**Palladium-Catalyzed, Carboxylic Acid-Assisted Allylic Substitution of Carbon
Nucleophiles with Allyl Alcohols as Allylating Agents in Water**

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Supporting Information

Experimental

General

IR spectra were measured with JASCO FT/IR-610 spectrometers. NMR spectra were recorded on a JEOL JNM-LA300 or JNM-LA400 spectrometer. Tetramethylsilane ($\delta = 0$) was used as an internal standard for ^1H NMR and CDCl_3 ($\delta = 77.0$) for ^{13}C NMR. HRMS was performed by using a JEOL SX-102. Preparative thin-layer chromatography (TLC) was carried out using Wakogel B-5F. Structures of **3a**,^[1] **3c**,^[2] **3g**,^[3] and **3h**^[4] were confirmed by comparison with published spectral data.

Typical Procedure of Allylic Substitution in Water (Table 1, entry 15)

Cinnamyl alcohol (**2a**, 0.44 mmol) and dibenzoylmethane (**1a**, 0.29 mmol) were suspended in water (1.8 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.029 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.0059 mmol) were added. The whole was heated under reflux conditions in an oil bath (oil bath temperature: 115 °C) for 15 min. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. To the resulting mixture, anthracene (0.066 mmol) as an internal standard was added, and the NMR yield (98%) was determined by ^1H NMR integration. The mixture was purified by silica gel preparative TLC (benzene) to give **3a** in 87% isolated yield.

Ethyl 2-benzoyl-2-methyl-5-phenylpent-4-enoate (3b)

Cinnamyl alcohol (**2a**, 0.36 mmol) and ethyl 2-benzoylpropionate (**1b**, 0.24 mmol) were suspended in water (1.4 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.024 mmol) and Pd(PPh₃)₄ (0.012 mmol) were added. The whole was heated under reflux conditions in an oil bath (oil bath temperature: 115 °C) for 5 h. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel preparative TLC (AcOEt/hexane = 1/10) to give **3b** in 90% isolated yield (69 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.05 (3H, t, *J* = 7.1 Hz), 1.57 (3H, s), 2.87 (1H, dd, *J* = 14.2, 7.6 Hz), 2.95 (1H, dd, *J* = 14.2, 7.6 Hz), 4.09-4.15 (2H, m), 6.08 (1H, dt, *J* = 15.8, 7.6 Hz), 6.38 (1H, d, *J* = 15.8 Hz), 7.18-7.21 (1H, m), 7.25-7.31 (4H, m), 7.42 (2H, t, *J* = 7.3 Hz), 7.53 (1H, t, *J* = 6.8 Hz), 7.85 (2H, d, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.83, 21.25, 40.35, 57.27, 61.40, 124.21, 126.20, 127.30, 128.44, 128.48, 128.56, 132.69, 133.95, 135.60, 137.12, 173.73, 197.28; IR (neat) 2981, 1733, 1683, 1240 cm⁻¹; HRMS (EI), calcd. for C₂₁H₂₂O₃: 322.1569, found: 322.1581.

Ethyl 2-oxo-1-(3-phenyl-2-propen-1-yl)-1-cyclopentanecarboxylate (3c)

Cinnamyl alcohol (**2a**, 0.34 mmol) and ethyl 2-oxocyclopentane-1-carboxylate (**1c**, 0.22 mmol) were suspended in water (1.3 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.023 mmol) and Pd(PPh₃)₄ (0.0045 mmol) were added. The whole was heated under reflux conditions in an oil bath (oil bath temperature: 115 °C) for 10 min. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel preparative TLC (AcOEt/hexane = 1/10) to give **3c** in 92% isolated yield (56 mg).

***tert*-Butyl 2-oxo-1-(3-phenyl-2-propen-1-yl)-1-cyclopentanecarboxylate (3d)**

Cinnamyl alcohol (**2a**, 0.42 mmol) and *tert*-butyl 2-oxocyclopentane-1-carboxylate (**1d**, 0.28 mmol) were suspended in water (1.7 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.028 mmol) and Pd(PPh₃)₄ (0.0056 mmol) were added. The whole was heated under reflux conditions in an oil bath (oil bath temperature: 115 °C) for 10 min. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel preparative TLC (AcOEt/hexane = 1/5, and then ether/hexane = 1/3) to give **3d** in 76% isolated yield (64 mg). Mp 69.4-69.5 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.44 (9H, s), 1.84-2.06 (3H, m), 2.14-2.26 (1H, m), 2.38-2.55 (3H, m), 2.75 (1H, dd, *J* = 14.1, 7.5 Hz), 6.10 (1H, dt, *J* = 15.8, 7.5 Hz), 6.44 (1H, d, *J* = 15.8 Hz), 7.18-7.34 (5H, m); ¹³C NMR (75 MHz, CDCl₃) δ 19.56, 27.87, 32.41, 36.87, 38.04, 60.74, 81.84, 124.87, 126.10, 127.28, 128.46, 133.81, 137.09, 170.18, 214.98; IR (film) 2975, 1749, 1721, 1368, 1251, 1144 cm⁻¹; Anal. calcd. for C₁₉H₂₄O₃: C, 75.97; H, 8.05, found: C, 76.05; H, 8.13.

