Palladium-catalyzed Aerobic anti-Markovnikov Oxidation of Aliphatic Alkenes to Terminal Acetals

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ABSTRACT: Terminal acetals were selectively synthesized from various unbiased aliphatic terminal alkenes and 1,2-, 1,3-, or 1,4-diols using a $PdCl_2(MeCN)_2$/CuCl catalyst system in the presence of *p*-toluquinone under 1 atm of O_2 and mild reaction conditions. The slow addition of terminal alkenes suppressed the isomerization to internal alkenes successfully. Electron-deficient cyclic alkenes, such as *p*-toluquinone, were key additives to enhance the catalytic activity and the anti-Markovnikov selectivity. The halogen groups in the alkenes were found to operate as directing groups, suppressing isomerization and increasing the selectivity efficiently.

INTRODUCTION

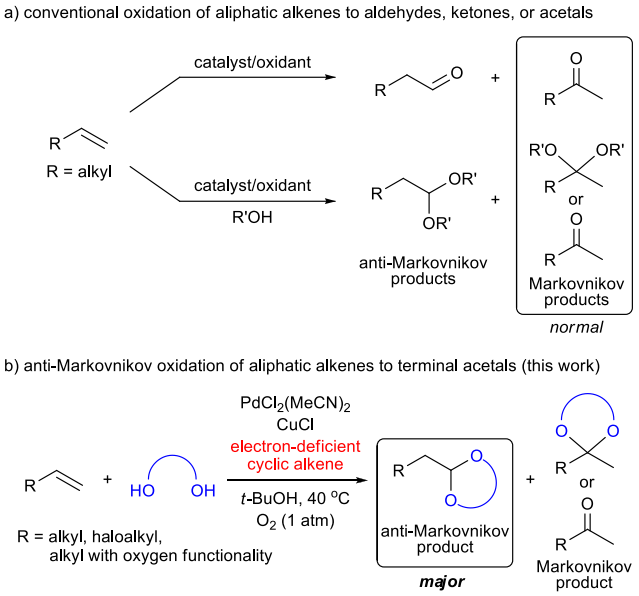
Realization of anti-Markovnikov selectivity in the oxidation of terminal alkenes is challenging.[1-3] Although ketones are typically obtained in palladium-catalyzed Wacker-type oxidation (Scheme 1a), aldehydes can be formed preferentially from terminal alkenes with oxygen or nitrogen directing groups[1,4-8] and vinylarenes.[1-3,9-12] In the case of vinylarenes, iron-[13,14] and ruthenium[15,16]-catalyzed reactions affording aldehydes have been reported; these reactions proceed via a tandem epoxidation–isomerization pathway. On the other hand, unbiased aliphatic terminal alkenes (other than ethylene) are known to be difficult to convert into aldehydes selectively.[17-19] Grubbs et al. reported anti-Markovnikov Wacker-type oxidation of the unbiased aliphatic alkenes using nitrite salts as co-catalysts under aerobic conditions.[20] Che et al. achieved iron porphyrin-catalyzed anti-Markovnikov oxidation in the presence of iodosylbenzene as an oxidant.[14]

The situation is similar in the formation of acetals, which are protected compounds of aldehydes or ketones, from terminal alkenes. Alkenes with electron-deficient groups,[21-25] alkenes with oxygen, nitrogen, or sulfur directing groups,[26-28] 1,5-dienes,[28] and vinylarenes[21,28-32] are known to afford terminal acetals preferentially by reactions with alcohols or diols, depending on the reaction conditions; however, unbiased aliphatic alkenes normally afford Markovnikov products (internal acetals[33-36] or ketones[19,21,30,34,37]) and remain challenging substrates for anti-Markovnikov oxidation (Scheme 1a). Here we report the palladium-catalyzed aerobic anti-Markovnikov oxidation of aliphatic alkenes to terminal acetals under mild reaction conditions (Scheme 1b). The key features of this reaction include: 1) the slow addition of alkenes, which can suppress the isomerization of terminal alkenes into internal alkenes, 2) addition of electron-deficient cyclic alkenes as auxiliary ligands, which enhance the catalytic activity and anti-Markovnikov selectivity,[9,29] and 3) halogen groups in alkenes, which act as directing groups despite their weakly coordinating ability, affording high anti-Markovnikov selectivity.

