JOC The Journal of Organic Chemistry

Article

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Palladium-Catalyzed Acylations: One-Pot Synthesis of Indenones

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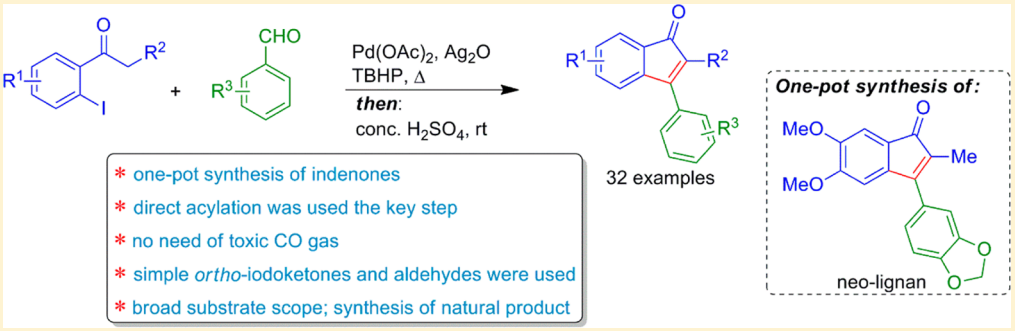
Supporting Information



ABSTRACT: An efficient, one-pot synthesis of substituted indenones was accomplished starting from simple *o*-iodoketones and aldehydes. [Pd]-catalyzed direct acylation of *o*-iodoketones with aldehydes was employed as the key step. Subsequent intramolecular aldol condensation afforded the indenones. Notably, a variety of indenones were achieved. Significantly, the natural product neolignan was accomplished in one pot.

INTRODUCTION

Indenones are ubiquitous structural units, which exhibit a broad biological spectrum and also serve as useful intermediates for the synthesis of natural products (Figure 1).[1] Until now,

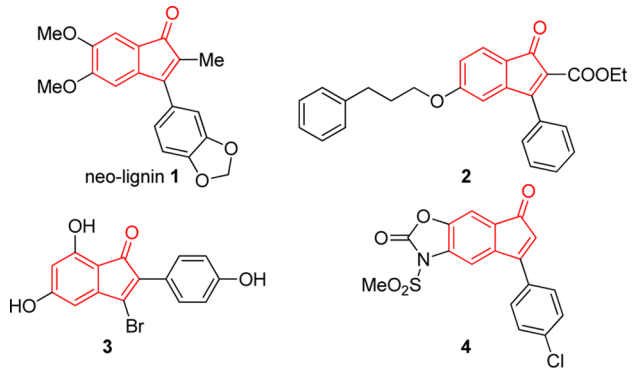
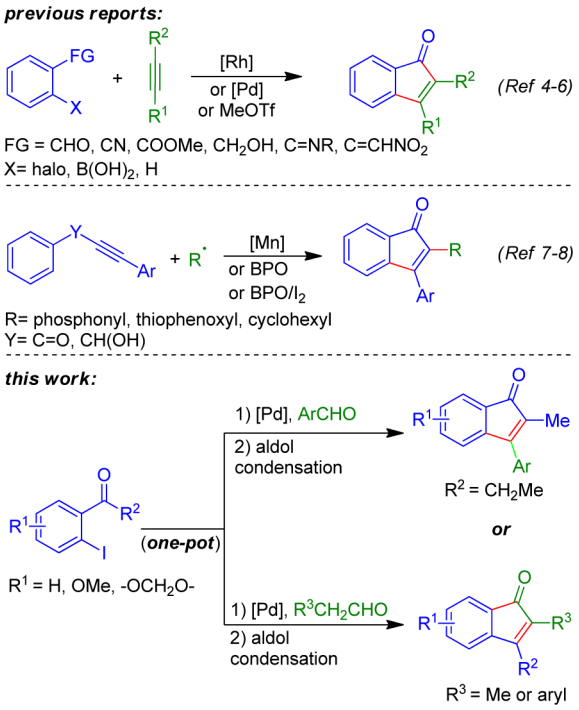


Figure 1. Compounds containing an indenone core.

various notable approaches have been reported on their synthesis.[2−8] For example, transition-metal-catalyzed annulations of alkynes were accomplished using carbon monoxide (CO) as carbonylating agent,[3] while annulations of internal alkynes with 2-halobenzaldehydes, 2-(methoxycarbonyl)phenylboronic acids, 2-bromophenylboronic acids, or 2-iodobenzonitriles have also been established using transition-metal catalysis (Scheme 1).[4−6] On the other hand, radical-mediated cyclizations were also reported (Scheme 1).[7,8]

Nevertheless, there are certain drawbacks with most of these methods. For example, regioselectivity is a common problem in transition-metal-mediated annulations, particularly when unsymmetrical alkynes were used.[9] Therefore, the development of

Scheme 1. Synthesis of Indenones



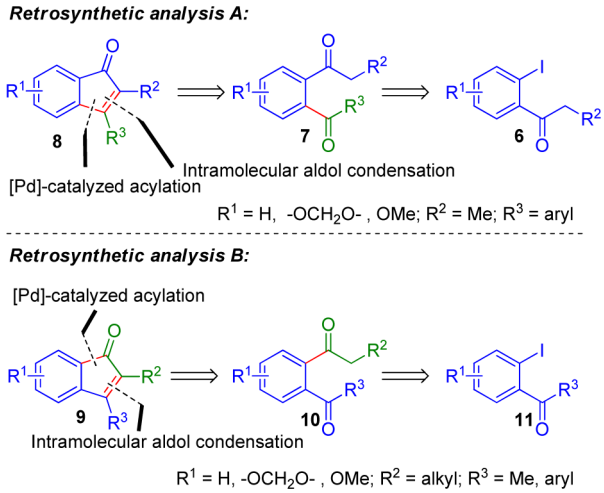
Received: October 7, 2016
Published: December 9, 2016

DOI: 10.1021/acs.joc.6b02453
J. Org. Chem. 2017, 82, 372−381

new synthetic methods with high regioselectivity is beneficial. In continuation of our ongoing research interest in transition-metal catalysis,[10] very recently, we have disclosed an environmentally benign acylation[10h] for the synthesis of various ketones. In this transformation, an iodoarene was coupled with an aldehyde in the presence of [Pd] catalyst and oxidant. Significantly, unlike previous reports, the reaction was feasible without activating the aldehyde functionality.[9f] On the other hand, we have developed acid-promoted domino one-pot synthesis of indanones and indenones from simple cinnamic acid esters.[11] Herein, we describe an efficient one-pot domino process for the synthesis of a wide variety of indenones starting from readily available *o*-iodoketones and aldehydes. Significantly, this strategy was applied to the one-pot synthesis of naturally occurring neolignan **1**.[1e]

Inspired by our recent results on [Pd]-catalyzed direct acylations,[10h] we envisioned that the indenones **8** could be obtained from 1,2-diketobenzenes **7** by employing intramolecular aldol condensation. The required 1,2-diketobenzenes **7** would be achieved from *o*-iodoketones **6** using [Pd]-catalyzed acylations (retrosynthetic analysis A; Scheme 2). Alternatively,

Scheme 2. Retrosynthetic Analysis



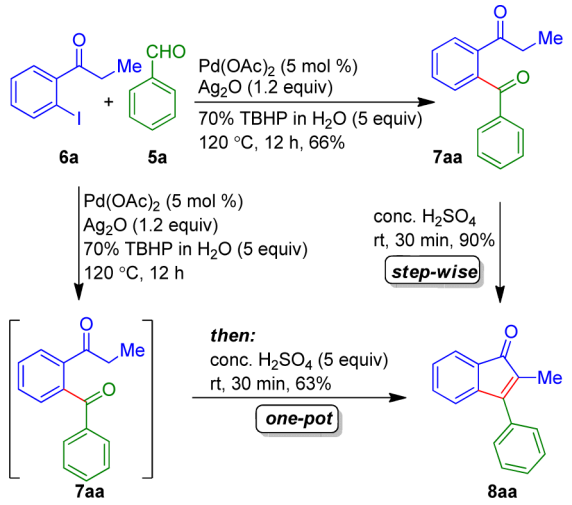
the indenones **9** could also be accomplished from 1,2-diketones **10**. These 1,2-diketones **7** would in turn would be synthesized from *o*-iodoketones **11** (retrosynthetic analysis B; Scheme 2).

