Lewis Acid Reagents

A Practical Approach

Edited by

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Preface

Lewis acids are becoming a powerful tool in many different modern reactions, such as the Diels-Alder reactions, Ene reactions, Sakurai reactions, and Aldol synthesis. In fact, the importance and practicality of Lewis acid reagents as valuable means of obtaining a variety of organic molecules is now fully acknowledged by chemists in the synthetic organic society. This prominence is due to the explosive development of newer and even more efficient methods during the last decade, and the numbered publications on these reagents is actually increasing exponentially each year. Research on asymmetric synthesis has become more important and popular in the total synthesis of natural products, pharmaceuticals, and agricultural agents, and Lewis acid chemistry plays a major role in this arena.

Comprehensive coverage of the literature on each area of Lewis acid is not necessarily provided here. Rather, the aim of the book is to furnish a detailed and accessible laboratory guide useful for researchers who are not familiar with the benefits of Lewis acids. It includes information on reagent purification, reaction equipment and conditions, work-up procedures, and other expert advice. The primary goal is thus to dispel the mystery surrounding Lewis acid reagents and to encourage more scientists to use these powerful synthetic tools to maximum effect. The book contains 14 independently referenced chapters describing a variety of Lewis acids using different metals. Each metal has different characteristic features of reagent preparation and practicality which clearly described in that chapter.

I would like to thank Professor K. Ishihara for helping to check parts of the manuscripts and for useful suggestions. I would also like to express my personal gratitude to all of the invited contributors who carefully honored the deadlines and thus made the editorial job much easier.

It is my strong hope that this book will be found an invaluable reference for graduate students as well as chemists at all levels in both academic and industrial laboratories.

Nagoya H. Y.
October 1998

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Contents

1

Introduction

HISASHI YAMAMOTO

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 $AlCl_3$, $TiCl_4$, $BF_3{\cdot}OEt_2$, 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).

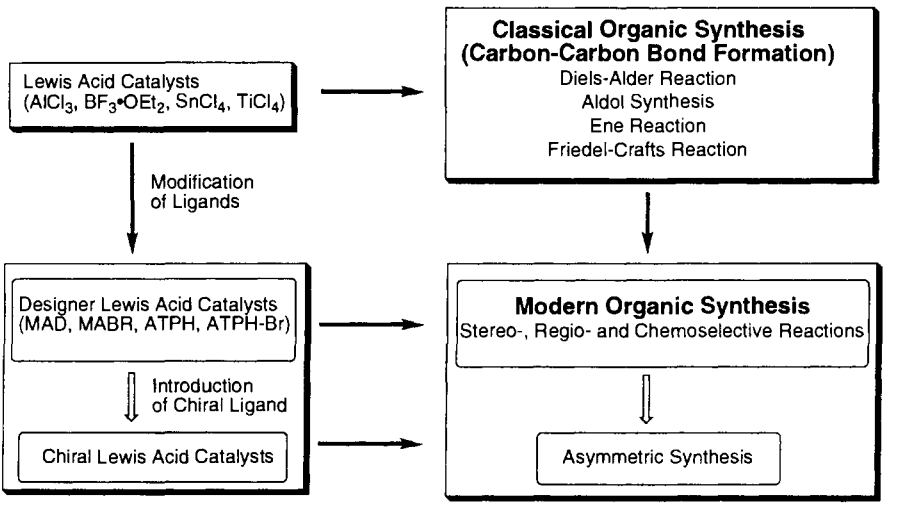

Fig. 1.1 Role of Lewis acid in organic synthesis.

