel chiral Brønsted acid and base catalysts as well as the utilization of transition-metal catalysts.

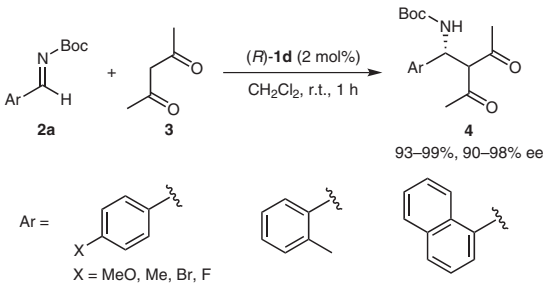
been established using other types of organocatalysts, such as proline and its derivatives, chiral secondary amines.[16]

In 2004, Terada and Uraguchi developed the chiral phosphoric acid **1** catalyzed enantioselective direct Mannich reaction of imine **2** with acetylacetone (**3**).[8] Chiral phosphoric acid **1a** exhibited extremely high catalytic activity for the direct Mannich reaction of *N*-Boc-protected imine **2aa** with acetylacetone (**3**) (Scheme 1). The resulting β-amino ketone **4a** 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 regards 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 the aromatic substitution to the *para*-position improved the enantioselectivity dramatically. Use of **1d** as the catalyst further increased the enantioselectivity to 95% ee, giving the product **4a** in nearly quantitative yield.



Scheme 1 Direct Mannich reaction catalyzed by **1**

The present catalytic reaction was applicable to *ortho*-, *meta*-, and *para*-substituted *N*-Boc-protected aromatic imines **2a** and the corresponding products were obtained in excellent chemical yields with high enantioselectivities (Scheme 2). 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.



Scheme 2 Direct Mannich reaction of imines **2a**

In the present direct Mannich reaction, it is considered that the dual function of the phosphoric acid moiety smoothly accelerates the reaction (Figure 3). The enol proton of the acetylacetone tautomer and the O-H proton of **1** function as acidic sites, while the nitrogen atom of **2a** and the phosphoryl oxygen function as basic sites. In the direct Mannich reaction of **2a** with **3**, **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 3a). Thus, phosphoric acid catalyst **1** electrophilically activates **2a** 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 the formation of Mannich product **4** and the regeneration of catalyst **1** (Figure 3b). More importantly, the reaction proceeds under a chiral environment created by the chiral conjugate base of **1** through hydrogen-bonding interactions to furnish optically active products **4**.

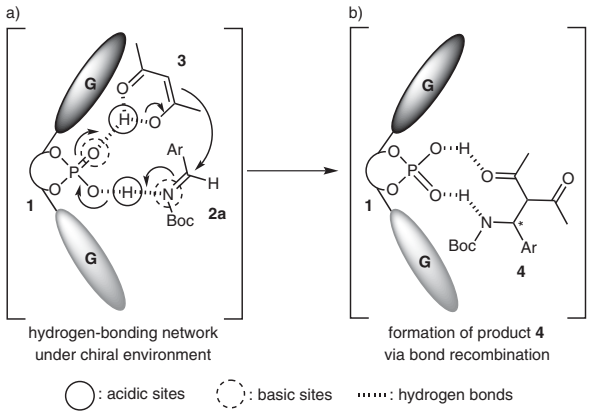
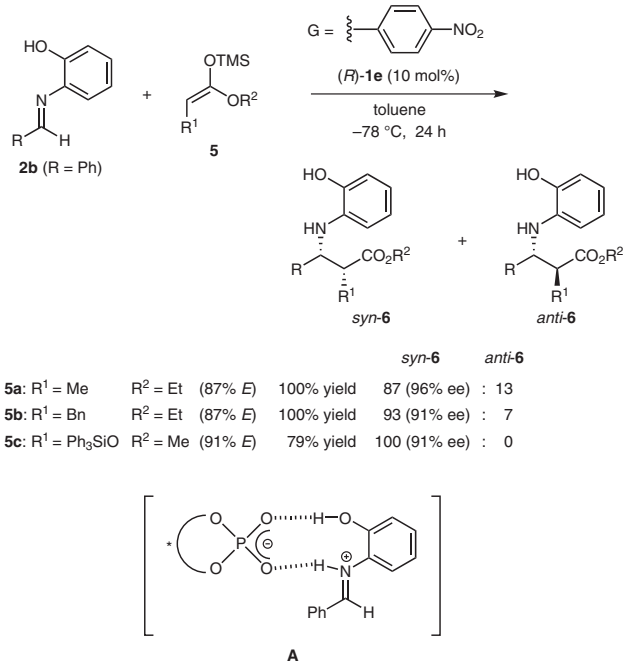


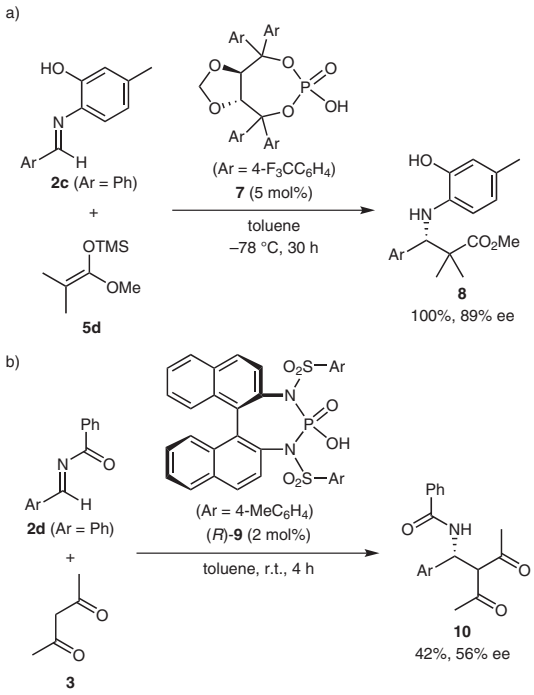
Figure 3 Assumed mechanism of enantioselective direct Mannich reaction catalyzed by chiral phosphoric acid **1**

Akiyama and co-workers independently reported the Mukaiyama-type Mannich reaction of ketene silyl acetals **5** with imines **2b** derived from 2-hydroxyaniline (Scheme 3).[7,17] The introduction of 4-nitrophenyl groups at the 3,3′-positions of the catalyst binaphthyl backbone, giving **1e**, yielded the best results in terms of catalytic activity and enantioselectivity. Mannich products **6** were obtained with high *syn*-selectivity and the enantioselectivity of the major *syn*-isomers reached as high as 96% ee. In the present Mannich reaction, an *ortho*-hydroxy functionality introduced onto the *N*-aryl moiety of the imine is essential to achieve the high stereoselectivities. Yamanaka, Akiyama, and co-workers rationalized the *re*-facial selectivity of the present reaction on the basis of experimental results and density functional theory (DFT) calculations,[18] in which the phosphoric acid catalyst and the imine form a nine-membered cyclic structure (**A**) through a double hydrogen-bonding interaction.

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



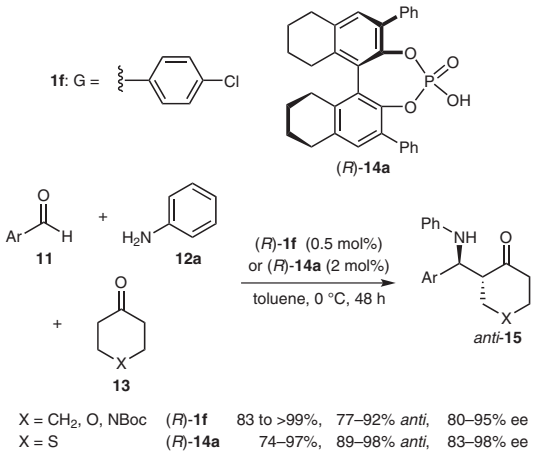
Scheme 3 Mukaiyama-type Mannich reaction of imines **2b** with ketene silyl acetals **5**



Scheme 4 Other structural motifs of chiral phosphoric acid catalysts

chiral phosphoric acid **7**, derived from TADDOL, functioned as an efficient enantioselective catalyst for the Mukaiyama-type Mannich reaction of imines **2c** with ketene silyl acetals **5d** (Scheme 4a).[19] Akiyama et al. also developed a phosphoric acid catalyst derived from an axially chiral biphenol,[20] which was also applied to the Mukaiyama-type Mannich reaction of ketene silyl acetals **5** with imines **2b**, affording Mannich products in good yields albeit with a slight decrease in enantioselectivities. Terada et al. also developed phosphorodiamidic acid **9** for use as an efficient Brønsted acid catalyst in the direct Mannich reaction of *N*-acyl imines **2d** with acetylacetone (**3**) (Scheme 4b).[21] Although the asymmetric induction of Mannich product **10** is still moderate, phosphorodiamidic acid **9** 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.

Gong and co-workers applied chiral phosphoric acid catalysts to the three-component direct Mannich reaction to realize a one-pot reaction among aromatic aldehyde **11**, aniline (**12a**), and ketones (Scheme 5).[22] The reaction of cyclic ketones **13** as the nucleophilic component proceeded smoothly in the presence of 0.5 mol% **1f** or 2 mol% **14a**, giving desired products **15** in good yields with high enantio- and *anti*-selectivities. They also extended the coupling method to the reaction of acyclic ketones, such as acetone and acetophenone, which gave products in good yields when the catalyst load was increased to 5 mol% and excess amounts of these ketones (10 equiv) were used, although slight decreases in enantioselectivities were observed. Shortly thereafter, Rueping et al. reported achiral Brønsted acid assisted chiral Brønsted acid catalysis in the direct Mannich reaction of acyclic ketones.[23] The reaction of *N*-aryl imines with acetophenone was conducted using a chiral phosphoric acid catalyst in combination with acetic acid as the co-catalyst. The corresponding products were obtained in acceptable yields even when the amount of acetophenone employed was decreased (2 equiv).

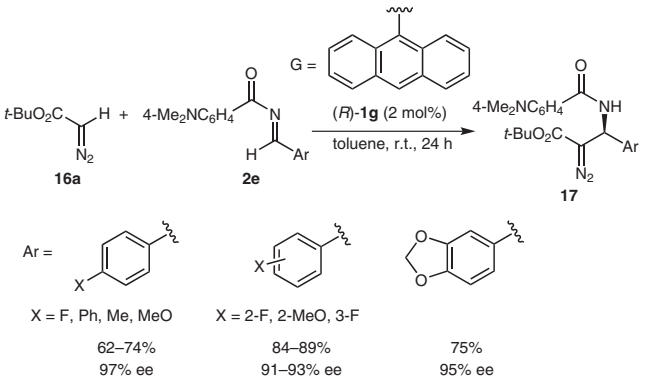


Scheme 5 Three-component direct Mannich reaction

3.2 Nucleophilic Addition of Diazoacetates to Aldimines

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[24] and Brønsted[25] acid catalyzed conditions. Meanwhile, Terada and co-workers reported an enantioselective direct substitution at the α-position of diazoacetate using a chiral phosphoric acid catalyst.[26] Phosphoric acid catalyst **1g** efficiently promoted the substitution reaction of α-diazoacetates **16** with *N*-acyl imines **2e** to give Mannich-type products **17**, which are β-amino esters having a diazo substituent at the α-position, in optically active forms (Scheme 6). 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, and the introduction of an electron-donating dimethylamino moiety gave the best results. A series of aromatic imines **2e** were applicable to these substitution reactions. *Para*-substituted aromatics showed excellent enantioselectivities irrespective of their electronic properties. *Ortho*- and *meta*-substitutions as well as fused-ring systems were also applicable. The thus-obtained β-amino-α-diazoester products **17** could be transformed into common synthetic intermediates, such as β-amino acid derivatives, via simple reduction or oxidation of the diazo moiety.



Scheme 6 α-Substitution reaction of diazoacetate with imines

The phosphoric acid is expected to promote the substitution reaction as a result of its dual function (Figure 4a). Intracomplex deprotonation from **B** by the basic phosphoryl oxygen would allow the direct substitution of diazoacetate, giving Mannich-type products without the formation of aziridine products.

Akiyama et al. reported the aziridine formation reaction (aza-Darzens reaction) using α-diazoacetate **16b** and *p*-methoxyphenyl (PMP)-protected imines **18** prepared in situ from glyoxal monohydrate **19** and 4-methoxyaniline (**12b**) in the presence of magnesium sulfate (Scheme 7).[27] Chiral phosphoric acid catalyst **1h** gave the corresponding aziridine products **20** with high enantioselectivities and the *cis*-isomer was formed exclusively. The PMP protective group would preserve the nucleophilicity of the nitrogen atom and hence the intramolecular substitution by the nitrogen atom would proceed predominantly via intermediate **C** (Figure 4b). This contrasts the reaction of *N*-benzoyl imines where Mannich-type products were obtained

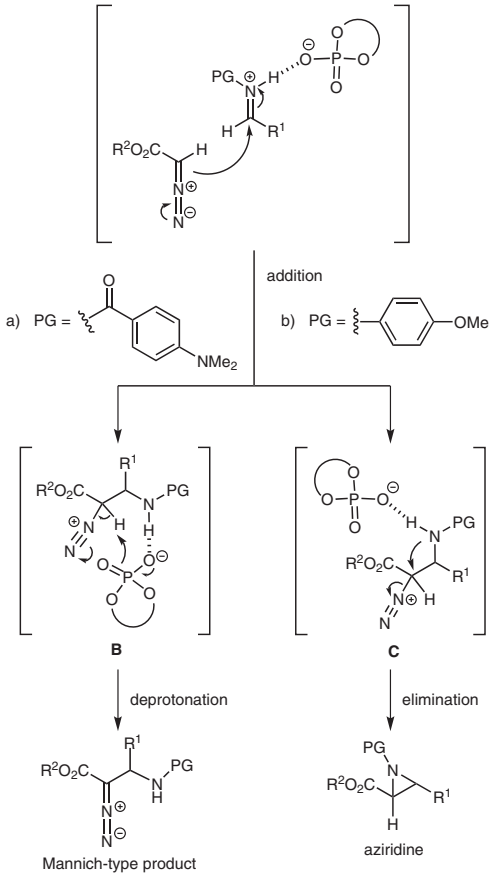
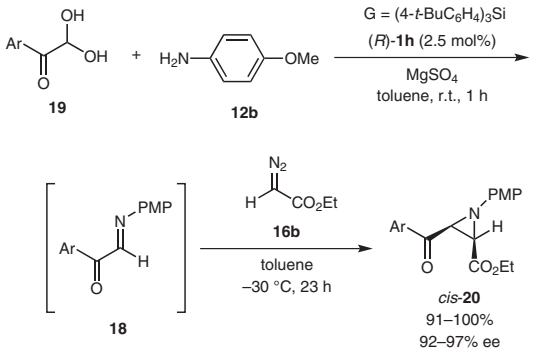


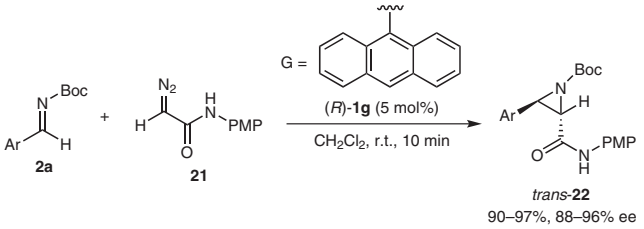
Figure 4 Mechanistic proposal for reactions of diazoacetate with imines

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.

Meanwhile, Zhong and co-workers reported the *trans*-selective aza-Darzens reaction of diazoacetamide **21** with *N*-Boc aromatic imines **2a** (Scheme 8).[28] In the presence of chiral phosphoric acid catalyst **1g**, the corresponding aziridine products **22** were obtained with excellent *trans*-selectivities, in this case, with high enantioselectivities. Although the dramatic changes in the stereochemical outcomes have not been clarified yet, the amide moiety may function as a hydrogen-bond donor site to the phosphoric



Scheme 7 Enantio- and *cis*-selective aza-Darzens reaction



Scheme 8 Enantio- and *trans*-selective aza-Darzens reaction

acid catalyst and affect the configuration of the transient assembly composed of ternary constituents.

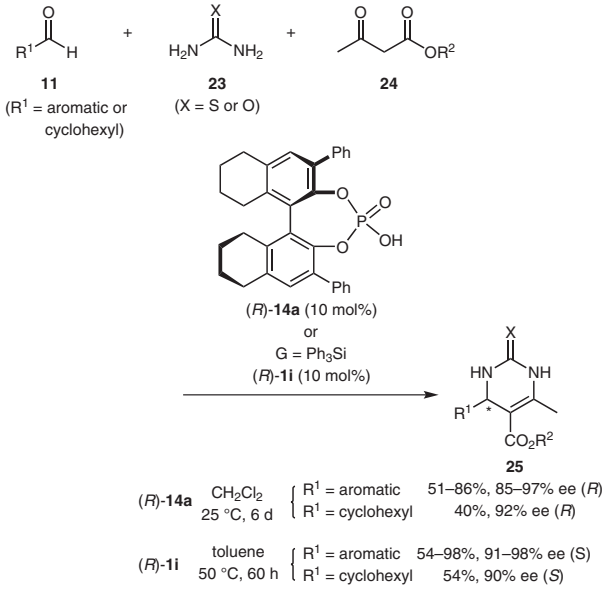
3.3 Biginelli Reaction

Gong and co-workers reported the enantioselective Biginelli reaction via the three-component coupling of aldehydes **11**, (thio)urea **23**, and β-keto esters **24** (Scheme 9).[29] Utilizing the Mannich reaction as the initial step, the method enabled efficient access to 3,4-dihydropyrimidine-2(1*H*)-one derivatives **25**[30] that possess a wide array of pharmaceutical properties and hence are considered to be medicinally relevant compounds. Catalyst **14a** having the H_8-binaphthyl backbone most effectively furnished the corresponding pyrimidinone derivatives in moderate to high yields with high enantioselectivities. A wide variety of aldehydes **11** are employable in this reaction. Gong and co-workers further optimized the substituent of catalyst **1** in the present Biginelli reaction.[31] Triphenylsilyl-substituted catalyst **1i** was found to provide higher enantioselectivity than that obtained by **14a** in most cases. In addition, the reaction catalyzed by (*R*)-**1i** gave product **25** whose enantiofacial selection is opposite that of catalyst (*R*)-**14a** even when using the same axial chirality of the catalysts. They performed transition-state analysis by DFT calculations to elucidate the reverse of the enantiofacial selection in these catalyses. They also demonstrated the synthetic utility of the enantioselective Biginelli reaction in the preparation of optically active intermediate **26** of (*S*)-L-771688,[32] a selective α_{1a} receptor antagonist (Scheme 10).

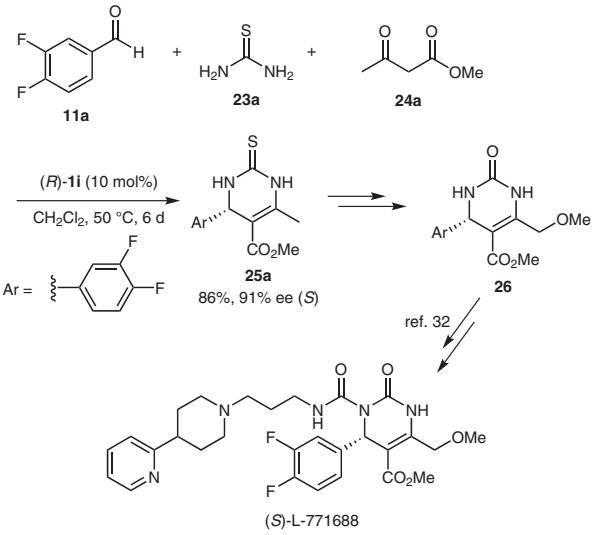
Gong and co-workers further applied this reaction using catalyst **1i** to the Biginelli-like condensation, employing enolizable ketones, including not only cyclic ketones **13** but also acyclic ketones **27**, in place of β-keto esters **24** (Scheme 11).[31] A broad range of cyclic ketones **13** and acyclic ketones **27** were applicable to the Biginelli-like condensation with aromatic aldehyde **11** and *N*-benzylthiourea (**28**), giving the corresponding products **29** and **30** with excellent enantioselectivities.

3.4 Vinylogous Mannich Reaction

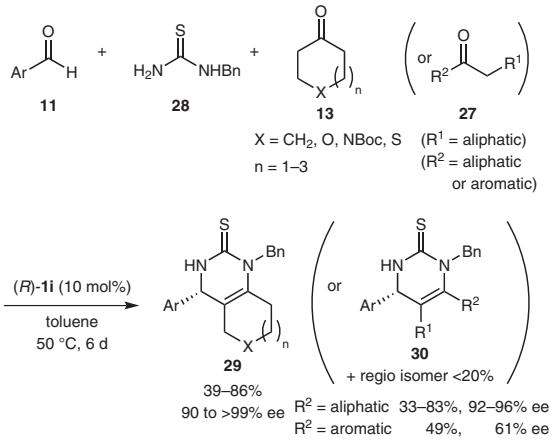
The asymmetric Mannich reaction is one of the most ubiquitous carbon–carbon bond-forming reactions in organic chemistry. The vinylogous extension of this fundamental carbon–carbon bond-forming reaction to nucleophilic components, namely, the vinylogous Mannich reaction,



Scheme 9 Biginelli reaction

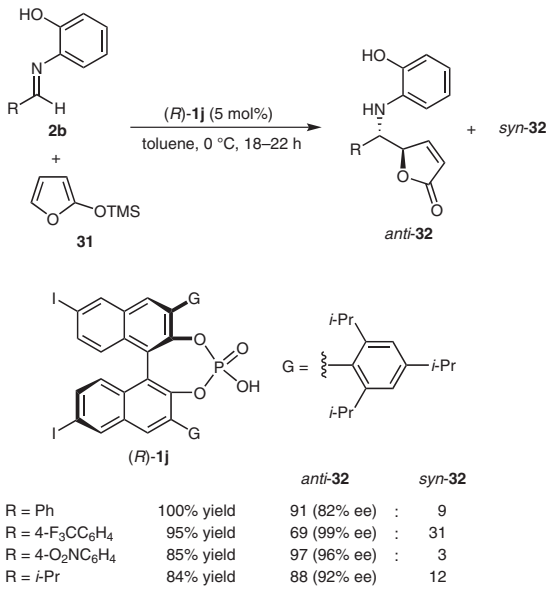


Scheme 10 Application to asymmetric synthesis of (*S*)-L-771688 precursor



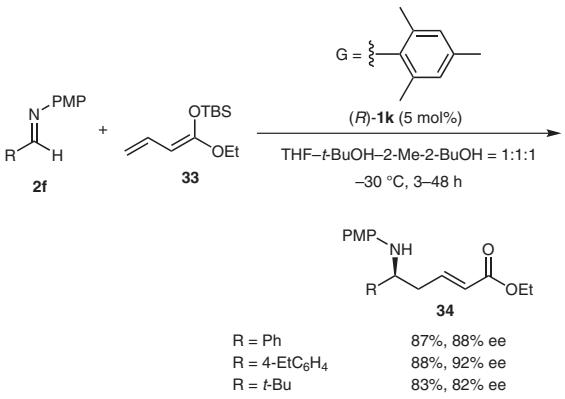
Scheme 11 Biginelli-like reaction via three-component coupling

has been little exploited[33] despite its potential to provide efficient access to highly functionalized δ-amino carbonyl compounds bearing a double bond. 2-Siloxyfuran **31** is an attractive vinylogous nucleophile that has been utilized extensively in vinylogous variants of fundamental transformations, such as the aldol reaction,[34] because the reactions provide γ-substituted butenolides, an important structural motif existing in naturally occurring products and biologically active compounds. Akiyama et al. successfully developed the enantioselective vinylogous Mannich reaction of 2-trimethylsiloxyfuran (**31**) with aldimines **2b** using chiral phosphoric acid catalyst **1j** bearing iodine groups at the 6,6′-positions of the binaphthyl backbone (Scheme 12).[35] A series of aldimines, including aliphatic ones, were utilized in the present reaction and γ-butenolide products **32** were obtained in good yields with moderate to high diastereo- and enantioselectivities.



		anti-32		syn-32
R = Ph	100% yield	91 (82% ee)	:	9
R = 4-$F_3CC_6H_4$	95% yield	69 (99% ee)	:	31
R = 4-$O_2NC_6H_4$	85% yield	97 (96% ee)	:	3
R = *i*-Pr	84% yield	88 (92% ee)		12

Scheme 12 Vinylogous Mannich reaction of 2-trimethylsiloxyfuran (**31**)



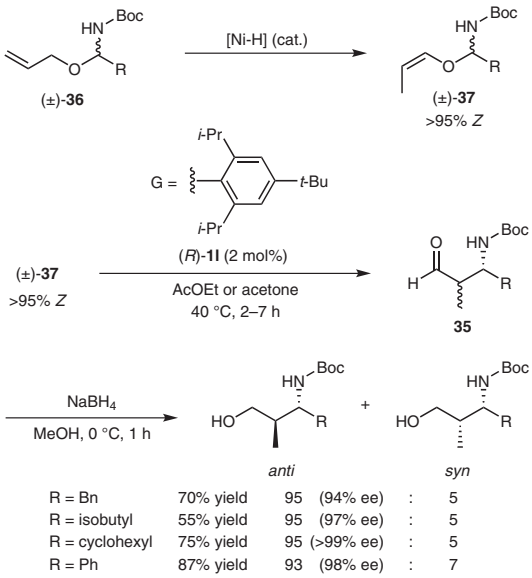
R = Ph	87%, 88% ee
R = 4-EtC_6H_4	88%, 92% ee
R = *t*-Bu	83%, 82% ee

Scheme 13 Vinylogous Mannich reaction of silyl dienol ether **33**

Schneider and Sickert were the first to demonstrate the catalytic and enantioselective vinylogous Mannich reaction of acyclic silyl dienol ether **33** with aldimines **2f** using chiral phosphoric acid catalyst **1k** (Scheme 13).[36] The reaction provided highly valuable δ-amino-α,β-unsaturated carboxylic esters **34** in optically active forms with complete regioselectivities. Schneider and co-workers also reported the enantioselective vinylogous Mannich reaction of vinylketene silyl *N*,*O*-acetals with aromatic imines.[37] The piperidine-derived vinylketene silyl *N*,*O*-acetals proved to be more suitable substrates than their dialkylamine- and pyrrolidine-derived counterparts, furnishing the corresponding vinylogous products, δ-amino-α,β-unsaturated amides, in good yields with high enantioselectivities.

3.5 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.[38] 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.[38c] Terada and Toda developed an alternative strategy to furnish optically active β-amino aldehydes **35** having an aliphatic substituent (R) at the β-position by combining two catalytic reactions (Scheme 14).[39] The sequence involves initial nickel complex catalyzed *Z*-selective isomerization of a double bond, followed by chiral phosphoric acid catalyzed aza-Petasis–Ferrier rearrangement,[40] using readily available hemiaminal allyl ethers **36** as the substrate. The aza-Petasis–Ferrier rearrangement of hemiaminal vinyl ethers **37** proceeded via carbon–oxygen bond cleavage of the ether moiety by acid catalyst **1l**, generating a reactive iminium intermediate and an enol form of the aldehyde. Subsequent recombination with carbon–carbon bond for-



R = Bn	70% yield	95 (94% ee)	:	5
R = isobutyl	55% yield	95 (97% ee)	:	5
R = cyclohexyl	75% yield	95 (>99% ee)	:	5
R = Ph	87% yield	93 (98% ee)	:	7

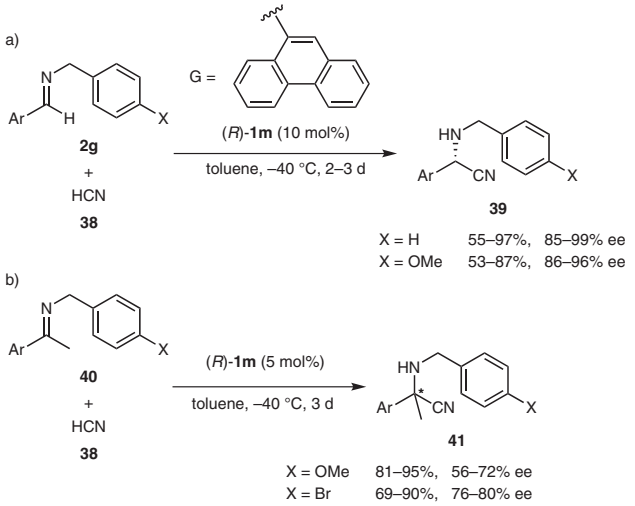
Scheme 14 Double-bond isomerization/aza-Petasis–Ferrier rearrangement sequence for the preparation of β-amino aldehydes **35**

mation resulted in rearranged products **35**, thus providing β-amino aldehydes having not only aliphatic but also aromatic substituents at the β-position with high *anti*- and enantioselectivities.

4 One-Carbon Homologation Reactions via Activation of Imines

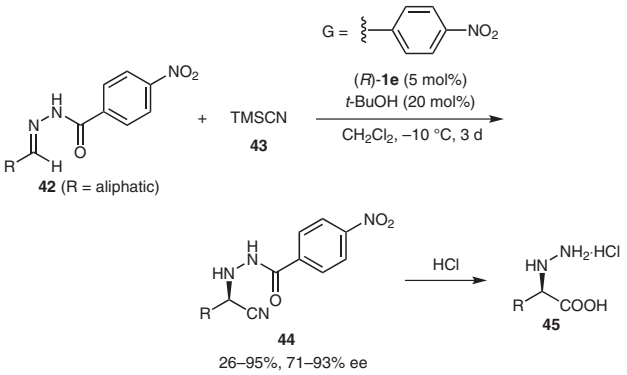
4.1 Strecker Reaction and Related Reactions

The hydrocyanation of imines, namely, the Strecker reaction, offers a practical route to α-amino acids or 1,2-diamines, which can be transformed from the corresponding α-amino nitrile products through simple hydrolysis or reduction of the nitrile moiety. The development of the catalytic enantioselective Strecker reaction is hence a vital step toward the efficient synthesis of these amines in optically active forms. A number of methods for the enantioselective Strecker reaction have been intensively investigated using either chiral metal catalysts or organocatalysts.[41] Chiral phosphoric acid catalysts were also successfully applied to the enantioselective Strecker reaction (Scheme 15). Rueping et al. were able to attain excellent performance using chiral catalyst **1m**, which has sterically demanding 9-phenanthryl substituents at the 3,3′-positions of the binaphthyl backbone.[42] The method offers efficient access to a broad range of aromatic amino nitriles **39** with high enantioselectivities (Scheme 15a). They also developed the enantioselective Strecker reaction of ketimines **40** catalyzed by the same chiral phosphoric acid **1m** to give products **41**, having a chiral quaternary stereogenic center, with moderate to high enantioselectivities (Scheme 15b).[43,44]



Scheme 15 Strecker reaction

In contrast to the Strecker reaction that involves the hydrocyanation of imines, the cyanation of hydrazone to give synthetically valuable α-hydrazinonitriles is poorly exploited[45] despite its ability to provide efficient access to α-hydrazino acids of therapeutically intriguing molecules. Tsogoeva and Zamfir developed a highly enantioselective Strecker-type reaction of hydrazones **42** using chiral phosphoric acid **1e** (Scheme 16).[46] Readily prepared and air-stable aliphatic hydrazones **42** are employable for this reaction, giving synthetically valuable α-hydrazinonitriles **44** in moderate to good yields with high enantioselectivities. The thus-obtained α-hydrazinonitriles **44** can be readily transformed into the corresponding α-hydrazino acids **45** in a quantitative manner under acid hydrolysis. The authors also proposed that the active catalyst is an in situ generated O-silylated BINOL-phosphate, thus shifting the mode of catalysis from a Brønsted acid catalysis to a Lewis acid catalysis.



