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Note

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Wacker-Type Oxidation of Internal Alkenes using Pd(Quinox) and TBHP

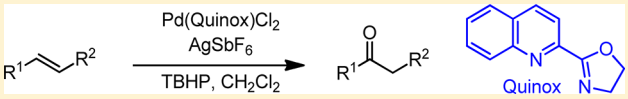
Ryan J. DeLuca,[†] Jennifer L. Edwards,[†] Laura D. Steffens,[†] Brian W. Michel,[†] Xiaoxiao Qiao,[‡] Chunyin Zhu,[‡] Silas P. Cook,*[,‡] and Matthew S. Sigman*[,†]

[†]Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States

[‡]Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405, United States

Supporting Information

ABSTRACT: The Pd-catalyzed TBHP-mediated Wacker-type oxidation of internal alkenes is reported. The reaction uses 2-(4,5-dihydro-2-oxazolyl)quinoline (Quinox) as ligand and TBHP(aq) as oxidant to deliver single ketone constitutional isomer products in a predictable fashion from electronically biased olefins. This methodology is showcased through its application on an advanced intermediate in the total synthesis of the antimalarial drug artemisinin.



The conversion of terminal olefins to methyl ketones using the Tsuji–Wacker oxidation has found extensive application in the synthesis of natural products, pharmaceuticals, and commodity chemicals.[1] In contrast, the use of the Tsuji–Wacker reaction for the selective oxidation of internal olefins has been sparsely reported, likely due to poor regioselectivity in the case of unbiased olefins.[2] Additionally, the reaction of internal alkenes is slow relative to that of terminal olefins due to the increased congestion of the substrate. The sluggish rate likely arises from turnover-limiting addition of the nucleophile to the activated Pd–alkene complex.[1a] There have been several notable reports demonstrating the potential utility of internal olefin oxidation for select substrate classes.[2] For example, Tsuji and co-workers have shown the regioselective oxidation of α,β-unsaturated ester **1** to give β-keto ester **2** (Figure 1).[3] The authors suggest the high regioselectivity observed results from coordination of the neighboring oxygen group to the catalyst.[3a] In addition, Feringa and co-workers have reported the oxidation of allylic phthalimide **3** to selectively deliver the methyl ketone **4**.[4] Kaneda and co-workers have demonstrated a copper-free oxidation of nitrile **5** to produce ketone **6**.[5] These examples illustrate that electronic bias is often required to achieve high selectivity in the Wacker oxidation, as unfunctionalized internal alkenes lead to multiple isomeric products.

Due to the potential utility of internal alkene oxidation to provide access to more highly substituted ketone products, we wanted to explore the versatility of our previously reported *tert*-butyl hydroperoxide (TBHP) mediated Wacker oxidation using Pd(Quinox) as the catalyst.[6] For a wide range of terminal olefin substrates, the use of this catalyst system results in excellent selectivity for formation of the methyl ketone product (Markovnikov addition). This has been proposed to arise from the use of a bidentate ligand and precoordination of TBHP, leaving only a single coordination site for alkene binding prior to a well-defined *syn*-peroxypalladation step[6,7] and precluding interactions with remote functional groups, in contrast to the proposal by Tsuji.[3a] Additionally, this method generally requires shorter reaction times and reduced catalyst loadings in comparison to the traditional Tsuji–Wacker oxidation.[6] Herein, we report the results of this investigation highlighted by a Wacker-type oxidation of a complex internal alkene en route to the synthesis of the antimalarial natural product artemisinin.

