ACCOUNTS
of chemical research

Brønsted-Acid-Catalyzed Asymmetric Multicomponent Reactions for the Facile Synthesis of Highly Enantioenriched Structurally Diverse Nitrogenous Heterocycles

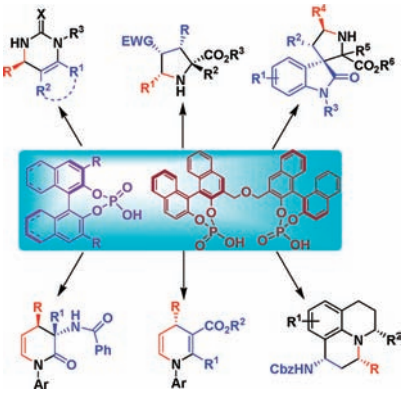
JIE YU,[†] FENG SHI,[‡] AND LIU-ZHU GONG*,[†]

[†]*Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. China, and* [‡]*School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou 221116, P. R. China*

RECEIVED ON FEBRUARY 13, 2011

CONSPECTUS

Optically pure nitrogenous compounds, and especially nitrogen-containing heterocycles, have drawn intense research attention because of their frequent isolation as natural products. These compounds have wide-ranging biological and pharmaceutical activities, offering potential as new drug candidates. Among the various synthetic approaches to nitrogenous heterocycles, the use of asymmetric multicomponent reactions (MCRs) catalyzed by chiral phosphoric acids has recently emerged as a particularly robust tool. This method combines the prominent merits of MCRs with organocatalysis, thus affording enantio-enriched nitrogenous heterocyclic compounds with excellent enantioselectivity, atom economy, bond-forming efficiency, structural diversity, and complexity. In this Account, we discuss a variety of asymmetric MCRs catalyzed by chiral phosphoric acids that lead to the production of structurally diverse nitrogenous heterocycles.



In MCRs, three or more reagents are combined simultaneously to produce a single product containing structural contributions from all the components. These one-pot processes are especially useful in the construction of heterocyclic cores: they can provide a high degree of both complexity and diversity for a targeted set of scaffolds while minimizing the number of synthetic operations. Unfortunately, enantioselective MCRs have thus far been relatively underdeveloped. Particularly lacking are reactions that proceed through imine intermediates, which are formed from the condensation of carbonyls and amines. The concomitant generation of water in the condensation reaction can deactivate some Lewis acid catalysts, resulting in premature termination of the reaction. Thus, chiral catalysts typically must be compatible with water for MCRs to generate nitrogenous compounds. Recently, organocatalytic MCRs have proven valuable in this respect. Brønsted acids, an important class of organocatalysts, are highly compatible with water and thereby offer great potential as chiral catalysts for multicomponent protocols that unavoidably release water molecules during the course of the reaction.

We present a detailed investigation of several MCRs catalyzed by chiral phosphoric acids, including Biginelli and Biginelli-like reactions; 1,3-dipolar cycloadditions; aza Diels–Alder reactions; and some other cyclization reactions. These approaches have enabled the facile preparation of 3,4-dihydropyrimidinones, pyrrolidines, piperidines, and dihydropyridines with high optical purity. The synthetic applications of these new protocols are also discussed, together with theoretical studies of the reaction transition states that address the regio- and stereochemistry. In addition, we briefly illustrate the application of a recently developed strategy that involves relay catalysis by a binary system consisting of a chiral phosphoric acid and a metal complex. This technique has provided access to new reactions that generate structurally diverse and complex heterocycles.

Enantioselective organocatalytic MCRs remain a challenge, but we illustrate success on several fronts with chiral phosphoric acids as the primary catalysts. Further progress will undoubtedly provide even better access to the chiral nitrogen-containing heterocycles that are not only prevalent as natural products but also serve as key chiral building blocks in organic synthesis.

Published on the Web 07/29/2011 www.pubs.acs.org/accounts
10.1021/ar2000343

1. Introduction

Both five- and six-membered, chiral nitrogenous heterocyclic structural skeletons are prevalent in biologically active natural products (Figure 1), and some of those constitute key intermediates with widespread application in organic synthesis.[1] Moreover, a large number of artificial molecules based on these structures hold great potential in pharmaceutical and medicinal research. For instance, MI-219 (**2**)[2a] is a potent, highly selective, and orally active inhibitor of the interaction between the tumor suppressor p53 and the E3 ubiquitin ligase MDM2. (*S*)-L-771688 (**5**)[2b] is a selective α_{1a} receptor antagonist for the treatment of benign prostatic hyperplasia (BPH). Thus, the development of new synthetic methods to readily access these targets in both highly structural diversity and stereoselectivity is undoubtedly appealing in organic and medicinal chemistry and their related fields as well.

Multicomponent reactions (MCRs) are strictly defined as one-pot processes where three or more accessible components are combined simultaneously in such a way that the single product contains significant portions of all reagents.[3] The MCRs are well amenable for the construction of heterocylic cores[4] and, more importantly, are at a premium for the achievement of a high degree of both complexity and diversity for a targeted set of scaffolds by minimizing the number of synthetic operations. However, the enantioselective version of MCRs has yet been underdeveloped. In particular, there lack reactions that proceed via imine intermediates, formed from condensation of carbonyls and amines, because the concomitant generation of water deactivates some Lewis acid catalysts and results in termination of the reaction prematurely. Thus, chiral catalysts are mostly required to be water (moisture) compatible for MCRs to generate nitrogenous compounds.[3a]

Recently, organocatalytic MCRs have emerged as robust synthetic tools as exemplified by many intriguing applications.[3d−g] Brønsted acids, one important class of organocatalysts, are essentially highly compatible with water and thereby hold great potential to be ideal chiral catalysts for the creation of new enantioselective multicomponent protocols that unavoidably release water molecules during reaction.[5] In 2004, Akiyama et al., and Terada and Uraguchi independently accomplished an innovative development of chiral Brønsted acid catalysts that possess strongly acidic functionalities.[6] These seminal events have prompted the chiral phosphoric acids to be accepted as a privileged class of Brønsted acid organocatalysts capable of affording numerous enantioselective transformations.[7] Indeed, the efficient

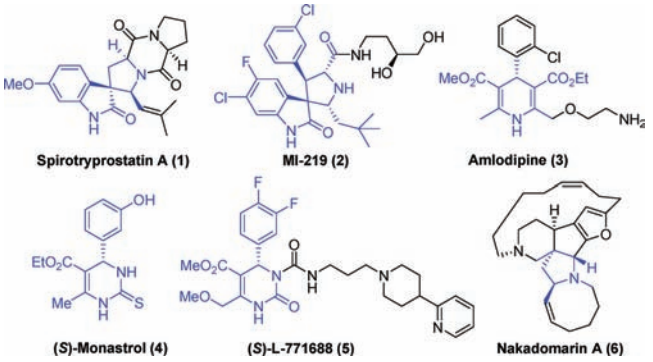


FIGURE 1. Biologically significant compounds containing nitrogenous heterocycles.

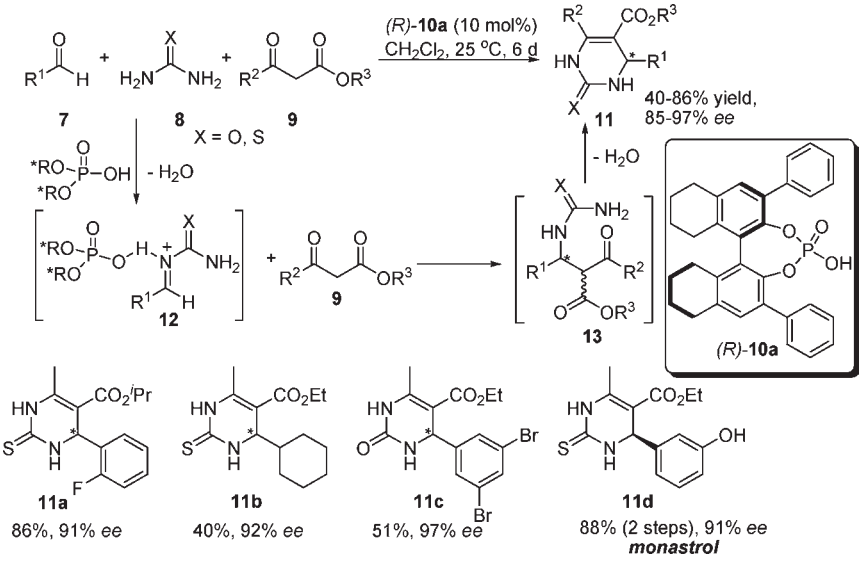
activation of imines[6] and structural tunability of binol-based phosphoric acids draw our attention to consider them as chiral catalysts for asymmetric MCRs to access optically pure nitrogenous heterocycles in structural diversity. In this Account, we will summarize chiral phosphoric-acid-catalyzed multicomponent reactions mainly coming from our group for the diversity-oriented synthesis of highly enantioenriched nitrogenous heterocycles.

2. Biginelli and Biginelli-like reaction

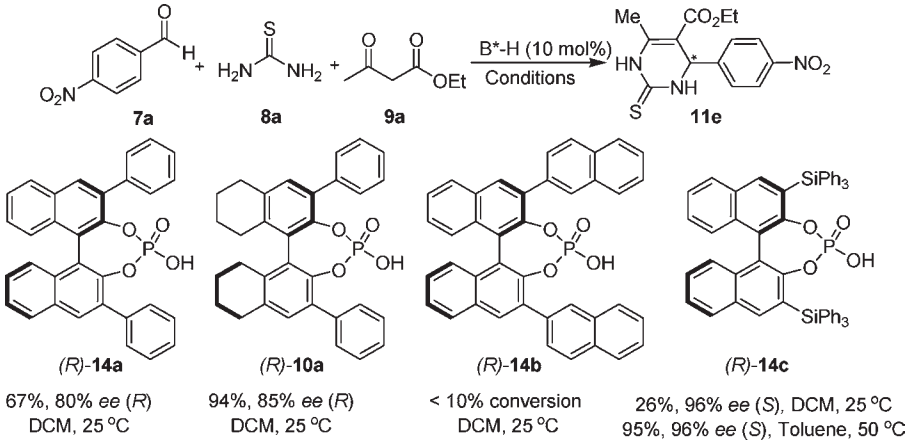
2.1. Biginelli Reaction. The Biginelli reaction,[8a] one of the most useful multicomponent reactions, offers an efficient way to access 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and related compounds, which show a wide scope of important pharmacological properties and make up a large family of medically relevant compounds.[8b] The absolute configuration of the inherent stereogenic center in DHPMs exerts great influence on the bioactivity,[8b] and asymmetric Biginelli reactions have therefore received renewed attention.[8c,d] However, this reaction unavoidably generates two molecules of water, which deactivates most of the Lewis acids and hence makes the chiral Lewis-acid-catalyzed enantioselective version continue to be a formidable challenge. The breakthrough in this field came from Zhu et al., who accomplished a highly enantioselective Biginelli reaction by using a moisture-compatible chiral ytterbium complex.[8e]

Inspired by the early success in the Mannich reactions catalyzed by phosphoric acids,[6] we disclosed the first highly enantioselective organocatalytic Biginelli reaction (Scheme 1).[9] Starting from an aldehyde **7**, thiourea or urea **8**, and acetoacetates **9**, H_8-BINOL-based chiral phosphoric acid **10a** exhibited the highest catalytic efficiency and afforded pyrimidinone derivatives **11** in moderate to good yields with high enantioselectivities. We proposed that chiral phosphoric acids would effectively catalyze the Biginelli reaction by

SCHEME 1. Chiral Phosphoric-Acid-Catalyzed Biginelli Reaction



SCHEME 2. Effect of the Substituents of the Phosphoric Acids on Stereochemistry



forming a chiral *N*-acyliminium phosphate ion pair **12**, to which the enantioselective addition of β-keto esters **9** could occur to generate optically active **11** via an enantioenriched intermediate **13**. Importantly, an active pharmaceutical ingredient monastrol (**11d**) could be accessed in two steps with high optical purity from the Biginelli reaction.

