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Activation of Lewis acid catalysts in the presence of an organic salt containing a non-coordinating anion: its origin and application potential†

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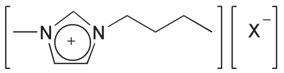
In the presence of a soluble organic salt containing non-coordinating anion (*e.g.*, [bmim][SbF_6] or [NR_4][SbF_6]), the catalytic activity of Lewis acid (MX_n) was dramatically enhanced due to the anion exchange between the Lewis acid and organic salt.

Lewis acids-catalyzed organic reactions play important roles in modern organic synthesis.[1] However, their relatively low turnover numbers often inhibit their application. Recently, several Lewis acid-catalyzed organic reactions have been conducted in ionic liquids (ILs) with great success.[2] In most of the examples studied, switching from an organic solvent to an IL not only facilitated the recycling of the catalyst but also led to positive changes in the course of the reaction (*e.g.*, significant rate acceleration).



X = SbF_6 (**1a**), PF_6 (**1b**)

In our earlier studies on catalysis in ILs,[3] we also found that the rates of the metal triflate-catalyzed C–C bond forming reactions (*e.g.* Friedel–Crafts alkylation[3b] and alkenylation[3h,i] reactions of aromatic compounds, and Diels–Alder reactions[3c]) were dramatically accelerated up to several hundred-fold in the presence of an IL containing very weakly coordinating anions such as [bmim][SbF_6] (**1a**) or [bmim][PF_6] (**1b**) (bmim = 1-butyl-3-methylimidazolium). In some cases,[3b,h,i] even the reactions that were not possible to conduct in conventional organic solvents proceeded smoothly in ILs. However, to date, the exact reasons behind this observed positive *"ionic liquid effect"* have not yet been elucidated. In this research, we performed for the first time detailed studies to elucidate the origin of the "*ionic liquid effect*" and found that an soluble organic salt having a "non-coordinating anion" such as PF_6^- or SbF_6^- activates the metal triflate catalysts, causing them to become more electrophilic by *in-situ* anion exchange, which dramatically enhances their catalytic activity. Moreover, on the basis of this result, we demonstrated that not only rare earth metal triflates but other types of Lewis acid catalysts can also be activated just by mixing them with an organic salt containing "non-coordinating anions".

The Lewis acidity of a metal ion is expected to increase with decreasing nucleophilicity of its counter anion, that is, metal salts with less nucleophilic counter anions are more electrophilic. For example, the stronger Lewis acidity of those Sc-complexes having very weakly coordinating anions,[4] such as $[B(C_6F_5)_4]^-$ rather than OTf^-, has already been confirmed by their much higher activity in many Sc-ion promoted electron transfer reactions.[5] In addition, we also observed the dramatic anion effect of ILs on the catalytic activity in the $Sc(OTf)_3$-catalyzed Friedel–Crafts alkylation reactions,[3b] and alkenylations.[3h] The catalytic activity generally increased with decreasing nucleophilicity of the IL anion. Considering all of these reported results, we postulated that the more Lewis-acidic (*i.e.*, more electrophilic) metal species **2** might be generated *in situ* by anion exchange between the metal triflate and ILs containing very weakly coordinating anions such as PF_6^- or SbF_6^- (Scheme 1).

To obtain evidence for the anion exchange between metal triflates and ILs **1**, we first carried out the reaction of $Sc(OTf)_3$ with 5 equivalents of Merrifield's resin-bound imidazolium hexafluoroantimonate **3**[6] in CH_2Cl_2 at room temperature (Scheme 2). After stirring for 4 h, the resin was filtered, washed thoroughly with THF, MeOH, H_2O, and again with MeOH, and dried *in vacuo*. The solid-state ^{19}F NMR spectra of the filtered resin **4** clearly indicated the anion exchange between the OTf anion of $Sc(OTf)_3$ and SbF_6 anion of resin **3**. As shown in Fig. 1, the filtered resin **4** contains the OTf anion as well as the SbF_6 anion.[7] The singlet peak at −82.5 ppm corresponds to the OTf anion (compare with the solid-state ^{19}F NMR spectrum (Inset (a) of Fig. 1) of resin-bound imidazolium triflate,[8] which was prepared independently). The formation of the superacidic species **2** was also detected from the analysis of the filtrate. Due to the instability of the superacidic species **2**, the same exchange experiment was carried out in d_6-DMSO–d_8-THF (1 : 1, v/v).[9] After stirring for 4 h, the resin was filtered off and the filtrate was subjected directly to ^{19}F NMR, and FAB-MS analysis. The ^{19}F NMR spectrum of the filtrate clearly (Fig. 2) showed that it contains the SbF_6^- moiety together with other unidentifiable species. The two coupling

$$M(OTf)_n + n\,[bmim][SbF_6]\,(\mathbf{1a}) \longrightarrow$$
$$[M(OTf)_{n-x}][SbF_6]_x\,(\mathbf{2}) + (n\text{-}x)\,[bmim][SbF_6] + (x)\,[bmim][OTf]$$

Scheme 1 *In-situ* formation of more electrophilic metal species **2** from metal triflates and **1a** by anion exchange.

