REVIEW

Post-functionalization of Organoboranes by Cu-Catalyzed Azide Alkyne [3+2]-Cycloaddition Reaction

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Abstract: The copper-catalyzed azide alkyne [3+2]-cycloaddition (CuAAC) reaction of organoboranes represents an attractive area of research within the field of click chemistry, with diverse applications in organic synthesis, medicinal chemistry, or materials science. Despite the potential issues caused by the copper insertion into the carbon-boron bond, significant progress has been made to harness the reactivity of organoboron compounds in CuAAC. This review provides an overview of the catalytic methods reported for CuAAC with various organoboranes, discussing the stability of the boron group and highlighting recent advancements in this area.

1. Introduction

Organoboranes represent an important class of molecules with various applications in the field of organic synthesis (Suzuki-Miyaura coupling, Chan Lam reaction, etc.), catalysis, optoelectronic, biomedical or materials science.[1] While borylation reactions, like Miyaura borylation, are well-established methods for introducing boron group into organic molecules, interest is growing in boron-selective transformations to prepare complex organoboron compounds.[2]

The copper-catalyzed azide alkyne [3+2]-cycloaddition (CuAAC), developed by Sharpless and Meldal, has emerged as the most popular reaction in click chemistry. A reason arises from the high tolerance toward functional groups and mild reaction conditions, allowing the rapid and modular synthesis of complex molecules such as glycoconjugates,[3] functionalized materials,[4] and so on. Merging CuAAC reaction with organoboranes is an appealing yet challenging strategy to build complex molecules incorporating a boron group. Copper is indeed well known for its ability to insert into the C–B bond as illustrated by the Chan–Lam coupling reaction widely employed for the construction of carbon-heteroatom bonds (C–N, C–O, C–Br, etc.).[5] In the context of the CuAAC reaction with organoboranes, copper insertion into the C–B bond frequently results in the formation of protodeborylation products, which in turn leads to a decrease in yields. Despite this potential drawback, several studies on CuAAC with organoboranes have shown that less protodeboronation is observed when the Lewis acidity of the boron atom is reduced, either by steric hindrance, by coordination to a Lewis base or by electron donation of an adjacent heteroatom to the empty p orbital of the boron. Nowadays, common organoboron compounds used in the CuAAC, include trifluoroborate salts **1**, boronic acids and esters **2**-**3**, tetracoordinated organoboranes **4**, amino boranes **5**, and triarylboranes **6** (Figure 1a).

Regarding the structure of the CuAAC partners, most examples have been focusing on azido or alkynyl organoboranes **7** and **10** (Figure 1b-c), with the boron group attached to an aryl or alkyl chain, leading to isomeric triazoles **9** and **13**. While less explored, another approach involves alkynylborane partners **11**, giving rise to triazolylboranes **14** with the boron atom directly connected to the triazole moiety (Figure 1c).

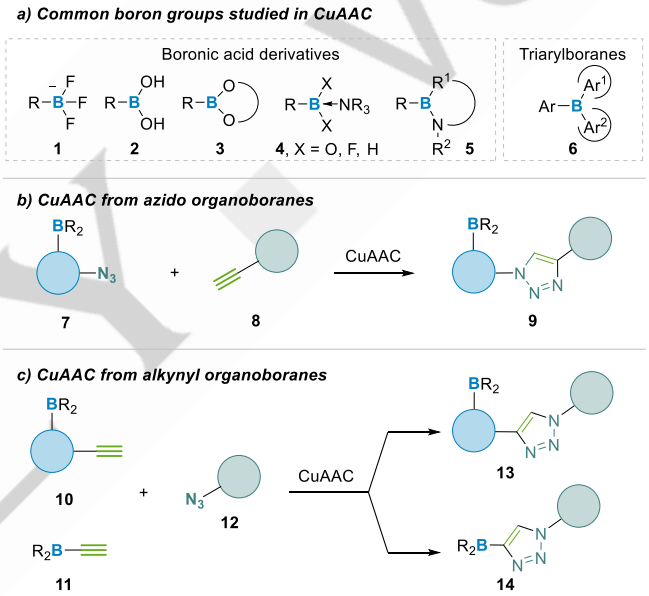

Figure 1. CuAAC with organoboranes.

The objective of this review is to provide an overview of the different catalytic methods reported in the literature for the CuAAC with organoboranes.[6] In addition, the stability of the boron group under the reaction conditions will also be addressed in the discussion, when relevant information is available.

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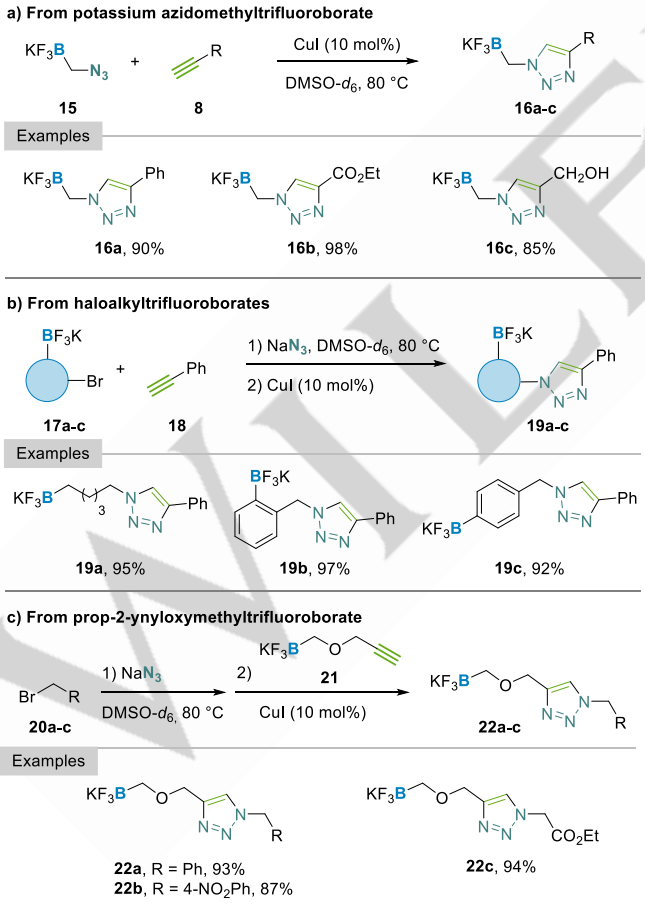
2. Fluoroorganoborates

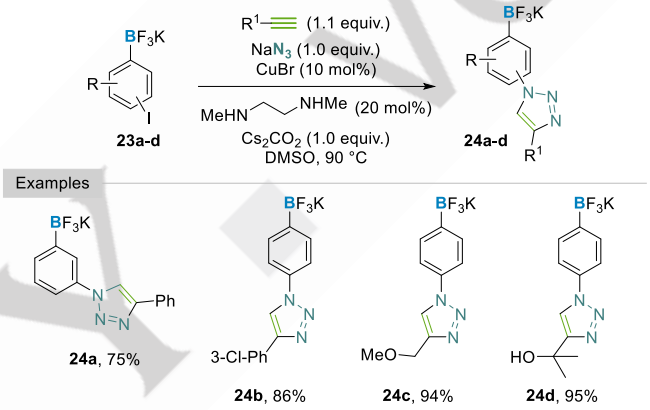
Potassium trifluoroborates have been used as stable organoboron reagents in various metal-catalyzed transformations.[7] In the context of the CuAAC reaction, early studies from Molander *et al.* demonstrated that potassium azido trifluoroborate **15** reacted efficiently with alkynes **8** in the presence of 10 mol% of Cu(I) in DMSO-d_6 at 80 °C (Scheme 1a).[8] Nine examples of triazoles **16** were described, with excellent yields ranging from 85% to 98%. An interesting efficient two-steps one-pot process from the corresponding bromides **17a-c** was developed as well, by direct nucleophilic substitution with NaN_3 followed by CuAAC (Scheme 1b).



Scheme 1. CuAAC with potassium trifluoroborates **15**, **17a-c, 20a-c**.

