Boronic Acids as Versatile Aryl Sources for the Highly Enantioselective Synthesis of Chiral Diarylmethanols on Multigram Scale

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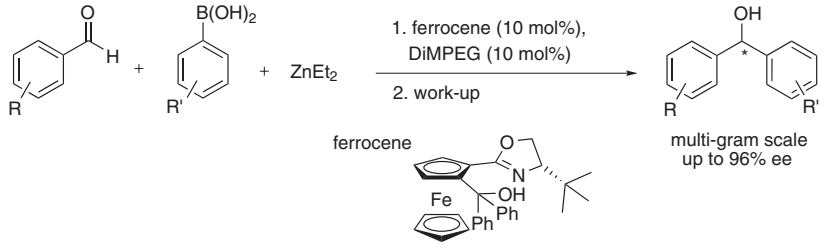
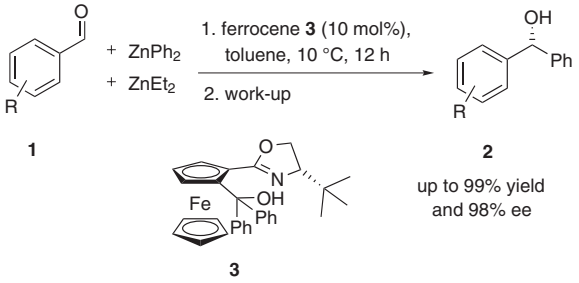
Abstract: Chiral diarylmethanols have been synthesized on gram scale in high yields with excellent enantioselectivities using a catalyst with a ferrocenyl oxazoline-based N,O-ligand and mixtures of diethylzinc and arylboronic acid as an aryl source.

Key words: diarylmethanols, zinc organyls, catalysis, arylboronic acids



Scheme 1

More and more the pharmaceutical and agricultural industries request highly enantioselective syntheses of chiral intermediates and final products due to their attractive biological activities and high market values.[1] From a practical and economical point of view, catalytic methods appear most desirable for such syntheses.[2] Enantiomerically pure diarylmethanols are particularly interesting target compounds because their structural skeleton can be found in many pharmaceutically and agriculturally important molecules. For example, diarylmethanols are key intermediates for the synthesis of antihistaminic agents such as neobenodine, orphenadrine, or carbinoxamine.[3] More recently, they have been used for the preparation for 1,1-diarylalkyl units, which are core structures of antimuscarinics, antidepressants, and endothelin antagonists.[4] Two general approaches exist for their synthesis: first, the enantioselective reduction of prochiral ketones[5,6] and second, the asymmetric phenyl- or aryl transfer onto aromatic aldehydes.[7,8] Despite vast improvements, both methods lack important criteria for their large-scale application in industry. For example, the reductive one is only applicable to substrates with significant steric and/or electronic difference between the two aryl groups. The aryl transfer protocol reported by us in 2000 (Scheme 2)[8b] requires 10 mol% of a catalyst stemming from ferrocene **3** and utilizes diphenylzinc (in combination with diethylzinc) as aryl source. Although high yields and excellent enantioselectivities in the formation of aryl phenyl methanols **2** have been achieved, the relatively high catalyst loading, the required use of expensive salt-free diphenylzinc, and the restriction to only phenyl transfer remained severe limitations of this approach.



Scheme 2

Recently, we described the applicability of arylboronic acids (instead of diphenylzinc) in the aryl transfer reactions and now almost any aryl group can be transferred to aromatic aldehydes with excellent enantioselectivities.[9] Furthermore, the catalyst loading could be reduced in the phenyl transfer to 1 mol% using polyethylene glycol-bound ligands[8f] or polyglycol ethers as additives.[10] Despite these major improvements, further optimizations appeared desirable, in particular when taking into account, that in large-scale processes the aryl transfer reagent should be easy to handle, low in cost and allow an aryl transfer to gain access to diarylmethanols. With respect to the two former aspects, a first breakthrough was achieved

