Supplementary Information: Experimental Section

Molecular Scaffolds with Remote Directing Groups for Selective Palladium-Catalyzed C-H Bond Functionalizations

Erin E. Stache, Curtis A. Seizert, and Eric M. Ferreira*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523

emferr@mail.colostate.edu
Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Materials and methods</td>
<td>S3</td>
</tr>
<tr>
<td>Experimental Section (from text)</td>
<td>S4</td>
</tr>
<tr>
<td>Additional Experiments</td>
<td>S33</td>
</tr>
<tr>
<td>Stereochemical Analysis</td>
<td>S38</td>
</tr>
</tbody>
</table>
Materials and Methods. All reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, N,N-dimethylformamide, dichloromethane, hexanes, and toluene were purified by passing through activated alumina columns. Diisopropylamine was distilled over CaH$_2$. 2-Fluoropyridine was freshly distilled before use. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Gelest (Morrisville, PA), Oakwood Products (West Columbia, SC), Strem (Newburport, MA), Mallinckrodt Chemicals (Phillipsburg, NJ), Spectrum (Gardena, CA) Fischer Scientific (Fair Lawn) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to either $p$-anisaldehyde or KMnO$_4$ solution followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). $^1$H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz), a Varian Inova 400 (at 400 MHz), or a Varian 400 MR (at 400 MHz) and are reported relative to SiMe$_4$ (δ 0.00). $^{13}$C NMR spectra were acquired on either a Varian Inova 400 (at 100 MHz), a Varian Mercury 300 (at 75 MHz), or a Varian 400 MR (at 100 MHz) and are reported relative to SiMe$_4$ (δ 0.0). All IR spectra were obtained on NaCl plates (film) with either a Nicolet Magna FTIR 760, a Nicolet 380 FTIR, or a Bruker Tensor 27. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS. Optical rotations were obtained with an Autopol-III automatic polarimeter.
Experimental Section (from text).

To a solution of (S)-proline (15.0 g, 130 mmol) in aq. NaOH (1 M, 261 mL) and dioxane (65.2 mL) at 0 °C was added Boc$_2$O (33.1 g, 154 mmol) portionwise over 20 min. The resulting mixture was stirred at 0 °C for 30 min, then allowed to warm to 23 °C and stirred overnight. The organic solvent was removed in vacuo. The remaining aqueous solution was acidified to pH ~2 with 1 M KHSO$_4$. The aqueous solution was extracted with CHCl$_3$ (3 x 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na$_2$SO$_4$ and concentrated to afford carbamate 1$^1$ (28.0 g, 99% yield, R$_f$ = 0.17 in 1:1 hexanes/EtOAc) as a white solid, which was sufficiently pure to be taken on to the next step.

To a solution of (S)-N-Boc proline (2.50 g, 11.6 mmol) in CH$_2$Cl$_2$ (38.7 mL) at 0 °C was added isobutyl chloroformate (1.67 mL, 12.8 mmol) and triethylamine (1.80 mL, 12.8 mmol). After stirring for 20 minutes at 0 °C, aniline (1.16 mL, 12.8 mmol) was added, and the reaction was warmed to 23 °C and stirred overnight. The reaction was washed sequentially with aq. KHSO$_4$ (1 M, 50 mL), sat. aq. NaHCO$_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated to afford a pale brown solid. The crude solid was suspended in hexanes (15 mL), cooled to 0 °C, and filtered to afford amide 35 (3.32 g, 98% yield, R$_f$ = 0.52 in 1:1 hexanes/EtOAc) as a light brown solid, which was sufficiently pure to be taken on to the next step.

To a solution of amide 35 (3.32 g, 11.4 mmol) in CH$_2$Cl$_2$ (22.8 mL) at 23 °C was added TFA (17.6 mL, 228 mmol). The solution was stirred at 23 °C for 1 h, and the solvent was removed under reduced pressure. The residue was taken up in CH$_2$Cl$_2$ (20 mL) and neutralized with solid Na$_2$CO$_3$ until pH ~9. Water (10 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to afford amino amide 2$^2$ (2.20 g, 99% yield, R$_f$ = 0.05 in 1:1 hexanes/EtOAc) as a light brown solid, which was sufficiently pure to be taken on to the next step.
To a solution of amino amide 2 (1.50 g, 7.88 mmol) in PhCH$_3$ (26.3 mL) at 23 °C was added isobutyraldehyde (1.10 mL, 11.8 mmol), TsOH·H$_2$O (75.0 mg, 0.394 mmol), and MgSO$_4$ (1.40 g, 11.8 mmol). The suspension was heated to reflux and stirred overnight. Upon cooling to 23 °C, the solution was quenched with sat. aq. NaHCO$_3$ (20 mL), and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated to afford aminal 4 (1.75 g, 91% yield, $R_f = 0.48$ in 1:1 hexanes/EtOAc) as a light yellow solid, which was sufficiently pure to be taken on to the next step.

**Aminal 4:**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44 (d, $J = 7.6$ Hz, 2H), 7.38 (t, $J = 7.7$ Hz, 2H), 7.19 (t, $J = 7.1$ Hz, 1H), 4.63 (app. s, 1H), 3.95 (dd, $J = 8.0$, 5.2 Hz, 1H), 3.31-3.26 (m, 1H), 2.77 (app. q, $J = 7.8$ Hz, 1H), 2.23-2.15 (m, 1H), 2.06-1.97 (m, 1H), 1.90-1.86 (m, 1H), 1.84-1.78 (comp m, 2H), 0.97 (d, $J = 6.7$ Hz, 3H), 0.81 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.0, 136.8, 129.1, 125.7, 123.4, 87.9, 66.4, 58.5, 31.3, 28.9, 25.1, 18.4, 14.6; [$\alpha$]$_D^{24} -28.2$ (c 0.29, CH$_2$Cl$_2$); IR (film) 2963, 3053, 1683, 1504, 1411, 758, 698 cm$^{-1}$; HRMS (ESI$^+$) m/z calc’d for (M+Na)$^+$ [C$_{15}$H$_{20}$N$_2$ONa]$^+$: 267.1468, found 267.1468.

To a solution of aminal 4 (500 mg, 2.04 mmol), 2-fluoropyridine (176 µL, 2.04 mmol) in PhCH$_3$ (10.2 mL) at -15 °C was added KHMDS (408 mg, 2.04 mmol) in THF (4.10 mL) slowly over 1 h. Upon completion of addition, the reaction was allowed to warm to 23 °C and stirred red overnight. The reaction was filtered over a pad of silica (5 x 5 cm, 100 mL EtOAC eluent) and concentrated. The crude product was purified by flash chromatography (3:1 → 1:1 hexanes/EtOAc eluent) to afford pyridine 6 (385 mg, 59% yield, 148 mg recovered 4: 83% yield, corrected, $R_f = 0.31$ in 1:1 hexanes/EtOAc) as a light beige solid.

**Pyridine 6:**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.69 (d, $J = 3.7$ Hz, 1H), 7.83 (d, $J = 7.9$ Hz, 1H), 7.64 (td, $J = 7.7$, 1.5 Hz, 1H), 7.41-7.34 (comp m, 4H), 7.21-7.13 (comp m, 2H), 4.64 (d, $J = 3.1$ Hz, 1H), 3.44 (dt, $J = 10.9$, 6.7 Hz, 1H), 3.03 (dt, $J = 11.2$, 5.7 Hz, 1H), 2.48 (app. t, $J = 7.0$ Hz, 2H), 1.93-1.81 (comp m, 3H), 0.93 (d, $J = 6.9$ Hz, 3H), 0.55 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.8, 162.2, 149.4, 136.6, 136.0, 129.0, 126.1, 124.3, 121.8, 120.8, 86.4, 77.7, 59.1, 38.8, 31.1, 25.6, 18.4, 15.1; [$\alpha$]$_D^{24} -1.8$ (c 0.22, CH$_2$Cl$_2$); IR (film) 2962, 1701, 1587, 1497, 1407, 752 cm$^{-1}$; HRMS (ESI$^+$) m/z calc’d for (M+H)$^+$ [C$_{20}$H$_{24}$N$_3$O]$^+$: 322.1914, found 322.1914.
To pyridine 6 (750 mg, 2.33 mmol) in a screw cap vial with Teflon cap was added CSA (542 mg, 2.33 mmol), NH₂Ph (106 µL, 1.17 mmol) and MeOH (4.66 mL). The reaction was heated to 110 °C for 24 h. Upon cooling, the reaction mixture was concentrated. To the residue was added sat. aq. NaHCO₃ (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by column chromatography (3:1 → 3:2 hexanes/EtOAc eluent) to afford amino amide 7 (874 mg, 70% yield (97% yield borm) R_f = 0.05 in 1:1 hexanes/EtOAc) as a beige solid.

Amide 7: ¹H NMR (400 MHz, CDCl₃) δ 10.45 (bs, 1H), 8.47 (ddd, J = 4.8, 1.9, 1.0 Hz, 1H), 7.89 (dt, J = 8.1, 1.0 Hz, 1H), 7.69 (td, J = 7.8, 1.8 Hz, 1H), 7.61-7.58 (comp m, 2H), 7.31-7.26 (comp m, 2H), 7.19 (ddd, J = 7.4, 4.9, 1.1 Hz, 1H), 7.08-7.03 (m, 1H), 4.29 (bs, 1H), 3.19 (dt, J = 10.3, 7.0 Hz, 1H), 3.11 (ddd, J = 10.3, 6.9, 5.6 Hz, 1H), 2.81 (ddd, J = 12.6, 6.9, 5.6 Hz, 1H), 2.11 (dt, J = 12.6, 7.9 Hz, 1H), 1.91-1.72 (comp m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 190.8, 173.2, 160.3, 147.4, 138.0, 136.7, 128.8, 123.8, 122.5, 122.4, 119.1, 74.2, 47.1, 39.1, 26.9; IR (film) 3262, 2968, 2869, 1682, 1601, 1516, 1441, 1312, 751, 692 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C₁₆H₁₈N₅O⁺]: 268.1444, found 268.1445.

Representative procedure for the formation of N,N-aminals:
To amino amide 7 (234 mg, 0.875 mmol), benzaldehyde (115 µL, 1.14 mmol) and MgSO₄ (158 mg, 1.31 mmol) was added PhCH₃ (3.65 mL) and AcOH (0.730 mL) at 23 °C. The suspension was heated to 110 °C for 24 h. Upon cooling to 23 °C, water (10 mL) was added to the suspension. The mixture was neutralized to pH ~9 with solid Na₂CO₃, and was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by column chromatography (3:1 → 1:1 hexanes/EtOAc eluent) to afford aminal 9 as a 4:1 ratio of diastereomers, which could be further purified to obtain analytically pure aminal 9 (276 mg, 89% yield, R_f = 0.53 in 40:1 EtOAc:MeOH eluent) as a beige solid.

Aminal 9: ¹H NMR (400 MHz, CDCl₃) δ 8.61 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.53-7.48 (comp m, 4H), 7.23 (d, J = 8.6 Hz, 2H), 7.20-7.15 (comp m, 5H), 7.10-7.04 (comp m,
2H), 5.68 (s, 1H), 3.48 (dt, \( J = 10.6, 6.4 \text{ Hz, 1H} \)), 3.20 (dt, \( J = 10.6, 6.6 \text{ Hz, 1H} \)), 2.70 (dt, \( J = 13.2, 7.6 \text{ Hz, 1H} \)), 2.57 (ddd, \( J = 13.4, 7.4, 6.2 \text{ Hz, 1H} \)), 2.04-1.91 (comp m, 2H); \( ^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 172.9, 161.1, 149.2, 139.74, 139.69, 137.2, 136.0, 128.3, 128.2, 127.0, 125.2, 122.1, 121.9, 121.0, 83.2, 77.9, 56.7, 37.6, 25.2; IR (film) 2966, 1704, 1587, 1495, 1382, 1299, 753, 692 cm\(^{-1}\); HRMS (ESI\(^+\)) \( m/z \) calc’d for (M+Na\(^+\)) \([\text{C}_{23}\text{H}_{21}\text{N}_3\text{ONa}]^{+}\): 378.1577, found 378.1574.

Representative procedure for the oxidation of amino amide 7-based aminals:

Pyridine 9 (84.7 mg, 0.238 mmol), Pd(OAc)\(_2\) (5.3 mg, 0.0238 mmol), and PhI(OAc)\(_2\) (115 mg, 0.357 mmol) were dissolved in AcOH (1.76 mL) and Ac\(_2\)O (1.76 mL) in a 2-dram vial. The vial was sealed with a Teflon cap and heated to 80 °C for 15.5 h, at which time PhI(OAc)\(_2\) (38.3 mg, 0.119 mmol) was added. The reaction was heated at 85 °C for an additional 9.5 h. Upon cooling, CH\(_2\)Cl\(_2\) (10 mL) and water (10 mL) were added and the mixture was neutralized with Na\(_2\)CO\(_3\) until pH ~9. The mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 15 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac\(_2\)O. The crude residue was purified by flash chromatography (4:1 \( \rightarrow \) 7:3 hexanes/acetone eluent) to afford acetate 10 (54.2 mg, 55% yield (61% borsm), R\(_f\) = 0.45 in 1:1 hexanes/acetone) as a beige solid and the corresponding diacetate (6.7 mg, 6% yield, R\(_f\) = 0.26 in 1:1 hexanes/acetone) as a beige solid.

