Synthetic Methods

DOI: 10.1002/ange.200502807

Difluoroallenyl Bromide as a Wide-Ranging Difluoromethylene Cation Equivalent: S_N2 Substitution of Difluoropropargyl Bromide through Sequential S_E2' and S_N2' Reactions**

*Bo Xu and Gerald B. Hammond**

Dedicated to Professor Chang N. Wu on the occasion of his 72nd birthday

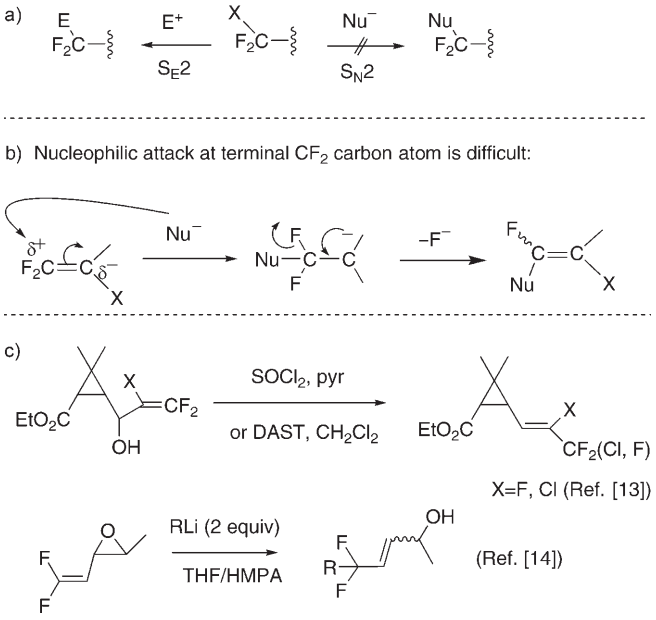
Unlike the other halogens, the small size of fluorine, the strong bond it forms with carbon, and its high electronegativity make it an ideal substituent to produce compounds with unique stereoelectronic and biological properties.[1] In this regard, *gem*-difluoromethylene-containing compounds have been sought after because of their inhibition of HIV protease,[2] and protein tyrosine phosphatase,[3] together with their ability to mimic phosphate,[4] carbonyl,[5] and retropeptide[6] units. In addition, the anomeric effects of heteroatom substituents, such as α-fluorinated ethers, α-fluorinated thioethers, and α-fluorinated amines, have sparked a flurry of new applications.[7] Overall, the significance of the incorporation of fluorine in organic molecules has spurred the development of novel synthetic strategies.[8] Despite these advances, a fundamental synthetic challenge persists, namely, the S_N2 synthesis of RCF_2Nu from RCF_2X

[*] B. Xu, Prof. G. B. Hammond
Department of Chemistry
University of Louisville
Louisville, KY 40292 (USA)
Fax: (+1) 502-852-3899
E-mail: gb.hammond@louisville.edu

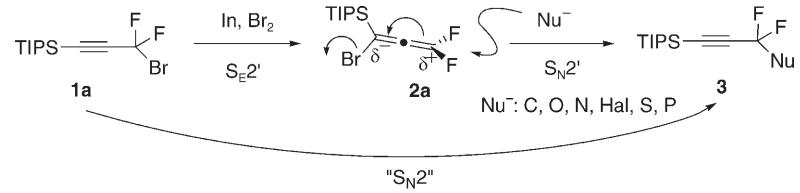
[**] Support of our work by the National Science Foundation (CHE-0513483) is gratefully acknowledged. The authors are also grateful to Professor Richard W. Fitch (Indiana State University) for his helpful advice on nitrogen nucleophiles and to the University of Kentucky for the use of its supercomputing facilities.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

(Scheme 1a). Whereas potent methodologies exist for S_E2-type electrophilic substitution using either difluoromethylene mono-[9] or dianion equivalents,[10] the shielding of the carbon atom by the surrounding fluorine atoms impedes substitution by a nucleophile (Nu), except under exceptional circumstances.[11] In some cases, nucleophilic substitution has been shown to proceed through a radical anion radical ($S_{RN}1$) process triggered by single electron-transfer, rather than S_N2 displacement.[12] In principle, RCF_2Nu could be synthesized by a nucleophilic reaction on *gem*-difluoroolefins (Scheme 1b), thus taking advantage of the preferential attack of nucleophiles at the terminal sp^2 difluoromethylene carbon atom. However, this approach usually yields addition–elimination products that arise from the facile β-elimination of a fluoride ion. In a couple of examples, this problem has been circumvented by using either 1,1-difluoro-2-halo-1-alken-3-ols[13] or 3,4-epoxy-1,1-difluorobutenes[14] for the synthesis of polyfluorinated pyrethroids or allylic alcohols, respectively (Scheme 1c). We now report what is in effect a widely applicable two-step S_N2 conversion of RCF_2Br into RCF_2Nu, whereby an indium-mediated S_E2' bromide substitution converts **1a** into **2a**, which in turn reacts with a nucleophile in a S_N2' fashion to produce **3** in high yield (Scheme 2). An added advantage of this strategy is that the resulting product **3** is equipped with a triisopropylsilyl (TIPS)–acetylenic linkage suitable for further synthetic manipulation.



