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Functionalization of Aromatic Amino Acids via Direct C−H Activation: Generation of Versatile Building Blocks for Accessing Novel Peptide Space

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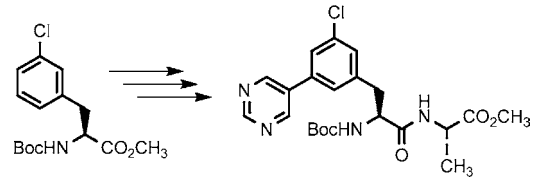
ABSTRACT



Functionalized α-amino acid building blocks have been prepared in good yield with high regiocontrol and preservation of stereochemistry via iridium-catalyzed borylation of suitably protected aromatic α-amino acid derivatives. The utility of these systems in peptide couplings and Suzuki reactions has been demonstrated.

The plethora of natural products and therapeutic agents which incorporate natural and non-natural α-amino acids provides continued impetus to the search for efficient new methods to construct these fragments with full control of stereochemistry.[1] Strategies for novel α-amino acid synthesis encompass resolution of racemic amino acids,[2] modification of readily available homochiral α-amino acids,[3] and de novo construction of α-amino acids with creation of the key α-stereocenter via asymmetric induction.[4] Methods which involve the modification of existing α-amino acids are particularly attractive, since the key α-stereocenter is already installed and synthetic routes can be very short.[5] However, they require mild reaction conditions and compatibility with sensitive functionality.

As part of a program to discover novel peptides for potential therapeutic use, we envisaged the incorporation of functionalized α-amino acids (bearing a concealed reactive center) into an intact peptide chain as an efficient means of introducing functional diversity (through organometallic

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coupling reactions) at a late stage in a synthetic sequence. In view of their stability and synthetic versatility, we were especially drawn to the incorporation of α-amino acids featuring an aryl boronate ester. Aryl boronic acids and esters have had an enormous impact on modern drug synthesis, potentially allowing access to a wide range of aryl, heteroaryl, vinyl, alkynyl, and acyl derivatives, and providing compatibility with peptide-based substrates.[6]

To implement this strategy, we envisaged that the necessary boronate derivatives could be generated by use of the emerging repertoire of C−H activation methodologies, applied directly on readily available α-amino acid systems. In particular, we were drawn to the pioneering work of Hartwig and Miyaura,[7] Smith and Maleczka,[8] and others using iridium-catalyzed aryl borylations, in the hope that it would enable the required functionalization under conditions compatible with typical amino acid protecting group strategies and preservation of stereochemical integrity.

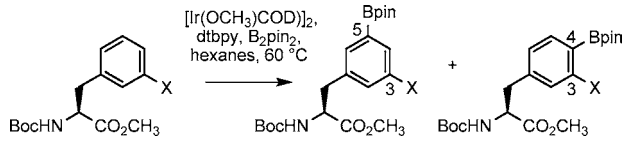
We report now the realization of this approach and describe the efficient construction of a series of *m*-arylboronate-substituted α-amino acid derivatives, generated via direct iridium-catalyzed borylation of protected, commercially available α-amino acids, together with examples of their incorporation and reactivity within simple peptides. During the course of our studies, the first report of such a transformation on a protected amino acid derivative appeared.[9]

A series of readily available meta-substituted *N*-Boc-phenylalanine methyl esters (prepared in one protection step from commercially available materials) were treated with bis(pinacolato)diboron (B_2pin_2) together with catalytic $[Ir(OCH_3)COD)]_2$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) to yield the corresponding borylated derivatives (Table 1). As expected, given the importance of steric effects on the regiochemistry of iridium-catalyzed borylation reactions,[7c] the products were predominantly or exclusively the 3,5-disubstituted derivatives.

