Synthetic Methods

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A Polycomponent Metal-Catalyzed Aliphatic, Allylic, and Benzylic Fluorination**

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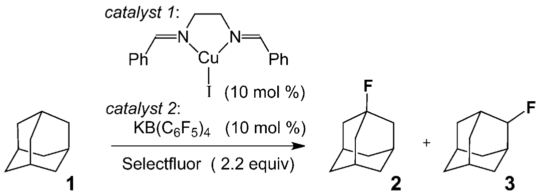
The selective incorporation of fluorine into organic molecules has advanced in dramatic ways over the last 30 years.[1] Although arene[2] and alkyne[3] fluorination using metal catalysis has received much attention, the corresponding methods for metal-catalyzed alkane fluorination remain only a promising goal [Eq. (1)].[4] To date, the most notable methods for alkane fluorination[5] involve the use of stoichiometric quantities of difficult-to-handle or indiscriminate reagents such as elemental fluorine,[6] cobalt trifluoride (polyfluorination),[7] or the potentially explosive cesium fluoroxysulfate.[8] We were particularly interested in the question of whether alkane fluorination could indeed be selectively catalyzed under mild reaction conditions, thus perhaps opening up a realm of fluorination catalysis in addition to the much-studied aromatic fluorination. What is more, a mild procedure using safe, commercially available alternatives would be complementary to pioneering methods, and perhaps be applicable to closely related allylic and benzylic substrates. Herein, we report the fluorination of a series of aliphatic, benzylic, and allylic substrates using a polycomponent catalytic system involving commercially available Selectfluor, the putative radical precursor *N*-hydroxyphthalimide (NHPI), an anionic phase-transfer catalyst ($KB(C_6F_5)_4$), and a copper(I) bisimine complex.[9,10]

$$\begin{matrix} R_2CH_2 \\ \text{or } R_3CH \end{matrix} \xrightarrow[R_3N\mathbf{F}^{\oplus}]{\textit{catalyst(s)}} \begin{matrix} R_2CH\mathbf{F} \\ \text{or } R_3C\mathbf{F} \end{matrix} \quad (1)$$

For the purposes of this study, we chose first to focus our efforts on the well-characterized adamantane system **1** and its fluorinated derivatives. Initial catalyst screening employed a variety of transition-metal salts, Selectfluor, and adamantane in dry MeCN (1 mL) and was stirred for 24 h at room temperature. Most notably, 10 mol% of CuI turned out to be a competent lead, thus yielding 1-fluoroadamantane (**2**) in 18% yield and in good selectivity [8:1 with respect to 2-fluoroadamantane (**3**)]. It should be noted that in the absence of a metal catalyst, the reaction produced no fluorinated products under the specified reaction conditions. At this point, a number of other copper(I) salts were screened (CuBr, CuCl, $CuClO_4$), but CuI proved to be the most effective. For example, CuCl afforded only trace amounts of product, whereas $CuClO_4$ resulted in a complex mixture of highly fluorinated adamantane-based products in variable quantities.

Our group has shown that reactions employing Selectfluor concomitant with a metal cocatalyst can be accelerated by the addition of a phase-transfer catalyst as a solubilizing agent and presumed metal counteranion exchanger.[10] To this end, we added $KB(C_6F_5)_4$ (10 mol%) to our reaction and were gratified to find a substantial increase in the rate of formation and yield of **2** (Table 1).[11] In a parallel effort toward making the reaction more homogeneous, we also sought the use of a ligand to bring CuI into solution more effectively and to modulate its reactivity. Bis(imine)-derived ligands are well established in copper catalysis, so we tried them at the outset.[12] For example, addition of *N*,*N*-bis(phenylmethylene)-1,2-ethanediamine (BPMED; 10 mol%) to our reaction afforded further increases in the yields of **2**. We then examined the effects of time, temperature, solvent, and the equivalency of Selectfluor on the reaction. Immediately, we

