CHAPTER-1

INTRODUCTION

BORONIC ACIDS: SYNTHESIS AND THEIR APPLICATIONS IN CHEMISTRY AND BIOLOGY

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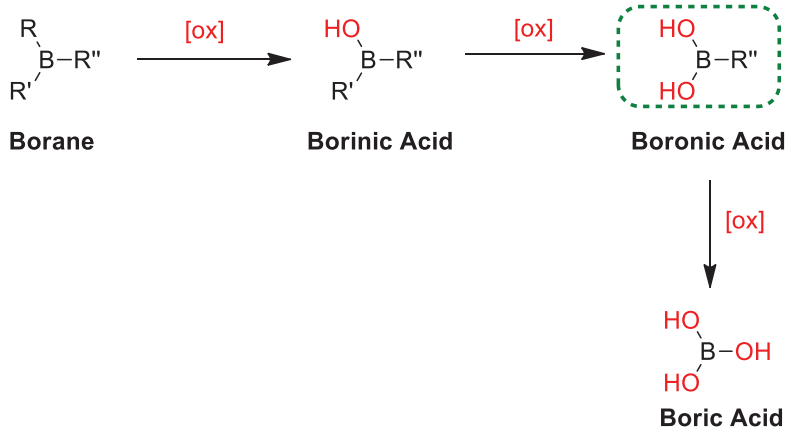
1.1 BRIEF HISTORY OF BORONIC ACID

Boronic acids are the class of organoboron compounds having trigonal planar geometry. The octet of boronic acid completes with one *C*-based substituent (*i.e.C-B* bond), two hydroxyl group and one vacant *p*-orbital, which is oriented orthogonal to the three substituents (**Scheme 1.1**). Boronic acid is the second oxidation product of borane. In general, boranes are unstable and undergo slow oxidation in air to provide borinic acid which subsequently oxidized to boronic acid. Boronic acids are relatively stable compounds which can be easily stored and handled. Oxidation of boronic acid results in the formation of boric acid which is more stable and environmentally benign compound. Boronic acids are also referred as green compounds since it degrades into boric acid [1].

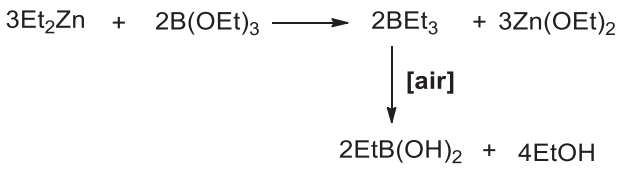


Scheme 1.1. Structures of different organo boron compounds.

In the past two decades, the importance of boronic acids has grown exponentially in synthetic organic chemistry. In 1981, Suzuki *et al*., made a breakthrough in the methodology of biaryl synthesis using arylboronic acids as a substrate in the presence of palladium catalysts (**Scheme 1.22**). Since then, arylboronic acids are extensively used in the synthesis of many complex natural products as well as bioactive molecules [2,3]. Besides the synthetic applications, considerable progresses have been made for the use of boronic acids in other fields including molecular recognition [4,5], material sciences [6] and catalysis [7,8]. Velcade, the first boronic acid containing anticancer drug, confirms the growing status of boronic acids as an important class of compounds not only in chemistry but also in medicine [9].

1.2 PREPARATION OF BORONIC ACIDS

Boronic acids can be achieved through numerous methods. In 1860, Frankland has reported the first preparation and isolation of a boronic acid, *i.e.* ethylboronic acid. The highly air-sensitive triethylborane was obtained by treating diethylzinc with triethylborate, which undergoes slow oxidation to provide ethylboronic acid (**Scheme 1.2**) [10-12].



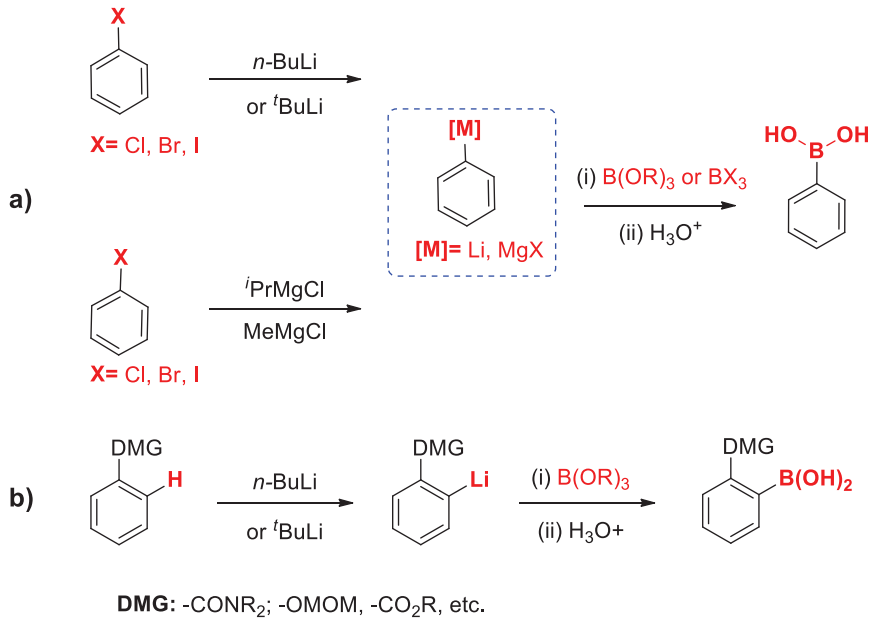
Scheme 1.2. Preparation of ethylboronic acid.

In continuation to this study, preparation of different varieties of boronic acids including aryl, alkyl, alkenyl, alkynyl and benzyl boronic acids were demonstrated in the literature [13]. In fact, in recent years significant advances have been made for the

straightforward synthesis of functionalized boronic acids from simple and commercially available starting materials [14]. Few synthetic strategies for the preparation of different types of boronic acids are discussed below.

1.2.1 Synthesis of arylboronic acids using organometallic intermediates

Among the different boronic acids, arylboronic acids remain the most popular class of boronic acids. Originally, phenylboronic acid was synthesized by Michaelis and Becker in 1880. The most common method for the preparation of arylboronic acids involves the reaction of organometallic species such as organolithium [15] or Grignard reagents [16] with trialkyl borate at low temperature, followed by acid hydrolysis.



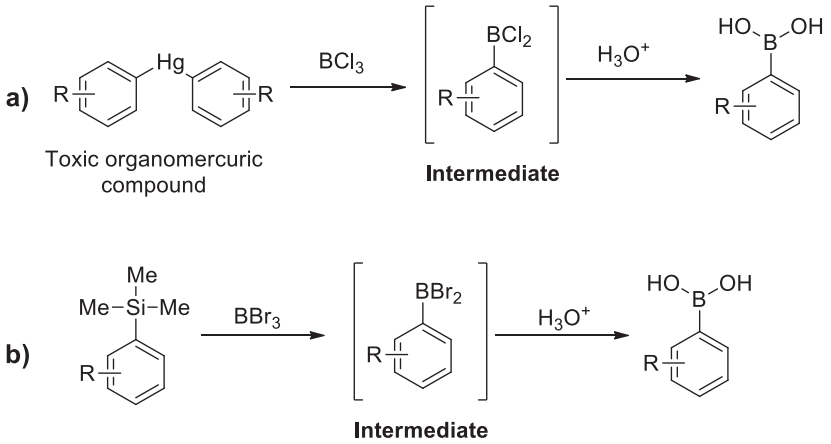
Scheme 1.3. Synthesis of arylboronic acid using organometallic compounds [DMG] = Directing metalation group.

This typical method provides the desired arylboronic acids in good to excellent yields (**Scheme 1.3a**) [17]. Basically, the organometallic species were generated *in situ* by metal-halogen exchange reaction of aryl halides with alkyllithium or metal insertion

reactions [18]. Alternatively, the reaction of alkyllithium with an arene bearing "Directed Metalation Group" (DMG) normally leads to *ortho*-lithiated intermediate which was trapped with borate esters to obtain arylboronic acids (**Scheme 1.3b**). In general, DMG's are known as chelating groups that direct the lithiation at *ortho*-position by increasing the acidity of the proton. DMG can be retained if needed or converted to a different functional group [19-21].

1.2.2 Synthesis of arylboronic acids from arylsilanes *via trans*-metallation

One of the oldest protocols for preparing arylboronic acids involves the reaction of boron trichloride with diaryl mercury compounds through *trans*-metallation. However, this method has remained unpopular due to the environmental toxicity of organomercury compounds (**Scheme 1.4 a**). In this context, environmentally benign aryl trialkylsilanes have found more suitable substrate which can be *trans*-metallated efficiently with boron halides.

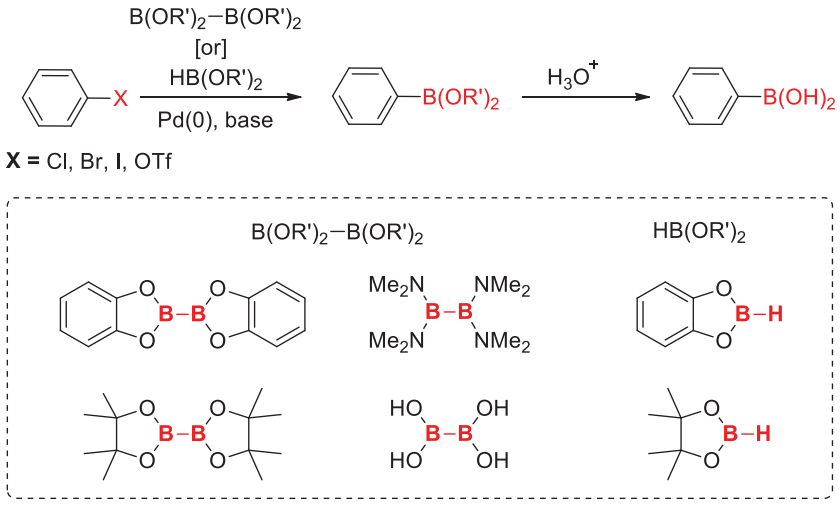


Scheme 1.4. Synthesis of arylboronic acid using arylsilane and boron tribromide.

For example, trimethyl arylsilane have been used for the preparation of arylboronic acids with boron tribromide. The reaction provides arylboron dibromide intermediate which subsequently undergoes for acid hydrolysis to form arylboronic acid (**Scheme 1.4 b**) [22]. Using this method, relatively simple arylboronic acids can be obtained.

