CHAPTER-1

INTRODUCTION

Introduction

1.1 Room Temperature Ionic Liquids, Solvents for Synthesis and Catalysis

Species in solution have been widely studied in the Chemistry. All the liquids can be used as a solvent, however very few are in general use. A major concern regarding cleaner technologies in both industry and academia, primarily demanding for alternative to the solvents those are of environmental hazard. The ionic liquids (ILs), a salt of poorly coordinated ions present in liquid form below 100°C, are potentially fulfills the requirements of the reaction in solvent media. Recent studies with ILs as solvents have shown significant impact on organic synthesis, and thus used in various reactions such as Pd-catalyzed allylation, Diels-Alder reaction, Fridel-Craft’s, and also in Asymmetric hydrogenation.

Furthermore, IL is a fused salt containing only ions. By meticulous selection of cation and its appropriate anionic partner, it is possible to synthesize the ILs those are liquid even at room temperature. The room temperature ILs have been known for many years, for instance ethylammonium nitrate ([EtNH$_3$],,[NO$_3$]), synthesized by P. Walden in 1914, has a melting point 12 °C. It has then proposed that such a ILs provide a useful extension to the range of solvents those are routinely used in the chemical synthesis.

Few of the physical properties of the ionic liquids which made them interesting as promising solvents in the synthetic chemistry are listed below.

1. ILs can solvate a wide range of organic as well as inorganic materials, with the routine combinations of reagents and bring them into the same phase.
2. The poorly coordinating ions in the IL, imparts the highly polar nature yet they are coordinating solvents.
3. Since ILs are immiscible with large number of organic solvents, they provide additional alternative for non-aqueous polar phase in the two-phase systems. Some of the ILs are Hydrophobic, and can be used as immiscible polar phase along with the water.
4. The non-volatile nature of the ILs, facilitates their use in the high vacuum systems and thereby eliminating many problems related to contamination.
Moreover the most of the ILs are air and/or moisture sensitive. The development of ILs, those are stable in both air and moisture has engendered the renewing strength in IL chemistry. The synthesis of various heterocyclic compounds has been carried out in the presence of nonvolatile molten salts i.e. ILs.\(^7\) The ILs such as 1-butyl-3-methyl imidazolium hexafluorophosphate\([\text{Bmim}]\text{PF}_6\) possess a valuable set of properties, viz. immiscible with non-polar alkanes and polar water, but it can readily solvate range of reagents and several metal catalysts.\(^8\) Such multiphase ionic system has efficiently enabled the simple extraction and isolation of the reaction products.

Table 1.1: Organic reactions catalyzed by ionic liquids

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Name of the ionic liquids</th>
<th>Structure of the ionic liquids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethylammonium nitrate</td>
<td>([\text{EtNH}_3]\text{.[NO}_3\text{]})</td>
</tr>
<tr>
<td>2</td>
<td>1-butyl-3-methyl-Imidazolium hexafluorophosphate</td>
<td>([\text{Bmim}]\text{PF}_6)</td>
</tr>
<tr>
<td>3</td>
<td>Aluminate (III) ionic liquids</td>
<td>([\text{Emim}]\text{Cl-AlCl}_3)</td>
</tr>
</tbody>
</table>

\[
\begin{array}{c}
\text{[N\text{N}}}\text{]}\text{[PF}_6\text{]}\text{]} \\
\text{[N\text{N}}}\text{]}\text{[PF}_6\text{]}\text{]} \\
\end{array}
\]

Fig. 1.1: 1-Butyl-3-methylimidazolium hexafluorophosphate and 1-Butyl-2,3-dimethylimidazoliumhexafluorophosphate.

Which study demonstrates that ionic liquids are potentially hazardous; it neither provide safe exposure limits nor does it recommend treatment procedures. As stated in Table 1.1 above the aluminate (III) ionic liquids react rapidly with water generating HCl, itself a toxic and irritant gas. Little is known of the toxic effect of halogen aluminate (III) ionic liquids. In a study of the effects of a basic \((X(\text{AlCl}_3) = 0.40)\ [\text{emin}]\text{Cl-AlCl}_3\) ionic liquid on the skin of rat, it was shown that the ionic liquids induced significant skin irritation, leading to ulceration in several cases.\(^9\) Penetration through the top layer of the skin of toxic material and damages to the underlying...
cells was observed. The washing of skin in contact using water led to a reduction in the degree of damage incurred. Therefore care is required to minimize exposure particularly while destroying the ionic liquids.

