Suzuki–Miyaura Cross-Couplings Mediated by *trans*-PdBr(*N*-Succ)(PPh₃)₂: A Convenient Synthetic Method for Diarylmethanes and Aryl(heteroaryl)-methanes

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Abstract: Diarylmethanes can be accessed efficiently by Suzuki–Miyaura cross-couplings of arylboronic acids with benzyl halides mediated by *trans*-PdBr(N-Succ)(PPh₃)₂. The methodology can be applied to the synthesis of aryl(heteroaryl)methanes. **Key words:** catalysis, palladium, pseudohalide, phosphine



Palladium(0)-catalysed carbon-carbon bond-forming processes are used widely in synthetic chemistry.^{1,2} The portfolio of catalyst systems available for the coupling of aryl and heteroaromatic components has increased commensurately with growing applications for such processes.^{3–5} Organ's recently developed PEPPSITM catalysts⁶ are of particular note. In the last few years we have exploited the reactivity of palladium(II) complexes⁷ possessing succinimide and related ligands in cross-coupling processes, for example, Sonogashira, Suzuki-Miyaura, and Stille. The synthesis of diarylmethanes⁸ is difficult using a variety of palladium catalyst systems,9 which led us to investigate the precatalyst, *trans*-PdBr(N-Succ)(PPh₃)₂ (1), for the cross-coupling of arylboronic acids with benzyl bromides 2.10 These reactions can be run at low palladium loadings (typically 1 mol%). For a few examples we were able to demonstrate that loadings as low as 0.01 mol%

SYNTHESIS 2009, No. 3, pp 0508–0510 Advanced online publication: 19.12.2008 DOI: 10.1055/s-0028-1083293; Art ID: Z20708SS © Georg Thieme Verlag Stuttgart · New York could be used on small-scale (0.8 mmol with respect to **2**). The central aim of this paper is to report convenient procedures for the gram-scale synthesis of diarylmethanes using exemplar cross-coupling substrates (Scheme 1). The broader scope of the methodology is also highlighted.

The reaction of 3-nitrobenzyl bromide (2a; 23 mmol) with phenylboronic acid (3a; 23 mmol) to give 1-benzyl-3-nitrobenzene (4a) was run initially using 0.1 mol% 1 at 60 °C (Procedure 1). A longer reaction time (40 h) was required than for the smaller-scale reaction (at 0.8 mmol), but pleasingly 4a was produced in 96% yield. Running the reaction under similar conditions, but using 1 at 0.01 mol% loading (Procedure 2), with increasing substrate quantities (0.116 mol), a 78% conversion into 4a was determined by ¹H NMR spectroscopy after 40 hours. Whilst unreacted 2a is inseparable from 4a by silica gel chromatography, heating the crude product mixture to 40 °C in aqueous ammonia in propan-2-ol for 15 hours allows 2a to be removed as the benzylammonium salt. The product 4a is then isolated by filtration through a short silica gel column in 70% yield.



^a Reactions were run at 60 °C, unless otherwise stated.

^b Amount of organoboronic acid used = 1.5 equiv.

 $^{\rm c}$ A small amount of protodeborylation was observed (~10%).

Scale-up was also carried out for the reaction of benzyl bromide (**2b**) with 4-fluorophenylboronic acid (**3b**) using 0.1 mol% of **1** at 60 °C for 40 hours, which afforded 1-benzyl-4-fluorobenzene (**4b**) in 88% yield (Procedure 1).

The broader scope of the methodology is exemplified by the cross-couplings of benzyl bromides or chlorides with a series of arylboronic acids or heteroarylboronic acids (Table 1).¹⁰

Both activated and deactivated arylboronic acids react with either benzyl bromide or benzyl chloride in good yields (entries 1 and 2, respectively). Several thiophene-2boronic acids are also effectively coupled (entries 3–6). Finally, cross-coupling of the hydrolytically sensitive furan-2-boronic acid with benzyl bromide is possible, provided that an excess of the boronic acid is used (entry 7).

