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Development of bis-thiourea-type organocatalyst for asymmetric Baylis–Hillman reaction ☆

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Abstract—A new chiral bis-thiourea-type organocatalyst **2** developed for the Baylis–Hillman reaction provided a drastic rate enhancement. Allylic alcohols were obtained with up to 90% ee in the case of cyclohexanecarboxaldehyde (**4i**).

The Baylis–Hillman reaction is a superior carbon–carbon bond-forming reaction since it gives synthetically useful chiral building blocks, that is, allylic alcohols, from simple aldehydes and electron-deficient alkenes without generating by-products.[1] This atoms economically superior reaction, however, is well known to be sluggish, and controlling the newly generated chirality in the product is also an issue.[2] To address these problems, various approaches,[3–5] especially focusing on Lewis acid catalysts[3] and/or chiral tertiary amine catalysts,[4] have been investigated. Herein, we report a novel approach to enhance the reaction rate, together with an asymmetric version of the Baylis–Hillman reaction of cyclohexenone with aldehydes, using a chiral bis-thiourea-type organocatalyst.

An organocatalyst, that is, an organic compound, which exhibits catalytic activities,[6] does not contain heavy metal, and so is advantageous from an environmental as well as a resource standpoint. The easy reproducibility and flexible design of such a catalyst are additional advantages. During our recent studies focusing on the development of efficient organocatalysts,[7] we independently found the urea/thiourea compounds **1**[8] having 3,5-bis-trifluoromethylphenyl groups activated the carbonyl compounds through hydrogen-bonding interactions, and drastically accelerated the hetero-Michael reaction of δ-lactone with pyrrolidine.[7e] These findings prompted us to apply the urea/thiourea catalyst **1** to the Baylis–Hillman reaction with the aim of enhancing the reaction between the ammonium enolate and the aldehyde, the rate-determining step, through promoting the enolate formation, as well as activating the aldehyde reactivity.[9] Asymmetric induction of the product was also expected as a result of the chirality in **1** (Chart 1).

First, the reactions of cyclohexenone (**3**) and benzaldehyde (**4a**) with DABCO in the presence of **1a** and **1b** as organocatalysts were examined without using solvent (Table 1). The allylic alcohol **5a** was obtained in 52% and 60% yields, respectively, which are more than 50-fold higher than the yield of the uncatalyzed reaction. ^{1}H NMR experiments showed that the thiourea **1b** interacted with both the enone **3** and aldehyde **4a**,[10]

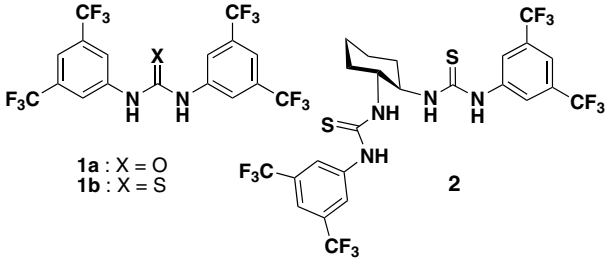

Chart 1. Structure of urea/thiourea and bis-thiourea compounds.

Keywords: Baylis–Hillman reaction; Organocatalyst; Bis-thiourea; Asymmetric reaction.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.05.137

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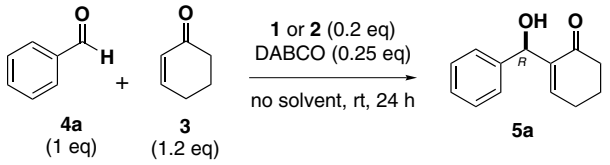
Table 1. Baylis–Hillman reaction catalyzed by **1** and **2**

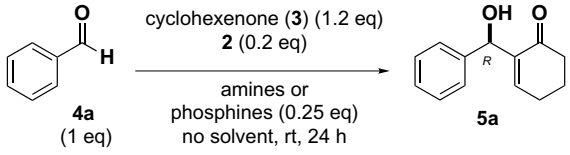


Entry	Catalyst	Yield (%)	Ee (%)[a]
1	None	1	—
2	**1a**	52	—
3	**1b**	60	—
4	**2**	72	33 (*R*)[b]

[a] The enantiomeric excess of **5a** was determined by HPLC analysis using a chiral column.[5e]

[b] Absolute stereochemistry was determined by comparison of the $[\alpha]_D$ value with that of reported by McDougal and Schaus.[5e]

Table 2. Reaction of **3** and **4a** with various amines and phosphines



Entry	Base	Yield (%)	Ee (%)[a]
1	DMAP	90	22
2	Et_3N	49	30
3	1-Methyl pyrrolidine	43	29
4	Imidazole	10	61
5	*N*-Methylimidazole	10	47
6	1,4-Dimethylpiperazine	9	31
7	Ph_3P	Trace	—
8	*n*-Bu_3P	Trace	—

