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Enantioselective Allyl-, and Allenylboration of Aldehydes Catalyzed by Chiral Hydroxyl Carboxylic Acid

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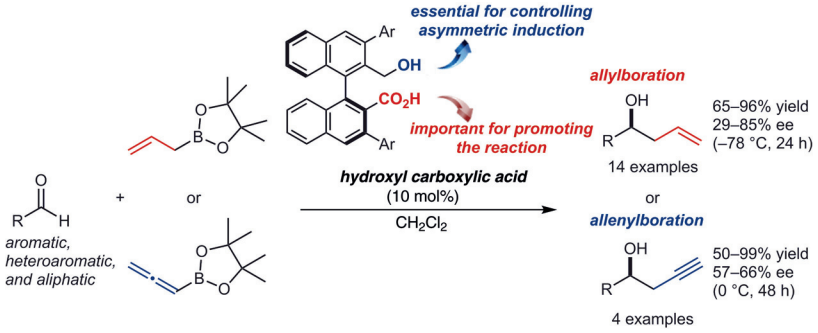

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Abstract Asymmetric allylboration of aldehydes with allylboronic acid pinacol ester catalyzed by chiral hydroxyl carboxylic acid is described. This reaction provides synthetically useful homoallyl alcohols in high yield with good to high enantioselectivity. The present catalytic protocol was also examined in asymmetric allenylboration of aldehydes at elevated temperature to afford chiral homopropargyl alcohols with reasonable asymmetric induction.

Key words Brønsted acid catalysis, chiral hydroxyl carboxylic acid, allylboration, homoallyl alcohol, allenylboration, homopropargyl alcohol

Organic acids constitute one of the most fundamental catalysts in organic chemistry. They are versatile because they can serve as a precursor of an anionic phase-transfer catalyst and as an anionic ligand of metal complexes in addition to functioning as a simple acidic promoter.[1] Since the first reports on binaphthol-derived chiral phosphoric acid catalyzed asymmetric Mannich type reactions by Akiyama[2a] and Terada,[2b] chiral phosphoric acid catalysis has progressed greatly in the last decade.[3] In contrast, despite its potential utility,[4] chiral carboxylic acids bearing a 1,1-binaphthyl framework have been less well explored, probably due to the limited availability of an efficient synthetic method.[4a] In this context, we recently reported a cost-effective and concise synthetic method for the construction of binaphthol-derived chiral dicarboxylic acids **1** (Figure 1).[5] By using this procedure, we were also able to synthesize a partially reduced hydroxyl carboxylic acid **2** on a gram scale as a result of desymmetrization of the dicarboxylic acid moiety. The corresponding carboxylate anion of **2** was found to serve as a novel bifunctional anionic phase-transfer catalyst, with which the first successful example of catalytic asymmetric fluorolactonization of ene-carboxylic acids with an electrophilic fluorinating reagent, Selectfluor® was achieved.[6] Our synthetic procedure allows for not only the fine-tuning of steric and electronic properties at the 3,3′-positions of **1** but also the incorporation of a hydrogen bond donor adjacent to the carboxylic acid functionality (Figure 1).

