A New Catalytic Conjugate Addition / Aldol Strategy That Avoids Preformed Metallated Nucleophiles

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Experimental Section:

All reagents were used as received unless otherwise noted. Tetrahydrofuran (THF), ether and benzene were freshly obtained from solvent purification system (Innovative Technology, Inc.). Ni(COD)_2 (Purchased from Strem Chemicals) was stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under an argon atmosphere.

General Procedure:

To a solution of Ni(COD)_2 (10 mol %) in 8.0 mL of THF at 0 °C was added acrylate (1.0 equiv), aldehyde (2.0 equiv) and aryl halide (2.0 equiv) under argon atmosphere. To this brown solution, dimethyl zinc (1.5 equiv) was slowly added at 0 °C, the mixture was stirred for 1h at 0 °C, and the mixture was allowed to warm to rt. After completion of the reaction, as judged by TLC analysis, the mixture was quenched with aqueous NH_4Cl solution at 0 °C, warmed to rt, extracted with ether (3 X 20 mL), washed with water and brine, and concentrated. The crude products were subjected to flash column chromatography on silica gel with hexane:ether (4:1) to give the desired products.

2-Benzyl-3-hydroxy-3-phenylpropionic acid *t*-butyl ester (Entry 1).

Following the general procedure, iodobenzene (224 μL , 2.0 mmol), benzaldehyde (202 μL , 2.0 mmol), *tert*-butyl acrylate (146 μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and Ni(COD)_2 (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, 276 mg (88 %, dr 86:14) as a colorless thick oil. ^1H

NMR (300 MHz, CDCl₃) δ 7.43-7.10 (m, 10H), 4.98 (m, 1H, major), 4.78 (dd, J = 5.4, 7.5 Hz, 1H, minor), 2.98-2.89 (m, 4H), 1.18 (s, 9H, minor), 1.10 (s, 9H, major); ¹³C NMR (75 MHz, CDCl₃) 174.0, 173.4, 142.2, 141.4, 139.2, 138.5, 129.0, 128.3, 128.2, 128.1, 127.7, 127.6, 126.4, 126.3, 126.0, 81.3, 81.0, 74.5, 74.4, 55.5, 54.9, 35.9, 33.7, 27.7, 27.5; IR (film) 3437, 2977, 1950, 1720, 1702, 1603, 1494 cm⁻¹; HRMS (EI) m/e Calcd for C₂₀H₂₄O₃ 312.1725, Found (M)⁺ 312.1731. Tentative assignments for the major compound include the following: ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.10, 4.98, 2.98-2.89, 1.10; ¹³C NMR (75 MHz, CDCl₃) 173.4, 141.4, 139.2, 129.0, 128.2, 128.1, 127.7, 126.5, 126.0, 81.0, 74.4, 55.5, 33.7, 27.5.

Evaluation of stereochemistry:

To a suspension of lithium aluminum hydride in ether at 0 °C was added 2-benzyl-3-hydroxy-3-phenylpropionic acid t-butyl ester (mixture) in ether. After completion of the reaction, as judged by TLC analysis, the mixture was quenched with water at 0 °C, warmed to rt, extracted with ether (3 X 10 mL), washed with water and brine, and concentrated to give diol.¹ The diol was then treated with 2,2-dimethoxypropane in the presence of PPTS in benzene at 0 °C, followed by stirring the mixture at RT. After completion of the reaction, as judged by TLC analysis, the mixture was quenched with aqueous NaHCO₃ solution, extracted with ether (3 X 10 mL), washed with water and brine, and concentrated to give 5-benzyl-2,2-dimethyl-4-phenyl-[1,3]dioxane as a colorless oil (inseparable mixture). Spectral data of the major compound and observed NOE's were consistent with the *syn* aldol stereochemistry.¹

^1H NMR (500 MHz, CDCl_3) δ 7.42-7.39 (m, 4H), 7.32-7.27 (m, 1H), 7.23 (t, $J = 7.0$ Hz, 2H), 7.15 (t, $J = 7.0$ Hz, 1H), 7.06 (d, $J = 7.0$ Hz, 2H), 5.30 (d, $J = 2.5$ Hz, 1H), 4.06 (d, $J = 11.0$ Hz, 1H), 3.67 (dd, $J = 1.5, 11.5$ Hz, 1H), 2.89 (dd, $J = 12.0, 13.3$ Hz, 1H), 2.26 (dd, $J = 3.5, 13.7$ Hz, 1H), 1.84 (d, $J = 10.5$ Hz, 1H), 1.62 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.9, 140.8, 129.3, 128.3, 128.2, 127.0, 125.7, 125.4, 99.1, 73.2, 61.8, 41.4, 29.9, 29.8, 19.0; IR (film) : 2991, 1604, 1496, 1450 cm^{-1} .

