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Asymmetric hydrogenation of chiral vinyloxazaborolidines under ambient conditions

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Dedicated to the memory of Professor Herbert C. Brown

Abstract—Novel homochiral vinyloxazaborolidines have been synthesized and subsequently hydrogenated using palladium on carbon under ambient conditions to produce, after oxidation of the boronate group, enantiomerically enriched secondary alcohols (up to 20% ee). Herein, the first example of asymmetric hydrogenation utilizing oxazaborolidines as chiral auxiliaries is reported.

1. Introduction

Chiral organoboron compounds are valuable synthetic intermediates due to their ability to undergo a wide range of transformations.[1] Such compounds are especially attractive because the stereogenic carbon atom directly attached to the boron will retain its configuration while boron is substituted for various functional groups.[2] Existing methods for the synthesis of chiral organoboron compounds include hydroboration of internal alkenes using an enantiomerically pure borane;[1,3–6] hydroboration using a metal-chiral phosphine catalyst,[7–11] rhodium-catalyzed diboration of alkenes,[12] and reaction of chiral (α-haloalkyl)boronic esters with nucleophiles.[13,14] Recently, a method whereby chiral organoboron compounds are obtained via asymmetric hydrogenation of prochiral alkenylboron compounds was reported.[15] However, since extreme reaction conditions were required to achieve good enantioselectivities,[†] we became interested in improving upon this methodology by exploring the possibility of hydrogenating these substrates under ambient conditions using a chiral auxiliary attached to boron. When the alkenylboron compound is fitted with a chiral auxiliary, the use of an achiral, heterogeneous catalyst is permitted. If optimized, such an approach would be an excellent addition to the current repertoire for synthesizing chiral organoboron compounds. Moreover, the use of a heterogeneous catalyst for asymmetric hydrogenations is highly desirable from an industrial standpoint due to the ease of catalyst recovery. Since the chiral auxiliary is not retained in the final product, it can be recovered and reused. Herein, we report preliminary results for the asymmetric hydrogenation of homochiral vinyloxazaborolidines under ambient conditions.

2. Results and discussion

We began our study by screening an array chiral diols and amino alcohols for their efficacy as chiral auxiliaries. (*Z*)-1-Methyl-1-propenyl boronic acid **1** was obtained in good yield and high purity by hydroboration of 2-butyne.[16,17] Various chiral 1,2-diols and 1,2-amino alcohols were reacted with **1** to form the corresponding chiral boronic esters and oxazaborolidines **2a**–**f** in situ. These compounds were then hydrogenated using Pd/C under ambient conditions, and subsequently oxidized with basic H_2O_2 to produce 2-butanol with varying degrees of asymmetric induction (Scheme 1). A few of the chiral auxiliaries surveyed are shown in Figure 1, where it can be seen that the best enantioselectivity was achieved with (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol (−)-**f**. To test the validity of this result, oxazaborolidine **2f** was synthesized, hydrogenated, and oxidized on three separate occasions. In each instance, (*R*)-2-butanol was produced in 20% ee.[‡]

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† Using a Rh-BINAP catalyst, the reaction was performed at −20 °C, under 9 atm of H_2 for 7 days.

‡ Use of the enantiomer, (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol, gave 20% ee of (*S*)-2-butanol.

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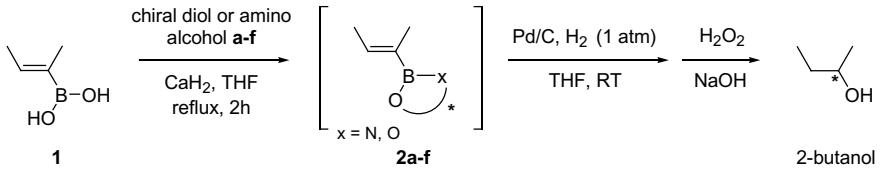


Scheme 1. Formation and subsequent hydrogenation of vinyloxazaborolidines.