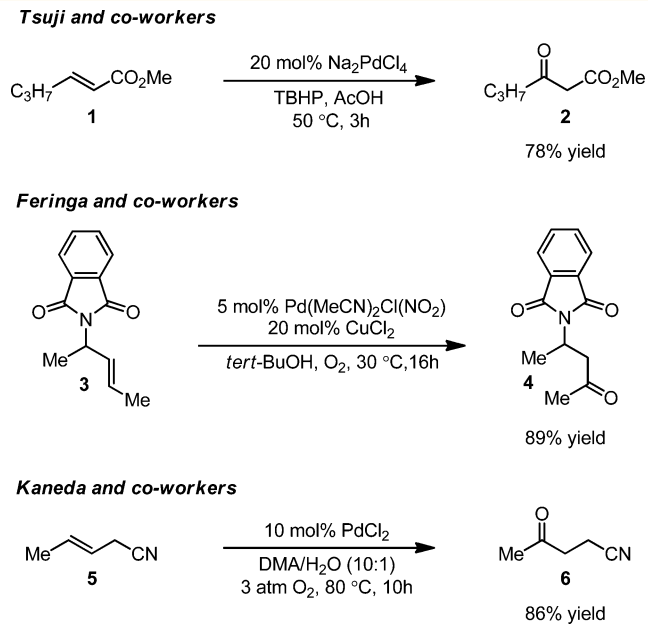


Figure 1. Previously reported Wacker oxidations using electronically biased internal alkenes.

To initiate our studies, the symmetrical alkene 4-octene was submitted to our previously reported optimized Pd(Quinox)–

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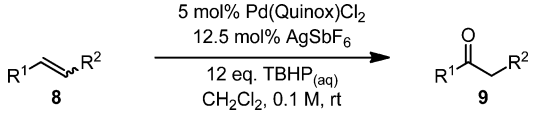
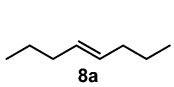
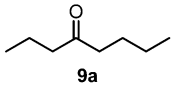
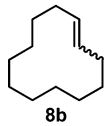
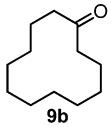
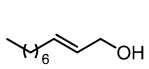
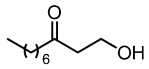
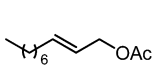
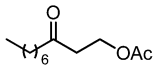
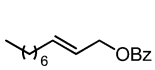
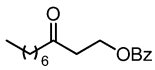
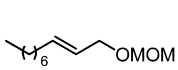
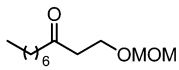
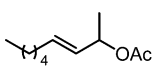
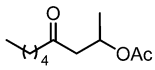
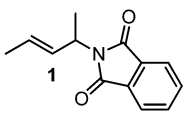
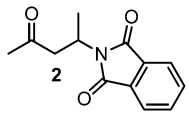
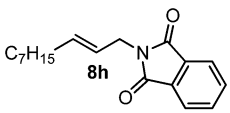
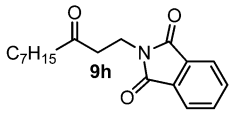
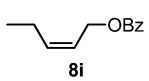
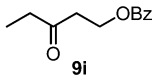
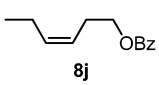
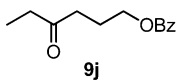
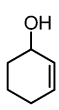
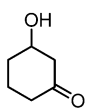
TBHP reaction conditions, which afforded a 71% yield of 4-octanone, with no appreciable amount of other ketone isomers observed (Table 1, entry 1). Notably, when anhydrous TBHP was used, significant isomerization was observed, which led to a complex mixture of ketone isomers. Next, the symmetric cyclic alkene cyclododecene, as a 70:30 mixture of trans and cis isomers (**8b**), was submitted to the reaction conditions, which gave a 76% yield of the ketone product **9b** (Table 1, entry 2). Submission of the unsymmetrical, nonbiased alkene 2-octene resulted in a ~1:1 mixture of 2- and 3-octanone. This result is consistent with previous observations supporting the hypothesis that electronic bias of the substrate is required for high selectivity.[3−5] Therefore, we sought to evaluate the type of functional groups necessary to achieve a highly regioselective alkene oxidation.

Table 1. Scope of the TBHP-Mediated Wacker Oxidation[b]

