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Hg(OTf)₂-Catalyzed Direct Vinylation of Tryptamines and Versatile Applications for Tandem Reactions†

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Graphical Abstract

We have developed a unique catalytic protocol for direct *gem*-vinylation of tryptamine derivatives employing Hg(OTf)₂ as the optimum catalyst. The intermolecular vinylations with a series of aromatic acetylenes proceeded under ambient temperature at the C2 positions of indoles with high functional group tolerance. Based on the mechanistic insights, we further developed the tandem reactions successfully constructing a quaternary center.

Introduction

The indole ring system is ubiquitous in natural products and has been exploited as a privileged motif for the development of pharmaceuticals and biologically active agents. During the course of our synthesis on naturally occurring alkaloids and their analogues,¹ we sought to develop a catalytic protocol that allows *gem*-selective vinylation of tryptamine derivatives with intentions to minimize the number of steps and amount of waste. Metal-catalyzed cross-couplings are one of the most reliable means to install alkenyl groups onto aromatic rings with exquisite control in regio-selectivity and olefin geometry.² However, it requires premodifications of both coupling partners (Scheme 1a). The direct C-H functionalization of aromatic systems without the need for premodifications emerged as a direct and atom-economical alternative to cross-couplings and the Mizoroki-Heck reaction.³ For example, the Fujiwara-Moritani reaction offers direct oxidative functionalization of arenes, yielding *trans*-substituted product as the major olefin isomer (Scheme 1b). With regards to catalytic direct vinylation of an indole system, two types of approaches have been exploited to date.⁴ The first approach involves an oxidative addition, which usually takes place at the electron-rich C3 position of indoles and thereby yields a C3-vinylated product.⁵ In most cases, catalytic functionalization of C-H at the C2 position poses a difficult problem and often requires a directing group at the N1 or C3 positions, entailing high temperature conditions (Scheme 1c).⁶ The

other approach employs a metal activator of alkynes, generating electrophilic metal complexes and subsequent hydroarylation reactions.⁷ In 2007, Echavarren and coworkers reported the direct C2 vinylation of 3-substituted indoles using a cationic gold (I)-catalyst.⁸ This conversion offers a rare example of the *gem*-selective C-H alkenylation at the indole C2 position (Scheme 1d), while related manipulations at the pyrrole C2 position have been explored a bit more due to the distinct regio-selectivities between indole and pyrrole systems as a nucleophile.⁹ To our knowledge, catalytic and chemo-selective protocols for the *gem*-2-vinylation of 3-substituted indole derivatives remain very limited,¹⁰ despite the importance on indole alkaloid synthesis.¹¹ Herein, we report a Hg(OTf)₂-catalyzed direct coupling reaction of indoles and aryl acetylenes yielding 2-vinylated tryptamine derivatives under mild conditions. Several applications for the tandem reactions are also described.

[Scheme 1]

Results and discussion

Employing tryptamine derivative **1** protected with a nosyl group and phenyl acetylene **2a** as the substrates, we screened catalytic conditions effecting the direct vinylation at the indole C2 position (Table 1). We first applied Echavarren's conditions exploiting a cationic gold (I) complex.⁸ The coupling of **1** and **2a** gave the desired product **3a** having a *gem*-substituted vinyl group in 38% yield (entry 1). A further reaction of the product **3a** gave the dimeric product **4** in a comparable yield (37%).¹² In order to achieve highly chemoselective intermolecular alkenylations without affecting the labile products bearing the vinyl group conjugated to an indole system, we found that Hg(OTf)₂, also known as Nishizawa reagent,¹³ was the optimum catalyst for the sensitive transformation.¹⁴ As shown in entry 2, treatment of **1** and **2a** (1.5 equiv.) in dichloromethane with Hg(OTf)₂ (5 mol%) at room temperature for 3 h afforded the desired vinylated product **3a** in 82% yield. Reducing the amount of catalyst to 1 mol% (entry 3) resulted in longer reaction time (24 h), giving a slightly lower yield (74%). Other mercury (II) salts, including Hg(OCOCF₃)₂ and Hg(OAc)₂, were not capable of performing the catalytic conversions (entry 4). Single application of trifluoromethanesulfonic acid as the Brønsted acid mediator resulted in no conversion (entry 5).

[Table 1]

We then investigated the scope of intermolecular vinylations, employing a series of aromatic terminal alkynes (Figure 1). The presence of electron withdrawing substituents on the aromatic ring

gave the corresponding products **3b-3d** in good yields. Alkynes **2e** and **2f**, conjugated with either coumarine or indole moieties, also afforded the functionalized tryptamine derivatives **3e** and **3f**. Conversion of the aromatic acetylene **2g**, bearing an electron donating methoxy substituent, also proceeded efficiently to give **3g** in 83% yield. In addition, this protocol was shown to be a successful application for direct vinylation of L-tryptophan derivative (**5** → **6**).¹⁵ On the whole, the intermolecular vinylation of tryptamine derivatives with various aromatic terminal alkynes occurs regioselectively at the indole C2 position under ambient temperature.¹⁶

[Figure 1.]

To gain mechanistic insights, we performed a conversion employing an internal acetylene **7** (Scheme 2). Hg(OTf)₂-catalyzed alkenylation with **7** also proceeded to afford **8** despite diminished reactivity and lower yield (66%). This implies a plausible reaction mechanism, shown in Scheme 3, initiated by the formation of π -complex **A**, and thereby activating the aromatic acetylene. Friedel-Crafts type C-C bond formation (intermediate **A** → **B**) would occur regioselectively at the indole C2 position due to the presence of alkyl substituent at the C3 position. Regeneration of the indole system could form an intermediate **C**. *In situ* generation of triflic acid would allow subsequent protonation at the terminal olefinic position (intermediate **C** → **D**), giving product **3a** and the regenerated catalyst. To verify the hypothesis, we then conducted the reaction with deuterated terminal acetylene **2a-D** (Scheme 2). In fact, the deuterium was incorporated on the vinylated product **3a-D** at both terminal olefinic positions at almost the same ratios (~25%). This is consistent with the proposed mechanism involving protonation and subsequent elimination of the mercury catalyst (**C** → **D** → **3a**) aside from the lower deuterium incorporation in **3a-D**. The substantial loss of deuterium (almost 50%) might be attributed to proton exchange between product **3a** and the cationic species **E** by a catalytic amount of triflic acid (Scheme 3).

