JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

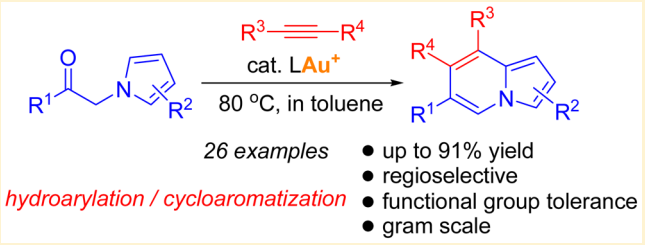
Gold(I)-Catalyzed Cascade Hydroarylation/Cycloaromatization to Indolizines via Pyridine Ring Construction

Xiangdong Li, Xin Xie, and Yuanhong Liu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, People's Republic of China

Supporting Information

ABSTRACT: An efficient and atom-economic method for the synthesis of multisubstituted indolizines via gold-catalyzed cascade hydroarylation/cycloaromatization reaction of α-(*N*-pyrrolyl)ketones with alkynes is described. The reaction is realized through the construction of the pyridine ring of indolizines, which allows the regioselective incorporation of a wide range of functionalities on the pyridine unit.

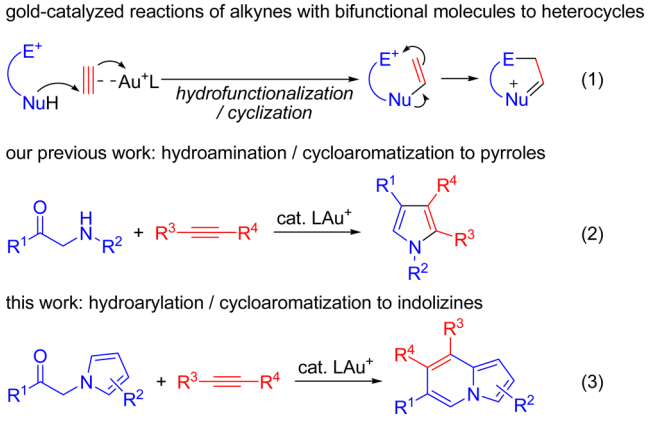


INTRODUCTION

Indolizines, which consist of a π-excessive pyrrole and a π-deficient pyridine ring, are known to possess a variety of important biological activities,[1] such as antibacterial,[1b] antiviral,[1c] anti-inflammatory,[1d] central nervous system (CNS) depressant activity,[1e] etc. They are also widely employed in the field of materials science[2] such as organic light-emitting devices (OLEDs),[2a] biological markers,[2b] and dyes.[2c] Consequently, the development of efficient methods for the construction of indolizines has gained much attention. Traditional synthetic methods to indolizines include Scholtz reaction,[3] Tschitschibabin reaction,[4] 1,3-dipolar,[5] or 1,5-dipolar[6] cycloadditions of pyridinium or related ylides with activated alkynes or alkenes. Recent published reports involve transition-metal-catalyzed cycloisomerization of alkynyl or propargyl pyridine derivatives,[7] transannulations of pyridotriazoles with alkynes,[8] oxidative cross-coupling/cyclization of alkenes and pyridine derivatives,[9] etc.[10] Although much progress has been achieved, most of these methods rely on the construction of the pyrrole ring of indolizines and lack a direct substituent variation on the pyridine ring.[11] Additionally, in some cases, they often involve elaborately designed starting materials and suffer from limited substrate availability. Therefore, a straightforward, convenient, and regioselective route to multiple-substituted indolizines using common chemical materials is highly attractive.

Alkynes have been recognized as versatile starting materials in synthetic chemistry because of their low cost and ready availability. Gold-catalyzed transformations of alkynes have received great attention over the years due to their high selectivity and efficiency, mild reaction conditions, and functional group compatibility.[12] In particular, gold-catalyzed hydrofunctionalization of alkynes via direct addition of a nucleophile to triple bonds is a powerful and atom-economical protocol for the formation of C−C and C−X bonds.[13] Recently, we realized that heterocycles could be conveniently constructed by gold-catalyzed reactions of alkynes with bifunctional compounds containing both nucleophilic and electrophilic groups initialized by hydrofunctionalization (Scheme 1, eq 1). Along this line, pyrroles have been synthesized by a gold-catalyzed hydroamination/cycloaromatization reaction of α-amino ketones with alkynes (Scheme 1, eq 2).[14] This strategy offers a convergent and one-step approach to heterocycles from alkynes. Herein, we report another successful example based on the above strategy for the synthesis of multiple-substituted indolizines from α-(*N*-pyrrolyl)ketones and alkynes, which involves a gold-catalyzed intermolecular hydroarylation/cycloaromatization cascade (Scheme 1, eq 3). To the best of our knowledge, the construction of indolizines from simple alkynes by intermolecular hydroarylation has not been reported.

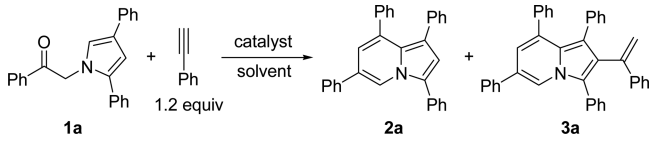
Scheme 1. Gold-Catalyzed Route to Heterocycles



Received: February 17, 2016
Published: April 1, 2016

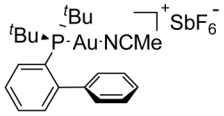
DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699

Table 1. Optimization of Reaction Conditions



1a 2a 3a

entry	catalyst (mol %)	solvent	temp (°C)	time (h)	yield(%)[a] 2a	yield(%)[a] 3a
1	catalyst **A** (5)	toluene	80	3	84	12
2	IPrAuCl/$AgSbF_6$ (5)	toluene	80	10	68	17
3[b]	PPh_3AuNTf_2 (5)	toluene	80	3	90	7
4	$PPh_3AuCl/AgSbF_6$ (5)	toluene	80	14	75	5
5	$PPh_3AuCl/AgPF_6$ (5)	toluene	80	14	45	2
6	PPh_3AuCl/AgOTs (5)	toluene	80	14	4	0
7	PPh_3AuNTf_2 (5)	DCE	80	12	84	8
8	PPh_3AuNTf_2 (5)	CH_3CN	80	22	68	4
9	PPh_3AuNTf_2 (5)	toluene	60	10	89	7
10	PPh_3AuNTf_2 (2)	toluene	80	12	88	8
11	PPh_3AuCl (5)	toluene	80	24	0	0
12	$AgNTf_2$ (5)	toluene	80	24	3	1
13	MsOH (20)	toluene	80	22	6	0



catalyst **A**

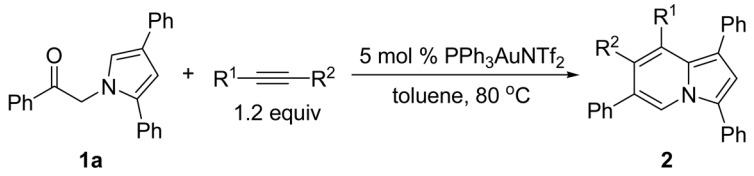
[a]All the reactions were carried out on a 0.3 mmol scale. NMR yields determined by ^1H NMR of the crude reaction mixture using CH_2Br_2 as an internal standard. [b]The isolated yields of **2a** and **3a** were 86% and 5%, respectively.

RESULTS AND DISCUSSION

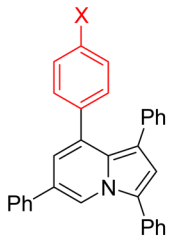
Compared with the gold-catalyzed intramolecular hydroarylation of alkynes with pyrroles,[15] few applications with limited substrate scope have been reported for the intermolecular variant,[16,17] possibly due to the following reasons: (i) Pyrrole possesses multiple nucleophilic sites; although pyrrole is known to undergo substitution predominantly at the α-position, the β-substitution can compete depending on the nature of the substituents on nitrogen and the substitution pattern on the pyrrole ring.[18] (ii) Double hydroarylation with two alkynes might occur at different reaction sites of pyrrole.[18a] (iii) In addition, double addition of pyrroles to acetylene to give the bis(pyrrolyl)alkane products might take place under gold catalysis.[16b,c] All of these challenges make the intermolecular hydroarylation of pyrroles with high selectivity a formidable task. We envisioned that employing an appropriate substituted pyrrole as the substrate may improve the selectivity of the intermolecular hydroarylation, since the hydroarylation at other positions of pyrrole or second hydroarylation might be inhibited by steric hindrance of the existing substituents on the pyrrole ring. To validate our hypothesis, α-(*N*-pyrrolyl)ketone **1a** bearing two substituents at the C-2 and C-4 positions on the pyrrole ring was chosen as a model substrate for optimization of the reaction conditions (Table 1). We were delighted to find that Echavarren's catalyst (catalyst **A**, 5 mol %) bearing a bulky biarylphosphine ligand (Johnphos) catalyzed the desired reaction of **1a** with phenylacetylene efficiently and regioselectively to afford 1,3,6,8-tetraphenylindolizine **2a** in 84% yield, accompanied by 12% of 2-vinylated indolizine **3a** in toluene at 80 °C for 3 h (Table 1, entry 1). **3a** might be formed via double hydroarylation of **1a** at its C-3 and C-5 positions, followed by cyclization, or through the hydroarylation of indolizine **2a** with the alkyne. In fact, reaction of **2a** with phenylacetylene under the reaction conditions shown in entry 1 did not afford **3a**, which reveals that **3a** was formed through the double hydroarylation pathway. To minimize the formation of the over-alkenylated product **3a**, gold catalysts with different ligands or counteranions were examined. The use of a cationic gold(I)-carbene complex of IPrAuCl/$AgSbF_6$ (IPr = 2,6-bis(diisopropylphenyl)imidazol-2-ylidene) gave a lower yield of **2a** with an increased amount of **3a** (Table 1, entry 2). Gratifyingly, the electron-neutral PPh_3AuNTf_2 turned out to be more efficient to provide **2a** in 90% yield with only 7% of **3a** (Table 1, entry 3). Gold catalysts with different counteranions such as SbF_6^-, PF_6^-, or OTs^- were less efficient (Table 1, entries 4–6). Performing the reaction in DCE also afforded **2a** in a high yield of 84%, whereas only 68% of **2a** was observed in CH_3CN (Table 1, entries 7 and 8). Decreasing the reaction temperature to 60 °C or lowering the catalyst loading to 2 mol % led to a prolonged reaction time (Table 1, entries 9 and 10). The use of PPh_3AuCl or $AgNTf_2$ alone failed to catalyze the reaction (Table 1, entries 11 and 12). Brønsted acid such as MsOH only provided little amounts of the desired products (Table 1, entry 13).

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688–3699

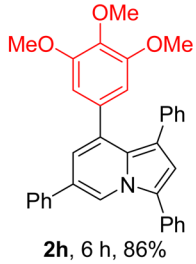
Table 2. Scope of the Alkynes[a]



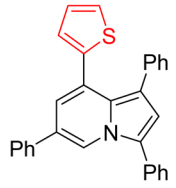
1a 2



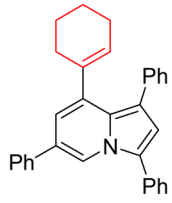
2a, X = H, 3 h, 86%[b]
2b, X = F, 10 h, 81%
2c, X = Cl, 10 h, 82%
2d, X = CO_2Et, 10 h, 86%
2e, X = Me, 10 h, 85%
2f, X = OMe, 4 h, 91%[c]
2g, X = NHCbz, 10 h, 87%



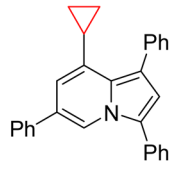
2h, 6 h, 86%



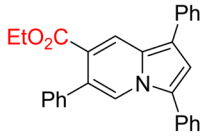
2i, 10 h, 80%



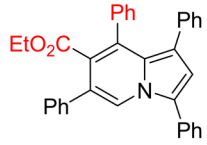
2j, 10 h, 71%



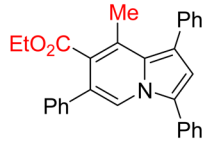
2k, 14 h, 54%



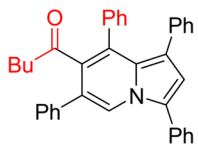
2l, 15 h, 44%



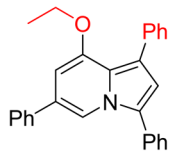
2m, 15 h, 77%



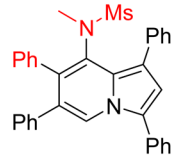
2n, 24 h, 63%



2o, 16 h, 85%



2p, 3 h, 40%[d]



2q, 36 h, 41%

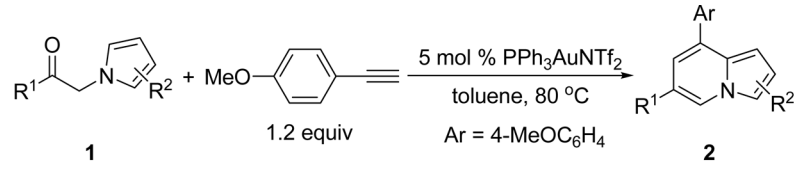
[a]Isolated yields. [b]2-Vinylated product **3a** was isolated in 5% yield. [c]2-Vinylated product **3f** was isolated in 7% yield. [d]5 mol % catalyst **A** and 2 equiv of ethoxyethyne were used.