2-Benzyl-3-hydroxy-3-phenylpropionic acid methyl ester (Entry 2).

Following the general procedure and stirring the reaction mixture at rt for 1 h, iodobenzene (224 μL , 2.0 mmol), benzaldehyde (202 μL , 2.0 mmol), methyl acrylate (90 μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and $\text{Ni}(\text{COD})_2$ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, syn-**2** (183 mg, 68 %) and anti-**2** (23 mg, 8 %) as a colorless solids.

Major isomer: ^1H NMR (500 MHz, CDCl_3) δ 7.41-7.35 (m, 4H), 7.32-7.28 (m, 1H), 7.26-7.22 (m, 2H), 7.18-7.15 (m, 1H), 7.08 (dd, $J = 1.5, 7.8$ Hz, 2H), 5.04 (m, 1H), 3.42 (s, 3H), 3.07-2.96 (m, 3H), 2.90 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.6, 141.3, 139.1, 128.7, 128.4, 128.3, 127.9, 126.3, 126.1, 74.1, 55.2, 51.5, 33.2; IR (film) 3456, 2951, 1729, 1603, 1494 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$ 270.1255, Found (M^+) 270.1248; m.p 52-53 $^\circ\text{C}$.

Minor isomer: ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.33 (m, 4H), 7.32-7.28 (m, 1H), 7.27-7.24 (m, 2H), 7.20-7.17 (m, 1H), 7.12-7.10 (m, 2H), 4.82 (d, J = 6.5 Hz, 1H), 3.52 (s, 3H), 3.07 (ddd, J = 5.5, 6.8, 9.5 Hz, 1H), 3.01 (s, 1H), 2.91 (dd, J = 9.5, 13.3 Hz, 1H), 2.73 (dd, J = 5.5, 13.8 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.0, 141.9, 138.3, 128.7, 128.6, 128.4, 128.1, 126.5, 126.2, 74.7, 54.9, 51.7, 35.7; IR (film) 3466, 2591, 1732, 1603, 1494. 1454 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$ 270.1255, Found (M) $^+$ 270.1258; m.p 84-85 $^\circ\text{C}$.

Evaluation of stereochemistry:

Both major and minor isomers were independently converted to their corresponding 5-benzyl-2,2-dimethyl-4-phenyl-[1,3]dioxane as shown in the case of entry 1. Spectral data and the observed NOE's of the major isomer were consistent with the *syn* aldol stereochemistry¹. (for data: see entry 1) and the minor isomer were consistent with the *trans* aldol stereochemistry.¹

2-Benzyl-3-hydroxy-3-(4-methoxyphenyl)-propionic acid *t*-butyl ester (Entry 3).

Following the general procedure and stirring the reaction mixture at rt for 4 h, iodobenzene (224 μL , 2.0 mmol), *p*-anisaldehyde (243 μL , 2.0 mmol), *tert*-butyl acrylate (146 μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and $\text{Ni}(\text{COD})_2$ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, 249 mg (73 %, dr 82:18) as a colorless thick oil. ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.12 (m, 7H), 6.88 (d, J = 9.3 Hz, 2H), 4.92 (q, J = 2.7 Hz, 1H, major), 4.74 (t, J = 6.0 Hz, 1H, minor), 3.81 (s, 3H), 3.02-2.84 (m, 4H), 1.20 (s, 9H, minor), 1.10 (s, 9H, major); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 173.4, 159.1, 139.2, 138.5, 134.3, 133.6, 129.1, 128.2, 128.1, 127.7, 127.4, 126.3, 126.1, 113.7, 113.6, 81.2, 80.9, 74.3, 74.1, 55.6, 55.2, 55.1, 35.9, 33.9, 27.7, 27.6; IR (film) : 3458,

