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A Simple, Modular Synthesis of C4-Substituted Tryptophan Derivatives

F. Bartoccini, S. Bartolucci, M. Mari and G. Piersanti*

The modular and versatile synthesis of C4-substituted tryptophan derivatives by direct functionalization of easily available *N*-acetyl 4-boronate tryptophan methyl ester via transition metal-catalyzed and metal-mediated cross coupling reactions is described. The versatility of the chemistry is highlighted by the gram-scale synthesis of 4-boronated *N*-acetyl-tryptophan methyl ester and the rapid synthesis of C4-aryl, C4-alkyl, C4-cyano, C4-trifluoromethyl, C4-azido, and C4-hydroxy tryptophan derivatives. The utility of our methodology is illustrated through the quick approach to the tricyclic azepino indole skeleton embedded in many natural products.

Introduction

Tryptophan (Trp), an essential amino acid, is an attractive compound for protein engineering for several reasons. Due to its indole aromatic side chains, it is, by far, a major source of UV absorption and fluorescence in proteins. It is also involved in important functions including ligand binding[1] as well as DNA-protein and protein-lipid interactions.[2] Thanks to its high brightness, it can be used to explore protein dynamics and folding.[3] It is abundantly found in most biologically active peptides that exhibit various physiological properties, in particular hormonal and antimicrobial activities.[4] In addition, tryptophan itself and tryptophan derivatives are also important biochemical precursor and/or synthetic intermediates of various natural products and biologically active compounds (Fig. 1).[5]

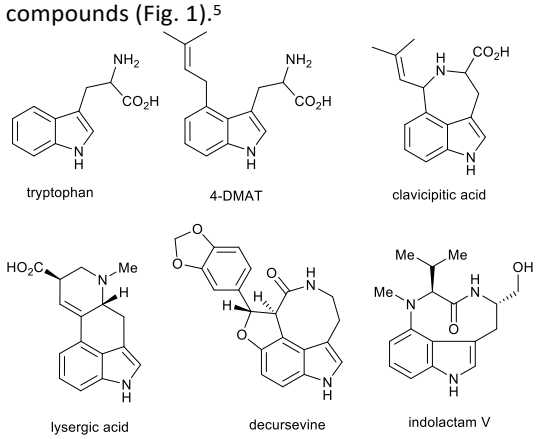
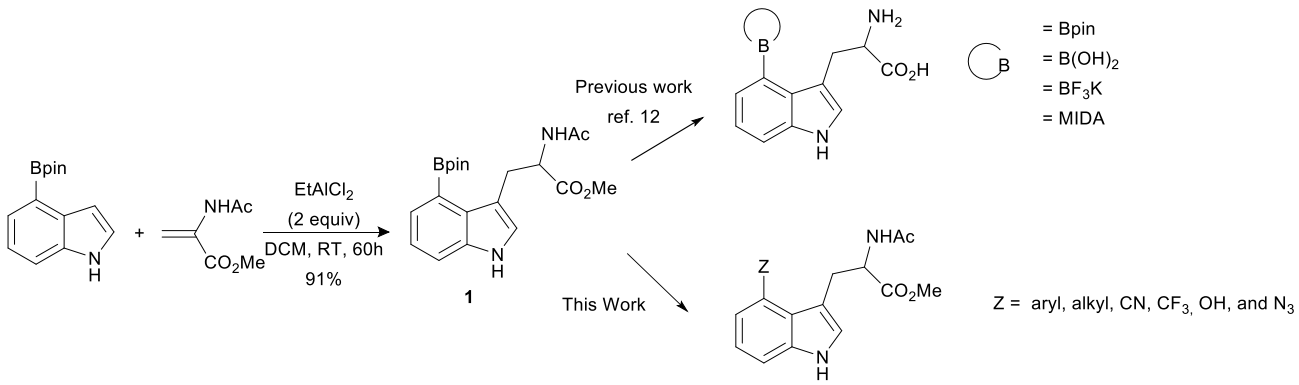


Fig. 1. Tryptophan and examples of natural products biosynthesized from tryptophan.

