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Copper Catalyzed β-Difluoroacetylation of Dihydropyrans and Glycals by Means of Direct C–H Functionalization

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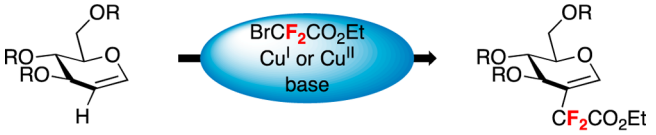
ABSTRACT



16 examples

A copper catalyzed direct functionalization of dihydropyrans and glycals has been developed. This method affords a new and straightforward access to C-2-CF_2 dihydropyrans and glycosides in a single step starting from readily available starting materials. This new copper based catalytic system, probably involving a Cu(III) species as supported by experiments, allows the formation of the valuable fluorinated glycosides in good yields.

Molecules containing a fluorine atom represent a remarkable class of compounds; the unique properties of the fluorine atom push it to the forefront of agrochemicals and drugs discovery. Its electronegativity, its small size, and the high energy of the C–F bond afford it the impressive ability to change the physical and biological properties of molecules.[1,2] On the other hand, fluorine is well recognized as a metabolically stable analog and/or surrogate of the hydrogen atom.[2] As a result, more than 20% of pharmaceuticals and 30% of agrochemicals bear at least one fluorine atom.[1] Thus, many synthetic efforts have been recently devoted to achieving the introduction of fluorine or fluorinated building blocks in an efficient manner[3] and particularly by means of C–H bond functionalization.[4] Quite recently, the introduction of fluorine and a CF_3 moiety onto aromatic and aliphatic backbones has attracted much attention, offering a wide range of elegant and efficient processes.[5] Surprisingly, the catalyzed direct introduction of a functionalized fluorinated moiety has been less explored, and such processes have remained scarce despite the high level of functionalization of the resulting products.[6] Among these fluorinated moieties, the CF_2CO_2Et moiety is extremely appealing due to the huge possibility of postfunctionalization. However, the introduction of the difluoroacetyl moiety onto an alkene or aromatic moiety usually focuses on (1) a radical addition of

(1) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.

(2) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.

(3) For review, see: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (c) Prakash, G. K. S.; Wang, F. *Chim. Oggi* **2012**, *5*, 30. For an early report on the radical of the fluorinated moiety on alkenes, see: (d) Chen, Q.-Y.; Yang, Z.-Y. *J. Fluorine Chem.* **1985**, *28*, 399. (e) Chen, Q.-Y.; He, Y.-B.; Yang, Z.-Y. *J. Fluorine Chem.* **1986**, *34*, 255. (f) Chen, Q.-Y.; Yang, Z.-Y.; Zhao, C.-X.; Qiu, Z.-M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 563. (g) Chen, Q.-Y.; Yang, Z.-Y. *J. Chem. Soc., Chem. Commun.* **1986**, 498. For selected examples, see: (h) Zhu, J.; Zhang, W.; Zhang, L.; Liu, J.; Zheng, J.; Hu, J. *J. Org. Chem.* **2010**, *75*, 5505. (i) Zhu, J.; Wang, F.; Huang, W.; Zhao, Y.; Ye, W.; Hu, J. *Synlett* **2011**, 899. (j) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560.

(4) Selected examples: (a) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (b) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (c) Mejía, E.; Togni, A. *ACS Catal.* **2012**, *2*, 521.

(5) Selected examples: (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (b) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (c) Novak, P.; Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 16167. (d) Hu, M.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 15257. (e) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.

(6) Surapanich, N.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V. *Eur. J. Org. Chem.* **2012**, 5943.

