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Noncovalent Modification Strategy with Achiral Phosphoric Acid Diesters for Designing a Chiral Brønsted Base Organocatalyst

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Abstract

A strategy for designing chiral Brønsted base organocatalysts through noncovalent modification of a chiral dibasic molecule with an achiral phosphoric acid diester is introduced for the first time. Such a molecular modification concept utilizing acid-base interactions may facilitate the on-demand design of asymmetric organocatalysts, as preliminarily demonstrated in this work.

Keywords: Organocatalyst, Achiral phosphoric acid diester, Noncovalent modification

There are many and various concepts and methods in molecular catalyst design.[1,2] However, they usually involve an experimental fine-tuning of molecular structure especially for the design of asymmetric catalysts, which is often time-consuming since it is not yet trivial to theoretically predict the optimal structure. Whereas such an optimization could generally be performed by varying a covalently linked moiety within the catalyst structure, it would be much easier if a noncovalent interaction could be utilized for molecular modification. For example, an acidic/basic site neighboring to the active center of catalyst may be used to readily modify its surrounding environment by adding diverse bases/acids. However, such a way is not general, arguably because a) noncovalent bonds are too weak and too flexible to predict and fix the conformation of catalyst and b) the active center of catalyst often has an acidic/basic nature that may be affected by an additional base/acid.

The history of organocatalysts involves plenty of developments of chiral Brønsted base catalysts that activate pronucleophilic substrates via deprotonation process. A breakthrough in such an activation mode has been achieved by Takemoto in 2003 by the development of a tertiary amine—thiourea bifunctional catalyst (so-called Takemoto's catalyst),[3] which has since boosted the evolution of bifunctional Brønsted base organocatalysis.[2] This type of catalyst allows for fine prediction and control of simultaneous activation of nucleophiles and electrophiles in the transition state of the reaction by introducing a basic site and an acidic (hydrogen bond donating) site at appropriate positions in the molecule via covalent bonds (Figure 1a).[4] If such a bifunctional situation can be constructed with a chiral/achiral dibasic molecule and an achiral/chiral monoacidic molecule through their specific acid-base interactions in situ, many variations in

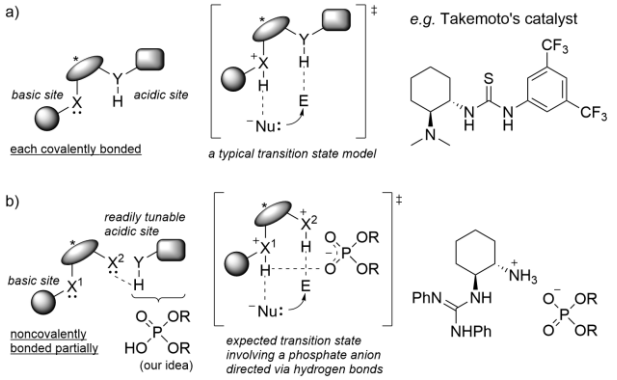


Figure 1. The design concept for a) typical chiral bifunctional acid-base type organocatalysts and b) our catalysts in this study.

catalyst structure and functionality may be quickly screened without synthesizing all the candidates in pure form. To realize this concept with our own approach, we envisioned to utilize achiral phosphoric acid diesters in an equimolar combination with optically active chiral dibasic molecules (Figure 1b, left). Achiral phosphoric acid diesters are readily accessible and structurally versatile, which may be potent as a noncovalent modifier of chiral dibasic scaffolds because a) they may have enough acidity to form a stable salt with general basic functional groups such as amino groups,[5] b) their conjugate bases, phosphate anions, may have appropriate basicity to be fixed as a pseudo-substituent of the chiral scaffold via hydrogen bonds in a transition state (Figure 1b, middle), and c) their inherent bulkiness may bring a good steric effect for controlling asymmetric induction. Although similar approaches for designing organocatalysts based on the chiral dibasic molecule—achiral acid combination have been reported,[6] to our knowledge, there are no examples of effectively using organic phosphoric acid as the achiral acid. Herein, we communicate the feasibility of such a noncovalent modification strategy utilizing achiral phosphoric acid diesters for designing a chiral Brønsted base organocatalyst.