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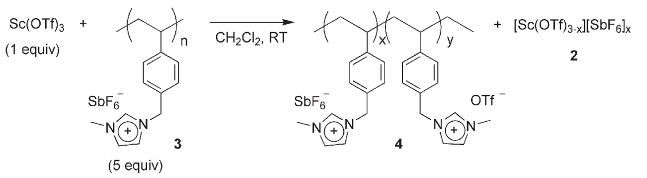


Scheme 2 The anion exchange reaction between $Sc(OTf)_3$ and the Merrifield's resin-bound imidazolium hexafluoroantimonate **3**.

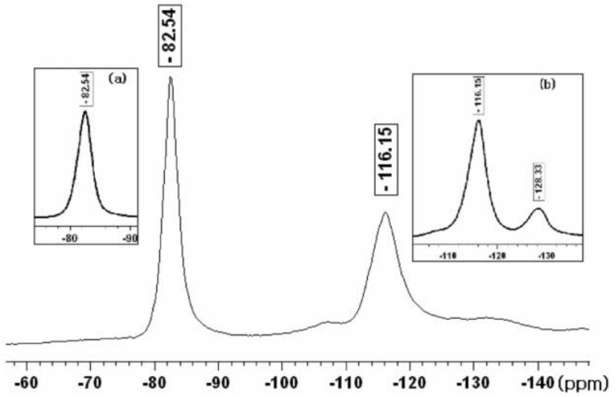


Fig. 1 Solid-state ^{19}F NMR spectra of polymer **4**. (Inset (a) is the solid-state ^{19}F NMR spectrum of the resin-bound imidazolium triflate, while inset (b) is the solid-state ^{19}F NMR spectrum of resin **3**.)

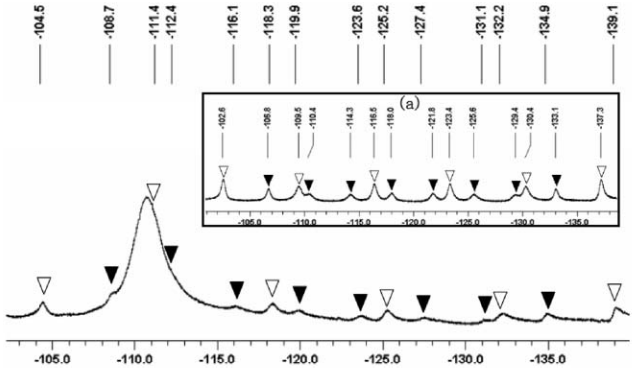
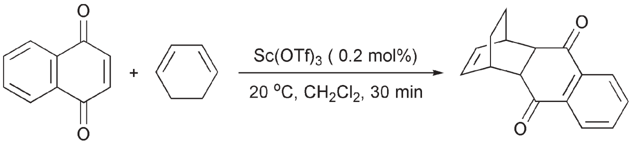


Fig. 2 ^{19}F NMR spectrum of the filtrate in d_6-DMSO. (Inset (a) is the spectrum of **1a**); (▽) the coupling between ^{19}F and the NMR-active Sb-nucleus (I = 5/2); (▼) the coupling between ^{19}F and the NMR-active Sb-nucleus (I = 7/2).)

patterns between ^{19}F and two NMR-active Sb-nuclides (I = 5/2 and 7/2) that were observed in the ^{19}F NMR spectrum of the filtrate are comparable with those in the spectrum of **1a** (inset (a) of Fig. 2).

