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Catalytic Asymmetric Hydrocarboxylation and Hydrohydroxymethylation. A Two-Step Approach to the Enantioselective Functionalization of Vinylarenes

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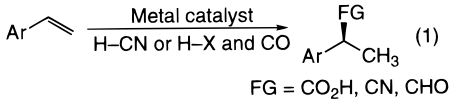
A method for the catalytic asymmetric hydrocarboxylation and hydrohydroxymethylation of vinylarenes is reported. By separating the step in which asymmetry is installed from the one where carbon−carbon bond formation takes place, a highly enantioselective and regioselective synthesis of Ibuprofen and its analogs is achieved. Stereochemistry is installed via an enantioselective hydroboration reaction, catalyzed by cationic rhodium BINAP complexes, and the homologation is carried out with halomethyllithium reagents. If CH_2Cl_2/*n*-BuLi is used as the homologating reagent, carboxylic acids are produced after oxidation. On the other hand, if CH_2ClBr is used in combination with *n*-BuLi, the corresponding primary alcohol is produced. This latter transformation represents a previously unknown asymmetric hydrohydroxymethylation reaction. In both cases, complete retention of stereochemistry is observed, yielding products in up to 97% ee. Superior results are obtained if the initially formed catecholate is converted into a pinacolate prior to homologation.

Introduction

Since the seminal experiments of Noyori and Nozaki on the use of chiral transition metal complexes for catalytic asymmetric synthesis,[1] research in this area has become a key focus for organic and organometallic chemists alike.[2] The ability to prepare enantiomerically enriched organic compounds using catalytic amounts of homochiral material is the most attractive feature of this approach to asymmetric synthesis. Since the specific biological properties of organic compounds are often closely related to their chirality, the drive to find efficient methods to prepare compounds in enantiomerically pure form is easily understood. Ibuprofen, Fluoxetine (Prozac), Allegra (Seldane), and Norastemizole (Hismal) are a few pharmaceutical compounds which are being targeted for synthesis as pure enantiomers.[3]

From the time of the original Nozaki/Noyori report, the field of catalytic asymmetric synthesis has advanced to encompass a wide range of transformations. Particularly useful are those reactions in which addition of a metal hydride across an olefin is followed by formation of a carbon−carbon bond. Some of the most successful asymmetric reactions, hydrocarboxylation,[4] hydrocyanation,[5] and hydroformylation,[6] belong to this type of transformation (eq 1).



All of these methods produce the basic carbon skeleton of Ibuprofen (**3d**) in one step starting from a vinylarene and either HCN or some other H−X species such as H_2O or H_2 in combination with CO. In terms of the synthesis of 2-arylpropionic acids, the hydrocarboxylation route[4] (CO and H_2O) is the most direct. We have recently reported a different approach to the enantioselective synthesis of Ibuprofen and its analogs in which the metal hydride addition step and the carbon−carbon bond-forming step are separated (Scheme 1).[7] This two-step hydrocarboxylation yields 2-arylpropionic acids using the relatively innocuous C-1 source, dichloromethane. We have recently extended this method to include an asymmetric synthesis of a key C-1 derivative of Ibuprofen which is not accessible using current asymmetric techniques, the hydroxymethyl derivative **4**. To the best of our knowledge, this reaction, which is essentially a catalytic asymmetric hydrohydroxymethylation, has not been previously reported.[8] In this paper, we describe the synthesis of asymmetric alcohols via the catalytic asymmetric hydrohydroxymethylation of vinylarenes, and provide a full account of our previously communicated approach to the synthesis of 2-arylpropionic acids from styrene derivatives and dichloromethane.

Results and Discussion

Synthetic Strategy. Our approach to the synthesis of compounds **3** and **4** is conceptually different from those previously employed in that we have separated the enantioselective metal hydride addition step from the carbon−carbon bond-forming step. This strategy requires the introduction of a carbon surrogate (**X** in eq 2) after the metal hydride addition. The surrogate will have to be reasonably stable, easily installable, and amenable to stereospecific replacement by carbon.

(1) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5239.
(2) (a) Ojima, I. Catalytic *Asymmetric Synthesis*; VCH Publishers: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley & Sons: New York, 1994.
(3) (a) *Chem. Eng. News* **1998**, Nov 30, 11. (b) *Chem. Eng. News* **1997**, Oct 20, 38.
(4) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.
(5) Rajanbabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 6325.
(6) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033.
(7) Chen, A.; Ren, L.; Crudden, C. M. *Chem. Commun.* **1999**, 611.
(8) Simple (non-enantioselective) hydrohydroxymethylations have been reported. See for example: Laine, R. M. *J. Am. Chem. Soc.* **1978**, *100*, 6451.

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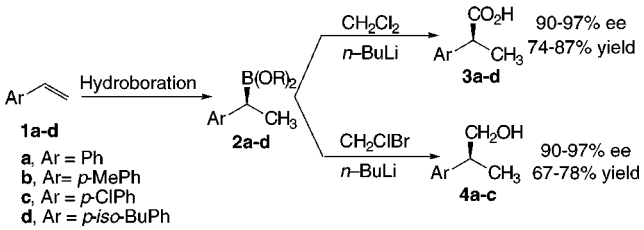
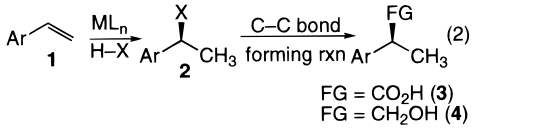
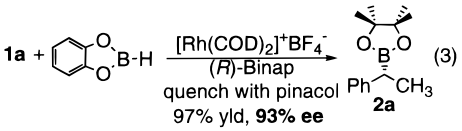
Scheme 1





This approach, although by definition lengthier than a one-pot method, provides greatly increased flexibility in terms of reagent choice for the key C−C bond-forming reaction. In the first demonstration of this strategy, we have employed boron as the carbon surrogate. Asymmetric catalytic hydroboration[9] is a well-precedented reaction known to occur with extremely high enantio- and regioselectivity. Several different catalytic asymmetric hydroboration systems have been reported, which are applicable to an increasingly large number of substrates.[9] Methods for the enantiospecific conversion of the installed B−C bond into a C−C bond were unknown for our particular system, but abound in related cases. H. C. Brown and co-workers in particular have reported several different one-carbon homologating agents which are reactive with trialkylboranes, including Cl_2CHOMe, CO, and CN^-.[10] Similarly, Tufariello has shown that sulfur ylides can homologate organoboranes,[11] as can the derived nitrogen ylides.[12] Several examples of the homologation of boronate esters have been previously reported, using reagents such as Brown's lithiated methoxyphenylthiomethyl ether,[13] Matteson's trimethylsilylchloromethyllithium,[14] or more simply dichloromethyllithium, also developed by Matteson.[15] With these facts in mind, we embarked on an investigation of the sequential hydroboration/homologation of vinylarenes.

