Communication

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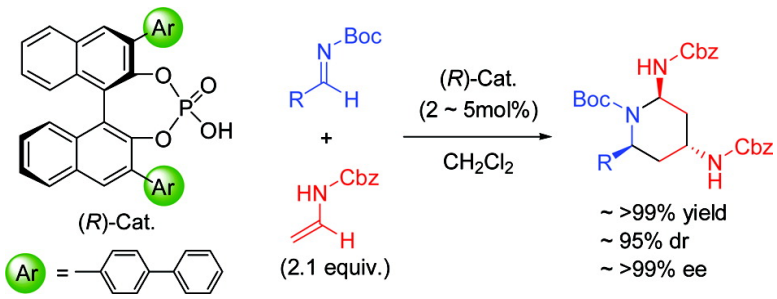

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Chiral Brønsted Acid-Catalyzed Tandem Aza-Ene Type Reaction/Cyclization Cascade for a One-Pot Entry to Enantioenriched Piperidines

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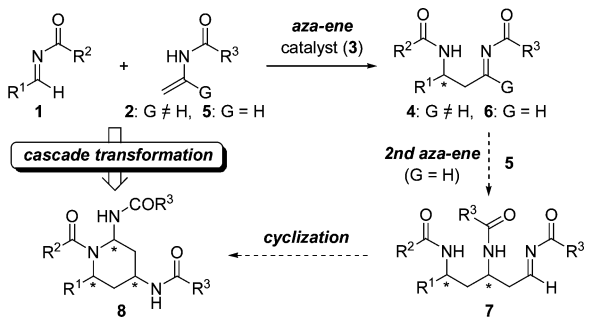
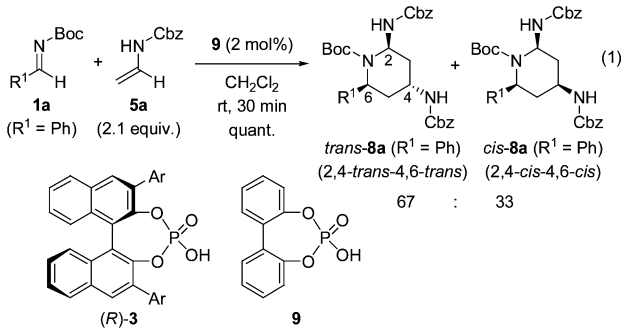
The development of efficient methods to access complex molecules with multiple stereogenic centers continues to be a substantial challenge in both academic research and industrial applications. One approach toward this challenge is the use of catalytic enantioselective cascade reactions,[1] which have emerged as powerful tools to give a rapid increase in molecular complexity from simple and readily available starting materials, thus producing enantioenriched compounds in a single operation. It is obvious that such transformations require less solvents, adsorbents, and energy, hence minimizing waste management as compared to a series of individual stepwise reactions. In recent years, considerable efforts have been devoted to the development of enantioselective organic transformations using chiral Brønsted acids as green catalysts.[2] Cascade reactions catalyzed by chiral Brønsted acids are attractive because such catalytic processes would allow the production of enantioenriched compounds by ecologically and economically favorable methods.[3] In this communication, we describe a chiral monophosphoric acid[4,5]-catalyzed tandem aza-ene type reaction/cyclization cascade that enables the rapid and highly enantio- and diastereoselective construction of piperidine derivatives with multiple stereogenic centers.

Recently, we successfully developed a highly efficient and enantioselective aza-ene type reaction[6] of *N*-acyl aldimines (**1**) with disubstituted enecarbamates (**2**: G ≠ H) catalyzed by chiral monophosphoric acid derivatives (**3**),[4d] in which the corresponding products (**4**) were obtained in ketimine form. Inspired by the formation of imines, we envisioned a sequential process using monosubstituted enecarbamates (**5**: G = H)[4g,6e] instead of the disubstituted versions (**2**). The acid-catalyzed reaction of initial aldimines (**1**) with **5** would generate aza-ene type products of *N*-acyl aldimines (**6**) as reactive intermediates and hence **6** would undergo further aza-ene type reactions leading to the subsequent generation of aldimines (**7**). If intramolecular cyclization of **7** could be enacted to terminate the tandem aza-ene type reaction sequence, our synthetic methodology would allow rapid access to piperidine derivatives (**8**) as key structural elements of numerous natural products (Scheme 1).[7]

