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Asymmetric synthesis of highly functionalized γ-lactams through an organocatalytic aza-Michael–Michael reaction cascade using fumaric acid amide esters as multi-reactive substrates

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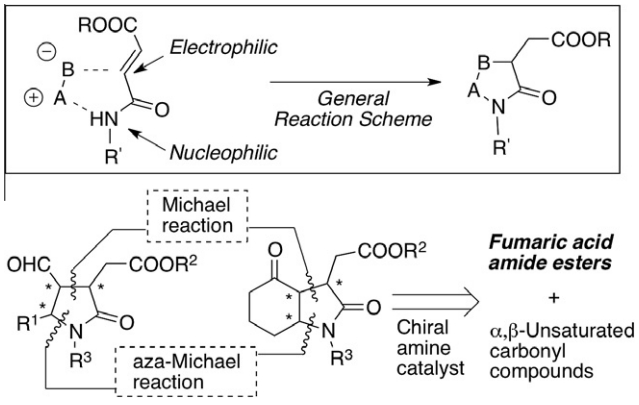
ABSTRACT

We developed a novel method for the asymmetric synthesis of highly functionalized γ-lactams through an organocatalytic aza-Michael–Michael reaction cascade using fumaric acid amide esters as multi-reactive substrates. Using chiral primary or secondary amine organocatalysts, we obtained two types of γ-lactams with three contiguous chiral centers in moderate to good yield with excellent enantioselectivity and diastereoselectivity.

Asymmetric cascade catalysis is an attractive method in modern organic synthesis that allows for the rapid and efficient construction of complex chiral molecules from relatively simple starting materials in a one-pot process, while minimizing cost and waste.[1] Various asymmetric cascade reactions have been reported using single-catalyst systems,[2] as well as multi-catalyst systems.[3] Among the reactions reported to date, secondary amine-catalyzed asymmetric C–C bond forming reaction cascades through sequential iminium/enamine catalysis are most impressive examples in the field. Using such cascade process, densely functionalized reaction products bearing more than three contiguous stereocenters have been produced in a highly enantioselective manner.[4]

Functionalized γ-lactams are ubiquitous structural motifs in various natural products, biologically active compounds, and pharmaceuticals. In addition, γ-lactams are useful synthetic precursors of pyrrolidine derivatives. These features have led to extensive efforts focused on the development of an efficient method for the stereoselective synthesis of functionalized γ-lactams.[5] To develop a novel method of synthesizing γ-lactams using asymmetric cascade catalysis, we envisioned that fumaric acid amide ester derivatives bearing both nucleophilic and electrophilic sites in a single molecule could be suitable building blocks. The application of such compounds to a chiral amine-catalyzed asymmetric aza-Michael–Michael reaction cascade using α,β-unsaturated carbonyl compounds as their reaction partners would afford 3,4,5-trisubstituted γ-lactams stereoselectively (Scheme 1). Herein we report an asymmetric synthesis of highly functionalized γ-lactams through an organocatalytic aza-Michael–Michael reaction cascade using fumaric acid amide esters as multi-reactive substrates.

We first examined aza-Michael–Michael reaction cascade using *N*-tosyl fumaric acid amide ester derivative **1** and *trans*-cinnamaldehyde **2** in the presence of (*S*)-diphenylprolinol trimethylsilyl ether (*S*)-**4** as a catalyst (Scheme 2(i)).[6] Although the experiments



Scheme 1. Cascade reaction using fumaric acid amide esters as multi-reactive substrates.

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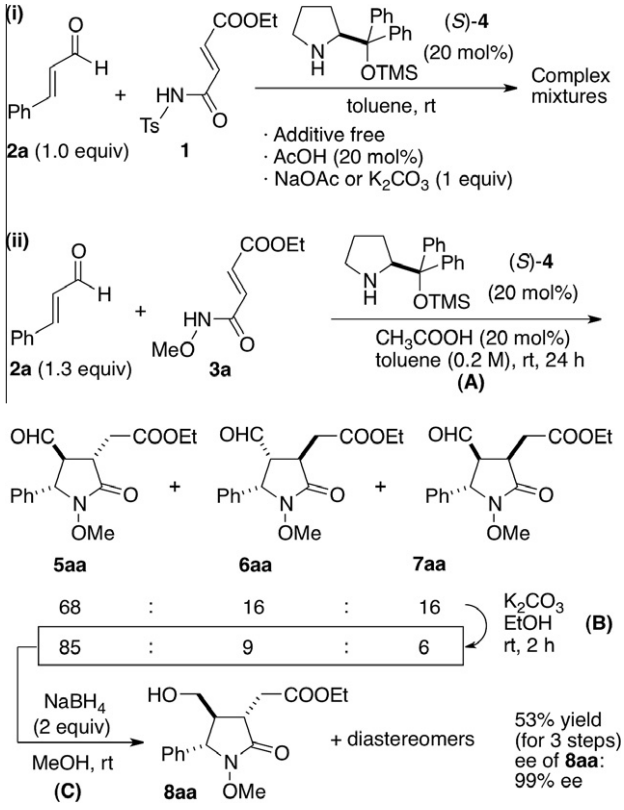


Scheme 2. Feasibility study of organocatalytic aza-Michael–Michael reaction cascade using *trans*-cinnamaldehyde **2a** with fumaric acid amide esters **1** and **3a**.

