Highly Chemoselective and Enantiospecific Suzuki–Miyaura Cross-Couplings of Benzylic Organoboronic Esters

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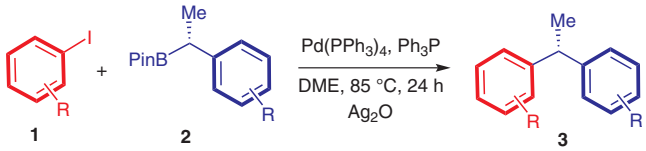
This paper is dedicated to Professor Scott E. Denmark, with thanks for his mentorship, his dedication to excellence and his extensive contributions to science.

Abstract: The use of potassium carbonate in addition to silver oxide is shown to increase the enantiospecificity of the Suzuki–Miyaura cross-coupling reaction of chiral secondary benzylic boronic esters. From mechanistic studies, it is shown that the reaction is compatible with Mizoroki–Heck coupling partners, even when they are present in considerable excess. This unique chemoselectivity provides the opportunity to carry out sequential reactions.

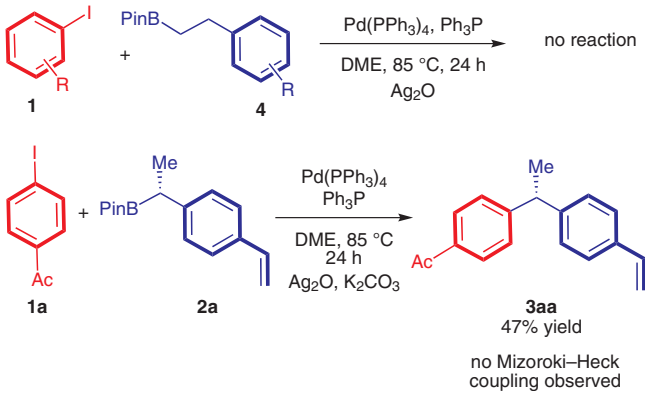
Key words: Suzuki, cross-coupling, palladium, chiral, enantiospecific

Since its discovery by Sneddon and Wilczynski[1] over 30 years ago, the metal-catalyzed hydroboration of unsaturated carbon–carbon bonds continues to be a reaction of considerable interest.[2] The ability to transform the boronic ester product into useful substrates is critical for the widespread use of this reaction in synthesis.[3] In 2009, our group reported an important advance in this area, namely the enantiospecific Suzuki–Miyaura cross-coupling of aryl iodides **1** and chiral, enantiopure organoboronic esters **2** (Scheme 1).[4] With the exception of the very specific class of cyclopropyl boronic esters,[5] this constituted the first example of a Suzuki–Miyaura cross-coupling reaction of a secondary chiral organoboronic ester, which occurred without loss of stereochemistry and with complete regiochemical fidelity.[6] Since our report,[4] other examples have appeared from the groups of Molander,[7] Suginome[8] and Hall,[9] whilst secondary allylic boronic ester coupling has been reported by our group,[10] and propargylic couplings by Aggarwal.[11]



Scheme 1 Enantiospecific Suzuki–Miyaura cross-coupling

In addition to the high enantiospecificity observed in this important reaction, we also found the reaction to be surprisingly chemoselective.[4] Notably, the linear hydroboration isomer **4**, obtained by hydroboration with iridium catalysts, and typically considered to be the more reactive regioisomer,[12] was completely unreactive under our optimized cross-coupling conditions (Scheme 2). Also, while studying the mechanistic details of this reaction, we discovered that in the presence of internal or large amounts of external Heck acceptors, complete selectivity was observed for the Suzuki–Miyaura product **3aa** (Scheme 2).[13,14] The exploration of this unique chemoselectivity and the rationale behind it is the subject of this paper.



Scheme 2 Chemoselective cross-coupling of secondary boronic ester in the presence of primary boronic ester or Heck acceptor

In our initial 2009 report, the Suzuki–Miyaura coupling was shown to proceed with high levels of retention of stereochemistry, although some erosion was observed.[4] Indeed, enantiospecificities in the order of 92% were obtained, leaving room for improvement. During a subsequent screen of conditions, we found that the enantiospecificity was improved markedly when potassium carbonate was used in conjunction with silver oxide as the base (Table 1).[15] Interestingly, these gains in enantiospecificity were undone when the phosphine loading was increased above the previously optimized triphenylphosphine–palladium ratio of 8:1 with regard to the isolated yield. This prompted us to further examine the effect of triphenylphosphine on both the yield and stereofidelity of the coupling.

