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Mechanism and Synthetic Utility of Boron Trifluoride Etherate Promoted Organolithium Additions

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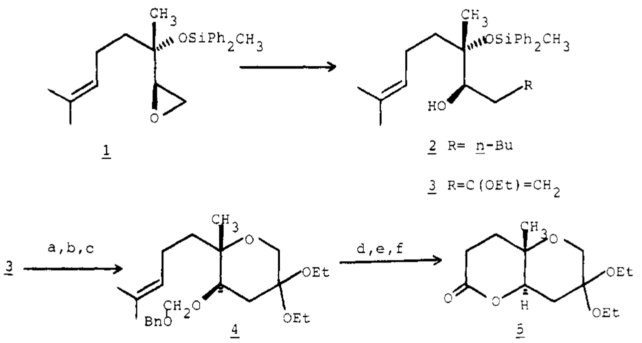
Much methodology in organic synthesis relies on the nucleophilic addition and substitution reactions of transition and main-group organometallics. In 1977, Yamamoto and Maruyama observed that boron trifluoride etherate ($BF_3{\cdot}Et_2O$) promoted allylic coupling and conjugate addition of organocopper compounds.[1,2] Others have recently reported that $BF_3{\cdot}Et_2O$ facilitated the addition of moderately basic main-group nucleophiles like alkynyllithiums, Grignard reagents, and enolates to a variety of electrophiles.[3-6] However, the mechanisms of these processes remain unclear. The role of the Lewis acid is complicated by the fact that boron halides (BX_3) undergo rapid displacement with organolithiums and magnesiums to furnish alkylhaloboranes and trisubstituted boranes (R_3B) regardless of stoichiometry.[7-9] Disproportionation and redistribution reactions of R_3B with BX_3 can subsequently intervene.[7] We now report that $BF_3{\cdot}Et_2O$ promotes the nucleophilic addition of *strongly basic alkyl, alkenyl, and aryllithiums* to organic substrates in synthetically useful ways. Evidence indicates that organolithiums and $BF_3{\cdot}Et_2O$ are reasonably stable together at low temperature and react independently as potent nucleophile and strong Lewis acid, respectively.

(2*R*,3*S*)-Linalool oxide silyl ether **1**,[10,11] reacted with 2 equiv of *n*-butyllithium or (α-ethoxyvinyl)lithium and $BF_3{\cdot}Et_2O$ (2 equiv, THF, -78 °C, 3 min) to afford **2** (95%) and **3** (85%), respectively. The organolithiums alone desilylated **1**, whereas cuprates gave **2** and **3** in low yield. No polymerization or enol ether decomposition was observed in these reactions. Adduct **3** has been converted to optically pure lactone **5**, an intermediate in the synthesis of polyether ionophores of the brevetoxin family (Scheme I).[12]

Minor amounts of 1-octanol were also produced with **2**, indicating the dramatic influence of the Lewis acid.[13] Oxetane reacted instantly and quantitatively at -78 °C with either *n*-butyllithium- or phenyllithium-$BF_3{\cdot}Et_2O$ to furnish 1-heptanol or 3-phenyl-1-propanol, respectively. No cyclic ether alkylations occurred in the absence of $BF_3{\cdot}Et_2O$. Table I lists a variety of other successful test cases.

Substituted fluoroboranes were logical reactive intermediates,[8,9] however, neither *n*-$BuBF_2$ nor *n*-Bu_2BF[8,14] converted THF to 1-octanol or epoxide **1** to **2**, even in the presence of added LiF or $BF_3{\cdot}Et_2O$.[15] THF solutions of *n*-BuLi and $BF_3{\cdot}Et_2O$ containing 1,10-phenanthroline as an indicator remained muddy-brown for 30-60 min at -78 °C but faded as the solution warmed. Only indicator-active solutions were capable of transforming **1** into **2**.

Scheme I[a]



1

2 R= n-Bu

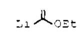
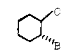
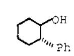
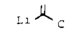
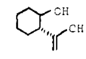
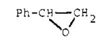
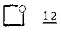
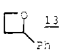
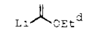
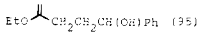
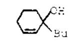
3 R=C(OEt)=CH2

4

5

[a] (a) $BnOCH_2Cl$, 80%; (b) NBS, EtOH, 80%; (c) Bu_4NF, KH, THF, 90%; (d) O_3, Jones oxidation; (e) H_2-Pd/C; (f) DCC, CH_2Cl_2, 55% from **4**.

