

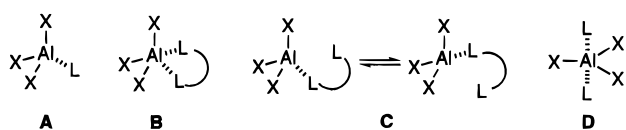
Fluorine-Assisted Selective Alkylation to Fluorinated Epoxides and Carbonyl Compounds: Implication of Pentacoordinate Trialkylaluminum Complexes

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Organoaluminum compounds have found numerous applications in organic synthesis.¹ Many of the reaction characteristics of organoaluminums associated with the availability of the empty p orbital of aluminum which makes these compounds electrophilic or Lewis acidic. Accordingly, organoaluminums (AlX₃) react readily with a variety of neutral or negatively charged Lewis bases (L) to form the corresponding tetra-coordinate complexes of type **A**. Although pentacoordination of



type **B** (X = Et; L = phosphine) in 1:1 Et₃Al/diphosphine complexes has been previously claimed with Ph₂PPPPh₂, MeN-(PPh₂)₂, and EtN(PPh₂)₂,² recent evidence obtained on the Me₃Al/Ph₂PCH₂PPh₂ complex only points to a highly fluxional molecule in solution with tetra-coordinate aluminum species of type **C** even at -80 °C.³ Recently, several restricted examples on neutral pentacoordinate, trigonal bipyramidal aluminum complexes of type **D** (X = halogen, hydrogen, alkyl; L = nitrogen or phosphine), where ligands L occupy two axial positions, have been isolated and characterized.⁴ However, little is known about the existence of another pentacoordinate organoaluminum complex **B**,⁵ and its nature still remains elusive despite its potential importance in the mechanistic as well as synthetic points of view. In this context, we have been interested for some time in the possibility of forming a previously uncertain pentacoordinate organoaluminum complex **B** and its synthetic application to, for example, chelation-controlled reactions. Among various metals to be chelated, aluminum has exceedingly high affinity toward fluorine as evident from the bond strengths in several diatomic molecules of metal-fluorine.^{6,7} The combination of this characteristic property with the well-known high oxygenophilicity of aluminum suggests that fluorine-assisted selective transformation of oxygen-containing organofluorine substrates seems to be quite suitable for our purpose. Here, we report such a selective alkylation with fluoro epoxides and fluoro carbonyl compounds as model substrates of our case study, which represents the

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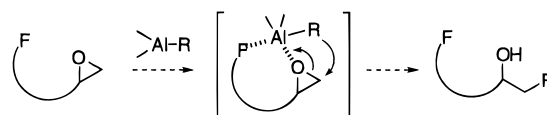
(2) Clemens, D. F.; Sisler, H. H.; Brey, W. S., Jr. *Inorg. Chem.* **1966**, *5*, 527.

(3) Schmidbaur, H.; Lauteschlager, S.; Muller, G. J. *Organomet. Chem.* **1985**, *281*, 25. For this argument, see: ref 4e.

(4) (a) Heitsch, C. W.; Nordman, C. E.; Parry, P. W. *Inorg. Chem.* **1963**, *2*, 508. (b) Palenick, G. *Acta Crystallogr.* **1964**, *17*, 1573. (c) Beattie, I. R.; Ozin, G. A. *J. Chem. Soc. A* **1968**, 2373. (d) Bennett, F. R.; Elms, F. M.; Gardiner, M. G.; Koutsantonis, G. A.; Raston, C. L.; Roberts, N. K. *Organometallics* **1992**, *11*, 1457. (e) Muller, G.; Lachmann, J.; Rufinska, A. *Ibid.* **1992**, *11*, 2970. (f) Fryzuk, M. D.; Giesbrecht, G. R.; Olovsson, G.; Rettig, S. J. *Ibid.* **1996**, *15*, 4832.

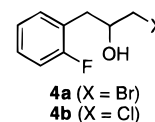
(5) For an intramolecular version of inorganic aluminum complex **B**, see: Rutherford, D.; Atwood, D. A. *Organometallics* **1996**, *15*, 4417.

Scheme 1



first experimental evidence of the intervention of pentacoordinate trialkylaluminum complexes **B** as plausible intermediates (Scheme 1).

