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Asymmetric Morita–Baylis–Hillman Reaction Catalyzed by Isophoronediamine-Derived Bis(thio)urea Organocatalysts

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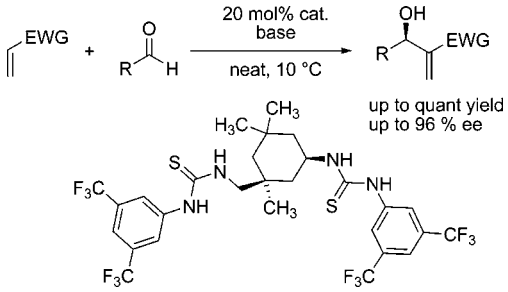
ABSTRACT



New and improved bis(thio)urea catalysts were synthesized from isophoronediamine (IPDA) and tested in the Morita–Baylis–Hillman reaction. The best results were achieved in the reaction of 2-cyclohexen-1-one with cyclohexanecarbaldehyde, using the catalyst depicted above, in combination with a novel base (*N,N,N′,N′*-tetramethylisophoronediamine, TMIPDA) in toluene. The desired Morita–Baylis–Hillman product was obtained in 75% yield and 96% ee.

The Morita−Baylis−Hillman (MBH) reaction is the addition of electron-deficient alkenes to aldehydes, promoted by nucleophilic bases such as DABCO.[1] The products of this versatile carbon−carbon bond forming reaction are highly functionalized allylic alcohols which can serve as valuable building blocks for the synthesis of complex natural products.[2] Hence, the development of a suitable asymmetric version of the MBH reaction has attracted considerable interest in recent years.[3] Hatakeyama et al. have described quinidine-derived chiral bases for the reaction of acrylates with aldehydes providing ee values up to 99%. However, the substrate scope of the latter transformation is rather narrow.[4] It was reported by Ikegami et al. that MBH reactions are further promoted by Brønsted acid cocatalysts.[5] Schaus et al. introduced an asymmetric Brønsted acid catalyst derived from BINOL that, in combination with PEt_3, led to ee values of up to 96% and good to moderate yields for a

(1) For reviews see: (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (c) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049. (d) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed; Wiley: New York, 1997; Vol. 51, p 201.

(2) For examples see: (a) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030. (b) Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867. (c) Anand, R. V.; Baktharaman, S.; Singh, V. K. *Tetrahedron. Lett.* **2002**, *43*, 5393. (d) Mateus, C. R.; Coelho, F. *J. Braz. Chem. Soc.* **2005**, *16*, 386.

(3) For recent advances in the asymmetric aza-Morita−Baylis−Hillman reaction see: (a) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701. (b) Shi, M.; Chen, L.-H. *Pure Appl. Chem.* **2005**, *77*, 2105. (c) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761.

(4) (a) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (b) Nakano, A.; Kawahara, S.; Akamatsu, S.; Morokuma, K.; Nakatani, M.; Iwabuchi, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Tetrahedron* **2006**, *62*, 381.

(5) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165.

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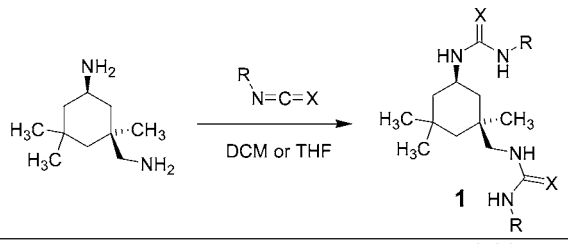
large variety of aldehydes in the reaction with 2-cyclohexen-1-one.[6] The first application of (thio)urea catalysts for the MBH reaction was reported by Connon et al., but no asymmetric version was investigated.[7] A chiral bifunctional catalyst was disclosed by Wang et al. carrying a Brønsted basic tertiary amine and a quasi-Lewis acidic thiourea group attached to a chiral scaffold.[8] Bis(thio)ureas derived from chiral *trans*-1,2-diaminocyclohexane were also proven to be suitable catalysts for the asymmetric MBH reaction, as described by Nagasawa et al.[9]

Herein, we report improved bis(thio)urea catalysts derived from isophoronediamine [3-(aminomethyl)-3,5,5-trimethylcyclohexylamine, IPDA]. IPDA is a readily available 1,4-diamine produced industrially on a multiton scale. IPDA and its derivative isophoronediisocyanate [5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane, IPDI] are used as monomers for urethane and epoxy resins.[10] The large scale optical resolution of IPDA was described recently by our group.[11]

The obvious advantages of bis(thio)urea catalysts are their facile and modular synthesis. Structurally diverse potential catalysts are easily accessible by condensation of a chiral diamine with 2 equiv of iso(thio)cyanate (Figure 1).

