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Synthesis of Non-canonical Tryptophan Variants via Rh-catalyzed C–H Functionalization of Anilines

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Abstract: Tryptophan and its non-canonical variants play critical roles in pharmaceutical molecules and enzymes. Facile access to this privileged class of amino acids from readily available building blocks remains a long-standing challenge. Here, we report a regioselective synthesis of non-canonical tryptophans bearing C4-C7 substituents via Rh-catalyzed annulation between structurally diverse *tert*-butyloxycarbonyl (Boc)-protected anilines and alkynyl chlorides readily prepared from amino acid building blocks. This transformation harnesses Boc-directed C–H metalation and demetalation to afford a wide range of C2-unsubstituted indole products in a redox-neutral fashion. This umpolung approach compared to the classic Larock indole synthesis offers a novel mechanism for heteroarene annulation and will be useful for the synthesis of natural products and drug molecules containing non-canonical tryptophan residues in a highly regioselective manner.

Tryptophan (Trp) is an indole-containing amino acid that plays myriad important roles in biology (**Figure 1A**).[1-8] It serves as a starting material for the biosynthesis of indole alkaloids and peptide natural products.[9-10] In proteins, Trp is responsible for numerous essential functions including steric, hydrophobic, and π-cation interactions as well as electron transfer (ET) and proton-coupled ET processes in redox-active enzymes.[4-12] Chemical modifications on the indole moiety of Trp drastically alter its structure and function.[13-14] The resulting non-canonical Trp variants are useful for the synthesis of Trp-containing natural products, drug molecules, and for studying the function of Trp in enzyme catalysis.[5]

We have been interested in the discovery and synthesis of peptide natural products carrying cross-linked Trp moieties.[15-17] Compared to the variety of existing methods for the preparation of indoles, efficient synthesis of non-canonical Trp remains underdeveloped. One of the most well-established methods for the synthesis of this class of molecules is the Larock indole synthesis, which entails Pd-catalyzed annulation between halogenated anilines and silyl alkynes (**Figure 1B**).[18,19] It has become a reliable transformation for the preparation of complex macrocyclic peptide natural products containing Trp modifications.[20-23] Despite these advantages, the method requires regioselective halogenation on the starting aniline and affords a C2-silylated indole as the precursor to C2-unsubstituted Trp.

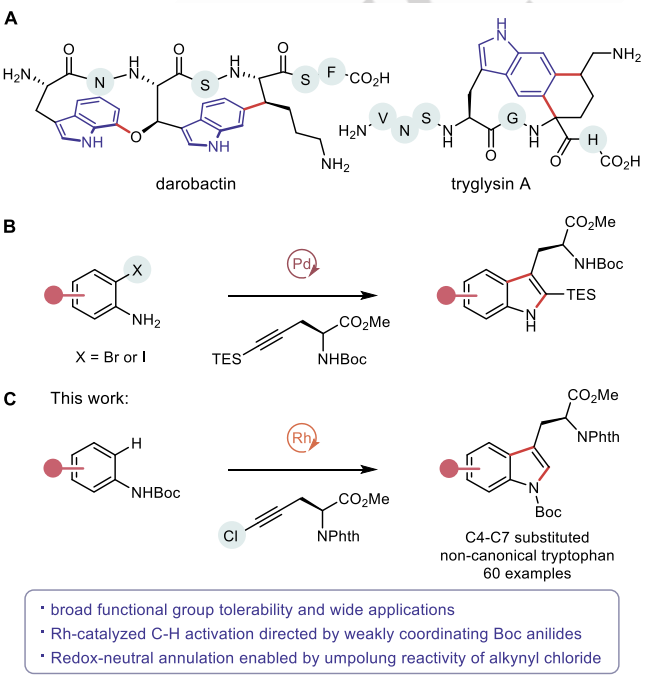

Figure 1. (A) Examples of Trp-containing natural products. (B) Larock indole synthesis. (C) This work: Rh-catalyzed C-H annulation between Boc-anilides and alkynyl chlorides.

