Aerobic Oxidative Cyclization Under Pd(II) Catalysis: A Regioselective Approach to Heterocycles

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Supporting Information

General procedure:

All reactions were performed in oven-dried flasks. Anhydrous ytterbium triflate and dichlorobis(acetonitrile)palladium(II) were purchased from Aldrich and Strem, respectively, and were used as received. Dichloroethane was distilled over calcium hydride under argon. 1,4-Dioxane (dried over molecular sieve) was purchased from Acros and used as received. THF was distilled from sodium metal-benzophenone ketyl before use. Thin-layer and flash column chromatography were performed on E. Merck silica gel 60 (230–400 mesh ASTM) using ethyl acetate/*n*-hexane as eluting solvents. Syringe pump addition was controlled by a Cole-Parmer[®] infusion dual-syringe pump.

¹H and ¹³C NMR spectra were recorded in deuteriochloroform (CDCl₃) with tetramethylsilane (TMS) as internal standard at ambient temperature unless otherwise indicated on a Bruker Avance DPX 300 Fourier Transform Spectrometer operating at 300 MHz for ¹H and 75 MHz for ¹³C, or a Bruker Avance DPX 400 Fourier Transform Spectrometer operating at 400 MHz for ¹H and 100 MHz for ¹³C. Infrared absorption spectra were recorded as a solution in CH₂Cl₂ with a Bio-Rad FTS 165 Fourier Transform spectrophotometer. Mass spectra were recorded with a Finnigan MAT 95 mass spectrometer for both low resolution and high resolution mass spectra.

Preparation of compounds 1a and 1c:

Reagents and conditions: (a) TsCl, Et₃N, CH₂Cl₂, 0 °C; (b) Allyl bromide, K₂CO₃, acetone, reflux; (c) *N,N*-dimethylacetamide, LDA, THF, -78 °C.

Typical procedure for the preparation of 4:

To a solution of glycine methyl ester hydrochloride (4.0 g, 31.9 mmol) in CH₂Cl₂ (120 mL) was added triethylamine (9.8 mL, 70.1 mmol). *p*-Toluenesulfonyl chloride (7.3 g, 38.2 mmol) in CH₂Cl₂ (40 mL) was added slowly to the reaction mixture via addition funnel at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water (60 mL) and extracted with diethyl ether (60 mL × 3). The combined organic layers were washed with brine (60 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash column chromatography to give **4a**¹ (7.60 g, 31.2 mmol, 98%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.12 (bs, 1H), 3.79 (d, *J* = 5.5 Hz, 2H), 3.64 (s, 3H), 2.42 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 169.6, 144.2, 136.5, 130.1, 127.6, 52.9, 44.4, 21.9.

4c:² Yield 100%; a white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.35 (bs, 1H), 3.97 (q, *J* = 7.3 Hz, 1H), 3.52 (s, 3H), 2.40 (s, 3H), 1.36 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 172.9, 143.9, 137.1, 129.9, 127.5, 52.8, 51.7, 21.8, 20.0.

Typical procedure for the preparation of **5**:

To a solution of **4c** (4.0 g, 15.6 mmol) in acetone (120 mL) was added anhydrous potassium carbonate (2.4 g, 17.1 mmol) and allyl bromide (1.5 mL, 17.1 mmol). The reaction mixture was then stirred and refluxed for 14 h. The mixture was diluted with water (60 mL) and acetone was evaporated. The residue was extracted with diethyl ether (60 mL $\times$ 3). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography to give **5c**³ (4.60 g, 15.5 mmol, 99%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 5.85–5.77 (m, 1H), 5.21–5.08 (m, 2H), 4.65 (q, J = 7.3 Hz, 1H), 3.95–3.81 (m, 2H), 3.55 (s, 3H), 2.41 (s, 3H), 1.40 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.0, 143.5, 137.4, 135.3, 129.7, 127.5, 117.7, 55.1, 52.2, 48.2, 21.7, 16.6.

5a: Yield 98%; a colorless oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, R_f = 0.26; ^1H NMR (300 MHz, CDCl_3) δ 7.71 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.73–5.60 (m, 1H), 5.18 (s, 1H), 5.15–5.12 (dd, J = 7.3, 1.1 Hz, 1H), 4.00 (s, 2H), 3.88 (d, J = 6.5 Hz, 2H), 3.61 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 169.6, 143.8, 137.0, 132.5, 129.8, 127.6, 120.1, 52.3, 51.0, 47.1, 21.8; IR (CH_2Cl_2) 3053, 2988, 2958, 1755, 1647, 1599, 1495, 1439, 1342, 1161 cm^{-1} ; LRMS (EI, 20 eV) m/z 224 ($\text{M}^+ - \text{COOMe}$, 50), 155 (Ts, 67), 128 ($\text{M}^+ - \text{Ts}$, 100); HRMS (EI) for $\text{C}_{13}\text{H}_{17}\text{O}_4\text{NS}$ (M^+): calcd 283.0878, found 283.0846.

Typical procedure for the preparation of **1**:

