

Room-Temperature Direct Arylation of Polyfluorinated Arenes under Biphasic Conditions

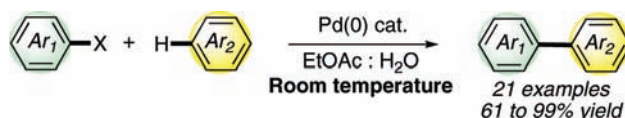
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ABSTRACT

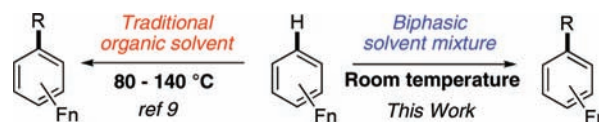


New biphasic conditions for the palladium-catalyzed direct arylation of electron-poor fluorinated arenes have been developed. Taking advantage of biphasic chemistry, the use of an immiscible mixture of water and an organic solvent allows complete solubilization of all components of the system, enabling the reaction to proceed at room temperature in yields up to 99%.

Transition-metal-catalyzed transformations at C–H bonds have undergone intensive development over the past decade.^{1,2} Tremendous efforts have focused on C–C bond-forming reactions to access biaryl systems using simple arenes in place of preactivated coupling partners.³ However, these processes require forcing conditions generally associated with the use of high temperatures, typically above 100 °C, which can represent serious limitations for both substrate compatibility and large-scale applications. To broaden the

applicability of these transformations, there is a need to develop milder reaction conditions that can proceed at lower temperatures.

Scheme 1. Precedent in C–H Functionalization of Polyfluoroarenes



An alternative to using traditional organic solvents in palladium-catalyzed direct arylation is to perform the transformation in an aqueous medium.⁴ This strategy was employed by Greaney and co-workers⁵ and proved to be efficient for the direct arylation of heteroarenes at temperatures as low as 50 °C. More recently, the urea-directed C–H

† Prof. Keith Fagnou passed away unexpectedly on November 11, 2009.

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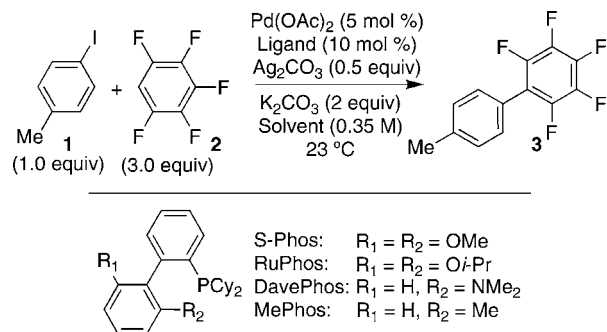
activation of electron-rich arenes under Pd(II) catalysis was accomplished at room temperature using water as the reaction solvent.⁶ To our knowledge, no reports have appeared where mild aqueous conditions were successfully employed for the direct arylation of electron-deficient arenes.⁷ Given the broad applicability of these types of polyarenes in material chemistry,⁸ their synthesis under mild conditions would be valuable.

Drawing inspiration from recent advances in the development of mild C–H functionalization conditions, we decided to investigate new strategies for the direct arylation of electron-deficient polyfluorinated arenes at lower temperature,⁹ employing water as a cosolvent in the reaction medium. Herein, we describe the successful development of a biphasic catalytic system¹⁰ that provides access to a variety of biaryls at ambient temperature.

Initial reaction development and optimization was performed with 4-iodotoluene **1** and pentafluorobenzene **2**. After extensive screening of solvents, the best results were obtained with the use of *i*-PrOAc, DMF or EtOAc. Under these conditions, no yields higher than 68% could be obtained without addition of water (Table 1, entries 1–3). Interestingly, the yield could be significantly increased when using a solvent mixture of water and EtOAc.¹⁰ We were pleased to find that the use of a 2.5:1 mixture of EtOAc and water could improve the reaction yield up to 83% (Table 1, entry 4). Taking advantage of biphasic chemistry, it was reasoned that by performing the reaction under such conditions, a complete solubilization of the inorganic components of the reaction could be achieved. In particular, the base, which has been shown to be crucial for the concerted metalation–deprotonation transition state to occur,¹¹ is only sparsely soluble in organic solvents.¹²

The phosphine ligand also exerted an important effect on the reaction outcome. For example, RuPhos allowed an improved yield of 91% over 16 h compared to S-Phos (Table 1, entry 5). Also, the reaction time could be decreased to 5 h using DavePhos (Table 1, entry 6), and ultimately the coupling product **3** could be obtained in 90% isolated yield in only 2 h with MePhos¹³ (Table 1, entry 7).

