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Highly Regioselective Synthesis of *gem*-Difluoroallenes through Magnesium Organocuprate S_N2' Substitution

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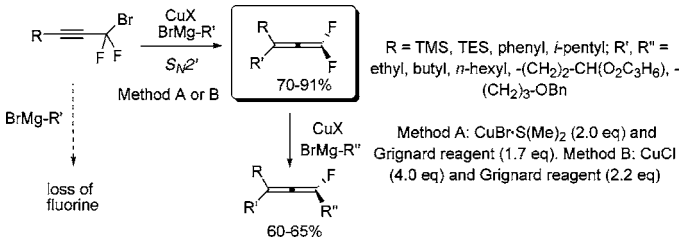
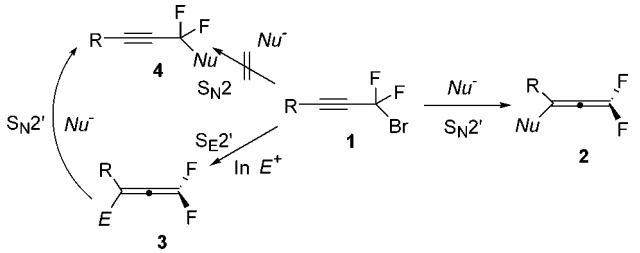
ABSTRACT



The reaction of *gem*-difluoropropargyl electrophiles with Grignard reagents is complicated by the inherent difficulty of executing nucleophilic substitutions on a CF_2 group, and the facile formation of carbenoid intermediates arising from α-elimination of fluoride. In the presence of an excess amount of a copper salt, a Grignard reagent reacts with *gem*-difluoropropargyl bromide via an S_N2' mechanism to produce *gem*-difluoroallene in high yield. If desired, the resulting difluoroallene can undergo a second nucleophilic attack on the CF_2 terminus to yield a trisubstituted monofluoroallene through an addition–elimination mechanism.

The selective substitution of hydrogen by fluorine is a valuable strategy that has made available fluoroorganic compounds with distinctive physicochemical and therapeutic properties.[1] Conceptually, the substitution of one or two fluorines on the terminal carbon of an allene moiety could lead to the discovery of novel nucleophilic, electrophilic, or cyclization reactions, en route to structural diverse targets with potential biological significance.[2] Whereas allenes are ubiquitous in organic chemistry, both as intermediates and targets,[3] less than a handful of fluorinated allene structures have been published.[4] Our interest in studying the effects of fluorine on the chemistry of alkynes led us to the discovery of an indium-mediated S_E2' conversion of *gem*-difluoropropargyl bromide **1** to allene **3** (Scheme 1).[5] If the electrophile

Scheme 1. Nucleophilic and Electrophilic Substitutions of **1**



was a leaving group (i.e., E = Br in **3**), it reacts with nucleophiles in an S_N2' fashion to produce **4**[6] thus overcom-

(1) For the most recent compilation of background references see: Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004.

(2) Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc.* **2002**, *124*, 6534−6535.

(3) For recent comprehensive coverage see: (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829−2871. (b) *Modern Allene Chemistry*; Krause, N., Hashmi, S., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vols. 1 and 2. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590−3593.

(4) Hammond, G. B. In *Fluorine-Containing Synthons*, Soloshonok, V. A., Ed.; ACS Symp. Ser. No. 911; Oxford University Press/American Chemical Society: Washington, DC, 2005; Chapter 10, pp 204−217.

(5) Wang, Z. G.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547−6552.

(6) Xu, B; Hammond, G. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7404−7407.

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ing the intrinsic barrier of RCF_2Br toward S_N2 substitutions.[7] In principle, a synthetically attractive approach to the nucleophilically substituted difluoroallene **2** is the copper-mediated S_N2'displacement of bromide from **1**—the only readily available difluoropropargyl electrophile.[8] Although this type of reaction has been utilized in the synthesis of allenes,[3b] its application to *gem*-difluoro systems is severely impaired because of the facile loss of fluorine through α-elimination, which may lead to carbenoid intermediates and complex mixtures.[9] We are now pleased to report a highly regioselective synthesis of difluoroallene **2** from difluoropropargyl **1**, employing an excess amount of a Grignard reagent and Cu(I) salt.

Ab initio calculations of NBO (natural bond order)[10] charge densities in propargyl bromide **5** vis-à-vis its fluorinated analogue **1** (Figure 1) demonstrate why S_N2' substitution is problematic in the fluorinated model. Electron densities on the C1- and C3-carbons of **5a** and **5b** indicate that the C3-carbon in both species is significantly more electrophilic than the C1-carbon and therefore prone to undergo an S_N2' attack. Conversely, the charge densities on the C1- and C3-carbons in *gem*-difluopropargyl bromides **1a** or **1b** reveal that both C1- and C3-carbons are electrophilic. To complicate matters further, the C1-carbon of difluoroallene **2b** has a positive charge density, whereas its nonfluorinated counterpart **6** does not (+0.337 vs −0.875).

