Asymmetric Synthesis

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High Substrate/Catalyst Organocatalysis by a Chiral Brønsted Acid for an Enantioselective Aza-Ene-Type Reaction**

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The enantioselective catalysis of organic reactions that involve small organic molecules, known as organocatalysis, has become a rapidly growing area of research, as it offers operational simplicity together with mild reaction conditions and is environmentally benign.[1] Although organocatalysis has proven to be beneficial in many respects, one critical drawback inherent in the methodologies reported to date is the inadequate catalytic efficiency.[2] Most organocatalytic reactions are performed at substrate-to-catalyst (S/C) molar ratios of 10 or less to achieve sufficient yields and avoid loss of

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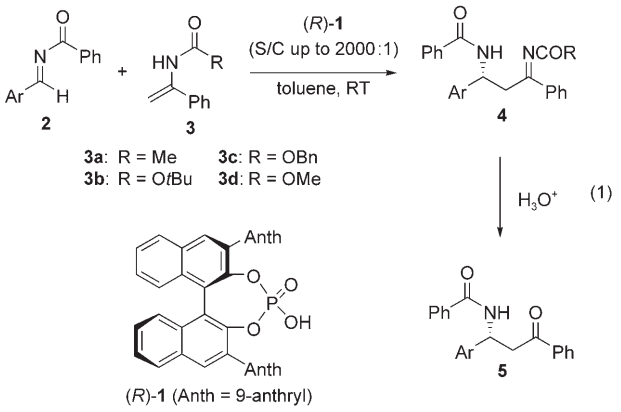
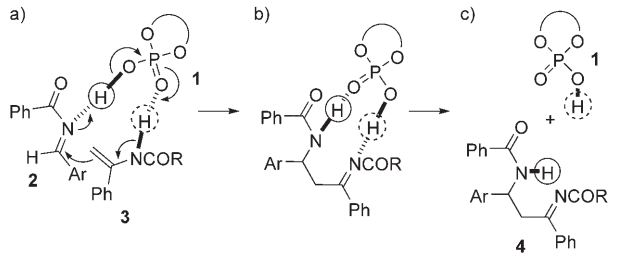
enantioselectivity. One of the greatest challenges in practical organocatalysis is to decrease the catalyst loading to ensure a high efficiency. Akiyama and co-workers and our group have independently developed binaphthol-derived monophosphoric acids **1** as organocatalysts for enantioselective carbon–carbon bond-forming reactions.[3,4] Herein, we report high S/C organocatalysis with **1** as the chiral Brønsted acid[5,6] for enantioselective reactions of *N*-benzoylimines **2** with enamides or enecarbamates **3**. The reaction conditions allow imine/catalyst molar ratios of up to 2000 to afford the corresponding β-aminoimine adducts **4** in high yields without considerable loss of enantioselectivity [Eq. (1)].



Recently Kobayashi and co-workers successfully demonstrated the first use of enamides and enecarbamates as nucleophiles in enantioselective reactions with either glyoxylates or glyoxylate-derived imines catalyzed by chiral copper complexes.[7] Their mechanistic proposal, in which the reaction proceeds by an aza-ene-type pathway, inspired us to develop a highly efficient organocatalytic reaction using a phosphoric acid catalyst **1** (Scheme 1). In our catalytic reaction, it is thought that **1** is assembled into the transient structure of the aza-ene-type reaction of **2** with **3** through a hydrogen-bonding network (Scheme 1a). Thus, the key aspect of catalysis is the dual function of the phosphoric acid moiety,[3c,4b] which electrophilically activates **2** through the proton (hollow circle) and accepts the NH proton (dashed circle) of **3** through the Lewis basic phosphoryl oxygen atom. Subsequent bond recombination, which leads to the aza-ene-type product and regeneration of the catalyst **1**, would ideally take place (Scheme 1b,c). On the basis of this mechanistic assumption, the dual function of **1** through these hydrogen-bonding interactions allows the reaction to operate under high S/C conditions.



Scheme 1. Mechanistic assumption of the aza-ene-type reaction catalyzed by **1**; see text for details.

