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Synthesis of Natural Product-like Polyheterocycles via One-Pot Cascade Oximation, C−H Activation, and Alkyne Annulation

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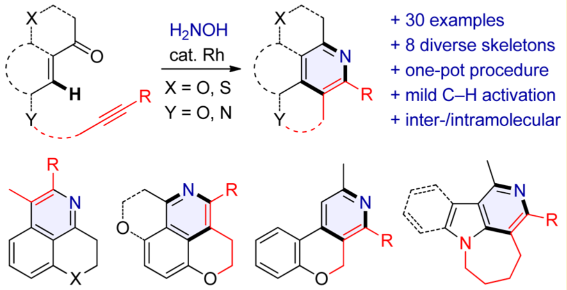
Supporting Information

ABSTRACT: An efficient protocol for the direct transformation of chroman-4-ones to tricyclic fused pyridines with the skeleton of cassiarins, a family of alkaloids with antimalarial activity, was developed. Also, a general strategy for modular construction of polyheterocycles with diverse natural product-like skeletons was developed by using ketone−alkyne bifunctional substrates. These reactions involved a one-pot cascade oximation of ketones, rhodium-catalyzed C−H activation, and intermolecular/intramolecular alkyne annulations under mild conditions with high atom, step, and redox economy.

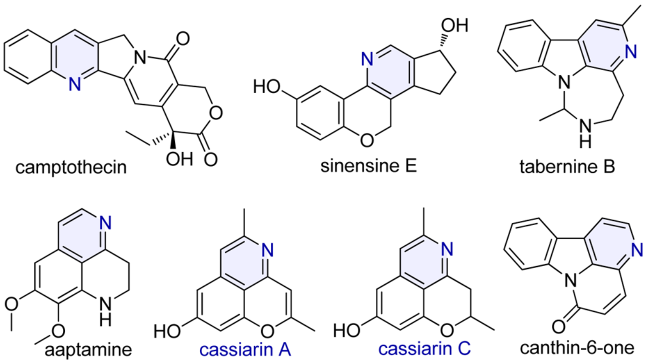


INTRODUCTION

Natural products are prevalidated starting points in the development of drugs and chemical biology toolkits,[1] which have specific interactions with diverse target biomacromolecules and access to a range of biologically relevant structural space.[2] Polyheterocycles containing privileged structures are widely used in drug discovery, for their ability to orient heteroatoms on well-defined scaffolds to bind multiple classes of proteins with high affinity.[3] Therefore, synthetic methods for the rapid construction of libraries of diverse natural product-like polyheterocycles[4,5] are in urgent need for high-throughput screening and navigating unexplored chemical space that is limited by the resources of the natural product. Polycyclic fused pyridine skeletons are ubiquitous in alkaloids,[6−9] such as camptothecin,[6a] sinensine E,[6b] and tabernine B,[6c] and the families of aaptamines,[6d] canthins,[6e] and cassiarins[7−9] (Scheme 1). Among them, we are particularly interested in cassiarins because of their unprecedented tricyclic skeleton[7] and a range of biological activities.[7,8]

Cassiarin A was isolated by Morita in 2007 from *Cassia siamea* and showed potent antimalarial activity.[7a] Since then, other members of this family such as cassiarin C have been isolated.[7] A series of studies on biological activities, such as antimalarial,[7,8a] vasorelaxant,[8b] anticancer,[8c] and anti-tobacco mosaic virus activity,[7e] as well as several total syntheses[7c,9] have been reported. However, the development of a general method for the rapid construction of their analogue library remains. With our continuous interest[10] in alkyne annulation via C−H activation[11−13] and previous work on isoquinoline synthesis,[10a] a one-pot assembly of cassiarin skeletons from 4*H*-chromen-4-ones or chroman-4-ones was proposed (Scheme 2a, strategy I). By shifting the nitrogen atom in the tricyclic skeleton of cassiarin C, we obtained an analogue skeleton that inspired us to design a ketone−alkyne bifunctional substrate, which could form a pyridine ring and a fused ring simultaneously via intramolecular alkyne annulation in a designable way[14−16] (strategy II). The traditional method for the synthesis of polycyclic fused pyridines via intramolecular hetero Diels−Alder reaction[14] typically needs a high temperature (180−200 °C), while the Larock approach[15] relies on brominated trifunctional substrates, which limits its atom economy and scope (Scheme 2b). Also, these two methods both need an additional step to form corresponding oximes or imines. Therefore, a general method for rapid and modular assembly of these skeletons under mild conditions is still needed. To meet this end, strategy II was extended to various substrates for one-pot construction of diverse polyheterocyclic skeletons.

Scheme 1. Examples of Natural Products with Polycyclic Fused Pyridine Skeletons



Herein, we report our progress on the synthesis of natural product-like polyheterocycles. By using strategy I, we built a

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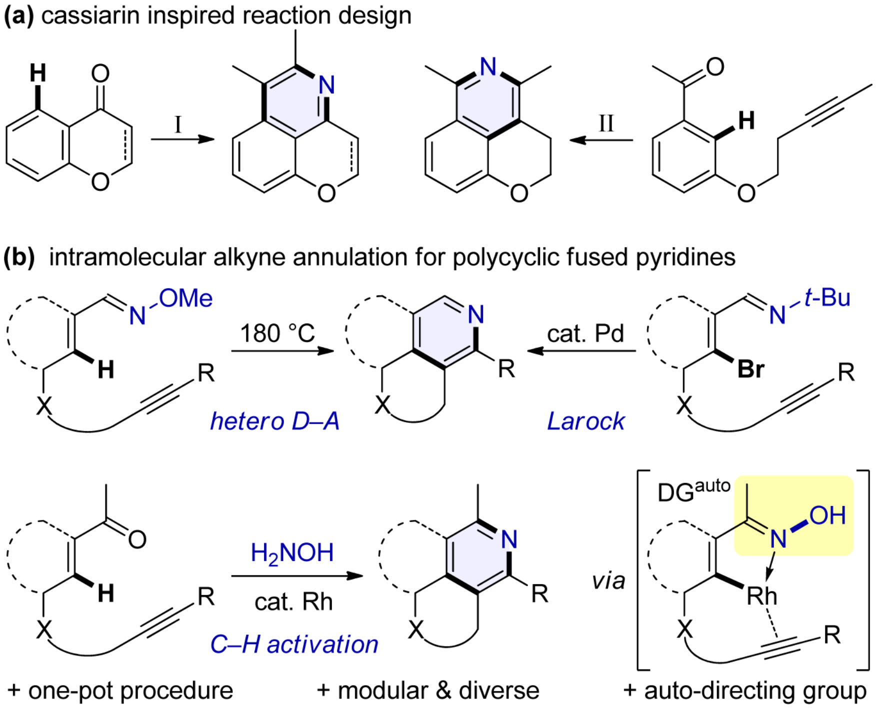
Scheme 2. Strategies for the Assembly of Polycyclic Fused Pyridine Skeletons

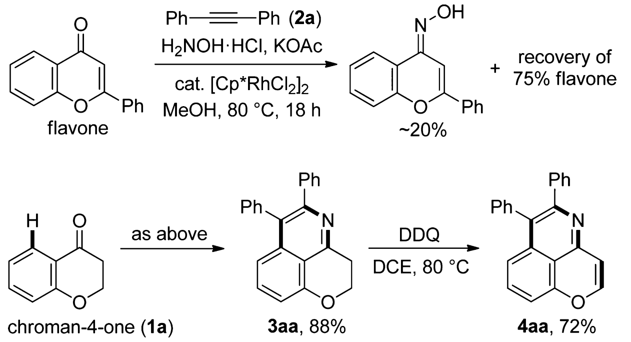


tricyclic library with cassiarin skeleton. By using strategy II, we developed a general method for diverse polyheterocycles, including chroman-fused pyridines and fused γ-carbolines. As a key feature for the realization of these strategies, oxime with a N−O bond as an internal oxidant[10a,17] served as an autoinstalled and autocleavable directing group[10b] for rhodium-catalyzed C−H activation and alkyne annulation, allowing one-pot construction of a pyridine ring[10a,18] with high atom, step, and redox economy.[19]

■ RESULTS AND DISCUSSION

We commenced our study by using flavone and diphenylacetylene (**2a**) as model compounds to test strategy I (Scheme 3).