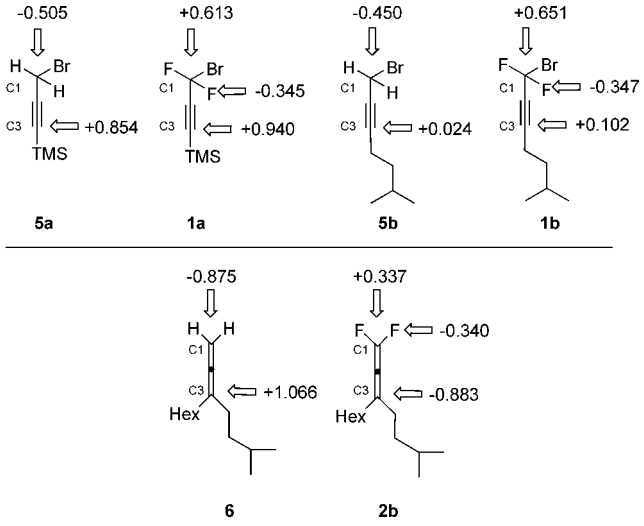
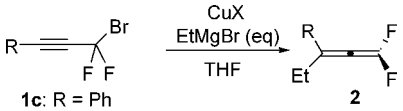


Figure 1. Ab initio calculation of *gem*-difluoropropargyl bromides and their nonfluorinated counterparts. Numbers refer to NBO (natural bond order) charge densities.

This difference in charge density is caused by the strong electron withdrawing effect of two fluorine atoms on the C1-carbon. If **2b** was synthesized from **1b** by using an S_N2' displacement, its CF_2 terminus would undergo a competitive nucleophilic attack—driven by an energetically favorable addition−elimination process (β-elimination of fluoride ion)[11]—yielding complicated mixtures of products (see also Scheme 2).

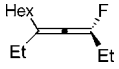
Table 1 summarizes the results of our S_N2' optimization study in the reaction between a Grignard nucleophile (EtMgBr) and difluoropropargyl bromides **1c** or **1d**. Loss of fluorine was observed in the absence of a copper source, most likely via a bromine−magnesium exchange, leading to a carbenoid intermediate that undergoes two succesive α-eliminations of F^- (Table 1, entry 1). The combination of CuCl and EtMgBr yields the desired product **2c** in low yield (8%, Table 1, entry 2). A purple color in the solution of the Grignard reagent and the copper salt signaled the formation

Table 1. Optimization of the Synthesis of Difluoroallene **2**



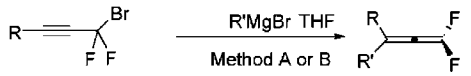
1c: R = Ph
1d: R = *n*-hexyl

entry	1	equiv of EtMgBr	CuX (equiv)	incubation[a] (°C, min)	temp, time (°C, h)	2 (%)[b]
1	**1c**	2.2	none	−40, 1	−40, 3	
2	**1c**	2.2	CuCl (1.1)	−40, 1	−40, 3	8
3	**1c**	2.2	CuCl (4.0)	−78, 1	−78, 1	NR
4	**1c**	2.2	CuCl (4.0)	−15, 5	−78, 1	81 (70)[c]
5	**1c**	2.2	CuCl (4.0)	+20, 5	−78, 1	14
6	**1c**	2.2	CuBr (4.0)	−15, 5	−78, 1	38
7	**1c**	2.2	CuCN (4.0)	−15, 5	−78, 1	NR
8	**1d**	2.2	CuCl (4.0)	−15, 5	−78, 1	51[d]
9	**1d**	1.0	CuBr (2.0) LiBr (2.0)	−60, 30	−60, 2	52
10	**1d**	1.5	CuBr (2.0) LiBr (2.0)	−60, 30	−60, 2	82
11	**1d**	1.7	CuBr (2.0) LiBr (2.0)	−60, 30	−60, 1	89
12	**1d**	1.7	CuBr (2.0) $S(Me)_2$ (2.0)	−60, 30	−60, 1	94 (91)[c]
13	**1c**	1.7	CuBr (2.0) $S(Me)_2$ (2.0)	−60, 30	−60, 1	80

