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Phenylboronic Acids

Isocyanide-Based Multicomponent Reactions of Free Phenylboronic Acids

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Abstract: Boronic acids are amongst the most useful synthetic intermediates, frequently used by modern drug design. However, their access and fast synthesis of libraries are often problematic. We present a methodology on the synthesis of drug-like scaffolds via IMCRs with unprotected phenylboronic acids. To demonstrate an application of our approach, we also performed one-pot Suzuki couplings on the primary MCR scaffolds. Moreover, we performed a thorough data-mining of the Cambridge Structural Database, revealing interesting geometrical features.

Introduction

Carbon's left neighbor in the periodic table boron, seems that has been neglected for many years. Even in nature, only few natural products are described, such as Boromycin.[1,2] Long in the domain of inorganic chemistry, boron has increasingly acquired an organic face.[3–5] Especially, boronic acids and their esters are of paramount importance to all facets of chemical science; from the Pd-catalyzed C-C Suzuki–Miyaura coupling reactions[6,7] and Petasis reaction[8] to metal-free catalysis, organic optoelectronic materials, pharmaceuticals and imaging agents.[9–11] Boronic acids, with appropriate substitution, are ideal to readily be converted from a neutral and trigonal planar sp^2 boron conformation to an anionic tetrahedral sp^3 boron under physiological conditions (pKa ranges 7–9). This property facilitates the use of boronic acid derivatives as enzyme inhibitors because they can mimic a tetrahedral sp^3-hybridized carbon atom in the transition state of enzyme-catalyzed hydrolytic processes. Moreover, based on this prosperity to engage various nucleophiles (alcohols or amines) with the empty *p*-orbital, allows boron to form a dative bond with many molecules of biological interest as carbohydrates and nucleic acids.[12–16] Despite the increasing interest in boron as an alternative to carbon in drug design the last decade,[15,17–20] boron in general has been overlooked by medicinal chemists even if there are five commercially available and late-stage clinical trials boronic acid-based drugs (Bortezomib, Ixazomib, Crisaborole, Tavaborole, Vaborbactam and VNRX-5133, Figure 1).[21,22] The perception of their potential intrinsic toxicity (although unproven),[23] and the late-stage functionalization of high-molecular weight boronic acids hamper their further utilization. Therefore, organoboron chemistry field is still underdeveloped; we neither have an extensive portfolio of chemical reactions to introduce boron into organic molecules, especially into complex molecular libraries for medicinal chemistry projects, nor do we have a good understanding of the compatibility of boron-containing molecules in common synthesis.[24] Unlike carboxylic acids which are ubiquitous in nature and inexpensive, boronic acids are almost entirely derived through synthesis.[24]

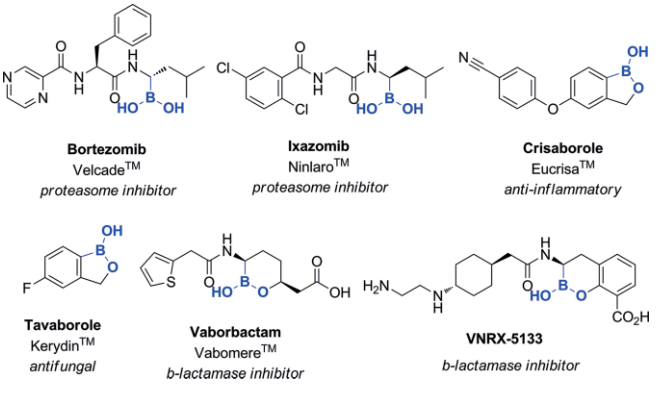

Figure 1. Commercially available and late-stage clinical trials boron-based drugs.

Our design should enable us, both to employ bifunctional unprotected phenylboronic acid derivatives into various isocyanide-based multi component reactions (IMCRs)[25] and directly perform post-modifications on those such as Suzuki couplings.[26] MCR-based synthesis gives us the opportunity to access a high degree of molecular complexity through minimal synthetic operations which is pivotal to the overall efficiency of