Given these limitations, a new one-step synthesis of non-canonical Trp analogs from readily available anilines is highly desirable. With recent developments, Rh-catalyzed C–H activation/annulation chemistry has become a powerful tool for the synthesis of various nitrogen-containing heterocycles.[24-29] Most of these transformations employ internal alkynes as the coupling partner and require stoichiometric oxidants for catalyst turnover. In these reactions, the C–H activation step is well-understood, whereas the subsequent redox process remains poorly defined.[30] One strategy to bypass this complication is embedding an internal oxidant in the directing group.[25-26,31] Alternatively, we envisioned that alkynyl halides that are easily prepared from free- or silyl-substituted terminal alkynes could be coupled with anilines bearing non-oxidative directing group for the synthesis of non-canonical Trp. The pre-installed halogen atom in the alkyne fragment would serve not only as the internal oxidant to balance the overall redox, but also as a cleavable progenitor for C2-unsubstituted indoles. Herein, we report a Rh-catalyzed

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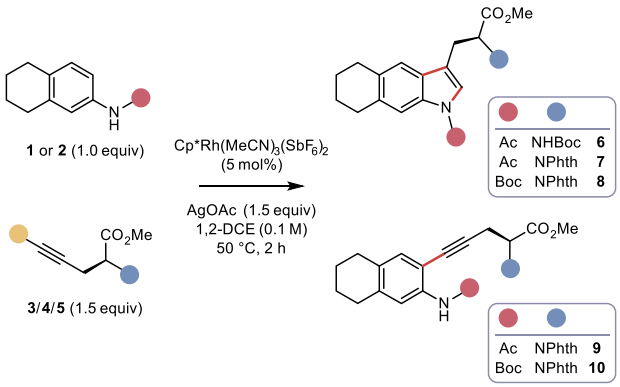
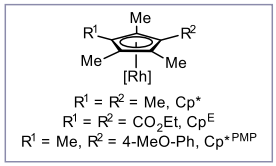
synthesis of C4-C7 substituted Trp and related 3-alkylindoles from Rh-catalyzed annulation between Boc-protected anilines and alkynyl chlorides (**Figure 1C**).

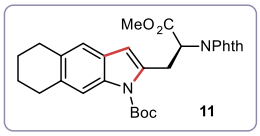
To test our hypothesis, acetanilide **1** bearing a tetralin moiety and alkynyl chloride **3** derived from (*S*)-propargyl alanine were chosen as model substrates for optimization studies (**Table 1**). In the presence of 5 mol% $[Cp^*Rh(MeCN)_3](SbF_6)_2$, 1.5 equivalents of AgOAc in 1,2-DCE at 50 °C for 2 h, 11% of desired indole product **6** was detected along with other byproducts (Entry 1 and **Figure S1** in SI). We reasoned that the strong Lewis acidity of the cationic Rh(III) complexes catalyze background cyclization of alkyne substrates bearing a nucleophilic Boc amide group. Consequently, switching Boc to a more inert phthalimide group in **4** gave 35% of desired indole product **7** and 23% of the alkynylation byproduct **9** at incomplete conversion of both starting material (Entry 2). To further optimize the ratio between the two products, we screened directing groups on the aniline (**Table S3** in SI). A weakly directing[32] and synthetically attractive Boc group is optimal for this transformation, providing 59% of the desired product and a 6:1 ratio between **8** and **10** at 70% conversion of the starting anilide (Entry 3). Using the alkynyl bromide **5** instead of **4** gave slightly diminished yield (49%), presumably due to the decreased stability (Entry 4). Screening of 14 Rh catalysts bearing different cyclopentadienyl (Cp) ligands[33] revealed that Cp* ligand on Rh is optimal for this chemistry (Entries 5-6 and **Table S1** in SI). Prolonging the reaction time to 6 h led to complete consumption of the starting anilide and 83% yield of the desired Trp product **8** along with 5% alkynylation byproduct **10** and 12% of a C2-Trp isomer **11** (Entry 9). No epimerization of the α-amino carboxylate stereogenic center was observed during the transformation (**Figure S4** in SI). Notably, the reaction can be performed at room temperature with prolonged reaction time (Entry 10).