Hydroboration. The Hayashi protocol[9a] was chosen for the hydroboration reaction since it could be effected with commercially available BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) as the chiral ligand, and was reported to occur with extremely high regio- and enantioselectivity in the reaction of styrene derivatives. After slight modifications of the reported procedure, we were able to install the carbon surrogate in the desired position with essentially complete regiochemical control and extremely high enantioselectivity (eq 3).[7]



One key modification which proved necessary for our purposes was the addition of pinacol after the reaction. In Hayashi's case, isolation of the boronate ester was not required, and methanol could be used to quench the hydroboration prior to oxidative workup. The use of a quenching reagent is particularly important to forestall less selective hydroboration from occurring as the reaction mixture warms. In our case, pinacol proved to be the optimal reagent since the resulting pinacolates could be isolated in high yield after chromatographic purification. Thus, the hydroboration of a variety of vinylarenes gave the corresponding boronate esters **2** in high yields, with enantioselectivities ranging from 90% to 97% ee (Table 1).[16] The enantioselectivities and yields were reproducible within 2% from run to run.

Homologation. We initially examined methoxyphenylthiomethyllithium (MPML) as a homologating reagent for the conversion of boronate ester **2** into acid **3**.[13] In our hands, treatment of substrate **2a** under the prescribed conditions did provide the one-carbon homologated product, but the yields were variable and difficult to reproduce. The requirement for a stoichiometric amount of mercuric chloride to assist the departure of the sulfur leaving group was another disagreeable feature of this route. Fortunately, a more palatable homologating reagent, $LiCHCl_2$, developed by Matteson et al. proved effective in the homologation of a variety of simple boronate esters as shown in Table 2. $LiCHCl_2$ can be generated by deprotonation of dichloromethane with *n*-BuLi or LDA; we employed *n*-BuLi.[15,17] Although $ZnCl_2$ is known to facilitate the migration, and was employed here, it is not strictly necessary for the homologation in this system.[15]

Table 2 demonstrates that, as expected, 2-arylpropionic acids are obtained with high ee (90−97%) resulting from a completely stereospecific homologation. The first two entries of Table 2 illustrate this fact. Treatment of boronate ester **2a** of 93% ee with $LiCHCl_2$ yields the corresponding carboxylic acid (*R*)-**3** with the same level of enantiomeric purity. Similarly, treatment of the enantiomer of **2a**, prepared by hydroboration with (*S*)-BINAP, yields (*S*)-**3** with complete retention of stereochemistry (90% ee). To achieve this level of enantiomeric purity, control of the pH of the reaction mixture during oxidation of the B−C bond in the intermediate chloroboronate is crucial. When chloroboronate **5** (Scheme 2) was treated with traditional oxidants such as $NaOH/H_2O_2$, no identifiable product could be isolated.[18] On the other hand,

(9) (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426. (b) Brown, J. M.; Hulmes, D. E.; Layzell, T. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1673. (c) Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 931. (d) Schnyder, A.; Togni, A.; Wiesli, U. *Organomet.* **1997**, *16*, 255. (e) Cheung, Y. K. *Organometallics* **1998**, *17*, 3236.

(10) Brown, H. C. *Organic Syntheses via Boranes*; John Wiley and Sons: London, 1975.

(11) Tufariello, J. J.; Wojtkowski, P.; Lee, L. T. C. *J. Chem. Soc., Chem. Commun.* **1967**, 505. (b) Tufariello, J. J.; Lee, L. T. C. *J. Am. Chem. Soc.* **1966**, *88*, 4757.

(12) Musker, W. K.; Stevens, R. R. *Tetrahedron Lett.* **1967**, 995.

(13) Brown, H. C.; Imai, T. *J. Am. Chem. Soc.* **1983**, *105*, 6285.

(14) Matteson, D. S.; Majumdar, D. *J. Organomet. Chem.* **1980**, *184*, C41.

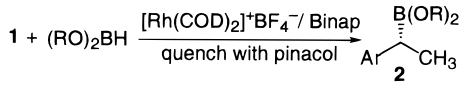
(15) (a) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588. (b) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529.

(16) Note that since boronate ester **2** is purified by chromatography prior to oxidation and analysis of the enantiomeric purity by gas chromatography, we cannot rule out unintentional enrichment in ee by physical separation of the enantiomerically pure material from the racemate. This type of separation has been observed for certain systems, but considering the high yields of the boronate ester obtained, we consider this will contribute little to the ee, if at all. For examples of separation of enantiomers by chromatography see: Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1994**, *59*, 370. Matusch, R.; Coors, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 626 and references therein.

(17) Matteson, D. S.; Peterson, M. L. *J. Org. Chem.* **1987**, *52*, 5116.

(18) This may be attributed to in situ generation of the corresponding peroxide from the aldehyde as has been previously observed: Matteson, D. S.; Moddy, R. J. *J. Org. Chem.* **1980**, *45*, 1091.

