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Selective Synthesis of Fluorinated Furan Derivatives via $AgNO_3$-Catalyzed Activation of an Electronically Deficient Triple Bond

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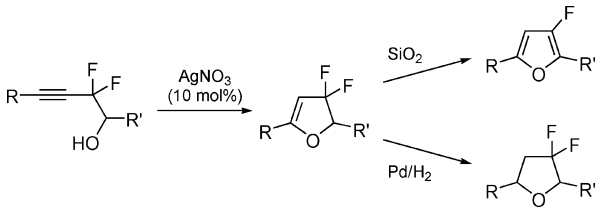

The transition metal-catalyzed direct activation of electron deficient triple bonds was investigated by using the combined electron withdrawing effects of two fluorine atoms to modulate the electronic density of the triple bond. With use of catalytic amounts of $AgNO_3$ (10 mol %) the synthesis of substituted 3,3-difluoro-4,5-dihydrofurans from *gem*-difluorohomopropargyl alcohols occurred in excellent NMR yields. Treatment of these dihydrofurans with SiO_2 or Pd/H_2 yielded the corresponding 3-fluorinated furans and 3,3-difluorotetrahydrofurans.

During the past decade there has been a concerted effort to develop transition metals capable of activating the triple bond to form new carbon−carbon bonds and carbon−heteroatom bonds.[1] It is well-known that complexes of group 11 metals (Cu,[2] Ag,[3] Au[4]) can activate electron-rich triple bonds; especially gold complexes have shown exceptional alkynophilicity under mild conditions. There are two types of transition metal-mediated triple bond activation: either through the formation of a vinylidene complex or through the direct activation of the π-bond. Because both activation methods are initiated from the metal−alkyne complex,[5] the coordination of an electron-rich triple bond with a Lewis acid is regarded as the keystone of this methodology.[6] Conversely, the activation of electronically deficient triple bonds with Lewis acids is hardly known.[3d] We now report the activation of an electronically deficient triple bond in *gem*-difluorohomopropargyl alcohol **1** using $AgNO_3$ as a Lewis acid. This discovery has resulted in new syntheses of fluorinated furan derivatives **2**, **3**, and **4**.

We decided to choose *gem*-difluorohomopropargyl alcohol[7] as a model because we envisaged a localized deactivation through inductive effects, of which the *gem*-difluoropropargyl group is capable of. As demonstrated by DFT calculations (Figure 1), the two fluorine atoms modulate the electronic density of the triple bond as compared with its nonfluorinated counterpart.

Another rationale for using fluorine is its impact on the biological activities of furan systems. The anti-HIV agents 3,3-*gem*-difluoromethylenated nucleoacids[8] and the anticancer drug Gemcitabine (2′-deoxy-2′-difluorocytidine), recently approved for the treatment of pancreatic cancer,[9] are cases in point.

Notwithstanding their potential usefulness, syntheses of fluorofurans and fluorohydrofurans are still tedious and there are no practical reactions that can generate substrate diversity. Furthermore, there are no reports of catalytic synthesis of these compounds.[10]

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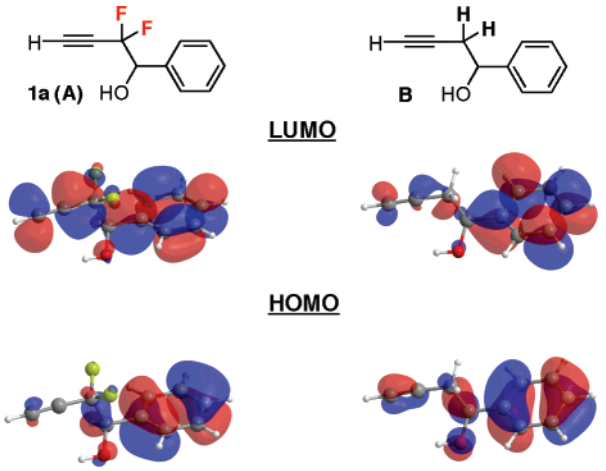
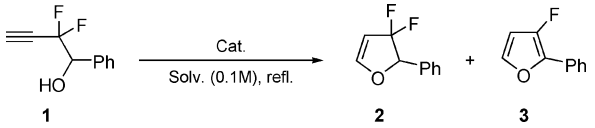


FIGURE 1. Comparison of the electronic states of the triple bond of *gem*-difluorohomopropargyl alcohol **1a** (A) and its nonfluorinated counterpart (B) [b3lyp/6-311g(d,p)5d].

TABLE 1. Screening of Metal Complexes of Group 11 Metals



entry	cat. X (mol %)	solvent	time,[a] h	yields of **2**/**3**,[b] %
1	$AuBr_3$ (5)	CH_2Cl_2	24	0/34
2	Me_3PAuCl (5)		24	no rxn
3	AgOTf (5)		12	0/34
4	$AgNO_3$ (5)		24	60/11
5	$AgNO_3$ (10)		24	45/31
6	Ag_2CO_3 (5)		24	no rxn
7	CuI (5)		24	0/34
8	CuOTf (5)		24	no rxn
9	$AgNO_3$ (10)	THF	6	94/0
10		Et_2O	6	no rxn
11		benzene	6	72/5

[a] The reaction time was determined by consumption of **1** as monitored by TLC. [b] Yields were determined by ^{19}F NMR.