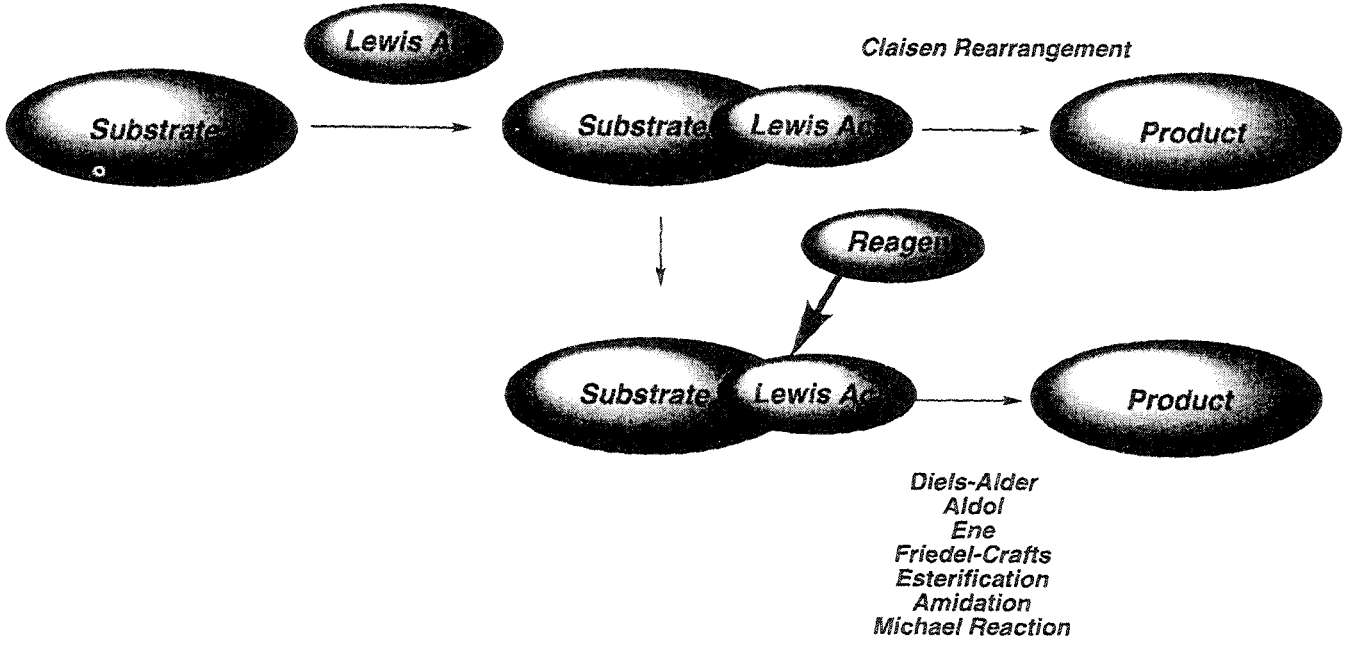

Fig. 1.2 Classification of Lewis acid promoted reactions.

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]

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2

Synthetic utility of bulky aluminium reagents as Lewis acid receptors

KEIJI MARUOKA

1. Introduction

Organoaluminium compounds, little known until the 1950s, have been widely accepted and increasingly important in the field of industry and in the laboratory,[1–13] particularly after K. Ziegler and colleagues discovered the direct synthesis of trialkylaluminiums and their brilliant application to the polymerization of olefins.[14,15] The chemistry of organoaluminium compounds has been understood in terms of the Lewis acidity of their monomeric species, which is directly related to the tendency of the aluminium atom to complete electron octets. Organoaluminium compounds possess a strong affinity for various heteroatoms in organic molecules, particularly oxygen. In fact, bond strength of aluminium and electronegative atoms such as oxygen is extremely strong; the bond energy of the Al–O bond is estimated to be 138 kcal mol^{-1}. In view of this high bond strength, most organoaluminium compounds are particularly reactive with oxygen and often ignite spontaneously in air. Accordingly, they easily generate 1:1 co-ordination complexes even with neutral bases such as ethers, which is in marked contrast with lithium and magnesium derivatives. Utilization of this property, commonly identified with 'oxygenophilicity', in organic synthesis allows facile reactions with hetero atoms particularly oxygen- and carbonyl containing compounds.

$$Me_3Al + Et_2O \rightarrow Me_3Al \cdots OEt_2 \qquad \Delta Hf = -20.21 \text{ kcal mol}^{-1}$$

The major difference between organoaluminium compounds and more common Lewis acids such as aluminium chloride and bromide is attributable to the structural flexibility of organoaluminium reagents. Thus, the structure of an aluminium reagent is easily modified by changing one or two of its ligands. Described below are our recent practical strategies to selective organic synthesis with modified organoaluminium reagents.

