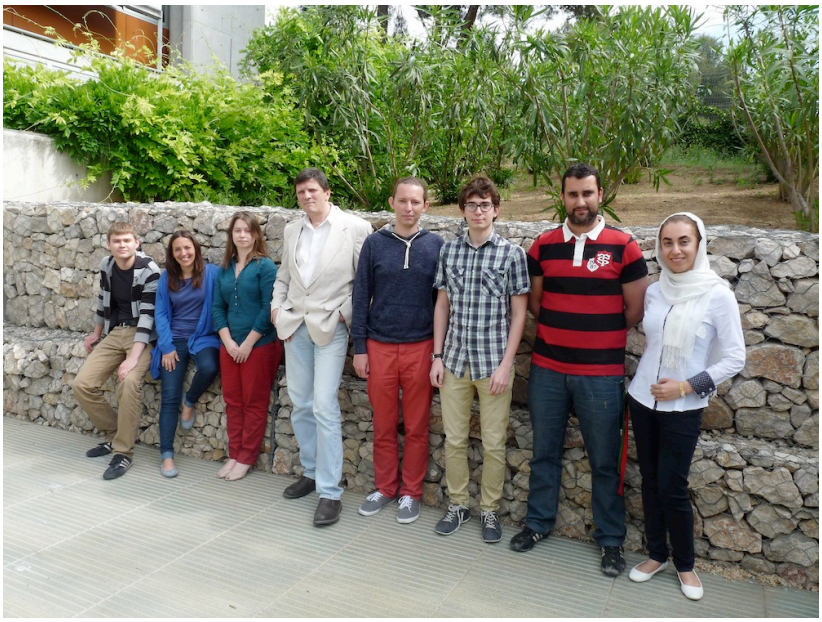
Grushin Research Group



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Postdoctoral Researchers: Anton Lishchynskyi / Hamidreza Samouei /Noel Nebra
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Abstract

Our research spans organic and inorganic chemistry with emphasis on metal complex catalysis and mechanistic studies. The main focus of the group is on new chemical transformations toward the development of highly challenging and practicable processes as well as deep understanding of elementary steps involved in the catalytic loop. Many of our projects are centered on organometallic fluorine chemistry, a new and exciting area for research. Our ultimate goal is the development of efficient methods for highly chemo- and regioselective, practicable fluorination, trifluoromethylation, and fluoroalkylation reactions of organic molecules with metal reagents and catalysts. Our other research interests include the synthesis of homogeneous catalysts, fine chemicals from renewable resources, inert bond activation, and new metal-catalyzed reactions of otherwise unreactive aromatic substrates.

ORGANOMETALLIC FLUORINE CHEMISTRY

Selectively fluorinated organic molecules often exhibit biological activity. Approximately 25% of all pharmaceuticals and nearly 50% of all agrochemicals on the current market are fluorine-containing compounds. Aromatic derivatives bearing a CF_3 group on the ring represent a particularly important class of biologically active materials. Trifluoromethylated aromatic compounds are currently manufactured by exhaustive chlorination of a methyl group on the aromatic ring, followed by the Swarts reaction of the $ArCCl_3$ intermediate with HF. This process generates large quantities of chlorine waste (HCl) and exhibits low functional group tolerance as it involves highly reactive, aggressive chemicals (Cl_2, HF). Although considerable progress has been made toward the development of new methods to introduce the CF_3 group into the aromatic ring, none of them is industrially feasible because of the high cost of the CF_3 sources employed, such as Ruppert's reagent CF_3SiMe_3.