In conclusion, we have developed a convenient method for the gram-scale synthesis of diarylmethanes. The broader scope of the method to give aryl(heteroaryl)methanes has been highlighted. Our methodology complements other recently reported conditions for the crosscoupling of benzyl chloride with various organoboronic acids [using Pd(PPh₃)₄].¹¹ The advantage of using precatalyst **1** is that both lower palladium loadings and lower reaction temperatures can be used.

All solvents were dried using standard procedures prior to use and stored under N₂. TLC analyses were performed using Merck 5554 aluminum-backed silica plates. Compounds were visualised using UV light (254 nm) and a solution of cerium sulfate tetrahydrate and phosphomolybdic acid in 10% aq H₂SO₄. Column chromatography was performed with silica gel 60 (35–70 µm) purchased from Aldrich. NMR spectra were recorded on a Jeol ECX400 or Jeol EX270 spectrometer, ¹H and ¹³C NMR spectra were referenced using residual solvent peak. Electron ionisation (EI) measurements were performed by Dr. T. A. Dransfield on a Fisons analytical VG Autospec instrument.

The benzyl halides and organoboronic acids are commercially available and were used as received: 3-nitrobenzyl bromide (98+%, Cat. No. A 14310), phenylboronic acid (98+%, Cat. No. A 14257), and benzyl bromide (99%, Cat. No. A 13535) were from Alfa Aesar; $Pd[(N-succ)Br(PPh_3)_2]$ (97%, Cat. No. 643742) was from Aldrich; and 4-fluorophenylboronic acid (97%, Cat. No. 006182) was from Fluorochem. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C.

Furan-2-boronic acid and thiophene-2-boronic acid were found to degrade rapidly at r.t. and repeatable results could only be achieved when these were stored at -20 °C and used within several weeks.

Procedure 1

Gram-Scale Synthesis of 1-Benzyl-3-nitrobenzene (4a) Using 0.1 mol% *trans*-Pd[(*N*-succ)Br(PPh₃)₂] (1)

A 250 mL three-necked flask was charged with 3-nitrobenzyl bromide (2a; 5.0 g, 23.1 mmol, 1.0 equiv), phenylboronic acid (3a; 2.82 g, 23.1 mmol, 1.0 equiv), and trans-Pd(N-succ)Br(PPh₃)₂ (18.7 mg, 23.1 µmol, 0.1 mol%) under N2. Degassed THF (58 mL) was added via cannula and the mixture was stirred at r.t. (ca. 23 °C) for 10 min until the starting materials were fully dissolved. A solution of anhyd Na2CO3 (2 M in degassed H2O, 29 mL) was added via syringe. The reaction flask was fitted with a reflux condenser under a stream of N₂. The mixture was then stirred vigorously and heated to 60 °C for 40 h. The mixture was cooled to r.t. and extracted with Et₂O (2×50 mL). The combined organic phases were dried (Na_2SO_4) , filtered, and evaporated with silica gel (50 g). The crude product adsorbed on silica gel was transferred onto a short silica gel column. Elution with PE-Et₂O (100:0 \rightarrow 90:10, v/v) gave the desired 1-benzyl-3-nitrobenzene (4a) as a light yellow oil; yield: 4.71 g (96%).

¹H NMR (400 MHz, CDCl₃): $\delta = 8.09-8.05$ (m, 2 H), 7.52 (d, J = 7.6 Hz, 1 H), 7.47–7.43 (m, 1 H), 7.33 (t, J = 7.3 Hz, 2 H), 7.25 (t, J = 7.3 Hz, 1 H), 7.19 (d, J = 7.2 Hz, 2 H), 4.08 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 148.4, 143.2, 139.3, 135.1, 129.3, 128.9, 128.8, 126.7, 123.7, 121.3, 41.5.

MS (EI): m/z (%) = 213 ([M⁺], 100), 196 (21), 165 (83), 152 (32).

