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# Palladium-Catalyzed Allylic Acyloxylation of Terminal Alkenes in the Presence of a Base

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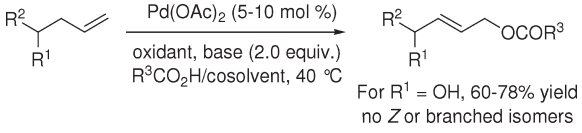


The efficiency and the selectivity of the Pd-catalyzed oxidation, in carboxylic acids, of terminal alkenes are strongly improved in the presence of a base. The methodology is particularly well adapted for the oxidation of homoallylic alcohols, for which the resulting acyloxylated products are obtained selectively as *E*-isomers in fair to good yields.

Palladium(II)-catalyzed allylic oxidation of internal or cyclic olefins in acetic acid is an efficient process for the synthesis of allylic acetates.[1] On the other hand, terminal olefins generally yield mixtures of allylic acetates, vinyl acetates, and ketones.[2] Recently, two important progresses have been achieved toward more selective transformations. White et al. demonstrated that the association of $Pd(OAc)_2$, benzoquinone (BQ), and DMSO or a bis(sulfoxide) ligand promoted the regio- and stereoselective allylic acetoxylation of terminal alkenes. In addition, either linear or branched products were selectively obtained depending on the reaction conditions.[3] This methodology has been applied in the total synthesis of 6-deoxyerythronolide B, through a C−H oxidative macrolactonization, increasing the overall efficiency of the synthesis and providing stereochemical control at a key lactone position.[4] Kaneda and co-workers described a regioselective process leading to linear allylic acetates using *N*,*N*-dimethylacetamide (DMA) as solvent and molecular oxygen as the sole oxidant, high pressures of $O_2$ (6 atm) being required, however.[5] Bipyrimidines as ligands were also found to improve the allylic acetoxylation of olefins.[6] The proposed mechanism of such transformations generally involves $\pi$-allyl-Pd(II) intermediates.[3f,6,7] Surprisingly, the influence of additives, such as acetate salts, has not received so much attention for the oxidation of terminal olefins.[8] Such compounds could act as bases to facilitate the formation of $\pi$-allyl complexes,[9] and as nucleophiles on such complexes. Herein, we disclose our results on the use of bases for the Pd-catalyzed oxidation of terminal alkenes.

The oxidation of allylbenzene (**1a**) in the presence of $Pd(OAc)_2$ (0.05 equiv) and BQ (2.0 equiv) in AcOH at 40 °C for 24 h led to a high conversion, but as observed before,[3g] to a low yield of cinnamyl acetate (**2a**) (Table 1, entry 1). The use of DMSO or DMA as the cosolvent improved the selectivity of the reaction, but dropped the conversion (entries 2 and 3). Almost full conversion was observed with $CH_3CN$ as cosolvent, leading to **2a** in 54% yield (entry 4). $CH_2Cl_2$ was not an efficient cosolvent (entry 5). In AcOH containing NaOAc as additive, **2a** can be produced in high yields but the results were inconsistent (entry 6). In contrast, reproducible results were obtained in $EtCO_2H$ containing $LiOH \cdot H_2O$ as a base,[10] affording **3a** in up to 75% yield, with high regioselectivity and good stereoselectivity (entries 7 and 8). The use of $MnO_2$, $MnO_2$/BQ, $O_2$/$Cu(OAc)_2$, or $O_2$ as oxidizing agents led to lower conversions and yields, but in some cases to higher L/B and *E*/*Z* ratios (entries 9−12).

