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Diarylmethanols by Catalyzed Asymmetric Aryl Transfer Reactions onto Aldehydes Using Boronic Acids as Aryl Source

Frank Schmidt,[a] Jens Rudolph,[a] and Carsten Bolm[a,*]

[a] Institut für Organische Chemie der RWTH Aachen, Landoltweg 1, 52074 Aachen, Germany
Fax: (+49)-241-809-2391; e-mail: Carsten.Bolm@oc.rwth-aachen.de

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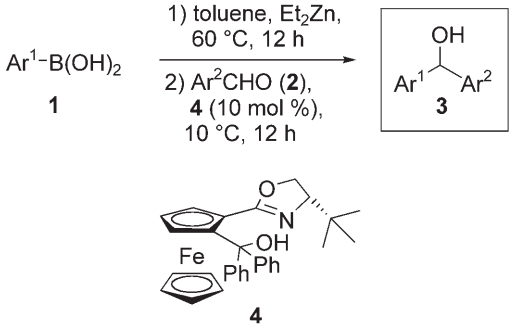
This paper is dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

Abstract: Using a planar-chiral ferrocene as catalyst and combinations of functionalized aldehydes and substituted arylboronic acids as starting materials, asymmetric aryl transfer reactions give access to structurally diverse, optically active diarylmethanols in high yields and enantioselectivities.

Keywords: arylboronic acids; C–C bond formation; diarylmethanols; enantioselective catalysis; organozinc reagents



Scheme 1. Aryl transfer to aromatic aldehydes.

Diarylmethanols **3** with defined stereochemistry at the hydroxy-bearing carbon are important intermediates for the synthesis of numerous compounds with high biological and/or physiological activity.[1] For example, neobenodine and orphenandrine show anticholinergic as well as anthihistaminic properties.[2] Recently, diarylmethanols have been used in the synthesis of pharmaceuticals containing asymmetrical 1,1′-diarylalkyl subunits.[3] The most common routes towards diarylmethanols are either enantioselective reductions of prochiral benzophenone derivatives[4] or asymmetric carbon-carbon bond formations starting from aromatic aldehydes and appropriate organometallic compounds.[5,6] Despite the fact that the latter strategy has attracted considerable attention due to its enormous synthetic potential, the so far evaluated substrate range appears rather limited. Thus mostly, aryl transfer reactions onto (unsubstituted) benzaldehyde (Scheme 1, $Ar^2 = Ph$) or *phenyl*-to-aldehyde transfers have been studied leading to aryl*phenyl*methanols. The synthesis of diarylmethanols with two differently substituted aryl groups *via* zinc reagents has, to the best of our knowledge, never been in the focus of an intensive study.[7]

In 2002, we described a general approach for aryl transfer reactions to aromatic aldehydes involving arylzinc species formed *in situ* from arylboronic acids **1** and diethylzinc. Ferrrocene **4** served as catalyst (Scheme 1).[8]

Noteworthy is the fact that with a single catalyst both enantiomers of **3** became accessible by choosing the appropriate combination of arylboronic acid **1** and aldehyde **2**. Also in this case, only aryl*phenyl*methanols were prepared.

Wondering about the flexibility of this method and with the goal to investigate the applicability of the approach in the preparation of more functionalized molecules, we have now studied the catalytic synthesis of 1,1′-disubstituted diarylmethanols (e.g., products with aryls other than phenyl). This involved structural variations of both the arylboronic acids **1** as well as the aldehydes **2**. The results are summarized in Table 1.

To our delight we found that most diarylmethanols **3** were formed in good yields and high enantioselectivities (Figure 1). For example, 4-chlorophenyl-2′-methylphenylmethanol (**3a**) was obtained with 91% *ee* in 71% yield (Table 1, entry 1). In the catalysis starting from 2-bromobenzaldehyde (**2c**) and 3-methoxyphenylboronic acid (**1c**) diarylmethanol *ent*-**3b** was formed with 88% *ee* in 66% yield (entry 3). Using the "reverse combination" of substrates, the enantiomeric product **3b** was obtained by aryl transfer from 2-bromophenylboronic acid (**1b**) onto 3-methoxybenzaldehyde (**2b**) with 86% *ee* in 38% yield (entry 2). Use of the same boronic acid (**1b**) in the ad-

Table 1. Catalyzed aryl transfer from boronic acids **1** to aldehydes **2**.[a]