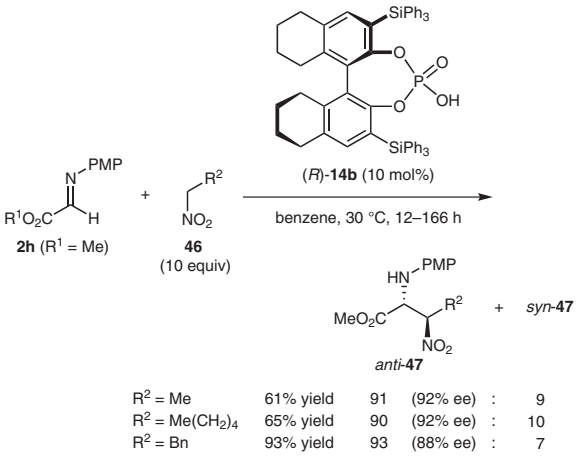
Scheme 16 Hydrocyanation of hydrazones **42** derived from aliphatic aldehydes

4.2 Aza-Henry Reaction

The synthesis of β-nitro amines via the addition of nitroalkanes to imines, or the so-called aza-Henry reaction, is an attractive tool for the creation of carbon–carbon bonds. The products obtained can be readily converted into vicinal diamines and α-amino acids by simple reduction and the Nef reaction, respectively, highlighting the several important synthetic applications of these compounds. In this context, enantioselective versions of the aza-Henry reaction have been actively investigated using chiral metal complexes and organocatalysts.[47] Rueping and Antonchick demonstrated the enantioselective direct aza-Henry reaction of α-imino esters **2h** with nitroalkanes **46** using chiral phosphoric acid catalysts (Scheme 17).[48] Catalyst **14b**, with its sterically demanding triphenylsilyl substituents, significantly accelerated the reaction to provide β-nitro-α-amino acid esters **47** in good yields. A variety of nitroalkanes were applicable to this reaction, giving desired products **47** with high diastereo- and enantioselectivities.

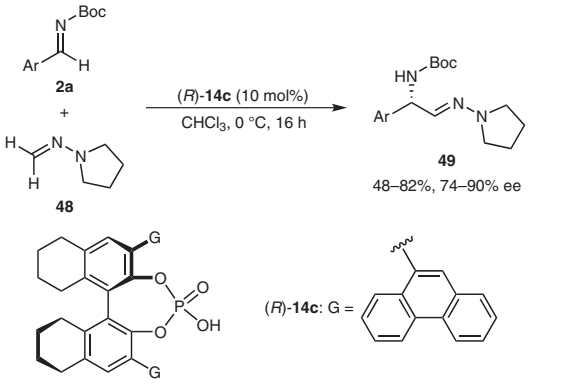
4.3 Imino-Azaenamine Reaction

Formaldehyde dialkylhydrazones, such as azaenamines (nitrogen analogues of enamines), possess a carbon atom that shows nucleophilic character, and are thus utilized as formyl anion equivalents.[49] The reaction enables efficient one-carbon homologation of electrophilic substrates. Rueping et al. utilized this nucleophilic species in a reac-



Scheme 17 Aza-Henry reaction of α-imino esters **2h**

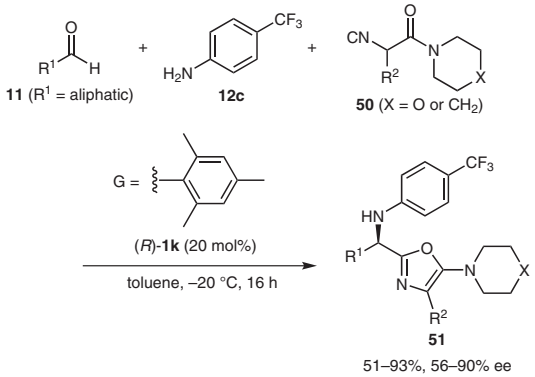
tion of imines **2a** under the influence of chiral phosphoric acid **14c** (Scheme 18).[50] The reaction of pyrrolidine-derived methylenehydrazine **48** with a series of *N*-Boc aromatic imines **2a** provided α-amino hydrazones **49** with moderate to high enantioselectivities. Products **49** have been proven to be useful synthetic intermediates that can be readily transformed into a diverse array of chiral nitrogen-containing compounds, such as α-amino aldehydes, α-amino nitriles, and 1,2-diamines, without racemization.



Scheme 18 Imino-azaenamine reaction of hydrazone **48**

4.4 Addition of Isocyanide to Aldimines

Isocyanides are useful one-carbon sources in organic synthesis. The Passerini three-component reaction[51] and the Ugi four-component reaction[52] are representative transformations that use isocyanides as one-carbon homologation reagents having a formally divalent carbon center, and the isocyanides can react with electrophiles and nucleophiles. Wang, Zhu, and co-workers developed enantioselective Ugi-type multicomponent reactions[53] that involved the α-addition of isocyanides to imines[54] catalyzed by chiral phosphoric acids (Scheme 19). Catalyst **1k** efficiently accelerated the three-component reaction of aliphatic aldehydes **11**, aniline derivative **12c**, and α-isocyanoacetamides **50**, giving 2-(1-aminoalkyl)-5-aminooxazoles **51** in good yields with moderate to high enantioselectivities.



Scheme 19 Three-component reaction of isocyanides, aldehydes, and anilines

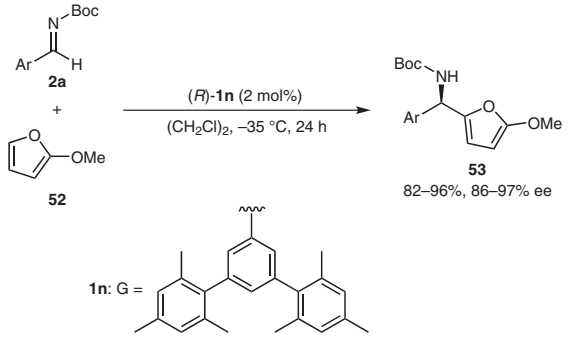
5 Friedel–Crafts and Related Reactions

Enantioselective Friedel–Crafts reactions using metal-based chiral catalysts or chiral organocatalysts have been investigated intensively, and provide atom-economical methods for the production of alkylated arenes in optically active forms.[55] The chiral phosphoric acid catalyzed Friedel–Crafts reaction was first accomplished via the activation of imines, but currently, the scope of electrophilic components has been broadened to include (α,β-unsaturated) carbonyl compounds, nitroalkenes, and others.

5.1 Friedel–Crafts Reaction via Activation of Aldimines or Hemiaminals

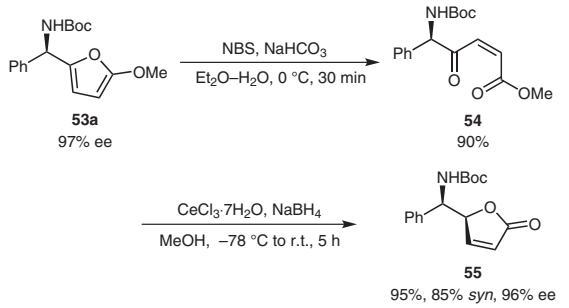
The Friedel–Crafts reaction via the activation of electrophiles functionalized by a nitrogen atom, such as imines, is undoubtedly the most practical approach to introduce a nitrogen-substituted side chain onto aromatic compounds. The enantioselective version of the Friedel–Crafts reaction of imines with electron-rich aromatic compounds enables efficient access to enantioenriched aryl methanamine derivatives. Several excellent approaches to highly enantioselective Friedel–Crafts reactions have been established using chiral phosphoric acid catalysts.

Terada and co-workers successfully demonstrated for the first time an enantioselective 1,2-aza-Friedel–Crafts reaction of 2-methoxyfuran (**52**) with *N*-Boc aldimines **2a** using a catalytic amount of chiral phosphoric acid (Scheme 20).[56] In the presence of 2 mol% **1n** having sterically hindered 3,5-dimesitylphenyl substituents, the corresponding Friedel–Crafts products **53** were obtained with excellent enantioselectivities, irrespective of the electronic properties of the aromatic imines **2a** employed. Most notable was that the reaction could be performed in the presence of as little as 0.5 mol% **1n** without any detrimental effects even on a gram scale (Ar = Ph: 95%, 97% ee).



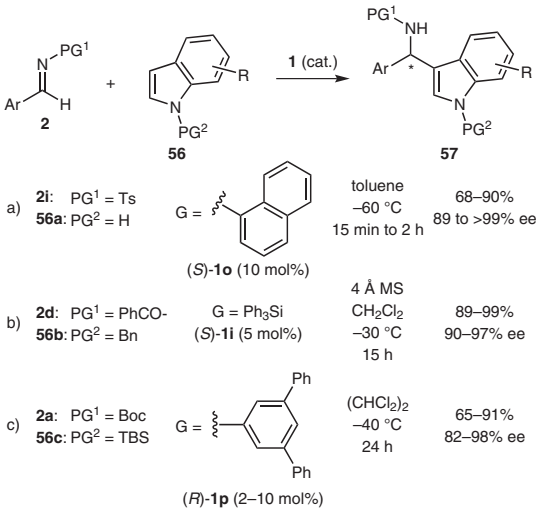
Scheme 20 1,2-Aza-Friedel–Crafts reaction of *N*-Boc imines **2a** with 2-methoxyfuran (**52**)

The synthetic utility of this transformation is highlighted by the derivatization of the furyl ring to form a γ-butenolide (Scheme 21). As the γ-butenolide architecture is a common building block in the synthesis of various natural products, Friedel–Crafts reaction product **53** represents a new addition to the synthetic precursors of nitrogen-containing molecules. The aza-Achmatowicz reaction, followed by reductive cyclization of 1,4-dicarbonyl intermediate **54** under Luche conditions, produced γ-butenolide **55** in good yield.



Scheme 21 Synthetic utility of furan-2-yl amine products

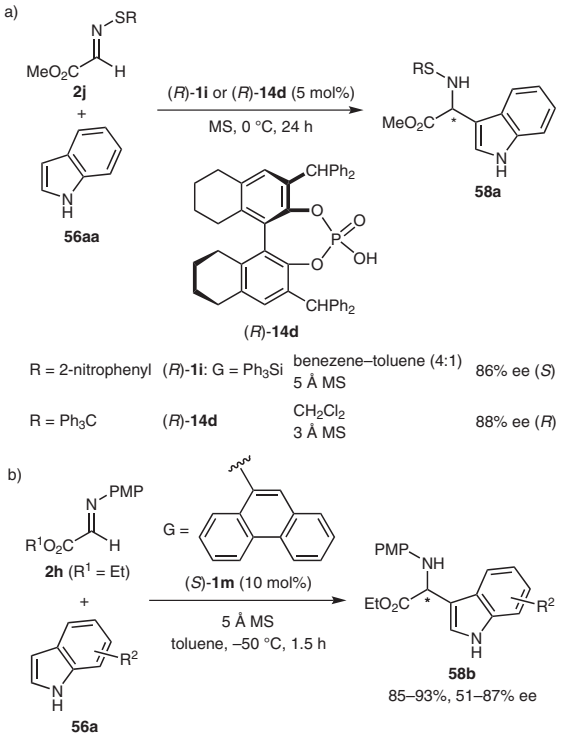
Further applications of the chiral phosphoric acid catalyzed 1,2-aza-Friedel–Crafts reaction were investigated by several research groups and the developed methods yielded a diverse array of optically active aryl methanamine derivatives with high enantioselectivities. In particular, the 1,2-aza-Friedel–Crafts reaction of indoles was intensively investigated because the enantioenriched products, namely, 3-indolyl methanamine derivatives, are widely known as valuable structures of pharmacophores and are present in thousands of natural products and many medicinal agents possessing versatile therapeutic effects.[57] You and co-workers (Scheme 22a),[58] Antilla and co-workers (Scheme 22b),[59] and Terada et al. (Scheme 22c)[60] almost simultaneously developed the highly enantioselective Friedel–Crafts reaction of indoles with aromatic imines. Their approaches differed in the substituents (G) of catalysts **1** introduced at the 3,3′-positions of the binaphthyl backbone and the protective group of imines **2**, and more interestingly, with or without the protective group at the nitrogen atom of indoles **56**. Goodman and Simón reported that, in the reaction of *N*-tosyl imine **2i** with unprotected indole **56a** (Scheme 22a), coordination between the phosphoric acid and both components, the imine and the indole, was observed by DFT calculations of the transition states.[61] These components were brought together under the chiral environment created by the chiral phosphoric acid catalyst through hydrogen bonds formed between the OH proton of the phosphoric acid and the nitrogen atom of imine **2i**, as well as the NH proton of indole **56a** and the phosphoryl oxygen. It is noteworthy that the enantioselectivities were as high as that observed in the reaction using unprotected indoles **56a**, even when N-protected indoles **56b** and **56c** were employed (Schemes 22b and 22c).



Scheme 22 1,2-Aza-Friedel–Crafts reaction of indoles **56** with aromatic imines

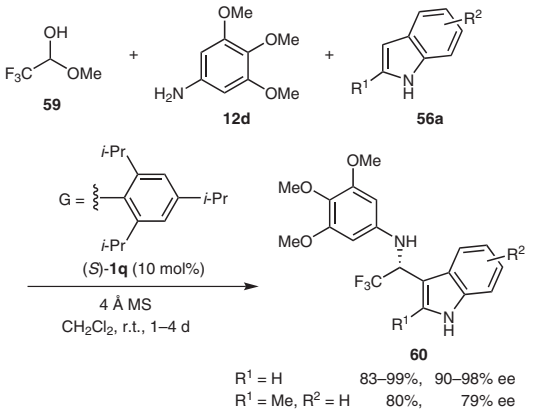
The reaction of α-imino esters as an electrophilic component was also reported independently by Hiemstra and co-workers (Scheme 23a)[62] and You and co-workers (Scheme 23b).[63] In Hiemstra's approach, indolyl glycine products **58a** were obtained with opposite absolute configurations, depending on the sulfur substituent as well as the structures of catalysts **1i** and **14d**, even when chiral phosphoric acids having axial chirality in the same *R*-configuration were employed.

Ma and co-workers reported an enantioselective synthesis of trifluoromethylated indole derivatives via the three-component coupling reaction among trifluoroacetaldehyde hemiaminal **59**, aniline derivative **12**, and indoles **56a** (Scheme 24).[64] Catalyst **1q** having bulky 2,4,6-triisopropylphenyl substituents worked well,[9b] giving the corresponding products **60** in excellent yields. In the present Friedel–Crafts reaction, the aniline derivative exhibited a marked effect on the enantioselectivity: 3,4,5-trimethoxyaniline (**12d**) gave products **60** with much higher enantioselectivities than 4-methoxyaniline (**12b**). Although the introduction of a substituent at the 2-position of the indole ring resulted in slight decreases in both reactivity and enantioselectivity, a wide range of functional groups, including electron-donating and electron-withdrawing sub-



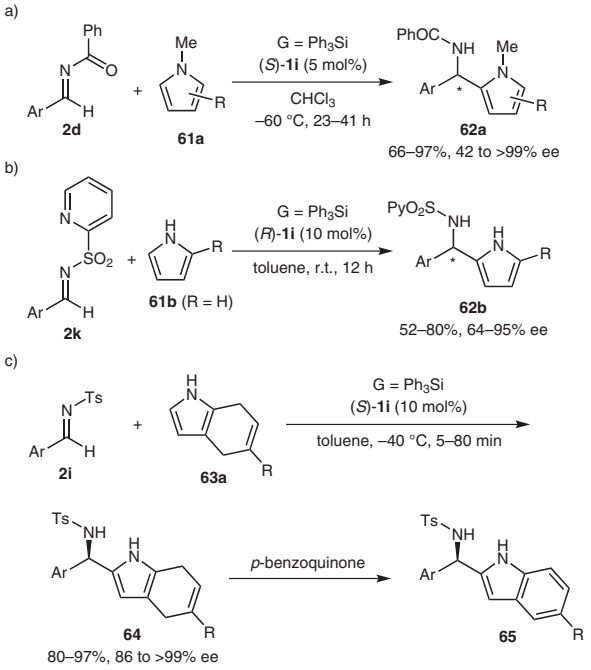
Scheme 23 1,2-Aza-Friedel–Crafts reaction of indoles **56** with α-imino esters

stituents, were tolerated by the indole ring. The authors extended this methodology to difluoroacetaldehyde hemiaminal to demonstrate the scope of this three-component reaction.



Scheme 24 Friedel–Crafts reaction via three-component coupling of trifluoroacetaldehyde hemiaminal **59**, aniline derivative **12d**, and indoles **56a**

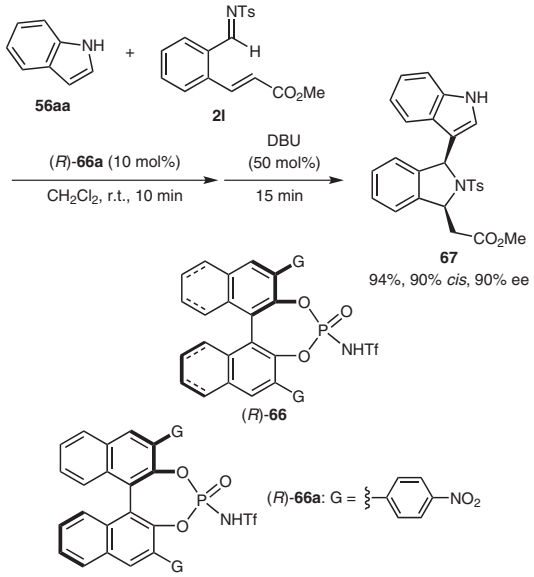
The enantioselective Friedel–Crafts reactions catalyzed by chiral phosphoric acids were further applied to such electron-rich aromatic compounds as pyrroles **61** (Schemes 25a and 25b)[65,66] and 4,7-dihydroindoles **63a** (Scheme 25c).[67] The reaction of 4,7-dihydroindoles **63a** yielded 2-substituted indole derivatives **65** after oxidation of Friedel–Crafts products **64**. This approach complements current studies of enantioselective Friedel–Crafts reactions of parent indoles **56**, where 3-substituted indole



Scheme 25 1,2-Aza-Friedel–Crafts reaction of pyrroles **61** and 4,7-dihydroindoles **63a**

derivatives **57** were obtained exclusively (see Scheme 22).

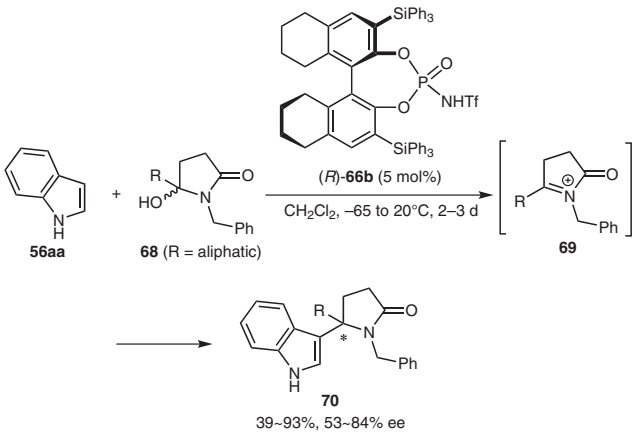
Enders et al. demonstrated the one-pot synthesis of enantioenriched isoindolines based on a consecutive transformation that involved a chiral Brønsted acid catalyzed Friedel–Crafts reaction followed by a base-catalyzed aza-Michael addition reaction using indole (**56aa**) and bifunctional ε-iminoenoates **2l** as substrates (Scheme 26).[68] In this one-pot transformation, the initial Friedel–Crafts reaction catalyzed by chiral BINOL-derived *N*-triflyl phosphoramide **66**, which was originally developed by



Scheme 26 One-pot synthesis of enantioenriched isoindolines **67** based on chiral Brønsted acid catalyzed Friedel–Crafts reaction/base-catalyzed aza-Michael addition sequence

Yamamoto and Nakashima,[69] followed by the DBU-promoted intramolecular aza-Michael addition, furnished isoindoline derivatives **67** in good yields with high diastereo- and enantioselectivities.

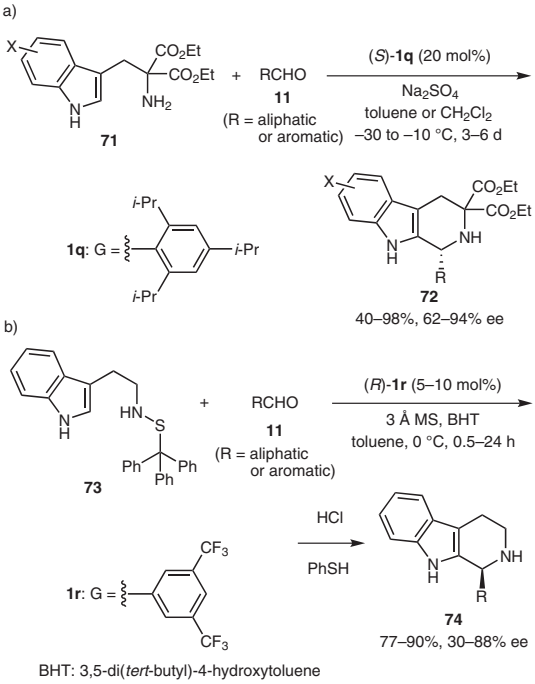
Rueping and Nachtsheim reported the nucleophilic substitution reaction of γ-alkyl-γ-hydroxylactams **68** with indole (**56aa**) catalyzed by chiral phosphoramide **66** (Scheme 27).[70] The reaction proceeds via in situ generated *N*-acyliminium ions **69** from **68** under the influence of **66b**. The reaction provides optically active γ-lactams **70** having a quaternary stereogenic center at the γ-position. The method furnishes an efficient approach to the γ-amino acid derivatives of biologically relevant molecules and can be extended to other nucleophilic components.



Scheme 27 Nucleophilic substitution reaction of γ-alkyl-γ-hydroxylactams **68** with indole

5.2 Pictet–Spengler Reaction

The Pictet–Spengler reaction of tryptamines and phenyl ethylamines with an aldehyde is a powerful and efficient method for the preparation of tetrahydro-β-carbolines and tetrahydroisoquinolines, respectively,[71] which are structural motifs of many alkaloids and related naturally occurring compounds. The enantioselective variants of the Pictet–Spengler reaction are in high demand because of the versatile synthetic applicability of the corresponding products to biologically active molecules. The reaction consists of a two-step transformation: an initial dehydrative imine formation, followed by an intramolecular Friedel–Crafts reaction. An excess amount of Brønsted acid is usually required to promote the reaction. List and co-workers accomplished the enantioselective Pictet–Spengler reaction by directly reacting substituted tryptamines **71** with aldehydes **11** in the presence of chiral phosphoric acid catalyst **1q** (Scheme 28a).[72] The method provided efficient access to tetrahydro-β-carboline derivatives **72** with high enantioselectivities, although the introduction of a *gem*-disubstituent adjacent to the reactive imine was required to suppress competing aldol pathways. Hiemstra and co-workers circumvented this intrinsic drawback, the requirement of a *gem*-disubstituent, by implementing an iminium ion strategy. They used *N*-sulfenyliminium ions as intermediates, generated from the reaction of *N*-sulfenyl tryptamines **73** with aldehydes **11**, in the Pictet–Spengler reaction and established an efficient method for the preparation of tetrahydro-β-carboline derivatives **74** in optically active forms using chiral phosphoric acid **1r** (Scheme 28b).[73] With this approach, not only aromatic but also aliphatic substituents can be introduced to the stereogenic center.

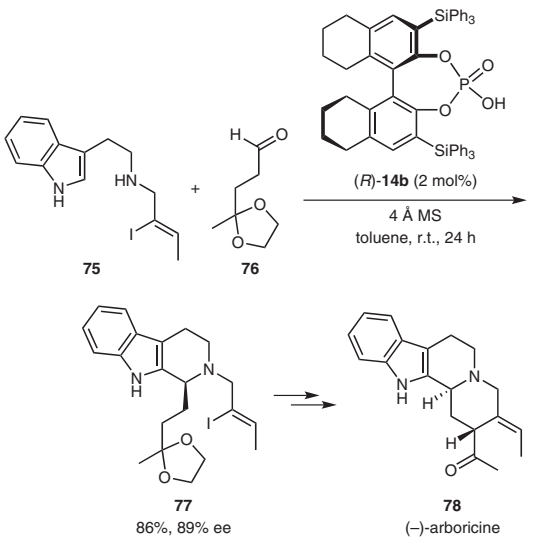


Scheme 28 Pictet–Spengler reaction of tryptamine derivatives with aldehydes

Hiemstra and co-workers applied their iminium ion strategy to natural product synthesis and accomplished the asymmetric total synthesis of the tetracyclic indole alkaloid (–)-arboricine (**78**) using the enantioselective Pictet–Spengler reaction as a key step (Scheme 29).[74] The Pictet–Spengler reaction of *N*-allyl-substituted tryptamine **75** with aldehyde **76** catalyzed by phosphoric acid **14b** gave the corresponding product **77** in good yield with high enantioselectivity.

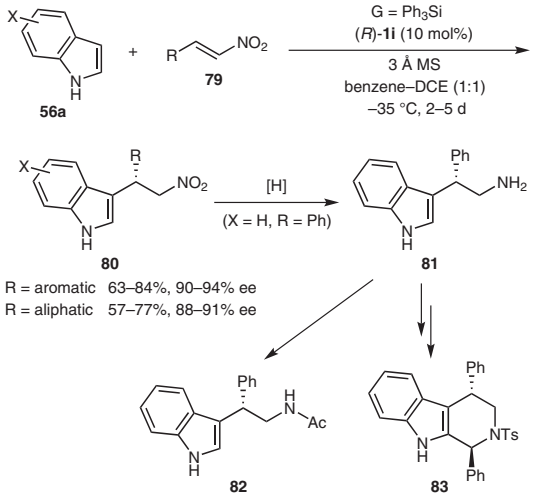
5.3 Friedel–Crafts Reaction via Activation of Nitroalkenes

The enantioselective Friedel–Crafts reaction of indoles with nitroalkenes has been known for a long time. This reaction offers considerable synthetic utility by enabling access to versatile precursors for the preparation of indole alkaloids. The enantioselective catalysis of this reaction has been investigated by using chiral catalysts, including metal complexes and organic molecules.[75] However, the enantioselectivities were not always good. Akiyama and co-workers developed a highly enantioselective Friedel–Crafts reaction of nitroalkenes **79** with indoles **56a** using chiral phosphoric acid **1i** (Scheme 30).[76] They pointed out



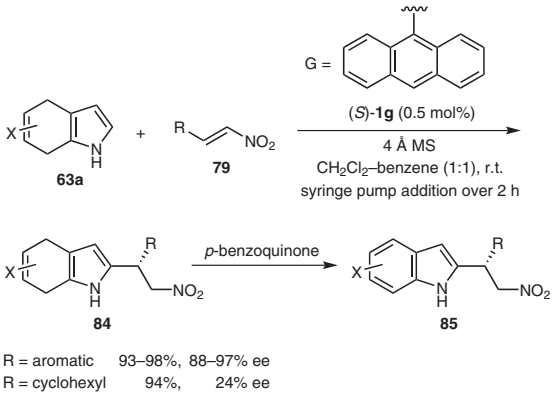
Scheme 29 Synthetic application of the enantioselective Pictet–Spengler reaction

the beneficial effects of molecular sieves on both chemical yield and enantioselectivity in the present Friedel–Crafts reaction. Among the molecular sieves tested, the MS 3A exhibited the best results, giving Friedel–Crafts products **80** in good yields with high enantioselectivities. The method is applicable not only to aromatic but also to aliphatic nitroalkenes. Friedel–Crafts product **80** can be readily transformed into tryptamine derivative **81** via a simple reduction of the nitro group, giving melatonin analogue **82** and tetrahydro-β-carboline derivative **83** without racemization. The reaction of *N*-methylindole **56d** provided a racemic Friedel–Crafts product in low yield and hence, the *N*-H moiety of indoles was deemed essential for accelerating the reaction as well as controlling the stereochemical outcome.



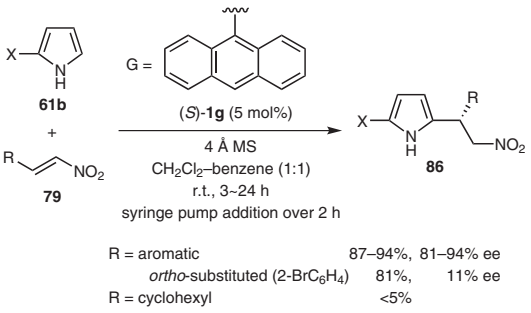
Scheme 30 Friedel–Crafts reaction of indoles **56** with nitroalkenes **79**

You and co-workers employed 4,7-dihydroindoles **63a**, instead of indoles **56**, in the Friedel–Crafts reaction with nitroalkenes **79** (Scheme 31).[77] Catalyst **1g** displayed excellent performance; however, the syringe pump technique was required to achieve high enantioselectivities because of considerable background reaction. Aromatic nitroalkenes **79** were useful substrates for this transformation. Meanwhile, the use of aliphatic nitroalkenes significantly decreased the enantioselectivity. Oxidation of Friedel–Crafts products **84** by *p*-benzoquinone provided 2-substituted indole derivatives **85** in excellent yield without racemization. As shown in Scheme 30, this approach complements the reaction of parent indoles **56** in which 3-substituted indole derivatives **80** are obtained exclusively.



Scheme 31 Friedel–Crafts reaction of 4,7-dihydroindoles **63a** with nitroalkenes **79**

Shortly thereafter, You and co-workers further extended the substrate scope to include pyrroles **61b** in the enantioselective Friedel–Crafts reaction of nitroalkenes **79**, giving products **86** in high yields and enantioselectivities (Scheme 32).[78]

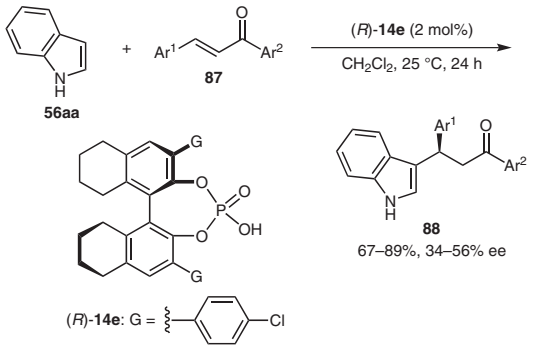


Scheme 32 Friedel–Crafts reaction of pyrroles **61b** with nitroalkenes **79**

5.4 Friedel–Crafts Reaction via Activation of Carbonyl Compounds

A number of enantioselective transformations have been established using chiral phosphoric acids via the activation of imines and related nitrogen-substituted functionalities. However, the activation of carbonyl compounds, including α,β-unsaturated carbonyl compounds, by chiral phosphoric acids has been limited and hence it is a challenging task to expand the synthetic utility of chiral phosphoric acid catalysts. Although the Friedel–Crafts

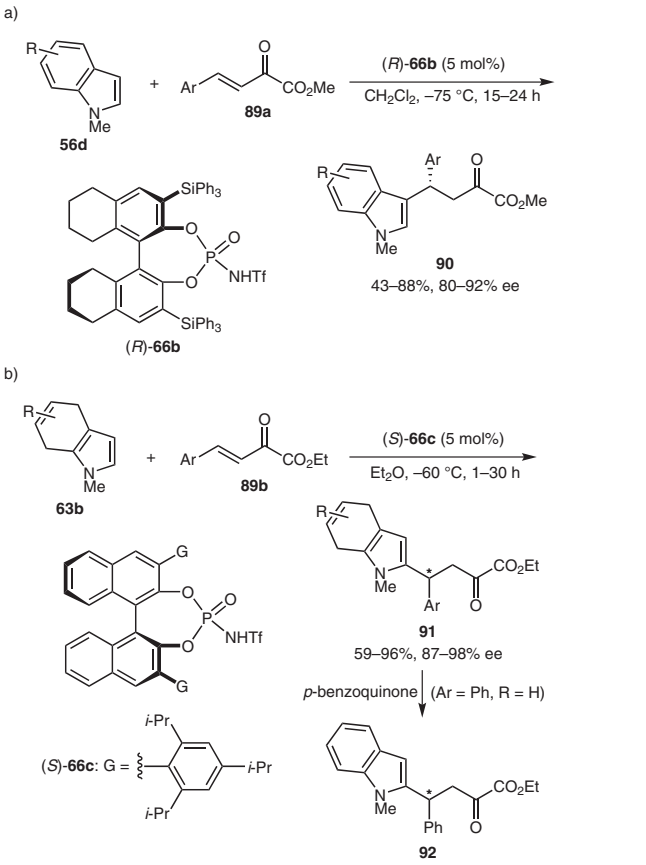
reaction with α,β-unsaturated carbonyl compounds involves fundamental transformations, simple α,β-unsaturated ketones are still challenging substrates in the chiral phosphoric acid catalyzed Friedel–Crafts reactions. Only moderate enantioselectivities were reported by Zhou, He, and co-workers in the Friedel–Crafts reaction of chalcone derivatives **87** with indole (**56aa**) using H_8-BINOL-derived chiral phosphoric acid **14e** as catalyst (Scheme 33).[79]



Scheme 33 Friedel–Crafts reaction of chalcone derivatives **87** with indole

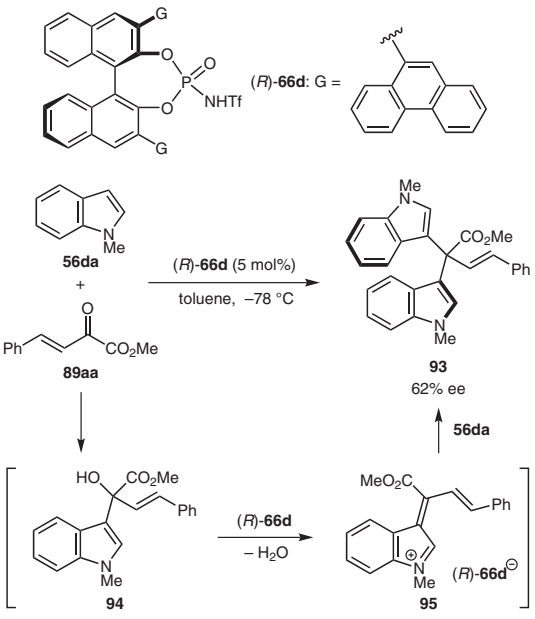
On the other hand, activated β,γ-unsaturated α-keto esters **89** functioned as efficient electrophiles in the enantioselective Friedel–Crafts reaction catalyzed by chiral phosphoramides **66** (Scheme 34). Rueping et al.[80] and You and co-workers[81] independently reported the enantioselective Friedel–Crafts reactions of β,γ-unsaturated α-keto esters **89** with *N*-methylindole **56d** (Scheme 34a) and *N*-methyl-4,7-dihydroindole **63b** (Scheme 34b), respectively. The use of chiral *N*-triflyl phosphoramide **66**, which was developed by Yamamoto and Nakashima[69] and is a stronger acid than chiral phosphoric acid, is crucial for the acceleration of the reaction. The C3 and C2 functionalization of the indole derivatives was accomplished to give **90** and **92**, respectively, in a highly enantioselective manner.

