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Iridium and phosphine promoted C–F bond activation: the C–S cross-coupling of aryl fluorides with diaryl disulfides to synthesize thioethers

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ABSTRACT

Carbon–fluorine bond is the strongest known single bond to carbon and proved very difficult to cleave. An iridium and phosphine promoted C–F bond activation was developed, for the first time achieving the C–S cross-coupling reaction of disulfides with aryl fluorides using iridium complex. The corresponding monoarylthiolation products were obtained at moderate to good yields. Thus, it represents a new method for the synthesis of aryl sulfides through C–F bond activation.

Transition metal catalyzed carbon–halogen bond activation and transformation into carbon–heteroatom bond has been considered a crucial aspect of organic synthesis in recent decades.[1] Among carbon–halogen bond, carbon–fluorine bond is the strongest known single bond to carbon and has proved very difficult to cleave,[2] the low reactivity of oxidative addition is attributable to the strength of the carbon–fluorine bond (154 kcal/mol for C_6F_6).[3] Despite the aforementioned difficulties, scientists have devoted great efforts to this area. Hitherto, several kinds of transition metals such as, Pd, Pt, Ni, Cu, Rh, Ti, Zr, Sm, Au have been proved to be effective to C–F bond activation and also achieved their catalytic C–F activations.[4,5] Among these examples, one of the strategies is to add activators involving Si, P, or B elements to make C–F bond activation easier.[6] Since Milstein reported the first example of M–F/P–R exchange reaction of metal–fluoride complexes,[7] several scientists (Macgregor, McGrady, Perutz, Li, et al.) have published their results in this area.[8–10] For example, Macgregor et al. explored the phosphine-assisted C–F activation by Pt, Ir, Pd, Rh complexes.[9] McGrady reported Ni-mediated C–F activation of pentafluoropyridine.[10] Li realized C–F activation of hexafluoropropene using cobalt and nickel complexes.10[d] Johnson described the reaction of $Ni(PEt_3)_2$ synthon with polyfluorinated pyridines and explored the reaction mechanism.[10e]

Recently, we have shown that the stoichiometric C–F bond activation of a chloro-bridged iridium(III) dimer bearing dfppy (2,4-difluorophenylpyridine) as a ligand leads to the formation of a heteroleptic cyclometalated iridium(III) fluorophenyl pyridine complex.[11] Having investigated the mechanism of this reaction, we were aware of the C–F bond activation was realized by the oxidative addition of iridium to the C–F bond. Therefore, it remains to be seen whether the amount of iridium complex involved in a C–F bond activation reaction can be reduced from a stoichiometric level to a catalytic level, or whether iridium complex can be used as a catalyst to realize the activation and even the transformation of C–F bond. Considering the availability of organic sulfur compounds and the significance of C–S bond formation, it is worthwhile to investigate the reaction between organofluorine compounds and organosulfur compounds. In this Letter, as a continuation of our previous iridium-involved C–F bond activation, we report on iridium promoted C–F bond activation and C–S bond cross-coupling reaction associated with phosphorus reagents by forming P–F bond and accordingly we propose a possible avenue for this process (Scheme 1).[10b]

We started with the coupling reaction of *p*-fluoronitrobenzene (**1a**) with bis(*p*-methoxyphenyl)disulfide (**2a**) in order to investigate the effect of iridium complex, phosphine and additive on the reaction. Arylthiolation product **3a** was obtained at a moderate yield (61%) when using $IrH(CO)(PPh_3)_3$ (2 mol%) dppBz (dppBz = 1,2-bis(diphenylphosphino)benzene, 4 mol%) and PPh_3

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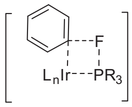


Scheme 1. The strategy of Ir-promoted C–F bond activation by forming P–F bond.

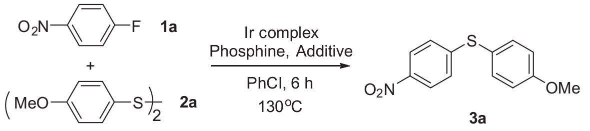
(1 equiv) in PhCl at 130 °C under an atmosphere of nitrogen (Table 1, entry 6) and no by-products like phosphine sulfides or thioethers were found. The yield of the desired product was lower than this when either of these reagents was absent. These results showed us that iridium complex, phosphine and additive were essential for getting a higher yield. And we considered the additive played an important role in the cleavage of C–F bond by serving as a fluorine-capture reagent and excess ligand to prohibit the quenching of catalyst by the product.