Entry	$Ar^1B(OH)_2$		Ar^2CHO		Product	Yield [%][b]	*ee* [%][c,d]
	Ar^1	No.	Ar^2	No			
1	2-methylphenyl	**1a**	4-chlorophenyl	**2a**	**3a**	71	91 (*S*)
2	2-bromophenyl	**1b**	3-methoxyphenyl	**2b**	**3b**	38[e]	86 (*S*)
3	3-methoxyphenyl	**1c**	2-bromophenyl	**2c**	*ent*-**3b**	66	88 (*R*)
4	2-bromophenyl	**1b**	4-methylphenyl	**2d**	**3c**	39[e]	86 (*S*)
5	4-methylphenyl	**1d**	2-bromophenyl	**2c**	*ent*-**3c**	78	88 (*R*)
6	1-naphthyl	**1e**	4-methylphenyl	**2d**	**3d**	67	86 (*S*)
7	4-methylphenyl	**1d**	1-naphthyl	**2e**	*ent*-**3d**	79	91 (*R*)
8	4-methoxyphenyl	**1f**	4-methylphenyl	**2d**	**3e**	79	91 (*S*)
9	4-methylphenyl	**1d**	4-methoxyphenyl	**2e**	*ent*-**3e**	83	91 (*R*)
10	2-thiophenyl	**1g**	4-methylphenyl	**2d**	**3f**	66	89 (*S*)
11	3-thiophenyl	**1h**	4-methylphenyl	**2d**	**3g**	71	95 (*S*)
12	2-methylphenyl	**1a**	2-thiophenyl	**2e**	**3h**	89	94 (*R*)
13	2-methylphenyl	**1a**	2-furyl	**2f**	**3i**	70	92 (*R*)

[a] All reactions were performed on a 0.25 mmol scale using 10 mol% of ferrocene **4**, 2.4 equivs. of diethylzinc, 10 mol% of DiMPEG in toluene.
[b] After column chromatography.
[c] Enantiomer ratios were determined by HPLC using a chiral stationary phase.
[d] The absolute configurations of the products were assigned based on the assumption of an analogous mechanism for all aryl transfers and the HPLC elution order.
[e] About 40% of the corresponding ethyl addition products were formed.

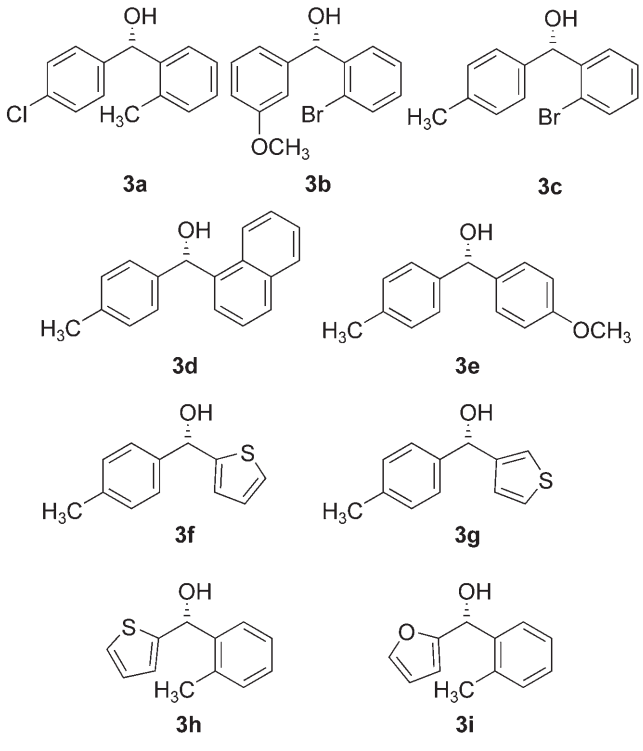


Figure 1. Products prepared by aryl transfer to aromatic aldehydes.