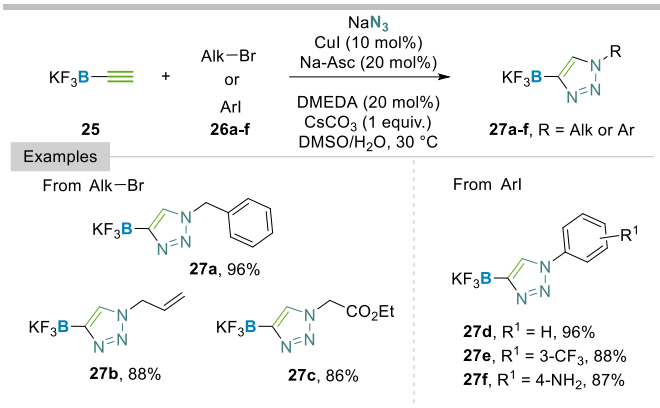
The CuAAC reaction was next extended by the same group to prop-2-ynyloxymethyltrifluoroborate **21** (Scheme 1c).[8] Bromides **20a-c** were first reacted with sodium azide to give the corresponding azide intermediates (not shown), which were then treated with alkyne **21** and CuI to provide triazoles **22a-c** in excellent yields. The authors did not mention the formation of protodeboronation products with any of these three methods.

Later on, Ham *et al.* reported the one-pot synthesis of aryl triazolyl trifluoroborates **24a-d** from aryl iodides **23a-d** and bromides (not shown). The reaction requests 10 mol% of CuBr and 20 mol% of *N,N'*-dimethylethylenediamine (DMEDA) as ligand, in presence of sodium azide and cesium carbonate (Scheme 2).[9] Under these conditions, the aryl iodide is first converted into the aryl azide intermediate, which reacts in the cycloaddition process with the terminal alkyne. A broad range of aryl halides and alkynes are compatible in this transformation, which does not affect the aryl trifluoroborate group.



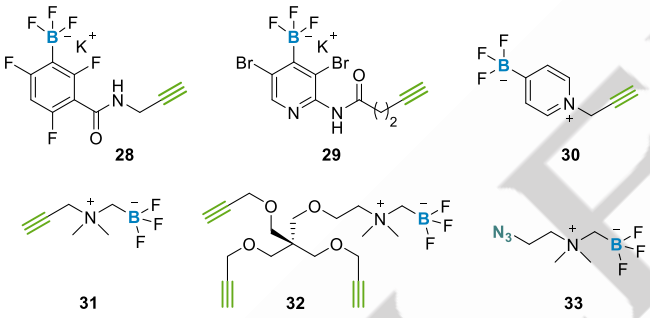
Scheme 2. One-pot CuAAC with potassium aryltrifluoroborates **24a-d**.

Following this work, the same group investigated the CuAAC of potassium ethynyltrifluoroborate and *in situ* generated alkyl or aryl azides (Scheme 3).[10] First attempt with BnBr, NaN_3 as azide source and CuI (10 mol%) catalyst in dry DMSO at 80 °C gave only protodeboronated triazole. The reaction outcome was not surprising, as alkynyltrifluoroborates are known to react with copper complexes.[11] However, the borylated triazole **27a** could be obtained in 96% yield when the reaction was carried out with Cs_2CO_3, sodium ascorbate (Na-Asc) and DMEDA as additives, in aqueous DMSO at 30 °C. Other substituted benzyl bromides as well as allyl bromides, α-bromo esters, and aryl iodides were regioselectively transformed into triazoles **27b-f** in good yields. A similar strategy was developed directly starting from alkyl and aryl azides.[12]



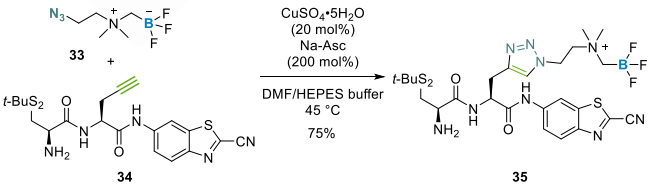
Scheme 3. One-pot CuAAC reaction with potassium ethynyltrifluoroborate **25**.

Perrin and his colleagues have developed a series of trifluoroborate salts for ^{18}F radiochemical labelling and PET imaging that can be directly used in CuAAC. These include aryl and pyridine potassium trifluoroborates **28**-**29**,[13] as well as zwitterionic pyridinium **30**,[14] and ammoniomethyl trifluoroborates ($AMBF_3$) bearing a propargyl (*ie* **31**-**32**)[14-15] or an azido group (*ie* **33**).[16] Compounds **31**-**33** are readily prepared by amine alkylation with iodomethyl pinacol boronate followed by treatment with KHF_2 (Scheme 4).[17]



Scheme 4. Examples of trifluoroorganoborates for ^{18}F radiosynthesis.

Several studies have emerged since then to label biomolecules or fluorescent probes with trifluoroborate salts **28**-**33**. This is usually achieved either with $CuSO_4$/Na-Asc, CuI or $Cu(CH_3N)_4PF_6$ as a copper catalytic system. It should be mentioned that some studies involving trifluoroborates **28**-**33** use a stoichiometric quantity of copper to carry out the cycloaddition. However, a typical example of catalytic CuAAC with azido $AMBF_3$ **33** is illustrated in Scheme 5 with the synthesis of the non-radioactive trifluoroborate **35**, the precursor of the radioactive analog.[18] The reaction carried out with the a combination of $CuSO_4 \cdot 5H_2O$ and Na-Asc, in a mixture of DMF and HEPES buffer, yields **35** in a good 75% yield, with no report of side product formation.



Scheme 5. Synthesis of trifluoroborate **35** by CuAAC.

3. Boronic acids and derivatives

3.1. Boronic acids and hemiesters

Boronic acids are commonly used in cross-coupling reactions to create new C–C or C–heteroatom bonds under transition-metal catalysis (Pd, Ni, Cu, etc.).[19] It is thus not surprising that some early examples of CuAAC with arylboronic acids describe the formation of by-products, such deboronation, leading to modest yields or complete degradation of cycloadducts.[20] In the course of their studies on the preparation of boronic acid–nucleotide conjugates by click chemistry, Wang *et al.* observed that the efficiency of the CuAAC in presence of catalytic amount of CuBr was highly dependent on the structure of the boronic acid.[20a] As shown in Figure 2, they investigated the stability of a series of boronic acids **36**-**39** by treating them with CuBr (40 mol%), tris(benzyltriazolylmethyl)amine (TBTA, 20 mol%) in a mixture of H_2O/DMF/*t*-BuOH for 5 h at room temperature. Although the quinoline boronic acid **36** was stable, partial degradation was observed for compounds **37**-**39**.

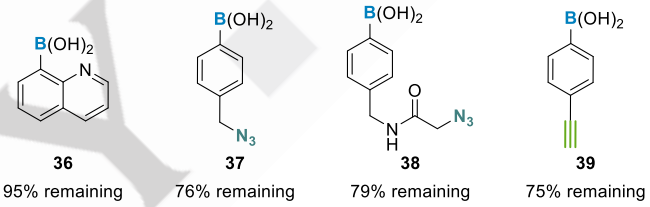
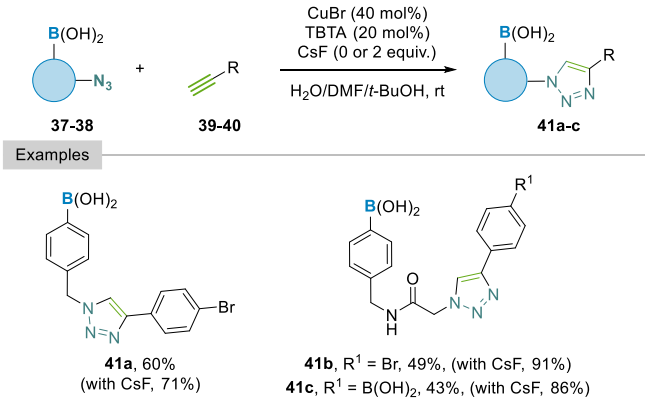


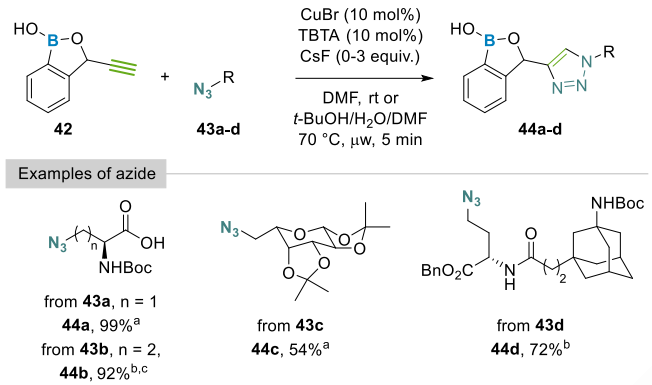
Figure 2. Study on the stability of boronic acids **36**-**39** with CuBr.