We first set the S/C ratio to 50:1 (2 mol%) using the binaphthol-derived monophosphoric acid **1** to ascertain the viability of the high S/C ratio in the aza-ene-type reaction. The catalytic efficiency was screened in the reaction of the benzaldehyde-derived *N*-benzoylimine (**2**; Ar = Ph) with an enamide **3a** in various solvents at room temperature. The yields and enantioselectivities were determined after the hydrolysis of imine adducts **4** to β-aminoketones **5** under acidic work-up conditions (concentrated HBr in MeOH).[8] Representative results are given in Table 1. Among the solvents tested, toluene was the best with respect to both yield and enantiomeric excess (Table 1, entries 1–3 versus 4), though the reaction also tolerated common organic solvents. In addition to the enamide **3a**, we examined enecarbamates **3b–d** (Table 1, entries 5–7). The steric bulk of the alkoxy moiety of the enecarbamates exhibited a dramatic effect on the enantioselectivity. That is, the enantioselectivity increased with the decrease in the steric demand of the alkoxy moiety, thus following the order *t*BuO **3b** < BnO **3c** < MeO **3d** and reaching 95% *ee* in the reaction with the less hindered methyl carbamate **3d** (Table 1, entry 7). Lowering the reaction temperature to 0°C led to a slight increase in the enantiomeric excess, although with some loss of catalytic efficiency (Table 1, entry 8). With successful results for the catalytic efficiency in the initial screening, we decreased the catalyst loading and set the S/C ratio to more than 1000:1 (0.1 mol%; Table 1, entries 9–11). The decrease in catalyst loading was clearly still effective, although a prolonged reaction time was required to achieve a comparable level of product formation (Table 1, entries 9 and 10); the enantioselectivity and the yield were maintained at an equally high level. It should be emphasized that the reaction can be performed without considerable loss of enantioselectivity, even when the S/C

Table 1: Chiral Brønsted acid-catalyzed reaction of imine **2** (Ar = Ph) with an enamide **3a** and enecarbamates **3b–d**.[a]

Entry	3	S/C[b] (mol%)	Solvent	*t* [h]	Yield [%][c]	*ee* [%][d]
1	**3a**	50:1 (2)	CH_2Cl_2	0.5	77	69
2	**3a**	50:1 (2)	$(CH_2Cl)_2$	0.5	61	70
3	**3a**	50:1 (2)	Et_2O	0.5	71	80
4	**3a**	50:1 (2)	toluene	0.5	90	86
5	**3b**	50:1 (2)	toluene	1	94	60
6	**3c**	50:1 (2)	toluene	1	55	83
7	**3d**	50:1 (2)	toluene	1	85	95
8[e]	**3d**	50:1 (2)	toluene	1	76	96
9	**3d**	1000:1 (0.1)	toluene	2	64	95
10	**3d**	1000:1 (0.1)	toluene	5	82	95
11	**3d**	2000:1 (0.05)	toluene	5	85	93

[a] Unless otherwise noted, all reactions were carried out with 0.10 mmol of **2** (Ar = Ph) and 0.12 mmol of **3** in a 0.1 M solution at room temperature. [b] Molar ratio of imine **2**/catalyst **1**. [c] Yield of the isolated product of **5** after hydrolysis of **4**. [d] Enantiomeric excess was determined by chiral HPLC analysis (see the Supporting Information). [e] Reaction performed at 0°C.

ratio was increased to as much as 2000:1 (0.05 mol%; Table 1, entry 11).

The applicability of the present high S/C organocatalysis to a series of *N*-benzoylimines **2** was investigated.[9] We set the S/C ratio to 1000:1 (0.1 mol%) to ensure the catalytic efficiency of **1**. Table 2 shows *para*- and *meta* substitution or

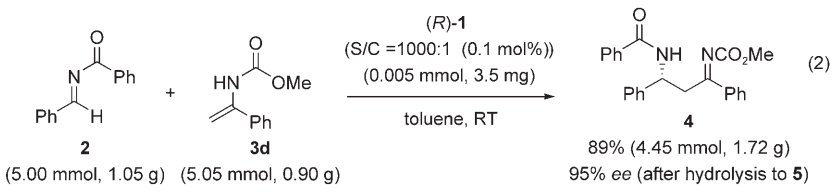
Table 2: Enantioselective aza-ene-type reaction of an enecarbamate **3d** with various *N*-benzoylimines **2** catalyzed by (*R*)-**1** with a S/C ratio of 1000:1 [0.1 mol%; Eq. (1)][a]

Entry	Ar	Yield [%][b]	*ee* [%][c]
1	*p*-Me-C_6H_4–	90	95
2	*m*-Me-C_6H_4–	83	93
3	*o*-Me-C_6H_4–	61	93
4[d]	*o*-Me-C_6H_4–	84	93
5	*p*-MeO-C_6H_4–	82	92
6	*p*-Br-C_6H_4–	89	96
7	*m*-Br-C_6H_4–	85	95
8[e]	*o*-Br-C_6H_4–	53	95
9[d]	*o*-Br-C_6H_4–	82	96
10	*p*-F-C_6H_4–	89	95
11	*p*-Cl-C_6H_4–	84	95
12	*p*-NC-C_6H_4–	97	98
13	1-naphthyl–	88	95
14	2-naphthyl–	91	95
15	(*E*)-C_6H_5-CH=CH–	81	93

[a] Unless otherwise noted, all reactions were carried out using 0.1 mmol of imine **2** in 0.1 M toluene solution at room temperature for 5 h. The molar ratio of imine **2**/enecarbamate **3d**/catalyst **1** was 1000:1200:1 (S/C = 1000:1). [b] Yield of the isolated product of **5** after hydrolysis of **4**. [c] Enantiomeric excess was determined by chiral HPLC analysis (see the Supporting Information). [d] The molar ratio of imine **2**/enecarbamate **3d**/catalyst **1** was 200:240:1 (S/C = 200:1). [e] Reaction performed for 12 h.

