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Conference paper

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Influence of fluorine substituents on the properties of phenylboronic compounds

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Abstract: Rapid development of research on the chemistry of boronic acids is connected with their applications in organic synthesis, analytical chemistry, materials' chemistry, biology and medicine. In many applications Lewis acidity of boron atoms plays an important role. Special group of arylboronic acids are fluoro-substituted compounds, in which the electron withdrawing character of fluorine atoms influences their properties. The present paper deals with fluoro-substituted boronic acids and their derivatives: esters, benzoxaboroles and boroxines. Properties of these compounds, i.e. acidity, hydrolytic stability, structures in crystals and in solution as well as spectroscopic properties are discussed. In the next part examples of important applications are given.

Keywords: benzoxaboroles; boronic acids; fluorine substituent; IMEBORON-16.

Introduction

Arylboronic acids have huge importance in chemistry. They are applied among others in organic synthesis, electrochemistry, separation techniques, building fluorophores and sensors, polymers, materials' chemistry and pharmacy [1, 2]. These applications require particular compounds of specific properties, both physical and chemical, e.g. acidity, solubility, stability or possibility of functionalization. Fluoroarylboronic acids and their derivatives play an important role in the above-mentioned applications and their role is still growing.

Introduction of a fluorine substituent into organic compounds significantly changes their physical properties such as: heat of vaporization, critical temperature, density, viscosity and other. Even more important is the influence of fluorine atom on the chemical properties of a given molecule [3]. The extreme electronegativity of fluorine substituent induces a strong withdrawing inductive effect, making fluorine a σ-electron acceptor, whereas the electron-donating resonance effect of its lone-pair electrons allows the fluorine atom to be considered as a π-electron donor as well. These electronic properties originating from the presence of fluorine in the molecule make the effects on, for example, acidity and basicity. Fluorine is inductively electron-withdrawing but electron-donating by resonance, while perfluoroalkyl groups (e.g. CF_3) are only electron-withdrawing [4]. Fluorine substituents change also the quadrupole moment in aromatic ring [5, 6] and the lipophilicity of compound. The ability of fluorine to participate in formation of hydrogen bonds is crucial to biological activity of fluorochemicals [3].

History of scientific interest in a fluorophenylboronic acids goes back to the beginning of the nineties of the twentieth century and was connected with Suzuki-Miyaura reaction used to synthesize receptor

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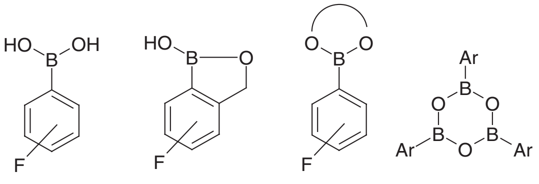


1 **2** **3** **4**

Scheme 1: Types of the compounds described in the paper (Ar=fluorinated aromatic ring).

antagonists [7] or enzyme inhibitors [8]. An interaction between fluorophenylboronic acid and some biologically significant ligands (i.e. NAD+, sorbitol, *L*-lactate) and enzyme – subtilisin was also investigated [9, 10].

As fluorinated boronic acids are used in various application, their properties are still explored. Basic research of fluorophenylboronic acid are focused on conformational analysis [11, 12], hydrogen bonding [11, 13–19] and acidity [14, 15, 20]. An important part of investigations is spectroscopic analysis – mainly by NMR [14–19, 21–23] and IR [13, 23], which in addition to characterize boronic acids [14, 15, 21, 23] can serve as a tool for studies of their complexation and aggregation [9, 10, 16–19, 22].

A more detailed discussion of numerous applications of fluoro-substituted phenylboronic acids is given later in this paper. The main areas are as follows:

- syntheses of fluorinated organic compounds, e.g. Suzuki-Miyaura cross-coupling or deboronation reaction [24–27],
- synthetic receptors used in detection of important analytes, e.g. fluoride anion, triethylamine, pyridine, glucose and dopamine [28–31],
- additives used to increase a conductivity of lithium ion battery electrolytes [32–39],
- building blocks in materials' chemistry to design special polymers or covalent organic frameworks (COF) systems [40–43],
- biologically active compounds used as antibacterial, antifungal or anticancer agents [44–49],
- application of the [^{10}B]borono-2-[^{18}F]fluoro-*L*-phenylalanine and its derivatives in Boron Neutron Capture Therapy, Positron Emission Tomography and Magnetic Resonance Imaging [50–62].

The subject of the present paper are fluoro-substituted phenylboronic acids (**1**) and their derivatives: benzoxaboroles (**2**), esters (**3**) and boroxines (**4**) (Scheme 1).

In the paper properties and application of these classes of boronic compounds are discussed.

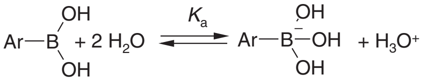
It is worth mentioning that there is a wide field of research related with application of boronic acids as fluoride ion receptors [63–68], which is not included in the current review.

Properties

Acidity

Boronic acids display Lewis acidic character described by equilibrium reaction (Scheme 2).

The increasing of electrophilic character of boron atom causes the rise of acidity of boronic acids [2], which can be achieved by introduction of electron withdrawing substituents into the aryl group. The pK_a values for fluoro-substituted phenylboronic compounds are collected in Table 1.



$$\mathrm{Ar{-}B(OH)_2} + 2\,\mathrm{H_2O} \overset{K_a}{\rightleftharpoons} \mathrm{Ar{-}B^{-}(OH)_3} + \mathrm{H_3O^+}$$

Scheme 2: Lewis acidity of boronic acids.

Table 1: pK_a values for fluoro-substituted phenylboronic compounds compared with unsubstituted compounds.

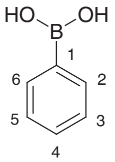
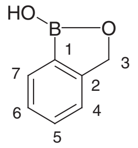
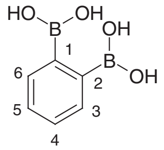
Substituents	pK_a	Method[a]	Reference
Boronic acids			
–	8.8	Spectr.	[69]
2-F	7.89±0.01	Spectr.	[70]
	7.85±0.07	Pot.	[70]
	7.83±0.02	Spectr.	[71]
3-F	8.09±0.01	Spectr.	[70]
	8.15±0.11	Pot.	[70]
	7.50±0.02	Spectr.	[71]
4-F	8.77±0.01	Spectr.	[70]
	8.71±0.10	Pot.	[70]
	8.66±0.05	Spectr.	[71]
	8.6	Spectr.	[69]
	9.1		[72]
2,3-F_2	6.99±0.04	Spectr.	[70]
	6.93±0.10	Pot.	[70]
2,4-F_2	7.75±0.01	Spectr.	[70]
	7.73±0.06	Pot.	[70]
	7.12±0.02	Spectr.	[71]
	7.6	Spectr.	[69]
2,5-F_2	7.06±0.03	Spectr.	[70]
	7.01±0.05	Pot.	[70]
	7.0	Spectr.	[69]
2,6-F_2	7.37±0.01	Spectr.	[70]
	7.41±0.09	Pot.	[70]
3,4-F_2	7.74±0.01	Spectr.	[70]
3,5-F_2	7.60±0.06	Spectr.	[70]
	7.52±0.11	Pot.	[70]
	7.08±0.03	Spectr.	[71]
2,3,4-F_3	6.97±0.01	Spectr.	[70]
	7.01±0.08	Pot.	[70]
	6.8	Spectr.	[69]
2,3,5-F_3	6.34±0.05	Spectr.	[70]
	6.38±0.11	Pot.	[70]
2,3,6-F_3	5.6	Spectr.	[70]
	6.5	Pot.	[70]
2,4,5-F_3	7.06±0.04	Spectr.	[70]
	6.98±0.10	Pot.	[70]
	6.7	Spectr.	[69]
2,4,6-F_3	7.1	Spectr.	[70]
	7.6	Pot.	[70]
3,4,5-F_3	7.34±0.02	Spectr.	[70]
	7.32±0.07	Pot.	[70]
	6.8	Spectr.	[69]
2,3,4,5-F_4	6.23±0.02	Spectr.	[70]
	6.17±0.03	Pot.	[70]
2,3,4,6-F_4	6.17±0.04	Spectr.	[70]
	6.19±0.05	Pot.	[70]
2-F, 5-NO_2	6.0	Spectr.	[69]
3-F, 2-CHO	5.74±0.02	Spectr.	[14]
4-F, 2-CHO	6.42±0.03	Spectr.	[14]

Table 1 (continued)

Substituents	pK_a	Method[a]	Reference
5-F, 2-CHO	6.72 ± 0.03	Spectr.	[14]
6-F, 2-CHO	6.05 ± 0.03	Spectr.	[14]
2,4-F_2, 3-CHO	6.5	Spectr.	[73]
Benzoxaboroles			
–	7.39	Spectr.	[74]
4-F	6.97 ± 0.02	Spectr.	[75]
5-F	6.57 ± 0.08	Spectr.	[75]
	6.63	Spectr.	[76]
6-F	6.36 ± 0.04	Spectr.	[75]
	6.45	Spectr.	[76]
7-F	7.42 ± 0.15	Spectr.	[75]
Diboronic acids			
–	6.0	Pot.	[15]
4,5-F_2	5.3	Pot.	[15]
3,6-F_2	4.1	Cond.	[15]
3,4,5,6-F_4	3.0	Cond.	[15]

[a] Spectr., spectrophotometric; pot., potentiometric; cond., conductometric.

