Synthesis of 1,2,3-triazol-1-yl-methaneboronic acids via click chemistry: an easy access to a new potential scaffold for protease inhibitors

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Abstract
Stereoselective synthesis of previously unreported 1,2,3-triazol-1-yl-methaneboronic acids has been achieved from azidomethaneboronates by Copper-catalyzed Azide-Alkyne Cycloaddition (CuAAC). The proximity of the cycloaddition reaction center to the boronic group is not detrimental for the stability of the $sp^3$-carbon-boron bond nor to the stereoisomeric composition, further expanding the field of application of click chemistry to new boronate substrates and offering a new potential scaffold for protease inhibitors.

Keywords
boron; Cu-catalyzed Azide-Alkyne Cycloaddition; click chemistry; bioisoster

Introduction
$\alpha$-Amidomethaneboronic acid is a recurring core-structure in biologically active and important boron-containing compounds. [1] After the approval of Velcade® (Figure 1a, A) and clarification on safety issue relatively to boron containing compounds, the use of this element in pharmaceutical research has become an attractive “hot” topic. As a result, several boron derivatives are currently in preclinical and clinical stage development.[2] Amongst others boronic acids exhibit excellent properties as competitive and reversible protease inhibitors. Due to their unique structural features, they act as transition state analogs: boron, with its open shell, interacts with nucleophilic active residues and in doing so converts from a neutral trigonal structure to an anionic tetrahedral adduct, which mimics the high-energy intermediate of the amide hydrolysis process. Whereas boron moiety acts as the “warhead” blocking the catalytic site, the $\alpha$-amido group enhances molecular recognition by mimicking natural substrates.[3]

$\alpha$-Amidomethaneboronate unit is the basic structure of peptidoboronic acids, a class of peptidomimetics largely explored to target different clinically relevant proteases. For example, the anticancer Velcade® (A) is a dipeptidyl boronic acid (Phe-boroLeu) acting as...
proteasome inhibitor, while derivatives of the type Val-boroPro or Pro-boroAla have been investigated as dipeptidyl peptidase-4 inhibitors for the treatment of diabetes.\textsuperscript{[4]} The same skeleton is part also of simpler acylamidomethaneboronic acids, reported as subtilisin and α-chymotripsin inhibitors and used as fluorescent carbohydrate sensors.\textsuperscript{[5]} In accordance with these developments, we investigated acylamidomethaneboronic acids B and C (Figure 1a) as potent and selective β-lactamase inhibitors.\textsuperscript{[6]}

In the course of our investigation, we were intrigued by the effect of α-amido group replacement with 1,4-disubstituted 1,2,3-triazole, which is a largely validated non-classical amide bioisostere (Figure 1b). These two groups share several chemical properties such as planarity, size, dipole moment and hydrogen-bond capabilities. However, they also have important differences: triazole hopping can restrict conformational flexibility and improve hydrolysis and oxidation stability.\textsuperscript{[7]} Furthermore, 1,2,3-triazoles 1,4-disubstituted are easily accessible through Copper-catalyzed Azide-Alkyne Cycloaddition (CuAAC). The latter is regarded as the click chemistry \textit{par excellence}, because it proceeds in mild conditions, using inexpensive reagents, with high versatility, high efficiency and simple product isolation.\textsuperscript{[8]} For all these reasons, click chemistry is gaining an ever-growing popularity in drug discovery and the use of triazole as amide surrogate is entering routine structure-activity relationship studies.\textsuperscript{[9]}

Surprisingly, this strategy has never been applied to α-amidomethaneboronic acids. A literature search of 1,2,3-triazol-1-yl-methaneboronic acids reveals that this is an unexplored scaffold. Investigation in this field has probably been discouraged by the known ability of copper to insert into the carbon-boron bond. Actually, this activation is exploited in several useful cross-coupling reactions, such as in a copper-variant of the Suzuki-Miyaura and in the Chan-Lam C-N and CO coupling with boronates.\textsuperscript{[10]} However, when undesired, it can leads to degradation promoting protodeboronation. To date some efforts on click reaction applied to boron derivatives have been done, but restricted to arylboronates, probably due to their greater availability and stability. Moreover, in these cases the alkyne and azide involved in CuAAC are remote with respect to the boronic moiety and the few examples reported in the literature do not proceed without difficulty. In some cases, unique approaches must be tried to succeed, such as fluoride addition to stabilize the carbon-boron bond or even inversion of the step sequence inserting the boron atom only after CuAAC was performed.\textsuperscript{[11]} On the other side, the literature reports a single case where the boronic group was directly linked to the alkyne, producing a 1,2,3-triazole-4-boronate.\textsuperscript{[12]}

Given this state of the art, the first milestone of our project was the assessment of 1,2,3-triazol-1-yl-methaneboronic acids chemical feasibility: their synthesis is reported herein.

**Results and Discussion**

Initial experiments focused on the synthesis of the simplest boronic ester, corresponding to triazolyl analogs of acyl-boroGly (Scheme 1).

Starting from chloromethaneboronate 1,\textsuperscript{[13]} substitution with sodium azide catalyzed by tetrabutylammonium iodide as phase transfer agent, yields azidomethaneboronate 2 (97%).\textsuperscript{[14]} The use of (+)-pinanediol as boronic esterifying group is justified by its strong
stability to hydrolysis, that allows for instance the use of TLC as reaction monitoring method. First investigation of CuAAC feasibility on the azido intermediate 2 was performed choosing ethyl propiolate as acetylene counterpart, according to the general observation that \( \alpha \)-carbonyl- are more reactive than alkyl- or aryl-alkynes. Among the wide variety of conditions described in the literature for CuAAC, we selected three. In two cases the copper(I) catalyst was directly added in the presence of a ligand (CuI, DIPEA, THF, or CuI, lutidine, CHCl\(_3\)); in the third case the catalytically active metal was generated \textit{in situ} by reduction of copper sulfate (CuSO\(_4\), sodium ascorbate, \textit{tert}-butanol, H\(_2\)O). Each experiment was performed at room temperature for 6 hours with a molar ratio of 2 : ethyl propiolate : catalyst 1 : 1.5 : 0.1. The crude product was analyzed by \(^1\)H-NMR and LC-MS and the formation of the expected and previously unreported product 3a in almost complete conversion was observed in all of the three experiments, confirming the robustness of CuAAC. Nevertheless, when the CuI catalyst was adopted, the NMR spectra revealed the presence of proto-deboronation by-products (5-20%), and these were more pronounced when the more basic DIPEA rather than lutidine was used as ligand. However DIPEA could be easily removed from the crude under reduced pressure, while lutidine was not. A superior performance in terms of purity of the recovered material and absence of deboronation by-products was observed for the aqueous conditions, which were therefore applied to cycloadditions of 2 with several other alkynes, selected among the many available on the market, including carbonyl, aromatic and aliphatic alkynes. In the optimized procedure, the azide 2 and an excess of the alkyne (1.5 equiv.) were dissolved in a 1:1 mixture of \textit{tert}-butanol and water, together with copper sulfate (0.05 equiv) reduced \textit{in situ} by sodium ascorbate (0.2 equiv.). Cyclizations were carried out at room temperature and followed by TLC until disappearance of the starting azidomethaneboronate 2: complete conversions were reached in two hours with propiolic acid and ethyl propiolate (Table 1, entries 1-2), while longer reaction times (up to sixteen hours) were required for alky- and aryl-alkynes (Table 1, entries 3-5). The expected 1,4-disubstituted triazoles were easily isolated by extraction and removal of the residual alkyne under reduced pressure, affording 3a-e in good to excellent yields (85-99%) as highly pure material. Cyclization was confirmed by a singlet downfield in the aromatic region in the \(^1\)H NMR spectra and the expected 1,4-regioselectivity was supported by bidimensional spectroscopy (particularly the \(^3\)J\(_{C,H}\) correlation between protons on the boron-bearing carbon atom and the unsubstituted carbon of the triazole ring). Final deprotection of (+)-pinanediol was accomplished by transesterification with phenylboronic acid in a biphasic system acetonitrile/\textit{n}-hexane, allowing to obtain final boronic acids 4a-e, purified by crystallization from acetonitrile (80-100%).

