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Regioselective functionalization of gem-bis(trifluoromethylated) alkanols

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Due to importance of alcohols in various fields,¹ numerous examples of functionalization of their sp³ C-H bond by radicals,^{2,3} metal complexes,⁴ H₂SO₄ and HF·SbF₅⁵ acids have been described. The potent superelectrophilic complexes $CX_4 \cdot 2AIX_3$ (X = Br or Cl)⁶ turned out to be effective for initiating sp^3 C–H functionalization of alkanes^{6(b)} and functional organic compounds⁷ including primary alcohols.^{7(d)}

Synthesis of alcohols containing polyfluorinated groups is of interest,⁸ since they possess valuable properties in comparison with their non-fluorinated analogues such as improved chemical and thermal stabilities, lower boiling points and increased hydrophobicity. Many polyfluorinated alcohols and their derivatives are biologically active compounds.⁹

The examples of free radical and transition metal initiated intermolecular functionalizations of sp³ C-H bond in fluorinated alcohols have been reported.¹⁰ Both of them, the free radical domino reaction^{10(a)} and ruthenium catalyzed C-C coupling with allenes^{10(b)} involved α -functionalization of short fluorinated alcohols. The superelectrophiles open the possibility of preparing products with neo- or tertiary structures and remote functional groups directly from linear functional organics.⁷

In this paper, we report on access to a new series of alcohols with polyflouoromethyl groups on the example of one-pot functionalization of 1,1,1-trifluoro-2-(trifluoromethyl)decan-2-ol 1 with CO and nucleophiles in the presence of CBr₄·2AlBr₃.

We could not predict a priori how two trifluoromethyl groups would affect activity of compound 1 in this reaction. On the one hand, the presence of two strong electron-withdrawing groups

could reduce its ability of coordinating superelectrophile and therefore facilitate the ionization of C-H bond. On the other hand, a functional group dramatically affects the sp^3 C–H bond functionalization. In the presence of superacids, functionalization of alkanes with CO and alcohols proceeds unselectively.¹¹ With $\mbox{CBr}_4{\cdot}\mbox{2AlBr}_3$ as the initiator, degradative functionalization of alkanes C6-C10 did not occur, however, two isomers with neoalkyl groups, such as Alk(Me)2COOR and Alk(Me)EtCOOR were formed.¹² On the contrary, the processing of functional organics, XC_nH_{2n+1} (X = ROCO, MeCO, MeCOO, NR₂, OH; n = 6-9) with CO and nucleophiles (NuH) occurred regioselectively, resulting in a sole *neo*-isomer, $XC_{n-3}H_{2(n-3)}C(Me)_2CONu.^7$

In fact, at -20 °C under atmospheric CO pressure and in the presence of 100% molar excess of CBr₄·2AlBr₃ in dry CH₂Br₂, carbonylation of polyfluoro alkanol 1 followed by in situ quenching with nucleophilic agents led to the corresponding bifunctional products of *neo* structures 2 in good or moderate yields (Scheme 1). No products of destructive functionalization with lower number of carbon atoms were detected.

The tentative mechanism of the process (see Scheme 1) involves the coordination of the hydroxyl group at the superelectrophilic complex ($CBr_3^+Al_2Br_7^-$) to form oxonium cation A at the first stage. The cleavage of sp^3 C–H bond leads to the secondary carbocation \mathbf{B} with cationic centre remoted from the oxonium group as a result of the repulsion of positive charges. The species **B** would isomerize into more stable tertiary cation **C**. The latter adds CO to form acylium cation D. Addition of nucleophile at cation **D** gives rise to product **2**.



Scheme 1 Reagents and conditions: i, CBr₄·2AlBr₃, CH₂Br₂, -20 °C, CO (1 atm), 2 h; ii, NuH, CO (1 atm), -20 °C, 10-20 min, heating to 0 °C (30 min), then H₂O.

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In the case of anisole, the acylation product **2e** was formed along with small amounts of the alkylation product **3** in yields of 8–25% depending on the reaction conditions (Scheme 2). Small amounts of **3** were detected by GC-MS spectra, when the reaction of **1** with anisole and CBr_4 ·2AlBr₃ was performed in the absence of CO.

Earlier, we observed the examples of alkylation of nucleophiles with cations $XC_nH_{2n}^+$ (to form the alkylation products similar to **3**) in analogous reactions.^{7(c)–(e)} The formation of alkylation products in CO atmosphere shows that generation of acylium cations can be reversible.¹³ Indeed, while the decarbonylation of MeCO⁺ is endothermic¹⁴ (by ~340 kJ mol⁻¹), the acylium salts, R_3CCO^+ (R = Me¹⁵, Ph¹⁶) are decarbonylated even at low temperature.

When ethanol was applied as a nucleophile, the conversion of substrate **1** was not full, and HOC(CF₃)₂(CH₂)₅CMe₂C(O)OEt was produced in a mixture with nonreacted compound **1**. The structure of this ester was supported by GC-MS spectra (M⁺ + H = 353). The use of octanethiol as a nucleophile led to the target thioester HOC(CF₃)₂(CH₂)₅CMe₂C(O)SC₈H₁₇ (M⁺ + H = 453) in a mixture with the dimeric dioctyl disulfide (M⁺ + H = 291), whose structure was proved by comparison with the authentic C₈H₁₇SSC₈H₁₇.

At 0 °C under CO atmosphere in the presence of CBr₄·2AlBr₃, compound 1 underwent oxidative functionalization to give a mixture of four isomeric cyclic esters with $M^+ = 306$ (the conversion within 2 h reached 92%). The reaction probably involved the generation of acylium cation **D** followed by its addition to the oxygen atom to form oxonium ion **E** which in turn eliminated proton and underwent cyclization (Scheme 3). Based on the NMR and GC-MS spectra of the isomeric mixture, structures **4a** and **4b** were assigned to the main isomers.



Scheme 3

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.11.030.

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