Department of Biomolecular Sciences, University of Urbino "Carlo Bo", P.zza Rinascimento 6, 61029 Urbino (PU), Italy
G. Piersanti. E-mail: giovanni.piersanti@uniurb.it
†Electronic supplementary information (ESI) available: General experimental details, copies of ^{1}H and ^{13}C NMR spectra.

In view of the central role that tryptophan plays, particularly in peptides and proteins, the preparation of new analogues is particularly attractive. A wide range of unusual tryptophans have been previously synthesized in search novel synthetic, medicinal, and other properties by using enzymatic and chemical methods.[6] When enzymes are involved, the accessibility of the enzyme active site may be sensibly restricted by substituents on the tryptophan indole ring. Substitution at the 4-position leads to a poor substrate, while substitution at the 5-, 6-, or 7-position is generally accepted.[7] Numerous tryptophan analogues also have become available through the versatility of indole chemistry,[8] and practical chemistry has been developed to functionalize different positions around the indole ring, mainly through the innate reactivity of the C2, C3, and C5 sites and to a lesser extent C6 and C7.[9] In contrast to these more accessible positions, methods for the selective introduction of a substituent at the C4 position on the indole ring of tryptophan derivatives is generally difficult and has received much less attention.[10]

In connection with a project exploiting the use of new boronated amino acids in organic synthesis,[11] we have focused our attention to the efficient and practical syntheses of tryptophans bearing a variety of substitution patterns at the C4 position, taking advantage of the broad utility of boronated reagents/compounds in synthesis. In particular, we recently reported a direct, regioselective, and chemoselective preparation of different protected 4-boron-containing tryptophans by Friedel-Crafts alkylation of easily accessible 4-boronated indoles[12] as a valid alternative to otherwise problematic halogen-metal exchange and Pd-catalyzed boronation of halogenated tryptophans or C4-regio-controlled Ir-catalyzed C-H boronation of unsubstituted tryptophans. Boronic esters are key reagents in organic synthesis and organometallic chemistry,[13] having displayed versatility in terms of the development of diverse carbon–carbon and carbon–heteroatom bond-forming transformations, such as,



Scheme 1. Background and reaction design of this work.

inter alia, Suzuki–Miyaura[14] and Chan–Evans–Lam[15] couplings and Hayashi–Miyaura conjugate addition.[16]

Results and discussion

Herein, we report the preparation of a wide range of desirable C4-substituted tryptophan analogues **2a–e** and **3–9** using known transformations such as arylation, alkylation, cyanation, trifluoromethylation, azidination, and hydroxylation, for which only very few syntheses have been reported. We demonstrate how our methodology provides quick access to a myriad of C4-substituted tryptophan derivatives that can be found in a variety of biologically active molecules and are useful intermediates for further elaboration to ergot alkaloids, for example.

