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Hydroxyl Group-Directed Organocatalytic Asymmetric Michael Addition of α,β-Unsaturated Ketones with Alkenylboronic Acids

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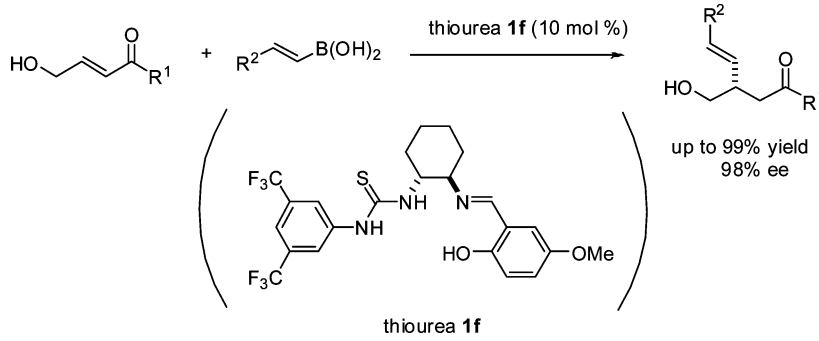
ABSTRACT



The organocatalytic asymmetric Michael addition of organoboronic acids to γ-hydroxy enones in the presence of an iminophenol-type thiourea catalyst is demonstrated. The hydroxyl group in the substrates plays a critical role in this reaction.

Asymmetric catalytic Michael addition of organoboronic acids to various electrophiles is a powerful tool for the construction of the carbon−carbon bonds.[1] Due to their stability toward air and moisture relative to other typical organometallic reagents such as Grignard reagents[2] and organolithium compounds,[3] organoboronic acids are considered to be some of the most useful carbon nucleophiles in organic chemistry. Most of the reported asymmetric catalytic Michael additions with organoboronic acids are in the presence of metallic catalysts such as rhodium and chiral phosphine ligands.[1] On the other hand, at the beginning of our research to achieve the organocatalytic asymmetric Michael addition of organoboronic acids, there were only two reported nonmetallic versions[4] of these reactions.[5] Chong et al. reported the Michael addition of alkenyl and alkynyl boronates to α,β-unsaturated ketones catalyzed by the

(1) For reviews, see: (a) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. For recent examples, see: (c) Navarro, C.; Moreno, A.; Csaky, A. G. *J. Org. Chem.* **2009**, *74*, 466. (d) Nishikawa, T.; Kiyomura, S.; Yamamoto, Y.; Miyaura, N. *Synlett* **2008**, 2487. (e) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J. P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (f) Nishimura, T.; Nagaosa, M.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 860.

(2) For recent examples, see: (a) Biswas, K.; Woodward, S. *Tetrahedron: Asymmetry* **2008**, *19*, 1702. (b) Wang, S.; Ji, S.; Loh, T. *J. Am. Chem. Soc.* **2007**, *129*, 276. (c) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 276.

(3) For recent examples, see: (a) Yamamoto, Y.; Suzuki, H.; Yasuda, Y.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **2008**, *49*, 4582. (b) Duguet, N.; Harrison-Marchand, A.; Maddaluno, J.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5745.

(4) For recent reviews of organocatalysts, see: (a) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5318. (e) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (f) Brekessel, H.; Groger, H. *Asymmetric Organocatalysis*, Wiley-VCH: Weinheim, 2004.