2976, 1719, 1611, 1513, 1495 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{21}\text{H}_{26}\text{O}_4$ 342.1831, Found $(\text{M})^+$ 342.1830. Tentative assignments for the major compound include the following: ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.12, 6.88, 4.92, 3.81, 3.02-2.84, 1.10; ^{13}C NMR (100 MHz, CDCl_3) δ 173.4, 159.1, 139.2, 133.6, 129.1, 128.1, 127.7, 126.1, 113.6, 80.9, 74.1, 55.6, 55.2, 33.9, 27.6.

2-Benzyl-3-furan-2-yl-3-hydroxy-propionic acid t-butyl ester (Entry 4).

Following the general procedure and stirring the reaction mixture at rt for 3 h, iodobenzene (224 μL , 2.0 mmol), 2-furaldehyde (166 μL , 2.0 mmol), *tert*-butyl acrylate (146 μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and $\text{Ni}(\text{COD})_2$ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, 229 mg (76 %, dr 84:16) as a colorless solid. ^1H NMR (300 MHz, CDCl_3) δ 7.39 (t, J = 1.5 Hz, 1H), 7.29-7.16 (m, 5H), 6.36-6.32 (m, 2H), 4.90 (t, J = 5.8 Hz, 1H, major), 4.73 (dd, J = 4.8, 9.3 Hz, 1H, minor), 3.14-3.05 (m, 2H), 2.99 (d, J = 7.2 Hz, 2H), 1.27 (s, 9H, minor), 1.22 (s, 9H, major); ^{13}C NMR (75 MHz, CDCl_3) δ 172.8, 154.0, 142.0, 138.9, 129.1, 128.2, 126.2, 110.2, 107.2, 81.3, 68.4, 52.8, 34.0, 27.2; IR (film) 3431, 2977, 1720, 1604, 1455 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4$ 302.1518, Found $(\text{M})^+$ 302.1519; m.p 56-57 $^\circ\text{C}$. Tentative assignments for the major compound include the following: ^1H NMR (300 MHz, CDCl_3) δ 7.39, 7.29-7.16, 6.36-6.32, 4.90, 3.14-3.05, 2.99, 1.22. ^{13}C NMR (75 MHz, CDCl_3) δ 172.8, 154.0, 142.0, 138.9, 129.1, 128.2, 126.2, 110.2, 107.2, 81.3, 68.4, 52.8, 34.0, 27.2.

Evaluation of stereochemistry:

Lithium aluminum hydride reduction of 2-benzyl-3-furan-2-yl-3-hydroxy-propionic acid t-butyl ester (major isomer) gave its corresponding diol, which was then treated with 2,2-dimethoxypropane in the presence of PPTS to give 5-benzyl-4-furan-2-yl-2,2-dimethyl-[1,3]dioxane as a colorless oil as shown in the case of entry 1. Spectral data of the compound and observed NOE's were consistent with the *syn* aldol stereochemistry.

Major

Syn isomer

^1H NMR (500 MHz, CDCl_3) δ 7.41 (s, 1H), 7.28-7.23 (m, 2H), 7.19-7.12 (m, 3H), 6.38 (dd, $J = 1.8, 3.0$ Hz, 1H), 6.32 (m, 1H), 5.30 (d, $J = 3.0$ Hz, 1H), 3.97 (dq, $J = 1.2, 11.0$ Hz, 1H), 3.61 (dd, $J = 1.2, 12.0$ Hz, 1H), 2.98 (dd, $J = 11.1, 13.8$ Hz, 1H), 2.43 (dd, $J = 3.0, 13.8$ Hz, 1H), 1.98-1.90 (m, 1H), 1.55 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.7, 141.5, 140.8, 129.3, 128.3, 125.8, 110.2, 106.2, 99.3, 69.8, 61.4, 39.6, 30.7, 29.7, 19.0; IR (film) : 2990, 1602, 1496, 1454, 1380 cm^{-1} .

2-Benzyl-3-hydroxypentanoic acid *t*-butyl ester (Entry 5).

