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Practical methylation of aryl halides by Suzuki–Miyaura coupling

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Abstract

A number of aryl halides (X = Cl, Br, I) can be converted to the corresponding toluenes in an operationally simple manner using trimethylboroxine (TMB) as a partner for palladium-catalysed Suzuki–Miyaura coupling. © 2000 Elsevier Science Ltd. All rights reserved.

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In the course of recent studies we became interested in methods for regiospecific incorporation of a methyl group into aromatic moieties. An obvious strategy is a metal-catalysed cross-coupling reaction of an organometallic methyl species ‘MeM’ and an aryl halide ArX (where M = Sn, Mg, Zn, B, Al. . .). In particular, the Suzuki–Miyaura coupling (M = B) appeared attractive to us, with mild conditions, broad functional group tolerance, non-toxic and easily removed by-products and conveniently handled reagents as notable features.¹

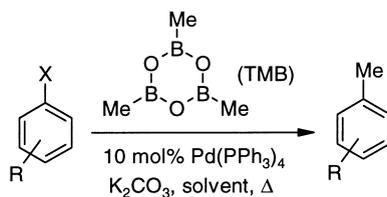
The prominent variant of this reaction is sp^2 – sp^2 coupling, although sp^3 – sp^2 coupling is also well established.^{2–7} There are limited reported examples using *methyl*boron derivatives; methylboronic acid (MBA) has been moderately useful to date,^{4–6} whereas methylboranes derived from 9-BBN are more reactive but less readily available.^{2,3,7} We were discouraged from the use of MBA because it is expensive and not readily available.

We now report that the anhydride, trimethylboroxine (TMB),[‡] is a useful and cheaper alternative reagent for methylation (Scheme 1). It has been used previously as a methylating agent for nickel catalysed coupling with allylamines.^{8,9}

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‡ Trimethylboroxine is commercially available on a large scale from Callery Chemical Co., Pittsburgh, PA 15230, USA.



Scheme 1.

A number of aryl halides were investigated to test the scope of the method (Table 1). Reactions were conducted at 100–115°C using tetrakis(triphenylphosphine)palladium(0) as catalyst, inexpensive potassium carbonate as base and one equivalent of the trimeric TMB.

The results shown in Table 1 are largely unoptimised,⁶ although preliminary optimisation has been carried out with the model case of 4-bromobenzophenone. The usual broad functional group tolerance of Suzuki–Miyaura coupling is mirrored in our results.

Methylation of electron-poor aryl bromides is efficient (entries 1–3), whereas with more electron rich substrates (entry 4), prolonged reaction times are required, although these can be shortened by the use of the polar solvent DMF at ca. 115°C.

Aryl chlorides are usually more readily available (and hence cheaper) than the corresponding aryl bromides or iodides, and pleasingly electron-poor chlorides, including a heteroaromatic chloride,⁶ provide the methylated products in good yield (entries 5–7). With aqueous dioxane as solvent, TLC analysis indicated complete consumption of starting material within a few hours (entries 6 and 7). Of note is the dimethylation of a dichloro substrate (entry 7) which indicates that nitrotoluenes can enter into the cross-coupling.[§] Significantly, entries 8 and 9 (naphthyl halides) demonstrate that, under largely unoptimised conditions, substrates without activating groups present can also be methylated in moderate to good yield.[¶] Yields obtained with the cheaper TMB are comparable to those obtained with MBA.

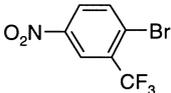
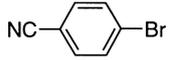
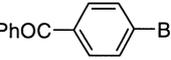
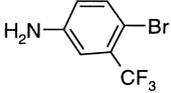
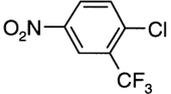
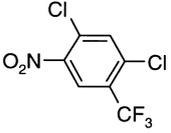
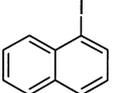
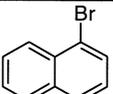
Using 4-bromobenzophenone as substrate, the effect of different bases, solvents, catalysts and methyl transfer reagents was investigated, primarily to address reaction rate. A number of experiments to generate relative data (cf. control conditions: Table 1, method A) were carried out using an SK-233TM workstation with on-line HPLC analysis. The inexpensive base potassium carbonate was one of the better studied, although cesium bases led to the highest conversions (e.g. 95% isolated yield with Cs₂CO₃). In the absence of base, only low level conversion is achieved. Aqueous dioxane or toluene were notable improvements over control conditions A (dioxane). Here isolated yields were essentially quantitative and, with the former, consumption of starting bromide was rapid. The best catalyst studied was PdCl₂(dppf), giving complete conversion within 3 h.^{**} Reactions with TMB in aqueous dioxane and with MBA in dioxane were both complete within 3 h. Using TMB in aqueous dioxane may involve in situ generation of MBA since hydration of TMB is a facile process.¹¹ MBA esters MeB(OR)₂ were inferior to TMB.

