JOC The Journal of Organic Chemistry

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Gold- and Iodine-Mediated Internal Oxygen Transfer of Nitrone- and Sulfoxide-Functionalized Alkynes

Dan Chen,[†,‡] Guoyong Song,[‡,§] Aiqun Jia,[†,*] and Xingwei Li[*,‡,§]

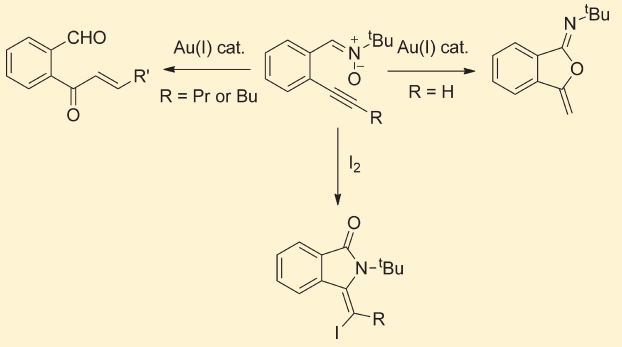
[†]School of Environmental and Biological Engineering, Nanjing University of Science and Technology, Nanjing 210014, China

[‡]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

[§]The Scripps Research Institute, Scripps Florida, Jupiter, Florida 33458, United States

Supporting Information

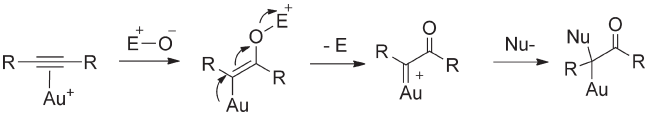
ABSTRACT: Intramolecular oxygen transfer of nitrone− and sulfoxide−alkynes was achieved using a catalytic amount of Au(I) and a stoichiometric amount of iodine. The Au(I)-catalyzed cyclization of a nitrone−terminal alkyne afforded a cyclic iminoester, while cyclization of analogous nitrone−internal alkynes yielded aldehyde−enones. The I_2-mediated cyclization of nitrone−alkynes afforded iodinated γ-lactams and the I_2-mediated internal redox of the closely related sulfoxide−alkynes gave diketones functionalized with a thioether.



Cyclization of heteroatom-functionalized alkynes and alkenes represents an important strategy in the construction of heterocycles. It is well-known that "soft" electrophilic reagents, particularly gold(I), platinum(II), and I^+, can promote the attack of a series of carbon, oxygen, and nitrogen nucleophiles at alkynes, leading to the construction of new skeletons. In these reactions, the electrophilic catalysts or reagents not only serve to activate the alkyne toward nucleophilic additions but also act in a unique way to stabilize the cationic species generated in the catalytic cycle. This area is rapidly growing owing to the wide scope of substrates that can be readily applied for the construction of diversified skeletons under mild conditions.[1]

Among various nucleophiles that added to alkynes, the polar E^+-O^- (E = N and S) groups in nitrones, nitro compounds, amine *N*-oxides, and sulfoxides are particularly interesting. They are both nucleophiles and O-atom donors. By using gold catalysis, the groups of Toste,[2] Zhang,[3] Liu,[4] and Shin[5] have successfully coupled the O-atom transfer with the subsequent C−O, C−N, C−S, and C−C bond-forming reactions, where O-atom transfer generates distinctive metal-stabilized α-oxo carbenoid intermediate, and this chemistry has been recently reviewed by us.[6] The oxo carbenoid intermediate was believed to result from an overall addition−elimination process that involves the backside addition of a polar E^+-O^- bond to a metal-activated alkyne followed by elimination of the E group (Scheme 1).[2,6] Although the structures of metal-stabilized oxo carbenoids are not well understood,[2g] they have been proposed in an increasing number of reports and they are susceptible to the attack of a series of nucleophiles including olefins,[5b,7] imines,[5a,b] arenes,[2f,3e,4a,8] and migrating hydrides[3a,b] and alkyls,[5c] leading to the construction of C−X bonds (X = C, O, S, N).[6]