[Scheme 2.]

[Scheme 3.]

Taking the mechanistic insights into account, we then envisioned tandem reactions by making use of the electrophilic nature of the vinylated product **3a**, presumably being in equilibrium with the cationic species **E**. As shown in Scheme 4, the stirred mixture of **1** and **2a** in the presence of Hg(OTf)₂ was subjected to sequential treatment of *N*-methylindole **9** at 45 °C. The expected tandem

coupling reactions gave a 66% yield of the bis-indole compound **10** with successful construction of a quaternary carbon center. Likewise, we also attempted the sequential reaction with the internal acetylene **11** bearing a hydroxyl group. Intermolecular alkenylation and subsequent intramolecular C-O bond formation produced **12** in 65% yield, allowing direct formation of the tetrahydrofuran ring attached to an indole system.¹⁷

[Scheme 4.]

Throughout our investigations so far, we found the unique conversion employing aromatic acetylene **2i** with a *N,N*-dimethylaniline group as a notable exception (Scheme 5). Treatment of **1** and **2i** with Hg(OTf)₂ (10 mol%) produced not only the expected **3i** (42%), but also significant amounts of **13** (18%) and **14** (24%). The unexpected products **13** and **14** are composed of the pyrrolidinoindoline skeleton,¹⁸ bearing one or two units of *N,N*-dimethyl-4-vinyl-aniline groups. The formation of **14** suggests a mechanistic rationale involving the C3 vinylation incorporating a quaternary carbon and subsequent cyclization between the resulting iminium species and sulphone amide, followed by a second vinylation at the N1 position. Despite a lower yield of the C2 vinylation product **3i**, the unique reactivity of the aromatic acetylene **2i**, capable of divergent C2/C3 *gem*-vinylation, prompted us to perform the conversion with tryptamine derivatives **15** bearing a methyl substituent at the indole C2 position. As expected, the intermolecular coupling of **15** with **2i** proceeded regioselectively at C3 with complete conversion of **15**. In addition to the expected mono-vinylated product **16**, bis-vinylated product **17**, containing two *N,N*-dimethyl-4-vinyl-aniline groups, was also formed. Since treatment of **16** and **2i** under identical conditions effected vinylation at the N1 position to form **17**, we assume intermolecular sequential alkenylations through C3 vinylation, followed by an ene-type reaction of **16** with an activated species of **2i** giving **17**. It is likely that the treatment of **2i** and Hg(OTf)₂ could generate an allenyl mercury intermediate **F** expected to exert anomalous reactivity with increased ionic and electrophilic properties compared to that of **2a**.

[Scheme 5.]

In summary, we have developed a Hg(OTf)₂-catalyzed protocol allowing direct and intermolecular alkenylation of tryptamines with aromatic acetylenes at room temperature. Derivatives of tryptamine and tryptophan were efficiently alkenylated at the C2 position in a highly chemoselective and regiocontrolled manner. A variety of functionalities and substituents on aryl

group attached to acetylenes were well tolerated except for the dimethyl amino substituent. Based on the mechanistic insights, we further realized a three-component coupling as well as a sequential cyclization demonstrating the versatile applicability of this protocol in the development of tandem reactions for assembling elaborated indole derivatives.

Experimental section

NMR spectra were recorded on JEOL JNM-ECX 400 ($^1\text{H}/400\text{ MHz}$, $^{13}\text{C}/100\text{ MHz}$) spectrometers. Chemical Shifts are reported in δ (ppm) using chloroform, acetonitrile and dimethyl sulfoxide as an internal standard of δ 7.26, 1.94, 2.50 and 77.16, 118.26, 39.52 for ^1H and ^{13}C -NMR, respectively. The medium pressure liquid chromatography (MPLC) purifications were performed on a YAMAZEN YFLC-AI-580. Analytical ultra performance liquid chromatography (UPLC) was carried out on WATERS ACQUITYTM UPLC[®] H-Class system with ACQUITY UPLC[®] BEH C18 1.7 μm 2.1 $\times$ 50 mm column and PDA detector (210-400 nm). Sample was dissolved in MeCN and UPLC fractionation conditions consisted of a linear gradient from 50% $\text{H}_2\text{O}/50\%$ MeCN to 5% $\text{H}_2\text{O}/95\%$ MeCN in 3 min at a flow rate of 0.5 mL/min, held at MeCN 100% for 0.50 min at a flow rate of 0.5 mL/min, then a convex gradient back to 80% $\text{H}_2\text{O}/20\%$ MeCN in 0.5 min at a flow rate of 0.5 mL/min, then held at 80% $\text{H}_2\text{O}/20\%$ MeCN for 0.5 min at a flow rate of 0.5 mL/min. Total run time for each injection was 4.5 min. Compound was detected by 252 nm UV absorption and characterized by photo diode array. Analytical high performance liquid chromatography (HPLC) was carried out on GILSON 321 pump equipped with a GILSON UV/VIS-151 detector, GILSON FC203B fraction collector and Inertsil[®] SIL-100A 10 $\times$ 250 mm column. Where necessary, solvents were distilled from appropriate drying agents prior to use. Flash column chromatography was performed using Kanto Silica Gel 60N.

General procedure for vinylation of tryptamine and tryptophane derivatives: 2-nitro-*N*-(2-(2-(1-phenylvinyl)-1*H*-indol-3-yl)ethyl)benzenesulfonamide (**3a**).

