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Nickel-Catalyzed Selective Defluorination to Generate Partially Fluorinated Biaryls

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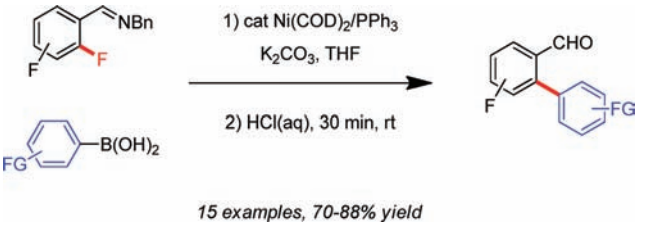
ABSTRACT



A Ni-catalyzed, chemoselective cross-coupling reaction of polyfluoroarenes under mild reaction conditions is reported. A variety of fluorine-containing biaryls are synthesized in good-to-excellent yields. A wide range of substitution patterns and functional groups are tolerated.

Aryl fluorides are important components of many biologically active molecules, including pharmaceuticals and agrochemicals.[1] Because no natural source of aryl fluorides has been identified, fluoroaromatic building blocks must be generated through synthesis.[2] The substitution patterns present in commercially available sources remain quite limited, which in turn limits the structural and functional diversity of drugs that can be readily constructed. Thus, a considerable need exists for the development of efficient, versatile methods of generating functionalized fluoroaromatic building blocks.

One approach is to fluorinate functionalized arenes.[2,3] Traditional methods rely on hazardous electrophilic fluorinating reagents and often exhibit low selectivity. Direct arylation of fluoroaromatics has been achieved, but the yields and selectivity are often low and diarylation is sometimes observed.[4] Reactions of diazonium salts with fluoride ions have been reported, but these suffer from the need to generate highly reactive intermediates. Suitably activated aryl halides can undergo halogen exchange reactions, although the scope remains limited. Recently, metal-catalyzed replacement of halides, boronic acids and stannanes with fluoride has emerged as a powerful strategy for fluoroarene synthesis.[5] However, these processes have yet to be used to generate functionalized polyfluorinated arenes, which are found in a number of top-selling drugs, including Januvia and Diflucan.

An alternative approach is to selectively functionalize polyfluoroaromatics via cross-coupling reactions.[6,7] Polyfluorinated arenes are typically more readily available and cheaper than their mixed halo counterparts. Toward this goal, our group has developed Pt(II)-catalyzed cross-coupling reactions of polyfluoroaryl imines, including methylation with zinc reagents[8] and methoxylation with silicon reagents.[9] A wide range of mono- and polyfluoroaryl

(1) (a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Purser, S.; Moore, P.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.

(2) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, *11*, 1804.

(3) Simizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.

(4) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (d) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (e) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (f) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506. (g) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2011**, *13*, 276.

(5) (a) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993. (b) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (c) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662. (d) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793. (e) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150. (f) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (g) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796. (h) Grushin, V. V.; Marshall, W. J. *Organometallics* **2007**, *26*, 4997. (i) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.

(6) Sun, A. D.; Love, J. A. *Dalton Trans* **2010**, *39*, 10362.

(7) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.

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imines can be generated. Potentially reactive functional groups are well-tolerated, and the reactions typically proceed with high yields and high selectivity for the fluorine adjacent to the imine directing group.

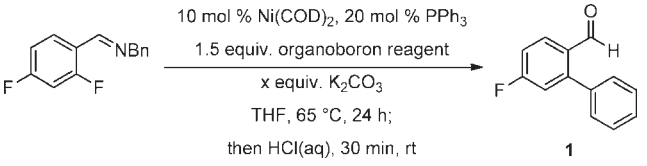
Despite these promising developments, these reactions have a number of limitations. A hydrogen in an ortho position results in C−H activation, which precludes cross-coupling. At least three electron-withdrawing groups in addition to the imine are required to render the substrate sufficiently reactive toward C−F activation, which is typically rate-limiting. Finally, the reaction has been principally limited to methylation and methoxylation. These limits need to be addressed for this strategy to be widely applicable. In particular, we sought to explore the use of Ni(0) catalysts for selective defluorination/cross-coupling with broad scope. We report herein a Ni(0)-catalyzed protocol that overcomes all of the limitations of the Pt(II) system.

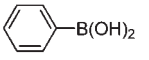
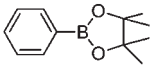
A number of groups have made important contributions in the field of Ni-catalyzed cross-coupling of mono- and polyfluoroarenes,[10] although the scope and functional group tolerance remains limited. We anticipated that the use of a suitable directing group, particularly one that can be easily modified, would permit a considerable extension of substrate scope without compromising synthetic utility. Boronic acids were chosen as the coupling partner because they are readily available and offer great functional group diversity.