The results of this study showed that the stereofidelity of the reaction decreased as the amount of triphenylphosphine was increased. This was juxtaposed with an increase in product yield as the phosphine loading was increased from more frugal loadings to the optimized triphenylphosphine–palladium (Ph_3P–Pd) ratio of 8:1.[16]

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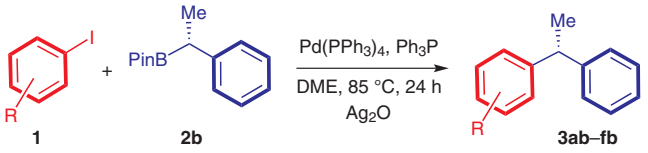
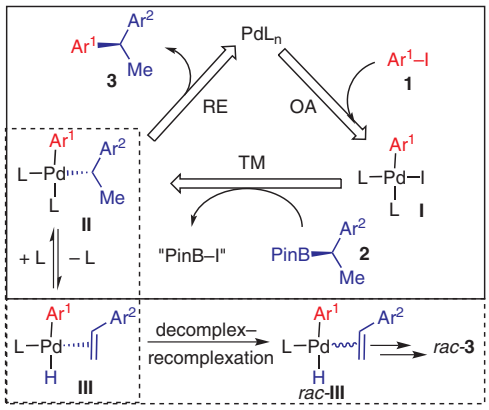
Thus, at high loadings of triphenylphosphine, a higher yield was obtained at the expense of the enantiomeric purity of the product.[13] Although the exact values of yield and enantioretention were found to vary slightly with the exclusion of potassium carbonate or the inclusion of trace amounts of water,[17] the trend was consistent over all the examined conditions.

Table 1 Effect of Potassium Carbonate on the Enantiospecificity of the Suzuki–Miyaura Cross-Coupling Reaction[a]



Ar–I (R)	Product	Yield (%)[b]	es[c]	es[c,d]
1a (4-Ac)	**3ab**	65 (63)[e]	92	98
1b (4-Cl)	**3bb**	81 (75)	91	99
1c (4-Me)	**3cb**	86 (60)	92	99
1d (4-MeO)	**3db**	(71)[e]	93	99
1e (2-Me)	**3eb**	(56)	93	96
1f (3,5-Me_2)	**3fb**	86 (64)	93	97

[a] Reaction conditions: $Pd(PPh_3)_4$ (8 mol%), Ph_3P (32 mol%), Ag_2O (1.5 equiv), K_2CO_3 (1.5 equiv, when added), DME (0.05 M), 85 °C, 24 h, N_2 atm.
[b] NMR yield determined vs the internal standard; yield of isolated product in parentheses.
[c] Enantiospecificity (es).[4]
[d] Enantiospecificity (es) in the presence of K_2CO_3 (1.5 equiv).
[e] $Pd_2(dba)_3$ was employed in place of $Pd(PPh_3)_4$.



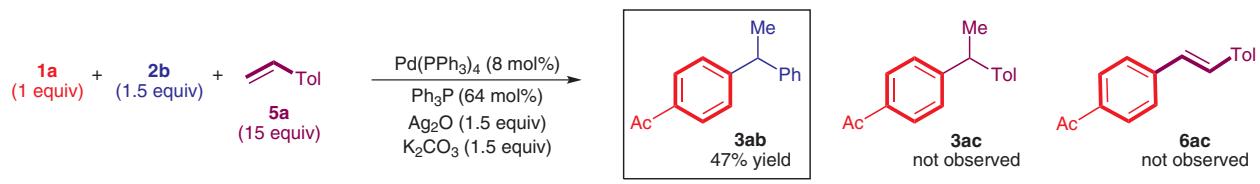
Scheme 3 Potential mechanism for the coupling of **1** and **2** with consideration of β-hydride elimination pathways

In order to probe the reason for the loss in stereoretention with added triphenylphosphine, we first explored potential racemization events. Thus exposure of cross-coupled product **3ab** (er = 97.5:2.5) to very harsh reaction conditions [Ph_3P (12 equiv with respect to Pd), DME, H_2O, 85 °C, 24 h, $Pd(PPh_3)_4$, Ag_2O, ArI, K_2CO_3] resulted in no loss of stereochemistry. The same experiment was performed with enantioenriched boronic ester **2b**, which, when added to the reaction mixture (without aryl iodide) under the same conditions, underwent less than 2% racemization. Therefore, scrambling of the stereochemistry of the product or starting material through the action of phosphine, base or palladium can be ruled out.