The data presented in Table 1 confirm that introduction of a fluorine substituent into phenylboronic compounds increases their acidity: the pK_a values for substituted compounds are lower than for unsubstituted ones. This effect is dependent on position of F substituent. The lowest effect, observed for *para* position, is the result of compensation of the inductive and resonance effects, which have comparable values [4]. For *meta* position the resonance effect is much weaker, which causes increased acidity. In the case of *ortho* derivative increased acidity can be caused by the formation of intramolecular B–O–H···F hydrogen bond [77]. It is interesting, that although introduction of the next fluorine substituents results in a further increase of acidity, the 2,6-substituted compounds have lower acidity than their 2,5-isomers. It can be explained by the formation of intramolecular hydrogen bond by only one of the *ortho* fluorine substituent [77], whereas the second *ortho* substituent can cause the opposite effect due to the steric hindrance [70].

4-, 5-, and 6-fluoro-substituted benzoxaboroles display considerably higher acidity than the unsubstituted compound. Surprisingly, 7-fluorobenzoxaborole has a higher pK_a value, similar to that of fluorine-substituted phenylboronic acids. Decrease of the acidity of this compound can be caused by the difficulty of the tetrahedral boronate ion formation caused by intramolecular hydrogen bond formation between fluorine atom and the neighboring B(OH) group [75].

1,2-Diboronic acids have extremely high acidity. It is explained by the increase stability of the anion resulting from the proximity of two boronic groups [15].

Noteworthy is to remark, that there are few examples of calculations of pK_a in literature [78, 79] and that the calculated values significantly differ from the experimental results.

The Lewis acidity of phenylboronic esters can be described by the value of Guttman's acceptor number [80, 81]. Acceptor number (AN), previously applied by Gutmann for quantitative description of electrophilic properties of solvents, is proportional to the change in ^{31}P NMR shift between complexed and uncomplexed triethylphosphine oxide (TEPO). This approach was used for a quantitative determination of Lewis acidity of fluorinated boronic esters [82]. Similarly as in the case of boronic acids, introduction of fluorine substituents increases the acidity of catechol boronates. In general, introduction of next substituents further increases the acidity. Value for catechol ester of pentafluorophenylboronic acid is even higher than that for the tris(pentafluorophenyl)borate (77.8 vs. 76.3) [82]. The acidity of other cyclic diols' esters of pentafluorophenylboronic acid was also investigated [83].

Stability of arylboronic acids. Hydrodeboronation reaction

Fluorinated arylboronic acids are susceptible to hydrodeboronation (Scheme 3).

As early as in 1965 Chambers and Chivers reported, that pentafluorophenylboronic acid rapidly hydrolyses to pentafluorobenzene and boric acid [84]. The rate and mechanism of deboronation of fluoro-substituted was further investigated and it was found, that deboronation can occur both in acidic and alkaline environment – by electrophilic or nucleophilic attack, respectively [24, 85]. Lozada et al. [86] investigated protodeboronation of several fluoro-substituted phenylboronic acids and proved that di-*ortho*-substituted species underwent facile C–B fission in aqueous basic conditions. Recently, Zarzeczańska et al. [70] reported study on the stability of all fluorinated phenylboronic acids. Noteworthy is, that the increase of acidity is not always followed by the rise in deboronation rate. It was confirmed, that 2,6-difluoro-substituted boronic acids deboronate faster than 3,4-difluoro, 3,5-difluorophenylboronic acid and even 3,4,5-trifluorophenylboronic acid [86].

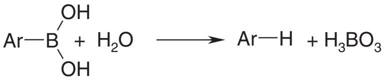
Crystal structure

Structural data for fluoro-substituted phenylboronic acids and their derivatives are collected in Table 2.

The most common structure of phenylboronic acid is a dimer with two intermolecular BOH · · · OB hydrogen bonds, in which boronic group has *syn-anti* conformation. This synthon is formed in almost all investigated fluoro-substituted phenylboronic acids (Fig. 1a). Fluorine substituents practically do not affect the B–C bond length which is similar for unsubstituted acid and for the investigated compounds. The presence of fluorine substituent at the *ortho* position enables the formation of the BO–H · · · F intramolecular hydrogen bond. The formation of such a bond can be assumed for all investigated *ortho*-fluorophenylboronic acids: the observed H · · · F distances range from 2.06 to 2.53 Å [77]. Interestingly, the second *ortho*-fluorine substituent does not form intramolecular hydrogen bond, as was stated for several 2,6-dialkoxy substituted phenylboronic acids [103]. Moreover, the majority of the molecules with *ortho*-fluorine substituents is not planar, contrary to what was for *ortho*-alkoxyphenylboronic acids [103]. These facts indicate that intramolecular BO–H · · · F hydrogen bonds are the weak ones and that they are insignificant compared to the O–H · · · O ones in dimers in controlling the *syn-anti* conformation of the boronic group.

The dimeric synthons serve as main building blocks for three-dimensional structures either by their close packing or by the aid of weak secondary interaction such as C–H · · · π, O–H · · · F, or C–H · · · F hydrogen bonds [77]. Dimeric hydrogen-bonded structure is also observed for fluoro-substituted benzoxaboroles (Fig. 1b), in which the B–C distance is the same as for the unsubstituted compound.

The 1,2-phenylenediboronic acids in solution are in equilibrium with their dehydrated forms. Stability of such cyclic semianhydrides is improved by fluorination of the aromatic ring and complexation of one of the boron



Scheme 3: Hydrodeboronation of arylboronic acids.

Table 2: Fluoro-substituted phenylboronic acids and their derivatives described in literature.

Substituents	Molecular structure	B–C distance (Å)	Dihedral angle[a] (°)	Reference
Boronic acids				
–	Dimer	1.56/1.56	6.6/21.0	[87]
2-F	Dimer, intramol. BOH···F	1.57	25.8	[77]
3-F	Dimer	1.56	25.9	[88]
2,3-F_2	Dimer, intramol. BOH···F	1.58/1.57	24.1/27.6	[77]
2,4-F_2	Dimer	1.57	5.91	[77]
	Dimer	1.57	4.9	[89]
2,5-F_2	Dimer, intramol. BOH···F; polymorphs	1.58/1.58	21.8/27.8	[77]
2,6-F_2	Dimer, intramol. BOH···F	1.59	25.0	[77]
2,3,4-F_3	Dimer, intramol. BOH···F	1.58	26.8	[77]
2,4,6-F_3	Dimer, one intramol. BOH···F	1.58	23.6	[77]
2,3,4,5,6-F_5	Dimer, one intramol. BOH···F	1.58	38.4	[90]
4-F, 2-CHO	Dimer	1.58	44.6	[14]
6-F, 2-CHO	With H_2O	1.55	74.7	[14]
2,3-F_2, 4-CHO	Intermol. BOH···HCO, intramol. BOH···F	1.59	18.5	[91]
3-F, 4-NH_2	Dimer	1.55	24.1	[20]
2-F, 6-$CH_2N(iPr)_2$	Dimer, intramol. BOH···N	1.60	26.0	[92]
2,6-$(CF_3)_2$	Dimer	1.60	68.2	[93]
2-CF_3, 6-$CH_2N(iPr)_2$	Dimer, intramol. BOH···N	1.59	21.8	[92]
2-F, 4-Fc	Dimer	1.57/1.56	6.4/5.9	[94]
3,4,5-F_3 * urea	Cocrystal	1.58	1.7	[95]
Benzoxaboroles				
–	Dimer	1.55/1.56		[96]
5-F	Dimer	1.55		[97]
	Dimer	1.55		[98]
6-F	Dimer	1.55		[75]
Diboronic acids (DBA)				
4,5-F_2 *o*-DBA	Dimer	1.58; 1.59	28.4;45.5	[15]
		1.58; 1.58	25.9;12.7	
3,4,5,6-F_4 *o*-DBA	Anhydride with coordinated water molecule and coordination dimer with B_4O_4 ring	see text	see text	[15]
2-F *p*-DBA		1.57	34.0	[99]
2,3-F_2 *p*-DBA		1.58	6.6	[99]
2,5-F_2 *p*-DBA		1.57	19.0	[99]
2,6-F_2 *p*-DBA		1.58	37.6	[99]
2,3,5,6-F_4 *p*-DBA		1.58	30.6	[99]
Boroxine				
4-F * pyridine	Complex with pyridine	1.56/1.61[b]	9.7/49.8[b]	[100]
Phenylboronic catechol esters				
4-F		1.53	1.9	[101]
2,6-F		1.55	3.5	[101]
2,4,6-F_3		1.55	1.6	[101]
3,4,5-F_3		1.55	5.6	[101]
2,3,4,5,6-F_5		1.56	1.6	[101]
4-CF_3*picoline	Co-crystal of 5 molecules of the complex with one picoline molecule	1.60		[102]

[a] Dihedral angle between benzene ring and O–B–O planes.

[b] Coordinated boron atom.

Numbering of the atoms is the same as in Table 1.

*Stands for cocrystal structures or complex.

centers with water, which is observed in two crystalline forms of the anhydrides [15]. For 1,4-phenylenediboronic acids different fluorine substitutions only slightly influence bond lengths between non-hydrogen atoms. Solely the presence of four fluorine atoms at the phenyl ring gives a significant B–C bond elongation [99].

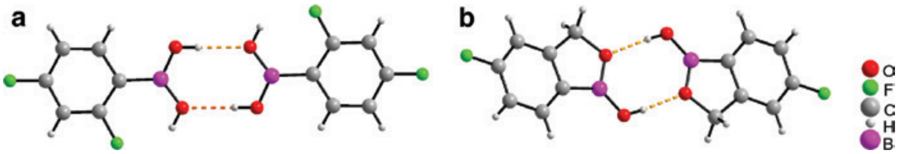


Fig. 1: Examples of dimeric structures of fluoro-substituted phenylboronic acid (a) and benzoxaborole (b).

