JOC The Journal of Organic Chemistry

Article

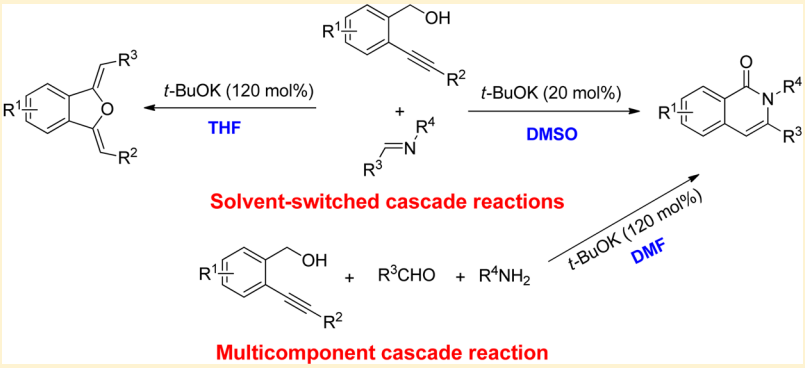
pubs.acs.org/joc

Transition Metal-Free Cascade Reactions of Alkynols to Afford Isoquinolin-1(2*H*)-one and Dihydroisobenzofuran Derivatives

Deng Yuan Li, Ke Ji Shi, Xiao Feng Mao, Guo Rong Chen, and Pei Nian Liu*

Shanghai Key Laboratory of Functional Materials Chemistry, Key Lab for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Meilong Road 130, Shanghai, 200237 China

Supporting Information



ABSTRACT: Transition metal-free cascade reactions of alkynols with imines have been achieved using potassium *tert*-butoxide as catalyst. Switching the reaction solvent gives two kinds of products in good yield: isoquinolin-1(2*H*)-one derivatives and dihydroisobenzofuran derivatives. This approach was used to generate the natural product 8-oxypseudopalmatine in a two-step procedure from commercially available starting materials. Additionally, multicomponent reactions of alkynols, aldehydes, and amines were also successfully achieved to afford isoquinolin-1(2*H*)-one derivatives.

INTRODUCTION

Direct transformations of alkynols have attracted extensive interest as methods for highly efficient synthesis of complex compounds, including bioactive compounds and natural products.[1] These reactions usually require transition metal catalysts,[2] such as tungsten,[3] gold,[4] platinum,[5] palladium,[6] and copper.[7] The reactions often involve cascade processes that start with intermolecular hydroalkoxylation of alkynes and continue via prins-type cyclization,[2c,g] Diels−Alder reaction,[4a−c] Povarov reaction,[5a] or other transformations.[2d−f,3a,b,4d−f,5c−g] Very few transition metal-free cascade reactions of alkynols have been reported.[8]

Isoquinolin-1(2*H*)-one derivatives show strong antihypertensive activity[9] and antitumor activity via different mechanisms.[10] In fact, isoquinolin-1(2*H*)-ones are the frequently used scaffolds for pharmaceutical drugs and natural products.[11] In recent years, diverse synthetic approaches to construct isoquinolin-1(2*H*)-one frameworks have been exploited,[12−16] while they are achieved usually by the cycloaddition reaction of benzamides and alkynes using transition metal catalysts such as Ni,[13] Cu,[14] Rh,[15] and Ru.[16] Thus, there remains a need for conceptually novel and versatile methodologies for the synthesis of isoquinolin-1(2*H*)-one from readily available building blocks with selective control of the substitution patterns.

Recently, we communicated the cascade reactions of *exo*-cyclic enol ethers with imines in the presence of potassium *tert*-butoxide (*t*-BuOK) to afford isoquinolin-1(2*H*)-one products in DMSO, or dihydroisobenzofuran products in THF (Scheme 1a).[17] Although the reactions gave good yields, the preparation of *exo*-cyclic enol ethers from alkynols usually require metal catalysts such as $Ln[N(SiMe_3)_2]_3$ (Ln = La, Sm, Y, Lu, Nd),[18] HgO[19] $Pd(OAc)_2/PdCl_2$,[20] Ag_2CO_3,[21] AuCl,[22] $Cu(OTf)_2$,[23] Cu(NHC)(Me) complex,[24] $\{M[N(SiMe_3)_2]_2\}$ (M = Ca, Sr, Ba),[25] or stoichiometric NaH,[26] which makes the protocol cumbersome. Herein we report the successful cascade reactions from alkynols and imines directly to afford the isoquinolin-1(2*H*)-ones in DMSO and dihydroisobenzofuran derivatives in THF with *t*-BuOK as the single catalyst (Scheme 1b). Moreover, the transition metal-free, three-component reactions of alkynols, aldehydes and amines were also successfully achieved to give isoquinolin-1(2*H*)-ones (Scheme 1c). The easy availability of alkynol starting materials makes this approach much more efficient and practical than the protocol via the previously reported functionalization of *exo*-cyclic enol ethers.

Received: March 18, 2014
Published: April 18, 2014

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

Scheme 1. Synthesis of Isoquinolin-1(2*H*)-ones and Dihydroisobenzofuran Derivatives

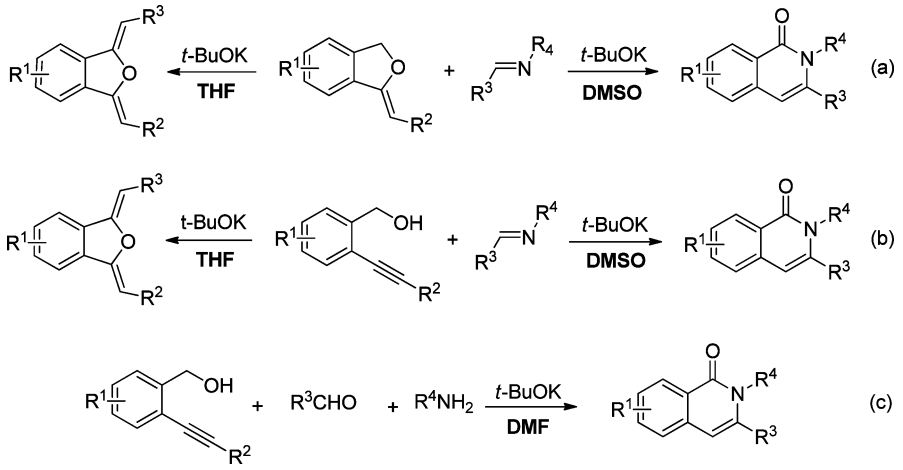
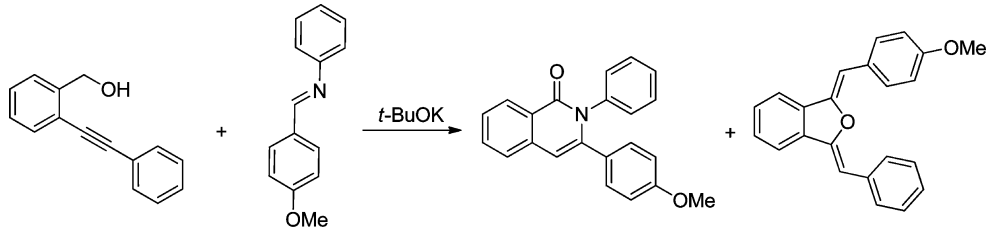


Table 1. Reactions of Alkynol 1a and Imine 2a under Various Conditions[a]



1a **2a** **3a** **4a**

entry	temp (°C)	time (h)	solvent	yield (**3a**, %)[b]	yield (**4a**, %)[b]
1	80	4	*t*-BuOH	0	0
2	80	4	dioxane	0	0
3	80	4	toluene	trace	trace
4	80	4	CH_3CN	trace	trace
5	80	4	NMP	trace	trace
6	80	4	DMF	44	15
7	80	4	DMSO	63	28
8	60	6	DMSO	76	trace
9	rt	6	DMSO	89	trace
10[c]	rt	6	DMSO	45	trace
11	80	4	THF	24	74
12[d]	80	4	THF	trace	89
13[d]	110	4	THF	trace	92
14[d]	rt	24	THF	29	17

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), *t*-BuOK (0.04 mmol), solvent (1.0 mL), unless otherwise noted. [b]Determined by ^{1}H NMR integration using $PhSiMe_3$ as the internal standard. [c]*t*-BuOK (0.02 mmol) was used. [d]*t*-BuOK (0.24 mmol) was used.

RESULTS AND DISCUSSION

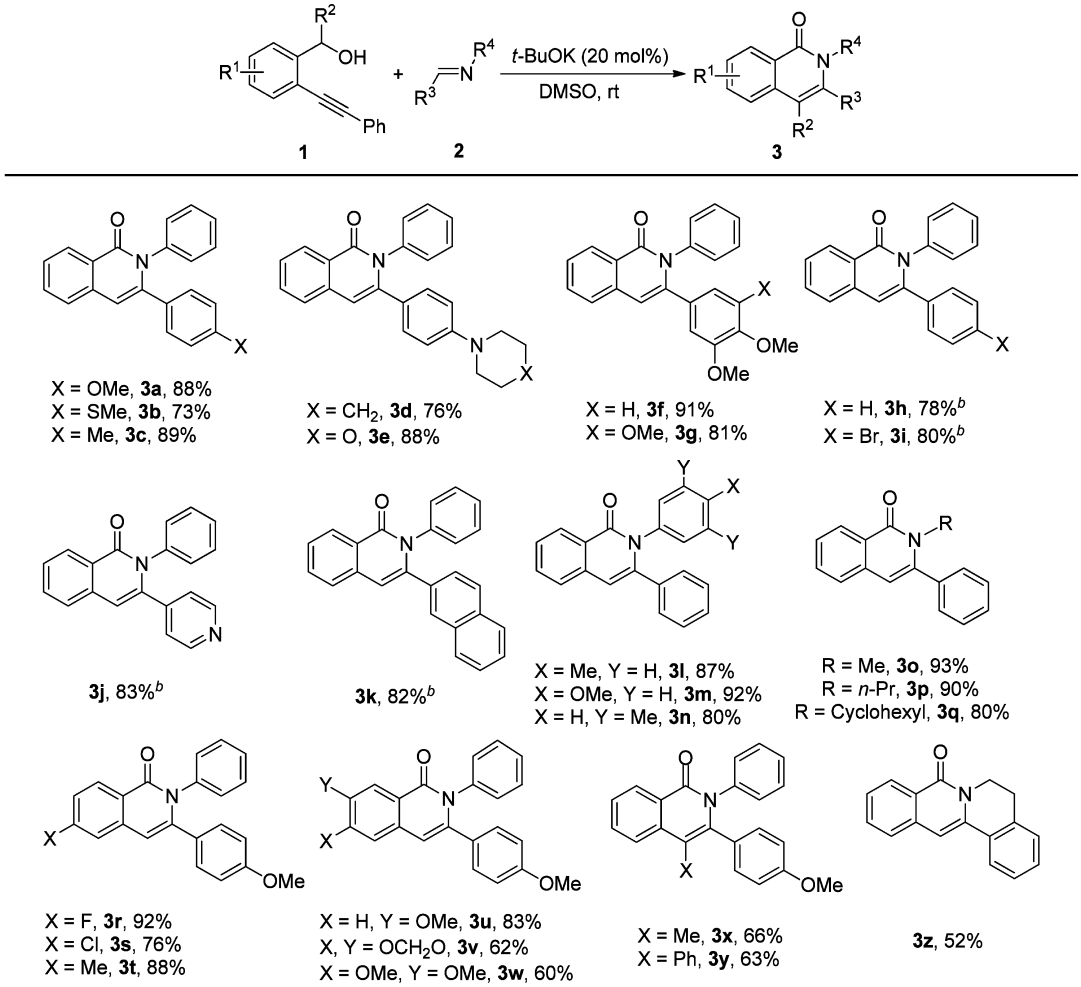
We began designing the new cascade processes by reacting alkynol **1a** and imine **2a** in the presence of *t*-BuOK (20 mol %) at 80 °C (oil bath temperature). As shown in Table 1, when *t*-BuOH, 1,4-dioxane, toluene, acetonitrile, or NMP were used as solvents, no desired products were obtained after 4 h (entries 1−5). When polar aprotic DMF was used as the solvent, the cascade reaction of **1a** and **2a** gave 3-(4-methoxyphenyl)-2-phenylisoquinolin-1(2*H*)-one (**3a**) in 44% yield, together with the dihydroisobenzofuran product **4a** in 15% yield (entry 6). Changing the solvent to DMSO increased the yield of **3a** to 63%, while also giving **4a** in 28% yield (entry 7). Decreasing the reaction temperature to 60 °C or room temperature substantially enhanced the yield of product **3a** to 76% or 89%, respectively, while formation of **4a** was inhibited (entries 8 and 9). Decreasing the catalyst loading of *t*-BuOK to 10 mol % remarkably reduced the yield of **3a** (entry 10).

