Non-Canonical Tryptophan Synthesis Enabled by Larock Umpolung

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Abstract

Tryptophan plays a critical role in diverse natural products, biological processes, and pharmaceutical molecules. Facile access to this amino acid and its analogues from readily available building blocks, however, remains a long-standing challenge. Here, we report a regioselective synthesis of tryptophan and unnatural variants bearing C4-C7 substituents via Rh-catalyzed annulation between structurally diverse *tert*-butyloxycarbonyl (Boc) protected anilines and a serine derived alkynyl chloride. This transformation features C-H activation directed by a weakly coordinating Boc group, the umpolung reactivity of alkynyl chloride, and acetic acid-mediated reverse C-H rhodation to afford the C2 unsubstituted indole products in a redox-neutral fashion. The wide utility of this chemistry is demonstrated for the synthesis of halogenated, borylated, and poly-oxygenated tryptophans, drug analogues, dipeptides with crosslinks on tryptophan, and heterocycle-containing tryptophan derivatives. This reaction will facilitate preparation of diverse compounds, notably a myriad of bioactive Trp-containing natural products.

Main Text

Tryptophan is an indole-containing essential amino acid that plays many important roles in proteins and small molecules (**Fig. 1a**) [1-7]. It serves as a starting material for the biosynthesis of indole alkaloids such as lysergic acid, the precursor to the psychedelic drug LSD[8]. It is widely distributed in peptide-derived drug molecules and natural products. Zosurabalpin, for example, is a tryptophan-containing macrocyclic antimicrobial drug developed recently for the treatment of carbapenem-resistant *Acinetobacter baumannii* infections[9]. More recently, aromatic ring modified tryptophan derivatives containing C-C, C-N and C-O cross-links have been identified in peptide natural products[10]. Darobactin and tryglysin are ribosomally synthesized and post-translationally modified peptides (RiPPs) that possess intricate ring structures and potent antimicrobial activities[11-13]. Due to the wide occurrence and importance of tryptophan, chemical modification on C4-C7 of the indole moiety occurs either naturally or artificially to drastically alter its chemical and functional properties[1-3,7,8,10]. 5-Hydroxylation of tryptophan is the initial step for the biosynthesis of serotonin and melatonin, hormones that mediate the sleep-wake cycle in vertebrates[1]. In proteins, tryptophan is responsible for many important functions, such as glycan-protein interactions[7], π-cation interactions[3,5], and as a redox-active amino acid capable of participating in electron transfer (ET) and proton-coupled electron transfer (PCET) processes (**Fig. 1b**) [4,6,14,15]. Incorporation of electronically and sterically modified tryptophan analogues has been a useful tool to study these functions of tryptophan in proteins. Indole is thus a widely distributed privileged scaffold with a variety of important biological roles[1,2,5,8].

We have been interested in the discovery and synthesis of peptide natural products that carry cross-linked tryptophan moieties. Compared to the myriad methods that exist for the preparation of indoles, efficient synthesis of unnatural tryptophan analogues bearing C4-C7 substituents remains underdeveloped[16,17]. One of the most well-established methods for the synthesis of this class of molecules is Pd-catalyzed coupling between halogenated anilines and silyl alkynes (**Fig. 1c**) [18]. It derives from Larock indole synthesis[19] and has become a robust and reliable transformation for the preparation of complex macrocyclic peptide natural products containing tryptophan modifications[20-23]. Despite these advantages, the method requires pre-installation of a halogen atom adjacent to the nitrogen in the starting aniline and affords a C2-silylated tryptophan analogue as the precursor to C2-unsubstituted tryptophan. Given these limitations, a novel synthesis of unnatural tryptophan from simple anilines in a single

transformation via *ortho*-directed C-H activation followed by a formal [3+2] annulation would be highly desirable (**Fig. 1d**). 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]. We envisioned that a rapid synthesis of tryptophan and its analogues may be achieved via Rh-catalyzed coupling between readily available anilines and serine-derived alkynyl halides. The pre-installed halogen atom (*i.e.* Cl or Br) in the alkyne fragment serves 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 synthesis of C4-C7 substituted tryptophan and related C3-alkylindoles from Boc-protected anilines.