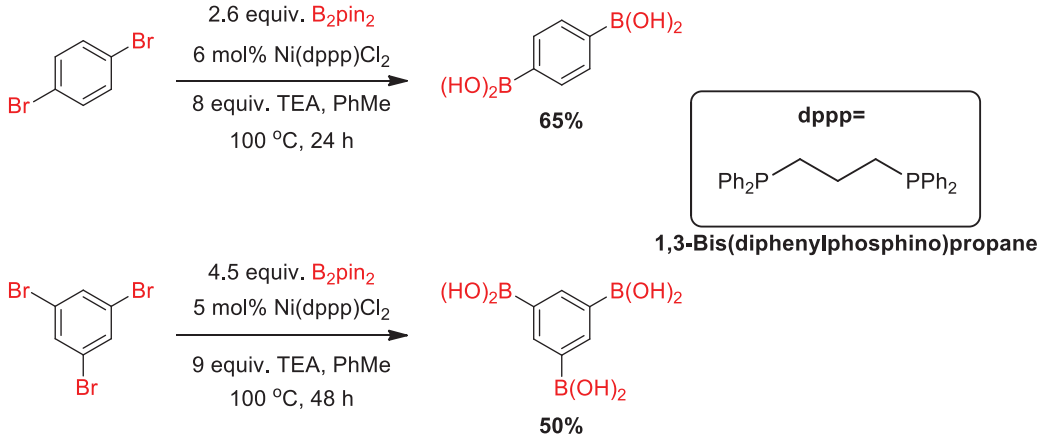
1.2.3 Palladium and Nickel catalyzed borylation of aryl halides and triflates with diboronyl esters

To some extent, the above said methods (*i.e.* reaction of organometallic reagents with borate esters) suffer from functional group incompatibility as well as requirement of extremely anhydrous conditions. In this context, Miyaura *et al.,* have demonstrated a simple method for the preparation of arylboronic acids involving the direct coupling of diboronyl esters (e.g. B_2pin_2, B_2Cat_2, etc.) with aryl halides and triflates in the presence of palladium catalysts (**Scheme 1.5**) [23-25].



Scheme 1.5. Palladium catalyzed synthesis of arylboronic acids.

This method shows a broad substrate scope and functional group tolerance. In some cases, tetrahydroxyborate [$B_2(OH)_4$], pinacolborane (HBpin) and catacolborane (HBcat) were also employed instead of diborateesters [26-31].

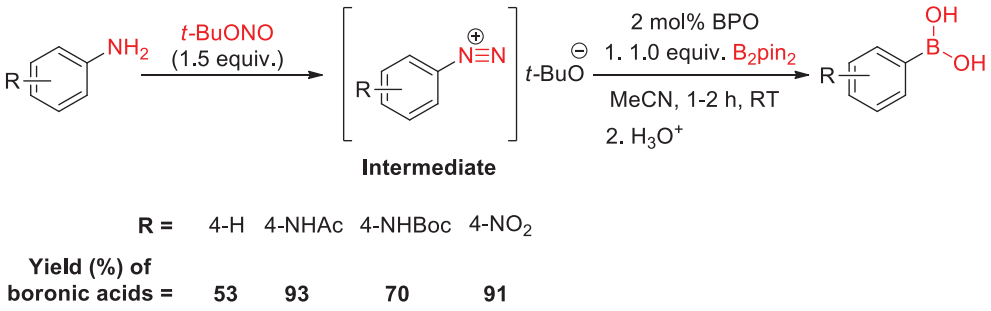


Scheme 1.6. Examples of Ni-catalyzed borylation of aryl halides. [dppp] = 1,3-bis(diphenylphosphino)propane.

Later, similar transformations were achieved using nickel catalysts such as Ni(dppe)Cl_2 and Ni(dppp)Cl_2. Using nickel catalysts, not only mono-borylation, but also di- and tri-borylations were achieved in reasonable yields (**Scheme 1.6**) [32].

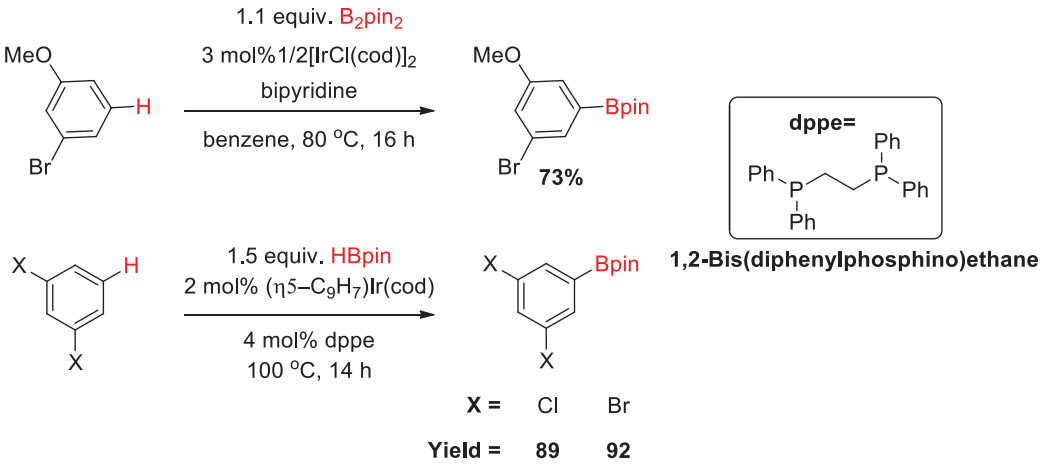
1.2.4 Synthesis of arylboronic acids from anilines

A metal-free *ipso*-borylation of aryl amines with B_2pin_2 has been explored in the presence of *tert.*-butyl nitrite (*t*-BuONO) and benzoyl peroxide (BPO) (**Scheme 1.7**) [33]. The reaction proceeds under mild condition through the formation of diazonium salt intermediate.



Scheme 1.7. Metal-free synthesis of arylboronates. [BPO]= Benzoyl peroxide.

1.2.5 Transition metal-catalyzed direct boronylation of arenes

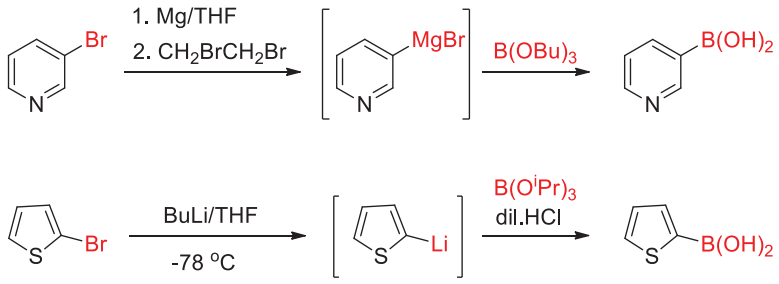


Scheme 1.8. Iridium catalyzed direct borylation of arenes.[dppe] = 1,3-bis(diphenylphosphino)ethane.

Recently, many research groups have developed a very attractive atom economy approaches, *i.e.* preparation of arylboronic acids by direct boronylation of arenes *via* iridium catalyzed *C*–H activation reactions (**Schemes 1.8**) [34-41]. These reactions usually provide good to excellent yields of arylboronic acids while many functional groups were found to be well tolerated.

1.2.6 Synthesis of heteroarylboronic acids

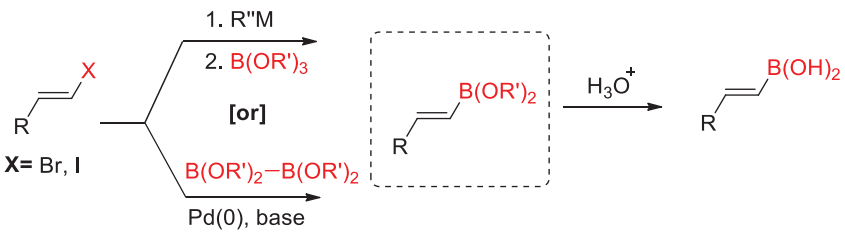
Similar to arylboronic acids,heteroarylboronic acids also play an important role in the synthesis of various natural products and bioactive compounds. Pyridinyl, pyrrolyl, thienyl, furyl and indolyl boronic acid derivatives have been synthesized from corresponding heteroaryl halides *via* metal-halogen exchange reactions (**Scheme 1.9**) [42, 43].



Scheme 1.9. Synthesis of different heterocyclic boronic acids.

1.2.7 Synthesis of alkenylboronic acids

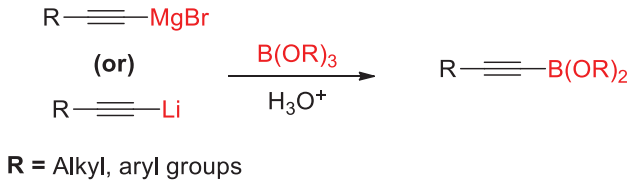
Alkenylboronic acids are another important class of synthetic intermediates employed in the preparation of various unsaturated compounds. Among the different routes: i) trapping of alkenyl-metal intermediates with borates, and ii) palladium-catalyzed direct coupling of diboronyl reagents with vinyl halides, are the most popular choice,widely employed in the preparation of alkenylboronic acids (**Scheme 1.10**) [44-48].



Scheme 1.10. Synthesis of alkenylboronic acids from vinylhalides.

1.2.8 Synthesis of alkynylboronic acids

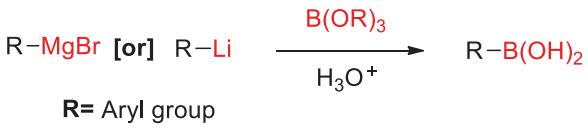
Similar to arylboronic acids, alkynylboronic acids can also be synthesized by replacement of Mg or Li acetylides with borate esters [13]. For instance, Matteson *et al.,* have demonstrated the synthesis of dibutylacetylene boronate from ethynylmagnesium bromide and trimethyl borate [49]. Similarly, Brown and his group synthesized alkynylboronic esters from ethynyllithium and trialkyl borate which provides a common access to alkynylboronic acids in good yields (**Scheme 1.11**) [50].



Scheme 1.11. Synthesis of alkynylboronic acids from Mg or Li acetylides.

1.2.9 Synthesis of alkylboronic acids

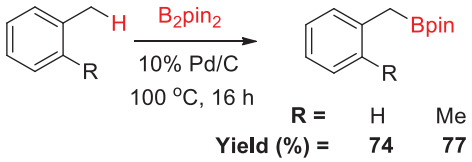
Alkylboronic acids have found limited uses in organic synthesis due to poor stability. In fact, *trans*-metallation of alkylboronic acid is relatively difficult when compared with arylboronic acids [51]. Alkylboronic acids are usually obtained by the reaction of alkyllithium or magnesium compounds with trialkylborates (**Scheme 1.12**). For example, the reaction of methyllithium with triisopropyl borate provides methylboronic acid in good yield [53].



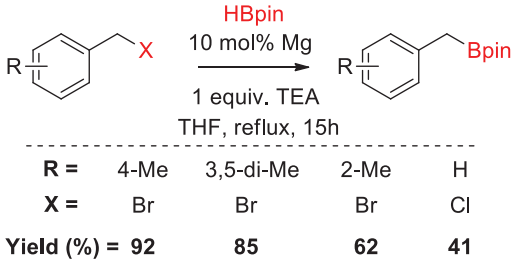
Scheme 1.12. Synthesis of alkylboronic acids from alkyllithium and magnesium compounds.

1.2.10 Synthesis of benzylboronic acids

Palladium-mediated benzylic *C*-H borylation of alkylbenzenes with bis(pinacolato)diboron or pinacol borane provides benzylboronic acids (**Scheme 1.13**) [52, 53]. On the other hand, benzyl halides can also be efficiently transformed into benzylboronate esters with pinacol borane in the presence of catalytic amount of magnesium (**Scheme 1.14**) [54]. These reactions provide benzylboronate esters in high yields.



Scheme 1.13. Pd-catalyzed *C*-H activation/borylation of benzylic positions.



Scheme 1.14. Mg-catalyzed borylation of benzyl halides.

