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Organoaluminum-Promoted Selective Addition to Fluorinated Carbonyl Compounds *via* Pentacoordinate Trialkylaluminum Complexes

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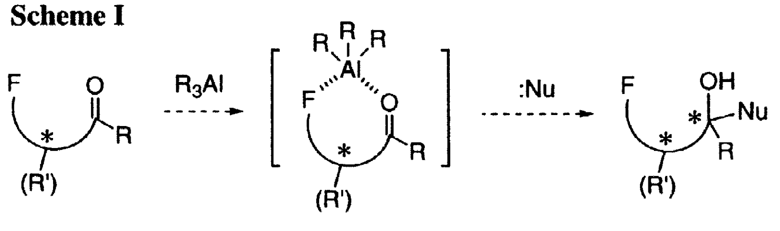
Abstract: A new organoaluminum-promoted selective alkylation with several nucleophiles has been developed which involves the chelation-controlled addition to fluoro carbonyl compounds with trialkylaluminums *via* pentacoordinate organoaluminum complexes. © 1998 Elsevier Science Ltd. All rights reserved.

Organofluorine compounds have been increasingly important in the area of theoretical, biochemical/biological, pharmacological, and material science,[1] and its sustained interest led to the rapid development of various new synthetic methodologies, which are mainly divided into two classes depending on the reaction pattern, *i.e.*, (i) the electrophilic or nucleophilic fluorine introduction to organic molecules,[2] and (ii) functional group transformation of organofluorine compounds.[3] Our attention has been focused on the latter approach by taking advantage of a characteristic feature of fluorine atom.[4] For example, 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: 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.[5] Accordingly, organoaluminum reagents seem to be quite valuable for fluorine-assisted selective transformation of oxygen-containing organofluorine substrates.[6] Here we wish to report such a selective addition reaction with fluoro carbonyl compounds as model substrates of our case study (Scheme I).

Scheme I



First, we carried out the discrimination experiment with 2-fluoro- and 4-fluoroisobutyrophenone in order to examine the advantage of aluminum reagents over other metal reagents for the high affinity to fluorine and oxygen. Thus, treatment of an equimolar mixture of 2-fluoro- and 4-fluoroisobutyrophenone in toluene at -78°C with Me_3Al (1 equiv) and subsequent addition of tributyltin hydride resulted in formation of two different alcohols **1** and **2** (82% combined yield) in a ratio of 34:1. Triethylaluminum showed similar selectivity. The discrimination ability is dramatically lowered by switching the metal reagents from Me_3Al to $TiCl_2(OPr^i)_2$ (1.9:1), $MgBr_2$ (1.9:1), $SiCl_4$ (2.3:1), and to $SnCl_4$ (1:1.3).[7] Use of Me_2AlCl as an aluminum reagent gave less satisfactory result.

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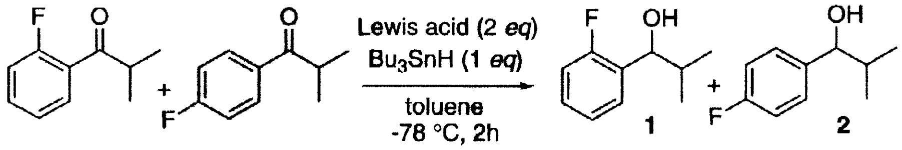
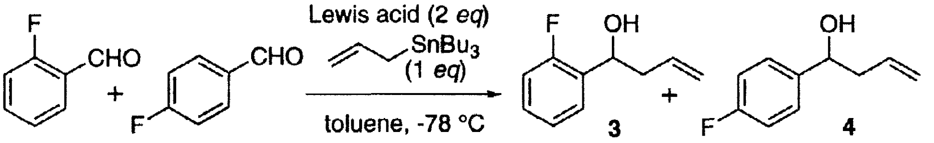