Acetate 10: \( ^{1} \)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.56 (ddd, \( J = 4.8, 1.7, 0.9 \text{ Hz, 1H} \)), 7.60-7.57 (comp m, 2H), 7.34-7.23 (comp m, 3H), 7.19-7.15 (comp m, 2H), 7.10-7.04 (comp m, 2H), 7.00 (ddd, \( J = 7.2, 4.8, 1.5 \text{ Hz, 1H} \)), 6.78-6.77 (comp m, 2H), 5.94 (s, 1H), 3.57 (dt, \( J = 9.8, 5.7 \text{ Hz, 1H} \)), 3.16 (ddd, \( J = 9.8, 7.8, 6.7 \text{ Hz, 1H} \)), 2.75 (dt, \( J = 13.3, 7.9 \text{ Hz, 1H} \)), 2.42 (s, 3H), 2.37 (td, \( J = 8.5, 4.7 \text{ Hz, 1H} \)), 1.98-1.86 (comp m, 2H); \( ^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 173.3, 168.9, 160.9, 148.9, 148.7, 137.6, 135.8, 131.1, 128.90, 128.86, 128.8, 128.3, 127.2, 125.4, 124.7, 122.8, 121.7, 121.0, 120.3, 77.6, 57.6, 38.2, 25.2, 21.1; IR (film) 3061, 2968, 1767, 1710, 1588, 1496, 1374, 1199, 754, 694 cm\(^{-1}\); HRMS (ESI\(^+\)) \( m/z \) calc’d for (M+H\(^+\)) \([\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_3]^{+}\): 414.1812, found 414.1814.
Table 1. Aminal formation and subsequent directed oxidation (reproduced).

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>aminal</th>
<th>yield (%)</th>
<th>dr (syn/anti)[j]</th>
<th>oxidation product</th>
<th>yield (%)</th>
<th>entry</th>
<th>aldehyde</th>
<th>aminal</th>
<th>yield (%)</th>
<th>dr (syn/anti)[j]</th>
<th>oxidation product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>49.0:1</td>
<td></td>
<td></td>
<td>55[k]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>66.0:1</td>
<td></td>
<td></td>
<td>43[k]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>78.6:1</td>
<td></td>
<td></td>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>87.1:1</td>
<td></td>
<td></td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Isolated yield.  [b] Diastereomeric ratio measured by [1H-NMR.  [c] Diastereomer product also observed (Entry 1: 6%, Entry 2: 16%, Entry 3: 13%)

Aminal formation

All aminals were synthesized via the same procedure as for aminal 9. With the exception of the aminals based on o-tolualdehyde, the major diastereomer was the syn product. See the discussion on Stereochemical Analysis, located later in the Supporting Information, for details of these assignments. Unless otherwise noted, the characterization data provided is for the major, syn diastereomer.

According to the general procedure, amino amide 7 (120 mg, 0.449 mmol), p-tolualdehyde (69.0 μL, 0.584 mmol), MgSO₄ (81.1 mg, 0.674 mmol), and PhCH₃/AcOH (5:1, 2.99 mL) were heated to 110 °C for 24 h. Aminal 30 was isolated as a 6.0:1 mixture of diastereomers (143 mg, 86 % yield, Rᵣ = 0.53 in 40:1 EtOAc:MeOH eluent) as
a beige solid. The major diastereomer could be further purified for characterization analysis.

**Aminal 30:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.63 (ddd, $J$ = 4.8, 1.8, 0.9 Hz, 1H), 7.56 (dt, $J$ = 8.0, 1.1 Hz, 1H), 7.50 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.45-7.42 (comp m, 2H), 7.25-7.21 (comp m, 2H), 7.12-7.04 (comp m, 4H), 7.00 (d, $J$ = 7.9 Hz, 2H), 5.63 (s, 1H), 3.42 (dt, $J$ = 10.7, 6.5 Hz, 1H), 3.18 (dt, $J$ = 10.7, 6.5 Hz, 1H), 2.72-2.57 (comp m, 2H), 2.25 (s, 3H), 2.03-1.89 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.7, 161.2, 149.2, 138.0, 137.1, 136.8, 136.0, 129.1, 128.7, 126.9, 125.2, 122.3, 121.9, 121.0, 83.1, 77.9, 56.4, 37.5, 25.2, 21.1; IR (film) 2925, 1707, 1598, 1499, 1381, 1313, 753, 693 cm$^{-1}$; HRMS (ESI$^+$) m/z calc’d for (M+H)$^+$ [C$_{24}$H$_{24}$N$_3$O]: 370.1914, found 370.1915.

According to the general procedure, amino amide 7 (150 mg, 0.561 mmol), m-tolualdehyde (85.7 µL, 0.729 mmol), MgSO$_4$ (101 mg, 0.842 mmol), and PhCH$_3$/AcOH (5:1, 3.74 mL) were heated to 110 °C for 24 h. Aminal 37 was isolated as a 5.8:1 mixture of diastereomers (157 mg, 76% yield, $R_f$ = 0.53 in 40:1 EtOAc:MeOH eluent). The major diastereomer could be further purified for characterization analysis.

**Aminal 37:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.61 (dd, $J$ = 4.8, 0.7 Hz, 1H), 7.53-7.44 (comp m, 4H), 7.23 (d, $J$ = 8.2 Hz, 2H), 7.10-7.03 (comp m, 3H), 6.98-6.94 (comp m, 2H), 5.63 (s, 1H), 3.49 (dt, $J$ = 10.5, 6.2 Hz, 1H), 3.19 (dt, $J$ = 10.5, 6.6 Hz, 1H), 2.70 (dt, $J$ = 13.3, 7.6 Hz, 1H), 2.55 (dt, $J$ = 13.4, 6.7 Hz, 1H), 2.19 (s, 3H), 2.01-1.93 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.0, 161.2, 149.1, 139.6, 138.0, 137.3, 135.9, 128.9, 128.7, 128.2, 127.6, 125.1, 122.0, 121.9, 121.0, 83.3, 78.0, 56.9, 37.7, 25.3, 21.3; IR (film) 2924, 1707, 1587, 1496, 1381, 1313, 753, 692 cm$^{-1}$; HRMS (ESI$^+$) m/z calc’d for (M+H)$^+$ [C$_{24}$H$_{23}$N$_3$ONa]: 392.1733, found 392.1732.

According to the general procedure, amino amide 7 (102 mg, 0.382 mmol), o-tolualdehyde (57.6 µL, 0.496 mmol), MgSO$_4$ (69.0 mg, 0.573 mmol), and PhCH$_3$/AcOH (5:1, 2.55 mL) were heated to 110 °C for 24 h. Aminals 39 and 39b were isolated as a
1:1.5 mixture of inseparable diastereomers (123 mg, 87% yield, $R_f = 0.58$ in 40:1 EtOAc:MeOH eluent).

**Aminal 39 (syn):** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.54 (dd, $J = 4.1$, 0.8 Hz, 1H), 7.56 (d, $J = 7.9$, 2H), 7.31-6.94 (comp m, 8H), 6.73-6.64 (comp m, 2H), 5.91 (s, 1H), 3.67 (dt, $J = 9.6$, 5.2 Hz, 1H), 3.18 (td, $J = 8.8$, 6.9 Hz, 1H), 2.87-2.73 (m, 1H), 2.57 (s, 3H), 2.35 (ddd, $J = 13.2$, 7.9, 5.3 Hz, 1H), 2.01-1.90 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.7, 161.1, 148.8, 138.0, 136.6, 135.7, 135.5, 130.6, 128.8, 128.3, 127.7, 126.2, 124.6, 121.6, 120.8, 120.5, 79.9, 77.7, 57.5, 38.3, 25.1, 19.4; IR (film) 3061, 2968, 1710, 1598, 1498, 1375, 1303, 748, 693 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+Na)$^+$ [C$_{24}$H$_{23}$N$_3$O$_3$Na]$^+$: 392.1733, found 392.1735.

**Aminal 39b (anti):** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.65 (dt, $J = 4.7$, 1.4 Hz, 1H), 7.72-7.65 (comp m, 2H), 7.30-7.14 (comp m, 7H), 7.04-6.95 (comp m, 3H), 6.61 (s, 1H), 2.84 (dt, $J = 13.2$, 8.8 Hz, 1H), 2.76 (td, $J = 9.4$, 6.8 Hz, 1H), 2.62 (s, 3H), 2.51-2.42 (comp m, 2H), 1.86-1.79 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.7, 160.3, 149.7, 137.1, 136.6, 132.4, 130.6, 128.4, 128.3, 127.9, 125.4, 122.3, 121.6, 120.7, 77.7, 75.0, 50.5, 36.3, 24.8, 19.0; IR (film) 2968, 1711, 1597, 1367, 1321, 747, 694 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+Na)$^+$ [C$_{24}$H$_{23}$N$_3$OCl]$^+$: 392.1733, found 392.1730.

According to the general procedure, amino amide 7 (106 mg, 0.397 mmol), $p$-chlorobenzaldehyde (72.4 mg, 0.515 mmol), MgSO$_4$ (71.7 mg, 0.596 mmol), and PhCH$_3$/AcOH (5:1, 2.65 mL) were heated to 110 °C for 24 h. Aminal 41 was isolated as a 3.8:1 mixture of diastereomers (104 mg, 67% yield, $R_f = 0.57$ in 40:1 EtOAc:MeOH eluent). The major diastereomer could be further purified for characterization analysis.

**Aminal 41:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.60 (d, $J = 4.7$ Hz, 1H), 7.51 (d, $J = 3.7$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.28-7.24 (m, 1H), 7.16-7.07 (comp m, 6H), 5.65 (s, 1H), 3.49 (dt, $J = 10.6$, 6.3 Hz, 1H), 3.17 (dt, $J = 10.6$, 6.6 Hz, 1H), 2.70 (dt, $J = 13.3$, 7.5 Hz, 1H), 2.57-2.54 (dt, $J = 13.4$, 6.8 Hz, 1H), 2.02-1.94 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.8, 161.0, 149.2, 138.3, 137.0, 136.1, 128.9, 128.5, 128.4, 125.4, 122.1, 122.0, 120.8, 82.6, 77.9, 56.8, 37.6, 25.3; IR (film) 2959, 2360, 1707, 1597, 1382, 1089, 753 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+H)$^+$ [C$_{23}$H$_{21}$N$_3$OCl]$^+$: 390.1368, found 390.1370.
According to the general procedure, amino amide 7 (109 mg, 0.408 mmol), p-anisaldehyde (64.5 µL, 0.530 mmol), MgSO$_4$ (73.7 mg, 0.612 mmol), and PhCH$_3$/AcOH (5:1, 2.72 mL) were heated to 110 °C for 24 h. Aminal 43 was isolated as a 5.8:1 mixture of diastereomers (123 mg, 78% yield, R$_f$ = 0.50 in 40:1 EtOAc:MeOH eluent). The major diastereomer could be further purified for characterization analysis. **Aminal 43**: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.62 (d, $J = 4.3$ Hz, 1H), 7.57 (d, $J = 7.9$ Hz, 1H), 7.51 (td, $J = 7.7$, 1.6 Hz, 1H), 7.42 (d, $J = 8.1$ Hz, 2H), 7.24 (t, $J = 8.0$ Hz, 2H), 7.13-7.04 (comp m, 4H), 6.71 (d, $J = 8.6$ Hz, 2H), 5.62 (s, 1H), 3.72 (s, 3H), 3.42 (dt, $J = 10.7$, 6.5 Hz, 1H), 3.17 (dt, $J = 10.8$, 6.4 Hz, 1H), 2.73-2.54 (comp m, 2H), 2.06-1.89 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.8, 161.2, 159.4, 149.2, 137.1, 136.0, 131.9, 128.7, 128.3, 125.2, 122.4, 121.9, 121.0, 113.7, 82.9, 77.9, 56.3, 55.2, 37.5, 25.2; IR (film) 2958, 1707, 1587, 1384, 1248, 753, 693 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+H)$^+$ [C$_{24}$H$_{24}$N$_3$O$_2$]: 386.1863, found 386.1849.

According to the general procedure, amino amide 7 (101 mg, 0.378 mmol), 2-naphthaldehyde (76.7 mg, 0.491 mmol), MgSO$_4$ (68.2 mg, 0.567 mmol), and PhCH$_3$/AcOH (5:1, 2.52 mL) were heated to 110 °C for 24 h. Aminal 45 was isolated as a 7.3:1 mixture of diastereomers (123 mg, 80% yield, R$_f$ = 0.50 in 40:1 EtOAc:MeOH eluent). The major diastereomer could be further purified for characterization analysis. **Aminal 45**: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.60 (d, $J = 4.7$ Hz, 1H), 7.57-7.37 (m, 1H), 7.71 (d, $J = 8.6$ Hz, 1H), 7.66-7.65 (m, 1H), 7.58 (s, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.49 (d, $J = 7.9$ Hz, 2H), 7.45-7.35 (comp m, 4H), 7.22 (t, $J = 7.9$ Hz, 2H), 7.04 (t, $J = 6.9$ Hz, 2H), 5.82 (s, 1H), 3.49 (dt, $J = 10.6$, 6.4 Hz, 1H), 3.26 (dt, $J = 10.7$, 6.5 Hz, 1H), 2.74 (dt, $J = 13.3$, 7.6 Hz, 1H), 2.64-2.57 (m, 1H), 2.08-1.92 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.9, 161.2, 149.2, 137.13, 137.08, 133.2, 132.8, 128.8, 128.6, 127.9, 127.6, 126.4, 126.2, 126.1, 125.3, 124.4, 122.2, 121.9, 120.9, 83.5, 78.0, 56.6, 37.7, 25.3; IR
Pd-Catalyzed Oxidations

The palladium-catalyzed oxidations of the synthesized aminals were performed via the same procedure as the oxidation of aminal 9. All reactions were conducted using the diastereomeric mixtures of aminals as the starting material. In all cases, the product was isolated as a single diastereomer, which was syn.

According to the general procedure, pyridine 30 (125 mg, 0.338 mmol), Pd(OAc)$_2$ (7.6 mg, 0.0338 mmol), PhI(OAc)$_2$ (109 mg, 0.338 mmol) and AcOH/Ac$_2$O (1:1, 3.38 mL) were stirred at 85 °C for 8 h. PhI(OAc)$_2$ (32.7 mg, 0.101 mmol) was added, and the mixture stirred an additional 10.5 h at 85 °C. Acetate 31 was isolated as a beige solid (68.2 mg, 47% yield, $R_f = 0.50$ in 1:1 hexanes/acetone) and diacetate 46 was isolated as a beige solid (26.0 mg, 16% yield, $R_f = 0.27$ in 1:1 hexanes/acetone).