RESULTS AND DISCUSSION

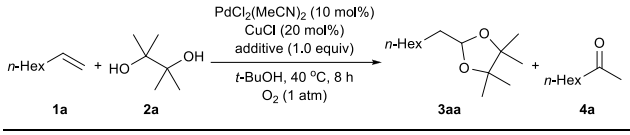
1-Octene (**1a**) and pinacol (**2a**, 3.0 equiv) were treated with

Scheme 1. Markovnikov and anti-Markovnikov Oxidation of Aliphatic Terminal Alkenes



catalytic amounts of $PdCl_2(MeCN)_2$ (10 mol%) and CuCl (20 mol%) in *t*-BuOH at 40 °C under 1 atm of O_2 (Table 1). Under these conditions, terminal acetal **3aa** was formed in only 8% yield along with the formation of 2- and 3-octanones (entry 1). Isomerization of **1a** to 2-octenes was also observed during the reaction (39%). The formation of 3-octanone would occur by the Wacker-type oxidation of 2-octenes. Because the isomerization would be catalyzed by in situ formed Pd-H species, we expected that, by maintaining the concentration of **1a** at a low level, the isomerization may be suppressed efficiently. When slow addition of **1a** to the reaction mixture by a syringe pump (7 h) was performed, the formation of 2-octenes was suppressed significantly (19%), and the yield of **3aa** and anti-Markovnikov selectivity were both increased (entry 2). The effect of electron-deficient cyclic alkenes as additives was then examined (entries 3–15). We previously found that these alkenes can operate as ligands to enhance the catalytic activity of the

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa 4a

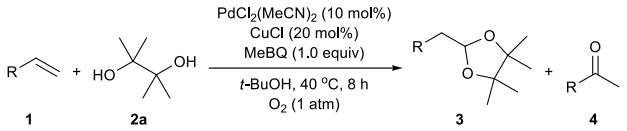
Entry	Additive	Yield of **3aa** (%)[b]	Yield of **4a** (%)[b]	Selectivity (%)[c]
1[d]	none	8	25[e]	24
2	none	34	28	55
3	maleic anhydride	50	17	75
4	maleimide	44	30	59
5	*N*-methylmaleimide	49	33	60
6	*N*-phenylmaleimide	49	18	73
7	BQ[f]	21	70	23
8	ClBQ	37	53	41
9	2,6-Cl_2BQ	25	60	29
10	Cl_4BQ	38	33	54
11	MeOBQ	32	16	67
12	PhBQ	51	35	59
13	MeBQ	53	34	61
14	MeBQ[g]	34	15	69
15[h]	MeBQ	25	53	32
16[i]	MeBQ	47	13	78
17[i,j]	MeBQ	5	13	28

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (1.50 mmol), $PdCl_2(MeCN)_2$ (0.050 mmol), CuCl (0.10 mmol), additive (0.50 mmol), *t*-BuOH (2.0 mL), 40 °C, O_2 (1 atm). **1a** was added over 7 h by a syringe pump, and the reaction mixture was stirred for an additional 1 h (8 h in total). [b] Determined by ^{1}H NMR. [c] Selectivity = **3aa**/(**3aa**+**4a**). [d] **1a** was added at a time (without a syringe pump). [e] Total yield of **4a** (11%) and 3-octanone (14%). [f] BQ = *p*-benzoquinone. [g] 10 mol% of MeBQ (0.050 mmol) was used. [h] *t*-AmylOH was used as a solvent. [i] Under Ar. [j] Without CuCl.

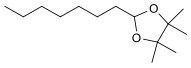
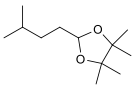
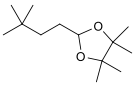
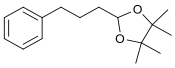
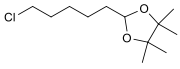
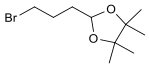
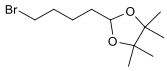
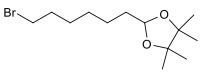
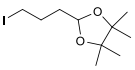
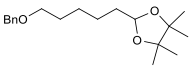
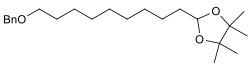
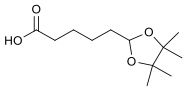
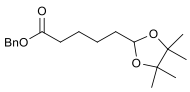
anti-Markovnikov oxidation of vinylarenes to aldehydes[9] and terminal acetals[29] under aerobic conditions. Maleic anhydride and maleimides were found to increase both the yield of **3aa** and the selectivity (entries 3–6). *p*-Benzoquinone (BQ), which is often used as an oxidant in Pd-catalyzed reactions, gave low selectivity for the product (entry 7). Halogen substituted BQs and MeOBQ were also inefficient (entries 8–11). On the other hand, PhBQ and MeBQ gave higher yields of **3aa** along with moderate selectivity (entries 12 and 13). Reducing the loading of MeBQ to 10 mol% was ineffective (entry 14). The use of *t*-amylOH instead of *t*-BuOH as a solvent lowered the yield of **3aa** and the selectivity (entry 15). Although the reaction proceeded even under an argon atmosphere (entry 16), the absence of both O_2 and CuCl resulted in low yield of **3aa** (entry 17). Thus, MeBQ also functioned as an oxidant, especially in the presence of CuCl. Indeed, in entries 13 and 16, 30% and 58% of MeBQ were converted into methyl-*p*-hydroquinone (MeHQ), respectively, according to ^{1}H NMR analysis.