We thus turned to the events of the catalytic cycle. As shown in Scheme 3, after oxidative addition (OA) and transmetallation (TM), a β-hydride elimination event would generate intermediate **III**. This would result in loss of stereochemistry only if the resulting vinyl arene decomplexes and recomplexes. Although the β-hydride elimination should be inhibited by added ligand, once formed, decomplexation of vinyl arene the from **III** is presumably a process that could be promoted by excess phosphine.[18] This would lead to *rac*-**III**, and eventually to racemic coupling product **3** after reductive elimination (RE).

In order to test this hypothesis, we attempted the Suzuki–Miyaura cross-coupling under our standard conditions, with the addition of exogenous 4-methylstyrene (**5a**). The formation of cross-over product **3ac** would be indicative that an alkene decomplexation–recomplexation pathway was operative. In the event, crossover product **3ac** was not observed, even in the presence of 15 equivalents of 4-methylstyrene (**5a**). This indicated that although trace levels of β-hydride elimination may have taken place,[18] alkene decomplexation was not occurring to an appreciable extent, even with 12 equivalents of triphenylphosphine (Scheme 4). An added factor, however, is the ability of potassium carbonate to deprotonate any small amounts of palladium hydride **III**, which would also prevent formation of a racemic product since it would prevent *rac*-**III** from equilibrating with **II**, and being converted into product. Consistent with this, Hünig's base, reported by Fu to be highly effective at deprotonating palladium hydrides,[19] was also effective at increasing the enantiospecificity.

Remarkably, less than 0.5% of the corresponding Mizoroki–Heck product **6ac** was observed, even when a tenfold excess of the styrene derivative was added to the reaction. Thus this mechanistic probe illustrated another significant aspect of the chemoselectivity of the conditions devel-

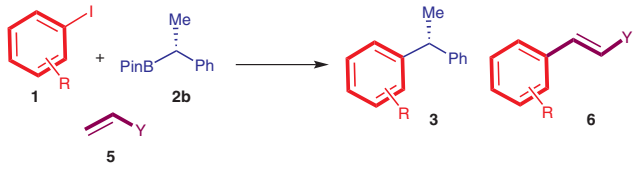


Scheme 4 Crossover experiment with vinyl arene demonstrating selectivity for Suzuki–Miyaura coupling rather than Mizoroki–Heck coupling

oped to cross-couple secondary benzylic boronic esters, namely the lack of reaction via competitive Mizoroki–Heck pathways, even in the presence of large excesses of styrenes. To explore this further, we examined the Suzuki–Miyaura cross-coupling in the presence of a variety of Heck acceptors and aryl iodides (Table 2).

As shown in Table 2, neither styrene derivatives nor methyl acrylate were competent Heck acceptors under the conditions where the Suzuki–Miyaura coupling of **2b** took place. This provides the interesting possibility that vinylated aromatic boronic esters such as **3aa** will be able to undergo sequential Suzuki–Miyaura coupling and then reaction at the styrene unit.

Table 2 Chemoselectivity in the Suzuki–Miyaura Cross-Coupling of Boronic Ester **2b** in the Presence of Mizoroki–Heck Acceptors **5**[a]



Entry	Ar–I (R)	Styrene **5** (Y)	Product	Yield (%)[b]
1	**1a** (4-Ac)	4-C_6H_4Me[c]	**3ab**	47
2	**1g** (H)	Ph[d]	**3gb**	(66)
3	**1h** (Naphth)[e]	Ph[d]	**3hb**	(70)
4	**1c** (4-Me)	Ph[d]	**3cb**	(40)
5	**1d** (4-MeO)	Ph[d]	**3db**	(56)
6	**1a** (4-Ac)	CO_2Me[d]	**3ab**	60 (52)
7	**1a** (4-Ac)	CO_2Me[f]	**3ab**	60