To a solution of tryptamine derivative **1** (128 mg, 0.371 mmol) and aryl acetylene **2a** (60 μL , 0.542 mmol) in dichloromethane (3.6 mL) was added $\text{Hg}(\text{OTf})_2$ (9.02 mg, 0.0181 mmol). After stirring for 3 h at room temperature, the mixture was added saturated NaHCO_3 (aq.) and extracted with EtOAc. The organic extracts were washed with saturated NaHCO_3 (aq.), water and brine, dried over Na_2SO_4 , and concentrated. The residue was purified by silica-gel column chromatography to afford **3a** (136 mg, 0.304 mmol, 82%) as a pale yellow amorphous. ^1H -NMR (400 MHz, CDCl_3) δ 2.85 (2H, t, $J = 7.3\text{ Hz}$), 3.30 (2H, td, $J = 7.3, 5.7\text{ Hz}$), 5.24 (1H, t, $J = 5.7\text{ Hz}$), 5.51 (1H, s), 5.68 (1H, s), 7.00 (1H, ddd, $J = 7.9, 7.0, 0.9\text{ Hz}$), 7.16 (1H, ddd, $J = 8.2, 7.0, 0.9\text{ Hz}$), 7.25 (1H, d, $J = 7.9\text{ Hz}$), 7.30-7.34 (5H, m), 7.37 (1H, d, $J = 7.9\text{ Hz}$), 7.59-7.65 (2H, m), 7.69 (1H, dd, $J = 5.9, 3.6\text{ Hz}$), 7.96 (1H, br-s), 7.98 (1H, dd, $J = 5.9, 3.4\text{ Hz}$); ^{13}C -NMR (100 MHz, CDCl_3) δ 25.00, 43.96, 110.08, 111.08, 117.31, 118.58, 119.92, 122.77, 125.53, 127.74, 128.20, 128.62, 128.70, 131.02, 132.74, 133.43, 133.47, 135.38, 135.44, 139.77, 141.04, 147.67; UPLC analysis: $t = 1.49\text{ min}$ (λ_{max} 300 nm); HR-MS (ESI) calcd. for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$ 470.1150, found 470.1161. According

to this procedure, deuterium labeling experiment was performed using deuterated **2a-D**.

***N*-(2-(2-(1-(2-bromophenyl)vinyl)-1*H*-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (3b).**

According to general procedure, tryptamine derivative **1** (70.8 mg, 0.205 mmol) was treated with corresponding aryl acetylene and Hg(OTf)₂ for 4.5 h to afford **3b** (90.6 mg, 0.172 mmol, 84%) as a pale yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ 2.70 (2H, t, *J* = 7.5 Hz), 3.20 (2H, td, *J* = 7.5, 5.9 Hz), 5.14 (1H, t, *J* = 5.9 Hz), 5.42 (1H, s), 5.74 (1H, s), 7.00 (1H, t, *J* = 7.5 Hz), 7.15 (1H, t, *J* = 7.5 Hz), 7.22-7.28 (2H, m), 7.34-7.43 (3H, m), 7.54 (1H, d, *J* = 7.7 Hz), 7.64 (1H, d, *J* = 3.2 Hz), 7.66 (1H, d, *J* = 3.4 Hz), 7.74 (1H, dd, *J* = 5.9, 3.2 Hz), 7.88 (1H, br-s), 8.02 (1H, dd, *J* = 5.9, 3.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 24.97, 43.86, 110.12, 111.05, 118.60, 118.72, 120.02, 123.10, 123.21, 125.50, 127.91, 128.76, 129.97, 131.11, 131.56, 132.76, 133.33, 133.44, 133.64, 133.98, 135.61, 141.12, 141.19, 147.84; UPLC analysis: *t* = 1.76 min (λ_{max} 304 nm); HR-MS (ESI) calcd. for C₂₄H₂₀N₃O₄BrSNa [M+Na]⁺ 548.0256, found 548.0264.

***N*-(2-(2-(1-(4-fluorophenyl)vinyl)-1*H*-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (3c).**

According to general procedure, tryptamine derivative **1** (107 mg, 0.309 mmol) was treated with corresponding aryl acetylene and Hg(OTf)₂ for 2 h to afford **3c** (121 mg, 0.259 mmol, 84%) as a pale yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ 2.84 (2H, t, *J* = 7.3 Hz), 3.29 (2H, td, *J* = 7.3, 5.7 Hz), 5.24 (1H, t, *J* = 5.7 Hz), 5.50 (1H, s), 5.64 (1H, s), 7.00 (1H, m), 7.01 (2H, d, *J* = 8.8 Hz), 7.16 (1H, ddd, *J* = 8.2, 7.0, 0.7 Hz), 7.26-7.33 (3H, m), 7.37 (1H, d, *J* = 8.2 Hz), 7.61-7.66 (2H, m), 7.69 (1H, dd, *J* = 5.9, 3.6 Hz), 7.95-8.00 (2H, m); ¹³C-NMR (100 MHz, CDCl₃) δ 24.96, 43.91, 110.12, 111.12, 115.60 (d, *J* = 21.9 Hz), 117.24, 118.59, 119.99, 122.88, 125.55, 128.13, 129.43 (d, *J* = 7.6 Hz), 130.97, 132.73, 133.35, 133.47, 135.19, 135.48, 135.87 (d, *J* = 2.9 Hz), 140.02, 147.63, 162.96 (d, *J* = 248.9 Hz); UPLC analysis: *t* = 1.72 min (λ_{max} 301 nm); HR-MS (ESI) calcd. for C₂₄H₂₀N₃O₄FSNa [M+Na]⁺ 488.1056, found 488.1082.