**Acetate 31:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.58 (ddd, $J = 4.8, 1.7, 1.0$ Hz, 1H), 7.58-7.55 (comp m, 2H), 7.38-7.30 (comp m, 3H), 7.28-7.23 (m, 1H), 7.08-7.00 (comp m, 2H), 6.90 (d, $J = 0.6$ Hz, 1H), 6.68-6.60 (comp m, 2H), 5.89 (s, 1H), 3.53 (dt, $J = 9.9, 5.8$ Hz, 1H), 3.15 (dt, $J = 9.9, 7.1$ Hz, 1H), 2.73 (dt, $J = 13.2, 7.8$ Hz, 1H), 2.45-2.38 (m, 1H), 2.40 (s, 3H), 2.24 (s, 3H), 1.98-1.85 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.2, 169.0, 161.0, 148.9, 148.5, 139.3, 137.5, 135.9, 128.8, 127.1, 126.3, 123.2, 121.7, 121.1, 120.4, 77.8, 77.6, 57.5, 38.1, 25.2, 21.1, 21.0; IR (film) 2968, 1766, 1708, 1497, 1373, 1200, 692 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+Na)$^+$ [C$_{26}$H$_{23}$N$_3$O$_3$Na]$^+$: 450.1788, found 450.1796.

**Diacetate 46:** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.71 (dd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 7.72-7.76 (m, 1H), 7.53-7.47 (comp m, 3H), 7.25-7.19 (comp m, 3H), 7.17-7.11 (m, 1H), 7.07-7.01 (m, 1H), 6.76 (s, 2H), 5.98 (s, 1H), 3.35 (dt, $J = 10.6, 6.6$ Hz, 1H), 3.12 (dt, $J = 10.6, 6.5$ Hz, 1H), 2.69-2.50 (comp m, 2H), 2.28 (s, 3H), 2.07-1.89 (comp m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.0, 168.4, 160.7, 149.3, 149.0, 139.7, 136.9, 135.9, 128.74, 128.68, 124.8, 121.8, 121.3, 120.8, 119.8, 119.6, 75.3, 56.6, 39.1, 25.0, 21.2, 21.0; IR (film) 2968, 1769, 1709, 1371, 1181, 1045, 753, 692 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+Na)$^+$ [C$_{28}$H$_{27}$N$_3$O$_5$Na]$^+$: 508.1843, found 508.1852.
According to the general procedure, pyridine 37 (124 mg, 0.336 mmol), Pd(OAc)$_2$ (7.5 mg, 0.0336 mmol), PhI(OAc)$_2$ (162 mg, 0.504 mmol), and AcOH/Ac$_2$O (1:1, 3.36 mL) were stirred at 80 °C for 15.5 h. PhI(OAc)$_2$ (54.1 mg, 0.168 mmol) was added, and the reaction stirred at 85 °C for an additional 9.5 h. Acetate 47 (104 mg, 72% yield, $R_f = 0.48$ in 1:1 hexanes/acetone) was isolated as a beige solid.

**Acetate 47**: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.57 (ddd, $J$ = 4.8, 1.7, 0.9 Hz, 1H), 7.60-7.57 (comp m, 2H), 7.08-7.04 (m, 1H), 7.00 (ddd, $J$ = 7.1, 4.9, 1.5 Hz, 1H), 6.95 (d, $J$ = 1.2 Hz, 2H), 6.53 (s, 1H), 5.87 (s, 1H), 3.56 (dt, $J$ = 9.7, 5.7 Hz, 1H), 3.16-3.10 (m, 1H), 2.75 (dt, $J$ = 13.3, 7.9 Hz, 1H), 2.38 (s, 3H), 2.38-2.32 (m, 1H), 1.91 (s, 3H), 1.97-1.90 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.5, 169.1, 161.2, 148.7, 146.4, 137.7, 135.7, 135.2, 130.6, 129.4, 128.9, 127.6, 124.7, 122.4, 121.1, 120.2, 77.8, 77.7, 57.5, 38.1, 25.2, 21.1, 20.6; IR (film) 3061, 2968, 1762, 1709, 1496, 1378, 1190, 755, 693 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc'd for (M+H)$^+$ [C$_{26}$H$_{26}$N$_3$O$_3$]: 428.1969, found 428.1974.

According to the general procedure, pyridines 39 and 39b (123 mg, 0.333 mmol), Pd(OAc)$_2$ (7.5 mg, 0.0333 mmol), PhI(OAc)$_2$ (107 mg, 0.333 mmol) and AcOH/Ac$_2$O (1:1, 3.33 mL) were stirred at 85 °C for 10 h. PhI(OAc)$_2$ (53.6 mg, 0.167 mmol) was added, and the reaction stirred an additional 10.5 h at 85 °C. Acetate 48 (128 mg, 85% yield, $R_f$ = 0.42 in 1:1 hexanes/acetone) was isolated as a beige solid. The $^1$H NMR spectrum featured highly broadened peaks, complicating characterization. Acetate 48 was therefore hydrolyzed to the phenol for characterization analysis.

**Acetate 48**: HRMS (ESI$^+$) $m/z$ calc'd for (M+Na)$^+$ [C$_{26}$H$_{26}$N$_3$O$_3$Na]: 450.1788, found 450.1786.
Pyridine 48 (33.7 mg, 0.0789 mmol) was dissolved in aq. HCl (1 M, 0.789 mL) and THF (1.47 mL), and the resulting solution was heated to reflux overnight. Upon cooling the reaction was quenched with solid Na\textsubscript{2}CO\textsubscript{3} until pH ~9. The mixture was then extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford phenol 49 (14.1 mg, 46% yield, R\textsubscript{f} = 0.28 in 1:1 hexanes/acetone) as a light yellow oil.

**phenol 49:** \( ^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3) \delta 12.13 (\text{br s}, 1\text{H}), 8.67 (\text{dt}, J = 4.8, 1.4 \text{ Hz}, 1\text{H}), 7.77-7.75 (\text{comp m}, 2\text{H}), 7.29-7.24 (\text{comp m}, 1\text{H}), 6.95-6.90 (\text{comp m}, 2\text{H}), 6.81 (d, J = 8.1 \text{ Hz}, 1\text{H}), 6.45 (d, J = 7.5 \text{ Hz}, 1\text{H}), 5.73 (s, 1\text{H}), 3.18 (\text{dt}, J = 12.5, 8.0 \text{ Hz}, 1\text{H}), 3.08 (\text{ddd}, J = 12.4, 7.8, 4.4 \text{ Hz}, 1\text{H}), 2.73-2.65 (\text{comp m}, 2\text{H}), 2.23-2.16 (\text{m}, 1\text{H}), 1.99-1.91 (\text{m}, 1\text{H}), 1.86 (s, 3\text{H}); \( ^{13}\text{C} \text{NMR} (100 \text{ MHz, CDCl}_3) \delta 171.5, 159.1, 148.5, 138.5, 136.9, 135.2, 130.7, 128.8, 128.0, 127.8, 122.9, 122.0, 121.3, 117.8, 116.8, 78.8, 50.9, 44.9, 34.8, 25.0, 19.4; \text{IR} \ (\text{film}) 3061, 2959, 1709, 1586, 1471, 1397, 1123, 749, 702 \text{ cm}^{-1}; \text{HRMS} \ (\text{ESI}^+) \text{ m/z calc'd for (M+Na)}^+ [\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_2\text{Na}]^+: 408.1682, \text{found 408.1690}.\)

According to the general procedure, pyridine 41 (104 mg, 0.267 mmol), Pd(OAc)\textsubscript{2} (6.0 mg, 0.0267 mmol), PhI(OAc)\textsubscript{2} (172 mg, 0.534 mmol) and AcOH/Ac\textsubscript{2}O (1:1, 2.67 mL) were stirred at 90 °C for 24 h with acetate 50 isolated as a beige solid (47.0 mg, 39% yield (51% borsm), R\textsubscript{f} = 0.48 in 1:1 hexanes/acetone).

**acetate 50:** \( ^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3) \delta 8.56 (\text{ddd}, J = 4.8, 1.8, 0.9 \text{ Hz}, 1\text{H}), 7.56-7.53 (\text{comp m}, 2\text{H}), 7.44-7.37 (\text{comp m}, 2\text{H}), 7.30-7.24 (\text{comp m}, 2\text{H}), 7.13 (d, J = 1.8 \text{ Hz}, 2\text{H}), 7.04 (\text{ddd}, J = 7.4, 4.8, 1.2 \text{ Hz}, 1\text{H}), 6.77 (\text{dd}, J = 8.4, 2.0 \text{ Hz}, 1\text{H}), 6.71 (d, J = 8.4 \text{ Hz}, 1\text{H}), 5.89 (s, 1\text{H}), 3.56 (\text{dt}, J = 9.8, 5.8 \text{ Hz}, 1\text{H}), 3.14 (\text{dt}, J = 9.7, 7.2 \text{ Hz}, 1\text{H}), 2.75 (\text{dt}, J = 13.3, 7.8 \text{ Hz}, 1\text{H}), 2.42 (s, 3\text{H}), 2.36 (\text{ddd}, J = 13.2, 7.5, 5.7 \text{ Hz}, 1\text{H}), 2.02-1.90 (\text{comp m}, 2\text{H}); \( ^{13}\text{C} \text{NMR} (100 \text{ MHz, CDCl}_3) \delta 173.3, 168.4, 160.8, 148.9, 137.3, 136.0, 134.0, 129.9, 129.0, 128.1, 125.6, 125.0, 123.3, 122.0, 121.9, 121.0, 120.3, 77.8, 57.6,
According to the general procedure, pyridine 43 (135 mg, 0.350 mmol), Pd(OAc)$_2$ (7.9 mg, 0.0350 mmol), PhI(OAc)$_2$ (113 mg, 0.350 mmol) and AcOH/Ac$_2$O (1:1, 3.50 mL) were stirred at 80 °C for 19 h. Acetate 51 was isolated as a beige solid (83.9 mg, 39% yield (45% borsm), $R_f = 0.40$ in 1:1 hexanes/acetone), as well as the corresponding diacetoxylation product (5.3 mg, 3% yield, $R_f = 0.23$ in 1:1 hexanes/acetone) as a beige solid.

**Acetate 51:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.58 (ddd, $J = 4.8, 1.8, 1.0$ Hz, 1H), 7.58-7.54 (comp m, 2H), 7.41-7.33 (comp m, 2H), 7.30-7.23 (m, 2H), 7.09-7.01 (comp m, 2H), 6.70 (d, $J = 8.7$ Hz, 1H), 6.64 (d, $J = 2.5$ Hz, 1H), 6.35 (dd, $J = 8.7, 2.5$ Hz, 1H), 5.85 (s, 1H), 3.70 (s, 3H), 3.52 (dt, $J = 9.9, 5.9$ Hz, 1H), 3.14 (dt, $J = 9.9, 7.1$ Hz, 1H), 2.73 (dt, $J = 13.3, 7.8$ Hz, 1H), 2.44-2.38 (m, 1H), 2.40 (s, 3H), 1.98-1.86 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.2, 168.8, 161.1, 159.9, 149.5, 148.9, 137.5, 135.9, 128.8, 128.0, 124.8, 123.3, 121.8, 121.0, 120.5, 111.1, 108.7, 77.8, 77.5, 57.3, 55.4, 38.0, 25.2, 21.1; IR (film) 2922, 1765, 1708, 1501, 1375, 1201, 753 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+Na)$^+$ [C$_{25}$H$_{25}$N$_3$O$_3$Na]$^+$: 466.1737, found 466.1734.

According to the general procedure, pyridine 45 (123 mg, 0.303 mmol), Pd(OAc)$_2$ (6.8 mg, 0.0303 mmol), PhI(OAc)$_2$ (127 mg, 0.394 mmol) and AcOH/acetamide (1:1, 3.03 mL) were stirred at 80 °C for 13 h. PhI(OAc)$_2$ (48.8 mg, 0.151 mmol) was added, and the reaction was stirred at 85 °C for an additional 5 h. Acetate 52 was isolated as a beige solid (81.5 mg, 58% yield, $R_f = 0.43$ in 1:1 hexanes/acetone).