To a solution of LDA [freshly prepared from diisopropylamine (0.91 mL, 6.5 mmol) and *n*-BuLi (2.45 M in hexane, 2.6 mL, 6.5 mmol) in THF (40 mL) at $-78\text{ }^{\circ}\text{C}$] was added *N,N*-dimethylacetamide (0.55 mL, 5.9 mmol) at $-78\text{ }^{\circ}\text{C}$. After 1 h, a solution of **5a** in THF (20 mL) was added slowly to the reaction mixture via a cannula. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and warmed to room temperature slowly. After 14 h, the reaction mixture was quenched with saturated NH_4Cl solution (60 mL) and extracted with ethyl acetate (60 mL $\times$ 3). The combined organic layers were washed with brine (60 mL), dried over MgSO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography to give **1a** (1.59 g, 4.7 mmol, 80%) as a yellow syrup. Analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, $R_f = 0.42$; ^1H NMR (400 MHz, CDCl_3) δ 14.87 (bs, $0.22 \times 1\text{H}$, enol) 7.72–7.68 (m, 2H), 7.31–7.28 (m, 2H), 5.65–5.54 (m, 1H), 5.36 (s, $0.22 \times 1\text{H}$, enol), 5.16–5.11 (m, 2H), 3.95 (s, $0.78 \times 2\text{H}$, keto), 3.86 (s, $0.22 \times 2\text{H}$, enol), 3.84 (d, $J = 6.6\text{ Hz}$, $0.22 \times 2\text{H}$, enol), 3.80 (d, $J = 6.7\text{ Hz}$, $0.78 \times 2\text{H}$, keto), 3.66 (s, $0.78 \times 2\text{H}$, keto), 3.00 (s, 2H, keto + enol), 2.95 (s, 4H, keto + enol), 2.42 (s, $0.78 \times 3\text{H}$, keto), 2.41 (s, $0.22 \times 3\text{H}$, enol); ^{13}C NMR (100 MHz, CDCl_3) δ 200.6, 172.4, 172.0, 166.9, 144.2, 143.8, 137.2, 135.9, 132.4, 132.1, 130.1, 130.0, 127.8, 127.6, 120.8, 120.0, 87.2, 55.7, 52.2, 51.3, 49.3, 46.3, 38.2, 35.7, 29.9, 21.8; IR (CH_2Cl_2) 3050, 2988, 2929, 1733, 1646, 1601, 1509, 1427, 1341, 1160 cm^{-1} ; LRMS (EI, 20 eV) m/z 224 ($\text{M}^+ - (\text{CO})\text{CH}_2\text{CONMe}_2$, 51), 183 ($\text{M}^+ - \text{Ts}$, 100), 155 (Ts, 54), 114 (44); HRMS (EI) for $\text{C}_{16}\text{H}_{22}\text{O}_4\text{N}_2\text{S}$ (M^+): calcd 338.1300, found 338.1306.

1c: Yield 50%; an orange syrup; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, R_f = 0.61; ^1H NMR (300 MHz, CDCl_3) δ 15.11 (s, $0.23 \times 1\text{H}$, enol) 7.74–7.70 (m, 2H), 7.33–7.29 (m, 2H), 5.85–5.64 (m, 1H), 5.21 (s, $0.23 \times 1\text{H}$, enol), 5.16–5.04 (m, 2H), 4.64–4.53 (m, 1H), 3.96 (d, J = 16.0 Hz, $0.77 \times 1\text{H}$, keto), 3.90–3.72 (m, 2H), 3.60 (d, J = 16.0 Hz, $0.77 \times 1\text{H}$, keto), 2.98–2.41 (m, 6H), 2.41 (s, $0.77 \times 3\text{H}$, keto), 2.39 (s, $0.23 \times 3\text{H}$, enol), 1.33 (d, J = 7.1 Hz, $0.23 \times 3\text{H}$, enol), 1.12 (d, J = 7.0 Hz, $0.77 \times 3\text{H}$, keto); ^{13}C NMR (75.5 MHz, CDCl_3) δ 202.4, 174.8, 171.9, 167.5, 144.0, 143.4, 138.0, 137.2, 136.1, 133.8, 130.1, 129.7, 127.6, 127.5, 119.7, 117.3, 87.1, 60.7, 56.2, 48.8, 47.8, 45.0, 37.9, 35.4, 21.7, 16.5, 12.7; IR (CH_2Cl_2) 3051, 2988, 2940, 1729, 1644, 1596, 1503, 1341, 1161 cm^{-1} ; LRMS (EI, 20 eV) m/z 239 ($\text{M}^+ - (\text{CO})\text{CH}_2\text{CONMe}_2$, 14), 238 (100), 197 ($\text{M}^+ - \text{Ts}$, 20), 155 (Ts, 34), 114 (33); HRMS (EI) for $\text{C}_{17}\text{H}_{24}\text{O}_4\text{N}_2\text{S}$ (M^+): calcd 352.1457, found 352.1447.

Preparation of compound 1b:

Reagents and conditions: (a) Methyl bromoacetate, KH, THF, 0 °C; (b) *N,N*-dimethylacetamide, LDA, THF, –78 °C.

Preparation of 6b:

To a suspension of KH (30% dispersion in oil, 4.1 g, 30.9 mmol) in THF (100 mL) was added a solution of *tert*-butyl *N*-allylcarbamate (4.4 g, 28.1 mmol) in THF (40 mL) via a cannula at 0 °C. After 30 min, methyl bromoacetate (2.8 mL, 30.9 mmol) was added slowly for 10 min. The resulting solution was stirred at room temperature for 14 h. The reaction mixture was quenched with saturated NH_4Cl solution (60 mL) and the solvent was evaporated. The residue was extracted with diethyl ether (60 mL

× 3). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by flash column chromatography to give **6b** (4.00 g, 17.4 mmol, 62%) as a yellow oil. Analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, *R_f* = 0.22; ¹H NMR (400 MHz, CDCl₃) δ 5.82–5.74 (m, 1H), 5.18–5.10 (m, 2H), 3.96 (s, 2H), 3.89 (d, *J* = 5.5 Hz, 1H), 3.84 (s, 1H), 3.73 (s, 3H), 1.47 (s, 5H, major conformer), 1.43 (s, 4H, minor conformer); ¹³C NMR (75.5 MHz, CDCl₃) δ 170.8, 155.9, 155.4, 134.0, 133.9, 117.9, 117.1, 80.7, 52.8, 52.2, 51.0, 50.6, 48.2, 47.8, 28.6, 28.5; IR (CH₂Cl₂) 3062, 3053, 2988, 2952, 1752, 1701, 1642, 1456, 1169 cm⁻¹; LRMS (EI, 20 eV) *m/z* 203 (*M*⁺ – CH=CH₂, 16), 199 (69), 185 (100), 171 (*M*⁺ – C(CH₃)₃, 60); HRMS (EI) for C₁₁H₁₉O₄N (*M*⁺): calcd 229.1314, found 229.1300.