The optimized reaction conditions using MeBQ as an additive were then applied to various aliphatic terminal alkenes (Table 2). By increasing the steric hindrance at the substituents, the anti-Markovnikov selectivity increased (entries 2 and 3). 4-

Table 2. Scope of Aliphatic Alkenes[a]



1 2a 3 4

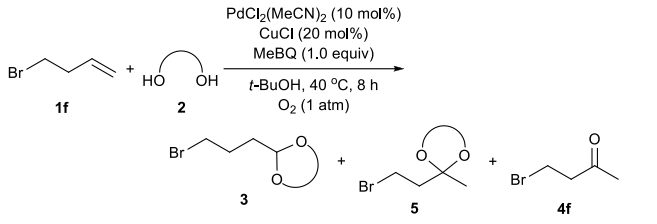
Entry	Product		Yield of **3** (%)[b,c]	Yield of **4** (%)[b]	Selectivity (%)[d]
1		**3aa**	53(37)	32	62
2		**3ba**	55(47)	18	75
3[e]		**3ca**	73(46)	12	86
4		**3da**	74(61)	25	75
5[f]		**3ea**	77(60)	8	91
6[g]		**3fa**	84(76)	3	97
7[f]		**3ga**	86(75)	7	92
8		**3ha**	77(63)	21	79
9[g]		**3ia**	40(33)	4	91
10[f]		**3ja**	60(49)	21	74
11[e]		**3ka**	56(52)	27	67
12[e,h]		**3la**	66(60)	18	79
13[e,h]		**3ma**	68(51)	12	85

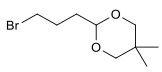
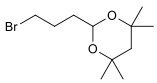
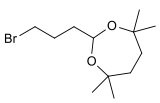
[a] Reaction conditions: **1** (2.0 mmol), **2a** (6.0 mmol), $PdCl_2(MeCN)_2$ (0.20 mmol), CuCl (0.40 mmol), MeBQ (2.0 mmol), *t*-BuOH (8.0 mL), 40 °C, O_2 (1 atm). **1** was added over 7 h by a syringe pump, and the reaction mixture was stirred for an additional 1 h (8 h in total). [b] Determined by ^{1}H NMR. [c] The values in parentheses are isolated yields. [d] Selectivity = **3**/(**3**+**4**). [e] For 12 h (slow addition 7 h + additional 5 h). [f] No slow addition, for 3 h. [g] No slow addition, for 1 h. [h] Maleic anhydride was used instead of MeBQ.

Phenyl-1-butene also gave a good product yield with good selectivity (entry 4). We found that linear alkenes with a chloro or

bromo group at the terminal carbon afforded high yields of terminal acetals with high selectivity (entries 5–8). The carbon–halogen bonds remained intact in these products. 4-Iodo-1-butene also gave the terminal acetal in high selectivity, albeit the yield was low (entry 9). The low conversion of 4-iodo-1-butene (47%) indicates that a side reaction such as carbon–iodine bond cleavage occurred, deactivating the catalyst. In entries 5–7 and 9, the slow addition of alkenes was not necessary because the isomerization of alkenes did not compete. As a control experiment, 1-bromobutane (1.0 equiv) was used as another additive for the reaction of 1-octene with pinacol to examine whether the bromo group in haloalkane is also effective. However, almost no improvement in the product yields (**3aa**: 53%, **4a**: 29%) and the selectivity (65%) was observed compared to those shown in entry 1, Table 2. These results indicate that the halogen substituents in the alkenes act as directing groups, even though they are regarded as weakly coordinating ligands in general. We also attempted terminal acetal formation from 4-bromo-1-butene and pinacol (10 equiv) using a $PdCl_2(MeCN)_2$ (10 mol%)/BQ (2.0 equiv, as an oxidant in this case)/DMF system (60 °C, 6 h), which has been used for vinylarenes, allyl ethers, and 1,5-dienes[28]; however, only 8% of **3fa** and 2% of **4f** were formed (89% conversion). Thus, because there are only weakly coordinating compounds in the present system (*t*-BuOH and pinacol would not be so favorable as ligands due to steric repulsion against other ligands on palladium), even halogen substituents, which are small and have weak coordination ability, may be able to coordinate to palladium. Related to the above results for haloalkenes, allylic fluorides are known to afford β-fluorinated aldehydes in a $PdCl_2(PhCN)_2/CuCl_2/AgNO_2$ catalyst system, although mechanistic investigations suggest that the anti-Markovnikov selectivity is attributed to the inductive effect of fluorine substituents, unlike the present reaction.[38] Other alkenes with oxygen functional groups such as ethers (entries 10 and 11), carboxy groups (entry 12), and ester groups (entry 13) also afforded moderate yields of the corresponding terminal acetals with good to high selectivity.