The scope of the process was then examined, under the experimental conditions of entry 8 of Table 1 (namely afterward, method A). An electron donating group on the arene decreases the regioselectivity of the oxidation (Table 2, **3b** and **3c**), while an electron withdrawing group did not affect it (**3d**). The methodology was found to be particularly well adapted to homoallylic alcohols and their derivatives. A protected homoallylic alcohol, such as 1-phenylbut-3-enyl acetate (**1e**), was regio- and stereoselectively oxidized into

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(8) A noncoordinating base was recently used as additive, but its exact role is unclear, see ref 3d. $AcO^-$ anions accelerate the reaction of $Pd(OAc)_2$ with alkenes in apolar solvents, due to better solubility of Pd(II) species in the presence of $(R_4N)^+AcO^-$, see: Kozitsyna, N. Y.; Bukharkina, A. A.; Martens, M. V.; Vargaftik, M. N.; Moiseev, I. I. *J. Organomet. Chem.* **2001**, *636*, 69.

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(10) NaOH and $LiOH \cdot H_2O$ afforded similar results, but the latter which is less hygroscopic was used for easier handling.

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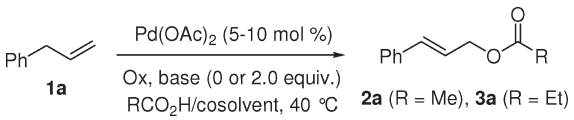
**TABLE 1. Optimization of the Oxidation of Allylbenzene (1a)**[a]




| entry | $RCO_2H$/cosolvent | $Pd(OAc)_2$, % | Ox (equiv) | base | conv.,[b] % | yield,[c] % | L/B, $E/Z$[d] |
|---|---|---|---|---|---|---|---|
| 1 | AcOH | 5 | BQ (2.0) | | 70 | (12) | |
| 2 | AcOH/DMSO, 1:1 | 5 | BQ (2.0) | | 38 | (25) | |
| 3 | AcOH/DMA, 1:1 | 5 | BQ (2.0) | | 29 | (18) | |
| 4 | AcOH/$CH_3CN$, 1:1 | 5 | BQ (2.0) | | 97 | (54) | |
| 5 | AcOH/$CH_2Cl_2$, 1:1 | 5 | BQ (2.0) | | 50 | (< 5) | |
| 6 | AcOH | 5 | BQ (2.0) | NaOAc | 80−100 | 60−76 (70−86) | 99.9, 21 |
| 7 | $EtCO_2H$ | 5 | BQ (2.0) | $LiOH·H_2O$ | 78 | (65) | |
| 8 | $EtCO_2H$ | 10 | BQ (2.0) | $LiOH·H_2O$ | 100 | 75 (86) | 99.9, 21 |
| 9 | $EtCO_2H$ | 10 | $MnO_2$ (2.0) | $LiOH·H_2O$ | 80 | 57 (67) | 99.9, 25 |
| 10 | $EtCO_2H$ | 10 | BQ (0.05), $MnO_2$ (2.0) | $LiOH·H_2O$ | 92 | 60 (71) | 99.9, 14 |
| 11 | $EtCO_2H$ | 10 | $Cu(OAc)_2$ (0.5), $O_2$[e] | $LiOH·H_2O$ | 85 | 61 (71) | 99.9, 50 |
| 12 | $EtCO_2H$ | 10 | $O_2$[e] | $LiOH·H_2O$ | 45 | 15 (24) | 99.9, 14 |

[a] **1a** (1.0 mmol), $Pd(OAc)_2$ (0.05 or 0.1 mmol), oxidant (0.5 or 2.0 mmol), base (0 or 2.0 mmol), $RCO_2H$/cosolvent (2.0 mL), 40 °C, 24 h. [b] Determined by GC. [c] GC yield in parentheses. [d] Determined by GC on isolated products. [e] Gas bag.

*E*-**3e** in medium yield. Interestingly, unprotected alcohols **1f**−**o** have been directly oxidized into corresponding linear (*E*)-4-hydroxy-esters **3f**−**o**. No *Z*, or branched isomers were detected by GC analysis. The allylic alcohol group is preserved, its oxidation or isomerization into a ketone function not being observed. Halogenated compounds (**1g**−**j**) were effectively oxidized allowing the possible elaboration of more complex compounds through further coupling reactions. While most products were isolated in fair to good yields (60−78%), **3k** and **3l** were obtained in low yields (∼10%). The oxidation of ether **1p** into *E*-**3p** was improved from 48% to 74% when the reaction was performed at rt for 72 h.

