Facile and Selective Alkylation of 3,3,3-Trifluoropropene Oxide (TFPO) with Organoaluminum Reagents *via* Pentacoordinate Trialkylaluminum Complexes

Takashi Ooi, Mayumi Furuya, and Keiji Maruoka*
Department of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810

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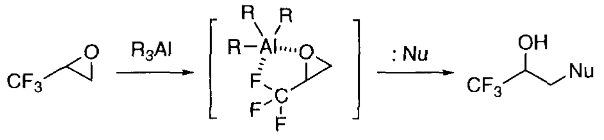
A new organoaluminum-promoted selective alkylation of 3,3,3-trifluoropropene oxide (TFPO) with several nucleophiles has been developed which involves the chelation-activated addition to fluoro epoxides *via* pentacoordinate trialkylaluminum complexes.

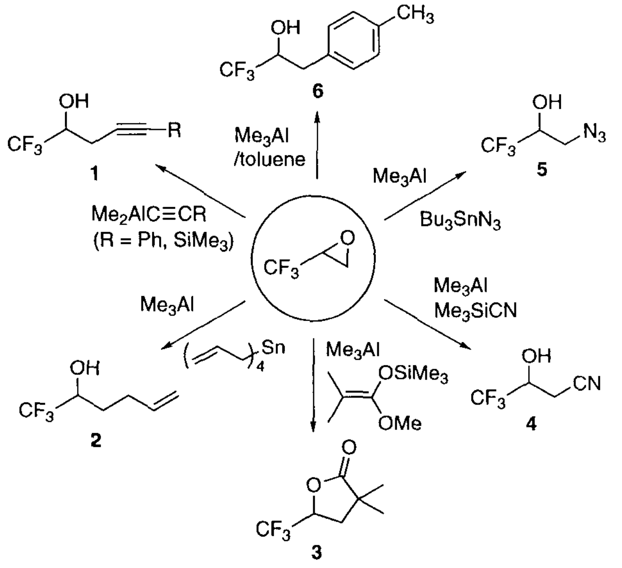
Organofluorine compounds have been of increasing and sustained interest to the synthetic and medicinal communities for a considerable time due to the unique physical and biological properties imparted by fluorine.[1,2] Accordingly, organofluorine chemistry has become a very important part of organic chemical research because of its utilization in the area of theoretical, biochemical/biological, pharmacological, and material science: drugs, pesticides, dyes, surfactants, textiles, etc.[2] This fact has enabled the rapid development of various new synthetic methodologies, and many reactive fluorinated building blocks have been elaborated for this purpose. Among these, 3,3,3-trifluoropropene oxide (TFPO) has been given much attention by numerous organic chemists as well as biochemists, since it is quite useful as a starting substrate for liquid crystals and biologically active compounds.[3-5] Despite a number of studies have been made on the cleavage reactions of TFPO,[3a,3c] only a few are known for the nucleophilic alkylation of TFPO with reactive organometallics.[5] Recently, Uneyama *et al.* reported the successful ring-opening reaction of TFPO with α-cyanocarbanions.[6] In conjunction with our recent finding on the fluorine-assisted selective alkylation to fluorinated epoxides and carbonyl compounds *via* pentacoordinate trialkylaluminum complexes,[7] we here wish to disclose our own results on the selective functionalization of TFPO with various nucleophiles *via* chelating pentacoordinate trialkylaluminum complexes (Scheme 1).



Scheme 1.

First, we examined the possibility of direct alkylation of TFPO with trialkylaluminum under mild reaction conditions. On treatment of TFPO with 1.2 equiv of dimethylaluminum phenylacetylide, which can be prepared from Me_2AlCl and lithium phenylacetylide, in toluene at 0 °C for 1 h and 25 °C for 3 h, the clean alkynylation reaction took place to furnish desired homopropargyl alcohol **1** (R = Ph) in 88% yield (entry 1, Table 1). The alkynylation with $Me_2AlC\equiv CSiMe_3$ proceeded equally well under similar conditions producing the corresponding *secondary* alcohol in good isolated yield (80%) (entry 2).