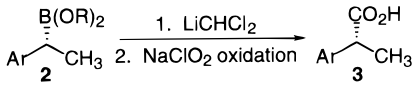
Table 1. Hydroboration of Vinylarenes



Ar	ligand	yield[a] (%)	enantioselectivity[b] (%)
Ph (**1a**)	(*R*)-Binap	99	93 (*R*)
Ph (**1a**)	(*S*)-Binap	95	90 (*S*)
p-MePh (**1b**)	(*R*)-Binap	99	97 (*R*)
p-ClPh (**1c**)	(*R*)-Binap	97	93 (*R*)
p-*i*BuPh (**1d**)	(*R*)-Binap	95	93 (*R*)

[a] Isolated yield of chromatographically and spectroscopically homogeneous material. [b] Enantiomeric excess of **2** determined by GC analysis of the alcohol resulting from oxidation with NaOH/H_2O_2. Chromatography of boronate ester **2** is performed prior to oxidation.[16]

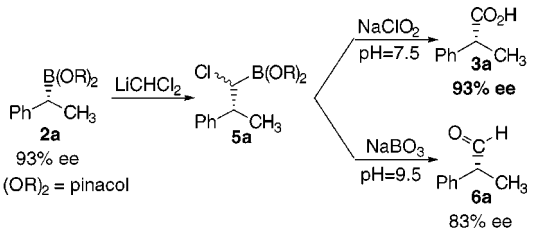
Table 2. Homologation with $LiCHCl_2$



Ar	conversion[a] (%)	yield[b] (%)	enantiomeric excess[c] (%)
Ph (**2a**)	93	87	93 (*R*)
Ph (*ent*-**2a**)	92	79	90 (*S*)
p-MePh (**2b**)	94	88[d]	97 (*R*)
p-ClPh (**2c**)	93	79[d]	93 (*R*)
p-*i*BuPh (**2d**)	90	79	93 (*R*)

[a] Determined by examination of crude chloroboronate (**5**) by ^{1}H NMR prior to oxidation. [b] Isolated yield of chromatographically and spectroscopically homogeneous material. [c] Enantiomeric excess determined by GC analysis of the alcohol resulting from reduction with BH_3·SMe_2. [d] Isolated yield after reduction with BH_3·SMe_2

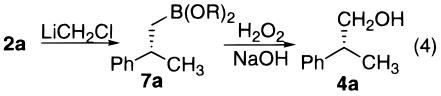
Scheme 2



oxidation with Kabalka's reagent, $NaBO_3$,[19] gave the expected aldehyde **6** in reasonable yield, but 5−30% racemization was observed. This is likely due to partial epimerization of the aldehyde under the basic conditions employed (pH 9.5).[19]

The use of $NaClO_2$ under buffered conditions (pH 7.5) was finally shown to be effective in terms of both yield and retention of enantiomeric purity.[20] This method has the added advantage that the carboxylic acid is obtained directly. We have recently found that the addition of $NaClO_2$ in two aliquots gives greatly increased yields (ca. 80%; see Table 2) compared with our previous report[7] in which 45−52% yield was obtained after addition of the oxidant in one portion.

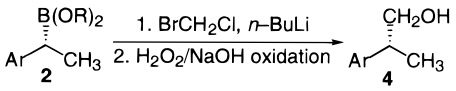
Hydrohydroxymethylation. Having developed a new method for the asymmetric hydrocarboxylation of vinylarenes, we then turned our attention to catalytic asymmetric hydrohydroxymethylation. As previously noted, we know of no literature reports of catalytic asymmetric hydrohydroxymethylations. This transformation was accomplished quite simply by replacing dichloromethane with bromochloromethane.[21] With the bromo derivative, lithium halogen exchange becomes the dominant reaction pathway upon treatment with *n*-BuLi, rather than deprotonation. As shown in eq 4, reaction of



boronate ester **2a** with $LiCH_2Cl$ gave the homologated boronate ester **7a**. Oxidation of **7a** yielded alcohol **4a** with complete retention of enantiomeric purity. Note that, in this synthetic sequence, the aldehyde is not present as an intermediate, so basic H_2O_2 can be employed without fear of compromising the stereochemistry.

This homologation protocol was then demonstrated on *ent*-**2a**, and pinacol boronates **2b**,**c**. As shown in Table 3, the corresponding chiral alcohols were obtained in high enantiomeric purity and with reasonable yields. As expected, the homologation proceeds with complete retention of stereochemistry for all substrates examined. The conversions using $LiCH_2Cl$ were occasionally lower than those obtained in the corresponding dichloromethane-based homologation, which translated into lower isolated yields of the product alcohols. Despite this fact, the overall sequence provides a unique method for the synthesis of enantiomerically enriched alcohols, via a formal hydrohydroxymethylation reaction.

Table 3. Preparation of 2-Arylpropanol Derivatives



Ar	conversion[a] (%)	yield[b] (%)	enantiomeric excess (%)
Ph (**2a**)	98	78	95 (*R*)
Ph (*ent*-**2a**)	88	68	88 (*S*)
p-MePh (**2b**)	87	69	96 (*R*)
p-ClPh (**2c**)	70	69	91 (*R*)

[a] Determined by examination of crude boronate ester **5** by ^{1}H NMR prior to oxidation. [b] Isolated yield of chromatographically and spectroscopically homogeneous material.

Conclusions

In conclusion, we have demonstrated that catalytic asymmetric hydrocarboxylations and hydrohydroxymethylations of vinylarenes can be effected using a strategy in which the enantioselective step is separated from the carbon−carbon bond-forming step. This method provides convenient access to highly enantiomerically enriched 2-arylpropionic acids and 2-arylpropanol derivatives. One of the key advantages of the two-step method is the ability to use a larger variety of homologating reagents than are usually employed in standard transition-metal-catalyzed processes. Using our method, Ibuprofen (**3d**) was prepared in 74% isolated yield and 93% ee from the corresponding vinylarene.

Experimental Section

General Procedures. Unless otherwise noted, all manipulations were carried out under an inert atmosphere (nitrogen

(19) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

(20) (a) Matteson D. S.; Beedle, E. C. *Tetrahedron Lett.* **1987**, *28*, 4499. (b) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(21) (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Michnik, T. J.; Matteson, D. S. *Synlett* **1991**, 631. (c) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8957.

