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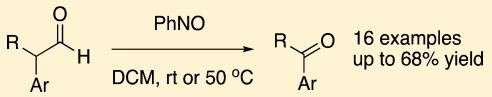
Metal- and O_2-Free Oxidative C−C Bond Cleavage of Aromatic Aldehydes

Guang Hu,[†] Kinthada Ramakumar,[†] and Stacey E. Brenner-Moyer*

Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

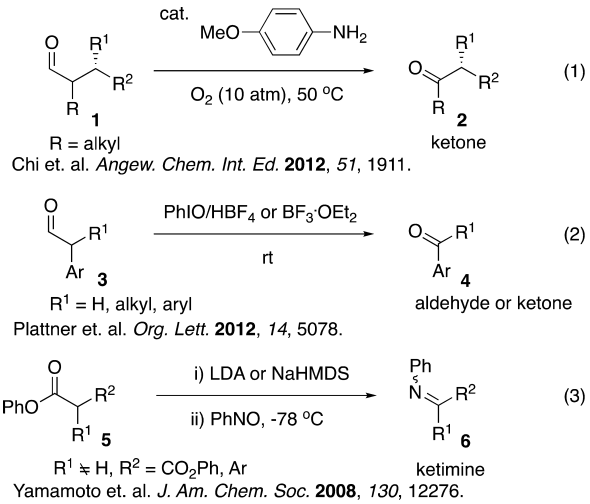
Supporting Information

ABSTRACT: An oxidative C−C cleavage of aldehydes requiring neither metals nor O_2 was discovered. Homobenzylic aldehydes and α-substituted homobenzylic aldehydes were cleaved to benzylic aldehydes and ketones, respectively, using nitrosobenzene as an oxidant. This reaction is chemoselective for aromatic aldehydes, as an aliphatic aldehyde was unreactive under these conditions, and other reactive functionality such as ketones and free alcohols are tolerated. A mechanism accounting for the fate of the lost carbon is proposed.



Aldehydes are one of the most versatile functional groups in organic chemistry and, as such, aldehyde intermediates are frequently employed in synthesis. Carbon−carbon bond cleavage of aldehydes, although desirable to the synthetic chemist, is difficult to achieve owing to the inherent stability of carbon−carbon bonds. Historically, this has required the preformation of enamines in conjunction with strong metal oxidants.[1−6] Although recent progress has allowed for direct C−C cleavage of aldehydes, strong metal oxidants or metals in combination with molecular oxygen or air are usually necessitated.[7−14] Very recently, however, metal-free methods have emerged for the direct oxidative carbon−carbon bond cleavage of aldehydes. In situ enamine formation in the presence of oxygen produced ketones (eq 1, Scheme 1) or esters.[15−17] To the best of our knowledge, there is only one example of metal- *and* oxygen-free oxidative carbon−carbon bond cleavage of aldehydes. In this example, α-aryl aldehydes were converted to aryl aldehydes or ketones using iodosylbenzene in conjunction with a strong Brønsted or Lewis acid (eq 2).[18] Moreover, we encountered only one example in the literature of carbon−carbon bond cleavage using nitrosobenzene.[19] This method entailed the formation of enolates of activated phenyl esters (i.e., β-diesters and α-aryl esters), followed by reaction with nitrosobenzene under cryogenic conditions to generate ketimines via an oxazetidin-4-one intermediate (eq 3). Reported herein is the serendipitous discovery of the use of nitrosobenzene as a reagent to directly cleave carbon−carbon bonds of α-aryl aldehydes. In contrast to the methods illustrated in Scheme 1, the method disclosed herein does not necessitate the use of high pressures of oxygen, strong Brønsted or Lewis acids, or cryogenic conditions. As such, with its comparatively mild conditions and broad functional group tolerance, this new method is amenable to providing benzylic aldehydes or aryl ketones, for structure−activity relationship (SAR) studies or relay synthesis, from aromatic ring-containing natural products. Moreover, this method is proposed to proceed via a novel mechanism that is distinct from that by which nitrosobenzene-mediated oxidative carbon−carbon bond cleavage of esters is reported to proceed.