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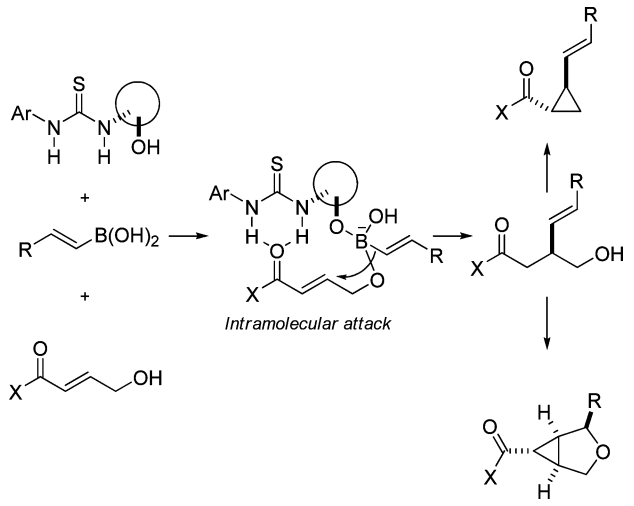
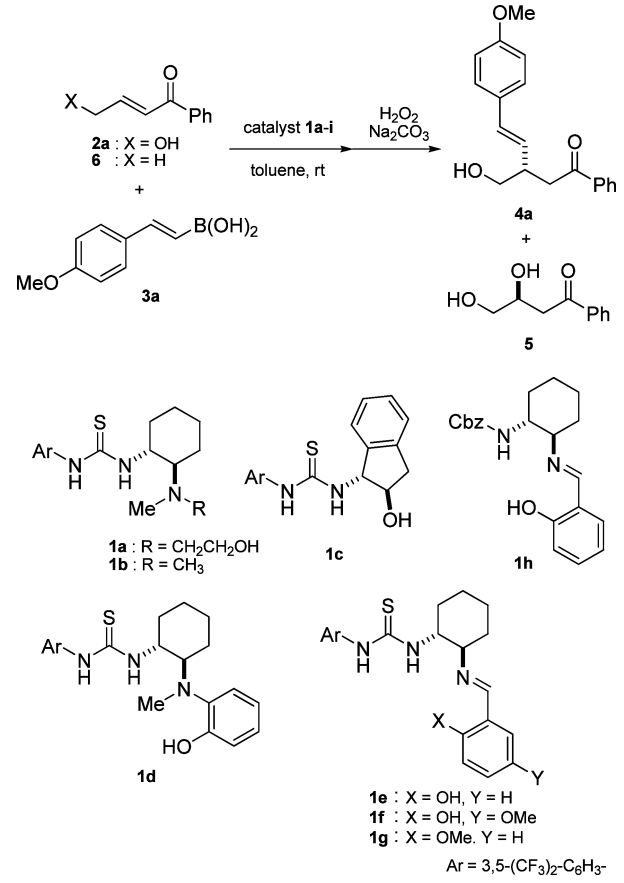
electron-deficient BINOL catalyst.[5] Recently, we reported that the bifunctional amino alcohol thiourea **1a** could be used for the 1,2-addition of organoboronic acids to acylquinolium species.[6,7] According to our and Chong's reports, it seemed that boronic acids were activated by the hydroxyl groups of the catalysts. Therefore, we speculate that if a hydroxyl group is added to the substrates, dual coordination of the substrate and the catalyst to the organoboronic acid should enhance the reactivity (Scheme 1).[8,9]

Scheme 1



Furthermore, the hydroxyl group of the products could be used for further transformations. We report here an organocatalytic asymmetric Michael addition of organoboronic acid to α,β-unsaturated ketones bearing a hydroxyl group at the γ-position together with its transformation to obtain unique cyclic compounds. Based on our hypothesis, we investigated the Michael addition of *p*-methoxyphenylvinyl boronic acid **3a** to γ-hydroxyenone **2a** in the presence of amino alcohol thiourea **1a** which had been developed previously.[6] Although the desired Michael adduct **4a** was indeed obtained in moderate yield, the enantiomeric excess of **4a** was somewhat low (36% ee). Recently, the oxy-Michael addition of arylboronic acids to **2a** catalyzed by the thiourea derived from a cinchona alkaloid was reported by Falck et al.[10] The obtained Michael adduct was converted to diol **5** under oxidative workup. When we treated the reaction mixture with H_2O_2 and Na_2CO_3, diol **5** was isolated in 22% yield with 64% ee (Table 1, entry 1). The same reaction with **1b**[11] gave

Table 1. Catalyst Screening of the Michael Addition[a]



			4a		5	
entry	catalyst	time (h)	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)
1	**1a**	36	52	36	22	64
2	**1b**	24	<1		88	88
3	**1c**[d]	72	20	8	0	
4	**1d**	72	38	47	0	
5	**1e**	36	91	95	0	
6	**1f**	24	92	97	0	
7	**1g**	72	36	26	16	33
8	**1h**	72	16	14	0	
9[e]	**1f**	36	0		0	

