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A GENERAL ROUTE TO IODINATED AROMATIC AMINO ACID BUILDING BLOCKS

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Abstract

Iodinated aromatic amino acids are valuable intermediates for peptide chemistry, medicinal chemistry, and chemical biology, enabling transition-metal-catalyzed cross-coupling while modifying aromatic side-chain electronics. However, iodination methods have largely been limited to tyrosine and tryptophan. Here, a silver-mediated iodination protocol was applied to a series of natural and unnatural Fmoc-protected amino acids, affording isolated yields of 70–90%. This work reports the first synthesis and characterization of Fmoc-2-iodo-1-naphthylalanine, Fmoc-1-iodo-2-naphthylalanine, and Fmoc-2-iodo-4-methylphenylalanine, with representative Suzuki–Miyaura coupling demonstrating the first synthesis of Fmoc-5-(2'piridinyl)-His-OH.

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Introduction

Aromatic amino acids play essential roles in protein structure and function through hydrophobic interactions, π-stacking interactions, cation–π interactions, and intrinsic fluorescent properties.[1] Beyond their biological importance, aromatic amino acids have become indispensable synthetic building blocks in peptide chemistry, medicinal chemistry, and chemical biology because they enable the incorporation of structurally and electronically diverse functionality into peptides and proteins.[2] While the twenty canonical amino acids provide only a limited range of aromatic side chains, noncanonical aromatic amino acids greatly expand accessible chemical space and provide opportunities to access molecular architectures unavailable through natural biosynthetic pathways.

One particularly attractive strategy for expanding the utility of aromatic amino acids is halogenation. Introduction of a halogen substituent can alter the electronic and physicochemical properties of an aromatic side chain while simultaneously providing a versatile synthetic handle for late-stage functionalization. Among the halogens, iodine is especially valuable because aryl iodides readily participate in transition-metal-catalyzed transformations including Suzuki–Miyaura, Sonogashira, and Heck cross-coupling reactions.[3-5] Consequently, iodinated amino acids have found widespread application as peptide building blocks, radiolabeled imaging probes, medicinal chemistry intermediates, and precursors for the preparation of structurally diverse noncanonical amino acids.[6-8]

For applications in peptide synthesis, iodinated amino acids must be compatible with standard solid-phase peptide synthesis (SPPS) methodologies. Accordingly, Fmoc protection is an essential feature of amino acid building blocks intended for peptide assembly.[9] However, the Fmoc protecting group itself contains an aromatic fluorene framework that could, in principle, undergo competing electrophilic substitution under iodination conditions.[10] An effective iodination methodology must therefore selectively functionalize the amino acid side chain while preserving the Fmoc protecting group.[11] Despite the widespread availability of Fmoc-protected aromatic amino acids, general iodination strategies compatible with Fmoc-protected peptide building blocks remain limited.

Most reported amino acid iodination methodologies rely on electrophilic aromatic substitution and have focused primarily on highly activated canonical aromatic amino acids, particularly tyrosine and tryptophan.[12] These electron-rich substrates undergo rapid iodination and consequently dominate the existing literature. Furthermore, histidine residues embedded within peptides have been iodinated using oxidative radioiodination methodologies for imaging and peptide labeling applications.[13] Unlike classical silver-mediated iodination chemistry, these transformations employ oxidative generation of electrophilic iodine species under aqueous conditions and are designed for isotopic labeling rather than the preparation of isolable synthetic intermediates. Consequently, this method is poorly suited for downstream peptide synthesis.[14]

Herein, we report a general silver-mediated iodination methodology employing molecular iodine and silver sulfate for the selective preparation of Fmoc-protected canonical and noncanonical aromatic amino acids. The methodology is compatible with standard solid-phase peptide synthesis protecting groups and establishes the relationship between aromatic electronic structure and iodination reactivity across a diverse substrate scope. To the best of our knowledge, this work represents the first synthesis and characterization of the Fmoc-protected mono-iodinated amino acid building blocks Fmoc-2-iodo-1-naphthylalanine, Fmoc-3-iodo-2-naphthylalanine, and Fmoc-2-iodo-4-methylphenylalanine. Representative Suzuki–Miyaura cross-coupling reactions further demonstrate the synthetic utility of these compounds as versatile intermediates for peptide diversification, and we further report the first synthesis of Fmoc-5-(2'-piridinyl)-His-OH

Materials and Methods

Materials

Fmoc-1-naphthylalanine-OH(Fmoc-1Nal-OH), Fmoc-2-naphthylalanine-OH (Fmoc-2Nal-OH), Fmoc-His(Trt)-OH, Fmoc-Tyr-OH, Fmoc-Tryptophan-OH, Fmoc-Phenylalanine-OH, and Fmoc-Phe(4-Me)-OH were obtained from Sigma-Aldrich, Fisher Scientific, TCI Chemicals, Oakwood Chemical, and used without further purification. Iodine, silver sulfate, methanol, sodium thiosulfate, and all other reagents and solvents were used as received unless otherwise noted.