dition onto 4-methylbenzaldehyde (**2d**) led to the corresponding product **3c** with good *ee* (86%), but also here the yield was relatively low (39%) (entry 4). In both reactions about 40% of the undesired ethyl addition products of the corresponding aldehydes were obtained. Starting from 4-methylphenylboronic acid (**1d**) and 2-bromobenzaldehyde (**2c**) diarylmethanol *ent*-**3c** was formed in good yield (78%) and *ee* (88%) (entry 5). Both 1-naphthylboronic acid (**1e**) and 4-methoxyphenylboronic acid (**1f**) reacted well with 4-methylbenzaldehyde (**2d**) to give **3d** and **3e** with 86 and 91% *ee* in yields of 67 and 79%, respectively (entries 6 and 8). The corresponding enantiomers *ent*-**3d** and *ent*-**3e** were both obtained with 91% *ee* in yields of 79% and 83%, respectively (entries 7 and 9). Noteworthy, heteroaromatic boronic acids **1g** and **1h** as well as heteroaromatic aldehydes **2e** and **2f** also reacted well. Thus, catalyzed aryl transfer reactions from 2-thiophenyl- and 3-thiophenylboronic acids (**1g** and **1h**) onto 4-methylbenzaldehyde (**2d**) gave the corresponding diarylmethanols **3f** and **3g** in 71 and 81% yield and 94 and 95% *ee*, respectively (entries 10 and 11). 2-Thiophencarbaldehyde (**2e**) and 2-methylphenylboronic acid (**1a**) afforded secondary alcohol **3h** in 89% yield and 94% *ee*. An excellent result was also achieved using 2-methylphenylbenzaldehyde (**1a**) and 2-furylcarbaldehyde (**2f**) as the aryl source affording the corresponding diarylmethanol (**3i**) with 92% *ee* in 70% yield. In contrast to other diarylmethanols the latter product appeared to be unstable and had to be stored under an argon atmosphere at below −20 °C. Decomposition was also observed under acidic conditions.

Attempted catalyses between 3-pyridinecarbaldehyde and 1-naphthylboronic acid as well as 2-furylcarbaldehyde and 2-methoxybenzaldehyde did not lead to the desired products. In both cases complexation of

the zinc reagent to the basic sites of the aldehydes was assumed, leading to a deactivation of the resulting species.

In conclusion, we demonstrated the applicability of the aryl transfer protocol using aryl boronic acids and aromatic aldehydes in the catalyzed enantioselective synthesis of 1,1′-disubstituted diarylmethanols. Generally, high enantioselectivities and good yields were achieved. Heteroaromatic aldehydes and heteroatom-containing arylboronic acids also reacted well. By the appropriate combination of arylboronic acid and arylaldehyde, both enantiomers of the desired products became available with the same catalyst, underlining the broad synthetic potential of the developed procedure.

Experimental Section

All air-sensitive manipulations were carried out under an inert atmosphere of Ar using sealed vials. Toluene was distilled under nitrogen from sodium/benzophenone ketyl radical. Diethyl ether and pentane for column chromatography were distilled before use. ^{1}H 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). IR spectra were measured on a Perkin–Elmer PE 1760 FT instrument as KBr pellets or neat (in case of liquid compounds); absorptions are given in wave numbers (cm^{-1}). Mass spectra were recorded on a Varian MAT 212 or on a Finnigan MAT 95 spectrometer with EI ionization. Optical rotation measurements were conducted at room temperature with a Perkin–Elmer PE 241 polarimeter at a wavelength of 589 nm. HPLC measurements were performed on a Dionex HPLC system (previously Gynkothek) with autosampler Gina 50, UV-detector UVD 170S, degasser DG 503 and gradient pump M480G. Alternatively, the Agilent HPLC system HP 1100 was used. For the enantiomer ratio determinations HPLC columns with chiral stationary phases from Chiral Technologies were used.

General Procedure

A 10-mL vial was charged with arylboronic acid **1** (0.6 mmol) and DiMPEG ($M_w = 2000\ g\,mol^{-1}$, 10 mol%, 50 mg, 0.025 mmol). After flushing with argon the vial was sealed with a septum. Freshly distilled toluene (2.5 mL) was then added followed by $ZnEt_2$ (184 μL, 1.8 mmol). The mixture was heated to 60 °C, stirred for 12 h at this temperature and subsequently cooled to room temperature. Another vial was charged with ferrocene **4** (10 mol%, 12.5 mg, 0.025 mmol), sealed with a septum and flushed with argon. Then, **4** was dissolved in toluene (1 mL), and this solution was then transferred to the first solution using a syringe. The mixture was stirred for 30 min at room temperature and then cooled to 10 °C. Stirring was continued for additional 10 min at this temperature. A third vial was charged with aldehyde **2** (0.25 mmol) and toluene (1 mL). After cooling of the solution to 10 °C, it was transferred into the other solution using a syringe, and the mixture was stirred for 12 h at this temperature. Then the reaction was quenched with water (0.7 mL). Subsequently it was filtered through a pad of celite and eluted with dichloromethane. The organic layer was washed with a saturated diluted HOAc[9a] and with brine, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give diarylmethanols **3**.

