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Benzoboroxoles: Synthesis and applications in medicinal chemistry

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Dedicated to Professor Narayan S. Hosmane on the occasion of his 70th birthday.

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ABSTRACT

Benzoboroxoles are cyclic boronic acids and they have gained significant attention amongst the organic and medicinal chemistry community in recent years with the approval of benzoboroxole based drugs such as tavaborole for onychomycosis and crisaborole for atopic dermatitis. There have been numerous other benzoboroxole-based compounds identified that exhibit excellent biological activity against wide variety of diseases. Much of the recent literature describes the preparation of functionalized benzoboroxoles and their applications in organic synthesis, materials, and medicinal chemistry. This review outlines the various methods reported for the synthesis of this class of compounds along with few recent applications of benzoboroxoles in medicinal chemistry.

1. Introduction

Boronic acids play an important role in organic and medicinal chemistry owing to their impressive chemical and biological profile as synthetic intermediates and drug candidates. The Lewis acidity of boronic acids coupled with their chemical stability and ease of disposal ideally makes them environmentally friendly replacements for other toxic and heavy metal counterparts in organometallic chemistry. Accordingly, boronic acids and their corresponding boronic acid esters (boronates) have been extensively utilized throughout organic chemistry as valuable synthons for reactions such as cross-coupling [1], homologation [2], aldol, and catalytic allylboration [3]. Several boronic acids have also been widely utilized in medicinal chemistry as chemotherapeutic [4] and boron-neutron capture therapy (BNCT) agents [5]. In the recent years benzoboroxoles (or benzoxaboroles), one such class of cyclic boronic acid hemiester analogs, have also gained popularity because of their remarkable chemical stability and impressive physicochemical properties. Accordingly, this class of compounds have found applications in materials, polymer chemistry, and particularly in drug discovery as lead candidates for wide variety of diseases [6]. Since there is an extensive amount of information available on this topic, this review is by no means exhaustive and it will mainly focus on various preparatory methods that have been reported in the literature for generating benzoboroxoles along with few of the recent applications in medicinal chemistry.

2. Boronic acids

Boronic acids **1** are boric acid derivatives in which one of the hydroxyl groups has been replaced with alkyl/aryl groups. Boronic acids hold a prominent place in medicinal chemistry because of their role as bioisosteric replacements for carboxylic acids **2** owing to their comparable stereoelectronic relationship. Aminoboronic acids are very similar in nature to amino acids and hence they have been utilized for several applications in peptidomimetics [7] and enzyme inhibition [8]. One of the major differences between boronates and carboxylates is the fact that the boronates are six electron species and they form a stable “ate” complex **3** when they

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interact with nucleophilic entities such as hydroxy termini of enzymes as opposed to the unstable tetrahedral carbonyl addition intermediate **4** obtained under similar conditions with carboxylates (Fig. 1). This in turn enables boronic acids to form a stable bond with the enzymes thereby leading to their reversible inhibition, and hence the boronic acids exhibit excellent therapeutic potential. This mode of action has led to the discovery of an anti-cancer drug bortezomib **5** (Velcade®, Fig. 2), which was approved by the FDA for the treatment of multiple myeloma [9]. The boronic acid unit in bortezomib binds to threonine residue and inhibits catalytic site of 26S proteasome via a reversible borate complex. Buoyed by the success of bortezomib, a second-generation drug ixazomib **6** (Ninlaro®, Fig. 2) was also identified based on a large-scale screening of boronated compounds and approved recently for the treatment of multiple myeloma [10]. The boronic acid unit in **6** inhibits 20S proteasome subunit beta-5 and **6** has significantly longer biological half-life compared to bortezomib **5**. Interestingly, ixazomib citrate **7**, is an orally bioavailable prodrug form of **6** which undergoes hydrolysis to release the free boronic acid. In addition to their medicinal applications, boronic acids have also been extensively utilized in organic chemistry. Some of the key reactions in which they are used include the Nobel prize winning Suzuki cross-coupling reaction [1], and C-C bond forming allylboration reaction [3]. There have been several reviews in the literature delineating the applications of boronic acids in medicinal [4], material [11], and polymer chemistry [12].

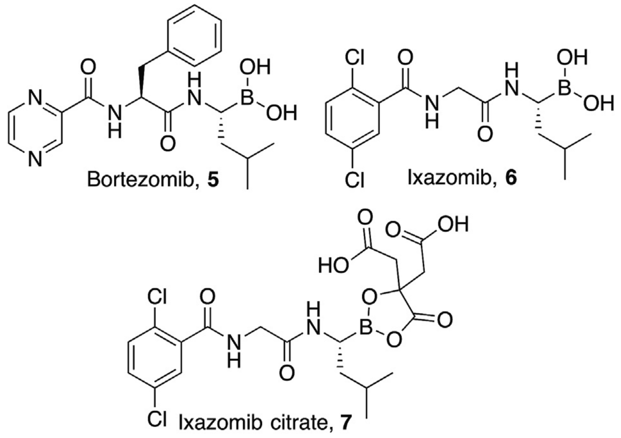


Fig. 2. Boronic acid containing anti-cancer agents in clinical use.

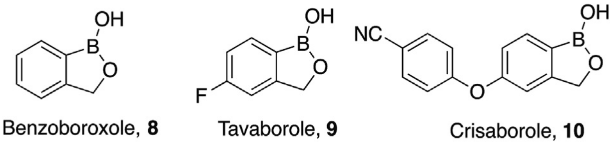


Fig. 3. Benzoboroxole based drugs in clinical use.

3. Benzoboroxoles

Benzoboroxoles **8** are cyclic boronic acid hemiesters that were first synthesized in 1957 by Torsell [13] and further explored by Snyder [14]. This area of research has piqued the interest of organic and medicinal chemists especially because of the approval of two drugs tavaborole **9** [15] and crisaborole **10** [16] (Fig. 3) for the treatment of onychomycosis and atopic dermatitis respectively. Tavaborole exhibits *anti*-fungal activity by inhibiting Leucyl-tRNA synthetase and this results in the inhibition of protein synthesis of fungal organism. Crisaborole shows anti-inflammatory activity via inhibition of the enzyme phosphodiesterase-4. Benzoboroxoles and their applications have been recently reviewed by Adamczyk-Wozniak as well as Benkovic [6]. Owing to our long-standing interest in boron chemistry [17], we have also been working on the functionalization of benzoboroxoles as therapeutic agents. This review provides a brief overview of the synthetic methods for the preparation of benzoboroxoles with focus on some recent applications in medicinal chemistry.