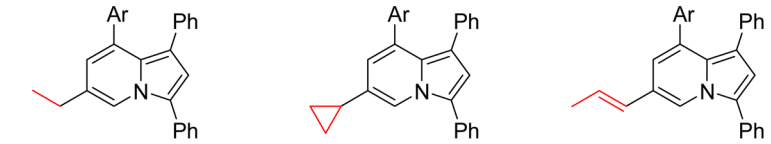
With the optimized reaction conditions established (Table 1, entry 3), we next examined the reaction scope (Table 2). First, the reactivity of terminal alkynes using **1a** as the reaction partner was investigated. In the cases of aryl substituted alkynes, a wide variety of functional groups on the aryl rings were tolerated well. For example, both of the electron-withdrawing (*p*-F, *p*-Cl, *p*-CO_2Et) and electron-donating (*p*-Me, *p*-MeO, *p*-NHCbz, 3,4,5-$(MeO)_3$) substituted aryl alkynes underwent the reaction smoothly to afford the corresponding indolizines **2b**–**2h** in 81–91% yields. The electronic nature of the aryl substituents had little influence on the reaction efficiency. Heteroaryl-substituted alkyne such as the thienyl-substituted one was also compatible in this reaction, furnishing **2i** in 80% yield. Notably, alkyne substituted with a 1-cyclohexenyl group underwent the reaction well to provide the desired **2j** in 71% yield, implying that the cationic Au(I) complexes activate the alkyne preferentially. Employing ethynylcyclopropane provided the desired indolizine **2k** in 54% yield. Activated terminal alkyne such as ethyl propiolate was also suitable to afford the expected **2l** in moderate yield. The reaction could be extended successfully to activated internal alkynes; for example, the use of alkynyl esters or ketone provided the corresponding indolizines **2m**–**2o** in 63–85% yields.[19] In addition, the reaction was also applicable to heteroatom substituted alkynes such as alkynyl ether or ynamide, furnishing **2p**–**2q** in 40–41% yields, which are difficult to be prepared by other methods. In the cases of **2l**, **2p**, and **2q**, some byproducts were also observed. These results are significant since C-8-O or N-functionalized indolizines have been found to be a potent sPLA2 inhibitor that can be used in the treatment of septic shock, pancreatitis, gout, and other diseases.[20] Our method provided a convenient route to these functionalized indolizines. The structure of indolizine was unambiguously confirmed by X-ray crystallographic analysis of **2f**.[21]

Next, the scope of *α*-(*N*-pyrrolyl)ketones **1** using 1-ethynyl-4-methoxybenzene as the reaction partner was examined (Table 3). We first examined the substituent effect (R^1) on the carbonyl group. Gratifyingly, substrates bearing an alkyl group,

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688–3699

Table 3. Scope of the α-(*N*-Pyrrolyl)ketones[a]

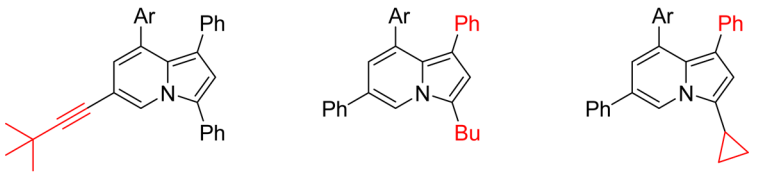




2r, 8 h, 81%

2s, 9 h, 82%

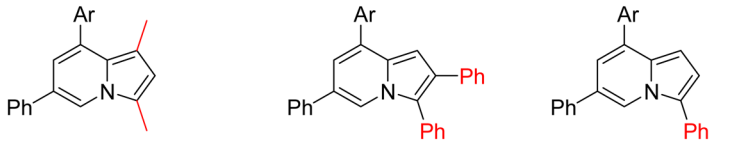
2t, 3 h, 81%



2u, 4 h, 88%

2v, 6 h, 78%

2w, 12 h, 86%



2x, 2 h, 55%[b]

2y, 22 h, 51%

2z, 4 h, 53%

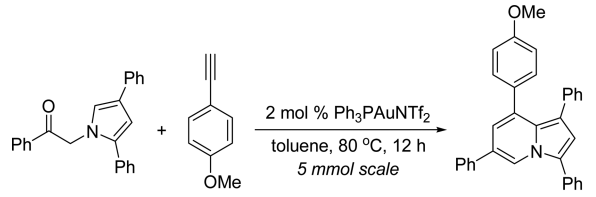
[a]Isolated yields. [b]2-Vinylated product **3x** was isolated in 13% yield.

such as ethyl or cyclopropyl, on the carbonyl moiety reacted well, furnishing **2r** and **2s** in high yields of 81% and 82%, respectively. When R^1 was a vinyl group such as a propenyl group, the corresponding indolizine **2t** was efficiently formed in 81% yield, while the vinyl group remained intact. Interestingly, alkynyl substituent with a bulky ^{t}Bu group on the alkyne terminus was proved to be well tolerated, providing alkynyl indolizine **2u** in 88% yield. As for the pyrrole moiety in α-(*N*-pyrrolyl)ketones, substrates derived from various 2,4-disubstituted pyrroles underwent facile cyclization to provide **2v**–**2x** in 55–86% yields. Among them, the more nucleophilic 2,4-dimethyl pyrrole substrate led to a moderate yield of the product **2x**. Substrates derived from 2,3-disubstituted pyrrole or 2-substituted pyrrole afforded the corresponding indolizines **2y**–**2z** in moderate yields, possibly due to the decreased regioselectivity in the hydroarylation step in these cases. It was also noted that trace amounts of byproducts **3** were generally observed in the above cases.

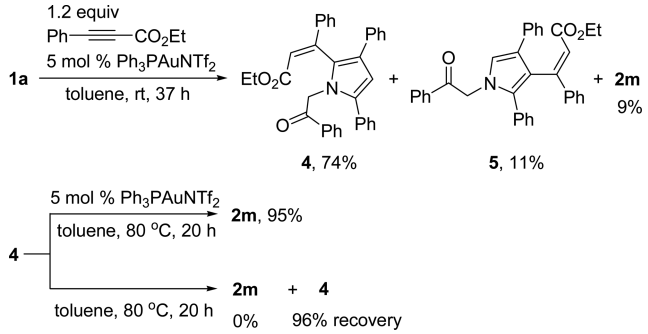
A gram-scale reaction was performed to demonstrate the practicality of our protocol. The reaction of **1a** with 1-ethynyl-4-methoxybenzene at 5 mmol scale using 2 mol % of PPh_3AuNTf_2 provided indolizine product **2f** in a high yield of 90% (Scheme 2).

To gain mechanistic insights, we tried to isolate the possible reaction intermediates. To our delight, C-5-alkenylated-pyrrole intermediate **4** was isolated in 74% yield by lowering the reaction temperature to room temperature, along with C-3-alkenylated-pyrrole **5** in 11% yield (Scheme 3). **4** cyclized smoothly in the presence of 5 mol % PPh_3AuNTf_2 to afford indolizine **2m** in 95% yield. However, in the absence of gold catalyst, formation of **2m** was not observed. These experiments indicated that the formation of C-5-alkenylated-pyrrole

Scheme 2. Gram-Scale Study



Scheme 3. Mechanistic Studies

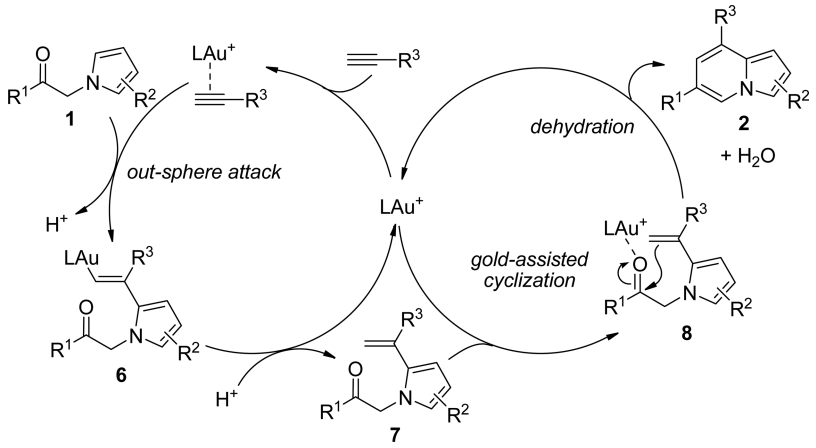


intermediate **4** was the initial step in this cascade reaction, and cyclization of **4** to indolizine was promoted by gold catalyst.

On the basis of the above observations, we propose the following reaction mechanism for this cascade reaction (Scheme 4). Initially, hydroarylation of **1** with terminal alkyne occurs regioselectively at the α-position of the pyrrole ring to afford the alkenyl gold intermediate **6**, which undergoes the

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688–3699

Scheme 4. Proposed Reaction Mechanism



protodeauration to give the intermediate **7**. Then, nucleophilic attack of the vinyl moiety in **7** to the carbonyl group, followed by elimination of water, leads to the indolizine products **2**. This process is also promoted by gold due to its Lewis acid property. In addition, the alkene moiety which conjugates with the pyrrole in **7** is more nucleophilic since the electrons on the pyrrole ring can delocalize onto the alkene unit, thus triggering an efficient ring closure. Alternatively, ring closure might occur directly from **6**, followed by deauration and dehydration.

CONCLUSION

In summary, we have developed a new and efficient method for the synthesis of multisubstituted indolizines based on gold-catalyzed hydroarylation/cycloaromatization reaction of α-(*N*-pyrrolyl)ketones with alkynes. A wide variety of the functional groups, particularly, esters, ketones, alkoxy, or amide groups, can be easily elaborated into the pyridine unit of the indolizine products. These results make the current method an attractive alternative and/or complement to the existing methods in which the functionality is usually incorporated into the pyrrole unit of the indolizines. Further studies to extend this chemistry for the synthesis of other heterocycles are in progress in our laboratory.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out using standard Schlenk techniques under argon unless otherwise noted. DCM and DCE were distilled from CaH_2. Toluene and THF were distilled from sodium and benzophenone. MeCN was dried using an Innovative Technology Solvent Purifier. Unless noted, all commercial reagents were used without further purification. Ph_3PAuCl[22] and $Ph_3PAuNTf_2$[23] were prepared according to the published method. 1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidenegold(I) chloride, $AgSbF_6$, and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (catalyst **A**) were purchased from a chemical supplier. ^{1}H NMR spectra were recorded at 400 or 600 MHz; ^{13}C NMR spectra were recorded at 100 or 150 MHz. ^{1}H NMR spectra were recorded with tetramethylsilane (δ = 0.00 ppm) as internal reference; ^{13}C NMR spectra were recorded with $CDCl_3$ (δ = 77.00 ppm) or C_6D_6 (δ = 128.06 ppm) as internal reference. High-resolution mass spectra were performed on a mass spectrometer with a TOF or LTQ analyzer.

Synthesis of *N-H* Pyrroles s-1a, s-1b, and s-1c. *Typical Procedure for the Synthesis of 2,4-Diphenyl-1H-pyrrole (**s-1a**).* To a solution of phenylacetylene (18.1 mL, 165 mmol) in THF (150 mL) was added *n*-BuLi (2.5 M in hexane, 60 mL, 150 mmol) at −78 °C. After stirring for 30 min at the same temperature, α-amino-acetophenone hydrochloride (8.58 g, 50.0 mol) was added; then the resulting mixture was warmed up to room temperature and stirred for 1 h. After the starting material was consumed, the mixture was quenched with water, extracted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by a short column chromatography on silica gel (eluent: dichloromethane:methanol = 25:1) to afford the crude product 1-amino-2,4-diphenylbut-3-yn-2-ol as an off-white solid.

