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Palladium-Catalyzed Synthesis of Indoles and Isoquinolines with *in Situ* Generated Phosphinimine

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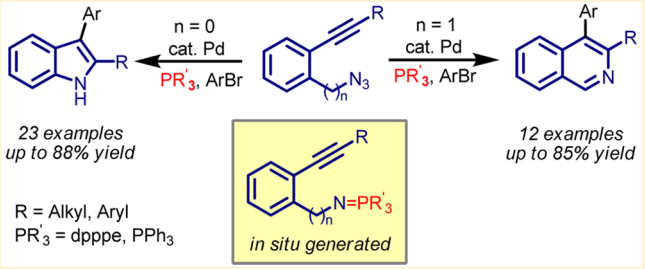
Supporting Information

ABSTRACT: A palladium-catalyzed synthesis of polysubstituted indoles and isoquinolines through the coupling of aryl bromides with 2-alkynyl arylazides or 2-alkynyl benzylazides has been developed. This method provides straightforward access to indoles and isoquinolines with high efficiency and excellent functional group compatibility. In this transformation, the iminophosphorane *in situ* generated from azides is served as the nucleophile that attacks the alkyne moiety in the cyclization process.

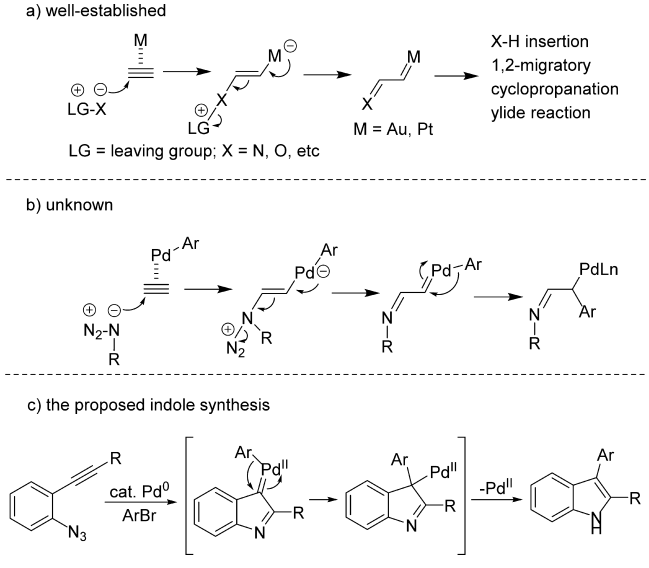


INTRODUCTION

Transition-metal-catalyzed carbene transfer reactions constitute one of the major domains of modern synthetic organic chemistry.[1] While diazo compounds are generally recognized as the most common precursors for the generation of metal carbene species, other metal carbene precusors, such as alkynes, cyclopropenes, and enynones, have also attracted significant attention in recent years.[2] In particular, alkynes are known to serve as carbene precursors by reacting with nucleophiles bearing a leaving group under Au- or Pt-catalyzed conditions (Scheme 1a).[3] Alkynes also serve as precursors for generating α-oxo and α-imino gold carbenes, which undergo typical carbene transformations, such as X−H bond insertion, 1,2-migration, cyclopropanation, ylide reaction, and others.[4] The azido moiety has been known as a useful nucleophile bearing an excellent leaving group (N_2). Consequently, the generation of a metal carbene intermediate from an azido and alkyne moiety has been recently established for the synthesis of nitrogen-containing heterocycles.[5]

On the other hand, diazo compounds have been extensively explored as palladium carbene precursors for cross-coupling reactions.[6,7] Recently, we have also demonstrated the use of ene-yne-ketones and allenyl ketones as the palladium carbene precursors in cross-coupling reactions.[8] As a continuation of our interest in carbene-based coupling reactions, we have conceived that the azido moiety may serve as a nucleophile for generating palladium carbenes from alkynes, similar to the corresponding Au- and Pt-catalyzed reactions (Scheme 1b).[3] With 2-alkynyl arylazides as the substrates, the palladium carbene generated may be involved in cross-coupling reactions for the synthesis of polysubstituted indole,[9] as proposed in Scheme 1c. Although generating palladium carbene from alkynes has been reported,[10] the combination of such type of transformation with cross-coupling is not known in the literature. A similar strategy should also be applied to the synthesis of isoquinolines by employing 2-alkynyl benzylazides as the substrates instead of 2-alkynyl arylazides.[11]

Scheme 1. Alkynes as Metal Carbene Precursors



RESULTS AND DISCUSSION

To achieve the proposed transformation, we have initially investigated the cross-coupling reaction by using alkynyl-substituted azide **1a** and aryl bromide **2a** as the substrates,

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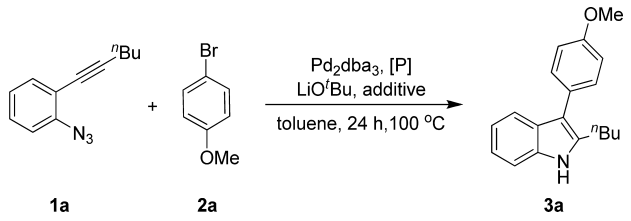
Table 1. Optimization of the Palladium-Catalyzed Synthesis of Indole[a]



1a 2a 3a

entry	Pd_2dba_3 (mol %)	base (equiv)	additive (equiv)	[P] (mol %)[d]	yield (%)[b]
1	5	LiO^{t}Bu (2)	Et_3B (1.5)	dpppe (20)	22
2	10	LiO^{t}Bu (2)	Et_3B (1.5)	dpppe (40)	58
3	10	LiO^{t}Bu (2)	Et_3B (1.5)	dpppe (20)	25
4	5	LiO^{t}Bu (2)	Et_3B (1.5)	dpppe (40)	68
5	2.5	LiO^{t}Bu (2)	Et_3B (1.5)	dpppe (40)	69
6	2.5	LiO^{t}Bu (2)	none	dpppe (50)	72
7[c]	2.5	LiO^{t}Bu (1.5)	none	dpppe (50)	75
8	2.5	LiO^{t}Bu (1.5)	H_2O (1)	dpppe (50)	52
9[c]	2.5	LiO^{t}Bu (1.5)	none	PPh_3 (100)	60
10	2.5	none	none	PPh_3 (100)	trace
11	2.5	NaO^{t}Bu (1.5)	none	PPh_3 (100)	33[e]
12	2.5	NaOMe (1.5)	none	PPh_3 (100)	67[e]
13	2.5	KOMe (1.5)	none	PPh_3 (100)	53[e]
14	2.5	LiOMe (1.5)	none	PPh_3 (100)	23[e]
15	2.5	K_2CO_3 (1.5)	none	PPh_3 (100)	29[e]
16	2.5	Cs_2CO_3 (1.5)	none	PPh_3 (100)	69[e]

[a]If not otherwise noted, the reaction was performed with **1a** (0.1 mmol) and **2a** (0.15 mmol) in toluene (2 mL) at 100 °C. [b]Yields of isolated product are given. [c]The reaction was carried out with **1a** (0.2 mmol) and **2a** (0.3 mmol) in toluene (2 mL) at 100 °C. [d]dpppe = 1,5-bis(diphenylphosphino)pentane. [e]NMR yields of the products are given.

and Et_3B was used as the reductant (Table 1, entry 1). The expected indole product **3a** could be isolated in 22% yield with 5 mol % Pd_2dba_3 and 20 mol % dpppe [1,5-bis(diphenylphosphino)pentane]. We suspected that the low yield might be attributed to the deactivation of the palladium catalyst. Indeed the reaction could be improved by increasing the loading of Pd_2dba_3 and dpppe (Table 1, entry 2). However, when the loading of dpppe was reduced, a sharp decrease of the yield was observed (Table 1, entry 3). In contrast, lowering the loading of Pd_2dba_3 alone does not lead to the reduction in yield (Table 1, entries 4 and 5). It was thus speculated that dpppe not only acted as the ligand but also played another vital role in this transformation. Since dpppe may play the role as a reductant in the reaction, the reaction was then carried out with 50 mol % dpppe but in the absence of Et_3B. Indeed the reaction went smoothly to afford the indole **3a** in an improved yield (Table 1, entry 6). When the concentration of the substrates was increased, the yield could be slightly improved with 1.5 equiv of base (Table 1, entry 7). The yield was diminished slightly when 1 equiv of water was added (Table 1, entry 8). Notably, while dpppe was replaced by PPh_3, the product was afforded with a slightly diminished yield (Table 1, entry 9). Moreover, a base was found to be necessary for the reaction (Table 1, entry 10). In addition to LiO^{t}Bu, other types of bases could also make the reaction work smoothly (Table 1, entries 11−16).