We further investigated the substituent effect of chiral phosphoric acids on the enantioselectivity of the Biginelli reaction.[10] By tuning the size of 3,3′-disubstituents of the phosphoric acids without changing the axial chirality of the catalysts, the stereochemistry of the Biginelli reaction can be reversed. For example, the enantioselectivity of (*R*)-**11e** could be improved from 80% to 85% ee (ee = enantiometric excess) by the replacement of phenyl-substituted catalyst **14a** with H_8-BINOL-based phosphoric acid **10a** (Scheme 2). However, a trace amount of product was obtained with **14b**, while triphenylsilyl-substituted catalyst **14c** was found to provide (*S*)-**11e** with the highest level of enantioselectivity.

Then we performed density functional theory (DFT) calculations to understand the reversal of the enantiofacial selection in these catalysts (Figure 2). In the case that involves **10a** as the catalyst, the dual activation model existed in both *si*-facial and *re*-facial attacking TSs while the *si*-facial attack (**TS-1-*R***) was favored and thereby gave a majority of the (*R*)-enantiomer. In contrast, in the reaction catalyzed by **14c**, the *re*-facial TS is favored in the dual activation mode (**TS-2-*S***), whereas the *si*-facial TS, with the phosphoric acid forming an 8-membered cyclic hydrogen bonding structure with the imine and a weaker hydrogen

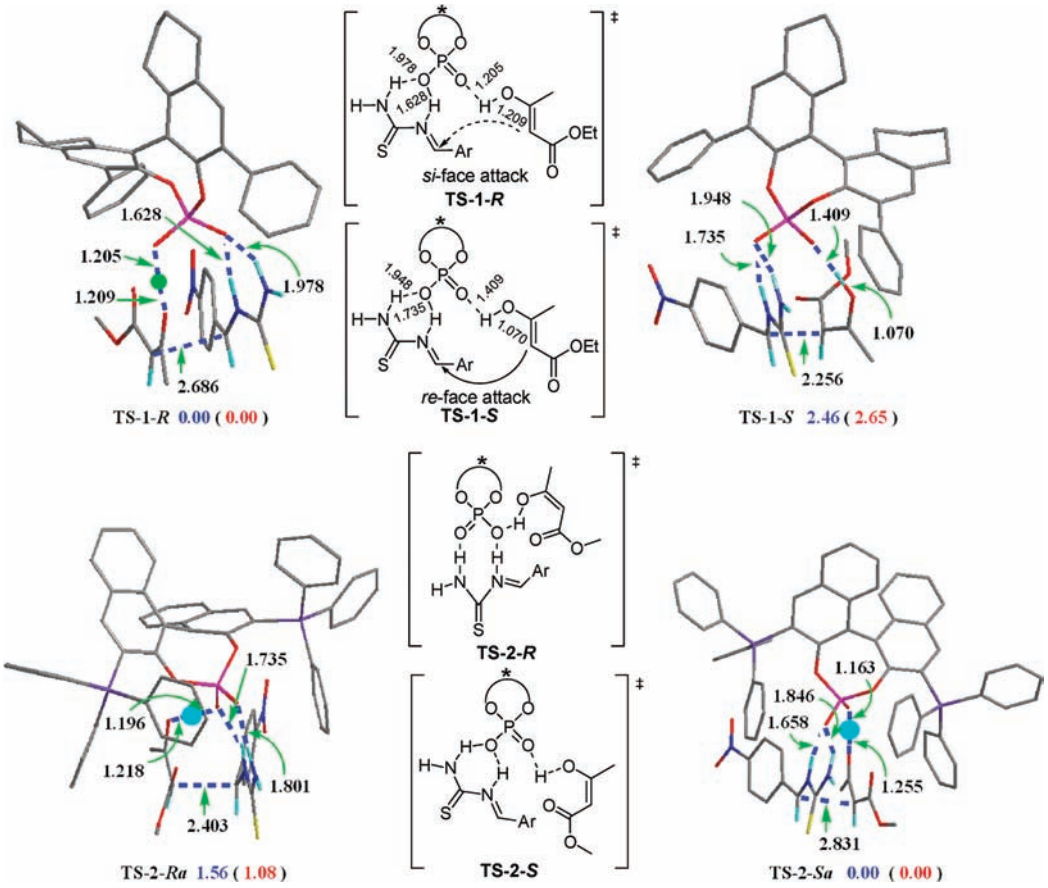
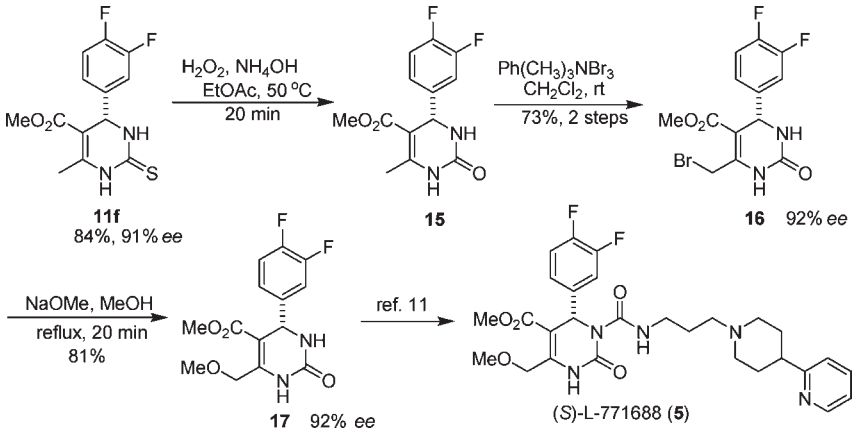


FIGURE 2. DFT calculation on how the 3,3′-substituents control the stereochemistry.

SCHEME 3. Synthesis of a Chiral Precursor to (*S*)-L-771688



bond to the enol, is not favored. Therefore, the (*S*)-enantiomer was preferentially produced.

The phosphoric acid (*R*)-**14c**-catalyzed Biginelli reaction tolerated a wide scope of aldehydes and could be practically used in the synthesis of a chiral precursor of (*S*)-L-771688 (**5**)[2b] (Scheme 3).[10] The dihydropyrimidinethione **11f** was first subjected to an oxidation and followed by a bromination, producing **16** in 73% yield without erosion of enantiomeric excess. Methoxylation of **16** afforded **17** in 81% yield. The compound **17** could be transformed into (*S*)-L-771688 (**5**) by following a known procedure.[11]

During our studies on the phosphoric-acid-catalyzed Biginelli reaction, we found a strong positive nonlinear effect (NLE) in the reaction of 4-nitrobenzaldehyde (**7a**), thiourea (**8a**),

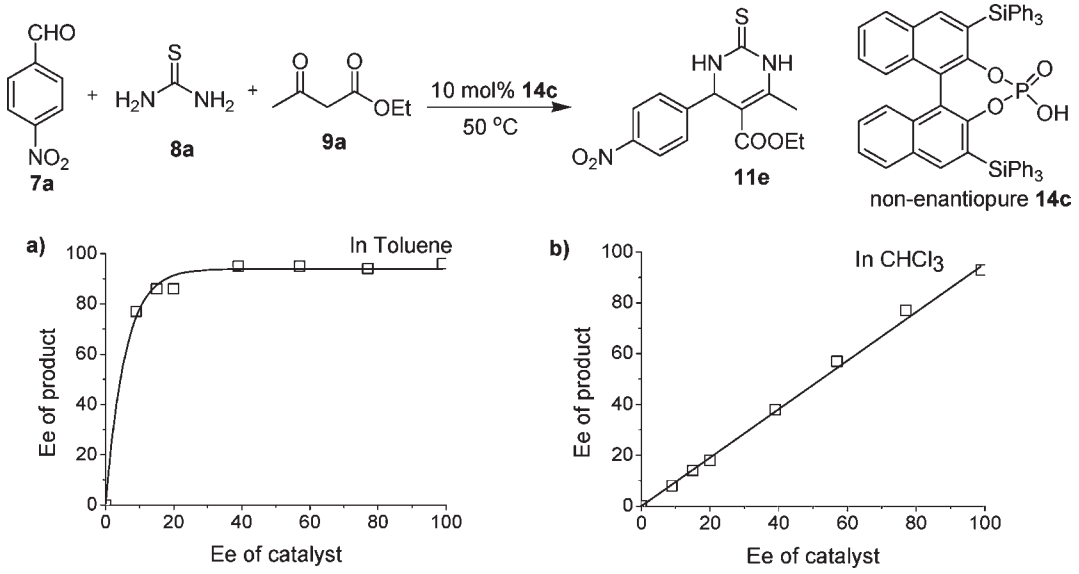
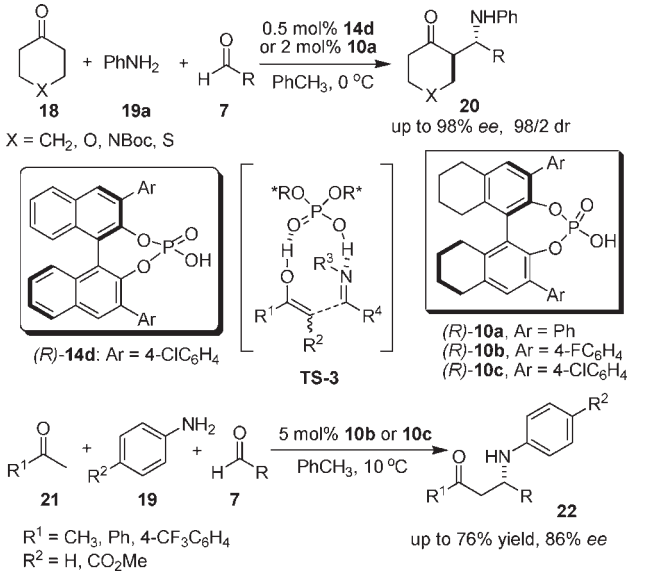


FIGURE 3. Asymmetric amplification in the Biginelli reaction catalyzed by **14c**.

