L-4-Boronophenylalanine (all around the one molecule)

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Dedicated to Prof. Irina Beletskaya on the occasion of her 75 anniversary

Abstract
L-4-Boronophenylalanine (L-BPA) is one of the two clinically approved drugs for boron neutron capture therapy of cancer. This mini-review describes various aspects of its chemistry: methods of synthesis, drug formulation, modifications directed to study its biodistribution and pharmaco-kinetics, as well as the application of L-BPA in organic synthesis.

Keywords: 4-Boronophenylalanine (BPA), synthesis, drug formulation, biodistribution and pharmacokinetics, Suzuki-Miyaura reaction, Boron Neutron Capture Therapy (BNCT)

Contents

1. Introduction

4-Boronophenylalanine (BPA, Scheme 1) is a boronated amino acid, which exhibits a specific affinity for tumors. Its ^{10}B-enriched form has been clinically approved for Boron Neutron

Capture Therapy (BNCT) of cancer, a binary method for the treatment of cancer, which is based on the nuclear reaction of two essentially nontoxic species, nonradioactive ^{10}B and low-energy thermal neutrons. The neutron-capture reaction by ^{10}B produces an α-particle ^{4}He^{2+} and ^{7}Li^{3+} ion together with 2.4 MeV of kinetic energy and a 480 keV photon. These high-linear-energy transfer ions dissipate their kinetic energy before traveling one cell diameter (5–9 μm) in biological tissues, ensuring their potential for precise cell killing. Therefore, high accumulation and selective delivery of boron into the tumor tissue are the most important requirements to achieve efficient neutron capture therapy of cancer.[1,2]
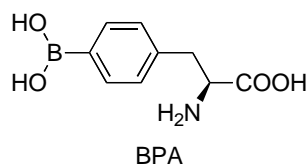
In this review, various aspects of the chemistry of 4-boronophenylalanine will be considered, including methods of its synthesis, drug formulation, modifications directed to study its biodistribution and pharmacokinetics, as well as the application of L-BPA in organic synthesis.

2. Synthesis of 4-Boronophenylalanine

The growing significance of BPA as a BNCT agent as well as its synthetic utility in the preparation of 4-substituted phenylalanine derivatives resulted in a development of numerous methods of its synthesis based on different synthetic methods. At present, preparation of this rather simple compound can be considered as a striking illustration of the wealth and diversity of the arsenal of organic syntheses.

All described methods of synthesis of BPA could be divided into three groups depending on the bond formed in the key step of BPA synthesis.

2.1 Introduction of the amino acid group

The first group includes methods based on the formation of the C1–C2 bond between various synthetic equivalents of the amino acid and the boron-containing benzyl or benzaldehyde fragment.
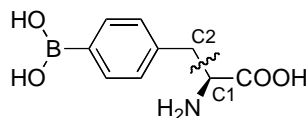

This approach was used in the first synthesis of BPA by Snyder et al.[3] featuring the reaction of 4-dihydroxyborylbenzyl bromide with diethyl acetamidomalonate followed by alkaline hydrolysis and decarboxylation (Scheme 1).
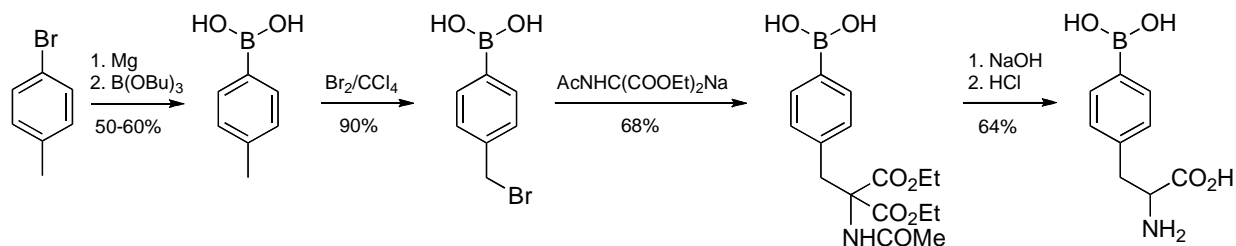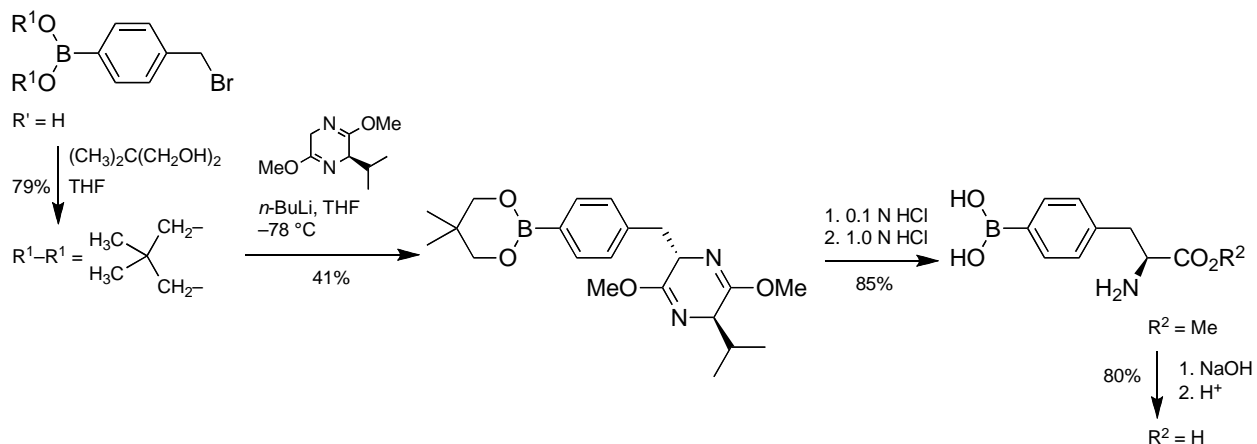
Scheme 1