RESULTS AND DISCUSSION

Thus, we initially examined the reaction with *o*-iodopropiophenone **6a** and benzaldehyde **5a**. In particular, the acylation reaction was carried out under the established conditions (i.e., reported conditions with iodoarenes and benzaldehydes). We were delighted to find that the reaction was amenable to this ketone **6a** as well. Then the isolated 1,2-diketobenzene **7aa** was subjected to an acid-mediated intramolecular aldol condensation. As expected, the desired indenone **8aa** was furnished (Scheme 3). With these encouraging results, we performed acylation and subsequent intramolecular aldol condensation[12] in a one-pot manner. To our delight, as anticipated, the indenone **8aa** was obtained in 63% overall yield (Scheme 3).

With these conditions, we next investigated the scope of this protocol by exploring the reaction between various *o*-iodopropiophenones **6a–d** and benzaldehydes **5a–m**. Gratifyingly, the reaction was found amenable and furnished

Scheme 3. Stepwise and One-Pot Synthesis of Indenone 8aa



the products **8aa–df** in fair to good yields (Table 1). Delightfully, the reaction proceeded smoothly with electron-deactivating (F, Cl, and Br) as well as electron-donating (alkyl, OMe, etc.) substituents on the aromatic ring of benzaldehydes **5e–p**. Significantly, the reaction was also successful with 2-furaldehyde **5m** (Table 1, **8am**). The reaction was also compatible with the protecting group free *p*-hydroxybenzaldehyde **5j** (Table 1, **8aj**). It is worth mentioning that in the case of electron-rich aromatic systems (iodoarenes or benzaldehydes) the direct formation of indenones was observed, albeit in minor amounts, before the addition of H_2SO_4 (Table 1, **8aj–df**). Presumably the aldol condensation would be induced either by the silver ions (Ag^+) from Ag_2O or the carboxylic acid that might be generated from the corresponding benzaldehyde. As in our previous report, the acylation reaction was unsuccessful with benzaldehydes bearing a strong electron-withdrawing nitro group and heteroaromatic aldehydes. These observations appear to be common under such radical-mediated conditions and may be due to the destabilizing nature of electron-withdrawing groups.[13]

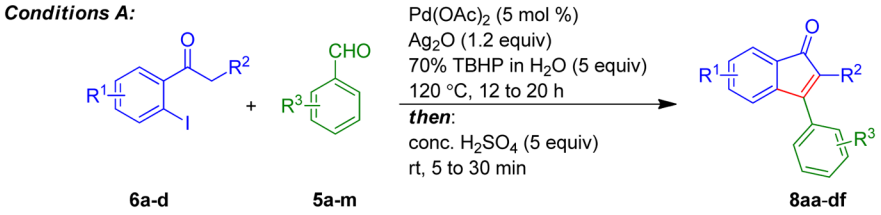
It was noticed that in the case of the electron-rich aromatic ring (benzaldehydes or iodoarenes) minor amounts of indenones **8** were formed before the addition of H_2SO_4. We supposed that the reaction could be driven to the target products if both or at least one of the aromatic rings is/are sufficiently electron rich. In such situations, even a mild acid(s) such as Ag^+ of Ag_2O or in situ formed carboxylic acids could promote the subsequent intramolecular aldol condensation. Therefore, the reaction was performed with the iodoarenes **6a–d** and benzaldehydes **5k–p**, under standard conditions, without the subsequent addition of H_2SO_4 (i.e., conditions B). To our delight, the reaction proceeded smoothly and furnished the indenones **8an–dk** (Table 2).

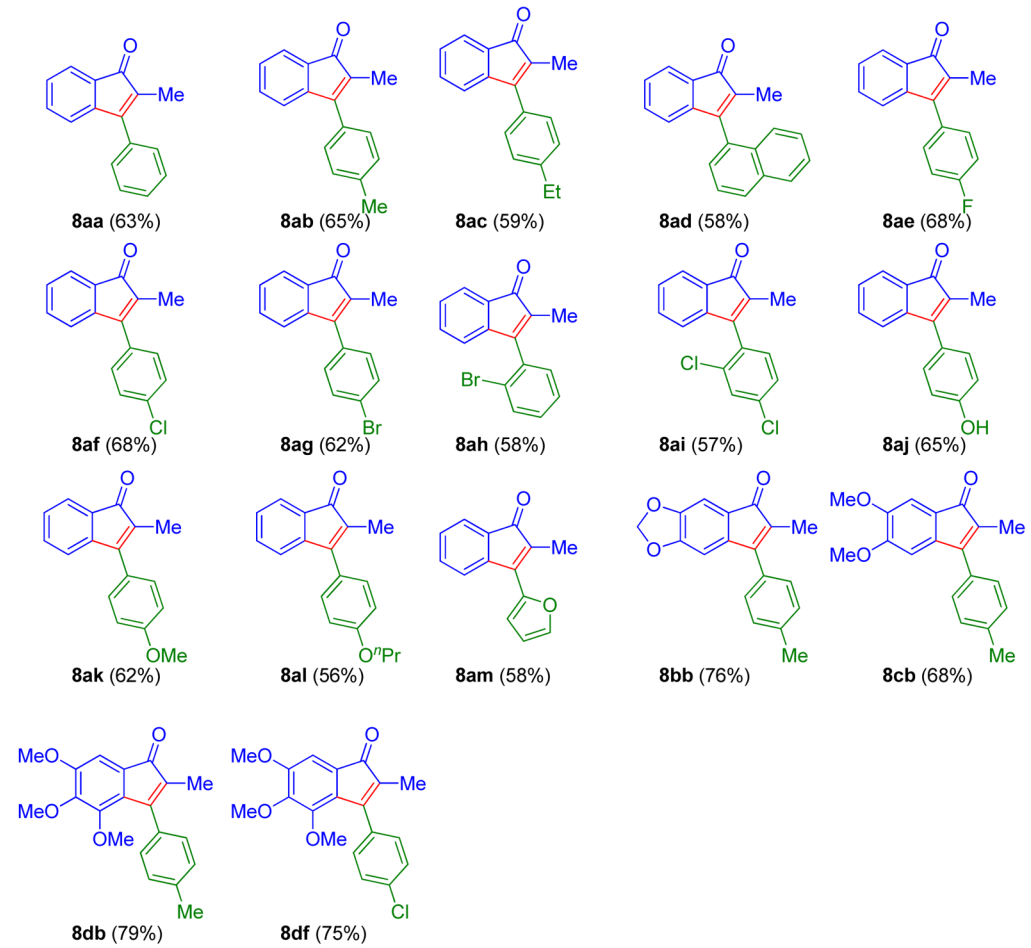
Furthermore, the structure of **8ap** was also confirmed by the single-crystal X-ray diffraction analysis (Figure 2).

