JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Transition-Metal-Free Alkynylation of 2-Oxindoles through Radical−Radical Coupling

Hong-Yan Huang,[†,‡] Liang Cheng,[*,†,‡] Jie-Jie Liu,[†,‡] Dong Wang,[†] Li Liu,[*,†,‡] and Chao-Jun Li[*,§]

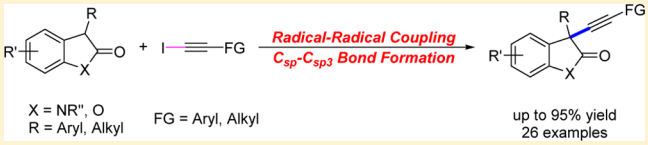
[†]Beijing National Laboratory for Molecular Sciences (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

[§]Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 0B8, Canada

Supporting Information

ABSTRACT: An effective transition-metal-free approach for the synthesis of 3-alkynyl-2-oxindoles through a radical−radical coupling process was developed. The reaction was general with respect to 2-oxindoles and iodoalkynes and provided the desired products bearing a quaternary center at C3 in good to excellent yields, making this method synthetically viable and attractive for the synthesis of spiro and fused 2-oxindole derivatives.

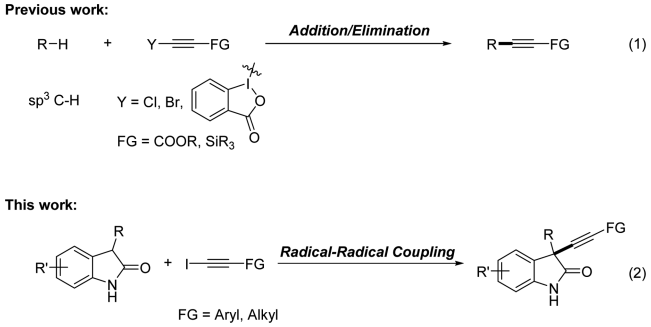


INTRODUCTION

The potential of C-alkynylation reactions in organic chemistry has been extensively exploited over the past decade, among which alkynylation of aromatic (sp^2) systems through nucleophilic or electrophilic C−H functionalization has been evaluated, and several methods offer solutions for the construction of new sp-sp^2 carbon−carbon bonds.[1] On the other hand, alkynyl-substituted alkyl groups are of particular importance for the pharmaceutical and pigment industries, as well as for materials science.[2] Therefore, the development of new synthetic methods for the installation of alkynyl groups onto an sp^3 C−H carbon is an emerging area of synthetic organic chemistry.[3] In contrast to the vast array of methods available for nucleophilic[3a−c] or electrophilic[3d] alkynylation to construct an sp−sp^3 bond, the installation of alkynyl moiety through radical activation of an sp^3 C−H bond is far less explored.[4]

As an important structural unit, 2-oxindoles with a quaternary carbon center at the C3 position constitute a ubiquitous class of heterocycles found in many natural products, clinical pharmaceuticals, and drug candidates.[5] Despite the great number of synthetic methods already available for other functional moieties, the introduction of a privileged alkynyl group at the C3 position of oxindoles to construct an all-carbon quaternary center has hardly been explored (Scheme 1, eq 1).[6] The installation of alkynyl groups onto an sp^3 carbon adjacent to carbonyl with concomitant formation of new C−C bonds can be achieved by nucleophilic addition of enolate to substituted alkynes.[7] In contrast, the direct introduction of alkynyl groups by C−H bond functionalization in 2-oxindoles is very rare.[6] Only two synthetic methods for the direct installation of propiolic ester groups at C3 of 2-oxindoles, via Lewis acid- or PTC-catalyzed alkynylations, have been reported.[6a,b] Recently, Veselý and co-workers described the alkynylation that proceeds by a β-addition−elimination mechanism, utilizing hypervalent iodine reagent IBX as the leaving group.[6c] Although these state-of-the-art alkynylation methods have demonstrated the possibility of directly introducing alkynyl moieties into the 2-oxindole systems, the narrow substrate scope, the forcing reaction conditions, the formation of complex reaction mixtures, and occasional selectivity problems still signify the need for further method development to efficiently introduce alkynyl groups by other more efficient pathways.

Scheme 1. Strategies for the Alkynylation of sp^3 C−H Bonds



In a continuation of our work on noble-metal-free olefination and radical arylation of 3-substituted 2-oxindoles with simple styenes and arenes to construct the C_{sp2}−C_{sp3} bonds,[8] we now present a highly effective alkynylation of 2-oxindoles with easily available 1-iodoalkynes without using external oxidants or transition-metal catalysts, which were expensive or hazardous and sometimes difficult to remove from the final compounds (Scheme 1, eq 2).[9] The products were formed in good to excellent yields with a broad substrate scope through the

Received: December 22, 2016
Published: February 7, 2017

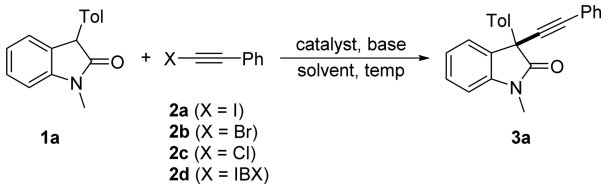
DOI: 10.1021/acs.joc.6b03057
J. Org. Chem. 2017, 82, 2656−2663

coupling of a 3-substituted 2-oxindole radical with an alkynyl radical, instead of previously reported addition/elimination pathways.[7]

RESULTS AND DISCUSSION

We started our investigations with a model reaction using 2-oxindole **1a** and 1-iodo-2-phenylacetylene **2a** (Table 1). When the reaction was conducted with photoredox catalysis or under UV conditions, which were commonly employed in radical cross-coupling reactions,[4b,10] no desired product was obtained (Table 1, entries 1 and 2). We envisioned that the alkynyl radical might be generated from the cleavage of C−I bond cleavage at a higher temperature.[11] Thus, we conducted the reaction at 120 °C for 24 h. To our delight, the desired alkynylation product **3a** was obtained in 54% without use of any catalyst (entry 3). Addition of strong bases as additives, beneficial to the generation of more reactive 2-oxindole enolate species,[12] resulted in inferior yields of **3a** (entries 4−9); whereas, with weak bases, which were not capable of producing 2-oxindolyl enolate but able to remove generated HI during the coupling process, better yields of the product were obtained (entries 10 and 11). A variety of different additional weak bases were then examined, with NaOAc providing the cross-coupling product in best yield (entry 11). A further optimization of the amount of NaOAc afforded the coupled product in 84% yield (entry 12). It is notable that this transformation can be conducted in an open flask without the need to remove oxygen and moisture from the air, producing the product in comparable yields (entry 13). The reaction was greatly inhibited by lowering the reaction temperature to 100 and 60 °C (entries 14 and 15). In comparison, when 1-chloro (**2b**),[6a] 1-bromo (**2c**),[6b] or 1-IBX (**2d**)[6c] substituted alkynes were used, as reported by Jorgensen, Feng, and Veselý, respectively, only trace amounts of the desired product were achieved (entries 16−18).

Table 1. Optimization of the Alkynylation of 2-Oxindole[a]



entry	catalyst	base	time (h)	temp (°C)	yield[b] (%)
1[c]	$[Ru(bpy)_3]Cl_2$		24	rt	
2[d]			24	rt	
3			24	120	54
4		KOH	12	120	45
5		Cs_2CO_3	12	120	50
6		DBU	12	120	
7		DMAP	12	120	
8		*t*-BuOK	12	120	53
9		*t*-BuONa	12	120	56
10		$KHCO_3$	24	120	80
11		NaOAc	12	120	74
12[e]		NaOAc	12	120	84
13[e,f]		NaOAc	12	120	80
14[e]		NaOAc	12	100	66
15[e]		NaOAc	12	60	
16[e,g]		NaOAc	24	120	
17[e,h]		NaOAc	12	120	
18[e,i]		NaOAc	12	120	9

[a]Unless noted, the reaction was carried out with **1a** (0.1 mmol), **2** (0.3 mmol), catalyst (1 mol %), base (1.0 equiv) in 2 mL of chlorobenzene under N_2. [b]Isolated yields. [c]Under the irradiation of a 16 W blue LED lamp. [d]Under the irradiation of an 8 W UV lamp (254 nm). [e]2.0 equiv of base was used. [f]Reaction under air. [g]**2b** was used. [h]**2c** was used. [i]**2d** was used.