Scheme 1. Relevant Examples of Metal-Free C−C Bond Cleavage



Recently, we reported a dienamine-catalyzed redox reaction between enals, **7**, and nitrosobenzene to yield γ-nitrone products **9** (Scheme 2).[20] The products of this reaction could be readily transformed into heterocycles **10** and **11** while still maintaining their aldehyde functionality, which could be elaborated further.

We were curious to see whether this method could be extended to saturated aldehydes to produce the corresponding α-nitrone products. Phenyl acetaldehyde, **12a**, was thus subjected to similar reaction conditions (entry 1, Table 1). While a trace amount of the nitrone product **13** was observed, surprisingly, the major identifiable product of the reaction was the product of oxidative cleavage: benzaldehyde (**14a**).

Seeking to learn more about this transformation, optimization and control experiments were initiated. The yield of

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Scheme 2. Reaction of α,β-Unsaturated Aldehydes with PhNO

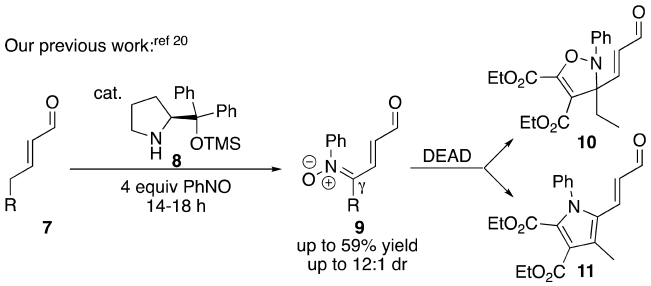
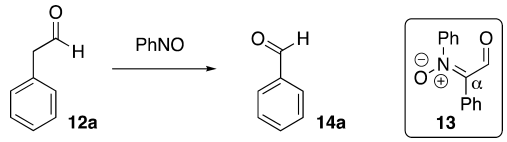


Table 1. Key Optimizations and Control Experiments[a]



entry	additive	T (°C)	yield[b] (%)
1	**8** (10 mol %)	rt	31
2	4-nitroaniline (10 mol %)	rt	63
3		rt	58
4		50	61
5[c]		rt	57
6	BHT (5 mol %)	rt	62
7	BHT (1 equiv)	rt	50
8	H_2O (10 equiv)	rt	60
9[d]		rt	45
10	4 Å mol. sieves (200 mg)	rt	26
11[e]		rt	0

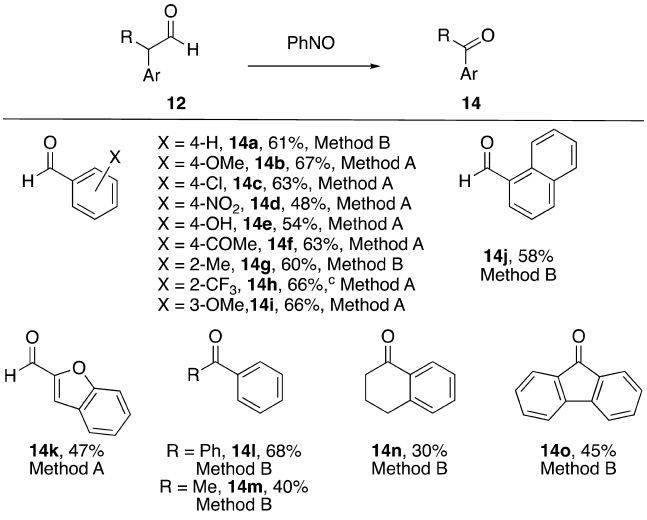
[a]Reaction conditions: **12a**, PhNO (4 equiv), additive, DCM (1 M), 24 h. [b]^{1}H NMR yield using cyclohexene as internal standard. [c]Rigorous exclusion of O_2 via freeze–pump–thaw technique. [d]Solvent = H_2O. [e]**13** used instead of **12a**. BHT = butylated hydroxytoluene.

benzaldehyde doubled when the amine additive was 4-nitroaniline instead of **8** (entry 2). However, the reaction proceeded nearly as well in the absence of an amine additive (entry 3). Thus, the reaction does not, in fact, proceed via an enamine intermediate. Rather, the low yield using **8** is possibly due to competing enamine-catalyzed reactions, whereas 4-nitroaniline is likely too weakly nucleophilic to generate an enamine species in the first place. Use of 2 equiv of nitrosobenzene is sufficient for this transformation, albeit slightly reduced product yields were obtained.[21] After extensive consideration of reaction variables, including equivalents of nitrosobenzene, solvent, additives, concentration, temperature, and time,[21] the conditions summarized in entries 3 and 4 were found to be optimal.

