Microwave-Mediated Suzuki–Miyaura Cross-Couplings of Thioether- and *ortho*-Substituted Methylphenylboronic Acid Esters

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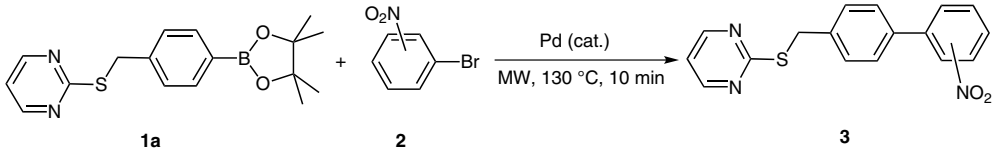
Abstract: Hiterto unsuccessful cross-couplings of *ortho*-substituted or thioether-substituted methylphenylboronates have now been achieved, under microwave conditions, enabling the synthesis of a library of novel biaryls. Tetrakis(triphenylphosphine)palladium and various bases, for example, sodium carbonate or cesium fluoride, were found to mediate the crucial C–C bond-forming cross-coupling reaction.

Key words: palladium, catalysis, cross-coupling, biaryls, microwaves

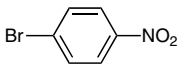
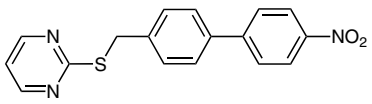
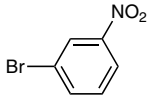
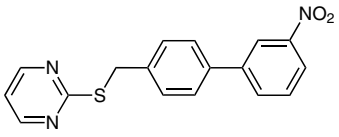
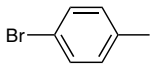
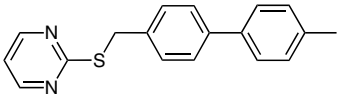
We have previously found that the attempted Suzuki–Miyaura (SM) coupling of sulfur-containing methylphenylboronic esters or *ortho*-substituted methylphenylboronic esters with aryl bromides was inefficient leading to mixtures of largely protodeborylated product or starting materials,[2] when employing standard microwave-mediated coupling conditions in water [$Pd(OAc)_2$, TBAB].[3] However, Itoh et al. recently found that $Pd(PPh_3)_4$ was an effective catalyst for the thermally mediated SM coupling of bromobenzenethioethers with aqueous Na_2CO_3 in toluene[4] which encouraged us to explore similar, albeit microwave-mediated, conditions for the coupling of our substituted methylphenylboronic acid esters (Scheme 1, example below).

A rapid screen of precatalysts, bases, and solvents using a parallel optimization method,[5] with automated solution dispensers, auto-sampler microwave, and an automated LC–MS analyzer, enabled us to determine suitable conditions for the coupling reactions of thioether-containing boronates **1** (see Supporting Information). The reaction optimization experiments were carried out on compound **1a** with 1-bromo-4-nitrobenzene (**2a**) under microwave irradiation at 130 °C for 10 minutes (Table 1).

Table 1 Opitimization of Reaction Conditions



1a + **2** → **3**

Entry	Aryl halide	Catalyst (mol%)	Conditions[6]	Product	Yield (%)[a]
1	**2a** 	5	A	**3a** 	91
2	**2b** 	3	B	**3a** 	85
3	**2c** 	5	A	**3c** 	50
4		3	C		81

[a] Isolated yields after purification by chromatography. Conditions A: **1a** (1.1 equiv), $Pd(PPh_3)_4$ (5 mol%), CsF (3 equiv), THF, 130 °C, 10 min, microwave irradiation (maximum power 300 W). Conditions B: **1a** (1.1 equiv), $Pd(PPh_3)_4$, Na_2CO_3 (3 equiv), toluene–EtOH–H_2O (1:1:1), 150 °C, 10 min, microwave irradiation (maximum power 300 W). Conditions C: **1a** (1.1 equiv), $Pd(PPh_3)_4$, Na_2CO_3 (3 equiv), toluene–EtOH–H_2O (1:1:1), 130 °C, 10 min, microwave irradiation (maximum power 300 W).