(*S*)-(4-Chlorophenyl)-(2′-methylphenyl)methanol (3a)[10]

The title compound was obtained from 2-methylphenylboronic acid (**1a**) (81.6 mg, 0.6 mmol) and 4-chlorobenzaldehyde (**2a**) (35.1 mg, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a pale yellow oil; yield: 0.18 mmol (71%, 91% *ee*); mp 63.2–65.9 °C; $[\alpha]_D^{20}$: −12 (*c* 1.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.12$ (sbr, 1H, OH), 2.23 (s, 3H, CH_3), 5.95 (s, 1H, CH), 7.14–7.32 (m, 7H, CH_{ar}), 7.38–7.42 (m, 1H, CH_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.5$ (CH_3), 75.4 (CH), 126.2 (CH), 126.3 (CH), 127.8 (CH), 128.4 (2CH), 128.6 (2CH), 130.7 (CH), 133.3 (C), 135.3 (C), 141.0 (C), 141.3 (C); IR (KBr): $\nu = 3265$, 2924, 1591, 1486, 1089, 1012, 863, 825, 751 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 232 (36, M^+), 179 (49), 119 (100), 91 (31), 77 (24); HR-MS: *m/z* = found 232.0654, calcd. for $C_{14}H_{13}ClO$: 232.0654. HPLC separation conditions: Chiralcel AD, 210 nm, 99:1 heptane/*i*-PrOH), 0.6 mL min^{-1}, t_R = 32.9 min (*R*), 35.0 min (*S*).

(*S*)-(2-Bromophenyl)-(3′-methoxyphenyl)methanol (3b)

The title compound was obtained from 2-bromophenylboronic acid (**1b**) (120.5 mg, 0.6 mmol) and 3-methoxybenzaldehyde (**2b**) (30.4 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a pale yellow oil; yield: 0.10 mmol (38%, 86% *ee*); Optical rotation: $[\alpha]_D^{20}$: +45 (*c* 2.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.51$ (sbr, 1H, OH), 3.77 (s, 3H, OCH_3), 6.15 (s, 1H, CH), 6.77–6.83 (m, 1H, CH_{ar}), 6.93–6.99 (m, 2H, CH_{ar}), 7.09–7.17 (m, 1H, CH_{ar}), 7.20–7.35 (m, 2H, CH_{ar}), 7.48–7.57 (m, 2H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 51.2$ (CH_3), 74.6 (CH), 112.7 (CH), 113.1 (CH), 119.3 (CH), 122.8 (C), 127.8 (CH), 128.6 (CH), 129.2 (CH), 129.5 (CH), 132.9 (CH), 142.5 (C), 143.9 (C), 159.7 (C); IR ($CHCl_3$): $\nu = 3382$, 3936, 1598, 1463, 1260, 1150, 1040, 725 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 292 (94, M^+), 195 (40), 184 (31), 182 (25), 109 (100), 77 (30); HR-MS: *m/z* = 292.0098, calcd. for $C_{14}H_{13}BrO_2$: 292.0099. HPLC separation conditions: Chiralcel OD-H, 220 nm, 90:10 heptane/*i*-PrOH), 0.5 mL min^{-1}, t_R = 25.1 min (*R*), 39.2 min (*S*).

(*R*)-(2-Bromophenyl)-(3′-methoxyphenyl)methanol (*ent*-3b)

The title compound was obtained from 3-methoxyphenylboronic acid (**1c**) (91.2 mg, 0.6 mmol) and 2-bromobenzaldehyde (**2c**) (29.0 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a pale yellow oil; yield: 0.16 mmol (66%, 88% *ee*).

(*S*)-(2-Bromophenyl)-(4′-methylphenyl)methanol (3c)[11]

The title compound was obtained from 2-bromophenylboronic acid (**1b**) (120.5 mg, 0.6 mmol) and 4-methylbenzaldehyde (**2d**) (29.5 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a pale yellow oil; yield: 0.10 mmol (39%, 86% *ee*); mp 69.0–70.6 °C; $[\alpha]_D^{20}$: −30 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 2.36 (sbr, 1H, OH), 6.14 (s, 1H, CH), 7.09–7.18 (m, 3H, CH_{ar}), 7.23–7.38 (m, 3H, CH_{ar}), 7.49–7.55 (m, 1H, CH_{ar}), 7.57–7.65 (m, 1H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 74.7 (CH), 122.7 (C), 127.1 (2CH), 127.7 (CH), 128.4 (CH), 129.0 (CH), 129.2 (2CH), 132.8 (CH), 137.5 (C), 139.3 (C), 142.0 (C); IR (KBr): ν = 3307, 1460, 1436, 1013, 810, 748 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 276 (100, M^+), 260 (79), 184 (54), 121 (32), 91 (41), 77 (34); HR-MS: *m/z* = 276.0147, calcd. for $C_{14}H_{13}BrO$: 276.0150. HPLC separation conditions: Chiralcel OD-H, 254 nm, 90:10 heptane/*i*-PrOH, 0.5 mL min^{-1}, t_R = 17.6 min (*R*), 23.5 min (*S*).

