Mono-Selective Ortho-C–H Functionalizations of Mandelic Acid and α-Phenylglycine

Supporting Information

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1. General Information

All commercial available reagents were purchased from Sigma-Aldrich, Fluka, Alfa Aesar, TCI, Oakwood, or Acros in the highest purity grade and used without further purification (only Boc-D-α-phenylglycine (10a) was purchased from Acros and recrystallized out of hexanes/EtOAc before usage). All small scale reactions were run in 8 mL sample vials heated in a Dynabloc heating block (VWR, Catalog Nr. 89083-386) calibrated to an external thermometer. Prior to beginning an experiment, the hot plate was turned on, and the block was allowed to equilibrate to the desired temperature for 30 minutes. Unless otherwise noted, all reactions were run under air and the indicated reaction temperature was that of the heating block. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker AV 400, Varian Inova 400 (400 MHz and 100 MHz, respectively), and Bruker DRX 600 (600 MHz and 150 MHz, respectively) instruments. Chemical shifts are reported in δ ppm referenced to an internal TMS standard for $^1$H NMR, CDCl$_3$ (δ 77.00) for $^{13}$C NMR. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. High-resolution mass spectra (HRMS) were obtained on an Agilent LC/MSD TOF mass spectrometer. Enantiomeric excesses (ee) were determined on a Hitachi LaChrow Elite HPLC system using commercially available chiral columns as described below.
2. Experimental Section

2.1 Optimization Studies for Arylation

![Chemical Reaction Diagram]

Table 1. Screening of Bases*  

| entry | base          | yield (%)^b |
|-------|---------------|-------------|
| 1     | --            | 11          |
| 2     | K$_3$PO$_4$   | 77          |
| 3     | K$_2$HPO$_4$  | 71          |
| 4     | Na$_3$PO$_4$  | 74          |
| 5     | KHCO$_3$      | 67          |
| 6     | K$_2$CO$_3$   | 50          |
| 7     | Cs$_2$CO$_3$  | 44          |
| 8     | KF            | 41          |
| 9     | LiOAc         | 23          |
| 10    | NaOAc         | 48          |
| 11    | KOAc          | 79          |
| 12    | CsOAc         | 33          |

*Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), Pd(OAc)$_2$ (0.005 mmol), AgOAc (0.2 mmol), base (0.3 mmol), HFIP (1 mL), air, 100 °C, 24 h. ^bYield determined by $^1$H-NMR analysis of crude reaction mixture using CH$_3$Br$_2$ as internal standard.

2.2 General procedure for the Pivaloyl Protection

The mandelic acid substrate (5 mmol, 1 equiv), pivaloyl chloride (7.5 mmol, 918 µL, 1.5 equiv) and DCM (5 mL) were stirred at r.t. for 24 h. The mixture was concentrated in vacuo and the resulting residue was purified by column chromatography (hexanes:EtOAc:HOAc = 75:25 with 0.2% HOAc).

(R)-2-phenyl-2-(pivaloyloxy)acetic acid (1a): The compound 1a was prepared according to the general procedure and was obtained as a colorless solid (1.14 g, 97% yield). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.52 – 7.46 (m, 2H), 7.43 – 7.37 (m, 3H), 5.90 (s, 1H), 1.28 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 177.78, 173.51, 133.45, 129.27, 128.80, 127.38, 73.74, 38.74, 27.00. HRMS (ESI-TOF) m/z Calcd for C$_{13}$H$_{16}$O$_4$ [M+H]$^+$: 237.1122, found: 237.1124.
(R)-2-(3-chlorophenyl)-2-(pivaloyloxy)acetic acid (1e): The compound 1e was prepared according to the general procedure and was obtained as a colorless solid (1.33 g, 98% yield). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.48 (t, $J = 1.8$ Hz, 1H), 7.39 – 7.35 (m, 2H), 7.35 – 7.31 (m, 1H), 5.86 (s, 1H), 1.28 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 177.63, 173.83, 134.21, 134.73, 130.08, 129.50, 127.43, 125.53, 73.06, 38.76, 26.97. HRMS (ESI-TOF) m/z Calcd for C$_{13}$H$_{15}$ClO$_4$ [M+H]$^+$: 271.0732, found: 271.0732.

(R)-2-(2-chlorophenyl)-2-(pivaloyloxy)acetic acid (1f): The compound 1f was prepared according to the general procedure and was obtained as a colorless solid (1.27 g, 94% yield). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.50 (dd, $J = 7.2$, 2.2 Hz, 1H), 7.44 (dd, $J = 7.5$, 1.7 Hz, 1H), 7.36 – 7.30 (m, 2H), 5.95 (s, 1H), 1.25 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 177.49, 173.99, 134.12, 131.75, 130.58, 130.01, 129.31, 127.25, 70.41, 38.75, 26.96. HRMS (ESI-TOF) m/z Calcd for C$_{13}$H$_{15}$ClO$_4$ [M+H]$^+$: 271.0732, found: 271.0731.

2-(4-chlorophenyl)-2-(pivaloyloxy)acetic acid (1g): The compound 1g was prepared according to the general procedure and was obtained as a colorless solid (1.12 g, 83% yield). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.44 – 7.40 (m, 2H), 7.39 – 7.35 (m, 2H), 5.86 (s, 1H), 1.27 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 177.66, 174.15, 135.39, 131.87, 129.06, 128.74, 73.07, 38.73, 26.96. HRMS (ESI-TOF) m/z Calcd for C$_{13}$H$_{15}$ClO$_4$ [M+H]$^+$: 271.0732, found: 271.0735.

2-(pivaloyloxy)-2-(4-(trifluoromethyl)phenyl)acetic acid (1h): The compound 1h was prepared according to the general procedure and was obtained as a colorless solid (1.29 g, 85% yield). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.67 (d, $J = 8.2$ Hz, 2H), 7.63 (d, $J = 8.2$ Hz, 2H), 5.95 (s, 1H), 1.28 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 177.58, 173.88, 137.15, 131.52 (q, $J_{CF3} = 32.7$ Hz), 127.71, 125.81, 123.76 (q, $J_{CF3} = 272.2$ Hz), 73.09, 38.78, 26.96. HRMS (ESI-TOF) m/z Calcd for C$_{14}$H$_{13}$F$_3$O$_4$ [M+H]$^+$: 305.0995, found: 305.0993.

2-(4-methoxyphenyl)-2-(pivaloyloxy)acetic acid (1i): The compound 1i was prepared according to the general procedure and was obtained as a colorless solid (996 mg, 75% yield). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.40 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.83 (s, 1H), 3.81 (s, 3H), 1.25 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 177.85, 174.93, 160.33, 128.86, 125.48, 114.22, 73.46, 55.31, 38.68, 26.97. HRMS (ESI-TOF) m/z Calcd for C$_{14}$H$_{18}$O$_5$ [M+H]$^+$: 267.1227, found: 267.1229.
2.3 General procedure for the Arylation of Mandelic acid

A 8 mL vial with fully covered solid Teflon lined screw cap equipped with a magnetic stir bar was charged with the substrate (0.1 mmol, 1.0 equiv), ArI (0.2 mmol, 2.0 equiv), Pd(OAc)$_2$ (1.1 mg, 0.005 mmol, 5 mol%), AgOAc (33 mg, 0.2 mmol, 2.0 equiv), KOAc (29 mg, 0.3 mmol, 3.0 equiv) and HFIP (1 mL). The vial was closed and stirred at 80 °C for 24 h. The reaction vessel was then cooled to rt. A 1.0 N HCl solution (1 mL) was then added, and the mixture was extracted with Et$_2$O (3 × 3 mL). The organic layers were combined, filtered through a pad of Celite® 545 and concentrated in vacuo. The resulting residue was purified by preparative TLC using 2:1 hexane:s:EtOAc (with 1% HOAc).

