Fluoroform Activation

DOI: 10.1002/ange.201306272

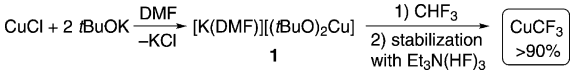
The Critical Effect of the Countercation in the Direct Cupration of Fluoroform with $[Cu(OR)_2]^-$**

*Andrey I. Konovalov, Jordi Benet-Buchholz, Eddy Martin, and Vladimir V. Grushin**

Trifluoromethane (CHF_3, fluoroform, HFC-23) is a gas (b.p. = −82 °C) that is formed as a side product (> 20000 t/a) in Teflon manufacturing. Being neither toxic nor ozone-depleting, fluoroform must nonetheless be destroyed because of its high global-warming potential ($> 10^4$ that of CO_2) and atmospheric lifetime of more than 250 years.[1] Incineration of CHF_3, a flame retardant, is, however, a costly and environmentally unfriendly process.

A vastly preferred alternative to the destruction of CHF_3 would be its utilization as a feedstock for the production of fluorochemicals. Fluoroform has long been viewed[2] as by far the best CF_3 source for the preparation of trifluoromethylated building blocks and intermediates that are in great demand for the synthesis of modern agrochemicals, pharmaceuticals, and specialty materials.[2–4] However, selective and efficient activation of CHF_3, a rather inert molecule, represents a considerable challenge. Until very recently, deprotonation of weakly acidic fluoroform ($pK_a = 27$ in H_2O)[5] with strong bases remained the only methodology[6] to employ CHF_3 in synthesis. This deprotonation approach may not be feasible for applications on a larger scale for a number of reasons, including the necessity to use low temperatures in order to avoid the exceedingly facile decomposition of the CF_3^- carbanionic intermediate to difluorocarbene.

A much more recent, distinctly different approach to CHF_3 activation is based on the previously proposed[6g] idea of direct metalation, leading to a stable M−CF_3 derivative in one step. In 2011, the first reactions of direct zincation and cupration of fluoroform were reported by Daugulis and co-workers[7] and our group,[2,8] respectively. Our cupration method[8] employs a novel reagent, dialkoxycuprate [K(DMF)][(tBuO)$_2$Cu] (**1**), which is prepared quantitatively from CuCl and two equivalents of tBuOK in DMF. Pre-isolated or in situ generated **1** reacts with CHF_3 at room temperature and 1 atm to give synthetically useful[8–10] $CuCF_3$ in > 90% yield within minutes (Scheme 1). Although evidence has been obtained[8] that neither CF_3^- nor CF_2 mediate this process, its mechanism remained unknown. Herein we report a combined experimental and computational study of the cupration reaction of fluoroform. Our investigations have revealed mechanistic features of this H−CF_3 activation that are as striking and unique as the reaction itself.



Scheme 1. Preparation of $CuCF_3$ from CHF_3.[8]

The $CuCF_3$ species that is directly produced in the reaction of [K(DMF)][(tBuO)$_2$Cu] (**1**) with CHF_3 decays in the course of hours and is too unstable for isolation.[8] This decomposition is caused by the potassium cation that abstracts F from the CF_3 ligand on Cu (α-F-elimination) to give KF and a Cu^I carbene. Freshly prepared solutions of fluoroform-derived $CuCF_3$ can be efficiently stabilized against this decomposition by the treatment with a source of HF, such as $Et_3N{\cdot}3HF$ or $Py(HF)_n$. The mechanism of this stabilization is the sequestering of the reactive potassium cations in the form of highly thermodynamically favored KF. The $CuCF_3$ species in the resultant solution is much more stable (for days at room temperature), yet insufficiently stable for isolation and structural studies.

We reasoned that adding a ligand with a strong affinity for K^+ after the cupration reaction would diminish its electrophilicity, thereby suppressing the decomposition of the just-produced $CuCF_3$. Unlike the treatment with the HF sources, this method was expected to provide a milder, more "non-invasive" technique to stabilize the originally formed $CuCF_3$ species for isolation and further studies. We were delighted to find that the addition of one equivalent of 18-crown-6 to the reaction mixture immediately after the cupration produced quantitatively a stable complex that was amenable to isolation and structure determination.