Thus, it turned out that under these conditions, the CuAAC of **37**-**39** led to modest or poor yields of triazoles **41a**-**c** (Scheme 6). However, addition of two equivalents of cesium fluoride prevented the decomposition of the organoboron species during the CuAAC, resulting in a significant improvement in isolated yields of **41a**-**c**, whether the boron group is on the azido or the alkyne partner. The authors argued that the fluoride anion coordinates to the boron atom to *in situ* generate a trifluoroborate salt that minimizes copper insertion into the C–B bond.[20a, 21]



Scheme 6. Effect of fluoride additive on the CuAAC with boronic acids **37**-**39**.

Cyclic boronic acid hemiester benzoboroxoles are recognized as effective binding agents for 1,2-diols and carbohydrates under physiological conditions.[22] In their research on the synthesis of lectin mimics, Maison *et al.* developed a "clickable" benzoboroxole **42** with a pending alkyne moiety (Scheme 7).[23] Under similar conditions as previously (CuBr 10 mol%, TBTA 10 mol%, CsF 3 equiv., DMF, rt), the regioselective synthesis of triazoles **44a** and **44c** was achieved in good to excellent yields. It is worth noting that product **44a** was obtained with a significant amount of the 1,5-regioisomer when $CuSO_4$ in the presence of TBTA, Na-Asc and CsF are used.



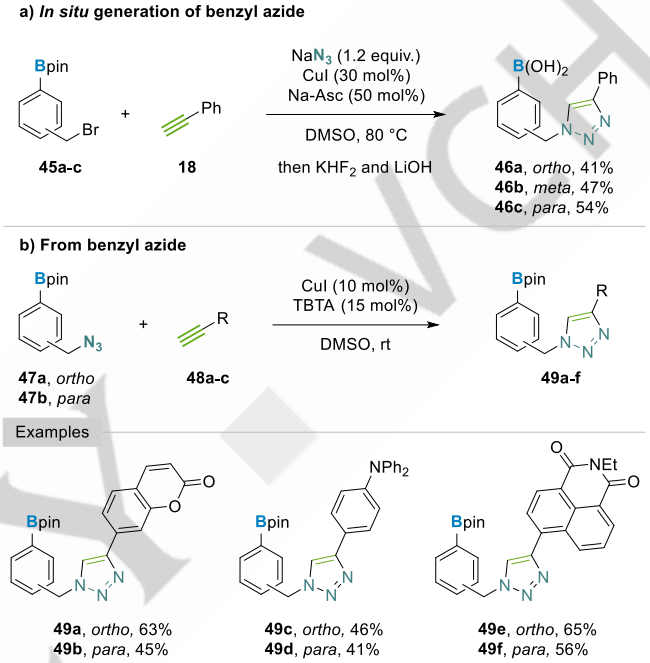
Scheme 7. CuAAC reaction with alkynyl benzoboroxole **42**. a) CuBr (10 mol%), TBTA (10 mol%), CsF (3 equiv.), DMF, rt. b) CuBr (10 mol%), TBTA (10 mol%), *t*-BuOH/H_2O/DMF, 70 °C, microwaves, 5 min. c) 8% of protodeboronation product was observed.

The optimized conditions have proved unsuitable for L-azidohomoalanine **43b** and triazidoadamantyl derivative **43d**, resulting in poor outcomes with the protodeboronation products mainly observed.[24] By running the reaction without cesium fluoride under microwave irradiation at 70 °C for 5 min, the formation of by-products was limited. As a result, both triazoles **44b** and **44d** were obtained in excellent yields of 92% and 72%, respectively, along with some protodeboronation with azide **43b**. Despite the degradation issues observed with boronic acids and hemiesters, several examples of CuAAC reaction have been described for preparation of complex molecules (H_2O_2-responsive multi-target delivery systems,[25] pro-theranostic nanoassemblies for cancer treatment),[26] post-modification of polymers,[27] cyclodextrins[28] and nanoparticles for saccharide recognition (*ie* lectin-type boronic acid modified NPs).[29] Either CuBr, $CuSO_4 \cdot 5H_2O$/Na-Asc or $Cu(PPh_3)I$ catalysts are used in these examples.

3.2. Hindered Boronic Esters (pinacol and pinanediol)

Pinacol boronates are extensively used in organic synthesis since they are more resistant to oxidation, protodeboronation, or metal insertion into the C–B bond, compared to boronic acids.[30] The CuAAC of organoboranes that bear a hindrered pinacol boronate group has received significant attention for preparing saccharide or reactive oxygen species sensors, fluorescent probes, etc. Due to their ease of deprotection under various conditions, boronic pinacol esters are also excellent alternatives for preparing boronic acids.

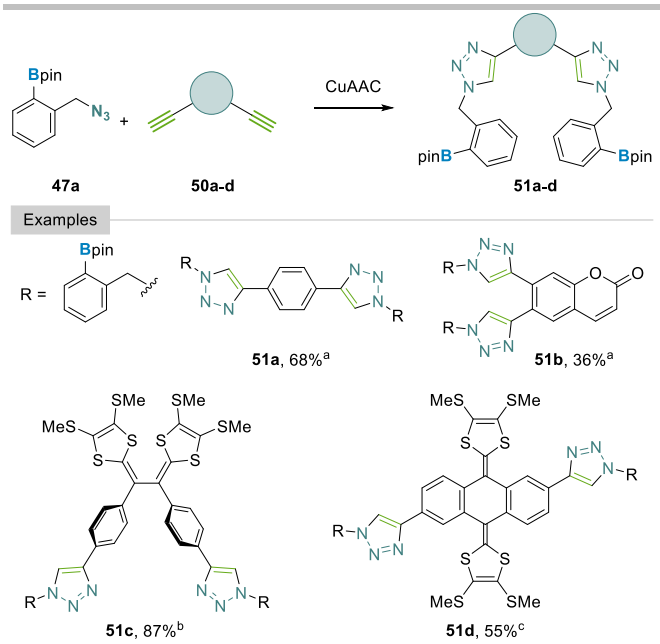
James and Fossey used this strategy to design a series of boronic acid-containing fluorescent triazoles acting as receptors for saccharides.[31] A one-pot process was developed from benzyl bromide **45a** using sodium azide, phenyl acetylene **18** and a catalytic system consisting of CuI/Na-Asc (Scheme 8a). In these conditions, they achieved the *in situ* formation of benzyl azide followed by CuAAC. After deprotection of the pinacol ester with KHF_2 then LiOH, the corresponding boronic acids **46a-c** were obtained with yields ranging from 41% to 54% over two steps.[31][32] It is worth noting that in addition to deprotection into boronic acids, the boron pinacol group of the click adducts could be used in Suzuki coupling[33] and Cu-mediated fluorination.[34]



Scheme 8. Examples of CuAAC with (azidomethyl) phenyl boronic pinacol esters **45a-c** and **47a-b**.

