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Electrophile and Lewis Acid

Edited by Takashiro Akitsu

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Meet the editor

Takashiro Akitsu, Ph.D., is a professor in the Department of Chemistry, Faculty of Science Division II, Tokyo University of Science, Japan. He obtained his Ph.D. in Physical and Inorganic Chemistry from Osaka University, Japan, in 2000. Dr. Akitsu studied at the Institute for Protein Research, Osaka University (metalloproteins), Keio University, Japan (photo and magnetic functional organic/inorganic hybrid compounds), and Stanford University, USA (physical and bioinorganic chemistry) before moving to the Tokyo University of Science. He has published 220 articles and book chapters. He has also served as an editorial board member and peer reviewer for many journals and was involved in the organizing committees for several international conferences.

Contents

Preface

One of the important principles or basic driving forces of chemical reactions is a charge. In common organic chemistry, electropositive (electron deficient) functional groups react with electronegative (electron-rich) demanding reactions. A similar situation is the bond formation between reagents where the concept of Lewis acids and bases applies. Synthesis of metal complexes often involves electrophilic or nucleophilic reactions of organic ligands and acid/base (catalytic) reactions.

It goes without saying that the transfer of "electrons" in a chemical reaction is an important factor in terms of bond formation and understanding of the reaction mechanism. This book focuses on the electron-receiving side and specializes in chemistry related to "electrophiles" and more extended "Lewis acids."

It should be noted that the chemical terms nucleophile and electrophile are more or less interchangeable with Lewis base and Lewis acid, respectively. In general, an electrophile is a chemical species that forms bonds with nucleophiles by accepting an electron pair. Electrophiles mainly interact with nucleophiles through addition and substitution reactions in organic reactions. Because electrophiles accept electrons, they are essentially Lewis acids.

Furthermore, Lewis acid is a chemical species that contains an empty orbital that is capable of accepting an electron pair from a Lewis. This concept also forms the basis of metal ions–ligands (Lewis base having a lone pair) coordination bond in metal complexes. In this way, the formation of coordination bonds between ligands and metal ions involves the process of association between Lewis bases and Lewis acids. As a concrete example of the concept of this book, this outlines the conditions for a new synthetic method targeting metal complexes.

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Chapter 1

Introductory Chapter: Electrophile and Lewis Acid

Shunsuke Aoki, Asaki Ishizuka, Daisuke Nakane
and Takashiro Akitsu

1. Introduction

Synthesis of metal complexes often involves electrophilic or nucleophilic reactions of organic ligands and acid/base (catalytic) reactions. Furthermore, the formation of coordination bonds between ligands and metal ions essentially involves the process of association between Lewis bases and Lewis acids (**Figure 1**). As a concrete example of the concept of this book, this chapter outlines the conditions for a new synthetic method targeting metal complexes.

Microfluidic device may be a tool for precise and systematic control of energy propagation in minute solutions [1, 2]. The solution in the channel becomes a Hagen–Poiseuille flow with a parabolic streamline distribution due to friction with the inner wall of the microchannel, causing collisions of molecules inside; the solution is mixed at a high speed at the same time as the molecular motion in the solution is activated, and a reaction field can be constructed in which the temperature of the solution is instantaneously switched. Inertial force and viscous force are related, and the smaller the container size, the shorter the solution mixing time. Such system may also be effective for weak intermolecular interactions recently.

We have reported the conventional synthesis of azo-salen type manganese(II) complexes in three steps [3]. Accurate pH control and adjustment of the reaction temperature are indispensable in this synthesis, and the reaction takes about 4 h. Synthetic experiments showed that both the conventional method and the microfluidic device method succeeded in obtaining azo compounds. This result proves that it is possible to synthesize azo compounds under mild pH control using a microfluidic device. In addition, by using a microfluidic device, the chemical reaction was promoted, and the reaction proceeded even with low-concentration hydrochloric acid. In addition, temperature control was unnecessary in microfluidic devices because reactions occur at interfaces. In steps II and III, the microfluidic device was operated at room temperature, and the conventional method was performed at 40°C. In addition, the conventional method required a reaction time of 4 h, but the microfluidic reaction was completed in less than 1 sec. Furthermore, the synthesis by the conventional method had to be performed in a nitrogen atmosphere, but it was possible to perform it in an air atmosphere by using microfluidics.

On the other hand, a reaction system fuses and dissociates “droplets” flowing through a microfluidic device with a nano-scale level solvent and reacts them [4, 5]. Microfluidic devices are tools that can precisely and systematically control energy propagation in microfluidic solutions. We would like to create a reaction system that fuses and dissociates droplets flowing through a microfluidic device and reacts and

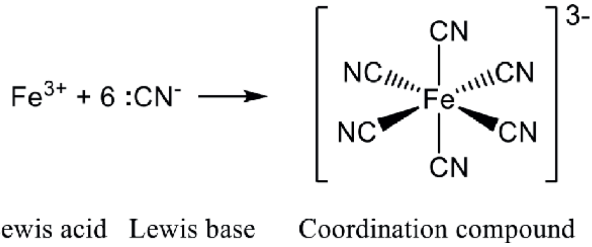

Figure 1.
Formation of coordination compounds from Lewis acid and Lewis base.

separates them in a nanoscale solvent. To demonstrate the usefulness of microfluidic devices/droplet synthesis, it is necessary to synthesize them.

In our laboratory, organic solvents are used to prepare and form single crystals of rare earth complexes of Schiff base. Since crystals are formed by volatilizing the organic solvent in the solution, there is a risk of leakage. Indeed, the results of environmental measurement in our laboratory may potentially suggest both fire and health hazards. When organic solvents volatilize to fill a room of laboratory, the vapor is harmful to human health.

In this context, information or knowledge of "interfacial organic solvents" used in preparation (two layers in test tubes) and crystallization (mutually dissolving solvents and solutes, vapor diffusion method) will be important or useful for experimental design of microfluid preparation devices in the near future. From the viewpoint of such analogy, in this chapter, we will present chemistry using interfacial organic solvents taken from our conventional experiments.

Herein, we present several examples that are difficult to synthesize in conventional ways. In order to demonstrate the usefulness of microfluidic/droplet synthesis, search for examples that cannot (or are difficult to) be synthesized in a beaker work (normal scale preparations) should be carried out. Comparing examples of metal complexes synthesized and crystallized at the interface of two solvents, we will study the accumulation of difficult conditions (so-called 'negative data') for synthesis by changing metals and substituents of salen-type lanthanide complexes that can be synthesized and crystallized depending on the metals.

2. Results

At first, preparations of metal complexes using two solutions systems are mentioned below.

These two-solvent cyano-bridged manganese salen complexes can be easily synthesized at the solution interface [6, 7]. However, if the substituents (X, Y) in aldehyde precursors and synthesis method are changed even slightly from the previously reported methods, conventional synthesis becomes difficult (**Figure 2**). Porous coordination polymers composed of metal ions and cyano groups exhibit magnetism, charge transfer, proton conductivity, etc. derived from metal ions. There are some expected advantages as follows: It is easy to design and synthesize. Previous studies with large spaces at the outer methoxy groups showed that the redox potential of salen complexes shifted due to substituent effects. Since there is a large space at the 3,3′-positions, it is possible to introduce a substituent to further construct the reaction space.

By slight modification of preparation conditions, many trials resulted in failure unfortunately, which are as follows:

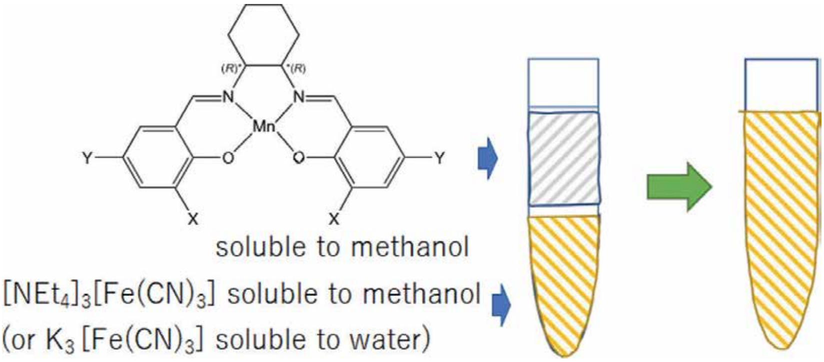

Figure 2.
Conventional preparation of cyano-bridged manganese salen complexes.

The pH adjustment (metal source is chloride and triethylamine, and no combination of pH > 7 is possible) was not appropriate. In addition, we were concerned about whether the deprotonation of phenol is possible and whether the form of manganese(II) ion exists (heating/stirring). (What are the stable species in the E vs. pH diagram?) What is the nature of the hydrolysis of the salt ($MnCl_2$) of a weak base ($Mn(OH)_2$) and a strong acid (HCl)? If no crystals precipitate, the concentration of the solution may be too low. The pH adjustment (metal source is chloride and triethylamine and impossible to combine pH > 7) was not proper. In addition, whether the deprotonation of phenol is possible and what is the mode of existence of manganese(II) ions (**Figure 3**)?

What is the nature of the hydrolysis of the salt ($MnCl_2$) of a weak base ($Mn(OH)_2$) and a strong acid (HCl)? From the beginning of ligand synthesis using manganese acetate, it should not make sense to add a counter anion (ClO_4^-). Here, methanol was used as the solvent and heated to 40°C. If manganese(II) is not oxidized to manganese(III), hexacyanoferrate(III) acid (anion) will not bind either. In rare cases, manganese(III) was generated during stirring (nitrate ions contained in the crystals were confirmed).

From the beginning of the ligand synthesis using manganese(II) acetate, even if counter anion (ClO_4^-) is added, it is meaningless. Here, the solvent used was methanol, which was heated to 40°C. If manganese(II) is not oxidized to manganese(III), hexacyanoferrate(III) acid (anion) also does not bind (**Figure 4**). In rare cases,

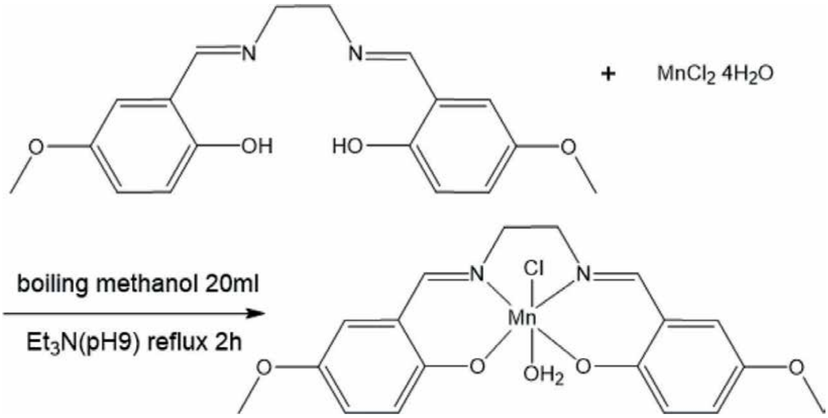

Figure 3.
Failure due to pH adjustment and redox of manganese(II) ion.

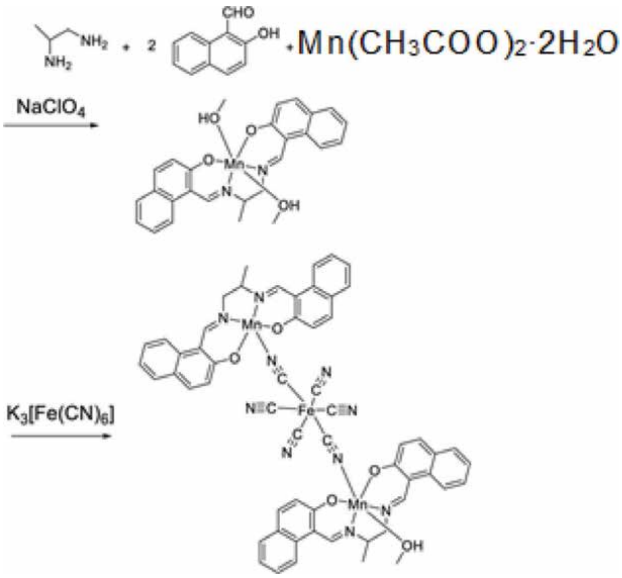

Figure 4.
Failure due to ClO_4^- ion.

manganese(III) was formed during stirring (which was confirmed nitrate ions included in the crystal).

Potassium hexacyanoferrate(III) is soluble in water and in methanol, but it is not necessary. Nitrogen does not oxidize or reduce iron(III) for cations that are soluble in methanol under a nitrogen atmosphere. Synthetic method for obtaining manganese(III) complexes, in one pot, ClO_4^- (−1 valence, acid) for isolation of salen-type manganese(III) complexes is added at the same time. Manganese(III) acetate alone is weakly acidic with acetate ions, and the added strong acid prevents deprotonation of phenol and inhibits coordination to manganese(III) ions. Furthermore, the ClO_4^- anion is more crystalline than the counterion and hexacyanoferrate(III) acid, which precipitates good ionic crystals. Therefore, it is difficult to form a cyano-bridged complex by such modified methods in contrast to established methods (**Figure 5**).

As for Schiff base lanthanide complexes, by the way, we have reported successful synthesis and crystal structure as well as crystallization of salen-type Schiff base mononuclear samarium(III) (or terbium(III)) complexes. These complexes were suitably prepared in methanol solutions by the conventional method [8]. Synthesis consisted of

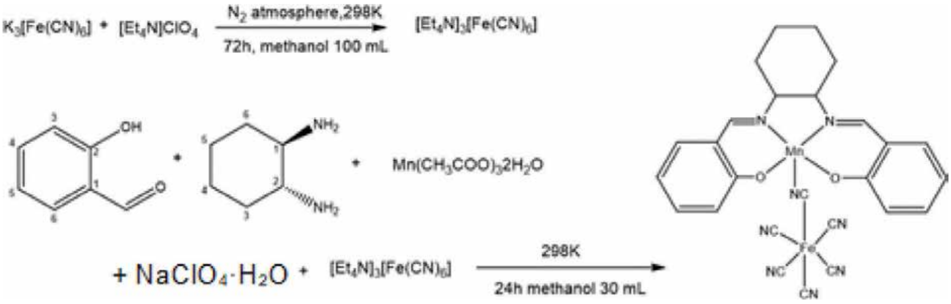

Figure 5.
Established methods of this preparation.

Figure 6.
Preparation of Schiff base lanthanide complexes. Hydrates and bases were not presented for clarity.

azo synthesis by diazo coupling with vanillin and aniline using the existing method, followed by Schiff base condensation with diphenylethylenediamine to synthesize ligands. The azo-free version was obtained by direct Schiff base condensation of *O*-vanillin and (chiral or racemic) diphenylethylenediamine without diazo coupling (**Figure 6**).

However, the formation of metal complexes was dependent on ligands or lanthanide metals in this series of complexes, which may be slightly different because of preparation conditions. In the presence of lanthanide(III) metal sources in methanol solution, only some ions were able to form salen-type complexes with two ligands. In the case of the cerium(III) complex, f-f transitions were not observed both with and without azo groups; in the neodymium(III) complex, both f-f transitions were observed; and in the dysrosium(III) complex, f-f transitions were observed only

	La	**Ce**	**Pr**	**Nd**	**Sm**	**Gd**	**Dy**	**Ho**	**Er**	**Tm**	**Yb**	**Lu**
Azo free	×	×	○	○	○	×	○	○	×	○	○	×
With azo	×	×	×	○	×	×	×	×	×	○	○	×

Table 1.
Summary of complexation of Schiff base lanthanide complexes (O: Success, X: Failure).

Figure 7.
Poor crystals.

without azo-groups. The results were able to be divided it into 3 patterns (**Table 1**). This is thought to be caused by differences in the ability of lanthanide(III) ions to form complexes with the same ligand, which are known in solvent extraction systems and differences in the hydrophobicity of azobenzene groups.

Investigation of poor solvents to test the vapor diffusion method was also carried out using diethyl ether, hexane, and toluene corresponding to azo-free dysrosium(III) complex. Toluene is useless because the substance inside turns into oil. When methanol and diethyl ether were used, grainy crystals appeared, but they did not appear to be single crystals (**Figure 7**).

3. Summary and perspective

To demonstrate the utility of microfluidic/droplet synthesis (two solvent systems), I'm looking for examples that cannot (or are difficult to) be synthesized in a beaker work. In particular, we will scrutinize examples of metal complexes that are synthesized and crystallized at the interface of two solvents, which are positioned as models of droplet synthesis in green chemistry, and organize viewpoints that should be considered. At the same time, some general knowledge about solvents is presented. In this review, we present the process of accumulating negative data for the synthesis of cyano-bridged iron and Schiff base salen-type manganese complexes and a series of salen-type lanthanide complexes. Schiff base ligand that can be synthesized and crystallized by metals and substituents (from hydrates) by changing various conditions, namely, solutions, will be discussed.

Microdroplet synthesis is expected to enable preparation under mild conditions in a short period of time. (These failure examples may be good examples for searching compounds and reaction conditions.) Slight modifications of the two solution reactions can be difficult to prepare and may be attractive targets for microdroplet methods. "Nanoscale thermodynamics" has not yet been established, but there may be useful hints in the field of basic chemistry.

Acknowledgements

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Chapter 2

Lewis Acidic Boron Reagents: Recent Advancement and Applications

Ababay Ketema Worku and Temesgen Atnafu Yemata

Abstract

Recently, the enthalpies of formation computed for different Lewis acid complexes of unsaturated molecules (e.g., aldehydes, imines, alkynes, and alkenes) offer a way to assess the suitability of a specific catalyst in a catalytic reaction. Main-group chemistry, in particular boron chemistry, which has resulted in a multitude of novel discoveries is one area of organometallic chemistry that has made significant strides during the past 20 years. In this review, the recent developments and applications of well-proven chemicals like tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) which has shown widespread applicability in a variety of chemistry have been discussed. Additionally, a number of brand-new Lewis acidic boranes and borocations have recently been reported, many of which are structurally suited for a particular use for main-group catalysis or borylation processes. These compounds undergo a variety of processes including borylation substitution and the addition of B-E across-bonds and they are used in the pharmaceutical and material sciences. Boron reagents also frequently make up the Lewis acid moiety of frustrated Lewis pairs (FLPs).

Keywords: Lewis acid, boron; catalysis, tris(pentafluorophenyl)borane, boron reagents, elementoboration reactions

1. Introduction

Boron reagents exhibit powerful electrophilic nature and utilized in Lewis acids due to the presence of a p-orbital (vacant) that can readily accept donor molecules electrons. The variety of boron reagents is growing as a result of growth in the field of boron chemistry. A string of catalysts boron with increasing structural complexity and tunable acidity arose over the recent years comprising triaryl, trialkyl, and trihalo-boranes [1].

The boron-based catalysts have different properties, for instance, boron trihalides with a chemical formula of BX_3 (X = F, Cl) are very sensitive to moisture and volatile in nature making them tough to handle. However, they are very effective as catalysts (**Figure 1**). According to studies conducted on perfluoroalkyl boranes are thermally unstable and are strong Lewis acid due to their highly electronegative fluorinated ligands [2]. Consequently, the emphasis was turned on halogenated triarylboranes, like tris(penta-fluorophenyl)-borane designated with a chemical formula, $B(C_6F_5)_3$ and are commonly referred to as BCF (**Figure 1**). Tris(pentafluorophenyl)borane, also known as BCF, was first synthesized by Massey in the 1960s [3, 4].

The field has not received much attention by the community (scientific) in spite of its exciting features until the advent of its application in the polymerization of olefins with metallocenes as activators. It has been reported by [6] that $B(C_6F_5)_3$ is among the well-defined and known activator in the area of polymerization (olefin) catalysis. Moreover, $B(C_6F_5)_3$ (Lewis acid) is capable of abstracting alkyl groups from a metal (transition) center. In hydrocarbons, the main-group (e.g., Al and Ga) alkyls may also react quickly with this borane at ambient temperature, resulting in complete alkyl/aryl group exchange. This is a reliable and an easy approach to obtain compounds of galane and tris(pentafluorophenyl)alane [7].

According to the findings reported by [8], Frustrated Lewis Pairs (FLPs) (e.g., H_2 and CO_2 *i.e.,* activate small molecules) can be formed from boranes bearing halogenated aryl groups using phosphines (**Figure 2**). Olefins can also react with these FLPs in an intramolecular addition.

2. Lewis acidic boron reagents synthesis

The preparation of halogenated triarylboranes (homoleptic) can be achieved by the application of either one of these two processes: the lithiation technique or the Grignard technique. Massey et al. [4] defined the BCF synthesis by employing a Grignard reagent with BCl_3 for the first time. Moreover, the lithiation method was reported somewhere else [9]. The general procedure for both methods is presented in **Figure 3**.

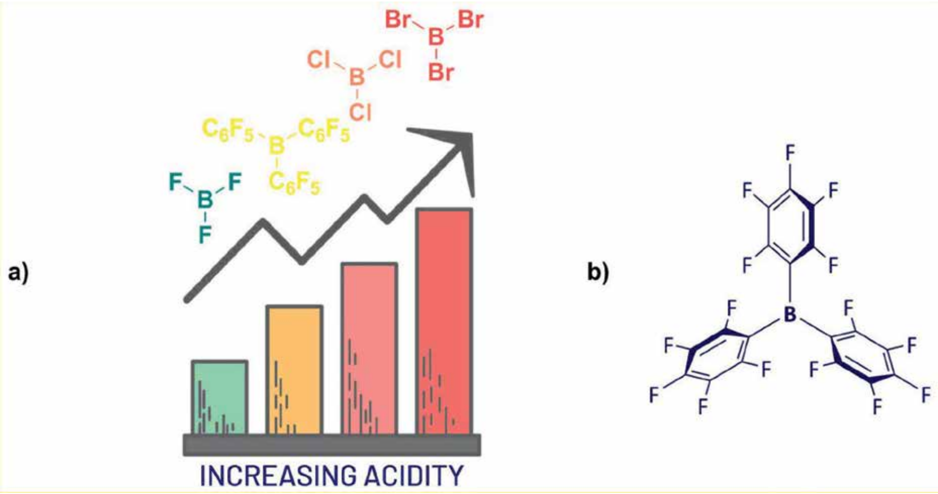


Figure 1.
(a) Acidity of various Lewis acids (boron-based) (b) (BCF). Reproduced with permission from ref. [5].

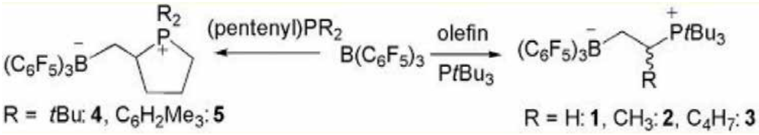


Figure 2.
Phosphine/borane pairs of olefins (inter- and intramolecular addition). Reproduced with permission from ref. [8].

Tris(perfluorotolyl)borane [$B(4\text{-}(CF_3)C_6F_4)_3$] has been synthesized by employing Grignard reagent to synthesis intermediate of arylcopper. This intermediate of copper then underwent reaction of transmetalation with BBr_3 to produce the desire product (**Figure 4**) [10].

Different purification strategies have been adopted for increasing the yield of the desired product. For instance, $B(4\text{-}FC_6H_4)_3$, $B(2\text{-}FC_6H_4)_3$, $B(2,6\text{-}F_2C_6H_3)_3$, $B(3,4,5\text{-}F_3C_6H_2)_3$, $B(3,5\text{-}(CF_3)_2C_6H_3)_3$, and $B(2,4,6\text{-}F_3C_6H_2)_3$ have been purified using sublimation after synthesis with Grignard method [11–15]. Moreover, lithiation approach has been employed to prepare boranes with groups of trifluoromethyl on

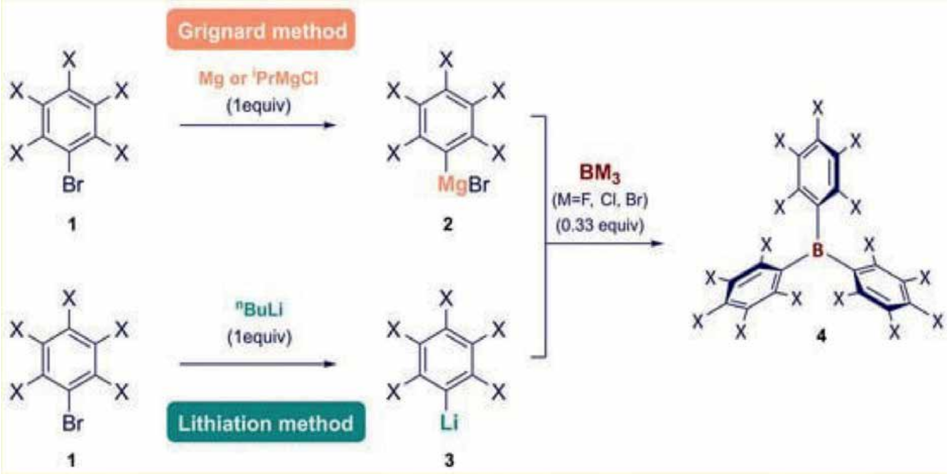


Figure 3.
Grignard and lithiation methods for synthesis of homoleptic halogenated triarylboranes. Reproduced with permission from ref. [5].

