Tetrahedron 64 (2008) 9423–9429

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Thiourea-catalyzed Morita–Baylis–Hillman reaction

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ARTICLE INFO

Article history:
Received 13 June 2008
Received in revised form 19 July 2008
Accepted 21 July 2008
Available online 26 July 2008

Keywords:
Bis-thiourea
Organocatalyst
Morita–Baylis–Hillman
Enantioselective reaction

ABSTRACT

Here, we describe our studies on the thiourea-catalyzed Morita–Baylis–Hillman (MBH) reaction. Chemoselective activation of carbonyl compounds via hydrogen bonding to thiourea as a catalyst is the key to drastic rate acceleration of this reaction. The application of chiral bis-thiourea-type organocatalysts, which can form a chiral double hydrogen-bonding network, is effective for enantioselective MBH reaction. A cooperative system of bis-thiourea compounds, synthesized from 1,2-diaminocyclohexane, and a Lewis base effectively promotes the MBH reaction at lower temperature, affording the MBH adducts in 33–95% yield with 44–90% ee. A plausible transition state model of the enantioselective MBH reaction is presented.

1. Introduction

Asymmetric catalytic reactions are a central topic in modern synthetic chemistry.[1] Since we reported catalytic enantioselective alkylation with chiral pentacyclic guanidine organocatalysts,[2,3] inspired by biologically active natural products,[4,5] we have continued to explore chiral hydrogen-bonding donors as asymmetric organocatalysts.[6–10] To promote the bond-forming process more effectively by means of synergistic proximity,[11] we have recently been focusing on the design of chiral hydrogen-bonding networks constituted from multiple hydrogen donors linked by a chiral spacer (Fig. 1). The highly tunable properties of such catalysts with respect to active sites, chiral spacer, and external bases have been utilized by us facilitate various classes of catalytic asymmetric bond-forming reactions.[9] Here, we describe our studies on catalytic enantioselective Morita–Baylis–Hillman (MBH) reaction.

MBH reaction is a versatile carbon–carbon bond-forming reaction for the synthesis of densely functionalized compounds from aldehydes and electron-deficient alkenes in the presence of Lewis bases such as tri-substituted phosphines and tertiary amines.[12,13] Attracted by the complexity of the reaction sequences[14] and the great potential utility of the products as chiral building blocks,[15] researchers have examined various approaches to make the reaction more efficient. The development of an asymmetric version of the reaction utilizing chiral catalysts is also of ongoing interest.[16–19] The first catalytic highly enantioselective MBH reaction with β-isocupredine (β-ICD) was reported by Hatakeyama's group in 1999.[16] Following their mechanistic proposals, enormous efforts have been devoted to the exploration of asymmetric Lewis base catalysts.[17] Only two precedents utilizing chiral Brønsted acid/Lewis base co-catalytic approaches had been reported by Ikegami's group[18a] and Schaus' group[18b] before our strategy was developed.[9b] Taking advantage of the ability of thiourea compounds to activate carbonyl compounds,[9a,20] we commenced a project to develop thiourea-catalyzed MBH reaction as a new approach in this field.[21] Herein, we describe (1) drastic rate acceleration of the MBH reaction by thiourea compounds, (2) design and development of bis-thiourea organocatalysts **1** (Fig. 2), leading to availability of the enantioselective MBH reaction, and (3) a possible mechanism for the rate enhancement and a plausible transition state model for enantioselective MBH reaction.

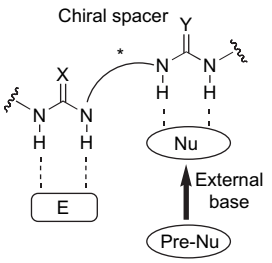

Figure 1. Our concept for catalyst design.

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doi:10.1016/j.tet.2008.07.087

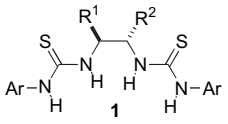


Figure 2. The structure of bis-thiourea organocatalysts **1**.

2. Results and discussion

2.1. Achiral diarylthiourea-catalyzed MBH reaction

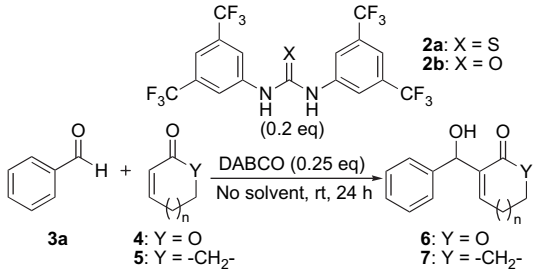
Since the MBH reaction is notoriously prone to be sluggish, selection of a suitable catalyst core to activate reaction components without decreasing the nucleophilicity of the Lewis base is particularly important. We previously reported that (thio)urea compounds can enhance the aza-Michael reaction of α,β-unsaturated carbonyl compounds with pyrrolidine.[9a] Based on those findings we planned to apply the (thio)urea compounds to catalytic MBH reaction via a tandem reaction sequence: aza-Michael, aldol, and elimination.[14] We hypothesized that if (thio)urea compounds could chemoselectively activate both aldehydes and Michael acceptors through double hydrogen-bonding interactions, the LUMO energy of the carbonyl group should decrease in each step, thereby resulting in rate acceleration of the reaction (Fig. 3).