or argon) in flame-dried glassware. All reaction solvents were dried according to literature procedures[22] immediately prior to use, and when necessary, they were purged of oxygen using repeated freeze−pump−thaw cycles and stored under argon in Schlenk flasks. With the exception of *p*-isobutylstyrene, which was prepared in three steps using a literature procedure,[23] all vinylarenes and other reagents were purchased from Aldrich Chemical Co. at the highest grade available and used without further purification unless otherwise noted. Prior to use, vinylarenes were distilled under partial vacuum and percolated through a column of dry, neutral alumina. Neat catecholborane was distilled under a partial vacuum of argon (bp 65 °C at 57 mm Hg) to remove B_2(catechol)$_3$ and stored under argon in a Schlenk flask at −25 °C. Pinacol (2,3-dimethylbutane-2,3-diol) was dried via azeotropic distillation with benzene and then recrystallized from anhydrous ether. It was subsequently stored in a vacuum desiccator over P_2O_5. Amylene (2-methyl-2-butene) was distilled under nitrogen before use. The catalyst precursor [Rh(COD)$_2$]BF_4 was prepared using a literature procedure[24] and stored under argon. The actual concentration of all organolithium bases used was elucidated by titration[25] against BHT and fluorene (Fluka). NMR spectra were recorded as follows: ^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{11}B at 128 MHz, all in $CDCl_3$ containing 0.03% TMS. Infrared spectra were obtained as thin films on NaCl disks. Mass spectra were recorded on a double-focusing mass spectrometer with 8 kV accelerating and 70 eV ionizing voltages. Gas chromatography (He carrier, 12.5 psi of head pressure, 1.15 mL/min flow) was performed with FID detection using split/splitless injector (split ratio 50) and hexane solutions. Retention times are given in minutes. All analyses were performed using a 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin column (30 m, 0.25 mm diameter, 0.25 μm thickness). Analytical thin-layer chromatography was performed on silica gel plates with an F-254 indicator, and visualization accomplished with UV light, $KMnO_4$, or *p*-anisaldehyde dip solutions. Column chromatography was carried out with flash grade silica gel (200−430 mesh) using Still's method. Internal reaction temperatures were monitored with a digital thermometer and a Teflon-coated probe.

Representative Hydroboration Experiment: Preparation of (*R*)-Pinacol(1-phenylethyl)boronate ((*R*)-2a). In a 10 mL round-bottomed flask (RBF), freshly prepared [Rh(COD)$_2$]$^+BF_4^-$ (24.1 mg, 0.061 mmol) and (*R*)-(+)-BINAP (44.0 mg, 0.071 mmol) were suspended in 4 mL of dried, deoxygenated DME. The suspension was stirred until a homogeneous, orange-red solution was obtained (usually <10 min at rt). Freshly purified styrene (**1a**) (0.35 mL, 3.1 mmol) was then added to the reaction mixture and the resulting solution stirred at rt for a further 10 min. Upon cooling to −66 °C (internal reaction temperature), catecholborane (0.40 mL, 3.8 mmol) was added as a solution in 2 mL of DME over 30 min. Care was taken to prevent the internal reaction temperature from rising above −63 °C during addition. The reaction solution was then kept between −66 and −63 °C for 4 h. Pinacol (759.2 mg, 6.4 mmol) was added rapidly in one batch, and the vessel was resealed and flushed with a vigorous flow of nitrogen. The reaction solution was allowed to warm slowly to rt overnight. The solvent was removed carefully at rt, and the resulting black, oily residue was purified via flash chromatography (silica gel, 24:1 hexane/EtOAc) to afford 709.9 mg (99% yield) of pinacol(1-phenylethyl)boronate (**(*R*)-2a**). IR: 2988 (s), 1490 (m), 1358 (s), 1146 (s). ^{1}H NMR: δ 7.11−7.28 (m, 5H), 2.43 (q, J = 7.6 Hz, 1 H), 1.33 (d, J = 7.6 Hz, 3 H), 1.21 (s, 6H), 1.20 (s, 6H). ^{13}C {^{1}H} NMR: δ 145.0, 128.3, 127.8, 125.0, 83.3, 24.61, 24.57, 17.0. ^{11}B NMR: δ 30.1. MS (EI, 70 eV): *m/e* (rel intens) 83.1 (59), 105.1 (81), 117.1 (29), 174.1 (16), 217.1 (40), 232.2 (100). HRMS: calcd for $C_{14}H_{21}BO_2$ 232.1635, obsd 232.1626.

Representative Elucidation of an Enantiomeric Excess of Hydroboration: Oxidation of (*R*)-Pinacol(1-phenylethyl)boronate to (*R*)-1-Phenylethanol. A small portion of boronate ester **(*R*)-2a** (39.6 mg, 0.17 mmol) was dissolved in 10 mL of diethyl ether. The flask was flushed with nitrogen,[26] and NaOH (1.5 mL of a 2 N aqueous solution, 3 mmol) was added at rt. Upon cooling to 0 °C, H_2O_2 (0.70 mL of a 30% w/v aqueous solution, 0.61 mmol) was added dropwise and the resulting solution stirred at 0 °C for 30 min and then at rt for 2 h. The ethereal layer was separated. The aqueous layer was extracted with ether (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), and dried with $MgSO_4$. A 19.4 mg (99% yield) sample of spectroscopically pure 1-phenylethanol was obtained by flash chromatography (silica gel, 4:1 hexane/Et_2O). Its spectral properties were consistent with the published data.[27] The enantiomeric excess was determined to be 93%[28] by chiral GC (temperature protocol, 80 °C, 3 min, then increase 1 °C per min to 130 °C for 30 min; retention time (*R*) = 33.5 min., (*S*) = 35.4 min).

(*S*)-Pinacol(1-phenylethyl)boronate ((*S*)-2a). [Rh(COD)$_2$]$^+BF_4^-$ (24.7 mg, 0.060 mmol), (*S*)-(−)-BINAP (44.2 mg, 0.071 mmol), styrene (**1a**) (0.35 mL, 3.1 mmol), catecholborane (0.40 mL, 3.8 mmol), and pinacol (749.9 mg, 6.3 mmol) were combined in a fashion identical to the preparation of **(*R*)-2a** to afford 684.0 mg (95% yield) of spectroscopically pure **(*S*)-2a**. Its spectroscopic properties were identical to those of its epimer.

(*S*)-1-Phenylethanol. A small portion of boronate ester **(*S*)-2a** (39.2 mg, 0.17 mmol) was oxidized in a fashion analogous to that of **(*R*)-2a** with basic hydrogen peroxide to afford, after flash chromatography (silica gel, 4:1 hexane/Et_2O), 19.3 mg (93% yield) of spectroscopically pure 1-phenylethanol. Its spectral properties were consistent with published data.[27] The enantiomeric excess was determined to be 90% by chiral GC using the same temperature protocol as its epimer.