Furthermore, to check the scope and applicability of the present protocol, the reaction was also performed with *o*-iodobenzophenones **11a–d** (Table 3). In contrast to the above, in this case, aliphatic aldehydes **5q–s** were employed for the [Pd]-catalyzed acylations. Gratifyingly, the protocol was also quite successful and gave the indenones **9ar–dr** (Table 3; conditions A or B). Notably, the reaction was compatible with heteroaromatic *o*-iodobenzophenone **11c** (Table 3).

DOI: 10.1021/acs.joc.6b02453
J. Org. Chem. 2017, 82, 372–381

Table 1. Scope and Generality of Formation of Indenones 8aa−df





To further demonstrate the applicability of the method, we investigated the coupling between the ketone **11e** and aliphatic aldehydes **5q** and **5r**. Notably, in the case of diketone intermediates derived from the *o*-iodoacetophenone **11e**, as anticipated, the reaction proceeded through the formation of relatively more stable enolate under acidic conditions and gave the indenones **9eq** and **9er** (Scheme 4, conditions A).

On the other hand, the reaction between the ketone **6a** and cyclohexanaldehyde **5s** furnished the inseparable mixture of indenone **8as** and spirocyclic ketone **9as** (Scheme 5). This may be due to the competitive enolization of both ketones and an independent subsequent intramolecular aldol condensation. When the reaction was conducted separately on the isolated mixture of **8as** and **9as** with H_2SO_4, no change was noticed in the ratio of **8as** and **9as** (i.e., conditions A). Thus, this indicates that the reaction might proceed through the irreversible independent path without equilibration for aldol condensation reaction.

In 1984, Gottlieb et al. isolated neolignan from the fruits of *Virola sebifera*.[1f] Later, in 1998, the research group of Harrowven revised its structure as neolignan **1** with the help of their synthetic, physical, and spectroscopic studies (see Figure 1).[1e] To further demonstrate the synthetic utility of the present strategy, it was investigated for one-pot synthesis of neolignan **1**. Thus, the *o*-iodoketone **6c** was subjected to the reaction with piperonaldehyde **5n** under standard conditions without H_2SO_4 (i.e., conditions B). Significantly, the natural product neolignan **1** was obtained in one pot (Scheme 6).

In summary, we have developed an efficient one-pot protocol for synthesis of substituted indenones starting from simple *o*-iodoketones and aldehydes. The [Pd]-catalyzed direct acylation was employed as the key step. Subsequent intramolecular aldol condensation afforded the indenones in one pot. Significantly, a variety of indenones were achieved. Delightfully, the strategy was applied to the one-pot synthesis of naturally occurring neolignan.

EXPERIMENTAL SECTION

IR spectra were recorded on an FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in

DOI: 10.1021/acs.joc.6b02453
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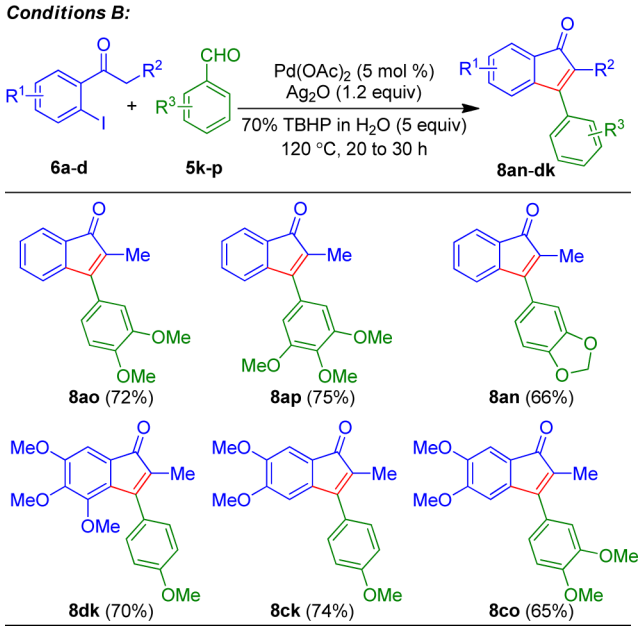
Table 2. Scope and Generality of Formation of Indenones 8an–dk



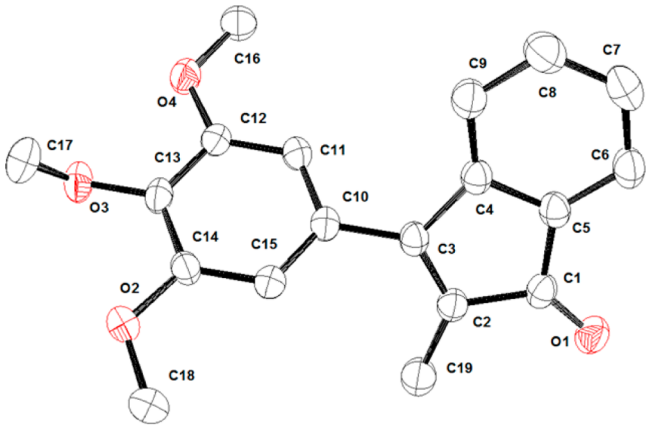
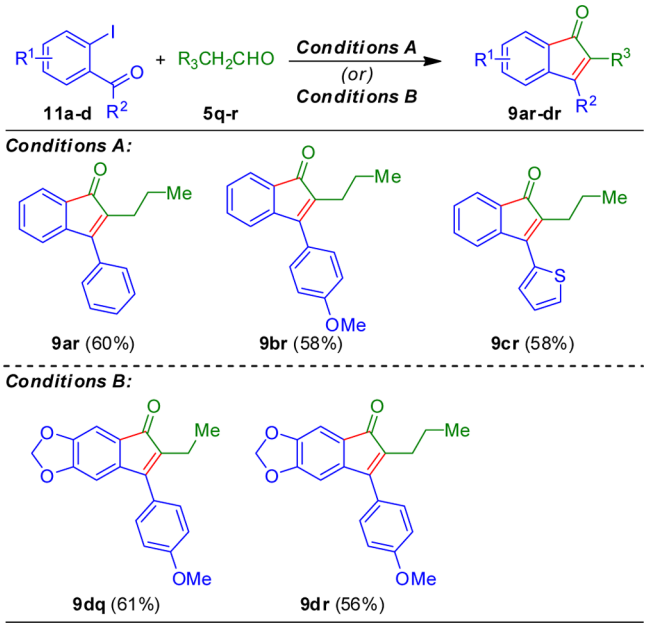


Figure 2. X-ray crystal structure of indenone **8ap**. Thermal ellipsoids is drawn at 50% probability level.

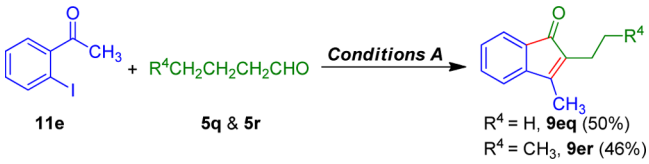
standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer at rt in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{13}C NMR, the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT-135 spectra. In the ^1H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, sept = septet, dd = doublet of doublet, m = multiplet, and br s = broad singlet. High-resolution mass spectra (HR-MS) were recorded on Q-TOF electron spray ionization (ESI) mode and atmospheric pressure chemical ionization (APCI) modes. Melting points were determined on an electrothermal melting point apparatus and are uncorrected.