1b: Yield 40%; a yellow oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, *R_f* = 0.39; ¹H NMR (300 MHz, CDCl₃) δ 14.93 (s, 0.07 × 1H, enol), 5.83–5.70 (m, 1H), 5.15–5.11 (m, 2H), 4.07 (s, 2H), 3.92–3.86 (m, 2H), 3.56 (s, 0.62 × 2H, major conformer), 3.52 (s, 0.38 × 2H, minor conformer), 3.01–2.97 (m, 6H), 1.46 (s, 0.62 × 9H, major conformer), 1.42 (s, 0.38 × 9H, minor conformer); ¹³C NMR (75.5 MHz, CDCl₃) δ 201.1, 200.6, 174.2, 172.2, 167.0, 166.4, 156.0, 155.3, 133.8, 133.6, 117.8, 117.1, 86.0, 85.0, 80.7, 80.4, 56.2, 51.4, 50.7, 49.1, 46.5, 46.3, 38.1, 35.7, 28.5; IR (CH₂Cl₂) 3051, 2988, 2929, 1744, 1693, 1647, 1464 cm⁻¹; LRMS (EI, 20 eV) *m/z* 284 (*M*⁺, 17), 228 (15), 211 (28), 184 (18), 129 (11), 114 (100); HRMS (EI) for C₁₄H₂₄O₄N₂ (*M*⁺): calcd 284.1736, found 284.1729.

Preparation of compounds 1d and 1e:

Reagents and conditions: (a) K_2CO_3 , KI, $\text{Br}(\text{CH}_2)_n\text{CH=CH}_2$, Acetone, reflux; (b) *N,N*-dimethylacetamide, LDA, THF, $-78\text{ }^\circ\text{C}$.

Typical procedure for the preparation of 7:

To a solution of **4a** (2.0 g, 8.22 mmol) in acetone (40 mL) was added anhydrous potassium carbonate (1.25 g, 9.04 mmol), anhydrous potassium iodide (682 mg, 4.11 mmol) and 5-bromo-1-pentene (1.1 mL, 9.04 mmol). The reaction mixture was stirred and refluxed for 18 h. The mixture was diluted with water (40 mL) and acetone was evaporated. The residue was extracted with diethyl ether (40 mL $\times$ 3). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography to give **7e** (2.06 g, 6.62 mmol, 81%) as a yellow oil. Analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f = 0.40$; ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, $J = 8.2$ Hz, 2H), 7.29 (d, $J = 8.3$ Hz, 2H), 5.78–5.69 (m, 1H), 4.99 (dd, $J = 15.5, 1.2$ Hz, 1H), 4.96 (dd, $J = 9.8, 1.2$ Hz, 1H), 4.04 (s, 2H), 3.63 (s, 3H), 3.23 (t, $J = 7.5$ Hz, 2H), 2.42 (s, 3H), 2.03 (q, $J = 7.0$ Hz, 2H), 1.63 (quintet, $J = 7.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.4, 143.4, 137.3, 136.7, 129.5, 127.3, 115.3, 52.1, 48.0, 30.5, 27.0, 21.5; IR (CH_2Cl_2) 3063, 3048, 2989, 2957, 1756, 1648, 1603, 1495, 1437, 1341, 1160 cm^{-1} ; LRMS (EI, 20 eV) m/z 256 ($\text{M}^+ - \text{CH}_2\text{CH}_2\text{CH=CH}_2$, 72), 252 (65), 198 (39), 155 (100); HRMS (EI) for $\text{C}_{15}\text{H}_{21}\text{O}_4\text{NS}$ (M^+): calcd 311.1191, found 311.1185.

7d: Yield 72% (based on 53% conversion) as a yellow oil; analytical TLC (silica gel 60), 20% EtOAc in *n*-hexane, $R_f = 0.40$; ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.73–5.66 (m, 1H), 5.06 (dd, $J = 15.6, 1.4$ Hz, 1H), 5.03 (dd, $J = 8.9, 1.4$ Hz, 1H), 4.07 (s, 2H), 3.63 (s, 3H), 3.31 (t, $J = 6.2$ Hz, 2H), 2.42 (s, 3H), 2.29 (q, $J = 6.1$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.4, 143.4,

136.8, 134.4, 129.5, 127.4, 117.3, 52.1, 48.1, 47.7, 32.6, 21.5; IR (CH₂Cl₂) 3074, 3050, 2956, 1755, 1642, 1600, 1495, 1439, 1343, 1160 cm⁻¹; LRMS (EI, 20 eV) *m/z* 256 (M⁺ – CH₂CH=CH₂, 100), 228 (11), 155 (73); HRMS (EI) for C₁₄H₁₉O₄NS (M⁺): calcd 297.1035, found 297.1023.

1d Keto : Enol = 4.0 : 1

1d: Yield 65%; an orange syrup; analytical TLC (silica gel 60), 100% EtOAc, *R_f* = 0.47; ¹H NMR (400 MHz, CDCl₃) δ 14.98 (s, 0.20 × 1H, enol), 7.73–7.68 (m, 2H), 7.32–7.29 (m, 2H), 5.73–5.63 (m, 1H), 5.36 (s, 0.20 × 1H, enol), 5.07–5.00 (m, 2H), 4.05 (s, 0.80 × 2H, keto), 3.90 (s, 0.20 × 2H, enol), 3.67 (s, 0.80 × 2H, keto), 3.28–3.21 (m, 2H), 3.01 (s, 2H, keto + enol), 2.96 (s, 4H, keto + enol), 2.43 (s, 0.80 × 3H, keto), 2.42 (s, 0.20 × 3H, enol), 2.31–2.23 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 200.6, 172.5, 171.9, 167.0, 144.0, 143.7, 136.8, 135.8, 134.6, 129.9, 127.7, 127.5, 117.4, 87.2, 57.1, 50.7, 49.1, 48.6, 45.7, 38.0, 35.6, 32.8, 32.5, 21.7; IR (CH₂Cl₂) 3051, 2988, 2928, 1720, 1646, 1598, 1496, 1450, 1340, 1161 cm⁻¹; LRMS (EI, 20 eV) *m/z* 312 (M⁺ – CH₂CH=CH₂, 14), 238 (25), 198 (100), 184 (27), 155 (48); HRMS (EI) for C₁₇H₂₄O₄N₂S (M⁺): calcd 352.1457, found 352.1454.

