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# Organoaluminum-Catalyzed New Alkylation of *tert*-Alkyl Fluorides: Synthetic Utility of Al-F Interaction

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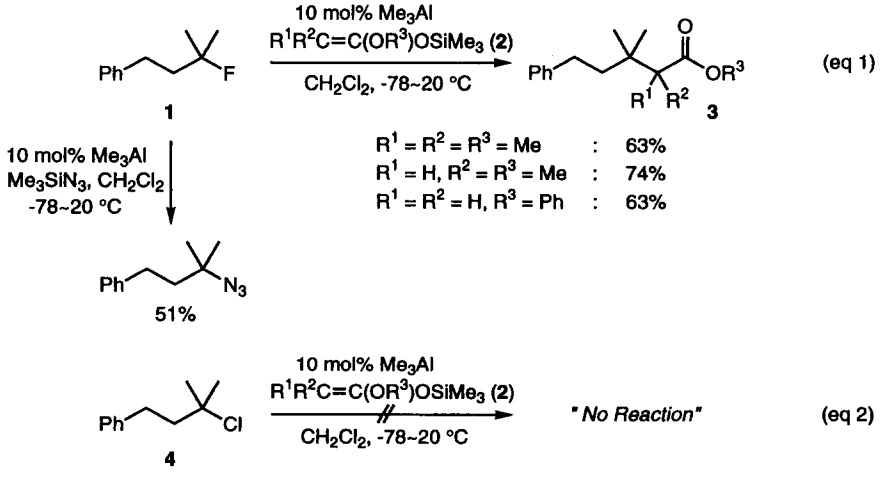
***Abstract:*** *tert*-Alkyl fluorides have been revisited as promising alkylation agents based on the activation of fluorine as a leaving group by organoaluminums through the eminent Al-F interaction. Trialkylaluminums were found to be excellent catalysts as well as alkylation agents. © 1997 Elsevier Science Ltd.

Despite its high electronegativity, fluorine has usually been recognized as a poor leaving group in substitution reactions. Hence, alkyl fluorides are relatively stable and have scarcely been used as alkylation agents in the entire picture of alkylation chemistry compared to other alkyl halides.[1] Upon considering the exceedingly high affinity of aluminum for fluorine atom (663.6±6.3 KJ/mol for Al-F bond),[2] however, we were intrigued by the possibility of activating fluorine as a leaving group by organoaluminums through the eminent Al-F interaction, thereby allowing the successful utilization of alkyl fluorides as promising alkylation agents for carbon-carbon bond formation reactions.[3] With the recent development of attractive methodologies for the selective introduction of fluorine atom into organic molecules,[4] we wish to disclose herein the new organoaluminum-catalyzed alkylation of *tert*-alkyl fluorides with certain nucleophiles as illustrated in eq 1, which provides a facile route to the construction of quaternary carbon centers in organic synthesis.

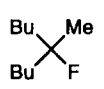
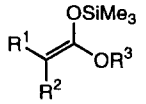
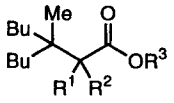
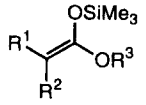
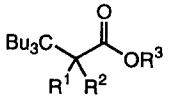



Treatment of 2-fluoro-2-methyl-4-phenylbutane (**1**)[5] and ketene silyl acetal **2** ($R^1 = R^2 = R^3 = Me$) in distilled $CH_2Cl_2$ with a catalytic amount of $Me_3Al$ (0.1 equiv) at -78~20 °C for 2 h gave rise to *α-tert*-alkylated ester **3** ($R^1 = R^2 = R^3 = Me$) in 63% yield. The less substituted ketene silyl acetals **2** ($R^1 = H$, $R^2 = R^3 = Me$

and $R^1 = R^2 = H$, $R^3 = Ph$) were also smoothly alkylated in a similar manner and the introduction of azide functionality appeared to be feasible with trimethylsilyl azide. In marked contrast, attempted reaction of chloro analogue **4** with **2** ($R^1 = R^2 = R^3 = Me$) under similar reaction conditions resulted in almost total recovery of the starting chloride **4** (eq 2). Attempted use of $TiCl_4$ as catalyst in the alkylation of **1** with **2** ($R^1 = R^2 = R^3 = Me$) caused significant rate retardation yielding **3** ($R^1 = R^2 = R^3 = Me$) in only 11% yield with the predominant formation of chlorination product **4** (39%) and the reaction did not proceed with $Ti(OPr^i)_4$ or $SnCl_4$.[6] These results clearly demonstrate the effectiveness of alkylaluminums to activate *tert*-alkyl fluorides.