Compounds 3g, 3h, and 3l were isolated as the corresponding methyl ester. Therefore, the residue after the workup and filtration was dissolved in toluene/MeOH (3:1, 0.5 mL) and 150 µl TMSCH$_2$N$_2$ (2N solution in hexane, CAUTION!!! Inhalation of TMSCH$_2$N$_2$ is potentially fatal and the chemical should be handled in the fume hood carefully.) was added dropwise to the reaction mixture. The solution was stirred for 30 min at r.t. and subsequently quenched with 0.5 mL AcOH. The mixture was concentrated in vacuo and purified by preparative TLC using 9:1 hexanes:EtOAc to give the corresponding methy ester.

(R)-2-(4'-methyl-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3a): The compound 3a was prepared according to the general procedure and was obtained as a colorless oil (29.1 mg, 89% yield). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.55 (d, $J_1 = 6.5$ Hz, 1H), 7.47 – 7.28 (m, 5H), 7.19 (d, $J_2 = 7.4$ Hz, 2H), 6.01 (s, 1H), 2.37 (s, 3H), 1.20 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 177.76, 174.63, 142.92, 137.29, 136.78, 131.60, 130.55, 129.29, 129.09, 129.00, 128.19, 127.65, 71.16, 38.62, 26.98, 21.17. HPLC chiralcel AD-H column (5% isopropanol in hexanes, with 0.2% TFA, 0.5 mL/min) tR= 14.53 min (minor), 17.35 min (major): 98% ee. HRMS (ESI-TOF) m/z Calcd for C$_{20}$H$_{22}$O$_4$ [M+H]$^+$: 327.1591, found: 327.1595.

(R)-2-acetoxy-2-(4'-methyl-[1,1'-biphenyl]-2-yl)acetic acid (3b): The compound 3b was prepared according to the general procedure and was obtained as a colorless oil (24.9 mg, 88% yield). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.56 (d, $J_1 = 7.9$ Hz, 1H), 7.46 – 7.36 (m, 2H), 7.30 – 7.24 (m, 2H), 7.21 (d, $J_2 = 7.7$ Hz, 2H), 6.08 (s, 1H), 2.38 (s, 3H), 2.10 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ $^{13}$C NMR (151 MHz, CDCl$_3$) δ 174.64, 170.11, 142.91, 137.40, 136.62, 131.14, 130.64, 129.33, 129.03, 128.08,
127.76, 70.99, 21.16, 20.59. HRMS (ESI-TOF) m/z Calcd for C_{17}H_{16}O_{4} [M+Na]^+: 307.0941, found: 307.0941.

(R)-2-(3'-methyl-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3e): The compound 3e was prepared according to the general procedure and was obtained as a colorless oil (25.4 mg, 78% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.55 (d, $J = 7.1$ Hz, 1H), 7.49 – 7.28 (m, 4H), 7.18 (s, 3H), 6.00 (s, 1H), 2.36 (s, 3H), 1.21 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.58, 174.54, 143.06, 139.62, 137.85, 131.39, 130.48, 130.13, 129.12, 128.36, 128.26, 128.17, 127.75, 126.44, 71.06, 38.61, 26.99, 21.44. HRMS (ESI-TOF) m/z Calcd for C$_{20}$H$_{22}$O$_4$ [M+H]^+: 327.1591, found: 327.1591.

(R)-2-(pivaloyloxy)-2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)acetic acid (3f): The compound 3f was prepared according to the general procedure and was obtained as a colorless oil (18.9 mg, 50% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.67 (d, $J = 8.0$ Hz, 2H), 7.60 (t, $J = 4.5$ Hz, 1H), 7.53 (d, $J = 7.9$ Hz, 2H), 7.46 (dd, $J = 6.2$, 2.9 Hz, 2H), 7.34 – 7.27 (m, 1H), 5.93 (s, 1H), 1.21 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.50, 174.38, 143.35, 141.29, 131.43, 130.40, 129.88, 129.87 (q, $J_{CF3} = 32.8$ Hz), 129.38, 128.59, 128.21, 125.29 (q, $J_{CF3} = 4.1$ Hz), 70.67, 38.64, 26.93. HRMS (ESI-TOF) m/z Calcd for C$_{20}$H$_{19}$F$_3$O$_4$ [M+H]^+: 381.1308, found: 381.1307.

(R)-methyl 2'-2-methoxy-2-oxo-1-(pivaloyloxy)ethyl]-[1,1'-biphenyl]-4-carboxylate (3g): The compound 3g was prepared according to the general procedure and was obtained as a colorless oil (23.1 mg, 60% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 8.5$ Hz, 2H), 7.56 (dd, $J = 6.6$, 2.6 Hz, 1H), 7.50 – 7.40 (m, 4H), 7.32 (dd, $J = 6.5$, 2.6 Hz, 1H), 5.95 (s, 1H), 3.95 (s, 3H), 3.66 (s, 3H), 1.23 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.42, 169.48, 166.82, 144.55, 141.69, 131.77, 130.24, 129.57, 129.46, 129.37, 129.14, 128.40, 128.34, 71.08, 52.45, 52.18, 38.64, 26.98. HRMS (ESI-TOF) m/z Calcd for C$_{22}$H$_{24}$O$_6$ [M+H]^+: 385.1646, found: 385.1646.

(R)-methyl 2'-2-methoxy-2-oxo-1-(pivaloyloxy)ethyl]-[1,1'-biphenyl]-3-carboxylate (3h): The compound 3h was prepared according to the general procedure and was obtained as a colorless oil (23.8 mg, 62% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.10 – 8.03 (m, 2H), 8.03 (d, $J = 8.5$ Hz, 2H), 7.56 (dd, $J = 6.6$, 2.6 Hz, 1H), 7.50 – 7.40 (m, 4H), 7.32 (dd, $J = 6.5$, 2.6 Hz, 1H), 5.95 (s, 1H), 3.95 (s, 3H), 3.66 (s, 3H), 1.23 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.42, 169.48, 166.82, 144.55, 141.69, 131.77, 130.24, 129.57, 129.46, 129.37, 129.14, 128.40, 128.34, 71.08, 52.45, 52.18, 38.64, 26.98. HRMS (ESI-TOF) m/z Calcd for C$_{22}$H$_{24}$O$_6$ [M+H]^+: 385.1646, found: 385.1646.
The compound 3i was prepared according to the general procedure and was obtained as a colorless oil (29.1 mg, 82% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.01 (d, $J = 8.0$ Hz, 2H), 7.64 – 7.58 (m, 1H), 7.52 (d, $J = 7.9$ Hz, 2H), 7.49 – 7.43 (m, 2H), 7.36 – 7.29 (m, 1H), 5.96 (s, 1H), 2.64 (s, 3H), 1.21 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 197.99, 177.50, 174.26, 144.62, 141.59, 136.16, 131.36, 130.22, 129.77, 129.32, 128.52, 128.40, 128.20, 70.65, 38.61, 26.93, 26.67. HRMS (ESI-TOF) m/z Calcd for C$_{21}$H$_{22}$O$_5$ [M+H]$^+$: 355.1540, found: 355.1539.

The compound 3j was prepared according to the general procedure and was obtained as a colorless oil (20.7 mg, 61% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 10.05 (s, 1H), 7.93 (d, $J = 8.0$ Hz, 2H), 7.64 – 7.55 (m, 3H), 7.51 – 7.43 (m, 2H), 7.36 – 7.29 (m, 1H), 5.95 (s, 1H), 1.21 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 192.02, 177.46, 174.18, 146.02, 141.42, 135.46, 131.38, 130.24, 130.20, 129.74, 129.39, 128.69, 128.31, 70.64, 38.62, 26.93. HRMS (ESI-TOF) m/z Calcd for C$_{20}$H$_{20}$O$_5$ [M+Na]$^+$: 363.1203, found: 363.1206.

