

Palladium/Iron-Catalyzed Wacker-Type Oxidation of Aliphatic Terminal and Internal Alkenes Using O₂

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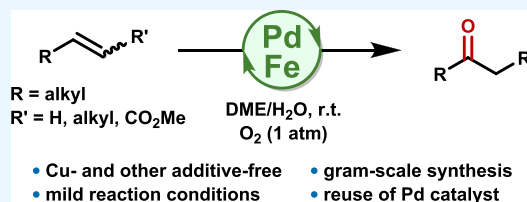


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ABSTRACT: The Wacker-type oxidation of aliphatic terminal alkenes proceeds using a Pd/Fe catalyst system under mild reaction conditions using 1 atm O₂ without other additives. The use of 1,2-dimethoxyethane/H₂O as a mixed solvent was effective. The slow addition of alkenes is also important for improving product yields. Fe(III) citrate was the most efficient cocatalyst among the iron complexes examined, whereas other complexes such as FeSO₄, Fe₂(SO₄)₃, Fe(NO₃)₃, and Fe₂O₃ were also operative. This method is also applicable to aliphatic internal alkenes, which are generally difficult to oxidize using conventional Pd/Cu catalyst systems. The gram-scale synthesis and reuse of the Pd catalysts were also demonstrated.



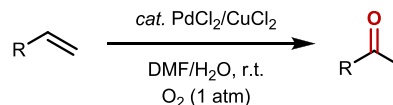
INTRODUCTION

Tsuji–Wacker oxidation is one of the most well-known homogeneous transition metal-catalyzed reactions.^{1–18} The Wacker-type oxidation furnishes methyl ketones from terminal alkenes, typically catalyzed by Pd and Cu salts under O₂ (Scheme 1a). However, Cu salts are generally moderately toxic,¹⁹ and alternative methods that do not use Cu salts as cocatalysts have been investigated. Catalyst systems that involve the direct oxidation of Pd(0) by O₂ in DMA, NMP,²⁰ DMA/H₂O,^{21,22} DMSO/H₂O (with 1 equiv of CF₃CO₂H),²³ MeOH/DMSO (with Pd NPs/ZrO₂),²⁴ MeOH/H₂O (with cationic Pd complexes with NN bidentate ligands),²⁵ *i*-PrOH (with Pd(OAc)₂/pyridine),²⁶ and ethylene carbonate²⁷ have been developed. These reactions require high temperatures (60–100 °C) and/or high O₂ pressures (2–10 atm) to smoothly promote the oxidation step. Polyoxometalates,^{28–32} alkyl nitrites and nitrite salts,^{33–37} and Ir or BiVO₄ photocatalysts³⁸ have been reported as cocatalyst alternatives to Cu salts. The nonredox metal ion Sc(III) can also operate as an efficient cocatalyst in the Pd(OAc)₂/Sc(OTf)₃/O₂ system.³⁹

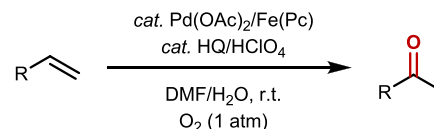
Fe complexes are generally less toxic than Cu complexes,¹⁹ and in addition, iron is more abundant and less expensive than copper. For Pd-catalyzed Wacker-type oxidations involving Fe complexes, Baekvall et al. developed an elegant biomimetic catalytic system that uses an Fe complex and *p*-hydroquinone (HQ) as cocatalysts, that is, Pd(OAc)₂/Fe(Pc) (Pc = phthalocyanine)/HQ/HClO₄/O₂ (Scheme 1b),⁴⁰ in which the Pd(0/II)–HQ/*p*-benzoquinone (BQ)–Fe(red/ox) triple catalytic system is operative. The addition of HClO₄ suppresses the precipitation of Pd(0).⁴⁰ Grubbs et al. successfully applied a Pd(OAc)₂/Fe(Pc)/BQ/HBF₄/O₂ catalyst system to internal alkenes.⁴¹ Fernandes et al. reported a Pd-catalyzed Wacker-type oxidation using a stoichiometric amount of Fe salts, such as Fe₂(SO₄)₃, as oxidants for Pd

Scheme 1. Pd-Catalyzed Wacker-Type Oxidations Using a Cu or Fe Complex as a Cocatalyst or an Oxidant

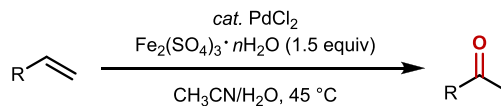
a) Conventional Pd/Cu catalyst system



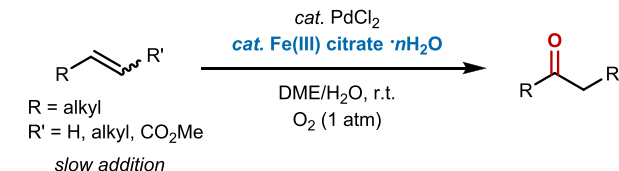
b) Pd/Fe/HQ/acid catalyst system



c) Pd catalyst system using Fe2(SO4)3 as a stoichiometric oxidant



d) Pd/Fe catalyst system (this work)



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(Scheme 1c).⁴² Because Fe complexes can be oxidized by O₂,⁴⁰ we hypothesized that a Pd/Fe/O₂ catalyst system without other additives could be developed. Herein, we report a simple, Cu- and other additive-free, Pd/Fe-catalyzed Wacker-type oxidation using 1 atm O₂ as the terminal oxidant that proceeds at room temperature (Scheme 1d). Aliphatic terminal and internal alkenes could be used as substrates. The gram-scale synthesis and reuse of the Pd catalyst were also demonstrated.