Changing the reaction solvent from DMSO to THF led to the dihydroisobenzofuran product **4a** in 74% yield and dramatically decreased the yield of **3a** to 24% (entry 11). The fact that changing solvent generated different products from the same starting material illustrates the solvent dependence of the cascade reaction pathway. Further optimization of the reaction conditions by increasing the temperature and catalyst dosage of *t*-BuOK led to 92% yield after 4 h (entries 12 and 13). In contrast, performing the reaction at room temperature in THF gave only 17% yield even after 24 h (entry 14).

To explore the scope of the cascade reactions, a wide range of imines were reacted with various alkynols in DMSO at room

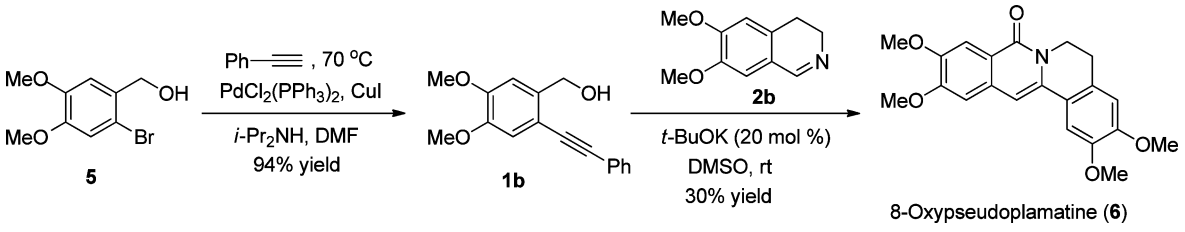
dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

Table 2. Reactions of Alkynols (1) and Imines (2) To Afford Isoquinolin-1(2*H*)-ones (3) in the Presence of *t*-BuOK[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), *t*-BuOK (0.04 mmol), DMSO (1.0 mL), room temperature, 6 h, unless otherwise noted. Isolated yields are shown. [b]THF was used as solvent at 80 °C for 6 h.

Scheme 2. Synthesis of the Natural Product 8-Oxypseudopalmatine (6)

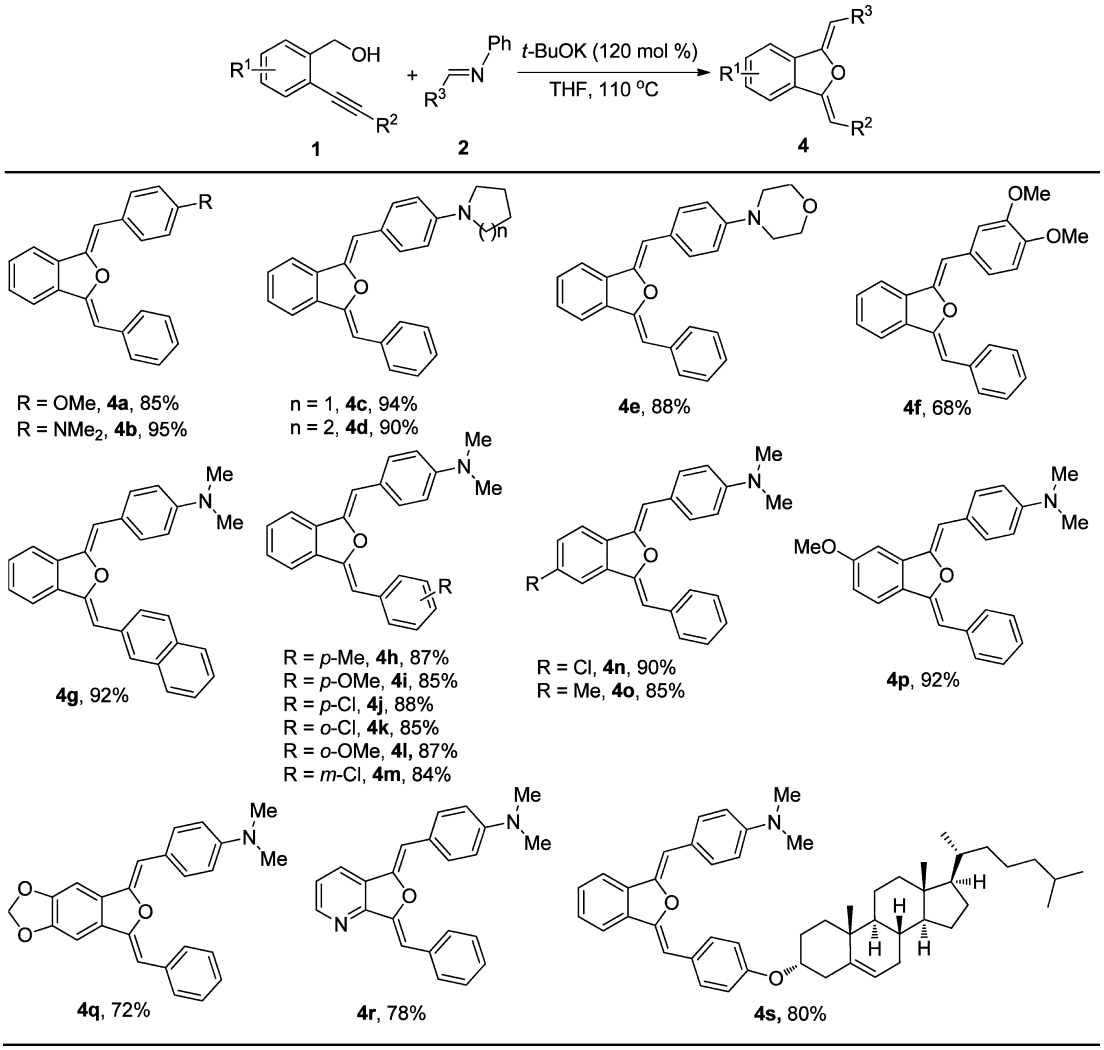


temperature with *t*-BuOK (20 mol %) as the catalyst. As shown in Table 2, *N*-phenylmethanimines substituted with benzene rings bearing electron-donating functional groups such as OMe, SMe, Me, piperidinyl, or morpholinyl reacted with **1a** to afford the products **3a**−**3g** in 73−91% isolated yields. These results indicate that electron-donating groups on the benzene ring do not inhibit the reaction. It is noteworthy that when *N*-phenylmethanimine was substituted with simple phenyl, 4-bromophenyl, or a pyridyl group or naphthyl group, the corresponding imines reacted with **1a** only in THF to give the products **3h**−**3k** in 78−83% yields. In contrast, when the 1-phenylmethanimine was substituted on the N atom with aromatic groups (4-Me-Ph, 4-MeO-Ph, 3,5-Me_2-Ph) or aliphatic groups (Me, *n*-propyl, cyclohexyl), the corresponding imines reacted smoothly with **1a** in DMSO to give products **3l**−**3q** in 80−93% yields.

Next the substrate scope with respect to alkynols was examined. Alkynols with various aryl substituents, such as 4-F-Ph, 4-Cl-Ph, 4-Me-Ph, and 5-MeO-Ph, participated in the cascade reactions to give **3r**−**3u** in 76−92% yields. In contrast, alkynols with a dimethoxyl or similar −OCH_2O- substituent generated **3v** and **3w** only in low yields of 62% or 63%, respectively. Alkynols carrying methyl or phenyl substitutions on the benzylic carbon reacted with imine **2a** to yield **3x** in 66% yield and **3y** in 63% yield. Interestingly, reacting **1a** with a cyclic

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

Table 3. Reactions of Alkynols (1) and Imines (2) To Afford Dihydroisobenzofuran Derivatives (4) in the Presence of *t*-BuOK[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), *t*-BuOK (0.24 mmol), THF (1.0 mL), 110 °C, 4 h. Isolated yields are shown.

imine produced the product **3z** in 52% yield, which represents the skeleton of protoberberine alkaloids.[27]

In order to demonstrate the synthetic usefulness of our cascade reaction, we applied it to the synthesis of the alkaloid 8-oxypseudopalmatine. Previous methods to synthesize this compound, which is found naturally in *Stephama suberosa* Forman (*Menispermaceae*),[28,29] require complicated starting materials[29b,e] and lengthy sequences with low overall yields.[29d] To use our approach, we first transformed the commercially available bromide **5** into alkynol **1b** in 94% yield, which was then reacted with the commercially available imine **2b** in DMSO with 20% mol *t*-BuOK as the catalyst. The alkaloid 8-oxypseudopalmatine **6** was obtained in 30% isolated yield (Scheme 2). In this way, our approach allowed the total synthesis of the natural product 8-oxypseudopalmatine in a two-step procedure and 28% total yield from commercial reagents, demonstrating the great potential of this cascade reaction for constructing complex compounds including natural products.

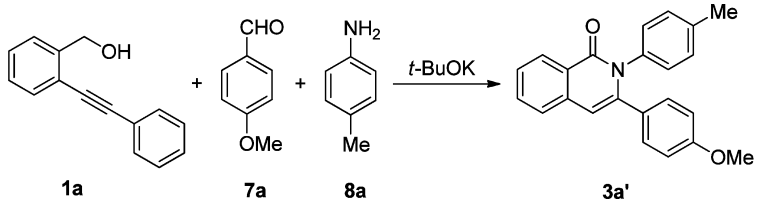
To explore the cascade reactions further, we reacted a variety of alkynols with various imines in THF at 110 °C (in sealed tubes) in the presence of 1.2 equiv of *t*-BuOK. A cascade cyclization/addition/elimination occurred to give the vinylogous analogues of 3-arylideneisobenzofuran-1(3*H*)-one compounds in the *Z*-configuration.[17] As shown in Table 3, various imines with electron-donating substituents on the benzene ring such as OMe, NMe_2, pyrrolidinyl, piperidinyl, or morpholinyl reacted efficiently with alkynol **1a** to give the corresponding products **4a**−**4f** in up to 95% yield.

We also tested the ability of a range of alkynols to react with *N*,*N*-dimethyl-4-((phenylimino)methyl)aniline **2c**. Alkynols carrying 2-OMe, 2-Cl, 3-Cl, 4-Me, 4-OMe, 4-Cl, or naphthyl at the R^2 position afforded **4g**−**4m** in 84−92% yield. Alkynols carrying 4-Me, 4-Cl, or 5-OMe at the R^1 position reacted with imine **2c** to give **4n**−**4p** in 85−92% yields. Alkynols with a cyclic −OCH_2O− substituent or pyridyl moiety smoothly reacted with **2c** to produce **4q** in 72% yield and **4r** in 78% yield, respectively. Finally, we applied the cascade reaction to the natural product derivatization: an alkynol derived from cholesterol reacted with imine **2c** in THF in the presence of *t*-BuOK, affording the desired product **4s** in 80% yield.

The multicomponent reaction (MCR) is a one-pot reaction with three or more starting materials to form a product, in which all or most of the atoms contribute to the newly constructed product.[30] Multicomponent reactions offer the unique opportunity of building up complex molecules with

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

Table 4. Optimization of Multicomponent Cascade Reaction of Alkynol 1a, Aldehyde 7a, and Amine 8a under Various Conditions[a]



entry	base	solvent	additive	temp (°C)	yied (**3a′**, %)[b]
1	*t*-BuOK	DMSO	—	rt	31
2	*t*-BuOK	DMF	—	rt	84 (81)[c]
3	*t*-BuOK	toluene	—	rt	0
4	*t*-BuOK	CH_2Cl_2	—	rt	0
5	*t*-BuOK	THF	—	rt	0
6	KHMDS	DMF	—	rt	40
7	KOH	DMF	—	rt	10
8	*t*-BuOK	DMF	—	60	75
9	*t*-BuOK	DMF	—	80	74
10	*t*-BuOK	DMF	—	0	68
12	*t*-BuOK	DMF	DCC	rt	44
13	*t*-BuOK	DMF	4 Å MS	rt	30
14	*t*-BuOK	DMF	18-Crown-6	rt	35

[a]Reaction conditions: **1a** (0.2 mmol), **7a** (0.24 mmol), **8a** (0.24 mmol), *t*-BuOK (0.24 mmol), solvent (1.0 mL), unless otherwise noted. [b]Determined by ^{1}H NMR integration using $PhSiMe_3$ as the internal standard. [c]Isolated yield is shown.

exceptional high synthetic efficiency and diversity with high stereoselectivity, from simple and easily available materials. Upon our interest in the development of multicomponent reactions, we explored the possibility of synthesizing isoquinolin-1(2*H*)-one derivatives in a one-pot reaction from alkynols, aldehydes, and amines.

Considered one equivalent of H_2O was generated to decompose one equivalent of *t*-BuOK in the MCR process, 1.2 equiv *t*-BuOK was used to initiate our studies for the reaction of alkynol **1a**, aldehyde **7a**, and aniline **8a** in DMSO at room temperature. As shown in Table 4, the reaction led to the formation of the desired product isoquinolin-1(2*H*)-one **3a′** in 31% yield (entry 1). This result encouraged us to explore the reaction conditions further. When the DMSO was changed to DMF, the yield of **3a′** drastically increased to 84% (entry 2). However, toluene, THF, and CH_2Cl_2 were inefficient for the reaction (entries 3−5). When the base *t*-BuOK was replaced by KHMDS or KOH, the results led to the decreased 40% or 10% yields of **3a′** (entries 6 and 7). The increase of reaction temperature was negative to the one-pot reaction (entries 8−10). With DCC, 4 Å MS was added to the reaction mixture, and worse results were observed (entries 12−13). Finally, the additive 18-Crown-6 also showed a negative effect to the reaction, forming product **3a′** (entry 14).