The unsubstituted phenylalanine derivative **1** yielded a statistical mixture of 3- and 4-isomers (**2a** and **2b** respectively), as well as diborylated material (**2c**, structure not shown), in high overall yield (Table 1). In contrast, the bromo, trifluoromethyl, methoxy, methyl, and chloro substituents were all sufficiently large to direct the reaction to exclusively one regioisomer, in very good to excellent yield (Table 1, **4a**, **6a**, **12a**, **14a**, and **16a**). Notably, the fluoro-substrate **9** yielded a similar product ratio to the unsubstituted system, reflecting the commonly held view that a fluoro substituent offers effectively the same steric hindrance as a hydrogen atom (Table 1, **10a** and **10b**). This finding is consistent with the obeservations of other workers.[10] A very small amount of 3,4-isomer could also be detected in the reaction of the 3-cyano derivative, reflecting the slightly smaller size of this substituent compared to, for example, a methyl group (Table 1, **8a** and **8b**).[10] These borylated phenylalanine derivatives were stable, readily isolated, and purified by column and/or preparative thin layer chromatography. Furthermore, preparation of the chloro derivative (Table 1, **16a**) could be run at multigram scale, with improved yields. The enantiopurity of a representative example, the *m*-trifluoromethyl derivative (Table 1, **6a**), was confirmed by chiral HPLC analysis of starting material and product (generated at 90 °C in this case), demonstrating that both were >98% ee.

As a control experiment, to confirm that regiochemical outcome was determined by steric effects, the 2-chlorophenylalanine derivative **17** was subjected to the standard reaction conditions. As expected, both 2,4- and 2,5-derivatives (**18a** and **18b**, respectively) were isolated as a 46:54 mixture in 86% combined yield (Scheme 1a). In addition, given the lack of regiocontrol observed with the 3-fluoro

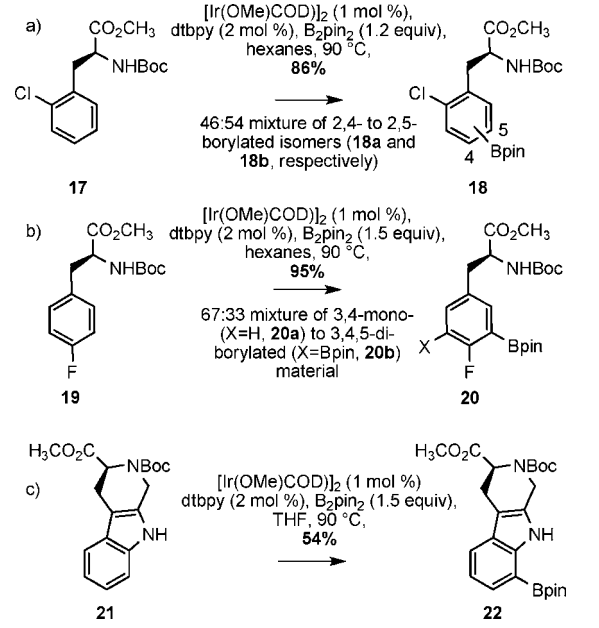
Table 1. Examples of Iridium-Catalyzed Borylation of Substituted Phenylalanine Derivates[a]



X	3,5-isomer [%]	3,4-isomer [%]	yield [%]
H (**1**)	60 (**2a**)	19 (**2b**)	81[b]
Br (**3**)	>98 (**4a**)	ND	80[c]
CF_3 (**5**)	>98 (**6a**)	ND	84
CN (**7**)	>95 (**8a**)	<5 (**8b**)	91
F (**9**)	66 (**10a**)	34 (**10b**)	91
OCH_3 (**11**)	>98 (**12a**)	ND	84[d]
CH_3 (**13**)	>98 (**14a**)	ND	77[c]
Cl (**15**)	>98 (**16a**)	ND	73[c]

[a] All reactions were performed at 0.5 mmol scale in 2.5 mL of hexanes at 60 °C with 1.2 equiv of B_2pin_2 in a sealed tube. Isomer ratio determined by ^1H NMR. [b] Yield includes 21% diborylated material (**2c**). [c] Conducted at 90 °C with 1.5 equiv of B_2pin_2. [d] (*R*)-Isomer used.

