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I_2O_5-Mediated 1,5-Cyclization of Aryldiynes with H_2O: A Way to Access 3-Acyl 1-Indenone Derivatives

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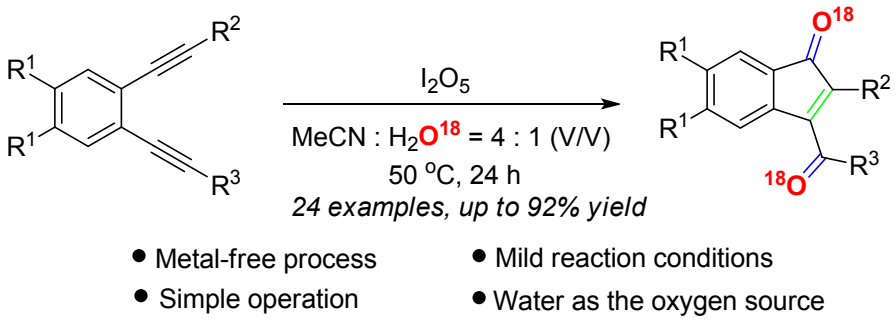
TOC graphic



ABSTRACT: A facile I_2O_5-mediated 1,5-cyclization of aryldiynes with H_2O has been successfully developed leading to a broad range of substituted 3-acyl 1-indenones in moderate to excellent yields. The protocol has advantages of metal-free process, mild reaction conditions, simple operation, and broad functional group tolerance. In the reaction, H_2O is used as both a co-solvent and an oxygen source.

INTRODUCTION

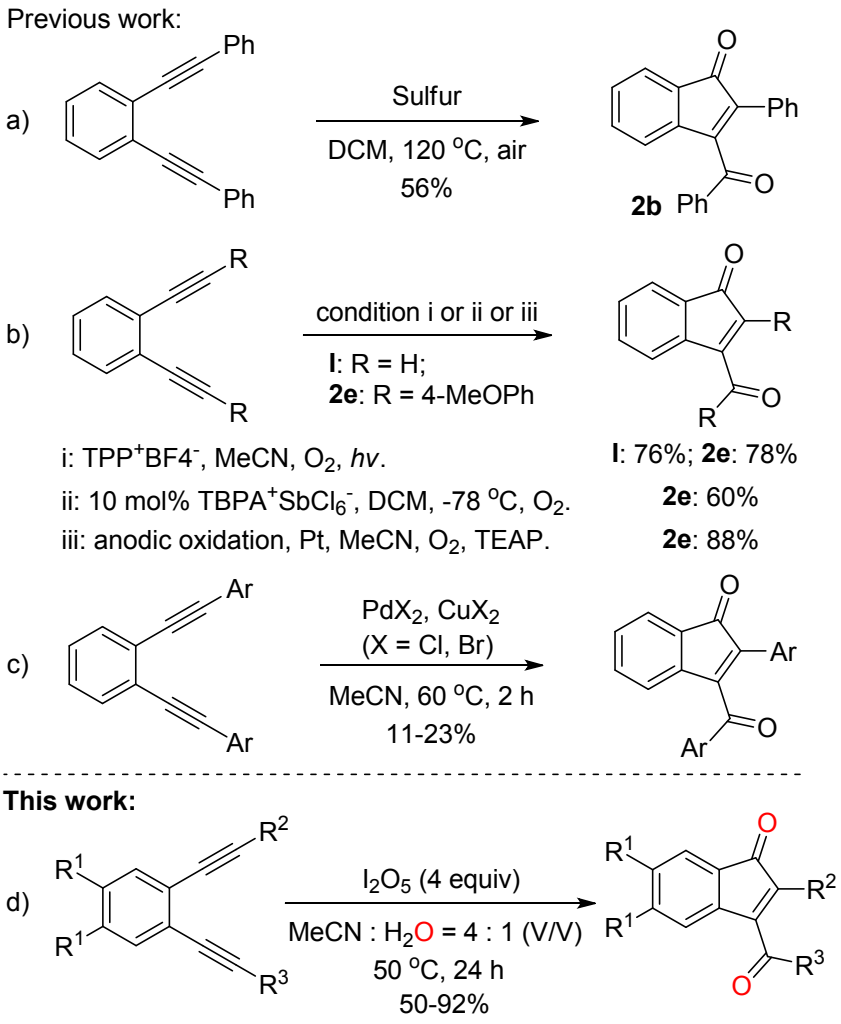
1-Indenones are known as an important class of carbocyclic compounds and their frameworks are found to widely exist in natural products and synthetically bioactive molecules.[1] The 1-indenone derivatives can exhibit versatile utilities in organic synthesis, drug discovery, materials science, and among others.[2] Consequently, it is of great interest to develop efficient and reliable methods for their synthesis. The intramolecular cyclization of aromatic carbonyl compounds under acidic conditions represents the most common way to access 1-indenones.[3] In recent years, most of methods for the construction of 1-indenones mainly focus on metal-involved cyclization reactions. For example, transition metal-catalyzed cross-coupling reactions[4] and direct C-H annulations[5] have been extensively studied in the last decade. More recently, the metal-free approaches via radical[6] or ionic pathway[7] for the synthesis of 1-indenone derivatives have received an increasing attention due to concerns about issues of environmental pollution and pharmaceutical purification. Despite some advances made over the past few years, it is still highly desirable to develop novel methods for the construction of diverse substituted 1-indenones from easily available precursors, in simple operation, and under metal-free reaction conditions.

Aryldiynes represent a class of valuable building blocks in synthetic chemistry which can undergo either a typical Bergman 1,6-cyclization[8] or the regio-variant 1,5-cyclization.[9-12] The latter transformation of aryldiynes enabled the formation of fulvenes induced by electrophiles,[9] radicals,[10] transition metals,[11] etc., and these types of reactions have been well studied.[9-12] In

contrast, the construction of 3-acyl 1-indenones from 1,5-cyclization reaction of aryldiynes has been less explored.[11b,13] Schumann and co-workers reported an annulation reaction of 1,2-bis(phenylethynyl)benzene with sulfur under air affording 3-benzoyl-2-phenyl-1*H*-inden-1-one (**2b**) in 56% yield (Scheme 1a), but the reaction required high temperature (120 ºC) and only gave one example.[13a] In 1996, Sankararaman et al described the synthesis of 3-acyl 1-indenones through the cyclization of aryldiynes via chemical, photochemical or electrochemical oxidation, but with narrow scope of substrates (Scheme 1b).[13b] Later, Wu et al synthesized 1-indenones as side products (yields of 11-23%) during the study of Pd-catalyzed cyclization of aryldiynes (Scheme 1c).[11b] As such, the development of general and efficient methods for the construction of diverse functionalized 1-indenones from aryldiynes is highly expected. Our current research interests focus on the development of nucleophilic hydroxyl group-triggered cascade reactions to access complex molecules using water as the hydroxyl source.[14,15] Previously, we disclosed that the Cu(0)/Selecfluor system may in situ generate an active XCuOH species (X = F or BF_4) in the presence of water which is readily to undergo the addition of hydroxyl group to carbon-carbon multiple bonds and induce successive tandem reactions.[14] Very recently, we found that an I_2O_5/H_2O system could undergo the generation of the hydroxyl radical species under metal-free conditions and induce tandem cyclization of 1,6-enynes to access strained 1*H*-cyclopropa[*b*]naphthalene-2,7-diones.[15] In this study, we describe an I_2O_5-mediated 1,5-cyclization of aryldiynes with H_2O, which provides an efficient and convenient approach for

the synthesis of 3-acyl 1-indenones in moderate to excellent yields under metal-free conditions (Scheme 1d).