(*R*)-Pinacol(1-(*p*-methylphenyl)ethyl)boronate (2b). [Rh(COD)$_2$]$^+BF_4^-$ (24.4 mg, 0.060 mmol), (*R*)-(+)-BINAP (43.6 mg, 0.070 mmol), *p*-methylstyrene (**1b**) (0.40 mL, 3.0 mmol), catecholborane (0.39 mL, 3.7 mmol), and pinacol (741.3 mg, 6.3 mmol) were combined in a fashion analogous to that of styrene (**1a**), except that the reaction solution was kept between −66 and −65 °C for 7 h, to afford 733.2 mg (99% yield) of spectroscopically pure **2b**. IR: 2982 (s), 1512 (s), 1358 (s), 1146 (s). ^{1}H NMR: δ 7.08 (m, 4 H), 2.38 (q, J = 7.6 Hz, 1 H), 2.29 (s, 3 H), 1.30 (d, J = 7.6 Hz, 3 H), 1.21 (s, 6H), 1.20 (s, 6H). ^{13}C {^{1}H} NMR: δ 141.9, 134.3, 129.0, 127.6, 83.2, 24.62, 24.59, 21.0, 17.3. ^{11}B NMR: δ 30.1. MS (EI, 70 eV): *m/e* (rel intens) 59.1 (77), 91.1 (44), 129.1 (100), 231.2 (6), 246.2 (10). HRMS: calcd for $C_{15}H_{23}BO_2$ 246.1792, found 246.1809.

(*R*)-1-(*p*-Methylphenyl)ethanol. A small portion of boronate ester **2b** (30.1 mg, 0.12 mmol) was oxidized in a fashion analogous to that of **(*R*)-2a** with basic hydrogen peroxide to afford, after flash chromatography (silica gel, 3:1 hexane/Et_2O), 15.8 mg (97% yield) of spectroscopically pure 1-(*p*-methylphenyl)ethanol. Its spectral properties were consistent with published data.[29] The enantiomeric excess was determined to be 97% by chiral GC (temperature protocol, 100 °C, 3 min, then increase 1 °C per min to 150 °C for 10 min; retention time (*R*) = 27.9 min, (*S*) = 29.8 min).

(*R*)-Pinacol(1-(*p*-chlorophenyl)ethyl)boronate (2c). [Rh(COD)$_2$]$^+BF_4^-$ (16.3 mg, 0.040 mmol), (*R*)-(+)-BINAP (28.9 mg, 0.046 mmol), *p*-chlorostyrene (**1c**) (0.24 mL, 2.0 mmol), catecholborane (0.25 mL, 2.3 mmol), and pinacol (531.8 mg, 4.5 mmol) were combined in a fashion analogous to that of styrene (**1a**), except that the reaction solution was kept between −66 and −64 °C for 6 h, to afford 518.3 mg (97% yield)

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(27) Nagai, U.; Shishido, T.; Chiba, R.; Mitsuhashi, H. *Tetrahedron* **1965**, *21*, 1701.
(28) A similar yield at up to 96% ee can be obtained by carrying out the reaction at −67 to −66 °C for 6 h.
(29) Ishizaki, T.; Miura, H.; Nohira, H. *Nippon Kagaku Kaishi* **1980**, 1381.

of spectroscopically pure product. IR: 2976 (s), 1482 (s), 1376 (s), 1140 (s). ^{1}H NMR: δ 7.18 (m, 4 H), 2.40 (q, J = 7.6 Hz, 1 H), 1.30 (d, J = 7.6 Hz, 3 H), 1.20 (s, 6H), 1.19 (s, 6H). ^{13}C {^{1}H} NMR: δ 143.5, 130.7, 129.1, 128.3, 83.4, 24.60, 24.57, 16.9. ^{11}B NMR: δ 31.4. MS (EI, 70 eV): *m/e* (rel intens) 83.1 (63), 104.1 (81), 166.0 (20), 231.2 (100), 251.1 (15), 266.1 (38). HRMS: calcd for $C_{14}H_{20}BO_2Cl$ 266.1246, found 266.1248.

(*R*)-1-(*p*-Chlorophenyl)ethanol. A small portion of boronate ester **2c** (41.9 mg, 0.16 mmol) was oxidized in a fashion analogous to that of **(*R*)-2a** with basic hydrogen peroxide to afford, after flash chromatography (silica gel, 3:1 hexane/Et_2O), 24.3 mg (97% yield) of spectroscopically pure 1-(*p*-chlorophenyl)ethanol. Its spectral properties were consistent with the published data.[30] The enantiomeric excess was determined to be 93% by chiral GC (temperature protocol, 100 °C, 3 min, then increase 1 °C per min to 160 °C for 15 min; retention time (R) = 43.9 min, (S) = 45.3 min).

(*S*)-Pinacol(1-(*p*-isobutylphenyl)ethyl)boronate (2d). [Rh(COD)$_2$]$^+$BF$_4^-$ (32.4 mg, 0.080 mmol), (*S*)-(−)-BINAP (54.8 mg, 0.088 mmol), *p*-isobutylstyrene (**1d**) (608.5 mg, 3.8 mmol), catecholborane (0.60 mL, 5.6 mmol), and pinacol (998.8 mg, 8.5 mmol) were combined in a fashion analogous to that of styrene (**1a**), except that the reaction solution was kept between −62 and −60 °C for 8 h, to afford 1.03 g (95% yield) of spectroscopically pure product. IR: 2966 (s), 1506 (m), 1376 (s), 1140 (s). ^{1}H NMR: δ 7.07 (m, 4 H), 2.42 (d, J = 7.2 Hz, 2 H), 2.40 (q, J = 7.6 Hz, 1 H), 1.83 (m, 1 H), 1.31 (d, J = 7.6 Hz, 3H), 1.21 (s, 6H), 1.19 (s, 6H), 0.89 (d, J = 6.4 Hz, 6H). ^{13}C {^{1}H} NMR: δ 142.0, 138.2, 129.0, 127.4, 83.2, 45.1, 30.2, 24.62, 24.57, 22.4, 17.1. ^{11}B NMR: δ 31.6. MS (EI, 70 eV): *m/e* (rel intens) 83.1 (13), 231.2 (32), 245.1 (100), 273.2 (9), 288.2 (50). HRMS: calcd for $C_{18}H_{29}BO_2$ 288.2262, found 288.2257.