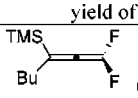
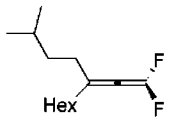
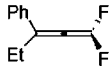
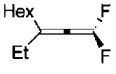
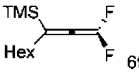
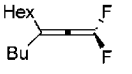
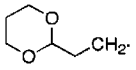
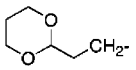
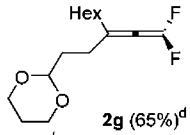
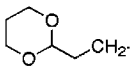
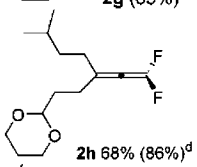
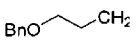
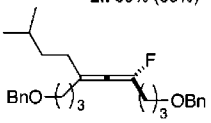
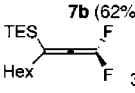
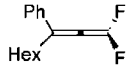
[a] Reactions were conducted in 1 mmol scale. A rbf was charged with the copper salt and THF and cooled to the temperature indicated, after which the Grignard reagent was introduced and the solution was stirred for an indicated period of time. Substrate was introduced at the end of the incubation time. [b] Yield was determined by ^{19}F NMR, using α,α,α-trifluorotoluene as an internal standard. [c] Isolated yield. [d] Major byproduct was monofluoro allene **7a**: 

(7) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing Ltd./CRC Press: Boca Raton, FL, 2004; p 123.
(8) Xu, B.; Mae, M.; Hong, J. A.; Li, Y.; Hammond, G. B. *Synthesis*. In press.
(9) Pohmakotr, M.; Ieawsuwan, W.; Tuchinda, P.; Kongsaeree, P.; Prabpai, S.; Reutrakul, V. *Org. Lett.* **2004**, *6*, 4547−4550.
(10) Computational analysis was carried out with Gaussian 03, Revision C.02 at the B3LYP/6-311+g(3d) level of theory. Frisch, M. J., et al., see Supporting Information.
(11) For synthetic applications that take advantage of fluoride elimination see: Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917−1936.

Table 2. Synthesis of Substituted *gem*-difluoroallenes



1a: R = TMS **1b**: R = *i*-pentyl
1c: R = phenyl **1d**: R = *n*-hexyl **1e**: R=TES

entry	1	R'	method	yield of 2[c]
1	**1a**	Bu	A[a]	 **2a** 69% (73%)[d]
2	**1b**	Hex	A	 **2b** 82% (90%)[d]
3	**1c**	Et	A	 **2c** 70% (82%)[d,e]
4	**1c**	Et	B	**2c** 70% (81%)
5	**1d**	Et	A	 **2d** 91% (94%)[d]
6	**1a**	Hex	A	 **2e** 69% (71%)[d,f]
7	**1d**	Bu	A	 **2f** 88% (92%)[d]
8	**1d**		A	NR
9	**1d**		B[b]	 **2g** (65%)[d]
10	**1b**		B	 **2h** 68% (86%)[d]
11	**1b**		B	 **7b** (62%)[g]
12	**1c**	Hex	A	 **2i** 37% (35%)[d]
13	**1c**	Hex	A	 **2j** 80%[h]

[a] Method A: $CuBr{\cdot}S(Me)_2$ (2.0 equiv) and Grignard reagent (1.7 equiv) were used. After the incubation time (30 min, −60 °C), the substrate was syringed in. [b] Method B: CuCl (4.0 equiv) and Grignard reagent (2.2 equiv) were used. After the incubation (10 min, ca. −20 °C), the mixture was cooled to −78 °C and the substrate was syringed in. [c] Isolated yield. [d] Yield in parentheses was determined by ^{19}F NMR, using α,α,α-trifluorotoluene as the internal standard. [e] Cold (−15 °C) jacketed column chromatography was used in the isolation. [f] Using CuCN (2.2 equiv)/HexMgBr (2.2 equiv), the ^{19}F NMR yield was only 58%. [g] Difluoroallene was obtained as the minor product (33%). [h] Product decomposed upon purification.

of the magnesium organocuprate complex (incubation). Increasing the temperature during the incubation, and the amount of copper(I), improved the yield of **2c** notably (Table 1, entry 4). Incubation at −78 °C or room temperature has a deleterious effect (Table 1, entries 3 and 5). Among the different copper salts screened (Table 1, entries 4, 6, and 7), the best yield of **2c** (R = phenyl) was recorded with CuCl; but when R = *n*-hexyl, the yield of **2d** was only 51% (Table 1, entry 8). Copper salts soluble in THF, such as CuBr·LiBr and $CuBr{\cdot}S(Me)_2$, yielded better results (Table 1, entries 9−13). The best results were obtained with 2 equiv of $CuBr{\cdot}S(Me)_2$ and 1.7 equiv of the Grignard reagent (method A) (Table 1, entries 12 and 13).

