Direct Alkynylation of Indole and Pyrrole Heterocycles**

Jonathan P. Brand, Julie Charpentier and Jérôme Waser*

Indoles and pyrroles occupy a privileged position in pharmaceuticals, material sciences and natural products.^[1] Consequently, methods to synthesize and functionalize these heterocycles are of utmost importance in organic chemistry.^[2] Metal-catalyzed cross-coupling is the most often used method for the introduction of (hetero)aryl, vinyl or acetylene groups to indoles and pyrroles, but it requires pre-modification of the heterocycle.^[3] Recently, the direct C-H functionalization of indoles and pyrroles has emerged as a more efficient alternative for the introduction of vinyl and aryl groups.^[4] In contrast, direct alkynylation of aromatic compounds are scarce.^[5] Recently reported methods include the Ga-catalyzed acetylenation of phenols and anilines,^[5a,5b] the Pd-catalyzed alkynylation of *N*-fused heterocycles,^[5c] anilines^[5d] and indoles,^[5e] the Ni-catalyzed alkynylation of azoles,^[5f] the reaction of pyrroles with bromo-acetylene ketone derivatives^[5g,5h] and the oxidative *N*-alkynylation of indoles.^[5i] In the single report on the alkynylation of indoles,^[5e] the reaction was limited to aryl and alkenyl bromo-acetylenes used in large excess (3 equivalents). These substrates cannot be converted into free acetylenes and the large excess of reagent needed limited the practicability of the reaction. Furthermore, the scope of indoles reported was limited, including only methyl, methoxy and ester functional groups. Indoles substituted at position 2 gave low yield, and 3-substituted indoles could not be used. In view of the limited scope reported in the case of indoles and pyrroles, there is an urgent need for new alkynylation methods, especially when considering the importance of acetylenes in organic synthesis.^[6] Herein, we report a functional group tolerant gold-catalyzed alkynylation of indole and pyrrole heterocycles. The reaction proceeded in high yield at room temperature under open flask conditions using benziodoxolone-derived hypervalent iodine reagent **1d** and gives easily deprotected silyl acetylenes products. (Scheme 1).

Equation 1.

Due to the limited results obtained with halogen-acetylene derivatives,^[5a-h] we considered using more reactive hypervalent iodine reagents.^[7,8] In particular, alkynyliodonium salts as electrophilic/oxidative reagents for acetylene transfer are well-established.^[8a-g] Surprisingly, their use for C-H functionalization has not been reported yet, although other hypervalent iodine reagents have been highly successful in arylation and heteroatom transfer reactions.^[4g,4h,9] However, when reaction conditions reported for the direct arylation of indole **2a** using Cu^[4g] and Pd^[4h] catalysts were examined with alkynyliodonium salts **1a** and **1b**^[8b,8d-f] and neutral benziodoxolone-derived reagents **1c** and **1d**,^[8h,8i] no product could be isolated (Table 1, Entries 1 and 2), as well as with several other metal catalysts.^[10] We then turned to Au catalysts.^[11] Their capacity to activate π -multiple bonds^[12] is well-established and they have also been used in C-C bond formation involving changes of oxidation state at Au.^[13] The functionalization of C-H bonds using Au catalysts has been realized in classical hydroarylation reactions.^[14] Other reports remained limited to stoichiometric methods^[15] or the introduction of heteroatoms.^[16] In the case of alkynes, hydroarylation reactions were shown to be favored, and no alkynylation methods based on Au catalysts could be developed so far.^[14a] The unique combination of 5 mol % AuCl and sterically hindered reagent **1d**^[17] in CH₂Cl₂ led to the formation of the 3-alkynylation product **3a** exclusively in 65% yield (Table 1, Entry 3). This constituted the first example of Au-catalyzed C-H alkynylation, as well as an unprecedented use of benziodoxolone-based hypervalent iodine reagents for acetylene transfer.

Table 1. Optimization of alkynylation of indole (**2a**).

Entry	Catalyst	Solvent	Yield ^[a]
1	Pd(OAc) ₂	AcOH	<5%
2	Cu(OTf) ₂	CH ₂ Cl ₂	<5%
3	AuCl	CH ₂ Cl ₂	65%
4	AuCl ₃	CH ₂ Cl ₂	56%
5	AuNHCCl ^[b]	CH ₂ Cl ₂	17%
6	AuCl	toluene	42%

[*] Jonathan P. Brand, Julie Charpentier and Prof. Dr. J. Waser
Laboratory of Catalysis and Organic Synthesis
Ecole Polytechnique Fédérale de Lausanne
EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne (CH)
Fax: (+) 41 21 693 97 00
E-mail: jerome.waser@epfl.ch
Homepage: <http://isic.epfl.ch/lcso>

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7	AuCl	Et ₂ O	84%
8	AuCl	THF	85%
9	AuCl	CH ₃ CN	82%
10	AuCl	DMF	62%
11	AuCl	<i>i</i> PrOH	81%
12	AuCl	MeOH	51%

[a] Reaction conditions: 0.20 mmol **2a**, 5-10% mol catalyst, 1.2 equiv reagent, 4 mL solvent. Yield was determined via GC-MS. [b] NHC = 1,3-di(2,6-di-*iso*-propylphenyl)-imidazol-2-ylidene.

Examination of several Au catalysts (Table 1, Entries 4 and 5)^[18] confirmed that AuCl was the best catalyst. The reaction worked in a broad range of solvents (Entries 6-12), with the best reproducibility and scope obtained in Et₂O (Entry 7). Inert conditions or dry solvents were not needed for the reaction and an 86% yield of **3a** was isolated on a 0.40 mmol scale after column chromatography (Table 2, Entry 1). Importantly, only a slight excess of reagent **1d** (20%) was needed to obtain good yields. This is a distinct advantage of Au catalyst when compared with Pd catalysts, for which extensive dimerization of the acetylene was observed.^{5c} On a 2.0 mmol scale with only 1 mol % of AuCl, 84% of **3a** was isolated, which constitutes the lowest catalyst loading reported so far for C-H alkynylation reactions. Furthermore, 63% of 2-iodobenzoic acid (**4**) was recovered via a simple extraction procedure, demonstrating a further advantage of benziodoxolone based reagent. The obtained 2-iodobenzoic acid (**4**) can then be used for the synthesis of reagent **1d** in two steps and 76% overall yield with one single recrystallization for purification. The preparation of **1d** is straightforward, and 6 g of pure **1d** has been obtained from 2-iodobenzoic acid (**4**) after a single day of work. Deprotection using TBAF allowed the isolation of the free acetylene indole in 94% isolated yield.

The scope of the reaction was then examined for several indole heterocycles (Table 2). *N*-Methylindole (**2b**) gave the desired product in 83% yield (Entry 2). Both electron-donating (Entries 3-4) and electron-withdrawing (Entries 5-9) groups were tolerated in the reaction, including OH (Entry 4), CN (Entry 5), CO₂H (Entry 6), NO₂ (Entry 7), Br (Entry 8) and I (Entry 9) groups, which have never been reported before. Importantly, yields higher than 90% were obtained for Br and I substituents (Entries 8 and 9), making the method orthogonal to classical Pd(0) cross-coupling chemistry, which is not the case for previously direct alkynylation methods also based on Pd(0).^[5c,5e] The reaction was also successful for 4, 6 and 7-Br substituted indoles (Entries 10-12). In contrast to previous reports,^[5e] good yields were obtained also in the case of 2-substituted indoles (Entries 13-15). Finally, 3-methyl indole, a substrate for which no successful alkynylation has ever been reported,^[5e] gave the 2-alkynylation product in 76% yield (Entry 16).

We then turned to the alkynylation of pyrroles (Table 3). Before our work, there was no report on metal-catalyzed direct alkynylation of these heterocycles. Pyrroles are sensitive compounds that usually require protection of the NH group.^[19] In the context of alkynylation reaction, NH unprotected bromo pyrroles are too unstable to be useful, and the use of classical Sonogashira reactions consequently involves multi-step procedures to give the free pyrrole acetylenes. Gratifyingly, free pyrroles could be used in our protocol (Table 3, Entries 1 and 4-8). For pyrrole itself, the 2-alkynylation product **6a** was obtained in 62% yield (Entry 1). By using 3 equivalents of pyrrole and one equivalent of **1d**, the yield could be increased to 83%. The reaction was sensitive to the steric hindrance on nitrogen:

2-alkynylation product **6a** was obtained exclusively for pyrrole (**5a**) (Entry 1), a significant amount of 3-alkynylation product **7b** was isolated for *N*-methyl-pyrrole (**5b**) (Entry 2) and 3-alkynylation was observed exclusively for *N*-TIPS-pyrrole (**5c**) (Entry 3). Consequently, the regioselectivity of the reaction can be controlled by the use of easily removable protecting groups. Monosubstituted (Entries 4-6), disubstituted (Entry 7) and trisubstituted (Entry 8) pyrroles could also be used. An electron-withdrawing group was tolerated at the 3-position (Entry 6), but not at the 2-position (result not shown). The use of monosubstituted pyrroles has been rarely reported in metal catalyzed C-H functionalization reactions,^[4f] and the use of di- and tri- substituted pyrroles is unprecedented.

Table 2. Scope of the Alkynylation Reaction of Indoles.

Entry	Substrate	Product	Isolated Yield ^[a]
1			86%
2			83%
3			80%
4	R = OH (2d)	3d	76%
5	R = CN (2e)	3e	80%
6	R = CO ₂ H (2f)	3f	67%
7	R = NO ₂ (2g)	3g	85% ^[b]
8	R = Br (2h)	3h	93%
9	R = I (2i)	3i	91%
10			80% ^[b]
11			77%
12			84%
13			90%
14			88%

[a] Reaction conditions: 0.40 mmol **2**, 0.48 mmol **1d** and 0.02 mmol AuCl in 8 mL Et₂O at 23 °C under air for 12–15 h. Yields are reported for products isolated after column chromatography. [b] >95% pure, small amounts of **2** could not be separated from the desired product.

Table 3. Scope of the Alkynylation Reaction of Pyrroles.

Entry	Substrate	Product	Isolated Yield ^[a]
1			62% (83%) ^[b]
2			48% (6b) 25% (7b) ^[b]
3			79%
4			58%
5			60%
6			58%
7			59% ^[b]
8			48%

[a] Reaction conditions: 0.40 mmol **5**, 0.48 mmol **1d** and 0.02 mmol AuCl in 8 mL Et₂O at 23 °C under air for 12–15 h. [b] Yields based on **1d** with 3 equiv **5**.

Considering the numerous precedents for Au mediated π systems activation^[12,14] and the rare other examples of C–H functionalization,^[15,16] at least two hypotheses could be considered for the mechanism: (1) Similar to the Cu system,^[4g] oxidation of Au(I) with **1d** to form a Au(III) acetylene complex **I**, followed by indole auration and reductive elimination^[15b] or (2) Au-mediated addition of indole to the triple bond of **1d** to form a vinyl Au complex **IIIa** or **IIIb**,^[14] followed either by β -elimination or a α -

elimination-1,2-shift sequence^[8b] depending on the regioselectivity of the addition. No Si shift was observed when using **1d** with a ¹³C label next to Si. Unfortunately, this result does not allow distinguishing between the proposed pathways, as an indole 1,2-shift could also account for this result. Obviously, further experiments are needed to fully understand the reaction mechanism.

