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Development of Chiral Organosuperbase Catalysts Consisting of Two Different Organobase Functionalities

Azusa Kondoh,[b] Masafumi Oishi,[a] Hikaru Tezuka,[a] and Masahiro Terada*[a]

[a] Dr. M. Oishi, H. Tezuka, Prof. Dr. M. Terada
Department of Chemistry, Graduate School of Science
Tohoku University
Aramaki, Aoba-ku, Sendai 980-8578 (Japan)
E-mail: mterada@tohoku.ac.jp
[b] Dr. A. Kondoh
Research and Analytical Center for Giant Molecules
Graduate School of Science, Tohoku University
Aramaki, Aoba-ku, Sendai 980-8578 (Japan)

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Abstract: In the field of chiral Brønsted base catalysis, a new generation of chiral catalysts has been highly anticipated to overcome the intrinsic limitation of pronucleophiles that are applicable to the enantioselective reactions. Herein, we reveal conceptually new chiral Brønsted base catalysts consisting of two different organobase functionalities, one of which functions as an organosuperbase and the other as the substrate recognition site. Their prominent activity, which stems from the distinctive cooperative function by the two organobases in a single catalyst molecule, was demonstrated in the unprecedented enantioselective direct Mannich-type reaction of α-phenylthioacetate as a less acidic pronucleophile. The present achievement would provide a new guiding principle for the design and development of chiral Brønsted base catalysts and significantly broaden the utility of Brønsted base catalysis in asymmetric organic synthesis.

The development of new molecular catalysts is one of the keys for paving the way to novel transformations in organic synthesis. In the field of chiral Brønsted base catalysis, which is one of the most fundamental and environmentally benign methodologies for the direct synthesis of enantio-enriched compounds,[1] a long-standing issue is the expansion of the scope of pronucleophiles that are applicable to the enantioselective reactions. Conventionally, chiral tertiary amines have been widely employed as chiral Brønsted base catalysts.[2] Recently, chiral uncharged organobases with higher basicity than tertiary amines, such as chiral guanidines, P1-phosphazenes, and cyclopentenimines, have also emerged as efficient chiral Brønsted base catalysts.[3-6] However, the insufficient basicity of these conventional chiral organobases limits the scope of pronucleophiles to highly acidic compounds, such as *β*-dicarbonyl compounds and nitroalkanes, which restricts the viable molecular transformations that are available under chiral Brønsted base catalysis. Therefore, the development of a new generation of chiral Brønsted base catalysts that can overcome the intrinsic limitations of pronucleophiles is highly desirable.[7] In this context, our research program has been focusing on the development of much stronger chiral uncharged organobases, namely chiral organosuperbases.[8] Our previous achievements, as well as the contributions of other groups, for the enantioselective reactions of less acidic pronucleophiles have revealed the benefit of chiral Brønsted bases having high basicity in developing new catalytic enantioselective reactions and expanding the scope of pronucleophiles.[9,10] However, development of chiral organosuperbase catalysts and the related chiral strong Brønsted base catalysts, which would provide the considerable progress in the field, are still less advanced due to the difficulty in designing catalyst molecules having both high basicity and high stereocontrolling ability. Herein, we report "chiral cooperative binary base catalysts" **1** as conceptually new chiral strong Brønsted base catalysts (Figure 1). The catalysts consist of two different organobase functionalities, one of which functions as an organosuperbase and the other as the substrate recognition site. Their prominent activity was demonstrated in the unprecedented enantioselective direct Mannich-type reaction of α-phenylthioacetate as a less acidic pronucleophile to construct a β-amino-α-thiocarbonyl scaffold.

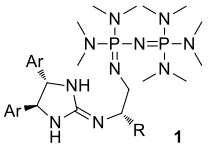

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Figure 1. Newly-developed Chiral Cooperative Binary Base Catalyst **1**.