Table 1. Optimization of reaction conditions.[a]



Entry	Substrate and Condition	Conv. of 1 or 2 (%)	Yield (%) 6/7/8	Yield (%) 9/10
1	● = Ac (**1**) ● = NHBoc ● = Cl (**3**)	24	11	--
2	Ac (**1**) NPhth Cl (**4**)	77	35	23
3	Boc (**2**) NPhth Cl (**4**)	70	59	10
4	Boc (**2**) NPhth Br (**5**)	65	49	9
5[b]	Same as 3, Cp^E instead of Cp* ligand	21	trace	6
6[b]	Same as 3, Cp^{*PMP} instead of Cp* ligand	72	50	10
7	Same as 3, AgOPiv instead of AgOAc	74	35	13
8	Same as 3, under N_2	53	42	9
9[c]	Same as 3, 6 h reaction time	99	83	5
10	Same as 3, rt, 24 h	87	71	8





[a] Reaction performed on 0.05 mmol scale. Conversion and yield were determined by ^{1}H-NMR using 1,2-dibromoethane as the internal standard. [b] Complexation was performed *in situ* using $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%) and MeCN (15 mol%). [c] 12% of the C2-substituted indole **11** was detected.

With the optimal conditions in hand, we evaluated the scope of anilide for this transformation (**Table 2**). A wide range of *para*- (**13-20**), *meta*- (**21-26**) and *ortho*- (**27-29**) substituted Boc-anilides can be smoothly converted to the corresponding C5-, C6- and C7-substituted Trp products ranging from 43% to 90% yield. Broad functional groups are tolerated in this transformation, including alkyl (**13** & **21**), aryl (**27**), full series of halogen (F, Cl, Br and I, **14-16**, **22**, **28**), methoxy and siloxy (**17-18**, **23**, **29**), boronic ester (Bpin, **19** & **24**), CF_3 (**20** & **25**) as well as carboxylic ester (**26**). In addition to mono-oxygenated Trp analogues, our method also allows direct access to di-oxygenated Trp products (**33-38**) as well as other oxygen-containing disubstituted Trp derivatives (**30**, **31**, **39**). An indolyne precursor[34] containing Trp (**40**) was obtained in 54% yield, demonstrating the potential for further diversification. While in most cases C-H activation occurs *ortho*- to a hydrogen atom, it can also occur adjacent to a methoxy group when the other *ortho*-position is blocked by a bromine (**30**) to generate a precursor for 4-methoxytryptophan, or in a case where symmetrical Boc protected 3,5-dimethoxyanilide was used as substrate (**35**). Notably, C–H activation occurs preferentially adjacent to a methylenedioxy (**38**) or fluorine (**41-43**) even when both *ortho*- and *meta*-positions are occupied by hydrogen atoms on the other side of the anilide. Carbocyclic substrates such as tetralin (**8**), indane (**44**) as well as 1- and 2-substituted naphthalene (**45** & **46**) are well tolerated. 5,7-dimethoxy-6-azatryptophan (**47**) and several heterocycle-fused Trp products including furan (**48**), thiophene (**49**), oxazolidone (**50**) and piperidone (**51**) can also be prepared using this method.