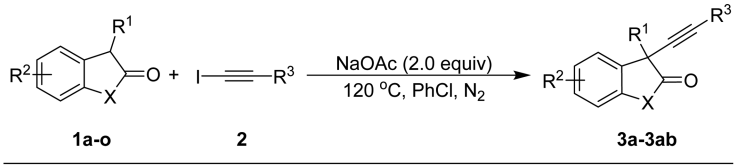
With the optimized reaction conditions in hand, we began to explore the substrate scope with respect to the 2-oxindoles **1a−o** and alkynyl iodides **2** (Scheme 2). A variety of 3-aryl-2-oxindoles underwent alkynylation with 1-iodo-2-phenylacetylene to furnish the desired products **3a−h** in good to excellent yields. In principle, electron-neutral (**3b**), electron-donating (**3a,c−e**), and electron-withdrawing (**3f−h**) substituents at the phenyl ring were all well tolerated under the standard reaction conditions. Substituents at the *ortho*- (**3d**), *meta*- (**3e**), or *para*- (**3a,c,f−h**) position did not affect the yields significantly. Other oxindole derivatives **3i−k** also provided the corresponding products in good to excellent yields. Notably, the acidic *N*-H in **1** was well tolerated in the reaction (**3j**). In addition, this alkynylation process also allows benzofuran-2(3*H*)-one[13] to serve as a cross-coupling partner, and the corresponding product **3l** was obtained in 84% yield.

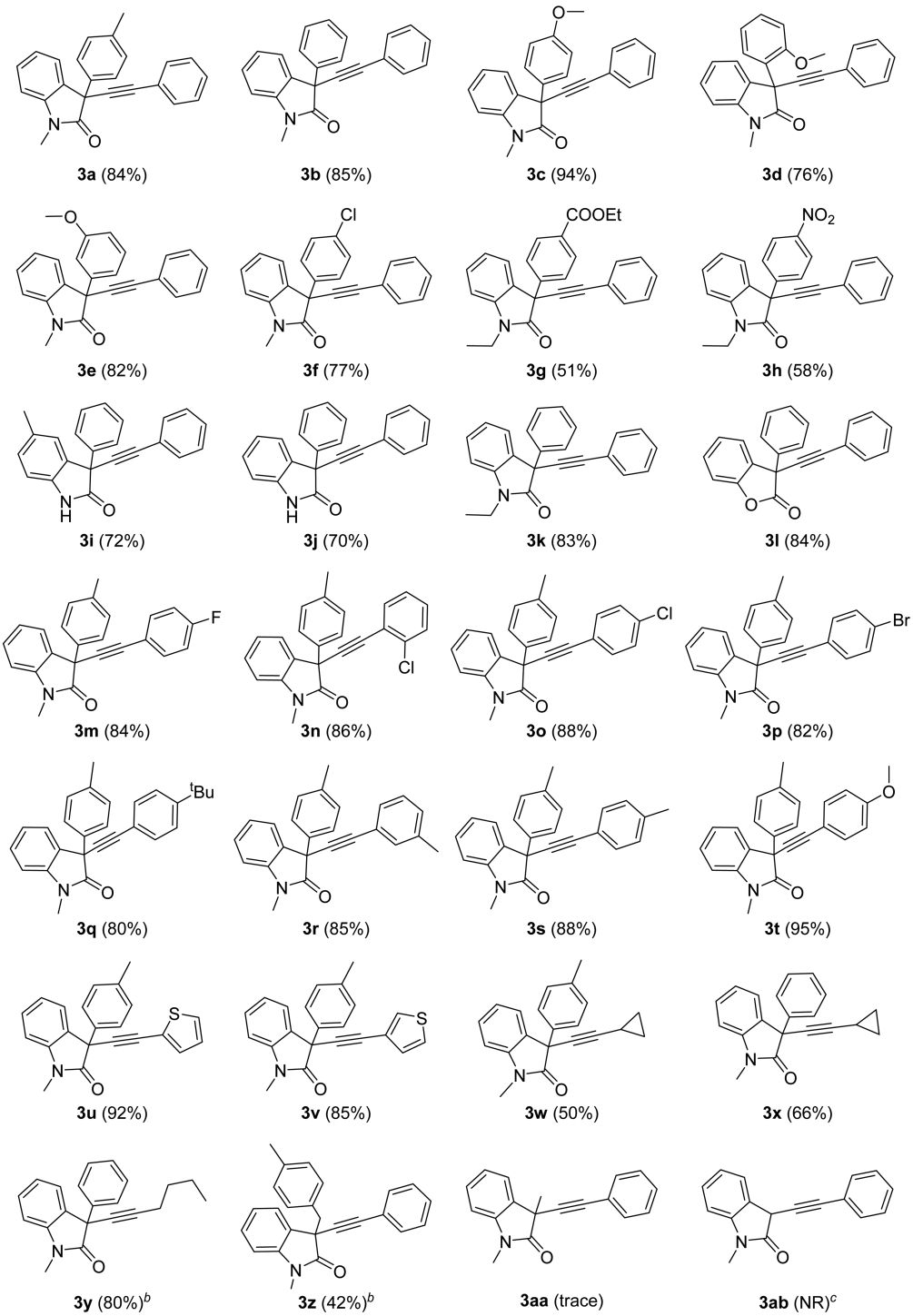
Next, we investigated this alkynylation process using alkynyl iodides as the cross-coupling partners. As expected, the reactions with alkynes in the presence of a variety of functional groups proceeded smoothly (**3m−t**). In addition, heterocyclic alkynes are also compatible with this transformation, thus providing the corresponding products **3u,v** in excellent yields (85−92%). Notably, alkyl-substituted alkynyl iodides bearing a cyclopropane and *n*-butyl group could also undergo this transformation (**3w−y**). When an alkyl-substituted oxindole like 1-methyl-3-(4-methylbenzyl)indolin-2-one was used, the desired product **3z** was isolated in moderate yield (42%). However, for 1,3-dimethylindolin-2-one, a dimer (1,1′,2,3′-tetramethyl[2,3′-biindoline]-2′,3-dione) was obtained as the major product (yield 66%) and only a trace amount of product **3aa** was observed. In addition, no reaction occurred when 1-methylindolin-2-one was used under the standard conditions after 24 h (**3ab**). To evaluate the practicality of the direct alkynylation reaction, a gram-scale reaction between **1a** (4.0 mmol, 0.95 g) and **2a** (12 mmol, 2.73 g) was carried out. As exhibited in Scheme 3, product **3a** was obtained in 86% yield, while 92% of the excess **2a** was recovered in the scaled up reaction.