1e Keto : Enol = 4.6 : 1

1e: Yield 69%; an orange syrup; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, *R_f* = 0.38; ¹H NMR (400 MHz, CDCl₃) δ 14.94 (s, 0.18 × 1H, enol), 7.72–7.68 (m, 2H), 7.33–7.31 (m, 2H), 5.78–5.68 (m, 1H), 5.39 (s, 0.18 × 1H, enol), 5.02–4.95 (m, 2H), 3.98 (s, 0.82 × 2H, keto), 3.87 (s, 0.18 × 2H, enol), 3.70 (s, 0.82 × 2H, keto), 3.20–3.10 (m, 2H), 3.03 (s, 2H, keto + enol), 2.97 (s, 4H, keto + enol), 2.43 (s, 0.82 × 3H, keto), 2.42 (s, 0.18 × 3H, enol), 2.05–2.01 (m, 2H), 1.65–1.57 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 200.8, 172.8, 172.1, 167.1, 144.1, 143.7, 137.6, 137.5,

137.0, 136.7, 130.1, 130.0, 127.9, 127.6, 115.8, 115.7, 87.3, 57.2, 50.9, 49.7, 49.1, 45.9, 38.2, 35.7, 31.1, 30.9, 30.0, 27.6, 27.4, 21.8; IR (CH₂Cl₂) 3058, 2990, 2940, 1729, 1655, 1596, 1493, 1326 cm⁻¹; LRMS (EI, 20 eV) *m/z* 252 (M⁺ – (CO)CH₂CONMe₂, 36), 211 (M⁺ – Ts, 100), 198 (27); HRMS (EI) for C₁₈H₂₆O₄N₂S (M⁺): calcd 366.1613, found 366.1607.

Preparation of compounds **1f** and **1h**:

Reagents and conditions: (a) *tert*-Butyl bromoacetate, 50% aqueous NaOH, (*n*-Bu)₄NHSO₄, benzene, 0 °C; (b) SOCl₂, MeOH, 0 °C; (c) *N,N*-dimethylacetamide, LDA, THF, –78 °C.

Typical procedure for the preparation of **8**:

To a solution of allyl alcohol (3.0 g, 51.6 mmol) in benzene (60 mL) was added tetrabutylammonium hydrogen sulfate (1.8 g, 5.2 mmol) and 50% aqueous NaOH solution (60 mL) at 0 °C. With vigorous stirring, *tert*-butyl bromoacetate (11.4 mL, 77.5 mmol) was added slowly and the mixture was warmed to room temperature. After 16 h, the mixture was diluted with *n*-pentane (60 mL) and water (60 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (60 mL × 3). The combined organic layers were concentrated in vacuo. The crude product was dissolved in methanol (170 mL). With vigorous stirring at 0 °C, thionyl chloride (11.2 mL, 155 mmol) was added via addition funnel for 10 min. After 12 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (*n*-pentane/ Et₂O as solvents) to give **8f**⁴ (5.00 g, 38.4 mmol, 74% over 2 steps) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.89–5.82 (m, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.3 Hz, 1H), 4.04 (s, 4H), 3.70 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 170.9, 133.9, 118.3, 72.5, 67.2, 51.9.

8h⁵: Yield 87% (over 2 steps); a yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 5.77–5.65 (m, 1H), 5.19 (d, *J* = 17.6 Hz, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 4.09 (d, *J* = 16.4 Hz, 1H), 4.00 (d, *J* = 16.4 Hz, 1H), 3.93 (quintet, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 1.31 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 171.4, 139.3, 117.5, 78.2, 65.7, 52.0, 21.4.

1f Keto : Enol = 3.2 : 1

1f: Yield 66%; a yellow oil; analytical TLC (silica gel 60), 60% EtOAc in *n*-hexane, *R_f* = 0.20; ¹H NMR (300 MHz, CDCl₃) δ 14.86 (s, 0.24 × 1H, enol), 5.97–5.84 (m, 1H), 5.46 (s, 0.24 × 1H, enol), 5.33–5.19 (m, 2H), 4.17 (s, 0.76 × 2H, keto), 4.07 (d, *J* = 5.6 Hz, 2H), 4.03 (s, 0.24 × 2H, enol), 3.60 (s, 0.76 × 2H, keto), 3.01 (s, 4H, keto + enol), 2.97 (s, 2H, keto + enol); ¹³C NMR (75.5 MHz, CDCl₃) δ 203.0, 173.6, 172.1, 166.8, 134.2, 133.9, 118.0, 117.6, 85.5, 75.0, 72.5, 72.1, 69.3, 45.4, 38.0, 35.4; IR (CH₂Cl₂) 3051, 2996, 2934, 1730, 1646, 1596 cm⁻¹; LRMS (EI, 20 eV) *m/z* 144 (*M*⁺ – CH₂CH=CH₂, 66), 129 (66), 127 (11), 114 (100); HRMS (EI) for C₉H₁₅O₃N (*M*⁺): calcd 185.1052, found 185.1050.

1h Keto : Enol = 2.4 : 1

1h: Yield 58%; a yellow oil; analytical TLC (silica gel 60), 60% EtOAc in *n*-hexane, *R_f* = 0.29; ¹H NMR (300 MHz, CDCl₃) δ 14.85 (s, 0.29 × 1H, enol), 5.80–5.65 (m, 1H), 5.46 (s, 0.29 × 1H, enol), 5.24–5.16 (m, 2H), 4.16 (d, *J* = 17.2 Hz, 1H), 4.07 (d, *J* = 17.3 Hz, 1H), 3.96–3.85 (m, 1H), 3.64 (d, *J* = 15.5 Hz, 0.71 × 1H, keto), 3.57 (d, *J* = 15.5 Hz, 0.71 × 1H, keto), 3.01 (s, 4H, keto + enol), 2.97 (s, 2H, keto + enol), 1.29 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 203.6, 174.3, 172.3, 166.9, 139.6, 139.2, 117.3, 116.8, 85.5, 78.2, 77.6, 73.5, 67.6, 45.8, 38.2, 35.6, 21.4, 21.3; IR (CH₂Cl₂) 3046, 2985, 2934, 1729, 1646, 1596 cm⁻¹; LRMS (EI, 20 eV) *m/z* 199 (*M*⁺,

12), 144 (61), 129 (45), 115 (100); HRMS (EI) for C₁₀H₁₇O₃N (M⁺): calcd 199.1208, found 199.1198.

Preparation of compound **1g**:

Reagents and conditions: (a) Allyl bromide, Ag₂O, Et₂O, rt; (b) *N,N*-dimethylacetamide, LDA, THF, −78 °C.

For the preparation of **9g**, see reference 6.

