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Acid–base organocatalysts for the aza-Morita–Baylis–Hillman reaction of nitroalkenes

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ABSTRACT

A new class of acid–base chiral organocatalysts **1a** and **2** for aza-Morita–Baylis–Hillman (aza-MBH) reaction of conjugated nitroalkenes is described. The acidic phenolic hydroxy groups and basic imidazole unit cooperatively activate nitroalkenes to promote the aza-MBH reaction in good yields with moderate enantioselectivities.

1. Introduction

The aza-Morita–Baylis–Hillman (aza-MBH) reaction is recognized as one of the most useful and atom-economical carbon–carbon bond forming reactions between the α-position of an electron-deficient alkene and an imine catalyzed by nucleophilic amines or phosphines.[1] The aza-MBH adducts are highly functionalized allylic amines, which prove to be valuable building blocks for biologically important compounds and natural products.[2] To date, a number of attractive systems have been developed for this asymmetric catalytic process.[3] Recently Xu et al. reported the first enantioselective aza-MBH reaction of the β-methyl substituted nitroalkene, although the applicability of their catalysts has been limited to trisubstituted β-styrene derivatives.[4] No reaction was observed when disubstituted nitroalkenes were used as starting materials. To the best of our knowledge, research on the enantioselective coupling of simple conjugated nitroalkenes and imines has not been reported. Obtaining efficient chiral catalysts for the aza-MBH reaction of simple conjugated nitroalkenes has been a challenge in organic synthesis.

Herein, BINOLate organocatalysts **1a** and **2** (Fig. 1) bearing an imidazole unit are expected to be effective for promoting the enantioselective aza-MBH reaction of conjugated nitroalkenes and *N*-tosylimines.

2. Results and discussion

Our work has focused on developing bifunctional catalysts that can promote enantioselective carbon–carbon bond forming reactions via a dual activation mechanism.[5] We envisioned that locating both acid and base units on one chiral skeleton would facilitate synergistic cooperation. A Lewis base unit, which would act as a reaction-promoting functionality, could be introduced onto the 3-position of BINOL as a chiral Brønsted acid, using an appropriate spacer (Fig. 2).

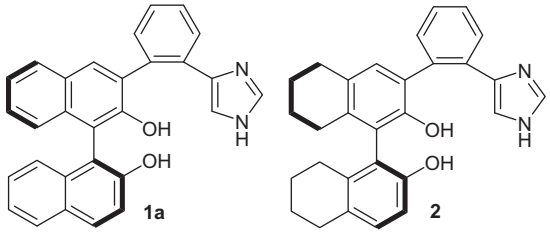

Figure 1. Acid–base organocatalysts for the aza-MBH reaction of nitroalkenes.

As the first step toward the development of the acid–base type organocatalyst, imidazole[6] units were attached through an aromatic ring to the 3-position of (*S*)-BINOL. The synthetic procedure for organocatalysts **1a**[7] and **2**[8] is shown in Scheme 1.[9] The reaction of prototypical substrates 2-(2-nitrovinyl)furan **10a** and 4-bromobenzyl *N*-tosylimine **11a** was initially attempted using organocatalyst **1a** or **2**. As expected, organocatalyst **1a**, with a 2-(1*H*-imidazol-4-yl)phenyl group at the 3-position of BINOL, promoted the reaction to give **12a** in 23% yield with 38% ee (Table 1, entry 5). In contrast, organocatalysts **1b–c**,[10,11] in which the possibility of synergistic cooperation between the Brønsted acid and the Lewis base in an intramolecular manner was eliminated, resulted in low asymmetric induction or no reaction (entries 6 and 7). The reaction was mediated by a mixed reagent (*S*)-BINOL (10 mol %) and imidazole (10 mol %) and produced **12a** in racemic form (entry 4). These results indicate that the introduction of acid–base units at the appropriate positions on one chiral skeleton improves the asymmetric induction efficiency. Known chiral organocatalysts **13**,[3e] **14**,[3m] **15**,[3d] and **16**[3a–c] for the aza-MBH reaction of α,β-unsaturated carbonyl compounds were ineffective in this reaction

