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Mild and General Conditions for the Cross-Coupling of Aryl Halides with Pentafluorobenzene and Other Perfluoroaromatics

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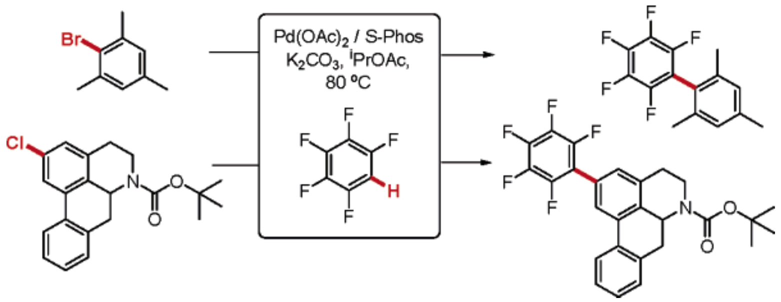
ABSTRACT



New reaction conditions are described that enable the direct arylation of pentafluorobenzene with sterically encumbered aryl bromides and aryl chlorides. These reactions occur in high yield and under mild conditions. Notably, the reactions can be performed at 80 °C in isopropyl acetate with a catalyst generated by the in situ mixing of Pd(OAc)$_2$ and S-Phos. The enhanced scope of these transformations should further reduce the need to use pentafluorophenylboronic acid in the construction of perfluoroarenes.

Palladium-catalyzed cross-coupling reactions of organometallic reagents and aryl halides constitute one of the most useful methods for the synthesis of biaryl molecules.[1] Despite their prevalence, there is significant waste built into these processes because both cross-coupling components must be activated (synthesized) prior to use. With respect to the organometallic, this typically requires the use of other strongly basic organometallic reagents such as butyllithium and often necessitates more than one step. Each of these pre-cross-coupling manipulations generates waste from reagents, solvents, and purification.

Other aspects of modern cross-coupling reactions that warrant attention are the challenges and limitations imposed by the reactivity itself. The need to activate one arene as a nucleophile (the organometallic) and the other as an electrophile (the aryl halide) can be problematic in cases where the substrates are challenging to activate in the necessary fashion. Such is the case with electron-deficient arenes when they must be preactivated as the nucleophilic component. With these limitations in mind, our group has been investigating the use of direct arylation[2−5] as a means of establishing new reactivity parameters for the resolution of

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(1) For reviews on this topic, see: (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Shulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) For recent reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (e) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2005**, 1253.

(3) For recent advances with electron-rich heterocycles, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Park, C. H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (c) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (d) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835. (e) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (f) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.

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long-standing challenges associated with the use of organometallic reagents in cross-coupling chemistry.[6]

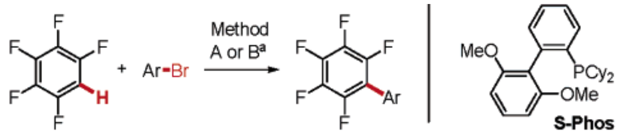
As noted, electron-deficient aryl (heteroaryl) organometallic reagents constitute a challenging substrate class in cross-coupling reactions and use of pentafluorophenyl organometallics is illustrative. Recent advances include the use of $C_6F_5B(OMe)_3Li$[7] or $C_6F_5BF_3K$[8] salts, which enable successful cross-coupling with aryl iodides. Very recently, the use of $C_6F_5B(OH)_2$ in conjunction with a stoichiometric silver additive was discovered to enable reactions with both aryl iodides and bromides.[9] To our knowledge, there are no reports of high-yielding cross-couplings with aryl chlorides or with more sterically encumbered aryl halides. Given the importance of perfluoroarenes in medicinal[10] and particularly materials chemistry,[11] a general solution to this limitation would be valuable in the synthesis of these molecules.

