SUPPORTING INFORMATION

Oxidative Synthesis of Cyclic Acyl Aminals Through Carbon-Carbon σ -Bond Activation

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General Procedures. THF and Et₂O were dried by distillation over Na/benzophenone under N₂. Toluene, 1,2-dichloroethane, and CH₂Cl₂ were dried by distillation over CaH₂. Photoirradiations were performed with a Hanovia 450 W medium pressure mercury lamp through Pyrex filtration. Reagents were used as purchased without further purification unless noted. Chemical shifts (δ) are reported in ppm. All compounds prepared from phenylalanine underwent racemization during aldehyde formation.¹

Reagents and Conditions

a) Allylmagnesium bromide, THF, 89%. b) MsCl, Et₃N, CH₂Cl₂. c) NaN₃, Bu₄Ni, DMF. d) Ph₃P, THF, H₂O, then C₅H₁₁COCl, Et₃N, 41% (three steps). e) 9-BBN, THF, then NaOOH, 44%.

Scheme 1.

Representative Stoichiometric Cyclization Protocol

Acylaminal **2a**

To **1a** (50 mg, 0.172 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 °C were added *N*-methylquinolinium hexafluorophosphate (59 mg, 0.206 mmol), and sodium acetate (100 mg, 1.21 mmol). The mixture was stirred at room temperature while irradiating for 5 h. The distance between the reaction flask and lamp was 4 cm. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product **2a** (29 mg, 86%): ¹H NMR (300 MHz, CDCl₃) δ 6.05 (d, *J* = 7.9 Hz, 1H), 5.09 (dt, *J* = 8.3, 2.3 Hz, 1H), 3.96 (m, 1H), 3.58 (m, 1H), 2.16 (m, 1H) 1.64–1.26 (m, 10H), 0.87 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 77.8, 36.9, 31.7, 31.5, 25.3, 25.2, 23.0, 22.5, 22.3, 14.0; IR (neat) 3286, 2950, 2855, 1660, 1544, 1453, 1208, 1083, 1032, 903 cm⁻¹; HRMS (EI) calcd for C₁₁H₂₁NO₂ 199.1572, found 199.1588.

Representative Catalytic Aerobic Cyclization Protocol

Acylaminal **2a**

To **1a** (89 mg, 0.306 mmol) in dichloroethane (10 mL) and toluene (2 mL) in a borosilicate flask at 20 °C were added *N*-methylquinolinium hexafluorophosphate (2 mg,

7 μmol), sodium acetate (178 mg, 2.17 mmol), and sodium thiosulfate (178 mg, 1.13 mmol). The mixture was stirred and irradiated at a distance of 4 cm for 3 h at room temperature while bubbling air gently. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product **2a** (45 mg, 75%).

Reagents and Conditions

a) NaH, DMF, then MeI, 82%. b) 9-BBN, THF, then NaOOH, 92%.

Scheme 2.

Acylaminal 2b

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **1b** (55 mg, 0.178 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (1 mg, 2 μmol), sodium acetate (100 mg, 1.2 mmol), and sodium thiosulfate (100 mg, 0.63 mmol). The mixture was irradiated for 4 h. Chromatographic purification (50% EtOAc in hexanes) provided the desired product (27 mg, 71%), which was analyzed as a 1:1 mixture of amide rotamers. ^1H NMR (300 MHz, CDCl_3) δ 5.64 (dd, J = 5.6, 3.3 Hz, 1H), 4.82 (dd, J = 8.5, 1.8 Hz, 1H), 4.02 (bt, J = 12.9 Hz, 2H), 3.58 (m, 1H), 2.91 (s, 3H), 2.88 (s, 3H), 2.41–2.25 (m, 4H), 1.99–1.24 (m, 12H), 0.88 (t, J = 5.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.3, 85.4, 81.2, 68.4, 34.1, 33.5, 31.7, 29.7, 29.2, 28.6, 27.3, 25.3, 25.2, 25.1, 24.5, 23.5, 23.4, 23.1, 22.6, 14.0; IR (neat) 2933, 2855, 1660, 1462, 1410, 1372, 1316, 1079, 1036, 911 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_2$ 213.1728, found 213.1732.