All small-scale reactions were carried out using a Schlenk tube. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Reactions were generally run under argon or a nitrogen atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 60–80 °C was used. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material). The aldehydes **5a–s** which were used are commercially available. The

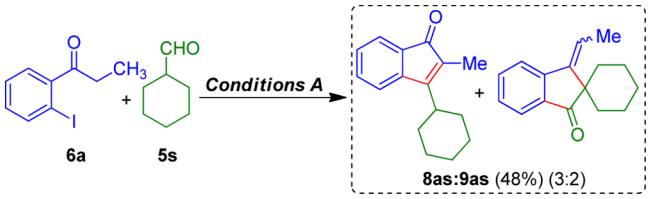
Table 3. Scope and Generality of Formation of Indenones 9aa–dr



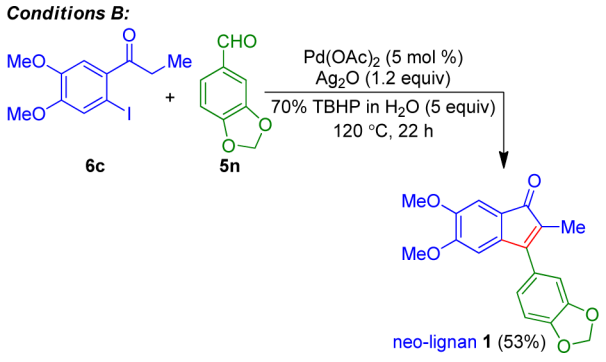
Scheme 4. Synthesis of Indenones 9eq and 9er



Scheme 5. Formation of Indenone Mixture 8as and 9as



Scheme 6. One-Pot Synthesis of Neolignan 1



o-iodo ketones **6a–d**, **11a–e** were synthesized from the corresponding *o*-iodo aldehydes by Grignard reaction followed by PCC oxidation, which is reported in the literature.[10a,14]

GP-1 [General Procedure for Preparation of 8 and 9 (Conditions A)]. GP-1 was carried out with *o*-iodoketone **6a–d**, **11a–e** (104–152 mg, 0.40 mmol), and aldehyde **5a–s** (166.4–366.5 mg, 1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %),

DOI: 10.1021/acs.joc.6b02453
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Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12−20 h. Progress of the reaction was monitored by TLC until the *o*-iodoketones **6a−d** and **11a−e** were consumed. The reaction mixture was removed from the oil bath and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature. Formation of the products **8aa−df** and **9ar−er** was monitored by TLC until the reaction was completed. The reaction mixture was quenched by the addition of aqueous $NaHCO_3$ solution and then extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the products **8** and **9** (34.0−112.0 mg, 46−79%) as viscous liquid/solids. The products **8am**, **8as**, **8dk**, **9er**, **9eq**, and **9ar** are reported in the literature.[15]

GP-2 [General Procedure for Preparation of 8 and 9 (Conditions B)]. GP-1 was carried out with *o*-iodoketones **6a−d**, and **11d** (104−152 mg, 0.40 mmol) and aldehyde **5** (166.4−366.5 mg, 1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 20−30 h. Progress of the formation of products **8an−dk** and **9dq−dr** was monitored by TLC until the reaction was completed. The reaction mixture was removed from the oil bath, allowed to reach room temperature, quenched by the addition of aqueous $NaHCO_3$ solution, and then extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the products **8** and **9** (68.7−104.0 mg, 65−75%) as a viscous liquid/solid.

*2-Methyl-3-phenyl-1H-inden-1-one (**8aa**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5a** (166.4 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol), and the reaction mixture was allowed to stir at 120 °C for 12 h. The reaction mixture was removed from the oil bath and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 35 min until the product **8aa** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to 95:5) furnished the product **8aa** (55.4 mg, 63%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 96:4), R_f(**6a**) = 0.50, R_f(**8aa**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 1870, 1680, 1591, 1470, 1280, 1189, 954, 718 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.53−7.43 (m, 6H), 7.31−7.26 (m, 1H), 7.20−7.16 (m, 1H), 7.05 (d, 1H, *J* = 7.3 Hz), 1.92 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.3 (C_q), 154.7 (C_q), 145.7 (C_q), 133.1 (CH), 132.7 (C_q), 131.1 (s, C═C), 131.0 (C_q), 129.2 (CH), 128.7 (2 × CH), 128.1 (CH), 128.0 (2 × CH), 122.5 (CH), 120.4 (CH), 8.6 (CH_3) ppm. HR-MS (ESI^+): *m*/*z* calcd for $[C_{16}H_{13}O]^+$ = $[M + H]^+$ 221.0961, found 221.0961.

*2-Methyl-3-(p-tolyl)-1H-inden-1-one (**8ab**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5b** (192.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 25 min until product **8ab** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3−95:5) furnished the product **8ab** (60.8 mg, 65%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 96:4), R_f(**6a**) = 0.50, R_f(**8ab**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 1812, 1686, 1597, 1456, 1287, 1189, 939, 718 $cm^{-11}H$ NMR ($CDCl_3$, 400 MHz): δ = 7.46 (d, 1H, *J* = 6.8 Hz), 7.39−7.37 (m, 2H), 7.33−7.26 (m, 3H), 7.18 (t, 1H, *J* = 7.0 Hz), 7.07 (d, 1H, *J* = 7.3 Hz), 2.43 (s, 3H) 1.92 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.4 (C_q), 154.8 (C_q), 145.7 (C_q), 139.3 (C_q), 133.0 (CH), 131.3 (C_q), 130.6 (C_q), 129.8 (C_q), 129.4 (2 × CH), 128.0 (3 × CH),122.4 (CH), 120.4(CH), 21.5 (CH_3), 8.6 (CH_3) ppm. HR-MS (ESI^+): *m*/*z* calcd for $[C_{17}H_{15}O]^+$ = $[M + H]^+$ 235.1117, found 235.1107.

*3-(4-Ethylphenyl)-2-methyl-1H-inden-1-one (**8ac**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5c** (214.6 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 13 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 30 min until product **8ac** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3−95:5) furnished the product **8ac** (58.5 mg, 59%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 96:4), R_f(**6a**) = 0.50, R_f(**8ac**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2938, 1819, 1686, 1599, 1457, 1287, 1088, 930, 718 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.46 (d, 1H, *J* = 7.3 Hz), 7.42−7.40 (m, 2H), 7.34 (d, 2H, *J* = 8.3 Hz), 7.28 (td, 1H, *J* = 7.4 and *J* = 1.2 Hz), 7.17 (t, 1H, *J* = 7.3 Hz), 7.07 (d, 1H, *J* = 7.3 Hz), 2.73 (q, 2H, *J* = 7.3 Hz), 1.93 (s, 3H), 1.30 (t, 3H, *J* = 7.3 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.4 (C_q), 154.8 (C_q), 145.7 (C_q), 145.6 (C_q), 133.0 (CH), 131.3 (C_q), 130.6 (C_q), 130.0 (C_q), 128.2 (2 × CH), 128.1 (2 × CH),128.0 (CH), 122.4(CH), 120.4(CH), 28.8 (CH_2), 15.4 (CH_2), 8.7 (CH_3) ppm. HR-MS (ESI^+): *m*/*z* calcd for $[C_{18}H_{17}O]^+$ = $[M + H]^+$ 249.1274, found 249.1274.

