JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

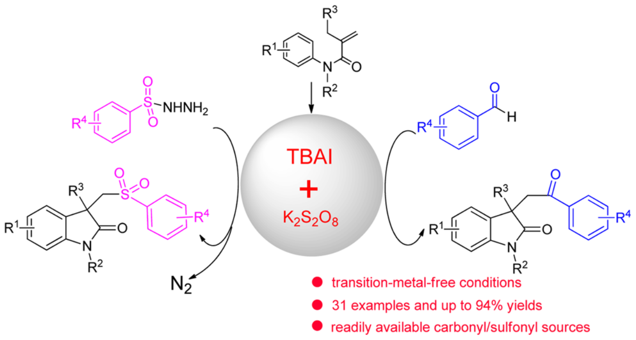
Transition-Metal-Free TBAI-Facilitated Addition−Cyclization of *N*-Methyl-*N*-arylacrylamides with Arylaldehydes or Benzenesulfonohydrazides: Access to Carbonyl- and Sulfone-Containing *N*-Methyloxindoles

Peng-Yi Ji, Ming-Zhong Zhang, Jing-Wen Xu, Yu-Feng Liu, and Can-Cheng Guo*

College of Chemistry and Chemical Engineering, Advanced Catalytic Engineering Research Center of the Ministry of Education, Hunan University, Changsha 410082, China

Supporting Information

ABSTRACT: A highly efficient addition−cyclization of *N*-methyl-*N*-arylacrylamides with arylaldehydes or benzenesulfonohydrazides was developed using a catalytic amount of the quaternary ammonium salt (TBAI) under metal-free conditions, leading to the carbonyl- and sulfone-containing oxindoles. Compared to previous methods, which require excessive amounts of explosive organic peroxides and precious or toxic metal reagents, the present protocol, which gave access to 3,3-disubstituted oxindoles, is a safe and green approach, resulting in the formation of various useful carbonyl- and sulfone-containing oxindoles in yields of 40−94%.



- transition-metal-free conditions
- 31 examples and up to 94% yields
- readily available carbonyl/sulfonyl sources

INTRODUCTION

The oxindole framework bearing a tetrasubstituted carbon stereocenter at the 3-position is a ubiquitous high-value heterocyclic motif[1] and can also be utilized to synthesize a series of pyrrolidinoindolines which exist in a number of natural products and bioactive molecules.[2] Owing to its importance and versatility, much effort has naturally gone into the asymmetric synthesis of a 3,3-disubstituted oxindole framework through a large family of intramolecular coupling reactions of activated alkenes,[3−9] including arylphosphorylation,[3] alkylarylation,[4] diarylation,[5] arylnitration,[6] aryltrifluoromethylation,[7] halogenation,[8] and azidoarylation.[9] Despite some success, however, room still exists for exploring a convenient, green, and general method to construct other important functionalized oxindoles.

Carbonyl-containing oxindoles, as synthetic intermediates of indole alkaloids,[10] exhibit extremely attractive bioactivities and widely exist in natural products.[11,12] The incorporation of arylcarbonyl groups into oxindole molecules has drawn increased attention. Recently, modern applications of transition-metal and photoredox catalysis have gained momentum as strategies for the formation of carbonyl-containing oxindoles from *N*-arylacrylamides; the vast majority of these elegant approaches undergo a 1,2-acylarylation of *N*-arylacrylamides to obtain the desired carbon stereocenters.[13] However, the use of toxic metal reagents, high-energy UV light, and precious photocatalysts might not be considered as advantages of the procedures. Consequently, there is still an urgent need for chemists to find out a safe and green process for the construction of carbonyl-containing oxindoles. Owing to our continuous interest in difunctionalization of activated alkenes,[8c,13h] we first disclose a metal-free TBAI-facilitated cascade cyclization strategy of activated alkenes for access to carbonyl-containing oxindoles. Most importantly, this mild, safe, and low toxicity catalytic system was successfully applied to the arylsulfonylation of arylacrylamides with readily available sulfonylhydrazides, resulting in the formation of various sulfone-containing oxindoles in moderate to high yields. As is well-known, sulfone-containing oxindoles, which possess inestimable roles in the structural library design and drug discovery,[14,12c] have been a source of interest for chemists, and a variety of inventive synthetic strategies were developed toward their preparation during the past few years.[14a,15]

Notably, among the previous protocols, there are still a dirth of articles which describe the work regarding the activated alkenes as carbon-based reagents via TBAI-catalyzed cycloaddition of arylacrylamides to obtain carbonyl- and sulfone-containing oxindoles. Herein, we wish to report a TBAI/$K_2S_2O_8$ combined strategy for the synthesis of carbonyl- and sulfone-containing oxindoles.

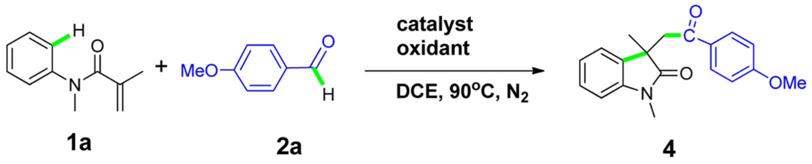
RESULTS AND DISCUSSION

Inspired by the elegant work of Wu and co-workers,[16] who demonstrated that the reaction of peroxydisulfate with TBAB under thermal conditions could generate activated tetrabutyl-

Received: April 8, 2016
Published: May 27, 2016

DOI: 10.1021/acs.joc.6b00773

Table 1. Screening Optimal Conditions of Synthesis of Product 4[a]



entry	catalyst (mol %)	oxidant (equiv)	T (°C)	yield[c] (%)
1	TBAI	$K_2S_2O_8$	90	71
2	TBAF	$K_2S_2O_8$	90	53
3	TBAC	$K_2S_2O_8$	90	63
4	TBAB	$K_2S_2O_8$	90	49
5	TEAB	$K_2S_2O_8$	90	36
6	TBAHS	$K_2S_2O_8$	90	49
7[b]	TBAI/KI	$K_2S_2O_8$	90	69
8	KI	$K_2S_2O_8$	90	trace
9	no catalyst	$K_2S_2O_8$	90	8
10	TBAI (5)	$K_2S_2O_8$	90	55
11	TBAI (20)	$K_2S_2O_8$	90	69
12	TBAI	$K_2S_2O_8$ (2 equiv)	90	55
13	TBAI	$K_2S_2O_8$ (4 equiv)	90	65
14	TBAI	$K_2S_2O_8$	70	39
15	TBAI	$K_2S_2O_8$	100	69
16	TBAI	$K_2S_2O_8$	110	66

[a] General reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), catalyst (10 mol %), oxidant (3 equiv), solvent (2 mL), 90 °C for 24 h. [b] TBAI (10 mol %), KI (10 mol %). [c] Yield detected by LC. TBAI: tetrabutylammonium iodide; TBAB: tetrabutylammonium bromide; TEAB: tetraethylammonium bromide; TBAF: tetrabutylammonium fluoride; TBAC: tetrabutylammonium chloride; TBAHS: tetrabutylammonium hydrogen sulfate.

