Chapter 4

A Mild and General Larock Indolization Protocol for the Synthesis of Unnatural Tryptophan Derivatives: Total Synthesis of (–)-Aspergilazine A.[†]

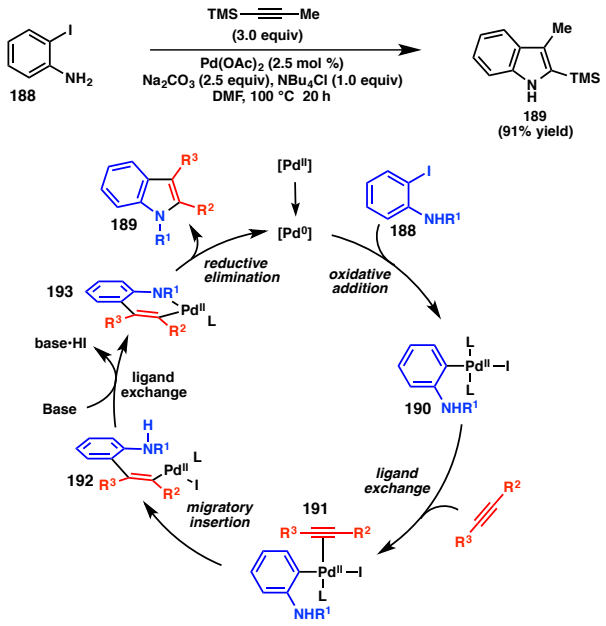
4.1 INTRODUCTION

The Pd(0)-catalyzed heteroannulation of disubstituted alkynes and 2-haloanilines, widely known as the Larock indole synthesis, is a powerful method for the preparation of structurally complex 2,3-disubstituted indoles that has found tremendous utility in accessing indole building blocks, unnatural tryptophan derivatives, and indole-containing natural products.[1,2,3,4] Mechanistically, it is expected to proceed through an active Pd(0) catalyst which can then undergo oxidative addition into 2-iodoaniline **188**. Coordination of an internal alkyne to adduct **190**, followed by migratory insertion and reductive elimination furnishes the indole product **189** and regenerates the Pd(0) catalyst. To date, Larock's original conditions – which couple an *o*-iodoaniline to an internal alkyne in the

[†] Portions of this chapter have been reproduced from submitted studies (Chuang, K. V.; Kieffer, M. E.; Reisman, S. E. *submitted*) and the supporting information found therein. Work was conducted in collaboration with Kangway V. Chuang.

presence of a "ligandless" Pd-catalyst, an inorganic base, and a chloride additive – still remain the most widely employed.[5]

Scheme 4.1. *The Larock indole synthesis catalytic cycle*



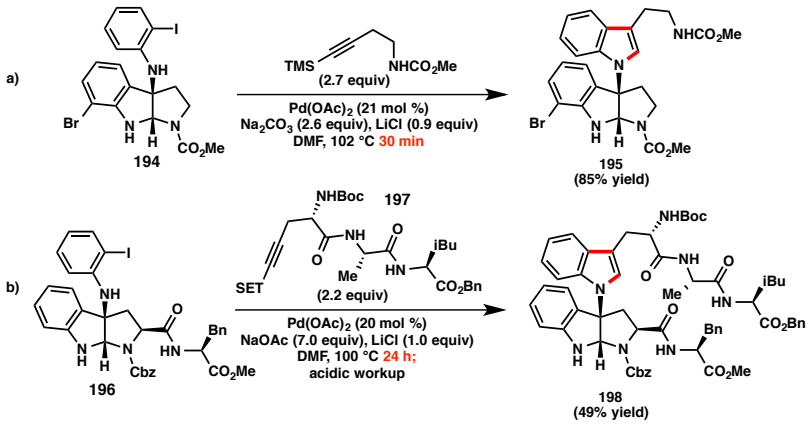
Despite the broad utility of the Larock indole synthesis, a surprisingly small portion of the literature has been dedicated to improving reaction conditions and expanding the substrate scope. From the standpoint of transition-metal catalysis, significant challenges remain, as the application of this reaction in the presence of more complex functionality requires increased catalyst loadings and reaction times due to diminished catalytic activity and poor catalyst turnover. These challenges were highlighted in our synthesis of (+)-naseseazines A and B (**Chapter 3**).[6] Specifically, low reactivity was observed with substoichiometric amounts of Pd catalyst, whereas use of higher Pd-loadings or more forcing conditions resulted in competitive hydrodehalogenation, problematic epimerization of the diketopiperazine, poor regioselectivity, and low mass recovery. This chapter describes our efforts to better

understand the intricacies of this transformation to aid in the development of a modified Larock indolization protocol. The mild procedure described herein enables the coupling of 2-bromoanilines with high functional group compatibility to provide structurally complex and synthetically useful indoles.

4.1.1 The Larock Indole Synthesis in Natural Products

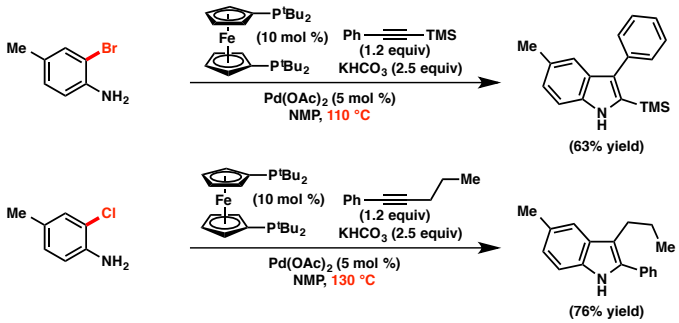
Following its initial disclosure in 1991, the Larock indole synthesis has been beautifully employed in a variety of total syntheses. Elegant examples from the Baran lab demonstrate the ability to quickly advance iodoaniline substrates **194** and **196** to highly functionalized intermediates *en route* to natural products such as psychotrimine and (+)-kapakahine B.[3] Despite the impressive and rapid generation of substrate complexity, these examples highlight the limitations of this catalyst system in tolerating functionalized substrates. For example, in their synthesis of kapakahine B, 20 mol % $Pd(OAc)_2$ is necessary to effect two productive turnovers on a complex iodoaniline substrate (**Scheme 4.2**, **b**). Generally, increased substrate complexity, especially with respect to *polar functionality* and *epimerizable centers*, necessitates increased catalyst loadings and reaction times, and typically results in lower product yields.

Scheme 4.2. *Iodoanilines in natural product synthesis*



It was not until 2004 that modifications to Larock's original conditions allowed for the successful implementation of bromo- and chloro-electrophiles. Employing 10 mol % of bidentate phosphine ligand 1,1'bis(di-*tert*-butylphosphino)ferrocene at elevated temperatures (110 – 130 °C), Senanayake and co-workers found that haloaniline substrates underwent smooth reaction to provide simple indoles in moderate to good yields (**Scheme 4.3**).[7]

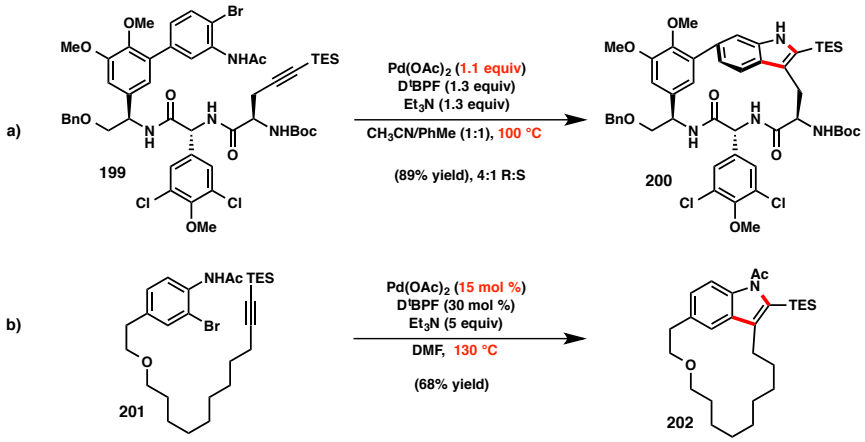
Scheme 4.3. *Larock modfications to include bromo- and chloroelectrophiles.*



Boger and co-workers have further explored the application of this phosphine ligand and bromoanilines in the context of total synthesis.[4] Utilizing a strategic intramolecular Larock reaction to assemble the key macrocyclic framework (**200**), early efforts resulted in poor mass recovery, competitive hydrodechlorination, and undesired epimerization of several critical α-stereocenters. Only after extensive optimization and

use of superstoichiometric Pd-catalyst and ligand were high yields obtained (**Scheme 4.4**, **a**). In a follow-up report, a catalytic Larock macrocyclization reaction was reported using 15 mol % $Pd(OAc)_2$ and 30 mol % ligand at 130 °C, but *only substrates without polar functionality and epimerizable centers* are competent in this transformation.[4]

Scheme 4.4. *Bromoanilines as electrophiles for the Larock indole synthesis*



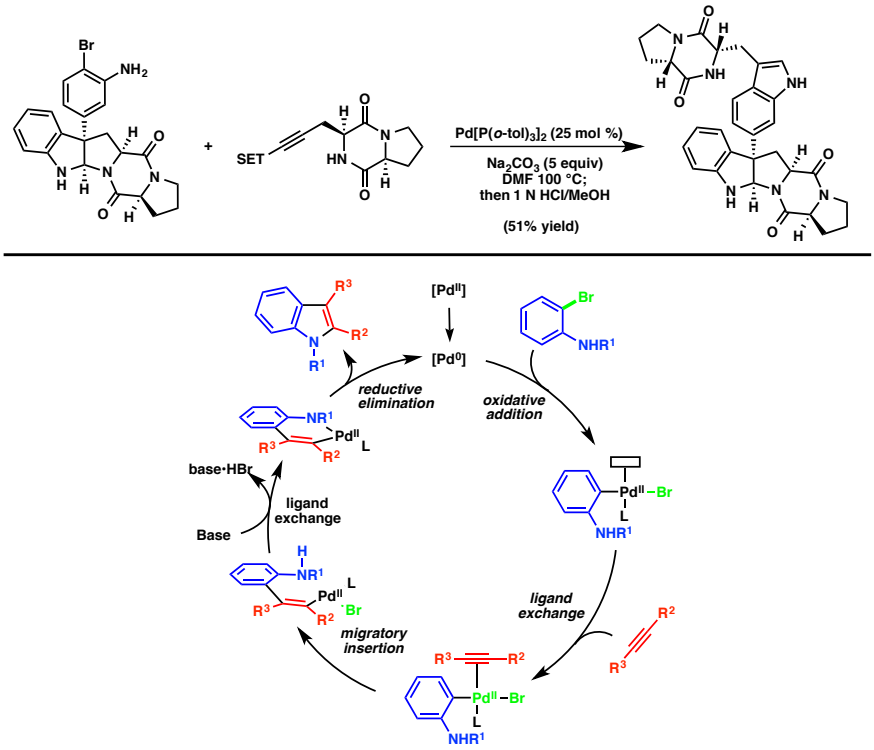
4.2 REACTION DESIGN

Our synthesis of (+)-naseseazines A and B constitutes the first *catalytic* Larock indolization on a bromoaniline in the context of total synthesis. We wondered whether these conditions could be further improved to create a low temperature, mild, and general protocol for the indolization of *2*-bromoaniline starting materials, which serve as more desirable substrates due to their increased ease of synthesis as well as commercial availability compared to *2*-iodoanilines. Specifically, we aimed to develop conditions compatible with highly functionalized substrates in order to directly access tryptophan derivatives. We hoped to identify conditions that would 1) increase substrate scope by enabling less reactive *2*-bromoaniline substrates; 2) proceed with synthetically useful

catalyst loadings; and 3) deliver products at lower temperatures in order to mitigate deleterious side reactivity. To accomplish this, we sought to understand why Pd[P(*o*-tol)$_3$]$_2$, our optimal catalyst in the preparation of the (+)-naseseazines, appeared to be uniquely effective in catalyzing our desired transformation.

