Asymmetric Morita–Baylis–Hillman Reaction Catalyzed by Simple Amino Alcohol Derived Thioureas

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Abstract: Thioureas straightforwardly derived from commercially available enantiopure amino alcohols have been found to promote the asymmetric Morita–Baylis–Hillman reaction of 2-cyclohexen-1-one and different aldehydes in the presence of triethylamine under solvent-free conditions. The corresponding allylic alcohols were obtained in good to high yields and up to 88% ee.

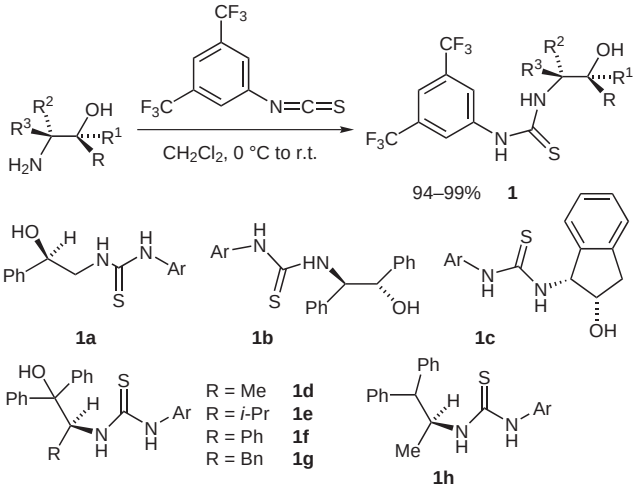
Key words: Morita–Baylis–Hillman reaction, chiral thioureas, asymmetric organocatalysis, amino alcohols

The Morita–Baylis–Hillman reaction (MBH) is an important synthetic tool for C–C bond formation.[1] The coupling of aldehydes with α,β-unsaturated carbonyl compounds, in the presence of a Lewis base such as DABCO or alkyl and aryl phosphines, affords a variety of densely functionalized allylic alcohols. In the asymmetric version of this reaction, enantioenriched allylic alcohols are obtained as valuable synthetic intermediates[2] and relatively few highly enantioselective and efficient protocols have been discovered up to now. A growing interest in this context has been recently directed to the development of catalytic versions[3] and the organocatalyzed protocols widen the opportunity to improve the reaction. Quinine-derived chiral bases,[4] BINOL-derived Brønsted acids,[5] amino acids,[6] and chiral diamines[7] derived from L-proline were successfully developed, affording MBH products in moderate to high yields and ee values. Enantiopure bisthioureas coupled with DABCO or DMAP have been proved valuable systems.[8] Both thiourea groups were found to be necessary for the activity and the asymmetric induction.[8a] An efficient bifunctional organocatalyst was developed by Wang and co-workers, who designed a binaphthyl-derived amine thiourea, which incorporated both Lewis base and acidic thiourea groups in the chiral scaffold.[9] Functionalized monothioureas have been used as organocatalysts in the aza-Baylis–Hillman reaction affording high enantioselectivity.[10]

Polar protic solvents as methanol and water are known to accelerate MBH reaction likely through hydrogen-bonding stabilization of the enolate intermediate and/or activation of the aldehyde.[11] Activation using basic and protic centers of variable range of acidity strength has been shown to be a successful strategy for the development of more efficient catalysts.[10,12]

Thus, we speculated that chiral 1,2-amino alcohols could have been a suitable platform to access novel monothioureas capable of promoting asymmetric MBH reaction. Herein, we report our findings that simple amino alcohol derived thioureas in the presence of triethyl amine can satisfactorily promote the asymmetric MBH reaction of 2-cyclohexen-1-one with aldehydes.

It has been well-documented that the most active thioureas are those having the 3,5-bistrifluoromethyl phenyl residue which makes them better H-bond donors.[13] Some commercially available enantiopure amino alcohols were then treated with the corresponding isothiocyanate in CH_2Cl_2 to give thioureas **1a**–**h** in almost quantitative yields (Scheme 1).[14] Compounds **1b** and **1c** were recently reported as promoters in the asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes.[15]



Scheme 1 Thioureas screened in the MBH reaction

A preliminary study was carried out by reacting cyclohexancarboxaldehyde and 2-cyclohexen-1-one under solvent-free conditions at room temperature in the presence of 20 mol% of thioureas **1a**–**h** and 20 mol% of DABCO (Table 1).

