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# Direct, Regioselective, and Chemoselective Preparation of Novel Boronated Tryptophans by Friedel–Crafts Alkylation

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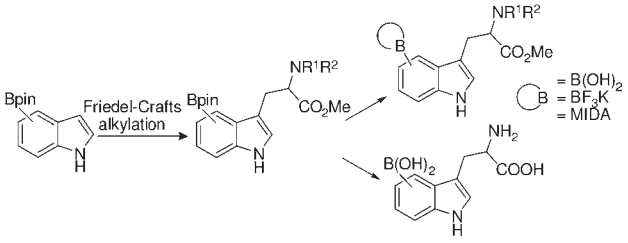
## ABSTRACT




**A facile synthetic approach to the direct preparation of various novel unnatural boronated protected tryptophans using a regio- and chemoselective electrophilic substitution of 4- and 5-boronated indoles with *N*-protected dehydroalanine is described. The gram-scale synthesis of two free tryptophan boronic acids is also reported.**

In the past decade, there has been considerable interest in functionalized amino acids bearing a hidden reactive center such as sulfur, selenium, phosphorus, fluorine, or boron.[1] Among them, boronated amino acids have received significant attention as potential pharmaceuticals due to their use as enzyme inhibitors,[2] as anti-HIV agents,[3] and for their preferential uptake by growing tumor cells. Hence, they have promising applications in boron neutron capture therapy (BNCT).[4] Remarkably, the recent biosynthetic incorporation of a boronate-containing amino acid into proteins allowed for selective protein modifications and easier protein purification.[5]

Additionally, amino acid derivatives with an organoboron functionality on the side chain have been prepared and used in Rh-, Ru-, Ni-, Cu- and Pd-catalyzed cross-coupling reactions to prepare new alkylated or arylated cross-linked amino acids and complex biologically active

(1) (a) Zhu, Y.; van der Donk, W. A. *Org. Lett.* **2001**, *3*, 1189. (b) Liu, S.; Dockendorff, C.; Taylor, S. D. *Org. Lett.* **2001**, *3*, 1571. (c) Martarello, L.; McConathy, J.; Camp, V. M.; Malveaux, E. J.; Simpson, N. E.; Simpson, C. P.; Olson, J. J.; Bowers, G. D.; Goodman, M. M. *J. Med. Chem.* **2002**, *45*, 2250. (d) Jacob, C.; Giles, G. I.; Niroshini, M.; Sies, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4742. (e) Volk, F.-J.; Wagner, M.; Frahm, A. W. *Tetrahedron: Asymmetry* **2003**, *14*, 497. (f) Wang, L.; Shultz, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 34. (g) Braga, A. L.; Ludtke, D. S.; Paixao, M. W.; Alberto, E. E.; Stefani, H. A.; Juliano, L. *Eur. J. Org. Chem.* **2005**, *20*, 4260. (h) Kaiser, P. F.; Churches, Q. I.; Hutton, C. A. *Aust. J. Chem.* **2007**, *60*, 799.

(2) Touchet, S.; Carreaux, F.; Carboni, B.; Bouillon, A.; Boucher, J.-L. *Chem. Soc. Rev.* **2011**, *40*, 3895.

(3) Chen, X.; Bastow, K.; Goz, B.; Kucera, L.; Morris-Natschke, S. L.; Ishaq, K. S. *AntiViral Chem. Chemother.* **1996**, *7*, 108.

(4) (a) Hawthorne, M. F.; Maderna, A. *Chem. Rev.* **1999**, *99*, 3421. (b) Barth, R. F.; Coderre, J. F.; Vicente, M. G. H.; Blue, T. E. *Clin. Cancer Res.* **2005**, *11*, 3987. (c) Kabalka, G. W.; Yao, M.-L. *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 111. (d) Kabalka, G. W.; Yao, M.-L.; Marepally, S. R.; Chandra, S. *Appl. Radiat. Isot.* **2009**, *67*, 374. (e) Kabalka, G. W.; Shaikh, A. L.; Barth, R. F.; Huo, T.; Yang, W.; Gordnier, P. M.; Chandra, S. *Appl. Radiat. Isot.* **2011**, *69*, 1778.