Chiral cyclic scaffolds embedded with an organobase functionality are common motifs in chiral Brønsted base catalysts (Figure 2a).[3,4,8] A cyclic scaffold facilitates the formation of an effective chiral environment around the reaction site by limiting the conformational flexibility of the catalyst molecules. We previously developed a chiral pseudo-C_2-symmetric 7,7-membered spirocyclic organosuperbase "**GP**" having a bis(guanidino)iminophosphorane as a core structure,[8] which could efficiently catalyze enantioselective reactions of less acidic pronucleophiles.[9] However, chiral cyclic organobases, in particular chiral cyclic organosuperbases having high basicity, are often difficult to synthesize, which limits their structural diversity and thus prevents their application to a wide range of reactions. Alternatively, chiral acyclic organobases with an additional acidic functionality as a substrate recognition site are also common motifs of chiral Brønsted base catalysts (Figure 2b).[2,5] Such so-called chiral "acid-base" bifunctional catalysts are more readily accessible than cyclic ones with more structural diversity. However, application of this motif to chiral

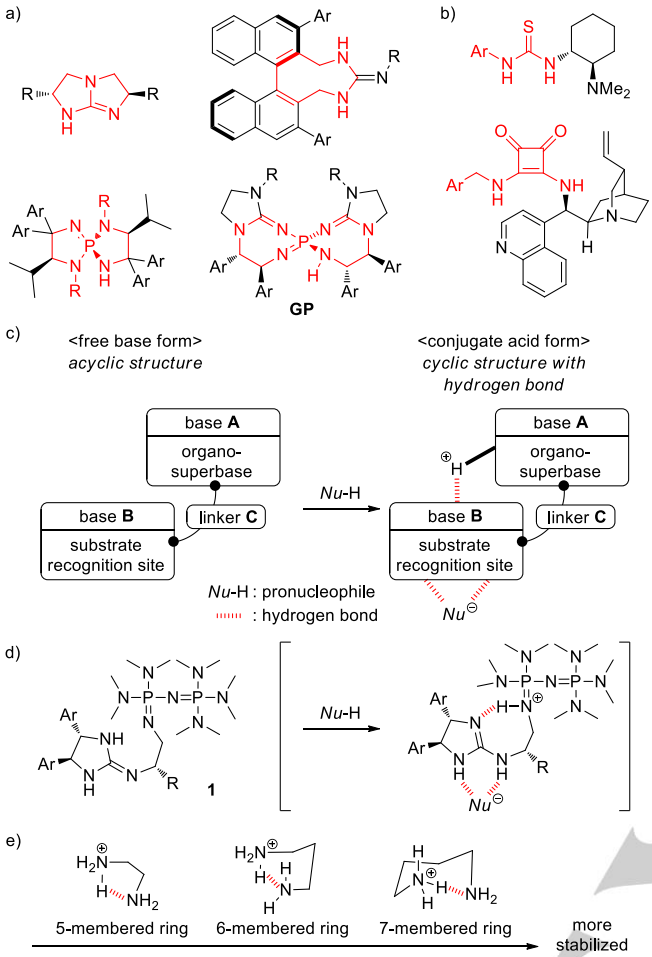
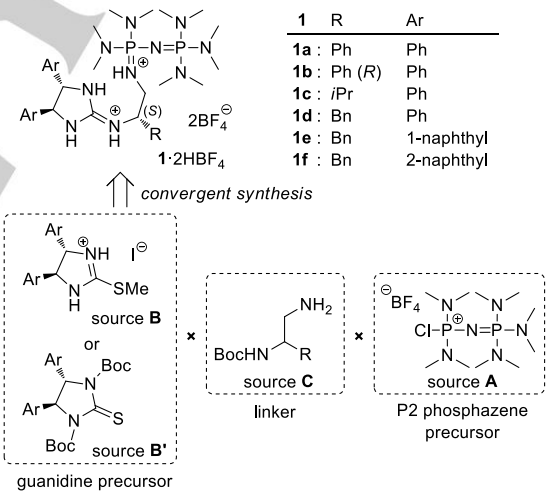


Figure 2. Molecular Design for Chiral Brønsted Base Catalysts. **a)** Typical chiral cyclic Brønsted base catalysts. **b)** Typical chiral "acid-base" bifunctional catalysts. **c)** Our molecular design for chiral organosuperbases consisting of two different organobase functionalities. **d)** Chiral cooperative binary base catalyst consisting of a P2-phosphazene and a guanidine. **e)** Formation of a cyclic structure with an intramolecular hydrogen bond in the conjugate acid form of diaminoalkanes.