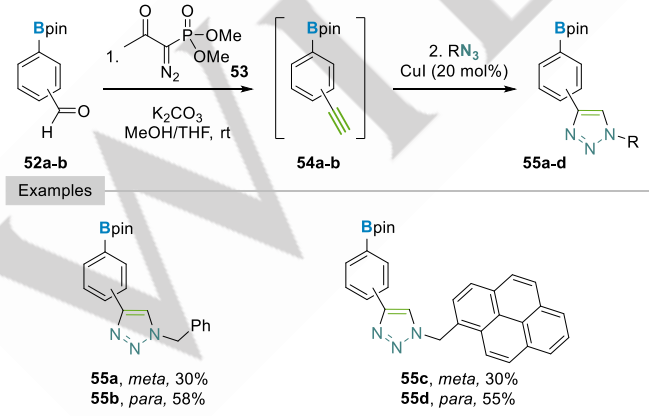
Under these optimized conditions, the one-pot [3+2]-cycloaddition from **45a** was less effective with alkynes **48a-c** containing fluorophores. The authors discovered that starting from azide derivatives **47a-b** (instead of *in situ* formation) and reducing the amount of copper iodide (10 mol%), while using TBTA ligand (15 mol %) resulted in better yields. For instance, triazole **49a** was isolated in 63% yield, while the one-pot procedure gave 29% yield, along with a mixture of protodeborylation and oxidation side-products. Other boronic pinacol esters **49b-f** were isolated in good yields from azides **47a-b**.

The CuAAC reaction with diynes has been documented in several publications for the development of bis-boronic acid saccharide sensors (Scheme 9). Fossey *et al.*, for instance, used their previously established conditions to produce glucose-selective fluorescent receptors **51a-b** with moderate yields of 68% and 36% respectively.[35][36] Similar conditions were applied for the synthesis of redox-active tetrathiafulvalene vinylogue **51c-d** designed for the electrochemical detection of saccharides and fluoride ion.[37] However, it was necessary to use a larger amount of copper iodide and raise up the temperature to obtain good isolated yields of 87% and 55%. Applications in the synthesis of functionalized polymers have also been developed to prepare micellar nanoparticles.[38]



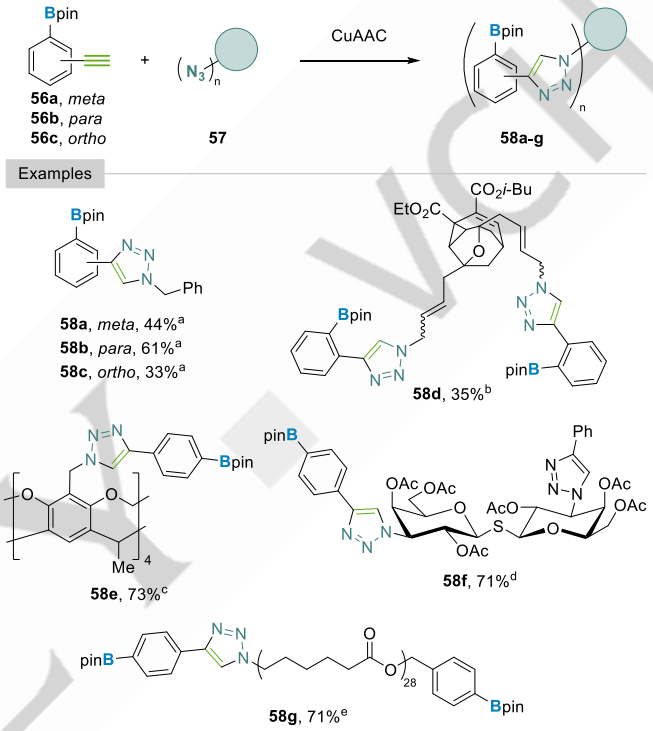
Scheme 9. Two-fold CuAAC with benzyl azido boronic pinacol ester **47a**. a) CuI (10 mol%), TBTA (30 mol%), DMSO, rt. b) CuI (50 mol%), *i*-Pr$_2$NEt (50 mol%), THF, 60 °C. c) CuI (90 mol%), THF, 65 °C.

A sequential Seyferth-Gilbert/CuAAC reaction was reported to directly convert aldehydes **52a-b** into triazoles **55a-d** by *in situ* formation of ethynyl phenyl boronic pinacol esters **54a-b** with Bestmann-Ohira reagent **53** (Scheme 10).[39] *Meta*- and *para*-substituted triazolylaryl boronates **55a-d** were produced with yields ranging from 30% to 58% in a one-pot process, using copper iodide as catalyst. The moderate yields were attributed to the low efficiency of the first step. Indeed, in a series of control experiments, the Seyferth–Gilbert reaction with *meta*- **52a** and *para*-substituted aldehydes **52b** gave the corresponding ethynylphenyl boronates **54a-b** in 45% and 75% yields respectively, while the *ortho* derivative (not shown) was obtained in only 8% yield.



Scheme 10. One-Pot synthesis of triazole boronates **55a-d** by Seyferth–Gilbert/CuAAC reactions (yields over 2 steps).

The CuAAC was later reported with ethynylphenyl boronates **56a-c** and benzyl azide *in situ* generated from benzylbromide and sodium azide (Scheme 11).[31a] CuI (10 mol%), in combination with Na-Asc (50 mol%), was used as catalyst in DMSO to obtain similar results to the one-pot process for *para*- and *meta*-derivatives **58a-b**. The *ortho*-substituted analogue **58c** was isolated in a modest 33% yield. The reaction of *ortho*-substituted ethynyl boronic ester **56c** is also illustrated in the two-fold CuAAC of bis-allylic azides. The transformation was performed with 5 mol% of Cu(CH$_3$CN)$_4$PF$_6$ catalyst in presence of TBTA ligand to suppress the protodeboronation. Here again a low yield of **58d** (35%) was obtained, showing the impact of the steric hindrance on the reactivity.[40]

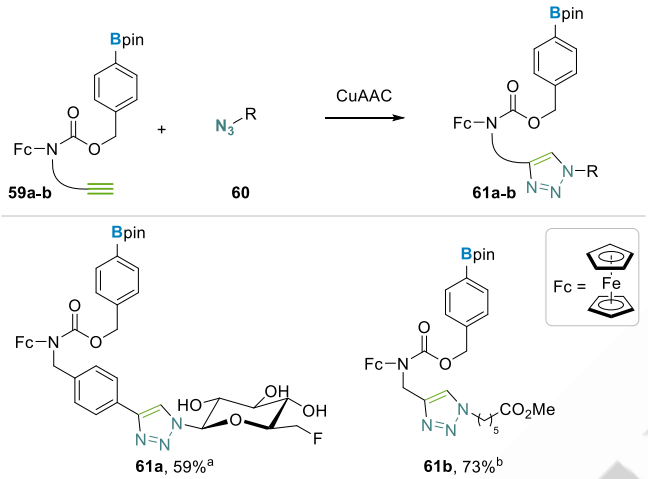


Scheme 11. Examples of CuAAC with ethynyl phenyl boronic pinacol esters **56a-c**. a) CuI (10 mol%), Na-Asc (50 mol%), DMSO, 80 °C. b) Cu(CH$_3$CN)$_4$PF$_6$ (5 mol%), TBTA (6 mol%), THF, 60 °C. c) CuI (50 mol%), Et$_3$N (10 equiv.), CH$_2$Cl$_2$/H$_2$O, rt. d) CuI (50 mol%), Et$_3$N (1 equiv.), CH$_3$CN, 50 °C. e) CuBr (36 mol%), PMDETA (36 mol%), CH$_2$Cl$_2$, rt.

Other examples involve *para*-ethynyl phenyl boronic pinacol ester **56b** to synthesize tetra-triazole cavitand **58e**[41] or disacharride **58f**, a precursor for ^{18}F radiolabelling.[42] In both cases, good yields were obtained, although 50 mol% of CuI was required. An interesting post-modification of polycaprolactone bearing a terminal benzyloxy pinacol boronic ester has been achieved with the same alkyne **56b**.[43] Using CuBr$_2$ in aqueous media, the authors observed the cleavage of C–B bond, and the conversion of the arylpinacolboronate into the aryl bromide.[44] However, switching to CuBr with *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylentriamine (PMDETA) as ligand in anhydrous conditions gave triazoles **58g** in 71% yield.