We chose optically pure *trans*-1,2-cyclohexanediamine as a starting point of catalyst design and thought up to convert one of the amino groups into *N,N'*-diphenyl substituted guanidino group that can be slightly less basic than the other amino group [see supporting information (SI)]. Because of the basicity contrast, the selective interaction of the remaining primary amino group with an external acid was expected (Figure 1b, right). In addition, the guanidino group having the controlled basicity and a certain bulkiness was envisioned to not only

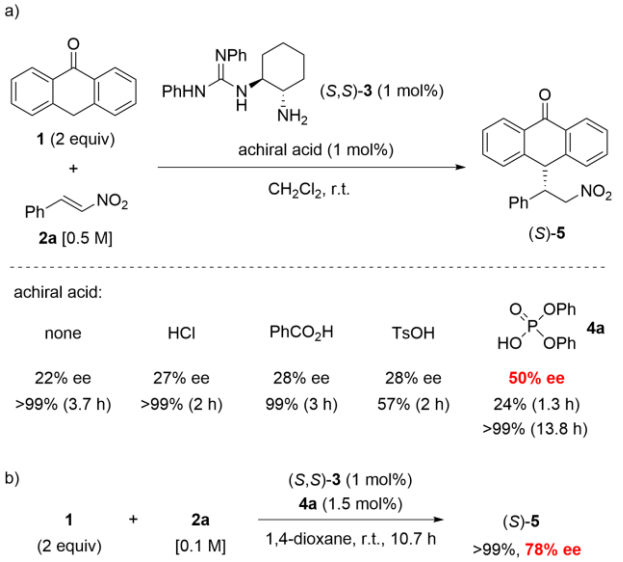


Figure 2. Conjugate addition reactions between **1** and **2a** catalyzed by (*S*,*S*)-**3** a) in the presence of different achiral acids, b) under optimized conditions in the presence of **4a**.

activate a pronuclephile via deprotonation but also then form hydrogen bonds with a bulky phosphate anion, the counter ion of the neighboring ammonium salt group, to create an effective chiral pocket for asymmetric induction in a transition state. With this rough vision in mind, we gave our hypothesis try in the conjugate addition reaction of anthrone (**1**) to *trans*-β-nitrostyrene (**2a**) selected as a model reaction that had previously been reported to be promoted by Brønsted base organocatalysis.[7] To our delight, the reaction performed using 2 equivalents of **1** to **2a** (0.5 M) in dichloromethane at room temperature for 13.8 h in the presence of 1 mol% of *N*-[(1*S*,2*S*)-2-aminocyclohexyl]-*N'*,*N"*-diphenylguanidine [(*S*,*S*)-**3**] and 1 mol% of phosphoric acid diphenyl ester [**4a**, pK_a = 1.9 (H_2O)][5] gave the corresponding adduct (*S*)-**5** in quantitative yield and an enantioselectivity of 50% ee, while only 22% ee was observed in the absence of **4a** under otherwise identical conditions (Figure 2a). The use of other achiral acids including hydrochloric acid, benzoic acid, and *p*-toluenesulfonic acid instead of **4a** led to only slight increase in enantioselectivity, indicating that phosphoric acid diesters could be specifically effective as an achiral cocatalyst. Further optimization of the reaction parameters showed that 1,4-dioxane is the best solvent in terms of stereoselectivity that becomes up to 78% ee by using 1.5 mol% of **4a** for 1 mol% of (*S*,*S*)-**3** and setting the initial concentration of **2a** to 0.1 M (Figure 2b). It should be noted that the stereoselectivity increased in proportion to the number of equivalents of **4a** to (*S*,*S*)-**3** and reached its maximum at 1.5 equivalents (1.5 mol%), whereas the catalytic activity decreased inversely and was completely lost at 2.0 equivalents (2.0 mol%) (see SI). Furthermore, a linear correlation was observed between the catalyst ee and the product ee (see SI). These observations indicate that a single molecular aggregate (salt) of (*S*,*S*)-**3** and **4a** is the catalytically active species most enantioselective and it is certainly Brønsted base organocatalysis.

To gain more insight into the catalytic species, the salt formation behavior of (*S*,*S*)-**3** with achiral phosphoric acid diesters was explored. X-ray crystal structure of a 1:1 salt of (*S*,*S*)-**3** with bis(4-nitrophenyl) hydrogen phosphate (**4b**) was initially analyzed, which unexpectedly suggested that such a salt could be stabilized via interaction between the guanidine moiety and the acid, at least in solid-state (see SI). However, a

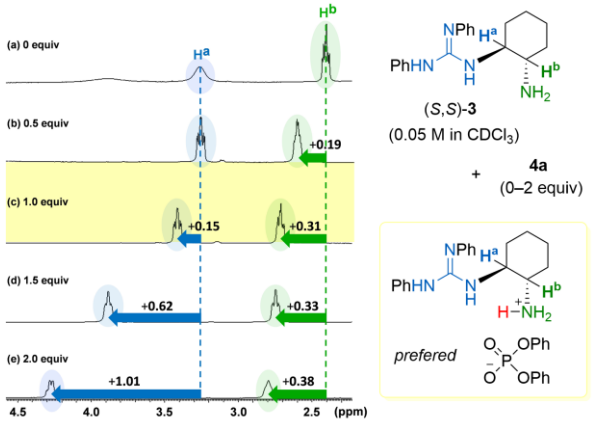


Figure 3. The salt formation behavior of (*S*,*S*)-**3** with varied amounts of **4a** observed by ^{1}H NMR spectroscopy.