organosuperbases is not feasible because intramolecular quenching of the organosuperbase moiety by the acid functionality would occur to form a zwitterionic species with considerable reduction of the basicity. By taking into account the virtues of both motifs, we have develop a conceptually new molecular design for chiral organosuperbases: a chiral acyclic organic molecule having two different organobase functionalities, one of which functions as an organosuperbase (base **A**) and the other as the substrate recognition site (base **B**) (Figure 2c). The key feature of the molecular design is *the distinctive cooperative function by two organobases in a single catalyst molecule*, namely, a chiral cooperative binary base catalyst. We expected that the conjugate acid of a chiral cooperative binary base catalyst, which is generated through the deprotonation of a pronucleophile and the actual key species in the stereo-determining step of the enantioselective reaction, would form a chiral cyclic structure with an intramolecular hydrogen bond between the two organobase functionalities **A** and **B**. Indeed, it is well-known that the conjugate acids of diaminoalkanes, as well as those of amidines and guanidines connected with an amino group, are highly stabilized by an intramolecular hydrogen bond between the two organobase functionalities to form a cyclic structure, in particular a seven-membered cyclic structure (Figure 2e).[11] Thus, the two organobase functionalities would work cooperatively to form an effective chiral environment around the substrate recognition site by limiting the conformational flexibility in the conjugate acid form. Importantly, our design permits chiral Brønsted base catalysts having both high basicity and a potential cyclic structure in the conjugate acid form, while avoiding tedious syntheses of cyclic catalyst molecules. As shown in Figure 2d, the newly-designed catalyst molecule **1** possesses a P2-phosphazene as an organosuperbase (base **A** in Figure 2c) and a chiral guanidine as a hydrogen bond donor for substrate recognition (base **B** in Figure 2c). The two organobase functionalities are connected by a chiral two-carbon linker (linker **C** in Figure 2c) derived from an α-amino acid, which allows the formation of a seven-membered cyclic structure with an intramolecular hydrogen bond in the conjugate acid form of the catalyst molecule. A series of catalyst molecules were successfully synthesized and isolated as stable HBF_4 complexes in a convergent manner from three readily accessible components including a triaminophosphonium (source **A**) as a P2-phosphazene precursor,[12] chiral cyclic thioureas (source **B** or **B'**) as a guanidine precursor,[13,14] and chiral 1,2-diaminoethane derivatives (source **C**) as a linker (Figure 3).[15] The established convergent synthesis would facilitate the optimization of the catalyst when applied to a variety of enantioselective reactions.

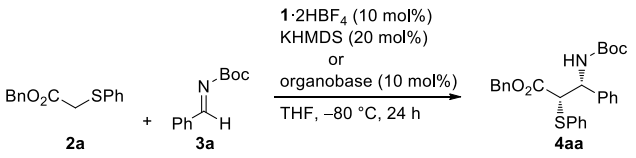


1	R	Ar
1a	Ph	Ph
1b	Ph (*R*)	Ph
1c	*i*Pr	Ph
1d	Bn	Ph
1e	Bn	1-naphthyl
1f	Bn	2-naphthyl

Figure 3. A Series of HBF_4 Complexes of **1**. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

In order to validate the catalytic performance of the newly-synthesized chiral organosuperbases, we applied them to a direct addition reaction of less acidic pronucleophiles. Specifically, the enantioselective direct Mannich-type reaction of α-phenylthioacetate[16] was selected as an ideal probe (Table 1). This unprecedented enantioselective reaction is a challenging catalytic reaction of less acidic acyclic ester derivative as a pronucleophiles.[17] It also provides direct access to an enantio-enriched α-thio-β-aminocarbonyl scaffold, which is a synthetically useful building block and often found in a family of sulfur-containing bioactive compounds.[18,19]

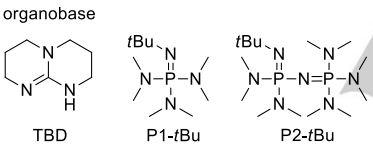
Table 1. Screening of Reaction Conditions.[a]