3.1. Preparation of benzoboroxoles

The boronic acid unit on the aryl ring in benzoboroxoles is typically introduced starting from the corresponding aryl halides/arenes using lithiation-borylation or transition metal-catalyzed borylation protocols [6].

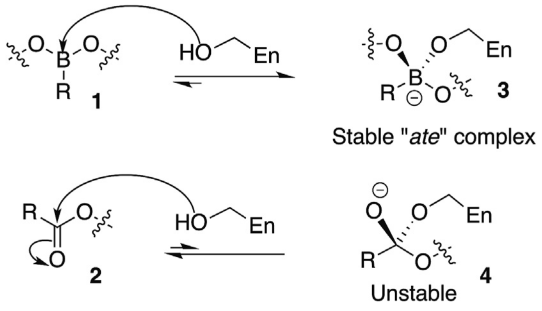
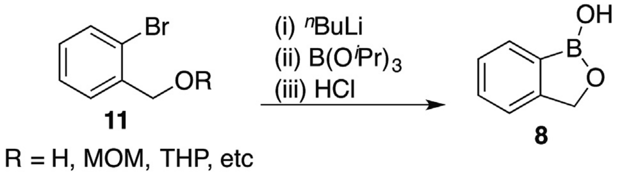


Fig. 1. Mechanism of action of boronic acid drugs.

3.1.1. Metalation-borylation protocol

One of the most commonly used methods for the preparation of benzoboroxoles involved the reaction of *o*-hydroxymethylhalobenzene **11** with *n*-butyllithium to generate the aryllithium which upon treatment with triisopropylborate yielded the “ate” complex, which when acidified resulted in the formation of benzoboroxoles via neutralization of the borate and concomitant cyclization (Scheme 1) [6,18]. The hydroxyl group in the starting material **11** typically did not interfere in the lithiation-borylation, however 2 equivalents of base were required for carrying out the deprotonation of alcohol and debromination respectively. Acid-labile protecting groups such as methoxymethyl (MOM), or tetrahydropyranyl (THP) were also frequently used in this methodology as the acidic work up could easily deprotect these protecting groups, thereby providing the benzoboroxoles essentially in a one-pot transformation (Scheme 1).

Al-Zoubi and co-workers recently described the synthesis of iodinated benzoboroxoles via consecutive metal-iodine exchange followed by borylation. The reaction of 3,4,5-triiodoanisole **12** with isopropylmagnesium chloride followed by the treatment with an aldehyde provided two regioisomeric benzyl alcohols **13a-b**. Regioselectivity was dependent on the nature of aldehyde being



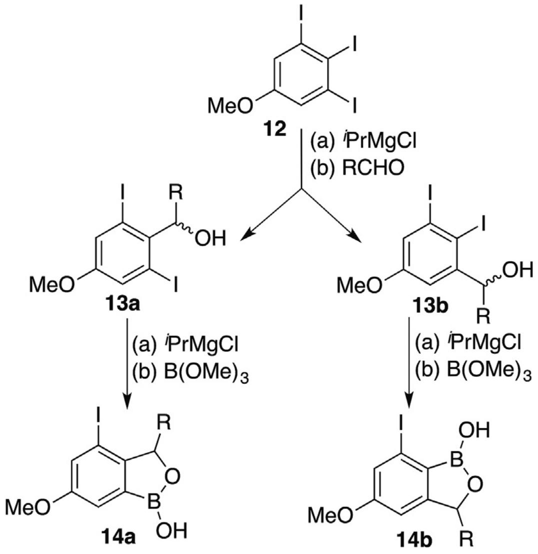
Scheme. 1. Dehalogenative lithiation-borylation protocol for the preparation of benzoboroxoles.

used, internal alcohol **13a** was obtained as the major product (~2–4:1) with aromatic aldehydes while alcohol **13b** predominated (~2–3:1) with aliphatic aldehydes. The alcohols were purified via flash chromatography and then subjected to another metal-halogen exchange with the same Grignard reagent, followed by borylation with trimethylborate to yield the target regioisomeric benzoboroxoles **14a-b** (Scheme 2) [19].

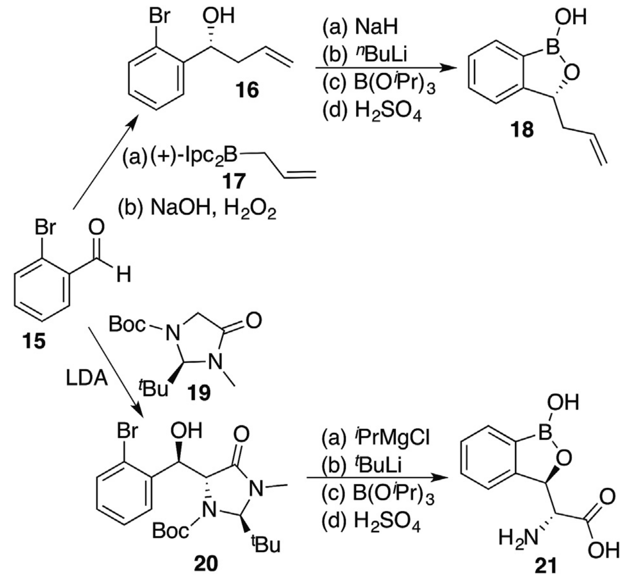
We were able to extend the lithiation-borylation protocol for the synthesis of chiral benzoboroxoles **18** via the enantioselective allylboration of *o*-bromobenzaldehyde **15** with *B*-allyldiisopinocampheylborane ($Ipc_2BAllyl$) **17** followed by sequential treatment of the resulting homoallylic alcohol **16** with sodium hydride, *n*-butyllithium, triisopropylborate, and sulphuric acid (Scheme 2) [17a]. Maison et al. reported the synthesis of chiral amino acid branched benzoboroxoles **21** via the reaction of *o*-bromobenzaldehyde **15** with lithiated imidazolidinone **19**, followed by lithiation-borylation methodology applied on the resulting benzylic alcohol **20** (Scheme 3) [20].

Britton and co-workers approached the synthesis of benzoboroxoles **23** via the directed lithiation of chiral hydrobenzoin **22** with *n*-butyllithium followed by borylation using trimethylborate and acidification (Scheme 4) [21].