The compound 3k was prepared according to the general procedure and was obtained as a colorless oil (40.1 mg, 87% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.62 (dd, $J = 7.2$, 2.1 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.30 – 7.28 (m, 1H), 5.99 (s, 1H), 4.10 – 3.96 (m, 4H), 3.21 (d, $J = 21.7$ Hz, 2H), 1.31 – 1.15 (m, 15H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.33, 171.82, 142.23, 138.70 (d, $J_{CP} = 3.8$ Hz), 132.33, 130.32, 129.75, 129.63, 129.58, 128.77, 128.20, 127.76, 71.01, 62.74 (dd, $J_{CP} = 18.5$, 6.8 Hz), 38.56, 33.31 (d, $J_{CP} = 138.1$ Hz), 27.00, 16.27 (d, $J_{CP} = 5.9$ Hz). HRMS (ESI-TOF) m/z Calcd for C$_{24}$H$_{31}$O$_7$P [M+H]$^+$: 463.1880, found: 463.1882.

The compound 3l was prepared according to the general procedure and was obtained as a colorless oil (24.3 mg, 61% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ $^1$H NMR (600 MHz, Chloroform-d) $\delta$ 7.54 (dd, $J = 7.5$, 1.6 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.39 – 7.34 (m, 3H), 7.33 (dd, $J = 7.3$, 1.6 Hz, 1H), 5.97 (s, 1H), 5.14 (s, 2H), 3.66 (s, 3H), 2.11 (s, 3H), 1.24 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.47, 170.83, 169.64, 142.27, 140.16, 135.98, 131.79, 130.51, 129.24, 129.06, 128.51, 128.31, 127.99, 127.49, 71.22, 66.08, 52.39, 38.63, 26.99, 20.99. HRMS (ESI-TOF) m/z Calcd for C$_{23}$H$_{26}$O$_6$ [M+H]$^+$: 399.1802, found: 399.1803.
(R)-2-(4'-methoxy-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3m): The compound 3m was prepared according to the general procedure and was obtained as a colorless oil (17.0 mg, 50% yield). 

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.56 (dd, $J = 7.5$, 1.7 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.36 – 7.28 (m, 3H), 6.93 (d, $J = 8.8$ Hz, 2H), 6.04 (s, 1H), 3.83 (s, 3H), 1.21 (s, 9H). 

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.51, 174.43, 159.14, 142.57, 132.00, 131.50, 130.72, 130.59, 129.16, 128.12, 127.61, 113.77, 70.81, 55.27, 38.62, 26.98. HRMS (ESI-TOF) m/z Calcd for C$_{20}$H$_{22}$O$_3$ [M+H]$^+$: 343.1540, found: 343.1543.

(R)-2-(4'-nitro-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3n): The compound 3n was prepared according to the general procedure and was obtained as a colorless oil (13.7 mg, 38% yield). 

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.26 (d, $J = 8.1$ Hz, 2H), 7.72 – 7.54 (m, 3H), 7.53 – 7.42 (m, 2H), 7.34 – 7.27 (m, 1H), 5.89 (s, 1H), 1.20 (s, 9H). 

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.45, 174.66, 144.54, 137.95, 135.41, 135.16, 133.09, 131.46, 130.53, 130.15, 129.49, 129.07, 128.29, 123.54, 70.50, 38.64, 26.92. HRMS (ESI-TOF) m/z Calcd for C$_{19}$H$_{19}$NO$_6$ [M+H]$^+$: 358.1285, found: 358.1287.

(R)-2-(4'-bromo-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3o): The compound 3o was prepared according to the general procedure and was obtained as a colorless oil (30.4 mg, 75% yield). 

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.63 – 7.48 (m, 3H), 7.48 – 7.37 (m, 2H), 7.35 – 7.26 (m, 4H), 5.96 (s, 1H), 1.21 (s, 9H). 

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.49, 174.12, 141.53, 138.57, 131.47, 131.39, 131.14, 130.40, 129.31, 128.26, 128.19, 122.10, 70.67, 38.62, 26.95. HRMS (ESI-TOF) m/z Calcd for C$_{19}$H$_{19}$BrO$_4$ [M+Na]$^+$: 413.0359, found: 413.0359.

(R)-2-(4'-chloro-4'-methyl-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3q): The compound 3q was prepared according to the general procedure and was obtained as a colorless oil (28.5 mg, 79% yield). 

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.57 (d, $J = 2.2$ Hz, 1H), 7.42 (dd, $J = 8.3$, 2.2 Hz, 1H), 7.31 – 7.18 (m, 5H), 6.01 (s, 1H), 2.40 (s, 3H), 1.25 (s, 9H). 

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 176.97, 173.84, 140.87, 137.30, 135.16, 133.09, 132.74, 131.47, 128.93, 128.78, 128.71, 127.56, 70.01, 38.18, 26.50, 20.73. HRMS (ESI-TOF) m/z Calcd for C$_{20}$H$_{21}$ClO$_4$ [M+Na]$^+$: 383.1020, found: 383.1019.

2-(5-chloro-4'-methyl-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3r): The compound 3r was prepared according to the general procedure and was obtained as a colorless oil (22.8 mg, 63% yield). 

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 8.4$ Hz, 1H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.32 (d, $J = 2.3$ Hz, 1H), 7.28 – 7.19 (m, 4H), 5.96 (s, 1H), 2.39 (s, 3H), 1.20 (s, 9H). 

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.41, 174.66, 144.54, 137.95, 135.41, 135.04, 130.50, 130.00, 129.49, 129.18, 129.10, 127.88, 70.26, 38.58, 26.92, 21.19. HRMS (ESI-TOF) m/z Calcd for C$_{20}$H$_{21}$ClO$_4$ [M+Na]$^+$: 383.1020, found:
2-(4'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3s): The compound 3s was prepared according to the general procedure and was obtained as a colorless oil (20.2 mg, 51% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.74 – 7.63 (m, 2H), 7.63 – 7.60 (m, 1H), 7.36 – 7.24 (m, 4H), 6.09 (s, 1H), 2.43 (s, 3H), 1.24 (s, 9H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 177.32, 174.21, 143.55, 138.17, 135.31, 135.18, 129.29, 129.17, 128.65, 127.51, 124.43, 123.72 (q, \(J_{CF3} = 32.5\) Hz), 70.23, 38.63, 26.92, 21.19. HRMS (ESI-TOF) m/z Calcd for C\(_{20}\)H\(_{21}\)F\(_3\)O\(_4\)[M+H]\(^+\): 395.1465, found: 395.1465.

2-(4'-methyl-[1,1'-biphenyl]-2-yl)acetic acid (5a\(_{mono}\)): The compound 5a\(_{mono}\) was prepared according to the general procedure and was obtained as a colorless oil (6.0 mg, 26% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.37 – 7.15 (m, 8H), 3.62 (s, 2H), 2.38 (s, 3H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 177.37, 142.09, 137.51, 136.44, 130.75, 129.87, 128.62, 128.51, 126.94, 126.87, 38.10, 29.26, 20.72. HRMS (ESI-TOF) m/z Calcd for C\(_{15}\)H\(_{14}\)O\(_2\)[M+H]\(^+\): 227.1067, found: 227.1069.

2-(4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)acetic acid (5a\(_{di}\)): The compound 5a\(_{di}\) was prepared according to the general procedure and was obtained as a colorless oil (21.6 mg, 68% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.39 – 7.33 (m, 1H), 7.26 – 7.23 (m, 2H), 7.23 – 7.16 (m, 8H), 3.53 (s, 2H), 2.39 (s, 6H). HRMS (ESI-TOF) m/z Calcd for C\(_{22}\)H\(_{20}\)O\(_2\)[M+H]\(^+\): 317.1536, found: 317.1536.

