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Gold-Catalyzed Tandem Cycloisomerization/Functionalization of in Situ Generated α-Oxo Gold Carbenes in Water

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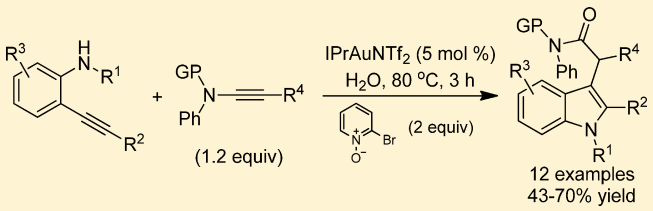
Supporting Information

ABSTRACT: A gold-catalyzed tandem cycloisomerization/functionalization of in situ generated α-oxo gold carbenes in water has been developed, which provides ready access to highly functionalized indole derivatives from *o*-alkynyl anilines and ynamides. Importantly, gold serves dual catalytic roles to mediate both the cycloisomerization of *o*-alkynyl anilines and the intermolecular oxidation of ynamides at the same time, thus providing a new type of concurrent tandem catalysis. The use of readily available starting materials, a simple procedure, and mild reaction conditions are other notable features of this method.



INTRODUCTION

Concurrent tandem catalysis (CTC),[1] which involves the cooperative action of two or more catalytic cycles in a single flask without purification between steps, has proven to be a powerful and widely used protocol strategy in chemical synthesis.[2] Generally, it can be divided into four types: (1) catalyst **I** transforms substrate **A** to give an intermediate **B**, which reacts with reagent(s) **C** to give product **P** by the same catalyst **I**; (2) similar to type **I** but catalyzed by a second catalyst **II** in the cycle **II**; (3) catalyst **I** transforms substrate **A** to give an intermediate **B**, which reacts again with substrate **A** to yield product **P** by the same catalyst **I**; (4) the products from two individual cycles are fed into a third independent cycle to produce the desired **P** (Figure 1). Despite the significant development in the past decades, CTC still remains a very challenging task as the catalyst must be compatible with residual materials such as substrates, intermediates, and other catalysts and must also exhibit reaction sequence selectivity.

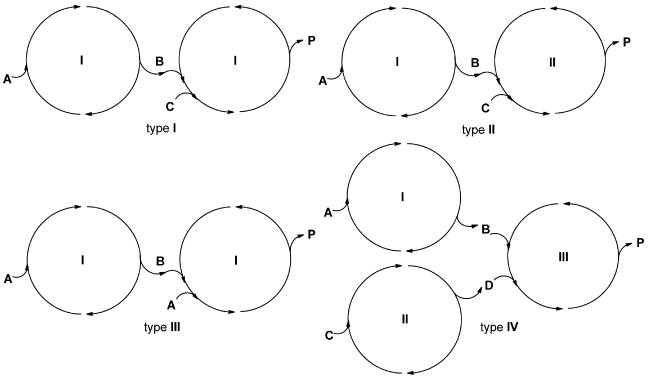


Figure 1. Types of concurrent tandem catalysis (CTC).

Significant progress in the gold-catalyzed intermolecular alkyne oxidation to make alkynes as equivalents of α-diazo ketones has been achieved in recent years, and an array of useful synthetic methods have been developed based on this strategy.[3,4] Very recently, we have developed the first example of generation of gold carbenes through intermolecular oxidation of ynamides in aqueous media.[5] Compared to traditional metal carbenoids, which were formed from metal-catalyzed decomposition of diazo compounds and normally in organic solvents, this carbenoid species is generated via gold-catalyzed intermolecular alkyne oxidation and its relevant reactions can be conducted in aqueous media, thereby making this nondiazo protocol very practical and environmentally friendly. More importantly, it was revealed for the first time that water could dramatically suppress the undesired overoxidation,[6] which might serve as a general solution to the problem of overoxidation in oxidative gold catalysis. By utilizing this approach, we have realized the first example of intermolecular C−H functionalization of indoles by α-oxo gold carbenes[7] generated via oxidation of ynamides.[8] In addition, this chemistry has also been successfully extended to a 2-substituted indole substrate, leading to the formation of the corresponding product in 76% yield (eq 1, Scheme 1).

Recently, gold-catalyzed cyclization of *o*-alkynyl anilines to construct indoles has also regained considerable attention (eq 2, Scheme 1).[9] Inspired by these results, we envisaged that this gold-catalyzed cycloisomerization reaction might be realized in water, and thus, the above-mentioned intermolecular C−H

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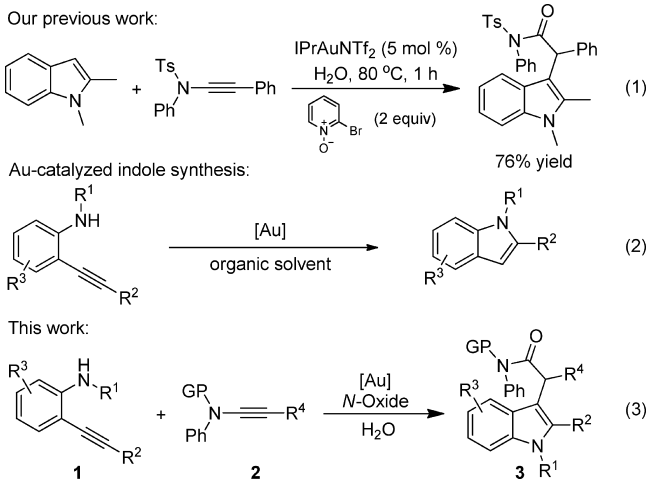
Scheme 1. Initial Reaction Design



functionalization of indoles by α-oxo gold carbenes would be achieved through a tandem one-pot strategy or concurrent tandem catalysis directly from the readily available *o*-alkynyl anilines (eq 3, Scheme 1). In this context, we describe herein the synthesis of highly functionalized indole derivatives in water by such a successful combination of the indole formation with its carbene functionalization. Significantly, the gold catalyst serves two distinct functions at the same time in such a tandem sequence, providing a new type of concurrent tandem catalysis.

