Rational Design of a New Chiral Lewis Acid Catalyst for Enantioselective Diels-Alder Reaction: Optically Active 2-Dichloroboryl-1,1'-binaphthyl

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Abstract: A novel chiral aryldichloroborane catalyst bearing binaphthyl skeletons with axial chirality was developed as an asymmetric catalyst for the Diels-Alder reaction of dienes and α , β -unsaturated esters, and could be reused as the corresponding boronic acid. In addition, a new convenient method for preparing arylboronic acids from aryl alcohols is described.

Spectacular advances have been achieved in recent years in the enantioselective Diels-Alder reaction of dienes and α , β -unsaturated aldehydes catalyzed by chiral Lewis acids.^{1,2} However, there has been relatively less progress in the development of asymmetric catalysts for the reaction with α,β -unsaturated esters as dienophiles because of their low reactivities.^{3,4} Alkyldihaloborane is one of the most powerful Lewis acids which can catalyze the latter reaction.^{3c,d} For example, Hawkins co-workers previously reported an effective and chiral alkyldicholoroborane catalyst prepared by hydroboration of 1-(1naphthyl)cyclohexene for the latter reaction, which gave high enantioselectivity.^{3d} However, in general, since alkyldichloroboranes readily decompose to alkanes or alkenes by protonolysis or β-hydride elimination, it is difficult to recover them as alkylboronic acids quantitatively.⁵ In addition, in the preparation of optically active alkyldihaloboranes, optical resolution or asymmetric hydroboration is required since they involve chiral carbons adjacent to boron.^{3c,d,5} Thus, the utility of chiral alkyldichloroboranes as strong Lewis acid catalysts in enantioselective synthesis encouraged us to seek new members of this class which would not have the disadvantages mentioned above. This paper describes novel and practical chiral aryldichloroborane catalysts 7a-c bearing binaphthyl skeletons with axial chirality which can be reused as the corresponding boronic acids 5a-c.6

For the synthesis of optically pure 2-dihydroxyboryl-1,1'-binaphthyl (5a), (R)-1,1'-bi-2-naphthol (1a) was first treated with Nphenyltrifluoromethanesulfonimide and the resulting monotriflate 2awas subjected to hydrogenolysis to give mono-ol 3a (Scheme 1).⁷ After transformation of the phenolic hydroxyl group to a diethylphosphate, 4a was treated with lithium-naphthalene and trimethylborate successively to give binaphthylboronic acid 5a.⁸ As far as we know, this is a new method for preparing arylboronic acid from aryl alcohol.9 Unfortunately, slight epimerization of 5a was revealed by conversion to the (2R,4R)-2,4-pentanediol ester and ¹H NMR analysis or by conversion to the pinacol ester and HPLC analysis. Therefore, boronic acid 5a was esterified with diethanolamine in 2-propanol, from which the boronate ester 6a was crystallized in good yield. Recrystallization of 6a and subsequent hydrolysis with dilute acid readily provided enantiomerically pure (R)-5a. (R)-6,6'-Diarylbinaphthylboronic acids $5b^8$ and $5c^8$ were synthesized from 1b and 1c, respectively, in a similar manner.

To activate chiral arylboronic acids **5a-c** as Lewis acid catalysts, conversion to the corresponding aryldichloroboranes **7a-c** was investigated.^{3d,10} As a result, two different procedures, *Method A* and *Method B*, were developed as shown in Scheme 2: one is *via* exchange of the methanol boronate with trichloroborane,¹¹ and the other is *via*



Scheme 1. Synthesis of (R)-2-Dihydroboryl-1,1'-binaphthyl Derivatives 5a-c

exchange of the anhydrides of boronic acids with trichloroborane.¹² The latter procedure is simpler and more convenient.^{10b}



Scheme 2. Preparation of (*R*)-2-Dichloroboryl-1,1'-binaphthyl Derivatives 7a-c

With these complexes **7a-c** in hand, we first explored their asymmetryinducing ability in the Diels-Alder reaction of cyclopentadiene and methyl acrylate as test materials. The results are summarized in Table 1. The reaction proceeded smoothly at -78 °C in the presence of 10 mol% of catalysts **7a-c** to give the endo-adduct in high yield with >99% diastereoselectivity. Catalyst **7b** showed the highest asymmetric induction, but even this was insufficient (entry 3). The substituents at the 6,6'-positions of the catalysts had remarkable effects on enantioselectivity and absolute stereochemistry. Sterically bulky substituents such as a mesityl group increased enantioselectivity (entry 1 vs. entry 3), while a phenyl substituent inverted the absolute enantioselectivity (entries 1-3 vs. entry 4).