Extensive study on hydrogen bonding in catechol phenylboronic esters was presented by Madura et al. [101]. All the investigated molecules are almost planar. Depending on the number and position of the fluorine substituents, the substantial differentiation of the molecular dipole moment is observed. The supramolecular motif of stacking columns directed by the antiparallel dipole–dipole interactions is observed in the case of highly polar molecules. The presence of *ortho*-F substituents enhances the proton acceptor character of oxygen atoms, which favors the formation of the intermolecular C–H · · · O hydrogen bonds.

Conformational analysis and equilibria in solution

Conformational analysis for isolated molecule of 2-fluorophenylboronic acid confirms its *syn-anti* conformation and the formation of BO–H · · · F intramolecular hydrogen bond [11, 12].

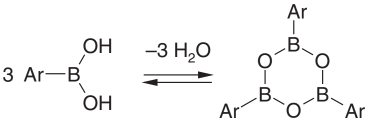
Phenylboronic acids display several equilibria in solution, one of which is the acid-boroxine equilibrium (Scheme 4) [40, 104, 105], which importance is connected with the formation of COFs systems [40] or self-healing polymers [41]. They can be investigated by various analytical methods, from which ^{19}F NMR seems to be very convenient due to several advantages of this method [21]. That will be discussed further in the next paragraph.

Ortho-formyl substituted phenylboronic acids display the tautomeric equilibria with the formation of the corresponding hydroxybenzoxaboroles (Scheme 5) [106].

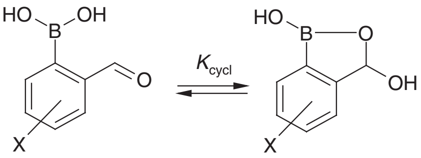
Equilibrium constant (K_{cycl}) values for this reaction depends on the substituent X and for the fluorine substituent vary from 0.08 to 0.69, depending on its position in the benzene ring [14].

Spectroscopic data

Spectroscopic techniques, especially in connection with computational methods, can serve as a useful tool for structural analysis. Such comprehensive study (FT-IR, Raman, ^{1}H and ^{13}C NMR, UV-Vis and DFT calculations) was carried out for several fluoro-substituted phenylboronic acids by Karabacak et al. [107–109]. Results of IR



Scheme 4: Formation of triarylboroxine from arylboronic acid.



Scheme 5: Tautomeric equilibrium for *ortho*-formylphenylboronic acids.

Table 3: ^{19}F NMR chemical shifts of fluorinated phenylboronic acids, benzoxaboroles and boroxines.

Aryl group	Solvent	Chemical shifts, ppm					Ref.
		2-F	3-F	4-F	5-F	6-F	
Phenylboronic acids							
2-F	Acetone-d_6	−105.99	–	–	–	–	[21]
3-F	Acetone-d_6	–	−115.01	–	–	–	[21]
3-F	CD_3OD	–	−114.8	–	–	–	[111]
4-F	Acetone-d_6	–	–	−111.07	–	–	[21]
4-F	Acetone-d_6	–	–	−110.98	–	–	[23]
4-F	Ether	–	–	−111.52	–	–	[23]
2,3-F_2	Acetone-d_6	−132.59	−140.54	–	–	–	[21]
2,4-F_2	Acetone-d_6	−101.7	–	−107.7	–	–	[21]
	Acetone-d_6	−101.37	–	−107.65	–	–	[23]
	CD_2Cl_2	−105.97	–	−105.72	–	–	[23]
	D_2O/Py	−101.64	–	−109.19	–	–	[85]
2,5-F_2	Acetone-d_6	−112.2	–	–	−120.8	–	[21]
2,6-F_2	Acetone-d_6	−103.10	–	–	–	−103.10	[21]
	Acetone-d_6	−103.16	–	–	–	−103.16	[23]
	D_2O/Py	−103.65	–	–	–	−103.65	[85]
3,4-F_2	Acetone-d_6	–	−140.90	−137.00	–	–	[21]
3,5-F_2	Acetone-d_6	–	111.59	–	−111.59	–	[21]
2,3,4-F_3	Acetone-d_6	−128.23	−164.19	−133.59	–	–	[21]
2,3,5-F_3	Acetone-d_6	−138.01	−136.10	–	−117.60	–	[21]
2,3,6-F_3	Acetone-d_6	−127.99	−144.95	–	–	−108.49	[21]
2,4,5-F_3	Acetone-d_6	−106.71	–	−131.75	−145.17	–	[21]
2,4,6-F_3	Acetone-d_6	−100.13	–	−107.85	–	−100.13	[21]
	Acetone-d_6	−99.95	–	−107.67	–	−99.95	[23]
	D_2O/Py	−100.79	–	−109.01	–	100.79	[85]
3,4,5-F_3	Acetone-d_6	–	−136.99	−160.05	−136.99	–	[21]
	Acetone-d_6 /D_2O	–	−136.41	−159.65	−136.41	–	[23]
	Ether	–	−136.41	−159.51	−136.41	–	[23]
	D_2O/Py	–	−139.08	−162.46	−139.08	–	[85]
2,3,4,5-F_4	Acetone-d_6	−131.99	−158.05	−154.72	−140.94	–	[21]
	Acetone-d_6/D_2O	−131.69	−158.17	−155.27	−141.14	–	[23]
	D_2O/Py	−130.66	−156.80	−154.64	−139.50	–	[85]
2,3,4,6-F_4	Acetone-d_6	−126.04	−168.07	−132.55	–	−105.98	[21]
	Acetone-d_6	−126.22	−168.26	−132.81	–	−106.12	[23]
	Acetonitrile-d_3	−125.56	−167.16	−131.51	–	−105.80	[23]
	D_2O/Py	−125.32	−166.79	−132.41	–	−105.20	[85]
	MeOH	−126.13	−167.44	−131.61	–	−106.20	[85]
	Py	−124.59	−166.31	−131.98	–	−104.65	[85]
2,3,5,6-F_4	Acetone-d_6	−133.60	−140.24	–	−140.24	−133.60	[21]
	Acetone-d_6	−133.70	−140.34	–	−140.34	−133.70	[23]
	Ether	−133.28	−140.27	–	−140.27	−133.28	[23]
	D_2O/Py	−133.48	−140.30	–	−140.30	−133.48	[85]
	MeOH	−133.59	−139.30	–	−139.30	−133.59	[85]
2,3,4,5,6-F_5	Acetone-d_6	−132.53	−163.38	−154.65	−163.38	−132.53	[21]
	Acetone-d_6	−132.61	−163.50	−154.72	−163.50	−132.61	[23]
	Acetone	−132.9	−164.1	−155.4	−164.1	−132.9	[84]
	Ether	−132.13	−163.35	−155.09	−163.35	−132.13	[23]
	CH_2Cl_2	−133.31	−162.06	−150.03	−162.06	−133.31	[23]
	CH_3CO_2H	−131.86	−162.72	−153.17	−162.72	−131.86	[23]
	MeOH	−132.44	−162.75	−154.11	−162.75	−132.44	[85]
	H_2O/MeOH	−132.14	−162.30	−153.69	−162.30	−132.14	[85]
3-F, 2-CHO	Acetone-d_6	–	−122.39 −120.81[a]	–	–	–	[14]
4-F, 2-CHO	Acetone-d_6	–	–	−112.75 −111.21[a]	–	–	[14]

Table 3 (continued)

Aryl group	Solvent	Chemical shifts, ppm					Ref.
		2-F	3-F	4-F	5-F	6-F	
5-F, 2-CHO	Acetone-d_6	–	–	–	−106.73 −116.12[a]	–	[14]
6-F, 2-CHO	Acetone-d_6	–	–	–	–	−106.03 −105.52[a]	[14]
Boroxines							
4-F	Ether	–	–	−106.34	–	–	[23]
2,6-F	Acetonitrile-d_3	−103.0	–	–	–	−103.0	[32]
2,4,6-F	Acetonitrile-d_3	−99.9	–	−106.8	–	99.9	[32]
3,4,5-F	Ether	–	−135.52	−156.50	−135.52	–	[23]
2,3,5,6-F	Ether	−131.60	−139.94	–	139.94	−131.60	[23]
2,3,4,5,6-F	Ether	−132.37	−163.66	−154.07	−163.66	−132.37	[23]
2,3,4,5,6-F	Acetonitrile-d_3	−132.4	−163.5	−153.7	−163.5	−132.4	[32]
Catechol esters							
2-F	$CDCl_3$	−102.61	–	–	–	–	[82]
3-F	$CDCl_3$	–	−113.46	–	–	–	[82]
4-F	$CDCl_3$	–	–	−106.45	–	–	[82]
2,4-F	$CDCl_3$	−98.47	–	−102.75	–	–	[82]
2,6-F	$CDCl_3$	−99.56	–	–	–	−99.56	[82]
3,4,5-F	$CDCl_3$	–	−134.36	−154.52	−134.36	–	[82]
2,4,6-F	$CDCl_3$	−96.13	–	−100.68	–	−96.13	[82]
2,3,4,5,6-F	$CDCl_3$	−128.43	−161.09	−146.620	−161.09	−128.43	[82]
Pinacol esters							
2-F	$CDCl_3$	−103.06	–	–	–	–	[82]
3-F	$CDCl_3$	–	−114.2	–	–	–	[112]
4-F	$CDCl_3$	–	–	−115.5	–	–	[111]
2,3-F	$CDCl_3$	−129.1	139.1	–	–	–	[112]
2,5-F	$CDCl_3$	−109.5	–	–	−120.6	–	[112]
3,5-F	$CDCl_3$	–	−110.9	–	−110.9	–	[112]
2,3,5-F	$CDCl_3$	−134.0	−133.6	–	−116.2	–	[112]
2,4,5-F	$CDCl_3$	−104.2	–	−128.5	−144.2	–	[112]
2,3,4,5-F	$CDCl_3$	−129.0	−156.1	−150.9	−139.8	–	[112]
		3-F	4-F	5-F	6-F	7-F	
Benzoxaboroles							
4-F	Acetone-d_6	–	−121.46	–	–	–	[75]
5-F	Acetone-d_6	–	–	−111.84	–	–	[75]
6-F	Acetone-d_6	–	–	–	−118.40	–	[75]
7-F	Acetone-d_6	–	–	–	–	−105.51	[75]

[a] Cyclic tautomer according to Scheme 5.
Numbering of the atoms is the same as in Table 1.

and multinuclear (^{1}H, ^{11}B, ^{13}C and ^{19}F) solid state NMR characterization together with DFT calculations were presented by Sene et al. [98] for 5-fluorobenzoxaborole and compared with the results of crystallographic research.