***N*-(2-(2-(1-(3,5-bis(trifluoromethyl)phenyl)vinyl)-1*H*-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (3d).**

According to general procedure, tryptamine derivative **1** (789 mg, 2.28 mmol) was treated with corresponding aryl acetylene and Hg(OTf)₂ for 3.5 h to afford **3d** (1.14 g, 1.95 mmol, 86%) as a pale yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ 2.82 (2H, t, *J* = 7.0 Hz), 3.30 (2H, td, *J* = 7.0, 5.9 Hz), 5.23 (1H, t, *J* = 5.9 Hz), 5.76 (1H, s), 5.84 (1H, s), 7.04 (1H, ddd, *J* = 8.2, 7.0, 0.9 Hz), 7.21 (1H, ddd, *J* = 8.2, 7.0, 0.9 Hz), 7.32 (1H, dd, *J* = 8.2, 0.9 Hz), 7.41 (1H, dd, *J* = 8.2, 0.9 Hz), 7.61-7.67 (2H, m), 7.67-7.71 (1H, m), 7.80 (2H, br-s), 7.87 (1H, br-s), 7.95 (1H, br-s), 7.98-8.02 (1H, m); ¹³C-NMR (100 MHz, CDCl₃) δ 25.34, 43.81, 111.13, 111.39, 118.97, 120.42, 120.50,

122.36 (q, $J = 3.8$ Hz), 123.27 (q, $J = 273.7$ Hz), 123.55, 125.59, 127.71, 128.10, 131.02, 132.29 (q, $J = 33.4$ Hz), 132.78, 133.50, 133.55, 133.60, 135.91, 138.97, 142.04, 147.78; UPLC analysis: $t = 2.18$ min ($\lambda_{\max}$ 285 nm); HR-MS (ESI) calcd. for $\text{C}_{26}\text{H}_{19}\text{N}_3\text{O}_4\text{F}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$ 606.0898, found 606.0905.

2-nitro-*N*-(2-(2-(1-(2-oxo-2*H*-chromen-3-yl)vinyl)-1*H*-indol-3-yl)ethyl)benzenesulfonamide (3e). According to general procedure, tryptamine derivative **1** (71.3 mg, 0.206 mmol) was treated with corresponding aryl acetylene and $\text{Hg}(\text{OTf})_2$ for 11 h to afford **3e** (89.7 mg, 0.174 mmol, 84%) as a pale yellow amorphous. ^1H -NMR (400 MHz, DMSO-d_6) δ 2.88-2.96 (2H, m), 3.08-3.16 (2H, m), 5.67 (1H, d, $J = 0.9$ Hz), 5.92 (1H, d, $J = 0.9$ Hz), 7.00 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz), 7.08 (1H, ddd, $J = 8.2, 7.0, 0.9$ Hz), 7.26 (1H, d, $J = 8.2$ Hz), 7.36 (1H, td, $J = 7.5, 0.9$ Hz), 7.45 (1H, d, $J = 8.4$ Hz), 7.46 (1H, d, $J = 7.9$ Hz), 7.64 (1H, ddd, $J = 8.4, 7.3, 1.6$ Hz), 7.74 (1H, dd, $J = 7.5, 1.6$ Hz), 7.78 (1H, td, $J = 7.6, 1.6$ Hz), 7.81 (1H, td, $J = 7.5, 1.8$ Hz), 7.91 (2H, m), 7.94 (1H, s), 8.19 (1H, s), 10.9 (1H, s); ^{13}C -NMR (100 MHz, DMSO-d_6) δ 25.59, 43.26, 109.04, 111.23, 115.92, 118.29, 118.82, 119.24, 120.79, 121.78, 124.43, 124.56, 126.88, 127.97, 128.80, 129.31, 131.98, 132.59, 132.96, 133.87, 133.93, 135.28, 135.56, 141.83, 147.62, 153.21, 159.06; UPLC analysis: $t = 1.50$ min ($\lambda_{\max}$ 297 nm); HR-MS (ESI) calcd. for $\text{C}_{27}\text{H}_{21}\text{N}_3\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$ 538.1049, found 538.1043.

2-nitro-*N*-(2-(2-(1-(1-tosyl-1*H*-indol-5-yl)vinyl)-1*H*-indol-3-yl)ethyl)benzenesulfonamide (3f).

According to general procedure, tryptamine derivative **1** (70.5 mg, 0.204 mmol) was treated with corresponding aryl acetylene and $\text{Hg}(\text{OTf})_2$ for 4 h to afford **3f** (104 mg, 0.162 mmol, 79%) as a pale yellow amorphous. ^1H -NMR (400 MHz, CDCl_3) δ 2.36 (3H, s), 2.84 (2H, t, $J = 7.3$ Hz), 3.29 (2H, td, $J = 7.3, 5.7$ Hz), 5.21 (1H, t, $J = 5.7$ Hz), 5.49 (1H, d, $J = 0.9$ Hz), 5.67 (1H, d, $J = 0.9$ Hz), 6.60 (1H, dd, $J = 3.6, 0.7$ Hz), 6.99 (1H, ddd, $J = 7.9, 7.3, 0.9$ Hz), 7.16 (1H, ddd, $J = 8.2, 7.3, 0.9$ Hz), 7.23-7.27 (3H, m), 7.30 (1H, dd, $J = 8.6, 1.8$ Hz), 7.36 (1H, d, $J = 7.9$ Hz), 7.45 (1H, d, $J = 1.8$ Hz), 7.55-7.62 (3H, m), 7.64-7.67 (1H, m), 7.79 (2H, d, $J = 8.4$ Hz), 7.89 (1H, br-s), 7.90-7.95 (2H, m); ^{13}C -NMR (100 MHz, CDCl_3) δ 21.69, 24.99, 43.92, 109.25, 110.03, 111.12, 113.55, 117.16, 118.53, 119.88, 120.74, 122.71, 124.31, 125.45, 126.93, 127.17, 128.09, 130.12, 130.84, 131.01, 132.69, 133.34, 133.42, 134.76, 135.14, 135.41, 135.60, 140.79, 145.35, 147.56; UPLC analysis: $t = 2.23$ min ($\lambda_{\max}$ 299 nm); HR-MS (ESI) calcd. for $\text{C}_{33}\text{H}_{28}\text{N}_4\text{O}_6\text{S}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 663.1348, found 663.1368.