Table 1. Enantioselective Diels-Alder Reaction of Cyclopentadienewith Methyl Acrylate Catalyzed by $7a-c^a$

$\begin{array}{c} & & & \\ \hline & & \\ \hline & \\ CO_2Me & + & \\ \hline & \\ \hline & \\ CH_2Cl_2, -78 \ ^\circ C \\ & \\ CO_2Me \\ \end{array} \right) \xrightarrow{2} \begin{array}{c} & & \\ \hline & \\ CO_2Me \\ & \\ \end{array} \right) \xrightarrow{99\% \text{ endo}}$									
	catalyst		adduct						
entry	7 a -c ^b m	nethod c	yield (%) d	ee (%) ^e	$\operatorname{config}^{f}$				
1	7a (82% ee)	Α	91	51 (62)	2R				
2	7a (>99% ee)	В	91	60	2 R				
3	7b (89% ee)	Α	92	65 (73)	2 R				
4	7c (92% ee)	Α	92	48 (53)	25				

^{*a*}Diels–Alder reaction of methyl acrylate (1 equiv) and cyclopentadiene (4 equiv) was carried out in dichloromethane [a dichloromethane to diene ratio of 12:1 (v/v)] in the presence of 10 mol% of the catalyst at -78 °C for 12 h. ^{*b*} Optical purity is indicated in parentheses. ^{*c*} See Scheme 2. ^{*d*} Isolated yield. ^{*e*} Determined by reduction with NaBH₄, conversion to the Mosher MTPA ester, and ¹H NMR (500 MHz) analysis; values in parentheses are corrected for the optical purity of **7**. ^{*f*} See ref. 3

The correlation between the enantioselectivity and the alkoxy moiety of alkyl acrylates in the Diels-Alder reaction with cyclopentadiene catalyzed by **7a** was also investigated. Sterically bulky alkoxy groups lowered the enantioselectivity: 48% ee (R) for ethyl acrylate, 11% ee (S) for *t*-butyl acrylate. However, the reaction of ethylene diacrylate (**8**), which is commercially available, and the following reduction with lithium aluminum hydride gave endo-5-norbornene-2-methanol with 78% ee (eq. 1). According to a control experiment (eq. 2), the enantioselectivity in the initial addition and the diastereoselectivity (double asymmetric induction) in the second addition were higher than that of methyl acrylate (Table 1, entry 2). Although it is not clear why the selectivities are increased by the link between dienophiles, similar effects are expected for other asymmetric reactions.

The proposed mechanism shown in Figure 1 can explain the absolute stereopreference in the above Diels-Alder reaction. The following features of the intermediates were predicted by a conformational analysis: boron complexes the carbonyl oxygen *anti* to the C-O bond of the ester,¹⁰ the enone unit is *s*-*trans*,¹³ and the carbonyl group is positioned over and approximately parallel to the naphthalene ring within the van der Waals radii (ca. 3 Å).^{3b} Thus, the absolute configuration of the major endo product using **7a** as a catalyst is consistent with the naphthyl shielding the *re* face of the coordinated methyl acrylate leading to attack by cyclopentadiene at the *si* face, as shown in **A**. Coordination of the methyl acrylate with the *re* face



Figure 1. Proposed mechanism on Diels–Alder reaction of cyclopentadiene with methyl acrylate catalyzed by 7a-c

exposed as shown in **B** is disfavored due to steric interaction of the alkene with the naphthyl. Increased enantioselectivity with the use of **7b** can be easily understood in terms of steric repulsion between the alkene and the mesityl group (see **C**). Although the reason for the inverse absolute stereopreference with the use of **7c** is not yet clear, intermediate **D** may be slightly favored due to some π - π attractive interaction between the alkene and the 6-phenylnaphthyl group.