Rueping et al. also reported interesting regioselectivity (1,2- vs. 1,4-addition) in the Friedel–Crafts reaction of β,γ-unsaturated α-keto esters **89** with *N*-methylindole **56d** by tuning the steric and electronic effects of the substituents introduced at the 3,3′-positions of phosphoramide catalysts **66**. When a sterically demanding triphenylsilyl group was introduced at the 3,3′-positions of the binaphthyl backbone to give catalyst **66b**, 1,4-addition products **90** were obtained exclusively (Scheme 34a). In contrast, when aryl groups were introduced at the 3,3′-positions, the catalytic reaction yielded predominantly bisindolyl product **93**, which was derived from intermediary 1,2-addition product **94** under the acid-catalyzed conditions (Scheme 35).[80] The formation of bisindolyl products is well known in the reactions of aldehydes, ketones, and 1,2-diketones with indole derivatives catalyzed by Lewis and Brønsted acids.[82] However, most interestingly, this bisindolyl product **93** exhibited atropisomerism and was



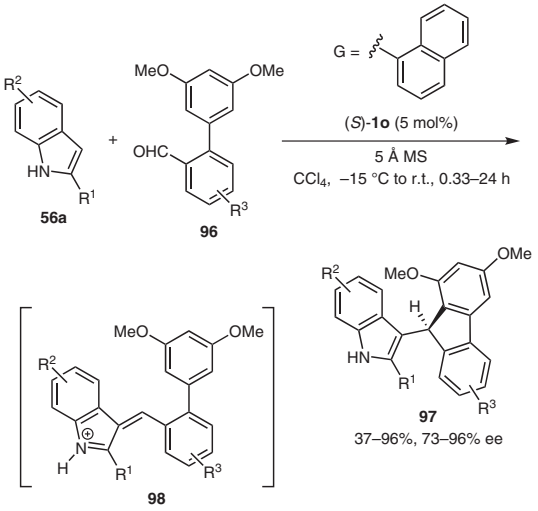
Scheme 34 Friedel–Crafts reaction of β,γ-unsaturated α-keto esters **89** with indole derivatives

separable as a stable isomer. After optimization of the catalyst substituents and the reaction conditions, the authors succeeded in obtaining bisindolyl product **93** in an atropisomeric ratio of 81:19 using catalyst **66d**.



Scheme 35 Formation of atropisomeric bisindolyl product **93** via 1,2-addition reaction

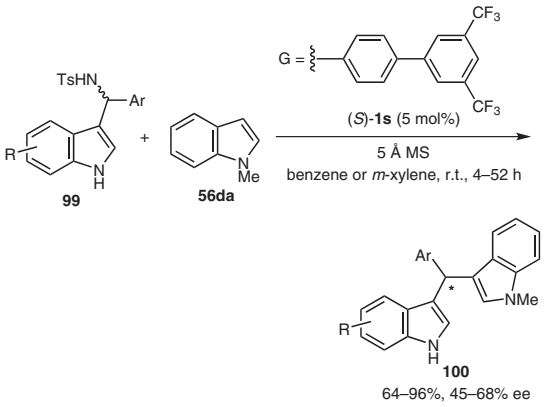
You and co-workers focused their attention on the formation of intermediary vinylogous iminium ion **95** during the transformation into bisindolyl products (Scheme 35). They successfully demonstrated the tandem intermolecular/intramolecular Friedel–Crafts reaction of indole **56a** with 2-formylbiphenyl derivatives **96** catalyzed by chiral phosphoric acid **1o** (Scheme 36).[83] In general, the use of molecular sieves enhanced the chemical yield and the enantioselectivity, because water is generated during the course of the second Friedel–Crafts reaction. Among those screened, MS 5A was the best, giving fluorene derivatives **97** in good yields with high enantioselectivities. In the reaction of *N*-methylindole derivative **56d**, both the reaction rate and the enantioselectivity (35% ee) deteriorated considerably and hence the *N*-H moiety of indoles **56a** functions not only to accelerate the reaction but also to efficiently control the stereoselectivity in the intermediary benzylidene indolium ion **98**.



Scheme 36 Tandem intermolecular/intramolecular Friedel–Crafts reaction of indole **56a** with 2-formylbiphenyl derivatives **96**

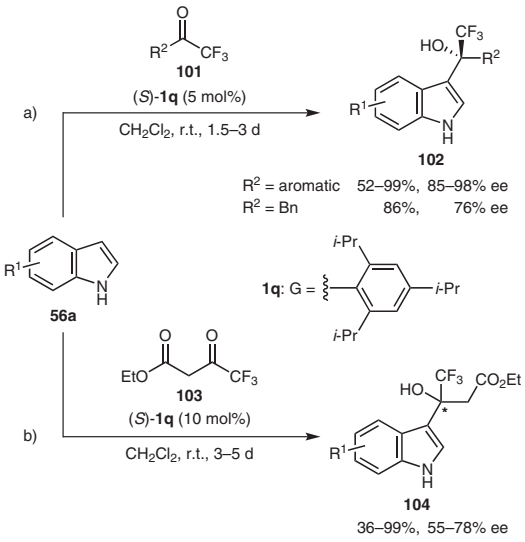
You and co-workers further applied the methodology to the in situ generation of the benzylidene indolium ion from *N*-tosyl(3-indolyl)methanamine **99** under the influence of chiral phosphoric acid **1s** (Scheme 37).[84] The method provides efficient access to the enantioselective synthesis of indole-containing unsymmetrically substituted triarylmethane derivatives **100**, albeit with moderate enantioselectivities. In this catalytic system, the authors observed an interesting feature: the kinetic resolution of racemic (3-indolyl)methanamine **99** by chiral phosphoric acid catalyst **1s**.

Ma and co-workers successfully developed the enantioselective Friedel–Crafts alkylation of indoles **56a** with trifluoromethyl ketones **101**, giving chiral tertiary alcohols **102** in good yields without the formation of bisindolyl byproducts (Scheme 38a).[85] Further substitution at the quaternary stereogenic center by indole **56a** would be efficiently suppressed by the trifluoromethyl group. Catalyst **1q** is also effective for the relatively less reactive



Scheme 37 Enantioselective synthesis of unsymmetrically substituted triarylmethanes **100**

trifluoromethyl alkyl ketone to afford the desired product in high yield albeit with a slight decrease in enantioselectivity. The method is applicable to the reaction of difluoromethyl- and perfluoroethyl-substituted phenyl ketones, giving the corresponding products with high enantioselectivities, and hence provides an efficient route to the asymmetric synthesis of tertiary alcohols bearing a fluorinated alkyl group in a highly enantioselective manner. Ma and co-workers also reported the enantioselective Friedel–Crafts alkylation of indoles **56a** with trifluoroacetoacetate **103** (Scheme 38b).[86] Optically active trifluoromethylated tertiary alcohols **104** were also obtained with moderate to high enantioselectivities.



Scheme 38 Friedel–Crafts reaction of trifluoromethyl-substituted ketones with indoles **56a**

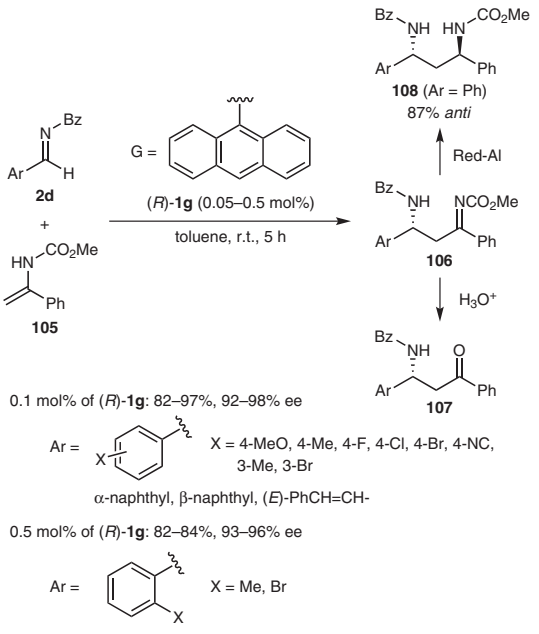
6 Ene (Type) Reactions

6.1 Aza-Ene-type Reaction of Aldimines with Enecarbamates

Kobayashi and co-workers pioneered the use of enamides or enecarbamates as nucleophiles in enantioselective reac-

tions with either glyoxylate-derived imines or glyoxylates catalyzed by chiral copper complexes.[87] The reaction using enamides or enecarbamates as nucleophilic components, namely, the aza-ene-type 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.

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 avoid loss of enantioselectivity. To ensure high efficiency, one of the greatest challenges in practical organocatalysis is to decrease the catalyst load.[3c,88] Terada et al. demonstrated a highly efficient organocatalytic reaction that uses phosphoric acid with a significantly low catalyst load in the aza-ene-type reaction (Scheme 39).[89] The reaction of aromatic imines **2d** with enecarbamates **105** could be accomplished in the presence of 0.1 mol% phosphoric acid catalyst **1g**. Both *para*- and *meta*-substitution to aromatic imines, or substitution to fused aromatic and α,β-unsaturated imines, resulted in excellent chemical yields and enantioselectivities, irrespective of the electronic properties of the substituents. Although *ortho*-substitution reduced the catalytic efficiency, giving products **106** in moderate chemical yields, the yields were improved by increasing the catalyst load to 0.5 mol%. It is noteworthy that the reaction can be performed without considerable loss of enantioselectivity even when the catalyst load is decreased to as little 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 predominantly the *anti*-1,3-diamine derivatives **108**.

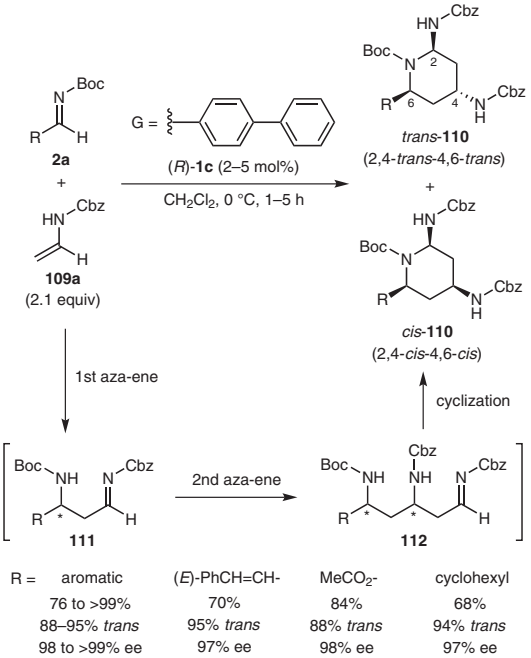


Scheme 39 Enantioselective aza-ene-type reaction under low catalyst load

6.2 Cascade Transformation 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 academia and industry. One approach is the use of catalytic enantioselective cascade reactions[90] 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.

Terada et al. successfully applied the aza-ene-type reaction to the cascade transformation by taking advantage of the formation of imine products (Scheme 40).[91] They employed monosubstituted enecarbamates **109**[87f] instead of the disubstituted versions and, as a result, piperidine derivatives **110** with multiple stereogenic centers were obtained with high stereoselectivities. The acid-catalyzed aza-ene-type reaction of initial aldimines **2a** with monosubstituted enecarbamates **109a** afforded aza-ene-type products of *N*-acyl aldimines **111** as reactive intermediates and **111** underwent further aza-ene-type reaction to generate aldimines **112**. The intramolecular cyclization of intermediate **112** 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 **2a** could be used in this 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 **110** with multiple ste-



Scheme 40 One-pot access to piperidine derivatives **110** via tandem aza-ene-type reaction/cyclization cascade

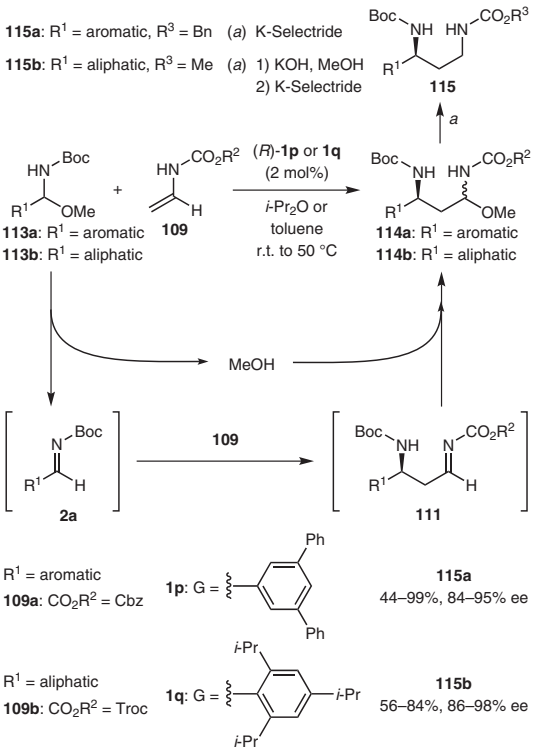
reogenic centers, as key structural elements of natural products.

6.3 Two-Carbon Homologation Reaction

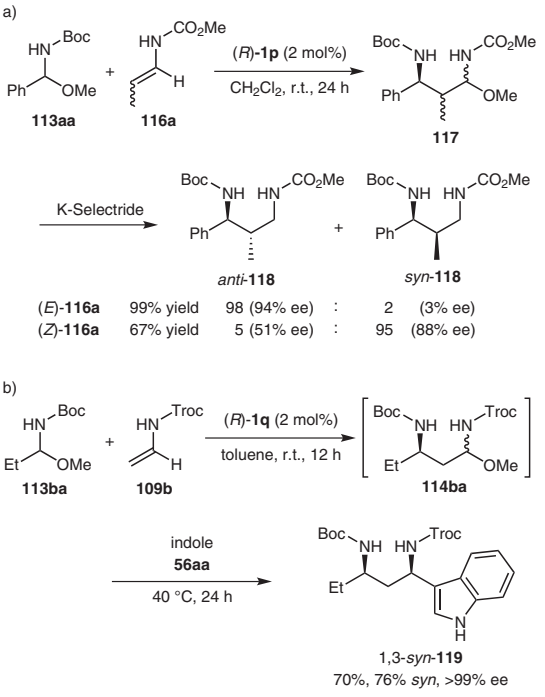
The homologation of a carbon unit is an important and fundamental methodology in the construction of carbon frameworks in synthetic organic chemistry. Much attention has been devoted to the development of the two-carbon homologation reaction using acetaldehyde anion equivalents, as these can be directly utilized in further transformations.[92] From a synthetic viewpoint, monosubstituted enecarbamates are attractive as acetaldehyde anion equivalents for the two-carbon homologation reaction because they are readily available and can provide aldimine products.[87f,93] These aldimines can be directly transformed into 1,3-diamine derivatives when the two-carbon homologation reactions are conducted with imines as the substrate.

Although the high reactivity of aldimine products **111** hindered the completion of the two-carbon homologation reaction because of overreaction, Terada et al. neatly demonstrated two-carbon homologation using enecarbamates **109** and hemiaminal ethers **113**, instead of imines **2a**, as the substrate (Scheme 41).[94] In the acid-catalyzed reaction of hemiaminal methyl ethers **113**, intermediary and reactive aldimine **111** was trapped by methanol that was generated during the formation of imine **2a**. A series of aromatic hemiaminal ethers **113a** were employable for this homologation reaction in the presence of phosphoric acid catalyst **1p**, giving hemiaminal products **114a** with high enantioselectivities. The enantioselectivities were determined only after the reduction of the hemiaminal moiety to 1,3-diamine derivatives **115**, although the reactivity of hemiaminal ethers **113a** was considerably dependent on the electronic properties of the substituents on the aromatic ring. Aliphatic hemiaminal ethers **113b** were also applicable to the present homologation, but in this case, protection of the nitrogen atom of **119** by the more electron-withdrawing trichloroethoxycarbonyl (Troc) group was required to suppress the formation of byproducts.

This homologation reaction can be applied to substituted enecarbamate **116a** (Scheme 42a). Either *anti*- or *syn*-products **118** were obtained in a highly diastereoselective manner from the respective geometric isomers of enecarbamates **116a**, and each of the major diastereomers **118**, furnished by the reduction of the hemiaminal moiety of **117**, exhibited good to high enantioselectivities. The synthetic utility of this homologation is highlighted by the sequential transformation of the homologation/Friedel–Crafts reaction in one pot (Scheme 42b). Catalyst **1q** also accelerated the Friedel–Crafts reaction of hemiaminal ether **114ba** with indole (**56aa**) to afford the desired 1,3-diamine derivatives **119** in good yields and nearly optically pure forms, albeit with only moderate *syn*-diastereoselectivities. The method enables facile access to highly enantioenriched 1,3-diamine derivatives as pharmaceutically and biologically intriguing molecules.



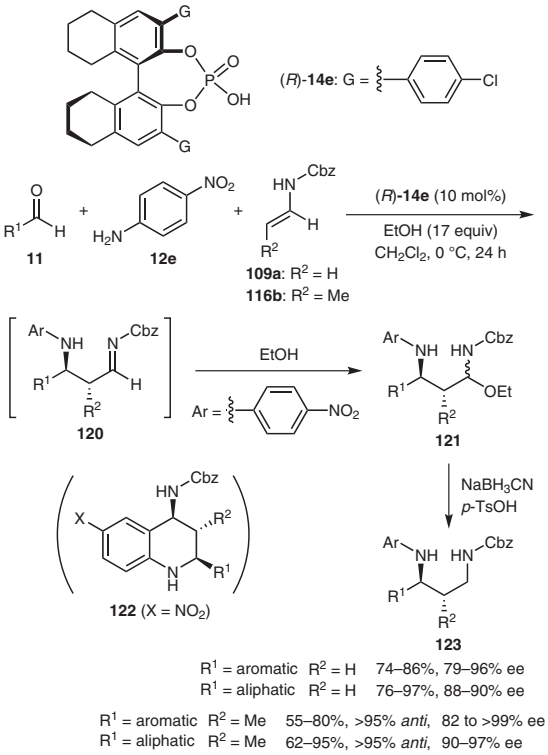
Scheme 41 Two-carbon homologation of hemiaminal ethers by enecarbamate



Scheme 42 Application of the two-carbon homologation reaction

Shortly thereafter, Masson, Zhu, and co-workers developed a multicomponent approach to the two-carbon homologation reaction among aldehydes **11**, anilines **12**, and enecarbamates **109** in the presence of excess ethanol as the trapping reagent to intercept initial product **120** (Scheme 43).[95] The use of aniline derivative **12e**, with its electron-withdrawing nitro group, resulted exclusively in

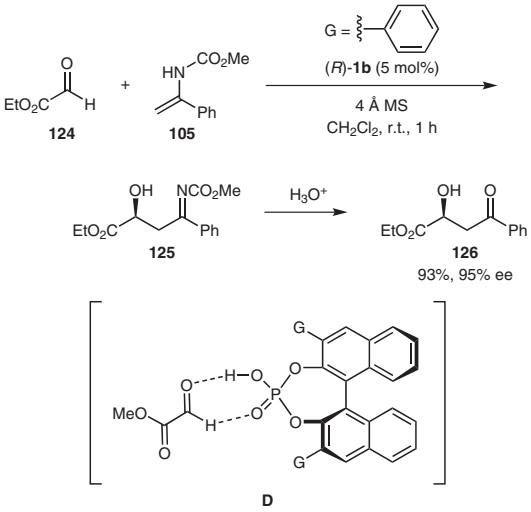
four-component adducts **121** at the expense of the Povarov products, tetrahydroquinolines **122**, which were formed from the inverse-electron-demand aza-Diels–Alder reaction of *N*-aryl imines with enecarbamate **109** (see Section 7.3).[96] In this regard, tetrahydroquinolines **122** were the only products obtained in the absence of ethanol under otherwise identical conditions. Aromatic as well as aliphatic aldehydes **11** can be used in the present four-component reaction, affording hemiaminal ethyl ethers **121** in good yields with high enantioselectivities. The potential of this multicomponent reaction is further demonstrated using substituted enecarbamate **116b**. The reaction of 4-nitroaniline (**12e**) and (*E*)-**116b** with a range of aromatic and aliphatic aldehydes **11** gave *anti*-products **123** with high diastereoselectivities (>95% *anti*) after the reduction of the hemiaminal moiety of **121**.



Scheme 43 Two-carbon homologation via multicomponent approach

6.4 Aza-Ene-type Reaction of Aldehyde with Enecarbamates

Terada et al. accomplished the enantioselective activation of aldehydes using a chiral phosphoric acid catalyst.[97] Their aza-ene-type reaction of glyoxylate **124** as a reactive aldehyde with enecarbamate **105** afforded the corresponding products **125** with excellent enantioselectivities (Scheme 44).[87d–g] Catalyst **1b** efficiently accelerated the aza-ene-type reaction of glyoxylate **124** in the presence of MS 4A, which was employed as a scavenger of acidic impurities.[98] After hydrolysis of products **125** to β-hydroxy ketones **126**, excellent enantioselectivities were observed even when catalyst **1b**, bearing unmodified phenyl groups (G = Ph), was used. 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, bulky ones in general, to achieve high enantioselectivities. To rationalize the stereochemical outcome, Terada and co-workers[97] proposed double hydrogen-bonding interaction **D** as the complexation mode[99] of glyoxylate **124** and phosphoric acids **1** on the basis of a screening of catalysts **1** having a series of substituted phenyl rings instead of simple phenyl groups, and DFT computational analysis of the hydrogen-bonding interaction between glyoxylate **124** and phosphoric acids **1** (Scheme 44). The additional hydrogen bond that exists between the formyl hydrogen atom and the phosphoryl oxygen atom creates a coplanar orientation between the formyl group and the phosphoric acid subunit,[100] and hence the formyl carbon of glyoxylate **124** would be exposed to an efficient chiral environment created by the phosphoric acid catalyst.

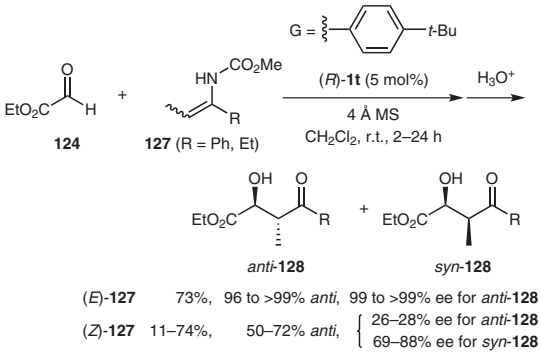


Scheme 44 Aza-ene-type reaction of glyoxylate **124** with enecarbamate **105** catalyzed by (*R*)-**1b**

The applicability of the aza-ene-type reaction of glyoxylate **124** with a series of substituted enecarbamates **127** demonstrates the stereochemical issue of enantio- and diastereoselection (Scheme 45). Catalysts **1t** exhibited excellent performance in the reaction of (*E*)-**127** to give *anti*-products **128** in nearly optically pure forms. However, (*Z*)-**127** retarded the reaction markedly and low enantioselectivity was observed for major *anti*-**128**. The exclusive formation of *anti*-products from the *E*-isomers could be attributed to the well-defined *exo*-transition state.[87d]

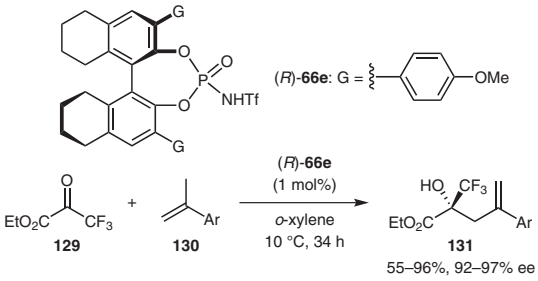
6.5 Carbonyl-Ene Reaction

The carbonyl-ene reaction is an important carbon–carbon bond-forming reaction that affords synthetically valuable homoallylic alcohols.[101] The enantioselective catalysis of the carbonyl-ene reaction has been extensively investigat-



Scheme 45 Diastereo- and enantioselective aza-ene-type reaction of glyoxylate **124** with enecarbamate **127**

ed using chiral metal complexes.[102] However, no highly enantioselective organocatalysis of the carbonyl-ene reaction was reported[103] until the work of Rueping et al.,[104] who used chiral phosphoramide **66**[69] as the strongly acidic catalyst (Scheme 46). The reaction of trifluoropyruvate **129** with α-methyl styrene derivatives **130** in the presence of chiral phosphoramide **66e** gave the corresponding homoallylic alcohols **131**, having the quaternary stereogenic center substituted by a trifluoromethyl group, with high enantioselectivities.

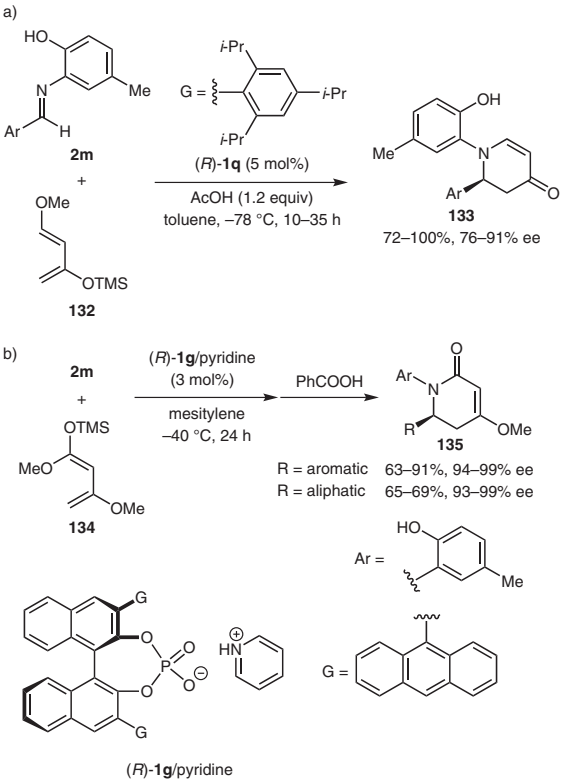


Scheme 46 Carbonyl-ene reaction of trifluoropyruvate **129** with α-methyl styrene derivatives **130**

7 Cycloaddition Reactions

7.1 Hetero-Diels–Alder Reaction of Aldimines

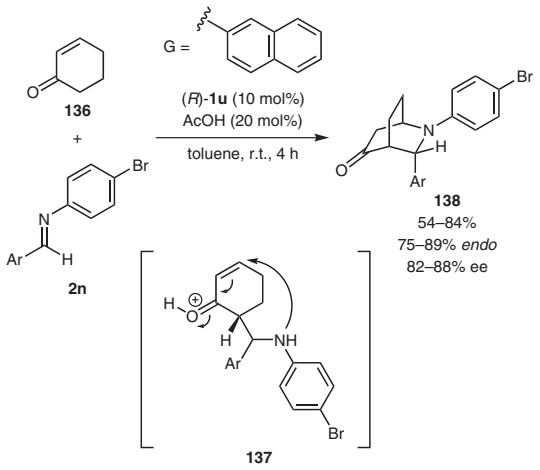
The enantioselective hetero-Diels–Alder reaction of siloxydienes, such as Danishefsky's and Brassard's dienes, with imines provides an efficient route for the preparation of functionalized nitrogen heterocycles in optically active forms, which can be utilized as synthetic precursors of biologically interesting alkaloid families and aza sugars. Akiyama et al. developed the enantioselective hetero-Diels–Alder reaction of Danishefsky's diene (**132**) with aromatic imines **2m** using chiral phosphoric acid catalyst **1q** (Scheme 47a).[105] The reaction catalyzed by **1q** provided dihydropyridin-4(1*H*)-one derivatives **133** in good yields with high enantioselectivities in the presence of acetic acid as the stoichiometric additive. Akiyama and co-workers also reported an enantioselective hetero-Diels–Alder reaction of Brassard's diene (**134**) with imines **2m** (Scheme 47b).[106] One of the intrinsic problems associated with Brassard's diene lies in its instability under acidic conditions. In order to suppress the decomposition of the diene by the phosphoric acid catalysts, they employed pyridinium salts of the catalysts. The pyridinium salt of **1g** displayed excellent performance for the hetero-Diels–Alder reaction of Brassard's diene with a broad range of imines, including aromatic and aliphatic derivatives. Uniformly high enantioselectivities and chemical yields of dihydropyridin-2(1*H*)-one products **135** were noted after treatment with an acid.



Scheme 47 Enantioenriched nitrogen heterocycles by hetero-Diels–Alder reaction of siloxydienes

7.2 Direct Cycloaddition Reaction of Aldimines with Cyclohexenone

Gong and co-workers[107] and Rueping and Azap[108] independently reported the enantioselective direct cycloaddition reaction of cyclohexenone **136** with aromatic imines **2n**. Rueping and Azap employed acetic acid as the co-catalyst to accelerate the tautomerization of cyclohexenone **136**, by which a reactive dienol for the enantioselective cycloaddition was generated in situ (Scheme 48). They proposed a stepwise mechanism for the reaction. The initial step is the chiral phosphoric acid **1u** catalyzed Mannich reaction of imines **2n** with the dienol generated in the presence of acetic acid, giving intermediate **137**. The subsequent intramolecular aza-Michael reaction provides the corresponding cycloaddition products **138**, the so-called isoquinuclidine derivatives, in moderate to good yields.