The rigorous exclusion of O_2 did not affect the reaction yield, affirming that adventitious O_2 is neither a catalyst nor reagent for this transformation (entry 5). Addition of the radical inhibitor BHT did not suppress the reaction, verifying that a radical mechanism is not operative (entries 6 and 7). While the addition of water was tolerated and water could be used as a reaction solvent, the rigorous exclusion of water resulted in significantly lower product yields after 24 h (entries 8–10). Water (and 4-nitroaniline) may help to stabilize the reactive enol form of **12a** and/or activate nitrosobenzene via hydrogen bonding interactions (vide infra). Finally, subjecting **13** to the reaction conditions did not yield any benzaldehyde, demonstrating that the nitrone is not an intermediate in this reaction (entry 11).

A variety of carbonyl compounds were evaluated under the reaction conditions at both rt and at 50 °C with only the isolated yield arising from the optimal method for each substrate being reported in Scheme 3. The reaction time was 24 h, which compares favorably with the only existing metal- and oxygen-free method for oxidative carbon–carbon bond cleavage of aldehydes (eq 2, Scheme 1), which required 6 days to generate aldehyde products from **12** (R = H). Substituted benzaldehydes **14a–14i** were all formed in comparable yields regardless of the electronic nature or position of the substituent. Even bulky 1-naphthaldehyde, **14j**, was generated in a similarly moderate yield. Heteroaromatic aldehydes such as **14k** could also be generated using this method. Interestingly, 3-phenylpropanal produced **14a** in 23% ^{1}H NMR yield at rt, while trace (<1%) **14a** was formed when 4-phenylbutanal was evaluated at rt.

Scheme 3. Substrate Scope[a,b]



[a]Reaction conditions: **12**, PhNO (4 equiv), DCM (1 M), 24 h. Method A = rt. Method B = 50 °C. [b]Yield = isolated yield. [c]Isolated yield of corresponding alcohol.

Ketone products could be formed by subjecting α-substituted homobenzylic aldehydes to the reaction conditions. In all cases, the higher temperature of Method B was required for ketone formation, as yields of <5% were obtained at rt. Biaryl ketones **14l** and **14o** were produced in yields higher than those of other aryl ketones **14m** and **14n**. Starting carbonyl compounds were recovered from a homobenzylic ketone (1-phenyl-2-butanone or 1,3-diphenyl-2-propanone), acid (phenylacetic acid), and ester (methyl phenylacetate), and from a β-dicarbonyl compound (3-benzyl-2,4-pentanedione) under the reaction conditions.

Importantly, whereas the only existing metal- and oxygen-free method for oxidative carbon–carbon bond cleavage of aldehydes utilizes a strong Brønsted or Lewis acid (eq 2, Scheme 1), our mild conditions are compatible with other reactive functionalities. Most notably, this reaction is chemoselective for aromatic aldehydes; for example, no reaction was observed with an aliphatic aldehyde (2-ethylhexanal) under these conditions. Additionally, a nucleophilic free alcohol (**14e**) as well as a reactive ketone (**14f**) were tolerated.

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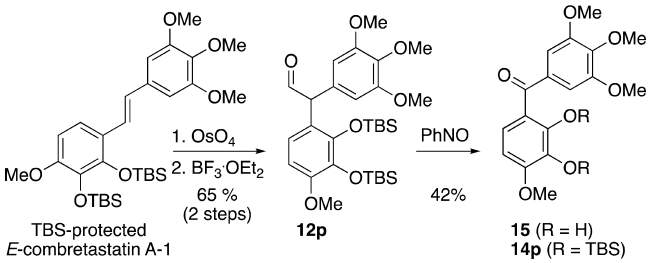
It is envisioned that this method will facilitate access to benzylic aldehydes and aryl ketones from complex homobenzylic aldehydes for synthetic and medicinal purposes. As an illustration of this application, diaryl ketone **14p** was furnished in 42% yield from homobenzylic aldehyde **12p** (Scheme 4).

