BF_3·OEt_2 and TMSOTf: A synergistic combination of Lewis acids†

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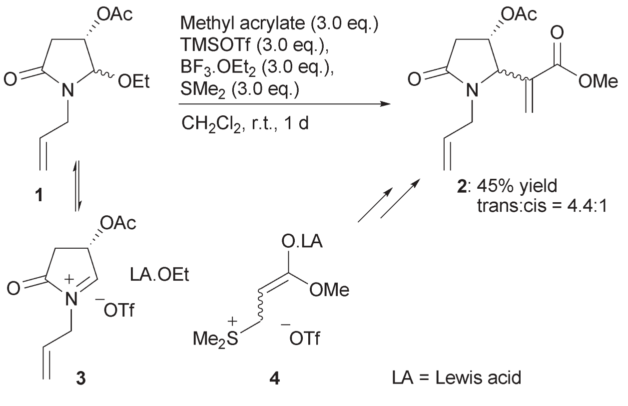
The combination of BF_3·OEt_2 and TMSOTf gives BF_2OTf·OEt_2, which is a more powerful Lewis acid than its components and especially effective in CH_3CN solvent; the complex formed has been characterised by ^1H, ^{19}F, ^{11}B and ^{31}P (using Et_3PO as an additive) NMR spectroscopy.

BF_3·OEt_2 and TMSOTf are powerful and commonly used Lewis acids in organic synthesis.[1] In the important and challenging area of glycosidation reactions, Nicolaou and Kishi and co-workers have found that the combination of both Lewis acids is more effective than the individual components.[2] In our own studies on the development of a novel Morita–Baylis–Hillman-type reaction, with (*S*)-malic acid-derived aminal **1** and methyl acrylate as partners, the combination of Lewis acids BF_3·OEt_2 and TMSOTf was found to be crucial for conversion (Scheme 1).[3] We were intrigued by such a requirement, since TMSOTf alone was sufficient to generate iminium ion **3** and β-sulfonium *O*,*O*-ketene acetal **4** when **1** or methyl acrylate were employed with more reactive partners. Furthermore, while BF_3·OEt_2 is capable of catalysing the generation of iminium ion, it is not suitably active for generating a sufficient concentration of **4**.

These findings suggested to us that this combination of reagents leads to a more powerful Lewis acid. We therefore set about identifying the nature of the Lewis acid generated from a 1 : 1 mixture of TMSOTf and BF_3·OEt_2 in $CDCl_3$ by ^1H, ^{11}B (Fig. 1) and ^{19}F (Fig. 2) NMR spectroscopy.[4] In addition to the relevant signals for TMSOTf and BF_3·OEt_2, the spectra also displayed signals for TMSF and a species characterised as BF_2OTf·OEt_2 (**5**). Evidence for the latter included: (a) a set of resonances in the ^1H NMR spectrum for a diethyl ether complex (1.52 and 4.44 ppm) downfield of BF_3·OEt_2, indicative of a more powerful Lewis acid (Fig. 1); (b) a new ^{11}B environment (−1.29 ppm) resonating upfield of BF_3·OEt_2 (Fig. 1, inset); (c) the ^{19}F NMR spectrum showed a new triflate signal appearing as a triplet (−76.8 ppm, $^5J_{F–F}$ = 2.8 Hz) (Fig. 2, inset), indicating that it is attached to BF_2, and a boron fluoride species (−146.4 and −146.3 ppm) downfield of BF_3·OEt_2, appearing as a broad signal accompanied by a downfield isotopic satellite (*i.e.*, those fluorides attached to ^{10}B) (Fig. 2).[5–7]



Scheme 1 Synthesis of Morita–Baylis–Hillman-type adduct **2**.

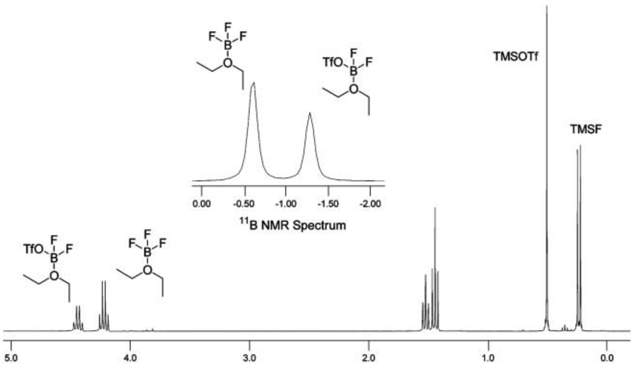


Fig. 1 ^1H and ^{11}B NMR (inset) spectra.

