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An Efficient Approach for Monofluorination via Highly Regioselective Fluorohydroxylation Reaction of 3-Aryl-1,2-allenes with Selectfluor

Chao Zhou,[†] Jing Li,[†] Bo Lu,[†] Chunling Fu,*[,†] and Shengming Ma*[,†,‡]

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, People's Republic of China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

masm@mail.sioc.ac.cn

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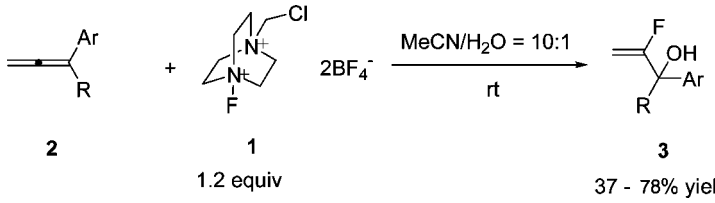
ABSTRACT



The internal C−C double bond in 3-aryl-1,2-allenes was highly regioselectively fluorohydroxylated to afford 2-fluoroalken-3-ols in 37−88% yields by using Selectfluor as the electrophilic reagent. The regioselectivity may be determined by the electronic effect, while the reactivity may be controlled by the stabilization effect of the aryl group in the allylic cationic intermediates.

Selectively fluorinated organic compounds are of current interest due to the rapidly increasing number of examples of these compounds with interesting and useful biological activity;[1] thus, development of efficient methodologies for monofluorination is of current interest. As a complement of nucleophilic fluorination reagents such as DAST,[2] a variety of electrophilic fluorination reagents[3] was developed for strategic fluorinations. The most successful one is Selectfluor[3−5] (1-chloromethyl-4-fluoro-1,4-diazonia-bicyclo[2.2.2]octanebis(tetrafluoroborate), also called F-TEDA-BF_4) **1**, which has been demonstrated to be one of the most reliable, mild, inexpensive, yet effective electrophilic fluorination reagents.[5]

Electrophilic additions of allenes have been demonstrated to be very powerful reactions in organic synthesis since two functionalities are introduced with one of the carbon−carbon

[†] Zhejiang University.
[‡] Chinese Academy of Sciences.

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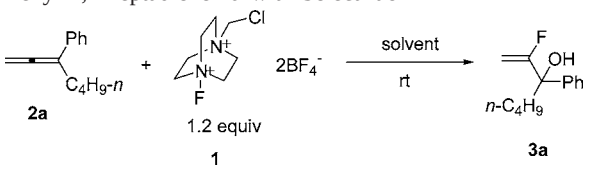
double bonds intact.[6−7] Many electrophilic reagents such as halogens,[7a−d] halogenic acids,[7e,f] and sulfenyl halides,[7g,h] may be used. Recently, we developed highly regio- and stereoselective halohydroxylations (X = Cl, Br, I) of heteroatom-substituted[8−9] and non-heteroatom-substituted allenes,[10] i.e, 1,2-allenyl sulfoxides,[8a,b] sulfones,[8c] sulfides,[9a,b] selenides,[9c] and furanones;[10] the reactions of sulfoxides and sulfones afforded *E*-products, while those of sulfides, selenides, and furanones afforded *Z*-products. However, we observed that such reactions of simple allenes are nonselective, affording a mixture of a couple of products. In this letter, we disclose our recent observations of highly regioselective fluorohydroxylation reactions of simple allenes, which provides an efficient way for monofluorinatin.[11]

The reaction of 3-phenyl-1,2-heptadiene **2a** with Selectfluor in aqueous DMF or DMA was very complicated (entries 1 and 2, Table 1); no reaction was observed in aqueous EtOH (entry 3, Table 1); however, the fluorination of **2a** in $MeNO_2/H_2O$ = 10:1 afforded 2-fluoro-3-phenyl-1-hepten-3-ol **3a** in 54% yield as the only product (entry 4, Table 1), which indicates that the reaction occurred highly regioselectively with the nonterminal relatively electron-rich C═C bond. Furthermore, the fluorinating reaction of allene **2a** with Selectfluor (1.2 equiv) in $MeCN/H_2O$ = 10:1 at room temperature for 2.0 h afforded **3a** in 62% yield (entry 5, Table 1). Reducing or increasing the amount of water led to a slight decrease in yield (entries 6−8, Table 1); the reaction in pure water afforded **3a** in only 5% yield (entry 9, Table 1); lower temperature led to a much slower reaction (entries 10−11, Table 1). Thus, the reaction conditions presented in entry 5 of Table 1 were defined as the standard conditions for further study.