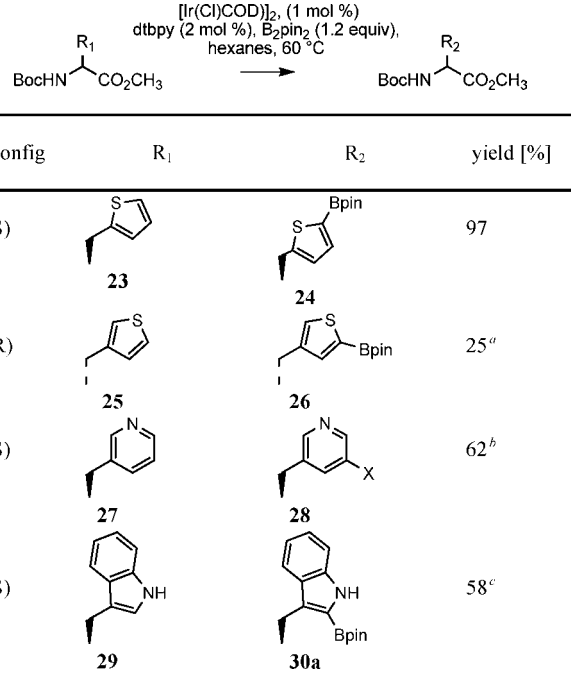
Scheme 1. Further Examples of Iridium-Catalyzed Borylation of Amino Acid Derivatives



derivative, the 4-fluoro derivative **19** was examined and yielded a 67:33 mixture of 3,4-monoborylated and 3,4,5-diborylated products (**20a** and **20b**, respectively), again illustrating the lack of steric control offered by the fluorine substituent (Scheme 1b).

Given the excellent yield and regiocontrol achieved with meta-substituted phenylalanine derivatives, we also explored a series of protected heteroarylalanine derivatives (Table 2).

Table 2. Examples of Iridium-Catalyzed Borylation of Heteroaryl Amino Acid Derivatives



config	R_1	R_2	yield [%]
(S)	**23**	**24**	97
(R)	**25**	**26**	25[a]
(S)	**27**	**28**	62[b]
(S)	**29**	**30a**	58[c]

[a] Reaction conducted at 25 °C with 0.5 equiv of B_2pin_2. [b] Reaction conducted at 80 °C overnight with $[Ir(OMe)(COD)]_2$ (3 mol %), dtbpy (6 mol %), and B_2pin_2 (0.9 equiv). Borylated product **28** (X = Bpin) unstable; yield based upon Suzuki coupling with *p*-nitroiodobenzene to yield product **28** (X = *p*-nitrophenyl). [c] Reaction conducted in a microwave reactor in MTBE with $[Ir(OMe)(COD)]_2$ (1.5 mol %), dtbpy (3 mol %), and B_2pin_2 (0.7 equiv). Isolated as a 6:1 mixture of 2-borylated **30a** to 2,7-diborylated **30b** material (structure not shown).

N-Boc-2-thienylphenylalanine methyl ester **23** yielded exclusively the 5-borylated product **24** in excellent yield (Table 2). In contrast, the 3-thienyl derivative **25** yielded a mixture of 3,5-monoborylated and 2,3,5-diborylated products, as a result of reaction at both positions adjacent to sulfur in this system. With careful control of reaction time and temperature, using only 0.5 equiv of B_2pin_2, a good yield of crude product, could be obtained, but as a result of protodeborylation on chromatography, only a 25% yield of the 3,5-substituted material **26** was finally isolated (Table 2). Both these thienyl substrates appeared significantly more reactive than their phenyl counterparts. In contrast, the reaction with the 3-pyridylalanine derivative **27** was sluggish, requiring elevated temperatures in order to achieve full conversion of the starting material. However, the reaction yielded a single 3,5-substituted product **28** (X = Bpin) in moderate yield (Table 2). Since this boronate ester was found to be unstable toward chromatographic purification, the reported yield corresponds to a two-step sequence including Suzuki−Miyaura coupling with *p*-nitroiodobenzene to yield **28** (X = *p*-nitrophenyl).

Tryptophan derivatives represent attractive substrates for this functionalization paradigm, given the abundance of tryptophan in biologically active peptides and the multiple possible positions open to iridium-catalyzed C−H activation, depending upon the protection regime employed. Thus, as recently reported,[11] the unsubstituted *N*-Boc-tryptophan methyl ester **29** yielded predominantly the 2-substituted product **30a**, in moderate yield (Table 2, entry 4). In contrast, the tryptophan derived tricyclic amino acid **21**, in which the 2-position is substituted, yielded predominantly the 7-borylated product **22** (Scheme 1c).[12] To again confirm the stereochemical integrity of the products in this series, chiral HPLC analysis of the 2-borylated product **30a** (Table 2) was undertaken, confirming that the enantiomeric excess was >98%.