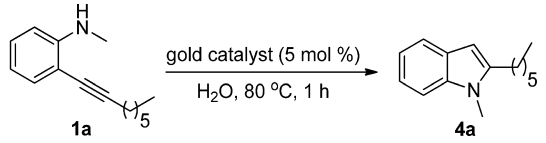
RESULTS AND DISCUSSION

Recently, the use of water as a medium for organic synthesis has garnered considerable attention with respect to environmental concerns, safety, and cost.[10] Although the development of various transition-metal-catalyzed reactions using water as a solvent is now extensively investigated, the gold-catalyzed reactions performed in aqueous medium remain limited.[11] A likely reason for this paucity is that the substrates may undergo the competitive hydration reaction when gold-catalyzed transformations of alkynes are carried out in water.[12] While the gold-catalyzed cyclization of *o*-alkynyl anilines for the synthesis of indoles has been well established,[9] to our best knowledge, such a reaction using water as a solvent remains unexploited. Therefore, we first investigated the gold-catalyzed 5-*endo*-*dig* cycloisomerization reaction in water. We set out to synthesize the *o*-alkynyl aniline **1a** as the model substrate to examine this gold-catalyzed cycloisomerization. As shown in Table 1, we were delighted to find that such a cycloisomerization could work well in water with various typical gold catalysts (Table 1, entries 1−6). In the presence of 5 mol % $IPrAuNTf_2$, which was the optimal gold catalyst for the next C−H functionalization step,[5] the reaction could afford the desired indole **4a** in 85% ^1H NMR yield (Table 1, entry 6). Notably, this result is even slightly better than the reaction in DCE (Table 1, entry 6 vs entry 7).

Inspired by the above results, we then sought to combine the gold-catalyzed cycloisomerization together with the gold-catalyzed alkyne oxidation, hoping to develop a two-step, one-pot strategy[13] to achieve the versatile functionalized indole **3a** (eq 4).

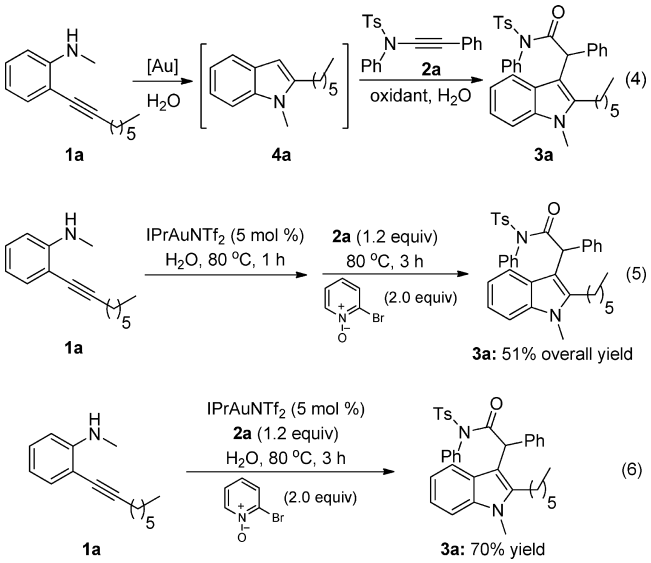
As shown in eq 5, treatment of *o*-alkynyl aniline **1a** with 5 mol % $IPrAuNTf_2$ in water at 80 °C for 1 h, followed by reacting with ynamide **2a** and 2-bromopyridine *N*-oxide for another 3 h in a one-pot process, led to the formation of the

Table 1. Formation of Indole 4a through Gold-Catalyzed Cycloisomerization Reaction in Water: Optimization of Reaction Conditions[a]



entry	gold catalyst	yield (%)[b]
1	$Ph_3PAuNTf_2$	80
2	$Et_3PAuNTf_2$	84
3	Cy-JohnPhosAuNTf$_2$	87
4	BrettPhosAuNTf$_2$	85
5	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	83
6	$IPrAuNTf_2$	85[c]
7[d]	$IPrAuNTf_2$	82

[a]Reaction conditions: [**1a**] = 0.10 M. [b]Estimated by ^1H NMR using diethyl phthalate as internal reference. [c]Yield of isolated **4a** was 83%. [d]In DCE.



functionalized indole **3a** in 51% two-step overall yield. Surprisingly, further studies showed that the reaction could offer a significant improvement through a direct tandem gold-catalyzed cycloisomerization/C−H functionalization (eq 5). Most importantly, in this case, the *N*-oxide can selectively attack the gold-activated alkyne of ynamide **2a**, but not the alkyne of **1a**.

Under the above optimized reaction conditions, various substituted *o*-alkynyl anilines **1** were reacted with different ynamides **2** to probe the generality of the reaction. The results are summarized in Table 2. Moderate to good yields (43−70%) of the corresponding highly functionalized indoles **3a**−**3l** were obtained. Importantly, by utilization of this tandem strategy, a range of functional groups could be readily introduced, including a remote chloro (Table 2, entry 2), azido (Table 2, entry 3), protected amino (Table 2, entry 4), and even the acid-sensitive protected hydroxy (Table 2, entries 5−6). Notably, these intermolecular oxidations of alkynes were highly regioselective as the 1,2-insertion product anticipated from intermolecular oxidation of *o*-alkynyl anilines **1** was not detected in each case,[14] highlighting the power of this tandem sequence.