SCHEME 4. Three-Component Direct Mannich Reaction



and ethyl acetoacetate (**9a**) catalyzed by 10 mol % of the nonenantiopure phosphoric acid **14c** in toluene (Figure 3a).[12] In contrast, a linear effect was observed for the same reaction under almost identical reaction conditions except chloroform was used as the solvent (Figure 3b).

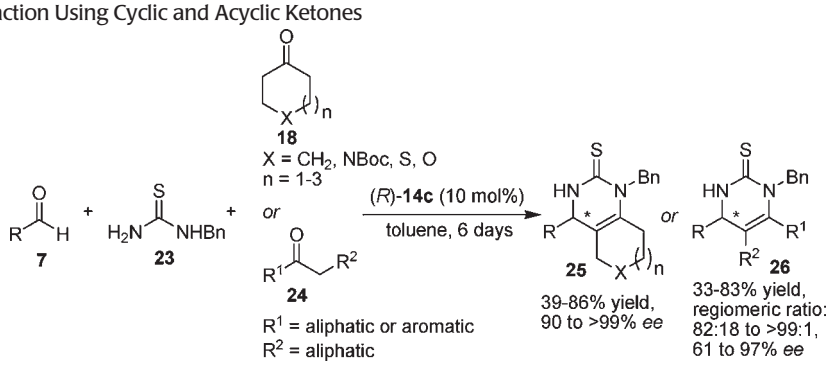
We found that the solution of optically pure phosphoric acid **14c** in toluene always remained clear while that of the racemic one formed a large amount of solid precipitate from the solution with stirring. In contrast, both racemic and optically pure samples were very soluble in chloroform and remained as clear solutions after being stirred. Further experimental studies underpinned the theory that, unlike the optically pure enantiomer, the racemic phosphoric acid formed energetically favored supramolecular aggregates that were less soluble in nonpolar solvents (e.g., toluene) through hydrogen bonds formed with crystalline water and led to the enhancement of the solution ee values. As a result, a dramatic positive NLE was observed in the phosphoric-acid-catalyzed Biginelli reaction.

The positive NLE turned out to be a general phenomenon in various phosphoric-acid-catalyzed reactions if the substrates and products did not contain hydrogen-bond-breaking elements and if the reaction was performed in a solvent that shows different solubility for optically pure phosphoric acid and its racemic aggregates.[12]

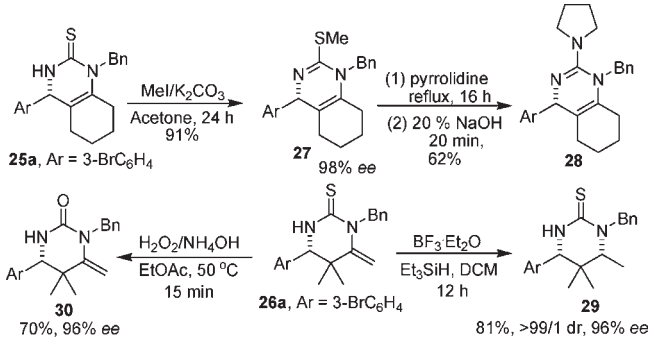
2.2. Biginelli-like Reaction. In contrast to numerous protocols available for Biginelli reactions, Biginelli-like reactions using enolizable ketones have been less explored even in a racemic manner.[13] The inferior reactivity of ketones, compared to that of β-keto esters, appears to be a key factor preventing the Biginelli-like reaction or the Mannich reaction from success under the catalysis of relatively mild Lewis or Brønsted acids.

We established a direct asymmetric three-component Mannich reaction of aromatic aldehyde **7**, anilines **19** with ketones **18** or **21** prior to our studies on the Biginelli-like reaction (Scheme 4).[14] We speculated that chiral phosphoric acids were able to activate enolizable ketones via **TS-3**. The reaction of cyclic ketone **18** as the nucleophilic component proceeded smoothly in the presence of 0.5 mol % **14d** or 2 mol % **10a**, giving *anti*-β-amino carbonyls in high yields with excellent enantioselectivities and high diastereomeric

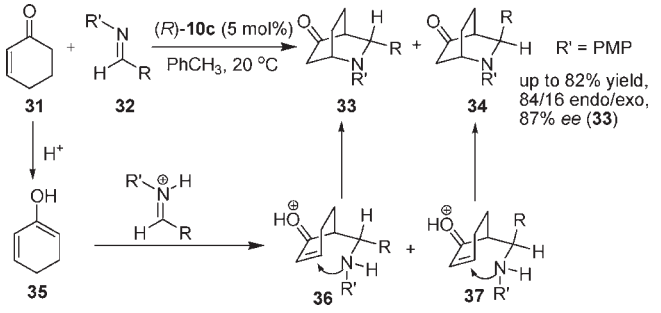
SCHEME 5. Biginelli-like Reaction Using Cyclic and Acyclic Ketones



SCHEME 6. Synthetic Applications of Biginelli-like Reaction



SCHEME 7. Direct aza-Diels-Alder Reaction of Imines with Cyclohexenone



ratios. Then acyclic ketones **21** were also examined as Mannich donors, such as acetone and acetophenone. Fairly good enantioselectivities were afforded for an aliphatic ketone in the presence of **10b**. The Mannich reaction involving aromatic ketones proceeded smoothly with good enantioselectivities catalyzed by 5 mol % of phosphoric acid **10c**.

Encouraged by these achievements on the Mannich reaction, we further performed the Biginelli-like condensation of enolizable ketones, including both cyclic ketones **18** and acyclic ketones **24** by using catalyst **14c** (Scheme 5).[10] A broad range of cyclic ketones **18** and acyclic ketones **24** were applicable to the Biginelli-like condensation with aromatic aldehyde **7** and *N*-benzylthiourea **23**, giving structurally diverse dihydropyrimidinethiones (**25** or **26**) with excellent optical purity.

Under standard reaction conditions, either dihydropyrimidinethione of type **25a** or **26a** could be transformed into synthetically useful chiral compounds, including 2-methylthiodihydropyrimidine **27**, guanidine **28**, chiral thiourea **29**, and dihydropyrimidinone **30** (Scheme 6).

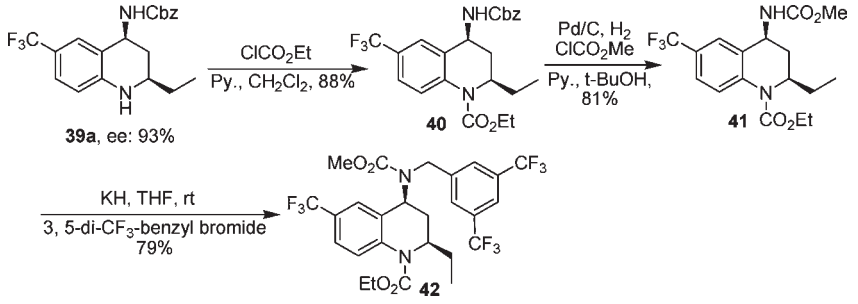
3. Multicomponent Aza-Diels–Alder Reaction

The asymmetric aza-Diels–Alder reaction is an efficient and versatile tool for the preparation of chiral piperidine derivatives, the precursors of a large family of biologically important compounds such as alkaloids, peptides, and azasugars.[15a] Thus, the catalytic asymmetric variants employing either metal complexes or organocatalysts have been disclosed over the past few years.[15b]

In 2006, Akiyama and co-workers developed an enantioselective hetero-Diels–Alder reaction of siloxydienes, including Danishefsky's and Brassard's dienes, with imines using a chiral phosphoric acid or a pyridinium salt as the catalyst.[16] Subsequently, we and Rueping and Azap independently reported an enantioselective direct aza-Diels–Alder reaction of cyclohexenone **31** with aromatic imines **32**.

Rueping and Azap found that the combined use of chiral phosphoric acid **14b** (10 mol %) and acetic acid (20 mol %) enables an efficient aza-Diels–Alder reaction of cyclohexenone **31** with aromatic imines to proceed with high stereoselecitivity.[17a] The stronger Brønsted acid **14b** is presumably to activate aldimine **32**, while the weaker Brønsted acid facilitates the keto–enol tautomerism of cyclohexenone **31**. Alternatively, we found that H_8-BINOL-based phosphoric acid **10c** was capable of offering comparable results without the assistance of extra acetic acid.[17b]

SCHEME 8. Synthesis of Torcetrapib **42**



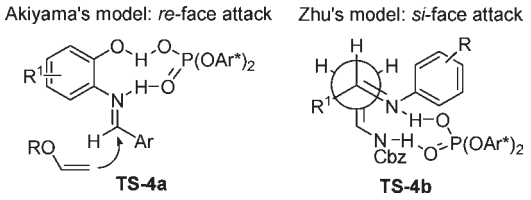
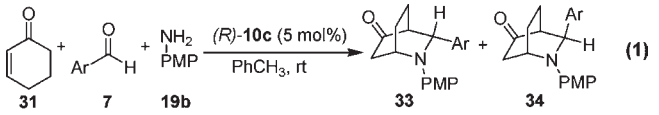


FIGURE 4. Activation modes and stereochemical outcomes of Povarov reaction.

We proposed that cyclohexenone would be enolized into **35** under the acidic conditions, which would first attack the protonated aldimine to undergo a Mannich reaction, generating intermediates **36** and **37**, followed by aza-Michael addition to afford products **33** and **34** in moderate to good enantioselectivities (Scheme 7).

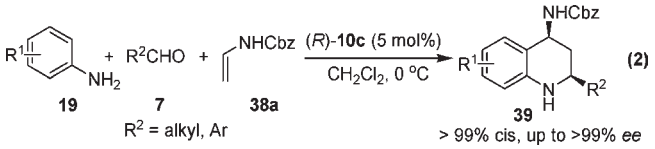
Moreover, a one-pot, three-component asymmetric aza-Diels–Alder reaction of cyclohexenone **31** with *p*-anisidine **19b** and a number of aromatic aldehydes **7** catalyzed by **10c** (5 mol %) was conducted to furnish the products in good yields with enantioselectivities similar to those observed for the corresponding reactions with preformed aldimines (eq 1).



Ar = 4-ClC$_6$H$_4$ (**33a**), 70% yield, endo/exo = 78/22, 83% *ee*;
Ar = 4-BrC$_6$H$_4$ (**33b**), 68% yield, endo/exo = 76/24, 84% *ee*;
Ar = 3-MeC$_6$H$_4$ (**33c**), 71% yield, endo/exo = 87/13, 85% *ee*.

