DOI: 10.1002/cjoc.201500468

Highly Enantioselective Intramolecular Morita-Baylis-Hillman Reaction Catalyzed by Mannose-Based Thiourea-phosphine

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The saccharide-based chiral bifunctional thiourea-phosphines were developed as chiral organocatalysts for the intramolecular Morita-Baylis-Hillman reaction of *ω*-formyl-enones. With only 2 mol% of thiourea-phosphine catalyst **3c**, chiral functionalized cyclohexenes were achieved under mild reaction conditions with excellent yields and enantioselectivities.

Keywords allylic alcohol, bifunctional thiourea-phosphine, chiral squaramide, enantioselective organocatalysis, Morita-Baylis-Hillman reaction

Introduction

The asymmetric Morita-Baylis-Hillman (MBH) reaction is an important C—C bond-forming reaction providing enantioenriched allylic alcohols, which are useful building blocks in organic synthesis.[1] Since Hatakeyama[2] developed the first highly enantioselective MBH reaction, great progress has been made in the past decade.[3] To our knowledge, there are but a few reports concerning the enantioselective intramolecular MBH reaction. Although the first example of an asymmetric intramolecular MBH reaction was reported by Fráter in 1992,[4] this enantioselective reaction was not explored further until recent decade. In 2005 Hong's group reported the intramolecular MBH reaction of hept-2-enedial using proline and imidazole as co-catalyst system.[5] At the same time, Miller's group developed a co-catalyst system involving pipecolinic acid and *N*-methylimidazole for the intramolecular MBH reaction of enone-al.[6] Later, the chiral rhenium-containing phosphine was used as catalyst for the enantioselective intramolecular MBH reaction.[7] We have found the chiral bifunctional phosphines were efficient for the intramolecular MBH reaction due to the nucleophilic activation by tertiary phosphine and the electrophilic activation by hydrogen-bonding (Figure 1).[8] Very recently, Chen and co-workers developed chiral ferrocene-based squaramide-phospines as the bifunctional organocatalyst for the intramolecular MBH reaction.[9] In addition, resin-supported proline could promote the intramolecular MBH reaction.[10]

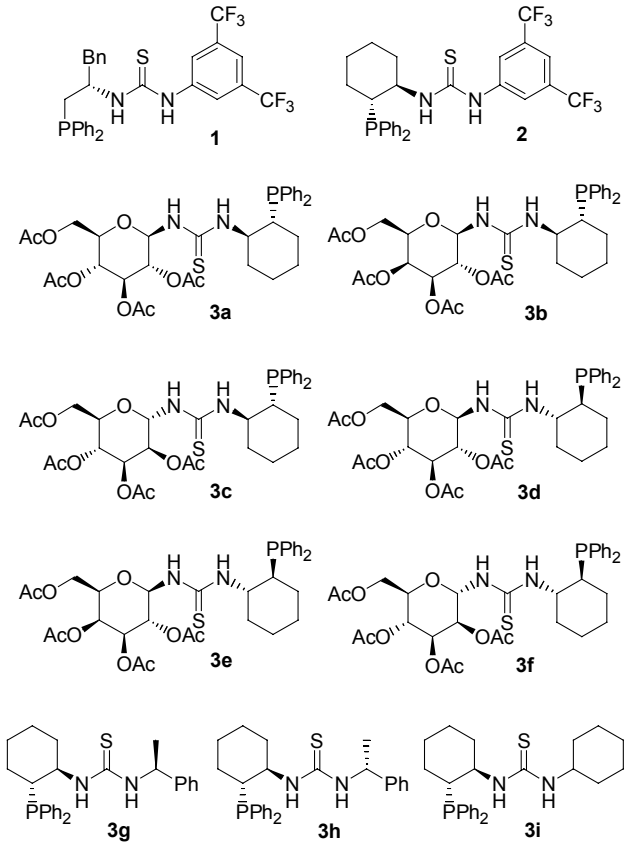

Figure 1 Structures of the chiral thiourea-phosphines.

Over the last decade, electrophile activation by chiral hydrogen-bond donors especially thiourea has emerged as an important tool for enantioselective synthesis.[11] It is demonstrated that introducing a saccharide scaffold into a bifunctional thiourea was a successful strategy to

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Received July 1, 2015; accepted September 20, 2015; published online September 29, 2015.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201500468 or from the author.

design efficient organocatalysts.[12] Compared with the previously developed tertiary thiourea-phosphine catalysts **1** and **2**,[13] saccharide-based thiourea-phosphine **3d** was more efficient in the intermolecular MBH reaction with higher reactivity and wider substrate scope (Figure 1).[14] Inspired by the previous work, we are interested in evaluating these catalysts in the intramolecular MBH reactions. Herein, we report the highly enantioselective intramolecular MBH reaction catalyzed by saccharide-based thiourea-phosphines.