Scheme 1. a) S_N2 and S_E2 reactions; b) nucleophilic substitution on a sp^2 fluorinated carbon atom; c) synthesis of polyfluorinated pyrethroids and propargyl alcohols using nucleophiles. Nu = nucleophile, pyr = pyridine, DAST = diethylaminosulfur trifluoride, HMPA = hexamethylphosphoramide.



Scheme 2. Planned strategy for the synthesis of **3** from **1a** using a S_N2 substitution. Hal = halide.

Functionalized allenes are of paramount importance in organic chemistry, both as building blocks and synthetic targets.[15] We have recently shown that fluorine substitution imparts profound changes to the chemistry of allenes.[16] On the basis of ab initio calculations,[17] we postulated that a vinylogous *gem*-difluoro-olefin, such as fluoroallene **2a** (Figure 1), would be ideally suited to acting as a difluoromethylene-cation equivalent because of the opposite NBO charges in **2a** (+0.765 on C1 and −0.449 on C3). This charge distribution would favor a S_N2' nucleophilic attack at C1, with concomitant bromide elimination at C3; the isomerization of the allene to a propargyl group is favorable and acts as a driving force. Conversely, its non-fluorinated counterpart **2b** has the electronic charge concentrated on the carbon termini, which is a deterrent towards nucleophilic attack. The synthesis of **1a** was carried out by using our previously reported procedure[18] on a multigram scale (92% yield). We treated **1a** with both hard and soft nucleophiles, including sodium 2-methyl malonate, Grignard reagents, triphenylphosphine, or sodium ethoxide, to demonstrate the lack of reactivity of the $-CF_2Br$ moiety towards nucleophilic substitution. In all cases, we obtained either starting material or intractable, defluorinated mixtures.

Prior to the present work, γ-bromodifluoroallenes were unknown.[19] We had reported earlier that the preformed indium propargyl complex **4**[20] yielded fluoroallenyl alcohol **5** when treated with a reactive electrophile, such as aqueous formaldehyde (Scheme 3).[21] Less reactive electrophiles, such as benzaldehyde or imines, produced homopropargyl alcohol or amines. If this premise is correct, then the reaction between **4** and a reactive electrophile, such as Br_2, should produce the γ-bromodifluoroallene **2a**. To our satisfaction, the S_E2' reaction of **4** and bromine proceeded quite readily at −78 °C in THF to yield the desired **2a** in 81% yield. This compound can be stored neat for months at −5 °C without any noticeable decomposition; in solution, it reverted to **1a** most

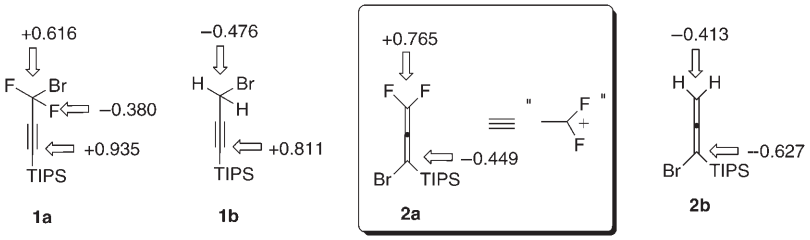
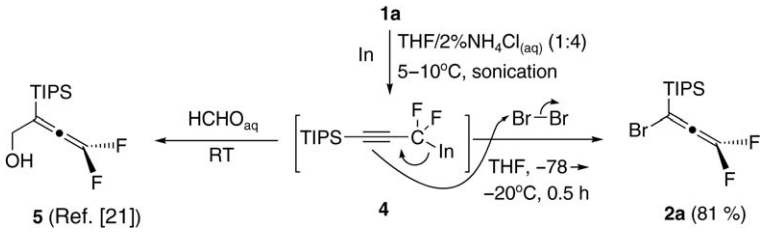


Figure 1. Ab initio calculation of *gem*-difluorinated propargyl and allenyl **1a** and **2a** and their non-fluorinated counterparts; the natural bond order (NBO) charge densities are given.