In assessing the existing limitations of the Larock indolization, we rationalized that the poor reactivity of 2-bromoanilines under Larock's ligandless conditions was likely due to slow rates of oxidative addition. Although this elementary step could be easily remedied by the addition of an electron-donating phosphine ligand, we recognized that the limited success of this approach might be due to diminished rates of alkyne insertion due to coordinative saturation of Pd.[8] We hypothesized that the use of sterically demanding phosphines, such as P(*o*-tol)$_3$ and P(^{t}Bu)$_3$, which have been demonstrated to proceed *via* Pd-monophosphine rather than Pd-bisphosphine intermediates as the active catalyst, may serve to balance these opposing factors by providing a vacant coordination site to facilitate alkyne insertion (**Scheme 4.5**).[9]

Scheme 4.5. *Improving the Larock indole synthesis*

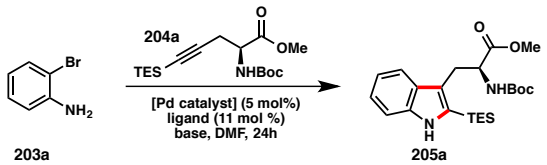


4.3 REACTION OPTIMIZATION

With the goal of identifying conditions tolerant of more complex functionality, we elected to study the coupling of 2-bromoaniline (**203a**) and alkyne **204a**[10] to afford 2-triethylsilyl-Boc-Trp-OMe (**205a**). Treatment with 5 mol % $Pd(OAc)_2$ with Na_2CO_3 at 100 °C, Larock's original conditions, surprisingly provided 27% yield of the desired coupling product. Turning our attention to the addition of phosphine ligands, the addition of 11 mol % PPh_3, PCy_3, DavePhos, or the dtbpf, the optimal ligand in Senanayake's report, suppressed the desired reactivity (**entries 2–5**). Returning to the preformed complex $Pd[P(o\text{-tol})_3]_2$, our most successful catalyst in the synthesis of the (+)-naseseazines, we were gratified to obtain 70% yield of the desired product. Moreover, by increasing the steric demand through the use of $Pd[P(^tBu)_3]_2$, a yield increase to 78% was

observed. We next investigated whether this reaction was competent at decreased temperatures. Lowering the temperature to 60 °C enabled a clean reaction and provided the product in an improved 85% yield (**entry 8**). To the best of our knowledge, this reaction represents the lowest temperature Larock indolization of *any 2-haloaniline* previously reported in the literature. Additionally, a soluble organic base (Cy_2NMe), and non-polar solvent could also be employed without loss in reaction efficiency (**entries 9 and 10**). Finally, in support of a highly active, Pd-monophosphine complex, use of a 1:1 [Pd]/L ratio generated by the addition of $Pd_2(dba)_3$ and $P(^tBu)_3$ offered improved initial rates of the reaction (**entry 11**). However, application of this catalyst system did not significantly reduce the overall reaction time, and furnished in the product in nearly identical yield. Although these final variations did not significantly affect yield, these data illustrate the robust nature of the active catalyst, as well as flexibility in the reaction conditions that may prove useful in individual substrate optimization. For simplicity of reaction setup, we elected to conduct our scope studies using the air-stable and crystalline $Pd[P(^tBu)_3]_2$.

Table 4.1. *Optimization Studies*



entry	[Pd cat.]	ligand	base	temp (°C)	yield (%)[b]
1	$Pd(OAc)_2$	–	Na_2CO_3	100	27
2	$Pd(OAc)_2$	PPh_3	Na_2CO_3	100	17
3	$Pd(OAc)_2$	DavePhos	Na_2CO_3	100	8
4	$Pd(OAc)_2$	PCy_3	Na_2CO_3	100	<5
5	$Pd(OAc)_2$	dtbpf	Na_2CO_3	100	<5
6	$Pd[P(o\text{-tol})_3]_2$	–	Na_2CO_3	100	70
7	$Pd[P(^t Bu)_3]_2$	–	Na_2CO_3	100	78
8	$Pd[P(^t Bu)_3]_2$	–	Na_2CO_3	60	85
9	$Pd[P(^t Bu)_3]_2$	–	Cy_2NMe	60	85
10[e]	$Pd[P(^t Bu)_3]_2$	–	Cy_2NMe	60	84 (87)[d]
11[e]	$Pd_2(dba)_3$	$P(^t Bu)_3$	Cy_2NMe	60	83

[a] Reactions conducted on 0.1 mmol scale with 2.0 equiv alkyne **204a** and 2.5 equiv base in DMF (0.5 mL). [b] Yield determined by ^1H NMR analysis of the crude reaction mixture relative to an internal standard. [c] 1:1 [Pd]/ligand used. [d] Isolated yield on 0.3 mmol scale. [e] Reaction performed in 1,4-dioxane.

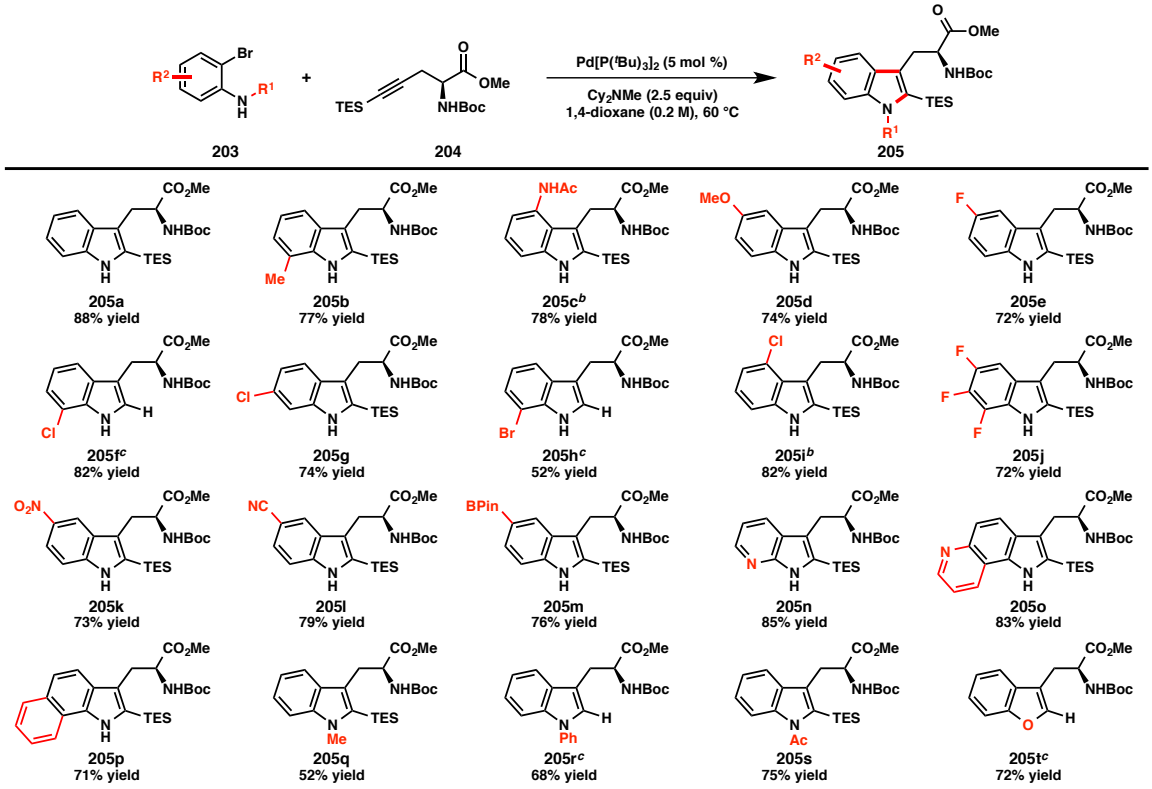
4.4 REACTION SCOPE

4.4.1 Bromoaniline scope

As shown in **Table 4.2**, the reaction exhibits excellent scope; both electron-rich (**205a**–**205d**) and electron-deficient (**205e**–**205l**) substrates react efficiently to provide a structurally diverse array of unnatural tryptophan derivatives. Substitution is readily tolerated at all positions of the indole, including the indole nitrogen, although the preparation of sterically demanding 4-substituted indoles requires slightly elevated temperatures to improve reaction rates (**205c** and **205l**). Halogenated substrates perform with excellent chemoselectivity for the aryl bromide over potentially reactive aryl chloride functionality, and a variety of useful chlorinated (**205f**, **205g**, **205l**) and fluorinated (**205e**, **205j**) tryptophans are readily accessed. Remarkably, even additional bromide functionality can be tolerated to provide bromotrytophan **205h**. Furthermore, we were pleased to find that Lewis-basic heterocycles also perform well under these

conditions (**205n** and **205o**). It is noteworthy that tryptophan **205o**, readily prepared here in two steps from commercially available materials, has recently been reported as a new fluorescent probe with interesting photophysical properties.[11] Finally, these conditions are also readily extended to 2-bromophenol to provide direct access to a substituted benzofuran derivative (**205t**). Importantly, chiral SFC analysis verified that this reaction proceeds without deleterious racemization, providing all products in enantiopure form. The 2-triethylsilyl group is easily removed using aqueous acid or fluoride sources, or alternatively can serve as a useful functional handle for a variety of transformations.[12]

Table 4.2. *Bromoaniline scope*

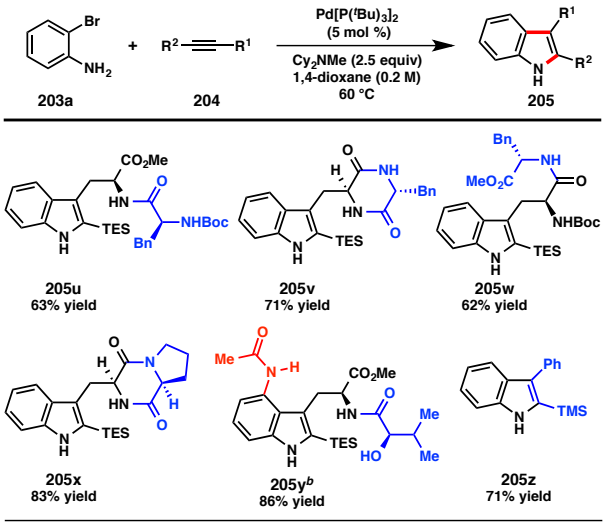


[a] Reactions conditions: Substituted 2-bromoaniline, alkyne (2.0 equiv), Cy2NMe (2.5 equiv) in 1,4-dioxane (0.2 M) at 60 °C. Isolated yields are reported. [b] Reaction performed at 80 °C. [c] To facilitate purification, desilylation with 1 M TBAF or 1 N HCl in MeOH was performed prior to chromatography.

4.4.2 Alkyne scope

To investigate the scope of the alkyne, several dipeptide-and diketopiperazine-based substrates were prepared and subjected to the reaction conditions (**Table 4.3**). In all cases, the products are obtained in good yields and with no observed epimerization of the α-stereocenters. Excellent functional group tolerance is demonstrated by the preparation of **205y** in 86% yield. Although the focus of this study was the coupling of peptide-based alkynes, simple alkynes such as TMS-phenyl acetylene can also be used (**3z**), reacting under considerably milder conditions than those previously reported.[13]

Table 4.3. *Alkyne scope*



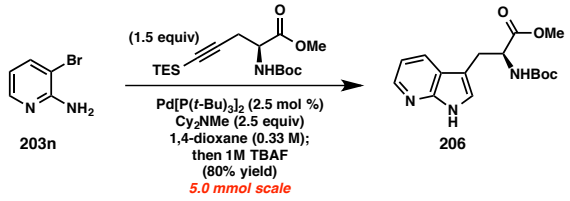
[a] Reactions conditions: **203a** (1.0 equiv), **204** (2.0 equiv), CyNMe (2.5 equiv), in 1,4-dioxane (0.2 M) at 60 °C. Isolated yields are reported. [b] Reaction performed at 80 °C.

4.4.3 Scale-up Reaction

The synthetic studies described above utilized 5 mol % catalyst for operational simplicity; however, individual couplings can be reoptimized for preparatively useful scales with lower catalyst loadings. For example, the coupling between 3-bromo-2-aminopyridine (**203n**) and alkyne **204a** was carried out on 5 mmol scale using 2.5 mol % $Pd[P(^tBu)_3]_2$ and 1.5 equiv alkyne, which upon quenching with 1M TBAF in THF to

effect protodesilylation, provided 1.28 g (80% yield) of *N*-Boc-7-aza-tryptophan methyl ester **206** (**Scheme 4.6**).

Scheme 4.6. *Reaction scale-up*

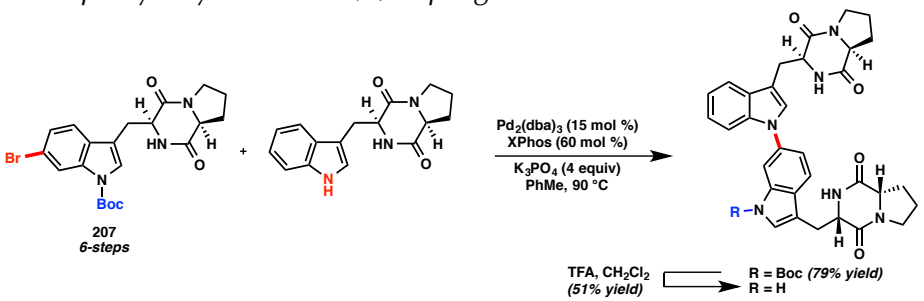


4.5 TOTAL SYNTHESIS OF (–)-ASPERGILAZINE A

4.5.1 Previous Synthesis of (–)-Aspergilazine A

With optimized conditions in hand, we set out to demonstrate the versatility and efficiency of this transformation through the total synthesis of (–)-aspergilazine A. (–)-aspergilazine A is (bis)diketopiperazine-containing indole natural product with a distinctive C6–N1 linkage.[14] First synthesized in 2014, Sperry and co-workers adopted a traditional approach utilizing a protecting group strategy.[15] In six-steps, they are able to synthesize Boc-protected 6-bromo tryptophan **207** via enzymatic resolution, which upon subjection to 30 mol % [Pd] and 60 mol % Xphos, undergoes C–N bond formation. Trifluoroacetic acid mediated removal of the Boc-protecting group then affords the natural product.