We proceeded to screen group 11 metals that would catalyze the cyclization of **1** to **2** (Table 1). In striking contrast to nonfluorinated systems,[11] gold(I) or -(III) complexes did not give satisfactory results (Table 1, entries 1 and 2). Instead, we found that $AgNO_3$ was the best catalyst for obtaining 3,3-difluoro-4,5-dihydrofuran **2a** (Table 1, entries 4 and 5). This reaction exhibited a remarkable solvent effect, THF being the best solvent for obtaining **2a** selectively (Table 1, entry 9). Product **2a** could not be isolated by silica gel chromatography or distillation, both purification methods yielded 3-fluorofuran **3a**.[12] Interestingly, our attempts to obtain **3a** by inducing aromatization of **2a** using basic (NaOH, *t*-BuOK, and NaH) or acidic (BF_3·Et_2O and BCl_3) conditions failed completely.

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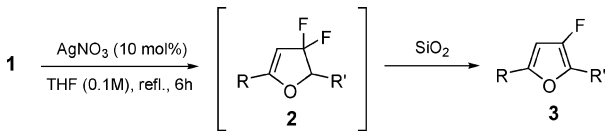
(12) A similar aromatization on silica gel has been reported; see ref 3a.

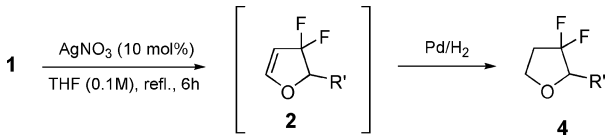
TABLE 2. Synthesis of 3,3-Difluoro-4,5-dihydrofuran 2 and 3-Fluorofuran 3



entry	R	R′	yields of products,[a] %	
1	H	Ph (**1a**)	94 (**2a**)	55 (**3a**)
2		4-Me-C_6H_4 (**1b**)	70 (**2b**)	55 (**3b**)
3		4-MeO-C_6H_4 (**1c**)	>99 (**2c**)	65 (**3c**)
4		3-MeO-C_6H_4 (**1d**)	>99 (**2d**)	79 (**3d**)
5		2,4-$(MeO)_2$-C_6H_3 (**1e**)	>99 (**2e**)	62 (**3e**)
6		4-Cl-C_6H_4 (**1f**)	>99 (**2f**)	32 (**3f**)
7		4-CF_3-C_6H_4 (**1g**)	>99 (**2g**)	52 (**3g**)
8		2-F-C_6H_4 (**1h**)	91 (**2h**)	49 (**3h**)
9		$BnOCH_2$ (**1i**)	81 (**2i**)	68 (**3i**)
10[b]	Ph (**1j**)	Ph		20 (**3j**)
11	TIPS (**1k**)			no rxn
12	*n*-Hex (**1*l***)			58 (**3*l***)
13	$BnOCH_2$ (**1m**)			65 (**3m**)

[a] Yields of **2** were determined by ^{19}F NMR; yields of **3** were calculated after isolation of pure product. [b] Reaction time was 24 h.

TABLE 3. Synthesis of 3,3-Difluorotetrahydrofuran 4



entry	R′	yields of **4**,[a,b] %
1	Ph (**1a**)	74 [81] (**4a**)
2	4-Me-C_6H_4 (**1b**)	41 [52] (**4b**)
3	3-MeO-C_6H_4 (**1d**)	63 [71] (**4d**)
4	2,4-$(MeO)_2$-C_6H_3 (**1e**)	52 [68] (**4e**)
5	4-Cl-C_6H_4 (**1f**)	49 [53] (**4f**)
6	4-CF_3-C_6H_4 (**1g**)	68 [92] (**4g**)
7	2-F-C_6H_4 (**1h**)	67 [73] (**4h**)
8	$BnOCH_2$ (**1i**)	50 [57] (**4i**)

[a] Isolated yields. [b] The values in brackets correspond to ^{19}F NMR yields.

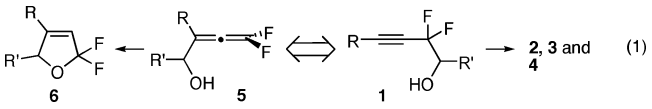
To explore the scope and limitations of the new Ag(I)-catalyzed cyclization, various *gem*-difluorohomopropargyl alcohols **1** were treated with $AgNO_3$ (10 mol %) in THF (Table 2).

In all cases ^{19}F NMR showed an excellent conversion to 4,5-dihydrofurans **2** regardless of the type of substrate R′ used [electron-donating (Table 2, entries 2−5), electron-withdrawing (Table 2, entries 6−8), and aliphatic substituents (Table 2, entry 9)]. After eluting through a silica gel column, 4,5-dihydrofurans **2** furnished the corresponding 3-fluorofurans **3** in good isolated yields (Table 2, entries 1−5 and 9); electron-withdrawing substituents (entries 6−8) produced **3** in moderate to low yields. In the case of internal alkynes, the Ag(I)-catalyzed cyclization funishes 3-fluorofuran **3**, albeit in low to moderate yields (Table 2, entries 10, 12, and 13). The reaction did not take place when R = TIPS (Table 2, entry 11).