The approach also allows for mono- or bis-annulation of 1,4-phenylenediamines, which can be controlled by the selection of TFA or Boc protecting groups on one of the nitrogen atoms. TFA protection facilitated the synthesis of 5-aminotryptophan analogue **54**, whereas a symmetrical bis-Boc protected 1,4-phenylenediamine enabled two successive reactions to give the bidirectional Trp **55** (**Scheme 1A**). Given the importance of cross-linked Trp residues in macrocyclic peptide natural products, we tested several dipeptides and found that our method is readily applicable to these structural motifs (**Scheme 1B**). The dipeptides include Trp-Ala bearing both acid-sensitive (Boc, **56**) and base-labile (Fmoc, **57**) groups, Trp-Val via diaryl amide linkage (**58**), Trp-Trp with bi-indole linkage (**59**) and Trp-Tyr via diaryl ether linkage (**60**). Triptans are anti-migraine drugs acting as serotonin receptor agonists, which share 5-substituted indole-3-alkylamine as the common structure.[1] Our method allows rapid access to Trp derivatives of triptans, including zolmitriptan (**61**) and almotriptan (**62**) analogues. Remarkably, besides Trp, a pyrrole-containing amino acid **63** can also be prepared analogously from *N*-Boc dehydroalanine methyl ester.

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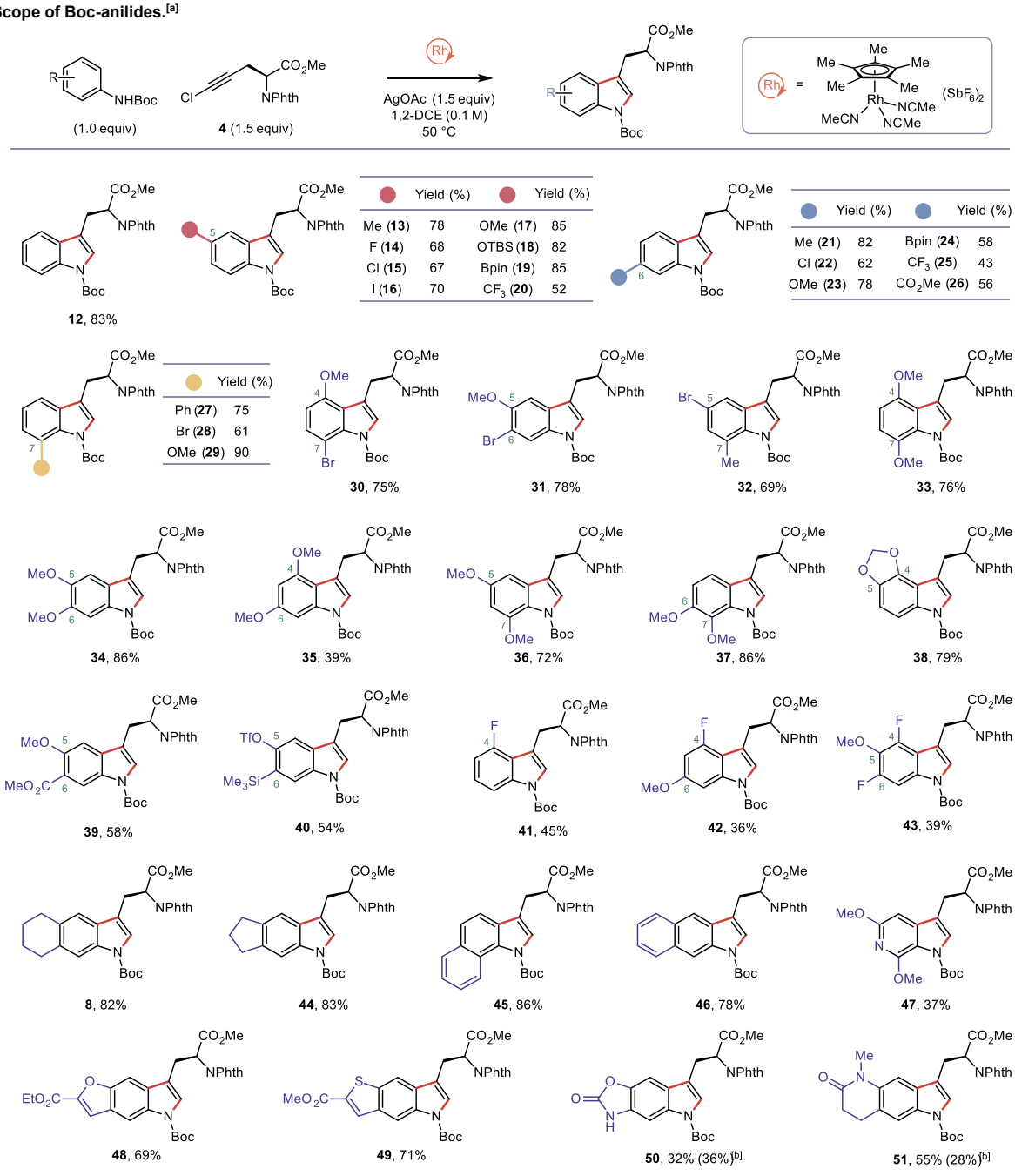
Table 2. Scope of Boc-anilides.[a]