We initially focused on the screening of suitable electrophiles in the presence of diaza[2.2.2]bicyclooctane (DABCO) (25 mol %) under solvent-free conditions.[22] The results with Schreiner's catalyst **2** (20 mol %)[20e] for the reaction of benzaldehyde (**3a**) with several electrophiles are summarized in Table 1. As we expected, significant rate enhancement was observed when both lactones **4** and cyclic enones **5** were used as substrates (entries 1–12). Among the electrophile investigated, cyclohexen-1-one (**5a**) gave promising results in terms of rate enhancement over the non-catalyzed reaction. When we examined the MBH reaction of **3a** with **5a**, the product was isolated in only 1% yield (entry 7). In contrast, addition of biarylthiourea **2a** gave the MBH adduct in 60% yield.[23]

To obtain structural insight into the catalytic activity of biarylthiourea **2a**, we performed experiments with structural variants (Fig. 4). Removal of the trifluoromethyl groups on the aromatic rings drastically decreased the reaction rate, suggesting the importance of electron-withdrawing groups to increase the acidity for catalytic activity. Since guanidinium salt **8** showed lower reactivity, the thiourea functionality appeared to be more effective than the corresponding guanidinium salt for carbonyl group activation. These observations are consistent with findings for the aza-Michael reaction,[9a] supporting the utility of a chemoselective carbonyl activation strategy for catalytic MBH reaction.

Crucial roles of hydrogen donors of **2a** were indicated by the results of ^{1}H NMR studies with reaction components and the corresponding MBH product (Table 2). As shown in Table 2, the ^{1}H

Table 1
MBH reaction using **2**



Entry	Catalyst	Substrate	Product	Yield[a] (%)
1	None		**6aa**	26
2	**2a**		**6aa**	62
3	**2b**		**6aa**	58
		4a		
4	None		**6ab**	1
5	**2a**		**6ab**	25
6	**2b**		**6ab**	15
		4b		
7	None		**7aa**	1
8	**2a**		**7aa**	60
9	**2b**		**7aa**	52
		5a		
10	None		**7ab**	3
11	**2a**		**7ab**	16
12	**2b**		**7ab**	38
		5b		

[a] Isolated yield.

NMR spectrum of a 1:1 mixture of **2a** and each substrate showed a downfield shift of N–*H* in **2a**, confirming the carbonyl group activation through hydrogen-bonding interaction between thiourea **2a** and the substrates. These observations strongly suggest that thiourea catalyst **2a** would promote all the expected reaction sequences, i.e., (1) aza-Michael reaction, (2) aldol reaction, and (3) elimination (Fig. 3).

2.2. Development of bis-thiourea organocatalyst for enantioselective MBH reaction

We next attempted to extend our strategy to develop an enantioselective variant of the reaction. Based on our proposed reaction mechanism (Fig. 3), we postulated that if two active sites were linked with a suitable chiral spacer, the carbon–carbon bond-forming process would take place more effectively owing to

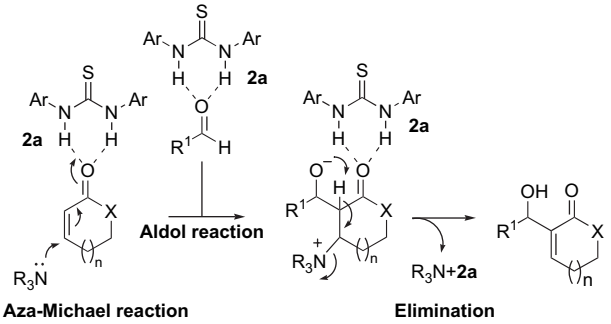


Figure 3. Working model of **2a**-catalyzed Morita–Baylis–Hillman reaction.

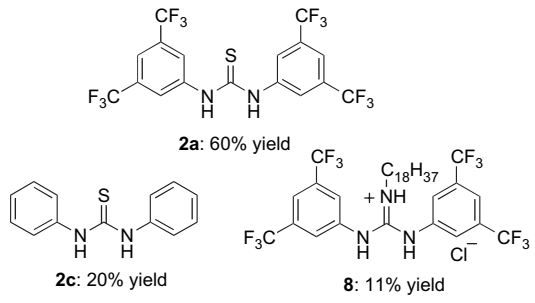


Figure 4. Reaction of **3a** and **5a** was conducted in the presence of **2a**, **2c**, and **8** under the same conditions as described in Table 1.

