A Brønsted Acid and Lewis Base Organocatalyst for the Aza-Morita–Baylis–Hillman Reaction

Katsuya Matsui, Shinobu Takizawa, Hiroaki Sasai*

The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki, Osaka 567-0047, Japan
Fax +81(6)68798469; E-mail: sasai@sanken.osaka-u.ac.jp

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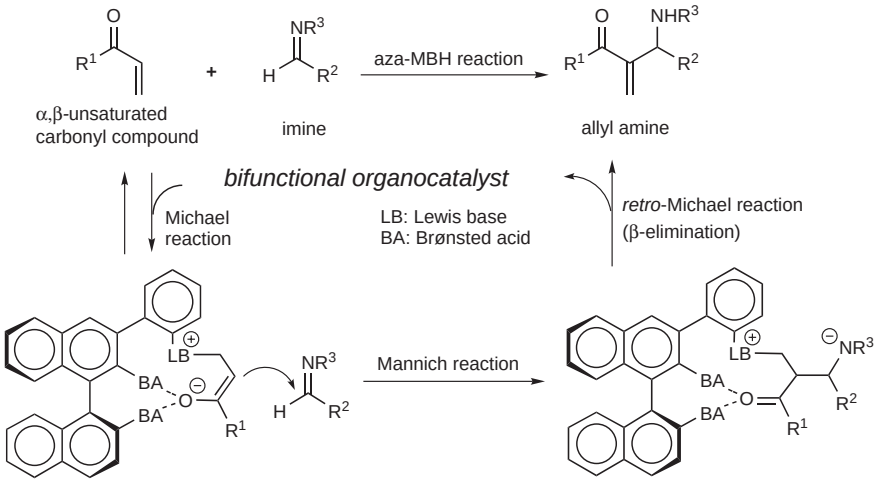
Abstract: (*S*)-3-[2-(Diphenylphosphino)phenyl]BINOL has been established as an efficient asymmetric bifunctional organocatalyst for the aza-Morita–Baylis–Hillman (aza-MBH) reaction. The Brønsted acid and Lewis base functionalities cooperate in substrate activation to promote the reaction with high enantiocontrol.

Key words: enantioselective aza-Morita–Baylis–Hillman reaction, bifunctional catalyst, Brønsted acid, Lewis base, organocatalysis

In enzyme-promoted asymmetric reactions, acid–base functionalities in the catalytic site activate substrates by a synergistic cooperation affording products in both high yield and enantioselectivity. The development of asymmetric catalysts using a small chiral molecule with enzyme-like activation for substrates has been a challenge to organic chemists.[1–3] Asymmetric bifunctional catalysts possessing two or more acid–base functionalities are representative examples of this type of artificial enzyme.[2,3] In this paper, we report (*S*)-3-[2-(diphenylphosphino)phenyl]BINOL (**1a**) as a novel asymmetric bifunctional organocatalyst for the aza-Morita–Baylis–Hillman (aza-MBH) reaction.[4] The Brønsted acid and Lewis base functionalities, for the activation of the substrate, performed harmoniously to promote the reaction with high enantiocontrol.

We envisioned locating both acid and base units on one chiral skeleton thereby facilitating a synergistic cooperation. To that end, a Lewis base unit, which would act as a reaction-promoting functionality in the aza-MBH reaction, could be introduced onto the 3-position of BINOL as a chiral Brønsted acid, using an aromatic ring as a spacer (Scheme 1).[5] Shi et al. also reported chiral phosphine–Lewis base organocatalyst for the aza-MBH reaction.[4e,f] As the first step towards development of our organocatalyst, phosphine units were attached through an aromatic ring to the 3-position of (*S*)-BINOL (Figure 1). As expected, organocatalyst **1a**,[6] with a 2-(diphenylphosphino)phenyl group attached to the 3-position of BINOL, promoted the reaction of methyl vinyl ketone (**2a**) and *p*-chlorophenyl *N*-tosylimine (**3a**) to give the adduct (*S*)-**4a** with 70% ee (entry 5, Table 1). In contrast, organocatalysts **1b**,**c**, in which the possibility of synergistic cooperation between the Brønsted acid and the Lewis base in an intramolecular manner has been eliminated, resulted in low asymmetric induction in **4a** (entries 6 and 7). The reaction mediated by a mixed reagent, (*S*)-BINOL (10 mol%) and triphenyl-