*2-Methyl-3-(naphthalen-1-yl)-1H-inden-1-one (**8ad**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5d** (249.6 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 15 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 30 min until product **8ad** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3−95:5) furnished the product **8ad** (62.7 mg, 58%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 96:4), R_f(**6a**) = 0.50, R_f(**8ad**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 2829, 1689, 1590, 1450, 1287, 1187, 938, 719 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.95 (dd, 2H, *J* = 8.3 and *J* = 4.4 Hz), 7.76 (d, 1H, *J* = 8.3 Hz), 7.60−7.54 (m, 1H), 7.53−7.51 (m, 2H), 7.47−7.44 (m, 2H), 7.20−7.18 (m, 2H), 6.65−6.63 (m, 1H), 1.76 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.2 (C_q), 154.9 (C_q), 146.8 (C_q), 133.8 (C_q), 133.4 (CH), 133.3 (C_q), 130.6 (C_q), 130.6 (C_q), 130.4 (C_q), 129.3 (CH), 128.6 (CH), 128.1 (CH), 126.3(CH), 126.3(CH), 125.8(CH), 125.7(CH), 125.4(CH), 122.3(CH), 120.8(CH), 8.8 (CH_3) ppm. HR-MS (ESI^+): *m*/*z* calcd for $[C_{20}H_{15}O]^+$ = $[M + H]^+$ 271.1117, found 271.1121.

*3-(4-Fluorophenyl)-2-methyl-1H-inden-1-one (**8ae**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5e** (198.4 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 30 min until product **8ae** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3−95:5) furnished the product **8ae** (64.7 mg, 68%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 96:4), R_f(**6aa**) = 0.50, R_f(**8ae**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 1891, 1687, 1597, 1460, 1287, 1089, 938, 728 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.48−7.44 (m, 3H), 7.30 (td, 1H, *J* = 7.4 and *J* = 1.2 Hz), 7.23−7.17 (m, 3H), 7.02 (d, 1H, *J* = 6.8 Hz), 1.90 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.0 (C_q), 164.2 (C_q, $^1J_{C-F}$ = 254 Hz), 161.7 (C_q), 153.7 (C_q), 145.5 (C_q), 133.2 (CH), 131.1 (C_q), 131.0 (C_q), 130.0 (CH), 129.9 (CH), 128.7 (C_q), 128.2 (CH), 122.6 (CH), 120.2 (CH), 116.0 (CH), 115.8 (CH), 8.6 (CH_3) ppm.

DOI: 10.1021/acs.joc.6b02453
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HR-MS (ESI$^+$): m/z calcd for $[C_{16}H_{12}FO]^+ = [M + H]^+$ 239.0867, found 239.0870.

*3-(4-Chlorophenyl)-2-methyl-1H-inden-1-one (**8af**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5f** (224.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 30 min until product **8af** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3−95:5) furnished the product **8af** (69.2 mg, 68%) as a yellow solid: Mp = 75−77 °C [TLC control (petroleum ether/ethyl acetate 96:4), R_f(**6a**) = 0.50, R_f(**8af**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2939, 1810, 1683, 1590, 1453, 1287, 1080, 938, 719 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.50−7.47 (m, 3H), 7.43−7.40 (m, 2H), 7.30 (td, 1H, J = 7.4 and J = 1.2 Hz), 7.19 (t, 1H, J = 7.8 Hz), 7.01 (d, 1H, J = 7.3 Hz), 1.90 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.9 (C_q), 153.4 (C_q), 145.3 (C_q), 135.1 (C_q), 133.2 (CH), 131.4 (C_q), 131.1 (C_q), 130.9 (C_q), 129.4 (d, 2 × CH), 129.1 (2 × CH), 128.3 (CH), 122.7 (CH), 122.2 (CH), 8.6 (CH_3) ppm. HR-MS (ESI$^+$) m/z calcd for $[C_{16}H_{12}ClO]^+ = [M + H]^+$ 255.0571, found 255.0567.

*3-(4-Bromophenyl)-2-methyl-1H-inden-1-one (**8ag**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5g** (296.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 15 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 30 min until product **8ag** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3−95:5) furnished the product **8ag** (73.8 mg, 62%) as a yellow solid. Mp = 71−74 °C [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**6a**) = 0.50, R_f(**8ag**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 2821, 1686, 1599, 1450, 1287, 1087, 945, 710 cm$^{-1.1}$H NMR ($CDCl_3$, 400 MHz): δ = 7.64 (d, 2H, J = 8.3 Hz), 7.47 (d, 1H, J = 7.3 Hz), 7.36−7.33 (m, 2H), 7.29 (td, 1H, J = 7.4 and J = 1.2 Hz), 7.20−7.17 (m, 1H), 7.0 (d, 1H, J = 7.3 Hz), 1.89 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.9 (C_q), 153.4 (C_q), 145.2 (C_q), 133.2 (CH), 132.0 (2 × CH), 131.5 (C_q), 131.4 (C_q), 130.9 (C_q), 129.6 (2C × CH), 128.2 (CH), 123.3 (C_q), 122.7(CH), 120.1 (CH), 8.6 (CH_3) ppm. HR-MS (ESI$^+$): m/z calcd for $[C_{16}H_{12}BrO]^+ = [M + H]^+$ 299.0066, found 299.0079.

*3-(2-Bromophenyl)-2-methyl-1H-inden-1-one (**8ah**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5h** (296.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 13 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 30 min until product **8ah** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3−95:5) furnished the product **8ah** (69.3 mg, 58%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**6a**) = 0.50, R_f(**8ah**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2933, 2829, 1689, 1598, 1450, 1287, 1087, 945, 710 cm$^{-1.1}$H NMR ($CDCl_3$, 400 MHz): δ = 7.72 (dd, 1H, J = 8.0 and J = 1.2 Hz), 7.47−7.41 (m, 2H), 7.32−7.23 (m, 3H), 7.18−7.15 (m, 1H), 6.70 (d, 1H, J = 7.3 Hz), 1.77 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.0 (C_q), 154.7 (C_q), 145.7 (C_q), 134.2 (C_q), 133.4 (CH), 133.3 (CH), 133.0 (C_q), 130.3 (C_q), 130.2 (CH), 129.6 (CH), 128.0 (CH), 127.5 (CH), 122.5 (CH), 122.2 (C_q), 120.5 (CH), 8.8 (CH_3) ppm. HR-MS (ESI$^+$) m/z calcd for $[C_{16}H_{12}BrO]^+ = [M + H]^+$ 299.0066, found 299.0060

*3-(2,4-Dichlorophenyl)-2-methyl-1H-inden-1-one (**8ai**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5i** (280.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 30 min until product **8ai** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3−95:5) furnished the product **8ai** (65.9 mg, 57%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**6a**) = 0.50, R_f(**8ai**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2939, 1810, 1683, 1590, 1453, 1287, 1080, 938, 719 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57 (d, 1H, J = 1.9 Hz), 7.47 (d, 1H, J = 6.8 Hz), 7.37 (dd, 1H, J = 8.0 and J = 2.2 Hz),7.29−7.23 (m, 2H), 7.18 (t, 1H, J = 7.3 Hz), 6.71 (d, 1H, J = 7.3 Hz), 1.77 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.6 (C_q), 151.9 (C_q), 145.3 C_q), 135.4 (C_q), 133.8 (C_q), 133.5 (CH), 130.5 (C_q), 130.5 (CH), 130.2 (2 × C_q), 130.2 (CH), 128.2 (CH), 127.4 (CH), 122.7 (CH), 120.3 (CH), 8.8 (CH_3) ppm. HR-MS (ESI$^+$): m/z calcd for $[C_{16}H_{11}Cl_2O]^+ = [M + H]^+$ 289.0181, found 289.0188.

