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Enantioselective Phospha-Michael Reaction of Diphenyl Phosphonate with Nitroolefins Utilizing Conformationally Flexible Guanidinium/Bisthiourea Organocatalyst: Assembly-State Tunability in Asymmetric Organocatalysis

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Abstract: A catalytic enantioselective phospha-Michael reaction of diphenyl phosphonate to nitroolefins was achieved by utilizing a 1,3-diamine-tethered guanidinium/bisthiourea organocatalyst. The procedure is applicable to nitroolefins having various aromatic and aliphatic substituents, and enables an efficient access to phospha-Michael products with 90–98% *ee*. Monomeric or oligomeric active species of the catalyst can be utilized, depending on the presence or absence of water.

Keywords: asymmetric synthesis; guanidinium species; organocatalysis; phospha-Michael reaction; thioureas

Hydrogen-bonding catalysis has recently emerged as an important strategy in asymmetric organocatalysis.[1,2] Although many H-bonding catalysts have been designed based on inspiration drawn from molecular recognition processes in enzyme-catalyzed reactions,[3] in general, their stereoselection processes are governed by a fundamentally different principle.[4] Since enzymes are conformationally flexible, their selectivities are controlled by the kinetically favored conformation, which affords substantial rate acceleration relative to competing reaction pathways *via* other conformations.[3] In sharp contrast, the vast majority of the H-bonding catalysts reported to date are predicated on the use of rigid chiral templates in order to reduce the number of distinct possible diastereomeric transiton states that can be involved.[1,2] In this context, our attention has been directed to the development of a catalytic system enabling the construction of versatile chiral environments by using a conformationally flexible organocatalyst, **1** or **2** (Figure 1).[5–8] We have successfully developed unique catalytic processes, such as retro-free,[5a,9] enantiodivergent[10] and entropy-controlled organocatalysis,[11] by exploiting the conformational flexibility of our catalysts.

Given the encouraging catalytic activity of 1,3-diamine-tethered guanidine/bisthiourea organocatalyst **2**,[12–14] which can selectively promote the Michael reaction of phenol enolates to nitroolefins,[11] we planned to extend this strategy to the asymmetric formation of phosphorus-carbon (P–C) bonds. The conjugate addition of phosphonates to nitroolefins (phospha-Michael reactions)[15–19] is a useful P–C bond-forming reaction that provides β-nitrophosphonates, which are precursors for the preparation of β-aminophosphonic acids.[20] However, only a few organocatalytic approaches to the phospha-Michael reaction, involving the use of conformationally constrained organocatalysts (i.e., quinines,[16a] axially chiral guanidines[16b] and squaramides that have chiral cyclohex-

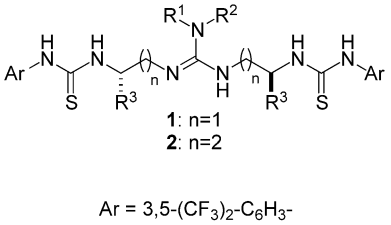


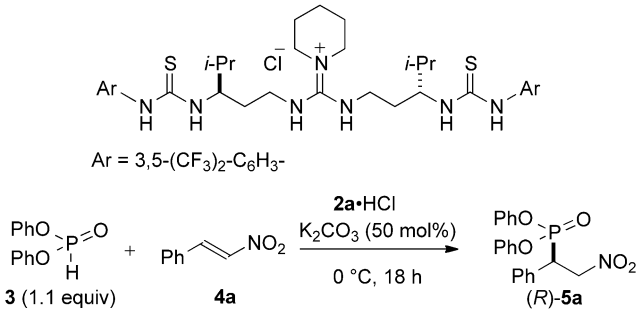
Figure 1. Structures of **1** and **2**.

anediamine[16c,d]), have been reported. Considering the diverse biological activities of P–C compounds,[20] additional studies to develop organocatalytic phospha-Michael reactions are desirable. Herein, we show that the conformationally flexible guanidinium/bisthiourea organocatalyst **2a**·HCl permits a highly enantioselective phospha-Michael reaction of diphenyl phosphonate with nitroolefins in 77–95% yield with 90–98% *ee*. The assembly-state tunability of the catalyst[21] by water in the reaction solution is also presented as a new aspect of guanidinium/bisthiourea organocatalysts.

