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Diastereoselective Generation of Lithium Carbenoid Reagent RCH(OMEM)CFBrLi and Its Reaction with Electrophiles

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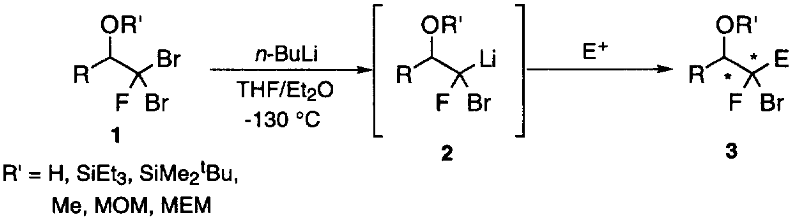
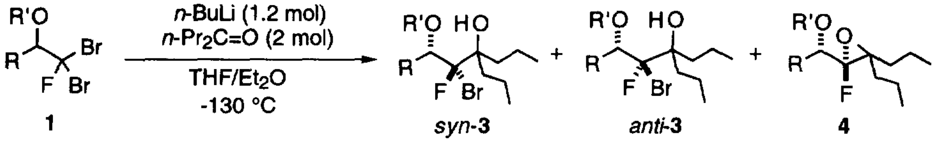
Abstract: Treatment of RCH(OMEM)CFBr$_2$ with *n*-BuLi at -130 °C in the presence of 4-heptanone gives the corresponding adduct diastereoselectively. The stereochemical outcome is explained in terms of the chelation between lithium and oxygen atoms of the MEM group. Starting with 2-phenylpropanal, a product is produced highly selectively containing three contiguous stereocenters including a -CFBr- moiety.

Much attention has been recently focused on the development of synthetic methods for organofluorine compounds because these frequently show unique biological and physical properties.[1] In particular, synthetic reactions using fluoroorganometallic reagents[2] derived from readily available fluorohalohydrocarbons are versatile to construct fluorinated target molecules. Thus, we have recently shown that dibromofluoromethyllithium can be generated from tribromofluoromethane by treatment with butyllithium at -130 °C and reacted with a variety of aldehydes and ketones smoothly to give fluorinated alcohols **1** (R' = H) in good yields.[3] We envisaged if a lithium-bromine exchange of **1** and subsequent reaction with an electrophile took place stereoselectively, **1** would be a new, versatile building block for monofluoro compounds.[4] Herein we describe diastereoselective generation of the lithium carbenoid **2** from **1** and its reaction with electrophiles as summarized in Scheme 1.[5] This methodology allowed us to selectively construct three contiguous stereocenters including a -CFBr- moiety.



Scheme 1

To a solution of RCH(OR')CFBr$_2$ (**1**) and 4-heptanone in THF–Et$_2$O (2 : 1) was added butyllithium at -130 °C. The resulting mixture was stirred for 1 h at -130 °C and allowed to warm up to -78 °C before quenching with sat. aq. NH$_4$Cl solution. Workup and purification by silica gel column chromatography gave the corresponding alcohol **3** as a mixture of diastereomers.[6] The results are shown in Scheme 2.

