Double Couplings of Dibromothiophenes Using Boronic Acids and Boronates

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Abstract: One-pot double couplings of dibromothiophenes have been investigated. Standard Suzuki couplings work well for 2,4-dibromothiophene, but are much more sensitive to steric effects in the case of 2,3-dibromothiophene. By using the recently reported potassium borates, though, good yields for both dibromothiophene isomers can be achieved.

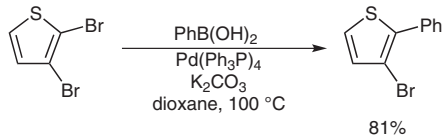
Key words: Suzuki couplings, regioselectivity, heteroaromatics, thiophenes, cross-coupling reactions, palladium catalysis

Substituted thiophenes are highly important molecules present in a wide range of compounds of biological and materials interest.[1] Although many routes have been developed for the preparation of such compounds, the most widely employed method for the installation of carbon substituents is transition-metal-catalyzed cross-coupling chemistry.[2] Such reactions have been used innumerable times and with great efficiency.

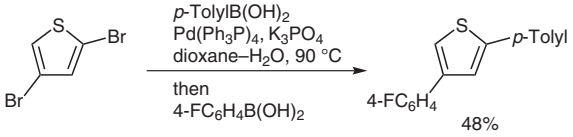
As part of a project aimed at improving the efficiency of cross-coupling chemistry for the preparation of multiply substituted heteroaromatics, we have been exploring the use of one-pot double Suzuki couplings.[3] Prior work has focused more on azoles,[4] but more recently has begun to examine thiophenes.[5]

The regioselectivity of couplings of dibromothiophenes is fairly well established.[6,7] In particular, the work of de Lera demonstrated that the initial site of coupling of 2,3-dibromothiophene in Stille, Suzuki, or Sonogashira couplings is always at C2 (Scheme 1).[7] Generally good yields were achieved for many of these couplings. At the same time, little was done with regard to the possibility of conducting a second coupling at the remaining bromide. Indeed, there have been no prior reports of one-pot double couplings on 2,3- or 2,4-dibromothiophenes.[8]

Initial efforts explored application of the conditions used successfully on 4,5-dibromothiophene-2-carboxaldehyde to a simple dibromothiophene such as 2,4-dibromothiophene (Scheme 2). Interestingly, although some dicoupled product was isolated, the overall yield was quite modest. Further analysis of the crude reaction mixture demonstrated that much of the material balance was monocoupled thiophenes.[9] Further attempts noted that catalyst decomposition appeared to be rapid. This decomposition could be greatly reduced by degassing the reaction mixture prior to the addition of the palladium catalyst. Further, reducing the temperature of the first coupling to 80 °C as well as cutting the reaction time to three hours also improved the yield of the dicoupled product. In a brief survey of reaction conditions, a slight increase in yield was noted by employing DMF as the solvent and aqueous sodium carbonate as the base.[10] The ratio of DMF to water was important, as highly aqueous conditions (>30% water by volume) resulted in poor conversion. Additionally, the use of 2 M sodium carbonate (as had been employed in many of our previous double couplings) resulted in poor reproducibility. The problem may be due to precipitation of the sodium carbonate upon addition to the DMF, which then appears to facilitate catalyst decomposition and precipitation as palladium black. Dilution to a 1 M sodium carbonate resolved this issue and proved generally satisfactory.



Scheme 1



Scheme 2

These reaction conditions proved quite satisfactory for a range of aryl boronic acids, including the sterically hindered 2-methoxyphenylboronic acid, as well as an alkenylboronic acid (Table 1). In general, overall yields are good, although the double coupling in which 2-thienylboronic acid is used in the first coupling is unexpected low (Table 1, entry 7), particularly in light of the much better result when this same boronic acid is used in the second coupling (entry 8).