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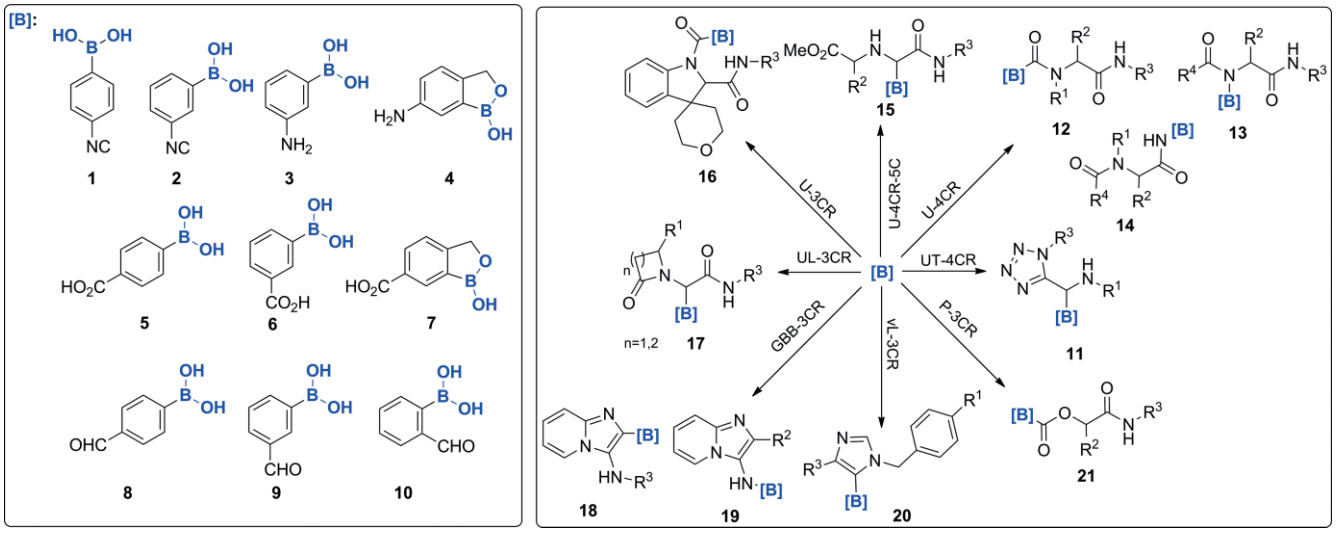


Figure 2. Overview of the bifunctional building blocks employed (left) along with the IMCRs performed (right). *Abbreviations*: U-4CR; Ugi-four component reaction (classical Ugi reaction), UT-4CR; Ugi-tetrazole-four component reaction, *P*3CR; Passerini three-component reaction, vL-3CR; van Leusen three-component imidazole synthesis, GBB-3CR; Gröbcke-Blackburn-Bienaymé three-component reaction, UL-3CR; Ugi-lactam three-component reaction, U-3CR; Ugi three-component reaction.

multistep organic syntheses.[27] Driven by the unmet need to develop chemoselective access to boron chemotypes[15] and to overcome all the issues of accessibility[28–30] and fast synthesis of large numbers of diverse derivatives, we describe herein the multi component reactions of free phenylboronic acids. Only scarce examples of IMCRs employing bifunctional substrates containing fully unprotected phenylboronic acids have so far been reported in literature without any extensive scope and limitation studies.[31–34]

In continuation and actually enhancement of our pioneer work on the high throughput screening via acoustic dispensing of complex boronic acids,[35] we employed the bifunctional boronic acid building blocks **1–10** (Figure 2, left) which bear the isocyano, amino, aldehyde and carboxy groups. In addition to the phenylboronic acids, we also utilize the benzoxaboroles **4** and **7** which consist of a benzene-fused oxaborole ring, introducing ring strain around the boron center.[36]

The synthesis of *p*- and *m*-isocyanophenylboronic acids, **1** and **2**, was accomplished by a classical formylation/dehydration procedure (see Supporting Information, SI) and - due to stability issues – immediately used after preparation. Using these boronic building blocks in combination with multiple complementary starting materials, we investigated a wide range of IMCRs (Figure 2, right); e.g. all the main Ugi variations; UT-4CR,[37] U-4CR,[38] U-4CR-5C,[39] U-3CR,[40] UL-3CR,[41] the GBB-3CR,[42–44] but also the van Leusen imidazole synthesis (vL-3CR)[45] and the Passerini reaction (*P*3CR)[46] (Figure 2).

Results and Discussion

The Ugi tetrazole variation (UT-4CR) gives easily access to tetrazole derivatives, which are very important to medicinal chemistry and drug design due to not only their bioisosterism to carboxylic acid and *cis*-amide moieties but also to their metabolic stability and other beneficial physicochemical properties.[47] Thus, we performed an UT-4CR with *p*-formyl-phenylboronic acid (**8**) yielding the adduct **11** in 85 % yield (Figure 3). Compound **11** combines the privileged tetrazole ring with the boronic acid moiety giving easy access to potential protease inhibitors.