Procedure 2

Gram-Scale Synthesis of 1-Benzyl-3-nitrobenzene (4a) Using 0.01 mol% *trans*-Pd[(*N*-succ)Br(PPh₃)₂] (1)

A 1000 mL three-necked flask was charged with 3-nitrobenzyl bromide (2a; 25.0 g, 115.7 mmol, 1.0 equiv), phenylboronic acid (3a; 14.11 g, 115.7 mmol, 1.0 equiv), and trans-Pd(N-succ)Br(PPh₃)₂ (9.4 mg, 11.6 µmol, 0.01 mol%) under N₂. Degassed THF (289 mL) was added via cannula and the mixture was stirred at r.t. (ca. 23 °C) for 10 min until the starting materials were fully dissolved. A solution of anhyd Na₂CO₃ (2 M in degassed H₂O, 145 mL) was added via syringe. The reaction flask was fitted with a reflux condenser under a stream of N₂. The mixture was then stirred vigorously and heated to 60 °C for 40 h after which time the reaction reached 78% conversion (¹H NMR spectroscopic analysis). The mixture was cooled to r.t. and extracted with Et_2O (2 × 200 mL). The combined organic phases were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was suspended in a mixture of 35% aq ammonia and propan-2-ol (1:1, v/v) and heated to 40 °C for 15 h after which time the remaining 3-nitrobenzyl bromide (2a) was completely consumed (TLC). The mixture was extracted with Et_2O (3 × 200 mL), the combined organic phases were then washed with 6 M aq HCl $(3 \times 100 \text{ mL})$, dried (Na₂SO₄), filtered, and evaporated with silica gel (100 g). The crude product adsorbed on silica gel was transferred onto a short silica gel column. Elution with PE-Et₂O (100:0 \rightarrow 90:10, v/v) gave the desired 1-benzyl-3-nitrobenzene (4a)¹² as a light yellow oil; yield: 17.19 g (70%). The characterisation data (NMR, MS) were identical to those reported above.

Gram-Scale Synthesis of 1-Benzyl-4-fluorobenzene (4b) Using 0.1 mol% *trans*-Pd[(*N*-succ)Br(PPh₃)₂] (1) (Procedure 1)

A 1000 mL three-necked flask was charged with benzyl bromide (**2b**; 12.5 g, 73.1 mmol, 1.0 equiv), 4-fluorophenylboronic acid (**3b**; 10.23 g, 73.1 mmol, 1.0 equiv), and *trans*-Pd(*N*-succ)Br(PPh₃)₂ (59.1 mg, 73.1 µmol, 0.1 mol%) under N₂. Degassed THF (183 mL) was added via cannula and the mixture was stirred at r.t. (ca. 23 °C) for 10 min until the starting materials were fully dissolved. A solution of anhyd Na₂CO₃ (2 M in degassed H₂O, 91 mL) was added via syringe. The reaction flask was fitted with a reflux condenser under a stream of N₂. The mixture was then stirred vigorously and heated to 60 °C for 40 h after which time the reaction reached 96% conver-

sion (by ¹H NMR spectroscopic analysis). The mixture was cooled to r.t. and extracted with Et₂O (2×100 mL). The combined organic phases were dried (Na₂SO₄), filtered, and evaporated with silica gel (100 g). The crude product adsorbed on silica gel was transferred onto a short silica gel column. Elution with PE gave the desired 1-benzyl-4-fluorobenzene (**4b**)¹³ as a colourless oil; yield: 12.02 g (88%).

¹H NMR (400 MHz, CDCl₃): δ = 7.30 (t, *J* = 7.3 Hz, 2 H), 7.23–7.12 (m, 5 H), 6.97 (t, *J* = 8.7 Hz, 2 H), 3.96 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 161.4 (d, $J_{C,F}$ = 243.9 Hz), 140.9 (d, $J_{C,F}$ = 1.0 Hz), 136.7 (d, $J_{C,F}$ = 3.2 Hz), 130.3 (d, $J_{C,F}$ = 7.8 Hz), 128.8, 128.5, 126.2, 115.2 (d, $J_{C,F}$ = 21.2 Hz), 41.0.

MS (EI): *m*/*z* (%) = 186 ([M⁺], 100), 171 (9), 165 (28), 109 (18), 91 (14).

The characterisation data for the compounds listed in Table 1 can be found in reference 10.

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