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FULL PAPER

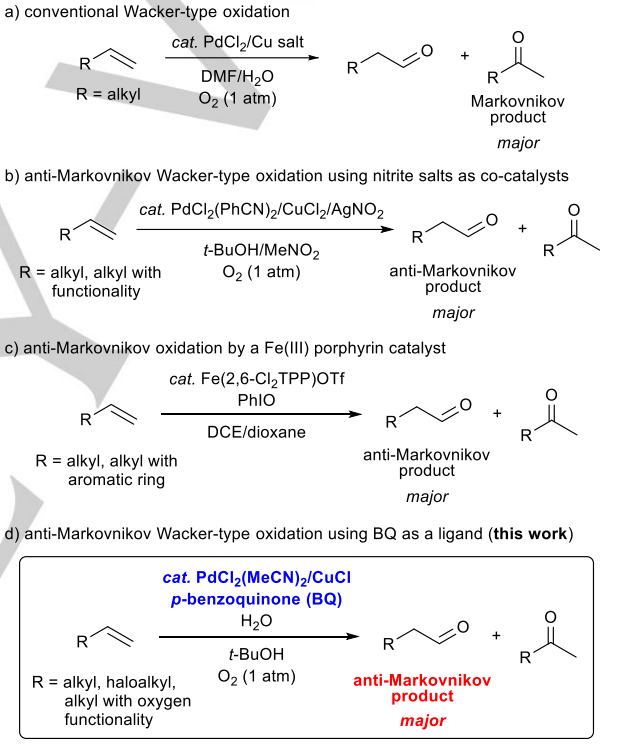
Palladium/Copper-catalyzed Oxidation of Aliphatic Terminal Alkenes to Aldehydes Assisted by *p*-Benzoquinone

Saki Komori,[a] Yoshiko Yamaguchi,[a] Yuka Murakami,[a] Yasutaka Kataoka,[a] and Yasuyuki Ura*[a]

Abstract: The development of an anti-Markovnikov Wacker-type oxidation for simple aliphatic alkenes is a significant challenge. Herein, a variety of aldehydes can be selectively obtained from various unbiased aliphatic terminal alkenes using $PdCl_2(MeCN)_2$/CuCl in the presence of *p*-benzoquinone (BQ) under mild reaction conditions. Isomerization of the terminal alkene to the internal alkene was suppressed via slow addition of the starting material to the reaction mixture. In addition to the Pd catalyst, CuCl and BQ were essential in order to obtain the anti-Markovnikov product with high selectivity. Terminal alkenes bearing a halogen substituent afforded their corresponding aldehydes with high anti-Markovnikov selectivity. The halogen acts as a directing group in the reaction. DFT calculations indicate that a μ-chloro Pd(II)–Cu(I) bimetallic species with BQ coordinated to Cu is the catalytically active species in the case of a terminal alkene without a directing group.

Introduction

The palladium/copper-catalyzed Wacker-type oxidation is a well-known and efficient method used to prepare carbonyl compounds from alkenes.[1] The reaction usually proceeds in a Markovnikov manner to afford methyl ketones from terminal alkenes (Scheme 1a). The development of the Wacker-type oxidation with anti-Markovnikov selectivity has been a longstanding synthetic target.[2] Alkenes with oxygen or nitrogen atom directing groups[1f, 1k, 2a, 3] and aromatic alkenes[2a-c, 4] are known to afford aldehydes with high selectivity. Alkenes with fluorine substituents such as 4,4,4-trifluoro-1-butene also preferentially form their corresponding aldehydes due to their strong inductive effect.[5] On the other hand, the conversion of simple aliphatic alkenes into aldehydes is still difficult.[6] Feringa has reported that a catalytic system consisting of $(MeCN)_2PdClNO_2$/$CuCl_2$/tertiary alcohol/O_2 can be used to prepare aldehydes from simple aliphatic terminal alkenes in low yield, but with up to 70% aldehyde selectivity.[6a] The importance of the steric effect of the alcohol solvents to achieve high selectivity was demonstrated by Hosokawa et al. using a $PdCl_2(MeCN)_2$/$CuCl_2$/O_2 system. Although 84% selectivity was attained by the use of 1-decene and *t*-BuOH, the total yield of aldehyde and ketone was still low (7%).[6c] Grubbs et al. developed an efficient $PdCl_2(PhCN)_2$/$CuCl_2$/$AgNO_2$/O_2 system in which the nitrite salt acts as a co-catalyst (Scheme 1b). Aldehydes were obtained in up to 70% yield with up to 90% selectivity from several aliphatic alkenes.[7] In this reaction, the key intermediate was proposed to involve a NO_2 radical acting as a ligand for the Pd catalyst. Other than Wacker-type oxidation, Che et al. reported a highly selective anti-Markovnikov oxidation catalyzed by Fe(2,6-Cl_2TPP)OTf (2,6-Cl_2TPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin) in the presence of PhIO as an oxidant (Scheme 1c).[8] This reaction proceeds via a tandem epoxidation–isomerization pathway. However, alternative approaches still need to be developed despite these previously reported methods.



Scheme 1. Markovnikov and anti-Markovnikov oxidation of aliphatic terminal alkenes used to prepare ketones and aldehydes.

In the present work, we have adopted a different catalytic system based on the Wacker-type oxidation using $PdCl_2(MeCN)_2$/CuCl/*p*-benzoquinone, to achieve high anti-Markovnikov selectivity for simple aliphatic alkenes (Scheme 1d). We have previously investigated the palladium-catalyzed anti-Markovnikov oxidation of terminal alkenes including the conversion of aromatic alkenes to aldehydes,[4a] aromatic alkenes, allyl ethers, and 1,5-dienes to terminal acetals,[9] and aliphatic alkenes to terminal acetals.[10] A catalytic system consisting of $PdCl_2(MeCN)_2$/CuCl/electron-deficient cyclic alkene/O_2 was discovered during these investigations, which exhibited good anti-Markovnikov selectivity. In the present work, we propose a μ-chloro Pd(II)-Cu(I) bimetallic complex as the catalytically active species in the reaction based on both experimental results and DFT calculations. BQ acts as a ligand coordinated to Cu(I), which

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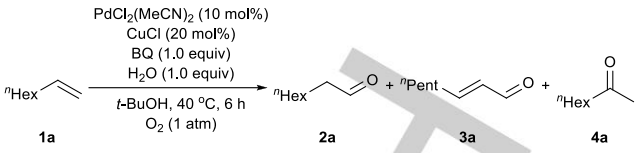
withdraws electrons from the Pd(II) center via Cu(I) to enhance the anti-Markovnikov selectivity. The steric hindrance between *t*-butyl group derived from *t*-BuOH and the alkyl group derived from the aliphatic alkene at the step after nucleophilic attack of *t*-BuOH to the coordinated alkene on Pd is also the factor to regulate the regioselectivity toward the anti-Markovnikov product.