Armed with these results, the same conditions were applied to 2,3-dibromothiophene (Table 2). The reactions again afforded generally good results, although the yields were definitely lower than those for the corresponding couplings on 2,4-dibromothiophene. The reduced yields are not the result of a less efficient first coupling. By simply running the first coupling under these reaction conditions, the monocoupled products could be isolated in 80–95% yield. Thus, the problem appears to be the steric hin-

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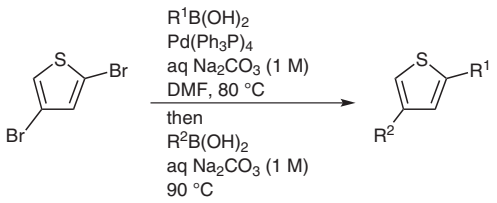
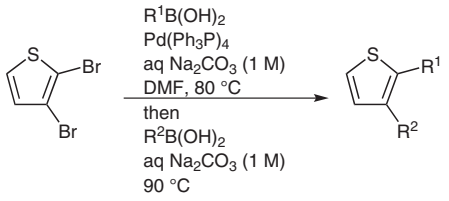
Table 1 Double Suzuki Couplings of 2,4-Dibromothiophene



Entry	R^1	R^2	Isolated yield (%)
1	4-MeC_6H_4	4-FC_6H_4	88
2	4-FC_6H_4	4-MeC_6H_4	80
3	(*E*)-PhC=CH	Ph	67
4	Ph	(*E*)-PhC=CH	64
5	2-$MeOC_6H_4$	Ph	54
6	Ph	2-$MeOC_6H_4$	42
7	2-thienyl	Ph	38
8	Ph	2-thienyl	75

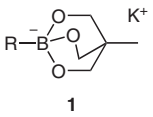
Table 2 Double Suzuki Couplings of 2,3-Dibromothiophene



Entry	R^1	R^2	Isolated yield (%)
1	4-MeC_6H_4	4-FC_6H_4	46
2	4-FC_6H_4	4-MeC_6H_4	40
3	(*E*)-PhC=CH	Ph	12
4	Ph	(*E*)-PhC=CH	18
5	2-$MeOC_6H_4$	Ph	21
6	Ph	2-$MeOC_6H_4$	15
7	2-thienyl	Ph	42
8	Ph	2-thienyl	38

drance that results from the presence of the initially coupled group at C2. It is possible that employing a more active catalyst may be sufficient to overcome this problem, but this option has not yet been explored.

Because catalyst stability was proving to be such an issue, we were interested in finding an even more mild set of reaction conditions or a more robust catalyst. Recently, Miyaura and co-workers reported the Suzuki-type coupling using stable boronate salts such as **1**[11] (Figure 1). Of great interest to us was their observation that these salts reacted under very mild conditions: no added base, palladium acetate as catalyst, and short, room temperature reactions. Gratifyingly, application of these same conditions to the double coupling of dibromothiophenes worked as well or better than the corresponding double Suzuki couplings using boronic acids.[12]



1

Figure 1 Structure of boronate salt **1**

Using the boronate salts, the yields of double couplings were generally higher for both the 2,3- and 2,4-dibromothiophenes (Table 3). Further, although the couplings of 2,3-dibromothiophenes still afforded slightly lower yields than those in the 2,4-dibromothiophene, the difference is quite modest. As a result, it appears that steric issues are less important.

Alkenyl boronate salts were also successful in these double couplings (Table 3, entries 3 and 4). Quite encouragingly, so was an ortho-substituted boronate (entries 5 and 6). It should be noted that the efficient preparation of this particular boronate salt did require the use of the organolithium route [halogen–metal exchange on 2-bromoanisole, followed by reaction with trimethyl borate and then treatment with 1,1,1-tris(hydroxymethyl)ethane] as attempts at preparing this boronate from the corresponding boronic acid resulted in very low yields of the product. Fortunately, the organolithium route afforded a nearly quantitative yield of the desired boronate salt.

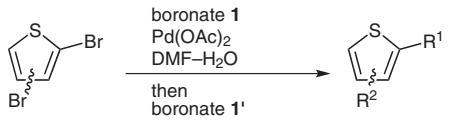
In conclusion, one-pot double couplings of dibromothiophenes are clearly readily achievable. The use of boronates as the coupling partners affords the products in good yield for either dibromothiophene isomer. In some preliminary studies, it appears that the same boronate reaction conditions are applicable to a range of heteroaromatics, including pyrroles, furans, and pyridines. This has not been the case in simple double Suzuki couplings, where a different set of reaction conditions are required for good yields with each different heteroaromatic. Thus, the boronate couplings hold promise for the development of a more general set of reaction conditions for these double couplings. Studies to this end are under way and will be reported in due course.