(*R*)-(2-Bromophenyl)-(4′-methylphenyl)methanol (*ent*-3c)

The title compound was obtained from 4-methylphenylboronic acid (**1d**) (82.0 mg, 0.6 mmol) and 2-bromobenzaldehyde (**2c**) (28.0 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a pale yellow oil; yield: 0.19 mmol (78%, 88% *ee*).

(*S*)-(1-Naphthyl)-(4′-methylphenyl)methanol (3d)[12]

The title compound was obtained from 1-naphthylboronic acid (**1e**) (103 mg, 0.6 mmol) and 4-methylbenzaldehyde (**2d**) (29.5 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a colorless oil; yield: 0.16 mmol (67%, 86% *ee*); $[\alpha]_D^{20}$: −24.1 (*c* 1.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 1H, CH_3), 3.32 (sbr, 1H, OH), 6.45 (s, 1H, CH), 6.07–6.87 (m, 2H, CH_{ar}), 7.17–7.27 (m, 2H, CH_{ar}), 7.36–7.48 (m, 3H, CH_{ar}), 7.60–7.65 (m, 1H, CH_{ar}), 7.76–7.86 (m, 2H, H_{ar}) 7.94–8.01 (m, 1H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (CH_3), 73.5 (CH), 124.0 (CH), 124.4 (CH), 125.3 (CH), 125.5 (CH), 126.1 (CH), 127.0 (2CH), 128.3 (CH), 128.7 (CH), 129.2 (2CH), 130.7 (C), 133.9 (C), 137.4 (C), 138.9 (C), 140.2 (C); IR (KBr): ν = 3136, 1508, 1445, 1312, 1061, 991, 826, 784, 571, 497 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 248 (75, M^+), 155 (27), 128 (43), 119 (100), 91 (15); anal. calcd. for $C_{18}H_{16}O$ (248.31): C 87.06, H 6.49; found C 86.84, H 6.60. HPLC separation conditions: Chiralcel AD, 210 nm, 95:5 heptane/*i*-PrOH, 0.6 mL min^{-1}, t_R = 36.7 min (*S*), 41.0 min (*R*).

(*R*)-(1-Naphthyl)-(4′-methylphenyl)methanol (*ent*-3d)

The title compound was obtained from 4-methylphenylboronic acid (**1d**) (82 mg, 0.6 mmol) and 1-naphthaldehyde (**2e**) (34.0 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a colorless oil; yield: 0.20 mmol (79%, 91% *ee*).

(*S*)-(4-Methoxyphenyl)-(4′-methylphenyl)methanol (3e)[13]

The title compound was obtained from 4-methoxyphenylboronic acid (**1f**) (91.2 mg, 0.6 mmol) and 4-methylbenzaldehyde (**2d**) (29.5 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a white solid; yield: 0.20 mmol (79%, 91% *ee*); mp 76.8–78.2 °C; $[\alpha]_D^{20}$: −5.2 (*c* 2.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (sbr, 1H, OH), 2.32 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 5.75 (s, 1H, CH), 6.79–6.88 (m, 2H, CH_{ar}), 7.08–7.16 (m, 2H, CH_{ar}), 7.18–7.29 (m, 4H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (CH_3), 55.3 (CH_3), 75.7 (CH), 113.8 (2CH), 126.4 (2CH), 127.8 (2CH), 129.1 (2CH), 136.4 (C), 137.1 (C), 141.2 (C), 159.0 (C); IR (KBr): ν = 3342, 1610, 1511, 1459, 1251, 1171, 1032, 811, 771 cm^{-1}; MS (EI, 70 eV): *m/z* (%) 228 (100, M^+),135 (96), 119 (66), 109 (65); HR-MS: *m/z* = 228.1149, calcd. for $C_{15}H_{16}O_2$: 228.1150. HPLC separation conditions: Chiralcel OD-H, 210 nm, 95:5 heptane/*i*-PrOH, 0.5 mL min^{-1}, t_R = 38.7 min (*R*), 45.0 min (*S*).

(*R*)-(4-Methoxyphenyl)-(4′-methylyphenyl)methanol (*ent*-3e)

The title compound was obtained from 4-methylphenylboronic acid (**1d**) (82.0 mg, 0.6 mmol) and 4-methoxybenzaldehyde (**2e**) (30.4 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a white solid; yield: 0.21 mmol (83%, 91% *ee*).