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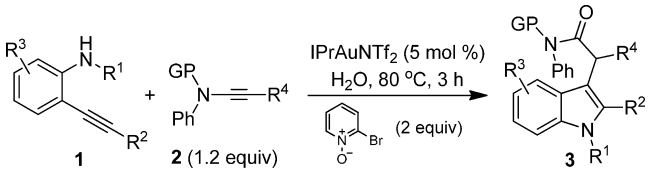
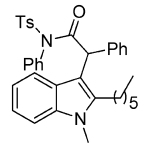
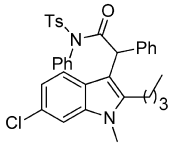
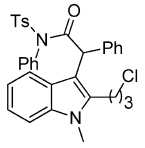
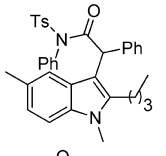
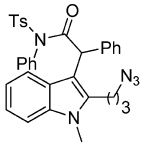
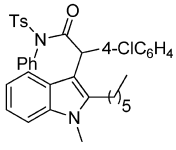
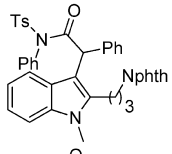
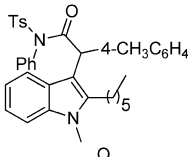
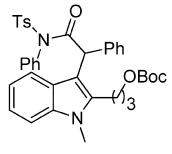
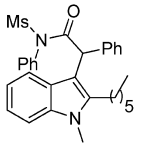
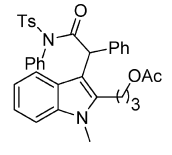
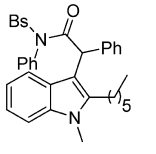
Table 2. Reaction Scope Study[a]

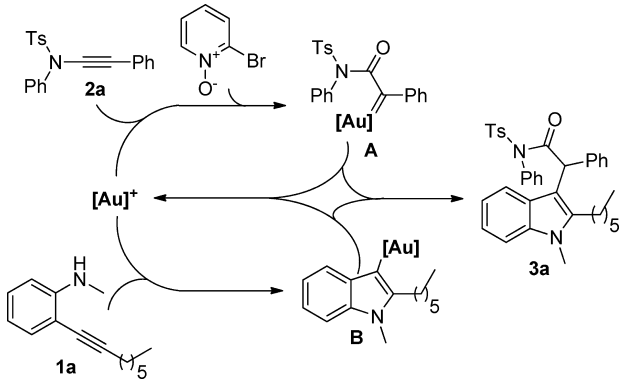


entry	product	3	yield	entry	product	3	yield
1		3a	70%	7		3g	60%
2		3b	64%	8		3h	43%
3		3c	50%	9		3i	57%
4		3d	56%	10		3j	67%
5		3e	53%	11		3k	61%
6		3f	55%	12		3l	65%

[a]Reactions run in vials. [**1a**] = 0.10 M; isolated yields are reported.

Finally, a plausible mechanism to rationalize the formation of indole **3a** is proposed (Scheme 2). The reaction pathway involving the complete formation of indole intermediate **4a** is much less possible, as the two-step, one-pot reaction exhibits a significantly lower efficiency than the concurrent tandem catalysis (eq 5 vs eq 6). Accordingly, we postulate that the reaction might go through a vinyl gold intermediate **B**, which would trap the α-oxo gold carbene intermediate **A**, generated through gold-catalyzed intermolecular oxidation of **2a**, to deliver the final product **3a**.

Scheme 2. Proposed Reaction Mechanism



CONCLUSION

In conclusion, we have developed a gold-catalyzed tandem cycloisomerization/intermolecular trapping of in situ generated α-oxo gold carbenes in water, which combines the indole formation with its carbene functionalization. Importantly, gold serves dual catalytic roles at the same time in such a tandem sequence, providing a new type of concurrent tandem catalysis. Studies to elucidate the detailed mechanism and further application of this tandem protocol into the synthesis of highly functionalized molecules and especially in the synthesis of natural products will be pursued further in our laboratory.

EXPERIMENTAL SECTION

General Information. Ethyl acetate (ACS grade), hexanes (ACS grade), and anhydrous 1,2-dichloroethane (ACS grade) were obtained commercially and used without further purification. Methylene chloride, tetrahydrofuran, and diethyl ether were purified according to standard methods unless otherwise noted. Commercially available reagents were used without further purification.

^{1}H NMR spectra were recorded in chloroform-d_3. Chemical shifts are reported in ppm (parts per million) with the internal TMS signal at 0.0 ppm as a standard. The data are being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, brs = broad singlet, coupling constant(s) in Hz, integration).

^{13}C NMR spectra were recorded in chloroform-d_3. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard.

Representative Synthetic Procedures for the Preparation of *o*-Alkynyl Anilines 1. To the corresponding aryl iodides (1.0 mmol) in Et_3N (5 mL) were added subsequently $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), and alkynes (1.2 mmol) at 25 °C. Stirring was continued for 16 h at 25 °C (for very electron-rich or sterically hindered aryl iodides, the temperature was raised to 50 °C). The reaction mixture was treated with saturated NH_4Cl solution (15 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired products **1**.