Unfortunately, in this method the BPA yield did not exceed 40% (based on *p*-tolylboronic acid). Better yields have been obtained after protection of the dihydroxyboryl group with diols resulting in cyclic ethers of boronic acid. For instance, the reaction of 4-dihydroxyborylbenzyl bromide with 2,3-dimethyl-2,3-butanediol gives 4-(pinacolylborono)benzyl bromide,[4] which in turn, reacts with ethyl 2-(diphenylmethyleneamino)acetate to give protected BPA[5] (Scheme 2).
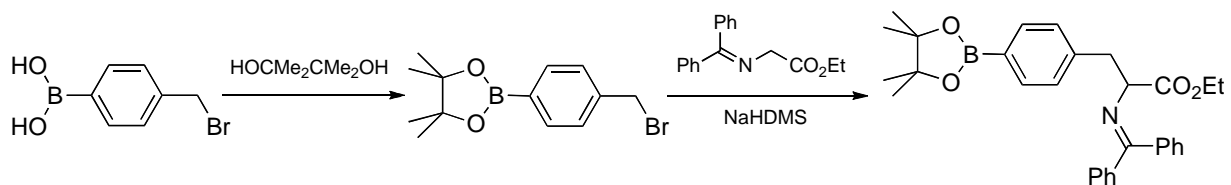
Scheme 2

The racemic mixture of L- and D-BPA can be separated by transformation of the amino acids into ethyl esters followed by selective hydrolysis of the L-isomer using the proteolytic enzyme chemotrypsin.[6]

The same approach can be used for the enantioselective synthesis of L-BPA. One synthesis is based on an enantioselective alkylation of (2*R*)-(−)-2,5-dihydro-2-isopropyl-3,6-dimethoxy-pyrazine and gives L-BPA in 22% yield[7] (Scheme 3).
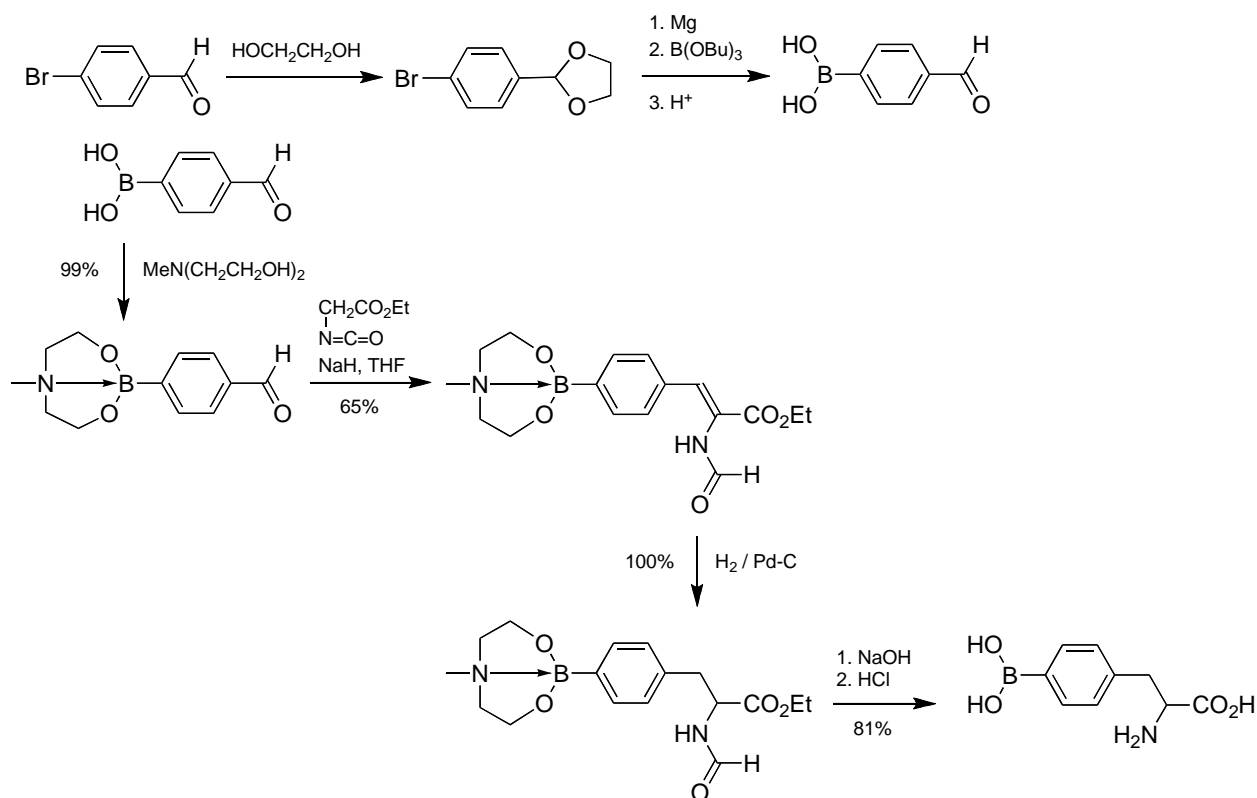