Particular NMR techniques have exceptional significance in characterization of phenylboronic compounds. A detailed ^{1}H, ^{13}C, ^{11}B, ^{19}F and ^{17}O NMR study of the series of all mono- and multi-fluoro substituted phenylboronic acids was carried out by Gierczyk et al. [21]. From the practical point of view the proton, boron and fluorine NMR methods are easy to use methods mainly due to the high natural abundance of the particular isotope. Of these three methods, ^{19}F NMR spectroscopy is of particular importance [110]. The advantages of this method are as follows:

- high sensitivity (83 % ^{1}H NMR), connected with the high natural abundance (100 % ^{19}F),
- spin number $I = ½$,

- short relaxation time T_1 (typical acquisition time 1.0 s, interscan 0.2 s),
- small half-width,
- range of chemical shifts more than 400 ppm (up to 1000 ppm),
- coupling constants: $J \ll \Delta\delta$, intensity and splitting as in ^{1}H spectra.

The ^{19}F NMR chemical shifts for the boronic acids and their derivatives are collected in Table 3.

Great differences in the chemical shifts makes the ^{19}F NMR spectroscopy an excellent tool in the research of structures, complexation, association as well as reaction kinetics. For instance, the differences in chemical shifts between 4-fluorophenylboronic acid, corresponding boroxine and pinacol ester are in order of 5 ppm. It is worth noting, that, in addition to chemical shifts, coupling constants values provide valuable information on structural parameters [21].

Useful tool in the investigation of oxygen-containing organoboron compounds is ^{17}O NMR spectroscopy [113]. However, the limitation of this method is very low natural abundance of ^{17}O nuclei ($3.7{*}10^{-2}$ %). In earlier works isotope enriched compounds were used. Contemporary spectrometers allow for a substantial acceleration of the spectral acquisition making the method more useful [114]. Selected ^{17}O NMR data for fluorinated phenylboronic compounds are collected in Table 4.

It is worth noting that ^{17}O chemical shifts are affected not only by electronic effect of fluorine substituents but also by their steric factors, which result in higher values for the *ortho*-substituted compounds [114].

^{1}H, ^{13}C and ^{11}B NMR data for fluoro-substituted boronic acids and their derivatives are collected in Supplementary material.

Table 4: ^{17}O NMR chemical shifts of fluorinated phenylboronic acids and benzoxaboroles.

Aryl group	Solvent	Chemical shifts, ppm		Ref.
Phenylboronic acids				
2-F	Acetone-d_6		82.0	[21]
3-F	Acetone-d_6		77.3	[21]
4-F	Acetone-d_6		74.6	[21]
2,3-F_2	Acetone-d_6		83.2	[21]
2,4-F_2	Acetone-d_6		80.9	[21]
2,5-F_2	Acetone-d_6		83.2	[21]
2,6-F_2	Acetone-d_6		91.9	[21]
3,4-F_2	Acetone-d_6		76.1	[21]
3,5-F_2	Acetone-d_6		78.4	[21]
2,3,4-F_3	Acetone-d_6		82.2	[21]
2,3,5-F_3	Acetone-d_6		84.3	[21]
2,3,6-F_3	Acetone-d_6		92.7	[21]
2,4,5-F_3	Acetone-d_6		82.1	[21]
2,4,6-F_3	Acetone-d_6		90.8	[21]
3,4,5-F_3	Acetone-d_6		76.7	[21]
2,3,4,5-F_4	Acetone-d_6		82.7	[21]
2,3,4,6-F_4	Acetone-d_6		91.4	[21]
2,3,5,6-F_4	Acetone-d_6		93.5	[21]
2,3,4,5,6-F_5	Acetone-d_6		92.1	[21]
		B–O–H	**B–O–C**	
Benzoxaboroles				
4-F	Acetone-d_6	68.0	96.3	[75]
5-F	Acetone-d_6	66.3	99.1	[75]
6-F	Acetone-d_6	67.2	100.9	[75]
7-F	Acetone-d_6	68.3	97.5	[75]

Numbering of the atoms is the same as in Table 1.

The molecular structure and adsorption mode onto the silver surface of the two groups of fluoro-substituted phenylboronic acids were investigated by experimental (FT-Raman, FT-IR, and SERS) and theoretical [DFT, B3LYP/6-311++G(d,p)] methods. The most stable structure of these absorbed molecules is a cyclic dimer. Conformational analysis for the absorbed molecules was also done [13].

Synthesis

Introduction of the boronic group

The fluorine-carbon bond is a stable one and does not react with common reagents used in the synthesis of boronic acids. Hence, typical reaction sequence shown in Scheme 6 can be applied.

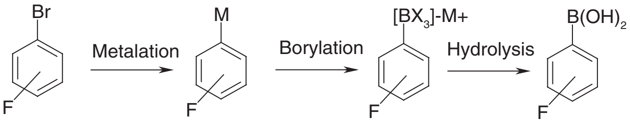
The most common metalating agents are n-butyllithium or lithium diisopropylamide (LDA) solutions, although an alternative method by Grignard reagent can be also used. Introduction of the boryl moiety can be achieved with trialkyl borates or cyclic pinacol esters. The synthesis of various fluorine-substituted phenylboronic acids was extensively investigated by Frohn et al. [23, 115]. Recently, the continuous process in a cryogenic flow reactor was described with the use of n-BuLi and $B(OMe)_3$ [116] or PinBOiPr [117]. Fluorinated phenylboronic acids with various functional groups in the phenyl ring can be synthesized in the same manner with optional protection of the functional group if necessary. For instance, several fluoroformylphenylboronic acids were synthesized with the protection of formyl group by acetal formation [14, 97].

The acidity of arenes is enhanced by fluorine substituent due to its electron-withdrawing inductive effect. Hence, direct metalation of fluorobenzene can be achieved at the *ortho* position. Thermodynamic and kinetic parameters of this reaction were discussed [118, 119]. Long range substituent effect was also investigated [120]. This effect is utilized in preparation of fluorophenylboronic acids by direct metalation, which is most often used for the syntheses of multi-fluoro derivatives, e.g. 2,3,5,6-tetrafluorophenylboronic acid (Scheme 7).

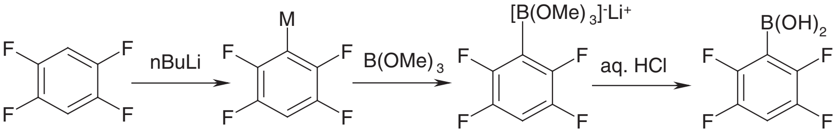
Similarly as in the reactions of aryl bromides, this approach can be applied in the synthesis of fluorinated phenylboronic acids containing functional groups [120].

Transformations of boronic acids

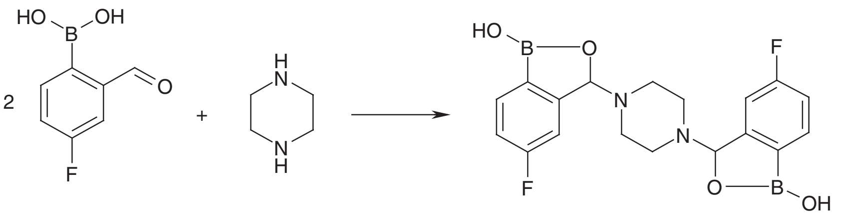
Derivatives of fluoro-substituted phenylboronic acids can be synthesized by typical reactions, e.g. esterification, dehydration, amination followed by dehydration, or reduction of the parent acids leading to esters, boroxines or benzoxaboroles, respectively. For instance, 3,3′-piperazine bis(5-fluorobenzoxaborole) was obtained from 4-fluoro-2-formylphenylboronic acid (Scheme 8) [121].