Scheme 1. Formation of Oxo Carbenoids

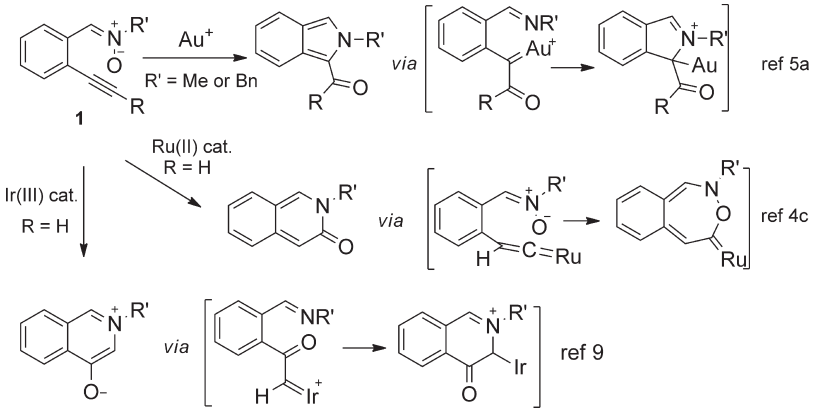


Previous reports have shown that three different types of products have been isolated for the catalytic cyclization of nitrone−alkynes. When gold catalysts such as IPrAuOTf were used (Scheme 2),[5a] isoindoles were isolated in moderate yield. In contrast, TpRu(II)-catalyzed (Tp = tris(pyrazolyl)borate) cyclization of the same terminal alkynes afforded 3-isoquinolones.[4c] Recently, we have reported a new selectivity of the cyclization of nitrone−terminal alkynes to rare ylidic azomethines using iridium(III) catalysts.[9] Notably, this selectivity cannot be achieved using gold catalysts.[5b] These different cyclization pathways indicated that intrinsically different metals can mediate the cyclization of nitrone−alkynes to yield complementary heterocycles. Achieving complementary reaction selectivity through rational design should be an important task. We noted that previously reported cyclization reactions of nitrone−alkynes are limited to those substrates with *N*-Me and -Bn groups.[4c,5a,5b] We now report that the selectivity of nitrone−alkyne cyclization can

Received: July 6, 2011

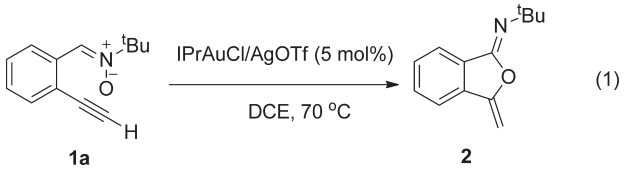
   dx.doi.org/10.1021/jo201347r | J. Org. Chem. XXXX, XXX, 000–000

Scheme 2. Reported Cyclization Products of Nitrone−Alkynes



be tuned by way of substrate control. Moreover, as a related electrophilic reagent, I_2 can also mediate the cyclization of nitrone- and sulfoxide-functionalized alkynes.

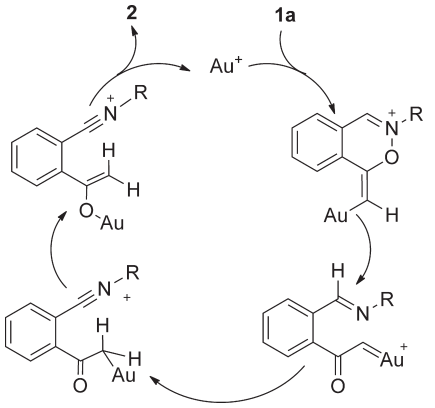
We started to apply the *N*-^{t}Bu-substituted nitrone−terminal alkyne as a substrate, where the introduction of the ^{t}Bu group should electronically and sterically tune the substrate. Smooth cyclization of **1a** occurred when IPrAuCl/AgOTf (5 mol %) was applied as a catalyst (eq 1). The cyclization product was isolated in 68% yield and was characterized as a cyclic iminoester on the basis of NMR spectroscopy (eq 1). In the ^{13}C NMR spectrum, the vinyl CH_2 resonates characteristically at δ 84.5 (benzene-d_6), and the ^{t}BuN=*C* signal appears at δ 155.9. The transformation of **1a** to iminoester **2** is proposed to occur via a reactive gold α-oxo carbenoid tethered to an aldimine group (Scheme 3). Instead of nucleophilically adding to the carbenoid, which was suggested in the reaction of *N*-Bn and -Me substituted nitrone−alkynes,[5a,b] the bulky aldimine group prefers to undergoes a hydride shift[3a,b] to the carbenoid to yield a nucleophilic gold enolate tethered to an electrophilic nitrilium. *O*-attack of the enolate at the nitrilium and subsequent deauration afforded the final product (Scheme 3). We noted that *O*-attack of gold enolates has not been previously suggested, although the *C*-attack is well-known.[5a,b] The switch of the reaction pathway of the oxo carbenoid intermediate is ascribed to the electronic and steric effects of the ^{t}Bu substituent. Sterically, the bulky ^{t}Bu group disfavors the nucleophilic attack of the imine nitrogen. Electronically, the stronger donating ability of the ^{t}Bu should favor the 1,5-migration of the aldimine hydrogen. Both factors contribute to the shift of the reaction selectivity to the observed iminoester product.