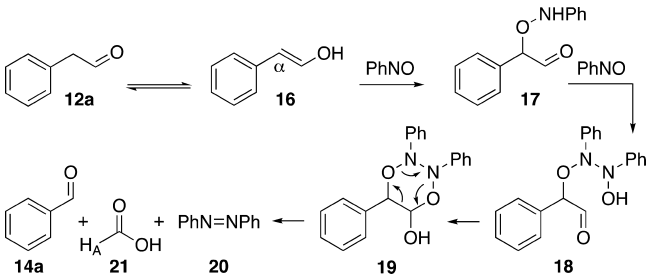
Scheme 4. Synthetic Utility



Upon subjecting **12p** to TBAF during the course of exploratory SAR studies on combretastatin A-1, Pettit and co-workers serendipitously generated the corresponding free alcohol of this diaryl ketone (**15**) in 49% yield.[22] Combretastatin A-1 is a natural product possessing potent activity as both a microtubule assembly inhibitor and as a sensitizer of multidrug-resistant cancer cells to other chemotherapeutic agents.[23,24] Diaryl ketone **15** was found to have activity identical to that of combretastatin A-1 in inhibition assays of both cancer cell growth and tubulin polymerization.[25] In contrast to Pettit's conditions, our conditions do not require O_2 and are orthogonal to silyl protecting groups and thus provide a more general method for producing benzylic aldehydes and aryl ketones of interest from the corresponding homobenzylic aldehydes.

A possible mechanism for this transformation is illustrated in Scheme 5. Homobenzylic aldehyde **12a** is in equilibrium with

Scheme 5. Possible Mechanism



its enol tautomer **16**. The enol tautomer of homobenzylic aldehydes should form more readily than that of aliphatic aldehydes, as the enol tautomer of homobenzylic aldehydes contains a π-bond in conjugation with the aromatic ring. Enol **16** possesses a nucleophilic α-carbon, which can react with the electrophile, nitrosobenzene.

Reaction of enol **16** with one equivalent of nitrosobenzene generates **17**. Due to the α-effect, **17** contains a highly nucleophilic nitrogen atom that can react with a second equivalent of nitrosobenzene to produce **18**. Intramolecular (or intermolecular) nucleophilic addition to the aldehyde initiates C−C bond cleavage, affording benzaldehyde **14a** along with byproducts azobenzene **20** and formic acid **21**. The driving force for bond cleavage is the formation of benzylic aldehydes, which contain a carbon−oxygen π-bond in conjugation with the aromatic ring.

The proposed mechanism is the culmination of several mechanistic probes as well as literature precedence. First, there are numerous reports of *O*-nitroso aldol reactions (i.e, **12a** → **17**) catalyzed by chiral secondary amines such as **8**.[26−35] In almost all of these reactions, nitrosobenzene is used in substoichiometric quantities,[26−32,34,35] often in a 1:3 ratio with the aldehyde reactants,[26,28−30,32,34,35] possibly to avoid overoxidation products (i.e., **13** and **14a**) that can arise in the presence of stoichiometric (or greater) amounts of this reagent. Moreover, in all of these reactions, the aldehyde products (i.e., **17**) are not isolated. Rather, an in situ reduction is performed, and it is the corresponding alcohols that are isolated. It was therefore not possible for us to isolate **17** and resubject it to our own reaction conditions to verify whether **14a** is formed.