(5) Brustad, E.; Bushey, M. L.; Wook Lee, J.; Groff, D.; Liu, W.; Schultz, P. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 8220.

(6) (a) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hintermann, T. *J. Am. Chem. Soc.* **2001**, *123*, 12411. (b) Yoburn, J. C.; Vranken, D. L. V. *Org. Lett.* **2003**, *5*, 2817. (c) Bois-Choussy, M.; Cristau, P.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4238. (d) Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032. (e) Hutton, C. A.; Skaff, O. *Tetrahedron Lett.* **2003**, *44*, 4895. (f) Albrecht, B. K.; Williams, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11949. (g) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldobskiy, M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6347. (h) Crowley, B. M.; Mori, Y.; McComas, C. C.; Tang, D.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 4310. (i) Meyer, F.-M.; Liras, S.; Guzman-Perez, A.; Perreault, C.; Bian, J.; James, K. *Org. Lett.* **2010**, *12*, 3870. (l) Colgin, N.; Flinn, T.; Cobb, S. L. *Org. Biomol. Chem.* **2011**, *9*, 1864.

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cyclic peptide natural products.[6] However, current preparations of boronated amino acids are somewhat limited due to the incompatibility of the boronic acid moiety/derivatives with the reagents and catalysts used in many synthetic methods, intermediate organometallic species, and reagents employed in their preparation.[7]

Tryptophan, an essential amino acid, functions as both a building block in protein biosynthesis and a biochemical precursor; it plays a crucial role in a large number of biochemical processes carried out by functional proteins. It is abundantly found in most biologically active peptides that exhibit various physiological properties, in particular hormonal, antimicrobial, and anticancer activities.[8] Tryptophan analogues are also important building blocks for the synthesis of peptidomimetics, natural products, and biologically active compounds.[9] Among tryptophans, those which are substituted at the 4- and 5-positions are particularly interesting because they might be useful intermediates for the synthesis of naturally occurring (−)-aurantioclavine, serotonin tryptamine, and indole alkaloids, such as the ergot alkaloids, indolactam V, Chuangxinmycin, and CC-1065, and also unnatural derivatives such as triptans.[10] Furthermore, 4-substituted tryptophans are particularly challenging substrates for steric and electronic reasons since most electrophilic attacks prefer the 2- or 7-position of tryptophan.[11] This problem has been circumvented by a wide variety of ingenious methods, but all suffer from low efficiency and practicability.[12]

In accordance with the above-reported renewed interest in the design and synthesis of new boron-containing amino acids as well as the central role that tryptophan plays particularly in peptides and proteins, new, simple, and reliable methods for the efficient synthesis of tryptophan analogues containing boronic acids on the indole ring are highly desirable (Figure 1). Tryptophan derivatives have been previously synthesized by using enzymatic and chemical methods.[13]

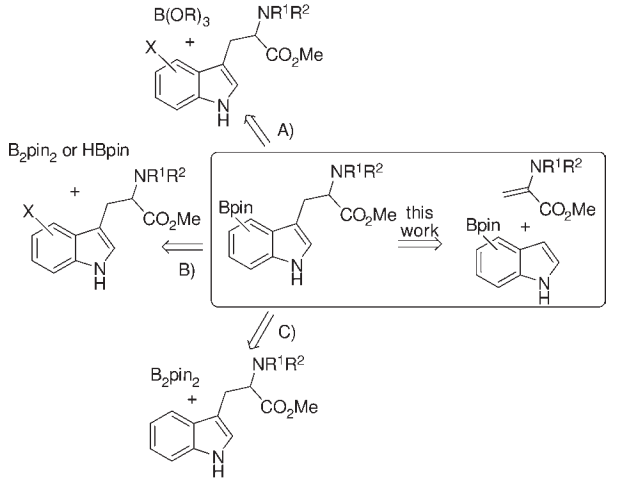



**Figure 1.** Possible approaches to boronated tryptophanes: path A (halogen−metal exchange), path B (Pd-catalyzed boronation), and path C (Ir-catalyzed C−H boronation).

