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# An enantioselective organocatalyzed aza-MBH domino process: application to the facile synthesis of tetrahydropyridines

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ABSTRACT

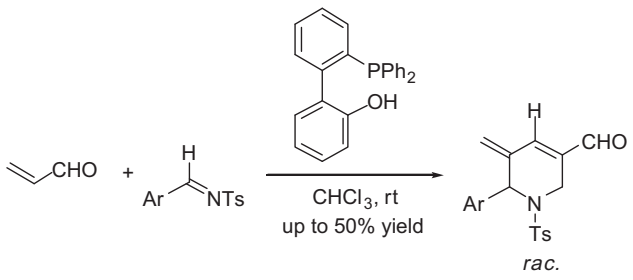
A chiral acid–base organocatalyst was found to promote an aza-MBH domino process between α,β-unsaturated carbonyl compounds and *N*-tosylimines to afford tetrahydropyridine derivatives with high enantioselectivity.



Simple construction of highly functionalized chiral molecules is an ongoing substantial challenge in current synthetic chemistry. Considerable efforts have been directed toward the development of asymmetric organocatalyzed domino reactions[1] that allow a rapid increase in molecular complexity from readily available materials under mild reaction conditions. These reactions can save the time, chemicals, energy, and labor typically required for isolation or purification of synthetic intermediates. In addition, there is no concern about metal contamination of the products and toxic metal waste since organocatalysts contain no toxic or expensive metals.

The aza-Morita–Baylis–Hillman (aza-MBH) reaction is one of the most useful and atom-economical C–C bond-forming reactions of activated alkenes with imines catalyzed by Lewis bases (**LB**).[2,3] The aza-MBH adducts are highly functionalized allylic amines that are valuable building blocks for medicinal chemistry.[4] Although until now a number of attractive systems have been developed for this asymmetric catalytic process,[5] few reports on the enantioselective domino reaction of activated alkenes with imines have been made.[6,7] As a recent excellent investigation of aza-MBH domino cyclizations, Prof. Huang reported achiral organocatalysis to produce highly functionalized heterocyclic compounds such as tetrahydropyridines (Scheme 1),[8a] dihydrobenzofurans,[8b] and chromans.[8c]

The aza-MBH reaction formally involves a sequence of reactions including a Michael addition, Mannich reaction, proton-transfer, and retro-Michael reaction (β-elimination) as shown in Scheme 2. In chiral acid–base organocatalysis of this process, Michael addition of the **LB** part of the catalyst to the activated alkene generates Brønsted acid (**BA**) stabilized chiral enolate **I**, which then reacts with the imine to afford the zwitterionic intermediate **II**. A proton shift from the α-carbon atom to the nitrogen anion in the intermediary ketone **II** followed by β-elimination of the **LB** catalyst yields the aza-MBH product with regeneration of the catalyst. With a suitable chiral acid–base organocatalyst, the nitrogen anion of intermediate **II** could react with a second equivalent of the activated alkene via an aza-Michael addition, followed by aldol/dehydration reactions to produce chiral tetrahydropyridines.[9] Herein, we report the chiral acid–base organocatalyzed domino process based on aza-MBH reactions of α,β-unsaturated carbonyl compounds with *N*-tosylimines to give highly functionalized tetrahydropyridines with up to 93% ee.