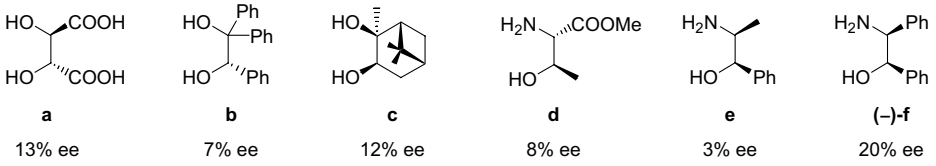


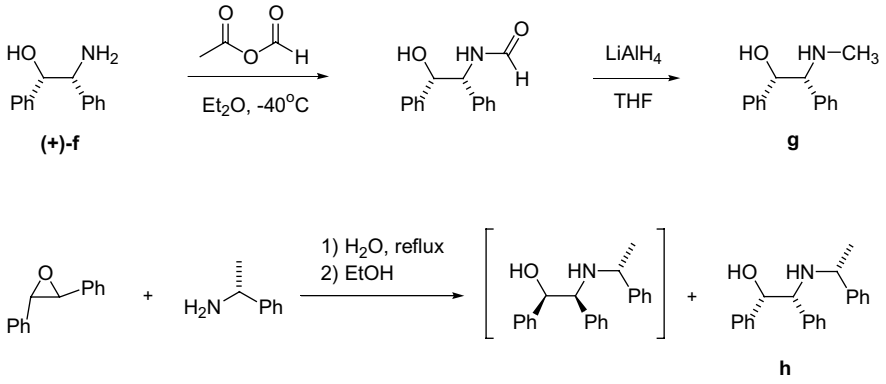
Figure 1. Chiral 1,2-diols and amino alcohols used as chiral auxiliaries on intermediate **2**. The ees obtained for 2-butanol were determined by chiral GC.

Encouraged by these results, we attempted to improve the enantioselectivity of this reaction by derivatization of ligand **f** at nitrogen. Thus, compounds **g** and **h** were synthesized (Scheme 2) and subsequently converted into oxazaborolidines by reaction with **1**. Hydrogenation and oxidation of these compounds however, resulted in decreased ees of 2-butanol (Table 1, entries 1 and 2). Reaction condition optimization studies were therefore carried out using the underivatized ligands (+)-**f** and (−)-**f**. The results obtained from varying the temperature, solvent, and catalyst, are summarized in Table 1.

Performing the hydrogenation at either high (65 °C) or low (−25 °C) temperature resulted in lowered enantioselectivities (Table 1, entries 6 and 7). The use of cinchonidine as a chiral surface modifier on palladium[18] also gave diminished ees (Table 1, entries 3 and 4). When ligand (−)-**f** was used as a chiral surface modifier, however, the enantioselectivity remained at 20% (Table 1, entry 5). Changes in solvent did not have any effect on the enantioselectivity of the reaction (Table 1, entries 9 through 11). Based on these results, the optimal reaction conditions were determined to be those which were employed initially (Scheme 1 with **2f**).

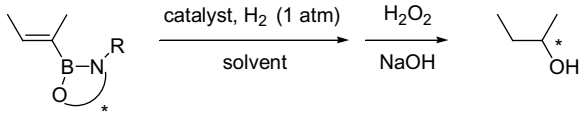
In order to examine whether the nature of the alkenylboron substrate had any effect on the reaction outcome, and to further explore the scope of this reaction, different boronic acid substrates were surveyed. Thus, commercially available 1-phenylethenylboronic acid was converted into the oxazaborolidine which, after hydrogenation and oxidation, yielded 1-phenylethanol in >99% conversion and 20% ee (Table 2, entries 1 and 2).

We speculated that the rotation of the B–C bond of the oxazaborolidine may account for the low enantioselectivity of this reaction. To test this hypothesis, we synthesized the geometric isomer (*E*)-1-methyl-1-propenyl oxazaborolidine **3f**, which we expected would have a higher barrier of rotation around the B–C bond due to the sterics of the β-methyl group (Fig. 2). Interestingly, hydrogenation of **3f**, followed by oxidation, gave 2-butanol with the same degree of induction obtained for the *Z*-isomer (Table 2, entries 3 and 4). This result suggests that B–C bond rotation is probably not responsible for the low enantioselectivity. Since the nature of the alkenylboron substrate seems inconsequential, we suspect that a more judicious choice of chiral ligand will enhance the enantioselectivity. It could be the case that the stereogenic centers of the ligand are too far removed from the double bond, and a system which allows for better transfer of chirality is required.



Scheme 2. Synthesis of *N*-substituted derivatives **g** and **h**.