The Povarov reaction, an inverse electron-demand aza-Diels–Alder reaction between 2-azadienes and electron-rich olefins, enables a rapid construction of tetrahydroquinoline derivatives. In 2006, Akiyama and co-workers reported an elegant Brønsted-acid-catalyzed Povarov reaction between vinyl ether and *N*-arylimines preformed from 2-hydroxylaniline and aldehydes.[18]

Subsequently, Zhu and co-workers reported a three-component variant using enecarbamates **38a** as electron-rich dienophiles (eq 2).[19] This protocol is amenable to a wide variety of aromatic and aliphatic aldehydes **7**, anilines **19**, and enecarbamates **38a** in the presence of chiral phosphoric acid **10c**, giving corresponding products **39** with excellent enantioselectivities.



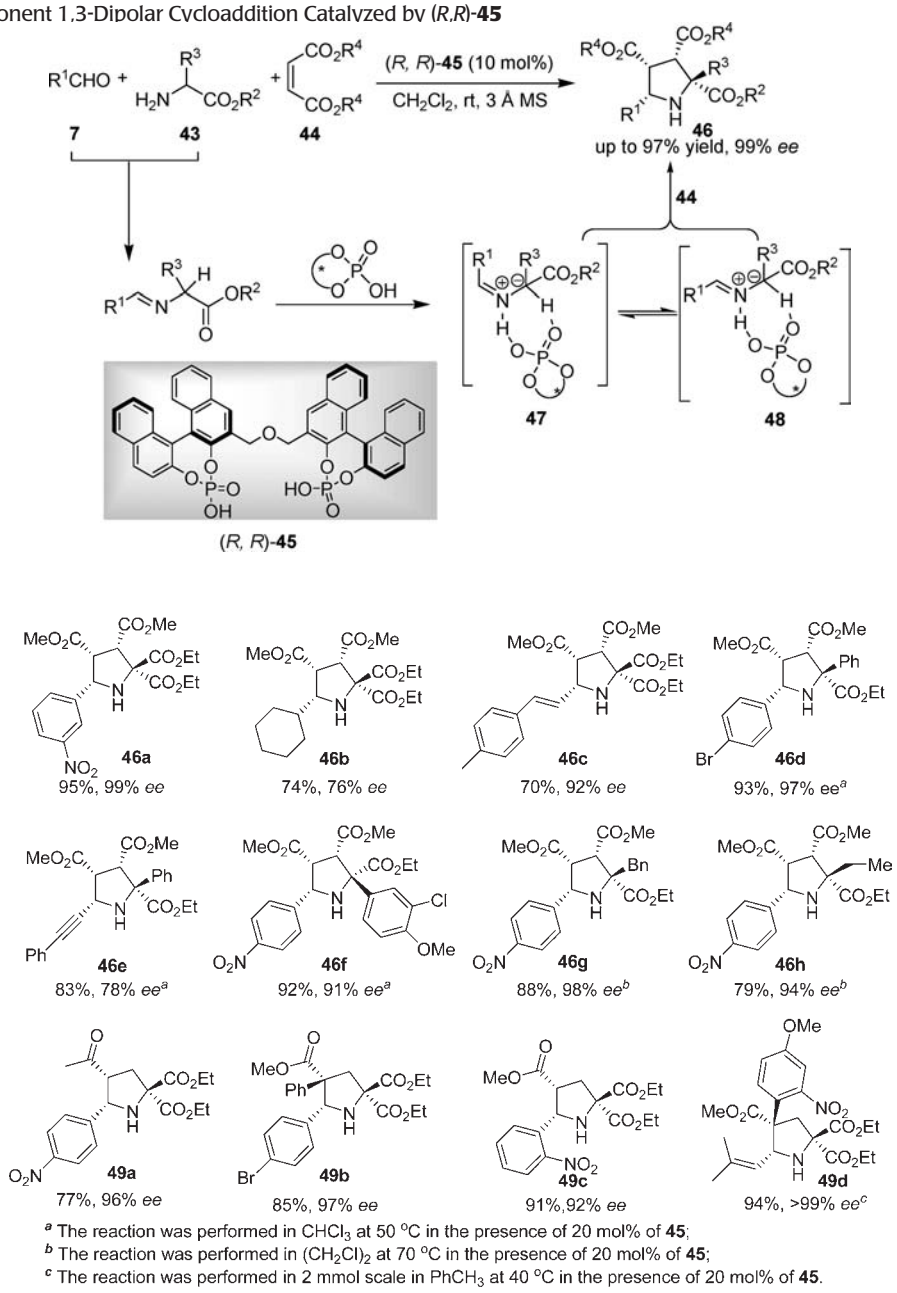
Interestingly, the absolute stereochemistry of the tetrahydroquinoline **39** is different from that obtained by Akiyama et al, although the chiral phosphoric acid catalysts have the same axial chirality (Figure 4).[19] In Akiyama's model, the phosphoric acid only activated the electrophile via the participation of the *o*-hydroxy group through the *re*-facial attacking **TS-4a**.[18] In Zhu's model, the phosphoric acid acted as a bifunctional catalyst that activates both the nucleophile and electrophile through the hydrogen bonds via the *si*-facial attacking **TS-4b**.

More importantly, the torcetrapib **42** (Scheme 8), an inhibitor of cholesteryl ester transfer protein,[20] could be concisely prepared starting with the present reaction. Ethoxycarbonylation of **39a** provided **40** in 88% yield. The deprotection of *N*-Cbz of **40**, followed by an acylation with methylchloroformate, furnished **41** in 81% yield. Finally, the benzylation of **41** at the secondary amide with 3,5-bis-(trifluoromethyl)benzyl bromide afforded torcetrapib **42**.[19]

4. 1,3-Dipolar Cycloaddition

The 1,3-dipolar cycloaddition of azomethine ylides with olefins gives rise to pyrrolidines, which represent structural elements frequently found in organocatalysts, natural products, and drug candidates.[21] Chiral Lewis-acid-catalyzed variants have received considerable attention over the past few years.[21a,b] In 2007, Vicario et al. and Córdova et al. reported the first ogranocatalytic asymmetric 1,3-dipolar addition of azomethine ylides to α,β-unsaturated aldehydes

SCHEME 9. Three-Component 1,3-Dipolar Cycloaddition Catalyzed by (*R*,*R*)-**45**



[a] The reaction was performed in $CHCl_3$ at 50 °C in the presence of 20 mol% of **45**;
[b] The reaction was performed in $(CH_2Cl)_2$ at 70 °C in the presence of 20 mol% of **45**;
[c] The reaction was performed in 2 mmol scale in $PhCH_3$ at 40 °C in the presence of 20 mol% of **45**.

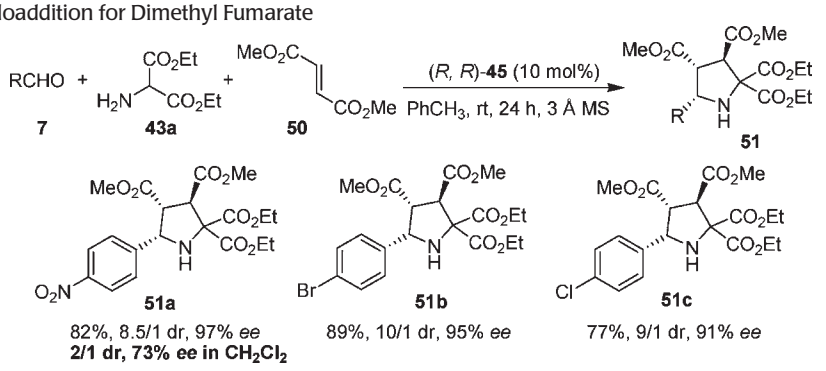
FIGURE 5. Scope of the asymmetric 1,3-dipolar cycloaddition reaction.

mediated by a chiral secondary amine via iminium activation strategy.[21c,d] However, this reaction is essentially unable to accommodate dipolarophiles other than enals and enones. Independently, we[21e] and Chen et al.[21f] established a 1,3-dipolar addition of azomethine ylides to nitroolefins by using thiourea-based bifunctional chiral organocatalysts.

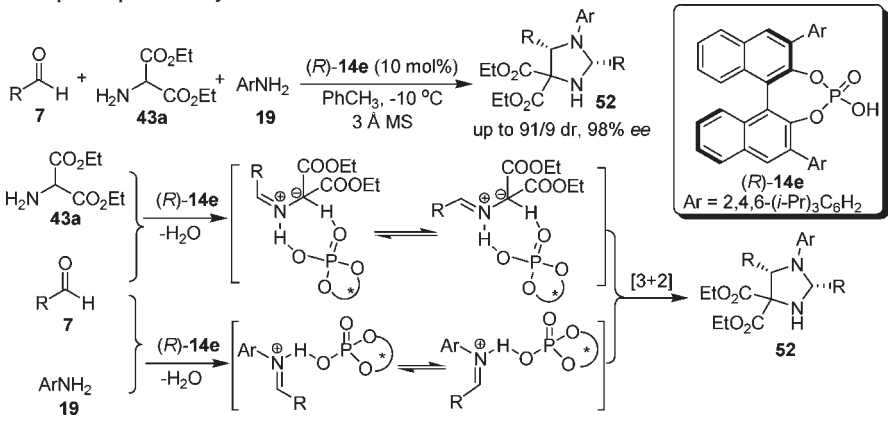
Simultaneously, we investigated a Brønsted-acid-catalyzed asymmetric three-component 1,3-dipolar cycloaddition[22] of aldehydes **7**, amino esters **43**, and maleates **44**, yielding multisubstituted pyrrolidines **46**. We initially proposed that the phosphoric acid theoretically forms a chiral azomethine ylide dipole **47** or **48** that would undergo an enantioselective 1,3-dipolar cycloaddition with dipolarophiles (Scheme 9). The bisphosphoric acid **45,** derived from (*R*,*R*)-linked BINOL,[23] turned out to be the best catalyst, which allowed the three-component 1,3-dipolar cycloaddition to proceed in high yields and excellent enantioselectivities.