Scheme 3

It should be noted that alkaline hydrolysis of the methyl ether at the last step results in some racemization of the amino acid. The racemization has been avoided by the enzymatic hydrolysis with chymotrypsin, however, the yield of this step drops to 64%.[7]

Another enantioselective synthesis of L-BPA utilizes Seebach's imidazolidinone (Scheme 4).[5]
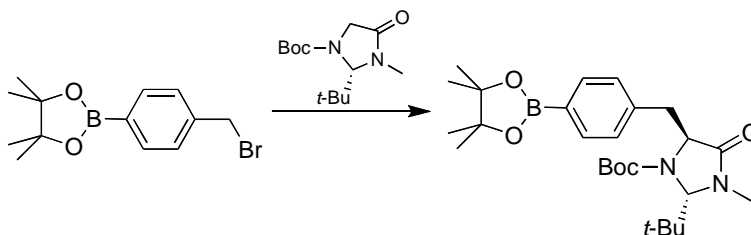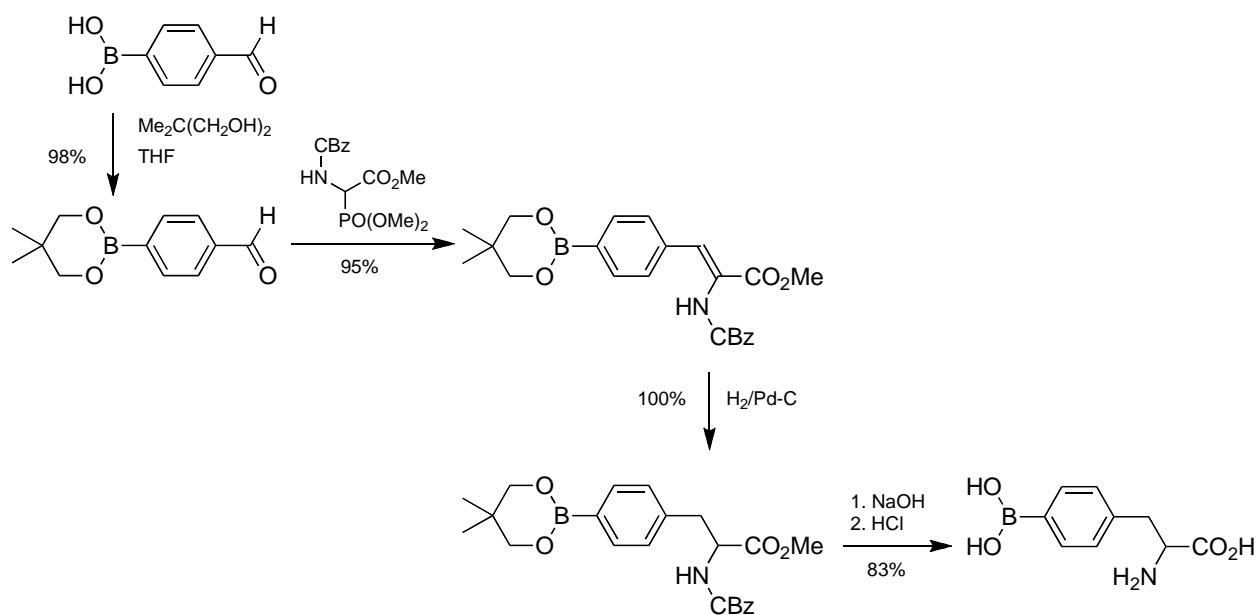

