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Chiral Amine-Catalyzed Enantioselective Cascade Aza–Ene-Type Cyclization Reactions

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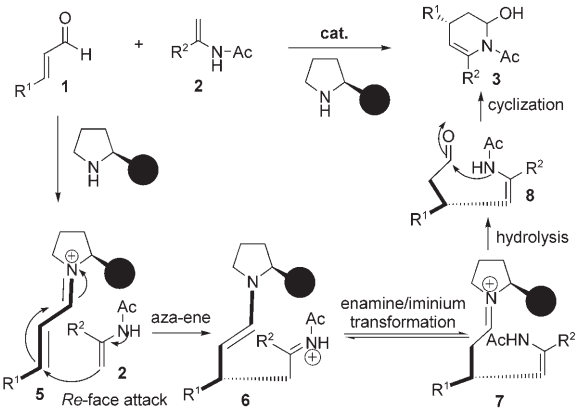
Despite the fact that enamides are versatile synthetic building blocks, only a handful of examples have been identified using them as nucleophiles in organic synthesis presumably due to their much lower reactivity compared with enamines and enols.[1] Kobayashi and co-workers have developed nice chiral Lewis acid catalyzed enantioselective nucleophilic addition of enamides and enecarbamates to highly reactive imines, aldehydes and alkylidenemalonates.[2] Recently, Terada et al. described elegant chiral Brønsted acid promoted aza–ene-type reactions between imines and enamides.[3] We envisioned that, by taking advantage of the capacity of a chiral secondary amine promoted activation of α,β-unsaturated aldehydes, relatively unreactive nucleophilic enamides could participate in a conjugate addition (aza–ene-type) process.[4] In this communication, we wish to report the results of the investigation, which has resulted in a novel organocatalytic highly enantioselective cascade aza–ene-type cyclization reaction.[5–8] To our knowledge this study represents the first example of an enantioselective cascade aza–ene-type cyclization process catalyzed by a chiral amine. The one-pot process affords enantioenriched synthetically useful six-membered ring hemiaminals. Moreover, significantly, we first observe that the cascade process involves an unprecedented multistep imminium/enamine transformation.

In the proposed cascade aza–ene-type cyclization sequence, we hypothesized that a chiral secondary amine activated enal **1** (e.g., iminium **5**) enabled a nucleophilic attack by enamide **2** (an aza–ene-type reaction) to give intermediate enamine/iminium **6**, which underwent a reversible enamine/iminium transformation to generate intermediate **7** (Scheme 1). Hydrolysis of **7** releasing catalyst was followed by spontaneous intramolecular cyclization to afford cyclic hemiaminal **3**.



Scheme 1. Proposed a chiral amine promoted cascade aza–ene-type cyclization reaction.

However, there are two challenging issues we might face in the designed cascade process. First, intermediate **6** could undergo an intramolecular Mannich-type reaction. Second, it would be more problematic if intermediate **7** participates in the second Mannich reaction because the process would poison the catalyst. We believed that these problems could be minimized. It is difficult for these two Mannich reactions to take place due to the significant steric hindrance in **6** and **7**, induced by the bulky organocatalyst and the highly substituted iminium/enamine moieties. Furthermore, the formation of strained four-membered cyclobutane is heavily energetically unfavorable. On the other hand, the steric effect imposed in **7** is a driving force to release catalyst and give less crowded enamide aldehyde **8**, which undergoes an intra-

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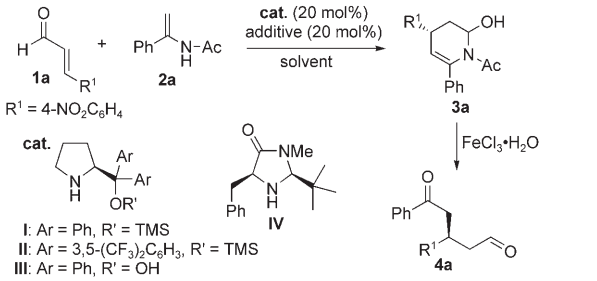
molecular cyclization giving rise to kinetically favorable six- against highly strained four-membered ring structure.