General Iodination Procedure

Aromatic amino acid substrate (1.0 equiv) was dissolved or suspended in methanol. The reaction mixture was cooled when required and treated with iodine (1.2 equiv) followed by silver sulfate (1.2 equiv). The vessel was flushed with nitrogen gas for 5 minutes and the reaction vessel was sealed. The reaction was performed without agitation at room temperature for 1.5 - 48 hours, depending on substrate. 1H NMR was used to monitor reaction progress.

Upon completion, the reaction mixture was filtered to remove insoluble salts, extracted in ethyl acetate, and quenched with aqueous sodium thiosulfate to remove residual iodine. The resulting mixture was extracted and concentrated under reduced pressure. Crude products were purified by recrystallization in methanol and water to afford the corresponding iodinated amino acid derivatives.

Liquid Chromatography-Mass Spectrometry

LC–MS analyses were performed on an Agilent 1100 Series LC/MS equipped with an electrospray ionization (ESI) source operating in positive-ion mode. Samples were dissolved in methanol and water (90:10, 0.1–1 mg mL^{-1}) prior to analysis. Mass spectra were acquired over an *m/z* range of 100–2200 and processed using Agilent ChemStation software.

Nuclear Magnetic Resonance Spectroscopy

H, ^{13}C, COSY, TOCSY, NOESY, HSQC, and HMBC spectra were acquired on a Varian 500 MHz spectrometer using the OneProbe at ambient temperature. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent resonance (CD_3OD: δH 4.78 ppm, δC 49.0 ppm.) Coupling constants (J) are reported in hertz (Hz). Spectra were processed using MestReNova.

General Suzuki Coupling Procedure

Iodinated amino acid substrate (1.0 equiv) was combined with phenylboronic acid (1.5 equiv), palladium catalyst ($Pd(PPh_3)_4$), and base (1.5eq Potassium Carbonate) in methanol and water (4:1). The reaction mixture was heated with stirring until conversion was observed by LC-MS. Upon completion, the reaction mixture was filtered, concentrated, and purified through recrystallization in MeOH/water to afford the coupled products. Product formation was confirmed by LC-MS analysis.

Results and Discussion

Scope and Electronic Dependence of Aromatic Amino Acid Iodination

Iodination chemistry has a range of reagents, including I_2 with an oxidant or Lewis acid, N-iodosuccinimide, or iodine monochloride.[23] The present study uses molecular iodine with silver sulfate as a Lewis acid. This reagent combination is inexpensive and scalable, making it attractive to gram-scale synthesis for Fmoc amino acid derivatization and subsequent peptide synthesis. The substrates included highly electron-rich phenolic and heteroaromatic systems (Fmoc-Tyr(OtBu)-OH, Fmoc-Trp-OH, and Fmoc-His(Trt)-OH), moderately activated fused aromatic systems (Fmoc-1Nal-OH and Fmoc-2Nal-OH), and comparatively electron-poor phenyl derivatives (Fmoc-Phe-OH and Fmoc-Phe(4-Me)-OH). As the reaction mechanism proceeds through electrophilic aromatic substitution (EAS), substrate electronics are expected to govern both reaction rate and product formation.

Initial reactions demonstrated the benefit of reaction progress monitoring via ^1H NMR spectroscopy, Figure 1. As anticipated, substantial differences in reaction time were observed across the substrate series. Fmoc-Tyr(tBu)-OH underwent rapid conversion within 1.5 h, consistent with the strong electron-donating influence of the phenolic oxygen. Fmoc-Trp-OH and Fmoc-His(Trt)-OH exhibited intermediate reactivity, followed by Fmoc-1Nal-OH and Fmoc-2Nal-OH, while Fmoc-Phe(4-Me)-OH required prolonged reaction times. Under identical reaction conditions, Fmoc-Phe-OH exhibited no detectable iodination. No quantitative kinetic analysis is given though product generation is shown with a one-phase exponential association model line fit and plotted on a logarithmic time scale, Figure 1. This gives a qualitative comparison of relative reaction rates and is not intended to match the experimental rate law.