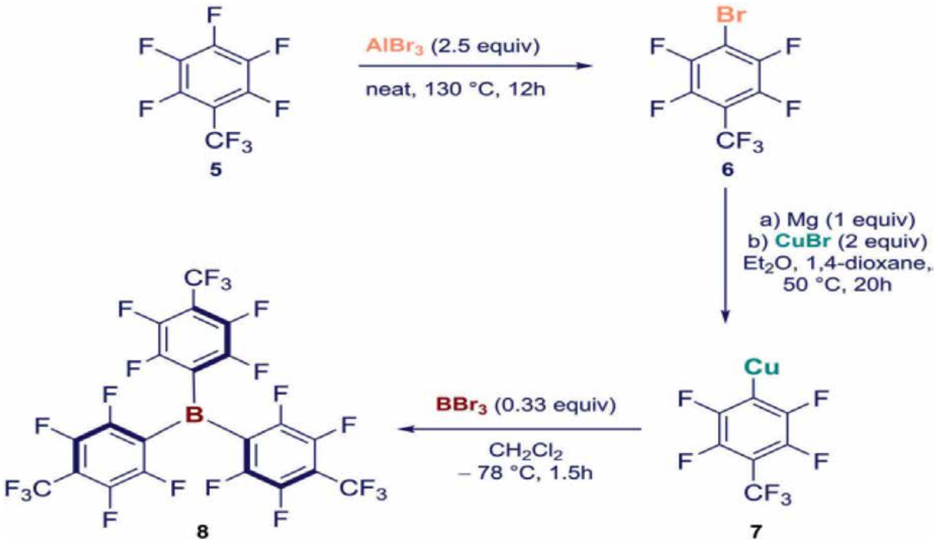


Figure 4.
Synthesis of [$B(4\text{-}(CF_3)C_6F_4)_3$] designated by No. 8 using the arylcopper intermediate designated by No. 7. Reproduced with permission from ref. [10].

aryl ring (*e.g.*, $B(2\text{-}(CF_3)C_6H_4)_3$ $B(2,5\text{-}(CF_3)_2C_6H_3)_3$, $B(3,5\text{-}(CF_3)_2C_6H_3)_3$, and $B(2,4\text{-}(CF_3)_2C_6H_3)_3$) [16–18]. The BCF was first synthesized in pentane (**Figure 5**) [4].

As a result of the complexity of the procedures, few heteroleptic boranes have been synthesized. The heteroleptic borane (e.g., $B(C_6F_5)_2(2\text{-}(C_6F_5)C_6F_4)$) that has been synthesized by substituting moiety of one perfluorophenyl by a motif of perfluorobiphenyl. The procedure for synthetic of 2-bromononofluoro-biphenyl portion comprised $(C_6F_5)Li$ and C_6F_5Br reaction followed by BCl_3 addition into $Sn(Me)_2(C_6F_5)_2$ and generated the $B(C_6F_5)_2Cl$. Eventually, $B(C_6F_5)_2(2\text{-}(C_6F_5)C_6F_4)$ was prepared by the reaction between 2-lithiumnonofluoro-biphenyl and $B(C_6F_5)_2Cl$ (**Figure 6**) [19].

The preparation of another heteroleptic boranes incorporating fluorinated and chlorinated aryl rings was reported somewhere else (**Figure 7**) [20]. The process included the dihalobenzene derivatives reacting with trimethyl borate and n-butyl lithium, resulting in boronic acids that were then transformed into salt of potassium trifluoroborate. Grignard reagents with various aryl frameworks reacted with the salt intermediates to yield the desired heteroleptic boranes. The resulting boranes

Figure 5.
Synthesis of BCF designated by No. 11. Reproduced with permission from ref. [4].

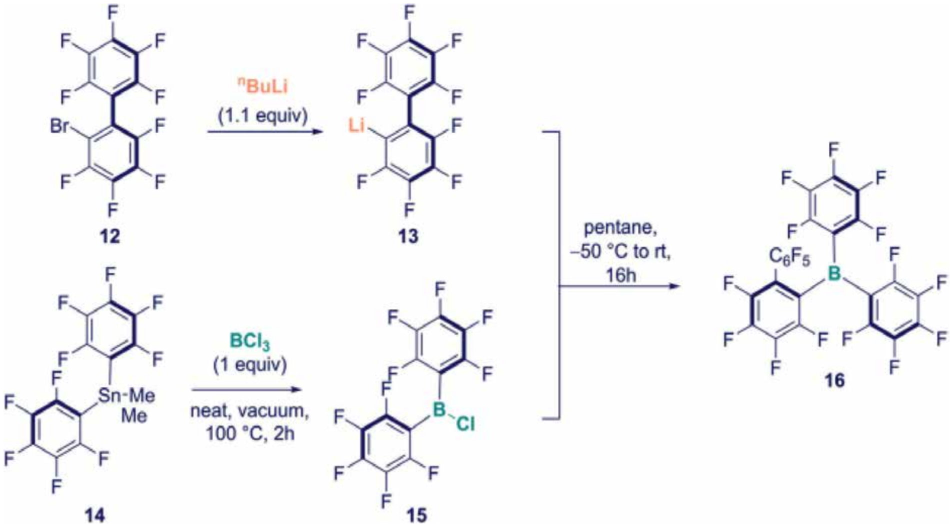


Figure 6.
Preparation of $B(C_6F_5)_2(2\text{-}(C_6F_5)C_6F_4)$ (simplest heteroleptic borane) designated by No. 16. Reproduced with permission from ref. [19].

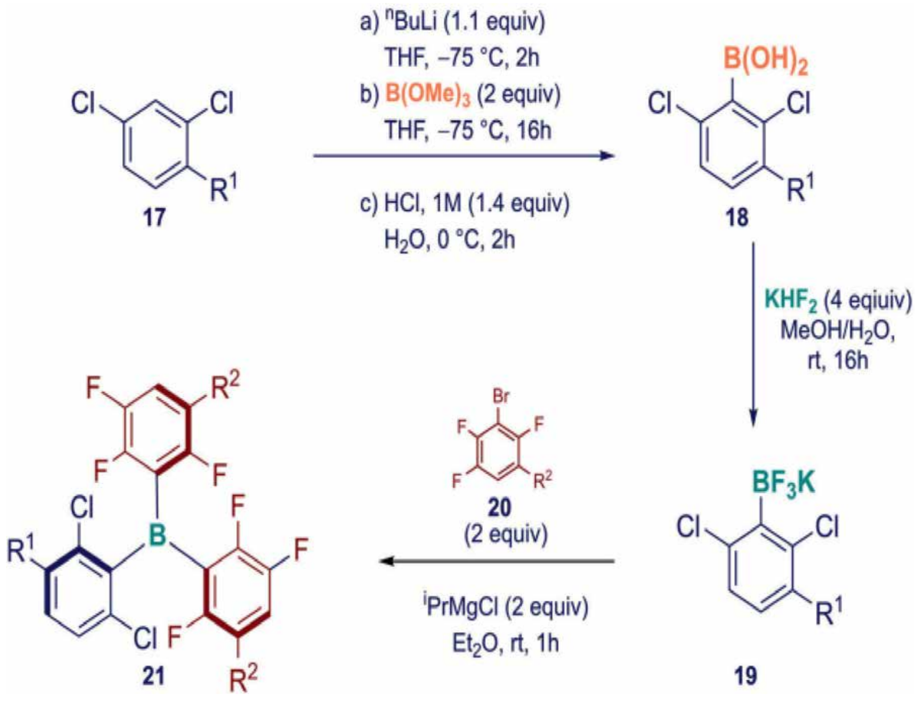


Figure 7.
Preparation path for boranes (heteroleptic) bearing fluorinated and chlorinated aryl rings designated by No. 21. Reproduced with permission from ref. [20].

exhibited an important property *i.e.,* moisture tolerance, due to the steric hindrance of the atoms of chlorine that avoid the binding of water molecules with the central boron.

Halogenated triarylborane comprising three types of aryl rings was first synthetized using a five-step process starting from dimethylsulfide [21]. In the first step, Li(C_6F_5) (single equivalent) was formed at the temperature of -78°C and then $H_3B(C_6F_5)$ was obtained by reacting with borane dimethylsulfide. The hydride (*i.e.,* excess) was subtracted from the resulting compound and with trimethylsilyl chloride (TMSCl) deriving the intermediate $H_2B(C_6F_5)$. Similarly, the aryl ring of trifluoromethyl bearing was installed by Li(3,5-$(CF_3)_2C_6H_3$) addition and the abstraction of surplus hydride with TMSCl, yielding HB(C_6F_5)(3,5-(CF_3)2C_6H_3) (*i.e.,* next intermediate). HB(C_6F_5)(3,5-(CF_3)2C_6H_3) has been treated by surplus methanol for an hour and then it was reacted with BBr_3 for three hours to yield BrB(C_6F_5)(3,5-(CF_3)C_6H_3). Then, bromoborane ultimately reacted with Zn$(C_6Cl_5)_2$ (*i.e.,* half an equivalent) and the last aryl ring attached resulting in desired heteroleptic borane (*i.e.,* B(C_6F_5)(C_6Cl_5)(3,5-$(CF_3)_2C_6H_3$)) (**Figure 8**).

3. Application of novel boranes and borocations

Many new boranes and borocation are utilized in borylation reactions such as hydroboration, dehydroborylation, haloboration, and carboboration. Since each of these reactions has some conditions (most prominently the kind of group bonded to the boron reagent) along with a range of substrates, the potential to functionalize the

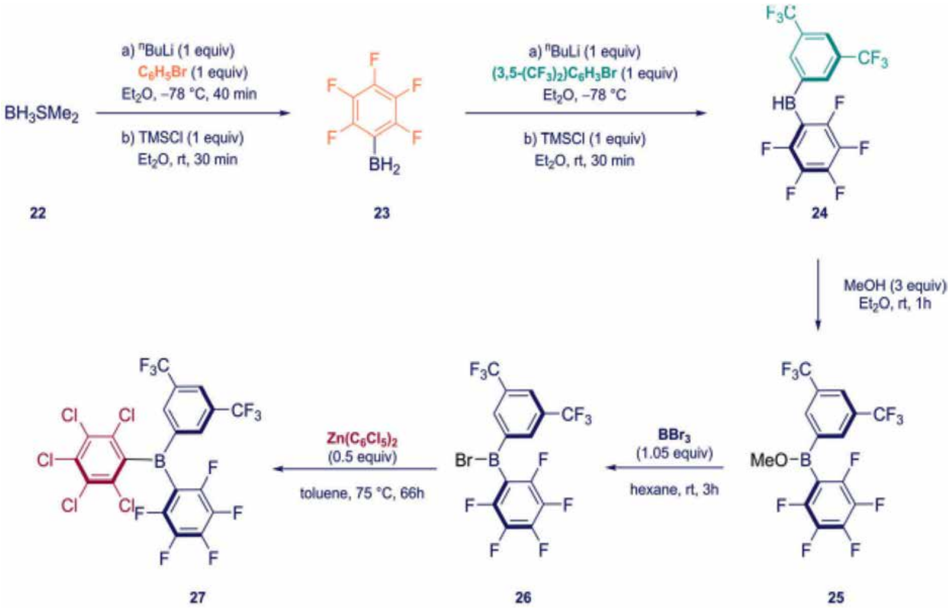


Figure 8.
The synthesizing process for $B(C_6F_5)(C_6Cl_5)(3{,}5\text{-}(CF_3)_2C_6H_3)$ *designated by No. 27. Reproduced with permission from ref. [21].*

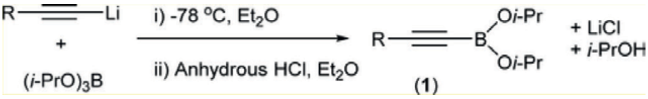


Figure 9.
Borylation of Lithiated alkynes. Reproduced with permission from refs. [22, 23].

structure and reduce the boron reagent's reactivity is essential. The results of these reactions might be viewed as intermediates on the way to the more diverse and valuable molecules, as the addition of a boron species enables further functionalization through future cross-coupling reactions.

Direct borylation substitution reaction (e.g., dehydroborylation) is one field of chemistry of borylation in which C-B bond forms from C-H bond. And also, in this reaction $B(C_6F_5)_3$ is inappropriate. It has been reported that trialkoxyboranes were appropriate reagents of borylation when joined with organolithiated species like alkynes to obtain alkynyl boronates (1) (**Figure 9**) [22, 23].

In a more contemporary method, the substrate is deprotonated using a base that can be integrated separately or, in the case of some borocations that can be added into the reagent structure and removing the need for lithiation. Certain species of borenium have been found to selectively dehydroborylate arenes and heteroarenes, according to recent research. Catechol-ligated borocations were used to catalyze arene borylation (intermolecular) (**Figure 10**) and generated a string of borylated arenes from benzene derivatives. $[CatB][CbBr_6]$ ($CbBr_6$ = [closo-1-H $CB_{11}H_5Br_6$]) is a catalytic quantity of $[CatB]^+$ [24].

Several amine-ligated catechol boreniums were created using $AlCl_3$ (halide abstraction catalyst) to obtain borocations [CatB (L)] $[AlCl_4]$ (*i.e.*, general formula).

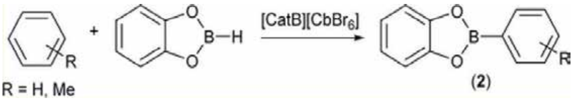


Figure 10.
Dehydroborylation of Arenes. Reproduced with permission from ref. [24].

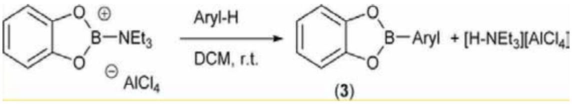


Figure 11.
Dehydroborylation of Arenes with Borocations. Reproduced with permission from ref. [24].

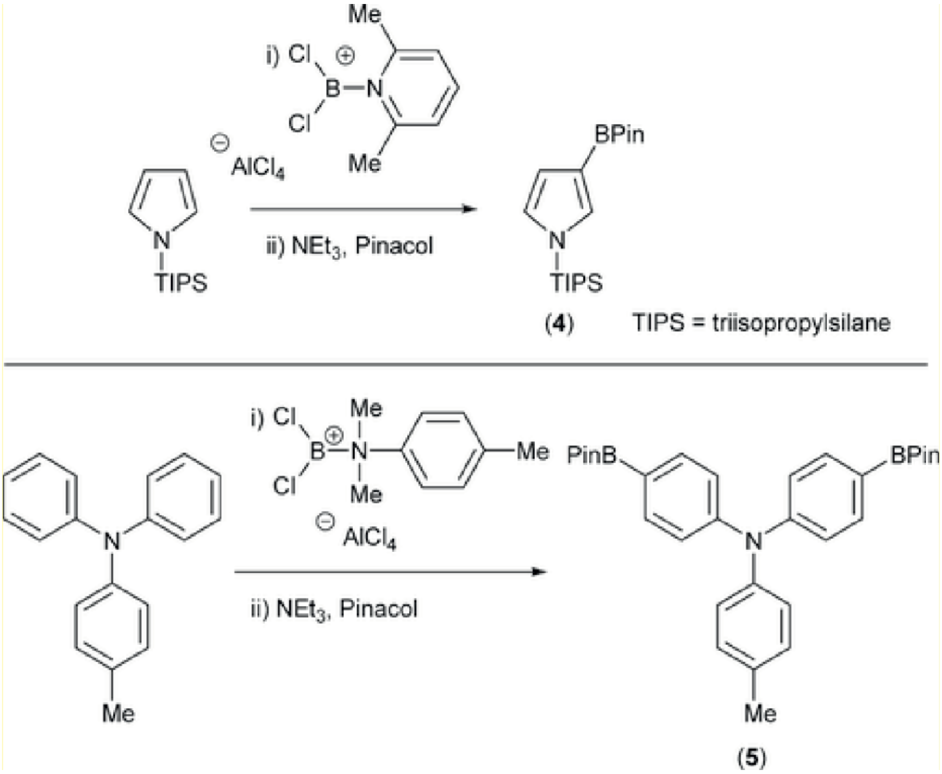


Figure 12.
(Hetero) arenes Dehydroborylation. Reproduced with permission from Ref. method [24].

For instance, as L = NEt3, this borenium was found to dehydroborylate many arenes, along with anilines, indoles, and pyrroles (**Figure 11**) [25]. Boreniums were used to boroylate N-heterocycles in a quantitative and highly regioselective way. The products (3) could merely be transesterified to create reagents (air-stable) for an extra cross-coupling process termed as pinacolboronate esters.

Furthermore, boreniums ([$Cl_2B(L)$][$AlCl_4$]) more reactive) were formed and used in arene dehydroborylation reactions (4) (**Figure 12**) [26, 27]. To boost the electrophilicity of the boreniums, the catechol ligand was replaced by two halides and allowed the reactions to continue rapidly at room temperature. The Lewis base alteration also provided access to many species of diborylated heteroaryl (5). These were isolated as esters of pinacolboronate, providing key synthetic molecules that can act as scaffolding for more complex molecules. For instance, Del Grosso et al. updated their research to include the haloarenes borylation [28] which was a crucial step in the creation of borylation chemistry (metal-free) as the deactivated arenes were not previously available with existing method [24].

Furthermore, the borylation of monohaloarenes principally created the para-substituted isomer (6), single product, revealing its ability to control regioselectivity (**Figure 13**). It was reported that of the haloarene (10 equivalents) and $AlCl_3$ (1 equivalent) were needed at the optimal conditions that were employed as the solvent [24].

Recently, catalytic method (metal-free) to borylation of arene that employed the borane $(1\text{-TMP-2-BH}_2C_6H_4)_2$ as a C-H bond activator has been reported [29] (**Figure 14**). First, the borane was reacted with the N-methylpyrrole (arene) followed by H_2 releasing after the C-H bond activation in the two positions. Then, the intermediate was reacted with H-BPin and regenerated the catalyst and produced the desire pinacolboronate ester (borylated arene) (8).

Indoles, furans, and electron-rich thiophene were added to the list of acceptable substrates besides N-substituted pyrroles (yield frequently exceeding 80%). In general, a single isomer of the products was produced with catalyst loading of 2.5 mol%. The employ of this system emphasizes the advantages over conventional pathways (*i.e.,* metal-catalyzed), eliminating the cost required to remove trace metals (impurities) from the products by maintaining the selectivity of the reaction.

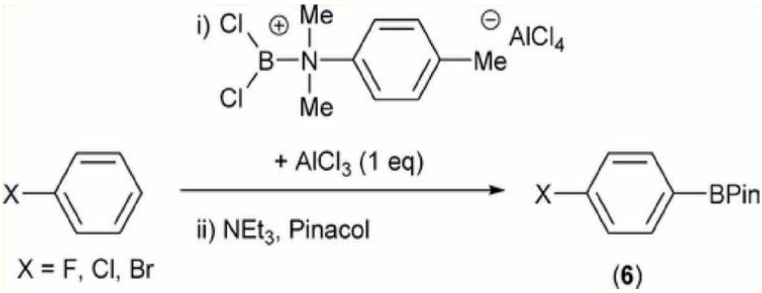


Figure 13.
Borocation for arenes dehydroborylation. Reproduced with permission from ref. [24].

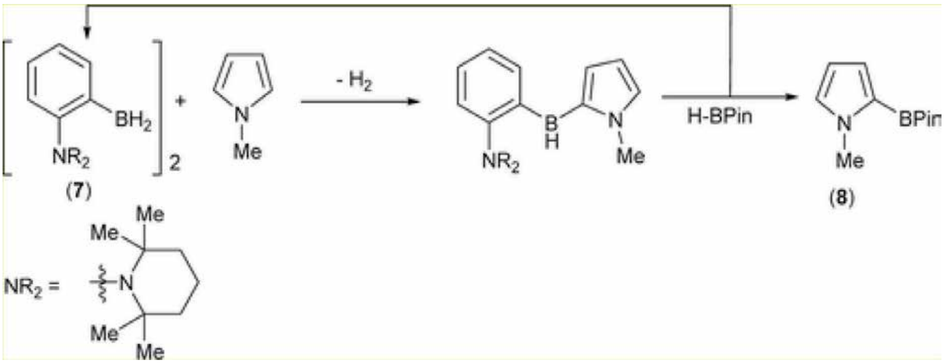


Figure 14.
Catalystic N-Methylpyrrole dehydroborylation. Reproduced with permission from ref. [29].

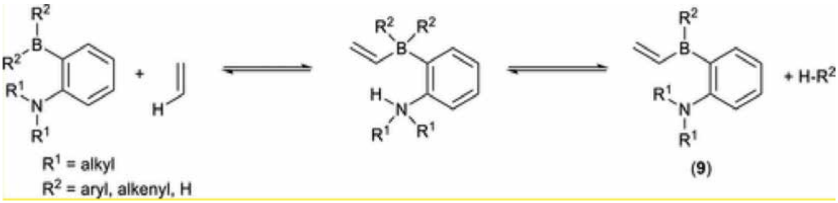


Figure 15.
Alkenes dehydroborylation. Reproduced with permission from ref. [30].

Moreover, 2-aminophenyl boranes (**Figure 15**) induced dehydroborylation of a variety of alkenes, arenes, and heteroarenes resulting in species of borylated [30]. This reaction is proposed to continue through an insertion of CH in an FLP-style, in which the amine and boron heterolytically split the CH bond. The close proximity of the Lewis base and acid promotes this reactivity, leading in a small kinetic barrier to reaction for thiophene with ΔG value of 21 Kcal/mol. The reaction of borylation was shown to be neutral (thermodynamically). Additionally, it was found that the equilibrium might be simply shifted by adding more substrate or might be eliminated the by-product (H-R^2) in the reaction mixture.

3.1 Elementoboration reactions

Borocations and boranes can be involved in substitution reactions like dehydroborylations and addition reactions like hydro-, carbo-, and haloboration. In an elementoboration, boron with another group is added to a π-system excluding the necessity of a substitution reaction. There are studies on addition of (1, n) of boron reagents to alkynes (n = 1–4) reported somewhere else [31] which allows the integration of a unit of boron while creating a species of vinyl catalyst [32]. However, many historical examples have required the use of a metal catalyst [32]. With the help of cross-coupling reactions with the boron unit, these borylated alkenes are effective building blocks for more compounds [33].

The drawbacks of $B(C_6F_5)_3$ become apparent when range of reactions is considered. For instance, despite the abundance of carboboration reaction the product utility was constrained by the need of transfer of C_6F_5 group. Moreover, further functionalizing challenge through boron group by employing cross-coupling reactions can be more difficult than those of conventional boronate esters and boronic acids [34].

In contrast, Lappert and Prokai's research focused on haloboration reactions, which involve combining halogen and boron with a nucleophile like an alkyne to create a vinylboron species [35]. The halogen addition makes a new site for functionalization via cross-coupling reactions (Suzuki reaction), even though the final products resemble those of carboboration processes [36]. This is beneficial when the relevant R group can be added to the intermediate product after borylation instead of by direct carboboration.

Until recently, the reaction of haloboration was believed to be a specialized field of main-group chemistry involving terminal alkynes and haloboranes like BCl_3 [37]. Recent findings have revealed that borocations with halides can resemble, if not surpass, the reactivity of trihalo-boranes. For instance, the structure and reactivity of a synthesized 2-dimethylaminopyridine (2-DMAP)-ligated borocation [Cl_2B-(2-DMAP)][$AlCl_4$] (10) were studied [38]. These classes were known as a boronium cation with acceptable moisture and air tolerance of 5% and decomposed after 24 hours.