Results and Discussion

1-Octene (**1a**) was treated with catalytic amounts of $PdCl_2(MeCN)_2$ (10 mol%) and CuCl (20 mol%) in the presence of BQ (1.0 equiv) and H_2O (1.0 equiv) in *t*-BuOH at 40 °C under 1 atm of O_2 (Table 1, Entry 1; also see Table S1 for further details). Both **1a** and H_2O were added via syringe pumps (over 5 h) to the reaction mixture. Under these conditions, octanal (**2a**) and *trans*-2-octenal (**3a**) were obtained in 34% and 20% yield (anti-Markovnikov products), respectively along with 2-octanone (**4a**) in 29% yield (Markovnikov product). The aldehyde selectivity ((**2a**+**3a**)/(**2a**+**3a**+**4a**)) was 65%. The α,β-unsaturated aldehyde **3a** was formed via the dehydrogenation of **2a** catalyzed by palladium in the presence of BQ as a hydrogen acceptor (vide infra).[11] Some bulky secondary and tertiary alcohols were examined as the reaction solvent because steric hindrance was expected to control the regioselectivity of the reaction to preferentially form the anti-Markovnikov product.[6c, 9a, 12] *t*-BuOH was found to be the optimal solvent (Table S2). As an additive, BQ gave the best results among the electron-accepting ligands examined in terms of the total yield of aldehydes (see Table S3). These included BQ derivatives, maleic anhydride, maleimide, acyclic α,β-unsaturated carbonyl compounds, and CO, some of which are known to enhance the catalytic activity and/or anti-Markovnikov selectivity in the Pd/Cu-catalyzed aerobic oxidation of aromatic alkenes to aldehydes[4a] and terminal acetals,[9b] as well as the oxidation of aliphatic alkenes to terminal acetals.[10] The absence of H_2O or the use of 2.0 equiv. of H_2O decreased the aldehyde selectivity (Entries 2 and 3). Isomerization of **1a** into its corresponding internal alkenes occurred when **1a** was added without the use of a syringe pump (total yield of the internal alkenes was 6% and 29% in Entries 1 and 4, respectively; see Table S1) and the selectivity of the reaction was decreased.[10] Thus, the high concentration of **1a** in the reaction mixture leads to the isomerization. The addition of H_2O without the use of a syringe pump also lowered the selectivity (Entry 5). The addition of both **1a** and H_2O without the use of syringe pumps resulted in a low total yield of **2a**, **3a**, and **4a** with low selectivity (Entry 6). The absence of CuCl resulted in low selectivity (30%, Entry 7).[13] Both the total yield of **2a** and **3a**, and the aldehyde selectivity were good when 20 mol% of CuCl was used when compared to 10 or 30 mol% CuCl (Entries 1, 8, and 9). In Entry 9, the mass balance was significantly poor (100% conversion of **1a** and 63% total yield of products including internal alkenes).[14] The absence of BQ also resulted in low selectivity (29%, Entry 10), which indicated that both CuCl and BQ are required to achieve high selectivity in the reaction. Upon increasing the amount of BQ to 2.0 equiv., the selectivity was increased up to 69% (Entry 11). The reactions performed under an Ar or air atmosphere also gave comparable results to those obtained in Entry 1, albeit the yields of **3a** were slightly low (Entries 12 and 13). The results shown in Entry 12 clearly indicate that BQ also acts as an oxidant for palladium in addition to $CuCl/O_2$ (Entry 10). The use of $CuCl_2$ instead of CuCl under an Ar atmosphere decreased the yield of **2a**, **3a**, and **4a** (the yield of the internal alkenes increased to 27% in Entry 14 when compared to 9% in Entry 12; see Table S1), albeit the selectivity was comparable in Entries 14 and 12 (67 and 63%, respectively). To further examine the difference between $CuCl_2$ and CuCl, one-tenth amounts (0.05 mmol, 10 mol% vs BQ) of **1a** and H_2O were subjected to the reaction conditions shown in Entries 14 and 12 (**1a** and H_2O were added without the use of syringe pumps) and the reactions were followed using ^1H NMR spectroscopy (Scheme S1, Figure S1). Although the former system gave **4a** in 1.5% yield (with a trace amount (<0.3%) of **2a** formed), the latter system afforded **2a** and **4a** in ca. 4 and 6% yield, respectively after 70 min. Thus, $CuCl_2$ was not effective in the anti-Markovnikov and Markovnikov oxidation. In Entry 14, $CuCl_2$ is gradually reduced in situ to CuCl upon reaction with Pd(0) and the as-formed CuCl will facilitate the oxidation when combined with Pd(II) and BQ.

Various aliphatic terminal alkenes were examined under the optimal conditions (Table 2). When α,β-unsaturated aldehyde **3** was formed along with saturated aldehyde **2**, catalytic hydrogenation using $(Cy_3P)_2Rh(H)Cl_2$[15] was applied to the reaction mixture to selectively hydrogenate **3** into **2** prior to isolating **2**. All the carbonyl compounds were isolated as their 2,4-

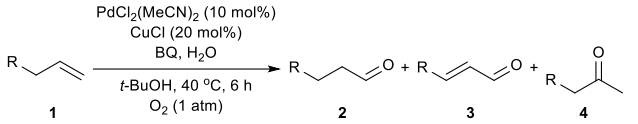
Table 1. Optimization of the reaction conditions.[a]



Entry	Change from standard conditions	Yield (%)[b]			Aldehyde Selectivity (%)[c]
		2a	**3a**	**4a**	
1	None	34	20	29	65
2	No H_2O	25	3	32	47
3	H_2O (2.0 equiv)	31	8	49	44
4[d]	No slow addition of **1a**	22	9	37	46
5[e]	No slow addition of H_2O	32	13	45	50
6[d,e]	No slow addition of **1a** and H_2O	15	10	29	46
7	No CuCl, no O_2 (under Ar)	15	5	46	30
8	CuCl (10 mol%)	29	12	44	48
9	CuCl (30 mol%)	31	9	20	67
10	No BQ	22	3	61	29
11	BQ (2.0 equiv)	45	13	26	69
12	No O_2 (under Ar)	35	12	28	63
13	Under air	35	13	31	61
14	$CuCl_2$ instead of CuCl, no O_2 (under Ar)	22	9	15	67

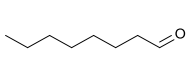
[a] Reaction conditions: **1a** (0.50 mmol), $PdCl_2(MeCN)_2$ (0.050 mmol), CuCl (0.10 mmol), BQ (0.50 mmol), H_2O (0.50 mmol), *t*-BuOH (2.0 mL), O_2 (1 atm), 40 °C, 6 h. **1a** and H_2O were added over 5 h via syringe pumps, and the reaction mixture was stirred for an additional 1 h (6 h in total). [b] Determined using ^1H NMR spectroscopy. [c] Selectivity = (**2a**+**3a**)/(**2a**+**3a**+**4a**). [d] **1a** was added without the use of a syringe pump. [e] H_2O was added without the use of a syringe pump.

Table 2. Anti-Markovnikov oxidation of aliphatic alkenes.[a]

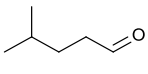


1 2 3 4

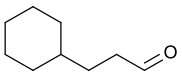
yield of **2** / yield of **3** / yield of **4** / aldehyde selectivity (%)[b]



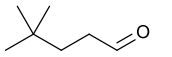
2a[c]
45(47)/13/26(26)/69



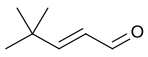
2b[c]
50(45)/18/24(23)/74



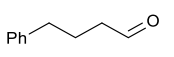
2c[c]
41(50)/21/26(25)/70



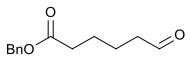
2d
41(40)/10(8)/10(10)/84



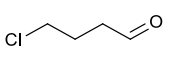
3d[d]
4/65(64)/14(7)/83



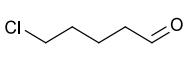
2e[c]
44(45)/11/17(10)/76



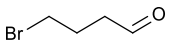
2f[c]
48(54)/15/22(22)/74



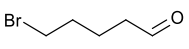
2g[e]
71(63)/0/4/95



2h[e]
56(55)/7(7)/10(10)/86



2i[e]
71(67)/4/3/96



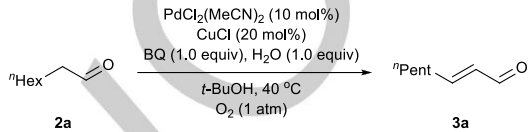
2j[e]
59(54)/6/17/79

[a] Reaction conditions: **1** (0.50 mmol), $PdCl_2(MeCN)_2$ (0.050 mmol), CuCl (0.10 mmol), BQ (0.50 or 1.0 mmol), H_2O (0.50 or 0.75 mmol), *t*-BuOH (2.0 mL), O_2 (1 atm), 40 °C, 6 h. **1** and H_2O were added over 5 h via syringe pumps, and the reaction mixture was stirred for an additional 1 h (6 h in total). [b] Determined using ^1H NMR spectroscopy. The values in the parentheses are the isolated yields for the corresponding 2,4-dinitrophenylhydrazone derivatives. Selectivity = (**2**+**3**)/(**2**+**3**+**4**). [c] Isolation of **2** was performed after hydrogenation of the reaction mixture (**3** was hydrogenated to **2**). [d] 48 h in total (**1** and H_2O were added over 5 h). [e] 3 h in total (**1** was added without the use of a syringe pump and H_2O was added over 2 h).

dinitrophenylhydrazone derivatives. Aliphatic alkenes containing a branched group at C4, such as 4-methyl-1-pentene (**1b**) and 3-cyclohexyl-1-propene (**1c**) gave 4-methylpentanal (**2b**) and 3-cyclohexylpropanal (**2c**) as the main product with 74 and 70% aldehyde selectivity, respectively. Bulky 4,4-dimethyl-1-pentene (**1d**) gave 4,4-dimethylpentanal (**2d**) with higher aldehyde selectivity than **1a**–**c**. In the case of **1d**, *trans*-4,4-dimethyl-2-pentenal (**3d**) was obtained selectively by prolonging the reaction time to 48 h. 4-Phenyl-1-butene (**1e**) and benzyl 5-hexenoate (**1f**) were also applicable to afford **2e** and **2f** with good selectivity. Haloalkenes were also employed as substrates in the reaction. Among them, 4-chloro-1-butene (**1g**) and 4-bromo-1-butene (**1i**) afforded their corresponding saturated aldehydes **2g** and **2i** with high selectivity (>95%). In these cases, the halogen groups act as directing groups and coordinate to the palladium center (vide infra).[10] The isomerization of terminal haloalkenes to internal alkenes was suppressed, even without the slow addition of **1**, which was attributed to the directing group.[10] The formation of α,β-unsaturated aldehyde **3** was effectively suppressed in the oxidation of haloalkenes due to the shorter reaction time. 5-Chloro-1-pentene (**1h**) and 5-bromo-1-pentene (**1j**) also afforded saturated aldehydes **2h** and **2j** with higher selectivity than that observed for **1a**.

