Organocatalysis

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Enantioselective Synthesis of Isoindolines: An Organocatalyzed Domino Process Based On the aza-Morita–Baylis–Hillman Reaction**

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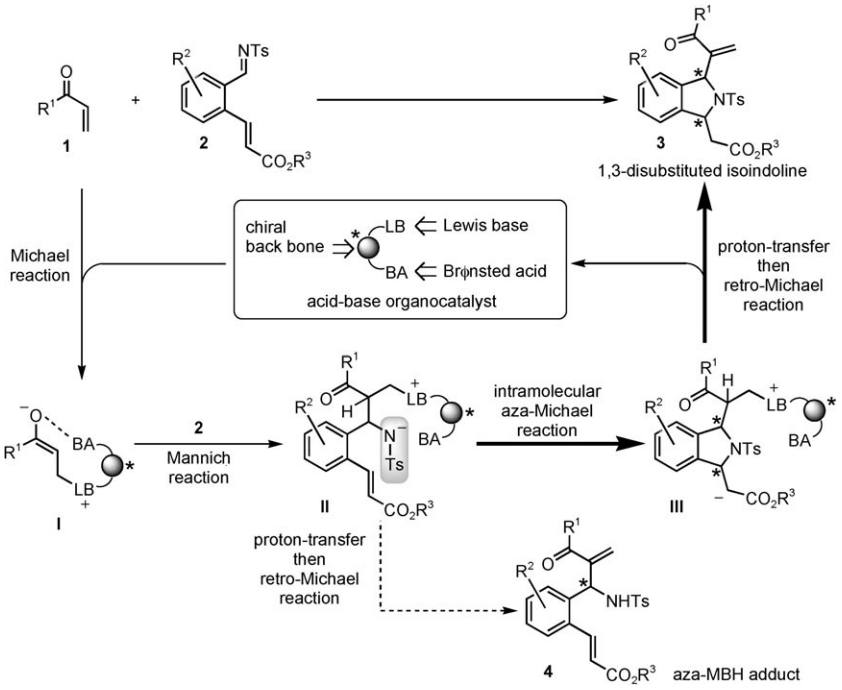
The organocatalytic asymmetric domino process is a very attractive method because of its ability to construct complex chiral molecules from readily available substrates under mild reaction conditions in two or more steps in a single operation. These reactions can save the time and the chemicals usually required for isolation or purification of the synthetic intermediates. In addition, no concern for metal contamination of the products is necessary because organocatalysts do not contain toxic or expensive metals. Examples of organocatalytic asymmetric domino reactions mediated by chiral secondary amines[1] and hydrogen phosphates have been recently reported;[2] these reactions are environmentally friendly and often proceed with excellent stereoselectivities.[3]

The aza-Morita–Baylis–Hillman (aza-MBH) reaction is known to be a useful and atom-economical C–C bond-forming reaction of electron-deficient alkenes with imines and is catalyzed by Lewis bases, such as nucleophilic amines or phosphines.[4] Highly functionalized allylic amines prepared with the aza-MBH reaction have proven to be valuable building blocks for biologically active compounds and natural products.[5] Although there are many reports in the field of the enantioselective aza-MBH processes,[6] to the best of our knowledge, no report on the organocatalyzed domino reaction of electron-deficient alkenes with imines has been published.[7]

We envisioned that chiral 1,3-disubstituted isoindoline **3** could be rapidly accessed from enone **1** and *N*-tosylimine **2** with a Michael acceptor moiety at the *ortho* position in the presence of an organocatalyst bearing both Brønsted acid (BA) and Lewis base (LB) units. A proposed catalytic cycle for the aza-MBH domino reaction is shown in Scheme 1. In the first step, the Michael addition of the Lewis base moiety to enone **1** generates chiral enolate **I** stabilized by BA, it then reacts with *N*-tosylimine **2** to form intermediate **II**. In the aza-MBH reaction pathway, proton-transfer from the α position of the carbonyl group to the amine group and subsequent retro-Michael reaction of the organocatalyst proceeds to form the normal aza-MBH adduct **4**. Alternatively, the nitrogen anion of intermediate **II** could react with the attached Michael acceptor intramolecularly, thus resulting in the formation of the chiral isoindoline **3** via intermediate **III** along with regeneration of the organocatalyst through proton-transfer and subsequent retro-Michael reaction.