To a solution of the above crude alcohol in DCE (150 mL) was added catalyst **A** (77.2 mg, 0.1 mmol), and then the flask was immersed into an oil bath preheated at 80 °C. After the reaction was complete as monitored by thin-layer chromatography (1 h), the mixture was cooled down. Then, anhydrous Na_2SO_4 was added to the reaction mixture to remove the byproduct water. Next, the mixture was filtered through a pad of Celite and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:dichloromethane = 1:1 to dichloromethane) to afford **s-1a** (7.73 g, 71% overall yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (bs, 1 H), 7.55 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 4H), 7.23−7.17 (m, 2H), 7.04−7.03 (m, 1H), 6.82−6.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.0, 132.4, 128.9, 128.7, 126.4, 126.4, 125.7, 125.1, 123.8, 115.7, 103.8. The spectroscopic data are in agreement with those previously reported.[24]

*2-Butyl-4-phenyl-1H-pyrrole (**s-1b**).* Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 30:1) afforded the title product in 57% overall yield (15 mmol scale, 1.71 g) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (bs, 1H), 7.49−7.46 (m, 2H), 7.30−7.26 (m, 2H), 7.13−7.09 (m, 1H), 6.75−6.74 (m, 1H), 6.19−6.18 (m, 1H), 2.45 (t, J = 7.2 Hz, 2H), 1.55−1.48 (m, 2H), 1.36−1.[27] (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 133.9, 128.5, 125.1, 124.8, 124.4, 112.8, 103.0, 31.5, 27.3, 22.3, 13.8; IR (film): 3326, 3059, 3029, 2958, 2931, 2862, 1687, 1604, 1524, 1493, 1449, 1378, 1265, 1182, 1124, 1072, 1032, 980, 926, 866, 794, 735, 696, 655 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}N$ [M]$^+$: 199.1361, found 199.1364.

*2-Cyclopropyl-4-phenyl-1H-pyrrole (**s-1c**).* Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 60:1:20) afforded the title product in 60% overall yield (15 mmol scale, 1.65 g) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (bs, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.31−7.28 (m, 2H), 7.17−7.11 (m, 1H), 6.84 (t, J = 2.0 Hz, 1H), 6.15 (t, J = 2.0 Hz, 1H), 1.78−1.72 (m, 1H), 0.83−0.78 (m, 2H), 0.64−0.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.5, 128.5, 125.2, 124.9, 124.6, 112.9, 102.1, 8.1, 6.5; IR (film): 3416, 3076, 3004, 1686, 1602, 1526, 1479, 1450, 1421, 1358, 1181, 1156, 1117, 1072, 1046, 1021, 970, 928, 903, 874, 799, 762, 743, 693, 676, 609 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}N$ [M + H]$^+$: 184.1121, found 184.1121.

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699

2,4-Dimethyl-1*H*-pyrrole (**s-1d**) was commercially available; 2,3-diphenyl-1*H*-pyrrole (**s-1e**)[25] and 2-phenyl-1*H*-pyrrole (**s-1f**)[26] were prepared according to published methods.

Synthesis of α-(*N*-Pyrrolyl)ketones 1a, 1f, 1g, 1i, and 1j. *Typical Procedure for the Synthesis of 2-(2,4-Diphenyl-1H-pyrrol-1-yl)-1-phenyl-ethan-1-one (**1a**).* Under argon, to a solution of 2,4-diphenyl-1*H*-pyrrole (2.19 g, 10.0 mmol) in DMF (40 mL) was added sodium hydride (60% w/w in mineral oil, 480 mg, 12.0 mmol) at 0 °C. After stirring for 30 min at the same temperature, 2-bromo-*N*-methoxy-*N*-methylacetamide (2.18 g, 12.0 mmol) was added; then the resulting mixture was warmed up to room temperature and stirred for 30 min. The mixture was quenched with water, extracted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by a short column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 3:1:1) to afford the crude product of 2-(2,4-diphenyl-1*H*-pyrrol-1-yl)-*N*-methoxy-*N*-methylacetamide as an off-white solid.

To a solution of the above crude product in DCM (50 mL) was added dropwise phenyl magnesium bromide (1.0 M in THF, 14.0 mL, 14.0 mmol) at −78 °C.[27] Then, the resulting mixture was warmed up to 0 °C and stirred for 1 h. After the starting material was consumed, the mixture was quenched with saturated NH_4Cl solution, extracted with DCM, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 50:1:20) to afford **1a** (2.86 g, 85% overall yield) as a light yellow solid.

*2-(2,4-Diphenyl-1H-pyrrol-1-yl)-1-phenylethan-1-one (**1a**).* Mp 140−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.83 (m, 2H), 7.59−7.52 (m, 3H), 7.44−7.41 (m, 2H), 7.35−7.26 (m, 7H), 7.17−7.13 (m, 1 H), 7.00 (d, J = 2.0 Hz, 1 H), 6.59 (d, J = 2.0 Hz, 1 H), 5.28 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 136.0, 135.4, 134.5, 133.9, 132.6, 128.9, 128.8, 128.6, 128.5, 127.9, 127.4, 125.5, 125.1, 125.0, 120.2, 107.1, 53.4; IR (film): 3059, 3032, 2925, 2338, 1955, 1889, 1814, 1698, 1602, 1580, 1524, 1485, 1450, 1422, 1402, 1350, 1300, 1211, 1182, 1160, 1074, 1057, 1012, 1000, 985, 929, 806, 751, 690, 667, 643, 616 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{20}NO$ $[M + H]^+$: 338.1539, found 338.1540.

*2-(2-Butyl-4-phenyl-1H-pyrrol-1-yl)-1-phenylethan-1-one (**1f**).* Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 100:1:30) afforded the title product in 16% overall yield (8.5 mmol scale, 432 mg) as a white solid. Mp 90−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2H), 7.63−7.59 (m, 1H), 7.50−7.47 (m, 4H), 7.31−7.27 (m, 2H), 7.14−7.10 (m, 1H), 6.83 (d, J = 1.6 Hz, 1H), 6.31 (s, 1H), 5.20 (s, 2H), 2.40 (t, J = 7.6 Hz, 2H), 1.67−1.59 (m, 2H), 1.42−1.33 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 135.9, 135.0, 134.6, 133.9, 128.9, 128.4, 127.9, 125.1, 124.9, 124.0, 117.8, 104.3, 52.9, 30.5, 25.8, 22.5, 13.9; IR (film): 3062, 3033, 2956, 2928, 2870, 2337, 1698, 1603, 1580, 1523, 1493, 1449, 1416, 1380, 1350, 1300, 1264, 1213, 1182, 1098, 1072, 1054, 1027, 989, 931, 834, 792, 752, 734, 688, 636, 617 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{24}NO$ $[M + H]^+$: 318.1852, found 318.1854.

*2-(2-Cyclopropyl-4-phenyl-1H-pyrrol-1-yl)-1-phenylethan-1-one (**1g**).* Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 50:1:20) afforded the title product in 62% overall yield (8.65 mmol scale, 1.61 g) as a white solid. Mp 130−131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 2H), 7.61−7.57 (m, 1H), 7.48−7.45 (m, 4H), 7.29−7.25 (m, 2H), 7.12−7.09 (m, 1H), 6.84 (s, 1H), 6.20 (s, 1H), 5.33 (s, 2H), 1.54−1.47 (m, 1H), 0.75−0.70 (m, 2H), 0.63−0.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 136.5, 135.8, 134.7, 133.8, 128.9, 128.4, 127.9, 125.1, 124.8, 123.6, 118.2, 104.0, 52.9, 6.6, 5.7; IR (film): 3055, 3004, 2927, 1698, 1601, 1580, 1527, 1450, 1411, 1389, 1352, 1265, 1215, 1183, 1140, 1067, 1052, 1027, 989, 889, 830, 799, 761, 730, 690, 646 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}NO$ $[M + H]^+$: 302.1539, found 302.1541.

*2-(2,3-Diphenyl-1H-pyrrol-1-yl)-1-phenylethan-1-one (**1i**).* Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 50:1:20) afforded the title product in 83% overall yield (10.0 mmol scale, 2.80 g) as a white solid. Mp 138−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.56−7.53 (m, 1H), 7.42−7.38 (m, 2H), 7.26−7.12 (m, 9H), 7.07−7.04 (m, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.55 (d, J = 2.0 Hz, 1H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 136.3, 134.5, 133.8, 132.4, 131.0, 130.8, 128.8, 128.6, 127.9, 127.8, 127.8, 127.6, 125.0, 122.9, 122.3, 108.9, 53.2; IR (film): 3049, 3031, 2907, 1701, 1599, 1578, 1504, 1474, 1449, 1416, 1347, 1273, 1226, 1182, 1160, 1077, 1029, 1015, 999, 984, 957, 924, 912, 852, 825, 783, 751, 724, 700, 690, 673, 639, 625, 611 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{20}NO$ $[M + H]^+$: 338.1539, found 338.1542.

*1-Phenyl-2-(2-phenyl-1H-pyrrol-1-yl)ethan-1-one (**1j**).* Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 50:1:20) afforded the title product in 72% overall yield (10.0 mmol scale, 1.87 g) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.83 (m, 2H), 7.59−7.54 (m, 1H), 7.45−7.41 (m, 2H), 7.33−7.20 (m, 5H), 6.72 (dd, J = 2.4, 1.6 Hz, 1H), 6.32−6.31 (m, 1H), 6.29−6.28 (m, 1H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 134.9, 134.5, 133.8, 132.8, 128.78, 128.76, 128.4, 127.8, 127.1, 123.5, 109.0, 108.8, 53.3; IR (film): 3059, 2925, 1961, 1892, 1816, 1698, 1597, 1579, 1546, 1493, 1470, 1448, 1424, 1353, 1313, 1221, 1182, 1159, 1074, 1056, 1026, 999, 975, 917, 884, 847, 823, 788, 754, 714, 700, 687, 642, 608 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}NO$ $[M + H]^+$: 262.1226, found 262.1228.

Synthesis of α-(*N*-Pyrrolyl)ketones 1b, 1c, 1d. *Synthesis of 2-(2,4-Diphenyl-1H-pyrrol-1-yl)-N-methoxy-N-methylacetamide.* Under argon, to a solution of 2,4-diphenyl-1*H*-pyrrole (877.2 mg, 4.0 mmol) in DMF (20 mL) was added sodium hydride (60% w/w in mineral oil, 192 mg, 4.8 mmol) at 0 °C. After stirring for 30 min at the same temperature, 2-bromo-*N*-methoxy-*N*-methylacetamide (874 mg, 4.8 mmol) was added; then the resulting mixture was warmed up to room temperature and stirred for 30 min. After the starting material was consumed, the mixture was quenched with water, extracted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 10:1:5) to afford 2-(2,4-diphenyl-1*H*-pyrrol-1-yl)-*N*-methoxy-*N*-methylacetamide (1.14 g, 89% yield) as a white solid. Mp 112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.38−7.37 (m, 4H), 7.31−7.28 (m, 3H), 7.15−7.11 (m, 1H), 7.04 (d, J = 2.0 Hz, 1 H), 6.54 (d, J = 2.0 Hz, 1 H), 4.75 (s, 2H), 3.44 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 135.8, 135.4, 132.6, 128.8, 128.4, 128.3, 127.2, 125.3, 124.9, 124.7, 120.2, 106.7, 61.1, 47.9, 32.3; IR (neat): 3062, 2966, 2936, 1672, 1602, 1579, 1522, 1489, 1478, 1455, 1443, 1422, 1385, 1317, 1250, 1211, 1173, 1160, 1119, 1095, 1076, 1058, 1035, 992, 959, 929, 917, 855, 814, 802, 780, 757, 749, 701, 685, 666, 639, 618, 606 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{21}N_2O_2$ $[M + H]^+$: 321.1598, found 321.1600.