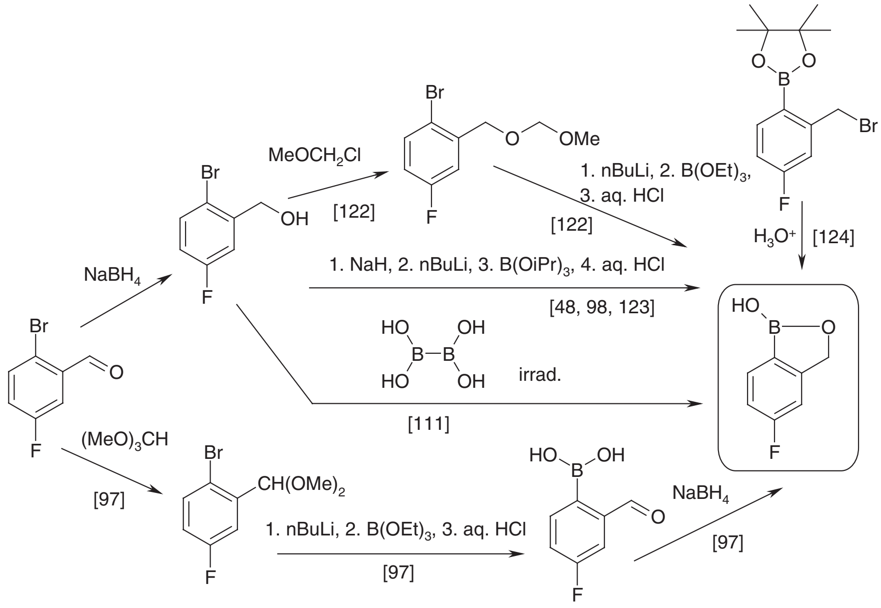
Scheme 6: Introduction of boronic group by aryl bromide metalation.



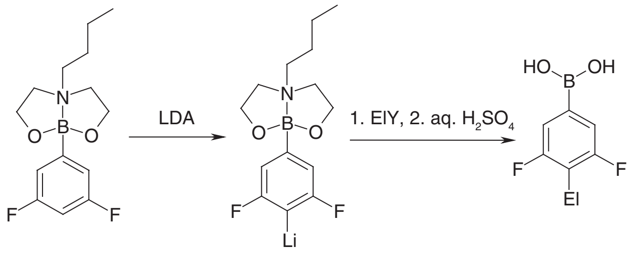
Scheme 7: Introduction of boronic group by direct metalation.



Scheme 8: Synthesis of bis-benzoxaborole from formylphenylboronic acid.



Scheme 9: Reported pathways in the synthesis of Kerydin [48, 97, 98, 111, 122–124].



Scheme 10: Metalation of protected phenylboronic acids ElY: electrophile.

In addition to the simple transformation of boronic acids, particular methods can be applied for the straightforward syntheses of these derivatives from different substrates. Scheme 9 shows various methods of preparation 5-fluorobenzoxaborole, which has been widely studied due to its antifungal properties and its recent use as the drug Kerydin.

The modification of this method is metalation of protected boronic acids (Scheme 10).

This method was applied to introduce additional functional groups (El: formyl, methoxycarbonyl, silyl, boronic) into phenyl ring [125]. Other isomers of difluorophenylboronic acids were also used in this approach [125]. Iodo-substituted compounds can be obtained from silyl derivatives by iododesilylation [126].

Applications

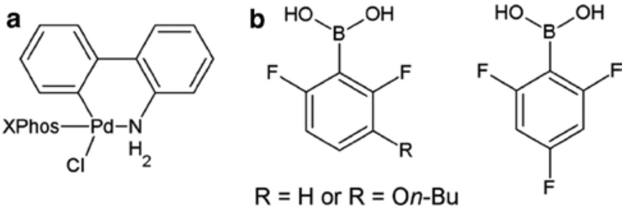
Organic synthesis

Suzuki-Miyaura cross-coupling

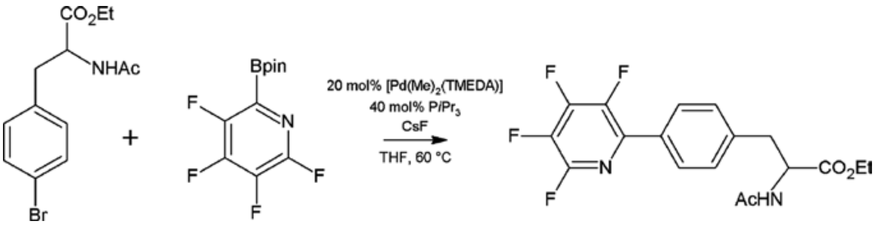
Suzuki-Miyaura cross-coupling (SMC) is the most widely used reaction to create bond between two sp^2 carbons [24, 127, 128]. SMC is regarded as the most significant discovery in chemistry of boronic acid [129]. Meaningful issue of using polyfluorinated boronic acids, which are easy to deboronate in SMC was described by Kinzel et al. [24]. In this article new palladium pre-catalyst was presented (Scheme 11), which enables carrying out of reaction in mild conditions – important for avoiding the deboronation reaction.

Recently published paper by Kohlmann et al. [130] shows an interesting example of SMC between pinacol 3,4,5,6-tetrafluoro-2-pyridinylboronate and phenylalanine precursors (Scheme 12). A variety of highly fluorinated amino acid derivatives were synthesized in this manner. These conversions gave access to building blocks with important functional moieties, such as 2-C_5F_4N, 4-$C_6H_4SF_5$, and 2-$C_6H_4SCF_3$.

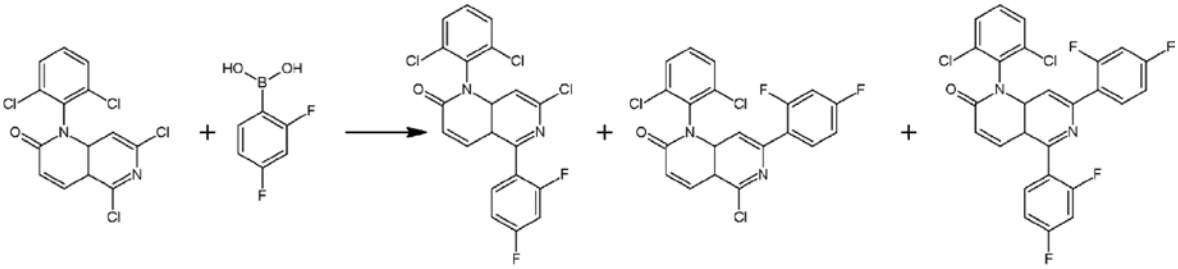
Regioselectivity of SMC reaction was investigated by Chung et al. [131] and by Cai et al. [132] for the reaction of 2,4-difluorophenylboronic acid with 1,6-naphthyridone dichloride, leading to an efficient intermediate in kinase inhibitor synthesis (Scheme 13).



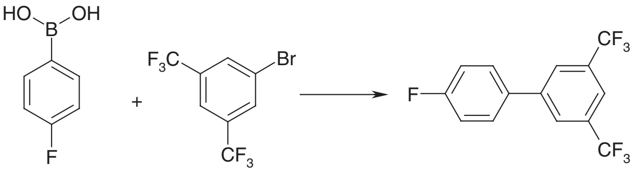
Scheme 11: (a) structure of palladium pre-catalyst, which is used in SMC of easily deboronating boronic acids, (b) structures of investigated fluorinated boronic acids [24].



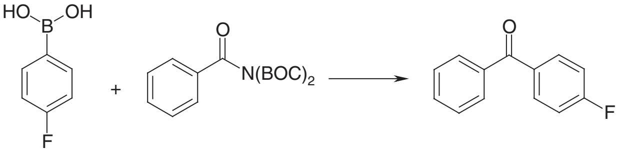
Scheme 12: SMC of pinacol 3,4,5,6-tetrafluoro-2-pyridinylboronate with phenylalanine derivative [130].



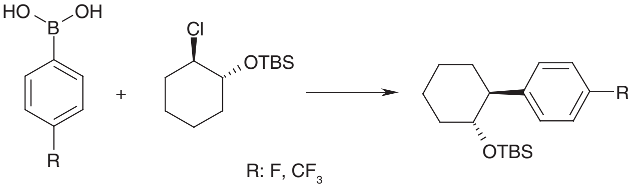
Scheme 13: SMC between 2,4-difluorophenylboronic acid and 1,6-naphthyridone [131, 132].



Scheme 14: SMC of 4-fluorophenylboronic acid with fluorinated phenyl bromide [25].



Scheme 15: SMC of fluorophenylboronic acids with amides [26].



Scheme 16: SMC of fluorinated phenylboronic acids and alkyl chlorides [134].

The extensive study of SMC between 4-fluorophenylboronic compounds and 3,5-bis(trifluoromethyl) phenyl bromide was presented by Butters et al. [25] (Scheme 14). Authors compare yields of the main product and side-products of protodeboronation, homocoupling and oxidation reactions.

Wide investigation has been carried on the SMC between aromatic amides and boronic acids resulting in diaryl ketones [26] (Scheme 15). Among others, fluoro and trifluoromethyl-substituted boronic acids were studied.

Interesting case of applying SMC is a site-specific introduction of 4-[18]fluorophenyl group into polypeptide [133]. This is an efficient way to obtain a tracer for the positron emission tomography (PET) imaging.