The most attractive CF_3 source is fluoroform (CHF_3; trifluoromethane; HFC-23) that is generated in large quantities (estimated 20 000 - 25 000 metric tons annually) as a side-product of the fluoropolymer and fluorochemical industries. While being nontoxic and ozone-friendly, fluoroform nonetheless must be treated as an exceptionally potent greenhouse gas with the global warming potential 11700 times that of CO_2. The long atmospheric lifetime of CHF_3 and the steady 5% annual increase of its concentration in the atmosphere pose a serious ecological danger. Therefore, side-produced CHF_3 should be (A) destroyed or (B) used as a feedstock for manufacturing valuable fluorinated compounds. Option (B) is evidently much more attractive, especially considering the fact that CHF_3 is difficult to incinerate and costly to destroy in the plasma process. Until recently, however, little progress was made toward the development of industrially feasible applications of fluoroform in the synthesis of organofluorine compounds. Activation of fluoroform, an inert molecule, is a great challenge.

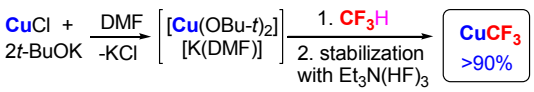

Fig. 1. *Direct cupration of fluoroform.*

In 2011, we reported our discovery of the long and highly sought-after reaction of direct cupration of fluoroform (*J. Am. Chem. Soc*. **2011**, *133*, 20901). The reaction of CuCl with *t*-BuOK (1:2 mol/mol) in an aprotic dipolar solvent such as DMF, gives the ate complex $[K(DMF)][Cu(OBu\text{-}t)_2]$ that easily and cleanly metalates fluoroform at 20 °C and 1 atm (Fig. 1). While employing only inexpensive materials, this reaction furnishes $CuCF_3$ in nearly quantitative yield and is expected to open up new horizons for trifluoromethylation reactions on a larger scale. The low cost of the CF_3 source would matter, however, only if we could find conditions to use it in equally cost-efficient, high-yielding, and safe trifluoromethylation processes. We have recently developed and reported two reactions that seem to meet these requirements, the oxidative trifluoromethylation of aryl boronic acids (*Angew. Chem., Int. Ed.* **2012**, *51*, 77670 and trifluoromethylation of α-holeketones (*J. Am. Chem. Soc.* **2012**, *134*, 16167. More recently, we demonstrated the exceptional efficacy of the fluoroform-derived $CuCF_3$ in trifluoromethylation of aryl and heteroaryl halides and established the mechanism of the cupration reaction.

Trifluoromethylation of Aryl and Heteroaryl Halides with Fluoroform-Derived $CuCF_3$

Aryl halides are the most attractive substrates for the synthesis of trifluoromethylated aromatic compounds. A broad variety of iodoarenes undergo smooth trifluoromethylation with fluoroform-derived, "ligandless" $CuCF_3$ at 20-50 °C to give the corresponding benzotrifluorides in nearly quantitative yield. A number of much less reactive aromatic bromides also have been trifluoromethylated, including pyridine, pyrimidine, pyrazine, and thiazole derivatives as well as aryl bromides bearing electron-withdrawing groups and/or ortho substituents. Only selected chloroarenes can be trifluoromethylated, e.g. 2-chloronicotinic acid.

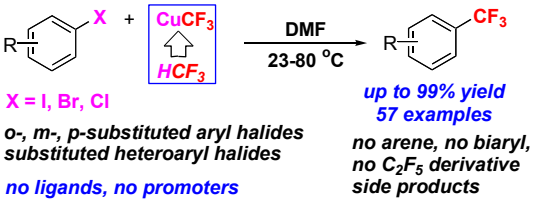

Fig. 2. *Trifluoromethylation of aryl halides with fluoroform-derived $CuCF_3$.*

Exceptionally high chemoselectivity of the reactions (no side-formation of arenes, biaryls, and C_2F_5 derivatives) has allowed for the isolation of a large number of trifluoromethylated products in high yield on a gram scale (up to 20 mmol). Interestingly and importantly, additional ligands do not benefit the reaction but rather make it less efficient in many instances. Our $CuCF_3$ reagent and its reactions with haloarenes provide an unmatched combination of reactivity, selectivity, and low cost.