The successful synthesis of these 1,2,3-triazol-1-yl-methaneboronic acids prompted us to expand our project toward chiral compounds introducing an \( \textit{R}_2 \)-substituent (see Figure 1b). To obtain an homochiral series with natural amino acids a stereoselective synthesis was required. At first we focused on triazolyl analogs of acyl-boroLeu bearing an isobutyl as \( \textit{R}_2 \) group (Scheme 2), a structure that is also part of Velcade® (A).

The configuration of the carbon in \( \alpha \) position to the boron is controlled through Matteson’ homologation of boronic esters, using (+)-pinanediol as chiral auxiliary agent. Following this procedure, isobutylboronate 5 was treated with dichloromethyl lithium
generated in situ at –100 °C for the insertion of an halogenated and asymmetrically substituted carbon on the carbon-boron bond. According to the literature, the use of (+)-pinanediol induced in 6 the S absolute configuration with high diastereoselectivity (d.e.>98%, 70%). Subsequent substitution with sodium azide afforded the azido boronate 7 (d.e.>98%, 97%). With respect to the synthesis of 2, the presence of a stereogenic center at the reactive site prevents using tetrabutylammonium iodide (TBAI) in favor of the non-nucleophilic tetrabutylammonium hydrogensulfate (TBAHS) to avoid epimerization (30% of undesired epimer using TBAI). Click reactions to 8a-e under the same conditions described for the synthesis of 3a-e performed equally well, without any effects on reaction efficiency neither in time reaction (2-16 h, see Experimental Section) nor in yields (81-97%). Most importantly, no effect on the diastereoisomeric composition was observed in the NMR spectra, as highlighted by comparison with spectra of 8a-e obtained starting from the epimeric mixture of 7. Final deprotection afforded enantiomerically pure triazolyl boronic acids 9a-e (Table 2, entries 1-5).

The same procedure was replicated for the synthesis of boroPhe analogs 18a-e and 19a-e (Scheme 3), bearing as R2 a benzyl or its meta-carboxy derivative, this latter being a recurring motif in β-lactamase inhibitors (Figure 1, C).

(+)-Pinanediol boronates 10 and 11 were subjected to two consecutive homologation steps: the first with chloromethylolithium for methylene insertion to 12 and 13, the second with dichloromethylolithium to introduce the halogenated carbon atom (14 and 15). Chlorine substitution with sodium azide in phase transfer conditions afforded 16 and 17. These key azido intermediates were then subjected to click reaction and deprotection to triazolyl analogs of acyl-boroPhe 18a-e and 19a-e (Table 2, entries 6-15).

The results reported in Table 2 indicates that the described procedure is reproducible and highly efficient, affording in all cases the expected triazolymethaneboronic acids in moderate to good overall yields as pure and stable solids that can be stored for months at +4 °C. The rate of CuAAC is not affected by the structure of azidomethaneboronates, but only by the electronic density of the alkyne partner: for a given alkyne, reaction times in fact are consistent for both primary (intermediate 2) and secondary azides (intermediates 16 and 17). Furthermore, for these latter derivatives cycloaddition reaction proceeds without any change in the diastereoisomeric composition, eventually affording enantiomerically-pure triazolymethaneboronic acids.

Conclusions

A synthetic procedure for enantiomerically-pure 1,2,3-triazol-1-yl-methaneboronic acids has been developed. This new scaffold can be obtained through CuAAC between stereoisomerically pure 1-azidoalkylboronates and terminal acetylenes, catalyzed by copper sulfate reduced in situ to Cu(I) by sodium ascorbate in tert-butanol/water system. In these conditions, the proximity of reaction center to the boronic group is not detrimental to the stability of the sp3 carbon-boron bond to copper(I) catalysis, further expanding the functional group compatibility of CuAAC beyond what is already known. Application of powerful click chemistry to boronates enables many analogs to be synthesized quickly.
Given the importance of α-amidomethaneboronic acids as proteases inhibitors, this efficient access to a new bioisosteric scaffold could promote further exploration of boronates as a promising class of biological active compounds.

**Experimental Section**

**General methods**

All reactions were performed under argon using oven-dried glassware and dry solvents. Dry tetrahydrofuran (THF) was obtained by standard methods and freshly distilled under argon from sodium benzenophenone ketyl prior to use. All of the reagents were used as purchased from commercial suppliers without further purification. The −100 °C bath was prepared by addition of liquid nitrogen to a pre-cooled (−78 °C) mixture of 1:1 ethanol/methanol. Preloaded (0.25 mm) glass supported silica gel plates (Kieselgel 60, Merck) were used for TLC analysis, and compounds were visualized by exposure to UV light and by dipping the plates in 1% Ce(SO$_4$)$_2$·4H$_2$O, 2.5% (NH$_4$)$_6$Mo$_7$O$_{24}$·4H$_2$O in 10% sulfuric acid followed by heating on a hot plate. Melting points were measured in open capillary tubes on a Stuart SMP30 Melting Point apparatus. Optical rotations were determined at +20 °C on a Perkin-Elmer 241 polarimeter and are expressed in 10$^{-1}$ deg cm$^2$ g$^{-1}$. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer. Chemical shifts (δ) are reported in ppm and were calibrated to the residual signals of the deuterated solvent.[20] Multiplicity is given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal; coupling constants (J) are given in Hz. Two-dimensional NMR techniques (COSY, HMBC, HSQC) were used to aid in the assignment of signals in $^1$H and $^{13}$C spectra. Particularly, in the $^{13}$C spectra, the signal of the boron-bearing carbon atom tends to be broadened, often beyond the detection limit; however, its resonance was always unambiguously determined by HSQC. Also the triazole ring carbon signals are often beyond the detection limit; when possible these were determined by HSQC and HMBC. High-resolution mass spectra were recorded on an Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS; elemental analysis were performed on a Carlo Erba Elemental Analyzer 1110.

**General procedure for CuAAC between azidomethaneboronates and terminal acetylenes**

Azidomethaneboronate (1.00 mmol), the selected terminal acryne (1.50 mmol), copper sulfate solution (50 mg/mL, 0.05 mmol) and sodium ascorbate (0.20 mmol) were dissolved in a 1:1 mixture of tert-Butanol and water (2.0 mL each). The reaction was magnetically stirred at room temperature for the proper time (2-16 hours as specified in each case), until disappearance of the azido boronate (TLC). The mixture was then partitioned between ethyl acetate (20 mL), water (10 mL) and saturated NaCl (8 mL); the aqueous phase extracted with ethyl acetate (2 × 20 mL). The pooled organic phases were washed with brine (15 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo, affording the expected 1,2,3-triazol-1-yl-methaneboronate.

**(+-)Pinanediol (4-ethoxycarbonyl-[1,2,3]triazol-1-yl)-methaneboronate (3a)**

Yellow viscous oil (reaction time 2h, 97%). [α]$^0_{D}$ = +13.6 (c 1.3, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): δ 0.76 (3H, s, pinanyl CH$_3$), 1.03 (1H, d, J = 11.1, pinanyl CH$_3$endo), 1.21 (3H, s, pinanyl CH$_3$), 1.32 (3H, t, J = 7.0, OCH$_2$CH$_3$), 1.35 (3H, s, pinanyl CH$_3$), 1.77-2.30 (5H,
m, pinanyl protons), 4.20 (2H, s, CH$_2$B), 4.29-4.35 (3H, m, CHOB, OCH$_2$CH$_3$), 8.19 (1H, s, CH$_{\text{triaz}}$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$14.2, 23.8, 26.4, 26.9, 28.3, 34.9, 35.9 (br, CB), 38.1, 39.2, 51.0, 61.0, 78.9, 87.7, 128.6, 139.9, 160.9. HRMS (ESI-TOF) m/z: [M+H]$^+$
Calcd for C$_{16}$H$_{25}$BN$_3$O$_4$ 334.1936; Found 334.1938.

