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Communication

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Palladium-Assisted Room-Temperature Nucleophilic Substitution of an Unactivated Aryl Fluoride

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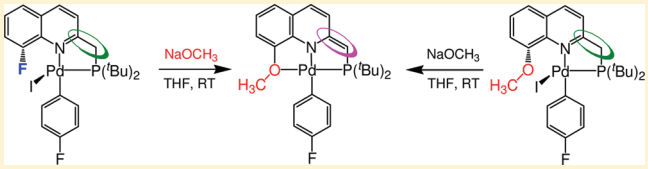
Supporting Information

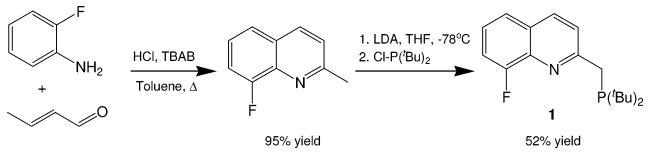
ABSTRACT: An organometallic palladium(II) complex of an 8-fluoroquinoline-based chelating ligand undergoes very facile nucleophilic substitution of the "unactivated" fluorine atom with the methoxy group upon simple stirring of its THF solution with sodium methoxide at room temperature. The final product of this reaction lacks the aromaticity in the heterocyclic ring of the quinoline moiety which might play an important role in the overall reactivity.



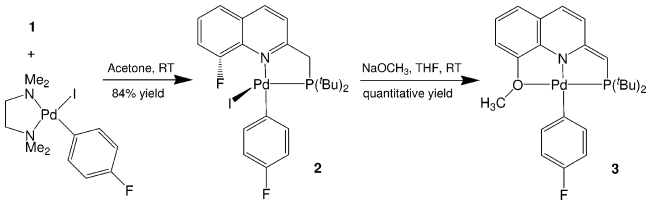
Activation of aryl−fluorine bonds by late-transition-metal complexes has remained a hot area of research for several decades.[1] For example, cleavage of these bonds can provide access to defluorinated compounds which are less persistent in nature than organic fluorides.[2] Fluoroaromatic substrates can also serve as valuable precursors for a variety of catalytic cross-coupling reactions.[3] In all cases, the emphasis of the late-transition-metal activation of C−F bonds was placed on the design of electron-rich metal complexes that can cleave these strong bonds giving new organometallic compounds,[4] the reaction usually requiring harsh reaction conditions.[5] Although polyfluoroaromatic compounds, as well as compounds having strong electron-withdrawing groups in the position ortho or para to the fluorine atom, are activated toward the nucleophilic substitution reaction that proceeds via S_NAr mechanism, the use of late-transition-metal complexes as activating groups in such reactions has not been reported.[6] Herein we present the first example of extremely facile nucleophilic replacement of unactivated aryl fluoride that is assisted by a Pd(II) complex.

Pincer ligands play an important role in bond activation studies and catalysis.[7] Heteroatoms, such as P, N, O, and S, are routinely used as "arms" of various metal pincer complexes. However, the use of halides as a part of the pincer system remains unknown. We were interested in exploring the possibility of using fluorine as a labile arm in pincer complexes. To facilitate the complexation to the metal center, we chose the rigid quinoline system, where the metal and fluoro substituents at the 8-position would be pitched together due to the steric requirements.[8] Toward this end, we prepared the fluorine-containing ligand **1** via the Doebner−Miller condensation of 2-fluoroaniline with crotonaldehyde[9] followed by a reaction with lithium diisopropylamide (LDA) and Cl-P(t-Bu)$_2$ (Scheme 1). The addition of 1 equiv of [Pd(4-FC$_6$H$_4$)I(tmeda)] (tmeda = tetramethylethylenediamine) to a solution of **1** in acetone resulted in the formation of complex **2** in 84% yield after 5 days at room temperature (Scheme 2). The yellow complex is only sparingly soluble in nonpolar benzene or toluene. The ^{31}P NMR spectrum of **2** in $CDCl_3$ showed a singlet at 60.7 ppm, 30 ppm downfield from the signal in free **1**. Unexpectedly, the ^{19}F NMR signal of the 8-fluoro substituent in **2** appears at −102.1 ppm, more than 25 ppm downfield from the fluorine signal in **1**. As we attributed such a significant shift in the spectrum to interactions between the fluorine atom and palladium, we were eager to determine the crystal structure of **2** (Figure 1; hydrogens are omitted). Yellow crystals suitable for crystallographic analysis were obtained upon slow evaporation of its benzene solution. Surprisingly, the distance between the two atoms was sufficiently long, 2.991 Å, to rule out bonding interactions. However, this distance, as well as the I- - -F distance of 3.301 Å, fall within the sum of the van der Waals radii of Pd and F (3.1 Å) and of I and F (3.45 Å), respectively. These factors may explain the significant change in the ^{19}F chemical shift upon Pd complexation. The steric congestion also results in the iodo ligand moving out of plane in this