Table 2
Effect of **3a**, **5a**, and **7aa** on the ^{1}H NMR signal of N–H in **2a**

Entry	Substrate	N–*H* in **2a** (ppm)
1	None	7.90
2	**3a**	8.30
3	**5a**	8.73
4	**7aa**	8.40

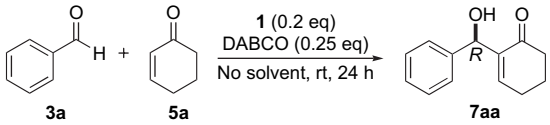
proximity effects, and simultaneously, asymmetric induction might be achieved. These speculations led us to prepare several types of chiral catalysts **1** having two thiourea functionalities (Fig. 5). The obvious advantages of the designed catalysts are facile synthesis and potent stereochemical diversity.[18e,f] The bis-thiourea compounds **1** can be easily prepared from isothiocyanate and chiral diamine simply by mixing them in THF and recrystallizing the product, without silica-gel column chromatography. With these thiourea compounds **1** in hand, the coupling reaction of benzaldehyde (**3a**) and cyclohexen-1-one (**5a**) was examined under the same conditions as described in Table 1 (Table 3).

Our investigation of the enantioselective MBH reaction revealed that cyclohexanediamine was one of the most suitable chiral spacers; **1a** gave **7aa** with 33% ee, favoring (*R*) configuration. It is interesting to note that bis-thiourea **1a** gave a greater rate-enhancing effect than biarylthiourea **2a** (**1a**; 72% vs. **2a**: 60%), although the H-bonding ability of **1a**, linked with a chiral spacer, should be less than that of **2a**. Compound **1b**, having a flexible chain-type chiral backbone, afforded the corresponding MBH product in 51% yield with 11% ee (entry 2). The unsymmetric thiourea **1c** gave unsatisfactory results in terms of selectivity (entry 3; 47% yield, 5% ee). The existence of the hypothetical proximity effect of two thiourea functionalities in **1a** was supported by experiments with the structural variant **1d** (entries 4 and 5). Monothiourea compound **1d** had significantly lower catalytic activity than **1a**, even with a higher catalyst loading (entry 5).

In the bis-thiourea **1a**-catalyzed MBH reaction, the Lewis base had a great influence on enantioselectivity, as shown in Table 4.[24] When we used phosphine, triazole, and triazine derivatives, almost no reaction occurred (entries 1–5). In the case of imidazole, the enantiomeric excess increased to 61% ee even at room temperature, although the yield was low (entry 8). On the other hand, a cooperative system of bis-thiourea **1a** and DMAP resulted in a smooth MBH reaction, giving **7aa** in 90% yield, with 22% ee (entry 12). Decreasing the temperature affected the reaction rate and slightly improved the selectivity (entry 13). As shown in entry 14, addition of MS4A was effective to increase the reactivity without loss of enantioselectivity.

Encouraged by these preliminary results, we examined the scope of substrates with the cooperative system of C_2 symmetric chiral thiourea compound **1a** and Lewis base (Table 5). We examined the feasibility of enantioselective MBH reaction of various aldehydes **3** with cyclic enones **5** by using 0.4 equiv of **1a** and Lewis base, respectively. In this system, high reactivity was consistently obtained when aromatic (entries 1–4) or aliphatic aldehydes including linear (entries 5–7), branched (entries 8–10) and cyclic compounds (entries 11–14) were used as electrophiles. As shown in

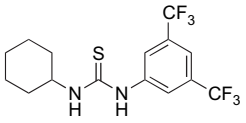
Table 3
MBH reaction using bis-thioureas **1**



3a **5a** **7aa**

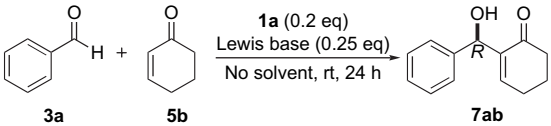
Entry	Thiourea	Yield[a] (%)	ee[b,c] (%)
1	**1a**	72	33
2	**1b**	51	11
3	**1c**	47	5
4	**1d**	20	—
5[d]	**1d**	46	—

[a] Isolated yield.
[b] ee values were determined by HPLC using a chiral column.
[c] Absolute stereochemistry of **7aa** was determined by comparison of $[\alpha]_D$ value with that reported by Schaus.[18b]
[d] 0.4 equiv of **1d** was used.