Optimization

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 ºC for 2 h, 11% of desired indole product **6** was detected along with other byproducts (Entry 1 and **Supplementary Fig. 1**). 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 (**Supplementary Table 3**). A weakly directing[30] 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[31] revealed that Cp* ligand on Rh is optimal for this chemistry (Entries 5-6 and **Supplementary Table 1**). Prolonging the reaction time to 6 h led to complete consumption of the starting anilide and 83% yield of the desired tryptophan product **8** along with 5% alkynylation byproduct **10** and 12% of a C2-tryptophan isomer **11** (Entry 9). No epimerization of the α-amino carboxylate stereogenic center was observed during the transformation (**Supplementary Fig. 4**). Notably, the reaction can be performed at room temperature with prolonged reaction time (Entry 10).

Scope & application

With the optimal conditions in hand, we started evaluating the scope of Boc-anilide for this transformation (**Fig. 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 tryptophan 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**). Aromatic hydroxylation is one of the major pathways for tryptophan metabolism. In addition to mono-oxygenated tryptophan analogues, our method also allows direct access to 4,7-(**33**), 5,6-(**34**), 4,6-(**35**), 5,7-(**36**), 6,7-(**37**), and 4,5-(**38**) di-oxygenated tryptophan products that covers all possible C4-C7 di-substitution patterns as well as other oxygen-containing disubstituted tryptophan derivatives (**30**, **31**, **39**). Beyond the tolerability of conventional functional handles such as halogens and boronic esters, an indolyne precursor[32] containing tryptophan (**40**) was obtained in 54% yield, demonstrating the potential for further diversification. While in most cases C-H activation occurs *ortho*- to hydrogen atom to minimize steric interactions with the bulky substituents, it can also occur adjacent to a methoxy group when the other *ortho*-position is blocked by a bromine atom (**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 group (**38**) or fluorine atom (**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 tryptophan products including furan (**48**), thiophene (**49**), oxazolidone (**50**) and piperidone (**51**) can also be prepared using this method. For the latter two cases, 2-chloronated tryptophan byproducts were also detected.

Beyond the scope of simple arylamines, mono- or bis-annulation of 1,4-phenylenediamines 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 tryptophan **55** (**Fig. 3a**). Given the importance of cross-linked tryptophan residues in macrocyclic peptide natural products, we tested several dipeptides and found that our method is readily

applicable to these structural motifs (**Fig. 3b**). 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 tryptophan derivatives of triptans, including zolmitriptan (**61**) and almotriptan (**62**) analogues. Remarkably, besides tryptophan, a pyrrole-containing amino acid **63** can also be prepared analogously using *N*-Boc protected dehydroalanine methyl ester in place of the anilide.

This method is generalizable for the synthesis of other 3-substituted indoles (**Fig. 3c**). 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[1,8]. 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 tryptophan (**Fig. 3d**). For example, pyridyl-substituted tryptophan **73** can be prepared by Suzuki-Miyaura coupling in 76% yield[33]. Likewise, pyridine-containing diarylamine **74** was synthesized in 55% yield using Chan-Lam coupling[34].

Mechanism

To gain insights into the reaction mechanism, we designed and performed a series of experiments (**Fig. 4**). 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 (**Fig. 4a**). 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[26,35,36]. We next investigated the reversibility of C-H metalation at

the *ortho*-position of starting anilide **75** and the C2-position of product **12** (**Fig. 4b**). 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[37]. 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** (**Fig. 4c**). This result, in addition to those in our observations during reaction optimization (**Table 1**, Entries 3 & 9), demonstrates that the C2-isomeric tryptophan product **77** is derived from the alkynylation intermediate **76**, whereas the formation of the desired tryptophan product **12** occurs independently to the alkynylation pathway.

Based on these observations and previous reports, we propose the following reaction mechanism (**Fig. 4d**). 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 rhodocycle **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**[26,27], or nucleophilic addition to a vinylidene rhodium carbene intermediate **V-b**[38]. 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 tryptophan 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 tryptophan product **77** as demonstrated above (**Fig. 4c**).

Conclusion

In summary, we report a novel and versatile synthesis of canonical and unnatural tryptophan analogues by Rh-catalyzed C-H activation / heteroannulation between Boc-protected anilines and alkynyl chlorides. We demonstrate more than 60 examples of this reaction with broad functional

group tolerability and synthetic applications including natural product fragments and drug analogues. The compatibility of functional handles such as boronic esters allows further diversification using cross-coupling chemistry. 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 and provides C2-free indoles for direct access to a diverse range of C4-C7 substituted unnatural tryptophan analogues and related 3-alkylindoles. Moreover, this work expands the utility of weak directing groups[30] in C-H activation chemistry for direct synthesis of tryptophan products with strategically protected *N*-Boc-indoles.