A low value of energy barrier to opening ring of the largely strained 4-membered ring molecule (*i.e.,*12.6 Kcal mol) allows to react efficiently like a cation of borenium (**Figure 16**).

Boronium (10) was done via syn-1,2-haloboration (selective) through a variety of alkynes terminal resulting in vinylpinacolboranes (11) (63–88% yields with isolation of good to high) (**Figure 17**). Moreover, the analogue bromo $[Br_2B$ (2-DMAP)$][BBr_4]$ (12) has been presented to undertake haloboration through certain internal and terminal alkynes (*e.g.,* 3-hexyne), resulting in the esters of vinylboronate (bromo-substituted) (13).

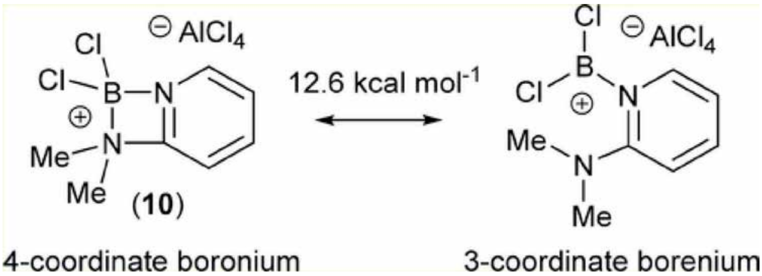


Figure 16.
Borocation energy barrier for opening ring. Reproduced with permission from ref. [38].

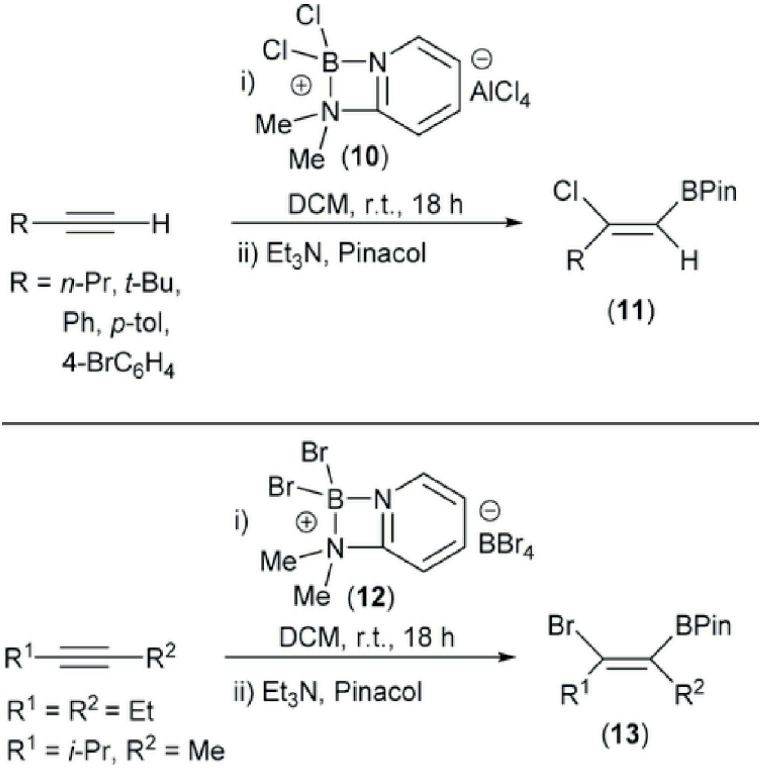


Figure 17.
Alkynes Haloboration through Borocations. Reproduced with permission from ref. [38].

Increasing the borocation of Lewis acidity resulted in a variety of internal alkynes that could be 1,2-haloborated. Several novel vinylboron molecules were identified as pinacolboronate esters by employing borenium [Cl_2B(lut)] [$AlCl_4$] (*i.e.,* lut = 2, 6-lutidine) (14). This system was found to be suitable for a broad range of alkynes (internal) with aliphatic and aromatic moieties along with tolerance of functional-group anisoles and thiophenes (**Figure 18**). Haloboration happened only at alkyne site when enzymes were used as targets, releasing the functionality constant of alkene. This product has been separated as stereoisomers and sole regioisomers that emphasize on the reaction's selectivity, showing a viable method for producing substituted alkenes (highly functionalized).

Cross-coupling reactions (sequential) of chloro and vinylboron substituents were used to obtain the alkene (highly functionalized) (15) (**Figure 19**) [39]. It was indicated that the reaction from alkyne to alkene (fully substituted) could be performed in a single pot. These alkenes (tetrasubstituted) are precursors and structural analogues to a number of drug molecules comprising Tamoxifen, Zuclomiphene, and a potent anticancer agent showing the significance of the reaction pathway [40].

Reactions of carboboration permit for quick creation of new bonds of C-B besides C-C across a p-system [41]. A range of trialkylboranes undergo carboboration with specific activated alkynes; nevertheless, $B(C_6F_5)_3$ has been recently confirmed as a predilection of these reactions without the necessity of alkynes (activated) [42]. One of the basic examples is the reaction between phenylacetylene and $B(C_6F_5)_3$ and 1,1-carboboration happens practically rapidly at room temperature but produces isomers of mixture of Z and E (**Figure 20**). Photoisomerization may be utilized to create a single isomer (16).

Employing $B(C_6F_5)_3$ for carboborations is inappropriate as the desired product lacks C_6F_5 group. $B(C_6F_5)_3$ was modified with reagents of $R\text{-}B(C_6F_5)_2$ that were prepared and used in reactions of carboboration by transfer of selective R-group

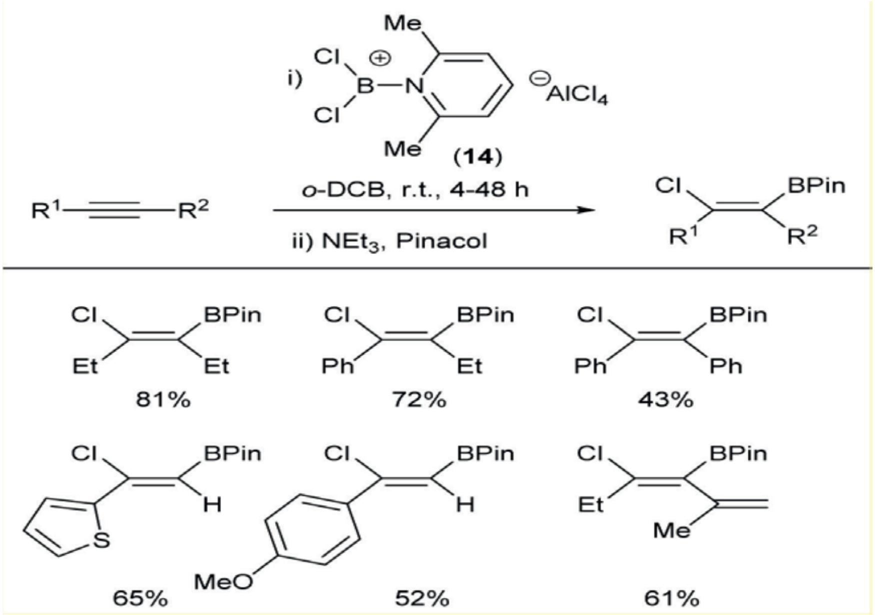
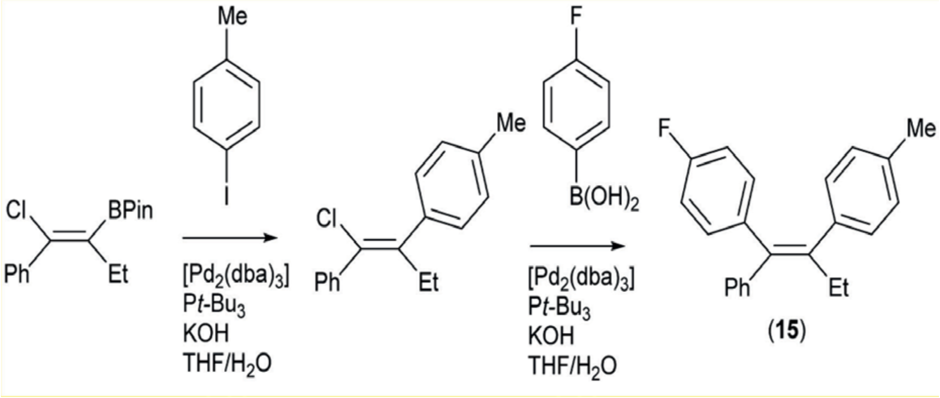
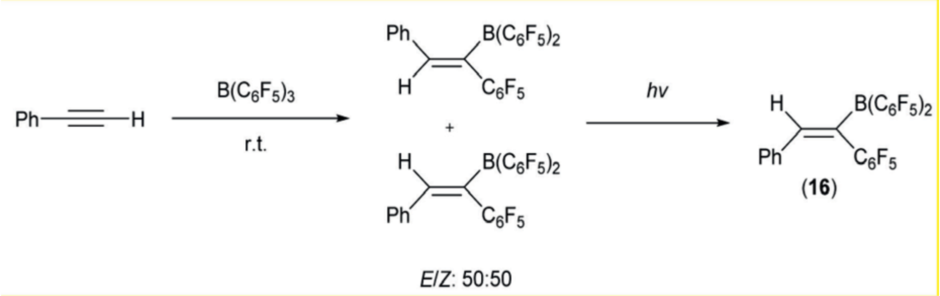


Figure 18.
Internal alkynes haloboration. Reproduced with permission from ref. [38].



(**15**)

Figure 19.
Haloboration products with cross-coupling (consecutive). Reproduced with permission from ref. [39].



(**16**)

Figure 20.
Phenylacetylene carboboration by $B(C_6F_5)_3$. Reproduced with permission from ref. [42].

(contrast to the transfer C_6F_5) [43]. However, this has left $B(C_6F_5)_2$ group into the molecule and prevented additional functionalization due to the difficult behavior of the reaction (cross-coupling) by using boron species (requires higher temperature) and resulted in a small yield than boronate esters [32].

So far, research has presented a variety of heteroleptic borocations and boranes that may be prepared and used in different reactions of carboboration. For instance, the species of neutral borane (general formula: Cl_2B-aryl) might be employed for 1,1-carboboration of trimethylsilyl (TMS) substituted alkynes as reported somewhere else [44]. In contrast, unlike other activated alkynes of carboborations, this process uses a group of BCl_2 that may be changed into a boronate ester, which is more valuable for synthetic purposes, than trialkyl/arylboranes. Using a range of TMS-alkynes and cheaply available $PhBCl_2$, single-products of vinylborane with outstanding regioselectivity and stereo were created. These products could then be isolated as pinacolboronates (17) (**Figure 21**). Along with arenes (triphenylamine and p-chlorobenzene) and heteroarenes ($PhBCl_2$) numerous dichloroboranes were also produced.

In contrast to haloboration, only a few cases of metal-catalyzed carboboration of alkynes have been reported in the literature [45]. However, some recent examples using borocations and boranes have been reported. For instance, quinolatoboreniums were synthesized (19) and when it was exposed to 3-hexyne resulted in 1,2-carboboration and then transferred into either a moiety of thiophenyl or phenyl and the resulting products were esterified by pinacol to yield vinylboronates (isolated) (20) (**Figure 22**) [46].

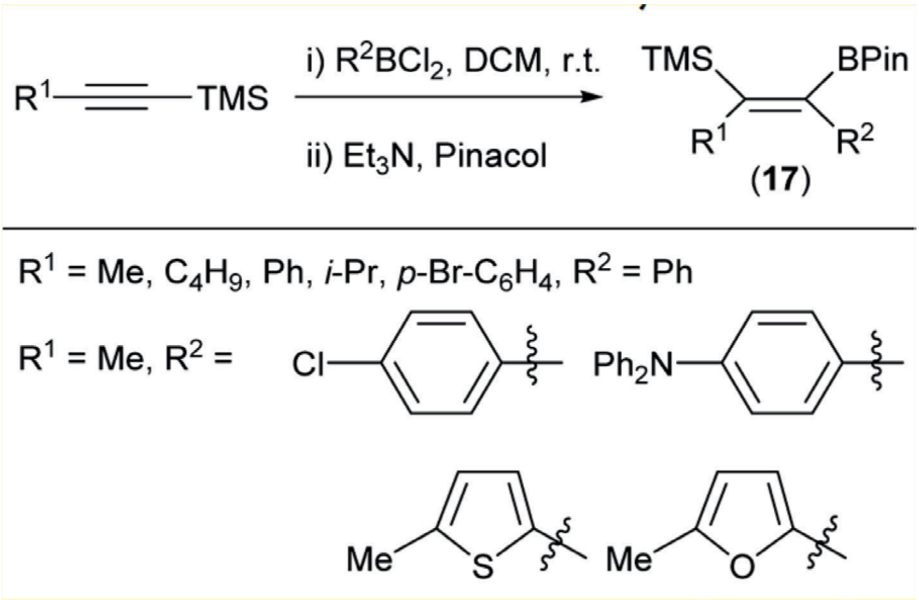


Figure 21.
TMS-alkynes carboboration. Reproduced with permission from ref. [44].

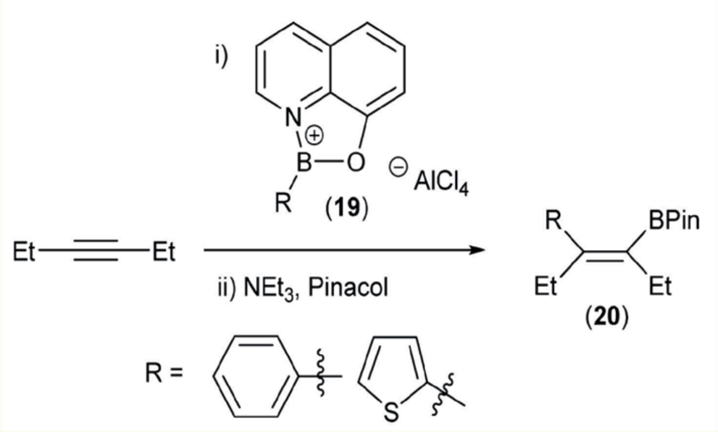


Figure 22.
Borocations of 1,2-carboboration of 3-Hexyne. Reproduced with permission from ref. [46].

Furthermore, 1,2-carboboration was obtained by employing boreniums in which 3-hexyne readily reacted with a phosphorus-coordinated borenium (21) (**Figure 23**) [47]. As shown in **Figure 23** a group mesityl was transferred and selectively generated the vinylboron species (22). The reagent comprises species of novel borenium that employs a scaffold of naphthalene to produce a strong interaction of intramolecular BP. Moreover, it has been shown to be stable, however, it showed an activation of H_2, highly reactive and carboboration of 3-hexyne indicating the broad utility of borocations.

Recently, Melen et al. presented 1,2-carboboration of allenes by employing boranes [48]. The reactions of esters and allenyl ketones in the presence of $B(C_6F5)_3$ gave 1, 2-carboboration products (**Figure 24**). The reactions (stoichiometric) with

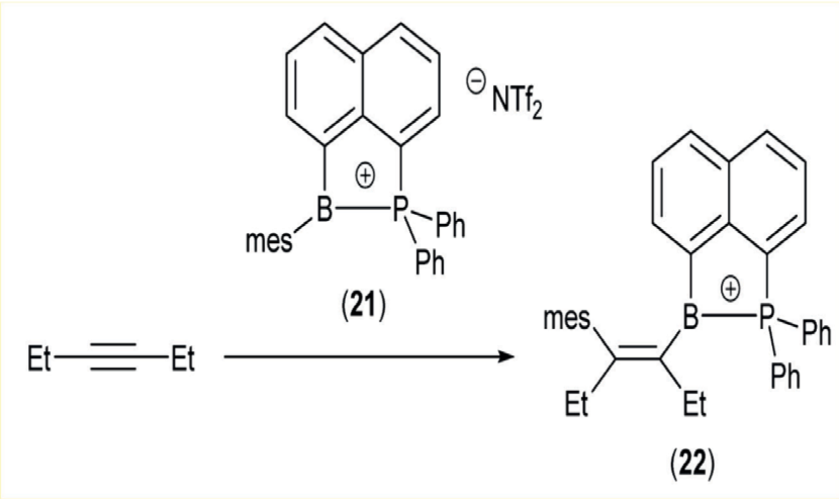


Figure 23.
3-Hexyne through 1,2-Carboboration with borocation. Reproduced with permission from refs. [46, 47].

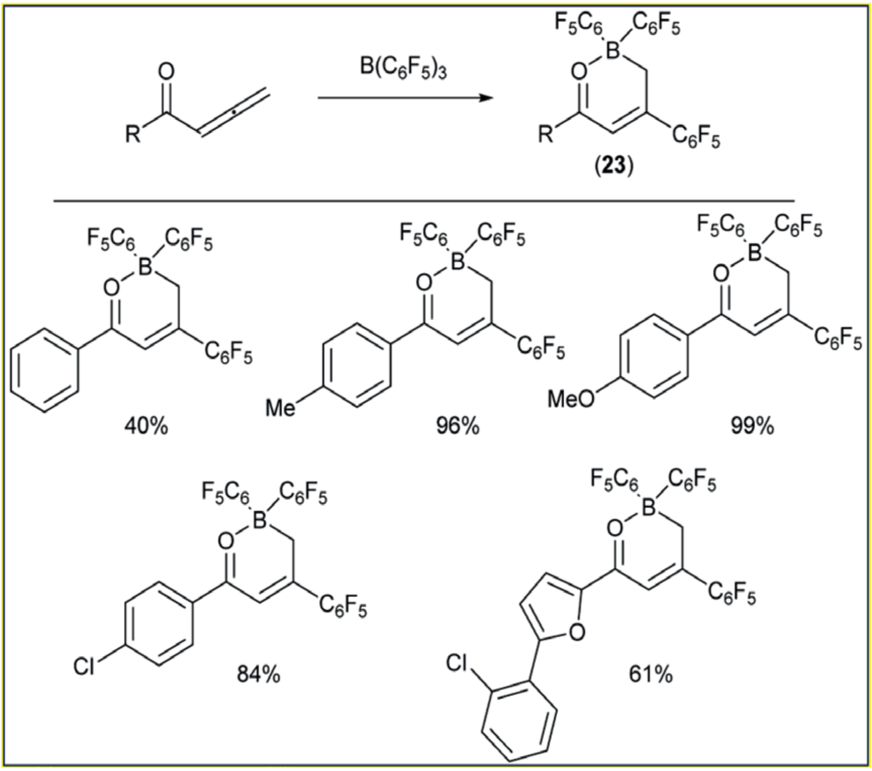


Figure 24.
Allenyl ketones (1,2-Carboboration) employing B(C_6F_5)$_3$. Reproduced with permission from ref. [48].

allenyl ketones continued at room temperature (30 minutes) confirming the intramolecular structure of chelating cyclic dihydroxyborinine products as confirmed using X-ray crystallography (23).

4. Main-group catalysis with boron reagents

Recently, there is a strong interest in using the main-group elements molecular catalysis than transition metals (TM) as there is a growing concern on the environmental and health impact of residues metals that remains in the products. The main group comprises Frustration Lewis Pair (FLP), single-site amphiphiles (e.g., singlet carbene (CR2) restricted phosphines, Di-coordinated borirene (LBR, L = Lewis donor), and di-coordination group with 14 cations) that begin to emerge as a powerful TM-free reagent for activation of inert substances and small molecules of interest as catalysts [49]. Boron reagents can function as Lewis acid due to their strong electrophilicity with vacancies of a p-orbital that can easily accept an electron from a donor molecule.

Numerous boranes (trialkyl-, triaryl-, and trihalo-boranes) have been produced and used over the past years. A series of boron-grounded catalysts with structural complexity and tunable acidity have been developed [1]. In 1950s, examinations were done on fluorinated ligands (largely electronegative) and perfluoroalkyl boranes and they showed a strong Lewis acidity to the boron center and less hydrolytically sensitivity of B-C bonds. Up to now, perfluoroalkyl boranes displayed thermal insecurity [5]. Catalysis is among the field of main-group chemistry that has flourished in recent times with borocations, boranes, and FLPs gaining features. This reagent has led to the development of carbon-carbon bond-forming responses, hydroboration, and hydrogenation which are conventionally essence-dominated paths [1].

Main-group catalysis comprises a rich soil in C-C bond-forming responses, hydroboration, hydrogenation, and numerous other metamorphoses which are conventionally attained by essence-grounded catalysis.

The low cost and less toxicity properties help in using the main-group elements for catalysis purposes. Recently, researchers are searching for the development of a new approach for greener catalysis. Moreover, less poisonous, earth-abundant, and first-row transition essence approaches are being developed to attain an environmentally-friendly catalysis [50]. Boranes can be used as Lewis acid catalysts as their central boron contains an empty p-orbital. The base of boranes intermediated Lewis acid catalysis is governed by the posterior release and attack of their empty p-orbital.

4.1 Boron catalysts for the formation of C-C bond

The development of a green method has fascinated tons attention all over the community (synthetic) as C-C bond construction in organic chemistry is among the vastest reactions. Among numerous C-C bonds protocols, compounds of organoboron are not simply confined to stoichiometric reagents. However, they owned an outstanding attainment as catalysts due to the easy change of the steric and electronic influences at the center of boron [51]. Tris(pentafluorophenyl)boran has attracted numerous attention among artificial chemists due to sterically hindered conformation at the center of boron (avoids the formation of Lewis adduct by Lewis base), stability (hydrolytic) (*i.e.,* permits the catalytic system even below a wet ecosystem), appropriate stability (thermal) up to 270°C with slight decomposition and high Lewis acidity (*i.e.,* between BCl_3 and BF_3) [51].

Carboboration reaction allows the facile creation of new bonds of both C-B and C-C throughout a π machine. Historically, trialkylboranes spread have been indicated to undertake carboboration through certain alkynes (activated). Currently, $B(C_6F_5)_3$ has been tested for a proclivity for this reaction without using of alkynes (activated). For instance, in B(C_6F_5)$_3$ and phenyl acetylene, 1,1-carboboration has been attained (instantly at room temperature), however, it generated an aggregate of Z and E isomers (**Figure 25**). Photoisomerization may be employed to produce the unmarried isomer (16) [1].

4.2 Boron-based catalyzed hydroborations

Hydroboration reactions have been extensively studied by employing metal catalysts. Currently, catalysis (metal-free) which provides a broader variety of substrates (borylated) access without eliminating impurities of trace metals has been reported. Many reactions of hydroboration are an atom-efficient with hydroboranes (e.g., pinacolborane (HBPin)) where selective addition is often detected. Now, numerous examples of boron-based catalysts have been reviewed somewhere else [52].

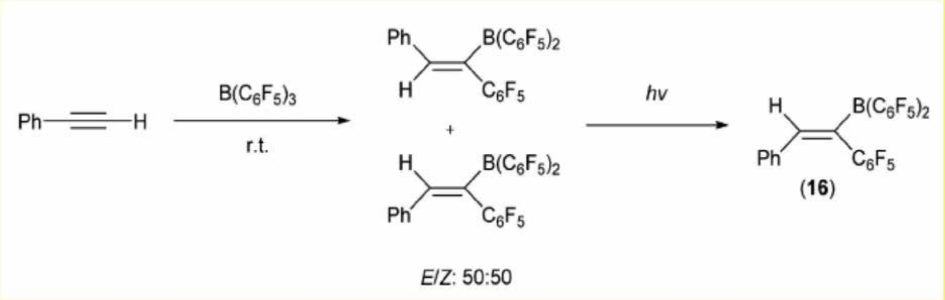


Figure 25.
Phenylacetylene carboboration with B(C_6F_5)$_3$. Reproduced with permission from ref. [52].