Driven by the seminal work of Suzuki and Miyaura,[13] boronic acids and their derivatives have become "the 'gold standard' for biaryl construction, arguably resulting in the ubiquity of this moiety in medicinal chemistry."[17] In addition, there is still an interest in unsymmetrical biaryls due to the unique properties conferred by the biaryl moiety and the fact that it is an important structural motif in a great number of biologically active compounds and functional molecules.[18] The Suzuki−Miyaura coupling of easily accessible and stable-to-storage *N*-acetyl tryptophan pinacol-boronated ester **1** was thus initially investigated (Fig. 2). According to previously reported conditions for Suzuki couplings,[19] **1** was coupled with bromobenzene and aryl bromide bearing either an electron-withdrawing or electron-donating substituent, such as *p*-bromobenzonitrile and *p*-bromoanisole, respectively. The coupled products (**2a–c**) were obtained chemoselectively in good yields. Although the *N*-arylation of a variety of azoles and amides has been reported,[20] no traces of *N*-arylated products were detected. The efficient arylation of tryptophan derivative **1** shows that it is possible to react selectively at the C4-B bond in preference to the competitive amide and indole N–H functional groups. The cross-coupling substrates also included nitrogen heterocycles. (Hetero)aromatic bromides and chlorides could be reacted according to the expected oxidative addition tendency of the halide and its position in the (hetero)cycle. Pharmacophore motifs such as 2-chloropyridine and 4-bromoindole could be introduced without difficulties. It should be emphasized that upon using the reverse approach, i.e. the direct coupling with heteroaryl boronic acids or pinacol esters, the observed functional and structural diversity was difficult to realize; in particular, *ortho*-nitrogen atom-containing boronic reagents were challenging coupling partners.[21] Moreover, the obtained mixed 4,4′-bisindole (**2e**) represents a new promising scaffold of this substructure, different from the most typical junction 2,2′- or 3,3′-bisindole, a natural product family derived from the oxidation and dimerization of two tryptophan monomers with potential use as anticancer, antibacterial, and antiviral agents.[22] The yields of the isolated products **2d** and **2e** were fair to moderate, and the compounds obtained were analytically pure by simple flash chromatography. We anticipate that this method will provide a flexible route to novel substituted polyaromatic amino acids, for which tryptophans are increasingly exploited as building blocks.

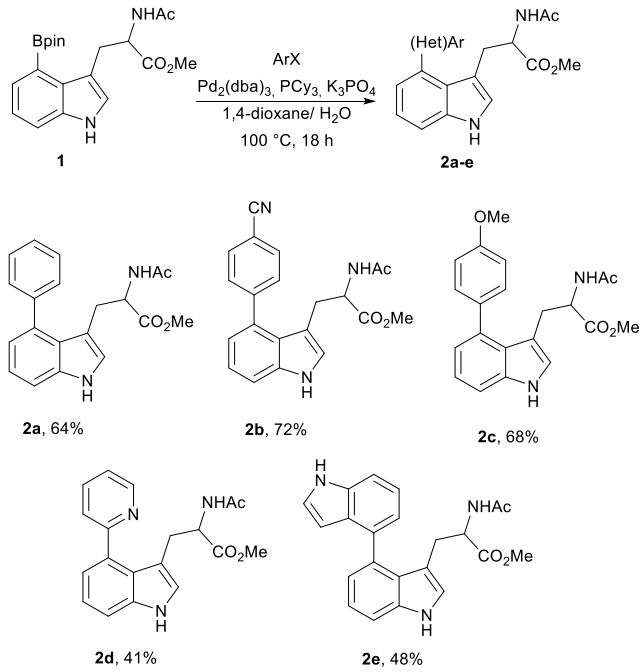


Fig. 2. Pd-catalyzed Suzuki−Miyaura cross-coupling of boronated tryptophan **1.**

In order to use these routes for the syntheses of clavine/ergot alkaloids, 4-alkylated tryptophans have to be applied. In particular, 4-dimethylallyl tryptophan (4-DMAT) is of interest, since it functions as the central intermediate in the biosynthetic pathways leading to numerous prenylated indole