During product purification, we were able to isolate two byproducts in the reaction of **1a** and **2e** under the optimized conditions: a small amount of unsubstituted alkyne **4** and a trace amount of the homocoupling diyne **5**, indicating the possible involvement of an alkynyl radical in this reaction (Scheme 4, eq 1). This finding was inconsistent with the addition/elimination mechanism proposed by Jorgensen and Feng when 1-chloro- or 1-bromoalkynes were used.[6a,b] Thus, to further shed light on the mechanism, several control experiments were carried out. When we added TEMPO to the standard reaction conditions, the alkynylation reaction was dramatically suppressed, with yield decreasing from 95% to 32% (Scheme 4, eq 2). It is well-known that the ring opening of the cyclopropylcarbinyl radical can serve as a radical clock.[14] Consistent with this hypothesis, a stoichiometric reaction of **1a** with **2e** in the presence of the radical clock (1-cyclopropylvinyl)benzene **6** afforded the ring-opening product **7** in 25% yield, while only a trace amount of alkynylation

DOI: 10.1021/acs.joc.6b03057
J. Org. Chem. 2017, 82, 2656−2663

Scheme 2. Substrate Scope for the Alkynylation of 2-Oxindoles[a]



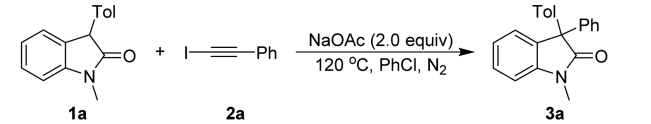


[a]The reaction was carried out with **1** (0.1 mmol), **2** (0.3 mmol), 0.2 mmol of NaOAc in 2 mL of chlorobenzene at 120 °C under N_2 for 12 h. Isolated yield. [b]6 equiv of 1-iodoalkyne was used. The alkynylation reaction mixture was stirred in *o*-xylene at 140 °C for 20 h. [c]NR: no reaction.

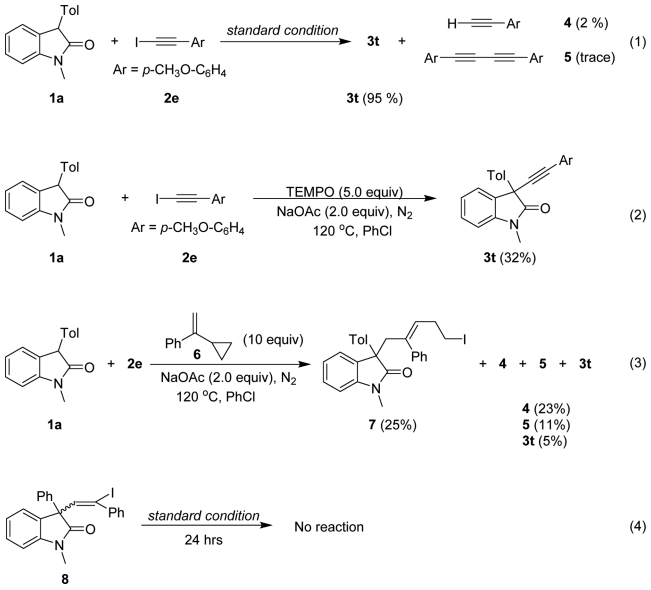
product **3t** (5%) was formed, together with a considerable amount of the byproducts **4** and **5** from alkyne, indicating the generation of alkynyl radical was a continuous process from the iodoalkyne (Scheme 4, eq 3). Finally, in order to exclude the

DOI: 10.1021/acs.joc.6b03057
J. Org. Chem. 2017, 82, 2656−2663

Scheme 3. Gram-Scale Reaction of 1a with 2a



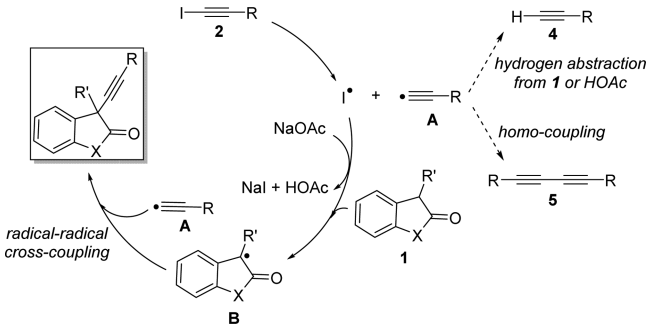
Scheme 4. Control Experiments



addition/elimination mechanism involving H or I atom transfer reactions, we prepared one of the possible intermediates, the vinyl iodide **8**, which turned out to be very inert under the standard condition, and no elimination of HI was observed (Scheme 4, eq 4).

Thus, based on these observations, we proposed that this alkynlation could proceed through another different pathway (Scheme 5) that involves a radical−radical-coupling process.[4b]

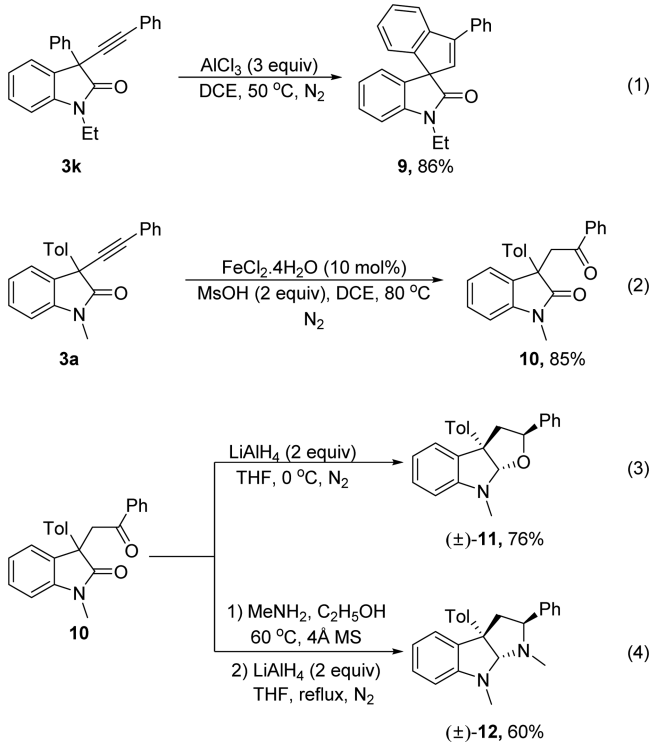
Scheme 5. Proposed Mechanism for the Cross-Coupling Reaction



We reasoned that the reaction might start with the homolytic decomposition of 1-iodoalkyne **2**, generating the highly reactive alkyne radical **A** and iodine radical species, in which the latter rapidly reacted with 2-oxindole (X = NR′′) or benzofuran-2(3*H*)-one (X = O) **1** to give the 2-oxindole radical **B**, while the generated HI was consumed by the base. The resulting 2-oxindole radical **B** underwent a selective cross-coupling with the alkyne radical **A** to give the product. On the other hand, the reactive alkyne radical **A** could also abstract one hydrogen from 2-oxindole **1** or HOAc to form the byproduct **4** or undergo a homodimerization to generate the diyne **5**. The persistent radical effect might provide a good explanation for the results of the cross-coupling reactions.[4b,15]

Finally, to illustrate the synthetic utility of this methodology, we examined its potential use for the construction of spiro and fused 2-oxindole skeletons, which have been recognized as a core in many natural products and biologically active molecules with great effort being devoted to their effective construction by synthetic and medicinal chemists.[16] Thus, the coupling product, oxindole-yne compound **3k**, underwent intramolecular Friedel−Crafts cyclization to afford the product spirocyclopentane-2-oxindole **9** in 86% yield (Scheme 6, eq 1). Selective hydration

Scheme 6. Subsequent Conversation of the Coupling Products



of product **3a** under the catalysis of $FeCl_2$ provided the key intermediate **10** (yield 85%) (Scheme 6, eq 2), which underwent reductive cyclization to afford biologically important 3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole and 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole derivatives (±)-**11** and (±)-**12** in 76% and 60% (two steps) yields, respectively, both with excellent diastereoselectivities (>20:1) (Scheme 6, eqs 3 and 4).

CONCLUSION

In summary, we have demonstrated a novel transition-metal-free approach to the synthesis of 3-alkynyl-2-oxindoles through a radical−radical coupling process. The reaction was general with respect to 2-oxindoles and iodoalkynes and provided the desired products bearing a quaternary center at C3 in good to excellent yields. These features make this method synthetically viable and attractive, as illustrated in the synthesis of biologically important 3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]-indole and 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole skeletons.