solution-state behavior, which is more realistic, analyzed by ^{1}H NMR spectroscopy was contrasting (Figure 3). In the absence of any acids in $CDCl_3$, the signal assignable to the methine proton on the guanidino group side, H^a, and that on the amino group side, H^b, in (*S*,*S*)-**3** appear at 3.26 ppm and 2.40 ppm, respectively (Figure 3a). When 0.5 equivalents of **4a** was added, only H^b was shifted 0.19 ppm downfield, which gradually reached +0.38 ppm as the addition amount was increased to 1, 1.5, and 2.0 equivalents (Figure 3b–e, green). On the other hand, H^a was significantly shifted downfield by +0.62 ppm and +1.01 ppm when the addition amount was 1.5 and 2.0 equivalents, respectively, although only 15% of the latter was shifted with 1 equivalent of **4a** (Figure 3b–e, blue). These results show that the salt formation of (*S*,*S*)-**3** with **4a** takes place preferentially on the amino group in solution, as expected. The no shift of H^a in the presence of 0.5 equivalents of **4a** may also support that the ammonium moiety little interacts with the neighboring guanidine group.

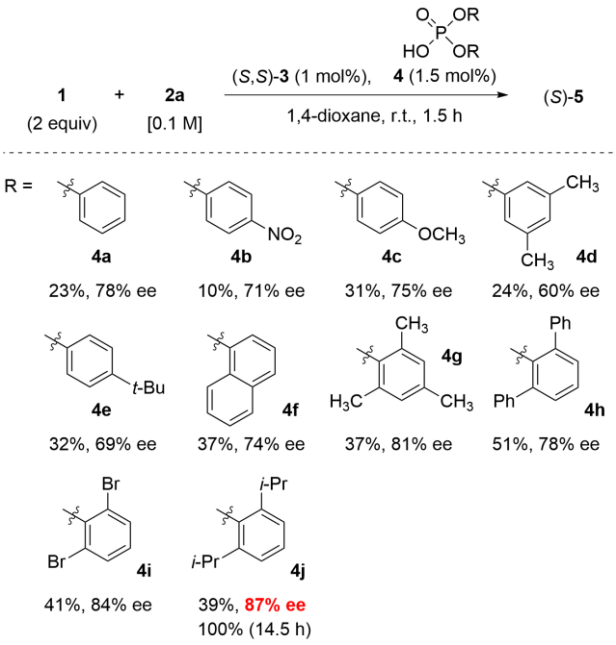


Figure 4. Conjugate addition reactions between **1** and **2a** catalyzed by (*S*,*S*)-**3** in the presence of different achiral phosphoric acid diesters **4a**–**4j**.

We explored whether the stereoselectivity of (*S*,*S*)-**3** in combination with **4a** can be further improved by just altering **4a** with different achiral phosphoric acid diesters **4b**–**4j** in the

conjugate addition reaction of **1** to **2a** under optimized conditions (Figure 4). As compared with **4a** (78% ee) bearing two non-substituted phenyl groups, the use of **4b**–**4e** bearing *meta*/*para*-substituted phenyl groups as well as **4f** bearing 1-naphthyl groups resulted in lowering the ee value regardless of their electronic properties. On the other hand, equal to or better enantioselectivity was achieved with **4g**–**4j** bearing 2,6-disubstituted phenyl groups, implying their positive steric effects for enantiodiscrimination. For the best result, the reaction between **2a** (0.1 M) and **1** (2 equiv) was smoothly catalyzed by 1 mol% of (*S*,*S*)-**3** in combination with 1.5 mol% of **4j** bearing 2,6-diisopropylphenyl groups in 1,4-dioxane at room temperature to afford (*S*)-**5** in quantitative yield and an enantioselectivity of 87% ee in 14.5 h.