Scheme 1. Working hypothesis for the mechanism of the alkynylation reaction

In conclusion, we have reported the first Au catalyzed direct alkynylation of indole and pyrrole heterocycles using a benziodoxolone-based hypervalent iodine reagent. When compared with the only reported method for the direct alkynylation of indoles,^{5e} functional group tolerance was greatly increased and unprecedented substitution patterns could be obtained. The reaction efficiency was improved (1 mol% catalyst, 1.2 equiv alkyne, 23 °C compared with 10 mol% catalyst, 3 equiv alkyne, 50 °C) and easily deprotected silyl acetylenes were obtained. The catalytic, regioselective alkynylation of pyrroles was reported for the first time. The reaction further constitutes a departure from classical Au-catalyzed hydroarylation reactions and was efficient at an unprecedentedly low catalyst loading for any direct alkynylation methods. The unique properties of benziodoxolone derived hypervalent reagents for acetylene transfer were discovered, which constitutes an important advance in the field of hypervalent iodine chemistry. The exceptional scope of the reaction, as well as the mild reaction conditions and simple experimental procedure (easily accessible reagent, no inert gas, no dry solvent) bode well for the application of the method in organic and medicinal chemistry.

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Direct Alkynylation

Jonathan P. Brand, Julie Charpentier
and Jérôme Waser *

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Easy C-H Alkynylation: The first AuCl-catalyzed direct alkynylation of indole and pyrrole heterocycles is described. The unique properties of benziodoxolone alkynyl periodinane **1d** and Au catalysts allowed the development of a high yielding, operatively simple (room temperature, no dry solvents or inert conditions, commercially available catalyst) reaction for the introduction of silyl acetylenes on a large range of indole and pyrrole heterocycles with broad functional groups and substitution patterns tolerance.

Supporting information

Direct Alkynylation of Indole and Pyrrole Heterocycles

*Jonathan P. Brand, Julie Charpentier and Jérôme Waser **

*Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH
4306, 1015 Lausanne, Switzerland*

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1 General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et₂O, CH₃CN, toluene, hexane and CH₂Cl₂ were dried by passage over activated alumina under nitrogen atmosphere (H₂O content < 10 ppm, *Karl-Fischer* titration). NEt₃ and pyridine were distilled under nitrogen from KOH. Gold chloride was purchased from Aldrich and kept in desiccator under anhydrous condition (decrease of reactivity has been observed for catalyst if prolonged exposition to air (*ca* 1 month)). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem, Maybrige, TCI or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F₂₅₄ TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ¹H-NMR spectra were recorded on a Bruker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-d₆ or CD₃OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation). ¹³C-NMR spectra were recorded with ¹H-decoupling on a Bruker DPX-400 100 MHz spectrometer in chloroform-d, DMSO-d₆ or CD₃OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm⁻¹ (w = weak, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API.

2 Preparation of Reagents

Phenyl(trimethylsilyl)ethynyl)iodonium triflate (1a).

Following a reported procedure,^[1] phenyliodonium diacetate (**8**) (3.22 g, 10.0 mmol, 1.00 equiv) was diluted with CH₂Cl₂ (10 mL) and the mixture was stirred for 5 minutes. Tf₂O (0.67 mL, 5.0 mmol, 0.50 equiv.) was added dropwise at 0 °C and the resulting yellow mixture was stirred 30 min. Bis(trimethylsilyl)acetylene (2.28 mL, 10.0 mmol, 1.00 equiv) was added. The mixture was then stirred 2 h

[1] T. Kitamura, M. Kotani, Y. Fujiwara, *Synthesis* **1998**, 10, 146.

and diethyl ether was added to precipitate the product. Filtration afforded **1a** (2.11 g, 4.67 mmol, 47%) as a colorless solid.

Mp (Dec.) 139-145°C; Lit.:^[1] 143-146°C;

¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, *J*(H,H)= 8.3 Hz, 2 H; ArH), 7.66 (s, 1 H; ArH), 7.55 (m, 2 H; ArH), 0.24 (s, 9 H; TMS);

¹³C NMR (100 MHz, CDCl₃) δ 133.9, 132.4, 132.2, 119.7 (q, ¹*J*(C,F) = 319 Hz), 119.1, 116.2, 43.3, -1.1;

IR ν 1448 (w), 1286 (m), 1253 (m), 1236 (s), 1222 (s), 1161 (m), 1026 (s), 988 (w), 863 (m), 847 (s), 742 (w), 714 (m), 678 (w), 637 (s).

Characterization data of **1a** corresponded to the literature values.^[1]

Phenyl(*triiso*-propylsilyl)iodonium triflate (**1b**)

Following a slight modification of the reported procedure,^[1] phenyliodonium diacetate (**8**) (2.53 g, 7.85 mmol, 1.00 equiv) was diluted with CH₂Cl₂ (7 mL) and the mixture was stirred for 5 minutes. Tf₂O (0.60 mL, 3.9 mmol, 0.50 equiv.) was added dropwise at 0 °C and the resulting yellow mixture was stirred 30 min. (Trimethylsilyl)(*triiso*-propylsilyl)acetylene (2.00 g, 7.86 mmol, 1.00 equiv) was added and the mixture was then stirred 2 h. Water was then added (30 mL) followed by extraction of the aqueous layer with CH₂Cl₂ (2 x 30 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. The resulting solid was triturated in hexane (10 mL). Filtration and removal of solvent in vacuo afforded phenyl(*triiso*-propylsilyl)iodonium triflate (**1b**) (2.90 g, 11.2 mmol, 70%) as a colorless solid.

Mp 109-114°C;

¹H NMR (400 MHz, CDCl₃) δ 8.09 (m, 2 H; ArH), 7.65 (m, 1 H; ArH), 7.52 (m, 2 H; ArH), 1.15-1.01 (m, 21 H; TIPS);

¹³C NMR (100 MHz, CDCl₃) δ 133.7, 132.5, 132.4, 120.3 (q, ¹*J*(C,F) = 319 Hz), 117.6, 117.6, 44.9, 18.3, 11.1;

IR ν 3288 (w), 3088 (m), 2949 (m), 2894 (m), 2869 (w), 1563 (m), 1467 (w), 1451 (w), 1388 (w), 1281 (s), 1236 (s), 1221 (s), 1174 (s), 1068 (w), 1028 (s), 988 (m), 916 (m), 884 (m), 736 (s), 679 (m), 639 (s);

HRMS (ESI) calcd for C₁₇H₂₆I⁺ (M-OTf) 385.0843; found 385.0812.

1-Hydroxy-1,2-benziodoxol-3(*1H*)-one (**9**)

Following a reported procedure,^[2] NaIO₄ (6.7 g, 31 mmol; 1.0 equiv) and 2-iodobenzoic acid (**4**) (7.4 g, 30 mmol, 1.0 equiv) were suspended in 30% (v:v) aq. AcOH (45 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (120 mL) and allowed to cool to room temperature, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 30 mL) and acetone (3 x 30 mL), and air-dried in the dark to give the pure product **9** (7.3 g, 19 mmol, 92%) as a colorless solid.

¹H NMR (400 MHz, (CD₃)₂SO) δ 8.02 (dd, $J(H,H)$ = 1.4, 7.7, Hz, 1 H; ArH), 7.97 (m, 1 H; ArH), 7.85 (dd, $J(H,H)$ = 0.7, 8.2, Hz, 1 H; ArH), 7.71 (td, $J(H,H)$ = 1.2, 7.6 Hz, 1 H; ArH);

¹³C NMR (100 MHz, (CD₃)₂SO) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4;

IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m);

The characterization data for compounds **9** corresponded to the reported values.^[2]

1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (**1c**)

Following a reported procedure,^[3] trimethylsilyltriolate (2.8 mL, 15 mmol, 1.4 equiv, freshly distilled) was added dropwise to a stirred solution of 2-iodosylbenzoic acid (**9**) (3.00 g, 11.4 mmol, 1.00 equiv) in acetonitrile (85 mL) until the mixture turned colorless. Bis(trimethylsilyl)acetylene (2.14 g, 12.5 mmol, 1.10 equiv) was then added dropwise, followed, after 20 min, by the addition of pyridine (1.2 mL, 15 mmol, 1.4 equiv). The mixture was stirred 30 min. The solvent was then removed under reduced pressure and the yellow crude oil was dissolved in dichloromethane (80 mL). The organic layer was washed with a large amount of water (130 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 x 65 mL). The organic layer was washed with brine (130 mL), dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (2.3 mL) afforded **1c** (2.35 g, 6.84 mmol, 60% yield) as a colorless solid.

Mp: 143-145°C (dec);

¹H NMR (400 MHz, CDCl₃) δ 8.42 (dd, $J(H,H)$ = 1.9, 6.4 Hz, 1 H; ArH), 8.19 (m, 1 H; ArH), 7.78 (m, 2 H; ArH), 0.32 (s, 9 H; TMS);

¹³C NMR (100 MHz, CDCl₃) 166.4, 134.9, 132.6, 131.7, 131.4, 126.1, 117.2, 115.4, 64.2, -0.5;

IR ν 3389 (w), 2967 (w), 1617 (s), 1609 (s), 1562 (m), 1440 (w), 1350 (m), 1304 (w), 1254 (w), 1246 (w), 1112 (w), 1008 (w), 852 (s), 746 (m), 698 (m), 639 (m);

The characterization data for compounds **1c** corresponded to the reported values.^[3]

[2] L. Kraszkiewicz, L. Skulski, *Arkivoc*, **2003**, 6, 120.

[3] V. V. Zhidankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, 61, 6547.

Triisopropylsilyl trimethylsilylacetylene (**11**)

Following a reported procedure,^[4] *n*-butyllithium (2.5 M in hexanes, 12.0 mL, 29.9 mmol, 0.98 equiv) was added dropwise to a stirred solution of ethynyltrimethylsilane (**10**) (3.0 g, 30 mmol, 1.0 equiv) in THF (48 mL) at -78°C . The mixture was then warmed to 0°C and stirred for 5 min. The mixture was then cooled back to -78°C and chlorotriisopropylsilane (6.4 mL, 30 mmol, 1.0 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and stirred overnight. A saturated solution of ammonium chloride (40 mL) was added, and the reaction mixture was extracted with diethyl ether (2 x 60 mL). The organic layer was washed with water and brine, then dried over MgSO_4 , filtered and concentrated under reduced pressure to obtain a colorless liquid which was further purified by Kugelrohr distillation ($56\text{--}57^\circ\text{C}/0.25\text{ mmHg}$) to yield **11** (7.16 g, 28.0 mmol, 92% yield) as a colorless liquid.