9g⁶: Yield 91%; a yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 5.99–5.86 (m, 1H), 5.29 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.15 (dd, *J* = 12.6, 5.5 Hz, 1H), 4.00 (q, *J* = 6.8 Hz, 1H), 3.94, (dd, *J* = 12.5, 6.1 Hz, 1H), 1.42 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 173.5, 134.5, 117.8, 74.3, 71.3, 61.0, 18.9, 14.5.

1g: Yield 48%; a yellow oil; analytical TLC (silica gel 60), 60% EtOAc in *n*-hexane, *R_f* = 0.39; ¹H NMR (300 MHz, CDCl₃) δ 14.83 (s, 0.49 × 1H, enol), 5.99–5.85 (m, 1H), 5.44 (s, 0.49 × 1H, enol), 5.33–5.17 (m, 2H), 4.12–3.87 (m, 3H), 3.76 (d, *J* = 16.1 Hz, 0.51 × 1H, keto), 3.63 (d, *J* = 16.1 Hz, 0.51 × 1H, keto), 3.01 (s, 3H), 2.99 (s, 0.51 × 3H, keto), 2.98 (s, 0.49 × 3H, enol), 1.40 (d, *J* = 6.6 Hz, 0.51 × 3H, keto), 1.37 (d, *J* = 6.8 Hz, 0.49 × 3H, enol); ¹³C NMR (75.5 MHz, CDCl₃) δ 206.9, 178.1, 172.6, 167.4, 134.9, 134.4, 117.8, 117.4, 84.5, 80.5, 75.5, 71.3, 70.7, 44.5, 38.3, 35.7, 20.4, 17.0; IR (CH₂Cl₂) 3052, 2990, 2948, 1732, 1643, 1596 cm^{−1}; LRMS (EI, 20 eV) *m/z* 199 (M⁺, 3), 143 (33), 127 (14), 114 (100); HRMS (EI) for C₁₀H₁₇O₃N (M⁺): calcd 199.1208, found 199.1211.

Preparation of compound **1i**:

Reagents and conditions: (a) Br₂, CHCl₃, 0 °C; (b) NaH, THF, , -78 °C.

Typical procedure for the preparation of **1i**:

Step (a)^{7a}: To a solution of *N,N*-dimethylacetoacetamide (20 g, 154.8 mmol) in chloroform (300 mL) over ice-water bath was added bromine (9.1 mL, 177.6 mmol) dropwise with vigorous stirring. The mixture was stirred overnight at room temperature. The solvent was distilled off to give a crude product of γ -bromo-*N,N*-dimethylacetoacetamide.

Step (b)^{7b}: To a suspension of sodium hydride (60% dispersion in oil, 724 mg, 18.1 mmol) in THF (60 mL) was added the crude product of γ -bromo-*N,N*-dimethylacetoacetamide slowly at -78 °C. After 2 h, a solution of alkoxide in THF [prepared from corresponding alcohol (16.5 mmol) and sodium hydride (18.1 mmol) in THF (60 mL) at 0 °C] was cannulated to the reaction mixture at -78 °C. After 5 h, the reaction was quenched by water (10 mL) and was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL), dried over Mg₂SO₄ and concentrated in vacuo. The crude product was purified by flash column chromatography to give **1i** (1.76 g, 8.3 mmol, 50%) as a yellow oil; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, *R_f* = 0.4; ¹H NMR (300 MHz, CDCl₃) δ 14.83 (bs, 0.22 $\times$ 1H, enol), 5.84–5.75 (m, 1H), 5.48 (s, 0.22 $\times$ 1H, enol), 5.21–5.14 (m, 2H), 4.10 (s, 0.78 $\times$ 2H, keto), 3.90 (s, 0.22 $\times$ 2H, enol), 3.62 (s, 0.78 $\times$ 2H, keto), 3.00 (s, 4H, keto + enol), 2.97 (s, 2H, keto + enol), 1.32 (s, 0.22 $\times$ 6H, enol), 1.30 (s,

0.78 $\times$ 6H, keto); ^{13}C NMR (75.5 MHz, CDCl_3) δ 203.5, 174.9, 172.7, 166.6, 142.6, 142.2, 114.8, 114.3, 86.8, 84.7, 76.3, 68.5, 62.4, 45.4, 44.9, 37.7, 35.1, 25.5, 25.3; IR (CH_2Cl_2) 3051, 2990, 2929, 1738, 1645, 1514 cm^{-1} ; LRMS (EI, 20 eV) m/z 213 (M^+ , 3), 154 (26), 144 (39), 114 (100); HRMS (EI) for $\text{C}_{11}\text{H}_{19}\text{O}_3\text{N}$ (M^+): calcd 213.1365, found 213.1365.

Ytterbium Triflate-Promoted Palladium(II)-Catalyzed Aerobic Oxidative Cyclizations:

- 1a,2a:** X = Ts-N; $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H}$; $n = 1$
1b,2b: X = Boc-N; $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H}$; $n = 1$
1c,2c: X = Ts-N; $\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{R}_4 = \text{H}$; $n = 1$
1d,2d: X = Ts-N; $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H}$; $n = 2$
1e,2e: X = Ts-N; $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H}$; $n = 3$
1f,2f: X = O; $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H}$; $n = 1$
1g,2g: X = O; $\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{R}_4 = \text{H}$; $n = 1$
1h,2h: X = O; $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{H}$, $\text{R}_4 = \text{Me}$; $n = 1$
1i,2i: X = O; $\text{R}_1 = \text{R}_2 = \text{H}$, $\text{R}_3 = \text{R}_4 = \text{Me}$; $n = 1$

Typical procedure for ytterbium triflate-promoted palladium(II)-catalyzed aerobic oxidative cyclization (Table 1):

In a two-necked 25-mL round-bottomed flask equipped with a magnetic stir bar, a mixture of $\text{PdCl}_2(\text{MeCN})_2$ (4 mg, 0.015 mmol) and anhydrous $\text{Yb}(\text{OTf})_3$ (93 mg, 0.15 mmol) in dry THF (5 mL) solution was stirred for 5 min at room temperature. To this mixture was added a dry THF (5 mL) solution of **1c** (53 mg, 0.15 mmol) *via* syringe under oxygen atmosphere (1 atm). The addition rate (5 mL over 3 hr) of **1c** was controlled accurately by using a syringe pump. After the addition, the reaction progress was monitored by TLC analysis. The reaction was complete after 4 hr. The mixture was filtered through a short pad of silica gel (EtOAc as eluent) and

concentrated in vacuo. The residue was purified by flash column chromatography (90–100% EtOAc in *n*-hexane) to give **2c** (47 mg, 90% yield).