Scheme 1



Scheme 2



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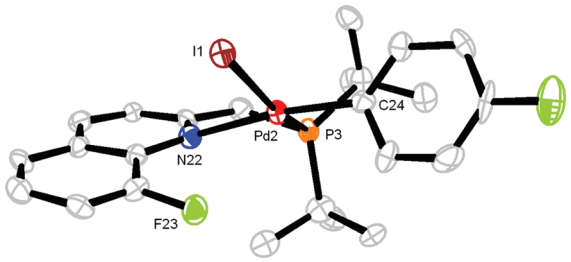


Figure 1. X-ray structure of a molecule of **2**.

distorted-square-planar Pd(II) complex with an I−Pd−P angle of 162.73(7)°. At the same time, the quinoline system became nonplanar near the metal center with an F−C−C−N dihedral angle of 8.62°.

We then explored the reactivity of **2**. Surprisingly, we found that the addition of 1 equiv of sodium methoxide in THF at room temperature resulted in an incomplete conversion of **2** to a new product that has only one signal in its ^{19}F NMR spectrum. Using a 10-fold excess of $NaOCH_3$ led, within 1 h, to a very clean formation of a product that exhibits a single resonance in the ^{19}F NMR spectrum at −120.7 ppm as well as a singlet at 89.8 ppm in the ^{31}P NMR spectrum (Scheme 2). The ^{1}H NMR spectrum of this new complex, **3**, confirmed the presence of the 4-FC_6H_4 group at the Pd center as well as a new OCH_3 group (2.87 ppm). The characteristic doublet due to the CH_2−P group (2H) that appeared at 3.84 ppm in **2** has been replaced by a doublet at 3.35 ppm which integrated as 1H in comparison with other signals in the system. As the NMR spectra clearly indicated dramatic changes in the overall structure of the Pd complex, together with the removal of the 8-fluoro substituent of the quinoline system, we sought to analyze **3** by X-ray crystallography. Dark orange crystals were obtained by slow evaporation of its benzene solution, and the structure is shown in Figure 2 (hydrogens are omitted). The

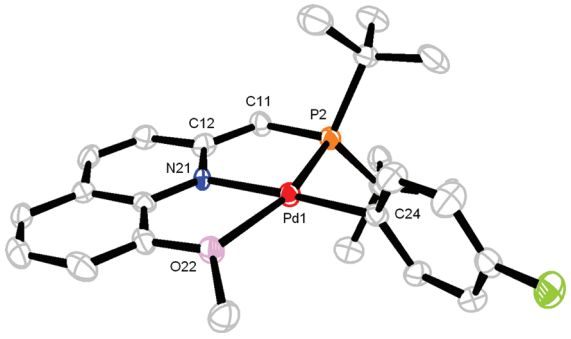
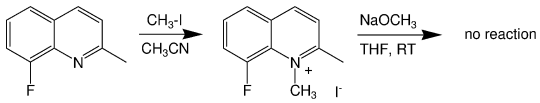


Figure 2. X-ray structure of a molecule of **3**.

structure of **3** shows that the 8-fluorine atom was replaced by a methoxy group which now coordinates to the metal center. In addition, dearomatization of the quinoline system took place due to the deprotonation of the CH_2−P group and formation of the C=C double bond. The latter is clearly observed in the structure, the distance C(11)−C(12) being 1.374(9) Å compared with 1.488(12) Å in **2**. The now covalent Pd(1)−N(21) bond is noticeably shorter (2.027(5) Å) than in **2** (2.178(7) Å), although this can be attributed to the enforced elongation due to steric repulsions in the latter. The C(12)−N(21) bond distance is significantly longer than that in **2** (1.376(8) Å vs 1.348(11) Å), while the C(20)−N(21) distance shortened to 1.359(8) Å from 1.385(11) Å in **2**. The change in the hybridization to sp^3 had no effect on the angles around the nitrogen atoms, which remain close to 120°, likely as a result of the formation of a rigid planar pincer system. Two five-membered chelating rings of the new pincer system are clearly unsymmetrical. The O(22)−Pd(1)−N(21) angle of 76.79(18)° is significantly smaller than the P(2)−Pd(1)−N(21) angle of 84.26(15)°. Conversely, the C(19)−O(22)−Pd(1) angle is substantially larger than C(11)−P(2)−Pd(1): 111.8(4)° vs 100.6(2)°, respectively. Due to the enforced planarity of the chelating rings, the 4-fluorophenyl group is now bent away from the bulky *tert*-butyl substituents of the phosphine ligand.