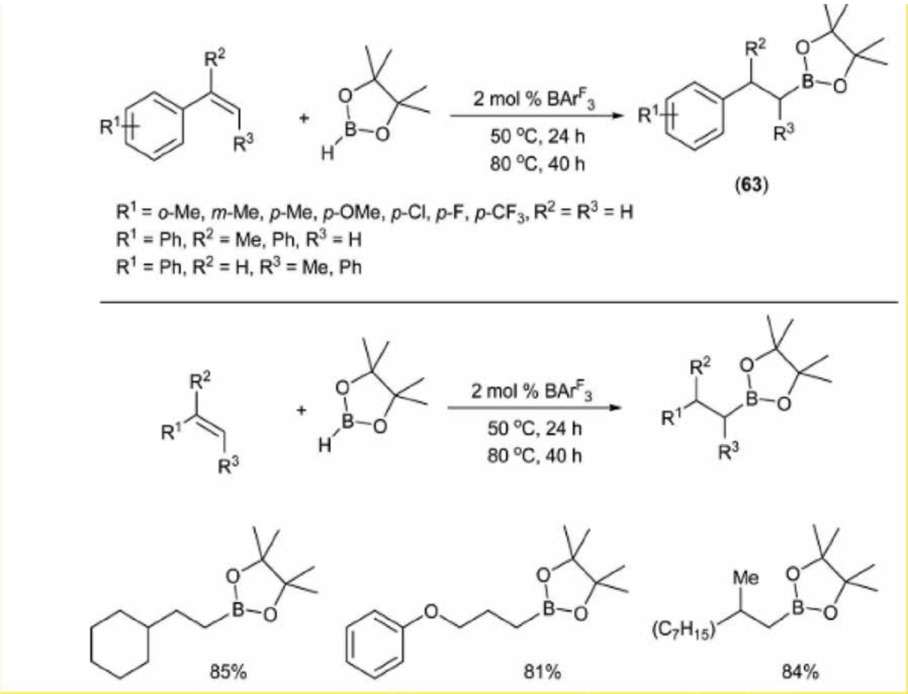


Figure 26.
1,2-hydroboration of aliphatic alkenes and styrenes. Reproduced with permission from ref. [53].

Hydroboration of alkenes by HBPin and catalyzed with tris[3,5-bis(trifluoromethyl) phenyl] borane $(BArF_3)_6$, $B(C_6F_5)_3$ turned out to be unusable. A series of selective products (*i.e.,* cis-1,2-hydroboration) were produced (63) (**Figure 26**). The reaction is a substituted aliphatic alkenes and styrene, often with excellent regioselectivity (anti-Markovnikov). BArF3 was employed as the catalyst precursor for alkene hydroboration. It has been participated in the redistribution of substituents with HBPin, resulting in an electron deficiency. Moreover, 1,2-hydroboration has undergone with these species. Alkene is followed by ligand exchange with HBPin to form pinacolboronic acid. It produces the ester product and regenerates the catalyst [53].

5. Conclusions and outlook

This chapter presents the review and discussion of the use of boranes in catalysis and exploring new reactivities as well as catalysis of boron that permits to perform identified reactions in milder situations.

The conclusion of this review focuses on Lewis acidic boron reagents synthesis, application of novel boranes and borocations, main-group catalysis with boron reagents, and halogenated triarylboranes design with careful consideration of their Lewis acidity. this relatively new field of catalysis will contribute to synthetic chemistry.

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Chapter 3

Developments and Uses of Lewis Acids: From Conventional Catalysts to Modern Green Catalysts

Hamad H. Al Mamari

Abstract

Lewis acids have played a pivotal role in organic synthesis. The inherent Lewis acidity of semimetal or metal ions, which stems from possession of empty orbitals or electron-accepting ability/electron pair affinity, has granted them the ability to catalyze various and numerous organic functional group transformations and methods for carbon-carbon (C-C) bond formation reactions. Lewis acids have developed from conventional catalysts to modern green ones that have enabled a wide range of chemical transformations and chemical processes of applications in various fields, such as pharmaceutical and petroleum/petrochemical industries. The chapter begins with a definition and description of Lewis acids and their significance in chemistry as an electronic science. The chapter then covers the uses and applications of Lewis acids as homogeneous catalysts in conventional organic reactions that employ and/or are Lewis-acids catalysts. Coverage continues on the importance of developments and inception of green and environmentally benign Lewis acids that can help preserve the environment, in a manifestation of green chemistry principles. Illustrations of the importance and applications of green Lewis acids in Lewis acid-catalyzed organic reactions and C-C bond formation reactions are covered. The chapter aims at introducing and stimulating the reader to Lewis acids, their description, and significance in synthetic organic chemistry in particular and in chemistry as a whole.

Keywords: Lewis acids, empty orbitals, Lewis-acid catalysis, homogenous catalysts, green Lewis acids

1. Introduction

According to Gilbert Lewis, a Lewis acid is a substance (atom, ion, or molecule) that contains or possesses an empty/vacant or unfilled atomic or molecular orbital that is capable of accepting or accommodating an electron pair [1–8]. This implies that substances with an incomplete or unsatisfied octet act as Lewis acids. An electron pair donor, a Lewis base, performs the donation of the electron pair from its highest

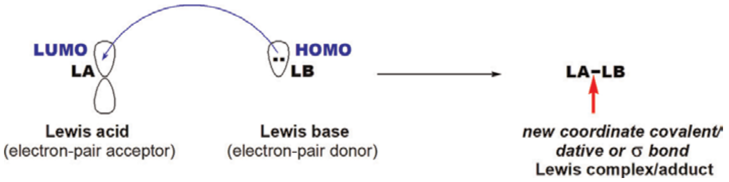

Figure 1.
The general reaction between a Lewis acid and a Lewis base.

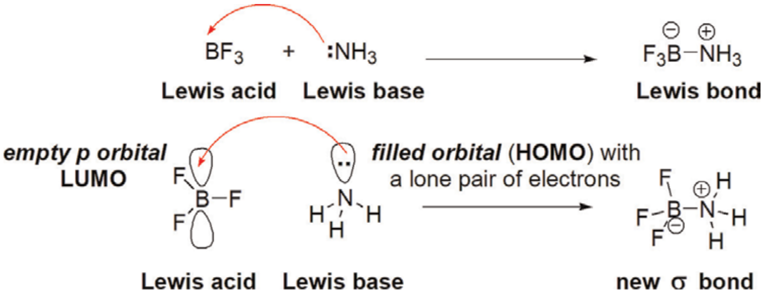

Figure 2.
Reaction between BF_3 (Lewis acid) and NH_3 (Lewis base).

occupied molecular orbital (HOMO) to the lowest occupied molecular orbital (LUMO) of the Lewis acid (**Figure 1**). Thus, in simple terms, a Lewis acid is an electron pair acceptor. The process of accepting an electron pair by a Lewis acid from a Lewis base results in the formation of a Lewis complex or adduct with a new coordinate covalent bond/dative bond or σ bond. Lewis acidity is closely linked and intertwined with electrophilicity. Thus, due to their electron deficiency, electrophiles with positive or partially positive characters as a result of electronic effects (inductive and electronic) manifest themselves as electron pair acceptors. Hence, Lewis acidity parallels electrophilicity in a similar manner that Lewis basicity parallels nucleophilicity.

Typical general examples of Lewis acids are based on B or boranes (BR_3) [6], such as BH_3 and BF_3 and aluminum compounds, AlR_3, such as $AlCl_3$. Other examples include alkali (M^+) metal ions, such as K^+ and alkaline earth metal ions (M^{2+}), such as Ca^{2+} and transition metal ions, such as Mn^{2+}. Other examples of Lewis acids include the proton, H^+, carbocations, R_3C+ [8], and electron-deficient π-systems. The vast majority of Lewis acids are metal-based, such as those based on Al, Ti, Mg, and Mn. Some are metalloid/semimetal-based, such as those based on B [6] and Si [7]. A typical example of a Lewis acid-Lewis base reaction is the reaction between BF_3 (Lewis acid) and NH_3 (Lewis base) (**Figure 2**).

Conventional Lewis acids have long been used as catalysts and played significant roles in various chemical transformations, particularly organic synthetic reactions. Notably, in oxidation and reduction reactions, electrophilic aromatic substitution reactions exemplified by Friedel-Crafts alkylation and acylation, and halogenation reactions of benzene. Conventional Lewis acids have catalyzed other numerous organic reactions typified by the Diels-Alder reaction, Alder-ene reaction, aldol reaction, reactions of silyl enol ethers (direct (1,2-) addition, and conjugate (1,4-) addition) and acylation of ketones.

2. Conventional uses of Lewis acids in organic synthesis

Lewis acids have been used and applied in numerous organic transformations. They have been in various functional group transformations and C-C/C-X bond formation reactions [9–11]. Below are selected representative reactions that are only intended to highlight the importance of Lewis acids in organic synthesis but by no means a comprehensive review of all organic transformations catalyzed by Lewis acids. For additional details, the reader is advised to consult the original literature.

2.1 Oxidation reactions

Primary alcohols and secondary alcohols can be oxidized to the corresponding aldehydes and ketones, respectively, using TPAP/NMO oxidation method (TPAP: tetrapropylammonium perruthenate, NMO: *N*-methyl morpholine *N*-oxide) (**Figure 3**) [12].

The perruthenate ion acts as a Lewis acid on its Ru center (**Figure 4**). The reaction is initiated by the reaction of the Lewis basic alcohol and the Lewis acidic Ru on the perruthenate ion to give an intermediate that leads to the product aldehyde. The resultant Lewis acidic Ru (RuO_3H) species then reacts with the O-Lewis basic NMO to regenerate the Lewis acidic perruthenate catalyst.

Allylic and benzylic alcohols can be selectively oxidized to the corresponding aldehydes using activated MnO_2 (**Figure 5**) [13, 14].

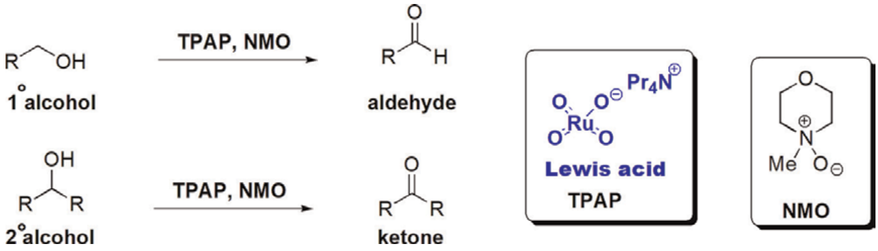

Figure 3.
Oxidation of alcohols using Lewis acidic TPAP/NMO.

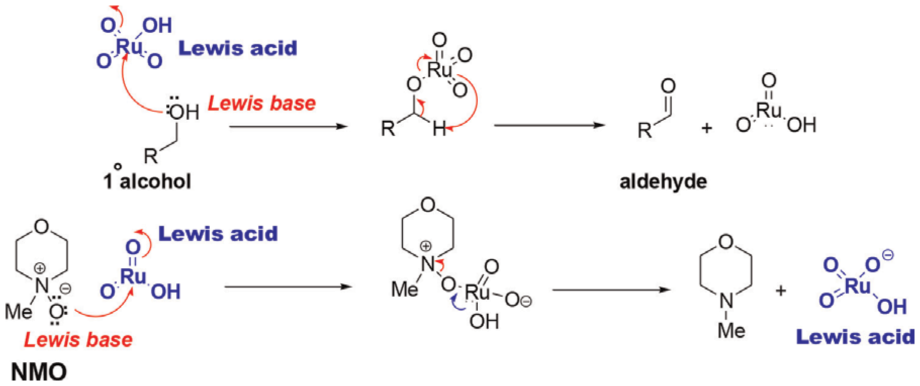

Figure 4.
Mechanism of the TPAP/NMO oxidation of alcohols.

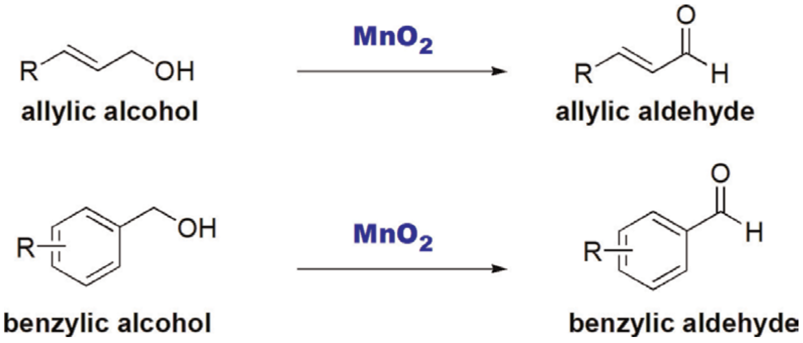

Figure 5.
Oxidation of allylic and benzylic alcohols with MnO_2.

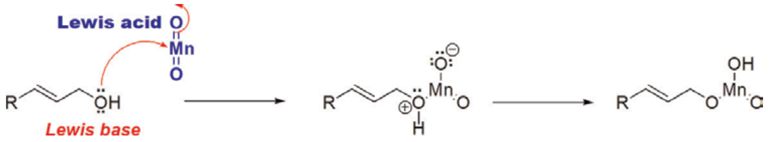

Figure 6.
The reaction between the Lewis acidic MnO_2 *with allylic alcohol.*

In the reaction, MnO_2 functions as a Lewis acid that accepts an electron pair from the Lewis basic O of the alcohol (**Figure 6**).

It has been reported that oxidation of alcohols to the corresponding ketones with potassium permanganate, $KMnO_4$, can be accelerated using Lewis acids, such as BF_3, Sc(OT*f*)$_3$, Zn (OT*f*)$_3$, Ca(OT*f*)$_3$, and Ba(OT*f*)$_3$ (**Figure** 7) [15]. The reaction is understood to be initiated by an initial reaction between the Lewis acid and the Lewis basic permanganate ion, MnO_4^-, leading to a Lewis adduct that affects the oxidation reaction (**Figure** 7).

Oxidation of sulfides to the corresponding ketones by $KMnO_4$ could be enhanced using the Lewis acidic $FeCl_3$ (**Figure** 8) [16]. The reaction is initiated by a Lewis complex that is formed upon the reaction of the Lewis basic permanganate, MnO_4^-, and the Lewis acidic $FeCl_3$ (**Figure** 8).

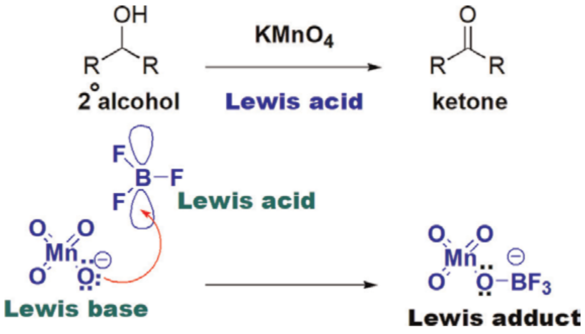

Figure 7.
Acceleration of alcohol $KMnO_4$ *oxidation by Lewis acids.*

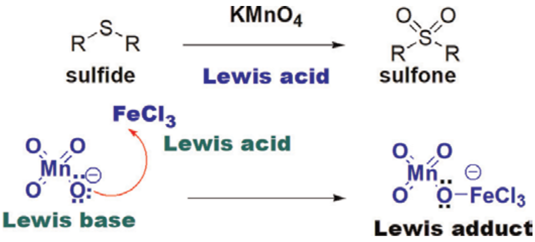

Figure 8.
Acceleration of sulfide $KMnO_4$ oxidation by Lewis acidic $FeCl_3$.

2.2 Reduction reactions

Esters can be reduced to the corresponding aldehydes using DIBAL-H (diisobutylaluminum hydride) at very low temperatures (−78°C) [17]. DIBAL-H acts as a Lewis acid, thus accepting an electron pair from the Lewis basic ester (**Figure 9**). The conversion of the ester into the corresponding aldehyde lies in the formation of the Lewis complex that leads to a tetrahedral intermediate that leads to the aldehyde upon aqueous workup.

Lewis acids have been used as reducing agents in various functional group transformations. Based on the electron deficiency of Lewis acids, which stems from the presence of empty orbitals, they react with electron-rich carboxylic acids and carboxylic acid derivatives, such as amides. In this regard, borane, BH_3, is found to be an excellent reducing agent for amides [18] and carboxylic acids [19] to primary amines (**Figure 10**) and primary alcohols, respectively. Borane, BH_3, is a mild reducing agent

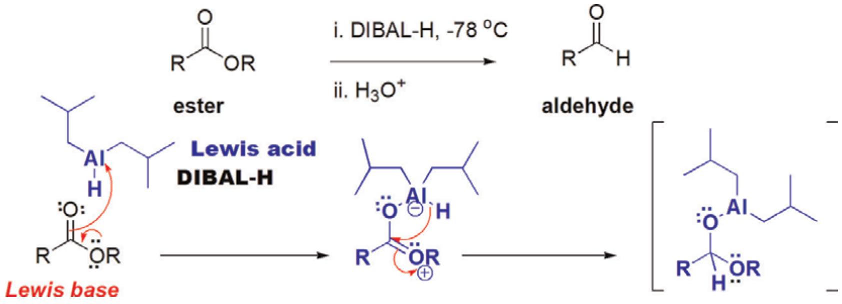

Figure 9.
Reduction of esters with Lewis acidic DIBAL-H at very low temperature.

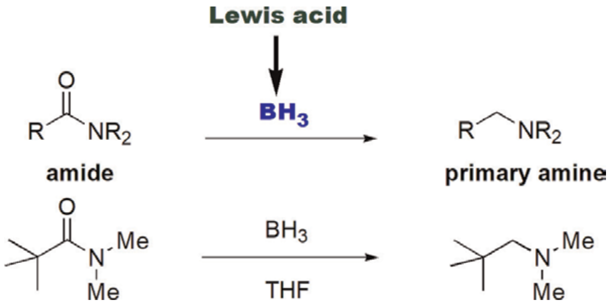

Figure 10.
Reduction of amides using borane, BH_3.

that is used instead of the more reactive $LiAlH_4$ that requires special handling procedures. The gaseous BH_3 is conveniently used as a liquid complex with diethyl ether ($BH_3.Et_2O$), tetrahydrofuran (BH_3.THF), or dimethyl sulfide (BH_3.DMS). The utility of BH_3 as an amide-reducing agent is extended to its chemoselective reduction ability of amides in the presence of less electron-rich carboxylic acid derivatives such as esters.

Mechanistically, amides utilize the *N* lone pair for donation to an empty p orbital in the Lewis acidic *B* in BH_3. In this manner, a Lewis adduct is formed from which a hydride transfer is initiated from the nucleophilic B to the electrophilic C affecting eventually leading to the reduction of the amide to the primary amine (**Figure 11**).

Similarly, carboxylic acids can conveniently be reduced with borane to give the corresponding primary alcohols (**Figure 12**). Borane has proven to be a highly efficient chemoselective reducing agent for carboxylic acids in the presence of less electron-rich carbonyl groups such as esters (**Figure 12**).

Sodium borohydride, $NaBH_4$, is known as a mild reducing agent for aldehydes and ketones. If an α,β-unsaturated carbonyl compound, such as the α,β-unsaturated ketone shown (**Figure 13**), is treated with $NaBH_4$, reduction of the both carbonyl group and the double bond takes place. Thus, the reaction is not regioselective/chemoselective. Chemoselective reduction of the carbonyl group in α,β-unsaturated ketone, while keeping the double bind intact, can be nicely achieved by adding the

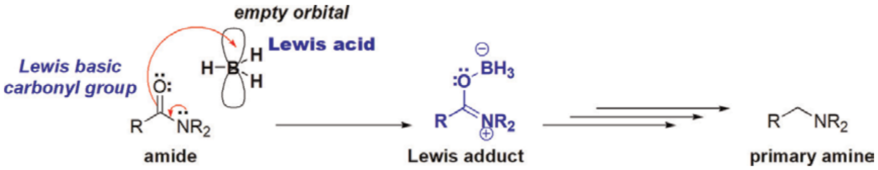

Figure 11.
The mechanism for the reduction of amides using borane, BH_3.

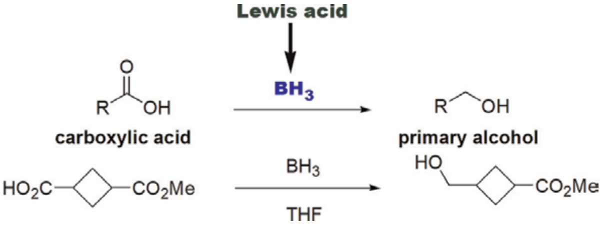

Figure 12.
Reduction of carboxylic acids using borane, BH_3.

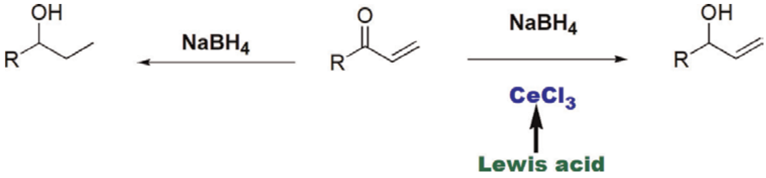

Figure 13.
Chemoselective reduction of α,β-unsaturated carbonyl compounds using $NaBH_4$-$CeCl_3$ *reduction (Luche reduction).*

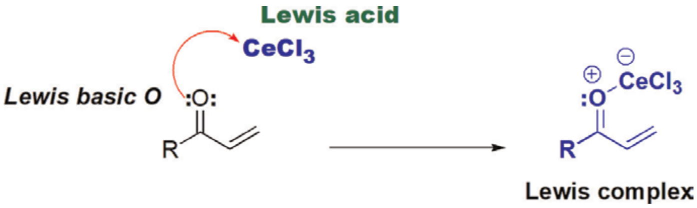

Figure 14.
The role of $CeCl_3$ in $NaBH_4$-$CeCl_3$ reduction (Luche reduction).

Lewis acidic cerium chloride, $CeCl_3$ (**Figure 13**). The $NaBH_4$-$CeCl_3$ reduction method is known as Luche reduction [20].

The role of the Lewis acidic $CeCl_3$ lies in its reaction with Lewis basic O of the carbonyl group. That is by donation of an electron pair from O to an empty orbital in Ce (**Figure 14**). The Lewis complex produced facilitates subsequent and chemoselective reduction of the ketone by $NaBH_4/CeCl_3$ in the presence of the C=C bond.

2.3 Electrophilic aromatic substitution: Friedel-crafts alkylation and acylation

Traditionally, Lewis acids have been used as catalysts in electrophilic aromatic substitution reactions of benzenes as typified by Friedel-Crafts alkylation and acylation reactions. The Friedel-Crafts alkylation employs benzene as a starting reactant that is reacted with an alkyl halide in the presence of AlX_3 as a catalyst (**Figure 15**) [21].

Due to the inherent stability of benzene, the Lewis acid catalyst is essential for the reaction. That is, no reaction would take place in the absence of a Lewis acid catalyst. Benzene needs a highly electrophilic species to react with in order for the electrophilic aromatic substitution to take place. Although alkyl halides are electrophilic by inductive effect, they are not sufficiently electrophilic for benzene to lose aromaticity and react with them. This will require a high-energy barrier to overcome. The role of the AlX_3 Lewis acid catalyst lies in its reaction with the Lewis basic alkyl halide. The alkyl halide donates one of the electron pairs on the halogen to the empty p orbital on Al in AlX_3. That is employing a HOMO from X in RX to the LUMO on Al in AlX_3. This results in the formation of the Lewis adduct, where a new σ bond between X and Al has formed. This Lewis adduct is a highly electrophilic species that is sufficiently electrophilic for the stable nucleophilic benzene (**Figure 16**).

The resultant Lewis adduct imparts a positive/electrophilic character on C bonded to X in the adduct. From a mechanistic point of view, this intermediate is susceptible to benzene nucleophilic attack. Alternatively, the electrophilic Lewis adduct can also

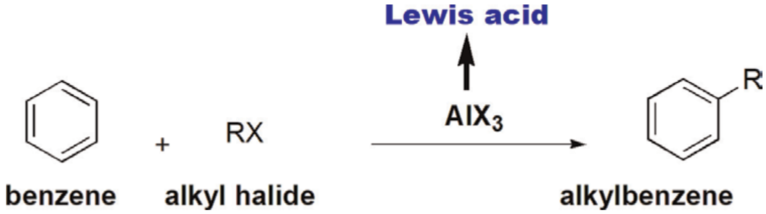

Figure 15.
Friedel-crafts alkylation of benzene.