Scheme 1. Synthesis of 3-Acyl 1-Indenones from Aryldiynes

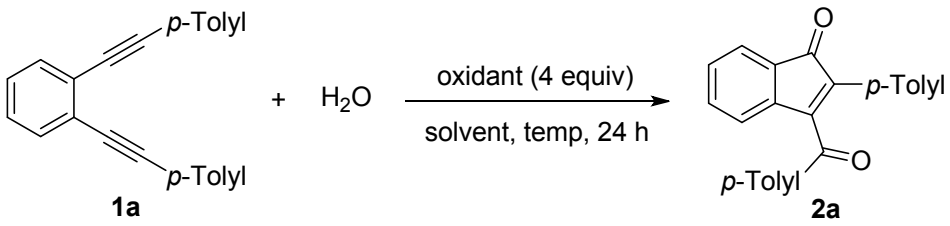


RESULTS AND DISCUSSION

Initially, 1,2-bis(*p*-tolylethynyl)benzene **1a** was chosen as the model substrate to optimize the reaction conditions (Table 1). We first carried out the reaction of **1a** with I_2O_5 and H_2O in acetonitrile at 50 °C for 24 hours and the desired product **2a** was obtained in 37% yield (entry 1, Table 1). It was

found that the volume ratio of acetonitrile versus H_2O has a significant effect on the yield of **2a** and a solvent mixture with a ratio of MeCN/H_2O = 4:1 (V/V) gave the best yield of **2a** (entries 2-5, Table 1). Either elevating the temperature (entry 7, Table 1) or prolonging the reaction time (entry 8, Table 1) could not further improve the yield. Solvent screening experiments indicated that a combined MeCN/H_2O = 4:1 (V/V) solvent system was the most suitable medium for the reaction (entries 9-13 vs 4, Table 1). In addition, several other oxidants ($PhI(OAc)_2$ and $K_2S_2O_8$) were investigated and all showed inferior efficiency than that of I_2O_5 (entries 14, 15 vs 4, Table 1). A controlled experiment revealed that no desired product was obtained in the absence of I_2O_5 (entry 16, Table 1). Finally, either decreasing or increasing the amount of I_2O_5 resulted in a reduced yield of **2a** (entries 17-18 vs 4, Table 1).

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

entry	catalyst	solvent[b]	temp (°C)	yield of **2a** (%)[c]
1	I_2O_5	MeCN:H_2O (400:1, V/V)	50	37
2	I_2O_5	MeCN:H_2O (40:1, V/V)	50	53
3	I_2O_5	MeCN:H_2O (5:1, V/V)	50	79
4	***I_2O_5***	***MeCN:H_2O (4:1, V/V)***	***50***	***87 (81[d])***

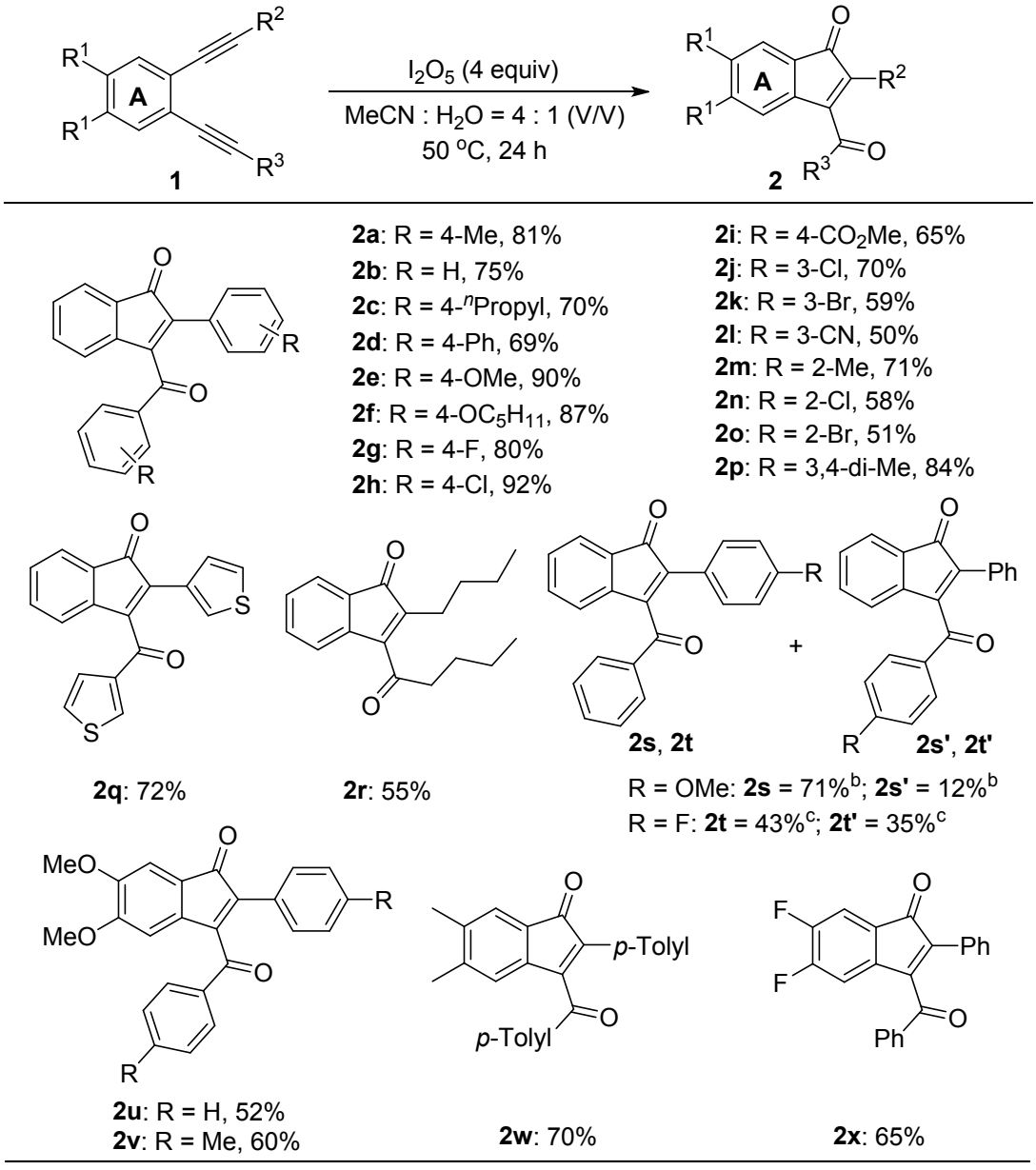
5	I_2O_5	MeCN:H_2O (3:1, V/V)	50	75
6	I_2O_5	MeCN:H_2O (4:1, V/V)	35	10
7	I_2O_5	MeCN:H_2O (4:1, V/V)	70	80
8	I_2O_5	MeCN:H_2O (4:1, V/V)	50	22[e], 85[f]
9	I_2O_5	THF:H_2O (4:1, V/V)	50	76
10	I_2O_5	DCM:H_2O (4:1, V/V)	50	71
11	I_2O_5	dioxane:H_2O (4:1, V/V)	50	73
12	I_2O_5	toluene:H_2O (4:1, V/V)	50	0
13	I_2O_5	DMF:H_2O (4:1, V/V)	50	58
14	$PhI(OAc)_2$	MeCN:H_2O (4:1, V/V)	50	14
15	$K_2S_2O_8$	MeCN:H_2O (4:1, V/V)	50	0
16	--[g]	MeCN:H_2O (4:1, V/V)	50	0
17	I_2O_5[h]	MeCN:H_2O (4:1, V/V)	50	79
18	I_2O_5[i]	MeCN:H_2O (4:1, V/V)	50	81