Table I. Alkylations Using RLi-$BF_3{\cdot}Et_2O$

electrophile	RLi (3 equiv)[a]	product (% yield)[b,c]
1	n-BuLi	2 (95)
1	 $Li\text{-}C(=CH_2)OEt$	3 (85)
1	PhLi	3 (R=Ph; 99)
 10	n-BuLi	 (97)
10	PhLi	 (96)
10	 $Li\text{-}C(=CH_2)CH_3$	 (95)
 Ph-CH—CH2 (O) 11	n-BuLi	$PhCH(OH)C_5H_{11}$ (64) $C_4H_9CH(Ph)CH_2OH$ (36)
11	PhLi	$PhCH(OH)CH_2Ph$ (84)
 12	n-BuLi	n-$C_7H_{15}OH$ (85)[e]
12	PhLi	$Ph(CH_2)_3OH$ (96)
12	$C_8H_{17}OLi$[d]	$C_8H_{17}O(CH_2)_3OH$ (53)
 13	n-BuLi	$C_6H_{13}CH(OH)Ph$ (96)
13	PhLi	$PhCH(OH)CH_2CH_2Ph$ (98)
13	 $Li\text{-}C(=CH_2)OEt$[d]	 $EtOC(=CH_2)CH_2CH_2CH(OH)Ph$ (95)
tetramethylethylene oxide	n-BuLi	no addition products
2-cyclohexenone	n-BuLi	 (95)

[a] Unless otherwise specified, organolithium solutions were added to $BF_3{\cdot}OEt_2$ in THF at -78 °C followed immediately by the electrophile. Reactions were terminated after 5-10 min. [b] Yields are reported for pure products, which, when necessary, were obtained by flash column chromatography. [c] Satisfactory NMR, IR, and mass spectral data were obtained for all products. In some cases, known compounds were identified by comparison with authentic samples. [d] In these experiments, $BF_3{\cdot}OEt_2$ was added to a mixture of organolithium and electrophile at -78 °C. Reactions were terminated after 5-10 min. [e] Actual yield is higher, but some product was lost due to volatility.

^{11}B NMR revealed the mechanism of both slow and fast BF_3-promoted alkylations. Alkylation of THF is slow, affording 1-octanol in 20% yield. Adding *n*-butyllithium to $BF_3{\cdot}Et_2O$ in THF at -78 °C immediately gave rise to a new peak at -0.5 ppm

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(13) For examples of THF cleavage by organocopper and silylmagnesium reagents, see: (a) Millon, J.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, 1095. (b) Steudel, W.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 6129.

(14) DeWitt, E. J. *J. Org. Chem.* **1961**, *26*, 4156.

(15) As this manuscript was being prepared, the reaction of dimethylboron bromide with 2-methyltetrahydrofuran was reported. Only ether cleavage to a mixture of bromopentanols was observed: Guindon, Y.; Yoakim, C.; Morton, H. E. *Tetrahedron Lett.* **1983**, *24*, 2969.

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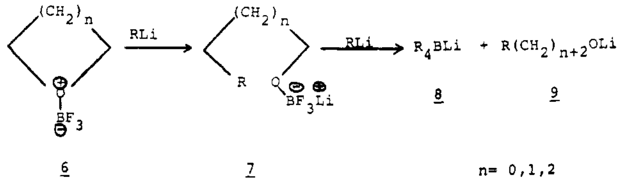
(upfield of $BF_3{\cdot}OR_2$ standard). A second peak gradually appeared at −17.8 ppm. Independent synthesis confirmed that the two signals corresponded, respectively, to lithium *n*-octyloxyboron trifluoride[16] and lithium tetrabutylborate. The much faster butylation of oxetane produced a signal at −0.5 ppm but only a very minor resonance at −17.8 ppm. None of the characteristic resonances of mono- and dibutylfluoroboranes could be detected.

These observations support a mechanism involving Lewis acid coordination then nucleophilic addition by *n*-butyllithium leading first to alkoxyboron trifluoride salt **7**. Complex **7** undergoes attack by residual alkyllithium much more rapidly than does $BF_3{\cdot}Et_2O$ to produce tetraalkylborate **8** and lithium alkoxide **9**. Low yields of 1-octanol from THF apparently result from deleterious consumption of the organolithium in this fashion. These reactions should find widespread use in organic synthesis.[17]



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(17) The following is a representative experimental procedure: *n*-Butyllithium (2.13 M in hexane; 1.4 mL, 3.0 mmol) was added dropwise to a stirred solution of $BF_3{\cdot}Et_2O$ (0.426 g, 3.0 mmol) in THF at −78 °C. Then neat cyclohexene oxide (0.098 g, 1.0 mmol) was added quickly. After 5 min of stirring, the reaction was quenched at −78 °C by addition of saturated aqueous $NaHCO_3$ (3 mL) and allowed to warm to room temperature. The bulk of solvent was removed in vacuo, more water added (3 mL), and the aqueous residue extracted using three 10-mL portions of 1:1 hexane:ether. Drying, evaporation, and then flash chromatography afforded *trans*-2-butylcyclohexanol (0.151 g, 97%).