*N-Methyl-2-(oct-1-ynyl)aniline (**1a**).* Pale yellow oil (172.3 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, 1H, J = 1.6 Hz, J = 7.6 Hz), 7.18−7.14 (m, 1H), 6.61−6.54 (m, 2H), 4.58 (s, 1H), 2.88 (s, 3H), 2.45 (t, 2H, J = 7.2 Hz), 1.65−1.57 (m, 2H), 1.49−1.42 (m, 2H), 1.38−1.28 (m, 4H), 0.91 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 131.8, 129.0, 116.0, 108.7, 108.4, 95.9, 77.0, 31.3, 30.3, 28.9, 28.6, 22.5, 19.6, 14.0; IR (neat): 3414, 2926, 2242, 1737, 1600, 1509, 1467, 1366, 1319, 1242, 1170, 1041, 748; MS (ESI, m/z) 238 (M + Na$^+$); HRESIMS Calcd for $[C_{15}H_{21}NNa]^+$ (M + Na$^+$) 238.1566, found 238.1574.

*2-(5-Chloropent-1-ynyl)-N-methylaniline (**1b**).* Pale yellow oil (153.9 mg, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, 1H, J = 1.2 Hz, J = 7.2 Hz), 7.02−7.16 (m, 1H), 6.62−6.55 (m, 2H), 4.57 (s, 1H), 3.71 (t, 2H, J = 6.4 Hz), 2.88 (s, 3H), 2.66 (t, 2H, J = 6.8 Hz), 2.09−2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 131.9, 129.4, 116.1, 108.8, 107.7, 93.5, 78.2, 43.7, 31.4, 30.3, 17.1; IR (neat): 3415, 2914, 2814, 2242, 1600, 1509, 1461, 1426, 1320, 1287, 1168, 747; MS (ESI, m/z) 230 (M + Na$^+$); HRESIMS Calcd for $[C_{12}H_{14}ClNNa]^+$ (M + Na$^+$) 230.0707, found 230.0712.

*2-(5-Azidopent-1-ynyl)-N-methylaniline (**1c**).* Pale yellow oil (137.1 mg, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, 1H, J =

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7.6 Hz), 7.19−7.15 (m, 1H), 6.61−6.53 (m, 2H), 4.56 (s, 1H), 3.43 (t, 2H, J = 6.4 Hz), 2.88 (s, 3H), 2.56 (t, 2H, J = 6.8 Hz), 1.87−1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 131.8, 129.3, 115.9, 108.7, 107.6, 93.6, 78.1, 50.2, 30.1, 27.9, 16.9; IR (neat): 3416, 2931, 2098(s), 1601, 1575, 1510, 1461, 1449, 1426, 1320, 1287, 1256, 1168, 747; MS (ESI, m/z) 237 (M + Na^+); HRESIMS Calcd for $[C_{12}H_{14}N_4Na]^+$ (M + Na^+) 237.1111, found 237.1112.

*2-(5-(2-(Methylamino)phenyl)pent-4-ynyl)isoindoline-1,3-dione (**1d**).* White solid (mp 75−77 °C, 229.3 mg, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, 2H, J = 2.4 Hz, J = 4.4 Hz), 7.67 (dd, 2H, J = 2.4 Hz, J = 4.0 Hz), 7.23−7.13 (m, 2H), 6.56−6.52 (m, 2H), 4.91 (s, 1H), 3.90 (t, 2H, J = 5.6 Hz), 2.93 (s, 3H), 2.53 (t, 2H, J = 5.6 Hz), 2.04−1.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 150.1, 133.9, 132.1, 131.8, 129.2, 123.2, 115.7, 108.7, 107.8, 93.9, 78.2, 37.0, 30.2, 27.5, 17.3; IR (neat): 3402, 2920, 2244, 1771, 1709(s), 1600, 1508, 1395, 1371, 1171, 748, 719; MS (ESI, m/z) 341 (M + Na^+); HRESIMS Calcd for $[C_{20}H_{18}N_2NaO_2]^+$ (M + Na^+) 341.1260, found 341.1263.

*5-(2-(Methylamino)phenyl)pent-4-ynyl Pivalate (**1e**).* White solid (mp 80−82 °C, 167.8 mg, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, 1H, J = 1.6 Hz, J = 8.0 Hz), 7.19−7.15 (m, 1H), 6.60−6.53 (m, 2H), 4.66 (s, 1H), 4.24 (t, 2H, J = 6.4 Hz), 2.88 (d, 3H, J = 5.2 Hz), 2.57 (t, 2H, J = 7.2 Hz), 1.98−1.92 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 149.8, 131.8, 129.2, 115.9, 108.7, 107.8, 93.8, 81.9, 77.9, 65.4, 30.1, 28.0, 27.7, 16.2; IR (neat): 3416, 2982, 2099, 1739(s), 1601, 1575, 1511, 1461, 1394, 1368, 1321, 1277, 1255, 1166, 1106, 747; MS (ESI, m/z) 312 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{23}NNaO_3]^+$ (M + Na^+) 312.1570, found 312.1581.

*5-(2-(Methylamino)phenyl)pent-4-ynyl Acetate (**1f**).* Pale yellow oil (141.0 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, 1H, J = 1.6 Hz, J = 7.6 Hz), 7.20−7.16 (m, 1H), 6.62−6.55 (m, 2H), 4.63 (s, 1H), 4.25 (t, 2H, J = 6.0 Hz), 2.89 (s, 3H), 2.57 (t, 2H, J = 7.2 Hz), 2.07 (s, 3H), 1.98−1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 149.8, 131.9, 129.3, 116.0, 108.8, 107.9, 94.0, 77.9, 63.0, 30.2, 28.0, 20.9, 16.4; IR (neat): 2920, 2239, 1737, 1702, 1591, 1488, 1470, 1365, 1241, 1173, 1150, 1087, 746, 695, 579, 562; MS (ESI, m/z) 254 (M + Na^+); HRESIMS Calcd for $[C_{14}H_{17}NNaO_2]^+$ (M + Na^+) 254.1151, found 254.1154.