Our study began with the Ni-catalyzed reaction of a 2,4-difluoroaryl imine. This substrate was selected for initial study, as it was unsuccessful in Pt-catalyzed cross-coupling reactions. This substrate undergoes efficient cross-coupling with 4-methoxylbenzeneboronic acid in THF in the presence of 10 mol % $Ni(COD)_2$, 20 mol % PPh_3 and 3.0 equiv of K_2CO_3.[11,12] The reaction resulted in exclusive functionalization of the ortho fluorine to generate the desired biaryl products in nearly quantitative conversion. The corresponding aldehyde was obtained in 85% yield after hydrolysis and column chromatography. This result demonstrated that the use of Ni(0) overcomes all of the limitations of the Pt system: an ortho C−H bond does not suppress catalysis, aryl coupling reagents can be used and a relatively unactivated polyfluoroarene can undergo efficient cross-coupling to yield the corresponding biaryl product.[13] Encouraged by this result, we were now poised to explore the scope in more detail.

Our first task was to explore the transmetalation reagent. In addition to organoboronic acids, organoboronic ester and trifluoroborate salt both proved viable in the reaction without compromising the yield (Table 1). In particular, the use of trifluoroborate salt precludes the need for added base (entry 3). Given the availability and ease of use organoboronic acids, we sought to use these reagents for further exploration.

Table 1. Exploration of Organoboron Sources



entry	organoboron reagent	reaction conditions[a]	yield[b]
1		A	74%
2		A	75%
3	$K[PhBF_3]$	B	69%

[a] A: 24 h, 3.0 equiv K_2CO_3. B: 48 h. No base added. [b] Isolated yield.

We next examined the scope of arylboronic acids. As shown in Table 2, a wide variety of arylboronic acids are compatible with the reaction conditions, providing the desired products in good-to-excellent yields after hydrolysis and isolation. Both electron-donating and electron-withdrawing are well-tolerated. An unprotected hydroxyl group does not diminish the yield (entry 4), although use of an ortho-substituted methoxyl group (entry 3) appears to suppress reactivity, presumably due to sterics. Of particular significance is that all of these products are 1,2,4-trisubstituted arenes, which is one of the most common motifs in pharmaceuticals aryl rings.[14] Moreover, fluoro- and trifluoromethyl groups (entries 5−7) can be incorporated as a means to generate more highly fluorinated building blocks.

(8) (a) Wang, T.; Alfonso, B. J.; Love, J. A. *Org. Lett.* **2007**, *9*, 5629. (b) Wang, T.; Love, J. A. *Organometallics* **2008**, *27*, 3290. (c) Buckley, H. L.; Sun, A. D.; Love, J. A. *Organometallics* **2009**, *28*, 6622. (d) Sun, A. D.; Love, J. A. *J. Fluorine Chem.* **2010**, *131*, 1237.

(9) Buckley, H. L.; Wang, T.; Tran, O.; Love, J. A. *Organometallics* **2009**, *28*, 2356.

(10) (a) Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973**, *50*, C12. (b) Braun, T.; Parsons, S.; Perutz, R.; Voith, M. *Organometallics* **1999**, *18*, 2254. (b) Braun, T.; Izundu, J.; Steffen, A.; Neumann, B.; Stammler, H.-G. *Dalton Trans.* **2006**, 5118. (d) Steffen, A.; Sladek, M. I.; Braun, T.; Neumann, B.; Stammler, H.-G. *Organometallics* **2005**, *24*, 4057. (e) Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 17978. (f) Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964. (g) Schaub, T.; Fischer, P.; Steffen, A.; Braun, T.; Radius, U.; Mix, A. *J. Am. Chem. Soc.* **2008**, *130*, 9304. (h) Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, 1771. (i) Ackermann, L.; Wechsler, C.; Kapdi, A.; Althammer, A. *Synlett* **2010**, 294.

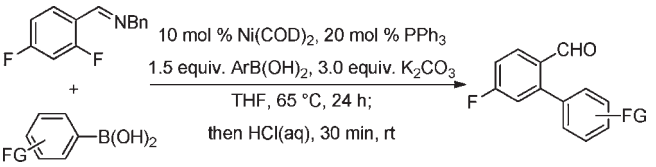
(11) Importantly, no reaction occurred in the absence of Ni, phosphine or base. Likewise, the corresponding 2,4-difluoroaryl aldehyde did not undergo cross-coupling.

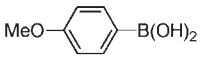
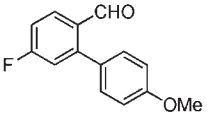
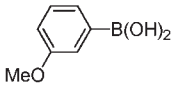
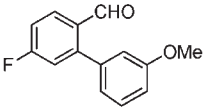
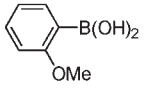
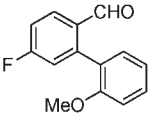
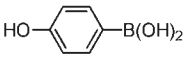
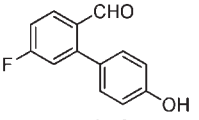
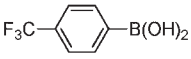
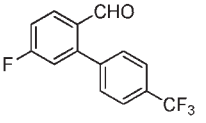
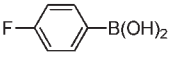
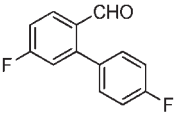
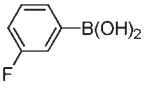
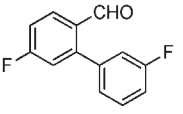
(12) Other phosphines were investigated but did not provide superior yields. Given the low cost and ease of handing, PPh_3 was used for the rest of the study. Details are provided in the Supporting Information.