[a] Reaction conditions: Boc-anilide (0.10 mmol), **4** (0.15 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), AgOAc (0.15 mmol) in 1,2-DCE (1.0 mL) at 50 °C for 4-48 h.
[b] Yield of C-2 chlorinated byproducts.

This method is generalizable for the synthesis of other 3-substituted indoles (**Scheme 1C**). Melatonin derivative **64** was prepared in 51% yield when excess HOAc is present during the reaction to inhibit C2 over-alkynylation (See SI for more details). Tryptophanol derivative **65** containing tosyl amide and acetonide protections was prepared in 75% yield. C3-alkylindoles **66** and **67** bearing pyrrolidine and piperidine moieties were synthesized in 81% and 52% yield respectively. Notably, these *N*-heterocyclic sidechains are widely present in triptans and psychedelic drugs.[1, 9] Dipeptide product **68** consisting of 5-methoxytryptophan and glycine was prepared in 42% yield. Besides nitrogen-containing alkynes, oxygen-substituted substrates including *C*-glycoside (**69**) as well as silyl protected secondary and tertiary propargyl alcohols (**70** & **71**) are also suitably converted into the C3-substituted indoles. In contrast to the C3-selectivity observed for alkyl substituted alkynes, 2-arylindole product **72** was obtained predominantly when phenyl-substituted alkynyl chloride was employed.

The facile preparation of **19** bearing a Bpin group provides opportunities to further incorporate drug-like heterocyclic moieties into Trp (**Scheme 1D**). For example, pyridyl-substituted Trp **73** can be prepared by Suzuki-Miyaura coupling in 76% yield.[35] Likewise, pyridine-containing diarylamine **74** was synthesized in 55% yield using Chan-Lam coupling.[36]