**Scheme 1.** Achiral acid–base organocatalyzed aza-MBH domino reaction reported by Huang.[8a]

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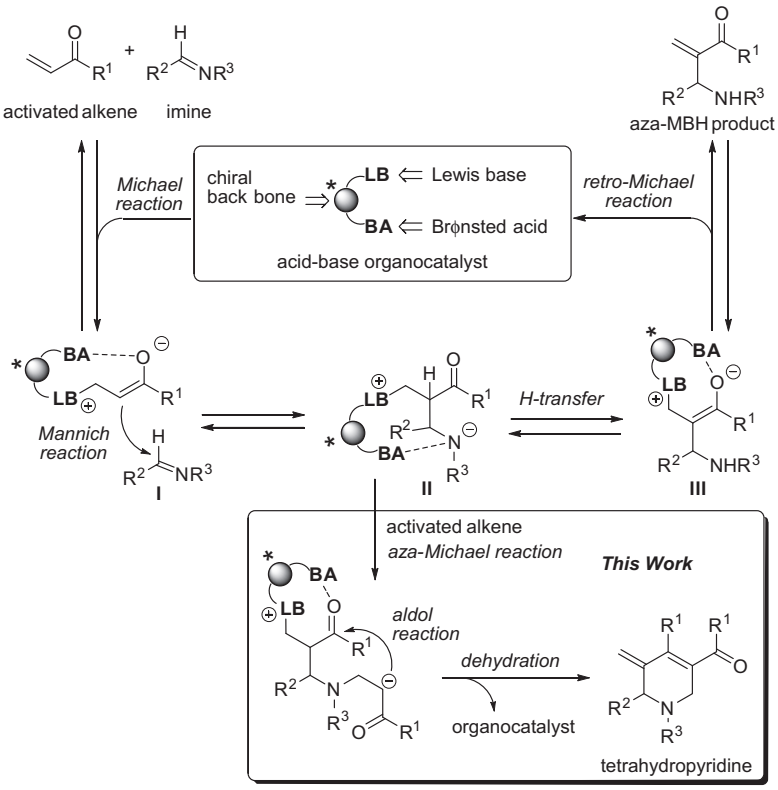
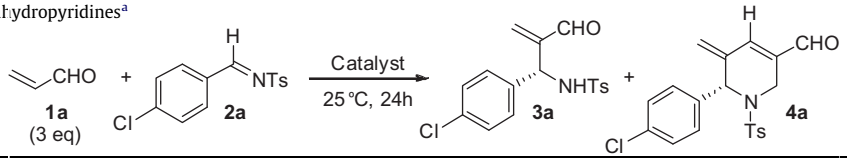



**Scheme 2.** Acid–base organocatalyzed domino process based on the enantioselective aza-MBH reaction.

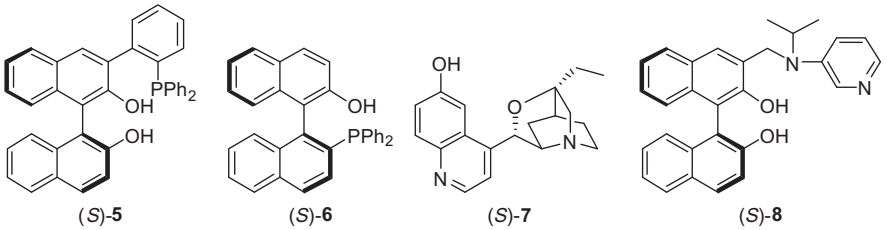
We first conducted experiments to assess the feasibility of using chiral acid–base organocatalysts to promote the enantioselective domino reaction of acrolein (**1a**) with 4-chlorophenyl *N*-tosylimine (**2a**) as shown in Table 1. Among the catalysts we examined for the aza-MBH reaction, including the known chiral organocatalysts (*S*)-**5**,[5m] (*S*)-**6**[5d,f] and (*S*)-**7**[5a–c] (Table 1, entries 1–3), the acid–base organocatalyst (*S*)-**8**[5e,k] promoted the domino reaction to give **3a** in high enantioselectivity (entry 4).[10] We then went on to study the effects of other conditions on the reaction of **1a** with **2a**. Solvent effects were crucial for accelerating the domino reaction. THF and cyclopentyl methyl ether (CPME) (entries 5 and 6), along with toluene (entry 7) gave mainly the normal aza-MBH adduct **3a**. In contrast, halogenated solvents such as chloroform, dichloromethane, and dichloroethane afforded **4a** as a major product with

**Table 1**
Enantioselective synthesis of tetrahydropyridines[a]




| Entry | Catalyst | Solvent | Ratio of **3a**:**4a** | Yield[b] (%) | Ee[c,d] (%) |
|---|---|---|---|---|---|
| 1 | (*S*)-**5** | $CHCl_3$ | 100:0 | 81 | 9[e] |
| 2 | (*S*)-**6** | $CHCl_3$ | 0:100 | 27 | 72 |
| 3 | (*S*)-**7** | $CHCl_3$ | 0:100 | 27 | 73 |
| 4 | (*S*)-**8** | $CHCl_3$ | 0:100 | 35 | 82 |
| 5 | (*S*)-**8** | THF | 96:4 | 100 | 81 |
| 6 | (*S*)-**8** | CPME | 99:1 | 37[f] | 81 |
| 7 | (*S*)-**8** | Toluene | 83:17 | 35[f] | 80 |
| 8 | (*S*)-**8** | $CH_2Cl_2$ | 0:100 | 31 | 83 |
| 9 | (*S*)-**8** | $(ClCH_2)_2$ | 37:63 | 18 | 84 |
| 10[g] | (*S*)-**8** | $(ClCH_2)_2$ | 38:62 | 58 | 85 |
| 11[g,h] | (*S*)-**8** | $(ClCH_2)_2$ | 98:2 | 98 | 92 |
| 12[g,i] | (*S*)-**8** | $(ClCH_2)_2$ | 0:100 | 60 | 87 |

[a] 20 mol % of catalyst was used.
[b] Isolated total yield of **3a** and **4a**.
[c] Ee of major product.
[d] Determined by HPLC (Daicel Chiralpak AS-H, EtOH/hexane = 35/65).
[e] (*R*)-form.
[f] Unreacted **2a** remained.
[g] MS 3A was added.
[h] At 0 °C for 48 h.
[i] At 0 °C for 48 h then 25 °C for 24 h.