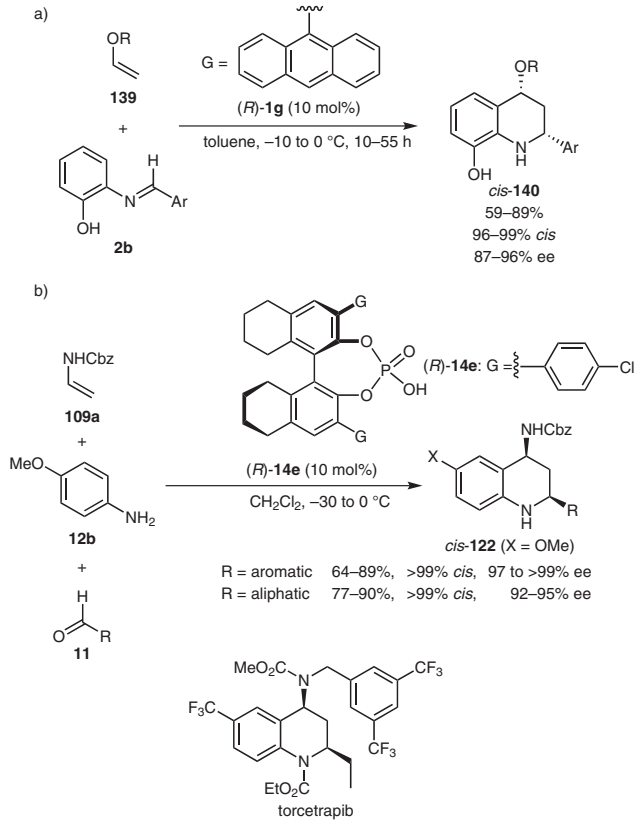


Scheme 48 Direct cycloaddition reaction of imines with cyclohexenone

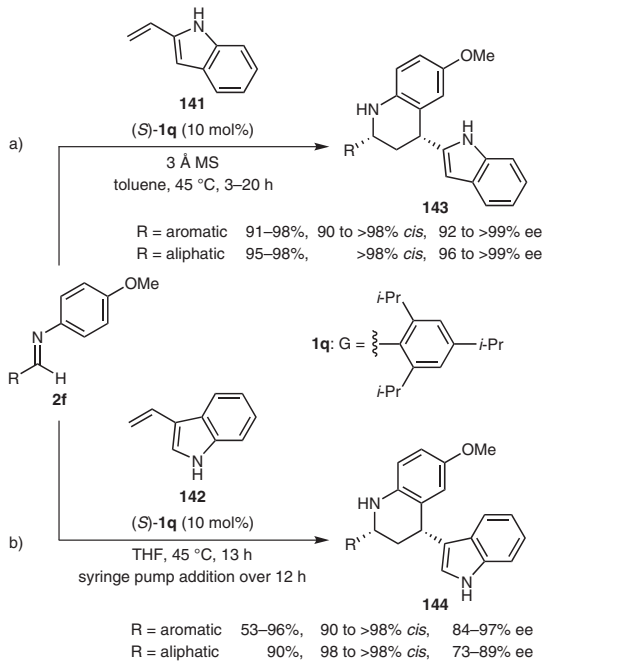
7.3 Inverse-Electron-Demand Aza-Diels–Alder Reaction (Povarov Reaction)

The Povarov reaction, an inverse-electron-demand aza-Diels–Alder reaction of 2-azadienes with electron-rich alkenes, enables facile access to tetrahydroquinoline derivatives of pharmaceutical and biological importance. Akiyama et al. developed the highly enantioselective Povarov reaction of *N*-aryl imines **2b** with vinyl ethers **139** using chiral phosphoric acid **1g** (Scheme 49a).[109] The method provides an efficient approach to enantioenriched tetrahydroquinolines **140** having an oxygen functionality at the 4-position. Masson, Zhu, and co-workers applied a three-component coupling process to the enantioselective Povarov reaction using enecarbamates **109**, instead of vinyl ethers **139**, as electron-rich alkenes (Scheme 49b).[96] The three-component approach employing 4-methoxyaniline (**12b**), enecarbamate **109a**, and aldehydes **11** in the presence of chiral phosphoric acid **14e** is applicable to a broad range of aromatic aldehydes, giving the corresponding products **122** with excellent enantioselectivities, irrespective of their electronic properties. Aliphatic aldehydes were also applicable to the present reaction. Interestingly, tetrahydroquinolines **140** and **122** have different absolute stereochemistries (Scheme 49a vs. 49b), although the chiral phosphoric acid catalysts have the same axial chirality. Masson, Zhu, and co-workers further demonstrated the power of the present reaction in the enantioselective synthesis of torcetrapib, an inhibitor of cholesteryl ester transfer protein.[96]

Vinylindole derivatives are also good candidates for the Povarov reaction because of their peculiar reactivity as electron-rich alkenes. Ricci and co-workers successfully demonstrated the enantioselective Povarov reaction of *N*-aryl imines with 2-vinylindoles and 3-vinylindoles (Scheme 50).[110] Phosphoric acid catalyst **1q** functioned as an efficient catalyst for the reaction of 2-vinylindole (**141**) with a variety of imines **2f**, affording the corresponding cycloadducts **143** in good yields with high stereoselectivities (Scheme 50a). However, the conditions that were optimized for the reaction of 2-vinylindole (**141**) could not be applied to that of 3-vinylindole (**142**), because **142** is much more sensitive to the acidic catalyst than **141**. After thorough optimization of the reaction conditions, namely,



Scheme 49 Inverse-electron-demand aza-Diels–Alder reaction (Povarov reaction)

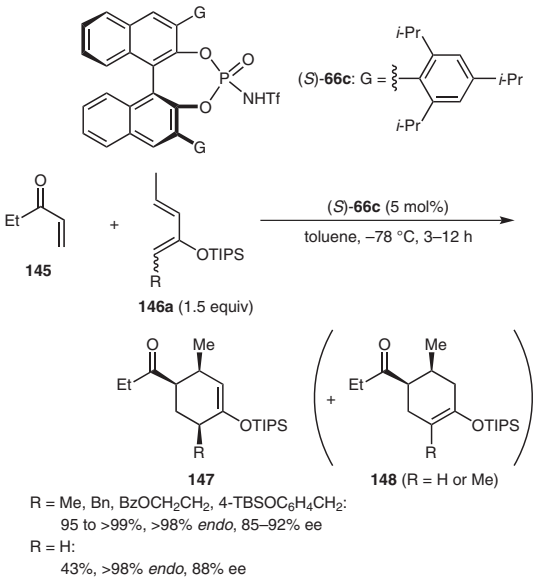


Scheme 50 Inverse-electron-demand aza-Diels–Alder reaction (Povarov reaction) of vinylindoles

use of a coordinating solvent such as tetrahydrofuran and the slow addition of **142** over 12 hours, cycloadducts **144** were obtained (Scheme 50b) with results that were comparable to those of **143** using the same catalyst **1q**. A variety of aryl substituents introduced at the nitrogen atom can be utilized in this reaction, giving the cycloadducts in high yields with excellent stereoselectivities.

7.4 Diels–Alder Reaction of Enone

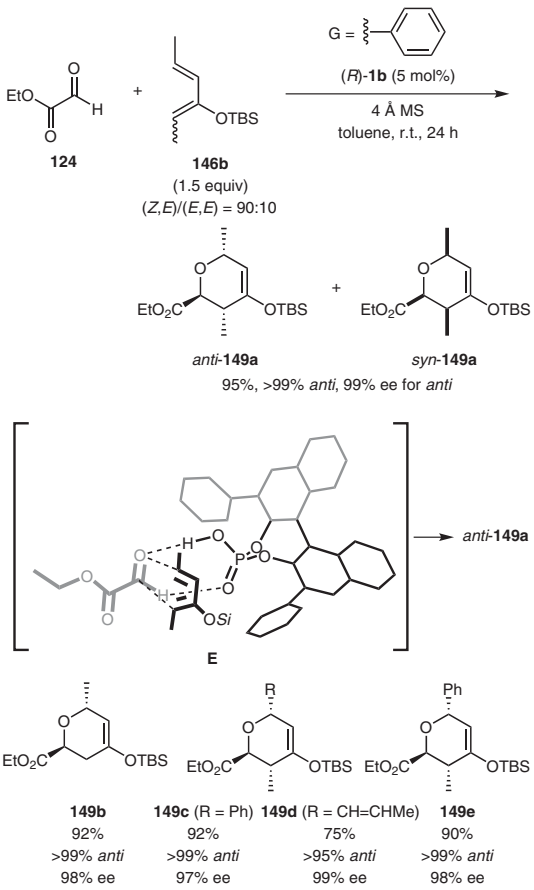
The enantioselective Diels–Alder reaction of α,β-unsaturated carbonyl compounds with dienes is one of the most well-studied transformations using chiral metal catalysts[111] and organocatalysts.[112] However, chiral phosphoric acids do not effectively accelerate the Diels–Alder reaction of α,β-unsaturated carbonyl compounds because they lack sufficient acidity to activate these dienophiles. Yamamoto and Nakashima overcame this intrinsic drawback by designing a novel chiral Brønsted acid catalyst with improved acidity (Scheme 51).[69] They successfully developed stronger chiral Brønsted acids, *N*-triflyl phosphoramides **66**, by introducing a strong electron acceptor, the TfN-H group,[113] into the phosphoric acid subunit in place of the phosphoric acid O-H group. *N*-Triflyl phosphoramide catalyst **66c** exhibited significant activity in the reaction of α,β-unsaturated ketone **145** with siloxydienes **146a**, affording enantioenriched cycloadducts **147** in excellent yields in most cases, although the yields were quite sensitive to the stability of the siloxydiene **146a**, because the protonation of the diene resulted in silylation and thus deactivation of the catalyst. In contrast, parent phosphoric acid **1b** (G = Ph) showed no catalytic activity and thus, the introduction of the electron-withdrawing NTf group into the phosphoric acid is quite effective in increasing the catalytic activity. The reaction of non-substituted and methyl-substituted siloxydienes at the R group furnished olefin regioisomers **148**. However, olefin migration was not observed when sterically demanding substituents, such as benzyl moieties, were employed as the R group.



Scheme 51 Diels–Alder reaction of enone **145** with siloxydienes **146** catalyzed by *N*-triflyl phosphoramide **66c**

7.5 Hetero-Diels–Alder Reaction of Aldehydes

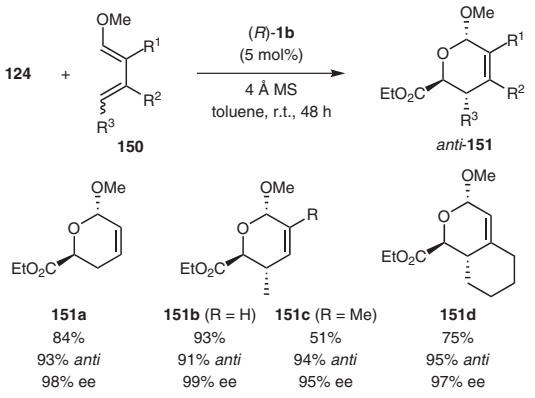
The hetero-Diels–Alder reactions of dienes with aldehydes are an efficient way to provide dihydropyran derivatives.[114] The development of catalytic enantio- and diastereoselective variants is an area of considerable importance.[115] Extensive studies of the use of chiral Lewis acid catalysts to control high levels of stereoselectivity have been conducted.[116] It is noteworthy that vicinal substituents of the dihydropyran are controlled exclusively in a *syn*-selective manner, where the diene approaches the aldehyde with an *endo*-orientation, presumably because of secondary π-orbital interactions and more importantly to avoid steric repulsion between the incoming diene and the sterically demanding Lewis acid catalyst.[117] In contrast, alternative *exo*-oriented enantioselective processes that afford *anti*-isomers have yet to be fully established.[118] Terada and co-workers developed an unprecedented *anti*- and enantioselective hetero-Diels–Alder reaction of siloxy- or methoxydienes with glyoxylate **124** using chiral phosphoric acid catalyst **1** (Schemes 52 and 53).[119] Catalyst **1b**, bearing unmodified phenyl groups (G = Ph), exhibited excellent performance in the hetero-Diels–Alder



Scheme 52 Hetero-Diels–Alder reaction of siloxydienes **146** with glyoxylate **124** catalyzed by (*R*)-**1b**

reaction of glyoxylate **124** with *tert*-butyldimethylsilyl-protected siloxydienes **146b**, giving the corresponding product **149a** in high yield with extremely high stereoselectivity (Scheme 52). It is noteworthy that chiral phosphoric acid **1b** is uniquely efficient in affording *anti*-cycloadduct **149a** as the single diastereomer in nearly optically pure form. In order to rationalize this unprecedented *anti*-selectivity observed in the **1b**-catalyzed reaction, they proposed *exo*-transition state **E**,[120] where the small phenyl groups at the 3,3′-positions of **1b** allow the diene to occupy an *exo*-position, giving the *anti*-isomer exclusively.

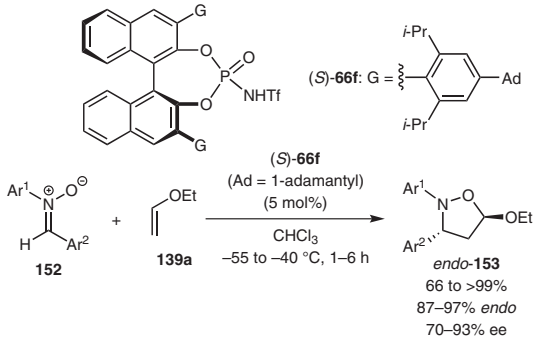
The *anti*- and enantioselective hetero-Diels–Alder reaction catalyzed by **1b** is applicable to a series of 2-siloxydienes, giving the corresponding products **149** in good yields with excellent stereoselectivities (Scheme 52). Although the alkenyl-substituted siloxydiene resulted in a decrease in reactivity, the stereoselectivity was maintained at a high level. Furthermore, methoxydienes **150** were also well tolerated, providing the corresponding *anti*-dihydropyrans **151** predominantly with excellent enantioselectivities (Scheme 53).



Scheme 53 Hetero-Diels–Alder reaction of methoxydienes **150** with glyoxylate **124** catalyzed by (*R*)-**1b**

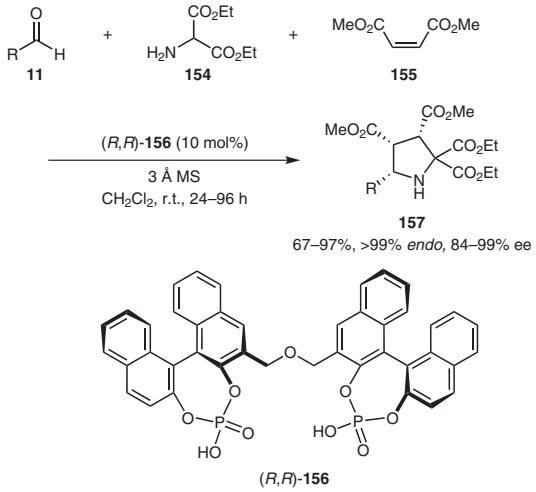
7.6 1,3-Dipolar Cycloaddition Reactions

The 1,3-dipolar cycloaddition reaction of nitrones with vinyl ethers provides an efficient route to 1,3-amino alcohols,[121] which can be transformed from the corresponding isoxazolidine products through reductive cleavage of the nitogen–oxygen bond. The development of the catalytic enantioselective 1,3-dipolar cycloaddition reaction is hence a vital step toward the efficient synthesis of these amino alcohols in optically active forms. Yamamoto and co-workers successfully developed the enantioselective 1,3-dipolar cycloaddition reaction of diaryl nitrones **152** with ethyl vinyl ether (**139a**) (Scheme 54).[122] They applied acidic NHTf-substituted chiral phosphoramide catalysts **66**, originally developed by the same research group,[69] to the present dipolar cycloaddition reaction. Chiral phosphoramide **66f** effectively catalyzed the cycloaddition reaction to give the corresponding isoxazolidine derivatives **153** in high yields. The introduction of an electron-withdrawing group to the aromatic ring, Ar^2, is necessary to ensure the high enantioselectivity. In addition, *endo*-**153** was furnished as the major diastereomer in the present reaction. The predominance of *endo*-products contrasted the formation of *exo*-isomers as major products under Lewis acid catalysis.[123]



Scheme 54 1,3-Dipolar cycloaddition reaction of nitrones **152** with ethyl vinyl ether (**139a**)

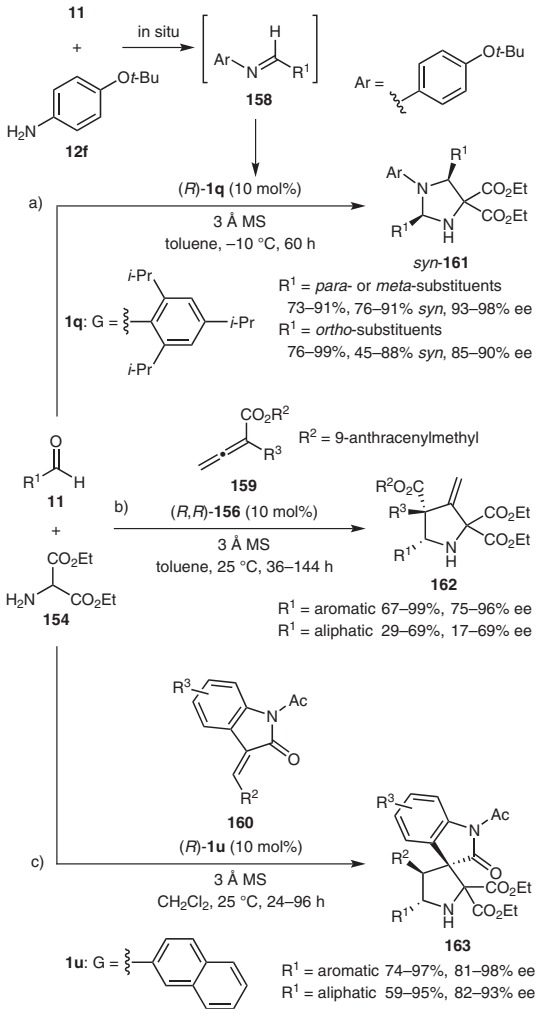
The asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides with electron-deficient olefins provides chiral pyrrolidine derivatives, an important class of nitrogen heterocycles,[121c,124] as the precursors of biologically active compounds. Gong and co-workers reported the enantioselective catalysis by chiral Brønsted acids in the three-component 1,3-dipolar cycloaddition reaction among aldehydes **11**, α-amino-1,3-dicarbonyl compounds **154**, and maleate **155** as an electron-deficient dipolarophile (Scheme 55).[125] As none of the chiral monophosphoric acids **1** provided sufficient enantioselectivities, they developed the new bisphosphoric acid **156**, derived from linked BINOL, that displayed excellent performance in this cycloaddition reaction in terms of diastereo- and enantioselectivities as well as catalytic efficiency. A broad range of aldehydes **11**, including aromatic and α,β-unsaturated aldehydes, were used in the reaction, giving



Scheme 55 1,3-Dipolar cycloaddition reaction via three-component coupling

the corresponding pyrrolidine derivatives **157** with excellent *endo*- and enantioselectivities.

Gong and co-workers further developed an enantioselective three-component 1,3-dipolar cycloaddition reaction among aldehydes **11**, α-amino-1,3-dicarbonyl compound **154**, and a series of electron-deficient dipolarophiles, namely, *N*-aryl imines **158**, 2,3-allenoates **159**, and methyleneindolinones **160** (Scheme 56). The reaction of *N*-aryl imines **158** as the dipolarophiles, generated in situ from aldehydes **11** and 4-*tert*-butoxyaniline (**12f**), afforded diastereomeric mixtures of cycloadducts **161** with excellent enantioselectivities under the influence of phosphoric acid **1q** (Scheme 56a).[126] The diastereoselectivities were markedly dependent on the substitution pattern of the aldehyde **11**. The s*yn*-isomers **161** were obtained predominantly in the reaction of *para*- and *meta*-substituted benzaldehydes, regardless of the electronic properties of these substituents. In contrast, *ortho*-substitution resulted in a significant decrease in diastereoselectivities. Meanwhile, in the reaction of 2,3-allenoates **159** as the dipolarophile, bisphosphoric acid catalyst **156** was the most effective in terms of enantioselectivity to give cycloadducts **162** as a single diastereomer having an *exo*-methylene moiety (Scheme 56b).[127] Although aliphatic aldehydes resulted in decreased chemical yields and enantioselectivities, excellent enantioselectivities were achieved using aromatic aldehydes as the 1,3-dipolarophile precursors in most cases. The activation of azomethine ylides by chiral phosphoric acid catalysts is also applicable to the cycloaddition reaction of methyleneindolinones **160** (Scheme 56c).[128] A broad range of aldehydes **11** and **160** were well tolerated for the cyclization reaction in the presence of chiral phosphoric acid **1u**, giving spirocyclic adducts **163** in good yields with high enantioselectivities. Thus, both aromatic and aliphatic aldehydes **11**, as well as **160** with either aromatic or aliphatic R^2 substituents, were adaptive substrates, despite the formation of regioisomeric byproducts when aliphatic R^2 substituents were introduced into **160**.

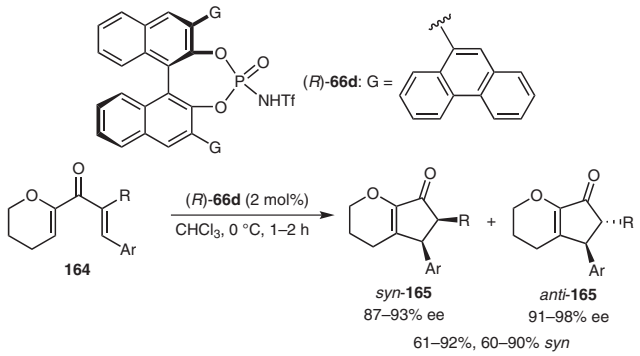


Scheme 56 1,3-Dipolar cycloaddition reaction of 1,3-dipolarophiles via multicomponent coupling

8 Cyclization Reactions

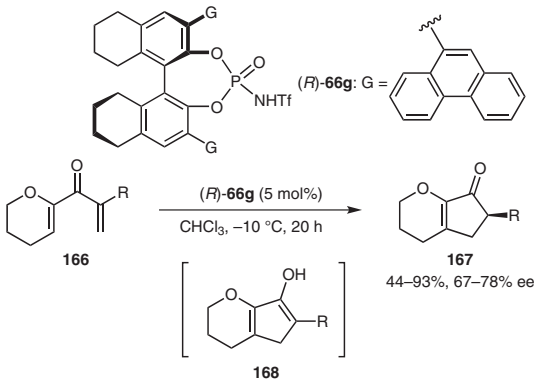
8.1 Electrocyclic Reactions

The Nazarov reaction is classified as an electrocyclic reaction and is one of the most versatile methods for the construction of five-membered cyclic enones, which are the key structural motif of numerous natural products.[129] In general, the Nazarov cyclization is accelerated by Lewis acid or Brønsted acid catalysts. However, the enantioselective Nazarov cyclization has rarely been exploited, even by using chiral metal complexes.[130] Rueping et al. developed for the first time an organocatalytic approach to the enantioselective Nazarov cyclization of dienones **164** using chiral phosphoramide **66** as the Brønsted acid catalyst (Scheme 57).[131] The reactivities and the enantioselectivities were strongly dependent on the solvent employed. While no reaction was observed in polar solvents, such as tetrahydrofuran and acetonitrile, the reaction proceeded smoothly in halogenated and aromatic solvents to afford diastereomeric mixtures of cyclized products **165**. The best enantioselectivities were achieved using chiral phosphoramide **66d** in chloroform, and a variety of dienones **164** were transformed into cyclopentenones **165** with moderate to high diastereoselectivities. Major product *syn*-**165** can be isomerized exclusively to *anti*-**165** under basic conditions without any loss of enantiomeric purity.



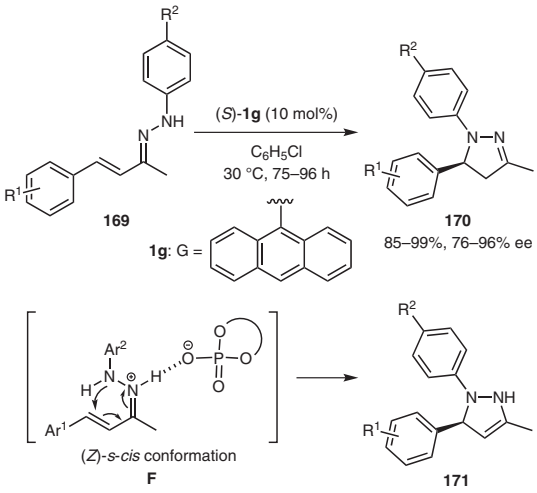
Scheme 57 Nazarov cyclization of dienones **164**

Rueping and Ieawsuwan further applied the enantioselective Nazarov cyclization to the preparation of α-substituted cyclopentenones **167**, lacking a β-substituent, using dienones **166** (Scheme 58).[132] In this transformation, the stereo-determining step is the Brønsted acid catalyzed enantioselective protonation of intermediately generated enol **168**.[130c] H_8-BINOL-derived phosphoramide **66g** exhibited the best performance in this case, giving cyclopentenones **167** with fairly good enantioselectivities.



Scheme 58 Nazarov cyclization of dienones **166**

In contrast to the Nazarov reaction, which is a 4π-electrocyclization, List and Müller reported the enantioselective catalysis of 6π-electrocyclization using benzylideneacetone-derived phenylhydrazone **169** as a 6π-electron system for the first time (Scheme 59).[133,134] Chiral phosphoric acid **1g** exhibited promising catalytic activity and enantioselectivity in the 6π-electrocyclization of **169**, giving the cyclized products, pyrazolines **170**, which are interesting synthetic targets in terms of broad potent biological activities, in excellent yields with high enantioselectivities. The electrocyclic reaction is well suited for hydrazones bearing either an electron-withdrawing or electron-donating substituent at the aromatic ring of the enone moiety. To undergo the cyclization, carbon–nitrogen double-bond isomerization of hydrazone (*E*)-**169** is required and this *E*/*Z* isomerization is also catalyzed by phosphoric acid **1g**. After adopting the cyclization-reactive *Z*-*s*-*cis*-conformation, protonated intermediate **F** undergoes 6π-electrocyclization in the chiral environment created by a chiral counteranion of the phosphoric acid, affording optically active 3-pyrazolines **171**. Subsequent isomerization of the double bond yields thermodynamically more stable 2-pyrazolines **170**. They also developed a direct method for the enantioselective 6π-electrocyclization from enones and hydrazines without the isolation of hydrazones **169**. In this direct method, the prior formation of hydrazones **169** using MS 4A was necessary in the absence of catalyst **1g**, because the overall reaction proceeded sluggishly when enones and phenylhydrazine reacted in the presence of the catalyst.

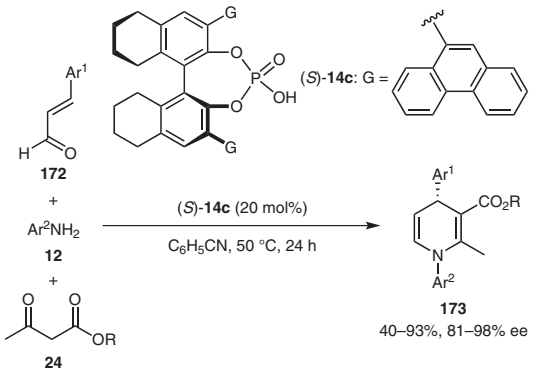


Scheme 59 6π-Electrocyclic reaction of phenylhydrazones **169** leading to pyrazolines **170**

8.2 Multicomponent Cyclization Reactions

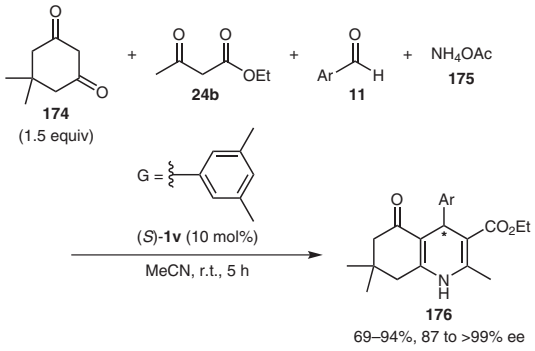
Multicomponent reactions, in which three or more reactants are combined in a single process to deliver new molecules containing substantial elements of all reactants, have received much attention with respect to synthetic efficiency and an increase in molecular diversity from the reactants.[135] Gong and co-workers developed an efficient three-component cyclization that involved α,β-unsaturated aldehydes **172**, aniline derivatives **12**, and β-keto esters **24** in the presence of chiral phosphoric acid catalyst **14c**, and 1,4-dihydropyridine derivatives **173** were obtained in the optically active forms (Scheme 60).[136] Both the reaction efficiency and the enantioselectivity displayed significant dependence upon the substituents of these reactants. Among the aniline derivatives **12** tested, 3-methoxyaniline (**12g**) gave the highest enantioselectivities albeit with accompanying decrease in chemical yields. In most cases, the reaction of ethyl or isopropyl β-keto esters **24** provided cyclized products **173** with higher enantioselectivities than the reaction of their methyl or allyl counterparts. α,β-Unsaturated aldehydes **172** with electron-withdrawing substituents, such as a nitro group or halogen atom, at the aromatic ring exhibited high enantioselectivities compared with the parent cinnamaldehyde and enals bearing an electron-donating group on the aromatic ring. The application of enantioenriched 1,4-dihydropyridines has been reported in the synthesis of alkaloids and a variety of biologically active molecules,[137] in particular, molecules that show activity against calcium channels,[138] and optically pure 4-substituted 1,4-dihydropyridine derivatives have been utilized as chiral models of NAD(P)H.[139] The present method enables efficient access to these dihydropyridine derivatives in a highly enantioselective manner.

The Hantzsch synthesis is one of the most efficient methods for the preparation of 1,4-dihydropyridine derivatives. Gestwicki and Evans reported the highly



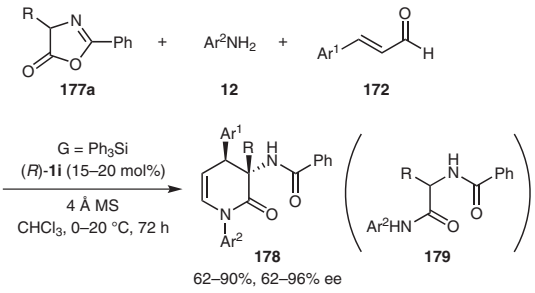
Scheme 60 1,4-Dihydropyridine synthesis via three-component coupling

enantioselective Hantzsch four-component coupling reaction of dimedone (**174**), ethyl acetoacetate (**24b**), aromatic aldehydes **11**, and ammonium acetate (**175**) using chiral phosphoric acid **1v** (Scheme 61).[140] The use of excess dimedone (**174**) was required to avoid the formation of byproducts, namely, symmetrical 1,4-dihydropyridines, and the desired four-component coupling products **176** were afforded in good yields with high enantioselectivities.



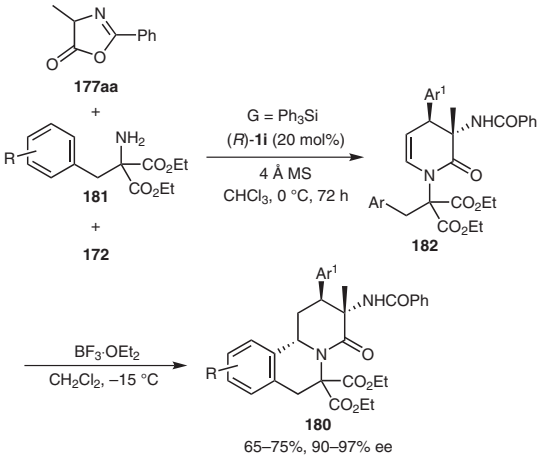
Scheme 61 1,4-Dihydropyridine synthesis via Hantzsch four-component coupling reaction

Azlactones **177** possess multiple reactive sites.[141] For example, the acidic nature at the C4 position allows for the formation of an enol tautomer that functions as a nucleophilic site and reacts with a variety of electrophiles, while the electrophilic nature of the carbonyl allows for nucleophilic attack to furnish a ring-opening product. Hence, the rich reactivity of the azlactone scaffold enables a large variety of transformations, making azlactones very useful as versatile reactants in the synthesis of biologically interesting molecules. Gong and co-workers developed an enantioselective cyclization reaction via three-component coupling by taking advantage of the multiple reactive sites of azlactones **177a** (Scheme 62).[142] Chiral phosphoric acid **1i** efficiently catalyzed the three-component coupling among azlactones **177a**, aniline derivatives **12**, and α,β-unsaturated aldehydes **172**, affording cyclized products **178** as a single diastereomer with high enantioselectivity, although aliphatic enals failed to give the desired products. The use of MS 4A was crucial to obtain desired products **178** in good yields. When the reaction was conducted in the absence of molecular sieves, considerable amounts of byproducts **179** were formed via direct nucleophilic ring opening of azlactones **177a** by **12**.