(*S*)-(4-Methylphenyl)-(2′-thienyl)methanol (3f)[14]

The title compound was obtained from 2-thiopheneboronic acid (**1g**) (76.8 mg, 0.6 mmol) and 4-methylbenzaldehyde (**2d**) (29.5 μL, 0.25 mmol) (28 mg, 23.4 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a white solid; yield: 0.16 mmol (66%, 89% *ee*); mp 64.2–64.9 °C; $[\alpha]_D^{20}$: +9.5 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ = 2.25 (s, 3H, CH_3), 2.85 (s, 1H, OH), 5.05 (d, *J* = 4.4 Hz, 1H, OH), 6.18 (d, *J* = 4.4 Hz, 1H, CH), 6.78–6.82 (m, 1H, CH_{ar}), 6.89 (dd, *J* = 4.3 Hz/5.0 Hz, 1H, CH_{ar}), 7.09–7.24 (m, 3H, CH_{ar}), 7.23 (dd, *J* = 1.1 Hz/5.0 Hz, 1H, CH_{ar}) 7.61 (dd, *J* = 1.1 Hz/7.4 Hz, 1H, CH_{ar}); ^{13}C NMR (100 MHz, acetone-d_6): δ = 18.5 (CH_3), 68.5 (CH), 124.4 (CH), 124.8 (CH), 125.8 (CH), 126.0 (CH), 126.2 (CH), 127.2 (CH), 130.1 (CH), 134.8 (C), 142.6 (C), 149.0 (C); IR (KBr): ν = 3323, 1270, 1155, 823, 702, 674, 469 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 204 (41, M^+), 119 (100), 110 (23), 91 (17); HR-MS: *m/z* = 204.0607, calcd. for $C_{12}H_{12}OS$: 204.0608. HPLC separation conditions: Chiralcel AD, 210 nm, 99:1 heptane/*i*-PrOH, 0.7 mL min^{-1}, t_R = 61.1 min (*S*), 71.0 min (*R*).

(*S*)-(4-Methylphenyl)-(3′-thienyl)methanol (3g)

The title compound was obtained from 3-thiopheneboronic acid (**1h**) (76.8 mg, 0.6 mmol) and 4-methylbenzaldehyde (**2d**) (29.5 μL, 0.25 mmol) (28 mg, 23.4 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a white solid; yield: 0.18 mmol (71%, 95% *ee*); mp 65.8–

67.2 °C; $[\alpha]_D^{20}$: +16.3 (*c* 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ = 2.27 (s, 3H, CH_3), 4.76 (d, *J* = 4.4 Hz, 1H, OH), 5.81 (d, *J* = 4.4 Hz, 1H, CH), 6.98 (dd, *J* = 5.0/0.8 Hz, 1H, CH_{ar}), 7.11 (d, *J* = 8.0 Hz, 2H, CH_{ar}), 7.22–7.25 (m, 1H, CH_{ar}), 7.28 (d, *J* = 8.0 Hz, 2H, CH_{ar}), 7.30–7.33 (m, 1H, CH_{ar}); ^{13}C NMR (100 MHz, acetone-d_6): δ = 20.3 (CH_3), 71.9 (CH), 120.4 (CH), 125.4 (CH), 126.3 (2CH), 126.6 (CH), 128.6 (2CH), 136.3 (C), 142.1 (C), 147.3 (C); IR (KBr): ν = 3238, 1614, 1416, 1279, 1028, 820, 795, 766, 738, 689 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 204 (100, M^+), 119 (86), 189 (18), 111 (40), 91 (24); anal. calcd. for $C_{12}H_{12}OS$ (204.29): C 70.55, H 5.92; found: C 70.42, H 5.75. HPLC separation conditions: Chiralcel AS, 210 nm, 98:2 heptane/*i*-PrOH, 0.5 mL min^{-1}, t_R = 33.5 min (*S*), 39.6 min (*R*).