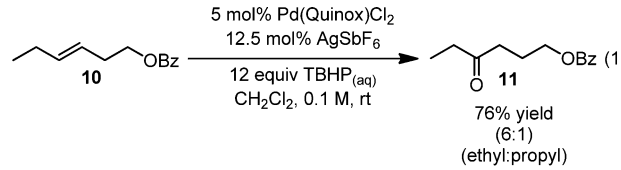


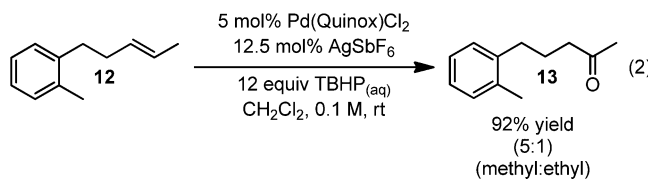
Entry	Substrate	Product	% Yield
1	 **8a**	 **9a**	71
2	 **8b**	 **9b**	76
3	 **8c**	 **9c**	48
4	 **8d**	 **9d**	68
5	 **8e**	 **9e**	61
6	 **8f**	 **9f**	93
7	 **8g**	 **9g**	57
8	 **1**	 **2**	66
9	 **8h**	 **9h**	79
10	 **8i**	 **9i**	31 (59)[a]
11	 **8j**	 **9j**	<1
12	 **8k**	 **9k**	<1

[a]10 mol % Pd(Quinox)Cl_2 and 25 mol % $AgSbF_6$. [b]All yields represent an average of two experiments on at least a 0.5 mmol scale.

The first functionalized substrate class to be evaluated was allylic alcohols. When the simple allylic alcohol **8c** was subjected to the standard reaction conditions, a highly selective oxidation occurred at the alkene carbon distal to the alcohol, albeit in a modest 48% yield (Table 1, entry 3). The starting material was entirely consumed, but no major byproducts were detected. To determine if a protected variant would improve the yield, three common alcohol protecting groups were evaluated (Table 1, entries 4−6). Both acetate **8d** (Table 1, entry 4) and benzoate **8e** (Table 1, entry 5) delivered the corresponding ketone products in improved yields and as single isomers (>20:1 by ^{1}H NMR) in 68% and 61% yields, respectively. Interestingly, the allylic methoxy ether (MOM) **8f** proved superior by producing ketone **9f** in 93% yield as a single regioisomer (Table 1, entry 6). When the secondary allylic acetate **8g** was subjected to the reaction conditions, the ketone product was isolated in 57% yield (Table 1, entry 7). In addition to allylic alcohol derivatives, allylic phthalimides were investigated, on the basis of our previous success with such substrates.[6d] While both the secondary (**1**) and primary (**8h**) allylic phthalimides produced single ketone products (>20:1 by ^{1}H NMR) distal to the phthalimide, substrate **1** delivered ketone **2** in 66% yield (Table 1, entry 8) and phthalimide **8h** provided ketone **9h** in 79% yield (Table 1, entry 9). Finally, *cis*-alkene **8i** was submitted to the reaction conditions, resulting in 31% yield (Table 1, entry 10). Increasing the catalyst loading to 10 mol % did enhance the yield of the process to 59%. In both cases, the remainder of the mass balance was unreacted starting material. Further efforts using *cis*-alkenes were unsuccessful (Table 1, entries 11 and 12). It remains unclear why *cis*-alkenes are less effective in the TBHP-mediated Wacker oxidation.

To test whether the selectivity arises from an electronic bias, a protected homoallylic alcohol substrate was evaluated. In the reaction, oxidation of homoallylic benzoate **10** (eq 1) delivered





a 6:1 mixture of the ethyl and propyl ketones in 76% yield. In this case, the mixture could be effectively separated by column chromatography. This result is consistent with the selectivity being dependent on the alkene's proximity to the directing group and suggests as the group is farther away from the alkene that poorer differentiation would result. Interestingly, an aryl group might facilitate directed oxidation, as observed in the

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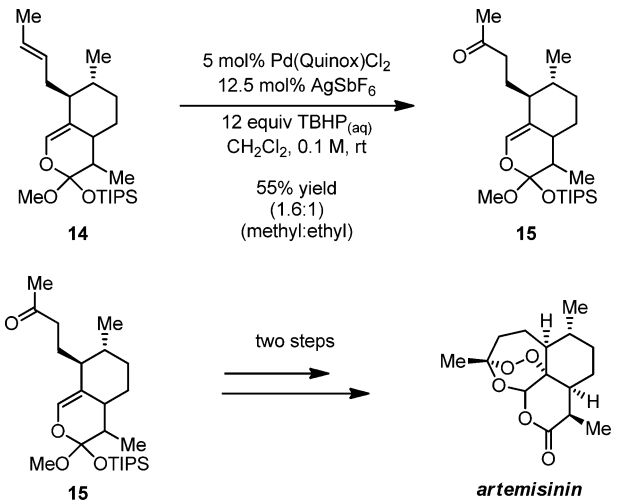
transformation of **12** to **13**, which results in a 92% yield of a 5:1 mixture of methyl and ethyl ketone products (eq 2).