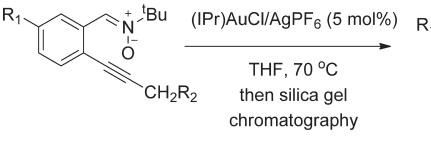
(1)

The substrate was then extended to nitrone−internal alkynes. Surprisingly, reactions conducted under essentially the same conditions afforded a different class of product. The isolated product (after chromatography) is acyclic. Thus, the internal redox reaction of substrates **1b**−**d** yielded aldehyde−enone products (**3b**−**d**) in 48−60% yield, and these products were fully characterized by NMR spectroscopy. A proposed mechanism for

Scheme 3. Suggested Mechanism of the Cyclization of Nitrone 1a



this transformation is given in Scheme 4. In line with the intermediacy of the oxo carbenoid suggested in the reaction of the nitrone−-terminal alkyne, this carbenoid prefers to undergo a formal 1,2-CH insertion and demetalation,[2f,3f] leading to an enone−imine intermediate. Similarly, the steric bulk of the *N*-^{t}Bu group in the imine group disfavors any nucleophilc addition to carbenoid. Hydrolysis of the imine readily occurred during the chromatographic separation, yielding the final product. We noted that an intramolecular version of the oxidation of alkynes to enones has been recently reported using pyridine *N*-oxides as oxidants.[3c] We noted that nitrones bearing diaryl-substituted alkynes failed to undergo any desired transformation, and only decomposition products were observed. The biased aryl and alkyl substituents in the alkyne unit should better polarize the alkyne toward nucleophilic attack. In addition, the reduced steric bulk of primary alkyl substituents also favors this transformation.



(2

3b: R_1 = H, R_2 = Et, 55%
3c: R_1 = H, R_2 = Pr, 48%
3d: R_1 = OMe, R_2 = Et, 66%

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Scheme 4. Proposed Pathway of Internal Redox Reaction of Nitrone−Internal Alkynes

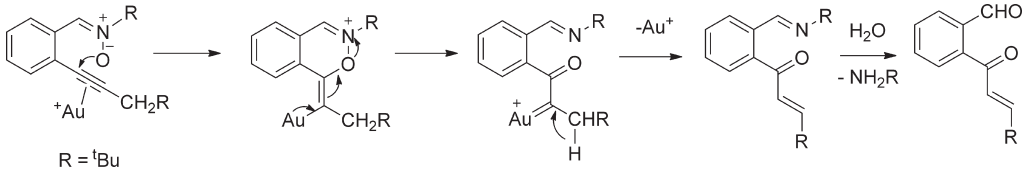
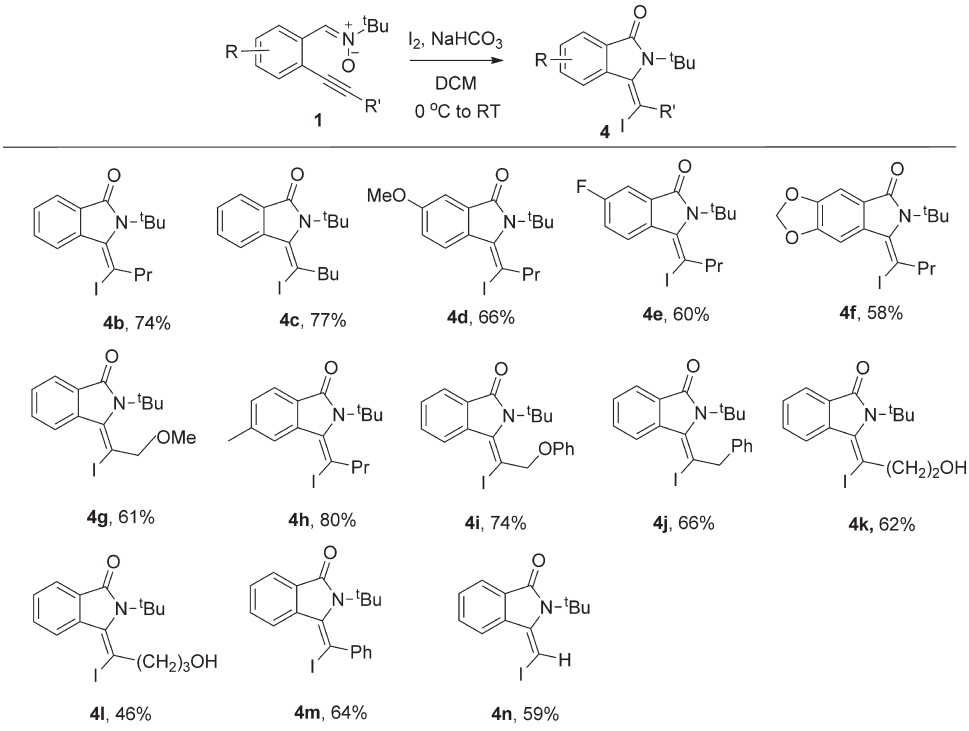


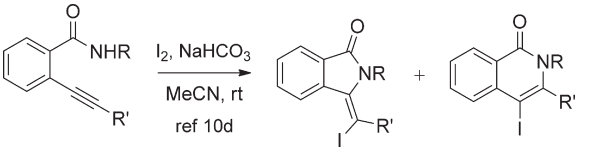
Table 1. Iodine-Induced Cyclization of Nitrone−Alkynes[a,b]



[a] Conditions: nitrone (0.21 mmol), $NaHCO_3$ (0.412 mmol, 2.0 equiv), iodine (0.412 mmol, 2.0 equiv), DCM (3 mL), 0 °C to rt, 8 h. [b] Isolated yield.