1.3 BORONIC ACID SURROGATES

In general, purification and characterization of some boronic acids are very difficult, thus they are often prepared as (or) converted into different surrogates and used in organic synthesis (Figure **1.1**). These surrogates are found to be stable which can be handled and stored easily when compared with un-protected boronic acids. Among them, the most common surrogates of boronic acids are boroxines, boronic

esters, potassium trifluoroborate salts and *N*-methyliminodiacetic acid (MIDA) boronate esters [55, 56]. A brief introduction of these boronic acid surrogates is discussed below.

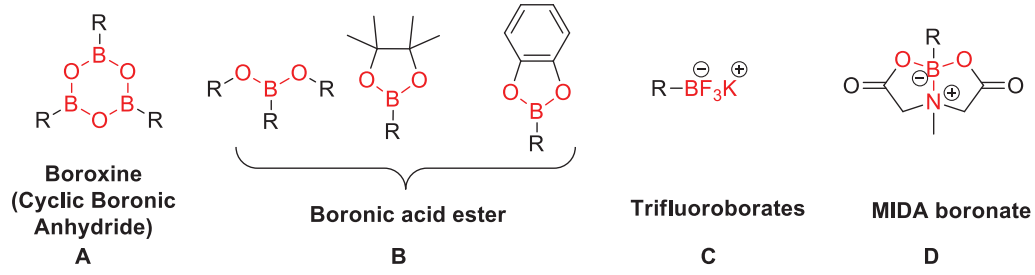
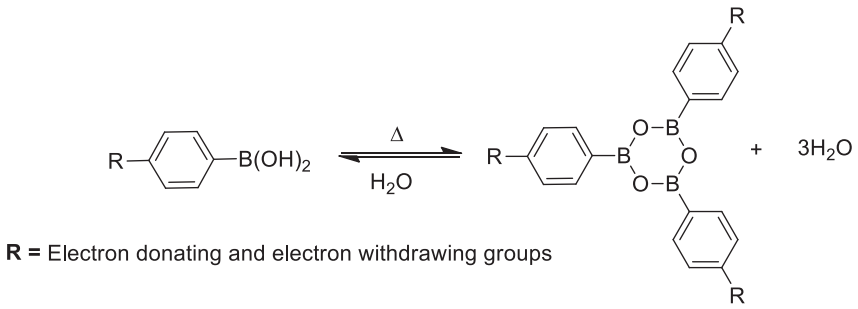


Figure1.1 Structures of some common boronic acid surrogates.

1.3.1 Boroxines

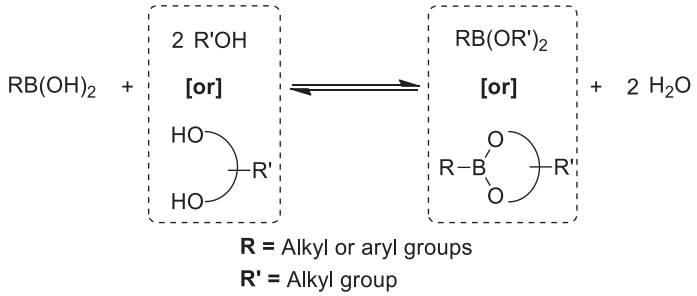
Boroxines, also known as boronic acid anhydrides, are the dehydration products of organoboronic acids (Figure **1.1**, **A**). They are isoelectronic to benzene thus expected to possess partial aromatic character due to the presence of vacant orbital on boron. Boroxines are generally prepared by thermal dehydration of boronic acids by azeotropic removal of water (**Scheme 1.15**). Alternatively, they can also be obtained by drying boronic acids over sulfuric acid or phosphorus pentoxide. These compounds have been employed in few synthetic transformations instead of boronic acids as well as found applications in materials and macromolecular architectures [57].



Scheme 1.15. Synthesis of boroxines from arylboronic acid.

1.3.2 Boronic esters

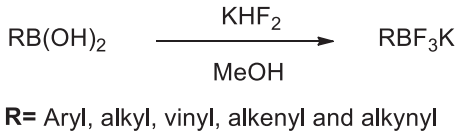
Boronic esters, also referred as boronate esters, are formed by the reaction of boronic acid with an alcohol through dehydration (**Scheme 1.16**). Boronate esters are quite stable under air and moisture which can be purified through column chromatography. Boronic esters can be classified as acyclic and cyclic esters,where in general, cyclic esters are more stable when compared with acyclic boronate esters. Among them, pinacol and catachol boronate esters are the most common surrogates used in many reactions [23, 58].



Scheme 1.16. Synthesis of boronic esters from boronic acids.

1.3.3 Potassium trifluoroborate salts

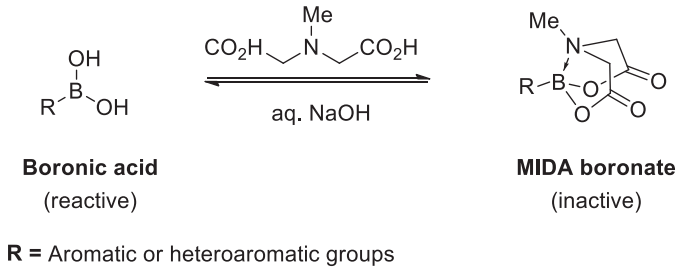
Potassium trifluoroborate salts (R-BF_3K) are a versatile class of air-stable boronic acid surrogate widely used in organic synthesis. Potassium trifluoroborates do not readily undergo trimerization as observed with boronic acids. Trifluoroborate salts are commonly employed in *Suzuki-Miyaura* cross-coupling reactions, 1,4-addition reactions and allylation of aldehydes, etc. Organotrifluoroborates are known as strong nucleophiles that react with electrophiles in the absence of catalysts [59]. These compounds can be easily prepared by the reaction of boronic acid with potassium hydrogen fluoridein methanol as described by Vedejs and co-workers (**Scheme 1.17**).



Scheme 1.17. Synthesis of potassium trifluoroborate salts from boronic acids.

1.3.4 *N*-Methyliminodiacetic acid (MIDA) boronate esters

It is known that some classes of boronic acids are difficult to prepare, store and use in coupling reactions since they are susceptible to quick decomposition. On the other hand, performing iterative *Suzuki-Miyaura* cross-couplings is limited due to the high reactivity of boronic acids. In order to overcome such issues, Burke and coworkers have used *N*-methyliminodiacetic acid (MIDA) for protecting the boronic acids (**Scheme 1.18**). The MIDA-protected boronate esters are stable under air, chromatographic purifications and high temperature (up to 80 °C). In addition, MIDA boronates are compatible with a wide range of reagents thus used in sequential *Suzuki-Miyaura* coupling reactions. Deprotection of MIDA ester can be achieved at room temperature using aqueous NaOH [60].

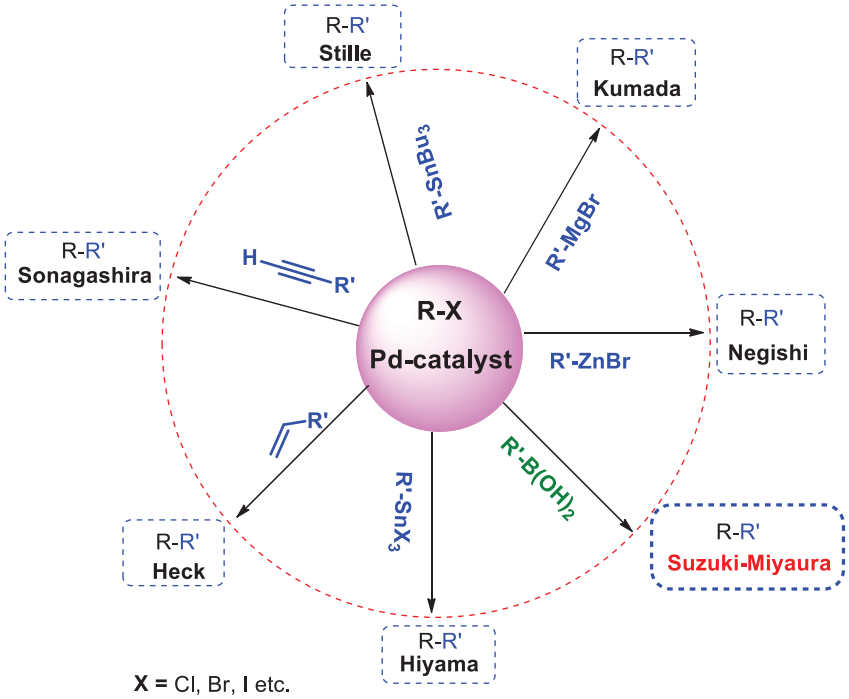


Scheme 1.18. Synthesis of MIDA-boronate esters from boronic acids.

1.4 APPLICATIONS OF BORONIC ACIDS IN ORGANIC SYNTHESIS

1.4.1 Transition metal-catalyzed cross-coupling reactions: *C-C* and *C*-heteroatom bond formation

Cross-coupling reactions have been widely used for introducing various functionalities into unsaturated (sp^2) and (sp) carbons such as aromatic rings, alkenes, alkynes, etc. Transition metal-mediated cross-coupling reactions are most useful synthetic tool for accessing various biologically relevant molecules and natural compounds.

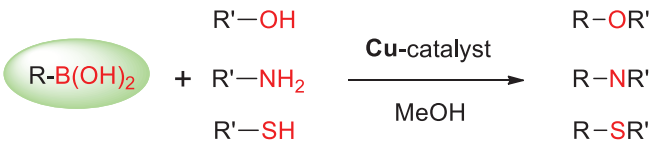


Scheme 1.19. Common Pd-catalyzed cross-coupling reactions.

In general, carbon-carbon bond formation are usually achieved by the reaction of aryl and vinyl halides/triflates with organometallic agents such as organomagnesium,

organoboron, organotin, organozinc compounds, etc. in the presence of transition metals [61]. In this context, *Heck*, *Hiyama*, *Suzuki-Miyaura*, *Negishi*,*Stille*, *Kumada* and *Sonogashira* reactions were developed and highly practiced in the modern organic synthesis (**Scheme 1.19**). Each of these name reactions uses a different kind of nucleophiles for *C-C* bond formation. Nobel Prize has been awarded to Richard F. Heck, Ei- ichi Negishi and Akira Suzuki jointly in 2010 for their valuable findings in *C-C* cross-coupling reactions [62].

The majority of organic compounds are made up of *C–C* bonds but their biological functions are usually derived from the heteroatoms (e.g. nitrogen, oxygen and sulphur) which are present in the molecule through *C*-heteroatom bonds. Therefore, not only *C-C* bond formation but also *C*-heteroatom bond formation reactions are equally important in organic synthesis, for example: aryl ethers (*C-O*), anilines (*C-N*), andthioethers (*C-S*) etc., formations (**Scheme 1.20**).

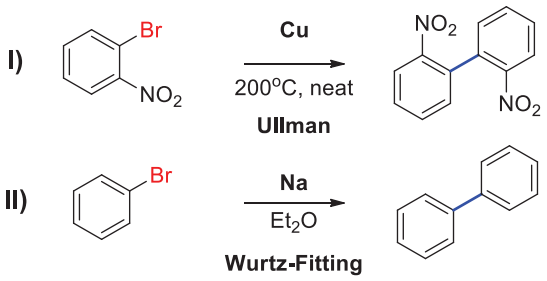


Scheme 1.20 *C*-heteroatom bond formation reactions.