[a] Reaction conditions: $Pd(PPh_3)_4$ (8%), Ph_3P (32%), Ag_2O (1.5 equiv), K_2CO_3 (1.5 equiv, when added), DME (0.05 M), H_2O (350 ppm) added to entries 2–5, 85 °C, 24 h, N_2 atm.
[b] Isolated yields in parentheses; GC yield for entry 1; NMR yields for entries 6 and 7. No Mizoroki–Heck product **6** was observed.
[c] Heck acceptor (15 equiv).
[d] Heck acceptor (2 equiv).
[e] 1-Iodonaphthalene was employed.
[f] Heck acceptor (10 equiv).

In order to determine which conditions prevent the Mizoroki–Heck reaction, we adjusted several of the reaction parameters and determined that under our conditions, the temperature and phosphine loading were responsible for the observed chemoselectivity. Thus, by omitting additional phosphine, above what is present with tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$], increasing the temperature, changing the solvent to *N*,*N*-dimethylformamide, and omitting silver oxide (Ag_2O), we were able to observe Mizoroki–Heck coupling of aryl iodide **1a** with methyl acrylate in 50% isolated yield; methyl cinnamate was also an effective partner.

In conclusion, it would appear that the conditions optimized to favor the Suzuki–Miyaura coupling of benzylic boronic esters **2** simultaneously disfavor the Mizoroki–Heck reaction, which provides the opportunity for considerable cross reactivity in coupling reactions of benzylic boronic esters. This is currently being explored in our group for the synthesis of π-extended aromatic systems using sequential hydroboration–coupling–hydroboration/diboration–coupling strategies. These results will be reported in due course.

Unless otherwise noted, all reactions were performed under an inert atmosphere using dried glassware. Solvents were dried by standard methods before being degassed by a minimum of three freeze-pump–thaw cycles and were stored over 4 Å molecular sieves. Aryl halides were purified before use following accepted protocols.[20] Ag_2O was purified by continuous hot water extraction in a Soxhlet condenser over three days, and dried under vacuum in the presence of P_2O_5. $Pd(PPh_3)_4$ was used as purchased from Strem. Ph_3P was purified by recrystallization from absolute ethanol. Cross-coupling reactions were assembled in a glovebox in 4 dram vials, sealed with air-tight Teflon caps and placed in an 85 °C oil bath for 24 h.[4] Once cooled, the reactions were filtered through Celite, washed with copious amounts of Et_2O and hexanes and concentrated in vacuo. Crude yields were determined by gas chromatography (GC) employing an internal standard (octadecane) with calibration curve, or by NMR with hexamethylbenzene (HMB) or dimethoxybenzene (DMB) serving as internal standards. Thin-layer chromatography was performed on EMD Chemicals Inc. TLC silica gel 60 aluminum-backed plates with F_{254} indicator. Visualization was accomplished with a UV source (254, 365 nm) and by treatment with phosphomolybdic acid. Column chromatography was performed with flash grade silica (Silicycle, 50 μm particle size, 60 Å porosity) and reagent grade solvents. NMR spectra were recorded at 400 MHz (^1H), and 100 MHz (^{13}C) in $CDCl_3$ using a Bruker Avance-400 spectrometer. High-resolution mass spectrometry (HRMS) was performed using a Micromass GCT (GC-Time of Flight Mass Spectrometer). GC analyses were performed on an HP 6850 network FID-GC fitted with an automatic injector. The column used was an HP-5 of 30 m in length with an internal diameter of 0.32 mm. The inlet conditions were 250 °C, 25 psi and a flow rate of 28.9 mL/min using a splitless injector with helium as the carrier gas. The method used had an initial temperature of 70 °C with an immediate increase to 240 °C using a 6°/min ramp. Determination of stereochemistry was performed by analysis on a Supercritical Fluid Chromatograph (SFC). Analytical SFC was performed on a Berger SFC HPLC using the specified chiracel Berger Silica column and appropriate co-eluent, flow rate and pressure conditions.