As shown in Figure 1, the product of this complexation is [K(18-crown-6)][(tBuO)Cu(CF_3)] (**2**),[11] a mixed ate species

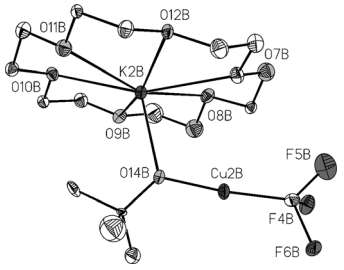


Figure 1. ORTEP drawing of [K(18-crown-6)][(tBuO)Cu(CF_3)] (**2**) with H atoms omitted and thermal ellipsoids drawn to the 50% probability level.

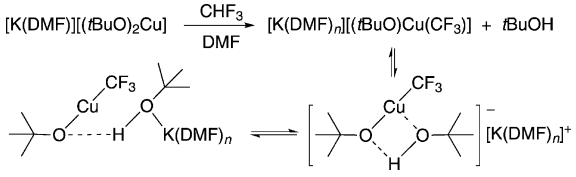
[*] A. I. Konovalov, Dr. J. Benet-Buchholz, Dr. E. Martin, Prof. V. V. Grushin
Institute of Chemical Research of Catalonia (ICIQ)
Avgda. Països Catalans 16, 43007 Tarragona (Spain)
E-mail: vgrushin@iciq.es

[**] We thank Prof. S. A. Macgregor and S. Kazandjian for discussions and preliminary computational studies. The ICIQ Foundation and The Spanish Government (Grant CTQ2011-25418) are acknowledged for support of this work.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201306272.

that bears one *t*BuO and one CF_3 ligand on the Cu^I center. The O atom of the *t*BuO ligand on Cu is coordinated to K^+ in the crown ether. The O-Cu-CF_3 fragments in the four independent molecules found in the crystal of **2** are nearly linear (174.5(5)–179.7(5)°) and the Cu–CF_3 bond distances (1.81(2), 1.868(14), 1.914(15), and 1.927(13) Å) are, on average, noticeably shorter than in the handful of previously reported structurally characterized Cu^I–CF_3 complexes.[12]

Under rigorously O_2- and H_2O-free conditions, **2** is stable in the solid state and decomposes only slowly in solution (DMF, THF, benzene). The isolation and structural characterization of **2** provides evidence for the reaction of CHF_3 with **1**, leading to $[(t\text{BuO})\text{Cu}(\text{CF}_3)]^-$ along with one equivalent of *t*BuOH (Scheme 2). These two undergo fast exchange, as follows from the observation of only one singlet resonance from the *t*BuO groups in the room temperature ^{1}H NMR spectrum of a freshly prepared cupration reaction mixture in $[D_7]$DMF. A possible mechanism for this exchange is shown in Scheme 2. In solutions of $[(t\text{BuO})\text{Cu}(\text{CF}_3)]^-$ prepared from



Scheme 2. Cupration of CHF_3 and *t*BuOCu/*t*BuOH exchange.

1 and CHF_3, the lack of strongly stabilizing ligands for the potassium cations accounts for their enhanced electrophilicity toward the F atoms and, as a consequence, the facile α-F elimination.

A striking observation was made when the synthesis of **2** was attempted by adding one equivalent of 18-crown-6 to a solution of **1** in DMF *before* rather than after the introduction of fluoroform. In the presence of 18-crown-6, the reaction was sluggish, producing **2** in only 15, 30, and 35% yield after 10, 40, and 60 min, respectively. The cupration was further slowed down in the presence of five equivalents of 18-crown-6 and even more so when the latter was replaced with one equivalent of [2.2.2]cryptand (crypt-222). No detectable change in the reaction rate occurred, however, when the amount of crypt-222 was doubled.