Following the general procedure and stirring the reaction mixture at rt for 1 h, iodobenzene (224 μL , 2.0 mmol), propionaldehyde (144 μL , 2.0 mmol), *tert*-butyl acrylate (146 μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and $\text{Ni}(\text{COD})_2$ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, anti-**5** (29 mg, 11 %) and syn-**5** (168 mg, 64 %) as a colorless oils.

Minor isomer : ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.20 (m, 5H), 3.53-3.46 (m, 1H), 3.04-2.92 (m, 2H), 2.82 (d, $J = 9.6$ Hz, 1H), 2.67-2.62 (m, 1H), 1.52 (m, 2H), 1.33 (s, 9H), 0.97 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5, 138.8, 129.1, 128.3, 126.3, 81.4, 73.3, 52.3, 35.9, 29.0, 27.9, 10.3; IR (film) 3439, 2976, 1721, 1496, 1455 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_3$ 264.1725, Found (M) $^+$ 264.1725.

Major isomer : ^1H NMR (400 MHz, CDCl_3) δ 7.25 (t, $J = 7.6$ Hz, 2H), 7.18 (d, $J = 7.2$ Hz, 3H), 3.75 (q, $J = 5.8$ Hz, 1H), 2.98 (dd, $J = 4.8, 13.6$ Hz, 1H), 2.91 (dd, $J = 10.0, 13.2$ Hz, 1H), 2.80 (s, 1H), 2.69 (dt, $J = 4.8, 10.4$ Hz, 1H), 1.55 (quintet, $J = 7.2$ Hz, 2H), 1.27 (s, 9H), 1.01 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 139.3, 129.0, 128.0, 126.1, 81.0, 73.3, 53.1, 33.3, 27.8, 27.1, 10.2; IR (film) 3445, 1721, 1702, 1605, 1496, 1455 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_3$ 264.1725, Found (M) $^+$ 264.1726.

Evaluation of stereochemistry:

Lithium aluminum hydride reduction of 2-benzyl-3-hydroxypentanoic acid *tert*-butyl ester (major isomer) gave its corresponding diol, which was then treated with 2,2-dimethoxypropane in the presence of PPTS to give 5-benzyl-4-ethyl-2,2-dimethyl-[1,3]dioxane as a colorless oil as shown in the case of entry 1. Spectral data of the compound and observed NOE's were consistent with the *syn* aldol stereochemistry.

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.26 (m, 2H), 7.22-7.17 (m, 3H), 3.95 (dt, $J = 2.4$, 7.0 Hz, 1H), 3.81 (dd, $J = 1.6$, 11.2 Hz, 1H), 3.55 (dd, $J = 1.6$, 11.6 Hz, 1H), 2.94 (dd, $J = 11.8$, 13.2 Hz, 1H), 2.73 (dd, $J = 3.6$, 13.6 Hz, 1H), 1.71-1.60 (m, 1H), 1.58-1.51 (m, 2H), 1.47 (s, 3H), 1.46 (s, 3H), 0.98 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.0, 129.4, 128.3, 125.8, 98.7, 73.5, 62.2, 38.5, 29.9, 29.4, 25.6, 19.1, 9.7.

2-Benzyl-3-hydroxy-4-methyl-pentanoic acid t-butyl ester (Entry 6).

Following the general procedure and stirring the reaction mixture at rt for 3 h, iodobenzene (224 μL , 2.0 mmol), isobutyraldehyde (183 μL , 2.0 mmol), *tert*-butyl acrylate (146 μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and $\text{Ni}(\text{COD})_2$ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, anti-**6** (25 mg, 9 %) and syn-**6** (193 mg, 69 %) as a colorless thick oils.

Minor isomer : ^1H NMR (300 MHz, CDCl_3) δ 7.30-7.19 (m, 5H), 3.23-3.15 (m, 1H), 3.00-2.99 (m, 1H), 2.97-2.90 (m, 2H), 2.82-2.75 (m, 1H), 1.70-1.58 (m, 1H), 1.30 (s, 9H), 0.99 (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.1, 139.0, 129.4, 128.5, 126.6, 81.6, 77.7, 50.1, 36.7, 33.3, 28.1, 19.5, 19.0; IR (film) 3497, 2964, 1704, 1455 cm^{-1} ; HRMS (ESI) m/e Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3 \text{Na}^+$ 301.1774, Found $(\text{M}^+\text{Na})^+$ 301.1771.