***N*-(2-(2-(1-(4-methoxyphenyl)vinyl)-1*H*-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (3g).**

According to general procedure, tryptamine derivative **1** (108 mg, 0.312 mmol) was treated with corresponding aryl acetylene and $\text{Hg}(\text{OTf})_2$ for 1.7 h to afford **3g** (123 mg, 0.258 mmol, 83%) as a

pale yellow amorphous. ^1H -NMR (400 MHz, CDCl_3) δ 2.85 (2H, t, $J = 7.3$ Hz), 3.30 (2H, td, $J = 7.3, 5.7$ Hz), 3.83 (3H, s), 5.22 (1H, br-t, $J = 5.7$ Hz), 5.40 (1H, s), 5.59 (1H, s), 6.86 (2H, d, $J = 8.6$ Hz), 6.99 (1H, ddd, $J = 7.9, 7.3, 0.7$ Hz), 7.15 (1H, ddd, $J = 8.2, 7.3, 0.9$ Hz), 7.25 (2H, d, $J = 8.6$ Hz), 7.26 (1H, d, $J = 7.9$ Hz), 7.36 (1H, d, $J = 8.2$ Hz), 7.63 (2H, dd, $J = 5.9, 3.4$ Hz), 7.69 (1H, dd, $J = 6.1, 3.4$ Hz), 7.95 (1H, br-s), 7.99 (1H, dd, $J = 5.9, 3.4$ Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 24.98, 43.97, 55.48, 109.94, 111.06, 114.02, 115.74, 118.57, 119.91, 122.71, 125.60, 128.26, 128.96, 131.06, 132.23, 132.72, 133.40, 133.53, 135.42, 135.71, 140.51, 147.71, 160.01; UPLC analysis: $t = 1.64$ min (λ_{max} 266, 295 nm); HR-MS (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$ 500.1256, found 500.1259.

(S)-methyl 2-(2-nitrophenylsulfonamido)-3-(2-(1-phenylvinyl)-1H-indol-3-yl)propanoate (6).

According to general procedure, tryptamine derivative **1** (124 mg, 0.307 mmol) was treated with corresponding aryl acetylene and $\text{Hg}(\text{OTf})_2$ for 3.5 h to afford **6** (129 mg, 0.256 mmol, 83%) as a pale yellow amorphous. ^1H -NMR (400 MHz, CDCl_3) δ 3.02 (1H, dd, $J = 14.5, 8.2$ Hz), 3.12 (1H, dd, $J = 14.5, 5.9$ Hz), 3.39 (3H, s), 4.39 (1H, td, $J = 8.2, 5.9$ Hz), 5.57 (1H, s), 5.73 (1H, s), 5.89 (1H, d, $J = 8.2$ Hz), 7.00 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz), 7.14 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz), 7.22 (1H, d, $J = 7.9$ Hz), 7.36 (5H, br-s), 7.40 (1H, d, $J = 7.9$ Hz), 7.53 (1H, td, $J = 7.5, 1.8$ Hz), 7.56 (1H, td, $J = 7.5, 1.8$ Hz), 7.68 (1H, dd, $J = 7.5, 1.8$ Hz), 7.80 (1H, dd, $J = 7.5, 1.8$ Hz), 7.99 (1H, br-s); ^{13}C -NMR (100 MHz, CDCl_3) δ 28.52, 52.49, 57.20, 107.89, 111.06, 117.69, 118.67, 120.14, 122.84, 125.54, 127.85, 128.27, 128.67, 128.75, 130.27, 132.72, 133.34, 133.87, 135.33, 136.15, 139.52, 141.09, 147.10, 171.38; UPLC analysis: $t = 1.59$ min (λ_{max} 301 nm); HR-MS (ESI) calcd. for $\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$ 528.1205, found 528.1222.

(Z)-2-nitro-N-(2-(2-(1-phenylprop-1-en-1-yl)-1H-indol-3-yl)ethyl)benzenesulfonamide (8).

According to general procedure, tryptamine derivative **1** (106 mg, 0.307 mmol) was treated with internal acetylene **7** and $\text{Hg}(\text{OTf})_2$ for 28 h to afford **8** (93.1 mg, 0.202 mmol, 66% yield, 13:1 mixture of *cis:trans* isomers), as a pale yellow amorphous. ^1H -NMR (400 MHz, CDCl_3) δ 1.80 (3H, d, $J = 7.0$ Hz), 2.82 (2H, t, $J = 7.5$ Hz), 3.28 (2H, td, $J = 7.5, 6.1$ Hz), 5.25 (1H, t, $J = 6.1$ Hz), 6.41 (1H, q, $J = 7.0$ Hz), 7.06 (1H, ddd, $J = 8.2, 7.0, 0.9$ Hz), 7.15-7.27 (6H, m), 7.31 (1H, d, $J = 8.2$ Hz), 7.45 (1H, d, $J = 7.9$ Hz), 7.60 (1H, td, $J = 7.7, 1.4$ Hz), 7.66 (1H, td, $J = 7.7, 1.4$ Hz), 7.74 (1H, dd, $J = 7.7, 1.4$ Hz), 7.88 (1H, br-s), 7.99 (1H, dd, $J = 7.7, 1.6$ Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 16.35, 25.45, 43.78, 110.18, 111.13, 118.44, 119.73, 122.23, 125.48, 126.62, 127.56, 127.84, 128.60, 129.31, 131.16, 132.73, 133.19, 133.45, 133.46, 133.57, 135.96, 140.61, 147.93; UPLC analysis: $t = 1.77$ min (λ_{max} 284 nm); HR-MS (ESI) calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$ 484.1307 found 484.1316.

Compound (10).