With the optimized reaction conditions in hand, we then proceeded to study the substrate scope of the reaction with a series of 2-alkynyl arylazides and aryl bromides (Scheme 2). The substrates with *para*-substituted aryl bromides all afforded the corresponding products in good yields (Scheme 2, **3a**−**j**), except the *p*-CO_2Me substituted bromide **2g**. With *meta*-substituted bromides, the reaction also went smoothly to give the corresponding products in good yields (Scheme 2, **3k**−**n**). The low yield in the case of **2p** may be attributed to the steric effect of the *ortho*-substitution (Scheme 2, **3p**). In addition, The reaction with 4-bromo-1,1′-biphenyl and 2-bromonaphthalene could deliever the corresponding indole products in good yields (Scheme 2, **3q**, **r**). Notably, the reaction with the azide substrates bearing an aryl substituent also afforded the corresponding products in moderate to good yields (Scheme 2, **3t**−**w**). The structure of indole product **3t** was further confirmed by X-ray crystallography.[13]

For the reaction mechanism, it was initially considered that the azido moiety of the substrate attack the arylpalladium(II)-activated triple bond to afford the cyclized intermediate. However, because the arylazide moiety can easily react with phosphine to generate phosphinimine under the current reaction conditions (Staudinger reaction),[14,15] it was thus speculated that the phosphinimine might be first formed and then the nucleophilic nitrogen of the phosphinimine attacked the arylpalladium(II)-activated triple bond. To substantiate such speculation, mechanistic experiments were carried out. The arylazide **1a** was first subjected to the reaction with triphenylphosphine in dichloromethane. After the reaction stirred at room temperature for 6 h, the arylazide **1a** completely disappeared. The solvent was removed and the formation of phosphinimine **4** was confirmed by ^{1}H and ^{13}C NMR spectra. The crude phosphinimine was then submitted to the Pd-catalyzed coupling reaction with aryl bromide. The expected indole product **3a** was obtained in 56% yield. A similar experiment with dpppe afforded the indole product **3a** in 72% yield (Scheme 3a).

In another control experiment, 2-alkynyl azidobenzene **1a** was replaced with 2-(hex-1-yn-1-yl)aniline **1a′** under the standard conditions. The formation of **3a** was not observed, as

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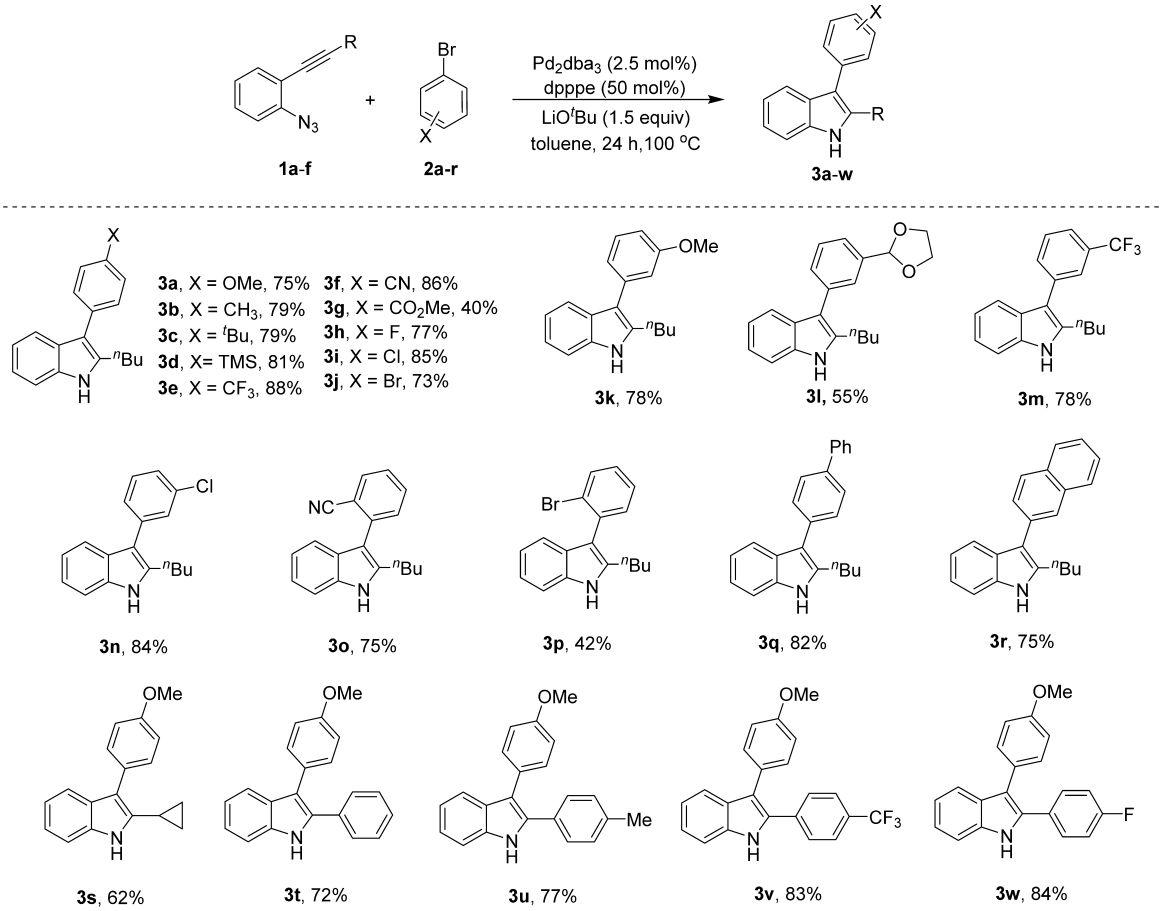
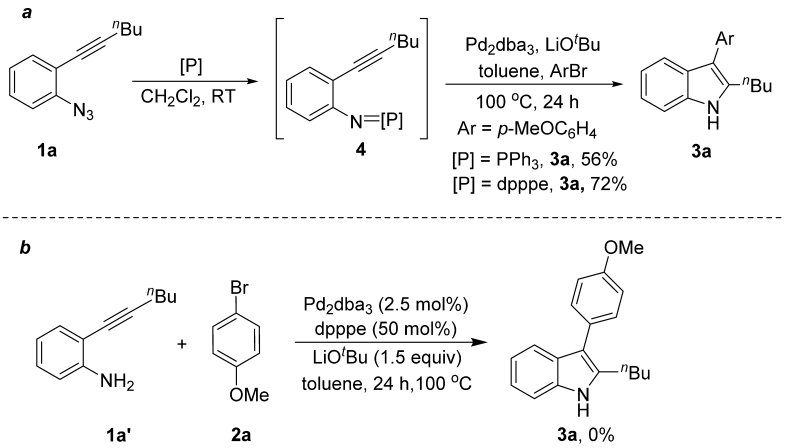
Scheme 2. Reaction Scope of the Aryl Bromides[a]



[a]If not otherwise noted, the reaction conditions are as follows: 2-alkynyl arylazides **1a−f** (0.2 mmol), ary bromides **2a−r** (0.3 mmol), Pd_2dba_3 (2.5 mol %), dppe (50 mol %), LiO^{t}Bu (1.5 equiv), toluene (2 mL), 100 °C, 24 h. [b]All the yields refer to the isolated indole products.