1d

Table 4
Enantioselective MBH reaction with various Lewis bases



3a **5b** **7ab**

Entry	Lewis base	Yield[a] (%)	ee[b] (%)
1	Ph_3P	Trace	—
2	*n*-Bu_3P	Trace	—
3	1*H*-1,2,4-Triazole	Trace	—
4	1*H*-1,2,3-Triazole	Trace	—
5	1,3,5-Triazine	Trace	—
6	1-Metylpyrrolidine	43	29
7	1,4-Dimethylpiperazine	9	31
8	Imidazole	10	61
9	*N*-Methylimidazole	10	47
10	Et_3N	49	30
11	*i*-Pr_2NEt	6	10
12	DMAP	90	22
13[c]	DMAP	25	33
14[c,d]	DMAP	45	33

[a] Isolated yield.
[b] ee values were determined by HPLC using chiral column.
[c] −10 °C.
[d] MS4A was added.

entries 1 and 3, the cooperative procedure with **1a** and DMAP smoothly enhanced the MBH reaction of aromatic aldehydes to give the corresponding MBH adducts even at subzero temperature with moderate ee (entry 1; 42% ee, entry 3; 33% ee). The use of imidazole instead of DMAP significantly improved the selectivity, giving the corresponding MBH products with 44–57% ee, although the reactivity was decreased (entries 2 and 4). In these bis-thiourea/

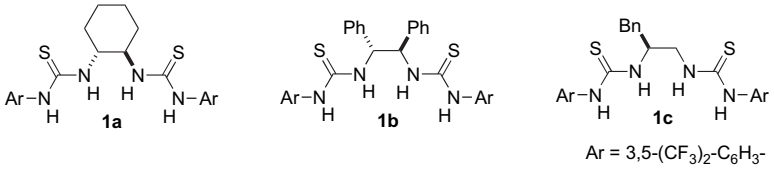
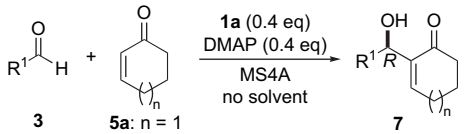
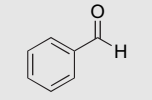
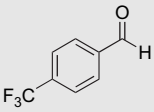
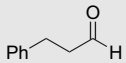
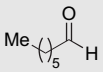
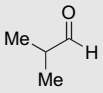
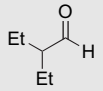
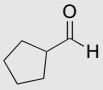
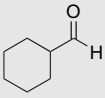


Figure 5. Structures of bis-thioureas **1a**, **1b**, and **1c**.

Table 5
Enantioselective MBH reaction with **1a**



Entry	Aldehyde	Enone	Temp (°C)	Time (h)	Product	Yield[a] (%)	ee[b,c] (%)
1	 **3a**	**5a**	−10	48	**7aa**	88	42
2[d]		**5a**	rt	120	**7aa**	40	57
3	 **3b**	**5a**	−5	72	**7ba**	99	33
4[d]		**5a**	4	120	**7ba**	95	44
5	 **3e**	**5a**	−5	72	**7ea**	33	59
6	 **3f**	**5a**	−5	72	**7fa**	63	60
7		**5b**	−20	48	**7fb**	50	56
8	 **3g**	**5a**	−5	72	**7ga**	67	60
9	 **3h**	**5a**	−5	72	**7ha**	53	72
10		**5b**	−40	72	**7hb**	55	70
11	 **3i**	**5a**	−5	72	**7ia**	55	86
12		**5b**	−40	48	**7ib**	62	75
13	 **3j**	**5a**	−5	72	**7ja**	72	90
14		**5b**	−40	48	**7jb**	71	85

[a] Isolated yield.
[b] ee values was determined by HPLC using a chiral column.
[c] Absolute stereochemistry of new products was determined by Sharpless epoxidation method.[18b]
[d] 0.4 equiv of imidazole was used as Lewis base.

imidazole co-catalyzed reactions of aromatic aldehydes, the C–C bond-forming process might take place predominantly through expected dual activation mode. It is noteworthy that aliphatic aldehydes having an enolizable carbonyl group gave only MBH adducts without generating self-aldol products (entries 5–14). Linear aldehydes afforded the MBH products with 59–60% ee (entries 5 and 6). In the present system, the five-membered enone **5b** was more reactive than **5a**, and the reaction was performed at −20 °C to give **7fb** with 56% ee. The ee values increased as the bulk at the α-position of the carbonyl group in **3** was increased (entries 8–14). α-Substituted aldehydes gave the products with 60–72% ee (entries 8–10). When this system was applied to cyclic aldehydes, the ee values reached up to 90% ee (entries 11–14). Thus, we have developed new enantioselective MBH reaction with a bis-thiourea/Lewis base co-catalytic system. Further improvement of the catalytic efficiency is under investigation.