DOI: 10.1021/acs.joc.6b03057
J. Org. Chem. 2017, 82, 2656−2663

EXPERIMENTAL SECTION

General Procedure for Sodium Acetate Promoted Cross-Coupling of 2-Oxindoles with Iodoalkynes. A solution of 2-oxindole **1** (0.1 mmol), iodoalkyne **2** (0.3 mmol), and NaOAc (0.2 mmol) in 2 mL of chlorobenzene was stirred at 120 °C under nitrogen atmosphere. The reaction mixture was stirred for 12−18 h until completion, which was monitored by TLC. Then solution was diluted by ethyl acetate (4 mL) and washed with brine (4 mL). The organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After removal of sodium sulfate through filtration, the solution was concentrated under reduced pressure, and the mixture was purified by flash column chromatography over silica gel (gradient: petroleum ether/ethyl acetate = 10/1) to afford the desired products **3**.

*1-Methyl-3-(phenylethynyl)-3-(p-tolyl)indolin-2-one (**3a**):* white solid, 28.4 mg, 84% yield; mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.46 (m, 2H), 7.35−7.28 (m, 4H), 7.27−7.25 (m, 3H), 7.14−7.10 (m, 3H), 6.93−6.91 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 143.3, 137.8, 135.6, 132.0, 129.5, 129.1, 128.4, 128.2, 126.8, 125.0, 123.6, 122.7, 108.6, 86.8, 84.2, 52.5, 27.0, 21.1; IR ν_{max} (KBr, film, cm^{-1}) 3054, 2921, 1726, 1608, 1509, 1490; HRMS (ESI) calcd for $C_{24}H_{20}ON$ [M + H$^+$] 338.1539, found 338.1535.

*1-Methyl-3-phenyl-3-(phenylethynyl)indolin-2-one (**3b**):* white solid, 27.4 mg, 85% yield; mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.40 (m, 4H), 7.40−7.26 (m, 8H), 7.16−7.12 (td, J = 7.6, 0.8 Hz, 1H), 6.96−6.94 (d, J = 7.8 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 143.3, 138.6, 132.1, 132.0, 129.2, 128.8, 128.3, 128.2, 128.1, 127.0, 125.1, 123.7, 122.7, 108.7, 86.6, 84.4, 52.9, 27.0; IR ν_{max} (KBr, film, cm^{-1}) 3054, 2922, 2237, 1724, 1609, 1500; HRMS (ESI) calcd for $C_{23}H_{18}ON$ [M + H$^+$] 324.1383, found 324.1379.

*3-(4-Methoxyphenyl)-1-methyl-3-(phenylethynyl)indolin-2-one (**3c**):* white solid, 33.2 mg, 94% yield; mp 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.44 (m, 2H), 7.39−7.25 (m, 7H), 7.15−7.12 (t, J = 7.5 Hz, 1H), 6.94−6.92 (d, J = 7.8 Hz, 1H), 6.86−6.84 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 159.4, 143.3, 132.0, 130.6, 129.1, 128.5, 128.2, 128.1, 125.1, 123.6, 122.7, 114.9, 114.2, 108.6, 86.9, 84.2, 55.4, 52.2, 27.0; IR ν_{max} (KBr, film, cm^{-1}): 3055, 2932, 2100, 1726, 1609, 1489; HRMS (ESI) calcd for $C_{24}H_{20}O_2N$ [M + H$^+$] 354.1489, found 354.1482.

*3-(2-Methoxyphenyl)-1-methyl-3-(phenylethynyl)indolin-2-one (**3d**):* white solid, 26.8 mg, 76% yield; mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22−8.10 (m, 1H), 7.49−7.46 (m, 2H), 7.32−7.25 (m, 5H), 7.10−7.06 (t, J = 7.4 Hz, 1H), 7.04−7.03 (d, J = 7.0 Hz, 1H), 6.99−6.96 (t, J = 7.5 Hz, 1H), 6.89−6.87 (d, J = 7.8 Hz, 1H), 6.77−6.75 (d, J = 8.1 Hz, 1H), 3.43 (s, 3H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 156.4, 143.7, 132.1, 132.1, 130.2, 129.6, 128.5, 128.3, 128.2, 126.9, 123.3, 122.9, 122.7, 121.1, 112.1, 107.8, 86.0, 85.8, 55.9, 51.3, 27.0. IR ν_{max} (KBr, film, cm^{-1}): 3054, 2933, 1726, 1609, 1491, 1470; HRMS (ESI) calcd for $C_{24}H_{20}O_2N$ [M + H$^+$] 354.1489, found 354.1483.

*3-(3-Methoxyphenyl)-1-methyl-3-(phenylethynyl)indolin-2-one (**3e**):* white solid, 28.9 mg, 82% yield; mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.44 (m, 2H), 7.38−7.31 (m, 2H), 7.31−7.22 (m, 4H), 7.15−7.10 (m, 1H), 7.09−7.06 (m, 1H), 7.00−6.96 (m, 1H), 6.93−6.91 (d, J = 7.8 Hz, 1H), 6.83−6.81 (dd, J = 8.2, 2.0 Hz, 1H), 3.78 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 159.8, 143.2, 140.0, 132.0, 131.9, 129.8, 129.2, 128.5, 128.2, 125.0, 123.6, 122.6, 119.2, 113.4, 113.0, 108.7, 86.5, 84.4, 55.3, 52.8, 27.0; IR ν_{max} (KBr, film, cm^{-1}) 3054, 2934, 1724, 1608, 1490, 1470; HRMS (ESI) calcd for $C_{24}H_{20}O_2N$ [M + H$^+$] 354.1489, found 354.1482.

*3-(4-Chlorophenyl)-1-methyl-3-(phenylethynyl)indolin-2-one (**3f**):* white solid, 27.5 mg, 77% yield; mp 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2H), 7.41−7.36 (m, 3H), 7.33−7.27 (m, 6H), 7.17−7.13 (t, J = 7.5 Hz, 1H), 6.96−6.94 (d, J = 7.8 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 143.2, 137.1, 134.1, 132.1, 131.4, 129.4, 128.9, 128.7, 128.5, 128.3, 125.1, 123.8, 122.4, 108.8, 86.2, 84.7, 52.4, 27.1; IR ν_{max} (KBr, film, cm^{-1}) 3055, 2933, 2237, 1726, 1609, 1489; HRMS (ESI) calcd for $C_{23}H_{17}ONCl$ [M + H$^+$] 358.0993, found 358.0988.

*Ethyl 4-(1-ethyl-2-oxo-3-(phenylethynyl)indolin-3-yl)benzoate (**3g**):* white solid, 21 mg, 51% yield; mp 56−58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.3 Hz, 2H), 7.53−7.48 (m, 4H), 7.38 (t, J = 7.8 Hz, 1H), 7.31−7.26 (m, 4H), 7.12 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 4.36 (q, J = 6.8 Hz, 2H), 3.94−3.74 (m, 2H), 1.38−1.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 166.3, 143.6, 142.3, 132.2, 131.9, 130.2, 130.1, 129.4, 128.7, 128.3, 127.0, 125.2, 123.6, 122.5, 109.1, 86.0, 85.0, 61.1, 53.0, 35.6, 14.4, 12.7; IR ν_{max} (KBr, film, cm^{-1}) 3056, 2925, 1720, 1609, 1487, 1466; HRMS (ESI): calcd for $C_{27}H_{24}O_3N$ [M + H$^+$] 410.1751, found 410.1749.

*1-Ethyl-3-(4-nitrophenyl)-3-(phenylethynyl)indolin-2-one (**3h**):* white solid, 22 mg, 58% yield; mp 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.51−7.48 (m, 2H), 7.44−7.40 (m, 1H), 7.34−7.31 (m, 4H), 7.16 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 3.94−3.75 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 147.7, 145.9, 142.4, 132.2, 131.1, 129.8, 129.0, 128.4, 128.1, 125.3, 124.1, 123.9, 122.1, 109.3, 85.5, 85.3, 52.9, 35.8, 12.7; IR ν_{max} (KBr, film, cm^{-1}) 3058, 2850, 1723, 1607, 1519, 1487; HRMS (ESI) calcd for $C_{24}H_{19}O_3N_2$ [M + H$^+$] 383.1390, found 383.1386.

