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Synthesis of Indolo[2,1-*a*]isoquinolines via a Triazene-Directed C−H Annulation Cascade

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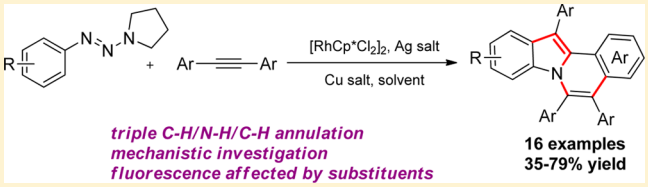
Supporting Information

ABSTRACT: Indole-containing polyaromatic scaffolds are widely found in natural products, pharmaceutical agents, and π-conjugated functional materials. Often, the synthesis of these highly valuable molecules requires a multistep sequence. Therefore, a simple, one-step protocol to access libraries of polyaromatic indole scaffolds is highly desirable. Herein we describe the direct synthesis of polysubstituted indolo[2,1-*a*]isoquinoline analogues via a double C−H annulation cascade using triazene as an internally cleavable directing group. Evidence from HRMS and theoretical calculations suggests that an unprecedented 1,2-alkyl migration might be responsible for the in situ cleavage of the directing group. Both kinetic isotope effects and DFT calculations suggested that the alkyne insertion step is rate-limiting for the second C,N annulation reaction.



INTRODUCTION

Indolo[2,1-*a*]isoquinolines are widely found in molecules with various functions, including tubulin-binding drugs,[1] HCV replicon inhibitors,[2] estrogen receptor modulators,[3] solid-state fluorescent materials, and organic semiconductors.[4] The specific functions of these molecules are often affected by the substituents on the flat, electron-rich, polyaromatic ring skeleton.[5] Therefore, intensive research has been directed toward the development of straightforward methods for the synthesis of substituted indolo[2,1-*a*]isoquinoline analogues.[6] The recently reported C−H/N−H activation−annulation reactions offer a very attractive approach to such scaffolds.[4a,7] The starting materials for these reactions, free NH indoles, can also be synthesized through an analogous C−H/N−H annulation reaction between an aniline derivative and an internal alkyne.[8,9] As common directing groups (DGs) for the indole synthesis are noncleavable in situ,[10] a separate synthetic operation is required to remove the DG, rendering the overall synthesis of indolo[2,1-*a*]isoquinolines a three-step sequence (Scheme 1a). Very recently, Glorius and our own group reported the direct synthesis of free NH indoles using removable directing groups (Scheme 1b).[11] Encouraged by our recent discovery of the synthesis of free NH indoles using triazene as an "internally cleavable" directing group,[12] we decided to intercept the free NH indole product in situ with another equivalent of the internal alkyne to generate the corresponding indolo[2,1-*a*]isoquinoline directly. To the best of our knowledge, this is the first direct synthesis of indolo[2,1-*a*]isoquinolines from readily available aniline derivatives.

RESULTS AND DISCUSSION

One significant limitation of our original triazene-directed indole synthesis was a very narrow substrate scope.[11b] The reaction worked well only for triazenylbenzenes bearing electron-neutral substituents. Strong electron-donating (e.g., MeO) and electron-withdrawing (e.g., Ac, CO_2Me, NO_2, etc.) groups were not tolerated, and very low yields of the indole products were obtained. Therefore, we decided to extend the substrate scope for the crucial free NH indole synthesis before attempting the cascade strategy. 2-Methoxy-4-nitrophenyltriazene **1aa**, a modest substrate in our previous indole synthesis, was chosen for development of the reaction conditions. Under our previously identified conditions, substrate **1aa** reacted with 1.1 equiv of diphenylacetylene (**2a**) in the presence of 5 mol % $[RhCp^*Cl_2]_2$, 20 mol % $AgSF_6$, and 2.0 equiv of $Cu(OAc)_2 \cdot H_2O$ in MeOH, yielding indole **3aa** in 61% yield. Various copper oxidants were examined, and $Cu(OPiv)_2$ was found to be significantly superior (Table 1, entry 5). Surprisingly, we observed a profound solvent effect. A 1:1 MeOH/*t*AmOH mixture led to a yield 30% higher than that with MeOH alone, while *t*AmOH resulted in a very slow reaction (50% yield). Combining $Cu(OPiv)_2$ and the solvent mixture improved the yield of **3aa** to 94%.

Having identified the critical copper oxidant and solvent combination, we examined many substrates beyond the scope of the previous reaction conditions. As shown in Table 2, for various triazenes examined, the yields were significantly higher

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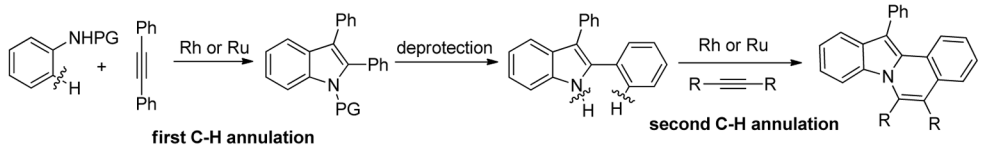
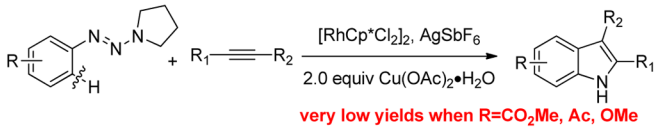
Scheme 1. C−H Annulation Strategy for the Synthesis of Indolo[2,1-*a*]isoquinolines

a) Three-step synthesis of indolo[2,1-*a*]isoquinolines via C-H annulation reactions

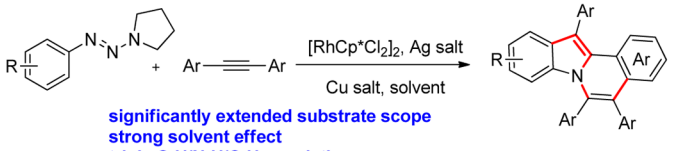


b) Triazene directed NH free indole synthesis via C-H annulation



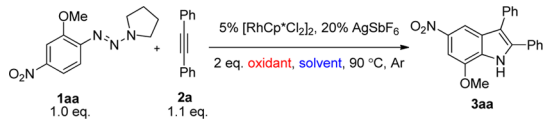
very low yields when R=CO_2Me, Ac, OMe

c) Triazene directed C-H annulation cascade (this work)



significantly extended substrate scope
strong solvent effect
triple C-H/N-H/C-H annulation
one-step cascade to indolo[2,1-*a*]isoquinolines
mechanistic insights
fluorescent tuning by substituents

Table 1. Investigation of Conditions for Triazene-Directed Indole Synthesis[a]



entry	solvent	oxidant	additive	yield (%)
1	MeOH	$CuCl_2$	$AgSbF_6$	trace
2	MeOH	CuO	$AgSbF_6$	trace
3	MeOH	$Cu(OTf)_2$	$AgSbF_6$	trace
4	MeOH	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	61
5	MeOH	$Cu(OPiv)_2$	$AgSbF_6$	82
6	MeOH/*t*AmOH	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	91
7	**MeOH/*t*AmOH**	**$Cu(OPiv)_2$**	**$AgSbF_6$**	**94**

[a]Reactions were carried out on a 0.2 mmol scale at 90 °C for 24 h.

than those using the previous $Cu(OAc)_2{\cdot}H_2O$/MeOH conditions. The nonsubstituted phenyltriazene resulted in a 76% yield, a more than 25% improvement. Substrates having strong electron-withdrawing substituents (CO_2Me, Ac, NO_2) were smoothly converted to the corresponding free NH indoles in moderate to high yields. Electron-donating groups were also tolerated. The reaction was slower when the other *ortho* position of the substrate was substituted. For alkyl,aryl-substituted asymmetric internal alkynes, excellent regioselectivity was observed.