Instead, we reproduced one of these procedures in which **12a** was reacted with 0.33 equiv of nitrosobenzene in $CHCl_3$ using 5 mol % *L*-proline as catalyst.[26] After 2 h, a new aldehyde peak and a small amount of benzaldehyde were observed by ^{1}H NMR. An in situ reduction was performed, and the corresponding alcohol of **17** was isolated in 60% yield, a quantity identical to that reported for this substrate in this procedure.[26]

We then reran the reaction. After 2 h, again, a new aldehyde peak and a small amount of benzaldehyde were observed by ^{1}H NMR. At this time, 3.67 equiv of nitrosobenzene were added to total the 4 equiv of nitrosobenzene that is employed in our conditions. Subsequently, the disappearance of the aldehyde peak corresponding to **17** and a dramatic increase in the aldehyde peak corresponding to benzaldehyde were observed. Collectively, these experiments suggest that **17** is a plausible intermediate in the formation of **14a**.

As mentioned above, due to the α-effect, **17** contains a highly nucleophilic nitrogen atom that can rapidly further react with nitrosobenzene.[20] The reaction of carbonyl compounds with 2 equiv of nitrosobenzene to form intermediates related to **18** has been reported previously.[20,33] These reports support the possible intermediacy of **18** in this transformation.

Finally, the byproducts formic acid and azobenzene were observed by various analytical methods. ^{1}H NMR spectra of the crude reaction mixture displayed a peak at 8.00 ppm, and a peak at 165.82 ppm was visible in crude ^{13}C NMR spectra, corresponding to H_A (Scheme 5) and the carbon in formic acid, respectively.[21] Moreover, through use of ReactIR, it was possible to observe the disappearance of the phenyl acetaldehyde (**12a**) carbonyl stretch peak at 1723 cm^{-1} over time and the emergence of peaks at 1704 and 1719 cm^{-1}, corresponding to the carbonyl stretch frequencies of benzaldehyde and formic acid, respectively (Figure 1). All three of these compounds were independently subjected to ReactIR to verify these frequencies and that solutions of these compounds obeyed Beer's law at the reaction concentration.[21] GC−MS spectra of the crude reaction displayed a prominent peak at 182 m/z (t_R = 13.63 min), corresponding to the mass of azobenzene.[21] The identity of this peak was confirmed by injection of commercially available pure azobenzene (t_R = 14.04 min).

In conclusion, reported herein is a novel, mild, metal- and O_2-free method for the oxidative carbon−carbon bond cleavage of aldehydes. Under these reaction conditions, nitrosobenzene selectively cleaves aromatic aldehydes; an aliphatic aldehyde was unreactive under these conditions, and a readily enolizable

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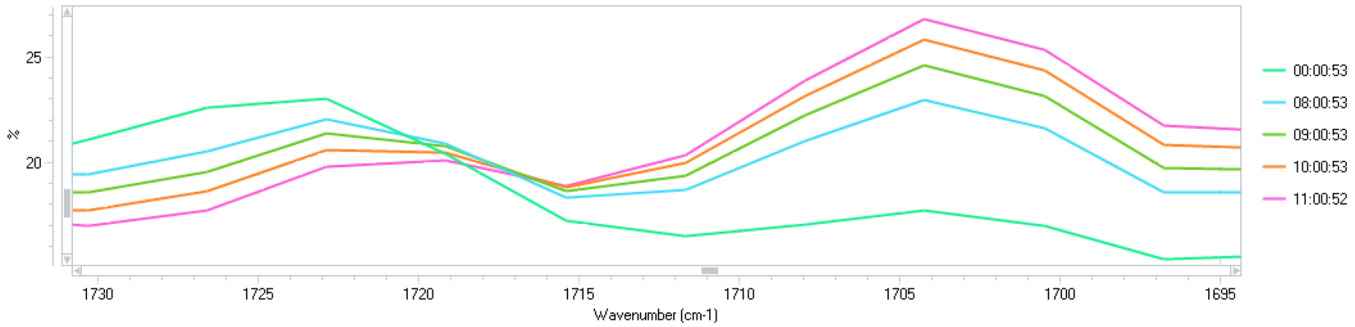

Figure 1. React-IR analysis of the reaction of phenylacetaldehyde with PhNO in dichloromethane at 0 (sea green), 8 (blue), 9 (green), 10 (orange), and 11 (pink) hours. Over time, phenylacetaldehyde (carbonyl vibration at 1723 cm^{-1}) decreases, while benzaldehyde (1704 cm^{-1}) increases. Additionally, the slope of the line from 1723 to 1719 cm^{-1} changes over time with the emergence of a peak at 1719 cm^{-1}, corresponding to the carbonyl vibration of formic acid.

