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Asymmetric Morita–Baylis–Hillman reactions of 2-cyclohexen-1-one catalyzed by chiral biaryl-based bis(thiourea) organocatalysts

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ABSTRACT

Newly-developed bis(thiourea) **1d** was found to be an efficient organocatalyst for the Morita–Baylis–Hillman reaction. High enantioselectivities were obtained in the reaction of 2-cyclohexen-1-one with both aromatic aldehydes (up to 84% ee) and aliphatic aldehydes (up to 96% ee).

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The Morita–Baylis–Hillman (MBH) reaction catalyzed by organocatalysts is a straightforward method for the synthesis of synthetically useful, functionalized allylic alcohols from simple aldehydes and electron-deficient alkenes. Furthermore, the high atom efficiency of the reaction has been drawing attention in recent years for its exemplification of green chemistry. Thus, the asymmetric version of the MBH reaction has received considerable interest in the field of organic synthesis.[1] In 1999, Hatakeyama and co-workers reported an asymmetric MBH reaction using quinidine-derived chiral bifunctional amino-phenol catalysts.[2] Subsequently, several types of organocatalysts have been developed for asymmetric MBH reactions, but the substrate scopes of these catalysts have proven to be rather limited. For example, BINOL-derived chiral Brønsted acids,[3a,b] chiral bis(thiourea)-bearing 1,2-cyclohexanediamine backbones,[3c,d] chiral amino-thioureas,[3e] chiral bis(thiourea)-bearing isophoronediamine backbones,[3f] and amino alcohol-derived thioureas[3g] have all exhibited high enantioselectivities in reactions of 2-cyclohexen-1-one and aliphatic aldehydes. However, reactions of aromatic aldehydes using the above catalysts have not exceeded 80% ee. In 2008, Shi and Liu reported that enantioselectivities of up to 88% ee were obtained in reactions of aromatic aldehydes with 2-cyclohexen-1-one using chiral bis(thiourea) bearing (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (H8-BINAM) backbones, although reactions with aliphatic aldehydes were not reported.[4a] Quite recently, Bugarin and Connell reported an asymmetric MBH reaction using a chiral DMAP catalyst in the presence of magnesium iodide.[4b] Although reactions of α,β-unsaturated and aromatic aldehydes with 2-cyclopenten-1-one exhibited high enantioselectivities (89–98% ee), reactions of aliphatic aldehydes showed only moderate enantioselectivities (53–63% ee). Other catalysts, such as amino acid-peptide,[5a,b] amino alcohol-proline,[5c,d] phosphinothiourea,[5e,f] brucine N-oxide,[5g] and valine-derived guanidine,[5h] have only been successfully used for the reaction of electron-deficient aromatic aldehydes with methyl vinyl ketone or acrylates. Thus, the development of a new catalyst for MBH reaction with wide applicability is still required.

Nagasawa and co-workers have proposed a transition-state model for the enantioselective MBH reaction of aldehydes and 2-cyclohexen-1-one with bis(thiourea) catalyst bearing chiral cyclohexanediamine backbones: two thiourea groups capture the carbonyl group of enone and enolate, respectively (Fig. 1).[3c,d] We considered the possibility that the substrate specificity of Nagasawa's bis(thiourea) catalyst in the MBH reaction was partially attributable to the relatively rigid structure of the chiral cyclohexanediamine backbone. We expected that a bis(thiourea) organocatalyst derived from a chiral diamine bearing flexible structure might be desirable for wide applicability in this reaction. Based on this working hypothesis, we designed a new class of bis(thiourea)/bis(urea) organocatalysts, **1a–d**, bearing flexible biaryl backbones, expecting that substrates would be captured in appropriate chiral environments by two thiourea/urea parts through double hydrogen bonding, irrespective of the types of substrates involved.

Synthesis of the new organocatalysts **1a–d** started from phenyl 3-chloropropionate (Scheme 1). The Friedel–Crafts reaction and subsequent trifluoromethanesulfonylation of the resulting phenol **2** gave ketone **3**. Ruthenium-catalyzed asymmetric reduction of **3** according to Noyori's procedure[6] gave (*R*)-alcohol **4** with 99% ee.[7] After acetylation of the secondary alcohol, acetate **5** was subjected

