VIP Pentafluoroethylation Very Important Paper

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Well-Defined CuC_2F_5 Complexes and Pentafluoroethylation of Acid Chlorides**

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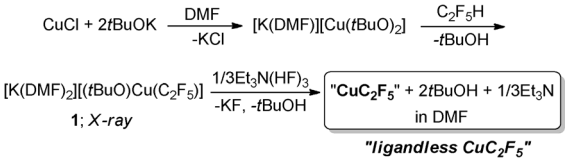
Abstract: *Four new well-defined Cu^I complexes bearing a C_2F_5 ligand have been prepared and fully characterized: $[(Ph_3P)_2CuC_2F_5]$ (**2**), $[(bpy)CuC_2F_5]$ (**3**), $[(Ph_3P)Cu(phen)C_2F_5]$ (**4**), and $[(IPr^*)CuC_2F_5]$ (**5**). X-ray structures of all four have been determined, showing that the C_2F_5-ligated Cu atom can be di- (**5**), tri- (**2** and **3**), and tetracoordinate (**4**). The mixed phen-PPh_3 complex **4** is a highly efficient fluoroalkylating agent for a broad variety of acid chlorides. This high-yielding transformation represents the first general method for the synthesis of $RCOC_2F_5$ from the corresponding RCOCl.*

Derivatives of Cu^I bearing a CF_3 ligand play a central role in the development of trifluoromethylation methods for the synthesis of biologically active compounds and specialty materials.[1] The so-called "$CuCF_3$", referred to as "an elusive and complex species" by Wiemers and Burton,[2] is particularly widely used in synthesis. However, $CuCF_3$ is not a well-defined compound but rather a variety of species of the general formula $[L_nCuCF_3]$, where L is a weakly bound ligand or a solvent molecule.[3] Fully characterized CF_3Cu^I complexes are very rare and only a handful of such compounds have been reported.[4]

Synthetic methodologies for the introduction of the C_2F_5 group into organic molecules are not nearly as developed as trifluoromethylation methods.[5] Nonetheless, examples have already been reported[6] of biologically active C_2F_5 derivatives that outperform their CF_3 congeners. For instance, some valylprolylvalylpentafluoroethyl ketones have been found to act as active inhibitors of human neutrophil elastase, whereas the corresponding CF_3 derivatives exhibit no activity.[6a] Given the clear need for new pentafluoroethylation methods, it is critical to study $C_2F_5Cu^I$ complexes as fluoroalkylating agents. Such well-defined complexes, however, are even scarcer than those bearing the CF_3 ligand. Daugulis and coworkers[7] have determined the crystal structure of the highly unstable $[K(DMPU)_3]^+[Cu(C_2F_5)Cl]^-$ that was formed in 14% yield by the thermal decomposition of a $CuCF_3$ derivative. The Hartwig group[8] have prepared $[(phen)Cu(C_2F_5)]$ (phen = 1,10-phenanthroline) for pentafluoroethylation of (hetero)aryl pinacolboronates and (hetero)aryl bromides. This complex has been isolated and shown[8a] to equilibrate with $[(phen)_2Cu]^+[Cu(C_2F_5)_2]^-$ in solution. Two of us[9] have developed the cupration of C_2F_5H with [K(DMF)]-$[(t\text{BuO})_2Cu]$, leading to $[K(DMF)_2][(t\text{BuO})Cu(C_2F_5)]$ (**1**), whose structure has been established by single-crystal diffraction. There have been no reports of efficient pentafluoroethylation reactions with a structurally defined $C_2F_5Cu^I$ complex. Herein we describe the first study targeting the synthesis and full characterization of pentafluoroethyl derivatives of copper. We also demonstrate the previously unknown pentafluoroethylation of acid chlorides with one of the new well-defined $C_2F_5Cu^I$ complexes. This new, broad-scope transformation is highly efficient and selective, affording ketones of the type $RCOC_2F_5$ in up to 95% yield.