[a] The enantiomeric excess of **5a** was determined by HPLC analysis using a chiral column.[5e]

which indicated that **1b** is involved in at least two steps of the Baylis–Hillman reaction, that is, (1) hetero-Michael reaction of the enone and tertiary amine, and (2) aldol reaction (Fig. 1). Based on these observations, we anticipated that compounds in which two urea/thiourea groups are connected with an appropriate spacer would accelerate the reaction by holding the two reaction components in a suitable position to react. The hypothetical structure of the complex further implies that chirality in the spacer might cause asymmetric induction of the product.[11] Therefore, we designed a bis-thiourea-functionalized chiral catalyst **2** to accommodate an enone and an aldehyde in a spatially restricted orientation.

The bis-thiourea catalyst **2** was prepared from isothiocyanate and diaminocyclohexane simply by mixing them, and purified by recrystallization.[12] Using the bis-thiourea catalyst **2**, coupling reaction of cyclohexenone (**3**) and benzaldehyde (**4a**) was examined under the same conditions as used for entries 1–3 in Table 1. In the presence of the bis-thiourea catalyst **2**, the yield of the allylic alcohol **5a** was increased to 72%, which indicates great effectiveness (72-fold versus the uncatalyzed reaction) of the bis-functionalized catalyst, as expected (Table 1).[13] In this case, the enantiomeric excess of **5a** was found to be 33%, favoring '*R*' configuration.[5e] Under these conditions, the reactions of various tertiary amines and phosphines were examined, and the results are summarized in Table 2.

In the case of DMAP, the reaction proceeded more effectively than with DABCO to give **5a** in 90% yield. Triethylamine and 1-methylpyrrolidine afforded moderate reaction enhancement and **5a** was obtained in 49% and 43% yields, respectively. In these cases, the enantiomeric excess was 22–30%. Interestingly, in the case of imidazole, the enantiomeric excess of **5a** was increased to 61%, though the yield was low. With these results in hand, we examined the feasibility of an asymmetric version of the Baylis–Hillman reaction of cyclohexenone (**3**) with various aldehydes **4** to investigate the utility and limitations of this bis-thiourea catalyst **2** (Table 3).

The Baylis–Hillman reaction with cyclohexenone (**3**) (2 equiv) and aldehydes **4** (1 equiv) was examined, using 0.4 equiv of base and bis-thiourea **2** in the absence of solvent. In the case of benzaldehyde (**4a**) with DMAP, **5a** was obtained in 33% ee with 88% yield. Changing the base to imidazole increased the ee value to 57% even

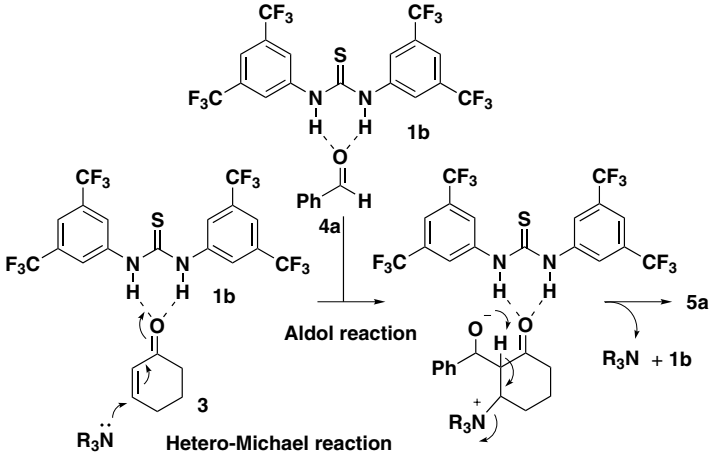
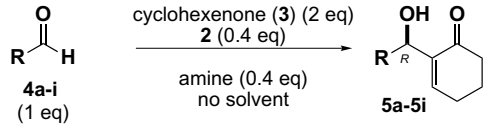
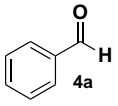
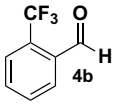
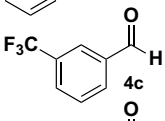
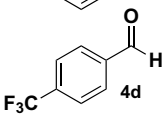
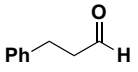
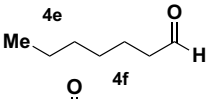
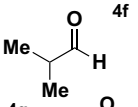
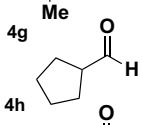
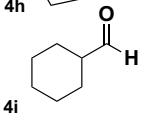


Figure 1. Baylis–Hillman reaction promoted by bis-thiourea catalyst.