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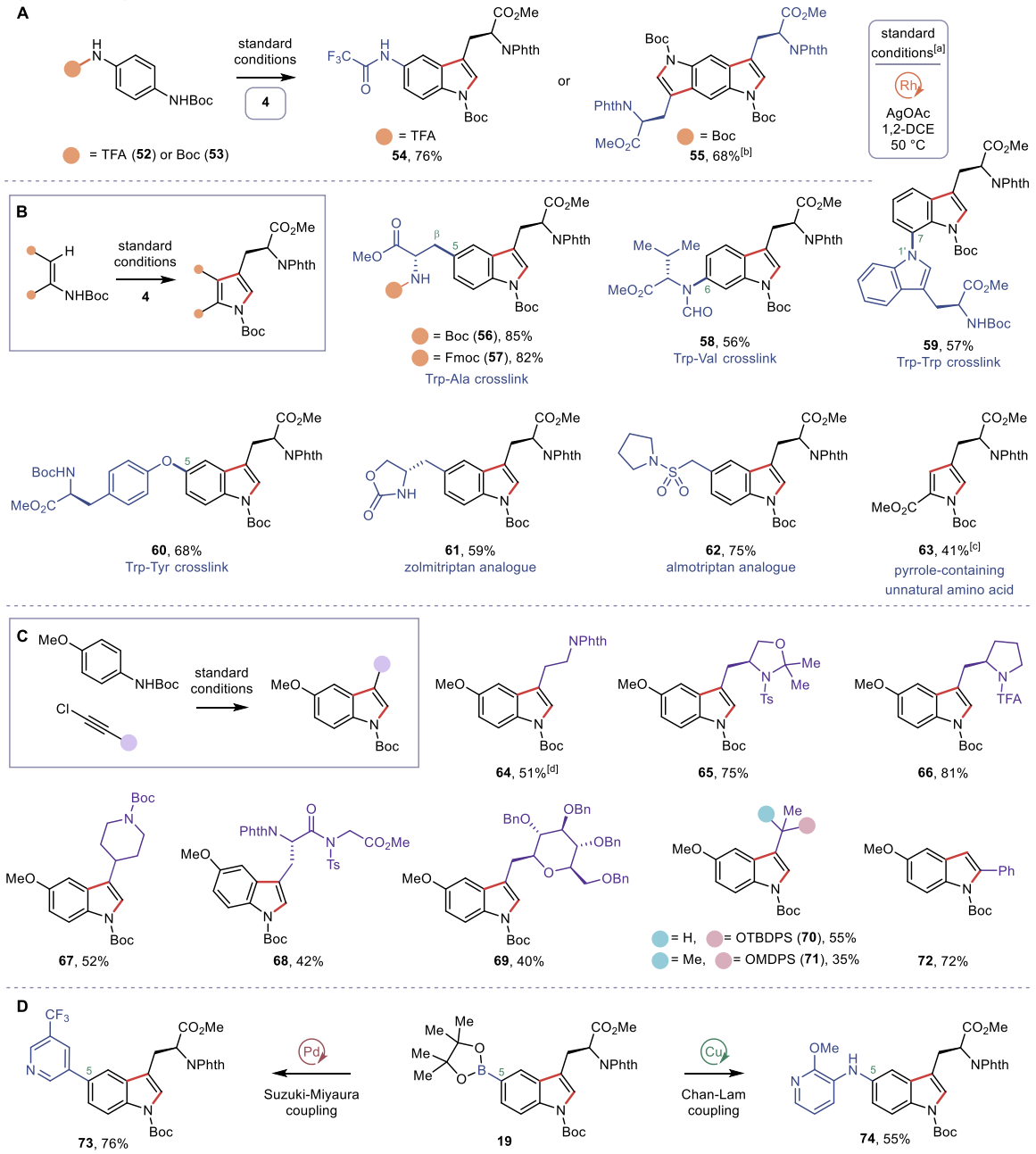
Scheme 1. Synthetic utility.



(A) Selective functionalization of 1,4-phenylenediamines. (B) Synthesis of complex Trp. (C) Scope of alkynyl chloride. (D) Synthetic diversification. [a] Standard conditions: Boc-anilide (0.10 mmol), alkynyl chloride (0.15 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), AgOAc (0.15 mmol) in 1,2-DCE (1.0 mL) at 50 °C. [b] 10 mol% of the Rh catalyst, 3.0 equiv. of **4**, and 3.0 equiv. of AgOAc were used. [c] Reaction performed at rt. [d] 5 equiv. of HOAc was added. See SI for more details.