2a **3a** **4aa**

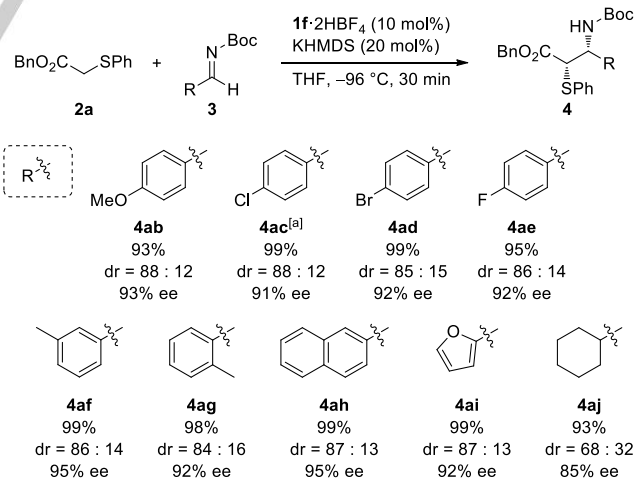
entry	**1** or organobase	R	Ar	yield [%][b]	dr[c]	ee [%][d]
1	**1a**	Ph	Ph	83	79 : 21	59
2	TBD	-	-	<1	-	-
3	P1-*t*Bu	-	-	<1	-	-
4	P2-*t*Bu	-	-	99[e]	58 : 42	-
5	**1b**	Ph (*R*)	Ph	99	52 : 48	46
6	**1c**	*i*Pr	Ph	95	59 : 41	59
7	**1d**	Bn	Ph	95	68 : 32	78
8	**1e**	Bn	1-naphthyl	94	65 : 35	18
9	**1f**	Bn	2-naphthyl	99	77 : 23	85
10[f]	**1f**	Bn	2-naphthyl	98	82 : 18	92
11[f,g]	**1f**	Bn	2-naphthyl	99	88 : 12	95

[a] Conditions: **2a** (0.10 mmol), **3a** (0.12 mmol), **1**·2HBF$_4$ (0.010 mmol) with KHMDS (0.020 mmol) or organobase (0.010 mmol), THF (1.0 mL), -80 °C, 24 h. [b] Isolated yields unless otherwise noted. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral stationary-phase HPLC analysis for the major diastereomer. [e] NMR yield. [f] Performed for 30 min. [g] Performed at -96 °C. THF = tetrahydrofuran



Our initial study was conducted with catalyst **1a** having phenyl groups on both the guanidine moiety and the linker. The catalyst was generated *in situ* by treating a HBF_4 complex of **1a** with two equivalents of potassium bis(trimethylsilyl)amide (KHMDS) prior to use. Treatment of benzyl α-phenylthioacetate (**2a**) with *N*-Boc imine **3a** in the presence of 10 mol% **1a** in THF at -80 °C for 24 h provided the desired product **4aa** in good yield (entry 1). In addition, substantial enantioselectivity was detected, which revealed that the newly-developed organosuperbase was indeed able to serve as a chiral Brønsted base catalyst. As a control experiment, the reaction was attempted with achiral bases possessing different basicities (entries 2-4). The use of less basic guanidine (TBD = 1,5,7-triazabicyclo[4.4.0.]dec-5-ene, pK_{BH+} = 26.0 in CH_3CN)[20] and P1-phosphazene (P1-*t*Bu, pK_{BH+} = 27.0 in CH_3CN, 15.7 in DMSO)[12,20] resulted in no reaction (entries 2 and 3). In contrast, the use of P2-phosphazene having much higher basicity (P2-*t*Bu, pK_{BH+} = 33.5 in CH_3CN, 21.5 in DMSO)[12] dramatically accelerated the reaction (entry 4). These results clearly indicate that the catalyst basicity imparted by the P2-phosphazene moiety of **1a** is essential for promoting this reaction. The effect of the substituents on the catalysts was then examined. First, the catalyst having the opposite absolute configuration at the chiral center on the linker was tested, which decreased the diastereoselectivity (entry 5). Interestingly, the absolute configuration of the major diastereomer was identical to that of the product obtained with the initial catalyst. This result suggests that the chiral guanidine moiety is the primary substrate recognition site for the enantioselective formation of the major diastereomer of **4aa**. Next, catalysts having various substituents on the guanidine moiety and the linker were applied to the reaction (entries 6-9). The substituents at both positions had an appreciable impact on the stereoselectivities, especially on the enantioselectivity. Among the catalysts tested, the catalyst having 2-naphthyl groups on the guanidine moiety and a benzyl group on the linker provided the highest stereoselectivities (entry 9). The reaction was found to be completed within 30 min with improvement in both the diastereomeric ratio and the ee value of the major diastereomer of **4aa** (entry 10). These results suggest that the product could be partially epimerized by extending the reaction time.[21] Further improvement of the stereoselectivities was achieved by reducing the reaction temperature from -80 °C to -96 °C, and these reaction conditions were used as the optimum reaction conditions for screening the scope of imines (entry 11). The absolute configuration of the major diasteromer of **4aa** was unambiguously determined to be (2*S*,3*R*) by single-crystal X-ray diffraction analysis.[22]

