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A simple and practical protocol for the palladium-catalyzed cross-coupling of boronic acids with methyl iodide

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A combination of palladium acetate and tri-1-naphthylphosphine was found to be a highly efficient catalyst system for the cross-coupling of arylboronic acids with methyl iodide at room temperature. The new process allows for a convenient introduction of methyl groups into various functionalized arenes under mild conditions. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: palladium; catalysis; cross-coupling reaction; boronic acid; methyl iodide

Palladium-catalyzed cross-coupling reactions of boronic acids have found widespread applications in organic synthesis, since they are easily performed and show excellent tolerance of functional groups.[1,2] Numerous protocols have been disclosed for the Suzuki coupling of aryl or vinyl boronic acids with vinyl,[3,4] aryl,[5] benzyl,[6] allyl,[7] and other carbon electrophiles.[8,9] However, only a few examples are known involving non-activated sp^3-hybridized electrophiles, and they require rather elaborate conditions.[10–16]

The reluctance of unactivated alkyl halides to oxidatively add to palladium(0) and the pronounced tendency of alkyl–palladium complexes to undergo β-hydride elimination are generally believed to be equally responsible for the difficulty in performing such reactions.[10–13] As a consequence, sensitive custom-made ligands that are both electron rich and sterically demanding have appeared, until now, to be indispensable for achieving reasonable yields in this type of transformation.[10–14]

We now found that for the cross-coupling of arylboronic acids with methyl iodide, which represents an unactivated alkyl halide without β-hydrogens, a much simpler reaction protocol is highly efficient.

We were interested in this particular cross-coupling since it potentially represented an attractive method for the introduction of methyl groups into functionalized molecules, especially if the transformation could be performed with commercially available, easy-to-use reagents and catalysts. In order to identify a suitable catalyst system for this type of transformation, we chose the coupling of phenylboronic acid with methyl iodide according to Scheme 1 as a model reaction and tested several palladium–phosphine complexes under various conditions (Table 1).

The nature of the phosphine ligand had a strong influence on the reaction outcome (entries 1–10). Using triphenylphosphine, only moderate turnovers and low yields were detected. Although changing the electron-donating ability of the ligand did not lead to satisfactory yields, the use of sterically demanding ligands significantly improved the catalyst performance. The best results were obtained with bulky tri-1-naphthylphosphine and with DPPF or DPE-Phos, both chelating phosphines with a large bite angle.

Since with tri-*o*-tolylphosphine only moderate yields were obtained, this ligand was used in further experiments to probe the efficiency of different bases and solvents (entries 11–20). Among the bases tested, potassium phosphate was found to be the most effective (entries 6, 11, 12). Like in other cross-coupling reactions involving boronic acids, the addition of water was found to be beneficial (entries 6, 14).[9,17,18] The reaction gave good yields in ethers, benzene and chlorinated solvents, but highly polar aprotic solvents were less effective (entries 6, 11–20). We considered tetrahydrofuran (THF) to be the most versatile solvent, since it solubilizes many functionalized boronic acids.

Overall, palladium acetate–tri-1-naphthylphosphine appeared to be the catalyst system of choice, since this phosphine not only showed a high activity, but is also inexpensive, robust and easy to handle. In combination with K_3PO_4 as the base and wet THF as the solvent, excellent yields were obtained

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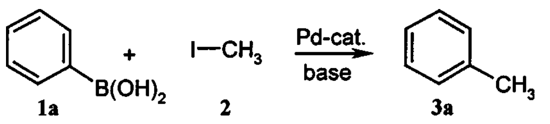
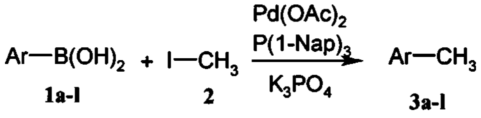


Scheme 1. Coupling of benzeneboronic acid and methyl iodide.



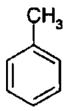
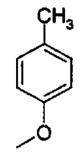
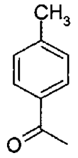
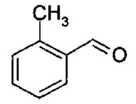
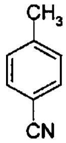
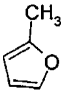
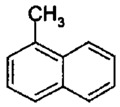
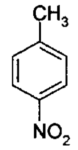
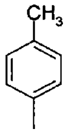
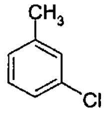
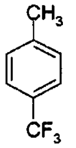
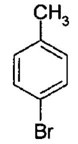
Scheme 2. Coupling of benzeneboronic acid and methyl iodide.