*3-(4-Hydroxyphenyl)-2-methyl-1H-inden-1-one (**8aj**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5j** (195.2 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 15 min until product **8aj** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−90:10) furnished the product **8aj** (61.3 mg, 65%) as a yellow solid. Mp = 168−171 °C [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**6a**) = 0.50, R_f(**8aj**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2878, 1710, 1686, 1589, 1451, 1297, 1187, 947, 711 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.46 (d, 1H, J = 6.3 Hz), 7.42−7.38 (m, 2H), 7.29 (td, 2H, J = 7.4 and J = 1.2 Hz), 7.20−7.16 (m, 1H), 7.08 (d, 1H, J = 7.3 Hz), 7.00−6.97 (m, 2H), 5.43 (brd. s, 1H), 1.92 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.5 (C_q), 156.5 (C_q), 154.6 (C_q), 145.7 (C_q), 133.0 (CH), 131.4 (C_q), 130.1 (C_q), 129.8 (2 × CH), 128.1 (CH), 125.2 (C_q), 122.4 (CH), 120.4 (CH), 115.6 (2 × CH), 8.7 (CH_3) ppm. HR-MS (ESI$^+$): m/z calcd for $[C_{16}H_{13}O_2]^+ = [M + H]^+$ 237.0910, found 237.0899.

*3-(4-Methoxyphenyl)-2-methyl-1H-inden-1-one (**8ak**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5k** (217.6 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 20 min until product **8ak** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−93:7) furnished the product **8ak** (62.1 mg, 62%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**6a**) = 0.50, R_f(**8ak**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2878, 1710, 1686, 1589, 1451, 1297, 1187, 947, 711 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.48−7.44 (m, 3H), 7.29 (td, 1H, J = 7.4 and J = 1.2 Hz), 7.20−7.16 (m, 1H), 7.09 (d, 1H, J = 7.3 Hz), 7.02 (d, 2H, J = 8.8 Hz), 3.88 (s, 3H), 1.92 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.3 (C_q), 160.3 (C_q), 154.5 (C_q), 145.7 (C_q), 133.0 (CH), 131.4 (C_q), 130.1 (C_q), 129.6 (2 × CH), 128.0 (CH), 125.1 (C_q), 122.3 (CH), 120.4 (CH), 114.1 (2 × CH), 55.4 (CH_3), 8.7 (CH_3) ppm. HR-MS (ESI$^+$): m/z calcd for $[C_{17}H_{15}O_2]^+ = [M + H]^+$ 251.1067, found 251.1063.

*2-Methyl-3-(4-propoxyphenyl)-1H-inden-1-one (**8al**).* GP-1 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol) and aldehyde **5l** (262.7 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 15 h, removed from the oil bath, and allowed to reach room temperature.

DOI: 10.1021/acs.joc.6b02453
J. Org. Chem. 2017, 82, 372−381

Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 20 min until product **8al** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−93:7) furnished the product **8al** (62.3 mg, 56%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 94:6), R_f(**6a**) = 0.50, R_f(**8al**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 2821, 1686, 1599, 1450, 1287, 1087, 945, 710 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45−7.42 (m, 3H), 7.27 (td, 1H, J = 7.4 and J = 1.2 Hz), 7.16 (t, 1H, J = 7.3 Hz), 7.09 (d, 1H, J = 6.8 Hz), 7.04−7.00 (m, 2H), 3.98 (t, 2H, J = 6.6 Hz), 1.92 (s, 3H), 1.89−1.80 (m, 2H), 1.06 (t, 3H, J = 7.5 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.3 (C_q), 159.9 (C_q), 154.5 (C_q), 145.7 (C_q), 132.9 (CH), 131.4 (C_q), 129.9 (C_q), 129.6 (2 × CH), 127.9 (CH), 124.7 (C_q), 122.2 (CH), 120.4 (CH), 114.6 (2 × CH), 69.6 (CH_2), 22.5 (CH_2), 10.5 (CH_3) 8.7 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{19}H_{19}O_2]^+ = [M + H]^+$ 279.1380, found 279.1382.

*3-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-1H-inden-1-one (**8an**).* GP-2 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol), aldehyde **5n** (256.0 mg,1.6 mmol), $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 28 h until product **8an** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−93:7) furnished the product **8an** (69.7 mg, 66%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**6a**) = 0.80, R_f(**8an**) = 0.30, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2878, 1710, 1689, 1596, 1481, 1287, 1187, 937, 721 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45 (d, 1H, J = 6.3 Hz), 7.28 (td, 1H, J = 7.4 and J = 1.2 Hz), 7.17 (t, 1H, J = 7.3 Hz), 7.06 (d, 1H, J = 6.8 Hz), 7.00−6.92 (m, 3H), 6.03 (s, 2H), 1.91 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.1 (C_q), 154.4 (C_q), 148.3 (C_q), 147.9 (C_q), 145.5 (C_q), 133.0 (CH), 131.2 (C_q), 130.4 (C_q), 128.0 (CH), 126.4 (C_q), 122.3 (CH), 122.3 (CH), 120.3 (CH), 108.6 (CH), 108.4 (CH), 101.4 (CH_2), 8.7 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{17}H_{13}O_3]^+ = [M + H]^+$ 265.0859, found 265.0848.

*3-(3,4-Dimethoxyphenyl)-2-methyl-1H-inden-1-one (**8ao**).* GP-2 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol), aldehyde **5o** (265.6 mg,1.6 mmol), $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 28 h until product **8ao** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 95:5−93:7) furnished the product **8ao** (80.7 mg, 72%) as yellow solid. Mp = 102−104 °C [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**6a**) = 0.70, R_f(**8ao**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2934, 1711, 1689, 1590, 1451, 1285, 1134, 1079, 930, 716 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45 (d, 1H, J = 6.3 Hz), 7.28 (td, 1H, J = 7.4 and J = 1.2 Hz), 7.19−7.15 (m, 1H), 7.11−7.07 (m, 2H), 6.99 (dd, 2H, J = 5.1 and J = 3.1 Hz), 3.94 (s, 3H), 3.91 (s, 3H), 1.93 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.2 (C_q), 154.6 (C_q), 149.8 (C_q), 148.9 (C_q), 145.6 (C_q), 133.0 (CH), 131.3 (C_q), 130.2 (C_q), 128.0 (CH), 125.3 (C_q), 122.3 (CH), 121.2 (CH), 120.3 (CH), 111.1 (CH), 111.0 (CH), 56.0 (CH_3), 55.9 (CH_3), 8.7 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{18}H_{17}O_3]^+ = [M + H]^+$ 281.1172, found 281.1173.

*2-Methyl-3-(3,4,5-trimethoxyphenyl)-1H-inden-1-one (**8ap**).* GP-2 was carried out with *o*-iodoketone **6a** (104.0 mg, 0.40 mmol), aldehyde **5p** (313.9 mg,1.6 mmol), $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 28 h until product **8ap** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−93:7) furnished the product **8ap** (93 mg, 75%) as a yellow solid. Mp = 109−112 °C [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**6a**) = 0.80, R_f(**8ap**) = 0.50, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2878, 1710, 1686, 1589, 1451, 1297, 1187, 947, 711 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45 (d, 1H, J = 6.8 Hz), 7.31−7.27 (m, 1H), 7.17 (t, 1H, J = 7.0 Hz), 7.09 (d, 1H, J = 7.3 Hz), 6.67 (s, 2H), 3.91 (s, 3H), 3.88 (s, 6H), 1.93 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.1 (C_q), 154.7 (C_q), 153.4 (3× C_q), 145.6 (C_q), 138.7 (C_q), 133.1 (CH), 131.1 (C_q), 130.7 (C_q), 128.1 (CH), 122.5 (CH), 120.3 (CH), 105.2 (2 × CH), 60.9 (CH_3), 56.2 (2 × CH_3), 8.7 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{19}H_{18}O_4]^+ = [M]^+$ 310.1205, found 310.1202.