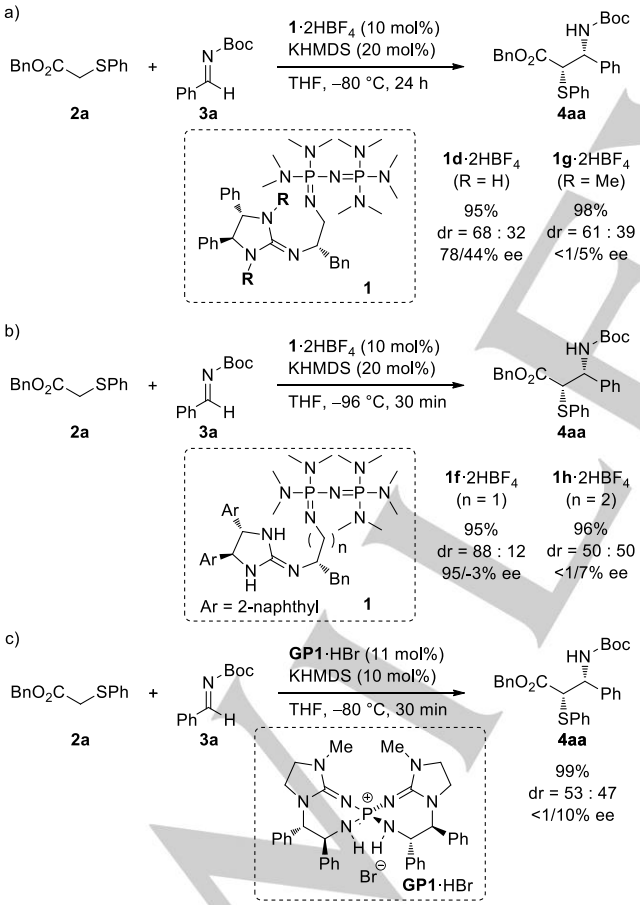
The scope of imines is summarized in Scheme 1. A variety of aromatic imines including those having an electron-donating group or an electron-withdrawing group at the *para* position, **3b**-**3e**, and sterically hindered *ortho*-tolyl imine **3g**, were applicable to this reaction, providing the corresponding adducts in high yields with a good level of diastereoselectivities and high enantioselectivities. The reaction of heteroaromatic 2-furyl imine **3i** also proceeded without any problem. Furthermore, aliphatic imine **3j** was applicable to this reaction, but the diastereomeric ratio was lower than those of aromatic imines. However, a high level of ee of the major diastereomer was still maintained.



Scheme 1. Scope of Imines. [a] Performed for 20 min.

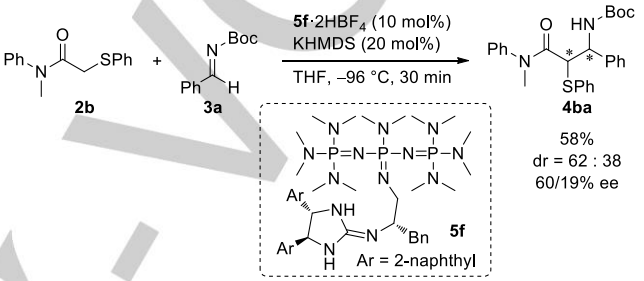
In order to gain insight into the requisite elements of the catalyst molecule for its high stereocontrolling ability, some control experiments were carried out (Scheme 2). First, the reaction was conducted with **1g** possessing the *N*-methylated guanidine moiety (Scheme 2a). The ee values of both enantiomers were