*Typical Procedure for the Synthesis of 1-(2,4-Diphenyl-1H-pyrrol-1-yl)butan-2-one (**1b**).* Under argon, to a solution of 2-(2,4-diphenyl-1*H*-pyrrol-1-yl)-*N*-methoxy-*N*-methylacetamide (1.46 g, 4.57 mmol) in DCM (20 mL) was added dropwise ethylmagnesium bromide (3.0 M in Et_2O, 2.13 mL, 6.40 mmol) at −78 °C. Then, the resulting mixture was warmed up to 0 °C and stirred for 1 h. After the starting material was consumed, the mixture was quenched with saturated NH_4Cl solution, extracted with DCM, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:dichloromethane = 1:1) to afford **1b** (1.07 g, 81% yield) as a white solid.

*1-(2,4-Diphenyl-1H-pyrrol-1-yl)butan-2-one (**1b**).* Mp 86−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.52 (m, 2H), 7.40−7.29 (m, 7H), 7.20−7.15 (m, 1H), 6.94 (d, J = 2.0 Hz, 1 H), 6.56 (d, J = 2.0 Hz, 1 H), 4.62 (s, 2H), 2.22 (q, J = 7.2 Hz, 2 H), 0.96 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 135.9, 135.1, 132.3, 128.8, 128.60, 128.55, 127.5, 125.6, 125.2, 125.0, 119.8, 107.4, 56.2, 32.4, 7.2; IR (neat): 3051, 2978, 2941, 2913, 2882, 1881, 1817, 1728, 1602, 1579, 1564, 1526, 1486, 1474, 1453, 1414, 1366, 1244, 1214, 1155,

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699

1111, 1073, 1042, 1011, 985, 929, 905, 802, 785, 755, 745, 692, 665, 639 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}NO$ $[M + H]^+$: 290.1539, found 290.1543.

*1-Cyclopropyl-2-(2,4-diphenyl-1H-pyrrol-1-yl)ethan-1-one (**1c**).* Cyclopropyl-magnesium bromide was used. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 20:1:4) afforded the title product in 36% yield (4.46 mmol scale, 489 mg) as a white solid. Mp 90−91 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 2H), 7.39−7.29 (m, 7H), 7.19−7.14 (m, 1H), 7.00 (d, J = 2.0 Hz, 1 H), 6.57 (d, J = 1.6 Hz, 1 H), 4.73 (s, 2H), 1.71−1.65 (m, 1 H), 1.03−0.99 (m, 2 H), 0.86−0.81 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 136.0, 135.1, 132.3, 128.8, 128.6, 128.5, 127.4, 125.6, 125.2, 125.0, 120.0, 107.3, 57.0, 17.4, 11.9; IR (neat): 3098, 3055, 3009, 2912, 2324, 2085, 1952, 1877, 1813, 1707, 1602, 1564, 1525, 1486, 1475, 1454, 1414, 1385, 1340, 1260, 1216, 1193, 1156, 1108, 1072, 1026, 964, 929, 893, 843, 803, 766, 752, 743, 692, 665, 645, 633, 617 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}NO$ $[M + H]^+$: 302.1539, found 302.1540.

*(E)-1-(2,4-Diphenyl-1H-pyrrol-1-yl)pent-3-en-2-one (**1d**).* Allylmagnesium bromide was used. In this case, double bond isomerization occurred to afford the α,β-unsaturated ketone product **1d**. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 50:1:10) afforded the title product in 40% yield (4.5 mmol scale, 548 mg) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.53 (m, 2H), 7.39−7.28 (m, 7H), 7.18−7.14 (m, 1H), 6.97 (d, J = 2.0 Hz, 1 H), 6.90 (dq, J = 15.6, 6.8 Hz, 1 H), 6.58 (d, J = 2.0 Hz, 1H), 5.99 (dq, J = 15.6, 1.6 Hz, 1 H), 4.75 (s, 2 H), 1.83 (dd, J = 6.8, 1.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 145.5, 136.0, 135.2, 132.4, 128.8, 128.6, 128.5, 127.4, 127.3, 125.6, 125.2, 125.0, 119.9, 107.3, 55.0, 18.5; IR (film): 3056, 3034, 2916, 1687, 1634, 1604, 1524, 1487, 1453, 1441, 1402, 1375, 1289, 1265, 1203, 1131, 1075, 1057, 1030, 1010, 968, 930, 808, 757, 732, 697, 668, 638, 617 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}NO$ $[M + H]^+$: 302.1539, found 302.1541.

Synthesis of α-(*N*-Pyrrolyl)ketone 1e. Under argon, to a solution of 3,3-dimethylbut-1-yne (530 mg, 6.45 mmol) in THF (10 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 2.41 mL, 6.02 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 30 min. Then, the in situ formed alkynyl lithium solution was added dropwise into the solution of the Weinreb amide (1.378 g, 4.3 mmol) in DCM (30 mL) through a syringe at −78 °C. After that, the resulting mixture was warmed up to 0 °C and stirred for 1 h. The mixture was quenched with saturated NH_4Cl solution, extracted with DCM, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 20:1) to afford **1e** (0.909 g, 62% yield) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 2H), 7.41−7.31 (m, 7H), 7.20−7.15 (m, 1H), 7.00 (d, J = 2.0 Hz, 1 H), 6.57 (d, J = 1.6 Hz, 1 H), 4.69 (s, 2H), 1.14 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 135.9, 135.3, 132.3, 128.9, 128.59, 128.55, 127.5, 125.6, 125.3, 125.0, 120.0, 107.4, 106.6, 77.1, 57.6, 29.6, 27.7; IR (film): 3392, 3061, 3032, 2972, 2930, 2869, 2211, 1676, 1603, 1492, 1476, 1450, 1365, 1261, 1202, 1135, 1072, 1030, 918, 790, 757, 736, 697, 671, 640 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{24}NO$ $[M + H]^+$: 342.1852, found 342.1852.

Synthesis of α-(*N*-Pyrrolyl)ketone 1h. *Synthesis of Precursor 1-Bromo-2,4-diphenylbut-3-yn-2-ol.* Under argon, to a solution of ethynylbenzene (7.14 mL, 65.0 mmol) in THF (100 mL) was added dropwise ethylmagnesium bromide (3.0 M in diethyl ether, 20 mL, 60 mmol) at 0 °C. Then, the resulting mixture was stirred at 0 °C for 1 h. Then, 2-bromo-1-phenylethan-1-one (9.95 g, 50 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for another 0.5 h. After the starting material was consumed, the mixture was quenched with saturated NH_4Cl solution, extracted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 60:1 to 20:1) to afford 1-bromo-2,4-diphenylbut-3-yn-2-ol (13.9 g, 92% yield) as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73−7.70 (m, 2H), 7.51−7.49 (m, 2H), 7.42−7.29 (m, 6H), 3.79 (d, J = 10.4 Hz, 1H), 3.72 (d, J = 10.4 Hz, 1H), 3.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 131.8, 128.8, 128.6, 128.4, 128.2, 125.7, 121.8, 89.0, 86.6, 72.3, 44.9; IR (film): 3541, 3433, 3060, 3030, 2963, 2231, 1954, 1883, 1758, 1680, 1597, 1574, 1489, 1445, 1412, 1335, 1268, 1231, 1167, 1068, 1031, 999, 970, 917, 844, 755, 689, 668, 615 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{13}OBr$ $[M]^+$: 300.0150, found 300.0146.

*Synthesis of 2-(2,4-Dimethyl-1H-pyrrol-1-yl)-1-phenylethan-1-one (**1h**).* Under argon, to a Schlenk tube were added KOH (898 mg, 16 mmol), DMSO (20 mL), and 2,4-dimethyl-1*H*-pyrrole (1.14 g, 12 mmol) sequentially. The resulting mixture was stirred at room temperature for 1 h. Then, 1-bromo-2,4-diphenylbut-3-yn-2-ol (2.41 g, 8 mmol) in DMSO (5 mL) was added in one portion. The reaction mixture was stirred at room temperature for another 3 h. Then, the mixture was quenched with water, extracted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 30:1:3) to afford **1h** (1.11 g, 65% yield) as a white solid. In this reaction, the alkynyl group was eliminated to furnish a ketone functionality. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96−7.94 (m, 2H), 7.63−7.59 (m, 1H), 7.51−7.47 (m, 2H), 6.31 (s, 1H), 5.82 (s, 1H), 5.14 (s, 2H), 2.08 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 134.7, 133.8, 128.9, 128.8, 127.8, 118.8, 118.1, 109.0, 52.7, 11.8, 11.7; IR (film): 3059, 2970, 2925, 2859, 1688, 1596, 1579, 1515, 1448, 1413, 1389, 1359, 1343, 1304, 1225, 1198, 1185, 1157, 1136, 1102, 1077, 1030, 995, 978, 925, 829, 797, 773, 756, 727, 687, 626, 612 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$: 214.1226, found 214.1228.

Synthesis of Indolizines 2. *Typical Procedure for the Synthesis of 1,3,6,8-Tetraphenylindolizine (**2a**).* Under argon, to a Schlenk tube were added PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), α-(*N*-pyrrolyl)-ketone **1a** (0.3 mmol, 101.2 mg), toluene (3 mL), and phenylacetylene (0.36 mmol, 39.5 μL). Then, the Schlenk tube was immersed into an oil bath preheated at 80 °C. After the reaction was complete as monitored by thin-layer chromatography (3 h), the mixture was cooled down. The solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: hexane:ethyl acetate = 100:1), followed by recycling preparative HPLC, to afford indolizine **2a** in 86% yield (108.6 mg) and **3a** in 5% yield (7.7 mg).

*1,3,6,8-Tetraphenylindolizine (**2a**).* Yellow solid. Mp 193−194 °C. ^1H NMR (400 MHz, C_6D_6) δ 8.48 (s, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.6 Hz, 2H), 7.21−6.92 (m, 18H); ^{13}C NMR (100 MHz, C_6D_6) δ 139.3, 138.9, 137.4, 134.7, 132.8, 130.0, 129.4, 129.3, 129.2, 128.8, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.0, 126.7, 125.3, 125.3, 120.6, 119.3, 118.1, 117.8; IR (film): 3055, 3031, 2987, 1955, 1888, 1598, 1500, 1488, 1470, 1448, 1396, 1347, 1314, 1264, 1220, 1172, 1149, 1074, 1027, 949, 896, 829, 734, 696, 656, 606 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{24}N$ $[M + H]^+$: 422.1903, found 422.1899.

*1,3,6,8-Tetraphenyl-2-(1-phenylvinyl)indolizine (**3a**).* Yellow sticky oil. ^1H NMR (400 MHz, C_6D_6) δ 8.39 (d, J = 1.2 Hz, 1H), 7.41 (d, J = 7.2 Hz, 2H), 7.33−7.30 (m, 4H), 7.21−6.86 (m, 17H), 6.80−6.79 (m, 3H), 5.66 (d, J = 1.2 Hz, 1H), 5.23 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 143.0, 142.0, 139.1, 138.9, 136.2, 134.8, 131.9, 131.2, 130.6, 129.6, 129.30, 129.27, 129.1, 128.2, 127.9, 127.6, 127.5, 127.4, 127.2, 127.1, 126.99, 126.96, 125.29, 125.26, 124.7, 120.9, 119.3, 118.7, 117.1; IR (film): 3057, 3028, 2961, 2924, 2854, 1975, 1953, 1888, 1739, 1658, 1600, 1577, 1493, 1470, 1446, 1396, 1312, 1261, 1179, 1075, 1026, 802, 761, 736, 696 cm^{-1}; HRMS (ESI) calcd for $C_{40}H_{30}N$ $[M + H]^+$: 524.2373, found 524.2370.

*8-(4-Fluorophenyl)-1,3,6-triphenylindolizine (**2b**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), 1-ethynyl-4-fluorobenzene (0.36 mmol, 43.2 mg), and 3 mL of toluene were stirred at 80 °C for 10 h. Column chromatography on silica gel (eluent: hexane:ethyl acetate:dichloromethane = 50:1:5), followed by recycling preparative HPLC, afforded the title product in 81% yield (106.4 mg) as a yellow solid. Mp 205−207 °C. ^1H NMR (400 MHz, C_6D_6) δ 8.47 (d, J = 1.2 Hz, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.30 (d, J =

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699

6.8 Hz, 2H), 7.21−6.94 (m, 14H), 6.86 (d, J = 1.2 Hz, 1H), 6.60 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 162.6 (d, $^1J_{C\text{-}F}$ = 246.1 Hz), 138.8, 137.2, 135.2 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 133.6, 132.7, 130.9 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 130.1, 129.4, 129.3, 128.8, 127.8, 127.52, 127.48, 127.0, 126.7, 125.5, 125.3, 120.4, 119.4, 118.0, 117.7, 114.6 (d, $^2J_{C\text{-}F}$ = 21.7 Hz); IR (film): 3054, 3031, 1951, 1879, 1682, 1598, 1536, 1502, 1469, 1447, 1417, 1396, 1347, 1314, 1266, 1220, 1174, 1155, 1095, 1075, 1028, 1014, 969, 949, 912, 867, 855, 831, 798, 758, 741, 696, 659, 645, 631, 612 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{23}FN$ [M + H]$^+$: 440.1809, found 440.1805.