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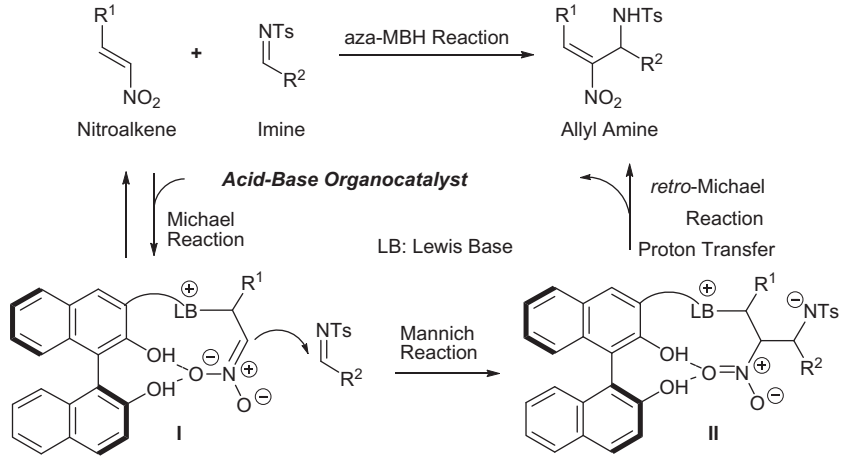
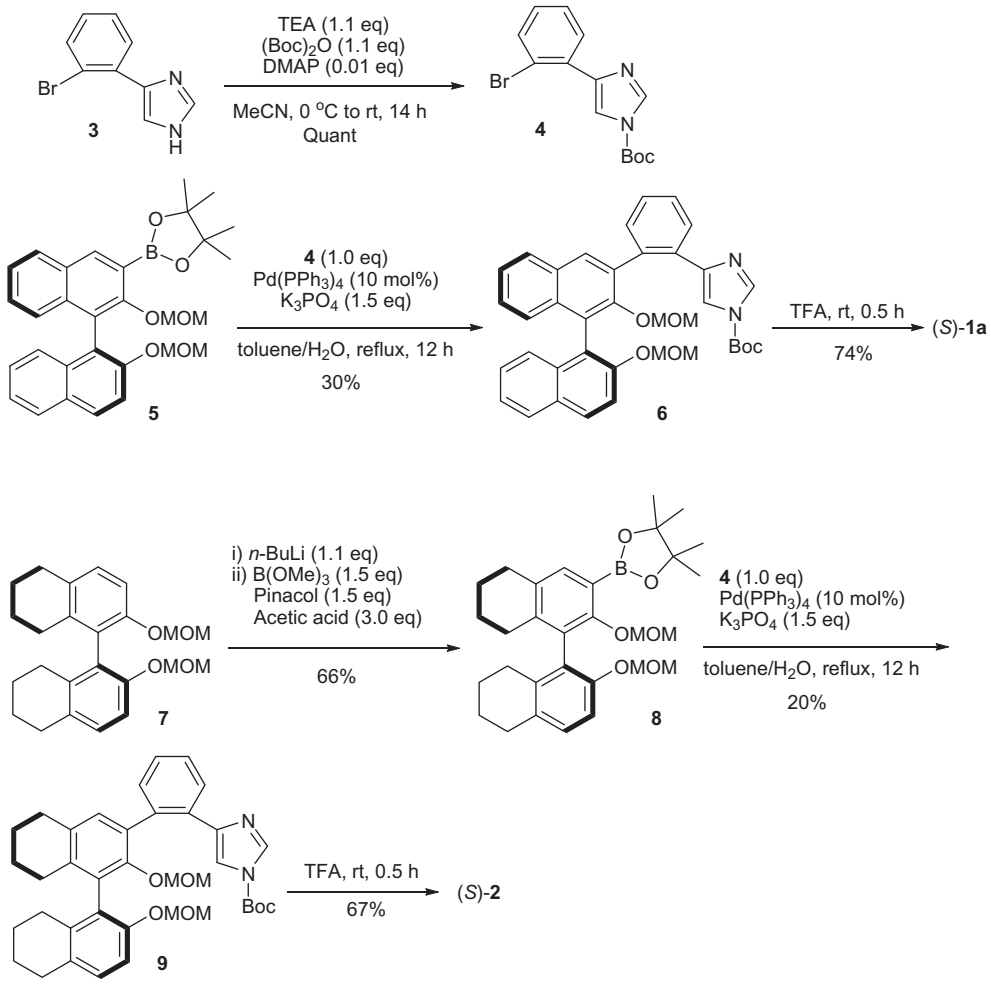


Figure 2. Acid–base organocatalyzed aza-MBH reaction of nitroalkenes.