Table 1: A test substrate: Screening of conditions for adamantane fluorination



1 2 3

Catalyst	Solvent	Ligand	*T* [°C]	**2/3**	**2** Yield [%]
	MeCN	–	25	–	0[a,b]
CuI	MeCN	–	25	8:1	18[a,b]
CuI	MeCN	BPMED	25	7:1	28[a,b]
CuI	MeCN	BPMED	25	5:1	35[a]
CuI	MeCN	BPMED	25	–	trace[a]
CuI	MeCN	BPMED	25	3:1	12[a]
CuI	**MeCN**	**BPMED**	**25**	**8.4:1**	**75[a]**

[a] Yield without $KB(C_6F_5)_4$. [b] MeCN was not degassed. [c] Yield after 1 . [d] Yield after 3 h. Otherwise yields were determined after 24 h by ^{19}F NMR spectroscopy using 2-fluorobenzonitrile as an internal standard, and also by column chromatography. Final entry indicates yield of isolated product.

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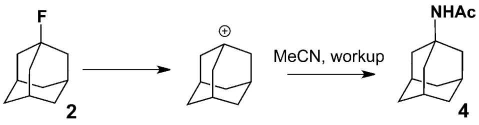
found the reaction proceeded well when MeCN was used as a solvent, and the yield of the fluorinated product depended significantly on reaction time. In this respect, longer reaction times were shown to give lower yields of **2** and an increased formation of the corresponding acetamide **4** [Eq. (2)].



(2)

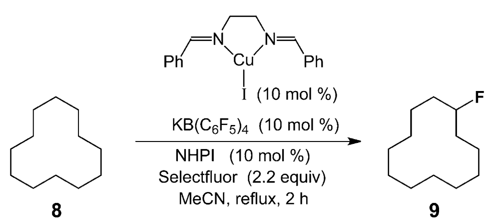
Furthermore, heating the reaction proved deleterious, whereas cooling of the reaction mixture to 0 °C remarkably yielded increased quantities of **3** over the anticipated **2** (40 %). Performing the reaction for 3 hours at room temperature provided for optimal yields of **2** (75 %; Table 1).

Although a detailed mechanistic study is forthcoming, a few observations point to the putative participation of radicals[5] (either free or metal-based) or single-electron transfer (SET) during fluorination: 1) yields in the strict absence of O_2 are much higher than in its presence;[13] 2) interference from the MeCN solvent is minimal (at least during the initial fluorination), and consistent with its sluggish reaction with free radicals.[14] 3) finally, there is precedent for Selectfluor engaging in SET chemistry.[15] In contrast, bare fluoro radicals are unlikely to be major participants in the optimized reaction; we would expect them to abstract H atoms with virtually equal facility from both tertiary and secondary alkyl sites in adamantane.[16] One final piece of evidence in support of the involvement of radicals may be discerned through the use of a radical trapping agent such as 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO). When the reaction is performed under optimized reaction conditions using a stoichiometric amount of adamantane and TEMPO, only trace amounts of **2, 3**, and **4** are evident.

The depletion of **2** involving a putative S_N1 solvolysis is likewise expected based on the formation of the corresponding acetamide after work-up [Eq. (2)].[17] Adamantyl cations are well-established intermediates in solvolysis reactions.[18] The higher stability of the 1-adamantyl cation relative to the 2-isomer would explain the relative depletion of product **2** versus **3** during longer reaction times. For example, as calculated at the B3LYP/6-311++G** level of theory, the 1-adamantyl cation is more stable than the 2-isomer by almost 11.3 kcal mol^{-1}.[19]

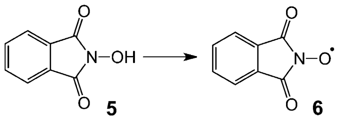
We turned our attention to an investigation of the scope of the reaction. A variety of aliphatic, allylic, and benzylic substrates were investigated. Unfortunately, upon initial screening, the reaction conditions optimized for reactive adamantane yielded only trace amounts of the desired fluorinated products on a variety of substrates. At this point, we chose to focus our efforts on a less-reactive model substrate such as cyclododecane (**8**; Table 2). We found that heating the reaction increased the yield of **9** greatly (43 %), likely a result from increased reaction rate, and as the product is a secondary fluoride, solvolysis in MeCN was not such a serious problem. In an effort to improve both the yield and the rate of the reaction, *N*-hydroxyphthalimide (**5**; 10 mol %), which is known to form the phthalimide *N*-oxyl (PINO) radical **6** in situ in the presence of redox active metals [Eq. (3)],[20] was examined as a possible cocatalyst. Interestingly enough, addition of NHPI provided additional increases in the yield of **9** (63 %; entry 3), and along with the additive KI, which forms the putative cuprate(I) complex **7** (10 mol %), the optimal yield of **9** (72 %; entry 4 was obtained.[21] When longer reflux times were employed, 1,1-difluorocyclododecane began to form in appreciable amounts (18 % after 24 h).