Scheme 1. Enantioselective aza-MBH/intramolecular aza-Michael domino reaction mediated by an acid–base organocatalyst. Ts = 4-toluenesulfonyl.

Optically active isoindolines are common substrates in a variety of natural products and pharmaceutical compounds.[8] However, research on the construction of the isoindoline core is clearly in the early stages, and only a few methods for its catalytic enantioselective preparation have been reported.[9] Herein, we describe the novel organocatalyzed aza-MBH/intramolecular aza-Michael domino reaction of α,β-unsaturated carbonyl compounds with *N*-tosylimines to furnish 1,3-

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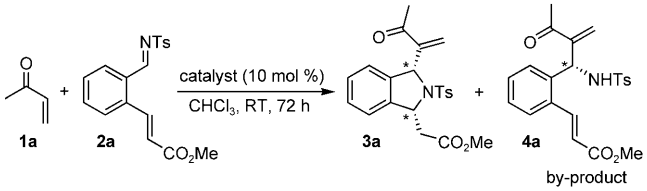
disubstituted isoindolines in high yields and high enantioselectivities.

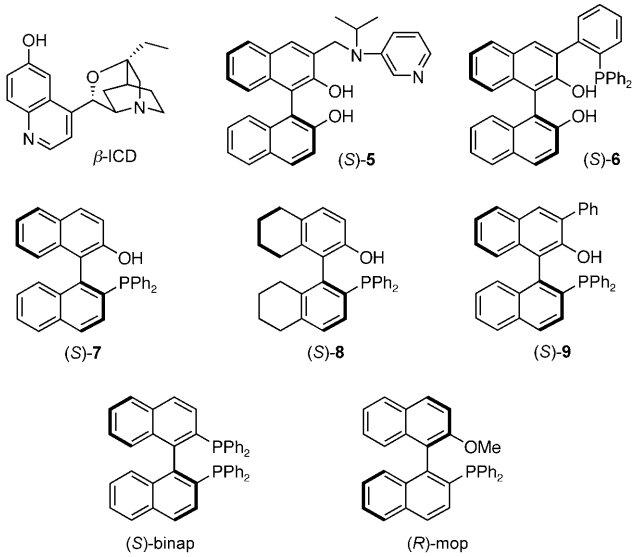
To explore the possibility of the proposed aza-MBH domino process, we began with the reaction of methyl vinyl ketone (**1a**; 3.0 equiv) and *N*-tosylimine **2a** in $CHCl_3$ at room temperature in the presence of organocatalysts (10 mol%; Table 1). 1,4-Diazabicyclo[2.2.2]octane (DABCO), 4-(dimethylamino)pyridine (DMAP), and PPh_3 as achiral Lewis bases catalyzed the reaction to afford only the desired isoindoline **3a** in moderate yields (64–73%; Table 1, entries 1–3). The reaction mediated by mixing PPh_3 (10 mol%) and (*S*)-binol (10 mol%) as the chiral Brønsted acid, formed racemic **3a** in slightly lower yield with decomposition of **2a** (Table 1, entry 4). Next, we applied known chiral acid–base organocatalysts, which can promote the aza-MBH reaction, for example, β-isocupreidine (β-ICD),[6a–c] (*S*)-**5**,[6e,j] and (*S*)-**6**.[6l] Organocatalyst β-ICD afforded **3a** in poor yield with no enantioselection together with small amounts of the aza-MBH adduct **4a** (Table 1, entry 5). Catalyst (*S*)-**5** was found to be inactive for the aza-MBH domino process (Table 1, entry 6), while catalyst (*S*)-**6** promoted the reaction to produce **3a** in low yield and *ee* (Table 1, entry 7). To our delight, we found that (*S*)-2-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol ((*S*)-**7**),[10] an acid–base organocatalyst developed by Shi et al.,[6d,f] mediated the reaction efficiently to afford **3a** in moderate yield with high enantioselectivity (Table 1, entry 8). The H_8-binol derivative (*S*)-**8**,[11] which has a larger dihedral angle than (*S*)-**7**, showed little improvement on the asymmetric induction (Table 1, entry 9). The catalytic activity was remarkably decreased with catalyst (*S*)-**9**,[6f] which has a phenyl group at the 3′-position (Table 1, entry 10). Activity was also low with catalysts (*S*)-**5** and (*S*)-**6**, owing to the steric bulkiness, thus resulting in the formation of aza-MBH adduct **4a** as the major product (Table 1, entries 6 and 7). Chiral phosphines as the sole Lewis base catalysts for example, (*S*)-binap and (*R*)-mop,[10] drastically decreased yields and *ee* values of **3a** and were accompanied by pronounced decomposition of **2a** (Table 1, entries 11 and 12). These outcomes indicate that the introduction of acid–base units at the appropriate positions on a single chiral skeleton assists in effectively promoting the aza-MBH domino reaction with high enantiocontrol. Notably, product **3a** was obtained as a single diastereomer for all entries. *cis*-1,3-Disubstited isoindoline is known to be thermodynamically more stable than the *trans* form.[12] Because the intramolecular aza-Michael process would be reversible, *cis*-**3a** could be formed as a single diastereomer ($\Delta E = 4.13$ kcal mol^{-1} based on MM2 calculations).