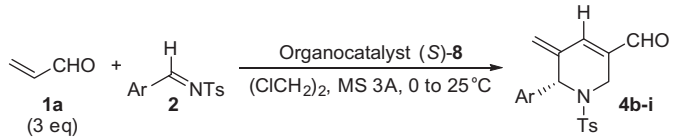

high enantioselectivity (entries 4, 8 and 9). The addition of MS 3A was beneficial for suppressing the decomposition of the moisture sensitive *N*-tosylimine, resulting in an improvement of the product yield (entry 10). The normal aza-MBH adduct **3a** was obtained in 96% yield with 92% ee at 0 °C, since the lower reaction temperature drastically diminished the reaction rate of the aza-Michael process between intermediate **II** and **1a** (entry 11). Finally, when the reaction mixture was stirred at 0 °C until the imine **2a** was consumed completely as determined by TLC analysis and then was slowly warmed up to 25 °C, tetrahydropyridine **4a** was obtained in 60% yield with 87% ee (entry 12).

The substrate scope under the optimized reaction conditions is summarized in Table 2. Regardless of whether the aromatic substituent of **2** is electron withdrawing or electron donating, acid–base organocatalyst (*S*)-**8** promotes the reaction with good to high enantioselectivities (Table 2, entries 1–7). α,β-Unsaturated *N*-tosylimine (**2i**) was able to use as a substrate (entry 8).

Being encouraged by the results obtained in Table 2, we attempted the cross domino reaction of the two different Michael acceptors **1a** and methyl vinyl ketone (MVK, **1b**) with imine **2b** in one-pot (Scheme 3). The reaction of **1b** and **2b** with catalyst (*S*)-**8** was allowed to proceed until **2b** was consumed and then **1a** was added. Although the normal aza-MBH product **3j** was formed in 93% yield and 93% ee, no desired domino product was obtained. To promote the following aza-Michael/aldol/dehydration sequence, various kinds of **LB** were tested. DBU, which can function as a strong **LB**[11] promoted the sequential reaction while maintaining the optical purity of **3** (Table 3).

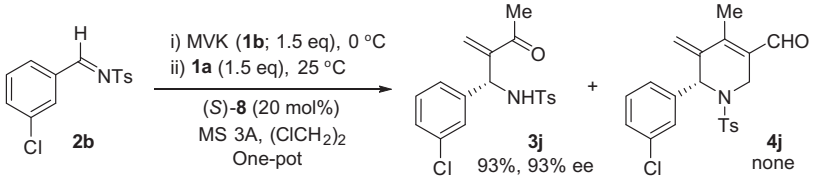
To provide mechanistic insight into the present domino reaction, we performed the aza-Michael/aldol/dehydration reaction of aza-MBH adduct **3h** (optical purity 90% ee) with **1a** catalyzed by (*S*)-**8** (Scheme 4). The domino reaction led to **4h** in 60% yield with 88% ee, along with the formation of 4-bromobenzaldehyde, tosylamine, and aldehyde **9**. These side products derived from the decomposition of imine **2h** via the retro-aza-MBH reaction of **3h**. Judging from these results, the present acid–base organocatalyzed