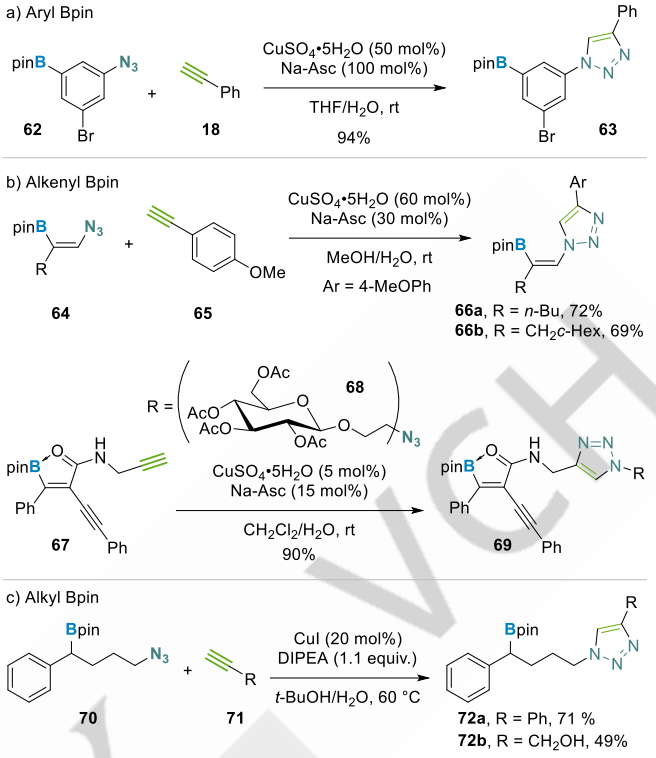
The CuAACs have also been used for the synthesis of substituted benzyloxy aryl pinacol boronic esters which have proved to be efficient tools for the detection of reactive oxygen species (ROS)[45], ROS-responsive drug delivery,[46] theranostic agents,[47] or materials.[48] In particular, the design of cancer-specific prodrugs has benefited from the progress made in the field of CuAAC of organoboranes. For example, Mohkir *et al.* have

developed a series of boron containing *N*-alkylaminoferrocene, which become activated when exposed to elevated levels of ROS, thereby mimicking the conditions specific to cancer.[49] Thanks to a CuAAC, the fluorinated prodrug **61a** was prepared in 59% yield using 20 mol% of CuI and triethylamine (Scheme 12).[50] In the same study, a [^{18}F]-radiolabelled analogue was also synthesized in the presence of $Cu(OAc)_2$, tris[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-ylmethyl]amine (THPTA) and sodium ascorbate. A second generation of *N*-alkylaminoferrocene bearing a pendant propargyl moiety has been developed and employed in the synthesis of triazole **61b**. The product was isolated in a good 73% yield using 20 mol% $Cu(PPh_3)_3Br$, together with DIPEA in CH_2Cl_2.[51]



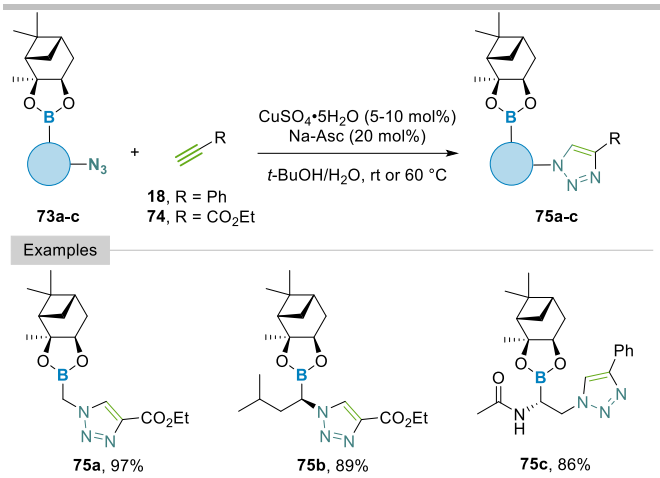
Scheme 12. Synthesis of boron containing *N*-alkylaminoferrocene by CuAAC. a) CuI (20 mol%), Et_3N (1.2 equiv.), THF, rt. b) $Cu(PPh_3)_3Br$ (20 mol%) DIPEA (2.5 equiv.), CH_2Cl_2, rt.

Other isolated examples of pinacol boronic esters employed in CuAAC should be underscored, and includes aryl **62**,[52] alkenyl **64**,[53] **67**[54] and alkyl boronates **70**[55] (Scheme 13). In these examples, the $CuSO_4{\cdot}5H_2O$ and Na-Asc catalytic system or CuI gave good results.



Scheme 13. Examples of CuAAC with aryl, vinyl and alkyl pinacol boronates.

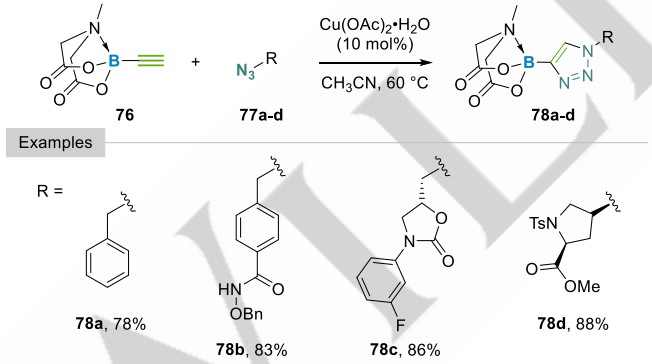
(+)-Pinanediol is now a well-established boron protective group for the synthesis of chiral amidomethylboronate,[56] a key structure in some boron-containing peptidomimetics. As part of their work on lactamase and protease inhibitors, Prati *et al.* synthesized a series of α- and β-azido boronates from pinanediol boronates **73a-c** (Scheme 14).[57] The authors selected (azidomethyl)boronate **73a** to test a range of three conditions of CuAAC with ethyl propiolate **74** (CuI with DIPEA or lutidine, $CuSO_4$/Na-Asc). Almost full conversion was observed in all cases; however using CuI led to 5% to 20 % protodeboronation. Under aqueous conditions with $CuSO_4$ (5-10 mol%), the cycloadduct **75a** was isolated in an excellent 97% yield. These reaction conditions were successfully applied to the CuAAC of a series of α- and β-azido boronates, and good performances were observed as demonstrated with triazoles **75b-c**.



Scheme 14. CuAAC with azido-containing pinanediol boronic esters **73a**-**c**.

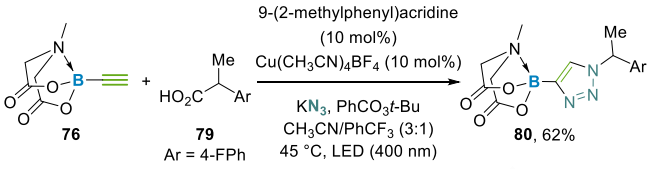
3.3. *N*-Coordinated Boronic Esters and (Fluoro)boranes

Among organoboranes, boron MIDA derivatives are known to be stable under a variety of metal catalyzed coupling conditions.[58] However, only few examples of these organoboranes have been reported within the frame of CuAAC.[59] In 2011, Grob and coworkers studied the reactivity of ethynyl MIDA boronate **76** in cycloaddition processes including CuAAC.[60] After a survey of different copper catalysts (i.e. $CuSO_4$/Na-Asc, CuI, CuCl, CuOAc or $Cu(OAc)_2$), they found that copper(II) acetate in acetonitrile at 60 °C provided the best results (Scheme 15). The air-stable MIDA derivatives **78a-d** were thus isolated with high yields after column chromatography. The authors did not observe any trace of the other regioisomer nor protodeboronation of **78a**-**d**.