*5-Methyl-3-phenyl-3-(phenylethynyl)indolin-2-one (**3i**):* white solid, 23.3 mg, 72% yield; mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.60−7.44 (m, 4H), 7.40−7.26 (m, 6H), 7.08−7.06 (m, 2H), 6.89−6.87 (d, J = 7.9 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 138.4, 137.8, 133.2, 132.8, 132.0, 129.4, 128.8, 128.5, 128.2, 128.0, 126.9, 125.8, 122.6, 110.2, 86.3, 84.8, 53.5, 21.2; IR ν_{max} (KBr, film, cm^{-1}) 3207, 2928, 2237, 1716, 1621, 1507; HRMS (ESI) calcd for $C_{23}H_{18}ON$ [M + H$^+$] 324.1383, found 324.1378.

*3-Phenyl-3-(phenylethynyl)indolin-2-one (**3j**):* white solid, 21.7 mg, 70% yield; mp 65−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.50−7.49 (d, J = 7.4 Hz, 4H), 7.36−7.24 (m, 8H), 7.09−7.06 (t, J = 7.6 Hz, 1H), 7.01−6.99 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 140.5, 138.3, 132.8, 132.1, 129.1, 128.9, 128.6, 128.3, 128.1, 127.0, 125.2, 123.6, 122.6, 110.7, 86.2, 84.9, 53.6; IR ν_{max} (KBr, film, cm^{-1}): 3237, 3060, 2237, 1721, 1617, 1600; HRMS (ESI) calcd for $C_{22}H_{16}ON$ [M + H$^+$] 310.1226, found 310.1221.

*1-Ethyl-3-phenyl-3-(phenylethynyl)indolin-2-one (**3k**):* white solid, 28 mg, 83% yield; mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.39 (m, 4H), 7.39−7.22 (m, 8H), 7.13−711 (dt, J = 7.6, 1.0 Hz, 1H), 6.97−6.95 (d, J = 7.8 Hz, 1H), 3.93−3.73 (m, 2H), 1.34−1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 142.6, 138.7, 132.4, 132.0, 129.0, 128.8, 128.4, 128.2, 127.9, 126.8, 125.2, 123.4, 122.7, 108.8, 86.5, 84.4, 52.9, 35.4, 12.6; IR ν_{max} (KBr, film, cm^{-1}) 3054, 2933, 2281, 1722, 1607, 1500; HRMS (ESI) calcd for $C_{24}H_{20}ON$ [M + H$^+$] 338.1539, found 338.1537.

*3-Phenyl-3-(phenylethynyl)benzofuran-2(3H)-one (**3l**):* white solid, 26.0 mg, 84% yield; mp 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.47 (m, 4H), 7.41−7.30 (m, 8H), 7.26−7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 152.9, 137.4, 132.1, 130.3, 130.1, 129.1, 129.0, 128.7, 128.4, 126.9, 125.4, 125.3, 122.0, 111.3, 85.8, 84.8, 51.5; IR ν_{max} (KBr, film, cm^{-1}): 3107, 2922, 2227, 1809, 1597, 1462; HRMS (ESI) calcd for $C_{22}H_{15}O_2$ [M + H$^+$] 311.1067, found 311.1063.

*3-((4-Fluorophenyl)ethynyl)-1-methyl-3-(p-tolyl)indolin-2-one (**3m**):* white solid, 29.8 mg, 84% yield; mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.40 (m, 2H), 7.39−7.35 (t, J = 7.7 Hz, 1H), 7.33−7.30 (m, 3H), 7.15−7.11 (m, 3H), 7.01−6.89 (m, 3H), 3.27 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.48, 162.6 (d, J = 248 Hz), 143.28, 137.90, 135.48, 134.0 (d, J = 8 Hz), 131.92, 129.51, 129.14, 126.76, 125.04, 123.62, 118.8 (d, J = 4 Hz), 115.5 (d, J = 22 Hz), 108.67, 86.55, 83.13, 52.53, 27.03, 21.11; IR ν_{max} (KBr, film, cm^{-1}): 3055, 2924, 1724, 1608, 1507; HRMS (ESI) calcd for $C_{24}H_{19}ONF$ [M + H$^+$] 356.1445, found 356.1440.

*3-((2-Chlorophenyl)ethynyl)-1-methyl-3-(p-tolyl)indolin-2-one (**3n**):* white solid, 31.9 mg, 86% yield; mp 65−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.47 (dd, J = 7.5, 1.4 Hz, 1H), 7.38−7.34 (m, 5H), 7.22−7.11 (m, 5H), 6.94−6.92 (d, J = 7.8 Hz, 1H), 3.27 (s, 3H),

DOI: 10.1021/acs.joc.6b03057
J. Org. Chem. 2017, 82, 2656−2663

2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 143.2, 137.9, 136.5, 135.4, 133.6, 131.8, 129.50, 129.46, 129.2, 129.1, 126.8, 126.3, 125.2, 123.6, 122.7, 108.6, 92.0, 81.1, 52.8, 27.0, 21.1; IR ν_{max} (KBr, film, cm^{-1}): 2926, 2237, 1724, 1608, 1508; HRMS (ESI) calcd for $C_{24}H_{19}ONCl$ [M + H^+] 372.1150, found 372.1146.

3-((4-Chlorophenyl)ethynyl)-1-methyl-3-(p-tolyl)indolin-2-one ***(3o)****:* pale yellow solid, 32.6 mg, 88% yield; mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 6H), 7.26−7.24 (d, J = 8.4 Hz, 2H), 7.15−7.11 (m, 3H), 6.94−6.92 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 143.3, 137.9, 135.4, 134.5, 133.3, 131.8, 129.5, 129.2, 128.6, 126.7, 125.0, 123.6, 121.2, 108.7, 87.9, 83.0, 52.6, 27.0, 21.1; IR ν_{max} (KBr, film, cm^{-1}) 2926, 2237, 1724, 1608, 1508; HRMS (ESI) calcd for $C_{24}H_{19}ONCl$ [M + H^+] 372.1150, found 372.1144.

3-((4-Bromophenyl)ethynyl)-1-methyl-3-(p-tolyl)indolin-2-one ***(3p)****:* white solid, 34.1 mg, 82% yield; mp 69−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.26 (m, 8H), 7.18−7.07 (m, 3H), 6.94−6.92 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 143.2, 137.9, 135.3, 133.4, 131.7, 131.4, 129.5, 129.2, 126.7, 125.0, 123.6, 122.7, 121.7, 108.7, 88.0, 83.1, 52.6, 27.0, 21.1; IR ν_{max} (KBr, film, cm^{-1}) 3054, 2924, 1726, 1608, 1509; HRMS (ESI) calcd for $C_{24}H_{19}ONBr$ [M + H^+] 416.0644, found 416.0640.

3-((4-tert-Butylphenyl)ethynyl)-1-methyl-3-(p-tolyl)indolin-2-one ***(3q)****:* white solid, 31.4 mg, 80% yield; mp 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.40 (d, J = 8.4 Hz, 2H), 7.37−7.26 (m, 6H), 7.13−7.11 (m, 3H), 6.93−7.91 (d, J = 7.8 Hz, 1H), 3.27 (s, 3H), 2.31 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 151.7, 143.3, 137.8, 135.8, 132.2, 131.8, 129.5, 129.0, 126.8, 125.2, 125.0, 123.6, 119.7, 108.6, 86.1, 84.4, 52.6, 34.8, 31.2, 27.0, 21.1; IR ν_{max} (KBr, film, cm^{-1}) 3053, 2962, 1721, 1608, 1508; HRMS (ESI) calcd for $C_{28}H_{28}ON$ [M + H^+] 394.2165, found 394.2160.