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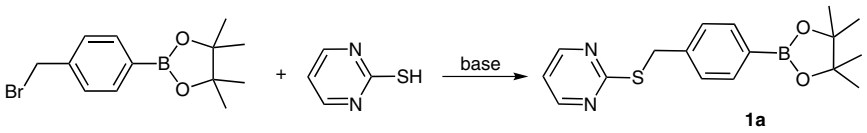
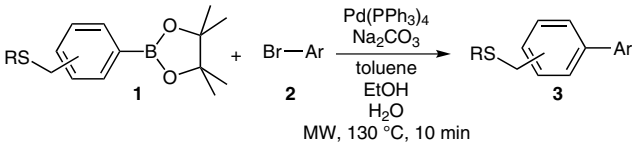
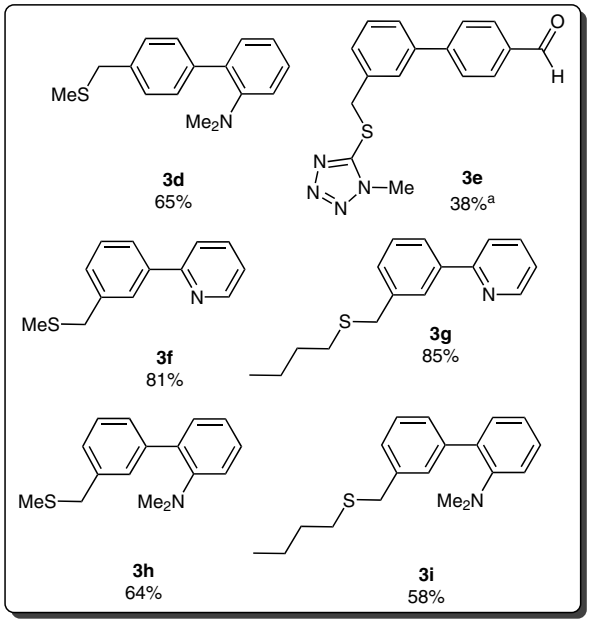


Scheme 1

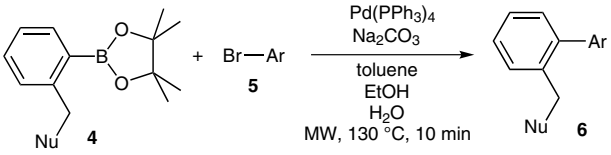


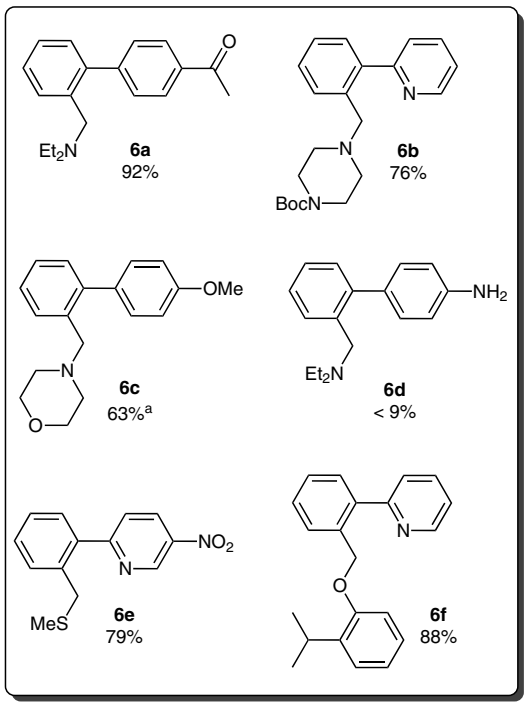


Scheme 2 Isolated yields given after purification by chromatography. [a] Mixture with biphenyl/boronic ester (84:16), calculated yield by ^{1}H NMR.