I_2 is also well-known as an electrophile to activate π bonds, and various reports have detailed the I_2-mediated activation of alkynes toward nucleophilic attack.[10] In this sense, I_2 and Au(I) behave similarly in inducing cyclization. We reasoned that I_2 could well activate the C≡C bond in nitrone−alkynes. Indeed, stirring a solution of nitrone−alkyne **1b** with I_2 afforded an iodinated lactam in good selectivity. The yield of the product was improved to 74% when $NaHCO_3$ was introduced to neutralize the released HI (0 °C to rt). Under these conditions, the cyclization of various nitrone−alkynes afforded lactams with an exocyclic double bond as the only isolated product in yields ranging from 46 to 80% (Table 1). The identity of the product **4b** has been confirmed on the basis of NMR spectroscopy. In particular, the *C*(vinyl)−I signal appears at a characteristic high field (δ 79.5) in ^{13}C NMR spectroscopy, and NOE spectroscopy revealed that the iodo and the amide are in a *trans* orientation. The scope of this cyclization reaction is broad (Table 1). Terminal and internal alkynes with a simple alkyl, aryl, or hydroxylalkyl group can be tolerated. This methodology readily allowed for the construction of γ-lactams under mild conditions. In addition, the presence of an iodo group should be an important handle for further functionalization of the cyclized products, giving rise to molecular complexity.[10d] The isoindolin-1-one ring system represents a key structural motif in various natural and synthetic products that exhibit a wide range of biological activities.[11] The current interest evoked by these fused phenanthrene lactams arises from their important pharmaceutical and biological activities as immunostimulant and anticancer agents.[11]

Larock has reported that I_2 can promote the electrophilic cyclization of structurally related *o*-(1-alkynyl)benzamides (eq 3).[10d] The selectivity of this reaction, however, can be an issue, and in many cases, both 1-isoquinolones and 1-isoindolones were isolated. In addition, no cyclization was observed for such terminal alkynes. In contrast, our current reaction system afforded 1-isoindolones as the only product.



(3)

To probe the mechanism of this reaction, amide **5** was synthesized and subjected to reaction conditions, and it gave

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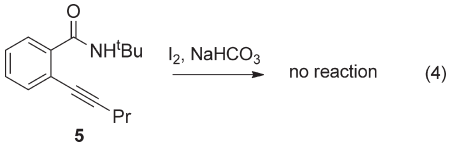
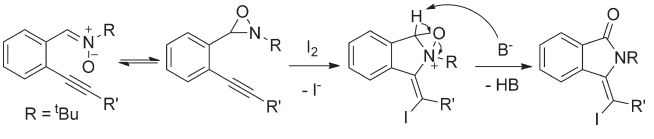
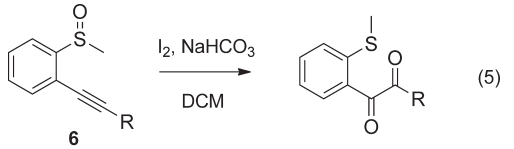
no cyclization product (eq 4). In addition, no isomerization product was observed when a simple *N-tert*-butyl-α-phenyl-nitrone was subjected to the standard conditions. These results indicate that the intermediacy of an amide is not relevant. Therefore, isomerization of nitrone to amide[12] is not plausible. To account for this reaction, a likely mechanism is given in Scheme 5. The nitrone moiety is proposed to undergo nucleophilic cyclization to give an oxaziradine intermediate, and this process can be catalyzed by a Lewis acid.[13] Activation of the C≡C bond by electrophilic I^+ is followed by nucleophilic addition of the oxaziradine nitrogen to give a vinyl iodide species, which is proposed to undergo base-promoted elimination of the amine group, leading to the scission of the strained oxaziradine ring and the formation of the final product.



Sulfoxides are the earliest substrates studied in Au-catalyzed internal redox cyclization reactions,[2h,3e] and the polar S^+-O^- bond is comparable to the N^+-O^- one in terms of both bond polarity and the O-atom donor character. Recent studies have shown that gold is well-known in mediating both inter- and intramolecular oxygen transfer from sulfoxides to alkynes.[4a,8,14] Although early examples suggested that this transformation involved the intermediacy of α-oxo carbenoids (Scheme 1), alternative mechanisms can be possible.[4a,8] In line with the above I_2-mediated cyclization of nitrone−alkynes, sulfoxide−alkynes smoothly reacted with I_2 under essentially the same conditions as nitrone−alkynes, leading to α-diones (benzil), with the sulfoxide group being reduced to a thioether (eq 5). Thus diones **7a**−**c** were isolated in 49−74% yield under mild conditions, where alkyne substrates bearing both alkyl and aryl substituents are applicable. Here the mild conditions and the use of cheap reagents make this system an attractive one. Very recently, Au(I)-catalyzed intermolecular oxidation of alkynes to diones has been achieved using a stoichiometric amount of PhS(O)Ph as an oxidant.[14] The isolation of the same type of product under either I_2 or Au(I) mediation suggests that these systems may follow similar pathways featuring the scenario of electrophilic activation of alkynes. A plausible mechanism to account for this internal redox transformation is given in Scheme 6. I_2 activation of the alkyne unit for the nucleophilic attack of the S^+-O^- bond gives an iodovinyl intermediate. In fact, this attack can follow either 5-exo or 6-endo selectivity (shown for 5-exo only). The resulting vinyl intermediate undergoes exocyclic nucleophilic addition of the iodide, leading to an α,α-diiodoketone, hydrolysis of which yields the final diketone product. α-Diketones are known to play an important role in organic synthesis.[15]