Complex **1** has been shown[9] to react with 4-IC_6H_4F to give a mixture of 4-$C_2F_5C_6H_4F$ and 4-$t\text{BuOC}_6H_4F$ in a 1:1.2 molar ratio. The undesired *tert*-butoxylation could be suppressed by the acidolysis of the Cu–O bond in **1** with $Et_3N{\cdot}3HF$ (TREAT HF). This reaction produces so-called "ligandless" CuC_2F_5, in which the Cu^I center is stabilized by coordination with weakly bound DMF solvent molecules, Et_3N released from the TREAT HF, and *t*BuOH coproduced in the cupration step (Scheme 1).[3,9,10] We reasoned that



Scheme 1. Preparation of $[K(DMF)_2][(t\text{BuO})Cu(C_2F_5)]$ (**1**) and "ligandless CuC_2F_5".[9]

replacing these weakly coordinated molecules with stronger binding ligands might produce new isolable complexes of the type $L_nCuC_2F_5$ for full characterization and use in pentafluoroethylation reactions.

The addition of triphenylphosphine (5 equiv) to ligandless CuC_2F_5 in DMF (Scheme 1), followed by evaporation and crystallization from benzene/hexane produced a PPh_3 complex. This complex was expected to be tetrahedral $[(Ph_3P)_3CuC_2F_5]$, akin to the previously characterized CF_3 analogue $[(Ph_3P)_3CuCF_3]$.[4d] Unexpectedly, however, X-ray diffraction showed that the Cu atom in the isolated product

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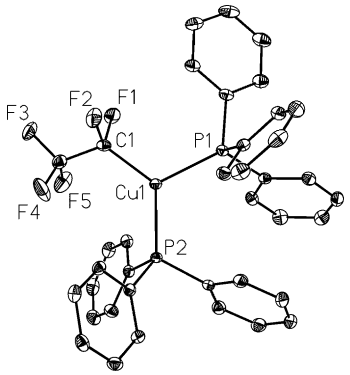


Figure 1. ORTEP drawing of $[(Ph_3P)_2CuC_2F_5]$ (**2**) with all H atoms omitted for clarity and thermal ellipsoids drawn at the 50% probability level.

$[(Ph_3P)_2CuC_2F_5]$ (**2**) is ligated with only two rather than three phosphines (Figure 1). Given the high lability of the PPh_3 ligands in $[(Ph_3P)_3CuCF_3]$,[4d] the bulkier C_2F_5 group apparently forces the third phosphine off the copper atom. A similar strategy was used to prepare $[(bpy)CuC_2F_5]$ (**3**; bpy = 2,2′-bipyridyl) and $[(Ph_3P)Cu(phen)C_2F_5]$ (**4**). Treatment of ligandless CuC_2F_5 in DMF with bpy or both PPh_3 and phen furnished **3** and **4**, which were also structurally characterized (Figures 2 and 3).

A different approach was used to complexes of the type $[(NHC)CuC_2F_5]$, where NHC is an N-heterocyclic carbene. Rather than reacting ligandless CuC_2F_5 with a preformed

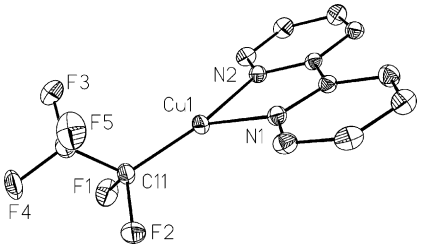


Figure 2. ORTEP drawing of $[(bpy)CuC_2F_5]$ (**3**) with all H atoms omitted for clarity and thermal ellipsoids drawn at the 50% probability level.

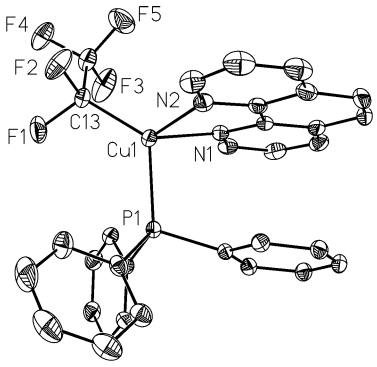


Figure 3. ORTEP drawing of $[(Ph_3P)Cu(phen)C_2F_5]$ (**4**) with all H atoms omitted for clarity and thermal ellipsoids drawn at the 50% probability level.