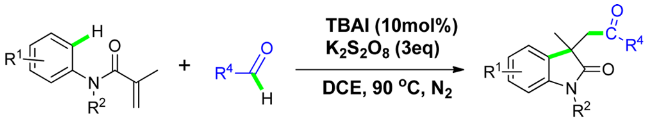
ammonium sulfate radical anions, which could mediate oxidative tandem coupling of alkynoates with aldehydes via a selective cycloaddition with an acyl radical. We hypothesized that the $K_2S_2O_8$/quaternary ammonium salt combined strategy could be applied to carboacylation/arylation of arylacrylamides under metal-free conditions. Then, *N*-methyl-*N*-phenylmethacrylamide **1a** and *p*-methoxybenzaldehyde **2a** were chosen as model substrates to optimize conditions for this reaction (Table 1). The results suggested that the catalysts employed, the oxidant ammounts, and the temperatures are variables that can be modulated to obtain the desired reactivity. First, in order to confirm the effects of the counterions on the reaction,[17] a series of quaternary ammonium salts as catalysts were tested, most of the quaternary ammonium salts especially TBAI and TBAC displayed good catalytic activity in this tandem reaction, and then catalytic amounts of potassium iodide were added alone or combined with TBAI, which gave the product **4** in a trace amount or 69% yields, which indicated that the counterions might have a minor effect on the reaction (entries 1−8, Table 1). By comparison, the TBAI may show a better catalytic compatibility since the iodide ion probably has a stronger separation ability to split from quaternary ammonium salts. Then, only 8% yields of **4** were detected without the presence of TBAI (entry 9, Table 1), so we chose the TBAI as the most suitable catalyst according to the experimental results thus obtained. It is worth to note that decreasing or increasing the amount of TBAI or $K_2S_2O_8$ both led to a lower yield of product **4**, suggesting that a suitable amount of catalyst and oxidant was necessary for good yield of the desired product (entries 10−13, Table 1). Finally, the temperature screening indicated that 90 °C was the most suitable temperature for this protocol (entries 14−16, Table 1).

With the optimized conditions in hand, we explored the scope of *N*-arylacrylamides and aldehydes for the annulation reaction (Table 2). Initially, a number of aldehydes without electron-withdrawing groups were investigated, and respective products were obtained in good isolated yields (69% and 65%, **4** and **5**). The strong electron-withdrawing substituent nitro group did not result in any desired product (**6**). However, F and CN groups at the para-position and the F group at the meta-position survived well to give the corresponding products in 40−48% yields (**7**−**9**), which enabled a potential application in further functionalization.[18] Subsequently, the effects of various substitution patterns on the *N*-aryl moiety of *N*-arylacrylamides were explored. Several substituents at the para-position provided the corresponding products in moderate yields (**10**−**11**). The nitro group at the para-position was also tried; unfortunately, we failed to get the desired product under optimal conditions (**12**). The iodo substituent at the meta-position was well tolerated (**13**), and the result encouraged us to take a step forward to test the compatibility of the *o*-Ph group under optimal conditions; to our delight, it eventually gained **14** in 49% yields. *N*-Benzyl *N*-phenylmethacrylamide could be smoothly converted into the desired oxindoles in 72% yields (**15**).

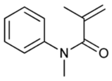
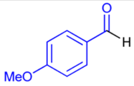
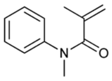
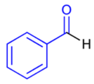
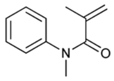
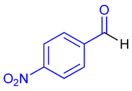
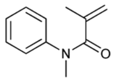
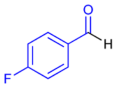
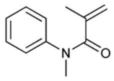
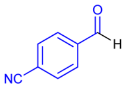
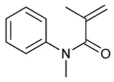
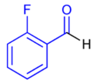
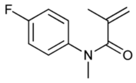
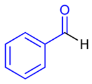
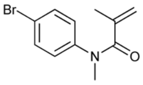
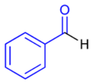
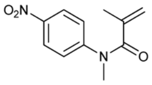
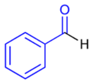
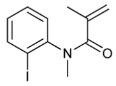
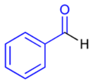
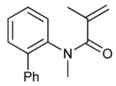
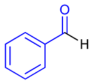
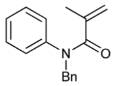
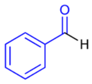
To demonstrate further the synthetic practicality of this quaternary ammonium salt catalytic oxidation system, we wondered whether this mild condition could acquit itself splendidly while *N*-methyl-*N*-phenylmethacrylamide **1a** and benzenesulfonohydrazide **3a** were employed as model substrates. Surprisingly, *N*-methyl-*N*-phenylmethacrylamide could be transformed into sulfone-containing oxindole with benzenesulfonohydrazide in excellent 85% isolated yields in the presence of a catalytic amount of TBAI and 3 equiv of $K_2S_2O_8$, even when the temperature dropped to 60 °C (Table S1; see the Supporting Information, p 2). The wonderful results inspired us to carry out further work about this coupling reaction.

DOI: 10.1021/acs.joc.6b00773
J. Org. Chem. 2016, 81, 5181−5189

Table 2. Synthesis of Carbonyl-Containing Oxindoles: Scope of *N*-Arylacrylamides[a]

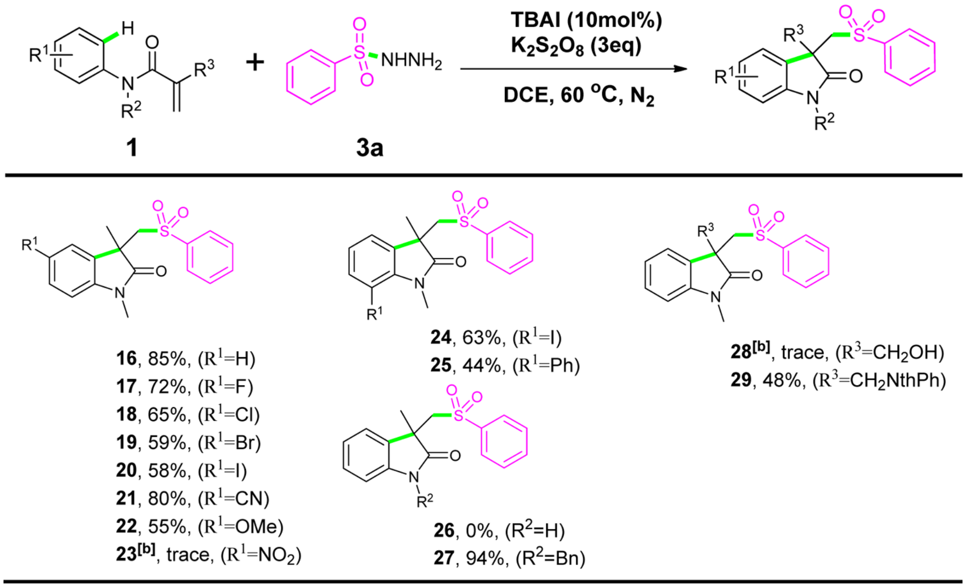


1 **2**

Entry	Amide **1**	Aldehyde **2**	Product (Yield [%][b])
1	 **1a**	 **2a**	**4** (69)
2	 **1a**	 **2b**	**5** (65)
3	 **1a**	 **2c**	**6** (0[c])
4	 **1a**	 **2d**	**7** (48)
5	 **1a**	 **2e**	**8** (40)
6	 **1a**	 **2f**	**9** (42)
7	 **1b**	 **2b**	**10** (45)
8	 **1c**	 **2b**	**11** (47)
9	 **1d**	 **2b**	**12** (Trace[c])
10	 **1e**	 **2b**	**13** (56)
11	 **1f**	 **2b**	**14** (49)
12	 **1g**	 **2b**	**15** (72)

[a] General reaction conditions: **1** (0.2 mmol), **2** (1.2 equiv), catalyst (10 mol %), oxidant (3 equiv), solvent (2 mL), 90 °C for 24 h. [b] Isolated yield. [c] Yield detected by GC−MS.