In this respect, boronic acids play an important role in both *C-C* and *C*-heteroatom bond formation reactions in the presence of palladium and copper catalysts. Some of these reactions are discussed below.

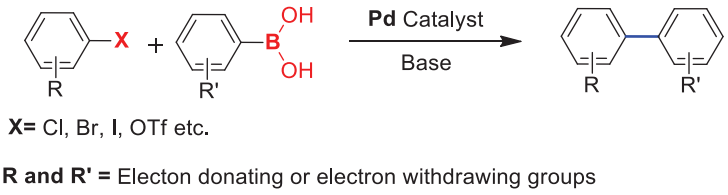
1.4.2 *Suzuki-Miyaura* cross-coupling reaction

Suzuki-Miyaura cross-coupling reaction is one of the important applications of arylboronic acids in organic synthesis. Biaryl moieties are the back bones of a wide range of natural products, pharmaceuticals, agrochemicals, dyes and catalysts.



Scheme 1.21. Synthesis of symmetrical biaryl compounds by traditional methods.

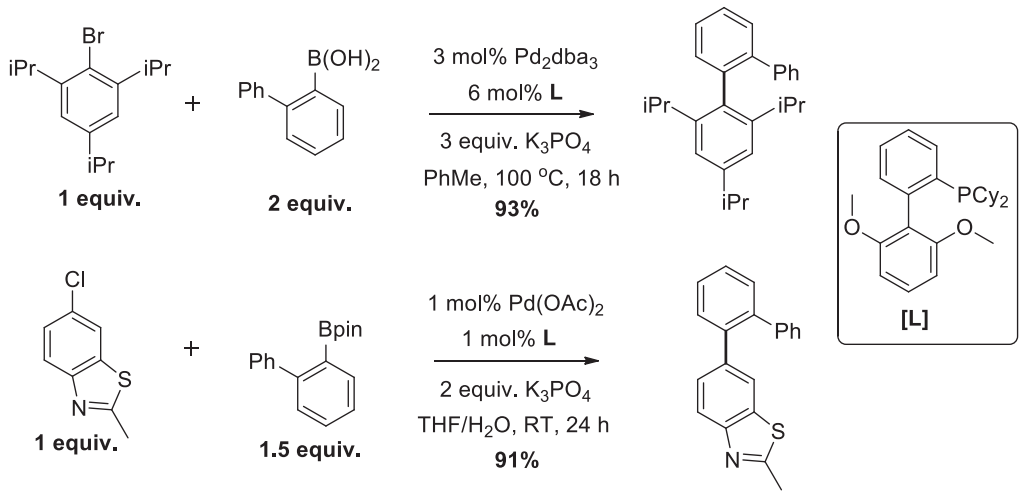
In early years, only limited synthetic protocols were available for the biaryl synthesis among which *Ullmann* reaction and *Wurtz–Fittig* reactions were fairly explored (**Scheme 1.21**). Poor selectivity, limited substrate scope and harsh reaction conditions are the major drawbacks of these methods [63, 64]. Under this circumstances, in 1981, Suzuki *et al*., made a breakthrough in the methodology of biaryl synthesis by using arylboronic acids as a coupling partner with aryl halides in the presence of palladium catalysts (**Scheme 1.22**).



Scheme 1.22. *Suzuki-Miyaura* cross-coupling reaction.

These reactions produce symmetrical as well as unsymmetrical biaryl compounds in high yields with good selectivity under mild conditions [65]. Since then,

this methodology has been modified and used in many complex natural products synthesis.



Scheme 1.23. *Suzuki-Miyaura* cross-coupling reaction of unactivated and sterically hindered arylhalides.

In general, *Suzuki-Miyaura* coupling reaction takes place at room temperature or slightly higher temperature which does not require any ligands for the activated substrates. On the other hand, phosphorus ligands were used in *Suzuki-Miyaura* reactions to demonstrate the coupling reaction of unactivated or sterically hindered substrates, e.g. arylbromides and chlorides with different arylboronic acids (**Scheme 1.23**) [66, 67]. *Suzuki-Miyaura* coupling reactions have been used as a synthetic tool for accessing many clinical drugs, for instance, boscalid (fungicide), losartan (anti-BB agent), ABT-963 (COX-inhibitor) etc., (Figure **1.2**) [68]. Syntheses of these bioactive molecules were employed in an industrial scale.

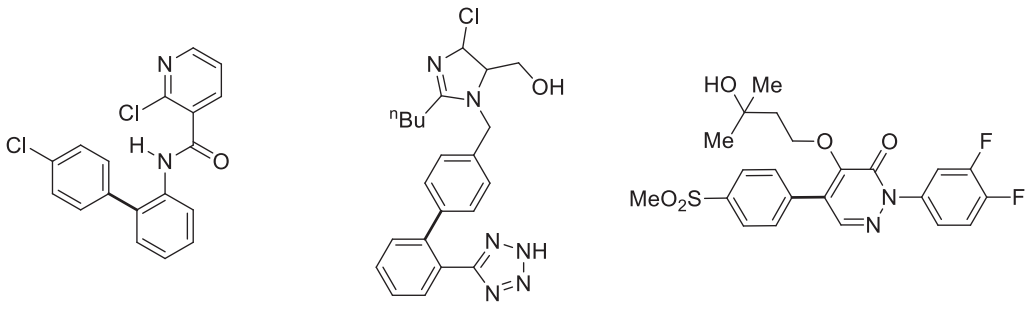
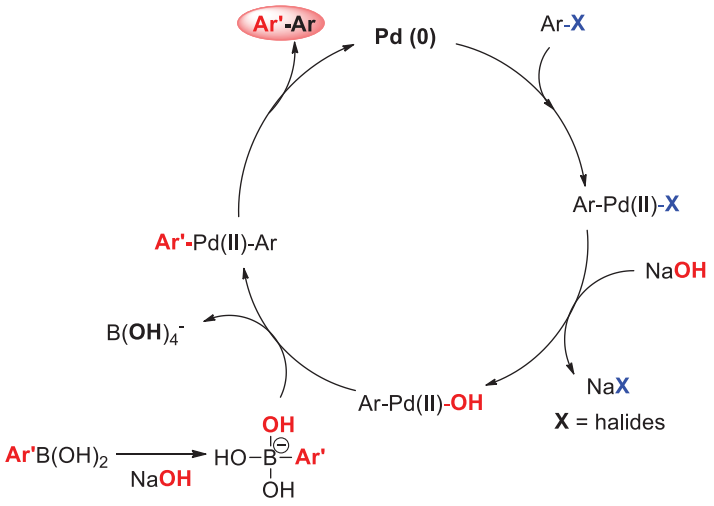


Figure1.2. Examples of clinical drugs accessed by *Suzuki-Miyaura* cross-coupling reactions.

1.4.3 Reaction mechanism of *Suzuki-Miyaura* cross-coupling reaction

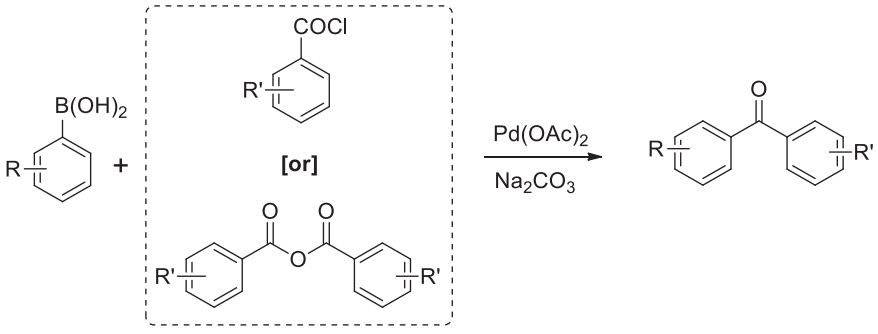
The general mechanism of *Suzuki-Miyaura* cross-coupling reaction involves three basic steps: i) oxidative addition, ii) *trans*-metalation, and iii) reductive eliminationas shown in **Scheme 1.24**. Oxidative addition of the aryl halide to the palladium (0) is the first step which results in the formation of Pd(II) complex. A molecule of the hydroxide ion replaces the halide on the palladium complex. Subsequently, boronic acid react with another molecule of sodium hydroxide to form a borate regent which undergoes *trans*-metalation during which the aryl group is transferred to palladium complex. Finally, reductive elimination gives the desired coupled product during which palladium (0) is regenerated. Depending on catalysts, ligands, and solvents, there may be additional processes/steps involves in the catalytic cycle.



Scheme 1.24. Proposed mechanism for the *Suzuki-Miyaura* cross-coupling reaction.

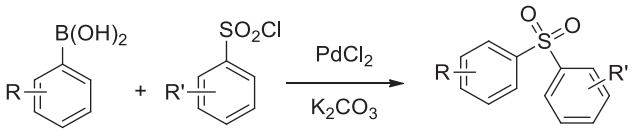
1.4.4 Other *C-C* bond forming reactions using arylboronic acids

Arylboronic acids readily undergo coupling/addition reactions with benzoyl chlorides, sulfonyl chlorides, benzoic anhydrides, benzaldehydes etc., in the presence of palladium catalysts. Reaction of arylboronic acid with carboxylic anhydride and acyl chloride was successfully demonstrated in the presence of palladium acetate which provides symmetrical as well as unsymmetrical aryl ketones (**Scheme 1.25**) [69].



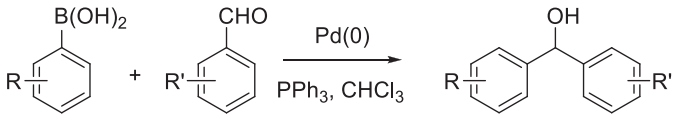
Scheme 1.25. Synthesis of diarylketones from arylboronic acids.

Similarly, unsymmetrical diaryl sulfones were obtained in excellent yields by the reaction of arylsulfonyl chlorides with arylboronic acids in the presence of palladium chloride (**Scheme 1.26**) [70]. On the other hand, arylboronic acids react with aryl aldehydes in the presence of palladium catalyst, affording the corresponding secondary alcohols in good yields (**Scheme 1.27**) [71]. Arylboronic acid also undergoes enantioselective 1,4-conjugate addition in the presence of rhodium-catalyst (Rh-catalyst) with high enantioselectivity (**Scheme 1.28**) [72, 73].



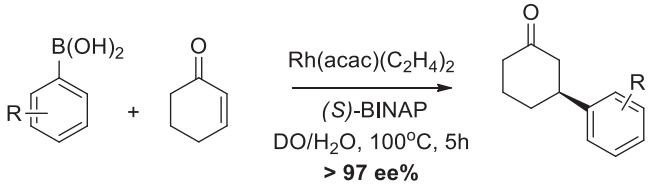
R and R' = Electron donating and electron withdrawing groups

Scheme 1.26. Synthesis of diarylsulfones from arylboronic acids.



R and R' = Electron donating and withdrawing groups

Scheme 1.27. Synthesis of diaryl methanol from arylboronic acids.

