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Testing the Veracity of Claims of Lewis Acid Catalysis

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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 employing Lewis acids indicated that the true catalyst is HOTf, through halogen bonding.

1. Introduction

The introduction of the concept of Lewis acidity, as opposed to Brønsted acidity, had a profound effect on synthetic organic chemistry. 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. Protonation has been demonstrated in metal “catalysed” hydroamination. In situ generation has been implicated in an intramolecular Friedel-Crafts reaction, and in THP formation. The participation of triflic acid derived from silver triflate has been established. We have shown that this is the case in deoxygenative allylation of benzyl alcohols. 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. Amongst others, Spencer, Evans, Vidovic, and Oestreich have used this test. Despite the availability of this simple test, the issue is “rarely alluded to”. We, therefore, set out to screen a series of reactions reported as being catalysed by Lewis acid 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.

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) and one ene or Prins-type reaction (Scheme 2). 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.

We further examined two deoxygenative allylations of benzyl substrates 5 and 7: one using FeCl₃.H₂O and one using Fe(OTf)₃, generated in situ from FeCl₃.H₂O and AgOTf (Scheme 3). 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). 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 1. Desilylation.

Scheme 2. Ene or Prins reaction.
A spectacular yttrium(III) catalysed route to eight membered rings has recently been reported (Scheme 5). 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. 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-tert-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-tert-butyl-4-methylpyridine resulted in a mere 20% conversion. It must be born in mind that when 2,6-di-tert-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.

Although the 2,6-di-tert-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. 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-tert-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. 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 acetoephonenes, such as 17, with aromatic aldehydes, such as 10, through halogen bonding (Scheme 6). When this reaction was tested in the presence of 2,6-di-tert-butyl-4-methylpyridine, no conversion could be detected. It therefore appears likely that the true catalyst is HBr. As commercially available CBr₄ is often supplied containing 5-10% water, hydrolysis on long term storage appears likely.

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, 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-tert-butyl-4-methylpyridine (10 mol%).

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References and notes

Supplementary Material

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