Oxidation of 1-decene (**1s**) in $EtCO_2H$ led to the expected product **3s** in good yield (Table 3, entry 1), but with low regio- and stereoselectivity (L/B and $E/Z$ < 10%). In addition, the product was contaminated with 10% of the homoallylic derivative. We have observed that the use of a higher carboxylic acid as solvent can improve the selectivity, but has a detrimental effect on the conversion, *i*-$PrCO_2H$ leading to only 62% conversion (entry 2). Interestingly, the addition of a cosolvent such as $CH_3CN$ to *i*-$PrCO_2H$ gave almost full conversion leading to **4s** in good yield, regio- and stereoselectivity, the amount of homoallylic derivative remaining relatively unchanged (entry 3), however. Medium conversion was obtained with *t*-$BuCO_2H/CH_3CN$, even in prolonging the reaction time to 72 h (entries 4 and 5), but the use of $MnO_2$ as oxidizing agent improved the conversion (entry 6), particularly when associated with BQ (entry 7). This latter acts probably as an electron-transfer mediator between the catalyst and the oxidant, and facilitates the overall transformation.[11]

**5s**−**v** were obtained in fair yields (59−69%) with good regio- and stereoselectivities (L/B 21−34, $E/Z$ 12−18), and were contaminated with only low amounts of the homallylic derivatives (Tables 2 and 3). The new procedure, based on the conditions of Table 3, entry 7 (called method B), is well adapted to the oxidation of homoallylic alcohols. Indeed, the efficiency of the oxidation of **1f** and **1g** was improved (Table 2: **3f**, 64%; **5f**, 78%; **3g**, 60%; **5g**, 77%), and interestingly, **1k** and **1***l* could be thus oxidized in high yields and regio- and stereoselectivities (**5k**, 80%; **5l**, 72%). Ethers were obtained in fair yields with method B (Table 2) in 72 (**5q**) or 24 h (**5r**). The oxidation of **1e** was slightly improved (**3e**, 55%; **5e**, 60%), but method B was less efficient than method A with allylarenes (**5a**, 60%; **5c**, 51%).

ESI-MS and the tandem version ESI-MS(/MS) are well adapted to the observation of short-lived molecular ions issued from metallocatalyzed reactions, and proposed species can be characterized from high resolution (HRMS) and ESI-MS(/MS) fragmentation.[12] The analysis by ESI/MS(+) of a mixture of $Pd(OAc)_2$ (0.1 mmol) and $LiOH·H_2O$ (2.0 mmol) in $EtCO_2H$ (2 mL) has shown two clusters at *m*/*z* 419.0661 and 499.1119, attributed to monomeric palladium species $[Li_2Pd(EtCO_2)_4,Li]^+$ and $[Li_2Pd(EtCO_2)_4,EtCO_2Li,Li]^+$, respectively. After addition of BQ and **1a**, and 45 min of stirring, two new clusters were observed at *m*/*z* 457.1002 and 537.1454, and were assigned to $[LiPd(\mathbf{1a})(EtCO_2)_3,Li]^+$ and $[LiPd(\mathbf{1a})(EtCO_2)_3,EtCO_2Li,Li]^+$, respectively (Figures S1−S6, Supporting Information). Palladium acetate exists as a trimer in the solid state, in which the $Pd(OAc)_2$ units are joined by double OAc bridges.[13] According to the ESI/MS studies, the acetate anion of the salt can act as a ligand for palladium leading to $M_2Pd(OAc)_4$ (**A**),[14] then coordination of **1** to **A** affords **B** (Scheme 1). The liganted $RCO_2^-$ in **B** can act as a base, facilitating the formation of $\pi$-allyl complex **C**.[9,15] Carefull