**(+)-Pinanediol (4-carboxy-[1,2,3]triazol-1-yl)-methaneboronate (3b)**

White solid (reaction time 2h, 85%). Mp 110-113 °C dec. [\(\alpha\)]$_{D}^{20}$ = +16.6 (c 1.3, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$0.82 (3H, s, pinanyl CH$_3$), 1.08 (1H, d, J = 11.1, pinanyl H$_{\text{endo}}$), 1.27 (3H, s, pinanyl CH$_3$), 1.42 (3H, s, pinanyl CH$_3$), 1.84-2.37 (5H, m, pinanyl protons), 4.29 (2H, s, CH$_2$B), 4.39 (1H, dd, J = 8.7, 4.4, CHOB), 8.37 (1H, s, CH$_{\text{triaz}}$). $^1$C NMR (100 MHz, CDCl$_3$): $\delta$24.1, 26.6, 27.1, 28.5, 35.1, 36.3 (br, CB), 38.3, 39.4, 51.1, 79.2, 88.0, 129.5, 139.3, 164.1. HRMS (ESI-TOF) m/z: [M+H]$^+$
Calcd for C$_{14}$H$_{21}$BN$_3$O$_4$ 306.1622; Found 306.1624.

**(+)-Pinanediol (4-phenyl-[1,2,3]triazol-1-yl)-methaneboronate (3c)**

Yellow viscous oil (reaction time 16h, 99%). [\(\alpha\)]$_{D}^{20}$ = +13.0 (c 2.2, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$0.83 (3H, s, pinanyl CH$_3$), 1.15 (1H, d, J = 11.1, pinanyl H$_{\text{endo}}$), 1.28 (3H, s, pinanyl CH$_3$), 1.43 (3H, s, pinanyl CH$_3$), 1.85-2.37 (5H, m, pinanyl protons), 4.24 (2H, s, CH$_2$B), 4.39 (1H, dd, J = 8.7, 1.8, CHOB), 7.29 (1H, t, J = 7.4, H$_{\text{Arom}}$), 7.39 (2H, t, J = 7.9, H$_{\text{Arom}}$), 7.82 (2H, d, J = 7.4, H$_{\text{Arom}}$), 7.89 (1H, s, CH$_{\text{triaz}}$). $^1$C NMR (100 MHz, CDCl$_3$): $\delta$24.0, 26.5, 27.0, 28.5, 35.1, 35.6 (br, CB), 38.2, 39.4, 51.1, 78.9, 87.5, 121.0, 125.7, 127.9, 128.8, 131.0, 147.6. HRMS (ESI-TOF) m/z: [M+H]$^+$
Calcd for C$_{19}$H$_{25}$BN$_3$O$_3$ 338.2038; Found 338.2031.

**(+)-Pinanediol (4-thiophen-3-yl-[1,2,3]triazol-1-yl)-methaneboronate (3d)**

Yellow viscous oil (reaction time 16h, 92%). [\(\alpha\)]$_{D}^{20}$ = +10.2 (c 0.9, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$0.83 (3H, s, pinanyl CH$_3$), 1.14 (1H, d, J = 11.1, pinanyl H$_{\text{endo}}$), 1.28 (3H, s, pinanyl CH$_3$), 1.43 (3H, s, pinanyl CH$_3$), 1.85-2.37 (5H, m, pinanyl protons), 4.23 (2H, s, CH$_2$B), 4.38 (1H, dd, J = 8.8, 1.7, CHOB), 7.34 (1H, dd, J = 5.0, 2.9, CHCHS), 7.45 (1H, dd, J = 5.0, 1.1, CHCHS), 7.64 (1H, dd, J = 2.9, 1.1, CHCHS), 7.79 (1H, s, CH$_{\text{triaz}}$). $^1$C NMR (100 MHz, CDCl$_3$): $\delta$24.0, 26.6, 27.0, 28.5, 35.1, 35.8 (br, CB), 38.2, 39.4, 51.1, 78.9, 87.6, 120.8, 120.9, 126.0, 126.1, 132.3, 143.8. HRMS (ESI-TOF) m/z: [M+H]$^+$
Calcd for C$_{17}$H$_{23}$BN$_3$O$_2$S 344.1602; Found 344.1610.

**(+)-Pinanediol (4-phenoxymethyl-[1,2,3]triazol-1-yl)-methaneboronate (3e)**

Yellow viscous oil (reaction time 8h, 97%). [\(\alpha\)]$_{D}^{20}$ = +13.1 (c 2.1, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$0.85 (3H, s, pinanyl CH$_3$), 1.13 (1H, d, J = 11.1, pinanyl H$_{\text{endo}}$), 1.30 (3H, s, pinanyl CH$_3$), 1.43 (3H, s, pinanyl CH$_3$), 1.85-2.39 (5H, m, pinanyl protons), 4.22 (2H, s, CH$_2$B), 4.39 (1H, dd, J = 8.8, 1.8, CHOB), 5.21 (2H, s, OCH$_2$), 6.96 (1H, t, J = 7.3, H$_{\text{Arom}}$), 7.00 (2H, d, J = 8.7, H$_{\text{Arom}}$), 7.28 (2H, dd, J = 8.7, 7.3, H$_{\text{Arom}}$), 7.77 (1H, s, CH$_{\text{triaz}}$). $^1$C NMR (100 MHz, CDCl$_3$): $\delta$24.0, 26.5, 27.0, 28.5, 35.1, 35.8 (br, CB), 38.2, 39.4, 51.1, 62.1, 78.9, 87.5, 114.9, 121.2, 124.1, 129.5, 143.9, 158.4. HRMS (ESI-TOF) m/z: [M+H]$^+$
Calcd for C$_{20}$H$_{27}$BN$_3$O$_3$ 368.2144; Found 368.2139.
General procedure for deprotection of pinanediol boronate esters via transesterification

To a solution of 1,2,3-triazol-1-yl-methaneboronate (0.50 mmol) in CH$_3$CN (3 mL), HCl (3M aqueous solution, 1.50 mmol), phenylboronic acid (0.47 mmol) and n-hexane (3 mL) were sequentially added and the resulting biphasic solution was vigorously stirred. After 30 min the n-hexane layer, containing the pinanediol phenylboronate, was removed and fresh n-hexane (3 mL) was added. This last procedure was repeated several times until a TLC analysis of the n-hexane layer not revealed anymore phenylboronate production (total reaction time 3 hours). The acetonitrile phase was then concentrated and the crude recrystallized from acetonitrile to afford 1,2,3-triazol-1-yl-methaneboronic acid.

The enantiomeric purity of chiral boronic acids was checked by reconversion into their pinanediol esters. In particular final compounds 9a-e, 18a-e and 19a-e were allowed to react with an equimolar amount of (+)-pinanediol in anhydrous THF: the NMR spectra of the crude products displayed the presence of a single diastereoisomer, proving that no epimerization occurred during transesterification.

(4-Ethoxycarbonyl-[1,2,3]triazol-1-yl)-methaneboronic acid (4a)
White solid (80%). Mp 123-125 °C dec. $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 1.38 (3H, t, $J = 7.1$, OCH$_2$C$_6$H$_5$), 4.27 (2H, s, CH$_2$B), 4.38 (2H, q, $J = 7.1$, OC$_2$H$_5$CH$_3$), 8.38 (1H, s, CH$_{triaz}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 14.6, 39.3 (br, CB), 62.1, 130.5, 140.4, COOEt not seen. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_6$H$_{11}$BN$_3$O$_4$ 200.0838; Found 200.0840.