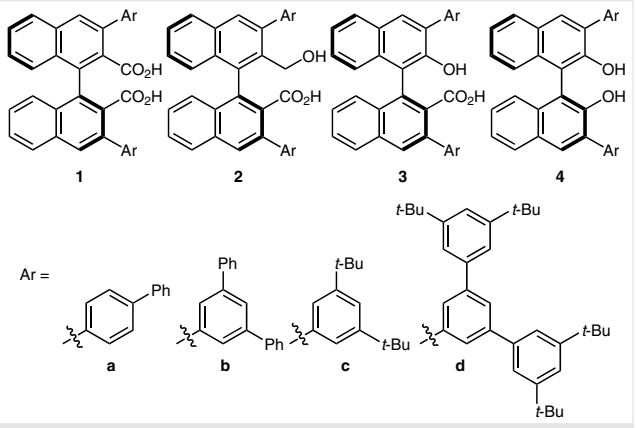


Figure 1 Chiral carboxylic acids and BINOL derivatives

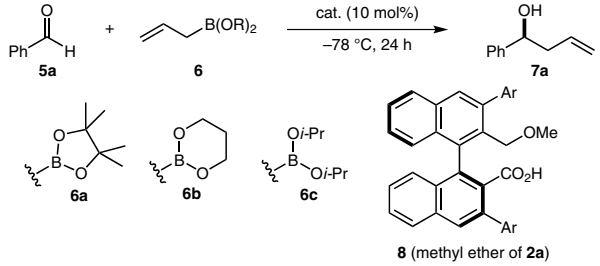
Asymmetric allylation of carbonyl compounds is a useful and reliable carbon–carbon bond-forming reaction for the preparation of chiral homoallyl alcohols.[7] Therefore, the development of catalytic variants is an important subject, and several catalytic systems with organoboronates were developed as a powerful method.[8] However, potentially toxic metal-based catalysts or additives were used to promote the reaction efficiently in many cases. Meanwhile, the organocatalytic version of this reaction has gained attention as a more environmentally benign synthetic strategy,[9–11] ever since Schaus and co-workers first reported the asymmetric allylboration of ketones catalyzed by chiral diols.[10a] In 2010, Antilla and co-workers first reported the highly

enantioselective allylboration of aldehydes catalyzed by a binaphthol-derived chiral phosphoric acid.[11a] Although high enantioselectivity was achieved, particularly with aromatic aldehydes (73–99% ee), reaction temperature and catalyst loading need to be improved. Therefore, further investigation of more efficient organocatalysts is desirable. In our continuing efforts to expand the utility of Brønsted acid catalysts, we applied such catalysts to the asymmetric allylboration of aldehydes (Equation 1). According to the precedent examples, we expected that our carboxylic acid catalysts would promote the reaction by enhancing the Lewis acidity of the boron center through either of the following two activation modes: (1) the formation of a mixed acid anhydride with the boronate ester,[12] or (2) the protonation of its oxygen atom. In this light, an investigation of the catalysis of **1** and **2** would offer fresh insight into the design of new catalysts that could show highly efficient and intriguing reactivity for asymmetric allylboration. Herein, we describe catalytic asymmetric allyl-, and allenylboration of aldehydes using chiral hydroxyl carboxylic acids.

Equation 1 Asymmetric allylboration of aldehydes promoted by chiral Brønsted acid catalysts

Initially, we set out to evaluate the various carboxylic acid catalysts in the reaction of benzaldehyde (**5a**) with allylboronic acid pinacol ester (**6a**) (Table 1). The reaction with dicarboxylic acid **1a** afforded the desired homoallyl alcohol **7a** in excellent yield with moderate enantiomeric excess at –78 °C (entry 1). Assuming that the high reactivity of the diacid catalyst affected the asymmetric induction negatively, partially reduced hydroxyl carboxylic acids, which are considered to be less acidic, were next examined. To our delight, the use of hydroxyl carboxylic acid **2a** resulted in significant improvements in the enantioselectivity, albeit with moderate chemical yield (entry 2). Phenol carboxylic acid **3a** also afforded the desired adduct **7a**, but the enantioselectivity dropped considerably (entry 3). In contrast, almost no conversion occurred in the reactions with BINOL catalyst **4a** or without any catalysts (entries 4 and 5), thus indicating that the carboxylic acid functionality is crucial to promote the reaction. In addition, in the presence of catalyst **2a**, the reactions with other boronate esters **6b** and **6c**, which are prone to ester exchange reaction, proceeded with extremely low enantioselectivity (entries 6 and 7). It should be noted that methylation of the hydroxyl group within **2a** led to a significant decrease in the efficiency of the reaction. Thus, the reaction with **8** gave **7a** in only 16% yield with a marginal enantioselectivity (2% ee), which strongly indicates that the co-presence of both the acid and the hydroxyl group at the defined position is essential (entry 8). From these results, the following presumptions regarding the reaction mechanism can be drawn: (1) The ester exchange on the boron with the catalyst may not be involved in this reaction, providing a contrasting example of Schaus' BINOL-catalyzed enantioselective allylation of ketones;[10a,10b] (2) If an ester exchange reaction occurs, it is an undesired process for high asymmetric induction; (3) Activation by protonation of the boronate oxygen is most likely, which is similar to the mode of action proposed by Antilla in his pioneering work on chiral phosphoric acid catalyzed allylboration of aldehydes;[11a] (4) The acidity of BINOL catalyst **4a** would be insufficient to activate the boronate ester, and ester exchange process between **4a** and **6b** and **6c** might be sluggish at –78 °C, thus resulting in no formation of the desired product **7a**; (5) Although the exact role of the alcohol func-