Table 1: Enantioselective aza-MBH domino reaction of **1a** with **2a**.[a]



Entry	Catalyst	**3a**		**4a**	
		Yield [%][b]	*ee* [%][c]	Yield [%][b]	*ee* [%][c]
1	DABCO	69	–	0	–
2	DMAP	64	–	0	–
3	PPh_3	73	–	0	–
4[d]	PPh_3	59	racemate	0	–
5	β-ICD	15	racemate	13	n.d.
6	(*S*)-**5**	trace	n.d.	56	48 (*R*)
7	(*S*)-**6**	14	19 (*R*,*S*)	36	racemate
8	(*S*)-**7**	62	87 (*R*,*S*)	0	–
9	(*S*)-**8**	58	84 (*R*,*S*)	0	–
10	(*S*)-**9**	12	82 (*R*,*S*)	36	82 (*R*)
11	(*S*)-binap	13	racemate	0	–
12	(*R*)-mop	27	14 (*R*,*S*)	0	–

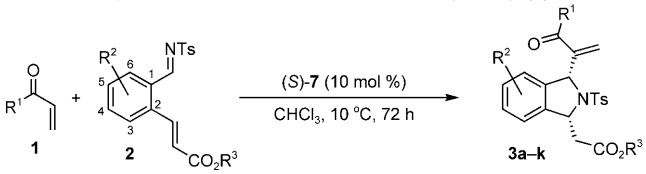
[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.050 mmol), catalyst (10 mol%), 0.25 M (concentration of **2a**) in $CHCl_3$, room temperature. [b] Yields were determined from the ^{1}H NMR spectra using benzyl phenyl ether as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase using a Daicel Chiralpak IA column. [d] In the presence of (*S*)-binol (10 mol%). binol = 1,1′-bi-2-naphthyl, n.d. = not determined.

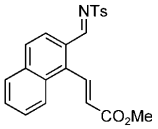
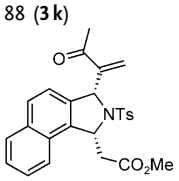
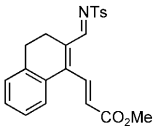
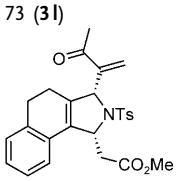


The optimal result (98% yield, 92% *ee*) was obtained when the reaction of **1a** with **2a** was performed in $CHCl_3$[13] (0.2 M for **2**) at 10 °C in the presence of molecular sieves (M.S.; 3 Å)[14] as an additive (Table 2, entry 1). Ethyl vinyl ketone (**1b**) and phenyl vinyl ketone (**1c**) were also suitable substrates and led to isoindolines **3b** and **3c**, respectively, with high *ee* values (Table 2, entries 2 and 3). Other α,β-unsaturated carbonyl compounds, for example, acrolein (**1d**) and phenyl acrylate (**1e**), promoted reactions with acceptable results (Table 2, entries 4 and 5). When the substituent R^3 on *N*-tosylimines **2** was changed, isoindolines **3f** and **3g** were formed in good yields (Table 2, entries 6 and 7). High enantioselectivities (Table 2, 89–93% *ee*) were obtained irrespective of the electronic nature of substituent groups at the 5-position on the aromatic ring of **2** (Table 2, entries 8–10). Substituent groups at the 6- and 3-positions led to **3k** and **3m** with 82 and 85% *ee*, respectively (Table 2, entries 11–13).