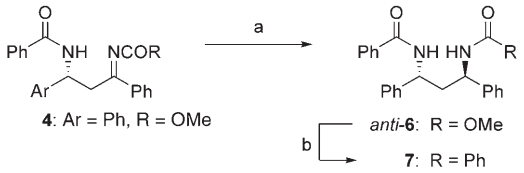
connection with a fused-ring system resulted in excellent yields and enantioselectivities, irrespective of the electronic nature of the substituents. Although *ortho* substitution led to a decrease in the catalytic efficiency, thus giving the product in moderate yields (Table 2, entries 3 and 8), the yields were improved in these cases by lowering the S/C ratio to 200:1 (0.5 mol%; Table 2, entries 4 and 9). An imine derived from an α,β-unsaturated aldehyde was also applicable to the present high S/C organocatalysis, thus giving the product in good yield with high enantioselectivity (Table 2, entry 15).

The utility of the high S/C process was further evaluated by performing a large-scale experiment [Eq. (2)]. The reaction proceeded smoothly without any detrimental effect even on a gram scale. It is noteworthy that only an amount of 3.5 mg of **1** was sufficient to yield 1.7 g of the β-aminoimine product **4** (Ar = Ph) with high enantiomeric excess on completion of the reaction.



(2)

Finally, the synthetic utility of this transformation was demonstrated by derivatization of **4** to C_2-symmetric 1,3-diamine **7**, which is potentially useful as a chiral ligand of metal complexes and a building block in the synthesis of natural products and pharmaceutical compounds (Scheme 2).[10] The reduction of **4** (Ar = Ph, R = OMe)[11] by



Scheme 2. Synthetic utility of β-aminoimine products **4**. Conditions: a) Red-Al, THF, −78→−60 °C, 24 h, 79% (*anti*/*syn* = 87:13); b) PhCOCl/NaI, CH_3CN, 60 °C, 12 h, 92%. Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.

Red-Al afforded *anti*-1,3-diamine **6** in predominantly good yield. A subsequent exchange reaction of the protecting groups[12] from a methoxycarbonyl to a benzoyl moiety led to C_2-symmetric (*R*,*R*)-**7** without any loss of enantiomeric excess during the course of the experiments.

In conclusion, we have successfully developed a highly efficient enantioselective aza-ene-type reaction of *N*-benzoylimines **2** with enecarbamates. The reaction can be performed at extremely low loading of the chiral Brønsted acid catalyst **1** without notable loss in enantioselectivity. The present method provides a practical route to synthetically useful β-aminoimine derivatives which can be readily transformed to 1,3-diamine derivatives of synthetic and biological importance. Further investigation of the reaction mechanisms and potential of the high S/C organocatalysis is in progress with the aim of developing practical organic transformations.

Experimental Section

A typical procedure for the enantioselective aza-ene-type reaction catalyzed by chiral Brønsted acid (*R*)-**1** (S/C = 1000:1): A dried test tube was charged with *N*-benzoylaldimine (**2**; Ar = Ph; 20.9 mg, 0.10 mmol) and the atmosphere replaced with nitrogen. After **2** (Ar = Ph) was dissolved in toluene (0.9 mL), a solution of chiral phosphoric acid (*R*)-**1** (0.1 mL, 0.0001 mmol) in toluene (0.001 M) and then enecarbamate **3d** (21.3 mg, 0.12 mmol) was added at room temperature.The reaction mixture was stirred for over 5 h at ambient temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, and the resulting solution was extracted with dichloromethane and dried over anhydrous Na_2SO_4. After the solvent was evaporated, the residue was dissolved in methanol (2.0 mL) and an aqueous solution of HBr (48%, 0.6 mL) was added. The reaction mixture was stirred at room temperature for 5 min, and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 °C. The resulting mixture was warmed up to room temperature and extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4. After the solvents were evaporated, the crude material was purified by chromatography (hexane/EtOAc, 8:1→1:1)

to give β-aminoketone **5** (Ar = Ph) in 82% yield (95% *ee*) as a white solid.

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[9] We employed the acetone-derived enecarbamate **8** instead of the acetophenone-derived enecarbamate **3d** to expand the substrate scope. The reaction of **8** with imine **2** (Ar = Ph) worked well under the high S/C conditions (0.1 mol% of **1**), and subsequent hydrolysis gave the corresponding product **9** in good yield (80%). Unfortunately, however, the enantiomeric excess was moderate (44% *ee*); further screening of the catalyst, reactants, and reaction conditions is required to improve the enantiomeric excess (see Supporting Information).

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