Organocatalysis

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Diphenylprolinol Silyl Ether as a Catalyst in an Enantioselective, Catalytic, Formal Aza [3+3] Cycloaddition Reaction for the Formation of Enantioenriched Piperidines**

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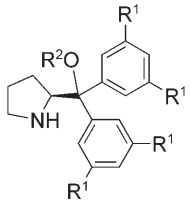
The piperidine ring system is one of the most common structural subunits in natural products and biologically significant compounds.[1] The aza Diels–Alder reaction[2] and the aza [3+3] cycloaddition reaction[3] are straightforward synthetic methods for making piperidine ring systems. Several methods have been developed for formal aza [3+3] cycloaddition reactions, such as reactions of 1,3-cyclic sulfonates with C/N dianions,[4] vinylogous amides with α,β-unsaturated iminium ions,[5] and aziridines with Pd–trimethylenemethane complexes.[6] In spite of these formal aza [3+3] cycloaddition methods, and to the best of our knowledge, an enantioselective catalytic version has not been reported.

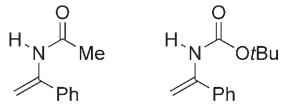
Asymmetric catalytic reactions promoted by organocatalysts is a rapidly growing area of research.[7] Our group developed diarylprolinol silyl ether as an effective catalyst in the Michael reaction,[8] the ene reaction,[9] the Diels–Alder reaction,[10] the tandem Michael/Henry reaction,[11] and the Michael reaction of nitroalkanes.[12] At the time of our first report, the group of Jørgensen also developed the same type of catalyst;[13] the diarylprolinol silyl ether catalyst has been widely used in enantioselective reactions.[14] We have applied diphenylprolinol silyl ether to the reaction of α,β-unsaturated aldehydes with enecarbamates and found that a formal aza [3+3] cycloaddition reaction proceeds in a highly enantioselective manner as reported herein (Figure 1).



catalyst	R^1	R^2
1	H	TMS
2	H	TBS
3	CF_3	TMS
4	H	H

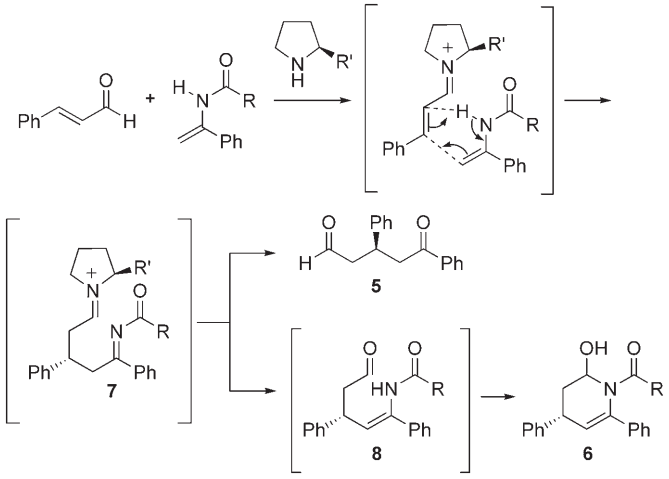
Figure 1. Organocatalysts examined in the present study.

Enecarbamates and enamides have been successfully utilized as reactive nucleophiles by the group of Kobayashi,[15] and Terada et al. recently used them in an aza-ene-type reaction.[16] Having reported the asymmetric ene reaction of cyclopentadiene,[9] we employed an enamide and an α,β-unsaturated aldehyde with the expectation that an ene reaction would occur. Notably, the asymmetric, catalytic intermolecular ene reaction of α,β-enals as enophiles is rare.[9] The reaction of cinnamaldehyde and *N*-(1-phenylvinyl)acetamide **9** was selected as a model reaction and we expected



9 **10**

that an amine catalyst and cinnamaldehyde would afford an iminium ion, which would react with enamide **9** to generate **7** by an ene reaction, to afford ketoaldehyde **5**[17] after hydration (Scheme 1). When cinnamaldehyde and enamide **9** were treated with a catalytic amount of diphenylprolinol trimethylsilyl ether (**1**), ketoaldehyde **5** was obtained in 18% yield in nearly optically pure form along with an unexpected piperidine derivative (**6**) in 47% yield as a mixture of α and β isomers (44:56). The α and β isomers were separated and their optical purities were found to be the same (87% *ee*, Table 1, entry 1). A pure sample of the α isomer resulted in a



Scheme 1. The reaction mechanism of **5** and **6**.