On the basis of the optimal conditions for the multicomponent reaction to form isoquinolin-1(2*H*)-ones **3**, the scope of this MCR was surveyed by probing the alkynols, the aldehydes, and the amines substrates (Table 5). A wide range of aldehydes substituted with various electron-donating substituents such as MeO, MeS, piperidinyl, or morpholinyl benzene ring were applicable to the reaction, giving the isoquinolin-1(2*H*)-ones product in 63−79% yields (**3a**, **3b**, **3d** and **3e**). Multisubstituted aldehydes were also tolerated to generate corresponding products **3f** and **3b′** in 68% and 69% yields, respectively. When benzaldehyde or 2-naphthaldehyde underwent the process with alkynol **1a** and aniline, the products **3h** and **3k** were obtained in 79% and 73% yields, respectively. Likewise, the reactions of alkynol **1a** with methyl- or methoxy-substituted amines and benzaldehydes proceeded smoothly to generate the corresponding products **3l**, **3m**, **3a′**, **3c′**, and **3d′** in 72−85% yields.

Subsequently, a variety of alkynols substituted with various substituents such as F, Cl, Me, MeO at position R^1 were examined in the reactions with aldehyde **7a** and aniline, giving the isoquinolin-1(2*H*)-ones product **3r−t** and **3u** in 67−75% yields. Interestingly, the steric hindered secondary alcohol with Me, Ph at position R^2 were applied to the reactions with aldehyde **7a** and aniline, the products **3x** and **3y** were obtained in 58% and 51% yields, respectively.

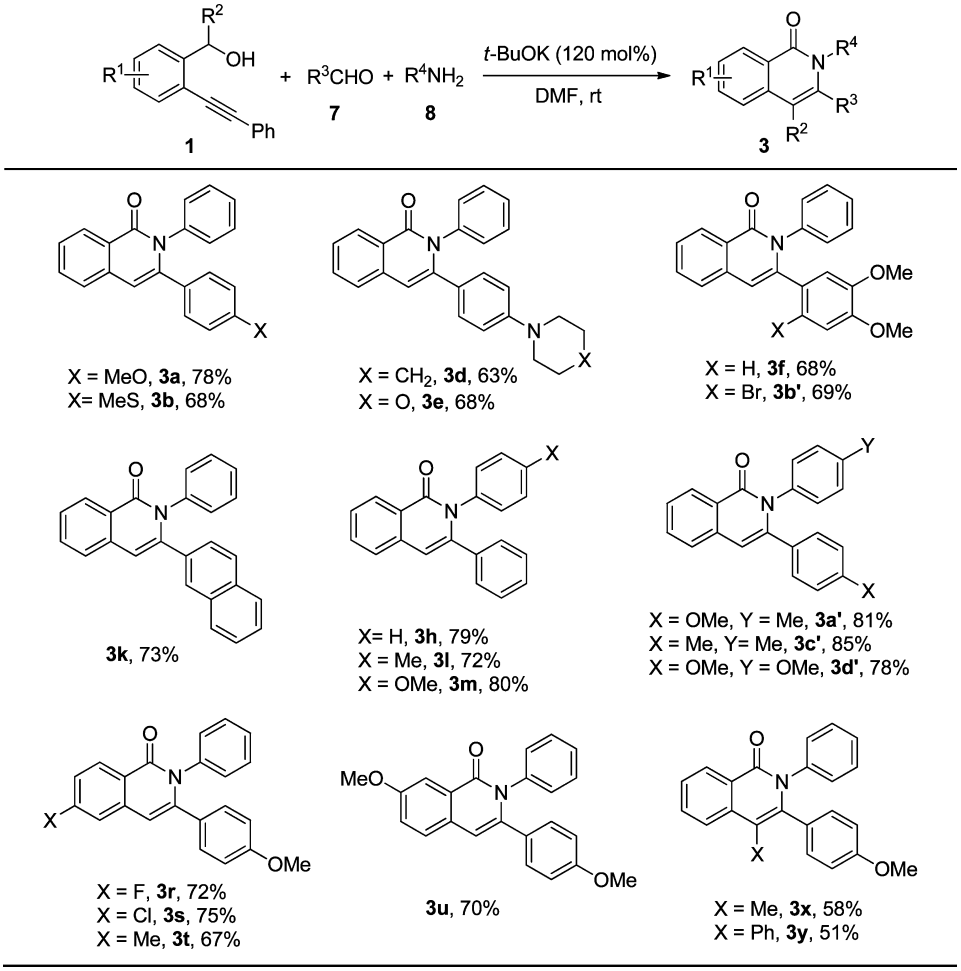
On the basis of the reaction mechanism described for the cascade reaction of *exo*-cyclic enol ether and imine catalyzed by *t*-BuOK,[17] we proposed the mechanism for the reactions of alkynols and imines as depicted in Scheme 3. First, deprotonation of alkynol by *t*-BuOK generates the benzyloxide anion **A**, which may undergo the nucleophilic attack on the alkynyl moiety to form the alkene anion **B**. After the protolysis, the *exo*-cyclic enol ether product **C** is formed, and this intermediate has been detected in the reactions. Then the deprotonated *exo*-cyclic enol ether **D** can be added to imine **2** to produce **E** and **F**. When the solvent is THF, proton H^1 of intermediate **F** can be selectively deprotonated to undergo the elimination to produce the product **4**. When the solvent is DMSO, H^2 of **F** can be deprotonated to undergo the intramolecular sp^3 C−O bond cleavage, leading to **I** after the proton exchange. After the intramolecular nucleophilic addition and C−C cleavage, the isoquinolin-1(2*H*)-one product **3** can be generated with Ar^1−CH_3 as the byproduct.

■ CONCLUSION

In summary, for the first time, we have developed the transition metal-free cascade reactions to convert alkynols and imines into derivatives of isoquinolin-1(2*H*)-one or dihydroisobenzofuran

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

Table 5. Reactions of Alkynols (1), Aldehydes (7) and Amines (8) To Afford Isoquinolin-1(2*H*)-ones (3) in the Presence of *t*-BuOK[a]



[a]Reaction conditions: **1** (0.25 mmol), **7** (0.30 mmol), **8** (0.30 mmol), *t*-BuOK (0.30 mmol), DMF (1.5 mL), room temperature, 8 h, unless otherwise noted. Isolated yields are shown.

using *t*-BuOK as the catalyst. The type of product depends on the solvent used: DMSO or THF, which demonstrated the solvent effect in the cascade process. On the basis of the cascade reaction, we accomplished the synthesis of alkaloid 8-oxypseudopalmatine in a two-step procedure, suggesting the usefulness of this method for constructing complex compounds including natural products. Additionally, the multicomponent reactions of alkynols, aldehydes, and amines were successfully achieved to afford the isoquinolin-1(2*H*)-ones. The cascade processes provide highly concise and effective protocols to the related complex compounds including the natural products.

EXPERIMENTAL SECTION

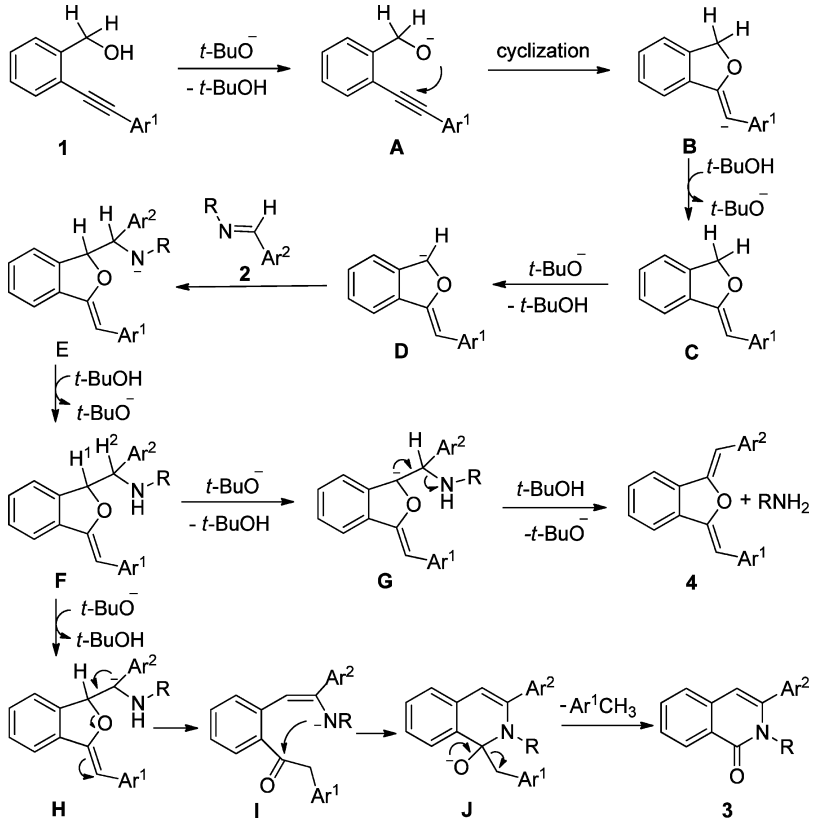
All manipulations were carried out under nitrogen atmosphere using standard Schlenk techniques, unless otherwise stated. Solvents DMSO and DMF were dried by the 4 Å molecular sieves and degassed with the nitrogen bubbling. THF was distilled under nitrogen from sodium benzophenone. Potassium *tert*-butoxide (1 M in THF) used in the catalytic reactions was purchased from a commercial source. The alkynols[23,31] and imines[32] were prepared according to the reported literature methods. Other chemicals were obtained from commercial sources, and were used without further purification. ^{1}H NMR spectra were recorded using TMS as internal standard. Chemical shifts in ^{13}C{^{1}H} NMR spectra were internally referenced to $CHCl_3$ (δ = 77.1 ppm).

Typical Procedure for the Cascade Reactions of Alkynols (1) and Imines (2) To Afford Isoquinolin-1(2*H*)-ones (3). To a mixture of alkynols (0.20 mmol) and imines (0.24 mmol) in DMSO (1.0 mL) at room temperature was added *t*-BuOK (0.04 mmol, 1 M in THF) via a syringe. The reaction mixture was stirred under nitrogen atmosphere, and the progress was monitored using TLC detection. After 6 h, the reaction mixture was diluted with saturated aq NH_4Cl (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with saturated brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent in vacuum, the crude product was purified by column chromatography on silica gel to afford the isoquinolin-1(2*H*)-one **3**. The products **3s**–**z** are new compounds, and the other products are known compounds.[17] (The syntheses of isoquinolin-1(2*H*)-ones **3a**–**z** were carried out using this procedure unless otherwise indicated.)

*3-(4-Methoxyphenyl)-2-phenylisoquinolin-1(2H)-one (**3a**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (58 mg, 88% yield). Mp: 187–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.45 (d, J = 8.00 Hz, 1H), 7.66–7.70 (m, 1H), 7.55 (d, J = 7.80 Hz, 1H), 7.48–7.56 (m, 1H) 7.27–7.30 (m, 2H), 7.19–7.21 (m, 1H), 7.12 (d, J = 7.24 Hz, 2H), 7.07 (d, J = 8.72 Hz, 2H), 6.68 (d, J = 8.72 Hz, 2H), 6.57 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.3, 159.3, 143.5, 139.3, 137.0, 132.8, 130.6, 129.5, 128.4, 127.7, 126.8, 126.0, 125.4, 113.3, 107.8, 55.3; HRMS (ESI, TOF) calcd for $C_{22}H_{18}NO_2^+$ [M + H]$^+$: 328.1332, found: 328.1333.

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602–4614

Scheme 3. Proposed Mechanism of the Cascade Reactions of Alkynols and Imines



3-(4-(Methylthio)phenyl)-2-phenylisoquinolin-1(2H)-one (**3b**). Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a white solid (50 mg, 73% yield). Mp: 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.45 (d, J = 8.04 Hz, 1H), 7.67−7.70 (m, 1H), 7.56 (d, J = 7.84 Hz, 1H), 7.49−7.53 (m, 1H), 7.27−7.31 (m, 2H), 7.22−7.24 (m, 1H), 7.12 (d, J = 7.84 Hz, 2H), 7.07 (d, J = 8.32 Hz, 2H), 7.02 (d, J = 8.44 Hz, 2H), 6.58 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.2, 142.2, 138.1, 138.0, 135.8, 131.9, 131.8, 128.6, 128.4, 127.8, 127.4, 126.8, 126.0, 125.1, 124.4, 124.3, 107.0, 14.3; HRMS (ESI, TOF) calcd for $C_{22}H_{18}NOS^+$ [M + H]$^+$: 344.1104, found: 344.1107.