Scheme 62 Cyclization reaction via three-component coupling among azlactones **177a**, aniline derivatives **12**, and α,β-unsaturated aldehydes **172**

Gong and co-workers also accomplished the enantioselective synthesis of benzo[*a*]quinolizidine derivatives **180** using aryl ethylamine derivative **181**, instead of aniline derivatives **12** (Scheme 63).[142] Aryl ethylamine derivative **181** participated in the smooth cyclization reaction of azlactone **177aa** with various cinnamaldehydes **172** in the presence of **1i**, affording cyclized products **182**. Subsequent treatment of **182** with boron trifluoride–diethyl ether complex resulted in the clean formation of benzo[*a*]quinolizidine derivatives **180** via the Pictet–Spengler-type cyclization in good overall yield with excellent diastereo- and enantioselectivities.

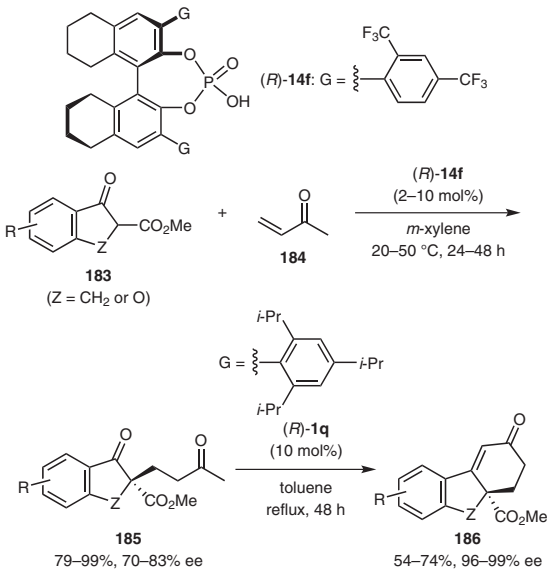


Scheme 63 Cyclization reaction via three-component coupling among azlactones **177aa**, aryl ethylamine derivative **181**, and α,β-unsaturated aldehydes **172**

8.3 Intramolecular Aldol Reaction (Robinson-type Annulation)

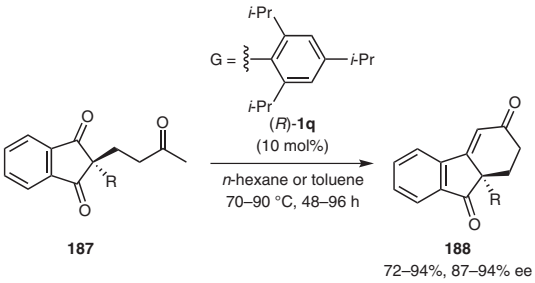
The Robinson annulation reaction is one of the most fundamental methods for providing cyclohexenone structural motifs and has been applied to a number of natural product syntheses. The enantioselective catalysis of the Robinson

annulation reaction is recognized as a prominent transformation in organocatalysis research.[143] The key step in the enantioselective Robinson annulation reaction is the initial enantioselective Michael addition to enones using the chiral catalysts. Akiyama et al. have developed a novel strategy for the enantioselective Robinson annulation reaction, which has two enantioselective processes. They combined a chiral phosphoric acid catalyzed enantioselective Michael addition of α-alkyl-β-keto esters **183** to methyl vinyl ketone (**184**) with a chiral phosphoric acid catalyzed kinetic resolution in the intramolecular aldol reaction followed by dehydration (Scheme 64).[144] Enantiomers **185** that were delivered predominantly by the enantioselective Michael addition were transformed preferentially by the kinetic resolution to give the corresponding Robinson-type annulation products **186** with excellent enantioselectivities.



Scheme 64 Robinson-type annulation reaction via two enantioselective processes

Akiyama and co-workers further developed the chiral phosphoric acid catalyzed desymmetrization of *meso*-1,3-diones **187** to yield optically active cyclohexenone derivatives **188** based on consecutive processes that included the enantioselective intramolecular aldol reaction as the key step (Scheme 65).[145] The method provides an efficient approach to cyclohexenone derivatives **188** in a highly enantioselective manner via the desymmetrization of σ-symmetric triketones **187** followed by dehydration in a one-pot operation.



Scheme 65 Desymmetrization of σ-symmetric triketones **187** leading to enantioenriched cyclohexenones **188**

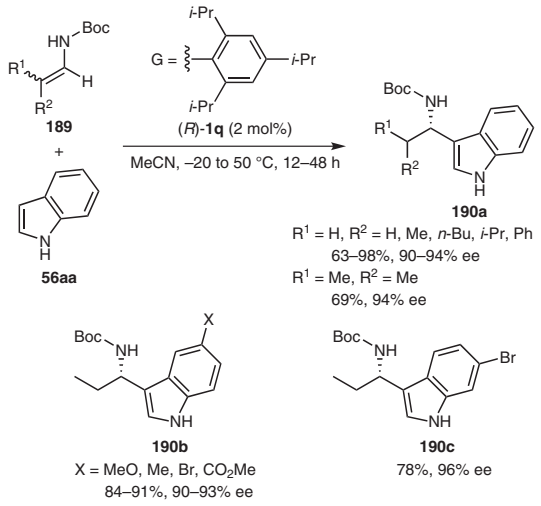
9 Transformations via Protonation of Electron-Rich Double Bonds

Brønsted acid activation of an electron-rich double bond is a fundamental method to generate reactive carbocation species. Brønsted acid catalyst molecules **1** undoubtedly possess relatively strong acidity and hence can be utilized as protonating agents of electron-rich double bonds to generate cationic species for further elaboration. The approach opens a new avenue for utilization of chiral phosphoric acids towards advanced enantioselective catalysis.

9.1 Carbon–Carbon Bond Formation via Protonation of Enamides or Enecarbamates

Enantioselective Friedel–Crafts reactions have been investigated intensively, using metal-based chiral catalysts or chiral organocatalysts.[55] These enantioselective catalyses have been accomplished via the activation of electron-deficient multiple bonds, such as C=O, C=NR, and C=C–X (X: electron-withdrawing group). The acid-catalyzed Friedel–Crafts 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 had been no reports of the enantioselective catalysis of the Friedel–Crafts reaction initiated by the activation of electron-rich multiple bonds, even using chiral metal catalysts, until 2007. Terada and Sorimachi successfully developed a highly enantioselective Friedel–Crafts reaction initiated by the activation of electron-rich multiple bonds using a chiral Brønsted acid catalyst for the first time. Chiral phosphoric acid **1q** exhibited excellent performance for the activation, enabling the catalytic reaction of indoles **56a** with enecarbamates **189** as electron-rich alkenes (Scheme 66).[146] Uniformly high enantioselectivities and chemical yields were achieved in the reaction of indole (**56aa**) with enecarbamates **189** bearing either a linear or a 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 **56a**, irrespective of their electronic properties. The present approach provides efficient access to enantioenriched 3-indolyl methanamines **190** with a variety of aliphatic substituents and effectively complements previous methods that afforded aromatic-group-substituted 3-indolyl methanamines **57** via the activation of aromatic imines (see Scheme 22).

The present Friedel–Crafts reaction proceeds through the in situ generation of aliphatic imines **191** that are delivered via the protonation of enecarbamates **189** by the phosphoric acid catalyst (Figure 5). Phosphoric acid functions as an efficient catalyst for the dual transformation



Scheme 66 Friedel–Crafts reaction via activation of enecarbamates **189** by phosphoric acid catalyst

that involves the in situ generation of imine **191** and the enantioselective carbon–carbon bond formation with indoles **56a**. This protocol offers the distinct advantage of generating, in situ, unstable aliphatic imines **191** from storable and thus easily handled enecarbamates **189**, and hence is applicable to other organic transformations. In fact, Terada et al. applied this method to an enantioselective direct Mannich reaction (Scheme 67).[147] The method provides an efficient pathway to produce β-alkyl-β-aminocarbonyl derivatives **192** in optically active forms.

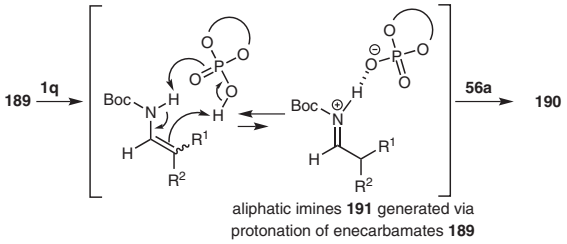
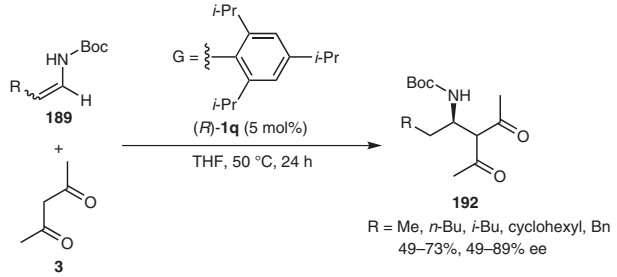
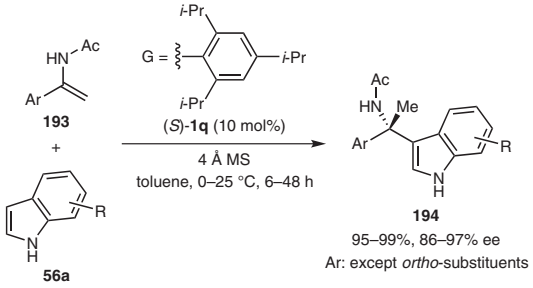


Figure 5 Mechanistic considerations of the Friedel–Crafts reaction of enecarbamates **189** with indole **56a**



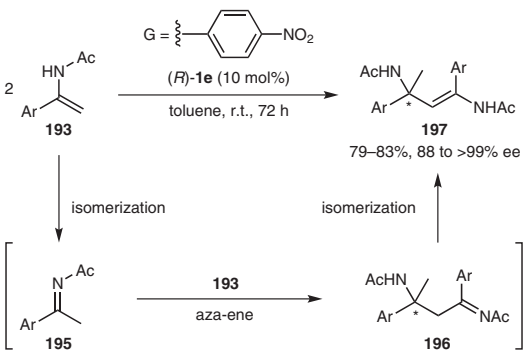
Scheme 67 Direct Mannich reaction via activation of enecarbamates **189**

Shortly thereafter, Zhou and co-workers independently reported the enantioselective Friedel–Crafts reaction of indoles **56a** with aryl-substituted enamides **193** catalyzed by chiral phosphoric acid catalyst **1q** (Scheme 68).[148] The yield of Friedel–Crafts products **194** was remarkably improved by the addition of MS 4A that prevented the hydrolysis of enamides **193**. It is noteworthy that in this catalytic Friedel–Crafts reaction, a quaternary stereogenic center bearing a nitrogen atom can be constructed in a highly enantioselective manner.



Scheme 68 Formation of quaternary stereogenic center bearing a nitrogen atom in the Friedel–Crafts reaction

Tsogoeva and co-workers reported the enantioselective formation of a quaternary stereogenic center bearing a nitrogen atom through the homo-coupling reaction of enamides **193** (Scheme 69).[149] Enamides **193** were isomerized in situ to ketimines **195** under the influence of phosphoric acid catalyst **1e**, as depicted in Scheme 69. Electrophilic ketimines **195** were generated under equilibrium conditions and their homo-coupling reaction with nucleophilic enamides **193** proceeded via the aza-ene-type mechanism to give the corresponding imine products **196**.[87,89] Resultant imines **196** were readily isomerized to the enamine form under acidic conditions, giving enamide products **197** with high enantioselectivities. Hydrolysis of the enamide moiety yielded optically active β-amino ketones having a quaternary carbon atom, which are potentially useful as synthetic building blocks.

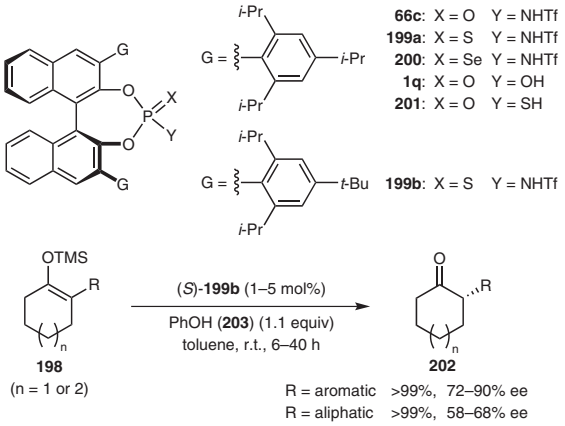


Scheme 69 Homo-coupling reaction of enamides **193**

9.2 Enantioselective Protonation of Silyl Enol Ethers

The enantioselective protonation of prochiral enol derivatives is an attractive route for the preparation of optically active α-substituted carbonyl compounds and has been studied extensively for the enantioselective catalysis using chiral metal complexes or a metal complex (Lewis

acid) assisted chiral Brønsted acid system in the presence of achiral proton sources.[150] Yamamoto and Cheon reported a highly enantioselective protonation of cyclic silyl enol ethers **198** using a metal-free chiral Brønsted acid for the first time (Scheme 70).[88i] They developed a new family of chiral phosphoramide catalysts **199** and **200** in order to achieve higher acidity to promote the enantioselective protonation.

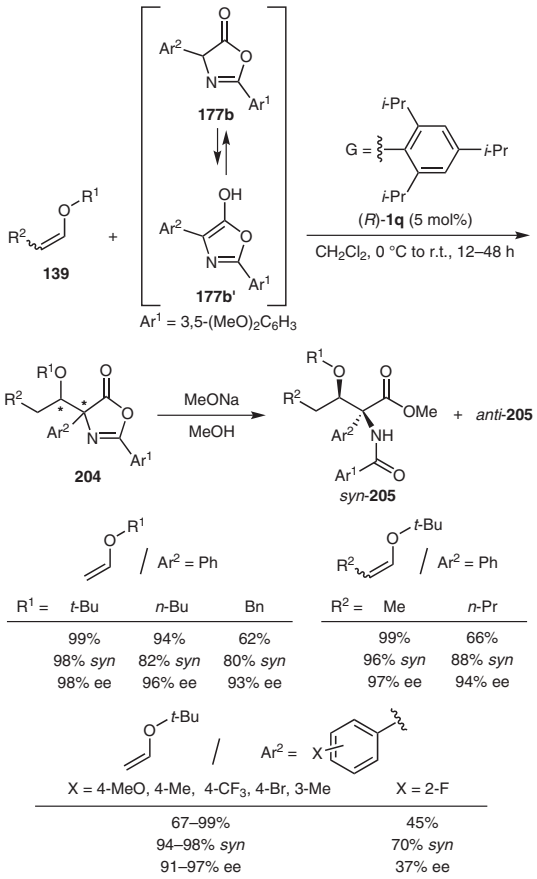


Scheme 70 Protonation of cyclic silyl enol ethers **198**

It is noteworthy that almost no reaction was observed when the parent chiral phosphoric acid **1q** and its thiol analogue **201**[151] were employed. Meanwhile, the introduction of an NHTf group into the phosphoryl moiety, i.e., phosphoramide catalyst **66c**, is crucial to enhance the catalytic activity, leading to the quantitative formation of enantioenriched product **202**. Further substitution of the oxygen with sulfur **199a** or selenium **200** in the phosphoramide catalyst improved enantioselectivity as well as reactivity. The enantioselectivities and the reactivities were also strongly dependent on the achiral proton sources and higher enantioselectivities could be achieved with sterically less hindered phenol or carboxylic acid derivatives. Among the catalytic systems tested, **199b** coupled with phenol (**203**) as the achiral proton source displayed the best result in terms of catalytic activity and enantioselectivity. Although moderate enantioselectivities were observed in the protonation of cyclic ketones having an aliphatic substituent at the α-position, the method is well suited for cyclic ketones bearing either an electron-withdrawing or an electron-donating aromatic substituent. More importantly, the catalyst load can be reduced to as little as 0.05 mol% without any significant loss of enantioselectivity.[88]

9.3 Aldol-type Reaction via Protonation 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 the protonation of vinyl ether **139**. Terada et al. developed chiral conjugate base controlled enantioselective transformations[152] involving the oxocarbenium ion as the reactive intermediate.[153] They applied the intermediary oxocarbenium[154] to a direct aldol-type reaction of azlactones **177b**[141] via their oxazole tautomers **177b′** (Scheme 71). 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.



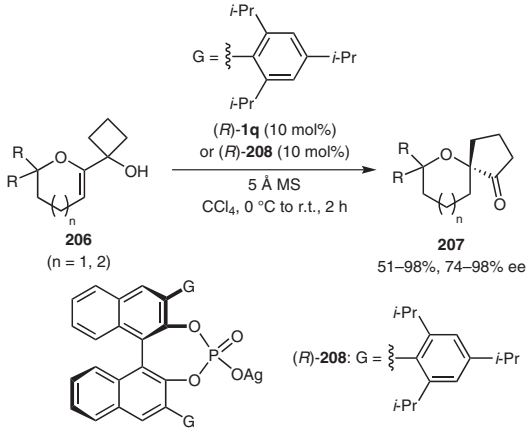
Scheme 71 Aldol-type reaction of azlactones **177b** via protonation of vinyl ethers **139**

The electronic manipulation of Ar^1 substituents introduced at the C2 position of azlactone **177** had a significant impact not only on the reactivity 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, giving **177b**, β-alkoxy-α-amino acid derivatives **205** were obtained with excellent enantio- and diastereoselectivities after opening the azlactone ring of initial aldol products **204**. An investigation of the substituent effect of vinyl ethers **139** showed that the sterically demanding *tert*-butyl ether is important to achieve high diastereoselectivity. Vinyl ethers **139** with an alkyl group substitution at the terminal position were also applicable,

affording β-alkoxy-α-amino acid derivatives **205** with high enantioselectivities. Azlactones **177b** having a series of aromatic groups (Ar^2) revealed uniformly high enantio- and diastereoselectivities for *para*- and *meta*-substituted aromatic rings (Ar^2), irrespective of their electronic properties. However, the *ortho* substitution led to a marked reduction of selectivity and chemical yield. Terada et al. 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,[153] and hence high stereoselectivities were achieved in this transformation.

9.4 Semi-Pinacol Rearrangement via Protonation of Vinyl Ethers

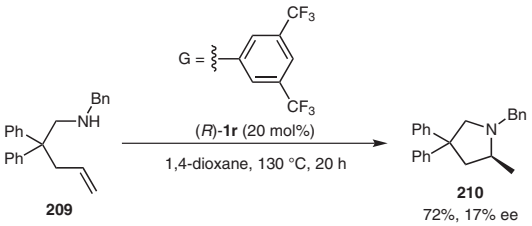
The semi-pinacol rearrangement is one of the most fundamental skeletal rearrangements of carbon frameworks and is considered to be a variant of the pinacol rearrangement, where a carbon–oxygen double bond is formed at C1 with concomitant migration of a group from C1 to adjacent C2, with or without loss of a leaving group, other than the hydroxy group, from C2.[155] Tu and co-workers accomplished the enantioselective synthesis of spiroethers that feature two fused rings joined by a single chiral oxo quaternary carbon center, on the basis of the semi-pinacol rearrangement (Scheme 72).[156] Although a highly strained cyclobutanol unit was necessary to promote the rearrangement, allylic alcohol derivatives **206** were rearranged to spiroethers **207** via protonation of the vinyl ether by chiral phosphoric acid catalyst **1q** and subsequent ring expansion of the cyclobutane skeleton. The addition of MS 5A was necessary for the reproducibility of the enantioselectivity, affording the corresponding products **207** in good yields with high enantioselectivities. The authors also attempted the in situ generation of phosphoric acid **1q**, using the corresponding silver phosphate **208** of **1q**, because of the lability of **206** under acidic conditions. This procedure, which involves a silver–proton exchange between alcohol **206** and silver phosphate **208**, provides relatively mild and weakly acidic conditions, effectively realizing the semi-pinacol rearrangement of **206**.



Scheme 72 Semi-pinacol rearrangement of allylic alcohols **206** via protonation of vinyl ether

9.5 Hydroamination via Protonation of Non-activated Alkenes

The intramolecular addition of amines to unsaturated carbon–carbon multiple bonds is one of the most direct methods for the preparation of nitrogen heterocycles. A variety of methodologies for the intramolecular hydroaminations of alkynes and allenes have been reported so far.[157] In contrast, the hydroamination of electronically nonactivated alkenes remains a challenging topic. The enantioselective hydroamination of nonactivated alkenes has relied thus far entirely on the use of chiral metal complexes. Ackermann and Althammer reported the enantioselective intramolecular hydroamination of nonactivated alkenes having a basic amine terminus under metal-free conditions (Scheme 73).[158] Chiral phosphoric acid **1r** enabled the hydroamination of aminoalkene **209**, giving the corresponding pyrrolidine derivatives **210** in optically active forms, although the enantioselectivity was not sufficiently high.



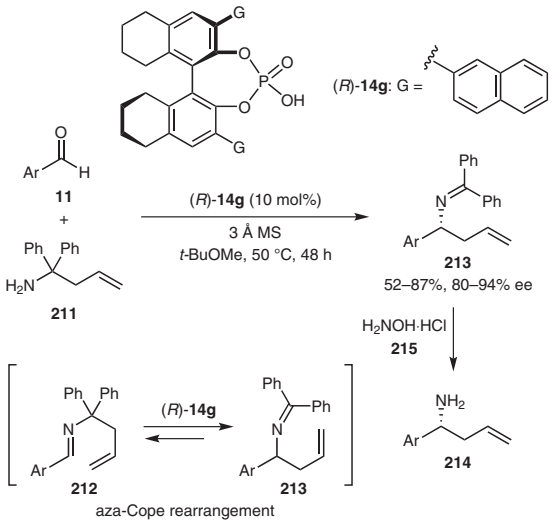
Scheme 73 Intramolecular hydroamination of nonactivated alkene **209**

10 Miscellaneous Carbon–Carbon Bond-Forming Reactions

10.1 Aza-Cope Rearrangement

Sigmatropic rearrangements are one of the most fundamental methods for the construction of carbon frameworks and have widespread application in the synthesis of biologically relevant molecules. A variety of enantioselective sigmatropic rearrangements have been established using chiral metal catalysts or organocatalysts.[159] Enantioselective versions of the aza-Cope rearrangement provide efficient routes to optically active homoallylic amines, which are useful precursors for the synthesis of natural products. However, this valuable transformation was not successfully developed until 2008. Rueping and Antonchick reported for the first time a highly enantioselective aza-Cope rearrangement that uses chiral phosphoric acid catalysts (Scheme 74).[160] The reaction of aromatic aldehydes **11** with achiral homoallylic amine **211** proceeds smoothly via the in situ generation of imines **212** in the presence of catalyst **14g** to afford rearranged products **213**, homoallylic amine derivatives, in good yields with high enantioselectivities. The method furnishes a practical

route to the catalytic enantioselective aminoallylation of aromatic aldehydes on the basis of a condensation–rearrangement sequence. Free primary homoallylic amines **214** were obtained by treating rearranged products **213** with hydroxylamine hydrochloride (**215**).



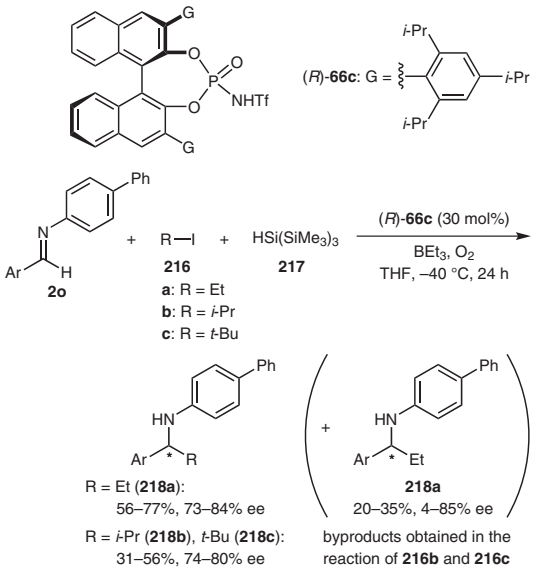
Scheme 74 Aza-Cope rearrangement of in situ generated imine **212**

10.2 Radical Reaction

Stereoselective radical reactions have received much attention due to the uniqueness of the radical processes and hence, the enantioselective catalysis of radical reactions has been approached in various ways.[161] In particular, because it is favorable for catalytic processes, reductive alkylation has been investigated extensively in enantioselective radical reactions, where the addition of alkyl radicals to multiple bonds, followed by trapping of the resulting radicals with a hydrogen atom source, leads to reduced products. Kim and Lee developed an enantioselective radical reaction of imines **2o** catalyzed by chiral phosphoramide **66c** on the basis of the reductive alkylation process using tris(trimethylsilyl)silane (**217**) as the hydrogen source and triethylborane as the initiator (Scheme 75).[162] The enantioselective reductive alkylation of imines **2o** by ethyl iodide (**216a**) gave the corresponding products **218a** in good yields with relatively high enantioselectivities. Meanwhile, in the reaction of isopropyl iodide (**216b**) and *tert*-butyl iodide (**216c**), desired products **218b** and **218c** were obtained in modest yields because of the considerable amount of byproduct **218a** furnished by the direct addition of an ethyl radical, generated from triethylborane, to imines **2o**.

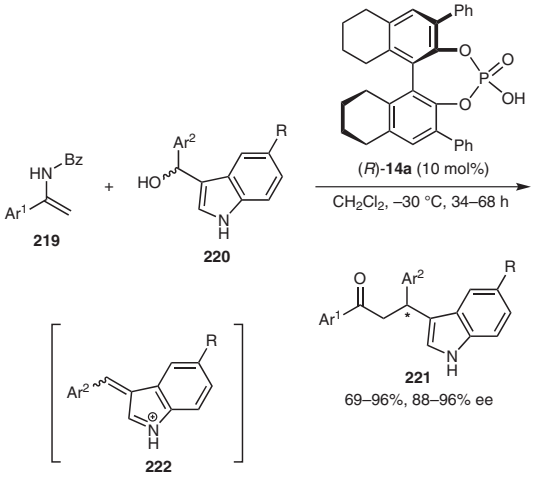
10.3 Alkylation of Enamides via Activation of Alcohols

The catalytic enantioselective α-alkylation of carbonyl derivatives is a highly valuable carbon–carbon bond-



Scheme 75 Reductive alkylation of imines **2o** catalyzed by chiral phosphoramide **66c**

forming strategy in organic synthesis. However, this important methodology has remained a longstanding issue in asymmetric catalysis and hence various approaches have been investigated. Among those approaches, Petrini, Melchiorre, and co-workers and Cozzi et al. accomplished efficient methods for the enantioselective α-alkylation of simple aldehydes with stable and unsymmetrically substituted diarylcarbocations using chiral secondary amine catalysts.[163] Shortly thereafter, Gong and co-workers reported that H_8-BINOL-derived phosphoric acid **14a** enabled the highly enantioselective α-alkylation of enamides **219** with indolyl alcohols **220** to give β-aryl-β-indolylpropanones **221** in good yields (Scheme 76).[164] The reaction proceeds via stabilized cation **222**, a vinylogous iminium intermediate, generated in situ from indolyl alcohols **219** under the influence of acid catalyst **14a**.



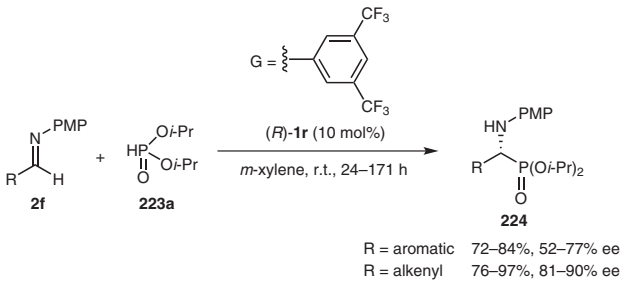
Scheme 76 α-Alkylation of enamides **219** with indolyl alcohols **220**

11 Carbon–Heteroatom Bond-Forming Reactions

11.1 Hydrophosphonylation (Kabachnik–Fields Reaction)

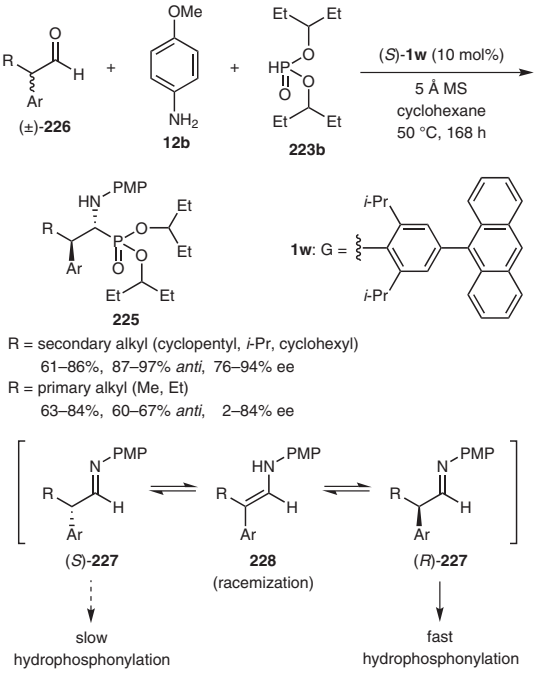
The Kabachnik–Fields reaction, which involves the hydrophosphonylation of phosphites with imines generated in situ from carbonyl compounds and amines, is an attractive method for the preparation of α-amino phosphonates. Optically active α-amino phosphonic acids and their phosphonate esters are an interesting class of compounds due to their potent biological activities as non-proteinogenic analogues of α-amino acids. Therefore, considerable attention has been paid to their enantioselective synthesis by the hydrophosphonylation of preformed imines, using either metal-based catalysts or organocatalysts.[165]

Akiyama et al. reported that chiral phosphoric acid **1r** functioned as an efficient catalyst in the addition reaction of diisopropyl phosphite (**223a**) with *N*-PMP-protected aldimines **2f** (Scheme 77).[166] Aromatic and α,β-unsaturated imines could be used in the reaction, giving α-amino phosphonate esters **224** in high yields. The use of sterically demanding dialkyl phosphites **223** and aldimines derived from cinnamaldehyde derivatives is essential to achieve high enantioselectivities. The same research group and Yamanaka and Hirata conducted DFT computational analysis of the hydrophosphonylation reaction.[167] Chiral phosphoric acid **1r** plays a significant role in the activation of both imine **2f** and phosphite **223** based on its dual functional catalysis.



Scheme 77 Hydrophosphonylation of imines

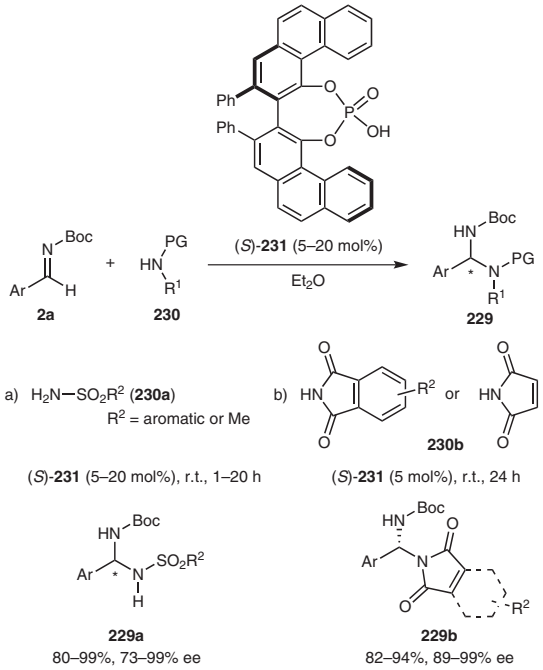
List and co-workers reported an excellent approach to the enantioselective synthesis of β-branched α-amino phosphonates **225**, which involved the dynamic kinetic resolution strategy (Scheme 78)[168] that they had previously applied to the enantioselective reductive amination of racemic α-branched aldehydes **226** (see Scheme 91).[169] They successfully accomplished the highly stereoselective direct three-component Kabachnik–Fields reaction of one equivalent each of racemic aldehyde **226**, 4-methoxyaniline (**12b**), and di(3-pentyl)phosphite (**223b**) in the presence of the newly developed chiral phosphoric acid **1w** by combining dynamic kinetic resolution with the parallel creation of an additional stereogenic center. The hydrophosphonylation proceeds through a tautomerization between imines **227** and enamines **228** with concomitant racemization at the α-position. Dynamic kinetic resolution occurs under the influence of catalyst (*S*)-**1w**, whereby the hydrophosphonylation of (*R*)-**227** proceeds faster than that of (*S*)-**227** to give β-branched α-amino phosphonates **225** with high diastereo- and enantioselectivities, especially for aldehydes **226** bearing a secondary alkyl group at the α-position.