RESULTS AND DISCUSSION

Initially, the effects of the reaction conditions were examined by using 1-octene (**1a**) as the substrate (Table 1). PdCl₂ (5 mol %) and Fe(III) citrate·*n*H₂O (5 mol %) were used as catalysts, and 1,2-dimethoxyethane (DME)/H₂O (3:1) was used as a mixed solvent. O₂ (1 atm) was used as the terminal oxidant. Substrate **1a** was slowly added (over 5 h) to the reaction solution at room temperature using a syringe pump, and the mixture was stirred for an additional 1 h. Standard conditions afforded 2-octanone (**2a**) in 97% yield (entry 1). Product **2a** was not obtained in the absence of PdCl₂ (entry 2). Although the reaction proceeded in the absence of the Fe complex, the yield of **2a** was moderate (entry 3). The slow addition of **1a** was also important for increasing the product yield (entry 4 vs 1). The use of air (1 atm) instead of O₂ decreased both the conversion of **1a** and the yield of **2a**, and increased the yield of internal alkenes via the isomerization of **1a** (entry 5). The catalytic activities of PdCl₂(MeCN)₂ and PdCl₂(PhCN)₂ were comparable to those of PdCl₂ (entries 6 and 7), whereas PdCl₂(cod) (cod = 1,5-cyclooctadiene) and Pd(OAc)₂ were inefficient (entries 8 and 9).

The effect of the solvents was also critical (entries 10–19). Varying the DME/H₂O ratio to 1:1 or 5:1 resulted in lower product yields (entries 10 and 11). The use of ethereal solvents miscible with H₂O other than DME, such as, diglyme, THF, and 1,4-dioxane, afforded **2a** in good to high yields (entries 12–14). In contrast, the use of Et₂O significantly reduced the product yield, probably due to its poor miscibility with H₂O (entry 15). Other polar solvents that are miscible with H₂O, such as MeOH, DMF, and MeCN, instead of DME decreased the yield of **2a** considerably, whereas EtOH produced a relatively good result (entries 16–19).

Fe complexes other than Fe(III) citrate·*n*H₂O were also examined as cocatalysts. Several Fe(II) and Fe(III) complexes, such as FeSO₄·7H₂O, Fe₂(SO₄)₃·*n*H₂O, Fe(NO₃)₃·9H₂O, and Fe₂O₃, were effective (entries 20–23). FeCl₂ afforded **2a** in good yield (entry 24), whereas FeCl₃ was almost ineffective (entry 25 vs 3). The Pd catalyst loading was also investigated. The use of 2, 1, or 0.5 mol % of PdCl₂ still afforded high product yields by increasing the Fe/Pd ratio and prolonging the reaction time (entries 26–28).

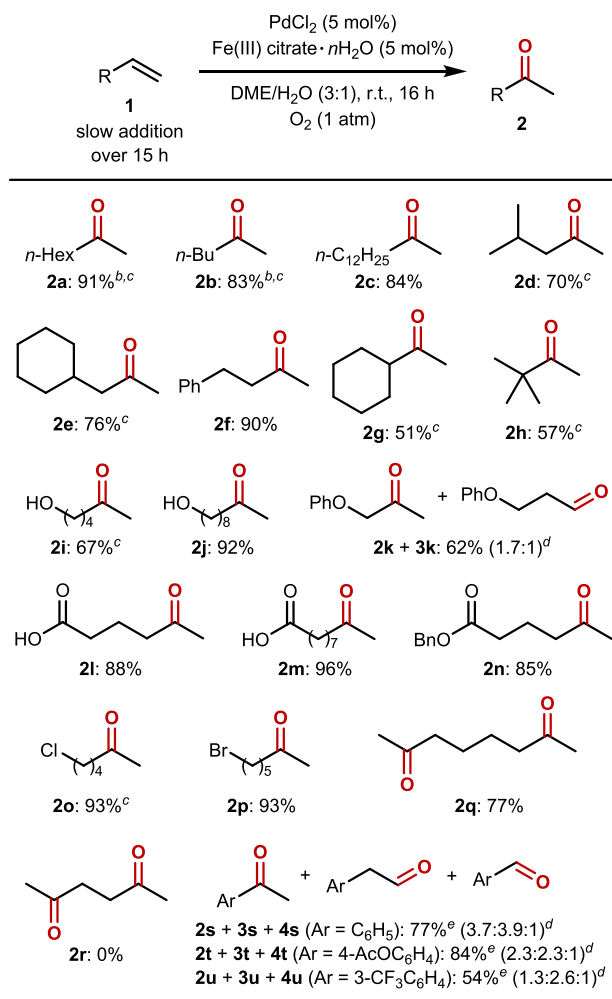
The optimized reaction conditions were then applied to various terminal alkenes (Scheme 2). In addition to linear alkenes **1a–1c**, branched alkenes such as 4-methyl-1-pentene (**1d**) and 3-cyclohexyl-1-propene (**1e**) also afforded the corresponding methyl ketones **2d** and **2e** in good yields. 4-Phenyl-1-butene (**1f**) was also suitable. Notably, bulky alkenes vinylcyclohexane (**1g**) and 3,3-dimethyl-1-butene (**1h**) furnished ketones **2g** and **2h** in moderate yields, respectively. 5-Hexen-1-ol (**1i**) and 9-decen-1-ol (**1j**) afforded the corresponding products in good to high yields. In the case of allyl phenyl ether (**1k**), methyl ketone **2k** and aldehyde **3k** were formed in a 1.7:1 ratio. The formation of the aldehyde could be due to the oxygen atom, which functions as a directing