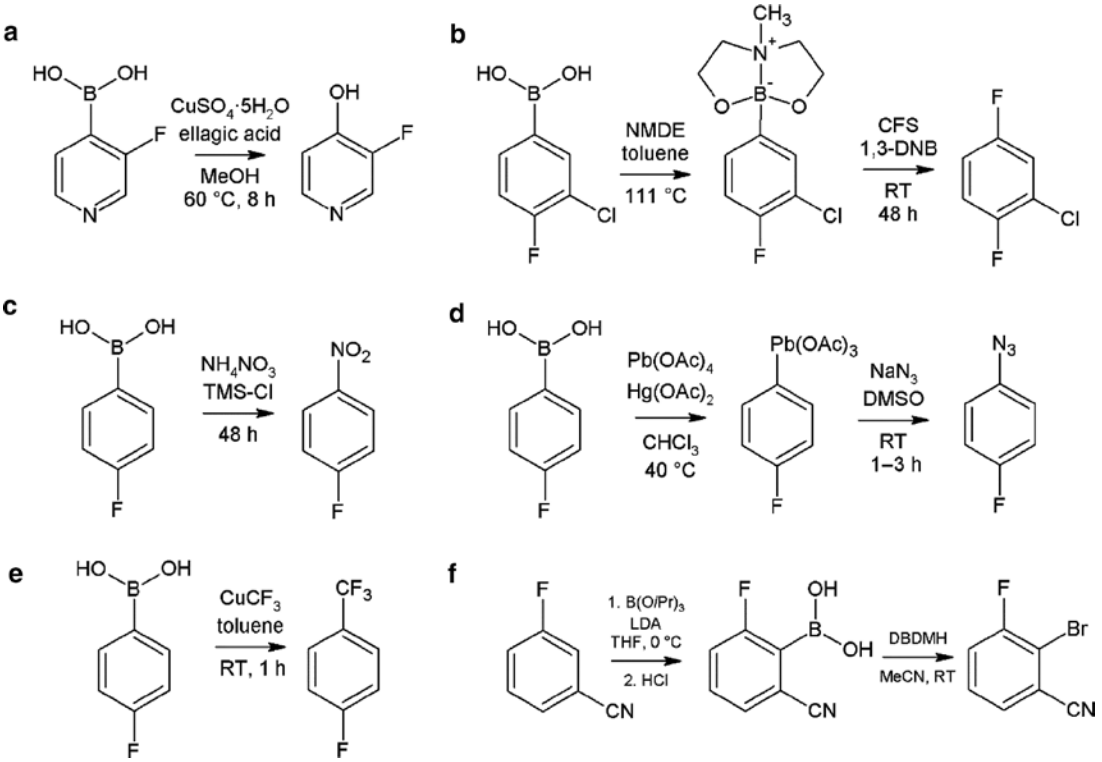
Reactions of primary and secondary alkyl chlorides with fluorophenylboronic acids can be accomplished through the use of nickel/amino alcohol-based catalysts (Scheme 16) [134].

Transformations of boronic group in fluorinated boronic acids

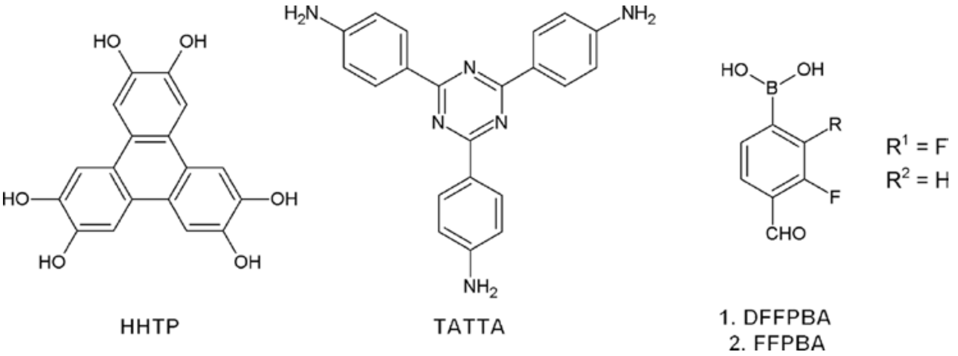
Fluorinated arylboronic acids have been transformed into various organic compounds by substitution of the boronic unit by other functional groups. Scheme 17 shows several examples of such reactions: hydroxylation of 2-fluoro-4-pyridinylboronic acid [135], fluorination with caesium fluoroxysulfate (CFS) [136], nitration by simple nitrates [137], creation of azides [138, 139], introduction of trifluoromethyl group [140] and bromination [141]. Generally, the presented transformations proceed with high yields.

Fluorinated boronic acids in covalent organic frameworks formation

Since boroxine-based COF-1 was synthesized [142] and similar COF-5 with *p*-diboronic acid as a linker, several COFs with the use of fluorinated phenylboronic acids were reported. Chen et al. [42] presented the HHTP-DFFPBA-TATTA COF with the use of DFFPBA as a linker, HHTP-FFPBA-TATTA COF with use FFPBA as a linker and



Scheme 17: Examples of fluorinated boronic acids' conversion into other organic compounds. NMDE, *N*-methyldiethanolamine; TMS-Cl, chlorotrimethylsilane; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin.



Scheme 18: Compounds used to create COFs: HHTP, 2,3,6,7,10,11-hexahydroxytriphenylene; TATTA, 4,4′,4″-(1,3,5-triazine-2,4,6-triyl)trianiline; DFFPBA, 2,3-difluoro-4-formyl-phenylboronic acid; FFPBA, 3-fluoro-4-formylphenylboronic acid [42].

boroxine-TATTA-based TATTA-DFFPBA COF and TATTA-FFPBA COF (Scheme 18). Porosity and gas adsorption in COFs, among others, was investigated. Li et al. [43] presented boroxine-based three-dimensional DL-COF-2 with use FFPBA and 1,3,5,7-tetraaminoadamantane (TAA). Gas adsorption in COF and catalytic properties in the cascade reaction with Knoevenagel-type condensation was investigated.

Other reactions

4-Fluorophenylboronic acid was used in palladium-catalyzed reaction of 1,1-fluoroarylation of aminoalkenes with addition of Selectfluor [143].

Fluoro-substituted phenylboronic acids were used in nickel-catalyzed cross-coupling with 2,2-difluoro-1-iodoethenyl tosylate to obtain difluoroalkylated arenes [144].

Reaction of *ipso*-iodination of silylated fluorophenylboronic acids was investigated [126].

Efficient two step synthesis of indoles with aryl and trifluoromethyl groups from substituted alkynes and various substituted 2-nitrophenylboronic acids – among others 4-fluoro-2-nitrophenylboronic acid – was reported [145].

Synthesis of bis- and tris(2,6-difluorophenylboronic) acids with the methylsilane core was reported by Gontarczyk et al. [146].

Enantioselective rhodium-catalyzed 1,4-addition of 3,5-difluorophenylboronic acid to α,β-unsaturated ester was reported. This is the key step of the multikilogram-scale synthesis of important pharmaceutical ingredients [147].

Binding to diols

General considerations

Ability of binding diols by phenylboronic acids is well known for many years. In 1959 Lorand and Edwards presented important paper about complexes between phenylboronic acid and *cis* diols, e.g. monosaccharides [148]. Westmark et al. discussed the mechanism and efficiency of sugars transport through lipid layer. Authors remarked, that in aqueous solution tetrahedral boronate anion is created, but in lipid layer it takes the trigonal form. Among others 4-fluorophenylboronic acid was investigated [72]. London and Gabel [9] showed changes in ^{19}F NMR chemical shifts depending on changes in pH of 4-fluorophenylboronic acid and 3-chloro-4-fluorophenylboronic acid. Moreover, it was remarked, that additional signal in the ^{19}F NMR spectra of boronic acid bound with diol or phosphate appears. It means, that ^{19}F NMR spectrometry could be useful to diol and phosphate binding monitoring for fluorinated boronic acids.

A detailed mechanism of diols binding and kinetics of binding was presented by Furikado et al. [149]. The influence of pH on reaction between 2,4-difluorophenylboronic acid and chromotropic acid was investigated in details.

Important insight into the binding affinity of diols to boronic acids depending on pK_a of the acids and pH of a solution was presented by Yan et al. [69]. Mono- and multifluorinated boronic acids were reacted with diols: glucose, fructose, catechol and Alizarin Red S (ARS). ARS is commonly used as spectrophotometric indicator of boronic acid binding affinity to diols [150, 151]. In the paper by Yan et al. [69] it was stated, that pK_a of acids and pH of a solution are not the only significant factors, but the presence of buffer and steric hindrance in boronic acid also influence the binding affinity. Significant conclusion from this paper is that increasing the acidity of boronic acid is not always followed by raise in the binding affinity. For example, at physiological pH (7.5) 3,4,5-trifluorophenyloboronic acid displays lower binding constant for glucose than 2,5-difluorophenylboronic acid despite higher pK_a of the latter. However, for fructose 3,4,5-trifluorophenylboronic acid has higher binding constant than 2,5-difluorophenylboronic acid. Introduction of nitro group to phenylboronic acids often diminishes affinity of diols, also to fluorinated acids, in spite of decreasing effect for pK_a [69, 152].

Binding of diols by boronic compounds is crucial from the point of view of their biological activity. It is discussed in the next chapter.

Applications in analytical chemistry – solid-phase extraction, enrichment of analytes, sensors and receptors

As it was stated earlier, introduction of fluorine substituents into phenylboronic acids decreases the pK_a value. In many cases it allows to make sensors suitable for sugar sensing at physiological pH [20, 30, 153].

In order to connect boronic acid to polymer matrix or other unit, additional functional group is required. It can be the amine [20, 29, 30], carboxyl [30] or formyl group [73, 154–158].

Important class of sensors is that based on hydrogels. In the paper of Zhang et al. [29] the binding of glucose by aminophenylboronic acids attached with polymerized crystalline colloidal arrays (PCCA) was described. Immobilization of boronic acids on PCCA was followed by creation of the amide bond between free carboxylic group from polyacrylic acid and amine group from boronic acid. Authors showed two mechanisms of glucose binding by immobilized boronic acids. In instance of shortage of glucose, the 2:1 complex boronic acid-glucose is formed, resulting in shrinking of the hydrogel. If the concentration of glucose in solution is higher – the 1:1 complex is formed, resulting in swelling of the hydrogel. In consequence, a huge shift in diffracted wavelength was observed. Aminophenylboronic acids with electron withdrawing groups (EWG) such as fluorine group were also investigated. However, introduction of EWG, which decreases pK_a, is not always a good way for optimization of response.