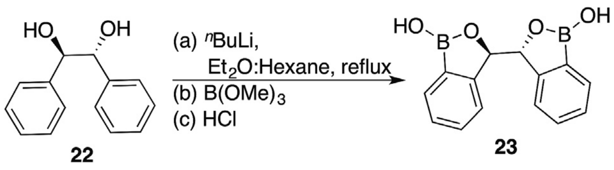
In an alternate protocol, Lulinski et al. described the synthesis of benzoboroxoles **27** via a dehalogenative lithiation of *o*-bromophenylboronate **26**. The requisite boronate **26** was prepared via the condensation of *o*-bromophenylboronic acid **24** with *N*-*n*-butyldiethanolamine **25**. The target benzoboroxoles **27** were prepared from **26** using metal-halogen exchange, trapping of the resulting aryllithium with aromatic aldehydes and subsequent acidic work up (Scheme 5) [22]. This methodology was further extended for the preparation of pyridinyl boroxoles **28** as well as benzosiloxaboroles **29** (Scheme 5) [23].



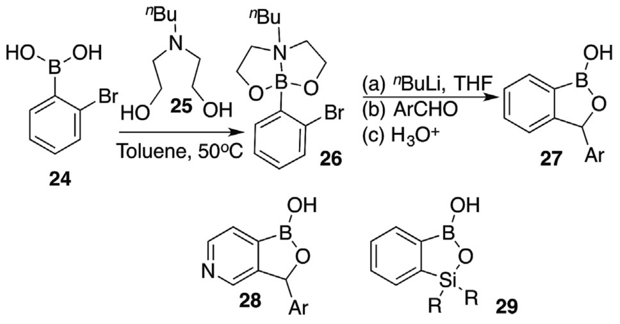
Scheme. 2. Dehalogenative lithiation-borylation protocol for the preparation of iodinated benzoboroxoles.



Scheme. 3. Dehalogenative lithiation-borylation protocol for the preparation of chiral benzoboroxoles.



Scheme. 4. Directed deprotonative lithiation-borylation protocol for the preparation of benzoboroxoles.



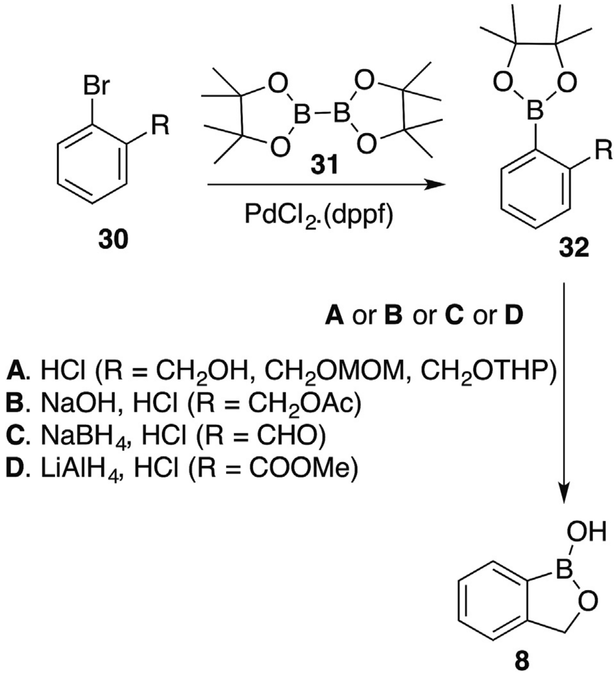
Scheme. 5. Preparation of benzoboroxoles via dehalogenative lithiation of *o*-bromoboronates.

3.1.2. Transition metal catalyzed borylation

Miyaura borylation [1,24] of haloarenes was extensively utilized for the preparation of densely functionalized benzoboroxoles owing to the mild experimental conditions employed to perform these reactions. In addition, the functional group compatibility of the reagents used in this reaction rendered further synthetic utility to this protocol. A wide variety of haloarenes **30** were utilized for borylation with bis(pinacolato)-diboron **31** in the presence of palladium catalysts. The substituents such as alcohols, ethers, esters, and aldehydes were well tolerated under these conditions to furnish the corresponding *B*-arylpinacolboronates **32**, which upon appropriate work up yielded the benzoboroxoles **8** (Scheme 6).

Recently, Huang et al. described the borylation of *o*-bromobenzyl alcohols directly without the need for protection of the alcohol moiety for the synthesis of benzoboroxoles **33** [25]. Lafitte et al. described the synthesis of boroxoles **34** in a similar manner using borylation of benzyl alcohols (Fig. 4) [26].

Peng and co-workers reported the synthesis of boroxoles **39** via Miyaura borylation of *o*-methyl-haloarenes **35** followed by radical bromination of methyl group in **35**, nucleophilic substitution with trimethylamine and cyclization of the resulting ammonium salt **36** via photoirradiation with methoxyamine (Scheme 7) [27].



Scheme. 6. Miyaura borylation protocol for the preparation of benzoboroxoles.

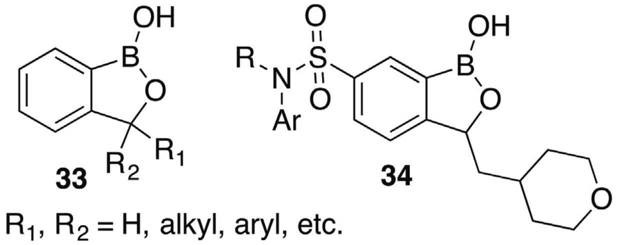


Fig. 4. Benzoboroxoles prepared using Miyaura borylation.

Larionov et al. described the synthesis of tavaborole **9** via metal-free borylation of 2-bromo-5-fluorobenzyl alcohol **40** with tetrahydroxydiboric acid **41** under photoirradiation conditions (Scheme 8) [28].

3.1.3. *Nucleophilic addition to o-formylphenylboronic acid*

Another strategy that was frequently employed for the synthesis of benzoboroxoles involved the addition of a variety of nucleophiles to *o*-formylphenylboronic acid **42** (Scheme 9). The aldehyde moiety in **42** is activated by the intramolecular hydrogen bonding between carbonyl oxygen and the boronic acid, which promoted facile cyclization upon reaction with a variety of nucleophiles to form the oxaborole ring **43**.

We reported the Barbier allylation of aldehyde **42** with α-bromomethylacrylates **44** to furnish the functionalized benzoboroxoles **45** (Scheme 10) [29]. The allyl bromides **44** were in turn prepared in two steps via Baylis-Hillman reaction [30] followed by bromination of the resulting alcohol.