2.3. Hypothetical transition state model

The origin of stereodiscrimination was examined by ^{1}H NMR analysis. As shown in Figure 6, complexation with (*R*,*R*)-**1a** and (*R*)-**7ga** (60% ee) caused significant splitting of the isopropyl signals of **7ga**. The observation that only the matched (*R*)-product showed a downfield shift with (*R*,*R*)-catalyst suggests the existence of interaction between the newly generated secondary alcohol moiety in (*R*)-**7ga** and thiourea functionality in (*R*,*R*)-**1a** (**III** in Scheme 1). Our hypothetical dual activation mode in the transition state can explain the results and the stereodiscrimination process. In the mechanism outlined in Scheme 1, two thiourea functionalities coordinate to the carbonyl groups of the aldehyde and enolate, respectively.[25] Substituent (R^1) in the aldehyde favors an *anti* relationship to avoid disrupting the hydrogen-bonding interaction between thiourea and enolate. We considered that carbonyl group activation by a thiourea functionality in **II** leads to rapid and irreversible elimination of tertiary amine, which is currently considered to be the rate-determining step,[14] to generate complex **III**. Thus, (*R*)-**7** should be produced as the major product. This model is consistent with previously proposed transition states in guanidinium/thiourea-catalyzed asymmetric nitroaldol reactions developed by our group.[9c–g]

3. Conclusions

We have developed a new approach to the MBH reaction utilizing a cooperative system of thiourea catalyst and Lewis base. First, basic methodology for the MBH reaction using achiral biarylthiourea was explored, and drastic rate acceleration was achieved. Second, based on mechanistic studies of the racemic version of the reaction, we developed novel bis-thiourea-type organocatalysts, which permit enantioselective MBH reaction. These two-center organocatalysts can be classified as homo-bifunctional organocatalysts in our proposed catalyst framework. Third, NMR studies yielded several mechanistic insights, and we propose a plausible transition state for thiourea-catalyzed MBH reaction. Precise mechanistic studies aimed at improving the catalyst efficiency in the enantioselective version of this reaction are ongoing. Further efforts to apply our concept to other classes of asymmetric C–C bond-forming reaction are also in progress.

4. Experimental

4.1. General

Flash chromatography was performed using Silica gel 60 (spherical, particle size 0.040–0.100 mm; Kanto Co., Inc., Japan). Optical rotations were measured with a JASCO DIP polarimeter 370. IR spectra were measured with JASCO VALOR-III FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL300 or JEOL JMN-EX400 or JEOL ALPHA500 instrument. Mass spectra were recorded on JEOL JMA-HX110 spectrometer.

4.2. Typical procedure for synthesis of bis-thiourea 1

To a solution of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (866 mg, 7.58 mmol) in THF (10 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (2.77 mL, 15.2 mmol) at 0 °C, and the mixture was stirred for 10 min. After warming to room

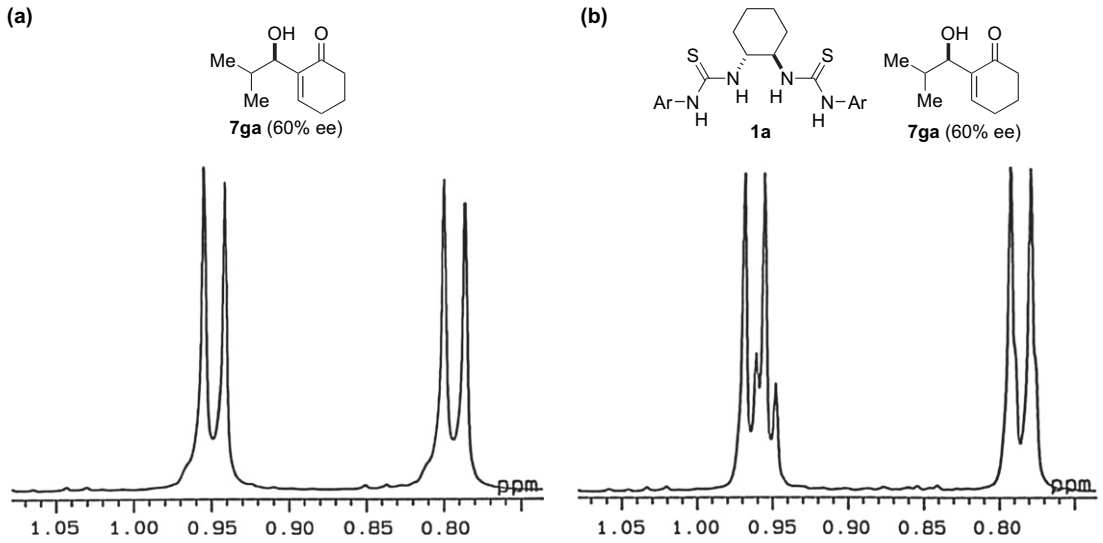


Figure 6. ^{1}H NMR spectra ($CDCl_3$) showing the methyl signals of **7ga**. (a) without **1a**. (b) **7ga**: **1a**=1:1 mixture.

temperature, the reaction mixture was stirred for 22 h and concentrated in vacuo. The residue was recrystallized from ethyl acetate–hexane to give **1a** (4.68 g, 94%) as a white solid.