Kinetic data for these reactions were obtained by ^{19}F NMR spectroscopy with an internal standard under pseudo-first-order conditions in CHF_3. The non-exponential curves (Figure 2) suggested autoinhibition, regardless of the presence or absence of the additives. In the latter case, this effect was difficult to recognize because the reaction was fast, reaching >90% conversion within about 5 min. It was confirmed by an independent experiment, however, that the *t*BuOH by-product (Scheme 2) does slow down the cupration. In the presence of 1.1 equivalents of *t*BuOH, deliberately added to **1** in DMF prior to the introduction of CHF_3, the yield of $CuCF_3$ was only about 65% after 20 min. Detailed kinetic analysis of the autoinhibition is the subject of a separate research project. Herein, we focus on the more

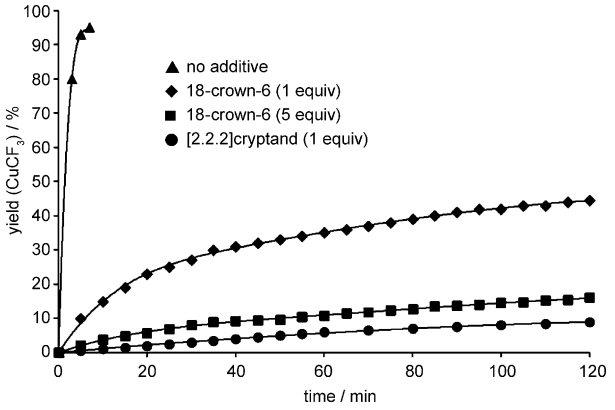


Figure 2. Kinetics of the cupration reaction of CHF_3 with [K(DMF)]-$[(t\text{BuO})_2\text{Cu}]$ (**1**) in DMF ([Cu] = 0.1 M) in the absence and presence of 18-crown-6 or [2.2.2]cryptand at 25 °C.

mechanistically significant, totally unexpected inhibiting effect of 18-crown-6 and crypt-222 that points to a crucial role of the alkali-metal counterion in the CHF_3 activation with **1**.

On addition of 18-crown-6 (1 equiv) to **1** in DMF, THF, or benzene, $[\text{K}(18\text{-crown-6})][(t\text{BuO})_2\text{Cu}]$ (**3**)[11] was cleanly formed with concomitant loss of the coordinated DMF molecule. The structure of isolated **3** (Figure 3) shows that

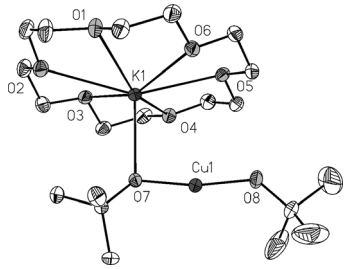


Figure 3. ORTEP drawing of $[\text{K}(18\text{-crown-6})][(t\text{BuO})_2\text{Cu}]$ (**3**) with H atoms omitted and thermal ellipsoids drawn to the 50% probability level.

the crowned K^+ is coordinated to one of the two O atoms of the dialkoxycuprate anion, with the K–O bond length of 2.668(2) Å being within the range found in the structures of **1** (2.629(2), 2.699(2), and 2.747(2) Å)[8] and **2** (2.652(11), 2.575(10), 2.600(10), and 2.625(10) Å). The Cu–O bond distances (1.804(2) and 1.829(2) Å) and the O-Cu-O angle (169.66(8)°) in **3** are similar to those determined for **1** (1.815(2) and 1.825(2) Å and 173.10(10)°, respectively). In spite of these similarities, however, **3** appeared to be much less reactive toward fluoroform (Figure 2).

Likewise, adding one equivalent of crypt-222 to a solution of **1** in $[D_7]$DMF led to the instantaneous complexation of the potassium cation, as was manifested by the characteristic changes in the ^{1}H NMR spectrum. The resultant salt $[\text{K}(\text{crypt-222})]^+$ $[(t\text{BuO})_2\text{Cu}]^-$ (**4**)[11] was also isolated and structurally characterized (Figure 4). Unlike **3**, **4** does not display coordination of the dialkoxycuprate anion to the K^+ that is