Scheme 3. Preliminary Results for the Assembly of the Cassiarin Skeleton



Our previous reported condition for one-pot isoquinoline synthesis[7a] was first employed, in which $H_2NOH{\cdot}HCl$, KOAc, and $[Cp^*RhCl_2]_2$ were used as the nitrogen source, base, and catalyst precursor, respectively. However, conversion of the oximation step was quite low, and no cyclization product was detected, even at elevated temperatures with higher hydroxylamine ratios and catalyst loadings. We speculated that this low reactivity may be caused by conjugation, which would reduce the reactivity of the ketone for oximation and weaken the coordinating ability of the formed oxime group. Therefore, the ketone substrate was changed to simple chroman-4-one (**1a**) to react with **2a**. Gratifyingly, desired product **3aa** with the skeleton of cassiarin C was obtained in good yield (88%) after a brief optimization of conditions (see Table S1 for details). Other nitrogen sources such as $H_2NOMe{\cdot}HCl$, $H_2NNMe_2{\cdot}HCl$, and $t\text{-}BuNH_2$ were not suitable for this reaction, while using $[Ru(p\text{-cymene})Cl_2]_2$[11e] as a catalyst precursor gave only a trace of product. **3aa** proceeded to dehydrogenation smoothly by employing DDQ as an oxidant to afford **4aa** with a skeleton of cassiarin A. Thus, strategy I proved to be feasible for assembly of the tricyclic cassiarin skeleton from chroman-4-ones and alkynes.

We then embarked on building a small library of multisubstituted tricyclic heterocycles. By using **1a** as the ketone partner, the scope of alkynes was evaluated (Scheme 4). Alkyl alkyne **2b** showed similar reactivity with aryl alkyne **1a**. Both electron rich and deficient aryl alkynes were compatible in the reaction to afford **3ac** and **3ad**. Similar to other Rh(III)-catalyzed alkyne annulations, aryl−alkyl asymmetric alkyne **2e** was reacted regioselectively to afford **3ae**. Notably, alkyl−alkyl asymmetric alkyne **2f** was also reacted well to give **3af** in high regioselectivity. The structures of **3ae** and **3af** were unambiguously identified by single-crystal X-ray analysis (Figure 1). In the search for the total syntheses of cassiarin A and C, propyne (gas or heptane solution) was also tested for the reaction, but no desired product was detected. Potential equivalent synthons of propyne were also tested. Using MeC≡CCOOH or MeC≡CC(OH)Me_2 gave a rather low conversion (<10%) of oxime **1a**. Conversion was improved to 30% by using MeC≡CTMS; however, the selectivity was low, and four cyclization products (two regioisomers, each with or without the TMS group) were detected via GC−MS.

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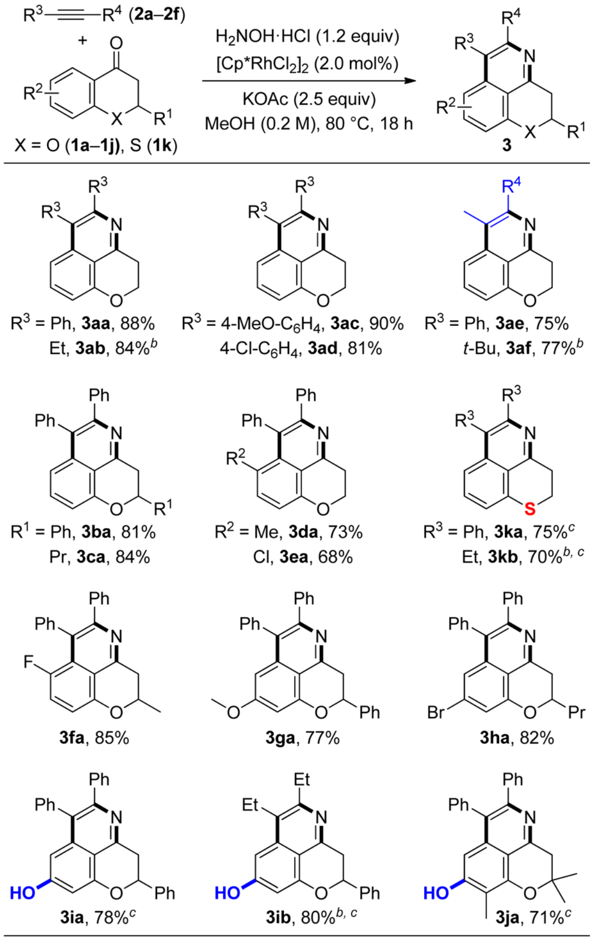
Scheme 4. Construction of a Multisubstituted Tricycle Library with a Cassiarin Skeleton



[a]Unless otherwise noted, reactions were performed using **1** (0.50 mmol), $H_2NOH{\cdot}HCl$ (0.60 mmol), and **2** (0.60 mmol) with $[Cp^*RhCl_2]_2$ (2.0 mol %) and KOAc (1.25 mmol) in MeOH (2.5 mL) under 80 °C for 18 h. [b]**2** (0.70 mmol) was used. [c]$[Cp^*RhCl]_2$ (3.0 mol %) was used.

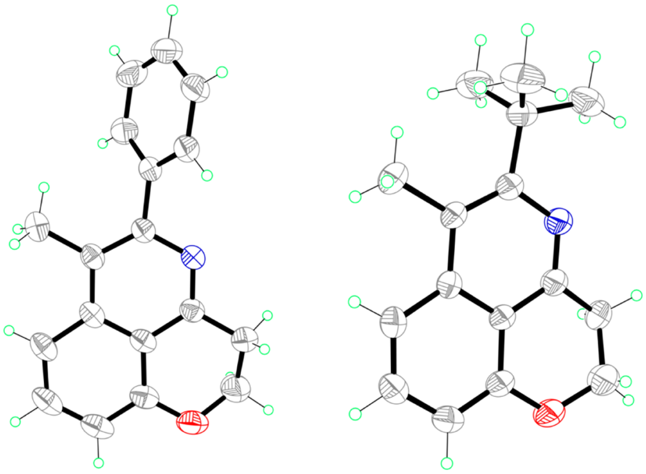
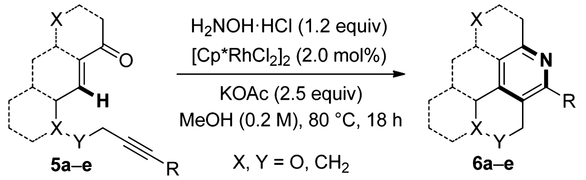


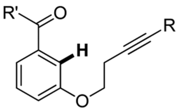
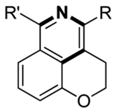
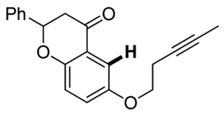
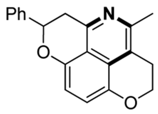
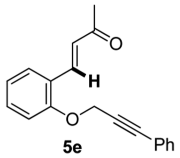
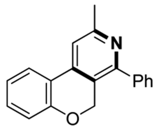
Figure 1. X-ray structures of **3ae** (left) and **3af** (right), shown as an ORTEP drawing with 35% probability ellipsoids.

Next, chroman-4-ones with various substituents at different positions were employed to couple with alkyne **2a** or **2b** under the standard condition. 2-Substituted chroman-4-ones with either an aryl group or an alkyl group reacted well to afford **3ab** or **3ac**, respectively. Both electron-donating groups (Me and OMe) and halogens (F, Cl and Br) were compatible for the reaction. Substituents such as Me and Cl at the meta position of the ketone group gave **3da** and **3ea** in lower yields, perhaps because of steric hindrance. Multisubstituted tricyclic products **3fa**, **3ga**, and **3ha** were obtained in good yield. Remarkably, substrates **1i** and **1j** reacted smoothly without protection, furnishing products **3ia**, **3ib**, and **3ja** with free a hydroxyl group at the same position as in cassiarins. Halides or a hydroxyl group in these products would facilitate further derivatization, such as cross-coupling or bioconjugation. As introducing a sulfur atom into the lead compounds is one of the efficient strategies for altering biological activities, thiochroman-4-one (**1k**) was employed for this reaction. **3ka** and **3kb** was obtained as expected and could be treated as thio analogues of cassiarins.

