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Stereoselective Synthesis of (*E*)-ArCF=CFR and (*E*)-ArCH=CFR from $ArCH(OH)CFBr_2$

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Abstract: (*E*)-*vic*-Difluoro olefin, RCF=CFBr, was synthesized by dehydrobromination of $RCFHCFBr_2$ using lithium 2,2,6,6-tetramethylpiperidide. (*E*)-Fluoro olefin, RCH=CFBr, was obtained by treatment of $RCH(OAc)CFBr_2$ with EtMgBr and $HN(i\text{-}Pr)_2$.

Fluoro olefins[1] are attracting attention in a wide area of liquid crystalline materials[2] and biologically active agents like peptide isosteres[3] and enzyme inhibitors.[4] Naturally, the physical properties and biological activities heavily depend on the configuration of fluoro olefins. However, previous synthetic efforts[5-10] have not focused on the stereoselective formation of fluorine substituted C=C bond. Herein we report highly stereoselective synthesis of (*E*)-difluoro olefins RCF=CFBr (**1**) is achieved *via* dehydrobromination of $RCHFCFBr_2$ (**4**). (*E*)-Monofluoro olefins of type RCH=CFBr (**2**) are found to be synthesized selectively by treatment of acetates $RCH(OAc)CFBr_2$ (**5**) or tosylate $RCH(OTs)CFBr_2$ (**6**) with a reagent consisting of EtMgBr and $HN(i\text{-}Pr)_2$. The remaining Br of **1** and **2** was lithiated and allowed to react with electrophile (E) to afford RCF=CFE and/or RCH=CFE, respectively, with complete retention of configuration.

We have demonstrated that $RCH(OH)CFBr_2$ (**3**) are successfully prepared by the reaction of $LiCFBr_2$ with aldehydes.[11] The substrates **4**, **5**, or **6** are easily obtained from **3** by fluorination, acetylation, or tosylation, respectively.

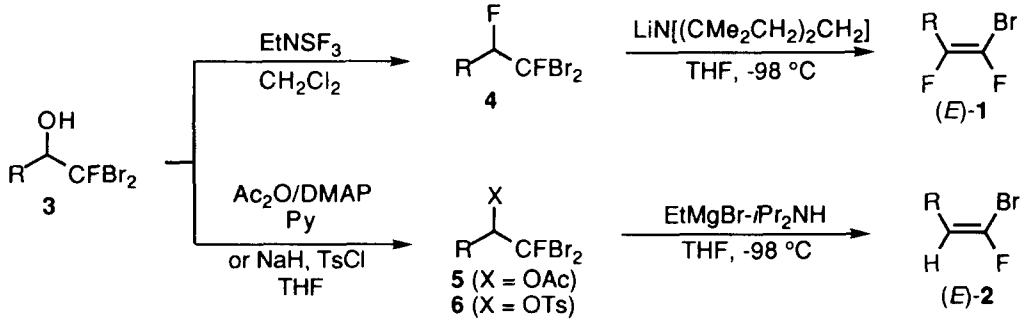


Table 1. Stereoselective Synthesis of Difluoro Olefin **1**.

Entry	R		Yield/%[a,b]	Base		Yield/%[a]	*E*/*Z*[c]
1	1-Naph	**4a**	76	LiN[$(CMe_2CH_2)_2CH_2$][d]	**1a**	82	>99 : <1
2				LiN*i*-Pr_2[d]		87	5.7 : 1
3				$KN(SiMe_3)_2$[e]		97	2.9 : 1
4				KO-*t*-Bu[f]		91	1 : 1.8
5				nBu_4NOH[g]		42[h]	1 : 6.9
6				DBU[i]		84	1 : 1.5
7				BEMP[i,k]		93	1 : 3.4
8	4-MeO-C_6H_4-	**4b**	59	LiN[$(CMe_2CH_2)_2CH_2$][d]	**1b**	79	11 : 1
9	3,4-$(MeO)_2C_6H_4$-	**4c**	49	LiN[$(CMe_2CH_2)_2CH_2$][d]	**1c**	78	10 : 1
10	4-MeC_6H_4	**4d**	57	LiN[$(CMe_2CH_2)_2CH_2$][d]	**1d**	52	10 : 1

a) Isolated Yield. b) Based on the aldehyde. c) *E*/*Z* ratio was determined by capillary gas chromatography. Stereochemistry was assigned on the basis of ^{19}F-NMR spectroscopy: J_{FF} = 7~11 Hz for *E*-isomers and 133~141 Hz for Z-isomers. d) THF, -98 °C, 10 min. e) THF/Et_2O/toluene, -130 °C, 20 min. f) THF, -78 °C, 30 min. g) CH_2Cl_2, -78 °C, 1 h. h) Starting material (40%) was recovered unchanged. i) CH_2Cl_2, -78~0 °C, 6 h. j) BEMP = $[CH_2(CH_2NMe)_2]P(NEt_2)(=NEt)$. k) CH_2Cl_2, rt, 12 h.

To a solution of $RCH(OH)CFBr_2$ **3** (R = aryl) in CH_2Cl_2 was added Et_2NSF_3 (1 equiv) at -78 °C, and the mixture was gradually warmed up to room temperature. Workup and column chromatography gave difluoroethanes **4** in yields shown in Table 1. Fluorination of **3** (R = alkyl) did not proceed even in refluxing CH_2Cl_2. When **4** was treated with lithium (2,2,6,6-tetramethyl)piperidide in THF at -98 °C for 10 min, (*E*)-2-aryl-1-bromo-1,2-difluoroethene ((*E*)-**1**) formed predominantly (Table 1, Entries 1, 8-10).[12] *E*/*Z* ratio dropped or was inverted when LiN*i*-Pr_2, $KN(TMS)_2$, or KO*t*-Bu was used (Entries 2-4). Thus the stereoselectivity depended on the character of the base. (*Z*)-**1** was obtained predominantly when *n*-Bu_4NOH was used as the base (Entry 5).