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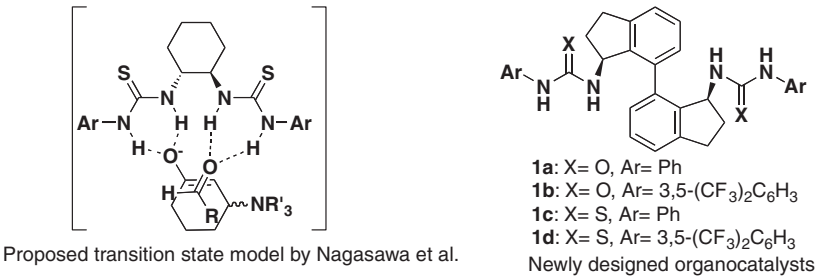
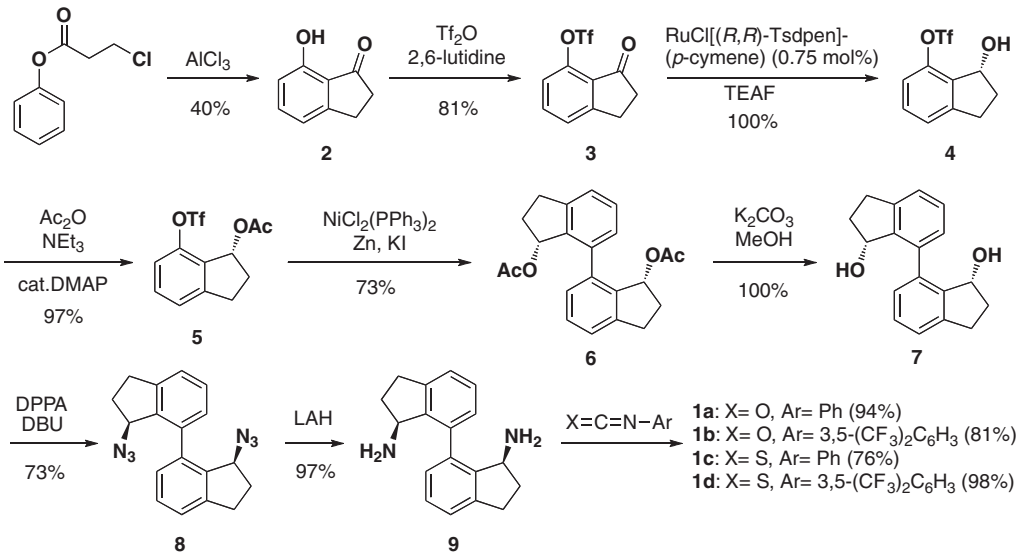
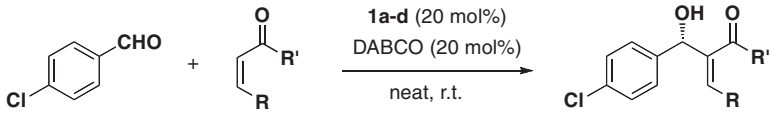


Figure 1. Bis(thiourea)/bis(urea) type organocatalysts.



Scheme 1. Synthesis of catalysts **1a–d**.

Table 1
Enantioselective MBH reaction using **1a–d** as catalysts[a]

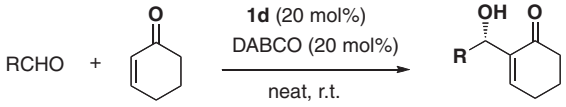


Entry	Catalyst	Enone	Time (h)	Yield (%)	% ee	Confign. [b]
1	**1a**	2-Cyclohexen-1-one	96	53	48[c]	*S*
2	**1b**	2-Cyclohexen-1-one	96	44	70[c]	*S*
3	**1c**	2-Cyclohexen-1-one	96	30	40[c]	*S*
4	**1d**	2-Cyclohexen-1-one	25	87	83[c]	*S*
5[d]	**1d**	2-Cyclohexen-1-one	96	86	82[c]	*S*
6[e]	**1d**	2-Cyclohexen-1-one	48	80	75[c]	*S*
7	**1d**	2-Cyclopenten-1-one	96	33	65[f]	*S*
8	**1d**	3-Buten-2-one	21	44	10[f]	*S*

[a] All reactions were carried out at room temperature with molar ratios of aldehyde/enone/**1a–d**/DABCO = 1:3:0.2:0.2, unless otherwise indicated.
[b] Determined by chiroptical comparison with the reported value (Refs. 4a and 5e).
[c] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralcel OD-H; hexane/*i*-PrOH = 95:5).
[d] Reaction was performed at 0 °C.
[e] Reaction was performed at 40 °C.
[f] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AS-H; hexane/*i*-PrOH = 90:10).

to a nickel-mediated homo-coupling reaction to give biaryl **6**. Deacetylation using K_2CO_3/MeOH gave diol **7**. Azidation of diol **7** with SN2 inversion was performed according to Shioiri's procedure[8] using diphenylphosphoryl azide (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). LAH reduction of the resulting diazide **8** gave diamine **9**. Enantiomeric purity of diamine **9** was determined to be >99% ee by HPLC analysis using chiral stationary phase column. Finally, diamine **9** was converted into the desired

Table 2
Enantioselective MBH reaction of aldehydes and 2-cyclohexen-1-one with **1d** as a catalyst[a]



Entry	*R* in RCHO	Time (h)	Yield (%)	% ee[b]
1	Phenyl	96	86	81
2	4-Methoxyphenyl	96	48	80
3	4-Fluorophenyl	43[c]	78	83
4	4-Nitrophenyl	10[c]	51	62
5	3-Chlorophenyl	96	54	78
6	3-Fluorophenyl	96	80	84
7	2-Phenylethyl	96	70	84
8	*n*-Hexyl	10[c]	54	86
9	*i*-Propyl	10[c]	61	96
10	*c*-Hexyl	10[c]	71	96
11[d]	*c*-Hexyl	18[c]	69	96

[a] All reactions were carried out at room temperature with molar ratios of aldehyde/enone/**1d**/DABCO = 1:3:0.2:0.2 unless otherwise indicated.
[b] Determined by HPLC analysis using chiral stationary phase column according to the literature (Refs. 3d–f and 4a).
[c] All the substrate was consumed.
[d] 10 mol % of **1d** was used.