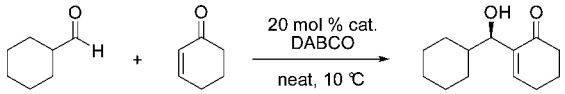


no.	structure	yield
	X = O	
1a	R = Ph	60 %[12]
1b	R = 3,5-$(CF_3)_2$-C_6H_3[13]	85 %
	X = S	
1c	R = Ph	quant[12]
1d	R = 3,5-$(CF_3)_2$-C_6H_3[13]	quant
1e	R = cyclohexyl	65 %
1f	R = adamantyl	quant

Figure 1. Synthesis of bis(thio)urea catalysts.

The catalytic activity of these bis(thio)ureas was tested in the model reaction of cyclohexanecarbaldehyde (**2**) with 2-cyclohexen-1-one (**3**) at 10 °C in the presence of 20 mol % of catalyst and base without any solvent (Table 1).

Table 1. Screening of the Bis(thio)ureas **1a**−**f** in the Reaction of 2-Cyclohexen-1-one (**3**) with Cyclohexanecarbaldehyde (**2**)[a]



2 **3** **4**

entry	catalyst	yield (%)[b]	ee (%)[b,c]
1	**1a**	10	86
2	**1b**	30	87
3	**1c**	11	93
4	**1d**	81	90
5	**1e**	3	70
6	**1f**	1	10

[a] The reaction was carried out with 1 equiv of **2** and 4 equiv of **3** in the presence of 20 mol % catalyst and DABCO under neat conditions at 10 °C for 72 h. [b] Yields and ee values were determined by GC on chiral stationary phase, using an internal standard. [c] Enantiomeric excess was in favor of the (*R*)-enantiomer. Absolute configuration was assigned by comparison of the retention times with those reported by Nagasawa et al.[9]

The bis(thio)urea **1d** was found to be the optimum catalyst for this reaction, providing the product **4** in 81% yield and 90% ee after 72 h (entry 3). The corresponding urea catalyst **1b** showed lower activity and selectivity (entry 1), while the alkyl-substituted bis(thio)ureas **1e** and **1f** were almost completely inactive (entries 5 and 6).

In general, the thiourea catalysts proved to be superior to urea catalysts for this transformation (entries 3 and 4). This is presumably due to the stronger H-bonding ability of thioureas compared to ureas, and therefore stronger interaction with the substrates.[14]

The nature of the nucleophilic base is known to have a pronounced influence on the MBH reaction.[15] Therefore various tertiary amine bases were screened in combination with catalyst **1d** for the test reaction (Table 2).

Tetramethylated IPDA [(1*R*,3*S*)-TMIPDA] was found to be the most effective base for this particular reaction, producing the allylic alcohol **4** with 90% yield and 91% ee (Table 2, entry 5). Under the conditions of this study, the amount of TMIPDA could be reduced from 20 mol % to 10 mol % without loss in activity or selectivity (Table 2, entries 5 and 6).

When the same reaction was carried out with DABCO, reduction of the amount of base from 20 mol % to 10

(6) (a) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094. (b) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231.

(7) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301.

(8) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.

(9) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.

(10) For examples see: (a) Hoenel, M.; Pfeil, A.; Budnick, T.; Schwan, H. German patent 4344510 A1, 1995. (b) Tillack, J.; Schmalstieg, L.; Puetz, W.; Ruttmann, G. German patent 19935329 A1, 2001.

(11) Berkessel, A.; Roland, K.; Schröder, M.; Neudörfl, J. M.; Lex, J. Submitted for publication.

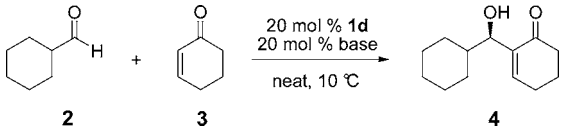
(12) X-ray crystallographic data for **1a** and **1c** are included in the Supporting Information.

(13) For synthesis of the catalysts **1b** and **1d** see: Berkessel, A.; Mukherjee, S.; Müller, T. N.; Cleeman, F.; Roland, K.; Brandenburg, M.; Neudörfl, J. M.; Lex, J. Submitted for publication.

(14) For recent reviews on catalysis by hydrogen-bond donors see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

(15) For examples of base influence on the MBH reaction see: (a) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311. (b) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692. (c) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369.