The in situ cleavage of the N−N bond of triazene was intriguing. To obtain insights into this puzzle, mass spectrometry studies aimed at capturing the leaving fragment were performed. Since a Ag salt was used to abstract chloride from the catalyst precursor and a Cu salt acted as an oxidant, stoichiometric $RhCp^*(OAc)_2$ was used for the mass spectrometry experiments. This rhodium "catalyst" gave the desired indole product in 47% yield under otherwise identical conditions. When the diluted reaction mixture (see the Supporting Information for details) was introduced to a high-resolution ESI mass spectrometer, a peak at m/z = 321, which might correspond to $[(C_{10}H_{14})RhN_2C_4H_8]^+$, was identified. Collision-induced dissociation (CID) of this species (Figure 1a) gave two major fragments at m/z = 292 and 237. The peak at m/z = 237 was assigned as $[Cp^*Rh - H]^+$ (Figure 1c),[13] suggesting the loss of the $N_2C_4H_8$ fragment. To confirm this fragmentation, a 2-methylpyrrolidine-derivatized triazene substrate was tested. As expected, a peak at m/z = 335 was found. The CID mass spectrum of the peak at m/z = 335 (Figure 1b) also showed a similar fragmentation pattern. On the basis of the loss of 84/29 and 98/43/29, respectively, a cyclic azo species from a 1,2-alkyl migration/ring expansion pathway was proposed. Preliminary free energy profiling revealed that such a process is highly exergonic (−44.4 kcal/mol).

During the substrate scope survey, we noticed a minor side product for the substrate bearing a *p*-Ac group. Isolation and structure elucidation revealed that this was the indolo[2,1-*a*]isoquinoline cascade product. We next surveyed various reaction parameters for the direct synthesis of indolo[2,1-*a*]isoquinolines (Table 3). It was found that combining the indole synthesis and the second N−H/C−H annulation was not trivial. Most of the conditions examined favored either the indole synthesis or the indole−aryl annulation but not both, and often, a large amount of indole or the triazene substrate remained at the end of the cascade. Both steps appeared to be most affected by the solvent. For 3-Ac-substituted triazenylbenzene **1q**, low yields were observed in most solvents. Surprisingly, mixing MeOH and *t*AmOH in a 1:1 ratio led to a very strong synergistic effect. The cascade reaction in either alcohol alone gave a yield of ≤10% (Table 3, entries 4 and 5), while a 65% yield was obtained using the solvent mixture (Table 3, entry 6). This unexpected yield was attributed to the difference in the rates of the two annulation steps in different solvents. Separate experiments showed that the second N−H/C−H annulation step was very slow in MeOH and quite facile in *t*AmOH. In sharp contrast, the first NH indole formation step was fast in MeOH and very slow in *t*AmOH. Therefore, a 1:1 MeOH/*t*AmOH mixture was required for the overall

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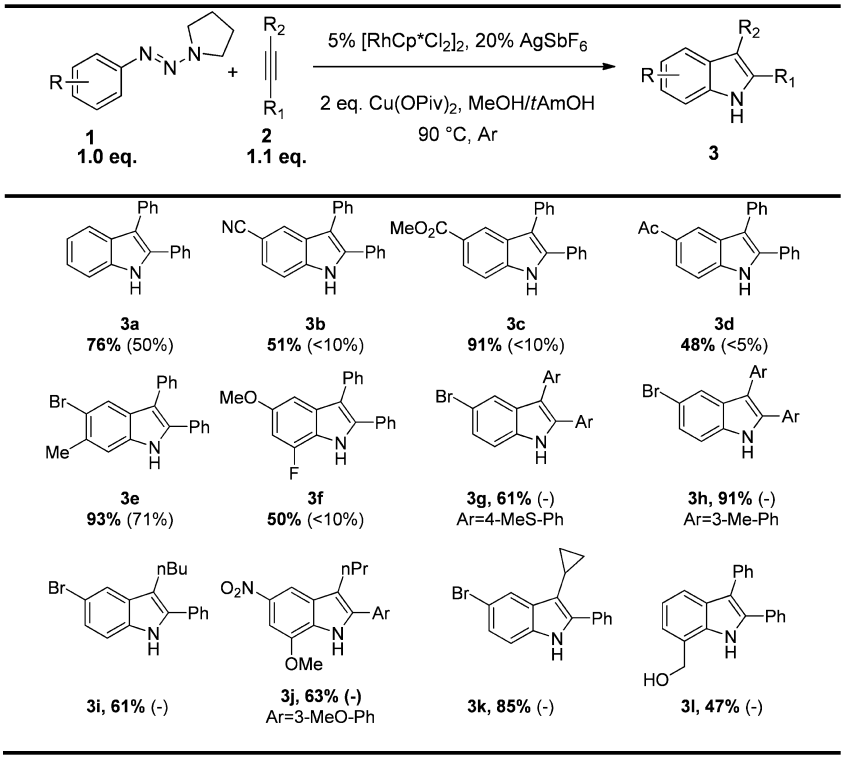
Table 2. Extended Substrate Scope beyond That of the Previous Triazene-Directed NH Indole Synthesis[a]



[a]Reactions were carried out on a 0.3 mmol scale at 90 °C for 24 h; numbers in parentheses represent yields using the $Cu(OAc)_2 \cdot H_2O$/MeOH conditions.

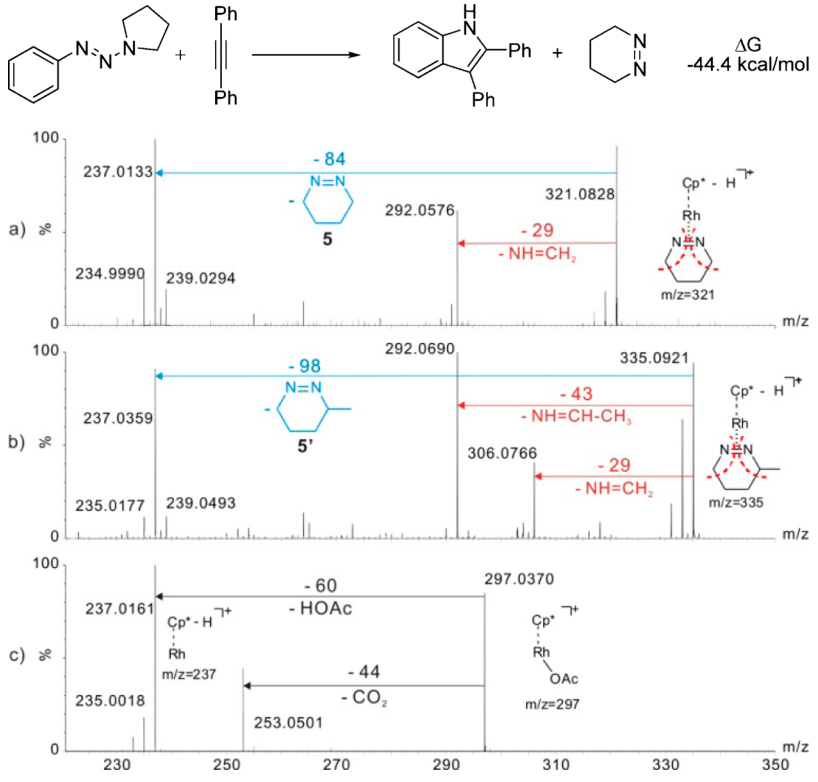


Figure 1. CID-HRMS evidence for the 1,2-alkyl migration/ring expansion mechanism of the N═N bond cleavage: (a) CID spectrum of the ion at m/z = 321.1 at E_{lab} = 15 eV; (b) CID spectrum of the ion at m/z = 335.1 at E_{lab} = 15 eV; (c) CID spectrum of the ion at m/z = 297.0 at E_{lab} = 10 eV. All of the CID experiments were performed with Ar as the collision gas.

cascade. Since the solvent mixture did not seem to slow down either step, it is likely that both solvents participated in both C−H activation processes. By contrast, when the non-substituted triazenylbenzene was examined, the MeOH/

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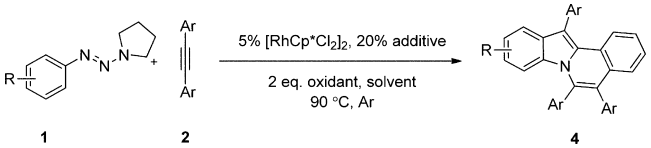
Table 3. Investigation of Conditions for the Direct Synthesis of Indolo[2,1-*a*]isoquinolines[a]



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entry	substrate	solvent	oxidant	additive	yield (%)[b]
1	**1q**	DCE	$Cu(OAc)_2$	$AgSbF_6$	8
2	**1q**	CH_3CN	$Cu(OAc)_2$	$AgSbF_6$	22
3	**1q**	*o*-xylene	$Cu(OAc)_2$	$AgSbF_6$	7
4	**1q**	*t*AmOH	$Cu(OAc)_2$	$AgSbF_6$	<5
5	**1q**	MeOH	$Cu(OAc)_2$	$AgSbF_6$	10
6	**1q**	MeOH/*t*AmOH	$Cu(OAc)_2$	$AgSbF_6$	65
7	**1q**	**MeOH/*t*AmOH**	**$Cu(OPiv)_2$**	**$AgSbF_6$**	**79**
8	**1a**	MeOH	$Cu(OAc)_2$	$AgSbF_6$	15
9	**1a**	MeOH/*t*AmOH	$Cu(OPiv)_2$	$AgSbF_6$	25
10	**1a**	*t*BuOH	$Cu(OAc)_2$	AgOAc	49
11	**1a**	*i*PrOH	$Cu(OAc)_2$	AgOAc	20
12	**1a**	DCE/*t*AmOH	$Cu(OAc)_2$	AgOAc	46
13	**1a**	MeOH/DCE	$Cu(OAc)_2$	AgOAc	<5
14	**1a**	**DCE**	**$Cu(OAc)_2$**	**AgOAc**	**53**

[a]Reactions were carried out on a 0.2 mmol scale for 48 h using 3.5 equiv of alkyne. [b]Conversion was calculated by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the external standard.