Scheme 3. Control Experiments



shown in Scheme 3b. The experiment rules out the mechanism in which the azide is first converted to the amine *in situ* and then the cyclization occurs. Notably, in Cacchi's aminopalladation/reductive elimination domino reaction for the construction of indole rings, a trifluoroacetyl substituent on the nitrogen is required.[9d,e] The proposed reaction mechanism is shown in Scheme 4. There are two possible pathways. In path *a*, arylpalladium(II) species **B** is first formed through oxidative addition of aryl bromide **2** to a Pd(0) catalyst, while iminophosphorane **C** is formed *in situ* from 2-alkynyl arylazide by a Staudinger reaction. Then, the 5-*endo-dig* cyclized intermediate **D** is generated through nucleophilic attack of the arylpalladium(II)-activated triple bond by the nitrogen of the phosphinimine moiety. Reductive elimination of intermediate **D** leads to the intermediate **J**, which is further converted to the product by hydrolysis. The alternative mechanism involving the carbene process is shown in path *b*. From intermediate **D**, palladium(II) carbene species

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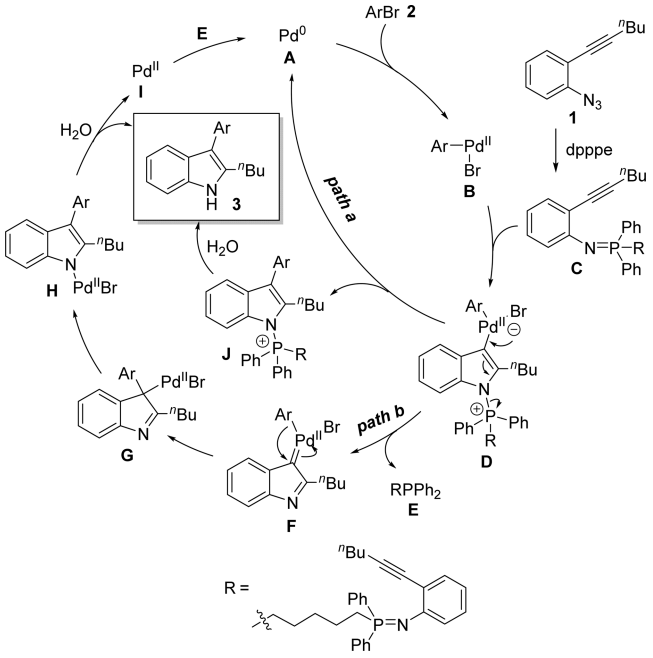
Scheme 4. Proposed Reaction Mechanism



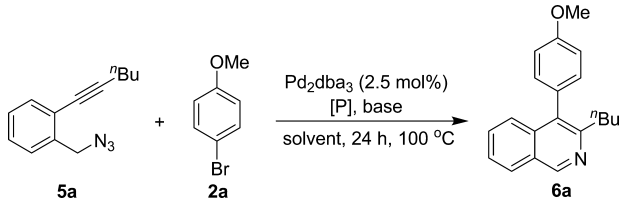
F is formed through back electron-donation from palladium. Subsequent migratory insertion gives intermediate **G**, which is isomerized to intermediate **H**. Protonation of the intermediate **H** affords product **3** and Pd(II) species, which is reduced to the Pd(0) catalyst by **E**.

Encourged by the above results, we further conceived to extend the reaction to the synthesis of polysubstituted isoquinolines with 2-alkynyl benzylazide **5a** (Table 2). However, when the reaction was performed under the standard conditions for indole synthesis as described above, the desired product **6a** was only obtained in 29% yield (Table 2, entry 1). We then optimized the reaction conditions by screening different bases; however, with K_2CO_3 and KOMe as the bases, only trace amounts of the products were detected (Table 2, entries 2, 3). To our delight, when dppe was replaced by PPh_3, the yield could be improved to 39% (Table 2, entry 4). The reaction with other solvents, such as dioxane, MeCN, and DCE, did not show improved results (Table 2, entries 5–7). Finally, it was observed that the yield of **6a** could be significantly improved by increasing the loading of aryl bromide **2a** (Table 2, entries 8–11).

With the optimized reaction conditions (with 3 equiv of aryl bromide) (Table 2, entry 11), we proceeded to investigate the scope of the reaction (Scheme 5). Moderate to good yields could be obtained with a series of aryl bromides (Scheme 5, **6a–i**). Besides, the reaction also worked well with 2-alkynyl benzylazides bearing various substituents (Scheme 5, **6j–l**).

For the synthesis of isoquinolines, the same control experiments as above-mentioned were carried out and similar results were obtained as shown in Scheme 6. Therefore, the mechanism for isoquinoline formation should be similar to that shown in Scheme 4.[12]

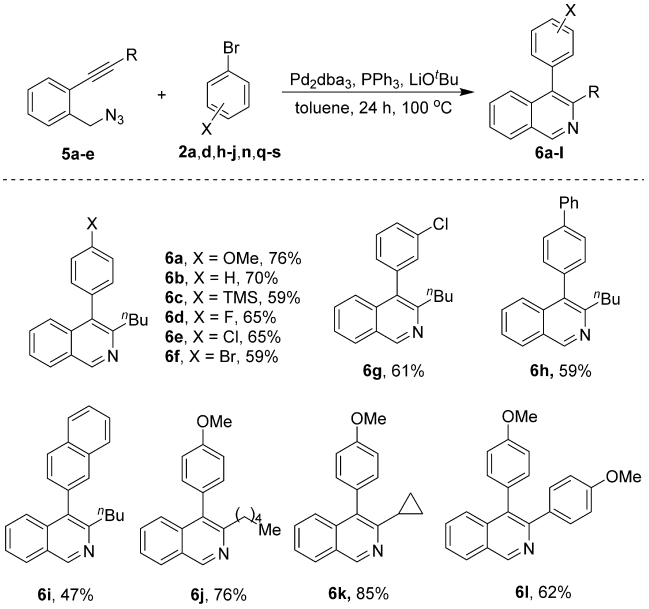
Table 2. Reaction Condition Optimization for Isoquinoline Synthesis[a]



entry	**2a** (equiv)	base (equiv)	solvent	[P] (mol %)	yield (%)[b]
1	1.5	LiO^{t}Bu (1.5)	toluene	dpppe (50)	29
2[c]	1.0	K_2CO_3 (1.5)	toluene	dpppe (50)	trace
3[c]	1.0	KOMe (1.5)	toluene	dpppe (50)	trace
4[c]	1.0	LiO^{t}Bu (3.0)	toluene	PPh_3 (100)	39
5[c]	1.0	LiO^{t}Bu (2.0)	dioxane	PPh_3 (100)	22
6[c]	1.0	LiO^{t}Bu (2.0)	MeCN	PPh_3 (100)	trace
7[c]	1.0	LiO^{t}Bu (2.0)	DCE	PPh_3 (100)	trace
8	1.5	LiO^{t}Bu (2.8)	toluene	PPh_3 (150)	45
9	2.0	LiO^{t}Bu (2.8)	toluene	PPh_3 (150)	58
10	2.5	LiO^{t}Bu (2.8)	toluene	PPh_3 (150)	68
11	3.0	LiO^{t}Bu (2.8)	toluene	PPh_3 (150)	76

[a]If not otherwise noted, the reaction was performed with **5a** (0.2 mmol) in toluene (1 mL) at 100 °C. [b]Yields refer to the isolated product. [c]The reaction was carried out with **5a** (0.1 mmol) in toluene (1 mL) at 100 °C.