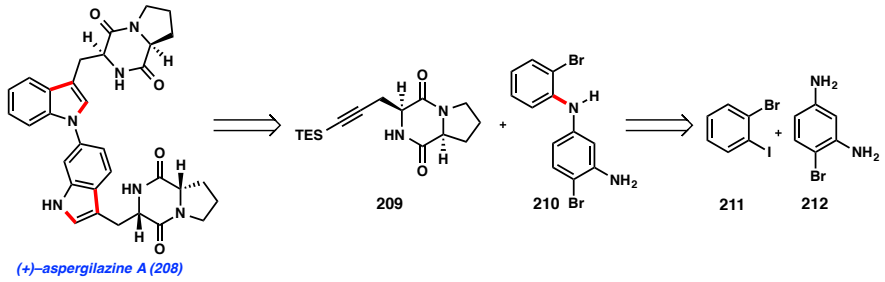
Scheme 4.6. *Sperry's synthesis of (–)-aspergilazine A*



4.5.2 Our Synthesis of (–)-Aspergilazine A

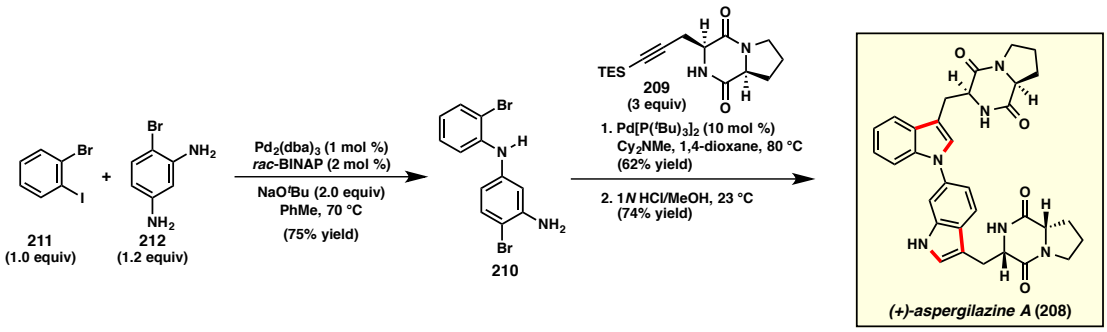
Retrosynthetically, we imagined a slightly more direct disconnection that could highlight our newly developed methodology. We proposed a disconnection through both tryptophan indoles *via* a sequential Larock indolization between known diketopiperazine **209** and diarylamine **210**. We hoped to synthesize diarylamine **210** using a selective Buchwald-Hartwig reaction of 1-bromo-2-iodobenzene (**211**) and commercially-available 4-bromo-1,2-diaminobenzene (**212**). Importantly, the success of this strategy hinges largely on the ability of this new protocol to enable the coupling of 2-bromoanilines; the preparation of the diiodinated analog of diarylamine **210** via C–N bond formation is a considerably more challenging synthetic undertaking.

Scheme 4.7. *Retrosynthetic analysis of (–)-aspergilazine A*



To this end, the requisite bis-bromoaniline (**210**) was readily prepared via coupling of 1-bromo-2-iodobenzene with 4-bromo-*m*-phenylenediamine (**212**).[16] Subjection of a mixture of dibromide **210** and alkyne **209** to 10 mol % Pd[P(^{t}Bu)$_3$] and 2.5 equiv of Cy_2NMe in 1,4-dioxane at 80 °C furnished bis-triethylsilyl-(–)-aspergilazine A in 62% isolated yield, representing an average reaction efficiency of 79% per indolization. Subsequent HCl-mediated desilylation cleanly provided the natural product. This highly convergent synthesis underscores the utility of this methodology in the direct preparation of complex molecular scaffolds.

Scheme 4.8. *Total synthesis of (–)-aspergilazine A*



4.6 CONCLUSION

In summary, this chapter describes the development of a mild and general protocol for the Pd-catalyzed synthesis of functionalized tryptophan derivatives. The reaction proceeds with low catalyst loadings, displays excellent substrate scope, and is readily scalable to provide gram quantities of synthetically useful indoles and unnatural tryptophans. Furthermore, the synthetic utility of this transformation has been demonstrated in the concise synthesis of the natural product (–)-aspergilazine A. We anticipate that this versatile protocol will find broad applicability in the preparation of complex indole and tryptophan scaffolds, and provide efficient entry to a broad array of natural products.

4.7 EXPERIMENTAL SECTION

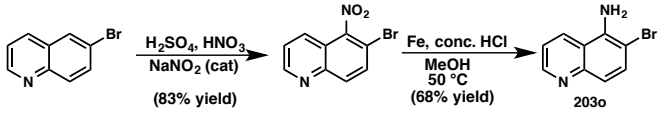
4.7.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. 1,4-Dioxane was dried by passing through activated alumina columns or purchased from Sigma-Aldrich (>99.8%, anhydrous).

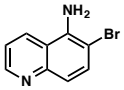
Triethylamine (Et_3N), diisopropylamine (i-Pr_2NH), diisopropylethylamine (i-Pr_2NEt), and dicyclohexylmethylamine (Cy_2NMe) were distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, p-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al. using silica gel (particle size 0.032-0.063) purchased from Silicyle. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$), MeCN (^1H, $\delta = 1.94$), or DMSO (^1H, $\delta = 2.50$), and $CDCl_3$ (^{13}C, $\delta = 77.0$), MeCN (^{13}C, $\delta = 118.26$), or DMSO (^{13}C, $\delta = 40.0$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Preparatory HPLC was performed with either an Agilent 1200 Series HPLC utilizing an Agilent XDB-C18 5μm column (30 x 250 mm). Analytical SFC was performed with a Mettler SFC supercritical CO2 analytical chromatography system with Chiralcel AD-H column (4.6 mm x 25 cm). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

4.7.2 Preparation of haloaniline substrates

Bromoaniline 203o

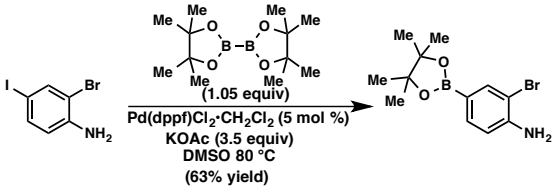


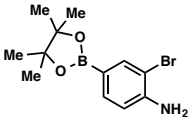
6-bromoquinoline was purchased from Combi-Blocks and nitrated using a known procedure. 5-nitro,6-bromo-quinloline (500 mg, 2.0 mmol, 1.0 equiv) was dissolved in MeOH (6 mL). Fe powder (331 mg, 5.9 mmol, 3.0 equiv) and concentrated HCl (2 mL) were added and the reaction was heated to 50 °C for 1 h. Upon cooling, the reaction was basified with NH_4OH to pH 9, filtered through celite, and extracted with EtOAc (2X, 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel (40% acetone, 60% hexanes) to provide a light yellow, amorphous solid (300 mg, 1.3 mmol, 68% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.16 (ddd, *J* = 8.6, 1.5, 0.9 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.45 (dd, *J* = 9.0, 0.7 Hz, 1H), 7.39 (dd, *J* = 8.6, 4.2 Hz, 1H) , 4.68 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.31, 148.1, 139.6, 133.3, 129.4, 120.7, 120.2, 118.7, 104.3; FTIR (NaCl, thin film): cm^{-1}; 3423, 3297, 3162, 1635, 1581, 1569, 1457, 1398, 1357, 1323; HRMS (MM) calc'd $[M+H]^+$ 222.9865, found 222.9862.

Bromoaniline 203m

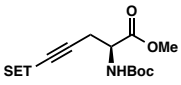




In a glovebox, a 2 dram vial was charged with 4-iodo,2-bromoaniline (500 mg, 1.7 mmol, 1.0 equiv), Pd(dppf)Cl_2•CH_2Cl_2 (69 mg, 0.08 mmol, 0.05 equiv), bis(pinacolato)diboron (448 mg, 1.8 mmol, 1.05 equiv), KOAc (557 mg, 5.9 mmol (3.5 equiv), and DMSO (5 mL). The vial was sealed, removed from the glove box and heated to 80 °C. After 24 h, the reaction was cooled, filtered through celite and flushed with ethyl acetate. This mixture was then washed with water (3 X), dried Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified by chromatography on silica gel (10% ethyl acetate, 90% hexanes) to give white, amorphous solid **203m** (315 mg, 1.1 mmol, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.3 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 1.32 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ146.6, 139.2, 135.0, 114.8, 108.8, 83.58, 24.8 (carbon adjacent to Boron was not observed); FTIR (NaCl, thin film): cm^{-1}; 3477, 3368, 2977, 2930, 1616, 1594, 1385, 1372, 1319, 1143, 1098; HRMS (MM) calc'd $[M+H]^+$ 297.0645, found 297.0637.

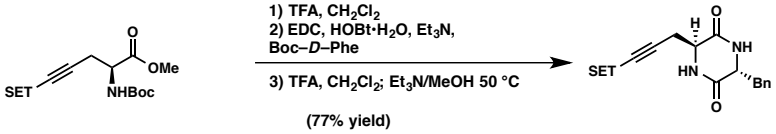
4.7.3 Preparation of alkyne substrates



Alkyne 204a

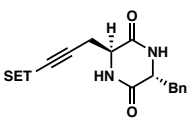
Alkyne **204a** was prepared on decagram scale according to the procedure reported by Baran and co-workers.

Alkyne 204v



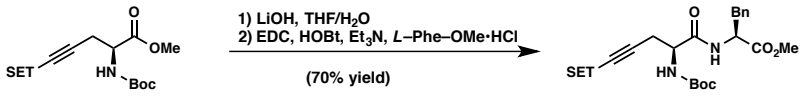
Methyl ester **204a** (1.02 g, 3.0 mmol, 1.00 equiv) was dissolved in a 5:1 mixture of CH_2Cl_2:TFA (20 mL) . After one hour, the reaction was concentrated and dissolved in 34 mL CH_2Cl_2. The solution was cooled to 0 °C under a positive pressure of N_2 and EDC•HCl (0.862 g, 4.5 mmol, 1.50 equiv), HOBt•H_2O (0.680 g, 4.5 mmol, 1.50 equiv) and Et_3N (1.88 mL, 13.5 mmol, 4.5 equiv) were added sequentially. The mixture was then stirred for 5 minutes, and Boc–*D*–phenylalanine (1.59 g, 6.0 mmol, 2.0 equiv) was added. The reaction was slowly warmed to 23 °C over 2 hours and stirring continued for 20 hours. The reaction was then quenched with 1 N HCl (500 mL) and extracted with EtOAc (3 x 250 mL), then the combined organics washed with saturated aqueous NaHCO3 (500 mL), and aqueous layer back extracted with EtOAc (200 mL). The combined organic layers were then dried over anhydrous Na2SO4, filtered, and concentrated in *vacuo* to afford crude dipeptide as a viscous oil.

The residue was then dissolved in CH_2Cl_2 (50 mL), and trifluoroacetic acid (15 mL) was added dropwise by addition funnel at room temperature over 10 minutes. Stirring was continued for 20 minutes, then the solution diluted with toluene (100 mL) and the mixture concentrated in *vacuo* to afford a thick oil. The residue was then redissolved in MeOH (35 mL) and the mixture cooled to 0 °C. Et_3N (27 mL) was then added dropwise the stirring solution over 10 minutes by addition funnel. Upon completion of the addition, the cooling bath was removed and the reaction was heated to 50 °C over 16 h. The mixture was cooled to 0 °C to yield a milky solution, which was filtered and washed with cold methanol to provide alkyne **204v** as a colorless solid (771 mg, 72% yield)

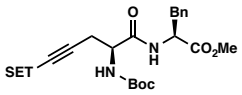


^{1}H NMR (500 MHz, DMSO) δ 8.35 (d, *J* = 1.6 Hz, 1H), 8.02 (d, *J* = 1.0 Hz, 1H), 7.29 – 7.19 (m, 3H), 7.18 – 7.12 (m, 2H), 4.15 (s, 1H), 3.19 – 3.11 (m, 2H), 2.88 (dd, *J* = 13.5, 4.9 Hz, 1H), 2.63 (dd, *J* = 16.9, 3.2 Hz, 1H), 2.40 (dd, *J* = 17.0, 4.7 Hz, 1H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.50 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (126 MHz, DMSO) δ 166.6, 166.0, 135.8, 130.1, 128.0, 126.7, 104.0, 83.9, 55.4, 52.6, 38.4, 24.8, 7.3, 3.9; FTIR (NaCl, thin film): cm^{-1}; 2916, 2350, 1732, 1651, 1557, 1455; $[\alpha]_D^{25}$ = –19.4 (*c* = 0.28, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 357.1993, found 357.1992.