Table 1. Fluorohydroxylation Reaction of 3-Phenyl-1,2-heptadiene **2a** with Selectfluor

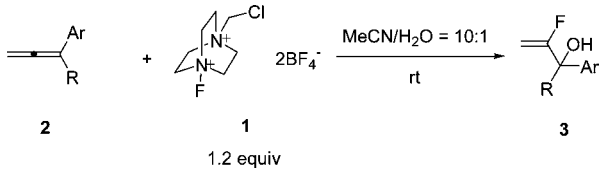


entry	solvent	reaction time (h)	NMR yield (%)
1	DMF/H_2O = 10:1	4.0	complicated
2	DMA/H_2O = 10:1	4.0	complicated
3	EtOH/H_2O = 10:1	4.0	no reaction
4	$MeNO_2/H_2O$ = 10:1	1.0	54
5	$MeCN/H_2O$ = 10:1	2.0	62
6	MeCN, 10 equiv H_2O	2.0	51
7	$MeCN/H_2O$ = 3:1	2.0	59
8	$MeCN/H_2O$ = 1:5	2.0	58
9	H_2O	22.0	5[a]
10[c]	$MeCN/H_2O$ = 10:1	12.0	64
11[d]	$MeCN/H_2O$ = 10:1	22.0	57

[a] 95% of **2a** was recovered. [b] Isolated yield. [c] Reaction was conducted at 0 °C. [d] Reaction was conducted at −40−0 °C.

The fluorohydroxylation of geminally disubstituted allenes with different types of R and Ar are conducted by applying the standard reaction conditions. The reaction of phenyl propadiene **2b** was very slow, affording the product **3b** in relatively low yield (entry 2, Table 2). The reaction of 1,1-

Table 2. Fluorohydroxylation Reaction of Aryl-Substituted Allenes with Selectfluor



	2			
entry	Ar	R	reaction time (h)	yield of **3** (%)
1	Ph	*n*-C_4H_9 (**2a**)	2.0	62 (**3a**)
2	Ph	H (**2b**)	12.0	37 (**3b**)
3	Ph	Et (**2c**)	2.0	65 (**3c**)
4	Ph	*n*-C_6H_{13} (**2d**)	2.0	57 (**3d**)
5	Ph	Ph (**2e**)	2.0	52 (**3e**)
6	*m*-MeC_6H_4	*n*-C_4H_9 (**2f**)	3.0	74 (**3f**)
7	*m*-MeC_6H_4	*n*-C_6H_{13} (**2g**)	3.0	71 (**3g**)
8	*m*-$CF_3C_6H_4$	*n*-C_4H_9 (**2h**)	20.0	40 (**3h**)
9	*p*-MeC_6H_4	*n*-C_4H_9 (**2i**)	2.0	77 (**3i**)
10	*p*-FC_6H_4	*n*-C_6H_{13} (**2j**)	3.0	78 (**3j**)
11	*o*-MeC_6H_4	*n*-C_4H_9 (**2k**)	15.0	45 (**3k**)
12[a]	*o*-MeC_6H_4	*n*-C_4H_9 (**2k**)	24.0	50 (**3k**)
13	*o*-MeC_6H_4	*n*-C_6H_{13} (**2l**)	15.0	40 (**3l**)
14[a]	*o*-MeC_6H_4	*n*-C_6H_{13} (**2l**)	24.0	45 (**3l**)

[a] 1.5 equiv of Selectfluor **1** were used.

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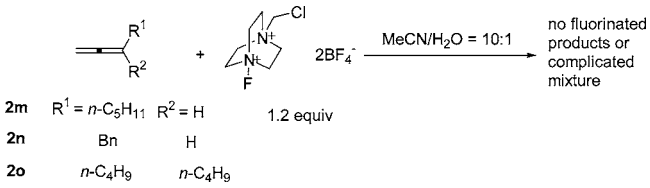
diphenyl propadiene afforded **3e** in 52% yield within 2 h (entry 5, Table 2). The substitution of the aryl group with *m*- or *p*-methyl group or fluorine atom led to a higher yield of **3** (entries 6, 7, 9, and 10, Table 2). However, when the methyl group is in the ortho position, the allenes are obviously less reactive, requiring more than 1.2 equiv of **1**, probably due to the steric effect (entries 11−14, Table 2).

Interestingly, we observed that with geminal bisalkyl-substituted allenes the reaction under the optimized reaction conditions failed to afford any fluorinated products (Scheme 1), which indicated the importance of the aryl group in this transformation.

Scheme 1. Reaction of Geminal Bisalkyl-Substituted Allenes with Selectfluor



In conclusion, we have developed a convenient method for the efficient synthesis of 2-fluoroalken-3-ols by the highly regioselective fluorohydroxylation reaction of 3-aryl substituted 1,2-allenes with Selectfluor. The observed results showed that fluorohydroxylation reaction demonstrates an aryl effect, which may be explained by its stabilization effect in the cationic allylic intermediate.[12] In addition, the aryl ring may also direct and/or activate the Selectfluor via a cation−π interaction. Due to easy availability of the starting allenes[13] and Selectfluor, as well as the potentials of the monofluorinated allylic alcohols, this reaction may be useful in organic synthesis. Further studies in this area are being conducted in our laboratory.

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Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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