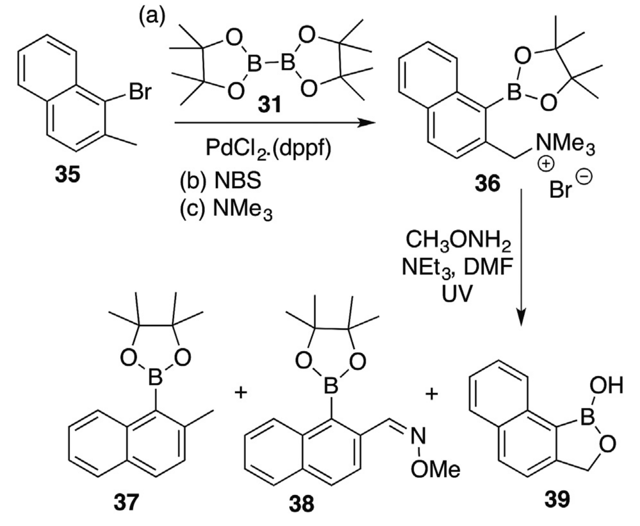
Reformatsky reaction with zinc reagent **46** was also reported with **42** for preparation of α-benzoboroxolylacetates **47** [31]. Recently, Wittig olefination of **42** was also reported using (2-aryl-2-oxoethylidene)triphenylphosphorane **48**. The resulting *o*-boronochalcone intermediate underwent spontaneous stereoselective oxa-Michael addition in the presence of cinchona alkaloid derived organocatalyst **49** to furnish the benzoboroxoles **50** in 74–99% ee (Scheme 10) [32].

Henry reaction of **42** with variety of nitroalkanes was reported for the formation of nitroalkylbenzoboroxoles **51** [33]. We reported the aldol reaction of **42** with ketones **52** and malonate **54** to yield the corresponding benzoboroxoles **53** and **55** respectively (Scheme 11) [34].

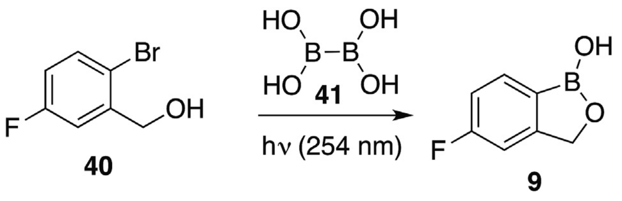
Adamczyk-Wozniak et al. reported the addition of secondary amines such as morpholine and piperidine to furnish 3-aminosubstituted benzoboroxoles **56** [35]. Interestingly, they noted that the addition of phenylethylamine **57** to aldehyde **42** resulted in the electrophilic *para* substitution to produce 3-arylbenzoboroxoles **58** [36]. Similar electrophilic substitution was also observed by Zhang et al. with indole **59** to yield indolylbenzoboroxoles **60** [37]. Adamczyk-Wozniak and co-workers demonstrated the synthesis of benzoboroxoles **62** via the addition of diamines such as piperazine **61** to aldehyde **42** (Scheme 12) [38].

We reported the synthesis of functionalized benzoboroxoles **64**, **66**, and **68** using Baylis-Hillman reaction and boronic acid aldehyde **42**. Baylis-Hillman reaction typically takes several days to one week of stirring at room temperature for completion. However, dramatic rate acceleration was observed with aldehyde **42** because of the activation of the aldehyde with *o*-boronic acid motif under the reaction conditions. Reaction of **42** with activated olefins such as acrylates, acrolein, and alkyl vinyl ketones **63** yielded benzoboroxoles **64**. Acrylonitrile **65** and cyclohex-2-enone **67** also reacted readily under these conditions to yield **66** and **68** respectively (Scheme 13) [29,34].

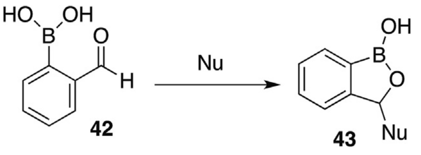
Snyder reported the addition of trimethylsilyl cyanide to **42** furnishing 3-cyanobenzoboroxole **69** in the presence of tetrabutylammonium cyanide [14b]. We were able to synthesize 3-



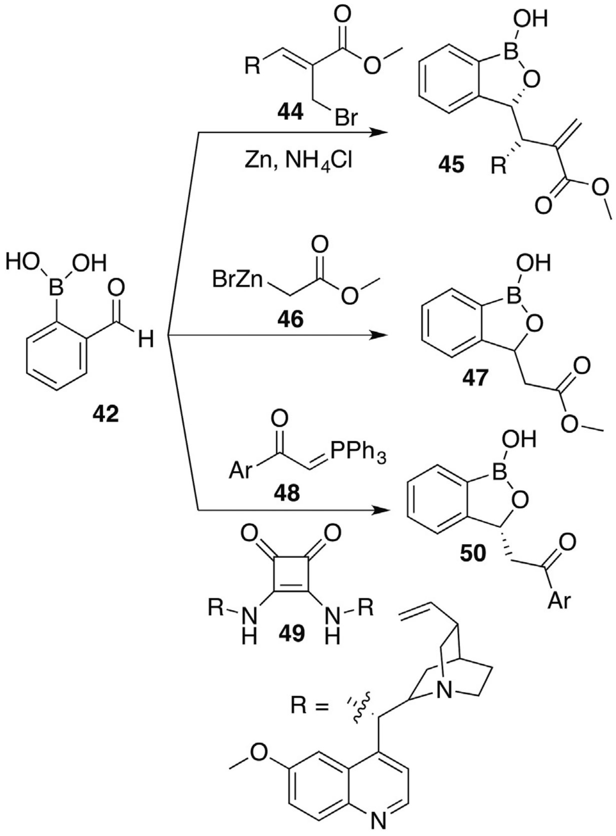
Scheme. 7. Preparation of benzoboroxoles via Miyaura borylation followed by photoirradiation.



Scheme. 8. Preparation of tavaborole via photoinduced metal free, borylation.



Scheme. 9. Preparation of benzoboroxoles via nucleophilic addition to *o*-formylphenylboronic acid.



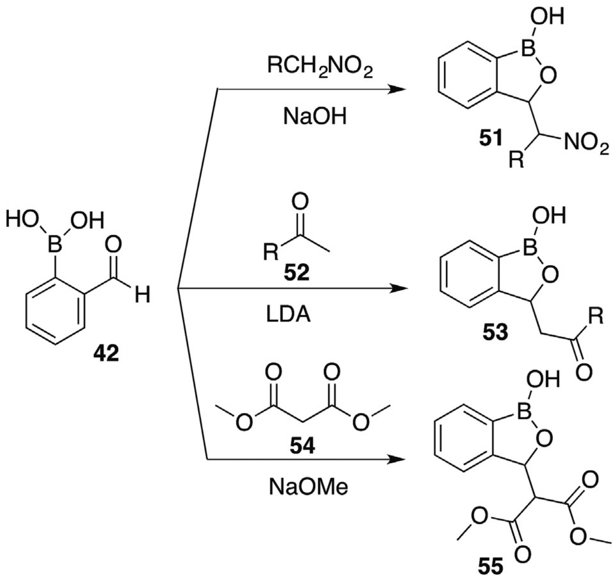
Scheme. 10. Preparation of benzoboroxoles via Barbier allylation, Reformatsky, and Wittig olefination reactions.

amidobenzoboroxoles **70** [39] via the nucleophilic addition between isocyanides and **42** under Passerini [40] reaction conditions (Scheme 14).