Table 2: Optimization of fluorination conditions for a secondary alkane.[a]

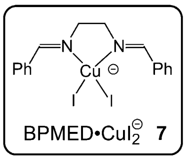


Entry	Catalyst	Cocatalyst	Cocatalyst	Yield [%]
1	(BPMED)CuI	–	–	26
2	(BPMED)CuI	$KB(C_6F_5)_4$	–	44
3	(BPMED)CuI	$KB(C_6F_5)_4$	NHPI	63
4	(BPMED)CuI	$KB(C_6F_5)_4$	NHPI[b]	72

[a] All reactions were performed at reflux for 2 h and yields were determined by ^{19}F NMR spectroscopy using 3-chlorobenzotrifluoride as an internal standard and isolation of the product by chromatography. [b] Reaction was performed with KI (10 mol%) as additive.



(3)

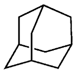
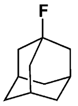
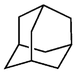
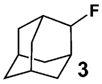
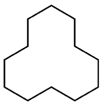
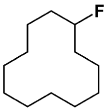
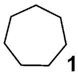
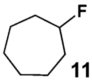
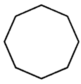
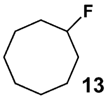
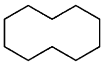
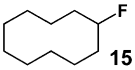
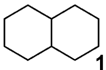
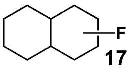
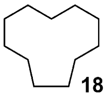
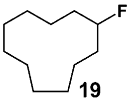
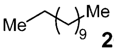
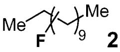
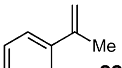
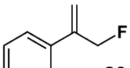
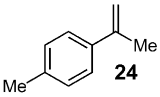
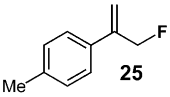
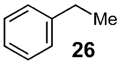
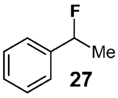
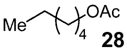
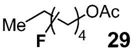
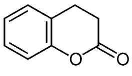
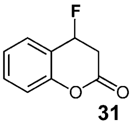
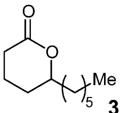
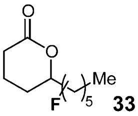
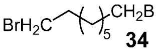
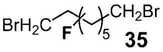


BPMED•CuI$_2^{\ominus}$ **7**

By using the optimized reaction conditions of Table 2, we explored other cycloalkanes, as they each give rise to one distinct monofluorinated product (Table 3). Medium sized rings such as cycloheptane (**10**), cyclooctane (**12**), and cyclodecane (**14**) worked as well (entries 5–7). Given the fact that an excess of cycloalkane is not used, it is remarkable that more polyfluorination is not observed. In fact, reaction conditions can be found under which the monofluoride is virtually the exclusive fluorinated product. In contrast, extended reaction times for **12** and **14** lead to diminished yields. It is clear that the products **13** and **15** undergo a slow solvolysis reaction, an unsurprising observation given the demonstrable release of Prelog strain[22] during S_N1 reactions of 8- and 10-membered ring systems, and that reaction times in MeCN reflect the susceptibility of substrates to solvolysis.

Straight-chain substrates such as *n*-dodecane (**20**) give rise to a virtual 1:1:1:1:1 mixture of monofluorinated products in 63 % yield, even though the necessity of 1.2 equivalents of KI at reflux may reflect their less reactive nature (Table 3, entry 9).[23] Allylic substrates proved to be interesting in their

Table 3: Catalytic substrate fluorinations.