Table 3. Synthesis of Sulfone-Containing Oxindoles: Scope of *N*-Arylacrylamides[a]



16, 85%, (R^1=H)
17, 72%, (R^1=F)
18, 65%, (R^1=Cl)
19, 59%, (R^1=Br)
20, 58%, (R^1=I)
21, 80%, (R^1=CN)
22, 55%, (R^1=OMe)
23[b], trace, (R^1=NO_2)

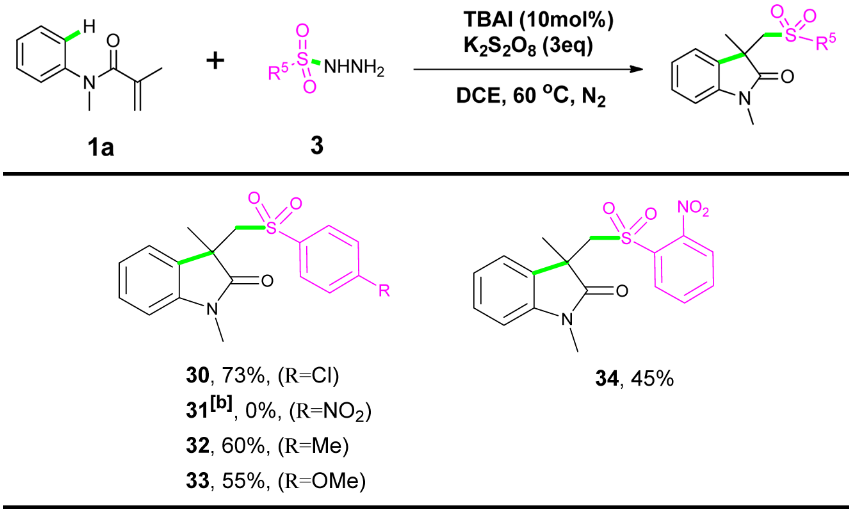
24, 63%, (R^1=I)
25, 44%, (R^1=Ph)

26, 0%, (R^2=H)
27, 94%, (R^2=Bn)

28[b], trace, (R^3=CH_2OH)
29, 48%, (R^3=CH_2NthPh)

[a]General reaction conditions: **1** (0.2 mmol), **3a** (1.2 equiv), catalyst (10 mol %), oxidant (3 equiv), solvent (2 mL), 60 °C for 24 h. [b]Yield detected by GC−MS.

Table 4. Scope of Sulfonylating Agents 3[a]



30, 73%, (R=Cl)
31[b], 0%, (R=NO_2)
32, 60%, (R=Me)
33, 55%, (R=OMe)

34, 45%

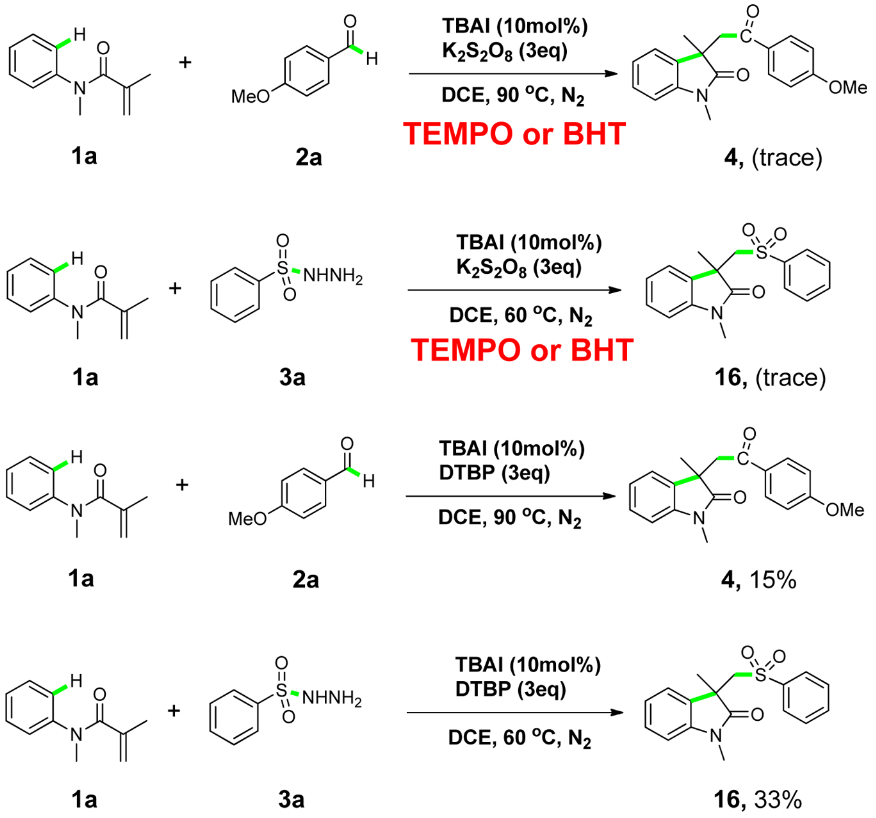
[a]General reaction conditions: **1a** (0.2 mmol), **3** (1.2 equiv), catalyst (10 mol %), oxidant (3 equiv), solvent (2 mL), 60 °C for 24 h. [b]Yield detected by GC−MS.

Subsequently, the scope of the *N*-arylacrylamides **1** was investigated, and the results are summarized in Table 3. A wide range of functional groups at the aryl ring reacted smoothly to give the desired products in good yields ranging from 55% to 85% (**16**−**22**); despite those well tolerated substituents, only a trace of **23** was detected by GC−MS. Ortho-substituted arylacrylamides, which could not be efficiently transformed in the reported protocol,[15b] were proved to be accessible under optimized conditions (**24**−**25**). Notably, 44% yields of **25** were obtained, even considering the great steric effects of the bezene group. *N*-unsubstituted *N*-methyl-*N*-phenylmethacrylamide failed to transform into the desired oxindole (**26**); subsequently, an electron-donating group such as a benzyl group was also examined under standard conditions to give the corresponding products in 94% yields (**27**). Finally, the substituent effect at the 2-position (R^3) of the acrylamide moiety was investigated. As shown in Table 3, the CH_2OH group was found to be not suitable as a substrate for this reaction (**28**), but it was noted that the 1,3-dioxoisoindolin-2-yl group was compatible with optimal conditions and transformed into the corresponding product in 48% isolated yields (**29**).

We next turned to evaluate the scope of the substituted sulfonylating agents through oxidative coupling reactions with *N*-methyl-*N*-phenylmethacrylamide **1a** (Table 4). Benzenesulfonohydrazides with different substituents (Cl, Me, OMe) at the para-position were tolerated in this reaction, which only failed in the transformation of substrate with a nitro group (**30**−**33**). The nitro group at the ortho-position was transformed into the desired product **34** in 45% yields.