Table 2. Optimization of the Base in the Reaction of 2-Cyclohexen-1-one (**3**) with Cyclohexanecarbaldehyde (**2**)[a]



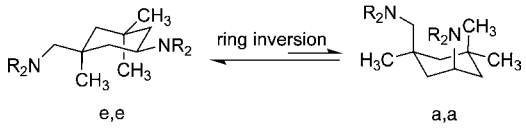
2 **3** **4**

entry	base	yield (%)[b]	ee (%)[b]
1	DABCO	81	90
2	DABCO[c]	48	90
3	DMAP	30	48
4	DBU	56	59
5	TMIPDA	90	91
6	TMIPDA[c]	90	90
7	quinuclidine	67	82
8	quinine	12	91
9	quinidine	12	90
10	brucine	2	72
11	NEt_3	3	

[a] Unless stated otherwise, the reaction was carried out with 1 equiv of **2** and 4 equiv of **3** in the presence of 20 mol % catalyst **1d** and base under neat conditions at 10 °C for 72 h. [b] See footnote b in Table 1. [c] 10 mol % of base.

mol % resulted in an approximately proportional reduction of the reaction rate (Table 2, entries 1 and 2). IPDA derivatives have a strong tendency to adopt the e,e rather than the a,a conformation of the cyclohexyl backbone, resulting in a large distance between the two nitrogen atoms (Scheme 1).[11] Compared to the rather compact structure of

Scheme 1



DABCO, steric hindrance will be much less in TMIPDA, allowing both tertiary amine moieties to act as base simultaneously. This hypothesis is further underlined by the X-ray crystal structure of **1a** (Figure 2). The N−N distance

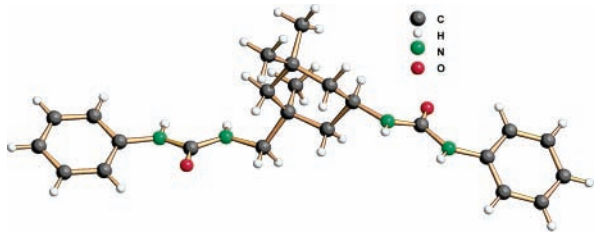


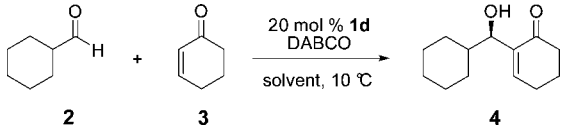
Figure 2. X-ray structure of catalyst **1a**.

of the backbone NH moieties in **1a** is 6.25 Å, compared to a N−N distance of 2.53 Å for DABCO.[16]

Although DBU is usually classified as a nonnucleophilic base, it is known to be very active in the MBH reaction.[15a] Unfortunately, in this case, the high activity of DBU led to lower selectivity and the formation of a significant amount of the aldol addition product of 2-cyclohexen-1-one (**3**) and cyclohexanecarbaldehyde (**2**) (Table 2, entry 4). Alkaloids were not particularly efficient in this reaction (Table 2, entries 8, 9, and 10). Nevertheless, the pseudoenantiomeric compounds quinine and quinidine provided the same product enantiomer, which shows that in this case, the chirality of the base has no significant influence on the enantioselectivity.

The MBH reaction of **3** and **2** was usually carried out under neat conditions in an excess of 2-cylohexen-1-one (**3**). For further optimization, the influence of a solvent on the reaction was investigated (Table 3). The concentration of

Table 3. Solvent Effects on the MBH Reaction of 2-Cyclohexen-1-one (**3**) with Cyclohexanecarbaldehyde (**2**)[a]



2 **3** **4**

entry	solvent	yield (%)[b]	ee (%)[b]
1	toluene	70	96
2[c]	toluene	75	96
3	DMF	14	25
4	DCM	55	95

[a] The reaction was carried out with 1 equiv of **2** (2.00 M in solvent) and 2 equiv of **3** in the presence of 20 mol % catalyst **1d** and DABCO at 10 °C for 72 h. [b] See footnote b in Table 1. [c] Result after 65 h with TMIPDA as base.

the aldehyde was kept constant, and only 2 equiv of **3** was added in these experiments. Toluene emerged as the best solvent for this reaction, affording the product **4** in 70% yield and 96% ee, which corresponds to the best result reported to date by Schaus et al.[6]

When TMIPDA was used as a base instead of DABCO, the reaction rate was slightly increased without loss in selectivity (Table 3, entry 2). In DCM, comparable asymmetric induction was achieved, although the reaction was significantly slower (Table 3, entry 4).