Scheme 78 Stereoselective synthesis of β-branched α-amino phosphonates **225** by Kabachnik–Fields reaction

11.2 Formation of (Hemi)Aminals

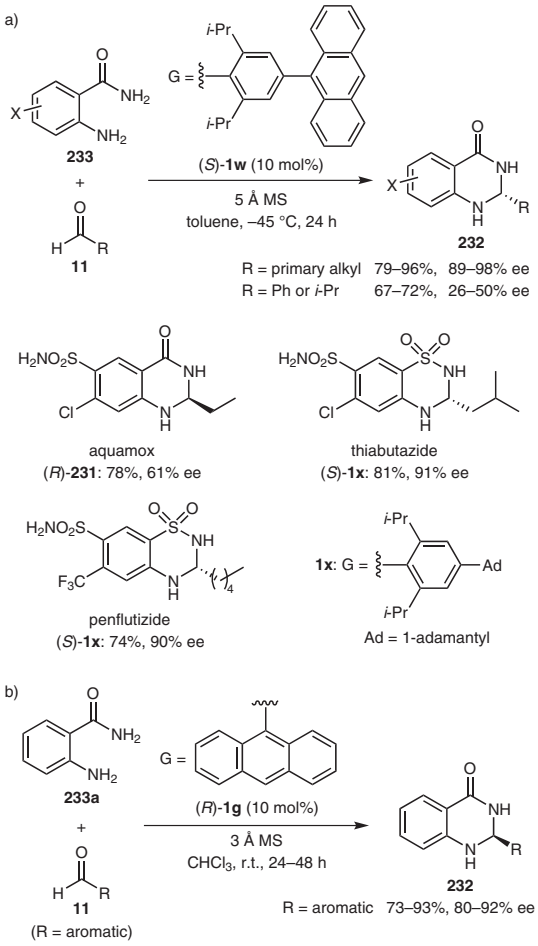
Aminals, compounds having two amino groups bound to the same carbon atom, are represented in many medicinal agents that have versatile therapeutic actions, such as proteinase inhibitors and neurotensins. Antilla and co-workers developed an enantioselective synthesis of protected aminals **229**, which involved the addition reaction of nitrogen nucleophiles **230** with *N*-Boc aromatic imines **2a** catalyzed by chiral phosphoric acids (Scheme 79).[170] In this novel enantioselective transformation, they employed a new type of axially chiral phosphoric acid **231**, derived from VAPOL (vaulted 3,3′-biphenanthrol), originally developed by Antilla's research group. Indeed, **231** exhibited excellent catalytic activity and enantioselectivity in the addition to *N*-Boc aromatic imines **2a**. Enantioenriched aminal products **229a** were obtained in the reaction of sulfonamides **230a** (Scheme 79a) and were stable on storage; neither decomposition nor racemization was observed in solution over several days. The same research group reported the enantioselective addition reaction of phthalimide or its derivatives **230b** with *N*-Boc aromatic imines **2a**, affording the corresponding aminals **229b** with excellent enantioselectivities (Scheme 79b).[171]



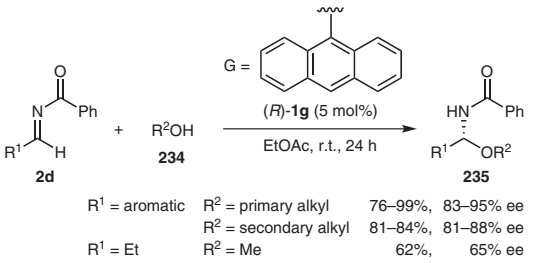
Scheme 79 Preparation of aminals via addition of nitrogen nucleophiles to imines

Cyclic aminals are relatively common structural elements of diverse pharmaceutical compounds. However, no efficient method was available to prepare these compounds until 2008. The research groups of List[172] and Rueping[173] independently reported a highly enantioselective direct synthesis of cyclic aminals **232** from aldehydes **11** and *o*-aminobenzamide derivatives **233** using chiral phosphoric acids (Scheme 80). The catalytic reaction involves the imine formation/intramolecular amine addition sequence using **11** and **233**. In List's approach, aliphatic aldehydes were mainly employed as the substrate and the corresponding dihydroquinazolinones **232** were furnished with excellent enantioselectivities when primary alkyl-substituted aldehydes and phosphoric acid catalyst **1w** were used (Scheme 80a). They also applied the enantioselective method to sulfonamide analogues instead of benzamides **233**. The method provides a practical and efficient route to pharmaceutically relevant compounds, namely, the benzo(thia)diazine class of cyclic aminals. In fact, they synthesized several benzo(thia)diazines, including aquamox, thiabutazide, and penflutizide, with high enantioselectivities using their modified methodology. Meanwhile, Rueping et al. focused on the preparation of aromatic-substituted cyclic aminals **232** using aromatic aldehydes and **233a** as the substrates (Scheme 80b). Phosphoric acid **1g** was the best catalyst in their case.

Antilla and co-workers further extended their methodology to the addition of an oxygen nucleophile, instead of a nitrogen nucleophile (see Scheme 79), to imines (Scheme 81).[174] They successfully developed the catalytic enantioselective addition reaction of alcohols **234** as oxygen nucleophiles with *N*-benzoyl imines **2d** using chiral



Scheme 80 Direct transformation of *o*-aminobenzamides **233** with aldehydes into cyclic aminals **232**



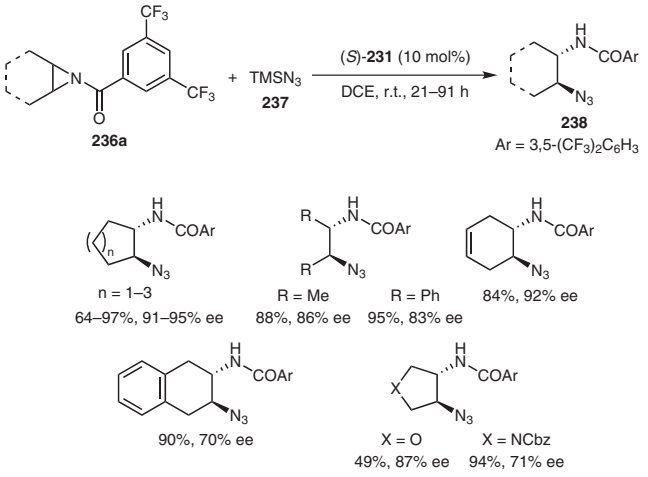
Scheme 81 Preparation of hemiaminal ethers **235** via addition of alcohols **234** to imines **2d**

phosphoric acid **1g**. The method provides straightforward access to chiral hemiaminal ethers **235** with high enantioselectivities.

11.3 Nucleophilic Ring Opening of Aziridines and Related Reactions

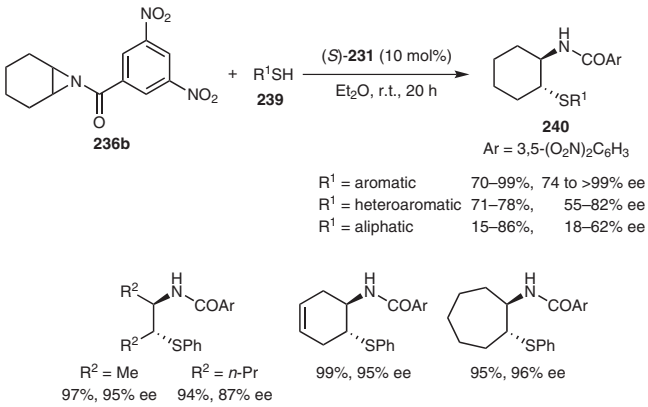
The ring opening of aziridines with nitrogen nucleophiles provides an efficient route to a vicinal diamine structural moiety[175] that exists in numerous biologically active compounds and medicinal agents, as well as chiral ligands of metal complexes. In this context, considerable effort has been devoted to their enantioselective synthesis. One of

the most direct methods for the preparation of enantioenriched vicinal diamines is the enantioselective desymmetrization of *meso*-aziridines **236** with nitrogen nucleophiles.[176] Antilla and co-workers developed a highly enantioselective synthesis of vicinal diamines based on the desymmetrization strategy using chiral phosphoric acid **231** and azidotrimethylsilylane (**237**) as the nitrogen nucleophile (Scheme 82).[177] The 3,5-bis(trifluoromethyl)benzoyl substituent introduced on the nitrogen atom of aziridines, giving **236a**, optimized both yield and enantioselectivity. A series of *meso*-aziridines **236a** derived from (hetero)cyclic and acyclic alkanes having aliphatic or aromatic substituents were applicable to the enantioselective aziridine ring opening reaction, giving the corresponding products **238** in optically active forms. They proposed that the silylated phosphate generated in situ by the reaction of chiral phosphoric acid with azidotrimethylsilylane (**237**) is a catalytically active species.



Scheme 82 Desymmetrization of *meso*-aziridines **236a** with azide

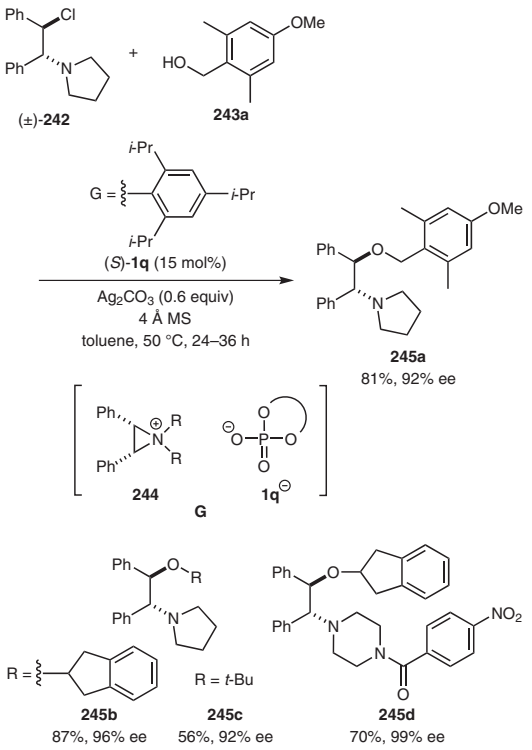
Antilla and co-workers further applied their method to the enantioselective ring opening of *meso*-aziridines **236** by a series of thiols **239**, instead of azide, as the nucleophile (Scheme 83).[178] This expansion of the substrate scope enabled the asymmetric synthesis of optically active β-amino thioether derivatives **240**. Phosphoric acid **231** also functioned as an efficient catalyst for the ring opening by thiols **239** in terms of catalytic activity and enantioselectivity. Interestingly, a silyl group is not required in this ring opening of aziridines **236**, which is in contrast to the reaction with azide as the nucleophile (Scheme 82). The introduction of 3,5-dinitrobenzoyl to the nitrogen atom of aziridine, giving **236b**, is highly desirable in achieving the high enantioselectivities. 3,5-Bis(trifluoromethyl)benzoyl, which was employed for the ring opening by azide (Scheme 82),[177] and 4-nitrobenzoyl protective groups displayed much lower enantioselectivities. Arylthiols are suitable for the reaction. Thus, a wide variety of electron-withdrawing and electron-donating substituents can be introduced to the *ortho*-, *meta*-, and *para*-positions of the aromatic ring. Meanwhile, heteroaryl- and alkylthiols proved to be relatively poor reaction partners, giving the corresponding products **240** with low to moderate enantioselectivities. Della Sala and Lattanzi independently reported the highly enantioselective ring opening of *meso*-aziridine **236** by (phenylthio)trimethylsilane (**241**; not shown), instead of thiols **239**, using the same catalyst **231**.[179] A range of *meso*-aziridines **236b** having a 3,5-dinitrobenzoyl group at the nitrogen atom could be used for this catalytic system, affording phenyl thioethers in good yields with high enantioselectivities. They also proposed that silylated phosphate generated in situ from catalyst **231** with silylated nucleophile **241** would be a catalytically active species, following Antilla's mechanistic proposal in the ring opening by azidotrimethylsilylane (**237**).[177]



Scheme 83 Desymmetrization of *meso*-aziridines **236b** with thiols **239**

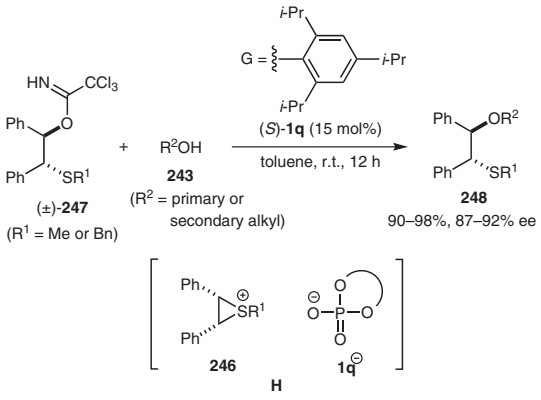
Toste and co-workers successfully demonstrated an enantioselective synthesis of β-alkoxy amines from racemic β-chloro tertiary amines **242** and alcohols **243** as an oxygen nucleophile under the influence of an equimolar amount of silver(I) salt and a catalytic amount of chiral phosphoric acid **1q** (Scheme 84).[180] The methodology is based on the chiral counteranion mediated enantioselective transformation.[152] The reaction proceeds via the asymmetric ring opening of intermediary *meso*-aziridinium ions **244** that were generated from the ring closure of β-chloro tertiary amines **242** by silver(I) salts. Subsequent nucleophilic ring opening of *meso*-aziridinium ions **244** by alcohols **243** provided the corresponding β-alkoxy amines **245**. Secondary, tertiary, and relatively hindered primary alcohols could be used in the reaction, giving β-alkoxy amines **245** with high enantioselectivities. The efficient desymmetrization of *meso*-aziridinium ion **244** was achieved under the influence of the chiral counteranion derived from phosphoric acid **1q**, as the ion pair **G** was formed between cationic **244** and the counteranion of **1q**. They pointed out that the resulting catalytic process can be regarded as chiral anion phase-transfer catalysis in analogy to the established chiral cation alternative.[181]

Toste and co-workers further extended their chemistry to the sulfur analogue of the ring opening reaction, namely, the desymmetrization of *meso*-episulfonium ions **246** (Scheme 85).[180a] However, in this application, the silver–



Scheme 84 Desymmetrization of *meso*-aziridinium ions **244** with alcohols **243**

halogen abstraction method for the generation of the cationic intermediate could not be utilized, because the sulfide would likely bind silver(I). Therefore, they employed trichloroacetimidate as the leaving group. The trichloroacetimidate moiety is directly activated by chiral phosphoric acid **1q**, and this is followed by ring closure with concomitant loss of trichloroacetamide from substrates **247** generating ion pair **H** of *meso*-episulfonium ions **246** and the chiral counteranion. The interception of intermediate **246** with an oxygen nucleophile, such as alcohols **243**, affords chiral sulfide products **248** in excellent yields with good enantioselectivities.



Scheme 85 Desymmetrization of *meso*-episulfonium ions **246** with alcohols **243**

12 Transfer Hydrogenation Reactions

12.1 Transfer Hydrogenation of Acyclic and Cyclic Imines

The enantioselective reduction of ketimines is a straightforward approach to synthesizing optically active amines. Although the catalytic enantioselective hydrogenations and the transfer hydrogenations of ketones and olefins have been intensively investigated using chiral metal complexes, the corresponding enantioselective reductions of imines are less advanced and hence the development of efficient methods for these transformations is still one of the greatest challenges in the practical synthesis of chiral amines. Most catalytic enantioselective hydrogenations of ketimines have been conducted using common hydrogen sources, such as high-pressure hydrogen gases, di- or trialkylsilanes, and ammonium formate, under the influence of chiral transition-metal complexes.[182] Recently, List and co-workers and MacMillan and co-workers independently reported the organocatalytic transfer hydrogenations of α,β-unsaturated aldehydes using Hantzsch esters **249** (Figure 6), which are dihydropyridine derivatives, as a biomimetic hydrogen source.[183] Following these excellent reports, Hantzsch esters gained popularity as an efficient hydrogen source for the enantioselective reduction of organic compounds, including imines.[184]

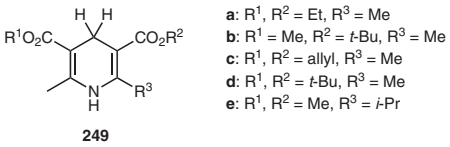
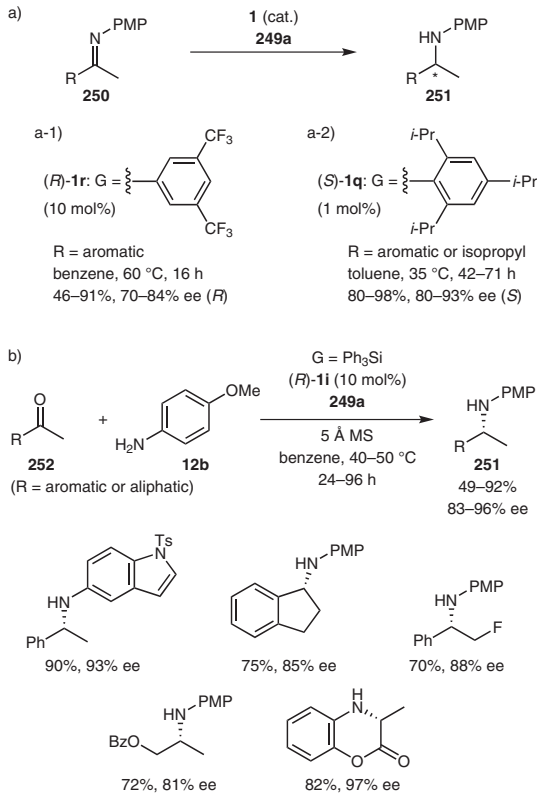


Figure 6 Hantzsch esters **249**

In 2005, Rueping et al. reported that chiral phosphoric acid **1r** functions as an efficient catalyst for the enantioselective reduction of ketimines **250** (Scheme 86a-1).[185] A variety of aryl methyl ketimines **250** were reduced to the corresponding amines **251** in optically active forms using Hantzsch ester **249a** as the hydrogenation transfer reagent.[186] In the same year, List and co-workers independently reported the highly enantioselective transfer hydrogenation reaction of ketimines **250** using Hantzsch ester **249a** by thorough optimization of the substituents (G) that were introduced onto the phosphoric acid catalyst (Scheme 86a-2).[187] Almost simultaneously, MacMillan and co-workers successfully developed the enantioselective reductive amination reaction using Hantzsch ester **249a** via simple fragment coupling between ketones **252** and aniline derivatives **12b** (Scheme 86b).[188] Acid catalyst **1i**, with its sterically demanding triphenylsilyl groups, was optimal for the enantioselectivity. Although the reaction required a methyl ketone subunit, this operationally simple method is applicable to not only aryl but also alkyl methyl ketones and provides a highly efficient route to structurally diverse chiral amines. In their conscientious studies on the reductive aminations, MacMillan and co-

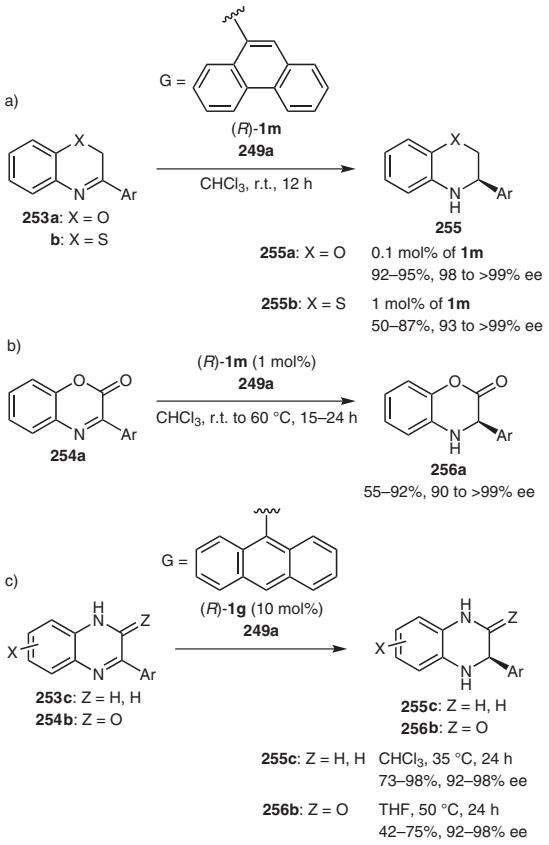


Scheme 86 Transfer hydrogenation of acyclic ketimines **250** using Hantzsch ester **249** as the biomimetic hydrogen source

workers also reported a couple of examples using cyclic imines as the substrate.

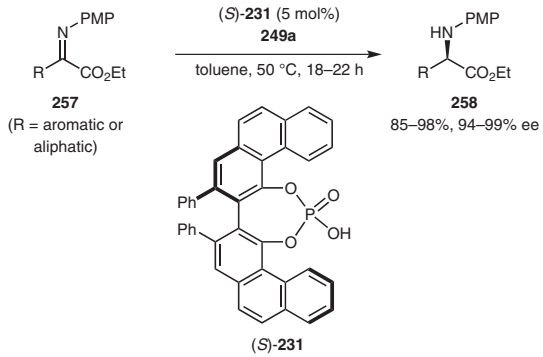
Shortly thereafter, a detailed investigation of the transfer hydrogenation of cyclic imines was conducted by Rueping et al. (Scheme 87a).[88g] Benzoxazines **253a** underwent the transfer hydrogenation in good yields with extremely high enantioselectivities even with a remarkably low catalyst load of **1m** (0.1 mol%). Benzothiazines **253b** (Scheme 87a) and benzoxazinones **254a** (Scheme 87b) were also hydrogenated by Hantzsch ester **249a** in the presence of the same catalyst **1m** (1 mol%) to give the corresponding products, **255b** and **256a**, with excellent enantioselectivities. They further extended the transfer hydrogenation to quinoxalines **253c** and quinoxalinones **254b** using **1g** (10 mol%) as the catalyst, giving rise to 2-tetrahydroquinoxalines **255c** and 3-dihydroquinoxalinones **256b**, respectively, with high enantioselectivities (Scheme 87c).[189]

Soon after these initial reports, the groups of Antilla[190] and You[191] independently applied the chiral phosphoric acid catalysis approach to the enantioselective hydrogenation of α-imino esters **257**. The method provides an alternative route to the enantioselective synthesis of α-amino esters **258**. Antilla and co-workers employed VAPOL-derived phosphoric acid **231**,[177] originally developed by his research group (Scheme 88), whereas **1g** was used in

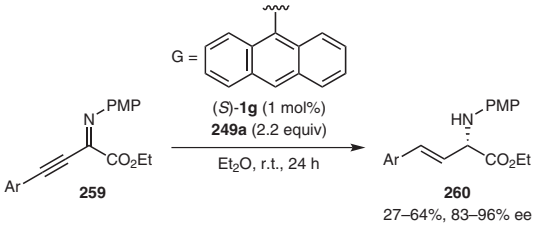


Scheme 87 Transfer hydrogenation of cyclic imines, **253** and **254**

You's studies. In both cases, excellent enantioselectivities were achieved. You and co-workers further applied the method to the enantioselective reduction of α-imino esters **259** having an alkynyl substituent at the α-position (Scheme 89).[192] Both alkyne and imine moieties were reduced under transfer hydrogenation conditions with an excess amount of Hantzsch ester **249a** (2.2 equiv) to give β,γ-unsaturated α-amino esters **260**. Although the chemical yields were moderate, high enantio- and *trans*-selectivities were achieved using the same chiral phosphoric acid catalyst **1g**.

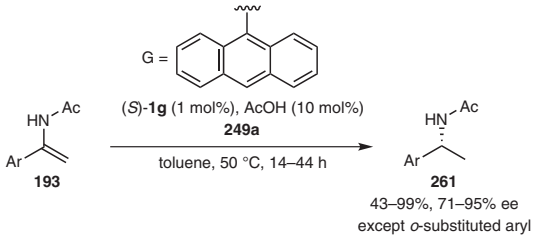


Scheme 88 Transfer hydrogenation of α-imino esters **257**



Scheme 89 Transfer hydrogenation of α-imino esters **259** having an alkynyl substituent at the α-position

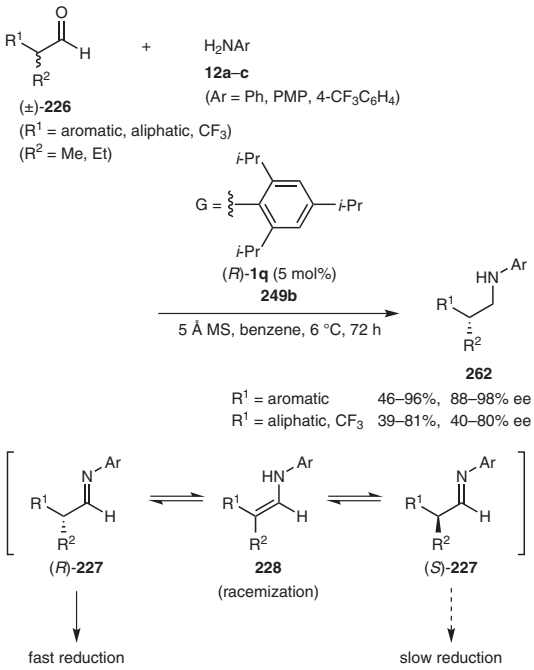
As shown in Schemes 86, 88, and 89, the reductive amination of ketones and the hydrogenation of ketimines catalyzed by chiral phosphoric acids were accomplished with high enantioselectivities. However, in these reductions, aryl derivatives, such as PMP, were primarily employed as the nitrogen protective group. The removal of these protective groups usually required somewhat harsh reaction conditions. Antilla and Li circumvented this drawback by using enamides **193** as the substrates (Scheme 90).[193] The reduction of enamides **193** proceeded via tautomerization to intermediary imines to give amine products **261** having an *N*-acetyl protective group that can be readily removed under standard conditions. Acetic acid was employed as the co-catalyst, which allowed for the reduction of the catalyst load of **1g** to 1 mol% while maintaining the high enantioselectivity. Acetic acid accelerated the tautomerization of the enamide to the imine, while it was inactive in the subsequent reduction and only chiral phosphoric acid **1g** functioned as the active catalyst for the successive transfer hydrogenation of the imine.



Scheme 90 Transfer hydrogenation of enamides **193**

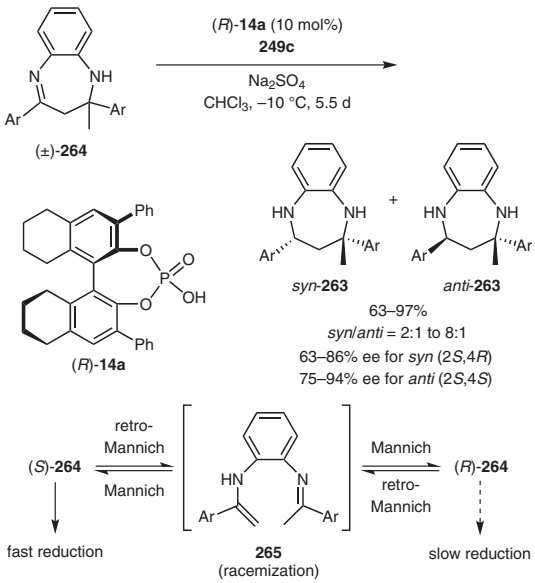
List and co-workers developed an excellent approach to synthesize β-branched amines in optically active forms by combining the enamine and reductive amination processes (Scheme 91).[169] The reductive amination of unsymmetrically α,α-disubstituted aldehydes **226** and aniline derivatives **12a–c** proceeded through a tautomerization between imine **227** and enamine **228**. Dynamic kinetic resolution occurred under the influence of catalyst (*R*)-**1q**, whereby the hydrogenation of (*R*)-**227** proceeded more rapidly than that of (*S*)-**227** to give β-branched amines **262** with moderate to high enantioselectivities (see Scheme 78).

Gong and co-workers reported a facial synthesis of chiral 1,3-diamine derivatives **263** bearing a quaternary stereo-



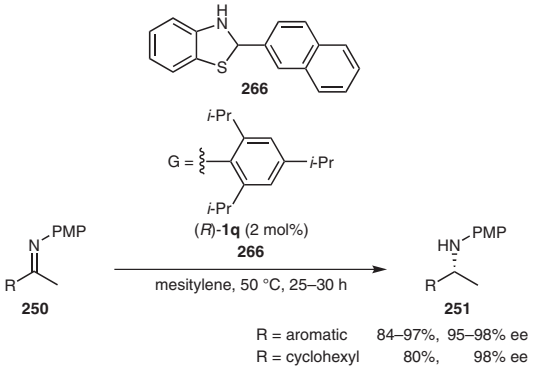
Scheme 91 Enantioselective synthesis of β-branched amines **262** through dynamic kinetic resolution

genic center via the transfer hydrogenation of 2,4-diaryl-2,3-dihydrobenzodiazepine derivatives **264** on the basis of dynamic kinetic resolution (Scheme 92).[194] The transfer hydrogenation of the *S*-enantiomer among racemic **264** proceeds rapidly in the presence of (*R*)-**14a** to afford (2*S*,4*R*)-*syn*-**263** predominantly along with (2*S*,4*S*)-*anti*-**263**. Meanwhile, the opposite enantiomer, (*R*)-**264**, undergoes slow transfer hydrogenation and the remaining (*R*)-**264** racemizes via intermediate **265** through the retro-Mannich and Mannich sequences.



Scheme 92 Enantioselective synthesis of 1,3-diamine derivatives **263** through dynamic kinetic resolution

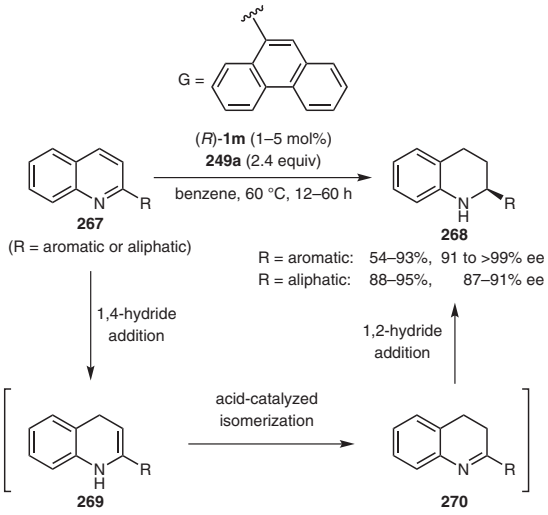
In organocatalytic hydrogenations, the hydrogen sources were, until recently, limited to Hantzsch esters **249**, which are the most well used cofactors in biochemical hydrogenation reactions.[184] Akiyama and Zhu utilized benzothiazoline derivative **266**,[195] which functioned as an efficient antioxidant with potent reducing ability,[196] as a novel hydrogen source, instead of Hantzsch esters **249** (Scheme 93). Aromatic methyl ketimines **250** having electron-donating and electron-withdrawing substituents were well tolerated in this hydrogenation system and even aliphatic ketimine underwent the reduction while maintaining excellent enantioselectivity. It is noteworthy that the present method, using **266** as a novel hydrogen source, provides the corresponding products **251** with higher enantioselectivities than those obtained in previous reports (see Scheme 86)[185,187,188] in which Hantzsch ester **249a** was employed. The distinct advantage of this protocol is that benzothiazoline **266** can be generated in situ from 2-naphthalenecarbaldehyde and 2-aminothiophenol. Thus, the three-component reaction between **250** and the in situ generated **266** becomes operative without considerable loss of enantioselectivity and chemical yield.