After demonstrating the requirement of a functional group to bias oxypalladation, we next challenged the methodology by subjecting an advanced precursor in the synthesis of the antimalarial drug artemisinin to our conditions. Ortho ester **14** has been previously subjected to an unusual variant of the Wacker oxidation ($PdCl_2$ and excess H_2O_2) for 4 days, giving the desired methyl ketone as a 2:1 mixture with the isomeric ethyl ketone in an overall 92% yield.[8] Using our variant, a similar result is observed after 24 h using this electronically unbiased alkene, furnishing product **15** in an overall 55% yield as a 1.6:1 mixture of methyl and ethyl ketones (Scheme 1).

Scheme 1. TBHP-Mediated Wacker Oxidation Providing Access to 15, an Intermediate in the Synthesis of the Natural Product Artemisinin



In summary, the palladium-catalyzed TBHP-mediated Wacker oxidation of internal olefins is a useful complement to the traditional Tsuji–Wacker system.[2a] The TBHP-mediated Wacker oxidation effectively differentiates the two internal alkene carbons using electronically biased substrates delivering single ketone product constitutional isomers. This system is highlighted by its high predictability and its attractive ease of setup and purification.

EXPERIMENTAL SECTION

A procedure for a one-pot synthesis of Quinox was outlined in a recent publication.[6d] *Caution!* Although no problems occurred during these studies, highly concentrated solutions of TBHP in the presence of transition metals can be explosive.

General Procedure for the Pd(Quinox)Cl_2–TBHP Oxidation. In the dark, $AgSbF_6$ (43 mg, 0.125 mmol, 0.125 equiv), Pd(Quinox)Cl_2 complex (19 mg, 0.05 mmol, 0.05 equiv), and a magnetic stir bar were placed in a 25 mL round-bottom flask. CH_2Cl_2 (3.3 mL) was charged into the flask, and the mixture was stirred for 10 min, after which aqueous 70 wt %/wt TBHP (1.7 mL, 12 mmol, 12 equiv) and the remaining CH_2Cl_2 (5.0 mL) were charged into the flask. The mixture, which turned a deep orange, was stirred for 10 min before the substrate (1.0 mmol, 1 equiv) was added. The reaction was monitored by TLC, and upon complete consumption of starting material (or 24 h), the reaction mixture was cooled to 0 °C and quenched with Na_2SO_3 (15 mL) to consume excess TBHP. The mixture was transferred to a separatory funnel and diluted with EtOAc (25 mL). The aqueous layer was back extracted with ethyl acetate (25 mL). The combined organics were washed with H_2O (4 × 10 mL) and brine (25 mL) and then dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude material was purified by silica gel flash chromatography and the product-containing fractions were combined and concentrated under reduced pressure.

General Procedure for Benzoyl Protection. Into a dry 250 mL round-bottom flask equipped with a stirbar were added the alcohol (10.0 mmol, 1.0 equiv), 244 mg of DMAP (2.0 mmol, 0.20 equiv), 1.8 mL of Et_3N (13.0 mmol, 1.3 equiv), and 50 mL of DCM. The flask was equipped with a septum and connected to a N_2 line. The resulting mixture was cooled to 0 °C, and 3.40 g of benzoic anhydride (15.0 mmol, 1.5 equiv) was dissolved in 5 mL of DCM and added dropwise. The mixture was warmed to room temperature and was stirred overnight. The solution was then washed with saturated aqueous NH_4Cl (50 mL) and H_2O (50 mL). The combined aqueous layers were extracted with DCM (50 mL). The combined organic layers were then washed with brine (30 mL), dried over Na_2SO_4, decanted, and concentrated in vacuo. The product was purified by silica gel flash column chromatography.