Scheme 5. Scope for the Synthesis of Isoquinoline[a]



[a]If not otherwise noted, the reaction conditions are as follows: 2-alkynyl benzylazides **5a–e** (0.2 mmol), ary bromides (0.6 mmol), Pd_2dba_3 (2.5 mol %), PPh_3 (1.5 equiv), LiO^{t}Bu (2.8 equiv), toluene (1 mL), 100 °C, 24 h. [b]All yields refer to the isolated products.

CONCLUSION

In conclusion, we have developed an efficient method for the synthesis of polysubstituted indoles and isoquinolines via the iminophosphorane intermediates generated *in situ* through a Staudinger reaction. The iminophosphoranes are versatile synthetic intermediates which have found many applications in organic chemistry. The reaction of iminophosphorane with a palladium-activated alkyne described herein opens up new possibilities for the application of iminophosphorane in developing new reactions.

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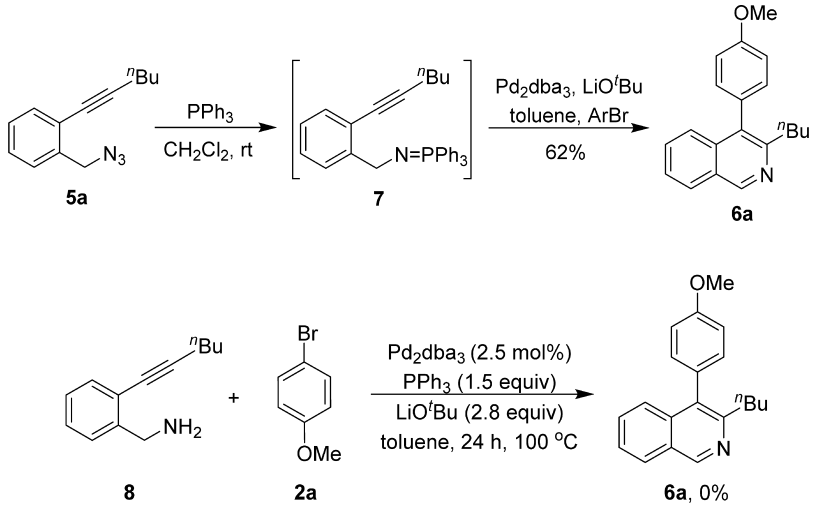
Scheme 6. Control Experiments for the Reaction of Isoquinolines Synthesis



EXPERIMENTAL SECTION

General Methods. All the reactions of palladium-catalyzed synthesis of polysubstituted indoles and isoquinolines were performed under a nitrogen atmosphere in a flame-dried reaction tube. All the solvents were distilled under a nitrogen atmosphere prior to use. Toluene was dried over Na with a benzophenone-ketyl intermediate as an indicator. For chromatography, 200−300 mesh silica gel was employed. Chemical shifts for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were reported relative to those of tetramethylsilane (TMS): chemical shifts (δ) were reported in ppm, and coupling constants (J) are in hertz (Hz). IR spectra were performed neat on an FT-IR spectrophotometer and reported in wavenumbers, cm^{-1}. For HRMS measurements, the mass analyzer is FT-ICR. 2-Alkynyl azidobenzenes and 2-alkynyl benzylazides were prepared according to the literature procedures.[16−18] Other starting materials were obtained from commercial suppliers and were used without further purification. PE, petroleum ether; EA, ethyl acetate.

General Procedure for the Synthesis of Polysubstituted Indoles. Under a N_2 atmosphere, Pd_2dba_3 (4.6 mg, 0.005 mmol, 2.5 mmol %), dpppe (44 mg, 0.1 mmol, 50 mmol %), and LiO^{t}Bu (24 mg, 0.3 mmol) were successively added to a flame-dried 10 mL Schlenk tube. The reaction tube was degassed three times with N_2, and dry toluene (2 mL) was added by syringe. Then, the 2-alkynyl azidobenzene (0.2 mmol) and the aryl bromides (0.3 mmol) were added with a syringe, respectively (Note: 2-alkynyl azidobenzenes or the aryl bromides in solid form were added to the reaction tube prior to LiO^{t}Bu). The reaction was heated at 100 °C with stirring for 24 h. Next, the reaction mixture was cooled to room temperature, and then it was filtered through a short plug of silica gel with ethyl acetate as eluents. The solvent was removed in *vacuo* to leave a crude mixture, which was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (10:1) to afford the pure indole product **3a**−**w**.

2-Butyl-3-(4-methoxyphenyl)-1H-indole (***3a***).[5b] Yield: 42 mg (75%), pale yellow liquid, R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.41−7.38 (m, 2H), 7.28 (d, J = 7.9 Hz, 1H), 7.16−7.07 (m, 2H), 7.02−6.99 (m, 2H), 3.85 (s, 3H), 2.79 (t, J = 7.8 Hz, 2H), 1.67−1.59 (m, 2H), 1.39−1.30 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 135.7, 135.1, 130.6, 128.1, 127.8, 121.4, 119.7, 118.8, 113.9, 110.3, 55.3, 32.0, 26.0, 22.5, 13.8; IR (film): 1330, 1459, 1487, 1557, 1613, 2931, 2957, 3408 cm^{-1}.

2-Butyl-3-(p-tolyl)-1H-indole (***3b***). Yield: 42 mg (79%), pale yellow liquid, R_f = 0.5 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 8.0, 2H), 7.29−7.25 (m, 3H), 7.17−7.07 (m, 2H), 2.81 (t, J = 7.8 Hz, 2H), 2.40 (s, 3H), 1.68−1.60 (m, 2H), 1.40−1.30 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.4, 135.2, 132.4, 129.5, 129.2, 128.0, 121.4, 119.7, 118.9, 114.2, 110.3, 32.0, 26.1, 22.5, 21.2, 13.8; HRMS (ESI, m/z): calcd for $C_{19}H_{22}N$ [M + H]$^+$ 264.1747, found 264.1750; IR (film): 1017, 1257, 1330, 1458, 1510, 1558, 2957, 3406 cm^{-1}.

2-Butyl-3-(4-(tert-butyl)phenyl)-1H-indole (***3c***). Yield: 48 mg (79%), pale yellow liquid, R_f = 0.5 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.48−7.41 (m, 4H), 7.30 (d, J = 7.9 Hz, 1H), 7.17−7.13 (m, 1H), 7.11−7.07 (m, 1H), 2.84 (t, J = 7.9 Hz, 2H), 1.71−1.63 (m, 2H), 1.43−1.33 (m, 11H), 0.90 (t, 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 135.9, 135.2, 132.4, 129.1, 128.0, 125.3, 121.4, 119.7, 119.1, 114.2, 110.3, 34.5, 32.1, 31.4, 26.1, 22.6, 13.9; HRMS (ESI, m/z): calcd for $C_{22}H_{28}N$ [M + H]$^+$ 306.2216, found 306.2219; IR (film): 1268, 1330, 1363, 1459, 1509, 1563, 2960, 3408 cm^{-1}.