Based on these considerations and taking into account the wide tolerance of the boronic acid ester, we envisioned the Lewis acid Friedel−Crafts alkylation of indoles with a dehydroamino acid for the synthesis of 4- or 5-boronated tryptophan derivatives.[14]

So, when we subjected the easily accessible boronated indoles (**1a**,**b**)[7c] to Friedel−Crafts conditions with *N*-acetyl dehydroalanine methyl ester (**2**) we obtained the boronated protected tryptophans **3a**,**b** in excellent yields with high regio- and chemoselectivity (Scheme 1).

To the best of our knowledge, this is the first reported example of direct Friedel−Crafts alkylation of boronated indoles. Notably, the widely used lithiation/trap with

(7) For a general overview of boronic acids, see: (a) *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*; Hall, D., Ed.; Wiley-VCH: 2005. For new approaches to prepare boronate with highly reactive functionalities, see: (b) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7164. For Miyaura cross-coupling reaction, see: (c) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (d) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359. For recent reviews of iridium-catalyzed direct boronation, see: (e) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (f) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992.

(8) (a) Chan, D. I.; Prenner, E. J.; Vogel, H. *J. Biochim. Biophys. Acta* **2006**, 1184. (b) Munoz, A.; Lopez-Garcia, B.; Perez-Paya, E.; Marcos, J. F. *Biochem. Biophys. Res. Commun.* **2007**, *354*, 172. (c) Yu, H.-Y.; Huang, K.-C.; Yip, B.-S.; Tu, C.-H.; Chen, H.-L.; Czeng, H.-T.; Cheng, J.-W. *ChemBioChem* **2010**, *11*, 2273.

(9) (a) Wen, S. J.; Yao, Z. J. *Org. Lett.* **2004**, *6*, 2721. (b) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5357. (c) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**, *6*, 2849. (d) Gonzalez-Vera, J. A.; Garcia-Lopez, M. T.; Herranz, R. *Org. Lett.* **2004**, *6*, 2641. (e) Miller, A.; Martin, S. F. *Org. Lett.* **2007**, *9*, 1113.

(10) Lead references, see: (a) Takano, S.; Nishimura, T.; Ogasawara, K. *Heterocycles* **1977**, *6*, 1167. (b) *The Alkaloids: Ergot Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 38, p 1. (c) Boger, D. L.; Yun, W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 2873. (d) Hopkins, S. J. *Drugs Today* **1992**, *28*, 155. (e) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1399. (f) Ishibashi, H.; Tabata, T.; Hanaoka, K.; Iriyama, H.; Akamatsu, S.; Ikeda, M. *Tetrahedron Lett.* **1993**, *34*, 489. (g) Khedkar, V.; Tillack, A.; Michalik, M.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 3123. (h) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohul, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745. (i) Brak, K.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2004.

(11) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.

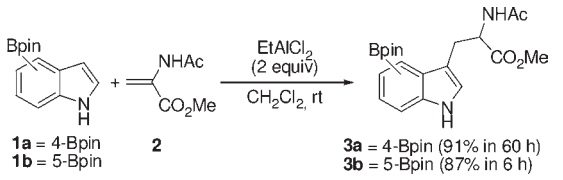
(12) (a) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815. (b) Li, L.; Martins, A. *Tetrahedron Lett.* **2003**, *44*, 5987. (c) Chae, J.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 3336. (d) Davies, H. M. L.; Manning, J. R. *J. Am. Chem. Soc.* **2005**, *128*, 1060. For metal-catalyzed processes: (e) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058. (f) Barluenga, J.; Jimenez-Aquino, A.; Aznar, F.; Valdes, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031.