Table 1. Effect of Reaction Conditions^a

entry	change from standard conditions	Conv. of 1a (%) ^b	yield of 2a (%) ^b	yield of internal alkenes (%) ^b
1	none	100	97	0
2	no PdCl ₂	52	0	0
3	no Fe(III) citrate· <i>n</i> H ₂ O	96	43	7
4	no slow addition of 1a	100	72	5
5	under air	56	29	24
6	PdCl ₂ (MeCN) ₂ instead of PdCl ₂	100	95	0
7	PdCl ₂ (PhCN) ₂ instead of PdCl ₂	100	95	0
8	PdCl ₂ (cod) instead of PdCl ₂	89	26	28
9	Pd(OAc) ₂ instead of PdCl ₂	40	10	0
10 ^c	DME/H ₂ O (1:1)	100	66	2
11 ^c	DME/H ₂ O (5:1)	100	86	3
12	diglyme/H ₂ O (3:1)	100	91	0
13	THF/H ₂ O (3:1)	100	67	6
14	1,4-dioxane/H ₂ O (3:1)	100	82	4
15	Et ₂ O/H ₂ O (3:1)	60	2	25
16	MeOH/H ₂ O (3:1)	100	23	16
17	EtOH/H ₂ O (3:1)	100	71	4
18	DMF/H ₂ O (3:1)	86	33	1
19	MeCN/H ₂ O (3:1)	75	44	18
20	FeSO ₄ ·7H ₂ O (5 mol %) instead of Fe(III) citrate· <i>n</i> H ₂ O	100	89	0
21	Fe ₂ (SO ₄) ₃ · <i>n</i> H ₂ O (2.5 mol %) instead of Fe(III) citrate· <i>n</i> H ₂ O	100	84	0
22	Fe(NO ₃) ₃ ·9H ₂ O (5 mol %) instead of Fe(III) citrate· <i>n</i> H ₂ O	100	91	0
23	Fe ₂ O ₃ (2.5 mol %) instead of Fe(III) citrate· <i>n</i> H ₂ O	100	83	0
24	FeCl ₂ (5 mol %) instead of Fe(III) citrate· <i>n</i> H ₂ O	100	76	8
25	FeCl ₃ (5 mol %) instead of Fe(III) citrate· <i>n</i> H ₂ O	90	49	20
26 ^d	PdCl ₂ (2 mol %), Fe(III) citrate· <i>n</i> H ₂ O (4 mol %), 16 h	100	96	0
27 ^e	PdCl ₂ (1 mol %), Fe(III) citrate· <i>n</i> H ₂ O (4 mol %), 16 h	100	92	0
28 ^f	PdCl ₂ (0.5 mol %), Fe(III) citrate· <i>n</i> H ₂ O (10 mol %), 70 h	100	88	3

^aReaction conditions: **1a** (0.50 mmol), PdCl₂ (0.025 mmol), Fe(III) citrate·*n*H₂O (0.025 mmol), DME (3.0 mL), H₂O (1.0 mL), r.t., O₂ (1 atm). **1a** was added over 5, 15, or 69 h using a syringe pump, and the reaction mixture was stirred for an additional 1 h (6, 16, or 70 h in total). ^bDetermined by ¹H NMR. ^cAverage of two runs. ^dPdCl₂ (0.010 mmol), Fe(III) citrate·*n*H₂O (0.020 mmol). ^ePdCl₂ (0.005 mmol), Fe(III) citrate·*n*H₂O (0.020 mmol). ^f**1a** (1.0 mmol), PdCl₂ (0.005 mmol), Fe(III) citrate·*n*H₂O (0.10 mmol).

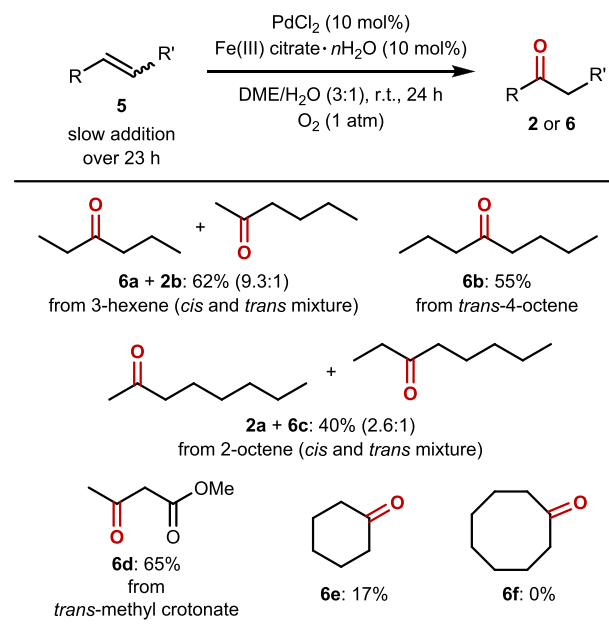
group.^{7,18} Alkenes with a carboxy or benzyloxycarbonyl group **1l–1n** are also applicable. Haloalkenes 6-chloro-1-hexene (**1o**) and 7-bromo-1-heptene (**1p**) afforded methyl ketones **2o** and **2p** in high yields, respectively, without damaging the halogen group. As for dienes, although 1,7-octadiene (**1q**) afforded the corresponding diketone **2q** in good yield, 1,5-hexadiene (**1r**) did not furnish the corresponding diketone **2r** at all. Styrene (**1s**), 4-acetoxystyrene (**1t**), and 3-trifluoromethylstyrene (**1u**) resulted in the corresponding mixtures of acetophenones **2s–2u**, arylacetaldehydes **3s–3u**,^{7,18,43–46} and arylaldehydes **4s–4u**.^{45,46}

Scheme 2. Scope of Terminal Alkenes^a

^aReaction conditions: 1 (0.50 mmol), PdCl₂ (0.025 mmol), Fe(III) citrate·*n*H₂O (0.025 mmol), DME (3.0 mL), H₂O (1.0 mL), r.t., O₂ (1 atm). 1 was added over 15 h using a syringe pump, and the reaction mixture was stirred for an additional 1 h (16 h in total). Isolated yields are shown. ^bSlow addition: 5 h + 1 h (6 h in total). ^cIsolated as 2,4-dinitrophenylhydrazone derivatives. ^dThe formation ratios of the mixtures are indicated in parentheses. ^eNMR yields.