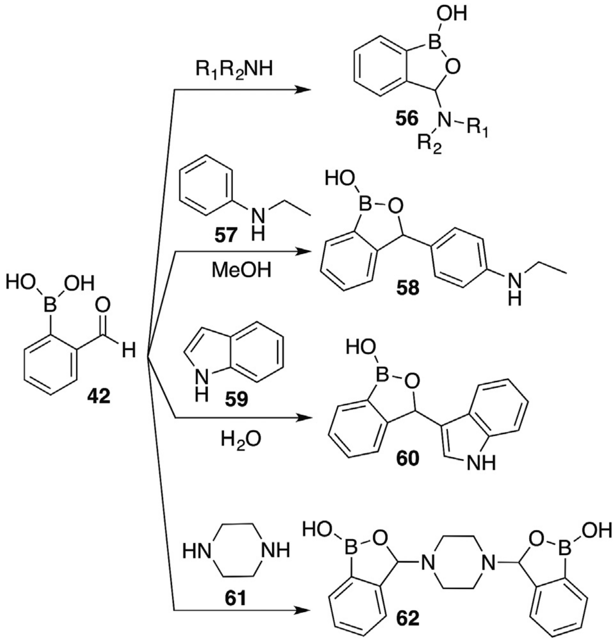
Maison et al. described the synthesis of acetylenyl benzoboroxoles **73**, which were further utilized for the synthesis of adamantane-based triazolylbenzoboroxoles **74** via click chemistry. The requisite alkynyl benzoboroxole **73** was obtained from the aldehyde **42** via protection of the boronic acid as pinacolboronate **71** followed by addition of acetylide. The resulting alcohol was treated with diethanolamine to generate **72**, which was readily purified via simple recrystallization. Acidification of **72** with HCl yielded the benzoboroxole **73** (Scheme 15) [41].

3.1.4. Miscellaneous methods

Benhamou et al. described the synthesis of 3,3-dimethylbenzoboroxole **76** via the addition of Bronsted acid (amberlyst 15) or Lewis acid ($PtCl_4$) catalyst to *o*-vinylphenylboronic acid **75** in *tert*-butanol medium (Scheme 16) [42]. Falck and co-workers described the synthesis 3-bromomethylbenzoboroxole **77** via the reaction of *o*-vinylphenylboronic acid **75** with NBS (Scheme 16) [43].



Scheme. 11. Preparation of benzoboroxoles via aldol chemistry.



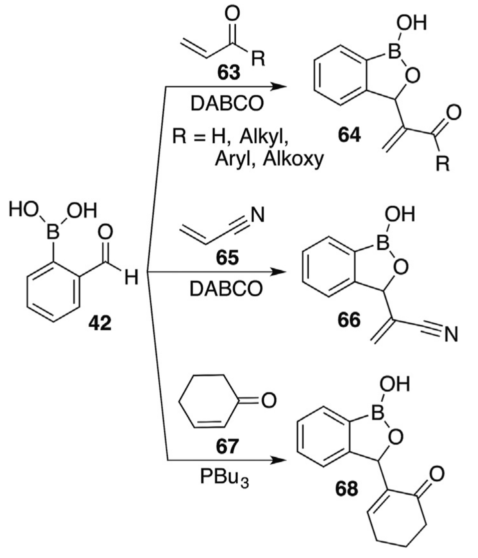
Scheme. 12. Preparation of aza-substituted benzoboroxoles.

Harrity and co-workers described the synthesis of benzoboroxoles **81** via directed 4 + 2 cycloaddition of alkynyl trifloroborates **79** to 2-pyrones **78** followed by the reduction of intermediate **80** with sodium borohydride (Scheme 17) [44].

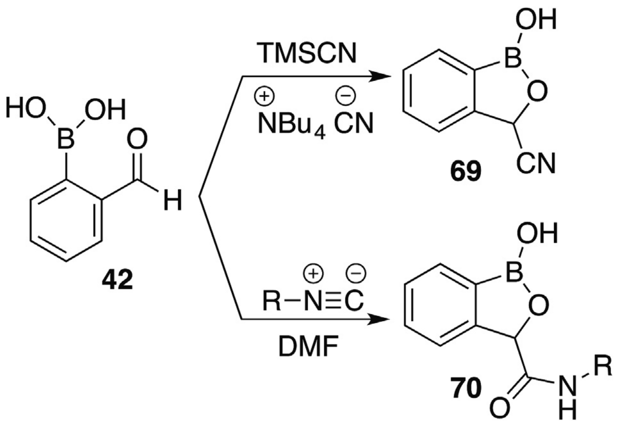
Cramer and Heinz utilized [2 + 2 + 2] cyclotrimerization of alkynes **85** and **86** for the synthesis of benzoboroxole **87**, which was subsequently utilized as a precursor in the synthesis of natural product Fijiolide A (Scheme 18) [45]. The alkyne **85** was prepared via borylation of disilyl diacetylide **82** to obtain diacetylenic boronate **83** and further reaction of **83** with propargyl alcohol **84**.