All boronic acids were from Frontier Scientific and used as received. All other reagents and solvents were from Acros or Aldrich and were used as received. Silica gel (Natlund) was used for all column chromatography and Sorbent Technologies silica TLC plates were used to monitor all reactions. NMR data were recorded on a JEOL ECX-300. IR spectra were recorded on a Varian 800 FTIR as solutions in deuterochloroform. Melting points were determined using a Fisher-Johns hot stage and are uncorrected. All coupling reactions were performed using a JKEM orbital shaker with a temperature-controlled multiwell heating block.

Double Suzuki Couplings; 4-(4′-Fluorophenyl)-2-(4′-tolyl)thiophene; Typical Procedure

2,4-Dibromothiophene (48.3 mg, 0.207 mmol) and 4-fluorophenylboronic acid (31.8 mg, 0.228 mmol) were combined in a vial and

Table 3 Double Boronate Couplings of Dibromothiphenes



Entry	R^1	R^2	Isolated yield (2,4 product, %)	Isolated yield (2,3 product, %)
1	4-MeC_6H_4	4-FC_6H_4	95	85
2	4-FC_6H_4	4-MeC_6H_4	71	64
3	(*E*)-PhC=CH	Ph	64	70
4	Ph	(*E*)-PhC=CH	65	67
5	2-$MeOC_6H_4$	Ph	81	64
6	Ph	2-$MeOC_6H_4$	94	61
7	2-thienyl	Ph	77	62
8	Ph	2-thienyl	81	73

dissolved in DMF (4 mL). Aq 1 M Na_2CO_3 (600 μL) was added and the resultant solution was degassed by bubbling argon through the solution for 10 min. $(Ph_3P)_4Pd$ (6.9 mg, 0.103 mmol) was added and the vial was sealed and shaken on an orbital shaker at 110 rpm at 80 °C for 3 h. Tolylboronic acid (27.8 mg, 0.228 mmol) and aq 1 M Na_2CO_3 (600 μL) were then added and the mixture was shaken at 110 rpm at 90 °C for an additional 16 h. The final reaction mixture was cooled, diluted with H_2O (15 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified on silica gel using 1:3 CH_2Cl_2–hexanes as eluent[13](Tables 1 and 2).

Double Boronate Couplings; 4-(4′-Fluorophenyl)-2-(4′-tolyl)thiophene; Typical Procedure

2,4-Dibromothiophene (80 mg, 0.33 mmol), 4-fluorophenyl boronate (87 mg, 0.34 mmol), and $Pd(OAc)_2$ (2.2 mg, 0.015 mmol) were combined in a vial and dissolved in DMF–H_2O (4:1, 1 mL). The vial was sealed and stirred at r.t. for 3 h. The mixture rapidly became dark brown. Tolyl boronate (86 mg, 0.34 mmol) was then added and the mixture was stirred for an additional 16 h. The final reaction mixture was diluted with H_2O (4 mL) and extracted with Et_2O (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified on silica gel using 1:3 CH_2Cl_2–hexanes as eluent (Table 3).

4-(4′-Fluorophenyl)-2-(4′-tolyl)thiophene

Brown solid; mp 26–28 °C.

IR ($CDCl_3$): 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.42 (m, 4 H), 7.28–7.02 (m, 6 H), 2.38 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 138.1, 129.8, 128.4 (d, *J* = 8 Hz), 127.6 (d, *J* = 6 Hz), 127.3 (d, *J* = 195 Hz), 125.8, 125.7, 122.0, 121.5, 116.2 (d, *J* = 22 Hz), 110.6, 21.3.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{13}FS$: 268.3546; found: 268.3544.

2-(4′-Fluorophenyl)-4-(4′-tolyl)thiophene

Yellow solid; mp 43–44 °C.

IR ($CDCl_3$): 3100, 3000, 1500, 1300, 1280, 1200, 900, 860, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.44 (m, 4 H), 7.33–7.02 (m, 6 H), 2.41 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.7, 138.4, 129.6 (d, *J* = 10 Hz), 128.5 (d, *J* = 210 Hz), 127.6 (d, *J* = 8 Hz), 125.7, 125.2, 122.0, 121.5, 116.2 (d, *J* = 25 Hz), 110.7, 110.5, 21.3.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{13}FS$: 268.3546; found: 268.3545.