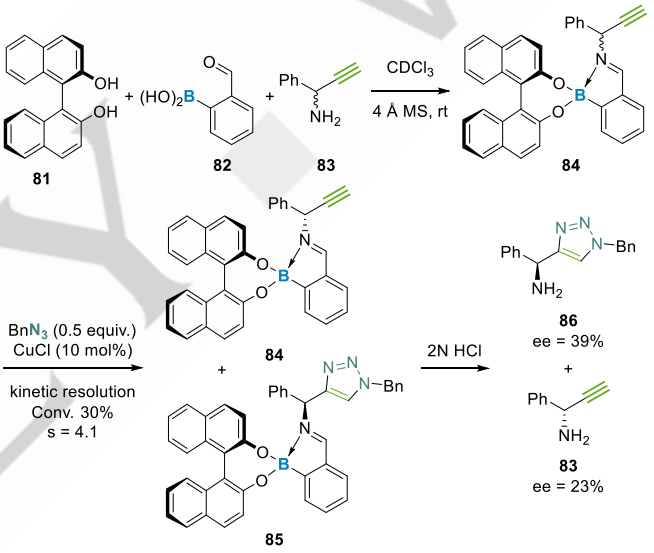
Scheme 15. CuAAC with ethynyl MIDA boronate **76**.

Larionov *et al.* recently provided an example of CuAAC with the same MIDA boronate derivative **76** (Scheme 16).[61] In their study, they developed a tandem three-component photocatalyzed decarboxylative triazolation/CuAAC reaction in presence of 10 mol% of acridine and copper catalyst. Under irradiation at 400 nm, carboxylic acid **79** was first converted into azide (not shown) that subsequently reacts with the alkyne **76** to give boronate **80** in 62% yield.



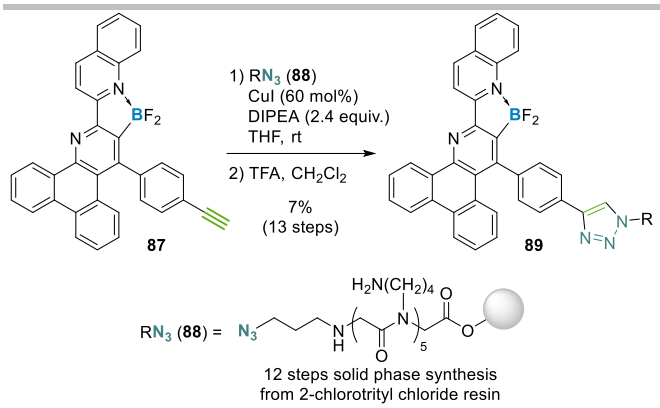
Scheme 16. Synthesis of triazole MIDA boronate **80** by a decarboxylative triazolation/CuAAC.

A more specific case of CuAAC on tetracoordinated organoborane **84** has been described for the kinetic resolution of primary amine **83** (Scheme 17).[62] In brief, condensation of (*R*)-BINOL **81**, boronic acid **82** and racemic amine **83** gave the coordinated imine **84**, which was subjected to the CuAAC with 10 mol% of CuCl and benzyl azide (0.5 equiv.). After 30% of conversion, both alkyne **84** and triazole **85** were obtained with a selectivity factor of 4.1. Hydrolysis furnished the enantioenriched starting alkyne **83** (ee = 23%) and triazole **86** (ee = 39%).



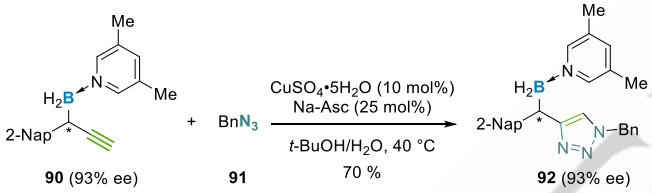
Scheme 17. Kinetic resolution of propargyl amine **83** by CuAAC.

Beyond the CuAAC with trifluoroborate salts discussed previously, Harrity *et al.* have applied the CuAAC to the synthesis of fluorescent tetracoordinated difluoroborane **89** (Scheme 18).[63] Peptoid **88** bearing an azide side chain was prepared on solid phase (12 steps from 2-chlorotrityl chloride resin), and then coupled with alkyne **87** using copper iodide and DIPEA in THF at room temperature. After removal from the resin, compound **89** was isolated in 7% yield over 13 steps. The authors did not discuss the stability of **87** or **89** in presence of copper.



Scheme 18. Synthesis of fluorogenic peptoid **89** by CuAAC.

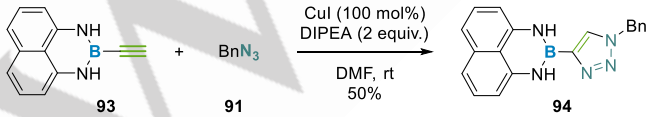
During their investigation into the synthesis of chiral propargylic organoboranes, Zhu and colleagues examined the reactivity of enantioenriched alkynyl pyridine borane complex **90** (Scheme 19).[64] Cycloaddition of alkyne **90** with benzyl azide **91** takes place smoothly at 40 °C in a mixture of *t*-BuOH/H_2O using $CuSO_4$/Na-Asc as catalytic system. No erosion of the enantiomeric excess of **92**, nor protodeboration, were reported.



Scheme 19. CuAAC with alkynyl pyridine borane complex **90**.

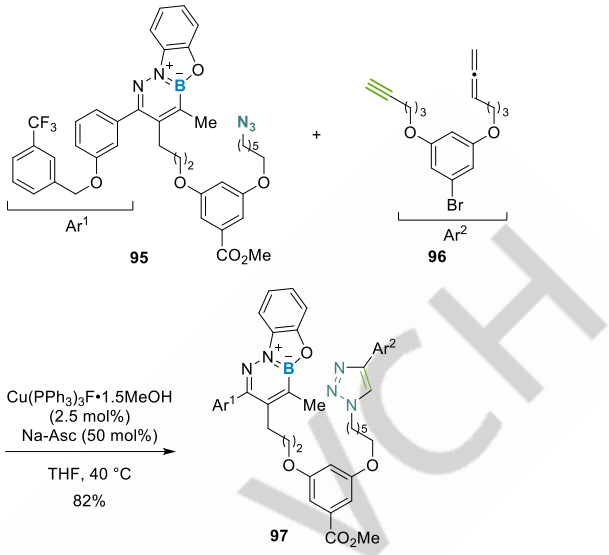
3.4. Organoboranes Embedded in a BN Heterocycle

1,8-Diaminonaphthalene (dan) is a well-established masking group for organoboranes which Lewis acidity and reactivity toward metal is diminished by electron donation of nitrogen atoms to the empty p orbital of the boron. Taking advantages in the stability of B(dan) derivatives, the group of Yoshida disclosed the CuAAC between ethynyl-B(dan) **93** and benzyl azide **91** (Scheme 20). In presence of a stoichiometric amount of CuI, B(dan)triazole **94** was isolated in 50 %.[65]



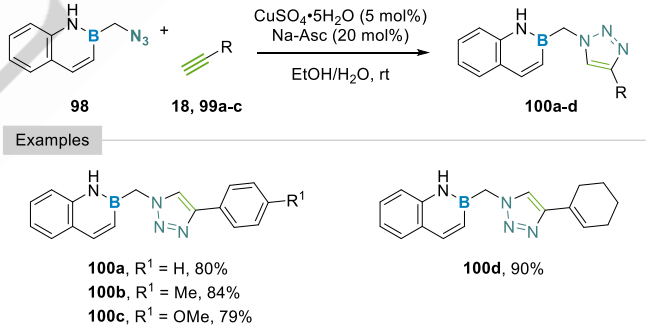
Scheme 20. CuAAC with ethynyl-B(dan) **93**

An example of CuAAC on azide **95** bearing a diazaborinine scaffold that displays a partial aromatic character, has been reported by Hoveyda and co-worker.[66] The reaction employs 2.5 mol% of $(Ph_3P)_3CuF{\cdot}1.5$ MeOH –a readily available and easy to handle Cu complex prepared in one step from triphenylphosphine and copper(II) fluoride–,[67] Na-Asc in THF at 40 °C (Scheme 21). The fluorescent diazaborinine **97** was isolated in an excellent 82% yield, demonstrating the robustness of diazaborinine in the CuAAC. Alternatively, $CuBr{\cdot}SMe_2$ also proved to be an efficient catalyst in this transformation.



Scheme 21. CuAAC with diazaborinine **95**.

