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Platinum(II)-Catalyzed Cross-Coupling of Polyfluoroaryl Imines

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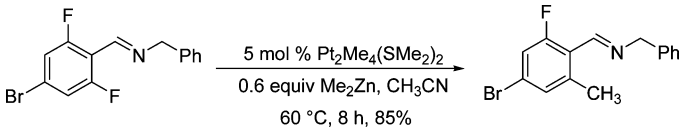
ABSTRACT



The introduction of fluorine into an organic molecule imparts unique physicochemical properties. Not surprisingly, fluorine is increasingly incorporated into new drugs and agrochemicals. However, aryl fluoride building blocks are only available through synthesis. The ability to cross-couple polyfluoroaromatics selectively could provide a convenient route to functionalized fluoroaromatics. We report herein the first examples of Pt-catalyzed cross-coupling of aryl fluorides. The methylated products can potentially serve as precursors to a wide range of functionalized fluorinated small molecules.

The introduction of fluorine into an organic molecule imparts unique physicochemical properties, including high metabolic stability, solubility, and lipophilicity, as well as the ability to hydrogen bond.[1] Recent estimates suggest that up to 20% of new drugs and approximately 30% of new agrochemicals contain fluorine;[1c,2] in particular, two of the world's top 10 best-selling drugs in 2005 (Pfizer's Lipitor and Johnson & Johnson's Risperdal) contain aryl fluorides. To date, fewer than 40 organofluoride natural products have been isolated, none of which contain an aryl fluoride.[3] Consequently, the building blocks used to generate aryl fluoride containing pharmaceuticals and materials must be obtained through synthesis. The ability to cross-couple polyfluoroaromatics selectively could provide a convenient route to functionalized fluoroaromatics. Toward this goal, we report herein the selective methylation of a series of polyfluorinated imines. This work represents the first examples of Pt-catalyzed cross-coupling of aryl fluorides. These results also provide rare examples of sp^2-sp^3 coupling of aryl fluorides. Moreover, the methylated products can serve as precursors to a wide range of functionalized fluorinated small molecules.

Catalytic cross-coupling of aryl fluorides has been a long-standing goal in organometallic chemistry, in part because of the challenge of activating the strong C−F bond.[4,5] Of the catalytic C−C bond forming reactions using aryl fluorides, Ni and Pd catalysts have been the most extensively explored.[6−8] However, these processes generally work only with monofluoroarenes and are thus not applicable to the synthesis of functionalized fluoroaromatics. Indeed, while

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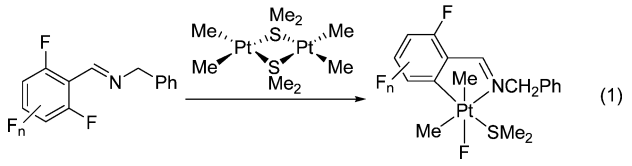
catalytic defluorination of polyfluoroarenes is well-established,[9] only a few examples of catalytic C−C bond formation have been reported.[8,10−12] Although these pioneering studies revealed the feasibility of such a process, the limited substrate scope in each case indicates that considerable challenges remain for selective cross-coupling of polyfluoroaromatics.

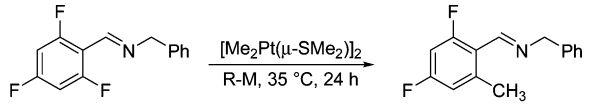
Inspired by the report from Crespo and Martinez that $[Me_2Pt(\mu\text{-}SMe_2)]_2$[13] promotes stoichiometric C−F activation of a series of aryl imines (eq 1),[14] we decided to explore the potential for this reaction to be part of a catalytic process. We reasoned that the Pt−F species could undergo transmetalation with an appropriate organometallic reagent. Subsequent reductive elimination would provide the functionalized product and would regenerate the Pt(II) catalyst.



(1)

Our study began with trifluoroimine **1a**. Attempts to use phenyl nucleophiles, such as $PhSi(OMe)_3$ (Table 1, entry 1),