General Procedure for the Mitsunobu Reaction. Into a dry 100 mL round-bottom flask equipped with a stirbar were added the corresponding allylic alcohol (10.0 mmol, 1.0 equiv) and 40 mL of dry THF. Next, 4.02 g of triphenylphosphine (15.0 mmol, 1.5 equiv) and 1.47 g of phthalimide (10.0 mmol, 1.0 equiv) were added to the reaction flask. The flask was equipped with a septum and connected to a N_2 line. The resulting mixture was cooled to 0 °C, and 2.9 mL of diispropyl azodicarboxylate (DIAD; 15.0 mmol, 1.5 equiv) was added dropwise. The mixture was warmed to room temperature and was stirred overnight. The crude reaction mixture was concentrated in vacuo, and the product was purified by silica gel flash column chromatography.

(*E*)-Oct-4-ene (8a). This commercially available compound was purchased and used without further purification.

Cyclododecene (8b). This commercially available compound was purchased and used without further purification. The cis:trans ratio was 30:70.

(*E*)-Dec-2-en-1-ol (8c). This commercially available compound was prepared according to the literature procedure.[9] Analytical data are consistent with the literature.[10]

(*E*)-Dec-2-en-1-yl Acetate (8d). This commercially available compound was prepared according to the literature procedure.[11] Analytical data are consistent with the literature.[12]

(*E*)-Dec-2-en-1-yl Benzoate (8e). This compound was prepared with the general procedure for benzoyl protection using 1.56 g of (*E*)-dec-2-en-1-ol. The product was purified by silica gel flash chromatography with 5% diethyl ether in hexanes as eluent to give the product as a colorless oil in 93% yield (2.42 g). R_f = 0.5 (10% Et_2O in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.6 Hz, 3H), 1.18–1.47 (m, 10H), 2.08 (q, J = 6.8 Hz, 2H), 4.76 (d, J = 6.4 Hz, 2H), 5.68 (dt, J = 15.6, 6.4 Hz, 1H), 5.86 (dt, J = 15.2, 6.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 8.05 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 22.9, 29.1, 29.3(2), 32.0, 32.5, 66.0, 123.9, 128.5, 129.5, 130.6, 133.1, 137.0, 166.7. IR (neat): 2924, 2853, 1717, 1450, 1377, 1265, 1107, 1068, 1025, 968, 935, 707, 686 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{24}O_2Na$ $[M + Na]^+$ 283.1674, found 283.1669.

(*E*)-1-(Methoxymethoxy)dec-2-ene (8f). This compound was prepared according to the literature procedure.[13] Analytical data are consistent with the literature.[13]

(*E*)-Non-3-en-2-yl Acetate (8g). This compound was prepared by the general procedure for benzoyl protection with the modification that 1.56 g of (*E*)-dec-2-en-1-ol was protected using 1.4 mL of acetic anhydride instead of benzoic anhydride. The product was purified by silica gel flash chromatography with DCM as eluent to give the product as a colorless oil in 56% yield (1.03 g). R_f = 0.7 (DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.23–1.41 (m, 11H), 2.03 (s, 3H), 5.31 (quint, J = 6.6 Hz, 1H), 5.45 (dd, J = 15.3, 6.8 Hz, 1H), 5.70 (dt, J = 15.3, 6.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 20.6, 21.7, 22.7, 28.8, 31.6, 32.3, 71.4, 129.5, 133.7, 170.6. IR (neat): 2957, 2927, 2857, 1735, 1456, 1369, 1235, 1135, 1041, 1014,

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967, 947, 841, 668, 609 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{11}H_{20}O_2Na$ $[M + Na]^+$ 207.1361, found 207.1364.

(*E*)-2-(Pent-3-en-2-yl)isoindoline-1,3-dione (1). This compound was prepared by the general procedure for the Mitsunobu reaction.[3] Analytical data are consistent with the literature.[3]