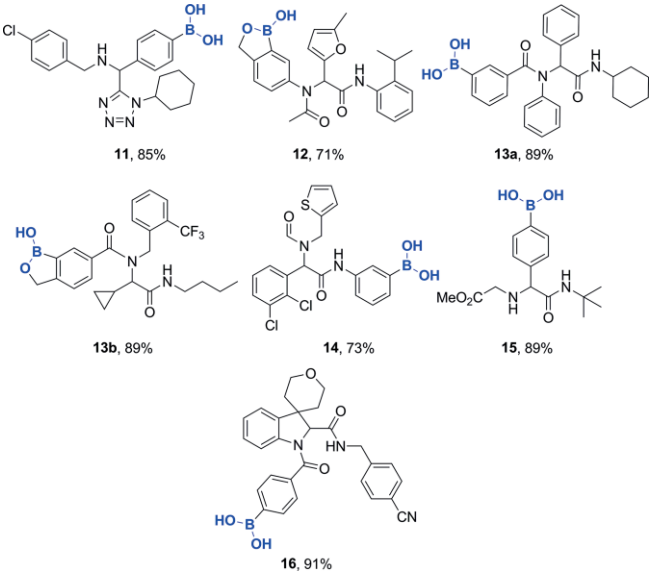


Figure 3. The UT-4CR adduct **11**; U-4CR adducts **12–14** utilizing different phenylboronic acids as the amine, acid and isocyanide component, respectively; the U-4CR-5C **15** with glycine; and the spiro indole **16** via an U-3CR.

The classical Ugi-4CR is the basis of an enormous number of secondary transformations. We used a diverse set of boronic building blocks such as **4**, **6**, **7** and **1** affording the peptidomimetics **12**, **13a**, **13b** and **14**, respectively (Figure 3).

Next, we synthesized an U-4CR-5C adduct, by employing an amino acid, glycine, and an alcohol (methanol from the solvent) yielding an iminodicarboxylic acid monoamide monoester, bearing the valuable boronic acid warhead **15** (Figure 3).

The spiroindole stands out as a privileged scaffold, represented not only in natural products but also in other bioactive compounds. For this reason, we wanted to insert the boronic acid functionality into this framework. Indeed, this type of U-3CR proceeded smoothly in a solvent combination of DCM/MeOH towards the spiro indole adduct **16** (Figure 3). In that variant of the classical Ugi reaction, a preformed cyclic imine (specifically a spiroindoline) is employed. All the aforementioned Ugi variations were run smoothly at r.t. for 24–48 h in good to excellent yields with great functional group tolerance.

The reaction of β- and γ-amino acids in the Ugi reaction yields strained β- and γ-lactams with widespread applications in both the synthesis of β-lactam antibiotics and other natural products, respectively. For that reason, we employed different β-amino acids or γ-aminobutyric acid[48] along with substituted formyl-phenylboronic acids (**8** and **9**) which under microwave conditions (100 °C, 1 h) afforded the lactams **17** in moderate to good yields (Figure 4). In case of the substituted β-amino acids, diastereomers (1:1) are formed.

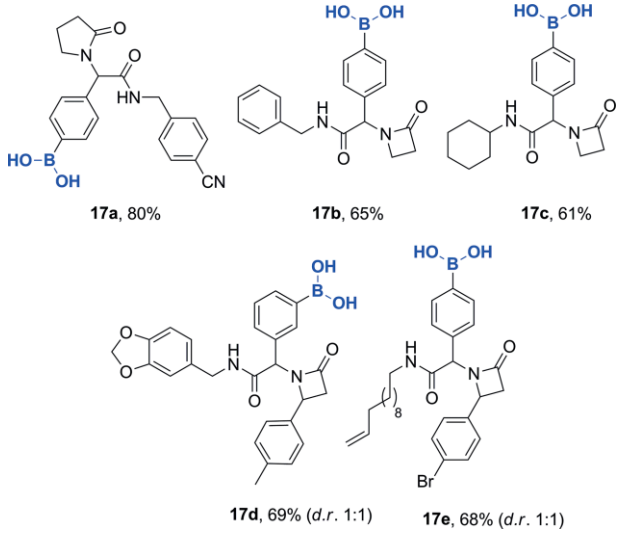


Figure 4. UL-3CR adducts **17a–e** utilizing 3- and 4-formylphenylboronic acids.