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Figures

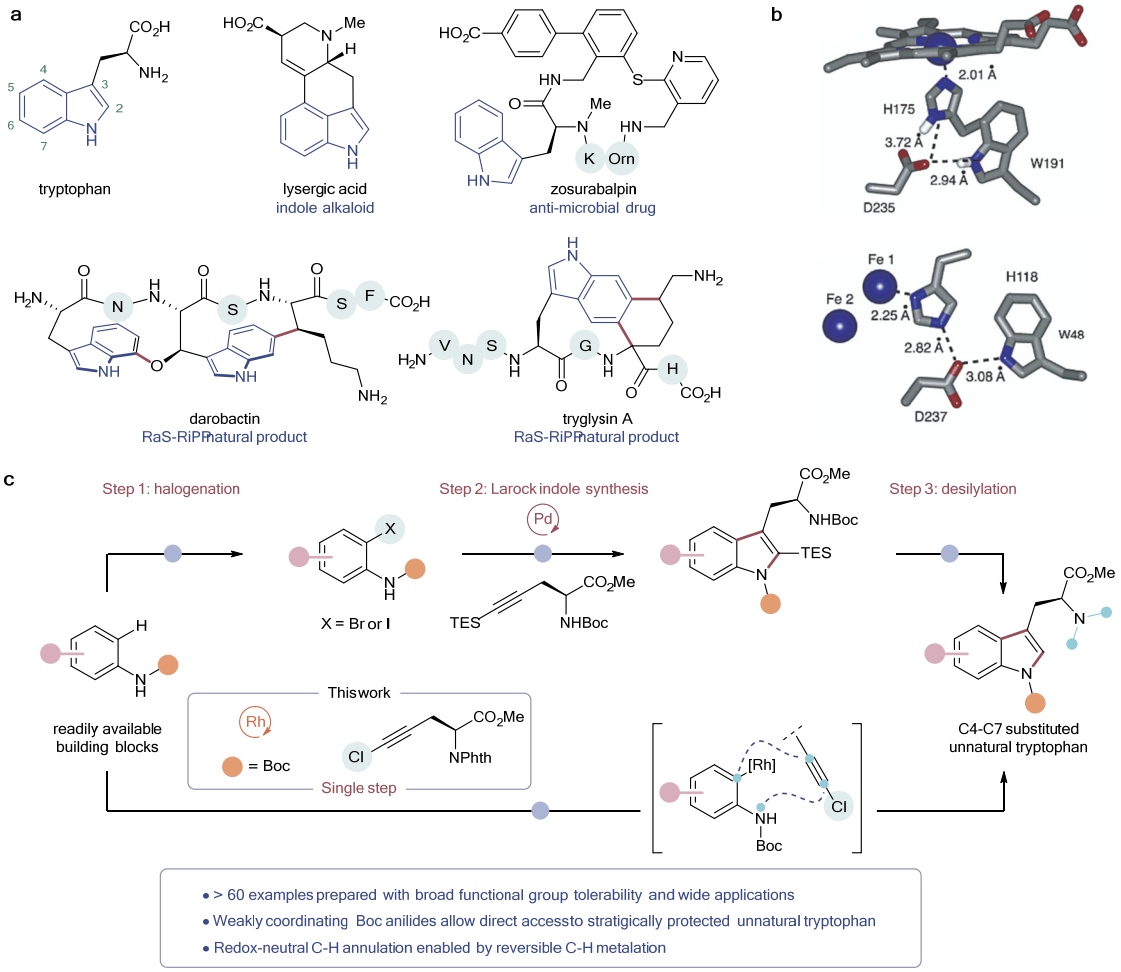
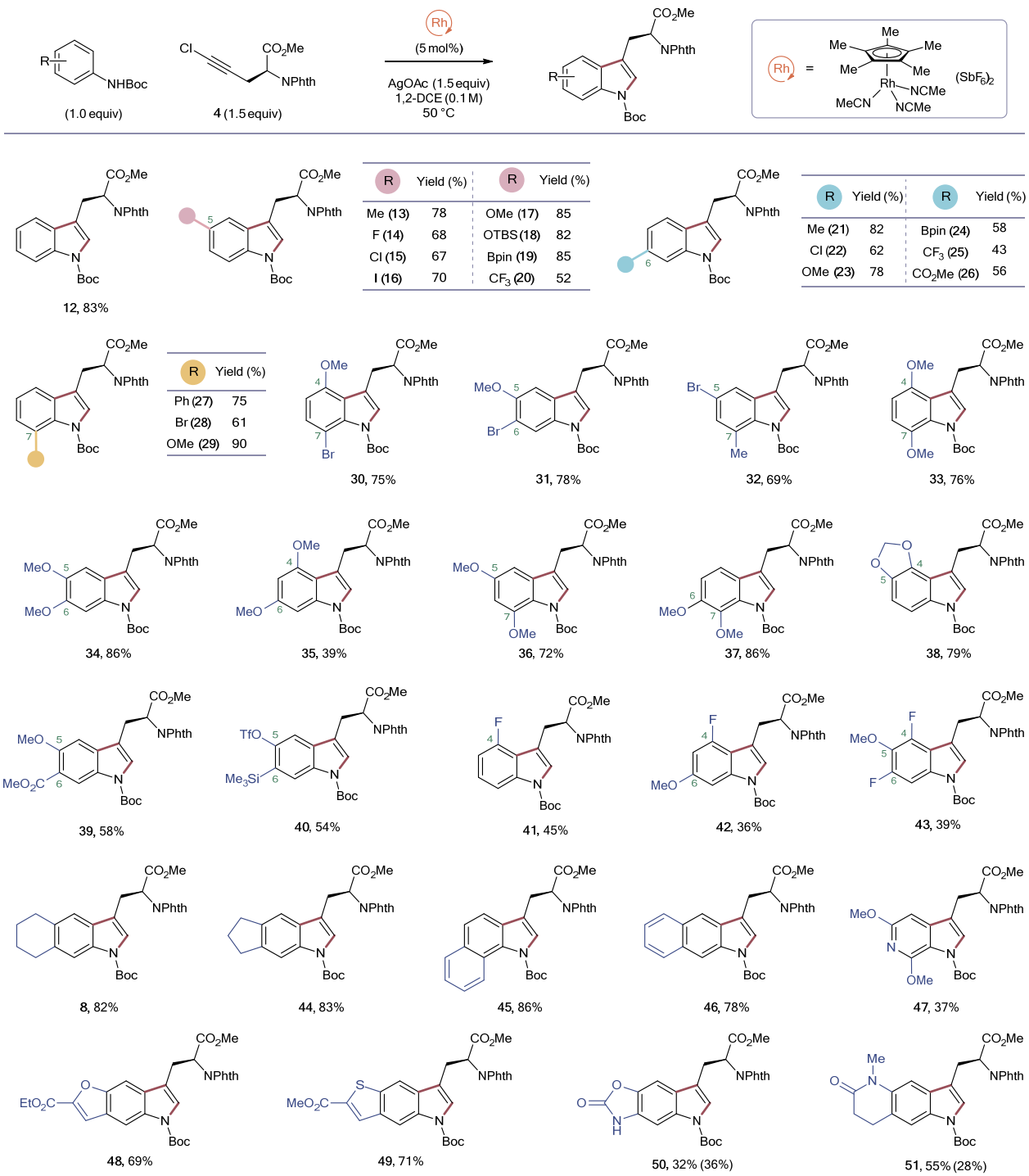