(4-Carboxy-[1,2,3]triazol-1-yl)-methaneboronic acid (4b)
White solid (80%). Mp 236-240 °C dec. $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 4.26 (2H, s, CH$_2$B), 8.39 (1H, s, CH$_{triaz}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 39.9 (br, CB), 130.7, 140.6, 163.3. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_4$H$_7$BN$_3$O$_4$ 172.0525; Found 172.0518.

(4-Phenyl-[1,2,3]triazol-1-yl)-methaneboronic acid (4c)
Grey solid (98%). Mp 122-124 °C dec. $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 4.48 (2H, s, CH$_2$B), 7.56-7.60 (3H, m, H$_{Arom}$), 7.83 (2H, dd, $J = 7.8$, 1.7, H$_{Arom}$), 8.78 (1H, s, CH$_{triaz}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 42.6 (br, CB), 126.0, 126.8, 127.6, 130.7, 131.9, 144.7. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_9$H$_{11}$BN$_3$O$_2$ 204.0941; Found 204.0940.

(4-Thiophen-3-yl-[1,2,3]triazol-1-yl)-methaneboronic acid (4d)
White solid (100%). Mp 170-172 °C dec. $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 4.47 (2H, s, CH$_2$B), 7.55 (1H, dd, $J = 5.1$, 1.1, CHCHS), 7.69 (1H, dd, $J = 5.1$, 2.8, CHCHS), 8.08 (1H, dd, $J = 2.8$, 1.1, CCHS), 8.70 (1H, s, CH$_{triaz}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 42.7 (br, CB), 126.4, 126.5, 126.6, 127.0, 129.6, 140.4. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_7$H$_9$BN$_3$O$_2$S 210.0504; Found 210.0498.

(4-Phenoxymethyl-[1,2,3]triazol-1-yl)-methaneboronic acid (4e)
White solid (100%). Mp 128-131 °C dec. $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 4.44 (2H, s, CH$_2$B), 5.33 (2H, s, OCH$_2$), 7.01 (1H, t, $J = 7.4$, H$_{Arom}$), 7.05 (2H, dd, $J = 8.7$, 0.8, H$_{Arom}$).
(+-)Pinanediol (1R)-1-azido-3-methylbutaneboronate (7)

To a solution of 6 [21] (800 mg, 2.81 mmol) in ethyl acetate (10 mL), sodium azide (1.83 g, 28.1 mmol), tetrabutylammonium hydrogensulfate (475 mg, 1.40 mmol) and water (24 mL) were added and the system was vigorously stirred at room temperature overnight. The mixture was then diluted with saturated ammonium chloride : water (1:1, 40 mL) and extracted twice with light petroleum (60 mL, 30 mL). The combined organic phases were washed again with saturated ammonium chloride : water (1:1, 20 mL), dried over Na₂SO₄ and filtered. Removal of solvent in vacuo afforded 7 as a colourless oil (794 mg, 97% yield). [α]²⁰D = −7.13 (c 1.7, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ 0.83 (3H, s, pinanyl CH₃), 0.92 (3H, d, J = 6.6, CH(CH₃)₂), 0.93 (3H, d, J = 6.6, CH(CH₃)₂), 1.09 (1H, d, J = 11.0, pinanyl Hendo), 1.28 (3H, s, pinanyl CH₃), 1.45 (1H, ddd, J = 14.0, 8.5, 5.4, BCH₂CH₂), 1.63 (1H, ddd, J = 14.0, 10.0, 5.4, BCH₂CH₂), 1.76-1.83 (1H, m, CH(CH₃)₂), 1.85-2.37 (5H, m, pinanyl protons), 3.11 (1H, dd, J = 6.5, CH(CH₃)₂), 3.62 (1H, d, J = 11.1, pinanyl Hendo), 1.25 (3H, s, pinanyl CH₃), 1.28-1.34 (1H, m, CH(CH₃)₂), 1.38 (3H, s, pinanyl CH₃), 1.38 (3H, s, pinanyl CH₃), 1.71-2.34 (7H, m, pinanyl protons, BCH₂CH₂), 4.32 (1H, d, J = 8.7, CHOB), 4.39 (2H, q, J = 7.0, OCH₂CH₃), 4.60 (1H, dd, J = 10.3, 5.5, BCH), 8.16 (1H, d, CHtriad). ¹³C NMR (100 MHz, CDCl₃): δ 34.21, 21.4, 22.8, 24.0, 25.0, 26.5, 27.0, 28.5, 35.2, 38.2, 39.3, 39.5, 46.4 (br, CB), 51.2, 78.5, 86.9. Anal. Calcd. for C₁₅H₂₃BN₃O₂: C, 61.87; H, 9.00; N, 14.43. Found: C, 61.66; H, 9.21; N, 14.29.

(+-)Pinanediol (1R)-1-(4-ethoxycarbonyl-[1,2,3]triazol-1-yl)-3-methylbutaneboronate (8a)

According to the general procedure reported above, CuAAC reaction between azido boronate 7 and ethyl propiolate (click reaction time 2h) afforded 8a as a yellow viscous oil (reaction time 2h, 89%). [α]²⁰D = +25.0 (c 0.9, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.80 (3H, s, pinanyl CH₃), 0.83 (3H, d, J = 6.6, CH(CH₃)₂), 0.90 (3H, d, J = 6.5, CH(CH₃)₂), 1.03 (1H, d, J = 11.1, pinanyl Hendo), 1.25 (3H, s, pinanyl CH₃), 1.28-1.34 (1H, m, CH(CH₃)₂), 1.38 (3H, s, pinanyl CH₃), 1.38 (3H, s, pinanyl CH₃), 1.71-2.34 (7H, m, pinanyl protons, BCH₂CH₂), 4.32 (1H, d, J = 8.7, CHOB), 4.39 (2H, q, J = 7.0, OCH₂CH₃), 4.60 (1H, dd, J = 10.3, 5.5, BCH), 8.16 (1H, d, CHtriad). ¹³C NMR (100 MHz, CDCl₃): δ 34.21, 21.4, 22.8, 24.0, 25.0, 26.5, 27.0, 28.5, 35.2, 38.2, 39.3, 39.4, 41.4, 47.1 (br, CB), 51.1, 61.2, 78.9, 87.6, 127.5, 140.1, 161.2. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₂₀H₃₃BN₃O₄ 390.2562; Found 390.2563.

(+-)Pinanediol (1R)-1-(4-carboxy-[1,2,3]triazol-1-yl)-3-methylbutaneboronate (8b)

Yellow viscous oil (reaction time 2h, 91%). [α]²⁰D = +19.5 (c 1.4, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.82 (3H, s, pinanyl CH₃), 0.86 (3H, d, J = 6.4, CH(CH₃)₂), 0.94 (3H, d, J = 6.3, CH(CH₃)₂), 1.04 (1H, d, J = 11.1, pinanyl Hendo), 1.28 (3H, s, pinanyl CH₃), 1.32-1.37 (1H, m, CH(CH₃)₂), 1.41 (3H, s, pinanyl CH₃), 1.83-2.37 (7H, m, pinanyl protons, BCH₂CH₂), 4.35 (1H, d, J = 8.7, 1.5, CHOB), 4.65 (1H, dd, J = 10.3, 5.5, BCH), 8.33 (1H, s, CHtriad), 8.74 (1H, br, COOH). ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 22.9, 24.0, 25.1, 26.5, 27.1, 28.5, 35.2, 38.3, 39.4, 41.4, 47.7 (br, CB), 51.1, 79.0, 87.8, 128.3, 139.4, 164.0. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C₁₈H₂₀BN₃O₄ 362.2249; Found 362.2254.

