Enantioselective conjugate addition of boronic acids to enones catalyzed by *O*-monoacyltartaric acids†

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We have found that *O*-monoacyltartaric acids catalyze asymmetric conjugate addition of boronic acids to enones with good enantioselectivity, and the 3,5-di(*tert*-butyl)benzoyl group provides the best results among the acyl groups examined.

Enantioselective 1,4- and 1,2-additions of boronic acids to α,β-unsaturated carbonyl compounds, aldehydes, ketones, or imines constitute effective C–C bond forming reactions in organic synthesis.[1] Although numerous efficient chiral transition metal catalysts are known, few organocatalysts (chiral biphenol derivatives,[2–4] thioureas,[5] and secondary amines)[6] have been successful in these transformations. Herein we report a class of chiral catalysts, *O*-monoacyltartaric acids **1** (Fig. 1),[7] capable of activating boronic acids.[8]

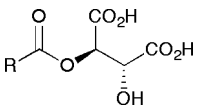
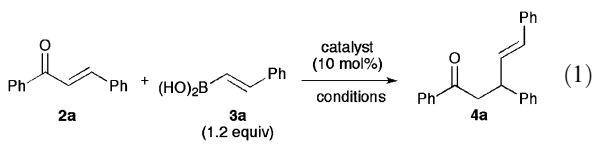


Fig. 1 *O*-Monoacyltartaric acids **1**.

Because α-hydroxycarboxylic acids are suitable scaffolds for boronic acids,[9] we hypothesized that they may activate boronic acids. Thus, we initially examined the activity of L-tartaric acid (10 mol%) for the conjugate addition of (*E*)-styrylboronic acid (**3a**) to chalcone (**2a**) (eqn (1)). The reaction in refluxing dichloromethane (0.05 M relative to **2a**) for 24 h gave the desired product **4a** in 89% yield with 25% ee. However, without L-tartaric acid under the same conditions, **4a** was obtained in 31%. Changing the solvent to toluene effectively suppressed the non-catalyzed reaction to 5% yield, whereas the presence of L-tartaric acid resulted in a similar yield and selectivity as the reaction in dichloromethane (97%, 24% ee).



(1)

Using toluene, we then examined the activity of other tartaric acid derivatives (10 mol%). For comparison, all reactions were conducted in toluene at 50 °C for 24 h. Protecting either the two carboxyl groups or the two hydroxy groups of L-tartaric acid significantly decreased the activity [dimethyl L-tartrate (6%, 0% ee), *O*,*O*-dibenzoyl L-tartaric acid (14%, 4% ee)]. On the other hand, an acceptable enantioselectivity (45% ee) was obtained with *O*-monobenzoyl L-tartaric acid (**1a**), but the yield was low (23%). Upon further examination, the addition of methanol (2 equiv. relative to **3a**) at a higher concentration (toluene, 0.3 M) improved both the yield and selectivity (38%, 59% ee; see Table 1, entry 1). Methanol suppressed the non-catalyzed reaction (6%) because **4a** was obtained in 35% yield in the absence of both **1a** and methanol.[10]

Under conditions using the methanol additive, various monoacylated L-tartaric acids[11] were investigated (Table 1). 1- and 2-Naphthoyl groups improved the chemical yield and selectivity (entries 2 and 3). Additionally, *meta*-substitution provided a superior selectivity compared to *ortho*- and *para*-substitution of the methyl substituent in the benzoyl group (entries 4–6). 3,5-Dimethylbenzoate **1g** was more selective than monomethylated **1e** (entry 7). Introducing electron-donating methoxy groups at the 3,5-positions significantly decelerated the reaction (entry 8), whereas electron-withdrawing trifluoromethyl groups exhibited a higher activity (entry 9). Moreover, bulkier alkyl substituents at the 3,5-positions increased the selectivity (entries 7, 10 and 11). These results suggest that not only the electronic effect but also the steric bulkiness of the substituent plays an important role for the activity and selectivity of the catalyst. Meanwhile, varying the reaction temperature with catalyst **1k** did not improve the selectivity (entries 12 and 13). Among the *O*-monoacylated L-tartaric acids (**1a–k**) tested, 3,5-di(*tert*-butyl)benzoate **1k** gave the best results (entry 11).