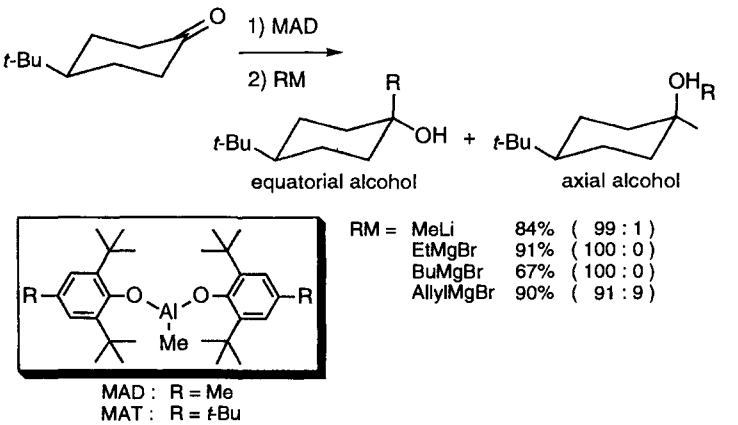
2. Amphiphilic alkylations

2.1 Amphiphilic carbonyl alkylations

Organoaluminium compounds are endowed with high oxygenophilic character, and hence are capable of forming long-lived monomeric 1:1 complexes with carbonyl substrates. For example, the reaction of benzophenone with Me_3Al in a 1:1 molar ratio gives a yellow, long-lived monomeric 1:1 species

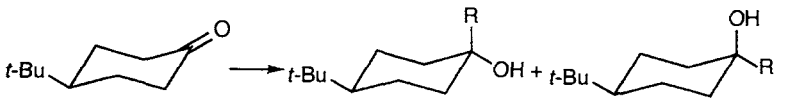
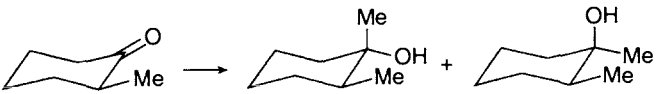
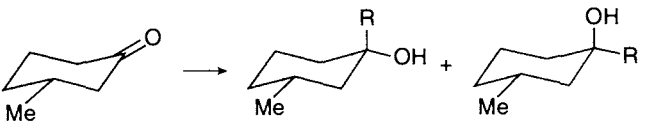
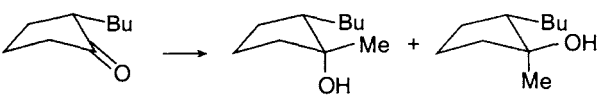
$$Ph_2C{=}O \xrightarrow[25\,^\circ C]{Me_3Al} \underset{\text{yellow complex}}{[Ph_2C{=}O \cdots AlMe_3]} \xrightarrow[80\,^\circ C]{} Ph_2\overset{\displaystyle Me}{\overset{|}{C}}{-}OAlMe_2$$

which decomposed unimolecularly to dimethylaluminum 1,1-diphenylethoxide during some minutes at 80 °C or many hours at 25 °C.[16] This unique property may be utilized for stereoselective activation of the carbonyl group. Among various organoaluminium derivatives examined, exceptionally bulky, oxygenophilic organoaluminium reagents such as methylaluminium bis(2,6-di-*tert*-butyl-4-alkylphenoxide) (MAD and MAT), have shown excellent diastereofacial selectivity in carbonyl alkylation.[17,18] Thus, treatment of 4-*tert*-butyl cyclohexanone with MAD or MAT in toluene produced a 1:1 co-ordination complex which on subsequent treatment with methyl-lithium or Grignard reagents in ether at −78 °C afforded the equatorial alcohol almost exclusively (Scheme 2.1). Methyl-lithium or Grignard reagents solely undergo preferential equatorial attack yielding axial alcohols as the major product. MAD and MAT have played a crucial role in the stereoselective synthesis of hitherto inaccessible equatorial alcohols from cyclohexanones as shown in Table 2.1.