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	6 (equiv)	Solvent	Yield (%)[b]	ee (%)[c]
1	**1a**	**6a** (1.1)	CH_2Cl_2	98	60
2	**2a**	**6a** (1.1)	CH_2Cl_2	43	77
3	**3a**	**6a** (1.1)	CH_2Cl_2	43	34
4	**4a**	**6a** (1.1)	CH_2Cl_2	<5	–
5	–	**6a** (1.1)	CH_2Cl_2	<5	–
6	**2a**	**6b** (1.1)	CH_2Cl_2	27	10
7	**2a**	**6c** (1.1)	CH_2Cl_2	99	20
8	**8**	**6a** (1.1)	CH_2Cl_2	16	2
9	**2b**	**6a** (1.1)	CH_2Cl_2	48	63
10	**2c**	**6a** (1.1)	CH_2Cl_2	27	86
11	**2d**	**6a** (1.1)	CH_2Cl_2	40	85
12	**2d**	**6a** (2.0)	CH_2Cl_2	73	85
13	**2d**	**6a** (2.0)	toluene	54	83
14	**2d**	**6a** (2.0)	hexane	84	62
15	**2d**	**6a** (2.0)	hexane/CH_2Cl_2 (1:5)	58	76
16	**2d**	**6a** (2.0)	hexane/CH_2Cl_2 (1:1)	80	69
17	**2d**	**6a** (2.0)	hexane/CH_2Cl_2 (5:1)	92	72
18	**2d**	**6a** (2.0)	THF	<5	–
19	**2d**	**6a** (2.0)	Et_2O	58	54

[a] Compound **5a** (0.05 mmol, 0.2 M).
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase.

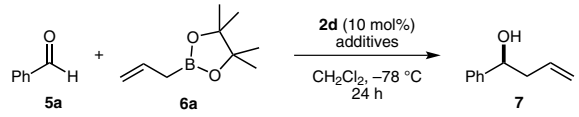
tionality of **2a** has yet to be elucidated, hydrogen bonding with the adjacent carboxylic acid is presumed to play an important role in the transition state.[13]

We next examined the effect of 3,3′-substitution patterns of the binaphthyl core of **2**. Bulky substituents appeared to be important to achieve high enantioselectivity, and **2d** was identified as the catalyst of choice, although the yield remained moderate (entries 9–11). When the reaction was run using 2 equivalents of **6a**, the yield was improved to 73% (entry 12). Whereas the use of toluene as solvent showed marginal differences in the outcome of the reaction, higher conversion was notable in hexane at the expense of the enantioselectivity (entries 13 and 14). The combination of hexane and CH_2Cl_2 in different ratios was then employed as the solvent (entries 15–17). Whereas a slight loss in the enantioselectivity was detected in hexane/CH_2Cl_2 (5:1), the yield was increased to 92%. While reaction in tetrahydrofuran (THF) barely afforded the desired product **7a**, the use of Et_2O gave the product in 58% yield with 54% ee (entries 18 and 19).

To improve the efficiency of the reaction, several additives were examined. With the assumption that inhibition of the catalyst might occur as a result of undesired interaction of the boronic acid ester of **7** with catalyst **2**, the effect of protic additives was then studied. Accordingly, both alcoholic and phenolic additives were found to accelerate the reaction (Table 2). 2,6-Di-*tert*-butyl-4-methoxyphenol gave **7a** in 90% yield, but a reduction of the enantioselectivity was observed (entry 7). Given that dicarboxylic acid catalyst **1a** showed superior performance in terms of the chemical yield (Table 1, entry 1), carboxylic acid was tested as an additive. However, the addition of benzoic acid resulted in drastic loss of the enantioselectivity, although the yield was high (entry 8).