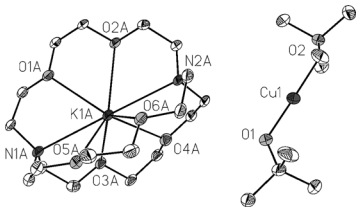
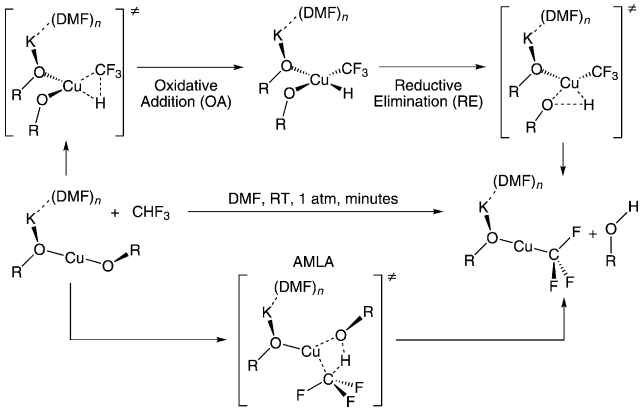


Figure 4. ORTEP drawing of [K(crypt-222)][(tBuO)$_2$Cu] (**4**) with H atoms omitted and thermal ellipsoids drawn to the 50% probability level.

confined in the cryptand cage: the two K···O(Cu) distances exceed 6.1 and 8.2 Å.

The observed order of reactivity toward fluoroform (**1** ≫ **3** > [**3** + 18-crown-6 (4 equiv)] > **4** ≈ [**4** + crypt-222 (1 equiv)] (see above and Figure 2) correlates with the concentration of "free" K^+ in these systems: $0.1 \gg 2.4\times10^{-3} > 1.2\times10^{-3} > 3.5\times10^{-5} \approx 2.5\times10^{-5}$ M, respectively. These [K^+] values were calculated given [**1**] = 0.1 M used in the experiments and the reported log K_S data for $[K(18\text{-crown-6})]^+$ (4.2–4.3)[14] and $[K(\text{crypt-222})]^+$ (7.9)[15] in the same solvent (DMF).[16] The observed correlation indicated that the potassium cation provides critical electrophilic assistance to the activation and cleavage of the H–CF_3 bond with the dialkoxycuprate. To understand the key role of K^+ in the cupration reaction, we studied its mechanism by theoretical calculations.

Analysis of mechanisms[17] of C–H activation with metals suggested that the cupration might proceed, as shown in Scheme 3, by a) oxidative addition of CHF_3 to the Cu^I center,



Scheme 3. OA/RE and AMLA mechanisms for H–CF_3 activation with $[K(DMF)_n][Cu(OR)_2]$ (R = alkyl).

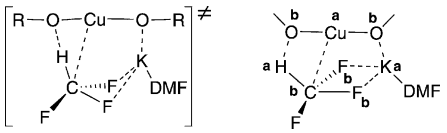
followed by reductive elimination of tBuOH (OA/RE) or b) proton transfer from CHF_3 to the O atom of the tBuO ligand on Cu with the simultaneous formation of the Cu–CF_3 bond (Scheme 3). This proton-transfer mechanism is similar to ambiphilic metal–ligand activation (AMLA), in which the cooperative effect of the F_3C–H···OCu hydrogen bond and the Lewis acidity of the 14e Cu^I center provides a low-energy route to fluoroform C–H bond cleavage and Cu–CF_3 bond formation. Each of these two mechanisms was probed with two sets of calculations, one for K^+-free, "naked" $[Cu(OR)_2]^-$ and one for $[K(DMF)][Cu(OR)_2]$ with R = Me (small model).

The ability of CHF_3 to form hydrogen bonds with O-donors has long been established.[18] Although such H-bonds are largely of electrostatic nature, the contribution of dispersion interactions needed to be taken into account in order to obtain accurate binding energies of CHF_3 to the dialkoxycuprate. Therefore, all calculations were performed at the DFT/B97D[19] level of theory with the Gaussian 09 package.[20]

In the study of the OA/RE pathway (Scheme 3), no agostic intermediates were located and the molecule always relaxed to the initial compound with a strong hydrogen bond between CHF_3 and $[Cu(OMe)_2]^-$ (r(O···H) = 1.76 Å). With K^+ omitted, a prohibitively high barrier of 47.3 kcal mol^{-1} was computed. Inclusion of $[K(DMF)]^+$ in the model resulted in electrostatic interactions between K^+ and F atoms of CHF_3, which changed the barrier to 49.6 kcal mol^{-1}. We therefore concluded that the OA/RE mechanism is unlikely to operate in the reaction.