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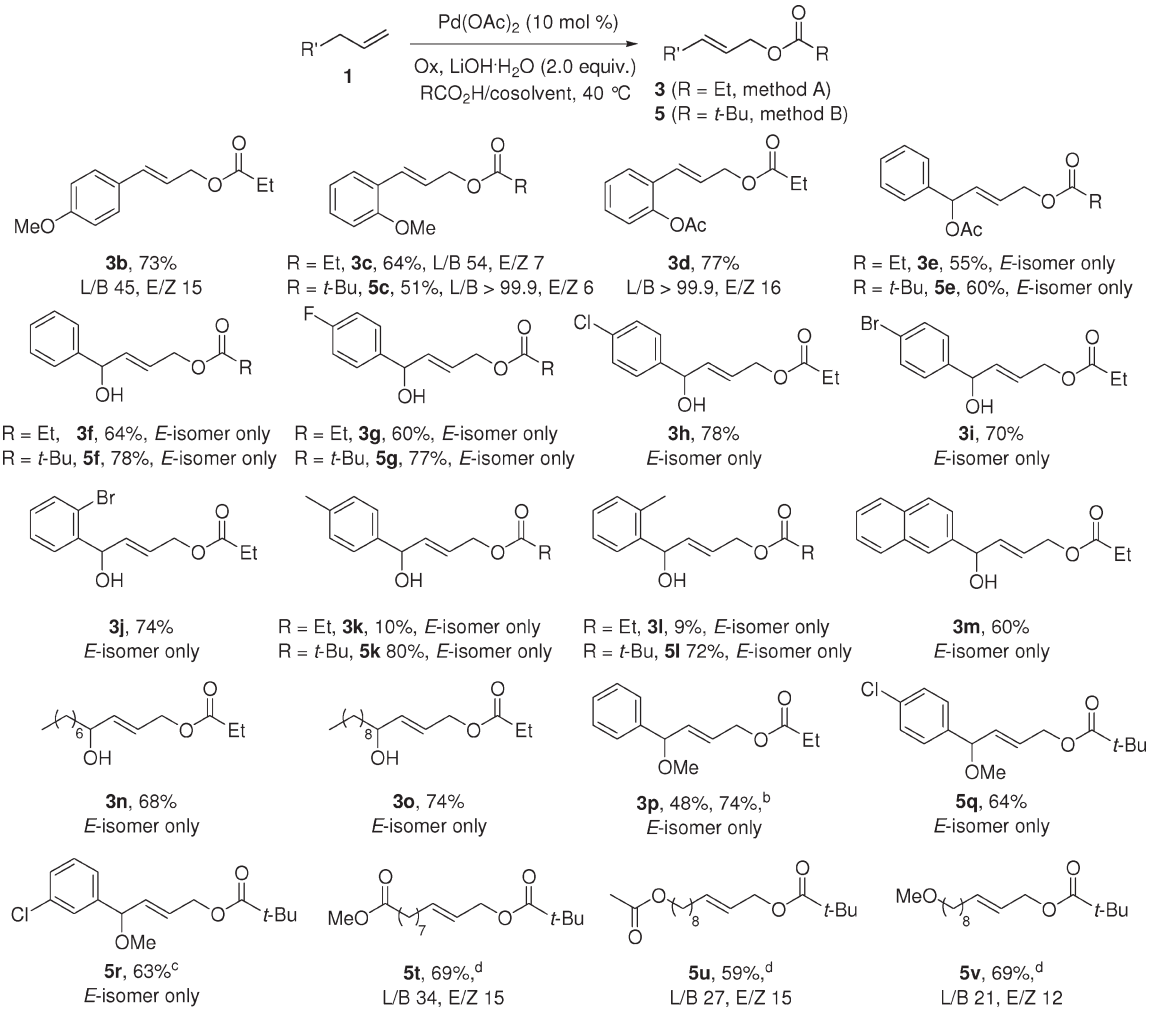
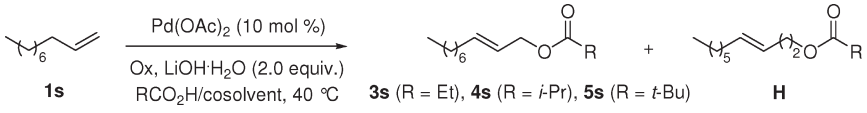
**TABLE 2. Oxidations with Method A or B[a]**