Catalyst **1a** afforded **4a** in modest yield and in almost racemic form (entry 1). Catalysts **1b** and **1c** having two chiral centers in flexible and rigid spatial arrangements slightly improved the enantioselectivity (entries 2 and 3).

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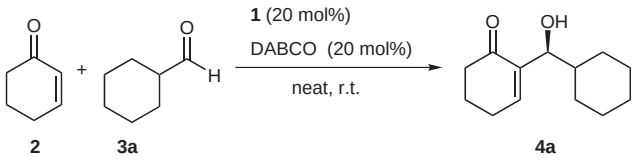
Table 1 MBH Reaction of **2** with **3** Catalyzed by 20 mol% of **1a**–**h** and DABCO Under Solvent-Free Conditions[a]



Entry	**1**	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	48	32	9
2	**1b**	48	31	30
3	**1c**	46	20	31
4	**1d**	65	56	46
5	**1e**	50	15	45
6	**1f**	88	50	63
7	**1g**	66	40	53
8	**1h**	65	31	60
9[d]	**1h**	65	46	47
10[e]	**1h**	65	27	55

[a] *Conditions*: **3a** (0.2 mmol), **2** (0.4 mmol), **1** (0.04 mmol), DABCO (0.04 mmol).
[b] Isolated yields after flash chromatography.
[c] Determined by HPLC analysis using Chiralpak AS-H column. Absolute configuration of the major enantiomer was determined to be *S* by comparison of optical rotation with that reported in the literature.
[d] The reaction was carried out adding 0.2 equiv of MeOH.
[e] The reaction was carried out adding 0.2 equiv of (–)-TADDOL.

Catalysts with only one chiral center, but having a sterically demanding diphenyl carbinol moiety were then checked. Suitable activation by the gem-diphenyl carbinol group has been suggested by our recent findings on nucleophilic asymmetric epoxidation of α,β-enones promoted by diaryl 2-pyrrolidinemethanols in the presence of *tert*-butyl hydroperoxide as oxidant.[16] The conversion to **4a** showed to be affected by the nature of the R group in organocatalysts **1d**–**g** and pleasingly a significant improvement of the enantioselectivity was achieved using compound **1f** which furnished the product in 50% yield and 63% ee (entry 6).

In order to prove the involvement of the hydroxyl group in the process, the reaction was performed using organocatalyst **1h**, which was identical to the most active compound **1d** devoid of the hydroxyl group (entry 8). After a comparable reaction time, the product was isolated in substantially lower yield, although an improved ee was observed (compare with entry 4). The reaction was then performed under the same conditions but adding 20 mol% of MeOH as external hydrogen-bonding donor (entry 9). The same level of asymmetric induction and a smaller conversion to **4a** was achieved when compared to the employment of catalyst **1d** (entry 4). Finally, 20 mol% of optically pure (–)-TADDOL was added to catalyst **1h** as external hydrogen-bonding donor (entry 10). In this case, a much slower conversion to **4a** was achieved while the enantioselectivity improved. These results confirmed the positive effect of the hydroxyl group of catalyst **1d** in accelerating the reaction, which was more pronounced than when using an external alcohol as hydrogen-bonding donor. Furthermore, it has been pointed out for the first time, that unfunctionalized monothioureas derived from simple chiral amines can catalyze the MBH reaction with reasonable level of asymmetric induction.

Reactions carried out with catalyst **1f** and DABCO at 20 mol% loading and room temperature in different solvents were very sluggish and only traces of the product were detected after 5 days.[17]

Given the importance of the nucleophilic base nature on the outcome of the MBH reaction,[18] its influence was investigated employing catalysts **1d**,**f** under solvent-free conditions (Table 2).