Table 3. Scope of Diols[a]



Entry	Product		Yield of **3** (%)[b,c]	Yield of **5** (%)[b,c]	Yield of **4f** (%)[b]	Selectivity (%)[d]
1		**3fb**	59 (46)[e]	28[f] (22)[e]	11	60
2[g]		**3fc**	90(66)	0	0	>99
3[h]		**3fd**	80(65)	0	2	98

[a] Reaction conditions: **1f** (2.0 mmol), **2** (6.0 mmol), $PdCl_2(MeCN)_2$ (0.20 mmol), CuCl (0.40 mmol), MeBQ (2.0 mmol), *t*-BuOH (8.0 mL), 40 °C, O_2 (1 atm), 8 h. [b] Determined by ^{1}H NMR. [c] The values in parentheses are isolated yields. [d] Selectivity = **3**/(**3**+**5**+**4f**). [e] Isolated as a mixture of **3fb** and **5fb**. [f] The value was calculated from the NMR yield of **3fb** and the ratio of **3fb** to **5fb** in the isolated mixture. [g] For 28 h. [h] For 3 h.

By using 4-bromo-1-butene as a terminal alkene, the scope of diols was then examined (Table 3). In the case of the primary diol 2,2-dimethyl-1,3-propanediol, internal acetal **5fb** was also formed as a by-product in addition to terminal acetal **3fb** and **4f**, resulting in decreased selectivity (entry 1). The relatively less bulky primary diol can also operate as a nucleophile, resulting in internal nucleophilic attack on the coordinated alkene (*vide infra*). On the other hand, the tertiary diols afforded high product yields with high selectivity (entries 2 and 3).

The reaction of 4-bromo-1-butene with pinacol was monitored by ^{1}H NMR spectroscopy (Figure 1). $CDCl_3$ was used as a co-solvent (*t*-BuOH/$CDCl_3$ = 1:1). We found that 3-bromobutanal, **6f**, an anti-Markovnikov Wacker-type oxidation product, was formed as the main oxidized compound in the early stages, and **6f** appeared to be gradually converted into **3fa** by reaction with pinacol catalyzed by an in situ generated acid. Because no induction period was observed in the formation of **3fa**, an alternative direct conversion from **1f** and pinacol to **3fa** (which does not go through **6f**) seems to be a competing reaction.

Based on these experimental results, a proposed mechanism for the formation of terminal acetals and ketones is shown in Scheme 2. To the $LPdCl_2$ species, terminal alkene **1** and MeBQ coordinate to afford **7**. Then, *t*-BuOH attacks the coordinated alkene preferentially at the terminal carbon to afford alkyl palladate **8**. Although electronic factors favor internal nucleophilic attack, the steric repulsion between R and *t*-Bu groups facilitates terminal nucleophilic attack. Subsequent elimination of HCl and β-H elimination result in the formation of alkenyl *t*-butyl ether **9**, which is converted into terminal acetal **3** via aldehyde **6** or directly, catalyzed by an acid. If *t*-BuOH attacks the internal carbon of the coordinated alkene in **7**, ketone **4** is formed via similar steps to those for the formation of **6**. The formed Pd-H species isomerizes the terminal alkene **1** into internal alkenes. The reduction of Pd(II) to Pd(0) with release of HCl and the reoxidation of the Pd(0) species by $CuCl_2$ reproduces the $PdCl_2$ species, and the reduced CuCl is reoxidized to $CuCl_2$ by O_2 and HCl. The Pd(0) species can be also reoxidized to Pd(II) by MeBQ and HCl, especially in the presence of CuCl, as observed in entry 16, Table 1. In the case of 4-bromo-1-butene, chelate coordination occurs and, thus, terminal nucleophilic attack is more favorable than internal nucleophilic attack because of the formation of a stable five-membered ring after the attack. The suppression of isomerization from the terminal alkene into internal alkenes by Pd-H species can be also rationalized by chelate coordination (Scheme 3). Other haloalkenes would also have similar chelate coordination effects. We propose that the electron-deficient cyclic alkenes such as MeBQ coordinate to Pd to facilitate the nucleophilic attack and the reduction of Pd(II) to Pd(0), as well as the stabilization of Pd(0) species, suppressing its deactivation to Pd black.[9,29] As another possibility, the catalytically active species may be Pd-Cu heterobimetallic complexes[17,39-42] and the electron-deficient cyclic alkenes may control the reactivity of the bimetallic complexes through the coordination to Cu.