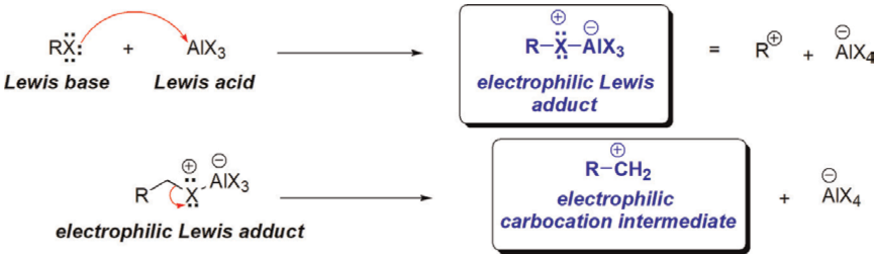

Figure 16.
Role of Lewis acidic $AlCl_3$ in Friedel-crafts alkylation of benzene.

be envisioned to undergo dissociation to an electrophilic carbocation intermediate setting stage for nucleophilic attack by benzene (**Figure 16**). The figure below shows examples of Friedel-Crafts alkylation of benzene (**Figure 17**).

Friedel-Crafts acylation of benzene is the reaction of benzene with an acid halide (or anhydride) in the presence of a Lewis acidic AlX_3 (**Figure 18**) [21].

As in the Friedel-Crafts alkylation reaction, the Lewis acid catalyst is essential for the Friedel-Crafts acylation reaction. The role of the AlX_3 Lewis acid catalyst lies in its reaction with the Lewis basic acid halide. The acid halide acts as a Lewis base employing one of the electron pairs on the halogen. Thus, an electron pair is donated from the Lewis basic X to the empty p orbital on Al in AlX_3. This results in the formation of the Lewis adduct, where a new σ bond between X and Al has formed. This Lewis adduct is a highly electrophilic species that is sufficiently electrophilic rendering its susceptibility to nucleophilic attack by benzene (**Figure 19**).

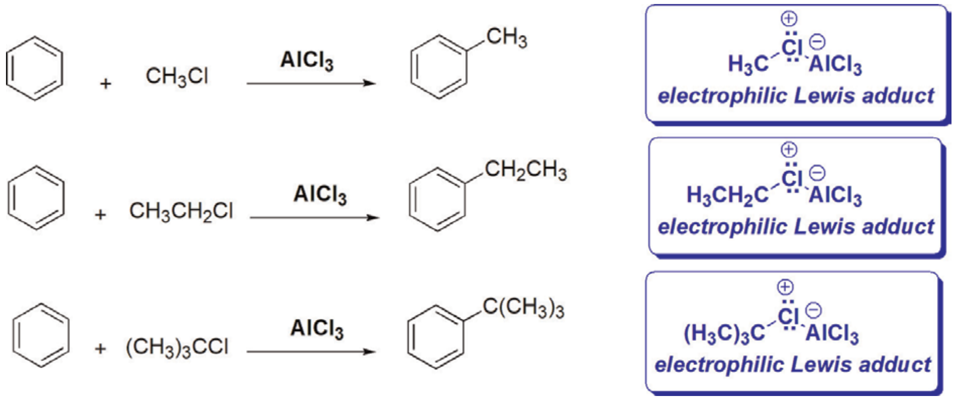

Figure 17.
Examples of Friedel-crafts alkylation of benzene.

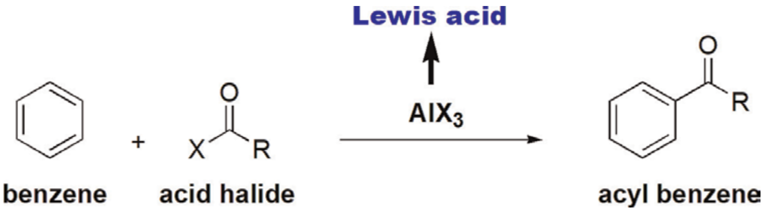

Figure 18.
Friedel-crafts acylation of benzene.

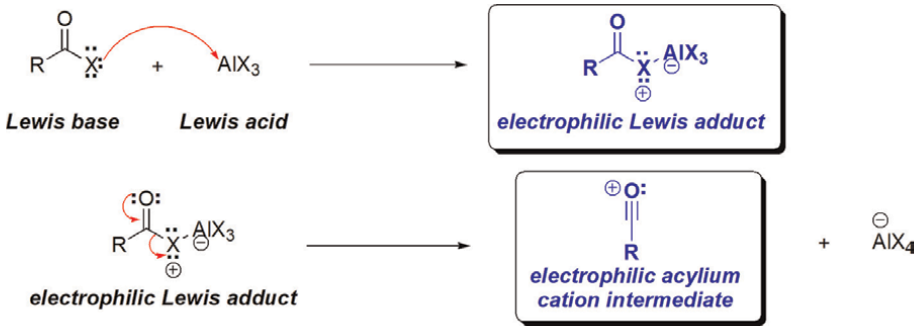

Figure 19.
Role of Lewis acidic $AlCl_3$ in Friedel-crafts acylation of benzene.

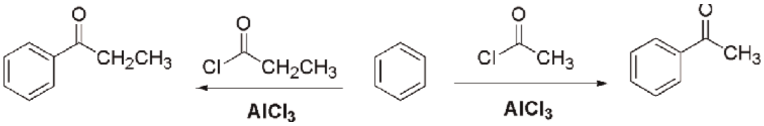

Figure 20.
Examples of Friedel-crafts acylation of benzene.

The electrophilic Lewis adduct formed can be envisioned to undergo dissociation to a highly electrophilic acylium cation intermediate. Thus, the stage is set for a facile Friedel-Crafts acylation reaction (**Figure 19**). The figure below shows examples of Friedel-Crafts acylation of benzene (**Figure 20**).

2.4 Electrophilic aromatic substitution: Halogenation

Halogenation of benzene using a halogen in the presence of FeX_3 is an example of electrophilic aromatic substitution reactions (**Figure 21**). In the reaction, FeX_3 acts as a Lewis acid, which is essential for the reaction [22].

The Lewis basic halogen, X_2 donates an electron pair from X to an empty orbital on Fe in FeX_3 to form an electrophilic Lewis adduct (**Figure 22**). This electrophilic intermediate is susceptible to nucleophilic attack by benzene at the terminal halogen (X) of the polarized X-X bond. This electrophilic Lewis adduct can be envisioned to undergo dissociation of the polarized X-X bond to give X^+ as an equivalent electrophilic intermediate (**Figure 22**). Thus, the stage is set for a benzene nucleophilic attack.

The Figure below shows examples of the halogenation of benzene (**Figure 23**).

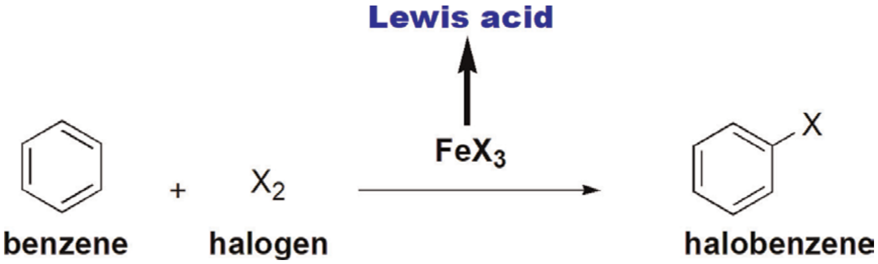

Figure 21.
Halogenation of benzene using X_2 in the presence of FeX_3.

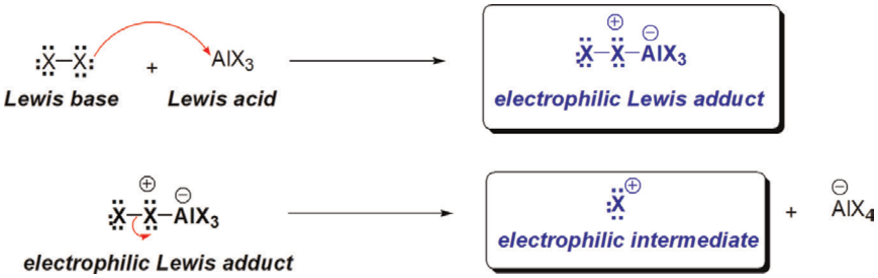

Figure 22.
Role of Lewis acidic FeX_3 in Friedel-crafts acylation of benzene.

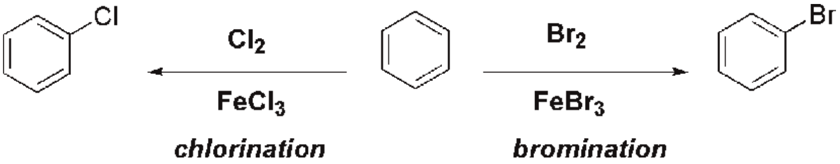

Figure 23.
Examples of halogenation of benzene using X_2 in the presence of FeX_3.

2.5 Hydroboration-oxidation

Hydroboration-oxidation is an electrophilic addition of borane, BH_3, to alkenes or alkynes. In the case of hydroboration of alkenes, the product is alcohol that ends at the less sterically hindered or more accessible C of C=C bond of the alkene (**Figure 24**) [23]. This method is a complementary method to the oxymercuration of alkenes that leads to the more substituted alcohol. Unlike oxymercuration, which follows Markovnikov's rule, hydroboration-oxidation is an anti-Markovnikov's alcohol formation. BH_3 acts as a Lewis acid/electrophile that utilizes its empty p orbital to accept an electron pair from the nucleophilic double bond in an alkene. The hydroboration addition takes place in a concerted manner, thus governed by steric control. As a result, the BH_2 group of the electrophilic BH_3 ends up at the less sterically hindered (more accessible) C of the C=C bond, while H bonds to the more sterically hindered C (less accessible).

2.6 Diels-Alder reaction

The Diels-Alder reaction is an electrocyclic [4 + 2] cycloaddition reaction between a diene and a dienophile [24, 25]. It is a robust and well-established C-C formation method. Typically, the diene is bonded with an electron-donating group (EDG), such as alkoxy (OR) or amino groups (NR_2), and thus electron-rich. The dienophile is

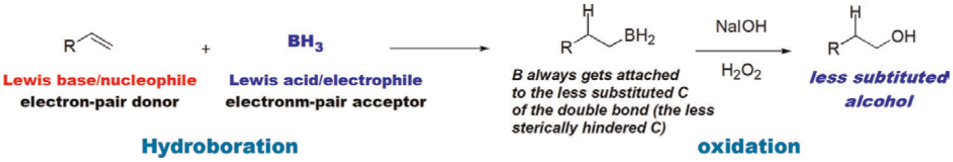

Figure 24.
Hydroboration-oxidation of alkenes.

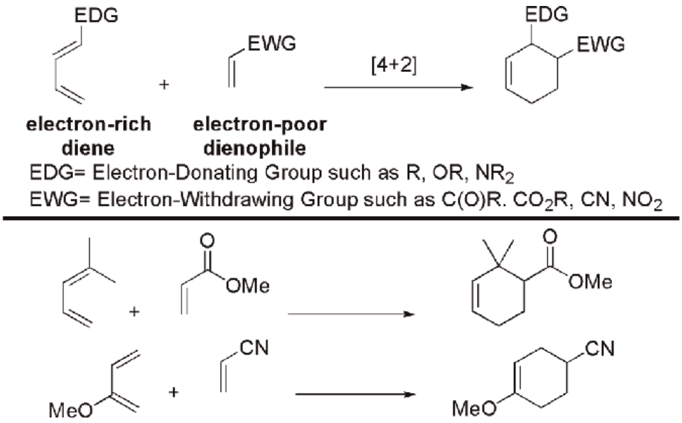

Figure 25.
Diels-Alder reaction.

typically electron-poor, because of attachment with an electron-withdrawing group (EWG), such as an ester (CO_2R), cyano (CN), or nitro (NO_2) groups (**Figure 25**). The regioselectivity is governed by proper interactions between the HOMO of the diene and the LUMO of the dienophile (**Figure 26**).

Diels-Alder reactions that do not meet the proper electron-demand/match involving an electron-rich diene and electron-poor dienophile may require Lewis acid catalysis. The role of Lewis acids lies in their activation of the Lewis basic dienophile by binding with it. Formation of the Lewis adduct results in lowering the LUMO of the dienophile (**Figure 26**). The result is a smaller energy gap between the HOMO of the diene and the LUMO of the dienophile, setting the stage for stronger orbital interactions and thus enhancement of reaction rates. Lewis acids, such as $AlCl_3$, BF_3, $ZnCl_2$, and $TiCl_4$, have been found to be efficient catalysts for the Diels-Alder reaction.

2.7 Alder-ene reaction

The Alder-ene reaction is an electrocyclic cycloaddition reaction between an ene and an enophile (**Figure 27**) [26, 27].

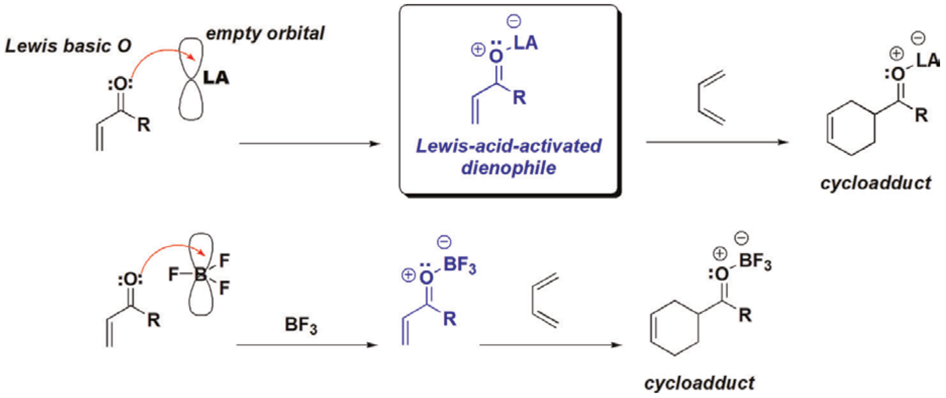

Figure 26.
Role of Lewis acids in activation of dienophiles as reaction partners in Diels-Alder reactions.

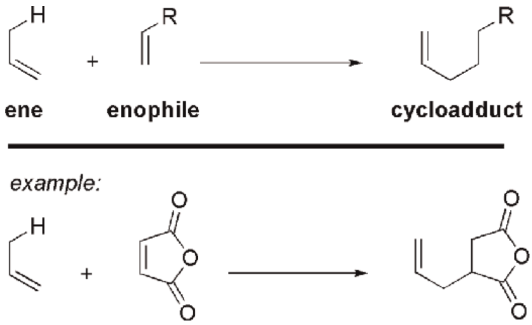

Figure 27.
The Alder-ene reaction.

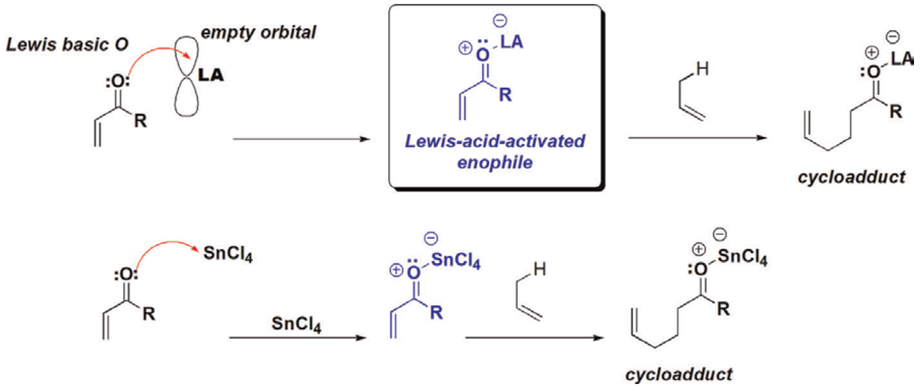

Figure 28.
Role of Lewis acids in activation of enophiles in the Alder-ene reaction.

The role of Lewis acids in the Alder-ene reaction lies in their activation of the enophile by binding with it thus lowering the LUMO of the enophile (**Figure 28**). As a result, the energy gap between the HOMO of the ene and the LUMO of the enophile is lowered. Therefore, the resultant stronger interactions facilitate the ene reaction.

2.8 Mukaiyama aldol reaction

The aldol reaction, which is a reaction between an enolate of a carbonyl compound and an aldehyde or ketone to form β-hydroxy carbonyl compound or α,β-unsaturated carbonyl compound. The Mukaiyama aldol reaction is a variant of the aldol reaction that employs a silyl enol ether, an enolate equivalent, as a nucleophile, an aldehyde or a ketone as an electrophile in the presence of $TiCl_4$ as a Lewis acid catalyst (**Figure 29**) [28].

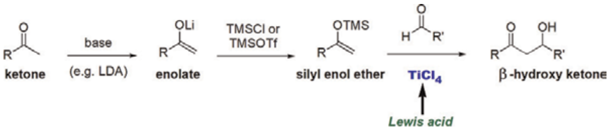

Figure 29.
The Mukaiyama aldol reaction employs $TiCl_4$ as a Lewis acid.

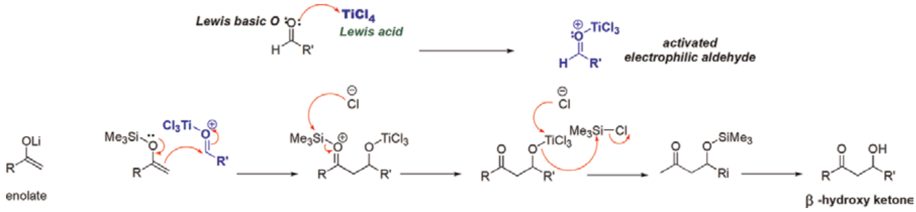

Figure 30.
The role of the Lewis acidic TiCl4 in the Mukaiyama aldol reaction.

The role of the $TiCl_4$ Lewis acid catalyst lies in its coordination with the electrophilic aldehyde or ketone. The Lewis basic O of the carbonyl group employs one of its lone pairs for donation to an empty orbital on the Lewis acidic Ti in $TiCl_4$. The result is the formation of a Lewis adduct that is an activated aldehyde with enhanced electrophilicity. The highly electrophilic aldehyde-$TiCl_3$ Lewis complex sets the stage for subsequent nucleophilic attack by the silyl enol ether (**Figure 30**). The reaction continues to ultimately give the β-hydroxy carbonyl compound.

2.9 C-F bond functionalization

The synthetic utility of Lewis acids has been extended to C-F bond functionalization reactions [29]. Lewis acids based on B, Si, and Al have affected the hydrodefluorination of alkyl fluorides, which is the transformation of C-F bond into C-H bond (**Figure 31**). Lewis acids based on B, Al, and Si (**Figure 30**) have achieved the ultimate functionalization of C-F bonds. Functionalization of C-F bonds has been achieved due to the high Lewis acidity of B, Al, and Si and to the high fluoride affinity, especially in the case of Si.

3. Green Lewis acids

3.1 Uses in various organic reactions

Typical Lewis acids, such as BF_3 and $AlCl_3$, are highly reactive with water. Thus, they are non-recoverable and end up as waste at the end of reactions. Catalysis is one of the 12 principles of green chemistry and this is due to the minimization of waste at the end of the reaction. Prevention of waste is another principle of the 12 principles of green chemistry. Therefore, it is a viable strategy to seek and develop green Lewis acid

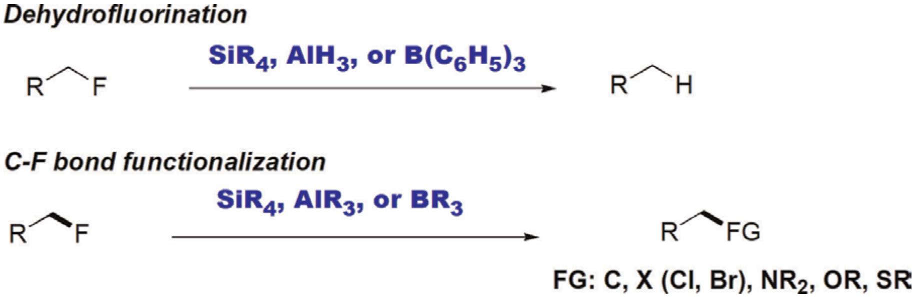

Figure 31.
Lewis acid-assisted C-F bond functionalization.

alternatives to the highly water-sensitive Lewis acids, such as BF_3 and $AlCl_3$ [30]. From a green chemistry point of view, the alternative should still function as a catalyst and it should not be water-sensitive. The idea is to minimize waste that is obtained at the end of reactions that employ BF_3 and $AlCl_3$. Lanthanide triflates (trifluoromethanesulfonate) are water-soluble and recyclable. The triflate group is a strongly electron-withdrawing group that imparts or enhances the Lewis acidity of the lanthanide. Thus, they are considered green Lewis acids. Examples of lanthanide triflates are $Yb(OTf)_3$, $Sc(OT\mathit{f})_3$, and $Ln(OT\mathit{f})_3$, which have been in various organic reactions (**Figure 32**) [31].

Developments of green alternatives to the classical stoichiometric oxidants, such as CrO_3 and MnO_2, that employ heavy metals producing metal waste, thus posing environmental problems, are sought. Ideal oxidants should be stable, active, and selective and ideally based on green oxidants, such as air or dilute H_2O_2. An example of green Lewis acidic oxidant is TS-1 (titanium silicate) (**Figure 33**) [32]. TS-1 is especially useful for oxidation reactions using H_2O_2 where the only by-product is water. Examples of its use include its catalytic conversion of cyclohexanone into cyclohexanone oxime, which is elaborated into caprolactam, a nylon 6 precursor (**Figure 33**).

A green Lewis acid-based zeolite, Sn-beta, was developed. Sn-beta [33] has been found to catalyze various oxidation methods/processes such as Baeyer-Villiger

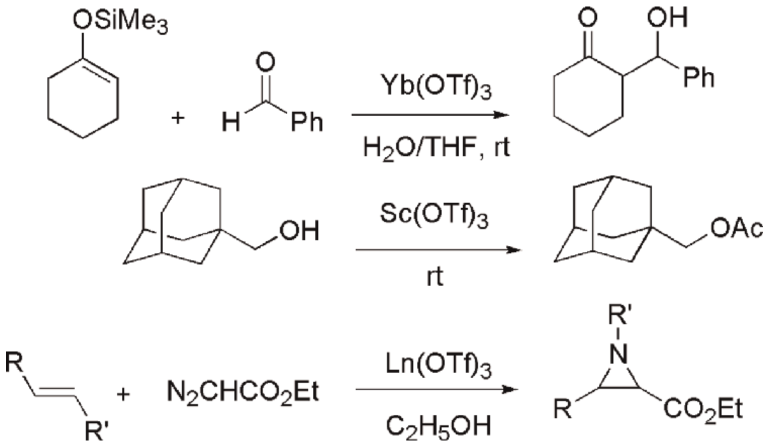

Figure 32.
Lanthanide triflates as Lewis acids in organic reactions.

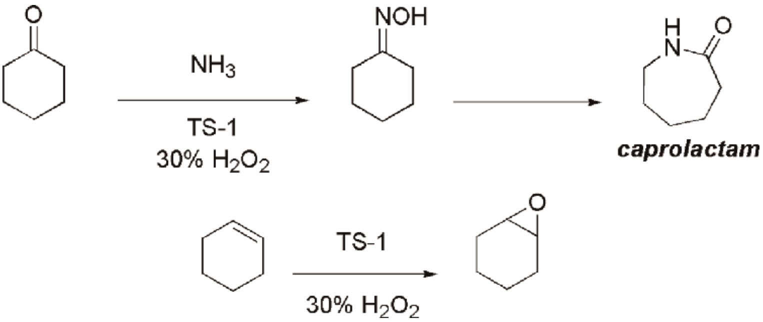

Figure 33.
Use of TS-1 in organic reactions.

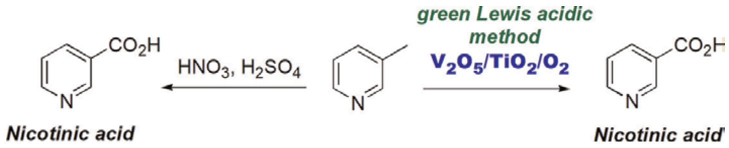

Figure 34.
Use of Lewis acids as green oxidant toward nicotinic acid.

oxidation reaction of ketones to produce the corresponding esters. Typical oxidations of alkylbenzene or aromatic compounds involve HNO_3/H_2SO_4 oxidation method (**Figure 34**). A green alternative to the harsh Lowry-Bronsted acidic method is using mild Lewis acid. An oxidation method that employs V_2O_5 and TiO_2 is found to oxidize 3-methyl pyridine into nicotinic acid [34].