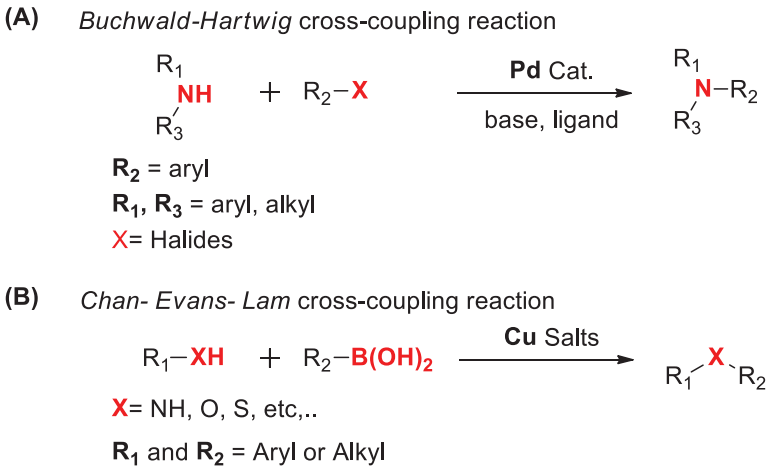


R = Electron donating and withdrawing groups

Scheme 1.28. Rhodium-catalyzed asymmetric conjugate addition of boronic acids to enones.

1.4.5 *Chan-Evans-Lam* cross-coupling reaction

Chan-Evans-Lam cross-coupling reaction is another popular reaction in organic synthesis discovered by Dominic Chan, David Evans and Patrick Lamin dependently in 1998. This reaction allows sp^2 *C*-heteroatom bond formation *via* an oxidative coupling of boronic acids with nucleophilic heteroatom containing substrates (e.g. *N-H*,*O-H*, *S-H*, etc.,) in the presence of copper salts (**Scheme 1.29**) [6]. Phenols, amines, anilines, amides, imides, ureas, carbamates, sulfonamides and thiols were used as a substrate in *Chan-Evans-Lam* cross-coupling reactions. Mostly, the reactions proceed at room temperature with catalytic or stoichiometric amount of copper salt under open-air condition (**Scheme 1.29 B**), which reveals certain advantages over the *Buchwald-Hartwig* cross-coupling reaction (**Scheme 1.29 A**). The reactions are usually carried out in methanol in the absence of any additives using air or oxygen as the terminal oxidant [74-76].

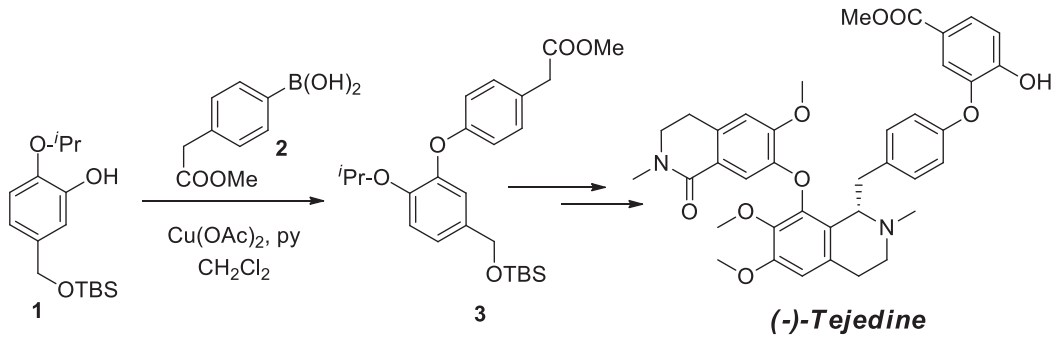


Scheme 1.29. *Buchwald-Hartwig* and *Chan-Evans-Lam* cross-coupling reactions.

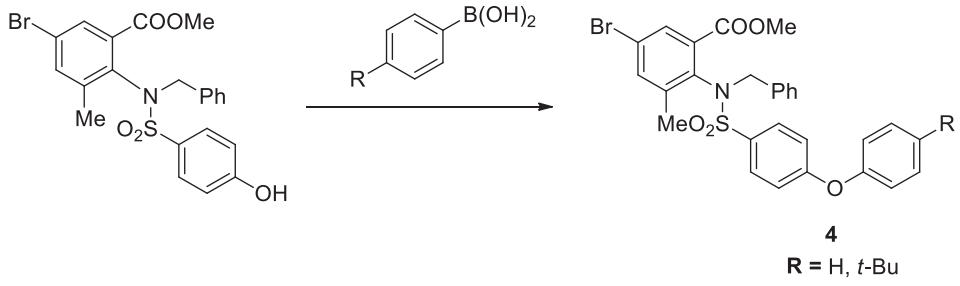
The methodologies of *Chan-Evans-Lam* cross-coupling reaction have been utilized in the synthesis of many biologically relevant compounds. The aryl ether **3** is an

important starting material for the synthesis of naturally occurring alkaloide*(-)-Tejedine*. The aryl ether **3** was obtained from phenol **1** and arylboronic acid **2** under *Chan-Evans-Lam* reaction condition in the presence of copper acetate (**Scheme 1.30**) [77].

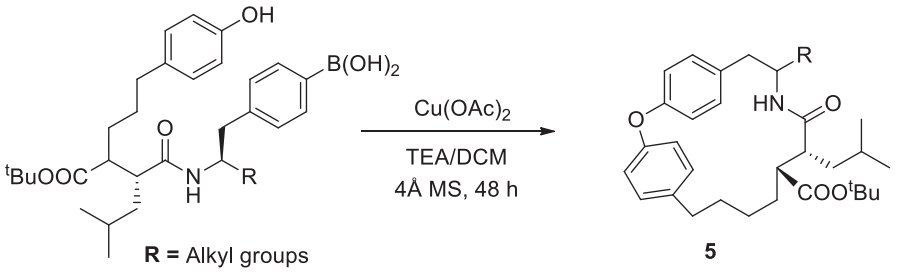
Synthesis of different types of matrix metalloproteinase (MMP) inhibitors such as *anthranilic acid-based* inhibitor **4** [78], *macrocyclic* inhibitor **5** [79], and *biphenyl* inhibitor **AG3433** [80] were demonstrated using *Chan-Evans-Lam* cross-coupling reaction strategies (**Schemes 1.31-1.33**). Later, the *N*-arylation methodology was used by Lam and co-workers for the synthesis of *pyrazole based* Factor Xa inhibitor (**Schemes 1.34**) [81].



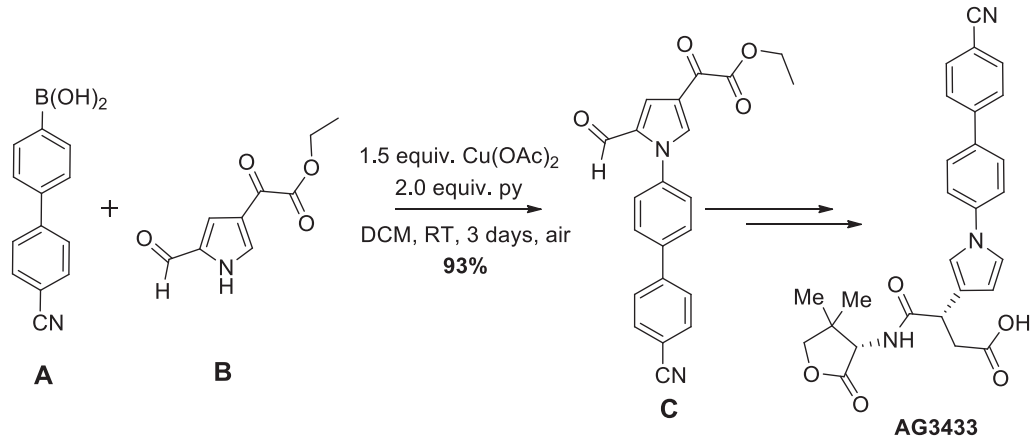
Scheme 1.30. Synthesis of aryl ether **3** under *Chan-Evans-Lam* reaction condition.



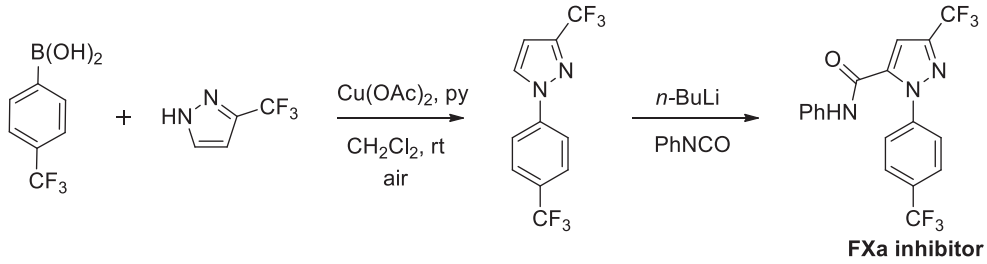
Scheme 1.31. Synthesis of *anthranilic acid-based* MMP inhibitor **4**.



Scheme 1.32. Synthesis of *macrocyclic* MMP inhibitor **5**.



Scheme 1.33. Synthesis of MMP inhibitor **AG3433**.

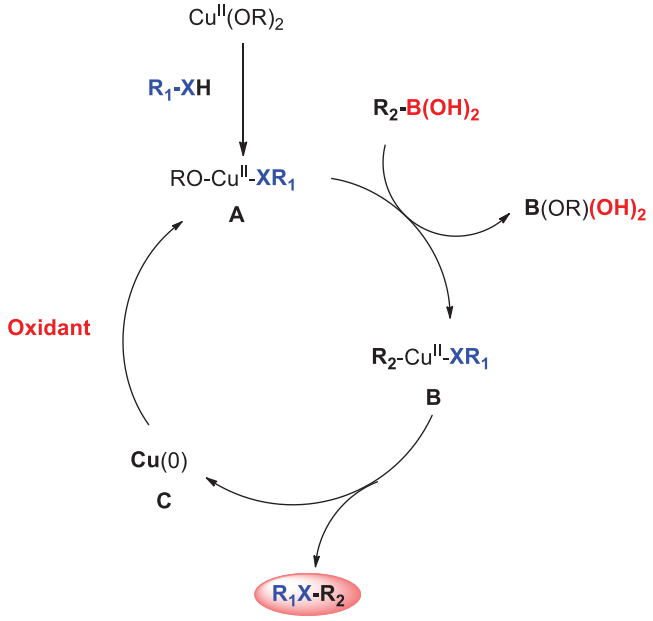


Scheme 1.34. Synthesis of Factor **Xa** inhibitor.

1.4.6 Proposed mechanism for *Chan-Evans-Lam* cross-coupling reaction

The proposed mechanism for *Chan-Evans-Lam* cross-coupling reaction is shown in the **Scheme 1.35**. At the outset, copper undergoes ligand exchange reaction with nucleophilic species (e.g. *NH*, *OH*, *SH*, etc.) to form intermediate **A**. Subsequently,

boronic acid undergoes *trans*-metalltion with copper to form the intermediate **B** which undergoes reductive elimination to provide the desired products and copper (0) species. In the presence of oxygen, copper (0) get oxidized to copper (II) to resume the catalytic cycle.