Scheme 5. Plausible Pathway of I_2-Mediated Cyclization of Nitrone−Alkynes





7a: R = ^{n}Pr, 74%
7b: R = Ph, 68%
7c: R = *p*-(C_6H_4)OMe, 49%

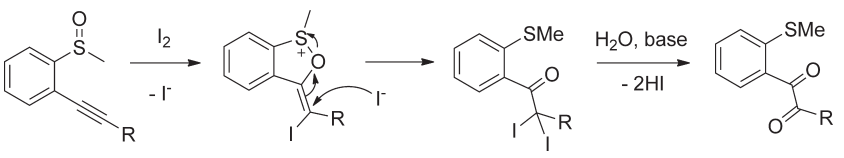
In summary, we achieved the intramolecular oxygen transfer of nitrone− and sulfoxide−alkynes mediated by a catalytic amount of Au(I) and a stoichiometric amount of I_2. Significant substituent effects in both the nitrone and the alkyne units were observed. The Au(I)-catalyzed cyclization of a nitrone−terminal alkyne with an *N*-^{t}Bu nitrone afforded a cyclic iminoester. In contrast, reactions of the directly analogous nitrone−internal alkynes yielded aldehyde−enones. In both cases, gold α-oxo carbenoids were suggested as key intermediates. These results stand in sharp contrast to those reported for nitroalkynes with *N*-Bn and -Me substituents under essentially the same conditions. The electronic and steric effects of the nitrone *N*-group clearly played a key role in controlling the reactions selectivity. It is the bulky and donating character the *N*-^{t}Bu group that changed the reaction patterns of the oxo carbenoid intermediate.

The I_2-mediated cyclization of nitrone−alkynes afforded iodinated γ-lactams, a process with formal 1,2-oxygen transfer from the N−O bond to the nitrone carbon. This transformation applied to a broad scope of nitrone−internal and −terminal alkynes with high selectivity under mild conditions. The I_2-mediated internal redox of the closely related sulfoxide−alkynes in the presence of water gave diketones functionalized with thioethers. In this reaction the transfer of the oxygen from S−O to the alkyne is also proposed to occur via an addition−elimination mechanism, a scenario similar to that in Au(I)-catalyzed internal redox of nitrone− and sulfoxide−alkynes. The versatility of the reaction patterns and the diversity of the reaction products may prove useful in the synthesis of complex structures.

EXPERIMENTAL SECTION

General Considerations. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, benzene-d_6, or acetone-d_6 on a 400 or 500 MHz spectrometer at 298 K. The chemical shift is given as dimensionless δ values and is frequency referenced to $SiMe_4$ in ^{1}H and ^{13}C NMR spectroscopy. Infrared

Scheme 6. Pathway of I_2-Mediated Internal Redox Reactions of Sulfoxide−Alkynes



dx.doi.org/10.1021/jo201347r |*J. Org. Chem.* XXXX, XXX, 000–000

spectra were obtained using neat films on a sodium chloride window. High-resolution mass spectra were obtained in ESI (cation mode). All other reagents were used as received from commercial sources. Nitrones were prepared according to literature reports.[4c,5a]

Synthesis and Characterization of Compound 2. Nitrone−alkyne **1a** (50 mg, 0.249 mmol), IPrAuCl (7.7 mg, 5 mol %), and AgOTf (3.2 mg, 5 mol %) were weighed into a pressure tube, to which was added dichloromethane (5 mL). After being purged with nitrogen, the mixture was stirred at 70 °C for 12 h. The mixture was then diluted with CH_2Cl_2 and filtered through Celite. All volatiles were removed under reduced pressure, and the residue obtained was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to give **2** (24.4 mg, 0.169 mmol, 68%). ^{1}H NMR (500 MHz, benzene-d_6): δ 7.67−7.64 (m, 1H), 6.86−6.85 (m, 1H), 6.78−6.72 (m, 2H), 4.59 (d, J = 2.5 Hz, 1H), 4.38 (d, J = 2.5 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, benzene-d_6): δ 155.9, 150.8, 135.9, 132.7, 131.1, 129.9, 123.6, 120.1, 84.5, 54.8, 30.8. HRMS (ESI): calcd for $[C_{13}H_{15}NO + H]^+$ 202.1232, found 202.1235.