For strategy II, we designed and synthesized an alkyne−ketone bifunctional substrate **5a** and employed it to react with $H_2NOH{\cdot}HCl$ under the Rh/KOAc conditions described above (Table 1, entry 1). To reduce the chance for intermolecular coupling of **5a**, the concentration of the reaction mixture was decreased. Desired intramolecular annulation product **6a** was obtained in 71% yield; this verified this strategy for the assembly of a tricyclic skeleton analogous to cassiarin C. The substituents on this skeleton can be tuned by using different substrates to afford **6b** and **6c** in similar yields (entries 2 and 3, respectively). Remarkably, substrate **5d**, an alkyne-tethered flavonone, reacted well to afford **6d** with a tetracyclic skeleton

Table 1. Synthesis of Diverse Chroman-Fused Pyridines



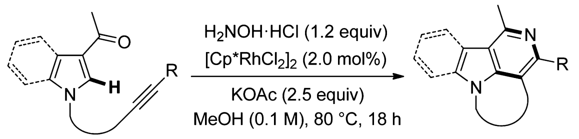
entry	substrate	product	yield (%)
			
1	R = R' = Me, **5a**	**6a**	68
2	R = *n*-Pr, R' = Me, **5b**	**6b**	71
3	R = Me, R' = Et, **5c**	**6c**	67
4	 **5d**	 **6d**	75
5[b]	 **5e**	 **6e**	61

[a]Unless otherwise noted, reactions were performed using **5** (0.50 mmol) and $H_2NOH{\cdot}HCl$ (0.60 mmol) with $[Cp^*RhCl_2]_2$ (2.0 mol %) and KOAc (1.25 mmol) in MeOH (5.0 mL) under 80 °C for 18 h. [b]$H_2NOH{\cdot}HCl$ (0.75 mmol) and K_2CO_3 (1.25 mmol) was used to react for 30 h.

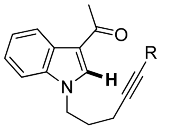
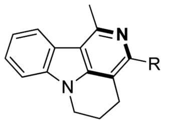
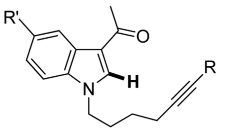
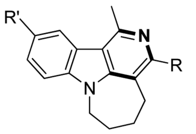
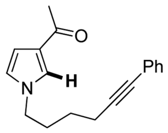
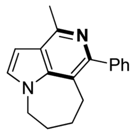
(entry 4). For substrate **5e** with an alkenyl C–H bond, only a trace of the product was obtained when using KOAc as a base. Replacing the base with K_2CO_3 gave the desired chroman-fused pyridine **6e** in acceptable yield (entry 5).

This strategy was further extended to alkyne-tethered 3-acetyl indoles **5f–k**, and a series of fused γ-carbolines **6f–k** were obtained (Table 2). Alkyne–indole substrates with a C3 or C4 alkyl chain linker were suitable for the reaction to afford γ-carbolines fused with a six-membered ring (entries 1 and 2) or a seven-membered ring (entries 3–6), respectively. The structure of **6h** was unambiguously identified by X-ray analysis (Figure 2). Substrates with electronic rich aryl alkyne **5j** gave a yield lower than that with electron deficient aryl alkyne **5k**, which is in contrast with the intermolecular cyclization. An alkyne-tethered 3-acetyl pyrrole **5l** also led to the reaction proceeding smoothly to afford **6l** with a 1*H*-pyrrolo[3,2-*c*]pyridine skeleton in moderate yield (entry 7).

Table 2. Synthesis of Fused γ-Carbolines and 1*H*-Pyrrolo[3,2-*c*]pyridine



5f–l **6f–l**

entry	substrate	product	yield (%)
			
1	R = Ph, **5f**	**6f**	70
2	R = Bu, **5g**	**6g**	72
			
3	R = Ph, R' = H, **5h**	**6h**	82
4	R = Ph, R' = Br, **5i**	**6i**	80
5	R = 4-MeO-C_6H_4, R' = H, **5j**	**6j**	64
6	R^2 = 4-Cl-C_6H_4, R' = H, **5k**	**6k**	79
			
7[b]	**5l**	**6l**	56

[a]Unless otherwise noted, reactions were performed using **5** (0.50 mmol) and $H_2NOH·HCl$ (0.60 mmol) with $[Cp*RhCl_2]_2$ (2.0 mol %) and KOAc (1.25 mmol) in MeOH (5.0 mL) under 80 °C for 18 h. [b]$[Cp*RhCl_2]_2$ (3.0 mol %) was used to react for 30 h.

However, γ-carbolines fused with a five-, eight-, or nine-membered ring were not obtained under the standard conditions by using corresponding substrates with a C2, C5, or C6 linker, which is a limitation for this reaction (Scheme 5). The corresponding oximes were formed, while only a trace of cyclized products can be detected via GC–MS even under enhanced conditions (100 °C, 4 mol % $[Cp*RhCl_2]_2$). As shown in a proposed mechanism (Scheme 5), this limitation was probably due to the difficulty of the corresponding tethered alkyne coordinating with Rh in rhodacycle intermediate **M1** to form **M2**. For a linker that is too short, the C≡C group would have a considerable energy barrier to access Rh and adjust a suitable orientation for coordination. For an alkyl linker that is too long, the flexibility and the number of conformations would increase, and it would have a stronger tendency to be randomly stretched in the solvent other than to keep a specific conformation for coordination. Also, the species (if formed) in this situation would be larger than that with a C3 or C4 linker. In this reaction, substrates with a C3 or C4 linker could keep this balance and result in γ-carbolines fused with a six- or seven-membered ring.

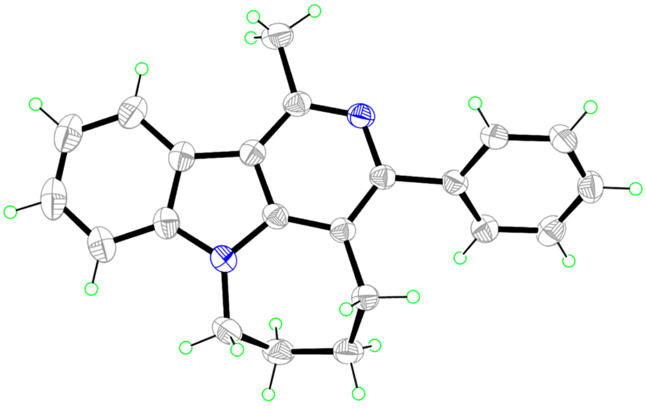
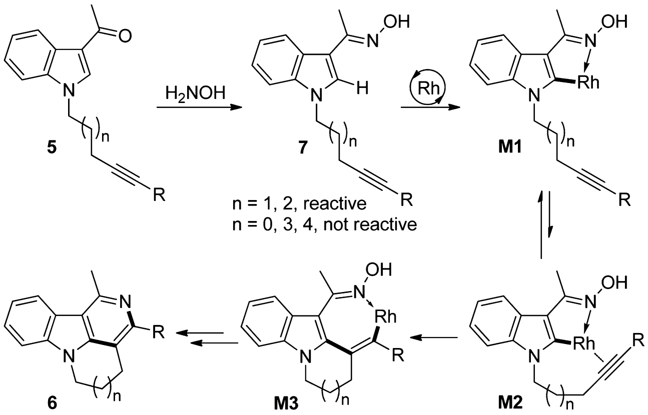


Figure 2. X-ray structure of **6h**, shown as an ORTEP drawing with 35% probability ellipsoids.

Scheme 5. Proposed Reaction Pathway and Limitation for the Synthesis of Fused γ-Carbolines



In summary, we have developed two strategies for the modular assembly of diverse natural product-like polyheterocycles via one-pot oximation of ketones, rhodium-catalyzed C–H activation, and alkyne annulations. Strategy I permitted the rapid assembly of the direct transformation of tricyclic heterocycles with a cassiarin skeleton and thio analogues from (thio)chroman-4-ones. Strategy II allowed the modular construction of diverse chroman-fused pyridines and fused γ-carbolines from bifunctional substrates in a designable fashion. The obtained natural product-like polyheterocycles could be treated as a small library for screening of lead compounds with biological activities related to the natural products, such as the antimalarial activity of cassiarins.

■ EXPERIMENTAL SECTION

General Methods. All organic compounds and inorganic salts were analytically pure and used directly after being purchased.