To clarify the pathway for the formation of α,β-unsaturated aldehyde **3**, aldehyde **2a** was subjected to the same reaction conditions as those used in the anti-Markovnikov oxidation. As a result, **2a** was converted into **3a** in moderate yield (Table 3, Entry 1). Although the dehydrogenation proceeded in the absence of O_2 (Entry 2), only a 6% yield of **3a** was formed in the absence of BQ after 24 h (Entry 3). Thus, BQ acts as a hydrogen acceptor under these conditions. This type of Pd-catalyzed dehydrogenation of carbonyl compounds to their corresponding α,β-unsaturated carbonyl compounds has been extensively investigated.[11]

Table 3. Pd-catalyzed dehydrogenation of **2a** to **3a**.[a]



2a **3a**

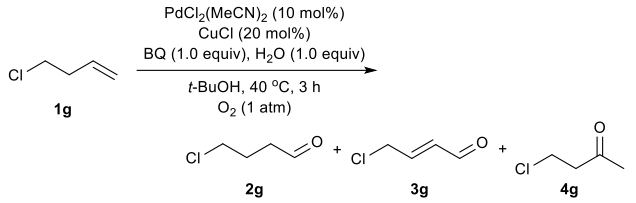
Entry	Change from standard conditions	Time (h)	Conv. of **2a** (%)[b]	Yield of **3a** (%)[b]
1	None	3	26	15
		24	78	49
2	No O_2 (under Ar)	3	20	14
		24	79	53
3	No BQ	3	19	0
		24	30	6

[a] Reaction conditions: **2a** (0.50 mmol), $PdCl_2(MeCN)_2$ (0.050 mmol), CuCl (0.10 mmol), BQ (0.50 mmol), H_2O (0.50 mmol), *t*-BuOH (2.0 mL), O_2 (1 atm), 40 °C. [b] Determined using ^1H NMR spectroscopy.

Subsequently, we examined the effect of CuCl and BQ on the aldehyde selectivity during the oxidation of haloalkene **1g** (Table 4; see Table S4 for further details). Again, the selectivity decreased in the absence of either CuCl or BQ (Entry 1 vs Entries 2 and 3), albeit the difference was not as large as that observed in the oxidation of **1a** (Table 1, Entry 1 vs Entries 7 and 10). The yield of **2g** was relatively low in Entries 2 and 3. Haloalkenes **1i** and **1j** were also examined in the same manner and a similar tendency was observed (Tables S5 and S6).

DFT calculations were performed to provide insight on the catalytically active species that regulate the regioselectivity of the reaction. Nucleophilic attack of *t*-BuOH to the coordinated alkene is considered as a key step determining the regioselectivity. Geometry optimization was performed using B3LYP/LANL2DZ for Pd, 6-311G(d) for Cu, and 6-31G(d) for all other atoms, and the frequency calculations were performed using M06/SDD for Pd, 6-311G(d) for Cu, and 6-311+G(d,p) for all other atoms, respectively. Propene was chosen as an aliphatic terminal alkene for simplicity. The Gibbs free energies (ΔG, kcal mol^{-1}) for the possible propene-coordinated Pd(II) or μ-chloro Pd(II)-Cu(I) heterobimetallic complexes (**A**–**F**) and their corresponding complexes formed after either Markovnikov ($\mathbf{G_M}$–$\mathbf{L_M}$) or anti-Markovnikov ($\mathbf{G_{AM}}$–$\mathbf{L_{AM}}$) nucleophilic attack of *t*-BuOH to the coordinated alkene were compared (Figure 1). MeCN or *t*-BuOH-coordinated Pd(II) complexes (**B** and **C**) were more stable than η^2-BQ-coordinated complex **A** by 8.4 and 4.6 kcal mol^{-1}, respectively, due to the low electron density on these Pd(II) centers and weak π-back donation to BQ. The energy differences $\Delta\Delta G_{\mathbf{G_{AM}\text{-}G_M}}$, $\Delta\Delta G_{\mathbf{H_{AM}\text{-}H_M}}$, and $\Delta\Delta G_{\mathbf{I_{AM}\text{-}I_M}}$ were 0.1, 7.0, and 5.7 kcal mol^{-1}, respectively, which indicates that BQ can stabilize the relatively electron-rich

Table 4. The effect of CuCl and BQ on the aldehyde selectivity during the oxidation of **1g**.[a]



Entry	Change from standard conditions	Conv. of **1g** (%)[b]	Yield (%)[b]			Aldehyde Selectivity (%)[c]
			2g	**3g**	**4g**	
1	None	96	72	2	4	95
2	No CuCl, no O_2 (under Ar)	90	63	1	7	90
3	No BQ	95	53	0	7	88

[a] Reaction conditions: **1g** (0.50 mmol), $PdCl_2(MeCN)_2$ (0.050 mmol), CuCl (0.10 mmol), BQ (0.50 mmol), H_2O (0.50 mmol), *t*-BuOH (2.0 mL), O_2 (1 atm), 40 °C, 3 h. **1** was added without the use of a syringe pump. H_2O was added over 2 h via a syringe pump, and the reaction mixture was stirred for an additional 1 h (3 h in total). [b] Determined using ^1H NMR spectroscopy. The reported values are the averages of two runs (see Table S4). [c] Selectivity = (**2g**+**3g**)/(**2g**+**3g**+**4g**).

Pd(II) species bearing a secondary alkyl ligand (**G_{AM}**) more than MeCN (**H_{AM}**) and *t*-BuOH (**I_{AM}**) due to its strong π-accepting ability. μ-Chloro Pd(II)-Cu(II) species are often considered as the catalytically active species in Wacker-type oxidation.[6a, 16] In addition, a polymeric complex $[(PdCl_2)_2CuCl_2(DMF)_4]_n$ incorporating μ-chloro Pd(II)-Cu(II) moieties has been isolated and revealed to have catalytic activity in the Wacker-type oxidation.[17] μ-Chloro Pd(II)-Cu(I) bimetallic complexes **D**–**F** containing either η^2-BQ, MeCN, or *t*-BuOH on Cu as a ligand were more stable than monometallic Pd complexes **A**–**C** with complex **D** the most stable among **D**–**F**. Complex **D** has a trigonal planar geometry around Cu (Figure 2), whereas **E** and **F** converged to linear geometries with Pd···Cu distances slightly shorter than the sum of van der Waals' radii of Pd (1.63 Å) and Cu (1.4 Å)[18] (Pd···Cu distances: 2.824 Å for **E** and 2.748 Å for **F**; Cl–Cu–X angles: 176.93° for **E** (X = N) and 179.03° for **F** (X = O); Pd–Cl–Cu angles: 72.66° for **E** and 69.89° for **F**) despite starting the optimizations from initial structures similar to **D**. **J_M** and **J_{AM}** were also the most stable among **J_M**–**L_M** and **J_{AM}**–**L_{AM}**, respectively. The energy differences $\Delta\Delta G_{J_{AM}\text{-}J_M}$, $\Delta\Delta G_{K_{AM}\text{-}K_M}$, and $\Delta\Delta G_{L_{AM}\text{-}L_M}$ were –0.9, 3.8, and 1.0 kcal mol^{-1}, respectively. This tendency was similar to that observed for $\Delta\Delta G_{G_{AM}\text{-}G_M}$, $\Delta\Delta G_{H_{AM}\text{-}H_M}$, and $\Delta\Delta G_{I_{AM}\text{-}I_M}$, indicating that BQ withdraws electrons from Pd via Cu. Thus, complex **D** is the most likely catalytically active species among **A**–**F**. Several Cu(I)-BQ complexes have been reported[19] and with both CuCl and BQ essential for high aldehyde selectivity in the anti-Markovnikov Wacker-type oxidation of **1a** (see Table 1), it is also reasonable to propose complex **D** as the catalytically active species based on these experimental findings. However, it should be noted that the formation of aldehydes also occurs even without CuCl albeit low selectivity (see Table 1, Entry 7), and hence other mechanisms without involvement of **D** may also be operative.