We also investigated the Gröbcke-Blackburn-Bienaymé (GBB-3CR) variant of the Ugi MCR using the 2-aminopyridine, the corresponding isocyanide from alanine methyl ester and the boronic acid **8** towards the derivative **18** (Figure 5). The isocyano phenylboronic acid **1**, in a one-pot fashion without further purification, also yielded the corresponding GBB adduct **19**. The reaction takes place either at r.t. or under MW conditions with $Sc(OTf)_3$ as catalyst.

The vL-3CR imidazole synthesis, which uses as reagent the tosylmethyl isocyanide (TosMIC) or substituted TosMICs,[49] is a very useful three component reaction towards 2- and 3-substituted imidazole derivatives. After quite some optimization (see SI) the formyl-phenylboronic acids (**8–10**) proved to be compatible with the basic reaction conditions, affording the very interesting imidazoles **20a-d** in good yields (Figure 5). Lastly, we successfully performed a *P*3̄CR, affording the derivative **21** in 70 % yield (Figure 5).

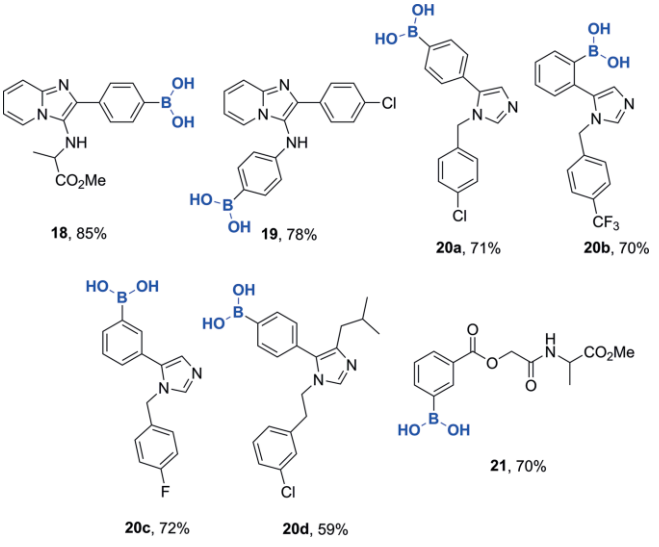
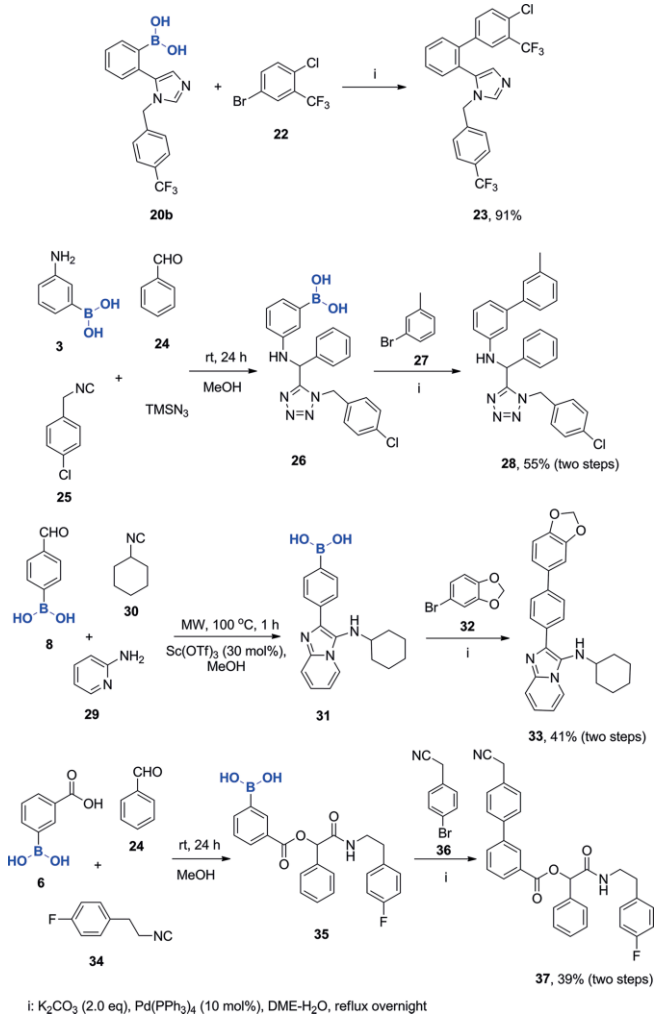


Figure 5. The GBB-3CR adducts **18**, **19**; vL-3CR adducts **20a-d** utilizing 2-, 3- and 4-formylphenylboronic acids; and the *P*3̄CR adduct **21**.