[a] Reactions were carried out with **2a** (1.0 equiv), **3a** (2.0 equiv), and catalyst **1a**−**h** (10 mol %) in toluene at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Catalyst loading was 20 mol %. [e] **6** was used instead of **2a**.

the diol **5** exclusively in high yield with 88% ee (entry 2). These results suggest that the basic amine might promote the production of diol, while the alcohol moieties promote the production of vinyl adduct **4a**. Therefore, we examined several thioureas bearing a hydroxyl group and no basic

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(7) Similar BINOL catalysts such as Chong's could be applied for the asymmetric 1,2-addition of organoboronic acids; see: (a) Lou, S.; Schaus, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 6922. (b) Lou, S.; Moquist, P. M.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398. (c) Lou, S.; Moquist, P. M.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.

(8) During the course of our investigation, a related report has appeared in the literature; see: (a) Kim, S.-G. *Tetrahedron Lett.* **2008**, *49*, 6148.

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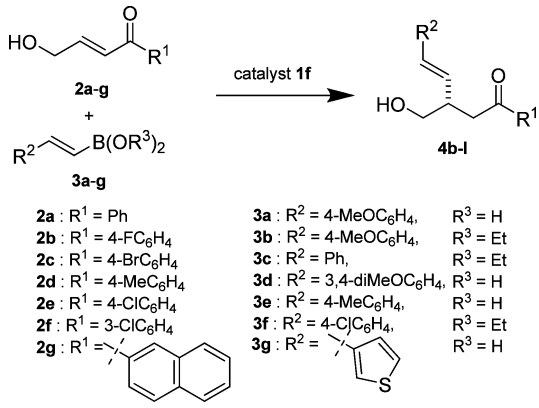
(11) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

amino group. Alcoholic catalyst **1c** showed poor reactivity for the Michael addition of the vinylboronic acid, but the production of **5** was completely suppressed (entry 3). The use of thiourea **1d**, which has a more acidic phenol group, resulted in an increase in the chemical yield of **4a** with no production of diol **5** (entry 4). Based on these results, we next screened the phenol thiourea catalysts. As a result, we found that iminothiourea **1e** provided the desired vinyl adduct **4a** in good yield and high ee (entry 5). Thiourea **1f**, which is derived from 2-hydroxy-5-methoxybenzaldehyde, showed increased reactivity in this reaction (entry 6). To investigate the role of the hydroxyl group and thiourea moiety of the catalyst, we synthesized catalysts **1g** and **1h**. These catalysts gave diminished yield and ee (entries 7 and 8). In addition, substrate **6** (X = H) gave neither the Michael adduct **4a** nor the diol **5** under the same conditions as in entry 5 (entry 9). Therefore, the hydroxyl groups of both the substrate and catalysts must participate in this reaction.

Having established the optimized catalyst for this Michael addition, we next screened several substrates **2b**−**g** and organoboronic acids **3a**−**g** (Table 2). First, the four substrates

Table 2. Substrate Scope of the Michael Addition[a]



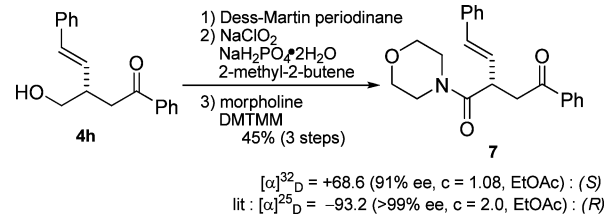
entry	2	3	time (h)	product	yield[b] (%)	ee[c] (%)
1	**2b**	**3a**	24	**4b**	81	97
2	**2c**	**3a**	24	**4c**	84	94
3	**2d**	**3a**	24	**4d**	86	95
4	**2e**	**3a**	24	**4e**	95	94
5	**2f**	**3b**	24	**4f**	82	97
6	**2g**	**3a**	36	**4g**	91	92
7[d]	**2a**	**3c**	72	**4h**	79	92
8	**2a**	**3d**	24	**4i**	99	98
9	**2a**	**3e**	36	**4j**	87	92
10[d]	**2a**	**3f**	72	**4k**	64	93
11	**2a**	**3g**	24	**4l**	84	91