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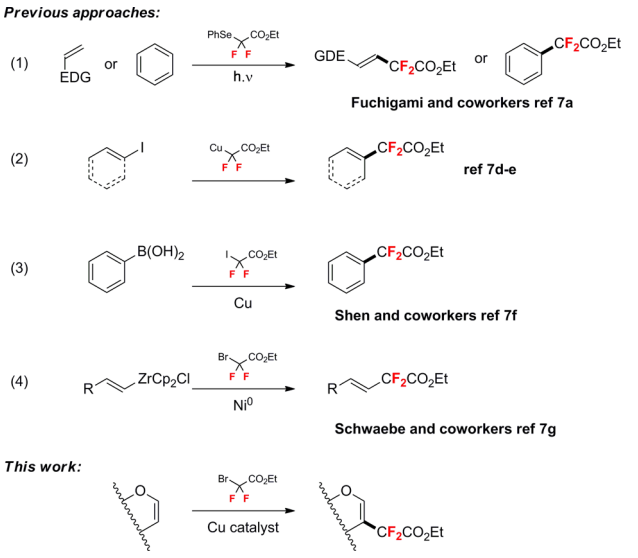
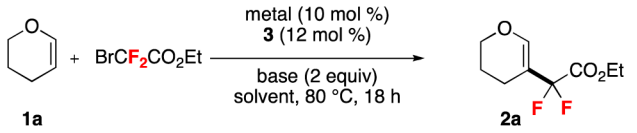
a halogenated or selenium based reagent on electron-rich olefins or electron-rich arenes;[7a−c] (2) the copper-bronze mediated reductive coupling of aryl or vinyl iodide with the copper species derived from the corresponding bromo, iodo, or trimethylsilyl difluoroacetate;[7d−e] (3) a copper mediated cross-coupling reaction of boronic acid with iododifluoroacetate in the presence of a stoichiometric amount of copper metal;[7f] or (4) a nickel catalyzed cross-coupling of vinyl zirconium species with bromodifluoroacetyl compounds.[7g] To the best of our knowledge no catalytic approach to the direct introduction of $BrCF_2CO_2Et$ by means of C−H bond functionalization has been reported to date. Thus, as our group is always interested in the preparation of fluorinated carbohydrates analogues, we report herein a catalytic radical free introduction of the CF_2CO_2Et moiety onto the C-2 position of dihydropyrans and glycals derivatives by means of direct copper catalyzed C−H functionalization (Scheme 1).

Scheme 1. Previous Examples of Difluoroacetylation Reactions



At the outset of the project, dihydropyran (DHP) was used as the model substrate to optimize the reaction conditions. Surprisingly, initial attempts using Pd catalysts led to the exclusive formation of the β-adduct **2a** albeit in low yield. Encouraged by these exciting results, we decided to improve this transformation. After extensive investigations, the corresponding adduct **2a** was obtained in 19% yield using $Pd(PPh_3)_4$ as a catalyst (Table 1, entry 1). The complete β-selectivity of the reaction contrasts with the typical Heck selectivity, which provides predominantly the α-product.[8] Thus, we hypothesized that the reaction might go through a different pathway: an electrophilic metalation. We next thought a more electrophilic metal, such as copper, might improve this chemical transformation, through a Cu(III) species, as a d^8 metal intermediate of the reaction.[9]

Table 1. Optimization of the Reaction Conditions



entry	metal	base	solvent	yield (%)[a]
1[b,c]	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	19
2[c]	$Cu(OTf)_2$	Cs_2CO_3	DMF	39
3	$Cu(OTf)_2$	Cs_2CO_3	DMF	47
4[c]	$Cu(OTf)_2$	–	DMF	NR[d]
5[c]	–	–	DMF	NR[d]
6	$Cu(OTf)_2$	Et_3N	DMF	21[f]
7	$Cu(OTf)_2$	K_3PO_4	DMF	4[f]
8	$Cu(OTf)_2$	K_2CO_3	DMF	49
9[e]	$Cu(OTf)_2$	K_2CO_3	DMF	73
10[e]	$Cu(OTf)_2$	Cs_2CO_3	NMP	65
11[e]	CuI	K_2CO_3	DMF	70
12[e]	$[Cu(OTf)]_2 \cdot C_6H_6$	K_2CO_3	DMF	62[f]
13[e]	$Cu(PF_6) \cdot (CH_3CN)_4$	K_2CO_3	DMF	52[f]

[a] Isolated yield. [b] Reaction was performed at 110 °C for 24 h. [c] Without **3**. [d] Starting material was fully recovered. [e] Reaction was performed under an air atmosphere. [f] Determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. **3**: 1,10-phenanthroline.

Pleasingly, the use of $Cu(OTf)_2$ affords a significant enhancement of the yield from 19% to 39% under milder conditions (entry 2). Moreover, a lower temperature and lower reaction time were required to ensure a full conversion along with a better isolated yield. The addition of a ligand (1,10-phenanthroline **3**) was beneficial, and the yield was improved to 47% (entry 3).[10] Noteworthy, control experiments revealed that the reaction did not occur in the absence of base[11] or copper catalyst (entries 4 and 5). The

(7) (a) Murakami, S.; Ishii, H.; Tajima, T.; Fuchigami, T. *Tetrahedron* **2006**, *62*, 3761. For a photocatalytic approach, see: (b) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (c) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560. (d) Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. *Tetrahedron* **1986**, *27*, 6103. (e) Ashwood, M. S.; Cottrell, I. F.; Cowden, C. J.; Wallace, D. J.; Davies, A. J.; Kennedy, D. J.; Dolling, U. H. *Tetrahedron Lett.* **2002**, *43*, 9271. (f) Qi, Q.; Shen, Q.; Lu, L. *J. Am. Chem. Soc.* **2012**, *134*, 6548. (g) Schwaebe, M. K.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **2000**, *41*, 791.