2a: Yield 98%; an orange oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, $R_f = 0.15$; ^1H NMR (300 MHz, CDCl_3) δ 7.68 (d, $J = 8.3$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H), 4.21 (d, $J = 18.2$ Hz, 1H), 4.12 (d, $J = 16.4$ Hz, 1H), 3.63 (d, $J = 18.2$ Hz, 1H), 3.44–3.38 (dd, $J = 16.3, 1.8$ Hz, 1H), 3.02 (s, 3H), 2.73 (s, 3H), 2.44 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 187.9, 165.5, 154.4, 145.0, 134.1, 132.8, 130.5, 128.1, 52.2, 48.9, 37.9, 34.8, 21.9, 19.3; IR (CH_2Cl_2) 3053, 3047, 2988, 2927, 1731, 1686, 1641, 1495, 1426, 1355, 1166 cm^{-1} ; LRMS (EI, 20 eV) m/z 336 (M^+ , 14), 181 (72), 153 (36), 136 (100); HRMS (EI) for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{N}_2\text{S}$ (M^+): calcd 336.1144, found 336.1139.

2b: Yield 68%; a yellow oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, $R_f = 0.20$; ^1H NMR (300 MHz, CDCl_3) δ 4.53–3.85 (m, 4H), 3.07 (s, 1H), 2.98 (s, 2H), 2.87 (s, 2H), 2.82 (s, 1H), 2.08–1.79 (m, 3H), 1.52–1.44 (m, 9H); ^{13}C NMR (76 MHz, CDCl_3) δ 189.9, 169.5, 166.3, 155.3, 133.6, 81.9, 52.5, 50.1, 38.0, 34.8, 28.5, 19.1; IR (CH_2Cl_2) 3052, 2990, 2940, 1733, 1646, 1378, 1246 cm^{-1} ; LRMS (EI, 20 eV) m/z 283 ($\text{M}^+ + \text{H}$, 18), 226 (50), 183 (41), 180 (71), 136 (100); HRMS (EI) for $\text{C}_{14}\text{H}_{22}\text{O}_4\text{N}_2$ (M^+): calcd 282.1580, found 282.1580.

2c: Yield 90%; a yellow oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, $R_f = 0.48$; ^1H NMR (300 MHz, CDCl_3) δ 7.69 (d, $J = 8.3$ Hz, $0.76 \times 2\text{H}$, major conformer), 7.64 (d, $J = 8.3$ Hz, $0.24 \times 2\text{H}$, minor conformer), 7.30 (d, $J = 8.1$ Hz, 2H), 4.53–4.27 (m, 2H), 4.05–3.94 (m, 1H), 2.99 (s, 1H), 2.96 (s, 2H), 2.73 (s, $0.24 \times 3\text{H}$, minor conformer), 2.43 (s, 1H), 2.40 (s, 2H), 2.37 (s, $0.76 \times 3\text{H}$, major conformer), 1.92 (s, $0.76 \times 3\text{H}$, major conformer), 1.87 (s, $0.24 \times 3\text{H}$, minor conformer), 1.36 (d, $J = 7.2$ Hz, $0.24 \times 3\text{H}$, minor conformer), 1.29 (d, $J = 7.2$ Hz, $0.76 \times 3\text{H}$, major conformer); ^{13}C NMR (75.5 MHz, CDCl_3) δ 191.5, 165.6, 153.2, 144.4, 137.0, 132.3, 130.5, 127.4, 56.4, 44.7, 37.4, 34.7, 21.8, 18.8, 15.3; IR (CH_2Cl_2) 3051, 2988, 2923, 1738, 1683, 1643, 1495, 1436, 1403, 1246, 1163 cm^{-1} ; LRMS (EI, 20 eV) m/z 350 (M^+ , 12), 209 (7), 195 (38), 167 (23), 150 (100); HRMS (EI) for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{N}_2\text{S}$ (M^+): calcd 350.1300, found 350.1296.

2d

2d: Yield 91%; a yellow oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, $R_f = 0.13$; ^1H NMR (500 MHz at -30 °C, CDCl_3) δ 7.70 (d, $J = 8.2$ Hz, 2H), 7.39 (d, $J = 8.2$ Hz, 2H), 4.42 (d, $J = 18.1$ Hz, 1H), 3.90–3.85 (m, 1H), 3.56 (d, $J = 18.2$ Hz, 1H), 3.10 (s, 3H), 3.08–3.03 (m, 1H), 3.02 (s, 3H), 2.76–2.63 (m, 2H), 2.48 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (126 MHz at -30 °C, CDCl_3) δ 197.2, 167.3, 151.9, 144.4, 136.0, 133.4, 130.0, 126.9, 55.9, 44.3, 38.0, 34.7, 34.4, 24.2, 21.7; IR (CH_2Cl_2) 3051, 2990, 2948, 1733, 1677, 1637, 1420, 1164 cm^{-1} ; LRMS (EI, 20 eV) m/z 350 (M^+ , 21), 237 (69), 195 (100), 150 (67); HRMS (EI) for $\text{C}_{17}\text{H}_{22}\text{O}_4\text{N}_2\text{S}$ (M^+): calcd 350.1300, found 350.1297.

Mixture of conformers

2e

2e: Yield 62%; a brown oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, $R_f = 0.15$; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.66–7.58 (m, 2H), 7.29–7.22 (m, 2H),

3.82 (s, 1H), 3.57 (m, 1H), 3.43–3.38 (m, 1H), 3.13 (t, $J = 5.8$ Hz, 1H), 2.98–2.79 (m, 6H), 2.35 (s, 3H), 2.33–2.27 (m, 2H), 1.70 (s, 3H), 1.34–1.13 (m, 2H); ^{13}C NMR (76 MHz, CD_2Cl_2) δ 197.5, 167.2, 155.2, 144.1, 136.3, 135.2, 130.0, 127.4, 55.7, 44.9, 38.0, 35.4, 31.7, 30.8, 21.5, 11.8; IR (CH_2Cl_2) 3050, 2985, 2940, 1744, 1688, 1637, 1495, 1420, 1164 cm^{-1} ; LRMS (EI, 20 eV) m/z 364 (M^+ , 23), 251 (88), 209 (100), 164 (99), 155 (33); HRMS (EI) for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{N}_2\text{S}$ (M^+): calcd 364.1464, found 364.1447.