(13) (a) Konda-Yamada, Y.; Okada, C.; Yoshida, K.; Umeda, Y.; Arima, S.; Sato, N.; Kai, T.; Takayanagi, H.; Harigaya, Y. *Tetrahedron* **2002**, *58*, 7851. (b) Goss, R. J. M.; Newill, P. L. A. *Chem. Commun.* **2006**, *47*, 4924. (c) Bittner, S.; Scherzer, R.; Harlev, E. *Amino Acids* **2007**, *33*, 19. (d) Sui, Y.; Liu, L.; Zhao, J. L.; Wang, D.; Chen., Y. J. *Tetrahedron Lett.* **2007**, *48*, 3779. (e) Blaser, G.; Sanderson, J. M.; Batsanov, A. S.; Howard, J. A. K. *Tetrahedron Lett.* **2008**, *49*, 2795. (f) E. Yokoyama, Y.; Nakakoshi, M.; Okuno, H.; Sakamoto, Y.; Sakurai, S. *Magn. Reson. Chem.* **2010**, *48*, 811. For an alternative route to completely protected boronated trypthophanes, see: (g) Prieto, M.; Mayor, S.; Lloyd-Williams, P.; Giralt *J. Org. Chem.* **2009**, *74*, 9202.

(14) (a) Angelini, E.; Balsamini, C.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *J. Org. Chem.* **2008**, *73*, 5654. (b) Lucarini, S.; Bartoccini, F.; Battistoni, F.; Diamantini, G.; Piersanti, G.; Righi, M.; Spadoni, G. *Org. Lett.* **2010**, *12*, 3844.

(15) Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551 and references therein.

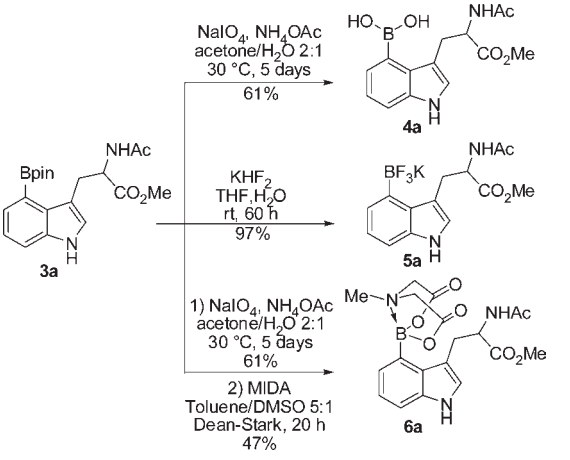
**Scheme 1.** Friedel–Crafts Alkylation of Boronated Indoles **1a**,**b** with *N*-Acetyl Dehydroalanine Methyl Ester **2**




boron electrophiles method (Figure 1, path A) and Pd-catalyzed Miyaura boronation (Figure 1, path B)[15] failed when applied to 4-bromotryptophan, showing the power of this approach. Nevertheless, Ir-catalyzed direct boronation of tryptophan (Figure 1, path C) led to a regioselective 2-boronated product in low yield.[16] Therefore this method is complementary for the synthesis of a series of boronated tryptophans that cannot be accessed by the above-mentioned methods, which are controlled by electronic and steric effects.