3-(4′-Fluorophenyl)-2-(4′-tolyl)thiophene

Pale yellow oil.

IR ($CDCl_3$): 3100, 3000, 1550, 1500, 1200, 960, 880, 840, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.51 (m, 4 H), 7.43–7.32 (m, 4 H), 7.06 (d, *J* = 6.8 Hz, 2 H), 2.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 136.9, 131.7, 130.8, 130.0, 129.5, 129.3, 129.0 (d, *J* = 8 Hz), 127.3 (d, *J* = 8 Hz), 126.9 (d, *J* = 210 Hz), 124.8, 116.7 (d, *J* = 25 Hz), 21.4.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{13}FS$: 268.3546; found: 268.3547.

2-(4′-Fluorophenyl)-3-(4′-tolyl)thiophene

Pale yellow oil.

IR ($CDCl_3$): 3100, 3000, 1500, 1220, 1160, 940, 880, 860 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.51 (m, 4 H), 7.39–7.32 (m, 3 H), 7.14 (t, *J* = 6.6 Hz, 2 H), 7.06 (d, *J* = 3.8 Hz, 1 H), 2.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 136.9, 131.7 (d, *J* = 8 Hz), 130.8, 130.0, 129.5 (d, *J* = 200 Hz), 129.3, 129.0, 127.3, 126.9, 124.8 (d, *J* = 10 Hz), 115.8 (d, *J* = 22 Hz), 21.2.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{13}FS$: 268.3546; found: 268.3543.

4-(2′-Methoxyphenyl)-2-phenylthiophene

Pale yellow oil.

IR ($CDCl_3$): 3100, 3000, 1500, 1250, 1140, 960, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.53 (m, 2 H), 7.42–7.24 (m, 5 H), 7.21 (t, *J* = 1 Hz, 1 H), 7.18 (d, *J* = 1 Hz, 1 H), 6.98 (d, *J* = 8 Hz, 2 H), 3.94 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.1, 129.2, 129.1, 128.4, 128.2, 127.8, 127.1, 125.8, 125.7, 122.6, 122.0, 121.1, 120.6, 111.7, 55.6.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}OS$: 266.3636; found: 266.3636.

2-(2′-Methoxyphenyl)-4-phenylthiophene

Pale yellow oil.

IR ($CDCl_3$): 3100, 3000, 1500, 1220, 1100, 960, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 1 Hz, 1 H), 7.69–7.61 (m, 3 H), 7.43 (d, *J* = 1 Hz, 1 H), 7.41–7.25 (m, 4 H), 7.02 (d, *J* = 8 Hz, 2 H), 3.92 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.1, 129.2, 129.1, 128.9, 128.7, 128.6, 127.8, 127.1, 126.4, 124.7, 123.6, 121.0, 120.6, 111.7, 55.2.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}OS$: 266.3636; found: 266.3633.

3-(2′-Methoxyphenyl)-2-phenylthiophene
Pale yellow oil.

IR ($CDCl_3$): 3100, 3000, 1500, 1240, 1140, 960, 800 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7 Hz, 2 H), 7.45–7.26 (m, 5 H), 7.05 (dd, *J* = 6, 1 Hz, 2 H), 7.00 (t, *J* = 7 Hz, 2 H), 3.84 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.1, 131.8, 130.6, 130.4, 129.2, 128.6, 128.2, 127.9, 125.5, 125.0, 120.0, 116.8, 116.4, 111.4, 55.7.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}OS$: 266.3636; found: 266.3638.

2-(2′-Methoxyphenyl)-3-phenylthiophene
Pale yellow oil.

IR ($CDCl_3$): 3100, 3000, 1500, 1260, 1140, 920, 840 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.16 (m, 10 H), 6.85 (d, *J* = 8 Hz, 1 H), 3.90 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.8, 131.0, 129.4, 129.3, 128.5, 128.2, 128.1, 127.6, 126.5, 125.2, 120.1, 120.0, 112.3, 109.7, 55.2.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}OS$: 266.3636; found: 266.3634.

4-Phenyl-2-(*trans*-styryl)thiophene
White solid; mp 44–46 °C.