Table 1. Optimization of Reaction Conditions



entry	solvent	ligand	time (h)	GC yield (%) ^a
1	<i>i</i> -PrOAc	S-Phos	16	47
2	DMF	S-Phos	16	59
3	EtOAc	S-Phos	16	68
4	EtOAc/H ₂ O (2.5:1)	S-Phos	16	83
5	EtOAc/H ₂ O (2.5:1)	RuPhos	16	91
6	EtOAc/H ₂ O (2.5:1)	DavePhos	5	92
7	EtOAc/H₂O (2.5:1)	MePhos	2	92 (90)
8 ^b	EtOAc/H ₂ O (2.5:1)	MePhos	16	0

^a Determined by GC analysis relative to tetradecane as an internal standard (isolated yield in parentheses). ^b No Ag₂CO₃ added.

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(10) For selected examples of transition metal catalyzed reactions under biphasic solvent conditions, see: (a) Kurahashi, T.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6336. (b) Bottarelli, P.; Costa, M. *J. Mol. Catal. A: Chem.* **2008**, *289*, 82. (c) Lautens, M.; Mancuso, J.; Grover, H. *Synthesis* **2004**, 2006. (d) Datta, A.; Plenio, H. *Chem. Commun.* **2003**, *13*, 1504.

(11) For an analysis of the CMD mechanism, see: Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

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The silver carbonate additive was required for the coupling reaction to proceed.¹⁴ Indeed, without the addition of Ag₂CO₃, no conversion to product **3** was observed (Table 1, entry 8) and only the starting materials were recovered. The role of silver(I) is attributed to a plausible abstraction of the iodine ligand from the Pd(II) complex, thereby generating an electrophilic cationic palladium intermediate.¹⁵

In the course of the optimization studies, we demonstrated that, under these biphasic conditions, the ratio of the two solvent components is crucial to ensure optimal conversion (Figure 1). There is a narrow window around a 2.5:1 ratio of EtOAc and water in which the highest yields are obtained, and any deviation from this ratio results in lower conversions.

(13) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

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(15) For examples of cationic Pd(II) complexes generated by Ag(I) abstraction of the iodide ligand, see: (a) Grove, D. M.; van Koten, G.; Louwen, J. N.; Noltes, J. G.; Spec, A. L. *J. Am. Chem. Soc.* **1982**, *104*, 6609. (b) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1995**, *60*, 1013. (c) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (d) Overman, L. E.; Poon, D. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 518.

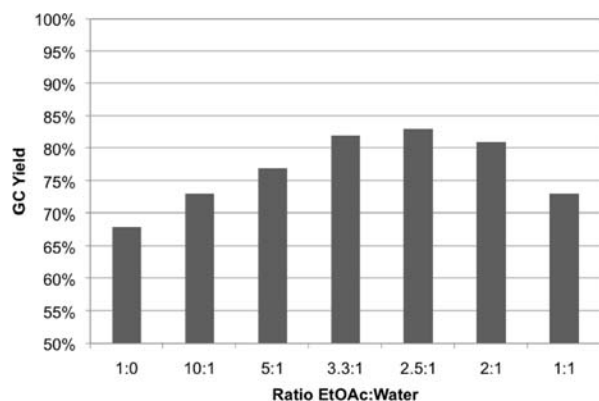


Figure 1. Effect of the ratio of EtOAc to water on the yield of the reaction using conditions from Table 1, entry 4.

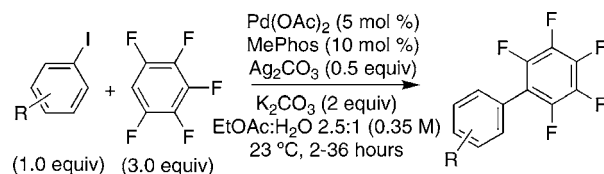
Illustrative examples with respect to the aryl iodide are shown in Table 2. In addition to 4-iodotoluene, which possesses a minimal steric and electronic bias, (Table 2, entry 1), electron-withdrawing groups such as a ketone, an ester, or a trifluoromethyl group are well tolerated, giving rise to the coupling products in 85% to 96% yields (Table 2, entries 2–4). Aryl iodides bearing electron-donating groups at the *para* and *ortho* positions also give excellent yields of 92% and 99% (Table 2, entries 5 and 6). Sterically demanding substrates are compatible as exemplified by products **9** and **10** obtained in 78% and 95% yields, respectively (Table 2, entries 7 and 8). Interestingly, 5-iodoindole is also tolerated to give biaryl **11** in 93% yield without arylation of the azole ring (Table 2, entry 9).

