Catalytic asymmetric carbon–carbon bond forming reactions: preparation of optically enriched 2-aryl propionic acids by a catalytic asymmetric hydroboration–homologation sequence†

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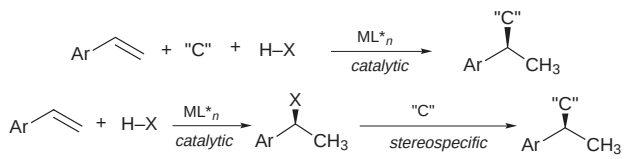
A new catalytic asymmetric one-carbon homologation strategy has been developed which employs a rhodium catalyzed asymmetric hydroboration followed by homologation with $LiCHCl_2$ and oxidation to generate 2-arylpropionic acids of high enantiomeric purity.

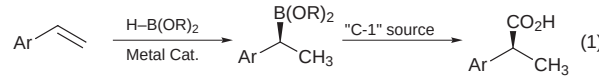
Asymmetric carbon–carbon bond forming reactions are among the most important transformations in organic synthesis.[1] Catalytic methods are the most efficient means to affect these reactions, since the source of chirality is also used in catalytic quantities. The asymmetric synthesis of 2-aryl substituted carboxylic acids is of particular importance since non-steroidal anti-inflammatory agents such as Ibuprofen™ and Naproxen™ are among this class of compounds. Furthermore, the positive medicinal effects of these pharmaceuticals are ascribed to only one of the enantiomeric forms.[2] State-of-the-art catalytic asymmetric C–C bond forming methods for the synthesis of 2-aryl substituted propionic acids include hydrocarbonylation techniques employing carbon monoxide.[3] The key step in these methods is the enantioselective addition of a transition metal hydride across an olefin, which is followed by C–C bond formation (carbonylation). It occurred to us that an alternative strategy would be to employ a catalytic asymmetric reaction to install the required stereocentre followed by a second, stereospecific C–C bond forming reaction (Scheme 1). This basic principle has been realized in our labs leading to a highly enantioselective synthesis of 2-arylpropionic acids with the aid of catalytic asymmetric hydroboration.[4]

The catalytic asymmetric hydroboration reaction occurs with essentially complete regiochemical control and extremely high enantiocontrol in the hydroboration of vinylarenes to give the corresponding chiral 2-aryl boronate esters.[4] Despite the success of this transformation, it has thus far been relegated to a method for the preparation of enantiomerically enriched aryl methyl alcohols,[4] and more recently extended to include the preparation of amines.[5]

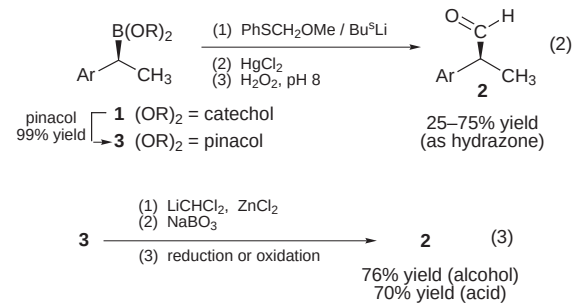
Although the application of chiral borane species prepared using *stoichiometric* amounts of chiral materials in C–C bond forming reactions has been reported in the elegant work of Matteson[6] and Brown,[7] no such use of the catalytically synthesized catecholate **1** has been described. We report herein a new asymmetric hydroboration–homologation method in which vinyl arenes are converted into 2-arylpropionic acids using only catalytic quantities of chiral material [eqn. (1)].



Scheme 1



Several potential 'C-1' sources can be employed for the stereospecific C–C bond forming reaction. We first examined lithiated methylthiophenyl methyl ether,[7] but found the reaction to be low yielding with substrate **1** [eqn. (2)]. Transesterification of catechol boronate **1** to the corresponding pinacol boronate **3** prior to homologation gave **2** in higher yields, up to 75% isolated (as the hydrazone), but the highly capricious procedure requiring large quantities of $HgCl_2$ prompted us to consider alternative homologating reagents. Matteson has described the use of $LiCHCl_2$ in his homologation–Grignard addition strategy carried out on boronate esters prepared with stoichiometric amounts of chiral borane reagents.[6] Indeed $LiCHCl_2$ could be reliably prepared using Matteson's detailed procedure[6] and reacted with boronate ester **3** to yield, after oxidative workup, the homologation product **2** in good yield: 79% isolated as the alcohol after $BH_3{\cdot}SMe_2$ reduction, or 70% as the carboxylic acid after Lindgren oxidation [eqn. (3)].