*t*AmOH conditions resulted in a yield of only 25% (Table 3, entry 9). For this substrate, the second step seemed to be problematic, and after an extensive search, DCE was found to be the best solvent (Table 3, entry 14). Eventually, we were able to identify two sets of conditions for the direct synthesis of indolo[2,1-*a*]isoquinolines. For triazenylbenzenes having an strong electron-withdrawing substituent, $Cu(OPiv)_2$ was used as the oxidant and a 1:1 mixture of MeOH and *t*AmOH was used as the solvent. For electron-neutral and -rich substrates, $Cu(OAc)_2{\cdot}H_2O$ and DCE were employed.

With the sets of optimized conditions in hand, we next examined the scope and functional group tolerance for both arenes and alkynes. As shown in Table 4, a number of triazenes and alkynes were smoothly converted to the desired indolo[2,1-*a*]isoquinolines. Triazenylbenzenes bearing electron-deficient substituents reacted in moderate to good yields under conditions A, while substrates having halogens, alkyls, and other electron-donating groups yielded only trace amounts of the desired polyaromatic products under the same conditions. The reactions of these substrates proceeded well under conditions B. *Para*, *meta*, or disubstituted triazenes were well-tolerated. Substrates having one *ortho* position substituted afforded low yields because of the unproductive indole synthesis step. Diarylacetylenes tolerated various substituents. Unfortunately, asymmetrically disubstituted acetylenes gave low yields and mixtures of regioisomers. Alkynes bearing an electron-withdrawing group such as ester, nitrile, etc. were not tolerated for this reaction. Rigorous efforts to address the selectivity issue of these substrates are currently ongoing.

A major limitation of the cascades described in Table 4 was the necessity to use the same alkyne twice. When two different alkynes were subjected to the conditions in Table 4, only the product from the more reactive alkyne was observed. Next, we tried sequential addition, where the second alkyne was introduced after the first alkyne was consumed. The "hybrid" indolo[2,1-*a*]isoquinoline product **5a** obtained from diphenylacetylene and 1,2-bis(4-bromophenyl)ethyne was isolated in 28% yield in the one-pot protocol. The efficiency of the synthesis of hybrid products was significantly improved by using a two-step sequence in which the free NH indole from one alkyne was isolated and treated with another alkyne under the cascade conditions (Scheme 2). Diphenylacetylenes bearing various substituents were well-tolerated.

The reaction of the free NH indole and an alkyne under either conditions A or B gave the desired indolo[2,1-*a*]isoquinoline in good yield, indicating that indole is an intermediate for this cascade reaction. The second catalytic cycle leading to the polyaromatic indole scaffold was investigated by density functional theory (DFT) calculations (see the Supporting Information for computational details). A catalytic cycle with its free energy profile is depicted in Scheme 3. The reaction is initiated by coordination of the indole to $Cp^*Rh(OAc)_2$.[14] Deprotonation of N−H via a low-barrier transition state (11.1 kcal/mol) gives **INT2**. Hence, N−Rh moiety serves as a directing group for the following C−H bond activation. A concerted metalation−deprotonation (CMD) process[15] then takes place with an activation free energy of 19.9 kcal/mol to afford intermediate **INT3**. It should be noted that the N−Rh moiety may also direct the Rh center to another adjacent C−H bond at the indole C7. However, the calculated high barrier (35.9 kcal/mol) strongly discourages this possibility. Through a dissociative ligand exchange step, AcOH is replaced by an alkyne to form intermediate **INT4**. Insertion of the alkyne into the Rh−C bond yields intermediate **INT5**. The congested environment in **TS3** causes repulsive interactions and consequently results in a high barrier for the insertion. The relative free energy of **TS3** was calculated to be 24.2 kcal/mol, which is still accessible under the current reaction conditions. Subsequently, **INT5** undergoes reductive elimination to release the product. Finally, Rh(I) in **INT6** is oxidized by $Cu(OAc)_2$ to regenerate the active Rh(III) species. Overall, the alkyne insertion is the rate-limiting step for this catalytic cycle. The potential energy surface shows that the C−H activation step is reversible, implying that the C−H activation should not exhibit a kinetic isotope effect. The small KIE of 1.1 measured experimentally (see the Supporting Information for details) verified our theoretical prediction and supported the proposed mechanism.

The isolated products displayed strong fluorescent color in both the solid and solution states. Variation of the substituents influences the energy levels and/or dipole moments in the ground and excited states of the core fluorophores, giving rise to different optical and photochemical properties of the fluorescent materials.[16] As expected, electron-donating groups blue-shifted the emission peaks by increasing the energy gap between the HOMO and LUMO (3.75 eV for compound **4f**; Scheme 4), while electron-withdrawing substituents red-shifted the emission peaks (3.29 eV for compound **4j**; Scheme 4). The fluorescence difference was more significant under UV light.

In summary, we have developed the first direct synthesis of indolo[2,1-*a*]isoquinolines using a Rh(III)-catalyzed triple C−H/N−H/C−H activation−annulation cascade. This transformation utilizes an internally cleavable triazene directing group. Collision-induced dissociation HRMS and theoretical calculations suggested that an unprecedented 1,2-alkyl migration/ring expansion mechanism is responsible for the in situ N−N cleavage. Detailed DFT studies of the second cascade step were carried out. The fluorescent properties of the

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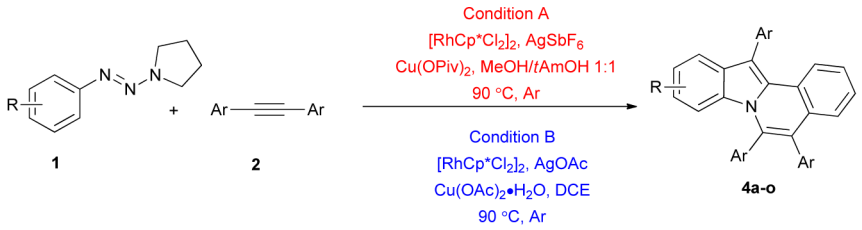
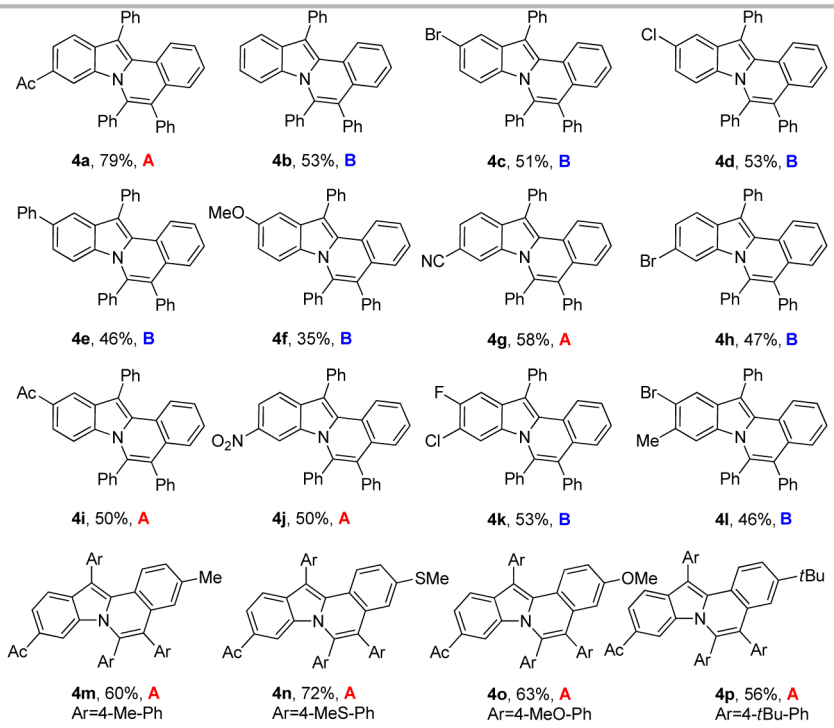
Table 4. Substrate Scope for the Synthesis of Indolo[2,1-*a*]isoquinolines via Cascade C−H Annulation[a]





[a]Reactions were carried out on a 0.2 mmol scale using 3.5 equiv of alkyne.

products are strongly influenced by the electronic characteristics of their substituents.