2-Butyl-3-(4-(trimethylsilyl)phenyl)-1H-indole (***3d***). Yield: 52 mg (81%), pale yellow liquid, R_f = 0.5 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 7.9 Hz, 1H), 7.18−7.07 (m, 2H), 2.83 (t, J = 7.9 Hz, 2H), 1.69−1.61 (m, 2H), 1.41−1.32 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H), 0.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 136.2, 135.9, 135.2, 133.5, 128.9, 127.8, 121.5, 119.8, 119.0, 114.3, 110.4, 32.1, 26.2, 22.6, 13.9, −1.0; HRMS (ESI, m/z): calcd for $C_{21}H_{28}NSi$ [M + H]$^+$ 322.1986, found 322.1988; IR (film): 839, 1108, 1248, 1329, 1459, 1600, 2956, 3409 cm^{-1}.

2-Butyl-3-(4-(trifluoromethyl)phenyl)-1H-indole (***3e***). Yield: 56 mg (88%), pale yellow liquid, R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.60 (t, J = 7.6 Hz, 3H), 7.35 (d, J = 8.0 Hz, 1H), 7.21−7.17 (m, 1H), 7.15−7.11 (m, 1H), 2.85 (t, J = 7.8 Hz, 2H), 1.72−1.64 (m, 2H), 1.42−1.33 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 136.8, 135.2, 129.6, 127.8 (q, J^2 = 32.3 Hz), 127.5, 125.4 (q, J^3 = 3.7 Hz), 124.5 (q, J^1 = 271.7 Hz), 121.9, 120.5, 120.3, 118.6, 113.2, 110.5, 31.9, 26.1, 22.5, 13.8; HRMS (ESI, m/z): calcd for $C_{19}H_{19}F_3N$ [M + H]$^+$ 318.1464, found 318.1467; IR (film): 1321, 1407, 1440, 1459, 1560, 1615, 2958, 3400 cm^{-1}.

4-(2-Butyl-1H-indol-3-yl)benzonitrile (***3f***). Yield: 47 mg (86%), yellow solid, mp: 120−121 °C; R_f = 0.2 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.50 (t, J = 8.7 Hz, 3H), 7.28 (d, J = 7.9 Hz, 1H), 7.14−7.09 (m, 1H), 7.07−7.03 (m, 1H), 2.76 (t, J = 7.8 Hz, 2H), 1.63−1.55 (m, 2H), 1.33−1.23 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 137.3, 135.2, 132.3, 129.7, 127.0, 122.0, 120.4, 119.4, 118.3, 112.7, 110.7, 108.7, 31.8, 26.1, 22.4, 13.7; HRMS (ESI, m/z): calcd for $C_{19}H_{19}N_2$ [M + H]$^+$ 275.1543, found 275.1545; IR (film): 1174, 1262, 1460, 1504, 1605, 2231, 2959, 3336 cm^{-1}.

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*Methyl 4-(2-Butyl-1H-indol-3-yl)benzoate (**3g**).*[19] Yield: 24 mg (40%), pale yellow solid, mp: 121−122 °C; R_f = 0.2 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.14−8.12 (m, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 7.9 Hz, 1H), 7.21−7.11 (m, 2H), 3.95 (s, 3H), 2.86 (t, J = 7.8, 2H), 1.72−1.64 (m, 2H), 1.41−1.31 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 140.7, 136.9, 135.2, 129.8, 129.2, 127.4, 127.2, 121.8, 120.2, 118.7, 113.5, 110.5, 52.0, 31.9, 26.2, 22.5, 13.8; IR (film): 1287, 1309, 1437, 1459, 1606, 1700, 2955, 3372 cm^{-1}.

*2-Butyl-3-(4-fluorophenyl)-1H-indole (**3h**).* Yield: 41 mg (77%), pale yellow solid, mp: 49−50 °C; R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.44−7.39 (m, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.18−7.08 (m, 4H), 2.79 (t, J = 7.8 Hz, 2H), 1.67−1.60 (m, 2H), 1.39−1.30 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (d, J = 244.4 Hz), 136.0, 135.1, 131.3 (d, J = 3.3 Hz), 131.0 (d, 7.6 Hz), 127.9, 121.6, 119.9, 118.6, 115.3 (d, J = 21,2 Hz), 113.4, 110.4, 31.9, 26.0, 22.4, 13.8; HRMS (ESI, m/z): calcd for $C_{18}H_{19}FN$ [M + H]$^+$ 268.1496, found 268.1497; IR (film): 1330, 1459, 1506, 1560, 2861, 2929, 2957, 3401 cm^{-1}.

*2-Butyl-3-(4-chlorophenyl)-1H-indole (**3i**).*[19] Yield: 48 mg (85%), pale yellow solid, mp: 41−43 °C; R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.42−7.38 (m, 4H), 7.31 (d, J = 7.9 Hz, 1H), 7.21−7.08 (m, 2H), 2.79 (t, J = 7.8 Hz, 2H), 1.67−1.60 (m, 2H), 1.39−1.30 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.1, 134.0, 131.6, 130.8, 128.6, 127.7, 121.7, 120.04, 118.6, 113.2, 110.4, 31.9, 26.0, 22.5, 13.8; IR (film): 1186, 1258, 1329, 1458, 1491, 1555, 2957, 3404 cm^{-1}.

*3-(4-Bromophenyl)-2-butyl-1H-indole (**3j**).* Yield: 48 mg (73%), pale yellow liquid, R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.58−7.55 (m, 3H), 7.35−7.31 (m, 3H), 7.17 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 2.80 (t, J = 7.8 Hz, 2H), 1.68−1.61 (m, 2H), 1.40−1.30 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.1, 134.4, 131.6, 131.2, 127.6, 121.7, 120.1, 119.7, 118.6, 113.3, 110.4, 31.9, 26.0, 22.5, 13.8; HRMS (ESI, m/z): calcd for $C_{18}H_{19}BrN$ [M + H]$^+$ 328.0695, found 328.0697; IR (film): 1186, 1257, 1329, 1458, 1488, 1552, 2958, 3406 cm^{-1}.

*2-Butyl-3-(3-methoxyphenyl)-1H-indole (**3k**).* Yield: 44 mg (78%), pale yellow liquid, R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.38−7.31 (m, 2H), 7.18−7.14 (m, 1H), 7.12−7.05 (m, 3H), 6.88−6.85 (m, 1H), 3.85 (s, 3H), 2.86(t, J = 7.8 Hz, 2H), 1.71−1.63 (m, 2H), 1.42−1.33 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 136.9, 136.1, 135.1, 129.4, 127.8, 122.1, 121.5, 119.9, 118.9, 115.1, 114.3, 111.5, 110.3, 55.2, 32.0, 26.1, 22.5, 13.8; HRMS (ESI, m/z): calcd for $C_{19}H_{22}NO$ [M + H]$^+$ 280.1696, found 280.1696; IR (film): 1262, 1329, 1419, 1490, 1571, 1603, 2956, 3406 cm^{-1}.

*3-(3-(1,3-Dioxolan-2-yl)phenyl)-2-butyl-1H-indole (**3l**).* Yield: 35 mg (55%), pale yellow liquid, R_f = 0.2 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.62−7.60 (m, 2H), 7.49−7.46 (m, 2H), 7.44−7.41 (m, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.17−7.13 (m, 1H), 7.11−7.07 (m, 1H), 5.89 (s, 1H), 4.16−4.13 (m, 2H), 4.06−4.03 (m, 2H), 2.82 (t, J = 7.8 Hz, 2H), 1.70−1.62 (m, 2H), 1.40−1.31 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 136.2, 135.6, 135.2, 130.4, 128.5, 127.9, 127.7, 123.9, 121.5, 119.9, 118.8, 114.1, 110.3, 103.9, 65.3, 32.0, 26.0, 22.5, 13.8; HRMS (ESI, m/z): calcd for $C_{21}H_{24}NO_2$ [M + H]$^+$ 322.1802, found 322.1801; IR (film): 1327, 1378, 1459, 1491, 1601, 1668, 2956, 3396 cm^{-1}.