The Mechanism of the Cupration Reaction of Fluoroform

Studying and understanding reaction mechanisms is one of the key research areas for our group. Although it was previously shown that the reaction of cupration of fluoroform (Fig. 1) is not mediated by CF_3^- formation, the mechanism of this unprecedented transformation remained unknown. We have recently found that the potassium counterion plays a crucial role in the Cu-CF_3 bond formation. Adding a ligand that binds efficiently to the K^+ such as 18-crown-6 or crypt-2.2.2 results in significant inhibition of the cupration process (Fig. 3). The efficient complexation of 18-crown-6 and crypt-2.2.2 with K[(*t*-BuO)$_2$Cu] has been demonstrated in separate experiments and both complexes have been structurally characterized (Fig. 4).

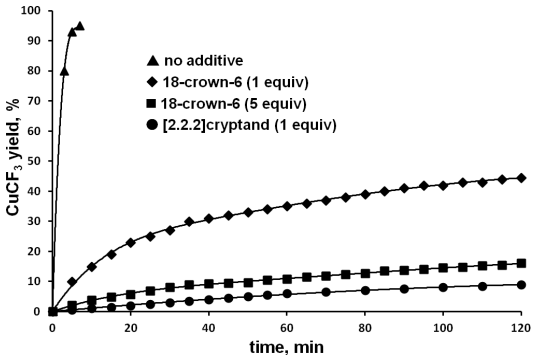

Fig. 3. *Kinetics of the cupration reaction of CHF_3 with [K(DMF)][(t-BuO)$_2$Cu] in DMF ([Cu] = 0.1M) in the absence and in the presence of 18-crown-6 or [2.2.2]cryptand at 25 °C.*

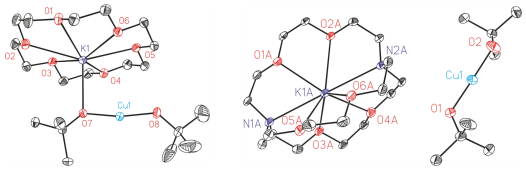

Fig. 4. *ORTEP drawings of [K(18-crown-6)][(t-BuO)$_2$Cu] (left) and [K(crypt-2.2.2)][(t-BuO)$_2$Cu] (right).*

The cupration rate correlates with the concentration of "free" K^+ in the system, pointing to the importance of electrophilic assistance from the alkali metal cation in the reaction. A combined experimental and computational study has shown that the cupration process is governed by a mechanism involving synchronous C-H bond cleavage and Cu-CF_3 bond formation. A total of eight Lewis acid and Lewis base centers interacting with one another are orderly arranged in a stable transition state providing a low-energy pathway for the transformation (Fig. 5; $\Delta G^{\neq}_{298K}$ = 21.5 kcal mol^{-1} computed in the gas phase).

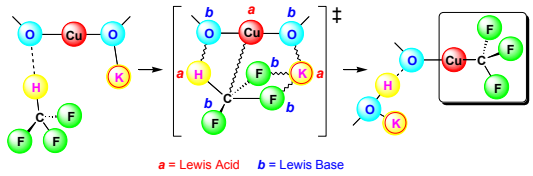

Fig. 5. *Schematic representation of the transition state for the CHF_3 cupration reaction, displaying interacting Lewis acid (a) and Lewis base (b) centers.*

Therefore, the alkali metal counter-cation to the dialkoxycuprate plays a dual role in the overall cupration process. As was shown previously (*J. Am. Chem. Soc.* **2011**, *133*, 20901), the cation slowly decomposes the $CuCF_3$ product via α-fluoride elimination. As is clear from our recent work, the electrophilic assistance of the alkali metal cation is paramount to the occurrence of the CHF_3 cupration in a highly efficient manner.

Interestingly, alkali metal-free [Me_4N][(*t*-BuO)$_2$Cu] (Fig. 6) made by the reaction of [Na(DMF)$_2$][Cu(OBu-*t*)$_2$] with [Me_4N]$^+$ F$^-$ still reacted with CHF_3, more slowly than [K(DMF)][Cu(OBu-*t*)$_2$] yet faster than [K(crypt-2.2.2)][(*t*-BuO)$_2$Cu] due to electrophilic assistance from NCH···O and CH···F interactions.