2.4 Gram-Scale Arylation of Mandelic acid

(R)-2-(4'-methyl-[1,1'-biphenyl]-2-yl)-2-(pivaloyloxy)acetic acid (3a): To a 150 mL pressure vessel was added (R)-2-phenyl-2-(pivaloyloxy)acetic acid 1a (5 mmol, 1.18 g, 1 equiv), 1-Iodo-4-methylbenzene 2a (10 mmol, 2.18 g, 2 equiv), Pd(OAc)\(_2\) (0.25 mmol, 56 mg, 5 mol%), AgOAc (10 mmol, 1.67 g, 2 equiv), KOAc (15 mmol, 1.47 g, 3 equiv) and HFIP (50 mL). The reaction tube was sealed using a plastic screw cap and the mixture was heated at 80 °C for 24 h. After completion, the reaction was allowed to cool to room temperature and a 1.0 N HCl solution (25 mL) was added to the solution. The solution was extracted with Et\(_2\)O (3 x 25 mL) and the combined organic extract was dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The crude product was purified by column chromatography (hexanes:EtOAc:HOAc = 66:33:1) to yield 3a (1.37 g, 84%).

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383.1020.
2.5 General Procedure for the Acetoxylation of Mandelic acid

A 8 mL vial with fully covered solid Teflon lined screw cap equipped with a magnetic stir bar was charged with the substrate (0.1 mmol, 1.0 equiv), PhI(OAc)\(_2\) (64 mg, 0.2 mmol, 2.0 equiv), Pd(OAc)\(_2\) (1.1 mg, 0.005 mmol, 5 mol%), KOAc (29 mg, 0.3 mmol, 3.0 equiv) and HFIP (1 mL). The vial was closed and stirred at 50 °C for 24 h. The reaction vessel was then cooled to rt. A 1.0 N HCl solution (1 mL) was then added, and the mixture was extracted with Et\(_2\)O (3 × 3 mL). The organic layers were combined, filtered through a pad of Celite® 545 and concentrated in vacuo. The resulting residue was purified by preparative TLC using 2:1 hexanes:EtOAc (with 1% HOAc) as the eluent.

(R)-2-(2-acetoxyphenyl)-2-(pivaloyloxy)acetic acid (6a): The compound 6a was prepared according to the general procedure and was obtained as a colorless oil (18.3 mg, 63% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.52 (dd, \(J = 7.8, 1.7\) Hz, 1H), 7.44 – 7.39 (m, 1H), 7.30 – 7.25 (m, 1H), 7.16 (dd, \(J = 8.1, 1.2\) Hz, 1H), 6.20 (s, 1H), 2.29 (s, 3H), 1.23 (s, 9H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 177.57, 172.84, 169.13, 148.58, 130.36, 129.73, 126.42, 126.32, 123.31, 69.06, 38.75, 26.97, 20.85. HPLC chiralcel AD-H column (10% isopropanol in hexanes, with 0.2% TFA, 0.5 mL/min) \(t_r = 20.98\) min (minor), 23.08 min (major): 99% ee. HRMS (ESI-TOF) \(m/z\) Calcd for C\(_{15}\)H\(_{18}\)O\(_6\)[M+H]\(^+\): 295.1176, found: 295.1177.

2.6 General Procedure for the Iodination of Mandelic acid

A 8 mL vial with fully covered solid Teflon lined screw cap equipped with a magnetic stir bar was charged with the substrate (0.1 mmol, 1.0 equiv), I\(_2\) (51 mg, 0.2 mmol, 2.0 equiv), Pd(OAc)\(_2\) (1.1 mg, 0.005 mmol, 5 mol%), AgOAc (33 mg, 0.2 mmol, 2.0 equiv), KOAc (29 mg, 0.3 mmol, 3.0 equiv) and HFIP (1 mL). The vial was closed and stirred at 50 °C for 24 h. The reaction vessel was then cooled to rt. A 1.0 N HCl solution (1 mL) was then added, and the mixture was extracted with Et\(_2\)O (3 × 3 mL). The organic layers were combined, filtered through a pad of Celite® 545 and concentrated in vacuo. The resulting residue was dissolved in toluene/MeOH (3:1, 0.5
mL) and 150 µl TMSCHN₂ (2N solution in hexane, CAUTION!!! Inhalation of TMSCH₂N₂ is potentially fatal and the chemical should be handled in the fume hood carefully.) was added dropwise to the reaction mixture. The solution was stirred for 30 min at r.t. and subsequently quenched with 0.5 mL AcOH. The mixture was concentrated in vacuo and purified by preparative TLC using 9:1 hexanes:EtOAc to give the corresponding methy ester.

(R)-1-(2-iodophenyl)-2-methoxy-2-oxoethyl pivalate (7a): The compound 7a was prepared according to the general procedure and was obtained as a colorless oil (19.3 mg, 51% yield). ¹H NMR (600 MHz, CDCl₃) δ 7.90 (dd, J = 8.0, 1.2 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.10 – 7.04 (m, 1H), 6.27 (s, 1H), 3.75 (s, 3H), 1.28 (s, 9H). ¹³C NMR (150 MHz, CDCl₃) δ 177.43, 169.06, 140.00, 137.38, 130.70, 128.90, 128.60, 99.62, 77.46, 52.61, 38.77, 27.05. HPLC chiralcel AD-H column (10% isopropanol in hexanes, with 0.2% TFA, 0.5 mL/min) tr= 9.00 min (major), 10.18 min (minor): 99% ee. HRMS (ESI-TOF) m/z Calcd for C₁₄H₁₇IO₄ [M+H]+: 377.0244, found: 377.0244.

2.7 General Procedure for the Olefination Reaction

A 8 mL vial with septum screw cap quipped with a magnetic stir bar was charged with the substrate (0.1 mmol, 1.0 equiv), Pd(OAc)₂ (1.1 mg, 0.005 mmol, 5 mol%), Ac-Leu-OH (2.6 mg, 0.015 mmol, 15 mol%) and KHCO₃ (20 mg, 0.2 mmol, 2.0 equiv). The vial was evacuated and flushed with O₂ (three times). After adding dry t-AmylOH (0.5 mL) and the olefin coupling partner (0.2 mmol, 2.0 mmol) to the reaction mixture, the vial was closed with a fully covered solid Teflon lined cap and stirred at 80 °C for 3 h (CAUTION!!! The reaction is run in a sealed vessel at elevated temperature under a 1 atm O₂ environment. Though no incidents have been encountered in the submitters’ laboratory, it is nonetheless recommended that a blast shield be used is used while heating in larger scale). The reaction vessel was then cooled to rt. A 1.0 N HCl solution (1 mL) was then added, and the mixture was extracted with Et₂O (3 × 3 mL). The organic layers were combined, filtered through a pad of Celite® 545 and concentrated in vacuo. The resulting residue was purified by preparative TLC using 2:1 hexanes:EtOAc (with 1% HOAc) as the eluent.

(R,E)-2-(2-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-2-(pivaloyloxy)acetic acid (9a mono): The reaction was performed with Ac-t-Leu-OH (2.6 mg, 0.015 mmol, 15 mol%) at 80 °C for 3 h under air. The title compound 9a mono was obtained as a colorless oil (23.8 mg, 71% yield). ¹H NMR (600 MHz, CDCl₃) δ 8.14 (d, J = 15.8 Hz, 1H), 7.63 –
(R,E)-2-acetoxy-2-(2-ethoxy-3-oxoprop-1-en-1-yl)phenyl)acetic acid (9b_mono): The reaction was performed with Ac-Gly-OH (1.8 mg, 0.015 mmol, 15 mol%) at 90 °C for 2 h. The title compound 9b_mono was obtained as a colorless oil (13.1 mg, 45% yield).\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.11 (d, \(J = 15.8\) Hz, 1H), 7.58 (dd, \(J = 7.1, 2.0\) Hz, 1H), 7.51 (dd, \(J = 6.8, 2.0\) Hz, 1H), 7.42 – 7.34 (m, 2H), 7.35 – 7.26 (m, 4H), 6.34 (d, \(J = 15.8\) Hz, 2H), 4.24 (q, \(J = 7.1\) Hz, 2H), 1.30 (t, \(J = 7.1\) Hz, 3H). \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 176.99, 172.26, 166.56, 141.32, 136.27, 134.65, 134.31, 130.15, 129.24, 128.54, 128.53, 128.47, 128.22, 127.33, 121.56, 76.29, 71.41, 60.66, 14.26. HRMS (ESI-TOF) m/z Calcd for C\(_{23}\)H\(_{26}\)O\(_5\) [M+H]\(^+\): 341.1857, found: 341.1857.