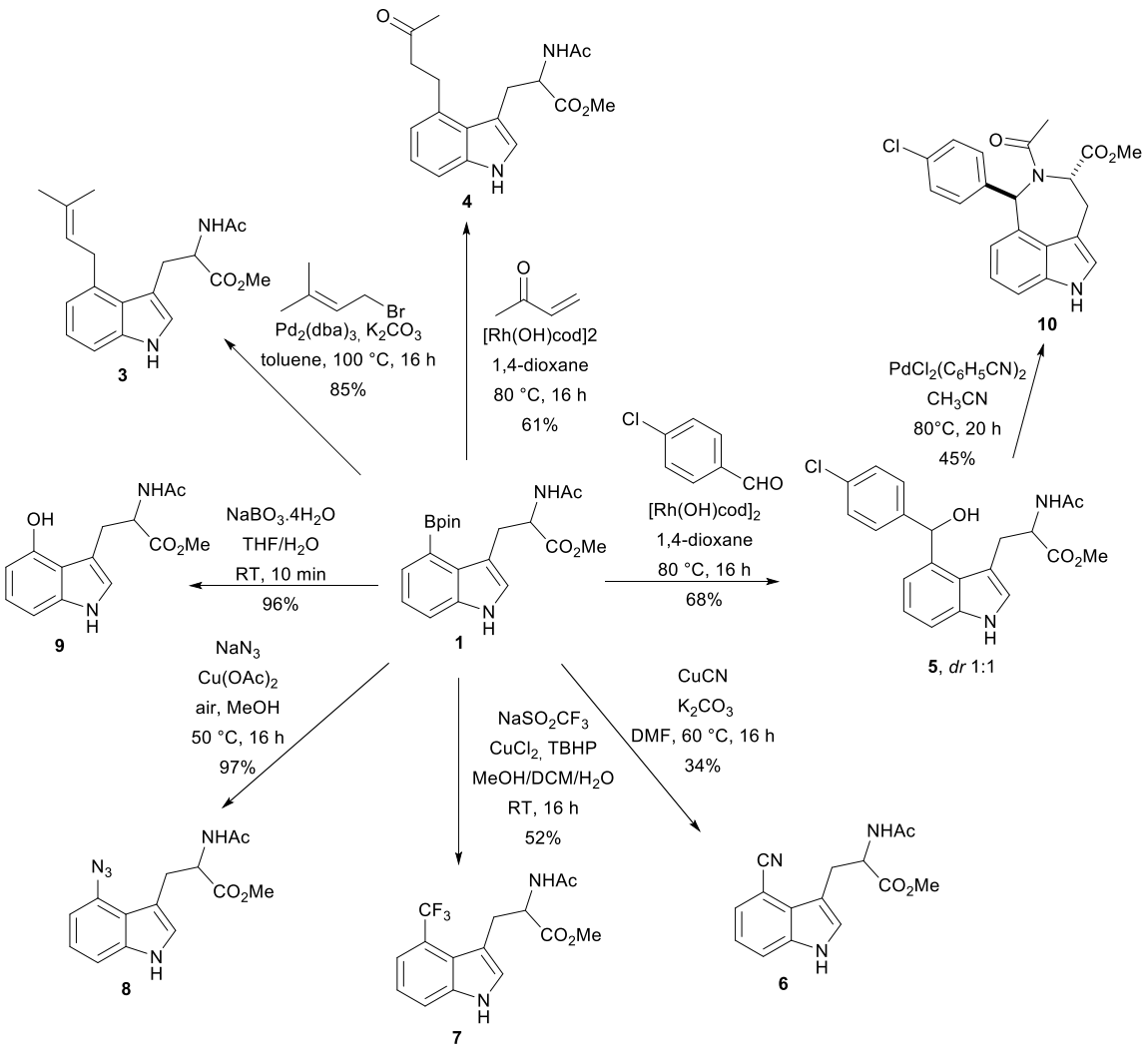
alkaloids, such as ergot alkaloids in normal biosynthesis and clavicipitic acid in derailment biosynthesis. It is biosynthetically derived primarily from tryptophan and dimethylallyl diphosphate using dimethylallyltryptophan synthase as the enzyme.[23] To study the insertion of prenyl side chains into tryptophan by aryl–allyl coupling, we carried out the reactions under different conditions than used for biaryl formation. As shown in Scheme 2, C4-prenylated cross-coupling product **3** was prepared in good yield with prenyl bromide by using the phosphane-free catalyst $[Pd_2(dba)_3]$ in toluene solution and in the presence of suspended potassium carbonate.[24] The reaction between **1** and prenyl bromide carried out in 1,4-dioxane/water in the presence of K_3PO_4 led to product **3** in low yield.

Among the most spectacular asymmetric C–C bond formation reactions in which organoboronates are involved, there are the rhodium-catalyzed 1,4-conjugate addition to a variety of Michael acceptors such as enones and enesters[25] and the 1,2-addition to carbonyls and imines.[26] Treating boronate tryptophan derivative **1** with both methyl vinyl ketone and 4-chlorobenzaldehyde in 1,4-dioxane at 80 °C for 16 h using the commercially available and very active catalyst $[Rh(OH)cod]_2$, the C4-substituted tryptophan derivatives containing a ketone (**4**) or a benzylic alcohol moiety (**5**) were obtained in good yield, respectively.

