Testing the Veracity of Claims of Lewis Acid Catalysis

Ivan Šolić, Hong Xuan Lin and Roderick W. Bates*

Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

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ABSTRACT

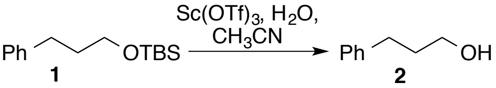
Are reactions employing Lewis acids really catalysed by those Lewis acids, or by "hidden Brønsted acids", i.e. Brønsted acids generated *in situ* by hydrolysis? Testing of a series of reactions using Sc(III), Fe(III), In(III) and Y(III) by addition of 2,6-di-*t*-butyl-4-methylpyridine reveal that all are likely to follow the latter pathway. A reaction claimed to be catalysed by CBr_4 through halogen bonding is also likely to be Brønsted acid catalysed.

1. Introduction

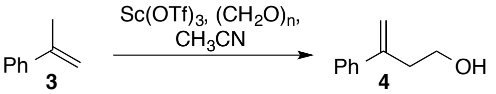
The introduction of the concept of Lewis acidity, as opposed to Brønsted acidity, had a profound effect on synthetic organic chemistry.[1] Numerous reactions, reagents and catalysts are based upon this concept. Many reagents employed as Lewis acids are metal salts. It is known that some salts can undergo hydrolysis *in situ* to generate a Brønsted acid. Thus, when such salts are used, it may be the case that they are not acting as Lewis acids, but as precursors for Brønsted acids, i.e. they may be pre-catalysts, and a so-called "hidden Brønsted acid" mechanism is operating. This has been demonstrated in a number of specific cases. In particular, Spencer *et al.* showed that this can operate in the context of aza-Michael additions.[2] Protonation has been demonstrated in metal "catalysed" hydroamination.[3] *In situ* generated Brønsted acid has been implicated in an intramolecular Friedel-Crafts reaction,[4] and in THP formation.[5] The participation of triflic acid derived from silver triflate has been established.[6] We have shown that this is the case in deoxygenative allylation of benzyl alcohols.[7] Despite these specific studies, there has not, to our knowledge, been a survey of reactions involving Lewis acids to screen for this phenomenon. A test is readily available: 2,6-di-*t*-butyl-4-methylpyridine is known to neutralise only Brønsted acids but not Lewis acids due to the steric crowding of the nitrogen lone pair.[8] Amongst others, Spencer,[2] Evans,[5] Vidović,[9] and Oestreich[10] as well as ourselves[7] have used this test.[11] Despite the availability of this simple test, the issue is "rarely alluded to".[10] We, therefore, set out to screen a series of reactions reportedly catalysed by Lewis acidic metal salts. While the independent verification (or otherwise) would appear to be a fundamental component of the scientific method, it appears to be the exception and not the rule in organic chemistry, especially in the context of mechanisms proposed in papers on synthetic methods.[12]

2. Results and Discussion

Our own experience with "hidden Brønsted acids" had been with $Sc(OTf)_3$, therefore we initially selected two simple, but useful, transformations in which this was claimed as a catalyst: one desilylation of TBS ether **1** (Scheme 1)[13] and one ene or Prins-type reaction (Scheme 2).[14] In each case, when the reaction was attempted in the presence of 2,6-di-*t*-butyl-4-methylpyridine, no conversion could be detected. We, therefore, conclude, that both of these reactions are really catalysed by *in situ* generated TfOH.[15]

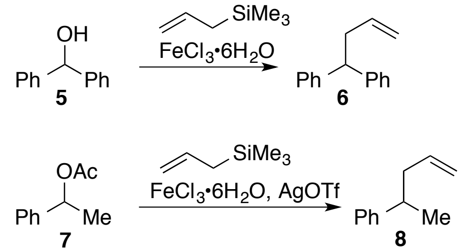


Scheme 1. Desilylation.

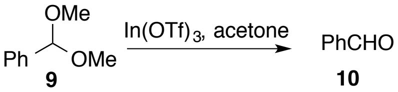


Scheme 2. Ene or Prins reaction.

We further examined two deoxygenative allylations of benzylic substrates **5** and **7**: one using $FeCl_3.6H_2O$[16] and one using $Fe(OTf)_3$ generated in situ from $FeCl_3.6H_2O$ and AgOTf (Scheme 3).[17] Again, each reaction failed to proceed in the presence of 2,6-di-*t*-butyl-4-methylpyridine indicating a hidden Brønsted acid mechanism. Indium salts have acquired a certain vogue in organic synthesis. We tested the reported indium(III) catalysed hydrolysis of acetal **9** (Scheme 4).[18] When the reaction was conducted in the presence of 2,6-di-*t*-butyl-4-methylpyridine, a mere trace of the aldehyde was detectable, although complete hydrolysis occurred under the same conditions in its absence. This, again, indicates that a hidden Brønsted acid mechanism operates and the true catalyst is HOTf.