***rac*-1-(Styren-4-yl)-1-(4-acetylphenyl)ethane (3aa)**

In an N_2-filled glovebox, 1-(4-iodophenyl)ethanone (**1a**) (6.91 mg, 245.9 g/mol, 0.0281 mmol), 4,4,5,5-tetramethyl-2-[1-(4-vinylphenyl)ethyl]-1,3,2-dioxaborolane (**2a**) (11.0 mg, 0.043 mmol, 1.53 equiv), Ag_2O (10.20 mg, 234 g/mol, 0.0436 mmol), $Pd(PPh_3)_4$ (2.85 mg, 1155.6 g/mol, 0.0025 mmol, 8.8 mol% Pd) and Ph_3P (2.31 mg, 262 g/mol, 0.009 mmol, 7.5:1 P/Pd) were taken up in DME (0.7 mL). The reaction vessel was sealed and the contents stirred at 85 °C for 24 h. Once cooled, the mixture was filtered through Celite and washed with copious amounts of Et_2O. The solvents were evaporated in vacuo and an internal NMR standard was added [hexamethylbenzene (HMB), 7.8 mg]. Product **3aa** was obtained in 54% NMR yield. The diaryl product was purified by column chromatography (hexanes–EtOAc, 20:1) to give 7.03 mg of a clear oil, representing a 48% isolated yield of product. The Mizoroki–Heck stilbene product was not detected in significant amounts by GC–MS or NMR.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 6.61 (dd, *J* = 17.6 Hz, 10.8 Hz, 1 H), 5.63 (dd, *J* = 17.6 Hz, 0.8 Hz,

1 H), 5.13 (dd, J = 10.8 Hz, 0.8 Hz, 1 H), 4.12 (q, J = 7.2 Hz, 1 H), 2.50 (s, 3 H), 1.58 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 145.0, 136.4, 135.8, 135.3, 128.6, 127.79, 127.73, 126.4, 113.5, 44.6, 26.6, 21.5, 15.3 (C=O signal not observed).

HRMS–TOF (EI): m/z $[M]^+$ calcd for $C_{18}H_{18}O$: 250.1358; found: 250.1351.

(*R*)-1-Phenyl-1-(4-acetylphenyl)ethane (3ab)[4]
Under an inert atm, 1-(4-iodophenyl)ethanone (**1a**) (12.45 mg, 0.051 mmol), (*R*)-4,4,5,5-tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane [(***R***)-**2b**] (17.41 mg, 0.075 mmol, er = 93.3:6.7), Ag_2O (17.68 mg, 0.076 mmol), K_2CO_3 (10.5 mg, 0.076 mmol), $Pd_2(dba)_3$ (1.186 mg, 0.0020 mmol, 8.1 mol% Pd) and Ph_3P (8.54 mg, 0.033 mmol) were taken up in DME (1.0 mL). The reaction vessel was sealed, and the contents stirred at 85 °C for 24 h. The desired product was isolated as a clear oil in 63% yield after column chromatography (hexanes–EtOAc, 20:1 to 10:1). The enantiomeric ratio was determined by SFC analysis [AD-H column, 5% MeOH (2 mL), 200 bar] to be 91.5:8.5 (98% retention of er).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.2 Hz, 2 H), 7.35–7.22 (m, 7 H), 4.23 (q, J = 7.2 Hz, 1 H), 2.59 (s, 3 H), 1.68 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 152.4, 146.0, 135.7, 128.9, 128.8, 128.1, 127.9, 126.7, 45.2, 26.8, 21.6.

HRMS–TOF (EI): m/z $[M]^+$ calcd for $C_{16}H_{16}O$: 224.1201; found: 224.1197.

(*R*)-1-Phenyl-1-(4-chlorophenyl)ethane (3bb)[4]
In an N_2-filled glovebox, 1-chloro-4-iodobenzene (**1b**) (35.96 mg, 0.151 mmol), (*R*)-**2b** (51.20 mg, 0.221 mmol, er = 94:6), Ag_2O (52.81 mg, 0.228 mmol), K_2CO_3 (32.20 mg, 0.233 mmol), $Pd(PPh_3)_4$ (13.82 mg, 0.012 mmol) and Ph_3P (12.58 mg, 0.0480 mmol) were weighed into a dried vial and taken up in DME (3 mL). The reaction vessel was sealed and the contents stirred at 85 °C for 24 h. The mixture was cooled and filtered through Celite. The desired product was isolated as a clear oil in 75% yield after column chromatography (pentane). The enantiomeric ratio was determined by SFC [OD, 1% MeOH (2 mL), 200 bar] to be 92.8:7.2 (a 98.7% retention of er).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.16 (m, 9 H), 4.15 (q, J = 7.2 Hz, 1 H), 1.64 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 145.0, 131.9, 129.1, 128.60, 128.59, 127.7, 126.4, 44.3, 21.9.