The pathways for Markovnikov and anti-Markovnikov selectivity starting from **D** to their corresponding complexes after β-H elimination (**P_M** and **P_{AM}**) were then calculated (Figure 3). Each pathway includes the nucleophilic attack of *t*-BuOH to the coordinated alkene, conformational change, dissociation of HCl, C_α–C_β bond rotation, and β-H elimination. In the transition states obtained for the nucleophilic attack step, internal attack (Markovnikov attack, **TS(D–J_M)**) was more favorable than terminal attack (anti-Markovnikov attack, **TS(D–J_{AM})**) by 2.7 kcal mol^{-1}.

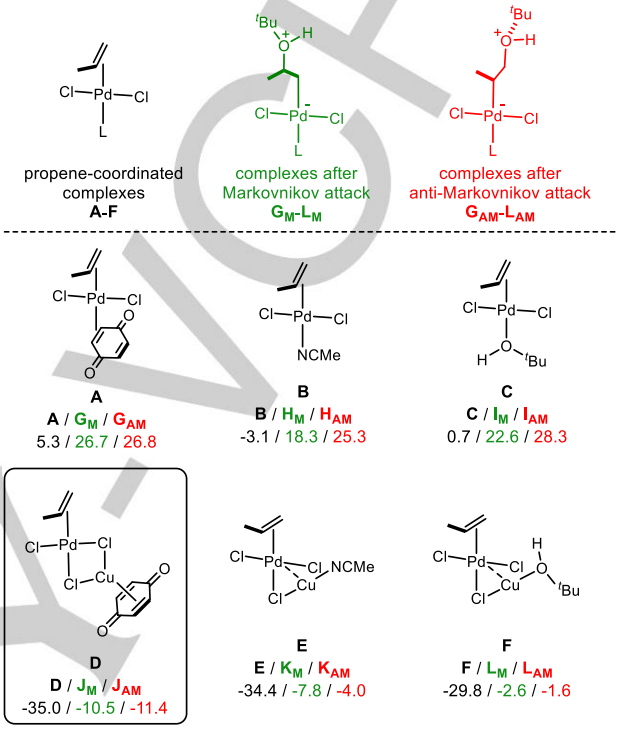


Figure 1. A comparison of the Gibbs free energy (Δ*G*, kcal mol^{-1}) calculated for the possible propene-coordinated Pd or Pd-Cu complexes (**A**–**F**, black) and their corresponding complexes formed after either Markovnikov (**G_M**–**L_M**, green) or anti-Markovnikov (**G_{AM}**–**L_{AM}**, red) nucleophilic attack of *t*-BuOH to the coordinated alkene. Δ*G* for $PdCl_2(MeCN)_2$ + propene + BQ + CuCl + 2 *t*-BuOH was defined as 0 kcal mol^{-1}.

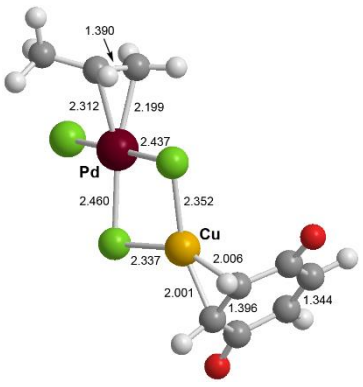


Figure 2. The optimized structure of **D**. Atomic distances are reported in Å.

After nucleophilic attack, conformational changes afford relatively stable structures **M_M** and **M_{AM}**, where the protic H and Cl atoms are positioned proximally. HCl is then dissociated from **M_M** and **M_{AM}** to generate *O*-coordinated complexes **N_M** and **N_{AM}**, respectively. The C_α–C_β bond rotation step was found to exhibit

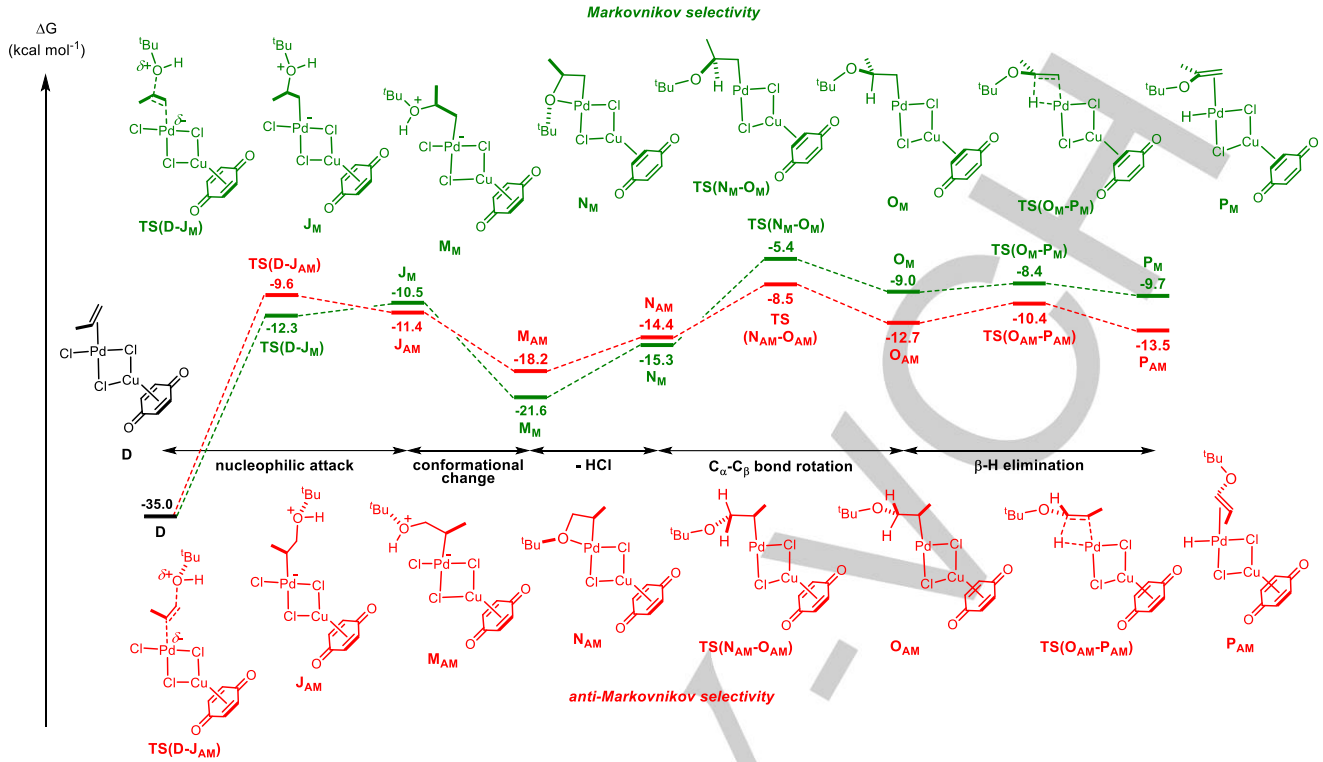


Figure 3. Energy profiles (ΔG, kcal mol^{-1}) for the reaction pathway from **D** to $\mathbf{P_M}$ and $\mathbf{P_{AM}}$ via Markovnikov and anti-Markovnikov nucleophilic attack, respectively. ΔG for $PdCl_2(MeCN)_2$ + propene + BQ + CuCl + 2 *t*-BuOH is defined as 0 kcal mol^{-1}.