Representative Procedure for the Synthesis of Compounds 3. Nitrone **1b** (50 mg, 0.206 mmol), IPrAuCl (6.4 mg, 5 mol %), and AgOTf (2.6 mg, 5 mol %) were weight into a 10 mL pressure tube, to which was added THF (5 mL). After being purged with nitrogen, the mixture was stirred at 70 °C for 12 h. The mixture was then diluted with CH_2Cl_2 and filtered through Celite. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (10% EtOAc in petroleum ether) to give **3b** as a yellow oil (21.3 mg, 0.113 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H), 7.91−7.89 (m, 1H), 7.59−7.56 (m, 2H), 7.49−7.47 (m, 1H), 6.71 (td, J = 15.8, 6.2 Hz, 1H), 6.51 (td, J = 15.8, 1.6 Hz, 1H), 2.27−2.23 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 191.0, 154.3, 141.8, 135.4, 133.1, 130.7, 129.5, 129.4, 128.4, 25.9, 12.0. HRMS (ESI): calcd for $[C_{12}H_{12}O_2 + H]^+$ 189.0916, found 189.0919.

Compound **3c** was obtained as a yellow oil in 48% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ 10.08 (s, 1H), 7.95 (dd, J = 7.2, 2.0 Hz, 1H), 7.79−7.67 (m, 3H), 6.77−6.70 (m, 1H), 6.63 (d, J = 17.2 Hz, 1H), 2.32−2.26 (m, 2H), 1.56−1.47 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 194.8, 191.9, 152.4, 142.6, 136.8, 134.0, 131.7, 131.0, 130.2, 129.4, 35.2, 21.9, 13.9. HRMS (ESI): calcd for $[C_{13}H_{14}O_2 + H]^+$ 203.1072, found 203.1076.

Compound **3d** was obtained as a yellow oil in 66% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ 10.11 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 2.8 Hz, 1H), 7.26 (dd, J = 8.4, 2.8 Hz, 1H), 6.97−6.90 (m, 1H), 6.78 (d, J = 16.0 Hz, 1H), 3.95 (s, 3H), 2.38−2.31 (m, 2H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 192.0, 191.7, 162.7, 152.6, 139.9, 134.4, 131.9, 128.3, 118.5, 113.6, 56.0, 26.0, 12.2. HRMS (ESI): calcd for $[C_{13}H_{14}O_3 + H]^+$ 219.1021, found 219.1024.

Representative Synthesis of Compounds 4. Nitrone **1b** (50 mg, 0.206 mmol), $NaHCO_3$ (34.6 mg, 0.412 mmol, 2.0 equiv), and dichloromethane (3 mL) were placed in a flask, to which was added dropwise a solution of iodine (104.4 mg, 0.412 mmol, 2.0 equiv) in DCM (2 mL) at 0 °C. The mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed (3×) with saturated aq $Na_2S_2O_3$. The combined organic extracts were dried with Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (5% EtOAc in petroleum ether) to give **4b** as a yellow oil (49.9 mg, 0.152 mmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.54 (t, J = 7.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 2.94 (t, J = 7.0 Hz, 2H), 1.71−1.64 (m, 2H), 1.44 (s, 9H), 0.98 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 147.6, 134.9, 133.2, 130.8, 129.7, 123.8, 123.4, 79.5, 54.3, 41.7, 30.2, 22.3, 13.0. IR (cm^{-1}): 1778, 1672, 1397, 1156, 1097, 997, 743. HRMS (ESI): calcd for $[C_{16}H_{20}INO + H]^+$ 370.0668, found 370.0671.

Compound **4c** was obtained as a yellow solid in 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.56−7.53 (m, 1H), 7.48−7.45 (m, 1H), 2.96 (t, J = 7.5 Hz, 2H), 1.66−1.60 (m, 2H), 1.44 (s, 9H), 1.42−1.39 (m, 2H), 0.96 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 147.4, 134.9, 133.3, 130.6, 129.6, 123.8, 123.4, 79.6, 54.3, 39.7, 31.3, 30.2, 21.7, 14.0. IR (cm^{-1}): 1774, 1684, 1385, 1146, 999, 760. HRMS (ESI): calcd for $[C_{17}H_{22}INO + H]^+$ 384.0824, found 384.0827.

Compound **4d** was obtained as a yellow solid in 66% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (d, J = 9.0 Hz, 1H), 7.25 (d, J = 3.0 Hz, 1H), 7.09 (dd, J = 8.5, 2.0 Hz, 1H), 3.89 (s, 3H), 2.90 (t, J = 7.5 Hz, 2H), 1.69−1.62 (m, 2H), 1.44 (s, 9H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 150.4, 147.5, 135.3, 128.0, 125.1, 119.6, 105.4, 55.8, 54.3, 41.4, 30.2, 29.9, 22.4, 13.0. IR (cm^{-1}): 1701, 1487, 1294, 1211, 1078, 1032, 822. HRMS (ESI): calcd for $[C_{17}H_{22}INO_2 + H]^+$ 400.0773, found 400.0775.