The substrate generality of the asymmetric allylboration reaction of aldehydes was then investigated under the optimum reaction conditions[14] identified above in Table 1, entry 12. Careful monitoring of the model reaction revealed that a similar chemical yield was obtained after a much shorter reaction time (Table 3, entry 1). However, the following reactions were run for 24 h, since a longer reaction time was sometimes necessary because of the low solubility of the aldehydes. A bulkier 2-naphthylaldehyde (**5b**) gave similar levels of yield and enantioselectivity (entry 2). Halogenated aldehydes generally gave the corresponding products in higher yield. Although moderate enantioselectivity was observed in the case of sterically congested *ortho*-substituted aldehydes **5c** and **5d** (entries 3 and 4), *meta*- and *para*-substituted halogenated substrates underwent the reaction with high enantioselectivity (entries 5–7). The reactions of aldehydes having an electron-withdrawing *para*-trifluoromethyl or *para*-cyano group proceeded smoothly with 85 and 80% ee, respectively (entries 8 and 9), whereas the reaction of **5j**, with an electron-donating *para*-methyl group, gave a low enantioselectivity (entry 10). Although the allylboration of heteroaromatic aldehyde **5k** and α,β-unsaturated aldehyde **5l** also proceeded nicely at higher

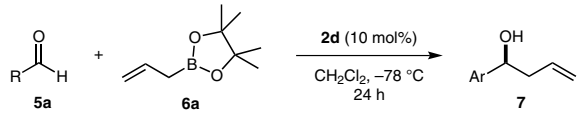
Table 2 Effect of Protic Additives[a]



Entry	Additives	Yield (%)[b]	ee (%)[c]
1	–	73	85
2	*t*-BuOH	81	46
3	CF_3CH_2OH	70	70
4	4-$MeOC_6H_4OH$	85	69
5	2,6-*t*-$Bu_2C_6H_3OH$	72	78
6	4-BrC_6H_4OH	77	48
7	2,6-*t*-Bu_2-4-$MeOC_6H_2OH$	90	65
8	$PhCO_2H$	93	39

[a] Reaction conditions: **5a** (0.05 mmol), **6a** (0.10 mmol), additives (0.15 mmol, 0.2 M).
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase.

Table 3 The Generality of the Reaction[a]



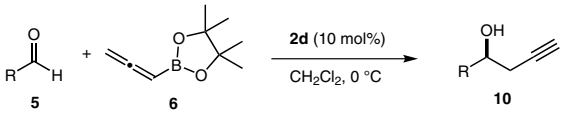
Entry	R		Product	Yield (%)[b]	ee (%)[c]
1[d]	Ph	**5a**	**7a**	74	85
2	2-naphthyl	**5b**	**7b**	70	75
3	2-ClC_6H_4	**5c**	**7c**	90	47
4	2-BrC_6H_4	**5d**	**7d**	92	49
5	3-ClC_6H_4	**5e**	**7e**	85	84
6	3-BrC_6H_4	**5f**	**7f**	96	83
7	4-BrC_6H_4	**5g**	**7g**	66	85
8	4-$F_3CC_6H_4$	**5h**	**7h**	74	85
9	4-NCC_6H_4	**5i**	**7i**	90	80
10	4-MeC_6H_4	**5j**	**7j**	90	29
11[e]	2-thienyl	**5k**	**7k**	93	43
12[f]	(*E*)-PhCH=CH	**5l**	**7l**	69	43
13	$PhCH_2CH_2$	**5m**	**7m**	65	35
14	*c*-C_6H_{11}	**5n**	**7n**	65	66

[a] Reaction conditions: **5a** (0.10 mmol), **6a** (0.20 mmol, 0.2 M).
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase.
[d] 5 h.
[e] Reaction was run in 1,2-dichloroethane at room temperature (2 h).
[f] Reaction was run at –35 °C.

reaction temperature, the enantioselectivity was unsatisfactory (entries 11 and 12). Aliphatic aldehydes were also applicable, albeit with moderate enantioselectivity (entries 13 and 14).