*4.2.1. Bis-thiourea **1a***

Mp=132–133 °C (decomposition). $[\alpha]_D^{25}$ −60.6 (*c* 1.0, $CHCl_3$). IR (KBr) 3357, 3280, 3065, 2950, 1688, 1573, 1473, 1389, 1279, 1189, 1124 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (br s, 2H), 7.81 (s, 4H), 7.69 (s, 2H), 7.07 (br s, 2H), 4.38 (br s, 2H), 2.20 (br s, 2H), 1.81 (br s, 2H), 1.35 (br s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 138.6, 132.8 (J_{CF}=33.1 Hz), 124.1 (br), 122.7 (J_{CF}=273.1 Hz), 119.7 (br), 59.5, 31.7, 24.4. HRMS (FAB, M+H) calcd for $C_{24}H_{21}F_{12}N_4S_2$ 657.1016, found 657.1031.

*4.2.2. Bis-thiourea **1b***

White solid. Mp=185–186 °C (decomposition). $[\alpha]_D^{25}$ −57.4 (*c* 1.0, $CHCl_3$). IR (KBr) 3300, 3111, 2940, 2864, 1644, 1582, 1471, 1446, 1388, 1283, 1230, 1181, 1130 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (br s, 2H), 7.72 (s, 4H), 7.70 (s, 2H), 7.51 (br s, 2H), 7.25–7.16 (m, 10H), 6.01 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, 138.4, 136.8, 133.0 (J_{CF}=33.1 Hz), 129.1, 128.7, 127.6, 124.0 (br), 122.6 (J_{CF}=273.1 Hz), 119.8 (br), 64.9. HRMS (FAB, M+H) calcd for $C_{32}H_{23}F_{12}N_4S_2$ 755.1173, found 755.1174.

*4.2.3. Bis-thiourea **1c***

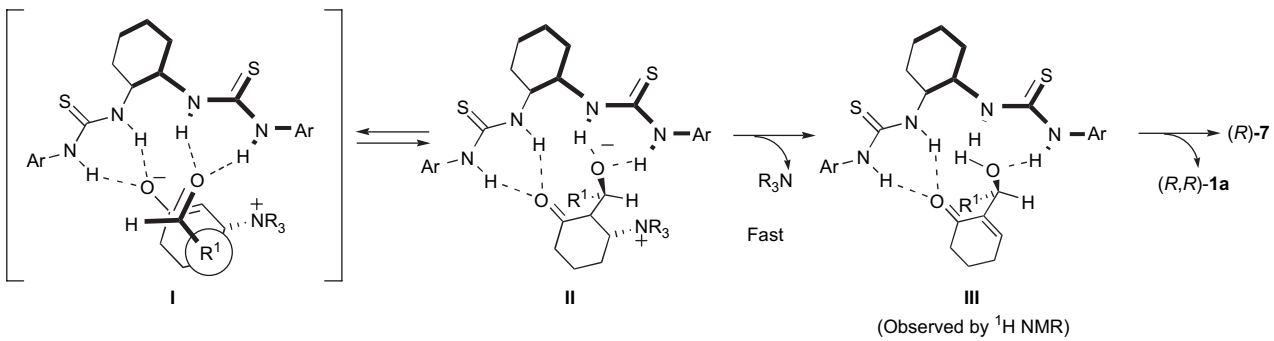
$[\alpha]_D^{25}$ −30.4 (*c* 1.5, CD_3OD). IR (neat) 3231, 1543, 1471, 1381, 1278, 1175, 1133 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 2H), 8.06 (s, 2H), 7.59 (s, 1H), 7.58 (s, 1H), 7.34–7.21 (m, 5H), 5.13 (br s, 1H), 4.06 (br s, 1H), 3.73 (br d, *J*=11.9 Hz, 1H), 3.30 (br, 2H). ^{13}C NMR (125 MHz, CD_3OD) δ 183.5, 182.9, 142.8, 142.7, 138.9, 132.7 (J_{CF}=33.1 Hz), 130.3, 129.6, 127.7, 124.7 (J_{CF}=273.1 Hz), 124.0 (br), 118.11, 57.0, 39.3. HRMS (FAB, M+H) calcd for $C_{27}H_{21}F_{12}N_4S_2$ 693.1016, found 693.1014.