[a]Reaction conditions: **1a** (0.1 mmol), oxidant (4 equiv), solvent (1.5 mL), given temperature for 24 h unless otherwise noted. [b]Solvent mixtures were prepared in terms of volume ratios (V/V). [c]LC yields were given. [d]Isolated yield shown in parentheses. [e]The reaction time is 12 h. [f]The reaction time is 28 h. [g]No oxidant; only the starting materials were recovered. [h]I_2O_5 (2 equiv). [i]I_2O_5 (6 equiv).

With the optimized reaction conditions in hand, we next examined the scope of aryldiynes **1** (Table 2). At first, a range of symmetric aryldiynes bearing *para*-substituted aryl rings at the alkyne moieties of **1** were evaluated under the standard reaction conditions (**2a-i**, Table 2). Substrates containing either electron-rich or electron-deficient aryl rings underwent the cyclization smoothly and gave the desired products in moderate to excellent yields. It was found that symmetric aryldiynes possessing *ortho*- or *meta*-substituted aryl rings at the alkyne moieties of **1** generally gave decreased yields of **2** compared to those of *para*-substituted ones presumably due to the steric hindrance effect (**2j-o** vs **2a-i**, Table 2). Aryldiynes bearing heteroaromatic rings or aliphatic groups at the alkyne moieties of **1** were also workable for the reaction and afforded the corresponding products in moderate yields (**2q**, **2r**, Table 2). In addition, asymmetric aryldiynes were also examined under the standard reaction conditions. For example, when **1s** was used, regioisomer **2s** was predominantly produced along with a small amount of **2s′** (total 83% yield of **2s** and **2s′** with a ratio of **2s** : **2s′** = 6 : 1 base on the ^{1}H NMR analysis; the structure of the major isomer is determined by the GC-MS analysis, see Supporting Information); when substrate **1t** was used, two regioisomers **2t** and **2t′** were obtained in a total yield of 78% with a ratio of **2t** : **2t′** = 1.2 : 1 base on the GC-MS analysis (see Supporting Information). According to our proposed mechanism (Scheme 3, *vide infra*), we presumed that **1s** may undergo *5-endo-dig* cyclization more favorably to mainly produce **2s** while **1t** may proceed via *5-exo-dig* cylization more favorably to mainly deliver **2t** (Scheme 3, *vide infra*). Furthermore, the substituents on phenyl ring **A** were investigated. Aryldiynes bearing either electron-donating or electron-withdrawing groups could

undergo the annulation smoothly and afford the target indenones in moderate yields (52-70%, **2u-x**, Table 2). Finally, a gram-scale (5 mmol of **1a** used) synthesis of **2a** was also tried, and the target indenone **2a** was obtained in 75% yield (eq. 1).

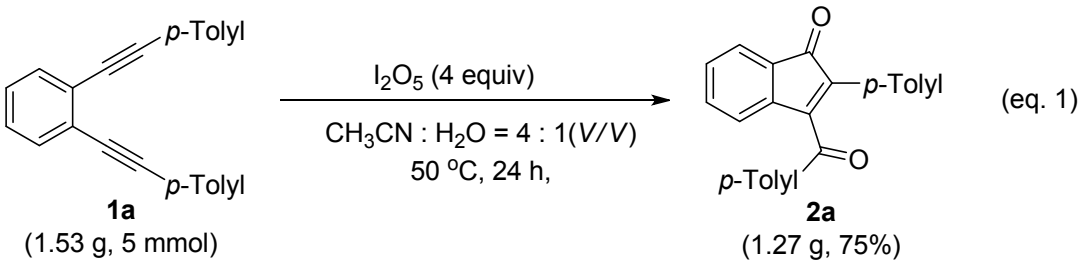
Table 2. Substrate scope for aryldiynes 1[a]



[a]Reaction conditions: **1** (0.3 mmol), I_2O_5 (4 equiv), MeCN/H_2O (4/1 (V/V), 4.5 mL), 50 ºC for 24 h.

[b]The structure of the major regioisomer **2s** was determined by the GC-MS analysis and the yield of **2s**

was calculated based on the ^{1}H NMR analysis. [c]The structure and yield of regioisomers were determined by the GC-MS analysis.



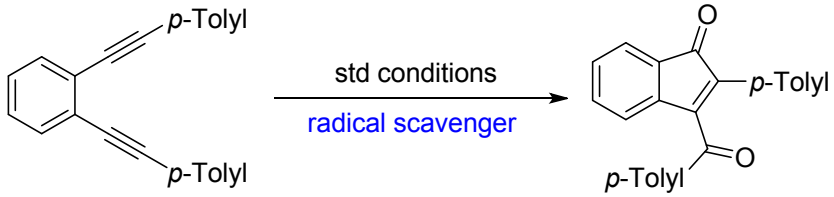
(eq. 1)

To gain insight into the reaction mechanism, we performed radical scavenging experiments by an extra addition of TEMPO[15,16] to the model reaction. As expected, the annulation reaction was almost suppressed and the similar result was obtained by using BHT (Butylated hydroxytoluene) as a radical scavenger (Scheme 2a). In these cases, the starting material **1a** was almost recovered. However, when *N-tert*-buthyl-α-phenylnitrone (PBN) was used as a radical scavenger, the reaction could still proceed well (Scheme 2a). We think that TEMPO and BHT may react with I_2O_5 directly under the reaction conditions, thus a cyclization may be inhibited.[17] To probe the source of the oxygen atoms in **2**, several additional experiments were carried out (Scheme 2b-d). It was found that an attempt to run the annulation of **1a** in a degassed acetonitrile-water mixture (4:1, V/V) could still give **2a** in 85% LC yield (Scheme 2b). Note that only small amount of product (8% LC yield) was detected when we performed the model reaction in a dehydrated acetonitrile (Scheme 2c). When substrate **1b** was subjected to the standard reaction conditions except using a MeCN/H_2O^{18} = 4:1 (V/V) solvent system, the

double-^{18}O-incorporated product **2b**-$[O^{18}]_2$ ($[M+H]^+$: m/z = 315) was detected by the MS analysis (Scheme 2d, also see Supporting Information). All these results disclosed that H_2O should be the sole oxygen source for the formation of the two carbonyl groups in 3-acyl 1-indenones **2**.