Major isomer : ^1H NMR (300 MHz, CDCl_3) δ 7.28-7.15 (m, 5H), 3.56 (m, 1H), 3.02 (dd, $J = 4.6, 13.8$ Hz, 1H), 2.90 (m, 1H), 2.76 (dt, $J = 4.8, 11.1$ Hz, 1H), 2.67 (d, $J = 3.6$ Hz, 1H), 1.85-1.74 (m, 1H), 1.23 (s, 9H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.6, 139.4, 129.1, 128.2, 126.2, 81.0, 77.0, 51.2, 33.2, 30.8, 27.8, 19.5, 17.5; IR (film) 3483, 2965, 1721, 1703, 1496, 1455 cm^{-1} ; HRMS (ESI) m/e Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3 \text{Na}^+$ 301.1774, Found (M^+Na^+) 301.1783.

2-Benzyl-3-hydroxy-4,4-dimethyl-pentanoic acid t-butyl ester (Entry 7).

Following the general procedure and stirring the reaction mixture at rt for 3 h, iodobenzene (224 μL , 2.0 mmol), pivalaldehyde (217 μL , 2.0 mmol), *tert*-butyl acrylate (146 μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and $\text{Ni}(\text{COD})_2$ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, anti-7 (70 mg, 24 %) and syn-7 (137 mg, 47 %) as a colorless solids.

Minor isomer : ^1H NMR (300 MHz, CDCl_3) δ 7.30-7.17 (m, 5H), 4.12 (d, $J = 9.0$ Hz, 1H), 3.20 (dd, $J = 1.5, 9.5$ Hz, 1H), 3.12 (dd, $J = 9.0, 13.4$ Hz, 1H), 2.97 (dd, $J = 6.6, 13.4$ Hz, 1H), 2.80 (ddd, $J = 1.8, 7.1, 8.9$ Hz, 1H), 1.25 (s, 9H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.0, 138.4, 129.3, 128.2, 126.4, 81.6, 80.4, 46.2, 38.8, 36.0, 27.6, 26.3; IR (film) 3497, 2964, 1704, 1455, 1367, 1150 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3$ 236.1412, Found ($\text{M}-(\text{CH}_3)_2\text{C}=\text{CH}_2$) $^+$ 236.1409; m. p. 109-110 $^\circ\text{C}$.

Major isomer : Recrystallized from Hexanes:ethyl acetate (4:1); ^1H NMR (300 MHz, CDCl_3) δ 7.28-7.15 (m, 5H), 3.61 (t, $J = 4.2$ Hz, 1H), 3.21-3.11 (m, 1H), 2.89-2.79 (m, 2H), 2.31 (d, $J = 4.2$ Hz, 1H), 1.16 (s, 9H), 1.0 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.0, 139.4, 129.3, 128.1, 126.1, 80.7, 78.9, 49.7, 35.9, 34.6, 27.6, 26.5; IR (film) 3499, 2977, 1723, 1705, 1480, 1367, 1149 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3$ 236.1412, Found $(\text{M}-(\text{CH}_3)_2\text{C}=\text{CH}_2)^+$ 236.1409; m. p. 82-84 $^\circ\text{C}$.

Evaluation of stereochemistry:

Lithium aluminum hydride reduction of 2-benzyl-3-hydroxy-4,4-dimethyl-pentanoic acid t-butyl ester (major isomer) gave its corresponding diol,¹ which was then treated with 2,2-dimethoxypropane in the presence of PPTS to give 5-benzyl-4-*tert*-butyl-2,2-dimethyl-[1,3]dioxane as a colorless oil as shown in the case of entry 1. Spectral data of the compound and observed NOE's were consistent with the *syn* aldol stereochemistry.