To understand the mechanism of this reaction, a number of control experiments were performed. As shown in Scheme 1, the presence of 2 equiv of radical inhibiters, such as TEMPO

Scheme 1. Experiments for Mechanism



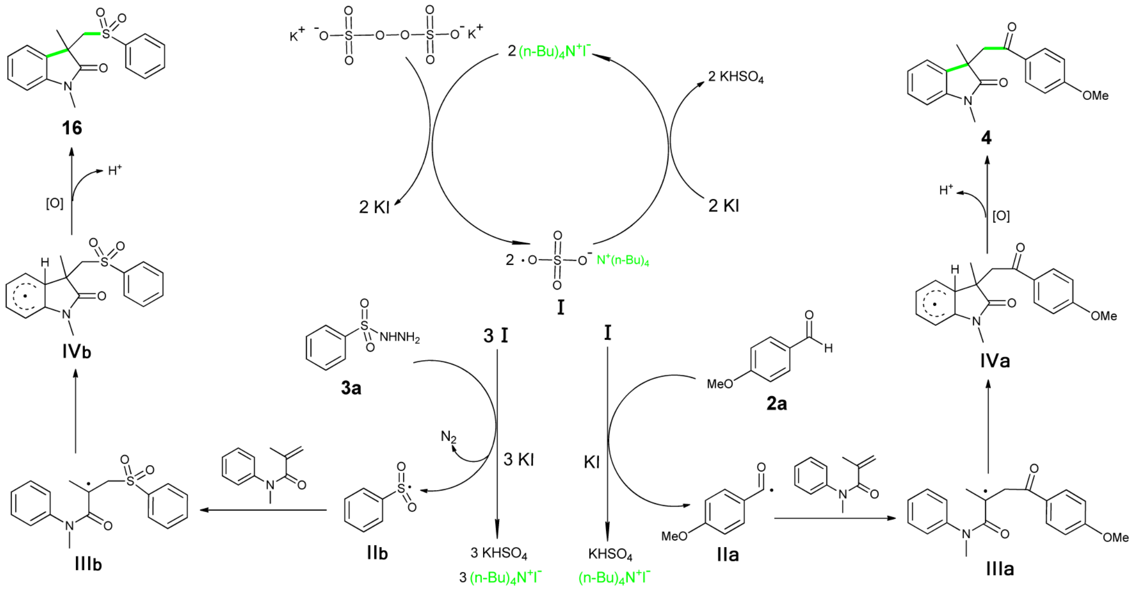


Figure 1. Proposed mechanism.

(2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (butylated hydroxytoluene), had obvious suppression to both reactions. In addition, in order to confirm that the cycloaddition process is via a radical pathway, 3 equiv of di-*t*-butyl peroxide (DTBP) was employed as the oxidant under general conditions. Interestingly, the corresponding products **4** and **16** were obtained in 15% and 33% isolated yields, respectively. From the above, the experimental results thus obtained may further prove the proposed mechanism.

On the basis of the experimental results and precedent literature,[13a,15b,16,19] a radical pathway has been proposed (Figure 1). At the beginning, potassium persulfate ($K_2S_2O_8$) is able to convert into the tetrabutylammonium sulfate radical anions **I** in the presence of a quaternary ammonium salt. The acyl radical **IIa** is obtained by hydrogen abstraction of aldehyde (**2a**) under the action of the resulting radical anions **I**,[13a] which probably is similar to the other process; in this process, the sulfonyl radical **IIb** is generated by hydrogen abstraction of benzenesulfonohydrazide (**3a**) with the release of N_2.[15b]

Simultaneously, an equal amount of $KHSO_4$ and tetrabutylammonium cations are released from the hydrogen abstraction process, and the tetrabutylammonium cations combine with KI to retrieve the catalysts TBAI. Then, the catalysts are ready to enter their next catalytic cycle. Subsequently, selective free-radical addition of **IIa** or **IIb** to activate alkene generates radical intermediate **IIIa** or **IIIb**, which is then followed by intramolecular cyclization of intermediate **IIIa** or **IIIb** with the aryl ring, leading to the formation of radical intermediate species **IVa** or **IVb**. Finally, corresponding products **4** or **16** are obtained via a deprotonation process of radical intermediate species **IVa** or **IVb**.

■ CONCLUSIONS

In summary, a mild, green, and versatile approach for access to carbonyl/sulfone-containing oxindoles has been systematically developed; the protocol allows a great progress on preparing these two kinds of significant functional oxindoles. At the same time, utilizing stable oxidant $K_2S_2O_8$ and a substoichiometric amount of readily available catalysts (TBAI) through intramolecular cyclization of arylacrylamides endows this protocol with great application prospect in pharmaceutical fields. Further experimental study to explicit a broader capability and application scope of this oxidative difunctionalization system is underway by our group.

■ EXPERIMENTAL SECTION

General Methods. Materials obtained from commercial suppliers were used as received unless mentioned otherwise. Products were purified by flash chromatography on silica gel (300−400 mesh) and were characterized by ^{1}H NMR and ^{13}C NMR. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer, and the chemical shifts (δ) were reported in ppm relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet; brs, broad singlet. The coupling constants, J values, are given in hertz (Hz). ^{13}C NMR spectra were obtained at a 100 MHz spectrometer and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$). Copies of ^{1}H NMR and ^{13}C NMR spectra are provided as Supporting Information. High-resolution mass spectra (HRMS) were measured on a double focusing mass spectrometer with an EI source.

Experimental Procedures for the Synthesis of Starting Materials 1. N-Arylacrylamide substrates **1** were prepared according to the literature.[12,13a,14]

Typical Experimental Procedure for the Formation of Carbonyl-Containing Oxindoles from *N*-Arylacrylamides. To a mixture of **1** (0.2 mmol), **2** (0.24 mmol) in 2.0 mL of DCE were added TBAI (7.4 mg, 10 mol %) and $K_2S_2O_8$ (162.2 mg, 3 equiv) at room temperature in a Schlenk tube. The resulting mixture was stirred at 90 °C under N_2 for 24 h. Then, the resulting reaction solution was cooled to room temperature, diluted, and washed with H_2O; the aqueous phase was extracted with ethyl acetate. The combined organic extracts was dried over anhydrous Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to afford the desired product.

Typical Experimental Procedure for the Formation of Sulfone-Containing Oxindoles from *N*-Arylacrylamides. To a mixture of **1** (0.2 mmol), **3** (0.24 mmol) in 2.0 mL of DCE were added TBAI (7.4 mg, 10 mol %) and $K_2S_2O_8$ (162.2 mg, 3 equiv) at room temperature in a Schlenk tube. The resulting mixture was stirred at 60 °C under N_2 for 24 h. Then, the resulting reaction solution was cooled to room temperature, diluted, and washed with H_2O; the aqueous phase was extracted with ethyl acetate. The combined organic extracts was dried over anhydrous Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to afford the desired product.

3-(2-(4-Methoxyphenyl)-2-oxoethyl)-1,3-dimethylindolin-2-one (**4**).[13a] Following the general procedure, the product was isolated as a colorless oil in 69% yield (46.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.87 (dd, J = 13.6, 8.3 Hz, 3H), 3.82 (s, 3H), 3.68 (d, J = 17.7 Hz, 1H), 3.60 (d, J = 17.7 Hz, 1H), 3.31 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 26.4, 45.3, 45.6, 55.4, 108.1, 113.5, 121.7, 122.0, 127.7, 129.4, 130.2, 133.8, 143.8, 163.4, 180.7, 194.5; HRMS m/z (EI) calcd for $C_{19}H_{19}NO_3$ [M$^+$]: 309.1365; found 309.1362.