(8) For examples of complete α-selectivity: (a) Gøgsig, T. M.; Kleimark, J.; Lill, S. O. N.; Korsager, S.; Lindhardt, A. T.; Norrby, P.-O.; Skrydstrup, T. *J. Am. Chem. Soc.* **2012**, *134*, 443. (b) Mo, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4152. (c) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858. For examples and discussions regarding the α/β regioselectivity: (d) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1987**, *52*, 3529. (e) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217. (f) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1993**, *58*, 7421. (g) Datta, G. K.; von Schenck, H.; Hallberg, A.; Larhed, M. *J. Org. Chem.* **2006**, *71*, 3896.

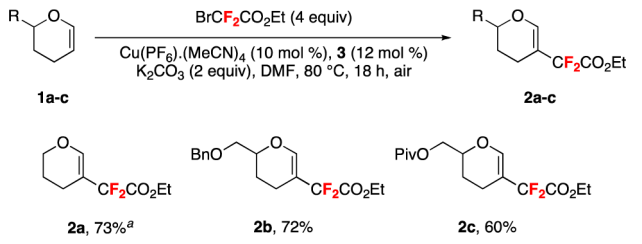
(9) (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (b) Gigant, N.; Chausset-Boissarie, L.; Belhomme, M.-C.; Poisson, T.; Pannecoucke, X.; Gillaizeau, I. *Org. Lett.* **2013**, *15*, 278. For well-defined Cu(III) species: (c) Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386.

(10) See Supporting Information for details.

(11) Starting material was fully recovered, precluding an addition–elimination process which would have afforded the α-bromo-β-CF_2CO_2Et pyran derivative.

nature of the base was crucial to achieve the transformation in good yield. Organic bases such as Et_3N were less efficient (entry 6), and a survey of inorganic bases highlighted K_2CO_3 as the most efficient base for this transformation (entry 8).[10] Then, a solvent screening showed that DMF and NMP were the most adequate solvents.[10] Nicely, a simple change from an argon to an air atmosphere led to the formation of **2a** in 73% yield (entry 9),[12] while the $Cu(OTf)_2/Cs_2CO_3$/NMP system gave a slightly lower yield (65%, entry 10). Another pertinent result is the effectiveness of Cu(I) catalysts as depicted in entries 11−13. To our delight, both CuI and $[Cu(OTf)]_2 \cdot C_6H_6$ led to the formation of **2a** in fairly decent yield, 70% and 62% respectively (entries 11 and 12), while $CuPF_6 \cdot (CH_3CN)_4$ gave a moderate yield along with unidentified side products (52%, entry 13). These last results clearly point out the fact that Cu(I) species might be the real active catalyst[13] involved in a Cu(I)/Cu(III) cycle. Next, functionalized dihydropyran derivatives **1b** and **1c** were engaged in the reaction, and pleasingly both benzyl and pivaloyl protecting groups were compatible affording the corresponding products **2b** and **2c** in 72% and 60% isolated yield respectively using $Cu(PF_6) \cdot (CH_3CN)_4$ as a catalyst instead of $Cu(OTf)_2$ (Scheme 2).

Scheme 2. Scope of Dihydropyran Derivatives[a]

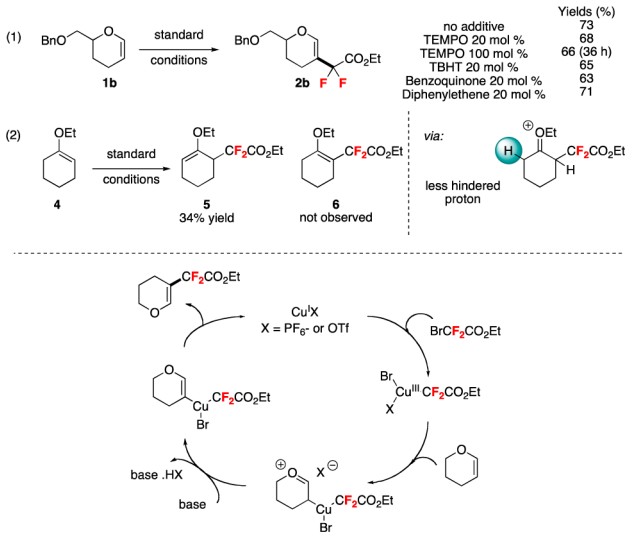


[a] $Cu(OTf)_2$ was used.