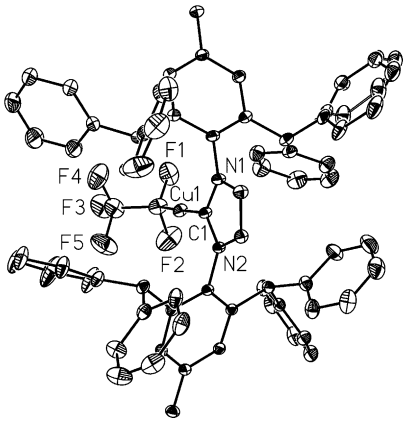


Figure 4. ORTEP drawing of $[(IPr^*)CuC_2F_5]\cdot C_6H_5CH_3$ (**5**$\cdot C_6H_5CH_3$) with the cocrystallized toluene molecule and all H atoms omitted for clarity and thermal ellipsoids drawn at the 50% probability level.

NHC ligand, the corresponding imidazolium salt was treated with basic **1** to prompt Cu–NHC bond formation through deprotonation. In this way, $[(IPr^*)CuC_2F_5]$ (**5**; IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) was prepared, isolated, and structurally characterized as a 1:1 toluene solvate (Figure 4). Less bulky imidazolium salts bearing *t*Bu or 2,6-(*i*Pr)$_2$C$_6$H$_3$ groups on the N atoms were found to react with **1** nonselectively, producing C_2F_5H (^{19}F NMR).

Both tricoordinate **2** and **3** are planar in the crystal. The Y-shaped molecule of **2** (Figure 1) displays noticeably different C–Cu–P bond angles (117.10(5)° and 126.58(5)°) and Cu–P bond distances (2.2845(5) and 2.2585(6) Å). With the N–Cu–N angle of 80.0(2)°, the Y geometry of **3** is considerably more distorted, as manifested by the C–Cu–N bond angles of 128.3(2)° and 151.3(2)° and Cu–N bond distances of 2.089(5) and 2.013(4) Å. On average, the Cu–C_2F_5 bond length in **2**–**5** (1.93–1.99 Å) is longer than in the $[Cu(C_2F_5)Cl]^-$ anion (1.916(9) Å)[7] and **1** (1.892(5) Å),[9] and more comparable with the value of 1.982(8) Å previously determined for the structure of a Cu^{III} complex $[(Et_2NCS_2)Cu(C_2F_5)_2]$.[11] In **4** and **5**, the C_2F_5 group is disordered over two (78:22) and three (61:23:16) positions, respectively. The Cu–CF_2–CF_3 bond angles in **2**–**5** (111–124°) are similar to those previously reported for the structures of $[Cu(C_2F_5)Cl]^-$ (116.8(5)°),[7] **1** (115.7(4)°),[9] and the Cu^{III} complex $[(Et_2NCS_2)Cu(C_2F_5)_2]$ (117.4(6)°).[11]

Of the four new $C_2F_5Cu^I$ derivatives synthesized and structurally characterized in the current study, only one (**4**) is a coordinatively saturated 18e species. Unsurprisingly, **4** is the most stable and easiest to isolate and purify CuC_2F_5 complex reported herein. Furthermore, the synthesis of this compound is scalable, as was demonstrated by the preparation of 3.52 g (90% yield) of **4** of >90% purity (^{19}F NMR). Additional purification by recrystallization from warm benzene/hexane furnished analytically and spectroscopically pure **4** as well-shaped red-orange crystals in 72% overall yield. Although **4** is air-sensitive and should be handled in an inert atmosphere, it is noticeably more robust than 16e tricoordinate **2** and **3**. The PPh_3 complex **2** was prepared and isolated analytically pure in