1,3-Dimethyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**5**).[13a] Following the general procedure, the product was isolated as a colorless oil in 69% yield (41.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.7 Hz, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.40 (m, 2H), 7.28 (s, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 3.69 (q, J = 17.9 Hz, 2H), 3.31 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 26.4, 45.2, 46.0, 108.1, 121.7, 122.1, 127.8, 127.9, 128.4, 133.1, 133.7, 136.3, 143.8, 180.5, 196.1; HRMS (EI) m/z calcd for $C_{18}H_{17}NO_2$ [M$^+$]: 279.1259; found 279.1258.

3-(2-(4-Fluorophenyl)-2-oxoethyl)-1,3-dimethylindolin-2-one (**7**).[13b] Following the general procedure, the product was isolated as a yellow oil in 48% yield (31.1 mg); mp = 108−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.84 (m, 2H), 7.28−7.24 (t, J = 7.7 Hz, 1H), 7.14−7.12 (d, J = 7.3 Hz, 1H), 7.08−7.04 (t, J = 8.3 Hz, 2H), 7.00−6.96 (t, J = 7.5 Hz, 1H), 6.91−6.89 (d, J = 7.8 Hz, 1H), 3.72−3.57 (m, 2H), 3.31 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 26.5, 45.2, 45.9, 108.1, 115.4, 115.7, 121.6, 122.1, 127.9, 130.5, 130.6, 132.7, 132.7, 133.6, 143.8, 165.7 (d, $1J_{\mathrm{C\text{-}F}}$ = 253.0 Hz), 180.2, 195.8; HRMS (EI) m/z calcd for $C_{18}H_{16}FNO_2$ [M$^+$]: 297.1165; found 297.1158.

4-(2-(1,3-Dimethyl-2-oxoindolin-3-yl)acetyl)benzonitrile (**8**).[13a] Following the general procedure, the product was isolated as a colorless oil in 40% yield (26.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 7.3 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 3.66 (s, 2H), 3.30 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.9, 26.5, 45.2, 46.2, 108.3, 116.5, 117.8, 121.7, 122.3, 128.1, 128.4, 132.4, 133.1, 139.1, 143.8, 180.1, 194.9; HRMS (EI) m/z calcd for $C_{19}H_{16}N_2O_2$ [M$^+$]: 304.1212; found 304.1208.

3-(2-(2-Fluorophenyl)-2-oxoethyl)-1,3-dimethylindolin-2-one (**9**).[13h] Following the general procedure, the product was isolated as a colorless oil in 42% yield (27.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.62 (m, 1H), 7.49−7.44 (dd, J = 13.3, 7.2 Hz, 1H), 7.28−7.24 (m, 1H), 7.14−7.08 (dd, J = 15.0, 7.5 Hz, 3H), 6.98 (m, 1H), 6.90 (d, J = 7.8 Hz, 1H), 3.78−3.61 (m, 2H), 3.31 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.4, 45.3, 50.8, 50.8, 108.0, 116.4, 116.6, 121.5, 122.0, 124.3, 124.7, 127.7, 130.6, 134.7, 133.7, 143.8, 161.9 (d, $1J_{\mathrm{C\text{-}F}}$ = 253.0 Hz), 180.5, 194.1; HRMS (EI) m/z calcd for $C_{18}H_{16}FNO_2$ [M$^+$]: 297.1165; found 297.1159.

5-Fluoro-1,3-dimethyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**10**).[13b] Following the general procedure, the product was isolated as a colorless oil in 45% yield (29.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.83 (d, J = 8.1 Hz, 2H), 7.52−7.51 (d, J = 8.0 Hz, 1H), 7.42−7.38 (d, J = 7.8 Hz, 2H), 6.97−6.89 (m, 2H), 6.83−6.80 (m, 1H), 3.66 (s, 2H), 3.30 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.7, 26.5, 45.6, 45.9, 108.5, 109.9, 110.2, 113.6, 113.9, 127.9, 128.4, 130.0, 133.3, 135.4, 136.0, 139.7, 159.1 (d, $1J_{\mathrm{C\text{-}F}}$ = 239.0 Hz), 180.2, 195.9; HRMS (EI) m/z calcd for $C_{18}H_{16}FNO_2$ [M$^+$]: 297.1165; found 297.1155.

5-Bromo-1,3-dimethyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**11**).[13h] Following the general procedure, the product was isolated as a yellow oil in 47% yield (37.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.9 Hz, 2H), 7.54 (m, 1H), 7.43−7.37 (dd, J = 17.2, 8.7 Hz, 3H), 7.23 (s, 1H), 6.78 (d, J = 8.2 Hz, 1H), 3.69 (s, 2H), 3.30 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 26.5, 45.3, 46.0, 109.5, 114.7, 124.9, 127.9, 128.5, 130.6, 133.3, 135.9, 136.0, 143.0, 179.9, 195.7; HRMS (EI) m/z calcd for $C_{18}H_{16}BrNO_2$ [M$^+$]: 357.0364; found 357.0357.

DOI: 10.1021/acs.joc.6b00773
J. Org. Chem. 2016, 81, 5181−5189

*7-Iodo-1,3-dimethyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**13**).*[13h] Following the general procedure, the product was isolated as a yellow oil in 56% yield (47.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.53 (m, 1H), 7.42−7.39 (t, J = 8.ii0 Hz, 2H), 7.04 (d, J = 7.2 Hz, 1H), 6.68−6.65 (t, J = 8.0 Hz, 1H), 3.69 (s, 5H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 30.3, 44.8, 46.3, 71.9, 121.2, 123.8, 127.9, 128.5, 133.3, 136.1, 136.8, 140.3, 144.2, 181.3, 195.8; HRMS (EI) m/z calcd for $C_{18}H_{16}INO_2$ [M$^+$]: 405.0226; found 405.0221.

*1,3-Dimethyl-3-(2-oxo-2-phenylethyl)-7-phenylindolin-2-one (**14**).*[13h] Following the general procedure, the product was isolated as a yellow oil in 49% yield (37.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.53 (dd, J = 17.4, 7.8 Hz, 3H), 7.43−7.39 (t, J = 8.0 Hz, 7H), 7.11 (d, J = 7.8 Hz, 1H), 7.04 (d, J = 7.05 Hz, 1H), 6.91−6.88 (t, J = 7.6 Hz, 1H), 3.93 (d, J = 14.5 Hz, 1H), 3.73 (d, J = 14.5 Hz, 1H), 2.71 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 30.5, 44.7, 46.5, 120.7, 121.5, 125.5, 127.5, 128.0, 128.5, 130.0, 130.8, 133.1, 134.8, 136.4, 139.2, 140.8, 181.7, 196.2; HRMS (EI) m/z calcd for $C_{24}H_{21}NO_2$ [M$^+$]: 355.1572; found 355.1565.

*1-Benzyl-3-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**15**).*[13b] Following the general procedure, the product was isolated as a white solid in 72% yield (54.5 mg); mp = 157−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.8 Hz, 2H), 7.53−7.49 (t, J = 8.0 Hz, 1H), 7.43−7.37 (dd, J = 14.7, 7.4 Hz, 4H), 7.35−7.31 (t, J = 8.0 Hz, 2H), 7.25−7.23 (d, J = 7.0 Hz, 1H), 7.14−7.08 (dd, J = 14.6, 7.4 Hz, 2H), 6.94−6.92 (d, J = 7.7 Hz, 1H), 6.74−6.72 (d, J = 7.7 Hz, 1H), 5.10−5.06 (d, J = 15.8 Hz, 1H), 4.98−4.94 (d, J = 15.8 Hz, 1H), 3.80−3.69 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 43.9, 45.3, 45.7, 109.2, 121.6, 122.1, 127.1, 127.3, 127.6, 127.9, 128.4, 128.6, 133.1, 133.7, 136.2, 142.8, 180.5, 195.8; HRMS (EI) m/z calcd for $C_{24}H_{21}NO_2$ [M$^+$]: 355.1572; found 355.1572.