Experimental

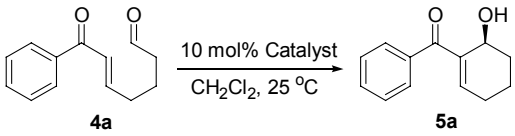
General procedure for the intramolecular Morita-Baylis-Hillman reaction: thiourea-phosphine **3c** (2.7 mg, 0.004 mmol) and *t*-BuOH (2.0 mL) were added to a vessel containing *ω*-formyl-enone **4**[15] (0.2 mmol) at 25 ℃. The resulting mixture was stirred at this temperature until the reaction was completed (monitored by TLC). Then the solvent was removed under reduced pressure, and the residue was purified by a flash column chromatography (silica gel, petroleum ether/EtOAc/CH_2Cl_2 as the eluent) to afford the desired product.[8a] The *ee* values were determined by HPLC analysis with a chiral column.

† Electronic Supplementary Information (ESI) available: HPLC spectra for the Morita-Baylis-Hillman products. See DOI: 10.1039/b000000x/.

Results and Discussion

Our initial investigation of enantioselective intramolecular MBH reaction of *ω*-formyl-enone **4a** was performed in CH_2Cl_2 with 10 mol% thiourea-phosphine **3** at 25 ℃. The results in Table 1 indicted that the sugar moiety of the catalysts had a remarkable effect on the reactivity and enantioselectivity of the intramolecular MBH reaction. The stereochemical control of the reaction resulted from the chirality of the cyclohexyl aminophosphine backbone (Entries 1—3 vs. 4—6). All the selected sugars (*D*-glucose, *D*-galactose and *D*-mannose) matched with an (*R*,*R*)-configuration of cyclohexyl aminophosphine to accelerate the MBH reaction with excellent yields (Entries 1—3). In contrast, their diastereomers **3d**—**3f** bearing the (*S*,*S*)-cyclohexyl aminophosphine exhibited poor reactivity (Entries 4—6). On the other hand, the enantioselectivity of the MBH reaction was highly affected by the configuration at the C1 and C2 carbon atom of the sugar scaffold.[12j,16] Thus *D*-mannose-based organocatalyst **3c** achieved higher enantioselectivity than *D*-glucose-based catalyst **3a** and *D*-galactose-based catalyst **3b**, while organocatalyst **3f** provided lower enantioselectivity than *D*-glucose derivative **3d** and *D*-galactose derivative **3e**. Among the screened thiourea-phosphine containing saccharide moiety, *D*-mannose-based organocatalyst **3c** provided the highest yield and enantioselectivity within 36 h (99% yield and 94% *ee*, Entry 3). To further prove the effect of the sugar scaffold, thiourea-phosphines **3g** and **3h** bearing a simple chiral group and cyclohexane-based thiourea-phosphines **3i** were also examined, and they could not provide good enantioselectivity (Entries 7—9). Compared with thiourea-phosphine **1** and **2** without saccharide scaffold, *D*-mannose-based thiourea-phosphine **3c** displayed a higher effectivity (Entries 3 vs. 10 and 11).[8] Moreover, the catalyst loading of **3c** could be decreased to 3 mol% displaying the same level of catalytic activity (Entry 13 vs. 3).

Table 1 Catalyst screening for the intramolecular MBH reaction of **4a**[a]



Entry	Catalyst	Time/d	Yield[b]/%	*ee*[c]/%
1	**3a**	3	99	69
2	**3b**	3	92	54
3	**3c**	1.5	99	94
4	**3d**	3	47	–83
5	**3e**	3	43	–88
6	**3f**	3	45	–80
7	**3g**	4.5	76	4
8	**3h**	4.5	61	12
9	**3i**	4.5	63	36
10	**1**	0.5	83	–76
11	**2**	1.5	99	76
12[d]	**3c**	3	99	91
13[e]	**3c**	5	90	90

[a] Unless stated otherwise, the reactions were performed on 0.2 mmol scale in 1.0 mL CH_2Cl_2 (0.2 mol/L) using 10 mol% of catalyst at 25 ℃. [b] Isolated yields. [c] The *ee* values were determined by chiral HPLC analysis, and the absolute configuration was assigned by comparison of optical rotation value with that reported in literature.[6] [d] Using 5 mol% **3c** as catalyst. [e] Using 3 mol% **3c** as catalyst.