Considering the absence of strong electron-withdrawing groups directly conjugated with the 8-position, it is very surprising that the nucleophilic replacement of the fluoro substituent with OCH_3 takes place under very mild conditions. Heating **1** with excess of sodium methoxide in THF did not result in the fluorine substitution reaction. In theory, the Pd center in **2** can be viewed as a Lewis acid that coordinates to the quinoline nitrogen activating the fluorine atom for the S_NAr-type reaction. To verify this, we prepared the salt *N*,2-dimethyl-8-fluoroquinolinium iodide, which possesses a quaternary nitrogen center as a very strong electron-withdrawing group (Scheme 3).[10] When this compound was treated with an

Scheme 3



excess of $NaOCH_3$ in THF or DMSO, no replacement of the fluoro atom with OCH_3 was observed, even upon moderate heating. Thus, it seems unlikely that the coordination of a neutral palladium center to the nitrogen atom is sufficient to activate the C−F bond toward nucleophilic substitution.

This suggests that the dearomatization of the quinoline moiety, via the deprotonation of the CH_2−P group, triggers the nucleophilic substitution.[11] In order to explore the feasibility of such a facile deprotonation reaction, we prepared ligand **4**, which already has the 8-CH_3O group installed, and reacted it with [Pd(4-FC_6H_4)I(tmeda)] (Scheme 4). The complete formation of the new complex **5** was observed within several hours at room temperature. Although we presently do not have the X-ray structure of **5**, we believe that the iodo ligand remains coordinated to the Pd center, similar to the case for **2**. In support, the removal of the iodine with $AgBF_4$, to give **6**, resulted in a significant shift in the ^{31}P NMR spectrum: 92.4 vs 73.0 ppm in **5**. The X-ray structure of **6** is shown in Scheme 4. The structure confirms the pincer-type coordination mode. The Pd−N coordination bond in the complex **6** is longer than that in the amide complex **3**, 2.056(4) Å vs 2.027(5) Å, while the Pd distance to the 4-FC_6H_4 group trans to it is now slightly shorter, 2.001(5) Å vs 2.013(6) Å, indicating a weaker trans influence of the aromatic nitrogen atom compared with that of the amide. The addition of 10 equiv of $NaOCH_3$ to a THF solution of **5** resulted in the quantitative formation of **3**. The reaction is reversible, and the addition of HI rapidly converts **3** to **5**. Thus, it is likely that the addition of the methoxide leads to the dearomatization of the quinoline ring in **2**, followed by the nucleophilic replacement of the 8-fluoro substituent via a Pd-assisted pathway.[12]

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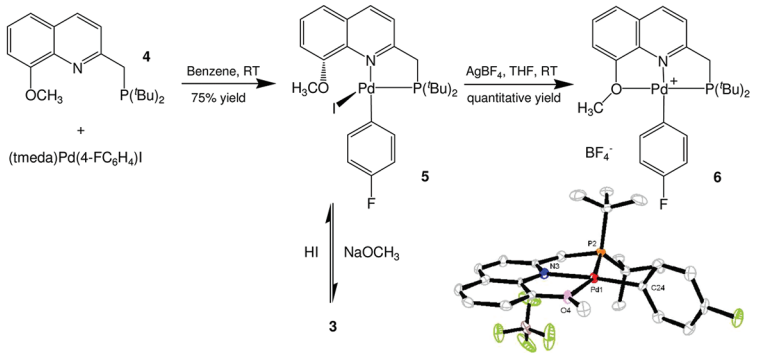
Scheme 4



In summary, we have presented the first example of a mild and selective nucleophilic substitution of an unactivated aromatic fluoride that is assisted by a late-transition-metal center. Although the detailed mechanism of the metal activation mode is presently under investigation, the facile base-promoted dearomatization of the quinoline system seems to play a role in the overall process. We are now exploring the scope of this and similar nucleophilic substitution reactions.

■ ASSOCIATED CONTENT

Supporting Information

Text giving complete experimental details and CIF files giving X-ray crystal data for complexes **2**, **3**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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