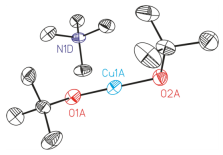

Fig. 6. *ORTEP drawing of [Me$_4$N][(t-BuO)$_2$Cu].*

Cupration of C_2F_5H and Highly Efficient Pentafluoroethylation Reactions

A logical extension of the CHF_3 cupration discovery was to examine whether or not this reaction could be applied to higher *H*-perfluoroalkanes (R_fH). To our surprise, under the conditions leading to the highly selective cupration of fluoroform, $CF_3(CF_2)_nH$ (n = 2, 5, 7), $HCF_2(CF_2)_4CF_2H$, and $(CF_3)_2CFH$ did not produce R_fCu but rather gave KF/KHF_2 and complex mixtures of organofluorine products. An even bigger surprise came when after all these failures pentafluoroethane C_2F_5H underwent smooth and clean cupration to give a C_2F_5Cu derivative in nearly quantitative yield (Fig. 7).

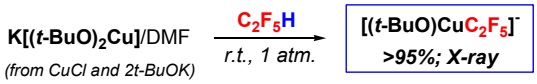

Fig. 7. *Cupration of C_2F_5H.*

The C_2F_5H cupration product is more stable than its CF_3 counterpart. As a result, the cuprated derivative, a mixed ate complex bearing one C_2F_5 and one *t*-BuO ligand on the Cu, $[K(DMF)_2][(t\text{-BuO})Cu(C_2F_5)]$, has been isolated and structurally characterized (Fig. 8).

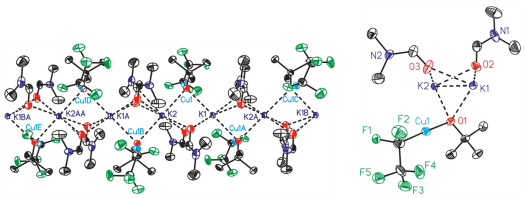

Fig. 8. *ORTEP drwaings of the C_2F_5H cupration product $[K(DMF)_2][(t\text{-BuO})Cu(C_2F_5)]$ displaying its polymeric structure (left) and the structural unit (right).*

There have been no literature reports on the preparation of CuC_2F_5 compounds directly from cheap and readily available C_2F_5H. Moreover, pentafluoroethylation methods are severely underdeveloped, despite the fact that in some cases C_2F_5 derivatives have been found to exhibit biological and material properties that are superior to those of their CF_3 counterparts. We have developed unprecedentedly efficient methods for pentafluoroethylation of (hetero)aryl halides, including *unactivated aryl bromides* using our C_2F_5H-derived Cu reagent (Fig. 9).

Efficient pentafluoroethylation of a variety of other substrates has also been demonstrated (Fig. 10). Also, the successful C_2F_5 transfer to Pd (Fig. 10) and a single-crystal X-ray diffraction study of the product, [(tmeda)Pd(C_2F_5)(Ph)], allowed us to conclude that the structural trans-influences of C_2F_5 and CF_3 on Pd are indistinguishable (within the experimental error).

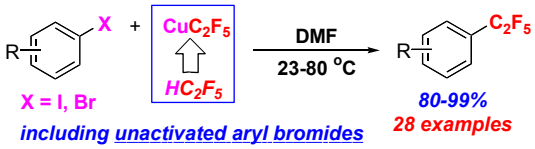

Fig. 9. *Pentafluoroethylation of (hetero)aryl halides with the C_2F_5H-derived Cu reagent.*

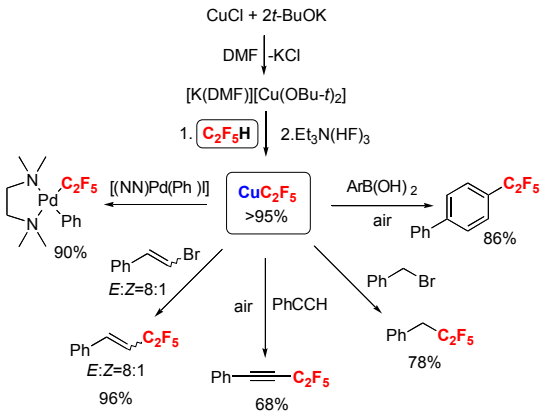

Fig. 10. *Pentafluoroethylation reactions with the C_2F_5H-derived Cu reagent.*

Activation of Fluoroform with Pd(II)