Fig. 1. Occurrence, function, and synthesis of tryptophan. (**a**) Examples of tryptophan-containing metabolites, natural products, and drug molecules. (**b**) Redox-active tryptophan residues in cytochrome c peroxidase (top) and the β2 subunit of the class I ribonucleotide reductase (bottom). (**c**) Previous synthesis of unnatural tryptophan analogues bearing C4-C7 substituents using Larock heteroannulation (top). This work: synthesis of unnatural tryptophan and related 3-alkylindoles via Rh-catalyzed C-H activation / annulation of *N*-Boc-anilines (bottom).



R	Yield (%)	R	Yield (%)
Me (13)	78	OMe (17)	85
F (14)	68	OTBS (18)	82
Cl (15)	67	Bpin (19)	85
I (16)	70	CF_3 (20)	52

R	Yield (%)	R	Yield (%)
Me (21)	82	Bpin (24)	58
Cl (22)	62	CF_3 (25)	43
OMe (23)	78	CO_2Me (26)	56

R	Yield (%)
Ph (27)	75
Br (28)	61
OMe (29)	90

Fig. 2. Scope of Boc-anilides in the Rh-catalyzed synthesis of tryptophan. Reactions were performed using 0.1 mmol of anilide for 4-48 h. Yields of C-2 chlorinated byproducts are reported in parentheses. See SI for more details.

