Hybrid Reagent of Ammonium Hydrogen Fluoride and Scandium Triflate: Highly Efficient Catalyst for Ring-opening Fluorination of 2,3-Epoxyalcohols

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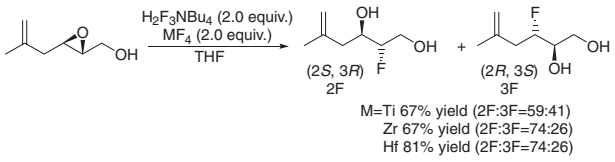
Ring-opening fluorination of 2,3-epoxy-alcohol is one of the most important ways of introducing fluorine atom into functionalized organic compounds. Catalytic ring-opening fluorination is shown to give excellent yield (88%) by catalytic amount of scandium triflate ($Sc(OTf)_3$) in DME.

The synthesis of organofluorine compounds has recently attracted explosive interest in material and biological sciences because of the anomalous physical properties and less availability of these compounds.[1] One of the simplest ways to obtain chiral organofluorine compounds involves the Katsuki-Sharpless asymmetric epoxidation[2] followed by ring-opening fluorination leading to enantio-enriched fluorohydrine. Among various fluorinating reagents, HF/amine complex such as HF/pyridine[3] can be used for epoxide ring-opening fluorination. We have already reported the combined use of stoichiometric amounts of Lewis acidic metal fluoride salts and ammonium hydrogen fluoride for ring-opening fluorination of epoxyalcohols (Scheme 1).[4] The reaction proceeded in good yield particularly by the use of HfF_4, although in stoichiometric amount. We herein report the development of *catalytic* ring-opening fluorination of epoxyalcohols by hybrid reagent of catalytic amount of scandium triflate ($Sc(OTf)_3$) and ammonium hydrogen fluoride.



Scheme 1.

When MF_4 was used in catalytic amount (30 mol %) (Scheme 1), the reaction did not proceed at room temperature. In order to find out the active species of fluorination, ^{19}F VT NMR analysis of the mixture of TiF_4 and $H_2F_3NBu_4$ was carried out. The 1:1 mixture of TiF_4 and $H_2F_3NBu_4$ in THF[5] showed two broad singlets at room temperature. When the solution was cooled to $-80\,^{\circ}C$, the signals split to 5 signals; 75 ppm (39%), 100 ppm (14%), 107 ppm (36%), 184 ppm (4%), 188 ppm (6%). In sharp contrast to 1:1 mixture, 0.15:1 mixture of TiF_4 and $H_2F_3NBu_4$ showed only one signal at 75 ppm even at $-80\,^{\circ}C$. According to the report on ^{19}F NMR of $[TiF_5]^-$ and $[TiF_6]^{2-}$ species,[6,7] the signal of 75 ppm corresponds to that of $[TiF_6]^{2-}$ and two sets of signals, (100, 184 ppm) and (107, 188 ppm) (relative intensity: ca. 4:1), are in good agreement with $[TiF_5]^-$. One set with large intensity, could be assigned to $[TiF_5(thf)]^-$ along with the other set corresponding to $[TiF_5(H_2O)]^-$.[7]

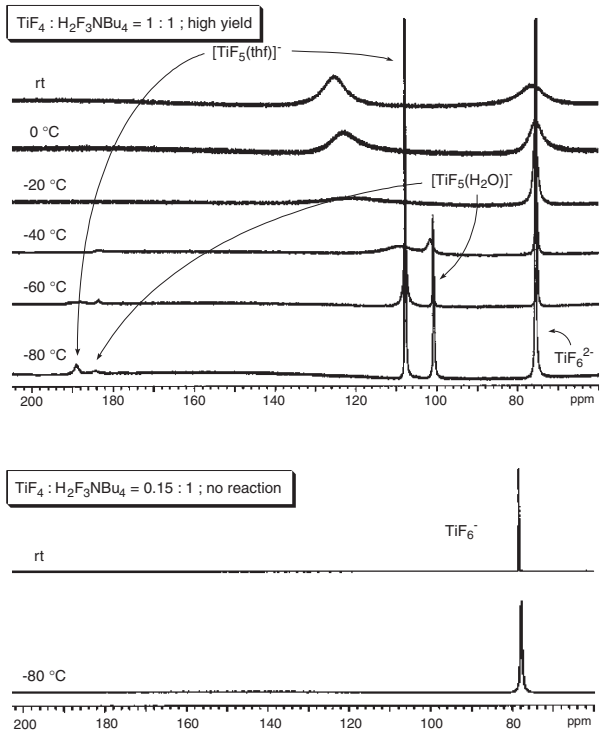


Figure 1. VT NMR (^{19}F) of the mixture of TiF_4:$H_2F_3NBu_4$ = 1:1 or 0.15:1 in THF.

It could be concluded that when TiF_4 and $H_2F_3NBu_4$ was mixed in 1:1 ratio, there is an equilibrium between $[TiF_6]^{2-}$ and $[TiF_5]^-$. $[TiF_5]^-$ with one coordination site could act as an active species. When a catalytic amount of TiF_4 and $H_2F_3NBu_4$ were mixed in 0.15:1 ratio, only $[TiF_6]^{2-}$ with no coordination site, was observed in the solution and hence the reaction did not proceed at all (Figure 2).