3.2. Use of benzoboroxoles in medicinal chemistry

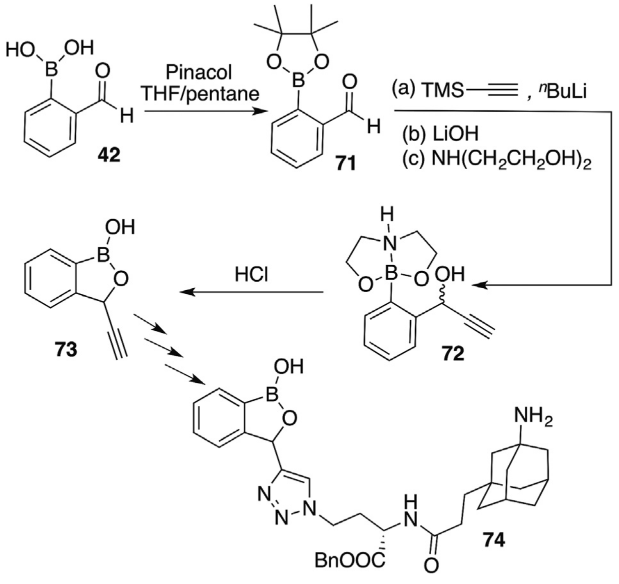
The development of tavaborole **9**, crisaborole **10**, and the related



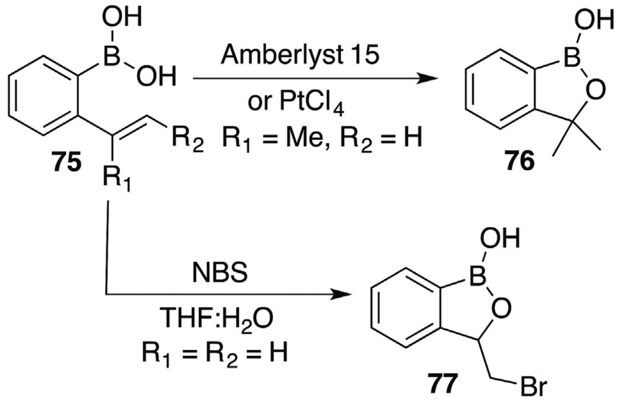
Scheme. 13. Preparation of benzoboroxoles via Baylis-Hillman chemistry.



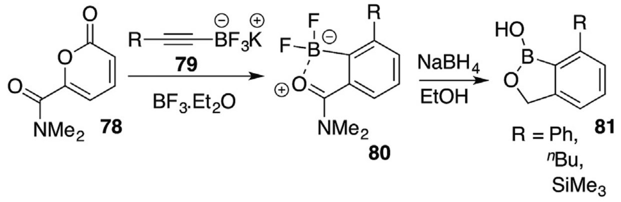
Scheme. 14. Preparation of benzoboroxoles via the reaction of *o*-formylphenylboronic acid with cyanides and isocyanides.



Scheme. 15. Preparation of benzoboroxoles via nucleophilic addition to *o*-formylphenylboronic acid.



Scheme. 16. Preparation of benzoboroxoles via *o*-vinyl phenylboronic acid.



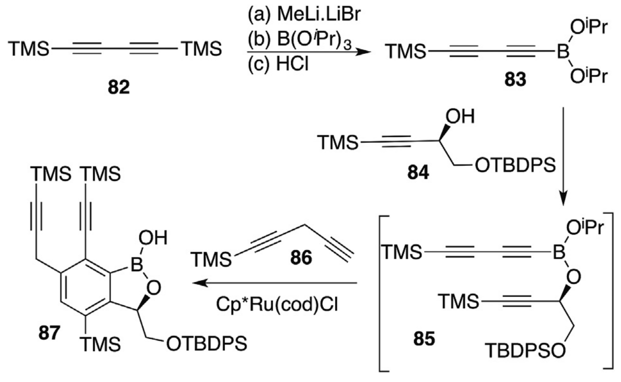
Scheme. 17. Preparation of benzoboroxoles via directed cycloaddition reaction.

series of benzoboroxoles have been extensively reviewed elsewhere [6,14,15]. The following are some of the recent applications of benzoboroxoles in medicinal chemistry.

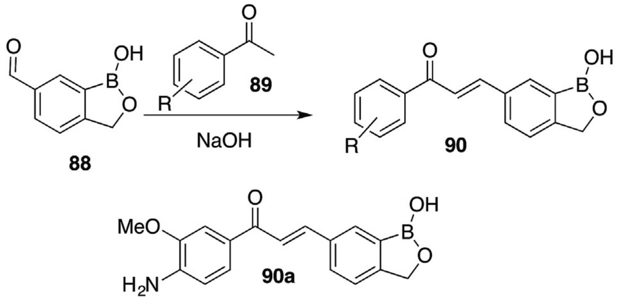
3.2.1. Anti-cancer agents

Zhou and coworkers recently described the preparation of benzoboroxole-chalcone conjugates **90** and tested these analogs as potential *anti*-cancer agents (Scheme 19) [46]. The borono chalcone **90a** was prepared via aldol coupling of *o*-nitroacetophenone **89** with formyl benzoboroxole **88**, followed by tin-mediated reduction of the nitro group to the corresponding amine. Some of these compounds, especially **90a**, showed promising cell proliferation inhibition properties against ovarian adenocarcinoma cell line SKOV3 while showing minimal toxicity towards normal cells, thus extending the application of this class of compounds as *anti*-cancer agents.

Winum et al. reported the synthesis of 6-urea and 6-thiourea substituted benzoboroxoles **91** and **92** (Fig. 5) [47] as potent carbonic anhydrase (CA) inhibitors, an emerging target for the



Scheme. 18. Preparation of benzoboroxoles via cyclotrimerization of alkynes.



Scheme. 19. Preparation of benzoboroxole-chalcone hybrids as *anti*-cancer agents.

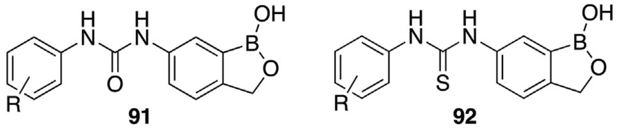
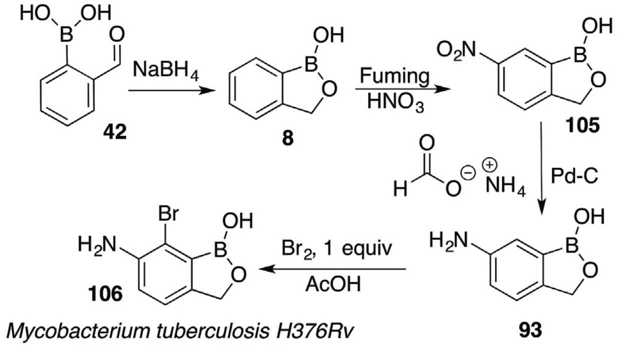


Fig. 5. Benzoboroxoles as carbonic anhydrase inhibitors.

development of cancer therapeutics [48].