An AMLA-type four-center transition state was found for H–CF_3 activation with $[Cu(OMe)_2]^-$ alone. The computed activation barrier $\Delta G^{\neq}_{298K} = 27.7$ kcal mol^{-1} is fairly consistent with the experimentally observed (Figure 2) slow reaction rate of CHF_3 with **4**, in which the K^+ cation is separated from the reactive centers by encapsulation inside the cryptand host (Figure 4).[21]

Placing a CHF_3 molecule in the $[K(DMF)][Cu(OMe)_2]$ environment produced a much more stable transition state with $\Delta G^{\neq}_{298K} = 21.5$ kcal mol^{-1}.[22] In addition to the expected pattern involving the H, O, Cu, and C centers, this striking transition state (Scheme 4) displays interactions of the



Scheme 4. Schematic representation of the computed transition state (left) displaying interacting Lewis acid (**a**) and Lewis base (**b**) centers (right) involved in the CHF_3 cupration reaction.

potassium ion not only with the other O atom on Cu, but also with two of the three F atoms of the fluoroform molecule. These additional K···O and K···F contacts provide extra stabilization to the transition state, thereby lowering considerably the activation barrier. As shown in Scheme 4, the presence of the potassium cation creates a remarkable template, in which a total of three Lewis acid centers (H, Cu, K) and five basic centers (O, O, C, F, F) are ideally preorganized for the C–H bond breakage and Cu–CF_3 bond formation. Apart from the template effect, this assembly facilitates the process by altering the electronic properties of the reactive centers. Thus, the K···F contacts increase the acidity of the H–CF_3 bond and the K–O interaction enhances the electrophilicity of the Cu center, as confirmed by NBO charge distribution analysis.[20]

The established Lewis acid effect of K^+ on the cupration reaction prompted us to synthesize a salt of $[(t\text{BuO})_2\text{Cu}]^-$

with a metal-free countercation in order to explore its reactivity toward CHF_3. The organic cation of choice was $[Me_4N]^+$ that is devoid of β-H atoms and hence cannot undergo Hofmann elimination. Attempts to prepare $[Me_4N]^+$ $[(t\text{BuO})_2\text{Cu}]^-$ (**5**) by metathesis between $[Me_4N]^+ X^-$ (X = Cl, BF_4) and **1** or $[\text{Na(DMF)}_2][(t\text{BuO})_2\text{Cu}]$[8] in various solvents were unsuccessful. The reaction of $[Me_4N]^+ F^-$ with $[\text{Na(DMF)}_2][(t\text{BuO})_2\text{Cu}]$ in THF, however, cleanly produced **5**, which was isolated and structurally characterized (Figure 5).[11]

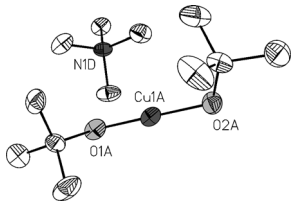


Figure 5. ORTEP drawing of $[Me_4N]$ $[(t\text{BuO})_2\text{Cu}]$ (**5**) with H atoms omitted and thermal ellipsoids drawn to the 50% probability level.

As anticipated, **5** appeared poorly reactive toward fluoroform in DMF, the reaction rate being roughly one half of that with [K(18-crown-6)][$(t\text{BuO})_2$Cu] (**3**). Somewhat unexpectedly, however, the cupration with **5** proceeded slightly faster than with **1** in the presence of five equivalents of 18-crown-6 and with [K(crypt-222)][$(t\text{BuO})_2$Cu] (**4**). We suspected that trace residual amounts of Na^+ in the sample of **5** after the synthesis might have catalyzed the cupration. Therefore, the reaction of CHF_3 with **5** was repeated in the presence of crypt-222 (1 equiv), which would efficiently sequester residual sodium ions in the form of inactive $[\text{Na(crypt-222)}]^+$. However, no change in the reaction rate was observed in this experiment, thus indicating that the sample of **5** was Na-free and that the measured rate of the reaction of **5** reflected its intrinsic reactivity toward fluoroform. A computational study was then performed and a transition state found where the $[Me_4N]^+$ plays essentially the same role as the potassium cation (Scheme 4), providing electrophilic assistance by means of NCH···O and NCH···F interactions. These interactions, however, are considerably weaker than those with K^+. As a consequence, the computed barrier ($\Delta G^{\ddagger}_{298K}$ = 26.9 kcal mol^{-1}) in this case is intermediate between those for the reactions in the presence of more Lewis acidic K^+ (21.5 kcal mol^{-1}; **1**) and in the absence of electrophilic assistance (27.7 kcal mol^{-1}; **4**). All three $\Delta G^{\ddagger}$ values are in excellent agreement with the experimentally observed reaction rates for **1**, **4**, and **5** (Figure 2).