Table 1. Optimization of Conditions for Catalytic Methylation

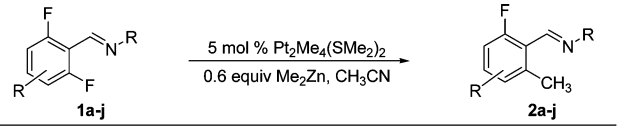


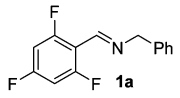
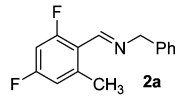
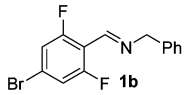
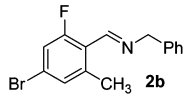
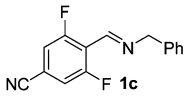
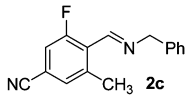
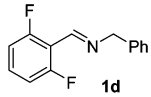
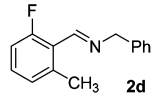
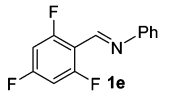
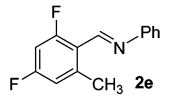
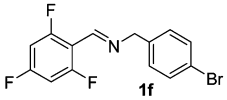
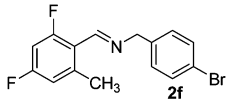
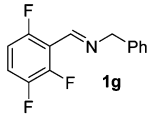
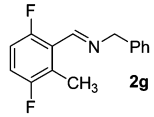
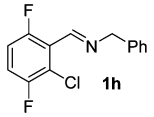
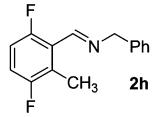
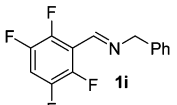
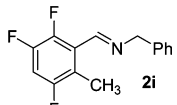
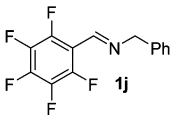
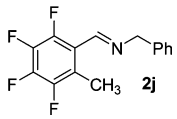
entry	R−M (equiv)	mol % Pt	solvent	yield[a]
1	$PhSi(OMe)_3$ (1.2)	5	acetone-d_6	4%
2	$MeSi(OMe)_3$ (1.2)	5	acetone-d_6	10%
3	Me_2Zn (1.2)	5	acetonitrile-d_3	***88%***
4	Me_2Zn (1.2)	0	acetonitrile-d_3	0%
5	Me_2Zn (0.6)	5	acetonitrile-d_3	***>95%***
6	MeLi (1.2)	5	THF-d_8	complex mixture
7	MeLi (1.2)	0	THF-d_8	complex mixture

[a] Yields based on ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

resulted in exclusive incorporation of methyl, presumably from the original Pt complex. Upon this discovery, we explored a variety of methylmetal reagents (entries 2−7). To our delight, Me_2Zn provided the monomethylated product (**2a**) in excellent yield and regioselectivity (entry 3). The selectivity for monomethylation indicates that C−F activation is faster for more highly fluorinated imines.[14] Importantly, no reaction occurs in the absence of catalyst (entry 4). Furthermore, the reaction can also proceed with a substoichiometric amount of Me_2Zn (entry 5), indicating that both methyl groups can be transferred from zinc. In comparison, the reaction of **1a** with MeLi provides a mixture of products (<5% of **2a**) in the presence and absence of Pt catalyst (entries 6 and 7).

Table 2. Scope of Pt-Catalyzed Methylation of Fluoroimines



entry	imine	product	cond, time, yield[a,b]
1	 **1a**	 **2a**	A, 8 h, 95%
2	 **1b**	 **2b**	A, 8 h, 85%
3	 **1c**	 **2c**	A, 4 h, 94%[c]
4	 **1d**	 **2d**	A, 24 h, <10%[c]
5	 **1e**	 **2e**	A, 8 h, 91%
6	 **1f**	 **2f**	A, 8 h, 86%
7	 **1g**	 **2g**	A, 8 h, 92%
8	 **1h**	 **2h**	A, 4 h, 99%[d,e]
9	 **1i**	 **2i**	B, 24 h, 70%[f]
10	 **1j**	 **2j**	B, 12 h, 74%[d]

[a] A: 60 °C; B: 80 °C. [b] Isolated yield, unless otherwise indicated. [c] Conversion based on ^{1}H NMR spectroscopy. [d] Yield based on ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [e] Note: product **2h** is identical to **2g**. [f] 1.2 equiv of Me_2Zn used.

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Inspired by this initial success, we sought to explore the ability of a series of polyfluoroaryl imines to undergo selective C−F cross-coupling with Me_2Zn. Of particular significance, **1b** reacts exclusively at the 2-position (Table 2, entry 2), an indication that the directing group permits the cleavage of the strong C−F bond in the presence of a considerably weaker C−Br bond. The desired product, **2b**, is formed in 85% isolated yield and is amenable to further functionalization at the aryl C−Br bond. Likewise, a cyano-substituted substrate (**1c**) reacts efficiently; no addition to the cyano group is observed (entry 3). In comparison, a difluoroimine (**1d**) without an additional electron-withdrawing group reacts sluggishly (entry 4).[14] Modification of the imine substituent is well-tolerated, as both aryl (entry 5) and aliphatic imines (entries 1 and 6) react uneventfully. As with **1b**, the bromine substituent within substrate **1f** is left untouched. Imine **1g** reacts exclusively at the more hindered site ortho to the imine (entry 7), consistent with the stoichiometric results.[14] This preference has been attributed to an electronic effect of the adjacent fluorine atom. Likewise, **1h** (entry 8) reacts at the more hindered site. In this case, however, the selectivity could also arise from preferential activation of the weaker C−Cl bond. Both the tetrafluoro substrate (**1i**) and pentafluoro substrate (**1j**) provide the corresponding monomethylated products **2i** and **2j**, respectively. Pentafluoroimine **1j** can undergo dimethylation with excess Me_2Zn.[15] These results clearly indicate the exceptional selectivity of this process.

The products are amenable to a wide range of further functionalization. For example, the imines are readily hydrolyzed to the corresponding aldehydes, which in turn can be converted to a broad range of functional groups. Furthermore, directed metalation of the methyl group of *ortho*-tolualdehydes and imines, followed by trapping with alkyl halides[16] and CO_2,[17] has been reported.

In summary, we have demonstrated the first examples of Pt-catalyzed C−F cross-coupling. A series of polyfluoroaryl imines react with Me_2Zn to generate functionalized fluoroarenes. The reaction is selective for ortho C−F activation in the presence of weaker aryl C−Br bonds. Outstanding selectivity is also achieved because the substrates are more reactive toward methylation than the products. Efforts to expand the substrate scope, as well as detailed mechanistic studies, are underway.

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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.

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(15) The dimethylated product can also be obtained by treating **2j** with Me_2Zn.

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