Alkyne 204w

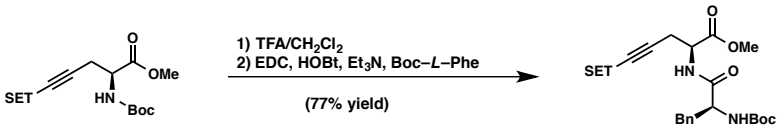


To a solution of methyl ester **204a** (550 mg, 1.5 mmol, 1.00 equiv) in THF/H_2O (4 mL/2 mL) at 0 °C under a positive pressure of N_2 was added aqueous LiOH (1 M, 1.9 mL, 1.2 equiv). After 1 hour, the reaction was quenched by slow addition of 1 M HCl (3 mL) and Et_2O (6 mL). The layers were separated and the aqueous was extracted with Et_2O (3X, 10 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a colorless oil. The oil was dissolved in 24 mL THF and cooled to 0 °C under a positive pressure of N_2. EDC (337 mg, 1.8 mmol, 1.2 equiv), anhydrous HOBt (277 mg, 2.0 mmol, 1.4 equiv) and Et_3N (610 μL, 4.4 mmol, 3.0 equiv) were added sequentially. After 5 minutes of stirring, a solution of (*l*)-Phe-OMe•HCl (347 mg, 1.6 mmol, 1.1 equiv) in THF (10 mL) was added via cannula. The reaction was warmed to room temperature and stirred for 12 h. The heterogeneous solution was concentrated and purified by chromatography on silica gel (20% ethyl acetate, 80% hexanes) to give white, amorphous solid **204w** (500 mg, 1.02 mmol, 70% yield)



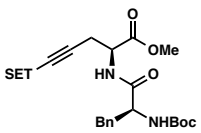
^{1}H NMR (500 MHz, $CDCl_3$, Major Rotamer) δ 7.30 – 7.19 (m, 3H), 7.13 – 7.04 (m, 2H), 6.84 (d, *J* = 4.9 Hz, 1H), 5.25 (s, 1H), 4.81 (ddd, *J* = 7.5, 6.0, 6.0 Hz, 1H), 4.22 (d, *J* = 4.9 Hz, 1H), 3.67 (s, 3H), 3.18 – 3.01 (m, 2H), 2.74 (dd, *J* = 17.1, 6.1 Hz, 1H), 2.65 (dd, *J* = 17.1, 6.5 Hz, 1H), 1.42 (s, 9H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.55 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 169.9, 155.3, 135.7, 129.1, 128.4, 127.0, 102.5, 85.5, 80.2, 53.4, 53.0, 52.2, 38.0, 28.1, 23.3, 7.7, 4.2; FTIR (NaCl, thin film): cm^{-1}; 3319, 2954, 2935, 2874, 2177, 1746, 1689, 1660, 1527, 1498, 1456, 1367, 1274, 1251, 1172, 1048, 1017; $[\alpha]_D^{25}$ = +39.2 (*c* = 4.29, $CHCl_3$); HRMS (MM) calc'd $[M–C_4H_9]^+$ 433.2153, found 433.2138.

Alkyne 204u



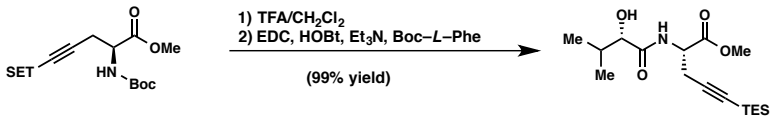
To a solution of Boc-alkyne **204a** (500 mg, 1.5 mmol, 1.00 equiv) in CH_2Cl_2 (15 mL) at 0 °C was added TFA (2.0 mL). The mixture was warmed to room temperature and stirred for 3 hours, after which PhMe (30 mL) was added and the reaction concentrated. The resultant oil was dissolved in THF (10 mL) and cooled to 0 °C under a positive pressure of N_2. In a separate flask, (*l*)-Boc-Phe-OH (466 mgs, 1.8 mmol, 1.2 equiv) was dissolved in THF (24 mL) and cooled to 0 °C. EDC (337 mg, 1.8 mmol, 1.2 equiv), anhydrous HOBt (277 mg, 2.0 mmol, 1.4 equiv) and Et_3N (610 μL, 4.4 mmol, 3.0 equiv) were added sequentially. After stirring for 5 minutes, the alkyne was transferred via cannula. The reaction was warmed to room temperature and stirred for 12 h. The heterogeneous reaction was concentrated and purified by chromatography on silica gel

(20% ethyl acetate, 80% hexanes) to provide the product as a colorless oil (552 mg, 1.13 mmol, 77% yield).



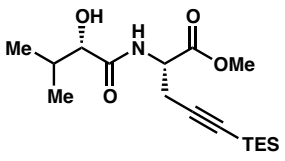
^{1}H NMR (500 MHz, $CDCl_3$, Major Rotamer) δ 7.28 – 7.22 (m, 2H), 7.19 (dd, *J* = 7.1, 7.1 Hz, 3H), 6.77 (d, *J* = 6.3 Hz, 1H), 5.16 (d, *J* = 5.9 Hz, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.44 (d, *J* = 6.1 Hz, 1H), 3.70 (s, 3H), 3.11 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.98 (dd, *J* = 12.8, 6.6 Hz, 1H), 2.73 (dd, *J* = 17.0, 4.0 Hz, 1H), 2.57 (dd, *J* = 17.1, 5.3 Hz, 1H), 1.35 (s, 9H), 0.98 – 0.87 (m, 9H), 0.57 – 0.46 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ170.8, 170.4, 155.2, 136.4, 129.2, 128.4, 126.7, 101.3, 85.5, 79.8, 55.3, 52.4, 50.8, 38.4, 28.1, 23.5, 7.3, 4.1; FTIR (NaCl, thin film): cm^{-1}; 3419, 3335, 2963, 2868, 2179, 1743, 1661, 1518, 1451, 1365; $[\alpha]_D^{25}$ = +52.7 (*c* = 5.4, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 489.2779, found 489.2793.

Alkyne 204y



To a solution of Boc-alkyne **204a** (1.00 g, 2.9 mmol, 1.00 equiv) in CH_2Cl_2 (30 mL) at 0 °C was added TFA (4 mL). The mixture was warmed to room temperature and stirred for 3 hours, after which PhMe (100 mL) was added and the reaction concentrated. The resultant oil was dissolved in THF (10 mL) and cooled to 0 °C under a positive pressure of N_2. In a separate flask, (*R*)-2-hydroxy-3-methylbutanoic acid (346 mgs, 2.9 mmol, 1.0 equiv) was dissolved in THF (100 mL) and cooled to 0 °C. EDC (674 mg, 3.5 mmol, 1.2 equiv), anhydrous HOBt (554 mg, 4.1 mmol, 1.4 equiv) and hünigs base (1.5 mL, 8.6 mmol, 3.0 equiv) were added sequentially. After stirring for 5 minutes, the alkyne was transferred via cannula. The reaction was warmed to room temperature and stirred for 12 h. The heterogeneous reaction was concentrated and purified by

chromatography on silica gel (100% ethyl acetate) to provide the product as a colorless oil (995 mg, 2.9 mmol, 99% yield).



^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 7.43 (d, *J* = 7.6 Hz, 1H), 4.59 (dt, *J* = 8.2, 5.3 Hz, 1H), 3.89 (dd, *J* = 5.5, 3.1 Hz, 1H), 3.71 (d, *J* = 5.6 Hz, 1H), 3.69 (s, 3H), 2.80 (dd, *J* = 17.2, 5.5 Hz, 1H), 2.73 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.07 (heptd, *J* = 6.9, 3.1 Hz, 1H), 1.01 – 0.93 (m, 12H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.61 – 0.52 (m, 6H); ^{13}C NMR (126 MHz, CD_3CN) δ 174.2, 171.7, 118.3, 103.6, 85.8, 76.4, 53.0, 51.4, 32.7, 23.9, 19.5, 15.9, 7.8, 5.0; FTIR (NaCl, thin film): cm^{-1}; 3385, 2952, 2863, 2176, 1744, 1653, 1507; $[\alpha]_D^{25}$ = -+89.4 (*c* = 3.40, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 342.2095, found 342.2087.

4.7.4 Optimization of reaction parameters

Optimization Procedure – In a glovebox, an oven-dried 1 dram vial was charged with 2-bromoaniline (17.2 mg, 0.1 mmol, 1.0 equiv), alkyne **204a** (68.3 mg, 0.2 mmol, 2.0 equiv), base (2.5 equiv), Pd-catalyst (0.05 equiv), and appropriate solvent (0.5 mL). The vial was sealed and heated to the required temperature for 2 – 36 h. Upon cooling, the crude reaction mixture was filtered through a silica plug, thoroughly washed with ethyl acetate and concentrated *in vacuo* to provide a crude oil.

The crude residue was dissolved in a standard solution of 2,3,5,6-tetrachloronitrobenzene in DMSO-d_6, and the yield of **205** was determined by ^{1}H NMR by integration relative to the internal standard.

** In entry 9 of Table 1, $Pd_2(dba)_3$ and P^tBu_3 were prestired for 1 h before being added to a vial containing the other reagents.

4.7.5 Substrate scope – characterization data

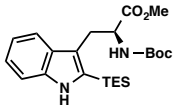
General Procedure I: In a glovebox, a 2 dram vial was charged with bromoaniline (0.3 mmol, 1.0 equiv), alkyne **204a** (0.6 mmol, 2.0 equiv), Cy_2NMe (0.75 mmol, 2.5 equiv), $Pd[P(P^tBu)_3]_2$ (0.015 mmol, 0.05 mmol) and anhydrous 1,4-dioxane (1.5 mL, 0.2 M). The vial was sealed and heated to 60 °C until there was complete consumption of starting material (12 – 72 h). In most cases the solution became cloudy as the reaction progressed. Upon cooling, the crude mixture was filtered through a plug of silica, which was subsequently flushed with ethyl acetate. The organics were concentrated and the crude residue was purified by chromatography on silica gel to provide tryptophan derivatives.

General Procedure II: In a glovebox, a 2 dram vial was charged with bromoaniline (0.3 mmol, 1.0 equiv), alkyne **204a** (0.6 mmol, 2.0 equiv), Cy_2NMe (0.75 mmol, 2.5 equiv), $Pd[P(P^tBu)_3]_2$ (0.015 mmol, 0.05 mmol) and anhydrous 1,4-dioxane (1.5 mL, 0.2 M). The vial was sealed and heated to 80 °C until there was complete consumption of starting material (12 – 72 h). In most cases the solution became cloudy as the reaction progressed. Upon cooling, the crude mixture was filtered through a plug of silica, which was subsequently flushed with ethyl acetate. The organics were concentrated and the crude residue was purified by chromatography on silica gel to provide tryptophan derivatives.

General Procedure III: In a glovebox, a 2 dram vial was charged with bromoaniline (0.3 mmol, 1.0 equiv), alkyne **204a** (0.6 mmol, 2.0 equiv), Cy_2NMe (0.75 mmol, 2.5

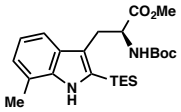
equiv), $Pd[P(P^tBu)_3]_2$ (0.015 mmol, 0.05 mmol) and anhydrous 1,4-dioxane (1.5 mL, 0.2 M). The vial was sealed and heated to 80 °C until there was complete consumption of starting material (12 – 72 h). In most cases the solution became cloudy as the reaction progressed. Upon cooling, the crude mixture was filtered through a plug of silica, which was subsequently flushed with ethyl acetate. The organics were concentrated and the crude residue was dissolved in 1M TBAF in THF. After 20 minutes, aqueous NH_4Cl was added and the reaction mixture was partitioned in a separatory funnel. The aqueous layer was back extracted with ethyl acetate (3 X 15 mL). The organics were then recombined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified using silica gel chromatography.