(R)-2-(2,6-bis((E)-3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-2-(pivaloyloxy) acetic acid (9a_di): The reaction was performed at 90 °C for 6 h. The title 9a_di compound was obtained as a colorless oil (35.3 mg, 82% yield).\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.22 (d, \(J = 15.6\) Hz, 2H), 7.56 (d, \(J = 7.8\) Hz, 2H), 7.41 (t, \(J = 7.8\) Hz, 1H), 6.61 (s, 1H), 6.31 (d, \(J = 15.6\) Hz, 2H), 4.23 (q, \(J = 7.1\) Hz, 4H), 1.50 (t, \(J = 7.1\) Hz, 6H), 1.22 (s, 9H). \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 176.99, 172.26, 166.38, 142.13, 136.12, 131.68, 129.58, 129.09, 122.68, 68.99, 60.80, 38.79, 26.88, 14.17. HRMS (ESI-TOF) m/z Calcd for C\(_{23}\)H\(_{26}\)O\(_5\) [M+H]\(^+\): 343.1857, found: 433.1857.
(R,E)-2-(5-chloro-2-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-2-(pivaloyloxy)acetic acid (9e): The compound 9e was prepared according to the general procedure and was obtained as a colorless oil (31.0 mg, 84% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.07 (d, \(J = 15.8\) Hz, 1H), 7.54 (d, \(J = 8.5\) Hz, 1H), 7.49 (d, \(J = 2.1\) Hz, 1H), 7.38 (dd, \(J = 8.4, 2.0\) Hz, 1H), 6.34 (d, \(J = 15.5\) Hz, 1H), 6.19 (s, 1H), 4.25 (q, \(J = 7.1\) Hz, 2H), 1.31 (t, \(J = 7.1\) Hz, 3H), 1.26 (s, 9H). \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 177.38, 172.48, 166.43, 140.14, 136.03, 134.38, 132.59, 129.79, 129.10, 128.69, 121.94, 71.02, 60.89, 38.77, 26.93, 14.20. HRMS (ESI-TOF) m/z Calcd for C\(_{18}\)H\(_{21}\)ClO\(_6\) [M+H]^+: 369.1099, found: 369.1098.

((R,E)-2-(2-(3-butoxy-3-oxoprop-1-en-1-yl)-5-chlorophenyl)-2-(pivaloyloxy)acetic acid (9f): The compound 9f was prepared according to the general procedure and was obtained as a colorless oil (35.7 mg, 90% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.07 (d, \(J = 15.8\) Hz, 1H), 7.55 (d, \(J = 8.4\) Hz, 1H), 7.49 (s, 1H), 7.37 (dd, \(J = 8.5, 2.1\) Hz, 1H), 6.35 (d, \(J = 15.7\) Hz, 1H), 6.18 (s, 1H), 4.19 (t, \(J = 6.7\) Hz, 2H), 1.71 – 1.62 (m, 2H), 1.45 – 1.37 (m, 2H), 1.26 (s, 9H), 0.94 (t, \(J = 7.4\) Hz, 3H). \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 177.33, 172.62, 166.48, 140.08, 136.01, 134.46, 132.60, 129.76, 129.11, 128.68, 121.96, 71.02, 64.76, 38.76, 30.64, 26.93, 19.11, 13.69. HRMS (ESI-TOF) m/z Calcd for C\(_{20}\)H\(_{25}\)ClO\(_6\) [M+H]^+: 397.1412, found: 397.1413.

(R,E)-2-(2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-5-chlorophenyl)-2-(pivaloyloxy)acetic acid (9g): The compound 9g was prepared according to the general procedure and was obtained as a colorless oil (35.2 mg, 89% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.98 (d, \(J = 15.6\) Hz, 1H), 7.52 (d, \(J = 8.4\) Hz, 1H), 7.48 (s, 1H), 7.35 (dd, \(J = 8.4, 2.0\) Hz, 1H), 6.26 (d, \(J = 15.4\) Hz, 1H), 6.18 (s, 1H), 1.50 (s, 9H), 1.25 (s, 9H). \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 177.31, 172.50, 165.74, 139.31, 135.70, 134.61, 134.48, 132.85, 129.67, 129.17, 128.68, 123.77, 81.09, 71.27, 38.76, 30.64, 26.93, 19.11, 13.69. HRMS (ESI-TOF) m/z Calcd for C\(_{20}\)H\(_{25}\)ClO\(_6\) [M+H]^+: 397.1412, found: 397.1409.

(R,E)-2-(2-(3-(benzyloxy)-3-oxoprop-1-en-1-yl)-5-chlorophenyl)-2-(pivaloyloxy)acetic acid (9h): The compound 9h was prepared according to the general procedure and was obtained as a colorless oil (31.1 mg, 72% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.14 (d, \(J = 16.1\) Hz, 1H), 7.52 (d, \(J = 8.4\) Hz, 1H), 7.48 (s, 1H), 7.42 – 7.31 (m, 6H), 6.37 (d, \(J = 15.4\) Hz, 1H), 6.16 (s, 1H), 5.22 (s, 2H), 1.21 (s, 9H). \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 177.37, 172.84, 166.24, 140.79, 136.13, 135.70, 134.61, 132.45, 129.75, 129.27, 128.65, 128.55, 128.27, 121.36, 71.28, 66.62, 38.73, 26.89. HRMS (ESI-TOF) m/z Calcd for C\(_{23}\)H\(_{22}\)ClO\(_6\) [M+H]^+: 431.1256, found: 431.1253.
(R,E)-2-(5-chloro-2-styrylphenyl)-2-(pivaloyloxy)acetic acid (9i): The compound 9i was prepared according to the general procedure and was obtained as a colorless oil (17.2 mg, 46% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.59 (d, $J = 8.5$ Hz, 1H), 7.50 – 7.44 (m, 4H), 7.37 – 7.33 (m, 3H), 7.30 – 7.27 (m, 1H), 6.97 (d, $J = 16.0$ Hz, 1H), 6.25 (s, 1H), 1.25 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.54, 173.00, 136.73, 135.68, 133.44, 132.90, 132.64, 129.69, 128.74, 128.65, 128.22, 127.93, 126.80, 123.91, 70.91, 38.76, 26.97. HRMS (ESI-TOF) m/z Calcd for C$_{21}$H$_{21}$ClO$_4$ [M+Na]$^+$: 395.1020, found: 395.1022.

(R,E)-2-(5-chloro-2-(4-methylstyril)phenyl)-2-(pivaloyloxy)acetic acid (9j): The compound 9j was prepared according to the general procedure and was obtained as a colorless oil (24.0 mg, 62% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.57 (d, $J = 8.4$ Hz, 1H), 7.44 (s, 1H), 7.42 – 7.32 (m, 4H), 7.15 (d, $J = 7.9$ Hz, 2H), 6.94 (d, $J = 16.1$ Hz, 1H), 6.25 (s, 1H), 2.35 (s, 3H), 1.25 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.60, 172.45, 138.15, 135.85, 134.04, 133.16, 132.83, 129.53, 129.44, 128.70, 127.75, 126.73, 122.99, 71.17, 38.77, 26.99, 21.29. HRMS (ESI-TOF) m/z Calcd for C$_{22}$H$_{23}$ClO$_4$ [M+Na]$^+$: 409.1177, found: 409.1175.