ketone and nucleophilic free alcohol were also tolerated. This reaction seemingly proceeds via a mechanism that is distinct from that by which nitrosobenzene-mediated oxidative carbon−carbon bond cleavage of esters is reported to proceed. Because carbon−carbon bond cleavage of aldehydes is a highly desirable process for synthetic chemists and because homobenzylic aldehydes react orthogonally to other highly reactive functionality under these mild conditions, this process may find utility in the synthesis of natural products or medicinal compounds containing aromatic rings. Moreover, the ability of nitrosobenzene to participate in a diverse array of chemical reactions via equally diverse reaction mechanisms warrants continued exploration into the use of this versatile organic reagent in new synthetic transformations.

EXPERIMENTAL SECTION

General Information. NMR data were acquired on a 500 MHz NMR spectrometer and use the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, brm = broad multiplet, brs = broad singlet. HRMS spectra were acquired using an MS spectrometer with Q-TOF mass analyzer. Flash chromatography was carried out with F60, 40−63 mm, 60 Å silica gel and EMD silica 60 F254 glass TLC plates. Solvents were dried and kept air-free in a solvent purification unit and were evaporated using a standard rotovapor and high vacuum. All reactions were carried out in oven-dried glassware. Phenyl acetaldehydes were prepared according to literature procedures.[18,36]

General Procedure. A: Phenyl acetaldehyde (60.07 mg, 0.5 mmol) and nitrosobenzene (214.22 mg, 2.0 mmol) were dissolved in dichloromethane (0.5 mL, 1 M) in a capped vial and stirred at rt for 24 h; then, the reaction mixture was passed through flash column chromatography using EtOAc/hexane, and the products were isolated.

B: Phenyl acetaldehyde (60.07 mg, 0.5 mmol) and nitrosobenzene (214.22 mg, 2.0 mmol) were dissolved in dichloromethane (0.5 mL, 1 M) in a sealed tube and heated at 50 °C for 24 h; then, the reaction mixture was passed through flash column chromatography using EtOAc/hexane, and the products were isolated.

Compound Characterization Data. *Benzaldehyde (**14a**).*[37] Prepared following procedure A and purified by column chromatography using 1/9 EtOAc/hexane and isolated as a colorless liquid (32 mg, 61%): ^{1}H NMR (500 MHz, CDCl3) δ 10.03 (s, 1H), 7.91−7.87 (m, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 192.4, 136.4, 134.5, 129.7, 129.0. HRMS (EI): exact mass calculated for $[M - H]^-$ ($C_7H_5O_1$) requires m/z 105.0340, found m/z 105.0338.

*4-Methoxybenzaldehyde (**14b**).*[37] Prepared following procedure A and purified by column chromatography using 1/9 EtOAc/hexane and isolated as an orange liquid (45 mg, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 3.89 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 190.8, 164.6, 132.0, 130.0, 114.3, 55.6. HRMS (ESI): exact mass calculated for $[M]^+$ ($C_8H_8O_2$) requires m/z 136.0524, found m/z 136.0526.

*4-Chlorobenzaldehyde (**14c**).*[37] Prepared following procedure A and purified by column chromatography using 1/9 EtOAc/hexane and isolated as a yellow solid (44 mg, 63%): mp 50 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.54 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.84, 141.0, 134.7, 130.9, 129.5. HRMS (EI): exact mass calculated for $[M - H]^-$ (C_7H_4OCl) requires m/z 138.9951, found m/z 138.9950.

*4-Nitrobenzaldehyde (**14d**).*[37] Prepared following procedure A and purified by column chromatography using 1/9 EtOAc/hexane and isolated as an orange solid (36 mg, 48%): mp 103 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.37 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.4, 151.1, 140.1, 130.5, 124.3. HRMS (EI): exact mass calculated for $[M]^+$ ($C_7H_5NO_3$) requires m/z 151.0269, found m/z 151.0269.