As a means of demonstrating the synthetic utility of these amino acid boronic esters, representative examples have been subjected to peptide coupling and Suzuki−Miyaura reactions in order to access biaryl and heterobiaryl amino acids typical of those used as components of biologically active molecules. Thus, in a "one-pot" process, *N*-Boc-2-thienylalanine methyl ester **23** (Table 2) could be selectively borylated and then treated directly, after removal of solvent, with methyl 3-iodobenzoate, under standard Suzuki−Miyaira reaction conditions, to yield the heterobiaryl-amino acid derivative **31** in 81% overall yield (Scheme 2a). This heterobiaryl motif is featured in recently claimed endothelin convertase inhibitors[13] and Factor IX/XI inhibitors,[14] and also represents a

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(11) The procedure reported in ref 9 yielded material with an optical rotation of similar magnitude but opposite sign to what we observed. In correspondence with the authors, we have confirmed that our data are correct.

(12) Small amounts of other borylated material were observed in the crude product but could not be characterized.

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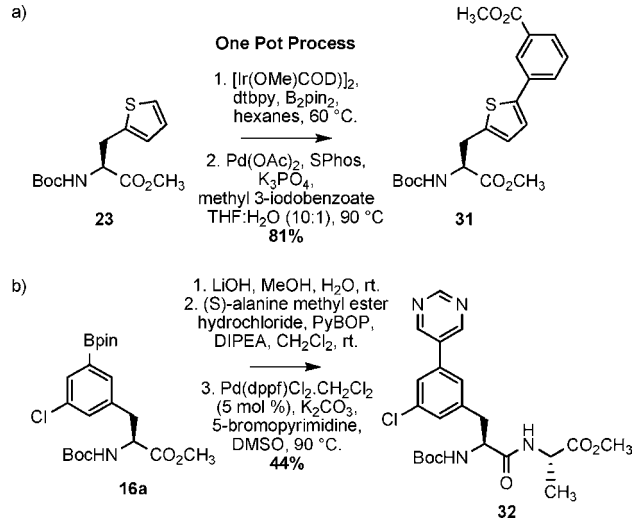
Scheme 2. Examples of Novel Amino Acid and Peptide Synthesis with Borylated Amino Acids



novel protected analogue of a recently published AMPA-kainate agonist.[15]

Further, the borylated amino acid **16a** derived from *N*-Boc-3-chlorophenylalanine methyl ester (Table 1) could be hydrolyzed and coupled smoothly to (*S*)-alanine methyl ester to yield a borylated dipeptide. This could be reacted directly under Suzuki−Miyaura conditions with 5-bromopyrimidine to furnish the novel, protected heterobiaryl-substituted dipeptide **12** in 44% overall yield for the three steps (Scheme 2b). While an interesting structure in itself, this chloro-substituted system also offers the possibility of further chemoselective modification, for example, further Suzuki−Miyaura couplings via the chlorine substituent, under more vigorous conditions, to yield trisubstituted systems, or hydrogenolytic removal of the chlorine atom (which would then have served as a regiochemical directing group).

In conclusion, we have developed an efficient synthesis of borylated aryl- and heteroaryl-amino acids, and explored the scope of this procedure with regard to regioselectivity and preservation of stereochemistry. We have applied this methodology in the construction of a novel set of usefully functionalized, homochiral amino acids, and confirmed their compatibility with both standard peptide coupling conditions and Suzuki−Miyaura coupling reactions. Furthermore, we have demonstrated their utility in the generation of other novel amino acid and peptide derivatives which feature functional groups commonly encountered in biologically active molecules. These meta-functionalized systems complement the more readily available para-substituted phenylalanine derivatives, accessible via, for example, the triflate of tyrosine.[16] Future synthetic studies will further explore the scope of reactivity of these borylated amino acids and their deployment in the construction of a broader range of biologically active peptides.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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