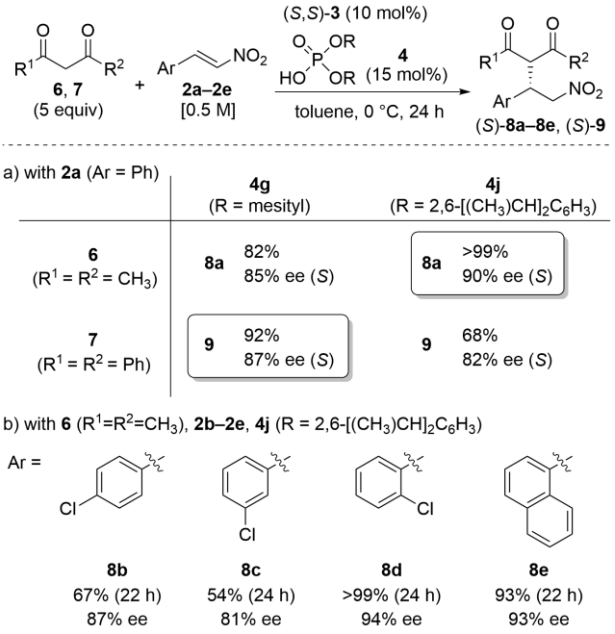
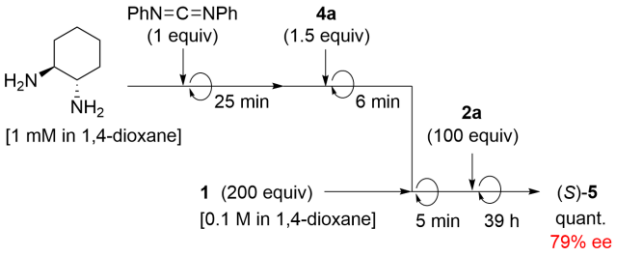


Figure 5. Conjugate addition reactions between **6**/**7** and **2a**–**2e** catalyzed by (*S*,*S*)-**3** in the presence of **4g**/**4j**.

Exploring the substrate scope of the conjugate addition reaction turned out that the optimal achiral phosphoric acid diester for (*S*,*S*)-**3** differed depending on whether the pronucleophile was acetylacetone (**6**)[8] or 1,3-diphenyl-1,3-propanedione (**7**)[9] under slightly modified conditions (10 mol% of the catalyst were used to promote the reaction at 0 °C with a reasonable reaction time): **4j** was optimal for **6**, while **4g** was optimal for **7**, in which the corresponding adducts (*S*)-**8a** and (*S*)-**9** were obtained in 90% ee and 87% ee, respectively (Figure 5a). These results suggest that the present catalyst design concept based on noncovalent molecular modification is amenable to the on-demand screening of optimal catalyst structures for each substrate, which is often costly in traditional molecular design that relies on covalent bonds and requires isolation of all candidates prior to use. Other facts on the scope of substrate currently available for the present catalytic system include that a) methyl acetoacetate seems to be more reactive than **6** despite its lower acidity (although much less suitable for asymmetric induction), while diethyl malonate is totally unreactive (see SI), b) the catalyst tends to be somewhat sensitive to the substituent of *trans*-β-nitroolefins to provide each adduct in moderate to high yields (46–>99%) and enantioselectivities (75–94% ee, see Figure 5b for some representatives and also SI for others). Although a clear explanation is not available for these results at the moment, it is plausible that the enantiotopic faces of nitroolefins are discriminated based on steric hindrance of the phosphate anion



Scheme 1. Asymmetric conjugate addition reaction between **1** and **2a** promoted by the present catalyst prepared in situ from the chiral diamine.

directed via noncovalent bonds in a transition state (see SI).

Finally, we show another advantage for the present chiral Brønsted base organocatalysts. When to the solution of (1*S*,2*S*)-1,2-cyclohexanediamine in 1,4-dioxane (1 mM) was added *N*,*N*′-diphenylcarbodiimide (1 equiv), **4a** (1.5 equiv), **1** (200 equiv), and **2a** (100 equiv) in sequence at appropriate intervals and the resulting mixture was stirred for 39 h at room temperature, (*S*)-**5** was quantitatively obtained with an enantioselectivity of 79% ee comparable to that observed in the reaction using pre-isolated (*S*,*S*)-**3** in combination with **4a** (Scheme 1 vs Figure 2b). This result suggests that our catalysts can be readily prepared in situ even from the chiral diamine ingredient via stepwise molecular assembly of the other two components. Not only the noncovalent bond site with achiral phosphoric acid diesters but also the substituents of the guanidino group may be quickly screened on demand.

In conclusion, we have proposed a strategy for designing chiral Brønsted base organocatalysts based on noncovalent modification of a chiral dibasic molecule with an achiral phosphoric acid diester, introducing a new type of such catalysts containing a guanidino group as a relatively mild basic site and a primary ammonium phosphate moiety as the essence of stereocontrol. The study may provide a guide for developing asymmetric catalysts readily available (pre-isolation free) and quickly designable on demand.

Supporting Information

Experimental procedures including the synthesis of (*S*,*S*)-**3** and achiral phosphoric acid diesters and the asymmetric conjugate addition reactions, characterization data of related compounds. This material is available on…

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Graphical Abstract

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<Summary>
Conjugate addition reactions of pronucleophiles including anthrone and 1,3-dicarbonyl compounds with nitroolefins were smoothly catalyzed by *N*-[(1*S*,2*S*)-2-aminocyclohexyl]-*N',N''*-diphenylguanidine noncovalently modified with achiral phosphoric acid diesters to afford the corresponding adducts with high enantioselectivity (up to 94% ee).

<Diagram>