**Acetate 52:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.48 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 7.72-7.69 (comp m, 3H), 7.58 (s, 1H), 7.42-7.37 (m, 1H), 7.33 (d, $J = 7.4$ Hz, 1H), 7.29-7.24 (comp m, 3H), 7.18 (s, 1H), 7.15 (dt, $J = 8.0, 1.0$ Hz, 1H), 7.08-7.02 (comp m, 2H), 6.78 (ddd, $J = 8.0, 6.0, 2.0$ Hz, 1H), 5.88 (s, 1H), 3.70 (s, 3H), 3.52 (dt, $J = 9.9, 5.9$ Hz, 1H), 3.14 (dt, $J = 9.9, 7.1$ Hz, 1H), 2.73 (dt, $J = 13.3, 7.8$ Hz, 1H), 2.43-2.37 (m, 1H), 2.40 (s, 3H), 1.98-1.86 (comp m, 2H); IR (film) 2922, 1765, 1708, 1501, 1375, 1201, 753 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+Na)$^+$ [C$_{25}$H$_{25}$N$_3$O$_3$Na]$^+$: 466.1737, found 466.1734.
= 7.4, 4.8, 1.2 Hz, 1H), 6.04 (s, 1H), 3.67 (dt, \( J = 9.5, 5.5 \) Hz, 1H), 3.24-3.18 (m, 1H), 2.82 (dt, \( J = 13.3, 8.0 \) Hz, 1H), 2.46 (s, 3H), 2.33 (ddd, \( J = 13.2, 7.7, 5.4 \) Hz, 1H), 2.01-1.91 (comp m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 173.8, 169.1, 161.1, 148.6, 146.3, 138.0, 135.7, 133.0, 130.5, 129.7, 128.9, 127.9, 127.0, 126.7, 125.8, 124.6, 121.5, 120.9, 120.3, 120.0, 79.4, 77.9, 57.9, 38.4, 25.2, 21.2; IR (film) 2968, 1763, 1708, 1376, 1198, 752 cm\(^{-1}\); HRMS (ESI\(^+\)) \( m/z \) calc’d for \((\text{M+H})^+\) \([\text{C}_{29}\text{H}_{26}\text{N}_3\text{O}_3]^+\): 464.1969, found 464.1969.
To a solution of amino amide 2 (1.50 g, 7.90 mmol) in PhCH₃ (26.3 mL) at 23 °C was added benzaldehyde (1.00 mL, 10.2 mmol), TsOH·H₂O (75.0 mg, 0.395 mmol), and MgSO₄ (1.40 g, 11.8 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 °C, the solution was quenched with sat. aq. NaHCO₃ (20 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated. The dark brown residue was purified by flash chromatography (7:3 hexanes/EtOAc eluent) to afford aminal 53 (1.77 g, 81% yield, Rf = 0.24 in 1:1 hexanes/EtOAc) as a light brown solid.

**Aminal 53**: ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 8.2 Hz, 2H), 7.36-7.25 (comp m, 7H), 7.11-7.07 (m, 1H), 5.67 (s, 1H), 4.03 (app. t, J = 6.6 Hz, 1H), 3.46-3.41 (m, 1H), 2.88 (app. q, J = 8.3 Hz, 1H), 2.20 (app. q, J = 8.3 Hz, 2H), 1.92-1.87 (comp m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.1, 139.6, 137.9, 129.3, 129.2, 128.7, 126.2, 125.3, 121.3, 83.8, 64.5, 56.2, 27.7, 25.0; [α]D²⁴ +8.9 (c 0.28, CH₂Cl₂); IR (film) 2969, 3032, 1699, 1598, 1498, 1384, 757 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H⁺) [C₁₈H₁₉N₂O]+: 279.1492, found 279.1492.

To a solution of freshly distilled diisopropylamine (933 µL, 6.60 mmol) in THF (8.00 mL) at -78 °C was added n-BuLi (2.60 mL, 2.5 M in hexanes, 6.40 mmol) dropwise. The solution was stirred for 10 min at -78 °C, at which time a solution of aminal 53 (1.77 g, 6.40 mmol) in THF (7.90 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 °C. To a suspension of NaH (638 mg, 60% dispersion in mineral oil, 15.9 mmol, washed 2 x 1.5 mL with hexanes) in DMF (14.0 mL) at 0 °C was added 2-(bromomethyl)pyridine hydrobromide (1.34 g, 5.30 mmol). The suspension was stirred at 0 °C for 30 min, at which time it was added to the enolate solution at -78 °C (flask rinsed with additional 1.90 mL DMF). The reaction mixture was warmed to 23 °C and stirred overnight. The reaction was quenched slowly with H₂O (40 mL) at 23 °C, and the resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford...
Pyridine 13 (250 mg, 0.677 mmol), Pd(OAc)$_2$ (15.2 mg, 0.0677 mmol), and PhI(OAc)$_2$ (327 mg, 1.02 mmol) were dissolved in AcOH (3.40 mL) and Ac$_2$O (3.40 mL) in a round-bottomed flask. The flask was capped and heated to 90 °C for 8 h, at which time PhI(OAc)$_2$ (109 mg, 0.338 mmol) was added. The reaction was heated at 90 °C for an additional 16 h. Upon cooling, the solvent was removed by azeotropic removal with heptanes (3 x 15 mL). The crude residue was purified by flash chromatography (17:3 → 4:1 hexanes/acetone eluent) to afford acetate 14 (131 mg, 45% yield, R$_f$ = 0.50 in 1:1 hexanes/acetone) as a beige solid.

Acetate 14: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.47 (dd, $J = 4.9, 0.9$ Hz, 1H), 7.52 (dd, $J = 8.7, 1.0$ Hz, 2H), 7.45 (td, $J = 7.7, 1.8$ Hz, 1H), 7.30-7.25 (comp m, 4H), 7.14 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.10-7.06 (comp m, 2H), 7.01 (td, $J = 7.6, 0.8$ Hz, 1H), 6.85-6.81 (comp m, 2H), 5.80 (s, 1H), 3.17 (dt, $J = 10.3, 6.2$ Hz, 1H), 3.08 (s, 2H), 2.95 (dt, $J = 10.2, 6.6$ Hz, 1H), 2.38 (s, 3H), 2.21 (app. t, $J = 7.2$ Hz, 2H), 1.71-1.62, (m, 1H), 1.37-1.28 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.8, 168.7, 157.3, 148.9, 148.3, 137.3, 135.8, 132.0, 129.0, 128.9, 126.6, 126.0, 125.9, 124.9, 122.8, 121.5, 120.7, 98.4, 77.7, 75.0, 57.4, 44.5, 34.7, 24.7, 21.1; [α]$_D^{24}$ +86.0 (c 0.40, CH$_2$Cl$_2$); IR (film) 3062, 2966, 1767.
1702, 1497, 1385, 1199 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H⁺) [C_{26}H_{26}N_{3}O_{3}]⁺: 428.1969, found 428.1976.

To a solution of (S)-N-Boc proline (0.500 g, 2.32 mmol) in CH₂Cl₂ (11.6 mL) at 0 °C was added isobutyl chloroformate (0.334 mL, 2.56 mmol) and Et₃N (0.359 mL, 2.56 mmol). After stirring for 20 minutes at 0 °C, p-anisidine (315 mg, 2.56 mmol) was added, and the reaction was allowed to warm to 23 °C and stirred overnight. The reaction mixture was washed sequentially with aq. KHSO₄ (1 M, 15 mL), sat. aq. NaHCO₃ (15 mL), and brine (15 mL). The organic layer was dried over Na₂SO₄ and concentrated to afford a pale brown solid. The crude solid was suspended in hexanes (5 mL), cooled to 0 °C and filtered to afford amide 56 (750 mg, 99% yield, Rₕ = 0.41 in 1:1 hexanes/EtOAc) as a light beige solid, which was sufficiently pure to be taken on to the next step.

To a solution of amide 56 (3.72 g, 11.6 mmol) in CH₂Cl₂ (23.2 mL) at 23 °C was added TFA (18.0 mL, 232 mmol). The resulting solution was stirred at 23 °C for 1 h, and the solvent was removed under reduced pressure. The residue was taken up in CH₂Cl₂ (20 mL) and neutralized with solid Na₂CO₃ until pH ~ 9-10. Water (10 mL) was added, and the mixture was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to afford amino amide 57 (2.03 g, 79% yield, Rₕ = 0.0 in 1:1 hexanes/EtOAc) as a white solid, which was sufficiently pure to be taken on to the next step.

To a solution of amino amide 57 (250 mg, 1.14 mmol) in PhCH₃ (5.70 mL) at 23 °C was added benzaldehyde (0.150 mL, 1.48 mmol), TsOH·H₂O (11.0 mg, 0.0578 mmol), and MgSO₄ (205 mg, 1.70 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 °C, the solution was quenched with sat. aq. NaHCO₃ (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The dark brown residue was purified by flash chromatography (7:3 → 1:1 hexanes/EtOAc eluent) to afford aminal 58 (264 mg, 75% yield Rₕ = 0.22 in 1:1 hexanes/EtOAc) as a light yellow solid.
**Aminal 58:** $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.26 (comp m, 6H), 6.83-6.78 (comp m, 3H), 5.56 (s, 1H), 4.07 (t, $J = 6.8$ Hz, 1H), 3.74 (s, 3H), 3.42 (dt, $J = 9.6$, 5.3 Hz, 1H), 2.92-2.86 (m, 1H), 2.23-2.17 (comp m, 2H), 1.93-1.87 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.4, 157.0, 139.6, 130.4, 128.9, 128.5, 126.2, 123.5, 114.2, 84.4, 64.4, 56.2, 55.3, 27.6, 24.8; [$\alpha$]$_D$ $^24$ +1.2 (c 0.78, CH$_2$Cl$_2$); IR (film) 2966, 1700, 1589, 1513, 1249, 749, 702 cm$^{-1}$; HRMS (ESI$^+$) m/z calc’d for (M+H)$^+$ [C$_{19}$H$_{21}$N$_2$O$_2$]$^+$: 309.1598, found 309.1595.

![Diagram of the reaction](image)

To a solution of freshly distilled diisopropylamine (484 µL, 3.45 mmol) in THF (4.10 mL) at -78 ºC was added n-BuLi (1.32 mL, 2.5 M in hexanes, 3.31 mmol). The solution was stirred for 10 min at -78 ºC, at which time a solution of aminal 58 (1.02 g, 3.31 mmol) in THF (7.00 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 ºC. To a suspension of NaH (331 mg, 60% dispersion in mineral oil, 8.27 mmol, washed 2 x 1.5 mL with hexanes) in DMF (9.10 mL) at 0 ºC was added 2-(bromomethyl)pyridine hydrobromide (697 mg, 2.76 mmol). The suspension was stirred at 0 ºC for 30 min, at which time it was added to the enolate solution at -78 ºC (flask rinsed with additional 2.00 mL DMF). The suspension was warmed to 23 ºC and stirred overnight. The reaction was quenched slowly with H$_2$O (30 mL) at 23 ºC, and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine 15 (663 mg, 60% yield, R$_f$ = 0.38 in 40:1 EtOAc/MeOH) as a beige solid and pyridine 15b (278 mg, 25% yield, R$_f$ = 0.22 in 40:1 EtOAc/MeOH) as a yellow oil.

**Pyridine 15:** $^1$H NMR (400 MHz, CDCl$_3$) δ 8.54 (dt, $J = 4.4$, 1.5 Hz, 1H), 7.51 (td, $J = 7.7$, 1.9 Hz, 1H), 7.17-7.11 (comp m, 7H), 6.83 (ddd, $J = 7.8$, 1.7 Hz, 2H), 6.76-6.72 (comp m, 2H), 5.30 (s, 1H), 3.69 (s, 3H), 3.36 (d, $J = 13.2$ Hz, 1H), 3.10-3.03 (comp m, 2H), 2.96 (ddd, $J = 11.4$, 6.5, 5.0 Hz, 1H), 2.30 (ddd, $J = 13.5$, 8.2, 5.5 Hz, 1H), 2.15 (dt, $J = 13.3$, 7.6 Hz, 1H), 1.83-1.76 (m, 1H), 1.66-1.60 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.5, 158.1, 157.2, 148.9, 140.1, 135.6, 129.7, 128.24, 128.20, 127.3, 125.3, 124.8, 121.4, 114.0, 83.7, 75.0, 55.30, 55.27, 45.6, 35.6, 24.6; [$\alpha$]$_D$ $^24$ +59.1 (c 1.82, CH$_2$Cl$_2$); IR (film) 2958, 1700, 1589, 1513, 1249, 749, 702 cm$^{-1}$; HRMS (ESI$^+$) m/z calc’d for (M+H)$^+$ [C$_{22}$H$_{24}$N$_3$O$_2$]$^+$: 400.2020, found 400.2024.

**Pyridine 15b:** $^1$H NMR (400 MHz, CDCl$_3$) δ 8.60 (ddd, $J = 4.9$, 0.9 Hz, 1H), 7.52 (td, $J = 7.7$, 1.9 Hz, 1H), 7.26-7.08 (comp m, 6H), 6.89-6.85 (comp m, 2H), 6.73-6.69 (comp m, 2H), 5.30 (s, 1H), 3.71 (s, 3H), 3.49 (d, $J = 13.1$ Hz, 1H), 3.13 (d, $J = 13.1$ Hz, 1H), 2.54 (td, $J = 9.1$, 6.7 Hz, 1H), 2.44-2.37 (comp m, 2H), 2.14-2.05 (m, 1H), 1.68-1.59 (comp m,
Supplementary Information: Stache, Seizert, and Ferreira

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 193.5, 177.4, 157.6, 156.7, 136.1, 134.4, 128.54, 128.47, 128.2, 124.7, 123.7, 121.7, 113.8, 78.8, 75.1, 55.3, 51.1, 46.2, 35.9, 24.6; [$\alpha$]$_D^{24}$ +4.0 (c 0.45, CH$_2$Cl$_2$); IR (film) 2961, 1703, 1512, 1248, 1032, 830, 702 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc'd for (M+H)$^+$ [C$_{25}$H$_{26}$N$_3$O$_2$]$^+$: 400.2020, found 400.2016.

Pyridine 15 (200 mg, 0.501 mmol), Pd(OAc)$_2$ (11.2 mg, 0.0501 mmol), and PhI(OAc)$_2$ (161 mg, 0.501 mmol) were dissolved in AcOH (3.5 mL) and Ac$_2$O (3.5 mL) in a round-bottomed flask. The flask was capped and heated to 95 °C for 8 h, at which time PhI(OAc)$_2$ (161 mg, 0.501 mmol) was added. The reaction was stirred an additional 16 h at 95 °C. Upon cooling the solvent was removed by azeotropic evaporation with heptanes (3 x 15 mL). Water (10 mL) was added, and the mixture was treated with solid Na$_2$CO$_3$ until pH $\sim$9. The mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL), and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified by flash chromatography (17:3 $\rightarrow$ 4:1 hexanes/acetone eluent) to afford acetate 16 (73.4 mg, 32% yield, $R_f = 0.30$ in 1:1 hexanes/acetone) as a light yellow residue.