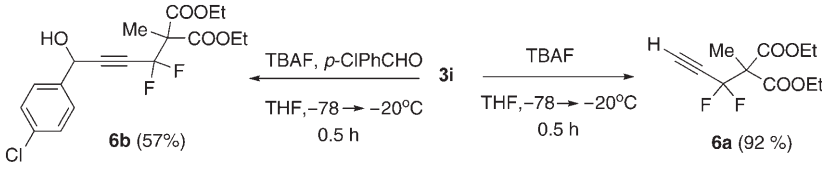


Scheme 3. Indium-mediated synthesis of **2a** via difluoropropargyl complex **4**.

likely through a S_N2' bromine displacement catalyzed by trace amounts of bromide. This proposition was later confirmed with the result obtained in entry **3g** in Table 1.

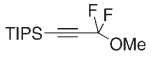
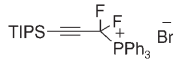
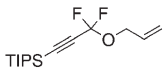
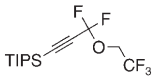
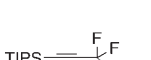
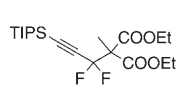
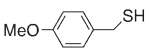
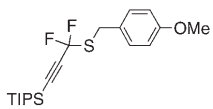
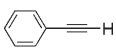
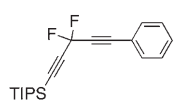
With a high-yielding synthesis of **2a** in hand, we proceeded to investigate its reactivity towards both soft and hard nucleophiles following the strategy depicted in Scheme 2. To our satisfaction, **2a** reacted readily with a wide range of weak and strong nucleophiles (P, O, S, C, N, and Br), in a S_N2' sense, thus furnishing **3** in good-to-excellent yields (Table 1). Aliphatic and aromatic amines produced complex mixtures. However, this problem was bypassed by using sodium azide as a nitrogen nucleophile, which produced a stable propargyl difluoroazide in almost 70% yield (entry **3h**). Notably, our new methodology also allowed the synthesis of hydrofluoroether **3c** in 68% yield by using trifluoroethanol as the nucleophile under very mild conditions. Prior to our disclosure, the synthesis of hydrofluoroethers could only be achieved under strongly basic conditions, which led to vinyl ether by-products, or through the very recently reported Pd^0-catalyzed hydroalkoxylation of hexafluoropropene.[22] In addition to the alkyne functionality present in **3**, the TIPS group is also a useful synthetic handle. It can be cleaved in excellent yield without loss of fluorine to yield **6a** by using TBAF. Alternatively, it can be further functionalized by using an electrophilic trap, such as *p*-chlorobenzaldehyde, to produce **6b** (see Scheme 4).

In conclusion, we have achieved a wide-ranging conversion of RCF_2Br into RCF_2Nu through a novel bromo-difluoroallene **2a**, which is the synthetic equivalent of a difluoromethylene cation. We are currently exploring the use of other substituents appended to the γ-carbon atom and probing the synthetic usefulness of the diverse repertoire of $-CF_2Nu$ synthons which have been obtained through this novel reaction.



Scheme 4. Deprotection and functionalization of **3i** using tetrabutylammonium fluoride (TBAF).

Table 1: S_N2' synthesis of difluoropropynes **3** from difluoroallene **2a**.

Nucleophile/conditions		Entry (yield [%])[a]	Nucleophile/conditions		Entry (yield [%])[a]
MeOH, K_2CO_3, 0°C, 3 h		**3a** (61)	PPh_3, diethyl ether, RT, 12 h		**3f** (92)
 K_2CO_3, 0°C, 4 h		**3b** (70)	NaBr, DMF, RT, 12 h		**3g** (78)
 K_2CO_3, 0°C, 4 h		**3c** (68)	NaN_3, CH_3CN, RT, 12 h		**3h** (68)
AcOH/AgOAc, RT, 12 h		**3d** (70)	 THF, NaH, 0°C 4 h		**3i** (70)
 *n*BuLi, THF, −78→0°C		**3e** (53)	 *n*BuLi, THF, −78→0°C		**3j** (55)

[a] Yield of the isolated products. All new compounds gave satisfactory spectral and analytical data. DMF = dimethylformamide.

Received: August 8, 2005
Published online: October 20, 2005

Keywords: allenes · cations · fluorine · nitrogen nucleophiles · nucleophilic substitution

[1] a) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell Publishing Ltd./CRC, Boca Raton, FL, **2004**; b) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**; c) T. Hiyama, *Organofluorine Compounds. Chemistry and Applications*, Springer, Berlin, **2000**; d) M. Schlosser, *Angew. Chem.* **1998**, *110*, 1538; *Angew. Chem. Int. Ed.* **1998**, *37*, 1496; e) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3.