We then directed our efforts to applying the catalytic conditions thus obtained to the enantioselective propargylation of aldehydes to produce synthetically useful homopropargylic alcohols (Table 4).[15] Recently, the utility of allenyl boronic acid pinacol ester (**9**) was explored in Brønsted acid catalyzed enantioselective propargylation of aldehydes, since **9** is a nontoxic and relatively air- and moisture-stable reagent.[16] Compared with **6a**, allenylboronate **9** was found to be less reactive. Although higher reaction temperature and longer reaction times were required to reach completion, the reaction of benzaldehyde (**5a**) and **9** afforded the desired homopropargyl alcohol **10a** in 81% yield with 57% ee (entry 1). This reaction was applicable to other aldehydes, furnishing the corresponding homopropargylic alcohol with promising enantioselectivities (entries 2–4).

Table 4 Asymmetric Allenylboration of Aldehydes[a]



Entry	R		Product	Yield (%)[b]	ee (%)[c]
1	Ph	**5a**	**10a**	81	57
2	3-BrC_6H_4	**5f**	**10f**	50	65
3	4-$F_3CC_6H_4$	**5h**	**10h**	92	63
4	4-NCC_6H_4	**5i**	**10i**	99	66

[a] Reaction conditions: **5a** (0.10 mmol), **9** (0.20 mmol), 0.2 M.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase.

In summary, we have developed a chiral hydroxyl carboxylic acid catalyzed asymmetric allylboration of aldehydes. This methodology provided synthetically useful homoallyl alcohols in high enantioselectivity. The present catalytic protocol was also applicable to the asymmetric propargylation of aldehydes with allenyl boronic acid pinacol ester. It is interesting that the co-presence of both the carboxylic acid and the hydroxyl group at the defined position was essential for high asymmetric induction. This study provides guidance for the design of novel catalysts, allowing the toolbox available for organocatalysis to be expanded. Further improvement of the efficiency of the reaction and elucidation of a more detailed reaction mechanism are currently underway in our laboratory.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588690.

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(14) **General Procedure:** To a flame-dried glass tube equipped with a three-way top were placed chiral acid catalyst **2d** (12.3 mg, 0.010 mmol), freshly distilled benzaldehyde (**5a**; 10 µL, 0.10 mmol), and anhydrous CH_2Cl_2 (0.5 mL) under Ar atmosphere. The resulting solution was cooled at –78 °C before allylboronic acid pinacol ester (**6a**; 37 µL, 0.20 mmol) was added by using a gas-tight syringe with a stainless steel needle. The reaction mixture was stirred at the same temperature for 5 h. The reaction was quenched with DIBAL-H (1.0 M in toluene, 15 µL). After stirring for 10 min, 4 M HCl was added to the mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the reaction mixture was purified by flash chromatography (EtOAc/hexanes, 1:9) to give **7a** (11.0 mg, 74%) as a colorless oil; $[\alpha]_D^{29}$ –56.3 (*c* 0.72, $CHCl_3$, 85% ee sample). ^{1}H NMR ($CDCl_3$): δ = 7.37–7.25 (m, 5 H), 5.82 (dddd, *J* = 17.2, 10.3, 7.5, 6.9 Hz, 1 H), 5.21–5.13 (m, 2 H), 4.75 (t, *J* = 6.3 Hz, 1 H), 2.57–2.47 (m, 2 H), 2.03 (br s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 143.9, 134.4, 128.4, 127.5, 125.8, 118.4, 73.3, 43.8. CHIRALCEL OD-H (ϕ 0.46 cm × 25 cm; 2-propanol/*n*-hexane, 5:95; flow rate 0.5 mL/min, detection at 210 nm; t_R = 14.5 (*R*), 16.6 (*S*) min.

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