IR ($CDCl_3$): 3100, 3000, 1500, 1280, 980, 920, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.21 (m, 13 H), 7.06 (d, *J* = 12 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.3, 129.4, 129.1, 128.9, 128.8, 128.4, 127.7, 127.3, 126.6, 126.5, 125.8, 125.8, 122.1, 110.8.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{14}S$: 262.3752; found: 262.3755.

2-Phenyl-4-(*trans*-styryl)thiophene
Yellow solid; mp 48–50 °C.

IR ($CDCl_3$): 3100, 3000, 1500, 1260, 980, 940, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 5 Hz, 2 H), 7.40–7.30 (m, 11 H), 7.26 (d, *J* = 12 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.4, 133.3, 129.4, 129.2, 128.9, 128.8, 128.4, 127.7 126.6, 126.5, 125.8, 125.7, 122.0, 110.6.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{14}S$: 262.3752; found: 262.3755.

3-Phenyl-2-(*trans*-styryl)thiophene
Yellow solid; mp 87–90 °C.

IR ($CDCl_3$): 3100, 3000, 1500, 1240, 980, 900, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–725 (m, 11 H), 7.08–6.93 (m, 2 H), 6.68 (d, *J* = 12 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4, 132.9, 131.3, 130.7, 130.1, 129.3, 129.2, 128.8, 128.4, 127.7, 126.6, 125.2, 123.8, 120.1.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{14}S$: 262.3752; found: 262.3754.

2-Phenyl-3-(*trans*-styryl)thiophene
White solid; mp 44–46 °C.

IR ($CDCl_3$): 3100, 3000, 1500, 1260, 980, 940, 840 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = Hz, 1 H), 7.60–7.25 (m, 10 H), 7.08–6.90 (m, 2 H), 6.65 (d, *J* = 12 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.6, 132.9, 131.4, 130.9, 130.1, 129.4, 129.2, 128.9, 128.6, 127.7, 126.5, 125.1, 124.0, 120.1.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{14}S$: 262.3752; found: 262.3753.

4-Phenyl-2-(2′-thienyl)thiophene
Mp 73–74 °C (Lit.[14] mp 74–76 °C).

IR ($CDCl_3$): 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–6.84 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1, 139.1, 137.3, 133.9, 129.2, 127.9, 127.8, 126.3, 124.1, 123.4, 122.2, 119.2.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}S_2$: 346.3972; found: 346.3970.

2-Phenyl-4-(2′-thienyl)thiophene
White solid; mp 70–72 °C.

IR ($CDCl_3$): 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 2 H), 7.53 (d, *J* = 1 Hz, 1 H), 7.48–7.40 (m, 2 H), 7.36–7.30 (m, 2 H), 7.28–7.23 (m, 2 H), 7.08 (dd, *J* = 5, 4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.2, 139.1, 137.4, 133.9, 129.1, 127.9, 127.8, 126.0, 124.1, 123.3, 122.2, 119.1.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}S_2$: 346.3972; found: 346.3973.

3-Phenyl-2-(2′-thienyl)thiophene
Mp 72–74 °C (Lit.[14] mp 75–76 °C).

IR ($CDCl_3$): 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.434 (m, 5 H), 7.30–6.85 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4, 129.8, 129.6, 128.0, 127.9, 126.3, 126.0, 125.7, 124.4, 124.0, 122.4, 118.6.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}S_2$: 346.3972; found: 346.3971.

2-Phenyl-3-(2′-thienyl)thiophene
Brown solid; mp 68–69 °C.

IR ($CDCl_3$): 3100, 3000, 1500, 1240, 1160, 940, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 765–7.47 (m, 2 H), 7.38–7.19 (m, 7 H), 7.08 (d, *J* = 5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.6, 129.8, 129.7, 128.0, 127.9, 126.3, 125.8, 125.7, 124.5, 123.9, 122.7, 118.7.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}S_2$: 346.3972; found: 346.3972.

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(12) The boronate salts were prepared as described in reference 11 starting from the commercially available boronic acids with the exception of the *o*-methoxyphenyl boronate salt, which was prepared via the organolithium route also described in reference 11.

(13) The use of CH_2Cl_2–hexane mixtures for chromatography was important as attempts to use EtOAc–hexanes or Et_2O–hexanes mixtures resulted in much lower isolated yields due to limited product solubility in these solvents.

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