4.3. Typical procedure for enantioselective Baylis–Hillman reaction

To a mixture of 2-cyclohexene-1-one (**5a**) (150 μL, 1.60 mmol), bis-thiourea catalyst **1a** (210 mg, 0.320 mmol), DMAP (39.1 mg, 0.320 mmol), and MS4A was added cyclohexanecarboxaldehyde (**3j**) (97.0 μL, 0.800 mmol) at −5 °C. The resulting mixture was stirred vigorously at −5 °C for 72 h. Then saturated NH_4Cl_{aq} was added, and the organic layer was extracted with ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=8/1, 2/1) to give **7ja** (119 mg, 72%). The enantiomeric excess of **7ja** (90% ee) was determined by the use of chiral HPLC analysis. (Chiralcel OB-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/2-propanol=99/1, 1.0 mL/min, (*R*) major; 13.5 min, (*S*) minor; 14.7 min). $[\alpha]_D^{24}$ +50.2 (*c* 1.03, $CHCl_3$). Characterization and spectroscopic data were in agreement with literature.[18b]

*4.3.1. **7ba** (Table 5, entry 3)*

Colorless oil. $[\alpha]_D^{23}$ −1.4 (*c* 0.80, benzene, 33% ee). IR (neat) 3424, 2952, 1666, 1415, 1376, 1326, 1258, 1164, 1121, 1067, 1017 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J*=8.1 Hz, 2H), 7.48 (d, *J*=8.1 Hz, 2H), 6.77 (t, *J*=4.1 Hz, 1H), 5.58 (d, *J*=4.7 Hz, 1H), 3.54 (d, *J*=5.6 Hz, 1H), 2.47–2.39 (m, 4H), 2.00 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$)



Scheme 1. Plausible transition state of (*R*,*R*)-**1a**-catalyzed MBH reaction.

δ 200.3, 145.8, 140.5, 126.7 (br), 125.2 (J_{CF}=4.1 Hz), 122.0 (J_{CF}=271.0 Hz), 72.2, 38.5, 25.7, 21.4. HRMS (FAB, M+H) calcd for $C_{14}H_{14}F_3O_2$ 271.0946, found 271.0970. HPLC (Chiralcel OB-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/2-propanol=75/5, 0.8 mL/min, (*S*) minor; 13.1 min, (*R*) major;14.8 min).

4.3.2. ***7fa*** *(Table 5, entry 6)*

Colorless oil. $[\alpha]_D^{23}$ +17.6 (*c* 0.87, $CHCl_3$, 60% ee). IR (neat) 3430, 2925, 2857, 1668, 1456, 1380, 1278, 1172, 1136 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (t, *J*=4.3 Hz, 1H), 4.27 (br, 1H), 2.87 (br s, 1H), 2.45–2.38 (m, 4H), 2.00 (m, 2H), 1.61 (m, 2H), 1.40–1.25 (m, 8H), 0.87 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 145.7, 140.9, 71.8, 38.7, 36.2, 31.8, 29.1, 26.0, 25.7, 22.6 (br), 14.1. HRMS (FAB, M+H) calcd for $C_{13}H_{23}O_2$ 211.1698, found 211.1731. HPLC (Chiralcel OD-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/2-propanol=99/1, 1.0 mL/min, (*R*) major; 18.3 min, (*S*) minor; 22.6 min).

4.3.3. ***7fb*** *(Table 5, entry 7)*

Colorless oil. $[\alpha]_D^{25}$ +3.1 (*c* 0.98, $CHCl_3$, 55% ee). IR (neat) 3274, 2927, 2856, 1691, 1629, 1520, 1366, 1279, 1173, 1137 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 4.43 (t, *J*=6.4 Hz, 1H), 2.62–2.61 (m, 2H), 2.45–2.43 (m, 2H), 1.69–1.64 (m, 2H), 1.47–1.42 (m, 1H), 1.33–1.25 (m, 7H), 0.87 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 157.8, 147.8, 67.9, 35.8, 35.2, 31.8, 29.1, 26.6, 25.4, 22.6, 14.1. HRMS (FAB, M+H) calcd for $C_{12}H_{21}O_2$ 197.1542, found 197.1537. HPLC (Chiralcel OD-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/2-propanol=98/2, 1.0 mL/min, (*R*) major; 30.9 min, (*S*) minor; 38.2 min).

4.3.4. ***7ha*** *(Table 5, entry 9)*

Colorless oil. $[\alpha]_D^{25}$ +5.9 (*c* 0.31, $CHCl_3$, 72% ee). IR (neat) 3447, 2959, 2873, 1667, 1459, 1378, 1172, 1138 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (t, *J*=4.0 Hz, 1H), 4.12 (d, *J*=6.7 Hz, 1H), 2.45–2.40 (m, 2H), 2.04–1.95 (m, 2H), 1.59–1.52 (m, 4H), 1.42–1.35 (m, 1H), 1.25–1.17 (m, 2H), 0.88–0.84 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 146.9, 139.8, 74.6, 44.8, 38.9, 25.8, 22.5, 22.3, 20.4, 10.9, 10.6. HRMS (FAB, M+H) calcd for $C_{12}H_{21}O_2$ 197.1542, found 197.1508. HPLC (Chiralcel OD-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/ethanol=98/2, 0.8 mL/min, (*R*) major; 6.7 min, (*S*) minor; 7.7 min).