(13) Stoichiometric and catalytic C−H activation in fluoroarenes have been reported recently: (a) Johnson, S. A.; Huff, C. A.; Mustafa, F.; Saliba, M. *J. Am. Chem. Soc.* **2008**, *130*, 17278. (b) Johnson, S. A.; Taylor, E. T.; Cruise, S. J. *Organometallics* **2009**, *28*, 3842. (c) Doster, M. E.; Hatnean, J. A.; Jeftic, T.; Modi, S.; Johnson, S. A. *J. Am. Chem. Soc.* **2010**, *132*, 11923. (d) Hatnean, J. A.; Beck, R.; Borrelli, J. D.; Johnson, S. A. *Organometallics* **2010**, *29*, 6077. (e) Johnson, S. A.; Mroz, N. M.; Valdizon, R.; Murray, S. *Organometallics* **2011**, *30*, 441. (f) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (g) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (h) Kanyiva, K. S.; Kashihara, N.; Nakao, Y.; Hiyama, T. *Dalton Trans.* **2010**, *39*, 10483.

(14) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

Table 2. Arylboronic Acid Scope and Limitation

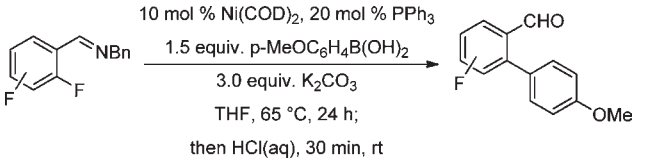


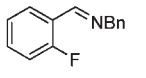
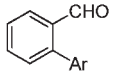
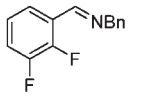
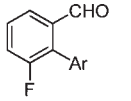
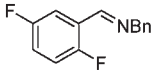
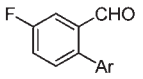
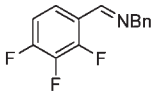
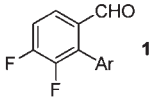
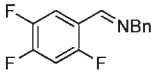
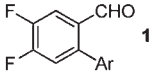
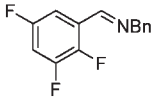
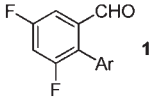
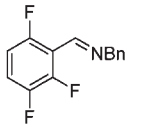
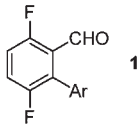
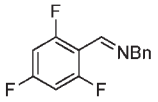
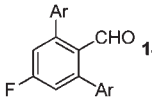
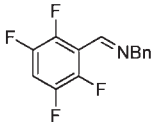
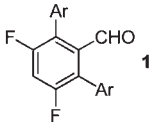
entry	boronic acid	product		yield[a]
1			**2**	85%
2			**3**	74%
3				<5%
4			**4**	88%
5			**5**	85%
6			**6**	77%
7			**7**	84%

[a] Isolated yield.

Having established the feasibility of this process, we then explored imines that would generate fluorinated building blocks after cross-coupling (Table 3). A broad range of substitution patterns are well-tolerated, with one exception (entry 3). One substrate with two ortho C−F bonds underwent monosubstition (entry 7). It is noteworthy that the product of this reaction has the same difluoro substitution pattern as the substrate in entry 3. Thus, it thus appears this substitution pattern is not tolerated for C−F activation. We are currently investigating the cause of this phenomenon. In contrast, two other substrates, both with at least one additional fluorine substituent, underwent efficient diarylation (entries 8 and 9). The monoarylated product was not detected even at incomplete conversion, suggesting that the second arylation is competitive with or faster than the initial arylation reaction. This reactivity is complementary to that observed with Pt(II) catalysts, in which monosubstitution occurs peferentially.

Table 3. Scopes and Limitations of Polyfluoroaryl Imines



entry	imine	product[a]		conditions (A or C), yield[b,c]
1			**8**	A, 82%
2			**9**	A, 78%
3				A or C, <5%
4			**10**	A, 91%
5			**11**	A, 75%
6			**12**	A, 70%
7			**13**	A or C, 70%
8			**14**	C, 81%
9			**15**	C, 84%

[a] Ar = 4-methoxylphenyl. [b] A: 1.5 equiv boronic acid, 24 h, C: 3.0 equiv boronic acid, 48 h. [c] Isolated yield.

In summary, we have found that $Ni(COD)_2/PPh_3$ catalyzes the cross-coupling of polyfluoroarenes to generate functionalized fluorinated building blocks under mild conditions. This work addresses the key limitations of our previously reported Pt-catalyzed aryl fluoride cross-coupling reactions and provides access to a broad range of fluorinated biaryl molecules. In general, the reactions are high yielding, and the process is tolerant of electron-donating, electron-withdrawing and protic functional goups. Arylboronic acids and ester and trifluoroborate salts provide comparable yields. Mechanistic analysis of this reaction is currently underway, as is the development of tandem functionalization reactions.

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Supporting Information Available. Complete experimental details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.