[a]Method A: **1** (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol), BQ (2.0 mmol), $LiOH \cdot H_2O$ (2.0 mmol), $EtCO_2H$ (2 mL), 40 °C, 24 h. Method B: **1** (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol), BQ (0.05 mmol), $MnO_2$ (2.0 mmol), $LiOH \cdot H_2O$ (2.0 mmol), *t*-$BuCO_2H$ (2 g), $CH_3CN$ (1 mL), 40 °C, 72 h. [b]Room temperature, 72 h. [c]24 h. [d]Presence of 1−3% of homoallylic derivatives.

**TABLE 3. Oxidation of 1-Decene[a]**



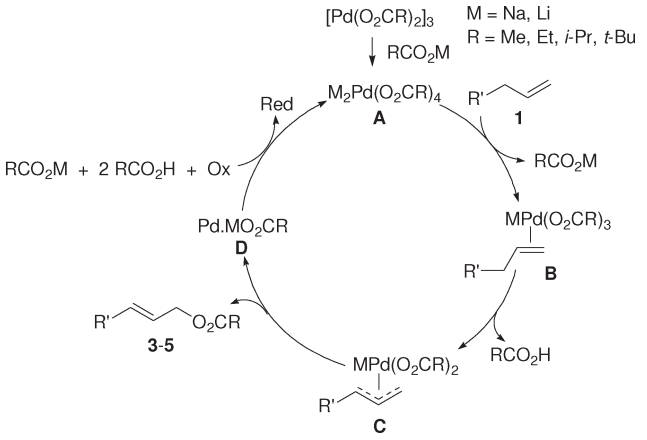

| entry | R | cosolvent | Ox (equiv) | time, h | conv.,[b] % | yield, % | L/B[c] | *E*/*Z*[c] | H[c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Et | | BQ (2.0) | 24 | 88 | 80 | 8 | 7 | 10 |
| 2 | *i*-Pr | | BQ (2.0) | 24 | 62 | 42 | 25 | 22 | 11 |
| 3 | *i*-Pr | $CH_3CN$ | BQ (2.0) | 24 | 94 | 74 | 17 | 19 | 10 |
| 4 | *t*-Bu | $CH_3CN$ | BQ (2.0) | 24 | 49 | 33 | 50 | 17 | 4 |
| 5 | *t*-Bu | $CH_3CN$ | BQ (2.0) | 72 | 66 | 43 | 43 | 15 | 4 |
| 6 | *t*-Bu | $CH_3CN$ | $MnO_2$ (2.0) | 72 | 76 | 54 | 27 | 20 | 3 |
| 7 | *t*-Bu | $CH_3CN$ | BQ (0.05), $MnO_2$ (2.0) | 72 | 90 | 61 | 29 | 18 | 3 |

[a]**1s** (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol), $LiOH \cdot H_2O$ (2.0 mmol), $RCO_2H$ (2.0 mL or 2.0 g), cosolvent (1.0 mL), 40 °C. [b]Determined by GC. [c]Determined by GC on isolated products (H: homoallylic derivative).

analysis of the ESI/MS spectra did not show the presence of clusters which could be attributed to **C**, suggesting that such a complex evolves rapidly under the reaction conditions. An intramolecular acetoxylation could lead to products **3**−**5** and **D**. The reoxidation of Pd(0) would then complete the catalytic cycle.

In conclusion, the use of a base for the Pd-catalyzed allylic oxidation of terminal alkenes in carboxylic acids as solvents

**SCHEME 1. Proposed Mechanism**




improved the efficiency and the selectivity of the process. The methodology is particularly convenient for the oxidation of homoallylic alcohols, corresponding *E*-acyloxylated products being obtained in fair to good yields.

