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Asymmetric Reaction Isophoronediamine-Derived Bis(thio)urea Organocatalysts	Morita-Baylis-Hillman Catalyzed by	Phản ứng Morita-Baylis-Hillman bất đối xứng xúc tác bằng chất xúc tác hữu cơ Bis(thio)urea có nguồn gốc từ Isophoronediamine
New and improved bis(thio)urea catalysts were synthesized from		Các chất xúc tác bis(thio)urea mới và tiên tiến hơn được tổng hợp từ

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

(1) For reviews see: (a) Berkessel, A.; Groger, 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.

isophoronediamine (IPDA) và được kiểm tra trong phản ứng Morita-Baylis-Hillman. Kết quả tốt nhất đạt được trong phản ứng của 2-cyclohexen-1-one với cyclohexanecarbaldehyde, khi dùng chất xúc tác được mô tả ở trên, kết hợp với một bazơ mới là (N,N,N',N'-tetramethylisophoronediamine, TMIPDA) trong toluene. Sản phẩm Morita-Baylis-Hillman đang xét có sản lượng 75% và ee 96%.

Phản ứng Morita-Baylis-Hillman (MBH) là sự bổ sung các anken thiếu electron cho các aldehyde, được thúc đẩy bởi các bazơ ưa nhân chẳng hạn như DABCO.¹ Sản phẩm của liên kết carbon—carbon đa năng này được chức hóa cao với rượu allylic, chất này đóng vai trò là thành phần cơ bản của quá trình tổng hợp các sản phẩm tự nhiên phức tạp.² Do đó, sự phát triển của phiên bản bất đối xứng thích hợp của phản ứng MBH rất được quan tâm

(d) Mateus, C. R.; Coelho, F. J. *Braz. Chem. Soc.* 2005, 16, 386.

interest in recent years. 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. It was reported by Ikegami et al. that MBH reactions are further promoted by Brønsted acid cocatalysts. Schaus et al. introduced an asymmetric Brønsted acid catalyst derived from BINOL that, in combination with PEt₃, led to ee values of up to 96% and good to moderate yields for a large variety of aldehydes in the reaction with 2-cyclohexen-1-one. The first application of (thio)urea catalysts for the MBH reaction was reported by Connon et al., but no asymmetric version was investigated. 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. 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.

Herein, we report improved bis(thio)urea catalysts derived from isophoronediamine [3-(aminomethyl)-3,5,5-trimethyl-cyclohexylamine, IPDA]. IPDA is a readily available 1,4-diamine produced industrially on a multiton scale. IPDA and its derivative isophoronediiisocyanate [5-isocyanato-1-(iso-cyanatomethyl)-1,3,3-

trimethylcyclohexane, IPDI] are used as monomers for urethane and epoxy resins. The large scale optical resolution of IPDA was described recently by our group.

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).

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

^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[^],3S)-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

(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.; Muller, T. N.; Cleeman, F.; Roland, K.; Brandenburg, M.; Neudorfl, 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.

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.

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.

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

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

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.