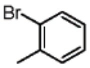
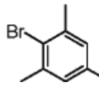
We recently reported the use of perfluorobenzenes as replacements for the corresponding organometallic reagents in cross-coupling reactions.[12] These reactions were found to occur in high yield with several aryl bromides but suffered from low yields with aryl chlorides or with ortho-substituted aryl bromides. These limitations prompted a reevaluation of the catalyst and reaction conditions, focusing on these more challenging substrates.

Herein, we report the discovery of new conditions for reaction with a wide range of sterically encumbered bromides and chlorides as well as aryl iodides, triflates, and heterocyclic aryl halides. Strikingly, these new reactions also occur at 80 °C, which is milder than our initially disclosed conditions at 120 °C, and are among the mildest conditions reported for this type of transformation. The successful realization of these reaction conditions should, in most cases, replace the use of pentafluorophenyl organometallics in the synthesis of these biaryl molecules.

Catalyst and reaction condition screens were performed with 2-bromotoluene (**1**) and bromomesitylene (**2**) as the model substrates in a reaction with pentafluorobenzene. Under the conditions we previously described,[12] very poor conversion was obtained with **1** (Table 1, entry 1) and no reaction was observed with **2** (entry 3). After extensive optimization, a catalyst generated by mixing $Pd(OAc)_2$ with 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos)[13] in isopropyl acetate at 80 °C with K_2CO_3 as the base emerged as an excellent catalyst−solvent system. Under these conditions, complete conversion was achieved with both aryl bromides **1** and **2**, resulting in 99% and 98% isolated yields, respectively. The combination of the $Pd(OAc)_2$/S-Phos catalyst and the ^{i}PrOAc[14] solvent appears to be an excellent combination for these reactions. Notably, use of our previously reported $Pd(OAc)_2/P^tBu_2MeHBF_4$ catalyst in ^{i}PrOAc or use of $Pd(OAc)_2$/S-Phos in DMA leads to significantly diminished outcomes. We also note that the reaction temperature can be lowered to 70 °C, but occasionally incomplete conversion is obtained; thus, we chose 80 °C as the standard reaction temperature for subsequent studies.

Table 1. Establishment of Conditions for Sterically Encumbered Aryl Bromides[a]



entry	aryl bromide	method	convn. (%)[b]	yield (%)[c]
1	 **1**	A	12	nd
2		B	100	99
3	 **2**	A	0	0
4		B	100	98

[a] Method A: $Pd(OAc)_2$ (5 mol %), $P^tBu_2MeHBF_4$ (10 mol %), K_2CO_3, DMA, 120 °C. Method B: $Pd(OAc)_2$ (5 mol %), S-Phos (10 mol %), K_2CO_3, ^{i}PrOAc, 80 °C. [b] Determined by GCMS analysis. [c] Isolated Yield.

The scope of the reaction with pentafluorobenzene and a range of aryl halides were investigated and are outlined in Table 2. In addition to ortho-substituted aryl bromides (entry 2), aryl iodides may also be employed (entry 3). With aryl iodides, 0.5 equiv of Ag_2CO_3 must be employed as an additive. An inhibitory effect of iodide salts on direct arylation has previously been observed,[5b,15] and we postulate

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(4) For recent examples involving metallacyclic intermediates, see: (a) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (c) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (d) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112.

(5) For recent examples of intramolecular reactions with simple arenes, see: (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (c) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (d) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

(6) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(7) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. *J. Fluorine Chem.* **2003**, *122*, 195.

(8) (a) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. *Tetrahedron Lett.* **2002**, *43*, 8111. (b) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

(9) Korenga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T. *Org. Lett.* **2005**, *7*, 4915.

(10) (a) Zahn, A.; Brotschi, C.; Leumann, C. *J. Chem. Eur.* **2005**, *11*, 2125. (b) Russell, M. G. N.; Carling, R. W.; Atack, J. R.; Bromidge, F. A.; Cook, S. M.; Hunt, P.; Isted, C.; Lucas, M.; McKernan, R. M.; Mitchinson, A.; Moore, K. W.; Narquizian, R.; Macaulay, A. J.; Thomas, D.; Thompson, S.-A.; Wafford, K. A.; Castro, J. L. *J. Med. Chem.* **2005**, *48*, 1367.