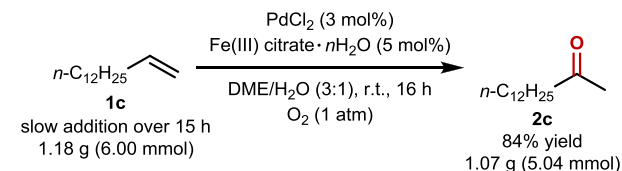
The same reaction conditions were applied to internal alkenes (Scheme 3). Because it is generally difficult for Pd/Cu catalyst systems to oxidize internal alkenes, Cu-free catalyst systems have predominantly been developed.^{37,41,47–56} 3-Hexene (5a, *cis* and *trans* mixture) afforded 3-hexanone (6a), along with a small amount of 2-hexanone (2b). *Trans*-4-octene (*trans*-5b) selectively furnished 4-octanone (6b) in a moderate yield. 2-Octene (5c, *cis* and *trans* mixture) yielded a mixture of 2-octanone (2a) and 3-octanone (6c) in a 2.6:1 ratio. *Trans*-methyl crotonate (5d) afforded methyl acetoacetate (6d) exclusively. As cycloalkenes, cyclohexene (5e) and cyclooctene (5f) were examined; however, cyclohexanone (6e) was obtained in a low yield (17%) and cyclooctanone (6f) was not formed at all. Although methyl (2*Z*)-2-methyl-2-butenate was used as a trisubstituted alkene, oxidation did not proceed.

Gram-scale synthesis was also attempted (Scheme 4). 1-Tetradecene (1c, 1.18 g, 6.00 mmol) was converted to 2-tetradecanone (2c, 1.07 g, 5.04 mmol) using 3 mol % of PdCl₂

Scheme 3. Scope of Internal Alkenes^a

^aReaction conditions: 5 (0.50 mmol), PdCl₂ (0.050 mmol), Fe(III) citrate·*n*H₂O (0.050 mmol), DME (3.0 mL), H₂O (1.0 mL), r.t., O₂ (1 atm). 5 was added over 23 h using a syringe pump, and the reaction mixture was stirred for an additional 1 h (24 h in total). Isolated yields are shown (the products were isolated as 2,4-dinitrophenylhydrazone derivatives). The formation ratios of the mixtures are indicated in parentheses.

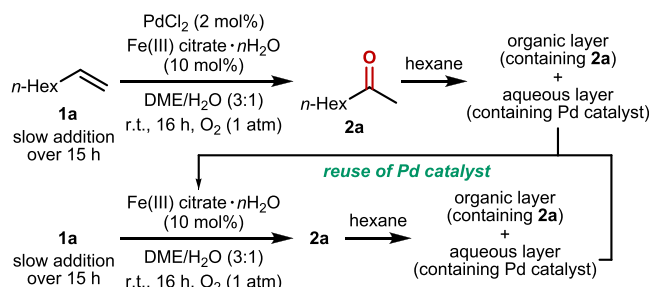
Scheme 4. Gram-Scale Synthesis



and 5 mol % of Fe(III) citrate·*n*H₂O without decreasing the product yield.

The reusability of the Pd catalyst was also examined (Scheme 5). After the first reaction using 1a as the substrate and PdCl₂ (2 mol %) and Fe(III) citrate·*n*H₂O (10 mol %) as

Scheme 5. Reuse of the Pd Catalyst

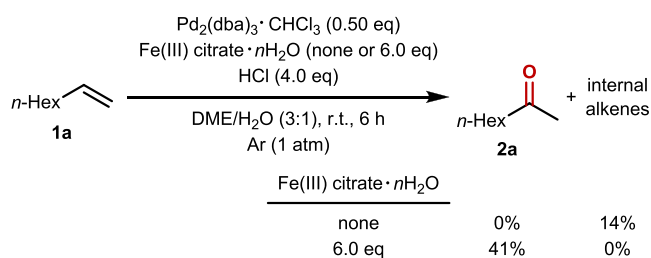


number of times reused	NMR yield of 2a (%)
-	99
1	98
2	91
3	78

the catalysts, the reaction mixture was extracted with *n*-hexane, and the aqueous layer containing the Pd catalyst was reused for the next reaction. Fe(III) citrate·*n*H₂O and DME were added to the aqueous layer, and **1a** was added over 15 h to the solution under O₂. This procedure was repeated thrice. Although the NMR yield of **2a** gradually decreased with each cycle, the overall recovery and reusability of the Pd catalysts were reasonable.

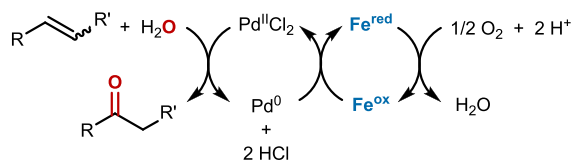
To clarify whether Fe(III) complexes can oxidize Pd(0) species, a Wacker-type oxidation was performed using a stoichiometric amount of Pd₂(dba)₃·CHCl₃ (dba = dibenzylideneacetone) in the absence or presence of Fe(III) citrate·*n*H₂O, under an argon atmosphere (Scheme 6). The results show that Fe(III) citrate is essential for the reaction to proceed and that Fe(III) can oxidize Pd(0) to Pd(II).