Entry	Substrate	Product	Yield [%]	*t* [h]	*T* [°C]
1	 **1**	 **2**	75[c]	3	25
2	 **1**	 **3**	40[c]	3	0
3	 **8**	 **9**	72[a]	2	81
4	 **10**	 **11**	66[b]	1	81
5	 **12**	 **13**	41[b]	0.5	81
6	 **14**	 **15**	47[b]	0.5	81
7	 **16**	 **17**	52[b]	2	25
8	 **18**	 **19**	33[b]	1	81
9	 **20**	 **21**	63[b]	2	81
10	 **22**	 **23**	53[c]	24	25
11	 **24**	 **25**	42[c] (88)	24	25
12	 **26**	 **27**	28[c] (70)	24	25
13	 **28**	 **29**	56[b] (81)	1.5	81
14	 **30**	 **31**	47[b]	3	25
15	 **32**	 **33**	62[b]	5	81
16	 **34**	 **35**	55[b]	3	81

[a] 10 mol% KI. [b] 1.2 equiv KI. [c] No KI. Yields within parentheses for entries 11–13 are based on recovered starting materials. All reactions were monitored by ^{19}F NMR spectroscopy and yields determined using 3-chlorobenzotrifluoride as an internal standard and/or isolation of the product by column chromatography. Compounds 2, 3, 9, 15, 29, 33, and 35 were isolated.

own way. For example, α-methylstyrenes **22** and **24** are known to fluorinate in MeCN to form fluoroacetamides (under so-called electrophilic conditions) admixed with variable quantities of allylic fluorides.[24] Under catalytic conditions at room temperature, as demonstrated herein, the allylic fluorides predominate to the virtual exclusion of the fluoroacetamides (entries 10 and 11). This result would seem to bolster the case for a different (non-electrophilic) mechanistic pathway as well.

A benzylic substrate, ethylbenzene (**26**), fluorinated to provide α-fluoroethylbenzene (**27**; Table 3, entry 12) in 28% yield (56% based on recovered substrate). Once again, this product is unlikely to form by a strictly electrophilic process under these reaction conditions. Although the yield of this reaction is modest, only very minor amounts of ring fluorinated products were observed. Especially intriguing results are shown in entries 13–15, in which oxygen-containing substrates (esters) fluorinate productively. For example, *n*-hexyl acetate (**28**) fluorinates predominately on the 3- and 5-positions of the hexyl chain (72%; 81% total fluorination, entry 13), whereas dihydrocoumarin (**30**) reacts at its benzylic position to afford product **31**, which is the equivalent of a conjugate addition of fluoride to coumarin (entry 14).[25] In contrast, the lactone **32** fluorinates exclusively on its side chain (entry 15).

At this point we undertook a preliminary UV/Vis study of components of the catalytic system. The main observations include: 1) BPMED + CuI affords a spectrum consistent with a Cu^{I} complex; 2) addition of KI maintains the oxidation state of Cu^{I}; 3) addition of Selectfluor gives rise to weak bands indicative of Cu^{II} and they disappear rapidly, concomitant with the appearance of a prominent I_3^- band.[26] In turn, addition of NHPI results in consumption of I_3^-.[27] Presumably, Cu^{I} is regenerated as well. Thus, along with electron transfer to Selectfluor from the cuprate complex, the addition of KI may aid in the production of PINO radicals and in the regeneration of the catalyst, thus allowing less reactive substrates to convert smoothly. Further investigations will prove essential to the elucidation of a reaction mechanism and additional study will address the utility of the reaction and its application to complex substrates and natural products.

Experimental Section

Representative procedure for the syntheses of fluorinated alkanes: An oven-dried, 10 mL round bottom flask equipped with a stir bar was placed under an atmosphere of N_2. $KB(C_6F_5)_4$ (22.0 mg, 0.025 mmol, 0.1 equiv), Selectfluor (195 mg, 0.55 mmol, 2.2 equiv), copper(I) iodide (5.0 mg, 0.025 mmol, 0.1 equiv), *N,N*-bis(phenylmethylene)-1,2-ethanediamine (6.0 mg, 0.025 mmol, 0.1 equiv), *N*-hydroxyphthalimide (4.0 mg, 0.025 mmol, 0.1 equiv), and potassium iodide (50.0 mg, 0.3 mmol, 1.2 equiv) were then added, followed by degassed MeCN (3.0 mL). The reaction mixture was then stirred for 10 min. Under a stream on N_2, cyclododecane (**8**; 42.0 mg, 0.25 mmol, 1.0 equiv) was added neat and the mixture heated to reflux for 2 h. The reaction was monitored by ^{19}F NMR at 30 min intervals. Final yields were determined either by ^{19}F NMR spectroscopy using 3-chlorobenzotrifluoride as an internal standard or column chromatography on silica (either method was in good agreement). Note that this procedure (omitting the addition of KI) also applies to the allylic and benzylic substrates (Table 3).