Next, the screening reaction conditions of additive was carried out for a better yield. The results are shown in Table 2. Arylthiolation product **3a** was obtained at a highest yield (85%) when using $IrH(CO)(PPh_3)_3$ (2 mol%) dppBz (4 mol%) and $^nBu_3$ P (1 equiv) in PhCl at 130 °C under an atmosphere of nitrogen (Table 2, entry 2). Thus, $^nBu_3P$ turned out to be the most suitable one.

Having delineated the optimal reaction conditions for the thiolation of fluorobenzene with disulfides to obtain the arylthiolation products through C–F bond activation (Table 2, entry 2), we applied them to a variety of substrates in order to determine the scope and limitations of the method. However, by changing 4-fluoronitrobenzene into 4-fluorobenzonitrile, the yield of desired product **3c** decreased dramatically into only 8%. So various iridium complexes were examined, it was exciting to find that product **3c** was obtained in higher yields (88%; Table 3) when $IrH(CO)(PPh_3)_3$ was replaced by $[Ir(COD)Cl]_2$ with addition of Cs_2CO_3 using dioxane as solvent. Cs_2CO_3 is crucial for this reaction to proceed for the reason that in the absence of Cs_2CO_3 the yields of the desired product were lower. As reported by some published articles[12], Cs_2CO_3 may play a role of a promoter in the activation of C–F bond especially for those fluorobenzenes which could not undergo this process easily. PhCl was changed into dioxane serving as solvent for the convenience of removal during the purification of product. Yields listed in Tables 3 and 4 showed us that dioxane could tolerate most substrates.

As depicted in Table 3, electron withdrawing groups on the phenyl ring of fluorobenzene were beneficial to the reaction (80–95% yield). Moreover, for the *m*-nitrile substrate, a monoarylthiolation product was obtained at a lower yield. This was probably due to the increased electron density at the *meta* position of such a substrate. While for the reaction involving fluorobenzene and fluorobenzene with electron donating group like methoxy as starting materials, the desired product could hardly be detected even though various methods involving different iridium complexes, phosphines, solvent with higher temperatures and longer reaction times have been tried. These results showed us the obvious influence of electron withdrawing groups on this reaction.

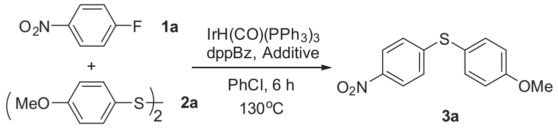
Table 1
Screen reaction conditions



Entry[a]	Ir complex/phosphine/additive	Yield[b] (%)
1	–/–/–	0
2	–/dppBz/–	23
3	–/–/PPh_3	34
4	–/dppBz/PPh_3	42
5	$IrH(CO)(PPh_3)_3$/–/–	<5
6	$IrH(CO)(PPh_3)_3$/dppBz/PPh_3	61

[a] Reaction conditions: **1a** (2.4 equiv), **2a** (0.25 mmol, 1.0 equiv), $IrH(CO)(PPh_3)_3$ (2%), dppBz (4%) and additive (1.0 equiv) in PhCl (2 mL).
[b] Isolated yields based on **2a** was reported.

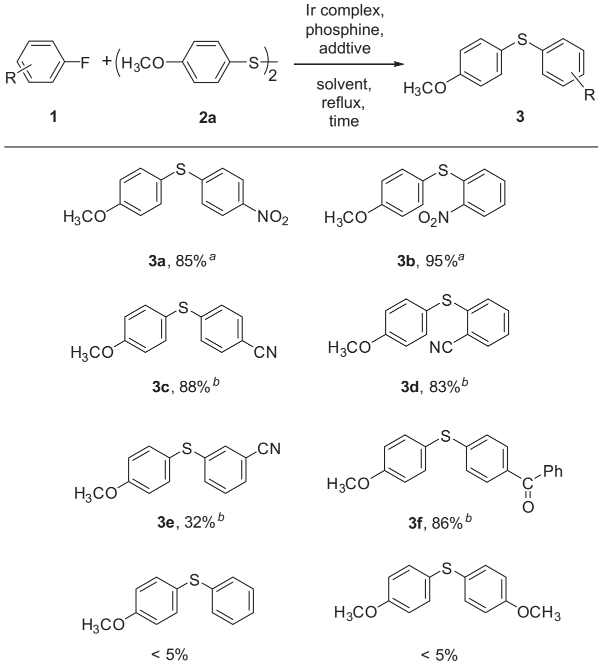
Table 2
Screen reaction conditions of additives



Entry[a]	Additive	Yield[b] (%)
1	Ph_3P	61
2	$^nBu_3P$	85
3	Cy_3P	79
4	$(p\text{-}MeC_6H_4)_3P$	32
5	$(p\text{-}MeOC_6H_4)_3P$	62
6	dppf	<5
7	dppe	76

[a] Reaction conditions: **1a** (2.4 equiv), **2a** (0.25 mmol, 1.0 equiv), $IrH(CO)(PPh_3)_3$ (2%), dppBz (4%) and additive (1.0 equiv) in PhCl (2 mL).
[b] Isolated yields based on **2a** was reported.