## Experimental Section

**Method A for the Oxidation of 1.** A round-bottomed flask was charged with $LiOH \cdot H_2O$ (2.0 mmol, 84 mg) and $EtCO_2H$ (1 mL) and the mixture was heated (oil bath, 40 °C) for 10 min. BQ (2.0 mmol, 216 mg), $Pd(OAc)_2$ (0.1 mmol, 22.4 mg), and $EtCO_2H$ (1 mL) were added, and the mixture was stirred at rt for 15 min. **1** (1.0 mmol) was added, and the mixture was heated (oil bath, 40 °C) for 24 h. After cooling to rt, the mixture was filtered through a $SiO_2$ pad, which was washed with $Et_2O$ (50 mL). NaOH (2 M, 25 mL) was added, and the mixture was stirred for 15 min. The organic phase was washed with $H_2O$ (25 mL). The aqueous combined phases were extracted with $Et_2O$ (25 mL). The combined organic phases were dried over $MgSO_4$, and then evaporated to dryness. Flash chromatography (petroleum ether/EtOAc, 95:5−60:40) led to **3**.

**Method B for the Oxidation of 1.** A round-bottomed flask was charged with $LiOH.H_2O$ (2.0 mmol, 84 mg) and *t*-$BuCO_2H$ (2 g), and the mixture was heated (oil bath, 40 °C) for 10 min. BQ (0.05 mmol, 5.5 mg), $MnO_2$ (2.0 mmol, 174 mg), $Pd(OAc)_2$ (0.1 mmol, 22.4 mg), and $CH_3CN$ (1 mL) were added, and the mixture was stirred at rt for 15 min. **1** (1.0 mmol) was added, and the mixture was heated (oil bath, 40 °C) for 72 h. After cooling to rt, the mixture was filtered through a $SiO_2$ pad, which was washed with $Et_2O$ (50 mL). NaOH (2 M, 25 mL) was added, and the mixture was stirred for 15 min. The organic phase was washed with $H_2O$ (25 mL). The aqueous combined phases were extracted with $Et_2O$ (25 mL). The combined organic phases were dried over $MgSO_4$, and then evaporated to dryness. Flash chromatography (petroleum ether/EtOAc, 95:52−60:40) led to **5**.

**(*E*)-4-Hydroxy-4-phenylbut-2-enyl propionate (3f):** pale yellow oil, 64%, L/B and $E/Z > 99.9$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.00 (t, 3H, $J = 7.6$ Hz), 2.20 (q, 2H, $J = 7.5$ Hz), 3.05 (br s, 1H), 4.43 (d, 2H, $J = 5.0$ Hz), 5.05 (d, 1H, $J = 5.2$ Hz), 5.65−5.85 (m, 2H), 7.21 (m, 5H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 9.1, 27.5, 64.1, 74.0, 124.7, 126.3, 127.7, 128.5, 136.2, 142.6, 174.4; IR (film) 3445, 2982, 2942, 1738, 1454, 1382, 1349, 1276, 1186, 1083, 1009, 974, 759, 701. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.63; H, 7.45.

**(*E*)-4-Hydroxy-4-phenylbut-2-enyl pivalate (5f):** colorless oil, 78%, L/B and $E/Z > 99.9$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.11 (s, 9H), 2.72 (br s, 1H), 4.46 (d, 2H, $J = 4.6$ Hz), 5.10 (d, 1H, $J = 4.9$ Hz), 5.80 (m, 2H), 7.21 (m, 5H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 27.6, 39.2, 64.5, 74.6, 125.5, 126.8, 128.2, 129.0, 136.2, 143.0, 178.8; IR (film) 3455, 2975, 1728, 1480, 1373, 1283, 1156, 1045, 971, 701; ESHRMS calcd for $C_{15}H_{20}O_3Na$ 271.1310, found 271.1304.

