Chiral phosphinothiourea organocatalyst in the enantioselective Morita–Baylis–Hillman reactions of aromatic aldehydes with methyl vinyl ketone

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ABSTRACT

A new class of chiral phosphinothioureas has been developed as efficient organocatalyst for the enantioselective Morita–Baylis–Hillman reaction of aromatic aldehydes with methyl vinyl ketone. The reaction proceeds under very mild conditions to afford the desired product in a short time period in good to excellent yields with up to 94% ee.

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The Morita–Baylis–Hillman (MBH) reaction is a powerful tool for the atom-economic construction of densely functionlized α-methylene-β-hydroxycarbonyl derivatives which serve as valuable building blocks in organic synthesis.[1] The development of a suitable asymmetric version of this reaction has attracted considerable interest in recent years.[2] Various chiral organocatalysts including quinidine-derived β-isocupreidine,[3] BINOL-derived Brønsted acid,[4] and bifunctional aminothiourea[5] have been notably developed for the asymmetric MBH reaction to achieve high enantiomeric excesses. Bis(thio)ureas derived from chiral *trans*-1,2-diaminocyclohexane, isophorone-diamine (IPDA), and H_8-BINAM were also proven to be efficient organocatalysts for the asymmetric MBH reactions of various aldehydes with 2-cyclohexen-1-one as described by Nagasawa, Berkessel and Shi, respectively.[6] However, Morita–Baylis–Hillman reactions involving methyl vinyl ketone (MVK) as reaction partner usually afforded the corresponding products in moderate enantioselectivities.[2,7] To the best of our knowledge, the highest enantioselectivity of this kind of MBH reaction was 83% ee using chiral tertiary amine/proline cocatalysts.[7d]

Cyclohexane-based aminothiourea has been extensively studied in recent years as a bifunctional organocatalyst for asymmetric catalysis.[8] In 2004, Yudin and co-workers reported cyclohexane-based iminophosphines derived from the ring-opening of aziridine for transition metal catalysis.[9] Due to the structural analogy between aminothiourea and iminophosphine, we envisioned that the overlapped structure, that is, phosphinothiourea (Fig. 1), could serve as a new class of bifunctional organocatalysts for enantioselective catalysis. As tertiary phosphines are effective catalysts for the MBH reaction, it is conceivable that the phosphinothiourea could catalyze this reaction in an enantioselective fashion.

The bifunctional phosphinothiourea was not documented before for asymmetric catalysis until recently Shi and Shi[10] reported the BINOL-derived phosphinothioureas as organocatalysts in the
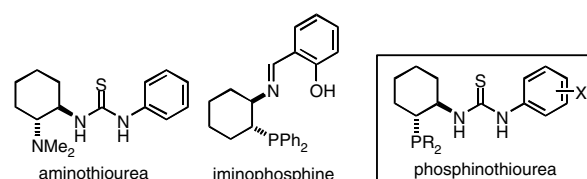

Figure 1. Overlap approach to design new catalyst.

presence of carboxylic acid as co-catalyst for the asymmetric aza-Morita–Baylis–Hillman reaction. However, the reaction usually takes a long time. Herein, we report a new class of phosphinothiourea organocatalysts, derived from *trans*-2-amino-1-(diphenylphosphino)cyclohexane (**1**),[11] which are fairly effective bifunctional organocatalysts for the enantioselective MBH reaction of arylaldehydes with MVK to give the corresponding adducts in up to 94% ee and good to excellent yields.

The organocatalysts **2a**–**f**[12] are easily prepared by condensation of (R,R)-2-amino-1-(diphenylphosphino)cyclohexane (**1**) with 1.1 equiv of the corresponding iso(thio)cyanate or isocyanate under mild conditions (Fig. 2, see Supplementary data).