2f

2f: Yield 97%; a brown oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, $R_f = 0.12$; ^1H NMR (400 MHz, CDCl_3) δ 4.37 (d, $J = 18.0$ Hz, 1H), 4.32 (d, $J = 17.5$ Hz, 1H), 4.21 (d, $J = 16.1$ Hz, 1H), 4.13 (d, $J = 16.1$ Hz, 1H), 3.08 (s, 3H), 2.91 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 190.6, 165.6, 157.4, 132.8, 71.5, 68.9, 38.1, 34.9, 17.4; IR (CH_2Cl_2) 3051, 2985, 2940, 1733, 1682, 1639 cm^{-1} ; LRMS (EI, 20 eV) m/z 183 (M^+ , 31), 153 (100), 139 (20); HRMS (EI) for $\text{C}_9\text{H}_{13}\text{O}_3\text{N}$ (M^+): calcd 183.0895, found 183.0889.

Mixture of conformer (1.9 : 1)

2g

2g: Yield 96%; a brown oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, $R_f = 0.21$; ^1H NMR (300 MHz, CDCl_3) δ 4.45–4.29 (m, 2H), 4.16–4.06 (m, 1H), 3.08 (s, 3H), 2.91 (s, 2H), 2.87 (s, 1H), 1.93 (s, 2H), 1.92 (s, 1H), 1.42 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.6, 166.1, 156.7, 156.3, 132.3, 76.5, 76.0, 68.7, 67.0, 38.2, 38.0, 34.8, 17.3, 17.2, 15.7, 15.5; IR (CH_2Cl_2) 3051, 2996, 2940, 1788,

1732, 1688, 1639 cm^{-1} ; LRMS (EI, 20 eV) m/z 197 (M^+ , 26), 167 (100), 153 (22), 136 (21); HRMS (EI) for $\text{C}_{10}\text{H}_{15}\text{O}_3\text{N}$ (M^+): calcd 197.1052, found 197.1035.

2h

2h: Yield 98%; a brown oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, R_f = 0.18; ^1H NMR (500 MHz at -30°C , CDCl_3) δ 4.52–4.46 (m, 1H), 4.39–4.32 (m, 1H), 4.20–4.17 (m, 1H), 3.12 (s, 3H), 2.98 and 2.94 (s, 3H), 1.98 (s, 3H), 1.53–1.50 (m, 3H); ^{13}C NMR (126 MHz at -30°C , CDCl_3) δ 191.2, 191.1, 165.7, 165.5, 131.9, 131.3, 125.9, 73.0, 72.5, 70.5, 67.4, 38.0, 34.5, 18.6, 18.1, 17.5, 16.6; IR (CH_2Cl_2) 3051, 2989, 2948, 1734, 1682, 1639 cm^{-1} ; LRMS (ESI) m/z 198 ($\text{M}^+ + \text{H}$, 90); HRMS (EI) for $\text{C}_{10}\text{H}_{15}\text{O}_3\text{N}$ (M^+): calcd 197.1052, found 197.1054.

2i

2i: Yield 92%; a brown oil; analytical TLC (silica gel 60), 80% EtOAc in *n*-hexane, R_f = 0.24; ^1H NMR (400 MHz, CDCl_3) δ 4.30 (d, J = 17.1 Hz, 1H), 4.21 (d, J = 17.1 Hz, 1H), 3.07 (s, 3H), 2.88 (s, 3H), 1.92 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.2, 166.3, 162.5, 131.9, 75.5, 66.8, 37.9, 34.8, 26.1, 23.6, 17.6; IR (CH_2Cl_2) 3051, 2988, 2929, 1732, 1684, 1639 cm^{-1} ; LRMS (EI, 20 eV) m/z 211 (M^+ , 63), 167 (52), 153 (100), 110 (50); HRMS (EI) for $\text{C}_{11}\text{H}_{17}\text{O}_3\text{N}$ (M^+): calcd 211.1208, found 211.1201.

Preparation of compounds 1fa:

Reagents and conditions: (a) LiAlD_4 , Et_2O , $0\text{ }^\circ\text{C}$ to rt then quench by H_2O ; (b) *tert*-Butyl bromoacetate, 50% aqueous NaOH , $(n\text{-Bu})_4\text{NHSO}_4$, benzene, $0\text{ }^\circ\text{C}$; (c) SOCl_2 , MeOH , $0\text{ }^\circ\text{C}$; (d) *N,N*-dimethylacetamide, LDA , THF , $-78\text{ }^\circ\text{C}$.

Typical procedure for the preparation of **8fa**:

To a solution of LiAlD_4 (2.83 g, 67.3 mmol; Aldrich, 98% deuterium) in dry diethyl ether (140 mL) was stirred at $0\text{ }^\circ\text{C}$. The mixture was slowly added acryloyl chloride (8.2 mL, 100.9 mmol) as an ethereal solution (40 mL) through addition funnel over 30 min. The resulting solution was warmed to room temperature and stirred for 14 h. The mixture was cooled to $0\text{ }^\circ\text{C}$ and H_2O (2.8 mL) was slowly added over a 10-min period. After stirring for another 15 min, 15% aqueous NaOH solution (2.8 mL) and then H_2O (2.8 mL) were added. The grey slurry was filtered via a short pad of celite and was washed by Et_2O (150 mL). The filtrate was concentrated in vacuo to give allyl-1- d_2 alcohol as a yellow oil.⁸

The crude product (allyl-1- d_2 alcohol) was converted to **8fa** in 22% yield (over 3 steps from acryloyl chloride) employing the procedure for the preparation of **8**.

8fa

>95% deuterium content by ^1H NMR

8fa: a yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 5.92 (dd, $J = 17.2, 10.4\text{ Hz}$, 1H), 5.35–5.23 (m, 2H), 4.10 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.1, 133.9, 118.8, 73.4 (m, $-\text{CD}_2-$), 67.3, 52.1.

1fa was prepared in 76% yield from **8fa** employing the procedure for the preparation of **1**.