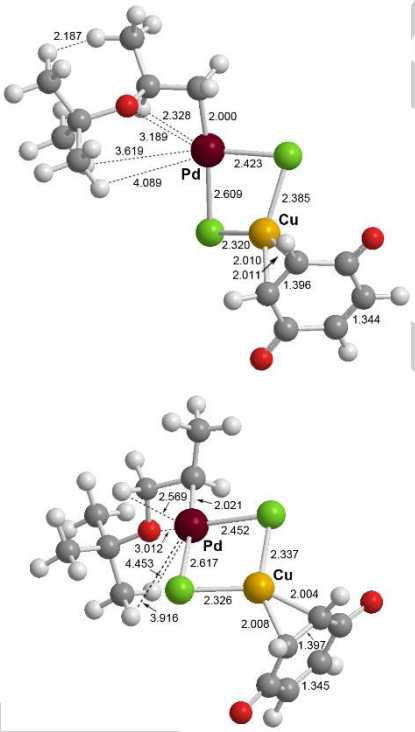


Figure 4. The optimized structures of **TS($\mathbf{N_M}$–$\mathbf{O_M}$)** (top) and **TS($\mathbf{N_{AM}}$–$\mathbf{O_{AM}}$)** (bottom). Atomic distances are reported in Å. The Pd–C_α–C_β–H_β dihedral angles for **TS($\mathbf{N_M}$–$\mathbf{O_M}$)** and **TS($\mathbf{N_{AM}}$–$\mathbf{O_{AM}}$)** were 27.91° and 47.32°, respectively.

the highest energy barrier in both pathways (29.6 kcal mol^{-1} between **D** and **TS($\mathbf{N_M}$–$\mathbf{O_M}$)**; 26.5 kcal mol^{-1} between **D** and **TS($\mathbf{N_{AM}}$–$\mathbf{O_{AM}}$)**). Thus, this step will control the regioselectivity toward the anti-Markovnikov product rather than the nucleophilic attack step. The energy barrier between $\mathbf{N_M}$ and **TS($\mathbf{N_M}$–$\mathbf{O_M}$)** (9.9 kcal mol^{-1}) is considerably higher than that between $\mathbf{N_{AM}}$ and **TS($\mathbf{N_{AM}}$–$\mathbf{O_{AM}}$)** (5.9 kcal mol^{-1}). The optimized structures of **TS($\mathbf{N_M}$–$\mathbf{O_M}$)** and **TS($\mathbf{N_{AM}}$–$\mathbf{O_{AM}}$)** are shown in Figure 4. In **TS($\mathbf{N_M}$–$\mathbf{O_M}$)**, the steric hinderance observed between *t*-butyl group and the methyl group on the C_β atom is responsible for destabilization when compared to $\mathbf{N_M}$ (the shortest H···H atomic distances: 2.187 Å for **TS($\mathbf{N_M}$–$\mathbf{O_M}$)** and 2.532 Å for $\mathbf{N_M}$). On the other hand, there is no such steric repulsion in $\mathbf{N_{AM}}$ and **TS($\mathbf{N_{AM}}$–$\mathbf{O_{AM}}$)**. After these transition states, $\mathbf{O_M}$ and $\mathbf{O_{AM}}$ which involve agostic interaction are formed, and the subsequent β-H elimination affords alkenyl ether-coordinated hydride complexes $\mathbf{P_M}$ and $\mathbf{P_{AM}}$, respectively. Because the energy barrier for Markovnikov selectivity is quite high as mentioned above (29.6 kcal mol^{-1}), the Markovnikov products would be formed via the nucleophilic attack of H_2O instead of *t*-BuOH to the coordinated alkene in practice.

On the other hand, in the case of haloalkenes, especially **1g** and **1i**, the aldehyde selectivity was very high (95 and 96%, see Table 2), which indicates that the chloro and bromo groups act as directing groups in the reaction. Thus, a Pd(II) complex coordinated by 4-chloro-1-butene in a bidentate manner was postulated (**Q**) and the Markovnikov and anti-Markovnikov nucleophilic attack steps were calculated (Figure 5). Because the absence of CuCl or BQ does not significantly decrease the aldehyde selectivity in the anti-Markovnikov Wacker-type oxidation of **1g** (see Table 4), CuCl and BQ were not included in

Q. The energy barrier for anti-Markovnikov attack (**Q** to **R_{AM}**) was smaller than that calculated for Markovnikov attack (**Q** to **R_M**) by 0.6 kcal mol^{-1} ($\Delta\Delta G^{\ddagger}$) due to more stable five-membered metallacycle being formed in **TS(Q-R_{AM})** compared to the six-membered metallacycle formed in **TS(Q-R_M)**. Although several pathways after the nucleophilic attack step to β-H elimination are possible, these calculations were not performed due to their complexity. The difference in the ring size of the metallacycles can explain the high aldehyde selectivity observed in the case of haloalkenes.

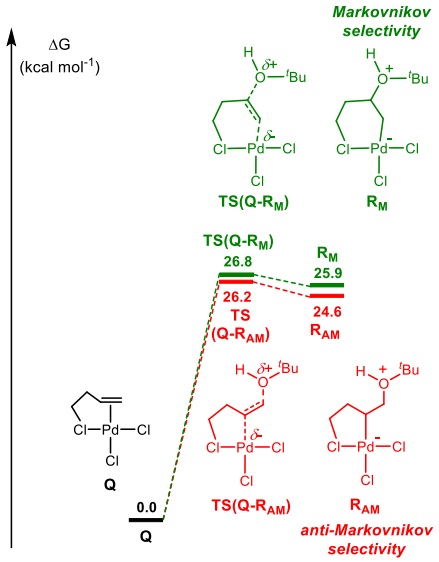
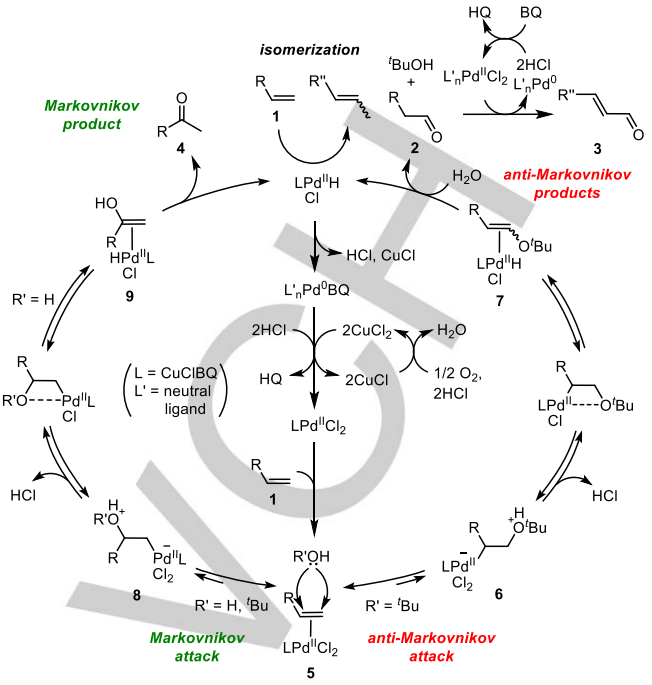


Figure 5. Energy profile (Δ*G*, kcal mol^{-1}) for the pathways from **Q** to **R_M** and **R_{AM}** via Markovnikov and anti-Markovnikov nucleophilic attack. Δ*G* for **Q** + *t*-BuOH is defined as 0 kcal mol^{-1}.

A proposed mechanism for the formation of aldehydes and ketones from aliphatic terminal alkenes in the absence of a directing group is shown in Scheme 2. Terminal alkene **1** coordinates to the $LPdCl_2$ species (L = CuClBQ) to afford **5**. *t*-BuOH then attacks terminal carbon atom of the coordinated alkene to afford secondary alkyl palladate **6**. Elimination of HCl, C_α–C_β bond rotation, and β-H elimination affords alkenyl *t*-butyl ether-coordinated Pd complex **7**. H_2O attacks the alkenyl *t*-butyl ether in **7** to provide aldehyde **2** and *t*-BuOH. The attack of H_2O to **7** rather than dissociation of the alkenyl *t*-butyl ether from **7** and subsequent hydrolysis of the ether rationalizes the experimental results that the reaction was retarded and free alkenyl *t*-butyl ether was not observed when the oxidation was performed without the addition of H_2O (see Table S1, Entry 2). Dehydrogenation of **2** by Pd/BQ affords α,β-unsaturated aldehyde **3**. In this reaction, Pd(II) is reduced to Pd(0) along with elimination of HCl again, and BQ reoxidizes Pd(0) to Pd(II).[11] On the other hand, nucleophilic attack of H_2O or *t*-BuOH on the internal carbon atom of the coordinated alkene in **5** affords primary alkyl palladate **8**. Methyl ketone **4** is formed via enol-coordinated Pd complex **9** in the case of the attack of H_2O (R' = H). Thus, although a certain concentration of H_2O is necessary to promote the formation of aldehyde **2** as mentioned above, high concentration of H_2O results in low aldehyde selectivity as observed in Entries 3, 5 and 6 in Table 1 (the use of 2.0 equiv. of H_2O or no slow addition of



Scheme 2. Proposed mechanism for aliphatic terminal alkenes in the absence of a directing group.