EXPERIMENTAL SECTION

General Methods and Materials. All of the reactions were performed under an argon atmosphere (balloon) with dry solvents under anhydrous conditions. Unless otherwise specified, all of the reagents and starting materials were purchased from commercial sources and used as received. The chromatography solvents were technical grade and distilled prior to use. Flash chromatography was performed using 200−300 mesh silica gel with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. The developed chromatograms were visualized by UV absorbance (254 nm). The ^{1}H and ^{13}C NMR data were recorded on 400 MHz NMR spectrometers, unless otherwise specified. Chemical shifts (δ) in parts per million are reported relative to the residual signals of chloroform (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Multiplicities are described as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet), and coupling constants (J) are reported in hertz. HRMS (ESI) analysis with a quadrupole time-of-flight mass spectrometer yielded ion mass/charge (m/z) ratios in atomic mass units. IR spectra were measured as dry films (KBr), and peaks are reported in terms of wavenumber (cm^{-1}).

General Procedure for the Synthesis of Free NH Indoles. $[Cp^*RhCl_2]_2$ (0.0015 mmol, 9.3 mg, 5 mol %), triazene substrate **1** (0.3 mmol, 1.0 equiv), $Cu(OPiv)_2$ (0.6 mmol, 159.5 mg, 2.0 equiv), and $AgSbF_6$ (0.060 mmol, 21 mg, 0.2 equiv) were weighed into an oven-dried Schlenk tube. The reaction vessel was capped and vacuum-flushed with argon three times. A solution of alkyne (0.33 mmol, 1.1 equiv) in 1:1 MeOH/*t*AmOH (3.0 mL) was added through the side arm using a syringe. The reaction mixture was stirred under an argon atmosphere at 90 °C for 24 h and then cooled to room temperature. Volatile solvent and reagents were removed by rotary evaporation, and the residue was purified by silica gel flash chromatography using ethyl acetate/petroleum ether (1:100 to 1:20) to afford product **3**.

*7-Methoxy-5-nitro-2,3-diphenyl-1H-indole (**3aa**).* Ethyl acetate/petroleum ether = 1:9, 94% yield (97.0 mg), yellow solid, mp 170−172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (s, 1H), 8.29 (s, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.43−7.34 (m, 10H), 4.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.4, 143.1, 136.3, 133.6, 131.6, 130.1, 129.7, 129.0, 128.6, 128.4, 128.2, 127.2, 117.6, 110.9, 104.3, 98.1, 56.1. HRMS (ESI): found 345.1231, calcd for $C_{21}H_{17}N_2O_3$ ([M + H]$^+$) 345.1239. IR (KBr) cm^{-1}: 3345, 1526, 1476, 1337, 1130, 1072, 797, 766, 743, 702.

*2,3-Diphenyl-1H-indole (**3a**).* Ethyl acetate/petroleum ether = 1:40, 76% yield (61.3 mg), yellow solid, mp 89−91 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.50−7.27 (m, 12H), 7.18 (td, J = 8.0, 0.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.0, 135.2, 134.2, 132.8, 130.3, 128.9, 128.8, 128.7, 128.3, 127.8, 126.4, 122.8, 120.6, 119.8, 115.2, 111.0. HRMS (APCI): found 270.1278, calcd for $C_{20}H_{16}N$ ([M + H]$^+$) 270.1283. IR (KBr) cm^{-1}: 3410, 3057, 2926, 1506, 1456, 1423, 1250, 1070, 764, 698.

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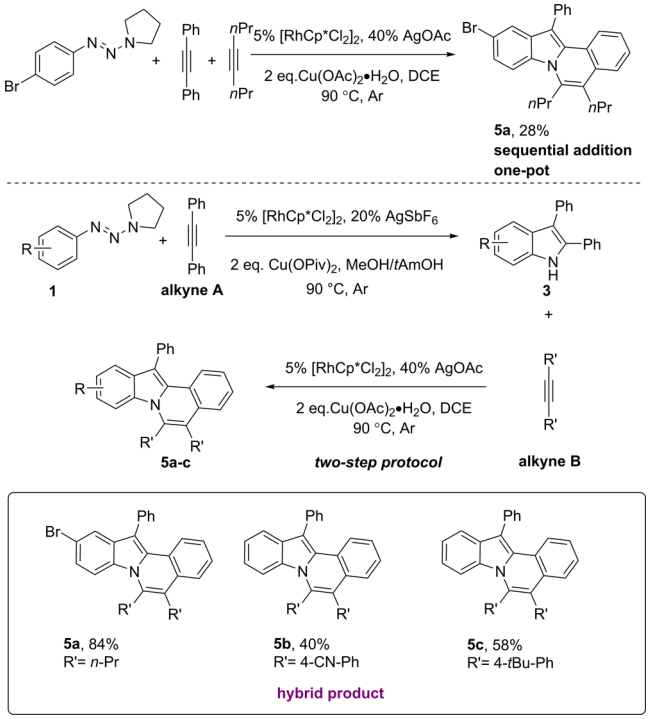
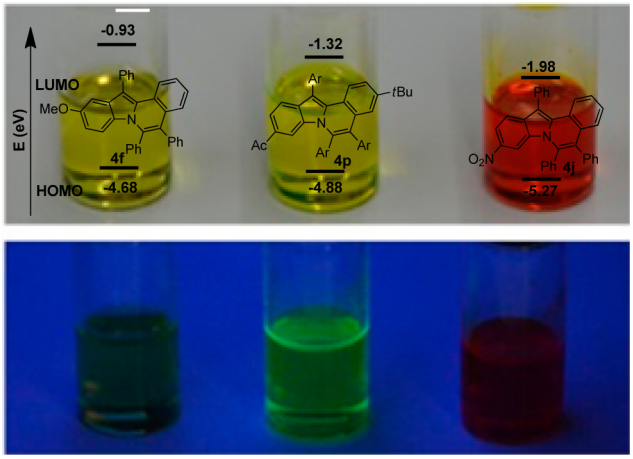
Scheme 2. Synthesis of "Hybrid" Indolo[2,1-*a*]isoquinolines Using Two Different Alkynes



*2,3-Diphenyl-1H-indole-5-carbonitrile (**3b**).* Ethyl acetate/petroleum ether = 1:9, 51% yield (45.0 mg), yellow solid, mp 129−131 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77 (s, 1H), 8.01 (s, 1H), 7.51−7.32 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.5, 136.1, 133.6, 131.5, 130.0, 128.89, 128.86, 128.7, 128.5, 128.2, 127.0, 125.5, 125.4, 120.7, 115.5, 111.8, 103.4. HRMS (APCI): found 295.1227, calcd for $C_{21}H_{15}N_2$ ([M + H]$^+$) 295.1235. IR (KBr) cm^{-1}: 3298, 2220, 1261, 1472, 762, 750, 700.

*Methyl 2,3-Diphenyl-1H-indole-5-carboxylate (**3c**).* Ethyl acetate/petroleum ether = 1:9, 91% yield (89.3 mg), yellow solid, mp 220−222 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 (s, 1H), 8.42 (s, 1H), 7.98 (dd, J = 1.4, 8.6 Hz, 1H), 7.46−7.31 (m, 11H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 138.5, 135.3, 134.3, 132.1, 130.2, 128.8, 128.7, 128.5, 128.1, 128.1, 126.7, 124.1, 122.7, 122.5, 116.2, 110.6, 51.9. HRMS (APCI): found 328.1332, calcd for $C_{22}H_{18}NO_2$ ([M + H]$^+$) 328.1338. IR (KBr) cm^{-1}: 3339, 1690, 1439, 1321, 1277, 1261, 1109, 758, 694.