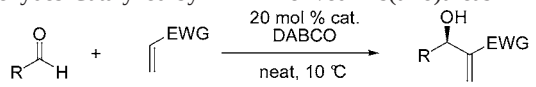
Polar solvents such as MeOH, DMF (Table 3, entry 3), THF, dioxane, and their mixtures with water were found to inactivate the catalyst, presumably by strong coordination to the thiourea moieties.[17]

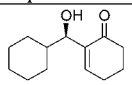
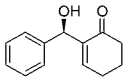
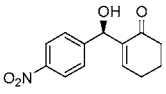
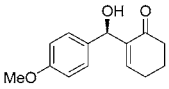
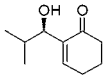
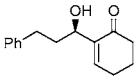
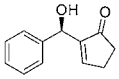
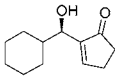
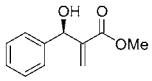
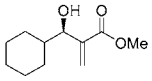
The use of nonpolar solvents provided enhanced selectivities, albeit at the expense of somewhat reduced reaction rates

(16) Wada, T.; Kishida, E.; Tomiie, Y.; Suga, H.; Seki, S.; Nitta, I. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1317.

(17) Polar solvents are assumed to catalyze the MBH reaction by a proton transfer mechanism. The same mechanism presumably underlies the frequently observed autocatalysis by the product. (a) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1734. (b) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762.

Table 4. MBH Reaction of Enones and Acrylates with Aldehydes Catalyzed by IPDA-Derived Bis(thio)ureas[a]



entry	product	cat.	yield (%)	ee (%)
1[b]		**1d**	75	96
2		**1a**	65[c]	77[e]
		1d	quant[c]	60[e]
3		**1a**	quant[d]	38[f]
		1d	65[d]	34[f]
4		**1a**	35[d]	79[f]
		1d	79[d]	50[f]
5		**1a**	62[d]	90[e]
6		**1a**	28[d]	79[f]
		1d	52[d]	69[f]
7		**1d**	quant[c]	*rac*
8		**1d**	22[c]	58[e]
9		**1d**	quant[c]	*rac*
10		**1b**	47[c]	22[e]

[a] The reaction was carried out with 1 equiv of aldehyde and 4 equiv of enone or acrylate in the presence of 20 mol % catalyst and DABCO at 10 °C for 72 h. [b] The reaction was carried out in toluene with 2 equiv of enone and 20 mol % TMIPDA as base. [c] GC yield. [d] Isolated yield. [e] ee determined by GC. [f] ee determined by HPLC.

(Table 2, entry 1 and Table 3, entry 1). The increase in enantioselectivity can be explained by the lower concentration of 2-cyclohexen-1-one (**3**) and consequently the suppression of the unselective background reaction catalyzed by DABCO. Unfortunately, for other substrates, in particular benzaldehyde, the decrease in rate was even more pronounced. Therefore, the general substrate scope of the reaction was studied under neat conditions with 4 equiv of 2-cyclohexen-1-one (**3**) (Table 4). We furthermore found that, with the exception of cyclohexanecarbaldehyde (**2**) as substrate (see Table 2), DABCO provides superior yields and ee values compared to TMIPDA.

Benzaldehyde is still one of the most challenging substrates for the MBH reaction with 2-cyclohexen-1-one (**3**). Catalyst **1a** effected this transformation with 65% yield and 77% ee (Table 4, entry 2). To the best of our knowledge, this is the best result for this pair of substrates reported so far. In general, aliphatic aldehydes gave better enantioselectivity compared to aromatic ones in the MBH with 2-cyclohexen-1-one (**3**). The same trend was observed for the reactions with 2-cyclopenten-1-one (Table 4, entries 7 and 8) and methyl acrylate (Table 4, entries 9 and 10).

In conclusion, we have found very active and enantioselective bis(thio)urea catalysts, derived in one step from the readily available 1,4-diamine IPDA. Good to excellent yields and enantiomeric excesses were obtained in the MBH reaction of a variety of aldehydes with 2-cyclohexen-1-one (**3**). Furthermore, it was shown for the first time that bis(thio)ureas are capable of activating Michael-acceptors besides 2-cyclohexen-1-one (**3**). Future investigations will include further probing of the substrate scope. Extensive kinetic and spectroscopic studies aiming at a mechanistic model for enantioselectivity are underway and will be published in due course.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie. We thank the BASF AG for a donation of IPDA. TMIPDA was kindly provided by Stefan Schnippering (this research group).

Supporting Information Available: Experimental procedures for the preparation of catalysts **1a**, **1c**, **1e**, and **1f** and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061298M