H_2O). Although both aldehydes **2a** and **3a** and ketone **4a** were formed even without the addition of H_2O (see Table 1, Entry 2), H_2O would be gradually generated via the elimination from *t*-BuOH catalyzed by an acid. Isomerization of terminal alkene **1** into internal alkenes is catalyzed by the Pd–H species formed in situ, and thus, keeping terminal alkene **1** at low concentration in the reaction mixture suppresses the isomerization. Reductive elimination of HCl from the Pd–H species affords a Pd(0) species, where BQ coordinates to Pd due to the stronger π-back donation of Pd(0) compared to Pd(II), to suppress the aggregation to Pd black. The Pd(0) species is re-oxidized to Pd(II) by either BQ/HCl or $CuCl_2$. O_2/HCl oxidizes CuCl to $CuCl_2$.

Conclusion

We have developed a Pd/Cu-catalyzed anti-Markovnikov Wacker-type oxidation of aliphatic terminal alkenes to form their corresponding aldehydes. As for simple alkenes, CuCl and BQ were found to be indispensable for high aldehyde selectivity. Slow addition of the terminal alkene efficiently suppressed its isomerization into the internal alkenes and increased the aldehyde selectivity. Slow addition of H_2O also improved the selectivity. Bulky 4,4-dimethyl-1-pentene selectively afforded an α,β-unsaturated aldehyde after a prolonged reaction time. Dehydrogenation from the saturated aldehyde to unsaturated aldehyde was also catalyzed by Pd in the presence of BQ, which acts as a hydrogen acceptor. On the other hand, in the case of haloalkenes, a higher aldehyde selectivity was observed when compared to the other alkenes studied, which was attributed to the halogen substituent acting as a directing group. The isomerization of the alkene was also suppressed due to the coordination of the halogen group. Thus, the slow addition of haloalkenes was not required.

DFT calculations indicated that a μ-chloro Pd(II)-Cu(I) bimetallic complex with BQ coordinated to Cu in an η^2 manner is the catalytically active species in the case of terminal alkenes without a directing group. The coordination of BQ decreases the electron density of Pd via Cu to facilitate the nucleophilic attack to the alkene. The anti-Markovnikov selectivity was also enhanced by stabilizing the secondary alkyl Pd intermediate more efficiently than the primary alkyl Pd intermediate. The C_α–C_β bond rotation step which precedes β-H elimination controls the regioselectivity of the reaction toward the anti-Markovnikov product (the $\Delta\Delta G^‡$ is 3.1 kcal mol^{-1}) rather than the nucleophilic attack step due to the difference in the steric hindrance between the *t*-butyl group derived from *t*-BuOH and the methyl group derived from propene in the transition states. For haloalkenes, the nucleophilic attack step controls the regioselectivity (the $\Delta\Delta G^‡$ is 0.6 kcal mol^{-1}). The difference in the ring size of the metallacycles formed in the transition states is the origin of the energy difference.

We envisage that the findings obtained in the present work will promote further development of the highly efficient and selective anti-Markovnikov Wacker-type oxidation of aliphatic terminal alkenes and related reactions.

Experimental Section

General Information. Unless otherwise indicated, all reactions were performed under an oxygen atmosphere (1 atm). $PdCl_2(MeCN)_2$,[20] 5-hexenyl benzyl ether,[21] 5-hexenoic acid benzyl ester,[22] and 5-chloro-1-pentene[23] were prepared as described in the literature. *t*-BuOH was purchased from Nacalai tesque Co. Ltd. and was purified by distillation using CaH_2. 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 (δ) were expressed relative to $SiMe_4$. High-resolution mass spectra were recorded on a JEOL JMS-T100LC spectrometer (ESI-TOF MS) with positive ionization mode. Elemental analysis was obtained using a J-SCIENCE LAB JM-10 analyzer.

General Procedure for the Synthesis of 2. Method A: To a reaction vessel, CuCl (9.9 mg, 0.10 mmol), $PdCl_2(MeCN)_2$ (13 mg, 0.05 mmol), BQ (108 mg, 1.0 mmol) were added, and O_2 was purged. To the mixture, *t*-BuOH (2 mL) was added and the reaction mixture was stirred at 40 °C. Immediately, a terminal alkene (0.50 mmol) and H_2O (9.0 μL, 0.50 mmol) were added slowly over 5 h by syringe pumps, and the reaction mixture was stirred for an additional 1 h (6 h in total). The reaction mixture was quenched by addition of *m*-xylene (1 mL). To another reaction vessel, the filtrate, *m*-xylene (1 mL), H_2O (0.2 mL), $(Cy_3P)_3Rh(H)Cl_2$ (7.4 mg, 0.01 mmol) were added, and H_2 was bubbled and purged. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched by addition of hexane (1.5 mL). The filtrate was added to another reaction vessel and products were derivatized to 2,4-dinitrophenylhydrazones using a literature procedure.[4b] The crude material was purified by silica gel column chromatography. Hydrazones were obtained as a mixture of *E* and *Z* isomers. **Method B:** To a reaction vessel, CuCl (9.9 mg, 0.10 mmol), $PdCl_2(MeCN)_2$ (13 mg, 0.05 mmol), BQ (108 mg, 1.0 mmol) were added, and O_2 was purged. To the mixture, *t*-BuOH (2 mL) was added and the reaction mixture was stirred at 40 °C. Immediately, a terminal alkene (0.50 mmol) and H_2O (9.0 μL, 0.50 mmol) were added slowly over 5 h by syringe pumps, and the reaction mixture was stirred for an additional 1 h or 43 h (6 h or 48 h in total). The reaction mixture was quenched by addition of hexane (1.5 mL). The filtrate was added to another reaction vessel and products were derivatized to 2,4-dinitrophenylhydrazones using a literature procedure.[4b] The crude material was purified by silica gel column chromatography. Hydrazones were obtained as a mixture of *E* and *Z* isomers. **Method C:** To a reaction vessel, CuCl (9.9 mg, 0.10 mmol), $PdCl_2(MeCN)_2$ (13 mg, 0.05 mmol), BQ (54 mg, 0.50 mmol) were added, and O_2 was purged. To the mixture, *t*-BuOH (2 mL) was added and the reaction mixture was stirred at 40 °C. Immediately, a terminal alkene (0.50 mmol) was added at one portion and H_2O (9.0 μL, 0.50 mmol) was added slowly over 2 h by a syringe pump, and the reaction mixture was stirred for an additional 1 h (3 h in total). The reaction mixture was quenched by addition of hexane (1.5 mL). The filtrate was added to another reaction vessel and products were derivatized to 2,4-dinitrophenylhydrazones using a literature procedure.[4b] The crude material was purified by silica gel column chromatography. Hydrazones were obtained as a mixture of *E* and *Z* isomers.

Octanal (2a) and 2-octanone (4a). Compounds **2a** and **4a** were isolated as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **2a'** and **4a'**. Method A was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) afforded a yellow solid (112 mg, 0.37 mmol, 73% yield (**2a'**/**4a'** = 47%/26%)). For **2a'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.00 (s, 1 H), 9.07 (d, *J* = 3.3 Hz, 1 H), 8.26 (dd, *J* = 9.6 Hz, 2.4 Hz, 1 H), 7.90 (d, *J* = 9.3 Hz, 1 H), 7.55 (t, *J* = 5.4 Hz, 1 H), 2.45–2.36 (m, 2 H), 1.64–1.56 (m, 2 H), 1.32–1.29 (m, 8 H), 0.90–0.86 (m, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.8, 145.1, 137.6, 129.8, 128.6, 123.4, 116.4, 32.5, 31.6, 29.1, 29.0. 26.2, 22.5, 14.0. For **4a'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.00 (s, 1 H), 9.09 (d, *J* = 3.0 Hz, 1 H), 8.26 (dd, *J* = 9.6 Hz, 2.4 Hz, 1 H), 7.93 (d, *J* = 8.7 Hz, 1 H), 2.45–2.36 (m, 2 H), 2.05 (s, 3 H), 1.64–1.56 (m, 2 H), 1.33–1.29 (m, 6 H), 0.90–0.86 (m, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.5, 145.2, 137.4, 129.8, 128.8, 123.4, 116.4, 39.0, 31.5, 28.8, 26.1, 22.5, 15.8, 14.0. HRMS (ESI): *m*/*z* calcd for $C_{14}H_{20}N_4O_4$ $[M+H]^+$ 309.1563, found 309.1574. Anal. Calcd for $C_{14}H_{20}N_4O_4$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.32; H, 6.48; N, 18.23.