Further evidence for **5** was obtained through complexation with triethylphosphine oxide, and in particular, examination of the ^{31}P and ^1H NMR spectra. Thus a 2 : 1 mixture of BF_3·OEt_2 and TMSOTf in $CDCl_3$ was treated with excess (4.7 equivalents) triethylphosphine oxide. The ^1H NMR spectrum showed free diethyl ether, free phosphine oxide, TMSF and two phosphine oxide complexes; furthermore, integration revealed that approximately 3 equivalents of phosphine oxide were complexed. The ^{31}P NMR spectrum (Fig. 3) showed free phosphine oxide and two downfield signals in the ratio 2 : 1. The most downfield signal at

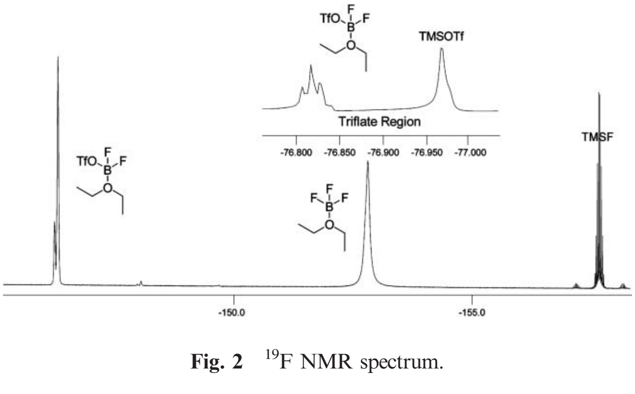


Fig. 2 ^{19}F NMR spectrum.

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† Electronic supplementary information (ESI) available: Full experimental details with supplementary spectra and discussion. See DOI: 10.1039/b611333h

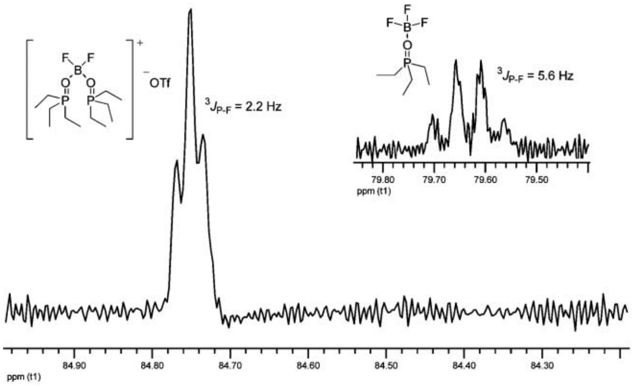


Fig. 3 ^{31}P NMR spectrum of phosphine oxide complexes.

84.8 ppm appeared as a triplet ($^3J_{P-F}$ = 2.2 Hz) and the other at 79.6 ppm as a quartet ($^3J_{P-F}$ = 5.6 Hz).[8] These signals were assigned to the bis-phosphine oxide boron difluoride complex $[BF_2(OPEt_3)_2]^+OTf^-$ and the $BF_3 \cdot OPEt_3$ complex, respectively.[9] When the same experiment was conducted with 0.7 equivalents of phosphine oxide, the predominant species was, tentatively, $BF_2OTf \cdot OPEt_3$, appearing downfield of $BF_3 \cdot OPEt_3$ and slightly upfield of the bis-phosphine oxide complex at 84.6 ppm; small amounts of the bis-complex were also observed.

The presence of significant amounts of the parent Lewis acids in solution suggested a dynamic equilibrium process. This was confirmed using Le Chatelier's principle. A 1.8 : 1 solution of $BF_3 \cdot OEt_2$:TMSOTf in $CDCl_3$ was prepared and the relative concentrations of all four species were obtained by integration of the relevant signals in the ^{1}H NMR spectrum. Using these values, the equilibrium constant K_{eq} (Scheme 2) was determined to be 0.74. After the introduction of additional TMSOTf (0.8 equivalents), bringing the ratio of $BF_3 \cdot OEt_2$: TMSOTf added to 1 : 1, the resulting relative concentrations were such that K_{eq} remained unchanged. In CD_2Cl_2, K_{eq} was determined to be 0.69.