(R,E)-2-(5-chloro-2-(2-(perfluorophenyl)vinyl)phenyl)-2-(pivaloyloxy)acetic acid (9k): The compound 9k was prepared according to the general procedure and was obtained as a colorless oil (30.6 mg, 66% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 17.0$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.48 (s, 1H), 7.40 (d, $J = 7.8$ Hz, 1H), 6.86 (d, $J = 16.6$ Hz, 1H), 6.18 (s, 1H), 1.25 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.44, 173.00, 144.85 (d, $J_{CF} = 252.0$ Hz), 140.18 (d, $J_{CF} = 253.2$ Hz), 137.75 (d, $J_{CF} = 251.7$ Hz), 134.88 (d, $J_{CF} = 8.5$ Hz), 133.37, 132.71, 129.88, 128.96, 128.01, 116.81, 111.77, 70.91, 38.77, 26.99, 21.29. HRMS (ESI-TOF) m/z Calcd for C$_{21}$H$_{16}$ClF$_5$O$_4$ [M+Na]$^+$: 485.0549, found: 485.0548.

(R,E)-2-(5-chloro-2-(2-diethoxyphosphoryl)vinyl)phenyl)-2-(pivaloyloxy)acetic acid (9l): The compound 9l was prepared according to the general procedure and was obtained as a colorless oil (32.4 mg, 75% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.00 (t, $J = 20.1$ Hz, 1H), 7.51 (s, 1H), 7.47 (d, $J = 8.5$ Hz, 1H), 7.32 (d, $J = 7.2$ Hz, 1H), 6.26 – 6.08 (m, 2H), 4.20 – 4.04 (m, 4H), 1.34 – 1.27 (m, 6H), 1.23 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.03, 169.73, 145.55, 135.98, 132.75 (d, $J_{CP} = 24.7$ Hz), 129.11, 128.16, 117.07, 115.73, 71.61, 62.64 (dd, $J_{CP} = 20.6$, 5.1 Hz), 38.70, 29.68, 26.98, 16.25 (d, $J_{CP} = 6.1$ Hz). HRMS (ESI-TOF) m/z Calcd for C$_{19}$H$_{26}$ClO$_3$P [M+H]$^+$: 433.1177, found: 433.1175.
(R,E)-2-(2-chloro-6-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-2-(pivaloyloxy)acetic acid (9m): The compound 9m was prepared according to the general procedure and was obtained as a colorless oil (13.9 mg, 38% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.16 (d, $J$ = 15.7 Hz, 1H), 7.50 (d, $J$ = 7.9 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.33 (t, $J$ = 7.9 Hz, 1H), 6.99 (s, 1H), 6.30 (d, $J$ = 15.4 Hz, 1H), 4.22 (q, $J$ = 7.1 Hz, 2H), 1.29 (t, $J$ = 7.1 Hz, 3H), 1.23 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 176.97, 172.70, 166.29, 141.49, 137.24, 135.91, 131.06, 130.29, 127.21, 126.24, 122.26, 68.99, 60.82, 38.84, 26.92, 14.15. HRMS (ESI-TOF) m/z Calcd for C$_{18}$H$_{21}$ClO$_6$ [M+H]$^+$: 369.1099, found: 369.1097.

(E)-2-(4-chloro-2-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-2-(pivaloyloxy)acetic acid (9n): The compound 9n was prepared according to the general procedure and was obtained as a colorless oil (22.4 mg, 61% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J$ = 15.8 Hz, 1H), 7.57 (d, $J$ = 2.1 Hz, 1H), 7.44 (d, $J$ = 8.4 Hz, 1H), 7.39 – 7.36 (m, 1H), 6.36 (d, $J$ = 15.7 Hz, 1H), 6.17 (s, 1H), 4.26 (q, $J$ = 7.1 Hz, 2H), 1.32 (t, $J$ = 7.1 Hz, 3H), 1.24 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.43, 172.90, 166.17, 139.92, 135.93, 135.73, 131.14, 130.48, 129.99, 127.37, 122.83, 71.03, 60.91, 38.74, 26.91, 14.21. HRMS (ESI-TOF) m/z Calcd for C$_{18}$H$_{21}$ClO$_6$ [M+H]$^+$: 369.1099, found: 369.1098.

(E)-2-(2-(3-ethoxy-3-oxoprop-1-en-1-yl)-4-(trifluoromethyl)phenyl)-2-(pivaloyloxy)acetic acid (9o): The compound 9o was prepared according to the general procedure and was obtained as a colorless oil (28.1 mg, 70% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.14 (d, $J$ = 15.9 Hz, 1H), 7.83 (s, 1H), 7.65 (s, 2H), 6.42 (d, $J$ = 15.1 Hz, 1H), 6.25 (s, 1H), 4.27 (q, $J$ = 7.1 Hz, 2H), 1.33 (t, $J$ = 7.0 Hz, 3H), 1.24 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.38, 172.44, 166.17, 140.00, 136.29, 135.06, 131.86 (q, $J_{CF}$ = 32.8 Hz), 129.68, 126.48, 124.34, 123.28, 122.54, 61.03, 38.78, 26.95, 14.19. (CF$_3$ peak is overlapping with other peaks) HRMS (ESI-TOF) m/z Calcd for C$_{19}$H$_{23}$F$_3$O$_7$ [M+H]$^+$: 403.1363, found: 403.1360.

(E)-2-(2-(3-ethoxy-3-oxoprop-1-en-1-yl)-4-methoxyphenyl)-2-(pivaloyloxy)acetic acid (9p): The compound 9p was prepared according to the general procedure and was obtained as a colorless oil (12.7 mg, 35% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.09 (d, $J$ = 15.7 Hz, 1H), 7.41 (d, $J$ = 8.6 Hz, 1H), 7.09 (d, $J$ = 2.7 Hz, 1H), 6.94 (dd, $J$ = 8.6, 2.7 Hz, 1H), 6.34 (d, $J$ = 15.7 Hz, 1H), 6.14 (s, 1H), 4.25 (q, $J$ = 7.1 Hz, 2H), 3.84 (s, 3H), 1.32 (t, $J$ = 7.1 Hz, 3H), 1.24 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.61, 173.55, 166.45, 160.22, 141.24, 135.58, 130.68, 125.05, 121.71, 115.87, 112.28, 71.38, 60.73, 55.41, 38.72, 26.99, 14.23. HRMS (ESI-TOF) m/z Calcd for C$_{19}$H$_{23}$O$_7$Na [M+Na]$^+$: 387.1414, found: 387.1416.
(R,E)-2-((tert-butoxycarbonyl)amino)-2-(2-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)acetic acid (11a): The compound 11a was prepared according to the general procedure and was obtained as a colorless oil (30.7 mg, 88% yield). H NMR (600 MHz, CDCl₃, a mixture of rotational isomers 4:1) δ 8.40 – 8.13 (m, 1.8H), 7.61 – 7.48 (m, 2H), 7.45 – 7.29 (m, 2H), 6.39 (d, J = 15.7 Hz, 1H), 5.83 – 5.44 (m, 1.2H), 4.42 – 4.17 (m, 2H), 1.40 (s, 1.5H), 1.35 (t, J = 7.1 Hz, 3H), 1.15 (s, 7.5H). ¹³C NMR (150 MHz, CDCl₃) δ 172.84, 166.98, 166.55, 141.05, 134.40, 132.53, 131.55, 131.17, 129.73, 129.19, 126.92, 123.71, 122.08, 60.58, 54.15, 14.20. HPLC chiralcel AD-H column (20% isopropanol in hexanes, with 0.2% TFA, 0.5 mL/min) tr= 14.03 min (major), 18.87 min (minor); 99% ee. HRMS (ESI-TOF) m/z Calcd for C₁₁H₁₂NO₆ [M+H]+: 350.1598, found: 350.1593.