*5-Chloro-2-(hex-1-yn-1-yl)-N-methylaniline (**1g**).* Pale yellow oil (168.3 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, 1H, J = 8.0 Hz), 6.55 (dd, 1H, J = 2.0 Hz, J = 8.0 Hz), 6.50 (d, 1H, J = 2.0 Hz), 4.65 (s, 1H), 2.85 (d, 3H, J = 4.8 Hz), 2.44 (t, 2H, J = 6.8 Hz), 1.63−1.54 (m, 2H), 1.51−1.42 (m, 2H), 0.94 (t, 2H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 134.9, 132.6, 116.0, 108.8, 106.9, 96.7, 76.2, 31.0, 30.1, 22.0, 19.3, 13.6; IR (neat): 2957, 2930, 2870, 1596, 1568, 1509, 1446, 1427, 1409, 1286, 1159, 1088, 884, 831, 794; MS (ESI, m/z) 244 (M + Na^+); HRESIMS Calcd for $[C_{13}H_{16}ClNNa]^+$ (M + Na^+) 244.0863, found 244.0861.

*2-(Hex-1-yn-1-yl)-N,4-dimethylaniline (**1h**).* Pale yellow oil (124.9 mg, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, 1H, J = 2.0 Hz), 6.98 (dd, 1H, J = 2.4 Hz, J = 8.0 Hz), 6.49 (d, 1H, J = 8.4 Hz), 4.41 (s, 1H), 2.86 (s, 3H), 2.45 (t, 2H, J = 6.8 Hz), 2.19 (s, 3H), 1.64−1.55 (m, 2H), 1.53−1.43 (m, 2H), 0.95 (t, 2H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 132.3, 129.8, 125.2, 109.0, 108.4, 95.7, 77.1, 31.1, 30.6, 22.1, 20.2, 19.4, 13.7; IR (neat): 2956, 2926, 2859, 2813, 1613, 1580, 1518, 1464, 1315, 1279, 1168, 882, 803; MS (ESI, m/z) 224 (M + Na^+); HRESIMS Calcd for $[C_{14}H_{19}NNa]^+$ (M + Na^+) 224.1410, found 224.1416.

Representative Synthetic Procedures for the Preparation of Ynamides 2. Alkynyl bromides (1.2 mmol) and DMEDA (0.2 mmol, 17.6 mg) were added to a stirred solution of amides (1.0 mmol), K_2CO_3 (2.0 mmol, 276.4 mg), $FeCl_3{\cdot}6H_2O$ (0.1 mmol, 27.0 mg), and toluene (5 mL) under air, and the resulting mixture was stirred at 100 °C for 12 h. The suspension was filtered, and the residue was washed with diethyl ether (3 × 15 mL). The purification of products was achieved by flash chromatography (eluent: hexanes/ethyl acetate) to afford the desired products **2**.

The data of the ynamides **2a** and **2c−2e** were reported in our previous work.[5]

*N-((4-Chlorophenyl)ethynyl)-4-methyl-N-phenylbenzenesulfonamide (**2b**).* Pale yellow oil (248.1 mg, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2H, J = 7.6 Hz), 7.45−7.21 (m, 11H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 138.7, 133.9, 132.9, 132.6, 129.5, 129.1, 128.6, 128.3, 128.2, 126.2, 121.1, 83.9, 69.5, 21.6; IR (neat): 2923, 2236, 1593, 1487, 1374, 1186, 1174, 1089, 1013, 689, 657; MS (ESI, m/z) 404 (M + Na^+); HRESIMS Calcd for $[C_{21}H_{16}ClNNaO_2S]^+$ (M + Na^+) 404.0482, found 404.0484.

General Procedure of the Synthesis of Highly Functionalized Indole Derivatives from *o*-Alkynyl Anilines and Ynamides. Ynamide **2** (0.36 mmol), 2-bromopyridine *N*-oxide (104.4 mg, 0.60 mmol), and $IPrAuNTf_2$ (13.5 mg, 0.015 mmol) were added in this order to a suspension of *o*-alkynyl aniline **1** (0.30 mmol) in H_2O (3.0 mL) at room temperature. The reaction mixture was stirred at 80 °C, and the progress of the reaction was monitored by TLC. The reaction typically took 3 h. Upon completion, the reaction was diluted with DCM (30 mL) and washed with H_2O (2 × 15 mL). The resulting solution was extracted again with DCM (30 mL), and the combined organic layers were dried with $MgSO_4$. The mixture was then concentrated, and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product **3**.

*2-(2-Hexyl-1-methyl-1H-indol-3-yl)-N,2-diphenyl-N-tosylacetamide (**3a**).* Pale yellow oil (121.5 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 2H, J = 8.4 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.30−7.04 (m, 12H), 7.02−6.84 (m, 2H), 6.77 (t, 1H, J = 7.2 Hz), 4.94 (s, 1H), 3.55 (s, 3H), 2.47 (s, 3H), 2.15−2.06 (m, 1H), 1.85−1.73 (m, 1H), 1.10−1.03 (m, 2H), 1.02−0.88 (m, 6H), 0.77 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 144.6, 139.6, 139.0, 136.5, 136.2, 136.1, 130.4, 129.6, 129.5, 129.2, 129.0, 128.8, 128.2, 127.1, 126.8, 120.6, 119.5, 119.2, 108.5, 106.2, 49.4, 31.3, 29.6, 29.1, 29.0, 24.2, 22.3, 21.7, 13.9; IR (neat): 2955, 2927, 2858, 2253, 2099, 1701(s), 1600, 1488, 1470, 1452, 1365, 1187, 1173, 1150, 1088, 912, 742, 695, 562; MS (ESI, m/z) 601 (M + Na^+); HRESIMS Calcd for $[C_{36}H_{38}N_2NaO_3S]^+$ (M + Na^+) 601.2495, found 601.2498.