2-Phenyl-3-(p-tolyl)isoquinolin-1(2H)-one (**3c**). Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a white solid (55 mg, 89% yield). Mp: 189−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.45 (d, J = 8.08 Hz, 1H), 7.66−7.70 (m, 1H), 7.55 (d, J = 7.84 Hz, 1H), 7.48−7.52 (m, 1H), 7.26−7.30 (m, 2H), 7.19−7.21 (m, 1H), 7.13 (d, J = 7.08 Hz, 2H), 7.04 (d, J = 8.12 Hz, 2H), 6.97 (d, J = 8.00 Hz, 2H), 6.58 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.3, 143.8, 139.3, 138.0, 137.0, 133.5, 132.9, 129.5, 129.2, 128.7, 128.6, 128.5, 127.7, 126.9, 126.1, 125.4, 107.9, 21.3; HRMS (ESI, TOF) calcd for $C_{22}H_{18}NO^+$ [M + H]$^+$: 312.1383, found: 312.1390.

2-Phenyl-3-(4-(piperidin-1-yl)phenyl)isoquinolin-1(2H)-one (**3d**). Column chromatography (eluent = petroleum ether/ethyl acetate 3:1 v/v) on silica gel gave a white solid (58 mg, 76% yield). Mp: 181−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.44 (d, J = 8.04 Hz, 1H), 7.64−7.68 (m, 1H), 7.54 (d, J = 7.76 Hz, 1H), 7.45−7.49 (m, 1H), 7.26−7.30 (m, 2H), 7.19−7.23 (m, 1H), 7.13 (d, J = 7.08 Hz, 2H), 7.00 (d, J = 8.84 Hz, 2H), 6.68 (d, J = 8.84 Hz, 2H), 6.57 (s, 1H), 3.12 (t, J = 5.64 Hz, 4H), 1.62−1.68 (m, 4H), 1.54−1.58 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.5, 151.4, 144.0, 139.5, 137.2, 132.8, 130.2, 129.5, 128.7, 128.4, 127.6, 126.6, 126.3, 126.0, 125.2, 114.9, 107.5, 49.8, 25.7, 24.3; HRMS (ESI, TOF) calcd for $C_{26}H_{25}N_2O^+$ [M + H]$^+$: 381.1961, found: 381.1961.

3-(4-Morpholinophenyl)-2-phenylisoquinolin-1(2H)-one (**3e**). Column chromatography (eluent = petroleum ether/ethyl acetate 2:1 v/v) on silica gel gave a white solid (67 mg, 88% yield). Mp: 282−284 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.44 (d, J = 8.08 Hz, 1H), 7.65−7.69 (m, 1H), 7.54 (d, J = 7.84 Hz, 1H), 7.47−7.51 (m, 1H), 7.27−7.31 (m, 2H), 7.20−7.24 (m, 1H), 7.14 (d, J = 7.04 Hz, 2H), 7.05 (d, J = 8.80 Hz, 2H), 6.67 (d, J = 8.84 Hz, 2H), 6.56 (s, 1H), 3.82 (t, J = 4.88 Hz, 4H), 3.11 (t, J = 4.84 Hz, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.4, 150.6, 143.7, 139.4, 137.1, 132.8, 130.3, 129.5, 128.8, 128.4, 127.7, 127.5, 126.8, 126.0, 125.3, 114.3, 107.7, 66.8, 48.6; HRMS (ESI, TOF) calcd for $C_{25}H_{23}N_2O_2^+$ [M + H]$^+$: 383.1754, found: 383.1760.

3-(3,4-Dimethoxyphenyl)-2-phenylisoquinolin-1(2H)-one (**3f**). Column chromatography (eluent = petroleum ether/ethyl acetate 3:1 v/v) on silica gel gave a white solid (65 mg, 91% yield). Mp: 182−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.45 (d, J = 8.04 Hz, 1H), 7.67−7.71 (m, 1H), 7.56 (d, J = 7.76 Hz, 1H), 7.48−7.52 (m, 1H), 7.27−7.32 (m, 2H), 7.20−7.24 (m, 1H), 7.15 (d, J = 7.12 Hz, 2H), 6.85−6.87 (m, 1H), 6.71 (d, J = 8.32 Hz, 1H), 6.62 (s, 1H), 6.51 (d, J = 2.00 Hz, 1H), 3.83 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.3, 148.9, 148.1, 143.4, 139.4, 136.9, 132.9, 129.5, 128.9, 128.8, 128.4, 127.8, 126.9, 126.0, 125.4, 122.1, 112.7, 110.4, 107.8, 55.9, 55.8; HRMS (ESI, TOF) calcd for $C_{23}H_{20}NO_3^+$ [M + H]$^+$: 358.1438, found: 358.1445.

2-Phenyl-3-(3,4,5-trimethoxyphenyl)isoquinolin-1(2H)-one (**3g**). Column chromatography (eluent = petroleum ether/ethyl acetate 2:1 v/v) on silica gel gave a foamed white solid (63 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.46 (d, J = 8.04 Hz, 1H), 7.68−7.72 (m, 1H), 7.58 (d, J = 7.76 Hz, 1H), 7.50−7.54 (m, 1H), 7.29−7.33 (m, 2H), 7.22−7.26 (m, 1H), 7.16 (d, J = 7.12 Hz, 2H), 6.65 (s, 1H), 6.36 (s, 2H), 3.78 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.2, 151.6, 142.4, 138.4, 136.9, 135.8, 132.0, 130.5, 128.3, 127.8, 127.5, 126.8, 126.1, 125.1, 124.5, 106.8, 106.0, 60.0, 55.2; HRMS (ESI, TOF) calcd for $C_{24}H_{22}NO_4^+$ [M + H]$^+$: 388.1543, found: 388.1544.

2,3-Diphenylisoquinolin-1(2H)-one (**3h**). The compound was prepared from (2-(phenylethynyl)phenyl)methanol (41.6 mg, 0.20 mmol) and *N*-benzylidene aniline (43.5 mg, 0.24 mmol) in the

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

presence of *t*-BuOK (0.04 mmol) in THF at 80 °C for 4 h. The product **3h** was obtained as a white solid (46 mg, 78% yield) after column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v). Mp: 177−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.47 (d, J = 8.08 Hz, 1H), 7.68−7.72 (m, 1H), 7.57 (d, J = 7.80 Hz, 1H), 7.50−7.54 (m, 1H), 7.25−7.29 (m, 2H), 7.11−7.22 (m, 8H), 6.61 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.2, 143.6, 139.1, 136.8, 136.3, 132.9, 129.5, 129.4, 128.7, 128.4, 128.1, 127.9, 127.8, 127.0, 126.1, 125.5, 108.0; HRMS (ESI, TOF) calcd for $C_{21}H_{16}NO^+$ $[M + H]^+$: 298.1226, found: 298.1232.

*3-(4-Bromophenyl)-2-phenylisoquinolin-1(2H)-one (**3i**).* The compound was prepared from (2-(phenylethynyl)phenyl)methanol (41.6 mg, 0.20 mmol) and *N*-(4-bromobenzylidene)aniline (62.4 mg, 0.24 mmol) in the presence of *t*-BuOK (0.04 mmol) in THF at 80 °C for 4 h. The product **3i** was obtained as a white solid (60 mg, 80% yield) after column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v). Mp: 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.46 (d, J = 8.04 Hz, 1H), 7.68−7.72 (m, 1H), 7.56 (d, J = 7.84 Hz, 1H), 7.51−7.53 (m, 1H), 7.28−7.32 (m, 4H), 7.22−7.24 (m, 1H), 7.11 (d, J = 7.08 Hz, 2H), 7.04 (d, J = 8.52 Hz, 2H), 6.58 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.1, 142.4, 138.9, 136.6, 135.2, 133.0, 131.2, 130.9, 129.4,129.0, 128.5, 128.0, 127.3, 126.2, 125.6, 122.5, 108.2; HRMS (ESI, TOF) calcd for $C_{21}H_{15}BrNO^+$ $[M + H]^+$: 376.0332, found: 376.0338.

*2-Phenyl-3-(pyridin-4-yl)isoquinolin-1(2H)-one (**3j**).* The compound was prepared from (2-(phenylethynyl)phenyl)methanol (41.6 mg, 0.20 mmol) and *N*-(pyridin-4-ylmethylene)aniline (43.7 mg, 0.24 mmol) in the presence of *t*-BuOK (0.04 mmol) in THF at 80 °C for 4 h. The product **3j** was obtained as a white solid (50 mg, 83% yield) after column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v). Mp: 201−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.48 (d, J = 8.04 Hz, 1H), 8.44 (d, J = 6.08 Hz, 2H), 7.71−7.75 (m, 1H), 7.55−7.61 (m, 2H), 7.29−7.33 (m, 2H), 7.24−7.27 (m, 1H), 7.14 (d, J = 7.00 Hz, 2H), 7.08 (d, J = 6.08 Hz, 2H), 6.64 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.9, 149.6, 143.9, 140.9, 138.5, 136.3, 133.1, 129.3, 129.0, 128.5, 128.3, 127.8, 126.5, 125.8, 123.6, 108.8; HRMS (ESI, TOF) calcd for $C_{20}H_{15}N_2O^+$ $[M + H]^+$: 299.1179, found: 299.1189.

*3-(Naphthalen-2-yl)-2-phenylisoquinolin-1(2H)-one (**3k**).* The compound was prepared from (2-(phenylethynyl)phenyl)methanol (41.6 mg, 0.20 mmol) and *N*-(naphthalen-2-ylmethylene)aniline (55.5 mg, 0.24 mmol) in the presence of *t*-BuOK (0.04 mmol) in THF at 80 °C for 4 h. The product **3k** was obtained as a white solid (57 mg, 82% yield) after column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v). Mp: 196−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.49 (d, J = Hz, 1H), 7.69−7.80 (m, 4H), 7.59 (d, J = 7.76 Hz, 1H), 7.51−7.56 (m, 2H), 7.44−7.49 (m, 2H), 7.12−7.25 (m, 6H), 6.71 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.2, 143.6, 139.1, 136.9, 133.9, 132.9, 132.8, 132.5, 129.5, 128.8, 128.6, 128.5, 128.1, 127.8, 127.7, 127.3, 127.1, 126.8, 126.6, 126.5, 126.2, 125.5, 108.5; HRMS (ESI, TOF) calcd for $C_{25}H_{18}NO^+$ $[M + H]^+$: 348.1383, found: 348.1383.

*3-Phenyl-2-(p-tolyl)isoquinolin-1(2H)-one (**3l**).* Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a white solid (54 mg, 87% yield). Mp: 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.46 (d, J = 8.04 Hz, 1H), 7.66−7.70 (m, 1H), 7.55 (d, J = 7.76 Hz, 1H), 7.48−7.50 (m, 1H), 7.16−7.19 (m, 5H), 7.06 (d, J = 8.20 Hz, 2H), 6.99 (d, J = 8.04 Hz, 2H), 6.58 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.3, 143.8, 137.5, 136.8, 136.5, 136.4, 132.8, 129.4, 129.3, 129.1, 128.4, 128.0, 127.9, 126.9, 126.1, 125.5, 107.9, 21.2; HRMS (ESI, TOF) calcd for $C_{22}H_{18}NO^+$ $[M + H]^+$: 312.1383, found: 312.1389.

*2-(4-Methoxyphenyl)-3-phenylisoquinolin-1(2H)-one (**3m**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (60 mg, 92% yield). Mp: 174−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.46 (d, J = 8.00 Hz, 1H), 7.66−7.70 (m, 1H), 7.55 (d, J = 7.84 Hz, 1H), 7.48−7.52 (m, 1H), 7.16−7.20 (m, 5H), 7.02 (d, J = 8.80 Hz, 2H), 6.70 (d, J = 8.76 Hz, 2H), 6.58 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.5, 158.7, 144.0, 136.8, 136.4, 132.8, 131.9, 130.3, 129.4, 128.4, 128.1, 128.0, 127.0, 126.1, 125.5, 114.0, 107.8, 55.4; HRMS (ESI, TOF) calcd for $C_{22}H_{18}NO_2^+$ $[M + H]^+$: 328.1332, found: 328.1336.

*2-(3,5-Dimethylphenyl)-3-phenylisoquinolin-1(2H)-one (**3n**).* Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a white solid (52 mg, 80% yield). Mp: 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.46 (d, J = 8.04 Hz, 1H), 7.66−7.70 (m, 1H), 7.55 (d, J = 7.80 Hz, 1H), 7.49−7.53 (m, 1H), 7.16−7.20 (m, 5H), 6.81 (s, 1H), 6.73 (s, 2H), 6.58 (s, 1H), 2.19 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.3, 143.9, 138.8, 138.3, 136.9, 136.4, 132.8, 129.5, 129.3, 128.5, 128.1, 127.8, 127.1, 126.9, 126.1, 125.5, 107.8, 21.2; HRMS (ESI, TOF) calcd for $C_{23}H_{20}NO^+$ $[M + H]^+$: 326.1539, found: 326.1545.