(*R*)-(2-Methylphenyl)-(2′-thienyl)methanol (3h)[15]

The title compound was obtained from 2-methylphenylboronic acid (**1a**) (81.5 mg, 0.6 mmol) and 2-thiophencarbaldehyde (**2e**) (28 mg, 23.4 μL, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/diethyl ether = 8:2) as a white solid; yield: 0.22 mmol (89%, 94% *ee*); mp 75.3–76.0 °C; $[\alpha]_D^{20}$: −3 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ = 2.25 (s, 3H, CH_3), 5.05 (d, *J* = 4.4 Hz, 1H, OH), 6.18 (d, *J* = 4.4 Hz, 1H, CH), 6.78–6.82 (m, 1H, CH_{ar}), 6.89 (dd, *J* = 4.3 Hz/5.0 Hz 1H, CH_{ar}), 7.09–7.24 (m, 3H, CH_{ar}), 7.23 (dd, *J* = 1.1 Hz/5.0 Hz, 1H, CH_{ar}) 7.61 (dd, *J* = 1.1 Hz/7.4 Hz, 1H, CH_{ar}); ^{13}C NMR (100 MHz, acetone-d_6): δ = 18.5 (CH_3), 68.5 (CH), 124.4 (CH), 124.8 (CH), 125.8 (CH), 126.0 (CH), 126.2 (CH), 127.2 (CH), 130.1 (CH), 134.8 (C), 142.6 (C), 149.0 (C); IR (KBr): ν = 3454, 3365, 1635, 1459, 1289, 1222, 1021, 785, 757, 700 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 204 (31, M^+), 171 (10), 119 (100), 91 8 (19); anal. calcd. for $C_{12}H_{12}OS$ (204.29): C 70.55, H 5.92; found: C 70.64, H 6.26. HPLC separation conditions: Chiralcel AD, 210 nm, 99:1 heptane/*i*-PrOH, 0.7 mL min^{-1}, t_R = 31.5 min (*S*), 40.0 min (*R*).

(*R*)-(2-Furanyl)-(2′-methylphenyl)methanol (3i)[9b]

The title compound was obtained from 2-methylphenylboronic acid (**1a**) (81.5 mg, 0.6 mmol) and furan-2-carbaldehyde (**2f**) (24 mg, 0.25 mmol) according to the general procedure after column chromatography (silica gel, eluents: pentane/ethylacetate = 9:1) as a pale yellow solid; yield: 0.18 mmol (70%, 92% *ee*); mp 44.6–45.2 °C; $[\alpha]_D^{20}$: −8.4 (*c* 0.82, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 1H, CH_3), 2.42 (sbr, 1H, OH), 6.27–6.32 (m, 1H, CH), 7.11–7.29 (m, 3H, CH_{ar}), 7.36–7.40 (m, 1H, CH_{ar}), 7.20–7.35 (m, 2H, CH_{ar}), 7.52–7.59 (m, 1H, H_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (CH_3), 67.1 (CH), 107.6 (CH), 110.3 (CH), 126.1 (CH), 126.2 (CH), 127.9 (CH), 130.4 (CH), 135.3 (C), 138.9 (C), 142.5 (CH), 155.6 (C); IR (KBr): ν = 3178, 1600, 1463, 1145, 1045, 1006, 729 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 188 (100, M^+), 171 (18), 119 (39), 97 (24), 91 (33); anal. calcd. for $C_{12}H_{12}O_2$ (188.22): C 76.57, H 6.43; found C 76.68, H 6.74. HPLC separation conditions: Chiralcel AD, 210 nm, 97:3 heptane/*i*-PrOH, 0.6 mL min^{-1}, t_R = 31.0 min (*S*), 33.2 min (*R*).