Table 1. Optimization of reaction conditions for asymmetric hydrogenation of **2f–h**[a]



Entry	Ligand	Catalyst	Temp. (°C)	Solvent	% Ee[c] (config.)[d]
1	**g**	Pd/C	25	THF	13 (*S*)
2	**h**	Pd/C	25	THF	11 (*S*)
3	(−)-**f**	Pd/C-cinchonidine[b]	25	THF	16 (*R*)
4	(+)-**f**	Pd/C-cinchonidine[b]	25	THF	14 (*S*)
5	(−)-**f**	Pd/C-ligand (−)-**f**[b]	25	THF	20 (*R*)
6[e]	(+)-**f**	Pd/C	−25	THF	14 (*S*)
7	(−)-**f**	Pd/C	65	THF	10 (*R*)
8	(−)-**f**	Pd/C	25	THF	20 (*R*)
9	(+)-**f**	Pd/C	25	CH_2Cl_2	20 (*S*)
10	(+)-**f**	Pd/C	25	CH_3CN	20 (*S*)
11	(−)-**f**	Pd/C	25	Toluene	19 (*R*)

[a] Unless otherwise noted, hydrogenations were carried out using 5 mol % catalyst for 16 h. By GC, all reactions gave 2-butanol with >99% conversion, with the exception of entry 6 which gave 16% conversion. % Conversions were determined from the ratio of 2-butanone to 2-butanol.
[b] 10% Pd/C was premixed with the chiral surface modifier in THF in a 1:1 molar ratio.
[c] Ee was determined by chiral GC.
[d] Configuration was determined by comparison of the retention time on chiral GC with an authentic sample.
[e] The reaction was run for 2 days.

3. Conclusion

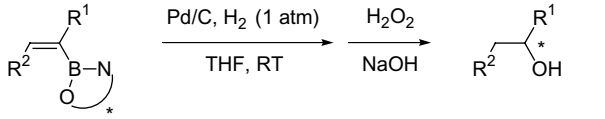
In summary, we have tested several commercially available, enantiomerically pure 1,2-chiral diols and 1,2-amino alcohols for their efficiency as chiral auxiliaries in the hydrogenation of alkenylboron compounds. Reaction condition optimization and ligand derivatization were also explored. The results obtained from this study demonstrate the asymmetric hydrogenation of vinyloxazaborolidines under ambient conditions. This is the first reported example of such a methodology, and although the degree of chiral induction achieved is modest, we expect to improve the enantioselectivity through studies currently aimed at systematic ligand design.

4. Experimental

4.1. General

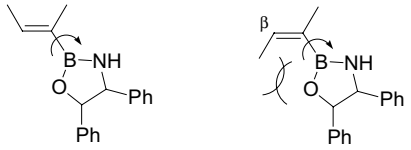
All reactions were performed using standard syringe techniques, and carried out in oven-dried glassware under an argon atmosphere. All solvents were dried prior to use: THF was distilled from sodium metal and benzophenone; CH_3CN, toluene, and CH_2Cl_2 were distilled from CaH_2. Reagents were purchased from Aldrich and used as received. ^1H NMR spectra were recorded on either a Bruker 250 MHz spectrometer or Varian 500 MHz spectrometer and are reported in ppm with respect to TMS ($\delta = 0$). Proton decoupled ^{13}C NMR spectra were recorded on a Bruker at 62.9 MHz or a Varian at 125 MHz and are reported in ppm.[§] ^{11}B NMR spectra were recorded on Bruker at 80.25 MHz and are reported in ppm with respect to BF_3/OEt_2 ($\delta = 0$). Analysis of enantioselectivity was accomplished using an HP 5890 gas chromatograph with a flame-ionization detector equipped with a Supelco β-cyclodextrin 120 chiral GC column (30 m × 0.25 mm). High-resolution mass measurements were obtained on a bench-top Mariner ESI-TOF mass spectrometer, or a JEOL HX-110 double focusing mass spectrometer for FAB. Optical rotations were recorded on a Jasco DIP-371 polarimeter.

Table 2. Asymmetric hydrogenation of various vinyloxazaborolidines[a]



Entry	R^1	R^2	Ligand	Product	% Ee[b](config.)[c]
1	Ph	H	(+)-**f**		20 (*R*)
2	Ph	H	(−)-**f**		20 (*S*)
3	H	CH_3	(+)-**f**		20 (*R*)
4	H	CH_3	(−)-**f**		20 (*S*)

[a] Hydrogenations were carried out using 5 mol % catalyst for 16 h. By GC, all reactions gave the alcohol with >99% conversion. % Conversions were determined from the ratio of 2-butanone to 2-butanol, or the ratio of acetophenone to 1-phenylethanol.
[b] Ee was determined by chiral GC.
[c] Configuration was determined by comparison of retention time on chiral GC with an authentic sample.



2f **3f**

Figure 2. Hindered rotation of the B–C bond in (*E*)-1-methyl-1-propenyl oxazaborolidine **3f**, as compared to **2f**.

[§] Due to relaxed ^{13}C–^{11}B spin–spin coupling, signals for carbons directly attached to boron are not observed.

