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Rhodium-Catalyzed Substitution Reaction of Aryl Fluorides with Disulfides: *p*-Orientation in the Polyarylthiolation of Polyfluorobenzenes

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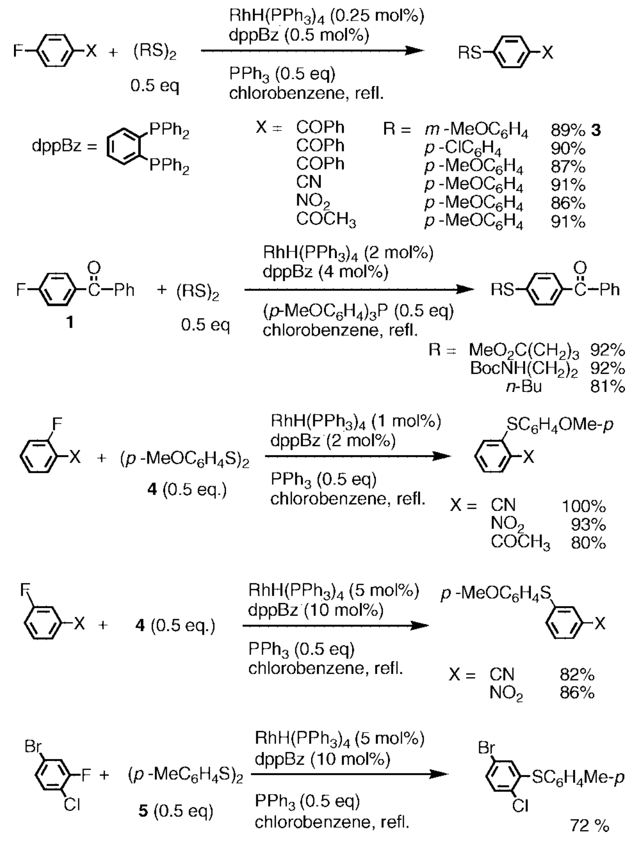
A variety of organofluorine compounds have become available in recent years, and their reactivity difference with organochlorine, organobromine, and organoiodine compounds can considerably broaden the potential of organic synthesis.[1] In this regard, the development of aromatic CF substitution reactions is desirable, and the use of transition metal catalysis has attracted much attention for organometallic reagents containing magnesium,[2] boron,[3] silicon,[4] tin,[5] copper,[6] or cesium,[7] which possess reactive and polarized metal-containing bonds. The reaction of less reactive reagents possessing unpolarized bonds with organofluorides, however, is rare; an exception is the hydrogenation reaction to convert CF bonds to CH bonds.[8] For the latter reactions to proceed, catalysts must be able simultaneously to activate a CF bond and another single bond of low polarity.

During our studies on the synthesis of organosulfur compounds utilizing rhodium catalysis, single bond metathesis reactions have become an important methodology. Rhodium complexes can cleave the SS bond and exchange bonds with SS, HH, CH, PS, PP, and CS bonds.[9] Described in this study is the finding that this methodology can be applied to the single bond metathesis of CF and SS bonds: Rhodium-catalyzed aryl- and alkylthiolation reactions of fluorobenzenes with disulfides. Synthesis of aryl sulfides using thiolates and aryl fluorides possessing strong electron-withdrawing substituents at the *o*- or *p*-positions has many precedents.[10] The present method employs disulfides without using strong bases.

Scheme 1



In the presence of $RhH(PPh_3)_4$ (0.25 mol%) and 1,2-bis(diphenylphosphino)benzene (dppBz) (0.5 mol%), bis(*m*-methoxyphenyl) disulfide **2** (0.5 equiv), *p*-fluorobenzophenone **1**, and PPh_3 (0.5 equiv) were reacted in refluxing chlorobenzene for 3 h giving 4-(*m*-methoxyphenylthio)benzophenone **3** in 89% yield (Scheme 1). The rhodium complex is essential, and **3** was not detected when **1** and **2** were treated with dppBz and PPh_3. $Rh_2(OAc)_4$ (70%), $Rh(acac)(C_2H_4)$ (84%), and $RhH(CO)(PPh_3)_4$ (71%) were active under identical conditions, whereas $RhCl(PPh_3)_3$, $[RhCl(cod)_2]_2$, $[RhCl_2Cp^*]_2$ (Cp* = pentamethylcyclopentadienyl), and $RhCl_3$ showed essentially no activity. **3** was not obtained in the absence of dppBz, and the use of other bidentate and monodentate ligands revealed a high efficiency of dppBz in this reaction: dppe, dppp, dppb, dpppentane, dpphexane, PPh_3, $(p\text{-}ClC_6H_4)_3P$, and $(p\text{-}MeOC_6H_4)_3P$ were not effective at all. In these unreactive cases, **2** was recovered in more than 80% yield. Added PPh_3 (0.5 equiv) trapped the fluoride to form Ph_3PF_2, which was confirmed by ^{31}P and ^{19}F NMR studies,[11] and as a result both arylthio groups of **2** could be used for the arylthiolation. It is presumed that rapid fluoride transfer from rhodium metal to phosphorus atom of the added PPh_3 took place,[12] or alternatively sulfenyl fluoride, which was formed by single bond metathesis of **1** and **2**, was rapidly converted to Ph_3PF_2. Essentially no reaction occurred in the absence of PPh_3. Dialkyl disulfides underwent alkylthiolation with **1**, when an electron-rich tris(*p*-methoxyphenyl)phosphine was employed as the fluoride trapping reagent.