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(+-)Pinanediol (1R)-3-methyl-1-(4-phenyl-[1,2,3]triazol-1-yl)butaneboronate (8c)

Yellow viscous oil (reaction time 16h, 81%). [a]D = +11.8 (c 1.8, CHCl3). 1H NMR (400 MHz, CDCl3): δ 0.84 (3H, s, pinanyl CH3), 0.88 (3H, d, J = 6.6, CH(CH3)2), 0.97 (3H, d, J = 6.5, CH(CH3)2), 1.13 (1H, d, J = 11.0, pinanyl Hendo), 1.29 (3H, s, pinanyl CH3), 1.33-1.41 (1H, m, CH(CH3)2), 1.42 (3H, s, pinanyl CH3), 1.73-2.38 (7H, m, pinanyl protons, BCHCH2), 4.37 (1H, dd, J = 8.7, 1.6, CHOB), 4.60 (1H, dd, J = 10.5, 5.6, BCH), 7.31 (1H, t, J = 7.5, HArom), 7.41 (2H, t, J = 7.5, HArom), 7.85 (2H, d, J = 7.5, HArom), 7.86 (1H, s, Ctriiaz). 13C NMR (100 MHz, CDCl3): δ 21.6, 23.0, 24.1, 25.2, 26.6, 27.1, 28.6, 35.3, 38.3, 39.5, 41.6, 46.5 (br, CB), 51.2, 78.9, 87.4, 119.7, 125.8, 128.0, 128.9, 131.2, 147.5. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C23H33BN3O3 394.2665; Found 394.2671.

(+-)Pinanediol (1R)-3-methyl-1-(4-thiophen-3-yl-[1,2,3]triazol-1-yl)butaneboronate (8d)

Yellow viscous oil (reaction time 16h, 85%). [α]D = +13.1 (c 1.6, CHCl3). 1H NMR (400 MHz, CDCl3): δ 0.84 (3H, s, pinanyl CH3), 0.87 (3H, d, J = 6.6, CH(CH3)2), 0.96 (3H, d, J = 6.5, CH(CH3)2), 1.12 (1H, d, J = 11.0, pinanyl Hendo), 1.29 (3H, s, pinanyl CH3), 1.33-1.38 (1H, m, CH(CH3)2), 1.42 (3H, s, pinanyl CH3), 1.72-2.37 (7H, m, pinanyl protons, BCHCH2), 4.36 (1H, d, J = 7.2, CHOB), 4.58 (1H, dd, J = 10.5, 5.5, BCH), 7.36 (1H, dd, J = 4.8, 2.8, CHCHS), 7.48 (1H, d, J = 4.8, CHCHS), 7.67 (1H, d, J = 2.8, CHS), 7.75 (1H, s, Ctriiaz). 13C NMR (100 MHz, CDCl3): δ 21.5, 23.0, 24.0, 25.1, 26.5, 27.1, 28.6, 35.3, 38.3, 39.5, 41.6, 46.6 (br, CB), 51.2, 78.8, 87.4, 119.5, 120.8, 126.0, 126.1, 132.4, 143.7. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C21H31BN3O2S 400.2228; Found 400.2225.

(+-)Pinanediol (1R)-3-methyl-1-(4-phenoxy methyl-3-yl-[1,2,3]triazol-1-yl)butaneboronate (8e)

Yellow viscous oil (reaction time 8h, 97%). [α]D = +17.0 (c 1.3, CHCl3). 1H NMR (400 MHz, CDCl3): δ 0.83 (3H, s, pinanyl CH3), 0.85 (3H, d, J = 6.6, CH(CH3)2), 0.94 (3H, d, J = 6.5, CH(CH3)2), 1.07 (1H, d, J = 11.0, pinanyl Hendo), 1.28 (3H, s, pinanyl CH3), 1.30-1.36 (1H, m, CH(CH3)2), 1.40 (3H, s, pinanyl CH3), 1.70-2.36 (7H, m, pinanyl protons, BCHCH2), 4.34 (1H, dd, J = 8.7, 1.8, CHOB), 4.55 (1H, dd, J = 10.2, 5.8, BCH), 5.21 (2H, s, OCH2), 6.96 (1H, t, J = 7.4, HArom), 6.99 (2H, d, J = 7.9, HArom), 7.28 (2H, t, J = 7.6, HArom), 7.69 (1H, s, Ctriiaz). 13C NMR (100 MHz, CDCl3): δ 21.5, 22.9, 24.0, 25.1, 26.5, 27.1, 28.5, 35.2, 38.3, 39.4, 41.5, 46.8 (br, CB), 51.2, 62.4, 78.8, 87.4, 115.0, 121.2, 122.8, 129.5, 144.0, 158.5. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C24H35BN3O3 424.2770; Found 424.2788.

(1R)-1-(4-ethoxycarbonyl-[1,2,3]triazol-1-yl)-3-methylbutaneboronic acid (9a)

Following the general procedure reported above, pinanediol removal from 8a via transesterification afford 9a as a white solid (76% yield). Mp 115-117 °C dec. [α]D = +9.2 (c 0.8, CH2OH). 1H NMR (400 MHz, CD3OD): δ 0.84 (3H, d, J = 6.5, CH(CH3)2), 0.92 (3H, d, J = 6.4, CH(CH3)2), 1.14-1.24 (1H, m, CH(CH3)2), 1.37 (3H, t, J = 6.8, OCH2CH3), 1.70-1.76 (1H, m, BCHCH2), 1.90-1.97 (1H, m, BCHCH2), 4.38 (2H, q, J = 6.8, OCH2CH3), 4.53 (1H, dd, J = 10.8, 3.8, BCH), 8.54 (1H, s, Ctriiaz). 13C NMR (100 MHz,
CD$_3$OD): $\delta$ 14.5, 21.4, 23.3, 26.2, 41.7, 51.3 (br, CB), 62.1, 129.4, 140.5, 162.2. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{10}$H$_{19}$N$_3$O$_4$ 256.1465; Found 256.1468.

(1R)-1-(4-Carboxy-[1,2,3]triazol-1-yl)-3-methylbutaneboronic acid (9b)

White solid (95%). Mp 123-127 °C dec. $[\alpha]_{D}^{20}$ = +4.5 (c 0.4, CH$_3$OH). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 0.86 (3H, d, $J$ = 6.6, CH(CH$_3$)$_2$), 0.94 (3H, d, $J$ = 6.5, CH(CH$_3$)$_2$), 1.20-1.27 (2H, m, CH(CH$_3$)$_2$), 1.72 (2H, m, CH(CH$_3$)$_2$), 1.94 (1H, d, $J$ = 14.3, 11.2, 4.7, BCH$_2$), 1.58 (1H, dd, $J$ = 11.2, 4.5, BCH$_2$), 8.51 (1H, s, CH$_{\text{triaz}}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 21.4, 23.3, 26.3, 41.7, 51.1 (br, CB), 129.8, 141.0, 163.1. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_8$H$_{15}$BN$_3$O$_4$ 228.1152; Found 228.1148.

(1R)-3-Methyl-1-(4-phenyl-[1,2,3]triazol-1-yl)-butaneboronic acid (9c)

Cream-colored solid (80%). Mp 127-132 °C dec. $[\alpha]_{D}^{20}$ = +8.0 (c 0.5, CH$_3$OH). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 0.92 (3H, d, $J$ = 6.6, CH(CH$_3$)$_2$), 0.98 (3H, d, $J$ = 6.5, CH(CH$_3$)$_2$), 1.31-1.38 (1H, m, CH(CH$_3$)$_2$), 1.84 (1H, d, $J$ = 14.6, 9.3, 4.1, BCH$_2$), 2.14 (1H, d, $J$ = 14.6, 11.5, 4.5, BCH$_2$), 2.69 (1H, d, $J$ = 11.5, 4.1, BCH$_2$), 7.51-7.58 (3H, m, H$_{\text{Arom}}$), 7.86 (2H, d, $J$ = 6.8, H$_{\text{Arom}}$), 8.94 (1H, s, CH$_{\text{triaz}}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 21.3, 23.3, 26.3, 40.8, 54.6 (br, CB), 125.7, 126.1, 127.6, 130.7, 131.9, 145.0. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{13}$H$_{19}$BN$_3$O$_2$ 260.1567; Found 260.1563.