*1,3-Dimethyl-3-((phenylsulfonyl)methyl)indolin-2-one (**16**).*[15a] Following the general procedure, the product was isolated as a white solid in 85% yield (64.8 mg); mp = 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.47 (m, 3H), 7.38−7.34 (t, J = 8.0 Hz, 2H), 7.29−7.25 (m, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.89−6.84 (dd, J = 13.2, 7.6 Hz, 2H), 3.88 (d, J = 14.6 Hz, 1H), 3.71 (d, J = 14.6 Hz, 1H), 3.16 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 26.4, 45.4, 61.7, 108.3, 122.4, 123.9, 127.6, 128.5, 128.7, 129.3, 133.2, 139.7, 143.1, 177.5; HRMS (EI) m/z calcd for $C_{17}H_{17}NO_3S$ [M]$^+$: 315.0929, found 315. 0926.

*5-Fluoro-1,3-dimethyl-3-((phenylsulfonyl)methyl)indolin-2-one (**17**).*[15a] Following the general procedure, the product was isolated as a white solid in 72% yield (57.5 mg); mp = 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.52 (m, 3H), 7.43−7.39 (m, 2H), 7.00−6.95 (dd, J = 8.8, 2.4 Hz, 1H), 6.79−6.70 (m, 2H), 3.87 (d, J = 14.6 Hz, 1H), 3.66 (d, J = 14.6 Hz, 1H), 3.19 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.2, 26.7, 46.0, 61.6, 108.8, 112.2, 112.4, 114.9, 115.1, 127.7, 129.0, 131.1, 133.6, 139.2, 139.9, 157.8, 160.2 (d, $1J_{C\text{-}F}$ = 240.0 Hz), 177.3; HRMS (EI) m/z calcd for $C_{17}H_{16}FNO_3S$ [M$^+$]: 333.0835; found, 333.0834.

*5-Chloro-1,3-dimethyl-3-((phenylsulfonyl)methyl)indolin-2-one (**18**).*[15a] Following the general procedure, the product was isolated as a white solid in 65% yield (54.0 mg); mp = 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.41−7.37 (t, J = 8.0 Hz, 2H), 7.22 (dd, J = 8.3, 1.9 Hz, 1H), 6.80 (dd, J = 8.7, 5.1 Hz, 2H), 3.89 (d, J = 14.7 Hz, 1H), 3.68 (d, J = 14.7 Hz, 1H), 3.21 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 26.6, 45.6, 61.6, 109.2, 124.4, 127.4, 127.7, 128.5, 128.8, 130.9, 133.5, 139.6, 141.9, 177.1; HRMS (EI) m/z calcd for $C_{17}H_{16}ClNO_3S$ [M$^+$]: 349.0539; found, 349.0538.

*5-Bromo-1,3-dimethyl-3-((phenylsulfonyl)methyl)indolin-2-one (**19**).*[15a] Following the general procedure, the product was isolated as a yellow solid in 59% yield (54.3 mg); mp = 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.57 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.41−7.38 (dd, J = 13.8, 7.7 Hz, 3H), 6.92 (s, 1H), 6.75 (d, J = 8.2 Hz, 1H), 3.89 (d, J = 14.8 Hz, 1H), 3.68 (d, J = 14.7 Hz, 1H), 3.21 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 26.6, 45.6, 61.6, 109.8, 115.0, 127.0, 127.4, 128.8, 131.3, 131.4, 133.6, 139.5, 142.4, 177.0; HRMS (EI) m/z calcd for $C_{17}H_{16}BrNO_3S$ [M$^+$]: 393.0034; found, 393.0031.

*5-Iodo-1,3-dimethyl-3-((phenylsulfonyl)methyl)indolin-2-one (**20**).*[14a] Following the general procedure, the product was isolated as a white solid in 58% yield (58.8 mg); mp = 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.52 (m, 2H), 7.44−7.37 (dd, J = 15.3, 7.6 Hz, 4H), 7.04 (s, 1H), 6.66−6.63 (d, J = 8.2 Hz, 1H), 3.88 (d, J = 14.8 Hz, 1H), 3.65 (d, J = 14.8 Hz, 1H), 3.20 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.2, 26.6, 45.4, 61.7, 85.1, 110.4, 127.4, 128.9, 131.6, 132.6, 133.8, 137.4, 139.6, 143.2, 176.8; HRMS (EI) m/z calcd for $C_{17}H_{16}INO_3S$ [M$^+$]: 440.9896; found, 440.9882.

*1,3-Dimethyl-2-oxo-3-((phenylsulfonyl)methyl)indoline-5-carbonitrile (**21**).*[14a] Following the general procedure, the product was isolated as a white solid in 80% yield (65.4 mg); mp = 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.58 (m, 2H), 7.51 (d, J = 7.7 Hz, 2H), 7.44 (m, 2H), 7.13 (s, 1H), 6.95 (d, J = 8.2 Hz, 1H), 3.91 (d, J = 14.7 Hz, 1H), 3.73 (d, J = 14.7 Hz, 1H), 3.28 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.8, 45.2, 61.4, 105.6, 108.8, 118.7, 127.2, 127.4, 129.1, 130.4, 133.8, 138.9, 139.6, 147.2, 177.4; HRMS (EI) m/z calcd for $C_{18}H_{16}N_2O_3S$ [M$^+$]: 340.0882; found, 340.0881.

*5-Methoxy-1,3-dimethyl-3-((phenylsulfonyl)methyl)indolin-2-one (**22**).*[14a] Following the general procedure, the product was isolated as a white solid in 55% yield (51.3 mg); mp = 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.48 (m, 3H), 7.40−7.36 (t, J = 8.0 Hz, 2H), 6.81−6.74 (m, 2H), 6.58 (s, 1H), 3.88 (d, J = 14.6 Hz, 1H), 3.67−3.64 (d, J = 11.5 Hz, 4H), 3.16 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 26.6, 46.0, 55.5, 61.8, 108.7, 111.1, 113.3, 127.8, 128.7, 130.6, 133.2, 136.7, 140.0, 155.8, 177.2; HRMS (EI) m/z calcd for $C_{18}H_{19}NO_4S$ [M$^+$]: 345.1035; found, 345.1030.

*7-Iodo-1,3-dimethyl-3-((phenylsulfonyl)methyl)indolin-2-one (**24**).* Following the general procedure, the product was isolated as a white solid in 63% yield (63.9 mg); mp = 180−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 1H), 7.59−7.52 (m, 3H), 7.45−7.41 (t, J = 7.7 Hz, 2H), 7.05−7.03 (d, J = 7.3 Hz, 1H), 6.64−6.61 (t, J = 7.7 Hz, 1H), 3.90 (d, J = 14.5 Hz, 1H), 3.65 (d, J = 14.5 Hz, 1H), 3.51 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.9, 30.5, 45.1, 61.8, 71.7, 123.9, 124.1, 127.8, 128.9, 132.3, 133.5, 139.5, 141.2, 143.6, 178.3; HRMS (EI) m/z calcd for $C_{17}H_{16}INO_3S$ [M$^+$]: 440.9896; found, 440.9888.