Although 3,3-difluoro-4,5-dihydrofurans **2** could not be isolated, we were in the position to readily prepare 3,3-fluorotetrahydrofuran **4** by catalytic hydrogenation of **2** with a simple one-step synthesis of **2** in hand (Table 3, entries 1−8). This reaction gave high ^{19}F NMR yields and satisfactory isolated

yields with all substrates tested. The reaction mechanism proposed for the cyclization of **1** to **2** contemplates activation of the triple bond through coordination with $AgNO_3$, followed by a 5-*endo*-*dig* cyclization and proton shift to produce 4,5-dihydrofuran **2**.

In conclusion, $AgNO_3$ (10 mol %) in THF was found to be an efficient catalyst for the activation of the electronically deficient triple bond of **1** and its cyclization to 3,3-difluoro-4,5-dihydrofuran **2**. This methodology is a nice regiochemical complement to our earlier synthesis of 2,2-difluorodihydrofurans **6** from the isomeric fluoroallenylalcohol **5** (eq 1).[13]



Experimental Section

Synthesis of 3,3-Difluoro-2-phenyl-4,5-dihyroduran (2a) and 3-Fluoro-2-phenylfuran (3a). Into the suspension of $AgNO_3$ (0.05 mmol, 10 mol %) in THF (3 mL) was added the THF solution starting material (**1a**) (0.5 mmol, 1.0 equiv) dropwise. The whole reaction mixture was heated at reflux for 6 h. The reaction was quenched by 10% HCl_{aq} (10 mL) and extracted by diethyl ether (3 × 10 mL) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After moderate evaporation of the solvent, the corresponding dihydrofuran (**2a**) was observed by ^{19}F NMR (δ −84.63 (ddd, J = 248.0, 23.1, 19.8 Hz, 1F), −87.16 (ddd, J = 248.0, 13.2, 13.2 Hz, 1F)), and ^{19}F NMR yield was obtained by using α,α,α-trifluoromethylbenzene as the internal reference. The residue was treated with silica gel and diethyl ether, and then the silica gel was dried with high vacuum after removing diethyl ether; finally compound **3a** was isolated by silica gel chromatography with hexane in 55%. ^1H NMR ($CDCl_3$) δ 6.44 (s, 1H), 7.26−7.28 (m, 2H), 7.12−7.45 (m, 2H), 7.71−7.72 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −165.29 (s, 1F); ^{13}C NMR ($CDCl_3$) δ 104.7 (d, J = 20.2 Hz), 123.7 (d, J = 4.8 Hz), 127.3, 128.9, 129.2 (d, J = 4.8 Hz), 136.8 (d, J = 21.1 Hz), 140.0 (d, J = 9.5 Hz), 149.5 (d, J = 253.1 Hz); IR (neat) 3155, 3056, 1633, 1432 cm^{-1}; MS *m*/*z* (%) 162 (100, M^+), 133 (27), 105 (6). Anal. Calcd: C, 74.07; H, 4.35. Found: C, 73.90; H, 4.36.

Synthesis of 3,3-Difluoro-2-phenyltetrahydrofuran (4a). After the standard preparation for compounds **2a** (0.5 mmol scale), which was described previously, the organic solvent was evaporated moderately. Pd black (0.1 g) and THF (1.5 mL) were added to the flask, and hydrogenation was carried out under 30 atm of hydrogen gas for 24 h at room temperature. After 24 h, Pd black was removed by the celite filtration, then Pd black (0.1 g) and THF (1.5 mL) were renewed and the reaction was maintained for another 15 h under the same condition. After the reaction, Pd black was removed by celite filtration and the solvent was evaporated. Compound **4a** was isolated by silica gel chromatography with hexane/EtOAc (15/1) in 74% yield. ^1H NMR ($CDCl_3$) δ 2.37−2.46 (m, 2H), 4.00 (dq, J = 8.5, 1.0 Hz, 1H), 4.20 (dt, J = 8.0, 1.0 Hz, 1H), 4.74 (dt, J = 12.5, 0.5 Hz, 1H), 7.26−7.31 (m, 5H); ^{19}F NMR ($CDCl_3$) δ −103.94 (dq, J = 230.1, 13.0 Hz, 1F), −104.57 (dq, J = 230.1, 13.0 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ 35.5 (t, J = 24.5 Hz), 65.3, 83.2 (t, J = 27.3 Hz), 126.8, 128.1 (t, J = 253.3 Hz), 128.2, 128.5; IR (neat) 3035, 2962, 2883, 1959, 1737, 1498, 1456, 1321, 1115 cm^{-1}; MS *m*/*z* (%) 184 (61, M^+), 165 (28), 135 (9), 105 (33). Anal. Calcd: C, 65.21; H, 5.47. Found: C, 65.20; H, 5.69.

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Supporting Information Available: Analytical and spectroscopic data for **3b**−**j**, **3*l***,**m**, and **4b** and **4d**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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