(1R)-3-Methyl-1-(4-thiophen-3-yl-[1,2,3]triazol-1-yl)-butaneboronic acid (9d)

Cream-colored solid (92%). Mp 130-132 °C dec. $[\alpha]_{D}^{20}$ = +6.2 (c 0.6, CH$_3$OH). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 0.91 (3H, d, $J$ = 6.6, CH(CH$_3$)$_2$), 0.98 (3H, d, $J$ = 6.5, CH(CH$_3$)$_2$), 1.26-1.38 (1H, m, CH(CH$_3$)$_2$), 1.82 (1H, d, $J$ = 14.6, 9.3, 4.3, BCH$_2$), 2.10 (1H, d, $J$ = 14.6, 11.5, 4.6, BCH$_2$), 4.66 (1H, d, $J$ = 11.5, 4.3, BCH$_2$), 7.67 (1H, d, $J$ = 4.2, CHCHS), 7.66 (1H, d, $J$ = 5.1, 2.8, CHCHS), 8.04 (1H, d, $J$ = 2.0, CCHS), 8.78 (1H, s, CH$_{\text{triaz}}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 21.3, 23.3, 26.3, 40.9, 54.3 (br, CB), 125.1, 126.3, 126.5, 127.3, 129.3, 141.3. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{11}$H$_{17}$BN$_3$O$_2$S 266.1131; Found 266.1137.

(1R)-3-Methyl-1-(4-phenoxymethyl-3-yl-[1,2,3]triazol-1-yl)-butaneboronic acid (9e)

White solid (77%). Mp 118-123 °C dec. $[\alpha]_{D}^{20}$ = +2.9 (c 1.2, CH$_3$OH). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 0.87 (3H, d, $J$ = 6.6, CH(CH$_3$)$_2$), 0.95 (3H, d, $J$ = 6.5, CH(CH$_3$)$_2$), 1.20-1.29 (1H, m, CH(CH$_3$)$_2$), 1.73 (1H, d, $J$ = 14.5, 9.1, 4.5, BCH$_2$), 1.97 (1H, d, $J$ = 14.5, 11.3, 4.6, BCH$_2$), 1.94 (1H, d, $J$ = 11.3, 4.5, BCH$_2$), 5.24 (2H, s, OCH$_2$), 6.98 (1H, tt, $J$ = 7.4, 1.0, H$_{\text{Arom}}$), 7.02 (2H, d, $J$ = 8.7, 1.0, H$_{\text{Arom}}$), 7.30 (2H, dd, $J$ = 8.7, 7.4, H$_{\text{Arom}}$), 8.30 (1H, s, CH$_{\text{triaz}}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 21.4, 23.3, 26.3, 41.4, 51.9 (br, CB), 61.4, 116.1, 122.7, 126.6, 130.6, 143.3, 159.3. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{14}$H$_{21}$BN$_3$O$_3$ 290.1673; Found 290.1673.

(+)-Pinanediol (1R)-1-azido-2-phenylethanaboronate (16)

Starting from 14 $^{[17]}$ and following the procedure described for the synthesis of 7, compound 16 was recovered as a yellowish oil (94%). $[\alpha]_{D}^{20}$ = +8.7 (c 1.0, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.83 (3H, s, pinanyl CH$_3$), 0.98 (1H, d, $J$ = 11.0, pinanyl H$_{\text{endo}}$), 1.29 (3H, 7, $J$ = 14.5, 9.1, 4.5, BCH$_2$), 1.94 (1H, d, $J$ = 11.3, 4.5, BCH$_2$), 5.24 (2H, s, OCH$_2$), 6.98 (1H, tt, $J$ = 7.4, 1.0, H$_{\text{Arom}}$), 7.02 (2H, d, $J$ = 8.7, 1.0, H$_{\text{Arom}}$), 7.30 (2H, dd, $J$ = 8.7, 7.4, H$_{\text{Arom}}$), 8.30 (1H, s, CH$_{\text{triaz}}$). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 21.4, 23.3, 26.3, 41.4, 51.9 (br, CB), 61.4, 116.1, 122.7, 126.6, 130.6, 143.3, 159.3. HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{14}$H$_{21}$BN$_3$O$_3$ 290.1673; Found 290.1673.

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s, pinanyl CH$_3$), 1.38 (3H, s, pinanyl CH$_3$), 1.85-2.37 (5H, m, pinanyl protons), 2.95 (1H, dd, $J$ = 14.0, 9.0, BCHCH$_2$), 3.03 (1H, dd, $J$ = 14.0, 5.7, BCHCH$_2$), 3.38 (1H, dd, $J$ = 9.0, 5.7, BCH), 4.33 (1H, dd, $J$ = 8.7, 1.7, CHOB), 7.19-7.32 (5H, m, H$_{Arom}$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 24.1, 26.5, 27.1, 28.6, 35.3, 36.9, 38.3, 39.5, 49.8 (br, CB), 51.2, 78.7, 87.1, 126.8, 128.6, 129.3, 138.8. Anal. Calcd. for C$_{13}$H$_{24}$BN$_3$O$_2$: C, 66.48; H, 7.44; N, 12.92. Found: C, 66.25; H, 7.68; N, 12.72.

### (+)-Pinanediol (1R)-1-azido-2-[(3-tert-butoxycarbonylphenyl)phenyletheneboronate (17)

Starting from 15 [17] and following the procedure described for the synthesis of 7, compound 17 was recovered as a yellowish oil (97%). [α]$^{20}_D$ = +11.9 (c 1.8, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.82 (3H, s, pinanyl CH$_3$), 0.93 (1H, d, $J$ = 11.0, pinanyl H$_{endo}$), 1.27 (3H, s, pinanyl CH$_3$), 1.37 (3H, s, pinanyl CH$_3$), 1.59 (9H, s, tBu), 1.86-2.38 (5H, m, pinanyl protons), 2.99 (1H, dd, $J$ = 13.9, 8.5, BCHCH$_2$), 3.05 (1H, dd, $J$ = 13.9, 6.0, BCHCH$_2$), 3.39 (1H, dd, $J$ = 8.5, 6.0, BCH), 4.34 (1H, d, $J$ = 7.6, CHOB), 7.34 (1H, t, $J$ = 7.7, H$_{Arom}$), 7.44 (1H, d, $J$ = 7.7, H$_{Arom}$), 7.86 (1H, d, $J$ = 7.7, H$_{Arom}$), 7.89 (1H, s, H$_{Arom}$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 24.0, 26.4, 27.1, 28.3, 28.5, 35.2, 36.7, 38.2, 39.5, 49.5 (br, CB), 51.1, 78.7, 81.0, 87.1, 128.0, 128.4, 130.2, 132.3, 133.4, 138.8, 165.7. Anal. Calcd. for C$_{23}$H$_{33}$BN$_3$O$_4$: C, 64.95; H, 7.58; N, 9.88. Found: C, 65.18; H, 7.81; N, 9.64.