1.2 Boronic Acids in organic synthesis

Boronic acids and their derivatives are among the most useful classes of organoboron molecules. Unlike many organometallic derivatives and most organoboranes, boronic acids are usually stable in air and moisture, and they have relatively low toxicity and environmental impact. The reactions of boronic acids can be divided into two categories according to involvement the boron-oxygen or the carbon-boron bonds are involved.

1.2.1 Reactions involving the B-O bonds
1.2.1.1 Boroxine formation

Most of the boronic acids readily undergo dehydration to form cyclic trimeric anhydrides (boroxines) (Scheme 1.1). The dehydration occurs spontaneously at room temperature, and make it difficult to obtain the acid free from their anhydride. Since in almost all cases, both will undergo the required reaction, they can usually be regarded as equivalent.

![Scheme 1.1: Boronic acid to Boroxine formation.](image)

1.2.1.2 Boronate formation

The ease with which boronic acids react with diols, to give cyclic boronic esters (boronates), by loosing of water, has led to their application in a number of areas, especially in the carbohydrate field.
1.2.1.3 Protection of diols

One of the main applications of boronic acids is as reagents for protection and derivatization of 1,2- and 1,3-diols as boronates (1,3,2-dioxaborolanes), particularly in carbohydrate chemistry. They have also been widely used to volatilize the diols using GC and GC-MS. The boronate derivatives are formed simply by stirring the boronic acid and diol together at ambient temperature, if necessary by warming, with azeotropic removal of water. Usually cleavage occurs readily under hydrolytic conditions, by exchange with a glycol or by treatment with hydrogen peroxide. Hindered boronic esters, such as pinacol may be relatively stable to hydrolysis and can often be purified by chromatography. A useful application of boronate protection is in the osmium tetroxide catalysed cis-dihydroxylation of alkenes under anhydrous conditions in the presence of a boronic acid. Further information on the applications of boronic acids as derivatizing and protecting agents can be found in various reviews and monographs.

1.2.1.3.4 Applications in carbohydrate chemistry

The formation of boronates with carbohydrate molecules has been utilized in numerous other applications, including the selective transport of sugars in lipophilic environments, and the design of artificial receptors, as discussed in several reviews.

1.2.1.3.5 Boronic acids and esters in asymmetric synthesis

a) Chiral boronates

Matteson has carried out extensive work on cyclic boronates, formed from chiral diols such as (1S,2S,3R,5S)-2,3-pinanediol or (R,R)-(−)-2,3-butanediol, which undergo carbon insertion with LiCHCl₂ in the presence of zinc chloride in up to 99% diastereomeric excess (de). Treatment of the resulting α-chloroboronic esters with various nucleophiles leads to α-substituted boronic esters which can be deprotected with hydrogen peroxide, or the sequence can be repeated to introduce a second chiral center, as illustrated in Scheme 1.2.
b) **Oxazaborolidines**

Reaction of various boronic acids with chiral amino alcohols gives oxazaborolidines, which were introduced by Corey as excellent catalysts for enantioselective borane reduction of ketones with very high ee.\(^{26}\) The reagents derived from \(\alpha,\alpha\)-diphenylprolinol have received the most attention, although the use of other amino alcohols has also been reported.\(^{27,28}\) Reviews on the use of oxazaborolidines as enantioselective catalysts,\(^{29,30}\) and the asymmetric reduction of ketones\(^{31,32}\) are available.

c) **Diels-Alder reactions**

Boronic acids form stable chiral acyloxyborane (CAB) catalysts with tartaric acid derivatives, which have been developed by Yamamoto as catalysts for asymmetric Diels-Alder\(^ {33}\) and hetero Diels-Alder\(^ {34}\) reactions, for example between aldehydes and Danishefsky’s diene [1-methoxy-3- (trimethylsiloxy)-1,3-butadiene, to give enantioselectively, dihydro-4-pyrone derivatives.\(^ {35}\)

### 1.3 Reactions involving cleavage of the C-B bond

In these reactions, displacement of boron by an electrophilic species takes place with formation of a new carbon-carbon or carbon-heteroatom bond.
1.3.1 C-C bond forming reactions: Suzuki biaryl coupling