We were interested in comparing the Lewis acidity of BF_2OTf with other Lewis acids; evidence already in hand (*i.e.*, in the ^{1}H NMR spectrum, the downfield shift of its etherate complex relative to that of BF_3) suggesting it to be the stronger Lewis acid (Fig. 1). Childs and co-workers determined a relative order of Lewis acidity by measuring the downfield shift of the H3 proton of crotonaldehyde [$\Delta\delta$(H3)] upon its complexation with a Lewis acid.[10]

As an initial test, a solution of $BF_3 \cdot OEt_2$ in $CDCl_3$ with 0.25 equivalents of crotonaldehyde was analysed by ^{1}H NMR spectroscopy at 15 °C. At this temperature, it became apparent that BF_3 was rapidly exchanging aldehyde and diethyl ether ligands, resulting in severely broadened resonances; Childs and co-workers used gaseous BF_3 as the source.[10] In order to slow down ligand exchange, the NMR sample was cooled to just above the freezing point of $CDCl_3$ (−55 °C). At this temperature, the spectrum showed well resolved resonances for unligated aldehyde, ligated aldehyde, unligated ether and ligated ether (Fig. 4). $\Delta\delta$(H3) was measured to be 1.10 ppm, which is within 0.1 ppm of the value given by Childs.[10]

$$BF_3 \cdot OEt_2 \quad TMSOTf \rightleftharpoons BF_2OTf \cdot OEt_2 \quad TMSF$$

$$K_{eq} = \frac{[BF_2OTf \cdot OEt_2]\,.\,[TMSF]}{[BF_3 \cdot OEt_2]\,.\,[TMSOTf]}$$

Scheme 2 Calculation of K_{eq}.

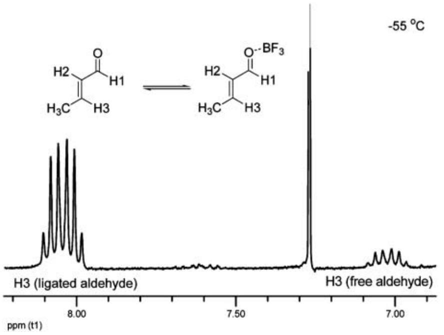


Fig. 4 Observance of BF_3–crotonaldehyde complex.

A similar experiment was conducted with TMSOTf as the Lewis acid in CD_2Cl_2. At room temperature, there was one set of sharp resonances for crotonaldehyde and TMSOTf, and $\Delta\delta$(H3) was found to be ~0.2 ppm.[11] The single set of sharp resonances suggest a ligand exchange process which is much faster than that with BF_3 as the Lewis acid, and the relatively small $\Delta\delta$(H3) suggests that the equilibrium lies very much towards unligated aldehyde. The ability of silicon to exchange ligands *via* an associative mechanism may account for this increased rate. Cooling to as low as −90 °C did not result in decoalescence (see ESI†).

A 1 : 1 solution of $BF_3 \cdot OEt_2$ and TMSOTf in $CDCl_3$ with crotonaldehyde (0.25 equivalents) was then analysed by ^{1}H NMR at room temperature and −55 °C. At room temperature, two sets of H3 resonances were apparent: a sharp signal and a broader one further upfield. Upon cooling to −55 °C, the former had shifted slightly downfield but remained sharp, while the latter split into two signals: a sharp downfield resonance and a broad upfield resonance close to the expected chemical shift of the free aldehyde (Fig. 5). Moving in an upfield direction, the resonances were assigned to the BF_2OTf complex [$\Delta\delta$(H3) = 1.4 ppm], the BF_3 complex [$\Delta\delta$(H3) = 1.1 ppm], and rapidly exchanging TMSOTf complex and free aldehyde. After comparison with the $\Delta\delta$(H3) data of a range of Lewis acids, as measured by Childs, it is clear that BF_2OTf is a very powerful Lewis acid, possessing a Lewis acidity that lies between those of BCl_3 and BBr_3.[10]

The success of the Morita–Baylis–Hillman-type reaction (Scheme 1) is tentatively attributed to a higher concentration of