Next, solvent effect was examined in the reaction of *ω*-formyl-enone **4a** using 3 mol% **3c** as the catalyst (Table 2). The survey of solvents indicated that the nonpolar solvents, such as *n*-hexane and toluene, led to moderate chemical yields (Entries 1 and 2), whereas the aprotic polar solvents afforded poor yields due to the low conversion of **4a** in these solvents (Entries 5—7). Comparatively, protic solvents examined except MeOH were evidently observed to accelerate the reaction rate (Entries 9—11), which usually possess a deleterious effect against the Michael additions for destructing the hydrogen bonds between substrates and the thiourea moiety.[17] The alcohol has probably acted as a shuttle to reduce the energy of the proton-transfer to activate MBH reaction.[18] *t*-BuOH was indicated to be a better solvent, leading to the desired product **5a** in 90% yield

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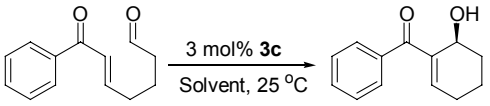
and 95% *ee* within 2 d (Entry 11). The addition of water to the *t*-BuOH solution could promote the proton of the solvent, but it caused a sharp decrease of both yield and enantioselectivity (Entry 12 vs. 11), which indicated that water had a negative influence towards the reaction. To our pleasure, the product **5a** could also be obtained in both excellent yield and enantioselectivity with lower load of catalyst (2 mol% of **3c**, Entry 13). Further decreasing the load of **3c** to 1 mol% led to the descent of chemical yield and enantioselectivity (Entry 14). As indicated in Entry 15, satisfying result could also be obtained when the concentration was decreased to 0.1 mol/L, leading to **5a** with 90% yield and 95% *ee*. Therefore, the optimal reaction condition was confirmed as described in Entry 15.

Table 2 The survey of solvents for the intramolecular MBH reaction of **4a**[a]



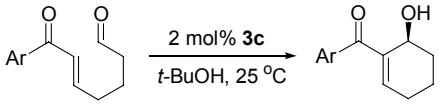
4a **5a**

Entry	Solvent	Time/d	Yield[b]/%	*ee*[c]/%
1	*n*-Hexane	5	60	95
2	Toluene	5	80	83
3	$CHCl_3$	5	87	86
4	CH_2Cl_2	5	90	90
5	THF	5	21	93
6	CH_3CN	5	10	90
7	DMF	4	trace	nd[d]
8	MeOH	5	30	6
9	EtOH	1.5	92	70
10	*i*-PrOH	2	93	90
11	*t*-BuOH	2	90	95
12[e]	*t*-BuOH/H_2O	2	65	66
13[f]	*t*-BuOH	2	90	94
14[g]	*t*-BuOH	4	84	85
15[f,h]	***t*-BuOH**	**2**	**90**	**95**

[a] Unless stated otherwise, the reactions were performed on 0.2 mmol scale in 1.0 mL solvent (0.2 mol/L) using 3 mol% of catalyst **3c** at 25 ℃. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Not determined. [e] 0.5 mL of *t*-BuOH and 0.5 mL of H_2O as solvent. [f] Using 2 mol% **3c** as catalyst. [g] Using 1 mol% **3c** as catalyst. [h] The reaction was performed on 0.2 mmol scale in 2.0 mL solvent (0.1 mol/L) at 25 ℃.

Under the optimized reaction conditions, the substrate scope of the intramolecular MBH reaction was investigated. It is noteworthy that the reactions took place very efficiently (Table 3, 86%—99% yield) with excellent levels of enantioselectivity (90%—99% *ee*) for all of the screened substrates except *ortho*-substituted aryl enone probably due to the *ortho* effect (Entry 2 vs. Entries 1 and 3—12). The enantioselectivity was gradually enhanced along with the electron enrichment on the phenyl group, while longer reaction times were required for complete conversion (Entries 9—12 vs. 1). Compared with thiourea-phosphine **1** and **2**,[8] *D*-mannose-based thiourea-phosphine **3c** exhibited better substrate generality and enantioselectivity in the intramolecular MBH reaction of *ω*-formyl-enones. Unfortunately, *D*-mannose-based thiourea-phosphine **3c** was still not efficient for the intramolecular MBH reaction of methyl *ω*-formyl-enone and phenyl *δ*-formylenone.

