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Microwave-Assisted Synthesis of Pinacol Boronates from Aryl Chlorides Catalyzed by a Palladium/Imidazolium Salt System

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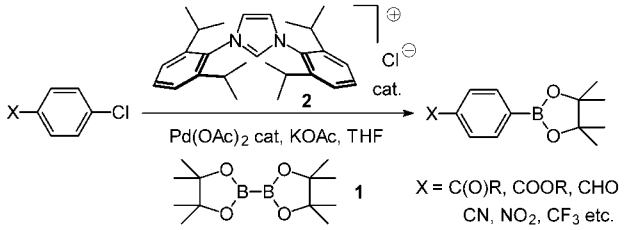
ABSTRACT



Aryl chlorides bearing electron-withdrawing groups react with bis(pinacol)borane 1 to give aryl boronates in good to excellent yields in the presence of a catalyst formed in situ from $Pd(OAc)_2$ and the imidazolium chloride 2. The reaction is greatly accelerated when carried out under microwave heating.

The widespread use of aryl boronic acids or aryl boronates in various metal-catalyzed C−C bond-forming reactions has created a substantial demand for these versatile nucleophiles.[1−3] While the conventional methods for their synthesis are not very compatible with polar substituents, a complementary entry into this class of compounds has recently been described which exhibits a much more favorable functional group tolerance. It consists of the palladium-catalyzed cross coupling of aryl bromides, iodides, or triflates with either tetraalkoxy diboron derivatives such as **1**[4] or pinacolborane, respectively.[5−7]

Aryl chlorides are the most attractive set of substrates due to their low cost and ready availability; however, they are not amenable to boronate formation under the conditions originally described ($PdCl_2$(dppf) cat., KOAc, DMSO, 80 °C).[5] Only very recently, Miyaura outlined a modified catalyst system comprising $Pd(dba)_2$ and PCy_3, which expands the scope of the method to aryl chlorides as well.[8] Prompted by this report, we want to disclose our preliminary studies on an alternative procedure which exploits the inherent advantages of imidazolium salts as cheap, readily available, and fully air stable substitutes for PCy_3.

Deprotonation of N,N′-disubstituted imidazolium salts affords the corresponding N-heterocyclic carbenes (NHC) which are excellent ligands for transitions metals in different oxidation states.[9] By virtue of their pronounced σ-donor but very weak π-acceptor properties, they render the resulting

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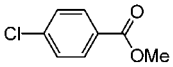
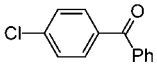
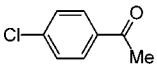
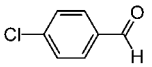
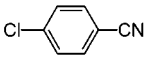
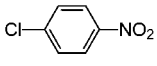
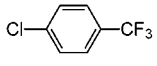
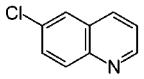
complexes very electron rich and hence facilitate all kinds of oxidative insertion processes. This notion is evident from previous applications of metal−NHC complexes to various types of cross coupling reactions[10] and olefin metathesis,[11,12] to mention just the most successful cases. The fact that the NHC complexes can usually be formed in situ and do not need to be isolated constitutes a significant advantage in practical terms.

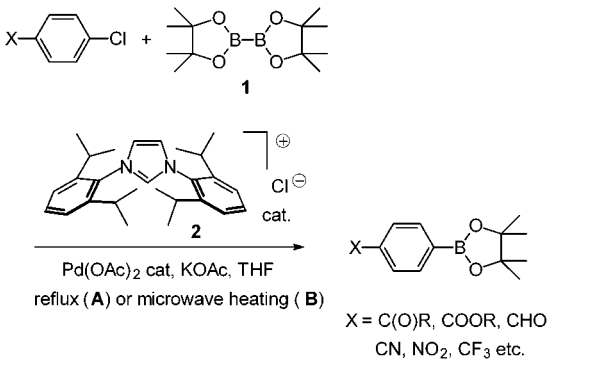
As outlined below, this concept also nicely pertains to the envisaged borylation of aryl chlorides. Specifically, reaction of a functionalized aryl chloride with the commercially available diboron derivative **1**[4] in the presence of $Pd(OAc)_2$ as the cheapest palladium source, imidazolium salt **2**,[13] and KOAc in refluxing THF affords the desired aryl pinacolboronates in good to excellent yields (Table 1, method **A**).[14] GC inspection of the crude mixtures shows that the conversion is quantitative in most cases, while some loss of products cannot be avoided during workup due to the physical properties of these compounds. As expected, the reaction is compatible with various substituents including ester, ketone, aldehyde, nitrile, nitro, and trifluoromethyl groups (Scheme 1). The use of THF as the solvent instead of DMSO[5a] is