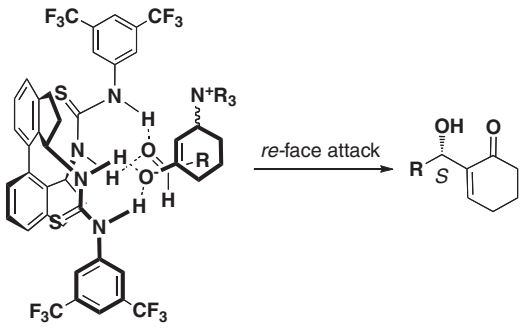


Figure 2. Possible transition state model for MBH reaction with **1d**.

bis(urea) **1a,b** and bis(thiourea) **1c,d** by treatment with isocyanate or isothiocyanate.

With chiral catalysts **1a–d** in hand, we first examined the reaction of 4-chlorobenzaldehyde with 2-cyclohexen-1-one without solvent at room temperature in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) and **1a–d** (Table 1). Reaction with bis(urea) **1a** showed a low chemical yield and enantioselectivity, while that with bis(urea) **1b** bearing trifluoromethyl groups on phenyl groups showed moderate enantioselectivity, although the chemical yield was still low (entries 1 and 2). Alternatively, bis(thiourea) **1c** was a less efficient catalyst in terms of chemical yield and enantioselectivity (entry 3). High enantioselectivity and chemical yield (83% ee, 87%) were obtained in the reaction with bis(thiourea) **1d** (entry 4).[9] With **1d**, we also examined the effect of temperature, but neither lowering nor raising the reaction temperature improved enantioselectivity (entries 5 and 6). Reactivity and/or enantioselectivity was also largely dependent on the structure of enone. The use of other enones instead of 2-cyclohexen-1-one resulted in a significant drop in chemical yield and enantioselectivity (entries 7 and 8).

To explore the scope of the present MBH reaction, we next examined the reactions of several other aldehydes with bis(thiourea) **1d** as a catalyst (Table 2). Equally high enantioselectivities, around 80% ee, were obtained, irrespective of the electronic nature of the aryl substituent, except for 4-nitrobenzaldehyde (entries 1–6). As we expected, the reactions of aliphatic aldehydes also showed high enantioselectivities (entries 7–10). In particular, excellent enantioselectivity (96% ee) was obtained in the reaction of cyclohexanecarboxaldehyde (entry 10).[10] It is noteworthy that the amount of the catalyst could be reduced to 10 mol % without diminishing enantioselectivity (entry 11).

Absolute configuration of all the products was determined to be *S*.[3d–f,4a] The observed stereochemistry can be explained by the transition state model, in which the re-face of aldehyde was preferentially attacked by the enolate (Fig. 2). However, further study is required to fully understand the mechanism of asymmetric induction.

In conclusion, we have demonstrated that the newly developed bis(thiourea) **1d** is an efficient chiral organocatalyst for asymmetric MBH reaction. To the best of our knowledge, this is the first example of high enantioselectivities in the reactions of 2-cyclohexen-1-one with both aromatic and aliphatic aldehydes using the same organocatalyst. Further studies on the scope of the reaction and clarification of the reaction mechanism are under way in our laboratory.

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7. Absolute configuration of alcohol **4** was determined by comparison of elution order of HPLC with the reported value (Ref. 6) after its conversion to known 1-indanol by hydrogenation.
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9. Reactions using other bases for this reaction gave less satisfactory results (DMAP: 96 h, 47% yield, 39% ee, imidazole: 96 h, 2% yield, 58% ee).
10. *Typical experimental procedure is exemplified by MBH reaction of cyclohexanecarboxaldehyde with 2-cyclohexen-1-one:* To a mixture of **1d**

(32.3 mg, 40.0 μmol), DABCO (4.5 mg, 40.0 μmol) and cyclohexanecarboxaldehyde (24 μl, 0.2 mmol) was added 2-cyclohexen-1-one (58 μl, 0.6 mmol) at room temperature. After being stirred for 10 h at the temperature, the mixture was directly subjected to silica gel chromatography (hexane-acetone = 100:0–90:10) and gave the desired product (29.4 mg, 71%). Enantiomeric excess of the product was determined to be 96% by HPLC using chiral stationary phase column (Ref. 3d). The specific rotation of the product was $[\alpha]_D^{26} = -67.4$ (c 1.00, $CHCl_3$). ^{1}HNMR (400 MHz, DMSO-d_6) of **1d**: δ = 1.67–1.72 (m, 2H), 2.44–2.47 (m, 2H), 2.74–2.81 (m, 2H), 2.90–2.96 (m, 2H), 6.33 (d, J = 7.8 Hz, 2H), 6.97–7.00 (m, 4H), 7.09 (t, J = 7.3 Hz, 2H), 7.64 (s, 2H), 7.80–7.91 (m, 6H), 9.09 (s, 2H).