The relative and absolute configurations of the isoindoline **3b** was determined by NMR spectroscopy and X-ray crystallographic analysis.[15] The aza-MBH/intramolecular aza-Michael domino reaction was found to be *cis* selective and (*R*,*S*)-configured isoindolines **3** were formed (Figure 1).

Table 2: Scope of aza-MBH domino reaction catalyzed by (*S*)-**7**.[a]



Entry	R^1	*N*-Tosylimine R^2, R^3		Yield [%][b]	*ee* [%][c]
1[d]	Me (**1a**)	H, Me	**2a**	98 (**3a**)	92
2[d]	Et (**1b**)	H, Me	**2a**	97 (**3b**)	92
3[d]	Ph (**1c**)	H, Me	**2a**	72 (**3c**)	88
4[d]	H (**1d**)	H, Me	**2a**	49 (**3d**)	87
5[d]	OPh (**1e**)	H, Me	**2a**	66 (**3e**)	68
6	**1a**	H, Et	**2b**	85 (**3f**)	93
7	**1a**	H, Bn	**2c**	78 (**3g**)	91
8[d]	**1a**	5-Me, Me	**2d**	75 (**3h**)	89
9	**1a**	5-F, Me	**2e**	80 (**3i**)	92
10[e]	**1a**	5-Cl, Me	**2f**	76 (**3j**)	93
11[d]	**1a**	6-Cl, Me	**2g**	88 (**3k**)	82
12	**1a**		**2h**	 73 (**3l**)	82
13[d]	**1a**		**2i**	 88 (**3m**)	85

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.050 mmol), catalyst (*S*)-**7** (10 mol%), 0.2 M (concentration of **2**) in $CHCl_3$, 10°C. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase (Daicel Chiralpak IA for **3a–d**, **3f–j**, and **3l**, **m**; Daicel Chiralpak IB for **3e**; Daicel Chiralpak IC for **3k**). [d] 3 Å M.S. was used as an additive. [e] 4 Å M.S. was used as an additive. M.S. = molecular sieves.

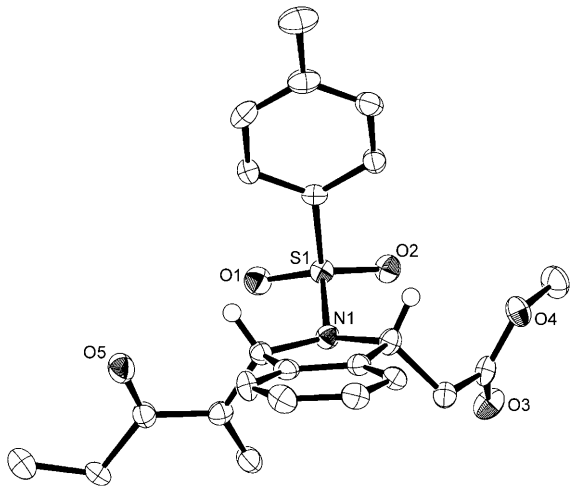
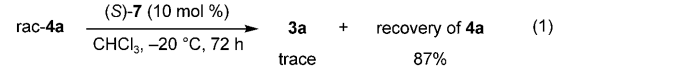
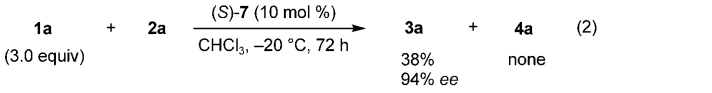


Figure 1. X-ray structure of the isoindoline (*R*,*S*)-**3b**. The hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

To provide mechanistic insight into this domino reaction, we performed the intramolecular aza-Michael reaction of racemic aza-MBH adduct **4a** catalyzed by (*S*)-**7** in $CHCl_3$ at −20°C. The reaction was very slow and only trace amounts of isoindoline **3a** were formed along with recovery of most of **4a** [Eq. (1)]. Under the same conditions, the domino reaction of