Scheme 1 The aza-MBH reaction promoted by asymmetric bifunctional catalysts

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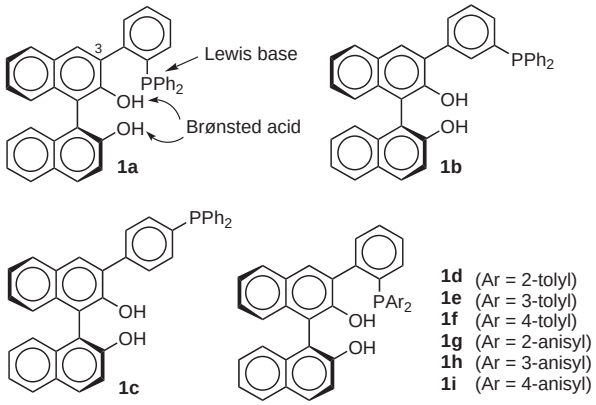


Figure 1 Asymmetric bifunctional organocatalysts for the aza-MBH reaction

phosphine (PPh_3, 10 mol%), also produced **4a** with low enantioselectivity (entry 4). These results indicate that the introduction of the acid and base units at the appropriate positions on one chiral skeleton dramatically improves the efficiency of the bifunctional asymmetric organocatalysts.

Ethereal solvents were relatively efficient when compared with other solvents (entries 5, and 8–10).[7] Although the organocatalysts **1d**–**i** bearing the ditolylphosphinophenyl or dianisylphosphinophenyl group on the 3-position of BINOL were employed, no improvement in catalytic activity was observed.[8] The best result (90% yield, 92% ee) was obtained when **1a** was used in *t*-BuOMe at –20 °C under a low concentration of the substrate **3a** (0.05 M, entry 11). As shown in Table 2, irrespective of whether the aromatic substituent R^2 of **3** is electron-withdrawing or electron-donating, organocatalyst **1a** promoted the reaction with high enantioselectivity. In addition, **1a** advances the substrate scope of the reported organocatalyst (*S*)-**5**[5a] (Figure 2 and Table 2, entries 6, and 12–14). Interestingly, the absolute configurations of the major adduct **4** obtained with catalyst (*S*)-**1a** were opposite to those obtained with (*S*)-**5** which contains a 3-pyridinylamino unit.

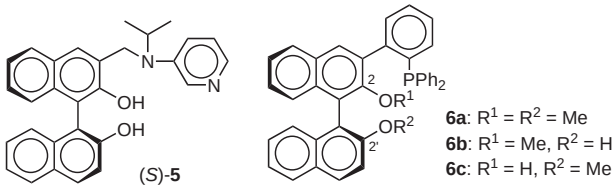
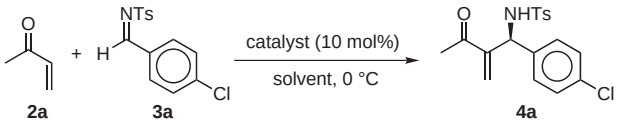


Figure 2

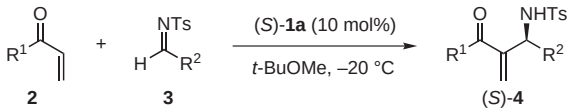
Table 1 Enantioselective Aza-MBH Reaction of **2a** with **3a** Catalyzed by Organocatalysts