Acetate 16: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.47 (dd, $J = 4.9, 0.9$ Hz, 1H), 7.45 (td, $J = 7.7, 1.9$ Hz, 1H), 7.38-7.34 (comp m, 2H), 7.26-7.22 (m, 1H), 7.11-7.06 (comp m, 2H), 6.99 (td, $J = 7.6, 1.1$ Hz, 1H), 6.89 (d, $J = 7.8$ Hz, 1H), 6.81-6.74 (comp m, 3H), 5.70 (s, 1H), 3.72 (s, 3H), 3.14-3.05 (comp m, 3H), 2.93 (dt, $J = 10.5, 6.4$ Hz, 1H), 2.34 (s, 3H), 2.27-2.15 (comp m, 2H), 1.75-1.61 (m, 1H), 1.42-1.31 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.2, 168.7, 157.3, 156.8, 148.9, 148.6, 135.6, 132.0, 130.3, 129.0, 126.9, 126.0, 125.7, 122.7, 121.4, 114.1, 77.7, 75.0, 57.0, 55.3, 44.9, 34.8, 24.7, 21.1; [$\alpha$]$_D^{24}$ +130.5 (c 2.64, CH$_2$Cl$_2$); IR (film) 2959, 1766, 1513, 1249, 1199, 832 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc'd for (M+H)$^+$ [C$_{27}$H$_{28}$N$_3$O$_4$]$^+$: 458.2074, found 458.2080.
To a solution of (S)-N-Boc proline (2.50 g, 11.6 mmol) in CH₂Cl₂ (33.2 mL) at 0 °C was added isobutyl chloroformate (1.67 mL, 12.8 mmol) and Et₃N (1.80 mL, 12.8 mmol). After stirring for 20 minutes at 0 °C, p-trifluoromethylaniline (1.59 mL, 12.8 mmol) was added and the reaction was warmed to 23 °C and stirred overnight. The reaction was washed sequentially with aq. KHSO₄ (1 M, 50 mL), sat. aq. NaHCO₃ (50 mL) and brine (50 mL). The organic layer was dried over Na₂SO₄ and concentrated to afford a pale brown solid. The crude solid was suspended in hexanes (15 mL), cooled to 0 °C and filtered to afford amide 60 (4.44 g, 89% yield, Rᵣ = 0.59 in 1:1 hexanes/EtOAc) as a light beige solid, which was sufficiently pure to be taken on to the next step.

To a solution of amide 60 (3.70 g, 10.3 mmol) in CH₂Cl₂ (20.7 mL) at 23 °C was added TFA (15.9 mL, 207 mmol). The solution was stirred at 23 °C for 1 h, at which point the solvent was removed under reduced pressure. The residue was taken up in CH₂Cl₂ (3 x 50 mL) and neutralized with solid Na₂CO₃ until pH ~9. Water (10 mL) was added, and the mixture was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to afford amino amide 61 (2.57 g, 96% yield, Rᵣ = 0.00 in 1:1 hexanes/EtOAc) as a white solid, which was sufficiently pure to be taken on to the next step.

To a solution of amino amide 61 (948 mg, 3.70 mmol) in PhCH₃ (18.3 mL) at 23 °C was added benzaldehyde (0.482 mL, 4.80 mmol), TsOH·H₂O (34.9 mg, 0.184 mmol), and MgSO₄ (663 mg, 5.50 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 °C, the solution was quenched with sat. aq. NaHCO₃ (20 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The dark brown residue was purified by flash chromatography (4:1 → 7:3 hexanes/EtOAc eluent) to afford aminal 62 (1.04 g, 82% yield, Rᵣ = 0.45 in 1:1 hexanes/EtOAc) as a light yellow solid.

**Aminal 62:** ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 7.40-7.34 (comp m, 3H), 7.33-7.28 (comp m, 2H), 5.74 (s, 1H), 4.03 (t, J = 6.7 Hz, 1H), 3.47 (dt, J = 9.6, 5.0 Hz, 1H), 2.87 (app. q, J = 8.6 Hz, 1H), 2.22 (dt, J = 8.1, 6.6, 2H), 1.95-1.87 (comp m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.5, 140.8, 138.6, 129.2,
128.8, 126.1 (q, J = 3.8 Hz), 125.8, 120.0, 83.1, 64.2, 56.0, 27.4, 24.8; [α]D24 +6.1 (c 0.49, CH2Cl2); IR (film) 3034, 2971, 1711, 1615, 1522, 1380, 1327, 1124 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C15H19F3N2O⁺]: 347.1366, found 347.1365.

To a solution of freshly distilled diisopropylamine (634 µL, 4.50 mmol) in THF (4.8 mL) at -78 °C was added n-BuLi (1.73 mL, 2.5 M in hexanes, 4.30 mmol) dropwise. The solution was stirred for 10 min at -78 °C, at which time a solution of aminal 62 (1.50 g, 4.30 mmol) in THF (6.00 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 °C. To a suspension of NaH (433 mg, 60% dispersion in mineral oil, 10.8 mmol, washed 2 x 1.5 mL with hexanes) in DMF (8.80 mL) at 0 °C was added 2-(bromomethyl)pyridine hydrobromide (913 mg, 3.60 mmol). The suspension was stirred at 0 °C for 30 min, at which time it was added to the enolate solution at -78 °C (flask rinsed with additional 2.00 mL DMF). The suspension was warmed to 23 °C and stirred overnight. The reaction was quenched slowly with H2O (30 mL) at 23 °C, and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na2SO4 and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine 17 (1.04 g, 66% yield, Rf = 0.58 in 40:1 EtOAc/MeOH) as a beige solid and pyridine 17b (498 mg, 32% yield, Rf = 0.19 in 40:1 EtOAc/MeOH) as a light beige solid.

Pyridine 17: ¹H NMR (400 MHz, CDCl3) δ 8.51 (dd, J = 4.9, 0.8 Hz, 1H), 7.55-7.47 (comp m, 5H), 7.22-7.19 (comp m, 3H), 7.17-7.14 (m, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.88 (dd, J = 7.6, 1.8 Hz, 2H), 5.49 (s, 1H), 3.19 (ABq, J = 13.2 Hz, Δν = 69.6 Hz, 2H), 3.21 (dt, J = 11.1, 6.8 Hz, 1H), 3.00 (dt, J = 11.4, 5.8 Hz, 1H), 2.31-2.19 (comp m, 2H), 1.84-1.74 (m, 1H), 1.65-1.55 (m, 1H); ¹³C NMR (100 MHz, CDCl3) δ 175.4, 157.3, 148.3, 140.12, 140.11, 139.5, 136.2, 128.6, 125.9 (q, J = 3.8 Hz), 125.5, 125.2, 121.7, 121.4, 82.6, 75.1, 56.0, 44.8, 35.6, 24.6; [α]D24 +63.2 (c 0.31, CH2Cl2); IR (film) 3063, 2967, 1713, 1615, 1380, 1327, 1122 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+Na)⁺ [C25H22F3N3ONa⁺]: 460.1607, found 460.1614.

Pyridine 17b: ¹H NMR (400 MHz, CDCl3) δ 8.50 (dd, J = 4.9, 0.9 Hz, 1H), 7.52 (td, J = 7.7, 1.8 Hz, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.24-7.21 (comp m, 4H), 7.17-7.14 (comp m, 3H), 7.09-7.07 (comp m, 2H), 5.32 (s, 1H), 3.50 (d, J = 13.2 Hz, 1H), 3.12 (d, J = 13.2, 1H), 2.54 (td, J = 9.0, 6.9 Hz, 1H), 2.46-2.37 (comp m, 2H), 2.16-2.10 (m, 1H), 1.70-1.62 (comp m, 2H); ¹³C NMR (100 MHz, CDCl3) δ 177.9, 149.1, 140.7, 136.1, 133.8, 128.8, 128.5, 128.2, 125.6 (q, J = 3.8 Hz), 124.5, 121.8, 121.4, 78.5, 74.9, 51.3, 46.3, 36.0, 24.5; [α]D24 +11.6 (c 0.59, CH2Cl2); IR (film) 2967, 1713, 1614, 1324, 1166, 1119, 844, 703 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C25H23F3N3O⁺]: 438.1788, found 438.1793.
Pyridine 17 (300 mg, 0.686 mmol), Pd(OAc)$_2$ (15.4 mg, 0.0686 mmol), and PhI(OAc)$_2$ (221 mg, 0.686 mmol) were dissolved in AcOH (3.50 mL) and Ac$_2$O (3.50 mL) in a round-bottomed flask. The flask was capped and heated to 95 °C for 12 h, at which time PhI(OAc)$_2$ (221 mg, 0.686 mmol) was added. The reaction was stirred an additional 12 h at 95 °C. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (3 x 15 mL). Water (10 mL) was added, and the mixture was treated with solid Na$_2$CO$_3$ until pH ~9. The aqueous mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL), and the combined organic phases were dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified by flash chromatography (17:3 → 4:1 hexanes/acetone eluent) to afford acetate 18 (218 mg, 64% yield, R$_f$ = 0.53 in 1:1 hexanes/acetone) as a light yellow residue.

**Acetate 18:** $^1$H NMR (400 MHz, CDCl$_3$) δ 8.46 (dd, $J = 4.6$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 2H), 7.53 (d, $J = 8.8$ Hz, 2H), 7.47 (td, $J = 7.7$, 1.8 Hz, 1H), 7.30 (td, $J = 8.4$, 1.6 Hz, 1H), 7.17 (d, $J = 7.3$ Hz, 1H), 7.10 (dd, $J = 6.9$, 5.4 Hz, 1H), 7.01 (t, $J = 7.5$ Hz, 1H), 6.80 (d, $J = 7.8$ Hz, 1H), 6.71 (dd, $J = 7.8$, 1.3 Hz, 1H), 5.80 (s, 1H), 3.21 (dt, $J = 7.8$, 4.6 Hz, 1H), 5.80 (s, 1H), 3.08 (ABq, $J = 13.2$ Hz, $\Delta v = 12.2$ Hz, 2H), 2.95 (dt, $J = 10.2$, 6.7 Hz, 1H), 2.39 (s, 3H), 2.26-2.19 (comp m, 2H), 1.71-1.64 (m, 1H), 1.38-1.31 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.3, 168.7, 156.9, 148.9, 148.2, 140.3, 136.0, 131.5, 129.3, 128.6, 126.22, 126.16, 126.1 (q, $J = 3.8$ Hz), 125.9, 123.1, 121.6, 119.9, 77.6, 75.0, 57.6, 44.3, 34.8, 24.7, 21.1; $[\alpha]_D^{24} +27.3$ (c 0.19, CH$_2$Cl$_2$); IR (film) 2968, 1768, 1712, 1379, 1326, 1199, 843, 736 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+H)$^+$ [C$_{27}$H$_{25}$F$_3$N$_3$O$_3$]$^+$ 496.1843, found 496.1843.

Pyridine 6 (200 mg, 0.622 mmol), Pd(OAc)$_2$ (69.8 mg, 0.311 mmol), and PhI(OAc)$_2$ (351 mg, 1.10 mmol) were dissolved in AcOH (3.10 mL) and Ac$_2$O (3.10 mL) in a round-bottomed flask. The flask was capped and heated to 85 °C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 15 mL). The residue
was treated with 1,2-bis(diphenylphosphino)ethane (249 mg, 0.622 mmol) in PhCH₃/CH₂Cl₂ (1:1, 6.20 mL) and stirred overnight at 23 °C. The solvent was removed by rotary evaporation, and the crude residue was purified by flash chromatography (4:1 → 3:1 hexanes/aceton eluent) to afford acetate 19 (>10:1 dr, 156 mg, 66% yield, Rₜ = 0.45 in 1:1 hexanes/acetone) as a light yellow oil and diacetate 20 (36.0 mg, 13% yield, Rₜ = 0.43 in 1:1 hexanes/acetone) as a light yellow oil.

**Acetate 19:** ¹H NMR (300 MHz, CDCl₃) δ 8.68 (d, J = 4.6 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.46-7.37 (comp m, 4H), 7.24-7.18 (comp m, 2H), 4.77 (d, J = 3.4 Hz, 1H), 3.80 (dd, J = 6.5, 3.1 Hz, 2H), 3.53 (dt, J = 10.7, 6.4 Hz, 1H), 3.05 (dt, J = 11.1, 5.7 Hz, 1H), 2.52 (dt, J = 13.3, 6.8 Hz, 1H), 2.39 (dt, J = 13.3, 6.7 Hz, 1H), 2.14-1.83 (comp m, 3H), 1.82 (s, 3H), 0.92 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.9, 170.6, 149.3, 136.7, 136.5, 129.1, 126.2, 124.1, 122.2, 120.6, 98.4, 84.6, 77.6, 65.5, 59.4, 38.9, 36.2, 25.6, 20.7, 14.0; [α]D₂⁴ +20.7 (c 2.05, CH₂Cl₂); IR (film) 3061, 2961, 1738, 1703, 1588, 1226, 1039, 753, 697 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C₂₂H₂₆N₃O₃]⁺: 380.1969, found 380.1970.

*Note:* The minor diastereomer of acetate 19 features the following diagnostic signals in the ¹H NMR: δ 4.97 (d, 1H), 2.06 (s, 3H), 0.51 (d, 3H).