Scheme 4

Another effective approach makes use of *p*-formylboronic acid as the starting material. Protection of the dihydroxyboryl group with *N*-methyldiethanolamine[8] followed by the reaction of the formyl group with sodium salt of ethyl isocyanoacetate, catalytical hydrogenation of the double bond formed, and deprotection affords BPA in 52% yield (Scheme 5).[9]
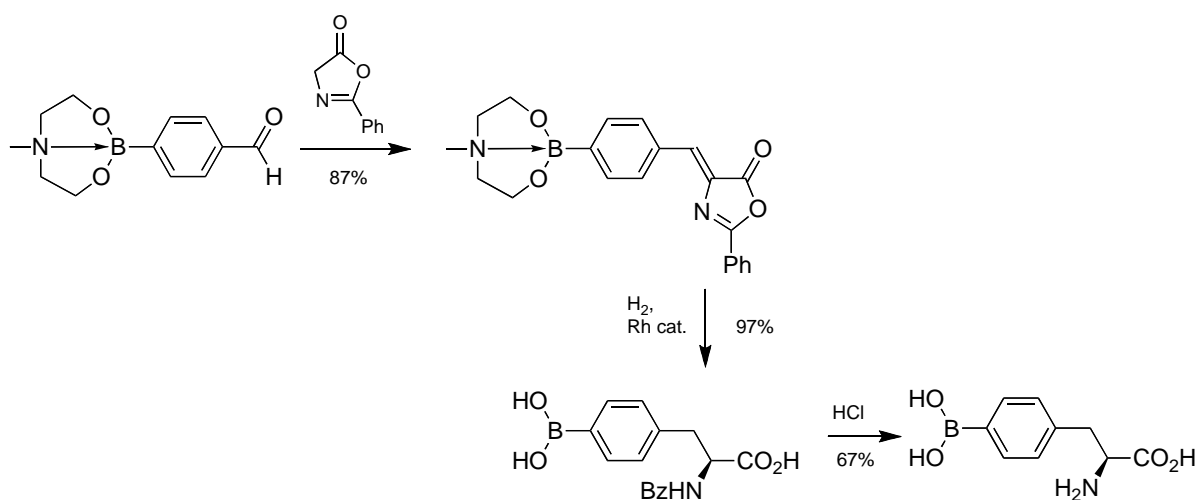

Scheme 5

The other method based on *p*-formylboronic acid includes protection of the dihydroxyboryl function with 2,2-dimethylpropan-1,3-diol followed by the reaction with *N*-(benzyloxycarbonyl) phosphonoglycine trimethyl ester. The subsequent catalytic hydrogenation of the double bond and deprotection results in formation of BPA in 62% yield (Scheme 6).[10]
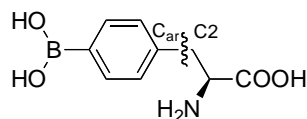

Scheme 6

The enantioselective synthesis of L-BPA based on catalytic hydrogenation with the chiral catalyst (1,5-cyclooctadiene)[*R*-1,2-bis(diphenylphosphino)propane]rhodium(I) tetrafluoroborate has been proposed (Scheme 7).[11]
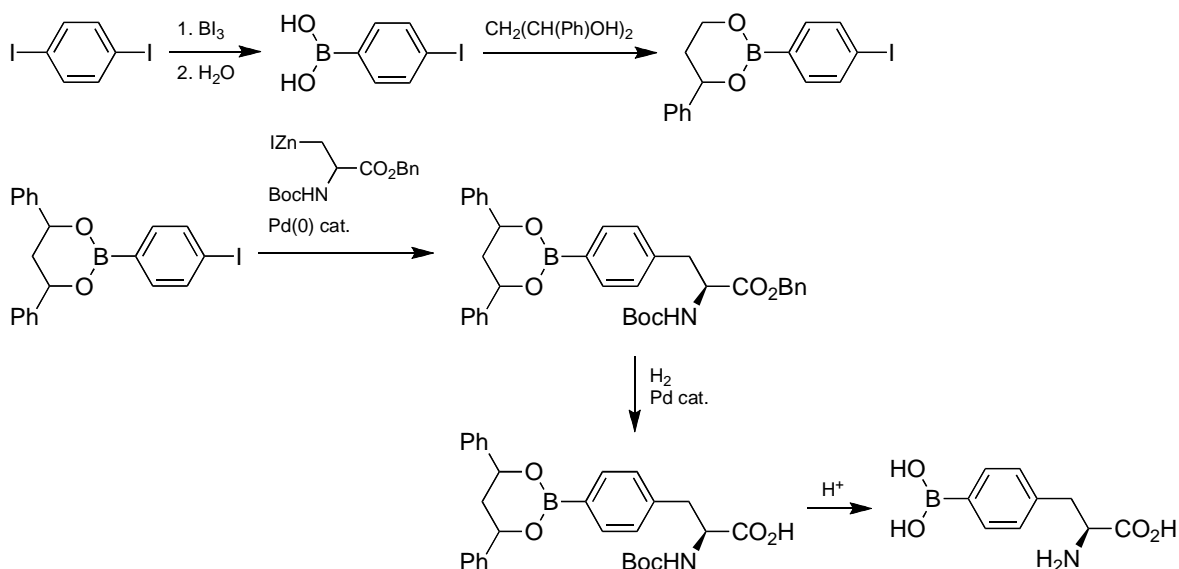

Scheme 7

2.2 Coupling of alanine with phenyl boronic acid

The second group of synthetic methods of BPA is based on the formation of the C2–C$_{ar}$ bond between the phenyl ring and the L-alanine fragment resulting in enantiomerically pure L-BPA.


At present, only one example of this approach has been reported (Scheme 8).[12] Unfortunately, this synthesis requires the preliminary preparation of an L-alanine zinc derivative and gives a rather low yield of the target product (~40% based on 4-iodophenylboronic acid and ~25 % based on the amino acid).