We initially chose the reaction of MVK with *p*-nitrobenzaldehyde to screen the phosphinothioureas as bifunctional organocatalysts for the MBH reaction. To our delight, when using CH_2Cl_2 as solvent, the reaction completed in 45 min with catalyst **2a** to provide the desired MBH product in 71% yield and 85% ee (Table 1, entry 3). Longer reaction time afforded lower chemical yield due
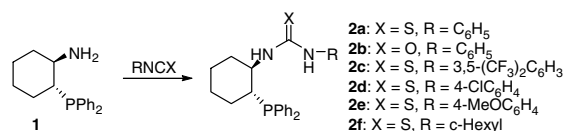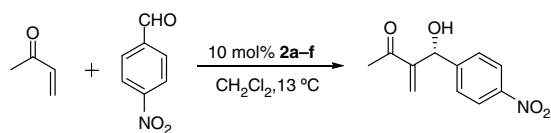

2a: X = S, R = C_6H_5
2b: X = O, R = C_6H_5
2c: X = S, R = 3,5-$(CF_3)_2C_6H_3$
2d: X = S, R = 4-ClC_6H_4
2e: X = S, R = 4-$MeOC_6H_4$
2f: X = S, R = *c*-Hexyl

Figure 2. New class of phosphinothiourea catalysts.

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Table 1
Screening of the catalysts for the reaction of MVK and 4-nitrobenzaldehyde[a]

Entry	Catalyst	t (min)	Yield[b] (%)	ee[c] (%)
1	**2a**	15	50	83
2	**2a**	30	66	85
3	**2a**	45	71	85
4	**2a**	60	64	85
5	**2a**	120	53	83
6[d]	**2a**	45	64	79
7	**2b**	45	trace	n.d.[e]
8	**2c**	45	83	4
9	**2d**	45	64	70
10	**2e**	45	62	83
11	**2f**	5	34	80

[a] Unless stated otherwise, the reactions were conducted with 10 mol % of organocatalyst, 5 equiv of MVK in CH_2Cl_2 (0.2 M) at 13 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] 5 mol % **2a** was used.
[e] Not determined.

to the over reaction with MVK (entries 4 and 5 vs 3). The thiourea moiety proved to be critical for the MBH reaction in terms of both yield and enantioselectivity. Urea derivative **2b** was ineffective under identical conditions (entry 7). Surprisingly, catalyst **2c** gave poor enantioselectivity, albeit with high yield (entry 8). Substitution at the 4-position of phenyl has no obvious effect on the enantioselectivity (entries 3, 9, and 10). Bearing an alkyl group, the phosphinothiourea **2f** afforded good level of enantioselectivity, but low yield (entry 11).

Further optimization including various solvents, temperature, and substrate concentration in the presence of catalyst **2a** led to the optimal reaction conditions (see Supplementary data): using **2a** as catalyst, the reaction of 5 equiv of MVK with 0.3 M of p-nitrobenzaldehyde in $CHCl_3$ completed in 15 min at 13 °C to provide the desired product in 75% yield and 94% ee.

Under the optimized conditions, the substrate scope in terms of aromatic aldehydes was first investigated. As indicated in Table 2, reaction of MVK with strong electron-deficient aldehydes usually proceeded very quickly (within 1 h) to provide the desired

Table 2
MBH reactions of MVK with aromatic aldehydes catalyzed by **2a**[a]
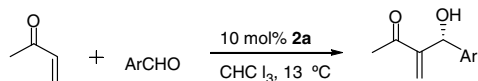
Entry	Ar	t (min)	Yield[b] (%)	ee[c] (%)
1	$4\text{-}NO_2C_6H_4$	15	75	94 (R)
2	$2\text{-}NO_2C_6H_4$	45	91	92 (R)
3	$3\text{-}NO_2C_6H_4$	20	71	94 (R)
4	$4\text{-}CNC_6H_4$	30	63	90 (R)
5	$4\text{-}CF_3C_6H_4$	60	65	92 (R)
6	$4\text{-}ClC_6H_4$	120	40	90 (R)
7	$2\text{-}ClC_6H_4$	120	62	87 (R)
8	$2,4\text{-}Cl_2C_6H_3$	60	61	89 (R)
9	$4\text{-}BrC_6H_4$	90	43	92 (R)
10	C_6H_5	180	48	90 (R)
11	2-Naphthyl	120	15	90 (R)

[a] Unless stated otherwise, the reactions were conducted with 10 mol % of organocatalyst, 5 equiv of MVK in $CHCl_3$ (0.3 M) at 13 °C.
[b] Isolated yields.
[c] The ee was determined by chiral HPLC, and the absolute configuration was determined by comparison of optical rotation with that of literature report.[7c,13]
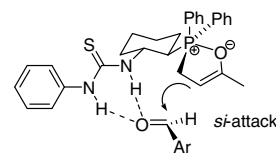