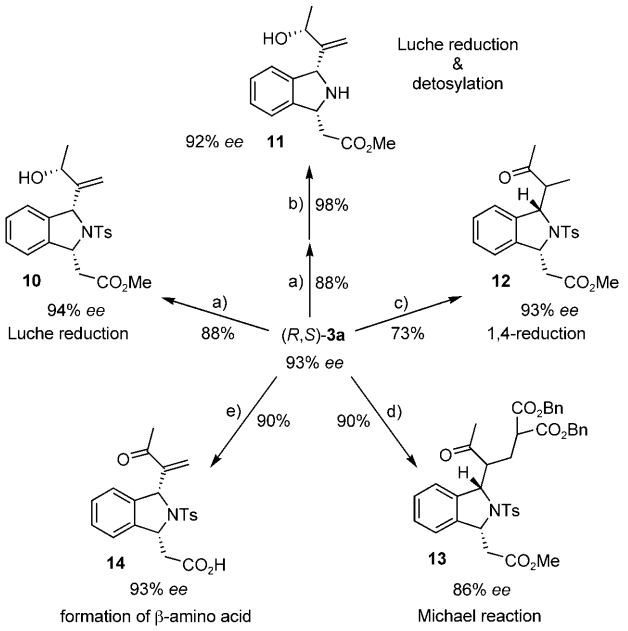


enone **1a** with *N*-tosylimine **2a** led to **3a** in 38% yield with 94% *ee* without formation of **4a** [Eq. (2)]. Judging from these experimental results, it is apparent that intramolecular



cyclization of aza-MBH intermediate **II** produces isoindoline **3** directly without forming aza-MBH adduct **4a** (Scheme 1).

To demonstrate the synthetic utility of the highly functionalized aza-MBH domino product **3a**, a variety of transformations were performed (Scheme 2). The allyl alcohol **10**



Scheme 2. Synthetic transformations of isoindoline (*R*,*S*)-**3a**. Reagents and conditions: a) $Yb(OTf)_3$ (1.5 equiv), $NaBH_4$ (1.5 equiv), MeOH, THF, 0°C, 30 min, 88% (d.r. = 77:23, determined by ^1H NMR spectroscopy); b) Mg (20 equiv), MeOH, RT, 2 h, 98%; c) Zn (20 equiv), aq NH_4Cl, THF, RT, 12 h, 73% (d.r. > 99:1, determined by HPLC analysis); d) dibenzyl malonate (1.2 equiv), DBU (1.2 equiv), THF, −40°C, 72 h, 90% (d.r. = 96:4, determined by HPLC analysis); e) LiOH (5.0 equiv) in aq., THF, RT, 26 h, 90%. Bn = benzyl, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

could be formed by Luche reduction of **3a** in the presence of $Yb(OTf)_3$.[16] Treatment of the major diastereomer **10** with Mg/MeOH[17] cleaved the Ts group to provide the amino alcohol **11** in 98% yield. The α-methyl ketone **12** was also obtained in good yield as a single diastereomer by 1,4-conjugate reduction of **3a** using Zn powder/NH_4Cl, without overreduction. Furthermore, the Michael addition of dibenzyl malonate to **3a** with DBU produced the adduct **13** in 90% yield with high diastereoselectivity (d.r. = 96:4). Finally, **3a** was easily hydrolyzed to β-amino acid **14** by exposure to aqueous LiOH/THF, and high enantiopurity was maintained.

In summary, we have developed the first enantioselective aza-MBH/intramolecular aza-Michael reaction of electron-deficient alkenes and *N*-tosylimines promoted by a chiral acid–base organocatalyst. The aza-MBH domino process described here was easily accessed to afford 1,3-disubstituted isoindolines in good yields with excellent diastereo- and enantioselectivities (up to 93% *ee*). The obtained product was transformed reliably into a variety of derivatives. Further investigations to extend the reaction scope and illustrate applications of this process in organic synthesis are underway.

Experimental Section

General procedure: Enone (0.10 mmol, 2.0 equiv) was added to a solution of organocatalyst (*S*)-**7** (10 mol%), *N*-tosylimine (0.050 mmol), and powdered M.S. (3 Å or 4 Å; 10 mg) in $CHCl_3$ (0.25 mL). The reaction mixture was stirred at 10 °C for 72 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel (*n*-hexane/EtOAc = 4:1) to afford the isoindoline product.

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[13] Solvent effects were crucial factors to help accelerate the domino reaction without formation of undesired aza-MBH adducts **4** (see the Supporting Information).

[14] The addition of M.S. (3 Å or 4 Å) was beneficial to suppress the decomposition of moisture sensitive *N*-tosylimines **2** (see the Supporting Information).
[15] CCDC 784114 ((*R*,*S*)-**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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