Scheme 1. One-Pot Entry to Piperidine Derivatives via Tandem Aza-ene Type Reaction/Cyclization Cascade



For the first step of the proposed cascade transformation, we examined the reaction of benzaldehyde-derived *N*-Boc aldimine (**1a**) with *N*-Cbz enecarbamate (**5a**) catalyzed by biphenol-derived phosphoric acid (**9**). To our delight, the cascade reaction proceeded smoothly to afford a diastereomeric mixture of the desired piperidine derivative (**8a**: R^1 = Ph) quantitatively (eq 1). Although the diastereoselectivity was moderate, only two diastereomers were obtained from among the four possible diastereomers that result from three stereogenic centers.[8]



This preliminary result prompted us to develop enantio- and diastereoselective variants of our cascade transformation. Our studies were commenced with the screening of chiral phosphoric acid catalysts (**3**) bearing various type of aromatic substituents (Ar) at the 3,3′-position on the binaphthyl backbone. As shown in Table 1, all of the chiral catalysts (**3**) exhibited excellent performance both in terms of catalytic efficiency and enantioselectivity. The cascade reaction of **1a** with **5a** was completed within 30 min in the presence of (*R*)-**3** (2 mol %) to afford the two diastereomers of the piperidine derivatives (*trans*- and *cis*-**8a**), as observed in the catalysis by **9** (entries 1−4 vs eq 1). Furthermore, excellent enantioselectivity was observed for the major *trans*-isomer, ir-

Table 1. Cascade Reaction of **1a** (R^1 = Ph) with **5a** Catalyzed by (*R*)-**3** Leading to Piperidine Derivatives (**8a**) (eq 1)[a]

entry	catalyst (**3**) (Ar)	yield (%)	*trans*:*cis*	ee (%)[b,c]	ee (%)[b,d]
1	**3a** (9-anthryl)	92	80:20	99	12[e]
2	**3b** (C_6H_5−)	92	86:14	95	19[e]
3	**3c** (3,5-Ph_2-C_6H_3−)	>99	86:14	96	31
4	**3d** (4-Ph−C_6H_4−)	>99	89:11	97	8[e]
5[f]	**3d**	>99	87:13	99	8
6[g]	**3d**	>99	91:9	99	14
7[h]	**3d**	97	92:8	99	14
8[i]	**3d**	>99	95:5	>99	40

[a] Unless otherwise noted, all reactions were carried out with 0.10 mmol of **1a**, 0.21 mmol of **5a**, and 0.002 mmol of (*R*)-**3** (2 mol %) in 1.0 mL of $CDCl_3$ at room temperature for 30 min. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] % ee of *trans*-**8a** (absolute stereochemistry: 2*R*,4*R*,6*S*). [d] % ee of *cis*-**8a** (absolute stereochemistry: 2*R*,4*S*,6*S*). [e] (2*S*,4*R*,6*R*)-**8a** as the major product. [f] In toluene for 1 h. [g] In $(CH_2Cl)_2$ for 1 h. [h] In CH_2Cl_2 for 1 h. [i] In CH_2Cl_2 at 0 °C for 1 h.