*8-(4-Chlorophenyl)-1,3,6-triphenylindolizine (**2c**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), 1-chloro-4-ethynylbenzene (0.36 mmol, 49.2 mg), and 3 mL of toluene were stirred at 80 °C for 10 h. Column chromatography on silica gel (eluent: hexane: ethyl acetate:dichloromethane = 50:1:5), followed by recycling preparative HPLC, afforded the title product in 82% yield (111.9 mg) as a yellow solid. Mp 210−212 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.46 (d, J = 1.6 Hz, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.29 (d, J = 6.8 Hz, 2H), 7.21−7.07 (m, 6H), 7.01−6.83 (m, 11H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.7, 137.6, 137.0, 133.36, 133.35, 132.6, 130.5, 130.0, 129.5, 129.3, 128.8, 127.9, 127.8, 127.5, 127.3, 127.0, 126.7, 125.6, 125.3, 120.4, 119.5, 118.0, 117.7; IR (film): 3050, 3032, 1679, 1597, 1574, 1487, 1447, 1415, 1348, 1314, 1266, 1252, 1174, 1148, 1089, 1015, 966, 948, 911, 827, 759, 742, 695, 658 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{23}ClN$ [M + H]$^+$: 456.1514, found 456.1511.

*Ethyl 4-(1,3,6-Triphenylindolizin-8-yl)benzoate (**2d**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), ethyl 4-ethynylbenzoate (0.36 mmol, 62.7 mg), and 3 mL of toluene were stirred at 80 °C for 10 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 30:1) afforded the title product in 86% yield (128.0 mg) as a yellow oil, which solidified upon standing. ^{1}H NMR (400 MHz, C_6D_6) δ 8.48 (d, J = 1.6 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.48−7.46 (m, 2H), 7.30−7.28 (m, 2H), 7.23−7.09 (m, 8H), 7.04−7.00 (m, 3H), 6.93−6.88 (m, 4H), 4.11 (q, J = 7.2 Hz, 2H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 166.2, 143.7, 138.6, 137.0, 133.6, 132.6, 129.9, 129.7, 129.5, 129.3, 129.24, 129.17, 128.8, 127.8, 127.6, 127.5, 127.1, 127.0, 126.8, 125.6, 125.2, 120.8, 119.8, 118.1, 117.8, 60.8, 14.3; IR (film): 3056, 3029, 2980, 2929, 2854, 2120, 1952, 1885, 1810, 1710, 1600, 1467, 1446, 1397, 1367, 1309, 1269, 1176, 1101, 1020, 949, 913, 845, 758, 736, 697, 656, 614 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{28}NO_2$ [M + H]$^+$: 494.2115, found 494.2109.

*1,3,6-Triphenyl-8-(p-tolyl)indolizine (**2e**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), 1-ethynyl-4-methylbenzene (0.36 mmol, 41.8 mg), and 3 mL of toluene were stirred at 80 °C for 10 h. Column chromatography on silica gel (eluent: hexane:ethyl acetate = 100:1), followed by recycling preparative HPLC, afforded the title product in 85% yield (110.7 mg) as a yellow solid. Mp 173−174 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.48 (s, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.30 (d, J = 7.2 Hz, 2H), 7.21−6.96 (m, 15H), 6.78 (d, J = 7.6 Hz, 2H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 139.0, 137.5, 136.8, 136.5, 134.8, 132.9, 130.1, 129.4, 129.2, 128.8, 128.5, 127.6, 127.4, 127.0, 126.6, 125.4, 125.1, 120.4, 119.2, 118.1, 117.8, 21.2; IR (film): 3050, 3028, 2920, 2862, 1951, 1887, 1802, 1674, 1598, 1537, 1501, 1485, 1468, 1447, 1416, 1397, 1346, 1314, 1264, 1221, 1174, 1147, 1111, 1073, 1029, 973, 949, 911, 854, 815, 757, 737, 695, 659, 634, 613 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{26}N$ [M + H]$^+$: 436.2060, found 436.2055.

*8-(4-Methoxyphenyl)-1,3,6-triphenylindolizine (**2f**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 4 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 100:1:2 to 50:1:2) afforded **2f** in 91% yield (123.9 mg) and **3f** in 7% yield (13.1 mg). For characterization data of **2f**: yellow solid. Mp 155−156 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.49 (d, J = 1.2 Hz, 1H), 7.50−7.48 (m, 2H), 7.34−7.33 (m, 2H), 7.22−6.95 (m, 15H), 6.58−6.56 (m, 2H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.6, 139.0, 137.5, 134.5, 132.8, 131.7, 130.4, 130.1, 129.4, 129.2, 128.8, 127.9, 127.6, 127.42, 127.36, 127.0, 126.6, 125.4, 125.1, 120.2, 119.0, 118.1, 117.7, 113.4, 54.9; IR (film): 3055, 3029, 2930, 2834, 2540, 2314, 1953, 1885, 1814, 1746, 1600, 1575, 1536, 1504, 1464, 1443, 1418, 1398, 1370, 1343, 1314, 1289, 1264, 1244, 1221, 1175, 1144, 1108, 1095, 1073, 1030, 1001, 973, 949, 912, 865, 830, 782, 758, 736, 696, 659, 645, 631, 613 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{26}NO$ [M + H]$^+$: 452.2009, found 452.2002.

*8-(4-Methoxyphenyl)-2-(1-(4-methoxyphenyl)vinyl)-1,3,6-triphenylindolizine (**3f**).* Yellow solid. Mp 126−127 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.45 (d, J = 1.6 Hz, 1H), 7.50 (d, J = 7.2 Hz, 2H), 7.36 (d, J = 6.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.15−7.07 (m, 10H), 7.02−6.98 (m, 1H), 6.85−6.79 (m, 3H), 6.61 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 5.65 (d, J = 1.2 Hz, 1H), 5.19 (d, J = 1.2 Hz, 1H), 3.30 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.43, 159.37, 142.3, 139.0, 136.5, 134.5, 134.4, 132.0, 131.5, 131.2, 130.6, 130.4, 129.8, 129.3, 129.1, 128.2, 128.0, 127.4, 127.0, 126.9, 125.3, 125.1, 124.5, 120.5, 119.0, 117.1, 116.8, 113.6, 113.3, 54.9, 54.6; IR (film): 3053, 2955, 2836, 2304, 1952, 1888, 1603, 1574, 1506, 1463, 1443, 1397, 1354, 1299, 1264, 1244, 1174, 1109, 1093, 1073, 1031, 987, 973, 895, 833, 804, 783, 759, 733, 698, 627 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{34}NO_2$ [M + H]$^+$: 584.2584, found 584.2577.

*Benzyl (4-(1,3,6-Triphenylindolizin-8-yl)phenyl)carbamate (**2g**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), benzyl (4-ethynylphenyl)carbamate (0.36 mmol, 90.5 mg), and 3 mL of toluene were stirred at 80 °C for 10 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 40:1:20) afforded the title product in 87% yield (149.7 mg) as a yellow solid. Mp 171−172 °C. ^{1}H NMR (600 MHz, C_6D_6, 70 °C) δ 8.47 (s, 1H), 7.50 (d, J = 5.2 Hz, 2H), 7.37 (d, J = 5.2 Hz, 2H), 7.24−7.22 (m, 4H), 7.18−7.06 (m, 13H), 7.00−6.94 (m, 5H), 6.20 (bs, 1H), 5.06 (s, 2H); ^{13}C NMR (150 MHz, C_6D_6, 70 °C) δ 153.4, 139.0, 137.8, 137.5, 137.0, 134.5, 134.4, 133.0, 130.3, 129.9, 129.4, 129.2, 128.9, 128.7, 128.6, 128.4, 127.9, 127.7, 127.5, 127.4, 127.0, 126.7, 125.5, 125.4, 120.4, 119.3, 118.3, 117.8, 67.1; IR (film): 3419, 3054, 3033, 1734, 1599, 1517, 1467, 1447, 1414, 1399, 1343, 1313, 1264, 1207, 1183, 1143, 1051, 1028, 1017, 949, 913, 896, 868, 834, 761, 733, 697, 611 cm^{-1}; HRMS (DART) calcd for $C_{40}H_{31}N_2O_2$ [M + H]$^+$: 571.2380, found 571.2368.

*1,3,6-Triphenyl-8-(3,4,5-trimethoxyphenyl)indolizine (**2h**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), 5-ethynyl-1,2,3-trimethoxybenzene (0.36 mmol, 69.2 mg), and 3 mL of toluene were stirred at 80 °C for 6 h. Column chromatography on silica gel (eluent: hexane:ethyl acetate:dichloromethane = 20:1:4) afforded the title product in 86% yield (131.5 mg) as a light yellow oil, which solidified upon standing. ^{1}H NMR (400 MHz, C_6D_6) δ 8.56 (d, J = 1.2 Hz, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.39 (d, J = 7.2 Hz, 2H), 7.25−7.08 (m, 10H), 6.99 (t, J = 7.2 Hz, 2H), 6.93−6.89 (m, 1H), 6.46 (s, 2H), 3.88 (s, 3H), 3.30 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 153.7, 139.1, 138.9, 137.8, 135.0, 134.5, 132.8, 129.8, 129.5, 129.3, 128.8, 127.8, 127.6, 127.5, 127.4, 127.0, 126.8, 125.43, 125.41, 120.2, 119.3, 118.1, 117.8, 107.5, 60.7, 55.7; IR (film): 3056, 2997, 2937, 2829, 2303, 1960, 1881, 1819, 1599, 1582, 1498, 1464, 1452, 1416, 1398, 1373, 1353, 1322, 1265, 1237, 1209, 1176, 1125, 1073, 1028, 1007, 958, 926, 835, 760, 733, 698, 665, 624, 608 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{30}NO_3$ [M + H]$^+$: 512.2220, found 512.2214.

*1,3,6-Triphenyl-8-(thiophen-2-yl)indolizine (**2i**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), 2-ethynylthiophene (0.36 mmol, 38.9 mg), and 3 mL of toluene were stirred at 80 °C for 10 h. Column chromatography on silica gel (eluent: hexane:ethyl acetate = 50:1), followed by recycling preparative HPLC, afforded the title product in 80% yield (102.2 mg) as a yellow sticky oil. ^{1}H NMR (400 MHz, C_6D_6) δ 8.41 (d, J = 1.2 Hz, 1H), 7.43 (d, J = 7.2 Hz, 2H), 7.28−7.01 (m, 15H), 6.75 (d, J = 4.8 Hz, 1H), 6.65−6.64 (m, 1H), 6.50 (dd, J = 5.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 140.1, 138.5, 137.7, 132.6, 129.5, 129.4, 129.2, 128.8, 128.2, 127.8, 127.6, 127.4, 127.3, 127.2, 127.0, 126.9, 126.8, 125.4, 125.1, 125.0, 121.7, 119.8, 118.4, 118.1; IR (film): 3055, 3028, 2303, 1952, 1886, 1806, 1599, 1497, 1467, 1446, 1399, 1311, 1264, 1223, 1158, 1135, 1073, 1028, 965, 942, 912, 855, 833, 798, 758, 734, 694, 664, 612 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{22}NS$ [M + H]$^+$: 428.1467, found 428.1463.