Having established a reliable homologation method, we then carried out the sequence under asymmetric conditions. Reaction of styrene with catechol borane in the presence of catalytic amounts of $[Rh(COD)_2]^+BF_4^-$ and (*S*)-BINAP[4] generated the boronate ester **1** asymmetrically. Conversion of boronate ester **1** to pinacolate **3** allowed us to isolate and purify this species by column chromatography. The enantioselectivity of the process was high (91% ee).‡ The purified material was then homologated with $LiCHCl_2$. Oxidation of the intermediate chloroboronate using Kabalka's procedure[8] yielded aldehyde **2**, which was further oxidized to the carboxylic acid under Pinnick-modified Lindgren conditions.[9] Analysis of this material by optical rotation and chiral GC§ showed that the homologation–oxidation had proceeded with some loss of enantiomeric purity, yielding the desired product in only 77% ee. This decrease in ee was determined by independent experiments to be occurring *via* the aldehyde. Thus direct oxidation of the intermediate chloroboronate to the acid under Lindgren conditions[10] was affected and yielded the desired product in a slightly reduced yield, but with complete retention of enantioselectivity [eqns. (4) and (5)].¶

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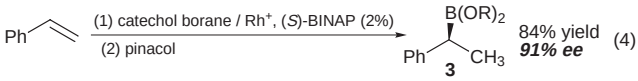

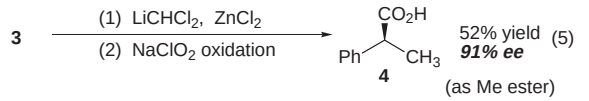

The slow addition of catechol borane as a solution in DME and maintenance of a low internal temperature were found to be crucial for achieving good enantioselectivities in our hands. (*R*)-BINAP gave slightly better enantioselectivities in the hydroboration, yielding **3** (*ent.*) in 95% ee (95% yield), which translated into 95% ee (45% yield) in the homologated carboxylic acid **4** (*ent.*).

The homologation method described herein is, to the best of our knowledge, the first use of chiral boronate esters prepared by *catalytic* hydroboration in a carbon–carbon bond forming reaction. With our method, the high regioselectivity observed in the catalytic asymmetric hydroboration is transferred to the subsequent C–C bond forming process, and the enantioselectivity is completely retained, offering a useful alternative to catalytic asymmetric hydrocarbonylation strategies. We are currently examining the application of this carbon monoxide-free hydrocarboxylation to more complex systems, and will report these results in due course.

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Notes and references

‡ Determined by oxidizing a small portion of the boronate ester, and subjecting the resulting alcohol to chiral gas chromatography: Column = 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin, (Suppelco, BETA DEX-225) 30 m, 0.25 mm diameter, 0.25 μm thickness, He carrier, 12.5 psi head pressure, 1.15 ml min^{-1} flow, FID detection. Retention time (t_R) = 44.6 (*R*) and 46.0 min (*S*) @ 70 °C for 5 min, then increase 1 °C per min to 150 °C for 30 min.

§ Column and conditions as above, **4**: (converted to Me ester by treatment with CH_2N_2) 154.1 (*S*) and 155.0 (*R*) min @ 50 °C for 100 min, then ramp at 1 °C per min to 160 °C.

¶ We thank a reviewer for pointing out this oxidation technique. The following procedure (styrene) is representative.

Hydroboration: In a flame dried round-bottomed flask, $[Rh(COD)_2]^+BF_4^-$ (32.4 mg, 0.078 mmol) and (*S*)-(−)-BINAP (54.8 mg, 0.088 mmol) were mixed. Dried, deoxygenated DME was added (4 ml) and the suspension stirred for 30 min. Styrene, previously distilled, was filtered through a plug of alumina and added to the mixture (0.46 ml, 4.0 mmol), which was then cooled to −66 °C. Catechol borane (0.5 ml, 4.7 mmol, distilled) was added as a solution in 2 ml DME dropwise over 45 min. During the addition, the internal temp did not exceed −66 °C. The solution was kept between −67 and −66 °C for 4 h. Pinacol (recrystallised and dried, 1.0121 g, 8.56 mmol) was added and the solution warmed slowly to room temperature overnight. Flash chromatography (silica gel, 24 : 1 hexane–EtOAc) yielded 761.4 mg (82%) of **3**. Enantioselectivity was determined to be 91% ee by oxidizing a small portion of this material under the conditions described in ref. 4, and analyzing the resulting material by chiral GC.

Homologation: this was carried out using $LiCHCl_2$ (1.25 mmol) generated by the slow addition of Bu^nLi (0.8 ml of a 1.57 M solution in hexane, 1.25 mmol) to a mixture of THF (6.5 ml) and CH_2Cl_2 (0.67 ml, 10 mmol) at −100 °C in a 95% EtOH–liq. N_2 bath. The clear colourless solution was stirred at −100 °C for 10 min before the rapid addition of boronate ester **3** (246 mg, 1.06 mmol) as a solution in 2 ml THF. $ZnCl_2$ (1.1 ml of a 1.0 M solution in Et_2O, 1.1 mmol) was then added. The reaction was left to warm to room temperature overnight. After this time, the volatiles were removed under a vigorous flow of N_2. The residue was quenched with 5 ml of sat. aq. NH_4Cl, extracted with light petroleum (4 × 20 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. NMR analysis of the material thus obtained (283 mg, 95% crude yield) indicated no starting material remained, and only the chloroboronate product was present. This material was then oxidized to the acid directly following the procedure in ref. 9, (48 h reaction time were necessary). Purification of acid **4** was affected by an acid–base extraction, followed by methylation with CH_2N_2 and flash chromatography (7 : 1 hexane–EtOAc) giving the methyl ester of **4** in 52% yield (91% ee).

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