Table 1. Effects of the reaction conditions[a] on the product distribution

Entry	Ligand	Base	Solvent	Yield (%)
1	PPh_3	K_2CO_3	THF	25
2	PCy_3	K_2CO_3	THF	29
3	$P(p\text{-MeO-}C_6H_4)$	K_2CO_3	THF	25
4	$P(p\text{-Cl-}C_6H_4)$	K_2CO_3	THF	19
5	$P(1\text{-Fur})_3$	K_2CO_3	THF	10
6	$P(o\text{-Tol})_3$	K_2CO_3	THF	55
7	DPE-Phos	K_2CO_3	THF	70
8	$P(1\text{-Nap})_3$	K_2CO_3	THF	65
9	DPPF	K_2CO_3	THF	69
10	BINAP	K_2CO_3	THF	31
11	$P(o\text{-Tol})_3$	KF	THF	25
12	$P(o\text{-Tol})_3$	K_3PO_4	THF	93
13[b]	$P(o\text{-Tol})_3$	K_2CO_3	THF	41
14	$P(o\text{-Tol})_3$	K_2CO_3	Benzene	85
15	$P(o\text{-Tol})_3$	K_2CO_3	Et_2O	67
16	$P(o\text{-Tol})_3$	K_2CO_3	DCM	62
17	$P(o\text{-Tol})_3$	K_2CO_3	DMF	5
18	$P(o\text{-Tol})_3$	K_2CO_3	NMP	20
19	$P(o\text{-Tol})_3$	K_2CO_3	DME	20
20	$P(o\text{-Tol})_3$	K_2CO_3	DMSO	13
21[c]	$P(Nap)_3$	K_3PO_4	THF	95

[a] Conditions: 1.0 mmol phenylboronic acid, 1.5 mmol methyl iodide, 0.03 mmol $Pd(OAc)_2$, 0.09 mmol ligand (0.05 for chelating phosphines), 2 mmol base, 2 mmol H_2O, 20 °C, 16 h.
[b] Without H_2O.
[c] 0.003 mmol $Pd(OAc)_2$, 0.009 mmol ligand.

Table 2. Palladium-catalyzed synthesis of methyl arenes[a]

Product	Yield[b] (%)	Product	Yield[b] (%)
	86 (92)		54 (88)
	58 (78)		80 (80)
	74 (87)		3 (90)
	54 (60)		89 (95)
	63 (67)		26 (98)[c]
	5 (80)[c]		54 (95)[c]

[a] Conditions: 1.0 mmol arylboronic acid, 1.5 mmol methyl iodide, 0.03 mmol $Pd(OAc)_2$, 0.07 mmol $P(1\text{-Nap})_3$, 2.0 mmol K_3PO_4, 2.0 mmol H_2O, 20 °C, THF; isolated yields.
[b] GC-determined yields in parentheses.
[c] The low isolated yields are due to the high volatility of the compound, which precluded an easy separation from the solvent.

even with low amounts of this catalyst (entry 21). These conditions are similar to those employed for the synthesis of arylacetic acid derivatives.[9]

In order to investigate the scope of the transformation, we applied the best protocol to the methylation of a variety of arylboronic acids (Scheme 2, Table 2). Gratifyingly, the reaction was found to be generally applicable to a large number of boronic acids. Both electron-rich and electron-poor substrates gave equally high yields, and many functional groups were tolerated. Boronic acids containing halo, keto, cyano, trifluoromethyl, formyl, or nitro groups were successfully converted. Even sterically demanding 1-naphthylboronic acid and sensitive 1-furylboronic acid were successfully methylated. It is also worth mentioning that no competing formation of biaryls was observed when *p*-bromophenylboronic acid was employed as the substrate.

In summary, the palladium-catalyzed cross-coupling reaction between arylboronic acids and methyl iodide disclosed here represents a mild and general method for the introduction of methyl groups into aromatic rings. The simple reaction protocol, which involves only air-stable, easy-to-handle chemicals and does not require dry solvents, makes this reaction a valuable alternative to the existing methods.

Synthesis of 4-nitrotoluene (3j)

A 20 ml flask was charged with palladium acetate (6.73 mg, 0.03 mmol), tri-1-naphthylphosphine (28.1 mg, 0.07 mmol) and an excess of potassium phosphate (424.6 mg, 2.00 mmol). The reaction vessel was purged with argon, then methyl iodide (93 µl, 1.50 mmol), a solution of *p*-nitrophenylboronic acid (167 mg, 1.00 mmol) in THF (4 ml), and water (36 µl, 2.0 mmol) were added via syringe, and the reaction mixture was stirred at 20 °C overnight. The reaction slurry was then poured into water (30 ml) and extracted three times with 10 ml portions of pentane. The combined organic layers were dried over $MgSO_4$, filtered through a plug of silica, and the volatiles were carefully distilled off. This way, **3j** was obtained as a white solid (123.0 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, tetramethylsilane (TMS)), δ ppm: 8.11 (d, ^3J(H,H) = 9 Hz, 2H), 7.31 (d, ^3J(H,H) = 9 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS), δ ppm: 146.3, 146.0, 130.1, 123.9, 22.0. MS (ion trap): m/z (%): 137(91) [M^+], 107(81), 91(100), 79(26), 77(34), 65(86), 63(24). The reactions in Tables 1 and 2 were performed accordingly. The products in Table 2 were isolated by column chromatography on SiO_2 and characterized by means of ^{1}H and ^{13}C NMR, as well as by gas chromatography–mass spectrometry.

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