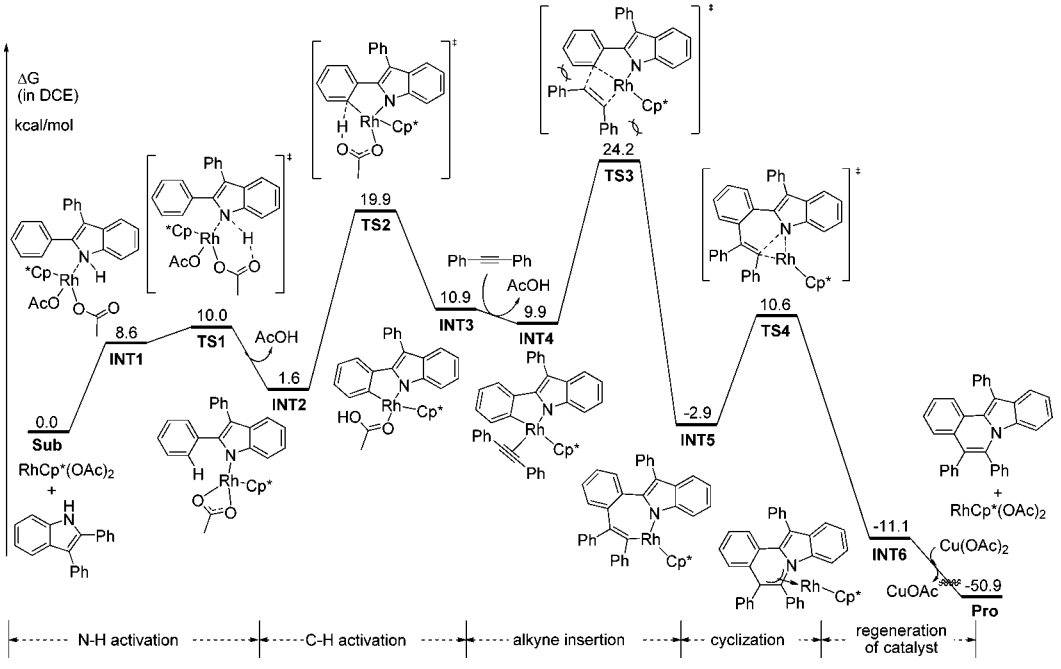
Scheme 4. Fluorescent Colors of Indolo[2,1-*a*]isoquinolines with Different Substituents: (top row) Under Natural Light; (bottom row) Under 254 nm UV Light



*1-(2,3-Diphenyl-1H-indol-5-yl)ethanone (**3d**).* Ethyl acetate/petroleum ether = 1:9, 48% yield (44.8 mg), yellow solid, mp 233−235 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (s, 1H), 8.31 (s, 1H), 7.95 (dd, J = 1.5, 8.6 Hz, 1H), 7.48−7.41 (m, 7H), 7.37−7.32 (m, 4H), 2.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.3, 138.5, 135.5, 134.2, 132.0, 130.6, 130.1, 128.83, 128.80, 128.5, 128.15, 128.12, 126.8, 123.1, 121.9, 116.4, 110.8, 26.7. HRMS (APCI): found 312.1388, calcd for $C_{22}H_{18}NO$ ([M + H]$^+$) 312.1388. IR (KBr) cm^{-1}: 3331, 1661, 1275, 1261, 766, 750, 698.

*5-Bromo-6-methyl-2,3-diphenyl-1H-indole (**3e**).* Ethyl acetate/petroleum ether = 1:40, 71% yield (76.9 mg), yellow semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (s, 1H), 7.64 (s, 1H), 7.51 (s, 1H)

Scheme 3. M06-Computed Free Energy Profile for the Formation of Indolo[2,1-*a*]isoquinolines



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7.41−7.30 (m, 10H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.2, 134.7, 134.7, 132.4, 130.1, 129.3, 128.7, 128.6, 128.5, 128.1, 127.9, 120.6, 119.2, 114.6, 114.3, 23.2. HRMS (ESI): found 362.0540, calcd for $C_{21}H_{17}BrN$ ($[M + H]^+$) 362.0544. IR (KBr) cm^{-1}: 3059, 2972, 1601, 1481, 1030, 982, 764, 698.

*7-Fluoro-5-methoxy-2,3-diphenyl-1H-indole (**3f**).* Ethyl acetate/petroleum ether = 1:40, 50% yield (47.5 mg), white solid, mp 59−61 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (s, 1H), 7.44−7.31 (m, 10H), 6.90 (d, *J* = 1.8 Hz, 1H), 6.71 (dd, *J* = 2.0, 12.1 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.0, 154.9, 150.4, 148.0, 135.6, 134.8, 132.3, 131.8, 131.7, 130.1, 128.7, 128.7, 128.1, 128.0, 126.5, 119.5, 119.4, 115.59, 115.56, 98.9, 98.7, 96.94, 96.91, 56.2. HRMS (APCI): found 318.1289, calcd for $C_{21}H_{17}FNO$ ($[M + H]^+$) 318.1294. IR (KBr) cm^{-1}: 3418, 1495, 1337, 1302, 1260, 1146, 859, 827, 770, 698.

*5-Bromo-2,3-bis(4-(methylthio)phenyl)-1H-indole (**3g**).* Ethyl acetate/petroleum ether = 1:40, 61% yield (80.3 mg), yellow solid, mp 118−120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (s, 1H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.33−7.28 (m, 8H), 7.20−7.18 (m, 2H), 2.54 (s, 3H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.9, 136.549, 134.8, 134.548, 131.1, 130.5, 130.4, 128.5, 128.4, 126.9, 126.4, 125.5, 122.0, 113.9, 113.7, 112.3, 15.8, 15.4. HRMS (APCI): found 440.0137, calcd for $C_{22}H_{19}BrNS_2$ ($[M + H]^+$) 440.0142. IR (KBr) cm^{-1}: 3273, 2920, 1591, 1504, 1186, 1013, 824, 795.

*5-Bromo-2,3-di-m-tolyl-1H-indole (**3h**).* Ethyl acetate/petroleum ether = 1:40, 91% yield (102.4 mg), white solid, mp 152−154 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1H), 7.79 (s, 1H), 7.32−7.14 (m, 10H), 2.39 (s, 3H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 138.2, 135.3, 134.4, 134.3, 132.1, 130.7, 130.6, 128.8, 128.6, 128.50, 128.46, 127.4, 127.2, 125.4, 125.3, 122.2, 114.7, 113.6, 112.3, 21.5, 21.5. HRMS (ESI): found 376.0696, calcd for $C_{22}H_{19}BrN$ ($[M + H]^+$) 376.0701. IR (KBr) cm^{-1}: 3420, 1506, 1456, 1314, 795, 764, 669.

*5-Bromo-3-butyl-2-phenyl-1H-indole (**3i**).* Ethyl acetate/petroleum ether = 1:40, 61% yield (59.8 mg), yellow semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (s, 1H), 7.76 (d, *J* = 1.5 Hz, 1H), 7.56−47 (m, 4H), 7.42−7.38 (m, 1H), 7.30−7.22 (m, 2H), 2.84 (t, *J* = 7.9 Hz, 2H), 1.71−1.66 (m, 2H), 1.45−1.36 (m, 2H), 0.97−0.92 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.5, 134.7, 133.1, 131.3, 129.1, 128.1, 128.0, 125.0, 122.0, 113.9, 112.8, 112.3, 33.3, 24.4, 23.1, 14.1. HRMS (APCI): found 328.0696, calcd for $C_{18}H_{19}BrN$ ($[M + H]^+$) 328.0701. IR (KBr) cm^{-1}: 3264, 2957, 1574, 1260, 1186, 974, 829, 704.

*7-Methoxy-2-(3-methoxyphenyl)-5-nitro-3-propyl-1H-indole (**3j**).* Ethyl acetate/petroleum ether = 1:9, 63% yield (64.3 mg), yellow semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (s, 1H), 8.29 (d, *J* = 1.7 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 1.9 Hz, 1H), 6.98 (dd, *J* = 2.4, 8.2 Hz, 1H), 4.04 (s, 3H), 3.88 (s, 3H), 2.87 (t, *J* = 7.9 Hz, 2H), 1.77−1.72 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 145.4, 142.3, 136.4, 133.6, 130.2, 129.7, 128.9, 120.5, 116.9, 113.9, 113.8, 110.7, 97.9, 56.1, 55.5, 26.8, 24.5, 14.5. HRMS (APCI): found 341.1495, calcd for $C_{19}H_{21}N_2O_4$ ($[M + H]^+$) 341.1501. IR (KBr) cm^{-1}: 3360, 2959, 1603, 1582, 1470, 1337, 1086, 872, 743.