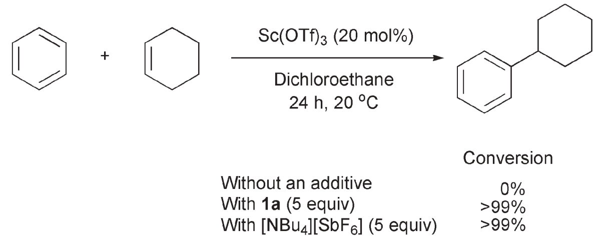
In addition, FAB-MS analysis provided more direct evidence for the existence of superacidic species **2** in the filtrate. In the FAB-MS spectrum, the molecular ion peak for $Sc(SbF_6)_3$ (m/z = 751.6, 753.6) was clearly detected, along with peaks for $Sc(OTf)_2(SbF_6)$ and $Sc(OTf)_2(SbF_6)\cdot 3DMSO$ (see ESI†). Based on these results, it can be concluded that the rate accelerations observed in metallic Lewis acid-catalyzed reactions in ILs containing very weakly coordinating anions such as PF_6^- or SbF_6^- may originate from the *in situ* generation of more highly Lewis-acidic metal species such as **2**, which were formed from the anion exchange between the metal triflate and ILs.

On the basis of our proposed anion-exchange mechanism for the activation of the catalyst, not only rare earth metal triflates but other types of Lewis acids, MX_n, would be activated merely by mixing them with any soluble organic salts containing non-coordinating anions. To demonstrate the validity of this concept, we next carried out a series of C–C bond forming reactions such as Diels–Alder reaction, Friedel–Crafts alkylation and Friedel–Crafts alkenylation using various Lewis acid catalysts ($Sc(OTf)_3$, $InCl_3$ or TMS-OTf) in the presence of a quaternary ammonium salt having the SbF_6 anion (*e.g.*, $[NBu_4][SbF_6]$) instead of the corresponding imidazolium salt **1a**. As we hoped, in all cases, $[NBu_4][SbF_6]$ produced a similar rate acceleration to $[bmim][SbF_6]$ (**1a**). Thus, the Diels–Alder reaction of naphthoquinone and cyclohexadiene using 0.2 mol% of Sc-catalyst in CH_2Cl_2 was completed within 30 min in the presence of 1 equiv. of $[NBu_4][SbF_6]$, whereas the same reaction without $[NBu_4][SbF_6]$ or **1a** is extremely sluggish (Scheme 3). Sc(III) triflate-catalyzed Friedel–Crafts alkylation of benzene with alkenes also proceeded readily in the presence of $[NBu_4][SbF_6]$, whereas the same reactions did not occur in dichloroethane. Thus, a quantitative yield of cyclohexylbenzene was obtained from benzene and cyclohexene using $Sc(OTf)_3$ and $[NBu_4][SbF_6]$ after 24 h (Scheme 4). In the Friedel–Crafts alkenylation of arenes with alkynes, the addition of $[NBu_4][SbF_6]$ also activated the catalysts markedly (Table 1). In the absence of a salt with a non-coordinating anion, $Sc(OTf)_3$ was totally inactive for the alkenylation of p-xylene with an electron-deficient alkyne such as p-chlorophenylacetylene (entry 1).[10] In contrast, in the presence of 5 equiv. of **1a** or $[NBu_4][SbF_6]$, the reaction was completed within 13 h and afforded the desired product in good yield (entries 2 and 3). More strikingly, metal chlorides such as $InCl_3$ (entry 6) or even non-metallic triflates such as TMS-OTf (entry 9), were also activated in the presence of the ammonium salt. For example, $InCl_3$ (entry 4) and TMS-OTf (entry 7) showed very low activity for the alkenylation of p-xylene with 1-phenyl-1-propyne, whereas in the presence of **1a** or $[NBu_4][SbF_6]$, the same reactions were completed within 1–3 h (entries 5, 6, 8 and 9).[11] We also carried out the same reaction using several quaternary ammonium salts bearing different anions such as PF_6^-, BF_4^- and OTf^- to clarify "the anion effect" on the activation of Lewis acid catalyst (in this case, TMS-OTf). As we expected, the Lewis acidity of the TMS-cation increased with decreasing nucleophilicity of the counter anion of salts in the order of $SbF_6^- > PF_6^- > BF_4^- > OTf^-$ (entries 9–12 in Table 1). According to the *ab initio* calculations, just as expected, the atomic charge at Si of



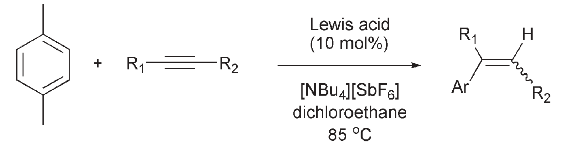
	Conv.	Yield	Endo/Exo
Without an additive	<10%	n.d.	n.d.
With **1a** (1 equiv)	>99%	96%	99/1
With $[NBu_4][SbF_6]$ (1 equiv)	>99%	95%	99/1

Scheme 3 $Sc(OTf)_3$-catalyzed Diels–Alder reaction of naphthoquinone with cyclohexadiene (for experimental details, see ESI†).