TPAP (tetrapropylammonium perruthenate), *vide supra*, a Lewis-acidic oxidizing agent for alcohols to aldehydes and ketones, has been heterogenized by reaction of $KRuO_4$ with NH_4Cl functionalized polystyrene [35]. Heterogenization is an environmentally benign process that converts a homogenous catalyst into a heterogeneous one by attaching the catalyst to a metal support, such as SiO_2, Al_2O_3, graphite, or zeolite. The process permits the separation and recovery of the Lewis acid and thus setting the stage for recycling and reuse. Hence, heterogenized Lewis acids fulfill the requirements of green Lewis acids.

3.2 Aqueous Diels-Alder reaction

The Diels-Alder reaction is one of the great C-C bond formation reactions. Its great utility in organic synthesis has been extended to its ability to take place in the presence of water in organic solvents or in water as the sole solvent [36–38]. Rates of Diels-Alder reactions have been tremendously accelerated in water/aqueous media. The enhancement of reaction rates is attributed to the association of water molecules with each other forcing organic molecules to come in proximity with each other and thus close contact commencing reactions. Lewis acid-catalyzed Diels-Alder reactions that have been carried out in water/in the presence of water have demonstrated the hydrophobic effect. Examples are shown below (**Figure 35**). Lewis acid-catalyzed aqueous Diels-Alder reactions manifest themselves as green organic reactions by fulfilling some great green chemistry principles, such as catalysis, prevention of waste, and use of environmentally benign solvents.

3.3 Aqueous aldol reaction

The aldol reaction is one of the great C-C bond formation reactions in organic synthesis. Their ability to take place in the presence of water has extended their utility/versatility in organic synthesis. Lewis acid-catalyzed aqueous aldol reactions have been possible employing silyl enol ether as masked nucleophilic enolates and a wide range of metal chloride, perchlorate of triflate (**Figure 36**) [31, 38].

3.4 As ionic liquids

Ionic liquids are produced from large, non-coordinating asymmetric ions with one of them being organic. Usually, the organic ion is a bulky heterocyclic cation that interacts with a small inorganic anion. Due to difference in size, the ion

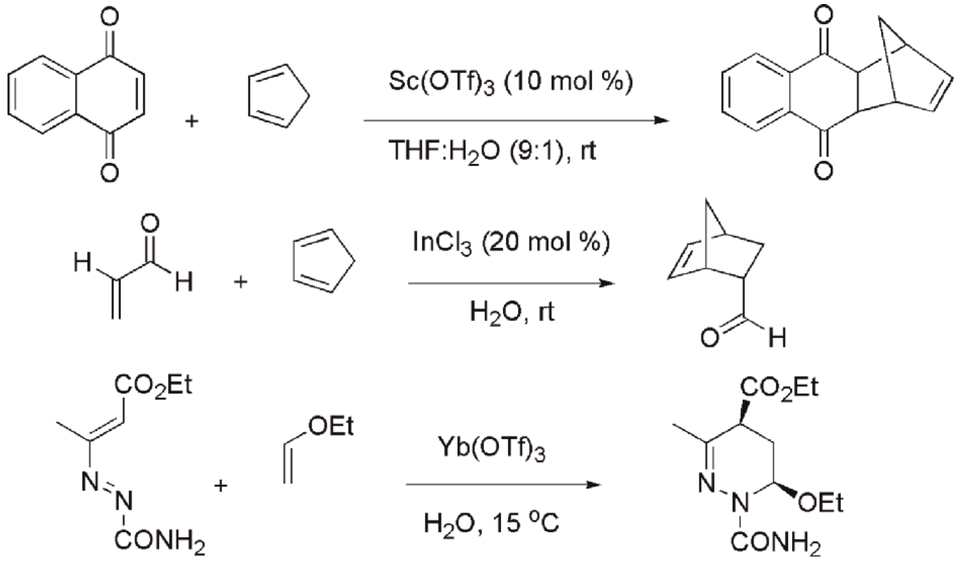

Figure 35.
Examples of Lewis acid-catalyzed Diels-Alder reactions in water.

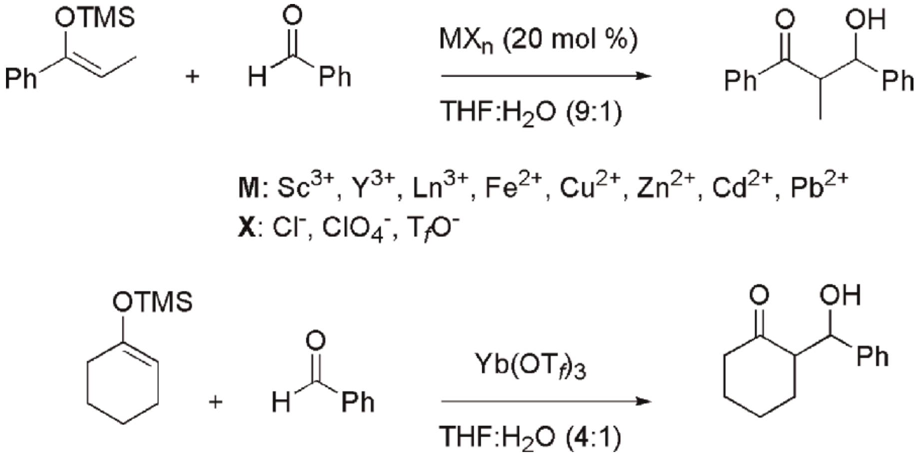

Figure 36.
Examples of Lewis acid-catalyzed aldol reactions in water.

packing in ionic liquids is poor, which makes them liquids at room temperature. Examples of ionic liquid include [(emim)$AlCl_4$], [(bmim)BF_4], and [(bmim)PF_6] (**Figure 37**) [39].

The positive/electrophilic character of the bulky organic ion imparts Lewis acidity to ionic liquids. Thus, they are used as catalysts. Ionic liquids Lewis acidic catalysts that are not miscible with organic solvents are separable from reaction mixtures, thus recoverable and recyclable/reusable. Therefore, catalytic Lewis acidic ionic liquids are green Lewis acids. Reactions involving ionic liquids may result in simpler workup procedures, especially if the organic product is immiscible with the ionic liquid. This allows easy and simple product separation and purification. [(emim)$AlCl_4$] has been used as a catalyst in oligomerization/polymerization reactions that occurred with a

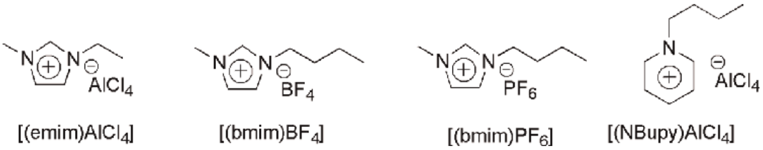

Figure 37.
Examples of ionic liquids.

high reaction rate and conversions. The Lewis acidity of ionic liquids can be enhanced by increasing the amount of the Lewis acid, the counter anion, in the formation process. Ionic liquids have been immobilized for uses and applications in alkylation reactions of aromatic compounds, such as benzene, toluene, and naphthalene with olefins [39].

3.5 Oil refining

Cracking of heavy oil fractions is required for the efficient production of gasoline. Original catalytic cracking methods were carried out thermally employing $AlCl_3$ as a Lewis acid. Such processes were considered inefficient due to their high-energy intensive feature and also due to the use of wasteful, corrosive, and environmentally non-friendly Lewis acid. Catalytic cracking currently and commonly employs zeolites such as zeolite Y. Zeolites are made of three-dimensional frameworks of crystalline hydrated aluminosilicates consisting of TO_4 (T: tetrahedral, Si or Al). Zeolites are hydrated, which imparts significant Brønsted acidity (**Figure 38**) [40].

The exact nature of zeolite is determined by important parameters, such as reaction conditions and *silica-to-alumina ratio*. ZSM-5 is an aluminosilicate mineral that is used to alkylate benzene with ethane to give ethylbenzene selectively. Many zeolites are not stable at high temperatures in the presence of water, due to the dealumination process (**Figure 39**). SiO_2 is added to obtain high silica zeolites, which are used in the bulk chemical industry.

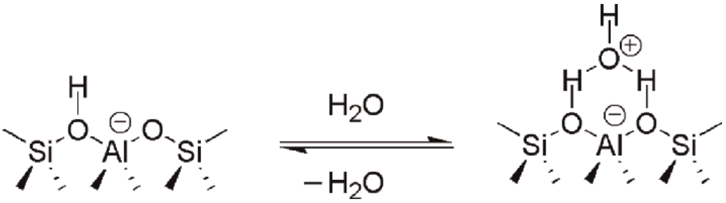

Figure 38.
The structure of zeolites.

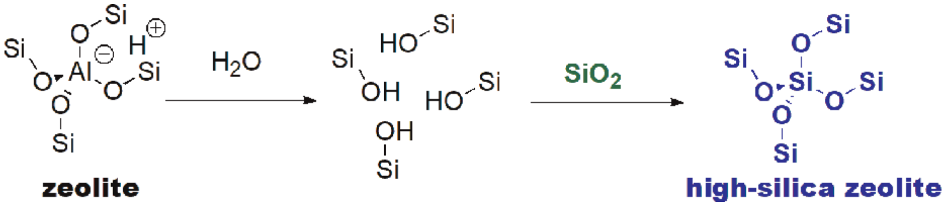

Figure 39.
Dealumination of zeolites and formation of high silica zeolites.

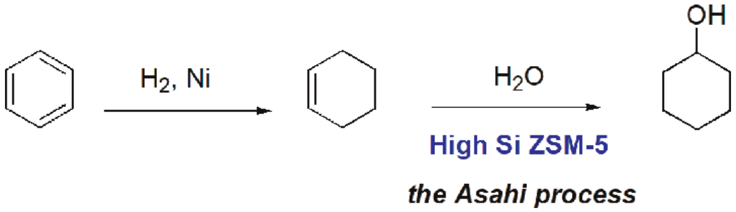

Figure 40.
Use of high silica zeolite.

High silica zeolites result in reactions with high yields and better selectivity. Green development is the *Asahi process*, hydration of cyclohexene to cyclohexanol (applications toward nylon 6 (*via* adipic acid) and nylon 6.6 (*via* caprolactam)) using high silica ZSM-5 with SiO_2/Al_2O_3 ratio of 25 (**Figure 40**) [40].

4. Concluding remarks

Due to their electron-pair affinity, Lewis acid catalysts have catalyzed various and numerous organic reactions, and C-C bond formation methods and processes. Their utility has been extended to their compatibility with water as a reaction medium. The catalytic feature of Lewis acids and the ability to use them in aqueous media make them environmentally benign and thus green catalysts. Applications of Lewis acids have been demonstrated by their ability to catalyze various organic transformations/reactions and in the ultimate and constantly sought reaction medium, water. The power of Lewis acids has affected the challenging C-F bond functionalization reactions. Lewis acids have seen applications in green processes/methods, such as ionic liquids, and in industrial processes, such as catalytic cracking in oil refining. It is envisioned that Lewis acids will have the potential to further contribute in the field of C-X bond functionalization reactions and other green transformations/processes.

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Chapter 4

Perspective Chapter: The Acidity Concept According to Lewis

Eylem Kuzu and Hasan Genç

Abstract

There are certain essential concepts that need to be considered before moving on to the reaction mechanisms in organic chemistry. Having learned basic concepts appropriately, one can understand reaction mechanisms better. For this reason, we will primarily focus on basic concepts such as electrophile and lewis acids in this part. This chapter presents electrophilic compounds, lewis acids, and bases, which are important in organic chemistry, with understandable examples. The reactivity of polarized bonds to be formed by groups attached to a compound, Lewis acid/base reactions and the reactions of metals with related concepts are clearly explained with examples. In addition, the reaction mechanisms mentioned in this chapter are presented according to the molecular orbital approach and acidity and basicity properties.

Keywords: electrophile, Lewis acid, HOMO, LUMO, reaction mechanism

1. Introduction: Electrophiles

1.1 Electrophilic compounds

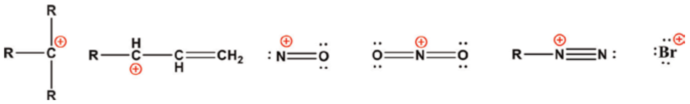
Chemical reactions are reactions based on the exchange of electrons. One compound gives out its electrons, while the other receives electrons. Meanwhile, atoms try to complete the number of electrons in their outer orbits in accordance with the octet rule. For a compound to accept electrons, it must be poor in electrons. Compounds that have fewer electrons and can receive electrons are called electrophilic compounds or electrophiles. Electrophile literally means electron loving. Electrophiles react with electron-rich compounds and try to fill or minimize the electron vacancy in their bodies [1].

It is possible to classify electrophilic compounds under certain groups.

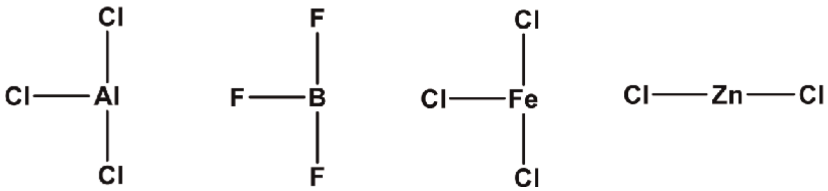
- Cations (compounds with positive (+) charge)
- Lewis acids
- Carbonyl compounds

1.1.1 Compounds containing polarized bonds

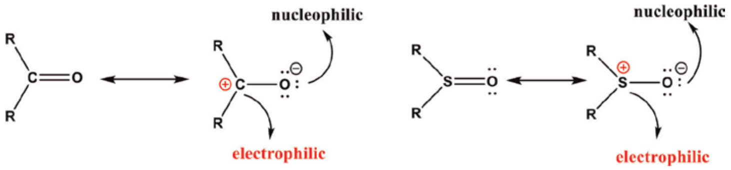
Positive (+) charged carbon, nitrogen, halogen compounds, etc. are classified in the cation group. Carbocations are sp^2 hybridized, positively (+) charged carbon compounds that bind three groups. They have electron vacancies. By reacting with nucleophiles, carbocations try to neutralize the positive (+) charge and to make the number of electrons in their bodies in line with the octet rule (1).


(1)

Lewis acids do not have protogenic properties like classical acids. Compounds that cannot donate protons but have an electron vacancy in their structure are included in this group. Compounds such as $AlCl_3$, BF_3, and $FeCl_3$ are neutral and the number of electrons in the outer orbit of the central atom does not comply with the octet rules. The number of electrons in the outer orbit is generally six. These compounds, easily reacting with these electron-rich ones, fill the electron vacancy in their outer orbits (2).

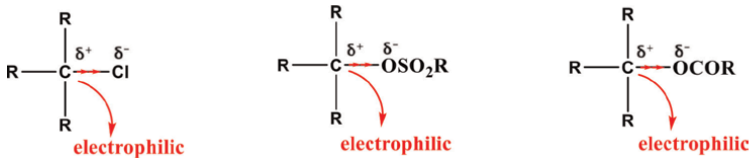

(2)

Carbonyl compounds are also potential electrophilic compounds. The double bonding electrons between carbon and oxygen become polarized because the oxygen attracts the electrons more. Therefore, the carbonyl carbon acquires a positive (+) charge, exhibits electrophilic properties, and reacts easily with nucleophiles. The double bond between the sulfur and oxygen also becomes polarized and the sulfur shows electrophilic properties (3).



(3)

Other than these compounds, all kinds of compounds with bond polarization show electrophilic properties. For example, since halogens are more electronegative than the carbon atom in alkyl halide, they attract the carbon halogen bond electrons towards them. As a result, the carbon atom becomes partially positively charged, while the halogen atom is negatively charged. Therefore, carbons attached to the halogen atom show electrophilic properties and react easily with nucleophiles (4).



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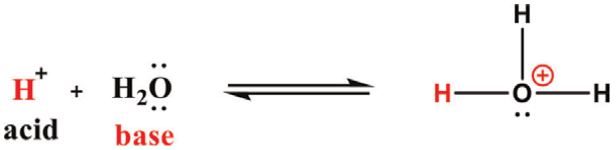
1.1.2 Lewis acid

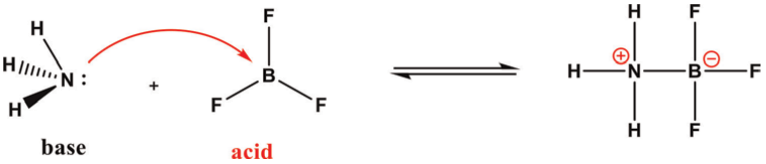
While the Arrhenius acid-base theory does not take into account the acid-base phenomenon in anhydrous environments, the Bronsted-Lowry acid-base theory completely excludes compounds that do not contain protons, since it is only about proton exchange. According to a theory that the American physical chemist Gilbert Newton Lewis (1875–1946) first brought up in 1923 and developed in 1938, compounds that can form a new bond by gaining a pair of electrons from a molecule or anion are called Lewis acids, and compounds that form a new bond by donating a pair of electrons to a molecule or cation are called Lewis bases. According to this definition, the proton is a Lewis acid. This definition covers many compounds that do not contain protons.



(5)

Let us examine the reaction between the proton and the H_2O molecule within the framework of Lewis acid-base theory. Since the proton has an electron vacancy in its outer orbit, it can easily accept a pair of electrons and is a Lewis acid. The oxygen of water, on the other hand, is a Lewis base because it can form a new bond by giving its free electrons to another atom. The proton forms a new sigma bond binding to the oxygen with a pair of free electrons on the oxygen (5).

Lewis acid-base theory explains why BF_3 reacts with NH_3 to form a complex. Since the hybridization of the boron atom in the BF_3 molecule is sp^2, the structure of the molecule is plane and there is also an empty p orbital on the boron. Boron trifluoride is a Lewis acid because the number of electrons in the outer orbital of the boron atom is six. This orbital takes a pair of electrons and turns them into a structure complying with the octet rule. In the ammonia molecule, there is a free electron pair that does not bind to the nitrogen atom. Thus, ammonia is a Lewis base. In the complex formation between NH_3 and BF_3, the nitrogen atom crosschecks the octet rule transferring its free electrons to the vacant p orbital of the boron atom (6).

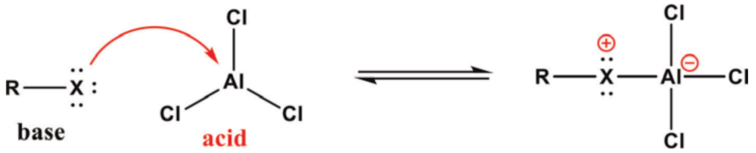


(6)

Likewise, $AlCl_3$ is also a Lewis acid because it has only six electrons in its aluminum outer shell (7). Compounds such as $ZnCl_2$, $FeCl_2$, $SnCl_4$, and $TiCl_4$, which have an electron vacancy in their outer orbits, also fall into the Lewis acid group.

(7)

In the Friedel-Crafts alkylation of aromatic compounds, compounds such as $AlCl_3$ are used as catalysts to increase the reactivity of alkyl halides. Aluminum trichloride forms a complex with a pair of nonbonding electrons of the alkyl halide. Aluminum trichloride is a Lewis acid because it has an electron vacancy in its outer shell. The halogen attached to the alkyl group is the Lewis base. The free electrons of the halogen attached to the alkyl group attack this vacancy and form a new covalent bond (8).



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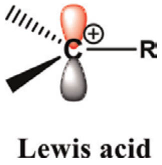
Carbocations are also classified in Lewis acids. A carbocation has, as shown earlier, three sp^2 hybrid orbitals and one vacant p orbital. Carbocations are compounds that are extremely prone to bond with Lewis bases (9).



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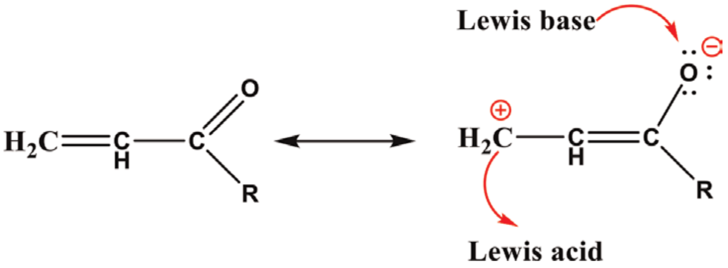
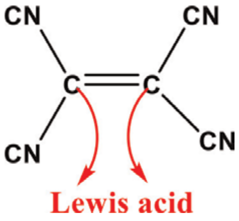
Double bonds with low electron density, for example, enon-type compounds (alpha, beta-unsaturated systems) react with Lewis bases and form covalent bonds due to the electron vacancy formed in the beta-position (10).



(10)

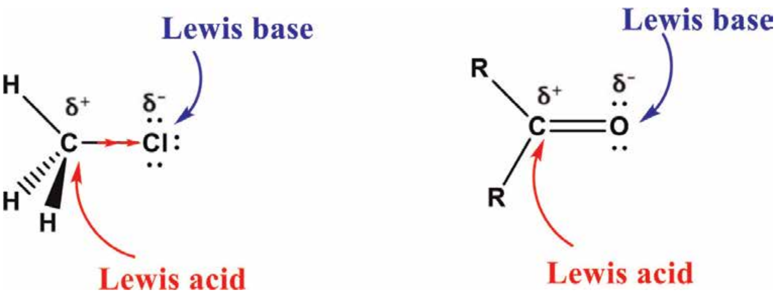
The carbon atoms of double bonds of tetracyanoethylene also have Lewis acid properties. Cyanide groups reduce the electron density of the double bond due to their strong electron-attracting properties. Therefore, nucleophiles (Lewis bases) attack carbon atoms of the double bond (11).



(11)

The hydride ion is the typical Lewis base. It reacts instantly with Lewis acids and forms covalent bonds. Unpolarized double-bond electrons are also Lewis bases. Since Lewis bases have high electron density, they instantly react with Lewis acids.

Polarized bonds form a dipole. One end of these bonds is a Lewis acid and the other end is a Lewis base. For example; carbon-halogen bonds are polarized bonds. Since the halogen atom attracts the sigma electrons between carbon and halogen more strongly and has non-free bonding electrons, it is a Lewis base. The carbon atom with reduced electron density acts as a Lewis acid. There is also a polarization in the carbonyl group. Therefore, the carbonyl carbon is the Lewis acid and the carbonyl oxygen is the Lewis base (12).



(12)

1.1.3 Lewis acid: Base definition

GN Lewis defined acids as substances that accept electron pairs and bases as substances that donate electron pairs. This definition is broader in scope than the Bronsted-Lowry definition. Reactions between compounds that do not contain protons are also acid-base reactions according to this definition. However, there is consistency between the two definitions. According to Bronsted-Lowry, acids are substances that donate positively charged particles (protons), whereas according to Lewis, acids are defined as substances that take negatively charged particles (electron pairs). According to the Lewis system, an example of a characteristic acid-base reaction is the reaction between trialkyl amine and boron trifluoride (13) [2].

$$\mathbf{R_3N:+BF_3 \rightleftharpoons R_3\overset{+}{N}——BF_3} \tag{13}$$

Trialkyl amine has an unshared electron pair on the nitrogen atom. In boron trifluoride, the boron atom has not completed its octet and has an electron pair deficiency. As the molecules combine, the unshared electron pair on the nitrogen atom forms the NB covalent bond. Since the nitrogen atom donates electrons during the reaction, the R_3N molecule containing this atom is Lewis base, and the BF_3 molecule containing the B atom that gains electrons is Lewis acid. The nitrogen atom is called a donor atom, meaning that it donates electrons, and the boron atom is called an acceptor atom, which means that it takes electrons.

Since the central atom or ion receives electrons in the formation of coordination compounds, they are Lewis acids. Ligands attached to the central atom are Lewis bases because they donate electrons.

$$\mathbf{4.CO + Ni \rightarrow Ni(CO)_4} \tag{14}$$

$$\mathbf{2.NH_3 + Ag^+ \rightarrow \left[Ag(NH_3)_2\right]^+} \tag{15}$$

In their reaction, CO and NH_3 are Lewis bases since they donate electron pairs, and Lewis acid, Ni, and Ag^+ accept electron pairs. In the formation of coordination compounds, since the central atom or ion gains electrons, Lewis acid. Ligands attached to the central atom are Lewis bases because they donate electrons (14 and 15).