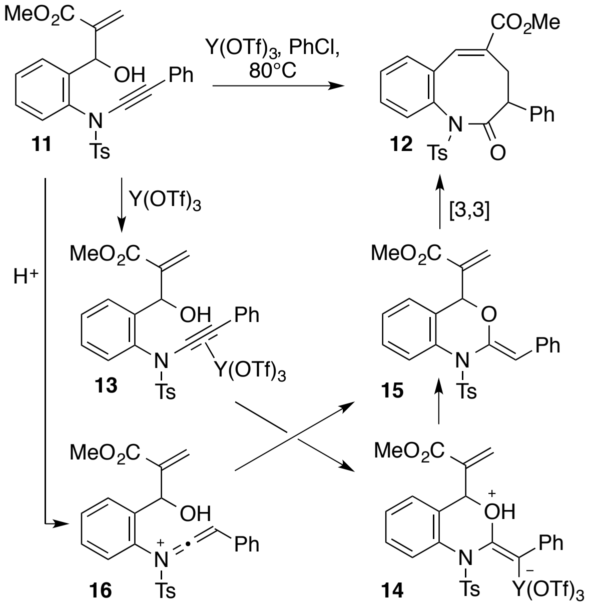


Scheme 3. Deoxygenative allylation.



Scheme 4. Acetal hydrolysis.

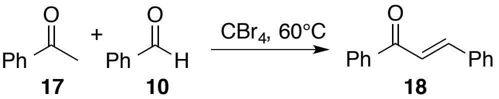
A spectacular yttrium(III) catalysed route to eight membered rings has recently been reported (Scheme 5).[19] The postulated mechanism involves formation of a η^1-vinyl yttrium species **14**, presumably arising from nucleophilic attack on a η^2-alkyne yttrium complex **13**.[20] The original report employed chlorobenzene as solvent. We found that the reaction works equally well in acetonitrile. Interestingly, when the reaction was carried out in chlorobenzene in the presence of 2,6-di-*t*-butyl-4-methylpyridine, the product **12** was still obtained in good yield. In contrast, repeating the cyclisation in acetonitrile in the presence of 2,6-di-*t*-butyl-4-methylpyridine resulted in a mere 20% conversion. It must be born in mind that when 2,6-di-*t*-butyl-4-methylpyridine reacts with a Brønsted acid, a new Brønsted acid, a pyridinium salt, is formed. Indeed, when ynamide **11** was treated with PPTS, complete conversion to the product **12** was observed. Ynamide **11** is, therefore, sufficiently acid sensitive that even a pyridinium salt is capable of catalysing this transformation. Ynamides are known to react with just carboxylic acids at room temperature.[21]



Scheme 5. Eight membered ring formation.

Although the 2,6-di-*t*-butyl-4-methylpyridine test is not as clear cut in this case as in the others, the operation of Occam's razor demands that the simplest explanation of this set of cyclisation experiments is that the reaction is Brønsted acid catalysed.[22] The initial cyclisation step would, therefore, be on ketene iminium ion **16**, giving **15** after deprotonation. This also illustrates that experiments with 2,6-di-*t*-butyl-4-methylpyridine as a test reagent must be interpreted with care.

Halogen bonding has been promulgated in recent years as a new method to facilitate reactions.[23] The concept is that vacant orbitals associated with the halogen atom accept electron density from the substrate i.e. they act as Lewis acids. To the best of our knowledge, the possibility of hidden Brønsted acid catalysis has not been suggested in this context. Recently, it has been reported that carbon tetrabromide can catalyse the Claisen-Schmidt condensation of acetophenones, such as **17**, with aromatic aldehydes, such as **10**, through halogen bonding (Scheme 6).[24] When this reaction was tested in the presence of 2,6-di-*t*-butyl-4-methylpyridine, no conversion could be detected. It therefore appears likely that the true catalyst is HBr. As commercially available CBr_4 is often supplied containing 5-10% water, hydrolysis on long term storage appears likely.



Scheme 6. Claisen-Schmidt condensation.

3. Conclusion

For all of the reactions examined in this study, the evidence strongly suggests that a hidden Brønsted acid mechanism operates in each case. It seems likely that this is also the case for many other reactions for which Lewis acid catalysis has been claimed or implied. It should be further noted that this phenomenon is not limited to metal triflates, although it is most often observed in such cases. The results presented here do not detract from the synthetic utility of the reported procedures. Indeed, the use of a metal salt as a Brønsted acid precursor may in some cases be more convenient than the use of the same acid directly. Nevertheless, a correct understanding of the mechanism is not only intellectually important, but also essential for further developments, such as asymmetric variants or use in flow chemistry. In addition, as hydrolysis and activity may vary with water content,[7] the reproducibility of the reported procedures may be in question.

4. Experimental section

All experiments were carried out as reported in the original literature, then repeated in the presence of 2,6-di-*t*-butyl-4-methylpyridine (10 mol%).

Acknowledgments

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Supplementary Material

^{1}H NMR spectroscopic results for all experiments (PDF file).