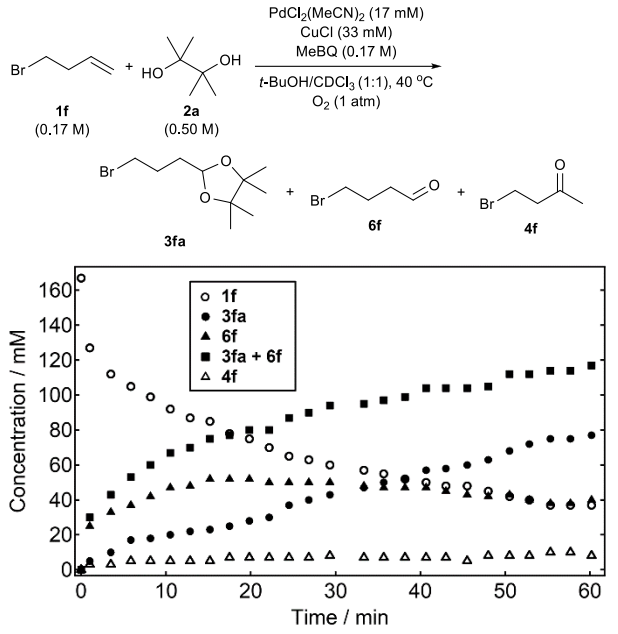
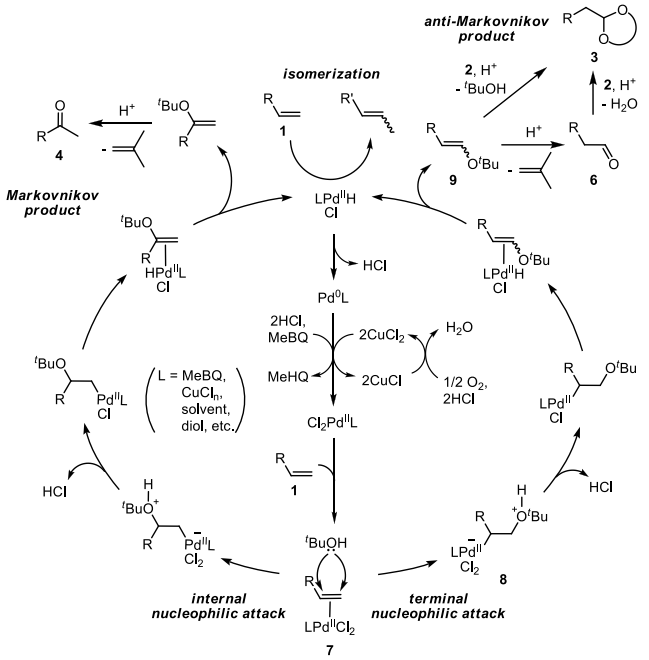
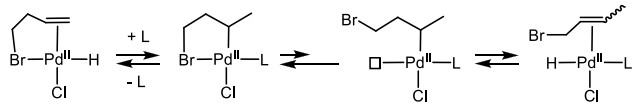


Figure 1. Time course of the conversion of **1f** into **3fa**, **6f**, and **4f**.

Scheme 2. Proposed Mechanism



Scheme 3. Suppression of the Isomerization by Chelate Coordination



CONCLUSION

We have developed a Pd-catalyzed aerobic anti-Markovnikov oxidation of aliphatic alkenes to terminal acetals. The use of a bulky nucleophile, *t*-BuOH, resulted in the anti-Markovnikov selectivity. Slow addition of terminal alkenes efficiently suppressed the isomerization into internal alkenes. The addition of electron-deficient cyclic alkenes such as MeBQ enhanced the catalytic activity and the selectivity. Halogen groups at appropriate positions in the alkenes were found to operate as directing groups to afford the corresponding terminal acetals in high yield and selectivity. We believe that these findings would be helpful for the further development of anti-Markovnikov Wacker-type oxidation and related reactions of aliphatic terminal alkenes.

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all reactions were performed under an oxygen atmosphere (1 atm). $PdCl_2(MeCN)_2$,[43] 4-iodo-1-butene,[44] 5-hexenyl benzyl ether,[45] 9-decenyl benzyl ether[45] and 5-hexenoic acid benzyl ester[46] were prepared as described in the literature. *t*-BuOH was purchased from Nacalai tesque Co. Ltd. and was purified by distillation. Other chemicals were also commercially available and were used without further purification. 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 (^{1}H), 75 MHz (^{13}C)) spectrometer or a JEOL JNM AL-400 (400 MHz (^{1}H), 100 MHz (^{13}C)) spectrometer. Chemical shift values (σ) were expressed relative to $SiMe_4$. Infrared spectra were measured on a JASCO FT/IR-6100 spectrophotometer. High-resolution mass spectra were recorded on a JEOL JMS-T100LC spectrometer (ESI-TOF MS) with positive ionization mode.