Because the conformationally flexible organocatalyst can potentially provide many different diastereomeric transition states,[10] it is important to kinetically control the stereoselectivity of bond formation through the ideal transition state of the catalyst in order to attain the maximum enantioselectivity with conformationally flexible organocatalysts. Accordingly, efforts directed at exploring the phospha-Michael reaction by utilizing conformationally flexible organocatalyst **2a**·HCl[22] were first focused on the solvent effect on the conjugate addition of diphenyl phosphonate (**3**) with β-nitrostyrene (**4a**). As shown in Table 1, the cooperative procedure using **2a**·HCl and potassium carbonate[23] promoted the smooth phospha-Michael reaction, giving the corresponding phospha-Michael adduct **5a** in 85–99% yield. A feature of this catalytic system is that (*R*)-**5a** predominates regardless of the solvent used (entries 1–6); these results contrast with the solvent-dependent enantioswitching in previously developed Mannich-type reactions[10] and Friedel–Crafts alkylations.[11,24] In comparison with polar solvents (entries 1–3: 7–42% *ee*), nonpolar solvents (entries 4–6: 88–89% *ee*) gave better enantioselectivities. Among the solvents tested, toluene gave the best enantioselectivity (entry 6, 89% *ee*). A significant improvement of the enantioselectivity was seen upon addition of water, and the *ee* value was increased to 95% *ee* (entry 7). The reaction proceeded with as little as 1 mol% of **2a**·HCl to give **5a** without loss of reactivity and enantioselectivity (entry 8, 99% yield, 95% *ee*). As shown in entry 9, the developed catalytic enantioselective phospha-Michael reaction was successfully performed on a 5-mmol scale with 1 mol% catalyst, giving the product **5a** in 99% yield with 95% *ee*. A single recrystallization of **5a** (95% *ee*) provided the optically pure compound in 91% yield by vapor diffusion of hexane into dichloromethane solution at 4 °C

Next, the scope of catalytic phospha-Michael reaction with a range of nitroalkenes **4** was examined (Table 2). For operational convenience, all reactions were performed with 5 mol% of **2a**·HCl under biphasic conditions. Fine-tuning of the reaction conditions by changing the amount of potassium carbonate or the reaction temperature in order to control the reaction rate (entries 7–11) led to high enantioselectivity for the reactions involving both aromatic and aliphatic nitroolefins. For example, *p*-substituted aromatic nitroolefins including an electron-withdrawing or electron-donating group gave the corresponding phospha-Michael adducts in 88–90% yield with 90–96% *ee* (entries 1–3). Disubstituted aromatic nitroolefin **4e** was also available as a substrate, giving the product **5e** in 81% yield with 96% *ee* (entry 4). Naphthyl-, 2-thienyl- and 2-furyl-substituted nitroolefins also afforded the corresponding phospha-Michael adducts in 77–84% yield with 95–98% *ee* (entries 5–8). Among the most challenging substrates reported to date in organocatalytic phospha-Michael reactions are sterically bulky aliphatic nitroolefins, which are well known to be poorly reactive.[16] Indeed, only one organocatalytic approach has been reported to afford a highly enantioselective reaction (>90% *ee*), and it required 20 mol% catalyst loading.[16c] As can be seen in entries 9 and 10, **2a** displayed extraordinary high catalytic activity for **4j** and **4k**, attaining high enantioselectivities with 5 mol% catalyst loading: **4j**: 98% yield,

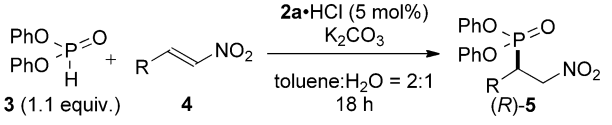
Table 1. Optimization studies.[a]

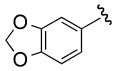


Entry	Catalyst (mol%)	Solvent	Yield [%][b]	*ee* [%][c,d]
1	5	MeCN	88	7
2	5	THF	85	20
3	5	EtOAc	94	42
4	5	CH_2Cl_2	99	88
5	5	Cl-benzene	91	88
6	5	toluene	94	89
7[e]	5	toluene: H_2O = 2: 1	99	95
8[e]	1	toluene: H_2O = 2: 1	99	95
9[f]	1	toluene: H_2O = 2: 1	99	95 (99)[g]