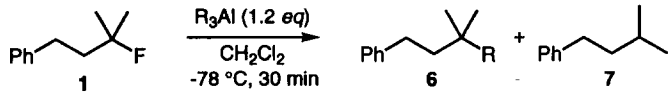
Some other examples are listed in Table I. The differently branched *tert*-alkyl fluorides uniformly experience the efficiency of this new catalytic *tert*-alkylation procedure except in the reaction of **5** and **2** ($R^1 = R^2 = R^3 = Me$) (entry 5), where both reaction partners are sterically demanding, thereby lowering the chemical yield.

**Table I.** $Me_3Al$-Catalyzed Alkylation of *tert*-Alkyl Fluorides. [a]

| entry | alkyl fluoride | nucleophile | product % yield [b] |
|---|---|---|---|
| |  |  |  |
| 1 | | $R^1 = R^2 = R^3 = CH_3$ | 65 |
| 2 | | $R^1 = H$, $R^2 = R^3 = CH_3$ [c] | 71 |
| 3 | | $R^1 = R^2 = H$, $R^3 = Ph$ | 76 |
| | | $Me_3SiN_3$ | $Bu_2MeC\text{-}N_3$ |
| 4 | | | 64 |
| | $Bu_3C\text{-}F$ **5** |  |  |
| 5 | | $R^1 = R^2 = R^3 = CH_3$ | 38 |
| 6 | | $R^1 = H$, $R^2 = R^3 = CH_3$ [c] | 60 |
| 7 | | $R^1 = R^2 = H$, $R^3 = Ph$ | 57 |
| | | $Me_3SiN_3$ | $Bu_3C\text{-}N_3$ |
| 8 | | | 61 |

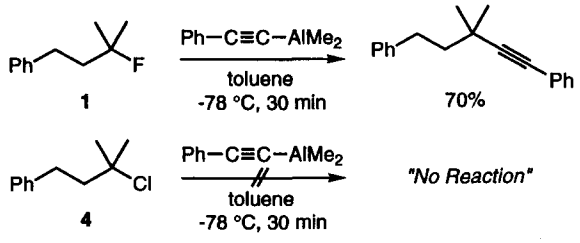
[a] Alkylation was carried out with 10 mol% $Me_3Al$ and 1.5 equiv of nucleophile in distilled $CH_2Cl_2$ at -78~20 °C. [b] Isolated yield. [c] Mixture of *E* and *Z* isomers.

As expected in the absence of external nucleophiles, use of stoichiometric amount of trialkylaluminum should lead to a simple *tert*-alkylation by direct transfer of the alkyl group from trialkylaluminum under mild conditions. Indeed, reaction of **1** with 1.2 equiv of $Me_3Al$ at -78 °C for 30 min afforded 2,2-dimethyl-4-phenylbutane (**6**, R = Me) in 70% yield. Other trialkylaluminums with higher alkyl groups are also employable giving alkylation product **6** (R = Et; 49%, R = Hex; 48%) predominantly with the concomitant formation of reduction product **7** (10% and 9%, respectively).