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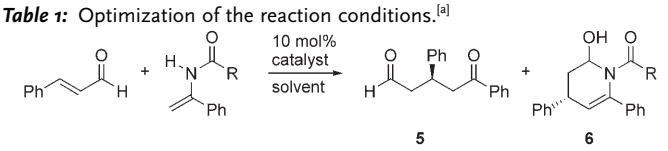
Table 1: Optimization of the reaction conditions.[a]



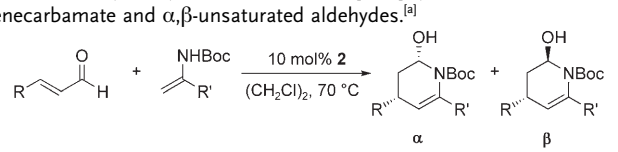
Entry	Catalyst	Ene	Solvent	*T* [°C]	Yield [%][b]		Ratio[c]	*ee* [%][d]		
					5	**6**	α:β	**5**	**6**α	**6**β
1	**1**	**9**	$(ClCH_2)_2$	40	18	47	44:56	99	87	86
2	**1**	**9**	PhH	40	29	14	45:55	99	87	87
3	**1**	**9**	CH_3CN	40	19	10	51:49	99	87	86
4	**1**	**9**	$(ClCH_2)_2$	70	17	68	45:55	n.d.	85	86
5	**2**	**9**	$(ClCH_2)_2$	70	18	69	46:54	n.d.	95	97
6	**3**	**9**	$(ClCH_2)_2$	70	< 5	< 5	n.d.	n.d.	n.d.	n.d.
7[e]	**2**	**10**	$(ClCH_2)_2$	70	0	90	34:66	n.d.	94	93

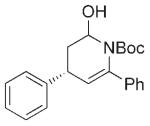
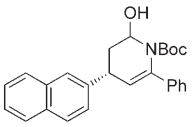
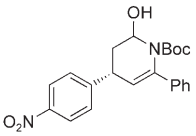
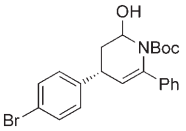
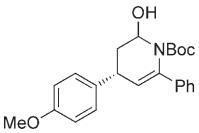
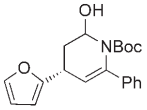
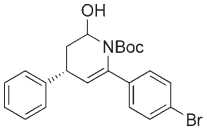
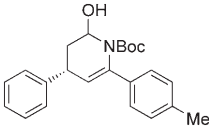
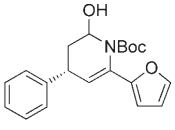
[a] Unless otherwise shown, the reaction was performed by employing cinnamaldehyde (0.5 mmol), enamide (1.0 mmol) or enecarbamate (0.75 mmol), and organocatalyst (0.05 mmol) in the indicated solvent (1.0 mL) at the indicated temperature for 22 h. n.d. = not determined. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral phase after separation of α and β isomers by TLC. [e] The reaction time was 34 h.

mixture of α and β isomers (44:56) upon standing at room temperature for two hours, indicating that there is an equilibrium between the isomers. Piperidine derivative **6** is proposed to be derived from acylimine **7**, which is generated by an ene reaction, with subsequent isomerization to enamide **8** and then successive cyclization (Scheme 1); formally, piperidine **6** was obtained by an enantioselective aza [3+3] cycloaddition reaction. Optimization of the reaction conditions was investigated in detail because a one-step synthesis of chiral piperidine rings by a catalytic asymmetric method is synthetically important (Table 1). First, the solvent was examined and benzene and CH_3CN were found to not be suitable as they led to a decreased yield of **6** (Table 1, entries 2 and 3). When the reaction was performed at a higher temperature (70 °C) in dichloroethane the yield of **6** increased without compromising the enantioselectivity (Table 1, entry 4). In the reaction catalyzed by a catalyst with a bulkier silyl substituent, such as a *tert*-butyldimethylsilyl (TBS) group (**2**), the enantioselectivity increased to 95% *ee* (Table 1, entry 5). Bis(trifluoromethyl) substituted arylprolinol silyl ether[13] **3** was not effective in the present reaction (Table 1, entry 6); and when enecarbamate **10** was employed instead of enamide **9** (Table 1, entry 7), piperidine derivative **6** was formed in excellent yield and high enantioselectivity without the formation of ketoaldehyde **5**. In the reaction of enecarbamate **10**, hydrolysis of **7** would be retarded and isomerization from **7** to **8** would be facilitated. The formation of **6** depends on a subtle balance of several competing reactions, such as the ene reaction, isomerization, hydrolysis, and aminoacetalization.

The scope of the reaction was investigated once the optimal reaction conditions were determined (Table 2). Phenyl- and naphthyl-substituted acrolein (Table 2, entries 1 and 2), as well as acrolein derivatives with aryl groups possessing electron-withdrawing (Table 2, entries 3, 4) and electron-donating (Table 2, entry 5) substituents are suitable

Table 2: Catalytic asymmetric formal aza [3+3] cycloaddition reaction of enecarbamate and α,β-unsaturated aldehydes.[a]



Entry	Product	*t* [h]	Yield [%][b]	Ratio[c] α:β	*ee* [%][d] α	β
1		34	90	34:66	94	93
2		38	83	29:71	91	90
3		22	83	29:71	95	97
4		22	88	31:69	91	92
5		48	73	19:81	97	97
6		96	80	27:73	99	99
7		48	89	14:86	90	90
8		29	89	26:74	90	88
9[e]		23	85	19:81	90	90

[a] Unless otherwise noted, the reaction was performed by employing α,β-unsaturated aldehyde (0.5 mmol), enecarbamate (0.75 mmol), and organocatalyst **2** (0.05 mmol) in dichloroethane (1.0 mL) at 70 °C. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral phase after separation of α and β isomers by TLC. [e] The reaction was performed at room temperature.

substrates that afford the piperidine derivatives in good yield with excellent enantioselectivity. In the reaction of acrolein substituted with a heteroaromatic group such as furyl, a nearly optically pure product was obtained (Table 2, entry 6).