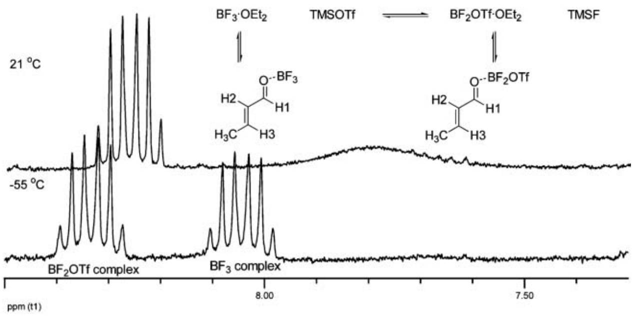
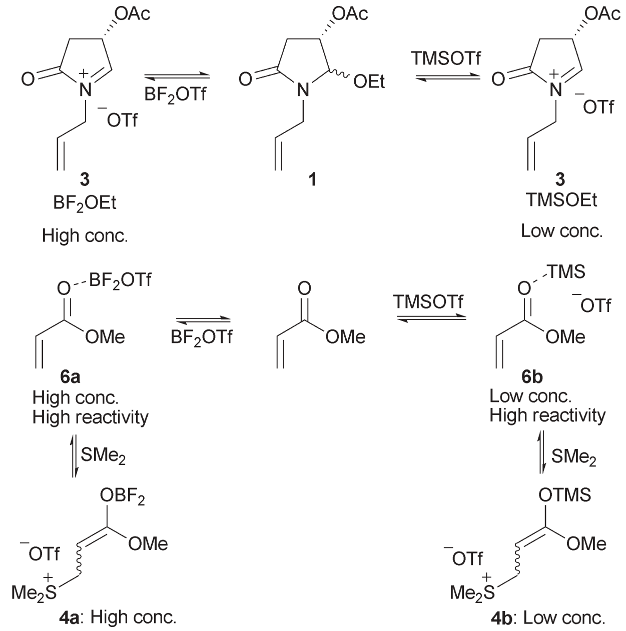


Fig. 5 Observance of a BF_2OTf–crotonaldehyde complex.



Scheme 3 Superiority of BF_2OTf over TMSOTf in synthesis.

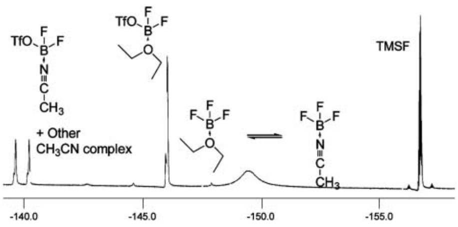


Fig. 6 ^{19}F NMR spectrum of $BF_3{\cdot}OEt_2$ and TMSOTf in CH_3CN.

iminium ion **3** and β-sulfonium enolate **4** due to the involvement of BF_2OTf. The above studies suggest that the superiority of BF_2OTf in achieving this is a reflection of its increased Lewis acidity over BF_3, the increased concentration of activated acrylate **6a**, and the increased stability (and thus concentration) of β-sulfonium enolate **4a** and BF_2OEt, the latter being a product of aminal fragmentation. Although TMSOTf-activated acrylate may be more reactive, its concentration is very low. Furthermore, the resultant silyl enol ether, **4b**, is less stable with respect to acrylate (Scheme 3).[12]

Since it has been demonstrated that mixtures of TMSOTf and $BF_3{\cdot}OEt_2$ in CH_3CN represent superior conditions for effecting glycosidation reactions,[2] the mixture in CH_3CN was also analysed by ^1H and ^{19}F NMR spectroscopy. The ^1H NMR spectrum (acquired with solvent suppression) showed TMSF, TMSOTf and two sets of etherate signals, the latter pair representing the BF_3 and BF_2OTf complexes. Integration revealed that **5** was present in much smaller proportions relative to $BF_3{\cdot}OEt_2$ ($\sim$3 : 1) in comparison to that observed in chlorinated solvents. Furthermore, the molar ratio of TMSF to **5** was 2.4 : 1. The reason for the anomalous integration value became clear following analysis of the ^{19}F NMR spectrum (Fig. 6). In addition to TMSF, $BF_2OTf{\cdot}OEt_2$ and a broad signal corresponding to rapidly exchanging $BF_3{\cdot}OEt_2$ and $BF_3{\cdot}CH_3CN$, the spectrum also contained two further ^{11}B-fluoride environments (140.2 and 139.7 ppm), which are tentatively assigned to $BF_2OTf{\cdot}CH_3CN$ and $[BF_2(CH_3CN)_2]^+OTf^-$.

When the Morita–Baylis–Hillman-type reaction (Scheme 1) was conducted in CH_3CN, the yield of **2** was substantially improved (85% yield). This can be attributed to the increased solvent stabilisation of ionic intermediates and/or $BF_2OTf{\cdot}CH_3CN$ being a more efficient transporter of Lewis acid to the substrate.