Ethyl 2-methyl-2-nitro-5-phenylpent-4-enoate (3e)

Cinnamyl alcohol (**2a**, 0.30 mmol) and ethyl 2-nitropropionate (**1e**, 0.20 mmol) were suspended in water (1.2 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.019 mmol) and Pd(PPh₃)₄ (0.0099 mmol) were added. The whole was heated under reflux conditions in an oil bath (oil bath temperature: 115 °C) for 1 h. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel preparative TLC (AcOEt/hexane = 1/10) to give **3e** in 78% isolated yield (40 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.29 (3H, t, *J* = 7.1 Hz), 1.81 (3H, s), 3.02 (1H, dd, *J* = 14.4, 7.6 Hz), 3.15 (1H, dd,

$J = 14.4, 7.3$ Hz), 4.28 (2H, q, $J = 7.1$ Hz), 6.02 (1H, ddd, $J = 15.6, 7.6, 7.3$ Hz), 6.52 (1H, d, $J = 15.6$ Hz), 7.23-7.34 (5H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 13.85, 21.26, 40.23, 62.86, 92.29, 120.68, 126.37, 127.93, 128.58, 136.19, 136.36, 167.07; IR (neat) 2984, 1749, 1553, 1255, 1130 cm^{-1} ; HRMS (EI), calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_4$: 263.1158, found: 263.1129.

2-Benzenesulfonyl-1,5-diphenylpent-4-en-1-one (3f)

Cinnamyl alcohol (**2a**, 0.26 mmol) and 2-benzenesulfonylacetophenone (**1f**, 0.23 mmol) were suspended in water (1.4 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.024 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.0047 mmol) were added. The whole was heated at 80 °C for 1.5 h. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel column chromatography (AcOEt/hexane = 1/15-1/5) to give **3f** in >99% isolated yield (88 mg). Mp 115.3-115.4 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.93-3.05 (2H, m), 5.21 (1H, dd, $J = 10.2, 4.2$ Hz), 5.92 (1H, dt, $J = 15.6, 7.1$ Hz), 6.40 (1H, d, $J = 15.6$ Hz), 7.15-7.20 (5H, m), 7.40-7.65 (6H, m), 7.80 (2H, d, $J = 7.6$ Hz), 7.92 (2H, d, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 31.64, 69.43, 122.94, 126.12, 127.58, 128.40, 128.71, 128.90, 128.94, 129.71, 134.00, 134.14, 134.29, 136.29, 136.39, 136.93, 191.85; IR (film) 1679, 1448, 1309, 1148, 744, 688 cm^{-1} ; HRMS (EI), calcd. for $\text{C}_{23}\text{H}_{20}\text{O}_3\text{S}$: 376.1133, found: 376.1153; Anal. calcd. for $\text{C}_{23}\text{H}_{20}\text{O}_3\text{S}$: C, 73.38; H, 5.35, found: C, 73.11; H, 5.57.

2,2-Dimethyl-4,6-dioxo-5,5-di(3-phenyl-2-propenyl)-1,3-dioxane (3g)

Cinnamyl alcohol (**2a**, 0.49 mmol) and Meldrum's acid (**1g**, 0.23 mmol) were suspended in water (1.3 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.022 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.0011 mmol) were added. The whole was heated at 80 °C for 30 min. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of

silica gel, and concentrated under vacuum. The mixture was purified by silica gel preparative TLC (AcOEt/hexane = 1/20) to give **3g** in 74% isolated yield (63 mg).

2-(2-Propen-1-yl)-1,3-diphenylpropane-1,3-dione (3h)

Allyl alcohol (**2c**, 0.42 mmol) and dibenzoylmethane (**1a**, 0.28 mmol) were suspended in water (1.7 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.028 mmol) and Pd(PPh₃)₄ (0.014 mmol) were added. The whole was heated at 80 °C for 30 min. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel preparative TLC (ether/toluene = 1/25) to give **3h** in 73% isolated yield (54 mg).

Benzyl 2-oxo-1-(2-propen-1-yl)-1-cyclopentanecarboxylate (3i)

Allyl alcohol (**2c**, 0.40 mmol) and benzyl 2-oxocyclopentane-1-carboxylate (**1h**, 0.27 mmol) were suspended in water (1.6 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.027 mmol) and Pd(PPh₃)₄ (0.013 mmol) were added. The whole was heated at 80 °C for 20 min. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel preparative TLC (AcOEt/hexane = 1/5) to give **3c** in 93% isolated yield (64 mg). ¹H NMR (300 MHz, CDCl₃) δ 1.85-2.06 (3H, m), 2.17-2.29 (1H, m), 2.34-2.50 (3H, m), 2.69 (1H, dd, *J* = 13.9, 7.1 Hz), 5.04-5.11 (2H, m), 5.14 (2H, s), 5.60-5.74 (1H, m), 7.30-7.37 (5H, m); ¹³C NMR (75 MHz, CDCl₃) δ 19.44, 32.04, 37.77, 38.02, 59.92, 66.98, 119.13, 127.85, 128.19, 128.50, 132.83, 135.52, 170.70, 214.23; IR (neat) 2968, 1749, 1726, 1220, 1155 cm⁻¹; HRMS (EI), calcd. for C₁₆H₁₈O₃; 258.1256, found: 258.1302.