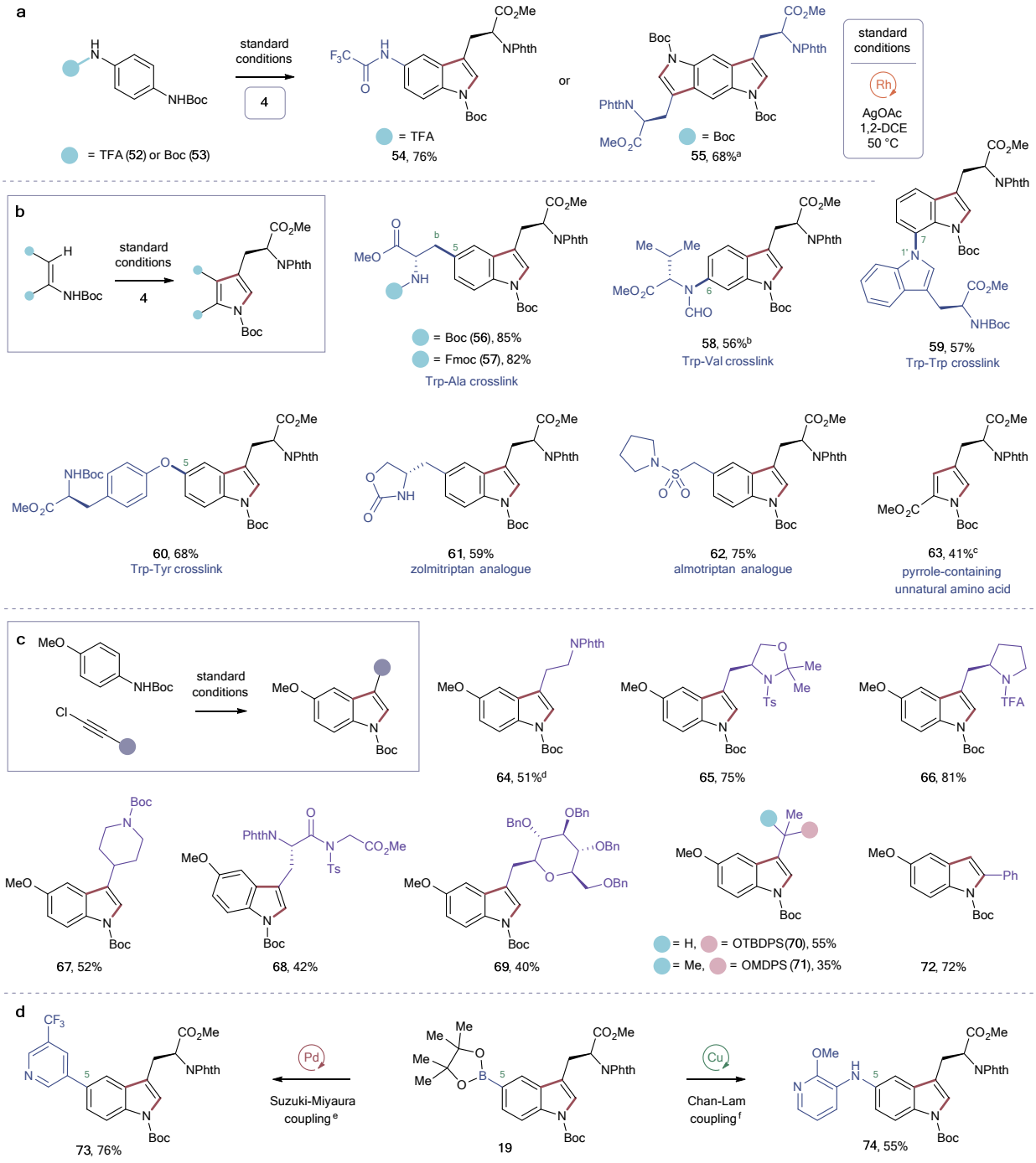


Fig. 3. Synthetic utility of Rh-catalyzed tryptophan synthesis. (**a**) Selective mono- and bis-functionalization of 1,4-phenylenediamines using TFA or Boc protecting groups. (**b**) Synthesis of dipeptides with C-C, C-N and C-O cross-links on tryptophan, a pyrrole-containing amino acid, and triptan analogues. (**c**) Scope of alkynyl chloride. (**d**) Synthetic diversification of the boron-containing tryptophan product using Suzuki-Miyaura coupling and Chan-Lam coupling. Reactions were performed using 0.1 mmol of anilide for 6-48 h. [a] 10 mol% of the Rh catalyst, 3.0 equiv. of **4**, and 3.0 equiv. of AgOAc were used. [b] A 78:22 e.r. mixture