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699

*8-(Cyclohex-1-en-1-yl)-1,3,6-triphenylindolizine (**2j**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), 1-ethynylcyclohex-1-ene (0.36 mmol, 38.2 mg), and 3 mL of toluene were stirred at 80 °C for 10 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 100:1), followed by recycling preparative HPLC, afforded the title product in 71% yield (90.2 mg) as a yellow sticky oil. ^{1}H NMR (400 MHz, C_6D_6) δ 8.40 (d, J = 1.2 Hz, 1H), 7.55−7.53 (m, 2H), 7.43−7.41 (m, 2H), 7.34−7.32 (m, 2H), 7.26 (t, J = 7.6 Hz, 2H), 7.21−7.04 (m, 7H), 6.97−6.95 (m, 2H), 5.85 (s, 1H), 2.069−2.065 (m, 2H), 1.92−1.91 (m, 2H), 1.41−1.35 (m, 2H), 1.20−1.19 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 139.1, 138.2, 137.3, 137.2, 132.9, 130.8, 129.3, 129.2, 128.8, 127.9, 127.8, 127.6, 127.5, 127.3, 127.0, 126.5, 126.0, 125.3, 119.0, 118.3, 117.8, 117.5, 30.0, 25.8, 22.4, 22.18; IR (film): 3056, 3029, 2931, 2860, 2831, 1951, 1884, 1724, 1640, 1599, 1577, 1515, 1493, 1447, 1399, 1328, 1313, 1264, 1213, 1177, 1158, 1136, 1072, 1028, 958, 937, 913, 836, 791, 759, 734, 697, 633, 614 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{28}N$ $[M + H]^+$: 426.2216, found 426.2201.

*8-Cyclopropyl-1,3,6-triphenylindolizine (**2k**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), ethynylcyclopropane (0.36 mmol, 23.8 mg), and 3 mL of toluene were stirred at 80 °C for 14 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 100:1:4), followed by recycling preparative HPLC, afforded the title product in 54% yield (62.7 mg) as a light yellow sticky oil. ^{1}H NMR (400 MHz, C_6D_6) δ 8.38 (s, 1H), 7.65 (d, J = 6.8 Hz, 2H), 7.44 (d, J = 7.2 Hz, 2H), 7.31−7.23 (m, 4H), 7.19−7.04 (m, 7H), 6.93 (s, 1H), 6.69 (s, 1H), 2.01−1.94 (m, 1H), 0.64−0.54 (m, 2H), 0.50−0.42 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 139.4, 139.1, 135.5, 133.0, 131.4, 130.1, 129.3, 129.2, 128.7, 127.7, 127.5, 127.3, 127.0, 126.4, 126.0, 125.2, 118.5, 117.9, 117.7, 114.7, 15.0, 8.5; IR (film): 3057, 3029, 3007, 2303, 1951, 1884, 1812, 1643, 1599, 1554, 1536, 1515, 1497, 1469, 1446, 1401, 1322, 1264, 1211, 1189, 1156, 1092, 1072, 1046, 1026, 956, 923, 828, 758, 735, 696, 667, 656, 613 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{24}N$ $[M + H]^+$: 386.1903, found 386.1895.

*Ethyl 1,3,6-Triphenylindolizine-7-carboxylate (**2l**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), ethyl propiolate (0.36 mmol, 35.3 mg), and 3 mL of toluene were stirred at 80 °C for 15 h. Column chromatography on silica gel (eluent: hexane:ethyl acetate = 20:1) afforded the title product in 44% yield (54.9 mg) as a yellow solid. Mp 156−157 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.76 (s, 1H), 8.05 (s, 1H), 7.68 (d, J = 7.6 Hz, 2H), 7.34−7.26 (m, 6H), 7.16−7.02 (m, 8H), 3.95 (q, J = 6.8 Hz, 2H), 0.75 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 166.8, 139.8, 135.8, 131.9, 129.37, 129.35, 129.2, 128.8, 128.4, 128.3, 128.2, 128.0, 127.2, 126.6, 126.0, 123.4, 122.3, 122.0, 120.6, 116.0, 60.6, 13.9; IR (film): 3057, 3027, 2979, 2927, 2902, 2870, 2853, 1950, 1887, 1808, 1702, 1617, 1599, 1574, 1546, 1501, 1472, 1454, 1428, 1403, 1379, 1364, 1331, 1285, 1270, 1230, 1204, 1155, 1109, 1076, 1021, 978, 965, 903, 835, 757, 736, 697, 665, 639, 616 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{24}NO_2$ $[M + H]^+$: 418.1802, found 418.1801.

*Ethyl 1,3,6,8-Tetraphenylindolizine-7-carboxylate (**2m**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), ethyl 3-phenylpropiolate (0.36 mmol, 62.7 mg), and 3 mL of toluene were stirred at 80 °C for 15 h. Column chromatography on silica gel (eluent: hexane:ethyl acetate:dichloromethane = 60:1:3) afforded the title product in 77% yield (114.1 mg) as a sticky yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 8.24 (s, 1H), 7.47−7.41 (m, 4H), 7.30−7.29 (m, 2H), 7.16−6.84 (m, 15H), 3.68 (q, J = 7.2 Hz, 2H), 0.54 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 167.9, 138.6, 137.0, 136.4, 132.4, 132.2, 130.3, 130.0, 129.4, 129.2, 128.69, 128.66, 127.9, 127.7, 127.7, 127.5, 127.4, 127.1, 126.6, 125.8, 125.3, 124.5, 121.1, 120.7, 118.7, 60.7, 13.6; IR (film): 3056, 3029, 2989, 2280, 1953, 1884, 1721, 1677, 1601, 1514, 1495, 1484, 1463, 1449, 1421, 1396, 1371, 1312, 1265, 1251, 1213, 1174, 1121, 1073, 1019, 974, 913, 893, 839, 812, 759, 734, 697, 654, 632, 608 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{28}NO_2$ $[M + H]^+$: 494.2115, found 494.2111.

*Ethyl 8-Methyl-1,3,6-triphenylindolizine-7-carboxylate (**2n**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), ethyl but-2-ynoate (0.36 mmol, 40.4 mg), and 3 mL of toluene were stirred at 80 °C for 24 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 50:1) afforded the title product in 63% yield (81.8 mg) as a sticky yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 8.09 (s, 1H), 7.44−7.42 (m, 2H), 7.39−7.37 (m, 4H), 7.24−7.20 (m, 2H), 7.18−7.04 (m, 7H), 6.85 (s, 1H), 3.88 (q, J = 6.8 Hz, 2H), 2.40 (s, 3H), 0.68 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 168.6, 139.4, 138.3, 132.3, 131.2, 129.3, 129.1, 128.7, 128.7, 128.6, 128.4, 127.9, 127.7, 127.4, 126.8, 126.4, 124.64, 124.55, 120.5, 120.0, 118.4, 60.7, 17.9, 13.8; IR (film): 3057, 3030, 2979, 1952, 1884, 1714, 1600, 1515, 1497, 1484, 1444, 1420, 1370, 1327, 1246, 1206, 1166, 1132, 1062, 1042, 1023, 1001, 964, 916, 834, 793, 759, 698, 665 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}NO_2$ $[M + H]^+$: 432.1958, found 432.1958.

*1-(1,3,6,8-Tetraphenylindolizin-7-yl)pentan-1-one (**2o**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), 1-phenylhept-1-yn-3-one (0.36 mmol, 67.1 mg), and 3 mL of toluene were stirred at 80 °C for 16 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 200:1) afforded the title product in 85% yield (128.6 mg) as a yellow solid. Mp 162−163 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.26 (s, 1H), 7.47−7.41 (m, 4H), 7.25−7.21 (m, 2H), 7.17−6.99 (m, 9H), 6.92−6.80 (m, 6H), 2.04 (t, J = 7.2 Hz, 2H), 1.20−1.12 (m, 2H), 0.79−0.70 (m, 2H), 0.50 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 205.8, 138.1, 137.1, 135.7, 134.0, 132.3, 131.1, 130.1, 129.9, 130.0, 129.5, 128.8, 128.7, 127.8, 127.6, 127.4, 127.1, 126.4, 125.2, 123.9, 121.4, 120.3, 118.7, 45.3, 25.5, 21.9, 13.8; IR (film): 3058, 3027, 2957, 2930, 2871, 1952, 1886, 1809, 1695, 1600, 1515, 1494, 1448, 1416, 1366, 1312, 1265, 1173, 1113, 1073, 1027, 973, 912, 837, 758, 736, 697, 673, 608 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{32}NO$ $[M + H]^+$: 506.2478, found 506.2478.

*8-Ethoxy-1,3,6-triphenylindolizine (**2p**).* Catalyst **A** (0.015 mmol, 11.6 mg), **1a** (0.3 mmol, 101.2 mg), ethoxyethyne (45% w/w in hexane, 0.6 mmol, 93.5 mg), and 3 mL of toluene were stirred at 80 °C for 3 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 100:1:5) afforded the title product in 40% yield (46.3 mg) as a light yellow solid. Mp 146−147 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.16 (d, J = 1.2 Hz, 1H), 7.81 (d, J = 6.8 Hz, 2H), 7.43 (d, J = 7.2 Hz, 2H), 7.39−7.33 (m, 4H), 7.25−7.05 (m, 7H), 6.93 (s, 1H), 6.16 (s, 1H), 3.58 (q, J = 6.8 Hz, 2H), 0.99 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 152.8, 139.7, 137.7, 132.9, 131.2, 129.3, 129.2, 128.8, 127.54, 127.53, 127.43, 127.39, 127.1, 125.8, 125.5, 123.1, 118.0, 116.5, 114.1, 96.4, 63.7, 14.3; IR (film): 3054, 3029, 2979, 2928, 2876, 1952, 1886, 1813, 1750, 1669, 1599, 1553, 1532, 1499, 1474, 1447, 1419, 1395, 1373, 1326, 1280, 1265, 1235, 1213, 1178, 1156, 1131, 1113, 1085, 1020, 962, 935, 912, 874, 816, 756, 737, 696, 677, 632, 613 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{24}NO$ $[M + H]^+$: 390.1852, found 390.1848.

*N-Methyl-N-(1,3,6,7-tetraphenylindolizin-8-yl)methanesulfonamide (**2q**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1a** (0.3 mmol, 101.2 mg), *N*-methyl-*N*-(phenylethynyl)methanesulfonamide (0.36 mmol, 75.3 mg), and 3 mL of toluene were stirred at 80 °C for 36 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 10:1 to 5:1) afforded the title product in 41% yield (64.9 mg) as a sticky yellow oil. ^{1}H NMR (600 MHz, C_6D_6, 70 °C) δ 8.24 (s, 1H), 7.68−7.67 (m, 2H), 7.40−7.38 (m, 2H), 7.30 (t, J = 5.2 Hz, 2H), 7.19−7.12 (m, 5H), 7.06−7.03 (m, 1H), 7.01−6.98 (m, 2H), 6.93−6.85 (m, 7H), 2.66 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6, 70 °C) δ 138.7, 138.0, 137.8, 134.5, 132.4, 131.7, 131.6, 130.4, 129.3, 128.8, 128.44, 128.35 (br), 128.2, 128.0, 127.8, 127.5, 127.2, 126.9, 126.8, 126.6, 122.3, 119.2, 118.1, 39.4, 37.8; IR (film): 3056, 3029, 2932, 2292, 1955, 1889, 1812, 1600, 1516, 1480, 1443, 1420, 1396, 1335, 1265, 1216, 1196, 1149, 1097, 1072, 1031, 1012, 999, 962, 938, 918, 835, 793, 760, 733, 699, 679, 663, 635, 624 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{29}N_2O_2S$ $[M + H]^+$: 529.1944, found 529.1944.

*6-Ethyl-8-(4-methoxyphenyl)-1,3-diphenylindolizine (**2r**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1b** (0.3 mmol, 86.8 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 8 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 100:1:10) afforded the title product in 81% yield (98.0 mg) as a yellow

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699

solid. Mp 161−162 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.05 (s, 1H), 7.54−7.52 (m, 2H), 7.24 (t, J = 7.2 Hz, 2H), 7.15−7.10 (m, 5H), 7.03 (s, 1H), 7.01−6.91 (m, 3H), 6.57−6.53 (m, 3H), 3.28 (s, 3H), 2.23 (q, J = 7.6 Hz, 2H), 1.02 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.5, 137.9, 134.3, 133.3, 131.9, 130.3, 130.1, 129.3, 128.9, 127.9, 127.5, 127.4, 126.5, 125.8, 124.9, 121.6, 118.3, 117.9, 116.9, 113.4, 54.9, 26.3, 15.3; IR (film): 3055, 3028, 2962, 2930, 2872, 2834, 2027, 1954, 1885, 1817, 1728, 1600, 1575, 1539, 1504, 1486, 1464, 1417, 1343, 1325, 1304, 1289, 1244, 1175, 1108, 1071, 1031, 951, 910, 826, 784, 759, 741, 697, 655, 640, 609 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{26}NO$ [M + H]$^+$: 404.2009, found 404.2003.