To gain insights into the reaction mechanism, a series of experiments was performed (**Figure 2**). Reaction of Boc-anilide **75** in comparison to its D_5-isotopologue revealed a pronounced primary kinetic isotope effect (KIE) value of 6.8 ± 0.5 (**Figure 2A**). This is in agreement with previously reported values for a concerted metalation deprotonation (CMD) mechanism for C–H activation, and suggests that the rate determining step of the transformation involves C-H bond cleavage by the Rh(III) catalyst.[25,37-38] We next investigated the reversibility of C–H metalation at the *ortho*-position of starting anilide **75** and the C2-position of product **12** (**Figure 2B**). The addition of 3 equivalents of acetic acid-d_4 to the standard reaction between **75** and alkynyl chloride **4** provides 40% deuterium incorporation at C2 position in **12**, with < 5% *ortho*-deuteration observed in the unreacted anilide **75**. In an independent control experiment, subjecting **12** into the standard reaction conditions gave <5% incorporation of deuterium at C2. The combination of both experimental results suggests that Boc-directed *ortho*- C-H activation of **75** is irreversible, and the generation of C2-unsubstituted indole **12** proceeds via acetic acid-mediated irreversible protodemetalation.[39] Lastly, to probe if alkynylation byproduct **76** is on route to **12** or its C2-isomer **77**, we subjected **76** to the standard reaction conditions, which resulted in the formation of 83% of product **77**, with no detection of C3-substituted indole **12** (**Figure 2C**). This result, in addition to those in our observations during reaction optimization (**Table 1**, Entries 3 & 9), demonstrates that the C2-isomeric Trp product **77**

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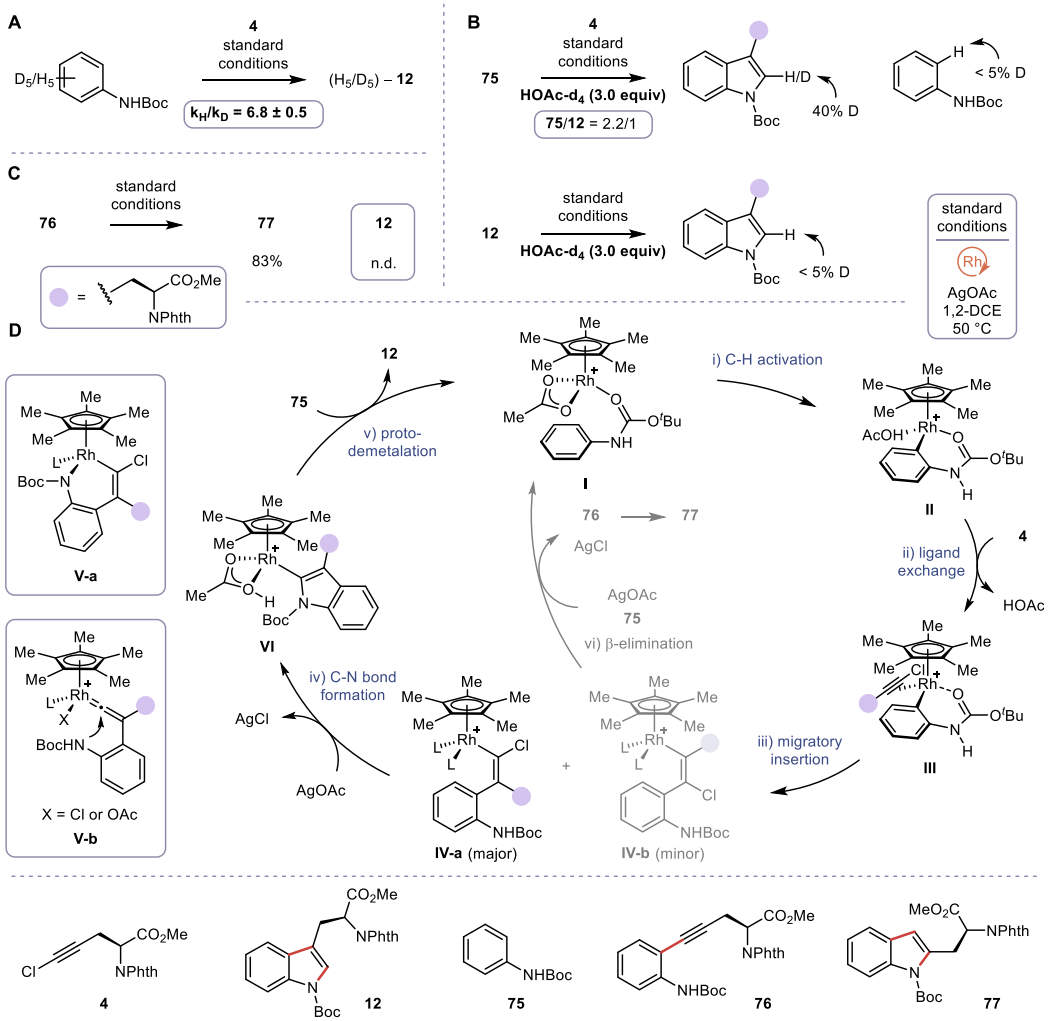