When using catalyst **1d** and DMAP, **4a** was recovered in better yield and improved ee (entry 1). A stronger base like DBU afforded the product in satisfactory yield after shorter reaction time, but with low ee (entry 2). *N*-Methyl imidazole did not furnish any trace of **4a** (entry 3). Triethylamine was slightly less efficient than DMAP (entry 4),

Table 2 MBH Reaction of **2** with **3a** Catalyzed by **1d**,**f** and Different Lewis Bases at Room Temperature Under Solvent-Free Conditions[a]

Entry	**1**	Base	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1d**	DMAP	64	65	52
2	**1d**	DBU	46	60	15
3	**1d**	*N*-Methyl imidazole	70	–	–
4	**1d**	Et_3N	70	52	54
5	**1d**	PPh_3	92	–	–
6	**1d**	Et_3P	78	50	0
7	**1f**	DMAP	70	24	46
8[d]	**1f**	Et_3N	93	61	79
9[e]	**1f**	Et_3N	122	67	84
10[f]	**1f**	DABCO	116	75	80
11[f]	**1f**	Et_3N	94	87	84

[a] *Conditions*: **3a** (0.2 mmol), **2** (0.4 mmol), **1** (0.04 mmol), base (0.04 mmol).
[b] Isolated yields after flash chromatography.
[c] Determined by HPLC analysis using Chiralpak AS-H column.[6] Absolute configuration of the major enantiomer was determined to be *S* by comparison of the optical rotation with that reported in the literature.
[d] The reaction was carried out using 0.2 equiv of **1f** and Et_3N and 4 equiv of **2**.
[e] The reaction was carried out at 4 °C using 0.2 equiv of **1f** and Et_3N and 4 equiv of **2**.
[f] The reaction was carried out at 4 °C using 0.3 equiv of **1f** and base and 4 equiv of **2**.

while phosphines proved to be ineffective for the reaction (entries 5 and 6). Then, the best candidate DMAP was checked with catalyst **1f** (entry 7), but no improvement was observed. Triethylamine was found to be the base of choice when used with promoter **1f**, in fact, the product was obtained in satisfactory yield and 79% ee (entry 8). When the temperature was decreased to 4 °C the product was isolated in good yield a higher ee (entry 9). A comparison was then made using catalyst **1f** at 30 mol% loading with DABCO (entry 10) and triethylamine (entry 11) at 4 °C with 4 equivalents of **2**. These experiments ascertained that triethylamine worked as a better base than DABCO. The scope of the MBH reaction was then evaluated reacting **2** with different aldehydes employing 20 mol% of **1f** and triethylamine at 4 °C under solvent-free conditions and the results are reported in Table 3.[19]

Cyclic aldehydes were converted into the corresponding allylic alcohols in good yields and fairly good enantioselectivities (entries 1 and 2). A significant decrease of the enantioselectivity and reactivity was observed when using aliphatic aldehydes of decresing steric hindrance (entries 3 and 4).[20] Interestingly, unsaturated *trans*-cinnamaldehyde furnished the product in high yield (entry 5), when compared to the saturated compound (entry 4), but with lower ee.

This protocol afforded good results even with more challenging aromatic aldehydes which were converted into products in high yields and moderate enantioselectivity (entries 6–8).[21] Carrying out the reactions at –8 °C helped to achieve higher ee (entries 1 and 2), especially for challenging benzaldehyde (entry 6), whose product was isolated in respectable 74 yield and 64% ee.[22]

Although more detailed mechanistic investigation is required, the catalyst hydroxyl group might be involved in the proton-transfer step. Indeed, Aggarwal and Lloyd-Jones have recently proposed that acceleration of MBH reaction by protic solvents as methanol, occurs through formal proton transfer from α-keto methine to the alkoxide in the zwitterion mediated by the alcohol.[12b] In our case, the thiourea moiety might be hydrogen-bonded with the carbonyl group of the zwitterionic intermediate and the proton transfer would be accordingly accelerated by the closely located hydroxyl group giving rise to the product and regenerating the catalyst through elimination (Figure 1).

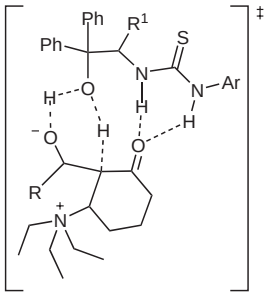
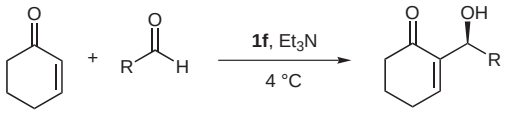
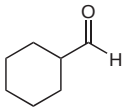
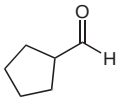
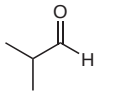
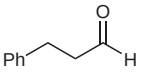
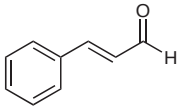
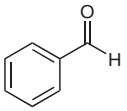
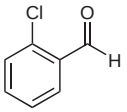
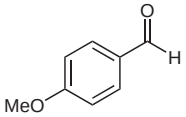