Reagents and Conditions

a) TBSCl, imidazole, DMF, 95%. b) Me_3Al , Cp_2ZrCl_2 , CH_2Cl_2 , then BnCl , $\text{Pd}(\text{PPh}_3)_4$, THF, 76%. c) $\text{BH}_3 \cdot \text{THF}$, THF, then NaOOH , 81%. d) MsCl , Et_3N , CH_2Cl_2 , 0 °C. e) NaN_3 , Bu_4NI , DMF, 55 °C. f) Ph_3P , THF, H_2O , then $\text{C}_5\text{H}_{11}\text{COCl}$, Et_3N , 61% (three steps). g) Bu_4NF , THF, 96%.

Scheme 3.

Acylaminal 4

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **3** (64 mg, 0.21 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μmol), sodium acetate (120 mg, 1.5 mmol), and sodium thiosulfate (120 mg, 0.76 mmol). The mixture was irradiated for 2.5 h. Chromatographic purification (30% hexanes in EtOAc) provided the desired product (32 mg, 72%) as a partially separable 2:1 mixture of *anti*- and *syn*-diastereomers. *Syn*-diastereomer, faster eluting: ^1H NMR (300 MHz, CDCl_3) δ 5.96 (bd, $J = 7.65$, 1H), 5.31 (dd, $J = 3.1$, 6.0 Hz, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.21 (t, $J = 7.4$ Hz, 2H), 1.98-1.31 (m, 13H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.90 (t, $J = 1.7$ Hz, 3H); ^1H NMR (300MHz, CDCl_3 , D_2O) δ 5.31 (d, $J = 2.4$ Hz, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.21 (t, $J = 7.4$ Hz, 2H), 1.98-1.31 (m, 13H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.90 (t, $J = 1.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.0, 79.1, 65.7, 37.1, 36.39, 31.92, 31.61, 29.0, 25.4, 22.5, 21.8, 14.1, 13.1; IR (neat) 3440, 2954, 2851, 1655, 1466, 1075, 997, 731 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_2$ 213.1728, found 213.1731. *Anti*-diastereomer, slower eluting: ^1H NMR (300 MHz, CDCl_3) δ 5.75 (bs, 1H), 4.79 (t, $J = 9.5$ Hz, 1H), 3.57 (m, 1H), 3.00 (m, 1H), 2.20 (t, $J = 7.15$ Hz, 2H), 1.90 (m, 1H), 1.63-1.26 (m, 12H), 0.89 (m, 6H); ^1H NMR (300 MHz, CDCl_3 , D_2O) δ 4.79 (d, $J = 9.3$ Hz, 1H), 3.57 (m, 1H), 3.00 (m, 1H), 2.20 (t, $J = 7.2$ Hz, 2H), 1.90 (m, 1H), 1.63-1.26 (m, 12H), 0.89 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.3, 82.9, 67.8, 37.1, 36.4, 32.1, 31.6, 26.0, 25.4, 22.5, 17.4, 14.1; IR (neat) 3441, 2955, 2852, 1656, 1466, 1075 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_2$ 213.1728, found 213.1731.

Scheme 4.

Reagents and Conditions

a) NaH, DMF, then MeI, 36%. b) 9-BBN, THF, then NaOOH, 78%.

Acylaminal 6

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **5** (98 mg, 0.31 mmol), dichloroethane (10 mL), toluene (2 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μ mol), sodium acetate (178 mg, 2.2 mmol), and sodium thiosulfate (178 mg, 1.1 mmol). The mixture was irradiated for 3 h. Purification by flash chromatography (50% EtOAc in hexanes) provided the desired product (47 mg, 67%), which was analyzed as a 1:1 mixture of amide rotamers: ^1H NMR (300 MHz, CDCl_3) δ 5.36 (d, J = 9.8 Hz, 1H), 4.45 (d, J = 9.4 Hz, 1H), 4.02 (m, 2H), 3.54 (m, 2H), 2.91 (d, J = 11.8 Hz, 3H), 2.31 (m, 3H), 1.99-1.25 (m, 6H), 0.90 (m, 3H), 0.80 (m, 3H); ^1H NMR (300 MHz, DMSO, 378 K) δ 4.85 (bs, 1H), 4.02 (m, 2H), 3.54 (m, 2H), 2.91 (d, J = 11.8 Hz, 3H), 2.31 (m, 3H), 1.99-1.25 (m, 6H), 0.90 (m, 3H), 0.80 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.3, 90.9, 86.0, 68.5, 34.3, 33.7, 33.3, 32.5, 32.2, 31.9, 26.4, 26.1, 25.4, 22.7, 17.0, 16.7, 14.1; IR (neat) 2952, 2853, 1654, 1456, 1073, 1005; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{25}\text{NO}_2$ 227.1885, found 227.1891.