Table 1 Enantioselective conjugated addition of **3a** to **2a** catalyzed by *O*-monoacyltartaric acid **1**[a]

Entry	R in **1**	%yield of **4a**	%ee of **4a**[b]
1	Ph (**1a**)	38	59
2	1-naphthyl (**1b**)	86	69
3	2-naphthyl (**1c**)	41	70
4	*o*-tolyl (**1d**)	63	64
5	*m*-tolyl (**1e**)	51	70
6	*p*-tolyl (**1f**)	58	62
7	$3,5\text{-Me}_2C_6H_3$ (**1g**)	77	80
8	$3,5\text{-(MeO)}_2C_6H_3$ (**1h**)	22	73
9	$3,5\text{-(F}_3C)_2C_6H_3$ (**1i**)	81	79
10	$3,5\text{-}^i\text{Pr}_2C_6H_3$ (**1j**)	74	82
11	$3,5\text{-}^t\text{Bu}_2C_6H_3$ (**1k**)	92	87
12[c]	**1k**	41	87
13[d]	**1k**	90	86

[a] Unless otherwise noted, reactions were carried out using chalcone (**2a**) (0.3 mmol), (*E*)-styrylboronic acid (**3a**) (0.36 mmol), *O*-monoacyltartaric acid (10 mol%), and methanol (0.72 mmol) in toluene (1 mL) at 50 °C for 24 h. [b] All cases gave the (*S*)-isomer. [c] At 40 °C. [d] At 60 °C.

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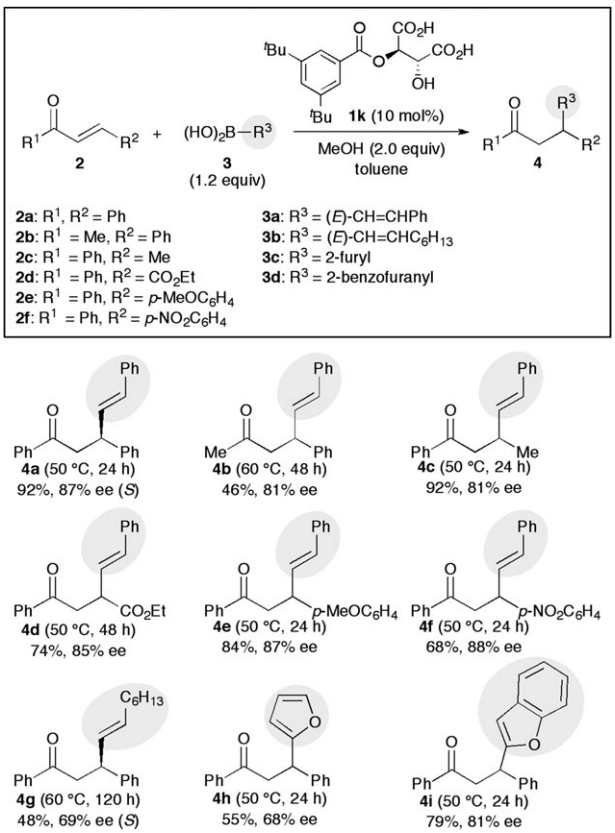

Scheme 1 *O*-3,5-Di(*tert*-butyl)benzoyltartaric acid (**1k**)-catalyzed conjugate addition. The values in parentheses indicate reaction temperatures and times.

Then the reactions of other enones with boronic acids were examined using catalyst **1k** (Scheme 1). Although methyl ketone-type enone **2b** afforded adduct **4b** in a low yield for reactions with styrylboronic acid (**3a**), phenyl ketone-type enones **2a** and **2c–f** showed good reactivities to give adducts **4a** and **4c–f** with good enantioselectivities (81–88% ee), respectively. Enone **2e**, which possessed *p*-$MeOC_6H_4$ as the R^2 group, reacted more smoothly than *p*-NO_2-substituted enone **2f**.[12] Furthermore, the effect of other boronic acids was examined for the reaction with chalcone (**2a**). Although alkenylboronic acid **3b** was much less reactive than **3a**, furan- and benzofuranboronic acids **3c** and **3d**[13] showed acceptable reactivities to give adducts **4h** and **4i** with good selectivities, respectively. These findings suggest that the enantioselectivity depends on the structure of boronic acids rather than that of enones. However, further studies are necessary to elucidate the precise mechanism.[14]

In summary, we have demonstrated for the first time that *O*-monoacylated tartaric acids, particularly 3,5-di(*tert*-butyl)-benzoyl derivative **1k**, are effective enantioselective catalysts for the asymmetric conjugate addition of boronic acids to enones. Further investigations to improve the catalytic activity and to extend the applicability to other reactions are underway.