4.2. Alkenylboronic acid syntheses

4.2.1. (2*Z*)-2-Buten-2-ylboronic acid 1. A 100-mL reaction flask, fitted with an addition funnel, was charged with 2-butyne (1.6 mL, 20 mmol) in anhydrous dichloromethane (8 mL) and cooled to −10 °C (ice-salt bath). $HBBr_2{\cdot}SMe_2$ (1 M, in dichloromethane, 20 mL, 20 mmol) was transferred to the addition funnel via syringe and added to the alkyne dropwise over 15 min. After stirring for 1 h at room temperature, the reaction was completed by ^{11}B NMR (2.8 ppm), then cooled to 0 °C and added, via cannula, to a stirred mixture of water (50 mL) and ether (75 mL) at 0 °C. After 15 min the water layer (bottom) was separated, and the organic layer was washed with cold water (2 × 25 mL) and brine (2 × 25 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield pure (2*Z*)-2-buten-2-ylboronic acid as a white solid (1.65 g, 83% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 1.77 (s, 3H), 1.81 (d, J = 6.75 Hz, 3H), 6.85 (qq, J = 6.5, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.76, 14.89, 143.73. ^{11}B NMR (80.25 MHz, $CDCl_3$): δ 28.28; HRMS (FAB) *m*/*z* calcd for $C_4H_8O_2B$ $(M-H)^-$: 99.0696, found 99.0618.

4.2.2. (2*E*)-2-Buten-2-ylboronic acid 3. 2-Bromo-*trans*-2-butene (1.01 mL, 10 mmol) was dissolved in THF (10 mL), cooled to −78 °C, and *t*-BuLi (1.7 M in pentane, 12.9 mL, 22 mmol) was added dropwise. The bright yellow solution was stirred at −78 °C for 1 h, and triisoproylborate (3.5 mL, 15 mmol) then added. The reaction mixture was stirred at −78 °C for 4 h and then let warm to 0 °C over the course of 3 h. Saturated NH_4Cl (10 mL) was added, and stirring continued at rt for 30 min. The reaction mixture was extracted with diethyl ether (2 × 20 mL), and the ether portions combined, washed with H_2O, and dried over $MgSO_4$. After filtration and evaporation, analytically pure **3** was obtained as a white solid (0.5 g, 50% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 1.84 (s, 3H), 2.04 (d, J = 7.5 Hz, 3H), 6.43 (q, J = 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.15, 22.56, 146.16. ^{11}B NMR (80.25 MHz, $CDCl_3$): δ 28.65; HRMS (FAB) *m*/*z* calcd for $C_4H_8O_2B$ $(M-H)^-$: 99.0696, found 99.0618.

4.3. Ligand synthesis

4.3.1. (1*S*,2*R*)-2-Methylamino-1,2-diphenylethanol g. This procedure was derived from that of Effenberger, who used a different but structurally similar substrate.[19] Acetic anhydride (0.94 mL, 10 mmol) and formic acid (0.38 mL, 10 mmol) were heated together at 60 °C for 30 min, cooled to room temperature, and added to a suspension of (+)-2-amino-1,2-diphenylethanol (1.07 g, 5 mmol) in dry diethyl ether (25 mL) at −40 °C (dry ice/CH_3CN). The suspension was left to stir at −40 °C for 2 h and then at room temperature for 10 min, at which point the reaction mixture solidified into a white mass. More ether (10 mL) was added, and the mass broken up, filtered, and washed several times with fresh ether. This yielded (1*S*,2*R*)-2-formyl-1,2-diphenylethanol as a fine white solid (1.15 g, 96% yield). ^1H NMR (500 MHz, DMSO-d_6): δ 4.76 (app. t, J = 5.7 Hz, 1H), 5.01 (dd, J = 9.3, 6.6 Hz, 1H), 5.52 (d, J = 5.0 Hz, O*H*), 7.17–7.23 (m, 10H), 7.88 (s, 1H), 8.54 (d, J = 10 Hz, N*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.89, 74.82, 126.76, 127.00, 127.20, 127.47, 127.57, 128.17, 139.98, 142.75, 159.97.