*2-(2-(3-Chloropropyl)-1-methyl-1H-indol-3-yl)-N,2-diphenyl-N-tosylacetamide (**3b**).* White solid (mp 169−171 °C, 109.6 mg, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 2H, J = 8.4 Hz), 7.42 (t, 1H, J = 7.2 Hz), 7.32−7.10 (m, 9H), 7.03−6.98 (m, 3H), 6.95−6.82 (m, 2H), 6.80 (t, 1H, J = 5.2 Hz), 4.99 (s, 1H), 3.59 (s, 3H), 3.22−3.12 (m, 2H), 2.47 (s, 3H), 2.41−2.33 (m, 1H), 2.10−2.02 (m, 1H), 1.48−1.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 144.7, 138.8, 137.8, 136.5, 136.1, 136.0, 130.4, 129.8, 129.5, 129.2, 129.1, 128.7, 128.3, 127.1, 127.0, 121.1, 119.7, 118.9, 108.7, 106.9, 49.1, 44.3, 31.6, 29.6, 21.7, 21.5; IR (neat): 2926, 2090, 1703(s), 1597, 1487, 1470, 1451, 1365, 1172, 1149, 1087, 695, 562; MS (ESI, m/z) 593 (M + Na^+); HRESIMS Calcd for $[C_{33}H_{31}ClN_2NaO_3S]^+$ (M + Na^+) 593.1636, found 593.1641.

*2-(2-(3-Azidopropyl)-1-methyl-1H-indol-3-yl)-N,2-diphenyl-N-tosylacetamide (**3c**).* Pale yellow oil (86.7 mg, 50%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 2H, J = 8.0 Hz), 7.42 (t, 1H, J = 7.2 Hz), 7.31−7.11 (m, 9H), 7.05−7.00 (m, 3H), 6.96−6.85 (m, 2H), 6.81 (t, 1H, J = 7.6 Hz), 4.98 (s, 1H), 3.58 (s, 3H), 2.94−2.86 (m, 2H), 2.47 (s, 3H), 2.33−2.21 (m, 1H), 2.02−1.92 (m, 1H), 1.29−1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 144.7, 138.8, 137.8, 136.5, 136.1, 136.0, 130.4, 129.8, 129.7, 129.5, 129.2, 129.1, 128.7, 128.3, 127.0, 121.1, 119.7, 118.9, 108.7, 106.9, 50.6, 49.1, 29.6, 28.1, 21.7, 21.3; IR (neat): 2920, 2096(s), 1702(s), 1476, 1363, 1276, 1172, 1149, 1087, 912, 747, 695, 562; MS (ESI, m/z) 600 (M + Na^+); HRESIMS Calcd for $[C_{33}H_{31}N_5NaO_3S]^+$ (M + Na^+) 600.2040, found 600.2042.

*2-(2-(3-(1,3-Dioxoisoindolin-2-yl)propyl)-1-methyl-1H-indol-3-yl)-N,2-diphenyl-N-tosylacetamide (**3d**).* Pale yellow oil (114.5 mg, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.85 (m, 4H), 7.77−7.23 (m, 2H), 7.37−7.32 (m, 1H), 7.27−7.19 (m, 5H), 7.14−7.11 (m, 4H), 7.05−6.98 (m, 3H), 6.95−6.82 (m, 2H), 6.80−6.76 (m, 1H), 4.90 (s, 1H), 3.55 (s, 3H), 3.38 (t, 2H, J = 7.2 Hz), 2.46 (s, 3H), 2.23−2.13 (m, 1H), 1.94−1.86 (m, 1H), 1.38−1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 168.0, 144.6, 138.7, 137.7, 136.5, 136.2, 136.1, 134.0, 132.0, 130.4, 129.7, 129.5, 129.2, 129.1, 128.6, 128.3, 127.0, 126.9, 123.2, 120.9, 119.6, 119.0, 49.2, 37.4, 29.6, 27.6, 21.8, 21.7; IR

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(neat): 3416, 2917, 2244, 2098(s), 1738(s), 1714, 1600, 1509, 1461, 1368, 1277, 1255, 1169, 747; MS (ESI, *m*/*z*) 704 (M + Na^+); HRESIMS Calcd for $[C_{41}H_{35}N_3NaO_5S]^+$ (M + Na^+) 704.2190, found 704.2188.