Guided by the above consideration and our previous successful use of chiral diarylprolinol silyl ethers as an effective promoter for activation of α,β-unsaturated aldehydes,[8,9] we initially investigated a reaction of *trans*-4-nitrocinnamaldehyde (**1a**) with enamide (**2a**) in the presence of an organic catalyst in CH_2Cl_2 (Table 1). It was found that the reaction highly depended on the organocatalysts and additives used. No reaction occurred with (*S*)-diphenylprolinol–TMS ether **I** without an additive (entry 1). We surmised that a base additive (NaOAc) could activate the enamide **2a** via facilitating deprotation. Disappointingly, the same outcome was obtained (Table 1, entry 2). However, to our delight, switching to an acid additive ($PhCO_2H$) led to a smooth transformation to afford desired cyclic hemiaminal (**3a**) in 80% yield and high enantioselectivity (90%) (Table 1, entry 3). The *ee* of the formed product was determined through conversion to acyclic ketoaldehyde **4a**. Notably, as designed, we did not observe the formation of cyclobutane products. Encouraged by the promising results, we probed more bulky prolinol ether **II** for the reaction under the same reaction conditions (Table 1, entry 8). The process proceeded much slower (48 h) with lower yield. Reactions did not take place for **III** and MacMillan's catalyst **IV** (Table 1, entries 9 and 10).

With the best promoter **I** in hand, we turned attention on optimizing reaction conditions. Probing acid additives resulted in the use of $PhCO_2H$ (Table 1, entries 3–5). Finally, screening of a variety of solvents revealed that $Cl(CH_2)_2Cl$ was the choice for the process (Table 1, entries 3, 6, and 7).

The optimal reaction conditions were exploited to probe the limitation of the organocatalyst **I** promoted cascade reactions. As revealed in Table 2, the cascade process serves as a general approach to the preparation of highly functionalized chiral cyclic hemiaminals. Notably, the new stereogenic center is created in high enantioselective control (90–97% *ee*) in all cases. Significant structural variation of both α,β-unsaturated aldehydes **1** and enamides **2** can be tolerated. The electronic and steric nature of the aryl rings of enals **1** has apparently limited influence on the stereochemical outcome. The similar trend is also observed for the enamides **2**. It is noted that in some cases (Table 2, entries 3–8 and 10), 2,4-dinitrobenzoic acid (DNBA) instead of $PhCO_2H$ as additive is used since $PhCO_2H$ gives much lower yields.

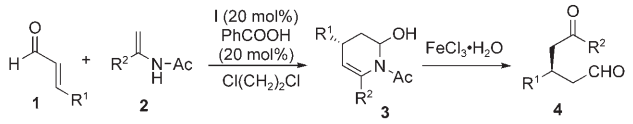
Table 1. Exploration of organocatalytic enantioselective cascade aza–ene-type cyclization reaction of *trans*-4-nitrocinnamaldehyde (**1a**) with enamide (**2a**).[a]



Entry	Cat.	Additive	Solvent	*t* [h]	Yield [%] **3a**[b]	*ee* [%] **4a**[c]
1	**I**	none	CH_2Cl_2	24	<5	nd[d]
2	**I**	NaOAc	CH_2Cl_2	24	<5	nd[d]
3	**I**	$PhCO_2H$	CH_2Cl_2	24	80	90
4	**I**	DNBA[e]	CH_2Cl_2	6	83	80
5	**I**	TMSCl	CH_2Cl_2	24	89	70
6	**I**	$PhCO_2H$	$Cl(CH_2)_2Cl$	24	85	90
7	**I**	$PhCO_2H$	EtOH	24	65	88
8	**II**	$PhCO_2H$	CH_2Cl_2	48	75	90
9	**III**	$PhCO_2H$	CH_2Cl_2	24	<5	nd[e]
10	**IV**	p-TsOH	CH_2Cl_2	24	<5	nd[e]

[a] Reaction conditions: unless specified, see Experimental Section. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Not determined. [e] 2,4-Dinitrobenzoic acid.

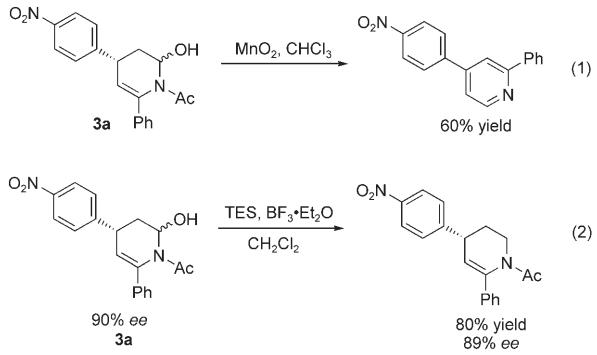
Table 2. Catalyst **I** promoted cascade aza–ene-type cyclization reactions of α,β-unsaturated aldehydes (**1**) with enamides (**2**).[a,10]