Synthesis of Terminal Acetals 3.

General Procedure for the Synthesis of 3. Method A: To a reaction vessel, CuCl (39.6 mg, 0.40 mmol), $PdCl_2(MeCN)_2$ (51.9 mg, 0.20 mmol), MeBQ (244 mg, 2.0 mmol), and pinacol (709 mg, 6.0 mmol) were added, and O_2 was purged. To the mixture, *t*-BuOH (8 mL) was added and the reaction mixture was stirred at 40 °C. Immediately, a terminal alkene (2.0 mmol) was added slowly over 7 h by a syringe pump, and the reaction mixture was stirred for an additional 1–5 h (8–12 h in total). The solvent and volatile materials were evaporated under vacuum. To the residue, dichloromethane (10 mL) and silica gel (2.5 g) were added, and the solvent was evaporated to adsorb the residue on the silica gel. Purification by silica gel column chromatography (hexane/ethyl acetate = 20/1 with 1% triethylamine) afforded the product as a pale yellow oil. **Method B:** This method is similar to Method A. After the reaction completed, the solvent and volatile materials were evaporated under vacuum. To the residue, a saturated aqueous $NaHCO_3$ solution and diethyl ether were added to extract. The aqueous layer was further extracted with diethyl ether (twice). The combined organic layer was washed with water and brine, and was dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under vacuum. To the residue, dichloromethane (10 mL) and silica gel (2.5 g) were added, and the solvent was evaporated to adsorb the residue on the silica gel. Purification by silica gel column chromatography (hexane/ethyl acetate = 20/1 with 1% triethylamine) afforded the product as a pale yellow oil. **Method C:** To a reaction vessel, CuCl (39.6 mg, 0.40 mmol), $PdCl_2(MeCN)_2$ (51.9 mg, 0.20 mmol), MeBQ (244 mg, 2.0 mmol), and pinacol (709 mg, 6.0 mmol) were added, and O_2 was purged. To the mixture, *t*-BuOH (8 mL) and a terminal alkene (2.0 mmol) were added and the reaction mixture was stirred at 40 °C for 1–28 h. The solvent and volatile materials were evaporated under vacuum. To the residue, dichloromethane (10 mL) and silica gel (2.5 g) were added, and the sol-

vent was evaporated to adsorb the residue on the silica gel. Purification by silica gel column chromatography (hexane/ethyl acetate = 20/1 with 1% triethylamine) afforded the product as a pale yellow oil. **Method D:** This method is similar to Method C. After the reaction completed, the solvent and volatile materials were evaporated under vacuum. To the residue, a saturated aqueous $NaHCO_3$ solution and diethyl ether were added to extract. The aqueous layer was further extracted with diethyl ether (twice). The combined organic layer was washed with water and brine, and was dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated under vacuum. To the residue, dichloromethane (10 mL) and silica gel (2.5 g) were added, and the solvent was evaporated to adsorb the residue on the silica gel. Purification by silica gel column chromatography (hexane/ethyl acetate = 20/1 with 1% triethylamine) afforded the product as a pale yellow oil.

2-Heptyl-4,4,5,5-tetramethyl-1,3-dioxolane (3aa). Method A was applied (0.17 g, 0.74 mmol, 37% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (t, J = 5.4 Hz, 1H), 1.61–1.54 (m, 2H), 1.40–1.27 (m, 10H), 1.19 (s, 12H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 101.0, 81.5, 36.5, 31.8, 29.6, 29.2, 24.5, 24.2, 22.6, 22.1, 14.1. HRMS (ESI): m/z calcd for $C_{14}H_{27}O_2$ [M-H]$^+$ 227.2011, found 227.2019.

2-(3-Methylbutyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ba). Method A was applied (0.19 g, 0.95 mmol, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (t, J = 5.1 Hz, 1H), 1.61–1.51 (m, 3H), 1.31–1.23 (m, 2H), 1.19 (s, 12H), 0.88 (d, J = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 101.2, 81.5, 34.3, 33.4, 28.0, 24.2, 22.5, 22.1. HRMS (ESI): m/z calcd for $C_{12}H_{23}O_2$ [M-H]$^+$ 199.1698, found 199.1691.

2-(3,3-Dimethylbutyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ca). Method A was applied (196 mg, 0.91 mmol, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (t, J = 5.1 Hz, 1H), 1.60–1.52 (m, 2H), 1.31–1.20 (m, 2H), 1.19 (s, 12H), 0.87 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 101.7, 81.6, 38.3, 31.7, 30.0, 29.2, 24.2, 22.1. HRMS (ESI): m/z calcd for $C_{13}H_{25}O_2$ [M-H]$^+$ 213.1855, found 213.1860.