Observation of the Novel Lithiated Pentacoordinate Carbocations $CH_nLi_{5-n}^+$ (n = 0–3) by Flash Vaporization Mass Spectroscopy

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On some occasions, theoretical predictions precede experiment as ideally they should. In 1978 in the course of ongoing dialogue of our laboratory with P.v.R. Schleyer, we were pleased to learn of the Schleyer–Pople prediction that the pentacoorindate carbocation CLi_5^+ would be stable and that its production by either of the two obvious ion–molecule reactions was favorable (exothermic) by some 60 kcal/mol:[1]

$$CLi_4 + Li^+ \rightarrow CLi_5^+$$

$$CLi_4^+ + Li \rightarrow CLi_5^+$$

When, in the course of our development of the flash vaporization mass spectra of polylithium organic compounds several years later, we observed the CLi_5^+ species among the ions produced by flash vaporization of tetralithiomethane, $(CLi_4)_n$, we congratulated Schleyer and Pople on the accuracy of their forecast and the result was a joint manuscript.[2]

Table I. Pentacoordinate Carbocations $Cli_{5-n}H_n^+$

ion	calculated mass	measured mass	source of ion
Cli_5^+	47.08000	47.08019	$(Cli_4)_n$
$CHLi_4^+$	41.07183	41.07196	$(CHLi_3)_n$
$CH_2Li_3^+$	35.06365	35.06380	$(CH_2Li_2)n$, $(CH_3Li)_4$
$CH_3Li_2^+$	29.05548	29.05559	$(CH_2Li_2)_n$, $(CH_3Li)_4$
CH_4Li^+	23.04730	[sought in CH_4 + Li reaction]	

We now report the observation of four of these unusual pentacoordinate carbocations by high-resolution mass spectroscopy. These novel ions are produced by the flash vaporization and electron impact of polylithium organic compounds. Some such species, $CH_2Li_3^+$ and $CLi_3H_2^+$, appear in the spectra of more than one lithium compound (Table I), while other species such as CLi_4H^+ appear to date only in the vapor species of a single new compound such as trilithiomethane, $(CHLi_3)_n$, which has been produced only very recently in our laboratory.[3] These new carbocations were forecast by Schleyer, Pople, and associates as well.[4]

Since the lithiated methanes are involatile below about 650 °C but thermally unstable above 225 °C[5] it was necessary to flash vaporize the lithiocarbons to obtain transient vapor species in a mass spectrometer. A conically wound, tungsten wire sample probe (which could be heated resistively from room temperature to incandescene [>1500 °C] in less than 2 s) was used for this propose and is illustrated and described elsewhere.[6]

High-resolution peak-matching studies were performed using a CEC model 21-110C double-focusing mass spectrometer (resolution 12000+). The EI ionizing energy was maintained at 70 eV, with the accelerating voltage held at 8 kV. In the actual experiments, the reference ion was positioned in the center of one oscilloscope channel, and the correct $\Delta m/m$ value was selected to position the desired sample ion in the center of the second oscilloscope channel. While sweeping rapidly (<0.5 s/cycle) across the sample ion channel, the appearance of a rising and falling peak with concomitant heating of the sample was confirmatory evidence for the existence of the lithiated carbocation. Each peak-matching experiment was performed a number of times to obtain a value for the relative error in the measured mass.

Halide-free methyllithium was prepared by transmetalation of dimethylmercury with lithium using the Wittig procedure.[7] Dilithiomethane, $(CH_2Li_2)_n$, was formed by the pyrolysis of methyllithium and is detailed elsewhere.[3,8] Trilithiomethane, $(CHLi_3)_n$, and tetralithiomethane, $(CLi_4)_n$, were prepared by metal vapor reactions using the appropriate chlorocarbon precursor.[3,9]

Table I contains calculated and measured masses of the pentacoordinate cations found. As can be seen, all of the lithium-stabilized methanonium ions except CH_4Li^+ are found in the EI mass spectra of the lithiated methanes. Numerous attempts to find this ion in the mass spectra of methyllithium and dilithiomethane were unsuccessful. Calculations predict that this ion may dissociate into CH_4 and Li^+ and probably be stable only at low temperatures.[4] However, the ion appears to be reasonably stable

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