We recently reported the synthesis of 6-aminobenzoboroxole derivatives **95**, **96**, **98**–**100**, **102**, and **104** as potential *anti*-cancer agents using reductive amination strategy. The reaction of amine **93** with variety of aldehydes followed by treatment with sodium borohydride furnished the secondary amine derivatives **94**, which were further converted to the *N*-nitrosoamines **95** upon treatment with sodium nitrite. The secondary amines **94** were further converted to urea derivatives **96** upon reaction with isocyanates. Alkylation of **93** and **94** was also achieved using bromomethylacrylate **97** and alkyl/benzyl bromides to furnish corresponding *N*-alkylated benzoboroxoles **98** and **99**. Acylation of 6-aminobenzoboroxole **93** with phthalic anhydride **101** and succinic anhydride **103** yielded corresponding imide **102** and amide **104** respectively. One of the secondary amine derivatives **94** and the urea-substituted benzoboroxole **96** showed significant cell proliferation inhibition activity against pancreatic (MIAPaCa-2) and triple negative breast (MDA-MB-231) cancer cell lines (Scheme 20) [49].



Mycobacterium tuberculosis H376Rv
MIC_{99} (7H9) = 7.8 μM
MIC_{99} (GAST) = 1.9 μM

Scheme. 21. Preparation of aminobenzoboroxoles as *anti*-tubercular agents.

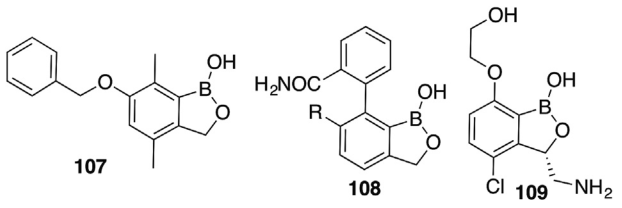
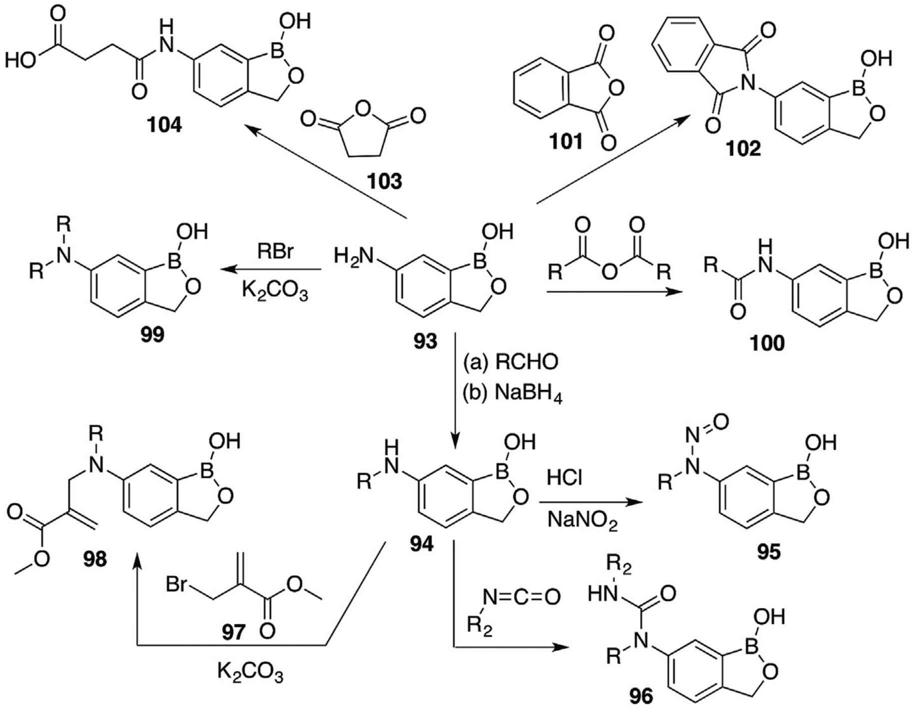
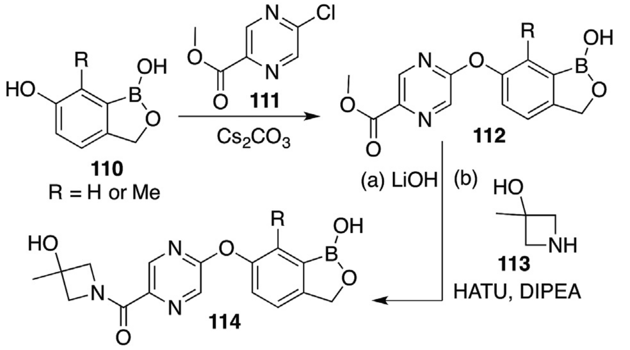


Fig. 6. *Substituted benzoboroxoles as anti-tubercular agents.*



Scheme. 20. Preparation of functionalized benzoboroxoles as *anti*-cancer agents.



Scheme. 22. Preparation of pyrazinylbenzoboroxoles as *anti*-malarial agents.

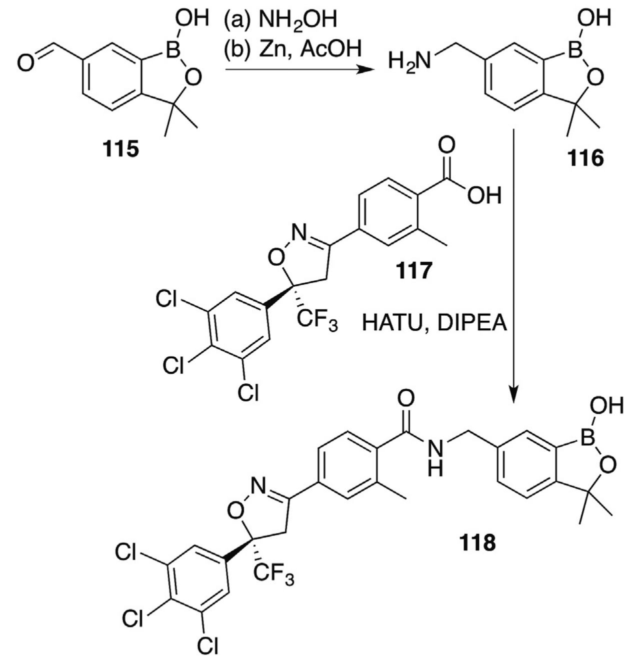
3.2.2. Anti-tubercular agents

We reported a simple synthesis of 6-amino-7-bromobenzoboroxole **106** via reduction of *o*-formylphenylboronic acid **42** followed by electrophilic nitration, reduction, and mono-bromination (Scheme 21) [50]. This analog showed promising activity against *Mycobacterium tuberculosis* H376Rv.

Recent reports from Anacor pharmaceuticals indicated that the benzoboroxoles **107**–**109** exhibit excellent activity against *M. tuberculosis* (Fig. 6) [51].