4.3.5. ***7hb*** *(Table 5, entry 10)*

Colorless oil. $[\alpha]_D^{25}$ +32.5 (*c* 1.01, $CHCl_3$, 70% ee). IR (neat) 3438, 2962, 2931, 2875, 1694, 1464, 1382, 1279, 1179, 1136 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.43 (m, 1H), 4.44 (d, *J*=5.8 Hz, 1H), 2.64–2.62 (m, 2H), 1.57–1.25 (m, 5H), 0.90 (t, *J*=7.5 Hz, 3H), 0.88 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 159.0, 146.7, 70.0, 45.2, 35.3, 26.6, 22.1, 20.6, 11.4, 11.2. HRMS (FAB, M+Na) calcd for $C_{11}H_{18}O_2$ Na 205.1204, found 205.1234. HPLC (Chiralcel OD-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/2-propanol=98/2, 1.0 mL/min, (*R*) major; 14.9 min, (*S*) minor; 17.8 min).

4.3.6. ***7ia*** *(Table 5, entry 11)*

Colorless oil. $[\alpha]_D^{23}$ +38.2 (*c* 0.96, $CHCl_3$, 85% ee). IR (neat) 3438, 2950, 2867, 1666, 1381, 1258, 1172, 1027 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (t, *J*=4.1 Hz, 1H), 3.94 (d, *J*=9.0 Hz, 1H), 2.44–2.38 (m, 4H), 2.19 (m, 1H), 1.97 (m, 2H), 1.82 (m, 1H), 1.62–1.42 (m, 6H), 1.07 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.93, 146.61, 140.30, 76.97, 44.99, 38.78, 29.93, 29.44, 25.72, 25.46 (br), 22.53. HRMS (FAB, M+H) calcd for $C_{12}H_{19}O_2$ 195.1385, found 195.1397. HPLC (Chiralcel OB-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/2-propanol=99/1, 1.0 mL/min, (*R*) major; 17.6 min, (*S*) minor; 19.8 min).

4.3.7. ***7ib*** *(Table 5, entry 12)*

Colorless oil. $[\alpha]_D^{25}$ +32.4 (*c* 1.08, $CHCl_3$, 75% ee). IR (neat) 3439, 2952, 2868, 1695, 1441, 1374, 1344, 1196 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (t, *J*=2.3 Hz, 1H), 4.22 (d, *J*=7.9 Hz, 1H), 2.62 (br d, *J*=4.0 Hz, 2H), 2.45–2.43 (m, 2H), 1.80–1.18 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 158.7, 147.1, 71.7, 44.6, 35.2, 29.2, 28.6, 26.7, 25.6, 25.6. HRMS (FAB, M+Na) calcd for $C_{11}H_{16}O_2Na$ 203.1048, found 203.1049. HPLC (Chiralcel OD-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/2-propanol=98/2, 0.8 mL/min, (*R*) major; 7.5 min, (*S*) minor; 8.5 min).

4.3.8. ***7jb*** *(Table 5, entry 14)*

Colorless oil. $[\alpha]_D^{28}$ +30.6 (*c* 1.09, $CHCl_3$, 85% ee). IR (neat) 3434, 2925, 2852, 1695, 1448, 1259, 1101 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J*=2.4 Hz, 1H), 4.18 (d, *J*=6.4 Hz, 1H), 2.80–2.62 (m, 2H), 2.45–2.44 (m, 2H), 1.83 (d, *J*=12.8 Hz, 1H), 1.76–1.70 (m, 2H), 1.66–1.57 (m, 2H), 1.52 (d, *J*=12.8 Hz, 1H), 1.25–0.95 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.2, 159.2, 146.2, 73.1, 42.6, 35.3, 29.5, 27.9, 26.7, 26.3, 26.0, 25.9. HRMS (FAB, M+Na) calcd for $C_{12}H_{18}O_2Na$ 217.1204, found 217.1242. HPLC (Chiralcel OB-H, 0.46 cm (φ)×25 cm (L), *n*-hexane/2-propanol=99.7/0.03, 1.0 mL/min, (*R*) major; 41.5 min, (*S*) minor; 47.2 min).

Acknowledgements

Y.S. gratefully acknowledges a JSPS Postdoctoral Fellowship for Research Abroad. This research was supported in part by grants from Mitubishi Chemical Corporation, the Uehara Memorial Foundation, and the Nagase Science and Technology Foundation.

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23. These results are not entirely novel; Connon and Maher also reported very similar results with the use of methyl acrylate and methyl vinyl ketone,[20k] at almost the same time as our report.[9b]
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