**Table 2**
Scope and limitations of the enantioselective synthesis of tetrahydropyridines[a]



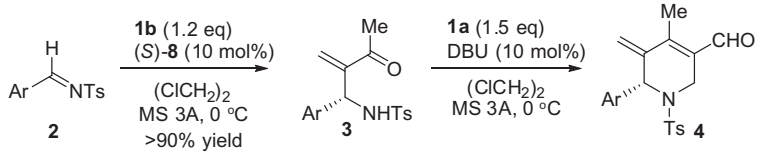

| Entry | Ar | | Time (h) | Product | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | 3-Cl–$C_6H_4$ | **2b** | 48 | **4b** | 55 | 80 |
| 2 | 2-Cl–$C_6H_4$ | **2c** | 48 | **4c** | 60 | 83 |
| 3 | 4-$NO_2$–$C_6H_4$ | **2d** | 24 | **4d** | 40 | 85 |
| 4 | Ph | **2e** | 48 | **4e** | 49 | 75 |
| 5 | 3,4-$(MeO)_2$–$C_6H_3$ | **2f** | 48 | **4f** | 58 | 83 |
| 6 | 4-NC–$C_6H_4$ | **2g** | 48 | **4g** | 45 | 84 |
| 7 | 4-Br–$C_6H_4$ | **2h** | 48 | **4h** | 60 | 88 |
| 8 | (*E*)-PhCH=CH | **2i** | 48 | **4i** | 43 | 78 |

[a] 20 mol % of catalyst was used.
[b] Isolated yield.
[c] Determined by HPLC (Daicel Chiralpak AS-H for **4b**,**c**,**e**,**h**, 2-propanol/hexane = 35/65; Daicel Chiralpak AD-H for **4d**,**g**,**i**, 2-propanol/hexane = 35/65; Daicel Chiralcel OJ-H for **4f**, 2-propanol/hexane = 35/65).



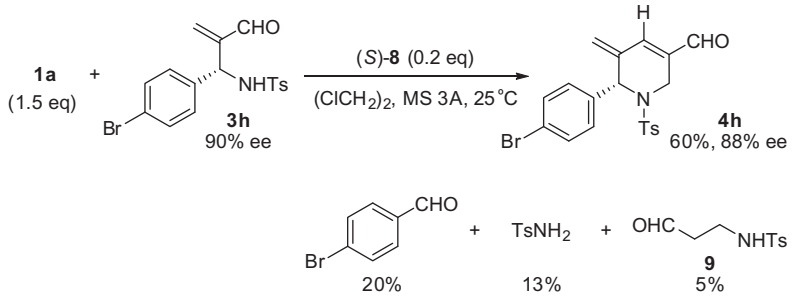

**Scheme 3.** Attempt at the cross aza-MBH domino reaction of **1a**, **1b** and **2b**.

**Table 3**
Stepwise synthesis of chiral tetrahydropyridines




| Entry | Ar | Product | Overall yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|
| 1 | 4-Cl–$C_6H_4$ | **4j** | 44 | 93 |
| 2 | 3-Cl–$C_6H_4$ | **4k** | 52 | 91 |
| 3 | Ph | **4l** | 40 | 87 |

[a] Isolated yield.
[b] Determined by HPLC (Daicel Chiralpak AS-H for **4j**,**k**, 2-propanol/hexane = 35/65; Daicel Chiralcel OD-H for **4l**, 2-propanol/hexane = 35/65).




**Scheme 4.** Aza-Michael/aldol/dehydration reaction of **1a** with **3h**.

aza-MBH reaction is likely reversible in halogenated solvents at 25 °C (Scheme 2).[12]

In conclusion, we have developed the enantioselective aza-MBH/aza-Michael/aldol/dehydration reaction of α,β-unsaturated carbonyl compounds and *N*-tosylimines promoted by a chiral acid–base organocatalyst.[13,14] The aza-MBH domino system described herein was easily accessed to give highly functionalized tetrahydropyridines in high enantioselectivities (up to 93% ee). Further investigations to extend the reaction scope and applications of this process in organic synthesis are underway.

## Acknowledgments

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## Supplementary data

Supplementary data associated with (experimental procedures and compound characterization data) this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.045.

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10. The self-condensation of **1a** and the formation of unidentified side-products were observed.
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12. The reversibility of aza-MBH reaction when using acrolein (**1a**) with chiral acid–base organocatalyst was reported. See Ref. 5f.
13. *Representative procedure for the domino reaction of* **1a** *with* **2a**: To a solution of organocatalyst (*S*)-**8** (5.1 mg, 0.012 mmol) and imine (**2a**, 0.059 mmol) in $(ClCH_2)_2$ (0.20 mL) was added acrolein (**1a**, 12 μL, 0.18 mmol) at 0 °C. The solution was stirred until **2a** was completely consumed as determined by TLC analysis and then allowed to slowly warm to 25 °C. The mixture was directly purified by preparative TLC ($SiO_2$, *n*-hexane/$CH_2Cl_2$ = 1/5 or $CH_2Cl_2$ only) to give the corresponding cyclic products **4a** as white solids.
14. We also attempted to utilize an aliphatic *N*-sulfonated imine (*c*-$C_6H_{11}CH{=}NTs$) for the reaction. However, the corresponding aza-MBH product was not formed.