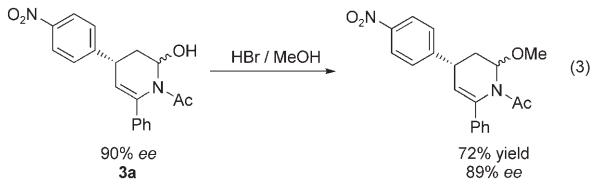


Entry	R^1	R^2	*t* [h]	Yield [%] **3**[b]	Yield [%] **4**[c]	*ee* [%][d]
1	$4\text{-}NO_2C_6H_4$	Ph	24	85[c], 88[b]	56	90
2	$3\text{-}FC_6H_4$	Ph	24	87	51	93
3[e]	$2\text{-}NO_2C_6H_4$	Ph	12	79,[c] 82[b]	55	93
4[e]	$4\text{-}MeOC_6H_4$	Ph	10	77	53	95
5[e]	$3\text{-}MeOC_6H_4$	Ph	10	80	54	94
6[e]	1-naphthyl	Ph	10	82	53	97
7[e]	$4\text{-}MeOC_6H_4$	$4\text{-}MeOC_6H_4$	15	82	54	90
8[e]	$4\text{-}MeOC_6H_4$	$4\text{-}FC_6H_4$	15	80	53	92
9	$4\text{-}NO_2C_6H_4$	$3\text{-}MeC_6H_4$	14	80,[c] 80[b]	51	94
10[e]	$4\text{-}MeOC_6H_4$	$3\text{-}MeC_6H_4$	14	73,[c] 78[b]	50	94[f]
11	$4\text{-}NO_2C_6H_4$	$3\text{-}BrC_6H_4$	40	45,[c] 50[b]	30	90

[a] Reaction conditions: unless specified, see Experimental Section. [b] Determined by ^1H NMR spectroscopy using BnOH as internal standard due to the difficulty of separation of product **3** from starting material **2**. [c] Isolated yields. [d] Determined by chiral HPLC analysis (Chiralpak AS-H or OJ-H) by converting **3** to **4**. [e] DNBA used as additive. [f] Determined by converting to corresponding enone with $Ph_3P{=}CHCOPh$.

Hemiaminals **3** as versatile building blocks can be explored for further synthetic elaborations. We have demonstrated they can be conveniently transformed to pyridines [Eq. (1)], enamides [Eq. (2)], aminals [Eq. 3)] in addition to 1,5-dicarbonyls (Table 1). Notably, the method affords an alterative approach to 1,5-dicarbonyls, which is complementary to that of our early strategy relying on the Mukaiyama–





Michael reaction of silyl enol ethers with α,β-unsaturated aldehydes.[10]

In conclusion, we have developed a new organocatalytic, highly enantioselective cascade aza–ene-type cyclization reaction. The process, efficiently catalyzed by readily available (*S*)-diphenylprolinol–TMS ether, establishes an unprecedented multistep iminium/enamine transformation in one-pot operation. Furthermore, the simplicity and practical nature of the asymmetric protocols presented here is underscored by the use of simple starting materials and the generation of synthetically useful, high optically active and heavily functionalized products. Future studies of the cascade reaction are aimed at investigating its full scope and applications in target-directed synthesis.

Experimental Section

General procedure (Table 2, entry 1): The reaction was carried out with **1a** (0.12 mmol) and **2a** (0.1 mmol) in the presence of 20 mol% catalyst **I** and 20 mol% $PhCO_2H$ in $ClCH_2CH_2Cl$ (0.2 mL) at room temperature for 24 h. Then the reaction mixture was treated with $FeCl_3{\cdot}6H_2O$ (27 mg, 0.1 mmol) in CH_2Cl_2 at room temperature for 6 h. The crude product was purified by column chromatography on silica gel to give product in 85% yield, 90% *ee* (HPLC on a Chiralpak AS-H column, hexanes/*i*PrOH 80:20 at 0.8 mL min^{-1}, $\lambda = 254$ nm); $t_{major} = 49.00$, $t_{minor} = 53.13$ min; $[\alpha]_D^{23} = +34.5$ ($c = 1.0$, $CHCl_3$).

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Keywords: aldehydes · cascade reactions · enamides · organocatalysis

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