The discovery by Suzuki and Miyaura that arylboronic acids undergo palladium-catalyzed cross-coupling with aryl halides in the presence of a base (Scheme 3) has stimulated enormous interest in the application of this (Suzuki reaction), and variants developed subsequently, to the synthesis of unsymmetrical biaryls and related compounds.\(^36\)

![Scheme 1.3](image)

**Scheme 1.3:** Synthesis of unsymmetrical biaryls.

Many of the methods previously employed for such syntheses involve the direct coupling of highly-reactive organometallic reagents (Grignard, Organolithium, etc.) with aryl halides in the presence of various catalysts. Such reactions are of limited utility, since the presence of many functional groups interferes. Boronic acids, on the other hand, which are air-stable materials of relatively low toxicity, will undergo the Suzuki reaction in the presence of a wide variety of functional groups. The highly versatile Stille coupling reaction,\(^37\) by comparison,\(^38\) involves toxic organotin species. Under the standard coupling conditions, aryl bromides are most frequently used as the electrophilic species, but iodides are more reactive. The successful coupling of the more readily available, but normally unreactive aryl chlorides has been achieved under modified conditions, using either palladium\(^39\) or nickel\(^40\) catalysts. A catalytic cycle for the Suzuki reaction\(^41,42\) is outlined in **Scheme 1.4.**
Scheme 1.4: Catalytic cycle for the Suzuki reaction.

Alternative illustrative experimental procedures for the biaryl synthesis have been reported. Useful reviews of the Suzuki and related reactions have been published by Suzuki and Miyaura and by Martin and Yang, and of biaryl synthesis via cross-coupling reactions by Stanforth. The more recent literature has been reviewed by Kotha et al.

1.4 Related coupling reactions

A variety of heterocyclic halides have been coupled with boronic acids, including thiophenes, furans, thiazoles, isoxazoles, pyridines, pyrimidines, and pyrazines. Aryl or vinyl triflates can undergo palladium-catalyzed boronic acid coupling, which usefully extends the scope of the reaction to phenols or enols. Coupling of boronate derivatives with aryl mesylates, catalyzed by nickel complexes, has also been reported, as has palladium-catalyzed coupling with sulfonium salts. Arenediazoniumtetrafluoroborates have been found to undergo coupling with arylboronic acids in dioxane or methanol, catalyzed by palladium acetate in the absence of both added base and phosphine ligand. This has been extended to the coupling of arenediazoniumtetrafluoroborates with potassium...
aryltrifluoroborates,\textsuperscript{58} which are more nucleophilic than the corresponding arylboronic acids, and also with potassium vinyl trifluoroborates,\textsuperscript{59} which are air-stable crystalline solids, more readily prepared and isolated than the corresponding vinylboronate esters. Alkenyl and aryl trifluoroborates have also been reported by Molander to couple with aryl halides, which greatly extends their usefulness.\textsuperscript{56} Coupling of arylboronic acids with, for example vinylic halides,\textsuperscript{60,61} or allenyl methyl carbonate,\textsuperscript{62} have also been described. Coupling reactions involving alkylboronic acids were reported to be difficult to accomplish.\textsuperscript{57} However, Molander has described, which primary alkylboronic acids could be coupled efficiently with aryl halides and triflates.\textsuperscript{58}

A further useful variation of the Suzuki reaction, shown in Scheme 1.5, is the carbonylative cross-coupling of arylboronic acids with aryl iodides in the presence of carbon monoxide at atmospheric pressure, to give substituted benzophenones.\textsuperscript{63}

Unsymmetrical ketones have also subsequently been prepared by cross-coupling of arylboronic acids with acyl chlorides, catalyzed either by (Ph\textsubscript{3}P)\textsubscript{2}Pd,\textsuperscript{64} or Pd(OAc)\textsubscript{2} with no added ligand.\textsuperscript{65}