Alkylation of terminal or 1,2-disubstituted epoxides normally provides a regioisomeric mixture of corresponding ring opening alcohols. For instance, treatment of 3-phenyl-1,2-epoxypropane (**1**, X = H) with Me₂AlC≡CPh (1.5 equiv) in toluene at -78 to -20 °C gave rise to a mixture of 1,5-diphenyl-4-pentyn-2-ol (**2**, X = H, R = Ph) and 2-benzyl-4-phenyl-3-butyn-1-ol (**3**, X = H, R = Ph) (64% combined yield) in a ratio of 1.1:1 (entry 2 in Table 1). In marked contrast, however, reaction of its fluoro analogue, 3-(2-fluorophenyl)-1,2-epoxypropane (**1**, X = F) with Me₂AlC≡CPh under similar reaction conditions afforded 1-(2-fluorophenyl)-5-phenyl-4-pentyn-2-ol (**2**, X = F, R = Ph) as a sole isolable product in 61% yield (entry 1 in Table 1).⁸ The metal effect on the regioselectivity for the present alkylation was also examined. Attempted reaction of fluoro epoxide **1** (X = F) with PhC≡CMgBr or PhC≡CTiCl(OPrⁱ)₂ furnished halohydrine **4a** or **4b**, respectively, as a sole isolable product.⁹ Use of PhC≡CLi for the substrate **1** (X = F) gave less



satisfactory results.¹⁰ These and other selected examples are included in Table 1, which clearly demonstrates the efficiency of the nucleophilic ring opening of fluoro epoxides with organoaluminum alkynides via the chelation between fluorine and aluminum, thereby permitting the otherwise difficult regioselective functionalization. A terminal epoxide with a fluorine atom on the aliphatic carbon chain underwent smooth alkylation with excellent selectivity in spite of its conformational flexibility (entry 5). For 1,2-*trans*-disubstituted epoxides, a high level of regioselectivity was observed as well (entries 7 and 9). Even a δ -fluoro epoxide showed moderate selectivity (entry 11 vs 12).

Although the hypothetical participation of neighboring fluorine atom in organoaluminum complexes with fluoro epoxides, *i.e.*, the existence of pentacoordinate trialkylaluminum complexes of type **B**, is strongly implicated by the above alkylation experiments, more direct and physical evidence was obtained by carrying out low-temperature ¹³C and ²⁷Al

(6) For example, the bond strengths in several diatomic molecules of metal-fluorine follow: Al-F, 663.6 ± 6.3 kJ/mol; Li-F, 577 ± 21 kJ/mol; Ti-F, 569 ± 34 kJ/mol; Si-F, 552.7 ± 2.1 kJ/mol; Sn-F, 466.5 ± 13 kJ/mol; Mg-F, 461.9 ± 5.0 kJ/mol. See: Weast, R. C. *Handbook of Chemistry and Physics*, 65th ed.; CRC Press: New York, 1984–1985.

(7) For the synthetic utility of forming the strong Al-F bonds, see: (a) Posner, G. H.; Ellis, J. W.; Ponton, J. J. *Fluorine Chem.* **1981**, *19*, 191. (b) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 1823.

(8) Use of exactly 1 equiv of Me₂AlC≡CPh under similar reaction conditions gave desired regioisomer **2** with excellent selectivity (>99: <1), but the yield of **2** was a little bit lower (56%) compared to that with 1.5 equiv of Me₂AlC≡CPh.

(9) For preparation of the alkynyltitanium reagent, PhC≡CTiCl(OPrⁱ)₂ from PhC≡CLi and Cl₂Ti(OPrⁱ)₂, see: Tabusa, F.; Yamamoto, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405.