Figure 1 Plausible transition state for the proton-transfer step promoted by amino alcohol derived thioureas

Table 3 Solvent-Free MBH Reaction of **2** with **3** Promoted by **1f** and Triethylamine at 4 °C[a]



2 **3** **4**

Entry	Aldehyde	Time (h)	Yield (%)[b]	ee (%, config)[c,d]
1		122 147	67 61	84 (*S*) 88[e]
2		139 120	67 45	76 (*S*) 81[e]
3		100	89	61 (*S*)
4		142	45	55 (*S*)
5		138	91	36 (*S*)
6[d]		118 119	92 74	57 (*S*) 64[e]
7		119	88	52 (nd)[f]
8		119	86	56 (*S*)

[a] *Conditions*: **3** (0.2 mmol), **2** (0.8 mmol), **1** (0.04 mmol), Et_3N (0.04 mmol).
[b] Isolated yields after flash chromatography.
[c] Determined by HPLC analysis using chiral columns.
[d] Absolute configuration was determined by comparison of optical rotations with those reported in the literature.
[e] The reaction was carried out at –8 °C using 0.3 equiv of **1f** and Et_3N.
[f] Not determined.

In summary, structurally simple monothiourea organocatalysts, readily obtained in one step and high yields from commercially available amino alcohols, have been discovered to promote the asymmetric MBH reaction of 2-cyclohexen-1-one and different aldehydes in the presence of triethylamine. The allylic alcohols were isolated in good to high yields and moderate to high

enantioselectivity. Given the broad variety of amino alcohols commercially available or accessible through asymmetric synthesis, it will be feasible to tune the activity and the enantioselectivity of amino alcohol derived thioureas as organocatalysts for the MBH reaction. Further study to address this issue and the scope of the MBH reaction are under way.