Tryptophan **205a**



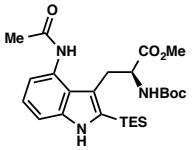
Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (88% hexanes, 12% ethyl acetate) to afford **3a** as a colorless oil (113.6 mg, 0.26 mmol, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$, Major Rotamer) δ 8.04 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.09 (dd, J = 7.4, 7.4 Hz, 1H), 4.93 (d, J = 7.7 Hz, 1H), 4.57 (dd, J = 14.4, 7.1 Hz, 1H), 3.63 (s, 3H), 3.36 – 3.18 (m, 2H), 1.36 (s, 9H), 1.05 – 0.98 (m, 9H), 0.97 – 0.89 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 155.1, 138.5, 132.8, 128.6, 122.4, 119.5, 119.3, 118.9, 110.8, 79.6, 54.2, 52.2, 29.3, 28.2, 7.4, 3.7; FTIR (NaCl, thin film): cm^{-1}; 3383, 2954, 2911, 2875, 1739, 1700, 1501, 1456, 1367, 1284, 1164; $[\alpha]_D^{25}$ = +1.4 (c = 1.4, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 433.2517, found 433.2519.

Tryptophan **205b**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (88% hexanes, 12% ethyl acetate) to afford **205b** as a colorless oil (102.9 mg, 0.230 mmol, 77% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 8.68 (s, 1H), 7.37 (dd, *J* = 7.0, 1.3 Hz, 1H), 6.99 – 6.91 (m, 2H), 5.41 (d, *J* = 7.8 Hz, 1H), 4.37 (dd, *J* = 14.9, 7.6 Hz, 1H), 3.57 (s, 3H), 3.29 (dd, *J* = 14.5, 6.7 Hz, 1H), 3.13 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.51 (s, 3H), 1.32 (s, 9H), 1.01 – 0.95 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.9, 156.1, 139.4, 133.2, 129.3, 123.6, 121.7, 121.5, 120.2, 117.2, 79.9, 56.1, 52.6, 29.6, 28.4, 17.4, 7.8, 4.3; FTIR (NaCl, thin film): cm^{-1}; 3396, 2954, 2912, 2874, 1704, 1498, 1366, 1279, 1217, 1163, 1018; $[\alpha]_D^{25}$ = –5.8 (*c* = 0.40, $CHCl_3$); HRMS (MM) calc'd $[M–C_4H_9]^+$ 391.2048, found 391.2038.

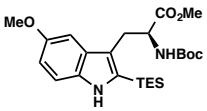
Tryptophan **205c**



Prepared following *General Procedure II* (12 h). The crude residue was purified by silica gel chromatography (80% hexanes, 20% acetone) to afford **205c** as a white, amorphous solid (114.3 mg, 0.234 mmol, 78% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.22 (s, 1H), 8.33 (s, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.4 Hz, 1H), 5.54 (s, 1H), 4.34 (dd, *J* = 15.7, 7.6 Hz, 1H), 3.60 (s, 3H), 3.37 (dd, *J* = 14.7, 6.1 Hz, 1H), 3.14 – 2.95 (m, 1H), 2.13 (s, 3H), 1.34 – 1.18 (m, 9H), 1.03 – 0.89 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 174.3, 171.1, 156.2, 141.6, 134.4, 130.5, 124.7, 122.8, 119.8, 118.5, 110.7, 79.9, 57.0, 52.6, 29.3, 28.4, 23.8, 7.7, 4.3; FTIR (NaCl, thin film): cm^{-1}; 3313, 2953,

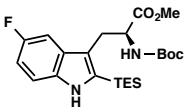
1700, 1672, 1506, 1367, 1168; $[\alpha]_D^{25}$ = –18.3 (*c* = 1.10, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 490.2732, found 490.2719.

Tryptophan **205d**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (85% hexanes, 15% ethyl acetate) to afford **205d** as a colorless oil (102.2 mg, 0.220 mmol, 74% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 8.95 (s, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.53 (d, *J* = 8.2 Hz, 1H), 4.36 (dd, *J* = 14.6, 8.2 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 3.26 (dd, *J* = 14.5, 6.1 Hz, 1H), 3.08 (dd, *J* = 14.5, 8.2 Hz, 1H), 1.28 (s, 9H), 1.01 – 0.95 (m, 9H), 0.95 – 0.91 (m, 6H); ^{13}C NMR (126 MHz, CD_3CN) δ 174.0, 156.1, 154.7, 135.2, 134.1, 130.0, 120.5, 113.3, 112.6, 101.1, 79.8, 56.3, 56.2, 52.6, 29.8, 28.4, 7.7, 4.2; FTIR (NaCl, thin film): cm^{-1}; 3379, 2953, 2874, 1700, 1620, 1506, 1437, 1391, 1366, 1218, 1164; $[\alpha]_D^{25}$ = +6.3 (*c* = 3.75, $CHCl_3$); HRMS (MM) calc'd $[M–C_4H_9]^+$ 407.1997, found 407.1994.

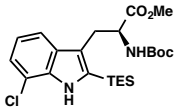
Tryptophan **205e**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (88% hexanes, 12% ethyl acetate) to afford **205e** as a colorless oil (97.2 mg, 0.216 mmol, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$, Major Rotamer) δ 8.01 (s, 1H), 7.26 – 7.22 (m, 1H), 7.21 – 7.14 (m, 1H), 6.91 (ddd, *J* = 8.9, 8.9, 2.2 Hz, 1H), 4.93 (d, *J* = 8.2 Hz, 1H), 4.53 (dd, *J* = 14.7, 7.0 Hz, 1H), 3.65 (s, 3H), 3.30 – 3.14 (m, 2H), 1.35 (s, 9H), 1.05 – 0.97 (m, 9H), 0.96 – 0.88 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.17, 157.69 (d, $J_{C\text{-}F}$ = 234.9 Hz), 155.00, 135.12 (d,

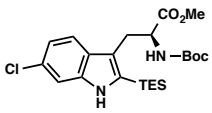
$J_{C\text{-}F}$ = 13.4 Hz), 129.00 (d, $J_{C\text{-}F}$ = 9.2 Hz), 119.56 (d, $J_{C\text{-}F}$ = 4.7 Hz), 111.30 (d, $J_{C\text{-}F}$ = 9.8 Hz), 110.83 (d, $J_{C\text{-}F}$ = 26.5 Hz), 103.61 (d, $J_{C\text{-}F}$ = 23.6 Hz), 79.75, 54.15, 52.26, 29.48, 28.17, 7.38, 3.62; FTIR (NaCl, thin film): cm^{-1}; 3372, 2956, 2875, 1734, 1718, 1700, 1502, 1437, 1367, 1166, 1073, 1010; $[\alpha]_D^{25}$ = +3.6 (*c* = 2.0, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 395.1797, found 395.1804.

Trytophan **205f**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (80% hexanes, 20% acetone) to afford **205f** as a colorless oil (114.3 mg, 0.245 mmol, 82% yield). ^1H NMR (500 MHz, CD_3CN, Major Rotamer) δ 8.87 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.08 – 6.97 (m, 1H), 5.50 (d, *J* = 8.1 Hz, 1H), 4.37 (dd, *J* = 15.1, 7.9 Hz, 1H), 3.56 (s, 3H), 3.29 (dd, *J* = 14.5, 6.5 Hz, 1H), 3.12 (dd, *J* = 14.5, 8.0 Hz, 1H), 1.29 (s, 9H), 1.02 – 0.96 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.7, 156.1, 136.6, 135.3, 131.5, 122.6, 122.4, 120.8, 118.6, 116.9, 79.9, 56.2, 52.6, 29.7, 28.4, 7.7, 4.2; FTIR (NaCl, thin film): cm^{-1}; 3380, 2954, 2875, 1734, 1718, 1507, 1499, 1366, 1164; $[\alpha]_D^{25}$ = +6.9 (*c* = 0.87, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 411.1501, found 411.1504.

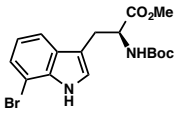
Tryptophan **205g**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (88% hexanes, 12% ethyl acetate) to afford **205g** as a colorless oil (103.9 mg, 0.222 mmol, 74% yield). ^1H NMR (500 MHz, $CDCl_3$, Major Rotamer) δ 7.98 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.33 (s, 1H),

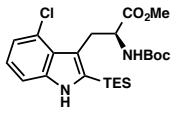
7.04 (d, J = 8.5 Hz, 1H), 4.92 (d, J = 8.1 Hz, 1H), 4.55 (dd, J = 14.7, 7.1 Hz, 1H), 3.61 (s, 3H), 3.22 (d, J = 6.6 Hz, 2H), 1.35 (s, 9H), 1.04 – 0.97 (m, 9H), 0.94 – 0.88 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 155.0, 138.8, 133.9, 128.4, 127.3, 120.1, 119.7, 110.7, 79.8, 54.2, 52.3, 29.5, 28.2, 7.4, 3.6; FTIR (NaCl, thin film): cm^{-1}; 3369, 2954, 2875, 1738, 1699, 1505, 1439, 1392, 1367, 1338, 1163, 1062; $[\alpha]_D^{25}$ = +7.1 (c = 1.63, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 467.2127, found 467.2129.

Tryptophan **205h**



Prepared following *General Procedure III* (36 h). The crude residue was purified by silica gel chromatography (80% hexanes, 20% acetone) to afford **205h** as a colorless oil (61.2 mg, 0.245 mmol, 52% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.33 (s, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 1.7 Hz, 1H), 7.00 (dd, J = 7.8, 7.8 Hz, 1H), 5.51 (d, J = 7.4 Hz, 1H), 4.43 (dd, J = 13.5, 7.6 Hz, 1H), 3.64 (s, 3H), 3.23 (dd, J = 14.7, 5.4 Hz, 1H), 3.10 (dd, J = 14.7, 7.7 Hz, 1H), 1.35 (s, 89H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.5, 156.2, 135.6, 130.0, 125.5, 125.0, 121.3, 119.0, 112.5, 105.2, 79.9, 55.3, 52.7, 28.4, 28.3; FTIR (NaCl, thin film): cm^{-1}; 3365, 2968, 1738, 1696, 1501, 1434, 1365, 1335; $[\alpha]_D^{25}$ = +44.0 (c = 0.385, $CHCl_3$); HRMS (MM) calc'd $[M–C_5H_{10}O_2]^+$ 297.0233, found 297.0229.

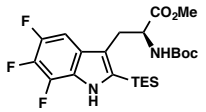
Tryptophan **205i**



Prepared following *General Procedure II* (12 h, 80 °C). The crude residue was purified by silica gel chromatography (88% hexanes, 12% ethyl acetate) to afford **205i** as a white, amorphous solid (113.7 mg, 0.243 mmol, 82%

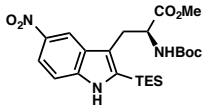
yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.29 (s, 1H), 7.38 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.06 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.02 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.41 (d, *J* = 7.7 Hz, 1H), 4.53 (dd, *J* = 15.2, 8.8 Hz, 1H), 3.61 (s, 3H), 3.55 (dd, *J* = 14.3, 5.7 Hz, 1H), 3.28 – 3.17 (m, 1H), 1.23 (s, 9H), 1.02 – 0.89 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.8, 156.1, 141.7, 136.0, 125.8, 125.7, 123.5, 121.1, 120.5, 111.4, 79.8, 57.2, 52.5, 29.8, 28.3, 7.7, 4.2; FTIR (NaCl, thin film): cm^{-1}; 3369, 2954, 2934, 2875, 1721, 1700, 1499, 1456, 1436, 1366, 1167; $[\alpha]_D^{25}$ = –9.0 (*c* = 4.1, $CHCl_3$); HRMS (MM) calc'd $[M–C_4H_9]^+$ 411.1501, found 411.1505.

Tryptophan **205j**



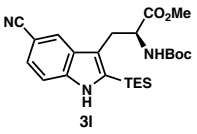
Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (88% hexanes, 12% ethyl acetate) to afford **205j** as a colorless oil (109.1 mg, 0.188 mmol, 72% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.36 (s, 1H), 7.25 (dd, *J* = 10.0, 7.1 Hz, 1H), 5.58 (d, *J* = 8.4 Hz, 1H), 4.32 (dd, *J* = 14.7, 8.5 Hz, 1H), 3.59 (s, 3H), 3.24 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.04 (dd, *J* = 14.6, 8.7 Hz, 1H), 1.27 (s, 9H), 1.03 – 0.90 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.5, 156.0, 147.0 (dd, $J_{C\text{-}F}$ = 236.4, 11.9 Hz), 139.5 – 137.1 (m), 137.4 (d, $J_{C\text{-}F}$ = 3.6 Hz), 137.2 (ddd, $J_{C\text{-}F}$ = 239.4, 18.9, 12.5 Hz), 125.8 (dd, $J_{C\text{-}F}$ = 9.1, 5.4 Hz), 124.3 (dd, $J_{C\text{-}F}$ = 10.4, 2.1 Hz), 122.5 – 122.1 (m), 101.08 (d, $J_{C\text{-}F}$ = 19.1 Hz), 79.87, 56.24, 52.70, 29.44, 28.32, 7.62, 4.04; FTIR (NaCl, thin film): cm^{-1}; 3351, 2956, 2876, 1700, 1514, 1467, 1436, 1367, 1350, 1165; $[\alpha]_D^{25}$ = +4.2 (*c* = 0.65, $CHCl_3$); LRMS (ESI) calc'd $[M–C_4H_9]^+$ 431.5, found 431.2.