Scheme 6. Stoichiometric Oxidation Using Pd₂(dba)₃



An outline of the proposed mechanism is presented in Scheme 7. Alkenes are oxidized to ketones by Pd(II), and the

Scheme 7. Outline of the Proposed Mechanism



formed Pd(0) species are reoxidized to Pd(II) by the higher oxidation state of the Fe complex (Fe^{ox}). The reduced Fe complex (Fe^{red}) is reoxidized by O₂. Etheral solvents may stabilize Fe complexes via coordination. In situ formed Pd–H species isomerize terminal alkenes to internal alkenes. Higher concentrations of terminal alkenes in the reaction mixture tend to promote isomerization into internal alkenes; thus, the slow addition of substrates inhibits isomerization.

CONCLUSIONS

We developed a Pd/Fe-catalyzed Wacker-type oxidation using O₂ as the terminal oxidant that proceeds under mild reaction conditions in the absence of other additives. Etheral solvent/H₂O systems, particularly DME/H₂O, are suitable reaction media. The addition of Fe cocatalysts, especially Fe(III) citrate, significantly promoted the reaction, and they functioned as reoxidants for the Pd(0) species. The slow addition of terminal alkenes is also a key factor in suppressing the isomerization to internal alkenes. Bulky terminal alkenes, such as 3,3-dimethyl-1-butene can also be oxidized. Aliphatic internal alkenes, which are generally difficult to oxidize by conventional Pd/Cu catalyst systems, were also converted to the corresponding ketones. The gram-scale synthesis proceeded successfully without a decrease in the product yield. The Pd catalyst was

reused by collecting and reusing the aqueous layer after each reaction. We believe that this Pd/Fe/O₂ catalyst system can be applied to other reactions related to the Wacker-type oxidation.

EXPERIMENTAL SECTION

General Information. All reactions were performed under an oxygen atmosphere unless otherwise noted using standard Schlenk techniques. PdCl₂ and Fe complexes were commercially available and used as received. Pd₂(dba)₃·CHCl₃ was prepared as described in the literature.⁵⁷ Because the number of water molecules in Fe(III) citrate·*n*H₂O is unknown, the mass was calculated as an anhydrous complex. DME (>99.0% purity), diglyme (>98.0% purity), and other organic solvents (>99.5% purities) were purchased from FUJIFILM Wako and used as received. THF was dried over Na/benzophenone and distilled. Ion-exchanged water was used for the reaction. Compound **1n** was prepared as described in the literature.⁵⁸ Alkenes other than **1n** were commercially available and used as received. Flash column chromatography was performed using silica gel SILICYCLE SiliaFlash F60 (40–63 μm, 230–400 mesh). NMR spectra were recorded on a Bruker AV-300N (300 MHz (¹H), 75 MHz (¹³C)) spectrometer or a JEOL JNM AL-400 (400 MHz (¹H), 100 MHz (¹³C)) spectrometer. Chemical shift values (δ) were expressed relative to SiMe₄ for ¹H and ¹³C NMR. Elemental analysis was performed using a PerkinElmer 2400II analyzer. High-resolution mass spectra were recorded on a JEOL JMS-T100LC spectrometer (ESI-TOF MS) with positive ionization mode. For identification of known isolated products, the spectral data were compared to those reported in the literature.

Wacker-Type Oxidation of Terminal Alkenes 1.

Method A: To a reaction vessel, PdCl₂ (4.4 mg, 0.025 mmol) and Fe(III) citrate·*n*H₂O (6.1 mg, 0.025 mmol) were added, and O₂ was purged. To the mixture were added DME (3.0 mL) and H₂O (1.0 mL), and the reaction mixture was stirred at room temperature. Immediately, **1** (0.50 mmol) was added slowly over 5 or 15 h by a syringe pump, and the reaction mixture was stirred for an additional 1 h (6 or 16 h in total). The product was derivatized to 2,4-dinitrophenylhydrazone using a literature procedure.⁴⁴ The crude material was purified by silica gel column chromatography. **Method B:** After the reaction completed, to the mixture was added CHCl₃. The aqueous layer was further extracted with CHCl₃ (thrice). The combined organic layer was dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under a vacuum. The crude material was purified by silica gel column chromatography.

2-Octanone (2a). Method A was applied. Compound **2a** was isolated as 2,4-dinitrophenylhydrazone derivatives **2a'** and **2a''**.⁵⁹ Purification by silica gel column chromatography (hexane/ethyl acetate = 60:1 to 7:1) afforded an orange solid (141 mg, 0.457 mmol, 91% yield).

2-Hexanone (2b). Method A was applied. Compound **2b** was isolated as 2,4-dinitrophenylhydrazone derivatives **2b'** and **2b''**. Purification by silica gel column chromatography (hexane/ethyl acetate = 40:1 to 5:1) afforded an orange solid (117 mg, 0.417 mmol, 83% yield). ¹H NMR for **2b'** (300 MHz, CDCl₃) δ 10.97 (s, 1H), 9.03 (d, *J* = 2.5 Hz, 1H), 8.23 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.90 (d, *J* = 9.6 Hz, 1H), 2.41 (t, *J* = 7.3 Hz, 2H), 2.04 (s, 3H), 1.65–1.55 (m, 2H), 1.44–1.32 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR for **2b'** (75 MHz, CDCl₃) δ 157.6, 144.2, 136.4, 128.9, 127.8, 122.4, 115.4, 37.7,

27.3, 21.3, 14.8, 12.9. HRMS (ESI): m/z calcd for $C_{12}H_{16}N_4O_4$ $[M + H]^+$ 281.1244, found 281.1254. Anal. Calcd for $C_{12}H_{15}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.10; H, 5.75; N, 19.80.

2-Tetradecanone (2c).⁶⁰ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 15:1) afforded a white solid (89 mg, 0.42 mmol, 84% yield).

4-Methyl-2-pentanone (2d). Method A was applied. Compound **2d** was isolated as 2,4-dinitrophenylhydrazone derivatives **2d'** and **2d''**.⁵⁹ Purification by silica gel column chromatography (hexane/ethyl acetate = 40:1 to 5:1) afforded an orange solid (99 mg, 0.35 mmol, 70% yield).