*1,3-Dimethyl-7-phenyl-3-((phenylsulfonyl)methyl)indolin-2-one (**25**).*[14a] Following the general procedure, the product was isolated as a yellow solid in 44% yield (40.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.52 (m, 3H), 7.42−7.39 (m, 7H), 7.11−7.03 (m, 2H), 6.91−6.87 (t, J = 8.0 Hz, 1H), 3.92 (d, J = 14.5 Hz, 1H), 3.72 (d, J = 14.5 Hz, 1H), 2.70 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 30.6, 45.0, 62.2, 121.8, 122.9, 125.7, 125.8, 127.7, 127.8, 128.9, 130.0, 130.3, 131.5, 133.3, 138.7, 140.1, 140.2, 178.6; HRMS (EI) m/z calcd for $C_{23}H_{21}NO_3S$ [M$^+$]: 391.1242; found, 391.1236.

*1-Benzyl-3-methyl-3-((phenylsulfonyl)methyl)indolin-2-one (**27**).*[14a] Following the general procedure, the product was isolated as a colorless oil in 94% yield (86.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.50 (dd, J = 7.1, 4.5 Hz, 3H), 7.38−7.24 (m, 7H), 7.14−7.10 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.82−6.79 (m, 1H), 6.70 (d, J = 7.9 Hz, 1H), 4.99 (d, J = 15.7 Hz, 1H), 4.79 (d, J = 15.8 Hz, 1H), 3.93 (d, J = 14.5 Hz, 1H), 3.75 (d, J = 14.6 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.9, 44.1, 45.6, 61.5, 109.4, 122.4, 123.8, 127.2, 127.5, 127.6, 128.3, 128.7, 128.8, 129.4, 133.3, 135.7, 140.0, 142.3, 177.7; HRMS (EI) m/z calcd for $C_{23}H_{21}NO_3S$ [M$^+$]: 391.1242; found, 391.1238.

*2-((1-Methyl-2-oxo-3-((phenylsulfonyl)methyl)indolin-3-yl)-methyl)isoindoline-1,3-dione (**29**).* Following the general procedure, the product was isolated as a white solid in 48% yield (50.5 mg); mp = 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.81 (dd, J = 4.7, 3.7 Hz, 2H), 7.73−7.71 (m, 2H), 7.55−7.49 (dd, J = 17.5, 7.8 Hz, 3H), 7.39−7.35 (t, J = 7.6 Hz, 2H), 7.33−7.29 (t, J = 7.7 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.89−6.85 (m, 2H), 4.07 (s, 2H), 3.96 (d, J = 14.2 Hz, 1H), 3.81 (d, J = 14.2 Hz, 1H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.7, 44.1, 49.3, 59.3, 108.6, 122.3, 123.6, 124.8, 125.4, 127.8, 128.8, 129.4, 131.5, 133.3, 134.2, 139.9, 143.8, 167.9, 174.8; HRMS (EI) *m*/*z* calcd for $C_{25}H_{20}N_2O_5S$ [M^+]: 460.1093; found, 460.1088.

*3-(((4-Chlorophenyl)sulfonyl)methyl)-1,3-dimethylindolin-2-one (**30**).*[15a] Following the general procedure, the product was isolated as a white solid in 73% yield (61.9 mg); mp = 169−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.28 (dd, *J* = 14.9, 8.0 Hz, 5H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.91−6.89 (m, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 3.91 (d, *J* = 14.6 Hz, 1H), 3.69 (d, *J* = 14.6 Hz, 1H), 3.17 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.5, 45.5, 61.9, 108.4, 122.5, 123.9, 128.7, 129.0, 129.2, 129.2, 138.1, 140.0, 143.2, 177.4; HRMS (EI) *m*/*z* calcd for $C_{17}H_{16}ClNO_3S$ [M^+]: 349.0539; found, 349.0535.

*1,3-Dimethyl-3-(tosylmethyl)indolin-2-one (**32**).*[15a] Following the general procedure, the product was isolated as a white solid in 60% yield (45.6 mg); mp = 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.94−6.90 (m, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.85 (d, *J* = 14.5 Hz, 1H), 3.66 (d, *J* = 14.5 Hz, 1H), 3.16 (s, 3H), 2.39 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 25.4, 26.4, 45.6, 61.8, 108.3, 122.4, 124.1, 127.8, 128.5, 129.4, 129.5, 137.0, 143.2, 144.2, 177.6; HRMS (EI) *m*/*z* calcd for $C_{18}H_{19}NO_3S$ [M^+]: 329.1086; found, 329.1081.

*3-(((4-Methoxyphenyl)sulfonyl)methyl)-1,3-dimethylindolin-2-one (**33**).*[15a] Following the general procedure, the product was isolated as a white solid in 55% yield (45.6 mg); mp = 120−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H), 7.31−7.27 (m, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.96−6.92 (m, 1H), 6.83 (m, 3H), 3.86 (d, *J* = 16.4 Hz, 4H), 3.66 (d, *J* = 14.5 Hz, 1H), 3.15 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.5, 45.6, 55.6, 62.0, 108.4, 114.0, 122.5, 124.1, 128.5, 129.6, 130.0, 131.4, 143.2, 163.4, 177.7; HRMS (EI) *m*/*z* calcd for $C_{18}H_{19}NO_4S$ [M] $^+$: 345.1035; found, 345.1026.

*1,3-Dimethyl-3-(((2-nitrophenyl)sulfonyl)methyl)indolin-2-one (**34**).* Following the general procedure, the product was isolated as a yellow solid in 45% yield (39.3 mg); mp = 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.8 Hz, 1H), 8.08 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.64−7.60 (t, *J* = 7.9 Hz, 1H), 7.24−7.20 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.79−6.71 (dt, *J* = 14.8, 7.3 Hz, 2H), 4.00 (d, *J* = 14.8 Hz, 1H), 3.75 (d, *J* = 14.8 Hz, 1H), 3.24 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.3, 26.6, 45.4, 62.1, 108.8, 122.3, 123.3, 127.8, 128.8, 129.0, 130.3, 133.1, 141.9, 143.5, 177.1; HRMS (EI) *m*/*z* calcd for $C_{17}H_{16}N_2O_5S$ [M^+]: 360.0780; found, 360.0770.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00773.

Copies of ^{1}H and ^{13}C spectra for all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ccguo@hnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Science Foundation of China (Nos. 21372068, 21572049) is gratefully acknowledged.

■ REFERENCES

(1) For some selected examples, see: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *2003*, 2209. (c) Lin, H.; Danishefsky, S. J. *Angew. Chem.* **2003**, *115*, 38; *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (d) Jensen, B. S. *CNS Drug Rev.* **2002**, *8*, 353. (e) da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273. (f) Zhou, F.; Liu, Y.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.

(2) For some selected examples, see: (a) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043. (b) Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. *13*, pp 163−236. (c) Takano, S.; Ogasawara, K. In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, CA, 1989; Vol. *36*, pp 225−251.

(3) For some selected examples of arylphosphorylation of activated alkenes, see: (a) Li, Y. M.; Sun, M.; Wang, H. L.; Tian, Q. P.; Yang, S. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972. (b) Li, Y. M.; Shen, Y.; Chang, K. J.; Yang, S. D. *Tetrahedron* **2014**, *70*, 1991.