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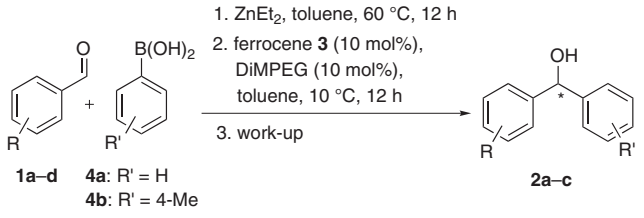
by the use of triphenylborane as phenyl source, which allowed the gram-scale synthesis of arylphenylmethanols. However, by this method only phenyl groups could be transfered.[11] Here, we report the catalytic asymmetric synthesis of diarylmethanols *on a gram-scale* using boronic acids as aryl source. These boron reagents are commercially available in large quantities, relatively inexpensive and easily prepared. Following a modified protocol in which diphenylzinc was substituted by an arylboronic acid and a slightly larger amount of diethylzinc was applied, excellent yields and very high enantioselectivities were achieved (Scheme 1 and Table 1). No problems were encountered in scaling up the reaction, and in all aspects the results of the 10 mmol scale studies were comparable to those previously obtained on the 0.25 mmol scale.[9]

Table 1 Gram Scale Synthesis of Diarylmethanols with Arylboronic Acids as Aryl Sources[a]



Entry	Aldehyde	Arylboronic Acid	Product	Yield (%)[b]	ee (%)[c]
1	4-chlorobenzaldehyde (**1a**)	**4a**	(*R*)-**2a**	93	96
2	4-methylbenzaldehyde (**1b**)	**4a**	(*R*)-**2b**	94	96
3	2-bromobenzaldehyde (**1c**)	**4a**	(*R*)-**2c**	99	93
4	benzaldehyde (**1d**)	**4b**	(*S*)-**2b**	95	94

[a] A mixture of 2.4 equiv of arylboronic acid and 7.2 equiv of $ZnEt_2$ was used in all experiments.
[b] After column chromatography.
[c] Enantiomer ratios were determined by HPLC analysis using a chiral column.

To our delight the previously reported protocol for the small scale syntheses of diarylmethanols using arylboronic acids worked well on a larger scale, emphasizing the synthetic value of the method.[9] In terms of the product yield, the larger-scale process proved highly efficient and even *ortho*-substituted diarylmethanol **2c**, which had been difficult to prepare in good yield before, was obtained in 99% yield.

In the syntheses of **2a** and **2b** a slight decrease of enantioselectivity (Δee = 1%) was observed upon scale-up. In contrast, the ee of **2c** raised (from 88%)[9] to 93% ee, which is a most striking result since *ortho*-substituted aromatic aldehydes are usually difficult substrates for stereoselective conversions. Interestingly, in the large-scale process using BPh_3 as aryl source the opposite effect was observed and a slight decrease in the enantioselective formation of **2c** occurred. Since we can exclude solvent and concentration effects, the reasons for these variations in the enantioselectivities still need to be elucidated.

Noteworthy is also that with the same catalyst both enantiomers of **2b** have been prepared with excellent enantiomeric excesses in high yields simply by using the appropriate combination of arylboronic acid and aldehyde (Table 1, entries 2 and 4).

Furthermore, ferrocene **3** could be recovered in almost quantitative yield by flash chromatography, and its reuse in the catalyzed aryl transfer revealed that it had retained its catalytic activity and enantioselectivity.

In summary, a protocol for the gram-scale catalytic synthesis of highly enantiomerically enriched diarylmethanols using boronic acids as versatile aryl source has been reported. The reaction is easy to perform, and the products are obtained in high yields and excellent enantioselectivities. Ferrocene **3** serves as catalyst precursor, which can be recovered almost quantitatively and reused in subsequent catalyses. By choosing the right combination of arylboronic acid and aldehyde both enantiomeric forms of the product are accessible.

Air sensitive manipulations were carried out under argon using standard Schlenk techniques. Toluene was distilled from sodium/benzophenone ketyl radical. Et_2O and pentane for column chromatograpy were distilled before use. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer (300 MHz and 75 MHz respectively) and on a Varian Inova 400 spectrometer (400 MHZ and 100 MHz respectively). HPLC measurements were performed on a Dionex HPLC system (previously Gynkotek) with autosampler Gina 50, UV-detector UVD 170S, degasser DG 503 and gradient pump M480G. Alternatively the HPLC system HP 1100 from Agilent Technologies was used. As stationary phase chiral HPLC columns from Chiral Technologies were used.