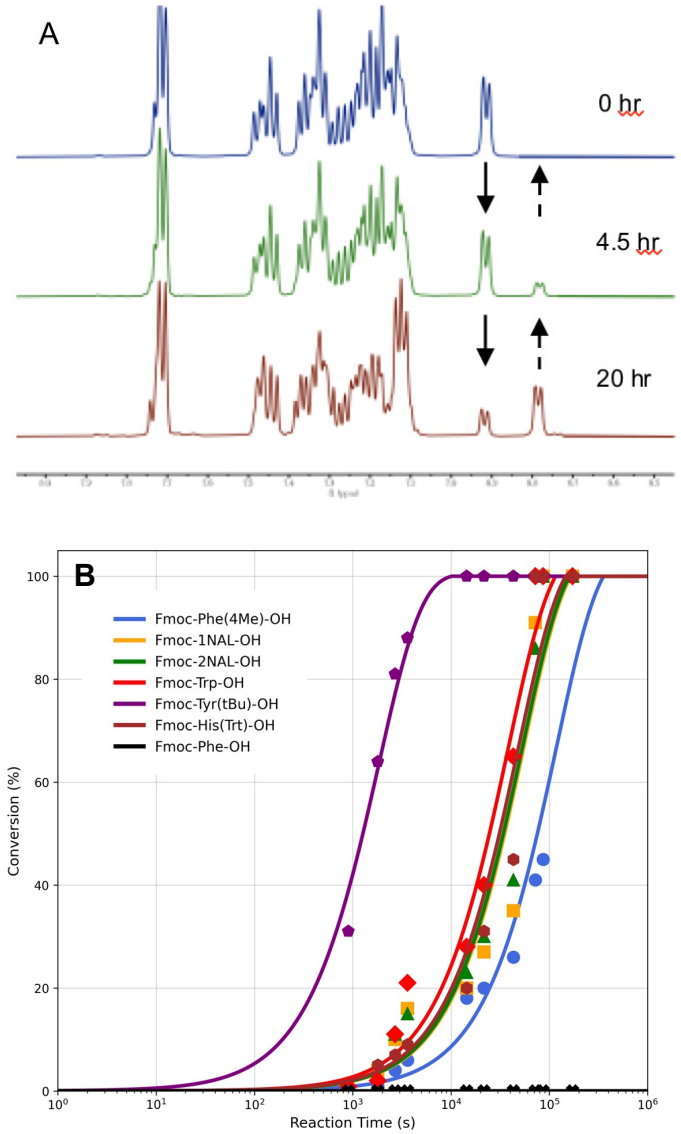


Figure 1: Reaction progress of electrophilic iodination of Fmoc-protected aromatic amino acids. A) 1D NMR of Fmoc-Phe(4-Me) after reacting for 0, 4.5 and 20 hours. Arrows indicate (dis)appearing resonances. B) Product formation with respect to time for aryl amino acids.

The observed reactivity trend is consistent with the proposed electrophilic aromatic substitution mechanism and Brown–Okamoto[15] electrophilic substituent constants. Electron-rich aromatic systems more readily stabilize the arenium-ion intermediate and therefore undergo iodination more rapidly than less activated aromatic rings.[16] This data is consistent with previous studies showing common iodination of Tyr and Trp, but not Phe. Importantly, productive iodination of the unnatural amino acids suggests the scope of successful iodination chemistry. Weak alkyl electron donation from the methyl substituent in Fmoc-Phe(4-Me)-OH was sufficient to yield iodination with extended time. Any substituent at or greater than this level of electron donation should likewise be amenable to aryl iodination under these reaction conditions.

Following optimization of reaction times through NMR monitoring, preparative-scale iodinations were performed for each substrate, Table 1. The methodology was successfully applied to Fmoc-Tyr(tBu)-OH, Fmoc-Trp-OH, Fmoc-His(Trt)-OH, Fmoc-1Nal-OH, Fmoc-2Nal-OH, and Fmoc-Phe(4-Me)-OH, affording isolated yields ranging from 70–90% following workup and recrystallization. Notably, successful monoiodination of the naphthylalanine derivatives and protected histidine expands the current substrate scope beyond the canonical amino acids for which literature precedent is well established.