Substrates **5** were synthesized via the Mitsunobu reaction[20] or cross-coupling of NH and alkyl chlorides[15]. All products of **3** and **6** are new compounds, which were characterized by ^{1}H and ^{13}C NMR and HRMS. Nuclear magnetic resonance (NMR) spectra were recorded at 298 K. ^{1}H NMR (300 or 400 MHz) chemical shifts (δ) were referenced to internal standard TMS (δ 0.00). ^{13}C NMR (75 or 100 MHz) chemical shifts were referenced to internal solvent $CDCl_3$ (δ 77.16) or DMSO-d_6 (δ 40.45). HRMS spectra were recorded on a high-resolution magnetic sector mass spectrometer with an electrospray ionization (ESI) source. The melting points were uncorrected. Single crystals of **3ae**, **3af**, and **6h** were obtained by slow evaporation using an acetone/hexane cosolvent. Single-crystal X-ray diffraction data were collected on a diffractometer equipped with graphite-monochromatized Mo Kα radiation at 294 ± 1 K.

Typical Procedure for the Synthesis of 3. To a 25 mL tube equipped with a magnetic stirrer were added chroman-4-one **1a** (74.1 mg, 0.5 mmol), 1,2-diphenylacetylene **2a** (106.9 mg, 0.6 mmol), hydroxylamine hydrochloride (41.7 mg, 0.6 mmol), $[Cp^*RhCl_2]_2$ (6.2 mg, 0.010 mmol, 2.0 mmol %), KOAc (122.7 mg, 1.25 mmol), and MeOH (2.5 mL). The tube was sealed and immersed in an oil bath (80 °C), and the contents were stirred for 18 h. After purification by flash column chromatography on silica gel with a petroleum ether/acetone (gradient mixture ratio from 100:0 to 80:20) eluant, **3aa** (142.0 mg, 88%) was obtained as a pale yellow solid.

*5,6-Diphenyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3aa**).* Pale yellow solid (142.0 mg, 88%): mp 170−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.08 (12H, m), 6.95 (1H, d, J = 7.5 Hz), 4.54 (2H, t, J = 5.9 Hz), 3.44 (2H, t, J = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 153.4, 150.1, 140.8, 137.4, 136.7, 131.5, 131.2, 130.2, 129.1, 128.1, 127.6, 127.1, 127.0, 117.7, 115.7, 110.7, 67.0, 32.8; HRMS (ESI) calcd for $C_{23}H_{17}NO$ [M + H]$^+$ 324.1383, found 324.1386.

*5,6-Diethyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ab**).* Pale yellow solid (91.1 mg, 80%): mp 40−41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.43 (2H, m), 6.89 (1H, dd, J = 7.2, 1.1 Hz), 4.50 (2H, t, J = 6.0 Hz), 3.32 (2H, t, J = 6.0 Hz), 3.02−2.92 (4H, m), 1.34 (3H, t, J = 7.6 Hz), 1.26 (3H, t, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 151.4, 151.1, 141.3, 136.9, 131.4, 129.7, 128.1, 127.4, 122.3, 115.6, 115.5, 110.5, 67.1, 32.6, 15.6; HRMS (ESI) calcd for $C_{15}H_{17}NO$ [M + H]$^+$ 228.1383, found 228.1387.

*5,6-Bis(4-methoxyphenyl)-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ac**).* Pale yellow solid (174.0 mg, 91%): mp 238−239 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.44 (1H, m), 7.33−7.26 (2H, m), 7.20−7.11 (3H, m), 6.98 (1H, dd, J = 7.6, 0.4 Hz), 6.91−6.87 (2H, m), 6.77−6.72 (2H, m), 4.62 (2H, t, J = 6.0 Hz), 3.82 (3H, s), 3.75 (3H, s), 3.47 (2H, t, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 155.0, 153.2, 150.0, 137.3, 133.6, 132.4, 131.6, 131.5, 130.0, 128.4, 117.9, 115.8, 113.9, 113.3, 110.6, 67.3, 55.30, 55.27, 33.0; HRMS (ESI) calcd for $C_{25}H_{21}NO_3$ [M + H]$^+$ 384.1594, found 384.1598.

*5,6-Bis(4-chlorophenyl)-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ad**).* Pale yellow solid (160.1 mg, 82%): mp 239−241 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.02 (11H, m), 4.63 (2H, t, J = 5.7 Hz), 3.47 (2H, t, J = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 154.1, 149.0, 139.2, 136.6, 135.8, 133.6, 133.5, 132.6, 132.1, 131.6, 128.8, 128.2, 117.5, 116.0, 111.4, 67.2, 32.9; HRMS (ESI) calcd for $C_{23}H_{15}Cl_2NO$ [M + H]$^+$ 392.0603, found 392.0605.

*6-Methyl-5-phenyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ae**).* Pale yellow solid (104.3 mg, 80%): mp 79−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.33 (7H, m), 6.97 (1H, d, J = 7.5 Hz), 4.52 (2H, t, J = 6.0 Hz), 3.36 (2H, t, J = 6.0 Hz), 2.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 151.4, 151.1, 141.3, 136.9, 131.4, 129.7, 128.1, 127.4, 122.3, 115.6, 115.5, 110.5, 67.1, 32.6, 15.6; HRMS (ESI) calcd for $C_{18}H_{15}NO$ [M + H]$^+$ 262.1226, found 262.1228.

*5-(tert-Butyl)-6-methyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3af**).* Pale yellow solid (87.0 mg, 72%): mp 82−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.44 (2H, m), 6.87 (1H, dd, J = 5.7, 2.7 Hz), 4.48 (2H, t, J = 6.0 Hz), 3.26 (2H, t, J = 5.9 Hz), 2.68 (3H, s), 1.53 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 155.1, 149.4, 138.2, 130.6, 121.9, 115.3, 115.1, 109.4, 67.4, 38.6, 32.8, 31.1, 16.4; HRMS (ESI) calcd for $C_{16}H_{19}NO$ [M + H]$^+$ 242.1539, found 242.1542.

*2,5,6-Triphenyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ba**).* Pale yellow solid (162.1 mg, 81%): mp 158−159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.06 (19H, m), 5.48 (1H, dd, J = 9.4, 5.6 Hz), 3.68−3.65 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 153.7, 150.4, 140.9, 139.9, 137.5, 136.7, 131.8, 131.3, 130.3, 129.3, 128.8, 128.5, 128.31, 128.25, 127.7, 127.3, 127.2, 126.3, 118.1, 115.6, 111.3, 79.2, 40.1; HRMS (ESI) calcd for $C_{29}H_{21}NO$ [M + H]$^+$ 400.1696, found 400.1703.

*5,6-Diphenyl-2-propyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ca**).* White solid (153.6 mg, 84%): mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, t, J = 8.1 Hz), 7.36−7.13 (11H, m), 6.97 (1H, d, J = 7.7 Hz), 4.52−4.43 (1H, m), 3.42 (1H, dd, J = 16.7, 3.1 Hz), 3.27 (1H, dd, J = 16.8, 11.1 Hz), 2.04−1.92 (1H, m), 1.86−1.75 (1H, m), 1.73−1.53 (2H, m), 1.02 (3H, t, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 153.8, 150.1, 140.8, 137.5, 136.5, 131.6, 131.2, 130.2, 128.9, 128.1, 128.0, 127.5, 127.0, 126.9, 117.3, 115.5, 110.7, 77.2, 38.0, 37.3, 18.4, 14.0; HRMS (ESI) calcd for $C_{26}H_{23}NO$ [M + H]$^+$ 366.1852, found 366.1852.

*7-Methyl-5,6-diphenyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3da**).* Pale yellow solid (114.0 mg, 68%): mp 221−222 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.09 (11H, m), 6.94 (1H, d, J = 7.9 Hz), 4.56 (2H, t, J = 6.0 Hz), 3.47 (2H, t, J = 6.0 Hz), 1.79 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 153.5, 152.2, 141.6, 140.1, 135.2, 134.6, 131.8, 129.9, 129.6, 127.4, 127.3, 127.2, 127.0, 126.6, 116.7, 111.2, 66.6, 33.3, 23.7; HRMS (ESI) calcd for $C_{24}H_{19}NO$ [M + H]$^+$ 338.1539, found 338.1541.