*6-Cyclopropyl-8-(4-methoxyphenyl)-1,3-diphenylindolizine (**2s**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1c** (0.3 mmol, 90.4 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 9 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 100:1) afforded the title product in 82% yield (102.6 mg) as a yellow solid. Mp 145−146 °C.^{1}H NMR (400 MHz, C_6D_6) δ 8.13 (s, 1H), 7.51 (d, J = 7.2 Hz, 2H), 7.22 (t, J = 7.2 Hz, 2H), 7.13−7.07 (m, 5H), 7.01−6.91 (m, 4H), 6.55−6.51 (m, 2H), 6.45 (s, 1H), 3.28 (s, 3H), 1.52−1.45 (m, 1H), 0.60−0.47 (m, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.5, 137.8, 134.2, 133.2, 131.8, 130.3, 130.1, 129.3, 128.8, 128.0, 127.5, 127.4, 126.2, 125.7, 124.9, 119.4, 118.4, 117.9, 117.0, 113.4, 54.9, 13.4, 7.0; IR (film): 3052, 3004, 1940, 1886, 1600, 1573, 1538, 1515, 1503, 1484, 1463, 1440, 1416, 1376, 1341, 1288, 1266, 1242, 1211, 1175, 1143, 1108, 1092, 1071, 1027, 992, 958, 911, 864, 830, 765, 736, 697, 656, 641, 629, 616, 608 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}NO$ [M + H]$^+$: 416.2009, found 416.1997.

*(E)-8-(4-Methoxyphenyl)-1,3-diphenyl-6-(prop-1-en-1-yl)indolizine (**2t**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1d** (0.3 mmol, 90.4 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 3 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 200:1:4) afforded the title product in 81% yield (100.4 mg) as a yellow solid. Mp 189−191 °C.^{1}H NMR (400 MHz, C_6D_6) δ 8.06 (s, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.23 (t, J = 7.6 Hz, 2H), 7.16−7.10 (m, 5H), 7.00−6.92 (m, 5H), 6.55 (d, J = 8.4 Hz, 2H), 5.97−5.85 (m, 2H), 3.28 (s, 3H), 1.65 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.6, 137.6, 134.3, 133.0, 131.8, 130.4, 130.1, 129.3, 129.0, 128.3, 127.9, 127.6, 127.4, 126.5, 125.1, 124.2, 122.5, 119.7, 118.6, 117.4, 117.3, 113.4, 54.9, 18.5; IR (film): 3054, 3026, 2957, 2930, 2835, 1949, 1889, 1801, 1602, 1505, 1443, 1404, 1343, 1324, 1290, 1245, 1176, 1108, 1031, 959, 828, 785, 763, 740, 698, 674 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}NO$ [M + H]$^+$: 416.2009, found 416.2002.

*6-(3,3-Dimethylbut-1-yn-1-yl)-8-(4-methoxyphenyl)-1,3-diphenylindolizine (**2u**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1e** (0.3 mmol, 102.4 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 4 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 100:1) afforded the title product in 88% yield (120.2 mg) as a yellow solid. Mp 169−171 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.53 (s, 1H), 7.36 (d, J = 7.2 Hz, 2H), 7.16−6.91 (m, 12H), 6.48 (d, J = 8.8 Hz, 2H), 3.27 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.5, 137.2, 134.1, 132.3, 131.0, 130.3, 130.1, 129.4, 128.8, 127.7, 127.4, 127.3, 126.5, 125.2, 124.4, 122.5, 118.8, 117.8, 113.3, 108.4, 98.6, 77.5, 54.9, 31.2, 28.3; IR (film): 3058, 3034, 2965, 1889, 1730, 1682, 1606, 1502, 1464, 1402, 1363, 1336, 1308, 1288, 1250, 1177, 1111, 1032, 961, 866, 827, 760, 738, 697, 666 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{30}NO$ [M + H]$^+$: 456.2322, found 456.2321.

*3-Butyl-8-(4-methoxyphenyl)-1,6-diphenylindolizine (**2v**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1f** (0.3 mmol, 95.2 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 6 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 200:1) afforded the title product in 78% yield (101.3 mg) as a sticky yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 7.76 (s, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.25 (t, J = 7.2 Hz, 2H), 7.18−7.12 (m, 5H), 7.02−6.93 (m, 4H), 6.78 (s, 1H), 6.56 (d, J = 8.4 Hz, 2H), 3.29 (s, 3H), 2.56 (t, J = 7.6 Hz, 2H), 1.67−1.59 (m, 2H), 1.35−1.30 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.5, 139.4, 138.0, 134.4, 132.0, 130.4, 130.2, 129.2, 127.4, 127.2, 126.5, 125.4, 124.9, 124.8, 118.8, 118.4, 116.6, 115.3, 113.4, 54.9, 29.5, 26.0, 23.0, 14.2; IR (film): 3057, 3031, 2956, 2930, 2871, 2835, 1950, 1885, 1738, 1715, 1640, 1607, 1575, 1505, 1462, 1444, 1422, 1396, 1375, 1341, 1316, 1290, 1245, 1205, 1175, 1121, 1107, 1071, 1030, 949, 910, 829, 809, 759, 734, 696, 660, 630 cm^{-1}; HRMS (DART) calcd for $C_{31}H_{30}NO$ [M + H]$^+$: 432.2322, found 432.2315.

*3-Cyclopropyl-8-(4-methoxyphenyl)-1,6-diphenylindolizine (**2w**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1g** (0.3 mmol, 90.4 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 12 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 50:1) afforded the title product in 86% yield (106.9 mg) as a light yellow solid. Mp 128−129 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 8.18 (d, J = 1.2 Hz, 1H), 7.56 (d, J = 7.6 Hz, 2H), 7.27 (t, J = 7.6 Hz, 2H), 7.19−7.09 (m, 5H), 7.03−6.92 (m, 4H), 6.73 (s, 1H), 6.55 (d, J = 8.8 Hz, 2H), 3.29 (s, 3H), 1.55−1.51 (m, 1H), 0.66−0.61 (m, 2H), 0.54−0.51 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.5, 139.5, 137.9, 134.3, 131.9, 130.4, 130.2, 129.3, 127.40, 127.37, 127.2, 127.1, 126.7, 124.9, 124.8, 119.5, 119.1, 116.2, 115.2, 113.4, 54.9, 6.8, 5.7; IR (film): 3053, 3004, 2836, 2339, 2307, 1950, 1883, 1600, 1504, 1444, 1407, 1372, 1317, 1290, 1264, 1244, 1175, 1127, 1108, 1071, 1030, 949, 894, 862, 831, 763, 734, 697, 660, 632, 610 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}NO$ [M + H]$^+$: 416.2009, found 416.1999.

*8-(4-Methoxyphenyl)-1,3-dimethyl-6-phenylindolizine (**2x**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1h** (0.3 mmol, 64.0 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 2 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 100:1 to 50:1) afforded indolizine **2x** in 55% yield (53.8 mg) and **3x** in 13% yield (17.5 mg). For characterization data of **2x**: sticky yellow oil. ^{1}H NMR (400 MHz, C_6D_6) δ 7.55 (d, J = 1.6 Hz, 1H), 7.48−7.46 (m, 2H), 7.37−7.35 (m, 2H), 7.25−7.22 (m, 2H), 7.17−7.13 (m, 1H), 6.86−6.83 (m, 2H), 6.80 (d, J = 1.6 Hz, 1H), 6.41 (s, 1H), 3.34 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.7, 139.6, 134.5, 132.9, 130.9, 129.1, 127.6, 127.12, 127.07, 124.0, 119.4, 118.4, 117.0, 116.7, 113.6, 109.2, 54.8, 14.2, 11.5; IR (film): 3055, 3034, 2930, 2836, 2057, 1891, 1693, 1627, 1609, 1576, 1538, 1507, 1446, 1418, 1369, 1346, 1314, 1288, 1244, 1175, 1106, 1029, 907, 832, 791, 761, 734, 697, 629 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{21}NO$ [M]$^+$: 327.1623, found 327.1624.

*8-(4-Methoxyphenyl)-2-(1-(4-methoxyphenyl)vinyl)-1,3-dimethyl-6-phenylindolizine (**3x**).* Yellow sticky oil. ^{1}H NMR (400 MHz, C_6D_6) δ 7.68 (d, J = 1.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 2H), 7.43−7.37 (m, 4H), 7.26 (t, J = 7.2 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 6.88 (d, J = 0.8 Hz, 1H), 6.85−6.82 (m, 2H), 6.79−6.76 (m, 2H), 5.88 (d, J = 2.0 Hz, 1H), 5.20 (d, J = 1.6 Hz, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 2.18 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.9, 159.7, 143.0, 139.5, 134.6, 134.4, 132.9, 130.9, 129.7, 129.2, 128.3, 127.4, 127.2, 127.0, 124.1, 118.5, 118.4, 117.5, 114.7, 114.1, 113.6, 108.6, 54.9, 54.8, 12.7, 10.4; IR (film): 3034, 2999, 2927, 2836, 2056, 1891, 1716, 1687, 1606, 1574, 1507, 1442, 1405, 1354, 1290, 1244, 1175, 1108, 1030, 899, 833, 792, 761, 735, 698, 654 cm^{-1}; HRMS (EI) calcd for $C_{32}H_{29}NO_2$ [M]$^+$: 459.2198, found 459.2203.

*8-(4-Methoxyphenyl)-2,3,6-triphenylindolizine (**2y**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1i** (0.3 mmol, 101.2 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 22 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 40:1:80) afforded the title product in 51% yield (68.8 mg) as a yellow solid. Mp 245−247 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.52−7.38 (m, 9H), 7.33−7.29 (m, 3H), 7.24−7.16 (m, 3H), 7.05 (d, J = 8.4 Hz, 2H), 6.98 (s, 1H), 6.86 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 138.7, 135.9, 132.4, 131.8, 131.43, 131.35, 131.0, 129.5, 129.2, 128.84, 128.76, 128.6, 128.2, 128.0, 127.2, 126.7, 126.1, 125.2, 122.7, 118.5, 117.6, 114.1, 100.0, 55.4; IR (neat): 3033, 2936, 2844, 2377, 2349, 2323, 1602, 1573, 1501, 1487, 1469, 1441, 1420, 1392, 1338, 1324, 1309, 1291, 1240, 1203, 1178, 1154, 1136, 1111, 1071, 1026, 918, 839, 830, 793, 768, 760, 728,

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699

701, 670, 665, 652, 641, 627, 607 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{26}NO$ $[M + H]^+$: 452.2009, found 452.2009.

*8-(4-Methoxyphenyl)-3,6-diphenylindolizine (**2z**).* PPh_3AuNTf_2 (0.015 mmol, 11.1 mg), **1j** (0.3 mmol, 78.4 mg), 1-ethynyl-4-methoxybenzene (0.36 mmol, 47.6 mg), and 3 mL of toluene were stirred at 80 °C for 4 h. Column chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 100:1 to 50:1) afforded the title product in 53% yield (59.7 mg) as a yellow solid. Mp 136−137 °C. ^1H NMR (400 MHz, C_6D_6) δ 8.43 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.32−7.30 (m, 2H), 7.21−7.06 (m, 6H), 6.99 (d, J = 0.8 Hz, 1H), 6.94−6.87 (m, 4H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 160.2, 139.3, 133.7, 133.3, 133.1, 132.1, 130.0, 129.4, 129.2, 128.6, 127.4, 127.3, 127.10, 127.08, 125.8, 118.9, 117.5, 115.5, 114.5, 101.2, 54.9; IR (film): 3056, 3031, 2957, 2931, 2835, 2280, 1953, 1893, 1717, 1601, 1574, 1529, 1502, 1466, 1445, 1415, 1390, 1353, 1338, 1306, 1289, 1264, 1245, 1177, 1109, 1075, 1029, 966, 906, 863, 832, 812, 799, 774, 757, 735, 698, 662, 650, 628, 609 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{22}NO$ $[M + H]^+$: 376.1696, found 376.1695.