Scheme 1. Synthesis of organocatalysts **1a** and **2**.

(entries 9–12). Among the acid–base organocatalysts we designed, catalyst **2** bearing an H8-BINOL[12] backbone also exhibited an acceptable outcome (entry 8), affording product **12a** in 56% yield and 51% ee. The absolute configurations of the major adduct **12a** obtained with catalyst (*S*)-**1a** were opposite to those obtained with (*S*)-**2**, which contains the H8-BINOL backbone (entries 5 and 8).

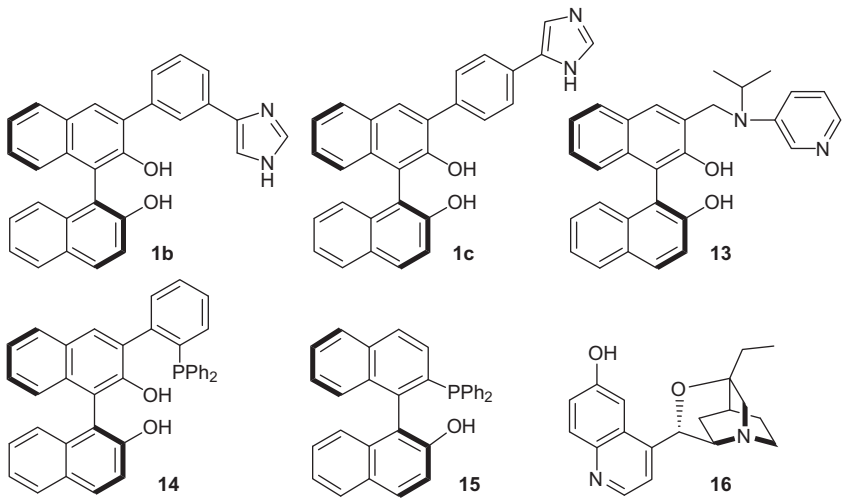
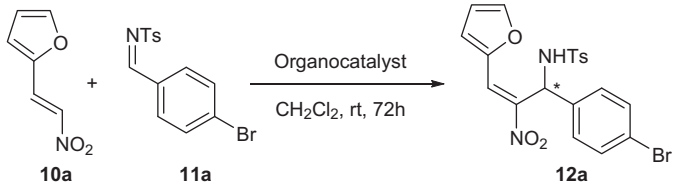


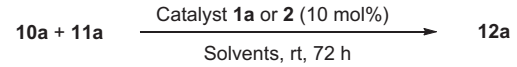
Table 1
Enantioselective aza-MBH reaction of **3a** with **4a** using organocatalysts



Entry	Organocatalyst (10 mol %)	Yield[a] (%)	ee[b,c] (%)
1	None	NR	—
2	(*S*)-BINOL	NR	—
3	Imidazole	25	—
4[d]	(*S*)-BINOL + imidazole	21	*rac*
5	**1a**	23	38 (−)
6	**1b**	12	5 (−)
7	**1c**	NR	—
8	**2**	56	51 (+)
9	**13**	NR	—
10	**14**	NR	—
11	**15**	NR	—
12	**16**	NR	—

[a] Isolated yield.
[b] Determined by HPLC (Daicel Chiralcel OD-H).
[c] The sign of specific rotation is indicated in parentheses.
[d] 10 mol % of (*S*)-BINOL and 10 mol % of imidazole were used.

Table 2
Effect of solvent and temperature on the reaction



Entry	Solvent	Catalysts	Yield[a] (%)	ee[b,c] (%)
1	MeCN	**1a**	NR	—
2		**2**	Trace	53 (+)
3	THF	**1a**	NR	—
4		**2**	19	31 (+)
5	Toluene	**1a**	30	47 (−)
6		**2**	55	21 (+)
7	Chlorobenzene	**1a**	64	45 (−)
8		**2**	34	37 (+)
9	$CHCl_3$	**1a**	48	47 (−)
10		**2**	67	55 (+)
11[d]		**2**	35	60 (+)
12	CCl_4	**1a**	81	45 (−)
13[d]		**1a**	NR	—
14		**2**	77	20 (+)

[a] Isolated yield.
[b] Determined by HPLC (Daicel Chiralcel OD-H).
[c] The sign of specific rotation is indicated in parentheses.
[d] At 0 °C for 168 h.