Lewis acids:

1. Since they can accept electron pairs, all cations are Lewis acid (16 and 17).

$$\mathbf{Fe^{3+} + 6CN^- \rightarrow \left[Fe(CN)_6\right]^{3-}} \quad (16)$$

$$\mathbf{Cr^{3+} + 6NH_3 \rightarrow \left[Cr(NH_3)_6\right]^{3+}} \quad (17)$$

2. Compounds containing a central atom that gains electrons in the valence shell and can increase the coordination number act as a Lewis acid (18–20).

$$\mathbf{AIF_3 + 3F_6 \rightarrow [AIF_6]^{3-}} \quad (18)$$

$$\mathbf{SnCl_4 + 2Cl^- \rightarrow [SnCl_6]^{6-}} \quad (19)$$

$$\mathbf{SbF_5 + F^- \rightarrow [SbF_6]^-} \quad (20)$$

3. Molecules such as CO_2 and SO_3 that have one or more multiple bonds in their central atoms act as Lewis acids (21).

$$\mathbf{CO_2 + OH^- \rightarrow HCO_3^-} \quad (21)$$

General grouping can be made for Lewis bases.

1. All anions are Lewis bases. Increasing the charge density increases the base force (22).

$$\mathbf{H^+ + OH^- \rightarrow H_2O}OH^- \text{ is lewis base.} \quad (22)$$

2. Molecules with unshared electron pairs, such as water, alcohol, and ether, act as Lewis bases (23).

$$\mathbf{Cu^{2+} + 4H_2O \rightarrow \left[Cu(H_2O)_4\right]^{2+}} \quad (23)$$

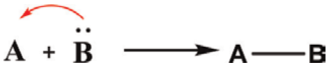
3. Alkynes that can form coordinate covalent bonds with metal ions acts as a Lewis base (24 and 25).

$$\mathbf{Ag^+ + C_2H_4 \rightarrow \left[Ag(C_2H_4)\right]^+} \quad (24)$$

$$\mathbf{Cr + 2C_6H_6 \rightarrow Cr(C_6H_6)_2} \quad (25)$$

1.1.4 Lewis definition

Lewis acid; electron pair acceptor; some defined it as a chemical species with an electron pair acceptor. A coordinate-covalent bond is formed as a result of electron pair transfer from B to A, with A Lewis acid and B Lewis base (26):



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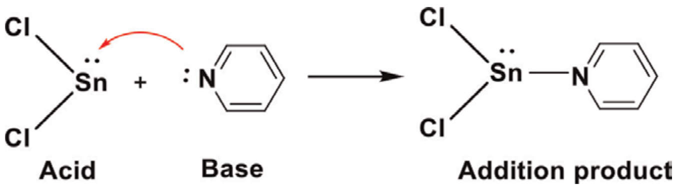
Lewis acid-base reaction from a two-electron reduction-oxidation (redox) reaction is the formation of a coordinate-covalent bond in the first. The oxidation numbers of atoms do not change in the formation of coordinate-covalent bonds. However, the characteristic feature of redox reactions is that the oxidation numbers change. Lewis acid-base reactions can be divided into three main groups:

a. Complex formation reactions: These are reactions in which Lewis acids and bases interact to form an addition product, as in the reaction. In the following reactions, the terms complex compound and complex ion are used for some of the products.

b. Pay attention (27–29):



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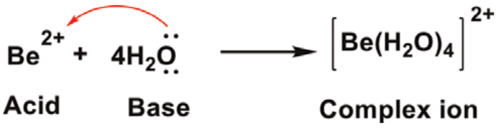

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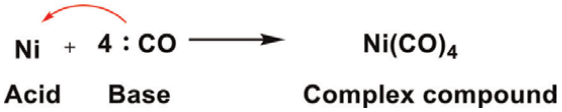
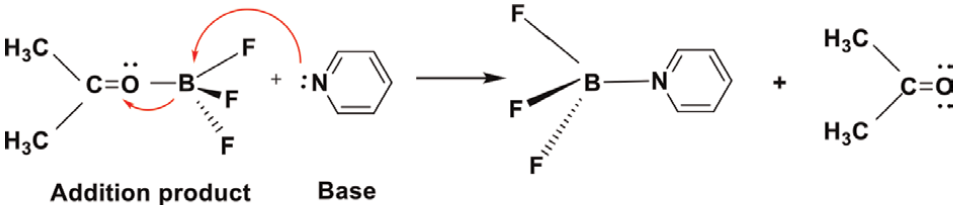


(29)

c. Substitution reactions: In these reactions, a Lewis base is replaced by another Lewis base, or a Lewis acid is replaced by another Lewis acid. The following reactions can be given as examples for the first group (30 and 31);



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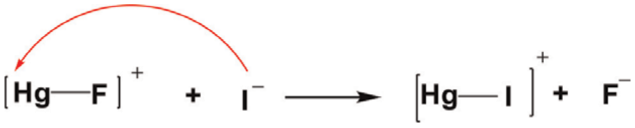
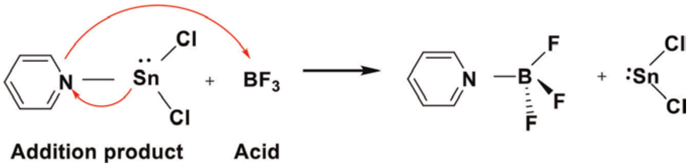


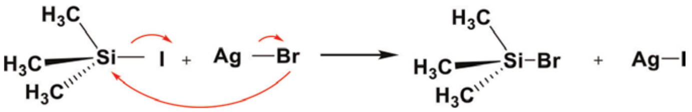
(31)

An acid can be replaced by another acid, as seen in the following reaction (32).



(32)

d. Metathesis (double displacement) reactions: Acids and bases are replaced in these reactions (33).



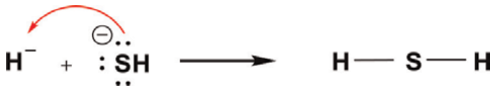
(33)

The Lewis acid-base concept is a very comprehensive one. It includes many chemical species defined as acids or bases according to Arrhenius, Brönsted-Lowry, and solvent system concepts. This definition is quite helpful in predicting whether two chemical species interact and, if so, the products formed. Therefore, it is widely used in inorganic chemistry and organic chemistry. Another benefit is that it allows us to explain acidity and basicity more easily with the molecular orbital approach. Some Lewis acids and bases listed below will provide more detailed information about Lewis acid-base reactions.

1.1.5 Lewis acids

For a chemical species to act as a Lewis acid, it must have either a low-energy vacant orbital to accept the electron pair or a positive center to attract the electron pair. According to the valence bond theory, the low energy orbital is the valence orbital. In the molecular orbital approach, it is the relatively low energy LUMO (lowest unoccupied molecular orbital). Some Lewis acids with these properties are given below [3].

a. H^+ Ion: It is the simplest Lewis acid, and its 1 s orbital is empty. It receives an electron pair from a Lewis base into its orbital. For example, its reaction with a Lewis base, HS^-, is (34):



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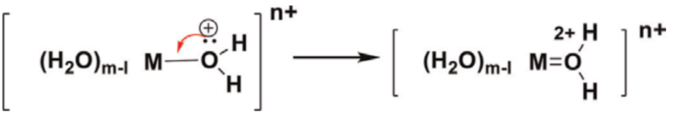
b. Major cations with high charge/radius ratio: Examples of these are Be^{2+}, Mg^{2+}, and A1^{3+}. The valence orbitals of these ions are empty. Be^{2+} has four vacant orbitals, and the other two have six (two of the 3d orbitals are considered low-energy. Look Coordination Chemistry section). Be^{2+} binds with four molecules of water, a Lewis base, and A1^{3+} with six molecules (35 and 36).

$$\mathbf{Be^{2+} + 4H_2O \;\rightarrow\; [Be(H_2O)_4]^{2+}} \tag{35}$$

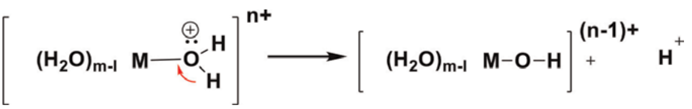
$$\mathbf{Al^{3+} + 6H_2O \;\rightarrow\; [Al(H_2O)_6]^{3+}} \tag{36}$$

Cations take an electron pair from each water molecule. As shown below, the formal charge of oxygen in the coordinating water molecule is (+1). If it donates the second pair of electrons, the formal charge becomes (+2). Ice is energetically unsuitable for oxygen, which is highly electronegative (37).



(37)

Instead, the following decomposition takes place (38):



(38)

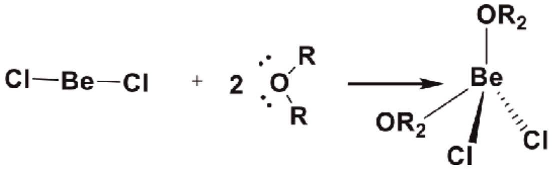
As can be seen, the acidity of aqueous solutions of such cations is a consequence of this dissociation. It is assumed that cations with low charge/radius ratios, such as Na^+, Rb^{+}, and Ba^{2+}, engage in ion-dipole interactions with Lewis bases, such as water, rather than coordinate-covalent bonding.

Transition metal cations: These cations contain empty valence orbitals. They receive electron pairs from Lewis bases such as NH_3, H_2O, F^-, and Cl^- (39 and 40).

$$\mathbf{Co^{2+} + 6NH_3 \rightarrow [Co(NH_3)_6]^{2+}} \tag{39}$$

$$\mathbf{Fe^{3+} + 4Cl^- \rightarrow FeCl_4} \tag{40}$$

c. Molecules with incomplete octets: These are molecules such as $BeCI_2$, BF_3, and $AlCl_3$. In the primary resonance structures of these molecules, the central atoms contain vacant valence orbitals. For example, $BeCl_2$ has two and one empty orbitals. For this reason, $BeCl_2$ reacts with two ether molecules and $B(CH_3)_3$ with one pyridine (C_5H_5N)) molecule (41 and 42).



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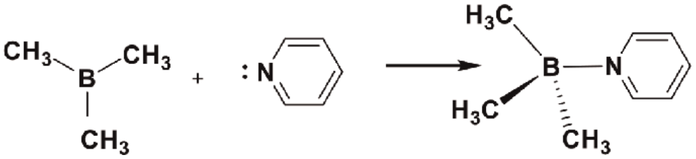
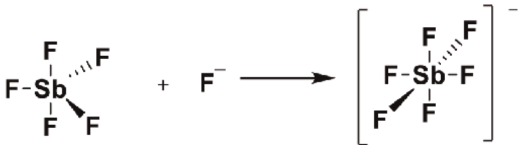


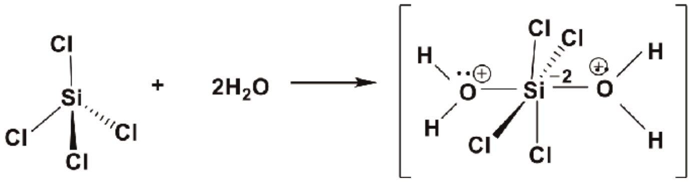
(42)

d. Molecules with empty d orbitals: As mentioned earlier, two of the valence d orbitals of the main elements can enter into a bonding. Molecules with at least one empty orbital behave as Lewis acids. Examples of these are $SnCl_2$, PCl_3, $SiCl_4$, and SbF_5. Since SbF_5 has a low energy d orbital, it receives a lone pair from the Lewis base (43).



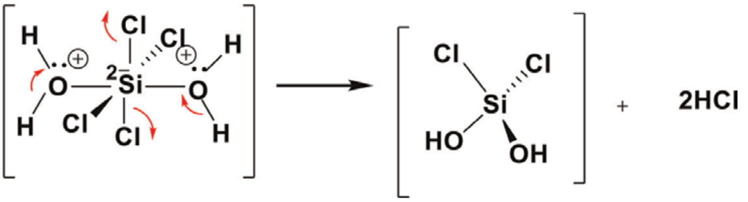
(43)

$SiCl_4$ has two low-energy d orbitals. To highlight the importance of the Lewis definition, let us consider the mechanism of the hydrolysis reaction of $SiCl_4$. Since $SiCl_4$ has two vacant d orbitals, it first binds to two H_2O molecules (44).



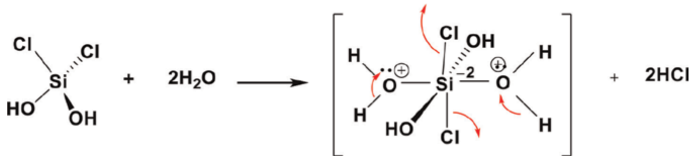
(44)

In the resulting structure, oxygens (+1) and silicon (−2) have formal charges. Therefore, the structure is unstable, and $2H^+$ and $2Cl^-$ leave the structure, as shown below (45).



(45)

Since it has two vacant d orbitals in $SiCl_2(OH)_2$, it binds two H_2O molecules again. $2H^+$ and $2Cl^-$ are separated from this structure and $Si(OH)_4$ is obtained (46).



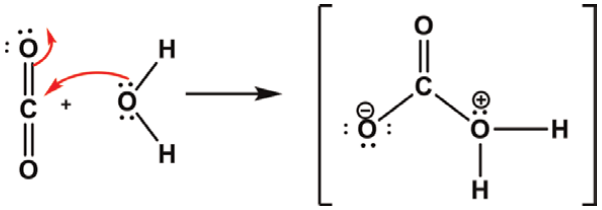
(46)

The hydrolysis reaction of $SiC1_4$ is (47),

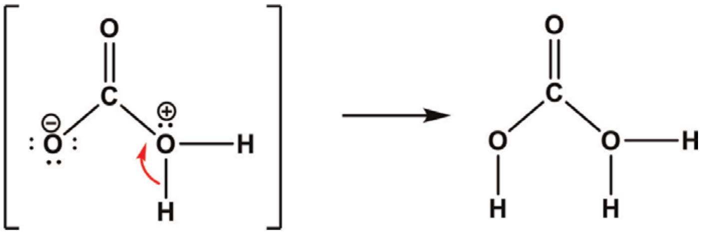
$$SiCl_4 + H_2O \rightarrow Si(OH)_4 + 4HCl \tag{47}$$

when reactions are summed side by side. This mechanism also explains why CCl_4 does not hydrolyze. It is because the valence shell of carbon does not contain the d orbital.

e. Molecules with multiple bonds between atoms with different electronegativity: In these molecules, the electropositive atom is partially positively charged. As a result of the attack of the electron pair of the Lewis base to this positive center, the electronegative atom receives the bond electrons as a lone pair. Thus, the Lewis base binds to the molecule. Examples of molecules in this group are CO_2, SO_2, SO_3, and $R_2C{=}O$ let us consider the reaction between CO_2 and H_2O as an example. Since carbon is the positive center, H_2O attacks this center, and an oxygen atom in CO_2 takes up the electrons of a π bond as a lone pair (48) [4].


(48)

Since oxygen has a positive formal charge in the resulting structure, it takes the electrons of an O—H bond and H^+ leaves. This ion binds to (−1) charged oxygen (49):


(49)

The sum of the two reactions gives the (50)

$$\mathbf{CO_2 + H_2O \rightarrow H_2CO_3} \tag{50}$$

reaction. As seen in the first step, CO_2 is a Lewis acid because it takes a lone pair from H_2O and forms a coordinate covalent bond.

f. Some transition elements: Atoms such as Cr, Fe, and Ni receive lone pairs from Lewis bases such as CO and NO (51) [5]:

$$\mathbf{Cr + 4NO \rightarrow Cr(NO)_4} \tag{51}$$

1.1.6 Acidity and basicity according to the molecular orbital approach

A significant role of the Lewis definition is that it allows us to explain acidity and basicity with molecular orbital theory. The highest occupied molecular orbital of a molecule is denoted by HOMO, and the lowest unoccupied molecular orbital is denoted by LUMO. According to the molecular orbital theory, the acidity of a molecule depends on LUMO, and its basicity depends on HOMO. Those with relatively low energy LUMOs act as acidic, and those with relatively high energy HOMOs and especially non-bonding molecular orbitals behave as basic. Because of non-bonding molecules, the electron pair in the orbital is under the influence of a single nucleus. The molecule has a higher tendency to donate these electrons. Molecules such as BF_3 and $SiCl_4$ behave as acids because they contain relatively low-energy LUMO. Likewise, the behavior of molecules such as CO and $H_2C{=}CH_2$ as π-acceptors is due to the relatively low energy π* molecules orbital (LUMO).

The molecular orbital theory explains the formation of coordinate-covalent bonds by the interaction of the LUMO of the acid with the HOMO of the base. A bonding and an antibonding molecular orbital are formed from the interaction of these two orbitals. The lone pair lower energy bond in the HOMO enters the molecular orbital. Since the counter-bonding molecular orbital is empty, a covalent bond is formed in the interaction of HOMO and LUMO. One point to consider here is the difference between the energy levels of HOMO and LUMO. If this difference is too high complete electron transfer from HOMO to LUMO will occur, and instead of covalent interaction, there will be electrostatic interaction. Since the Lewis definition requires covalent interaction, the chemical species would not be defined as acid and base in such a case [6].

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Chapter 5

An Overview of *N*-Heterocyclic Carbene: Properties and Applications

Norein Sakander, Ajaz Ahmed, Bisma Rasool
and Debaraj Mukherjee

Abstract

In 1991, *N*-heterocyclic carbenes were isolated and characterised successful introduced an entirely new class of organic compounds for research. From these origin as scientific curiosities, N-heterocyclic carbenes today rank among organic chemistry's most powerful tool, having a wide applicability in commercially important processes. In this chapter, we summarise the general properties and uses of N-heterocyclic carbenes in modern chemistry and demonstrates how these properties are being exploited.

Keywords: N-heterocyclic carbene, asymmetric catalysis, umpolung, organocatalysis, coordination chemistry

1. Introduction

Carbenes, a fascinating family of carbon-containing compounds, are described as neutral compounds having a divalent carbon atom with a six-electron valence shell. Nevertheless, unbound carbenes are extremely unstable due to their incomplete electron octet and coordinative unsaturation, and they have only ever been thought of as highly reactive transitory intermediates in organic transformations like cyclopropanation. Despite attempts at synthesis dating back to 1835 [1], it wasn't until groundbreaking investigations in the late 1980s and early 1990s that a free, uncoordinated carbene was finally isolated and given a clear characterisation [2]. Bertrand and colleagues described the creation of the first isolable carbene in a seminal study from 1988, stabilising it through advantageous interactions with nearby silicon and phosphorus substituents [3]. A nitrogen heterocycle with a carbene that can be isolated and "bottled" was described by Arduengo et al. three years later [4]. The remarkable stability and relatively easy synthesis of the first N-heterocyclic carbene (NHC), 1,3-di(adamantyl)imidazol-2-ylidene (IAd, compound labelled 1a), spurred an explosion of experimental and theoretical studies, with libraries of novel NHCs being synthesised and studied. These structural features were inspired by earlier insightful studies by Wanzlick [5] and O fele [6] on metal-carbene complexes. As more of the complex chemistry of these compounds has been uncovered and utilised as a result of these discoveries, NHCs have been raised from simply laboratory curiosities to substances of immense practical value. NHCs have several uses in some of the most

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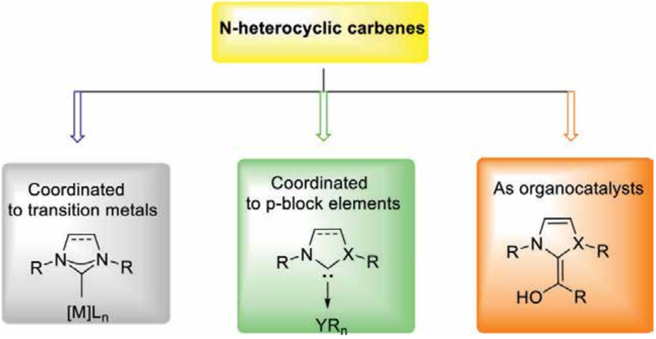


Figure 1.
Major applications of NHCs.

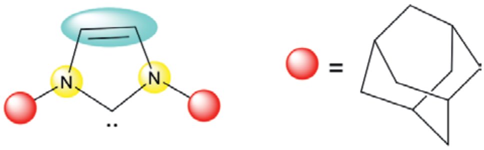
significant catalytic transformations in the chemical industry as good ligands for transition metals, and their reactivity upon coordination to main group elements and as organocatalysts has opened up new study avenues.

In order to serve as an introduction and reference for researchers interested in investigating and using these significant chemicals, we have attempted to present a condensed review of the features and wide range of uses of NHCs in this chapter. Following a general overview of the structure and characteristics of NHCs, three sections are loosely divided to discuss NHCs' reactivity and uses in contemporary chemistry. These sections cover their use as ligands for transition metals, when they are coordinated to p-block elements, and as organocatalysts. For further in-depth reading, each part includes a brief summary of the salient characteristics and essential applications, as well as references to seminal works and thorough expert evaluations. The discussion is highlighted by more thorough summaries of a few recent research that illustrate the state of the art today and anticipated developments as an increasing number of NHCs continue to find novel and interesting uses throughout the chemical sciences (**Figure 1**).

2. Structure and general properties of NHCs

NHCs are categorised as heterocyclic entities with at least one nitrogen atom and a carbene carbon inside the ring structure [7, 8]. Several diverse types of carbene compounds with varying substitution patterns, ring diameters, and levels of heteroatom stabilisation fit under these criteria [9]. The first known compound, IAd (1a), serves as an illustration of the general structures of NHCs in **Figure 2**. The exceptional stability of the carbene centre C2 can be partially explained by the overall electrical and steric impact of these structural characteristics.

NHCs typically have bulky substituents next to the carbene carbon, as shown in IAd by the two adamantyl groups attached to the nitrogen atoms. These substituents work to kinetically stabilise the species by sterically disfavoring dimerization to the corresponding olefin (the Wanzlick equilibrium). Yet, the nitrogen atoms' ability to stabilise electrons is a much more crucial feature. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), which are best defined as a formally sp2-hybridised lone pair and an unoccupied p-orbital at the C2 carbon, respectively, in NHCs such as IAd are different from conventional carbenes (**Figure 3**).



IAd (1a)

Figure 2.
Structure of carbene.

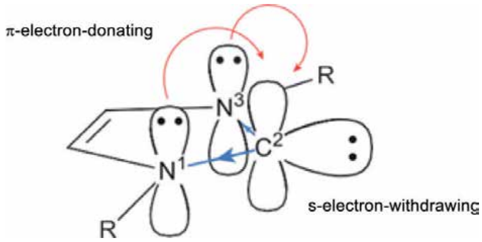


Figure 3.
Molecular orbital diagram of NHC.

The nearby nitrogen atoms maintain this structure both mesomerically and inductively by contributing electron density into the vacant p-orbital and reducing the energy of the occupied s-orbital, respectively. Because NHCs are cyclic, this forces the carbene carbon into a configuration that is more sp2-like and favours the singlet state. The C-N bond lengths (1.37 A) found in IAd, which lie between those of its equivalent imidazolium salt (IAdH1, 1.33 A)4 and its C_2-saturated counterpart (IAdH2, 1.49 A) [10], reflect this ground-state structure and indicate that the C_{22} nitrogen bonds have partial double-bond character. All classes of NHC can be stabilised using these broad principles, however the proportional importance of each effect differs from compound to compound (**Figure 4**).