Table 3
Scope of the thiolation of fluorobenzene with diaryl disulfides



[a] Yield of **3a**, **3b** was obtained using method in entry 2 of Table 2.
[b] Yield of **3c**–**3f** were obtained under following conditions: **1** (3.0 equiv), **2a** (0.25 mmol, 1.0 equiv), $[Ir(COD)Cl]_2$ (2%), dppBz (4%), $^nBu_3P$ (1.0 equiv) and Cs_2CO_3 (3.0 equiv) in refluxed dioxane (2 mL) for 20 h. All yields listed in table were isolated yields based on **2a**.

Given the optimal conditions with which to obtain the arylthiolation product by C–F bond activation, we then examined the substrate scope with respect to disulfides. As shown in Table 4, a series of electron-donating groups in disulfides (such as *p*-tolyl, *p*-chlorophenyl and *n*-butyl) afforded the corresponding arylthiolation products **4a–f** at moderate to good yields (Table 4).

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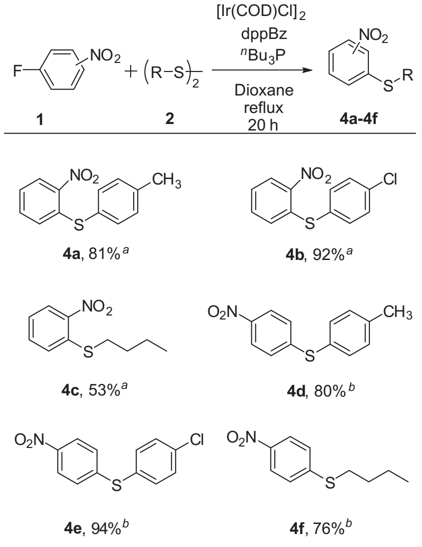
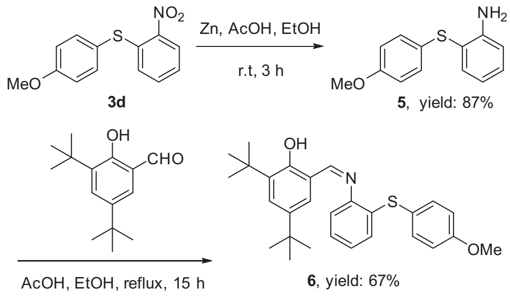
Table 4
Scope of the thiolation of fluorobenzene with diaryl disulfides



[a] Reaction conditions: **1d** (3.0 equiv), **2** (0.25 mmol, 1.0 equiv), [Ir(COD)Cl]$_2$ (2%), dppBz (4%) and ^{n}Bu$_3$P (1.0 equiv) in dioxane (2 mL).

[b] Reaction conditions: **1b** (3.0 equiv), **2** (0.25 mmol, 1.0 equiv), [Ir(COD)Cl]$_2$ (2%), dppBz (4%), ^{n}Bu$_3$P (1.0 equiv) and Cs$_2$CO$_3$ (3.0 equiv) in dioxane (2 mL). All yields listed in table were isolated yields based on **2**.



Scheme 2. The derivatization reactions.

This methodology of iridium-promoted C–F activation provides a convenient means to synthesize monoarylthiolation products from very cheap starting materials, such as fluorobenzene. For example, one of a series of useful ligands of titanium complexes exhibiting high activity in the polymerization of ethylene[13] was easily synthesized from the C–F activation product **3d** through the steps mentioned hereunder (Scheme 2).

In conclusion, we have demonstrated a novel iridium and phosphine promoted cross-coupling of aryl fluoride with diaryl disulfides by C–F bond activation. This reaction proceeds under mild conditions and tolerates some functional groups, and the reaction products are strongly influenced by substrates. Moreover, this is a new methodology for the construction of aryl sulfides from fluorinated organics. Further work seeks to investigate competitive processes between C–H bond and C–F bond cleavage under oxidative iridium complex catalysis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.133. These data include MOL files and InChiKeys of the most important compounds described in this article.

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