Scheme 2. Preliminary Mechanistic Studies

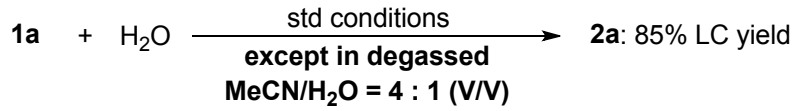
a) Radical scavenging experiments



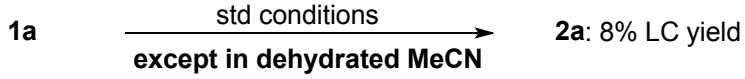
1a **2a**

TEMPO	Yield of **2a**	BHT	Yield of **2a**	PBN	Yield of **2a**
4 equiv	39%	4 equiv	23%	4 equiv	74%
8 equiv	2%	8 equiv	trace	8 equiv	69%

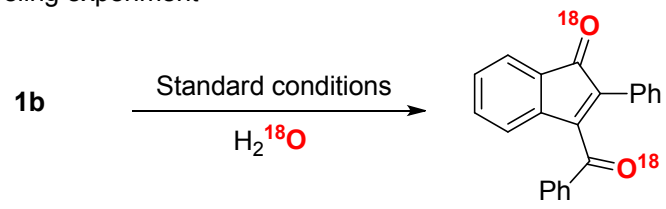
b) Reaction of **1a** under standard reaction conditions except under a degassed MeCN-H_2O mixture



c) Control experiment by removal of H_2O



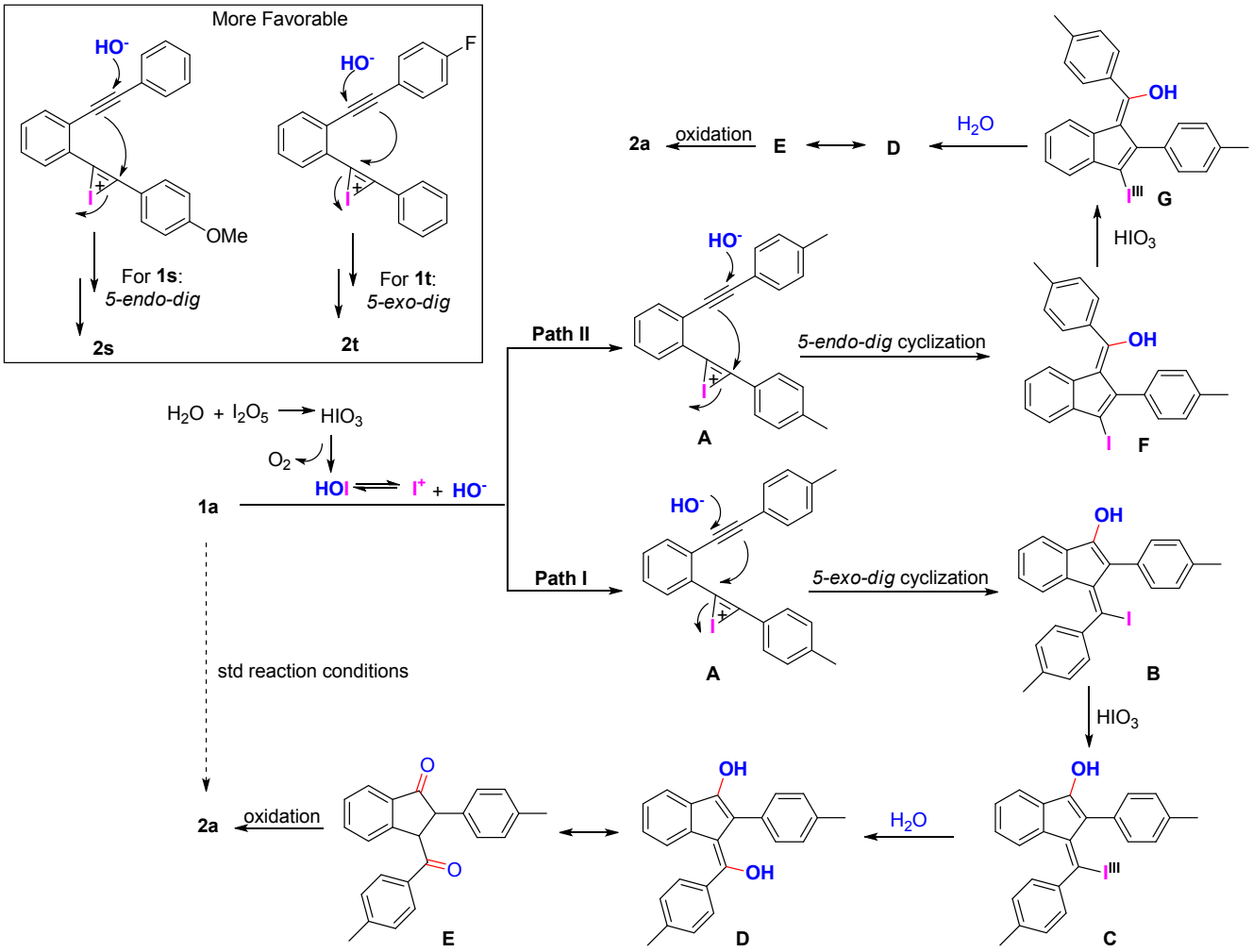
d) ^{18}O-labeling experiment



2b-$[^{18}O]_2$: detected by MS

On the basis of our mechanistic experiments and previous literature,[15,18-22] a possible mechanism for the I_2O_5-mediated annulation of **1a** with H_2O is proposed in Scheme 3. First, HIO_3 was produced upon the hydrolysis of I_2O_5 by water.[18] Then the decomposition of HIO_3 may generate HOI and O_2.[19] In solution, HOI may release I^+ and OH^- species. Activation of the carbon-carbon triple bond of **1a** by I^+ may produce intermediate **A**.[19] *5-Exo-dig* cyclization of **A** may generate intermediate **B** (Path I).[15,19,20] The redox reaction between **B** and HIO_3 yielded an vinyl-λ^3-iodane intermediate **C** that underwent substitution by H_2O to generate intermediate **D**.[15,21a,22] Alternatively, *5-Endo-dig* cyclization of **A** followed by the oxidation of the resulting intermediate **F** by HIO_3 may deliver intermediate **G**.[15,21a] Substitution of I^{III} moiety in **G** by H_2O could also deliver intermediate **D** (Path II).[15,21a,22] Finally, the tautomerization of **D** to **E** followed by the oxidation of the resulting intermediate **E** gave the final product **2a**.