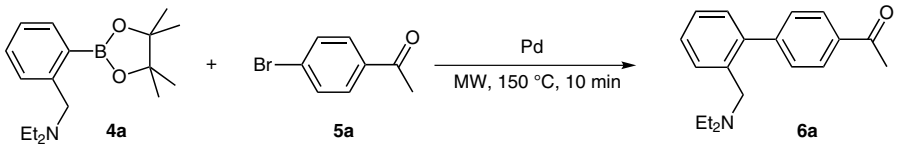
Table 1 summarizes some of the results obtained. The reaction was first achieved using an aryl bromide containing an electron-withdrawing group to ensure favorable coupling conditions. A number of salient observations can be made: high reaction temperatures in the microwave do not appear to be deleterious to reaction yields – at 150 °C an 85% yield for **3b** was observed (Table 1, entry 2) and at 130 °C, a 91% yield for **3a** was noted (Table 1, entry 1). An electron-rich aryl bromide, 1-bromotoluene (**2c**), was also tested, affording a moderate yield when using conditions A (e.g., 50% yield, Table 1, entry 3) although a better yield was observed when using conditions C (81% yield, Table 1, entry 4). Conditions C were deemed to be optimal since the biphenyl products were obtained in good yields employing a relatively low catalyst loading.

It is pertinent to mention that the SM coupling reaction is better if the thioether-substituted boronic ester is purified by chromatography on silica gel first. Hence, following the preparation of **1**, supported scavenger agents are usually unable to remove traces of thiol, which are known to act as poisons towards palladium catalysts.[4]





Scheme 4 Percentage yields given after purification by chromatography. [a] Mixture with protodeborylated product (87:13), calculated yield by ^{1}H NMR.



Scheme 3

A range of sulfur-containing phenylboronic acid pinacol esters were coupled in a SM reaction with several aryl bromides using the previously established conditions C (Scheme 2). The biaryl products **3** were generally obtained in very good yields, even with electron-rich aryl bromide coupling partners, although moderate yields were achieved when using a 2-substituted aryl bromide (e.g., 85% for **3g**, 58% for **3i**).

Following on from the success of the optimization process with thioether derivatives, a screen of catalysts, bases, ligands, and solvent systems was undertaken in order to optimize the coupling reactions of *ortho*-substituted boronates using 2-(*N*,*N*-diethylaminomethyl)phenylboronic acid pinacol ester (**4a**) as the boronate coupling partner and 4-bromoacetophenone (**5a**) as the aryl bromide for the SM coupling (Scheme 3, also Supporting Information, Figure S2).

The best conditions found were once again where $Pd(PPh_3)_4$ was used as precatalyst with either CsF as a base in THF or with K_3PO_4 or Na_2CO_3 as base in toluene–EtOH–H_2O (1:1:1). The latter conditions were selected for the SM coupling of 2-substituted phenylboronic esters in order to synthesize a library of 2-substituted biaryls **6** (Scheme 4). The latter were obtained mainly in good yields (e.g., 92% for **6a**, 88% for **6f**) and this appears to also operate for the coupling of a 2-substituted thioether methylphenylboronic acid ester (to afford **6e**), which, gratifyingly, satisfies both the criteria that we wished to resolve. However, a very low yield was observed for the aniline product **6d**.

Once the optimal conditions for the SM coupling of *ortho*-substituted phenylboronic esters were ascertained, the synthesis of a twenty-member library of *ortho*-substituted piperazin-1-ylmethylbiaryls was undertaken, which, post-