[§] Treatment of the dichloride with Me₃Al¹⁰ (1.1 equiv. DMF, 10 mol% Pd(PPh₃)₄, 70°C internal, overnight) leads to monomethylation *ortho* to the nitro function (84% yield).

[¶] Complete consumption of 5-bromo-*m*-xylene was achieved under conditions C (24 h) as evidenced by ¹H NMR and TLC analysis of the crude product; however, the purified yield of mesitylene was low, possibly due to volatility.

^{**}The cheaper and more robust Pd(OAc)₂/4PPh₃ combination has proved comparable to Pd(PPh₃)₄ for certain substrates.

Table 1
Methylation of aryl halides with trimethylboroxine (TMB)

Entry	Substrate	Reaction Time, h	Yield, % ^a	Method ^b
1		23	75 [#]	A
2		23	64 [#]	A
		23	81	B
3		27	82	A
		23	86	B
4		42	68 [#]	A
		71	90	A
		17	95	B
5		21	54	A
		46	72	A
		17	40 ^c	B
6		24	77	C
7		6	84 ^d	C
8		28	55 [#]	A
9		71	72 [#]	A
		23	57 [#]	B

^a Yield of substituted toluene after chromatography, calculated from ¹H NMR of isolated Me/X mixtures where indicated (#). Products were identified by comparison to authentic materials and/or ¹H, ¹³C NMR and HRMS. Reactions were conducted on 1g scale with 10 mol% Pd(PPh₃)₄, 3 equiv K₂CO₃, 1 equiv TMB and 10 mL solvent.

^b **A** = 1,4-dioxane, reflux; **B** = DMF, 115-120°C; **C** = 10% aq. 1,4-dioxane, reflux.

^c Minor amounts of *N,N*-dimethyl-3-nitro-2-pyridinamine also isolated.

^d Dimethyl product isolated.

In conclusion, trimethylboroxine (TMB) is a practical methylating agent for a variety of aryl halides under palladium catalysis.

Typical experimental procedure (entry 7)

1,5-Dichloro-2-nitro-4-(trifluoromethyl)benzene (1.02 g, 3.92 mmol), potassium carbonate (1.63 g, 11.76 mmol), Pd(PPh₃)₄ (0.45 g, 0.39 mmol), 10% aq. 1,4-dioxane (10 mL) and TMB

(0.55 mL, 3.92 mmol) were charged to a flask and the contents heated to 105–115°C (oil bath temperature) under nitrogen for 6 h and then stirred overnight at ambient temperature. The reaction mixture was filtered through a pad of Celite[®], washed with THF and concentrated in vacuo. Flash column chromatography (SiO₂, 10:1 hexane:Et₂O) afforded 1,5-dimethyl-2-nitro-4-(trifluoromethyl)benzene as a low melting solid, 0.72 g (84%); R_f 0.45 (5:1 hexane:Et₂O); ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.30 (s, 1H), 2.65 (s, 3H), 2.54 (q, ⁵J(H,F) = 1.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 146.5 (bs), 142.3 (q, ³J(C,F) = 1.5 Hz), 137.5 (q, ⁵J(C,F) = 1.0 Hz), 136.5 (bs), 127.8 (q, ²J(C,F) = 31.7 Hz), 123.3 (q, ¹J(C,F) = 273.6 Hz), 122.7 (q, ³J(C,F) = 5.4 Hz), 20.3 (s), 19.0 (q, ⁴J(C,F) = 2.4 Hz); LRMS (EI⁺) *m/z* (relative intensity) 219 (M⁺, 22), 202 (100), 189 (5); HRMS (EI⁺) *m/z* calcd for C₉H₈NO₂F₃ 219.0507, found 219.0496.

Acknowledgements

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