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High Stereoselective Preparation of O-Protected 2-Trifluoromethyl 3-Bromoallylic Alcohols from 1,1-Dibromo-1-alkenes

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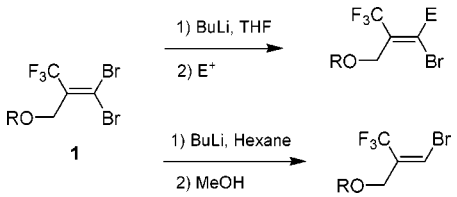
ABSTRACT



A highly stereoselective lithium−bromine exchange reaction of 2-trifluoromethyl-3,3-dibromoallylic alcohols is described. (*E*)- and (*Z*)-2-trifluoro-3-bromoallylic alcohols were obtained in THF and hexane, respectively. The lithium carbenoid intermediate was stable even at −40 °C and could be trapped by various electrophiles to afford functionalized 2-trifluoromethyl-3-bromoallylic alcohols.

Considerable attention has been given to fluorinated organic compounds due to their potential use in medicinal and agricultural chemistry.[1] Our group has put forth much effort to develop new fluorine-containing building blocks for the synthesis of such fluorinated organic compounds.[2] As a part of our research program, we wish to develop fluorinated 3-bromoallylic alcohol building blocks and investigate their use in organic synthesis. Here, we report our preliminary results on the synthesis of (*E*)- or (*Z*)-2-trifluoromethyl-3-bromoallylic alcohols and their functionalized derivatives with high stereoselectivity.

3-Bromoallylic alcohols are versatile building blocks in organic synthesis for the vinyl bromide and allylic alcohol functional groups.[3] Vinyl bromides[4] are very useful for their use as precursors to vinyl anions and as coupling partners in a wide range of transition-metal-mediated coupling reactions. Reduction of *gem*-dibromides was a practical process for the stereoselective synthesis of vinyl bromides. Several methods have been reported including the hydrogenolysis with tributyltin hydride[5] and diethyl phosphonate[6] or monometalation with lithium and zinc.[7]

The monometalation reaction of *gem*-dibromidealkenes, which possess a metal carbenoid intermediate, attracted a

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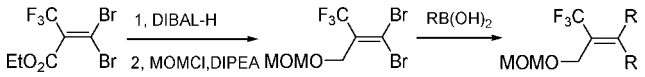
great deal of interest for its unique stereoselectivity and reactivity.[8] (*E*)-Products were obtained when trisubstituted 1,1-dibromoalkenes were treated with lithium reagents due to the steric effects or the chelation of oxygen.[7a−e] Harada et al. also studied the stereochemistry of tetrasubstituted *gem*-dibromoalkenes with lithium and zinc reagents.[7f,g] They found the order of addition affected the selectivity dramatically. To the best of our knowledge, there is no report about the bromine−lithium exchange reaction of fluorine-containing *gem*-dibromoalkenes, and the influence of fluorine on the stereochemistry of this reaction is unclear.

In a previous paper, we reported the synthesis of a protected 2-trifluoromethyl-3,3-dibromoallylic alcohol **1a** and its bis-Suzuki coupling reaction for the synthesis of fluorinated tetrasubstituted alkenes (Scheme 1).[2c] We are also

Scheme 1. Preparation of **1a** and Its Bis-Suzuki Coupling

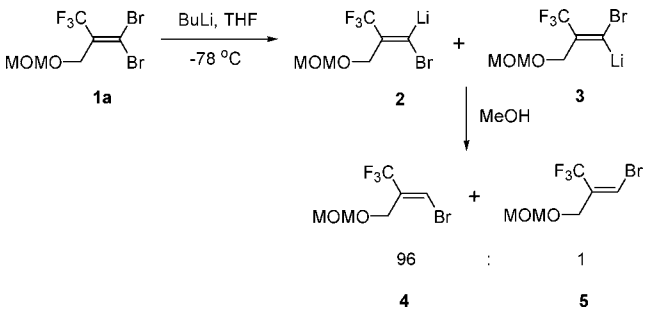


1a

interested in the monobromine−lithium exchange reaction of this *gem*-dibromidealkene **1a**. The stereoselectivity may be controlled by the chelation of fluorine or oxygen atom affording geometrically pure (*E*)- or (*Z*)-3-bromoallylic alcohol.