In conclusion, we have uncovered the critical role of the countercation in the cupration of fluoroform with dialkoxy Cu^I ate complexes such as **1**. In accordance with the previous observations,[8] this reaction is not mediated by free CF_3^- and/or difluorocarbene. Both experimental and computational studies rather indicate that the cupration process is governed by a unique mechanism that involves synchronous C–H bond cleavage and Cu–CF_3 bond formation with electrophilic assistance from the alkali-metal counterion. A total of eight Lewis acid and Lewis base centers interacting with one another are cleverly arranged in the computed stable transition state that provides a low-energy pathway for the transformation. Therefore, the alkali-metal counterion M^+ (e.g., M = K or Na) to the dialkoxycuprate is highly important, as it plays a dual role in the overall cupration process. As was shown previously,[8] the cation slowly decomposes the $CuCF_3$ product through α-fluoride elimination. As we demonstrate in the current work, the electrophilic assistance of M^+ is paramount to the occurrence of the CHF_3 cupration in a highly efficient manner.

Received: July 18, 2013
Published online: September 13, 2013

Please note: Minor changes have been made to this manuscript since its publication in *Angewandte Chemie* Early View. The Editor.

Keywords: C–H activation · copper · fluorine · fluoroform · trifluoromethylation

[1] W. Han, Y. Li, H. Tang, H. Liu, *J. Fluorine Chem.* **2012**, *140*, 7.
[2] O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475.
[3] For selected recent monographs, see: a) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**; b) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, UK, **2006**; c) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, UK, **2009**; d) V. A. Petrov, *Fluorinated Heterocyclic Compounds. Synthesis Chemistry and Applications*, Wiley, Hoboken, **2009**.
[4] For selected recent reviews of trifluoromethylation methods, see: a) M. Schlosser, *Angew. Chem.* **2006**, *118*, 5558; *Angew. Chem. Int. Ed.* **2006**, *45*, 5432; b) D. Cahard, J.-A. Ma, *J. Fluorine Chem.* **2007**, *128*, 975; c) K. Uneyama, T. Katagiri, H. Amii, *Acc. Chem. Res.* **2008**, *41*, 817; d) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1; e) N. Shibata, A. Matsnev, D. Cahard, *Beilstein J. Org. Chem.* **2010**, *6*, 65; f) K. Sato, A. Tarui, M. Omote, A. Ando, I. Kumadaki, *Synthesis* **2010**, 1865; g) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161; h) F.-L. Qing, F. Zheng, *Synlett* **2011**, 1052; i) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455; j) Y. Macé, E. Magnier, *Eur. J. Org. Chem.* **2012**, 2479.
[5] E. A. Symons, M. J. Clermont, *J. Am. Chem. Soc.* **1981**, *103*, 3127.
[6] a) T. Shono, M. Ishifune, T. Okada, S. Kashimura, *J. Org. Chem.* **1991**, *56*, 2; b) N. Roques, J. Russell, PCT Int. Appl. WO 97/19038, **1997**; c) N. Roques, J. Russell, U.S. Patent 6355849, **2002**; d) J. Russell, N. Roques, *Tetrahedron* **1998**, *54*, 13771; e) R. Barhdadi, M. Troupel, M. Perichon, *Chem. Commun.* **1998**, 1251; f) B. Folléas, I. Marek, J.-F. Normant, L. Saint-Jalmes, *Tetrahedron Lett.* **1998**, *39*, 2973; g) B. Folléas, I. Marek, J.-F. Normant, L. Saint-Jalmes, *Tetrahedron* **2000**, *56*, 275; h) T. Billard, S. Bruns, B. R. Langlois, *Org. Lett.* **2000**, *2*, 2101; i) S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848; j) B. R. Langlois, T. Billard, *ACS Symp. Ser.* **2005**, *911*, 57; k) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324; l) H. Kawai, Z. Yuan, E. Tokunaga, N. Shibata, *Org. Biomol. Chem.* **2013**, *11*, 1446.
[7] I. Popov, S. Lindeman, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 9286.
[8] A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901.
[9] P. Novák, A. Lishchynskyi, V. V. Grushin, *Angew. Chem.* **2012**, *124*, 7887; *Angew. Chem. Int. Ed.* **2012**, *51*, 7767.