60% yield. The orange bpy complex **3** (59% yield, 95% purity) is particularly air-sensitive and poorly stable, showing signs of decomposition (darkening) within a few days even if stored in an argon-filled glove-box. It is noteworthy that highly air-sensitive **3** is the C_2F_5 congener of [(bpy)$CuCF_3$], an active complex[12] in the oxidative trifluoromethylation of arylboronic acids.[13] The NHC complex **5** was isolated spectroscopically pure in 68% yield. Recrystallization from benzene/hexanes gave analytically pure **5**. As mentioned above, [(phen)CuC_2F_5] exists in equilibrium with $[(phen)_2Cu]^+[Cu(C_2F_5)_2]^-$.[8] Similarly, solutions of **2**, **3**, and **4** were found to contain 8%, 11%, and 5% of $[Cu(C_2F_5)_2]^-$, respectively (^{19}F NMR). In contrast, the NHC complex **5** does not equilibrate with $[(IPr^*)_2Cu]^+[Cu(C_2F_5)_2]^-$ in solution, apparently due to the exceptional steric bulk of the IPr* ligand.[14]

As mentioned above, pentafluoroethyl ketones are of particular importance for the synthesis of biologically active C_2F_5 derivatives. Readily available and inexpensive acid chlorides RCOCl would be ideal precursors to $RCOC_2F_5$ by pentafluoroethylation of the C–Cl bond. However, the only currently available one-step transformation of this type proceeds via a ketene intermediate and is, therefore, inapplicable to a broad variety of acid chlorides devoid of H atoms in the α position.[15] In general, $C_2F_5Cu^I$ reagents seem promising for pentafluoroethylation of the RCO–Cl bond. Neither **1** nor ligandless CuC_2F_5, however, could be used for this transformation. First, complex **1** bearing C_2F_5 and *t*BuO ligands on the Cu center both pentafluoroethylates and *tert*-butoxylates electrophiles[9] (see above). Second, the *t*BuOH by-product present in the ligandless CuC_2F_5 solutions (Scheme 1) could esterify RCOCl, especially in the presence of Cu. Finally, the DMF solvent can react with acid chlorides to generate $[RCOOCH{=}NMe_2]^+Cl^-$, a Vilsmeyer–Haack-type adduct that is reactive toward nucleophiles, alcohols included.[16] In contrast, the well-defined pre-isolated $C_2F_5Cu^I$ complexes **2**–**5** in an inert solvent are devoid of these problems. Therefore, we explored the possibility of using them as pentafluoroethylating agents for acid chlorides. The initial tests were performed with 4-FC_6H_4COCl as the substrate to obtain additional information by ^{19}F NMR spectroscopic analysis of the reaction mixtures.

Exploratory experiments indicated that 4-FC_6H_4COCl reacted with 1.05 equiv of **2** or **5** (THF, 65 °C) in a nonselective manner to give 4-$FC_6H_4COC_2F_5$ in only about 5–25% yield (^{19}F NMR) at > 90% conversion. The bpy complex **3** was not considered as a reagent because of its poor stability and exceedingly facile oxidizability (see above). We were delighted to find, however, that the mixed phen-PPh_3 complex **4** smoothly pentafluoroethylated 4-FC_6H_4COCl in a highly selective manner. To achieve high chemoselectivity and avoid the formation of by-products, **4** used for the fluoroalkylation should be thoroughly purified by recrystallization. THF was a particularly convenient solvent for the reaction because the Cu by-product, [(Ph_3P)Cu(phen)Cl] (**6**), appeared to be poorly soluble in THF and precipitated out as the pentafluoroethylation occurs. Only 1 equiv of **4** was needed to reach > 95% conversion of 4-FC_6H_4COCl after 3 h at 65 °C. During that time, the red color from **4** vanished and a yellow precipitate of **6** was produced. The structure of **6** in the form of a 1:1 1,2-dichloroethane solvate was established by X-ray analysis (Figure 5).