^1H NMR (400 MHz, CDCl_3) δ 7.30-7.27 (m, 2H), 7.22-7.16 (m, 3H), 3.69 (dd, $J = 2.0$, 11.0 Hz, 1H), 3.66 (d, $J = 1.6$ Hz, 1H), 3.47 (dd, $J = 1.6$, 12.4 Hz, 1H), 3.00 (dd, $J = 12.0$, 12.6 Hz, 1H), 2.91 (dd, $J = 4.4$, 14.2 Hz, 1H), 1.74-1.67 (m, 1H), 1.48 (s, 3H), 1.42 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.0, 129.3, 128.3, 125.7, 98.8, 78.9, 63.2, 38.2, 34.2, 31.2, 29.8, 27.0, 18.8; IR (film) : 2955, 1603, 1496, 1479, 1378 cm^{-1} .

2-Benzyl-3-hydroxy-3-methyl-butiric acid tert-butyl ester (Entry 8).

Following the general procedure and stirring the reaction mixture at rt for 12 h, iodobenzene (224 μL , 2.0 mmol), acetone (146 μL , 2.0 mmol), *tert*-butyl acrylate (146 μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and $\text{Ni}(\text{COD})_2$ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, 143 mg (54 %) as a colorless thick oil; ^1H NMR (300 MHz, CDCl_3) δ 7.28-7.23 (m, 2H), 7.20-7.17 (m, 3H), 3.25 (s, 1H), 3.04-2.90 (m, 2H), 2.59 (dd, $J = 5.4$, 11.1 Hz, 1H), 1.30 (s, 6H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 139.2, 129.2, 128.2, 126.2, 81.3, 71.0, 57.6, 33.7, 29.2, 27.7, 26.8; IR (film) 3466, 2976, 1693, 1604, 1495, 1455, 1390 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3$ 208.1099, Found ($\text{M}-(\text{CH}_3)_2\text{C}=\text{CH}_2$) $^+$ 208.1100.

3-Hydroxy-2-naphthalen-1-ylmethyl-3-phenyl-propionic acid t-butyl ester (Entry 9).

Following the general procedure and stirring the reaction mixture at rt for 3 h, iodonaphthalene (292 μL , 2.0 mmol), benzaldehyde (202 μL , 2.0 mmol), *tert*-butyl acrylate (146

μL , 1.0 mmol), dimethyl zinc (750 μL , 2.0 M solution in toluene, 1.5 mmol) and $\text{Ni}(\text{COD})_2$ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, syn-**9** (212 mg, 59 %) and anti-**9** (32 mg, 9 %).

Major isomer

Major isomer: Recrystallized from hexanes:ethyl acetate (4:1); ^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.45-7.37 (m, 4H), 7.36-7.31 (m, 2H), 7.28-7.26 (m, 1H), 5.10 (m, 1H), 3.54 (dd, J = 3.4, 13.2 Hz, 1H), 3.35 (dd, J = 11.4, 13.8 Hz, 1H), 3.19 (d, J = 2.4 Hz, 1H), 3.10-3.03 (m, 1H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.9, 141.3, 135.4, 133.8, 131.8, 128.6, 128.3, 127.8, 127.2, 127.0, 126.5, 125.8, 125.3, 125.2, 123.7, 81.0, 74.5, 54.5, 30.3, 27.6; IR (film) 3464, 2977, 1701, 1597, 1455, 1366 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{24}\text{H}_{26}\text{O}_3$ 362.1881, Found (M) $^+$ 362.1883; m. p. 80-81 $^\circ\text{C}$.

Minor isomer

Minor isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.87-7.81 (m, 1H), 7.80-7.76 (m, 1H), 7.75-7.70 (m, 1H), 7.49-7.44 (m, 2H), 7.41-7.30 (m, 7H), 4.87 (dd, J = 6.0, 7.5 Hz, 1H), 3.39 (dd, J = 8.7, 13.4 Hz, 2H), 3.30 (dd, J = 6.0, 13.8 Hz, 1H), 3.14 (dt, J = 6.0, 9.9 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 142.3, 134.7, 133.8, 131.8, 128.8, 128.4, 127.8, 127.4, 127.3, 126.2, 125.9, 125.4, 125.3, 123.4, 81.4, 74.8, 54.0, 32.9, 27.7; IR (film) 3472,

2977, 1701, 1597, 1453, 1366 cm^{-1} ; HRMS (EI) m/e Calcd for $\text{C}_{24}\text{H}_{26}\text{O}_3$ 362.1881, Found (M)⁺ 362.1880.