**Diacetate 20:** ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, J = 4.5 Hz, 1H), 7.75-7.67 (comp m, 2H), 7.47-7.39 (comp m, 4H), 7.23-7.19 (comp m, 2H), 5.02 (d, J = 3.9 Hz, 1H), 4.12 (dd, J = 11.3, 7.3 Hz, 1H), 4.04 (dd, J = 11.3, 5.5 Hz, 1H), 3.95 (dd, J = 11.3, 5.5 Hz, 1H), 3.85 (dd, J = 11.3, 7.3 Hz, 1H), 3.53 (dt, J = 10.6, 6.5 Hz, 1H), 3.04 (dt, J = 11.1, 5.8 Hz, 1H), 2.56 (dt, J = 13.3, 6.8 Hz, 1H), 2.40 (dt, J = 13.3, 6.8 Hz, 1H), 2.30 (dddd, J = 7.2, 5.5, 3.9, 1.7 Hz, 1H), 2.03 (s, 3H), 2.02-1.97 (m, 1H), 1.89-1.85 (m, 1H), 1.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.0, 170.4, 161.6, 149.4, 136.5, 136.2, 129.1, 126.4, 123.7, 122.3, 120.5, 80.5, 77.8, 62.0, 61.4, 59.1, 41.0, 38.9, 25.7, 20.8, 20.7; [α]D₂⁴ +26.6 (c 0.50, CH₂Cl₂); IR (film), 2961, 1738, 1703, 1588, 1226, 1039, 753, 697 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C₂₄H₂₆N₃O₅]⁺: 438.2023, found 438.2023.

To a solution of freshly distilled diisopropylamine (177 µL, 1.30 mmol) in THF (3.00 mL) at -78 °C was added n-BuLi (0.480 mL, 2.5 M in hexanes, 1.20 mmol) dropwise. The solution was stirred for 10 min at -78 °C, at which time a solution of aminal 4 (295 mg, 1.20 mmol) in THF (3.10 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 °C. To a suspension of NaH (121 mg, 60% dispersion in mineral oil, 3.00 mmol, washed 2 x 1.0 mL with hexanes) in DMF (5.00 mL) at 0 °C was added 2-(bromomethyl)pyridine hydrobromide (255 mg, 1.00 mmol). The suspension was stirred at 0 °C for 30 min, at which time it was added to the enolate solution at -78 °C (flask rinsed with additional 1.10 mL DMF). The suspension was warmed to 23 °C and stirred overnight. The reaction was quenched by slow addition of H₂O (20 mL) at 23 °C,
and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 35 mL), dried over Na₂SO₄ and concentrated. The crude residue was purified by flash chromatography (7:3 → 1:1 hexanes/EtOAc eluent) to afford pyridine 21 (272 mg, 81% yield, Rₜ = 0.74 in 40:1 EtOAc/MeOH) as a beige solid.

**Pyridine 21:**

- **¹H NMR (400 MHz, CDCl₃)** δ 8.56 (d, J = 3.8 Hz, 1H), 7.62 (t, J = 6.8 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.40-7.34 (comp m, 4H), 7.23-7.19 (m, 1H), 7.15 (t, J = 5.6 Hz, 1H), 4.47 (d, J = 2.8 Hz, 1H), 3.27 (ABq, J = 13.2 Hz, Δν =18.5 Hz, 2H), 2.76 (app. s, 2H), 2.19-2.06 (comp m, 2H), 1.78-1.74 (m, 1H), 1.64-1.57 (m, 1H), 1.49-1.45 (m, 1H), 0.89 (d, J = 6.9 Hz, 3H), 0.58 (d, J = 6.2 Hz, 3H);
- **¹³C NMR (100 MHz, CDCl₃)** δ 174.1, 158.1, 148.8, 136.4, 129.0, 126.1, 125.3, 124.4, 121.5, 98.3, 86.4, 74.9, 58.4, 45.4, 34.9, 30.6, 24.7, 18.4, 14.3; [α]D₂⁴ +85.0 (c 0.38, CH₂Cl₂); IR (film) 2969, 2870, 1676, 1600, 1524, 1443, 755 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+Na)⁺ [C₂₁H₂₅N₃ONa]⁺: 358.1890, found 358.1894.

![Diagram](image)

(At 55 °C) Pyridine 21 (50.4 mg, 0.150 mmol), Pd(OAc)₂ (3.4 mg, 0.0150 mmol), and PhI(OAc)₂ (72.5 mg, 0.225 mmol) were dissolved in AcOH (0.750 mL) and Ac₂O (0.750 mL) in a round-bottomed flask. The flask was capped and heated to 55 °C for 24 h. Water (10 mL) was added, and the mixture was treated with solid Na₂CO₃ until pH ~9. The aqueous solution was extracted with CH₂Cl₂ (3 x 15 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac₂O. The crude residue was purified by flash chromatography (3:1 → 1:1 hexanes/acetic acid eluent) to afford acetate 22 (25.1 mg, 43% yield, 10:1 dr, Rₜ = 0.48 in 1:1 hexanes/acetone) as a light yellow amorphous solid and diacetate 23 (8.7 mg, 13% yield, Rₜ = 0.35 in 1:1 hexanes/acetone) as a light yellow amorphous solid.

(At 70 °C) Pyridine 21 (50.0 mg, 0.149 mmol), Pd(OAc)₂ (3.3 mg, 0.0149 mmol), and PhI(OAc)₂ (72.0 mg, 0.224 mmol) were dissolved in AcOH (0.750 mL) and Ac₂O (0.750 mL) in a round-bottomed flask. The flask was capped and heated to 70 °C for 13 h. Water (10 mL) was added, and the mixture was treated with solid Na₂CO₃ until pH ~9. The aqueous solution was extracted with CH₂Cl₂ (3 x 15 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac₂O. The crude
residue was purified by flash chromatography (3:1 → 1:1 hexanes/acetone eluent) to afford acetate 22 (28.0 mg, 48% yield, 5.7:1 dr, Rf = 0.48 in 1:1 hexanes/acetone) as a light yellow amorphous solid and diacetate 23 (12.9 mg, 19% yield, Rf = 0.35 in 1:1 hexanes/acetone) as a light yellow amorphous solid.

**Acetate 22:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.56 (dd, $J$ = 4.9, 0.9 Hz, 1H), 7.62 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.45-7.34 (comp m, 5H), 7.22 (tt, $J$ = 6.8, 1.8 Hz, 1H), 7.15 (ddd, $J$ = 7.4, 5.0, 1.0 Hz, 1H), 4.54 (d, $J$ = 3.5 Hz, 1H), 3.83 (d, $J$ = 6.3 Hz, 2H), 3.23 (ABq, $J$ = 13.2 Hz, $\Delta$ν = 35.9 Hz, 2H), 2.92-2.85 (m, 1H), 2.83-2.77 (m, 1H), 2.23-2.07 (comp m, 2H), 1.93 (s, 3H), 1.85 (qd, $J$ = 6.6, 3.5 Hz, 1H), 1.68-1.53 (comp m, 2H), 0.83 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.0, 170.7, 157.9, 148.9, 136.5, 135.9, 129.0, 126.3, 125.1, 124.3, 124.0, 121.7, 84.4, 74.9, 65.0, 58.2, 45.6, 36.3, 35.3, 24.7, 20.9, 14.0; [α]$_D^{24}$ +70.4 (c 0.50, CH$_2$Cl$_2$); IR (film) 2965, 1739, 1702, 1593, 1409, 1226 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+H)$^+$ [C$_{23}$H$_{27}$N$_3$O$_3$]+: 394.2125, found 394.2126.

**Note:** The minor diastereomer of acetate 22 features the following diagnostic signals in the $^1$H NMR: $\delta$ 4.78 (d, 1H), 2.06 (s, 3H), 0.60 (d, 3H).

**Diacetate 23:** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.55 (dd, $J$ = 4.1 Hz, 1H), 7.62 (td, $J$ = 7.6, 1.5 Hz, 1H), 7.43-7.35 (comp m, 5H), 7.23-7.21 (m, 1H), 7.15 (dd, $J$ = 6.8, 5.4 Hz, 1H), 4.78 (d, $J$ = 3.6 Hz, 1H), 3.94 (dd, $J$ = 13.6, 6.1 Hz, 4H), 3.23 (ABq, $J$ = 13.2 Hz, $\Delta$ν = 33.8 Hz, 2H), 2.93-2.84 (m, 1H), 2.80-2.73 (m, 1H), 2.22-2.08 (comp m, 2H), 1.66-1.57 (comp m, 2H), 2.02 (s, 3H), 1.92 (s, 3H), 1.99-1.92 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.9, 170.5, 170.4, 157.6, 149.0, 136.1, 135.9, 129.1, 126.6, 125.1, 124.0, 121.8, 80.3, 75.0, 61.9, 60.8, 57.9, 45.5, 41.0, 35.6, 24.7, 20.79, 20.76; [α]$_D^{24}$ +72.8 (c 0.43, CH$_2$Cl$_2$); IR (film) 2965, 1739, 1702, 1593, 1409, 1226 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+Na)$^+$ [C$_{23}$H$_{29}$N$_3$O$_3$Na]$^+$: 474.1999, 474.1997.

A 2-dram vial was charged with pyridine 6 (31.9 mg, 0.0992 mmol), H$_2$[PMo$_{11}$V$_0$O$_{40}$]:32H$_2$O (2.4 mg, 0.00102 mmol, 1 mol %), Cu(OAc)$_2$ (19.8 mg, 0.109 mmol), and Pd(OAc)$_2$ (2.2 mg, 0.00992 mmol). The materials were dissolved in 0.992 mL CF$_3$CH$_2$OH, and methyl acrylate (35.6 µl, 0.397 mmol) was added. The vial was sealed under air and heated to 110 °C with vigorous stirring for 16 h. The reaction mixture was allowed to cool, diluted with CHCl$_3$ (15 mL) and washed with 10%aq. NH$_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with CHCl$_3$ (10 mL). The combined organic layers were concentrated in vacuo, and the residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford alkene 25 (17.3 mg, 43% yield, >10:1 dr, Rf = 0.10 in 1:1 hexanes/EtOAc) as a pale yellow oil.
**Alkene 25:**

^1^H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.68 (d, \(J = 4.7\) Hz, 1H), 7.77 (d, \(J = 8.2\) Hz, 1H), 7.66 (td, \(J = 7.6, 1.6\) Hz, 1H), 7.42-7.34 (m, 5H), 7.22 (tt, \(J = 5.7, 2.9\) Hz, 1H), 7.17 (dd, \(J = 6.8, 5.3\) Hz, 1H), 6.62-6.52 (m, 1H), 5.49 (d, \(J = 15.60\) Hz, 1H), 4.68 (d, \(J = 3.12\) Hz, 1H), 3.63 (s, 3H), 3.48 (dt, \(J = 10.92, 6.63\) Hz, 1H), 3.08-3.00 (m, 1H), 2.54-2.47 (m, 1H), 2.43 (s, 1H), 2.09-1.67 (m, 4H), 0.90 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 172.1, 166.8, 162.2, 149.6, 140.5, 127.3, 1173 cm\(^{-1}\); HMRS (ESI\textsuperscript{+}) m/z calc’d for (M+H\textsuperscript{+}) \([C\textsubscript{24}H\textsubscript{28}N\textsubscript{3}O\textsubscript{3}]^+\) : 406.2125, found 406.2129.

![Chemical Structure](image)

To a solution of acetate 22 (118 mg, 0.300 mmol) in MeOH (3.0 mL) at 23 °C was added K\textsubscript{2}CO\textsubscript{3} (83.0 mg, 0.600 mmol), and the resulting mixture was stirred overnight. The reaction was partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated to afford alcohol 63 (93.1 mg, 88% yield, \(R_f = 0.34\) in 1:1 hexanes/acetone) as a white solid, which was sufficiently pure to be taken on to the next step.

**Alcohol 63:**

^1^H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.55 (dd, \(J = 4.8, 0.8\) Hz, 1H), 7.62 (td, \(J = 7.7, 1.8\) Hz, 1H), 7.41-7.35 (comp m, 2H), 7.30-7.28 (comp m, 3H), 7.26-7.21 (m, 1H), 7.16 (ddd, \(J = 7.5, 4.9, 0.9\) Hz, 1H), 4.51 (d, \(J = 3.4\) Hz, 1H), 3.71 (dd, \(J = 12.0, 1.6\) Hz, 1H), 3.35 (dd, \(J = 12.0, 5.6\) Hz, 1H), 3.26 (ABq, \(J = 13.2\) Hz, \(\Delta\nu = 12.8\) Hz, 2H), 2.82-2.77 (m, 1H), 2.72-2.65 (m, 1H), 2.16-2.11 (m, 1H), 2.01-1.94 (m, 1H), 1.82-1.74 (m, 1H), 1.65-1.54 (m, 1H), 1.38-1.31 (m, 1H), 0.97 (d, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 174.3, 156.8, 149.0, 136.2, 129.2, 126.7, 125.2, 124.9, 123.7, 121.7, 118.5, 74.4, 62.0, 57.7, 45.1, 37.7, 34.3, 24.6, 14.1; [\(\alpha\)]\textsubscript{D}\textsuperscript{24} +54.0 (c 0.45, CH\textsubscript{2}Cl\textsubscript{2}); IR (film) 3332, 2961, 1696, 1594, 1476, 753, 698 cm\(^{-1}\); HRMS (ESI\textsuperscript{+}) m/z calc’d for (M+H\textsuperscript{+}) \([C\textsubscript{21}H\textsubscript{26}N\textsubscript{3}O\textsubscript{2}]^+\) : 352.2020, found 352.2024.