With regard to the polyfluoroarene coupling partner, tetrafluoro- and trifluoroarenes were found to be efficient for the coupling reaction (Table 3). For example, tetrafluorinated biaryls **12**–**14** (Table 3, entries 1–3) can be obtained in excellent yields ranging from 91% to 98%. Symmetrical arenes having more than one potential site of arylation require a larger excess of the polyfluoroarene component in order for the monoarylated product **15** and **16** to be obtained in 90% and 88% yields, respectively (Table 3, entries 4 and 5). Furthermore, trifluorinated arenes can also be coupled efficiently and selectively to give only monoarylation products in 81–99% yields (Table 3, entries 6–8).

A preliminary investigation of the applicability of our new biphasic direct arylation conditions to classes of substrates other than polyfluorinated arenes led to promising results. We were pleased to observe that the method is suitable for the direct arylation of halogenated thiophenes. We recently demonstrated that introduction of a chlorine atom enhances the propensity for heteroarenes to undergo C–H bond functionalization.¹⁶

Whereas our previous examples with chlorinated heterocycles required elevated temperatures,¹⁶ under these new biphasic conditions, 2-chlorothiophene reacts regioselectively

Table 2. Scope of Aryl Iodides with Pentafluorobenzene

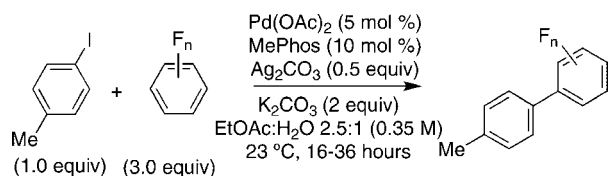


entry	aryl iodide	product	isolated yield
1			90%
2			95%
3			96%
4			85%
5			92%
6			99%
7			78%
8			95%
9			93%

at the C5 position at only 60 °C to afford products **20** and **21** in 77% and 61% yields, respectively (Table 4, entries 1 and 2).¹⁷ 3-Chlorothiophene also reacts selectively at the C2 position, providing biaryl product **22** in good yield (Table 4, entry 3).¹⁸ More interestingly, 3-bromothiophene is a compatible coupling partner and C–H bond cleavage occurs

(16) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

(17) A yield of 31% was obtained with 2-chlorothiophene at ambient temperature after 16 h.

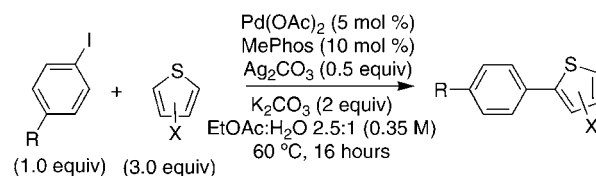
Table 3. Scope of Polyfluoroarenes with 4-Iodotoluene

entry	perfluoroarene	product	isolated yield
1			95%
2			91%
3			98%
4 ^a			90%
5 ^a			88%
6			99%
7			81%
8			98%

^a 10 equiv of polyfluoroarene was used.

in the presence of a reactive C–Br bond (Table 4, entry 4). The presence of the chlorine and bromine substituents on these products are valuable synthetic handles that can be used for subsequent transformations.^{2,3}

(18) Traces of another regioisomer were observed by GC–MS with the use of 3-chloro- and 3-bromothiophene.

Table 4. Arylation of Halogenated Thiophenes

entry	aryl iodide	thiophene	product	isolated yield
1				77%
2				61%
3				73%
4				72%

In conclusion, we have developed mild biphasic conditions for the direct arylation of electron-deficient arenes at room temperature. The conditions are general and effective for a variety of aryl iodides and polyfluorinated arenes as coupling partners, and excellent yields are generally obtained. Other halogenated thiophenes are also compatible and led to the heterobiaryl products in good yields. In addition to its synthetic utility, the beneficial influence of a biphasic solvent mixture in a direct arylation process should demonstrate the viability of water as a cosolvent in the development of milder reaction conditions.

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Note Added after ASAP Publication. Figure 1 was missing the x axis of the graph in the version published asap April 9, 2010; the correct version reposted April 16, 2010.

Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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