(*R*)-1-(*p*-Isobutylphenyl)ethanol. A small portion of boronate ester **2d** (98.9 mg, 0.34 mmol) was oxidized in a fashion analogous to that of **(*R*)-2a** with basic hydrogen peroxide to afford, after flash chromatography (silica gel, 3:1 hexane/Et_2O), 53.9 mg (89% yield) of spectroscopically pure 1-(*p*-isobutylphenyl)ethanol. Its spectral properties were consistent with the published data.[23] The enantiomeric excess was determined to be 93% by chiral GC (temperature protocol, 80 °C, 90 min, then increase 1 °C per min to 160 °C for 15 min; retention time (R) = 148.9 min, (S) = 149.3 min).

Representative Homologation Experiment: Preparation of (*R*)-2-Phenylpropionic Acid, ((*R*)-3a). In a 50 mL two-necked RBF, $LiCHCl_2$ (2.67 mmol) was generated by the dropwise addition of *n*-BuLi (1.7 mL of a 1.57 M solution in hexane, 2.67 mmol) down the side of the flask to a mixture of dichloromethane (1.4 mL, 22 mmol) and THF (10 mL) at −100 °C in a 95% EtOH−liquid N_2 bath. The clear colorless solution was stirred at −100 °C for a further 10 min[31] before the rapid addition of boronate ester **(*R*)-2a** (360.1 mg, 1.55 mmol, 93% ee) as a solution in 2 mL of THF. $ZnCl_2$ (1.5 mL of a 1.0 M solution in Et_2O, 1.5 mmol) was then added.[32] The reaction was left to warm to ambient temperature overnight. After this time, the volatiles were removed under a vigorous flow of N_2. The residue was quenched with 6 mL of saturated aqueous ammonium chloride, extracted with light petroleum ether (4 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. NMR analysis of the material **(*R*)-5a** thus obtained (435.0 mg) indicated 93% conversion. A portion of this material (401.5 mg, 1.43 mmol) was then dissolved in *t*-BuOH (35 mL) and amylene (11 mL) in a 100 mL RBF. An aqueous solution (25 mL) of sodium chlorite (1.0089 g, 8.9 mmol) and potassium hydrogen phosphate (1.4511 g, 10.7 mmol) was then added dropwise to the reaction mixture, and the reaction was then left to stir at ambient temperature for 24 h. Another batch of the above aqueous sodium chlorite−potassium hydrogen phosphate solution[33] was added and the reaction stirred for another 48 h. The volatiles were removed in vacuo, and the resulting aqueous residue was extracted with ether (3 × 30 mL) and ethyl acetate (2 × 25 mL). The combined organic extracts were washed with distilled water (4 × 10 mL) and then extracted with saturated aqueous sodium bicarbonate (4 × 25 mL). The basic extracts were then slowly acidified to pH 2 with concentrated HCl.[34] The resulting aqueous solution was subsequently extracted with ethyl acetate (4 × 50 mL). The organic extracts were then combined, washed with distilled water (2 × 20 mL) and brine (75 mL), and finally dried over $MgSO_4$. Filtration and concentration in vacuo furnished a yellow oil (**(*R*)-3a**), which can be rendered spectroscopically pure by bulb-to-bulb distillation. A 0.2039 g (87% yield) sample of acid **(*R*)-3a** was obtained as a colorless oil whose spectral properties were consistent with published data.[35]

Representative Elucidation of Enantiomeric Excess of Hydrocarboxylation: Reduction of (*R*)-2-Phenylpropionic Acid ((*R*)-3a) to (*R*)-2-Phenylpropanol ((*R*)-4a). In a 25 mL RBF acid **(*R*)-3a** (58.9 mg, 0.39 mmol) was dissolved in ether (10 mL). The reaction solution was then cooled to 0 °C before borane·SMe_2 complex (0.200 mL, 2.2 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h and then at ambient temperature for a further 3 h. The solution was recooled to 0 °C, and unreacted borane was quenched with the dropwise addition of water. When no further evolution of H_2 was observed with further addition of water, NaOH (2 mL of a 2 N aqueous solution, 4 mmol) was added dropwise. The biphasic solution was then poured into a separatory funnel, and the ether layer was separated. The aqueous layer was further extracted with ether (3 × 5 mL), and the combined ether extracts were washed with brine (10 mL), dried with $MgSO_4$, and filtered. Concentration of the filtrate in vacuo followed by flash chromatography (silica gel, 4:1 hexane/Et_2O) afforded 49.7 mg (94% yield) of spectroscopically pure alcohol **(*R*)-4a** as a colorless oil whose spectral properties were consistent with published data.[36] The enantiomeric excess was determined to be 93% by chiral GC (temperature protocol, 80 °C, 3 min, then increase 1 °C per min to 130 °C for 30 min; retention time (R) = 38.6 min, (S) = 40.8 min).

(*S*)-2-Phenylpropionic Acid, ((*S*)-3a). Boronate ester **(*S*)-2a** (364.1 mg, 1.57 mmol, 90% ee) was homologated with *n*-BuLi (1.7 mL of a 1.57 M solution in hexanes, 2.67 mmol), dichloromethane (1.4 mL, 22 mmol), and $ZnCl_2$ (1.5 mL of a 1.0 M solution in Et_2O, 1.5 mmol) in a fashion analogous to that of **(*R*)-2a**. A 424.0 mg (91% conversion by ^{1}H NMR analysis) sample of the corresponding chloroboronate product **(*S*)-5a** was obtained. A 394.0 mg (0.71 mmol) sample of this material was then oxidized with sodium chlorite (1.0190 g, 9.0 mmol × 2), potassium hydrogen phosphate (1.4111 g, 10.4 mmol × 2), amylene (11 mL), and *t*-BuOH (35 mL) to afford 127.6 mg (79% yield) of acid **(*S*)-3a** as a colorless oil. Its spectroscopic properties were consistent with published data.[35]

(*S*)-2-Phenylpropanol ((*S*)-4a). A portion of acid **(*S*)-3a** (105.3 mg, 0.70 mmol) was reduced in a fashion analogous to that of **(*R*)-3a** with borane·SMe_2 complex (0.40 mL, 4.2 mmol) to afford, after flash chromatography (silica gel, 4:1 hexane/Et_2O), 92.5 mg (97% yield) of spectroscopically pure alcohol **(*S*)-4a**. Its spectral properties were consistent with published data.[36] The enantiomeric excess was determined to be 90% by chiral GC using the same temperature protocol as for its epimer.