To our surprise, use of a reagent prepared from EtMgBr and *i*-Pr_2NH resulted in reduction of **4** to give monofluoroethenes **2** instead of dehydrobromination. For this transformation, acetates **5** and tosylates **6** were found to be better substrates. Acetylation of **3** was carried out with Ac_2O in pyridine and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at 60 °C for 1 h. Both **3** (R = aryl) and **3** (R = alkyl) gave the corresponding acetate **5** in good yields. Tosylation of **3** was carried out by consequent treatment with NaH and TsCl in THF at 0 °C. The results are summarized in Table 2.

The requisite reagent was prepared by addition of THF solution of EtMgBr (15 equiv) to THF solution of *i*-Pr_2NH (5 equiv) at 0 °C. After 5 min, acetate **5** was added to this mixture at -98 °C. The reaction mixture was stirred for 10 min, workup, and purification afforded 2-aryl-1-bromo-1-

fluoroethenes **2** in good yields. Examples are shown in Table 2. It is worthy to note that the substrate **5** (R = aryl) gave (*E*)-**2** predominantly (Entries 1-4). Diethylmagnesium in 1,4-dioxane also could effect the same transformation (**2b**, 93%, *E*/*Z* = 22:1), but a magnesium amide *i*-Pr_2NMgBr,[13] prepared from an equimolar amounts of EtMgBr and *i*-Pr_2NH (room temperature, 12 h) promoted dehydrobromination instead of reductive elimination. Use of less amount of EtMgBr or *i*-Pr_2NH reduced the *E*/*Z* ratio to 18~3 : 1. Zinc or magnesium metal also promoted the reductive elimination of **5a** and gave **2a** but stereoselectivity was lower: Zn: 50 °C, DMF, 80% yield, *E*/*Z* = 1.4 : 1; Mg: room temperature, THF, 42% yield, *E*/*Z* = 1 : 1.2.

On the other hand, reduction of **5g** gave (*Z*)-**2g** as the major product. The *Z*/*E* ratio was improved up to 16 : 1 (Entry 6) when the corresponding tosylate **6g** was reacted with Et_2Mg (1.5 equiv).

Table 2. Stereoselective Synthesis of Monofluoro Olefins **2**.

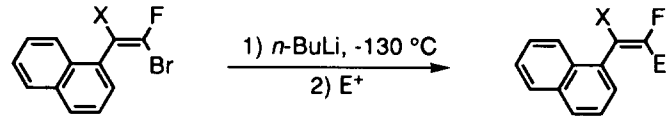
Entry	R		Yield/%[a, b]		Yield/%[a]	*E* : *Z*[c]
1	1-Naph	**5a**	85	**2a**	81	>99 : <1
2	4-MeO-C_6H_4-	**5b**	86	**2b**	84	>99 : <1
3	4-NC-C_6H_4-	**5e**	78	**2e**	89	>99 : <1
4	3,4-$(OCH_2O)C_6H_3$-	**5f**	76	**2f**	88	>99 : <1
5	$PhCH_2CH_2$-	**5g**	78	**2g**	80	1 : 2
6	$PhCH_2CH_2$-	**6g**	72	**2g**	87	1 : 16

a) Isolated Yield. b) Based on the aldehyde. c) *E*/*Z* ratio was determined by capillary gas chromatography. Stereochemistry was assigned on the basis of ^1H- and ^{19}F-NMR spectroscopy: J_{HF} = 30~32 Hz for *E*-isomers and 12~13 Hz for Z-isomers.

The remaining bromine is a key handle to elaborate extension of carbon framework. Bromine-lithium exchange of (*E*)-**1** and (*E*)-**2** by treatment with *n*-BuLi at -130 °C followed by reaction with an electrophile gave the corresponding di- or monofluoroethenes **8-11** with complete retention of stereochemistry (Scheme 3). Therefore, the configuration of RCF=CFLi and RCH=CFLi involved in the reactions of Scheme 3 are apparently stable enough in spite of their carbenoid character.

In summary, we have demonstrated that the stereoselective synthesis of mono- and difluoro olefins $R^1CX{=}CFR^2$ (X = H or F) are stereoselectively prepared starting with $CFBr_3$ and aldehyde under control of the stereochemistry of elimination. This methodology allows us to obtain a wide variety of fluoro olefins. Other type of reaction of **1** and **2**, such as cross-coupling reaction, is studying in our laboratories.

Scheme 3.



X = F,	$E^+ = CD_3OD$	E = D	**8**	97%
F,	Me_3SiCl	Me_3Si	**9**	96%
F,	PhCHO, Ac_2O	PhCH(OAc)	**10**	66%
H,	PhCHO, Ac_2O	PhCH(OAc)	**11**	39%

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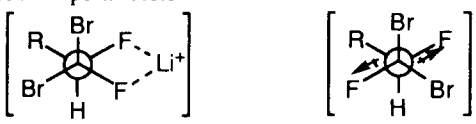
12. Dehydrobromination of **4** with $LiN[(CMe_2CH_2)_2CH_2]$ was assumed to proceed *via* the transition state (i) involving Li-F chelate. Elimination of HBr occurred with n-Bu_4NOH from the transition state (ii) wherein dipole-dipole repulsion of C-F bonds plays an important role.



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