*2-Butyl-3-(3-(trifluoromethyl)phenyl)-1H-indole (**3m**).*[20] Yield: 50 mg (78%), pale yellow liquid, R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.75 (s, 1H), 7.67−7.64 (m, 1H), 7.60−7.54 (m, 3H), 7.33 (d, J = 7.9 Hz, 1H), 7.21−7.11 (m, 2H), 2.82 (t, J = 7.8 Hz, 2H), 1.70−1.63 (m, 2H), 1.41−1.32 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 136.3, 135.2, 132.7, 130.8 (q, J = 31.9 Hz), 128.9, 127.5, 126.1 (q, J = 3.8 Hz), 124.3 (q, J = 272.4 Hz), 122.5 (q, J = 3.8 Hz), 121.9, 120.3, 118.4, 113.1, 110.5, 31.9, 26.0, 22.4, 13.7; IR (film): 1322, 1460, 1492, 1558, 1612, 2931, 2958, 3396 cm^{-1}.

*2-Butyl-3-(3-chlorophenyl)-1H-indole (**3n**).* Yield: 48 mg (84%), pale yellow liquid, R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.47−7.46 (m, 1H), 7.36−7.35 (m, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.28−7.25 (m, 1H), 7.21−7.15 (m, 1H), 7.13−7.09 (m, 1H), 2.81 (t, J = 7.8 Hz, 2H), 1.68−1.61 (m, 2H), 1.40−1.31 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 136.4, 135.1, 134.2, 129.7, 129.4, 127.7, 127.6, 125.9, 121.7, 120.1, 118.6, 113.1, 110.4, 31.9, 26.0, 22.4, 13.8; HRMS (ESI, m/z): calcd for $C_{18}H_{19}ClN$ [M + H]$^+$ 284.1201, found 284.1204; IR (film): 1253, 1327, 1404, 1458, 1561, 1596, 2957, 3402 cm^{-1}.

*2-(2-Butyl-1H-indol-3-yl)benzonitrile (**3o**).* Yield: 41 mg (75%), pale yellow liquid, R_f = 0.2 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.79−7.77 (m, 1H), 7.66−7.61 (m, 1H), 7.56−7.54 (m, 1H), 7.42−7.38 (m, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.18−7.08 (m, 2H), 2.83−2.67 (m, 2H), 1.69−1.48 (m, 2H), 1.30−1.19 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.8, 135.2, 133.3, 132.5, 131.9, 127.8, 126.7, 121.8, 120.1, 119.0, 118.3, 113.5, 111.0, 110.6, 31.2, 26.4, 22.2, 13.6; HRMS (ESI, m/z): calcd for $C_{19}H_{19}N_2$ [M + H]$^+$ 275.1543, found 275.1545; IR (film): 1017, 1327, 1459, 1491, 1597, 2226, 2957, 3390 cm^{-1}.

*3-(2-Bromophenyl)-2-butyl-1H-indole (**3p**).* Yield: 27 mg (42%), pale yellow liquid, R_f = 0.5 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.36−7.33 (m, 3H), 7.28 (d, J = 7.8 Hz, 1H), 7.24−7.19 (m, 1H), 7.18−7.14 (m, 1H), 7.07 (t, J = 7.5 Hz, 1H), 2.76−2.60 (m, 2H), 1.66−1.53 (m, 2H), 1.34−1.26 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 136.3, 134.8, 133.1, 132.8, 128.4, 128.2, 127.0, 125.7, 121.4, 119.7, 119.2, 114.1, 110.3, 31.4, 26.4, 22.3, 13.7; HRMS (ESI, m/z): calcd for $C_{18}H_{19}BrN$ [M + H]$^+$ 328.0695, found 328.0697; IR (film): 1025, 1056, 1256, 1330, 1458, 1474, 2955, 3407 cm^{-1}.

*3-([1,1′-Biphenyl]-4-yl)-2-butyl-1H-indole (**3q**).* Yield: 54 mg (82%), pale yellow liquid, R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.70−7.66 (m, 5H), 7.57−7.55 (m, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.35−7.30 (m, 2H), 7.19−7.10 (m, 2H), 2.86 (t, J = 7.8 Hz, 2H), 1.71−1.63 (m, 2H), 1.42−1.33 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 138.5, 136.2, 135.2, 134.6, 129.9, 128.8, 127.9, 127.1, 127.0, 127.0, 121.5, 119.9, 118.9, 113.9, 110.4, 32.0, 26.2, 22.5, 13.8; HRMS (ESI, m/z): calcd for $C_{24}H_{24}N$ [M + H]$^+$ 326.1903, found 326.1903; IR (film): 1331, 1458, 1488, 1561, 1610, 2927, 2956, 3414 cm^{-1}.

*2-Butyl-3-(naphthalen-2-yl)-1H-indole (**3r**).*[5b] Yield: 45 mg (75%), pale yellow liquid, R_f = 0.4 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.84 (m, 5H), 7.70−7.64 (m, 2H), 7.50−7.43 (m, 2H), 7.32 (t, J = 7.9 Hz, 1H), 7.20−7.10 (m, 2H), 2.87 (t, J = 7.8 Hz, 2H), 1.70−1.62 (m, 2H), 1.39−1.30 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 135.2, 133.8, 133.1, 131.9, 128.4, 128.1, 127.9, 127.8, 127.7, 125.9, 125.3, 121.6, 120.0, 118.9, 114.3, 110.4, 32.0, 26.1, 22.5, 13.8; IR (film): 1324, 1458, 1503, 1601, 1629, 2928, 2956, 3415 cm^{-1}.

*2-Cyclopropyl-3-(4-methoxyphenyl)-1H-indole (**3s**).*[5b] Yield: 33 mg (62%), pale yellow liquid, R_f = 0.3 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.56−7.53 (m, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.16−7.07 (m, 2H), 7.03−7.00 (m, 2H), 3.86 (s, 3H), 2.22−2.15 (m, 1H), 0.98−0.93 (m, 2H), 0.73−0.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 135.8, 134.7, 130.6, 128.2, 127.7, 121.5, 119.9, 118.6, 114.7, 113.8, 110.4, 55.3, 8.1, 7.5; IR (film): 1241, 1333, 1461, 1512, 1558, 1612, 1655, 3403 cm^{-1}.

*3-(4-Methoxyphenyl)-2-phenyl-1H-indole (**3t**).*[21] Yield: 43 mg (72%), yellow solid, mp: 179−181 °C; R_f = 0.3 (PE/EA = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.43−7.40 (m, 3H), 7.37−7.36 (m, 1H), 7.35−7.32 (m, 2H), 7.30−7.28 (m, 1H), 7.25−7.21 (m, 2H), 7.16−7.12 (m, 1H), 6.95−6.91 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 135.8,

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133.7, 132.8, 131.2, 129.0, 128.6, 128.0, 127.5, 127.3, 122.6, 120.3, 119.7, 114.7, 114.0, 110.8, 55.2; IR (film): 746, 1036, 1177, 1245, 1284, 1456, 1513, 2969 cm^{-1}.

*3-(4-Methoxyphenyl)-2-(p-tolyl)-1H-indole (**3u**).*[22] Yield: 48 mg (77%), yellow solid, mp: 109−110 °C; R_f = 0.3 (PE/EA = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.40−7.30 (m, 5H), 7.21−7.19 (m, 1H), 7.15−7.11 (m, 3H), 6.95−6.91 (m, 2H), 3.84 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 137.4, 135.7, 133.8, 131.1, 129.9, 129.4, 129.0, 127.9, 127.5, 122.4, 120.2, 119.5, 114.2, 114.0, 110.7, 55.2, 21.2; IR (film): 1175, 1244, 1285, 1329, 1455, 1520, 2959, 3408 cm^{-1}.