On the basis of this new transformation mechanism, mechanistic experiments were carried out. First, in order to rule out a radical pathway, the addition of radical inhibitors or radical scavengers to the reaction mixture was performed (Scheme 3, eq 1).

Interestingly, the addition of radical inhibitors or radical scavengers had a negligible effect on the yield of the reaction. In the presence of 20 mol % of TEMPO, TBHT, benzoquinone, or diphenylethene, a slight drop in the reaction yield was observed. Noteworthy, the reaction carried out with 1 equiv of TEMPO still proceeded smoothly although a longer reaction time was required (66%, 36 h). Additional evidence of the reaction mechanism was obtained with enol

Scheme 3. Evidence of the Reaction Mechanism



ether **4**. Under standard conditions an isomerization of the double bond of the product was observed, supporting the presence of an oxonium intermediate. Indeed, two sites of deprotonation are available, and it occurred on the less hindered position affording the trisubstituted enol ether **5** as the sole product (Scheme 3, eq 2). According to these results, we proposed the following mechanism. The *in situ* generated Cu(I) complex[12] is involved in an oxidative addition into the C−halogen bond of $BrCF_2CO_2Et$ leading to the formation of an highly electrophilic Cu(III) species.[14a] Then, the last one reacts with DHP forming an oxonium species, which is then released as an enol ether by the base. A final reductive elimination delivers the desired product and regenerates the copper catalyst (Scheme 3).[14b]

Finally, in order to highlight this new reactivity, we turned our attention to the functionalization of much more complex and challenging substrates: carbohydrate derivatives. Indeed, fluorinated carbohydrates are extremely appealing,[15] as the feature of the fluorine atom or fluorinated group to enhance the stability or to mimic the glycosidic linkage might afford metabolically stable carbohydrate-based drugs.[14] Thus, the design and synthesis of *in vivo* stable glycomimetic compounds appear as a real challenge toward the discovery of new biologically active compounds. In addition, to the best of our knowledge no catalytic C−H-bond functionalization of the glycosidic

(12) The use of an oxygen atmosphere supressed the reaction.

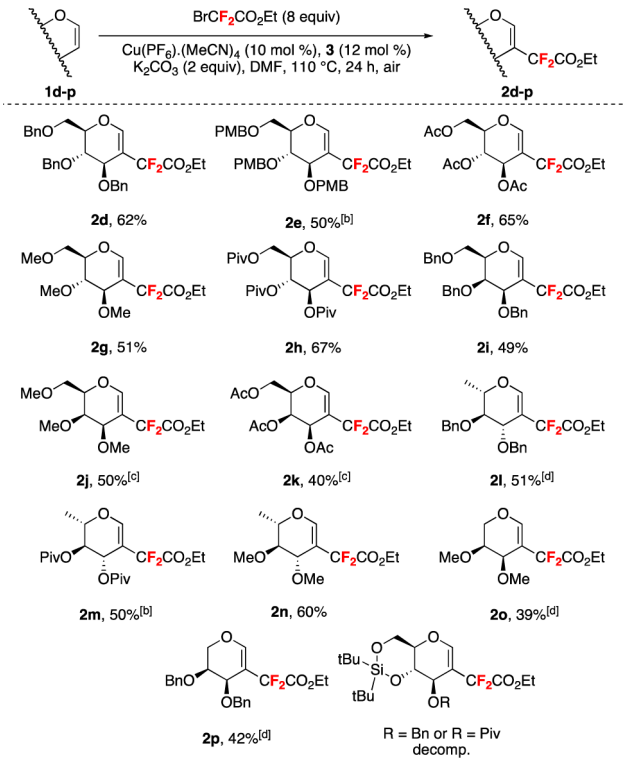
(13) The active Cu(I) can be generated through either the reduction or the disproportionation of Cu(II). For reduction, see: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. For disproportion, see: (b) Ribas, X.; Calle, C.; Poater, A.; Casitas, A.; Gomez, L.; Xifra, R.; Parella, T.; Benet-Buchholz, J.; Schweiger, A.; Mitrikas, G.; Sola, M.; Llobet, A.; Stack, T. D. P. *J. Am. Chem. Soc.* **2010**, *132*, 12299 and references herein.