^1H NMR (400 MHz, CDCl_3) δ 1.08 (m, 21 H; TIPS), 0.18 (s, 9 H; TMS);

IR ν 2959 (m), 2944 (m), 2896 (w), 2867 (m), 1464 (w), 1385 (w), 1250 (m), 996 (w), 842 (s), 764 (s), 675 (m), 660 (m).

Characterization data of **11** corresponded to the literature values.^[4]

1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**1d**)

Following a reported procedure,^[3] trimethylsilyltriflate (3.6 mL, 20 mmol, 1.1 equiv, freshly distilled) was added dropwise to a stirred solution of 2-iodosylbenzoic acid (**9**) (4.7 g, 18 mmol, 1.0 equiv) in acetonitrile (140 mL). (Trimethylsilyl)(triisopropylsilyl)acetylene (**11**) (5.0 g, 20 mmol, 1.1 equiv) was then added dropwise, followed, after 15 min, by the addition of pyridine (1.5 mL, 20 mmol, 1.1 equiv). The mixture was stirred 10 min. The solvent was then removed under reduced pressure and the yellow crude oil was dissolved in dichloromethane (50 mL). The organic layer was washed with HCl 1 M (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The organic layers were combined, washed with a saturated solution of NaHCO_3 (2 * 50 mL), dried over MgSO_4 , filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (*ca* 35 mL) afforded **1d** (6.3 g, 15 mmol, 83%) as a colorless solid.

Mp (Dec.) $170\text{--}176^\circ\text{C}$;

^1H NMR (400 MHz, CDCl_3) δ 8.44 (m, 1 H; ArH), 8.29 (m, 1 H; ArH), 7.77 (m, 2 H; ArH), 1.16 (m, 21 H; TIPS);

^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 134.6, 132.3, 131.4, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1;

[4] C J. Helal, P. A. Magriotis, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 10938.

IR ν 2943 (m), 2865 (m), 1716 (m), 1618 (m), 1604 (s), 1584 (m), 1557 (m), 1465 (m), 1439 (w), 1349 (m), 1291 (m), 1270 (w), 1244 (m), 1140 (m), 1016 (m), 999 (m), 883 (m), 833 (m), 742 (m), 702 (s), 636 (m).

Characterization data of **1d** corresponded to the literature values.^[3]

2-Iodo-1-triisopropylsilyl acetylene (**13**)

Following a reported procedure,^[5] MeLi·LiBr (1.5 M in diethyl ether, 1.1 mL, 1.6 mmol, 1.0 equiv) was added to a stirred solution of triisopropylsilylacetylene (**12**) (0.36 mL, 1.6 mmol, 1.0 equiv) in dry THF (1.8 mL), cooled at -78°C , and the mixture was allowed to react for 1 h at that temperature. A solution of I₂ (457 mg, 1.80 mmol, 1.25 equiv) in dry THF (2.7 mL) was then added dropwise and the mixture was stirred for 1.5 h at -78°C . The mixture was then diluted with brine (6 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with a saturated aqueous solution of Na₂S₂O₃ (3 x 20 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane) afforded 2-iodo-1-triisopropylsilyl acetylene (**13**) (470 mg, 1.52 mmol, 94%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 1.10–1.04 (m, 21 H; TIPS);

¹³C NMR (100 MHz, CDCl₃) δ 100.8, 18.5, 11.4 (one acetylene carbon was not resolved).

Characterization data of **13** corresponded to the literature values.^[5]

Substrate synthesis:

2-Phenyl-1H-pyrrole

Following a slightly modified procedure,^[6] pyrrole (2.1 mL, 30 mmol, 12 equiv) was added to a stirring solution of Pd(OAc)₂ (34 mg, 0.15 mmol, 0.05 equiv) in AcOH (30 mL) under air. After 5 min stirring, Ph₂IOTf (1.1 g, 2.6 mmol, 1.0 equiv) was added. The reaction was stirred at room temperature for 15 h and then filtrated over celite. After concentration under reduced pressure, the mixture was dissolved in DCM (50 mL) and washed twice with a saturated solution of NaHCO₃ (2x30 mL). The organic layer was dried over MgSO₄ and concentrated under vacuum. Purification by column chromatography (PET/EtOAc 95/5, R_f=0.2) afforded 2-Phenyl-1H-pyrrole **5e** (171 mg, 1.07 mmol, 41% yield) as a colorless oil. Purity $\geq$ 90%.

¹H NMR (CDCl₃, 400MHz) δ 8.46 (br s, 1 H; NH), 7.51 (dm, $J(\text{H},\text{H}) = 7.2$ Hz, 2 H; PhH), 7.39 (m, 2 H; PhH), 7.24 (m, 1 H; PhH), 6.90 (m, 1 H; pyrrole H), 6.56 (m, 1 H; pyrrole H), 6.33 (m, 1 H; pyrrole H);

[5] S. López, F. Fernández-Trillo, P. Midón, L. Castedo, L. Saá, *J. Org. Chem.*, **2005**, 70, 6346.

[6] N. R. Deprez, D. Kalyani, D. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, 128, 4972.

^{13}C NMR (CDCl_3 , 100MHz) δ : 132.8, 132.1, 128.9, 126.2, 123.9, 118.8, 110.2, 106.0.

Characterization data of **5e** corresponded to the literature values.^[6]

3 Alkynylation Reaction

Optimization procedure:

1d (103 mg, 0.240 mmol, 1.2 equiv) was added to a stirring solution of catalyst (0.010 mmol, 0.05 equiv) and indole (**2a**) (23 mg, 0.20 mmol, 1.0 equiv) in the indicated solvent (4 mL) under air (see Table 1). The reaction was sealed and stirred at room temperature for 12-15 hrs. The reaction mixture was then filtered over silica gel and the filtrate was concentrated *in vacuo*. The residue was diluted with dichloromethane (1 mL, solution **A**). 0.1 mL of a solution of decane 0.02 M in dichloromethane and 0.8 mL of dichloromethane were added to 0.1 mL of solution **A**. The resulting solution was injected into GC-MS and the following oven program was followed: Initial temperature: 50°C, Ramp: 10.0 °C/min to 250 °C, hold 25 min at 250 °C.

General procedure (Table 2 and 3):

1d (206 mg, 0.480 mmol, 1.2 equiv) was added to a stirring solution of AuCl (4.6 mg, 0.020 mmol, 0.05 equiv) and the corresponding indole/pyrrole (0.400 mmol, 1.0 equiv) in Et_2O (8 mL) under air. The reaction was sealed and stirred at room temperature for 12-15 hrs. Et_2O (10 mL) was added, the organic layer was washed twice with NaOH 0.1 M (15 mL). The aqueous layers were combined and extracted with Et_2O (20 mL). The organic layers were combined, washed with saturated NaHCO_3 (20 mL), brine (20 mL), dried with MgSO_4 and concentrated under reduced pressure.

3-((Triisopropylsilyl)ethynyl)-1H-indole (**3a**)

Purification by flash chromatography (PET/ Et_2O 8/2) afforded **3a** (102 mg, 0.342 mmol, 86 %) as brown solid. R_f 0.4 (PET/ Et_2O 7:3, UV/Anisaldehyde).

Large scale procedure: **1d** (1.0 g, 2.4 mmol, 1.2 equiv) was added to a stirring solution of AuCl (4.6 mg, 0.020 mmol, 0.01 equiv) and **2a** (0.24 g, 2.0 mmol, 1.0 equiv) in Et_2O (40 mL) under air. The reaction was sealed and stirred at room temperature for 12-15 h. Et_2O (50 mL) was added, the organic layer was washed twice with NaOH 0.1 M (50 mL). The aqueous layers were combined and extracted with Et_2O (50 mL). The organic layers were combined, washed with saturated NaHCO_3 (50 mL), brine (50 mL), dried with MgSO_4 and concentrated under reduced pressure. Purification by flash chromatography (PET/ Et_2O 8/2) afforded **3a** (498 mg, 1.68 mmol, 84 %) as brown solid.

R_f 0.4 (PET/ Et_2O 7/3, UV/Anisaldehyde);

Mp 55-58°C;

^1H NMR (CDCl_3 , 400MHz) δ 8.11 (br s, 1 H; NH), 7.79 (m, 1 H; ArH), 7.40 (d, $J(\text{H},\text{H}) = 2.7$ Hz, 1 H; ArH), 7.36 (m, 1 H), 7.26 (m, 2 H; ArH), 1.22 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 135.1, 128.9, 128.3, 123.1, 120.8, 120.1, 111.4, 100.4, 99.3, 92.19, 18.8, 11.5;

IR ν 3407 (m), 3062 (w), 2942 (s), 2891 (m), 2864 (s), 2152 (s), 1620 (w), 1532 (w), 1457 (s), 1416 (m), 1383 (w), 1341 (w), 1325 (m), 1239 (s), 1128 (m), 1071 (m), 996 (m), 910 (m), 883 (s), 774 (s), 742 (s), 676 (s), 658 (s), 628 (s);

HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{28}\text{NSi}^+$ ($\text{M}+\text{H}$) 298.1991, found 298.2001.

2-Iodobenzoic acid was recovered by adjusting the pH of the NaOH fraction to 1 with conc. HCl and extracting with CH_2Cl_2 (3x100 mL). The organic layers were combined, dried over MgSO_4 and concentrated under reduced pressure to afford 2-Iodobenzoic acid (375 mg, 1.45 mmol, 63% recovered) as a colorless solid.

1-Methyl-3-((triisopropylsilyl)ethynyl)-1H-indole (3b)

Purification by flash chromatography (PET/ Et_2O 99/1) afforded **3b** (103 mg, 0.331 mmol, 83 %) as yellow solid.

R_f 0.6 (PET/ Et_2O 99:1, UV/Anisaldehyde);

Mp 60-61 °C;

^1H NMR (CDCl_3 , 400MHz) δ 7.81 (dd, $J(\text{H},\text{H}) = 0.3, 7.4$ Hz, 1 H; ArH), 7.36-7.24 (m, 4 H; ArH), 3.78 (s, 3 H; CH_3), 1.26 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 136.0, 132.6, 129.6, 122.6, 120.3, 120.1, 109.4, 100.5, 97.5, 91.4, 32.9, 18.8, 11.4;

IR ν 3129 (w), 3051 (w), 2957 (s), 2939 (s), 2889 (m), 2863 (s), 2721(w), 2365 (w), 2144 (s), 1715 (w), 1616 (w), 1538 (m), 1462 (s), 1424 (w), 1381 (s), 1349 (m), 1328 (m), 1249 (m), 1162 (m), 1130 (m), 1075 (m), 1016 (m), 992 (m), 919 (w), 883 (s), 804 (m), 768 (m), 727 (s), 705 (s), 674 (s), 648 (s), 608 (m);

HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{30}\text{NSi}^+$ ($\text{M}+\text{H}$) 312.2148, found 312.2162.

5-Methoxy-3-((triisopropylsilyl)ethynyl)-1H-indole (3c)

Purification by flash chromatography (PET/Et₂O 8/2) afforded **3c** (105 mg, 0.321 mmol, 80 %) as brown amorphous solid.