A broad range of aldehydes **7**, including aromatic, α, β-unsaturated, and aliphatic aldehydes, with aminomalonates as well as α-arylglycine esters and phenylalanine esters were accommodated in the reaction, giving the corresponding pyrrolidine derivatives **46** with excellent *endo*- and

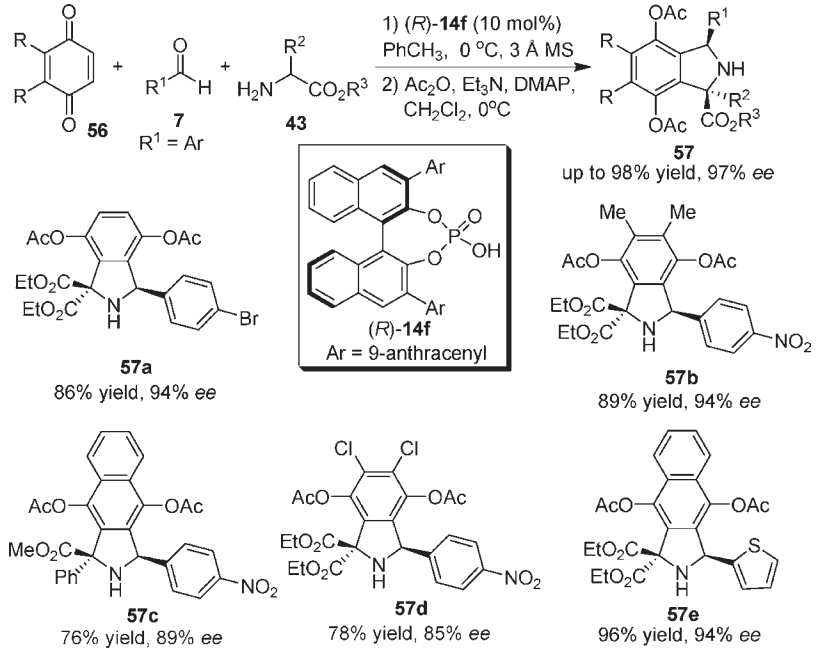
SCHEME 10. 1,3-Dipolar Cycloaddition for Dimethyl Fumarate



SCHEME 11. Imines Used as Dipolarophiles to Synthesize Imidazolidines **52**

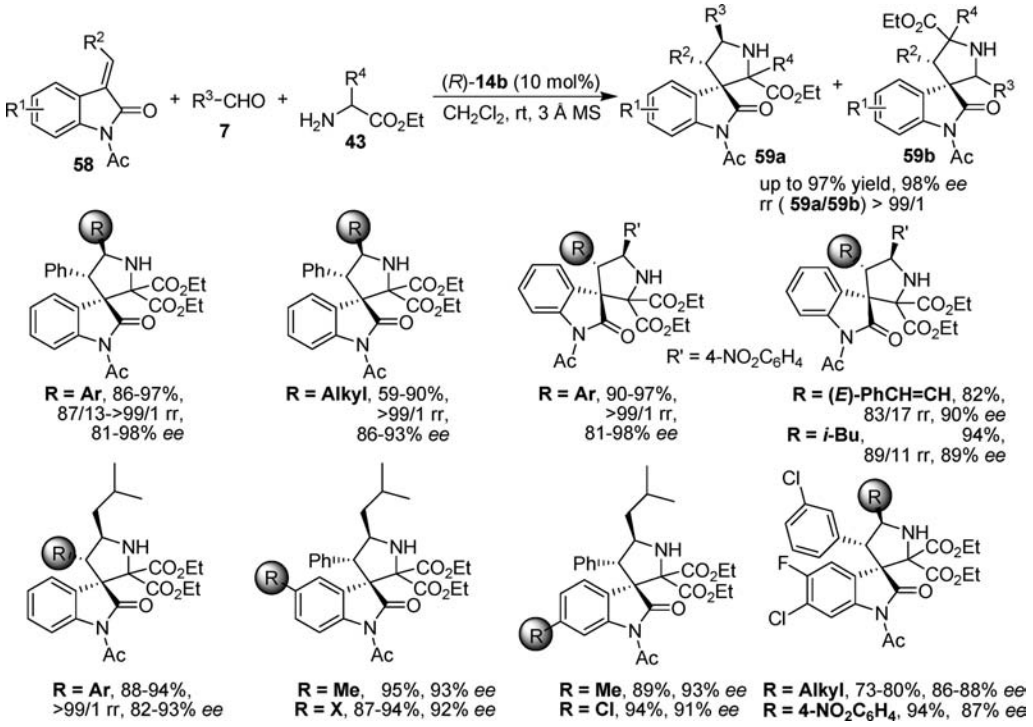


SCHEME 12. Synthesis of Isoindoline Derivatives **57**



enantioselectivities. In addition, this protocol tolerated electronically deficient olefin dipolarophiles other than maleate, such as vinyl ketones and esters (Figure 5).[24a] More interestingly, methyl 2-(2-nitrophenyl)acrylate can

SCHEME 13. Synthesis of Spiro[pyrrolidin-3,3′-oxindoles]

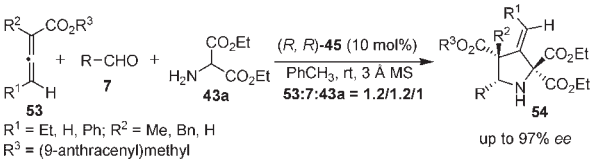


also participate in the 1,3-dipolar cycloaddition reaction of azomethine ylides with 3-methylbutenal to yield highly enantioenriched pyrrolidine derivative **49d** bearing an all-carbon quaternary stereogenic center.[24b]

In comparison with maleates **44**, dimethyl fumarate **50** represents an even more challenging dipoloraphile in the asymmetric 1,3-dipolar cycloaddition reaction. Indeed, when we applied the optimal conditions to the 1,3-dipoalr addition involving dimethyl fumarate **50**, the reaction proceeded smoothly to give the *endo*-product **51a** in high yield but with a moderate enantioselectivity and low diastereoselectivity. After screening solvents, the best results were attained by conducting the reaction in toluene (Scheme 10).[24a]

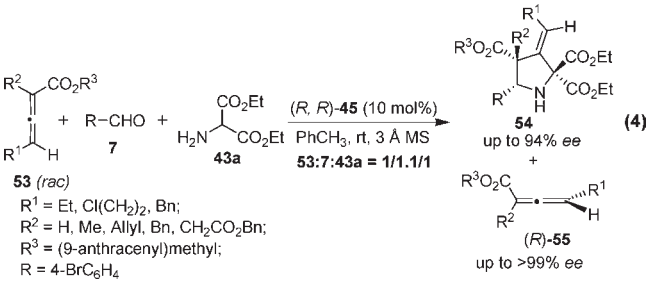
We also found that the reaction could be expanded to a series of electron-deficient dipolarophiles other than electronically poor olefins. *N*-Aryl imines, generated in situ from aldehydes **7** and anilines **19**, are suitable dipolarophiles capable of reacting with azomethine ylides to generate chiral imidazolidines **52** with high stereoselectivity catalyzed by phosphoric acid **14e** (Scheme 11).[25] The studies on the relationship between ee of the catalyst **14e** versus that of the product found a negative NLE, revealing that two molecules of phosphoric acids are probably involved in the catalysis for the activation of both azomethine ylides and imines.

The reaction involving 2,3-allenoates **53** as the dipolarophiles occurred readily in the presence of chiral bisphosphoric acid **45** to give 3-methylenepyrrolidine derivative **54** as a single diastereomer (eq 3).[26] Although aliphatic aldehydes resulted in diminished enantioselectivities, excellent ee values were obtained using aromatic aldehydes in most cases.



(3)

In view of the widespread applications of axially chiral 2,3-allenoates,[27] we established a kinetic resolution of *rac*-2,3-allenoates via (*R,R*)-**45** catalyzed 1,3-dipolar cycloaddition, providing an alternative access to both 3-methylene-pyrrolidine derivatives (**54**) and the recovered (*R*)-2,3-allenoates (**55**) in high yields and excellent enantioselectivities (eq 4).[28]



(4)

We also developed a one-pot synthesis of chiral isoindoline derivatives based on consecutive transformations that

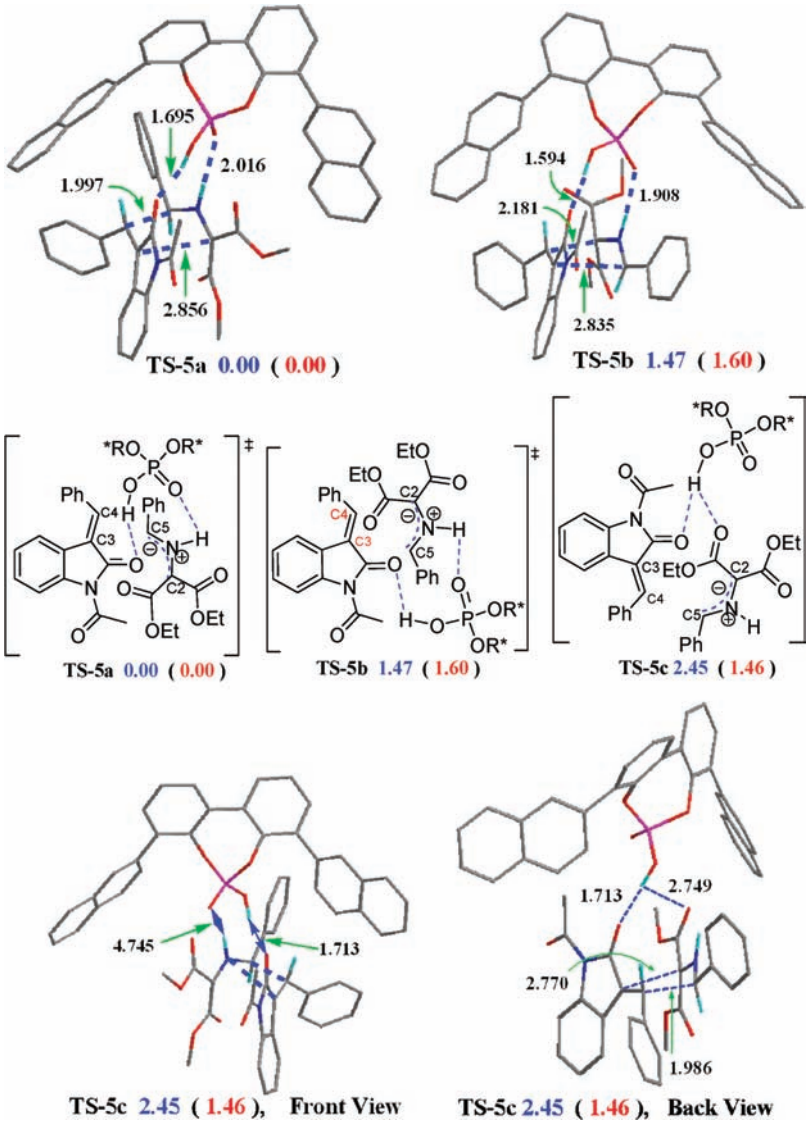


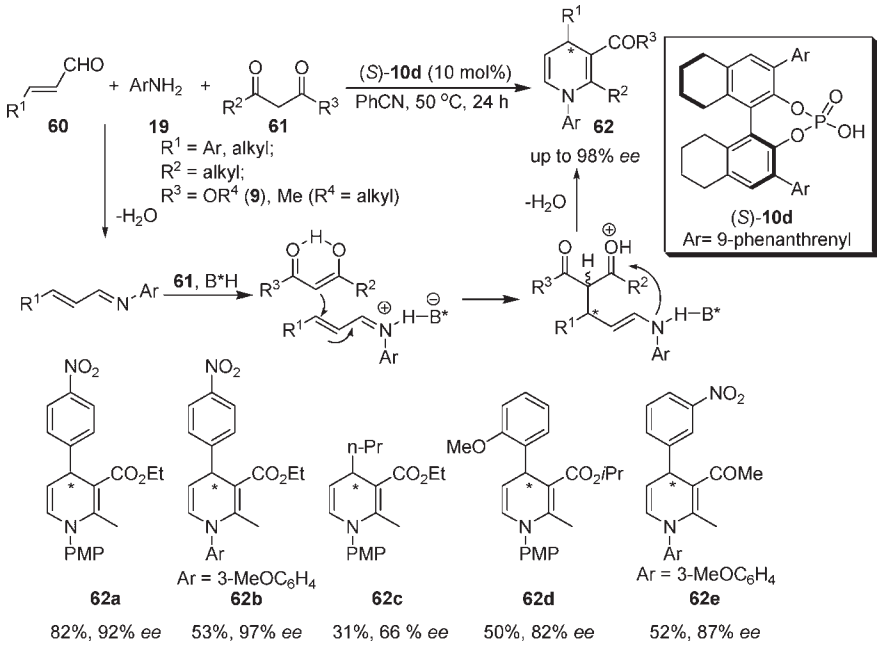
FIGURE 6. Located transition states for the 1,3-dipolar cycloaddition.