Evaluation of stereochemistry:

Lithium aluminum hydride reduction of 3-hydroxy-2-naphthalen-1-ylmethyl-3-phenylpropionic acid t-butyl ester (major isomer) gave its corresponding diol, which was then treated with 2,2-dimethoxypropane in the presence of PPTS to give 2,2-dimethyl-5-naphthalen-1-ylmethyl-4-phenyl-[1,3]dioxane as a colorless oil as shown in the case of entry 1. Spectral data of the compound and observed NOE's were consistent with the *syn* aldol stereochemistry.

^1H NMR (500 MHz, CDCl_3) δ 7.99 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 8.4 Hz, 1H), 7.53-7.47 (m, 4H), 7.44-7.40 (m, 2H), 7.39-7.34 (m, 2H), 7.32-7.30 (m, 2H), 5.44 (d, J = 3.2 Hz, 1H), 4.01 (d, J = 11.6 Hz, 1H), 3.65 (d, J = 12.0 Hz, 1H), 3.27 (dd, J = 12.0, 14.2 Hz, 1H), 2.78 (d, J = 14.0 Hz, 1H), 1.95 (m, 1H), 1.67 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.8, 136.9, 133.8, 131.9, 128.6, 128.3, 127.8, 127.2, 126.6, 125.6, 125.4, 125.3, 123.8, 99.2, 73.5, 62.0, 40.3, 30.0, 26.6, 19.0; IR (film) : 2989, 1596, 1509, 1450, 1378 cm^{-1} .

3-Hydroxy-2-(4-methylbenzyl)-3-phenyl-propionic acid t-butyl ester (Entry 10).

Following the general procedure and stirring the reaction mixture at rt for 3 h, 4-iodotoluene (436 mg, 2.0 mmol), benzaldehyde (202 μ L, 2.0 mmol), *tert*-butyl acrylate (146 μ L, 1.0 mmol), dimethyl zinc (750 μ L, 2.0 M solution in toluene, 1.5 mmol) and Ni(COD)₂ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, 258 mg (79 %, dr 88:12) as a colorless thick oil; ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.38-7.34 (m, 2H), 7.31-7.26 (m, 1H), 7.09-7.03 (m, 4H), 4.93 (d, *J* = 1.6 Hz, 1H, major), 4.77 (t, *J* = 6.6 Hz, 1H, minor), 3.20 (m, 1H), 3.0-2.71 (m, 3H), 2.31 (s, 3H), 1.22 (s, 9H, minor), 1.13 (s, 9H, major); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 173.4, 142.0, 141.5, 136.0, 135.7, 135.4, 128.9, 128.7, 128.2, 128.1, 127.7, 127.5, 126.5, 126.1, 81.2, 80.8, 74.4, 74.3, 55.6, 54.9, 35.4, 33.3, 27.7, 27.5, 20.9; IR (film) 3460, 2977, 1721, 1703, 1515, 1455, 1367 cm⁻¹; HRMS (EI) *m/e* Calcd for C₂₁H₂₄O₂ 308.1776, Found (M-H₂O)⁺ 308.1776. Tentative assignments for the major compound include the following: ¹H NMR (400 MHz, CDCl₃) δ 7.42, 7.38-7.34, 7.31-7.26, 7.09-7.03, 4.93, 3.20, 3.0-2.71, 2.31, 1.13; ¹³C NMR (100 MHz, CDCl₃) δ 173.4, 141.5, 136.0, 135.4, 128.9, 128.7, 128.1, 127.7, 126.5, 80.8, 74.4, 55.6, 33.3, 27.5, 20.9.

3-(2-*t*-Butoxycarbonyl-3-hydroxy-3-phenyl-propyl)-benzoic acid ethyl ester (Entry 11).