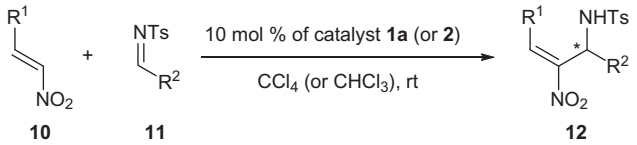
Encouraged by the results obtained with **1a** and **2**, the effect of other reaction conditions were investigated (Table 2). Halogenated solvents such as chlorobenzene, $CHCl_3$, and CCl_4 (entries 7–14), along with toluene (entries 5 and 6), gave relatively good results compared with MeCN (entries 1 and 2) and THF (entries 3 and 4). The product was obtained with 60% ee when using **2** at 0 °C (entry 11), although lower reaction temperature drastically diminished the reaction rates (entries 11 and 13).

Next, we investigated the substrate scope of this catalyst system under the optimized reaction conditions (Table 3).[13] Regardless of whether the aromatic substituent R^2 of **11** is electron withdrawing or electron donating, organocatalysts **1a** and **2** promoted the reaction (entries 1–10). 2-Naphthyl *N*-tosylimine **11g** could be used as a substrate (entries 11 and 12). The reactions of 4-methoxy-1-(2-nitrovinyl)benzene **10b** and 2,4-dimethoxy-1-(2-nitrovinyl)benzene **10c** produced the corresponding adducts **12h** and **12i** but with low yields and enantioselectivities (entries 13 and 14). When using (2-nitrovinyl)benzene **10d** as a substrate, no reaction was observed (entry 15).

3. Conclusion

In conclusion, acid–base organocatalysts (*S*)-3-(2-(1*H*-imidazol-4-yl)phenyl)BINOL **1a** and (*S*)-3-(2-(1*H*-imidazol-4-yl)phenyl)-5,5',6,6',7,7',8,8'-octahydro-BINOL **2** for the aza-MBH reaction of conjugated nitroalkenes have been prepared. The acid–base functionalities suitably positioned on the skeleton work synergistically to furnish the product with up to 60% ee. Efforts are currently underway to improve the catalytic efficacy and investigate the reaction mechanism.

Table 3
Substrate scope using organocatalysts **1a** and **2**



10 **11** **12**

Entry	R^1	R^2	Cat	Time (h)	Yield[a] (%)		ee[b,c] (%)
1	2-Furyl **10a**	Ph **11b**	**1a**	72	77	**12b**	57 (−)
2	**10a**	**11b**	**2**	120	54	**12b**	57 (+)
3	**10a**	4-F–C_6H_4 **11c**	**1a**	96	77	**12c**	51 (−)
4	**10a**	**11c**	**2**	120	60	**12c**	47 (+)
5	**10a**	4-Cl–C_6H_4 **11d**	**1a**	72	94	**12d**	47 (−)
6	**10a**	**11d**	**2**	72	76	**12d**	51 (+)
7	**10a**	4-MeO–C_6H_4 **11e**	**1a**	96	35	**12e**	43 (−)
8	**10a**	**11e**	**2**	168	14	**12e**	40 (+)
9	**10a**	4-NC–C_6H_4 **11f**	**1a**	72	98	**12f**	51 (−)
10	**10a**	**11f**	**2**	72	85	**12f**	47 (+)
11	**10a**	2-Naphthyl **11g**	**1a**	72	89	**12g**	47 (−)
12	**10a**	**11g**	**2**	120	47	**12g**	47 (+)
13	4-MeO–C_6H_4 **10b**	4-Br–C_6H_4 **11a**	**1a**	72	23	**12h**	29 (−)
14	2,4-diMeO–C_6H_3 **10c**	**11a**	**1a**	72	16	**12i**	21 (−)
15	Ph **10d**	**11a**	**1a**	72	NR		—

[a] Isolated yield.
[b] Determined by HPLC (Daicel Chiralcel OD-H).
[c] The sign of specific rotation is indicated in parentheses.