To a solution of tryptamine derivative **1** (70.6 mg, 0.204 mmol) and phenyl acetylene (29 μ l, 0.260 mmol) in 1,2-dichloroethane (3.0 ml) was added to Hg(OTf)₂ (5.00 mg, 0.0100 mmol). After stirring for 5.5 h at room temperature, *N*-methyl indole **9** (62 μ l, 0.496 mmol) was then added to the reaction mixture and stirred at room temperature for 12 h and at 45 °C for 10.5 h. The mixture was cooled to room temperature and added saturated NaHCO₃ (aq.) and extracted with EtOAc. The organic extracts were washed with saturated NaHCO₃ (aq.), water and brine, dried over Na₂SO₄, and concentrated. The residue was purified by silica-gel column chromatography to afford **10** (77.9 mg, 0.135 mmol, 66%) as a pale yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ 2.36 (3H, s), 2.74 (1H, dd, *J* = 9.7, 0.9 Hz), 2.76 (1H, d, *J* = 8.6 Hz), 2.92-3.02 (2H, m), 3.72 (3H, s), 5.07 (1H, br-t, *J* = 5.9 Hz), 6.40 (1H, s), 6.95 (1H, ddd, *J* = 7.9, 7.0, 0.9 Hz), 7.02 (1H, ddd, *J* = 7.9, 7.0, 1.1 Hz), 7.10 (1H, ddd, *J* = 8.2, 7.0, 1.1 Hz), 7.17 (1H, d, *J* = 8.2 Hz), 7.19-7.30 (7H, m), 7.34 (1H, d, *J* = 8.2 Hz), 7.40 (1H, d, *J* = 7.9 Hz), 7.60 (1H, td, *J* = 7.7, 1.4 Hz), 7.66 (1H, td, *J* = 7.7, 1.6 Hz), 7.76 (1H, dd, *J* = 7.7, 1.4 Hz), 7.94 (1H, dd, *J* = 7.7, 1.6 Hz), 7.97 (1H, br-s); ¹³C-NMR (100 MHz, CDCl₃) δ 26.06, 29.03, 32.90, 43.41, 44.97, 107.03, 109.75, 111.04, 118.03, 119.34, 119.55, 121.32, 121.48, 121.58, 121.87, 125.46, 126.29, 126.79, 127.76, 128.35, 128.51, 129.33, 131.15, 132.76, 133.39, 133.68, 133.85, 137.96, 141.56, 146.87, 147.86; UPLC analysis: *t* = 2.21 min (λ_{max} 284 nm); HR-MS (ESI) calcd. for C₃₃H₃₀N₄O₄SNa [M+Na]⁺ 601.1885, found 601.1883.

Compound (12).

To a solution of tryptamine derivative **1** (70.8 mg, 0.205 mmol) and **11** (61.2 mg, 0.300 mmol) in 1,2-dichloroethane (3.0 ml) was added Hg(OTf)₂ (5.00 mg, 0.0100 mmol). After stirring at room temperature for 14 h, the mixture was treated with additional **11** (50.0 mg, 0.245 mmol) and stirred for 5 h. The mixture was then added saturated NaHCO₃ (aq.) and extracted with EtOAc. The organic extracts were washed with saturated NaHCO₃ (aq.), water and brine, dried over Na₂SO₄, and concentrated. The residue was purified by silica-gel column chromatography to afford **12** (73.5 mg, 0.134 mmol, 65%) as a pale yellow amorphous. ¹H-NMR (400 MHz, CDCl₃) δ 2.01 (1H, m), 2.15 (1H, m), 2.68 (2H, dd, *J* = 7.7, 6.6 Hz), 2.89 (2H, td, *J* = 7.0, 2.9 Hz), 3.15 (1H, m), 3.25 (1H, m), 3.90 (3H, s), 4.14 (1H, td, *J* = 8.2, 5.2 Hz), 4.23 (1H, q, *J* = 7.7 Hz), 5.95 (1H, t, *J* = 5.0 Hz), 6.91 (1H, t, *J* = 7.7 Hz), 7.09 (1H, t, *J* = 7.7 Hz), 7.23 (1H, d, *J* = 7.7 Hz), 7.27 (1H, d, *J* = 7.7 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 7.53 (2H, m), 7.58 (1H, m), 7.93 (1H, m), 7.96 (2H, d, *J* = 8.4 Hz), 8.33 (1H, br-s); ¹³C-NMR (100 MHz, CDCl₃) δ 24.41, 25.87, 38.53, 43.38, 52.28, 68.45, 85.02, 107.11, 111.16, 118.23, 119.81, 122.14, 125.29, 125.79, 128.63, 129.43, 129.87, 131.12, 132.42, 133.03, 133.30, 134.41, 138.94, 147.49, 149.71, 166.84; UPLC analysis: *t* = 1.59 min (λ_{max} 283 nm);

HR-MS (ESI) calcd. for $C_{28}H_{27}N_3O_7SNa$ $[M+Na]^+$ 572.1467, found 572.1474.

***N*-(2-(2-(1-(4-(dimethylamino)phenyl)vinyl)-1*H*-indol-3-yl)ethyl)-2-nitrobenzenesulfonamide (3i).**

To a solution of tryptamine derivative **1** (86.4 mg, 0.250 mmol) and aryl acetylene **2i** (109 mg, 0.751 mmol) in dichloromethane (3.5 ml) was added $Hg(OTf)_2$ (12.5 mg, 0.0251 mmol). After stirring at room temperature for 24 h, the mixture was added saturated $NaHCO_3$ (aq.) and extracted with EtOAc. The organic extracts were washed with saturated $NaHCO_3$ (aq.), water and brine, dried over Na_2SO_4 , and concentrated. The residue was purified by silica-gel column chromatography to afford **3i** (51.0 mg, 0.104 mmol, 42%), **13** (21.8 mg, 0.0444 mmol, 18%) and **14** (38.1 mg, 0.0599 mmol, 24%).