Entry	Organocatalyst	Solvent[a]	Time (h)	Yield (%)[b]	ee (%)[c]
1	None	THF	24	NR	–
2	(*S*)-BINOL	THF	24	NR	–
3[d]	PPh_3	THF	3	70	–
4[d,e]	(*S*)-BINOL + PPh_3	THF	4	75	1
5	**1a**	THF	20	62	70
6	**1b**	THF	18	93	5
7[d]	**1c**	THF	12	88	1
8	**1a**	Et_2O	20	44	79
9	**1a**	DME	20	36	67
10	**1a**	*t*-BuOMe	20	72	82
11[f]	**1a**	*t*-BuOMe	144	90	92

[a] 0.5 M (substrate concentration of **3a**) and 3 equiv of **2a**.
[b] Isolated yield.
[c] Determined by HPLC (Daicel Chiralpak AD-H).
[d] Decomposition of **3a** was observed.
[e] 10 mol% of (*S*)-BINOL and 10 mol% of PPh_3 were used.
[f] Performed at –20 °C in 0.05 M (concentration of **3a**).

Table 2 Enantioselective Aza-MBH Reaction of **2** with **3** Catalyzed by (*S*)-**1a**[9]



2 **3** (*S*)-**4**

Entry	R^1	R^2	Time (d)	Yield (%)[a]	ee (%)[b,c]
1	Me (**2a**)	*p*-Cl-C_6H_4 (**3a**)	6	90	92 (95)
2	Me (**2a**)	Ph (**3b**)	9	97	87 (87)
3	Me (**2a**)	*p*-Et-C_6H_4 (**3c**)	8	Quant.	93 (93)
4	Me (**2a**)	*p*-Br-C_6H_4 (**3d**)	4	87	92 (94)
5	Me (**2a**)	*p*-MeO-C_6H_4 (**3e**)	9	90	95 (94)
6	Me (**2a**)	*o*-Cl-C_6H_4 (**3f**)	6	96	92 (62)
7	Me (**2a**)	*p*-NO_2-C_6H_4 (**3g**)	2	95	82
8[d]	Me (**2a**)	*p*-NO_2-C_6H_4 (**3g**)	4	93	88 (91)
9	Et (**2b**)	*p*-NO_2-C_6H_4 (**3g**)	2.5	87	85
10[d]	Et (**2b**)	*p*-NO_2-C_6H_4 (**3g**)	6	87	89 (88)
11	Ph (**2c**)	*p*-NO_2-C_6H_4 (**3g**)	3	89	82
12[d]	Ph (**2c**)	*p*-NO_2-C_6H_4 (**3g**)	8	85	84 (58)
13	Me (**2a**)	2-Furyl (**3h**)	3	93	94 (88)
14	Me (**2a**)	1-Naphthyl (**3i**)	12	85	90 (70)
15	Me (**2a**)	2-Naphthyl (**3j**)	8	91	89 (91)

[a] Isolated yield.
[b] Determined by HPLC (Daicel Chiralpak AD-H or OD-H).
[c] The ee in parentheses were obtained by using (*S*)-**5** under optimal conditions (a mixed solvent system consisting of toluene and cyclopentyl methyl ether in a 1:9 ratio, –15 °C).
[d] Performed at –40 °C.

Since the diprotected catalyst **6a** and the monoprotected catalysts **6b**,**c** resulted in no activity or low selectivity, both the phenolic hydroxyl groups in **1a** seem to be required to promote the aza-MBH reaction.[10]

In conclusion, efficient asymmetric bifunctional organocatalysis for the aza-MBH reaction has been established with (*S*)-3-[2-(diphenylphosphino)phenyl]BINOL (**1a**) bearing the phenyl-binaphthyl skeleton for the positioning of functionalities. The acid and base functionalities suitably positioned on the skeleton work synergistically to furnish the product with high enantioselectivity. Efforts are currently underway to provide the mechanistic information.