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Table 2. Scope of Substrates in Cascade Reaction of **1** with **5a** Catalyzed by (*R*)-**3d** (eq 1)[a]

entry	**1** (R^1)	yield (%)	*trans*:*cis*	ee (%)[b,c]	ee (%)[b,d]
1	**1b**: *p*-Br−C_6H_4−	>99	94:6	99	23
2	**1c**: *p*-Me−C_6H_4−	>99	95:5	98	4
3[e]	**1d**: 2-furyl	76	88:12	99	14
4[e]	**1e**: Ph−CH=CH−	70	95:5	97	36
5[e]	**1f**: MeO_2C−	84	88:12	98	ND[f]
6[e]	**1g**: *c*-C_6H_{11}−	68	94:6	97	48

[a] Unless otherwise noted, all reactions were carried out with 0.10 mmol of **1**, 0.21 mmol of **5a**, and 0.002 mmol of (*R*)-**3d** (2 mol %) in 1.0 mL of CH_2Cl_2 at 0 °C for 5 h. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] % ee of *trans*-**8**. [d] % ee of *cis*-**8**. [e] Reaction was carried out using 0.005 mmol of (*R*)-**3d** (5 mol %). [f] Not determined % ee.

respective of the Ar substituent of the chiral catalysts (**3**) (entries 1−4). Interestingly, the simple phenyl-substituted catalyst (**3b**) also gave high enantioselectivity for the major *trans*-isomer (entry 2). In contrast, the diastereoselectivity was affected by the Ar substituents; among the catalysts examined, the *para*-biphenyl-substituted catalyst (**3d**) exhibited the highest diastereoselectivity (entry 4). Further optimization of reaction conditions by changing either solvents or reaction temperature was performed using **3d** (entries 5−8). As a result, nearly enantiopure piperidine derivatives (**8a**) were obtained with high diastereoselectivity in CH_2Cl_2 at 0 °C (entry 8).

To investigate the scope of the present cascade transformations, the reaction of **5a** with a series of aldimines (**1**) was examined using (*R*)-**3d**. Representative results are summarized in Table 2. It should be emphasized that, in most cases, one stereoisomer was formed exclusively from among the eight possible stereoisomers consisting of four pairs of enantiomers. Excellent enantioselectivities along with high diastereoslectivities were attained using aromatic aldimines (**1b** and **1c**), regardless of their electronic nature (entries 1 and 2). Heteroaromatic and α,β-unsaturated aldimines (**1d** and **1e**) were also encouraging, giving the corresponding products (**8d** and **8e**) in acceptable yields (entries 3 and 4). Moreover, the glyoxylate-derived aldimine (**1f**) could be transformed to the highly functionalized piperidine derivative (**8f**) in excellent enantioselectivity (entry 5). An aliphatic aldimine (**1g**) was also applicable to the present reaction, giving the product (**8g**) in high stereoselectivity (entry 6).

The high enantio- and diastereoselectivities observed can be attributed to the double asymmetric induction[9] arising from the matched combination between the optically active aldimine intermediates (**6**) and (*R*)-**3**. As shown in eq 1, catalysis of the cascade reaction by biphenol-derived phosphoric acid (**9**) resulted in 4,6-*trans* selectivity, although the selectivity was moderate. The observed 4,6-*trans* diastereofacial selectivity induced by the chirality of **6** is identical to the stereochemical outcome in enantioselective catalysis, where (*R*)-**3** preferentially directs attack of both the initial aldimines (**1**) and **6** onto the *si* face, giving a 4,6-*trans* relationship as the predominant relative stereochemistry. It is likely that the final step of the stereoselective cyclization proceeded under substrate control rather than enantioselective catalysis by (*R*)-**3**, because the reaction catalyzed by **9** also affords only two of the possible four diastereomers.

In summary, we have developed an efficient and highly diastereo- and enantioselective tandem aza-ene type reaction/cyclization cascade, featuring a chiral monophosphoric acid catalyst, for a one-pot entry to piperidine derivatives. With the control of three stereogenic centers, the cascade transformations can be widely applied using simple enecarbamates and a broad range of aldimines to provide a rapid increase in molecular complexity. Further investigations of this cascade transformation are currently underway in our laboratory to elucidate the origin of the stereoselectivity and to construct more complex heterocyclic systems.

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Supporting Information Available: Representative experimental procedure, spectroscopic data for cascade reaction products (**8**), determination of relative stereochemistry of **8**, and absolute stereochemistry of **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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