Chemoselective removal of the pinacol group of compound **3a** through oxidative cleavage with sodium periodate[17] provided the free tryptophan boronic acid **4a** in high yield, whereas the hydrolysis of the boron ester through trans-boro-esterification with phenyl boronic acid and 2 N HCl led to only a trace amount of the desired product (Scheme 2). Thus, 4-boronic acid protected tryptophan **4a** is easily obtainable through this method. This is quite important, since in some reactions, such as the Petasis reaction,[18] carbon–heteroatom couplings,[19] and oxidative homocoupling reactions,[20] free boronic acids have proven to be more efficient. However, boronic acids are never ideal because they exhibit several drawbacks, such as the partial formation of dimeric and cyclic trimeric boroxines (which depend on storage water content). Yet, in some cases, these reagents may suffer from long-term instability and protodeboronation. This has led to increased use of potassium aryltrifluoroborates[21] and *N*-methyliminodiacetyl (MIDA) boronates[22] which were recently developed. They are the next generation of boron synthetic intermediates that meet the challenge of stability and reactivity for all boronated compounds. Recently, Molander[23] and Burke[24] made superb efforts to advance the transition-metal-catalyzed Suzuki–Miyaura coupling using organotrifluoroborate salts and MIDA boronates as coupling partners.[25] Using standard conditions, compounds **5a** and **6a** were obtained from boronate and boronic acid tryptophans respectively, in almost quantitative yield after conventional flash chromatography on silica gel without specific precautions (Scheme 2).[26] Thus, four different protected boron-containing tryptophans (**3a**–**6a**) can be obtained and employed according to the use and purpose. In addition, **5a** and **6a** were exposed to air at rt for a period of 2 months and no detectable degradation was observed.[27]

**Scheme 2.** Conversion of Boronated Tryptophan **3a** to Boronic Acid **4a**, Trifluoroborate **5a**, and MIDA Boronated **6a**




We then turned our attention to preparing completely deprotected free amino acids **9a** and **9b**. Whereas the ester hydrolysis worked fine under standard conditions, the

(16) (a) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056. (b) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649. (c) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924. (d) Mertins, K.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2004**, *207*, 21. (e) Tagata, T.; Nishida, M. *Adv. Synth. Catal.* **2004**, *346*, 1655. (f) Paul, S.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 15552. (g) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E.; Smith, M. R. *J. Org. Chem.* **2009**, *74*, 9199. (h) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E., Jr.; Smith, M. R., III. *J. Org. Chem.* **2009**, *74*, 9199. (i) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068.

(17) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757.

(18) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.

(19) (a) Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029. (b) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381.

(20) (a) Gao, X.; Zhang, Y.; Wang, B. *Org. Lett.* **2003**, *5*, 4615. (b) Coskun, A.; Akkaya, E. U. *Org. Lett.* **2004**, *6*, 3107. (c) Nishiyabu, R.; Kubo, Y.; James, T. D.; Fossey, J. S. *Chem. Commun.* **2011**, *47*, 1106.

(21) (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020. (b) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (c) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (e) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. (f) Bagutski, V.; Ros, A.; Aggarwal, V. K. *Tetrahedron* **2009**, *65*, 9956.

(22) (a) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716. (b) Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17.

(23) (a) Molander, G. A.; Sandrock, D. L. *Curr. Opin. Drug Discovery* **2009**, *12*, 811. (b) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240.

(24) (a) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084. (b) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466. (c) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961. (d) Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130. (e) Lee, S. J.; Anderson, T. M.; Burke, M. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8860. (f) Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 6941. (g) Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314. (h) Struble, J. R.; Lee, S. J.; Burke, M. D. *Tetrahedron* **2010**, *66*, 4710.

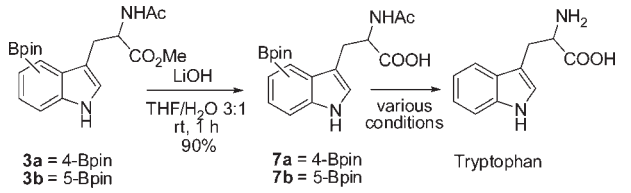
(25) For elegant examples of different coupling using organotrifluoroborates, see: (a) Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438. (b) Abel, R.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6289. (c) Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 18057. (d) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940.

(26) Ballmer, S. G.; Gillis, E. P.; Burke, M. D. *Org. Synth.* **2009**, *86*, 344.