Scheme 3. Proposed Mechanism for the Oxidative Annulation of 1a



CONCLUSION

In summary, we have successfully developed a facile 1,5-cyclization of aryldiynes with water by using commercially available, inexpensive, and easily handled I_2O_5 as the oxidant. The present protocol provides an efficient and convenient way to access a range of diverse functionalized 3-acyl indenones by using water as the green oxygen source under metal-free reaction conditions. Further studies on cyclization reactions involving the I_2O_5/H_2O system are underway in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, commercially available reagents were purchased from chemical suppliers and used without purifications. The ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer at 25 °C in $CDCl_3$ or DMSO-d_6 at 500 MHz and 125 MHz, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Chemical shifts of ^{13}C NMR were reported relative to the solvent signal ($CDCl_3$: δ = 77.16 ppm; DMSO-d_6: δ = 39.51 ppm). GC-MS experiments were performed with EI source; high resolution mass spectra (HRMS) were obtained on a TOF MS instrument with EI or ESI source. Acetonitrile is dehydrated by CaH_2 before preparation of the combined MeCN/H_2O solvent system. Flash column chromatography was performed on silica gel (100-200 mesh) with the indicated solvent mixtures.

Preparation of the starting material aryldiynes 1.[23] $Pd(PPh_3)_2Cl_2$ (28.1 mg, 0.04 mmol, 2 mol %) and CuI (3.8 mg, 0.02 mmol, 1 mol %) were placed to a septum-capped one neck flask which was then charged with Et_3N (15 mL) and the resulting mixture was degassed by freeze-pump-thaw technique. An aryl halide (2 mmol) and an appropriate acetylene (1.2 equiv based on aryl halide) were successively added via syringe to the stirred reaction mixture. After that the reaction mixture was stirred at room temperature until all the aryl halide has been consumed (monitored by TLC or GC). The Et_3N was removed under reduced pressure and the residue was dissolved in toluene (10 mL) and filtered through a small pad of silica gel, which then was rinsed with toluene (10 mL × 2). The combined organic layer was concentrated under reduced pressure and the residue was purified by flash chromatography using hexane or hexane/EtOAc mixture as an eluent. Enediynes **1a-x** were synthesized according to this general procedure from the corresponding *o*-diiodobenzenes with appropriate terminal alkynes. Their ^{1}H and ^{13}C NMR spectra were in line with the previous literature.[9f,10b,11c,20]

Typical procedure for the I_2O_5-mediated 5-*exo-dig* cyclization of aryldiynes with H_2O. To a 25 mL Schlenk tube were added 1,2-bis(*p*-tolylethynyl)benzene **1a** (91.8 mg, 0.3 mmol), I_2O_5 (400.8 mg, 4 equiv, 1.2 mmol) and mixed solvent (MeCN:H_2O = 4:1 (V/V), 4.5 mL). The mixture was stirred at 50 ºC for 24 h. H_2O (4 mL) and saturated $Na_2S_2O_3$ (4 mL) were added at room temperature. Then, the reaction mixture was extracted with CH_2Cl_2 and purified by flash column chromatography (petroleum ether/EtOAc, = 10 : 1 (V/V)). The product was isolated as a yellow solid (82.0 mg, 81%).

3-(4-methylbenzoyl)-2-(p-tolyl)-1H-inden-1-one ***(2a)***. Yellow solid (82.0 mg, 81%); m.p. 152-155 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 7.0 Hz, 1H), 7.38-7.34 (m, 3H), 7.29-7.26 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 7.2 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.3, 194.4, 150.1, 145.6, 144.4, 139.0, 134.3, 134.0, 132.8, 129.6, 129.5, 129.2, 129.11, 129.09, 126.9, 123.7, 121.5, 21.8, 21.3; HRMS (ESI) for $C_{24}H_{19}O_2$ $[M+H]^+$: calcd 339.1380, found 339.1385.

3-benzoyl-2-phenyl-1H-inden-1-one ***(2b)***.[13b] Yellow solid (70.1 mg, 75%); m.p. 113-115 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95-7.93 (m, 2H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.54-7.50 (m, 1H), 7.45-7.43 (m, 2H), 7.40-7.35 (m, 3H), 7.32-7.29 (m, 1H), 7.25-7.22 (m, 3H), 7.06 (d, *J* = 7.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.0, 194.6, 150.4, 144.1, 135.2, 134.6, 134.39, 134.36, 129.7, 129.6, 129.4, 129.3, 129.0, 128.8, 128.3, 123.9, 121.8.

3-(4-propylbenzoyl)-2-(4-propylphenyl)-1H-inden-1-one ***(2c)***. Yellow solid (83.2 mg, 70%); m.p. 159-161 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.39-7.34 (m, 3H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.06-7.02 (m, 3H), 2.60-2.57 (m, 2H), 2.51-2.48 (m, 2H), 1.64-1.52 (m, 4H), 0.91-0.85 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.4, 194.3, 150.0, 149.9, 144.4, 143.7, 134.4, 134.3, 133.1, 129.6, 129.5, 129.2, 129.0, 128.9, 128.4, 127.1, 123.7, 121.6, 38.0, 37.7, 24.1, 23.9, 13.6; HRMS (ESI) for $C_{28}H_{27}O_2$ $[M+H]^+$: calcd 395.2006, found 395.2003.

3-([1,1'-biphenyl]-4-carbonyl)-2-([1,1'-biphenyl]-4-yl)-1H-inden-1-one ***(2d)***. Yellow solid (96.3 mg,

69%); m.p. 209-211 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08-8.05 (m, 2H), 7.67 (d, *J* = 6.8 Hz, 1H), 7.64-7.60 (m, 3H), 7.59-7.58 (m, 1H), 7.58-7.55 (m, 2H), 7.54-7.51 (m, 4H), 7.46-7.39 (m, 6H), 7.35-7.31 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.1, 194.2, 150.5, 147.2, 144.3, 141.6, 140.2, 139.5, 134.5, 134.0, 133.9, 130.0, 129.8, 129.7, 129.4, 129.0, 128.8, 128.7, 128.5, 127.6, 127.55, 127.3, 127.1, 127.0, 123.9, 121.8; HRMS (ESI) for $C_{34}H_{23}O_2$ $[M+H]^+$: calcd 463.1693, found 463.1688.