Table 3 Substrate scope of intramolecular MBH reaction catalyzed by **3c**[a]



4 **5**

Entry	Ar	Time/d	Yield[b]/%	*ee*[c]/%
1	Ph	2	90	95
2	2-BrC_6H_4	2	96	29
3	3-BrC_6H_4	3	92	90
4	4-BrC_6H_4	2	92	90
5	3-ClC_6H_4	2.5	95	90
6	4-ClC_6H_4	2	93	92
7	4-FC_6H_4	2	90	93
8	2-Naphthyl	2	97	96
9	3-MeC_6H_4	2.5	99	97
10	4-MeC_6H_4	2.5	93	97
11	4-$MeOC_6H_4$	4	93	99
12	4-$Me_2NC_6H_4$	6	86	99

[a] The reactions were performed on 0.2 mmol scale in 2.0 mL *t*-BuOH (0.1 mol/L) using 2 mol% of catalyst **3c** at 25℃. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

Conclusions

In conclusion, we have developed a highly enantioselective intramolecular MBH reaction catalyzed by the *D*-mannose-based chiral thiourea-phosphine. The intramolecular MBH reaction of *ω*-formyl-enones could be performed efficiently using 2 mol% of thiourea-phosphine **3c** under mild conditions to provide chiral cyclic allylic alcohols in excellent yields and enantioselectivities. Further applications of the sugar-based chiral thiourea-phosphines in enantioselective reactions are currently undergoing in our group.

Acknowledgement

We acknowledge the financial support from National Natural Science Foundation of China (Nos. 20772029, 21242007), the Program for New Century Excellent Talents in University (No. NCET-07-0286), and the Fundamental Research Funds for the Central Universi-

ties.

References

[1] Selected papers on the application of chiral allylic alcohols, see: (a) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534; (b) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun*. **2001**, 2030; (c) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616; (d) Adam, W.; Alsters, P. L.; Neumann, R.; Saha-Möller, C. R.; Sloboda-Rozner, D.; Zhang, R. *J. Org. Chem*. **2003**, *68*, 1721; (e) Fournier, J.-F.; Mathieu, S.; Charette, A. B. *J. Am. Chem. Soc*. **2005**, *127*, 13140; (f) Griesbeck, A. G.; El-Idreesy, T. T.; Lex, J. *Tetrahedron* **2006**, *62*, 10615; (g) Hamed, O.; Henry, P. M.; Becker, D. P. *Tetrahedron Lett*. **2010**, *51*, 3514; (h) Kanbayashi, N.; Onitsuka, K. *Angew. Chem.*, *Int. Ed*. **2011**, *50*, 5197; (i) Li, Z.; Parr, B. T.; Davies, H. M. L. *J. Am. Chem. Soc*. **2012**, *134*, 10942.

[2] Iwabuchi, Y.; Nakatani, M.; Yodoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc*. **1999**, *121*, 10219.

[3] For reviews on the asymmetric MBH reactions, see: (a) Masson, G.; Housseman, C.; Zhu, J. *Angew*. *Chem.*, *Int*. *Ed*. **2007**, *46*, 4614; (b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem*. *Soc*. *Rev*. **2007**, *36*, 1581; (c) Krishna, P. R.; Sachwani, R.; Reddy, P. S. *Synlett* **2008**, 2897; (d) Carrasco-Sanchez, V.; Simirgiotis, M. J.; Santos, L. S. *Molecules* **2009**, *14*, 3989; (e) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005; (f) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174; (g) Mansilla, J.; Saa, J. M. *Molecules* **2010**, *15*, 709; (h) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659; (i) Wei, Y.; Shi, M. *Chem.-Asian J.* **2014**, *9*, 2720.

[4] Roth, F.; Gygax, P.; Fráter, G. *Tetrahedron Lett.* **1992**, *33*, 1045.

[5] Chen, S.-H.; Hong, B.-C.; Su, C.-F.; Sarshar, S. *Tetrahedron Lett*. **2005**, *46*, 8899.

[6] (a) Aroyan, C. E.; Vasbinder, M. M.; Miller, S. J. *Org*. *Lett*. **2005**, *7*, 3849; (b) Selig, P. S.; Miller, S. J. *Tetrahedron Lett.* **2011**, *52*, 2148.

[7] Seidel, F.; Gladysz, J. A. *Synlett* **2007**, 986.