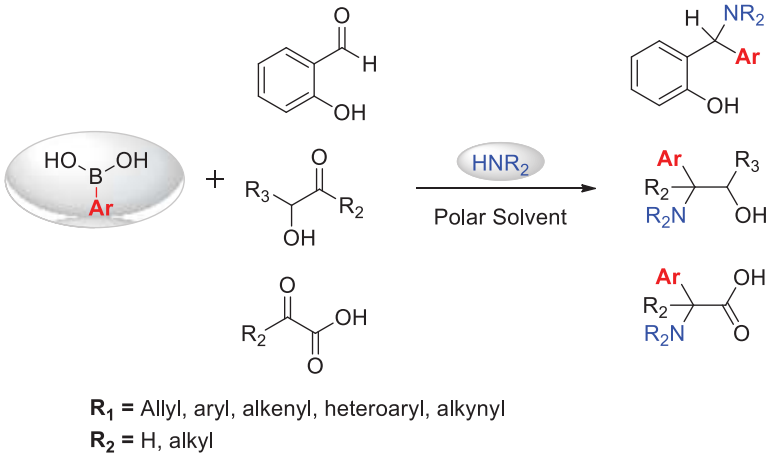


Scheme1.35. Proposed mechanism for *Chan-Evans-Lam* cross-coupling reaction.

1.4.7 *Petasis* reaction or *Petasis Borono-Mannich* reaction

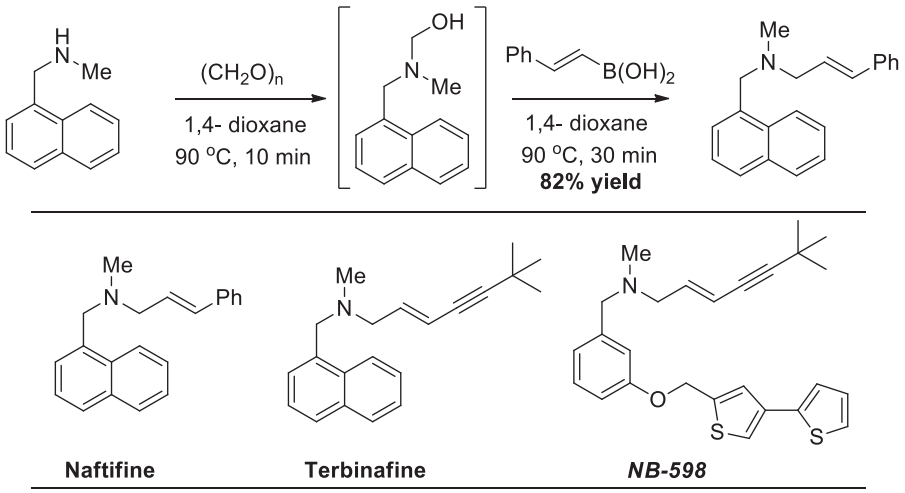
Multi-component reactions (MCR) are one of the most important reactions in modern organic synthesis. Multi-component reactions involve the coupling of three or more reactants in an atom economical manner to provide highly functionalized organic molecules. *Petasis* reaction,also known as *Petasis Borono-Mannich* (PBM) reaction, is a three-component coupling reaction involving boronic acids, carbonyl compounds, and primary or secondary amines. In 1993, Petasis *et al.,* disclosed the preparation of functionalized allyl amines in one-pot by the reaction of secondary amines,

paraformaldehyde and 1-alkenylboronic acids. Since then, several reports were demonstrated the coupling of allylic, alkenyl, aryl, and alkynylboronic acids and their surrogates with iminium ion generated from the reaction of amine and carbonyl compounds. The reaction works mainly with α-hydroxyaldehydes, salicylaldehydes, and glyoxylic acid in polar solvents. *Petasis* reaction resembles the *Mannich* reaction and enables the preparation of amines and their derivatives such as α-amino acids (**Scheme 1.36**) [82].

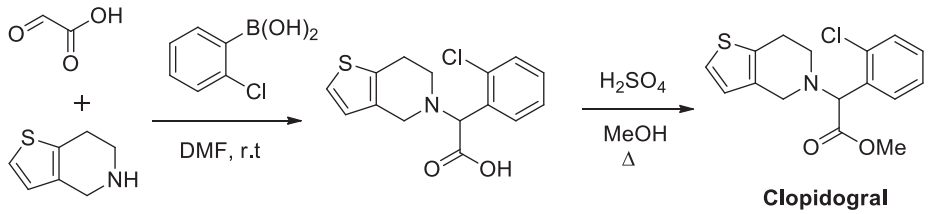


Scheme 1.36. Multi-component *Petasis Borono-Mannich* reaction.

Petasis reaction plays significant role in the synthesis of various biologically relevant molecules and natural products. Petasis and co-workers have demonstrated the one-pot synthesis of **Naftifine** (a potent antimycotic) in excellent yield (**Scheme 1.37**). **Terbinafine** and ***NB598*** are other antifungal agents easily accessed *via Petasis* reaction (**Scheme 1.37**) [82b, 83]. *Petasis* reaction is the key for the synthesis of antiplatelet agent **Clopidogrel** (**Scheme 1.38**) [84].



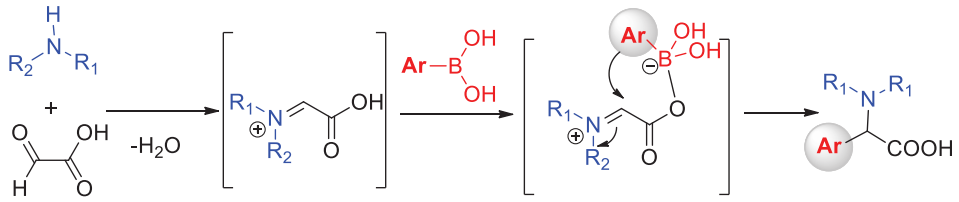
Scheme 1.37. Synthesis of Naftifine and other antifungal agents.



Scheme 1.38. Synthesis of antiplatelet agent Clopidogrel using *Petasis* reaction.

1.4.8 A proposed mechanism for *Petasis* reaction

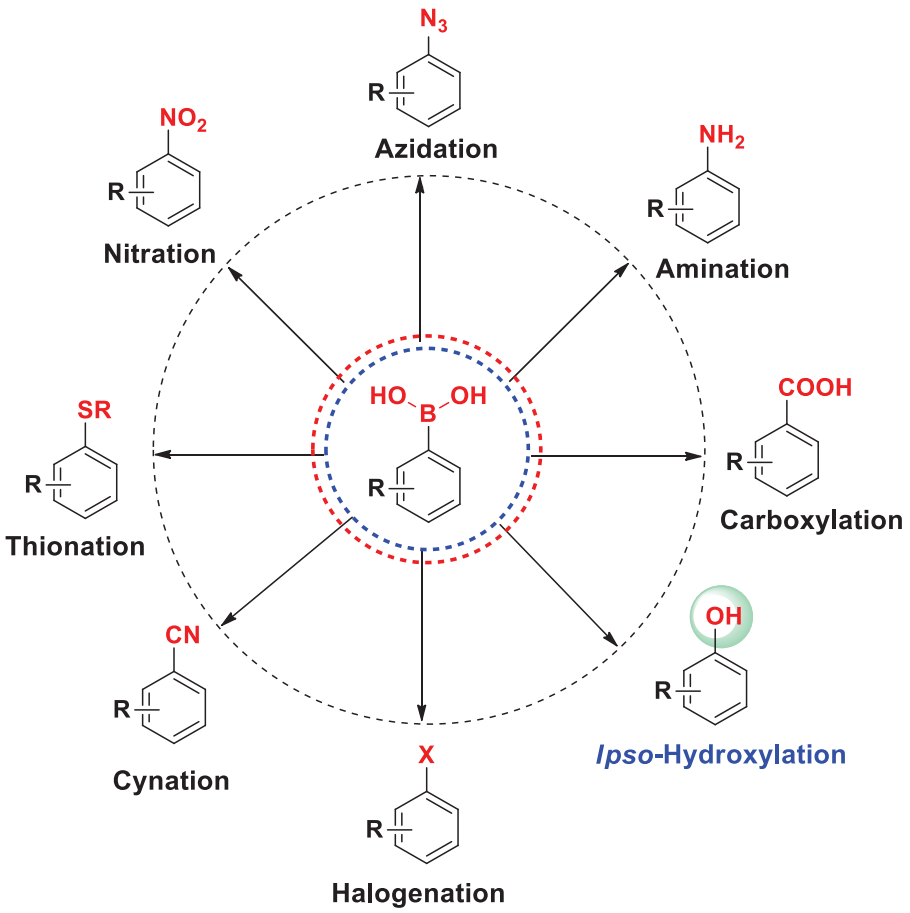
A plausible mechanism of *Petasis* reaction is shown in **Scheme 1.39** [82b]. Similar to *Mannich* reaction, imine or iminium salt is formed at first after which aryl group is delivered intramolecularly with assistance of neighboring hydroxyl group.



Scheme 1.39. Proposed mechanism for *Petasis Borono-Mannich* reaction.

1.5 *ipso*-FUNCTIONALIZATION OF BORONIC ACIDS

Functionalized arenes, e.g. aryl halides, aryl amines, aryl azides etc., play important role in synthetic organic chemistry and they have been usually achieved by nucleophilic substitution reaction (or) *C-H* activation of aryl ring under harsh reaction conditions. In this respect, numerous methods have been developed for the *ipso*-functionalization of arylboronic acids with suitable reagents to obtain aryl halide, aryl azide, aryl amine, phenols and benzonitrile, nitrobenzene, benzoic acid, aryl sulphide, etc., under mild reaction conditions (**Scheme 1.40**) [85-92].



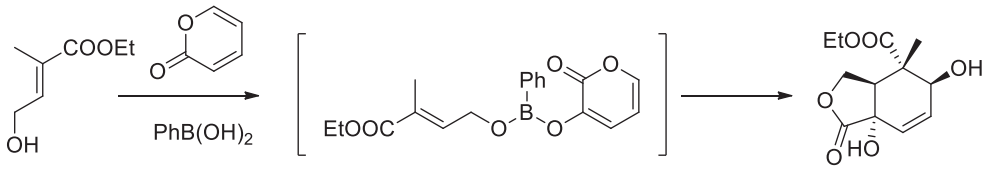
R= Electron donating and electron withdrawing group

Scheme1.40. Conversion of boronic acids into different functionalities.

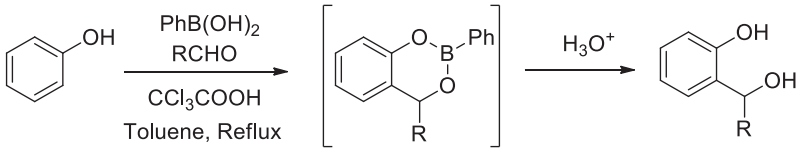
1.6 BORONIC ACIDS AS REAGENTS AND CATALYSTS IN ORGANIC TRANSFORMATIONS

Boronic acids are attractive class of synthetic intermediates explored in many organic reactions including *C*-*C* and *C*-heteroatom bond formation, *Petasis* reaction, *ipso*-functionalization, etc. Besides that boronic acids are also used as reagents and catalysts in many organic transformations [93].

Boronic acids can make covalent bonds with alcohols and carboxylic acids in a reversible manner. In this context, boronic acids act like a template where reactants can be brought closer in order to accelerate reactions. Using phenylboronic acid as a template, Nicolaou and co-workers have demonstrated synthesis of anticancer drug Taxol through *Diels-Alder* reaction (**Scheme 1.41**) [93, 94]. Similarly, Nagata *et al*., disclosed phenylboronic acid mediated *ortho*-α-hydroxyalkylation of phenols with different aldehydes (**Scheme 1.42**) [95].