Acknowledgment

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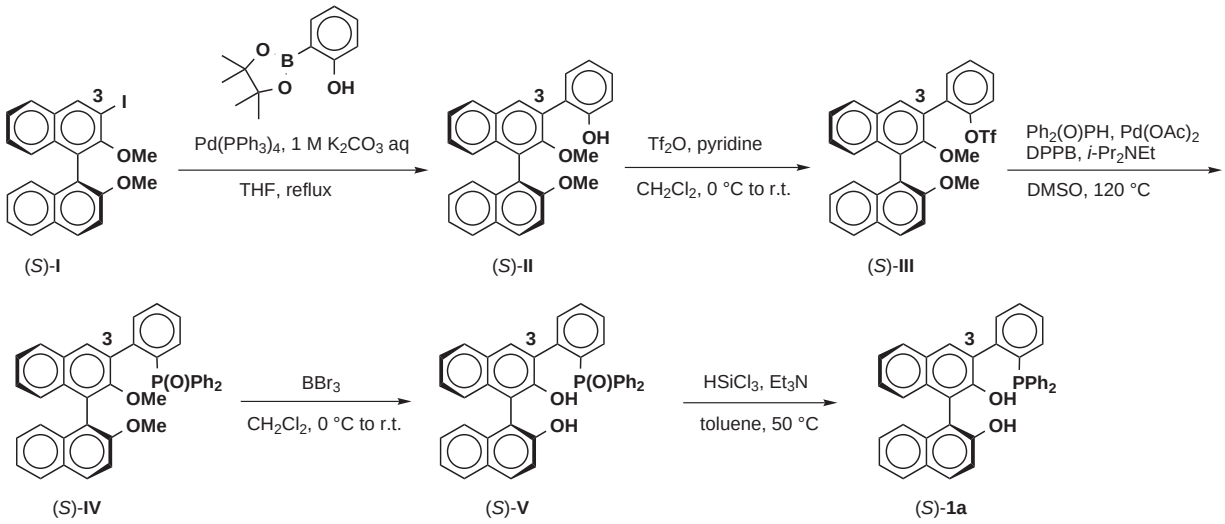
(6) **General Procedure for the Synthesis of (S)-1a** (Scheme 2)
To a solution of (*S*)-**I**[11] (132.0 mg, 0.3 mmol) and 2-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (79.2 mg, 0.36 mmol) in THF (6 mL) were added 1 M K_2CO_3 aq (3 mL) and $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol). The mixture was refluxed for 12 h, and then cooled to r.t. Then, CH_2Cl_2 (5 mL) was added and the organic phase was separated. The aqueous phase was extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc–hexane = 1:4) to give the compound (*S*)-**II** (121.9 mg, 0.3 mmol, 100%).
Compound (*S*)-**II**: orange solid; mp 58–59 °C (EtOAc–hexane). IR (neat): ν = 3354, 3039, 2915, 2830 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 8.02 (1 H, d, *J* = 9.2 Hz), 8.00 (1 H, s), 7.93 (1 H, d, *J* = 8.6 Hz), 7.89 (1 H, d, *J* = 8.6 Hz), 7.59 (1 H, d, *J* = 7.8 Hz), 7.46 (1 H, dt, *J* = 8.6, 1.3 Hz), 7.41–7.17 (8 H, m), 7.08 (1 H, d, *J* = 8.9 Hz), 3.82 (3 H, s), 3.24 (3 H, s). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ = 154.6, 153.8, 152.2, 133.8, 133.2, 131.8, 131.5, 131.3, 131.1, 129.8, 129.4, 128.8, 128.1, 127.9, 126.8, 126.6, 126.3, 125.8, 125.5, 125.3, 124.8, 123.5, 121.1, 118.2, 113.2, 61.4, 56.3. HRMS (ESI): *m/z* calcd for $C_{28}H_{22}NaO_3$: 429.1467 [M + Na]$^+$; found: 429.1466. $[\alpha]_D^{20}$ –63.9 (*c* 0.6, $CHCl_3$).
