Asymmetric Morita-Baylis-Hillman Reaction of Arylaldehydes with 2-Cyclohexen-1-one Catalyzed by Chiral Bis(Thio)urea and DABCO
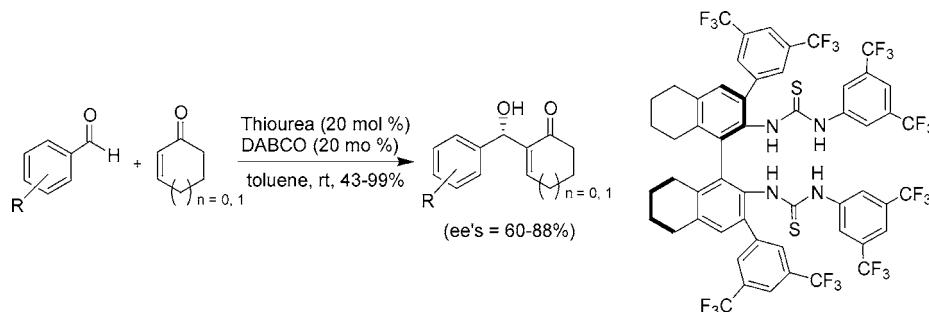
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ABSTRACT

Novel bis(thio)urea organocatalysts were synthesized from axially chiral (*R*)-(−)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (H$_8$-BINAM), and their catalytic abilities have been examined in the Morita-Baylis-Hillman reaction of 2-cyclohexen-1-one or 2-cyclopenten-1-one with a wide range of aromatic aldehydes in combination with DABCO. The best result was achieved in the reaction of 3-fluorobenzaldehyde with 2-cyclohexen-1-one to give the desired Morita-Baylis-Hillman product in 79% yield and 88% ee.

The Morita-Baylis-Hillman reaction (MBH reaction), one of the most important methods for converting simple starting materials to densely functionalized products in a catalytic and atom economic way, has attracted much attention since the first report in a patent in 1972.[1] As for the great potential of the products for further transformation and the superior mild reaction conditions, the development of a suitable asymmetric version of this reaction has attracted considerable interest in recent years. Various chiral catalysts and cocatalysts were developed, and very recently, a chiral medium for this reaction was also reported.[2,2p]

The first breakthrough in catalytic, asymmetric MBH reaction was disclosed by Hatakeyama and co-workers with quinidine-derived chiral bases as organocatalysts for the reaction of 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) with aldehydes, providing the adducts with ee values up to 99%, although the substrate scope and the latter transformation are very narrow.[3] In 2003, Schaus et al. described that an axially chiral Brønsted acid catalyst derived from BINOL in combination with PEt$_3$ led to ee values of the adducts up to 96% and good to moderate yields for a huge variety of aldehydes in the MBH reaction with 2-cyclohexen-1-one.[4] Later on, Connon et al. first used the (thio)ureas to accel-

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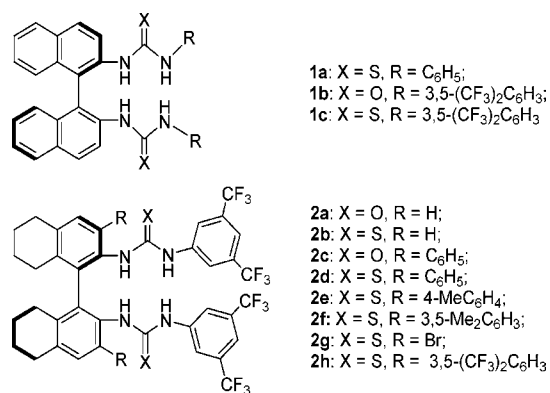† Fax: (+86)(21)64166128.
‡ Chinese Academy of Sciences.
§ East China University of Science and Technology.
(1) For reviews, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062. (b) Drewes, S. E.; Roo, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (d) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−892. (e) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4514−4528. (f) Shi, Y. L.; Shi, M. *Eur. J. Org. Chem.* **2007**, *18*, 2905−2916. (g) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581−1588. (h) Iwabuchi, Y.; Hatakeyama, S. *J. Synth. Org. Chem. Japan* **2002**, *60*, 2−14.

erate the DABCO-promoted MBH reaction of arylaldehydes with methyl acrylate as recoverable H-bonding organocatalysts.[5] In 2005, Wang's group reported a novel type of bifunctional organocatalyst, the chiral amine-thiourea compound derived from 1,1′-binaphthyl-2,2′-diamine (BINAM), for catalyzing highly enantioselective MBH reactions of 2-cyclohexen-1-one with various aldehydes to give the corresponding adducts in high yields and enantiomeric excesses.[6] Recently, Lattanzi described a simple chiral amino alcohol derived thiourea for the same MBH reaction to produce the corresponding adducts in up to 88% ee.[7] On the other hand, bis(thio)ureas derived from chiral *trans*-1,2-diaminocyclohexane and isophorone-diamine [3-(aminomethyl)-3,5,5-trimethylcyclohexylamine, IPDA] were also proven to be suitable organocatalysts for the asymmetric MBH reactions of various aldehydes with 2-cyclohexen-1-one as described by Nagasawa and Berkessel.[8]