R_f 0.3 (PET/Et₂O 8/2, UV/Anisaldehyde);

¹H NMR (CDCl₃, 400MHz) δ 8.18 (br s, 1 H; NH), 7.37 (d, *J*(H,H)= 2.6 Hz, 1 H; ArH), 7.27 (d, *J*(H,H)= 2.2 Hz, 1 H; ArH), 7.24 (d, *J*(H,H)= 8.8 Hz, 1 H; ArH), 6.93 (dd, *J*(H,H)= 2.4, 8.8 Hz, 1 H; ArH), 3.93 (s, 3 H; CH₃), 1.24 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 154.8, 130.0, 129.7, 128.6, 113.3, 112.2, 101.4, 100.5, 98.8, 92.0, 55.6, 18.7, 11.4;

IR ν 3473 (w), 3394 (w), 2945 (w), 2892 (w), 2867 (w), 2253 (w), 2155 (w), 1625 (w), 1587 (w), 1486 (w), 1464 (w), 1439 (w), 1288 (w), 1249 (w), 1213 (w), 1177 (w), 1062 (w), 1026 (w), 907 (s), 884 (w), 838 (w), 802 (w), 731 (s), 676 (w), 651 (m), 644 (w);

HRMS(ESI) calcd for C₂₀H₃₀NOSi⁺ (M+H) 328.2097, found 328.2090.

3-((Triisopropylsilyl)ethynyl)-1*H*-indol-5-ol (**3d**)

Following the general procedure except that the work up was modified as following: Et₂O (10 mL) was added to the reaction mixture, the organic layer was washed twice with NaHCO₃ (15 mL). The aqueous layers were combined and extracted with Et₂O (20 mL). The organic layers were combined, dried with MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (PET/Et₂O 7/3) afforded **3d** (96 mg, 0.31 mmol, 76%) as a tan solid.

R_f 0.3 (PET/Et₂O 7/3, UV/Anisaldehyde);

Mp 124-126 °C;

¹H NMR (CDCl₃, 400MHz) δ 8.10 (br s, 1 H; NH), 7.40 (d, *J*(H,H)= 2.6 Hz, 1 H; ArH), 7.22 (d, *J*(H,H)= 8.8 Hz, 1 H; ArH), 7.16 (d, *J*(H,H)= 2.2 Hz, 1 H; ArH), 6.84 (dd, *J*(H,H)= 2.4, 8.8 Hz, 1 H; ArH), 4.87 (br s, 1 H; OH), 1.19 (s, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 150.4, 130.3, 129.9, 129.2, 112.9, 112.1, 104.6, 100.2, 98.8, 91.8, 18.8, 11.5;

IR ν 3407 (m), 2943 (s), 2865 (s), 2147 (m), 1627 (w), 1585 (w), 1489 (m), 1463 (s), 1419 (w), 1365 (w), 1315 (w), 1245 (m), 1191 (m), 1102 (w), 1053 (m), 997 (w), 936 (m), 936 (m), 884 (m), 837 (m), 799 (m), 740 (s), 678 (s);

HRMS(ESI) calcd for C₁₉H₂₈NOSi⁺ (M+H) 314.1940, found 314.1925.

3-((Triisopropylsilyl)ethynyl)-1*H*-indole-5-carbonitrile (**3e**)

Purification by flash chromatography (PET/Et₂O 6/4) afforded **3e** (103 mg, 0.319 mmol, 80 %) as tan solid.

R_f 0.25 (PET/Et₂O 6/4, UV/Anisaldehyde);

Mp 164-167 °C;

¹H NMR (CDCl₃, 400MHz) δ 9.06 (br s, 1 H; NH), 8.09 (d, *J*(H,H)= 0.7 Hz, 1 H; ArH), 7.58 (d, *J*(H,H)= 2.6 Hz, 1 H; ArH), 7.50 (m, 2 H; ArH), 1.20 (s, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 136.9, 130.5, 128.8, 125.9, 125.6, 120.7, 112.6, 103.5, 100.3, 98.4, 93.6, 18.8, 11.4;

IR ν 3282 (m), 2941 (m), 2864 (m), 2226 (s), 2153 (s), 1620 (m), 1464 (m), 1432 (m), 1361 (w), 1288 (w), 1244 (s), 1178 (m), 1104 (m), 1073 (w), 996 (m), 910 (s), 883 (s), 822 (m), 804 (m), 769 (m), 737 (s), 718 (s), 672 (s), 638 (s);

HRMS(ESI) calcd for C₂₀H₂₇N₂Si⁺ (M+H) 323.1944, found 323.1952.

3-((Triisopropylsilyl)ethynyl)-1*H*-indole-5-carboxylic acid (**3f**)

Following the general procedure except that the work up was modified as following: the reaction mixture was concentrated and the crude mixture purified by flash chromatography (PET/Et₂O 4/6) affording **3f** (92 mg, 0.27 mmol, 67 %) as a colorless solid.

R_f 0.3 (PET/Et₂O 4/6, UV/Anisaldehyde);

Mp 157-160°C;

¹H NMR (MeOD, 400MHz) δ 8.42 (m, 1 H; ArH), 7.89 (dd, *J*(H,H)= 1.7, 8.6 Hz, 1 H; ArH), 7.56 (s, 1 H; ArH), 7.44 (dd, *J*(H,H)= 0.5, 8.6 Hz, 1 H; ArH), 1.16 (m, 21 H);

¹³C NMR (MeOD, 100MHz) δ 171.1, 139.6, 131.6, 129.8, 125.0, 123.6, 123.6, 112.5, 101.8, 100.6, 92.3, 19.2, 12.6;

IR ν 3370 (m), 2943 (s), 2874 (m), 2865 (s), 2501 (m), 2245 (w), 2151 (m), 2075 (w), 1680 (s), 1616 (m), 1575 (w), 1463 (m), 1417 (m), 1355 (m), 1313 (m), 1267 (s), 1242 (s), 1119 (m), 1072 (m), 977 (m), 917 (m), 884 (s), 818 (s), 772 (s), 753 (s), 671 (s);

HRMS(ESI) calcd for $C_{20}H_{28}NO_2Si^+$ (M+H) 342.1889, found 342.1890.

5-Nitro-3-((triisopropylsilyl)ethynyl)-1H-indole (**3g**)

Purification by flash chromatography (PET/Et₂O 7/3) afforded **3g** (116 mg, 0.339 mmol, 85 %) as yellow solid as an inseparable mixture 95/5 with 5-nitroindole.

R_f 0.3 (PET/Et₂O 7/3, UV/Anisaldehyde);

Mp 193-195 °C;

¹H NMR (CDCl₃, 400MHz) δ 9.10 (br s, 1 H; NH), 8.70 (d, $J(H,H)$ = 2.1 Hz, 1 H; ArH), 8.17 (dd, $J(H,H)$ = 2.1, 8.9 Hz, 1 H; ArH), 7.63 (d, $J(H,H)$ = 2.6 Hz, 1 H; ArH), 7.50 (d, $J(H,H)$ = 8.9 Hz, 1 H; ArH), 1.21 (s, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 142.4, 138.1, 131.3, 128.5, 118.6, 117.3, 111.8, 102.0, 98.1, 94.3, 18.8, 11.4;

IR ν 3319 (m), 2943 (m), 2865 (m), 2153 (m), 1621 (w), 1463 (m), 1329 (s), 1282 (m), 1244 (m), 1113 (m), 1041 (w), 995 (w), 909 (s), 883 (m), 843 (w), 818 (w), 796 (m), 769 (m), 736 (s), 675 (s);

HRMS(ESI) calcd for $C_{19}H_{27}O_2N_2Si^+$ (M+H) 343.1842, found 343.1835.

5-Bromo-3-((triisopropylsilyl)ethynyl)-1H-indole (**3h**)

Purification by flash chromatography (PET/Et₂O 8/2) afforded **3h** (140 mg, 0.372 mmol, 93 %) as brown amorphous solid.

R_f 0.3 (PET/EtOAc 7/3, UV/Anisaldehyde);

¹H NMR (CDCl₃, 400MHz) δ 8.19 (br s, 1 H; NH), 7.85 (dd, $J(H,H)$ = 0.5, 1.2 Hz, 1 H; ArH), 7.38 (d, $J(H,H)$ = 2.7 Hz, 1 H; ArH), 7.32 (dd, $J(H,H)$ = 1.9, 8.6 Hz, 1 H; ArH), 7.20 (d, $J(H,H)$ = 8.6 Hz, 1 H; ArH), 1.19 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 133.6, 130.5, 129.2, 126.0, 122.6, 114.1, 112.8, 99.3, 99.1, 92.6, 18.7, 11.4;

IR ν 3539 (w), 3464 (m), 3387 (m), 2960 (m), 2941 (m), 2864 (m), 2150 (m), 1649 (w), 1567 (w), 1526 (w), 1462 (s), 1415 (w), 1273 (m), 1238 (m), 1102 (w), 1063 (w), 998(w), 908 (s), 884 (s), 796 (s), 733 (s), 670 (s), 652 (s);

HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{27}^{79}\text{BrNSi}^+$ ($\text{M}+\text{H}$) 376.1096, found 378.1103.

5-Iodo-3-((triisopropylsilyl)ethynyl)-1H-indole (**3i**)

Purification by flash chromatography (PET/Et₂O 7/3) afforded **3i** (154 mg, 0.363 mmol, 91 %) as brown solid.

R_f 0.2 (PET/Et₂O 7/3, UV/Anisaldehyde);

Mp 75-77 °C;

^1H NMR (CDCl_3 , 400MHz) δ 8.20 (br s, 1 H; NH), 8.09 (d, $J(\text{H,H})$ = 1.0 Hz, 1 H; ArH), 7.51 (dd, $J(\text{H,H})$ = 1.5, 8.4 Hz, Hz, 1 H; ArH), 7.35 (d, $J(\text{H,H})$ = 2.6 Hz, 1 H; ArH), 7.12 (d, $J(\text{H,H})$ = 8.6 Hz, 1 H; ArH), 1.22 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 134.1, 131.6, 131.3, 129.0, 128.9, 113.4, 99.4, 98.8, 92.7, 84.5, 18.9, 11.5;

IR ν 3388 (m), 2941 (s), 2863 (s), 2152 (m), 1644 (w), 1527 (w), 1450 (s), 1413 (m), 1334 (w), 1272 (m), 1240 (m), 1139 (w), 110 (w), 1074 (m), 996 (w), 909 (m), 880 (s), 795 (s), 736 (s), 666 (s);

HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{27}\text{INSi}^+$ ($\text{M}+\text{H}$) 424.0958, found 424.0943.

4-Bromo-3-((triisopropylsilyl)ethynyl)-1H-indole (**3j**)

Purification by flash chromatography (PET/Et₂O 7/3) afforded **3j** (120 mg, 0.319 mmol, 80 %) as brown solid as an inseparable 96/4 mixture with 4-bromoindole.