*3-(4-Methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-1H-indole (**3v**).* Yield: 61 mg (83%), pale yellow liquid, R_f = 0.3 (PE/EA = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.52 (q, J = 8.4 Hz, 4H), 7.41 (d, J = 8.1 Hz, 1H), 7.34−7.30 (m, 2H), 7.26−7.23 (m, 1H), 7.17−7.13 (m, 1H), 6.97−6.93 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ158.5, 136.3, 136.1, 131.9, 131.2, 129.1 (q, J = 32.5 Hz), 128.9, 128.0, 126.7, 125.6 (q, J = 3.7 Hz), 124.1 (q, J = 272.0 Hz), 123.3, 120.6, 120.0, 116.3, 114.3, 111.0, 55.23; HRMS (ESI, m/z): calcd for $C_{22}H_{17}F_3NO$ $[M + H]^+$ 368.1257, found 368.1258; IR (film): 734, 843, 1064, 1125, 1244, 1323, 1523, 1616 cm^{-1}.

*2-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1H-indole (**3w**).*[22] Yield: 54 mg (84%), pale yellow liquid, R_f = 0.2 (PE/EA = 10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.37−7.30 (m, 5H), 7.21−7.19 (m, 1H), 7.15−7.11 (m, 1H), 7.01−6.95 (m, 2H), 6.94−6.91 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J = 247.9 Hz), 158.1, 135.8, 132.8, 131.1, 129.8 (d, J = 8.0 Hz), 128.9 (d, J = 3.4 Hz), 128.8, 127.1, 122.7, 120.4, 119.6, 115.7 (d, J = 21.7 Hz), 114.6, 114.1, 110.8, 55.2; IR (film): 1035, 1159, 1244, 1454, 1496, 1519, 1598, 2971 cm^{-1}.

Experiments for Mechanistic Investigations (eq 1). To a solution of PPh_3 (52.4 mg, 0.2 mmol) in dried dichloromethane (1 mL) was added the 2-alkynyl azidobenzene **1a** (40 mg, 0.2 mmol) at room temperature, and the mixture was stirred for 6 h. 2-Alkynyl azidobenzene completely disappeared as judged by TLC (thin-layer chromatography). The solvent was then removed under vacuum to afford phosphinimine **4** as the crude product. The structure of phosphinimine **4** was confirmed by comparing the ^1H and ^{13}C NMR spectra with standard spectra.[24] Then Pd_2dba_3 (4.6 mg, 0.005 mmol, 2.5 mol %), LiO^tBu (24 mg, 0.3 mmol), dry toluene (2 mL), aryl bromide **2a** (56 mg, 0.3 mmol), and the phosphinimine **4** were added to the reaction tube under N_2 gas, and the solution was stirred at 100 °C for 24 h. The product **3a** could be isolated in 56% yield. A similar reaction with dppe afforded **3a** in 72% yield.

General Procedure for the Synthesis of Polysubstituted Isoquinolines. Under N_2 gas, Pd_2dba_3 (4.6 mg, 0.005 mmol, 2.5 mol %), PPh_3 (78.6 mg, 0.3 mmol), and LiO^tBu (44.8 mg, 0.56 mmol) were successively added to a flame-dried 10 mL Schlenk tube. The reaction tube was degassed three times with N_2, and dry toluene (1 mL) was added by syringe. Then, 2-alkynyl benzylazide (0.2 mmol) and aryl bromide (0.6 mmol) were added by syringe, respectively. Note that aryl bromide in solid form was added to the reaction tube prior to LiO^tBu. The reaction was heated at 100 °C with stirring for 24 h, and then it was cooled to room temperature and filtered through a short plug of silica gel with ethyl acetate as the eluent. The solvent was removed in *vacuo* to leave a crude mixture, which was purified to afford the pure product **6a−l**.

*3-Butyl-4-(4-methoxyphenyl)isoquinoline (**6a**).* Yield: 45 mg (76%), pale yellow liquid, R_f = 0.3 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.96−7.94 (m, 1H), 7.55−7.48 (m, 2H), 7.41−7.39 (m, 1H), 7.21 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 3.90 (s, 3H), 2.74 (t, J = 7.9 Hz, 2H), 1.71−1.63 (m, 2H), 1.32−1.22 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158. 9, 153.4, 151.3, 136.3, 131.2, 130.1, 130.0, 129.5, 127.3, 126.7, 125.9, 125.2, 113.8, 55.2, 35.3, 32.5, 22.7, 13.9; HRMS (ESI, m/z): calcd for $C_{20}H_{22}NO$ $[M + H]^+$ 292.1696, found 292.1689; IR (film): 1235, 1286, 1377, 1463, 1514, 1573, 1610, 2929, 2957 cm^{-1}.

*3-Butyl-4-phenylisoquinoline (**6b**).* Yield: 36 mg (70%), pale yellow liquid, R_f = 0.5 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.97−7.95 (m, 1H), 7.54−7.43 (m, 5H), 7.37−7.34 (m, 1H), 7.30−7.28 (m, 2H), 2.72 (t, J = 7.9 Hz, 2H), 1.71−1.63 (m, 2H), 1.30−1.21 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 151.5, 137.5, 135.9, 130.4, 130.2, 130.1, 128.4, 127.4, 127.3, 126.6, 126.0, 125.2, 35.3, 32.5, 22.7, 13.9; HRMS (ESI, m/z): calcd for $C_{19}H_{20}N$ $[M + H]^+$ 262.1590, found 262.1585; IR (film): 1249, 1376, 1443, 1500, 1573, 1619, 2928, 2957 cm^{-1}.

*3-Butyl-4-(4-(trimethylsilyl)phenyl)isoquinoline (**6c**).* Yield: 39 mg (59%), pale yellow liquid, R_f = 0.4 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.96−7.94 (m, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.53−7.48 (m, 2H), 7.39−7.36 (m, 1H), 7.27 (d, J = 8.0 Hz, 2H), 2.72 (t, J = 7.9 Hz, 2H), 1.72−1.64 (m, 2H), 1.31−1.22 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H), 0.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 151.5, 139.5, 137.8, 135.9, 133.3, 130.5, 130.0, 129.5, 127.3, 126.6, 126.0, 125.3, 35.3, 32.5, 22.6, 13.9, −1.0; HRMS (ESI, m/z): calcd for $C_{22}H_{28}NSi$ $[M + H]^+$ 334.1986, found 334.1988; IR (film): 818, 857, 967, 1105, 1249, 1377, 1572, 2955 cm^{-1}.

*3-Butyl-4-(4-fluorophenyl)isoquinoline (**6d**).* Yield: 36 mg (65%), pale yellow liquid, R_f = 0.4 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.98−7.96 (m, 1H), 7.57−7.50 (m, 2H), 7.34−7.32 (m, 1H), 7.28−7.19 (m, 4H), 2.70 (t, J = 7.9 Hz, 2H), 1.70−1.62 (m, 2H), 1.31−1.22 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J = 246.5 Hz), 153.2, 151.7, 136.0, 133.3 (d, J = 3.6 Hz), 131.8 (d, J = 8.0 Hz), 130.3, 129.4, 127.4, 126.6, 126.1, 124.9, 115.5 (d, J = 21.3 Hz), 35.3, 32.4, 22.7, 13.8; HRMS (ESI, m/z): calcd for $C_{19}H_{19}FN$ $[M + H]^+$ 280.1496, found 280.1493; IR (film): 1222, 1378, 1507, 1573, 1604, 1619, 2929, 2958 cm^{-1}.