*7-Chloro-5,6-diphenyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ea**).* Pale yellow solid (130.3 mg, 73%): mp 248−249 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, J = 8.4 Hz), 7.21−7.12 (10H, m), 6.98 (1H, d, J = 8.3 Hz), 4.62 (2H, t, J = 6.0 Hz), 3.49 (2H, t, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 153.8, 153.5, 141.2, 138.3, 135.0, 132.4, 131.9, 130.0, 128.5, 127.6, 127.2, 127.1, 127.0, 122.3, 117.4, 112.2, 66.9, 33.0; HRMS (ESI) calcd for $C_{23}H_{16}ClNO$ [M + H]$^+$ 358.0993, found 358.0995.

*7-Fluoro-2-methyl-5,6-diphenyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3fa**).* Pale yellow solid (150.8 mg, 85%): mp 156−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.06 (12H, m), 6.89 (1H, dd, J = 8.5, 3.3 Hz), 4.53 (1H, dqd, J = 12.3, 6.2, 3.3 Hz), 3.37 (1H, dd, J = 16.8, 3.2 Hz), 3.22 (1H, dd, J = 16.8, 11.2 Hz), 1.58 (3H, d, J = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 152.3 (d, J_{CF} = 249.9 Hz), 152.0, 151.1 (d, J_{CF} = 3.3 Hz), 140.6, 138.8 (d, J_{CF} = 3.5 Hz), 130.6 (d, J_{CF} = 3.5 Hz), 130.5 (d, J_{CF} = 2.8 Hz), 130.1, 127.5, 127.3, 127.2, 127.0, 126.8, 125.9 (d, J_{CF} = 3.3 Hz), 125.2 (d, J_{CF} = 10.9 Hz), 117.1 (d, J_{CF} = 23.8 Hz), 116.0 (d, J_{CF} = 2.6 Hz), 110.9 (d, J_{CF} = 7.1 Hz), 73.7, 39.6, 21.2; HRMS (ESI) calcd for $C_{24}H_{18}FNO$ [M + H]$^+$ 356.1445, found 356.1441.

*8-Methoxy-2,5,6-triphenyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ga**).* Pale yellow solid (165.7 mg, 77%): mp 154−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.14 (16H, m), 6.75 (1H, d, J = 2.2 Hz), 6.55 (1H, d, J = 2.1 Hz), 5.47 (1H, dd, J = 9.9, 5.0 Hz), 3.73−3.59 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 156.4, 153.0, 151.1, 141.0, 139.8, 138.1, 137.7, 131.2, 130. 2, 128.8, 128.6, 128.44, 128.35, 128.29, 127.6, 127.2, 127.0, 126.3, 111.9, 102.4, 98.2, 79.4, 55.4, 39.7; HRMS (ESI) calcd for $C_{30}H_{23}NO_2$ [M + H]$^+$ 430.1802, found 430.1801.

*8-Bromo-5,6-diphenyl-2-propyl-2,3-dihydropyrano[2,3,4-ij]isoquinoline (**3ha**).* White solid (181.7 mg, 82%): mp 116−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.24 (6H, m), 7.19−7.09 (6H, m), 4.47−4.38 (1H, m), 3.36 (1H, dd, J = 16.7, 3.1 Hz), 3.20 (1H, dd, J = 16.9, 11.2 Hz), 1.98−1.87 (1H, m), 1.81−1.68 (1H, m), 1.66−1.50 (2H, m), 0.99 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 153.8, 151.3, 140.4, 137.3, 136.7, 131.1, 130.1, 128.33, 128.29, 128.0, 127.6, 127.3, 127.2, 126.2, 119.7, 114.5, 114.2, 77.8, 37.7, 37.1, 18.3, 14.0; HRMS (ESI) calcd for $C_{26}H_{22}BrNO$ [M + H]$^+$ 444.0958, found 444.0961.

*2,5,6-Triphenyl-2,3-dihydropyrano[2,3,4-ij]isoquinolin-8-ol (**3ia**).* Pale yellow solid (162.5 mg, 78%): mp 218−221 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 (1H, s), 7.63−7.16 (15H, m), 6.68 (1H, s), 6.43 (1H, s), 5.59 (1H, d, J = 8.9 Hz), 3.65−3.39 (3H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.8, 157.2, 153.7, 150.8, 141.9, 141.1, 140.8, 138.7, 138.6, 131.9, 131.0, 129.5, 129.3, 128.2, 128.1, 127.8, 127.6, 111.3, 103.6, 101.2, 79.5; HRMS (ESI) calcd for $C_{29}H_{21}NO_2$ [M + H]$^+$ 416.1645, found 416.1649.

*5,6-Diethyl-2-phenyl-2,3-dihydropyrano[2,3,4-ij]isoquinolin-8-ol (**3ib**).* Pale yellow solid (128.0 mg, 80%): mp 264−267 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.26 (1H, s), 7.59−7.38 (5H, m), 6.82 (1H, s), 6.58 (1H, s), 5.49−5.48 (1H, m), 3.49−3.23 (m, 3H), 2.88−2.80 (m, 4H), 1.28−1.17 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 157.4, 154.0, 151.7, 141.0, 137.7, 129.4, 129.1, 127.5, 126.2, 111.1, 102.4, 98.7, 79.5, 28.6, 21.4, 15.5, 15.5; HRMS (ESI) calcd for $C_{21}H_{21}NO_2$ [M + H]$^+$ 320.1645, found 320.1647.

*2,2,9-Trimethyl-5,6-diphenyl-2,3-dihydropyrano[2,3,4-ij]isoquinolin-8-ol (**3ja**).* Pale yellow solid (135.0 mg, 71%): mp 288−291 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (1H, s), 7.36−7.14 (10H, m), 6.50 (1H, s), 3.21 (2H, s), 2.16 (3H, s), 1.44 (6H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.7, 152.8, 152.1, 149.8, 142.0, 138.8, 135.8, 131.9, 131.0, 129.2, 128.1, 127.9, 127.7, 127.5, 112.5, 110.5, 99.8, 78.1, 43.7, 27.8, 9.5; HRMS (ESI) calcd for $C_{26}H_{23}NO_2$ [M + H]$^+$ 382.1802, found 382.1805.

*5,6-Diphenyl-2,3-dihydrothiopyrano[2,3,4-ij]isoquinoline (**3ka**).* Pale yellow solid (127.7 mg, 75%): mp 143−145 °C (acicular crystals), 163−165 °C (granular crystals); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.09 (13H, m), 3.68 (2H, t, *J* = 5.9 Hz), 3.23 (2H, t, *J* = 5.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 149.4, 140.6, 137.4, 137.1, 134.9, 131.2, 130.1, 130.0, 129.3, 128.1, 127.5, 127.1, 127.0, 124.0, 122.6, 122.1, 36.4, 26.2; HRMS (ESI) calcd for $C_{23}H_{17}NS$ [M + H]$^+$ 340.1154, found 340.1157.

*5,6-Diethyl-2,3-dihydrothiopyrano[2,3,4-ij]isoquinoline (**3kb**).* Pale yellow solid (85.4 mg, 70%): mp 68−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (1H, dd, *J* = 8.4, 1.0 Hz), 7.43 (1H, dd, *J* = 8.4, 7.4 Hz), 7.34 (1H, dd, *J* = 7.3, 1.0 Hz), 3.57 (2H, dd, *J* = 6.8, 5.3 Hz), 3.23 (2H, dd, *J* = 6.9, 5.3 Hz), 3.03−2.90 (4H, m), 1.33 (3H, t, *J* = 7.6 Hz), 1.26 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 152.9, 136.3, 135.3, 129.1, 128.4, 123.1, 122.2, 119.9, 36.4, 28.5, 26.4, 21.1, 15.1, 14.8; HRMS (ESI) calcd for $C_{15}H_{17}NS$ [M + H]$^+$ 244.1154, found 244.1156.

Synthesis of 4aa. To a 25 mL tube equipped with a magnetic stirrer were added **3aa** (129.4 mg, 0.4 mmol) and DDQ (136.2 mg, 0.6 mmol). The tube was evacuated and backfilled with nitrogen for three cycles, and anhydrous DCE (4.0 mL) was added under nitrogen. The tube was sealed and immersed in an oil bath (80 °C), and the contents were stirred for 18 h. Full conversion of **3aa** was confirmed by TLC. After purification by flash column chromatography on silica gel with a petroleum ether/acetone (gradient mixture ratio from 100:0 to 90:10) eluant, **4aa** (96.7 mg, 75%) was obtained as a pale yellow solid.