Compound **4e** was obtained as a yellow solid in 60% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (dd, J = 9.0, 4.5 Hz, 1H), 7.49 (dd, J = 8.0, 2.5 Hz, 1H), 7.26−7.22 (m, 1H), 2.91 (t, J = 7.5 Hz, 2H), 1.70−1.63 (m, 2H), 1.42 (s, 9H), 0.98 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.6 (d, J_{F-C} = 250.3 Hz), 148.9, 147.1, 135.8 (d, J_{F-C} = 9.8 Hz), 131.0 (d, J_{F-C} = 3.0 Hz), 125.7 (d, J_{F-C} = 9.4 Hz), 118.5 (d, J_{F-C} = 23.6 Hz), 109.8 (d, J_{F-C} = 24.9 Hz), 79.0, 54.5, 41.6, 30.2, 22.3, 13.0. IR (cm^{-1}): 1711, 1479, 1285, 1217, 1078, 995, 947, 880, 816, 683, 629. HRMS (ESI): calcd for $[C_{16}H_{19}FINO + H]^+$ 388.0574, found 388.0577.

Compound **4f** was obtained as a yellow solid in 58% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.17 (s, 1H), 6.07 (s, 2H), 2.89 (t, J = 7.5 Hz, 2H), 1.68−1.61 (m, 2H), 1.41 (s, 9H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5, 149.9, 149.7, 147.3, 130.2, 128.6, 103.6, 102.6, 102.3, 77.9, 54.2, 41.6, 30.3, 22.4, 13.0. IR (cm^{-1}): 1676, 1474, 1387, 1341, 1308, 1032, 988, 930, 876. HRMS (ESI): calcd for $[C_{17}H_{20}INO_3 + H]^+$ 414.0566, found 414.0565.

Compound **4g** was obtained as a yellow solid in 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.58 (td, J = 7.5, 1.0 Hz, 1H), 7.52 (td, J = 7.5, 1.0 Hz, 1H), 4.62 (s, 2H), 3.37 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.9, 149.3, 134.5, 133.6, 131.0, 130.6, 124.3, 123.5, 74.4, 74.2, 57.2, 54.6, 30.3. IR (cm^{-1}): 1705, 1628, 1460, 1356, 1283, 1086, 1026, 982, 772, 643. HRMS (ESI): calcd for $[C_{15}H_{18}INO_2 + H]^+$ 372.0460, found 372.0462.

Compound **4h** was obtained as a yellow solid in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 2.93 (t, J = 7.0 Hz, 2H), 2.47 (s, 3H), 1.70−1.63 (m, 2H), 1.44 (s, 9H), 0.98 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.4, 147.6, 141.3, 135.2, 130.9, 130.8, 124.0, 123.1, 79.1, 54.2, 41.8, 30.3, 22.3, 22.1, 12.9. IR (cm^{-1}): 1707, 1636, 1458, 1360, 1275, 1213, 1011, 934, 826, 675. HRMS (ESI): calcd for $[C_{17}H_{22}INO + H]^+$ 384.0824, found 384.0826.

Compound **4i** was obtained as a yellow solid in 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 7.59−7.51 (m, 2H), 7.29−7.26 (m, 2H), 7.03−7.01 (m, 2H), 6.99−6.96 (m, 1H), 5.20 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8, 149.8, 148.9, 134.4, 133.5, 131.0, 130.7, 129.5, 124.4, 123.6, 121.4, 115.4, 72.3, 70.0, 54.7, 30.4. IR (cm^{-1}): 1707, 1597, 1497, 1460, 1271, 1215, 1003, 976, 750, 669. HRMS (ESI): calcd for $[C_{20}H_{20}INO_2 + H]^+$ 434.0617, found 434.0620.

Compound **4j** was obtained as a yellow solid in 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.57−7.47 (m, 2H), 7.34−7.25 (m, 5H), 4.34 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 147.8, 138.7, 134.8, 133.4, 130.9, 130.0, 129.0, 128.5, 126.8, 124.0, 123.4, 77.3, 54.5, 45.6, 30.3. IR (cm^{-1}): 1705, 1560, 1460, 1269, 993, 760, 702, 671. HRMS (ESI): calcd for $[C_{20}H_{20}INO + H]^+$ 418.0668, found 418.0670.

Compound **4k** was obtained as a yellow solid in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H),

dx.doi.org/10.1021/jo201347r |J. Org. Chem. XXXX, XXX, 000–000

7.57 (t, J = 6.8 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 3.92 (s, 2H), 3.25 (t, J = 6.0 Hz, 2H), 1.45(s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 149.2, 134.7, 133.4, 130.9, 130.1, 123.9, 123.5, 72.9, 61.5, 54.5, 43.0, 30.3. IR (cm^{-1}): 1686, 1638, 1467, 1458, 1271, 1049, 1009, 760, 675. HRMS (ESI): calcd for $[C_{15}H_{18}INO_2 + H]^+$ 372.0460, found 372.0462.