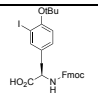
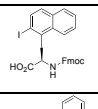
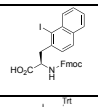
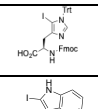
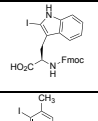
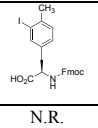
The modest electronic activation of Fmoc-Phe(4-Me)-OH showed a unique side product. Methanol-mediated methyl esterification of the amino acid carboxylic acid was observed. For the most electronically activated substrates, iodination occurred rapidly with little evidence of competing chemistry. Only the prolonged reaction time required for the less reactive Fmoc-Phe(4-Me)-OH substrate appears to result in methyl ester formation. This competition is in concordance with literature precedent for silver-mediated iodination,[18] however, it has only been previously observed under harsher temperature conditions than currently employed. Notably, elevated temperature also yielded side chain deprotection, which was not observed under the present mild iodination conditions.

Holistically, the present room-temperature conditions seem well-suited to scalable, Fmoc-protected iodination. The reaction times are longer than previous heated trials, but far fewer side reactions are observed. Notably, despite the presence of an aromatic fluorene moiety, the Fmoc protecting group remained intact and unreacted throughout the entire substrate scope. This chemo-selectivity demonstrates that aromatic iodination proceeds preferentially over both carboxylic acid methyl esterification and Fmoc functionalization. Collectively, these results establish the relative reactivity of the competing processes under the reaction conditions as aromatic iodination > methyl esterification >> Fmoc modification, providing practical considerations for iodination with any Fmoc-protected amino acid.

Structural Characterization of Iodinated Products

Table 1 shows the iodination of the queried Fmoc amino acids. The structures were characterized using a combination of LC-MS and multidimensional NMR spectroscopy. Notably, all products demonstrated mass changes consistent with mono-iodination. LC–MS analyses confirmed the expected molecular ions for all isolated iodinated products. Figure 2 shows the isolated Fmoc-2-iodo-1-naphthylalanine product. A singly charged peak is observed at 563.8 a.m.u. consistent with the calculated mass of 563.6 a.m.u. There are additional signals at 282.3 a.m.u., the doubly charged product, and 304.3 a.m.u., doubly charged with a sodium ion. Minor signals corresponding to de-iodinated species and ionization-derived adducts were observed across the substrate scope, consistent with the known susceptibility of aryl iodides to

Table 1: Scope of aromatic amino acid iodination reactions

Substrate	Product	Relative Activation	Time (h)	Isolated Yield (%)	LCMS Expected (a.m.u)	LCMS Observed (a.m.u.)*
Fmoc-Tyr(tBu)		High (σ^+ **-0.92)**	1.5	84	586.10	586.30
Fmoc-1-NAL		Moderate	24	87	564.06	563.6
Fmoc-2-NAL		Moderate	24	78	564.06	563.6
Fmoc-His(Trt)		Moderate-High	20	82	746.16	746.2
Fmoc-Trp		Moderate-High	20	89	553.06	553.1
Fmoc-Phe(4-Me)		Low-Moderate (σ^+ **-0.31)**	48	77 (55)**	528.06	527.8, 542.6**
Fmoc-Phe	N.R.	Low (σ^+ **0.00)**	72	0	N/A	N/A

* *Reported masses correspond to positive-ion ESI-LCMS analyses.*

***Total iodination yield is 77%, iodination with methyl esterification was 22% of total yield.*

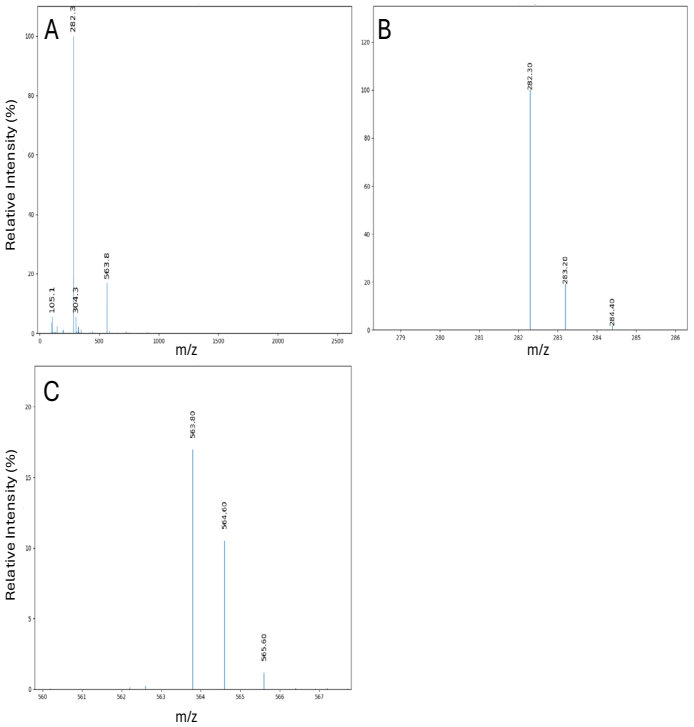


Figure 2: ESI-MS of Fmoc-2-iodo-1-napthylalanine. A) full m/z representation B) isotopic distribution near $[M+2H]^{+2}$ product C) isotopic distribution near $[M+H]^+$ peak.