*5,6-Diphenylpyrano[2,3,4-ij]isoquinoline (**4aa**).* Pale yellow solid (96.7 mg, 75%): mp 168−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (1H, dd, *J* = 8.4, 7.9 Hz), 7.34−7.25 (6H, m), 7.19−7.15 (5H, m), 7.07 (1H, d, *J* = 8.4 Hz), 6.99 (1H, d, *J* = 7.9 Hz), 6.49 (1H, d, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 151.9, 149.8, 149.5, 141.0, 137.6, 137.2, 131.5, 131.1, 130.2, 128.6, 127.7, 127.3, 127.2, 119.4, 117.5, 110.4, 109.2; HRMS (ESI) calcd for $C_{23}H_{15}NO$ [M + H]$^+$ 322.1226, found 322.1230.

Typical Procedure for the Synthesis of 5a−5e. To a 25 mL tube equipped with a magnetic stirrer were added 1-(3-hydroxyphenyl)ethanone (272.3 mg, 2.0 mmol) and PPh_3 (786.9 mg, 3.0 mmol). The tube was evacuated and backfilled with nitrogen for three cycles, and dry THF (10.0 mL) was added. After the solid was dissolved, nitrogen bubbling was conducted for several miniutes. Under nitrogen protection, the tube was immersed in an ice/water bath. Diethyl azodicarboxylate (522.5 mg, 3.0 mmol) was added dropwise while the mixture was being stirred, followed by the addition of pent-3-yn-1-ol (201.9 mg, 2.4 mmol, dissolved in 2.0 mL of dry THF). The tube was sealed, and the contents were stirred at room temperature for 18−24 h (full conversion was confirmed by TLC). After purification by flash column chromatography on silica gel with petroleum ether as the eluant, **5a** (316.7 mg, 78%) was obtained. **5b**−**5e** was synthesized from corresponding ketone−phenols and alkyne−alcohols in yields that range from 64 to 80%.

*1-[3-(Pent-3-yn-1-yloxy)phenyl]ethanone (**5a**).* White solid (316.7 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.46 (2H, m), 7.34 (1H, t, *J* = 7.9 Hz), 7.11−7.07 (1H, m), 4.06 (2H, t, *J* = 7.1 Hz), 2.65−2.57 (2H, m), 2.56 (3H, s), 1.78 (3H, t, *J* = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 158.7, 138.3, 129.5, 121.1, 119.8, 113.2, 77.3, 74.8, 66.6, 26.5, 19.6, 3.3; HRMS (ESI) calcd for $C_{13}H_{14}O_2$ [M + H]$^+$ 203.1067, found 203.1065.

*1-[3-(Hept-3-yn-1-yloxy)phenyl]ethan-1-one (**5b**).* Colorless liquid (346.5 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.47 (2H, m), 7.34 (1H, t, *J* = 7.9 Hz), 7.10 (1H, dd, *J* = 8.2, 2.6 Hz), 4.08 (2H, t, *J* = 7.1 Hz), 2.65 (2H, tt, *J* = 7.1, 2.3 Hz), 2.57 (3H, s), 2.14 (2H, tt, *J* = 7.0, 2.3 Hz), 1.57−1.45 (2H, m), 0.97 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 158.8, 138.4, 129.5, 121.2, 120.0, 113.2, 82.0, 75.7, 66.8, 26.6, 22.3, 20.7, 19.8, 13.4; HRMS (ESI) calcd for $C_{15}H_{18}O_2$ [M + H]$^+$ 231.1380, found 231.1383.

*1-[3-(Pent-3-yn-1-yloxy)phenyl]propan-1-one (**5c**).* Colorless liquid (344.7 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.43 (2H, m), 7.30 (1H, t, *J* = 7.9 Hz), 7.06−7.02 (1H, m), 4.00 (2H, t, *J* = 7.1 Hz), 2.90 (2H, q, *J* = 7.2 Hz), 2.62−2.54 (2H, m), 1.76 (3H, t, *J* = 2.5 Hz), 1.16 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 158.4, 137.8, 129.1, 120.2, 119.0, 112.7, 76.9, 74.6, 66.3, 31.3, 19.3, 7.7, 2.9; HRMS (ESI) calcd for $C_{14}H_{16}O_2$ [M + H]$^+$ 217.1223, found 217.1226.

*6-(Pent-3-yn-1-yloxy)-2-phenylchroman-4-one (**5d**).* Pale yellow solid (472.3 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.31 (6H, m), 7.09 (1H, dd, *J* = 9.0, 3.1 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 5.36 (1H, dd, *J* = 13.3, 2.9 Hz), 3.99 (2H, t, *J* = 7.0 Hz), 2.99 (1H, dd, *J* = 16.9, 13.3 Hz), 2.81 (1H, dd, *J* = 16.9, 3.0 Hz), 2.61−2.54 (2H, m), 1.77 (3H, t, *J* = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 156.0, 152.9, 138.7, 128.6, 128.5, 126.0, 125.4, 120.6, 119.2, 108.3, 79.4, 77.2, 75.0, 66.9, 44.2, 19.5, 3.3; HRMS (ESI) calcd for $C_{20}H_{18}O_3$ [M + H]$^+$ 307.1329, found 307.1330.

*(E)-4-{2-[(3-Phenylprop-2-yn-1-yl)oxy]phenyl}but-3-en-2-one (**5e**).* Pale yellow solid (353.2 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 16.5 Hz), 7.55 (1H, dd, *J* = 7.7, 1.5 Hz), 7.42−7.26 (6H, m), 7.11 (1H, d, *J* = 8.3 Hz), 6.99 (1H, t, *J* = 7.5 Hz), 6.75 (1H, d, *J* = 16.5 Hz), 4.97 (2H, s), 2.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 156.3, 138.3, 131.6, 131.5, 128.7, 128.2, 128.1, 127.8, 123.9, 121.9, 121.5, 113.0, 87.6, 83.4, 57.0, 27.1; HRMS (ESI) calcd for $C_{19}H_{16}O_2$ [M + H]$^+$ 277.1223, found 277.1220.

*Typical Procedure for the Synthesis of **5f**−**5l**.* To a 25 mL tube equipped with a magnetic stirrer were added 1-(1*H*-indol-3-yl)ethanone (159.2 mg, 1.0 mmol), K_2CO_3 (207.3 mg, 1.5 mmol), KI (199.2 mg, 1.2 mmol), (6-chlorohex-1-yn-1-yl)benzene[15] (231.2 mg, 1.2 mmol), and 7.5 mL of acetone. The tube was sealed and immersed in an oil bath (100 °C), and the contents were stirred for 18−24 h. After purification by flash column chromatography on silica gel with a petroleum ether/acetone (gradient mixture ratio from 100:0 to 90:10) eluant, **5h** (276.6 mg, 88%) was obtained. Other compounds of **5f**−**5l** were synthesized from corresponding NH−ketones and Cl−alkynes in yields that range from 75 to 92%.

*1-[1-(5-Phenylpent-4-yn-1-yl)-1H-indol-3-yl]ethan-1-one (**5f**).* White solid (272.0 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43−8.41 (1H, m), 7.67 (1H, s), 7.41−7.21 (8H, m), 4.17 (2H, t, *J* = 6.7 Hz), 2.42 (3H, s), 2.29 (2H, t, *J* = 6.6 Hz), 2.00 (2H, p, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 136.4, 135.0, 131.3, 128.1, 127.7, 126.1, 123.1, 123.0, 122.3, 122.2, 116.6, 109.7, 87.8, 81.9, 45.2, 28.2, 27.2, 16.4; HRMS (ESI) calcd for $C_{21}H_{19}NO$ [M + H]$^+$ 302.1539, found 302.1536.

*1-[1-(Non-4-yn-1-yl)-1H-indol-3-yl]ethanone (**5g**).* White solid (257.5 mg, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41−8.35 (1H, m), 7.72 (1H, s), 7.37−7.23 (3H, m), 4.23 (2H, t, *J* = 6.7 Hz), 2.47 (3H, s), 2.22−2.09 (4H, m), 2.01−1.92 (2H, m), 1.56−1.37 (4H, m), 0.93 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 136.4, 135.0, 126.0, 122.8, 122.2, 122.0, 116.4, 109.6, 81.7, 77.7, 45.1, 30.8, 28.5, 27.0, 21.7, 18.1, 15.7, 13.3; HRMS (ESI) calcd for $C_{19}H_{23}NO$ [M + H]$^+$ 282.1852, found 282.1855.