2-(3-Phenylpropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3da). Method A was applied (0.30 g, 1.21 mmol, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.11 (m, 5H), 5.02 (t, J = 5.1 Hz, 1H), 2.62 (t, J = 7.5 Hz, 2H), 1.76–1.66 (m, 2H), 1.63–1.57 (m, 2H), 1.16 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.2, 128.4, 128.2, 125.6, 100.7, 81.6, 35.8, 35.7, 26.1, 24.2, 22.1. HRMS (ESI): m/z calcd for $C_{16}H_{23}O_2$ [M-H]$^+$ 247.1698, found 247.1707.

2-(5-Chloropentyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ea). Method C was applied (284 mg, 1.20 mmol, 60% yield). ^{1}H NMR (300MHz, $CDCl_3$) δ 5.02 (t, J = 5.4 Hz, 1H), 3.52 (t, J = 6.9 Hz, 2H), 1.82–1.73 (m, 2H), 1.64–1.56 (m, 2H), 1.52–1.37 (m, 4H), 1.19 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 100.7, 81.6, 45.0, 36.2, 32.5, 26.9, 24.2, 23.8, 22.0. HRMS (ESI): m/z calcd for $C_{12}H_{22}ClO_2$ [M-H]$^+$ 233.1308, found 233.1306.

2-(3-Bromopropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3fa). Method C was applied (384 mg, 1.53 mmol, 76% yield). The spectral data for **3fa** were in accordance with those reported in the literature.[47]

2-(4-Bromobutyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ga). Method C was applied (395 mg, 1.49 mmol, 75% yield). ^{1}H NMR (300MHz , $CDCl_3$) δ 5.03 (t, J = 4.8 Hz, 1H), 3.40 (t, J = 6.9 Hz, 2H), 1.95–1.85 (m, 2H), 1.64–1.48 (m, 4H), 1.19 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 100.5, 81.7, 35.4, 33.6, 32.7, 24.2, 23.2, 22.0. HRMS (ESI): m/z calcd for $C_{11}H_{20}BrO_2$ [M-H]$^+$ 263.0647, found 263.0637.

2-(6-Bromohexyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ha). Method A was applied (366 mg, 1.25 mmol, 63% yield). ^{1}H NMR (300MHz, $CDCl_3$) δ 5.02 (t, J = 5.1 Hz, 1H), 3.39 (t, J = 6.9 Hz, 2H), 1.90–1.80 (m, 2H), 1.62–1.55 (m, 2H), 1.46–1.35 (m, 6H), 1.19 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 100.8, 81.6, 36.3, 33.9, 32.7, 28.7, 28.0, 24.2 (2C), 22.0. HRMS (ESI): m/z calcd for $C_{13}H_{24}BrO_2$ [M-H]$^+$ 291.0960, found 291.0970.

2-(3-Iodopropyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ia). Method D was applied (196 mg, 0.66 mmol, 33% yield). The spectral data for **3ia** were in accordance with those reported in the literature.[47]

2-(5-Benzyloxypentyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ja). Method D was applied (299 mg, 0.97 mmol, 49% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.17 (m, 5H), 4.96 (t, J = 5.1 Hz, 1H), 4.43 (s, 2H), 3.39 (t, J = 6.6 Hz, 2H), 1.59–1.50 (m, 4H), 1.37–1.32 (m, 4H), 1.13 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.4, 100.8, 81.5, 72.8, 70.3, 36.4, 29.7, 26.2, 24.3, 24.2, 22.0. HRMS (ESI): m/z calcd for $C_{19}H_{30}O_3Na$ [M+Na]$^+$ 329.2093, found 329.2076.

2-(9-Benzyloxynonyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ka). Method B was applied (374 mg, 1.03 mmol, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.16 (m, 5H), 4.97 (t, J = 5.1 Hz, 1H), 4.43 (s, 2H), 3.39 (t, J = 6.6 Hz, 2H), 1.59–1.49 (m, 4H), 1.34–1.22 (m, 12H), 1.13 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.5, 128.2, 127.4, 127.3, 100.8, 81.3, 72.7, 70.3, 36.3, 29.6, 29.5, 29.3 (3C), 26.0, 24.3, 24.1, 21.9. HRMS (ESI): m/z calcd for $C_{23}H_{38}O_3Na$ [M+Na]$^+$ 385.2719, found 385.2703.