3i: 1H -NMR (400 MHz, $CDCl_3$) δ 2.89 (2H, t, $J = 7.3$ Hz), 2.99 (6H, s), 3.33 (2H, td, $J = 7.3, 5.9$ Hz), 5.24 (1H, t, $J = 5.9$ Hz), 5.29 (1H, d, $J = 1.1$ Hz), 5.55 (1H, d, $J = 1.1$ Hz), 6.66 (2H, d, $J = 8.8$ Hz), 6.98 (1H, ddd, $J = 7.9, 7.0, 0.9$ Hz), 7.14 (1H, ddd, $J = 8.2, 7.0, 1.1$ Hz), 7.19 (2H, d, $J = 8.8$ Hz), 7.25 (1H, d, $J = 8.2$ Hz), 7.35 (1H, d, $J = 7.9$ Hz), 7.59-7.65 (2H, m), 7.68 (1H, m), 7.94 (1H, s), 8.00 (1H, m); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 25.00, 40.55, 44.05, 109.71, 111.00, 112.15, 113.95, 118.50, 119.79, 122.48, 125.54, 127.40, 128.31, 128.58, 131.07, 132.70, 133.34, 133.69, 135.34, 136.24, 140.64, 147.72, 150.74; UPLC analysis: $t = 1.88$ min (λ_{max} 300 nm); HR-MS (ESI) calcd. for $C_{26}H_{27}N_4O_4S$ $[M+H]^+$ 491.1753, found 491.1760.

13: 1H -NMR (400 MHz, $CDCl_3$) δ 2.27 (1H, ddd, $J = 12.0, 5.4, 1.1$ Hz), 2.57 (1H, ddd, $J = 12.0, 11.1, 7.5$ Hz), 2.92 (6H, s), 3.21 (1H, ddd, $J = 11.1, 10.0, 5.4$ Hz), 3.67 (1H, ddd, $J = 10.0, 7.5, 1.6$ Hz), 4.77 (1H, br-s), 5.04 (1H, d, $J = 0.9$ Hz), 5.13 (1H, s), 5.58 (1H, d, $J = 1.6$ Hz), 6.52 (2H, d, $J = 8.8$ Hz), 6.59 (1H, d, $J = 7.7$ Hz), 6.80 (2H, d, $J = 8.8$ Hz), 6.80 (1H, td, $J = 7.5, 1.1$ Hz), 7.07 (1H, d, $J = 7.5$ Hz), 7.12 (1H, td, $J = 7.7, 1.1$ Hz), 7.58 (1H, td, $J = 7.7, 1.6$ Hz), 7.61 (1H, dd, $J = 7.9, 1.6$ Hz), 7.67 (1H, td, $J = 7.7, 1.4$ Hz), 7.86 (1H, dd, $J = 7.9, 1.4$ Hz); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 37.18, 40.60, 47.95, 63.96, 82.53, 109.62, 111.91, 114.95, 119.66, 124.29, 129.03, 129.24, 130.46, 131.03, 131.78, 133.29, 133.48, 148.35, 149.31, 149.81, 150.70; UPLC analysis: $t = 2.13$ min (λ_{max} 243 nm); HR-MS (ESI) calcd. for $C_{26}H_{27}N_4O_4S$ $[M+H]^+$ 491.1753, found 491.1750.

14: 1H -NMR (400 MHz, CD_3CN) δ 2.29-2.34 (2H, m), 2.91 (6H, s), 2.93 (6H, s), 3.24 (1H, m), 4.00 (1H, m), 4.73 (1H, s), 5.00 (1H, d, $J = 1.1$ Hz), 5.07 (1H, s), 5.22 (1H, d, $J = 1.1$ Hz), 5.81 (1H, s), 6.37 (1H, d, $J = 7.7$ Hz), 6.42 (2H, d, $J = 9.1$ Hz), 6.61 (2H, d, $J = 9.1$ Hz), 6.64 (2H, d, $J = 9.1$ Hz), 6.66 (2H, d, $J = 9.1$ Hz), 6.78 (1H, td, $J = 7.5, 0.9$ Hz), 7.06 (1H, ddd, $J = 7.9, 7.5, 1.4$ Hz), 7.19 (1H, dd, $J = 7.5, 0.9$ Hz), 7.57 (1H, ddd, $J = 7.9, 6.8, 1.8$ Hz), 7.64-7.72 (3H, m); ^{13}C -NMR (100 MHz, CD_3CN) δ 40.20, 40.50, 40.63, 49.22, 64.16, 86.93, 105.83, 108.82, 112.65, 112.83, 114.51, 119.65, 124.95, 125.03, 125.11, 128.20, 129.66, 129.69, 130.62, 131.42, 132.35, 133.01,

133.95, 135.02, 145.66, 148.64, 150.37, 151.16, 151.72, 152.91; UPLC analysis: $t = 3.11$ min ($\lambda_{\max}$ 294 nm); HR-MS (ESI) calcd. for $C_{36}H_{38}N_5O_4S$ $[M+H]^+$ 636.2645, found 636.2639.

Compounds (16 and 17).

A solution of tryptamine derivative **15** (73.0 mg, 0.203 mmol) and aryl acetylene **2i** (35.0 mg, 0.241 mmol) in dichloromethane (3.0 ml) was added to $Hg(OTf)_2$ (10.0 mg, 0.0201 mmol) and stirred for 17.5 h at room temperature. Additional aryl acetylene **2i** (29.0 mg, 0.200 mmol) was added and stirred again for 5.5 h. The mixture was added sat $NaHCO_3$ aq. and extracted with EtOAc. The organic extracts were washed with sat $NaHCO_3$ aq., water and brine, dried over Na_2SO_4 , and concentrated. The residue was purified by silica-gel column chromatography to afford **16** (48.8 mg, 0.0967 mmol, 48%) and **17** (49.4 mg, 0.0761 mmol, 37%).