of the starting anilide was used. [c] Reaction performed at rt. [d] Reaction performed in the presence of 5 equivalents of HOAc.

[e] Conditions for the Suzuki-Miyaura coupling: **19** (0.1 mmol), 3-Bromo-5-(trifluoromethyl)pyridine (0.15 mmol), SPhos-Pd-G3 (10 mol%), 0.5 M K_3PO_4 (0.4 mL), THF (0.8 mL), 65 °C, 4 h. [f] Conditions for the Chan-Lam coupling: **19** (0.1 mmol), 3-amino-2-methoxypyridine (0.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), $B(OH)_3$ (0.2 mmol), 4 Å M.S., MeCN (0.5 mL), 80 °C, 32 h, O_2 balloon. See SI for more details.

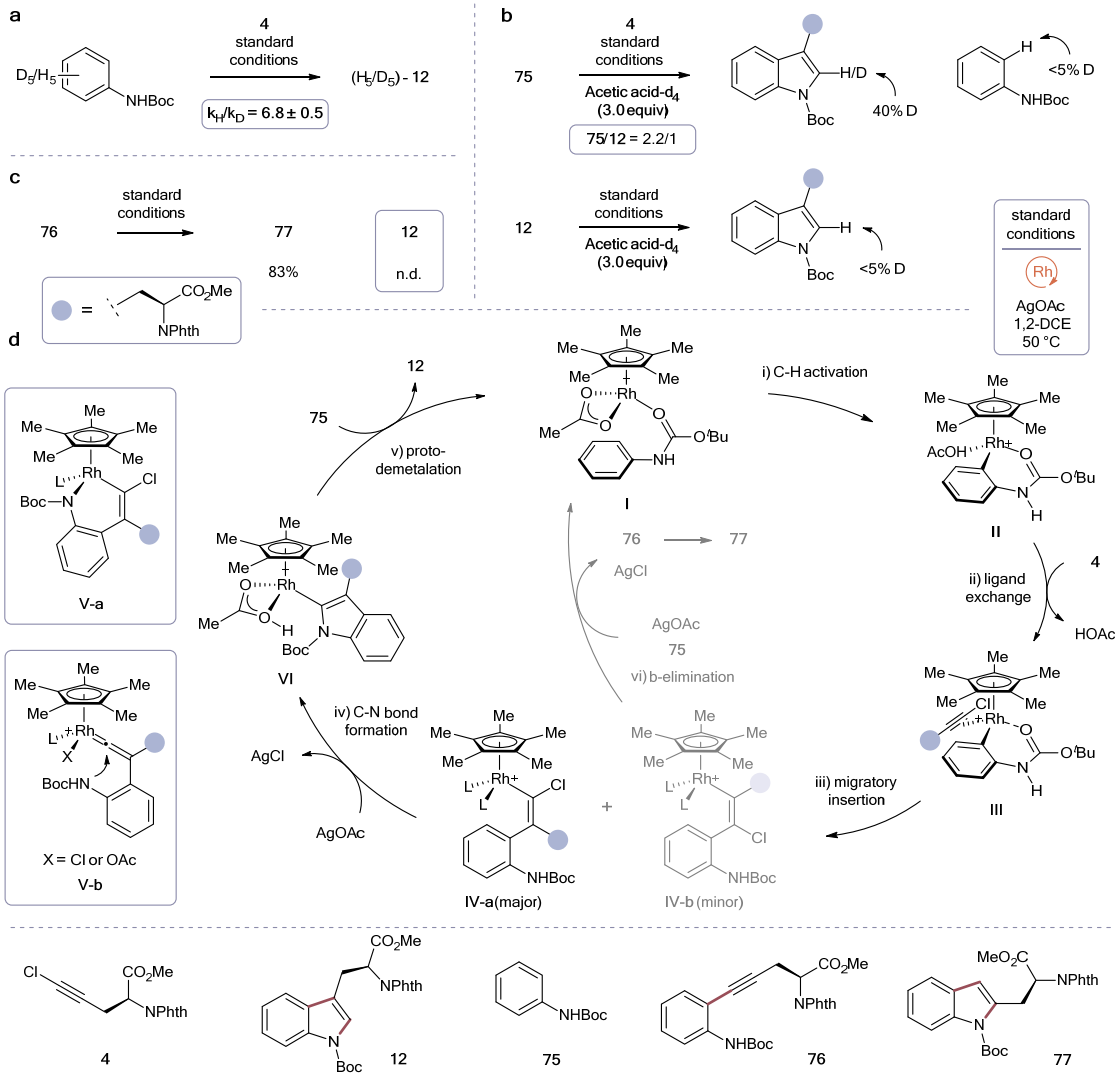
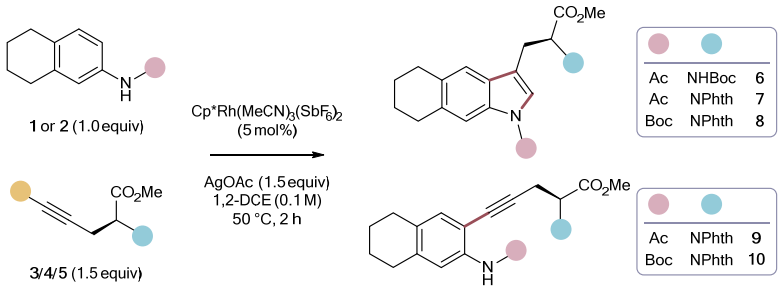
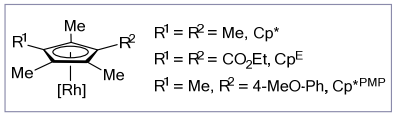