*6-Methyl-7-(p-tolyl)-5H-indeno[5,6-d][1,3]dioxol-5-one (**8bb**).* GP-1 was carried out with *o*-iodoketone **6b** (121.6 mg, 0.40 mmol) and aldehyde **5b** (192.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 14 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 15 min until product **8bb** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−90:10) furnished the product **8bb** (84.6 mg, 76%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**6b**) = 0.30, R_f(**8bb**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 1757, 1690, 1590, 1450, 1286, 1089, 930, 719 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.34−7.29 (m, 4H), 6.98 (s, 1H), 6.59 (s, 1H), 5.97 (s, 2H), 2.42 (s, 3H), 1.86 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 196.9 (C_q), 152.9 (C_q), 151.2 (C_q), 146.9 (C_q), 142.4 (C_q), 139.2 (C_q), 129.7 (C_q), 129.6 (C_q), 129.4 (2 × CH), 127.9 (2 × CH), 125.1 (C_q), 105.0 (CH), 103.5 (CH), 101.9 (CH_2), 21.4 (CH_3) 8.7 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{18}H_{15}O_3]^+ = [M + H]^+$ 279.1016, found 279.1011.

*5,6-Dimethoxy-2-methyl-3-(p-tolyl)-1H-inden-1-one (**8cb**).* GP-1 was carried out with *o*-iodoketone **6c** (128.0 mg, 0.40 mmol) and aldehyde **5b** (192.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 13 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 10 min until product **8cb** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−90:10) furnished the product **8cb** (80.0 mg, 68%) as a yellow solid. Mp = 158−160 °C [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**6c**) = 0.30, R_f(**8cb**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 1808, 1680, 1595, 1450, 1287, 1189, 936, 710 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.34 (dd, 4H, J = 7.3, J = 1.2 Hz), 7.10 (s, 1H), 6.63 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.43 (s, 3H), 1.86 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.9 (C_q), 153.1 (C_q), 152.3 (C_q), 148.2 (C_q), 140.2 (C_q), 139.2 (C_q), 129.9 (C_q), 129.4 (C_q), 129.4 (2 × CH), 127.9 (2 × CH), 123.4 (C_q), 107.4 (CH), 105.4 (CH), 56.3 (CH_3), 56.3 (CH_3), 21.4 (CH_3) 8.6 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{19}H_{19}O_3]^+ = [M + H]^+$ 295.1329, found 295.1324.

*5,6-Dimethoxy-3-(4-methoxyphenyl)-2-methyl-1H-inden-1-one (**8ck**).* GP-2 was carried out with *o*-iodoketone **6c** (128.0 mg, 0.40 mmol), aldehyde **5k** (217.6 mg,1.6 mmol), $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 28 h until product **8ck** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−90:10) furnished the product **8ck** (91.8 mg, 74%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**6c**) = 0.50, R_f(**8ck**) = 0.70, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2931, 1729, 1689, 1591, 1456, 1287, 1088, 934, 722 cm^{-1}.^1H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (d, 2H, J = 8.8 Hz), 7.10 (s, 1H), 7.02 (d, 2H, J = 8.8 Hz), 6.65 (s, 1H), 5.28 (DCM), 3.88 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 1.87 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.8 (C_q), 160.2 (C_q), 152.9 (C_q), 152.2 (C_q), 148.2 (C_q), 140.2 (C_q), 129.5 (2 × CH), 129.0 (C_q), 125.2 (C_q), 123.6 (C_q), 114.2 (2 × CH), 107.4 (CH), 105.5 (CH), 56.4 (CH_3), 56.3 (CH_3), 55.3 (CH_3), 8.7 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{19}H_{19}O_4]^+ = [M + H]^+$ 311.1278, found 311.1274.

*3-(Benzo[d][1,3]dioxol-5-yl)-5,6-dimethoxy-2-methyl-1H-inden-1-one (**8cn**).*[1e] GP-2 was carried out with *o*-iodoketone **6c** (128.0 mg, 0.40 mmol), aldehyde **5n** (240.0 mg,1.6 mmol), $Pd(OAc)_2$ (5.0 mg,

DOI: 10.1021/acs.joc.6b02453
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5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 28 h until product **8cn** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−85:15) furnished the product **8cn** (68.7 mg, 53%) as a yellow solid. Mp = 214−216 °C [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**6c**) = 0.50, R_f(**8cn**) = 0.70, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2931, 1719, 1685, 1590, 1456, 1287, 1088, 935, 728 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.11 (s, 1H), 6.96−6.93 (m, 3H), 6.64 (s, 1H), 6.05 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 1.87 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.3 (C_q), 152.9 (C_q), 152.3 (C_q), 148.3 (C_q), 148.2 (C_q), 148.0 (C_q), 140.1 (C_q), 129.3 (C_q), 126.6 (C_q), 123.4 (C_q), 122.1 (CH), 108.7 (CH), 108.3 (CH), 107.5 (CH), 105.4 (CH), 101.4 (CH_2), 56.4 (2 × CH_3), 8.8 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{19}H_{17}O_5]^+$ = $[M + H]^+$ 325.1071, found 325.1063.

*3-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-2-methyl-1H-inden-1-one (**8co**).* GP-2 was carried out with *o*-iodoketone **6c** (128.0 mg, 0.40 mmol), aldehyde **5o** (265.6 mg,1.6 mmol), $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 28 h until product **8co** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10−85:15) furnished the product **8co** (88.4 mg, 65%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**6c**) = 0.50, R_f(**8co**) = 0.70, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2934, 1719, 1689, 1587, 1451, 1387, 1243, 1084, 905, 708 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.10 (s, 1H), 7.06 (dd, 1H, J = 7.3 and J = 1.9 Hz), 7.01−6.97 (m, 2H), 6.67 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 1.89 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.7 (C_q), 153.0 (C_q), 152.2 (C_q), 149.7 (C_q), 149.0 (C_q), 148.3 (C_q), 140.2 (C_q), 129.0 (C_q), 125.4 (C_q), 123.5 (C_q), 121.0 (CH), 111.3 (CH), 111.0 (CH), 107.4 (CH), 105.5 (CH), 56.4 (CH_3), 56.3 (CH_3), 56.0 (CH_3), 55.9 (CH_3), 8.8 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{20}H_{21}O_5]^+$ = $[M + H]^+$ 341.1384, found 341.1383.

*4,5,6-Trimethoxy-2-methyl-3-(p-tolyl)-1H-inden-1-one (**8db**).* GP-1 was carried out with *o*-iodoketone **6d** (140.0 mg, 0.40 mmol) and aldehyde **5b** (192.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 10 min until product **8db** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−90:10) furnished the product **8db** (101.9 mg, 79%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**6d**) = 0.30, R_f(**8db**) = 0.70, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2898, 1719, 1686, 1588, 1451, 1345, 1297, 1187, 947, 711 cm^{-1}.NMR ($CDCl_3$, 400 MHz): δ = 7.32 (d, 2H, J = 7.8 Hz), 7.24 (d, 2H, J = 7.8 Hz), 6.99 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.33 (s, 3H), 2.41 (s, 3H), 1.77 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.3 (C_q), 155.6 (C_q), 153.4 (C_q), 148.4 (C_q), 147.2 (C_q), 138.4 (C_q), 131.1 (C_q), 130.4 (C_q), 129.3 (C_q), 128.4 (2 × CH), 128.0 (2 × CH), 127.2 (C_q), 104.6 (CH), 61.2 (CH_3), 61.0 (CH_3), 56.4 (CH_3), 21.4 (CH_3), 8.4 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{20}H_{21}O_4]^+$ = $[M + H]^+$ 325.1434, found 325.1438.