(30) Okamoto, K.; Kinoshita, T.; Takemura, Y.; Yoneda, H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1426.

(31) The solution should remain colorless. Color indicates decomposition of the homologation reagent (this will occur if the addition is too rapid and/or the internal reaction temperature exceeds −80 °C) to the corresponding carbene, and colored reagents should not be used for the homologation. Precipitation of the homologation reagent may also be observed near the end of the 10 min period, but it can be used for the homologation without any deleterious effect on the yield or the enantiomeric excess.

(32) $ZnCl_2$ separates from the ether solvent at room temperature and thus should be added rapidly with a syringe previously chilled to −25 °C in a desiccator.

(33) Sodium chlorite has a limited lifetime in water at room temperature, so the oxidant must be introduced in two batches to ensure quantitative conversion.

(34) Care should be taken to maintain the internal temperature below 35 °C to minimize decomposition of product acid.

(35) *The Aldrich Library of NMR Spectra*; Aldrich Chemical Co.: Milwaukee, 1974; Vol. 6, p 105d.

(36) Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832.

(*R*)-2-(*p*-Methylphenyl)propanol (4b). Boronate ester **2b** (360.0 mg, 1.47 mmol, 97% ee) was homologated with *n*-BuLi (1.3 mL of a 1.57 M solution in hexanes, 2.0 mmol), dichloromethane (1.3 mL or 20 mmol), and $ZnCl_2$ (1.4 mL of a 1.0 M solution in Et_2O, 1.4 mmol) in a fashion analogous to that of **(*R*)-2a**. A 419.3 mg (94% conversion by ^{1}H NMR analysis) sample of the corresponding chloroboronate product **5b** was obtained. A 389.6 mg (1.30 mmol) sample of this material was oxidized with sodium chlorite (900.0 mg, 8.0 mmol × 2), potassium hydrogen phosphate (1.3770 g, 10.1 mmol × 2), amylene (10 mL), and *t*-BuOH (30 mL). After removal of the volatiles in vacuo, the reaction mixture was worked up by extraction of the aqueous residue with ether (3 × 30 mL) and ethyl acetate (2 × 50 mL). The organic extracts were combined, washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated to give **3b** as a pale yellow oil. The crude product was directly reduced with borane·SMe_2 complex (0.500 mL, 5.3 mmol) in a manner analogous to the reduction of **(*R*)-3a** to afford, after flash chromatography (silica gel, 7:1 hexane/EtOAc), 180.9 mg (88% yield) of spectroscopically pure alcohol **4b**. Its spectral properties were consistent with published data.[37] The enantiomeric excess was determined to be 97% by chiral GC (temperature protocol, 80 °C, 3 min, then increase 1 °C per min to 130 °C for 15 min; retention time (*R*) = 48.8 min, (*S*) = 50.6 min).

(*R*)-2-(*p*-Chlorophenyl)propanol (4c). Boronate ester **2c** (360.4 mg, 1.36 mmol, 93% ee) was homologated with *n*-BuLi (1.4 mL of a 1.57 M solution in hexanes, 2.2 mmol), dichloromethane (1.2 mL, 19 mmol), and $ZnCl_2$ (1.4 mL of a 1.0 M solution in Et_2O, 1.4 mmol) in a fashion analogous to that of **(*R*)-2a**. A 425.2 mg (93% conversion by ^{1}H NMR analysis) sample of the corresponding chloroboronate product **5c** was obtained. A 409.2 mg (1.30 mmol) sample of this material was then oxidized with sodium chlorite (910.0 mg, 8.0 mmol × 2), potassium hydrogen phosphate (1.4117 g, 10.3 mmol × 2), amylene (10 mL), and *t*-BuOH (35 mL). After the removal of the volatiles in vacuo, the reaction mixture was worked up by extraction of the aqueous residue with ether (3 × 30 mL) and ethyl acetate (2 × 50 mL). The organic extracts were combined, washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated to give **3c** as a pale yellow solid. The crude product was directly reduced with borane·SMe_2 complex (0.500 mL, 5.3 mmol) in a manner analogous to the reduction of **(*R*)-3a** to afford, after flash chromatography (silica gel, 7:1 hexane/EtOAc), 180.2 mg (79% yield) of spectroscopically pure alcohol **4c**. Its spectral properties were consistent with published data.[37] The enantiomeric excess was determined to be 93% by chiral GC (temperature protocol, 80 °C, 5 min, then increase 1 °C per min to 160 °C for 30 min; retention time (*R*) = 73.2 min, (*S*) = 75.5 min).

(*S*)-Ibuprofen (3d). Boronate ester **2d** (420.0 mg, 1.46 mmol, 92% ee) was homologated with *n*-BuLi (1.6 mL of a 1.57 M solution in hexanes, 2.51 mmol), dichloromethane (1.3 mL, 20 mmol), and $ZnCl_2$ (1.4 mL of a 1.0 M solution in Et_2O, 1.4 mmol) in a fashion analogous to that of **(*R*)-2a**. A 472.0 mg (90% conversion by ^{1}H NMR analysis) sample of the corresponding chloroboronate product **5d** was obtained. A 363.8 mg (1.11 mmol) sample of this material was then oxidized with sodium chlorite (750.0 mg, 6.6 mmol × 2), potassium hydrogen phosphate (1.1085 g, 8.1 mmol × 2), amylene (7.5 mL), and *t*-BuOH (30 mL) to afford 191.4 mg (84% yield) of Ibuprofen (**3d**) after bulb-to-bulb distillation. This was purified further by loading the acid onto a column of basic alumina and rinsing the column with ether (4 × 150 mL). The acid was then flushed off the column with 100 mL of TFA. Removal of the solvent followed by another bulb-to-bulb distillation furnished 179.9 mg (79% yield) of Ibuprofen (**3d**) as a crystalline solid. Its spectroscopic properties were consistent with published data.[38]

(*S*)-2-(*p*-Isobutylphenyl)propanol ((*S*)-4d). A portion of Ibuprofen (**3d**) (43.1 mg, 0.21 mmol) was reduced in a fashion analogous to that of **(*R*)-3a** with borane·SMe_2 complex (0.100 mL, 1.1 mmol) to afford, after flash chromatography (silica gel, 3:1 hexane/Et_2O), 39.8 mg (99% yield) of spectroscopically pure alcohol **4d**. Its spectral properties were consistent with published data.[39] The enantiomeric excess was determined to be 93% by chiral GC (temperature protocol, 85 °C, 100 min, then increase 1 °C per min to 180 °C for 35 min; retention time (*R*) = 161.0 min, (*S*) = 161.8 min).