3-(4-methoxybenzoyl)-2-(4-methoxyphenyl)-1H-inden-1-one ***(2e)***.[11b] Red solid (99.9 mg, 90%); m.p. 120-122 °C (lit.[11b] 116-117 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 -7.92 (m, 2H), 7.57 (d, *J* = 7.1 Hz, 1H), 7.46-7.43 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.86-6.83 (m, 4H), 6.79-6.77 (m, 2.4 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.6, 193.2, 164.6, 160.1, 149.1, 144.5, 134.3, 133.3, 131.8, 130.8, 129.6, 128.9, 128.3, 123.6, 122.4, 121.3, 114.1, 113.9, 55.5, 55.1.

3-(4-(pentyloxy)benzoyl)-2-(4-(pentyloxy)phenyl)-1H-inden-1-one ***(2f)***. Red solid (126.1 mg, 87%); m.p. 191-193 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94-7.91(m, *J* = 5.8 Hz, 2H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.45-7.43 (m, 2H), 7.36-7.33 (m, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.85-6.83 (m, 2H), 6.79-6.78 (m, 2H), 3.98 (t, *J* = 6.6 Hz, 2H), 3.90 (t, *J* = 6.6 Hz, 2H), 1.81-1.72 (m, 4H), 1.44-1.33 (m, 8H), 0.95-0.91 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.8, 193.3, 164.3, 159.7, 149.1, 144.7, 134.3, 133.4, 131.9, 130.8, 129.7, 128.8, 128.1, 123.6, 122.2, 121.4, 114.60, 114.5, 68.4, 68.0, 28.9, 28.7, 28.2, 28.1, 22.42, 22.38, 13.98, 13.96; HRMS (ESI) for $C_{32}H_{35}O_4$ $[M+H]^+$: calcd 483.2530, found 483.2535.

3-(4-fluorobenzoyl)-2-(4-fluorophenyl)-1H-inden-1-one ***(2g)***. Yellow solid (83.1 mg, 80%); m.p. 106-109 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.93 (m, 2H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.44-7.39 (m, 3H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.07-7.03 (m, 3H), 6.98-6.93 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.9, 192.9, 166.6 (d, *J* = 257.8 Hz) , 163.2 (d, *J* = 250.7 Hz), 149.8, 143.9, 134.6, 133.7, 132.2 (d, *J* = 9.7 Hz), 131.6 (d, *J* = 2.9 Hz), 131.4 (d, *J* = 8.3 Hz), 129.6, 129.4, 125.8 (d, *J* = 3.3 Hz), 124.1, 121.9,

116.3 (d, J = 22.2 Hz), 115.7 (d, J = 21.8 Hz); HRMS (ESI) for $C_{22}H_{13}F_2O_2$ $[M+H]^+$: calcd 347.0878, found 347.0884.

3-(4-chlorobenzoyl)-2-(4-chlorophenyl)-1H-inden-1-one ***(2h)***. Yellow solid (104.9 mg, 92%); m.p. 140-143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88-7.85 (m, 2H), 7.63 (d, J = 7.0 Hz, 1H), 7.41-7.31 (m, 6H), 7.25-7.22 (m, 2H), 7.03 (d, J = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.5, 193.1, 150.1, 143.6, 141.3, 135.4, 134.6, 133.4, 133.3, 130.7, 130.6, 129.7, 129.4, 129.4, 128.8, 128.0, 124.2, 121.9; HRMS (ESI) for $C_{22}H_{13}Cl_2O_2$ $[M+H]^+$: calcd 379.0287, found 379.0281.

methyl 4-(3-(4-(methoxycarbonyl)benzoyl)-1-oxo-1H-inden-2-yl)benzoate ***(2i)***. Yellow solid (83.2 mg, 65%); m.p. 120-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01-7.99 (m, 2H), 7.97-7.94 (m, 2H), 7.90-7.88 (m, 2H), 7.67 (d, J = 6.8 Hz, 1H), 7.48-7.46 (m, 2H), 7.45-7.42 (m, 1H), 7.38-7.35 (m, 1H), 7.11 (d, J = 7.2 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.2, 193.7, 166.4, 165.8, 151.0, 143.4, 138.1, 135.1, 134.7, 134.1, 133.9, 130.4, 130.1, 130.0, 129.6, 129.5, 129.3, 129.2, 124.3, 122.2, 52.6, 52.2; HRMS (ESI) for $C_{26}H_{19}O_6$ $[M+H]^+$: calcd 427.1176, found 427.1172.

3-(3-chlorobenzoyl)-2-(3-chlorophenyl)-1H-inden-1-one ***(2j)***. Yellow solid (79.5 mg, 70%); m.p. 135-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (t, J = 1.8 Hz, 1H), 7.75-7.73 (m, 1H), 7.66-7.64 (m, 1H), 7.51-7.49 (m, 1H), 7.44-7.37 (m, 2H), 7.37-7.29 (m, 2H), 7.25-7.21 (m, 2H), 7.19-7.16 (m, 1H), 7.10 (d, J = 7.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.1, 192.9, 150.3, 143.4, 136.6, 135.3, 134.6, 134.4, 134.4, 133.9, 131.2, 130.2, 129.9, 129.7, 129.3, 129.26, 129.0, 127.5, 127.5, 124.3, 122.1; HRMS (ESI) for $C_{22}H_{13}Cl_2O_2$ $[M+H]^+$: calcd 379.0287, found 379.0297.

3-(3-bromobenzoyl)-2-(3-bromophenyl)-1H-inden-1-one ***(2k)***. Red-brown solid (82.1 mg, 59%); m.p. 127-129 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (t, J = 1.7 Hz, 1H), 7.78-7.76 (m, 1H), 7.64-7.62 (m, 2H), 7.56 (t, J = 1.7 Hz, 1H), 7.43-7.40 (m, 1H), 7.37-7.32 (m, 2H), 7.28-7.26 (m, 1H), 7.23 (t, J = 7.9 Hz, 1H), 7.10 (t, J = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.1, 192.7, 150.1, 143.3, 137.2, 136.8, 134.6, 133.9, 132.2, 132.1, 131.9, 131.4, 130.4, 129.8, 129.3, 127.9, 127.8, 124.2, 123.2, 122.4, 122.1; HRMS (ESI) for $C_{22}H_{13}Br_2O_2$ $[M+H]^+$: calcd 466.9277, found 466.9283.

3-(3-(3-cyanobenzoyl)-1-oxo-1H-inden-2-yl)benzonitrile ***(2l)***. Black solid (54.2 mg, 50%); m.p. 181-183 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (t, *J* = 1.4 Hz, 1H), 8.11-8.09 (m, 1H), 7.83-7.81 (m, 1H), 7.71-7.68 (m, 2H), 7.61-7.59 (m, 1H), 7.57-7.53 (m, 2H), 7.48-7.44 (m, 1H), 7.42-7.38 (m, 2H), 7.10 (d, *J* = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.4, 191.8, 150.4, 142.8, 137.3, 135.7, 134.9, 133.5, 133.4, 133.0, 132.8, 132.7, 132.6, 130.6, 130.4, 130.14, 129.4, 129.0, 124.7, 122.4, 117.9, 117.2, 113.7, 113.0; HRMS (ESI) for $C_{24}H_{13}N_2O_2$ $[M+H]^+$: calcd 361.0972, found 361.0967.