Due to their partial aromaticity, NHCs generated from heteroaromatic compounds benefit from a higher level of stability. As less proximal steric bulk is required due to this effect, which has been estimated to be about 25 kcal/mol for model imidazol-2-ylidenes [11], the simple methyl-substituted NHC 1,3- di(methyl)imidazol-2-ylidene (IMe) is persistent in solution [12]. The first example of a stable carbene that does not benefit from aromaticity was described by Arduengo and coworkers in 1995 [13] and is known as 1,3-di(mesityl)imidazolin-2-ylidene (SIMes). Therefore, stabilising the carbene centre does not need two nearby nitrogen atoms [14]. Stable carbenes containing only one nitrogen substituent, as the series of cyclic (alkyl) (amino)carbenes (CAACs,) discovered by Bertrand et al. [15], have also garnered significant research

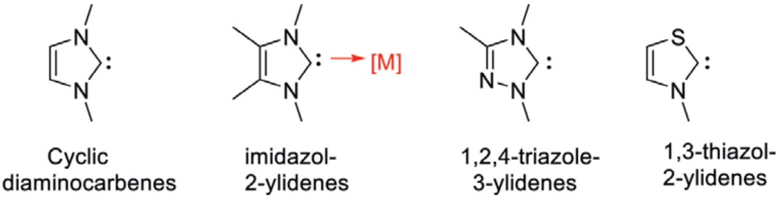


Figure 4.
Different types of N-heterocyclic Carbenes.

interest. NHCs bearing alternate heteroatoms, such as sulphur and oxygen, are accessible. When the carbene centre is generated at places other than C2, similar compounds stabilised by a single nitrogen atom may arise. These mesoionic or “abnormal” carbenes, for which it is impossible to sketch a neutral, non-zwitterionic carbene resonance structure, tend to be more electron-donating than their “normal” equivalents and can exhibit a wide range of distinct characteristics [16, 17]. There have also been reports of remote NHCs, in which the carbene carbon is not located close to a nitrogen heteroatom. The characteristics of the carbene can be significantly influenced by the size and substitution pattern of the nitrogen heterocycle. Although while instances of NHCs with smaller or bigger ring sizes, such as N, N9- diamidocarbenes (DACs), have also been described, the greatest class of NHCs is still 5-membered rings. Due to the higher N-C-N bond angle in these later compounds, which in turn effectively moves the nitrogen substituents closer to the carbene centre, there is an increase in steric shielding. Bigger rings also have an electrical impact because the cyclic structure’s geometric constraints change the kind and extent of heteroatom stabilisation. It is also important to note that numerous related groups of stable carbenes exist, which, although not being NHCs, benefit from related methods of stabilisation. These include cyclic derivatives and cyclic species featuring different ring heteroatoms such as phosphorus instead of nitrogen [7, 14, 17].

Understanding the reactivity of NHCs is made possible by their ground-state electrical structure. The lone pair located in the plane of the heterocyclic ring of NHCs makes these compounds nucleophilic in contrast to the normal electrophilicity of the majority of transitory carbenes. The main effect of this property is that NHCs are inclined to function as s-donors and bind to a variety of metallic and non-metallic species. The extraordinary power and distinctive characteristics of these interactions, as well as their impact on the stability, structure, and reactivity of the resulting complexes or adducts, are what have driven NHC interest to such a high level. The following sections go into more detail about this extensive coordination chemistry and the various applications of NHCs that result from it.

The relative simplicity with which libraries of structurally varied analogues may be created and researched is another appealing aspect of NHCs. Synthetic approaches to NHCs profit from years of study on the synthesis of heterocyclic compounds since, in the majority of situations, the carbene is produced following deprotonation of the matching cationic heterocyclic azolium salt [18]. The steric and electrical characteristics of the resultant carbene may be easily changed for most classes of N-heterocycles by simply changing the starting materials in a modular synthetic procedure. With various kinds of heterocycles having essentially varied steric needs, the nitrogen-substituents or other groups located next to C2 have the most impact on the steric environment at the carbene centre. The heterocycle class is the main factor controlling the NHC electronics, however the ring backbone substitution pattern is also crucial. The evaluation of these characteristics enables straightforward comparisons between NHCs as well as between NHCs and other related compounds like phosphines, enabling better informed choice of the best carbene for any particular application [19, 20].

3. Coordination of NHCs to transition metals

The vast majority of N-heterocyclic carbene applications require coordination to transition metals (**Figure 5**). About 20 years prior to the discovery of a free NHC, Wanzlick [5] and Ofele [6] separately synthesised imidazol-2-ylidene-containing

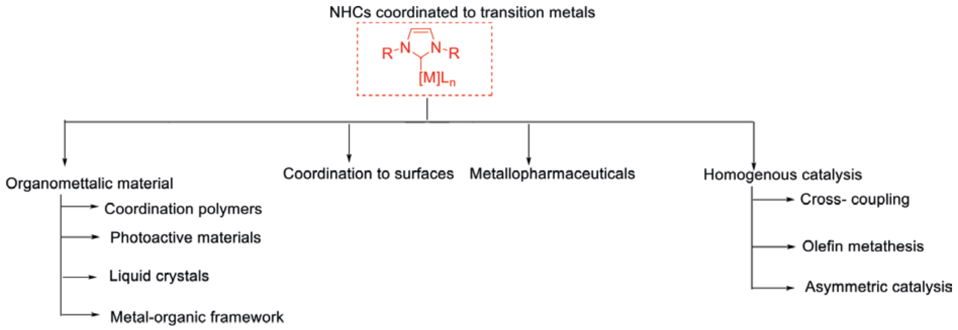


Figure 5.
Coordination of NHC to transition metals.

species carrying mercury(II) and chromium(0), respectively, in 1968. These reactions resulted in the first instances of NHC-metal complexes. Before IAd was isolated, Lappert and colleagues had carried out insightful experiments in the early 1970s [21]. As was already indicated, NHCs aptitude as ligands for transition metals may be explained by the fact that they naturally possess the capacity to donate an official sp2-hybridised lone pair into an orbital of the transition metal.

Many groups have investigated the complete nature of bonding in these complexes, and Cavallo and colleagues [22] and D'ez-Gonzalez and Nolan [23] have both written reviews on the issue. While p-back-bonding into the carbene p-orbital and p-donation from the carbene p-orbital may not have a significant impact, s-donation is still the most significant factor in metal–ligand interaction. For instance, Frenking and coworkers determined that group 11 metal-imidazol-2-ylidene and imidazolin-2-ylidene complexes account for around 20% of the total bond energy [24]. In practice, metal-C-coordination is typically depicted as a single bond rather than a double bond in actuality, with p-contributions limited to delocalization inside the NHC ring (often depicted by a curved line between the ring heteroatoms). This illustration highlights the distinctions between NHCs and traditional Fischer or Schrock carbene ligands and most accurately captures the experimentally found potential for rotation around the metal-C-bond. NHCs were previously thought of potential analogues for this common class of auxiliary ligand in transition-metal coordination chemistry because of their strong s-donor and relatively weak p-acceptor features, which resemble the coordination properties of phosphines [25].

4. Medicinal and materials applications of NHC-metal species

Organometallic materials can be developed because of the great thermal stability of metal-NHC complexes and the possibility to customise their steric and electronic properties [26]. In order to create organometallic complexes within the material's pores, imidazolium salts have been effectively coordinated to transition metals when used as linker molecules in metal–organic frameworks [27]. It is also possible for transition-metal complexes with hydrophobic long alkyl chain N-substituents to self-assemble into extremely air- and moisture-resistant liquid crystals that are thermally stable after the clearing point [28]. Many studies have been conducted on the addition of NHC-metal complexes to the side chains or primary chain of polymers. Bielawski and colleagues created a number of distinct palladium(II) and

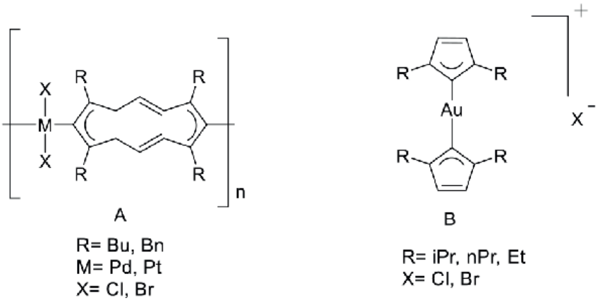


Figure 6.
NHC showing medicinal properties.

platinum(II) organometallic polymers A using benzene-linked bis(NHC) units which exhibit self-healing qualities due to the intrinsic reversibility of metal–ligand coordination [29]. The conjugated bis-NHC linkers in these materials, which enable electronic interaction between the two coordinated metal centers, make them promising as electrical conductors. There have also been reports of NHC-transition metal complexes that function as phosphors and other photoactive substances [30]. The therapeutic uses of NHC-transition-metal complexes as metallopharmaceuticals have received more attention in recent years, with silver(I) and gold(I) species showing particular promise as antibacterial and anticancer agents, respectively [31]. A variety of Gram-positive and Gram-negative bacteria are resistant to several imidazol-2- and imidazolin-2-ylidene-Ag complexes, which have astonishingly low minimum inhibitory concentration values (10 mg/ ml^{21}). These species often remain therapeutically active for longer than the usual reference $AgNO_3$, which might be explained by a delayed release of active Ag^1 ions from the NHC-stabilised complexes. Based on the targeting of mitochondria, NHC -metal species containing gold have demonstrated potential as anticancer medications. Since anticancer action is heavily dependent on penetration across the mitochondrial membrane, it is essential for these systems to be able to precisely control the lipophilicity of the complexes by change of the N-substituents on the NHC. The cationic gold(I) complexes were demonstrated to induce apoptosis by selective inhibition of the selenoenzyme thioredoxin reductase, which is over expressed in many human cancers in a seminal publication by Berners-Price, Filipovka and co-workers (**Figure 6**) [32].

5. NHCs as organocatalysts

A third significant class of applications, in which NHCs function as organocatalysts, has been made possible by their tendency to coordinate to carbon-electrophiles [33, 34]. The bulk of these reactions begin as a result of a carbene's nucleophilic assault on carbonyl groups found in organic substrates. The majority of the transformations that NHCs mediate as organocatalysts involve an initial assault of the NHC onto a carbonyl group. The bulk of NHC-catalysed reactions use aldehydes as substrates, in addition to trans esterification and related transformations of esters, which are particularly relevant in the production of polymers. In these reactions, the functional group is umpolunged, and the carbonyl carbon behaves more like a transitory nucleophile than an electrophile. There are also other related transformations that include an umpolung at the b-position of α,β-unsaturated substrates. These

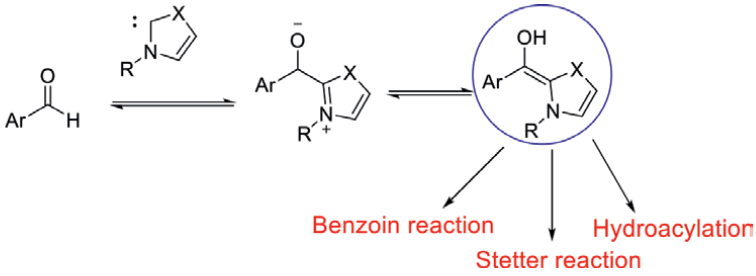


Figure 7.
NHC as organocatalyst.

procedures involve direct NHC assault on α,β-unsaturated esters as well as "conjugate umpolung" reactions of α,β-unsaturated aldehydes (Michael umpolung). Azolium intermediates with leaving groups in the a-position or those produced from aldehydes by in-situ oxidation constitute another family of reactions (**Figure** 7).

The cationic N-heterocyclic fragment created by nucleophilic attack is electron-withdrawing by nature, which plays a crucial part in the adduct's subsequent reactivity. An acyl azolium salt is produced in the case of esters by adding the NHC to the carbonyl and then releasing the alkoxy group. This species may interact with alcohols to produce transesterification products and is noticeably more electrophilic than the parent ester. In step growth and ring-opening polymer synthesis, reactions of this kind are often used, and NHCs provide an alternative to conventional organometallic catalysts and initiators [35]. Due to their strong Bronsted basicity, NHCs play a further role in these processes by hydrogen attaching to the alcohol and activating it for nucleophilic attack.

The nucleophilic attack of NHCs on aldehydes leads to the widest and most varied range of NHC-organocatalyzed reactions. The earliest instance of this type of transformation, which was reported in 1943 by Ukai and colleagues and included the homo-dimerization of aldehydes to benzoins catalysed by a thiazolium salt [36], was not well understood at the time. The mechanism of this method is based on the amphiphilic properties of an in situ produced NHC active catalyst, as suggested by Breslow in 1958 [37]. The previously aldehydic proton in the resultant compound is made acidic by the negative inductive impact of the cationic azolium group following the first nucleophilic assault of the NHC on the aldehyde. The enamine-like "Breslow intermediate", which is nucleophilic at carbon as a result of p-donation from the ring heteroatoms.

The isolation and characterisation of representative samples taken from SIPr by Berkessel and coworkers [38] has recently validated the role of these species in NHC organocatalysis. In the aforementioned benzoin condensation, product production is caused by intermediate nucleophilic attack on another aldehyde equivalent followed by the elimination of the NHC. The aldehyde substrate's natural reactivity is effectively flipped during the reaction (also known as "umpolung"), with the typically electrophilic carbonyl carbon serving as a momentary nucleophile. Hence, umpolung reactions of this kind are examples, and Breslow intermediates may be thought of as acyl anion equivalents [39].

The study of NHC-catalysed umpolung has advanced significantly over the past few decades, and [33, 34]. **Figure 8** provide an overview of the main reaction classes. In general, pre-forming the free carbene is not necessary in reactions facilitated by NHC coordinated with the transition-metal complexes. Rather, the equivalent

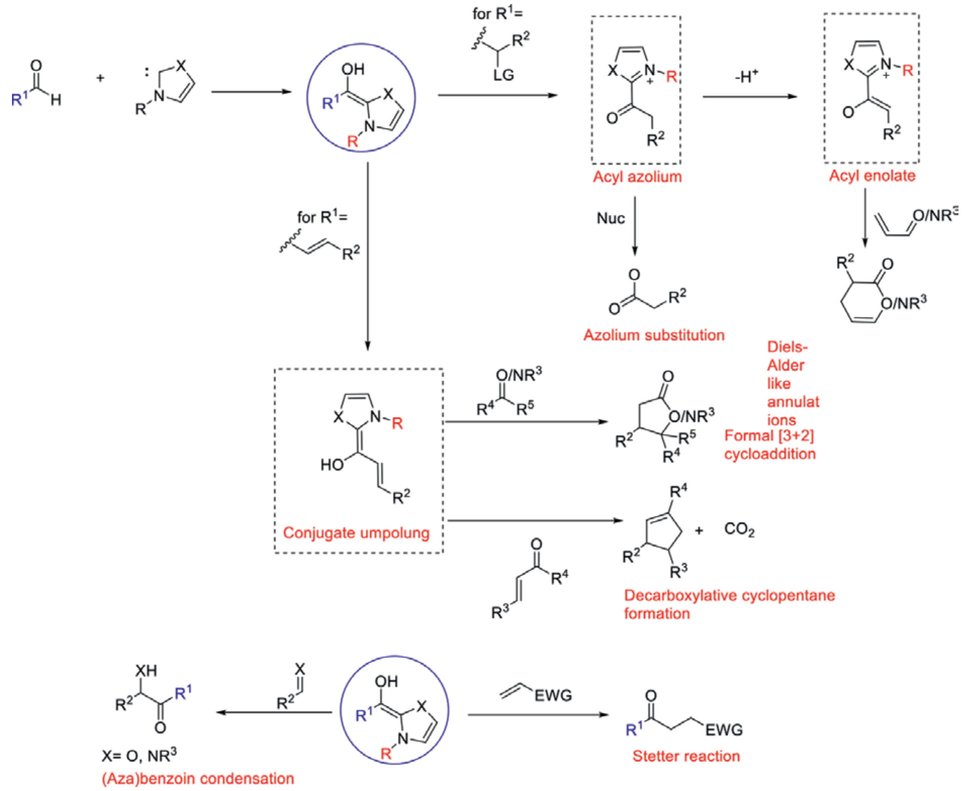


Figure 8.
Different reactivity of Breslow intermediate.

azolium salt precursor is often deprotonated in order to produce the active catalyst in situ. The creation of asymmetric variants utilising chiral NHCs has significantly increased the syntactic value of several of these transformations. The most successful enantioselectivity-inducing catalysts have been those based on the triazol-2-ylidene motif, with systems that include a chiral nitrogen substituent into a rigid polycyclic structure being commonly used.

One geometric isomer of the Breslow intermediate is preferred over the other when using these asymmetrical catalysts, and the electrophile approaches the least hindered enantiotopic face. Since the benzoin condensation is reversible, the Breslow intermediary may potentially attack other electrophiles nucleophilically. In particular, aldehyde addition reactions to activated alkenes, like Michael acceptors, have received a great deal of attention (the Stetter reaction). The researchers have been focusing on expanding the pool of appropriate olefinic coupling partners for this process [40]. Recently, the application of relatively electron-neutral styrene derivatives was accomplished utilising an electron-rich 2,6-dimethoxyphenyl N-substituted triazol-2-ylidene catalyst [41].

There are additional Breslow intermediate reactivity routes that do not need a formal umpolung at the carbonyl carbon [42]. For instance, removing a leaving group from the a-position can lead to the same kind of acyl azolium salts as those produced by adding NHC to esters. Similar species can also be produced via the direct in situ oxidation of the Breslow intermediate in the presence of an external oxidant or by pre-oxidised substrates like ketenes. Upon addition-elimination of a nucleophile, these intermediates may release the NHC fragment immediately, or they may first react as enolate or enone equivalents with the azolium moiety as a bystander [43].

The reactivity of α,β-unsaturated aldehydes is a potent and well-studied class of transformations. Because to the extended p-system of the Breslow-type intermediates produced with these substrates, nucleophilic attack may take place conjugately to produce products with an umpolung at the β-position (referred to as a "conjugate umpolung" [44]). In these methods, sterically demanding NHC catalysts that inhibit competitive functionalization at the traditional "carbonyl" position are frequently advantageous. The first conjugate addition of the NHC to the β-position as opposed to the carbonyl group occurs in another category of reactions with a,b-unsaturated carbonyl compounds. After this, the resultant adducts can react to produce products that are a- or b-functionalized as a consequence of chemistry of the Morita-Baylis-Hillman type or a formal umpolung at the b-position, respectively [45]. Accessing the umpolung reactivity seen with aldehydes from other kinds of substrates is one very fascinating topic of current study endeavour. Chi and coworkers recently published an exquisite proof of this idea in a number of annulation reactions of saturated aliphatic esters [46]. **Figure 9** provides a mechanistic explanation for these events and illustrates how the critical diamino dienol Breslow-type intermediate is formed. The acyl azolium salt that results from the first nucleophilic addition-elimination of the NHC to the ester group tautomerizes to produce an enol species. The azolium group in this molecule has an electron-withdrawing property that makes the b-CH2 protons very acidic. If there is an excess of DBU base (where DBU is 1,8-diazabicyclo [5.4.0] undec-7-ene, 1.5–2 equiv.), deprotonation can take place to produce the homoenolate equivalent. The high degree of conjugation present in the resultant intermediate with b-aryl-substituted substrates can also help to explain the extraordinary selectivity for this deprotonation step over more traditional a-functionalization methods. The Breslow-type species, which may react as a nucleophile through conjugate umpolung to produce b-functionalized products, is comparable to that synthesised under standard circumstances using a,b-unsaturated aldehyde substrates.

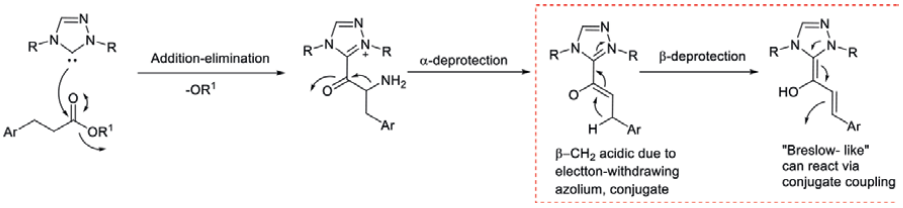


Figure 9.
Mechanistic explanation for diamino dienol Breslow-type intermediate formation.

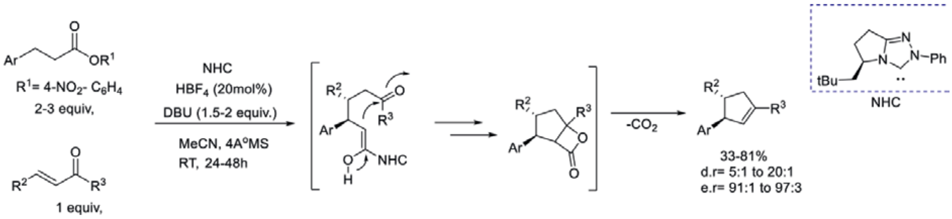


Figure 10.
Reaction of NHC with enones.

Aliphatic esters are often used as feedstocks in organic chemistry, but there are few other synthetic techniques for specifically activating the b-position of these substrates. This approach also permits high degrees of enantiocontrol during the annulation processes utilising the chiral triazol-2-ylidene catalyst, delivering five-membered heterocycles in enantiomeric ratios using enone, trifluoroketone, or hydrazone electrophiles (the reaction with enones is shown in **Figure 10**).

6. Conclusions

One of the most significant achievements in contemporary chemical research is undoubtedly the discovery and development of N-heterocyclic carbenes. Since Arduengo and colleagues originally described the first "bottleable" NHC 23 years ago, significant research on the structure, coordination chemistry, and reactivity of these compounds by other groups has resulted in a wide range of applications in numerous industries. NHCs are currently the mainstays of organic and organometallic chemistry, competing with phosphines in the role of auxiliary ligands in transition metal catalysis and opening up new avenues in main-group chemistry and organocatalysis.

However, the rapid growth of NHCs is far from over, as our hope is evident from the examples of current research discussed in this review. NHCs continue to play a variety of novel functions in the chemical sciences in addition to their existing ones. Heterogeneous catalysis is one promising area where the strength of NHC-metal binding might provide improved stability of metallic colloids or surfaces with the potential to change the catalyst's capabilities by in situ functionalization of the ligand. The growing usage of NHCs in metallopharmaceuticals may also be explained by the stability and strength of the metal–ligand connection as well as the ease with which one can modify the structural characteristics of organometallic complexes. The use of NHCs is becoming more widely accepted in domains where significant progress is also being achieved. Recent ground-breaking research in the field of organocatalysis has concentrated on the creation of novel reactivity pathways that broaden the spectrum of acceptable reaction partners beyond the conventional aldehydes.

The creation of novel NHCs with unique characteristics and reactivities is one of the main forces behind the most innovative research currently being conducted. In the area of homogeneous transition-metal catalysis, new chelating imidazolin-2-ylidene ligands on ruthenium catalysts have made it easier to catalyse Z-selective olefin metathesis, while recently created chiral NHC ligands have showed promise in asymmetric hydrogenation processes. The stability of hitherto inaccessible non-metallic species and the activation of tiny molecules have both been made possible by new classes of NHCs, such as DACs and CAACs, which have displayed an unheard-of reactivity. The recent report of an organic radical that had been stabilised by a CAAC and was "bottleable" serves as an example of how well CAACs are suited to this type of stabilisation. The future of NHCs appears to be highly promising given the significant advancements made over the previous two decades and the high calibre research now being carried out.

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Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

Ac	Acetyl
aq	Aqueous
Boc	*tert*-Butoxycarbonyl
Bu	n-Butyl
Bn	Benzyl
CAN	Ceric ammonium nitrate
CH_3CN	Acetonitrile
Cbz	Benzyloxycarbonyl
CuAAC	CuI-catalysed azide-alkyne cycloaddition
$Cu(OAc)_2$	Copper acetate
$CuSO_4$	Copper sulphate
Cy	Cyclohexyl
d.r.	Diastereomeric ratio
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
Et	Ethyl
h	Hours
IPA	Isopropanol
m.p.	Melting point
Me	Methyl
mCPBA	Meta perchloro benzoic acid
min	Minutes
n-Bu	n-Butyl
NaN_3	Sodium azide
NH_3	Ammonia
NHC	N-heterocyclic carbene
Ph	Phenyl
Py	Pyridine
R_f	Retention factor
RT	Room temperature
TBS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tosylate	*p*-Toluenesulfonate
Triflate	Trifluoromethanesulfonate
Ts	*p*-Toluenesulfonyl

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The subject of this book is the basics of chemistry that “want” electrons to form chemical bonds. Covalent bonds are generally represented by “lines” in structural formulas in organic chemistry. A single line of a single bond represents an “electron pair.” Organic chemistry textbooks use arrows to indicate the flow of electrons to represent the creation or disappearance of bonds between atoms. There are electron-rich atoms and electron-poor atoms, which are donors (nucleophiles) and acceptors (electrophiles), respectively. Protonated ions and metal complexes form “coordination bonds.” An electron pair (i.e., two electrons) is given from one atom (Lewis base, coordinating atom) to another atom (Lewis acid, metal ion), that is, there is a “bias” in donating electrons. However, once the coordination bonds are formed, the four N–H bonds of the ammonium ion are just four indistinguishable “equivalent” covalent bonds. They are classified according to the nature of the atoms that form chemical bonds, but the actual subjects are potentially wide-ranging from organic chemistry to inorganic coordination chemistry, from s- or p-block elements to d- or f-block elements, and from basics to applications.

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