Tryptophan **205k**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (85% hexanes, 15% ethyl acetate) to afford **205k** as a yellow oil (105.0 mg, 0.219 mmol, 73% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.66 (s, 1H), 8.30 (d, *J* = 2.0 Hz, 1H), 7.91 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 5.59 (d, *J* = 8.4 Hz, 1H), 4.37 (dd, *J* = 15.0, 8.3 Hz, 1H), 3.57 (s, 3H), 3.32 (dd, *J* = 14.6, 6.3 Hz, 1H), 3.15 (dd, *J* = 14.6, 8.4 Hz, 1H), 1.26 (s, 9H), 1.05 – 0.92 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.5, 156.1, 144.0, 142.1, 138.1, 134.1, 121.9, 119.8, 114.9, 108.6, 79.9, 56.3, 52.7, 29.6, 28.3, 7.6, 4.0; FTIR (NaCl, thin film): cm^{-1}; 3380, 2968, 2873, 1736, 1716, 1696, 1508, 1330, 1162, 1065, 1004; $[\alpha]_D^{25}$ = +7.9 (*c* = 0.75, $CHCl_3$); LRMS (ESI) calc'd $[M+H]^+$ 478.3, found 478.3.

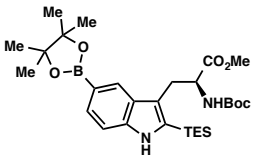
Tryptophan **205l**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (80% hexanes, 20% ethyl acetate) to afford **205l** as a white, amorphous solid (109.0 mg, 0.238 mmol, 79% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.48 (s, 1H), 8.03 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.38 (dd, *J* = 8.5, 1.5 Hz, 1H), 5.66 (d, *J* = 8.8 Hz, 1H), 4.35 (ddd, *J* = 9.0, 9.0, 5.5 Hz, 1H), 3.62 (s, 3H), 3.31 (dd, *J* = 14.6, 5.4 Hz, 1H), 3.10 (dd, *J* = 14.6, 9.2 Hz, 1H), 1.23 (s, 9H), 1.00 – 0.93 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.5, 155.9, 141.4, 136.9, 129.6, 126.0, 125.3, 122.3, 121.8, 113.0, 102.4, 79.8, 56.5, 52.7, 29.6, 28.3, 7.6, 4.0; FTIR (NaCl, thin film): cm^{-1}; 3350, 2953, 2878, 2218, 1728, 1696, 1508, 1370,

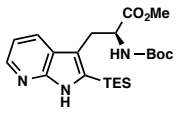
1167; $[\alpha]_D^{25}$ = –2.3 (*c* = 2.2, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 458.2470, found 458.2454.

Tryptophan **205**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (85% hexanes, 15% ethyl acetate – 80% hexanes, 20% ethyl acetate) to afford **205m** as a white, amorphous solid (127.0 mg, 0.227 mmol, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$, Major Rotamer) δ 8.10 – 7.98 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 4.90 (d, *J* = 8.1 Hz, 1H), 4.56 (dd, *J* = 14.4, 6.7 Hz, 1H), 3.75 (s, 3H), 3.39 – 3.24 (m, 2H), 1.36 (d, *J* = 2.8 Hz, 12H), 1.32 (s, 9H), 1.03 – 0.97 (m, 9H), 0.96 – 0.90 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ173.1, 155.2, 140.5, 133.1, 128.6, 128.4, 126.7, 120.1, 110.2, 83.4, 79.5, 54.0, 52.3, 28.8, 28.2, 24.9, 7.4, 3.7 (carbon adjacent to Boron was not observed); FTIR (NaCl, thin film): cm^{-1}; 3379, 2976, 2874, 1741, 1700, 1499, 1351, 1146; $[\alpha]_D^{25}$ = +15.0 (*c* = 1.0, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 558.3406, found 558.3388.

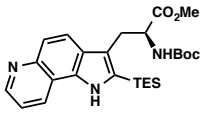
Tryptophan **205n**



Prepared following *General Procedure I* (12 h). The crude residue was purified by silica gel chromatography (98% dichloromethane, 2% methanol) to afford **205n** as a light yellow oil (111.2 mg, 0.256 mmol, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$, Major Rotamer) δ 9.78 (d, *J* = 14.4 Hz, 1H), 8.28 (d, *J* = 3.8 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.03 (dd, *J* = 7.7, 4.8 Hz, 1H), 5.14 (d, *J* = 8.4 Hz, 1H),

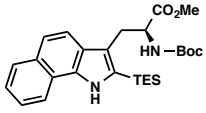
4.59 (dd, *J* = 15.0, 7.1 Hz, 1H), 3.59 (s, 3H), 3.25 (d, *J* = 6.8 Hz, 2H), 1.33 (s, 9H), 1.02 – 0.88 (m, 15H); ^{13}C NMR (126 MHz, $CDCl_3$) δ173.3, 155.0, 150.8, 143.3, 134.0, 127.3, 120.9, 118.1, 115.2, 79.7, 54.2, 52.2, 29.8, 28.1, 7.3, 3.6; FTIR (NaCl, thin film): cm^{-1}; 3380, 3226, 2953, 1743, 1691, 1582, 1496, 1439, 1367, 1283, 1172; $[\alpha]_D^{25}$ = +8.7 (*c* = 2.5, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 434.2470, found 434.2490.

Tryptopahn **205o**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (98% dichloromethane, 2% methanol) to afford **205o** as a light yellow oil (119.5 mg, 0.249 mmol, 83% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.79 (s, 1H), 8.78 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.76 (ddd, *J* = 8.3, 1.5, 0.7 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.47 (dd, *J* = 8.3, 4.3 Hz, 1H), 5.60 (d, *J* = 8.3 Hz, 1H), 4.40 (dd, *J* = 15.0, 7.8 Hz, 1H), 3.57 (s, 3H), 3.37 (dd, *J* = 14.5, 6.6 Hz, 1H), 3.22 (dd, *J* = 14.5, 8.0 Hz, 1H), 1.26 (s, 9H), 1.01 (s, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.8, 156.1, 148.6, 147.4, 133.9, 133.3, 130.0, 125.6, 123.3, 123.1, 122.0, 121.2, 117.8, 80.0, 56.6, 52.7, 29.5, 28.4, 7.8, 4.4; FTIR (NaCl, thin film): cm^{-1}; 3350, 2953, 2873, 1734, 1717, 1700, 1696, 1570, 1496, 1377, 1164; $[\alpha]_D^{25}$ = +8.7 (*c* = 1.2, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$484.2626, found 484.2621.

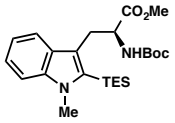
Tryptophan **205p**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (88% hexanes, 12% ethyl

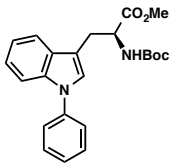
acetate) to afford **205p** as a colorless foam (103.2 mg, 0.213 mmol, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$, Major Rotamer) δ 8.67 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.44 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 4.97 (d, *J* = 7.9 Hz, 1H), 4.61 (*app* q, *J* = 7.1 Hz, 1H), 3.62 (s, 3H), 3.34 (d, *J* = 6.8 Hz, 2H), 1.35 (s, 9H), 1.08 – 1.02 (m, 9H), 1.02 – 0.97 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ173.3, 155.1, 133.6, 130.7, 130.6, 128.8, 125.4, 124.6, 124.2, 121.4, 121.3, 120.4, 119.4, 118.9, 79.7, 54.4, 52.3, 28.2, 24.7, 7.5, 3.8; FTIR (NaCl, thin film): cm^{-1}; 3409, 3350, 2953, 2868, 1743, 1694, 1501, 1392, 1362, 1165; $[\alpha]_D^{25}$ = +54.8 (*c* = 0.97, $CHCl_3$); HRMS (MM) calc'd $[M–C_4H_9]^+$ 427.2048, found 427.2066.

Tryptophan **205q**



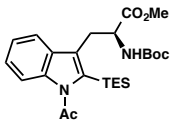
Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (88% hexanes, 12% ethyl acetate) to afford **205q** as a colorless oil (70.1 mg, 0.156 mmol, 52% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.20 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.04 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H), 5.41 (d, *J* = 7.3 Hz, 1H), 4.33 (dd, *J* = 15.1, 7.5 Hz, 1H), 3.83 (s, 3H), 3.52 (s, 3H), 3.33 (dd, *J* = 14.6, 7.1 Hz, 1H), 3.18 (dd, *J* = 14.5, 7.4 Hz, 1H), 1.37 – 1.23 (m, 9H), 1.03 – 0.95 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.9, 156.1, 141.0, 135.5, 129.6, 123.2, 121.8, 119.6, 119.5, 110.2, 80.0, 56.4, 52.5, 33.8, 28.9, 28.4, 7.9, 5.2; FTIR (NaCl, thin film): cm^{-1}; 3350, 2956, 2876, 1700, 1516, 1465, 1367, 1165; $[\alpha]_D^{25}$ = +4.9 (*c* = 0.34, $CHCl_3$); HRMS (MM) calc'd $[M–C_4H_9]^+$ 391.20480, found 391.2034.

Tryptophan **205r**



Prepared following *General Procedure III* (12 h). The crude residue was purified by silica gel chromatography (20% acetone, 80% hexanes) to afford **205r** as a colorless oil (80.2 mg, 0.203 mmol, 68% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ7.63 (d, *J* = 7.8 Hz, 1H), 7.58 – 7.50 (m, 5H), 7.41 – 7.35 (m, 1H), 7.31 (s, 1H), 7.25 – 7.19 (m, 1H), 7.19 – 7.14 (m, 1H), 5.58 (d, *J* = 7.8 Hz, 1H), 4.51 (dd, *J* = 13.5, 7.7 Hz, 1H), 3.67 (s, 3H), 3.31 (dd, *J* = 14.7, 5.4 Hz, 1H), 3.18 (dd, *J* = 14.7, 7.6 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.6, 156.3, 140.4, 136.7, 130.7, 130.0, 127.9, 127.3, 124.8, 123.5, 121.1, 120.0, 118.3, 113.0, 111.4, 79.9, 55.2, 52.7, 28.5; FTIR (NaCl, thin film): cm^{-1}; 3380, 2966, 2930, 1741, 1714, 1501, 1455, 1367; $[\alpha]_D^{25}$ = +32.1 (*c* = 1.86, $CHCl_3$); HRMS (MM) calc'd $[M–C_4H_9]^+$ 339.1339, found 339.1326.

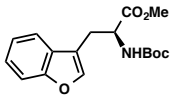
Tryptophan **205s**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (86% hexanes, 14% ethyl acetate) to afford **205s** as a colorless oil (107.0 mg, 0.226 mmol, 75% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 7.75 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.35 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.27 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 5.57 (d, *J* = 8.3 Hz, 1H), 4.40 (dd, *J* = 15.2, 8.0 Hz, 1H), 3.54 (s, 3H), 3.37 (dd, *J* = 14.4, 6.7 Hz, 1H), 3.20 (dd, *J* = 14.3, 8.2 Hz, 1H), 2.78 (s, 3H), 1.30 (s, 9H), 1.00 – 0.89 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.4, 171.0, 156.1, 138.0, 137.1, 133.7, 131.2, 125.9, 123.4,

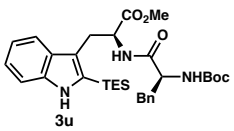
120.4, 115.2, 80.0, 55.9, 52.7, 28.8, 28.4, 27.0, 8.6, 6.9; FTIR (NaCl, thin film): cm^{-1}; 3373, 2953, 2874, 1746, 1700, 1499, 1435, 1369, 1321, 1223, 1167, 1109; $[\alpha]_D^{25}$ = +5.0 (*c* = 0.69, $CHCl_3$); HRMS (MM) calc'd $[M–C_4H_9]^+$ 419.1997, found 419.1986.

Tryptophan **205t**



Prepared following *General Procedure III* (24 h). The crude residue was purified by silica gel chromatography (25% acetone, 75% hexanes) to afford **205t** as a colorless oil (68.9 mg, 0.216 mmol, 72% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.58 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.27 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 5.63 (d, *J* = 6.5 Hz, 1H), 4.48 (dd, *J* = 13.5, 7.9 Hz, 1H), 3.67 (s, 3H), 3.20 (dd, *J* = 14.8, 5.3 Hz, 1H), 3.07 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.2, 156.0, 144.1, 128.8, 125.4, 123.6, 120.7, 118.3, 116.8, 112.2, 80.0, 54.5, 52.8, 28.4, 26.6; FTIR (NaCl, thin film): cm^{-1}; 3375, 2977, 2925, 1744, 1716, 1690, 1505, 1455, 1367, 1165; $[\alpha]_D^{25}$ = +16.8 (*c* = 0.64, $CHCl_3$); LRMS (MM) calc'd $[M–C_4H_9]^+$ 263.2, found 263.2.