(R,E)-2-((1,3-dioxoisindolin-2-yl)-2-(2-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)acetic acid (11b): The reaction was performed with Ac-Gly-OH (1.8 mg, 0.015 mmol, 15 mol%) at 90 °C for 2 h. The title compound 11b was obtained as a colorless oil (27.7 mg, 73% yield). H NMR (600 MHz, CDCl₃) δ 8.17 (d, J = 15.6 Hz, 1H), 7.82 (dd, J = 5.6, 3.3 Hz, 2H), 7.77 (d, J = 7.9 Hz, 1H), 7.69 (dd, J = 5.5, 3.0 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 6.42 (s, 1H), 6.31 (d, J = 15.6 Hz, 1H), 4.33 – 4.17 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 172.50, 166.98, 166.55, 141.05, 134.40, 132.53, 131.55, 131.17, 129.73, 129.19, 126.92, 123.71, 122.08, 60.82, 52.36, 14.22. HRMS (ESI-TOF) m/z Calcd for C₂₃H₂₄NO₆ [M+H]+: 380.1129, found: 380.1127.

(R,E)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-(2-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)acetic acid (11c): The reaction was performed with Ac-Gly-OH (1.8 mg, 0.015 mmol, 15 mol%) at 90 °C for 2 h. The title compound 11c was obtained as a colorless oil (31.6 mg, 67% yield). H NMR (600 MHz, CDCl₃, mixture of rotational isomers) δ 8.26 (t, J = 17.0 Hz, 1.5H), 7.76 (d, J = 7.5 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.62 – 7.51 (m, 2H), 7.48 – 7.22 (m, 5H), 7.19 – 7.00 (m, 2H), 6.93 (d, J = 7.4 Hz, 1H), 6.37 (dd, J = 30.2, 15.5 Hz, 1H), 6.11 (s, 0.5H), 5.73 (d, J = 21.3 Hz, 1H), 4.46 – 4.12 (m, 4H), 4.01 (s, 1H), 1.34 – 1.25 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 173.69, 172.77, 166.92, 166.65, 157.05, 155.41, 143.72, 143.63, 143.32, 143.21, 141.53, 141.19, 141.01, 140.95, 136.84, 135.75, 134.00, 133.89, 130.36, 128.86, 128.62, 127.64, 127.57, 127.49, 127.03, 127.00, 126.86, 125.06, 124.78, 124.65, 121.67, 119.88, 68.51, 67.25, 60.84, 60.65, 54.49, 47.01, 46.64, 14.20. HRMS (ESI-TOF) m/z Calcd for C₂₈H₂₃NO₆ [M+H]+: 472.1755, found: 472.1758.

(R,E)-2-(2-(3-butoxy-3-oxoprop-1-en-1-yl)phenyl)-2-((tert-butoxycarbonyl)amino)acetic acid (11e): The compound 11e was prepared according to the general procedure and was obtained as a colorless oil (32.1 mg, 85% yield). H NMR (600 MHz, CDCl₃, a mixture of
rotational isomers 4:1) δ 8.28 (d, J = 15.5 Hz, 1.8H), 7.60 – 7.49 (m, 2H), 7.34 (m, 2H), 6.39 (d, J = 15.7 Hz, 1.2H), 5.77 – 5.49 (m, 1H), 4.31 – 4.14 (m, 2H), 1.75 – 1.64 (m, 2H), 1.51 – 1.33 (m, 3.7H), 1.15 (s, 7.4H), 0.97 (t, J = 7.4 Hz, 3H). 13C NMR (150 MHz, CDCl3) δ 172.85, 166.76, 156.73, 141.91, 138.11, 133.68, 130.11, 128.10, 126.82, 126.64, 121.34, 81.97, 64.50, 54.12, 30.70, 27.93, 19.17, 13.72. HRMS (ESI-TOF) m/z Calcd for C20H27NO6 [M+H]+: 378.1911, found: 378.1911.

(R,E)-2-(2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)phenyl)-2-((tert-butoxycarbonyl)amino)acetic acid (11f): The compound 11f was prepared according to the general procedure and was obtained as a colorless oil (30.2 mg, 80% yield).1H NMR (600 MHz, CDCl3, a mixture of rotational isomers 4:1) δ 8.29 – 8.03 (m, 1.8H), 7.52 (t, J = 7.0 Hz, 2H), 7.41 – 7.28 (m, 2H), 6.31 (d, J = 15.6 Hz, 1H), 5.71 – 5.48 (m, 1.2H), 1.54 (s, 9H), 1.41 (s, 2H), 1.16 (s, 7H). 13C NMR (150 MHz, CDCl3) δ 172.90, 165.98, 156.68, 140.91, 137.98, 133.89, 129.88, 128.06, 126.84, 126.67, 123.21, 81.89, 80.62, 54.16, 28.19, 27.96. HRMS (ESI-TOF) m/z Calcd for C20H27NO6 [M+H]+: 378.1911, found: 378.1911.

(R,E)-2-(2-(3-(benzyloxy)-3-oxoprop-1-en-1-yl)phenyl)-2-((tert-butoxycarbonyl)amino)acetic acid (11g): The compound 11g was prepared according to the general procedure and was obtained as a colorless oil (32.9 mg, 80% yield).1H NMR (600 MHz, CDCl3, a mixture of rotational isomers) δ 8.42 – 8.23 (m, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.46 – 7.28 (m, 7H), 6.44 (d, J = 15.7 Hz, 1H), 5.71 – 5.49 (m, 1H), 5.32 – 5.21 (m, 2H), 1.41 (s, 2H), 1.13 (s, 7H). 13C NMR (150 MHz, CDCl3) δ 172.79, 166.42, 156.84, 137.46, 136.62, 136.35, 132.40, 128.57, 128.21, 128.17, 128.15, 126.84, 126.69, 120.90, 82.02, 66.39, 54.13, 27.93. HRMS (ESI-TOF) m/z Calcd for C23H25NO6 [M+H]+: 412.1755, found: 412.1752.

(R,E)-2-((tert-butoxycarbonyl)amino)-2-(2-styrylphenyl)acetic acid (11h): The compound 11h was prepared according to the general procedure and was obtained as a colorless oil (21.9 mg, 62% yield).1H NMR (600 MHz, CDCl3, a mixture of rotational isomers 2:1) δ 8.39 (s, 0.7H), 7.71 – 7.47 (m, 4H), 7.41 – 7.20 (m, 5H), 7.13 – 7.03 (m, 1H), 7.00 (d, J = 16.0 Hz, 1H), 5.73 (s, 0.35H), 5.51 (d, J = 4.5 Hz, 0.7H), 5.43 (s, 0.35H), 1.40 (s, 2.5H), 1.16 (s, 6.5H). 13C NMR (150 MHz, CDCl3) δ 173.62, 156.42, 156.73, 142.52, 138.16, 135.98, 133.55, 130.24, 128.57, 128.21, 128.17, 128.15, 126.84, 126.69, 120.90, 82.02, 66.39, 54.13, 27.93. HRMS (ESI-TOF) m/z Calcd for C21H23NO4 [M+H]+: 354.1700, found: 354.1694.