dramatically decreased. This result indicates that the N-H proton on the guanidine moiety plays a key role in the stereoselective C-C bond forming event. The catalyst **1h** having a one-carbon elongated linker was also examined (Scheme 2b). In this case, the product was obtained in high yield but low stereoselectivities. This result reveals the importance of the relative arrangement of the two organobase functionalities in the catalyst molecule, implying that the distinctive cooperative function by the P2-phosphazene moiety and the guanidine moiety is indeed operative to control the stereoselectivities of the reaction. Chiral bis(guanidino)iminophosphorane having typical substituents **GP1**, of which potential has been exhibited in several reactions,[8] was then applied to this reaction to compare its catalytic activity (Scheme 2c). The reaction proceeded smoothly to provide **4aa** in quantitative yield, but with very low diastereo- and enantioselectivities albeit under unoptimized reaction conditions for **GP**. Considering the fact that no chiral organobases other than **GP** possess comparable basicity to **1**, this result not only shows the advantage of the newly-developed catalyst, but also strongly demonstrates the importance of the development of novel chiral organosuperbases to open up new avenues for unprecedented molecular transformations under chiral Brønsted base catalysis.



Scheme 2. Control Experiments.

Finally, an exploratory study of the reaction of α-phenylthioacetamide **2b** revealed another promising aspect of our molecular design (Scheme 3). Whereas the reaction of much less acidic **2b** did not proceed with P2-phosphazene-based catalyst **1** even at the higher temperature of -40 °C, the P3-phosphazene based-catalyst **5f** possessing enhanced basicity promoted the reaction to provide the corresponding Mannich adduct **4ba** in moderate yield with moderate stereoselectivities. Thus, our molecular design for chiral Brønsted base catalysts potentially allows for the fine tuning of the catalyst basicity with an organosuperbase functionality in addition to fine tuning of a chiral environment around the reaction site with substituents on a chiral organobase functionality as a substrate recognition site and a linker. These tunable properties of the newly-designed catalysts are markedly beneficial for further development of new catalytic enantioselective reactions with the expansion of the scope of pronucleophiles.



Scheme 3. Exploratory Study of Direct Mannich-type Reaction of α-Phenylthioacetamide.

In conclusion, we have developed chiral Brønsted base catalysts consisting of a P2-phosphazene as an organosuperbase and a chiral guanidine as a hydrogen bond donor for substrate recognition. The molecular design is based on a conceptually new idea for a distinctive cooperative function by two organobases in a single catalyst molecule. The prominent catalytic activity of the chiral cooperative binary base catalyst was demonstrated in the enantioselective direct Mannich-type reaction of α-phenylthioacetate as a less acidic pronucleophile to construct a β-amino-α-thiocarbonyl scaffold in a highly enantioselective manner. The results of our investigation would provide a new guiding principle for the design and development of chiral Brønsted base catalysts and would broaden the utility of chiral Brønsted base catalysis in organic synthesis. Further studies are in progress to develop novel catalytic enantioselective reactions and expand the scope of pronucleophiles by using the newly-developed catalysts and to develop highly efficient catalysts based on the newly-established molecular design.

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Keywords: organocatalyst • organosuperbase • asymmetric catalysis • phosphazene • guanidine

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[21] As a control experiment, treatment of enantio-enriched **4aa** with **1f** generated *in situ* in toluene at -80 °C for 24 h resulted in partial epimerization. See the Supporting Information for details.

[22] CCDC No. 1942446. See the Supporting Information for details.

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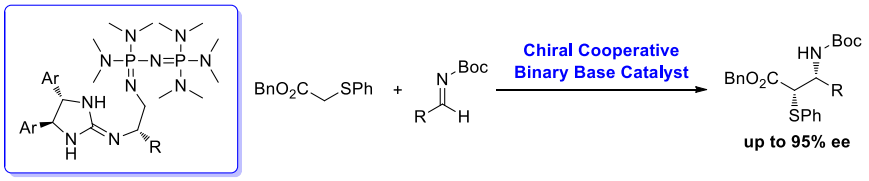

Chiral Brønsted base catalysts, which consist of a P2-phosphazene as an organosuperbase and a chiral guanidine as a hydrogen bond donor for substrate recognition, were developed based on a conceptually new idea for a distinctive cooperative function by two organobases in a single catalyst molecule. The prominent catalytic activity was demonstrated in the enantioselective direct Mannich-type reaction of less acidic α-phenylthioacetate.