*5-Bromo-3-cyclopropyl-2-phenyl-1H-indole (**3k**).* Ethyl acetate/petroleum ether = 1:40, 85% yield (79.3 mg), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.91 (d, *J* = 1.7 Hz, 1H), 7.73−7.71 (m, 2H), 7.50−7.36 (m, 3H), 7.31−7.21 (m, 2H), 2.06−1.97 (m, 1H), 0.97−0.92 (m, 2H), 0.53−0.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.0, 134.3, 132.5, 132.0, 131.9, 128.7, 128.0, 127.9, 125.1, 122.4, 122.1, 114.2, 113.0, 112.3, 6.9, 6.2. HRMS (APCI): found 312.0382, calcd for $C_{17}H_{15}BrN$ ($[M + H]^+$) 312.0388. IR (KBr) cm^{-1}: 3285, 1574, 1514, 1493, 1379, 1184, 991, 829, 702.

*(2,3-Diphenyl-1H-indol-7-yl)methanol (**3l**).* Ethyl acetate/petroleum ether = 1:5, 47% yield (42.1 mg), white semisolid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.19 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.49−7.27 (m, 10H), 7.13−7.06 (m, 2H), 5.10 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.2, 134.7, 134.4, 132.7, 130.2, 129.3, 128.6, 128.5, 128.3, 127.7, 126.2, 123.1, 120.8, 120.1, 119.7, 115.0, 64.5. HRMS (APCI): found 300.1391, calcd for $C_{21}H_{18}NO$ ($[M + H]^+$) 300.1388. IR (KBr) cm^{-1}: 3441, 3354, 3057, 2926, 1614, 1267, 1026, 768, 745, 698.

General Procedures for the Direct Synthesis of Indolo[2,1-*a*]isoquinolines. *Conditions A.* $[Cp^*RhCl_2]_2$ (0.0010 mmol, 6.4 mg, 5 mol %), triazene substrate **1** (0.2 mmol, 1.0 equiv), $Cu(OPiv)_2$ (0.4 mmol, 106.3 mg, 2.0 equiv), and $AgSbF_6$ (0.040 mmol, 13.8 mg, 0.2 equiv) were weighed into an oven-dried Schlenk tube. The reaction vessel was capped and vacuum-flushed with argon three times. A solution of alkyne (0.7 mmol, 3.5 equiv) in 1:1 MeOH/*t*AmOH (2.0 mL) was added through the side arm using a syringe. The reaction mixture was stirred under an argon atmosphere at 90 °C for 48 h and then cooled to room temperature. Volatile solvent and reagents were removed by rotary evaporation, and the residue was purified by silica gel flash chromatography using ethyl acetate/petroleum ether (1:100 to 1:10) to afford product **4**.

Conditions B. $[Cp^*RhCl_2]_2$ (0.0010 mmol, 6.4 mg, 5 mol %), triazene substrate **1** (0.2 mmol, 1.0 equiv), $Cu(OAc)_2{\cdot}H_2O$ (0.4 mmol, 80 mg, 2.0 equiv), and AgOAc (0.080 mmol, 13.4 mg, 0.4 equiv) were weighed into an oven-dried Schlenk tube. The reaction vessel was capped and vacuum-flushed with argon three times. A solution of alkyne (0.7 mmol, 3.5 equiv) in DCE (2.0 mL) was added through the side arm using a syringe. The reaction mixture was stirred under an argon atmosphere at 90 °C for 48 h and then cooled to room temperature. Volatile solvent and reagents were removed by rotary evaporation, and the residue was purified by silica gel flash chromatography using ethyl acetate/petroleum ether (0:100 to 1:10) to afford product **4**.

*1-(5,6,12-Triphenylindolo[2,1-a]isoquinolin-9-yl)ethanone (**4a**).* Conditions A, ethyl acetate/petroleum ether = 1:9, 79% yield (76.9 mg), yellow solid, mp 234−236 °C. ^{1}H NMR (DMSO- d_6, 400 MHz): δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.72−7.21 (m, 19H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.56 (s, 1H), 2.03 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 197.0, 136.4, 136.2, 135.4, 135.1, 133.8, 133.3, 131.9, 131.5, 131.12, 131.08, 130.5, 130.0, 129.9, 129.6, 128.9, 128.5, 128.4, 127.7, 127.4, 126.4, 125.1, 124.5, 122.6, 121.4, 118.7, 117.2, 112.3, 26.5. HRMS (APCI): found 488.2009, calcd for $C_{36}H_{26}NO$ ($[M + H]^+$) 488.2014. IR (KBr) cm^{-1}: 2920, 1670, 1263, 764, 714, 700.

*5,6,12-Triphenylindolo[2,1-a]isoquinoline (**4b**).* Conditions B, ethyl acetate/petroleum ether = 1:100, 53% yield (47.2 mg), yellow solid, mp 186−188 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 7.6 Hz, 1H), 7.69−7.63 (m, 4H), 7.61−7.52 (m, 2H), 7.41 (s, *J* = 9.5 Hz, 5H), 7.30−7.15 (m, 9H), 6.90−6.86 (m, 1H), 6.06 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.9, 136.5, 136.0, 135.6, 131.9, 131.6, 131.2, 131.1, 130.9, 130.7, 130.6, 129.1, 128.74, 128.69, 127.9, 127.3, 127.0, 126.8, 126.5, 126.1, 125.9, 124.5, 121.7, 121.6, 120.8, 119.0, 114.5, 112.1. HRMS (APCI): found 446.1901, calcd for $C_{34}H_{24}N$ ($[M + H]^+$) 446.1909. IR (KBr) cm^{-1}: 2926, 1449, 1275, 1261, 750, 700.

*10-Bromo-5,6,12-triphenylindolo[2,1-a]isoquinoline (**4c**).* Conditions B, ethyl acetate/petroleum ether = 1:100, 51% yield (53.3 mg), yellow solid, mp 259−261 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 4.4 Hz, 5H), 7.60−7.53 (m, 1H), 7.40−7.33 (m, 5H), 7.28−7.15 (m, 8H), 6.94−6.91 (dd, *J* = 1.9, 9.2 Hz, 1H), 5.86 (d, *J* = 9.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.6, 135.7, 135.6, 135.2, 132.2, 131.8, 131.7, 131.13, 131.10, 130.8, 130.2, 129.3, 128.9, 128.8, 128.0, 127.6, 127.4, 126.9, 126.7, 126.3, 125.6, 124.7, 123.6, 122.2, 121.2, 115.9, 115.4, 111.4. HRMS (APCI): found 524.1015, calcd for $C_{34}H_{23}BrN$ ($[M + H]^+$) 524.1014. IR (KBr) cm^{-1}: 1591, 1443, 1373, 1339, 957, 866, 760, 704.

*10-Chloro-5,6,12-triphenylindolo[2,1-a]isoquinoline (**4d**).* Conditions B, ethyl acetate/petroleum ether = 1:100, 53% yield (50.8 mg), yellow solid, mp 258−260 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (dd, *J* = 0.5, 8.1 Hz, 1H), 7.62 (d, *J* = 4.3 Hz, 4H), 7.56−7.51 (m, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.41−7.34 (m, 5H), 7.31−7.15 (m, 8H), 6.81 (dd, *J* = 2.2, 9.2 Hz, 1H), 5.92 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.6, 135.8, 135.7, 135.2, 131.9, 131.8, 131.7, 131.1, 130.8, 129.9, 129.3, 128.9, 128.8, 128.0, 127.6, 127.4, 126.9, 126.7, 126.3, 125.6, 124.6, 122.2, 121.0, 118.0, 115.6, 111.5. HRMS (APCI): found 480.1513, calcd for $C_{34}H_{23}ClN$ ($[M + H]^+$) 480.1519. IR (KBr) cm^{-1}: 3065, 1595, 1443, 1072, 961, 872, 762, 704.

*5,6,10,12-Tetraphenylindolo[2,1-a]isoquinoline (**4e**).* Conditions B, ethyl acetate/petroleum ether = 1:50, 46% yield (47.9 mg), yellow

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solid, mp 230−232 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, J = 8.2 Hz, 1H), 7.71−7.68 (m, 3H), 7.65−7.64 (t, J = 3.7 Hz, 2H), 7.62−7.53 (m, 3H), 7.41−7.36 (m, 7H), 7.30−7.13 (m, 10H), 6.09 (d, J = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.9, 136.9, 136.3, 135.9, 135.5, 134.9, 131.9, 131.4, 131.3, 131.1, 131.02, 130.96, 129.2, 128.81, 128.75, 128.6, 127.9, 127.4, 127.1, 126.8, 126.6, 126.5, 126.2, 125.9, 124.6, 121.8, 120.5, 117.0, 114.7, 112.5. HRMS (APCI): found 522.2214, calcd for $C_{40}H_{28}N$ ([M + H]$^+$) 522.2222. IR (KBr) cm^{-1}: 3057, 1599, 1452, 1375, 1263, 1028, 878, 760, 700.