Alkyl-substituted acrolein did not afford a good result. With regard to the ene component, enecarbamates substituted with aryl groups having electron-deficient (Table 2, entry 7) and electron-donating (Table 2, entry 8) substituents, as well as heteroaromatic groups (e.g. furyl; Table 2, entry 9) can be successfully employed.

Piperidine derivative **6a** was converted into **11** by treatment with 2 M HCl, and subsequent oxidation without compromising the enantioselectivity [Eq. (1)]; the absolute configuration was determined by comparison of the optical rotation with that reported in the literature.[18] This absolute configuration is reasonable considering that the ene component approaches opposite to the face with the bulky diphenyl(*tert*-butyldimethylsiloxy)methyl group (Figure 2)

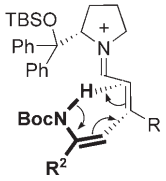
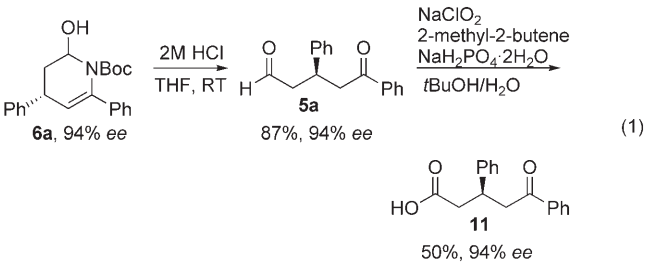
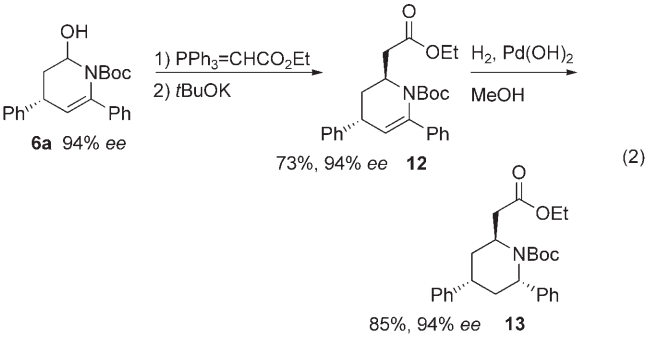


Figure 2. The transition state of the reaction.

Compound **6a** possesses alkene and hemiaminal moieties, which makes it an important synthetic intermediate because there are several additional transformations that are possible. For instance, a



Wittig reaction and subsequent intramolecular Michael reaction stereoselectively provided **12** in good yield. Hydrogenation of **12** also proceeded in a highly stereoselective manner to afford 2,4,6-trisubstituted piperidine **13** as a single isomer without affecting the enantioselectivity [Eq. (2)]. The relative configuration of **13** was determined by using coupling constants and NOESY spectra.[19]



In summary, we have reported the highly enantioselective formal aza [3+3] cycloaddition reaction of α,β-unsaturated aldehydes and enecarbamates catalyzed by diphenylprolinol silyl ether as an organocatalyst. The reaction consists of four consecutive reactions that include an asymmetric ene reaction, an isomerization from an imine into an enecarbamate, hydrolysis, and hemiacetal formation in one pot to afford synthetically important piperidine derivatives with excellent enantioselectivities from simple starting materials. Notably, the intermolecular asymmetric, catalytic ene reaction of α,β-unsaturated aldehydes as the enophile is rare, and the present reaction is one of the few successful examples of such a reaction.

Typical procedure (Table 2, entry 1): A dichloroethane solution (0.66 mL) of enecarbamate **10** (164.5 mg, 0.75 mmol) was added to a dichloroethane solution (0.33 mL) of catalyst **2** (18.3 mg, 0.05 mmol) and *trans*-cinnamaldehyde (62.5 μL, 0.5 mmol) at room temperature. After stirring the reaction mixture at 70 °C for 34 h, the resulting mixture was quenched with 1 N HCl at 0 °C and the organic materials were extracted three times with ethyl acetate. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1:30) to afford **6a** as a mixture of α and β isomers (158.1 mg, 0.45 mmol, 90 %) as a yellow solid. The ratio of α and β isomers was determined by ^{1}H NMR spectroscopy. A small portion of the mixture was purified by TLC to afford α and β isomers, the enantioselectivities of which were determined by HPLC analysis by using a chiral column.

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[19] See the Supporting Information.