2-(4-Carboxybutyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3la). Method B was applied. Maleic anhydride was used instead of MeBQ as an additive. Water was used instead of a saturated aqueous $NaHCO_3$ solution for extraction. After filtration of the drying agent, the solvent was evaporated and volatile materials were further removed under vacuum at 40 ℃ overnight to afford **3la** as a pale yellow oil (276 mg, 1.20 mmol, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (br, 1H), 5.00 (t, J = 5.2 Hz, 1H), 2.32 (t, J = 7.6 Hz, 2H), 1.68–1.55 (m, 4H), 1.47–1.38 (m, 2H), 1.16 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 179.7, 100.5, 81.7, 35.9, 33.9, 24.6, 24.1, 23.9, 21.9. IR (neat) ν 1710 cm^{-1} (C=O). HRMS (ESI): m/z calcd for $C_{12}H_{21}O_4$ [M-H]$^+$ 229.1440, found 229.1431.

2-(4-Benzyloxycarbonylbutyl)-4,4,5,5-tetramethyl-1,3-dioxolane (3ma). Method B was applied. Maleic anhydride was used instead of MeBQ as an additive (326 mg, 1.02 mmol, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5H), 5.11 (s, 2H), 5.01 (t, J = 5.1 Hz, 1H), 2.37 (t, J = 7.5 Hz, 2H), 1.74–1.56 (m, 4H), 1.48–1.38 (m, 2H), 1.18 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.4, 136.1, 128.5, 128.1, 100.6, 81.6, 66.1, 36.0, 34.2, 24.9, 24.2, 24.0, 22.0. IR (neat) ν 1738 cm^{-1} (C=O). HRMS (ESI): m/z calcd for $C_{19}H_{27}O_4$ [M-H]$^+$ 319.1909, found 319.1922.

2-(3-Bromopropyl)-5,5-dimethyl-1,3-dioxane (3fb) and 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane (5fb). Method D was applied. 2,2-Dimethyl-1,3-propanediol was used instead of pinacol. Purification by silica gel column chromatography afforded a mixture of **3fb** and **5fb** as a pale yellow oil (323 mg, 1.36 mmol, 68% total yield, **3fb**:**5fb** = 2.1:1). ^{1}H NMR for **3fb**

(300MHz, $CDCl_3$) δ 4.46 (t, J = 4.8 Hz, 1H), 3.61–3.38 (m, 6H), 2.06–1.97 (m, 2H), 1.81–1.75 (m, 2H), 1.18 (s, 3H), 0.72 (s, 3H). ^{1}H NMR for **5fb** (300MHz, $CDCl_3$) δ 3.61–3.38 (m, 6H), 2.28 (t, J = 8.4 Hz, 2H), 1.38 (s, 3H), 1.03 (s, 3H), 0.85 (s, 3H). $^{13}C\{^1H\}$ NMR for **3fb** (75 MHz, $CDCl_3$) δ 101.1, 77.2, 33.7, 33.3, 30.1, 27.2, 22.9, 21.8. $^{13}C\{^1H\}$ NMR for **5fb** (75 MHz, $CDCl_3$) δ 98.3, 70.4, 42.9, 29.8, 27.2, 22.8, 22.3, 19.9. HRMS (ESI): m/z calcd for $C_9H_{17}BrKO_2$ $[M+K]^+$ 275.0049, found 275.0045.

2-(3-Bromopropyl)-4,4,6,6-tetramethyl-1,3-dioxane (3fc). Method D was applied. 2,4-Dimethyl-2,4-pentanediol was used instead of pinacol (347 mg, 1.31 mmol, 66% yield). ^{1}H NMR (300MHz , $CDCl_3$) δ 4.91 (t, J = 4.8 Hz, 1H), 3.43 (t, J = 6.9 Hz, 2H), 2.03–1.94 (m, 2H), 1.73–1.66 (m, 2H), 1.58 (d, J = 13.8 Hz, 1H), 1.45 (d, J = 13.8 Hz, 1H), 1.32 (s, 6H), 1.22 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 89.2, 71.0, 45.5, 34.1, 33.8, 33.3, 27.7, 25.1. HRMS (ESI): *m/z* calcd for $C_{11}H_{21}O_2$ $[M-Br]^+$ 185.1542, found 185.1550.

2-(3-Bromopropyl)-4,4,7,7-tetramethyl-1,3-dioxepane (3fd). Method D was applied. 2,5-Dimethyl-2,5-hexanediol was used instead of pinacol (360 mg, 1.29 mmol, 65% yield). ^{1}H NMR (300MHz , $CDCl_3$) δ 4.73 (t, J = 5.7 Hz, 1H), 3.40 (t, J = 6.9 Hz, 2H), 1.94–1.84 (m, 2H), 1.79–1.60 (m, 6H), 1.22 (s, 6H), 1.18 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 90.9, 74.7, 35.5, 35.3, 33.7, 30.0, 28.7, 25.8. HRMS (ESI): *m/z* calcd for $C_{12}H_{23}O_2$ $[M-Br]^+$ 199.1698, found 199.1693.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx.

^{1}H and ^{13}C NMR spectra for **3** (PDF)

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The authors declare no competing financial interest.

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