(R,E)-2-((tert-butoxycarbonyl)amino)-2-(2-(4-methylstyryl)phenyl)acetic acid (11i): The compound 11i was prepared according to the general procedure and was obtained as a colorless oil (23.5 mg, 64% yield).1H NMR (600 MHz, CDCl3, a mixture of rotational isomers 2:1)
δ 8.39 (s, 0.7H), 7.70 – 7.02 (m, 9H), 6.97 (d, J = 15.9 Hz, 1H), 5.73 (s, 0.3H), 5.50 (d, J = 4.9 Hz, 0.7H), 5.40 (s, 0.3H), 2.33 (s, 3H), 1.41 (s, 3H), 1.15 (s, 6H). 13C NMR (150 MHz, CDCl3) δ 173.64, 156.85, 137.64, 136.81, 136.27, 134.71, 131.91, 129.39, 127.94, 127.52, 126.77, 126.20, 124.82, 123.92, 81.60, 55.40, 28.02, 21.26. HRMS (ESI-TOF) m/z Calcd for C_{22}H_{25}NO_4 [M+H]^+: 368.1856, found: 368.1858.

(R,E)-2-(((tert-butoxycarbonyl)amino)-2-(2-(perfluorophenyl)vinyl)phenyl)acetic acid (11j): The compound 11j was prepared according to the general procedure and was obtained as a colorless oil (37.6 mg, 85% yield).^1H NMR (600 MHz, CDCl3, a mixture of rotational isomers 3:1) δ 8.28 (s, 0.75H), 8.00 (d, J = 16.6 Hz, 0.75H), 7.88 (d, J = 15.8 Hz, 0.25H), 7.58 (d, J = 7.5 Hz, 1H), 7.48 (s, 1H), 7.40 – 7.28 (m, 2H), 6.88 (d, J = 16.5 Hz, 1H), 5.64 (s, 0.25H), 5.52 (s, 0.25H), 5.50 (d, J = 4.9 Hz, 0.75H), 1.41 (s, 2H), 1.14 (s, 7H). 13C NMR (150 MHz, CDCl3) δ 173.04, 156.79, 144.85 (d, J_{CF} = 250.6 Hz), 139.89 (d, J_{CF} = 253.9 Hz), 137.76 (d, J_{CF} = 249.7 Hz), 137.14, 136.05, 134.99, 129.02, 128.26, 127.14 (d, J_{CF} = 58.0 Hz), 126.62, 126.39, 115.92, 112.41, 81.85, 54.63, 28.17. HRMS (ESI-TOF) m/z Calcd for C_{21}H_{18}F_{5}NO_4 [M+H]^+: 444.1229, found: 444.1230.

2.8 Gram-Scale Olefination of α-Phenylglycine

(R,E)-2-2-(4-acetoxy styryl)phenyl-2-(((tert-butoxycarbonyl)amino)acetic acid (11k): The compound 11k was prepared according to the general procedure and was obtained as a colorless oil (30.5 mg, 74% yield).^1H NMR (600 MHz, CDCl3, a mixture of rotational isomers 2:1) δ 8.37 (s, 0.8H), 7.67 – 7.41 (m, 4H), 7.31 – 7.19 (m, 2H), 7.16 – 7.02 (m, 3H), 6.97 (d, J = 16.0 Hz, 1H), 5.72 (s, 0.4H), 5.54 – 5.39 (m, 1H), 2.29 (s, 3H), 1.40 (s, 3H), 1.15 (s, 6H). 13C NMR (150 MHz, CDCl3) δ 173.57, 169.46, 156.84, 150.17, 136.42, 136.33, 135.28, 130.93, 128.05, 127.91, 127.78, 126.27, 126.13, 121.82, 81.71, 55.37, 28.01, 21.14. HRMS (ESI-TOF) m/z Calcd for C_{23}H_{25}NO_6 [M+H]^+: 412.1755, found: 412.1757.

(R,E)-2-(((tert-butoxycarbonyl)amino)-2-(2-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)acetic acid (11a): An oven-dried, 350 mL Schlenk-type sealed tube with a Teflon high-pressure valve and side arm (the reaction vessel contains a high-vacuum valve with PTFE O-ring at the tip and PTFE wiper to protect the O-ring on the shaft, purchased from Synthware (product F588350)) was equipped with a magnetic stir bar. Palladium(II) acetate (56 mg, 0.25 mmol, 5 mol%), Ac-Leu-OH (130 mg, 0.75 mmol, 15 mol%), Boc-D-α-phenylglycine (10a) (1.26 g, 5.0 mmol, 1.0 equiv), and potassium bicarbonate (1.0 g, 10.0 mmol, 2.0 equiv) were added to the Schlenk tube. t-AmylOH (25.0 mL) and ethyl acrylate (8a) (1.09 mL, 10.0 mmol, 2.0 equiv) were added via syringe addition. The reaction tube was sealed using a plastic screw cap.
The side arm is fitted with a piece of rubber tubing, which, in turn, is connected to a three-way stopcock attached by rubber tubing to a high vacuum line and to a balloon filled with O₂. The reaction tube was evacuated briefly and charged with O₂; this process was repeated three times, and the vessel was sealed tightly. The reaction mixture was stirred at room temperature for 5 min, during which time it is yellow to orange in color. The temperature was then increased to 80 °C for 4 h (CAUTION!!! The reaction is run in a sealed vessel at elevated temperature under a 1 atm O₂ environment. Though no incidents have been encountered in the submitters’ laboratory, it is nonetheless recommended that a blast shield be used while heating). The reaction was allowed to cool to room temperature and a 1.0 N HCl solution (25 mL) was added to the solution. The solution was extracted with EtOAc (3 x 25 mL) and the combined organic extract was dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by column chromatography (hexanes:EtOAc:HOAc = 66:33:1) to yield 11a (1.29 g, 74%).
3. HPLC

Area % Report

Data File:  C:\EZChrom Elite\Enterprise\Projects\Default\Data\Tetsuya\TT02-033_5IPrOH
Method:  C:\EZChrom Elite\Enterprise\Projects\Default\Method\untitled.met
Acquired:  6/20/2014 7:28:36 PM
Printed:  12/8/2014 5:27:37 PM

DAD-CH2 205 nm Results

| Retention Time | Area     | Area % | Height  | Height % |
|----------------|----------|--------|---------|----------|
| 14.533         | 994438   | 1.11   | 54255   | 2.28     |
| 17.353         | 88427713 | 98.89  | 2321766 | 97.72    |
| Totals         | 89422151 | 100.00 | 2376021 | 100.00   |
**DAD-CH2**

**205 nm Results**

| Retention Time | Area   | Area % | Height   | Height % |
|----------------|--------|--------|----------|----------|
| 20.98          | 44560  | 0.12   | 2211     | 0.24     |
| 23.080         | 3713388 | 99.88 | 921266   | 99.76    |
| **Totals**     | **37829039** | **100.00** | **1091362** | **100.00** |

**Area % Report**

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\Navid\nav_234i
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\untitled.met
Acquired: 9/1/2014 4:09:33 PM
Printed: 12/8/2014 5:31:34 PM

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**DAD-CH2**

**205 nm Results**

| Retention Time | Area   | Area % | Height   | Height % |
|----------------|--------|--------|----------|----------|
| 9.000          |        |        |          |          |
| 10.180         |        |        |          |          |
### DAD-CH2
#### 205 nm Results

| Retention Time | Area    | Area % | Height  | Height % |
|----------------|---------|--------|---------|----------|
| 11.813         | 1110226 | 1.45   | 72236   | 2.51     |
| 13.727         | 75687050| 98.55  | 2800318 | 97.49    |
| **Totals**     | 76797276| 100.00 | 2872554 | 100.00   |

### Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\Navid\nav_142ac3
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\untitled.met
Acquired: 5/27/2014 6:37:11 PM
**DAD-CH2**

**205 nm Results**

| Retention Time | Area      | Area % | Height   | Height % |
|----------------|-----------|--------|----------|----------|
| 14.033         | 23856740  | 99.88  | 901073   | 99.54    |
| 18.871         | 27931     | 0.12   | 4167     | 0.46     |
| **Totals**     | **23884671** | **100.00** | **905240** | **100.00** |
4. NMR Spectra for New Compounds