R_f 0.3 (PET/Et₂O 7/3, UV/Anisaldehyde);

Mp 73-74 °C;

^1H NMR (CDCl_3 , 400MHz) δ 8.29 (br s, 1 H; NH), 7.46 (d, $J(\text{H},\text{H}) = 2.7$ Hz, 1 H; ArH), 7.34 (m, 1 H; ArH), 7.27 (m, 1 H; ArH), 7.04 (t, $J(\text{H},\text{H}) = 7.7$ Hz, 1 H; ArH), 1.21 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 135.9, 131.2, 126.1, 125.2, 123.9, 115.4, 110.8, 100.4, 100.0, 93.5, 18.8, 11.7;

IR v 3398 (m), 2940 (m), 2863 (m), 2148 (m), 1612 (w), 1561 (w), 1525 (w), 1462 (m), 1416 (m), 1336 (w), 1297 (m), 1240 (w), 1192 (m), 1143 (w), 1108 (w), 1076 (w), 1044 (w), 998 (w), 911 (m), 882 (m), 772 (s), 738 (s), 673 (s), 661 (s), 636 (m);

HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{27}^{79}\text{BrNSi}^+$ (M+H) 376.1096, found 376.1075.

6-Bromo-3-((triisopropylsilyl)ethynyl)-1H-indole (3k)

Purification by flash chromatography (PET/Et₂O 85/15) afforded **3k** (115 mg, 0.306 mmol, 77 %) as brown oil.

R_f 0.4 (PET/Et₂O 8/2, UV/Anisaldehyde);

^1H NMR (CDCl_3 , 400MHz) δ 8.16 (br s, 1 H; NH), 7.63 (d, $J(\text{H},\text{H}) = 8.4$ Hz, 1 H; ArH), 7.48 (d, $J(\text{H},\text{H}) = 1.5$ Hz, 1 H; ArH), 7.38 (d, $J(\text{H},\text{H}) = 2.6$ Hz, 1 H; ArH), 7.35 (dd, $J(\text{H},\text{H}) = 1.4, 8.4$ Hz, 1 H; ArH), 1.22 (s, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 135.7, 128.7, 127.7, 124.1, 121.2, 116.5, 114.3, 113.9, 99.4, 92.6, 18.7, 11.3;

IR v 3418 (m), 3123 (w), 2943 (s), 2874 (m), 2864 (s), 2152 (m), 1706 (w), 1614 (m), 1531 (w), 1452 (m), 1391 (m), 1318 (m), 1239 (m), 1136 (m), 1099 (m), 1069 (s), 996 (m), 920 (w), 895 (m), 883 (s), 848 (w), 803 (s), 775 (s), 728 (w), 670 (s);

HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{27}^{79}\text{BrNSi}^+$ (M+H) 376.1096, found 376.1111.

7-Bromo-3-((triisopropylsilyl)ethynyl)-1H-indole (3l)

Purification by flash chromatography (PET/Et₂O 97/3) afforded **3l** (125 mg, 0.332 mmol, 84 %) as colorless solid.

R_f 0.4 (PET/Et₂O 7/3, UV/Anisaldehyde);

Mp 57-59 °C;

^1H NMR (CDCl_3 , 400MHz) δ 8.35 (br s, 1 H; NH), 7.70 (d, $J(\text{H,H}) = 7.9$ Hz, 1 H; ArH), 7.50 (d, $J(\text{H,H}) = 2.6$ Hz, 1 H; ArH), 7.41 (m, 1 H; ArH), 7.11 (t, $J(\text{H,H}) = 7.7$ Hz, 1 H; ArH), 1.19 (s, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 133.9, 130.1, 128.6, 125.4, 121.9, 119.4, 104.8, 100.9, 99.5, 92.5, 18.8, 11.4;

IR ν 3401 (s), 3117 (w), 2942(s), 2864 (s), 2146 (m), 1564 (w), 1489 (w), 1430 (m), 1404 (m), 1382 (w), 1318 (m), 1238 (m), 1201 (m), 1139 (w), 1077 (m), 997 (m), 910 (w), 883 (s), 832 (s), 769 (s), 736 (s), 676 (s), 664 (s), 619 (m);

HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{27}^{79}\text{BrNSi}^+$ (M+H) 376.1096, found 376.1102.

2-Methyl-3-((triisopropylsilyl)ethynyl)-1H-indole (3m)

Purification by flash chromatography (PET/Et₂O 7/3) afforded **3m** (112 mg, 0.360 mmol, 90 %) as brown amorphous solid.

R_f 0.3 (PET/Et₂O 7:3, UV/Anisaldehyde);

^1H NMR (CDCl_3 , 400MHz) δ 7.75 (br s, 1 H; NH), 7.71 (m, 1 H; ArH), 7.28-7.17 (m, 3 H; ArH), 2.48 (s, 3 H; CH₃), 1.25 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 140.3, 134.5, 129.3, 122.1, 120.5, 119.2, 110.6, 100.7, 96.9, 93.2, 18.8, 12.6, 11.4;

IR ν 3462 (w), 3394 (m), 2943 (m), 2865 (m), 2251 (w), 2147 (m), 1461 (m), 1430 (w), 1307(m), 1243 (m), 1161 (w), 1072 (w), 1013 (m), 997 (m), 908 (s), 883 (m), 777 (m), 734 (s), 673 (m), 653 (m), 628 (m);

HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{30}\text{NSi}^+$ (M+H) 312.2148, found 312.2150.

2-Phenyl-3-((triisopropylsilyl)ethynyl)-1H-indole (3n)

Purification by flash chromatography (PET/Et₂O 85/15) afforded **3n** (132 mg, 0.353 mmol, 88 %) as slightly yellow amorphous solid.

R_f 0.4 (PET/Et₂O 8:2, UV/Anisaldehyde).

^1H NMR (CDCl_3 , 400MHz) δ 8.32 (br s, 1 H; NH), 8.11 (m, 2 H; ArH), 7.80 (m, 1 H; ArH), 7.49 (m, 2 H; ArH), 7.40 (m, 2 H; ArH), 7.27 (m, 2H; ArH), 1.24 (s, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 139.7, 135.1, 131.3, 130.8, 128.7, 128.3, 126.4, 123.4, 120.9, 120.1, 110.9, 101.2, 96.5, 95.1, 18.8, 11.5;

IR ν 3420 (w), 3060 (w), 2942 (m), 2874 (m), 2864 (m), 2141 (m), 1604 (w), 1489 (w), 1459(m), 1327(m), 1237(m), 1177(w), 998(m), 908(s), 883(m), 787(m), 768(m), 740(s), 691(s), 676(s), 660(s), 633(m);

HRMS(ESI) calcd for $\text{C}_{25}\text{H}_{32}\text{NSi}^+$ (M+H) 374.2304, found 374.2307.

(3-((Triisopropylsilyl)ethynyl)-1H-indol-2-yl)methanol (**3o**)

Purification by flash chromatography (PET/Et₂O 1/1) afforded **3o** (107 mg, 0.326 mmol, 82 %) as orange solid.

R_f 0.4 (PET/Et₂O 1/1, UV/Anisaldehyde);

Mp 93-94°C;

^1H NMR (CDCl_3 , 400MHz) δ 8.65 (br s, 1 H; NH), 7.71 (m, 1 H; ArH), 7.24 (m, 3 H; ArH), 4.94 (d, $J(\text{H,H}) = 2.6$ Hz, 2 H; CH₂), 2.71 (br s, 1 H; OH), 1.21 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 141.5, 135.0, 129.0, 123.2, 120.8, 119.4, 111.4, 99.4, 96.6, 94.6, 57.3, 18.8, 11.4;

IR ν 3538 (m), 3273 (m), 2940 (m), 2864 (m), 2147 (m), 1460 (m), 1390 (w), 1327 (m), 1246 (m), 1187 (w), 1001 (m), 968 (m), 910 (m), 883 (m), 782 (s), 736 (s), 677 (s), 659 (s), 628 (s);

HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{30}\text{NOSi}^+$ (M+H) 328.2097, found 328.2104.

3-Methyl-2-((triisopropylsilyl)ethynyl)-1H-indole (**3p**)

Purification by flash chromatography (PET/Et₂O 99/1) afforded **3p** (95 mg, 0.31 mmol, 76 %) as amorphous orange solid.

R_f 0.1 (PET/Et₂O 99/1, UV/Anisaldehyde);

Mp 75-77 °C;

^1H NMR (CDCl_3 , 400MHz) δ 7.98 (br s, 1 H; NH), 7.59 (d, $J(\text{H,H}) = 7.9$ Hz, 1 H; ArH), 7.28 (m, 2 H; ArH), 7.17 (m, 1 H; ArH), 2.47 (d, $J(\text{H,H}) = 0.5$ Hz, 3 H; Me), 1.23 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100MHz) δ 135.6, 127.8, 123.7, 119.8, 119.3, 118.9, 117.0, 110.7, 98.5, 97.4, 18.8, 11.4, 9.6;

IR ν 3478 (m), 3415 (m), 3059 (w), 2942 (m), 2865 (m), 2145 (m), 1455 (m), 1383 (w), 1362 (m), 1338 (m), 1243 (w), 1154 (w), 1115 (w), 1073 (w), 997 (m), 909 (w), 883 (m), 858 (w), 733 (s), 710 (m), 676 (s);

HRMS(ESI) calcd for $\text{C}_{20}\text{H}_{30}\text{NSi}^+$ (M+H) 312.2148, found 312.2160.

2-((Triisopropylsilyl)ethynyl)-1H-pyrrole (6a)

Following the general procedure: purification by flash chromatography (PET/ Et_2O 98/2) afforded **6a** (62 mg, 0.25 mmol, 62 %) as green oil.

Following general procedure but using **5a** (84 μL , 1.2 mmol, 3 equiv) and **1d** (171mg, 0.400 mmol, 1 equiv): purification by flash chromatography (PET/ Et_2O 98/2) afforded **6a** (82 mg, 0.33 mmol, 83 %) as green oil.

R_f 0.3 (PET/ EtOAc 98:2, UV/ KMnO_4);

^1H NMR (CDCl_3 , 400MHz) δ 8.36 (br s, 1H, NH), 6.19 (td, $J(\text{H,H}) = 2.7, 3.4$ Hz, 1H, ArH), 6.51 (ddd, $J(\text{H,H}) = 1.5, 2.4, 3.8$ Hz, 1H, ArH), 6.75 (dt, $J(\text{H,H}) = 1.4, 2.7$ Hz, 1H, ArH), 1.14-1.13 (m, 21H, TIPS).

^{13}C NMR (CDCl_3 , 400MHz) δ 119.1, 118.7, 115.3, 109.1, 99.0, 91.9, 18.7, 11.4;

IR ν 3478 (m), 3405 (m), 2943 (s), 2865 (s), 2364 (w), 2146 (s), 1716 (w), 1550 (w), 1463 (m), 1384 (w), 1254 (w), 1119 (m), 1119 (m), 1094 (m), 1034 (m), 997 (m), 962 (m), 911 (m), 883 (s), 804 (m), 755 (s), 728 (s), 676 (s), 658 (s);

HRMS(ESI) calcd for $\text{C}_{15}\text{H}_{26}\text{NSi}^+$ (M+H) 248.1835, found 248.1847.