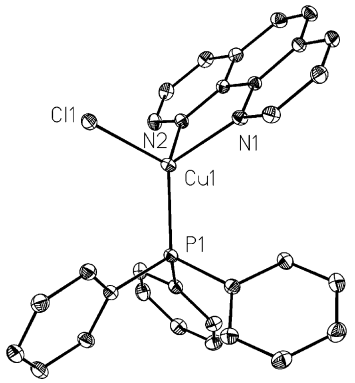
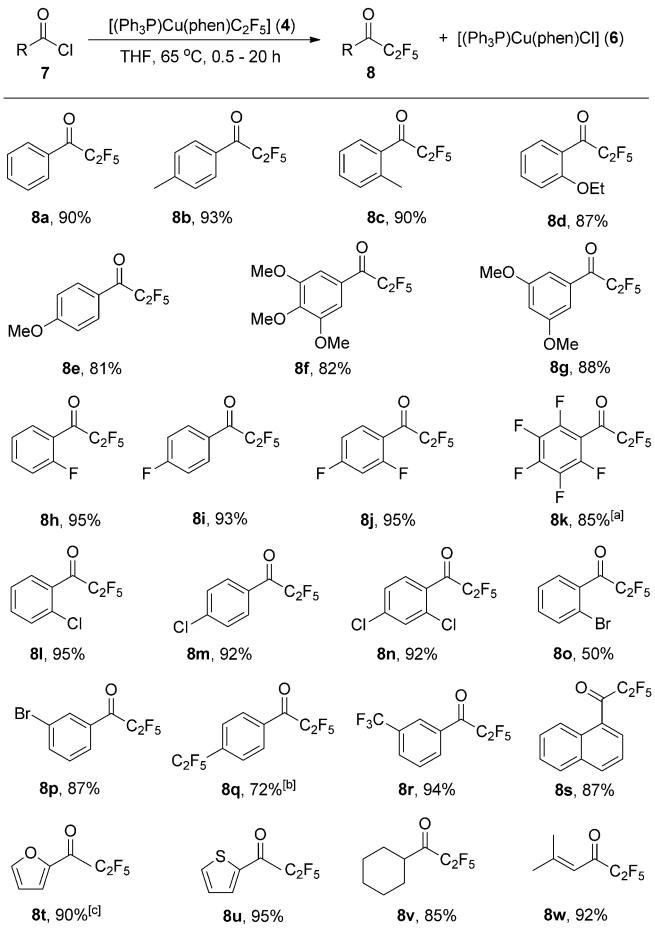


Figure 5. ORTEP drawing of [(Ph_3P)Cu(phen)Cl]·$C_2H_4Cl_2$ (**6**·$C_2H_4Cl_2$) with the cocrystallized molecule of 1,2-dichloroethane and all H atoms omitted for clarity and thermal ellipsoids drawn at the 50% probability level.

Various acid chlorides **7** cleanly reacted with **4** (1 equiv) to give the corresponding ketones **8** in high yield (Scheme 2). The reaction proceeded smoothly with benzoic acid chlorides bearing electron-withdrawing and electron-donating substituents in the *ortho*, *meta*, and *para* positions of the benzene ring (**7a**–**r**) and 1-naphthoic acid chloride (**7s**). Both 2-furancarboxylic acid chloride (**7t**) and 2-thiophenecarboxylic acid chloride (**7u**) underwent pentafluoroethylation in nearly quantitative yield. The aliphatic (**7v**) and vinylic (**7w**) derivatives were also converted into the corresponding pentafluoroethyl ketones in 85% and 92% yield, respectively. In all reactions, the conversion was close to quantitative.