4-Methylpentanal (2b) and 4-methyl-2-pentanone (4b). Compounds **2b** and **4b** were isolated as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **2b'** and **4b'**. Method A was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) afforded an orange solid (94 mg, 0.34 mmol, 68% yield (**2b'**/**4b'** = 45%/23%)). For **2b'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.00 (s, 1 H), 9.09 (d, *J* = 2.7 Hz, 1 H), 8.28 (dd, *J* = 9.3 Hz, 2.7 Hz, 1 H), 7.91 (d, *J* = 9.6 Hz, 1 H), 7.54 (t, *J* = 5.4 Hz, 1 H), 2.47–2.35 (m, 2 H), 1.69–1.46 (m, 3 H), 0.95 (d, *J* = 6.6 Hz, 6 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.0, 145.0, 137.5, 129.8, 128.6, 123.4, 116.4, 35.0, 30.5, 27.6, 22.3. For **4b'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.03 (s, 1 H), 9.11 (d, *J* = 2.7 Hz, 1 H), 8.28 (dd, *J* = 9.3 Hz, 2.7 Hz, 1 H), 7.95 (d, *J* = 9.9 Hz, 1 H), 2.30 (d, *J* = 7.2 Hz, 2 H), 2.10–2.01 (m, 1 H), 2.05 (s, 3 H), 0.98 (d, *J* = 6.9 Hz, 6 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.8, 145.1, 137.4, 129.8, 128.8, 123.4, 116.2, 47.9, 26.0, 22.4, 15.9. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{16}N_4O_4$ $[M+H]^+$ 281.1250, found 281.1245. Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.34; H, 5.76; N, 19.94.

3-Cyclohexylpropanal (2c) and 3-cyclohexyl-2-propanone (4c). Compounds **2c** and **4c** were isolated as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **2c'** and **4c'**. Method A was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 20/1) afforded an orange solid (120 mg, 0.37 mmol, 75% yield (**2c'**/**4c'** = 50%/25%)). For **2c'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1 H), 9.10 (d, *J* = 2.7 Hz, 1 H), 8.29 (dd, *J* = 9.6 Hz, 2.4 Hz, 1 H), 7.92 (d, *J* = 9.6 Hz, 1 H), 7.54 (t, *J* = 5.1 Hz, 1 H), 2.47–2.40 (m, 2 H), 1.78–1.66 (m, 5 H), 1.53–1.46 (m, 2 H), 1.30–1.12 (m, 4 H), 1.00–0.87 (m, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.0, 145.1, 137.7, 129.9, 128.7, 123.5, 116.5, 37.2, 33.7, 33.1, 30.0, 26.5, 26.2. For **4c'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.04 (s, 1 H), 9.12 (d, *J* = 2.7 Hz, 1 H), 8.30 (ddd, *J* = 9.6 Hz, 2.7 Hz, 0.6 Hz, 1 H), 7.95 (d, *J* = 9.6 Hz, 1 H), 2.31 (d, *J* = 6.6 Hz, 2 H), 2.05 (s, 3 H), 1.77–1.68 (m, 5 H), 1.35–1.34 (m, 4 H), 1.06–0.89 (m, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.6, 145.2, 137.6, 130.0, 128.9, 123.6, 116.5, 46.7, 35.5, 33.2, 26.3, 26.1, 16.1. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}N_4O_4$ $[M+H]^+$ 321.1563, found 321.1577. Anal. Calcd for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29; N, 17.49. Found: C, 56.03; H, 6.13; N, 17.21.

4,4-Dimethylpentanal (2d), 4,4-dimethyl-2-pentenal (3d), and 4,4-dimethyl-2-pentanone (4d). Compound **2d**, **3d**, and **4d** were isolated as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **2d'**, **3d'**, and **4d'**. Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) afforded an orange solid (89 mg, 0.29 mmol, 58% yield (**2d'/3d'/4d'** = 40%/8%/10%)). For **2d'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.00 (s, 1 H), 9.09 (d, *J* = 2.4 Hz, 1 H), 8.28 (dd, *J* = 9.6 Hz, 2.1 Hz, 1 H), 7.92 (d, *J* = 9.6 Hz, 1 H), 7.55 (t, *J* = 5.4 Hz, 1 H), 2.44–2.37 (m, 2 H), 1.52–1.46 (m, 2 H), 0.96 (s, 9 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.3, 145.1, 137.6, 129.9, 128.7, 123.5, 116.5, 40.1, 30.3, 29.2, 28.3. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}N_4O_4$ $[M+H]^+$ 295.1406, found 295.1398.

4,4-Dimethyl-2-pentenal (3d) and 4,4-dimethyl-2-pentanone (4d). Compounds **3d** and **4d** were isolated as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **3d'** and **4d'**. Method B was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) afforded an orange solid (103 mg, 0.35 mmol, 71% yield (**3d'/4d'** = 64%/7%)). For **3d'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.10 (s, 1 H), 9.12 (d, *J* = 2.7 Hz, 1 H), 8.30 (ddd, *J* = 9.6 Hz, 2.4 Hz, 0.6 Hz, 1 H), 7.93 (d, *J* = 9.6 Hz, 1 H), 7.77 (t, *J* = 4.2 Hz, 1 H), 6.28 (d, *J* = 1.2 Hz, 1 H), 6.27 (s, 1 H), 1.13 (s, 9 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.5, 150.8, 144.8, 137.9, 129.9, 129.1, 123.5, 121.8, 116.5, 34.2, 29.0. For **4d'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1 H), 9.11 (d, *J* = 2.7 Hz, 1 H), 8.29 (dd, *J* = 9.6 Hz, 2.4 Hz, 1 H), 7.94 (d, *J* = 9.6 Hz, 1 H), 2.34 (s, 2 H), 2.10 (s, 3 H), 1.03 (s, 9 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.0, 145.1, 137.6, 130.0, 129.0, 123.5, 116.5, 52.3, 32.0, 29.9, 18.5. HRMS for **3d'** (ESI): *m*/*z* calcd for $C_{13}H_{16}N_4O_4$ $[M+H]^+$ 293.1250, found 293.1249. Anal. Calcd for **3d'** $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.04; H, 5.42; N, 18.98.

4-Phenylbutanal (2e) and 4-phenyl-2-butanone (4e). Compounds **2e** and **4e** were isolated as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **2e'** and **4e'**. Method A was applied. $(Cy_3P)_3Rh(H)Cl_2$ (29.4 mg, 0.04 mmol) was used. Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) afforded an orange solid (90 mg, 0.28 mmol, 55% yield (**2e'/4e'** = 45%/10%)). The spectral data for **2e'** was in accordance with those reported in the literature.[24] For **4e'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.96 (s, 1 H), 9.04 (d, *J* = 2.7 Hz, 1 H), 8.22 (dd, *J* = 9.5 Hz, 2.7 Hz, 1 H), 7.83 (d, *J* = 9.6 Hz, 1 H), 7.28–7.14 (m, 5 H), 2.94 (t, *J* = 7.2 Hz, 2 H), 2.68 (t, *J* = 7.5 Hz, 2 H), 2.02 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.1, 145.0, 140.7, 137.7, 129.8, 128.7, 128.4, 126.0, 123.4, 116.4, 40.4, 32.2, 16.2.

6-Oxohexenoic acid benzyl ester (2f) and 5-oxohexenoic acid benzyl ester (4f). Compounds **2f** and **4f** were isolated as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **2f'** and **4f'**. Method A was applied. BQ (54 mg, 0.50 mmol) was used. Purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) afforded an orange oil (151 mg, 0.38 mmol, 76% yield (**2f'/4f'** = 54%/22%)). For **2f'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.91 (s, 1 H), 8.98 (d, *J* = 2.1 Hz, 1 H), 8.17 (dd, *J* = 9.6 Hz, 2.1 Hz, 1 H), 7.81 (d, *J* = 9.6 Hz, 1 H), 7.44 (t, *J* = 5.1 Hz, 1 H), 7.26 (s, 5 H), 5.04 (s, 2 H), 2.43–2.34 (m, 4 H), 1.74–1.57 (m, 4 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.0, 151.9, 144.9, 137.5, 135.8, 129.7, 128.5, 128.4, 128.11, 128.07, 128.0, 123.2, 116.3, 66.1, 37.9, 33.7, 25.4, 24.2. For **4f'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.91 (s, 1 H), 8.98 (d, *J* = 2.1 Hz, 1 H), 8.13 (dd, *J* = 13.5 Hz, 2.1 Hz, 1 H), 7.81 (d, *J* = 9.6 Hz, 1 H), 7.26 (s, 5 H), 5.04 (s, 2 H), 2.43–2.34 (m, 4 H), 1.97 (s, 3 H), 1.74–1.57 (m, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.8, 156.9, 144.9, 137.4, 135.7, 129.8, 128.8, 128.4, 128.11, 128.07, 128.03, 127.99, 123.1, 116.2, 66.1, 33.2, 32.0, 20.9, 15.9. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{20}N_4O_6$ $[M+H]^+$ 401.1461, found 401.1464.