1-Methyl-3-(p-tolyl)-3-(m-tolylethynyl)indolin-2-one ***(3r)****:* white solid, 29.9 mg, 85% yield; mp 44−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.23 (m, 6H), 7.18−7.09 (m, 5H), 6.93−6.91 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 143.3, 137.9, 137.8, 135.6, 132.7, 132.1, 129.5, 129.3, 129.1, 129.0, 128.1, 126.8, 125.0, 123.6, 122.5, 108.6, 86.4, 84.4, 52.6, 27.0, 21.2, 21.1; IR ν_{max} (KBr, film, cm^{-1}): 3054, 2922, 1727, 1608, 1508; HRMS (ESI) calcd for $C_{25}H_{22}ON$ [M + H^+] 352.1696, found 352.1691.

1-Methyl-3-(p-tolyl)-3-(p-tolylethynyl)indolin-2-one ***(3s)****:* white solid, 30.9 mg, 88% yield; mp 49−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.31 (m, 6H), 7.13−7.07 (m, 5H), 6.92−6.90 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 143.3, 138.5, 137.8, 135.7, 132.2, 131.9, 129.4, 129.01, 128.96, 126.8, 125.0, 123.6, 119.6, 108.6, 86.0, 84.4, 52.6, 27.0, 21.5, 21.1; IR ν_{max} (KBr, film, cm^{-1}) 3054, 2922, 1727, 1608, 1508; HRMS (ESI) calcd for $C_{25}H_{22}ON$ [M + H^+] 352.1696, found 352.1692.

3-((4-Methoxyphenyl)ethynyl)-1-methyl-3-(p-tolyl)indolin-2-one ***(3t)****:* white solid, 34.9 mg, 95% yield; mp 54−56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.29 (m, 6H), 7.13−7.10 (m, 3H), 6.92−6.91 (d, J = 7.8 Hz, 1H), 6.81−6.79 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 3.26 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 159.7, 143.2, 137.7, 135.8, 133.5, 132.3, 129.4, 129.0, 126.8, 125.0, 123.5, 114.8, 113.8, 108.6, 85.3, 84.2, 55.3, 52.6, 27.0, 21.1; IR ν_{max} (KBr, film, cm^{-1}): 3054, 2932, 2238, 1724, 1607, 1510; HRMS (ESI) calcd for $C_{25}H_{22}O_2N$ [M + H^+] 368.1645, found 368.1640.

1-Methyl-3-(thiophene-2-ylethynyl)-3-(p-tolyl)indolin-2-one ***(3u)****:* white solid, 31.6 mg, 92% yield; mp 157−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.35 (m, 4H), 7.33−7.27 (m, 3H), 7.16−7.13 (t, J = 7.3 Hz, 1H), 6.95−6.94 (d, J = 7.8 Hz, 1H), 6.82−6.80 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 159.9, 143.3, 137.3, 134.1, 133.6, 131.7, 129.3, 128.9, 128.5, 125.1, 123.8, 114.5, 113.9, 108.8, 84.71, 84.66, 55.4, 52.4, 27.1; IR ν_{max} (KBr, film, cm^{-1}) 2921, 2851, 2231, 1723, 1606, 1510; HRMS (ESI) calcd for $C_{22}H_{17}ONNaS$ [M + Na^+] 366.0923, found 366.0919.

1-Methyl-3-(thiophene-3-ylethynyl)-3-(p-tolyl)indolin-2-one ***(3v)****:* white solid, 29.2 mg, 85% yield; mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.43 (m, 1H), 7.38−7.30 (m, 4H), 7.23−7.21 (dd, J = 5.0, 3.0 Hz, 1H), 7.15−7.10 (m, 4H), 6.93−6.91 (d, J = 7.8 Hz, 1H), 3.27 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 143.3, 137.8, 135.5, 132.0, 130.2, 129.5, 129.4, 129.1, 126.8, 125.15, 125.08, 123.6, 121.7, 108.6, 86.3, 79.4, 52.6, 27.0, 21.1. IR ν_{max} (KBr, film, cm^{-1}): 3105, 2925, 2231, 1724, 1608, 1508; HRMS (ESI) calcd for $C_{22}H_{18}ONS$ [M + H^+] 344.1104, found 344.1100.

3-(Cyclopropylethynyl)-1-methyl-3-(p-tolyl)indolin-2-one ***(3w)****:* white solid, 15.0 mg, 50% yield; mp 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (t, J = 7.7 Hz, 1H), 7.25−7.21 (m, 3H), 7.10−7.08 (m, 3H), 6.90−6.88 (d, J = 7.8 Hz, 1H), 3.23 (s, 3H), 2.29 (s, 3H), 1.23−1.26 (m, 1H), 0.78−0.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 143.2, 137.6, 136.0, 132.6, 129.4, 128.8, 126.7, 124.8, 123.5, 108.5, 88.0, 72.5, 52.0, 26.9, 21.1, 8.42, 8.40, −0.2; IR ν_{max} (KBr, film, cm^{-1}) 3158, 2930, 2238, 1724, 1610, 1492; HRMS (ESI) calcd for $C_{21}H_{20}ON$ [M + H^+] 302.1539, found 302.1536.

3-(Cyclopropylethynyl)-1-methyl-3-phenylindolin-2-one ***(3x)****:* white solid, 19.0 mg, 66% yield; mp 84−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 4H), 7.27−7.20 (m, 3H), 7.11−7.07 (t, J = 7.5 Hz, 1H), 6.91−6.89 (d, J = 7.8 Hz, 1H), 3.25 (s, 3H), 1.34−1.26 (m, 1H), 0.83−0.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 143.2, 139.0, 132.6, 128.9, 128.6, 127.8, 126.8, 124.9, 123.5, 108.5, 88.2, 72.4, 52.4, 27.0, 8.43, 8.41, −0.2; IR ν_{max} (KBr, film, cm^{-1}) 3011, 2923, 2238, 1724, 1608, 1509; HRMS (ESI) calcd for $C_{20}H_{18}ON$ [M + H^+] 288.1383, found 288.1379.

3-(Hex-1-yn-1-yl)-1-methyl-3-phenylindolin-2-one ***(3y)****:* pale yellow oil, 24.3 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.23 (m, 7H), 7.12−7.08 (t, J = 7.4 Hz, 1H), 6.91−6.89 (d, J = 7.8 Hz, 1H), 3.25 (s, 3H), 2.29−2.25 (m, 2H), 1.53−1.51 (m, 2H), 1.46−1.40 (m, 2H), 0.92−0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 143.2, 139.0, 132.7, 128.9, 128.6, 127.8, 126.9, 124.8, 123.5, 108.5, 85.4, 52.4, 30.8, 27.0, 22.1, 18.7, 13.7; IR ν_{max} (KBr, film, cm^{-1}) 2955, 2932, 2237, 1727, 1610, 1508; HRMS (ESI) calcd for $C_{21}H_{22}ON$ [M + H^+] 304.1696, found 304.1692.

1-Methyl-3-(4-methylbenzyl)-3-(phenylethynyl)indolin-2-one ***(3z)****:* white solid, 14.7 mg, 42% yield; mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.42 (m, 2H), 7.29−7.25 (m, 4H), 7.12−7.11 (d, J = 7.1 Hz, 1H), 7.06−7.02 (t, J = 7.5 Hz, 1H), 6.96−6.90 (m, 4H), 6.70−6.68 (d, J = 7.8 Hz, 1H), 3.46−3.43 (d, J = 13.0 Hz, 1H), 3.42−3.21 (d, J = 13.0 Hz, 1H), 3.08 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 142.8, 136.6, 131.9, 131.6, 130.4, 129.9, 128.6, 128.3, 128.2, 128.1, 124.7, 122.8, 122.6, 108.1, 86.7, 84.1, 49.2, 44.5, 26.4, 21.1; IR ν_{max} (KBr, film, cm^{-1}): 2922, 2852, 1722, 1610, 1507; HRMS (ESI) calcd for $C_{25}H_{22}ON$ [M + H^+] 352.1696, found 352.1691.