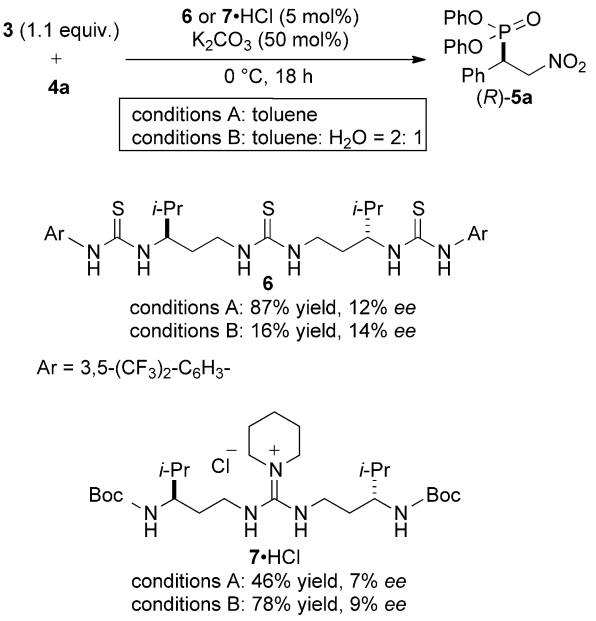
[a] Reactions were carried out on a 0.1-mmol scale in 1.0 mL of the solvent.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] The absolute configuration of **5a** was determined to be (*R*) on the basis of its optical rotation.[16]
[e] Reactions were carried out on a 0.1-mmol scale in 1.0 mL of toluene and 0.5 mL H_2O.
[f] The reaction was carried out on a 5-mmol scale in 50 mL of toluene and 25 mL H_2O.
[g] The *ee* value after single recrystallization.

Table 2. Catalytic phospha-Michael reactions with various nitroolefins using **2a**·HCl.[a]



Entry	4: R	K_2CO_3 (mol%)	Temp. [°C]	Product	Yield [%][b]	*ee* [%][c,d]
1	**4b**: 4-Me-C_6H_4	50	0	**5b**	88	91
2	**4c**: 4-Cl-C_6H_4	50	0	**5c**	88	90
3	**4d**: 4-MeO-C_6H_4	50	0	**5d**	90	96
4	**4e**: 	50	0	**5e**	81	96
5	**4f**: 1-naphthyl	50	0	**5f**	84	96
6	**4g**: 2-naphthyl	50	0	**5g**	81	98
7[e]	**4h**: 2-thienyl	25	0	**5h**	77	95
8[e]	**4i**: 2-furyl	25	0	**5i**	78	95
9[f,g]	**4j**: *c*-C_6H_{11}	10	–10	**5j**	98	92
10[e]	**4k**: *t*-Bu	25	0	**5k**	95	92
11[f,g]	**4l**: $PhCH_2CH_2$	10	–30	**5l**	95	92

[a] Reactions were carried out on a 0.1-mmol scale in 1.0 mL of toluene.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] The absolute configuration of **5** was determined to be (*R*) on the basis of the optical rotation.[16]
[e] The reactions were carried out in 0.5 mL toluene and 0.25 mL H_2O.[f] The reactions were carried out in 0.5 mL toluene and 0.1 mL H_2O.
[g] Ice was formed in the reaction media.



Scheme 1. The phospha-Michael reaction of **3** with **4a** utilizing **6** or **7**·HCl.

92% *ee* (entry 9) and **4k**: 95% yield, 92% *ee* (entry 10).

To gain insight into the reaction mechanism, we next investigated the structure/catalytic activity relationship with respective to possible catalytic sites (Scheme 1). Use of the structural variants **6** and **7**·HCl under the same reaction conditions as employed in Table 1, entry 6 (conditions A) and entry 7 (conditions B) resulted in a drastic decline of the enantioselectivity (7–14% *ee*). These observations strongly suggest that the stereodiscrimination process in catalytic phospha-Michael reactions using **2a**·HCl is governed by cooperative activation of the substrates[25] by guanidinium and thiourea in **2a**·HCl under both homogeneous and biphasic conditions. As regards reactivity, a significant difference between **6** and **7**·HCl was observed. For example, the addition of water drastically decreased the reactivity of **6**, in which the guanidinium group in **2a**·HCl is replaced by a thiourea group (toluene: 87% yield *vs.* toluene/H_2O = 2/1: 16% yield). On the other hand, significantly higher reactivity upon addition of water (toluene: 46% yield *vs.* toluene/H_2O = 2/1: 78% yield) was observed in the reaction using guanidinium **7**·HCl. Thus, the guanidinium cation in the catalyst plays a key role in enhancement of the reaction rate of the phospha-Michael reaction under biphasic conditions in the presence of water,[26] suggesting that the P–C bond-forming reaction might take place through the interaction of guanidinium/phosphite at the interfacial layer.[22]