Scheme 8

## 2.3 Introduction of boronic acid group into phenylalanine

The third group of methods of BPA synthesis is based on the introduction of the dihydroxyboryl substituent directly to the phenylalanine fragment with formation of the C–B bond. This approach allows using commercially available enantiomeric amino acids and minimizes transformations of the [10]B-enriched product.
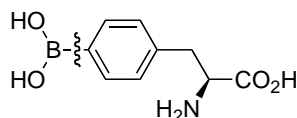
The first synthesis applying this approach was proposed by Malan and Morin in 1998.[13] It includes the Pd-catalyzed cross-coupling of protected L-4-iodophenyl alanine with diboronic acid dipinacolate followed by removal of protecting groups and results in L-BPA in 53% yield (based on the amino acid) (Scheme 9).
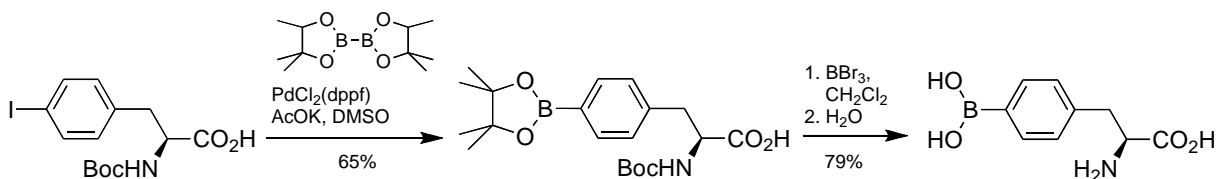
Scheme 9

The yield of the cross-coupling stage can be boosted up to 88% by protecting the carboxylic acid of the phenylalanine reactant as benzyl ester.[13] Another modification of this synthesis protects the carboxylic acid as methyl ester (Scheme 10).[14,15]
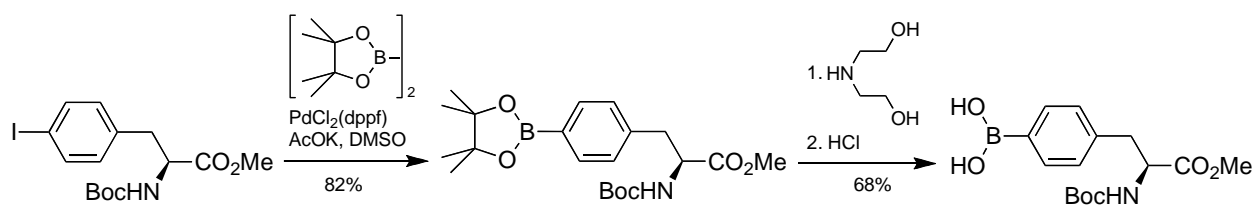
Scheme 10

Further development of this approach utilizes the more readily available L-tyrosine triflate (instead of L-4-iodophenylalanine) and 1,3-diphenyl-1,3-propanediol ester of diboronic acid (instead of diboronic acid dipinacolate).[16] In the last case the yield of the target product is 48% (based on the amino acid) (Scheme 11).
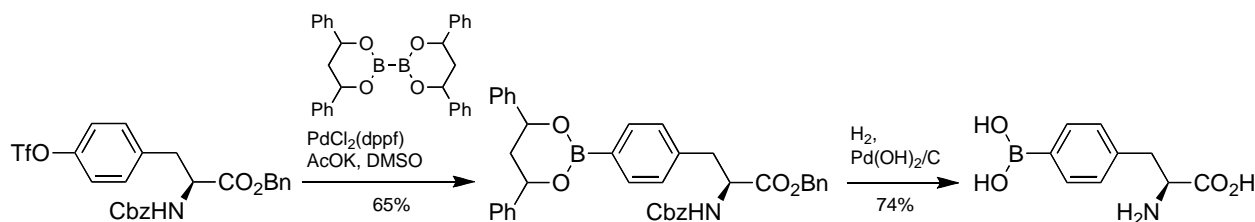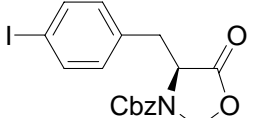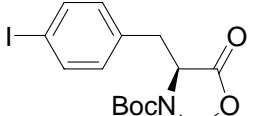
Scheme 11

The main disadvantages of these good-looking synthetic schemes are low-yields for the multi-step syntheses of the boronating agents[13,16] and loss of more than 50% of [10]B-enriched materials at the coupling stage.

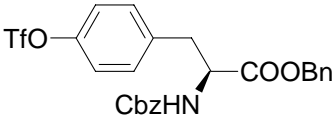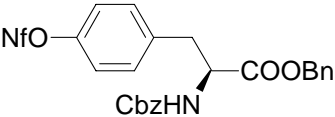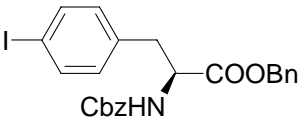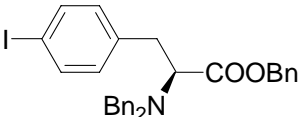A breakthrough took place when the boronating agents were changed for pinacolborane,[17] which can be easily prepared by the reaction of commercially available borane-dimethylsulfide complex with pinacol.[18] Surprisingly, in this case the 4-iodo-L-phenylalanine derivatives have been found to be more effective than L-tyrosine triflates and nonaflates (Table 1).[19]