Similar example of a hydrogel sensing material is the photonic colloidal crystal based on polyacrylamide-poly(ethylene glycol) with attached 4-amino- and 4-carboxy-3-fluorophenylboronic acids and then amplified by applying 4-carboxy-3-fluorophenylboronic acid [153].

Interesting example is the use of 2,4-difluoro-3-formylphenylboronic acid (DFFPBA) attached to various materials, firstly reported in 2013 by Li et al. [73] Authors presented a column for selective enrichment of nucleosides – also from urine sample. The preparation of this type of columns has been described in details [158]. Important application of DFFPBA is also the capillary electrophoresis, which is a fast, accurate and precise way for measuring association constant of binding monosaccharides by boronic acids. Binding with fructose, mannose, *N*-acetylneuraminic acid (Neu5Ac), xylose and fucose was investigated [159]. DFFPBA has significantly higher association constant for fructose than others boronic acids. Also for other sugars – xylose, fucose, mannose – stronger affinity was observed [159]. Therefore monolithic column (copolymer poly(MBAA-co-GMA) covered by PEI) with use of DFFPBA for enrichment of trace glycoproteins from urine samples was prepared. MALDI-TOF MS spectrum shows, that this method of enrichment by solid-phase extraction succeeded. Lowered binding pH of DFFPBA profitably influenced the selectivity of binding glycoproteins [156]. Similar method is the enrichment of nucleosides by the use of aminated magnetic attapulgite as a bottom support for DFFPBA [154].

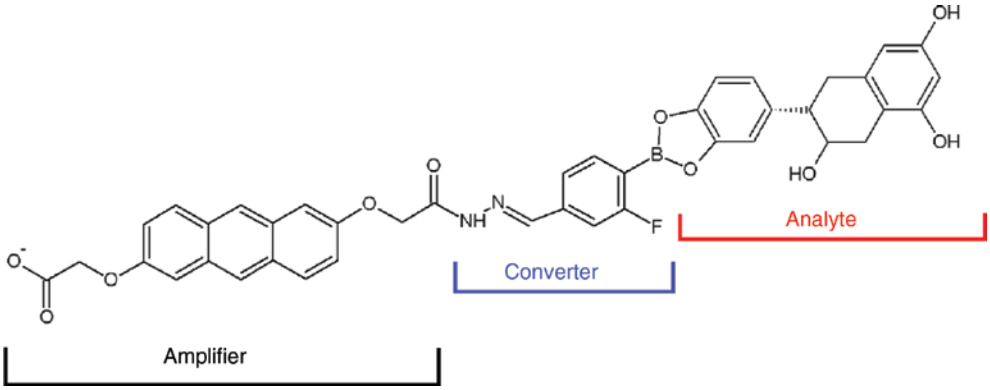
Interesting way was to create a hybrid method of selection of aptamers for binding glycoproteins – alkaline phosphatase (ALP) and ribonuclease B (RNase B) was investigated. Magnetic beads with attached DFFPBA enable enriching binding sequences, which is followed by capillary electrophoresis separation [160].

Novel amplification in creating specific receptors for glycans, glycoproteins and monosaccharides is creating molecularly imprinted polymers (MIPs) with use of DFFPBA as binding agent for template and analyte [157]. Xing et al. described the process of preparation and evaluations of molecularly imprinted receptor (MIR). MIR based on 3D arrays was created for specific glycoprotein recognition (RNase B) [155], which is part of a sensor, connected with display electrode. On the latter a reduction of Prussian blue to Prussian white takes place. The idea assumes absorbance measuring of fading blue color, which indicates quantitatively the concentration of RNase B in solution. DFFPBA is also used as a linker between the base surface and template or analyte.

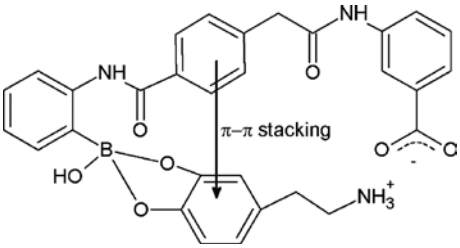
Interesting examples of receptors for fluoride ion recognition are macrocycles, one of which is made of two particles of DFFPBA, 3-aminophenylboronic acid and pentaerythritol. It was found, that such macrocycles can include some small compounds, e.g. chloroform, benzene and tetrabutylammonium fluoride (TBAF). TBAF was used to investigate receptor properties of macrocycles. Fluoride ion inclusion was observed by significant changes in ^{11}B NMR spectrum [161].

2-Fluoro-4-formylphenylboronic acid can be used as linker – converter between diol (analyte) and anthracene (amplifier) (Scheme 19). Amplifier and converter noncovalently interact with synthetic pores. This sensing system was used to detect polyphenols in green tea [162].

Important achievement in the research of boronic receptors was a computational design of receptor based on phenylboronic acid for recognition of dopamine. It was possible to predict distances between molecules and to project three binding parts involving: (i) covalent bonding with creating boronic ester with



Scheme 19: Applying 2-fluoro-4-formylphenylboronic acid as converter in sensing system for polyphenols [162].



Scheme 20: Computer-designed complex of receptor and dopamine [31].

analyte, (ii) π–π stacking between aromatic ring in receptor and dopamine, (iii) and ionic interaction between amine group of dopamine and geminal diol in receptor (Scheme 20). One of the discussed boronic acids was 2-amino-5-fluorophenylboronic acids [31].

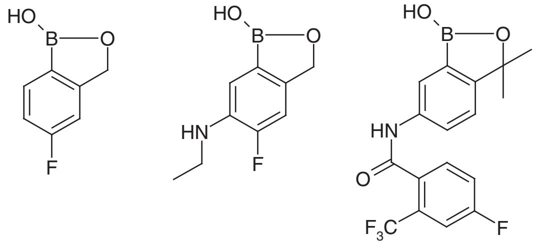
Biological activity

Inhibitory properties of fluoroarylboronic acids

The above-mentioned ability to bind diols molecules by arylboronic acids is also the basis of their biological activity, which depends on enzyme inhibition. London and Gabel investigated interaction of 4-fluorophenylboronic acid and 3-chloro-4-fluorophenylboronic acid, with the active site of subtilisin Carlsberg. The reaction was monitored by ^{19}F NMR spectrometry [10]. 2-Fluoro-, 4-fluorophenylboronic acid and 4-fluoro-3-pyridinylboronic acid, among others, were investigated as inhibitors for fatty acid amide hydrolase. Fluoro- and trifluoromethylphenylboronic acids were found to be potent inhibitors. However, these acids are far from the best one investigated compound, 4-nonylphenylboronic acid [163].

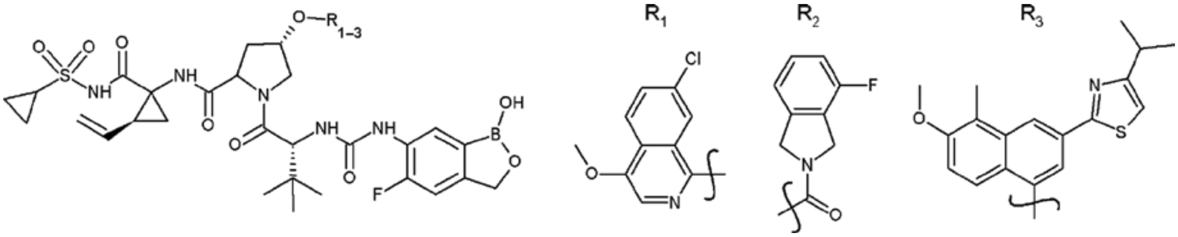
Medical applications

Substantial increase of interest in benzoxaborole chemistry is associated with the discovery of biological activity of 5-fluorobenzoxaborole, AN2690 (tavaborole) [122]. AN2690 is a novel antifungal drug, which is applied for the topical treatment of toenail onychomycosis [164–166]. Improved nail penetration by this compound in comparison with earlier applied drugs is connected with its small molar mass. Tavaborole is described as a safe, non-toxic substance [166]. It is available as a 5 % solution, brand name – Kerydin [46, 166]. Potential formulation of drugs containing AN2690 in inorganic Mg–Al double hydroxide matrix and in

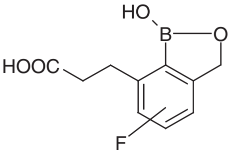


AN2690 AN3018 AN5568

Scheme 21: Fluorinated benzoxaboroles with biological activity.



Scheme 22: AN2690-containing potential HCV NS3 inhibitors [47].



Scheme 23: Fluoro-substituted benzoxaboroles (three isomers) – compounds investigated for possible treatment disease caused by malarial parasite *Plasmodium falciparum* [49].

poly-*L*-lactic acid matrix was described by Sene et al. [167, 168]. The mechanism of AN2690 antifungal activity is connected with enzyme inhibition: trapping tRNA by creation stable adduct tRNA^{Leu} in the editing site of the leucyl-tRNA synthetase [44]. Other active fluorobenzoxaborole is the 5-fluoro-6-ethylamino-derivative, AN3018. Its interaction with enzyme is based on the formation of additional hydrogen bond to ethylamine group and was proved by crystallography of the complex [45]. Another fluorinated benzoxaborole, AN5568, is active against human African trypanosomiasis [98, 169] (Scheme 21).