\textbf{Scheme 1.5:} Synthesis of substituted benzophenones

Originally the tetrakis(triphenylphosphine)palladium(0) was the catalyst employed for the biaryl coupling,\textsuperscript{36} and it is still the most popular. A wide variety of alternative catalysts have been reported for Suzuki and related couplings, including: (Ph\textsubscript{3}P)\textsubscript{2}PdCl\textsubscript{2},\textsuperscript{49,63} dppbPdCl\textsubscript{2},\textsuperscript{50,66} Pd(dba)\textsubscript{2},\textsuperscript{67} Pd(OAc)\textsubscript{2},\textsuperscript{57,68} Pd(OAc)\textsubscript{2}/o-tol\textsubscript{2}P,\textsuperscript{51,69} Pd(OAc)\textsubscript{2}/dppf,\textsuperscript{51} (PhCN)\textsubscript{2}PdCl\textsubscript{2}/Ph\textsubscript{3}As,\textsuperscript{61} (CH\textsubscript{3}CN)\textsubscript{2}PdCl\textsubscript{2},\textsuperscript{63} Pd-C,\textsuperscript{70} (Ph\textsubscript{3}P)\textsubscript{2}NiCl\textsubscript{2},\textsuperscript{55} and the palladacycle complex trans-di-µ-acetatobis[2-(di-o-tolylphosphino)-benzyl]- dipalladium(II).\textsuperscript{71}

Alternative bases to sodium carbonate include: NaHCO\textsubscript{3},\textsuperscript{49,72} K\textsubscript{2}CO\textsubscript{3},\textsuperscript{59} Cs\textsubscript{2}CO\textsubscript{3},\textsuperscript{48b} K\textsubscript{3}PO\textsubscript{4},\textsuperscript{54} EtsN,\textsuperscript{51,69a} Ag\textsubscript{2}O,\textsuperscript{61} Ba(OH)\textsubscript{2},\textsuperscript{73} good for sterically-hindered biaryls, and CsF,\textsuperscript{74} compatible with readily-hydrolyzed functionality, such as esters.
Suzuki and Miyaura\textsuperscript{36} reported that stronger bases such as ethoxide or hydroxide gave poorer yields than carbonate; sodium acetate was also found to be ineffective.

The palladium-catalyzed coupling of boron compounds with aryl halides has been extended by Miyaura’s group to the cleavage of a boron-boron bond in the one-step conversion of aryl halides to boronic esters using the novel reagent Bis(pinacolato)diboron,\textsuperscript{75} allowing access to boronic acid derivatives without protection of functionalities such as ester, ketone, cyano or nitro groups.

### 1.4.1 1,2- and 1,4-additions to carbonyl compounds

Miyaura has also described the conjugate addition of arylboronic acids to enones, in the presence of a rhodium catalyst and a chelating phosphine, to give good yields of saturated ketones.\textsuperscript{76} Under similar conditions, both aryl- and alkenylboronic acids can add to aldehydes to give secondary alcohols in high yield (Scheme 1.6).\textsuperscript{77}

\begin{center}
\textbf{Scheme 1.6}: Arylboronic acids addition in enones and aldehydes
\end{center}

An extension of these reactions to the addition of potassium alkenyl- and aryltrifluoroborates to aldehydes and enones has also been reported.\textsuperscript{78}

### 1.4.2 C-O, C-N and C-S bond-forming reactions

One of the simplest reactions of arylboronic acids is their oxidative cleavage, usually with hydrogen peroxide,\textsuperscript{79} to give phenols. Other oxidative reactions with N-Bromosuccinimide to give aryl halides are known.\textsuperscript{80} More usefully, arylboronic acids undergo Ullmann-type C-O and C-N coupling reactions with phenols,\textsuperscript{81,82} amines, amides and imides,\textsuperscript{82,83} ureas, sulfonamides and carbamates,\textsuperscript{80} and N-heteroaromatics\textsuperscript{84} in the presence of copper(II) acetate Scheme 1.7 to give the corresponding diaryl ethers, arylamines or N-aryl heterocycles.
Formation of unsymmetrical thioethers from arylboronic acids and thiols, mediated by copper(II) acetate has also been reported.  

1.5 Water Promoted Organic Reaction

The use of water as a solvent in organic chemistry was rediscovered in the eighties. For the most part of studies water as a solvent was ruled out in the preceding decades due to several reasons. Among them the insolubility of the reactants and the incompatibility of the intermediates with water are the primary. However many biochemical processes occur in the presence of water, and the diversity of the reactions in vivo should prompt chemists to discover the potential of water, as a solvent. As a matter of fact that the hydrophobic effect, a principal force determining the folding of proteins and the binding of enzymes to substrate, was utilized for the first time in 1980 for water promoted Diels-Alder reaction.