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Notes and references

1 For reviews on 1,4- and 1,2-additions of organoboronic acids, see: (*a*) K. Yoshida and T. Hayashi, in *Boronic Acids*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005, ch. 4; (*b*) R. A. Batey, in *Boronic Acids*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005, ch. 7.

2 For 1,4-addition to enones catalyzed by chiral biphenols, see: (*a*) T. R. Wu and J. M. Chong, *J. Am. Chem. Soc.*, 2005, **127**, 3244; (*b*) T. R. Wu and J. M. Chong, *J. Am. Chem. Soc.*, 2007, **129**, 4908. For a theoretical study, see: ; (*c*) S. C. Pellegrinet and J. M. Goodman, *J. Am. Chem. Soc.*, 2006, **128**, 3116; (*d*) R. S. Paton, J. M. Goodman and S. C. Pellegrinet, *J. Org. Chem.*, 2008, **73**, 5078.

3 For 1,2-addition to ketones catalyzed by chiral biphenols, see: (*a*) S. Lou, P. N. Moquist and S. E. Schaus, *J. Am. Chem. Soc.*, 2006, **128**, 12660; (*b*) D. S. Barnett, P. N. Moquist and S. E. Schaus, *Angew. Chem., Int. Ed.*, 2009, **48**, 8679.

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5 For reactions of boronic acids catalyzed by thioureas, see: (*a*) Y. Yamaoka, H. Miyabe and Y. Takemoto, *J. Am. Chem. Soc.*, 2007, **129**, 6686; (*b*) T. Inokuma, K. Takasu, T. Sakaeda and Y. Takemoto, *Org. Lett.*, 2009, **11**, 2425.

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7 Yamamoto *et al.* employed boron complexes of *O*-monoacyltartaric acids as asymmetric Lewis acid catalysts for Diels–Alder reactions, aldol-type reactions, allylations, *etc.*, and found 2,6-dialkoxybenzoyl derivatives to be effective. For leading references, see: (*a*) K. Furuta, Y. Miwa, K. Iwanaga and H. Yamamoto, *J. Am. Chem. Soc.*, 1988, **110**, 6254; (*b*) K. Furuta, T. Maruyama and H. Yamamoto, *J. Am. Chem. Soc.*, 1991, **113**, 1041; (*c*) K. Ishihara, Q. Gao and H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 10412; (*d*) K. Ishihara, M. Mouri, Q. Gao, K. Furuta and H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 11490.

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9 D. G. Hall, *Boronic Acids*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005, ch. 1.

10 The addition of methanol (1 equiv.) or the use of water or *tert*-butylalcohol (2 equiv.) instead of methanol afforded comparable results. However, methanol (4 equiv.) cut in the yield in half. It has recently been reported that the presence of a small amount of alcohol improves the outcome of binaphthol-catalyzed allylboration of ketones, see ref. 3*b*.

11 *O*-Monoacylated L-tartaric acids were prepared *via* monoacylation of dibenzyl L-tartarate and subsequent hydrogenolysis of the benzyl esters, according to the reported procedure, see: K. Furuta, Q.-Z. Gao and H. Yamamoto, *Org. Synth.*, 1998, **Coll. Vol. 9**, 722. See also ref. 7.

12 Due to the conjugation of the *p*-MeO group, enone **2e** has a more negatively charged carbonyl oxygen and a more positively charged β-carbon than **2a**, which may facilitate the coordination of the catalyst–boronic acid complex and the migration of the R^3 group.

13 For enantioselective conjugate additions of furanboronic acids to enals, see ref. 6.

14 Rapid complexation between boronic acids and catalyst **1k** could be observed by ^{1}H-NMR at room temperature. Catalysis by the **1**·boron complex instead of **1** itself cannot be excluded at this stage.