involved a chiral phosphoric acid **14f** catalyzed 1,3-dipolar cycloaddition using quinone **56** as dipolarophiles, followed by isomerization mediated by an organic base, providing isoindoline derivatives **57** with high enantiomeric purity (Scheme 12).[29]

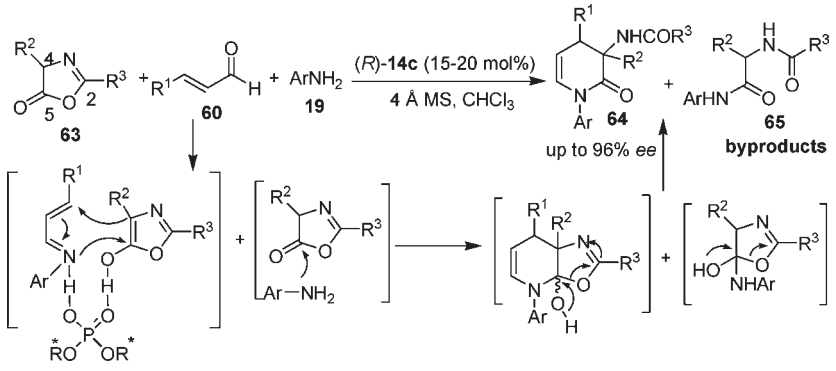
The spiro[pyrrolidin-3,3′-oxindole] ring system is a core structural element found in a large family of natural alkaloids and unnatural compounds exhibiting important bioactivities, as typically exemplified in Figure 1.[1] Encouraged by the success in the Brønsted-acid-catalyzed 1,3-dipolar cycloaddition, we developed an asymmetric three-component 1,3-dipolar cycloaddition of methyleneindolinones **58** with aldehydes **7** and amino esters **43** catalyzed by phosphoric acid **14b**, affording spiro[pyrrolidin-3,3′-oxindole] derivatives **59** with high enantioselectivity and structural diversity (Scheme 13).[30a]

Interestingly, the unusual regioisomers of type **59a** were predominantly formed, rather than **59b** that was predicted to be generated according to conventional regulation.[21a,b] To understand this regioselectivity, we performed theoretical calculations on the transition states.[30] As shown in Figure 6, the most favored transition structure **TS-5a**, wherein both the methyleneindolinone and the azomethine ylide are hydrogen-bonded with the hydroxyl proton and phosphoryl oxygen of the catalyst and thereby allows for dual activation of the two substrates simultaneously by Brønsted acid and Lewis base, affords the major product observed. The **TS-5a** is found to be more stable than **TS-5b**, which corresponds to the minor regioisomer, presumably due to the stabilization stemming from the favorable $\pi-\pi$ stacking interaction between the oxo-indole

SCHEME 14. Three-Component Cyclization to Form 4-Substituted DHPs **62**



SCHEME 15. Chiral Phosphoric Acid (*R*)-**14c** Catalyzed Cyclization of Azlactones **63**



ring and the conjugated esters in **TS-5a**. Moreover, **TS-5c**, which leads to the formation of the enantiomer of the major regiomer, is considerably less stable than **TS-5a** in energy.

5. Multicomponent Cyclization Reactions for Synthesis of Dihydropyridines

Dihydropyridines (DHPs) exhibit a wide spectrum of pharmaceutical activities.[8b] In particular, 4-aryl-substituted 1,4-dihydropyridines have been recognized as an important class of organic calcium-channel modulators for the treatment of cardiovascular diseases. Optically pure DHPs have been widely applied in the synthesis of alkaloids as chiral building blocks, and the C4-substituted 1, 4-dihydropyridines have also been utilized as chiral models of NAD(P)H.[31]

We accomplished an asymmetric three-component cyclization reaction of cinnamaldehydes **60** and aromatic primary amines **19** with 1,3-dicarbonyl compounds **61** catalyzed by H_8-BINOL-based chiral phosphoric acid **10d** to afford the 1, 4-dihydropyridine derivatives **62** in moderate to high yields and with excellent enantioselectivities (Scheme 14).[32]

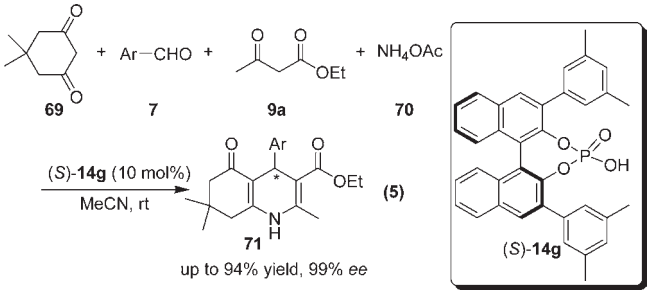
The reaction tolerated a broad scope of substrates including various cinnamaldehydes, β-ketoesters, and acetyl acetones. Among the anilines **19** explored, 3-methoxy-aniline gave the highest ee value, but was accompanied by comparative erosion of the yields. α,β-Unsaturated aldehydes **60** with electron-withdrawing substituents on the aromatic

ring exhibited high enantioselectivities, whereas the use of aliphatic α,β-unsaturated aldehydes resulted in low yield and inferior enantioselectivity (**62c**).

Azlactones **63** possessing three reactive sites at C-2, C-4, and C-5, of which both C-2 and C-5 are electrophilic, while C-4 is nuleophilic, have been versatile reactants participating in various synthetically important reactions.[33] The enantioselective cyclization reaction of azlactones with cinnamaldehydes **60** and aniline derivatives **19** catalyzed by chiral phosphoric acid **14c** proceeded nicely to furnish 3-amino-3,4-dihydropyridinones **64** as a single diastereomer with high enantioselectivities (Scheme 15).[34] Interestingly, the use of 4 Å MS was crucial to obtaining high yields of the desired products **64**. When the reaction was carried out in the absence of 4 Å MS, considerable amounts of byproducts **65** were formed from the nuleophilic ring-opening of azlactones **63** by amines **19**.

Furthermore, aryl ethylamine derivatives **66** were able to participate in the reactions with azlactone **63a** and various cinnamaldehydes **60** in the presence of **14c** to give products **67** in high yields. Subsequent treatment of **67** with trifluoroborane resulted in a clean Pictet-Spengler type cyclization reaction, generating benzo[*a*]quinolizidine derivatives **68** in high overall yields and with excellent enantioselectivities (Scheme 16).[34]

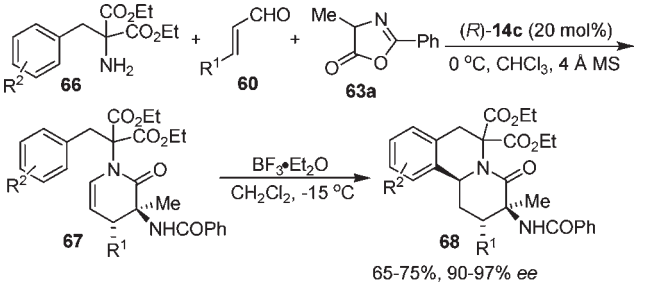
Subsequently, Gestwicki and Evans reported a four-component Hantzsch condensation reaction of dimedone **69**, ethyl acetoacetate **9a**, aromatic aldehydes **7**, and ammonium acetate **70** catalyzed by chiral phosphoric acid **14g**, giving the desired products **71** in good yields with high enantioselectivities (eq 5).[35]



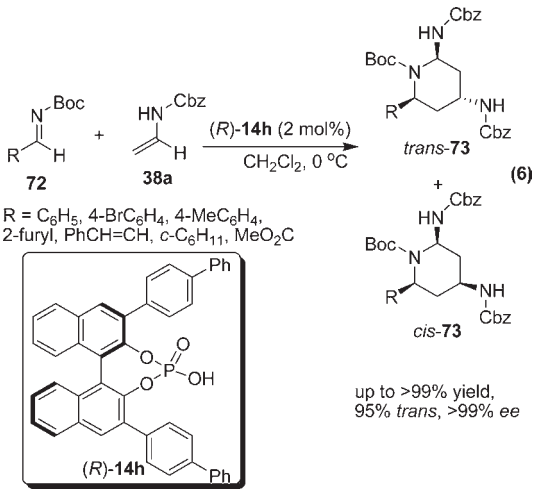
6. Other Multicomponent Reactions to Access Nitrogenous Heterocycles

In 2007, Terada and co-workers successfully accomplished a cascade aza-ene-type reaction/cyclization of monosubstituted enecarbamates **38a** with aldimines **72** catalyzed by the chiral phosphoric acid **14h** to afford piperidine

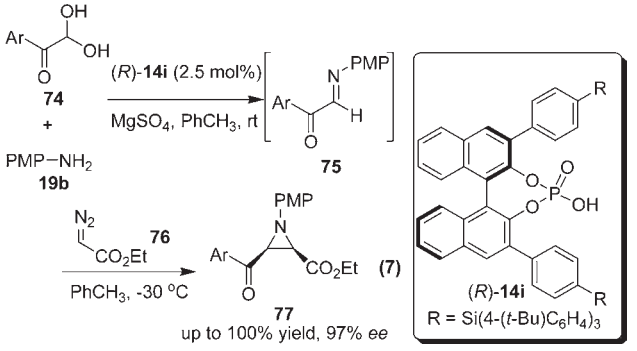
SCHEME 16. Synthesis of Benzo[*a*]quinolizidine Derivatives **68**