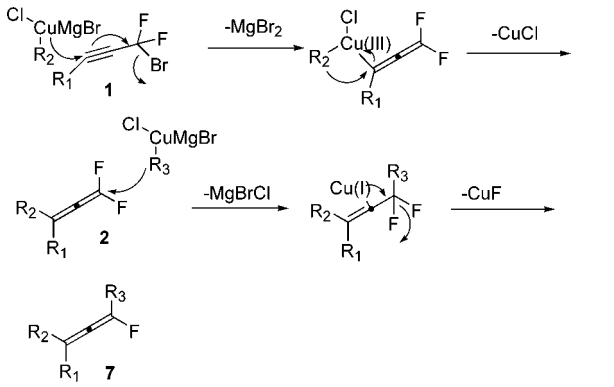
With optimized reaction conditions in hand, we investigated the scope of the reaction (Table 2). Method A or B (CuCl, 4.0 equiv; R′MgBr, 2.2 equiv) gave very good to excellent yields of **2a**−**f** (Table 2, entries 1−7). Method A failed with 1,3-dioxolan-2-ylmethylmagnesium bromide (Table 2, entry 8). This was attributed to a stabilizing complexation of the copper intermediate with the oxygen atoms of the dioxolane moiety. To our satisfaction, Method B overcame this problem, producing **2g** and **2h** (Table 2, entries 9 and 10) in good yields. With benzyloxypropylmagnesium bromide, the major product obtained was monofluoroallene **7b** (62% yield) (Table 2, entry 11). A bulkier substitutent on the C3-carbon reduced the efficiency of the S_N2' attack (Table 2, entry 12).

Difluoroarylallenes are highly unstable. Of all the aryl-containing substrates screened, only phenyl difluoroallene **2c** could be isolated by using a refrigerated column. Its homologue **2i** decomposed during purification (Table 2, entry 13). On the other hand, alkyl- and silyl-substituted difluoroallenes can be chromatographed at room temperature.

Decomposition with loss of fluorine was observed if the product was stored at ambient temperatures for 24 h. At 0 °C, these difluoroallenes could be stored neat for a month without noticeable decomposition. Electron-donating (*p*-OMe, *o*-Me) or -withdrawing (*p*-CF_3) aryl substitutents led to highly unstable arylallenes.[12]

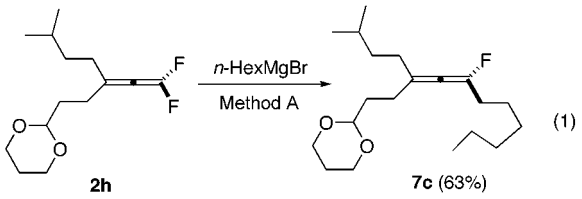
Scheme 2 illustrates a plausible mechanism for the copper-mediated S_N2' substitution reaction. The initially formed

Scheme 2. Proposed Mechanism for the Formation of Difluoroallene **2** and Monofluoroallene **7**



copper intermediate reacted at the C3-carbon of difluoropropargyl bromide **1** in an S_N2' fashion, with elimination of bromide. The interaction of a copper-centered d-orbital with σ and π^* orbitals of the substrate led to the formation of a σ-copper(III) species,[3b] which undergoes a reductive elimination to furnish the nucleophilically substituted difluoroallene **2**. If the reaction conditions are not properly controlled, a second nucleophilic attack by the cuprate complex produces monofluoroallene **7**.

Experimental evidence that supports the formation of **7** from **2** is shown in eq 1; the trisubstituted monofluoroallene



2h **7c** (63%) (1)

7c was obtained in 63% (unoptimized yield), using similar reaction conditions to those employed for the synthesis of the parent material **2h**. The ease of formation of monofluoroallene **7** could prove advantageous if one seeks to prepare a trisubstituted fluoroallene. Trisubstituted monofluoroallenes **7b**, and **7c** were significantly more stable than their difluorinated counterparts.

In summary, disubstituted *gem*-difluoroallenes have been synthesized from their difluoropropargyl bromide precursors in good to excellent yields, using a magnesium organocuprate intermediate. Aryl substitution destabilizes difluoroallenes. Difluoroallenes can react again with a magnesium organocuprate to give trisubstituted monofluoroallenes. Synthetic applications from these reactions are ongoing in our laboratory.

Acknowledgment. The authors are grateful to the National Science Foundation (CHE-0513483) for its financial support and to the University of Kentucky for use of its supercomputing facility.

Supporting Information Available: Experimental procedures and analytical or spectroscopic data for compounds **1a**−**d**, **2a**−**h**, **7b**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052816G

(12) Using method A and HexMgBr the ^{19}F NMR yields were as follows: 38% (R = *p*-MeC_6H_4); 34% (R = *p*-$MeOC_6H_4$); 37% (R = *p*-$CF_3C_6H_4$).