Table 1. Synthesis of Pinacol Arylboronates from Aryl Chlorides Catalyzed by $Pd(OAc)_2$ and the Imidazolium Chloride **2** either in Refluxing THF (Method **A**) or under Microwave Heating (Method **B**)

substrate	[a]	mol%[b]	t (min)[b]	GC (%)	Yield[c]
	**A**	3	360	100	85%
	B	6/6	10/10	95	72%
	**A**	6	240	81	74%
	B	6/6	10/10	84	63%
	**A**	3	360	98	73%
	B	6/6	10/10	88	57%
	**A**	3	300	100	72%
	B	6/6	10/10	100	63%
	**A**	3	240	100	90%
	B	6	10	100	
	**A**	3	300	100	63%
	B	6	10	90	
	**A**	3	300	100	77%
	B	6/6	10/10	100	61%
	**A**	6	360	100	53%[d]
	B	6/6	10/10	66	

[a] Method **A**: aryl chloride (1 equiv), compound **1** (1.16 equiv), $Pd(OAc)_2$ (mol % as indicated), imidazolium chloride **2**, KOAc (2.5 equiv), THF, reflux. Method **B**: aryl chloride (1 equiv), compound **1** (1.16 equiv), $Pd(OAc)_2$ (mol % as indicated), imidazolium chloride **2**, KOAc (2.5 equiv), THF, 110 °C (sealed tube), microwave heating. [b] Two values indicate that the catalyst had to be replenished once. [c] Isolated yields. [d] Purified by Kugelrohr distillation.

Scheme 1



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(14) **Representative procedure for method A**: A solution of 4-chlorobenzoic acid methyl ester (171 mg, 1.0 mmol), 4,4,5,5-tetramethyl[1,3,2]-dioxaborolane **1** (294 mg, 1.16 mmol), KOAc (245 mg, 2.50 mmol), $Pd(OAc)_2$ (6.70 mg, 0.03 mmol), and imidazolium chloride **2** (26 mg, 0.06 mmol) in THF (12 mL) is refluxed under Ar for 6 h. For workup, the reaction mixture is filtered through a short pad of silica, the filtrate is evaporated, and the residue is purified by flash chromatography (silica, ca. 10 cm, ∅ 2 cm, hexane/EtOAc, 10/1 → 4/1) to give 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)benzoic acid methyl ester (222 mg, 85%) as a colorless solid. The analytical and spectroscopic data are in full agreement with those previously reported, cf. ref 5a.

beneficial from a practical point of view. Electron-rich substrates such as 4-methoxychlorobenzene or 3,5-dimethoxychlorobenzene, in contrast, lead to significantly lower yields due to competing reduction of their C−Cl bonds.

A particularly noteworthy aspect concerns the very significant rate acceleration that can be reached if the borylation is carried out under dielectric heating using microwave technology (method **B**).[15,16] This allows the reduction of the overall reaction time from several hours to 10−20 min without affecting the yields. A somewhat higher catalyst loading, however, turned out to be necessary because the precipitation of Pd black is fast under these conditons.

Since the available equipment allows us to perform these reactions in preparatively useful amounts (up to ca. 0.5 g scale), we believe that this simple and rapid protocol for aryl boronate formation is particularly relevant for combinatorial chemistry and high-throughput syntheses.[7] Studies along those lines and further investigations into the favorable properties of metal−NHC complexes[17] are underway and will be reported soon.

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(15) **Representative procedure for method B** (SAFETY ASPECT): As described below, the catalyst tends to decompose under microwave heating with formation of a precipitate likely consisting of (colloidal) palladium black. Although no safety hazards have ever been encountered when applying method **B**, it must be kept in mind that microwave irradiation of metallic particles can result in substantial overheating. Therefore, the use of equipment allowing the automatic control of temperature and pressure in the reaction flask is strongly recommended. A 10 mL SmithProcess vial containing a magnetic stir bar is charged with 4-(trifluoromethyl)chlorobenzene (94 mg, 0.52 mmol), 4,4,5,5-tetramethyl[1,3,2]dioxaborolane **1** (157 mg, 0.62 mmol), KOAc (118 mg, 1.20 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), imidazolium chloride **2** (26 mg, 0.06 mmol), and THF (4.5 mL). The vial is sealed and the suspension is heated to 110 °C for 10 min in a microwave oven, with constant control of the reaction temperature and the internal pressure in the vial (Smith Creator reactor, Personal Chemistry, Konstanz, Germany). After that time, the suspension is replenished with the same amounts of $Pd(OAc)_2$ and imidazolium chloride **2**, and the mixture is reexposed to dielectric heating (110 °C) for another 10 min. For workup, the insoluble residues are filtered off through a short pad of silica, the filtrate is evaporated, and the product is purified by rapidly passing it through a small silica gel column (ca. 5 cm, ∅ 2 cm) using hexane/EtOAc (10/1) as the eluent. This affords 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-benzotrifluoride as colorless crystals (86 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.3 Hz, 2H), 7.61 (d, 2H), 1.35 (s, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.0, 132.8 (J_{CF} = 32 Hz), 124.3 (J_{CF} = 3.8 Hz), 124.1 (J_{CF} = 272 Hz), 84.3, 24.8. ^{11}B NMR (96 MHz, $CDCl_3$): δ = 30.6. MS: *m/z* (rel intensity) 272 ([M^+], 19), 257 (100), 229 (9), 215 (5), 186 (90), 173 (84), 153 (6), 85 (17), 58 (23), 43 (32).

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