Fluorine and chlorine atoms on the aromatic ring are well-tolerated (**8h**–**n**), and so is bromine in the *meta* position (**8p**), as manifested by the high yields (85–95%) of the corresponding ketone products. In contrast, the reaction of 2-bromobenzoic acid chloride furnished the desired product (**8o**) in only 61% yield, as a consequence of competing pentafluoroethylation of the aromatic C–Br bond. The so-called "*ortho* effect",[3,17] that is, the enhanced reactivity of halogen atoms in the 2-position of the ring, evidently brought about the side formation of 2-(C_2F_5)$C_6H_4COC_2F_5$ (15%) and 2-(C_2F_5)C_6H_4COCl (10%) in the reaction of 2-BrC_6H_4COCl. Likewise, the reaction of 4-IC_6H_4COCl, which contains an even more reactive Ar–I bond, with 1 equiv of **4** gave rise to 4-$IC_6H_4COC_2F_5$, 4-(C_2F_5)C_6H_4COCl, and 4-(C_2F_5)$C_6H_4COC_2F_5$ in an approximately 3:4:6 molar ratio. With 2 equiv of **4**, this reaction afforded the disubstituted product (**8q**) in 72% yield. The aromatic C–Cl (**7l**–**n**) and certain C–Br (**7p**) bonds staying intact in the reaction provide an opportunity for further functionalization of the pentafluoroethylated products by a variety of metal-catalyzed cross-coupling reactions. Such chloroarenes bearing the strongly electron-withdrawing COC_2F_5 group on the ring (**8l**–**n**) are electron-deficient and therefore "activated" toward C–Cl bond functionalization with transition metals.[18]

Electron-withdrawing groups on the ring of substituted benzoic acid chloride derivatives facilitate the reaction. The



Scheme 2. Pentafluoroethylation of acid chlorides (0.4 mmol) with **4** (0.4 mmol) in THF (0.5–0.9 mL). The yields were determined by ^{19}F NMR spectroscopy with 1,3-bis(trifluoromethyl)benzene as an internal standard. For details, see the Supporting Information. [a] 10 min at 23 °C. [b] With 0.5 equiv of 4-IC_6H_4COCl. [c] With 1.1 equiv of **7t**.

particularly electron-deficient pentafluorobenzoic acid chloride (**7k**) reacted with **4** within 10 min at room temperature to give $C_6F_5COC_2F_5$ (**8k**) in 85% yield. A nitro group on the ring, however, is not tolerated: *meta*- and *para*-nitrobenzoic acid chlorides and 3,5-dinitrobenzoic acid chloride did not yield the corresponding ketones upon treatment with **4**. Instead, these reactions gave rise to C_2F_5H as the main product. A detailed study of this change in reactivity was beyond the scope of the current work. It is conceivable, however, that coordination of the NO_2 group to the Cu^I center[3] triggers single-electron transfer and the formation of $C_2F_5^{\cdot}$ radicals that abstract hydrogen from the solvent (THF).[19] Apart from the nitro derivatives, all other substrates (Scheme 2) reacted with **4** in a highly chemoselective manner, showing no signs of radical processes. We therefore propose that, like the trifluoromethylation of aryl halides, the pentafluoroethylation of RCOCl is governed by a nonradical mechanism, possibly involving C–Cl oxidative addition to Cu^I, followed by C–C_2F_5 reductive elimination from the resultant Cu^{III} intermediate.[3] Phosphine dissociation from coordinatively saturated **4** is likely a prerequisite for the oxidative addition to occur. It is noteworthy that, like other Cu^I perfluoroalkyl compounds,[1,4,7–10,12,13,17] **4** and its equilibrium partner $[Cu(C_2F_5)_2]^-$ (see above) are unreactive toward C=O bonds. Therefore, no C_2F_5 addition to the carbonyl group of the desired $RCOC_2F_5$ product takes place even if **4** is used in excess for the reaction with RCOCl.