[2] a) E. Specker, J. Bottcher, H. Lilie, A. Heine, A. Schoop, G. Muller, N. Griebenow, G. Klebe, *Angew. Chem.* **2005**, *117*, 3200; *Angew. Chem. Int. Ed.* **2005**, *44*, 3140; b) A. G. Myers, J. K. Barbay, B. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 7207.

[3] L. Bialy, H. Waldmann, *Angew. Chem.* **2005**, *117*, 3880; *Angew. Chem. Int. Ed.* **2005**, *44*, 2.

[4] D. O'Hagan, H. S. Rzepa, *Chem. Commun.* **1997**, 645.

[5] C. Leriche, X. He, C. Chang, H. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 6348.

[6] M. Sani, L. Bruche, G. Chiva, S. Fustero, J. Piera, A. Volonterio, M. Zanda, *Angew. Chem.* **2003**, *115*, 2106; *Angew. Chem. Int. Ed.* **2003**, *42*, 2060.

[7] F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827.
[8] a) For leading general references: *Fluorine-Containing Synthons*, ACS Symposium Series 911 (Ed.: V. A. Soloshonok), Oxford University Press/American Chemical Society, Washington, DC, **2005**; for leading references on asymmetric fluorination: b) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826; c) M. Marigo, D. Fielenbach, A. Braunton, A. Kjaersgaard, K. A. Jorgensen, *Angew. Chem.* **2005**, *117*, 3769; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703; d) D. D. Steiner, N. Mase, C. F. Barbas III, *Angew. Chem.* **2005**, *117*, 3772; *Angew. Chem. Int. Ed.* **2005**, *44*, 3706.
[9] a) M. Mae, J. A. Hong, K. Uneyama, G. B. Hammond, *Tetrahedron Lett.* **2005**, *46*, 1787; b) T. Kobayashi, T. Nakagawa, H. Amii, K. Uneyama, *Org. Lett.* **2003**, *5*, 4297; D. J. Burton, L. Lu, *Top. Curr. Chem.* **1997**, *193*, 45, and references therein.
[10] G. K. S. Prakash, J. Hu, T. Mathew, G. A. Olah, *Angew. Chem.* **2003**, *115*, 5374; *Angew. Chem. Int. Ed.* **2003**, *42*, 5216, and references therein.
[11] A case in point is the substitution of R-C≡C-CF_2Br with I: a) P.-Y. Kwok, F. W. Muellner, C.-K. Chen, J. Fried, *J. Am. Chem. Soc.* **1987**, *109*, 3684; b) M. G. Barlow, S. Tajammal, A. E. Tipping, *J. Fluorine Chem.* **1993**, *64*, 61; another example is the Arbuzov reaction of CF_2Br_2 with $P(OEt)_3$.
[12] V. N. Boiko, G. M. Shchupak, *J. Fluorine Chem.* **1994**, *69*, 207.
[13] M. Fujita, T. Hiyama, *Tetrahedron Lett.* **1986**, *27*, 3659.
[14] H. Ueki, T. Chiba, T. Yamazaki, T. Kitazume, *J. Org. Chem.* **2004**, *69*, 7616.
[15] For a comprehensive coverage, see: a) *Modern Allene Chemistry, Vol. 1–2* (Eds.: N. Krause, A. S. K. Hashmi) Wiley-VCH, Weinheim, **2004**; b) A. Hoffmann-Roder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196.
[16] Q. L. Shen, G. B. Hammond, *J. Am. Chem. Soc.* **2002**, *124*, 6534, and references therein.
[17] Computational analysis was carried out using Gaussian 03, Revision C.02 at the HF/6-311++g level of theory; Gaussian 03, Revision C.01, M. J. Frisch et al., Gaussian, Inc., Wallingford, CT, **2004**.
[18] Z. Wang, G. B. Hammond, *Chem. Commun.* **1999**, 2545.
[19] The synthesis and chemistry of bromoallenes has been recently reported: H. Ohno, H. Hamaguchi, M. Ohata, T. Tanaka, *Angew. Chem.* **2003**, *115*, 1791; *Angew. Chem. Int. Ed.* **2003**, *42*, 1749.
[20] Preliminary results from our ongoing investigation on the nature of the indium complex support the propargyl nature of **4**: B. Xu, G. B. Hammond, unpublished results.
[21] Z. G. Wang, G. B. Hammond, *J. Org. Chem.* **2000**, *65*, 6547.
[22] Y. Matsukawa, J. Mizukado, H. Quan, M. Tamura, A. Sekiya, *Angew. Chem.* **2005**, *117*, 1152; *Angew. Chem. Int. Ed.* **2005**, *44*, 1128.