3-Cyclohexyl-2-propanone (2e). Method A was applied. Compound **2e** was isolated as 2,4-dinitrophenylhydrazone derivative **2e'**.⁵⁹ Purification by silica gel column chromatography (hexane/ethyl acetate = 60:1 to 7:1) afforded an orange solid (122 mg, 0.38 mmol, 76% yield).

4-Phenyl-2-butanone (2f).⁶⁰ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 30:1 to 3:1) afforded a colorless oil (67 mg, 0.45 mmol, 90% yield).

1-Cyclohexylethanone (2g). Method A was applied. Compound **2g** was isolated as 2,4-dinitrophenylhydrazone derivative **2g'**. Purification by silica gel column chromatography (hexane/ethyl acetate = 40:1 to 5:1) afforded an orange solid (78 mg, 0.25 mmol, 51% yield). ¹H NMR for **2g'** (300 MHz, $CDCl_3$) δ 11.02 (s, 1H), 9.12 (d, $J = 2.6$ Hz, 1H), 8.29 (dd, $J = 9.6, 2.6$ Hz, 1H), 7.96 (d, $J = 9.6$ Hz, 1H), 2.38–2.25 (m, 1H), 2.04 (s, 3H), 1.92–1.73 (m, 5H), 1.46–1.18 (m, 5H). ¹³C{¹H} NMR for **2g'** (75 MHz, $CDCl_3$) δ 160.7, 144.4, 136.5, 128.9, 127.9, 122.5, 115.5, 46.2, 29.1, 24.99, 24.97, 13.5. HRMS (ESI): m/z calcd for $C_{14}H_{18}N_4O_4Na$ $[M + Na]^+$ 329.1226, found 329.1240. Anal. Calcd for $C_{14}H_{19}N_4O_4$ (**2g'**·0.6 H₂O): C, 53.02; H, 6.10; N, 17.67. Found: C, 53.16; H, 5.95; N, 17.31.

3,3-Dimethyl-2-butanone (2h). Method A was applied. Compound **2h** was isolated as 2,4-dinitrophenylhydrazone derivative **2h'**.⁵⁹ Purification by silica gel column chromatography (hexane/ethyl acetate = 60:1 to 7:1) afforded an orange solid (81 mg, 0.29 mmol, 57% yield). ¹H NMR for **2h'** (300 MHz, $CDCl_3$) δ 11.01 (s, 1H), 9.12 (d, $J = 2.6$ Hz, 1H), 8.28 (dd, $J = 9.6, 2.4$ Hz, 1H), 7.96 (d, $J = 9.6$ Hz, 1H), 2.04 (s, 3H), 1.24 (s, 9H). ¹³C{¹H} NMR for **2h'** (75 MHz, $CDCl_3$) δ 163.7, 145.5, 137.5, 129.9, 129.0, 123.5, 116.6, 39.3, 27.5, 12.1. HRMS (ESI): m/z calcd for $C_{12}H_{17}N_4O_4$ $[M + H]^+$ 281.1244, found 281.1254. Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.27; H, 5.82; N, 19.74.

6-Hydroxy-2-hexanone (2i). Method A was applied. Compound **2i** was isolated as 2,4-dinitrophenylhydrazone derivatives **2i'** and **2i''**. Purification by silica gel column chromatography (hexane/ethyl acetate = 8:1 to ethyl acetate only) afforded an orange solid (99 mg, 0.33 mmol, 67% yield). ¹H NMR for **2i'** (300 MHz, $CDCl_3$) δ 11.04 (s, 1H), 9.11 (d, $J = 2.5$ Hz, 1H), 8.28 (dd, $J = 9.6, 2.4$ Hz, 1H), 7.94 (d, $J = 9.6$ Hz, 1H), 3.72 (t, $J = 6.1$ Hz, 2H), 2.48 (t, $J = 7.6$ Hz, 2H), 2.07 (s, 3H), 1.81–1.60 (m, 4H), 1.47 (br s, 1H). ¹³C{¹H} NMR for **2i'** (75 MHz, $CDCl_3$) δ 157.9, 145.2, 137.6, 130.0, 128.9, 123.5, 116.4, 62.4, 38.7, 32.0, 22.3, 15.9. HRMS (ESI): m/z calcd for $C_{12}H_{16}N_4O_5Na$ $[M + Na]^+$ 319.1018, found 319.1021. Anal. Calcd for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.45; N, 18.91. Found: C, 48.54; H, 5.32; N, 18.89.

10-Hydroxy-2-decanone (2j).⁶¹ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 2:1) afforded a white solid (79 mg, 0.46 mmol, 92% yield).

1-Phenoxy-2-propanone (2k)⁶² and 3-Phenoxypropanal (3k).⁶³ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 20:1 to 2:1) afforded a pale yellow oil (46 mg, 0.31 mmol, 62% yield (**2k**/**3k** = 1.7:1)).

5-Oxohexanoic Acid (2l).⁶⁴ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 1:1) afforded a colorless oil (57 mg, 0.44 mmol, 88% yield).

9-Oxodecanoic Acid (2m).⁶⁵ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 1:1) afforded a white solid (89 mg, 0.48 mmol, 96% yield).

5-Oxohexanoic Acid Benzyl Ester (2n).⁶⁶ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 20:1 to 3:1) afforded a pale yellow oil (94 mg, 0.43 mmol, 85% yield).