1.5.1 Structure of Water

Liquids (solvent) can be divided in two groups. In the first one, molecules are held together by weak non-directional Vender Waals forces and fill space in a regular manner. In these unstructured liquids, molecules have 10-11 neighbors on average. The second group concerns the structured liquid, such as hydrogen bonds. In this case, molecules do not fill space efficiently and as a consequence, the structured liquids display cavities. The microscopic structure of liquid water can be visualized by considering the hexagonal ice structure in which each water molecule shares four hydrogen bonds (2 donar& 2 accepter) with its neighbors. Such an extremely structured network of low entropy and low density displays many cavities which can easily accommodate solutes. In two state mode, liquid water is represented as an equilibrium between such “structured water” constituted between by ice type clusters.
and “unstructured water” having higher entropy and density in which each molecule has many more neighbors. This equilibrium can be influenced by temperature, pressure and additives. At room temperature and under normal pressure, water molecules in the pure liquid have 4.4 neighbors. On average as seen by neutron diffraction, the structure and the importance of water clusters are under investigations.

1.5.2 Reactivity in Water

Solvent effects are rationalized by studying the relative solvation of the initial (reactants) and transition states. This effect includes the solute-solvent interaction and the reorganization of solvent around the solute. Due to the hydrophobic interaction, they have a tendency to aggregate, but this association is not sufficient to explain the rate enhancement. Noteworthy is the high surface tension of water (72 dynes/cm), a consequence of its high c,e,d (550 cal/cm³ or 22000 atm), which tends to induce a diminution of the surface of contact between hydrophobic and water molecule. Following Aldolation shows the reactivity of molecule in different solvents.

Scheme 1.8: Synthesis of 2R, 2S-2-(hydroxyl(phenyl) methyl) cyclohexanone
CHAPTER-1

INTRODUCTION

Table 1.2: Optimization of reaction.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp.</th>
<th>Time</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>R:S</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_2)Cl(_2)</td>
<td>20°C</td>
<td>2h</td>
<td>1 eq. TiCl(_4)</td>
<td>82</td>
<td>25:75</td>
</tr>
<tr>
<td>CH(_2)Cl(_2)</td>
<td>60°C</td>
<td>9 days</td>
<td>10000 atm</td>
<td>90</td>
<td>75:25</td>
</tr>
<tr>
<td>H(_2)O</td>
<td>20°C</td>
<td>5 days</td>
<td>stirring</td>
<td>23</td>
<td>85:15</td>
</tr>
<tr>
<td>H(_2)O:THF (1:1)</td>
<td>20°C</td>
<td>5 days</td>
<td>stirring</td>
<td>45</td>
<td>74:26</td>
</tr>
</tbody>
</table>

Table 1.3: Water promoted organic reactions.

<table>
<thead>
<tr>
<th>No.</th>
<th>Type of reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Michael-type reaction</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>Reduction reaction using SmI(_2) in water, reduction or ketones as well as alkyl and aryl iodides.</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>Decarboxylation of malonic acid derivatives in water under microwave irradiation.</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>Stereoselective bromination of stibene and chalcone.</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>Preparation of ylidenemalononitriles without catalyst in water</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>InBr(_3)-water chemoselectivedithioacetalization of aldehyde.</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>Deprotection of alkyl TBS ethers.</td>
<td>95</td>
</tr>
</tbody>
</table>

1.6 Rare-Earth Metal Triflates in Organic Synthesis

Lewis-acid (LA)-catalyzed reactions are of enormous interest because of their exclusivereactivities and mild reaction conditions.\(^{96,97}\) A broadmultiplicity of reactions using Lewis acids have been developed, and they have been applied to the synthesis of natural compounds also Usually, Lewis acids such as AlCl\(_3\), BF\(_3\), TiCl\(_4\), SnCl\(_4\), etc., are used in these reactions, however, more than stoichiometric amount of the LA is required are needed in many cases. Moreover, these LAs are moisture sensitive and easily decomposed or deactivated in the presence of even a small amount of water. Furthermore, these Lewis acids cannot be recovered and reused after the completion of reaction. The first report on water-compatible Lewis acids, lanthanide triflates
[Ln(OTf)\textsubscript{3}], appeared in 1991.\textsuperscript{98,99} Before 1991, Earlier, only one report on amidine synthesis in an organic solvent using a lanthanide triflate as a catalyst was known, under strictly anhydrous conditions.\textsuperscript{100} It was thus accepted that the LA catalysis must be performed under strictly anhydrous conditions.