(4) For some selected examples of alkylarylation of activated alkenes, see: (a) Li, Z.; Zhang, Y.; Zhang, L.; Liu, Z. Q. *Org. Lett.* **2014**, *16*, 382. (b) Xie, J.; Xu, P.; Li, H.; Xue, Q.; Jin, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 5672. (c) Wei, W.-T.; Zhou, M.-B.; Fan, J.-H.; Liu, W.; Song, R.-J.; Liu, Y.; Hu, M.; Xie, P.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638. (d) Zhou, S.-L.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem.—Eur. J.* **2013**, *19*, 12970. (e) Meng, Y.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 7540. (f) Wang, H.; Guo, L.-N.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 10370.

(5) For some selected examples of diarylation of activated alkenes, see: Fu, W.; Xu, F.; Fu, Y.; Zhu, M.; Yu, J.; Xu, C.; Zou, D. *J. Org. Chem.* **2013**, *78*, 12202.

(6) For some selected examples of arylnitration of activated alkenes, see: (a) Li, Y. M.; Wei, X. H.; Li, X. A.; Yang, S. D. *Chem. Commun.* **2013**, *49*, 11701. (b) Li, Y. M.; Shen, Y.; Chang, K. J.; Yang, S. D. *Tetrahedron Lett.* **2014**, *55*, 2119. (c) Shen, T.; Yuan, Y.; Jiao, N. *Chem. Commun.* **2014**, *50*, 554.

(7) For some selected examples of aryltrifluoromethylation of activated alkenes, see: (a) Yang, F.; Klumphu, P.; Liang, Y. M.; Lipshutz, B. H. *Chem. Commun.* **2014**, *50*, 936. (b) Wang, J. Y.; Su, Y. M.; Yin, F.; Bao, Y.; Zhang, X.; Xu, Y. M.; Wang, X. S. *Chem. Commun.* **2014**, *50*, 4108. (c) Li, L.; Deng, M.; Zheng, S. C.; Xiong, Y. P.; Tan, B.; Liu, X. Y. *Org. Lett.* **2014**, *16*, 504. (d) Wei, W.; Wen, J.; Yang, D.; Liu, X.; Guo, M.; Dong, R.; Wang, H. *J. Org. Chem.* **2014**, *79*, 4225. (e) Xu, P.; Xie, J.; Xue, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem.—Eur. J.* **2013**, *19*, 14039. (f) Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 504. (g) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G.-S. *J. Am. Chem. Soc.* **2012**, *134*, 878. (h) Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480. (i) Kong, W. Q.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086.

(8) For some selected examples of halogenation of activated alkenes, see: (a) Wei, H.-L.; Piou, T.; Dufour, J.; Neuville, L.; Zhu, J. P. *Org. Lett.* **2011**, *13*, 2244. (b) Fabry, D. C.; Stodulski, M.; Hoerner, S.; Gulder, T. *Chem.—Eur. J.* **2012**, *18*, 10834. (c) Zhang, M.-Z.; Sheng, W.-B.; Jiang, Q.; Tian, M.; Yin, Y.; Guo, C.-C. *J. Org. Chem.* **2014**, *79*, 10829.

(9) For some selected examples of azidoarylation of activated alkenes, see: (a) Wei, X. H.; Li, Y. M.; Zhou, A. X.; Yang, T. T.; Yang, S. D. *Org. Lett.* **2013**, *15*, 4158. (b) Yuan, Y.; Shen, T.; Wang, K.; Jiao, N. *Chem.—Asian J.* **2013**, *8*, 2932. (c) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985.

(10) For some selected examples, see: (a) Cordell, G. A.; Saxton, J. E. In *Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1981; Vol. *20*, p 3. (b) Hino, T.; Nakagawa, M. *Alkaloids* **1989**, *34*, 1. (c) Sevenet, T.; Pusset, J. *Alkaloids* **1996**, *48*, 1. (d) Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical & Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Amsterdam, 1999; Vol. *13*.

(11) For some selected examples, see: (a) Jensen, B. S. *CNS Drug Rev.* **2002**, *8*, 353. (b) Sevenet, T.; Pusset, J. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1996; Vol. *48*, pp 1−73. (c) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (d) Brown, D. A.; Garthwaite, J.; Hayashi, E.; Yamada, S. *Br. J. Pharmacol.* **1976**, *58*, 157.

(12) (a) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (b) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758. (c) Zhou, F.; Liu, Y.-L.;

Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381 and references cited therein.

(13) (a) Zhou, M.-B.; Song, R.-J.; Ouyang, X.-H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690. (b) Wang, H.; Guo, L.-N.; Duan, X.-H. *Adv. Synth. Catal.* **2013**, *355*, 2222. (c) Ouyang, X.-H.; Song, R.-J.; Li, J.-H. *Eur. J. Org. Chem.* **2014**, *2014*, 3395. (d) Niu, B.; Xie, P.; Zhao, W.; Zhou, Y.; Bian, Z.; Pittman, C. U.; Zhou, A. *RSC Adv.* **2014**, *4*, 43525. (e) Zheng, L.; Huang, H.; Yang, C.; Xia, W. *Org. Lett.* **2015**, *17*, 1034. (f) Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2015**, *47*, 1195. (g) Bergonzini, G.; Cassani, C.; Wallentin, C. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14066. (h) Zhang, M.-Z.; Ji, P.-Y.; Liu, Y.-F.; Guo, C.-C. *J. Org. Chem.* **2015**, *80*, 10777.

(14) For some selected examples, see: (a) Shen, T.; Yuan, Y.; Song, S.; Jiao, N. *Chem. Commun.* **2014**, *50*, 4115. (b) Fontecave, M.; Ollagnier-de-Choudens, S.; Mulliez, E. *Chem. Rev.* **2003**, *103*, 2149. (c) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, *2011*, 6821. (d) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *2009*, 3003. (e) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (f) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *2003*, 2209. (g) Lu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 7156.

(15) (a) Wei, W.; Wen, J.; Yang, D.; Du, J.; You, J.; Wang, H. *Green Chem.* **2014**, *16*, 2988. (b) Li, X.; Xu, X.; Hu, P.; Xiao, X.; Zhou, C. *J. Org. Chem.* **2013**, *78*, 7343. (c) Tian, Q.; He, P.; Kuang, C. *Org. Biomol. Chem.* **2014**, *12*, 6349. (d) Shi, L.; Wang, H.; Yang, H.; Fu, H. *Synlett* **2015**, *26*, 688. (e) Zuo, J.; Wu, Z.-J.; Zhao, J.-Q.; Zhou, M.-Q.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 634. (f) Xia, D.; Miao, T.; Li, P.; Wang, L. *Chem.—Asian J.* **2015**, *10*, 1919. (g) Liu, J.; Zhuang, S.; Gui, Q.; Chen, X.; Yang, Z.; Tan, Z. *Eur. J. Org. Chem.* **2014**, *2014*, 3196.

(16) Mi, X.; Wang, C.; Huang, M.; Wu, Y.; Wu, Y. *J. Org. Chem.* **2015**, *80*, 148.

(17) Kiyokawa, K.; Kosaka, T.; Minakata, S. *Org. Lett.* **2013**, *15*, 4858.

(18) For some selected examples, see: (a) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. *I*, pp 213−1119. (b) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004, and references therein. (c) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486.

(19) Wen, J.; Wei, W.; Xue, S.; Yang, D.; Lou, Y.; Gao, C.; Wang, H. *J. Org. Chem.* **2015**, *80*, 4966.