Synthesis of Intermediates 4 and 5. To a Schlenk tube were added PPh_3AuNTf_2 (73.9 mg, 0.1 mmol), **1a** (675 mg, 2.00 mmol), toluene (20 mL), and ethyl 3-phenylpropiolate (418 mg, 2.40 mmol) under argon. The resulting solution was stirred at room temperature for 37 h. Then, the solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate:dichloromethane = 60:1:3 to 30:1:3) to afford **2m** in 9% yield (84.7 mg), **4** as a yellow solid in 74% yield (761 mg), and **5** as a light yellow solid in 11% yield (110.5 mg), respectively. The structures of **4** and **5** were confirmed by X-ray crystallographic analysis.

*Ethyl (Z)-3-(1-(2-Oxo-2-phenylethyl)-3,5-diphenyl-1H-pyrrol-2-yl)-3-phenyl Acrylate (**4**).* Mp 126−127 °C. ^1H NMR (400 MHz, C_6D_6) δ 7.64 (d, J = 7.2 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H), 7.45−7.43 (m, 2H), 7.39 (d, J = 7.6 Hz, 2H), 7.12−7.05 (m, 4H), 7.01−6.95 (m, 3H), 6.93−6.81 (m, 6H), 6.53 (s, 1H), 5.32−5.11 (m, 2H), 4.06−3.94 (m, 2H), 0.96 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 193.6, 165.6, 147.2, 139.1, 137.6, 136.7, 135.3, 133.9, 133.2, 129.8, 129.6, 128.83, 128.81, 128.62, 128.61, 128.5, 127.8, 127.7, 127.7, 126.2, 125.9, 122.5, 110.0, 60.3, 51.9, 14.3; IR (film): 3058, 3030, 2980, 2929, 2854, 1960, 1890, 1814, 1701, 1601, 1576, 1521, 1489, 1470, 1449, 1424, 1392, 1364, 1346, 1264, 1223, 1157, 1096, 1074, 1028, 1000, 918, 876, 845, 804, 754, 736, 696 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{30}NO_3$ $[M + H]^+$: 512.2220, found 512.2222.

*Ethyl (Z)-3-(1-(2-Oxo-2-phenylethyl)-2,4-diphenyl-1H-pyrrol-3-yl)-3-phenyl Acrylate (**5**).* Mp 122−123 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.60−7.56 (m, 1H), 7.46−7.38 (m, 4H), 7.34 (d, J = 7.2 Hz, 2H), 7.19−7.04 (m, 11H), 6.96 (s, 1H), 6.25 (s, 1H), 5.28−5.19 (m, 2H), 3.90 (q, J = 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 166.0, 150.3, 141.0, 135.4, 134.7, 133.8, 133.3, 131.4, 130.1, 128.8, 128.8, 128.0, 128.0, 127.93, 127.89, 127.8, 127.6, 127.2, 125.4, 125.2, 120.5, 119.5, 118.9, 59.6, 53.6, 14.0; IR (film): 3059, 3028, 2978, 2937, 1963, 1810, 1699, 1601, 1575, 1554, 1531, 1486, 1446, 1401, 1350, 1266, 1214, 1173, 1073, 1024, 983, 906, 867, 839, 790, 766, 747, 696, 686, 662, 651, 638, 625, 612 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{30}NO_3$ $[M + H]^+$: 512.2220, found 512.2223.

Control Experiments: Reaction of 4 in the Presence of Gold Catalyst. To a Schlenk tube were added PPh_3AuNTf_2 (11.1 mg, 0.015 mmol), **4** (153.5 mg, 0.3 mmol), and toluene (3 mL) under argon. The resulting solution was stirred at 80 °C for 20 h. Then, the solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:dichloromethane = 60:1:3) to afford **2m** in 95% yield (140.0 mg).

Control Experiments: Reaction of 4 in the Absence of Gold Catalyst. To a Schlenk tube were added **4** (153.5 mg, 0.3 mmol) and toluene (3 mL) under argon. The resulting solution was stirred at 80 °C for 20 h. Then, the solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:dichloromethane = 30:1:3) to recover **4** in 96% yield (147.5 mg).

Gram-Scale Synthesis of Indolizine 2f. Under argon, to a Schlenk tube were added PPh_3AuNTf_2 (0.10 mmol, 73.9 mg), α-(*N*-pyrrolyl)ketone **1a** (5.0 mmol, 1.687 g), toluene (50 mL), and 1-ethynyl-4-methoxybenzene (6.0 mmol, 793 mg). The Schlenk tube was immersed into an oil bath preheated at 80 °C. After the reaction was complete as monitored by thin-layer chromatography (12 h), the mixture was cooled down. Then, the solvent was evaporated under the reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum ether:dichloromethane = 5:2) to afford indolizine **2f** in 90% yield (2.026 g).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00346.

Spectroscopic characterization of all new compounds, X-ray crystallography and the crystal data of compounds **2f**, **3f**, **4**, and **5** (PDF)

Crystallographic data for **2f** (CIF)

Crystallographic data for **3f** (CIF)

Crystallographic data for **4** (CIF)

Crystallographic data for **5** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yhliu@sioc.ac.cn. Fax: (+86) 021-64166128.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Grant Nos. 21125210, 21421091, 21372244) for financial support.

■ REFERENCES

(1) For a review, see: (a) Sharma, V.; Kumar, V. *Med. Chem. Res.* **2014**, *23*, 3593. For selected papers, see: (b) Gundersen, L.-L.; Charnock, C.; Negussie, A. H.; Rise, F.; Teklu, S. *Eur. J. Pharm. Sci.* **2007**, *30*, 26. (c) Huang, W.; Zuo, T.; Jin, H.; Liu, Z.; Yang, Z.; Yu, X.; Zhang, L.; Zhang, L. *Mol. Diversity* **2013**, *17*, 221. (d) Dawood, K. M.; Abdel-Gawad, H.; Ellithey, M.; Mohamed, H. A.; Hegazi, B. *Arch. Pharm.* **2006**, *339*, 133. (e) Harrell, W. B. *J. Pharm. Sci.* **1970**, *59*, 275.

(2) (a) Wan, J.; Zheng, C.-J.; Fung, M.-K.; Liu, X.-K.; Lee, C.-S.; Zhang, X.-H. *J. Mater. Chem.* **2012**, *22*, 4502. (b) Sonnenschein, H.; Hennrich, G.; Resch-Genger, U.; Schulz, B. *Dyes Pigm.* **2000**, *46*, 23. (c) Weidner, C. H.; Wadsworth, D. H.; Bender, S. L.; Beltman, D. J. *J. Org. Chem.* **1989**, *54*, 3660.

(3) (a) Scholtz, M. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 734. (b) Boekelheide, V.; Windgassen, R. J. *J. Am. Chem. Soc.* **1959**, *81*, 1456.

(4) (a) Tschitschibabin, A. E. *Ber. Dtsch. Chem. Ges. B* **1927**, *60*, 1607. (b) Hurst, J.; Melton, T.; Wibberley, D. G. *J. Chem. Soc.* **1965**, 2948.

(5) (a) Wu, K.; Chen, Q.-Y. *Synthesis* **2003**, 0035. (b) Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2015**, *17*, 2800.

(6) (a) Sasaki, T.; Kanematsu, K.; Kakehi, A.; Ito, G. *Tetrahedron* **1972**, *28*, 4947. (b) Pohjala, E. *Tetrahedron Lett.* **1972**, *13*, 2585.

(7) For selected papers, see: (a) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (b) Liu, Y.; Song, Z.; Yan, B. *Org. Lett.* **2007**, *9*, 409. (c) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (d) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783. (e) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (f) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547.

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699

(g) Chernyak, D.; Gadamsetty, S. B.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 2307. (h) Zhang, L.; Li, X.; Liu, Y.; Zhang, D. *Chem. Commun.* **2015**, *51*, 6633. (i) Xu, T.; Alper, H. *Org. Lett.* **2015**, *17*, 4526.
(8) (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (b) Helan, V.; Gulevich, A. V.; Gevorgyan, V. *Chem. Sci.* **2015**, *6*, 1928.
(9) Liu, R.; Hong, J.; Lu, C.; Xu, M.; Gao, J.; Jia, Y. *Org. Lett.* **2015**, *17*, 3050.
(10) For other methods, see: (a) Shen, Y.; Zhang, Y.; Jiang, G.-F. *Synthesis* **2002**, *2002*, 714. (b) Kaloko, J., Jr.; Hayford, A. *Org. Lett.* **2005**, *7*, 4305. (c) Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 8976. (d) Barluenga, J.; Lonzi, G.; Riesgo, L.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2010**, *132*, 13200. (e) Zhu, H.; Stöckigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011**, *13*, 2792. (f) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 15545.
(11) For indolizine synthesis by construction of the pyridine ring, see: (a) Zhu, H.; Stöckigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011**, *13*, 2792. (b) Lee, J. H.; Kim, I. *J. Org. Chem.* **2013**, *78*, 1283. (c) Kucukdisli, M.; Opatz, T. *J. Org. Chem.* **2013**, *78*, 6670. (d) Kim, M.; Jung, Y.; Kim, I. *J. Org. Chem.* **2013**, *78*, 10395. (e) Hao, W.; Wang, H.; Ye, Q.; Zhang, W.; Xi, Z. *Org. Lett.* **2015**, *17*, 5674.
(12) For reviews, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028.
(13) For a review, see: Shen, H. C. *Tetrahedron* **2008**, *64*, 3885.
(14) Li, X.; Chen, M.; Xie, X.; Sun, N.; Li, S.; Liu, Y. *Org. Lett.* **2015**, *17*, 2984.
(15) (a) Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 1517. (b) Gruit, M.; Michalik, D.; Krüger, K.; Spannenberg, A.; Tillack, A.; Pews-Davtyan, A.; Beller, M. *Tetrahedron* **2010**, *66*, 3341. (c) Borsini, E.; Broggini, G.; Fasana, A.; Baldassarri, C.; Manzo, A. M.; Perboni, A. D. *Beilstein J. Org. Chem.* **2011**, *7*, 1468. (d) Sarkar, S.; Bera, K.; Jalal, S.; Jana, U. *Eur. J. Org. Chem.* **2013**, *2013*, 6055. (e) Pan, B.; Lu, X.; Wang, C.; Hu, Y.; Wu, F.; Wan, B. *Org. Lett.* **2014**, *16*, 2244. (f) Hack, D.; Loh, C. C. J.; Hartmann, J. M.; Raabe, G.; Enders, D. *Chem.—Eur. J.* **2014**, *20*, 3917. (g) Boiaryna, L.; Azizi, M. S.; El Bouakher, A.; Picard, B.; Taillier, C.; Othman, M.; Trabelsi-Ayadi, M.; Dalla, V. *Org. Lett.* **2015**, *17*, 2130. (h) Li, Z.; Kumar, A.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. *Tetrahedron* **2015**, *71*, 3333.
(16) (a) Matsuda, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem.—Eur. J.* **2015**, *21*, 1463. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358. (c) Luo, C.; Yang, H.; Mao, R.; Lu, C.; Cheng, G. *New J. Chem.* **2015**, *39*, 3417.
(17) For gold-catalyzed intermolecular hydroarylation of alkynes with other arenes or heteroarenes, see: (a) Reetz, M.; Sommer, K. *Eur. J. Org. Chem.* **2003**, *2003*, 3485. (b) Hashmi, A. S. K.; Blanco, M. C.; Kurpejović, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709. (c) Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem.* **2006**, *2006*, 4340. (d) Reference 16b.
(18) (a) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Eur. J. Org. Chem.* **2007**, *2007*, 1648. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528.
(19) For Pt-catalyzed regioselective hydroarylation of alkynyl esters with pyrroles, see: Oyamada, J.; Kitamura, T. *Tetrahedron* **2009**, *65*, 3842.
(20) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636.
(21) The X-ray crystallography of **2f**, **3f**, **4**, and **5** is shown in the Supporting Information.
(22) Braunstein, P.; Lehner, H.; Matt, D. *Inorg. Synth.* **1990**, *27*, 218.
(23) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.
(24) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926.
(25) Yu, S.; Xiong, M.; Xie, X.; Liu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11596.
(26) Wen, J.; Zhang, R.; Chen, S.; Zhang, J.; Yu, X. *J. Org. Chem.* **2012**, *77*, 766.
(27) Ueda, H.; Yamaguchi, M.; Kameya, H.; Sugimoto, K.; Tokuyama, H. *Org. Lett.* **2014**, *16*, 4948.

DOI: 10.1021/acs.joc.6b00346
J. Org. Chem. 2016, 81, 3688−3699