Among other organoboron reagents employed in the CuAAC, azaborine **98** containing an azido group have been investigated as coupling partner (Scheme 22).[68] The reaction proceeds well in aqueous media with $CuSO_4$/Na-Asc, accommodating alkynes **18**, **99a-c** bearing either aryl or alkenyl substitutions. These results underline the stability of the borazaronaphthalene core under these conditions.

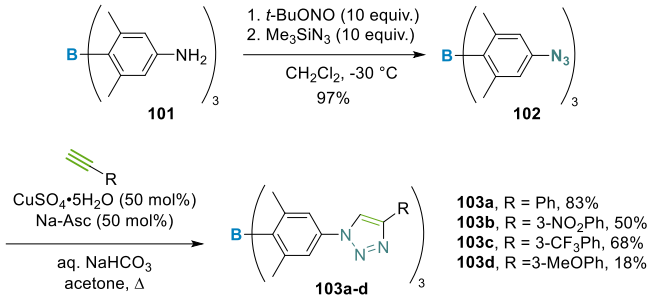


Scheme 22. CuAAC with 2-azidomethyl azaborine **98**.

4. Hindered Triarylboranes

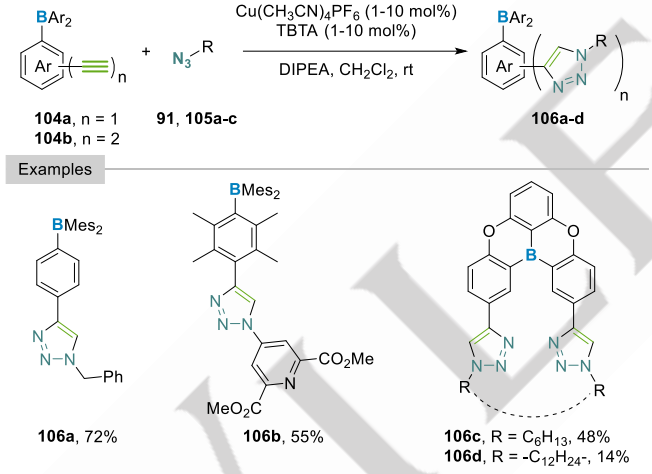
Triarylboranes display a variety of photophysical properties that can be finely tuned by modifying their molecular structure. This versatility makes them valuable for developing materials used in OLEDs and other optoelectronic devices. In the context of CuAAC, sterically hindered triarylboranes are usually employed, which prevent the insertion of copper into the C–B bond. For example, extension of the π-conjugated system of hindered triarylborane **102** has been successfully achieved by CuAAC with phenyl acetylene derivatives (Scheme 23).[69] Tris-azide **102** was first synthesized from tris-aniline **101** through diazotization then treatment with $TMSN_3$. Compound **102** then underwent a three-fold CuAAC reaction with different alkynes in the presence of 50

mol% of $CuSO_4$/Na-Asc in acetone and saturated aqueous sodium hydrogen carbonate solution. Tris-triazoles **103a-d** were isolated in modest to good yields after purification over silica gel.



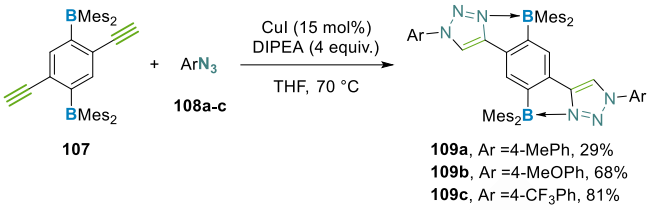
Scheme 23. Three-fold CuAAC with azido triarylborane **102**.

In the alkynyl triarylborane series, Wang and co-workers have demonstrated that hindered dimesitylboranes **104a-b** react with benzyl azide **91** or dimethyl 4-azidopyridine-2,6-dicarboxylate *via* CuAAC to produce **106a-b**. These triazoles are then employed as ligands for Pt(II) or lanthanide(III) complexes (Scheme 24).[70] The cycloaddition was performed with 1 or 10 mol% of cationic copper complexe $Cu(CH_3CN)_4PF_6$, TBTA as stabilizing ligand and DIPEA as base. Under similar conditions, 5,9-dioxa-13*b*-boranaphtho[3,2,1-*de*]anthracene derivatives **106c-d** were prepared by a two-fold cycloaddition process.[71][72]



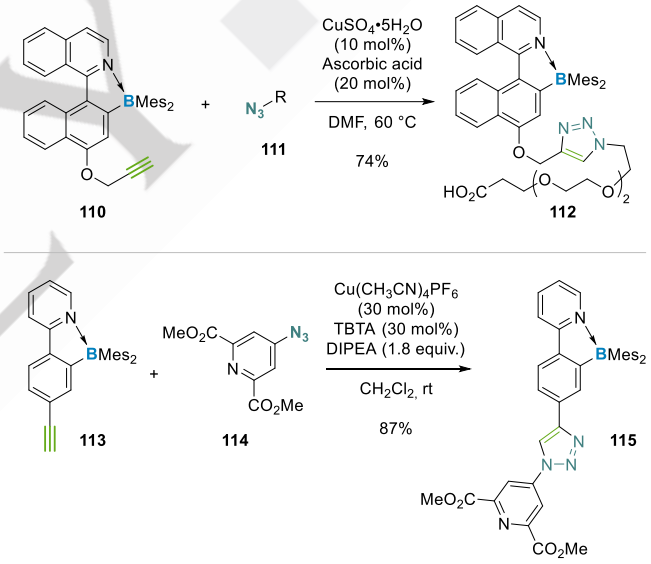
Scheme 24. CuAAC on mono- and di-alkynyl triarylboranes **104a-b**.

A series of conjugated triazole-coordinated triarylboranes **109a-c** were prepared from dialkynyl bis borane **107** in the presence of CuI (15 mol%) and DIPEA (Scheme 25).[73] An excess of aryl azide, and running the reaction at 70 °C were necessary to achieve complete conversion of **107**, probably because of the steric hindrance caused by the dimesitylboryl groups. Nevertheless, various substituted aryl azides were found to be compatible, providing **109a-c** with yields ranging from 29 to 81%. This synthetic approach was also applied to the preparation of polymers starting from 1,12-diazidodecane (not shown).[73]



Scheme 25. Synthesis of triazole-coordinated triarylboranes **109a-c** by CuAAC.

In the previous scenario, the boron coordinating group emerges during the triazole formation process. It is noteworthy that CuAAC can be directly conducted on coordinated triarylboranes, as depicted with the functionalization of luminescent triarylboranes **112**, bearing a carboxylic acid-terminated polyethylene glycol to enhance its water solubility (Scheme 26).[74] The CuAAC reaction was performed with $CuSO_4$ and ascorbic acid, leading to **112** in 74% yield. A similar 1,3-dipolar cycloaddition was harnessed to prepare photochromic organoborane ligand for lanthanide complexes. The same catalytic system failed to give good results likely due to the competing chelation with the pyridine unit. However, the combination of $Cu(CH_3CN)_4PF_6$ with TBTA and DIPEA yielded triazole **115** in an excellent 87% yield.[75]

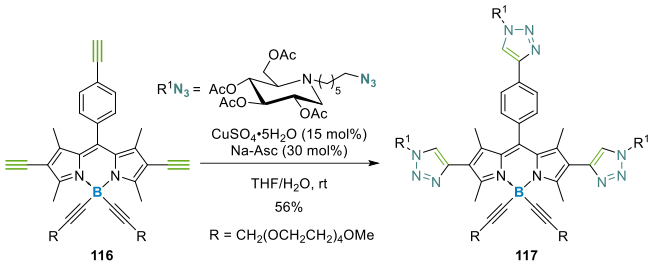


Scheme 26. CuAAC on tetracoordinated triarylboranes **110** and **113**.