### (1R)-1-(4-Ethoxycarbonyl-[1,2,3]triazol-1-yl)-2-phenyletheneboronic acid (18a)

According to the general procedures reported above, CuAAC reaction between azido boronate 16 and ethyl propiolate (click reaction time 2h) followed by deprotection of pinanediol boronate ester via transesterification afford 18a as a white solid (75% overall yield). Mp 147-149 ºC dec. [α]$^{20}_D$ = −53.7 (c 1.1, CH$_3$OH). $^1$H NMR (400 MHz, CD$_2$OD): $\delta$ 1.34 (3H, t, $J$ = 7.1, OCH$_2$CH$_3$), 3.20 (1H, dd, $J$ = 14.0, 9.9, BCHCH$_2$), 3.25-3.31 (1H, m, BCHCH$_2$ and CD$_3$OD), 4.33 (2H, q, $J$ = 7.1, OCH$_2$CH$_3$), 4.62 (1H, dd, $J$ = 9.9, 4.9, BCH), 6.97 (2H, d, $J$ = 7.0, H$_{Arom}$), 7.14-7.20 (3H, m, H$_{Arom}$), 8.16 (1H, s, CH$_{triaz}$). $^{13}$C NMR (100 MHz, CD$_2$OD): $\delta$ 14.5, 39.2, 55.4 (br, CB), 62.2, 127.7, 129.5, 129.7, 130.4, 139.3, 162.3, C-4 triazole ring not seen. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{17}$BN$_3$O$_4$ 290.1309; Found 290.1295.

### (1R)-1-(4-Carboxy-[1,2,3]triazol-1-yl)-2-phenyletheneboronic acid (18b)

White solid (click reaction time 2h, 85% overall yield). Mp 120-122 ºC dec. [α]$^{20}_D$ = −43.4 (c 1.0, CH$_2$OH). $^1$H NMR (400 MHz, CD$_2$OD): $\delta$ 3.18 (1H, dd, $J$ = 14.0, 10.0, BCHCH$_2$), 3.27-3.32 (1H, m, BCHCH$_2$ and CD$_3$OD), 4.68 (1H, dd, $J$ = 10.0, 5.6, BCH), 7.00 (2H, d, $J$ = 6.6, H$_{Arom}$), 7.14-7.22 (3H, m, H$_{Arom}$), 8.15 (1H, s, CH$_{triaz}$). $^{13}$C NMR (100 MHz, CD$_2$OD): $\delta$ 39.3, 53.5 (br, CB), 127.8, 129.5, 129.8, 130.3, 139.2, 140.4, 163.2. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{11}$H$_{13}$BN$_3$O$_4$ 262.0996; Found 262.0994.

### (1R)-1-(4-Phenyl-[1,2,3]triazol-1-yl)-2-phenyletheneboronic acid (18c)

White solid (click reaction time 16h, 70% overall yield). Mp 151-153 ºC dec. [α]$^{20}_D$ = −62.3 (c 1.3, CH$_2$OH). $^1$H NMR (400 MHz, CD$_2$OD): $\delta$ 3.25-3.31 (1H, m, BCHCH$_2$ and CD$_3$OD), 3.39 (1H, dd, $J$ = 14.1, 5.7, BCHCH$_2$), 4.84 (1H, dd, $J$ = 10.0, 5.7, BCH), 7.12 (2H, d, $J$ = 6.9, H$_{Arom}$), 7.16-7.25 (3H, m, H$_{Arom}$), 7.44-7.52 (3H, m, H$_{Arom}$), 7.73 (2H, d, J $\delta$ 9.9, 4.9, BCH), 6.97 (2H, d, $J$ = 7.0, H$_{Arom}$), 7.14-7.20 (3H, m, H$_{Arom}$), 8.16 (1H, s, CH$_{triaz}$). $^{13}$C NMR (100 MHz, CD$_2$OD): $\delta$ 14.5, 39.3, 55.4 (br, CB), 127.8, 129.5, 129.8, 130.3, 139.2, 140.4, 163.2. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{17}$BN$_3$O$_4$ 290.1309; Found 290.1295.
[1R]-2-Phenyl-1-(4-thiophen-3-yl-[1,2,3]triazol-1-yl)-ethaneboronic acid (18d)

Cream-colored solid (click reaction time 16h, 80% overall yield). Mp 141-143 °C dec. [α]D 20 = −67.3 (c 1.1, CH3OH). 1H NMR (400 MHz, CD3OD): δ3.25-3.32 (1H, m, BCHCH2 and CD3OD), 3.40 (1H, dd, J = 14.2, 5.7, BCHCH2), 4.87 (1H, dd, J = 10.6, 5.7, BCH), 7.13 (2H, d, J = 6.9, HAr), 7.17-7.25 (3H, m, HAr), 7.47 (1H, d, J = 5.0, HAr), 7.63 (1H, dd, J = 5.0, 2.8, HAr), 7.94 (1H, d, J = 1.9, HAr), 8.57 (1H, s, CHtri). 13C NMR (100 MHz, CD3OD): δ38.7, 56.7 (br, CB), 125.3, 126.0, 126.5, 127.5, 128.1, 129.1, 129.7, 129.8, 138.6, 141.5. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C14H15BN3O2S 300.0975; Found 300.0987.

[1R]-2-Phenyl-1-(4-phenoxymethyl-3-yl-[1,2,3]triazol-1-yl)-ethaneboronic acid (18e)

White solid (click reaction time 2h, 55% overall yield). Mp 108-110 °C dec. [α]D 20 = −54.9 (c 1.2, CH3OH). 1H NMR (400 MHz, CD3OD): δ1.35 (3H, t, J = 7.1, OCH2CH3), 3.24 (1H, dd, J = 14.0, 10.0, BCHCH2), 3.34 (1H, dd, J = 14.0, 5.2, BCHCH2), 4.34 (2H, q, J = 7.1, OCH2CH3), 4.75 (1H, m, BCH), 7.26 (1H, d, J = 7.6, HAr), 7.33 (1H, t, J = 7.6, HAr), 7.69 (1H, s, HAr), 7.85 (1H, d, J = 7.6, HAr), 8.23 (1H, s, CHtri). 13C NMR (100 MHz, CD3OD): δ14.5, 39.1, 54.4 (br, CB), 62.1, 128.5, 129.2, 129.6, 130.3, 131.2, 134.5, 139.9, 162.1, 169.4, C-4 triazole ring not seen. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C14H15BN3O6 334.1517; Found 334.1513.

[1R]-1-(4-Carboxy-[1,2,3]triazol-1-yl)-2-(3-carboxyphenyl)ethaneboronic acid (19a)

According to the general procedures reported above, the product of CuAAC reaction between azido boronate 17 and ethyl propiolate (click reaction time 2h) was firstly subjected to tert-butyl group removal (TFAA 25% v/v in DCM, 2 mL, rt, 5h) followed by deprotection of pinanediol boronate ester via transesterification affording 19a as a white solid (64% overall yield). Mp 157-159 °C dec. [α]D 20 = 54.9 (c 1.2, CH3OH). 1H NMR (400 MHz, CD3OD): δ1.35 (3H, t, J = 7.1, OCH2CH3), 3.24 (1H, dd, J = 14.0, 10.0, BCHCH2), 3.34 (1H, dd, J = 14.0, 5.2, BCHCH2), 4.34 (2H, q, J = 7.1, OCH2CH3), 4.75 (1H, m, BCH), 7.26 (1H, d, J = 7.6, HAr), 7.33 (1H, t, J = 7.6, HAr), 7.69 (1H, s, HAr), 7.85 (1H, d, J = 7.6, HAr), 8.23 (1H, s, CHtri). 13C NMR (100 MHz, CD3OD): δ14.5, 39.1, 54.4 (br, CB), 62.1, 128.5, 129.2, 129.6, 130.3, 131.2, 134.5, 139.9, 162.1, 169.4, C-4 triazole ring not seen. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C14H17BN3O6 334.1204; Found 334.1208.