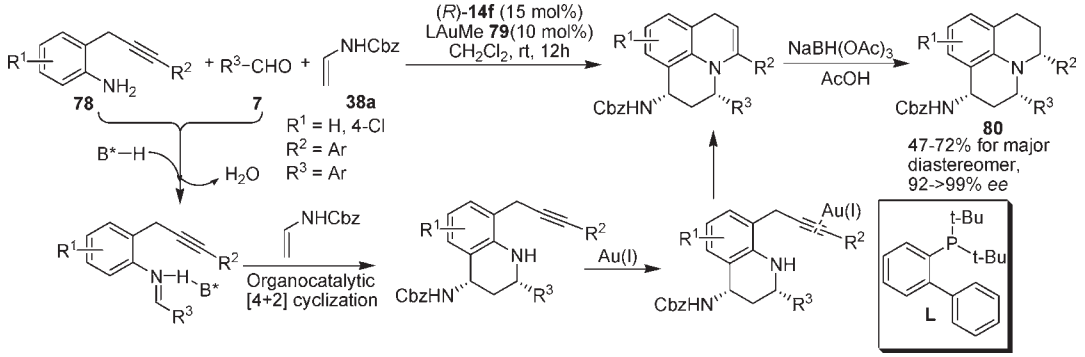
derivatives **73** with high diastereo- and enantioselectivities (eq 6).[36]



Aziridine derivatives not only have antitumor and antibiotic activities[37] but also serve as versatile intermediates in organic synthesis.[38] In 2009, Akiyama and co-workers reported an elegant enantioselective one-pot synthesis of aziridines **77** via chiral phosphoric acid **14i** catalyzed aza-Darzen reactions of α-diazoacetate **76** with aldimines **75**, which were generated in situ from glyoxal monohydrates **74** and 4-methoxyaniline **19b** (eq 7).[39]



SCHEME 17. Synthesis of Julolidines by Cascade Reactions under Relay Catalysis



7. Relay Catalytic Asymmetric Multicomponent Reaction

Traditionally, either metal-based catalysts or organocatalysts are generally used alone to promote fundamentally different reactions in asymmetric catalytic processes. Recently, the combination of metal complexes and organic molecules in cooperative and relay catalysis has attracted much attention for its potential to realize unprecedented transformations.[40] Particularly, relay catalysis holds great potential in creation of new transformations, which rely on the compatibility of metal catalysis with phosphoric acid catalysis.[40e] Notably, elegant advances have corroborated the robustness of this concept to establish new asymmetric catalytic reactions.[40c,d]

Very recently, the chiral phosphoric-acid-catalyzed Povarov reactions have been established.[19] We[41a] and Che and Liu[41b] have respectively demonstrated that gold complexes and Brønsted acid can work compatibly in the relay catalysis for the consecutive hydroamination/transfer hydrogenation of alkynes. Inspired by these achievements, we then designed a relay catalytic sequential Pavarov reaction/intramolecular hydroamination reaction by using a gold(I)/Brønsted acid binary system for the synthesis of polycyclic heterocycles. The three-component cascade reaction of 2-(2-propynyl)aniline derivatives **78**, aldehyde **7**, and enecarbamates **38a** consists of an enantioselective [4 + 2] cycloaddition reaction catalyzed by chiral phosphoric acid **14f** and a subsequent catalytic intramolecular hydroamination by a gold(I) complex **79**. This approach provides a unique method for the preparation of structurally diverse and complex julolidine derivatives **80** in high optical purity (Scheme 17).[42] Kinetic studies revealed that the phosphoric acid is not only a chiral catalyst for the Povarov reaction but also an assistant to facilitate the gold complex-catalyzed hydroamination reaction.

8. Conclusion

Enantioselective organocatalytic multicomponent reactions hold great importance in organic synthesis and medicinal chemistry, but still remain a challenging field in current asymmetric catalysis. We have accomplished several stereoselective multicomponent reactions by using chiral phosphoric acids as the main catalysts. The reactions turn out to be useful and efficient for the creation of structurally diverse and complex nitrogenous heterocycles in high optical purity. Importantly, chiral nitrogen-containing heterocyles obtained from these reactions, such as DHPMs, tetrahydroquinolines, pyrolidines, and dihydropyridines, are not only prevalent in natural products and pharmaceutically relevant compounds but also serve as key chiral building blocks in organic synthesis. In addition, our attempts presented in this Account might open a window for the future development of unprecedented asymmetric organocatalytic multicomponent reactions, particularly using Brønsted acids as catalysts. Furthermore, we have demonstrated that the use of a chiral phosphoric acid/metal binary catalyst system might be a new strategy allowing for the creation of unprecedented enantioselective cascade reactions in the construction of structurally diverse nitrogen-containing molecules.

BIOGRAPHICAL INFORMATION

Jie Yu received his B.S. degree from the University of Science and Technology of China in 2006. Then he began his graduate studies under the direction of Prof. Gong. His present research area involves chiral phosphoric-acid-catalyzed cyclization reactions.

Feng Shi received her B.S. and M.S. degrees from Xuzhou Normal University. In 2010, she joined the group of Prof. Gong to pursue her Ph.D. degree. Her research focuses on asymmetric multicomponent reactions leading to the synthesis of bioactive heterocycles.

Liu-Zhu Gong graduated from Henan Normal University in 1993 and received his Ph.D. in 2000 from Institute of Chemistry, Chinese Academy of Sciences. He became an associate professor

of Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences in 2000 and was promoted to full professor in 2001. Since 2006, he has been a full professor at University of Science and Technology of China. He was appointed the Cheung Kong Scholar Professor of organic chemistry in 2008. His current research interest is focused on the organo- and transition-metal-catalyzed asymmetric synthesis and total synthesis of natural products.

We sincerely thank all co-workers and collaborators whose names appear in the related references for their great contribution to the project. The financial support from NSFC (20732006), CAS, MOST (973 project 2010CB833300), and the Ministry of Education is gratefully acknowledged. We also thank Dr. Fei Liu in Australia for polishing English.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: gonglz@ustc.edu.cn.

REFERENCES

1 *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Fattorusso, E., Taglialatela-Scafati, O., Eds; Wiley-VCH: Weinheim, Germany, 2008.

2 (a) Shangary, S.; et al. Temporal Activation of p53 by A Specific MDM2 Inhibitor is Selectively Toxic to Tumors and Leads to Complete Tumor Growth Inhibition. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 3933–3938. (b) Barrow, J. C.; et al. In Vitro and in Vivo Evaluation of Dihydropyrimidinone C-5 Amides as Potent and Selective α_{1A} Receptor Antagonists for the Treatment of Benign Prostatic Hyperplasia. *J. Med. Chem.* **2000**, *43*, 2703–2718.

3 For some reviews, see: (a) *Multicomponent Reactions*. Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Ramón, D. J.; Yus, M. Asymmetric Multicomponent Reactions (AMCRs): The New Frontier. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. (c) Dömling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev.* **2006**, *106*, 17–89. (d) Ramachary, D. B.; Jain, S. Sequential One-pot Combination of Multi-component and Multi-catalysis Cascade Reactions: An Emerging Technology in Organic Synthesis. *Org. Biomol. Chem.* **2011**, *9*, 1277–1300. (e) Ramachary, D. B.; Kishor, M.; Reddy, G. B. Development of Drug Intermediates by Using Direct Organocatalytic Multi-component Reactions. *Org. Biomol. Chem.* **2006**, *4*, 641–1646. For some early studies in organocatalytic MCRs: (f) Ramachary, D. B.; Barbas, C. F., III. Towards Organo-click Chemistry: Development of Organocatalytic Multi-component Reactions through Combinations of Aldol, Wittig, Knoevenagel, Michael, Diels-Alder and Huisgen Cycloaddition Reactions. *Chem.—Eur. J.* **2004**, *10*, 5323–5331. (g) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. Organocatalytic Asymmetric Domino Knoevenagel/Diels-Alder reactions: A Bioorganic Approach to the Diastereospecific and Enantioselective Construction of Highly Substituted Spiro[5,5]undecane-1,5,9-triones. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233–4237.

4 (a) Orru, R. V. A.; de Greef, M. Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds. *Synthesis* **2003**, 1471–1499. (b) Sunderhaus, J. D.; Martin, S. F. Applications of Multicomponent Reactions to the Synthesis of Diverse Heterocyclic Scaffolds. *Chem.—Eur. J.* **2009**, *15*, 1300–1308.

5 (a) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis by Chiral Hydrogen-Bond Donors. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543. (b) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107*, 5713–5743.

6 (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568. (b) Uraguchi, D.; Terada, M. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

7 For recent reviews, see: (a) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744–5758. (b) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. Chiral BINOL-Derived Phosphoric Acids: Privileged Brønsted Acid Organocatalysts for C-C Bond Formation Reactions. *Org. Biomol. Chem.* **2010**, *8*, 5262–5276. (c) Terada, M. Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations. *Synthesis* **2010**, 1929–1982 and references cited therein.

8 For reviews, see: (a) Biginelli, P. Aldehyde-Urea Derivatives of Aceto- and Oxaloacetic Acids. *Gazz. Chim. Ital.* **1893**, *23*, 360–416. (b) Kappe, C. O. Biologically Active Dihydropyrimidones of the Biginelli-type—a Literature Survey. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052. (c) Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from the Old Dog. *Acc. Chem. Res.* **2000**, *33*, 879–888. (d) Gong, L.-Z.; Chen, X.-H.; Xu, X.-Y. Asymmetric Organocatalytic Biginelli Reactions: A New Approach to Quickly Access Optically Active 3,4-Dihydropyrimidin-2-(1H)-ones. *Chem.—Eur. J.* **2007**, *13*, 8920–8926. and references cited therein. For example, see: (e) Huang, Y.; Yang, F.; Zhu, C. Highly Enantioseletive Biginelli Reaction Using a New Chiral Ytterbium Catalyst: Asymmetric Synthesis of Dihydropyrimidines. *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387.

9 Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. Highly Enantioselective Organocatalytic Biginelli Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 14802–14803.

10 Li, N.; Chen, X.-H.; Song, J.; Luo, S.-W.; Fan, W.; Gong, L.-Z. Highly Enantioselective Organocatalytic Biginelli and Biginelli-Like Condensations: Reversal of the Stereochemistry by Tuning the 3,3′-Disubstituents of Phosphoric Acids. *J. Am. Chem. Soc.* **2009**, *131*, 15301–15310.

11 Goss, J. M.; Schaus, S. E. Enantioselective Synthesis of SNAP-7941: Chiral Dihydropyrimidone Inhibitor of MCH1-R. *J. Org. Chem.* **2008**, *73*, 7651–7656.