Figure 2. Mechanistic studies. (A) Deuterium kinetic isotope effects for Boc-anilide and its isotopologue. (B) C2 deuterium incorporation experiments. (C) Isomerization of the alkynylation product. (D) Proposed catalytic cycle.

is derived from the alkynylation intermediate **76**, whereas the formation of the desired Trp product **12** occurs independently to the alkynylation pathway.

Based on these observations and previous reports, [25, 37-39] we propose the following reaction mechanism (**Figure 2D**). Cationic Cp*Rh(III) intermediate **I** is formed after ligand exchange of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ with AgOAc and the Boc-anilide **75**, which sets the stage for subsequent C-H activation via CMD with an observed primary KIE of 6.8. The resulting rhodacycle **II** then undergoes ligand exchange with the alkynyl chloride, followed by migratory insertion into the aryl-rhodium bond to afford a mixture of regio-isomeric intermediates **IV-a** and **IV-b**. From the major isomer **IV-a**, C-N bond formation that closes the indole ring can occur via either a reductive elimination/oxidative addition sequence from intermediate **V-a**, [25-26] or nucleophilic addition to a vinylidene rhodium carbene intermediate **V-b**. [40] Both pathways give rise to a C2-rhodium substituted indole intermediate **VI** after ligand exchange between Cl and HOAc. Finally, proto-derhodation occurs to regenerate **I** from **VI** and release the Trp product **12**. From the minor isomer **IV-b**, β-Cl elimination occurs to provide the alkynylation product **76** and regenerate **I** following ligand exchange. **76** is then converted into the C2-isomeric Trp product **77** as demonstrated above (**Figure 2C**).

In summary, we report a novel and versatile synthesis of non-canonical Trp and related 3-alkylindoles by Rh-catalyzed C-H activation/heteroannulation between Boc-protected anilines and alkynyl chlorides. We demonstrate broad scope of this reaction with wide functional group tolerability and synthetic applications including natural product fragments and drug analogues. Different from traditional C-H activation / annulation chemistry, which often involves internal alkynes and requires external oxidants, our method uses alkynyl halides as the coupling partner to enable a redox-neutral annulation that provides direct access to C2-free indoles. Moreover, this work expands the utility of weak directing groups[32] in C-H activation chemistry for direct synthesis of tryptophan products with strategically protected *N*-Boc-indoles.

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Keywords: Non-canonical Amino Acid • Tryptophan Synthesis • Rhodium Catalysis • C-H Activation • Umpolung

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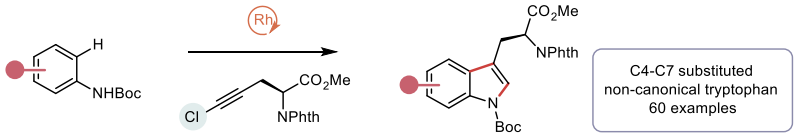

We report a regioselective synthesis of non-canonical tryptophan variants bearing C4-C7 substituents via Rh-catalyzed annulation between simple anilines and alkynyl chlorides. This umpolung approach compared to the classic Larock indole synthesis offers a novel mechanism for heteroarene annulation and will be useful for the synthesis of complex non-canonical tryptophan moieties in a highly regioselective manner.