*3-(1-Methyl-3-(2-(4-methyl-N-phenylphenylsulfonamido)-2-oxo-1-phenylethyl)-1H-indol-2-yl)propyl Pivalate (**3e**).* Pale yellow oil (103.7 mg, 53%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 2H, *J* = 8.4 Hz), 7.40 (t, 1H, *J* = 7.6 Hz), 7.30−7.25 (m, 4H), 7.22−7.09 (m, 5H), 7.04−6.99 (m, 3H), 6.96−6.88 (m, 2H), 6.81−6.77 (m, 1H), 4.97 (s, 1H), 3.71 (t, 2H, *J* = 6.0 Hz), 3.56 (s, 3H), 2.47 (s, 3H), 2.32−2.45 (m, 1H), 2.01−1.93 (m, 1H), 1.48 (s, 9H), 1.33−1.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 153.4, 144.7, 138.8, 138.1, 136.5, 136.2, 136.1, 130.4, 129.7, 129.5, 129.2, 129.1, 128.7, 128.3, 127.0, 126.9, 120.9, 119.6, 119.0, 108.7, 106.8, 82.0, 66.0, 49.1, 29.5, 28.1, 28.0, 21.7, 20.7; IR (neat): 2923, 2850, 2096, 1738(s), 1600, 1470, 1366, 1277, 1254, 1172, 1152, 1087, 912, 743, 695, 562; MS (ESI, *m*/*z*) 675 (M + Na^+); HRESIMS Calcd for $[C_{38}H_{40}N_2NaO_6S]^+$ (M + Na^+) 675.2499, found 675.2496.

*3-(1-Methyl-3-(2-(4-methyl-N-phenylphenylsulfonamido)-2-oxo-1-phenylethyl)-1H-indol-2-yl)propyl Acetate (**3f**).* Pale yellow oil (98.1 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 2H, *J* = 8.4 Hz), 7.42−7.38 (m, 1H), 7.30−7.09 (m, 9H), 7.04−7.01 (m, 3H), 6.97−6.86 (m, 2H), 6.82−6.77 (m, 1H), 4.97 (s, 1H), 3.75−3.65 (m, 2H), 3.56 (s, 3H), 2.45 (s, 3H), 2.29−2.18 (m, 1H), 2.03−1.91 (m, 4H), 1.34−1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 170.6, 144.6, 138.7, 138.1, 136.4, 136.0, 130.3, 129.7, 129.4, 129.2, 129.0, 128.6, 128.2, 126.9, 120.9, 119.6, 118.9, 108.6, 106.6, 63.4, 49.1, 29.5, 27.8, 21.6, 20.8, 20.7; IR (neat): 3360, 2958, 2921, 2851, 1696(s), 1494, 1469, 1350, 1167, 1152, 1084, 743; MS (ESI, *m*/*z*) 617 (M + Na^+); HRESIMS Calcd for $[C_{35}H_{34}N_2NaO_5S]^+$ (M + Na^+) 617.2081, found 617.2086.

*2-(2-Butyl-6-chloro-1-methyl-1H-indol-3-yl)-N,2-diphenyl-N-tosylacetamide (**3g**).* Pale yellow oil (105.2 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 2H, *J* = 8.4 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.35−7.24 (m, 4H), 7.24−7.13 (m, 4H), 7.00 (dd, 2H, *J* = 2.8 Hz, *J* = 6.4 Hz), 6.96−6.89 (m, 3H), 6.70 (dd, 1H, *J* = 1.6 Hz, *J* = 8.4 Hz), 4.90 (s, 1H), 3.52 (s, 3H), 2.48 (s, 3H), 2.13−2.02 (m, 1H), 1.81−1.70 (m, 1H), 1.37−1.20 (m, 4H), 1.04−0.87 (m, 4H), 0.66 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 144.8, 140.3, 138.6, 137.0, 136.1, 130.4, 129.8, 129.5, 129.2, 129.1, 128.6, 128.2, 127.0, 126.8, 125.5, 120.1, 120.0, 108.6, 106.4, 49.2, 31.0, 29.7, 23.9, 22.4, 21.7, 13.5; IR (neat): 2954, 2923, 1703(s), 1597, 1487, 1472, 1453, 1362, 1187, 1172, 1146, 1087, 659; MS (ESI, *m*/*z*) 607 (M + Na^+); HRESIMS Calcd for $[C_{34}H_{33}ClN_2NaO_3S]^+$ (M + Na^+) 607.1793, found 607.1795.

*2-(2-Butyl-1,5-dimethyl-1H-indol-3-yl)-N,2-diphenyl-N-tosylacetamide (**3h**).* White solid (mp 165−167 °C, 72.7 mg, 43%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89−7.86 (m, 2H), 7.42−7.37 (m, 1H), 7.30−7.22 (m, 5H), 7.19−7.14 (m, 3H), 7.11−7.04 (m, 3H), 6.96−6.86 (m, 3H), 4.94 (s, 1H), 3.52 (s, 3H), 2.43 (s, 3H), 2.22 (s, 3H), 2.11−2.03 (m, 1H), 1.83−1.75 (m, 1H), 1.05−0.95 (m, 2H), 0.94−0.86 (m, 2H), 0.65 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 144.4, 139.7, 139.1, 136.4, 136.1, 134.9, 130.5, 129.5, 129.4, 129.2, 129.0, 128.8, 128.5, 128.1, 126.8, 124.2, 122.2, 118.8, 108.2, 105.4, 49.3, 31.0, 29.6, 23.9, 22.4, 21.7, 21.4, 13.5; IR (neat): 2957, 2920, 2850, 1703(s), 1658, 1631, 1597, 1488, 1470, 1453, 1363, 1243, 1187, 1172, 1146, 1087, 1045, 695; MS (ESI, *m*/*z*) 587 (M + Na^+); HRESIMS Calcd for $[C_{35}H_{36}N_2NaO_3S]^+$ (M + Na^+) 587.2339, found 587.2340.