16: 1H -NMR (400 MHz, $CDCl_3$) δ 2.13 (3H, s), 2.14-2.22 (1H, m), 2.40-2.49 (1H, m), 2.49-2.61 (2H, m), 2.82 (6H, s), 5.15 (1H, t, $J = 5.7$ Hz), 5.36 (1H, s), 5.49 (1H, s), 6.35 (2H, d, $J = 8.8$ Hz), 6.46 (2H, d, $J = 8.8$ Hz), 7.22 (1H, td, $J = 6.8, 0.9$ Hz), 7.25 (1H, d, $J = 1.8$ Hz), 7.33 (1H, ddd, $J = 7.7, 6.8, 1.8$ Hz), 7.44 (1H, d, $J = 7.7$ Hz), 7.62-7.71 (2H, m), 7.80 (1H, m), 7.85 (1H, m); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 16.77, 35.24, 39.19, 40.38, 65.69, 111.68, 115.65, 120.25, 122.75, 125.47, 126.06, 127.65, 128.42, 128.60, 131.04, 132.89, 133.33, 133.66, 141.53, 147.84, 147.93, 149.97, 155.62, 184.79; UPLC analysis: $t = 1.47$ min ($\lambda_{\max}$ 269 nm); HR-MS (ESI) calcd. for $C_{27}H_{28}N_4O_4SNa$ $[M+Na]^+$ 527.1729, found 527.1732.

17: 1H -NMR (400 MHz, CD_3CN) δ 2.13 (1H, td, $J = 12.0, 5.0$ Hz), 2.44 (1H, td, $J = 12.0, 5.0$ Hz), 2.53 (1H, m), 2.85 (6H, s), 2.88 (6H, s), 3.07 (1H, m), 3.77 (1H, d, $J = 1.4$ Hz), 3.89 (1H, d, $J = 1.4$ Hz), 4.83 (1H, s), 5.00 (1H, d, $J = 0.9$ Hz), 5.34 (1H, d, $J = 0.9$ Hz), 5.60 (1H, s), 5.83 (1H, br-t, $J = 5.7$ Hz), 6.19 (1H, d, $J = 7.5$ Hz), 6.41 (2H, d, $J = 9.1$ Hz), 6.44 (2H, d, $J = 9.1$ Hz), 6.61 (2H, d, $J = 9.1$ Hz), 6.72 (2H, br-d, $J = 9.1$ Hz), 6.80 (1H, td, $J = 7.5, 1.1$ Hz), 7.01 (1H, td, $J = 7.5, 1.1$ Hz), 7.08 (1H, dd, $J = 7.5, 1.1$ Hz), 7.72 (1H, td, $J = 7.7, 1.6$ Hz), 7.76 (1H, td, $J = 7.7, 1.6$ Hz), 7.83 (1H, dd, $J = 7.7, 1.6$ Hz), 7.85 (1H, dd, $J = 7.7, 1.6$ Hz); ^{13}C -NMR (100 MHz, CD_3CN) δ 40.46, 40.57, 40.91, 41.31, 56.93, 80.17, 108.13, 109.86, 112.00, 112.68, 113.48, 120.15, 123.47, 124.46, 125.97, 127.81, 129.33, 130.85, 131.50, 132.15, 133.58, 133.67, 135.04, 143.93, 148.76, 148.84, 150.54, 151.76, 153.46, 155.92; UPLC analysis: $t = 2.86$ min ($\lambda_{\max}$ 279, 301 nm); HR-MS (ESI) calcd. for $C_{37}H_{40}N_5O_4S$ $[M+H]^+$ 650.2801, found 650.2785.

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Figure and Scheme Legends:

Table 1. Screening of catalyst for coupling of **1** with **2a**.

Figure 1. Intermolecular *gem*-alkenylation of either tryptamine or tryptophan derivative (**1**, **5**) with aromatic acetylene **2**.

Scheme 1. Synthesis of branched olefins.

Scheme 2.

Scheme 3. Proposed mechanism.

Scheme 4.

Scheme 5.

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(12) The dimer **4** was obtained as 5:1 mixture of diastereomers. Although **4** was not fully characterized, NMR spectra of **4** were consistent with the data reported in ref. 8a.

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(14) Similar conversion using indium catalyst, see: (a) Tsuchimoto, T.; Kanbara, M. *Org. Lett.* **2011**, *13*, 912-915. (b) Bhaskar, G.; Saikumar, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 3141-3145.

(15) The stereogenic center in **5** was almost completely retained through the vinylation, see supporting information.

(16) In place of the CH₂CH₂NHNs substituent at indole C3 position, substrates bearing CH₂CH₂NHBoc or CH₂CH₂-phthalimide group were also applicable for the *gem*-vinylation without substantial decrease of the yields. The intermolecular alkenylation of **1** with aliphatic acetylenes were not successful.

(17) (a) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* **2007**, *13*, 8285-8293. (b) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178-3181.

(18) Crich, D.; Banerjee, A. *Acc. Chem. Rec.* **2007**, *40*, 151-161.

Entry	Catalyst	Time	Yield: 3a
1	$[\text{AuCl}(\text{PPh}_3) + \text{AgSbF}_6]$ (7 mol%)	8 h	38% ^a
2	$\text{Hg}(\text{OTf})_2$ (5 mol%)	3 h	82%
3	$\text{Hg}(\text{OTf})_2$ (1 mol%)	24 h	74% ^b
4	$\text{Hg}(\text{OCOCF}_3)_2$ (10 mol%)	18 h	9%
5	TfOH (10 mol%)		

^a **4** (37%): dimer of **3a**, ^b Recovery of **1** (17%)

a) cross-couplings

X, Y: metal or halogen etc.

b) Mizoroki-Heck / Fujiwara-Moritani reactions

c) Alkenylation of indole C2 position

d) Direct alkenylation of 3-substituted indoles