To a solution of alcohol 63 (87.2 mg, 0.248 mmol), p-nitrobenzoic acid (45.6 mg, 0.273 mmol), EDC (57.0 mg, 0.298 mmol), HOBT (38.0 mg, 0.248 mmol) in CH\textsubscript{3}CN (2.50 mL) at 23 °C was added Et\textsubscript{3}N (38.0 \(\mu\)L, 0.273 mmol). The reaction was stirred at 23 °C for 3 d. The volatile organic solvent was removed, and the residue was partitioned between H\textsubscript{2}O (15 mL) and EtOAc (15 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude product was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford benzoate 26 (119 mg, 96% yield, \(R_f = 0.47\) in 1:1 hexanes/acetone) as a white solid. The solid was crystallized by a layering technique with CH\textsubscript{2}Cl\textsubscript{2} and hexanes.
Ester 26: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.62 (dd, $J = 5.0$, 0.9 Hz, 1H), 8.31-8.21 (comp m, 2H), 7.72 (td, $J = 7.7$, 1.7 Hz, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.39-7.29 (comp m, 4H), 7.25-7.20 (comp m, 2H), 4.59 (d, $J = 3.4$ Hz, 1H), 3.99 (dd, $J = 10.9$, 8.0 Hz, 1H), 3.34 (ABq, $J = 13.2$ Hz, Δν = 67.7 Hz, 2H), 3.10 (dt, $J = 11.5$, 7.3 Hz, 1H), 2.88 (dt, $J = 11.4$, 5.7 Hz, 1H), 2.14 (app. t, $J = 7.2$ Hz, 2H), 2.01-1.95 (m, 1H), 1.79-1.69 (comp m, 4H), 1.56-1.49 (m, 1H), 1.34-1.32 (m, 1H), 0.93 (d, $J = 1.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.7, 164.2, 157.3, 150.4, 148.2, 137.0, 136.1, 135.5, 130.5, 129.2, 126.6, 125.5, 124.3, 123.4, 122.3, 84.1, 75.2, 66.2, 57.8, 36.4, 35.9, 24.7, 22.0, 14.8; [α]$_D$ +61.0 (c 1.14, CH$_2$Cl$_2$); IR (film) 2968, 1723, 1721, 1527, 1276, 1103, 720 cm$^{-1}$; HRMS (ESI$^+$) $m$/z calc’d for (M+H)$^+$ [C$_{28}$H$_{29}$N$_4$O$_5$]$^+$: 500.2132, found 500.2137; mp 110-116 °C.

To a solution of freshly distilled diisopropylamine (167 µL, 1.19 mmol) in THF (5.00 mL) at -78 °C was added n-BuLi (0.460 mL, 2.5 M in hexanes, 1.15 mmol) dropwise. The solution was stirred for 10 min at -78 °C, at which time a solution of aminal 4 (200 mg, 0.818 mmol) in THF (3.20 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 °C. Benzyl bromide (256 µL, 1.64 mmol) was added at -78 °C, and the reaction was warmed to 23 °C and stirred overnight. The reaction was quenched with water (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent) to afford aminal 27 (195 mg, 71% yield, $R_f$ = 0.74 in 4:1 hexanes/EtOAc) as a white amorphous solid.

Aminal 27: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.43-7.36 (comp m, 6H), 7.30-7.20 (comp m, 4H), 4.48 (d, $J = 2.8$ Hz, 1H), 3.06 (ABq, $J = 13.6$ Hz, Δν = 76.8 Hz, 2H), 2.73-2.72 (comp m, 2H), 2.08-2.02 (m, 1H), 1.89-1.78 (comp m, 2H), 1.56-1.49 (m, 1H), 1.34-1.32 (m, 1H), 0.93 (d, $J = 1.1$ Hz, 3H), 0.72 (d, $J = 3.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.7, 137.6, 136.5, 131.0, 129.0, 127.9, 126.4, 126.1, 124.4, 86.9, 75.0, 58.8, 42.8, 34.5, 30.8, 24.8, 18.5, 14.8; [α]$_D$ +63.7 (c 0.16, CH$_2$Cl$_2$); IR (film) 3029, 2964, 1700, 1498, 1409, 698 cm$^{-1}$; HRMS (ESI$^+$) $m$/z calc’d for (M+H)$^+$ [C$_{22}$H$_{27}$N$_2$O]$^+$: 335.2118, found 335.2120.
Aminal 27 (20.0 mg, 0.0598 mmol), Pd(OAc)$_2$ (1.3 mg, 5.98 µmol), and PhI(OAc)$_2$ (28.9 mg, 0.0897 mmol) were dissolved in AcOH/Ac$_2$O (1:1, 0.600 mL) in a scintillation vial. The vial was heated to 80 °C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (2 x 10 mL). Water (10 mL) was added to the residue, and the mixture was neutralized with solid Na$_2$CO$_3$ until pH ~9. The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Only starting material was observed by $^1$H NMR.

To a solution of amino amide 7 (25.4 mg, 0.0950 mmol) in PhCH$_3$ (0.950 mL) at 23 °C was added benzaldehyde (12.5 µL, 0.124 mmol), TsOH·H$_2$O (1.0 mg, 4.75 µmol) and MgSO$_4$ (17.2 mg, 0.143 mmol). The suspension was heated to 110 °C for 10 h. Upon cooling to 23 °C, the solution was quenched with sat. aq. NaHCO$_3$ (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue was purified by column chromatography (7:3 → 3:2 hexanes/EtOAc eluent) to afford aminal 9b (29.4 mg, 87 % yield, R$_f$ = 0.45 in 9:1 CH$_2$Cl$_2$/MeOH) as a beige solid.

**Aminal 9b**: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.66 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.70-7.60 (comp m, 2H), 7.33-7.27 (comp m, 7 H), 7.23-7.17 (comp m, 3H), 7.06-7.02 (m, 1H), 6.47 (s, 1H), 2.85-2.77 (comp m, 2H), 2.57-2.53 (m, 1H), 2.50-2.44 (m, 1H), 1.92-1.81 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.0, 160.1, 149.6, 137.8, 136.6, 134.4, 128.68, 128.66, 128.5, 128.3, 124.8, 122.4, 122.1, 121.1, 78.3, 78.0, 50.5, 36.2, 25.0; IR (film) 2969, 2869, 1708, 1497, 1373, 1303, 746, 694 cm$^{-1}$; HRMS (ESI$^+$) m/z calc’d for (M+Na)$^+$ [C$_{23}$H$_{21}$N$_3$ONa]$^+$ : 378.1577, found 378.1581.
Pyridine 9b (15.0 mg, 0.0422 mmol), Pd(OAc)$_2$ (0.9 mg, 4.22 µmol) and PhI(OAc)$_2$ (20.4 mg, 0.0633 mmol) were dissolved in PhCH$_3$ (0.422 mL) in a 2-dram vial. The vial was sealed and heated to 90 °C for 18 h. Upon cooling, the solvent was removed by rotary evaporation. Acetoxylated product 10b was not observed by $^1$H NMR.

Pyridine 9b (63.4 mg, 0.178 mmol), Pd(OAc)$_2$ (4.0 mg, 0.0178 mmol), PhI(OAc)$_2$ (57.3 mg, 0.178 mmol), $p$-tolualdehyde (63.0 µL, 0.534 mmol), and H$_2$O (6.4 µL, 0.356 mmol) were dissolved in AcOH (0.890 mL) in a 2-dram vial. The vial was capped and heated to 90 °C for 20 h. Pd(OAc)$_2$ (4.0 mg, 0.0178 mmol), PhI(OAc)$_2$ (86.0 mg, 0.267 mmol) and Ac$_2$O (0.890 mL) were added and the reaction heated for an additional 18 h at 90 °C. Upon cooling, the solvent was removed and the resulting mixture was neutralized with solid Na$_2$CO$_3$ and water (10 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude mixture was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford pyridine 9 (7.0 mg, 11% yield), acetate 10 (3.6 mg, 5% yield), pyridine 30 (10.8 mg, 16% yield) and acetate 31 (14.1 mg, 19% yield).
Pyridine 13 (10.0 mg, 0.0271 mmol) and Pd(OAc)$_2$ (6.1 mg, 0.0271 mmol) were dissolved in AcOH (0.270 mL) in a scintillation vial. The vial was sealed and heated to 85 °C for 1 h. The reaction was cooled to 23 °C, and the organic solvent was removed azeotropically with heptane (3 x 5 mL) to afford palladacycle 32 (17.9 mg, 99% yield) as a light brown solid. The solid was crystallized by a layering technique with CH$_2$Cl$_2$ and hexanes.

**Palladacycle 32:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.93 (dd, $J =$ 5.5, 1.4 Hz, 1H), 7.85 (td, $J =$ 7.7, 1.4 Hz, 1H), 7.43-7.37 (comp m, 5H), 7.09-6.96 (comp m, 4H), 6.71 (t, $J =$ 7.3 Hz, 1H), 6.17 (d, $J =$ 7.5 Hz, 1H), 5.43 (s, 1H), 4.51 (d, $J =$ 14.5 Hz, 1H), 3.60 (d, $J =$ 14.5 Hz, 1H), 3.55 (dd, $J =$ 13.0, 5.9 Hz, 1H), 2.83-2.75 (m, 1H), 2.61 (dd, $J =$ 12.2, 7.6 Hz, 1H), 2.04 (s, 3H), 1.98-1.84 (m, 1H), 1.82-1.71 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.9, 154.3, 151.7, 146.7, 146.3, 138.5, 134.0, 133.3, 129.4, 128.9, 128.7, 127.4, 126.5, 124.3, 124.2, 123.7, 93.3, 75.8, 62.2, 46.7, 33.6, 24.6; IR (film) 3051, 2970, 1712, 1598, 1402, 730, 702 cm$^{-1}$; mp 250 °C dec.
Additional Experiments

Isomerization of anti diastereomer 9b

A solution of aminal 9b (96.3 mg, 0.271 mmol) in AcOH (1.08 mL) in a 2-dram vial was sealed with a Teflon cap and heated to 105 °C for 68 h. The reaction was partitioned between CH₂Cl₂ (10 mL) and H₂O (10 mL). The mixture was treated with solid Na₂CO₃ until pH 9. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc to EtOAc eluent) to afford aminal 9 (72.6 mg, 75% yield) as 5:1 mixture of syn and anti diastereomers.

Acetoxylation of anti diastereomer 9b

Pyridine 9b (100 mg, 0.281 mmol), Pd(OAc)₂ (6.3 mg, 0.0281 mmol), and Phl(OAc)₂ (90.5 mg, 0.281 mmol) were dissolved in AcOH (1.76 mL) and Ac₂O (1.76 mL) in a 2-dram vial. The vial was sealed with a Teflon cap and heated to 85 °C for 12 h, at which time Phl(OAc)₂ (90.5 mg, 0.281 mmol) was added. The reaction was heated at 85 °C for an additional 12 h. Upon cooling, CH₂Cl₂ (10 mL) and water (10 mL) were added and the mixture was neutralized with Na₂CO₃ until pH ~9. The mixture was extracted with CH₂Cl₂ (2 x 15 mL). The combined organics were dried over Na₂SO₄ and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac₂O. The crude residue was purified by flash chromatography (4:1 → 7:3 hexanes/acetone eluent) to afford acetate 10 (55.2 mg, 48% yield, Rₜ = 0.45 in 1:1 hexanes/acetone) as a beige solid.
Control experiment with benzaldehyde analog of aminal 27

To a solution of freshly distilled diisopropylamine (146 µL, 1.04 mmol) in THF (4.00 mL) at -78 °C was added n-BuLi (0.400 mL, 2.5 M in hexanes, 1.01 mmol). The solution was stirred for 10 min at -78 °C, at which time aminal 53 (250 mg, 0.720 mmol) in THF (3.20 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 °C. Benzyl bromide (225 µL, 1.44 mmol) was added at -78 °C, and the reaction was warmed to 23 °C, and stirred overnight. The reaction was quenched with water (10 mL). The aqueous was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash chromatography (7:1 → 4:1 hexanes/EtOAc eluent) to afford 65 and 65b as a 2.33 : 1 ratio of inseparable diastereomers (225 mg, 85% yield, Rᵣ = 0.29 in 1:4 EtOAc:hexanes) as a white amorphous solid.

To a solution of aminal 65 (25.0 mg, 0.0678 mmol) in AcOH/Ac₂O (0.678 mL) was added Pd(OAc)₂ (10 mol %), PhI(OAc)₂ (1.5 equiv), and the mixture was heated to 90 °C for 22 h. The reaction was partitioned between CH₂Cl₂ (10 mL) and H₂O (10 mL). The mixture was treated with Na₂CO₃ until pH 9. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was concentrated from heptanes (3 x 5 mL). The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc eluent) to afford starting material 65 (15.7 mg, 63% yield) and amide 66 (4.8 mg, 18% yield).
Aminal hydrolysis

Acetate 14 (122 mg, 0.284 mmol) was dissolved in aq. HCl (1 M, 2.80 mL) and THF (5.70 mL), and the resulting solution was heated to reflux overnight. Upon cooling the reaction was quenched with solid Na₂CO₃ until pH ~9-10. The mixture was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was taken up in ether (20 mL), and extracted with Claisen’s alkali (17.5 g KOH dissolved in 12.5 mL H₂O, then 37.5 mL MeOH added, 3 x 15 mL). The combined aqueous layers were acidified to pH ~9-10 and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford phenol 68 (98.0 mg, 89% yield, Rf = 0.42 in 1:1 acetone:hexanes) as a beige solid.

**Phenol 68**: ¹H NMR (400 MHz, CDCl₃) δ 8.60 (d, J = 4.8 Hz, 1H), 7.63 (td, J = 7.7, 1.8 Hz, 1H), 7.29-7.25 (m, 1H), 7.23-7.20 (comp m, 3H), 7.17-7.10 (comp m, 2H), 7.06-7.04 (comp m, 2H), 6.78 (d, J = 7.8 Hz, 1H), 6.65 (dd, J = 7.6, 1.6 Hz, 1H), 6.57 (td, J = 7.4, 1.0 Hz, 1H), 5.34 (s, 1H), 3.32 (ABq, J = 14.1 Hz, Δν = 93.0 Hz, 2H), 3.10 (dt, J = 12.4, 8.0 Hz, 1H), 2.99 (ddd, J = 12.4, 7.9, 4.6 Hz, 1H), 2.38-2.24 (comp m, 2H), 2.16-2.07 (m, 1H), 1.95-1.85 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 173.5, 157.5, 156.8, 149.2, 136.6, 135.8, 130.7, 130.6, 128.9, 127.0, 125.7, 124.9, 122.0, 119.7, 118.7, 117.8, 82.0, 74.5, 50.8, 43.0, 33.1, 23.9; [α]D²⁴ -1.2 (c 0.46, CH₂Cl₂); IR (film) 3061, 2965, 1699, 1597, 1499, 1399, 755 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C₂₄H₂₄N₃O₂]⁺: 386.1863, found 386.1865.