(*E*)-2-(Dec-2-en-1-yl)isoindoline-1,3-dione (8h). This compound was prepared by the general procedure for the Mitsunobu reaction using 1.56 g of (*E*)-dec-2-en-1-ol. The product was purified by silica gel flash chromatography with 5% ethyl acetate in hexanes as eluent to give the product as a colorless oil in 98% yield (2.80 g). R_f = 0.5 (5% EtOAc in hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 7.0 Hz, 3H), 1.18−1.37 (m, 10H), 1.99 (q, J = 7.2 Hz 2H), 4.23 (d, J = 6.0 Hz, 2H), 5.50 (dt, J = 15.5, 6.6 Hz, 1H), 5.74 (dt, J = 15.5, 7.1 Hz, 1H), 7.69−7.72 (m, 2H) 7.82−7.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 29.1, 29.3, 32.0, 32.3, 39.8, 71.4, 123.2, 123.4, 132.4, 134.0, 135.6, 168.2. IR (neat): 2923, 2853, 1771, 1709, 1466, 1390, 1354, 1186, 1099, 966, 716 cm^{-1}. HRMS (AP-TOF): m/z calculated for $C_{18}H_{24}NO_2$ $[M + H]^+$ 286.1807, found 286.1802.

(*Z*)-Pent-2-en-1-yl Benzoate (8i). This compound was prepared by the general procedure for benzoyl protection using 861 mg of (*Z*)-pent-2-en-1-ol. The product was purified by silica gel flash chromatography with 5% ethyl acetate in hexanes as eluent to give the product as a colorless oil in 90% yield (1.71 g). Analytical data are consistent with the literature.[14]

(*Z*)-Hex-3-en-1-yl Benzoate (8j). This compound was prepared by the general procedure for benzoyl protection using 1.00 g of (*Z*)-hex-3-en-1-ol. The product was purified by silica gel flash chromatography with 5% ethyl acetate in hexanes as eluent to give the product as a colorless oil in 86% yield (1.76 g). Analytical data are consistent with the literature.[15]

(*E*)-Hex-3-en-1-yl Benzoate (10). This compound was prepared by the general procedure for benzoyl protection using 1.56 g of (*E*)-dec-2-en-1-ol. The product was purified by silica gel flash chromatography with 10% ethyl acetate in hexanes as eluent to give the product as a colorless oil in 95% yield (1.94 g). Analytical data are consistent with the literature.[15]

(((7*R*,8*S*)-8-((*E*)-But-2-en-1-yl)-3-methoxy-4,7-dimethyl-4,4a,5,6,7,8-hexahydro-3*H*-isochromen-3-yl)oxy)-triisopropylsilane (14). This compound was prepared according to the literature procedure.[8] Analytical data are consistent with the literature.[8]

Octan-4-one (Table 1, Entry 1; 9a). The general procedure for the TBHP-mediated Wacker oxidation was followed using 112 mg of (*E*)-oct-4-ene (1.0 mmol). The crude mixture was purified by flash chromatography with 5% ethyl acetate in hexanes as eluent to afford the product as a colorless oil in 71% yield (91 mg). The spectral data were in accordance with those of the known commercially available compound.

Cyclododecanone (Table 1, Entry 2; 9b). The general procedure for the TBHP-mediated Wacker oxidation was followed using 166 mg of cyclododecene (1.0 mmol). The crude mixture was purified by flash chromatography with 5% ethyl acetate in hexanes as eluent to afford the product as a white solid in 76% yield (138 mg). The spectral data were in accordance with those of the known commercially available compound.

1-Hydroxydecan-3-one (Table 1, Entry 3; 9c). The general procedure for the TBHP-mediated Wacker oxidation was followed using 78 mg of (*E*)-dec-2-en-1-ol (0.5 mmol). The crude mixture was purified by flash chromatography with 40% ethyl acetate in hexanes as eluent to afford the product as a colorless oil in 32% yield (55 mg). R_f = 0.5 (40% EtOAc in hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.22−1.34 (m, 8H), 1.59 (quint, J = 7.3 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H), 2.67 (t, J = 5.3 Hz, 2H), 3.85 (t, J = 5.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 23.9, 29.3, 29.4, 31.9, 43.6, 44.5, 58.2, 212.3. IR (neat): 3420, 2924, 2854, 1701, 1457, 1375, 1047, 668 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{10}H_{20}O_2Na$ $[M + Na]^+$ 195.1361, found 195.1361.