Although the MBH reactions of aliphatic aldehydes with 2-cyclohexen-1-one have achieved very high yields and ee's by these organocatalysts mentioned above, using aromatic aldehydes usually afforded the corresponding products in moder-ate yields and moderate ee's. To the best of our knowledge, the highest ee of this kind of MBH reaction regarding aromatic aldehyde is 77%. Herein, we report that the improved bis(thio)urea organocatalysts, derived from axially chiral (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (H$_8$-BINAM), were fairly effective chiral organocatalysts for the enantioselective MBH reaction of arylaldehydes with 2-cyclohexen-1-one to give the corresponding adducts in up to 88% ee and good to excellent yields.

The organocatalysts **1a**−**c** and **2a**−**h** are easily accessible by condensation of chiral BINAM and H$_8$-BINAM with 2 equiv of the corresponding iso(thio)cyanate under mild conditions (see Supporting Information) (Figure 1). Organo-

with 2-cyclohexen-1-one (**4a**) in toluene at room temperature in combination with 1,4-diazabicyclo[2.2.2]octane (DABCO) to find out the best catalyst and the results of these experiments are summarized in Table 1. As can be seen from Table 1, the structure of these organocatalysts significantly affects the enantioselectivities and chemical yields of **5a** (Table 1, entries 1−11). Three structural features of these catalysts were found to be important for achieving high enantioselectivity: (1) Bisthioureas are better catalysts because bisthioureas **1c**, **2b**, and **2d** are slightly more effective than those of bisureas **1b**, **2a**, and **2c** under identical conditions, presumably due to the stronger H-bonding ability of thiourea than that of urea, which makes them more effectively interact with the substrates (Table 1, entries 2−7).[11] (2) H$_8$-BINAM derived organocatalysts are more effective than those BINAM derived ones since bisthiourea **2b** derived from (*R*)-H$_8$-BINAM was found to be the optimum catalyst for this reaction, providing the corresponding product **5a** in 66% yield and 29% ee after 72 h, whereas the bis(thio)ureas **1a** and **1c** derived from BINAM gave very low enantioselectivities (Table 1, entries 1, 3, and 5), and (3) Substitution at the 3,3′-positions gave higher ee than others (Table 1, entries 6−11). When the substituents at the 3,3′-positions are phenyl group, 4-methylphenyl group, or

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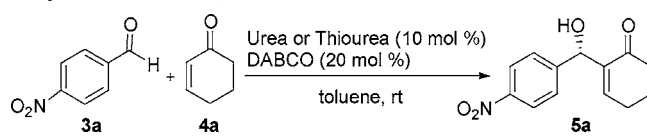
(7) Lattanzi, A. *Synlett.* **2007**, 2106−2110.

(8) (a) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589−5592. (b) Berkessel, A.; Roland, K.; Neudörfl, J. M. *Org. Lett.* **2006**, *8*, 4195−4198. (c) Roussel, C.; Roman, M.; Andreoli, F.; Delrio, A.; Faure, R.; Vanthuyne, N. *Chirality* **2006**, *18*, 762−771.

(9) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037−7042.

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(11) For recent reviews on organocatalysis by hydrogen-bonding donors with thioureas, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299−4306. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (c) Connon, S. J. *Chem.−Eur. J.* **2006**, *12*, 5418−5427. (d) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999−1010.

Figure 1. Screened organocatalysts.

catalysts **1a**−**c** and **2b** were first prepared by Connon's group, which have been used for a Friedel−Crafts type reaction.[9] Organocatalysts **2a** and **2c**−**h** were first prepared by our group, and **2a**−**f** have been already used in asymmetric Henry reaction.[10]

The chiral organocatalysts **1a**−**c** and **2a**−**h** were first examined in the MBH reaction of 4-nitrobenzaldehyde (**3a**)

Table 1. Screening of the Bis(thio)ureas **1a−c** and **2a−h** in the MBH Reaction of 4-Nitrobenzaldehyde (**3a**) with 2-Cyclohexen-1-one (**4a**) in the Presence of DABCO[a]

entry	catalyst	yield (%)[b] 5a	ee (%)[c] 5a
1	**1a**	60	0
2	**1b**	69	2
3	**1c**	67	5
4	**2a**	76	2
5	**2b**	66	29
6	**2c**	49	13
7	**2d**	53	39
8	**2e**	44	39
9	**2f**	65	35
10	**2g**	77	57
11	*2h*	*67*	*72*

[a] Unless stated otherwise, the reaction was carried out with 1.0 equiv of **3a** and 3 equiv of **4a** in the presence of catalyst (10 mol %) and DABCO (20 mol %) in toluene at room temperature for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC.