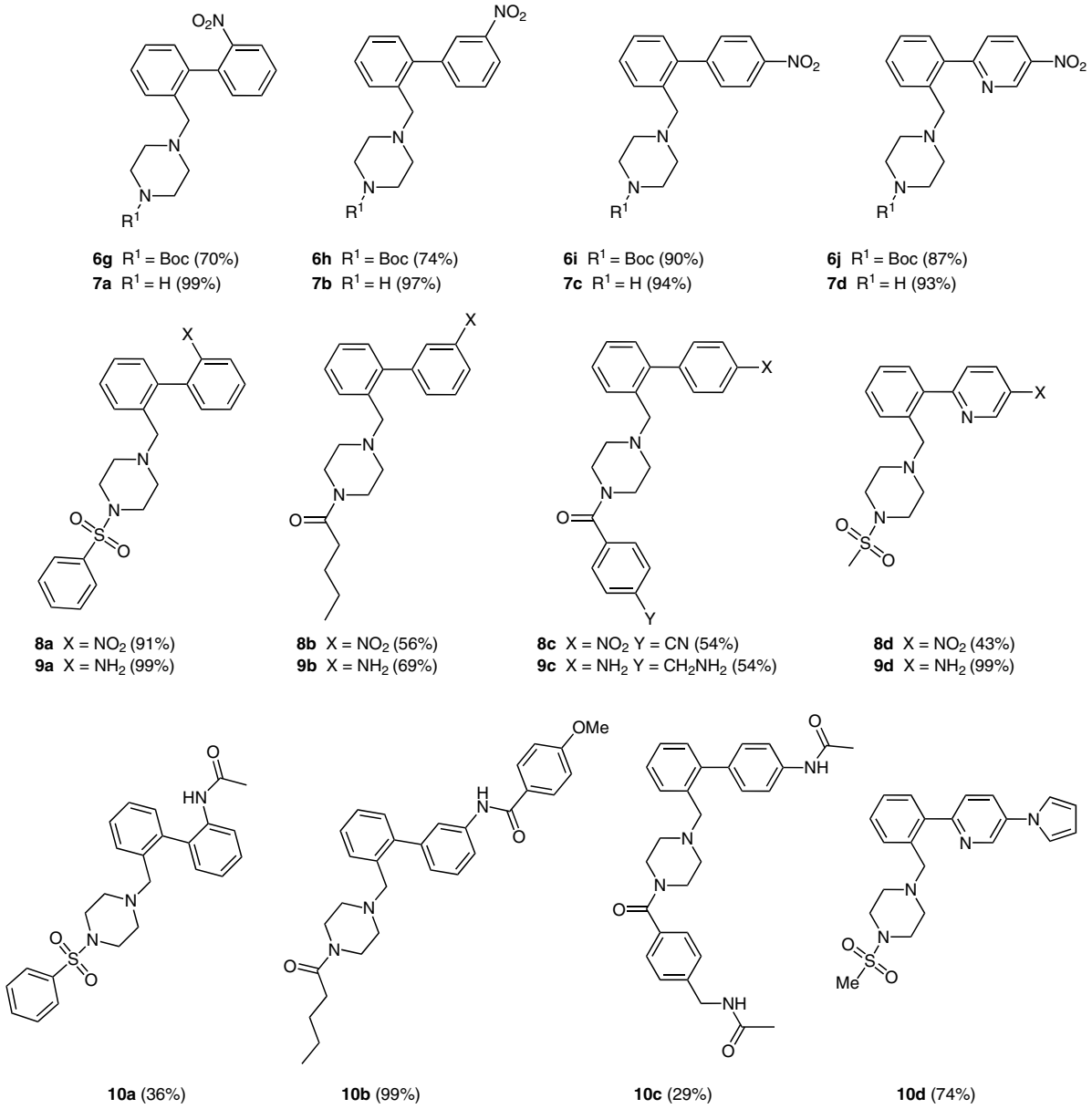


Figure 1

biphenyl synthesis (**6g–j**), used conditions recently reported by us. Hence, Boc group removal (TFA–CH_2Cl_2, then a basic wash), giving **7a–d**, was followed by piperazine functionalization to an amide or a sulfonamide, affording **8a–d**.[2c] The nitro group was reduced [flow-chemistry hydrogenation (H-Cube) catalyzed by Raney nickel], giving **9a–d**, and the resulting amino group was functionalized to an amide, a sulfonamide, or a pyrrole, finally yielding **10a–d** (Figure 1).

In conclusion, our biphenyl-building methodology relying on an initial nucleophilic displacement of a bromomethylbenzene boronic acid ester is now complete since it is now amenable to both 2-substituted and thioether-containing boronate starting materials. Applications of this reaction sequence include the synthesis of novel biphenyls, with the potential for drug discovery, and potential ligands **3f–i** for the synthesis of unsymmetrical SCN pincer palladacycles,[7] with potential for catalysis. Studies in the latter direction are currently underway, having already yielded a number of interesting pincer palladacycles,[8] and will be reported in due course.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(5) A total of 27 conditions were evaluated: catalysts: $PdCl_2$, $Pd(OAc)_2$, and $Pd(PPh_3)_4$; bases: CsF, K_3PO_4, and Na_2CO_3; solvents: H_2O, THF, and toluene–EtOH–H_2O (1:1:1).