*4-Hydroxybenzaldehyde (**14e**).*[38] Prepared following procedure A and purified by column chromatography using 1/9 EtOAc/hexane and isolated as a beige powder (33 mg, 54%): mp 114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.81 (d, J = 7.4 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.30 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1, 161.5, 132.5, 130.0, 116.0. HRMS (ESI): exact mass calculated for $[M]^+$ ($C_7H_6O_2$) requires m/z 122.0368, found m/z 122.0371.

*4-Acetylbenzaldehyde (**14f**).*[39] Prepared following procedure A and purified by column chromatography using 1/9 EtOAc/hexane and isolated as an orange liquid (45 mg, 63%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.08 (d, J = 7.8 Hz, 2H), 7.96 (d, J = 7.8 Hz, 2H), 2.65 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.4, 191.6, 141.2, 139.1, 129.8, 128.8, 27.0. HRMS (EI): exact mass calculated for $[M]^+$ ($C_9H_8O_2$) requires m/z 148.0524, found m/z 148.0529.

*2-Methylbenzaldehyde (**14g**).*[40] Prepared following procedure B and purified by column chromatography using 1/9 EtOAc/hexane and isolated as a colorless liquid (40 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 140.5, 134.1, 133.6, 132.0, 131.7, 126.3, 19.5. HRMS (EI): exact mass calculated for $[M]^+$ (C_8H_8O) requires m/z 120.0575, found m/z 120.0576.

*3-Methoxybenzaldehyde (**14i**).*[37] Prepared following procedure A and purified by column chromatography using 1/9 EtOAc/hexane and isolated as a colorless liquid (45 mg, 66%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.51−7.45 (m, 2H), 7.42 (s, 1H), 7.20 (d, J = 6.7 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 160.1, 137.8, 130.0, 123.5, 121.5, 112.0, 55.4. HRMS (EI): exact mass calculated for $[M]^+$ ($C_8H_8O_2$) requires m/z 136.0524, found m/z 136.0526.

*1-Naphthaldehyde (**14j**).*[37] Prepared following procedure B and purified by column chromatography using 1/19 EtOAc/hexane and isolated as a yellow liquid (45 mg, 58%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1H), 9.28 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 6.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H). ^{13}C NMR (125 MHz,

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$CDCl_3$) δ 193.5, 136.7, 135.3, 133.7, 131.4, 130.6, 129.1, 128.5, 127.0, 124.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_8O$) requires m/z 156.0575, found m/z 156.0577.

*Benzofuran-2-carbaldehyde (**14k**).*[41] Prepared following procedure A and purified by column chromatography using 1/19 EtOAc/hexane and isolated as a yellow liquid (34 mg, 47%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.57 (s, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 179.8, 156.3, 152.8, 129.2, 126.7, 124.2, 123.7, 117.7, 112.76. HRMS (ESI): exact mass calculated for $[M + H]^+$ ($C_9H_7O_2$) requires m/z 147.0446, found m/z 147.0445.

*Benzophenone (**14l**).*[18] Prepared following procedure B and purified by column chromatography using 1/99 EtOAc/hexane and isolated as a white solid (62 mg, 68%): mp 47 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.7 Hz, 4H), 7.59 (t, J = 7.3 Hz, 2H), 7.49 (t, J = 7.5 Hz, 4H).^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 137.6, 132.4, 130.1, 128.3. HRMS (ESI): exact mass calculated for $[M + H]^+$ ($C_{13}H_{11}O$) requires m/z 183.0810, found m/z 183.0814.

*Acetophenone (**14m**).*[18] Prepared following procedure B and purified by column chromatography using 1/19 EtOAc/hexane and isolated as a colorless liquid (24 mg, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 7.9 Hz, 2H), 7.59−7.54 (m, 1H), 7.46 (t, J = 7.4 Hz, 2H), 2.61 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 137.2, 133.1, 128.6, 128.3, 26.6. HRMS (EI): exact mass calculated for $[M]^+$ (C_8H_8O) requires m/z 120.0575, found m/z 120.0575.