*2-(4-Chlorophenyl)-2-(2-hexyl-1-methyl-1H-indol-3-yl)-N-phenyl-N-tosylacetamide (**3i**).* Pale yellow oil (104.7 mg, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2H, *J* = 8.4 Hz), 7.40 (t, 1H, *J* = 7.6 Hz), 7.29−7.22 (m, 6H), 7.14−7.09 (m, 3H), 7.07−6.97 (m, 3H), 6.91−6.82 (m, 1H), 6.76 (t, 1H, *J* = 7.6 Hz), 4.88 (s, 1H), 3.55 (s, 3H), 2.47 (s, 3H), 2.06−1.99 (m, 1H), 1.70−1.63 (m, 1H), 1.01−0.86 (m, 8H), 0.76 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 144.7, 139.6, 137.6, 136.3, 135.8, 135.7, 132.6, 130.2, 130.1, 129.7, 129.4, 129.2, 128.9, 128.2, 126.6, 120.6, 119.5, 118.8, 108.6, 105.2, 48.8, 31.2, 29.5, 28.9, 28.8, 23.9, 22.2, 21.6, 13.8; IR (neat): 2954, 2928, 2857, 2253, 1703(s), 1596, 1489, 1470, 1406, 1365, 1187, 1088, 1015, 813, 739, 696, 653; MS (ESI, *m*/*z*) 635 (M + Na^+); HRESIMS Calcd for $[C_{36}H_{37}ClN_2NaO_3S]^+$ (M + Na^+) 635.2106, found 635.2114.

*2-(2-Hexyl-1-methyl-1H-indol-3-yl)-N-phenyl-2-(p-tolyl)-N-tosylacetamide (**3j**).* White solid (mp 162−164 °C, 119.1 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 2H, *J* = 8.4 Hz), 7.43−7.37 (m, 1H), 7.32−7.23 (m, 6H), 7.20−7.07 (m, 2H), 6.99−6.85 (m, 5H), 6.79−6.73 (m, 1H), 4.89 (s, 1H), 3.55 (s, 3H), 2.47 (s, 3H), 2.24 (s, 3H), 2.12−2.03 (m, 1H), 1.83−1.71 (m, 1H), 1.13−0.89 (m, 8H), 0.77 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 144.5, 139.5, 136.4, 136.4, 136.1, 136.0, 135.9, 130.4, 129.6, 129.5, 129.2, 129.0, 128.9, 128.6, 127.0, 120.5, 119.4, 119.1, 108.4, 106.2, 49.0, 31.3, 29.1, 29.0, 24.2, 22.4, 21.7, 21.0, 13.9; IR (neat): 2954, 2921, 2850, 1708(s), 1658, 1632, 1596, 1487, 1469, 1452, 1365, 1142, 1087, 1020, 739, 695; MS (ESI, *m*/*z*) 615 (M + Na^+); HRESIMS Calcd for $[C_{37}H_{40}N_2NaO_3S]^+$ (M + Na^+) 615.2652, found 615.2654.

*2-(2-Hexyl-1-methyl-1H-indol-3-yl)-N-(methylsulfonyl)-N,2-diphenylacetamide (**3k**).* Pale yellow oil (91.7 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 1H, *J* = 8.0 Hz), 7.41 (t, 1H, *J* = 7.6 Hz), 7.33−7.15 (m, 9H), 7.07 (t, 1H, *J* = 7.6 Hz), 6.93 (s, 2H), 5.06 (s, 1H), 3.60 (s, 3H), 3.43 (s, 3H), 2.28−2.12 (m, 1H), 1.89−1.77 (m, 1H), 1.16−0.95 (m, 8H), 0.77 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 139.9, 138.7, 136.6, 135.2, 130.2, 129.8, 129.2, 128.7, 128.3, 127.0(2), 126.9(9), 121.0, 119.7, 119.3, 108.9, 105.9, 49.2, 42.4, 31.3, 29.6, 29.2, 29.1, 24.2, 22.4, 14.0; IR (neat): 2954, 2926, 2850, 1704(s), 1594, 1490, 1470, 1452, 1356, 1170, 1145, 964, 742, 695; MS (ESI, *m*/*z*) 525 (M + Na^+); HRESIMS Calcd for $[C_{30}H_{34}N_2NaO_3S]^+$ (M + Na^+) 525.2182, found 525.2185.

*N-((4-Bromophenyl)sulfonyl)-2-(2-hexyl-1-methyl-1H-indol-3-yl)-N,2-diphenylacetamide (**3l**).* Pale yellow oil (125.3 mg, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.81 (m, 2H), 7.61−7.55 (m, 2H), 7.41 (t, 1H, *J* = 7.6 Hz), 7.28 (t, 2H, *J* = 7.6 Hz), 7.25−7.10 (m, 6H), 7.08−7.00 (m, 3H), 6.84−6.79 (m, 2H), 4.92 (s, 1H), 3.55 (s, 3H), 2.12−1.99 (m, 1H), 1.75−1.62 (m, 1H), 1.10−0.85 (m, 8H), 0.75 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 139.6, 138.6, 138.0, 136.4, 135.6, 131.9, 131.0, 130.3, 129.8, 129.1, 129.0, 128.7, 128.2, 127.0, 126.8, 120.7, 119.6, 118.8, 108.6, 105.6, 49.4, 31.2, 29.6, 29.0, 28.9, 24.0, 22.3, 13.9; IR (neat): 2951, 2928, 2856, 2250, 1711(s), 1573, 1487, 1470, 1452, 1390, 1366, 1173, 1010, 744, 698; MS (ESI, *m*/*z*) 665 (M + Na^+); HRESIMS Calcd for $[C_{35}H_{35}BrN_2NaO_3S]^+$ (M + Na^+) 665.1444, found 665.1442.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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