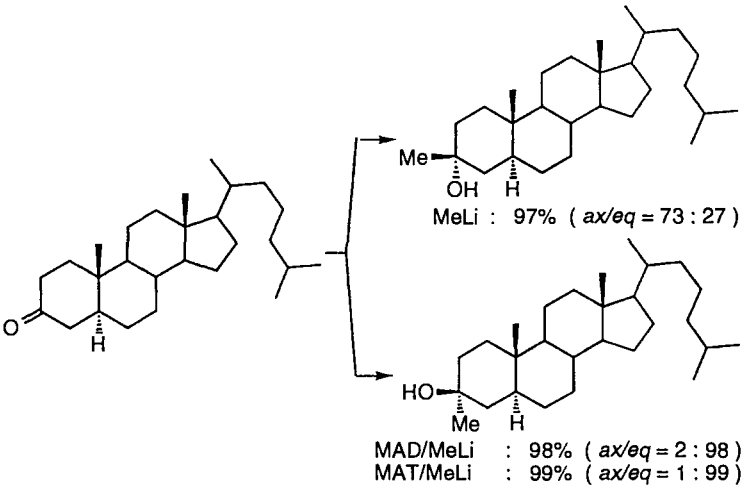


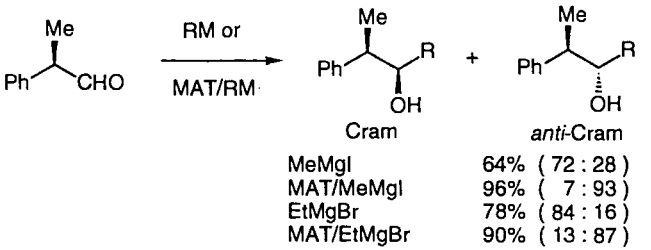
Scheme 2.1

Table 2.1 Stereoselective alkylation of cyclic ketones

Entry	Alkylation agent	Chemical yield (ax/eq ratio)
		
1	MeLi	75% (79 : 21)
2	MAD/MeLi	84% (1 : 99)
3	MAT/MeLi	92% (0.5 : 99.5)
4	EtMgBr	95% (48 : 52)
5	MAD/EtMgBr	91% (0 : 100)
6	BuMgBr	58% (56 : 44)
7	MAD/BuMgBr	67% (9 : 100)
		
8	MeLi	73% (92 : 8)
9	MAD/MeLi	84% (14 : 86)
10	MAT/MeLi	80% (10 : 90)
		
11	MeLi	80% (83 : 17)
12	MAD/MeLi	69% (9 : 91)
13	MAT/MeLi	95% (3 : 97)
14	BuMgBr	86% (79 : 21)
15	MAD/BuMgBr	75% (1 : 99)
		
16	MeLi	77% (75 : 25)
17	MAD/MeLi	82% (1 : 99)

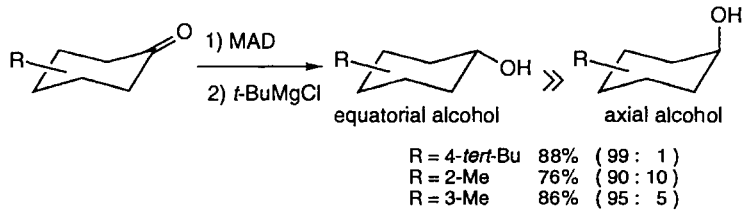
This approach has been quite useful in the stereoselective alkylation of steroidal ketones. Reaction of 3-cholestanone with MeLi gave predominantly 3β-methylcholestan-3α-ol (axial alcohol), whereas amphiphilic alkylation of the ketone with MAD/MeLi or MAT/MeLi afforded 3α-methylcholestan-3β-ol (equatorial alcohol) exclusively (Scheme 2.2). In addition, unprecedented *anti*-Cram selectivity was achievable in the MAD- or MAT-mediated alkylation of α-chiral aldehydes possessing no ability to be chelated.





Scheme 2.2

In contrast to the facile MAD- or MAT-mediated alkylation of cyclic ketones with primary organolithium or Grignard reagents, reduction takes precedence over alkylation with hindered alkylation agents such as *t*-butylmagnesium chloride in the presence of MAD[18] (Scheme 2.3). This amphiphilic reduction system appears to be complementary to the existing methodologies using L-Selectride for obtaining axial selectivity.



Scheme 2.3