

Introduction

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Are enzymatic reactions really good models for laboratory chemical reactions? An enzyme is a giant molecule, large enough to support a substrate, whereas chemical reagents are composed of much smaller molecules. Still, the much smaller molecular apparatus of human-made reagents is expected to induce reactions with selectivities comparable to those of a large enzyme. Clearly, the design of new reagents requires careful abstraction and simplification of the true mechanism of an enzyme, much like the design of an aircraft might be based on the aerodynamics of a bird.

A case in point is the important role of hydrogen bonding during enzymatic reactions. In the course of such processes, the giant template of the enzyme will specify quite accurately the position and direction of a proton for hydrogen bonding, before and after the reaction. However, a proton by itself cannot behave in this fashion. A perfect sphere, it has no directional selectivity for hydrogen bonding outside the domain of the enzyme, thus it is unable to act as a 'delicate finger' in an ordinary organic reaction as it does in the enzymatic transformation. It is natural to wonder whether an appropriate substitute for the proton might induce human-made reactions capable of selectivities comparable to those afforded by enzymes.

An excellent candidate as a proton substitute is a Lewis acid. The observation that organoaluminium, organolithium, organoboron and many other organometallic compounds immediately ignite when exposed to air, reflecting the high affinity of these metals for oxygen, inspired us to devise a new series of reagents based on those metals: true 'Designer Lewis Acids' for organic synthesis. For example, since an organoaluminium compound would have three ligands around the metal, the structural design of such a catalyst could be quite flexible. The goal, then, was to engineer an artificial proton of a special shape, which could be utilized as an effective tool for chemical reactions, by harnessing the high reactivity of the metal atom towards oxygen. Such a concept was initially researched by examining the influence of specially designed Lewis acid compounds.

In the *Encyclopedia of reagents for organic synthesis* edited by Paquette,

the reagent function index listed the following metals as being used as Lewis acid reagents:¹

Aluminum, Antimony, Boron, Cadmium, Cerium, Cobalt, Copper, Europium, Germanium, Hafnium, Iron, Lanthanum, Lithium, Magnesium, Molybdenum, Nickel, Palladium, Phosphorus, Silicon, Silver, Sulfur, Thallium, Tin, Titanium, Vanadium, Ytterbium, Zinc, Zirconium

A truly varied group of elements are used as the Lewis acid reagent and each metal has its own characteristic features. We therefore decided in this book to classify these reagents according to their metals.

It need not be pointed out that Lewis acid-promoted carbon-carbon bond formation reaction is one of the most important processes in organic synthesis. Classically, Friedel-Crafts reaction, ene reaction, Diels-Alder reaction, and Mukaiyama aldol synthesis are catalysed with ordinary Lewis acids such as AlCl_3 , TiCl_4 , $\text{BF}_3 \cdot \text{OEt}_2$, or SnCl_4 (Fig. 1.1). These classical Lewis acids activate the functional groups of substrates, and the reactions proceed in relatively low stereo-, regio-, or chemoselectivities. On co-ordination with well-designed ligand(s), a Lewis acid exhibits substantially new reactivity. Furthermore, a designer Lewis acid leads to an isolation of monomeric Lewis acid species whose structural features can be easily understood and easily extended to designer chiral catalysts for asymmetric syntheses. Thus, metal ligand tunings are the most essential component in the design of Lewis acid reagents.²⁻⁴

Lewis acid-mediated reactions can be classified as follows. The complex between substrate and Lewis acid rearranges to produced the product (type 1).

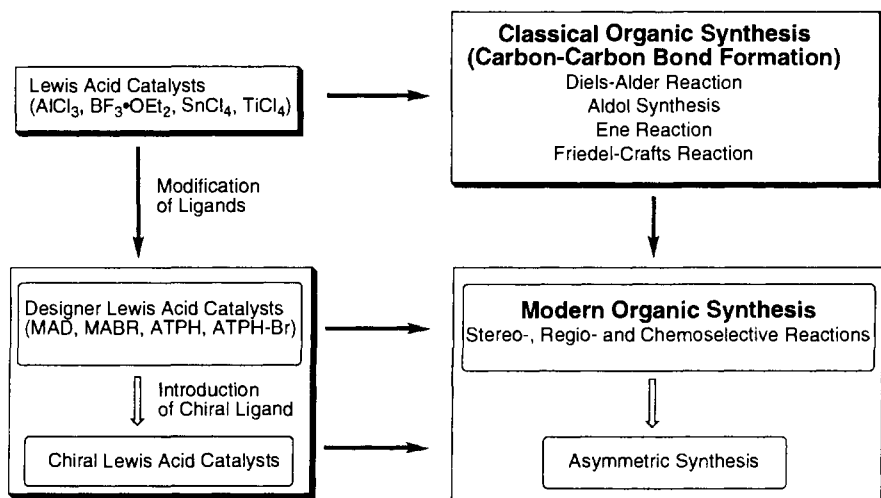


Fig. 1.1 Role of Lewis acid in organic synthesis.