As explained above, chemoselective activation of fluoroform, an industrially side-produced potent greenhouse gas, is a critical task of

modern chemical research. In 2011, the first examples of CHF_3 activation with transition metals were reported by Daugulis (Zn), Goldman (Ir), and our group (Cu; see above). We have now added palladium to this short list. It has been found that [(dppp)Pd(Ph)(OH)], a new compound (X-ray), smoothly reacts with fluoroform in the presence of a basic promoter to give [(dppp)Pd(Ph)(CF_3)] (Fig. 11).

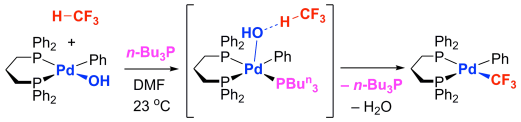

Fig. 11. *Base-promoted/catalyzed activation of Fluoroform with [(dppp)Pd(Ph)(OH)].*

The promoter (e.g., *n*-Bu_3P) is released after the Pd-CF_3 bond formation step and therefore can be used not only in stoichiometric but also in catalytic quantities.

A combined experimental and computational study points to a new mechanism that involves H-bonding Pd-O(H)···H-CF_3 (experimentally observed by ^1H and ^{31}P NMR) and nucleophilic attack of the promoter on the metal, followed by a push-pull-type collapse of the resultant five-coordinate Pd(II) intermediate via a polar transition state. Fig. 12 displays the computed reaction profile for CHF_3 activation with a small model [(dpp)Pd(Ph)(OH)]/PMe_3 (dpp = 1,3-diphosphinopropane) in DMF. The key transition state **TS2** is shown in Fig. 13.

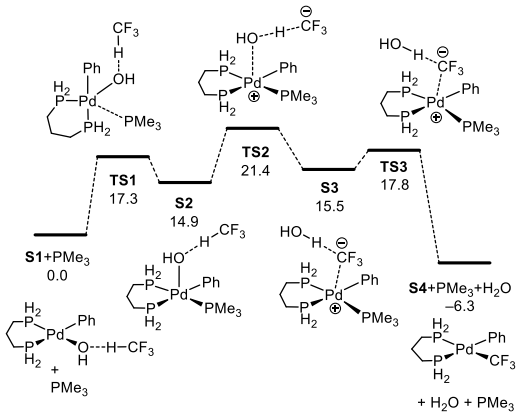

Fig. 12. *Computed reaction profile for PMe_3-mediated reaction of [(dpp)Pd(Ph)(OH)] with CHF_3 in DMF.*

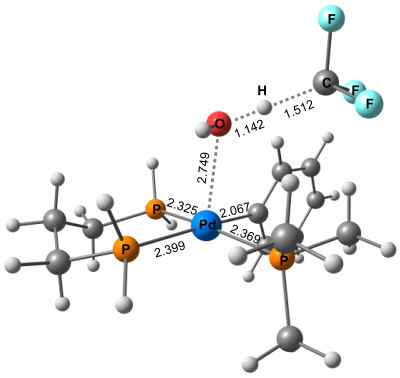

Fig. 13. *Optimized structure of **TS2** (see Fig. 12).*

This *nucleophile*-assisted push-pull mechanism (Fig. 12) of CHF_3 activation with the Pd complex is distinctly different from the one that operates in the direct cupration of fluoroform and involves *electrophilic* assistance from the alkali metal cation interacting with fluorines on the CHF_3 molecule (see above). Given (i) the exceptional attractiveness of fluoroform as a CF_3 source and (ii) palladium being one of the very few metals that can mediate Ar-CF_3 bond formation, our results are expected to prompt further developments in the area of trifluoromethylation.