The stability & usefulness of the [Ln(OTf)\textsubscript{3}] as LA in water was the appealing. After the first report, not only Ln(OTf)\textsubscript{3} but also scandium and yttrium triflates were shown to be water-compatible LA, and these rare-earth metal triflates[RE(OTf)\textsubscript{3}] was regarded as new types of LAs. Only catalytic amounts of triflates are enough to complete the reactions in most cases. Furthermore,[RE(OTf)\textsubscript{3}] can be recovered easily after reactions and reused without loss of activity.[RE(OTf)\textsubscript{3}] are available not only in aqueous media but also in many organic solvents. The triflate are still active in the coexistence of many Lewis bases containing nitrogen, oxygen, phosphorus, and sulfur atoms. In almost all cases, catalytic use, recovery, and reuse of the triflates are possible. While large amounts of conventional LAs are required treatment of the residues after reactions, which may induce some serious environmental problems. On the other hand triflate-catalyzed reactions are clean and the triflates are regarded as eco-friendly catalysts.

The catalytic efficiency of rare-earth metal triflates vary from one reaction to another. Generally, [Sc(OTf)\textsubscript{3}] shows a higher catalytic activity than [Ln(OTf)\textsubscript{3}] and [Y(OTf)\textsubscript{3}]. Recently, the relative Lewis acidity of rare earth metal triflates were evaluated based on their competitive ligand dissociation from complexes, M(OTf)\textsubscript{3}(L)\textsubscript{4}(L=hexamethylphosphoramide, triethylphosphine oxide, or trimethyl phosphate) using tandem mass spectrometry.\textsuperscript{101} The results are in accordance to the extraordinary catalytic activity of Sc(III) and Yb(III). The high Lewis acidity of Sc(III) and Yb(III) may be attributed to their small ionic radii.\textsuperscript{102}

Rare-earth metal triflates are readily prepared by heating the corresponding metal oxides or chlorides in an aqueous trifluoromethanesulfonic acid (TfOH) solution.\textsuperscript{103,104} They are also prepared by the reaction of aqueous solutions of the corresponding metal halides with silver triflate. Typically, eight or nine molecules of water are contained in the triflates after removal of water at room temperature. Anhydrous samples are obtained after drying at elevated temperature under high vacuum.
1.6.1 Applications of rare earth metal triflates

1) **Aldol Reaction**

Kobayashi and his group reported the use of Yb(OTf)$_3$ for hydroxymethylation reaction of silyl enol ethers with commercial aqueous formaldehyde solution.\(^9\) Yb(OTf)$_3$ catalyzed hydroxyl methylation of Silyl Enol Ethers with Aqueous Formaldehyde Sol.

\[
\text{Me}_3\text{SiO} + \text{R}_1 \overset{\text{Yb(OTf)$_3$; (10 mol\%)}\text{aq. HCHO}}{\rightleftharpoons} \text{R}_2 \xrightarrow{\text{THF/H}_2\text{O; r.t.}} \text{R}_1 \text{OH} \]

**Scheme 1.9**: Synthesis of hydroxymethylation.

2) **Mannich type reaction**

A novel Mannich-type reaction of \(N-(\alpha\text{-aminoalkyl})\)-benzotriazoles with silyl enol ethers has been developed.\(^7\) Yb(OTf)$_3$ was also useful for three-component coupling reactions of aldehydes, amines, and silyl enol ethers.\(^1\) Three component coupling Reactions of Aldehyde, Amine and Silyl Enol ethers Catalyzed.

\[
\text{R}_1\text{O} + \text{R}_2\text{NH}_2 + \text{Me}_3\text{SiO} \overset{\text{Yb(OTf)$_3$; (5-10 mol\%)}\text{MgSO}_4; \text{r.t.}}{\rightleftharpoons} \text{R}_1\text{NH} \text{R}_2 \text{O} \]

**Scheme 1.10**: Novel Mannich-type reaction.

3) **Pictet-Spengler Reaction**

Sc(OTf)$_3$ catalyzed in situ invention of the acyliminium ion from methoxyindolone and successive cyclization to give the corresponding carboline in moderate yield.\(^1\) The same reaction was also mediated by Cu(OTf)$_2$ in a better yield.
CHAPTER-1

INTRODUCTION

Scheme 1.11: Transition metal mediated organic reaction.