HRMS–TOF (EI): m/z $[M]^+$ calcd for $C_{14}H_{13}Cl$: 216.0706; found: 216.0702.

(*R*)-1-Phenyl-1-(4-methylphenyl)ethane (3cb)[4]
In an N_2-filled glovebox, 1-iodo-4-methylbenzene (**1c**) (33.09 mg, 0.152 mmol), (*R*)-**2b** (53.26 mg, 0.229 mmol, er = 94:6), Ag_2O (52.66 mg, 0.227 mmol), K_2CO_3 (32.68 mg, 0.237 mmol), $Pd(PPh_3)_4$ (14.82 mg, 0.0128 mmol) and Ph_3P (12.56 mg, 0.0479 mmol) were weighed into a dried vial and taken up in DME (3 mL). The reaction vessel was sealed and the contents stirred at 85 °C for 24 h. The mixture was cooled and filtered through Celite. The desired product was isolated as a clear oil in 60% yield after column chromatography (pentane). The enantiomeric ratio was determined by SFC [OD, 1% MeOH (2 mL), 200 bar] to be 93:7 (99% retention of er).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.07 (m, 9 H), 4.11 (q, J = 7.2 Hz, 1 H), 2.30 (s, 3 H), 1.62 (d, J = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 143.4, 135.5, 129.0, 128.3, 127.54, 127.46, 125.9, 44.4, 21.9, 20.9.

HRMS–TOF (EI): m/z $[M]^+$ calcd for $C_{15}H_{16}$: 196.1252; found: 196.1256.

(*R*)-1-Phenyl-1-(4-methoxyphenyl)ethane (3db)[4]
In an N_2-filled glovebox, 4-iodoanisole (**1d**) (35.08 mg, 0.150 mmol), (*R*)-**2b** (52.67 mg, 0.227 mmol, er = 94:6), Ag_2O (52.34 mg, 0.226 mmol), K_2CO_3 (32.12 mg, 0.232 mmol), $Pd(PPh_3)_4$ (13.55 mg, 0.0117 mmol) and Ph_3P (12.33 mg, 0.0470 mmol) were weighed into a dried vial and taken up in DME (3 mL). The reaction vessel was sealed and the contents stirred at 85 °C for 24 h. The mixture was cooled and filtered through Celite. The desired product was isolated as a clear oil in 71% yield after column chromatography (pentane–Et_2O, 50:1). The enantiomeric ratio was determined by SFC [OD, 1% MeOH (2 mL), 200 bar] to be 93.1:6.9 (99% retention of er).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.17 (m, 7 H), 6.89–6.85 (m, 2 H), 4.15 (q, J = 7.2 Hz, 1 H), 3.82 (s, 3 H), 1.66 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 146.9, 138.7, 128.6, 128.5, 127.7, 126.1, 113.8, 55.4, 44.1, 22.2.

HRMS–TOF (EI): m/z $[M]^+$ calcd for $C_{15}H_{16}O$: 212.1201; found: 212.1211.

(*R*)-1-Phenyl-1-(2-methylphenyl)ethane (3eb)[4]
In an N_2-filled glovebox, 1-iodo-2-methylbenzene (**1e**) (31.20 mg, 0.143 mmol), (*R*)-**2b** (50.15 mg, 0.216 mmol, er = 94:6), Ag_2O (51.21 mg, 0.221 mmol), K_2CO_3 (30.40 mg, 0.220 mmol), $Pd(PPh_3)_4$ (13.05 mg, 0.0113 mmol) and Ph_3P (12.11 mg, 0.0462 mmol) were weighed into a dried vial and taken up in DME (3 mL). The reaction vessel was sealed and the contents stirred at 85 °C for 24 h. The mixture was cooled and filtered through Celite. The desired product was isolated as a clear oil in 64% yield (containing ca. 8% of the homo-coupled product) after column chromatography (pentane–Et_2O, 50:1). The enantiomeric ratio was determined by SFC [OJ, 1.5% *i*-PrOH (2 mL), 200 bar] to be 89.9:10.1 (96% retention of er).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.15 (m, 9 H), 4.34 (q, J = 7.2 Hz, 1 H), 2.26 (s, 3 H), 1.63 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 144.0, 136.2, 130.5, 128.4, 127.8, 126.8, 126.21, 126.15, 125.9, 41.1, 22.3, 19.9.