partial fragmentation during electrospray ionization.

Assignment of the iodination regiochemistry was obtained from NMR analysis, Table 2. For Fmoc-Tyr(OtBu)-OH, Fmoc-Trp-OH, Fmoc-His(trt)-OH, the observed NMR chemical shift data were consistent with previous literature reports.[8, 12, 13] Among the other amino acids, mild substitution differences arose. Fmoc-1NAL-OH, Fmoc-2NAL-OH and Fmoc-Phe(4-Me)-OH underwent substitution ortho to the Cβ substituent. For Fmoc-1NAL-OH only the 2 position is available for substitution. Fmoc-2NAL-OH can be ortho-substituted at either the 1 or 3-position. ^{1}H NMR shows the elimination of the starting material singlet, consistent with iodination at the 1-position. Fmoc-Phe(4-Me)-OH shows ortho iodination at the 2 position, suggesting that Cβ backbone is more electron donating than the methyl group, unlike Tyr where the substituent dictates regiochemistry.[19] The iodo-substituted aryl carbon is readily identified as it becomes shielded to ~90 ppm. HSQC and HMBC shows a cross peak to the Cβ hydrogens whereas no correlation is observed to the 4-methyl substituent. Further, NOE contacts between the 4-methyl hydrogens are observed between an aromatic singlet, and an aromatic doublet, the 3,5 positions, Figure 3.

Table 2: NMR Peak Assignments

Compound	^{1}H NMR (500 MHz)
Fmoc-2-iodo-1-naphthylalanine-OH	CD_3OD: δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.80–7.70 (m, 3H), 7.59–7.50 (m, 3H), 7.47 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.42–7.20 (m, 7H), 4.59 (dd, *J* = 9.2, 5.6 Hz, 1H), 4.26–4.04 (m, 4H), 3.75–3.60 (m, 1H, partially overlapped with residual solvent).
Fmoc-3-iodo-2-naphthylalanine-OH	CD_3OD: δ 7.82–7.71 (m, 1H), 7.69 (s, 1H), 7.51 (dd, *J* = 7.6, 3.0 Hz, 1H), 7.43 (qd, *J* = 6.8, 3.5 Hz, 1H), 7.38–7.30 (m, 1H), 7.25–7.10 (m, 2H), 4.56 (dd, *J* = 9.7, 5.3 Hz, 1H), 4.26–4.16 (m, 2H), 4.12–4.05 (m, 1H), 3.35 (d, *J* = 5.1 Hz, 1H, partially overlapped with residual solvent), 3.10 (dd, *J* = 13.9, 9.7 Hz, 1H).
Fmoc-iodo-Phe(4-Me)-OH	CD_3OD: δ 7.72 (dd, *J* = 11.5, 7.3 Hz, 1H), 7.45 (dd, *J* = 16.4, 7.6 Hz, 1H), 7.38–7.25 (m, 2H), 7.23–7.09 (m, 2H), 6.95–6.76 (m, 2H), 4.77–4.50 (m, 1H), 4.43–4.12 (m, 3H), 4.09–4.01 (m, 1H), 3.35–3.21 (m, 1H, partially overlapped with residual solvent), 3.10–2.91 (m, 2H).
Fmoc-3-iodo-Tyr(tBu)-OH	$CDCl_3$: δ 7.77 (dd, *J* = 7.6, 3.9 Hz, 1H), 7.65–7.55 (m, 2H), 7.40 (td, *J* = 7.5, 4.0 Hz, 1H), 7.35–7.29 (m, 1H), 7.10–6.98 (m, 1H), 4.67–4.59 (m, 1H), 4.44 (dd, *J* = 10.4, 7.0 Hz, 1H), 4.34 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.22 (t, *J* = 7.2 Hz, 1H), 3.72 (d, *J* = 8.5 Hz, 1H), 3.12–3.00 (m, 2H), 1.44 (s, 9H).
Fmoc-2-iodo-Trp-OH	CD_3OD: δ 7.80–7.68 (m, 4H), 7.60–7.46 (m, 5H), 7.40–7.25 (m, 5H), 7.25–7.18 (m, 1H), 7.12–7.04 (m, 2H), 7.00 (t, *J* = 7.4 Hz, 1H), 4.64–4.44 (m, 3H), 4.30–4.15 (m, 3H), 4.10 (t, *J* = 7.1 Hz, 1H), 3.14 (dd, *J* = 14.7, 8.3 Hz, 1H), 2.64–2.41 (m, 1H).
Fmoc-2-iodo-His(Trt)-OH	CD_3OD: δ 8.30 (s, 1H) δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.60 (dd, *J* = 11.8, 7.5 Hz, 1H), 7.45 (t, 2H), 7.25 (m, 10H), 7.11 (dd, *J* = 6.7, 2.8 Hz, 4H), 4.53 (dd, *J* = 10.1, 4.7 Hz, 1H), 4.34–4.27 (m, 1H), 4.22–4.09 (m, 1H), 3.15–3.00 (m, 1H, partially overlapped/weak).