*2-Methyl-3-phenylisoquinolin-1(2H)-one (**3o**).* Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a white solid (44 mg, 93% yield). Mp: 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.46 (d, J = 7.72 Hz, 1H), 7.62−7.66 (m, 1H), 7.51 (s, 1H), 7.47−7.49 (m, 4H), 7.40−7.42 (m, 2H), 6.46 (s, 1H), 3.43 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.5, 144.0, 136.5, 136.3, 132.4, 129.1, 128.9, 128.8, 128.0, 126.7, 126.0, 125.0, 107.6, 34.3; HRMS (ESI, TOF) calcd for $C_{16}H_{14}NO^+$ $[M + H]^+$: 236.1070, found: 236.1056.

*3-Phenyl-2-propylisoquinolin-1(2H)-one (**3p**).* Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a pale-yellow oil (47 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.45 (d, J = 7.56 Hz, 1H), 7.61−7.65 (m, 1H), 7.45−7.50 (m, 5H), 7.39−7.43 (m, 2H), 6.40 (s, 1H), 3.90 (t, J = 7.76 Hz, 2H), 1.55−1.64 (m, 2H), 0.73 (t, J = 7.44 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.9, 143.8, 136.4, 132.3, 129.1, 128.9, 128.5, 128.0, 126.6, 125.8, 125.3, 107.8, 47.2, 22.2, 11.3; HRMS (ESI, TOF) calcd for $C_{18}H_{18}NO^+$ $[M + H]^+$: 264.1383, found: 264.1383.

*2-Cyclohexyl-3-phenylisoquinolin-1(2H)-one (**3q**).* Column chromatography (eluent = petroleum ether/ethyl acetate 25:1 v/v) on silica gel gave a white solid (48 mg, 80% yield). Mp: 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.41 (d, J = 7.92 Hz, 1H), 7.59−7.63 (m, 1H), 7.43−7.47 (m, 5H), 7.36−7.39 (m, 2H), 6.35 (s, 1H), 3.69−3.77 (m, 1H), 2.76−2.86 (m, 2H), 1.74 (d, J = 13.32 Hz, 2H), 1.65 (d, J = 14.68 Hz, 2H), 1.51 (d, J = 13.16 Hz, 1H), 1.18−1.28 (m, 1H), 0.89−0.99 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.5, 144.7, 137.4, 136.2, 132.2, 128.9, 128.6, 128.5, 127.8, 126.8, 126.6, 125.6, 108.2, 62.0, 28.9, 26.4, 25.2; HRMS (ESI, TOF) calcd for $C_{21}H_{22}NO^+$ $[M + H]^+$: 304.1696, found: 304.1699.

*6-Fluoro-3-(4-methoxyphenyl)-2-phenylisoquinolin-1(2H)-one (**3r**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (64 mg, 92% yield). Mp: 207−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.09 (dd, J_1 = 2.72 Hz, J_2 = 9.28 Hz, 1H), 7.54−7.57 (m, 1H), 7.39−7.44 (m, 1H), 7.26−7.29 (m, 2H), 7.20−7.24 (m, 1H), 7.11 (d, J = 7.16 Hz, 2H), 7.06 (d, J = 8.80 Hz, 2H), 6.68 (d, J = 8.76 Hz, 2H), 6.56 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.5 (d, J_{C-F} = 3.64 Hz), 161.6 (d, J_{C-F} = 247.01 Hz), 159.4, 142.9 (d, J_{C-F} = 2.40 Hz), 139.1, 133.6 (d, J_{C-F} = 2.13 Hz), 130.7, 129.4, 128.8, 128.4 (d, J_{C-F} = 21.90 Hz), 128.4, 127.9, 127.0 (d, J_{C-F} =8.01 Hz), 121.7 (d, J_{C-F} = 23.75 Hz), 113.6, 113.4, 107.1, 55.3; HRMS (ESI, TOF) calcd for $C_{22}H_{17}FNO_2^+$ $[M + H]^+$: 346.1238, found: 346.1245.

*6-Chloro-3-(4-methoxyphenyl)-2-phenylisoquinolin-1(2H)-one (**3s**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (55 mg, 76% yield). Mp: 218−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.41 (d, J = 2.16 Hz, 1H), 7.62 (dd, J_1 = 8.44 Hz, J_2 = 2.20 Hz, 1H), 7.49 (d, J = 8.44 Hz, 1H), 7.27−7.31 (m, 2H), 7.21−7.24 (m, 1H), 7.10 (d, J = 7.20 Hz, 2H), 7.06 (d, J = 8.76 Hz, 2H), 6.68 (d, J = 8.80 Hz, 2H), 6.54 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.3, 159.4, 143.9, 139.0, 135.4, 133.3, 132.7, 130.6, 129.4, 128.9, 128.4, 127.9, 127.6, 126.5, 113.4, 107.1, 55.3; HRMS (EI, TOF) calcd for $C_{22}H_{16}ClNO_2$ $[M]^+$: 361.0870, found: 361.0869.

*3-(4-Methoxyphenyl)-6-methyl-2-phenylisoquinolin-1(2H)-one (**3t**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (60 mg, 88% yield). Mp: 238−

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

240 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.24 (s, 1H), 7.50 (dd, J_1 = 8.24 Hz, J_2 = 1.72 Hz, 1H), 7.46 (d, J = 8.04 Hz, 1H), 7.26−7.30 (m, 2H), 7.19−7.22 (m, 1H), 7.11 (d, J = 7.16 Hz, 2H), 7.06 (d, J = 8.76 Hz, 2H), 6.68 (d, J = 8.76 Hz, 2H), 6,54 (s, 1H), 3.74 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.3, 159.2, 142.6, 139.5, 137.0, 134.7, 134.4, 130.7, 129.6, 129.0, 128.8, 128.0, 127.7, 126.0, 125.3, 113.3, 107.7, 55.3, 21.7; HRMS (EI, TOF) calcd for $C_{23}H_{19}NO_2$ $[M]^+$: 341.1416, found: 341.1415.

*7-Methoxy-3-(4-methoxyphenyl)-2-phenylisoquinolin-1(2H)-one (**3u**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (59 mg, 83% yield). Mp: 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.36 (d, J = 8.88 Hz, 1H), 7.25−7.29 (m, 2H), 7.18−7.22 (m, 1H), 7.11 (d, J = 7.20 Hz, 2H), 7.06−7.08 (m, 3H), 6.91 (d, J = 2.40 Hz, 1H), 6.68 (d, J = 8.72 Hz, 2H), 6.49 (s, 1H), 3.93 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.3, 163.0, 159.3, 144.2, 139.4, 139.1, 130.6, 129.6, 128.9, 128.7, 127.6, 119.2, 116.3, 113.3, 107.6, 106.9, 55.7. 55.3; HRMS (EI, TOF) calcd for $C_{23}H_{19}NO_3$ $[M]^+$: 357.1365, found: 357.1369.

*7-(4-Methoxyphenyl)-6-phenyl-[1,3]dioxolo[4,5-g]isoquinolin-5(6H)-one (**3v**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (46 mg, 62% yield). Mp: 228−230 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.79 (s, 1H), 7.26−7.29 (m, 2H), 7.18−7.22 (m, 1H), 7.11 (d, J = 7.48 Hz, 2H), 7.05 (d, J = 8.72 Hz, 2H), 6.89 (s, 1H), 6.67 (d, J = 8.76 Hz, 2H), 6.45 (s, 1H), 6.10 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.5, 159.2, 152.4, 147.9, 142.3, 139.4, 134.3, 130.7, 129.5, 128.8, 127.7, 120.8, 113.3, 107.7, 106.3, 103.9, 101.8, 55.3; HRMS (EI, TOF) calcd for $C_{23}H_{17}NO_4$ $[M]^+$: 371.1158, found: 371.1160.

*6,7-Dimethoxy-3-(4-methoxyphenyl)-2-phenylisoquinolin-1(2H)-one (**3w**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (46 mg, 60% yield). Mp: 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.83 (s, 1H), 7.26−7.30 (m, 2H), 7.19−7.23 (m, 1H), 7.12 (d, J = 7.08 Hz, 2H), 7.06 (d, J = 8.76 Hz, 2H), 6.91 (s, 1H), 6.69 (d, J = 8.76 Hz, 2H), 6.50 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.7, 159.2, 154.0, 149.4, 142.2, 139.5, 132.5, 130.7, 129.6, 129.0, 128.7, 127.6, 119.2, 113.3, 108.3, 107.4, 106.1, 56.3, 55.3; HRMS (ESI, TOF) calcd for $C_{24}H_{22}NO_4^+$ $[M + H]^+$: 388.1543, found: 388.1541.

*3-(4-Methoxyphenyl)-4-methyl-2-phenylisoquinolin-1(2H)-one (**3x**).* Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a white solid (45 mg, 66% yield). Mp: 239−241 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.54 (d, J = 7.96 Hz, 1H), 7.76 (d, J = 3.56 Hz, 2H), 7.53−7.57 (m, 1H), 7.20−7.24 (m, 2H), 7.12−7.16 (m, 1H), 7.02 (d, J = 7.20 Hz, 2H), 6.96 (d, J = 8.68 Hz, 2H), 6.70 (d, J = 8.68 Hz, 2H), 3.73 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.8, 158.9, 140.1, 140.0, 137.8, 132.8, 131.9, 129.6, 128.7, 127.8, 127.6, 126.8, 125.9, 123.5, 113.3, 110.9, 55.2, 15.1; HRMS (EI, TOF) calcd for $C_{23}H_{19}NO_2$ $[M]^+$: 341.1416, found: 341.1418.

*3-(4-Methoxyphenyl)-2,4-diphenylisoquinolin-1(2H)-one (**3y**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (51 mg, 63% yield). Mp: 213−215 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.56 (d, J = 7.84 Hz, 1H), 7.57−7.60 (m, 1H), 7.50−7.54 (m, 1H), 7.20−7.26 (m, 5H), 7.12−7.18 (m, 4H), 7.10 (d, J = 7.40 Hz, 2H), 6.78 (d, J = 8.64 Hz, 2H), 6.42 (d, J = 8.64 Hz, 2H), 3.60 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.9, 158.3, 141.0, 139.7, 137.8, 136.7, 132.6, 132.4, 131.7, 129.6, 128.8, 128.4, 128.1, 127.6, 127.3, 126.9, 125.7, 125.6, 119.2, 112.7, 55.0; HRMS (ESI, TOF) calcd for $C_{28}H_{22}NO_2^+$ $[M + H]^+$: 404.1645, found: 404.1649.

*5H-Isoquinolino[3,2-a]isoquinolin-8(6H)-one (**3z**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (26 mg, 52%). Mp: 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.45 (d, J = 8.08 Hz, 1H), 7.83−7.85 (m, 1H), 7.62−7.66 (m, 1H), 7.58 (d, J = 7.56 Hz, 1H), 7.45−7.49 (m, 1H), 7.36−7.38 (m, 2H), 7.27−7.29 (m, 1H), 7.04 (s, 1H), 4.39 (t, J = 6.12 Hz, 2H), 3.03 (t, J = 6.16 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 162.3, 137.5, 136.7, 135.6, 132.4, 130.4, 129.4, 128.1, 127.6, 126.7, 126.4, 125.2, 125.1, 103.0, 39.8, 28.7; HRMS (ESI, TOF) calcd for $C_{17}H_{14}NO^+$ $[M + H]^+$: 248.1070, found: 248.1069.

*(4,5-Dimethoxy-2-(phenylethynyl)phenyl)methanol (**1b**).* To a mixture of the (2-bromo-4,5-dimethoxyphenyl)methanol (494.2 mg, 2.0 mmol) in DMF (10 mL) at room temperature were added $PdCl_2(PPh_3)_2$ (7.1 mg, 0.01 mmol) and CuI (1.9 mg, 0.01 mmol) under nitrogen. After the reaction mixture was stirred for 5 min, *N*,*N*-diisopropylamine (815.2 g, 8.0 mmol) was added via a syringe. The reaction mixture was then heated to 70 °C. A solution of the phenylacetylene (1.5 equiv) in DMF (5 mL) was added dropwise over 10 min, the mixture was allowed to stir at 70 °C for several hours, and the progress was monitored using TLC detection. After 2 h, the reaction mixture was washed with saturated aq NH_4Cl and brine and then extracted with EtOAc (3 × 25 mL). The combined organic extract was washed with saturated brine (50 mL) and dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent in vacuum, the crude product was purified by column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel to give **1b** as a white solid (504 mg, 94% yield). Mp: 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.51−7.53 (m, 2H), 7.34−7.37 (m, 3H), 7.02 (d, J = 8.32 Hz, 2H), 4.86 (d, J = 6.40 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 2.06 (t, J = 6.12 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 149.7, 148.1, 136.3, 131.5, 128.5, 128.4, 123.2, 114.5, 113.2, 110.7, 92.8, 87.0, 63.8, 56.2, 56.0; HRMS (EI, TOF) calcd for $C_{17}H_{16}O_3$ $[M]^+$: 268.1099, found: 268.1100.