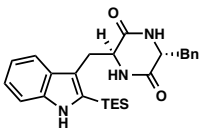
Tryptophan **205u**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (80% hexanes, 20% acetone) to afford **205u** as a colorless oil (109.1 mg, 0.188 mmol, 63% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.10 (s, 1H), 7.59 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.29 – 7.19 (m, 3H), 7.16 – 7.05 (m, 3H), 7.05 – 7.01 (m, 1H), 6.69 (d, *J* = 6.1 Hz, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 4.62 (dd, *J* = 13.1, 6.8 Hz, 1H), 4.23 (ddd, *J*

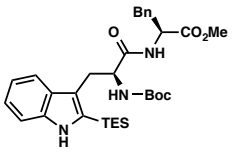
= 8.4, 8.4, 5.7 Hz, 1H), 3.60 (s, 3H), 3.24 (ddd, *J* = 14.4, 6.5, 4.7 Hz, 1H), 3.08 – 2.91 (m, 3H), 1.25 (s, 9H), 1.03 – 0.88 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ173.2, 172.1, 156.2, 139.8, 138.3, 133.3, 130.2, 129.7, 129.1, 127.4, 122.8, 120.4, 119.8, 119.4, 112.1, 79.9, 56.2, 55.4, 52.6, 38.4, 29.7, 28.4, 7.7, 4.2; FTIR (NaCl, thin film): cm^{-1}; 3380, 2948, 2878, 1736, 1666, 1506, 1367, 1244, 1165; $[\alpha]_D^{25}$ = –4.2 (*c* = 1.6, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 580.3201, found 580.3206.

Tryptophan **205v**



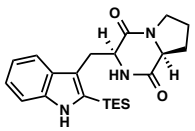
Prepared following *General Procedure I* (72 h). The crude residue was purified by silica gel chromatography (55% hexanes, 40% ethyl acetate, 5% methanol) to afford **205v** as a colorless oil (95.2 mg, 0.213 mmol, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.29 (ddd, *J* = 6.3, 5.1, 2.1 Hz, 2H), 7.22 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.18 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.10 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 1H), 5.64 (s, 1H), 4.24 (ddd, *J* = 5.2, 5.2, 2.5 Hz, 1H), 3.59 (dd, *J* = 14.5, 3.8 Hz, 1H), 3.45 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.14 (d, *J* = 5.1 Hz, 2H), 2.87 (dd, *J* = 14.5, 11.5 Hz, 1H), 1.02 – 0.94 (m, 9H), 0.90 – 0.82 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 167.0, 138.7, 134.8, 133.9, 129.9, 128.9, 127.6, 127.6, 122.8, 119.7, 118.7, 118.0, 111.1, 56.6, 53.3, 40.2, 30.0, 7.4, 7.4, 3.7; FTIR (NaCl, thin film): cm^{-1}; 3356, 3226, 2958, 2864, 1676, 1451, 1437, 1316; $[\alpha]_D^{25}$ = +5.6 (*c* = 0.47, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 448.2415, found 448.2426.

Tryptophan **205w**



Prepared following *General Procedure I* (36 h). The crude residue was purified by silica gel chromatography (80% hexanes, 20% acetone) to afford **205w** as a colorless oil (108.0 mg, 0.186 mmol, 62% yield).[1]H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.10 (s, 1H), 7.59 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.29 – 7.19 (m, 3H), 7.16 – 7.05 (m, 3H), 7.05 – 7.01 (m, 1H), 6.69 (d, *J* = 6.1 Hz, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 4.62 (dd, *J* = 13.1, 6.8 Hz, 1H), 4.23 (ddd, *J* = 8.4, 8.4, 5.7 Hz, 1H), 3.60 (s, 3H), 3.24 (ddd, *J* = 14.4, 6.5, 4.7 Hz, 1H), 3.08 – 2.91 (m, 3H), 1.25 (s, 9H), 1.03 – 0.88 (m, 15H); ^{13}C NMR (126 MHz, CD_3CN) δ 172.6, 172.3, 156.0, 140.1, 137.6, 133.4, 130.3, 129.6, 129.3, 127.7, 122.9, 121.0, 119.8, 119.7, 112.0, 80.0, 57.1, 54.3, 52.7, 38.2, 29.6, 28.3, 7.8, 4.3, 4.2; FTIR (NaCl, thin film): cm^{-1}; 3370, 2953, 2878, 1745, 1666, 1508, 1449, 1370, 1241, 1170; $[\alpha]_D^{25}$ = +10.0 (*c* = 1.06, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 580.3201, found 580.3206.

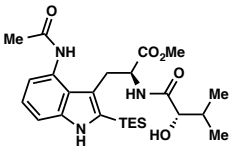
Tryptophan **205x**



Prepared following *General Procedure I* (72 h). The crude residue was purified by silica gel chromatography (55% hexanes, 40% ethyl acetate, 5% methanol) to afford **3x** as an amorphous, white solid (98.6 mg, 0.249 mmol, 83% yield). [1]H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.56 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.40 (ddd, *J* = 8.2, 0.8, 0.8 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H), 5.59 (s, 1H), 4.42 (dd, *J* = 11.8, 2.4 Hz, 1H), 4.07 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.84 (dd, *J* = 15.0, 3.9 Hz, 1H), 3.75 – 3.66 (m, 1H), 3.65 – 3.54 (m, 1H), 3.00 (dd, *J* = 15.0, 11.8 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.13 – 2.00 (m, 2H), 1.99 – 1.87 (m, 1H), 1.04

– 0.98 (m, 9H), 0.94 – 0.85 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 165.7, 138.9, 133.6, 127.9, 123.0, 119.9, 118.8, 118.3, 111.3, 59.2, 54.8, 45.4, 28.4, 27.5, 22.6, 7.4, 3.8; FTIR (NaCl, thin film): cm^{-1}; 3365, 2953, 2873, 1671, 1456, 1412, 1303, 1239; $[\alpha]_D^{25}$ = –34.4 (*c* = 0.82, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 398.2258, found 398.2272.

Tryptophan **205y**

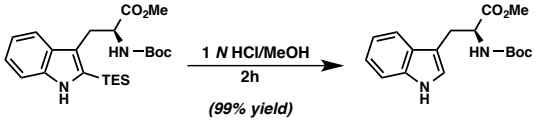


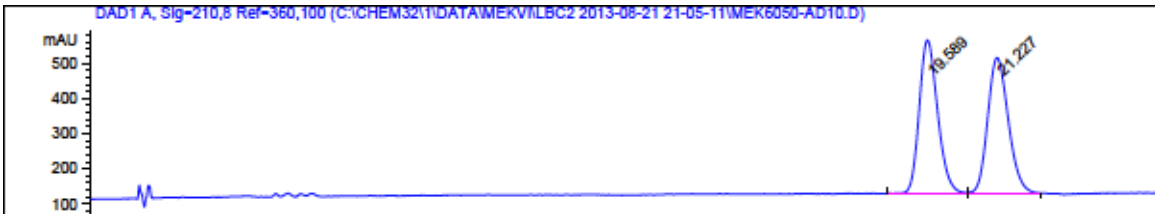
Prepared following *General Procedure II* (0.87 mmol scale, 12 h). The crude residue was purified by silica gel chromatography (100% ethyl acetate) to afford **205y** as a light yellow oil (370.2 mg, 0.756 mmol, 86% yield). ^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 9.28 (s, 1H), 8.44 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 5.6 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 4.53 (dt, *J* = 10.3, 6.3 Hz, 1H), 3.65 (s, 3H), 3.64 – 3.62 (m, 1H), 3.59 (d, *J* = 5.9 Hz, 1H), 3.45 (dd, *J* = 14.7, 6.2 Hz, 1H), 3.17 (dd, *J* = 14.7, 10.3 Hz, 1H), 2.19 (s, 3H), 1.91 – 1.79 (m, 1H), 1.07 – 0.94 (m, 15H), 0.87 (dd, *J* = 15.7, 4.0 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CD_3CN) δ 174.4, 173.6, 171.5, 141.7, 134.9, 130.2, 124.9, 122.9, 119.4, 118.9, 110.9, 76.3, 52.6, 32.6, 29.5, 29.3, 23.8, 19.4, 15.6, 7.7, 4.3; FTIR (NaCl, thin film): cm^{-1}; 3324, 2956, 2875, 1742, 1657, 1516, 1435, 1369; $[\alpha]_D^{25}$ = –1.8 (*c* = 1.3, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 490.2732, found 490.2772.

4.7.6 Stability of tryptophan center

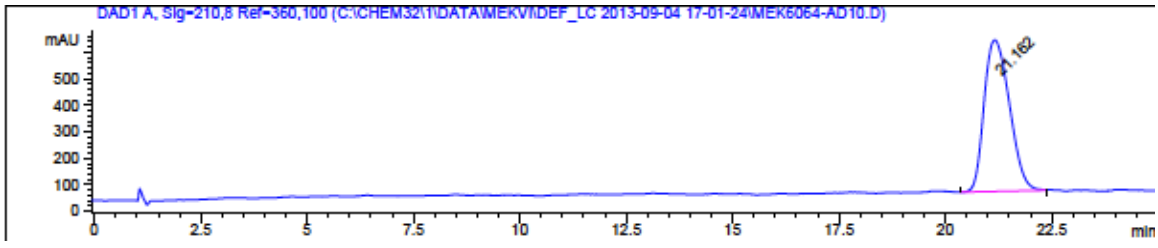
In order to confirm that the tryptophan products were not undergoing deleterious racemization under the reaction conditions, tryptophan **205a** was desilylated with 1 *N* HCl/MeOH and compared to *racemic N*-Boc-tryptophan methyl ester through chiral SFC

analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(minor) = 19.6 min, t_R(major) = 21.2 min. We observed no racemization of the tryptophan stereocenter under the reaction conditions. Additionally, Larock indole syntheses using dipeptide-derived alkynes to provide tryptohans **205u** – **205y** show the formation of a single diastereomer of product by crude ^{1}H NMR and LCMS, further supporting the stability of the tryptophan stereocenter under Larock conditions. The low optical rotations exhibited by tryptophans **205a** – **205z** are consistent with literature values of related compounds.





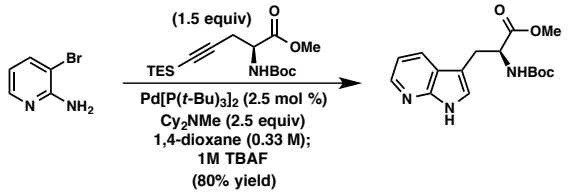
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.589	BV	0.4601	1.31030e4	436.62933	50.0927
2	21.227	VB	0.5243	1.30545e4	386.23413	49.9073



Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.162	VB	0.6657	2.36458e4	570.35565	100.0000

4.7.7 Scale-up and desilylation of tryptophan 205o

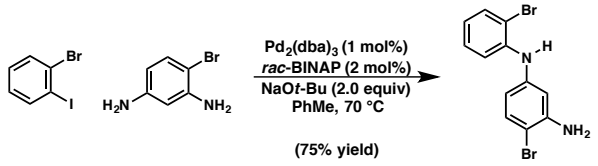


In a glovebox, pyridyl aniline **203o** (865 mg, 5.0 mmol, 1.0 equiv), alkyne **204a** (2.56 g, 7.5 mmol, 1.5 equiv), $Pd[P(^tBu)_3]_2$ (64 mg, 0.125 mmol, 0.025 equiv), and Cy_2NMe (2.7 mL, 12.5 mmol, 2.5 equiv) were combined in a 50 mL flask. The solids were dissolved in 15 mL 1,4-dioxane and the solution was heated to 60 °C for 30 h. Upon cooling, the milky yellow solution was filtered through a silica plug, which was washed thoroughly with ethyl acetate. The solution was concentrated and then redissolved in 50 mL ethyl acetate and 1 M TBAF in THF (5 mL). After 20 minutes, aqueous NH_4Cl was added and the reaction mixture was partitioned in a separatory funnel. The aqueous layer was back extracted with ethyl acetate (3 X 150 mL). The organics were then recombined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified using silica gel chromatography (60% hexanes, 35% ethyl acetate, 5% methanol) to afford tryptophan as a light yellow solid (1.28 g, 80% yield).