Procedure of a Gram-Scale Reaction of 1a with 2a. A solution of 1-methyl-3-(*p*-tolyl)indolin-2-one **1a** (4.0 mmol, 0.95 g), (iodoethynyl)benzene **2a** (12 mmol, 2.37 g), and NaOAc (8.0 mmol, 0.66 g) in 40 mL of chlorobenzene was stirred at 120 °C under nitrogen atmosphere. The reaction mixture was stirred for 14 h until completion as monitored by TLC. Then solution was washed with brine (20 mL). The organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After removal of sodium sulfate through filtration, the solution was concentrated under reduced pressure and the mixture was purified by flash column chromatography over silica gel (gradient: petroleum ether/ethyl acetate = 10/1) to afford the desired product **3a** (1.16 g, yield 86%).

Radical-Trapping Experience. A solution of 1-methyl-3-(*p*-tolyl)indolin-2-one **1a** (0.1 mmol), (iodoethynyl)benzene **2e** (0.3 mmol), (1-cyclopropylvinyl)benzene **6** (10 mmol), and NaOAc (0.2 mmol) in 2 mL of chlorobenzene was stirred at 120 °C under nitrogen atmosphere. The reaction mixture was stirred for 12 h until completion as monitored by TLC. Then solution was diluted with ethyl acetate (4 mL) and washed with brine (4 mL). The organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After removal of sodium sulfate through filtration, the solution was concentrated under reduced pressure, and the mixture was purified by flash column chromatography over silica gel (gradient: petroleum ether/ethyl acetate = 30/1) to afford the desired product **7**.

DOI: 10.1021/acs.joc.6b03057
J. Org. Chem. 2017, 82, 2656−2663

*3-(5-Iodo-2-phenylpent-2-en-1-yl)-1-methyl-3-(p-tolyl)indolin-2-one (**7**):* white solid, 12.7 mg, 25% yield; mp 66−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.22 (m, 3H), 7.11−7.04 (m, 5H), 7.03−7.01 (dd, J = 7.4, 1.4 Hz, 1H), 6.98−6.94 (td, J = 7.4, 1.0 Hz, 1H), 6.70−6.68 (d, J = 7.8 Hz, 1H), 6.55−6.52 (m, 2H), 5.45−5.35 (m, 1H), 3.87−3.83 (dd, J = 13.4, 1.4 Hz, 1H), 3.16−3.13 (d, J = 13.6 Hz, 1H), 2.91−2.87 (td, J = 7.3, 1.4 Hz, 2H), 2.73 (s, 3H), 2.30−2.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 144.2, 139.3, 138.4, 138.1, 137.0, 130.6, 130.0, 129.1, 128.3, 127.9, 127.5, 126.8, 126.6, 126.5, 122.0, 107.9, 55.9, 46.9, 32.7, 26.0, 20.9, 5.2; IR ν_{max} (KBr, film, cm^{-1}) 3024, 2933, 1620, 1514, 1445; HRMS (ESI) calcd for $C_{27}H_{26}IONNa$ [M + Na$^+$] 530.0951, found 530.0941.

Procedure for the Synthesis of Compound 9. A solution of **3k** (0.1 mmol in 1 mL of 1,2-dicholoethane) was slowly dropped into the solution of aluminum chloride (0.3 mmol in 1 mL of 1,2-dicholoethane) at 50 °C under the nitrogen atmosphere. The reaction mixture was stirred for 3 h until completion as monitored by TLC. Then the reaction mixture was quenched with a saturated ammonium chloride solution (4 mL). The organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After removal of sodium sulfate through filtration, the solution was concentrated under reduced pressure. Silica gel column chromatography (gradient: petroleum ether/ethyl acetate = 15/1) gave the desired product **9**.

*1′-Ethyl-3-phenylspiro[indene-1,3′-indolin]-2′-one (**9**):* white solid, 29.0 mg, 86% yield. The ^{1}H NMR spectra were identical with previous reports.[17]

Procedure for the Synthesis of Compound 10. A solution of **3a** (0.1 mmol), iron(II) chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$, 0.01 mmol), and methanesulfonic acid (0.22 mmol) in 1.5 mL of 1,2-dicholoethane was stirred at 80 °C under nitrogen atmosphere. The reaction mixture was stirred for 12 h until completion as monitored by TLC. Then the reaction mixture was diluted with ethyl acetate (4 mL) and quenched with 10% (w/w) sodium bicarbonate solution (4 mL). The organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After removal of sodium sulfate through filtration, the solution was concentrated under reduced pressure, and the mixture was purified by flash column chromatography over silica gel (gradient: petroleum ether/ethyl acetate = 10/1) to afford the desired product **10**.

*1-Methyl-3-(2-oxo-2-phenylethyl)-3-(p-tolyl)indolin-2-one (**10**):* white solid, 30.2 mg, 85% yield; mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.83 (d, J = 7.4 Hz, 2H), 7.52−7.49 (t, J = 7.4 Hz, 1H), 7.40−7.36 (t, J = 7.7 Hz, 2H), 7.33−7.29 (m, 3H), 7.26−7.24 (d, J = 7.1 Hz, 1H), 7.12−7.10 (d, J = 8.1 Hz, 2H), 7.05−7.01 (t, J = 7.5 Hz, 1H), 6.93−6.91 (d, J = 7.8 Hz, 1H), 4.16−4.12 (d, J = 16.0 Hz, 1H), 4.09−4.05 (d, J = 16.0 Hz, 1H), 3.27 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 178.8, 144.9, 137.4, 136.6, 136.4, 133.3, 131.8, 129.4, 128.6, 128.4, 128.0, 126.7, 124.1, 122.2, 108.5, 52.9, 47.0, 26.8, 21.0; IR ν_{max} (KBr, film, cm^{-1}) 3054, 2933, 1715, 1688, 1613, 1509; HRMS (ESI) calcd for $C_{24}H_{22}O_2N$ [M + H$^+$] 356.1645, found 356.1640.

Procedure for the Synthesis of Compound 11. A solution of **10** (0.1 mmol) and lithium aluminum hydride (0.2 mmol) in 1.5 mL of tetrahydrofuran was stirred at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 6 h until completion as monitored by TLC. Then the reaction mixture was quenched with saturated ammonium chloride solution (4 mL). The organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After removal of sodium sulfate through filtration, the solution was concentrated under reduced pressure. Silica gel column chromatography (dichloromethane) gave the desired product **11**.

*(±)-8-Methyl-2-phenyl-3a-(p-tolyl)-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole (**11**):* pale yellow oil, 26.0 mg, 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.12 (m, 10H), 6.93−6.91 (dd, J = 7.3, 1.2 Hz, 1H), 6.68−6.64 (dt, J = 7.4, 1.0 Hz, 1H), 6.50−6.48 (d, J = 7.8 Hz, 1H), 5.45 (s, 1H), 5.27−5.25 (dd, J = 8.2, 6.8 Hz, 1H), 3.24−3.19 (dd, J = 13.0, 6.8 Hz, 1H), 3.04 (s, 3H), 2.57−2.52 (dd, J = 13.0, 8.2 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 141.9, 140.8, 136.4, 135.2, 129.4, 128.2, 128.1, 127.3, 126.4, 125.9, 124.4, 118.2, 107.6, 106.7, 80.0, 60.6, 48.6, 31.7, 21.0; IR ν_{max} (KBr, film, cm^{-1}) 3026, 2927, 1606, 1512, 1449; HRMS (ESI) calcd for $C_{24}H_{24}ON$ [M + H$^+$] 342.1852, found 342.1846.