Scheme 93 Transfer hydrogenation using benzothiazoline derivative **266** as a novel hydrogen source

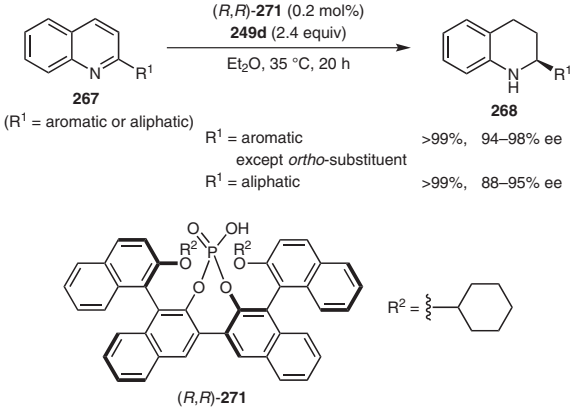
12.2 Tandem Transfer Hydrogenation of Quinolines and Pyridine Derivatives

The asymmetric hydrogenation of nitrogen-substituted heteroaromatic compounds provides a straightforward and attractive route to enantioenriched nitrogen heterocycles. In contrast, the enantioselective hydrogenation of these heteroaromatics using chiral transition-metal catalysts has not been fully established and successful examples of these transformations are limited.[197] The use of Hantzsch esters **249** as the hydrogen source was proven to be beneficial for the asymmetric hydrogenation of these heteroaromatics by Rueping et al. The enantioselective reduction of quinolines **267** to tetrahydroquinolines **268** using Hantzsch ester **249a** proceeded smoothly in the presence of chiral phosphoric acid catalyst **1m** (Scheme 94).[198] The method is applicable to a variety of 2-aryl- and 2-alkyl-substituted quinolines **267** and provides direct access to tetrahydroquinoline alkaloids **268** in a highly enantioselective manner. They proposed that the reaction proceeds via a tandem hydrogenation cascade. The first step of the cascade generates enamines **269** via the 1,4-hydride addition to quinolines **267**. Under acidic conditions, the subsequent isomerization of **269** provides imines **270**, which are delivered to the second step of the cascade. The 1,2-hydride addition to imines **270** with generation of the stereogenic center provides enantioenriched tetrahydroquinoline products **268**.



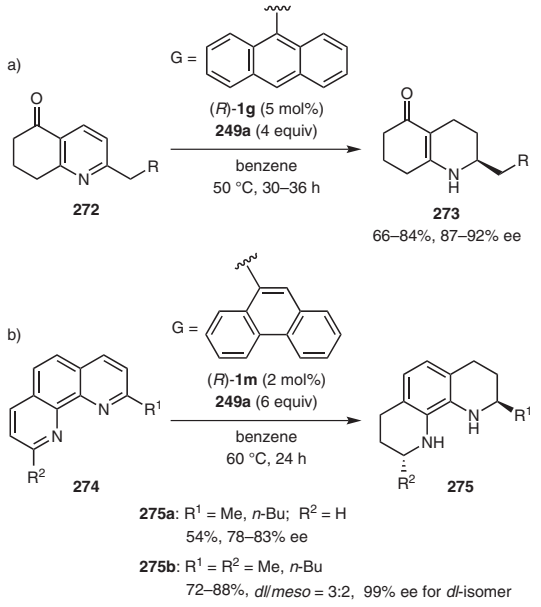
Scheme 94 Transfer hydrogenation of 2-substituted quinolines **267** to tetrahydroquinolines **268**

Du and co-workers reported the enantioselective hydrogenation of quinolines using a new type of axially chiral phosphoric acid catalyst **271** having a bis-BINOL scaffold (Scheme 95).[88h] Newly developed catalyst **271** showed higher efficiency than the parent mono-BINOL-derived phosphoric acid catalysts. The enantioselectivities of alkyl and aryl 2-substituted quinolines **267** were uniformly high and the corresponding tetrahydroquinolines **268** were obtained quantitatively even when the catalyst load was reduced to as little as 0.2 mol%. 2,3-Disubstituted quinolines were also hydrogenated with high diastereo- and enantioselectivities.

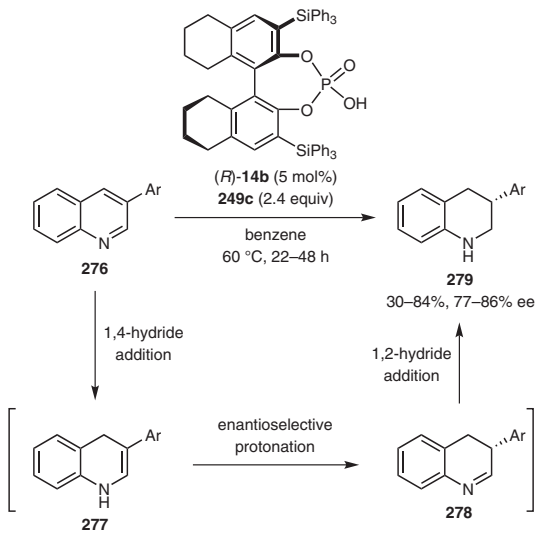


Scheme 95 Transfer hydrogenation of quinolines **267** using newly developed chiral phosphoric acid catalyst **271**

Rueping and Antonchick successively applied the cascade transfer hydrogenation strategy to the enantioselective reduction of pyridine derivatives (Scheme 96a).[199] Catalyst **1g** functioned efficiently in the hydrogenation of pyridine derivatives **272** to furnish the corresponding products **273**, hexahydroquinolinones, with high enantioselectivities. The method allows access to enantioenriched nitrogen heterocycles as useful precursors of various natural products. Metallinos et al. reported the enantioselective reduction of 2-substituted and 2,9-disubstituted 1,10-phenanthrolines **274** (Scheme 96b).[200] Although considerable amounts of *meso*-isomers were formed in the hydrogenation of 2,9-disubstituted 1,10-phenanthrolines **274b**, *dl*-octahydrophenanthrolines **275b** were obtained with excellent enantioselectivities.



Scheme 96 Transfer hydrogenation of pyridine and 1,10-phenanthroline derivatives



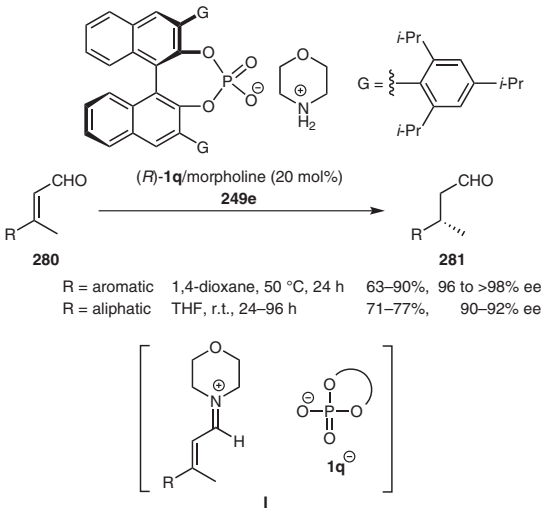
Scheme 97 Transfer hydrogenation of 3-substituted quinolines to tetrahydroquinolines

Rueping et al. further extended the method to the hydrogenation of 3-substituted quinolines **276** (Scheme 97).[201] Here, the key step is the enantioselective protonation of intermediary enamine **277**. The mechanisms of the stereodetermining step are entirely different from those of the asymmetric hydrogenation of 2-substituted quinolines **267**, where the 1,2-hydride addition step is the key to determining the stereochemical outcome (see Scheme 94). After thorough optimization of the phosphoric acid catalyst, **14b** was found to be the best, giving 3-substituted tetrahydroquinolines **279** with good enantioselectivities.

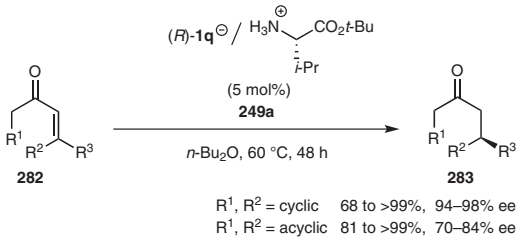
12.3 Transfer Hydrogenation of α,β-Unsaturated Carbonyl Compounds

Most organic transformations proceed via ionic intermediates or transition states and hence are influenced by the counterion, particularly in organic solvents, because ion pairs are ineffectively solvated in these media. Although efficient asymmetric catalytic transformations involving anionic intermediates have been realized using chiral cationic catalysts, such as phase-transfer catalysts,[181] an analogous version of inverse polarity was not accomplished until recently. In this context, List and Mayer introduced the concept of 'asymmetric counteranion directed catalysis (ACDC)' as a useful strategy in enantioselective organocatalytic transformations[152] and applied their ACDC concept to a metal-free biomimetic transfer hydrogenation of α,β-unsaturated aldehydes **280**,[183] in which a binary catalytic system of an achiral amine and a chiral phosphoric acid was employed (Scheme 98).[152] They found that the morpholine salt of **1q**, prepared readily by simple mixing, was a widely applicable and highly enantioselective catalyst for the transfer hydrogenation of α,β-unsaturated aldehydes **280**. The catalytic salt of morpholine and **1q** generates the ion pair, **I**, of achiral iminium cation and chiral phosphate anion, where the chiral phosphate anion could induce the asymmetry in the process. α,β-Unsaturated aldehydes having aromatic substituents at the β-position were reduced to their corresponding saturated aldehydes **281** in good yields with excellent enantioselectivities. The method is also applicable to α,β-unsaturated aldehydes with less sterically hindered aliphatic substituents, the transfer hydrogenations of which could not be achieved by previous methods using chiral amine base catalysts in a highly enantioselective manner.[183,184]

List and Martin further applied their salt catalyst to the enantioselective hydrogenation of α,β-unsaturated ketones **282** (Scheme 99).[202] Although, in the reduction of **282**, the morpholine/chiral phosphoric acid salt system failed to provide the corresponding saturated ketones **283** in satisfactory yields and enantioselectivities, ammonium phosphate, derived from (*R*)-**1q** and primary amine (*S*)-valine *tert*-butyl ester, proved to be effective for the present transfer hydrogenation. It is noteworthy that the salt derived from the opposite enantiomer of **1q**, namely, (*S*)-**1q**, and (*S*)-valine *tert*-butyl ester displayed a consid-



Scheme 98 Asymmetric counteranion directed organocatalytic transfer hydrogenation of α,β-unsaturated aldehydes **280**

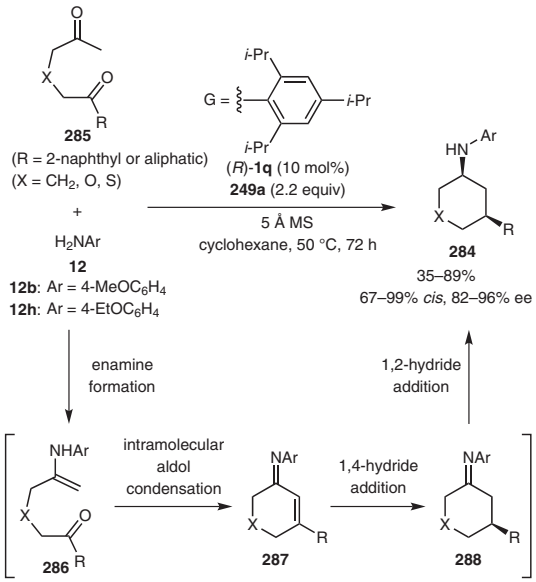


Scheme 99 Transfer hydrogenation of α,β-unsaturated ketones **282**

erable decrease in yields and enantioselectivities. Not only cyclic but also acyclic ketones **282** were reduced efficiently in the presence of (*R*)-**1q** and (*S*)-valine *tert*-butyl ester, giving saturated products **283** in good yields and enantioselectivities.

12.4 Application of Transfer Hydrogenation to Cascade Reaction

Cascade transformations involving different organocatalytic processes have emerged as a powerful and efficient method for the rapid construction of complex molecules starting from simple materials in one pot.[90] In particular, organocatalyses by amines or their salts were intensively applied to cascade transformations, including enamine or iminium ion, as the reactive intermediate.[203] List and Zhou successfully combined chiral phosphoric acid catalysis with these amine catalyses based on enamine and iminium ion mechanisms (Scheme 100).[204] They developed a highly enantioselective synthesis of 3-substituted (hetero)cyclohexylamines **284** from 2,6-diketones **285** via a three-step organocatalysis,[205] namely, (i) intramolecular aldol condensation via enamine **286** formation to give cyclized product **287**; (ii) 1,4-hydride addition under the iminium ion mechanism to give saturated imine **288**; and (iii) 1,2-hydride addition cascade catalyzed by chiral phosphoric acid and accelerated by aniline substrate **12b** or **12h**. Acid catalyst **1q** exhibited excellent performance for the cascade transformation, giving the corresponding 3-substituted (hetero)cyclohexylamines **284** with high enantio- and *cis*-selectivities. The reductive amination of 3-substituted cyclohexanones, intermediate **288** of the present cascade, generally provides the corresponding *trans*-isomer under standard reductive amination conditions. In contrast, in the present cascade transformation, *cis*-**284** was obtained predominantly.



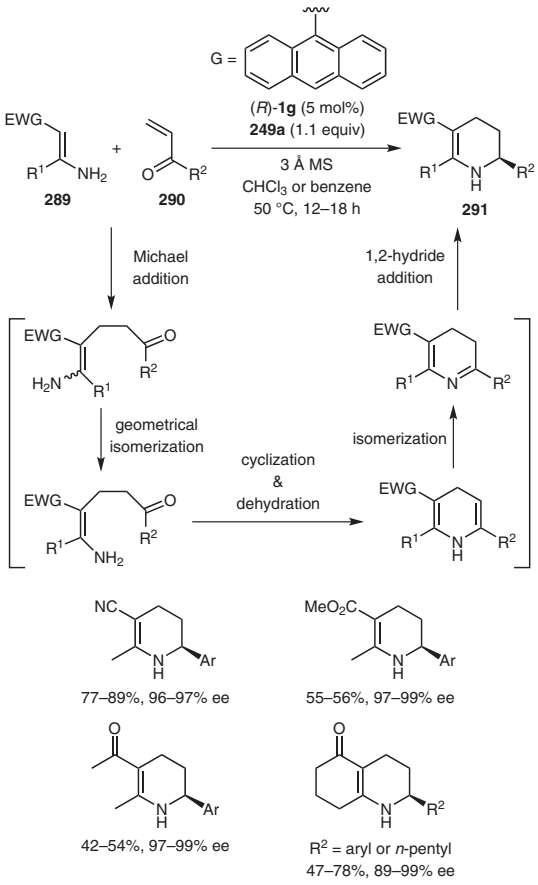
Scheme 100 Intramolecular aldol condensation/tandem transfer hydrogenation cascade

Rueping and Antonchick developed an organocatalytic multiple-cascade sequence using enamines **289** and α,β-unsaturated ketones **290** as substrates to obtain enantioenriched nitrogen heterocycles **291** (Scheme 101).[206] The multiple-cascade sequence comprises Michael addition, geometrical isomerization, cyclization, dehydration, isomerization, and 1,2-hydride addition, in which each single step is efficiently catalyzed by chiral phosphoric acid catalyst **1g**. The method enables direct, rapid, and efficient access to a diverse set of tetrahydropyridine and azadecalinone derivatives **291** with excellent enantioselectivities.

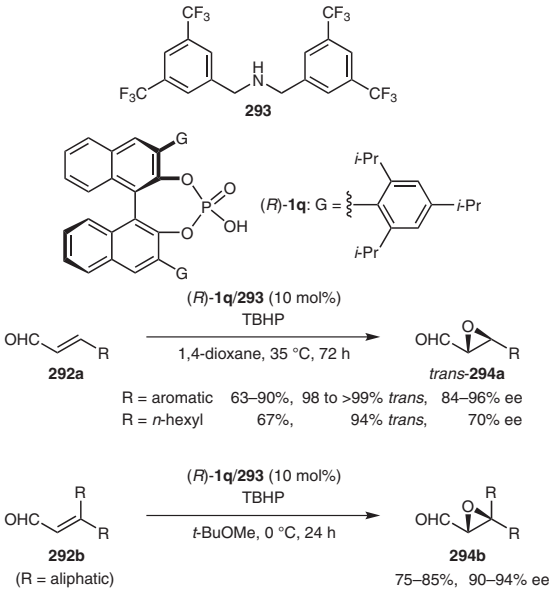
13 Oxidations

13.1 Epoxidation

Catalytic asymmetric epoxidation occupies a privileged position in organic synthesis owing to the fundamental importance of enantioenriched epoxides as key synthetic intermediates. A number of efficient protocols for the enantioselective epoxidation using chiral metal catalysts[207] and organocatalysts[208] have been reported to date. The Julia–Colonna epoxidation is one of the most efficient synthetic methods for the enantioselective functionalization of α,β-unsaturated ketones using hydrogen peroxide under basic conditions.[209] Since its discovery in



Scheme 101 Multiple-cascade sequence leading to tetrahydropyridine and azadecalinone derivatives **291**



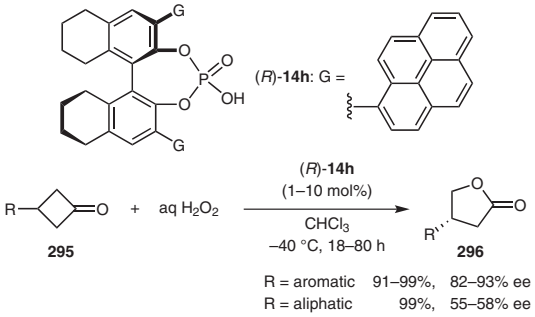
Scheme 102 Stereoselective epoxidation using ammonium phosphate salt catalyst

1980, the enantioselective epoxidation of α,β-unsaturated carbonyl compounds has emerged as an efficient route for preparing highly functionalized synthetic intermediates.[210]

List et al. applied their ACDC concept[152] to the development of the enantioselective epoxidation of α,β-unsaturated aldehydes **292** using an ammonium phosphate salt catalytic system (Scheme 102).[211] They identified a new catalytic salt that was derived from dibenzylamine derivative **293** and phosphoric acid **1q**, and functioned as an efficient enantioselective catalyst for 1,2-disubstituted enals **292a** having aromatic substituents at the β-position. The corresponding epoxides **294a**, with excellent *trans*- and enantioselectivities, were obtained in the presence of *tert*-butyl hydroperoxide (TBHP) as the oxidant, although an enal having an aliphatic substituent at the β-position exhibited a slight decrease in stereoselectivity. Notably, this salt-catalyzed reaction is well suited for trisubstituted enals **292b** to afford trisubstituted epoxides **294b** with high enantioselectivities, because these enals **292b** have previously been elusive substrates for all types of enantioselective epoxidation.

13.2 Baeyer–Villiger Oxidation

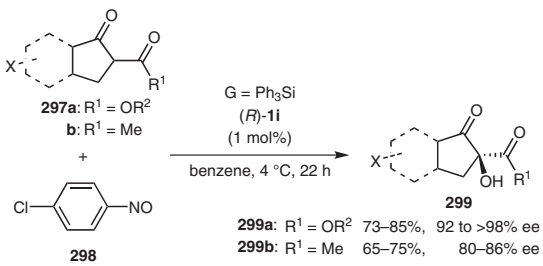
The Baeyer–Villiger reaction represents one of the most fundamental and widely applied reactions in organic synthesis.[212] However, the enantioselective Baeyer–Villiger reaction is largely unexplored in comparison with other catalytic enantioselective transformations. In addition, there are only a few cases where aqueous hydrogen peroxide is utilized as the terminal oxidant in the enantioselective Baeyer–Villiger reactions, despite the distinct advantage that its reduction product is water. Ding and coworkers successfully developed a highly enantioselective Baeyer–Villiger reaction of cyclobutanone derivatives **295** using chiral phosphoric acid catalyst **14h** in combination with aqueous hydrogen peroxide as the oxidant (Scheme 103).[213] A variety of 3-aryl- and alkyl-substituted cyclobutanones **295** can be oxidized by 10 mol% **14h** with hydrogen peroxide. High enantioselectivities were achieved in the reaction of cyclobutanones having aromatic substituents. It is noteworthy that the value (R = Ph: 88% ee) represents the highest enantioselectivity obtained in the asymmetric Baeyer–Villiger oxidation of **295a** (R = Ph) with chemical catalysts, although the oxidation of **295** having aliphatic substituents gave the corresponding γ-butyrolactones **296** with modest enantioselectivities. Ding, Li, and co-workers also elucidated the mechanism of the Baeyer–Villiger oxidation on the basis of experimental and theoretical studies.[213b] The phosphoric acid catalyst participates in both the carbonyl addition and the subsequent rearrangement steps in a synergistic manner through hydrogen-bonding interactions. The catalyst simultaneously enhances the electrophilicity of the carbonyl carbon via protonation and the nucleophilicity of the hydrogen peroxide through Brønsted basic site in the addition step followed by the rearrangement step, in which the dissociation of the hydroxy group from the Criegee intermediate is also accelerated by the catalyst.



Scheme 103 Baeyer–Villiger reaction of cyclobutanone derivatives **295**

13.3 α-Hydroxylation of 1,3-Dicarbonyl Compounds

The α-hydroxylation of 1,3-dicarbonyl compounds has been well utilized, affording α-hydroxy carbonyl compounds that serve as key structural elements in a number of natural products and pharmaceuticals. In this regard, considerable effort has been devoted to the establishment of efficient methods for the preparation of α-hydroxy 1,3-dicarbonyl compounds in optically active forms. However, the development of catalytic enantioselective α-hydroxylations of 1,3-dicarbonyl compounds has faced limited success.[214] Zhong and co-workers developed a highly enantioselective α-hydroxylation of 1,3-dicarbonyl compounds **297** using chiral phosphoric acid catalyst **1i** (Scheme 104).[215] In general, α-hydroxylation reactions are accomplished by using oxaziridines and peroxides as oxygen sources. Zhong and co-workers, however, employed 4-chloronitrosobenzene (**298**) as the oxygen source.[216] Chiral phosphoric acid catalyst **1i** activates the nitroso compound via protonation of the basic nitrogen atom of the nitroso moiety and promotes bond formation between the oxygen atom and the α-carbon atom of 1,3-dicarbonyl compounds **297**. Subsequent nitrogen–oxygen bond cleavage affords α-hydroxylation products **299** in optically active forms. β-Keto esters **297a** bearing a five-membered ring were well tolerated in the α-hydroxylation, giving the corresponding products **299a** with excellent enantioselectivities, irrespective of the steric demand of the ester moiety. Although in the reaction of 1,3-diketones **297b**, a slight decrease in enantioselectivities was observed, the α-hydroxylation of 1,3-diketones was achieved in high yields with good enantioselectivities for the first time.



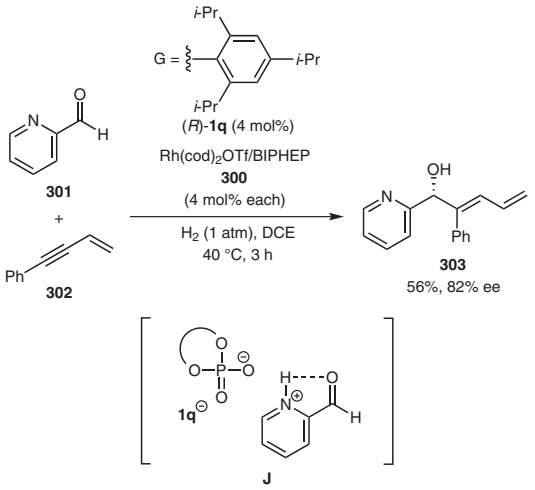
Scheme 104 α-Hydroxylation of 1,3-dicarbonyl compounds **297** by 4-chloronitrosobenzene (**298**)

14 Combined Use of Metal Complex and Phosphoric Acid Catalysts

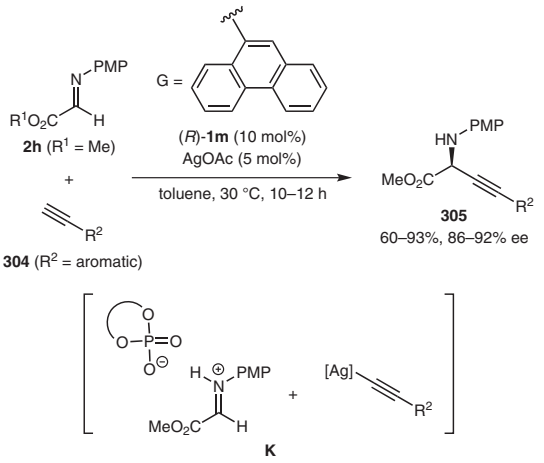
In the past decade, tremendous progress has been made in the field of catalysis using small organic molecules, namely, organocatalysis.[1] Meanwhile, catalysis by transition-metal complexes has continued to be applied to a broad range of organic transformations and it occupies a privileged position in 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 to construct binary catalytic systems,[217] and this has attracted much attention as it has the potential to realize unprecedented transformations. Recently, several excellent approaches were established with the chiral phosphoric acid/metal complex binary catalytic system in catalytic enantioselective transformations. There are two types of combination in the binary catalytic system. One is that each reactant is activated simultaneously by one type of catalyst; thus, the metal complex activates nucleophiles, while the phosphoric acid activates electrophiles in a cooperative manner. The other is the consecutive transformation using a binary catalytic system, that is, relay catalysis for a multi-step sequence in which each catalyst promotes one type of reaction in a one-pot sequential manner.

14.1 Cooperative Catalysis by Metal Complex and Phosphoric Acid

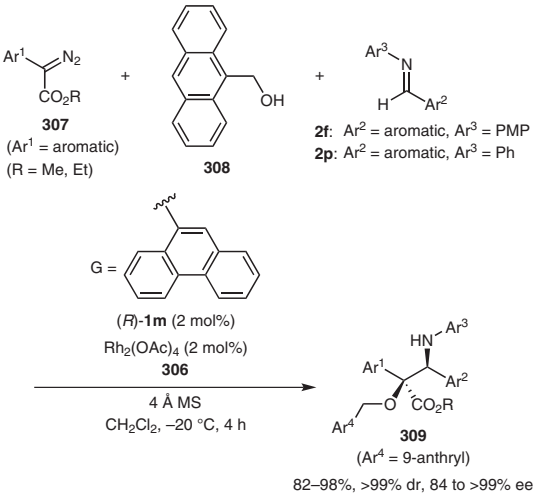
Krische and Komanduri developed a highly enantioselective reductive coupling reaction of 1,3-enynes with heteroaromatic aldehydes and ketones catalyzed by a chiral rhodium complex under hydrogenation conditions.[218] In the course of their studies, they found that a Brønsted acid co-catalyst accelerated the rate of the reaction significantly. In order to elucidate the role of the Brønsted acid co-catalyst, they attempted to use a combination of achiral rhodium complex **300** with chiral phosphoric acid **1q** in the reductive coupling between 2-pyridinecarboxaldehyde (**301**) and 1,3-enyne **302** (Scheme 105). The product **303** was obtained in an optically active form, although the enantioselectivity obtained in this combination was lower than that observed in the parent combination of the chiral rhodium complex and the achiral Brønsted acid co-catalyst. This result indicates that the rhodium complex and the Brønsted acid functioned as the cooperative catalyst. Thus, **1q** protonates 2-pyridinecarboxaldehyde (**301**) to give intermediate **J** in advance of the carbon–carbon bond-forming step, hence accelerating the coupling reaction because of the lowered LUMO of aldehyde **301**. Furthermore, the enantioenrichment of product **303** suggests that the chiral counteranion of **1q** is incorporated into the transient assembly of the coupling reaction through hydrogen-bonding interactions. The authors disclosed that the protonation of **301** by **1q** is responsible for the asymmetric induction and not the ion pairing to the rhodium



Scheme 105 Rhodium complex/chiral phosphoric acid cooperative catalysis for reductive coupling between heteroaromatic aldehyde **301** and 1,3-enyne **302**



Scheme 106 Silver complex/chiral phosphoric acid cooperative catalysis for enantioselective alkynylation of α-imino ester **2h**



Scheme 107 Rhodium complex/chiral phosphoric acid cooperative catalysis for three-component coupling reaction

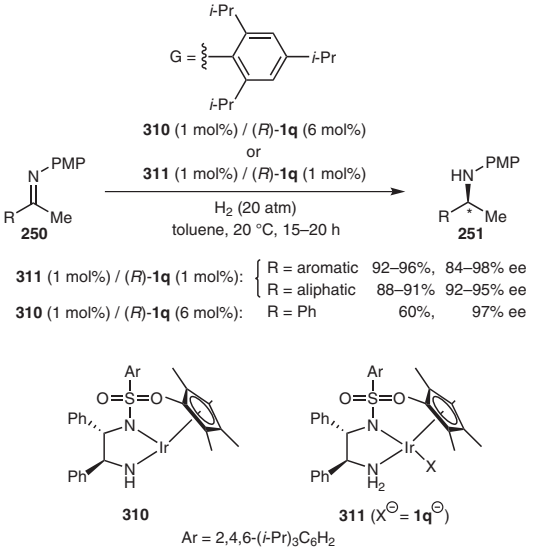
complex, on the basis of these results coupled with their previous studies.[219]

Rueping et al. developed an excellent cooperative process that comprised an enantioselective Brønsted acid and silver complex catalyzed alkynylation (Scheme 106).[220] The enantioselective alkynylation under binary catalytic conditions was accomplished in the reaction of α-imino ester **2h** with a series of aryl-substituted terminal alkynes **304**, in which the α-imino ester and the alkyne were activated by phosphoric acid **1m** and the silver complex, respectively. α-Amino acid products **305** having an alkynyl substituent were obtained in good yields with high enantioselectivities. Although, from a mechanistic viewpoint, an exchange of the metal counteranion from acetate to chiral phosphate, leading to the formation of a chiral silver complex, cannot be ruled out, both catalysts are required for the reaction to proceed, and, more importantly, the reaction that proceeded under the influence of a chiral silver complex and an achiral phosphoric acid catalyst resulted in racemic products **305**. As shown in reactive intermediate **K**, the simultaneous activation of both α-imino ester **2h** and alkyne **304** by cooperative organic and metallic catalyses is crucial in furnishing α-amino ester products **305** in optically active forms.

Hu, Gong, and co-workers developed a system that involved cooperative catalysis by chiral phosphoric acid **1m** and achiral rhodium complex **306** (Scheme 107).[221] They applied the binary catalytic system to a three-component coupling reaction among α-diazoesters **307**, primary alcohols, and aldimines **2**. The steric bulk of the primary alcohol had a significant effect on both diastereo- and enantioselectivities. The sterically demanding 9-anthracenemethanol (**308**) was the best component to give β-amino-α-alkoxy esters **309** with excellent stereoselectivities under cooperative catalysis by phosphoric acid **1m** and rhodium complex **306**. Hu and co-workers further applied this cooperative catalysis approach to a four-component coupling reaction among α-diazoesters, primary alcohols, aromatic aldehydes, and aniline derivatives.[222]

The enantioselective reduction of imines provides direct access to chiral amines, one of the most important functionalities in fine chemical and pharmaceutical compounds. As shown in Schemes 86–97, the organocatalytic approach has been established to provide an efficient route to the enantioselective transfer hydrogenation of ketimines using Hantzsch ester **249** as the hydrogen source. However, in the hydrogenation of ketimines using chiral metal catalysts, this transformation remains challenging, particularly in the case of acyclic ketimines **250**. Xiao and co-workers successfully developed a binary catalytic system for the enantioselective hydrogenation of acyclic ketimines **250**, where diamine-ligated iridium complex **310**, in combination with chiral phosphoric acid **1q**, enabled the highly enantioselective hydrogenation of **250**, affording the corresponding amines **251** in good yields with excellent enantioselectivities (Scheme 108).[223] Notably, the preformed iridium complex **311**, prepared from **310** and **1q**, functioned as an efficient catalyst with-

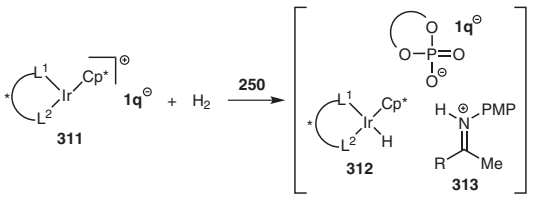
out any detrimental effect on the enantioselectivity. More interestingly, the addition of **1q** to preformed **311** markedly enhanced the catalytic activity with higher conversion being observed at 1 mol% each of **311** and **1q**. Xiao and co-workers further applied the present cooperative catalysis to the enantioselective reductive amination reaction of ketones with aniline derivatives under hydrogenation conditions.[224]



Scheme 108 Iridium complex/chiral phosphoric acid cooperative catalysis for enantioselective hydrogenation of ketimines **250**

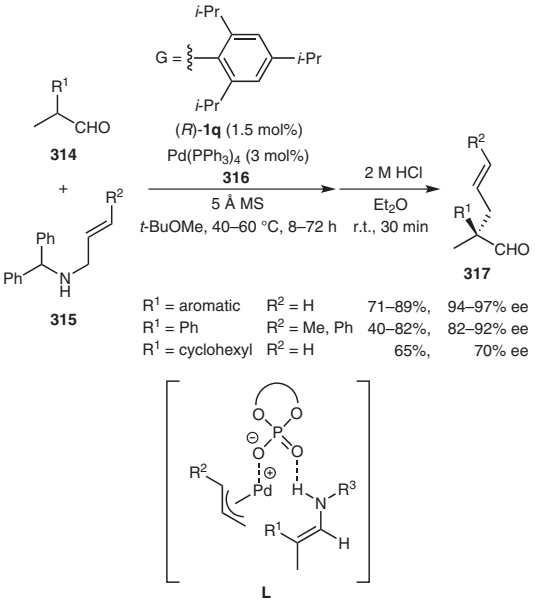
Xiao and co-workers established the present cooperative catalysis by taking into consideration Norton's mechanistic studies on ruthenium-catalyzed ionic hydrogenation of iminium cations where imines can be reduced through an ionic pathway,[225] while it is generally believed that the metal-catalyzed hydrogenation proceeds via the coordination between the nitrogen atom of imine and the metal center. Hydrolytically hydrogen-activating catalyst **312** is associated with chiral counteranion **1q**$^-$, which influences the enantio-discrimination by ion pairing with resulting iminium cation **313** (Scheme 109). In fact, the enantioselectivity observed was significantly affected by the chiral phosphoric acids employed.