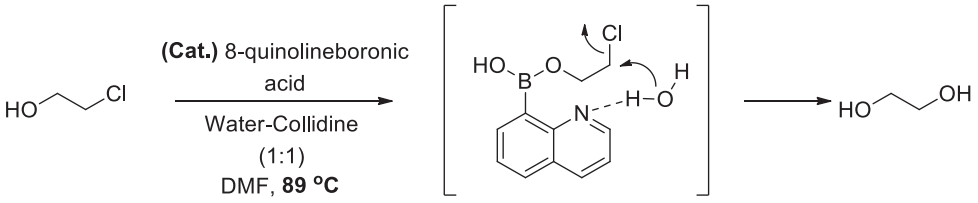


Scheme 1.41. Use of boronic acid as a template for the *Diels-Alder* reactions.



Scheme 1.42. Boronic acid-mediated *ortho*-α-hydroxyalkylation of phenol with aldehyde.

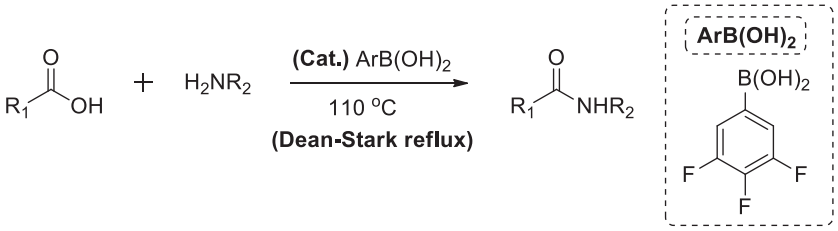
Besides using boronic acids as reagents, in 1963,Letsinger and coworkers have introduced, for the first time, quinolin-8-ylboronic acid as a catalyst for the hydrolysis/alcoholysis of chlorine-functionalized aliphatic alcohols in the presence of collidine (**Scheme 1.43**) [96]. Recently, arylboronic acids have emerged as a unique class of organocatalyst for many reactions including activation of carboxylic acids andcarbonyl groups, *Diels-Alder* reactions, dipolar cycloadditions, *Friedel-Crafts* alkylations, *Nazarov* cyclization, *Meyer-Schuster* reaction, *Biginelli* reaction, elimination and cascade reactions, etc. The major advantage of using arylboronic acids as catalysts is that their Lewis acidity can be easily modulated depending on the requirement of reaction by simply changing the substituents on the aryl ring. Few of the above mentioned catalytic reactions are discussed below.



Scheme 1.43. Quinolin-8-ylboronic acid catalyzed hydrolysis chlorine-functionalized aliphatic alcohols.

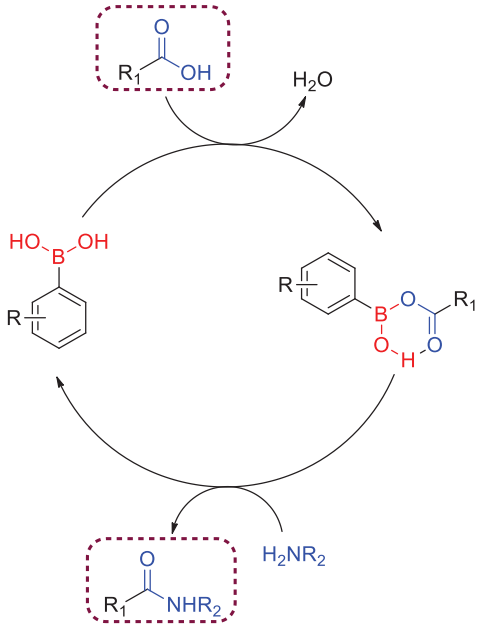
In 1996, Yamamoto *et al.,* disclosed the first catalytic use of arylboronic acids for the direct amidation of carboxylic acids. In this study, electron-deficient poly-fluorinated arylboronic acids were found more active, perhaps, due to enhanced Lewis acidity. Among the used boronic acids, 3,4,5-trifluorophenylboronic acid showed better catalytic activity while the reactions were carried out in non-polar solvents at 110ºC for several hours (**Scheme 1.44**) [96, 97]. Since this first report, numerous groups have

demonstrated the catalytic applications of various substituted arylboronic acids in the amidation reactions of carboxylic acids.



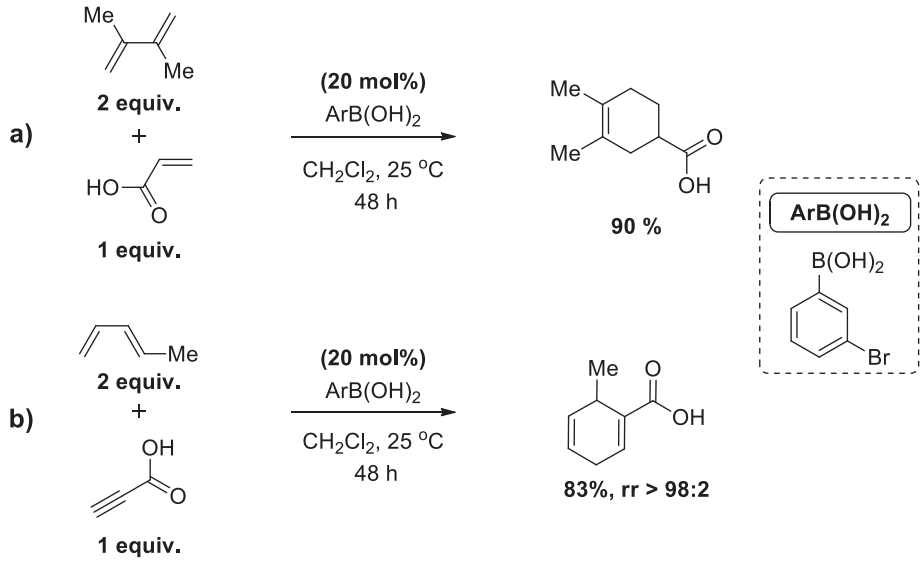
Scheme 1.44. Arylboronic acids catalyzed direct amidation of carboxylic acids.

A general mechanism for the arylboronic acid catalyzed amidation reaction is shown in **Scheme 1.45**. Reaction of carboxylic acid with arylboronic acid results in the formation of mono-acyl boronate species which is augmented through an intramolecular hydrogen bond. The nucelophilic amine attacks on the electrophilic carbonyl group which results in the formation of desired amidation product and regeneration of the catalyst.



Scheme 1.45. Mechanism of arylboronic acids catalyzed direct amidation of carboxylic acids.

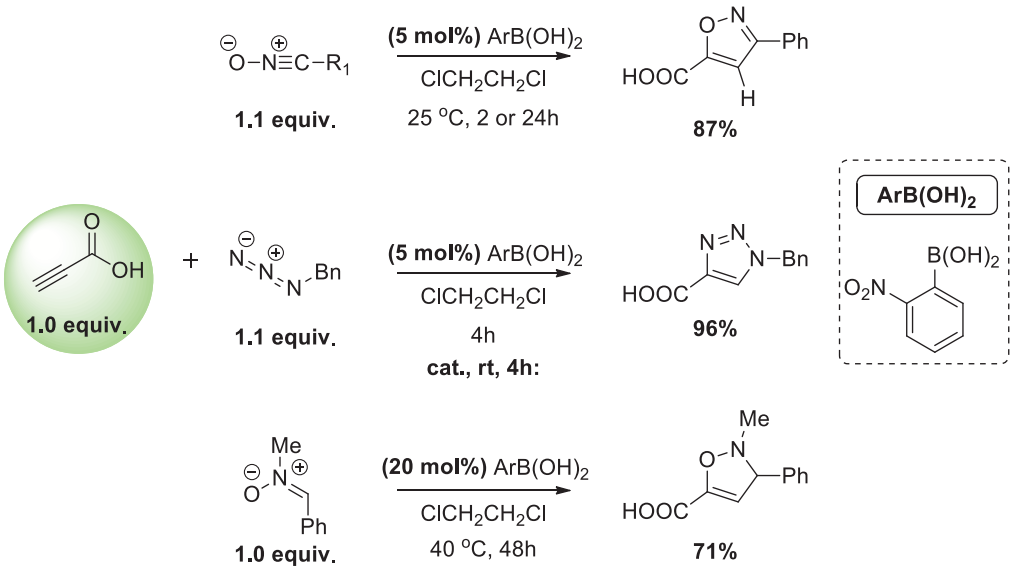
In a similar fashion, arylboronic acids also facilitate the *Diels-Alder* reactions (**Scheme 1.46**) [93, 98]. For example, 2,3-dimethyl-1,3-butadiene undergoes [4+2] cycloaddition with acrylic acid in the presence of 3-bromophenylboronic acid at room temperature. Similarly, 3-bromophenylboronic acid also catalyze the cycloaddition of 1,3-pentadiene with propynoic acid in excellent regioselectivity. Later, several methodologies were established for arylboronic acid catalyzed [3+2] dipolar cycloaddition reactions involving propynoic acid with azides, nitrile oxides, and nitrones. In all these reactions, 2-nitrophenylboronic acid has been used as a catalyst for [3+2] dipolar cycloaddition reactions (**Scheme 1.47**) [96, 99].



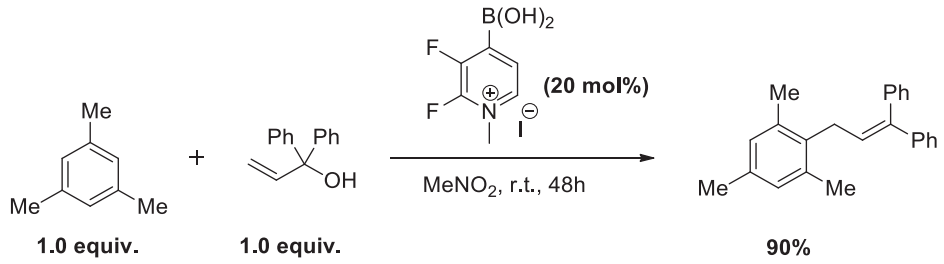
Scheme 1.46. Arylboronic acids catalyzed *Diels-Alder* reactions.

Furthermore, arylboronic acids can activate not only carboxylic acids, but also hydroxyl group of alcohols. It facilitates the partial or complete (or) ionization of the *C–O* bond to generate carbocation intermediate. McCubbin and co-workers

demonstrated the *Friedel-Crafts* reaction of allylic alcohols using fluoropyridylboronic acid as a catalyst at room temperature (**Scheme 1.48**) [96].



Scheme 1.47. Arylboronic acids catalyzed [3+2] dipolar cycloaddition reactions.



Scheme 1.48. Arylboronic acids catalyzed *Friedel-Crafts* alkylation reaction.

1.7 APPLICATIONS OF BORONIC ACIDS IN BIOLOGICAL AND MEDICINAL CHEMISTRY

Beside the applications in synthetic organic chemistry, boronic acids have tremendous utility in medicinal chemistry and biological science. In biological point of

view, boronic acids have been explored as enzyme inhibitors, molecular receptors and probe for detecting reactive oxygen species.