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[1] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; b) D. Cahard, X. Xu, S. Couve-Bonnaire, X. Pannecoucke, *Chem. Soc. Rev.* **2010**, *39*, 558 – 568.

[2] a) D. Watson, S. Mingjuan, G. Teverovskiy, Y. Zhang, G. F. Jorge, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661 – 1664; b) T. Furuya, J. E. M. N. Klein, T. Ritter, *Synthesis* **2010**, 1804 – 1821; c) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 2265 – 2268; *Angew. Chem. Int. Ed.* **2010**, *49*, 2219 – 2222; d) Y. Ye, S. Lee, M. S. Sanford, *Org. Lett.* **2011**, *13*, 5464 – 5467; e) R. N. Loy, M. S. Sanford, *Org. Lett.* **2011**, *13*, 2548 – 2551.

[3] a) J. A. Akana, K. X. Bhattacharyya, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2007**, *129*, 7736 – 7737; b) B. C. Gorske, C. T. Mbofana, S. J. Miller, *Org. Lett.* **2009**, *11*, 4318 – 4321.

[4] Considerable progress has been made in aliphatic C–H bond activation; see: "C–H activation": H. M. Davies, A. R. Dick, *Top. Curr. Chem.* **2010**, 303 – 346; and for a representative example, see: M. S. Chen, M. C. White, *Science* **2007**, *318*, 783 – 787.

[5] Fluorination of alkane derived free radicals has been recently observed: M. Rueda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquins, G. M. Sammis, *J. Am. Chem. Soc.* **2012**, *134*, 4026 – 4029.

[6] a) W. T. Miller, A. L. Dittman, *J. Am. Chem. Soc.* **1956**, *78*, 2793 – 2797; b) W. T. Miller, D. D. Koch, F. W. McLafferty, *J. Am. Chem. Soc.* **1956**, *78*, 4992 – 4995; c) W. T. Miller, S. D. Koch, *J. Am. Chem. Soc.* **1957**, *79*, 3084 – 3089; d) D. H. R. Barton, R. H. Hesse, R. F. Markwell, M. M. Pechet, H. T. Toh, *J. Am. Chem. Soc.* **1976**, *98*, 3034 – 3035; e) S. Rozen, *Acc. Chem. Res.* **1988**, *21*, 307 – 312.

[7] a) R. W. Fowler, W. B. Burford, J. M. Hamilton, R. G. Sweet, C. E. Weber, J. S. Kasper, I. Litant, *Preparation, Properties and Technology of Fluorine and Organic Fluoro Compounds*, McGraw Hill, New York, **1951**, pp. 349 – 371; b) B. D. Joyner, *J. Fluorine Chem.* **1986**, *33*, 337 – 346; c) J. Burdon, J. C. Creasey, L. D. Proctor, R. G. Plevey, J. R. N. Yeoman, *J. Chem. Soc. Perkin Trans. 2* **1991**, 445 – 447.

[8] a) G. G. Furin, *New Fluorinating Agents in Organic Synthesis*, Springer, Berlin, **1989**, pp. 135 – 168; b) M. Zupan, S. Stavber, *Tetrahedron* **1989**, *45*, 2737 – 2742.

[9] For our interest in polyfunctional catalysis, see: a) D. H. Paull, M. T. Scerba, E. Alden-Danforth, L. R. Widger, T. Lectka, *J. Am. Chem. Soc.* **2008**, *130*, 17260 – 17261; b) J. Erb, D. H. Paull, L. Belding, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2011**, *133*, 7536 – 7546.

[10] S. Bloom, M. T. Scerba, J. Erb, T. Lectka, *Org. Lett.* **2011**, *13*, 5068 – 5071.