Reagents and Conditions

a) DMSO, oxalyl chloride, CH_2Cl_2 , -78°C , then Et_3N , 74%. b) $\text{HONH}_2\cdot\text{HCl}$, NaOAc, EtOH, 88%. c) LiAlH_4 , NiCl_2 , Et_2O . d) $\text{C}_5\text{H}_{11}\text{COCl}$, Et_3N , THF, 63% (two steps). e) NaH, DMF, then MeI. f) Bu_4NF , THF.

Scheme 5.

Acylaminal 6

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **7** (29 mg, 0.09 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μ mol), sodium acetate (60 mg, 0.73 mmol), and sodium thiosulfate (60 mg, 0.38 mmol). The mixture was irradiated for 3 h. Purification by flash chromatography (50% EtOAc in hexanes) provided the desired product (12 mg, 56%).

Scheme 6.²

Reagents and Conditions

a) MsCl , Et_3N , CH_2Cl_2 . b) NaN_3 , DMF, 55°C . c) Ph_3P , THF, H_2O . d) $p\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$, Et_3N , CH_2Cl_2 , 34% (four steps).

Aminal 9

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **8** (55 mg, 0.11 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μ mol), sodium acetate (100 mg, 1.2 mmol), and sodium thiosulfate (100 mg, 0.63 mmol). The mixture was irradiated for 5 h. Purification by flash chromatography (10% EtOAc in hexanes) provided the desired product (31 mg, 68%). ^1H NMR (300 MHz, CDCl_3) δ 8.35 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.9 Hz, 2H), 5.22 (m, 1H), 3.61 (dd, J = 2.9, 10.0 Hz, 1H), 3.36 (m, 2H), 3.07 (t, J = 2.7, 10.1 Hz, 1H), 1.89 (m, 1H), 1.62-1.23 (m, 18H), 0.88, (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 130.1, 124.2, 84.6, 67.9, 63.2, 41.5, 33.1, 29.9, 29.6, 29.5, 26.4, 24.8, 22.7, 21.2, 18.1, 14.3, 14.1; IR (neat) 3561, 3101, 2924, 2855, 1604, 1535, 1466, 1350, 1165, 1105, 937, 847, 744; HRMS (EI) calcd for $\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}_5\text{S}$ 398.1875, found 398.1868.

Reagents and Conditions

a) MsCl , Et_3N , CH_2Cl_2 . b) NaN_3 , DMF, 55 $^\circ\text{C}$. c) Ph_3P , THF, H_2O . d) $p\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$, Et_3N , CH_2Cl_2 , 36% (four steps).

Scheme 7.

(*N,N*)-Acylaminal 11

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **10** (40 mg, 0.084 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μ mol), sodium acetate (100 mg, 1.2 mmol), and sodium thiosulfate (100 mg, 0.63 mmol). The mixture was irradiated for 5 h. Purification by flash chromatography (10% EtOAc in hexanes) provided the desired product (21 mg, 64%). ^1H NMR (300 MHz, CDCl_3) δ 8.30 (d, J = 8.9 Hz, 2H), 8.04 (d, J = 8.9 Hz, 2H), 6.10 (m, 1H), 5.90 (m, 1H), 3.80 (m, 1H), 2.91 (dt, J = 8.3, 3.2 Hz, 1H), 1.79 (m, 4H), 1.22 (m, 10H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.0, 150.0, 146.0, 128.8, 124.5, 58.4, 42.0, 36.6, 31.4, 31.1, 25.2, 22.4, 18.8, 14.0; IR (neat) 3313, 2939, 2861, 1650, 1527, 1354, 1147, 1097, 924, 740 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{26}\text{N}_3\text{O}_5\text{S}$ 384.1593, found 384.1583.

Reagents and Conditions

a) LiAlH_4 , THF, reflux, then $(\text{Boc})_2\text{O}$, NaOH , H_2O , CH_2Cl_2 . b) Oxalyl chloride, DMSO, CH_2Cl_2 , -78 $^\circ\text{C}$, then Et_3N . c) Allylmagnesium bromide, THF, 0 $^\circ\text{C}$. d) NaH , DMF, then MeI , 54% (4 steps). e) $\text{BH}_3\cdot\text{THF}$, THF, 0 $^\circ\text{C}$, then NaOOH , 65%. f) Dihydropyran, PPTs, CH_2Cl_2 , 0 $^\circ\text{C}$, 91%.

Scheme 8.