1-Methyl-2-((triisopropylsilyl)ethynyl)-1H-pyrrole (6b), 1-Methyl-3-((triisopropylsilyl)ethynyl)-1H-pyrrole (7b)

Following the general procedure but using **5b** (107 μL , 1.20 mmol, 3 equiv) and **1d** (171 mg, 0.400 mmol, 1 equiv): purification by flash chromatography (PET) afforded **6b** (50 mg, 0.19 mmol, 48 %) as orange amorphous solid and **7b** (26 mg, 0.099 mmol, 25 %) as violet amorphous solid.

6b:

R_f 0.1 (PET, UV/KMnO₄);

¹H NMR (CDCl₃, 400MHz) δ 6.62 (dd, *J*(H,H)= 1.9, 2.6 Hz, 1 H; ArH), 6.44 (m, 1 H; ArH), 6.06 (m, 1 H; ArH), 3.69 (d, *J*(H,H)= 0.3 Hz, 3 H; CH₃), 1.14 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 125.5, 123.4, 115.0, 107.8, 98.4, 94.5, 34.6, 18.7, 11.4;

IR ν 3108 (w), 3108(s), 2943 (m), 2892 (s), 2865 (w), 2724 (w), 2363 (w), 2145 (s), 1716 (w), 1645 (w), 1572 (w), 1528 (w), 1463 (m), 1420 (w), 1383 (w), 1366 (w), 1310 (m), 1233 (m), 1177 (m), 1073 (w), 1053 (m), 1014 (m), 996 (m), 918 (m), 883 (s), 780 (s), 717 (s), 689 (s), 675 (s), 661 (s);

HRMS(ESI) calcd for C₁₆H₂₈NSi⁺ (M+H) 262.1991, found 262.1994.

7b:

R_f 0.4 (PET, UV/KMnO₄);

¹H NMR (CDCl₃, 400MHz) δ 6.83 (m, 1 H; ArH), 6.47 (t, *J*(H,H)= 2.2 Hz, 1 H; ArH), 6.24 (m, 1 H; ArH), 3.61 (s, 3 H; CH₃), 1.10 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 126.3, 121.5, 112.5, 104.8, 102.6, 87.5, 36.3, 18.7, 11.5;

IR ν 3127 (w), 2942 (s), 2892 (m), 2865 (s), 2722 (w), 2364 (w), 2342 (w), 2145 (m), 1716 (w), 1543 (w), 1509 (w), 1463 (m), 1422 (w), 1382 (w), 1364 (m), 1346 (m), 1231 (w), 1170 (w), 1075 (w), 982 (m), 918 (w), 883 (s), 779 (s), 764 (s), 700 (m), 668 (s), 641 (s);

HRMS(ESI) calcd for C₁₆H₂₈NSi⁺ (M+H) 262.1991, found 262.1990.

1-(Triisopropylsilyl)-3-((triisopropylsilyl)ethynyl)-1H-pyrrole (7c)

Purification by flash chromatography (PET/Et₂O 98/2) afforded **7c** (127 mg, 0.315 mmol, 79 %) as yellow oil.

R_f 0.5 (PET/Et₂O 99/1, UV/KMnO₄).

¹H NMR (CDCl₃, 400MHz) δ 7.01 (m, 1 H; ArH), 6.67 (t, *J*(H,H)= 2.6 Hz, 1 H; ArH), 6.43 (dd, *J*(H,H)= 1.0, 2.4 Hz, 1 H; ArH), 1.47 (m, 3 H; TIPS), 1.14 (m, 39 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 128.9, 123.9, 114.4, 106.9, 103.0, 88.1, 18.8, 17.8, 11.6, 11.5;

IR ν 2945 (m), 2866 (m), 2362 (w), 2151 (m), 1463 (m), 1385 (w), 1296 (m), 1222 (w), 1097 (s), 1074 (m), 1017 (m), 985 (m), 909 (s), 883 (s), 790 (m), 735 (s), 674 (s), 659 (s);

HRMS(ESI) calcd for C₂₄H₄₆NSi₂⁺ (M+H) 404.3169, found 404.3155.

2-Ethyl-5-((triisopropylsilyl)ethynyl)-1H-pyrrole (6d)

Purification by flash chromatography (PET → PET/CH₂Cl₂ 99/1) afforded **6d** (64 mg, 0.23 mmol, 58 %) as colorless oil. Turning then green without impurities appearing in NMR.

R_f 0.1 (PET/CH₂Cl₂ 99/1, UV/KMnO₄);

¹H NMR (CDCl₃, 400 MHz) δ 8.04 (br s, 1 H; NH), 6.40 (dd, *J*(H,H) = 2.9, 3.4 Hz, 1 H; ArH), 5.86 (m, 1 H; ArH), 2.62 (q, *J*(H,H) = 7.7 Hz, 2 H; CH₂), 1.25 (t, *J*(H,H) = 7.6 Hz, 3 H; CH₃), 1.12 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100 MHz) δ 135.9, 115.8, 111.7, 105.5, 99.5, 91.3, 21.0, 18.7, 13.5, 11.4;

IR ν 3472 (w), 3384 (w), 2943 (s), 2865 (s), 2141 (s), 1572 (w), 1463 (m), 1386 (w), 1330 (w), 995 (m), 882 (m), 761 (s), 676 (s), 657 (s);

HRMS(ESI) calcd for C₁₇H₃₀NSi⁺ (M+H) 276.2148, found 276.2158.

2-Phenyl-5-((triisopropylsilyl)ethynyl)-1H-pyrrole (6e)

Purification by flash chromatography (PET/DCM 95/5) afforded **6e** (79 mg, 0.24 mmol, 60 %) as pink amorphous solid.

R_f 0.2 (PET/Et₂O 5/95, UV/KMnO₄);

¹H NMR (CDCl₃, 400 MHz) δ 8.54 (br s, 1 H; NH), 7.52 (m, 2 H; PhH), 7.41 (m, 2 H; PhH), 7.28 (m, 1 H; PhH), 6.60 (dd, *J*(H,H) = 2.2, 3.4 Hz, 1 H; PyrH), 6.50 (dd, *J*(H,H) = 2.7, 3.6 Hz, 1 H; PyrH), 1.19 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100 MHz) δ 133.1, 131.9, 129.0, 126.9, 124.2, 117.3, 114.3, 106.8, 99.0, 93.1, 18.8, 11.4;

IR ν 3471 (w), 3424 (w), 2942 (m), 2864 (m), 2142 (m), 1604 (w), 1505 (m), 1461 (m), 1383 (w), 1305 (w), 1243 (w), 1073 (w), 1044 (w), 996 (m), 892 (w), 882 (m), 781 (m), 755 (s), 677(s);

HRMS(ESI) calcd for C₂₁H₃₀NSi⁺ (M+H) 324.2148, found 324.2139.

1-(5-((Triisopropylsilyl)ethynyl)-1H-pyrrol-3-yl)ethanone (6f)

Purification by flash chromatography (PET/Et₂O 7/3) afforded **6f** (67 mg, 0.23 mmol, 58 %) as tan solid.

R_f 0.3 (PET/Et₂O 7/3, UV/KMnO₄);

Mp 120-122 °C;

¹H NMR (CDCl₃, 400MHz) δ 9.52 (br s, 1 H; NH), 7.37 (dd, *J*(H,H) = 1.2, 2.6 Hz, ArH), 6.87 (m, 1H; ArH), 2.44 (s, 3 H; Ac), 1.10 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 193.7, 126.2, 124.1, 115.3, 115.1, 97.4, 93.4, 27.3, 18.6, 11.3;

IR ν 3554 (m), 3223 (m), 2866 (m), 2151 (m), 1645 (s), 1562 (w), 1496 (m), 1464 (m), 1394 (m), 1342 (m), 1247 (w), 1204 (m), 1149 (w), 1077 (w), 998 (w), 935 (m), 884 (m), 832 (m), 767 (m), 738 (m), 660 (m);

HRMS(ESI) calcd for C₁₇H₂₈ONSi⁺ (M+H) 290.1940, found 290.1938.

2,5-Dimethyl-3-((triisopropylsilyl)ethynyl)-1H-pyrrole (7g)

Purification by flash chromatography (PET/Et₂O 85/15) afforded **7g** (65 mg, 0.24 mmol, 59 %) as yellow oil.

R_f 0.3 (PET/Et₂O 85:15, UV/KMnO₄);

¹H NMR (CDCl₃, 400MHz) δ 7.58 (br s, 1 H; NH), 5.90 (d, *J*(H,H) = 1.7 Hz, 1 H; ArH), 2.32 (s, 3 H; Me), 2.20 (s, 3 H; Me), 1.14 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 132.3, 125.5, 108.8, 103.1, 102.3, 89.1, 18.8, 12.8, 12.0, 11.5;

IR ν 3374 (m), 2942 (s), 2865 (s), 2146 (s), 1594 (w), 1463 (m), 1384 (w), 1371 (w), 1307 (m), 1244 (w), 1157 (w), 1127 (w), 1074 (w), 996 (m), 919 (w), 882 (s), 812 (s), 788 (s), 702 (s), 675 (s), 658 (s);

HRMS(ESI) calcd for C₁₇H₃₀NSi⁺ (M+H) 276.2148 found 276.2150.

3-Ethyl-2,4-dimethyl-5-((triisopropylsilyl)ethynyl)-1H-pyrrole (6h)

Purification by flash chromatography (PET/DCM 99/1) afforded **6h** (58 mg, 0.19 mmol, 48 %) as yellow oil.

R_f 0.25 (PET/ CH₂Cl₂ 99/1, UV/KMnO₄);

¹H NMR (CDCl₃, 400MHz) δ 7.74 (br s, 1 H; NH), 2.40 (q, *J*(H,H) = 7.6 Hz, 2 H; CH₂), 2.19 (s, 3 H; Me), 2.14 (s, 3 H; Me), 1.15 (m, 21 H; TIPS), 1.08 (t, *J*(H,H) = 7.7 Hz, 3 H; CH₂CH₃);

^{13}C NMR (CDCl_3 , 100MHz) δ 125.5, 124.7, 121.4, 108.9, 99.4, 93.6, 18.8, 17.6, 15.4, 11.4, 11.2, 10.0;

IR ν 3478 (w), 3398 (w), 2960 (s), 2942 (s), 2865 (s), 2133 (s), 1587 (w), 1462 (m), 1382 (w), 1329 (w), 1309 (w), 1243 (w), 1138 (w), 1066 (w), 1016 (w), 996 (m), 916 (m), 883 (s), 851 (m), 775 (w), 724 (m), 703 (m), 674 (s), 658(s);

HRMS(ESI) calcd for $\text{C}_{19}\text{H}_{34}\text{NSi}^+$ (M+H) 304.2461, found 304.2453.