(14) (a) Ethyl bromoacetate does not react, even at higher temperature. We suppose that the CF_2 moiety strengthens the electrophilicity of the Cu(III) intermediate, supporting the hypothesis of a nucleophilic attack of the DHP ring on the electrophilic metal center. All our attempts to characterize the Cu(III) species were unsuccessful. (b) We cannot rule out that the reductive elimination proceeds before the proton abstraction.

(15) For a review, see: Leclerc, E.; Pannecoucke, X.; Ethève-Quelquejeu, M.; Sollogoub, M. *Chem. Soc. Rev.* **2013**, *42*, 4270.

(16) For examples of C−H functionalization of glycosides, see: (a) Frihed, T. G.; Heuckendorff, M.; Pedersen, C. M.; Bols, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 12285. (b) Bai, Y.; Zeng, J.; Cai, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 4394. (c) Farr, R . N.; Outten, R. A.; Cheng, J. C.-Y.; Daves, G. D. *Organometallics* **1990**, *9*, 3151.

Scheme 4. Synthesis of Fluorinated Glycal Derivatives[a]



[a] Reaction conditions: **1** (0.24 mmol), $BrCF_2CO_2Et$ (8 equiv, 1.92 mmol), $Cu(PF_6)\cdot(MeCN)_4$ (0.024 mmol), **3** (0.029 mmol), K_2CO_3 (0.48 mmol), DMF (1.2 mL), 110 °C. [b] 110 °C, 30 h. [c] The isolated product contained some impurities. [d] CuI was used.

moiety by a fluorinated building block has been reported to date.[16] This new site selective introduction of the CF_2CO_2Et moiety applied to glycal derivatives could provide a straightforward and practical access to the unstudied C-2-CF_2 glycomimetics.[17] Initial attempts revealed that further optimizations were required to ensure a full conversion and decent yields as well. After optimizations, we found that the use of $Cu(PF_6)\cdot(CH_3CN)_4$ instead of $Cu(OTf)_2$, an increase in the number of $BrCF_2CO_2Et$ equivalents from 4 to 8 equiv, and enhancement of the reaction temperature to 110 °C furnish the corresponding tri-*O*-Bn-D-glucal **2d** in 62% yield (Scheme 4). The same protocol was used for glucal derivatives **2e**, **2f**, and **2g** affording the CF_2 glycosides in 50%, 65%, and 51% yield respectively.[18] Galactal derivatives reacted smoothly under our optimized conditions furnishing the fluoroglycosides **2i**, **2j**, and **2k** in moderate yield. The 6-deoxy-L-glucal derivatives **1l**, **1m**, and **1n** were submitted to the reaction conditions. The benzyl protected glycomimetic **2l** and the pivaloyl-protected CF_2 derivatives **2m** were obtained in 51% and 50% yield respectively, while the methyl protected fluorinated glycoside **2m** was isolated in 60% yield. We then turned our attention to the arabinal derivatives; surprisingly the methyl and benzyl protected glycals **2o** and **2p** gave lower yields compared to the previous glycosides, 39% and 42% respectively.[18b]

In conclusion we report herein an unsual nonradical addition of $BrCF_2CO_2Et$ to dihydropyran and glycal derivatives. This straightforward methodology based on a copper catalyzed C−H bond functionalization process afforded an easy access to C-2 CF_2-dihydropyrans and C-2 CF_2-glycosides. Mechanistic studies support a plausible Cu(I)/Cu(III) catalytic cycle involving a highly electrophilic organometallic species. This new methodology was successfully applied to a broad range of glycal derivatives giving an easy access to a new class of fluorinated compounds with potential applications as glycomimetics. Further applications of this new intriguing reactivity is currently underway in our laboratory.

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Supporting Information Available. Experimental procedures along with spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For an example of introduction of a fluorinated moiety at the C2 position of the carbohydrate, see: Wegert, A.; Miethchen, R.; Hein, M.; Reinke, H. *Synthesis* **2005**, 1850 and references herein.

(18) (a) The PMB protected glucal **1e** gave a lower yield, probably due to a partial deprotection of the PMB ether. *p*-Anisaldehyde was detected by ^1H NMR of the crude product. (b) We suspect that the ring conformation and particularly the C-4 center might affect the reactivity and stability of the resulting product.

The authors declare no competing financial interest.