*2,3,10,11-Tetramethoxy-5H-isoquinolino[3,2-a]isoquinolin-8(6H)-one (**6**).* The compound was prepared from (4,5-dimethoxy-2-(phenylethynyl)phenyl)methanol (**1b**, 134.2 mg, 0.50 mmol) and 6,7-dimethoxy-3,4-dihydroisoquinoline (**2b**, 114.7 mg, 0.60 mmol) in the presence of *t*-BuOK (0.10 mmol) in DMSO at room temperature for 48 h. The product **6** was obtained as a white solid (55 mg 30% yield) after column chromatography (eluent = petroleum ether/ethyl acetate 1:2 v/v). Mp: 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.81 (s, 1H), 7.25 (s, 1H), 6.94 (s, 1H), 6.84 (s, 1H), 6.75 (s, 1H), 4.37 (t, J = 6.12 Hz, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H), 2.95 (t, J = 6.12 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 161.6, 153.6, 150.2, 149.1, 148.5, 136.3, 132.3, 128.5, 122.6, 118.7, 110.6, 107.9, 107.7, 106.0, 101.3, 56.4, 56.3, 56.2, 39.9, 28.2; HRMS (EI, TOF) calcd for $C_{21}H_{21}NO_5$ $[M]^+$: 367.1420, found: 367.1418.

Typical Procedure for the Reactions of Alkynols (1) and Imines (2) To Afford Dihydroisobenzofuran Derivatives (4). To a mixture of alkynols (0.20 mmol) and imines (0.24 mmol) in THF (1.0 mL) at room temperature was added *t*-BuOK (0.24 mmol, 1 M in THF) via a syringe. The reaction mixture was then heated to 110 °C in a sealed tube under nitrogen atmosphere and stirred for 4 h. After the mixture cooled to ambient temperature, it was diluted with saturated aq NH_4Cl (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with saturated brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent in vacuum, the crude product was purified by column chromatography on silica gel to afford the dihydroisobenzofuran derivatives **4**. The products **4j** and **4m**−**4s** are new compounds and the other products are known compounds.[17] (The syntheisis of dihydroisobenzofuran derivatives **4a**−**4s** were carried out using this procedure unless otherwise indicated.)

*(1Z,3Z)-1-Benzylidene-3-(4-methoxybenzylidene)-1,3-dihydroisobenzofuran(**4a**).* Column chromatography (eluent = petroleum ether/ethyl acetate 50:1 v/v) on silica gel gave a yellow solid (55 mg, 85% yield). Mp: 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.90 (d, J = 7.40 Hz, 2H), 7.86 (d, J = 8.84 Hz, 2H), 7.61−7.66 (m, 2H), 7.39−7.45 (m, 4H), 7.23−7.27 (m, 1H), 6.97 (d, J = 8.84 Hz, 2H), 6.17 (s, 1H), 6.15 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 158.5, 152.0, 150.5, 135.3, 134.1, 133.6, 129.9, 129.3, 128.9, 128.7, 128.4, 127.9, 126.5, 120.0, 119.7, 114.2, 99.6, 99.2, 55.5; HRMS (ESI, TOF) calcd for $C_{23}H_{19}O_2^+$ $[M + H]^+$: 327.1380, found: 327.1389.

*4-((Z)-((Z)-3-Benzylidene-isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (**4b**).* Column chromatography (eluent =

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

petroleum ether/ethyl acetate 40:1 v/v) on silica gel gave a yellow solid (64 mg, 95% yield). Mp: 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.92 (d, J = 7.32 Hz, 2H), 7.82 (d, J = 8.88 Hz, 2H), 7.60−7.64 (m, 2H) 7.36−7.45 (m, 4H), 7.222−7.25 (m, 1H), 6.79 (d, J = 8.92 Hz, 2H), 6.14 (s, 2H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.3, 149.3, 135.6, 134.4, 133.3, 129.8, 129.2, 128.6, 128.4, 126.2, 123.5, 119.9, 119.4, 112.5, 100.5, 98.5, 40.6; HRMS (ESI, TOF) calcd for $C_{24}H_{22}NO^+$ [M + H]$^+$: 340.1696, found: 340.1705.

*1-(4-((Z)-((Z)-3-Benzylidene-isobenzofuran-1(3H)-ylidene)-methyl)phenyl)pyrrolidine (**4c**).* Column chromatography (eluent = petroleum ether/ethyl acetate 30:1 v/v) on silica gel gave a yellow solid (69 mg, 94% yield). Mp: 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.93 (d, J = 7.36 Hz, 2H), 7.82 (d, J = 8.76 Hz, 2H), 7.59−7.64 (m, 2H), 7.33−7.45 (m, 4H), 7.21−7.26 (m, 1H), 6.63 (d, J = 8.84 Hz, 2H), 6.14 (s, 1H), 6.13 (s, 1H), 3.37 (t, J = 6.52 Hz, 4H), 2.04 (t, J = 6.52 Hz, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.4, 148.8, 146.8, 135.6, 134.6, 133.2, 129.9, 129.1, 128.6, 128.3, 128.2, 126.1, 122.4, 119.9, 119.3, 111.8, 100.9, 98.3, 47.7, 25.6; HRMS (ESI, TOF) calcd for $C_{26}H_{24}NO^+$ [M + H]$^+$: 366.1852, found: 366.1860.

*1-(4-((Z)-((Z)-3-Benzylidene-isobenzofuran-1(3H)-ylidene)-methyl)phenyl)piperidine (**4d**).* Column chromatography (eluent = petroleum ether/ethyl acetate 30:1 v/v) on silica gel gave a yellow solid (68 mg, 90% yield). Mp: 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.91 (d, J = 7.32 Hz, 2H), 7.82 (d, J = 8.84 Hz, 2H), 7.60−7.65 (m, 2H), 7.37−7.45 (m, 4H), 7.22−7.26 (m, 1H), 6.98 (d, J = 8.88 Hz, 2H), 6.15 (s, 1H), 6.14 (s, 1H), 3.25 (t, J = 5.60 Hz, 4H), 1.71- 1.77 (m, 4H), 1.59−1.64 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.2, 150.7, 149.9, 135.4, 134.3, 133.5, 129.6, 129.2, 128.6, 128.4, 126.3, 125.7, 119.9, 119.5, 116.1, 100.2, 98.8, 50.3, 25.9, 24.5; HRMS (ESI, TOF) calcd for $C_{27}H_{26}NO^+$ [M + H]$^+$: 380.2009, found: 380.2017.

*4-(4-((Z)-((Z)-3-Benzylidene-isobenzofuran-1(3H)-ylidene)-methyl)phenyl)morpholine (**4e**).* Column chromatography (eluent = petroleum ether/ethyl acetate 30:1 v/v) on silica gel gave a yellow solid (67 mg, 88% yield). Mp: 192−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.91 (d, J = 7.52 Hz, 2H), 7.85 (d, J = 8.80 Hz, 2H), 7.61−7.66 (m, 2H), 7.39−7.45 (m, 4H), 7.23−7.26 (m, 1H), 6.97 (d, J = 8.84 Hz, 2H), 6.17 (s, 1H), 6.14 (s, 1H), 3.90 (t, J = 4.80 Hz, 4H), 3.24 (t, J = 7.76 Hz, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.1, 150.3, 149.8, 135.4, 134.2, 133.6, 129.6, 129.2, 128.8, 128.6, 128.4, 126.8, 126.4, 120.0, 119.6, 115.5, 99.8, 99.1, 67.0, 49.1; HRMS (ESI, TOF) calcd for $C_{26}H_{24}NO_2^+$ [M + H]$^+$: 382.1802, found: 382.1803.

*(1Z,3Z)-1-Benzylidene-3-(3,4-dimethoxybenzylidene)-1,3-dihydroisobenzofuran (**4f**).* Column chromatography (eluent = petroleum ether/ethyl acetate 15:1 v/v) on silica gel gave a yellow solid (48 mg, 68% yield). Mp: 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.89 (d, J = 7.32 Hz, 2H), 7.62−7.67 (m, 3H), 7.35−7.43 (m, 4H), 7.29−7.31 (m, 1H), 7.21−7.25 (m, 1H), 6.92 (d, J = 8.36 Hz, 1H), 6.18 (s, 1H), 6.16 (s, 1H), 4.00 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.1, 150.5, 149.1, 148.2, 135.3, 134.1, 133.7, 129.3, 129.0, 128.6, 128.4, 128.2, 126.6, 121.9, 119.9, 119.6, 111.3, 111.2, 100.0, 99.3, 56.3, 56.0; HRMS (ESI, TOF) calcd for $C_{24}H_{21}O_3^+$ [M + H]$^+$: 357.1485, found: 357.1495.

*N,N-Dimethyl-4-((Z)-((Z)-3-(naphthalen-2-ylmethylene)-isobenzofuran-1(3H)-ylidene)methyl)aniline (**4g**).* Column chromatography (eluent = petroleum ether/ethyl acetate 50:1 v/v) on silica gel gave a yellow solid (72 mg, 92% yield). Mp: 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.55 (s, 1H),7.90−7.94 (m, 4H), 7.82−7.87 (m, 2H), 7.67−7.69 (m, 1H), 7.62−7.64 (m, 1H), 7.38−7.50 (m, 4H), 6.86 (d, J = 8.84 Hz, 2H), 6.29 (s, 1H), 6.19 (s, 1H), 3.06 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 151.7, 148.4, 148.3, 133.4, 133.0, 132.3, 132.1, 131.2, 128.8, 128.2, 127.4, 127.1, 126.9, 126.7, 126.2, 125.7, 125.1, 124.5, 122.5, 118.9, 118.4, 111.5, 99.7, 97.6, 39.6; HRMS (ESI, TOF) calcd for $C_{28}H_{24}NO^+$ [M + H]$^+$: 390.1852, found: 390.1861.

*N,N-Dimethyl-4-((Z)-((Z)-3-(4-methylbenzylidene)isobenzofuran-1(3H)-ylidene)methyl)aniline (**4h**).* Column chromatography (eluent = petroleum ether/ethyl acetate 30:1 v/v) on silica gel gave a yellow solid (62 mg, 87% yield) Mp: 162−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.82 (d, J = 8.56 Hz, 4H), 7.59−7.63 (m, 2H), 7.35−7.38 (m, 2H), 7.25 (d, J = 8.60 Hz, 2H), 6.80 (d, J = 8.92 Hz, 2H), 6.13 (s, 1H), 6.12 (s, 1H), 3.04 (s, 6H), 2.40 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 151.7, 149.4, 149.3, 136.0, 134.4, 133.5, 132.7, 129.7, 129.4, 129.0, 128.4, 128.3, 123.6, 119.8, 119.4, 112.6, 100.2, 98.6, 40.7, 21.5; HRMS (ESI, TOF) calcd for $C_{25}H_{24}NO^+$ [M + H]$^+$: 354.1852, found: 354.1855.

*4-((Z)-((Z)-3-(4-Methoxybenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (**4i**).* Column chromatography (eluent = petroleum ether/ethyl acetate 30:1 v/v) on silica gel gave a yellow solid (63 mg, 85% yield). Mp: 156−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.87 (d, J = 8.80 Hz, 2H), 7.81 (d, J = 8.88 Hz, 2H), 7.59−7.62 (m, 2H), 7.35−7.37 (m, 2H), 6.98 (d, J = 8.84 Hz, 2H), 6.80 (d, J = 8.64 Hz, 2H), 6.12 (s, 1H), 6.10 (s, 1H), 3.88 (s, 3H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 158.1, 150.9, 149.5, 149.2, 134.2, 133.6, 129.6, 128.8, 128.4, 123.7, 119.6, 119.4, 114.1, 112.6, 99.9, 98.3, 55.5, 40.7; HRMS (ESI, TOF) calcd for $C_{25}H_{24}NO_2^+$ [M + H]$^+$: 370.1802, found: 370.1810.

*4-((Z)-((Z)-3-(4-Chlorobenzylidene)isobenzofuran-1(3H)-ylidene)-methyl)-N,N-dimethylaniline (**4j**).* Column chromatography (eluent = petroleum ether/ethyl acetate 30:1 v/v) on silica gel gave a pale-yellow solid (66 mg, 88% yield). Mp: 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.84 (d, J = 8.60 Hz, 2H), 7.78 (d, J = 8.88 Hz, 2H), 7.60−7.63 (m, 2H), 7.35−7.42 (m, 4H), 6.79 (d, J = 8.92 Hz, 2H), 6.16 (s, 1H), 6.08 (s, 1H), 3.04 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.7, 149.4, 149.2, 134.5, 134.2, 133.1, 131.4, 129.8, 129.4, 128.7, 128.4, 123.3, 119.9, 119.4, 112.6, 100.9, 97.3, 40.6; HRMS (EI, TOF) calcd for $C_{24}H_{20}ClNO$ [M]$^+$: 373.1233, found: 373.1230.