*1-[1-(6-Phenylhex-5-yn-1-yl)-1H-indol-3-yl]ethanone (**5h**).* Pale yellow solid (276.6 mg, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41−8.39 (1H, m), 7.66 (1H, s), 7.36−7.21 (8H, m), 4.08 (2H, t, *J* =

7.2 Hz), 2.45 (3H, s), 2.39 (2H, t, J = 6.9 Hz), 2.02−1.94 (2H, m), 1.59−1.52 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 192.9, 136.6, 134.8, 131.4, 128.2, 127.7, 126.3, 123.5, 123.1, 122.5, 122.4, 116.8, 109.8, 89.0, 81.4, 46.4, 28.8, 27.5, 25.6, 18.8; HRMS (ESI) calcd for $C_{22}H_{21}NO$ $[M + H]^+$ 316.1700, found 316.1696.

1-[5-Bromo-1-(6-phenylhex-5-yn-1-yl)-1H-indol-3-yl]ethanone ***(5i)***. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51 (1H, d, J = 1.7 Hz), 7.63 (1H, d, J = 1.1 Hz), 7.34−7.32 (2H, m), 7.26−7.23 (4H, m), 7.10 (1H, dd, J = 8.7, 2.9 Hz), 4.05 (2H, td, J = 7.1, 4.1 Hz), 2.41−2.38 (5H, m), 2.01−1.93 (2H, m), 1.58−1.52 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 192.4, 135.4, 135.2, 131.3, 128.1, 127.7 (overlapped), 125.9, 124.8, 123.4, 116.1, 115.8, 111.3, 88.9, 81.4, 46.6, 28.7, 27.3, 25.5, 18.8; HRMS (ESI) calcd for $C_{22}H_{20}BrNO$ $[M + H]^+$ 394.0801, found 394.0806.

1-{1-[6-(4-Methoxyphenyl)hex-5-yn-1-yl]-1H-indol-3-yl}ethanone ***(5j)***. Pale yellow solid (301.3 mg, 87%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.38 (1H, dd, J = 6.0, 2.6 Hz), 7.70 (1H, s), 7.35−7.24 (5H, m), 6.78 (2H, d, J = 8.8 Hz), 4.13 (2H, t, J = 7.2 Hz), 3.74 (3H, s), 2.47 (3H, s), 2.41 (2H, t, J = 6.8 Hz), 2.06−1.99 (2H, dt, J = 14.9, 7.4 Hz), 1.64−1.53 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 192.8, 159.1, 136.7, 134.8, 132.8, 126.3, 123.1, 122.5, 122.4, 116.8, 115.6, 113.8, 109.8, 87.4, 81.2, 55.2, 46.5, 28.9, 27.5, 25.7, 18.9; HRMS (ESI) calcd for $C_{23}H_{23}NO_2$ $[M + H]^+$ 346.1802, found 346.1805.

1-{1-[6-(4-Chlorophenyl)hex-5-yn-1-yl]-1H-indol-3-yl}ethanone ***(5k)***. Pale yellow solid (298.8 mg, 85%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.39 (1H, dd, J = 6.3, 2.4 Hz), 7.69 (1H, s), 7.34−7.19 (7H, m), 4.13 (2H, t, J = 7.1 Hz), 2.47 (3H, s), 2.41 (2H, t, J = 6.9 Hz), 2.05−1.98 (2H, m), 1.62−1.55 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 192.9, 136.7, 134.7, 133.6, 132.7, 128.5, 126.4, 123.2, 122.6, 122.4, 122.1, 116.9, 109.8, 90.1, 80.4, 46.5, 28.9, 27.6, 25.6, 19.0; HRMS (ESI) calcd for $C_{22}H_{20}ClNO$ $[M + H]^+$ 350.1306, found 350.1308.

1-[1-(6-Phenylhex-5-yn-1-yl)-1H-pyrrol-3-yl]ethanone ***(5l)***. Pale yellow solid: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34−7.32 (2H, m), 7.23−7.19 (4H, m), 6.54−6.51 (2H, m), 3.80 (2H, t, J = 7.0 Hz), 2.33 (2H, t, J = 6.9 Hz), 2.30 (3H, s), 1.87−1.80 (2H, m), 1.51−1.43 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 192.9, 131.2, 128.0, 127.5, 125.6, 125.5, 123.4, 122.0, 108.9, 89.0, 81.1, 49.3, 30.0, 26.8, 25.3, 18.7; HRMS (ESI) calcd for $C_{18}H_{19}NO$ $[M + H]^+$ 266.1539, found 266.1539.

Typical Procedure for the Synthesis of 6. To a 25 mL tube equipped with a magnetic stirrer were added **5a** (101.1 mg, 0.5 mmol), hydroxylamine hydrochloride (41.7 mg, 0.6 mmol), $[Cp^*RhCl_2]_2$ (6.2 mg, 0.010 mmol, 2.0 mmol %), KOAc (122.7 mg, 1.25 mmol), and MeOH (5.0 mL). The tube was sealed and immersed in an oil bath (80 °C), and the contents were stirred for 18 h. After purification by flash column chromatography on silica gel with a petroleum ether/acetone (gradient mixture ratio from 100:0 to 90:10) eluant, **6a** (67.6 mg, 68%) was obtained as a white solid.

4,6-Dimethyl-2,3-dihydropyrano[4,3,2-de]isoquinoline ***(6a)***. White solid (67.6 mg, 68%): mp 77−79 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.59 (1H, d, J = 8.3 Hz), 7.40−7.34 (1H, m), 7.05 (1H, d, J = 7.6 Hz), 4.38 (2H, t, J = 5.8 Hz), 3.08 (2H, t, J = 5.7 Hz), 2.87 (3H, s), 2.57 (3H, s); ^{13}C NMR (75 MHz, CDCl$_3$) δ 155.5, 152.4, 144.5, 126.5, 126.3, 124.9, 118.1, 117.8, 113.2, 65.9, 25.7, 22.5, 20.8; HRMS (ESI) calcd for $C_{13}H_{13}NO$ $[M + H]^+$ 200.1070, found 200.1072.

6-Methyl-4-propyl-2,3-dihydropyrano[4,3,2-de]isoquinoline ***(6b)***. Pale yellow semisolid (81.1 mg, 71%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.60 (1H, dd, J = 8.4, 0.8 Hz), 7.40−7.35 (1H, m), 7.06 (1H, dd, J = 7.6, 0.8 Hz), 4.38 (2H, t, J = 5.7 Hz), 3.14 (2H, t, J = 5.7 Hz), 2.88 (3H, s), 2.86−2.80 (2H, m), 1.81−1.69 (2H, m), 1.00 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 155.5, 152.6, 148.4, 126.4, 126.2, 124.7, 117.6, 113.1, 65.9, 36.2, 25.4, 23.0, 22.4, 14.1; HRMS (ESI) calcd for $C_{15}H_{17}NO$ $[M + H]^+$ 228.1383, found 228.1385.

6-Ethyl-4-methyl-2,3-dihydropyrano[4,3,2-de]isoquinoline ***(6c)***. Pale yellow solid (71.1 mg, 67%): mp 49−51 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 (1H, d, J = 8.4 Hz), 7.39−7.34 (1H, m), 7.04 (1H, d, J = 7.6 Hz), 4.38 (2H, t, J = 5.8 Hz), 3.23 (2H, q, J = 7.6 Hz), 3.09 (2H, t, J = 5.8 Hz), 2.58 (3H, s), 1.40 (3H, t, J = 7.6 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.4, 152.6, 144.7, 126.4, 125.4, 125.3, 118.0, 117.5, 113.0, 65.8, 28.9, 25.8, 20.9, 14.3; HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$ 214.1226, found 214.1228.