[a] Reactions were carried out with **2** (1.0 equiv), **3** (2.0 equiv) and catalyst **1h** (10 mol %) in toluene at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Catalyst loading was 20 mol %.

with several substituents at the para position of the phenyl groups were treated with *p*-methoxyphenylvinylboronic acid **3a** in the presence of iminothiourea **1f** to give the desired products **4b**−**e** in good yields and ee's (entries 1−4). In the case of meta-substituted substrate **2f**, the reaction with **3a** and **1f** gave slightly diminished enantioselectivity (94% yield, 77% ee, data not shown). After several examinations, we found that the use of ethylboronate **3b**[6]a instead of **3a** improved the stereoselectivity (entry 5). The substrate with a bulky naphthyl group **2g** also gave a good result (entry 6). With regard to the boronic acids, the electrodensity of the reagents significantly affected the yield. When relatively electron-deficient nucleophiles **3c** and **3f** were used in this reaction, 20 mol % of the catalyst **1f** and a prolonged reaction time were necessary to achieve a good yield (entries 7 and 10).[12] In contrast, electron-rich nucleophiles **3d** and **3e** gave good results under the same reaction conditions as with **3a** (entries 8 and 9). In addition, the heteroaromatic vinylboronic acid **3g**[6] could be used for this transformation (entry 11).

The absolute configuration of the Michael adduct **4** was determined by the conversion of **4h** into known compound **7**,[13] as shown in Scheme 2. Dess−Martin oxidation[14] of **4h**

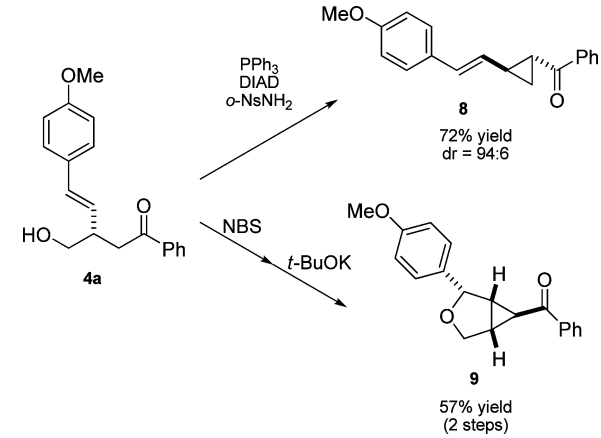
Scheme 2. Determination of the Absolute Configuration of the Michael Adduct **4h**



was followed by Pinnick oxidation[15]and condensation with morpholine in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[16] to give ketone **7** in 45% yield in three steps. Comparison of the specific rotation of synthetic **7** with that reported in the literature showed that the Michael adduct **4h** has an *S*-configuration.

We explored the transformation of the Michael adduct **4a** into unique cyclic compounds (Scheme 3). Unexpectedly, the

Scheme 3. Transformations of the Michael Adduct **4a**



reaction of Michael adduct **4a** with *o*-nitrobenzenesulfonamide under Mitsunobu conditions[17] produced the cyclopropyl ketone **8** in 72% yield with high diastereoselectivity. In addition, successive treatment of **4a** with *N*-bromosuccinimide and *t*-BuOK provided the bicycle [3.1.0] compound **9** in 57% yield.

In summary, we have developed a novel catalyst **1f** for the asymmetric Michael addition of various organoboronic acids or organoboronates to γ-hydroxyenones. The Michael adducts obtained were successfully transformed into cyclopropyl and bicyclic compounds. Further studies are currently underway to clarify the precise mechanism of the thiourea-catalyzed asymmetric Michael addition of organoboronic acids.

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Supporting Information Available: Experimental procedures and spectroscopic data for catalysts **1d**−**h**, substrates **2a**−**g**, products **4a**−**l**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) When less reactive nucleophiles were used, 2-phenylfuran was produced as the byproduct, and the yield of the desired products had been decreased. For the reactions of γ-hydroxy enones, see: Greatrex, B. W.; Kimber, M. C.; Taylor, D. K.; Tiekink, T. K. *J. Org. Chem.* **2003**, *68*, 4239.

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