Following the general procedure and stirring the reaction mixture at rt for 12 h, 3-iodobenzoic acid ethyl ester (336 μ L, 2.0 mmol), benzaldehyde (202 μ L, 2.0 mmol), *tert*-butyl acrylate (146 μ L, 1.0 mmol), dimethyl zinc (750 μ L, 2.0 M solution in toluene, 1.5 mmol) and

Ni(COD)₂ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, 207 mg (54 %, dr 87:13) as a colorless thick oil. ¹H NMR (300 MHz, CDCl₃) δ 7.87-7.84 (m, 1H), 7.81 (s, 1H), 7.43-7.29 (m, 7H), 4.99 (dd, *J* = 2.4, 5.4 Hz, 1H, major), 4.79 (dd, *J* = 5.7, 7.2 Hz, 1H, minor), 4.35 (q, *J* = 6.0 Hz, 2H), 3.03-2.93 (m, 4H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 9H, minor), 1.10 (s, 9H, major); ¹³C NMR (100 MHz, CDCl₃) δ 173.6, 173.1, 166.6, 141.9, 141.3, 139.6, 138.9, 133.7, 130.2, 130.0, 129.9, 128.3, 128.2, 128.1, 127.8, 127.6, 127.4, 126.5, 126.2, 81.2, 81.1, 74.7, 74.4, 60.8, 55.4, 54.8, 35.6, 33.6, 27.6, 27.5, 14.3; IR film 3481, 2978, 1717, 1605, 1587, 1454; HRMS (EI) *m/e* Calcd for C₂₃H₂₈O₅ 384.1936, Found (*M*⁺) 384.1934. Tentative assignments for the major compound include the following: ¹H NMR (300 MHz, CDCl₃) δ 7.87-7.84, 7.81, 7.43-7.29, 4.99, 4.35, 3.03-2.93, 1.37, 1.10; ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 166.6, 141.3, 139.6, 133.7, 130.2, 130.0, 128.2, 128.1, 127.8, 127.4, 126.5, 81.1, 74.4, 60.8, 55.4, 33.6, 27.5, 14.3.

2-[3-(*t*-Butyldimethylsilanyloxymethyl)-benzyl]-3-hydroxy-3-phenylpropionic acid *t*-butyl ester (Entry 12).

Following the general procedure and stirring the reaction mixture at rt for 12 h, *t*-butyl-(3-iodobenzoyloxy)-dimethylsilane (696 mg, 2.0 mmol), benzaldehyde (202 μL, 2.0 mmol), *tert*-butyl acrylate (146 μL, 1.0 mmol), dimethyl zinc (750 μL, 2.0 M solution in toluene, 1.5 mmol) and Ni(COD)₂ (27 mg, 0.1 mmol) were employed to produce the title compound, after flash chromatography, 334 mg (73 %, dr 88:12) as a colorless thick oil. ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.13 (m, 7H), 7.05 (s, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 4.98 (q, *J* = 2.4 Hz, 1H, major), 4.78 (dd, *J* = 5.4, 7.4 Hz, 1H, minor), 4.67 (s, 2H), 3.03 (d, *J* = 3.0 Hz, 1H), 2.97-2.78 (m, 3H), 1.18 (s, 9H, minor), 1.11 (s, 9H, major), 0.93 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 141.4, 141.2, 139.0, 128.3, 128.0, 127.7, 127.6, 126.7, 126.4, 123.9, 81.0, 74.3, 64.9, 55.4, 33.5, 27.7, 27.6, 25.9, 18.4, -5.2; IR (film): 3437, 2955, 1721, 1703; cm⁻¹; HRMS (EI) *m/e* Calcd

for $C_{23}H_{31}O_4$ Si 399.1992, Found $(M-C(CH_3)_3)^+$ 399.1991. Tentative assignments for the major compound include the following: 1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.13, 7.05, 6.99, 4.98, 4.67, 3.03, 2.98-2.79, 1.11, 0.93, 0.08; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 141.4, 141.2, 139.0, 128.3, 128.0, 127.7, 127.6, 126.7, 126.4, 123.9, 81.0, 74.3, 64.9, 55.4, 33.5, 27.7, 27.6, 25.9, 18.4, -5.2.

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Unit 300 spectrometer

Unity 300 spectrometer

K5-11-141

Mercury 400 spectrometer

Minor Isomer

Unity 300 spectrometer

Major Isomer

Unity 300 spectrometer

Unity 300 spectrometer

Major Isomer

Unity 300 spectrometer

Unity 300 spectrometer

Mercury 400 spectrometer

Major Isomer

Unity 300 spectrometer

Minor Isomer

Unity 300 spectrometer

Unity 300 spectrometer