Table 2. Enantioselective Diels–Alder Reaction of Cyclopentadiene with Versatile Dienophiles Catalyzed by $7a^{a}$

dienophile	major adduct	yield (%) ^b	endo /exo ^e	ee (%)	config
MeO ₂ C CO ₂ Me	MeO ₂ C 2 CO ₂ Me	80 ^c	-	70 ^f	2 <i>S</i> ^{<i>i</i>}
		30 ^d	<1/99	72 ^g	2 <i>R</i> ^j
СНО	OHC 2	>95	18/82	55 ^h	2 <i>S</i> ^{<i>h</i>}

^a Unless otherwise noted, Diels-Alder reaction of α , β -unsaturated esters (1 equiv) and cyclopentadiene (4 equiv) was carried out in dichloromethane [a dichloromethane to diene ratio of 12:1 (v/v)] in the presence of 10 mol% of **7a** (>99% optical purity) prepared by *method B* at -78 °C for 12 h. ^b Isolated yield. ^c 5 equiv of cyclopentadiene was used; a dichloromethane to diene ratio of 3:1 (v/ v). d 5 equiv of cyclopentadiene was used; a dichloromethane to diene ratio of 5:1 (v/v). ^e Determined by ¹H NMR (300 MHz) analysis. f Determined by GC analysis (Chiraldex G-TA). ^h Furuta, K.; Determined by GC analysis (Chiraldex B-TA). Shimizu, S.; Miwa, Y.; Yamamoto, H. J. Org. Chem. 1989, 54, 1481. ⁱ Van Gastel, F. J. C.; Klunder, A. J. H.; Zwanenburg, B. Recl. Trav. Chim. Pays-Bas 1991, 110, 175. ^j Determined by reduction with LiAlH₄ and comparison of optical rotation values with data in the literature; Mattay, J.; Mertes, J.; Maas, G. Chem Ber. 1989, 122, 327.



Next, the enantioselectivity and absolute stereochemistry in the Diels-Alder reaction of cyclopentadiene and other dienophiles were explored using non-substituted catalyst **7a**. The results are summarized in Table 2. Dimethyl fumarate reacted with cyclopentadiene with better enantioselectivity than methyl acrylate, and the absolute stereopreference was consistent with that of methyl acrylate. The reaction with 2,2-dimethyl-5-methylene-1,3-dioxolan-4-one¹⁴ as a cyclic dienophile also gave good enantioselectivity but low yield, and the absolute stereopreference could be explained in terms of the sterically favored intermediate **E**. The enhanced enantioselectivity in both cases may be ascribed to conformational restriction of the enone unit. Low enantioselectivity was seen with methacrolein as a dienophile. Nevertheless, the absolute stereopreference could be explained in terms of the most favorable intermediate **F**.

In conclusion, a new and effective chiral arylboronic acid and its dichloroborane derivative with a binaphthyl skeleton was developed, and its utility has been demonstrated in Diels-Alder reactions with both α , β -unsaturated esters and aldehydes, although the enantioselectivity is insufficient. Preliminary studies indicate that this area of research may yield other catalyst structures and other useful enantioselective reactions.

References and Notes

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- (*R*)-1,1'-Binaphthyl-2-boronic Acid (**5a**): IR (Kbr) 3670-3150 (br), 3057, 1470, 1458, 1375, 1350, 1317, 1248 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+D₂O) δ 7.15 (d, J=8.7 Hz, 1H), 7.23-7.36 (m, 3H), 7.48-7.56 (m, 3H), 7.67 (t, J=7.2 Hz, 1H), 7.95 (d, J=8.3 Hz, 1H), 7.99 (d, J=8.5 Hz, 1H), 8.00 (d, J=8.3 Hz, 1H), 8.06 (d, J=8.5 Hz, 1H), 8.14 (d, J=8.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃+D₂O) δ 126.0, 126.5, 127.1, 127.3, 127.4, 127.8, 128.1, 128.3, 128.8, 129.4, 131.3, 133.1, 133.2, 134.1, 135.1, 138.6, 144.7. ¹¹B NMR (96 MHz, C₆D₆) δ 30.5; HREIMS calcd for C₂₀H₁₅O₂B [M⁺] 298.1165, found 298.1159.