NEW EFFICIENT PREPARATIVE METHODS

New, Highly Efficient, Simple, Safe, and Scalable Synthesis of [$(Ph_3P)_3Ru(CO)(H)_2$]

The title complex, [$(Ph_3P)_3Ru(CO)(H)_2$], is one of the most important and widely used homogeneous catalysts for a broad variety of transformations, including efficient C-H activation and functionaliaztion, the borrowing hydrogen methodology, and polymerization. The known methods to prepare this important complex, however, suffer from numerous drawbacks, including modest yields, unscalability, and the need to use toxic reagents and solvents. For instance, to prepare 20 g of crude [$(Ph_3P)_3Ru(CO)(H)_2$] by the most widely used procedure (*Inorg. Synth*. **1974**, *15*, 45), one would have to use nearly 50 g of PPh_3, over 300 mL of toxic 40% aqueous formaldehyde (ca. 130-fold excess), and almost 3 L of ethanol.

We have developed a novel method to prepare [$(Ph_3P)_3Ru(CO)(H)_2$], which does not employ toxic and hazardous materials, uses PPh_3 in the

minimal possible excess, and produces the desired complex in unprecedented nearly quantitative yield (Fig. 14). For most purposes, no purification is needed for the product that precipitates out of the reaction mixture spectroscopically and analytically pure. The reaction is conducted in ethanol, the "greenest" organic solvent. Importantly, the latter can be used in small quantities, thereby enabling scalability, as we have demonstrated by preparing up to over 17 g of pure $[(Ph_3P)_3Ru(CO)(H)_2]$ in one batch. The new method is likely to find use in both academic and industrial research.

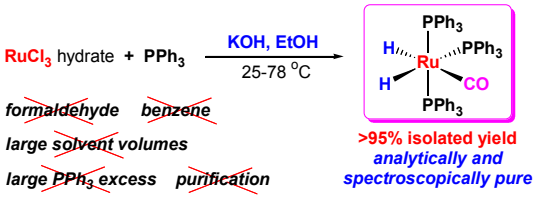

Fig. 14. *The new highly efficient, simple, safe, and scalable synthesis of* $[(Ph_3P)_3Ru(CO)(H)_2]$.

Articles

"Cupration of C_2F_5H: Isolation, Structure, and Synthetic Applications of $[K(DMF)_2][(t\text{-}BuO)Cu(C_2F_5)]$. Highly Efficient Pentafluoroethylation of Unactivated Aryl Bromides"
J. Am. Chem. Soc. **2013**, *135*, 12584-12587.
Lishchynskyi, A.; Grushin, V. V.

"The Critical Effect of the Countercation in the Direct Cupration of Fluoroform with $[Cu(OR)_2]^-$"
Angew. Chem. Int. Ed. **2013**, *52*, 11637-11641.
Konovalov, A. I.; Benet-Buchholz, J.; Martin, E.; Grushin, V. V.

"Nucleophile-Catalyzed, Facile, and Highly Selective C−H Activation of Fluoroform with Pd(II)"
J. Am. Chem. Soc. **2013**, *135*, 16837-16840.
Takemoto, S.; Grushin, V. V.

"New, Highly Efficient, Simple, Safe, and Scalable Synthesis of $[(Ph_3P)_3Ru(CO)(H)_2]$"
Organometallics **2013**, *32*, 4440-4443.
Samouei, H.; Grushin, V. V.

"Trifluoromethylation of Aryl and Heteroaryl Halides with Fluoroform-Derived $CuCF_3$: Scope, Limitations, and Mechanistic Features"
J. Org. Chem. **2013**, 78, 11126-11146.
Lishchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero-Adán, E. C.; Novák, P.; Grushin, V. V.

"Trifluoromethylation"
Science of Synthesis: C-1 Building Blocks in Organic Synthesis 2. van Leeuwen, P. W. N. M., Ed.; Thieme: Stuttgart, **2013**, 367-408.
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