Next, we sought to identify a relatively new transformation that has received much less "field testing" on molecules of significance in pharmaceutical synthesis such as copper-mediated cyanation and copper-mediated trifluoromethylation with Langlois' reagent (Scheme 2).[27] Thus, the reaction of the boronate tryptophan derivative **1** with $Zn(CN)_2$ in the presence of CsF or KOH with 1.5 equiv. of added $Cu(OAc)_2$ generated the corresponding benzonitrile product **6** in less than 10% yield. However, this reaction with 1.5 equiv. of CuCN in place of copper acetate, K_2CO_3 as the base, and DMF as the solvent formed product **6** in 34% yield after 16 h at 60 °C. Whereas the trifluoromethyl derivative **7** was obtained in 52% yield by reaction with sodium triflate in the presence of CuCl and *t*BuOOH. The cyanation and trifluoromethylation reactions are particularly valuable because direct cyanation and trifluoromethylation of C−H bonds still remain a significant challenge. Furthermore, the cyano-containing tryptophan **6** could be further elaborated to generate products containing functionality resulting from the selective reaction of the cyano group such as hydrolysis to the amide and carboxylic acid, or reduction to the aldehyde and primary amine.

Additionally, the boronated derivatives participated in a broad selection of high yielding transformations for carbon-heteroatom bond formation, with complete preservation of the tryptophan (Scheme 2). The boron substituent could be replaced by a large number of functional groups using classical transformations such the Chan–Lam–Evans coupling, including the use of sodium azide as a nitrogen counterpart, leading to product **8** in 97% yield and simple hydroxylation by oxidation. Moreover, the corresponding phenol **9** was obtained using Borax in high yield (96%) after an easy purification by column chromatography on silica gel. Both products azidotryptophan derivative **8** and hydroxytryptophan derivative **9** have proven difficult to make; however, photoreactive tryptophan analogs have been shown to be useful as photoaffinity labeling agents.[28]

The application of our protocol to the synthesis of 3,4-disubstituted indole natural product analogs was pursued (Scheme 2). The unique fused tricyclic azepinoindole skeleton, the core structural unit of clavicipitic acids and other related natural products, was accessible from the 4-substituted tryptophan derivative **5** by intramolecular benzylic amination.[29] Treatment of benzhydryl alcohol **5** with bis(benzonitrile)dichloropalladium(II) in acetonitrile allowed the aminocyclization to occur, providing the seven-membered nitrogen-containing ring compound **10** in decent yield (Scheme 2). Notably, by simple modifications and changing the aldehyde used, this strategy could easily allow the synthesis of many analogues of the natural product clavicipitic acid, which could be used as probes for elucidating the mode of action.[30]



Scheme 2. Versatile and valuable transformations of the borylated tryptophan **1**

Conclusion

In conclusion, we have demonstrated that *N*-acetyl 4-boronate tryptophan methyl ester **1** reacted with a series of electrophiles to regioselectively and rapidly generate a wide range of C4-functionalized free (N–H) tryptophans that are important building blocks in medicinal and biological chemistry. Thus, 4-aryl- and 4-alkyltryptophans (**2a–e** and **3**), ketone and benzylic alcohol tryptophans (**4** and **5**), 4-cyano and 4-trifluoromethyl tryptophans (**6** and **7**), and also 4-azido- and 4-hydroxytryptophans (**8** and **9**) were easily produced in a direct and efficient manner. The generality inherent in this approach offers a flexible and rapid new route to various C4-substituted tryptophan derivatives for application in natural product synthesis, as exemplified by the synthesis of the fused azepinoindole core (**10**). These reactions point to broad new possibilities for incorporating 4-boronate tryptophan precursors into more complex chemical environments.

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