3-(2-methylbenzoyl)-2-(o-tolyl)-1H-inden-1-one ***(2m)***. Yellow solid (72.0 mg, 71%); m.p. 120-122 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.63 (d, *J* = 7.1 Hz, 1H), 7.56-7.54 (m, 1H), 7.45-7.42 (m, 1H), 7.35-7.29 (m, 2H), 7.26-7.23 (m, 1H), 7.12-7.03 (m, 4H), 7.01-7.00 (m, 2H), 2.52 (s, 3H), 2.23 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 195.9, 195.8, 152.4, 143.9, 138.9, 138.7, 136.5, 136.1, 134.2, 132.2, 131.6, 130.2, 123.0, 129.7, 129.7, 129.6, 129.2, 128.8, 125.2, 125.1, 123.9, 122.3, 20.7, 20.5; HRMS (ESI) for $C_{24}H_{19}O_2$ $[M+H]^+$: calcd 339.1380, found 339.1387.

3-(2-chlorobenzoyl)-2-(2-chlorophenyl)-1H-inden-1-one ***(2n)***. Yellow solid (66.0 mg, 58%); m.p. 153-155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.1 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.53-7.48 (m, 2H), 7.39-7.36 (m, 1H), 7.19-7.16 (m, 1H), 7.15-7.12 (m, 2H), 7.11-7.06 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.4, 193.1, 150.3, 143.0, 137.2, 137.1, 134.5, 133.7, 132.5, 132.0, 130.9, 130.2, 130.0, 129.9, 129.6, 129.5, 129.2, 129.1, 126.5, 126.1, 124.2, 123.3; HRMS (ESI) for $C_{22}H_{13}Cl_2O_2$ $[M+H]^+$: calcd 379.0287, found 379.0282.

3-(2-bromobenzoyl)-2-(2-bromophenyl)-1H-inden-1-one ***(2o)***. Red-brown solid (72.3 mg, 51%); m.p. 115-118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67-7.65 (m, 2H), 7.54-7.51 (m, 1H), 7.45-7.43 (m, 1H), 7.40-7.37 (m, 1H), 7.35-7.33 (m, 2H), 7.14-7.06 (m, 4H), 7.01-6.98 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.1, 193.8, 149.6, 143.1, 139.3, 139.0, 134.5, 133.0, 132.32, 132.31, 131.2, 130.8, 130.1, 123.0, 129.5, 127.0, 126.7, 124.2, 123.4, 123.4, 120.1; HRMS (ESI) for $C_{22}H_{13}Br_2O_2$ $[M+H]^+$: calcd 466.9277, found 466.9284.

3-(3,4-dimethylbenzoyl)-2-(3,4-dimethylphenyl)-1H-inden-1-one ***(2p)***. Yellow solid (92.3 mg, 84%);

m.p. 154-156 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.68-7.67 (m, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.36-7.33 (m, 1H), 7.29-7.25 (m, 2H), 7.19-7.17 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.01-6.96 (m, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 2.18 (s, 3H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.5, 194.7, 150.3, 144.5, 144.3, 137.7, 137.3, 136.5, 134.3, 134.1, 133.3, 130.4, 130.2, 130.1, 129.7, 129.6, 129.0, 127.4, 126.8, 123.6, 121.5, 20.2, 19.7, 19.6, 19.6; HRMS (ESI) for $C_{26}H_{23}O_2$ $[M+H]^+$: calcd 367.1693, found 367.1698.

3-(3,4-dimethylbenzoyl)-2-(3,4-dimethylphenyl)-1H-inden-1-one ***(2q)***. Yellow solid (69.6 mg, 72%); m.p. 130-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09-8.08 (m, 1H), 7.94-7.93 (m, 1H), 7.63 – 7.62 (m, 1H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.38-7.33 (m, 2H), 7.29–7.26 (m, 1H), 7.21-7.19 (m, 1H), 7.15-7.14 (m, 1H), 7.02 (d, *J* = 7.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.3, 188.1, 148.3, 144.4, 140.6, 136.0, 134.5, 130.1, 129.5, 129.2, 128.5, 127.7, 127.5, 127.3, 126.9, 125.6, 123.9, 121.7; HRMS (ESI) for $C_{18}H_{11}O_2S_2$ $[M+H]^+$: calcd 323.0195, found 323.0189.

2-butyl-3-pentanoyl-1H-inden-1-one ***(2r)***. Yellow solid (44.6 mg, 55%); m.p. 87-89 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29-8.27 (m, 1H), 8.13-8.11 (m, 1H), 7.88-7.82 (m, 2H), 2.42-2.39 (m, 2H), 2.12-2.08 (m, 2H), 1.61-1.55 (m, 2H), 1.37-1.30 (m, 6H), 0.92-0.84 (m, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.5, 172.6, 160.4, 135.2, 134.6, 131.1, 130.5, 128.0, 126.1, 102.3, 37.7, 33.1, 26.4, 24.0, 22.5, 22.0, 13.7, 13.6; HRMS (ESI) for $C_{18}H_{23}O_2$ $[M+H]^+$: calcd 271.1693, found 271.1698.

3-benzoyl-2-(4-methoxyphenyl)-1H-inden-1-one ***(2s)*** *and 3-(4-methoxybenzoyl)-2-phenyl -1H-inden-1-one* ***(2s')***. Inseparable regioisomers: **2s**:**2s'** = 6:1; Red solid (85.0 mg, 83% total yield); m.p. 123-126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (peaks for major product **2s**): δ 7.95-7.93 (m, 2H), 7.61 (d, *J* = 7.0 Hz, 2H), 7.55-7.52 (m, 1H), 7.42-7.35 (m, 5H), 7.29-7.26 (m, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.79-6.76 (m, 2H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) (peaks for major product **2s**): δ 196.6, 195.0, 160.3, 148.5, 144.5, 135.3, 134.5, 134.4, 131.0, 129.6, 129.5, 129.0, 128.9, 123.9, 122.3, 121.5, 114.1, 114.0, 55.3; HRMS (ESI) for $C_{23}H_{17}O_3$ $[M+H]^+$: calcd 341.1172, found 341.1177.

3-benzoyl-2-(4-fluorophenyl)-1H-inden-1-one ***(2t)*** *and 3-(4-fluorobenzoyl)-2-phenyl-1H-inden*

*-1-one **(2t')***. Inseparable regioisomers: **2t**:**2t'** = 1.2:1; Yellow solid (77.2 mg, 78% total yield); m.p. 101-103 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.96 (m, 2H), 7.64-7.62 (m, 1H), 7.45-7.38 (m, 4H), 7.37-7.23 (m, 3H), 7.09-7.00 (m, 2H), 6.95-6.92 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): we failed to assign those peaks for each isomer due to the substantial overlaps appearing in ^{13}C NMR spectra; HRMS (ESI) for $C_{22}H_{14}FO_2$ $[M+H]^+$: calcd 329.0972, found 329.0976.