^{1}H NMR (500 MHz, CD_3CN, Major Rotamer) δ 10.06 (s, 1H), 8.30 – 8.18 (m, 1H), 7.94 – 7.85 (m, 1H), 7.20 (s, 1H), 7.06 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.64 (d, *J* = 7.7 Hz, 1H), 4.45 (dd, *J* = 13.4, 7.6 Hz, 1H), 3.64 (s, 3H), 3.23 (dd, *J* = 14.7, 5.4 Hz, 1H), 3.11 (dd, *J* = 14.7, 7.5 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, CD_3CN) δ 173.6, 156.2, 149.6, 143.8, 127.8, 125.0, 120.7, 116.3, 110.0, 79.9, 55.3, 52.7, 28.4, 28.4; FTIR (NaCl, thin

film): cm^{-1}; 3365, 2978, 1743, 1698, 1511, 1434, 1362; $[\alpha]_D^{25}$ = 49.1 (*c* = 1.25, $CHCl_3$); HRMS (MM) calc'd $[M+H]^+$ 320.1605, found 320.1594.

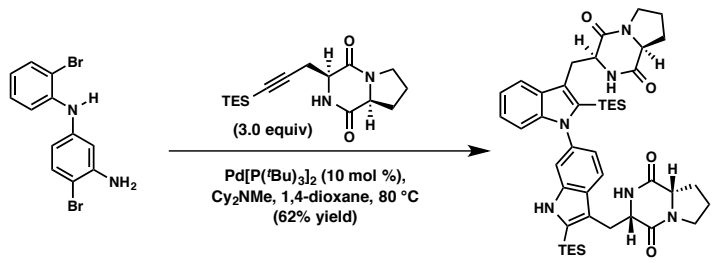
4.7.8 Total synthesis of (–)-aspergilazine A



In a glove box, a flame-dried 250 mL flask was charged with iodobromobenzene (771 μL, 6.0 mmol, 1.0 equiv), dianiline **212** (1.34 g, 7.2 mmol, 1.2 equiv), $Pd_2(dba)_3$ (54 mg, 0.06 mmol, 0.01 equiv), *rac*-BINAP (75 mg, 0.12 mmol, 0.02 equiv), and NaO^{t}Bu (865 mg, 9.0 mmol, 1.5 equiv). 60 mL of PhMe was added and the reaction flask was sealed and heated to 70 °C for 3.5 hours. Upon cooling, the reaction mixture was filtered through a plug of silica gel, which was flushed with ethyl acetate. The organics were concentrated and purified by silica gel chromatography (20% acetone, 80% hexanes) to provide the diarylamine **7** as a light yellow oil (1.54 g, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.31 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.27 – 7.20 (m, 1H), 6.83 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 6.49 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.03 (s, 1H), 4.11 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ144.6, 141.9, 140.7, 132.9, 132.8, 128.0, 121.2, 116.6, 112.5, 111.2, 106.3, 101.9; FTIR (NaCl, thin film): cm^{-1}; 3464, 3380, 1612, 1582, 1511, 1459, 1407, 1330, 1303, 1276; HRMS (MM) calc'd $[M+H]^+$ 340.9284, found 340.9264.

Synthesis of bis-triethylsilyl-(–)-aspergilazine A



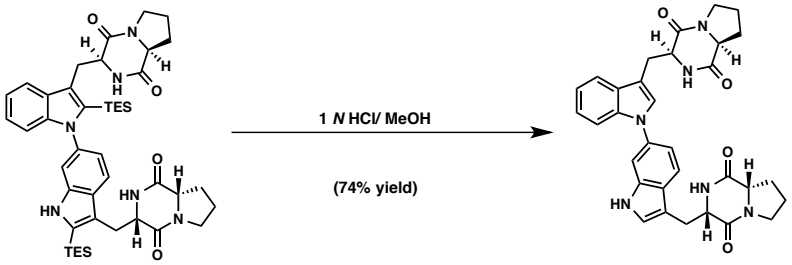
In a glovebox, a one dram vial was charged with diarylamine (35 mg, 0.1 mmol, 1.0 equiv), alkyne **209** (94 mg, 0.3 mmol, 3.0 equiv), Cy_2NMe (55 μL, 0.25 mmol, 2.5 equiv), $Pd[P(^tBu)_3]_2$ (5.2 mg, 0.01 mmol, 0.1 equiv) and 1,4-dioxane (500 μL). The vial was sealed and heated to 80 °C for 4 hours. Upon cooling, the reaction mixture was filtered through celite, which was washed with ethyl acetate (15 mL). The organics were concentrated and the crude reaction mixture was purified by preparative reverse phase HPLC (65–85% acetonitrile in H_2O, 30 mL/min, 20 min) to give the product as a colorless solid (49.5 mg, 62% yield).

^{1}H NMR (500 MHz, CD_2Cl_2, Major Rotamer) δ 8.47 (d, J = 11.0 Hz, 1H), 7.72 (dd, J = 8.3, 2.5 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.47 (dd, J = 7.6, 1.6 Hz, 1H), 7.21 – 7.11 (m, 3H), 7.03 – 6.94 (m, 1H), 5.71 (s, 1H), 5.56 (s, 1H), 4.60 – 4.52 (m, 1H), 4.52 – 4.47 (m, 1H), 4.25 – 4.08 (m, 2H), 3.98 – 3.84 (m, 2H), 3.78 – 3.68 (m, 2H), 3.67 – 3.57 (m, 2H), 3.22 (ddd, J = 14.7, 11.7, 2.9 Hz, 1H), 3.11 (ddd, J = 14.9, 11.7, 1.4 Hz, 1H), 2.46 – 2.30 (m, 2H), 2.18 – 2.03 (m, 4H), 2.05 – 1.89 (m, 2H), 1.19 – 1.08 (m, 9H), 1.08 – 0.98 (m, 6H), 0.98 – 0.84 (m, 9H), 0.75 – 0.52 (m, 6H); FTIR (NaCl, thin film): cm^{-1}; 3375, 2963, 2859, 1671, 1446, 1414; $[\alpha]_D^{25}$ = –79.5 (c = 0.055, 1:1 DCM:MeOH); HRMS (MM) calc'd $[M–SiC_6H_{15}]^+$ 679.3423, found 679.3426.

The ^{1}H NMR was found to coalesce in deuterated acetonitrile at 60 °C. The ^{13}C NMR was still rotameric, even at elevated temperature.

^{1}H NMR (400 MHz, CD_3CN) δ 9.42 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.72 – 7.65 (m, 1H), 7.51 (s, 1H), 7.22 – 7.04 (m, 3H), 6.94 (s, 1H), 5.60 (s, 1H), 5.49 (s, 1H), 4.47 (dd, *J* = 11.4, 11.4 Hz, 2H), 4.15 (t, *J* = 7.7 Hz, 2H), 3.85 (d, *J* = 14.7 Hz, 1H), 3.79 (dd, *J* = 15.0, 4.2 Hz, 1H), 3.72 – 3.58 (m, 2H), 3.50 (ddd, *J* = 11.6, 8.1, 3.8 Hz, 2H), 3.28 – 3.16 (m, 1H), 3.12 (dd, *J* = 14.9, 10.8 Hz, 1H), 2.33 – 2.15 (m, 2H), 2.06 – 1.70 (m, 6H), 1.23 – 0.94 (m, 11H), 0.88 (t, *J* = 7.7 Hz, 6H), 0.74 – 0.51 (m, 5H).

Synthesis of (–)-aspergilazine A



The silylated compound (49.5 mg, 0.06 mmol, 1.0 equiv) was dissolved in 1 *N* HCl in MeOH (10 mL) and allowed to stir for 15 minutes. The reaction was quenched by addition of aqueous $NaHCO_3$ and diluted with ethyl acetate. The organics were removed *in vacuo* and the aqueous extracted with ethyl acetate (3 X 20 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (5% MeOH, 95% CH_2Cl_2) to provide (–)-aspergilazine A as a colorless solid (26.0 mg, 74% yield).

Spectroscopic and physical data, including ^{1}H, ^{13}C NMR in DMSO-*d6,* IR, and MS obtained for (–)-aspergilazine A matched that as reported during isolation by Gu et. Al and data obtained by Sperry and co-workers. See below for ^{1}H and ^{13}C comparison table.

^{1}H NMR (500 MHz, DMSO) δ 11.05 (s, 1H), 7.98 (s, 1H), 7.87 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.14 – 7.11 (m, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 4.39 (t, *J* = 4.8 Hz, 1H), 4.35 (t, *J* = 4.7 Hz, 1H), 4.12 – 4.05 (m, 2H), 3.45 – 3.35 (m, 3H), 3.33 – 3.20 (m, 3H), 3.19 – 3.10 (m, 2H), 2.05 – 1.89 (m, 2H), 1.79 – 1.49 (m, 4H), 1.47 – 1.31 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 169.6, 169.5, 165.9, 165.9, 136.5, 136.0, 133.5, 129.0, 128.8, 126.5, 126.2, 122.5, 120.2, 119.9, 115.7, 111.4, 110.5, 110.2, 107.1, 58.9, 55.7, 55.6, 45.1, 28.2, 26.3, 26.2, 22.3, 22.3; FTIR (NaCl, thin film): cm^{-1}; 3365, 3246, 2933, 1666, 1459, 1414; $[\alpha]_D^{25}$ = –90.6 (*c* = 0.625, 1:1 CH_2Cl_2:MeOH); HRMS (MM) calc'd $[M+H]^+$ 565.2558, found 565.2555.

Comparison of ^{1}H NMR data for Natural vs. Synthetic (-)-Aspergilazine A

Isolation (–)-Aspergilazine A ^{1}H NMR, 600 MHz, DMSO	**This Work (–)-Aspergilazine A ^{1}H NMR, 500 MHz, DMSO**
δ 11.09 (s, 1H)	11.05 (s, 1H)
8.00 (s, 1H)	7.98 (s, 1H)
7.89 (s, 1H)	7.87 (s, 1H)
7.75 (br d, *J* = 8.4 Hz, 1H)	7.73 (d, *J* = 8.4 Hz, 1H)
7.68 (br d, *J* = 7.8 Hz, 1H)	7.67 (d, *J* = 7.9 Hz, 1H)
7.48 (d, *J* = 8.2 Hz, 1H)	7.47 (d, *J* = 8.3 Hz, 1H)
7.47 (s, 1H)	7.45 (s, 1H)
7.45 (d, *J* = 1.9 Hz, 1H)	7.43 (d, *J* = 1.7 Hz, 1H)
7.29 (d, *J* = 1.7 Hz, 1H)	7.28 (d, *J* = 2.0 Hz, 1H)
7.16 (ddd, *J* = 7.7, 7.4, 1.0 1H)	7.18 – 7.14 (m, 1H)
7.14 (dd, *J* = 8.3, 1.9, 1H)	7.14 – 7.11 (m, 1H)
7.09 (ddd, *J* = 7.4, 7.4, 0.8 1H)	7.09 (t, *J* = 7.4 Hz, 1H)
4.41 (dd, *J* = 4.9, 5.0 Hz, 1H)	4.39 (dd, *J* = 4.8, 4.8 Hz, 1H)
4.37 (dd, *J* = 5.0, 5.0 Hz, 1H)	4.35 (t, *J* = 4.7 Hz, 1H)
4.07 (dd, *J* = 8.3, 8.3 Hz, 2H)	4.12 – 4.05 (m, 2H)
3.38 (m, 3H)	3.45 – 3.35 (m, 3H)
3.26 (m, 3H)	3.33 – 3.20 (m, 3H)
3.16 (m, 2H)	3.19 – 3.10 (m, 2H)
1.98 (m, 2H)	2.05 – 1.89 (m, 2H)
1.65 (m, 4H)	1.79 – 1.49 (m, 4H)
1.37 (m, 2H)	1.47 – 1.31 (m, 2H)

Comparison of ^{13}C NMR data for Natural vs. Synthetic (–)-Aspergilazine A

Isolation (–)-Aspergilazine A ^{13}C NMR, 150 MHz, DMSO	**This Work (–)-Aspergilazine A ^{13}C NMR, 126 MHz, DMSO**	**Chemical Shift Difference, Δδ**
169.7	169.6	0.1
169.6	169.5	0.1
166.0	165.9	0.1
165.9	165.9	0.0
136.7	136.5	0.2
136.2	136.0	0.2
133.6	133.5	0.1
129.1	129.0	0.1
128.9	128.8	0.1
126.6	126.5	0.1
126.3	126.2	0.1
122.6	122.5	0.1
120.3	120.2	0.1
119.9	119.9	0.0
115.8	115.7	0.1
111.5	111.4	0.1
110.6	110.5	0.1
110.3	110.2	0.1
107.2	107.1	0.1

59.0	58.9	0.1
59.0	58.9	0.1
55.8	55.7	0.1
55.7	55.6	0.1
45.2	45.1	0.1
45.2	45.1	0.1
28.3	28.2	0.1
28.3	28.2	0.1
26.4	26.3	0.1
26.3	26.2	0.1
22.4	22.3	0.1
22.4	22.3	0.1

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