In all the aforementioned IMCRs we employed a set of different aromatic and aliphatic amines, aldehydes, acids and isocyanides. Moreover, we were able to uncover interesting reactivity details. Interestingly, formyl boronic acids react quite well, especially in the GBB reaction, with the exception of the *ortho*-substituted one. The *ortho* substituted formyl-derivatives reacted less efficient than the corresponding *meta* or *para* in all the described MCRs. A plausible reason would be that due to steric hindrance, the key step of Schiff base formation might be hampered or the possible formation of iminoboronate adducts. In addition, the monoester benzoxaboroles reacted in general, worse than their free derivatives, although their solubility was much better than the phenylboronic acids which might point to a catalytic effect of the boronic acid during these reactions.[50]

To underscore the usefulness of our approach, we envisioned to increase the complexity and diversity of our scaffolds. Boronic acids serve as an excellent hub for secondary transformations e.g. Suzuki C-C couplings. So, we successfully performed the Suzuki coupling of the imidazole derivative **20b** towards the compound **23** (Scheme 1). Next, we envisioned using a one-pot strategy; we performed an UT-4CR, GBB-3CR and *P*3̄CR and without purification of the intermediate MCR adduct, we continued with the Suzuki coupling, affording smoothly the derivatives **28**, **33** and **37** in very good yields in a fast manner (Scheme 1).

We were able to obtain the X-ray structures of compounds **17b** and **17c** (Figure 6). It is known that boronic acid derivatives can form dimeric units via an extended hydrogen bond network. This dimerization, as expected,[51] is observed in the crystal structure of **17b** (Figure 6, A). The hydrogen bond of O-H···O-H was measured at 2.0 Å whereas the extended hydrogen bond network can be seen in Figure 6. In the case of **17c**, one hydroxyl group was substituted by a methoxy group (55 % of the molecules) during the recrystallization process (see SI and Figure 6, B). This has an impact on the hydrogen bond network (approximately of 1.8 Å), since the aforementioned dimerization cannot be observed (see SI).



Scheme 1. Suzuki couplings as post-modifications of the phenylboronic acids IMCR adducts.

A data miming exercise of the Cambridge Structural Database (CSD)[52] revealed some of the geometrical features of similar phenylboronic acids (Figure 7, A). 282 Hits were found, which revealed that the average distance of C4–B3 (namely DIST1) is 1.58 Å and the B3–O1 (namely DIST2) is 1.37 Å. The average angle of O1–B3–O2 (namely ANG1) is 118.7° whereas the C4–B3–O1 (namely ANG 3) is 119.7° revealing the sp^2 character (Figure 7). The average torsion angle of H-O1–B3–O2 (namely TOR1) is 8° with a higher density of values, as expected, at ±180° and 0° (Figure 7). In this way, we confirm that the preferred H-O1–B3–O2 torsion angle is synperiplanar.

The comparison of ANG1 with TOR1 revealed that the angle ANG1 (O1–B3–O2) increases while the phenylboronic acid gets its coplanar conformation (TOR1: –180°/0°/+180°). This makes sense as the two oxygens are repulsed by each other (Figure 7, B). That fact is also verified by the comparison analysis of ANG1 and DIST2; the distance DIST2 (B3–O1) increases as the angle gets smaller. In the average bond length of 1.37 Å, the angle is increasing to ca. 118° (Figure 7, B). We also performed comparison analyses of the two planes of the aromatic ring and the boronic acid warhead, which were found to be almost coplanar