12 Li, N.; Chen, X.-H.; Zhou, S.-M.; Luo, S.-W.; Song, J.; Ren, L.; Gong, L.-Z. Asymmetric Amplification in Phosphoric Acid-Catalyzed Reactions. *Angew. Chem., Int. Ed.* **2010**, *49*, 6378–6381.

13 For example, see: Zhu, Y.-L.; Huang, S.-L.; Pan, Y.-J. Highly Chemoselective Multicomponent Biginelli-Type Condensations of Cycloalkanones, Urea or Thiourea and Aldehydes. *Eur. J. Org. Chem.* **2005**, 2354–2367.

14 Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. Chiral Brønsted Acid-Catalyzed Direct Asymmetric Mannich Reaction. *J. Am. Chem. Soc.* **2007**, *129*, 3790–3791.

15 (a) *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Rubiralta, M., Giralt, E., Diez, A., Eds.; Elsevier: Amsterdam, the Netherlands, 1991. (b) Kobayashi, S.; Ishitani, H. Catalytic Enantioselective Addition to Imines. *Chem. Rev.* **1999**, *99*, 1069–1094.

16 (a) Itoh, J.; Fuchibe, K.; Akiyama, T. Chiral Brønsted Acid Catalyzed Enantioselective Aza-Diels-Alder Reaction of Brassard's Diene with Imines. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796–4798. (b) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. Enantioselective Aza-Diels-Alder Reaction Catalyzed by a Chiral Brønsted Acid: Effect of the Additive on the Enantioselectivity. *Synlett* **2006**, 141–143.

17 (a) Rueping, M.; Azap, C. Cooperative Coexistence: Effective Interplay of Two Brønsted Acids in the Asymmetric Synthesis of Isoquinuclidines. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832–7835. (b) Liu, H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. Enantioselective Direct Aza Hetero-Diels-Alder Reaction Catalyzed by Chiral Brønsted Acids. *Org. Lett.* **2006**, *8*, 6023–6026.

18 Akiyama, T.; Morita, H.; Fuchibe, K. Chiral Brønsted Acid-Catalyzed Inverse Electron-Demand Aza Diels-Alder Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 13070–13071.

19 Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. Chiral Brønsted Acid-Catalyzed Enantioselective Three-Component Povarov Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599.

20 Guinó, M.; Phua, P. H.; Caille, J.-C.; Hii, K. K. A Concise Asymmetric Synthesis of Torcetrapib. *J. Org. Chem.* **2007**, *72*, 6290–6293.

21 For some reviews, see: (a) Coldham, I.; Hufton, R. Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides. *Chem. Rev.* **2005**, *105*, 2765–2810. (b) Pandey, G.; Banerjee, P.; Gadre, S. R. Construction of Enantiopure Pyrrolidine Ring System via Asymmetric [3 + 2]-Cycloaddition of Azomethine Ylides. *Chem. Rev.* **2006**, *106*, 4484–4517. For examples, see: (c) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. Organocatalytic Enantioselective [3 + 2] Cycloaddition of Azomethine Ylides and α,β-Unsaturated Aldehydes. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168–5170. (d) Ibrahem, I.; Rios, R.; Vesely, J.; Córdova, A. Organocatalytic Asymmetric Multi-Component [C+NC+CC] Synthesis of Highly Functionalized Pyrrolidine Derivatives. *Tetrahedron. Lett.* **2007**, *48*, 6252–6257. (e) Xue, M.-X.; Zhang, X.-M.; Gong, L.-Z. The First Organocatalytic Enantio- and Diastereoselective 1,3-Dipolar Cycloaddition of Azomethine Ylides with Nitroalkenes. *Synlett* **2008**, 691–694. (f) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. Reaction Control in the Organocatalytic Asymmetric One-Pot, Three-Component Reaction of Aldehydes, Diethyl α-Aminomalonate and Nitroalkenes: Toward Diversity-Oriented Synthesis. *Chem.—Eur. J.* **2008**, *14*, 9873–9877.

22 Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. Asymmetric Organocatalytic Three-Component 1,3-Dipolar Cycloaddition: Control of Stereochemistry via a Chiral Brønsted Acid-Activated Dipole. *J. Am. Chem. Soc.* **2008**, *130*, 5652–5653.

23 Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. Catalytic Enantioselective meso-Epoxide Ring Opening Reaction with Phenolic Oxygen Nucleophile Promoted by Gallium Heterobimetallic Multifunctional Complexes. *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260.

24 (a) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. Binaphthol-derived Bisphosphoric Acids Serve as Efficient Organocatalysts for Highly Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides to Electron- Deficient Olefins. *J. Am. Chem. Soc.* **2011**, *133*, in press, DOI: 10.1021/ja204218h. (b) Cheng, M.-N.; Wang, H.; Gong, L.-Z. Asymmetric Organocatalytic 1,3-Dipolar Cycloaddition of Azomethine Ylide to Methyl 2-(2-Nitrophenyl)acrylate for the Synthesis of Diastereoisomers of Spirotryprostatin A. *Org. Lett.* **2011**, *13*, 2418−2421.

25 Liu, W.-J.; Chen, X.-H.; Gong, L.-Z. Direct Assembly of Aldehydes, Amino Esters, and Anilines into Chiral Imidazolidines via Brønsted Acid Catalyzed Asymmetric 1,3-Dipolar Cycloadditions. *Org. Lett.* **2008**, *10*, 5357–5360.

26 Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. Highly Enantioselective Catalytic 1,3-Dipolar Cycloaddition Involving 2,3-Allenoate Dipolarophiles. *Org. Lett.* **2009**, *11*, 4946–4949.

27 For some reviews, see: (a) Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* **2005**, *105*, 2829–2871. (b) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds; Wiley-VCH: Weinheim, Germany, 2004.

28 Yu, J.; Chen, W.-J.; Gong, L.-Z. Kinetic Resolution of Racemic 2,3-Allenoates by Organocatalytic Asymmetric 1,3-Dipolar Cycloaddition. *Org. Lett.* **2010**, *12*, 4050–4053.

29 Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. Asymmetric Organocatalytic Formal Double-Arylation of Azomethines for the Synthesis of Highly Enantiomerically Enriched Isoindolines. *Chem. Commun.* **2010**, 1275–1277.

30 (a) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. Organoatalytic Synthesis of Spiro[pyrrolidin-3, 3′-Oxindoles] with High Enantiopurity and Structural Diversity. *J. Am. Chem. Soc.* **2009**, *131*, 13819–13825. For Lewis acid-catalyzed variant, see: (b) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. Highly Enantioselective Synthesis and Cellular Evaluation of Spirooxindoles Inspired by Natrual Products. *Nat. Chem.* **2010**, *2*, 735–740.

31 For review, see: (a) Lavilla, R. Recent Developments in the Chemistry of Dihydropyridines. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141–1156. For example, see: (b) Franke, P. T.; Johansen, R. L.; Bertelsen, S.; Jørgensen, K. A. Organocatalytic Enantioselective One-Pot Synthesis and Application of Substituted 1,4-dihydropyridines—Hantzsch Ester Analogues. *Chem.—Asian J.* **2008**, *3*, 216–224.

32 Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. Organocatalytic Asymmetric Three-Component Cyclization of Cinnamaldehydes and Primary Amines with 1,3-Dicarbonyl Compounds: Straightforward Access to Enantiomerically Enriched Dihydropyridines. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458–2462.

33 Hewlett, N. M.; Hupp, C. D.; Tepe, J. J. Reactivity of Oxazol-5-(4H)-ones and Their Application toward Natural Product Synthesis. *Synthesis* **2009**, 2825–2839.

34 Jiang, J.; Qing, J.; Gong, L.-Z. Asymmetric Synthesis of 3-Amino-δ-Lactams and Benzo[a]quinolizidines by Catalytic Cyclization Reactions Involving Azlactones. *Chem.—Eur. J.* **2009**, *15*, 7031–7034.

35 Evans, C. G.; Gestwicki, J. E. Enantioselective Organocatalytic Hantzsch Synthesis of Polyhydroquinolines. *Org. Lett.* **2009**, *11*, 2957–2959.

36 Terada, M.; Machioka, K.; Sorimachi, K. Chiral Bronsted Acid-catalyzed Tandem Aza-ene Type eaction/Cyclization Cascade for A One-pot Entry to Enantioenriched Piperidines. *J. Am. Chem. Soc.* **2007**, *129*, 10336–10337.

37 Fürmeier, S.; Metzger, J. O. Fat-derived Aziridines and Their N-substituted Derivatives: Biologically Active Compounds Based on Renewable Raw Materials. *Eur. J. Org. Chem.* **2003**, 649–659.

38 Watson, I. D. G.; Yu, L.; Yudin, A. K. Advances in Nitrogen Transfer Reactions Involving Aziridines. *Acc. Chem. Res.* **2006**, *39*, 194–206.

39 Akiyama, T.; Suzuki, T.; Mori, K. Enantioselective Aza-Darzens Reaction Catalyzed by A Chiral Phosphoric Acid. *Org. Lett.* **2009**, *11*, 2445–2447.

40 For reviews, see: (a) Shao, Z.; Zhang, H. Combining Transition Metal Catalysis and Organocatalysis: A Broad New Concept for Catalysis. *Chem. Soc. Rev.* **2009**, *38*, 2745–2755 and references cited therein. (b) Zhou, J. Recent Advances in Multicatalyst Promoted Asymmetric Tandem Reactions. *Chem. Asian J.* **2010**, *5*, 422–434. (c) Zhong, C.; Shi, X. When Organocatalysis Meets Transition-Metal Catalysis. *Eur. J. Org. Chem.* **2010**, 2999–3025. (d) Hashmi, A. S. K.; Hubbert, C. Gold and Organocatalysis Combined. *Angew. Chem., Int. Ed.* **2010**, *49*, 1010–1012 and references cited therein. For first example illustrating the compatibility: (e) Sorimachi, K.; Terada, M. Relay Catalysis by A Metal-complex/Brønsted Acid Binary System in A Tandem Isomerization/Carbon- Carbon Bond Forming Sequence. *J. Am. Chem. Soc.* **2008**, *130*, 14452–14453.

41 (a) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. Consecutive Intramolecular Hydroamination/Asymmetric Transfer Hydrogenation under Relay Catalysis of An Achiral Gold Complex/Chiral Brønsted Acid Binary System. *J. Am. Chem. Soc.* **2009**, *131*, 9182–9183. (b) Liu, X.-Y.; Che, C.-M. Highly Enantioselective Synthesis of Chiral Secondary Amines by Gold/Chiral Brønsted Acid Catalyzed Tandem Intermolecular Hydroamination and Transfer Hydrogenation Reactions. *Org. Lett.* **2009**, *11*, 4204–4207.

42 Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. Highly Enantioselective Relay Catalysis in the Three-Component Reaction for Direct Construction of Structurally Complex Heterocycles. *Org. Lett.* **2010**, *12*, 2266–2269.