Diarylmethanols 2a–d; General Procedure

A well-dried Schlenk flask was charged with arylboronic acid **4** (24 mmol) and dimethylpolyethyleneglycol (M_w = 2000 g·mol^{-1}, 2 g, 1 mmol) and was sealed with a septum. Freshly distilled toluene (100 mL) was added followed by $ZnEt_2$ (7.4 mL, 72 mmol). The mixture was heated to 60 °C, stirred for 12 h at this temperature and afterwards cooled to r.t. In another Schlenk flask, ferrocene **3** (500 mg, 1 mmol) was dissolved in toluene (35 mL) and transferred via syringe to the first solution. The mixture was stirred for 30 min at r.t. and then also cooled to 10 °C. Stirring was continued for additional 10 min at this temperature. A third Schlenk flask was charged with aldehyde **1** (10 mmol) and dissolved in toluene (35 mL). After cooling to 10 °C, this solution was transferred via syringe into the other flask. The reaction was stirred for 12 h at 10 °C. Then the reaction was carefully quenched with H_2O (10 mL) and stirred for additional 10 min. Subsequently it was filtered through a pad of Celite and washed vigorously with CH_2Cl_2 (400 mL). The organic layer was washed with AcOH (20% in H_2O, 250 mL) and H_2O, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Column chromatography (silica gel, eluents: pentane–Et_2O, 9:1 to 8:2) of the crude product afforded pure **2**.

(*R*)-(4-Chlorophenyl)phenylmethanol (2a)[12]
Obtained from 4-chlorobenzaldehyde (**1a**; 1.405 mg, 10 mmol) and phenylboronic acid (**4a**; 2.926 g, 24 mmol) according to the general procedure as a pale yellow solid; yield: 2.030 g (93%); 96% ee. HPLC separation conditions: Chiralcel OB-H, 30 °C, 230 nm, 90:10 heptane–*i*-PrOH, 0.5 mL/min; t_R = 25.7 min (*R*), 33.6 min (*S*).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.23 (br s, 1 H, OH), 5.78 (s, 1 H, CH), 7.23–7.45 (m, 9 H, H_{arom}).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 75.7 (CH), 126.6 (2 CH), 127.9 (3 CH), 128.7 (2 CH), 128.7 (2 CH), 133.3 (C), 142.3 (C), 143.5 (C).

(*R*)-(4-Methylphenyl)phenylmethanol (2b)[13]
Obtained from 4-methylbenzaldehyde (**1b**; 1.18 mL, 1.202 g, 10 mmol) and phenylboronic acid (**4a**; 2.926 g, 24 mmol) according to the general procedure as a pale yellow solid; yield: 1.870 g (94%); 96% ee.

(*S*)-(4-Methylphenyl)phenylmethanol (2b)[13]
Obtained from benzaldehyde (**1d**; 1.02 mL, 1.061 g, 10 mmol) and 4-methylphenylboronic acid (**4b**; 3.263 g, 24 mmol) according to the general procedure as a pale yellow solid: 1.890 g (95%); 94% ee. HPLC separation conditions: Chiralcel OD, 30 °C, 230 nm, 98:2 heptane–*i*-PrOH, 0.9 mL/min; t_R = 28.1 min (*S*), 31.3 min (*R*).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.04 (s, 1 H, OH), 2.31 (s, 3 H CH_3), 5.76 (s, 1 H, CH), 7.08–7.37 (m, 9 H, H_{arom}).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.2 (CH_3), 76.2 (CH), 126.6 (2 CH), 126.7 (2 CH), 127.5 (CH), 128.5 (2 CH), 129.3 (2 CH), 137.3 (C), 141.0 (C), 144.0 (CH).

(*R*)-(2-Bromophenyl)phenylmethanol (2c)[14]
Obtained from 2-bromobenzaldehyde (**1c**; 1.17 mL, 1.850 g, 10 mmol) and phenylboronic acid (**4**; 2.926 g, 24 mmol) according to the general procedure as a pale yellow oil: 2.620 g (99%); 93% ee. HPLC separation conditions: Chiralcel OD, 25 °C, 230 nm, 90:10 heptane–*i*-PrOH, 0.8 mL/min; t_R = 11.6 min (*R*), 14.9 min (*S*).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.47 (s, 1 H, OH), 6.17 (s, 1 H, CH), 7.20–7.42 (m, 7 H, H_{arom}), 7.50–7.59 (m, 2 H, H_{arom}).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 74.9 (CH), 122.9 (C), 127.1 (2 CH), 127.8 (CH), 127.9 (CH), 128.6 (2 CH), 129.2 (CH), 129.7 (CH), 132.9 (CH), 142.2 (C), 142.6 (C).

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