The aforementioned precipitation of **6** during the process facilitates the workup of the reaction mixtures and isolation of the desired product. On the other hand, the enhanced volatility of pentafluoroethyl ketones can cause considerable losses during their isolation, especially from reactions performed on a small scale. Four less-volatile (GC) pentafluoroethyl ketone products **8f**, **8n**, **8p**, and **8s** were selected for the synthesis on a larger scale and isolation. The reactions of **7f**, **7n**, and **7s** performed with 0.2 g of **4** (0.32 mmol) furnished the corresponding desired isolated products in 68%, 72%, and 82% yield, respectively. From a larger scale-up experiment with 1 g of **4** (1.6 mmol), **8p** was isolated in 93% yield. The synthesis of **8p** was chosen for the largest scale reaction due to the presence on its molecule of the Br atom for further functionalization, if desired.

In summary, four novel Cu^I complexes bearing C_2F_5 ligands have been prepared and characterized in solution and in the solid state.[20] Depending on the nature of the ligands, the C_2F_5-ligated Cu atom in these complexes can be di-, tri-, or tetracoordinate. In contrast with tetrahedral $[(Ph_3P)_3CuCF_3]$,[4d] its C_2F_5 analogue, $[(Ph_3P)_2CuC_2F_5]$ (**2**), is trigonal-planar Y-shaped, containing only two PPh_3 ligands per Cu. The mixed phen-PPh_3 complex $[(Ph_3P)Cu(phen)C_2F_5]$ (**4**) is a highly efficient fluoroalkylating agent for a broad variety of acid chlorides. This high-yielding transformation represents the first general method for the synthesis of pentafluoroethyl ketones from the corresponding acid chlorides in one step.

Keywords: copper · fluorine · organometallic synthesis · pentafluoroethylation · pentafluoroethyl ketones

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Angew. Chem. **2015**, *127*, 5307–5311

[1] For selected recent reviews, see a) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475; b) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161; c) T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, 6679; d) X. Liu, X. Wu, *Synlett* **2013**, 1882; e) A. Lishchynskyi, P. Novák, V. V. Grushin in *Science of Synthesis: C-1 Building Blocks in Organic Synthesis 2* (Ed.: P. W. N. M. van Leeuwen), Thieme, Stuttgart, **2013**, p. 367; f) P. Chen, G. Liu, *Synthesis* **2013**, 2919; g) J. Xu, X. Liu, Y. Fu, *Tetrahedron Lett.* **2014**, *55*, 585; h) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors, F. R. Leroux, *Beilstein J. Org. Chem.* **2013**, *9*, 2476; i) K. Jouvin, C. Guissart, C. Theunissen, G. Evano in *Copper-Mediated Cross-Coupling Reactions* (Eds.: G. Evano, N. Blanchard), Wiley, Hoboken, NJ, **2014**, p. 515.
[2] D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.* **1986**, *108*, 832.
[3] A. I. Konovalov, A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2014**, *136*, 13410.
[4] a) G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600; b) G. G. Dubinina, J. Ogikubo, D. A. Vicic, *Organometallics* **2008**, *27*, 6233; c) H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2011**, *50*,

3793; *Angew. Chem.* **2011**, *123*, 3877; d) O. A. Tomashenko, E. C. Escudero-Adán, M. Martínez Belmonte, V. V. Grushin, *Angew. Chem. Int. Ed.* **2011**, *50*, 7655; *Angew. Chem.* **2011**, *123*, 7797; e) Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K.-W. Huang, *Organometallics* **2011**, *30*, 3229; f) A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901; g) A. I. Konovalov, J. Benet-Buchholz, E. Martin, V. V. Grushin, *Angew. Chem. Int. Ed.* **2013**, *52*, 11637; *Angew. Chem.* **2013**, *125*, 11851; h) J. Jover, F. M. Miloserdov, J. Benet-Buchholz, V. V. Grushin, F. Maseras, *Organometallics* **2014**, *33*, 6531.

[5] See, for example: O. Kazakova, G.-V. Röschenthaler in *Efficient Preparations of Fluorine Compounds* (Ed.: H. W. Roesky), Wiley, Hoboken, NJ, **2013**, p. 205.