Figure 3. Proposed transition state.

products in very good yields and excellent enantioselectivities (90–94% ee, entries 1–5). Both mono- and di-halogen substituted arylaldehydes are tolerated to generate the products in high enantioselectivities (87–92% ee) albeit with moderate yields (entries 6–9). The reactions with non-substituted benzaldehyde and 2-naphthylaldehyde proceeded slowly to afford the product in high enantioselecitvity (90% ee), but low yields (entries 10 and 11). As a general trend, the reaction with electron-rich arylaldehyde proved to be difficult and complex mixture was observed.

The observed absolute configuration could be explained by the plausible transition state illustrated in Figure 3. The thiourea moiety forms hydrogen-bond with the aldehyde carbonyl. The cyclohexyl scaffold forces the phosphinoyl associated enolate to attack the activated carbonyl from the si-face to generate the R configuration.

In summary, we have developed a highly enantioselective Morita–Baylis–Hillman reaction involving the addition of MVK to aromatic aldehydes catalyzed by a phosphinothiourea organocatalyst derived from trans-2-amino-1-(diphenylphosphino)cyclohexane. The reaction proceeds under very mild conditions to afford the desired product in a short time period in good to excellent yields with generally excellent enantiomeric excesses (87–94% ee). Further efforts are underway with a focus on improving the catalyst activity and the scope of substrate as well as the mechanism of the asymmetric MBH reaction.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.042.

References and notes

1. For reviews, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. Tetrahedron 1996, 52, 8001–8062; (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Chem. Rev. 2003, 103, 811–892.
2. For reviews, see: Organocatalytic Enantioselective Morita–Baylis–Hillman (MBH) Reactions: (a) Menozzi, C.; Dalko, P. I. In Dalko, P. I., Ed.; Enantioselective Organocatalysis, Reactions and Experimental Procedures; Wiley-VCH: Weinheim, 2007; pp 151–187; (b) Masson, G.; Housseman, C.; Zhu, J. Angew. Chem., Int. Ed. 2007, 46, 4614–4628; (c) Basavaiah, D.; Rao, K. V.; Reddy, R. J. Chem. Soc. Rev. 2007, 36, 1581–1588.
3. (a) Iwabuchi, Y.; Nakatani, M.; Yodoyama, N.; Hatakeyama, S. J. Am. Chem. Soc. 1999, 121, 10219–10220; (b) Nakano, A.; Kawahara, S.; Morokuma, K.; Nakatami, M.; Iwabuchi, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. Tetrahedron 2006, 62, 381–389.
4. (a) McDougal, N. T.; Schaus, S. E. J. Am. Chem. Soc. 2003, 125, 12094–12095; (b) McDougl, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. Adv. Synth. Catal. 2004, 346, 1231–1240.
5. (a) Wang, J.; Yu, X.; Zu, L.; Wang, W. Org. Lett. 2005, 7, 4293–4296; (b) Lattanzi, A. Synlett 2007, 2106–2110.
6. (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) Shi, M.; Liu, X.-G. Org. Lett. 2008, 10, 1043–1046.

7. (a) Krishna, P. R.; Kannan, V.; Reddy, P. V. N. *Adv. Synth. Catal.* **2004**, *346*, 603–606; (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601–610; (c) Vasbinder, M. M.; Imbriglio, J. E.; Miller, S. J. *Tetrahedron* **2006**, *62*, 11450–11459; (d) Tang, H.; Zhao, G.; Zhou, Z.; Zhou, Q.; Tang, C. *Tetrahedron Lett.* **2006**, *47*, 5717–5721.

8. Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923–925 and references therein.

9. Dalili, S.; Caiazzo, A.; Yudin, A. K. *J. Organomet. Chem.* **2004**, *689*, 3604–3611.

10. Shi, Y.-L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129–2135.

11. Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597–2600.

12. During the preparation of this manuscript, Jacobsen reported *ent*-**2c** and similar organocatalysts for the asymmetric [3+2] cycloaddition: Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660–5661.

13. (a) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741–3743; (b) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal.* **2004**, *346*, 1106–1110.