[10] P. Novák, A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2012**, *134*, 16167.
[11] CCDC 950993 (**2**), 950994 (**3**), 950995 (**4**), and 950996 (**5**) 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.
[12] Reported Cu–CF_3 bond lengths: [(TMS-IPr)Cu(CF_3)] (1.967(6) Å),[13a] [(SI*i*Pr)Cu(CF_3)] (2.022(4) Å),[13a] [(SIMes)$_2$Cu][(CF_3)$_2$Cu] (1.970 (6) Å),[13b] [(phen)Cu(PPh_3)(CF_3)] (1.985(1) Å),[13c] [(bathophen)Cu(CF_3)] (1.907(9) Å),[13d] [(Ph_3P)$_3$Cu(CF_3)] (2.018(7), 2.025(7), and 2.031(10) Å),[13e] and [Cu$_4$(CF_3)$_2$(C(OBu-t)$_2$)$_2$(μ^3-OBu-t)$_2$] (1.8908(16) Å).[8]
[13] 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.* **2011**, *123*, 3877; *Angew. Chem. Int. Ed.* **2011**, *50*, 3793; d) Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K.-W. Huang, *Organometallics* **2011**, *30*, 3229; e) O. A. Tomashenko, E. C. Escudero-Adan, M. Martinez Belmonte, V. V. Grushin, *Angew. Chem.* **2011**, *123*, 7797; *Angew. Chem. Int. Ed.* **2011**, *50*, 7655.
[14] a) I. Takeda, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3133; b) K. Ozutsumi, K. Ohtsu, T. Kawashima, *J. Chem. Soc. Faraday Trans.* **1994**, *90*, 127.
[15] J. Gutknecht, H. Schneider, J. Stroka, *Inorg. Chem.* **1978**, *17*, 3326.
[16] The reported[14,15] $\log K_S$ values were obtained for $KClO_4$. As [(*t*BuO)$_2$Cu]$^-$ is a stronger coordinating anion than ClO_4^-, the calculations might somewhat underestimate the actual concentrations of 18-crown-6- and crypt-222-free K^+. The overall trend in [K^+] and its correlation with the reactivity toward CHF_3, however, remain unaffected.
[17] D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749.
[18] See, for example: a) C. J. Creswell, A. L. Allred, *J. Am. Chem. Soc.* **1963**, *85*, 1723; b) S. Andreades, *J. Am. Chem. Soc.* **1964**, *86*, 2003; c) I. Alkorta, S. Maluendes, *J. Phys. Chem.* **1995**, *99*, 6457; d) M. L. Chabinyc, J. I. Brauman, *J. Am. Chem. Soc.* **1998**, *120*, 10863; e) A. Mukhopadhyay, P. Pandey, T. Chakraborty, *J. Phys. Chem. A* **2010**, *114*, 5026; f) S. J. Grabowski, *J. Phys. Chem. A* **2011**, *115*, 12789; g) P. Ramasami, T. A. Ford, *J. Mol. Struct.* **2012**, *1023*, 163.
[19] S. Grimme, *J. Comput. Chem.* **2006**, *27*, 1787.
[20] See the Supporting Information for details.
[21] Replacing the MeO ligands in the small model with *t*BuO raised the barrier by 2.5 kcal mol^{-1}.
[22] Recomputing this transition state at the DFT/B3LYP and the DFT/PBE levels produced higher activation barriers of 25.7 and 23.7 kcal mol^{-1}, respectively, thus indicating that the contribution from the London dispersion forces is not negligible.