*3,4-Dihydronaphthalen-1(2H)-one (**14n**).*[18] Prepared following procedure B and purified by column chromatography using 1/9 EtOAc/hexane and isolated as an orange liquid (22 mg, 30%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 2.97 (t, J = 5.8 Hz, 2H), 2.66 (t, J = 6.4 Hz, 2H), 2.16−2.13 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 144.4, 133.3, 132.5, 128.7, 127.0, 126.5, 39.1, 29.6, 23.2. HRMS (ESI): exact mass calculated for $[M + H]^+$ ($C_{10}H_{11}O$) requires m/z 147.0810, found m/z 147.0816.

*9H-Fluoren-9-one (**14o**).*[18] Prepared following the procedure **B**, purified by column chromatography using 1/99 EtOAc/hexane and isolated as a yellow solid (41 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.0 Hz, 4H), 7.25 (t, J = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9, 144.4, 134.7, 134.1, 129.1, 124.3, 120.3.

*(2,3-bis((tert-Butyldimethylsilyl)oxy)-4-methoxyphenyl)(3,4,5-trimethoxyphenyl)methanone (**14p**).* To a solution of TBS-protected *E*-combretastatin A-1 (112 mg, 0.2 mmol) in acetone (1 mL) and H_2O (40 μL) was added NMO (44 mg, 0.36 mmol) followed by *t*-BuOH (132 μL). The solution was cooled to 0 °C and stirred for 5 min. OsO_4 (4% in H_2O, 0.2 mL, 0.024 mmol) was added dropwise, and the reaction stirred at 0 °C for 15 min. The reaction was brought to room temperature and stirred until complete consumption of olefin, as observed by TLC. The reaction was quenched with a 10% solution of $Na_2S_2O_3$ and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude diol was concentrated under reduced pressure and purified by flash chromatography (30% EtOAc/petroleum ether) to obtain pure diol (107 mg, 90%).

$BF_3{\cdot}OEt_2$ (45 μL, 0.358 mmol) was added dropwise to a stirred solution of diol (107 mg, 0.179 mmol) in anhydrous THF (2.5 mL) under argon at room temperature for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ (aq) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude aldehyde was concentrated under reduced pressure and purified by flash chromatography (10% EtOAc/petroleum ether) to obtain pure aldehyde **12p** as an oil (74 mg, 72%).

Aldehyde **12p** (23 mg, 0.04 mmol) and nitrosobenzene (17 mg, 0.16 mmol) were dissolved in dichloromethane (0.040 mL, 1 M) in a sealed tube and heated at 80 °C for 10 h, and then the reaction mixture was directly purified by flash chromatography (8% EtOAc/petroleum ether) to obtain pure **14p** as a yellow liquid (10 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 9H), 1.01 (s, 9H), 0.66 (s, 9H), 0.17 (s, 6H), −0.02 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.9, 154.5, 152.8, 145.6, 142.4, 137.0, 133.3, 126.5, 123.1, 108.0, 105.2, 61.0, 56.2, 55.1, 26.1, 25.8, 18.8, 18.0, −3.5, −3.8. HRMS (ES+): exact mass calculated for $[M + H]^+$ ($C_{29}H_{47}O_7Si_2$) requires m/z 563.2860, found m/z 563.2856.

*(2-(Trifluoromethyl)phenyl)methanol (**22h**).*[42] Prepared following procedure B and further reduced by $NaBH_4$ and purified by column chromatography using 1/9 EtOAc/hexane and isolated as an orange liquid (58 mg, 66% over 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 4.87 (s, 2H), 2.16 (brs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 132.2, 128.8, 127.5, 127.2 (q, ^3J(C,F)=30.8 Hz) 125.8 (q, ^1J(C,F)=5.7 Hz), 124.4 (q, ^2J(C,F)=5.7 Hz), 61.4 (q, ^4J(C,F)=2.9 Hz). HRMS (ESI): exact mass calculated for $[M + H]^+$ ($C_8H_8F_3O$) requires m/z 177.0522, found m/z 177.0512.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00784.

Further details about reaction optimization and mechanistic studies and copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: seb244@rutgers.edu.

ORCID

Stacey E. Brenner-Moyer: 0000-0002-4535-8167

Author Contributions

†G.H. and K.R. contributed equally.

Notes

The authors declare no competing financial interest.

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