Table 1. Palladium-catalyzed cross-coupling of pinacolborane with 4-iodo-L-phenylalanine and L-tyrosine derivatives

Amino acid derivative	Yield[a] %	Total chemical yield (%) of L-BPA	
		based on pinacolborane	based on amino acid
TfO—⟨aryl⟩—COOBn, CbzHN	> 5	–	–
NfO—⟨aryl⟩—COOBn, CbzHN	58[b]	21	18
I—⟨aryl⟩—COOBn, CbzHN	82	29	16
I—⟨aryl⟩—COOBn, Bn₂N	84	20	19
I—⟨aryl⟩—CbzN oxazolinone	72	29	35
I—⟨aryl⟩—BocN oxazolinone	71	32	21

[a] Conditions: 3 mol% [PdCl2(dppf)], triethylamine, 1,4-dioxane, 80–100 °C, 16–36 h.
[b] [PdCl$_2$(PPh$_3$)$_2$] used as a catalyst.

Overall the best yield of L-BPA was obtained starting from 4-iodo-L-phenylalanine protected with 3-(benzyloxycarbonyl)oxazolin-5-one (Scheme 12).[19]
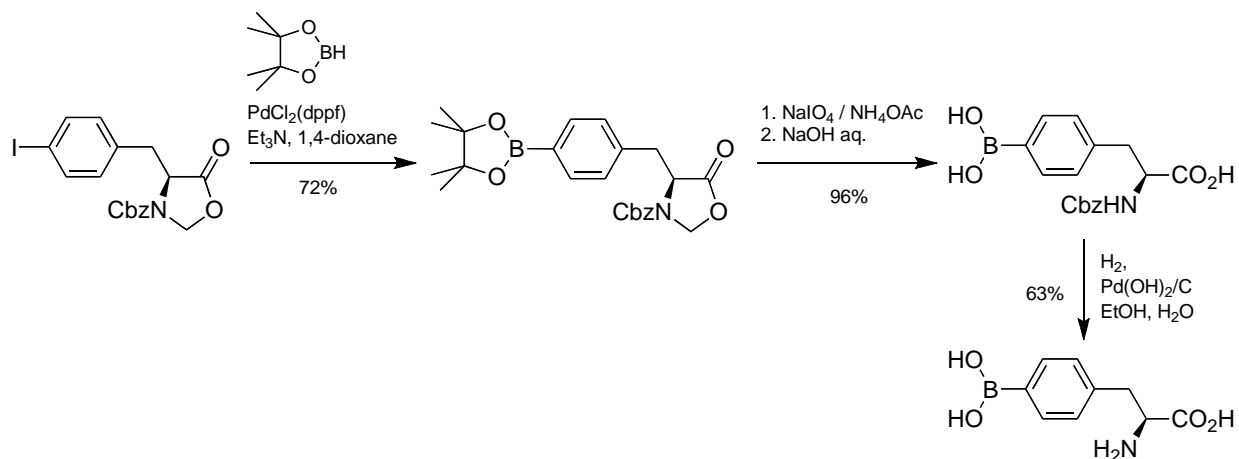
Scheme 12

The most recent improvement of this method employs ionic liquids [*bmim*][X], (*bmim* = 1-butyl-3-methylimidazolium, X = BF$_4$, PF$_6$) at the cross-coupling stage. The reaction was completed in 20 min producing the boronated phenylalanine in high yield (Scheme 13). The product is readily isolated by simple separation of phases.[20]
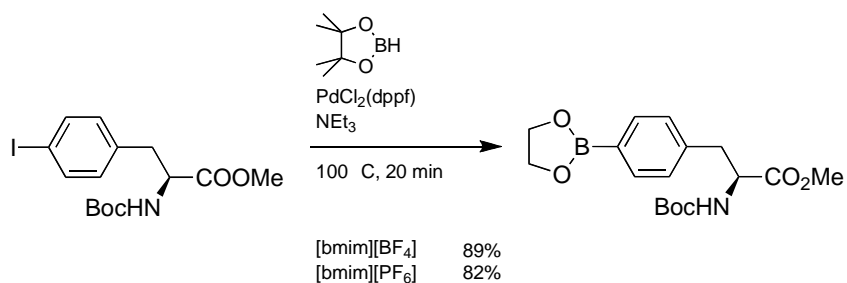
Scheme 13

In general, contemporary methods of organic synthesis allow synthesizing L-BPA with high efficiency. Some further improvement of the synthetic methods could be achieved by proper choice of the protective groups and deprotection reactions.

3. Drug Formulation and Delivery

Drug formulation and delivery is a very important factor, especially if a drug has poor solubility; this is the case for L-BPA having very limited water solubility (1.6 g/L). The crystal structure of L-BPA, established by X-ray diffraction method, shows an extended pattern of hydrogen bonding involving the boronic acid, carboxylate and ammonium groups.[21]

The first attempt to solve the water solubility problem made use of the hydrochloride salt L-BPA·HCl.[22] However, the acidity of a 0.1 M solution has been reported with a pH ≈ 1.5.