With these initial results at hand, our attention has been focused on the Me_3Al-promoted ring opening of TFPO in the presence of various external nucleophiles as illustrated in Scheme II and the results are summarized in Table I. Me_3Al-promoted allylation with tetraallyltin proceeded at 0 °C for 1 h and 25 °C for 20 h to give olefinic alcohol **2** as a sole isolable product in good yield (entry 3). It should be added that attempted allylation of simple propylene oxide under similar reaction conditions exhibited total lack of regioselectivity, producing 44:56 mixture of 5-hexen-2-ol and 2-methyl-4-penten-1-ol in 51% combined yield. Use of silyl ketene acetal as a nucleophile resulted in the facile formation of five-membered cyclic lactone **3** having a trifluoromethyl group, which is a synthetically useful building block (entry 4). Introduction of both cyano and azide functionalities also appeared feasible with Me_3SiCN and Bu_3SnN_3, respectively (entries 5 and 6). Interestingly, simple treatment of TFPO with 1.2 equiv of Me_3Al in toluene in the absence of nucleophiles caused the Friedel-Crafts type reaction with toluene as solvent and afforded alcohol **6** in 53% yield (entry 7).



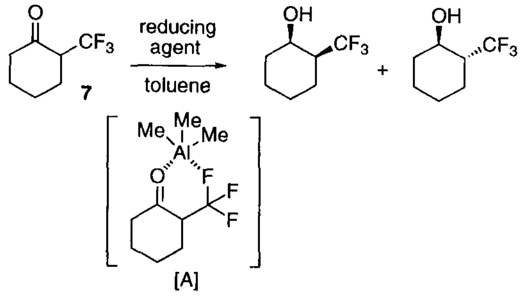
Scheme 2.

This approach is, in principal, applicable to selective functionalization of carbonyl substrates possessing trifluoromethyl group on an appropriate position as exemplified by the diastereoselective reduction of 2-trifluoromethyl cyclohexanone (**7**). Indeed, initial treatment of **7** with Me_3Al (1.2 equiv) and subsequent addition of Bu_3SnH (1.2 equiv) in toluene at -78 °C for 3.5 h gave rise to 2-trifluoromethyl cyclohexanol in 69% yield with the *syn*/*anti* ratio of 81:19. This selectivity can be interpreted by the formation of the intermediary chelate-like pentacoordinate Me_3Al complex [A].[8] When DIBAH was employed as a reducing agent, total lack of the selectivity was observed and the reduction with $NaBH_4$ in methanol at 0 °C exhibited the opposite diastereoselectivity (Scheme 3).

Table I. Me_3Al-promoted alkylation of TFPO [a]

entry	promotor	nucleophile	condition (°C, h)	product	% yield [b]
1		$Me_2AlC\equiv CPh$ [c]	0, 1; 25, 3 [d]	**1** (R = Ph)	88
2		$Me_2AlC\equiv CSiMe_3$ [c]	0. 1; 25, 3 [d]	**1** (R = $SiMe_3$)	80
3	Me_3Al	$(CH_2{=}CHCH_2)_4Sn$	0, 1; 25, 20	**2**	59
4	Me_3Al	$Me_2C{=}C(OMe)OSiMe_3$	0, 0.5; 25, 2	**3**	62
5	Me_3Al	Me_3SiCN	0, 1; 25, 7	**4**	51
6	Me_3Al	Bu_3SnN_3	0, 1; 25, 19	**5**	64
7	Me_3Al	(toluene)	0, 1; 25, 2.5 [d]	**6**	53

[a] Unless otherwise specified, the reaction was carried out in CH_2Cl_2 with 1.2 equiv of Me_3Al and 1~2 equiv of nucleophile under the indicated reaction conditions. [b] Isolated yield. [c] Dimethylaluminum alkynide was prepared by treatment of corresponding alkynyllithium with Me_2AlCl in toluene at 0 °C for 30 min. [d] Use of toluene as solvent.



Me_3Al/Bu_3SnH, -78 °C, 3.5 h : 69% (81 : 19)
DIBAH, -78 °C, 1.5 h : 56% (57 : 43)
$NaBH_4$ (in MeOH), 0 °C, 20 min : 57% (20 : 80)

Scheme 3.

Typical experimental procedure for the Me_3Al-promoted ring opening reaction of TFPO is as follows (entry 4): To a solution of TFPO (43 μL, 0.5 mmol) and methyl trimethylsilyl dimethylketene acetal (200 μL, 1 mmol) in CH_2Cl_2 (3 mL) was added a 1 M hexane solution of Me_3Al (0.6 mL, 0.6 mmol) at -78 °C under argon. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for additional 2 h. This mixture was then poured into 1 N HCl and extracted with ether. The combined ethereal extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:3 as eluant) gave five-membered lactone **3** (56.4 mg, 0.31 mmol) as a colorless oil (62% isolated yield).

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