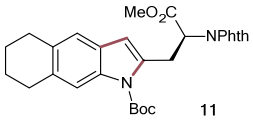
Fig. 4. Mechanistic studies and proposed catalytic cycle. (**a**) Deuterium kinetic isotope effects for Boc-anilide and its penta-deuterated isotopologue. (**b**) C2 deuterium incorporation experiments in the presence of perdeuterated acetic acid. (**c**) Isomerization of the alkynylation product to the C2-tryptophan isomer under standard conditions. (**d**) Proposed mechanism of the transformation based on experimental observations and previous reports.

Table 1. Optimization of reaction conditions.[a]



Entry	Substrate and Condition	Conv. of 1 or 2 (%)	Yield (%) 6/7/8 [b]	Yield (%) 9/10 [c]
1	= Ac (1) = NHBoc = Cl (3)	24	11	--[d]
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[e]	Same as 3, Cp^E instead of Cp* ligand	21	trace	6
6[e]	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[f]	Same as 3, 6 h reaction time	99	83	5
10	Same as 3, rt, 24 h	87	71	8





[a] Reaction performed using 0.05 mmol of anilide. Conversion and yield were determined by ^{1}H-NMR using 1,2-dibromoethane as the internal standard. [b] **6** was formed in Entry 1, **7** was formed in Entry 2, **8** was formed in Entries 3-10. [c] **9** was formed in Entry 2, **10** was formed in Entries 3-10. [d] Other types of byproducts were detected. [e] Complexation was performed *in situ* using $[Cp^xRhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%) and MeCN (15 mol%). [f] 12% of the C2-substituted indole **11** was also detected. See SI for more details.

Reporting Summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data Availability Statement

Experimental data supporting the conclusions of this study are available within the article and its Supplementary information. X-ray data are available in the Cambridge Crystallographic Data Center under CCDC number 2343679.

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Author contributions

J.Z.H., V.Y.Y. and M.R.S. conceived of the idea for the study. J.Z.H. and V.Y.Y. performed all experiments. J.Z.H., V.Y.Y. and M.R.S. analyzed data and prepared the manuscript.

Competing interests

The authors declare that they have no competing interests.

Additional information

Supplementary information

This report contains Supplementary Text, Supplementary Tables S1-S11, and Supplementary Figs. S1-S9.

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