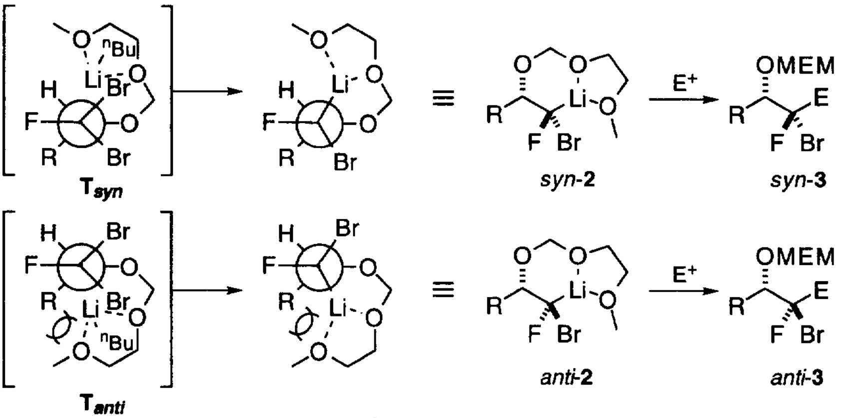


	R'	R	Yield (%)	Product ratio				
				syn-**3**	:	*anti*-**3**	:	**4**
a	$SiEt_3$	1–naphthyl-	38	57	:	25	:	18
b	$SiMe_2$*t*-Bu	1–naphthyl-	47	67	:	0	:	33
c	Me	1–naphthyl-	49	60	:	40	:	0
d	MOM	1–naphthyl-	55	85	:	15	:	0
e	MEM	1–naphthyl-	55	83	:	17	:	0
f	MEM	Ph-	58	50	:	50	:	0
g	MEM	$Ph(CH_2)_2$-	62	62	:	38	:	0
h	MEM	*c*-Hex-	51	92	:	8	:	0
i	MEM	*i*-Pr-	46	92	:	8	:	0

Scheme 2

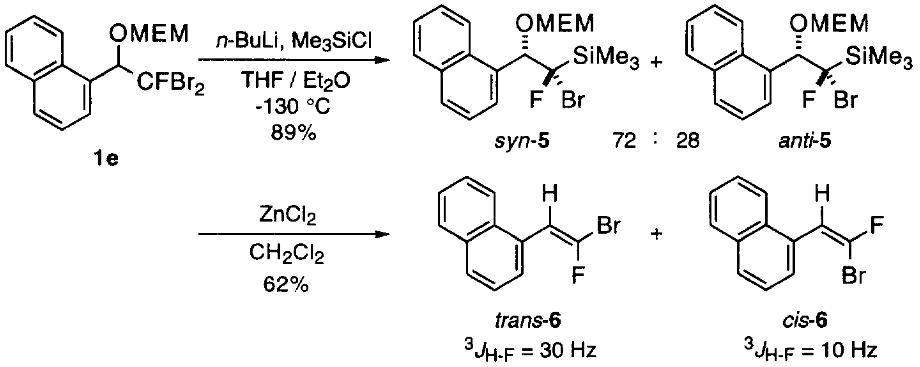
Silyl and methyl ethers **1a**~**1c** were allowed to react with 4-heptanone to give **3a**~**3c** with 57~67% *syn*-selectivity. It is particularly noted that silyl ethers **1a** and **1b** afforded oxiranes **4a** and **4b**, respectively, which apparently were produced from *anti*-**3a** and **3b**, respectively, via intramolecular cyclization. On the other hand, methoxymethyl (MOM) ether **1d** and methoxyethoxymethyl (MEM) ether **1e**, having one or two ethereal oxygen(s) afforded *syn*-**3d** and **3e**, respectively, with relatively high diastereoselectivity. These results show that the protecting group plays an important role in the diastereoselective generation of the lithium carbenoid **2**.[7] The diastereoselectivity is also affected by the substituent R. Substrate **1** (R = Ph or CH_2CH_2Ph) exhibited moderate selectivities, whereas high *syn*–selectivities were observed with **1** (R = *c*-Hex or *i*-Pr). Thus, the bulkier the substituent R, the higher *syn*–diastereoselectivity resulted. The yields were generally moderate, probably because the fluorine–containing carbenoid **2** was thermally unstable even at -130 °C and also underwent proton abstraction from 4-heptanone.

The stereochemical outcome is tentatively attributed to the chelation effect as illustrated in Scheme 3. We assume that the conformations in which the carbon–fluorine bond and carbon–oxygen bond are oriented *anti* are favorable due to the dipole–dipole repulsion.[8] Thus, two transition states (T_{syn} and T_{anti}) are possible.[9] While T_{anti} involves the steric interaction between the substituent R and lithium chelating with the MEM group, such interaction is absent in T_{syn}. Accordingly, exchange of *pro*-(*R*)-bromine-lithium with retention of configuration proceeds preferentially via T_{syn}, and the resulting carbenoid *syn*-**2** undergoes carbonyl addition with retention to give rise to *syn*–**3**. Based on the transition state model T_{syn}, it can reasonably be explained that the sense of diastereoselectivity should be *syn* and the degree of the selectivity should depend on the size of substituent R.