(*R*)-1-Phenyl-1-(3,5-dimethylphenyl)ethane (3fb)[4]
In an N_2-filled glovebox, 1-iodo-3,5-dimethylbenzene (**1f**) (32.58 mg, 0.140 mmol), (*R*)-**2b** (53.47 mg, 0.230 mmol, er = 94:6), Ag_2O (52.01 mg, 0.224 mmol), K_2CO_3 (31.11 mg, 0.225 mmol), $Pd(PPh_3)_4$ (13.15 mg, 0.0114 mmol) and Ph_3P (12.80 mg, 0.0488 mmol) were weighed into a dried vial and taken up in DME (3 mL). The reaction vessel was sealed and the contents stirred at 85 °C for 24 h. The mixture was cooled and filtered through Celite. The desired product was isolated as a clear oil in 77% yield (containing ca. 10% of the homo-coupled product) after column chromatography (pentane–Et_2O, 50:1). The isolated yield without K_2CO_3 was 64% (^{1}H NMR yield = 86%). The enantiomeric ratio was determined by SFC [OD, 1% *i*-PrOH (2 mL), 100 bar] to be 91.3:8.7 (97% retention of er).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.15 (m, 5 H), 6.83 (m, 3 H), 4.07 (q, J = 7.2 Hz, 1 H), 2.27 (s, 6 H), 1.61 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 146.4, 137.9, 128.5, 127.91, 127.86, 127.8, 127.7, 126.0, 125.6, 44.8, 22.1, 21.5.

HRMS–TOF (EI): m/z $[M]^+$ calcd for $C_{16}H_{18}$: 210.1409; found: 210.1402.

(*rac*)-1-(1-Phenylethyl)naphthalene (3hb)[4]
In an N_2-filled glovebox, 1-iodonaphthalene (**1h**) (12.7 mg, 0.05 mmol, 1.0 equiv), *rac*-**2b** (17.4 mg, 0.075 mmol), $Pd(PPh_3)_4$ (4.62 mg, 0.004 mmol), Ph_3P (4.19 mg), Ag_2O (17.4 mg, 0.075 mmol), K_2CO_3 (10.4 mg, 0.075 mmol), styrene (10.4 mg, 0.1 mmol) and DME (1 g), were weighed into a 5 mL vial containing a Teflon-coated stir bar. The reaction vessel was sealed inside the glovebox with a Teflon cap possessing a rubber septum, and then removed. Out-

side the glovebox, a mixture of H_2O–DME (7.40 mg, 7.33 mg of deionized, degassed H_2O in 145.3 mg of anhyd DME) was added via a microsyringe through the rubber septum. The vial was placed in an 85 °C oil bath for 24 h. After cooling to r.t., the crude mixture was filtered through a silica plug, washed with copious amounts of EtOAc, and then concentrated in vacuo. The crude residue was purified by column chromatography (hexanes–EtOAc, 50:1 to 20:1) to provide the product in 70% yield (8.13 mg, 0.035 mmol) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.78 (m, 1 H), 7.64–7.59 (m, 1 H), 7.54–7.50 (m, 1 H), 7.28–7.16 (m, 4 H), 7.06–6.90 (m, 4 H), 6.96–6.90 (m, 1 H), 4.70 (q, *J* = 7.1 Hz, 1 H), 1.54 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 141.7, 134.1, 131.8, 128.9, 128.6, 127.8, 127.1, 126.1, 125.9, 125.6, 125.5, 124.5, 124.1, 40.7, 22.7.

HRMS–TOF (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{16}$: 232.1252; found: 232.1258.

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