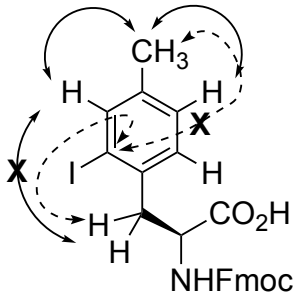


Figure 3. Regiochemistry determination from NMR. Solid lines represent NOE correlations, dashed lines HMBC correlations.

Synthetic Utility of Iodinated Amino Acid Building Blocks

To demonstrate the utility of the iodinated amino acids as synthetic intermediates, a representative Suzuki-Miyura cross-coupling reaction was performed. Fmoc-5-Iodo-His(Trt)-OH was treated with 2'-pyridinyl boronic acid, Figure 4. The substrate underwent productive cross-coupling in moderate isolated yield, 53%. LC-MS analysis, Figure 5, shows a prominent peak at 455.2 a.m.u., which corresponds well with the calculated product of 455.17 a.m.u. The only other minor peak corresponds to a fragment with a mass of 243.1 a.m.u., consistent with the calculated trityl cation mass of 243.11 a.m.u. It should be noted that the reaction conditions are anticipated to remove the trityl side chain protection. However, the small trityl peak observed on the LCMS appears to result from coelution and not fragmentation of the protecting group's C-N bond during ionization. NMR confirmed formation of the desired coupled product, highlighting the versatility of the iodinated synthetic intermediates.

Acknowledgements

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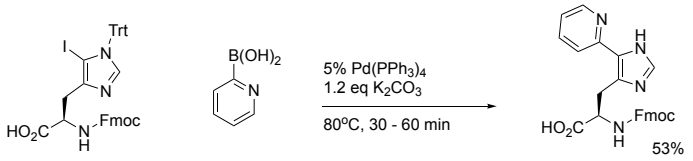

Figure 4. Suzuki- Miyura elaboration of iodinated amino acid.

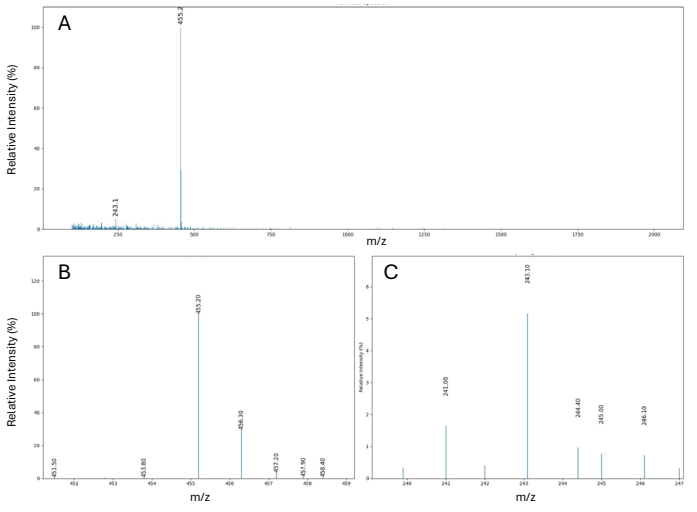

Figure 5: ESI-MS of Suzuki cross-coupling reaction. A) full m/z representation B) isotopic distribution near major product C) isotopic distribution near minor peak.

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