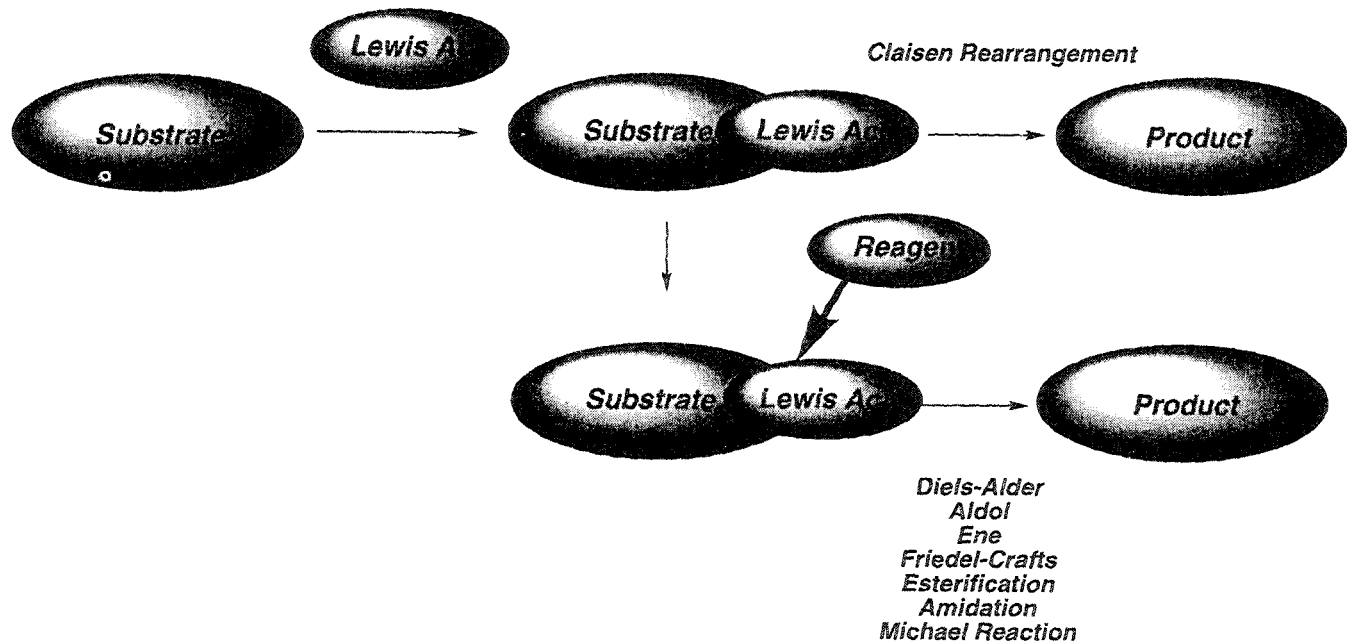


Fig. 1.2 Classification of Lewis acid promoted reactions.

Claisen rearrangement promoted by Lewis acid catalyst is a typical example of type 1. On the other hand, some complexes between Lewis acids and substrates are stable enough and the formed complexes react with a variety of reagents from outside the system to generate the product (type 2). The reaction between the Lewis acid activated unsaturated carbonyl compounds with dienes, Diels–Alder reaction, is an example of type 2 (see Fig. 1.2).

A Lewis basic carbonyl group can be activated through co-ordination with a metal-centred Lewis acid, with profound reactivity and stereochemical consequences. In the context of asymmetric synthesis, many of the Lewis acid-mediated reactions are known to proceed with improved stereoselectivities as compared to their non-catalysed counterparts; very recently, a number of chiral Lewis acids have been used as remarkably efficient catalysts for carbonyl addition processes. Although the origins of many of the effects brought about by Lewis acids are still poorly understood, it is clear that the conformational preferences of the Lewis acid carbonyl complex are ultimately responsible for determining the stereochemical course of Lewis acid-mediated reactions.^{5,6}

References

1. Paquette, L. A. (ed.) *Encyclopedia of reagents for organic synthesis*, John Wiley & Sons, Chichester, New York, Brisbane, Toronto, Singapore, **1995**.
2. Schinzer, D. (ed.) *Selectivities in Lewis acid promoted reaction*, Kluwer Academic Publishers, Dordrecht, Boston, London, **1988**.
3. Sasntelli, M.; Pons, J.-M., *Lewis acids and selectivity in organic synthesis*, CRC Press, Boca Raton, New York, London, Tokyo, **1996**.
4. *Methods of Organic Chemistry* (Houben-Weyl), Additional and Suppl. Vol. of the 4th Edn, Vol. E 21b; *Stereoselective Synthesis* (ed. G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**.
5. Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 256.
6. Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.*, **1993**, **115**, 3133.