1.7 Polymer-supported reagents

The use of polymer supports in organic synthesis began with solid-phase synthesis where the synthetic target is attached to the polymer. For a variety of reasons, like ease of reaction monitoring and product characterization, shorter method development time, the role of the polymer has gradually shifted to supporting reagents for reacting with solution-phase substrates in synthesis, which sometimes referred as polymer-assisted synthesis. Nowadays's such use of polymer-supported reagents is common, than solid-phase synthesis, and a great number of such reagents have been reported in the literature, which are commercially available. Despite intensive research efforts over the past few years, the number of polymer-supported reagents known is still a small fraction of the reagents commonly used in traditional solution-phase organic synthesis. Therefore, with the increased desire for faster production of compound collections with greater structural complexity, the need has grown for polymer supported reagents capable of affecting different reactions and greater efficiency. This highlights some of the recent progress in developing polymer-supported reagents and showcases some of the different strategies for enhancing their performance and improving methods for their preparation.

The applications of polymer supports in organic synthesis has specific requirements of the polymer regarding solvent compatibility, reactivity, porosity, etc. Thus, one polymer does not fit all applications, just as there is no universal solvent, and striking the proper balance between polymer structure and synthetic use is essential. Some of the polymer supports used in the research described in Table 1.4. Judging by the number and variety of materials listed, it is quite clear that the research
regarding polymer-supported reagents and catalysts the polymers used. To support them is an active and dynamic field and that many important discoveries are still to be made.

Table 1.4: Applications of polymer supported reagent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reported Reaction Condition</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{R-SO}_2\text{Na} + \text{Ar}^+ \rightarrow \text{Ar}^-$</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>$\text{PEG-400}$ $\text{MW (200 W), 50°C, 10 min}$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$\text{Ar-X + (HO)}_2\text{B-Ar'} \rightarrow \text{Ar-}\text{Ar'}$</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>$1.2 \text{eq.}$ $\text{1 mol-% Pd / FVC (13 wt-%)}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$2 \text{eq. Na}_2\text{CO}_3$ $\text{EtOH/H}_2\text{O (1:1)}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{X: Cl, Br, I}$ $\text{r.t., 2-6 h}$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$\text{R-X + Y-B(OH)}_2 \rightarrow \text{R-Y}$</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>$\text{(1 mol-%)}$ $\text{DMF/Water}$ $\text{Na}_2\text{CO}_3$ $\text{50°C}$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>$\text{PEG} \rightarrow \text{PEG-}\text{NH}_2 \rightarrow \text{PEG-N}$</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>$\text{Suzuki Coupling}$ $\text{Knoevenagel Condensation}$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$\text{KAPs}$ $\text{Pd/CKN}$</td>
<td>111</td>
</tr>
</tbody>
</table>
1.8 Photocatalysis of organic reaction

Decarboxylative cross-coupling of alkyl carboxylic acids with vinyl halides and Enantioselective decarboxylative arylation of α-amino acids are merger of photoredox and nickel catalysis. The mechanistic evaluation of a mode of catalytic activation that achieve the highly selective photoredox α-alkylation/lactonization of alcohols with methyl acrylate via a hydrogen atom transfer mechanism. The combination of photoredox catalysis and enamine catalysis has enabled the development of an enantio selective α-cyanoalkylation of aldehydes. Benzylic ethers with schiff bases has been successfully reacted, direct benzylic C–H activation by a combination of a thiol catalyst with an iridium photocatalyst and subsequent radical radical coupling with secondary aldimes affords a variety of β-amino ether products in good to excellent yields. The direct α-hetero arylation of tertiary amines has been achieve via photoredox catalysis to generate valuable benzylic amine pharmacophores. An efficient route towards biologically relevant pentose derivatives were described, by de novo synthetic strategy features an enantioselective α-oxidation reaction enabled by a chiral amine in conjunction with copper(II) catalysis. Alkyl oxalates are new bench-stable alcohol activating groups for radical generation under visible light photoredox conditions. The direct β-coupling of cyclic ketones with aryl ketones has been achieved via the synergistic combination of photoredox catalysis and organocatalysis. Visible light photoredox catalysis with transition metal complexes used in organic synthesis. Serendipity has long been a welcome yet elusive phenomenon in the advancement of chemistry. The mechanism directly couples tertiary amines with cyano aromatics by using mild and operationally trivial conditions. Redox processes and radical intermediates are found in many biochemical processes, including deoxyribonucleotide synthesis and oxidative DNA damage. One of the core principles underlying DNA biosynthesis is the radical-mediated elimination of H2O to deoxygenate ribonucleotides, an example of ‘spin-centreshift’ during which an alcohol C–O bond is cleaved, resulting in a carbon-centred radical intermediate. Although spin-centre shift is a well-understood biochemical process, it is underused by the synthetic organic chemistry community. Photoredox Catalysis, a mild, operationally simple approach to the
synthesis of trifluoromethyl carbonyl compounds.\textsuperscript{124} The direct b-activation of saturated aldehydes and ketones has long been an elusive transformation. The photoredox catalysis in combination with organo catalysis can lead to the transient generation of 5p-electron b-enaminyl radicals from ketones and aldehydes. This rapidly couple with cyano-substituted aryl rings at the carbonyl b-position. This mode of activation is suitable for a broad range of carbonyl b-functionalization reactions and is amenable to enantioselective catalysis.\textsuperscript{125}