**(*E*)-4-(4-Chlorophenyl)-4-hydroxybut-2-enyl propionate (3h):** pale yellow oil, 78%, L/B and $E/Z > 99.9$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.09 (t, 3H, $J = 7.3$ Hz), 2.30 (q, 2H, $J = 7.3$ Hz), 3.19 (br s, 1H), 4.53 (d, 2H, $J = 4.0$ Hz), 5.12 (d, 1H, $J = 4.1$ Hz), 5.84 (m, 2H), 7.25 (m, 4H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 8.9, 27.3, 63.8, 73.2, 125.0, 127.6, 128.5, 133.2, 135.6, 140.8, 174.2; IR (film) 3417, 2979, 1731, 1491, 1383, 1187, 1090, 1014, 911, 735; ESHRMS calcd for $C_{13}H_{15}O_3NaCl$ 277.0607, found 277.0614.

**(*E*)-4-(2-Bromophenyl)-4-hydroxybut-2-enyl propionate (3j):** pale yellow oil, 74%, L/B and $E/Z > 99.9$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.88 (t, 3H, $J = 7.6$ Hz), 2.08 (q, 2H, $J = 7.5$ Hz), 3.11 (br, 1H), 4.31 (m, 2H), 5.35 (s, 1H), 5.66 (m, 2H), 6.89 (dt, 1H, $J = 1.5$ Hz, $J = 7.9$ Hz), 7.08 (dd, 1H, $J = 4.6$ Hz, $J = 9.6$ Hz), 7.28 (m, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 8.9, 27.3, 64.0, 72.1, 122.1, 125.0, 127.6, 127.7, 128.9, 132.5, 134.0, 141.3, 174.2; IR (film) 3436, 2980, 1729, 1465, 1349, 1190, 1084, 1016, 910, 733; ESHRMS calcd for $C_{13}H_{15}O_3NaBr$ 321.0102, found 321.0095.

**(*E*)-4-Hydroxy-4-*p*-tolylbut-2-enyl pivalate (5k):** colorless oil, 80%, L/B and $E/Z > 99.9$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.08 (s, 9H), 2.21 (s, 3H), 3.23 (br s, 1H), 4.41 (d, 2H, $J = 4.8$ Hz), 5.00 (d, 1H, $J = 4.4$ Hz), 5.71 (td, 1H, $J = 4.9$ Hz, $J = 15.6$ Hz), 5.79 (dd, 1H, $J = 5.2$ Hz, $J = 15.7$ Hz), 7.01 (d, 2H, $J = 7.6$ Hz), 7.10 (d, 2H, $J = 7.8$ Hz); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 20.8, 27.0, 38.5, 64.0, 73.5, 124.3, 126.0, 128.9, 135.8, 137.0, 139.5, 178.1; IR (film) 3439, 2973, 1728, 1480, 1397, 1283, 1156, 1088, 970, 819; ESHRMS calcd for $C_{16}H_{22}O_3Na$ 285.1467, found 285.1457.

**(*E*)-4-(4-Chlorophenyl)-4-methoxybut-2-enyl pivalate (5q):** colorless oil, 64%, L/B and $E/Z > 99.9$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.13 (s, 9H), 3.23 (s, 3H), 4.53 (m, 3H), 5.74 (m, 2H), 7.21 (m, 4H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 27.0, 38.5, 56.2, 63.6, 82.5, 126.6, 128.0, 128.5, 133.2, 133.5, 139.0, 177.8; IR (film) 2976, 1729, 1482, 1462, 1282, 1152, 1090, 1015, 968, 824; ESHRMS calcd for $C_{16}H_{21}O_3NaCl$ 319.1077, found 319.1082.

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**Supporting Information Available:** General information, analytical data of compounds **3a**−**3e**, **3g**, **3i**, **3m**−**3p**, **5a**, **5c**, **5e**, **5g**, **5l**, and **5r**−**5v**, ESI/MS(+) spectra (Figures S1−S6), and the copies of $^1$H NMR and $^{13}$C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.