*4-((Z)-((Z)-3-(2-Chlorobenzylidene)isobenzofuran-1(3H)-ylidene)-methyl)-N,N-dimethylaniline (**4k**).* Column chromatography (eluent = petroleum ether/ethyl acetate 40:1 v/v) on silica gel gave a yellow solid (64 mg, 85% yield). Mp: 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.55 (dd, J_1= 7.96 Hz, J_2 = 1.12 Hz, 1H), 7.78 (d, J = 8.80 Hz, 2H), 7.72 (d, J = 7.04 Hz, 1H), 7.61 (d, J = 7.16 Hz, 1H), 7.37−7.44 (m, 4H), 7.14−7.18 (m, 1H), 6.76 (d, J = 8.84 Hz, 2H), 6.55 (s, 1H), 6.16 (s, 1H), 3.02 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 153.6, 149.4, 149.0, 134.6, 133.4, 133.2, 132.4, 129.8, 129.7, 129.6, 128.5, 127.1, 126.8, 123.2, 120.4, 119.4, 112.5, 101.2, 94.0, 40.6; HRMS (ESI, TOF) calcd for $C_{24}H_{21}ClNO^+$ [M + H]$^+$: 374.1306, found: 374.1306.

*4-((Z)-((Z)-3-(2-Methoxybenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (**4l**).* Column chromatography (eluent = petroleum ether/ethyl acetate 30:1 v/v) on silica gel gave a yellow solid (64 mg, 87% yield). Mp: 182−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.50 (dd, J_1 = 7.72 Hz, J_2 = 1.48 Hz, 1H), 7.81 (d, J = 8.84 Hz, 2H), 7.69−7.71 (m, 1H), 7.58−7.60 (m, 1H), 7.35−7.38 (m, 2H), 7.21−7.23 (m, 1H), 7.10−7.13 (m, 1H), 6.93 (d, J = 8.08 Hz, 1H), 6.78 (d, J = 8.88 Hz, 2H), 6.59 (s, 1H), 6.12 (s, 1H), 3.92 (s, 3H), 3.02 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 156.3, 152.4, 149.4, 149.3, 134.4, 133.8, 129.7, 129.2, 129.0, 128.3, 127.3, 124.6, 123.7, 120.9, 120.2, 119.3, 112.6, 110.6, 100.2, 92.2, 55.8, 40.6; HRMS (ESI, TOF) calcd for $C_{25}H_{24}NO_2^+$ [M + H]$^+$: 370.1802, found: 370.1775.

*4-((Z)-((Z)-3-(3-Chlorobenzylidene)isobenzofuran-1(3H)-ylidene)-methyl)-N,N-dimethylaniline (**4m**).* Column chromatography (eluent = petroleum ether/ethyl acetate 50:1 v/v) on silica gel gave a yellow solid (63 mg, 84% yield). Mp: 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.22 (t, J = 1.68 Hz, 1H), 7.82 (d, J = 8.88 Hz, 2H), 7.63 (dd, J_1 = 7.28 Hz, J_2 = 4.48 Hz, 2H), 7.52 (d, J = 7.76 Hz, 1H), 7.35−7.43 (m, 2H), 7.29−7.33 (m, 1H), 7.20 (dd, J_1= 7.96 Hz, J_2 = 1.00 Hz, 1H), 6.84 (d, J = 8.80 Hz, 2H), 6.19 (s, 1H), 6.08 (s, 1H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 153.3, 149.5, 149.0, 137.4, 134.6, 134.5, 132.9, 129.8, 129.6, 129.5, 128.4, 127.8, 126.5, 126.0, 123.1, 120.0 119.4, 112.7, 101.3, 97.1, 40.6; HRMS (EI, TOF) calcd for $C_{24}H_{20}ClNO$ [M]$^+$: 373.1233, found: 373.1229.

*4-((Z)-((Z)-3-Benzylidene-5-chloroisobenzofuran-1(3H)-ylidene)-methyl)-N,N-dimethylaniline (**4n**).* Column chromatography (eluent = petroleum ether/ethyl acetate 50:1 v/v) on silica gel gave a yellow

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

solid (67 mg, 90% yield). Mp: 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.90 (d, J = 7.48 Hz, 2H), 7.79 (d, J = 8.88 Hz, 2H), 7.60 (d, J = 1.48 Hz, 1H), 7.51 (d, J = 8.32 Hz, 1H), 7.42−7.46 (m, 2H), 7.34 (dd, J_1 = 8.32 Hz, J_2 = 1.72 Hz, 1H), 7.24−7.27 (m, 1H), 6.78 (d, J = 8.88 Hz, 2H), 6.11 (s, 2H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 151.1, 149.4, 148.4, 135.1, 134.9, 134.2, 132.9, 129.8, 129.5, 128.7, 128.5, 126.6, 123.1, 120.5, 119.9, 112. 5, 101.1, 99.6, 40.6; HRMS (EI, TOF) calcd for $C_{24}H_{20}ClNO$ $[M]^+$: 373.1233, found: 373,1234.

*4-((Z)-((Z)-3-Benzylidene-5-methylisobenzofuran-1(3H)-ylidene)-methyl)-N,N-dimethylaniline (**4o**).* Column chromatography (eluent = petroleum ether/ethyl acetate 50:1 v/v) on silica gel gave a yellow solid (60 mg, 85% yield). Mp: 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.91 (d, J = 7.84 Hz, 2H), 7.81 (d, J = 8.72 Hz, 2H), 7.50 (d, J = 7.96 Hz, 1H), 7.41−7.44 (m, 3H), 7.20−7.25 (m, 2H), 6.79 (d, J = 8.64 Hz, 2H), 6.11 (s, 1H), 6.08 (s, 1H), 3.02 (s, 6H), 2.45 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.3, 149.5, 149.2, 138.6, 135.7, 133.7, 132.2, 130.6, 129.6, 128.6, 128.4, 126.1, 123.8, 120.0, 119.2, 112.7, 99.7, 98.3, 40.7, 21.8; HRMS (EI, TOF) calcd for $C_{25}H_{23}NO$ $[M]^+$: 353.1780, found: 353.1781.

*4-((Z)-((Z)-3-Benzylidene-6-methoxyisobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (**4p**).* Column chromatography (eluent = petroleum ether/ethyl acetate 25:1 v/v) on silica gel gave a yellow solid (68 mg, 92% yield). Mp: 177−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.88 (d, J = 7.52 Hz, 2H), 7.82 (d, J = 8.84 Hz, 2H), 7.52 (d, J = 8.52 Hz, 1H), 7.40−7.43 (m, 2H), 7.21 (t. J = 7.36 Hz, 1H), 7.02 (d, J = 2.04 Hz, 1H), 6.95 (dd, J_1 = 8.52 Hz, J_2 = 2.20 Hz, 1H), 6.79 (d, J = 8.88 Hz, 2H), 6.10 (s, 1H), 6.00 (s, 1H), 3.90 (s, 3H), 3.02 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 161.1, 152.3, 149.4, 149.2, 136.1, 135.9, 129.8, 128.6, 128.1, 126.7, 125.8, 123.4, 121.2, 117.4, 112.6, 102.0, 100.5, 97.1, 55.8, 40.6; HRMS (EI, TOF) calcd for $C_{25}H_{23}NO_2$ $[M]^+$: 369.1729, found: 369.1732.

*4-((Z)-((Z)-7-Benzylidene-[1,3]dioxolo[4,5-f]isobenzofuran-5(7H)-ylidene)methyl)-N,N-dimethylaniline (**4q**).* Column chromatography (eluent = petroleum ether/ethyl acetate 25:1 v/v) on silica gel gave a yellow solid (55 mg, 72% yield). Mp: 206−208 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.87 (d, J = 7.48 Hz, 2H), 7.78 (d, J = 8.88 Hz, 2H), 7.39−7.43 (m, 2H), 7.19−7.23 (m, 1H), 6.99 (s, 1H), 6.96 (s, 1H), 6.78 (d, J = 8.88 Hz, 2H), 6.06 (s, 2H), 5.93 (s, 2H), 3.02 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.3, 149.9, 149.3, 149.2, 135.7, 129.5, 128.6, 128.2, 128.1, 125.9, 123.6, 112.6, 102.0, 99.3, 99.2, 98.9, 97.3, 40.7; HRMS (EI, TOF) calcd for $C_{25}H_{21}NO_3$ $[M]^+$: 383.1521, found: 383.1523.

*4-((Z)-((Z)-7-Benzylidenefuro[3,4-b]pyridin-5(7H)-ylidene)-methyl)-N,N-dimethylaniline (**4r**).* Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a yellow solid (53 mg, 78% yield). Mp: 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.59 (dd, J_1 = 4.72 Hz, J_2 = 1.32 Hz, 1H), 7.96 (d, J = 7.36 Hz, 2H), 7.89 (dd, J_1 = 7.88 Hz, J_2 = 1.32 Hz, 1H), 7.83 (d, J = 8.88 Hz, 2H), 7.43−7.47 (m, 2H), 7.27−7.30 (m, 2H), 6.80 (d, J = 8.96 Hz, 2H), 6.63 (s, 1H), 6.16 (s, 1H), 3.04 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 151.9, 150.4, 149.7, 146.7, 135.0, 130.1, 129.0, 128.7, 128.3, 127.2, 126.9, 123.5, 122.8, 112.5, 102.9, 100.3, 40.6; HRMS (EI, TOF) calcd for $C_{23}H_{20}N_2O$ $[M]^+$: 340.1576, found: 340.1577.

*4-((Z)-((Z)-3-(4-(((3R,8S,9S,10R,13R,14S,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)benzylidene)-isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (**4s**).* Column chromatography (eluent = petroleum ether/ethyl acetate 30:1 v/v) on silica gel gave a yellow solid (116 mg, 80% yield). Mp: 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.79−7.84 (m, 4H), 7.58−7.60 (m, 2H), 7.32−7.38 (m, 2H), 6.98 (d, J = 8.72 Hz, 2H), 6.80 (d, J = 8.68 Hz, 2H), 6.11 (s, 1H), 6.09 (s, 1H), 5.32 (br, 1H), 4.60 (s, 1H), 3.03 (s, 6H), 2.56 (d, J = 14.56 Hz, 1H), 2.41 (d, J = 15.08 Hz, 1H), 1.95−2.04 (m, 3H), 1.76−1.85 (m, 2H), 0.83−1.68 (m, 33H), 0.69 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 156.4, 150.8, 149.5, 149.2, 138.8, 134.2, 133.7, 129.6, 129.5, 128.8, 128.4, 128.3, 122.4, 123.8, 119.6, 119.4, 117.1, 112.7, 99.8, 98.5, 73.3, 56.9, 56.3, 50.0, 42.5, 40.7, 39.9, 39.7, 37.1, 36.5, 36.3, 36.0, 33.3, 32.0, 29.8, 28.4, 28.2, 26.0, 24.4, 24.0, 23.0, 22.7, 20.9, 19.2, 18.9, 12.0; HRMS (EI, TOF) calcd for $C_{51}H_{65}NO_2$ $[M]^+$: 723.5015, found: 723.4990.

Multicomponent Cascade Reactions of Alkynols (1), Aldehydes (7) and Amines (8) To Afford Isoquinolin-1(2*H*)-ones (3). To a mixture of alkynols (0.25 mmol), aldehydes (0.30 mmol), and amines (0.30 mmol) in DMF (1.5 mL) at room temperature was added *t*-BuOK (0.30 mmol, 1 M in THF) via a syringe. The reaction mixture was stirred under nitrogen atmosphere, and the progress was monitored using TLC detection. After 8 h, the reaction mixture was diluted with saturated aq NH_4Cl (3 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with saturated brine (15 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent in vacuum, the crude product was purified by column chromatography on silica gel to afford the isoquinolin-1(2*H*)-one **3**. The products **3a′−3d′** are new compounds, and the other products are known compounds.[17] (The synthesis of isoquinolin-1(2H)-ones **3a**, **3b**, **3d−3f**, **3h**, **3k−3m**, **3r−3u**, **3x**, **3y** and **3a′−3d′** were also carried out using this procedure unless otherwise indicated.)

*3-(4-Methoxyphenyl)-2-(p-tolyl)isoquinolin-1(2H)-one (**3a′**).* Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a white solid (69 mg, 81% yield). Mp: 212−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.44 (d, J = 8.08 Hz, 1H), 7.65−7.69 (m, 1H), 7.54 (d, J = 7.76 Hz, 1H), 7.47−7.51 (m, 1H), 7.06−7.10 (m, 4H), 6.99 (d, J = 8.24 Hz, 2H), 6.70 (d, J = 8.80 Hz, 2H), 6.55 (s, 1H), 3.75 (s, 3H), 2.29 (s, 3H).^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.4, 159.2, 143.6, 137.4, 137.0, 136.6, 132.7, 130.6, 129.4, 129.1, 128.9, 128.4, 126.7, 126.0, 125.4, 113.3, 107.7, 55.3, 21.2; HRMS (ESI, TOF) calcd for $C_{23}H_{20}NO_2^+$ $[M + H]^+$: 342.1489, found: 342.1494.