The *N*-formyl compound, (1*S*,2*R*)-2-formylamino-1,2-diphenylethanol, (1.15 g, 4.76 mmol) was suspended in dry THF (30 mL) and cooled to −10 °C. Lithium aluminum hydride (1 M in THF, 7 mmol) was added dropwise via syringe to the suspension, which turned clear during the addition. After stirring at room temperature for 24 h, more $LiAlH_4$ (3 mmol) was added, and the reaction let to stir for another 24 h. After cooling to 0 °C, the reaction mixture was quenched with 3 M NaOH and extracted with ether (3 × 20 mL). The ether layers were dried with $MgSO_4$ and evaporated to give a white solid (0.98 g), which still contained 15% aldehyde by ^1H NMR. Recrystallization from ethyl acetate provided pure **g** (0.84 g, 77% yield) as shiny white needles $[\alpha]_D^{25} = -6.8$ (*c* 4.4, $CHCl_3$). ^1H NMR (500 MHz, DMSO-d_6): δ 1.75 (br s, N*H*), 2.02 (s, 3H), 3.58 (d, J = 5.5 Hz, 1H), 4.64 (app. t, J = 5.3 Hz, 1H), 5.23 (d, J = 4.0 Hz, O*H*), 7.12–7.21 (m, 10H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 34.15, 70.61, 76.19, 126.46, 126.74, 126.94, 127.35, 127.41, 128.50, 140.88, 143.23; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{17}NO$ $(M+H)^+$: 228.1391, found 228.1383.

4.3.2. (1*S*,2*R*,1′*R*)-2-(1′-Phenylethyl)amino-1,2-diphenylethanol h. A 50-mL flask fitted with a reflux condenser was charged with (±)-*trans*-stilbene oxide (1.96 g, 10 mmol), (*R*)-(+)-α-methylbenzylamine (3.87 mL, 30 mmol) and deionized water (2 mL). The mixture was refluxed for 24 h and monitored by TLC for the disappearance of starting epoxide. After cooling to room temperature, 10 mL of water was added. Large chunks of off-white sticky solid separated from the reaction mixture. The liquid was decanted off, and the solid sonicated in 10 mL of ethanol. The white crystalline solid was filtered and washed with cold ethanol to give the title compound as a single diastereomer (1.35 g, 43%). Recrystallization from ethanol gave shiny white needles $[\alpha]_D^{25} = +40$ (*c* 4.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.36 (d, J = 6.5 Hz, 3H), 1.81 (br s, N*H*), 3.55 (d, J = 4.0 Hz, O*H*), 3.78 (q, J = 6.5 Hz, 1H), 4.0 (d, J = 4.5 Hz, 1H), 4.96 (t, J = 4.5 Hz, 1H), 6.98–7.00 (m, 5H), 7.17–7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.11, 54.62, 65.65, 75.41, 126.51, 126.68, 127.21, 127.37, 127.54, 127.85, 128.13, 128.22, 128.66, 139.25, 140.54, 145.56; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{23}NO$ $(M+H)^+$: 318.1877, found 318.1852.

4.4. General procedure for the synthesis of vinyloxazaborolidines and vinylboronic esters

The preparation of (*Z*)-1-methyl-1-propenyl oxazaborolidine **2f** is representative. An oven-dried 50 mL round-bottom flask equipped with a side arm, condenser, and stir bar was charged with (2*Z*)-2-buten-2-ylboronic acid (0.3 g, 3 mmol) and (−)-2-amino-1,2-diphenylethanol (0.64 g, 3 mmol). The solids were dissolved in THF (10 mL), and CaH_2 (0.25 g, 6 mmol) then

added. After 2 h at reflux, the reaction mixture was cooled to room temperature, and the CaH_2 filtered under argon. The filtrate was transferred under argon to a dry round-bottom flask via cannula. ^1H NMR (250 MHz, $CDCl_3$) of the reaction mixture in THF with TMS referenced at zero showed the following peaks representative of product formation: δ 1.82 (m, 6H), 4.99 (d, $J = 8.5$ Hz, 1H), 5.74 (d, $J = 8.5$ Hz, 1H), 6.45 (q, $J = 5.5$ Hz, 1H), 6.86–7.12 (m, 10H). ^{11}B NMR (80.25 MHz, $CDCl_3$): δ 32.66.

4.5. General procedure for asymmetric hydrogenation

To the vinyloxazaborolidine or vinylboronic ester (0.3 M in THF) was quickly added 10% Pd/C (0.16 g), and the reaction flask evacuated and purged with argon (3 cycles). After stirring overnight under a balloon of H_2, the reaction mixture was filtered under argon. To the filtrate was added 3 M NaOH (1 mL, 3 mmol), followed by 30% H_2O_2 (0.7 mL, 3 mmol). After stirring for 30 min, K_2CO_3 was added, and stirring continued for 15 min. The THF layer (top) was removed, dried over $MgSO_4$, filtered, and after dilution with ether, analyzed for % conversion and ee by chiral GC. Evaporation of the THF layer under reduced pressure gave back the chiral auxiliary, 2-amino-1,2-diphenylethanol, in analytically pure form, and in 75% yield.

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