The unique solvent/water effects described above,[24,26] along with our wish to explore assembly-state-tunable organocatalysis, stimulated us to investigate the relationship between the *ee* of the catalyst **2a**·HCl and the *ee* of the phospha-Michael product **5a** in the presence or absence of water.[27] A linear relationship between the % *ee* of **2a**·HCl and that of **5a** was obtained for the reaction in the absence of water, suggesting that the stereoselectivity in this process is controlled by the inherent structure of monomeric **2a**·HCl.[10,11] In contrast, a negative non-linear effect was observed upon addition of water.[9c] These observations indicate the importance of catalyst assembly for the construction of a favorable chiral environment for attainment of higher *ee* of (*R*)-**5a** in the phospha-Michael reaction of **3** with **4a** (Table 1, entry 6 *vs.* entry 7). Thus, the results shown in Figure 2 support the idea that the assembly state of the **2a**·HCl can be tuned depending on the presence or absence of water. We believe that assembly-state tunability of the catalyst[21] is a potentially useful strategy for modulation of the chiral environments of conformationally flexible guanidinium/bisthiourea organocatalysts. Further mechanistic studies are ongoing.

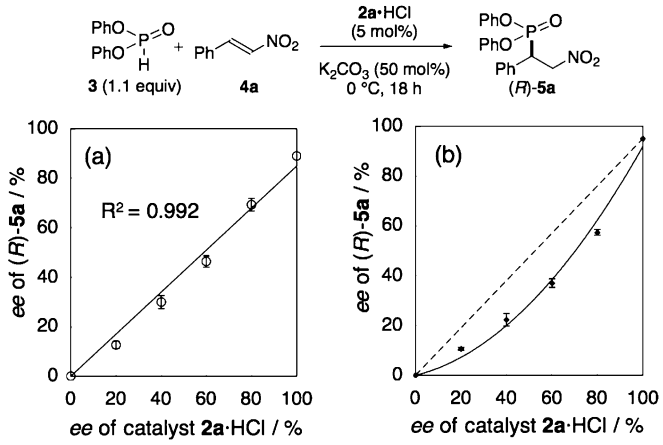


Figure 2. Relationships between *ee* of **2a** and that of (*R*)-**5a**; (**a**) conditions A: toluene, (**b**) conditions B: toluene: H_2O = 2:1.

In conclusion, we have developed the organocatalytic phospha-Michael reaction of diphenyl phosphonate with nitroolefins by utilizing a conformationally flexible organocatalyst. The availability of monomeric or oligomeric active species of the catalyst, depending on the presence or absence of water, may serve to extend the concept of constructing diverse chiral environments with a single chiral catalyst. Further efforts to apply assembly-state-tunable organocatalysis to other classes of asymmetric transformations, including enantio-switching, diastereo-switching and organocascade reactions, are under way.

Experimental Section

Typical Procedure

To a mixture of **2a**·HCl (4.5 mg, 0.005 mmol) and β-nitrostyrene (**4a**) (14.9 mg, 0.100 mmol) in toluene (1.0 mL) and 0.1 M aqueous K_2CO_3 (0.5 mL) was added diphenyl phosphonate (**3a**) (21.1 μL, 0.11 mmol) at 0 °C. The mixture was stirred for 18 h at 0 °C, then the reaction was quenched with saturated aqueous NH_4Cl. The resulting mixture was diluted with CH_2Cl_2 and poured into water. The aqueous layer was extracted with CH_2Cl_2 (×3) and the combined organic layer was washed with brine, and dried over $MgSO_4$. Solvents were evaporated under reduced pressure, and the residue was purified by flash column chromatography (*n*-hexane/EtOAc = 10/1) to afford (*R*)-**5a** (yield: 36.4 mg, 95% yield) and **2a**·HCl (recovery: 4.5 mg, 99%). The enantiomeric excess of (−)-(*R*)-**5a** (95% *ee*) was determined by means of chiral HPLC analysis (Chiralpak IA, 0.46 cm (ϕ) × 25 cm (L), *n*-hexane/ethanol = 80/20, 1.0 mL min^{-1}): major; 17.9 min, minor; 13.6 min.

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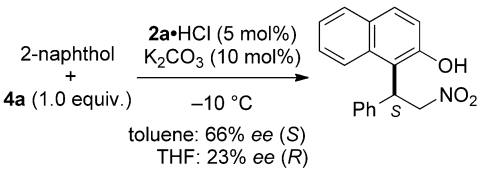
[24] Solvent-dependent enantioswitching occurred in the catalytic Friedel–Crafts reaction of 2-naphthol with **4a** using **2a**·HCl and potassium carbonate. Thus, conformationally flexible catalyst **2a**·HCl may provide an



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[27] C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922.