Table 2. Solvent and Base Effect on the MBH Reaction of 4-Nitrobenzaldehyde (**3a**) with 2-Cyclohexen-1-one (**4a**)[a]

entry	solvent	base	yield (%)[b] 5a	ee (%)[c] 5a
1	toluene	DMAP	75	33
2	toluene	imidazole	27	26
3	toluene	*N*-methylimidazole	46	33
4	toluene	pyridine	NR[e]	—[d]
5	toluene	DUB	61	3
6	toluene	Et$_3$N	12	30
7	*toluene*	*DABCO*	*77*	*57*
8	THF	DABCO	54	29
9	CH$_3$CN	DABCO	<10	—[d]
10	DMF	DABCO	16	32
11	CH$_2$Cl$_2$	DABCO	12	40
12	neat	DABCO	66	34

[a] Unless stated otherwise, the reaction was carried out with 1 equiv of **3a** and 3 equiv of **4a** in the presence of catalyst (10 mol %) and base (20 mol %) in solvent at room temperature for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Not determined. [e] No reaction.
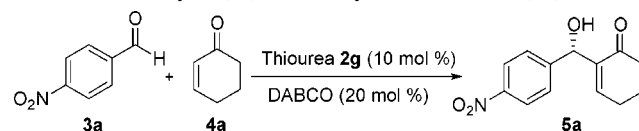
3,5-dimethylphenyl group, product **5a** was produced in 35−39% ee's, suggesting that sterically more congested organocatalyst could improve the enantioselectivity (Table 1, entries 7−9). When the substituents at the 3,3′-position are bromine (bisthiourea **2g**), the ee of **5a** was improved to 57% (Table 1, entry 10). The highest level of enantioselectivity (72% ee) was achieved if using (*R*)-3,3′-[3,5-bis(tifluoromethyl)phenyl]-H$_8$-BINAM-bisthiourea **2h** as the organocatalyst under identical conditions (Table 1, entry 11).

The nature of the nucleophilic base is known to have a pronounced influence on the MBH reaction.[12] Therefore various tertiary amino bases were screened in combination with organocatalyst **2g** for the reaction, and the results of these experiments are summarized in Table 2. DABCO was found to be the most effective base for this MBH reaction, producing the corresponding product **5a** in 77% yield and 57% ee (Table 2, entry 7). Although DBU is usually classified as a nonnucleophilic base, it is known to be very active in the MBH reaction.[12b] Unfortunately, in this case, the high activity of DBU led to lower enantioselectivity (Table 2, entry 5). It should be noted that pyridine was almost totally inactive in this reaction (Table 2, entry 4).

The examination of solvent effects revealed that a variety of solvents such as tetrahydrofuran (THF), dimethylforamide (DMF), and dichloromethane (DCM) could be employed for the bis(thio)urea/DABCO-cocatalyzed MBH reaction and toluene was the best solvent for the reaction (Table 2, entries 7−12).[4,8b] Acetonitrile (CH$_3$CN) gave very poor result in this reaction (Table 2, entry 9).

To further optimize the reaction conditions, the employed amounts of catalysts were examined using bisthiourea **2d** or **2g**, which can be more easily prepared, as the catalyst under the standard conditions and the results of these ex-

periments are summarized in Table 3. Product **5a** was obtained in higher yields and enantioselectivities when bisthiourea **2d** or **2g** (20 mol %) and DABCO (20 mol %) were employed under otherwise identical conditions (Table 3, entries 2 and 7).

Therefore, the best reaction conditions are to carry out the MBH reaction with 1 equiv of aromatic aldehyde **3** and 3 equiv of 2-cyclohexen-1-one **4a** in the presence of catalyst **2h** (20 mol %) and DABCO (20 mol %) at room temperature in toluene.