5-Methyl-2-phenyl-2,3,6,7-tetrahydrodipyrano[4,3,2-de:2′,3′,4′-ij]isoquinoline ***(6d)***. Yellow solid (113.2 mg, 75%): mp 168−170 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (2H, d, J = 7.7 Hz), 7.42−7.32 (1H, m), 6.96 (1H, d, J = 8.2 Hz), 6.86 (1H, d, J = 8.2 Hz), 5.28 (1H, dd, J = 11.3, 3.2 Hz), 4.39−4.27 (2H, m), 3.48 (1H, dd, J = 16.7, 11.4 Hz), 3.39 (1H, dd, J = 16.7, 3.2 Hz), 3.03 (2H, t, J = 5.6 Hz), 2.57 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.7, 148.4, 145.6, 145.5, 140.1, 128.7, 128.3, 126.3, 124.1, 118.8, 114.6, 114.3, 110.3, 79.1, 65.9, 39.6, 25.6, 20.7; HRMS (ESI) calcd for $C_{20}H_{17}NO_2$ $[M + H]^+$ 304.1332, found 304.1336.

2-Methyl-4-phenyl-5H-chromeno[3,4-c]pyridine ***(6e)***. White solid (83.2 mg, 61%): mp 101−102 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72−7.70 (1H, m), 7.44−7.38 (5H, m), 7.35 (1H, s), 7.29−7.25 (1H, m), 7.04 (1H, t, J = 7.5 Hz), 6.95 (1H, d, J = 8.1 Hz), 5.09 (2H, s), 2.62 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 157.7, 155.7, 155.3, 138.9, 138.7, 131.3, 128.8, 128.5, 128.4, 124.1, 122.3, 121.3, 121.2, 117.5, 114.6, 65.6, 24.8; HRMS (ESI) calcd for $C_{19}H_{15}NO$ $[M + H]^+$ 274.1226, found 274.1227.

1-Methyl-3-phenyl-5,6-dihydro-4H-indolo[3,2,1-ij][1,6]naphthyridine ***(6f)***. Pale yellow solid (104.0 mg, 70%): mp 178−180 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.10 (1H, d, J = 7.8 Hz), 7.69−7.67 (2H, m), 7.46−7.26 (6H, m), 4.07 (2H, t, J = 5.7 Hz), 3.08−3.00 (5H, m), 2.15−2.07 (2H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ 150.5, 149.8, 143.0, 140.2, 129.4, 128.2, 127.5, 125.5, 122.4, 122.2, 120.1, 114.8, 111.5, 108.5, 40.7, 23.7, 23.5, 22.5; HRMS (ESI) calcd for $C_{21}H_{18}N_2$ $[M + H]^+$ 299.1543, found 299.1547.

3-Butyl-1-methyl-5,6-dihydro-4H-indolo[3,2,1-ij][1,6]naphthyridine ***(6g)***. Pale yellow solid (100.4 mg, 72%): mp 105−106 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.04 (d, J = 7.8 Hz, 1H), 7.41 (dd, J = 7.8, 7.4 Hz, 1H), 7.29−7.22 (2H, m), 4.03−4.01 (2H, m), 2.95−2.83 (7H, m), 2.25−2.18 (2H, m), 1.76−1.65 (2H, m), 1.50−1.38 (2H, m), 0.95 (3H, t, J = 7.3 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.4, 149.8, 143.0, 140.0, 125.2, 122.4, 122.1, 119.9, 114.1, 110.9, 108.4, 40.4, 34.3, 32.5, 23.2, 23.0, 22.3, 21.4, 14.1; HRMS (ESI) calcd for $C_{19}H_{22}N_2$ $[M + H]^+$ 279.1856, found 279.1854.

1-Methyl-3-phenyl-4,5,6,7-tetrahydro-2,7a-diazacyclohepta[jk]fluorene ***(6h)***. Pale yellow solid (128.1 mg, 82%): mp 170−172 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.13 (1H, d, J = 7.8 Hz), 7.57 (2H, d, J = 7.1 Hz), 7.50−7.29 (6H, m), 4.39−4.36 (2H, m), 3.14−3.11 (2H, m), 3.03 (3H, s), 2.25−2.19 (2H, m), 2.10−2.13 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.3, 150.5, 146.9, 141.7, 141.6, 129.8, 128.2, 127.5, 125.7, 122.4, 122.4, 120.3, 117.1, 116.5, 109.1, 44.3, 28.01, 27.99, 26.8, 24.0; HRMS (ESI) calcd for $C_{22}H_{20}N_2$ $[M + H]^+$ 313.1699, found 313.1696.

10-Bromo-1-methyl-3-phenyl-4,5,6,7-tetrahydro-2,7a-diazacyclohepta[jk]fluorene ***(6i)***. White solid (156.6 mg, 80%): mp 170−171 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.10 (1H, d, J = 1.6 Hz), 7.53 (2H, d, J = 7.1 Hz), 7.46−7.39 (3H, m), 7.36−7.32 (1H, m), 7.12 (1H, d, J = 8.7 Hz), 4.23−4.20 (2H, m), 3.07−3.04 (2H, m), 3.03 (3H, s), 2.16−2.10 (2H, m), 2.03−1.97 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.6, 150.4, 146.9, 141.2, 140.0, 129.7, 128.1, 128.1, 127.5, 124.6, 123.8, 116.4, 115.9, 113.0, 110.3, 44.3, 27.8, 27.7, 26.6, 23.7; HRMS (ESI) calcd for $C_{22}H_{19}BrN_2$ $[M + H]^+$ 391.0804, found 391.0809.

3-(4-Methoxyphenyl)-1-methyl-4,5,6,7-tetrahydro-2,7a-diazacyclohepta[jk]fluorene ***(6j)***. Pale yellow solid (110.2 mg, 64%): mp 145−147 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.09 (1H, d, J = 7.8 Hz), 7.49 (2H, d, J = 8.6 Hz), 7.46−7.43 (1H, m), 7.34 (d, J = 8.2 Hz, 1H), 7.29−7.26 (1H, m), 6.96 (2H, d, J = 8.6 Hz), 4.32−4.29 (2H, m), 3.81 (s, 3H), 3.11−3.08 (2H, m), 3.01 (s, 3H), 2.20−2.14 (2H, m), 2.10−1.99 (2H, m); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.1, 152.7, 150.2, 146.9, 141.5, 133.9, 131.0, 125.6, 122.25, 122.22, 120.2, 116.7, 116.2, 113.5, 109.0, 55.3, 55.3, 44.0, 27.9, 27.8, 26.7, 23.7.; HRMS (ESI) calcd for $C_{23}H_{22}N_2O$ $[M + H]^+$ 343.1805, found 343.1809.

3-(4-Chlorophenyl)-1-methyl-4,5,6,7-tetrahydro-2,7a-diazacyclohepta[jk]fluorene ***(6k)***. Pale yellow solid (137.0 mg, 79%): mp 168−170 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14 (1H, d, J = 7.8 Hz), 7.54−7.49 (3H, m), 7.44−7.39 (3H, m), 7.35−7.32 (1H, m), 4.37−4.34 (2H, m), 3.12−3.09 (2H, m), 3.04 (3H, s), 2.25−2.17 (2H, m), 2.10−2.04 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 150.5, 146.7, 141.6, 139.9, 133.4, 131.2, 128.2, 125.8, 122.3, 122.1, 120.3, 117.1, 116.4, 109.1, 44.1, 27.8, 26.7, 23.8; HRMS (ESI) calcd for $C_{22}H_{19}ClN_2$ $[M + H]^+$ 347.1310, found 347.1309.

*3-Methyl-5-phenyl-6,7,8,9-tetrahydro-4,9a-diazabenzo[cd]azulene (**6l**).* Pale yellow solid (73.5 mg, 56%): mp 95−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.30 (5H, m), 6.98 (1H, d, $J = 2.6$ Hz), 6.50 (1H, d, $J = 2.4$ Hz), 4.23−4.20 (2H, m), 3.05−3.02 (2H, m), 2.74 (3H, s), 2.16−2.10 (2H, m), 2.00−1.94 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 149.0, 142.0, 141.2, 129.9, 128.0, 127.0, 124.3, 117.1, 100.4, 49.2, 28.9, 28.6, 27.1, 21.7; HRMS (ESI) calcd for $C_{18}H_{18}N_2$ $[M + H]^+$ 263.1543, found 263.1546.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01460.

Table S1, X-ray structural details **3ae**, **3af**, and **6h** (Figures S1−S3 and Tables S2−S4), and copies of ^{1}H and ^{13}C NMR spectra (PDF)
Crystallographic information for **3ae** (CIF)
Crystallographic information for **3af** (CIF)
Crystallographic information for **6h** (CIF)

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Notes

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