For the photocatalysis reaction on semiconductors, the absorbed irradiation functions as thermal energy and excites the electrons from valence band to conduction band. Therefore, the width of band gap is one of the most important properties which strongly influence the electrical and optical properties of the material. Broader band gap needs more energy to excite the electrons which means only the irradiation carrying higher energy such as ultraviolet light and microwave can be used for the energy source during the reaction process. The irradiation with lower energy, visible light and infrared for example, can only drive catalysts with narrow band gap.\textsuperscript{125b}

These differences shown in fig 1.2.

![Diagram](image)

**Fig 1.3:** Different band gap and their light adsorption.

Recently, gold loaded TiO\textsubscript{2} catalyst has been reported that can facilitate this reaction by a photocatalytic process under moderate temperature and atmosphere pressure.\textsuperscript{126}
Advantage of the photo catalyst reaction

1. Free, clean and renewable solar energy can be used as a driving force for chemical reactions.
2. The photo catalytic organic reactions, in which O$_2$ usually involved, offer possible capability of finishing a chemical process in a sustainable and eco-friendly way.
3. Compared with the thermal activation, photochemical excitation can be conducted under a moderate temperature and pressure.
4. The mild condition of photochemical reactions can minimize by-products and produce high-purity products in organic synthesis.

1.9 Phase-transfer Catalyst

A variety of solvent-free N-alkylation reactions have been reported which entail the use of phase transfer agents such as tetrabutylammonium bromide (TBAB) under microwave irradiation conditions. The important recent examples are N-alkylation of phthalimides$^{127}$ or its potassium salt$^{128}$ in the presence of potassium carbonate and TBAB. The approach has been extended to a variety of heterocyclic systems, namely carbazole,$^{129}$ other azaheterocycles using K$_2$CO$_3$/KOH and TBAB,$^{130}$ including pyrrolidino [60]fullerenes.$^{131}$ The scope and limitations of the transition-metal-free Suzuki-type coupling of aryl halides and arylboronic acids to form biaryls are also presented.$^{132}$

Fig 1.4: Universal reaction of photosynthesis.
No Transition Metal Catalyst Required

Scheme 1.12: Transition metal-free Suzuki-type coupling reaction.

The first theory for the phase transfer catalysis is the extraction mechanism proposed by Starks (see scheme 1.13) which is based on the hypothesis that PTC (denoted as Q′X′ below) can move freely across organic and aqueous layers. The inorganic base (MOH) and PTC undergo ion exchange and the resulting Q′OH− is extracted into the organic layer. The Q′OH− species, which is highly polarized and thus is highly basic, deprotonates the reactant. The deprotonated species (Q′R−) is also a highly polarized species with the highly reactive.$^{133}$

Scheme 1.13: Phase transfer catalysis Starks extraction mechanism.

Advantages of phase transfer catalyst
- Elimination of dangerous, inconvenient, and expensive reactants
- High reactivity and selectivity of the active species
- High yield and purity of products
- Simplicity of the procedure
- Low investment cost
- Low energy consumption
- Minimization of industrial waste
Elimination of organic solvents (when organic reactants are liquid)
mild reactions conditions, which increase process reliability and flexibility;
viability in the presence of water and avoidance of run-away conditions;
the ability to use NaOH as a base rather than the more expensive and hazardous organic bases such as sodium methoxide;
compatibility with a broad range of solvents.
1.10 References.


CHAPTER-1

INTRODUCTION