Table 3. Effects of the Employed Amounts of Catalysts for the MBH Reaction of 4-Nitrobenzaldehyde (**3a**) with 2-Cyclohexen-1-one (**4a**)[a]
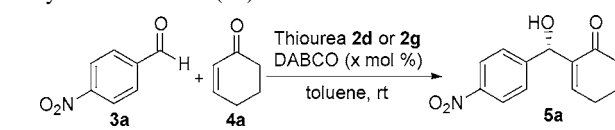
entry	catalyst	yield (%)[b] 5a	ee (%)[c] 5a
1	**2d** (10 mol %)	53	39
2	*2d (20 mol %)*	*90*	*57*
3	**2d** (30 mol %)	69	51
4	**2g** (5 mol %)	43	49
5	**2g** (10 mol %)	77	57
6[d]	**2g** (10 mol %)	40	54
7	*2g (20 mol %)*	*97*	*63*
8	**2g** (30 mol %)	94	55

[a] Unless stated otherwise, the reaction was carried out with 1 equiv of **3a** and 3 equiv of **4a** in the presence of catalyst (10 mol %) and DABCO (20 mol %) in toluene at room temperature for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] DABCO (10 mol %) was used.

Table 4. MBH Reaction between 2-Cyclohexen-1-one and Various Aromatic Aldehydes under These Optimized Conditions

entry	product	yield (%)[b]	ee (%)[c]
1	5a	94	72
2	5b	94	74
3	5c	90	85
4	5d	99	75
5	5e	67	86
6	5f	99	62
7	5g	98	63
8	5h	95	83
9	5i	64	77
10	5j	71	83
11	5k	88	84
12	5l	79	88
13	5m	50	78
14	5n	99	81
15	5o	99	83
16[d]	5p	85	76
17[d]	5q	67	80

[a] The reaction was carried out with 1 equiv of aldehyde and 3 equiv of 2-cyclohexen-1-one in the presence of catalyst **2h** (20 mol %) and DABCO (20 mol %) at room temperature for 72 h. [b] Isolated yield. [c] Determined by HPLC. [d] The reaction was carried out for 96 h.

With these optimized reaction conditions in hand, we next turned our interest to the reaction generality. A variety of aromatic aldehydes **3** were examined under these optimal conditions and the results are shown in Table 4. As can be seen from Table 4, the reaction proceeded smoothly to afford the corresponding adducts **5** in good to excellent yields and good enantioselectivities for various aromatic aldehydes **3**

(12) For selected examples of base influence on the MBH reaction. see: (a) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692−700. (b) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311− 2312.

bearing electron-withdrawing substituents on the benzene ring as well as pyridyl aldehyde (Table 4, entries 1−14). As for aromatic aldehydes **3** having a moderately electron-donating group on the benzene ring, prolonged reaction time was required to afford the corresponding adducts **5p** and **5q** in 76 and 80% ee's (Table 4, entries 16 and 17). The best result was achieved in the reaction of 3-fluorobenzaldehyde with 2-cyclohexen-1-one to give the desired Morita-Baylis-Hillman product **5l** in 79% yield and 88% ee (Table 2, entry 12).

Benzadehyde is still one of the most challenging substrates for the MBH reaction with 2-cyclohexen-1-one. Organo-catalyst **2h** effected this transformation in 99% yield and 81% ee (Table 4, entry 14). To the best of our knowledge, this is the best result for this kind of MBH reaction reported so far.

The MBH reaction between the 2-cyclopenten-1-one (**4b**) and 4-nitrobenzaldehyde could also proceed smoothly under the standard conditions, affording the corresponding product **6** in 43% yield and 60% ee (Scheme 1). It should be noted

Scheme 1. MBH Reaction between 2-Cyclopenten-1-one (**4b**) and 4-Nitrobenzaldehyde
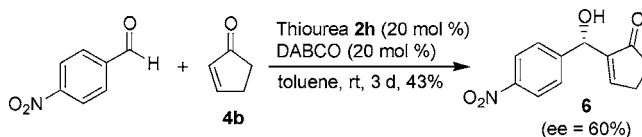
that the corresponding adducts **5** and **6** were obtained as S-configuration according to previous literature.[4]

In summary, we have developed a fairly effective asymmetric Morita-Baylis-Hillman reaction involving the addition of 2-cyclohexen-1-one or 2-cyclopenten-1-one to aromatic aldehydes catalyzed by bis(thio)urea organocatalysts derived from (R)-(−)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (H8-BINAM) and DABCO. The corresponding adducts were obtained in good to excellent yields and moderate to good enantiomeric excesses in most cases. For 4-chlorophenylaldehyde, 3-chlorophenylaldehyde, and 3-fluorophenylaldehyde, up to 85−88% ee's can be achieved under mild conditions. Further efforts are underway with a focus on improving the catalyst activity and reaction enantio-selectivity as well as to elucidate the mechanistic details of this asymmetric MBH reaction.

Supporting Information Available: The spectroscopic data (¹H, ¹³C spectroscopic data), HRMS of the compounds shown in Figure 1, Table 4, and Scheme 1, along with the detailed description of experimental procedures as well as the chiral HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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