[1R]-2-(3-Carboxyphenyl)-1-(4-ethoxycarbonyl-[1,2,3]triazol-1-yl)-ethaneboronic acid (19b)

White solid (click reaction time 2h, 55% overall yield). Mp 108-110 °C dec. [α]D 20 = −54.9 (c 1.2, CH3OH). 1H NMR (400 MHz, CD3OD): δ3.26 (1H, dd, J = 14.0, 10.1, BCHCH2), 3.31-3.41 (1H, m, BCHCH2 and CD3OD), 4.71 (1H, br, BCH), 7.22 (1H, d, J = 7.7, HAr), 7.32 (1H, t, J = 7.7, HAr), 7.71 (1H, s, HAr), 7.84 (1H, d, J = 7.7, HAr), 8.18 (1H, s, CHtri). 13C NMR (100 MHz, CD3OD): δ39.1, 53.9 (br, CB), 128.5, 129.2, 129.6, 131.2,
132.2, 134.6, 139.9, 140.8, 163.5, 169.6. HRMS (ESI-TOF) m/z: [M–H]– Calcd for C_{12}H_{11}BN_3O_6 304.0749; Found 304.0739.

(1R)-2-(3-carboxyphenyl)-1-(4-Phenyl-[1,2,3]triazol-1-yl)-ethaneboronic acid (19c)
White solid (click reaction time 16h, 79% overall yield). Mp 88-90 °C dec. [α]^{20}_D = –70.0 (c 1.0, CH₃OH). ^1H NMR (400 MHz, CD₃OD): δ 3.26-3.32 (1H, m, BCHC₂ and CD₃OD), 3.39 (1H, dd, J = 14.1, 5.8, BCHCH₂), 4.74 (1H, dd, J = 9.9, 5.8, BCH), 7.29-7.44 (5H, m, H_{Arom}), 7.71 (2H, d, J = 7.4, H_{Arom}), 7.76 (1H, s, H_{Arom}), 7.85 (1H, d, J = 7.2, H_{Arom}), 8.17 (1H, s, C₃H₄triaz). ^13C NMR (100 MHz, CD₃OD): δ 39.1, 54.0 (br, C₂B), 123.6, 126.8, 129.2, 129.7, 130.00, 130.06, 131.2, 132.2, 134.7, 140.0, 147.1, 169.6, C-4 triazole ring not seen. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C_{17}H_{17}BN_3O_4 338.1310; Found 338.1310.

(1R)-2-(3-carboxyphenyl)-1-(4-thiophen-3-yl-[1,2,3]triazol-1-yl)-ethaneboronic acid (19d)
Cream-colored solid (click reaction time 16h, 60% overall yield). Mp 185-187 °C dec. [α]^{20}_D = –69.4 (c 0.7, CH₃OH). ^1H NMR (400 MHz, CD₃OD): δ 3.32 (1H, dd, J = 14.2, 10.2, BCHC₂), 3.41 (1H, dd, J = 14.2, 5.6, BCHC₂), 4.76 (1H, dd, J = 10.2, 5.6, BCH), 7.30-7.44 (3H, m, H_{Arom}), 7.54 (1H, dd, J = 5.0, 2.9, H_{Arom}), 7.75 (1H, s, H_{Arom}), 7.79 (1H, d, J = 1.9, H_{Arom}), 7.84 (1H, d, J = 6.8, H_{Arom}), 8.28 (1H, s, C₃H₄triaz). ^13C NMR (100 MHz, CD₃OD): δ 38.8, 55.2 (br, C₂B), 124.1 (2C), 126.6, 128.3, 129.3, 129.7, 131.1, 132.2, 134.5, 134.6, 139.7, 142.9, 169.5. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C_{15}H_{15}BN_3O_4S 344.0874; Found 344.0873.

(1R)-2-(3-carboxyphenyl)-1-(4-phenoxymethyl-3-yl-[1,2,3]triazol-1-yl)-ethaneboronic acid (19e)
White solid (click reaction time 8h, 54% overall yield). Mp 182-184 °C dec. [α]^{20}_D = –37.1 (c 1.3, CH₃OH). ^1H NMR (400 MHz, CD₃OD): δ 3.21 (1H, dd, J = 14.1, 10.1, BCHC₂), 3.32 (1H, dd, J = 14.1, 5.6, BCHCH₂), 4.72 (1H, dd, J = 10.1, 5.6, BCH), 5.10 (2H, s, OCH₂), 6.92-6.96 (3H, m, H_{Arom}), 7.17-7.28 (4H, m, H_{Arom}), 7.71 (1H, s, H_{Arom}), 7.82 (1H, d, J = 7.7, H_{Arom}), 7.89 (1H, s, C₃H₄triaz). ^13C NMR (100 MHz, CD₃OD): δ 39.2, 53.6 (br, C₂B), 62.1, 116.0, 122.3, 127.1, 129.1, 129.6, 130.5, 131.2, 132.1, 134.6, 139.9, 159.6, 169.6, C-4 triazole ring not seen. HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C_{18}H_{19}BN_3O_5 368.1416; Found 368.1411.

Supplementary Material
Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

a. Examples of α-amidomethaneboronic acids found in biologically active compounds. b. Bioisosteric amide replacement with 1,2,3-triazole-1,4-disubstituted.
Scheme 1.
Synthesis of triazolyl analog of acyl-boroGly 3a. Tested conditions for CuAAC: a) CuI, DIPEA, THF; b) CuI, lutidine, CHCl₃; c) CuSO₄, Sodium ascorbate, tert-BuOH, H₂O.
Scheme 2.
Stereoselective synthesis of triazolyl analogs of acyl-boroLeu. (i) LiCHCl₂, ZnCl₂, THF, –100 °C→r.t.; (ii) NaN₃, TBAHS, EtOAc, H₂O, r.t.; (iii) Alkyne, CuSO₄, Sodium ascorbate, tert-BuOH, H₂O, r.t.; (iv) Phenylboronic acid, HCl, Acetonitrile, n-Hexane, r.t.
Scheme 3.
Stereoselective synthesis of triazolyl analogs of acyl-boroPhe. (i) LiCH$_2$Cl, THF, $-80$ °C→r.t.; (ii) LiCHCl$_2$, THF, $-100$ °C→r.t.; (iii) NaN$_3$, TBAHS, EtOAc, H$_2$O, r.t.; (iv) Alkyne, CuSO$_4$, Sodium ascorbate, tert-BuOH, H$_2$O, r.t.; (v) Phenylboronic acid, HCl, Acetonitrile, n-Hexane, r.t.
Table 1
Copper-catalyzed Azide-Alkyne Cycloaddition between α-azidomethaneboronate 2 and alkynes.

| Entry | R₁ | Click reaction | Deprotection |
|-------|----|----------------|--------------|
|       |    | Product | Time (h) | Yield (%) | Product | Yield (%) |
| 1     | 3a | 2 | 97 | 4a | 80 |
| 2     | 3b | 2 | 85 | 4b | 80 |
| 3     | 3e | 16 | 99 | 4e | 98 |
| 4     | 3d | 16 | 92 | 4d | 100 |
| 5     | 3e | 8 | 97 | 4e | 100 |
Table 2

Copper-catalyzed Azide-Alkyne Cycloaddition between chiral α-azidomethaneboronates and alkynes.

![Chemical Reaction Diagram]

| Entry | Product | R₂ | R₁ | Overall Yield (%) |
|-------|---------|----|----|------------------|
| 1     | 9a      |    |    | 68               |
| 2     | 9b      |    |    | 86               |
| 3     | 9c      |    |    | 65               |
| 4     | 9d      |    |    | 78               |
| 5     | 9e      |    |    | 75               |
| Entry | Product | $R_2$ | $R_1$ | Overall Yield (%) |
|-------|---------|-------|-------|-------------------|
| 6     | 18a     |       |       | 75                |
| 7     | 18b     |       |       | 85                |
| 8     | 18c     |       |       | 70                |
| 9     | 18d     | (boroPhe) |       | 80                |
| 10    | 18e     |       |       | 79                |
| 11    | 19a     | (boro-m-COOH-Phe) |       | 64                |
| Entry | Product | R₂ | R₁   | Overall Yield (%) |
|-------|---------|----|------|-------------------|
| 12    | 19b     |    |      | 55                |
| 13    | 19c     |    |      | 79                |
| 14    | 19d     |    |      | 60                |
| 15    | 19e     |    |      | 54                |