Scheme 4 Sc(OTf)$_3$-catalysed Friedel–Crafts alkylation of benzene and cyclohexane (for experimental details, see ESI†).

Table 1 Lewis acid-catalyzed Friedel–Crafts alkenylation of *p*-xylene with alkyne[a]



Entry	R_1	R_2	Catalyst	Additive (5 equiv.)	*t*/h	Yield (%)
1	*p*-ClPh	H	Sc(OTf)$_3$	None	48	0[c]
2	*p*-ClPh	H	Sc(OTf)$_3$	**1a**	12	63[c]
3	*p*-ClPh	H	Sc(OTf)$_3$	NBu$_4$SbF$_6$	13	61
4[b]	Ph	Me	InCl$_3$	None	72	7
5[b]	Ph	Me	InCl$_3$	**1a**	3	94
6[b]	Ph	Me	InCl$_3$	NBu$_4$SbF$_6$	3	88
7	Ph	Me	TMS-OTf	None	2	9
8	Ph	Me	TMS-OTf	**1a**	1	93
9	Ph	Me	TMS-OTf	NBu$_4$SbF$_6$	2	95
10	Ph	Me	TMS-OTf	NBu$_4$PF$_6$	2	89
11	Ph	Me	TMS-OTf	NBu$_4$BF$_4$	2	46
12	Ph	Me	TMS-OTf	NBu$_4$OTf	2	5

[a] For experimental details, see ESI. [b] 20 mol% of InCl$_3$ was used. [c] See ref. 3*h*.

[TMS][SbF$_6$] was found to be much more positive than that of TMS-OTf and eventually close to the charge of naked TMS-cation.[12] These experimetal and theoretical results strongly indicate that the anionic nature of organic salts plays a crucial role for the activation of Lewis acids. Thus, the acidity of an metallic or non-metallic Lewis acid could be very simply tuned by proper selection of counter anions of salts.

In summary, the origin of the acceleration effect of ILs in Lewis acid-catalyzed reactions was clearly elucidated for the first time. An imidazolium IL having very weakly coordinating anions such as PF_6^- or SbF_6^- activates metal triflate catalysts so that they become more electrophilic (*i.e.*, more Lewis acidic) by anion exchange, which dramatically enhances the catalytic activity. As evidence for the anion exchange, solid- and solution-state ^{19}F NMR and FAB-MS analyses were conducted. Moreover, it was also demonstrated that several types of Lewis acid can be activated, according to the catalyst activation mechanism, merely by mixing them with a soluble organic salt containing non-coordinating anions. Furthermore, the acidity of Lewis acids can be very simply tuned by proper selection of counter anions of soluble organic salts. We believe that the present study will open up new perspectives for Lewis acid chemistry.

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6 For the preparation of Merrifield's resin-bound imidazolium hexafluoroantimonate **3**, see ESI†.

7 The solid ^{19}F NMR of **3** (Inset (b) of Fig. 1) and **4** did not show a fine coupling pattern between ^{19}F and two NMR-active Sb-nuclides (I = 5/2 and 7/2) which can be attributed to the inhomogeneous chemical environment of the SbF$_6$ moiety in the polymer matrix).

8 For the preparation of Merrifield's resin-bound imidazolium triflate, see ESI†.

9 Since species **2** was shown to be unstable in the absence of electron donor ligands, we carried out the exchange experiment in the presence of DMSO.

10 T. Tsuchimoto, T. Maeda, E. Shirakawa and Y. Kawakami, *Chem. Commun.*, 2000, 1573.

11 The alkenylation of *p*-xylene with 1-phenyl-1-propyne using TMS-OTf as a catalyst was also carried out with a reduced amount (1 equiv.) of [NBu$_4$][SbF$_6$]. However, the reaction proceeded more slowly than when 5 equiv. of the same additive was used and thus only 45% yield was obtained after the same reaction time (2 h).

12 The calculated atomic charges at Si of TMS$^+$ from TMS-OTf and TMS-SbF$_6$ in gas/dichloromethane/DMSO are as following[a] (see ESI† for full data):

Species	Gas	DCM	DMSO
TMS$^+$	2.102	2.138	2.145
TMS-SbF$_6$	2.007	2.009	2.009
TMS-OTf	1.991	1.974	1.974

[a]Charges were obtained from the natural bond orbital populations. Charges are in e$^+$.