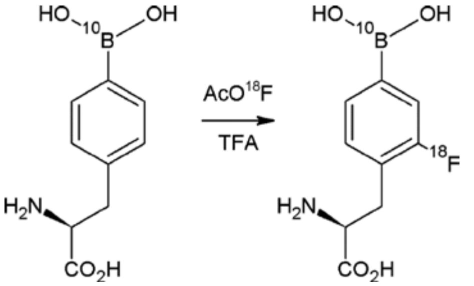
Biological activity of 2,4,6-trifluorophenylboronic acid and its catechol ester against several fungi and bacteria was investigated and compared with that of AN2690 [170]. Results show significant advantage of AN2690 over others compounds. Other extensive comparison of biological activity between diversely fluoro-substituted benzoxaboroles was presented by Baker et al. [122]. Again, AN2690 had the lowest minimum inhibitory concentrations. Rock et al. [44] investigated several fluorinated boronic compounds and showed significant difference in the inhibitory concentration between AN2690 and investigated compounds.

AN2690 was used also as a part of more complex compounds. AN2690-containing molecules were investigated as HCV NS3 protease inhibitors (Scheme 22) [47]. Noteworthy is, that this potential inhibitors have 6-amino group as in AN3018. The best inhibition properties is displayed by compounds with R_1 and R_3 moieties (from similar 10 compounds studied). Akin AN2690-containing macrocycles were also investigated as HCV NS3 protease inhibitors [48].

Among 22 benzoxaborole-based compounds investigated against malarial parasite *Plasmodium falciparum*, three monofluoro-substituted isomers (Scheme 23) have the lowest IC_{50} values. The most effective was the 4-fluorosubstituted isomer [49].

$^{10}B + {}^{1}n \rightarrow [^{11}B] \rightarrow {}^{7}Li + {}^{4}He\ (\alpha) + 2.79\ MeV$

Scheme 24: The fission reaction of ^{10}B atom. Basic process in BNCT [50].



Scheme 25: Radiosynthesis of 4-[^{10}B]borono-2-[^{18}F]fluoro-*L*-phenylalanine (18F-PBA) [171].

Boron neutron capture therapy. Positron emission tomography

In contrast to traditional radiotherapy, the boron neutron capture therapy (BNCT) is a biologically-targeted one. It means, that BNCT saves normal tissue around tumor [171]. ^{10}B atom captures a neutron and converts it to an unstable ^{11}B isotope, than decays to ^{7}Li and α particle (Scheme 24) [50, 171]. The penetration range of particles is as short as dimension of a cell. For efficient delivery of radionuclides to tumour issue, suitable carrier is needed. Approved for clinical use are mercapto[^{10}B]borane (BSH) [172–174] and *p*-[^{10}B]boronophenylalanine (PBA) [170, 173]. To monitor by positron emission tomography (PET) Imaging pharmacokinetics, incorporation in cells and metabolism of PBA, 4-[^{10}B]borono-2-[^{18}F]fluoro-*L*-phenylalanine (18F-PBA, Scheme 24) was investigated [50–60].

Connection between BNCT and magnetic resonance imaging (MRI) was also proposed [62] basing on 4-[^{10}B]borono-2,6-fluorophenylalanine, 4-[^{10}B]borono-2,6-fluorophenylalaninol (racemate) and on 2-trifluoromethyl analogs (all with [^{19}F]fluorine). The 4-[^{10}B]borono-2,6-fluorophenylalaninol has over eight-fold solubility in water than 4-[^{10}B]borono-2,6-fluorophenylalanine and 4-[^{10}B]boronophenylalanine. Moreover the former compound has the lowest IC_{50} – 0.8. For comparison, 4-[^{10}B]borono-2,6-fluorophenylalanine and 4-[^{10}B]boronophenylalanine have IC_{50} value over 6 and 4, respectively and the best incorporation values into tumour cells (over 1.0 μg/1.0 × 10^{7} of [^{10}B]boron concentration).

Although various similar to ^{18}F-PBA radiocompounds are obtained by activation of nitro groups (such as radiofluorinated DOPA and phenylalanine), nucleophilic approaches to ^{18}F-PBA are not appropriately efficient because of Lewis acidic character of boron [175]. Radiosynthesis of ^{18}F-PBA with use of acetyl [^{18}F]hypofluorite in trifluoroacetic acid (TFA) was reported (Scheme 25) [171, 176–178]. Another approach is applying gas [^{18}F]fluorine ([^{18}F]F$_2$) in freon-11 (CCl_3F) and TFA [175]. The desired product was isolated from by-products by semi-preparative RP-HPLC. Similar method was applied into automated module, in which [^{18}F]F$_2$ is added into 4-[^{10}B]borono-*L*-phenylalanine dissolved in TFA [179].

Pinacol and benzopinacol 2,6-difluoro-4-carboxyphenylboronates' and a biotin derivatives' conversion to corresponding [^{18}F]-labeled trifluorophenylborates was reported [180]. Stability of benzopinacol esters is appropriate for PET imaging (stability over two-fold of the half-life of the ^{18}F). Condensation of benzopinacol 3-carboxy-2,4,6-trifluorophenylboronate with biotinylated piperazine and conversion to the corresponding [^{18}F]-labeled trifluoroborane yielded a novel radiotracer. Tests of distribution of radiotracer in mice were presented [181]. Conversion to labeled trifluoroboranes was also investigated for chromophoric BODIPY derivative of benzopinacol 2,4,6-trifluoroboronate [182]. Benzopinacol 3-carboxy-2,4,6-trifluorophenylboronate was also linked with marimastat – drug for breast cancer – by diether chain and converted to [^{18}F]fluoro-[^{19}F]difluoroborane [183]. The final compound enables matrix metalloproteases' activity in vivo monitoring by PET, which would be helpful in breast cancer treatment.

It was established, that isotope ^{18}F introduces some difficulties, such as time constrains, recombination and fragmentation [174]. Therefore, 4-[^{10}B]borono-2-fluorophenylalanine with [^{19}F]fluorine (2-F PBA) was investigated. To improve solubility of 2-F PBA in water, the complex with fructose was created by boronic group.

Apart from applying boronic acid in BNCT, ^{18}F-radiolabeling of various peptides by Suzuki-Miyaura cross-coupling (SMC) was reported [133]. SMC of chemically modified subtilisin from *Bacillus lentus* containing *p*-iodobenzylcysteine [183] with 4-[^{18}F]fluorophenylboronic acid was investigated. SMC was successfully carried out also with synthesized decamer polypeptide called comprehensive carcinoma homing peptide (CCHP) [133], containing 4-iodo-*L*-phenylalanine. CCHP was characterized as widely cancer-targeting [184].

Fluorophenylboronic acids as catalysts

3,4,5-Trifluorophenylboronic acid was found to be a catalyst in the condensation reaction of carboxylic acids and ureas (Scheme 26) [186].

Another application of fluorinated phenylboronic acids is the catalysis of dipeptide synthesis. 3,4,5-Trifluorophenylboronic acid and *o*-nitrophenylboronic acid – among others investigated boronic acids – gave good or excellent yields [187].

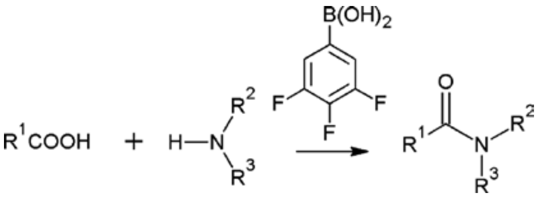
Other example is catalysis of Friedel-Crafts prenylation and alkylation with use of perfluorophenylboronic acid, 2,3,4,5-tetrafluorophenylboronic acid and 2,3-difluoro-4-pyridiniumboronic acid chloride – two last gave the best yields (80 %) [188].

Fluorinated phenylboronic acid in electrochemistry – anion complexing properties

Important application of fluorinated phenylboronic acids chemistry is their use in electrochemistry as anion complexing agents. Additives to lithium-ion battery increase solubility of salts in non-aqueous solution, with increases conductivity [33–39]. As additives for battery electrolytes phenylboronic esters [33, 37–39], borates [34, 35] and borinates can be used [36]. Nair et al. [32] reported, that introduction of fluorine substituents into phenyl rings in boroxines increases the fluoride anion binding energy. Similar tendency can be observed for esters [82], where increase of conductivity was also remarked [38]. The influence of other fluoro-substituted phenylboronic esters on conductivity of polymer electrolytes was also investigated [33, 39].

The concept of a fluorine tag

High sensitivity of ^{19}F NMR chemical shift on the changes in the organic molecule allows to use the fluorine substituent as “fluorine tag”. 2-Formyl-4-fluorophenylboronic acid was used as a derivatizating agent in a three-component coupling reaction with (*rac*)-α-methyl-benzylamine with diol to afford diastereomeric imino-boronate esters. This method was applied to determine enantiomeric purity of chiral diols [189]. Recently, Axthelm et al. [190] described an array of three water-soluble boronic acid receptors in combination with ^{19}F NMR spectroscopy to discriminate diol-containing bioanalytes: catechol, dopamine, fructose, glucose, glucose-1-phosphate, glucose-6-phosphate, galactose, lactose, and sucrose at low mM



Scheme 26: Phenylboronic acid-catalyzed amide condensation [186].

concentrations. Another example is the use of fluorinated boronic acid appended pyridinium salts in combination with ^{19}F NMR spectroscopy to screen a pool of 59 analytes [191].

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