3.2.3. Anti-malarial agents

Zhang and co-workers reported the synthesis of 6-aryloxy-7-alkylbenzoboroxoles **112** and **114** (Scheme 22) [52]. Synthesis of **112** involved *ipso* substitution of chloropyrazole ester **111** with phenolic benzoboroxole **110**. Pyrazinylbenzoboroxoles **114** were obtained upon saponification of ester **112** to carboxylic acid and subsequent coupling with cyclobutylamine **113**. These molecules showed impressive *in vitro* biological activity against cultured *Plasmodium falciparum*. The *in vivo* evaluation of these compounds in mice infected with drug-resistant strains of *P. falciparum* showed excellent potential for their development as *anti*-malarial agents.



Scheme. 23. Preparation of functionalized benzoboroxoles as ectoparasiticidic agents.

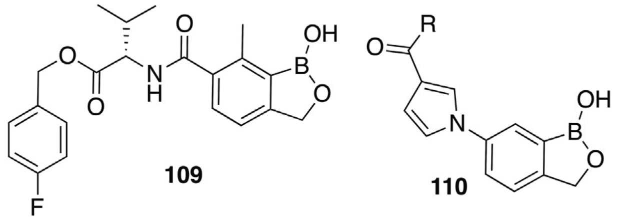


Fig. 7. Development of functionalized benzoboroxoles for the treatment of African trypanosomiasis.

3.2.4. Ectoparasiticidic agents

Zhang et al. reported the synthesis of isoxazoline-based benzoboroxoles **118** as long acting animal ectoparasiticide against dog ticks and cat fleas [53]. The synthesis of **118** was accomplished starting from 3,3-dimethyl-6-formylbenzoboroxole **115** in three steps involving the formation of oxime, reduction in zinc/acetic acid, followed by peptide coupling with isoxazolinylbenzoic acid **117** (Scheme 23).

3.2.5. Efficacy against African Trypanosomiasis

Recently, a valine amide substituted benzoboroxole **109** was identified as a lead compound for clinical development as *anti*-protozoal agent based on a detailed SAR investigation against *Trypanosoma congolense* and *T. vivax*. These two protozoan parasites are primarily responsible for African trypanosomiasis in animals. Similarly, 6-pyrrolobenzoboroxole derivative **110** was identified as a lead candidate for human African trypanosomiasis or sleeping sickness (Fig. 7) [54]..

3.2.6. Miscellaneous applications in medicinal chemistry

Lapa and co-workers reported the synthesis of clarithromycin-benzoboroxole conjugate **121** as a more potent derivative than the parent drug clarithromycin against gram-positive bacterial strains [55]. Tevyashova et al. reported the synthesis of a series of amphotericin benzoboroxole conjugates, of which the compounds

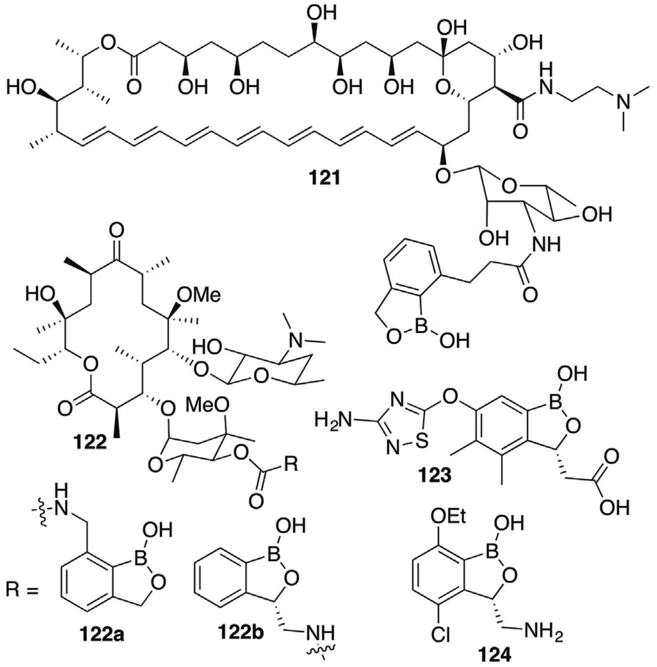


Fig. 8. Miscellaneous applications of benzoboroxoles in medicinal chemistry.

122a-b showed the best antifungal activity against *Candida albicans, Cryptococcus humicolus, Aspergillus niger,* and *Fusarium oxysoprum* while showing low cytotoxicity and hemolytic potency [56]. Verheizen et al. described thiadiazolyloxy benzoboroxole derivative **123** as potent inhibitor of serine β-lactamase [30]. Palencia and co-workers recently reported the use of a 3-aminomethylbenzoboroxole **124** as an effective inhibitor of human protozoan pathogens such as *Toxoplasma* and *Cryptosporidium* (Fig. 8) [57].

In addition to the analogs mentioned above, several other benzoboroxole analogs were developed that exhibited *anti*-inflammatory [58], and *anti*-viral (HCV protease) [59] activities as well. Numerous benzoboroxole-based compounds were also developed for applications in polymer and materials chemistry as hydrogels, and oligosaccharide detection [60].

4. Conclusions

In conclusion, benzoboroxoles have gained prominence in organic, material and medicinal chemistry. The clinical introduction of boronic acid based drugs bortezomib and ixazomib, and benzoboroxole drugs tavaborole and crisaborole marks a new era in developing novel boron containing drugs for the treatment of wide variety of diseases. Apart from already approved drugs, the fact that there have been numerous other benzoboroxole derived candidate compounds that exhibit excellent biological activity against several diseases should provide huge impetus in further exploring this class of molecules as novel drug candidates. This review provides a brief overview of the synthetic methods available for the preparation of benzoboroxoles along with some of their recent applications in drug discovery.

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Abbreviations

Boc	*t*-Butoxycarbonyl
^{t}Bu	*t*-Butyl
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene
cod	1,5-cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DIPEA	*N,N*-Diisopropylethylamine
dppf	1,1′-Bis(Diphenylphosphino)ferrocene
dtbpy	Di-*tert*-butyl-2,2′-bipyridine
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo [4,5-*b*]pyridinium 3-oxide hexafluorophosphate
Ipc$_2$BAllyl	*B*-Allyldiisopinocampheylborane
LDA	Lithium diisopropylamide
MOM	Methoxymethyl
NBS	*N*-Bromosuccinimide
SAR	Structure Activity Relationship
THP	Tetrahydropyranyl
TMS	Trimethylsilyl
XPhos Pd G2	Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-iphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)

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