>95% deuterium content by ^1H NMR

1fa: a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 14.88 (s, $0.35 \times 1\text{H}$, enol), 5.93–5.86 (m, 1H), 5.46 (s, $0.35 \times 1\text{H}$, enol), 5.34–5.22 (m, 2H), 4.18 (s, $0.65 \times 2\text{H}$, keto), 4.03 (s, $0.35 \times 2\text{H}$, enol), 3.60 (s, $0.65 \times 2\text{H}$, keto), 3.01 (s, 4H, keto + enol), 2.97 (s, 2H, keto + enol); ^{13}C NMR (100 MHz, CDCl_3) δ 203.2, 173.9, 172.3, 166.9, 134.3, 133.9, 118.5, 118.1, 85.6, 75.1, 71.7 (m, $-\text{CD}_2-$), 69.4, 45.7, 38.2, 35.7; LRMS (EI, 20 eV) m/z 187 (M^+ , 6), 144 (64); HRMS (EI) for $\text{C}_9\text{H}_{13}\text{D}_2\text{O}_3\text{N}$ (M^+): calcd 187.1178, found 187.1180.

Preparation of compound 1fb:

Reagents and conditions: (a) LiAlD_4 , Et_2O , 0 °C to rt then quench by H_2O ; (b) *tert*-Butyl bromoacetate, 50% aqueous NaOH, (*n*-Bu)₄NHSO₄, benzene, 0 °C; (c) SOCl_2 , MeOH, 0 °C; (d) *N,N*-dimethylacetamide, LDA, THF, −78 °C.

Typical procedure for the preparation of 8fb:

To a solution of LiAlD_4 (2.00 g, 47.6 mmol; Aldrich, 98% deuterium) in dry diethyl ether (140 mL) was stirred at −10 °C. The mixture was slowly added propargyl alcohol (2.67 g, 47.6 mmol) as an ethereal solution (30 mL) through addition funnel over 30 min. The resulting solution was warmed to room temperature and stirred for 14 h. The mixture was cooled to 0 °C and H_2O (2.0 mL) was slowly added over a 10-min period. After stirring for another 15 min, 15% aqueous NaOH solution (2.0 mL)

and then H₂O (2.0 mL) were added. The grey slurry was filtered via a short pad of celite and was washed by Et₂O (100 mL). The filtrate was concentrated in vacuo to give allyl-2-*d*₁ alcohol as a yellow oil.⁹

The crude product (allyl-2-*d*₁ alcohol) was converted to **8fb** in 49% yield (over 3 steps from propargyl alcohol) employing the procedure for the preparation of **8**.

8fb

95% deuterium content by ¹H NMR

8fb: a yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 5.18 (s, 1H), 5.11 (s, 1H), 3.98 (s, 4H), 3.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.8, 133.5 (t, *J*_{CD} = 23.9 Hz), 118.0, 72.3, 67.1, 51.7.

1fb was isolated in 91% yield from **8fb** employing the procedure for the preparation of **1**.

1fb Keto : Enol = 2.2 : 1

95% deuterium content by ¹H NMR

1fb: a yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 14.88 (s, 0.31 × 1H, enol), 5.46 (s, 0.31 × 1H, enol), 5.30 (s, 1H), 5.23 (s, 1H), 4.29–4.24 (m, 1H), 4.18 (s, 0.69 × 1H, keto), 4.13 (s, 0.31 × 1H, enol), 4.07 (s, 0.69 × 2H, keto), 4.03 (s, 0.31 × 2H, enol), 3.60 (s, 0.69 × 2H, keto), 3.01 (s, 4H, keto + enol), 2.97 (s, 2H, keto + enol); ¹³C NMR (75.5 MHz, CDCl₃) δ 203.2, 173.9, 172.3, 166.9, 133.7 (t, *J*_{CD} = 23.9 Hz), 118.2, 117.8, 85.6, 75.2, 72.6, 72.3, 69.5, 58.9, 45.7, 38.2, 35.7; LRMS (EI, 20 eV) *m/z* 186 (*M*⁺, 1), 129 (78), 114 (100); HRMS (EI) for C₉H₁₄DO₃N (*M*⁺): calcd 186.1115, found 186.1099.

Typical procedure for the aerobic oxidative cyclization of **1fa** and **1fb** (eq 2 and 3):

2fa and **2fb** were obtained employing the procedure for the preparation of **2a–i** except that the loading of Yb(OTf)₃ was 30 mol %.

Figure S1. ^1H NMR Spectra of **2f**, **2fa** and **2fb**

Figure S2. ^{13}C NMR Spectra of **2f**, **2fa** and **2fb**

Expanded Region of ^{13}C NMR Spectrum of 2fa

2fa: Yield 65%; >95% deuterium content; a brown oil; ^1H NMR (300 MHz, CDCl_3) δ 4.21 (d, $J = 16.1$ Hz, 1H), 4.13 (d, $J = 16.1$ Hz, 1H), 3.07 (s, 3H), 2.91 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 190.7, 165.6, 157.4, 132.8, 71.4, 68.1 (m, $-\text{CD}_2-$), 38.1, 34.9, 17.4; LRMS (EI, 20 eV) m/z 185 (M^+ , 7), 153 (100); HRMS (EI) for $\text{C}_9\text{H}_{11}\text{D}_2\text{O}_3\text{N}$ (M^+): calcd 185.1021, found 183.1029. See Figure S1 and S2.

2fb: Yield 48%; 90% deuterium content; a brown oil; ^1H NMR (300 MHz, CDCl_3) δ 4.34 (s, 2H), 4.22 (d, $J = 16.1$ Hz, 1H), 4.13 (d, $J = 16.1$ Hz, 1H), 3.08 (s, 3H), 2.91 (s, 3H), 1.93 (t, $J_{\text{HD}} = 2.3$ Hz, 2H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 190.6, 165.6, 157.2, 133.0, 71.5, 68.9, 38.1, 34.9, 17.1 (t, $J_{\text{CD}} = 19.8$ Hz, $-\text{CH}_2\text{D}$); LRMS (EI, 20 eV) m/z 184 (M^+ , 14), 154 (100); HRMS (EI) for $\text{C}_9\text{H}_{12}\text{DO}_3\text{N}$ (M^+): calcd 184.0958, found 184.0962. See Figure S1 and S2.

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