5. Others organoboranes

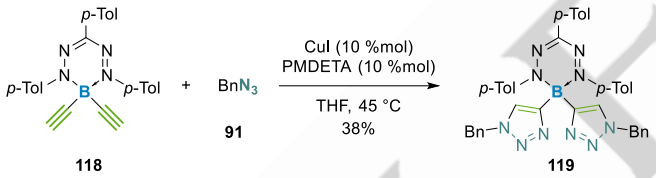
Fluoride-substituted boron dipyrromethenes (BODIPY) and azadipyrromethene (aza-BODIPY) are a widely studied class of molecular dyes among the *N*,*N* π-conjugated tetracoordinate boron compounds. They have been extensively used in CuAAC to prepare fluorescence probes and imaging agents as well as luminescent materials.[76] In the context of *N*,*N*-chelate of organoboranes (containing at least one C–B bond), the CuAAC has been applied to BODIPY containing either an azido[77] or an alkynyl group. A representative example is shown in Scheme 27 with the three-fold cycloaddition of dialkynylborane complex **116**.[78] Initial attempts to carry out the CuAAC reaction with $CuBr{\cdot}SMe_2$ at room temperature resulted in a complex mixture.

However, $CuSO_4$ and sodium ascorbate gave better results under carefully degassed conditions, leading to the desired product **117** in modest 56% yield after silica gel purification. The main by-product observed is likely to be the cycloadduct formed between the azidoiminosugar and the terminal alkyne, arising from the cleavage of the C–B bond.



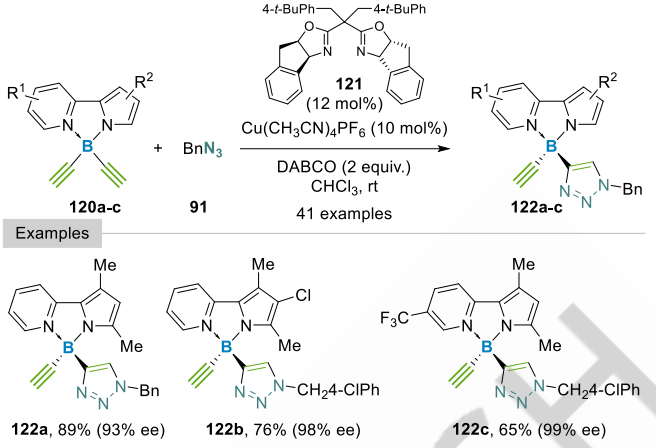
Scheme 27. Three-fold CuAAC of triyne BODIPY **116**.

Due to their properties, formazanate BF_2 complexes are becoming increasingly popular as replacements for BODIPYs. They are currently used in polymer science but also as dye for NIR-II fluorescence imaging.[79] In this regard, Gilroy *et al.* conducted a study on a range of dialkynyl formazanate borane complexes to investigate their properties and reactivities. They showed that terminal bis-alkynes **118** reacted with benzyl azide **91** in presence of CuI (10 mol%) and PMDETA to give bis-(triazolyl)borane **119** in 38% yield (Scheme 28).[80][81] The authors attributed the deceiving yield to the sterically congested environment around the boron.



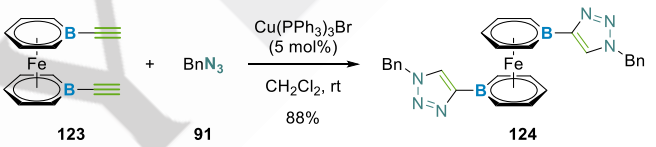
Scheme 28. CuAAC of formazanate dialkynylborane complex **118**.

Recently, an original application of enantioselective CuAAC has been described on *N,N*-chelated dialkynylboranes **120a-c** to create stereogenic tetracoordinated boron compounds through a desymmetrization process (Scheme 29).[82] The reaction was carried out in presence of 10 mol% of $Cu(CH_3CN)_4PF_6$, indane-fused BOX ligand **121** bearing two pendant bulky benzyl groups, and DABCO in chloroform. Up to 41 examples of chiroptical triazolyl organoboranes **122a-c** exhibiting bright fluorescence and circular polarized luminescence properties have been reported. These compounds were typically prepared with good yields and excellent enantioselectivities.



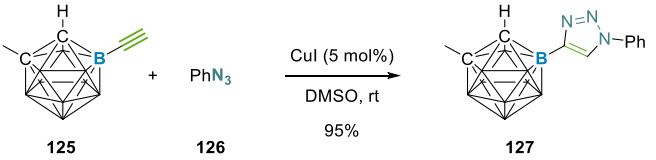
Scheme 29. Desymmetrization of **120a-c** by enantioselective CuAAC.

With the aim of preparing metallopolymers, Jäkle outlined a double CuAAC involving the unusual dialkynyl boratabenzene iron(II) complex **123** (Scheme 30).[83] Employing a 5 mol% loading of $Cu(PPh_3)_3Br$ catalyst, bis-triazole **124** was isolated with 88% yield, demonstrating the compatibility of this substrate under these specific conditions.



Scheme 30. Two-fold CuAAC with boratabenzene iron complexe **123**.

B-Alkynylated *o*-carborane **125**, a class of carbon-boron clusters, has also proven to be suitable for the click reaction with phenyl azide **126**.[84] Under simple reaction conditions (5 mol% CuI in DMSO), cycloadduct **127** was isolated in an impressive 95% yield.



Scheme 31. CuAAC with of B-alkynylated *o*-carborane **125**.

6. Summary and Outlook

The CuAAC reaction has attracted considerable interest and applications over the past decade, and is now widely used within organic, medical and bioorganic chemistry, as well as in materials science. However, when applied to organoboron compounds, the CuAAC still presents some challenges due to the propensity for copper to insert into the C–B bond and mediates degradation. Along the years, the studies have allowed to decipher the reactivity of organoboranes in the CuAAC. The boron group can still be preserved from this side-reaction, either by adjusting the reaction conditions (i.e. use of fluoride) and/or the nature of the substituents onto the boron atom. As a general trend,

organoboranes with reduced Lewis acidity, coordinated to a Lewis base or sterically hindered are generally less prone to protodeboronation and lead to better efficiency. Among the catalytic systems, CuX (with X = I, Br, Cl) and $CuSO_4$/Na-Asc are the most common, employed with or without stabilizing ligands such TBTA. A few examples illustrate the use of complexes soluble in organic solvent ($Cu(PPh_3)_3X$ with X = Br, F) or cationic complexes ($Cu(CH_3CN)_4X$ with X = PF_6, BF_4). Interestingly, the aforementioned complex, associated to a chiral ligand, was used in the enantioselective synthesis of boron-stereogenic compounds, which open new avenues in the field of organoboranes with chiroptical properties. Beyond the copper-catalyzed cycloaddition, it should be mentioned that the Huisgen azide alkyne [3+2]-cycloaddition with organoboranes have also been reported with strained alkynes[85] or under thermal conditions.[86] An appealing, yet underexplored field is the ruthenium-catalyzed azide alkyne cycloaddition with organoboranes that would provide a complementary approach to the CuAAC. Indeed, the RuAAC is not only selective for the formation of 1,5-disubstituted 1,2,3-triazoles, but also compatible with internal alkynes. Although the reactivity of some other organoboron reagents is still to be explored, overall the CuAAC have already greatly expanded the utility of organoboranes with exciting applications in imaging, medicinal chemistry or materials science.

Acknowledgements

The authors are grateful to the University of Bordeaux, CNRS and ANR (ANR-19-CE06-0003), for financial support.

Keywords: boron • click chemistry • copper catalysis • cycloaddition • organoborane •

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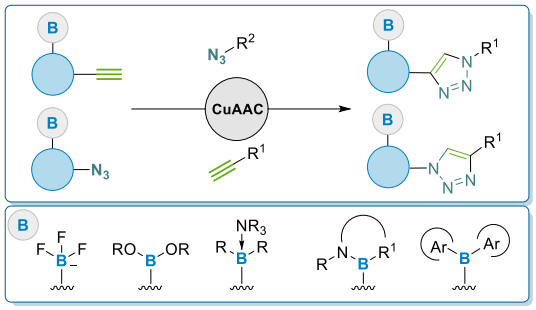

This review presents an overview of the advancements in Cu-catalysed azide alkyne [3+2]-cycloaddition reactions with organoboranes. It discusses the different organoboron groups employed and their stability under CuAAC.