4-Chlorobutanal (2g). Compound **2g** was isolated as 2,4-dinitrophenylhydrazone derivatives **2g'**. Method C was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) afforded a yellow solid (91 mg, 0.32 mmol, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.06 (s, 1 H), 9.11 (d, *J* = 2.4 Hz, 1 H), 8.30 (dd, *J* = 9.6 Hz, 2.1 Hz, 1 H), 7.91 (d, *J* = 9.6 Hz, 1 H), 7.60 (t, *J* = 4.8 Hz, 1 H) 3.67 (t, *J* = 6.3 Hz, 2 H), 2.67–2.60 (m, 2 H), 2.20–2.11 (m, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.3, 145.0, 138.0, 130.0, 128.9, 123.5, 116.4, 44.0, 29.8, 28.8. HRMS (ESI): *m*/*z* calcd for $C_{10}H_{11}ClN_4O_4$ $[M+Na]^+$ 309.0367, found 309.0374. Anal. Calcd for $C_{10}H_{11}ClN_4O_4$: C, 41.90; H, 3.87; N, 19.54. Found: C, 41.82; H, 3.80; N, 19.64.

5-Chloropentanal (2h), 5-chloro-2-pentenal (3h), and 5-chloro-2-pentanone (4h). Compounds **2h**, **3h**, and **4h** were isolated as a mixture of corresponding 2,4-dinitrophenylhydrazone derivatives **2h'**, **3h'**, and **4h'**. Method C was applied. Purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) afforded an orange solid (108 mg, 0.36 mmol, 72% yield (**2h'/3h'/4h'** = 55%/7%/10%)). For **2h'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1 H), 9.03 (d, *J* = 2.4 Hz, 1 H), 8.25 (dd, *J* = 9.6 Hz, 1.8 Hz, 1 H), 7.88 (d, *J* = 9.6 Hz, 1 H), 7.58 (t, *J* = 5.1 Hz, 1 H), 3.59 (t, *J* = 6.3 Hz, 2 H), 2.51–2.40 (m, 2 H), 1.93–1.77 (m, 4 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 151.7, 145.0, 137.6, 129.8, 128.6, 123.3, 116.4, 44.5, 31.7, 31.6, 23.3. For **3h'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.09 (s, 1 H), 9.03 (d, *J* = 2.4 Hz, 1 H), 8.25 (dd, *J* = 9.6 Hz, 1.8 Hz, 1 H), 7.88 (d, *J* = 9.6 Hz, 1 H), 7.81 (d, *J* = 9.0 Hz, 1 H), 6.46–6.38 (m, 1 H), 6.30–6.20 (m, 1 H), 3.65 (t, *J* = 6.6 Hz, 2 H), 2.73 (q, *J* = 6.6 Hz, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 149.3, 145.0, 139.9, 137.6, 130.0, 128.9, 128.6, 123.2, 116.5, 42.9, 35.6. For **4h'**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1 H), 9.03 (d, *J* = 2.4 Hz, 1 H), 8.25 (dd, *J* = 9.6 Hz, 1.8 Hz, 1 H), 7.88 (d, *J* = 9.6 Hz, 1 H), 3.65 (t, *J* = 6.6 Hz, 2 H), 2.61 (t, *J* = 7.2 Hz, 2 H), 2.18–2.13 (m, 2 H), 2.08 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.4, 144.6, 137.6, 129.9, 128.6, 123.3, 116.2, 44.2, 35.9, 28.5, 16.3. HRMS for **2h'** and **4h'** (ESI): *m*/*z* calcd for $C_{11}H_{13}ClN_4O_4$ $[M+Na]^+$ 323.0523, found 323.0514.

4-Bromobutanal (2i). Compound **2i** was isolated as a pure (*E*)-2,4-dinitrophenylhydrazone derivative **2i'**. Method C was applied. H_2O (13.5 μL, 0.75 mmol) was used. Purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) afforded a yellow solid (111 mg, 0.34 mmol, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.07 (s, 1 H), 9.12 (d, *J* = 2.7 Hz, 1 H), 8.31 (dd, *J* = 9.3 Hz, 2.1 Hz, 1 H), 7.91 (d, *J* = 9.6 Hz, 1 H), 7.58 (t, *J* = 4.8 Hz, 1 H) 3.53 (t, *J* = 6.3 Hz, 2 H), 2.67–2.61 (m, 2 H), 2.28–2.19 (m, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 150.1, 145.0, 138.0, 130.0, 128.9, 123.5, 116.4, 32.4, 31.0, 28.9. HRMS (ESI): *m*/*z* calcd for $C_{10}H_{11}BrN_4O_4$ $[M+H]^+$ 331.0042, found 331.0053. Anal. Calcd for $C_{10}H_{11}BrN_4O_4$: C, 36.27; H, 3.35; N, 16.92. Found: C, 36.53; H, 3.31; N, 17.12.

5-Bromopentanal (2j). Compound **2j** was isolated as 2,4-dinitrophenylhydrazone derivatives **2j'**. Method C was applied. H_2O (13.5 μL, 0.75 mmol) was used. Purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) afforded a yellow solid (92 mg, 0.27 mmol, 54% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.04 (s, 1 H), 9.12 (d, *J* = 2.4 Hz, 1 H), 8.30 (ddd, *J* = 9.6 Hz, 2.7 Hz, 0.6 Hz, 1 H), 7.93 (d, *J* = 9.6 Hz, 1 H), 7.55 (t, *J* = 4.8 Hz, 1 H) 3.47 (t, *J* = 6.3 Hz, 2 H), 2.52–2.45 (m, 2 H), 2.03–1.94 (m, 2 H), 1.89–1.76 (m, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 151.3, 145.1, 137.9, 130.2, 123.5, 116.5, 33.1, 31.9, 31.6, 24.6. HRMS (ESI): *m*/*z* calcd for $C_{11}H_{13}BrN_4O_4$ $[M+H]^+$ 345.0199, found 345.0198. Anal. Calcd for $C_{11}H_{13}BrN_4O_4$: C, 38.28; H, 3.80; N, 16.23. Found: C, 38.37; H, 3.82; N, 15.99.

Theoretical Calculations. Calculations were carried out using density functional theory (DFT)-optimized geometries using the Gaussian 09 Revision E.01[25] implementation of B3LYP [Becke three-parameter exchange functional (B3)[26] and the Lee–Yang–Parr correlation functional (LYP)[27]]. The geometry optimization was performed using the basis set consisted of the combination of LANL2DZ[28] for Pd, 6-311G(d) for Cu, and 6-31G(d) for other atoms. The frequency calculation was performed using M06[29] and the basis set consisted of the combination of the Stuttgart-Dresden-Bonn energy-consistent pseudopotential (SDD)[30] for Pd, 6-311G(d) for Cu, and 6-311+G(d,p) for other atoms. The SMD method[31] was applied to incorporate a solvent effect (*t*-BuOH). Frequency calculations on optimized species established that the energy minima possessed only real frequencies and the transition states possessed a

single imaginary frequency. Zero-point energy and thermodynamic functions were computed at standard temperature (298.15 K) and pressure (1 atm). Spatial plots of the optimized geometries were obtained from Gaussian 09 output using Cambridge Soft Corporation's ChemBio3D Ultra ver. 11.0.1.

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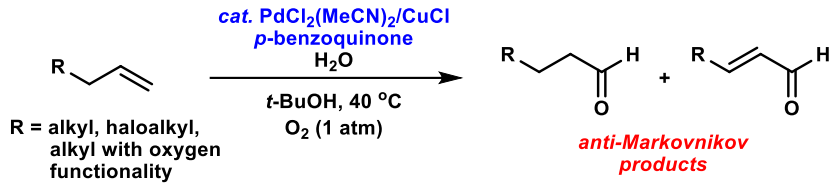

Anti-Markovnikov Wacker-type oxidation: Aldehydes were selectively obtained from various unbiased aliphatic terminal alkenes using $PdCl_2(MeCN)_2$/CuCl in the presence of *p*-benzoquinone under mild reaction conditions.