Acylaminal 15

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **14** (55 mg, 0.13 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μ mol), sodium acetate (100 mg, 1.2 mmol), and sodium thiosulfate (100 mg, 0.63 mmol). The mixture was irradiated for 5 h. Chromatographic purification (30% acetone in hexanes) provided the desired product (19 mg, 63%) as a separable 2:1 mixture of *anti*- and *syn*-diastereomers. *Anti*-diastereomer, faster eluting: ^1H NMR (300 MHz, CDCl_3) δ 5.70 (bs, 1H), 4.90 (bd, J = 9.4 Hz, 1H), 3.93 (m, 1H), 3.53 (dt, J = 2.3, 9.5 Hz, 1H), 3.38 (s, 3H), 3.31 (m, 1H), 2.11 (m, 1H), 1.80-1.25 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.3, 79.8, 75.5, 66.2, 56.7, 28.4, 25.5, 20.3; IR (neat) 3443, 3338, 2930, 1719, 1490, 1367, 1163, 1064, 984, 878 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{21}\text{NO}_4$ 231.1471, found 231.1471. *Syn*-diastereomer, slower eluting: ^1H NMR (300 MHz, CDCl_3) δ 5.11 (bs, 1H), 4.66 (t, J = 8.4 Hz, 1H), 3.88 (m, 1H), 3.50 (dt, J = 2.2, 9.2 Hz, 1H), 3.38 (s, 3H), 2.98 (m, 1H), 2.22 (m, 1H), 1.68-1.44 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.3, 83.0, 80.4, 66.5, 56.7, 29.9, 28.5, 24.8; IR (neat) 3444, 3339, 2931, 1719, 1491, 1367, 1163, 1064, 984, 878 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{21}\text{NO}_4$ 231.1471, found 231.1484.

Reagents and Conditions

a) 2,2-dimethoxypropane, PPTs, PhMe, 34%. b) $\text{BH}_3\cdot\text{THF}$, THF, 0 $^\circ\text{C}$, 71%.
c) Dihydropyran, PPTs, CH_2Cl_2 , 90%.

Scheme 9.

Acylaminal 18

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **17** (100 mg, 0.23 mmol), dichloroethane (10 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μ mol), sodium acetate (200 mg, 2.4 mmol), and sodium thiosulfate (200 mg, 1.3 mmol). The mixture was irradiated for 2 h. Chromatographic purification (45% EtOAc in hexanes) provided the desired product (53 mg, 85%) as a single diastereomer. ^1H NMR (300 MHz, CDCl_3 , 323K) δ 5.15 (bs, 1H), 3.97 (m, 1H), 3.88 (m, 2H), 3.43 (dt, J = 2.8, 8.5 Hz, 2H), 2.13-2.08 (m, 2H), 1.95-1.38 (m, 17H); ^{13}C NMR (75 MHz, CDCl_3) δ 151.9, 128.4, 100.2, 93.9, 83.2, 71.2, 63.7, 31.5, 28.4, 24.8, 22.5, 19.7; IR (neat) 2974, 2934, 2871, 1706, 1457, 1394, 1263, 1180, 1081, 1017 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{20}\text{NO}_4$ 242.1392, found 242.1402.

Reagents and Conditions

a) LiAlH_4 , THF, reflux, then $(\text{Boc})_2\text{O}$, NaOH, H_2O , CH_2Cl_2 . b) Oxalyl chloride, DMSO, CH_2Cl_2 , -78°C , then Et_3N . c) Allylmagnesium bromide, THF, 0°C . d) NaH, DMF, then MeI. e) $\text{BH}_3\cdot\text{THF}$, THF, 0°C , then NaOOH, 43%.

Scheme 10.³

Acylaminal 18

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **19** (30 mg, 0.07 mmol), dichloroethane (2.5 mL), toluene (0.5 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μmol), sodium acetate (60 mg, 0.7 mmol), and sodium thiosulfate (60 mg, 0.4 mmol). The mixture was irradiated for 2.5 h. Chromatographic purification (45% EtOAc in hexanes) provided the desired product (10 mg, 56%) as a single diastereomer. 0.379 mmol).

1. For a method to prepare *N*-protected α -amino aldehydes from amino alcohols without racemization, see Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, 41, 1359.
2. For the preparation of the starting structure in this sequence, see Kumar, V. S.; Floreancig, P. E. *J. Am. Chem. Soc.* **2001**, 123, 3842.
3. For the synthesis of *m*-trifluoromethylphenylalanine, see Pirrung, M. C.; Krishnamurthy, N. *J. Org. Chem.* **1993**, 58, 957.