(6) **General Procedure for the SM Coupling of Sulfur-Substituted Methylphenylboronic Esters Using Conditions A: 2-[(4′-Nitrobiphenyl-4-yl)methylthio]pyrimidine (3a)**
1a (164 mg, 0.5 mmol,), **2a** (111 mg, 0.55 mmol), CsF (228 mg, 1.5 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), and THF (2 mL) were placed in a sealed microwave vial and stirred under microwave irradiation (maximum power 300 W) at 130 °C for 10 min. The mixture was cooled to r.t., diluted with EtOAc (20 mL) and H_2O (10 mL), and extracted with EtOAc. The organic layer was washed with a sat. NaCl solution, dried over anhyd $MgSO_4$, filtered, and concentrated under reduced pressure to give 269 mg of an orange solid. The crude product was purified by chromatography on silica gel (hexane–EtOAc, 8:2) to give 147 mg of the expected product as a yellow solid in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, 2 H, *J* = 4.8 Hz), 8.29 (d, 2 H, *J* = 8.8 Hz), 7.72 (d, 2 H, *J* = 8.8 Hz), 7.57 (m, 4 H), 6.70 (dd, 1 H, $J_{1\text{ and }2}$ = 4.8 Hz), 4.47 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 157.3 (2 C), 147.2, 147.1, 138.8, 137.6, 129.9 (2 C), 127.7 (2 C), 127.5 (2 C), 124.1 (2 C), 116.7, 34.8 ppm. HRMS (ES): *m/z* calcd for $[C_{17}H_{13}O_2N_3S + H]^+$ 324.0801; found: 324.0805. Anal. Calcd for $C_{17}H_{13}N_3O_2S$: C, 63.1; H, 4.1; N, 13.0. Found: C, 62.9; H, 4.1; N, 12.9.
General Procedure for the SM Coupling of Sulfur-Substituted Methylphenylboronic Esters Using Conditions C: 2-[(3′-Nitrobiphenyl-4-yl)methylthio]pyrimidine (3b)
1a (125 mg, 0.38 mmol), 3-bromonitrobenzene (**2b**, 85 mg, 0.42 mmol), Na_2CO_3 (121 mg, 1.14 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), toluene (1 mL), EtOH (1 mL), and H_2O (1 mL) were placed in a sealed microwave vial and stirred under microwave irradiation (maximum power 300 W) at 130 °C for 10 min. The mixture was cooled to r.t., diluted with EtOAc (20 mL) and H_2O (10 mL), and extracted with EtOAc. The organic layer was washed with a sat. NaCl solution, dried over anhyd $MgSO_4$, filtered, and concentrated under reduced pressure to give 195 mg of a brown oil. The crude product was purified by chromatography on silica gel (hexane–EtOAc, 8:2) to give 104 mg of the expected product as a yellow solid in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, 2 H, *J* = 4.8 Hz), 4.41 (m, 1 H), 8.17 (dd, 1 H, J_1 = 7.9 Hz, J_2 = 2.2 Hz), 7.87 (d, 1 H, *J* = 7.9 Hz), 7.62–7.52 (m, 5 H), 6.98 (dd, 1 H, $J_{1\text{ and }2}$ = 4.8 Hz), 4.46 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 157.3 (2 C), 148.8, 142.5, 138.3, 137.5, 132.9, 129.9 (2 C), 129.7, 127.2 (2 C), 122.0, 121.8, 116.7, 34.8 ppm. HRMS (ES): *m/z* calcd for $[C_{17}H_{13}O_2N_3S+H]^+$ 324.0801; found: 324.0804. Anal. Calcd for $C_{17}H_{13}N_3O_2S$: C, 63.1; H, 4.1; N, 13.0. Found: C, 62.9; H, 4.0; N, 13.1.

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