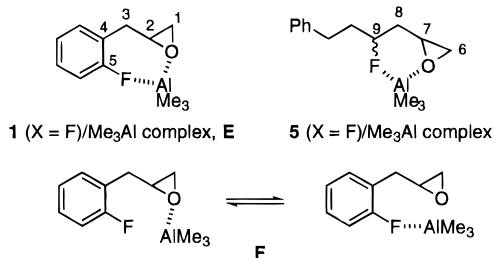
(10) The ring opening reaction of epoxide **1** (X = H or F) was carried out with 1.5 equiv of PhC≡CLi in toluene at 25 °C for 42 h giving the secondary alcohol **2** (X = H or F; R = Ph) exclusively in only 8–9% yield. Attempted reaction of *trans*-1,2-disubstituted epoxide under similar reaction conditions resulted in the almost total recovery of the starting epoxide (*cf.* entry 7 in Table 1).

Table 1. Regioselective Alkylation of Fluoro Epoxides with Organoaluminum Alkynides^a

entry	epoxide	reagent Me ₂ AlC≡C-R	conditions (°C, h)	products % yield ^b (ratio) ^{c,d}
1			-78, 0.1 -20, 5.5	
2	X = F, R = Ph			61 (>99 : <1)
3	X = H			64 (1.1 : 1)
4	X = F, R = SiMe ₃			69 (>99 : <1)
5	X = H			70 (1.8 : 1)
5			-78, 0.1 -78-0, 2 0, 3.5	
6	X = F, R = Ph			64 (>99 : <1)
7	X = H			73 (1 : 1)
7			-20, 3.5 0, 3.5 rt, 2	
8	X = F, R = Ph ^e			74 (>99 : <1) ^g
9	X = H ^f			78 (6.3 : 1) ^h
9			-78, 0.1 -20, 5.5	
10	X = F, R = Ph			70 (>99 : <1) ⁱ
11	X = H			42 (1 : 1.2)
11			-78, 1.5 -40, 2 -20, 2 0, 3	
12	X = F, R = Ph			64 (3.8 : 1)
13	X = H			65 (2 : 1)

^a Unless otherwise specified, the reaction was carried out in toluene with 1.5 equiv of reagent under the given reaction condition. ^b Isolated yield. ^c Determined by capillary GLC, HPLC, and/or 300-MHz ¹H NMR analysis. ^d The regio- and stereochemical assignment of alkylation products were made by independent syntheses, i.e., the carbonyl alkylation of aldehydes with propargylic Grignard reagents (Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225). ^e Ratio of *trans/cis* = 2.7:1. ^f Ratio of *trans/cis* = 8.3:1. ^g *Syn/anti* ratio of the major regioisomer = 4.3:1. ^h *Syn/anti* ratios of each regioisomer are 41:1 and 1:4.6, respectively. ⁱ Two equivalents of aluminum alkynide was used.

NMR studies of these aluminum complexes. The original signals of epoxide carbons C-1 and C-2 in **1** (X = F) occurred at δ 46.27 and 50.83, respectively, and the signal of the fluorine bearing aromatic carbon C-5 appeared at δ 161.09 (d, *J* = 245 Hz). When **1** (X = F) was complexed with Me₃Al in a 1:1.1

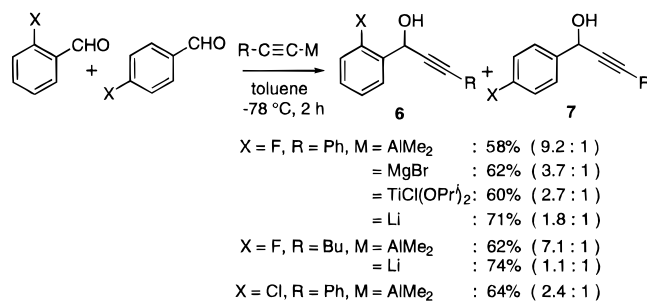


molar ratio in CD₂Cl₂ at -78 °C, the significant downfield shift of epoxide carbons C-1 and C-2 in structure **E** was observed at δ 53.60 and 59.67, respectively, with concomitant upfield shift of C-F carbon C-5 at δ 160.08 (d, *J* = 246 Hz) by ¹³C NMR analysis at -78 °C; this supported the expected chelate formation of aluminum with fluoro epoxide **1** (X = F). It should be added that the upfield shift of fluorine bearing carbon was also observed in the ¹³C NMR measurement of fluorobenzene with Me₃Al (1.1 equiv) in CD₂Cl₂ at -78 °C, where the original peak of the C-F carbon at δ 162.77 (d, *J* = 245 Hz) shifted to δ 161.61 (d, *J* = 245 Hz).¹¹ Similarly, epoxide **5** (X = F)/Me₃Al chelate complex in CD₂Cl₂ at -78 °C showed that the original signals of free, diastereomeric epoxide carbons C-6 and

(11) The similar upfield effect is observed in several metal complexes of fluorinated macrocycles: Plenio, H.; Diodone, R. *J. Am. Chem. Soc.* **1996**, *118*, 356.