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References

[1] A. F. Harms, W. Hespe, W. T. Nauta, R. F. Rekker, *Drug Design* **1976**, *6*, 1.
[2] R. F. Rekker, H. Timmerman, A. F. Harms, W. T. Nauta, *Arzneim. Forsch.* **1971**, *21*, 688.
[3] Y. Bolshan, C. Y. Chen, J. R. Chilenski, F. Gosselin, D. J. Mathre, P. D. O'Shea, A. R. R. D. Tillyer, *Org. Lett.* **2004**, *6*, 111, and references cited therein.
[4] a) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40; *Angew. Chem. Int. Ed.* **2001**, *40*, 40; b) T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *2*, 659; c) C.-y. Chen, R. A. Reamer, J. R. Chilenski, C. J. McWilliams, *Org. Lett.* **2003**, *5*, 5039; d) R. Schmid, E. A. Broger, M. Cereghetti, Y. Crameri, J. Foricher, M. Lalonde, R. K. Muller, M. Scalone, G. Schoettel, U. Zutter, *Pure Appl. Chem.* **1996**, *68*, 131; e) A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, *J. Chem. Soc., Chem. Commun.* **1981**, 315; f) J. Wright, L. Frambes, P. Reeves, *J. Organomet. Chem.* **1994**, *476*, 215; g) J. Peyronel, J. Fiaud, H. Kagan, *J. Chem. Res. Synop.* **1980**, 320; h) H. Brunner, A. Kuerzinger, *J. Organomet. Chem.* **1988**, *346*, 413.
[5] a) W.-S. Huang, L. Pu, *J. Org. Chem.* **1999**, *64*, 4222; b) W.-S. Huang, L. Pu, *Tetrahedron Lett.* **2000**, *41*, 145; c) C. Bolm, K. Muñiz, *Chem. Commun.* **1999**, 1295; d) C. Bolm, N. Hermanns, J. P. Hildebrand, K. Muñiz, *Angew. Chem.* **2000**, *112*, 3607; *Angew. Chem. Int. Ed.* **2000**, *39*, 3465; e) G. Zhao, X.-G. Li, X.-R. Wang, *Tetrahedron: Asymmetry* **2001**, *12*, 399; f) I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2320; g) D.-H. Ko, K. H. Kim, D.-C. Ha, *Org. Lett.* **2002**, *4*, 3759; h) M. G. Pizzuti, S. Superchi, *Tetrahedron: Asymmetry* **2005**, *16*, 2263; i) M. Fontes, X. Verdaguer, L. Solà, M. A. Pericàs, A. Riera, *J. Org. Chem.* **2004**, *69*, 2532; j) M. Hatano, T. Miyamoto, K. Ishihara, *Adv. Synth. Catal.* **2005**, *347*, 1561; k) 25 Y.-C. Qin, L. Pu, *Angew. Chem.* **2005**, 118, 279; *Angew. Chem. Int. Ed*. **2006**, *45*, 273; l) K. Ito, Y. Tomita, T. Katsuki, *Tetrahedron Lett.* **2005**, *46*, 6083; m) J. Rudolph, C. Bolm, P.-O. Norrby, *J. Am. Chem. Soc.* **2005**, *127*, 1548; n) A. L. Braga, D. S. Lüdtke, F. Vargas, M. W. Paixão, *Chem. Commun.* **2005**, 2512; o) A. L. Braga, S. S. Lüdtke, P. H. Schneider, F. Vargas, A. Schneider, L. A. Wessjohann, M. W. Paixão, *Tetrahedron Lett.* **2005**, *46*, 7827; p) J.-X. Ji, J. Wu, T. T.-L. Au-Yeung, C.-W. Yip, R. K. Haynes, A. S. C. Chan, *J. Org. Chem.* **2005**, *70*, 1093; q) S. Özçubukçu, F. Schmidt, C. Bolm, *Org. Lett.* **2005**, *7*, 1407; r) P.-Y. Wu, H.-L. Wu, B.-J. Uang, *J. Org. Chem.* **2006**, *71*, 833; s) W.-S. Huang, Q.-S. Hu, L. Pu, *J. Org. Chem.* **1999**, *64*, 7940.

[6] For a review see: F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454.
[7] a) After finishing our experimental work a very interesting paper describing the synthesis of unsymmetrically disubstituted diarylmethanols involving lithium-to-zinc transmetalations was published. J. G. Kim, P. J. Walsh, *Angew. Chem.* **2006**, *118*, 4281; *Angew. Chem. Int. Ed.* **2006**, *45*, 4175; b) for a rhodium-catalyzed synthesis of unsymmetrical diarylmethanols, see: H.-F. Duan, J.-H. Xie, W. J. Shi, Q. Zhang, Q.-L. Zhou, *Org. Lett.* **2006**, *8*, 1479.
[8] a) C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850; b) J. Rudolph, F. Schmidt, C. Bolm, *Synthesis* **2005**, 840.
[9] a) Diarylmethanols **3f–i** were only washed with brine; b) fast decomposition of compound **3i** under acetic conditions was noticed.
[10] C. Krug, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 1674.
[11] a) W. P. Almeida, P. R. R. Costa, *Synth. Commun.* **1996**, *26*, 4507; b) T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokuzawa, R. Noyori, *Org. Lett.* **2000**, *2*, 659.
[12] M. Artico, G. Stefancich, R. Silvestri, S. Massa, G. Apuzzo, M. Artico, G. Simonetti, *Eur. J. Med. Chem.* **1992**, *27*, 693.
[13] T. van Pham, R. A. McClelland, *Can. J. Chem.* **2001**, *79*, 1887.
[14] W.-S. Cho, H.-J. Kim, B. J. Littler, M. A. Miller, C.-H. Lee, J. S. Lindsey, *J. Org. Chem.* **1999**, *64*, 7890.
[15] G. de Martino, G. La Regina, A. Di Pasquali, R. Ragno, A. Bergamini, C. Ciaprini, A. Sinistro, G. Maga, E. Crespan, M. Artico, R. Silvestri, *J. Med. Chem.* **2005**, *48*, 4378.