10-Methoxy-5,6,12-triphenylindolo[2,1-a]isoquinoline (**4f**). Conditions B, ethyl acetate/petroleum ether = 1:50, 35% yield (33.2 mg), yellow solid, mp 212−214 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 7.7 Hz, 1H), 7.67−7.60 (m, 4H), 7.55−7.53 (m, 1H), 7.39−7.35 (m, 5H), 7.28−7.14 (m, 8H), 6.89 (d, J = 2.5 Hz, 1H), 6.52−6.49 (dd, J = 2.6, 9.4 Hz, 1H), 5.91 (d, J = 9.1 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.3, 137.0, 136.6, 135.8, 135.5, 131.9, 131.40, 131.38, 131.2, 131.0, 130.9, 129.2, 128.74, 128.71, 127.9, 127.3, 126.9, 126.8, 126.7, 126.3, 126.1, 125.6, 124.4, 121.2, 115.4, 111.7, 111.2, 99.5, 55.6. HRMS (APCI): found 476.2008, calcd for $C_{35}H_{26}NO$ ([M + H]$^+$) 476.2014. IR (KBr) cm^{-1}: 2920, 1611, 1441, 1375, 1227, 1200, 1126, 1032, 764, 723, 700.

5,6,12-Triphenylindolo[2,1-a]isoquinoline-9-carbonitrile (**4g**). Conditions A, ethyl acetate/petroleum ether = 1:9, 58% yield (54.5 mg), yellow solid, mp 234−236 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, J = 7.9 Hz, 1H), 7.61−7.20 (m, 20H), 6.23 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.2, 135.6, 135.2, 134.6, 134.1, 133.0, 131.6, 131.5, 131.0, 130.6, 130.2, 129.5, 129.4, 129.3, 128.2, 128.1, 127.9, 127.1, 127.0, 126.5, 125.2, 125.0, 124.1, 123.2, 120.7, 119.8, 119.6, 112.6, 102.6. HRMS (APCI): found 471.1855, calcd for $C_{35}H_{23}N_2$ ([M + H]$^+$) 471.1861. IR (KBr) cm^{-1}: 2920, 1597, 1472, 1454, 1339, 822, 762, 700.

9-Bromo-5,6,12-triphenylindolo[2,1-a]isoquinoline (**4h**). Conditions B, ethyl acetate/petroleum ether = 1:100, 47% yield (49.2 mg), yellow solid, mp 257−259 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, J = 7.8 Hz, 1H), 7.62−7.60 (m, 4H), 7.55−7.52 (m, 1H), 7.46−7.14 (m, 15H), 6.03 (d, J = 1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.6, 135.8, 135.7, 135.0, 131.9, 131.8, 131.2, 131.1, 131.0, 130.8, 129.3, 129.2, 129.0, 128.9, 128.0, 127.5, 127.3, 126.9, 126.7, 126.3, 125.7, 124.8, 124.5, 122.1, 120.0, 117.6, 114.1, 112.0. HRMS (APCI): found 524.1007, calcd for $C_{34}H_{23}BrN$ ([M + H]$^+$) 524.1014. IR (KBr) cm^{-1}: 3057, 1458, 1369, 1335, 1277, 955, 764, 702.

1-(5,6,12-Triphenylindolo[2,1-a]isoquinolin-10-yl)ethanone (**4i**). Conditions A, ethyl acetate/petroleum ether = 1:9, 50% yield (48.7 mg), yellow solid, mp 246−248 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.1 (s, 1H), 7.9 (d, J = 4.3 Hz, 1H), 7.65 (d, J = 4.4 Hz, 4H), 7.58−7.56 (m, 1H), 7.49−7.48 (d, J = 1.8 Hz, 1H), 7.47−7.35 (m, 5H), 7.30−7.13 (m, 8H), 6.04 (d, J = 9.1 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.3, 136.5, 135.6, 135.5, 135.2, 133.7, 132.1, 131.7, 131.1, 131.0, 130.9, 130.2, 129.3, 129.0, 128.8, 128.0, 127.7, 127.5, 127.0, 126.8, 126.4, 125.7, 124.7, 122.9, 120.7, 120.5, 114.4, 113.4, 26.7. HRMS (APCI): found 488.2007, calcd for $C_{36}H_{26}NO$ ([M + H]$^+$) 488.2014. IR (KBr) cm^{-1}: 3057, 2924, 2853, 1676, 1437, 1256, 764, 700.

9-Nitro-5,6,12-triphenylindolo[2,1-a]isoquinoline (**4j**). Conditions A, ethyl acetate/petroleum ether = 1:4, 50% yield (49.0 mg), orange solid, mp 222−224 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.64−7.50 (m, 9H), 7.49−7.46 (m, 3H), 7.40−6.98 (m, 7H), 6.97 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.4, 136.0, 136.0, 135.8, 135.0, 134.3, 134.3, 131.7, 131.5, 131.0, 130.4, 129.73, 129.68, 129.5, 129.4, 128.5, 128.1, 128.0, 127.2, 127.1, 126.6, 125.2, 125.1, 123.5, 118.4, 116.9, 112.7, 112.4. HRMS (APCI): found 491.1759, calcd for $C_{34}H_{23}N_2O_2$ ([M + H]$^+$) 491.1760. IR (KBr) cm^{-1}: 3360, 2920, 2849, 1645, 1470, 1329, 706.

9-Chloro-10-fluoro-5,6,12-triphenylindolo[2,1-a]isoquinoline (**4k**). Conditions B, ethyl acetate/petroleum ether = 1:100, 53% yield (52.7 mg), yellow solid, mp 256−258 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, J = 5.4 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.32−7.27 (m, 5H), 7.21−7.19 (m, 7H), 7.06 (t, J = 7.5 Hz, 1H), 6.93−6.84 (m, 5H), 6.69 (d, J = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.2, 153.6, 143.8, 139.7, 139.7, 139.32, 139.30, 138.8, 138.6, 138.5, 138.3, 135.82, 135.78, 135.51, 133.48, 133.22, 133.17, 131.6, 131.5, 131.2, 130.17, 130.15, 129.8, 128.0, 127.7, 127.6, 127.3, 127.1, 126.7, 126.6, 125.9, 123.9, 122.0, 121.1, 120.0, 119.8, 119.6, 119.5. HRMS (APCI): found 498.1420, calcd for $C_{34}H_{22}ClFN$ ([M + H]$^+$) 498.1425. IR (KBr) cm^{-1}: 3057, 2922, 1443, 1024, 758, 696.

10-Bromo-9-methyl-5,6,12-triphenylindolo[2,1-a]isoquinoline (**4l**). Conditions B, ethyl acetate/petroleum ether = 1:100, 46% yield (49.4 mg), yellow solid, mp >270 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 4.3 Hz, 4H), 7.54−7.52 (m, 1H), 7.45−7.40 (m, 3H), 7.36−7.13 (m, 11H), 6.07 (s, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.7, 136.0, 135.7, 135.1, 131.8, 131.2, 130.7, 130.5, 130.0, 129.0, 128.9, 127.9, 127.4, 127.2, 126.987, 126.6, 126.2, 125.7, 124.5, 121.6, 119.3, 118.1, 117.5, 111.4, 23.1. HRMS (APCI): found 538.1166, calcd for $C_{35}H_{25}BrN$ ([M + H]$^+$) 538.1170. IR (KBr) cm^{-1}: 2918, 1441, 764, 739, 721, 698.