(*R*)-6,6'-Dimesityl-1,1'-binaphthyl-2-boronic Acid (**5b**): IR (KBr) 3675-3150 (br), 2920, 1622, 1470, 1377, 1360, 1350, 1312 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+D₂O) δ 2.02 (s, 6H), 2.06 (s, 6H), 2.35 (s, 6H), 6.99 (s, 4H), 7.12 (dd, *J*=1.6, 8.6 Hz, 1H), 7.18 (dd, *J*=1.6, 8.6 Hz, 1H), 7.32 (d, *J*=8.8 Hz, 1H), 7.43 (d, *J*=8.6 Hz, 1H), 7.58 (dd, *J*=1.1, 6.9 Hz, 1H), 7.70 (t, *J*=8.2 Hz, 1H), 7.72 (s, 1H), 7.77 (d, *J*=0.8 Hz, 1H), 7.97 (d, *J*=8.5 Hz, 1H), 8.02 (d, *J*=8.4 Hz, 1H), 8.16 (d, *J*=8.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃+D₂O) δ 21.8 (6C), 126.2, 126.7, 127.6, 127.9, 128.1, 128.5, 128.7, 128.9, 129.5, 129.7, 131.7, 132.1, 132.2, 134.4, 135.4, 136.49, 136.53, 136.6, 136.7, 137.34, 137.39, 138.6, 138.9, 139.0, 140.1, 140.3, 144.9.

(*R*)-6,6'-Diphenyl-1,1'-binaphthyl-2-boronic Acid (**5c**): IR (KBr) 3675-3250 (br), 3050, 1489, 1395, 1375, 1360, 1352, 1320 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+D₂O) δ 7.28 (d, *J*=8.8 Hz, 1H), 7.35-7.43 (m, 3H), 7.44-7.62 (m, 7H), 7.67-7.75 (m, 5H), 8.07 (d,

1055

 $\begin{array}{l} \textit{J=8.0 Hz, 1H}, 8.12 (d, \textit{J=9.1 Hz, 1H}), 8.17 (d, \textit{J=9.7 Hz, 1H}), \\ 8.18 (d, \textit{J=9.8 Hz, 1H}), 8.19 (d, \textit{J=8.3 Hz, 1H}); \\ ^{13}\text{C NMR} (75 \\ \text{MHz, CDCl}_3 + \text{D}_2\text{O}) \\ \delta 125.8, 125.9, 126.2, 126.3, 126.80, 126.84, \\ 127.5, 127.7, 127.8, 129.0, 129.4, 131.5, 131.9, 132.1, 134.1, \\ 135.1, 138.1, 139.5, 139.6, 140.65, 140.73, 144.2. \end{array}$

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- 11. Method A: A dry, 25-mL round flask fitted with a stirring bar and a reflux condenser was charged with chiral boronic acid **5a** (14.9 mg, 0.05 mmol) and dry methanol (1 mL). An argon atmosphere was secured, and the solution was brought to reflux. After being refluxed for 2 h, the methanol and water generated were removed under vacuum at room temperature. After the above treatment of **5a** with methanol was repeated three times, the resulting solid was dissolved in dichloromethane (150 μ L) and boron trichloride solution in hexane (1 *M*, 150 μ L, 0.15 mmol) at 0 °C. After being stirred at 0 °C for 12 h, the volatile boron compounds and solvents were removed under vacuum at room temperature. The treatment with boron trichloride was repeated twice. The residual oil obtained as **7a** was immediately used as a catalyst for the Diels-Alder reaction without isolation.

- Method B: A dry, 25-mL round flask fitted with a stirring bar and 12 a 10-mL pressure-equalized addition funnel (containing a cotton plug and CaH2 and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with chiral boronic acid 5a (14.9 mg, 0.05 mmol) and benzene (3 mL). An argon atmosphere was secured, and the solution was brought to reflux. After 7 h, the reaction mixture was cooled to room temperature and boron trichloride (1 M in hexane, 300 µL, 0.3 mmol) was added. After being refluxed for 3 h, the resulting mixture was cooled to room temperature and the addition funnel and condenser were quickly removed and replaced with a septum. The volatile boron compounds and solvents were then removed under vacuum at room temperature. The residual oil obtained as 7a was immediately used as a catalyst for the Diels-Alder reaction without isolation. (R)-2-Dichloroboryl-1,1'-binaphthyl (7a): ¹¹B NMR (96MHz, C₆D₆) δ 57.4.
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