Deprotection procedure:

3-Ethynyl-1H-indole (14)

Tetrabutylammonium fluoride (1 M in THF, 0.80 mL, 0.80 mmol, 2.0 equiv) was added to a stirring solution of **3a** (119 mg, 0.400 mmol, 1 equiv) in THF (5 mL). The reaction was stirred at room temperature for 15 h. The reaction was quenched with a saturated solution of NH_4Cl (10 mL) and extracted twice with Et_2O (15 mL). The organic layers were combined, washed with saturated NaHCO_3 (20 mL), brine (20 mL), dried with MgSO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexane/ Et_2O 7/3) to afford **14** (53 mg, 0.38 mmol, 94%) as a tan solid.

R_f 0.25 (hexane/ Et_2O 7/3, UV/ KMnO_4);

Mp 109-111°C;

^1H NMR (CDCl_3 , 400MHz) δ 8.16 (br s, 1 H; NH), 7.82 (d, $J(\text{H},\text{H})$ = 7.4 Hz, 1 H; ArH), 7.45 (d, $J(\text{H},\text{H})$ = 1.7 Hz, 1 H; ArH), 7.39 (m, 1 H; ArH), 7.28 (m, 2 H; ArH), 3.28 (s, 1 H; acetylene);

^{13}C NMR (CDCl_3 , 100MHz) δ 134.9, 128.8, 128.5, 123.2, 120.9, 119.9, 111.4, 97.5, 78.8, 77.4;

^{13}C DEPT 135 NMR (CDCl_3 , 100MHz) δ : 128.9, 123.3, 120.9, 119.9, 111.5, 78.9, 77.5;

IR ν : 3407(s), 3266 (s), 3125 (w), 3052 (w), 2926 (w), 2852 (w), 2106 (w), 1653 (w), 1618 (w), 1526 (w), 1458 (m), 1421 (m), 1362 (w), 1342 (w), 1325 (w), 1242 (m), 1126 (w), 1104 (w), 1091 (w), 1061 (w), 1005 (w), 912 (w), 829 (w), 767 (w), 756 (w), 744 (m), 714 (m), 685 (w), 676 (w), 649 (w), 635 (m);

HRMS(ESI) calcd for $\text{C}_{10}\text{H}_8\text{N}^+$ (M+H) 142.0657, found 142.0674.

The data are consistent with reported data^[7] excepted the ^{13}C peak reported at 122.5 ppm by authors which has not been observed in our case. In contrast the peak at 77.4 ppm was not reported maybe due to the proximity of CDCl_3 signal. DEPT 135 confirmed the presence of this signal, which can be attributed to one of the acetylene carbons.

DEPT experiments (see spectra) was not conclusive to differentiate definitively the two acetylene carbons at 78.8 and 77.4 ppm, as even the quaternary carbon displayed a significant signal in all DEPT

[7] D. W. M. Benzie, P. M. Fresneda, R. A. Jones, H. McNab, *J. Chem. Soc. Perkin Trans. 1* **1986**, 1651.

experiments. To confirm further the assignment, **14** was deprotonated with *n*BuLi in THF and the resulting organolithium was quenched with D₂O. The obtained C-D coupling was much larger at 78.8 ppm (38.2 Hz vs 7.7 Hz), confirming definitively this carbon to be the terminal one.

¹H NMR (CDCl₃, 400MHz) δ 8.15 (br s, 1 H; NH), 7.84 (d, *J*(H,H)= 6.9 Hz, 1 H; ArH), 7.41 (d, *J*(H,H)= 2.4 Hz, 1 H; ArH), 7.37 (m, 1 H; ArH), 7.30 (m, 2 H; ArH);

¹³C NMR (CDCl₃, 100MHz) δ: 135.1, 129.0, 128.6, 123.3, 120.9, 119.9, 111.6, 97.5, 78.8 (t, *J*¹(C,D)= 38.2 Hz, C≡CD), 77.2 (t, *J*²(C,D)= 7.7 Hz, C≡CD).

4. Mechanistic Investigations

Preparation and reaction of ¹³C-labeled reagent **1d'**

2-(4-Methoxybenzyloxy)ethanol (**17**)

Following a reported procedure,^[8] sodium hydride (60% in mineral oil, 0.70 g, 17 mmol, 1.0 equiv) was added to a solution of ethylene glycol (**15**) (freshly distilled from drierite (p = 0.3 mbar, T = 46 °C), 2.8 mL, 50 mmol, 3.0 equiv) in THF (30 mL). After stirring 30 min at RT, 4-methoxybenzyl chloride (**16**) (2.60 g, 16.6 mmol, 1.00 equiv) and Bu₄NI (0.61 g, 1.7 mmol, 0.10 equiv) were added, and the reaction mixture was heated to reflux. After 4.5 h, the reaction mixture was cooled to RT, the reaction was quenched with sat. NH₄Cl (30 mL) and extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 5/1-1/1) to yield protected alcohol **17** (2.54 g, 13.9 mmol, 84%) as a yellow oil.

R_f (PET/AcOEt 1/1, KMnO₄) 0.25;

¹H NMR (CDCl₃, 400 MHz) δ 7.27 (dm, *J*(H,H)= 8.2 Hz, 2 H; ArH), 6.89 (dm, *J*(H,H)= 8.6 Hz, 2 H; ArH), 4.49 (s, 2 H; benzyl CH₂), 3.81 (s, 3 H; OCH₃), 3.74 (t, *J*(H,H)= 4.3 Hz, 2 H; CH₂OPMB), 3.57 (m, 2 H; CH₂OH), 2.08 (br s, 1 H; OH).

¹H NMR corresponded to the literature values.^[8]

2-(4-Methoxybenzyloxy)acetaldehyde (**20**)

Following a reported procedure,^[9] Dess-Martin Periodinane (**19**) (0.53 g, 1.3 mmol, 1.1 equiv) was added to a solution of alcohol **18** (0.21 g, 1.2 mmol, 1.0 equiv) in wet CH₂Cl₂ (9 mL). After stirring 2.5 h at RT, the reaction was quenched with sat. NaHCO₃ (10 mL) and sat. sodium thiosulfate solution (10 mL) and the mixture was stirred vigorously for 10 min until two clear layers were obtained. The layers were separated and the water layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure to give aldehyde **20** (0.21 g, 1.2 mmol, quant.) as a yellow oil, which was used immediately in the next step without further purification.

R_f (PET/AcOEt 1/1, KMnO₄) 0.35;

¹H NMR (CDCl₃, 400 MHz) δ 9.71 (t, *J*(H,H)= 0.9 Hz, CHO), 7.29 (dm, *J*(H,H)= 8.8 Hz, 2 H; ArH), 6.90 (dm, *J*(H,H)= 8.8 Hz, 2 H; ArH), 4.57 (s, 2 H; benzyl CH₂), 4.07 (d, *J*(H,H)= 0.9 Hz, 2 H; CH₂CHO), 3.81 (s, 3 H; OCH₃).

¹H NMR corresponded to the literature values.^[9]

Labeled 1-((3,3-dibromoallyloxy)methyl)-4-methoxybenzene (23) and triisopropyl(3-(4-methoxybenzyloxy)prop-1-ynyl)silane (24)

Following a slightly modified literature procedure,^[10] a solution of PPh₃ (**22**) (1.6 g, 6.0 mmol, 2.0 equiv) in CH₂Cl₂ (9 mL) was added to a solution of CBr₄ (**21**) (1.0 g, 3.0 mmol, 1.0 equiv, 20% ¹³C, prepared from 0.80 g natural CBr₄ and 0.20 g 99% ¹³C-enriched CBr₄) in CH₂Cl₂ (12 mL) at 0 °C over 15 min. After stirring for 15 min at 0 °C, the yellow-orange solution was cooled to −78 °C and a solution of aldehyde **20** (freshly synthesized, 0.66 g, 3.6 mmol, 1.2 equiv) in CH₂Cl₂ (9 mL) was added over 10 min, whereas the reaction mixture turned dark red-brown. The reaction mixture was left to warm to RT over 17 h, quenched with sat. NaHCO₃ (30 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/CH₂Cl₂ 3/1-1.5/1) to yield dibromide **23** (501 g, 1.55 mmol, 52%) as a slightly yellow oil, which was used directly in the next step.

R_f (PET/ CH₂Cl₂ 2/1, KMnO₄) 0.30;

¹H NMR (CDCl₃, 400 MHz) δ 7.28 (dm, *J*(H,H)=8.6 Hz, 2 H; ArH), 6.90 (dm, *J*(H,H)= 8.6 Hz, 2 H; ArH), 6.64 (tm, *J*(H,H)= 6.1 Hz, 1 H; alkene H), 4.46 (s, 2 H; benzyl CH₂), 4.04 (m, 2 H; alkene CH₂), 3.81 (s, 3 H; OCH₃);

[9] I. Collins, J. Caldwell, T. Fonseca, A. Donald, V. Bavetsias, L. J. K. Hunter, M. D. Garrett, M. G. Rowlands, G. W. Aherne, T. G. Davies, V. Berdini, S. J. Woodhead, D. Davis, L. C. A. Seavers, P. G. Wyatt, P. Workman, E. McDonald, *Bioorg. Med. Chem.* **2006**, *14*, 1255.

[10] L. A. Paquette, J. Y. Chang, Z. S. Liu, *J. Org. Chem.* **2004**, *69*, 6441.

^{13}C NMR (CDCl_3 , 100 MHz) δ 159.3, 135.6, 129.5, 129.4, 113.8, 91.3 (labeled 20x more intensive), 72.2, 69.4, 55.2;

Following a literature procedure,^[11] $n\text{BuLi}$ (2.5 M in hexane, 1.4 mL, 3.4 mmol, 2.2 equiv) was added dropwise to a solution of dibromide **23** (0.50 g, 1.5 mmol, 1.0 equiv) in THF (9 mL) at -78°C . The yellow solution was stirred 1 h at -78°C and 1 h at RT. After cooling to -78°C , TIPSCl (0.43 mL, 2.0 mmol, 1.3 equiv) was added and the reaction was left to warm to RT over 12 h. The reaction was quenched with sat. NaHCO_3 (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/ CH_2Cl_2 4/1-2/1) to yield alkyne **24** (372 g, 1.12 mmol, 72%) as a colorless oil. Comparison of the ^{13}C NMR with an unlabeled sample (synthesized following the same procedure) showed 20% ^{13}C incorporation at the indicated position only.

R_f (PET/ CH_2Cl_2 2/1, KMnO_4) 0.35;

^1H NMR (CDCl_3 , 400 MHz) δ 7.30 (dm, $J(\text{H},\text{H}) = 8.4$ Hz, 2 H; ArH), 6.89 (dm, $J(\text{H},\text{H}) = 8.6$ Hz, 2 H; ArH), 4.59 (s, 2 H; benzyl CH_2), 4.19 (s, 2 H; alkyne CH_2), 3.81 (s, 3 H; OCH_3), 1.12 (m, 21 H; TIPS);

^{13}C NMR (CDCl_3 , 100 MHz) δ 159.3, 129.8, 129.5, 113.8, 103.4, 87.7 (labeled 20x more intensive), 70.6, 57.4, 55.2, 18.6, 11.1;

IR ν 2961 (w), 2944 (w), 2931 (w), 2866 (w), 2171 (w), 1663 (w), 1614 (w), 1515 (w), 1463 (w), 1444 (w), 1378 (w), 1250 (w), 1078 (m), 1036 (w), 907 (s), 730 (s), 651 (m);

HRMS(ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3^+$ ($\text{M}+\text{H}$) 333.2250, found 333.2254.