A recent approach is based on tight and reversible esterification of the boronic acid moiety with 1,2- and 1,3-diols (Scheme 14).[23-25] The interaction between a boronic acid and a diol is known to be one of the strongest single-pair reversible functional group interactions in an aqueous environment and it is widely used for construction of boronic acid-based sugar sensors.[24,26-31]
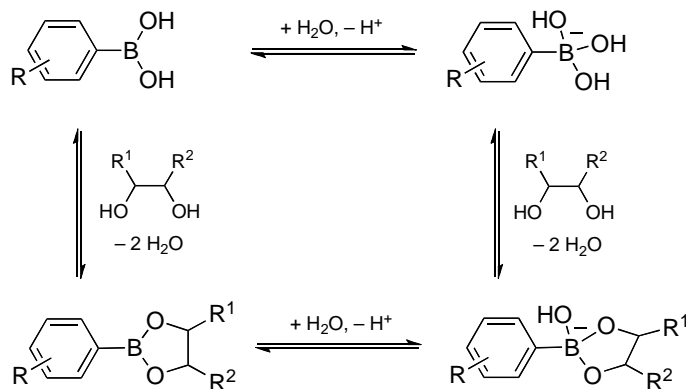
Scheme 14

Therefore, it is not surprisingly that the formation of esters of L-BPA with monosaccharides (fructose, in particular) was proposed to produce a water soluble form of L-BPA for BNCT.[32–36] Intravenous injection of the L-BPA-fructose complex is now the standard method for its clinical use. According to multinuclear NMR spectroscopy data the L-BPA-fructose complex in water buffered at physiological pH has been found to adopt the structure of β-D-fructofuranose 2,3,6-(p-phenylalanylorthoboronate).[37]
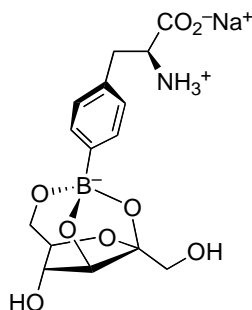
Another approach proposed to obtain water-soluble forms of BPA is the transformation into amides containing water-solubilizing hydroxyl groups. These forms have a high water solubility and lower cytotoxicity than BPA itself and might be suitable boron carriers on BNCT for malignant brain tumor.[38-40]
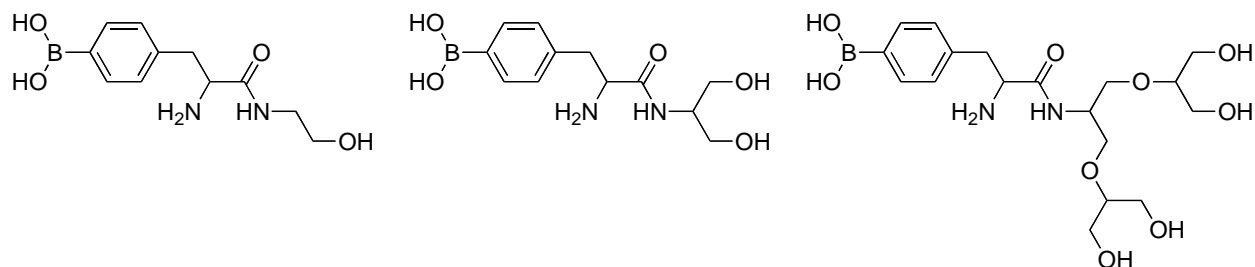
4. Study of Biodistribution and Pharmacokinetics

Studying the biodistribution of pharmacokinetics of boron compounds (particularly BPA) is of great importance both for biomedical studies and for planning of patient treatment. Several methods have been developed to determine the boron content of biological research samples taken at biopsy and in tissues obtained from animal biodistribution experiments. These samples are often available in macroscopic quantities of 50–100 mg or more. Following the oxidative dissolution of weighed tissue samples, boron analysis of the aqueous sample is accomplished with inductively coupled plasma- or direct current plasma-atomic emission spectroscopy (ICP-AES and DCP-AES, respectively). These methods determine boron in tissue reliably at a level of 1 ppm.[41] However, none of these methods can be applied non-invasively for monitoring the in situ boron distribution in patients.

For in vivo imaging of boron compounds, radio-labeled derivatives are of particular interest because their biodistribution can be easily monitored. In many cases, radio-labeling provides detailed information about boron pharmacokinetics that can be used to generate improved patient treatment protocols, for example, by providing information about the required dosage of tumor-seeking boron conjugates, and optimal treatment time. Positron emission tomography (PET) using ^{18}F-labeled L-BPA (Scheme 15)[42] has been developed for this purpose and at present is widely used for patient treatment.[43–48]
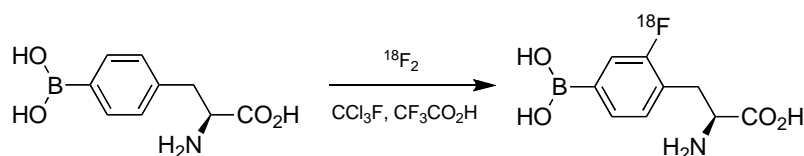
Scheme 15