The *p*- and *o*-derivatives of cyano- and nitrofluorobenzene reacted with bis(*p*-methoxyphenyl) disulfide **4** in the presence of the rhodium complex (0.25−2 mol%) to give the corresponding aryl sulfides in high yields (Scheme 1). Fluorobenzene, however, was inert under these conditions indicating the important role of electron-withdrawing groups. It should be noted that *m*-cyano- and *m*-nitrofluorobenzene reacted smoothly with **4**, provided that a higher catalyst loading (5 mol%) was employed. The reactivity of aryl fluoride was higher than bromide and chloride as indicated by the reaction of 1-bromo-4-chloro-3-fluorobenzene with di(*p*-tolyl) disulfide **5** giving the fluorine substituted product.

Mechanistically, the rhodium complex should be involved in the cleavage of the CF bond in aryl fluorides and the SS bond in disulfides, and the mode of CF cleavage is a subject of interest. Nucleophilic aromatic substitution of the aryl fluoride with rhodium

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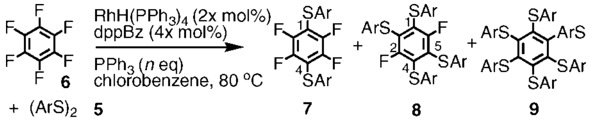
Scheme 2

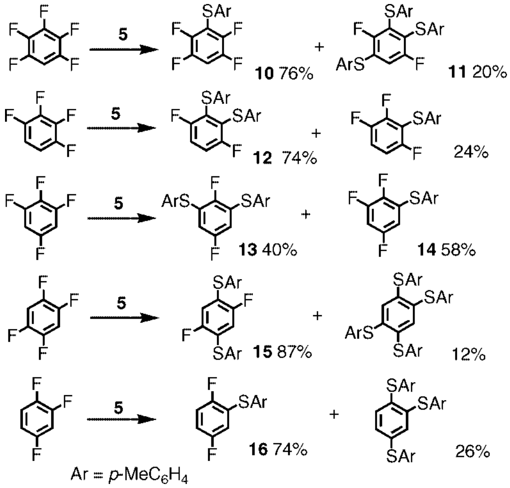


Ar = *p*-MeC$_6$H$_4$

	7	8	9
n = 0.5, x = 1	95%	5%	n.d.
2, 2	n.d.	95%	5%
3, 5	3%	3%	92%

n. d. = not detected

Scheme 3



thiolate is a possible pathway. However, oxidative addition to the CF bond or electron transfer of a low valent rhodium complex can also be conceivable at present.[13]

The polyarylthiolation reaction proceeded with polyfluorobenzenes, and a notable tendency to form *p*-difluorides was observed. When hexafluorobenzene **6** (2 equiv) was reacted with **5** and PPh$_3$ (0.5 equiv) for 4 h in the presence of RhH(PPh$_3$)$_4$ (2 mol%) and dppBz (4 mol%), 1,4-bis(*p*-tolylthio)-2,3,5,6-tetrafluorobenzene **7** was obtained in 95% yield with a small amount of 1,2,4,5-tetrakis-(*p*-tolylthio)-3,6-difluorobenzene **8** (5%) (Scheme 2). The reaction using 0.5 equiv of **6** resulted in the formation of **8** (95%) and a small amount of hexakis(*p*-tolylthio)benzene **9** (5%), which required a longer reaction time (12 h) for completion; under forced conditions and larger catalyst loading, the use of 0.33 equiv of **6** gave **9** in 92% yield after 48 h. Notably, bis-, tetrakis-, and hexakis-(*p*-tolylthio) derivatives, **7**, **8**, and **9**, were formed sequentially, and mono-, tris-, and pentakis(*p*-tolylthio) derivatives were not detected.[14] The results indicated very rapid second, fourth, and sixth arylthiolation reactions compared to the first, third, and fifth reactions.

The reaction of pentafluorobenzene and **5** (0.5 equiv) in the presence of RhH(PPh$_3$)$_4$ (5 mol%) and dppBz (10 mol%) gave 1-(*p*-tolylthio)-2,3,5,6-tetrafluorobenzene **10** in 76% yield along with 1,2,4-tris(*p*-tolylthio)-3,6-difluorobenzene **11** in 20% yield (Scheme 3). Three isomers of tetrafluorobenzene were reacted: 1,2,3,4-tetrafluorobenzene predominantly gave 3,6-difluoro-1,2-bis(*p*-tolylthio)benzene **12**; 1,2,3,5-tetrafluorobenzene gave comparable amounts of 2,5-difluoro-1,3-bis(*p*-tolylthio)benzene **13** and 2,3,5-trifluoro-1-(*p*-tolylthio) derivative **14**; 1,2,4,5-tetrafluorobenzene gave 2,5-difluoro-1,4-bis(*p*-tolylthio)benzene **15**. 1,2,4-Trifluorobezene gave 2,5-difluoro-1-(*p*-tolylthio)benzene **16** in 74% yield. These reactions clearly showed a tendency to form *p*-difluoro derivatives (*p*-difluoride rule). Related orientations were observed in the nucleophilic substitution reactions of polyfluorobenzenes with sodium methoxide in a nonexplicit manner as shown here.[15]

The origin of the *p*-difluoride rule is an interesting subject. An explanation is the minimization of the dipole moment by the formation of the *p*-difluoride structure. Alternatively, it can be due to an unusually high reactivity of *p*-arylthiolated fluorobenzenes toward the rhodium catalyzed.

A rhodium complex catalyzes arylthiolation of aromatic fluorides. The rhodium-catalyzed method contains a notable mode of CF activation by a transition metal catalyst and may offer an extremely broad scope for the manipulation of organosulfur compounds.

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

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