*3-(4-Chlorophenyl)-4,5,6-trimethoxy-2-methyl-1H-inden-1-one (**8df**).* GP-1 was carried out with *o*-iodoketone **6d** (140.0 mg, 0.40 mmol) and aldehyde **5f** (224.0 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed stir at 120 °C for 14 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 15 min until product **8df** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−90:10) furnished the product **8df** (102.9 mg, 75%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**6d**) = 0.30, R_f(**8df**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 1910, 1689, 1592, 1453, 1288, 1089, 930, 738 $cm^{-1}$$^1H$ NMR ($CDCl_3$, 400 MHz): δ = 7.41 (d, 2H, J = 8.8 Hz), 7.36 (d, 2H, J = 8.8 Hz), 6.99 (s, 1H,), 3.87 (s, 3H), 3.85 (s, 3H), 3.33 (s, 3H), 1.75 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 196.9 (C_q), 154.0 (C_q), 153.6 (C_q), 148.3 (C_q), 147.3 (C_q), 134.3 (C_q), 132.6 (C_q), 131.1 (C_q), 129.6 (2 × CH), 128.9 (C_q), 128.0 (2 × CH), 126.9 (C_q), 104.9 (CH), 61.1 (CH_3), 61.0 (CH_3), 56.5 (CH_3), 8.4 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{19}H_{18}ClO_4]^+$ = $[M + H]^+$ 345.0888, found 345.0881.

*3-(4-Methoxyphenyl)-2-propyl-1H-inden-1-one (**9br**).* GP-1 was carried out with *o*-iodoketone **11b** (135.2 mg, 0.40 mmol) and aldehyde **5r** (137.6 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 12 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 20 min until product **9br** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−93:7) furnished the product **9br** (64.5 mg, 58%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**11b**) = 0.30, R_f(**9br**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2978, 1700, 1689, 1590, 1452, 1297, 1187, 945, 721 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45 (d, 1H, J = 6.8 Hz), 7.40 (d, 2H, J = 8.8 Hz), 7.28 (td, 1H, J = 7.5 and J = 0.9 Hz), 7.20−7.16 (m, 1H), 7.05−7.02 (m, 3H), 3.88 (s, 3H), 2.33−2.29 (m, 2H), 1.58−1.47 (m, 2H), 0.89 (t, 3H, J = 7.3 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.4 (C_q), 160.2 (C_q), 154.9 (C_q), 145.9 (C_q), 134.6 (C_q), 133.0 (CH), 131.2 (C_q), 129.3 (2 × CH), 128.1 (CH), 125.1 (C_q), 122.2 (CH), 120.4 (CH), 114.1 (2 × CH), 55.3 (CH_3), 25.4 (CH_2), 22.6 (CH_2), 14.3 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{19}H_{19}O_2]^+$ = $[M + H]^+$ 279.1380, found 279.1385.

*2-Propyl-3-(thiophene-2-yl)-1H-inden-1-one (**9cr**).* GP-1 was carried out with *o*-iodoketone **11c** (125.6 mg, 0.40 mmol) and aldehyde **5r** (137.6 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 17 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 20 min until product **9cr** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−93:7) furnished the product **9cr** (59.0 mg, 58%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**11c**) = 0.50, R_f(**9cr**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2930, 1790, 1686, 1590, 1455, 1277, 1099, 984, 716 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.49 (dd, 1H, J = 5.1 and J = 1.2 Hz), 7.41−7.40 (m, 2H), 7.34 (d, 1H, J = 7.3 Hz), 7.29−7.25 (m, 2H), 7.17−7.12 (m, 2H), 2.44−2.40 (m, 2H), 1.56−1.46 (m, 2H), 0.90 (t, 3H, J = 7.3 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.4 (C_q), 147.2 (C_q), 144.9 (C_q), 135.0 (C_q), 134.3 (C_q), 133.0 (CH), 131.1 (C_q), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 122.4 (CH), 120.8 (CH), 25.7 (CH_2), 22.5 (CH_2), 14.3 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{16}H_{15}O_S]^+$ = $[M + H]^+$ 255.0838, found 255.0841.

*6-Ethyl-7-(4-methoxyphenyl)-5H-indeno[5,6-d][1,3]dioxol-5-one (**9dr**).* GP-1 was carried out with *o*-iodoketone **11d** (152.8 mg, 0.40 mmol) and aldehyde **5q** (115.3 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 18 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 5 min until product **9dr** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5 to 90:10) furnished the product **9dr** (75.1 mg, 61%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**11d**) = 0.30, R_f(**9dr**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2878, 1714, 1696, 1589, 1461, 1297, 1187,

DOI: 10.1021/acs.joc.6b02453
J. Org. Chem. 2017, 82, 372−381

947, 741 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (d, 2H, J = 8.8 Hz), 7.01 (d, 2H, J = 8.8 Hz), 6.97 (s, 1H), 6.56 (s, 1H), 5.97 (s, 2H), 3.87 (s, 3H), 2.29 (q, 2H, J = 7.3 Hz),1.08 (t, 3H, J = 7.3 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 196.9 (C_q), 160.2 (C_q), 152.6 (C_q), 151.1 (C_q), 147.0 (C_q), 142.4 (C_q), 134.9 (C_q), 129.2 (2 × CH), 125.1 (C_q), 125.1 (C_q), 114.2 (2 × CH), 104.8 (CH), 103.6 (CH), 101.9 (CH_2), 55.3 (CH_3), 16.8 (CH_2), 14.1 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{19}H_{17}O_4]^+$ = $[M + H]^+$ 309.1121, found 309.1126.

*7-(4-Methoxyphenyl)-6-propyl-5H-indeno[5,6-d][1,3]dioxol-5-one (**9dr**).* GP-1 was carried out with *o*-iodoketone **11d** (152.8 mg, 0.40 mmol) and aldehyde **5r** (137.6 mg,1.6 mmol) in the presence of $Pd(OAc)_2$ (5.0 mg, 5 mol %), Ag_2O (111.3 mg, 0.48 mmol), and TBHP (257.1 mg, 2.0 mmol). The reaction mixture was allowed to stir at 120 °C for 20 h, removed from the oil bath, and allowed to reach room temperature. Concentrated H_2SO_4 (0.1 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 10 min until product **9dr** was formed. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5−90:10) furnished the product **9dr** (72.1 mg, 56%) as a yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**11d**) = 0.30, R_f(**9dr**) = 0.80, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2931, 1871, 1687, 1590, 1459, 1281, 1189, 933, 728 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (d, 2H, J = 8.8 Hz), 7.01 (d, 2H, J = 8.8 Hz), 6.97 (s, 1H), 6.54 (s, 1H), 5.97 (s, 2H), 3.87 (s, 3H), 2.26−2.22 (m, 2H), 1.51−1.45 (m, 2H), 0.87 (t, 3H, J = 7.3 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.0 (C_q), 160.1 (C_q), 153.1 (C_q), 151.1 (C_q), 146.9 (C_q), 142.4 (C_q), 133.6 (C_q), 129.2 (2 × CH), 125.1 (C_q), 125.0 (C_q), 114.2 (2 × CH), 104.8 (CH), 103.5 (CH), 101.8 (CH_2), 55.3 (CH_3), 25.4 (CH_2), 22.7 (CH_2), 14.2 (CH_3) ppm. HR-MS (ESI^+): m/z calcd for $[C_{20}H_{19}O_4]^+$ = $[M + H]^+$ 323.1278, found 323.1280.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02453.

Synthesis of precursors; X-ray data for compound **8ap**; ^1H NMR and ^{13}C NMR spectra of all compounds (PDF)
X-ray data for compound **8ap** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Department of Science and Technology-Science and Engineering Research Board (DST-SERB) [No. SB/S1/OC-39/2014], New Delhi, for financial support. B.S. thanks MHRD for the award of a research fellowship.

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