To a solution of (*S*)-**II** (121.9 mg, 0.3 mmol) with pyridine (72 μL, 0.9 mmol) in CH_2Cl_2 (3 mL) was added trifluoromethanesulfonic anhydride (100 μL, 0.6 mmol) at 0 °C. The mixture was then warmed to r.t. and was kept overnight. The mixture was quenched with H_2O and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4). The filtrate was evaporated in vacuo, and the residue was purified by flash chromatography (SiO_2, EtOAc–hexane = 1:4) to give (*S*)-**III** (159.9 mg, 0.297 mmol, 99%).
Compound (*S*)-**III**: orange solid; mp 42–43 °C (EtOAc–hexane). IR (neat): ν = 3056, 2917, 2833, 1389, 1182 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.99 (1 H, d, *J* = 9.2 Hz), 7.93 (1 H, s), 7.90 (1 H, d, *J* = 8.6 Hz), 7.85 (1 H, d, *J* = 7.3 Hz), 7.69–7.65 (1 H, m), 7.48–7.16 (9 H, m), 3.80 (3 H, s), 3.06 (3 H, s). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ = 154.7, 153.6, 147.6, 134.2, 133.9, 132.7, 132.5, 131.0, 130.2, 129.7, 129.2, 129.1, 128.9, 128.0, 127.7, 126.6, 125.4, 125.2, 125.1, 124.9, 123.6, 121,2. 118.8, 113.2, 60.4, 56.3. HRMS (ESI): *m/z* calcd for $C_{29}H_{21}F_3NaO_5S$: 561.0960 [M + Na]$^+$; found: 561.0955. $[\alpha]_D^{20}$ –78.4 (*c* 0.5, $CHCl_3$).
To a solution of (*S*)-**III** (161.6 mg, 0.3 mmol) in DMSO (6 mL) were added $Ph_2(O)PH$ (121.3 mg, 0.6 mmol) and DPPB (12.8 mg, 0.03 mmol) at r.t. followed by $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and *i*-Pr_2NEt (209 μL, 1.2 mmol). After the mixture was stirred for 12 h at 100 °C, it was cooled to r.t., and EtOAc (10 mL) was added. The organic phase was washed twice with H_2O, dried over Na_2SO_4 and evaporated