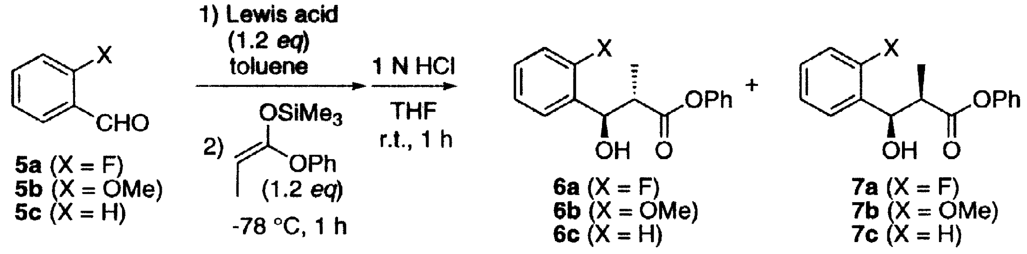
Lewis acid:	Me_3Al	: 82% (34 : 1)
	Et_3Al	: 67% (26 : 1)
	Me_2AlCl	: 75% (7.3 : 1)
	$TiCl_2(OPr^i)_2$	: 71% (1.9 : 1)
	$MgBr_2$	: 71% (1.9 : 1)
	$SiCl_4$	: 12% (2.3 : 1)
	$SnCl_4$	: 17% (1 : 1.3)
	$LiClO_4$	*no reaction*

The advantage of aluminum reagents over other metal reagents was also seen in the Lewis acid-promoted allylation of fluoro carbonyl compounds. Thus, Me_3Al-promoted selective allylation of an equimolar mixture of 2- and 4-fluorobenzaldehydes with allyltributyltin afforded the homoallylic alcohol **3** almost exclusively. Again, unsatisfactory results were obtained with Ti, Mg, Li, Sn, Si reagents in terms of chemical yield and selectivity.[7]

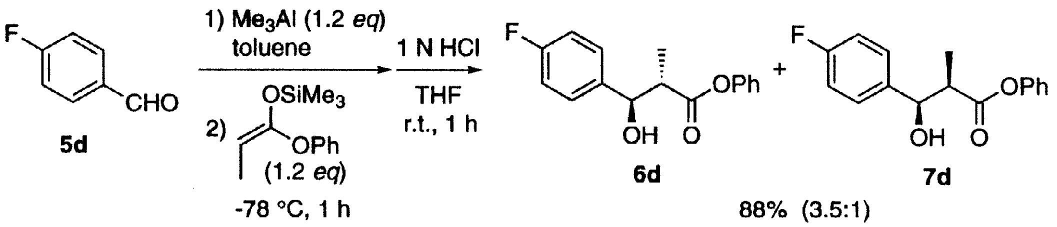


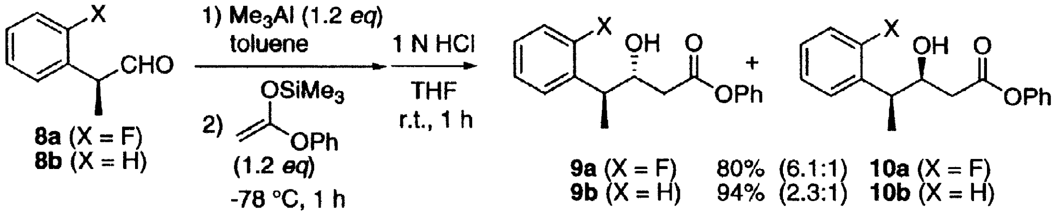
Lewis acid:	Me_3Al	: 74% (31 : 1)
	$TiCl_2(OPr^i)_2$	: 56% (9.8 : 1)
	$MgBr_2$	: 18% (7.1 : 1)
	$LiClO_4$	: 17% (4.1 : 1)
	$SiCl_4$	: 30% (3.8 : 1)
	$SnCl_4$	: 84% (3.9 : 1)