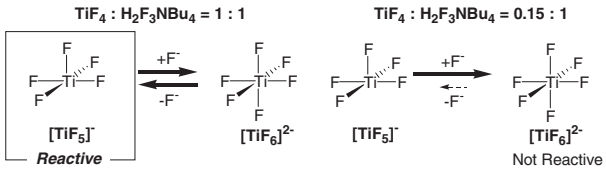


Figure 2. Active species of the ring opening fluorination.

With these information in hand, we focused on catalytic fluorination by metal triflate catalysts ($M(OTf)_n$) by changing the counter anion from fluorine to triflate. Triflate anion should leave a coordination site available for the epoxyalcohols, because of less nucleophilicity and hence weakly coordinative ability.

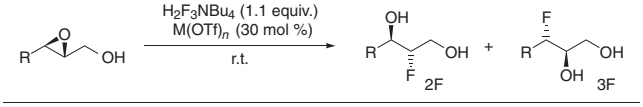
First of all, ring-opening fluorination of *trans*-epoxyalcohol was examined with 30 mol % of $Hf(OTf)_4$ in several solutions as compared with HfF_4 in $H_2F_3NBu_4$ (200 mol % each) conditions. $Sc(OTf)_3$ was also examined in view of a similar ionic radii (Hf: 0.78 Å, Sc: 0.75 Å) (Table 1). When $Hf(OTf)_4$ was used, the fluorinated product was obtained in poor to fair yield (Entries 1–4). On the other hand, when $Sc(OTf)_3$ was used, the fluorinated product was obtained in good yield. However, in dichloromethane, starting epoxyalcohol was almost consumed but the fluorohydrin was obtained in low yield and non-fluorinated by-products were mainly formed. It could be considered that high Lewis acidity in dichloromethane led to decomposition of the starting epoxyalcohol (Entries 7, 8). The reactions in THF (Entries 5 and 6), acetonitrile (Entries 9 and 10) and DME (Entry 11) gave good yields. Among all the solvents investigated, DME was the best to give 80% yield. Each of the reaction shows C-3 regioselectivity and the ratio of C-2 *vs* C-3 fluorination is about 35 to 65. Other metal triflates such as $Yb(OTf)_3$ (Entry 12), $Y(OTf)_3$ (Entry 13), and $La(OTf)_3$ (Entry 14) gave the fluorinated product only in trace amount.

The 2F and 3F products showed only one ^{19}F NMR peak, which are the same as previously reported.[4] Therefore, it could be suggested that this reaction proceeds via complete inversion process.

With this success in fluorination of 2,3-epoxyalcohol, 5-methyl-2,3-epoxyhex-5-en-1-ol, the synthetic intermediate for fluorinated 19-nor-vitamin D analogue,[8] could be fluorinated in good yield (88%) when using 30 mol % of $Sc(OTf)_3$ and DME (Scheme 2).

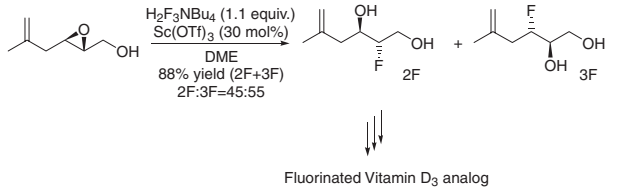
In summary, $Sc(OTf)_3$ could act as an effective catalyst in ring opening fluorination of 2,3-epoxyalcohol by ammonium hydrogen fluoride. Further investigation of the regioselective ring-opening fluorination of epoxyalcohols is in progress.

Table 1. Ring opening fluorination by 30 mol % $M(OTf)_n$ in various solvent systems



Entry	$M(OTf)_n$	Solvent	R	Time (h)	% yield (2F + 3F)[a]	2F:3F[a]
1	$Hf(OTf)_4$	THF	*n*-Pr	2	0	—
2[b]		CH_2Cl_2		27	5	—
3[c]		CH_3CN		4	43	26:74
4		DME	*i*-Pr	4	33	51:49
5	$Sc(OTf)_3$	THF	*n*-Pr	24	59	30:70
6			*i*-Pr	4	47	40:60
7		CH_2Cl_2	*n*-Pr	96	20	22:78
8			*i*-Pr	4	8	13:87
9		CH_3CN	*n*-Pr	4	74	25:75
10			*i*-Pr	4	71	36:64
11		DME	*i*-Pr	4	80	37:63
12	$Yb(OTf)_3$	DME	*i*-Pr	4	trace	—
13	$Y(OTf)_3$			4	trace	—
14	$La(OTf)_3$			4	trace	—

[a]Determined by ^{19}F NMR using BTF as an internal standard.
[b]The reaction was carried out at −20–0 °C.
[c]The reaction was carried out at 0 °C.



Scheme 2.

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5 Small amount of C_6D_6 was added for D-lock.

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