Scheme 3

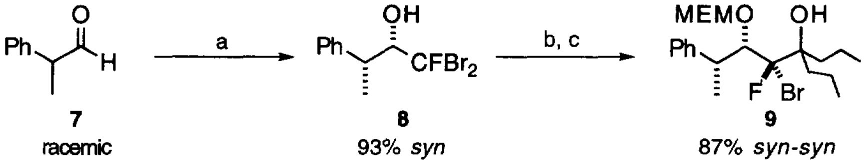
Silylation of **1e** with chlorotrimethylsilane also occurred stereoselectively to give *syn*-**5** as the major diastereomer in good yield (Scheme 4). The stereochemistry of **5** was assigned by conversion of **5** into **6** with zinc chloride via deprotection of the MEM group followed by the Peterson elimination in one pot and by the ^{1}H NMR analysis of $^3J_{\text{H-F}}$ of **6**.



Scheme 4

Finally, we explored the stereocontrol of the three contiguous chiral centers starting with (±)-2-phenylpropanal (**7**) as the starting substrate (Scheme 5). Thus, treatment of $CFBr_3$ with butyllithium at -130 °C in the presence of **7** gave **8** with 93% *syn*-selectivity.[10] The alcohol **8** was protected with the MEM group and treated with butyllithium in the presence of 4-heptanone to give **9**, whose Me, MEMO, and Br substitutents were found to be arranged *syn–syn* with 87% stereoselectivity.

In summary, we have demonstrated that diastereoselective bromine-lithium exchange of $RCH(OR')CFBr_2$ is realized by use of the MEM protecting group for R' and bulky substituent for R. The present method through a fluorine-substituted lithium carbenoid and its reaction with electrophiles constitutes a highly efficient route to stereo-defined organofluorine compounds.



a) $CFBr_3$, *n*-BuLi, THF/Et_2O, -130 °C (69%) b) MEMCl, $(i\text{-}Pr)_2NEt$, $(CH_2Cl)_2$, 60 °C (60%) c) *n*-Pr_2CO, *n*-BuLi, THF/Et_2O, -130 °C (35%)

Scheme 5

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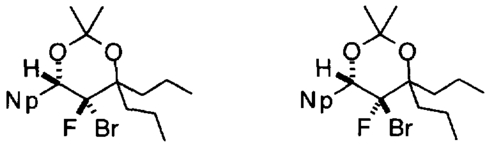
4. Review: Takeuchi, Y. *Yuki Gosei Kagaku Kyokai Shi* **1988**, *46*, 145-159.
5. Hoffmann *et al.* studied the diastereoselective bromine-lithium exchange of 3-alkoxy-1,1-dibromoalkanes extensively, but 1,1-dibromo-3-methyl-2-(trimethylsilyloxy)butane was tested only for diastereoselective generation of β-alkoxy-α-bromoalkyllithium. (a) Hoffmann, R. W.; Stiasny, H. C.; Kruger J. *Tetrahedron* **1996**, *52*, 7421-7434. (b) Hoffmann, R. W.; Julius, M. *Liebigs Ann. Chem.* **1991**, 811-822 and references cited therein.
6. The diastereomeric ratio was determined by ^{19}F NMR. The stereochemistry of **3e** was assigned on the basis of $^3J_{H\text{-}F}$ of the acetonides prepared through deprotection followed by acetalization.



$^3J_{F\text{-}H}$ = 0 Hz
major

$^3J_{F\text{-}H}$ = 24 Hz
minor

7. When OR' was OAc or F, only β-elimination reaction occurred, giving rise to 1-bromo-1-fluoro-2-(1-naphthyl)ethene in good yields (*E* : *Z* = 2 : 1).
8. Ishihara, T.; Ichihara, K.; Yamanaka, H. *Tetrahedron Lett.* **1995**, *36*, 8267-8270.
9. Conformations involving the interaction between lithium and fluorine also may be possible, but this model does not explain the size effect of the substituent. For the interaction between lithium and fluorine, see Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Org. Chem.* **1995**, *60*, 8140-8141 and references cited therein.
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