*3-(2-Bromo-4,5-dimethoxyphenyl)-2-phenylisoquinolin-1(2H)-one (**3b′**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (75 mg, 69% yield). Mp: 186−188 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.48 (d, J = 7.96 Hz, 1H), 7.69−7.73 (m, 1H), 7.58 (d, J = 84 Hz, 1H), 7.52−7.56 (m, 1H), 7.19−7.26 (m, 5H), 6.88 (s, 1H), 6.60 (s, 1H), 6.56 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.2, 149.5, 147.7, 141.7, 138.8, 136.6, 132.9, 129.2, 129.1, 128.8, 128.5, 128.3, 127.3, 126.3, 125.9, 114.8, 114.6, 114.5, 108.8, 56.2; HRMS (EI, TOF) calcd for $C_{23}H_{18}BrNO_3$ $[M]^+$: 435.0470, found: 435.0469.

*2,3-Di-p-tolylisoquinolin-1(2H)-one (**3c′**).* Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a white solid (69 mg, 85% yield). Mp: 202−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.44 (d, J = 8.08 Hz, 1H), 7.65−7.69 (m, 1H), 7.54 (d, J = 7.80 Hz, 1H), 7.47−7.51 (m, 1H), 7.04−7.08 (m, 4H), 6.97−7.00 (m, 4H), 6.56 (s, 1H), 2.29 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.4, 143.9, 137.9, 137.4, 136.9, 136.6, 132.8, 129.4, 129.2,129.1, 128.6, 128.4, 126.8, 126.0, 125.4, 107.8, 21.3; HRMS (ESI, TOF) calcd for $C_{23}H_{20}NO^+$ $[M + H]^+$: 326.1539, found: 326.1542.

*2,3-Bis(4-methoxyphenyl)isoquinolin-1(2H)-one (**3d′**).* Column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v) on silica gel gave a white solid (76 mg, 78% yield). Mp: 205−207 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.44 (d, J = 8.00 Hz, 1H), 7.65−7.69 (m, 1H), 7.47−7.55 (m, 2H), 7.08 (d, J = 8.76 Hz, 2H), 7.02 (d, J = 8.76 Hz, 2H), 6.79 (d, J = 8.88 Hz, 2H), 6.70 (d, J = 8.88 Hz, 2H), 6.56 (s, 1H), 3.76 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 163.6, 159.2, 158.6, 143.8, 137.0, 132.8, 132.0, 130.6, 130.3, 128.9, 128.4, 126.8, 126.0, 125.3, 114.0, 113.3, 107.6, 55.4, 55.3; HRMS (ESI, TOF) calcd for $C_{23}H_{20}NO_3^+$ $[M + H]^+$: 358.1438, found: 358.1441.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H spectra for products **3a−3z, 3a′−3d′**, **4a−4s** and **6**, ^{13}C NMR spectra for new compounds **3s−3z, 3a′−3d′**, **4j**, **4m−s** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/jo5006312 | J. Org. Chem. 2014, 79, 4602−4614

AUTHOR INFORMATION

Corresponding Author

*E-mail: liupn@ecust.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Project Nos. 21172069, 21190033, and 21372072), the Innovation Program of Shanghai Municipal Education Commission (Project No. 12ZZ050), the Basic Research Program of the Shanghai Committee of Science and Technology (Project No. 13NM1400802), NCET (NCET-13-0798), and the Fundamental Research Funds for the Central Universities.

REFERENCES

(1) (a) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304. (b) McDonald, F. E.; Reddy, K. S. *Anew. Chem., Int. Ed.* **2001**, *40*, 3653. (c) Trost, B. M.; Rhee, Y. H. *Org. Lett.* **2004**, *6*, 4311. (d) Davidson, M. H.; MacDonald, F. E. *Org. Lett.* **2004**, *6*, 1601−1603. (e) Balthaser, B. R.; McDonald, F. E. *Org. Lett.* **2009**, *11*, 4850. (f) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Soc. Chem.* **2012**, *134*, 1930.

(2) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528. (c) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091. (d) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (e) Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031. (f) Borghèse, S.; Drouhin, P.; Bénéteau, V.; Louis, B.; Pale, P. *Green Chem.* **2013**, *15*, 1496. (g) Barluenga, J.; Fernández, A.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Chem.—Eur. J.* **2009**, *15*, 11660. (h) Alcaide, B.; Almendros, P.; del Campo, T. M.; Carrascosa, R. *Eur. J. Org. Chem.* **2010**, 4912. (i) Li, S.; Ma, S. *Org. Lett.* **2011**, *13*, 6046. (j) Wong, C. M.; Vuong, K. Q.; Gatus, M. R. D.; Hua, C.; Bhadbhade, M.; Messerle, B. A. *Organometallics* **2012**, *31*, 7500. (k) Reddy, M. S.; Kumar, Y. K.; Thirupathi, N. *Org. Lett.* **2012**, *14*, 824.

(3) (a) Barluenga, J.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J.; Sordo, T.; Campomanes, P. *Chem.—Eur. J.* **2005**, *11*, 5735. (b) Barluenga, J.; Diéguez, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 126.

(4) (a) Barluenga, J.; Calleja, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Chem.—Eur. J.* **2010**, *16*, 7110. (b) Han, Z.-Y.; Chen, D.-F.; Wang, Y.-Y; Guo, R.; Wang, P.-S.; Wang, C.; Gong, L.-Z. *J. Am. Chem. Soc.* **2012**, *134*, 6532. (c) Guo, R.; Li, K.-N; Gong, L.-Z. *Org. Biomol. Chem.* **2013**, *11*, 6707. (d) Wu, H.; He, Y.-P.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 460. (e) Wang, P.-S.; Li, K.-N.; Zhou, X.-L.; Wu, X.; Han, Z.-Y.; Guo, R.; Gong, L.-Z. *Chem.—Eur. J.* **2013**, *19*, 6234. (f) Cala, L.; Mendoza, A.; Fañanás, F. J.; Rodríguez, F. *Chem. Commun.* **2013**, *49*, 2715.

(5) (a) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7044. (b) Barluenga, J.; Mendoza, A.; Rodríguez, F.; Fañanás, F. J. *Chem.—Eur. J.* **2008**, *14*, 10892. (c) Patil, N. T.; Kavthe, R. D.; Raut, V. S.; Reddy, V. V. N. *J. Org. Chem.* **2009**, *74*, 6315. (d) Patil, N. T.; Kacthe, R. D.; Raut, V. S.; Shinde, V. S.; Scridhar, B. *J. Org. Chem.* **2010**, *75*, 1277. (e) Patil, N. T.; Kavthe, R. D.; Shinde, V. S.; Scridhar, B. *J. Org. Chem.* **2010**, *75*, 337. (f) Pardo, P.; Fernández, A.; Fañanás, F. J.; Rodríguez, F. *Adv. Synth. Catal.* **2012**, *354*, 2141. (g) Galván, A.; Calleja, J.; Fañanás, F. J.; Rodríguez, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 6038.

(6) (a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (b) Jiang, H.; Gao, Y.; Wu, W.; Huang, Y. *Org, Lett.* **2013**, *15*, 238.

(7) Cao, H.; Jiang, H.; Yao, W.; Liu, X. *Org. Lett.* **2009**, *11*, 1931.

(8) (a) Chavre, S. N.; Choo, H.; Cha, J. H.; Pae, A. N.; Choi, K. II; Cho, Y. S. *Org. Lett.* **2006**, *8*, 3617. (b) LaPorte, M.; Hong, K. B.; Xu, J.; Wipf, P. *J. Org. Chem.* **2013**, *78*, 167.

(9) (a) Guastavino, J. F.; Barolo, S. M.; Rossi, R. A. *Eur. J. Org. Chem.* **2006**, 3898. (b) Saeed, A.; Ashraf, Z. *Pharm. Chem. J.* **2008**, *42*, 277.

(10) (a) Cushman, M.; Jayaraman, M.; Vroman, J. A.; Fukunaga, A. K.; Fox, B. M.; Kohlhagen, G.; Strumberg, D.; Pommier, Y. J. *J. Med. Chem.* **2000**, *43*, 3688. (b) Yang, S. H.; My Van, H. T.; Le, T. N.; Khadka, D. B.; Cho, S. H.; Lee, K.-T.; Lee, E.-S.; Lee, Y. B.; Ahn, C.-H.; Cho, W.-J. *Eur. J. Med. Chem.* **2010**, *45*, 5493. (c) Li, S. W.; Nair, M. G.; Edwards, D. M.; Kisliuk, R. L.; Gaumont, Y.; Dev, I. K.; Duch, D. S.; Humphreys, J.; Smith, G. K.; Ferone, R. *J. Med. Chem.* **1991**, *34*, 2746.

(11) Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077.

(12) (a) Yeung, C. S.; Hsieh, T. H. H.; Dong, V. M. *Chem. Sci.* **2011**, *2*, 544. (b) Walker, E. R.; Leung, S. Y.; Barrett, A. G. M. *Tetrahedron Lett.* **2005**, *46*, 6537. (c) Grigg, R.; Sridharan, V.; Xu, L.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1903. (d) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921. (e) Mehta, G.; Shah, S. R.; Venkateswarlu, Y. *Tetrahedron* **1994**, *50*, 11729.

(13) (a) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (b) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (c) Liu, C.-C.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2010**, *12*, 3518.

(14) (a) Too, P. C.; Chiba, S. *Chem. Commun.* **2012**, *48*, 7634. (b) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2009**, *11*, 2469.

(15) (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (b) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592.

(16) (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (b) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2011**, *17*, 12573.

(17) Li, D. Y.; Shang, X. S.; Chen, G. R.; Liu, P. N. *Org. Lett.* **2013**, *15*, 3848.

(18) (a) Seo, S. Y.; Yu, X.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 263. (b) Sun, Y.; Wu, G.; Cen, D.; Chen, Y.; Wang, L. *Dalton Trans.* **2012**, *41*, 9682.

(19) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255.

(20) (a) Luo, F.-T.; Schreuder, I.; Wang, R.-T. *J. Org. Chem.* **1992**, *57*, 2213. (b) Gabriele, B.; Mancuso, R.; Salerno, G. *J. Org. Chem.* **2008**, *73*, 7336.

(21) (a) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019. (b) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447.

(22) (a) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2007**, *48*, 1439. (b) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409.

(23) Praveen, C.; Iyyappan, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 4767.

(24) Pouy, M. J.; Delp, S. A.; Uddin, J.; Ramdeen, V. M.; Cochrane, N. A.; Fortman, G. C.; Gunnoe, T. B.; Cundari, T. R.; Sabat, M.; Myers, W. H. *ACS Catal.* **2012**, *2*, 2182.

(25) Brinkmann, C.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A.; Reid, S. *Organometallics* **2012**, *31*, 7287.

(26) Weingarten, M. D.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 4717.

(27) (a) Bhakuni, D. S.; Jain, S. Protoberberine Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. *28*, Chapter 2. (b) Shamma, M. The Protoberberines and Retroprotoberberines. In *The Isoquinoline Alkaloids. Chemistry and Pharmacology*; Blomquist, A. T., Wasserman, H., Eds.; Academic Press: New York, 1972; Vol. *25*, pp 268. (c) Southon, I. W.; Buckingham, J. *Dictionary of Alkaloids*; Chapman and Hall: London, 1989. (d) Bentley, K. W. Berberines and Tetrahydroberberines. In *The Isoquinoline Alkaloids*; Ravindranath, B., Ed.; Harwood Academic: Bangalore, 1998; Vol. *1*, pp 219.

(28) Patra, A.; Montgomery, C. T.; Freyer, A. J.; Guinaudeau, H.; Shamma, M.; Tantisewie, B.; Pharadai, K. *Phytochemistry* **1987**, *26*, 547.

(29) (a) Cobas, A.; Guitán, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 6765. (b) Suau, R.; López-Romero, J. M.; Ruiz, A.; Rico, R. *Tetrahedron* **2000**, *56*, 993. (c) Lee, C.-S.; Yu, T.-C.; Luo, J.-W.;

Cheng, Y.-Y.; Chuang, C.-P. *Tetrahedron Lett.* **2009**, *50*, 4558. (d) My Van, H. T.; Yang, S. H.; Khadka, D. B.; Kim, Y.-C.; Cho, W.-J. *Tetrahedron* **2009**, *65*, 10142. (e) Chen, A.; Zhao, K.; Zhang, H.; Gan, X.; Lei, M.; Hu, L. *Monatsh. Chem.* **2012**, *143*, 825.

(30) (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Zhu, J.; BienaymG, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (e) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234. (f) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (g) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.

(31) Mancuso, R.; Mehta, S.; Gabriele, B.; Salerno, G.; Jenks, W. S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 897.

(32) (a) Naka, H.; Koseki, D.; Kondo, Y. *Adv. Synth. Catal.* **2008**, *350*, 1901. (b) Ruano, J. L. G.; Alwmán, J.; Alonso, I.; Parra, A.; Marcos, V.; Aguirre, J. *Chem.—Eur. J.* **2007**, *13*, 6179.