[11] Toste et al. have recently developed a system involving an asymmetric phase-transfer-catalyzed fluorination of silyl ethers: V. Rauniyar, A. D. Lackner, G. L. Hamilton, F. D. Toste, *Science* **2011**, *334*, 1681 – 1683.

[12] CuI·bisimine complexes are known: A. Toth, C. Floriani, M. Pasquali, A. Chiesi-Villa, A. Gaetani-Manfredotti, C. Guastini, *Inorg. Chem.* **1985**, *24*, 648 – 653.

[13] a) K. Okamura, Y. Takahashi, T. Miyashi, *J. Phys. Chem.* **1995**, *99*, 16925 – 16931; b) F. Wilkinson, *Pure Appl. Chem.* **1997**, *69*, 851 – 856. In contrast, this observation may also be explained by suppression of the formation of catalytically deactivated $Cu\text{-}O_2$ complexes; see: c) N. Kitajima, Y. Moro-oka, *Chem. Rev.* **1994**, *94*, 737 – 757; d) Z. Tyeklar, R. Jacobson, N. Wei, N. N. Murthy, J. Zubieta, K. D. Karlin, *J. Am. Chem. Soc.* **1993**, *115*, 2677 – 2689.

[14] P. S. Engel, W. K. Lee, G. E. Marschke, H. J. Shine, *J. Org. Chem.* **1987**, *52*, 2813 – 2817.

[15] a) P. T. Nyffeler, S. G. Durón, M. D. Burkhart, S. P. Vincent, C. H. Wong, *Angew. Chem.* **2005**, *117*, 196 – 217; *Angew. Chem. Int. Ed.* **2005**, *44*, 192 – 212; b) X. Zhang, H. Wang, Y. Guo, *Rapid Commun. Mass Spectrom.* **2006**, *20*, 1877 – 1882; c) Y. A. Serguchev, M. V. Ponomarenko, L. F. Lourie, A. A. Fokin, *J. Phys. Org. Chem.* **2011**, *24*, 407 – 413.

[16] M. L. Poutsma in *Free Radicals*, *Vol. II* (Ed.: J. K. Kochi), Wiley, New York, **1973**.

[17] Q. Michaudel, D. Thevenet, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 2547 – 2550.

[18] P. von R. Schleyer, R. C. Fort, W. E. Watts, M. B. Comisarow, G. H. Olah, *J. Am. Chem. Soc.* **1964**, *86*, 4195 – 4197.

[19] Geometry optimizations were performed using the Spartan‘06 program, Wavefunction, Inc.

[20] a) S. Coseri, *Catal. Rev. Sci. Eng.* **2009**, *51*, 218 – 292; b) S. Coseri, *Eur. J. Org. Chem.* **2007**, 1725 – 1729; c) B. Orlińska, I. Romanowska, *Cent. Eur. J. Chem.* **2011**, *9*, 670 – 676.

[21] It is known that aqueous solutions of CuI and KI react to form a host of copper halide species in which the ate complex CuI_2^- predominates: K. Endo, K. Yamamoto, K. Deguchi, K. Matsushita, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2803 – 2807.

[22] Y. I. Gol'dfarb, L. I. Belen'kii, *Russ. Chem. Rev.* **1960**, *29*, 214 – 235.

[23] A chart based on substrate reactivity under given reaction conditions was recommended and is provided in the Supporting Information.

[24] J. S. Yadav, B. V. Subba Reddy, D. Narasimha Chary, D. Chandrakanth, *Tetrahedron Lett.* **2009**, *50*, 1136 – 1138.

[25] Compound **31** is prone to dehydrofluorination over time.

[26] Similarly, unstable CuI_2 rapidly disproportionates to give a mixture of CuI and soluble I_2 in acetonitrile; see: Y.-L. Wang, X.-B. Wang, X.-P. Xing, F. Wie, J. Li, L.-S. Wang, *J. Phys. Chem. A* **2010**, *114*, 11244 – 11251.

[27] Selectfluor is also known to react with I_3^- and I^-: a) R. E. Banks, M. K. Besheesh, S. N. Mohialdin-Khaffaf, I. Sharif, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2069 – 2076; b) S. Stavber, P. Kralj, M. Zupan, *Synlett* **2002**, *4*, 598 – 600.