*3-benzoyl-5,6-dimethoxy-2-phenyl-1H-inden-1-one **(2u)***. Purple solid (58.2 mg, 52%); m.p. 145-147 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91-7.89 (m, 2H), 7.50-7.47 (m, 1H), 7.37-7.35 (m, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.23 (s, 1H), 7.21-7.18 (m, 3H), 6.70 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.5, 194.7, 153.7, 149.4, 148.3, 138.8, 135.3, 134.5, 134.2, 129.9, 129.4, 129.3, 128.7, 128.7, 128.2, 121.8, 108.2, 106.1, 56.4, 56.4; HRMS (ESI) for $C_{24}H_{19}O_4$ $[M+H]^+$: calcd 371.1278, found 371.1270.

*5,6-dimethoxy-3-(4-methylbenzoyl)-2-(p-tolyl)-1H-inden-1-one **(2v)***. Purple solid (71.8 mg, 60%); m.p. 152-154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.21 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.63 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.9, 194.6, 153.6, 149.3, 148.1, 145.5, 139.1, 138.79, 133.78, 132.9, 129.61, 129.55, 129.2, 129.1, 127.2, 121.8, 108.1, 105.9, 56.5, 56.4, 21.8, 21.3; HRMS (ESI) for $C_{26}H_{23}O_4$ $[M+H]^+$: calcd 399.1591, found 399.1597.

*5,6-dimethyl-3-(4-methylbenzoyl)-2-(p-tolyl)-1H-inden-1-one **(2w)***. Black solid (77.0 mg, 70%); m.p. 138-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.21 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.63 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.9, 194.6, 153.6, 149.3, 148.1, 145.5, 139.1, 138.8, 133.8, 132.9, 129.6, 129.6, 129.2, 129.1, 127.2, 121.8, 108.1, 105.9, 56.5, 56.4, 21.8, 21.3; HRMS (ESI) for $C_{26}H_{23}O_2$ $[M+H]^+$: calcd 367.1693, found 367.1697.

*3-benzoyl-5,6-difluoro-2-phenyl-1H-inden-1-one **(2x)***. Yellow solid (67.5 mg, 65%); m.p. 124-127 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77-7.75 (m, 2H), 7.56-7.53 (m, 1H), 7.48-7.45 (m, 1H), 7.38-7.35

(m, 2H), 7.34-7.31 (m, 2H), 7.20-7.16 (m, 3H), 7.07-7.04 (m, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 192.3, 190.0, 158.8 (dd, J_1 = 248.8 Hz, J_2 = 71.3 Hz), 158.3 (dd, J_1 = 253.8 Hz, J_2 = 17.5 Hz), 135.0, 132.0, 131.8 (d, J = 1.3 Hz), 129.9, 129.7, 129.1, 128.6, 122.7 (dd, J_1 = 15.0 Hz, J_2 = 6.3 Hz), 121.6, 120.8 (d, J = 26.3 Hz), 120.6 (dd, J_1 = 18.8 Hz, J_2 = 11.3 Hz), 116.4 (dd, J_1 = 25.0 Hz, J_2 = 3.8 Hz), 100.2 (d, J = 2.5 Hz), 81.2 (d, J = 2.5 Hz); HRMS (ESI) for $C_{22}H_{13}F_2O_2$ $[M+H]^+$: calcd 347.0878, found 347.0871.

Gram-scale synthesis of 2a. To a 50 mL round-bottomed flask were added 1,2-bis(*p*-tolylethynyl)benzene **1a** (1.5 g, 5 mmol), I_2O_5 (6.7 g, 4 equiv, 20 mmol), MeCN/H_2O (4/1 (V/V), 25 mL). The reaction was stirred at 50 °C for 24 h. After completion of the reaction, H_2O (10 mL) and saturated $Na_2S_2O_3$ (15 mL) was added at room temperature. Then, the reaction mixture was extracted with DCM and purified by flash chromatography on silica gel (petroleum ether/EtOAc, V/V =10 : 1). The product was isolated as a yellow solid (1.27 g, 75%).

Radical inhibition reactions. To a 25 mL Schlenk tube were added 1,2-bis(*p*-tolylethynyl)benzene **1a** (91.8 mg, 0.3 mmol), I_2O_5 (400.8 mg, 4 equiv, 1.2 mmol), TEMPO, butylated hydroxytoluene (BHT), or *N*-*tert*-buthyl-α-phenylnitrone (PBN), MeCN/H_2O (4/1 (V/V), 4.5 mL). The reaction was stirred at 50 °C for 24 h. After completion, samples were taken for LC analysis.

Controlled experiment by removal of O_2. 1,2-Bis(*p*-tolylethynyl)benzene **1a** (91.8 mg, 0.3 mmol), I_2O_5 (400.8 mg, 4 equiv, 1.2 mmol), MeCN/H_2O (4/1 (V/V, 4.5 mL) were added to a 10-mL flask equipped with a high-vacuum PTFE valve-to-glass seal. Then the resultant mixture in the sealed tube was frozen by immersion of the flask in liquid N_2. When solvent was completely frozen, the flask was

opened to the vacuum (high vacuum) and pumped for 2-3 minutes, with the flask still immersed in liquid N_2. The flask was then closed and warmed until solvent completely melted. This process was repeated three times and after the last cycle the flask was backfilled with an inert Ar gas. The reaction was stirred at 50 °C for 24 h under Ar atmosphere. After completion, samples were taken for LC analysis.

Controlled experiment by removal of H_2O. To a 25 mL Schlenk tube were added 1,2-bis(*p*-tolylethynyl)benzene **1a** (91.8 mg, 0.3 mmol), I_2O_5 (400.8 mg, 4 equiv, 1.2 mmol) and anhydrous acetonitrile (4 mL). The reaction was stirred at 50 °C for 24 h. After completion, samples were taken for LC analysis.

^{18}O-Labeling experiment. To a 25 mL Schlenk tube were added 1,2-bis(phenylethynyl)benzene **1b** (83.5 mg, 0.3 mmol), I_2O_5 (400.8 mg, 4 equiv, 1.2 mmol) and MeCN/H_2O^{18} (4/1 (V/V), 4.5 mL). The reaction was stirred at 50 °C for 24 h. H_2O (4 mL) and saturated $Na_2S_2O_3$ (4 mL) was added at room temperature. Then, the reaction mixture was extracted with DCM and purified by flash chromatography on silica gel (petroleum ether/EtOAc = 10 : 1 (V/V)) as a yellow solid (68.0 mg, 73%). The double-^{18}O-incorporated product **2b**-$[O^{18}]_2$ (m/z = 315 $[M+H]^+$) was detected by the MS analysis (see Figure *S1* in Supporting Information).

ASSOCIATED CONTENT

Supporting Information

Charts for mechanistic studies as well as copies of ^{1}H and ^{13}C NMR spectra of the products. This

material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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