(27) For the MIDA derivatives, prolonged exposure to water and/or moisture showed, by $^1$H NMR and TLC, formation of the hydrolyzed boronic acid.

removal of the acetyl group was difficult. *N*-Acetyl derivatives require prolonged heating in concentrated acid or base which is not compatible with sensitive compounds. Different acidic and basic conditions were tested, but in all cases protodeboronation or decomposition occurred both from **7a,b** or directly from **3a,b**. Also, the use of acylase enzymes from *Aspergillus melleus* under very mild conditions (pH 7.4, temperature 37 °C) did not provide the desired product (Scheme 3).[13a,28]

**Scheme 3.** Hydrolysis of *N*-Acetyl Boronated Indoles **3a**,**b**

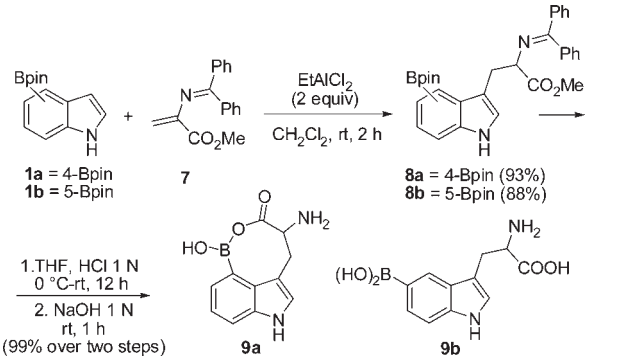



A different dehydroamino acid was then necessary. We sought to use the stable and readily available methyl 2-(diphenylmethyleneamino)acrylates[29] in our sequence, based on its reported good reactivity and the mild and selective reaction conditions for the deprotection of the amino group in the final compounds. We predicted that the use of dehydroalanine **7** should rapidly give access to useful quantities of boronated tryptophans with unprecedented levels of ease and efficiency. Dehydroamino acid **7** was then coupled to boronated indoles **1a**,**b** to give the boronated protected tryptophans **8a**,**b**. Again, the Friedel–Crafts reaction proceeded in excellent yield and the boronated protecting group remained intact.

The adducts **8a,b** were readily converted to free tryptophan boronic acids **9a**,**b** by conventional sequences (1 N HCl and 1 N NaOH) in one pot, two steps, and almost quantitative overall yield, which presented a straightforward route to 4- and 5-substituted tryptophans (Scheme 4). Selective deprotection of either the amino or the ester was possible as well.

Notably, in the case of 4-boronated derivatives the treatment of **8a** with aqueous sodium hydroxide converted the ester into a carboxy group, which simultaneously cyclized to the adjacent boron derivative to form the unknown eight-membered ring **9a** (Scheme 4).

**Scheme 4.** Friedel–Crafts Alkylation of Boronated Indoles **1a**,**b** with Methyl 2-(Diphenylmethyleneamino)acrylates **7** and Hydrolysis of Compounds **8a**,**b**




In summary, we have prepared various novel protected boronate tryptophans (**3a,b**–**8a,b**) via a regio- and chemoselective Friedel–Crafts alkylation between boronate indoles and *N*-protected dehydroalanine. Therefore, this methodology offers an alternative approach to access protected tryptophan boronates in cases where the Miyaura boronation or more traditional stoichiometric metalating reagent approaches fail and where Ir-catalyzed boronation does not give the correct regioisomer. We are currently in the process of investigating further applications of protected boronate tryptophans as building blocks in the preparation of biaryl-containing peptide natural products. The proper choice of protective groups in the dehydroalanine enables easy and practical access to two novel free boronic acid tryptophans **9a,b**. Evaluation of these boron-containing amino acids as BNCT agents is currently under way.

**Acknowledgment.** We would like to thank Prof. Gilberto Spadoni, University of Urbino, for useful discussions.

**Supporting Information Available.** Experimental procedure and spectral data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

(28) (a) Chenault, H. K.; Dahmer, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 6354. (b) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2716.

(29) Tarzia, G.; Balsamini, C.; Spadoni, G.; Duranti, E. *Synthesis* **1988**, *7*, 514.