[8] (a) Gong, J.-J.; Yuan, K.; Song, H.-L.; Wu, X.-Y. *Tetrahedron* **2010**, *66*, 2439; (b) Yuan, K.; Song, H.-L.; Hu, Y.; Fang, J.-F.; Wu, X.-Y. *Tetrahedron*: *Asymmetry* **2010**, *21*, 903.

[9] Zhang, X.; Ma, P.; Zhang, D.; Yang, L.; Zhang, S.; Jiang, R.; Chen, W. *Org. Biomol. Chem.* **2014**, *12*, 2423.

[10] Akagawa, K.; Sakamoto, S.; Kudo, K. *Synlett* **2011**, 817.

[11] For recent reviews on the chiral bifunctional thioureas, see: (a) Dalko, P. I. *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH, Weinheim, **2009**; (b) Connon, S. J. *Chem.-Eur. J.* **2006**, *12*, 5418; (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 1520; (d) Takemoto, Y. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1139; (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; (f) Yu, X.; Wang, W. *Chem.-Asian J.* **2008**, *3*, 516; (g) Zhang, Z. G.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187; (h) Connon, S. J. *Synlett* **2009**, 354; (i) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, 1; (j) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593; (k) Huang, Y.-B.; Yi, W.-B.; Cai, C. *Top. Curr. Chem.* **2012**, *308*, 191; (l) Narayanaperumal, S.; Rivera, D. G.; Silva, R. C.; Paixão, M. W. *ChemCatChem* **2013**, *5*, 2756.

[12] (a) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923; (b) Li, X.-J.; Liu, K.; Ma, H.; Nie, J.; Ma, J.-A. *Synlett* **2008**, 3242; (c) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707; (d) Lu, A.; Gao, P.; Wu, Y.; Wang, Y.; Zhou, Z.; Tang, C. *Org. Biomol. Chem.* **2009**, *7*, 3141; (e) Pu, X.; Li, P.; Peng, F.; Li, X.; Zhang, H.; Shao, Z. *Eur. J. Org. Chem.* **2009**, 4622; (f) Gu, Q.; Guo, X.-T.; Wu, X.-Y. *Tetrahedron* **2009**, *65*, 5265; (g) Ma, H.; Liu, K.; Zhang, F.-G.; Zhu, C.-L.; Nie, J.; Ma, J.-A. *J. Org. Chem.* **2010**, *75*, 1402; (h) Pu, X.-W.; Peng, F.-Z.; Zhang, H.-B.; Shao, Z.-H. *Tetrahedron* **2010**, *66*, 3655; (i) Nie, J.; Li, X.-J.; Zheng, D.-H.; Zhang, F.-G.; Cui, S.; Ma, J.-A. *J. Fluorine Chem.* **2011**, *132*, 468; (j) Agarwal, J.; Peddinti, R. K. *Eur. J. Org. Chem.* **2012**, 6390; (k) Yuan, H.-N.; Wang, S.; Nie, J.; Meng, W.; Yao, Q.; Ma, J.-A. *Angew*. *Chem.*, *Int*. *Ed*. **2013**, *52*, 3869; (l) Yuan, H.-N.; Li, S.; Nie, J.; Zheng, Y.; Ma, J.-A. *Chem.-Eur. J.* **2013**, *19*, 15856.

[13] (a) Gong, J.-J.; Yuan, K.; Wu, X.-Y. *Tetrahedron*: *Asymmetry* **2009**, *20*, 2117; (b) Yuan, K.; Song, H.-L.; Hu, Y.; Wu, X.-Y. *Tetrahedron* **2009**, *65*, 8185.

[14] Yang, W.-H.; Sha, F.; Zhang, X.; Yuan, K.; Wu, X.-Y. *Chin. J. Chem.* **2012**, *30*, 2652.

[15] (a) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41; (b) Denney, D. B.; Smith, L. C.; Song, J.; Rossi, C. J.; Hall, C. D. *J. Org. Chem.* **1963**, *28*, 778; (c) Yagi, K.; Turitani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111; (d) Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913.

[16] (a) Henderson, A. S.; Bower, J. F.; Galan, M. C. *Org. Biomol. Chem.* **2014**, *12*, 9180; (b) Zhao, J.; Zhang, Y.; Han, F.; Zhao, S. *Carbohydr. Res*. **2009**, *344*, 61.

[17] (a) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713; (b) Mandai, H.; Shimowaki, K.; Mitsudo, K.; Suga, S. *Asian J. Org. Chem.* **2014**, *3*, 437.

[18] (a) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723; (b) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 1706; (c) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513.

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