As shown in Schemes 106– 108, one type of catalyst activates each reactant simultaneously: the phosphoric acid activates imines as the electrophilic component while the metal complex activates nucleophiles in a cooperative manner.

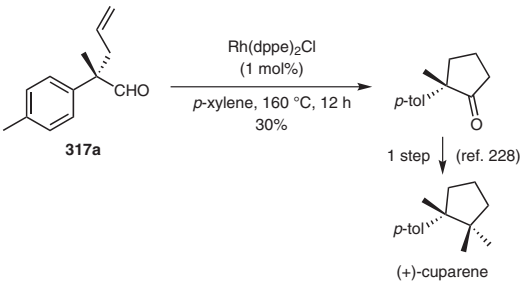


Scheme 109 Cooperative catalysis by iridium complex/chiral phosphoric acid binary system

List and Mukherjee developed the enantioselective α-allylation of α-branched aldehydes **314** using cooperative catalysis (Scheme 110).[226] The transformation of **314** with allylamine derivatives **315** was mediated in a highly enantioselective manner under the influence of chiral phosphoric acid **1q** with achiral palladium complex **316**, $Pd(PPh_3)_4$. The reaction likely proceeded through reactive intermediate **L**, including a π-allyl palladium complex, an enamine, and chiral phosphate counteranion **1q**$^-$, to afford the corresponding chiral aldehydes **317** bearing a quaternary stereogenic center with high enantioselectivities. In this transformation, the chiral phosphate counteranion activates the nucleophilic enamine and this activation mode is in contrast to the previous cooperative catalyses where the phosphoric acid activates electrophilic imines (see Schemes 106–108). The method enables efficient access to the enantioselective construction of all-carbon quaternary stereogenic centers, which represents an important yet considerable challenge in organic synthesis.[227] The same authors also demonstrated a concise synthesis of (+)-cuparene by taking advantage of this method for preparing **317a** as the key building block (Scheme 111).[228]



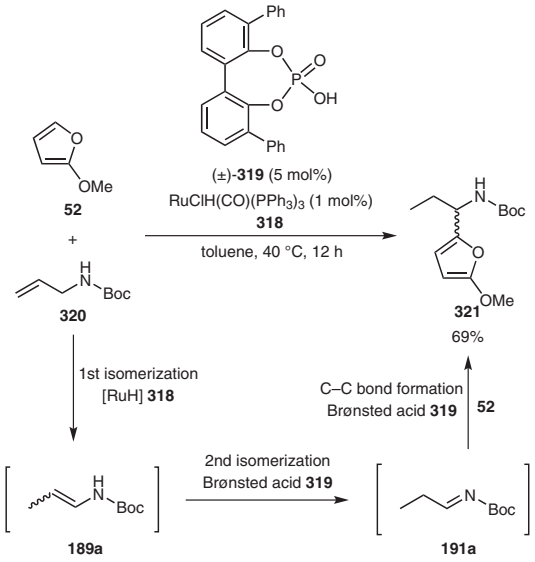
Scheme 110 Palladium complex/chiral phosphoric acid cooperative catalysis for α-allylation of α-branched aldehydes **314**



Scheme 111 Synthetic application of palladium complex/chiral phosphoric acid cooperative catalysis

14.2 Relay Catalysis by Metal Complex and Phosphoric Acid

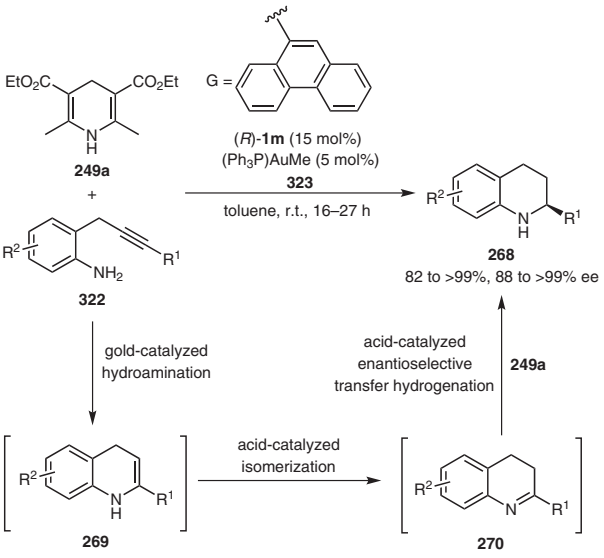
As shown in Schemes 105– 108 and 110, each reactant was activated by one type of catalyst simultaneously. Terada and Sorimachi reported an unprecedented consecutive transformation using a binary catalytic system, that is, relay catalysis for the tandem isomerization/carbon–carbon bond-formation sequence promoted by a binary catalyst consisting of ruthenium hydride complex **318** and Brønsted acid **319** (Scheme 112).[229] The reaction of *N*-Boc-protected allylamine **320** with 2-methoxyfuran (**52**) proceeded smoothly to give product **321**, with a nitrogen functionality at the stereogenic center, in good yield. Control experiments revealed that both catalysts, ruthenium complex **318** and Brønsted acid **319**, are indispensable to the sequential processes. Although a racemic acid catalyst was employed in this case, an enantioselective version would also be applicable, considering recent progress in enantioselective Friedel–Crafts reactions using chiral phosphoric acid catalysts (see Sections 5.1 and 9.1).



Scheme 112 Relay catalysis by ruthenium complex/Brønsted acid binary system

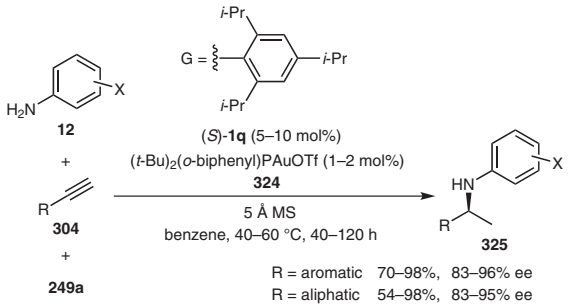
The present sequential transformation involves a three-step relay catalysis where: (i) the isomerization of *N*-allylcarbamate **320** to enecarbamate **189a** is catalyzed by the ruthenium hydride complex **318**; (ii) the subsequent isomerization of **189a** to intermediary imine **191a** is relayed by acid catalyst **319**; and (iii) the catalytic sequence is terminated by a carbon–carbon bond-forming reaction of **191a** with electron-rich aromatic compounds **52** as a nucleophilic component under the influence of acid catalyst **319**. The advantage of this relay catalysis is that the method enables the generation of reactive imines **191** from readily available allylcarbamates in a one-pot reaction via tandem isomerization. Terada and Sorimachi also applied the present relay catalysis to the reaction of a 1,3-dicarbonyl compound, instead of 2-methoxyfuran (**52**), as the nucleophilic component (see Section 9.1). The corresponding Mannich product was obtained in an acceptable yield.

The enantioselective version of the relay transformation by organic and metallic catalyses was successfully demonstrated by Gong and co-workers (Scheme 113).[230] They accomplished the direct transformation of *o*-propargylaniline derivatives **322** into tetrahydroquinolines **268** in a highly enantioselective manner through the hydroamination of alkynes/isomerization/enantioselective transfer hydrogenation (see Section 12.2) sequence under the relay catalysis of an achiral gold complex **323**/chiral phosphoric acid **1m** binary system. A control experiment using chiral gold phosphate, prepared from the silver salt of **1m** and Ph_3PAuCl, showed that the reaction was incomplete and the enantioselectivity was lower than that obtained in the binary catalytic system. Therefore, it can be excluded that the chiral gold phosphate, even if it were generated in situ, functions as the dominant catalytic species at the last step, namely, the enantioselective transfer hydrogenation of **270**. Instead, chiral phosphoric acid **1m** plays the dominant role in the actual enantioselective catalyst.



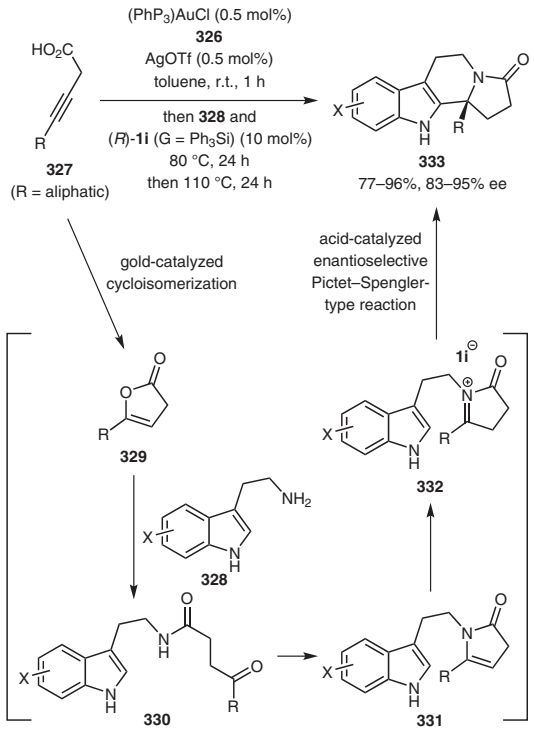
Scheme 113 Enantioselective relay catalysis by gold complex/chiral phosphoric acid binary system for tetrahydroquinoline synthesis

Meanwhile, Che and Liu reported an intermolecular version of Gong's relay catalysis, that is, the hydroamination of alkynes/isomerization/enantioselective transfer hydrogenation sequence (Scheme 114).[231] The intermolecular relay catalysis was accomplished via a three-component reaction among terminal alkynes **304**, aniline derivatives **12**, and Hantzsch ester **249a** in the binary catalytic system composed of gold complex **324** and chiral phosphoric acid **1q**. This relay catalysis exhibited a very broad substrate scope toward diversely substituted chiral amines **325** in good yields with high enantioselectivities.



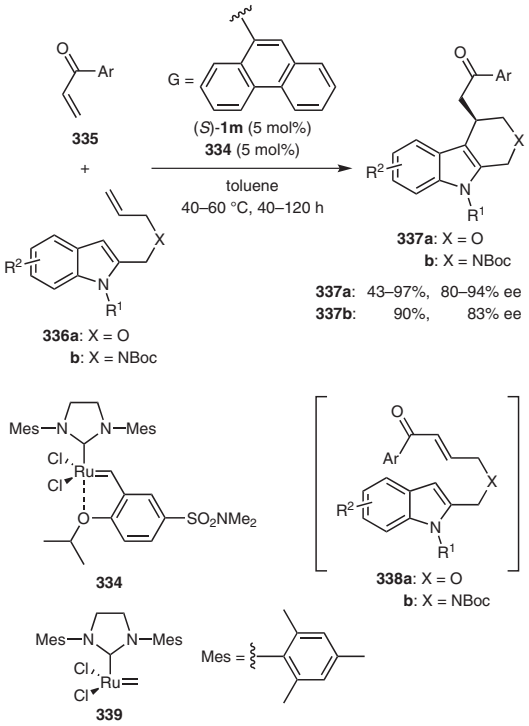
Scheme 114 Relay catalysis by gold complex/chiral phosphoric acid binary system for amine synthesis

Shortly thereafter, Dixon and co-workers reported a binary catalytic system composed of gold complex **326** and chiral phosphoric acid **1i** for a one-pot sequential transformation of alkynoic acids **327** and tryptamines **328** (Scheme 115).[232] The initial step of this sequential transformation is the gold-catalyzed cycloisomerization of **327**, affording substituted furanones **329**. In a previous publication, it was pointed out that this initial cycloisomerization is not promoted by Brønsted acid catalysts.[233] Subsequent steps were conducted by adding tryptamines **328** and phosphoric acid catalyst **1i** in a one-pot procedure; nucleophilic ring opening of furanone derivatives **329** by tryptamines **328** led to acyclic ketoamide intermediate **330**, and this was followed by dehydrative recyclization to afford enamides **331**. Resulting enamides **331** generated *N*-acyl iminium ions **332** as the reactive intermediate under the influence of chiral phosphoric acid catalyst **1i** and, following Pictet–Spengler-type ring closure, polycyclic tetrahydro-β-carboline derivatives **333** were formed in good yields with high enantioselectivities.



Scheme 115 Relay catalysis by gold complex/chiral phosphoric acid binary system for polycyclic tetrahydro-β-carboline synthesis

You and co-workers combined olefin cross-metathesis with intramolecular Friedel–Crafts reaction in a one-pot sequence using ruthenium complex **334** and chiral phosphoric acid **1m** (Scheme 116).[234] This sequential transformation involves two distinct catalytic cycles: the first cycle is the olefin cross-metathesis between aryl vinyl ketones **335** and allyl indolylmethyl ethers **336a** by ruthenium complex **334**, giving rise to enones **338**, and the subsequent catalytic cycle involves the intramolecular Friedel–Crafts reaction of **338** under the influence of chiral phosphoric acid **1m**. This binary catalytic process indeed worked well in the reaction of **335** with **336a** to afford the corresponding cyclized products **337a** in good yields with high enantioselectivities. However, this method affords products **337a** with slightly lower enantioselectivities than that observed in the chiral phosphoric acid catalyzed intramolecular Friedel–Crafts reaction of **338a** (e.g., **337aa**: R^1 = Me, R^2 = H, Ar = Ph, 94% ee vs. 96% ee), presumably owing to the generation of Lewis acidic ruthenium complex **339** during the course of the first catalytic cycle.[235] Thus, the activation of enones **338** by achiral ruthenium complex **339** leads to undesired racemic product **337a**, although this achiral catalytic process is not a dominant cycle because of little loss of enantioselectivity during the sequential catalysis. The method is also applicable to the construction of the tetrahydro-β-carboline skeleton: the reaction of nitrogen analogue **336b** with phenyl vinyl ketone (**335a**) provided cyclized product



Scheme 116 Relay catalysis by ruthenium complex/chiral phosphoric acid binary system in olefin cross-metathesis/intramolecular Friedel–Crafts reaction sequence

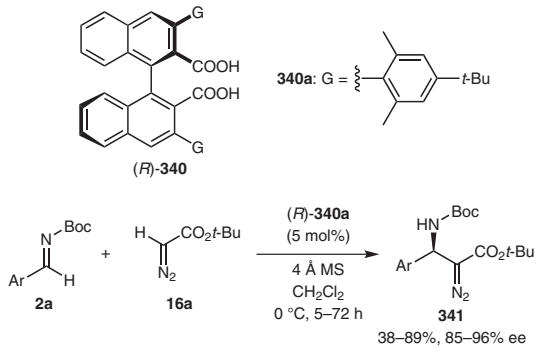
337b (R^1 = Me, R^2 = H, Ar = Ph) in good yield, albeit with a slight decrease in enantioselectivity.

15 New Aspects in the Development of Chiral Brønsted Acid Catalysts

Since the development of chiral phosphoric acids and their analogues as enantioselective catalysts, continuous effort has been made to cultivate novel structural motifs of chiral Brønsted acid catalysts having acidic functionalities other than phosphoric acid, and several efficient chiral acid catalysts have been reported to date. This section reviews recent progress in the development of chiral Brønsted acid catalysts, especially those bearing strongly acidic functionalities.

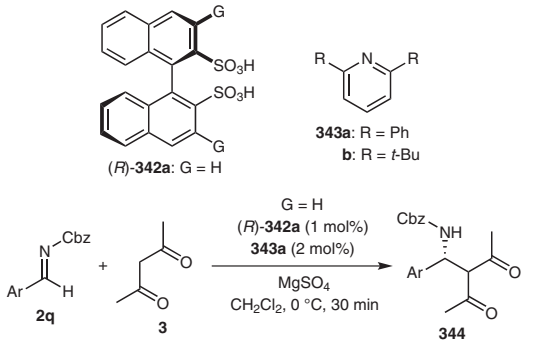
15.1 Chiral Brønsted Acid Catalysts Other Than Phosphoric Acid Catalysts

One of the key principles in the design of chiral Brønsted acid catalysts is the choice of a catalyst having an appropriate acidity. Although an important class of moderate Brønsted acids, carboxylic acids, is often utilized as one of the most fundamental acid catalysts in a variety of organic transformations, these carboxylic acids have rarely been employed in enantioselective catalyses,[236] presumably because of the poor catalytic activity of the carboxylic acid and the difficulty of constructing an efficient chiral environment around it. Maruoka and Hashimoto overcame these intrinsic problems by introducing two carboxylic acid moieties in the catalyst molecule. They developed novel chiral Brønsted acid catalysts **340**, which consist of two carboxylic acids and an axially chiral binaphthyl moiety (Scheme 117).[237] Dicarboxylic acid **340a** functioned as an efficient enantioselective catalyst in the Mannich-type reaction of *N*-Boc imines **2a** with diazoacetate **16a**, affording the corresponding products **341** with high enantioselectivities. They also applied dicarboxylic acid catalysts **340** to the enantioselective aziridination of diazoacetamides with *N*-Boc imines[238] and the enantioselective imino azaenamine reaction of arylaldehyde *N*,*N*-dialkylhydrazones with *N*-Boc imines.[239]



Scheme 117 Mannich-type reaction of *N*-Boc imines **2a** with diazoacetate **16a**, catalyzed by a novel chiral Brønsted acid having two carboxylic acids

Combined acid and base salts, such as pyridinium *p*-toluenesulfonate (PPTS), are one of the most utilized acid catalysts in organic synthesis. These acid–base salts have several advantages over single-molecule catalysts in terms of flexibility in the design of their dynamic complexes. Ishihara and co-workers focused their attention on the superior properties of these acid–base combined organic salts and developed novel chiral Brønsted acids derived from binaphthyldisulfonic acid **342** and pyridine derivatives **343** (Scheme 118).[240] The salt catalyst generated in situ from **342a** (G = H)[241] and 2,6-diphenylpyridine (**343a**) exhibited excellent performance in the direct Mannich reaction of *N*-Cbz imines **2q** with acetylacetone (**3**), affording the corresponding products **344** with high enantioselectivities. The distinct advantage of the salt catalyst is that both the Brønsted acidity and the bulk can be readily controlled by achiral pyridine derivatives **343** without substituents at the 3,3′-positions of the binaphthyl backbone (G = H). In fact, catalytic activities and enantioselectivities were markedly dependent on the achiral pyridine **343** employed. The use of pyridine derivative **343b**, with its sterically bulky *tert*-butyl substituents at the 2,6-positions, resulted in a considerable decrease in chemical yield with slightly lower enantioselectivity (76% ee). The importance of the salt formation with the pyridine derivative is obvious, because a significant decrease in enantioselectivity (to only 17% ee) was observed in the absence of pyridine derivatives, despite furnishing **344a** in good yield.

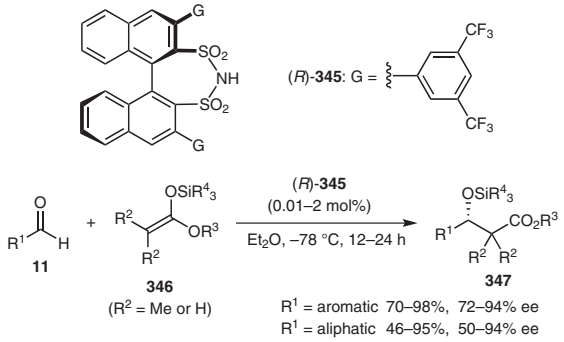


acid–base combined salt catalysts	yield of **344a** (Ar = Ph)	
(*R*)-**342a** (5 mol%)/**343a** (10 mol%)	74%	92% ee
(*R*)-**342a** (5 mol%)/**343b** (10 mol%)	32%	76% ee
(*R*)-**342a** (5 mol%)/ –	81%	17% ee

Scheme 118 Mannich reaction of *N*-Cbz imines **2q** with acetylacetone (**3**) catalyzed by chiral disulfonic acid/pyridine derivative combined organic salts

Strong chiral Brønsted acids have great potential for high-performance enantioselective catalysis in general and are particularly promising for the activation of important but less basic substrate classes, such as aldehydes. List and co-workers reported that a disulfonimide is a promising acid catalyst for the activation of simple aldehydes (Scheme 119).[242] They identified that the newly developed chiral cyclic disulfonimide **345**, with a binaphthyl

backbone, functioned as a powerful enantioselective catalyst for the Mukaiyama aldol reaction of aldehydes **11** with ketene silyl acetals **346**.

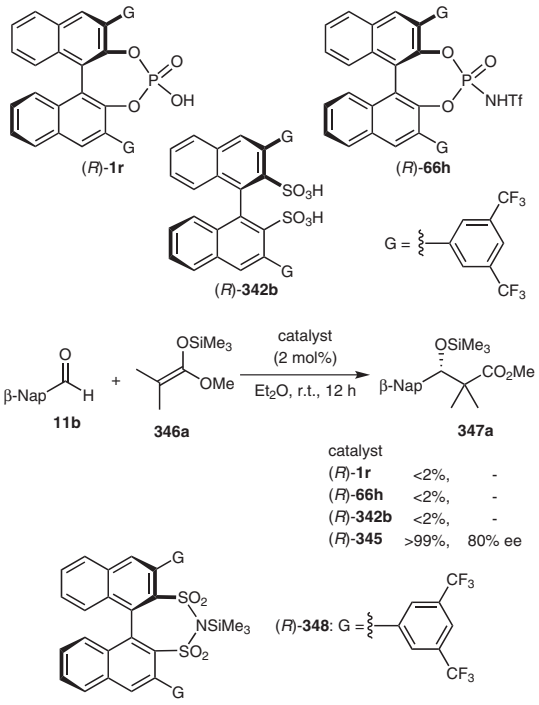


Scheme 119 Mukaiyama aldol reaction catalyzed by chiral disulfonimide **345**

Their basic idea in the design of chiral disulfonimide catalysts originates from the resemblance in relative reactivity between triflic acid (TfOH) and triflylimide (Tf_2NH), which are both powerful Brønsted acid catalysts: TfOH (pK_a –5.9 in water) is much more Brønsted acidic than Tf_2NH (pK_a 1.7 in water); however, the relationship is reversed if one regards the Lewis acidity of the corresponding silylated species, with that of $TMSNTf_2$ being much stronger than that of TMSOTf.[243] Furthermore, the C_2-symmetric binaphthyl disulfonimide topology is of particular interest as it differs from that of the corresponding pseudo-C_2-symmetric phosphoric acids, and hence the corresponding silylated species may serve as promising chiral Lewis acid catalysts. Indeed, a comparison of phosphoric acid **1r** and phosphoramide **66h** with disulfonic acid **342b** and disulfonimide **345** revealed that disulfonimide catalyst **345** was not only far more active than the alternative catalysts, **1r**, **66h**, and **342b**, but also provided product **347a** with high enantioselectivity in the Mukaiyama aldol reaction of **11b** with **346a** (Scheme 120). List and co-workers concluded that the Lewis acid mechanism seems to be more plausible than the Brønsted acid catalysis in this Mukaiyama aldol reaction.[242] Thus, sulfonimide catalyst **345** is first silylated by ketene acetal **346**, affording *N*-silyl disulfonimide **348** that is responsible for the active enantioselective catalyst through the O-silylation of aldehyde **11**. They also pointed out that *N*-silyl disulfonimide **348** represents a powerful catalyst for enantioselective silicon catalysis and a number of reactions catalyzed by $TMSNTf_2$, and similar catalysts should be accessible in an enantioselective fashion.

15.2 Chiral Conjugate Acid Catalysts Derived from Chiral Bases

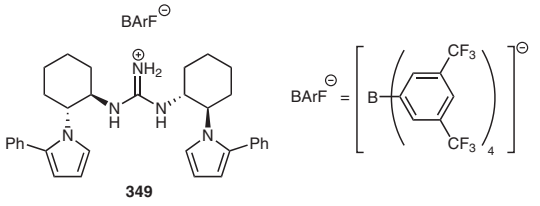
Most of the chiral Brønsted acid catalysts developed can be classified as nonionic compounds.[2] In contrast, the hydrogen-bonding donor capability of a cationic organic molecule with a less coordinatable anion, such as tetraarylborate, has been well investigated. This type of chiral

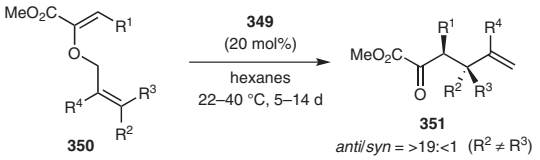


Scheme 120 Mukaiyama aldol reaction catalyzed by various chiral acid catalysts

Brønsted acid is generated as the conjugate acid of a chiral organic Brønsted base. However, the development of cationic Brønsted acid catalysts for enantioselective transformations has been largely unexploited in comparison with that of nonionic chiral Brønsted acid catalysts.[244] Jacobsen and Uyeda successfully developed a cationic chiral Brønsted acid catalyst that was furnished from a chiral guanidine base (Scheme 121).[245] Thus, chiral guanidinium ion **349** having a fluorinated tetraarylborate as the counteranion functioned as an efficient enantioselective catalyst for the Claisen rearrangement of ester-substituted allyl vinyl ethers **350**. Notably, the enantioselectivity is strongly dependent on the substrate employed; introduction of the ester substituent on the allyl vinyl ethers is indispensable for achieving high enantioselectivity, although the guanidinium catalyst induces rate enhancements in the rearrangement of a variety of substituted allyl vinyl ethers. Substrates having an alkyl group (Me or Et) at the vinyl terminus afforded rearranged products **351** with high enantioselectivities. Although the introduction of substituents at the allyl terminus resulted in a slight decrease in enantioselectivities, not only *anti*-isomers but also products having a quaternary stereogenic center were obtained with high diastereoselectivities.

Meanwhile, Ooi and co-workers designed and synthesized novel cationic chiral Brønsted acid catalyst **352** (Scheme 122).[246] Their strategy for the molecular design was to employ a chiral *P*-spiro tetraaminophosphonium cation framework as the primary structure, which is a unique structural motif introduced by their research group,[247] where the core structure of HN-P^+-NH interacts with electrophiles through two hydrogen bonds that seem to regulate the relative location between the electrophile





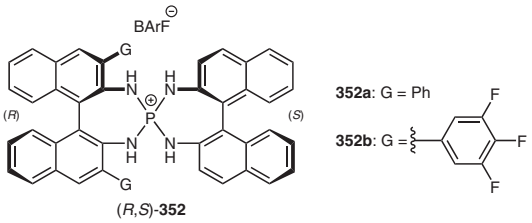
R^1	R^2	R^3	R^4		
Me or Et	H	H	H	80–86%,	92% ee
Et	*n*-Pr or Ph	H	H	91–92%,	81–85% ee
Me	H	H	Me	73%,	96% ee
Et	Me	Me	H	89%,	81% ee
Et	Ph or alkyl chain	Me	H	73–89%,	82–84% ee

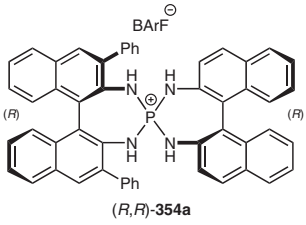
Scheme 121 Claisen rearrangement catalyzed by chiral guanidinium ion **349**

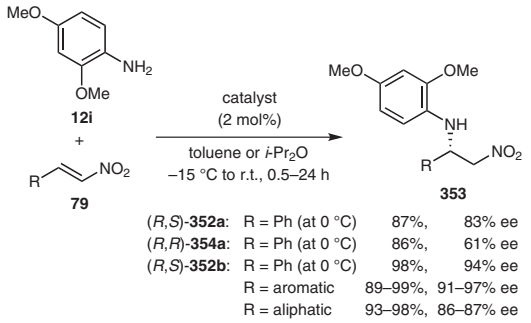
and the chiral catalyst. In addition, they introduced a binaphthyl-derived axially chiral diamine as a readily accessible and modifiable chiral source, instead of chiral aliphatic diamines,[247] to the phosphorus center by taking into consideration the enhancement of the acidity of NH protons. A newly developed arylaminophosphonium cation (*R*,*S*)-**352**, with the [7.7]-spirocyclic core, exhibited excellent catalytic activity in the conjugate addition of aniline derivative **12i** to nitroalkenes **79**, affording products **353** in good yields. The enantioselectivity is markedly dependent on the axial chiralities of the diamines introduced; switching the unsubstituted binaphthyl unit to the opposite enantiomer, which gives rise to homochiral arylaminophosphonium cation (*R*,*R*)-**354a**, results in a considerable decrease in the enantioselectivity [(*R*,*S*)-**352a**: 83% ee vs. (*R*,*R*)-**354a**: 61% ee]. Heterochiral catalyst **352b**, with its 3,4,5-trifluorophenyl groups, facilitated the reaction, affording **353a** (R = Ph) in nearly quantitative yield with the highest enantioselectivity. A broad range of nitroalkenes **79**, including aromatic, heteroaromatic, and aliphatic ones, can be transformed into the corresponding products **353** in high yields with high enantioselectivities in the presence of catalyst **352b**.

16 Conclusions

This review focused on recent advances in the chemistry of chiral Brønsted acid catalysis using BINOL-derived phosphoric acids of general type **1** for enantioselective transformations. In initial studies, chiral phosphoric acids were utilized for the activation of imines in most cases. As introduced in this review, it has been convincingly demonstrated that tremendous progress has been made in the development of chiral phosphoric acid catalysis and the broadening of the scope of functionalities that can be activated by chiral phosphoric acid catalysts and their ana-







(*R*,*S*)-**352a**:	R = Ph (at 0 °C)	87%,	83% ee
(*R*,*R*)-**354a**:	R = Ph (at 0 °C)	86%,	61% ee
(*R*,*S*)-**352b**:	R = Ph (at 0 °C)	98%,	94% ee
	R = aromatic	89–99%,	91–97% ee
	R = aliphatic	93–98%,	86–87% ee

Scheme 122 Conjugate addition of aniline derivatives **12i** to nitroalkenes **79** catalyzed by arylaminophosphonium cation

logues. Numerous bond-forming reactions, including carbon–carbon, carbon–heteroatom, and carbon–hydrogen bond-forming reactions, have been successfully established in a highly enantioselective manner by using these acid catalysts. However, the enantioselective versions of many reactions remain to be developed using chiral phosphoric acids or other types of chiral Brønsted acids. Further elaboration of novel chiral Brønsted acids derived not only from other types of chiral backbones, such as diols, diamines, and amino alcohols, but also from stronger acid functionalities could lead to the discovery of even more selective and efficient methods for a wide variety of enantioselective organic transformations.

Note Added in Proof

After acceptance of this review article, Ishihara and co-workers reported the direct Mannich reaction of *N*-Boc imine **2aa** with acetylacetone (**3**) using chiral phosphoric acids and their metal salt derivatives, where calcium salt of chiral phosphoric acid (*R*)-**1d** (G = 4-β-naphthylphenyl) functioned as an efficient catalyst to yield the corresponding product (*R*)-**4a** with high enantioselectivity.[248] The result obtained with the calcium salt of (*R*)-**1d** is comparable to that using (*R*)-**1d** which was purified by silica gel (the result shown in Scheme 1). However, an HCl wash of the silica gel purified (*R*)-**1d** resulted in the formation of **4a** with low and opposite enantioselectivity. They also reported that chiral phosphoric acid (*R*)-**1g** (G = 9-anthryl) washed with HCl exhibited good performance in the direct Mannich reaction, giving rise to (*S*)-**4a** with high enantioselectivity under optimal reaction conditions.

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