Slow addition of *n*-BuLi (1 equiv, 2 M in cyclohexane) to a THF solution of **1a** at −78 °C, after the mixture was quenched with methanol, gave a mixture of **4** and **5** in a ratio of 96:1 (Scheme 2). The major product was assigned to (*E*) configuration according to the coupling constants of vinyl hydrogen.[9] NOE experiments also supported our conclusion, which reflects the interaction between vinyl hydrogen and allylic hydrogen in **5**. Braun[7a,b] and Harada[7f] reported that thermodynamic products could be obtained when a lithium reagent was slowly added to *gem*-dibromoalkenes. During the slow addition, rapid exchange equilibrium was observed between the carbenoid intermediate and unreacted starting material. Under the same addition order, we thought that the product was thermodynamic

Scheme 2. Stereoselective Bromine−Lithium Exchange Reaction of **1a**



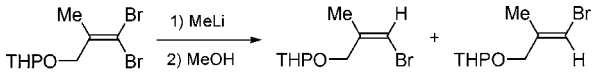
1a **2** **3** **4** **5**

controlled. The intermediate **2**, in which the lithium is cis to the CF_3, was more stable than **3**. To confirm this conclusion, 0.5 equiv of BuLi was used to achieve complete exchange equilibrium. The result (*E*/*Z* = 88:1, along with unreacted **1a**) agreed with the former experiment.

On the other hand, generation of the carbenoid, by adding dibromoalkene **1a** to 2 equiv of BuLi in THF (kinetic condition), only gave moderate selectivity (*E*/*Z* = 3:1).

These results were opposite to the nonfluorinated substrate reported by Paquette[5e] in which the bromine trans to the methyl group was exchanged (Scheme 3). Comparing two

Scheme 3



substrates showed that the selectivity was reversed completely due to substituting the methyl with CF_3 group. The stronger chelation between fluorine and lithium proposed the predominant factor to change the selectivity of this bromine−lithium exchange reaction.

There are many reports[10] about the chelation of N or O with lithium to control the selectivity, but few about F−Li interaction.[11] The introduction of fluorine affected the selectivity greatly and thus stimulated our interest to give further investigation of this reaction from temperature, solvent and additives. The addition order of these experiments was the same as the previous one to give a thermodynamic controlled product.

Temperature had a minor influence on the *E*/*Z* ratio. The treatment of **1a** with BuLi at −90 to −40 °C (entries 1−3, Table 1) in THF gave similar results. (*E*)-Product **4** was

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Table 1. Bromine−Lithium Exchange Reaction of **1a** under Thermodynamic Controlled Conditions

entry	solvent	T (°C)	yield[a] (%)	**4**/**5**[b]
1	THF	−90	40	100:0
2	THF	−78	64	96:1
3	THF	−40	45	100:0
4	Et_2O	−78	68	2:1
5	hexane	−78	58	1:5
6	hexane	−78	61[c]	2:1
7	THF	−78	65[c]	100:0

[a] Isolated yield; low yields because of the low boiling point of **4** and **5**. [b] The ratio was determined on the basis of ^{19}F NMR. [c] Addition of 2 equiv of TMEDA.

obtained predominantly. Interestingly, the intermediates **2** and **3** were very stable even at −40 °C, and no isomerization or Fritsch−Buttenberg−Wiechell (FBW) rearrangement[12] products were detected. A possible reason was deduced to the electron withdrawing nature of trifluoromethyl group that stabilized the vinyl anion. However, when the reaction was performed at 0 °C, only decomposition of **1a** was observed.

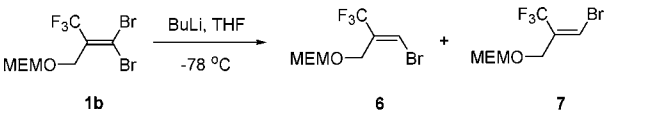
On the other hand, solvent had a great influence on the selectivity. When the reaction was conducted in Et_2O at −78 °C, the *E*/*Z* ratio was dramatically decreased to 2:1 (entry 4, Table 1). We determined that the donor ability of solvent was very important to the selectivity. We conducted the same reaction in weak donor solvent such as hexane and *Z* selectivity was observed (*E*/*Z* = 1:5, entry 5, **Table 1**).

It was reported that donor additives could chelate lithium[13] and therefore affect the structure of lithium carbenoid to change the selectivity. As we expected, when 2 equiv of TMEDA was added to the reaction mixture, the *E* selectivity was increased both in THF and hexane. The ratio (*E*/*Z*) was 1:5 to 2:1 in hexane, and it was up to 100:0 in THF (entry 6 and 7, Table 1). Therefore, we can control the selectivity of this bromine−lithium exchange reaction by the choice of solvents and additives.

The isolated yields of **4** or **5** were relatively low (40−65%) due to the low boiling point of products. The problem could be resolved by changing the protective group to MEM. The yields were increased to 84% (in THF, *E*/*Z* = 63:1) and 83% (in hexane, *E*/*Z* = 1:3), respectively. The selectivity of **1b** was similar to **1a** (Scheme 4).