2-Hex-2-enyl-1,3-diphenylpropane-1,3-dione (3j)

2-Hexen-1-ol (**2d**, 0.42 mmol) and dibenzoylmethane (**1a**, 0.28 mmol) were suspended in water (1.7 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.028 mmol) and Pd(PPh₃)₄ (0.014 mmol) were added. The whole was heated at 80 °C for 2 h. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel preparative TLC (AcOEt/hexane = 1/15) to give **3j** and **4** in 80% yield (70 mg, **3j**:**4** = 76:4). ¹H NMR (300 MHz, CDCl₃) δ 0.80 (3H, t, *J* = 7.3 Hz), 1.27 (2H, sextet, *J* = 7.3 Hz), 1.86-1.92 (2H, dt, *J* = 7.3, 5.3 Hz), 2.82 (2H, t, *J* = 6.2 Hz), 5.27 (1H, t, *J* = 6.6 Hz), 5.45-5.50 (2H, m), 7.44 (4H, t, *J* = 7.5 Hz), 7.55 (2H, t, *J* = 7.5 Hz), 7.96 (4H, d, *J* = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 13.52, 22.29, 32.63, 34.42, 57.33, 126.40, 128.55, 128.78, 133.38, 133.44, 136.10, 195.73; IR (neat) 2958, 1695, 1671, 1597, 1449, 1268 cm⁻¹; HRMS (EI), calcd. for C₂₁H₂₂O₂: 306.1620, found: 306.1626.

2-(1,3-diphenyl-2-propen-1-yl)-1,3-diphenylpropane-1,3-dione (3k)

1,3-Diphenyl-2-propen-1-ol (**2e**, 0.26 mmol) and dibenzoylmethane (**1a**, 0.24 mmol) were suspended in water (1.4 mL) at rt under argon, and then 1-adamantanecarboxylic acid (0.024 mmol) and Pd(PPh₃)₄ (0.012 mmol) were added. The whole was heated under reflux conditions in an oil bath (oil bath temperature: 115 °C) for 30 min. After the mixture was cooled to rt, water (5 mL) and brine (5 mL) were added. The organic materials were extracted with ethyl acetate, dried over sodium sulfate, passed through a short pad of silica gel, and concentrated under vacuum. The mixture was purified by silica gel column chromatography (AcOEt/hexane = 1/20) to give **3k** in 88% isolated yield (88 mg). Mp 132.4-133.4 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.80 (1H, dd, *J* = 10.5, 6.8 Hz), 5.95 (1H, d, *J* = 10.5 Hz), 6.26-6.36 (2H, m), 7.07-7.24 (8H, m), 7.31-7.35 (4H, m), 7.42-7.48 (3H, m), 7.55 (1H, t, *J* = 7.3 Hz), 7.82 (2H, d, *J* = 7.3 Hz), 8.03 (2H, d, *J* = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 49.98,

62.56, 126.20, 126.83, 127.29, 128.26, 128.47, 128.55, 128.60, 128.74, 128.85, 129.86, 131.80, 133.19, 133.41, 136.81, 136.84, 137.21, 140.88, 193.70, 194.36; IR (KBr) 1688, 1595, 1494, 1447, 1260, 1201, 965, 744, 686 cm^{-1} ; HRMS (EI), calcd. for $\text{C}_{30}\text{H}_{24}\text{O}_2$: 416.1776, found: 416.1736; Anal. calcd. for $\text{C}_{30}\text{H}_{24}\text{O}_2$: C, 86.51; H, 5.81, found: C, 86.30; H, 6.02.

Plot of yield vs. time for the reactions of 1b with 2a or 2b at 100 °C in the presence of 1-AdCO₂H in water

Conditions: $\text{Pd}(\text{PPh}_3)_4$ (2 mol %), 1-AdCO₂H (10 mol %), **1b:2a (2b)** = 1:1.5, at 100 °C in water. Open square: **1b + 2a**, closed square: **1b + 2b**.

References

- [1] M. Sekiya, K. Suzuki, *Chem. Pharm. Bull.* **1970**, *18*, 1530.
- [2] Y. Masuyama, K. Yamada, S. Shimizu, Y. Kurusu, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2913.
- [3] M. Prat, M. Moreno-Manas, J. Ribas, *Tetrahedron* **1988**, *44*, 7205.
- [4] J. R. Hwu, C. N. Chen, S.-S. Shiao, *J. Org. Chem.* **1995**, *60*, 856.