Boronic acids have also been employed as MRI and PET agents for *in vivo* carbohydrate imaging, protein manipulations and modifications. Further, in cell permeable sensors, separation and purification of glycosylated products, feed-back controlled drug delivery and in diagnostic or therapeutic products, boronic acids have achieved significant attention. Besides, many more biological applications of boronic acids reveal their importance in biological chemistry (Figure **1.3**) [100].

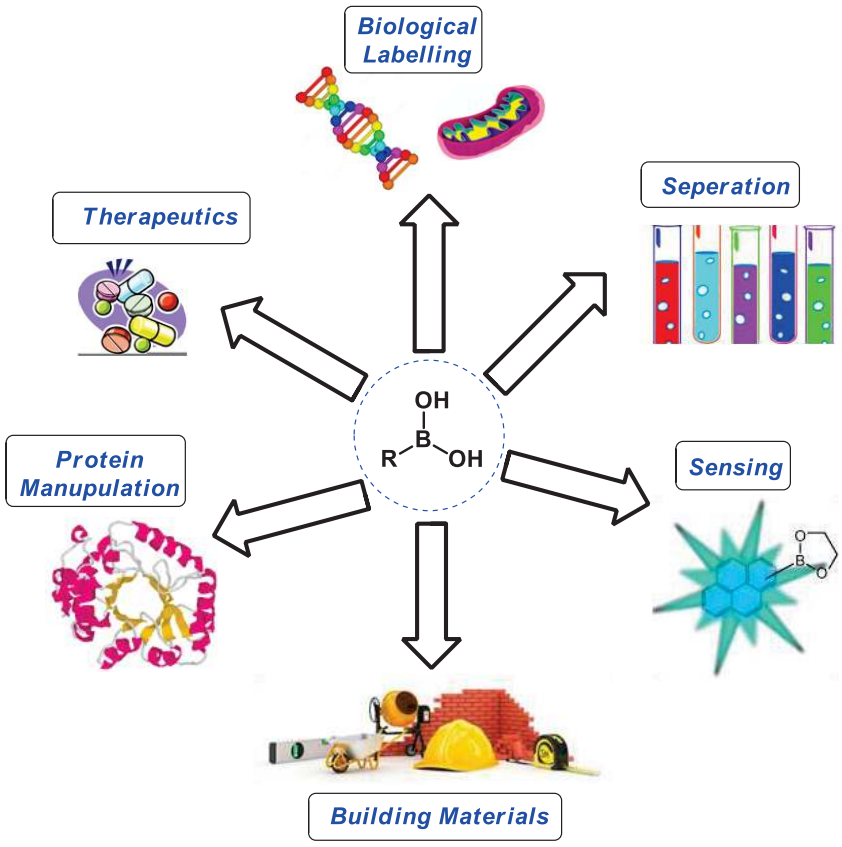
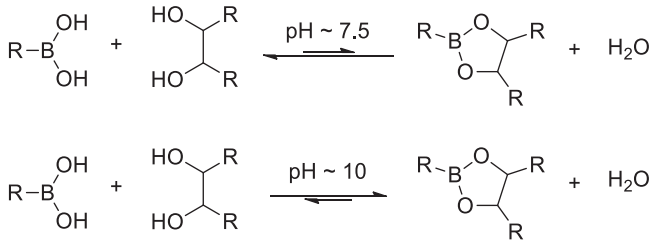


Figure 1.3 Applications of boronic acids in various fields.

1.7.1 Applications of boronic acids as sensors

The use of boronic acids in diverse areas of research is significantly increased in recent years. In modern biological science, boronic acids are mainly used as a molecular receptor for the selective recognition of a wide range of analytes in biological system [100a &100d]. The interactions of boronic acids with diols lead to their utility in various sensing applications (**Scheme 1.49**).

For instance, boronic acids have been explored as the sensors for carbohydrates, amino acids, amino alcohols etc., due to their unique electronic and chemical properties. In 1959, Lorand and Edwards were reported first quantitative evaluation of interactions between saccharides and boronic acid, since then, the field of molecular recognition with boronic acids has been well explored (**Figure 1.4**).



Scheme 1.49. Interaction of boronic acid with diols in different pH.

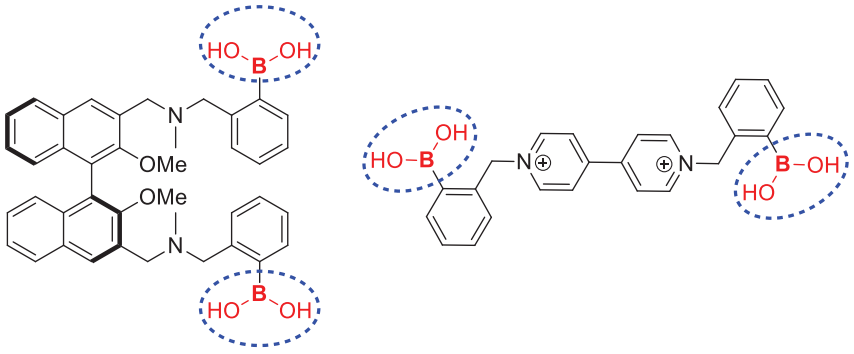


Figure 1.4 Structures of some glucose sensors.

1.7.2 Applications of boronic acids as therapeutic agents

Boronic acids are Lewis acids that have tendency to interact strongly with bases and nucleophiles. Considering this property as a key factor, numerous boronic acids have been designed and developed as inhibitors for various enzymes including β-lactamase, lipase, apoptotic tubulin polymerization, fatty acid amide hydrolase (FAAH), etc. Bortezomib is a boron-containing proteasome inhibitor (anti-neoplastic or anticancer agent) used for the treatment of multiple myeloma and mantle cell lymphoma (**Figure1.5**) [101].

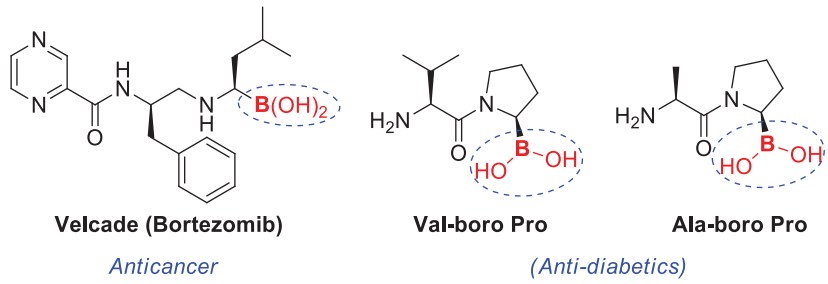


Figure 1.5 Boronic acids as proteasome and DPP-IV enzyme inhibitors.

Proteasomes are cellular complexes that break down proteins. Bortezomib catalytically binds the active site of the 26S proteasome with high affinity and specificity, thereby resulting in cell cycle arrest and apoptosis [101a]. Similarly, Val-boro Pro and Ala-boroPro are boronic acid containing dipeptidyl Peptidase (DPP-IV) inhibitors reported in 1990 [101b]. DPP-IV inhibitors reduce glucagon and blood glucose levels and used for the treatment of diabetes mellitus type 2 (**Figure1.5**) [101]. Besides, plenty of designed drugs with boronic acid moiety exhibit anticancer, antiviral, antifungal, antibacterial activities, etc. (**Figure 1.6**) [102].

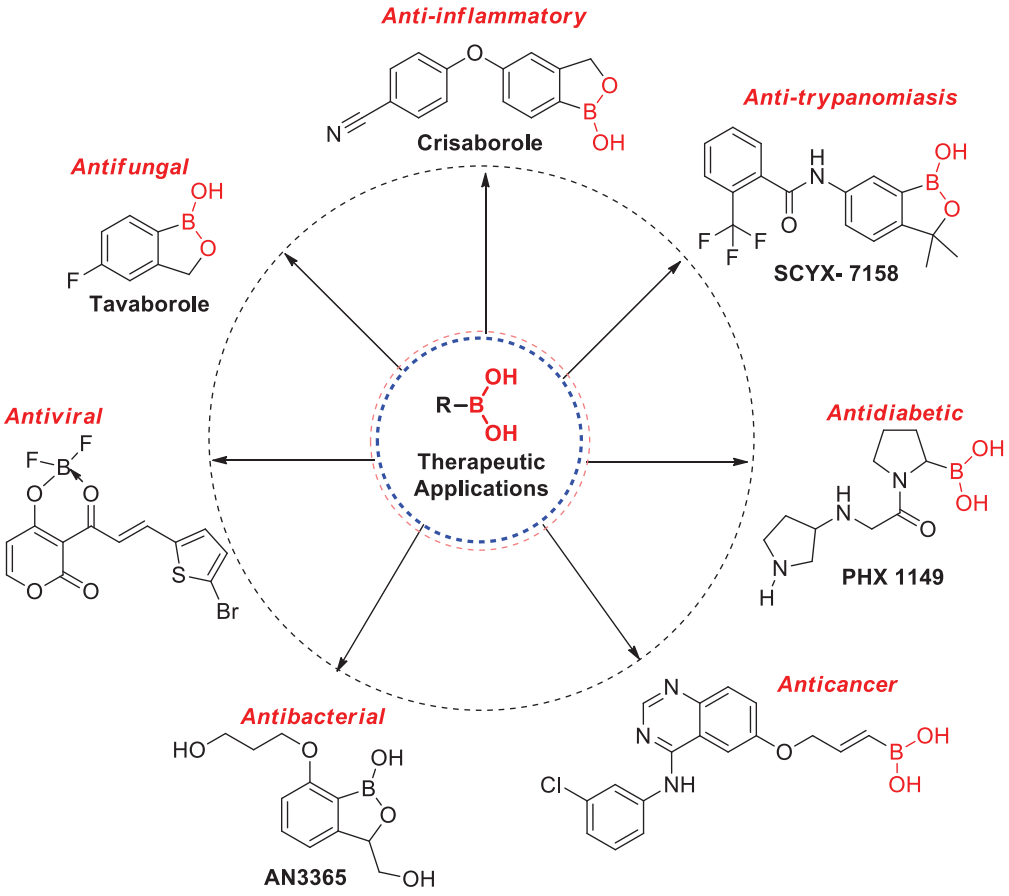


Figure 1.6 Therapeutic applications of boronic acids.

1.8 OBJECTIVES OF THE THESIS WORK

From this brief introduction, it is clear that boronic acids have found wide applications in various fields including organic synthesis, biochemistry, medicinal chemistry, material sciences, agriculture, etc. In spite of all these accomplishments, we believe that more applications of boronic acids as starting material, reagent and catalyst in organic synthesis are rather yet to be explored. **Thus, our objective is to develop an efficient and greener synthetic methodology using boronic acids as starting material or reagent in different organic transformations**.

In the next chapters, we have introduced and discussed new applications of boronic acids as **Aryl and Alkyl donors** as well as **Reductant** in organic synthesis.

The main focus of the current thesis work is aimed,

1. To investigate *ipso*-hydroxylation of arylboronic acids into phenol under catalyst-free reaction condition using green oxidant hydrogen peroxide and solid adduct of hydrogen peroxide *i.e.* urea-hydrogen peroxide.
2. To demonstrate a copper-mediated *N*-arylation and *N*-alkylation of sulfoximines using arylboronic acids and alkylboronic acids, respectively.
3. To explore arylboronic acid as a deoxygenating reagent for the deoxygenation of *tertiary* amine *N*-oxides.

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