Scheme 2

in vacuo. The residue was purified by flash chromatography (SiO_2, EtOAc–hexane = 4:1) to give the compound (*S*)-**IV** (147.1 mg, 0.249 mmol, 83%).
Compound (*S*)-**IV**: white solid; mp 77–78 °C (EtOAc–hexane). IR (neat): ν = 3055, 2932, 2844, 1438, 1158 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.96 (1 H, d, *J* = 9.2 Hz), 7.75 (1 H, s), 7.85–7.04 (22 H, m), 7.54 (1 H, d, *J* = 7.5 Hz), 6.99 (1 H, d, *J* = 8.1 Hz), 3.78 (3 H, s), 2.99 (3 H, s). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ = 154.6, 153.6, 144.6, 134.1, 133.9, 133.8, 133.5, 133.3, 133.2, 133.2, 133.1, 132.0, 131.9, 131.6, 131.5, 131.4, 131.4, 131.3, 131.2, 131.0, 130.9, 130.9, 129.4, 129.3, 129.2, 128.8, 128.8, 128.3, 128,1, 128.0, 127.9, 127.7, 127.4, 127.4, 126.4, 126.2, 126.2, 125.9,124.9, 124.2, 123.4, 113.6, 60.1, 56.8. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.37, 28.95. HRMS (ESI): *m/z* calcd for $C_{40}H_{31}NaO_5P$: 613.1909 $[M + Na]^+$; found: 613.1898. $[\alpha]_D^{20}$ –64.3 (*c* 0.4, $CHCl_3$).
To a solution of (*S*)-**IV** (177.2 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) was added BBr_3 (0.9 mL, 0.9 mmol, 1 M in CH_2Cl_2) at 0 °C and the resulting solution was stirred for 30 min. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (SiO_2, EtOAc–hexane = 1:4) to give the compound (*S*)-**V** (153.6 mg, 0.273 mmol, 91%).
(*S*)-**V**: white solid; mp 149–150 °C (EtOAc–hexane). IR (neat): ν = 3356, 3053, 2912, 2853, 1448, 1166 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.89 (1 H, d, *J* = 8.9 Hz), 7.84 (1 H, d, *J* = 7.8 Hz), 7.80–6.98 (22 H, m). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ = 153.3, 150.9, 143.1, 134.0, 133.3, 133.0, 132.8, 132.7, 132.3, 132.1, 132.0, 131.8, 131.7, 131.5, 131.4, 131.2, 130.8, 130.6, 129.8, 129.8, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.0, 126.9, 126.8, 126.2, 126.0, 124.9, 124.8, 123.1, 122.8, 119.6, 115.0, 112.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 31.17. HRMS (ESI): *m/z* calcd for $C_{38}H_{27}NaO_5P$: 585.1596 $[M + Na]^+$; found: 585.1615. $[\alpha]_D^{20}$ +86.4 (*c* 0.6, $CHCl_3$).
To a solution of (*S*)-**V** (112.5 mg, 0.2 mmol) and Et_3N (279 μL, 2.0 mmol) in toluene (6.7 mL) was added $HSiCl_3$ (404 μL, 4.0 mmol) at 0 °C. After being stirred at 50 °C for 12 h, the mixture was cooled to r.t., diluted with EtOAc and then quenched with a small amount of sat. aq $NaHCO_3$. The resulting suspension was filtered through Celite® and the solid was washed with EtOAc (2 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexane = 1:4) to give the compound (*S*)-**1a** (65.6 mg, 0.12 mmol, 60%).
Compound (*S*)-**1a**: white solid; mp 105–106 °C (EtOAc–hexane). IR (neat): ν = 3370, 3050, 2902, 2824, 1444 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.96 (1 H, d, *J* = 9.2 Hz), 7.88 (1 H, d, *J* = 7.3 Hz), 7.80–6.98 (23 H, m), 5.18 (1 H, br s). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ = 152.8, 150.2, 149.7, 143.1, 142.7, 133.8, 133.6, 133.5, 133.3, 132.0, 131.9, 130.9, 129.2, 129.2, 129.2, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 126.9, 126.9, 125.2, 124.7, 123.8, 123.6, 118.1, 111.8, 111.7. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –10.46, –11.71. HRMS (ESI): *m/z* calcd for $C_{38}H_{27}NaO_2P$: 569.1646 $[M + Na]^+$; found: 569.1631. $[\alpha]_D^{20}$ –73.2 (*c* 0.6, $CHCl_3$).

(7) Results of the aza-MBH reaction of **2a** with **3a** catalyzed by **1a** using various solvents (0.5 M; substrate concentration of **3a**) at 0 °C for 20 h: CH_2Cl_2 (36% yield, 45% ee), toluene (24% yield, 56% ee), MeCN (38% yield, 48% ee), DMF (34% yield, 21% ee), MeOH (22% yield, 21% ee).

(8) Results of the aza-MBH reaction of **2a** with **3a** catalyzed by organocatalysts **1d–i** in *t*-BuOMe (0.05 M; substrate concentration of **3a**) at –20 °C for 144 h: **1d** (no reaction), **1e** (71% yield, 88% ee), **1f** (80% yield, 86% ee), **1g** (no reaction), **1h** (14% yield, 73% ee), **1i** (29% yield, 77% ee).

(9) **General Experimental Procedure (Table 2)**
To a solution of organocatalyst **1a** (2.7 mg, 0.005 mmol, 10 mol%) in *t*-BuOMe (1.0 mL) were added **2** (0.15 mmol) and imine **3**[12] (0.05 mmol) at –20 °C. The 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, EtOAc–hexane = 1:2) to give the corresponding adduct **4**. All products were characterized by ^1H NMR, ^{13}C NMR, MS, and IR spectroscopy. Absolute configurations of **5** were determined by comparing the assign of the optical rotations with those in the literature.[4]

(10) The aza-MBH reaction of **2a** with **3a** was performed in *t*-BuOMe (0.05M; substrate concentration of **3a**) at 0 °C; **6a**: no reaction; **6b**: (*S*)-**4a**, 86 h, 5% yield, 63% ee; **6c**: (*R*)-**4a**, 48 h, 95% yield, 61% ee.

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