Another approach includes PET imaging using ^{11}C-labelled L-BPA prepared by a modified Bucherer-Strecker procedure (Scheme 16) followed by separation of the enantiomers by chiral HPLC.[49]
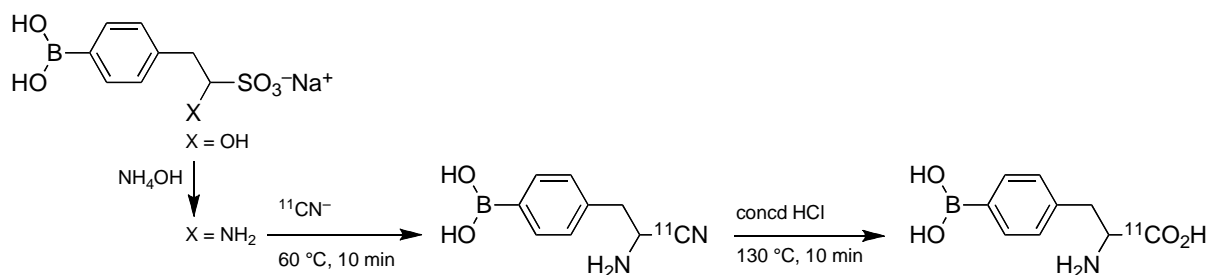
Scheme 16

^{10}B and ^{11}B magnetic resonance imaging (MRI) was proposed as a non-invasive method for the in vivo assessment of BNCT agents, but its practical utilization still remains to be proven.[50,51] The other recently developed approach is ^{19}F MRI of fluorine-containing BPA derivatives.[52,53]
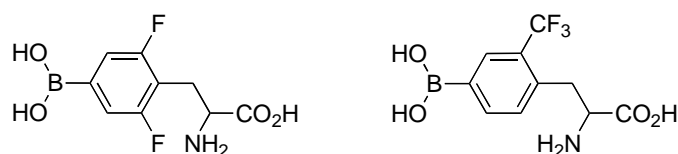
5. Non-medical Applications – BPA in Organic Synthesis

Development of effective methods of BPA synthesis resulted in active use of this amino acid and its derivatives in organic synthesis utilizing Pd-catalyzed cross-coupling (Suzuki-Miyaura reaction). This approach was applied to the synthesis of 4-vinyl[5], 4-aryl[5,15,54,55] and 4-heteroaryl (thiophene,[5,15,54,55] pyridine,[5,15,55] pyrimidine,[5,55] pyrazine,[55] pyridazinone,[56] quinoline,[5] benz–imidazole[55]) derivatives of phenylalanine. Very recently this methodology was used for the introduction of the L-phenylalanine moiety into purine bases, nucleosides and nucleotides.[57,58] Other examples are the Pd-catalyzed synthesis of L-phenylalanine-based amidine[59] and the Cu-mediated reaction with phenols.[14] Some examples are shown below.
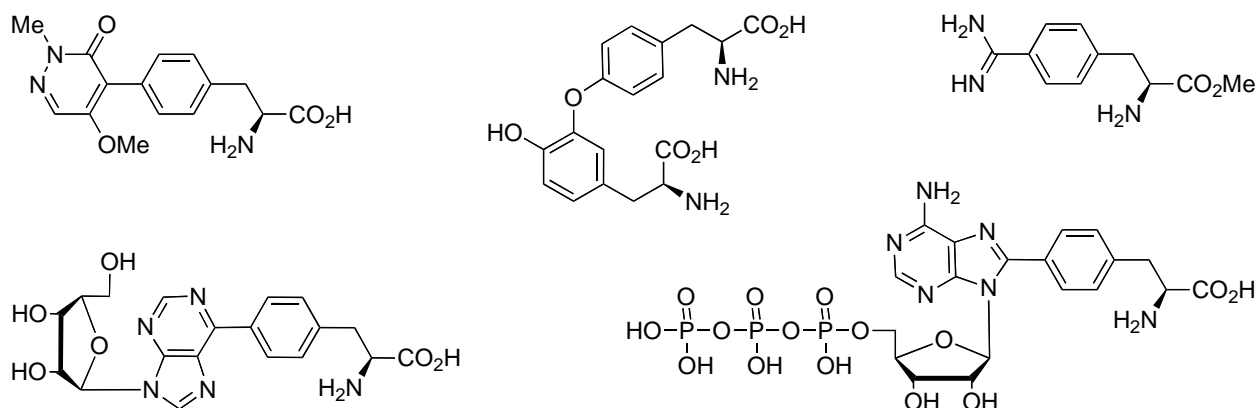
6. Conclusions

Contemporary methods of organic synthesis open ways to the synthesis of L-BPA with high efficiency. Some further improvement of the developed synthetic methods could be achieved by proper choice of the protective groups and deprotection reactions. At present, good availability of L-BPA allows its use in organic synthesis for the preparation of various substituted phenyl-alanines.

Presently, BPA is the most studied boron-containing amino acid; however, it should be remembered that progress of BNCT caused the synthesis of a wide arsenal of boronated amino acids;[60] probably, some of these compounds or their analogues could soon find an application as BNCT drugs.

Acknowledgements

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