With this information on the metal effect at hand, our attention has been focused on the diastereoselective aldol reactions of fluoroaldehydes with ketene silyl acetals in the presence of trimethylaluminum. Despite the numerous studies for achieving *syn*-selective aldol reactions with ordinary aldehydes, the corresponding *anti*-selectivity has not been easily attainable for the lack of appropriate methodologies.[8,9] Indeed, the *syn/anti* problem has been one of the long-standing concern relating to the 1,2- and 1,3-asymmetric induction in acyclic systems.[9] We have found that high *anti*-selectivity is achieved in the aldol reactions of fluoro aldehydes with ketene silyl acetals in the presence of trimethylaluminum. For example, Me_3Al-induced reaction of *o*-fluorobenzaldehyde (**5a**) with a substituted ketene silyl acetal gave rise to a mixture of fluoro β-hydroxy esters, **6a** and **7a** with high diastereoselectivity probably due to the effective fixation of carbonyl moiety (**6a/7a** = 16:1), while the selectivity was dramatically lowered by use of other common Lewis acids such as $BF_3 \cdot OEt_2$, $TiCl_4$ and Me_3SiOTf.[10,11] In contrast, however, *o*-anisaldehyde (**5b**) and benzaldehyde (**5c**) exhibited moderate selectivity (**6b/7b** = **6c/7c** = 5.3:1).[10] The importance of chelate formation for obtaining high *anti* selectivity was also emphasized by performing the aldol reaction with *p*-fluorobenzaldehyde (**5d**), where further decrease of the diastereoselectivity was observed (**6d/7d** = 3.5:1).[10] In a similar manner, fluoro aldehyde **8a** was treated with a ketene silyl acetal in the presence of trimethylaluminum to furnish fluoro β-hydroxy ester **9a** again with good selectivity (**9a**/**10a** = 6.1:1).[10]

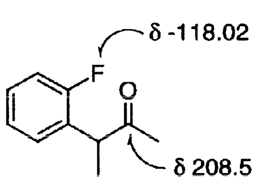


Lewis acid		
	BF_3•OEt_2 :	70% (**6a**:**7a** = 1:1.8)
	$TiCl_4$:	74% (2.9:1)
	Me_3SiOTf :	85% (1:1.5)
	Me_3Al :	96% (16:1)
	:	89% (**6b**:**7b** = 5.3:1)
	:	88% (**6c**:**7c** = 5.3:1)

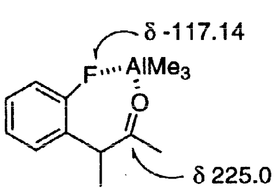




The high diastereoselectivity observed herein is ascribed to the effective chelate formation of Me_3Al with fluoro carbonyl compounds via pentacoordinate organoaluminum complexe **A**. Convincing physical evidence was obtained by carrying out low temperature ^{13}C and ^{19}F NMR study of these aluminum complexes. The original signal of carbonyl carbon in fluoro ketone **11a** appeared at δ 208.5. When **11a** was complexed with Me_3Al in a 1:1 molar ratio in CD_2Cl_2 at -50 °C, a significant downfield shift of carbonyl carbon was observed at δ 225.0 by ^{13}C NMR analysis. Furthermore, ^{19}F NMR mearsurement of the complex **A** under similar conditions showed the F signal at δ -117.4 which originally occurred at δ -118.02 in **11a**.[12] These results indicate the formation of the intermediary pentacoordinate Me_3Al complex **A**.



11a



11a/Me3Al complex, **A**

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(7) Lewis acids such as $MgBr_2$ and $LiClO_4$ can be utilized in ether solvent at 0-25 °C because of their solubility problem in toluene.

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(9) For a recent example, see: Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527 and references cited therein.

(10) The relative configuration in the aldols thus obtained has been determined by the use of ^1H NMR spectroscopy according to the aldol stereostructural assignment described by Heathcock. See: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2.

(11) According to a usual manner, catalytic amount (20 mol%) of Me_3SiOTf was used. See: Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

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