3-Oxodecyl Acetate (Table 1, Entry 4; 9d). The general procedure for the TBHP-mediated Wacker oxidation was followed using 198 mg of (*E*)-dec-2-en-1-yl acetate (1.0 mmol). The crude mixture was purified by flash chromatography with 10% ethyl acetate in hexanes as eluent to afford the product as a colorless oil in 68% yield (146 mg). R_f = 0.3 (10% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H), 1.21−1.33 (m, 8H), 1.54−1.62 (m, 2H), 2.04 (s, 3H), 2.44 (t, J = 7.4 Hz, 2H), 2.74 (t, J = 6.3 Hz, 2H), 4.34 (t, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.0, 22.7, 23.7, 29.2, 29.3, 31.8, 41.3, 43.4, 59.6, 171.0, 208.2. IR (neat): 2926, 2855, 1739, 1715, 1366, 1233, 1036, 668 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{12}H_{22}O_3Na$ $[M+Na]^+$ 237.1467, found 237.1469.

3-Oxodecyl Benzoate (Table 1, Entry 5; 9e). The general procedure for the TBHP-mediated Wacker oxidation was followed using 130 mg of (*E*)-dec-2-en-1-yl benzoate (0.5 mmol). The crude mixture was purified by flash chromatography with 20% diethyl ether in hexanes as eluent to afford the product as a colorless oil in 61% yield (84 mg). R_f = 0.5 (20% Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 6.6 Hz, 3H), 1.20−1.32 (m, 8H), 1.57−1.64 (m, 2H), 2.47 (t, J = 7.4 Hz, 2H), 2.87 (t, J = 6.3 Hz, 2H), 4.60 (t, J = 6.3 Hz, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 8.00 (d, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.7, 23.8, 29.2(2), 31.8, 41.5, 43.4, 60.1, 128.4, 129.7, 130.1, 133.1, 166.5, 208.1. IR (neat): 2925, 2854, 1717, 1602, 1451, 1271, 1110, 964, 708, 686 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{24}O_3Na$ $[M + Na]^+$ 299.1623, found 299.1622.

1-(Methoxymethoxy)decan-3-one (Table 1, Entry 6; 9f). The general procedure for the TBHP-mediated Wacker oxidation was followed using 100 mg of (*E*)-1-(methoxymethoxy)dec-2-ene (0.5 mmol). The crude mixture was purified by flash chromatography with 10% diethyl ether in hexanes as eluent to afford the product as a colorless oil in 93% yield (100 mg). R_f = 0.2 (10% Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.5 Hz, 3H), 1.21−1.34 (m, 8H), 1.55−1.62 (m, 2H), 2.45 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 6.1 Hz, 2H), 3.37 (s, 3H), 3.80 (t, J = 6.0 Hz, 2H) 4.60 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 22.8, 23.8, 29.2, 29.3, 31.9, 42.8, 43.6, 55.4, 62.9, 96.7, 209.4. IR (neat): 3743, 2925, 2855, 1715, 1457, 1379, 1213, 1149, 1110, 1041, 918, 668 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{12}H_{24}O_3Na$ $[M + Na]^+$ 239.1623, found 239.1624.

4-Oxononan-2-yl Acetate (Table 1, Entry 7; 9g). The general procedure for the TBHP-mediated Wacker oxidation was followed using 92 mg of (*E*)-non-3-en-2-yl acetate (0.5 mmol). The crude mixture was purified by flash chromatography with dichloromethane as eluent to afford the product as a colorless oil in 57% yield (57 mg). R_f = 0.3 (DCM). ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H), 1.20−1.34 (m, 7H), 1.52−1.60 (m, 2H), 2.00 (s, 3H), 2.40 (t, J = 7.3 Hz, 2H), 2.52 (dd, J = 16.2, 5.8 Hz, 1H), 2.76 (dd, J = 16.3, 7.0 Hz, 1H), 5.27 (sext., J = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 20.3, 21.4, 22.6, 23.5, 31.5, 43.6, 48.7, 67.4, 170.5, 208.1. IR (neat): 2956, 2932, 2872, 1736, 1714, 1457, 1370, 1236, 1141, 1037, 956, 668, 607 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{11}H_{20}O_3Na$ $[M + Na]^+$ 223.1310, found 223.1305.