Procedure for the Synthesis of Compound 12. A mixture of **10** (0.1 mmol), methylamine (0.4 mmol, 33 wt % solution in absolute ethanol), and 4 Å molecular sieves (100 mg) in 1 mL of ethanol was stirred at 60 °C under nitrogen atmosphere. The reaction mixture was stirred for 72 h until completion as monitored by TLC. After removal of molecular sieves through filtration, the solution was concentrated under reduced pressure. The residue and lithium aluminum hydride (0.2 mmol) in 1.5 mL of tetrahydrofuran were stirred at 60 °C under nitrogen atmosphere. The reaction mixture was stirred for 6 h until completion as monitored by TLC. Then the reaction mixture was quenched by saturated ammonium chloride solution (4 mL). The organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After removal of sodium sulfate through filtration, the solution was concentrated under reduced pressure. Silica gel column chromatography (dichloromethane) gave the desired product **12**.

*(±)-1,8-Dimethyl-2-phenyl-3a-(p-tolyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**12**):* white solid, 21.1 mg, 60% yield; mp 157−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 4H), 7.27−7.24 (m, 3H), 7.17−7.10 (m, 3H), 6.93−6.92 (m, 1H), 6.72−6.68 (m, 1H), 6.56−6.54 (d, J = 7.9 Hz, 1H), 4.85 (s, 1H), 3.70−3.63 (dd, J = 10.5, 5.3 Hz, 1H), 3.04 (s, 3H), 2.65−2.54 (m, 2H), 2.31 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 144.2, 142.0, 135.7, 135.2, 129.1, 128.4, 128.03, 127.6, 127.3, 126.4, 124.8, 117.9, 107.1, 98.2, 66.5, 58.9, 51.8, 38.0, 34.0, 21.0; IR ν_{max} (KBr, film, cm^{-1}) 3026, 2933, 1602, 1511, 1455; HRMS (ESI) calcd for $C_{25}H_{27}N_2$ [M + H$^+$] 355.2161, found 355.2169.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03057.

Details on mechanism experiments; ^{1}H and ^{13}C NMR spectra of all products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chengl@iccas.ac.cn.
*E-mail: lliu@iccas.ac.cn.
*E-mail: cj.li@mcgill.ca

ORCID

Liang Cheng: 0000-0001-7427-2939
Chao-Jun Li: 0000-0002-3859-8824

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Program on Key Research Project (2016YFA0602900). We also thank the National Natural Science Foundation of China (21372224, 21420102003, 21232008, and 21502201), Shandong Province Independent Innovation and Achievements Transformation of Special (2014XGC06001), Beijing Natural Science Foundation (2162049), the Young Elite Scientist Sponsorship Program by CAST (2015QNRC001), and the Chinese Academy of Sciences for financial support.

■ REFERENCES

(1) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470. (b) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874−922. (c) Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *40*,

DOI: 10.1021/acs.joc.6b03057
J. Org. Chem. 2017, 82, 2656−2663

5084−5121. (d) Haro, T. d.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512−1513. (e) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522−2523. (f) Jie, X.; Shang, Y.; Hu, P.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3630−3633. (g) Shang, M.; Wang, H.; Sun, S.; Dai, H.; Yu, J. *J. Am. Chem. Soc.* **2014**, *136*, 11590−11593.
(2) Hirsch, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3803−3804.
(3) For selected examples, see: (a) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810−11811. (b) Xiang, S.-K.; Zhang, B.; Zhang, L.-H.; Cui, Y. X.; Jiao, N. *Sci. China: Chem.* **2012**, *55*, 50−54. (c) Xu, X.; Li, X. *Org. Lett.* **2009**, *11*, 1027−1029. (d) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165−4179.
(4) (a) Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486−4487. (b) Xie, J.; Shi, S.; Zhang, T.; Mehrkens, N.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6046−6050. (c) Tang, S.; Wang, P.; Li, H.; Lei, A. *Nat. Commun.* **2016**, *7*, 11676.
(5) For reviews, see: (a) Vine, K. L.; Matesic, L.; Locke, J. M.; Ranson, M.; Skropeta, D. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 397−414. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (c) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105−2108. (d) Jensen, B. S. *CNS Drug Rev.* **2002**, *8*, 353−360. (e) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758−776. (f) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36−51. (g) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381−1407.
(6) (a) Wang, Z.; Zhang, Z.; Yao, Q.; Liu, X.; Cai, Y.; Lin, L.; Feng, X. *Chem. - Eur. J.* **2013**, *19*, 8591−8596. (b) Poulsen, T. B.; Bernardi, L.; Aleman, J.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 441−449. (c) Kamlar, M.; Císařová, I.; Veselý, J. *Org. Biomol. Chem.* **2015**, *13*, 2884−2889.
(7) For selected examples, see: (a) Beringer, F. M.; Galton, S. A. *J. Org. Chem.* **1965**, *30*, 1930−1934. (b) Miller, S. I.; Dickstein, J. I. *Acc. Chem. Res.* **1976**, *9*, 358−363. (c) Vita, M. V.; Mieville, P.; Waser, J. *Org. Lett.* **2014**, *16*, 5768−5771. (d) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281−8283. (e) Moloney, M. G.; Pinhey, J. T.; Roche, E. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 333−341.
(8) (a) Huang, H.-Y.; Wu, H.-R.; Wei, F.; Wang, D.; Liu, L. *Org. Lett.* **2015**, *17*, 3702−3705. (b) Wu, H.-R.; Huang, H.-Y.; Ren, C.-L.; Liu, L.; Wang, D.; Li, C.-J. *Chem. - Eur. J.* **2015**, *21*, 16744−16748.
(9) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219−9280.
(10) Liu, W.; Li, L.; Li, C.-J. *Nat. Commun.* **2015**, *6*, 6526.
(11) For homocleavage of the C−I bond under high temperature, see: (a) Chen, Z.; Jiang, H.; Wang, A.; Yang, S. *J. Org. Chem.* **2010**, *75*, 6700−6703. (b) Jin, F.; Zhong, Y.; Zhang, X.; Zhang, H.; Zhao, Q.; Han, W. *Green Chem.* **2016**, *18*, 2598−2603. (c) Zhang, C.-P.; Chen, Q.-Y.; Guo, Y.; Xiao, J.-C. *Tetrahedron* **2013**, *69*, 10955−10989.
(12) For pK_a values of 2-oxindoles, see: (a) Zhu, X.-Q.; Zhou, J.; Wang, C.-H.; Li, X.-T.; Jing, S. *J. Phys. Chem. B* **2011**, *115*, 3588−3603. For selected reviews and work, see: Ouyang, K.; Xi, Z. *Huaxue Xuebao* **2013**, *71*, 13−25. (b) Wei, W. T.; Yang, X. H.; Li, H. B.; Li, J. H. *Adv. Synth. Catal.* **2015**, *357*, 59−63. (c) Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2015**, *47*, 1195−1209.
(13) Yang, C.; Liu, Y.; Yang, J.-D.; Li, Y.-H.; Li, X.; Cheng, J.-P. *Org. Lett.* **2016**, *18*, 1036−1039.
(14) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197−1212.
(15) (a) Frenette, M.; Aliaga, C.; Font-Sanchis, E.; Scaiano, J. C. *Org. Lett.* **2004**, *6*, 2579−2582. (b) Gu, X.; Guo, Y.; Zhang, F.; Mebel, A. M.; Kaiser, R. I. *Chem. Phys. Lett.* **2007**, *436*, 7−14.
(16) (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432−3435. (b) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. *J. Am. Chem. Soc.* **2005**, *127*, 10130−10131. (c) Morales-Rios, M. S.; Santos-Sanchez, N. F.; Joseph-Nathan, P. *J. Nat. Prod.* **2002**, *65*, 136−141. (d) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503.
(17) Basavaiah, D.; Reddy, K. R. *Org. Lett.* **2007**, *9*, 57−60.

DOI: 10.1021/acs.joc.6b03057
J. Org. Chem. 2017, 82, 2656−2663