Representative Hydrohydroxymethylation Experiment: Preparation of (*S*)-2-Phenylpropanol ((*S*)-4a). In a 10 mL RBF boronate ester **(*S*)-2a** (312.5 mg, 1.4 mmol, 95% ee) and bromochloromethane (0.100 mL, 1.54 mmol) in 2.0 mL of THF were dissolved. Upon cooling of the reaction solution to −78 °C using a 95% EtOH−liquid N_2 bath, *n*-BuLi (0.71 mL of a 2.17 M solution in hexanes, 1.54 mmol) was added dropwise to the middle of the stirring vortex over a period of 15 min. The reaction was then left to warm to ambient temperature overnight. After this time, the volatiles were removed under a vigorous flow of N_2. The residue was quenched with 10 mL of saturated aqueous ammonium chloride, extracted with light petroleum (4 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. NMR analysis of the material (**(*S*)-7a**) thus obtained (321.5 mg) indicated 98% conversion. A portion of this material (300.8 mg, 1.22 mmol) was then dissolved in diethyl ether (10 mL). To the reaction mixture were added, sequentially, at room temperature, methanol (2 mL) and NaOH (4.0 mL of a 2 N aqueous solution, 8.0 mmol) and then, at 0 °C, H_2O_2 (0.300 mL of a 30% aqueous w/v solution, 2.6 mmol). The resulting reaction mixture was warmed slowly to room temperature overnight. The biphasic solution was then poured into a separatory funnel, and the ether layer was separated. The aqueous layer was further extracted with ether (3 × 20 mL) and the combined ether extracts were washed with brine (10 mL), dried with $MgSO_4$, and filtered. Concentration of the filtrate in vacuo followed by flash chromatography (silica gel, 9:1 hexane/EtOAc) afforded 134.4 mg (78% yield) of spectroscopically pure alcohol **(*S*)-4a**. Its spectroscopic properties were consistent with published data.[36] The enantiomeric excess was determined to be 95% by chiral GC (temperature protocol, 80 °C, 3 min, then increase 1 °C per min to 130 °C for 30 min; retention time (*R*) = 38.6 min, (*S*) = 40.8 min).

(*R*)-2-Phenylpropanol ((*R*)-4a). Boronate ester **(*R*)-2a** (233.6 mg, 1.0 mmol, 88% ee), bromochloromethane (0.072 mL, 1.1 mmol), and *n*-BuLi (0.51 mL of a 2.17 M solution in hexanes, 1.1 mmol) were combined in the manner described for the hydrohydroxymethylation of **(*S*)-2a**. NMR analysis of the resulting product **(*R*)-7a** (254.1 mg) indicated 88% conversion. This material (254.1 mg, 0.97 mmol) was then oxidized with methanol (2 mL), NaOH (4.0 mL of a 2 N aqueous solution, 8.0 mmol), and H_2O_2 (0.285 mL of a 30% aqueous w/v solution, 2.5 mmol). Flash chromatography (silica gel, 9:1 hexane/EtOAc) afforded 92.0 mg (68% yield) of spectroscopically pure alcohol **(*R*)-4a**. Its spectroscopic properties were consistent with published data.[36] The enantiomeric excess was determined to be 88% by chiral GC using the same temperature protocol as for its epimer.

(*R*)-2-(*p*-Methylphenyl)propanol (4b). Boronate ester **2b** (254.1 mg or 1.03 mmol, 96% ee), bromochloromethane (0.074 mL or 1.14 mmol), and *n*-BuLi (0.52 mL of a 2.17 M solution in hexanes, 1.14 mmol) were combined in the manner described above for the hydrohydroxymethylation of **(*S*)-2a**. NMR analysis of the resulting product **7b** (261.7 mg) indicated 87% conversion. This material (261.7 mg, 1.01 mmol) was then oxidized with methanol (2 mL), NaOH (4.0 mL of a 2 N aqueous solution, 8.0 mmol), and H_2O_2 (0.280 mL of a 30% aqueous w/v solution, 2.5 mmol). Flash chromatography (silica gel, 9:1 hexane/EtOAc) afforded 106.5 mg (69% yield) of spectroscopically pure alcohol **4b**. Its spectral properties were consistent with published data.[37] The enantiomeric excess was determined to be 96% by chiral GC (temperature protocol, 80 °C, 3 min, then increase 1 °C per min to 130 °C for 15 min; retention time (*R*) = 48.8 min, (*S*) = 50.6 min).

(37) DePuy, C. H.; Storm, D. L.; Frey, J. T.; Naylor, C. G. *J. Org. Chem.* **1970**, *35*, 2746.
(38) Nugent, W. A.; McKinney, R. J. *J. Org. Chem.* **1985**, *50*, 5370.
(39) Takano, S.; Ogasawara, K.; Nagayama, I.; Kutsuma, T. *Synth. Commun.* **1976**, *6*, 349.

(*R*)-2-(*p*-Chlorophenyl)propanol (4c). Boronate ester **2c** (267.7 mg, 1.00 mmol, 91% ee), bromochloromethane (0.072 mL, 1.10 mmol), and *n*-BuLi (0.51 mL of a 2.17 M solution in hexanes, 1.10 mmol) were combined in the manner described above for the hydrohydroxymethylation of **(*S*)-2a**. NMR analysis of the resulting product **7c** (268.0 mg) indicated 70% conversion. This material (268.0 mg, 0.96 mmol) was then oxidized with methanol (2 mL), NaOH (4.0 mL of a 2 N aqueous solution, 8.0 mmol), and H_2O_2 (0.280 mL of a 30% aqueous w/v solution, 2.5 mmol). Flash chromatography (silica gel, 9:1 hexane/EtOAc) afforded 117.2 mg (69% yield) of spectroscopically pure alcohol **4b**. Its spectral properties were consistent with published data.[37] The enantiomeric excess was determined to be 93% by chiral GC (temperature protocol, 80 °C, 5 min, then increase 1 °C per min to 160 °C for 30 min; retention time (*R*) = 73.2 min, (*S*) = 75.5 min).

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