Isotope repartition: expected for about 20% incorporation was obtained.

Labeled triisopropyl acetylene (**12'**)

Following a literature procedure,^[12] DDQ (0.38 g, 1.7 mmol, 1.5 equiv) was added to a solution of protected alcohol **24** (372 mg, 1.12 mmol, 1.00 equiv) in CH_2Cl_2 (11 mL) and water (1.1 mL) at 0°C . The reaction mixture was stirred 15 min at 0°C and 3 h at RT. The resulting dark red thick suspension was quenched with sat. NaHCO_3 (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with sat. NaHCO_3 (20 mL) and brine (20 mL), dried over MgSO_4 and the solvent was removed under reduced pressure. TLC (PET/ AcOEt 6/1, KMnO_4) showed a mixture of two products, which were shown to be the corresponding propargylic alcohol ($R_f = 0.50$) and anisaldehyde ($R_f = 0.45$) by ^1H NMR. This mixture was directly used as such in the next step.

Following a literature procedure,^[13] the obtained mixture was diluted in Et_2O (14 mL) and MnO_2 (Aldrich activated, 1.2 g, 13 mmol, 12 equiv) and KOH (freshly grounded, 0.38 g, 6.8 mmol, 6.0 equiv) were added in 4 portions every hour. After stirring for further 3 h, TLC (PET/ AcOEt 6/1, KMnO_4) showed

[11] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, 3769.

[12] P. Dimopoulos, A. Athlan, S. Manaviazar, J. George, M. Walters, L. Lazarides, A. E. Aliev, K. J. Hale, *Org. Lett.* **2005**, 7, 5369.

[13] H. Kukula, S. Veit, A. Godt, *Eur. J. Org. Chem.* **1999**, 277.

complete conversion and the reaction mixture was filtered over SiO₂ and the filter cake was washed with Et₂O (50 mL). The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (PET) to yield alkyne **12'** (167 mg, 0.915 mmol, 82%) as a colorless oil. Comparison of the ¹³C NMR with an unlabeled sample (synthesized following the same procedure) showed 20% ¹³C incorporation at the indicated position only.

R_f (PET, KMnO₄) 0.80;

¹H NMR (CD₂Cl₂, 400 MHz) δ 2.38 (s, 1 H; alkyne H), 1.07 (m, 21 H; TIPS);

¹³C NMR (CD₂Cl₂, 100 MHz) δ 94.9, 86.2 (labeled 20x more intensive), 18.3, 11.1.

Labeled tri*iso*-propyl((trimethylsilyl)ethynyl)silane (**11'**)

*n*BuLi (2.5 M in hexane, 0.44 mL, 1.1 mmol, 1.2 equiv) was added to a solution of acetylene **12'** (167 mg, 0.915 mmol, 1.00 equiv) in THF (2 mL) at −78 °C. The reaction mixture was stirred 15 min at 0 °C and the yellow solution was cooled back to −78 °C. TMSCl (freshly distilled, 0.15 mL, 1.2 mmol, 1.3 equiv) was added and the colorless solution was left to warm to RT over 6 h. The reaction was quenched with sat. NH₄Cl (3 mL) and extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (PET) to yield protected alkyne **11'** (184 g, 0.722 mmol, 79%) as a colorless oil. Comparison of the ¹³C NMR with an unlabeled sample showed 20% ¹³C incorporation at the indicated position only.

R_f (PET, KMnO₄) 0.80;

¹H NMR (CDCl₃, 400 MHz) δ 1.07 (m, 21 H; TIPS), 0.17 (s, 9 H; TMS);

¹³C NMR (CDCl₃, 100 MHz) δ 116.2, 110.1 (labeled 20x more intensive), 18.6, 11.1, 0.0;

IR ν 2959 (m), 2944 (m), 2896 (w), 2867 (m), 1464 (w), 1385 (w), 1250 (m), 996 (w), 842 (s), 764 (s), 675 (m), 660 (m).

¹H NMR corresponded to the literature values.^[4]

Labeled 1-[(tri*iso*--propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (**1d'**)

Following a slightly modified literature procedure,³ TMSOTf (freshly distilled, 0.15 mL, 0.82 mmol, 1.1 equiv) was added to a suspension of iodine **9** (freshly synthesized, 0.19 g, 0.72 mmol, 1.0 equiv) in CH₃CN (6.5 mL). After 10 min, a solution of acetylene **11'** (0.18 g, 0.72 mmol, 1.0 equiv) in CH₂Cl₂ (1.0

mL) was added to the slightly yellow solution. After stirring 15 min at RT, pyridine (70 μ L, 0.87 mmol, 1.2 equiv) was added and the solvent was removed under reduced pressure below 30 °C. The reaction mixture was diluted with CH₂Cl₂ (15 mL) and washed with 1 M HCl (5 mL). The water layer was extracted with CH₂Cl₂ (2 x 5 mL) and the combined organic layers were washed with sat. Na₂CO₃ (2 x 10 mL). The combined basic aqueous layers were extracted with CH₂Cl₂ (10 mL) and the combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure to give iodine **1d'** (>95% pure by ¹H NMR, containing traces of acetylene **11'**, 259 mg, 0.604 mmol, 84%) as a slightly yellow solid. Comparison of the ¹³C NMR with an unlabeled sample showed 20% ¹³C incorporation at the indicated position only.

¹H NMR (CDCl₃, 400 MHz) δ 8.40 (m, 1 H; Ar H), 8.28 (m, 1 H; Ar H), 7.74 (m, 2 H; Ar H), 1.13 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100 MHz) δ 166.3, 134.6, 132.4, 131.5, 131.4, 126.0, 115.6, 114.1 (labeled 20x more intensive), 64.7, 18.4, 11.1.

Labeled 3-((Triisopropylsilyl)ethynyl)-1H-indole (3a')

Following the general procedure on a 0.20 mmol scale using **1d'** (103 mg, 0.240 mmol, 10% ¹³C, prepared from 51.5 mg 20 % labeled 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one and 51.5 mg natural **1d**). Purification by flash chromatography (PET/Et₂O 8/2) afforded **3a'** (51 mg, 0.17 mmol, 86%) as a brown solid.

R_f 0.4 (PET/Et₂O 7/3, UV/Anisaldehyde);

¹H NMR (CDCl₃, 400MHz) δ 8.11 (br s, 1 H; NH), 7.79 (m, 1 H; ArH), 7.41 (d, *J*(H,H) = 2.6 Hz, 1 H; ArH), 7.36 (m, 1 H; ArH), 7.26 (m, 2H; ArH), 1.22 (m, 21 H; TIPS);

¹³C NMR (CDCl₃, 100MHz) δ 135.1, 128.9, 128.2, 123.1, 120.8, 120.1, 111.4, 100.3, 99.2, 92.9 (labeled 10x more intensive), 18.8, 11.5;

Comparison of the ¹³C NMR with an unlabeled sample showed 10% ¹³C incorporation at the indicated position only.

Labeled 3-Ethynyl-1H-indole 14'

Tetrabutylammonium fluoride (1 M in THF, 0.34 mL, 0.34 mmol, 2.0 equiv) was added to a stirring solution of **3b'** (50 mg, 0.17 mmol, 1 equiv) in THF (2.5 mL). The reaction was stirred at room temperature for 15 h. The reaction was quenched with a saturated solution of NH₄Cl (5 mL) and extracted twice with Et₂O (10 mL). The organic layers were combined, washed with saturated NaHCO₃ (10 mL), brine (10 mL), dried with MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (PET/Et₂O 9/1 to 9/2) to afford **14** (17 mg, 0.12 mmol, 71%) as a tan solid.

R_f 0.2 (PET/Et₂O 9/1, UV/KMnO₄);

¹H NMR (CDCl₃, 400MHz) δ: 8.19 (br s, 1 H; NH), 7.80 (dd, *J*(H,H) = 0.5, 7.4 Hz, 1 H; ArH), 7.47 (dd, *J*(H,H) = 1.0, 2.4 Hz, ArH), 7.40 (m, 1 H; ArH), 7.27 (m, 2 H; ArH), 3.26 (d, *J*(H,H) = 0.7 Hz, 1 H; acetylene H);

¹³C NMR (CDCl₃, 100MHz) δ: 135.0, 128.8, 128.5, 123.2, 120.9, 120.0, 111.4, 97.7, 78.9 (labeled 10x more intensive), 77.5;

Comparison of the ¹³C NMR with an unlabeled sample showed 10% ¹³C incorporation at the indicated position only.

5. Spectra of New Compounds

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Frequency: 400.13MHz

solvent: <CDCl3>
Frequency: 100.61MHz

solvent: <CDCl3>
Frequency: 400.13MHz

solvent: <CDCl3>
Frequency: 100.61MHz

solvent: <MeOD>
Frequency: 400.13 MHz

solvent: <MeOD>
Frequency: 100.61 MHz

solvent: <CDCl₃>
Frequency: 400.13 MHz

solvent: <CDCl₃>
Frequency: 100.61 MHz

solvent: <CDCl3>
Frequency: 400.13MHz

solvent: <CDCl3>
Frequency: 100.61MHz

solvent: <CDCl3>
Frequency: 400.13 MHz

solvent: <CDCl3>
Frequency: 100.61 MHz

solvent: <CDCl₃>
Frequency: 400.13MHz

solvent: <CDCl₃>
Frequency: 100.61MHz

solvent: <CDCl3>
Frequency: 400.13MHz

solvent: <CDCl3>
Frequency: 100.61MHz

solvent: <CDCl₃>
Frequency: 400.13 MHz

solvent: <CDCl₃>
Frequency: 100.61 MHz

solvent: <CDCl3>
Frequency: 400.13MHz

solvent: <CDCl3>
Frequency: 100.61MHz

solvent: <CDCl3>
Frequency: 400.13MHz

solvent: <CDCl3>
Frequency: 100.61MHz

solvent: CDCl₃
Frequency: 400.13 MHz

solvent: <CDCl₃>
Frequency: 100.61 MHz

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Frequency: 400.13MHz

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Frequency: 100.61MHz

solvent: <CDCl3>
Frequency: 100.61MHz
DEPT 135

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Frequency: 400.13 MHz

solvent: <CDCl3>
Frequency: 100.61 MHz

solvent: <CDCl₃>
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solvent: <CDCl₃>
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solvent: <CDCl₃>
Frequency: 100.61MHz

solvent: <CDCl3>
Frequency: 400.13MHz

1d'

solvent: <CDCl3>
Frequency: 100.612769MHz

1d'

solvent: <CDCl3>
Frequency: 100.61MHz

1d

solvent: <CDCl3>
Frequency: 400.13MHz

solvent: <CDCl3>
Frequency: 100.61MHz

solvent: <CDCl3>
Frequency: 100.61MHz