C-7 at δ 45.27/46.52 and 47.93 (d, *J* = 4 Hz)/48.01 (d, *J* = 4 Hz), respectively, shifted downfield to δ 52.85/54.10 and 57.87 (d, *J* = 3.6 Hz)/58.07 (d, *J* = 3.6 Hz), respectively, and the uncomplexed, diastereomeric C-F carbon C-9 at δ 90.40 (d, *J* = 167 Hz) and 90.66 (d, *J* = 167 Hz) shifted upfield to δ 88.95 (d, *J* = 169 Hz) and 89.07 (d, *J* = 169 Hz), respectively. Since these ¹³C NMR data may not rigorously rule out the possibility of the involvement of a fluxional complex **F**, we further carried out the low-temperature ²⁷Al NMR analysis of several trialkyl-aluminum complexes.¹² The original signal of Me₃Al appeared at δ 153 in CD₂Cl₂ at -50 °C. Addition of fluorobenzene to Me₃Al in CD₂Cl₂ showed the Al signal at δ 152, while the coordination of epoxide **1** (X = H) to Me₃Al caused significant downfield shift to δ 195. However, when Me₃Al was complexed with fluoro epoxide **1** (X = F), the upfield shift of the Al signal in the complex **E** relative to the non-fluoro epoxide **1** (X = H)/Me₃Al complex was observed at δ 182. Moreover, the Al signal of the epoxide **5** (X = H)/Me₃Al complex at δ 167 significantly shifted upfield to δ 146 in the spectrum of fluoro epoxide **5** (X = F)/Me₃Al complex probably due to the formation of a six-membered chelate as well as the participation of more basic alkyl fluoride compared to the case of epoxide **1** (X = F). The data presented herein, together with alkylation experiments, argue against the possibility of fluxional organoaluminum complexes with fluoro epoxides by a rapid metal site exchange as shown in **F**.

Our concept is also applicable to the selective alkylation of carbonyl compounds with organoaluminum reagents. Indeed, treatment of an equimolar mixture of 2-fluorobenzaldehyde and 4-fluorobenzaldehyde in toluene at -78 °C with Me₂AlC≡CPh (1 equiv) resulted in formation of two different propargyl alcohols **6** and **7** (X = F, R = Ph; 58% combined yield) in a ratio of 9.2:1. The selectivity is lowered by switching the metals



of PhC≡C-M from Al to Mg (3.7:1), Ti (2.7:1),^{9,13} and Li (1.8:1). The similar tendency is also observed with BuC≡C-M (M = AlMe₂ or Li). The high affinity of aluminum to fluorine compared to other halogens is evident from the discrimination experiment between chloro analogues with Me₂AlC≡CPh, which shows only moderate selectivity (2.4:1).

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Supporting Information Available: Representative experimental procedures as well as spectroscopic characterization of all new compounds including some analytical data (6 pages). See any current masthead page for ordering and Internet access instructions.

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(12) Benn, R.; Rufinska, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 861. The ²⁷Al NMR chemical shifts are highly dependent on the ligands and structural types of organoaluminum compounds and on the coordination number of the Al atom. However, as the general tendency, the higher coordination number of the Al atom in organoaluminum compounds always causes the more upfield shift. See also: van Vliet, M. R. P.; Buysingh, P.; van Koten, G.; Vrieze, K.; Kojic-Prodic, B.; Spek, A. L. *Organometallics* **1985**, *4*, 1701. See: refs 4e,f and 5.

(13) Reaction of an equimolar mixture of 2-fluoro- and 4-fluorobenzaldehyde with (PhC≡C)₂Ti(OPrⁱ)₂ in toluene at -78 °C gave **6** and **7** in a ratio of 1.7:1.