This bromine−lithium exchange reaction provided a functionalized vinyl anion, which could be trapped by various electrophiles. However, little is known about the use of 1-halo-1-lithioethenes (halo = Cl,[14] Br,[15] I[16]) as synthetic intermediates, presumably due to concerns over the rearrangement or decomposition of such lithium carbenoids. Our intermediates **2** and **3** were stable even in −40 °C,

Scheme 4. Stereoselective Bromine−Lithium Exchange Reaction of **1b**

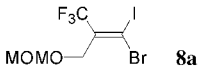
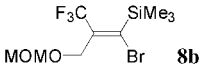
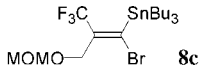
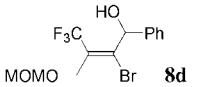
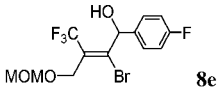
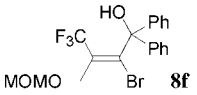
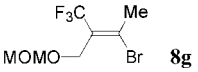


1b **6** **7**

THF	63	:	1	84%
Hexane	1	:	3	83%

providing the possibility of reaction to various electrophiles. Therefore, intermediate **2** was trapped by a variety of electrophiles with retention of configuration giving **8a**−**g** in moderate to excellent yields (Table 2).

Table 2. Reaction of Lithium Carbenoid **2** with Electrophiles

entry	electrophile	product	yield (%)[a]
1	I_2	 **8a**	95
2	TMSCl	 **8b**	91
3	Bu_3SnCl	 **8c**	87
4	PhCHO	 **8d**	93
5	*p*-F-C_6H_4CHO	 **8e**	75
6	Ph(CO)Ph	 **8f**	63
7	MeI	 **8g**	68

[a] Isolated yield based on **1a**.

Reaction of lithium carbenoid **2** with iodine afforded stereospecific iodobromoalkenes **8a** in 95% yield (entry 1). Similarly, reaction with trimethylsilyl chloride (TMSCl) and tributyltin chloride gave 3-vinylsilyl (**8b**) and vinyltin (**8c**) functionalized derivatives in 91% and 87% yields, respectively (entries 2 and 3). On the other hand, quenching **2** with benzaldehyde afforded 2-bromoallyl alcohol **8d** in 93% yield (entry 4). The introduction of the fluorine at 4-position of phenyl provided us with further evidence for the stereo-

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selectivity, since we established the structure of **8e** by X-ray diffraction studies (Figure 1).[17]

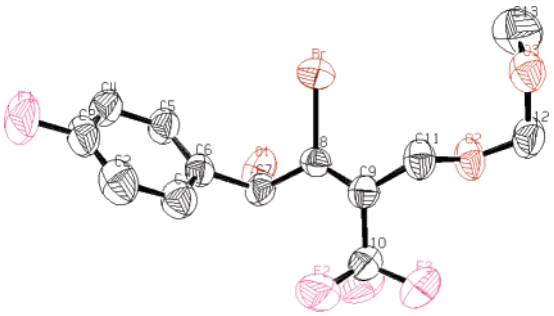

Figure 1. ORTEP drawing of **8e** with all H atoms omitted for clarity.

Figure 1 illustrated that the bromine is trans to CF_3 in **8e**; i.e., the bromine cis to CF_3 was exchanged and reacted with electrophiles. 2-Bromoallyl alcohols are versatile building blocks in synthetic chemistry.[18] Our method provided an approach to synthesize such fluorine-containing polysubstituted 2-bromoallyl alcohols with high stereoselectivity. Reaction with steric benzyl phenone also gave 2-bromoallyl alcohols **8f** in 63% yield (entry 6). Alkylated product **8g** could also be obtained by using methyl iodide as electrophile in 68% yield (entry 7). Otherwise, reaction of **2** with DMF affords 2-bromo-α,*β*-unsaturated aldehyde **8h** in 33% yield (entry 8). The low yield of **8h** was reasoned by its low boiling point. Unfortunately, **2** could not react with phenyl nitrile and decomposed after being warmed to room temperature.

In summary, we have developed a facile method to stereoselectively prepare O-protected 2-trifluoromethyl-3-bromoallylic alcohols and their functionalized derivatives. Their applications in organic synthesis are under investigation. More detailed results will be reported soon.

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Supporting Information Available: Analytical data for all new compounds as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Crystallographic data for X-ray structure have been deposited with the Cambridge Crystallographic Centre as CCDC 242759. Copies of the data can be obtained free of charge via from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk.

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