[6] a) M. R. Angelastro, L. E. Baugh, P. Bey, J. P. Burkhart, T.-M. Chen, S. L. Durham, C. M. Hare, E. W. Huber, M. J. Janusz, J. R. Koehl, A. L. Marquart, S. Mehdi, N. P. Peet, *J. Med. Chem.* **1994**, *37*, 4538; b) M. Andrzejewska, L. Yépez-Mulia, R. Cedillo-Rivera, A. Tapia, L. Vilpo, J. Vilpo, Z. Kazimierczuk, *Eur. J. Med. Chem.* **2002**, *37*, 973; c) A. Johansson, A. Poliakov, E. Åkerblom, K. Wiklund, G. Lindeberg, S. Winiwarter, U. H. Danielson, B. Samuelsson, A. Hallberg, *Bioorg. Med. Chem.* **2003**, *11*, 2551; d) G. Kokotos, Y.-H. Hsu, J. E. Burke, C. Baskakis, C. G. Kokotos, V. Magrioti, E. A. Dennis, *J. Med. Chem.* **2010**, *53*, 3602; e) C. Philippe, J. Kaffy, T. Milcent, D. Bonnet-Delpon, *J. Fluorine Chem.* **2012**, *134*, 136; f) K. Nickisch, W. Elger, J. Cessac, N. Kesavaram, B. Das, R. Garfield, S.-Q. Shi, O. Amelkina, R. Meister, *Steroids* **2013**, *78*, 255.

[7] I. Popov, S. Lindeman, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 9286.

[8] a) N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 536; *Angew. Chem.* **2012**, *124*, 551; b) M. G. Mormino, P. S. Fier, J. F. Hartwig, *Org. Lett.* **2014**, *16*, 1744.

[9] A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2013**, *135*, 12584.

[10] H. Serizawa, K. Aikawa, K. Mikami, *Org. Lett.* **2014**, *16*, 3456.

[11] D. Naumann, T. Roy, B. Caeners, D. Hütten, K.-F. Tebbe, T. Gilles, *Z. Anorg. Allg. Chem.* **2000**, *626*, 999.

[12] N. Nebra, V. V. Grushin, *J. Am. Chem. Soc.* **2014**, *136*, 16998.

[13] L. Chu, F.-L. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513.

[14] G. Berthon-Gelloz, M. A. Siegler, A. L. Spek, B. Tinant, J. N. H. Reek, I. E. Markó, *Dalton Trans.* **2010**, *39*, 1444.

[15] a) C. Baskakis, V. Magrioti, N. Cotton, D. Stephens, V. Constantinou-Kokotou, E. A. Dennis, G. Kokotos, *J. Med. Chem.* **2008**, *51*, 8027; b) V. Magrioti, A. Nikolaou, A. Smyrniotou, I. Shah, V. Constantinou-Kokotou, E. A. Dennis, G. Kokotos, *Bioorg. Med. Chem.* **2013**, *21*, 5823.

[16] a) J. Barluenga, P. J. Campos, E. Gonzales-Nuñez, G. Asensio, *Synthesis* **1985**, 426; b) A. F. Popov, O. V. Lobanova, V. A. Savelova, Y. S. Sadovskii, T. N. Solomoichenko, Z. P. Piskunova, *Russ. J. Org. Chem.* **2002**, *38*, 1624.

[17] A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adán, P. Novák, V. V. Grushin, *J. Org. Chem.* **2013**, *78*, 11126.

[18] For reviews of metal-catalyzed coupling reactions of aryl chlorides, see a) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047; b) V. V. Grushin, H. Alper, *Top. Organomet. Chem.* **1999**, *3*, 193; c) A. F. Littke, G. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; *Angew. Chem.* **2002**, *114*, 4350; d) R. B. Bedford, C. S. Cazin, D. Holder, *Coord. Chem. Rev.* **2004**, *248*, 2283.

[19] W. R. Dolbier, Jr., *Chem. Rev.* **1996**, *96*, 1557.

[20] CCDC 1042807 (**2**), 1042808 (**3**), 1042809 (**4**), 1042810 (**5**), and 1042811 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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