6-Chloro-2-hexanone (2o). Method A was applied. Compound **2o** was isolated as 2,4-dinitrophenylhydrazone derivatives **2o'** and **2o''**. Purification by silica gel column chromatography (hexane/ethyl acetate = 20:1 to 2:1) afforded an orange solid (146 mg, 0.464 mmol, 93% yield). ¹H NMR for **2o'** (300 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.14 (d, $J = 2.5$ Hz, 1H), 8.31 (dd, $J = 9.6, 2.6$ Hz, 1H), 7.96 (d, $J = 9.6$ Hz, 1H), 3.61 (t, $J = 6.0$ Hz, 2H), 2.48 (t, $J = 6.9$ Hz, 2H), 2.08 (s, 3H), 1.91–1.80 (m, 4H). ¹³C{¹H} NMR for **2o'** (75 MHz, $CDCl_3$) δ 157.2, 145.1, 137.6, 130.0, 128.9, 123.5, 116.4, 44.6, 38.0, 31.8, 23.1, 16.0. HRMS (ESI): m/z calcd for $C_{12}H_{16}ClN_4O_4$ $[M + H]^+$ 315.0855, found 315.0845. Anal. Calcd for $C_{12}H_{15}ClN_4O_4$: C, 45.80; H, 4.80; N, 17.80. Found: C, 45.54; H, 4.57; N, 17.93.

7-Bromo-2-heptanone (2p).⁶⁷ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 10:1) afforded a pale yellow oil (90 mg, 0.47 mmol, 93% yield).

2,7-Octanedione (2q).⁶⁸ Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 3:1) afforded a pale yellow oil (55 mg, 0.39 mmol, 77% yield).

Wacker-Type Oxidation of Internal Alkenes 5. To a reaction vessel, $PdCl_2$ (8.9 mg, 0.050 mmol) and Fe(III) citrate· nH_2O (12 mg, 0.050 mmol) were added, and O_2 was purged. To the mixture, DME (3.0 mL) and H_2O (1.0 mL) were added and the reaction mixture was stirred at room temperature. Immediately, **5** (0.50 mmol) was added slowly over 23 h by a syringe pump, and the reaction mixture was stirred for an additional 1 h (24 h in total). The product was derivatized to 2,4-dinitrophenylhydrazone using a literature procedure.⁴⁴ The crude material was purified by silica gel column chromatography.

3-Hexanone (6a). Compounds **6a** and **2b** were obtained as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **6a'**, **6a''**, and **2b'** from 3-hexene (**5a**, *cis* and *trans* mixture). Purification by silica gel column chromatography (hexane/ethyl acetate = 40:1 to 5:1) afforded an orange solid (87 mg, 0.31 mmol, 62% yield ((**6a'** + **6a''**)/**2b'** = 9.3:1)). ¹H NMR for **6a'** and **6a''** (300 MHz, $CDCl_3$) δ 11.24 (s, 1H for **6a'** or **6a''**), 11.21 (s, 1H for **6a'** or **6a''**), 9.11 (d, $J = 2.6$ Hz, 1H), 8.28 (dd, $J = 9.6, 2.5$ Hz, 1H), 7.96 (d, $J = 9.6$ Hz, 1H for

6a' or 6a"), 7.95 (d, $J = 9.6$ Hz, 1H for 6a' or 6a'), 2.48–2.36 (m, 4H), 1.76–1.60 (m, 2H), 1.23 (t, $J = 7.8$ Hz, 3H for 6a' or 6a"), 1.21 (t, $J = 7.4$ Hz, 3H for 6a' or 6a'), 1.07 (t, $J = 7.3$ Hz, 3H for 6a' or 6a"), 1.00 (t, $J = 7.4$ Hz, 3H for 6a' or 6a"). $^{13}\text{C}\{^1\text{H}\}$ NMR for 6a' and 6a" (75 MHz, CDCl_3) δ 162.83, 162.80, 145.3, 137.4, 129.9, 128.8, 123.55, 123.53, 116.34, 116.31, 38.8, 32.2, 30.7, 23.2, 19.4, 18.8, 14.4, 13.8, 10.4, 9.4. HRMS (ESI): m/z calcd for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 303.1069, found 303.1059. Anal. Calcd for $\text{C}_{12}\text{H}_{16.2}\text{N}_4\text{O}_{4.1}$ (6a'·0.1 H_2O): C, 51.10; H, 5.79; N, 19.86. Found: C, 51.07; H, 5.95; N, 19.56.

4-Octanone (6b). Compound 6b was obtained as 2,4-dinitrophenylhydrazone derivatives 6b' and 6b" from *trans*-4-octene (*trans*-5b). Purification by silica gel column chromatography (hexane/ethyl acetate = 60:1 to 7:1) afforded an orange solid (85 mg, 0.28 mmol, 55% yield). ^1H NMR for 6b' and 6b" (300 MHz, CDCl_3) δ 11.22 (s, 1H), 9.09 (d, $J = 2.6$ Hz, 1H), 8.29–8.24 (m, 1H), 7.93 (d, $J = 9.6$ Hz, 1H), 2.42–2.35 (m, 4H), 1.74–1.34 (m, 6H), 1.10–0.94 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR for 6b' and 6b" (75 MHz, CDCl_3) δ 162.22, 162.16, 145.25, 145.23, 137.3, 129.87, 129.86, 128.7, 123.5, 116.30, 116.27, 39.4, 37.1, 32.2, 30.1, 28.2, 27.2, 23.0, 22.4, 19.5, 18.8, 14.4, 13.9, 13.8, 13.7. HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 331.1382, found 331.1381. Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_4$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.55; H, 6.70; N, 17.80.