To conclude, we have demonstrated that in chlorinated solvents, $BF_3{\cdot}OEt_2$ and TMSOTf are in equilibrium with TMSF and $BF_2OTf{\cdot}OEt_2$. In CH_3CN, there is evidence for the competing complex $BF_2OTf{\cdot}CH_3CN$. BF_2OTf has a Lewis acidity similar to that of BCl_3/BBr_3, but with the advantage of being tolerant to a wide range of functional groups (the latter reagents can release nucleophilic halide, which may nurture unwanted processes). Our laboratory and others have demonstrated that the employment of such a mixture in synthesis can be more effective than the parent Lewis acids alone. We are currently investigating other applications, particularly harnessing the mixture's potential as a source of bidentate Lewis acid.

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Notes and references

1 *Lewis Acids in Organic Synthesis*, ed. H. Yamamoto, Wiley-VCH, Weinheim, 2000, vol. **1**; A. D. Dilman and S. L. Ioffe, *Chem. Rev.*, 2003, **103**, 733.

2 K. C. Nicolaou, C.-K. Hwang and M. E. Duggan, *J. Am. Chem. Soc.*, 1989, **111**, 6682; C. Y. Hong and Y. Kishi, *J. Am. Chem. Soc.*, 1991, **113**, 9693.

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4 ^1H NMR spectra were referenced to the residual solvent signal (7.27 ppm for $CDCl_3$), while the ^{19}F, ^{11}B and ^{31}P NMR spectra were externally referenced against CCl_3F, $BF_3{\cdot}OEt_2$ and H_3PO_4 (85%), respectively.

5 Gray, Jun and co-workers observed a similar phenomenon with mixtures of $BF_3{\cdot}OEt_2$ and TMSOMs while investigating conditions for the reductive cleavage of per-O-methylated D-glucans and D-fructans. Upon addition of 0.2 equivalents of $BF_3{\cdot}OEt_2$ to 1.0 equivalent of TMSOMs in $CDCl_3$, "in addition to the expected resonances of diethyl ether," the ^1H NMR spectrum exhibited signals corresponding to TMSF, TMSOMs and a new (OMs) signal: J.-G. Jun and G. R. Gray, *Carbohydr. Res.*, 1987, **163**, 247; J.-G. Jun, T. H. Ha and D.-W. Kim, *Tetrahedron Lett.*, 1994, **35**, 1235. Olah and co-workers have demonstrated that neat mixtures of BBr_3 or BCl_3 and silyl triflate undergo a similar ligand exchange process: G. A. Olah, K. Laall and O. Farooq, *Organometallics*, 1984, **3**, 1337.

6 Integration of the ^1H and ^{19}F NMR signals revealed a non-equimolar relationship between TMSF and the most downfield etherate or boron fluoride signal, respectively, favouring the former (1.25 : 1). Upon tilting the NMR tube, a transparent grainy material was observed adhering to the inner surface, suggestive of hydrolysed Lewis acid and/or a sparingly soluble **5**. Decantation of the mixture and introduction of fresh solvent confirmed that **5** is indeed sparingly soluble in $CDCl_3$.

7 Small amounts of Me_2SiF_2 ($\sim$2%) were also detected.

8 Fine coupling was not observed in the ^{19}F spectrum due to broadening.

9 The triethylphosphine oxide complex of BF_3 is known: M. A. Beckett, G. C. Strichland, J. R. Holland and K. S. Varma, *Polymer*, 1996, **37**, 4629.

10 R. F. Childs, D. L. Mulholland and A. Nixon, *Can. J. Chem.*, 1982, **60**, 801.

11 It is known that the addition of crotonaldehyde to a solution of TMSOTf results in a relatively small downfield shift of the H3 proton. On the other hand, the use of $TMSNTf_2$ results in a very large downfield shift [$\Delta\delta(H3) = 1.81$ ppm]: B. Mathieu and L. Ghosez, *Tetrahedron Lett.*, 1997, **38**, 5497.

12 The ^{31}P chemical shifts of the triethylphosphine oxide complexes formed from TMSOTf, $BF_2OTf{\cdot}OEt_2$ and $BF_3{\cdot}OEt_2$ suggest the following decreasing order of Lewis acidity: $TMS^+ > BF_2OTf > BF_3$. See the ESI† for spectra and a discussion.