Compound **4l** was obtained as a yellow solid in 46% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 3.74 (t, J = 6.8 Hz, 2H), 3.08 (t, J = 7.2 Hz, 2H), 1.96−1.89 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 147.9, 134.8, 133.3, 130.9, 129.9, 123.8, 123.5, 77.9, 61.6, 54.4, 36.4, 32.1, 30.3. IR (cm^{-1}): 1686, 1636, 1460, 1360, 1267, 1047, 1003, 762, 675. HRMS (ESI): calcd for $[C_{16}H_{20}INO_2 + H]^+$ 386.0617, found 386.0619.

Compound **4m** was obtained as a yellow solid in 64% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 8.5 Hz, 1H), 7.55−7.50 (m, 3H), 7.37 (t, J = 7.5 Hz, 2H), 7.29−7.25 (m, 1H), 1.23 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 147.9, 141.2, 135.0, 133.3, 130.9, 130.3, 130.1, 128.1, 127.8, 124.5, 123.5, 71.6, 54.4, 30.1. IR (cm^{-1}): 1705, 1460, 1360, 1263, 1211, 997, 762, 671. HRMS (ESI): calcd for $[C_{19}H_{18}INO + H]^+$ 404.0511, found 404.0514.

Compound **4n** was obtained as a yellow solid in 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.59−7.50 (m, 2H), 6.11 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.1, 150.0, 134.6, 133.7, 131.0, 130.6, 123.9, 123.5, 54.7, 49.5, 30.4. IR (cm^{-1}):1707, 1626, 1473, 1276, 1002, 796, 673. HRMS (ESI): calcd for $[C_{13}H_{14}INO + H]^+$ 328.0198, found 328.0207.

Representative Synthesis of Compounds 7a−c. Compound **6a** (50 mg, 0.249 mmol), $NaHCO_3$ (41.8 mg, 0.498 mmol, 2.0 equiv), and dichloromethane (3 mL) were placed in a flask to which was added dropwise a solution of iodine (126.3 mg, 0.498 mmol, 2.0 equiv) in DCM (2 mL) at 0 °C. The mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed (3×) with saturated aq $Na_2S_2O_3$. The combined organic extracts were dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (5% EtOAc in petroleum ether) to give **7a** as a yellow oil (41.0 mg, 0.184 mmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (dd, J = 7.5, 1.0 Hz, 1H), 7.53 (td, J = 7.5, 1.0 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.28 (td, J = 8.5, 1.5 Hz, 1H), 2.92 (t, J = 6.5 Hz, 2H), 2.41 (s, 3H), 1.78−1.71 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 202.7, 195.0, 142.4, 134.1, 133.1, 132.6, 128.9, 125.7, 40.3, 17.1, 16.9, 13.6. IR (cm^{-1}): 1707, 1657, 1587, 1460, 1435, 1121, 743. HRMS (ESI): calcd for $[C_{12}H_{14}O_2S + H]^+$ 223.0793, found 223.0795.

Compound **7b** was synthesized as a yellow solid in 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99−7.97 (m, 2H), 7.73 (dd, J = 8.5, 1.5 Hz, 1H), 7.65−7.61 (m, 1H), 7.55 (td, J = 8.0, 1.5 Hz, 1H), 7.52−7.48 (m, 2H), 7.44 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.9, 193.0, 143.5, 134.5, 133.8, 133.4, 133.2, 131.6, 129.9, 128.8, 126.9, 124.5, 16.7. IR (cm^{-1}): 1668, 1651, 1580, 1545, 1458, 1261, 1207, 798, 644. HRMS (ESI): calcd for $[C_{15}H_{12}O_2S + H]^+$ 257.0636, found 257.0654.

Compound **7c** was synthesized as a yellow solid in 49% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96−7.93 (m, 2H), 7.72 (dd, J = 8.0, 1.0 Hz, 1H), 7.54 (td, J = 8.5, 2.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.19 (td, J = 8.0, 1.5 Hz, 1H), 6.97 (dd, J = 6.5, 2.0 Hz, 2H), 3.88 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.2, 191.9, 164.7, 143.7, 133.7, 133.6, 132.4, 131.3, 126.4, 126.3, 124.2, 114.2, 55.6, 16.4. IR (cm^{-1}): 1665, 1643, 1599, 1572, 1423, 1263, 1213, 1171, 1016, 887, 744, 611. HRMS (ESI): calcd for $[C_{16}H_{14}O_3S + H]^+$ 287.0742, found 287.0745.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xwli@dicp.ac.cn; jiaaiqun@gmail.com.

■ ACKNOWLEDGMENT

We gratefully acknowledge the financial support from the Dalian Institute of Chemical Physics, Chinese Academy of Sciences. We thank Prof. Roy Periana (Scripps Florida) and Prof. Jing Zhao (Nanjing University) for discussions. X.L. conceived and designed all the experiments.

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