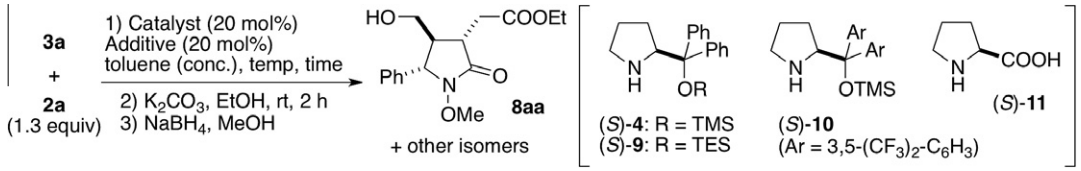
were performed under several reaction conditions, all reactions gave complex mixtures.[7] To increase the nucleophilicity of the amide nitrogen, hydroxylamine derivative **3a** was selected as the substrate (Scheme 2(ii)). Using 20 mol % of (*S*)-**4** and 20 mol % of acetic acid, the target reaction cascade proceeded at room temperature to give a diastereomeric mixture of γ-lactam derivatives (Reaction (A)). Among the four possible diastereomers, compound **5aa** was formed as the major isomer, and isomers **6aa** and **7aa** were also detected in ^{1}H NMR analysis (**5aa**:**6aa**:**7aa** = 68:16:16). Based on the structure of the reaction products, the diastereomeric ratio was expected to change under thermodynamic control through the retro-Michael reaction. In practice, the ratio of the obtained mixture improved to 85:9:6 by treatment with K_2CO_3 in ethanol (Reaction (B)). Because of the instability of the obtained aldehydes, the overall yield of this reaction process was determined after converting into the corresponding alcohol, such as **8aa** (Reaction (C)) (53% yield in 3 steps). Chiral HPLC analysis revealed that the enantiomeric excess of **8aa** was 99% ee. The relative stereochemistry of **8aa** was determined by NOE experiments, and the absolute stereochemistry of **8aa** (3*S*,4*S*,5*S*) was unambiguously determined by transforming it into the known compound.[8,9]

The promising results of the feasibility study led us to optimize the reaction conditions (Table 1). We first screened chiral amine catalysts **4** and **9**–**11** (entries 1–4). Chiral amine catalyst **4** was the best for chemical yield and enantiomeric excess. Less satisfactory results were obtained using more acidic additives such as benzoic acid (entry 5). There was a slight improvement in the yield and diastereomeric ratio when the reaction was performed at 40 °C under diluted reaction conditions (entries 6, 7). The best results were obtained when the reaction was performed in the absence of acetic acid (67% yield in 3 steps) (entry 8).

Having established the optimized conditions, we examined the scope and limitations of the developed cascade reaction (Table 2). When β-aryl α,β-unsaturated aldehydes were utilized as substrates, the aza-Michael–Michael reaction cascade proceeded at 40 °C in the presence of 20 mol % of (*S*)-**4**, providing a mixture of chiral γ-lactams. Base-promoted epimerization of the obtained diastereomeric mixtures, followed by the reduction of their aldehydes, afforded the corresponding γ-lactams in moderate to good overall yield with high stereoselectivity. Substrates involving an electron-donating group on the aromatic ring tended to result in a higher yield (entries 2–4), compared with those bearing an electron-withdrawing group on the aromatic ring (entries 5–8), or a substrate with a hetero-aromatic ring (entry 9). β-Alkyl α,β-unsaturated aldehydes were also applicable to this cascade reaction process. When crotonaldehyde **2j** and 3-benzyloxycarbamoyl-acrylic acid ethyl ester **3b** were utilized as the substrates, the corresponding γ-lactams were obtained in a 49% overall yield with high diastereoselectivity and enantioselectivity (entry 10). On the other hand, there was a decreased reactivity and selectivity when 3-cyclohexyl-2-propenal **2k** was used (entry 11).[10]

The satisfactory results of the asymmetric synthesis of functionalized γ-lactams using α,β-unsaturated aldehydes prompted us to apply cyclohexenone **12** to the present sequential reaction process (Table 3). We first tried an aza-Michael–Michael reaction cascade

Table 1
Optimization of the reaction conditions



Entry	Catalyst	Additive	Conc. (M)	Temp.	Time (h)	Yield[a] (%)	Ratio (**6aa**: sum of other isomers)[b]	Ee (% ee)[c]
1	(*S*)-**4**	AcOH	0.2	rt	22	53	85:15	99
2	(*S*)-**9**	AcOH	0.2	rt	22	49	86:14	98
3	(*S*)-**10**	AcOH	0.2	rt	43	19	—	—
4	(*S*)-**11**	AcOH	0.2	rt	30	No reaction	—	—
5	(*S*)-**4**	PhCOOH	0.2	rt	14	28	73:27	98
6	(*S*)-**4**	AcOH	0.05	rt	26	50	92:8	98
7	(*S*)-**4**	AcOH	0.05	40 °C	35	57	92:8	99
8	(*S*)-**4**	—	0.05	40 °C	35	67	91:9	99

[a] Isolated yield of the mixture of diastereomers in 3 steps.
[b] Determined by ^{1}H NMR analysis.
[c] Enantiomeric excess of the major isomer **8aa**, which was determined by chiral HPLC analysis.