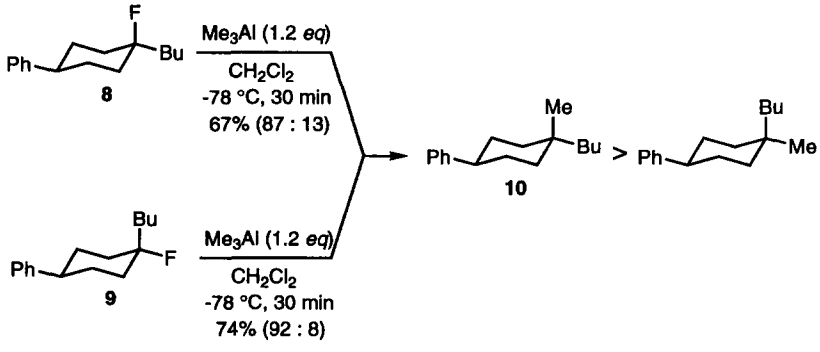



R = Me : 70%
R = Et : 49% + 10%
R = Hex : 48% + 9%

One of the characteristic features of our approach is the successful *tert*-alkyl-alkynyl coupling with dialkylaluminum alkynides which permits the introduction of a quaternary carbon in a position adjacent to an alkynyl group. Such transformation was previously attained by the cross-coupling reaction of *tert*-alkyl chlorides with trialkynylaluminums.[7] The reaction of **1** with dimethylaluminum phenylacetylide (1.5 equiv), readily prepared from lithium phenylacetylide and $Me_2AlCl$, in toluene at -78 °C for 30 min resulted in formation of a cross-coupling product in 70% yield. This result indicates the *efficient and selective transfer of the alkynyl group* from the aluminum center in dialkylaluminum alkynides. Again, the importance of fluoro leaving group has been demonstrated by comparing the unsuccessful alkylation of the chloro analogue **4** with dimethylaluminum phenylacetylide under similar reaction conditions.

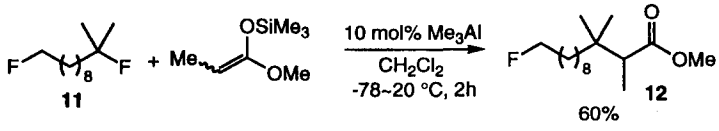



The stereochemical aspect of this alkylation was examined with stereochemically defined cyclic *tert*-alkyl fluorides **8** and **9**,[8] which on separate treatment with $Me_3Al$ (1.2 equiv) yielded thermodynamically more stable product **10**[9] as a major product irrespective of the stereochemistry of the starting fluorides **8** or **9**. This stereochemical outcome suggests the intervention of the intermediary carbocation for effecting $S_N1$-type alkylations.




The present new *tert*-alkylation method was highlighted by the selective functionalization of difluoroalkane with different reactivity profile including *tert*-alkyl/*prim*-alkyl and *tert*-alkyl/*sec*-alkyl fluorides. This method provides a facile route to new types of organofluorine compounds, which are increasingly important in the area of biochemical/biological, pharmacological, and material science.[10] For instance, reaction

of difluoroalkane **11** with ketene silyl acetal **2** ($R^1$ = H, $R^2$ = $R^3$ = Me) was catalyzed by 10 mol% $Me_3Al$ to afford alkylation product **12** in 60% yield, leaving the *primary* alkyl fluoride moiety intact.

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(5) *tert*-Alkyl fluoride **1** can be readily prepared from benzylacetone by the following sequences: (a) MeLi, ether, 0 °C; (b) DAST, $CH_2Cl_2$, -78~20 °C (see ref. 4a).

(6) Although $BF_3$•$OEt_2$ also functions as catalyst, its inapplicability as alkylation agents compared to trialkylaluminums significantly diminishes the synthetic utility. In addition, attempted use of catalytic $Me_2AlCl$ lowered the yield of alkylation product (58%) due to the chlorination and elimination, and these side reactions become predominant with $AlCl_3$ or $AlCl_nF_{3-n}$ (ACF). For the defluorination of perfluoroalkyl compounds mediated by aluminum halides, see: Krespan, C. G.; Petrov, V. A. *Chem. Rev.* **1996**, *96*, 3269.

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(8) The stereochemistry of the starting *tert*-alkyl fluorides **8** and **9** was determined by the orientation of the axial and equatorial butyl carbons adjacent to the quaternary carbon centers by $^{13}C$ NMR analysis. See: Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: Weinheim, 1987.

(9) The stereochemical assignment of **10** was made by comparison of the signals of axial and equatorial methyl carbons of the methylation products in $^{13}C$ NMR spectrum. Generally, the equatorial-methyl signal of substituted cyclohexane derivatives appears downfield relative to the corresponding axial-methyl signal. See ref. 8.

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