*3-Butyl-4-(4-chlorophenyl)isoquinoline (**6e**).* Yield: 38 mg (65%), pale yellow liquid, R_f = 0.4 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.98−7.96 (m, 1H), 7.57−7.52 (m, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.34−7.31 (m, 1H), 7.25−7.23 (m, 2H), 2.70 (t, J = 7.9 Hz, 2H), 1.70−1.62 (m, 2H), 1.31−1.22 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 151.9, 135.9, 135.7, 133.6, 131.6, 130.3, 129.2, 128.7, 127.5, 126.6, 126.2, 124.8, 35.3, 32.4, 22.7, 13.9; HRMS (ESI, m/z): calcd for $C_{19}H_{19}ClN$ $[M + H]^+$ 296.1201, found 296.1193; IR (film): 1376, 1455, 1487, 1498, 1572, 1619, 2926, 2956 cm^{-1}.

*4-(4-Bromophenyl)-3-butylisoquinoline (**6f**).* Yield: 40 mg (59%), pale yellow liquid, R_f = 0.4 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.99−7.96 (m, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.57−7.51 (m, 2H), 7.34−7.31 (m, 1H), 7.18 (d, J = 8.3 Hz, 2H), 2.70 (t, J = 7.9 Hz, 2H), 1.70−1.62 (m, 2H), 1.31−1.22 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 151.8, 136.4, 135.7, 131.9, 131.7, 130.4, 129.2, 127.5, 126.6, 126.2, 124.8, 121.7, 35.3, 32.5, 22.7, 13.9; HRMS (ESI, m/z): calcd for $C_{19}H_{19}BrN$ $[M + H]^+$ 340.0695, found 340.0689; IR (film): 1377, 1455, 1486, 1497, 1572, 1619, 2927, 2955 cm^{-1}.

*3-Butyl-4-(3-chlorophenyl)isoquinoline (**6g**).* Yield: 36 mg (61%), pale yellow liquid, R_f = 0.4 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.98−7.96 (m, 1H), 7.58−7.51 (m, 2H), 7.46−7.45 (m, 2H), 7.34−7.31 (m, 2H), 7.21−7.18 (m, 1H), 2.71 (t, J = 7.9 Hz, 2H), 1.71−1.64 (m, 2H), 1.32−1.23 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 152.0, 139.4, 135.6, 134.4, 130.4, 130.2, 129.7, 129.0, 128.5, 127.8, 127.5, 126.6, 126.12, 124.8, 35.3, 32.4, 22.6, 13.8; HRMS (ESI, m/z): calcd for $C_{19}H_{19}ClN$ $[M + H]^+$ 296.1201, found 296.1194; IR (film): 1078, 1374, 1496, 1571, 1594, 1619, 2927, 2957 cm^{-1}.

*4-([1,1′-Biphenyl]-4-yl)-3-butylisoquinoline (**6h**).* Yield: 40 mg (59%), pale yellow liquid, R_f = 0.3 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.99−7.96 (m, 1H), 7.76−7.71 (m, 4H), 7.55−7.44 (m, 5H), 7.41−7.36 (m, 3H), 2.77 (t, J = 7.9 Hz, 2H), 1.74−1.67 (m, 2H), 1.33−1.24 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 151.6, 140.6, 140.2, 136.5, 135.9, 130.7, 130.1, 128.8, 127.4, 127.4, 127.1, 126.7, 126.0, 125.2, 35.4, 32.5, 22.7, 13.9; HRMS (ESI, m/z): calcd for $C_{25}H_{24}N$

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$[M + H]^+$ 338.1903, found 338.1897; IR (film): 733, 765, 1377, 1485, 1573, 1619, 2927, 2956 cm^{-1}.

3-Butyl-4-(naphthalen-2-yl)isoquinoline (6i). Yield: 29 mg (47%), pale yellow liquid, R_f = 0.4 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.99−7.95 (m, 3H), 7.89−7.86 (m, 1H), 7.78 (s, 1H), 7.58−7.53 (m, 2H), 7.52−7.47 (m, 2H), 7.43−7.40 (m, 1H), 7.37−7.35 (m, 1H), 2.78−2.73 (m, 2H), 1.74−1.66 (m, 2H), 1.28−1.19 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 151.7, 136.0, 135.0, 133.3, 132.6, 130.3, 130.1, 129.1, 128.4, 128.1, 128.0, 127.8, 127.4, 126.7, 126.4, 126.2, 126.0, 125.2, 35.4, 32.5, 22.6, 13.9; HRMS (ESI, m/z): calcd for $C_{23}H_{22}N$ $[M + H]^+$ 312.1747, found 312.1749; IR (film): 1242, 1377, 1465, 1494, 1572, 1618, 2927, 2957 cm^{-1}.

4-(4-Methoxyphenyl)-3-pentylisoquinoline (6j). Yield: 46 mg (76%), pale yellow liquid, R_f = 0.4 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.96−7.94 (m, 1H), 7.54−7.47 (m, 2H), 7.41−7.39 (m, 1H), 7.22−7.19 (m, 2H), 7.06−7.03 (m, 2H), 3.90 (s, 3H), 2.75−2.71 (m, 2H), 1.72−1.65 (m, 2H), 1.24−1.21 (m, 4H), 0.84−0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 153.4, 151.4, 136.3, 131.2, 130.1, 130.0, 129.6, 127.3, 126.7, 125.9, 125.2, 113.8, 55.2, 35.6, 31.8, 30.0, 22.4, 13.9; HRMS (ESI, m/z): calcd for $C_{21}H_{24}NO$ $[M + H]^+$ 306.1852, found 306.1849; IR (film): 1228, 1286, 1377, 1514, 1573, 1610, 2928, 2956 cm^{-1}.

3-Cyclopropyl-4-(4-methoxyphenyl)isoquinoline (6k). Yield: 47 mg (85%), yellow solid, mp: 135−136 °C; R_f = 0.5 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.91−7.88 (m, 1H), 7.52−7.48 (m, 1H), 7.46−7.42 (m, 2H), 7.33−7.30 (m, 2H), 7.08−7.04 (m, 2H), 3.89 (s, 3H), 1.99−1.92 (m, 1H), 1.18−1.15 (m, 2H), 0.86−0.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 152.9, 151.4, 135.8, 131.7, 130.0, 129.4, 129.4, 127.3, 126.4, 125.4, 124.7, 113.9, 55.2, 14.4, 9.7; HRMS (ESI, m/z): calcd for $C_{19}H_{18}NO$ $[M + H]^+$ 276.1383, found 276.1382; IR (film): 1033, 1176, 1228, 1287, 1453, 1513, 1573, 1610 cm^{-1}.

3,4-Bis(4-methoxyphenyl)isoquinoline (6l).[23] Yield: 42 mg (62%), pale yellow solid, mp: 157−159 °C; R_f = 0.2 (PE/EA = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.03−8.01 (m, 1H), 7.70−7.68 (m, 1H), 7.62−7.55 (m, 2H), 7.35−7.32 (m, 2H), 7.18−7.15 (m, 2H), 6.95−6.91 (m, 2H), 6.78−6.75 (m, 2H), 3.86 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 158.6, 151.5, 150.4, 136.3, 133.4, 132.3, 131.5, 130.3, 129.7, 129.6, 127.5, 127.2, 126.5, 125.5, 113.9, 113.1, 55.2, 55.1; IR (film): 829, 1033, 1176, 1244, 1513, 1608, 2834, 2930 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01864.

Copies of ^1H and ^{13}C spectra for all products (PDF)

X-ray crystallographic data for product **3t** (CIF)

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Notes

The authors declare no competing financial interest.

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