Acknowledgments

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7. (*S*)-**1a**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.48–7.75 (17H, m); ^{13}C NMR (37.7 MHz, $CDCl_3$): δ 153.0, 149.3, 135.7, 135.2, 134.4, 134.0, 133.5, 131.3, 130.9, 130.2, 128.9, 128.7, 128.5, 128.0, 127.9, 127.7, 126.9, 126.5, 124.8, 124.7, 123.7, 123.1, 118.3, 113.1; HRMS (ESI) *m/z* calcd for $C_{29}H_{21}N_2O_2$, 429.1525 [$(M+H)^+$]: found, 429.1515; $[\alpha]_D^{20} = -56.3$ (*c* 0.5, $CHCl_3$).
8. (*S*)-**2**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.66–7.64 (9H, m), 2.74 (4H, br s), 2.18 (4H, br s), 1.20–1.70 (8H, m); ^{13}C NMR (37.7 MHz, $CDCl_3$): δ 148.3, 147.7, 136.4, 136.3, 135.8, 134.9, 134.1, 131.0, 130.8, 130.6, 129.5, 129.3, 129.3, 127.9, 127.3, 127.1, 127.0, 126.2, 125.1, 122.7, 121.6, 119.0, 28.9, 26.9, 23.0, 22.9, 22.6; HRMS (ESI) *m/z* calcd for $C_{29}H_{29}N_2O_2$, 437.2151 [$(M+H)^+$]: found, 437.2169; $[\alpha]_D^{20} = -109$ (*c* 0.5, $CHCl_3$).
9. Known compounds **3**, **5** and **7** were synthesized following their reported procedures. Compound **3**, Young, M. B.; Barrow, J. C.; Glass, K. L.; Lundell, G. F.; Newton, C. L.; Pellicore, J. M. Rittle, K. E.; Selnick, H. G. Stauffer, K. J.; Vacca, J. P.; Williams, P. D.; Bohn, D.; Clayton, F. C.; Cook, J. J.; Krueger, J. A.; Kuo, L. C. S.; Lewis, D.; Lucas, B. J.; McMasters, D. R.; Miller-Stein, C.; Pietrak, B. L.; Wallace, A. A.; White, R. B.; Wong, B.; Yan, Y.; Nantermet, P. G. *J. Med. Chem.* **2004**, *47*, 2995. Compound **5**, Ma, L.; Jin, R.-Z.; Lü, G.-H.; Bian, Z.; Ding, M. X.; Gao, L.-X. *Synthesis* **2007**, 2461. Compound **7**, Takasaki, M.; Motoyama, Y.; Yoon, S.-H.; Mochida, I.; Nagashima, H. *J. Org. Chem.* **2007**, *72*, 10291.
10. (*S*)-**1b**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.08–7.77 (17H, m); ^{13}C NMR (37.7 MHz, $CDCl_3$): δ 153.1, 146.9, 138.0, 134.8, 133.7, 133.0, 131.6, 130.7, 130.5, 130.2, 129.1, 129.1, 128.6, 128.5, 128.1, 126.9, 126.8, 125.8, 124.4, 124.2, 123.9, 123.5, 128.5, 118.3, 114.1, 112.2; HRMS (ESI) *m/z* calcd for $C_{29}H_{21}N_2O_2$, 429.1525 [$(M+H)^+$]: found, 429.1511; $[\alpha]_D^{20} = -94.8$ (*c* 0.5, $CHCl_3$).
11. (*S*)-**1c**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.96–7.94 (17H, m); ^{13}C NMR (37.7 MHz, $CDCl_3$): δ 154.6, 151.3, 138.5, 136.8, 135.7, 134.7, 132.7, 132.2, 131.0, 130.7, 130.4, 130.3, 129.0, 128.9, 127.3, 126.9, 125.5, 125.5, 125.3, 124.2, 123.9, 119.2, 116.9, 114.8; HRMS (ESI) *m/z* calcd for $C_{29}H_{21}N_2O_2$, 429.1525 [$(M+H)^+$]: found, 429.1511; $[\alpha]_D^{20} = -104$ (*c* 0.5, $CHCl_3$).
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13. *General experimental procedure* (Table 3): To a solution of organocatalyst (10 mol %) in solvent (0.2 mL) was added nitroalkene **10** (0.2 mmol) and imine **11** (0.1 mmol) at rt. The reaction mixture was stirred until the reaction had reached completion by monitoring with TLC analysis. The mixture was directly purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc = 7/2) to give the corresponding adduct **12** as a yellow solid. All products were characterized by ^{1}H, ^{13}C NMR, MS, and IR spectroscopy, and were identical in all respects with reported by Namboothiri et al.[6d] Determination of absolute configurations of **12** is now in progress.