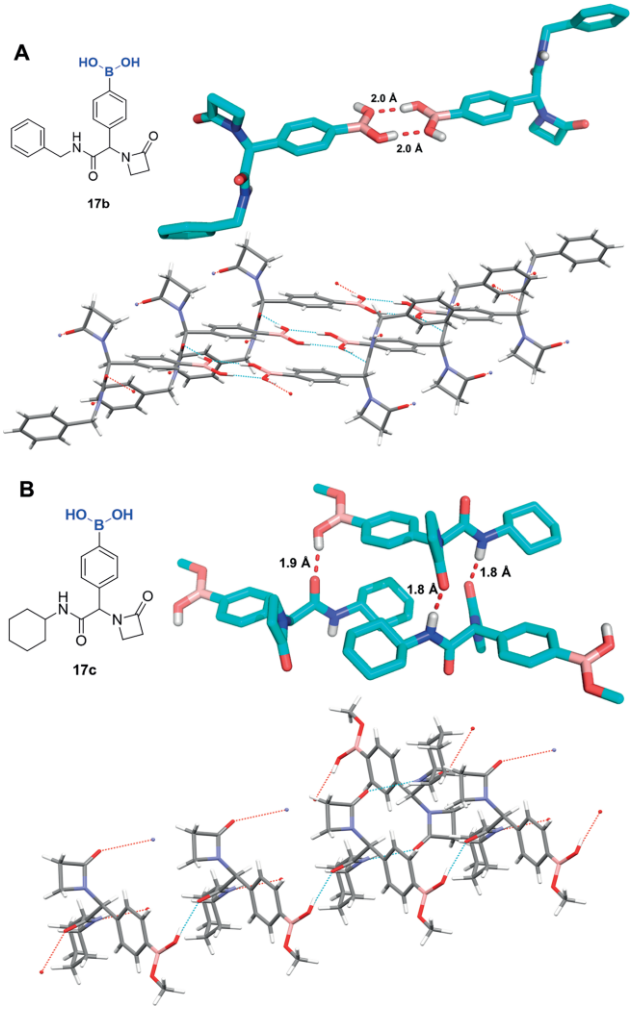


Figure 6. (A) Molecular geometry observed in the crystal structures of compound **17b** (CCDC 1825508), showing the atom labelling scheme and intermolecular hydrogen network of the dimer; (B) molecular geometry observed in the crystal structure of compound **17c** (CCDC 1819623), showing the atom labelling scheme. In the crystal structure, approximately 55 % of molecules are methylated in the boronic acid fragment.

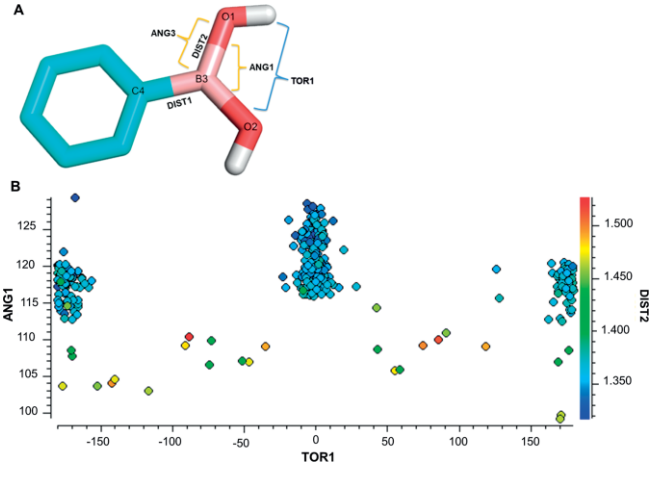


Figure 7. (A) Phenylboronic acids found in CSD (282 hits) and their geometrical features; (B) scatterplot of the ANG1 with TOR1 and DIST2, demonstrating that ANG1 gets its highest values when the conformation of boronic acid is almost coplanar while DIST2 (B3–O1) increases as the ANG1 gets smaller.

(0°-6°, see SI), except of some special cases of *o*-substituted phenylboronic acids. In addition, it was found that in the observed in CSD dimerization, the average intermolecular hydrogen bond O-H•••O-H is 2.4 Å with a coplanar conformation of the dimer (see SI).

Conclusion

We have shown the broad compatibility of free boronic acid building blocks in several IMCRs. It is significant, since very short syntheses can be established to complex molecules containing a free boronic acid. This is in contrast to the conventionally used strategy of late-stage-functionalization. A crystallographic analysis of boronic acids revealed their special geometrical features, along with the inter and intramolecular network of interactions, which could enhance the design of scaffolds with a specific binding mode. Since boronic acids are an upcoming class of bioactive molecules we predict that our findings will rapidly be adapted by the synthetic chemical community.

Experimental Section

General Methods

All the reagents and solvents were purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros and were used without further purification. All microwave irradiation reactions were carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography was performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 μm). Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometers {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)}. Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in Hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR were reported in ppm relative to the solvent peak. Flash chromatography was performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 × 250 mm, 5 μm particle size) or Viridis 2-ethyl pyridine column (4.6 × 250 mm, 5 μm particle size). High resolution mass spectra were recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400.

Experimental procedures, analytical data, single-crystal X-ray structure determination and analysis and data mining are given in the Supporting Information.

CCDC 1819623 (for **17b**), and 1825508 (for **17c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgments

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Keywords: Multicomponent reactions · Boron · Ugi reaction · C-C coupling · Structure elucidation

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