1-(3-Methyl-5,6,12-tri-p-tolylindolo[2,1-a]isoquinolin-9-yl)-ethanone (**4m**). Conditions A, ethyl acetate/petroleum ether = 1:9, 60% yield (65.2 mg), orange solid, mp 207−209 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J = 8.3 Hz, 1H), 7.81−7.94 (d, J = 8.6 Hz, 1H), 7.49−7.46 (m, 3H), 7.41−7.39 (d, J = 7.6 Hz, 2H), 7.30−7.27 (m, 4H), 7.10−7.05 (m, 5H), 6.98 (s, 1H), 6.60 (s, 1H), 2.53 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H), 2.29 (s, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 139.0, 137.8, 137.1, 136.4, 136.0, 134.5, 133.8, 133.5, 132.7, 132.6, 131.8, 131.5, 130.9, 130.7, 130.4, 129.9, 128.7, 128.1, 126.2, 124.9, 123.1, 122.4, 120.7, 118.4, 117.7, 111.7, 25.8, 21.7, 21.5, 21.4, 21.3. HRMS (APCI): found 544.2635, calcd for $C_{40}H_{34}NO$ ([M + H]$^+$) 544.2640. IR (KBr) cm^{-1}: 2920, 1668, 1595, 1558, 1472, 1395, 951, 816, 739.

1-(3-(Methylthio)-5,6,12-tris(4-(methylthio)phenyl)indolo[2,1-a]-isoquinolin-9-yl)ethanone (**4n**). Conditions A, ethyl acetate/petroleum ether = 1:9, 72% yield (96.6 mg), yellow solid, mp 216−218 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.51−7.46 (m, 5H), 7.33−7.29 (m, 4H), 7.18−7.10 (m, 5H), 7.01 (s, 1H), 6.67 (s, 1H), 2.63 (s, 3H), 2.53 (s, 3H), 2.50 (s, 3H), 2.35 (s, 3H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 140.8, 139.1, 137.9, 137.5, 136.2, 134.1, 133.7, 132.5, 132.0, 131.94, 131.90, 131.4, 131.3, 131.0, 130.5, 129.8, 127.1, 126.4, 125.9, 125.2, 124.9, 122.9, 122.5, 121.7, 121.1, 118.4, 117.4, 111.4, 26.0, 15.7, 15.39, 15.37, 15.2. HRMS (APCI): found 672.1517, calcd for $C_{40}H_{34}NOS_4$ ([M + H]$^+$) 672.1523. IR (KBr) cm^{-1}: 1667, 1593, 1470, 1435, 1265, 1098, 816, 768, 750.

1-(3-Methoxy-5,6,12-tris(4-methoxyphenyl)indolo[2,1-a]-isoquinolin-9-yl)ethanone (**4o**). Conditions A, ethyl acetate/petroleum ether = 1:9, 63% yield (76.5 mg), yellow solid, mp 227−229 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, J = 9.0 Hz, 1H), 7.83 (dd, J = 1.2, 8.6 Hz, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.13 (t, J = 8.2 Hz, 4H), 6.99 (d, J = 8.6 Hz, 2H), 6.86−6.82 (m, 3H), 6.68−6.66 (m, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.8, 160.0, 159.12, 159.05, 158.3, 136.5, 134.7, 133.8, 132.6, 132.2, 132.0, 130.4, 129.2, 128.7, 127.8, 126.5, 122.2, 120.8, 119.3, 118.2, 117.5, 114.7, 114.6, 114.5, 113.6, 110.5, 109.5, 55.4, 55.4, 55.2, 55.1, 26.0. HRMS (APCI): found 608.2432, calcd for $C_{40}H_{34}NO_5$ ([M + H]$^+$) 608.2437. IR (KBr) cm^{-1}: 2934, 1663, 1605, 1512, 1290, 1211, 1032, 831.

1-(3-(tert-Butyl)-5,6,12-tris(4-(tert-butyl)phenyl)indolo[2,1-a]-isoquinolin-9-yl)ethanone (**4p**). Conditions A, ethyl acetate/petroleum ether = 1:9, 56% yield (79.6 mg), yellow solid, mp >270 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.62−7.50 (m, 5H), 7.41−7.22 (m, 8H), 7.09 (d, J = 7.6 Hz, 2H), 6.97 (s, 1H), 2.06 (s, 3H), 1.49 (s, 9H), 1.31 (s, 9H), 1.28 (s, 9H), 1.21 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.8, 151.9, 150.8, 150.3, 149.5, 135.9, 134.4, 133.9, 133.3, 132.62, 132.59, 131.3, 130.7, 130.5, 130.4, 129.3, 126.0, 125.6, 124.6, 124.5, 124.4, 123.3, 123.2, 122.6, 120.5, 118.6, 117.8, 111.7, 34.9, 34.77, 34.75, 34.4, 31.6, 31.3, 31.1, 26.1. HRMS (APCI): found 712.4510, calcd for $C_{52}H_{58}NO$ ([M + H]$^+$): 712.4518. IR (KBr) cm^{-1}: 2966, 2923, 1676, 1404, 1366, 1271, 1116, 1023, 823.

10-Bromo-12-phenyl-5,6-dipropylindolo[2,1-a]isoquinoline (**5a**). Ethyl acetate/petroleum ether = 1:20, 84% yield (19.1 mg), yellow

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solid, mp 183−185 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (t, J = 9.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.59−7.55 (m, 2H), 7.52−7.48 (m, 3H), 7.44−7.37 (m, 2H), 7.14−7.10 (m, 1H), 3.38 (t, J = 8.2 Hz, 2H), 2.93 (t, J = 8.1 Hz, 2H), 1.99−1.93 (m, 2H), 1.75−1.69 (m, 2H), 1.28 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.3, 136.2, 132.6, 132.2, 131.2, 129.9, 129.6, 129.4, 127.63, 127.56, 125.8, 125.7, 125.4, 124.0, 123.4, 121.6, 117.3, 116.2, 115.2, 111.1, 31.7, 30.0, 23.7, 21.8, 14.7, 14.1. HRMS (APCI): found 456.1322, calcd for $C_{28}H_{27}BrN$ ($[M + H]^+$) 456.1327. IR (KBr) cm^{-1}: 3671, 3057, 2953, 2877, 2315, 1947, 1886, 1707, 1593, 1540, 1439, 1366, 1320, 1274, 1228, 1157, 1058, 945, 900, 867, 750, 699, 487.

*4,4′-(12-Phenylindolo[2,1-a]isoquinoline-5,6-diyl)dibenzonitrile (**5b**).* Ethyl acetate/petroleum ether = 1:9, 40% yield (10.0 mg), yellow solid, mp >270 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.62−7.47 (m, 10H), 7.31−7.20 (m, 5H), 6.98−6.91 (m, 2H), 5.99 (d, J = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.7, 139.7, 135.8, 134.1, 132.9, 132.7, 132.2, 131.8, 131.3, 131.1, 131.0, 130.5, 129.7, 129.4, 127.8, 127.7, 127.6, 126.3, 125.8, 124.9, 122.4, 121.7, 120.7, 119.7, 118.6, 118.2, 113.7, 113.5, 113.3, 111.7. HRMS (APCI): found 496.1810, calcd for $C_{36}H_{22}N_3$ ($[M + H]^+$) 496.1814. IR (KBr) cm^{-1}: 3657, 3060, 2982, 2892, 2391, 2226, 1926, 1807, 1731, 1602, 1555, 1445, 1384, 1332, 1246, 1149, 1105, 1024, 961, 842, 742, 673, 619, 554, 498, 436.

*5,6-Bis(4-(tert-butyl)phenyl)-12-phenylindolo[2,1-a]isoquinoline (**5c**).* Ethyl acetate/petroleum ether = 1:20, 58% yield (16.2 mg), yellow solid, mp >270 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, J = 8.0 Hz, 1H), 7.67−7.59 (m, 4H), 7.53 (d, J = 7.8 Hz, 2H), 7.34−7.15 (m, 10H), 7.08 (d, J = 7.8 Hz, 2H), 6.87 (t, J = 7.9 Hz, 1H), 6.20 (d, J = 8.7 Hz, 1H), 1.33 (s, 9H), 1.28 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.7, 149.4, 136.7, 136.4, 134.0, 132.8, 131.7, 131.6, 131.4, 130.9, 130.7, 130.6, 129.2, 127.3, 127.0, 126.3, 126.0, 125.3, 124.61, 124.57, 121.9, 121.7, 120.7, 118.9, 114.9, 112.0, 34.8, 34.5, 31.4. HRMS (APCI): found 558.3157, calcd for $C_{42}H_{40}N$ ($[M + H]^+$) 558.3161. IR (KBr) cm^{-1}: 3060, 3033, 2960, 2903, 2869, 2313, 1911, 1770, 1669, 1607, 1557, 1449, 1386, 1333, 1258, 1213, 1152, 1110, 1022, 839, 747, 707, 622, 574, 433, 408.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds, CID-HRMS data, and computational details. 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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