2-(4-Oxopentan-2-yl)isoindoline-1,3-dione (Table 1, Entry 8; 2). The general procedure for the TBHP-mediated Wacker oxidation was followed using 430 mg of (*E*)-2-(pent-3-en-2-yl)isoindoline-1,3-dione (2.0 mmol). The crude mixture was purified by flash chromatography with 15% ethyl acetate in hexanes as eluent to afford the product as a colorless oil in 66% yield (305 mg). The spectral data were in accordance with the previous report.[3]

2-(3-Oxodecyl)isoindoline-1,3-dione (Table 1, Entry 9; 9h). The general procedure for the TBHP-mediated Wacker oxidation was followed using 258 mg of (*E*)-2-(dec-2-en-1-yl)isoindoline-1,3-dione (1.0 mmol). The crude mixture was purified by flash chromatography with 10% ethyl acetate in hexanes as eluent to afford the product as a white solid in 79% yield (237 mg). R_f = 0.3 (10% EtOAc in hexanes). Mp: 88−90 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 6.9 Hz, 3H), 1.19−1.31 (m, 8H), 1.56 (quint, J = 7.3, 2H), 2.41 (t, J = 7.6 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 3.96 (t, J = 7.4 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 7.83 (dd, J = 5.3, 3.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 23.9, 29.3, 29.4, 31.9, 33.3, 40.8, 43.2, 123.5, 132.3, 134.2, 168.4, 208.5. IR (neat): 2923, 2853, 1704, 1652, 1436,

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1360, 1221, 1091, 721, 668 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{23}NO_3Na$ $[M + Na]^+$ 324.1576, found 324.1574.

3-Oxopentyl Benzoate (Table 1, Entry 10; 9i). The general procedure for the TBHP-mediated Wacker oxidation was followed using 190 mg of (*Z*)-pent-2-en-1-yl benzoate (1.0 mmol). The crude mixture was purified by flash chromatography with 10% ethyl acetate in hexanes as eluent to afford the product as a colorless oil in 31% yield (64 mg). R_f = 0.3 (10% EtOAc in hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 1.09 (t, J = 7.3 Hz, 3H), 2.50 (q, J = 7.3 Hz, 2H), 2.88 (t, J = 6.5, 2H), 4.59 (t, J = 6.3 Hz, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 7.8, 36.6, 41.3, 60.2, 128.5, 129.8, 130.2, 133.2, 166.6, 208.5. IR (neat): 2976, 1711, 1601, 1451, 1314, 1369, 1111, 1070, 1025, 973, 708, 617 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{12}H_{14}O_3Na$ $[M + Na]^+$ 229.0841, found 229.0837.

4-Oxohexyl Benzoate (11). The general procedure for the TBHP-mediated Wacker oxidation was followed using 204 mg of (*E*)-hex-3-en-1-yl benzoate (1.0 mmol). The crude mixture was purified by flash chromatography with 10% ethyl acetate in hexanes as eluent to afford the product as a colorless oil in 65% yield (143 mg). The spectral data were in accordance with the previous report.[16]

5-(*o*-Tolyl)pentan-2-one (13). The general procedure for the TBHP-mediated Wacker oxidation was followed using 200 mg of (*E*)-1-methyl-2-(pent-3-en-1-yl)benzene (1.25 mmol). The crude mixture was purified by flash chromatography with 5% ethyl acetate in hexanes as eluent to afford the product as a colorless oil in 92% yield (202 mg). The spectral data were in accordance with the previous report.[17]

4-((7*R*,8*S*)-3-Methoxy-4,7-dimethyl-3-((triisopropylsilyl)oxy)-4,4a,5,6,7,8-hexahydro-3*H*-isochromen-8-yl)butan-2-one (15). The general procedure for the TBHP-mediated Wacker oxidation was followed using 48 mg of (((7*R*,8*S*)-8-((*E*)-but-2-en-1-yl)-3-methoxy-4,7-dimethyl-4,4a,5,6,7,8-hexahydro-3*H*-isochromen-3-yl)oxy)-triisopropylsilane (**14**; 0.11 mmol). The crude mixture was purified by flash chromatography with 10% ethyl acetate in hexanes as eluent to afford the products as a colorless oil in 55% yield (27 mg) as a 1.6:1 mixture. The spectral data were in accordance with the previous report.[8]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sicook@indiana.edu (S.P.C.); sigman@chem.utah.edu (M.S.S.).

Notes

The authors declare no competing financial interest.

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