Table 3. Reaction of **3** with various aldehydes in the presence of **2**



Entry	4	Base	Temp (°C)	Time (h)	Yield (%)	Ee (%)[a]
1		DMAP	−5	72	88	33
		Imidazole	rt	120	40	57
2		DMAP	−5	72	38	30
3		DMAP	−5	72	88	19
4		DMAP	−5	72	99	33
		Imidazole	4	120	95	44
5		DMAP	−5	72	33	59
6		DMAP	−5	72	63	60
7		DMAP	−5	72	67	60
8		DMAP	−5	72	55	86
9		DMAP	−5	72	72	90

[a] The enantiomeric excess of **5** was determined by HPLC analysis using a chiral column.[5e,14]

though the reaction was conducted at room temperature. *ortho*-, *meta*-, and *para*-substituted benzaldehyde derivatives reacted to give **5b**–**d** in 30%, 20%, and 33% ee, respectively (runs 3–5). The chemical yields of aromatic aldehydes were quite high, except for *ortho*-substituted derivatives. The *ortho*-substituent presumably disturbs the coordination of the carbonyl group in **4b** to the thiourea moiety. Although asymmetric induction with aromatic aldehydes was low, the aliphatic aldehydes **4e**, **4f**, and branched aldehyde **4g** gave the corresponding allylic alcohols **5e**–**g** with 60% ee. More excitingly, five- and six-membered cyclic aliphatic aldehyde **4h** and **4i**, gave the alcohols **5h** and **5i** with very high enantiomeric excess, that is, 86% and 90% ee, respectively.

Since the newly generated stereochemistry of the alcohol in **5** is '*R*',[5e,14] the transition state of this Baylis–Hillman reaction can be considered to be as shown in Figure 2. The aldehyde **4** and the enone **3** coordinate to the thiourea groups in **2** through hydrogen-bonding interactions, such that the 'R' group in the aldehyde is located on the opposite side from the thiourea group,

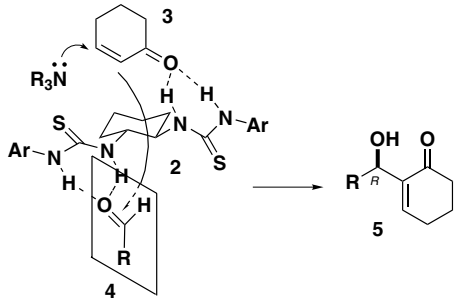


Figure 2. Proposed transition state of the bis-thiourea-catalyzed Baylis–Hillman reaction.

which interacts with the enone, and these two components interact to form the new carbon–carbon bond. This would afford (*R*)-**5** as the major coupling product.

In summary, we have developed the new bis-thiourea-type catalyst **2** for the Baylis–Hillman reaction. This catalyst drastically improved the reaction rate. Further, the produced allylic alcohol **5** showed induction of

chirality up to 90% ee in the case of cyclohexanecarboxaldehyde (**4i**). It should be noted that the bis-thiourea catalyst **2** can be easily recovered quantitatively by silica-gel column chromatography. This catalyst could also be easily modified by introducing an appropriate chiral spacer, which might improve the asymmetric induction with a variety of substrates. Further efforts to improve the catalyst are in progress.

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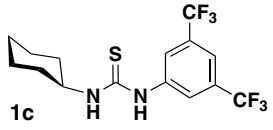
9. Maher and Connon recently reported **1** as an efficient catalyst for the Baylis–Hillman reaction: Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301.
10. The ^{1}H NMR spectrum of a 1:1 mixture of the thiourea **1b** and enone **3** showed a downfield shift of N-*H* in **1b** from 7.90 to 8.73 ppm. In the case of a 1:1 mixture of **1b** and **4a**, a downfield shift of N-*H* in **1b** was also observed from 7.90 to 8.30 ppm.
11. Bifunctional catalysts, see: (a) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539; (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 2672; (c) Okino, T.; Nakamura, S.; Fukuzawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.
12. The bis-thiourea catalyst **2** was prepared as follows: 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 temperature, the reaction mixture was stirred for 22 h and concentrated in vacuo. The residue was recrystallized from ethyl acetate–hexane to give **2** (4.68 g, 94%) as a white solid. Mp = 132–133 °C (decomposition). $[\alpha]_D^{25}$ −60.6 (*c* 1, $CHCl_3$). 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 180.54, 138.59, 132.78 (J_{CF} = 33.1 Hz), 124.08 (br), 122.71 (J_{CF} = 273.1 Hz), 119.67 (br), 59.45, 31.74, 24.39. HRMS (FAB, M+H) calcd for $C_{24}H_{21}F_{12}N_4S_2$ 657.1016, found 657.1031.
13. When **1c**[11a] was used as catalyst, **5a** was obtained in 20% yield. This result clearly indicates the importance of the bis-functionality of catalyst **2**.



1c

14. The absolute stereochemistries of **5b–d**, **5f**, **5h** and **5i** are determined by Sharpless epoxidation method.[5e]