3-Octanone (6c). Compounds 2a and 6c were obtained as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives 2a', 2a", 6c', and 6c" from 2-octene (5c, *cis* and *trans* mixture). Purification by silica gel column chromatography (hexane/ethyl acetate = 60:1 to 7:1) afforded an orange solid (61 mg, 0.20 mmol, 40% yield ((2a' + 2a")/(6c' + 6c") = 2.6:1)). ^1H NMR for 6c' and 6c" (300 MHz, CDCl_3) δ 11.20 (s, 1H for 6c' or 6c"), 11.02 (s, 1H for 6c' or 6c"), 9.10 (d, $J = 2.6$ Hz, 1H), 8.27 (dd, $J = 9.6, 2.5$ Hz, 1H), 7.96 (d, $J = 9.6$ Hz, 1H), 2.48–2.37 (m, 4H), 1.67–1.58 (m, 2H), 1.43–1.29 (m, 4H), 1.23 (t, $J = 7.7$ Hz, 3H for 6c' or 6c"), 1.20 (t, $J = 7.4$ Hz, 3H for 6c' or 6c"), 0.94–0.88 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR for 2a', 6c' and 6c" (75 MHz, CDCl_3) δ 163.0, 159.5, 145.31, 145.27, 145.1, 137.40, 137.37, 129.9, 128.8, 128.7, 123.52, 123.51, 116.3, 116.2, 36.8, 32.0, 31.44, 31.36, 31.1, 30.7, 30.3, 29.4, 25.8, 25.1, 24.9, 23.7, 23.2, 22.45, 22.41, 22.3, 13.97, 13.94, 13.8, 10.4, 9.4. Some signals for 2a", 6c', and 6c" were overlapped with those for 2a'. HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 331.1382, found 331.1396. Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_4$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.39; H, 6.74; N, 17.93.

Methyl Acetoacetate (6d). Compound 6d was obtained as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives 6d' and 6d". Purification by silica gel column chromatography (hexane/ethyl acetate = 12:1 to 1:1) afforded an orange solid (97 mg, 0.33 mmol, 65% yield). ^1H NMR for 6d' (300 MHz, CDCl_3) δ 11.04 (s, 1H), 9.05 (d, $J = 2.6$ Hz, 1H), 8.26 (dd, $J = 9.6, 2.5$ Hz, 1H), 7.90 (d, $J = 9.6$ Hz, 1H), 3.74 (s, 3H), 3.48 (s, 2H), 2.15 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR for 6d' (75 MHz, CDCl_3) δ 169.6, 150.7, 144.8, 138.0, 129.9, 129.3, 123.2, 116.4, 52.3, 44.1, 16.1. HRMS (ESI): m/z calcd for $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_6\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 319.0655, found 319.0644. Anal. Calcd for $\text{C}_{11}\text{H}_{12.4}\text{N}_4\text{O}_{6.2}$ (6d'·0.2 H_2O): C, 44.06; H, 4.17; N, 18.69. Found: C, 44.10; H, 4.02; N, 18.53.

Cyclohexanone (6e).⁶⁹ Compound 6e was obtained as a corresponding 2,4-dinitrophenylhydrazone derivative 6e'. Purification by silica gel column chromatography (hexane/

ethyl acetate = 30:1 to 7:1) afforded a yellow solid (23 mg, 0.083 mmol, 17% yield).

Gram-Scale Synthesis of 2c. To a reaction vessel, PdCl_2 (32 mg, 0.18 mmol) and Fe(III) citrate· $n\text{H}_2\text{O}$ (73 mg, 0.30 mmol) were added, and O_2 was purged. To the mixture, DME (36 mL) and H_2O (12 mL) were added, and the reaction mixture was stirred at room temperature. Immediately, 1c (1.53 mL, 1.18 g, 6.00 mmol) was added slowly over 15 h by a syringe pump, and the reaction mixture was stirred for an additional 1 h (16 h in total). After the reaction was completed, the mixture was filtered by Celite. CHCl_3 was added to the filtrate, and the aqueous layer was extracted with CHCl_3 (five times). The combined organic layer was dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under a vacuum. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate = 50:1 to 7:1). Compound 2c was obtained as a white solid (1.07 g, 5.04 mmol, 84% yield).

Reuse of the Pd Catalyst. To a reaction vessel, PdCl_2 (5.3 mg, 0.030 mmol) and Fe(III) citrate· $n\text{H}_2\text{O}$ (37 mg, 0.15 mmol) were added, and O_2 was purged. To the mixture were added DME (9.0 mL) and H_2O (3.0 mL), and the reaction mixture was stirred at room temperature. Immediately, 1a (235 μL , 1.50 mmol) was added slowly over 15 h by a syringe pump, and the reaction mixture was stirred for an additional 1 h (16 h in total). After the reaction was completed, to the mixture was added hexane. The aqueous layer was further extracted with hexane (thrice). After the organic layer was removed, the remaining organic solvents were evaporated under a vacuum. To the reaction vessel with only the aqueous layer remaining, Fe(III) citrate· $n\text{H}_2\text{O}$ (37 mg, 0.15 mmol) and DME (9.0 mL) were added and the reaction mixture was stirred at room temperature. Immediately, 1a (235 μL , 1.50 mmol) was added slowly over 15 h by a syringe pump, and the reaction mixture was stirred for an additional 1 h (16 h in total). Thereafter, these manipulations were repeated.

Stoichiometric Oxidation Using $\text{Pd}_2(\text{dba})_3$. To a reaction vessel were added $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (26 mg, 0.025 mmol) and Fe(III) citrate· $n\text{H}_2\text{O}$ (none or 73 mg, 0.30 mmol), and Ar was purged. To the mixture, DME (1.5 mL), H_2O (0.50 mL), HCl in 1,4-dioxane (50 μL , 4 M solution), and 1a (7.8 μL , 0.050 mmol) were added, and the reaction mixture was stirred at room temperature for 6 h. A portion of the reaction mixture (0.20 mL) and CDCl_3 (0.40 mL) were mixed and the samples were filtered. The organic layers were analyzed by ^1H NMR spectroscopy.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c07577>.

Copies of ^1H and ^{13}C NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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