(11) (a) Sakamoto, Y.; Suzuki, T.; Miura, A.; Fujikawa, H.; Tokito, S.; Taga, Y. *J. Am. Chem. Soc.* **2000**, *122*, 1832. (b) Hwang, D. H.; Song, S. Y.; Ahn, T.; Chu, H. Y.; Do, L. M.; Kim, S. H.; Shim, H. K.; Zyung, T. *Synth. Met.* **2000**, *111*, 485. (c) Montes, V. A.; Li, G.; Pohl, R.; Shinar, J.; Anzenbacher, P. *Adv. Mater.* **2004**, *16*, 2001. (d) Tsuzuki, T.; Shirasawa, N.; Suzuki, T.; Tokito, S. *Adv. Mater.* **2003**, *15*, 1455. (e) Kitamura, T.; Wada, Y.; Yanagida, S. *J. Fluorine Chem.* **2000**, *105*, 305. (f) Weck, M.; Dunn, A. R.; Matsumoto, K.; Coates, G. W.; Lobkovsky, E. B.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2741. (g) Nitschke, J. R.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 10183.

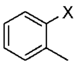
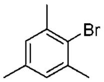
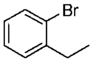
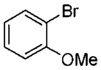
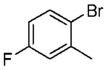
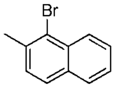
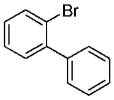
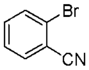
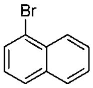
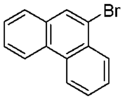
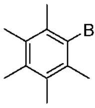
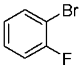
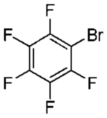
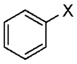
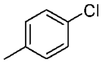
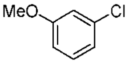
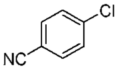
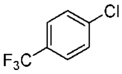
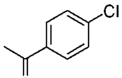
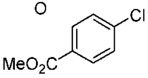
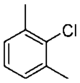
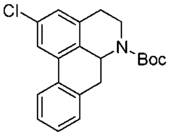
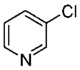
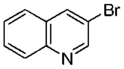
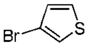
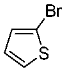
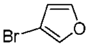
(12) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.

(13) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(14) EtOAc can also be employed. However, the lower volatility and slightly higher boiling point of ^{i}PrOAc results in greater reproducibility and greater ease in performing the reactions. Notably, it allows the reactions to be run below the solvent boiling point (85−91 °C).

(15) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

Table 2. Scope of Aryl Halide−Pentafluorobenzene Cross-Coupling[a]

entry	aryl halide	product	yield[b]
1 2 3	 X = Cl X = Br X = I	**3** **3** **3**	97 99 82
4		**4**	98
5		**5**	82
6		**6**	99
7		**7**	96
8		**8**	96
9		**9**	92^c
10		**10**	73^d
11		**11**	99
12		**12**	97
13		**13**	85^d
14		**14**	99
15		**15**	83^d
16 17	 X= Cl X= OTf	**16** **16**	99 98
18		**17**	99
19		**18**	89
20		**19**	97
21		**20**	97
22		**21**	62
23		**22**	99
24		**23**	90
25		**24**	99
26		**25**	79
27		**26**	92
28		**27**	70
29		**28**	63^d
30		**29**	55^d