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(14) **Procedure for the Synthesis of Catalysts 1**
To a solution of amino alcohol (0.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise 3,5-bis(trifluoromethyl)phenyl isothiocyanate (92 μL, 0.5 mmol) at 0 °C under N_2. After stirring the reaction mixture for 3–5 h at r.t., the solvent was removed under reduced pressure and residue was purified by flash chromatography (PE–Et_2O, 90:10) to provide **1**.
Spectral data for catalyst **1a**: white solid, mp 145–147 °C; $[\alpha]_D^{20}$ –55.0 (*c* 0.30, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.56 (br s, 1 H), 7.80 (br s, 2 H), 7.67 (s, 1 H), 7.50–7.27 (m, 5 H), 6.91 (br s, 1 H), 5.02 (br s, 1 H), 4.18 (br s, 1 H), 3.65–3.56 (m, 2 H), 3.00 (br s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 180.7, 140.5, 138.9, 132.8, 128.9, 128.6, 125.7, 123.8, 119.4, 76.2, 52.1. IR (neat): 3261, 3066, 1538, 1385, 1278, 1133, 700, 682 cm^{-1}. MS (EI): *m/z* (%) = 271 (100), 213 (37), 202 (58), 163 (30).
Catalyst **1d**: white solid, mp 66–68 °C; $[\alpha]_D^{19}$ –53.8 (*c* 0.34, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.5 (br s, 1 H), 7.70–7.20 (m, 14 H), 6.88 (br s, 1 H), 5.64 (br s, 1 H), 2.95 (br s, 1 H), 1.15 (br s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 178.8, 144.3, 138.4, 133.0, 128.9, 128.7, 127.7, 127.5, 126.0, 125.7, 125.4, 125.2, 123.5, 119.3, 81.3, 56.7, 14.9. IR (neat): 3369, 3062, 1528, 1449,1382, 1278, 1176, 1136, 701, 682 cm^{-1}. MS (EI): *m/z* (%) = 271 (100), 229 (42), 213 (72), 202 (76), 182 (48), 163 (50).
Catalyst **1e**: white solid, mp 66–68 °C; $[\alpha]_D^{20}$ –16.7 (*c* 0.32, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (br s, 1 H), 7.71–7.18 (m, 12 H), 6.92–6.87 (m, 1 H), 5.59 (br s, 1 H), 2.84 (br s, 1 H), 2.04 (br s, 1 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 180.6, 144.9, 144.4, 138.4, 133.9, 128.5, 128.1, 127.3, 125.6, 125.5, 125.3, 125.1, 123.8, 122.8, 119.3, 83.1, 63.4, 29.7, 23.4, 18.4. IR (neat): 3350, 3063, 2963, 1562, 1449, 1277, 1381, 1176, 1135, 703, 683 cm^{-1}. MS (EI): *m/z* (%) = 271 (100), 229 (40), 202 (34), 182 (34), 163 (64).
Catalyst **1f**: white solid, mp 81–83 °C; $[\alpha]_D^{22}$ –251.7 (*c* 0.34, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (br s, 1 H), 7.68–7.59 (m, 3 H), 7.42–7.26 (m, 5 H), 7.15–7.05 (m, 8 H), 7.00–6.95 (m, 2 H), 6.46 (br s, 1 H), 2.76 (br s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 179.3, 143.6, 143.4, 138.3, 136.3, 133.2, 128.9, 128.7, 128.1, 127.9, 127.3, 125.9, 125.5, 123.7, 119.6, 81.7, 64.7. IR (neat): 3255, 3062, 1518, 1449, 1381, 1278, 1176, 1137, 699, 682 cm^{-1}. MS (EI): *m/z* (%) = 271 (100), 213 (34), 202 (28), 163 (42).
Catalyst **1g**: white solid, mp 79–82 °C; $[\alpha]_D^{21}$ –75.1 (*c* 0.33, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (br s, 1 H), 7.64–7.15 (m, 15 H), 7.03–7.00 (m, 2 H), 6.78 (s, 1 H), 5.91 (br s, 1 H), 3.17 (br s, 1 H), 2.85–2.78 (m, 2 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 179.5, 144.2, 138.0, 131.9, 129.5, 128.7, 128.6, 127.5, 127.4, 126.9, 126.4, 125.6, 125.2, 124.0, 122.7, 119.3, 81.8, 60.2, 37.4. IR (neat): 3320, 3063, 1539, 1449, 1383, 1277, 1181, 1135, 701, 681 cm^{-1}.

MS (ESI$^+$): *m/z* (%) = 575 (70) [M + H$^+$], 557 (100) [M – 17]. Catalyst **1h**: white solid, mp 49–51 °C; $[\alpha]_D^{21}$ –8.50 (*c* 0.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (br s, 1 H), 7.67 (s, 1 H), 7.33–7.14 (m, 12 H), 5.84 (br s, 1 H), 5.38 (br s, 1 H), 4.90–4.85 (m, 1 H), 3.93 (d, *J* = 9.9 Hz, 1 H), 1.21 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 179.5, 141.5, 141.1, 138.0, 133.2, 129.0, 128.9, 128.6, 128.3, 128.2, 127.9, 127.2, 127.1, 124.3, 122.7, 119.9, 58.1, 54.2, 19.6. IR (neat): 3063, 1532, 1382, 1279, 1176, 1135, 888, 752, 702 cm^{-1}. MS (ESI$^+$): *m/z* (%) = 483 (100) [M + H$^+$].

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(19) **Typical Procedure for the MBH Reaction**
To a capped vial containing catalyst **1f** (22.4 mg, 0.04 mmol) was added 2-cyclohexen-1-one (78 mL, 0.8 mmol) and Et_3N (4.4 mL, 0.04 mmol). The mixture was stirred for 5 min and then the aldehyde was added (0.2 mmol). After 100–147 h, the reaction was directly purified by flash silica gel chromatography eluting with PE–Et_2O mixtures (98:2 to 80:20) to give a clear oil. Spectral data of allylic alcohols matched those reported in the literature.[2,3,5]

(20) A similar outcome for aliphatic aldehydes was observed in organocatalyzed MBH reaction, see ref. 5a,b, 8, and 9.

(21) The corresponding products are generally obtained in moderate yields and ee, see ref. 5a,b, 8, and 9.

(22) The best result achieved up to now for the allylic alcohol obtained when reacting benzaldehyde and 2-cyclohexen-1-one is 65% yield and 77% ee, see ref. 8b.