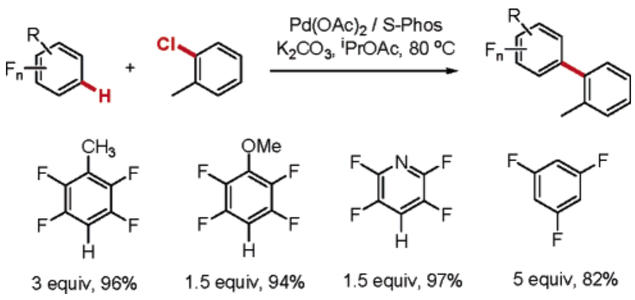
[a] Conditions: aryl halide, pentafluorobenzene (1.5 equiv), Pd(OAc)$_2$ (5 mol %), S-Phos (10 mol %), and K$_2$CO$_3$ (2 equiv) dissolved in ^{i}PrOAc and heated at 80 °C. [b] Isolated yield. [c] Performed using Pd(OAc)$_2$ with P^{t}Bu$_3$HBF$_4$ in DMA at 120 °C. [d] 3 equiv of pentafluorobenzene was used.

that the silver salts are serving to remove the iodide salts from the mixture as they are generated by the catalytic cycle. The silver carbonate may also be facilitating a bromide−carbonate ligand exchange, which may facilitate C−H bond cleavage.[16] A variety of ortho substituents can be present including sp^3 (entries 1−5, 7, 8, and 13) and sp^2 carbons (entries 8, 9, 11, and 12), methoxy (entry 6), nitrile (entry 10), and fluoro groups (entries 14 and 15). Even more sterically encumbered bis-ortho-substituted aryl bromides can be arylated in high yield (entries 4 and 13).

Given the low yields associated with aryl chlorides in Suzuki cross-coupling reactions of pentafluorophenylboronic acid and in direct arylation of pentafluorobenzene in our previous report,[12] we were pleased to find that a wide range of aryl chlorides can now be employed with these new conditions. Both activated and deactivated aryl chlorides are compatible (entries 16 and 18−23) as are sterically encumbered aryl chlorides (entries 1 and 24). More functionalized aryl chlorides can also be employed as illustrated by the high-yielding reaction of the C2 chlorinated aporphine to generate **24** in 99% yield (entry 25). An aryl triflate may also be employed as illustrated by entry 17. We also evaluated the compatibility of these new reaction conditions with heterocyclic aryl halides. For example, 3-chloropyridine can be cross-coupled in good yield (entry 26) as can 3-bromoquinoline (entry 27). In contrast, the use of 2- and 4-chloropyridine results in less than 50% of the desired product and is a focus of continuing effort and study. Additionally, 3- and 2-bromothiophene (entries 28 and 29) and 3-bromofuran (entry 30) may be arylated in 70, 63, and 55% yields, respectively.

Other perfluoroaromatic compounds can also be arylated in high yield. To evaluate the applicability of these conditions to other aromatic compounds, 2-chlorotoluene was employed as a model aryl halide to maintain the challenging oxidative addition and steric bulk (Scheme 1). Under the standard conditions, 2,3,5,6-tetrafluoroanisole and 2,3,5,6-tetrafluoropyridine both reacted to give 94 and 97% isolated yields,

Scheme 1. Arylation of Substituted Perfluoroaromatics



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[16] For a mechanistic discussion, see: Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066 and ref 12.

respectively. With 2,3,5,6-tetrafluorotoluene, 3 equiv was found to give a better yield, allowing the isolation of the arylated product in 96% yield. 1,3,5-Trifluorobenzene can also be employed. In this case, 5 equiv of the arene was employed to give 82% isolated yield.

In conclusion, the combination of $Pd(OAc)_2$ with S-Phos generates a catalyst that, in the presence of K_2CO_3 in ^{i}PrOAc at 80 °C, is very effective for the direct arylation of pentafluorobenzene and other polyfluorinated aromatics with a wide range of aryl halides including sterically hindered aryl chlorides and bromides and heterocyclic aryl halides. The relative mildness of the reaction conditions and the broad scope should make this method useful in the synthesis of perfluoroaryl molecules and reduce the current reliance on the use of stoichiometric organometallic species when the synthesis of these molecules is called for.

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Supporting Information Available: Complete characterization data for all new metal complexes and biaryl products as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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