To a solution of phenol 68 (76.0 mg, 0.198 mmol) and AlCl₃ (66.9 mg, 0.502 mmol) in DCE (1.30 mL) at 23 °C was added PhNH₂ (69.0 µL, 0.753 mmol). The resulting mixture was heated to 90 °C and stirred for 8 h. Upon cooling, the reaction mixture was poured into water, and sat. Rochelle’s salt (10 mL) was added. The aqueous was extracted with EtOAc (3 x 15 mL), the organics washed with brine (20 mL) and dried over Na₂SO₄ and concentrated. To the crude mixture was added aq. HCl (6 M, 2.50 mL) and heated to 70 °C for 3 h. Upon cooling, the mixture was poured into water and the aqueous extracted with EtOAc (3 x 10 mL), dried over Na₂SO₄ and concentrated to afford a mixture of salicylaldehyde (9.3 mg, 38% yield) and imine 70 (5.2 mg, 13% yield).
Additional exchange experiments

Aminal 19 (30 mg, 0.0791 mmol), isobutyraldehyde (144 µL, 1.58 mmol), CSA (20.2 mg, 0.0870 mmol) and H₂O (2.8 µL, 0.158 mmol) were dissolved in MeOH (0.800 mL) in a scintillation vial. The vial was sealed with a Teflon cap and stirred 24 h at 100 °C. The volatile organic material was removed. Sat. aq. NaHCO₃ (10 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The organic layers were dried over Na₂SO₄ and concentrated in vacuo. ¹H NMR showed an approximately 4:1 ratio of aminals 6 and 19.

To a solution of amino amide 61 (1.00 g, 3.87 mmol) in PhCH₃ (19.4 mL) at 23 °C was added isobutyraldehyde (0.530 mL, 5.81 mmol), TsOH·H₂O (37.0 mg, 0.194 mmol), and MgSO₄ (0.700 g, 5.81 mmol). The mixture was heated to reflux overnight. Upon cooling to 23 °C, the solution was quenched with sat. aq. NaHCO₃ (20 mL), and the resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified via flash chromatography (4:1 hexanes/EtOAc eluent) to give aminal 71 (1.12 g, 92% yield, Rₜ 0.49 in 1:1 hexanes/EtOAc) as a light yellow oil.

Aminal 71: ¹H NMR (400 MHz, CDCl₃) δ 7.64 (s, 4H), 4.72 (d, J = 2.1 Hz, 1H), 3.97 (dd, J = 9.0, 5.2 Hz, 1H), 3.32 (dt, J = 9.9, 5.1 Hz, 1H), 2.76 (ddd, J = 9.5, 8.4, 6.4 Hz, 1H), 2.26-2.19 (m, 1H), 2.05-1.76 (comp m, 4H), 1.01 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.6, 140.1, 126.3 (q, J = 3.8 Hz), 122.4, 87.3, 66.4, 58.5, 31.3, 28.9, 25.1, 18.4, 14.6; [α]D²⁴ -2.2 (c 0.98, CH₂Cl₂); IR (film) 2967, 1704, 1614, 1328, 1122, 1068, 843 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+Na)+ [C₁₆H₂₀N₂O₃F]⁺: 313.1522, found 313.1531.

To a solution of freshly distilled diisopropylamine (516 µL, 3.68 mmol) in THF (5.00 mL) at -78 °C was added n-BuLi (1.41 mL, 2.5 M in hexanes, 3.52 mmol) dropwise. The
solution was stirred for 10 min at -78 °C, at which time a solution of aminal 71 (1.10 g, 3.52 mmol) in THF (6.80 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 °C. To a suspension of NaH (368 mg, 60% dispersion in mineral oil, 9.19 mmol, washed 2 x 1.5 mL) in DMF (10.0 mL) at 0 °C was added 2-(bromomethyl)pyridine hydrobromide (775 mg, 3.06 mmol). The suspension was stirred at 0 °C for 30 min, at which time it was added to the enolate solution at -78 °C (flask rinsed with additional 1.80 mL DMF). The suspension was warmed to 23 °C and stirred overnight. The reaction was quenched slowly with H₂O (25 mL) at 23 °C, and the resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 1.5 mL), dried over Na₂SO₄ and concentrated. The crude residue was purified by flash chromatography (7:3 → 1:1 hexanes/EtOAc eluent) to afford pyridine 72 (905 mg, 73% yield, Rᵢ = 0.21 in 1:1 hexanes/EtOAc) as a light yellow solid.

**Pyridine 72:** \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 8.55 (dd, \(J = 4.9, 0.9\) Hz, 1H), 7.65-7.59 (comp m, 3H), 7.53 (d, \(J = 8.5\) Hz, 2H), 7.48 (d, \(J = 7.8\) Hz, 1H), 7.15 (ddd, \(J = 7.4, 5.0, 1.0\) Hz, 1H), 4.53 (d, \(J = 3.0\) Hz, 1H), 3.24 (ABq, \(J = 12.2\) Hz, \(\Delta \nu = 20.5\) Hz, 2H), 2.82-2.75 (comp m, 2H), 2.20-2.15 (m, 1H), 2.10-2.03 (m, 1H), 1.79 (septet of doublets, \(J = 6.8, 3.0\) Hz, 1H), 1.65-1.54 (m, 1H), 1.51-1.42 (m, 1H), 0.91 (d, \(J = 6.9\) Hz, 3H), 0.55 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 174.4, 157.9, 148.8, 139.6, 135.8, 126.1 (q, \(J = 3.8\) Hz), 125.2, 123.8, 121.6, 85.9, 74.8, 58.5, 45.4, 35.0, 30.5, 24.6, 18.3, 14.3; \([\alpha]_D^{24}\) +69.4 (c 0.65, CH₂Cl₂); IR (film) 2966, 1704, 1614, 1325, 1124, 845, 748 cm\(^{-1}\); HRMS (ESI⁺) m/z calc’d for (M+Na)⁺ [C₂₂H₂₅N₃O₂F₃Na]⁺: 426.1764, found 426.1766.

Pyridine 72 (100 mg, 0.248 mmol), Pd(OAc)₂ (2.8 mg, 0.0124 mmol), PhI(OAc)₂ (80.0 mg, 0.248 mmol), PhCHO (50.0 µL, 0.496 mmol), and H₂O (18.0 µL, 0.992 mmol) were dissolved in AcOH (2.50 mL) in a scintillation vial. The vial was capped and heated to 105 °C for 10 h. The reaction was cooled to 95 °C and Pd(OAc)₂ (5.6 mg, 0.0248 mmol) and PhI(OAc)₂ (160 mg, 0.496 mmol) were added, and the reaction was stirred for another 24 h at 95 °C. Upon cooling, the solvent was removed, and the resulting mixture was neutralized with solid Na₂CO₃ and water (10 mL). The mixture was extracted with CH₂Cl₂ (3 x 10 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated. The crude mixture was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford pyridine 17 (33.0 mg, 30% yield) and acetate 18 (8.6 mg, 7% yield).
Stereochemical Analysis

Diastereomeric analysis of aminals

The assignment of diastereomers was done via NOE experiments, reaction evaluation, and $^1$H-NMR acquisition. One of the complicating factors in this analysis was the observed isomerization of the syn and anti diastereomers, particularly in the oxidation reactions. This isomerization could be sufficiently suppressed using toluene as the solvent, which allowed for reaction assessment.

For aminals 13 and 13b, NOE studies were performed. An interaction was observed between the highlighted protons in 13b. No interaction was observed in the opposite diastereomer. Based on this result, 13b was assigned as the anti diastereomer, and aminal 13 was assigned as syn. Both diastereomers were subjected to the Pd-catalyzed acetoxylation using PhCH$_3$ as solvent; only the syn diastereomer was reactive, albeit in low yield (<10%).

NOE studies on analogous diastereomeric compounds 9 and 9b revealed a key interaction between the aminal proton and a pyrrolidine proton, indicating that 9 was the syn diastereomer. The same reaction analysis was also performed, and corroborated this assignment. Based on the NOE studies and the decisive role of the pyridyl group on the oxidation, aminal 9 was assigned as syn, and 9b was assigned anti.
NMR data of the aminal protons in 9 and 9b allowed for analogous assignments of other diastereomeric mixtures in aromatic aldehyde-based aminals. Some illustrative examples are below.

The condensation of amino amide 7 with aromatic aldehydes using PhCH$_3$/AcOH (5:1) gave, in all but one case, the syn diastereomer as the major product. Alternatively, the
condensation utilizing TsOH·H₂O in PhCH₃ gave the anti diastereomer as the major product.

The acetoxylated arene products warrant further discussion. In each case, only one diastereomer is observed. This has been assigned as the syn product based on the following analysis. The aminal proton of 10, the oxidation product, is at 5.94 ppm, more similar to the chemical shift of the syn diastereomers of the aminal precursors. Furthermore, amino amide 7 was condensed with O-acetylsalicylaldehyde (3) to afford the opposite diastereomer (10b). The chemical shift of the aminal proton of this structure is 6.54 ppm, more consistent with the anti diastereomers of the aminal precursors. This aminal (10b) was further isomerized using AcOH, and a 1:1 mixture of the two diastereomers was observed. The other diastereomer correlated to the oxidation product (10), confirming the identification of these species as the acetoxylated arenes. The chemical shifts of the aminal protons in the oxidation products were 5.85-6.04 ppm, and were thus also assigned as syn.
For all aminals based on isobutyraldehyde and subsequently functionalized species, only one diastereomer was observed by NMR. The reactivity of compounds 6 and 21 in the Pd-catalyzed transformations is consistent with the reactivity observed in the aromatic systems. The X-ray crystal structure of 26 also indicates a syn relationship of the pyridyl and the aliphatic group. It is highly likely, therefore, that all aminals of the aliphatic systems are syn diastereomers.

Related experimental details
Pyridine 13b (10.0 mg, 0.0271 mmol), Pd(OAc)$_2$ (1.2 mg, 5.41 µmol), and PhI(OAc)$_2$ (13.1 mg, 0.0406 mmol) were dissolved in PhCH$_3$ (0.300 mL) in a scintillation vial. The vial was sealed and heated to 100 °C for 24 h. Upon cooling, the solvent was removed by rotary evaporation. Starting material, trace isomerization to pyridine 13 and benzylic oxidation were observed by $^1$H NMR.

To a solution of amino amide 7 (50 mg, 0.187 mmol) in THF (1.87 mL) at 23 °C was added aldehyde 71 (39.9 mg, 0.243 mmol), TFA (1.4 µL, 0.0187 mmol) and MgSO$_4$ (33.8 mg, 0.281 mmol). The suspension was heated to 75 °C for 12 h. Upon cooling to 23 °C, the solution was quenched with sat. aq. NaHCO$_3$ (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified by column chromatography (7:3 to 1:1 hexanes/EtOAc eluent) to afford acetate 10b (65.6 mg, 85% yield, $R_f = 0.50$ in EtOAc) as a beige solid.

Acetate 10b: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.60 (dd, $J = 4.1$, 0.8 Hz, 1H), 7.69–7.62 (comp m, 2H), 7.33–7.17 (comp m, 6H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.07–7.02 (comp m, 3H), 6.54 (s, 1H), 2.83 (dt, $J = 13.5$, 8.9 Hz, 1H), 2.74 (td, $J = 9.5$, 6.7 Hz, 1H), 2.59–2.55 (m, 1H), 2.42 (ddd, $J = 12.9$, 8.4, 4.0 Hz, 1H), 2.35 (s, 3H), 1.90–1.79 (comp m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.9, 169.4, 160.3, 149.7, 149.3, 137.8, 136.4, 129.6, 129.0, 128.5, 126.9, 125.6, 124.7, 123.3, 122.4, 121.8, 120.9, 77.9, 72.6, 50.1, 36.0, 24.7, 20.8; IR (film) 2967, 1766, 1711, 1587, 1369, 1198, 753 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ calc’d for (M+Na)$^+$ [C$_{25}$H$_{23}$N$_3$O$_3$Na]$^+$: 436.1632, found 436.1632.

Acetate 10b (7.0 mg, 0.0169 mmol) was dissolved in AcOH (0.169 mL) and heated to 90 °C for 18 h. Upon cooling, the solvent was removed by azeotropic removal with heptanes (3 x 15 mL). $^1$H NMR revealed a 1:1 mixture of acetate 10 and acetate 10b.
Summary of $^1H$ NMR diagnostic signals for diastereomeric analysis

**ISOPROPYL SUBSTRATES**

6
4.64 ppm

19 (major)
4.77 ppm

19 (minor)
4.97 ppm

20
5.02 ppm

21
4.47 ppm

22 (major)
4.54 ppm

22 (minor)
4.78 ppm

23
4.78 ppm

**PHENYL SUBSTRATES**

**SYN DIASTEREOMERS**

9
5.68 ppm

10
5.94 ppm

**ANTI DIASTEREOMERS**

9b
6.47 ppm

10b (independently synthesized)
6.54 ppm

13
5.44 ppm

14
5.80 ppm

13b
5.34 ppm
does not functionalize

14b
not synthesized
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2012

Supplementary Information: Stache, Seizert, and Ferreira

Molecular structures and NMR data:

6: Aminal 4.64 ppm, d
Methyl 0.93 ppm, d
0.55 ppm, d

Acetate 1.82 ppm, s

19 (major): Aminal 4.77 ppm, d
Methyl 0.92 ppm, d

19 (minor): Aminal 4.97 ppm, d
Methyl 0.51 ppm, d

Acetate 1.82 ppm, s

20: Acetates 2.06 ppm, s
2.03 ppm, s

21: Aminal 4.47 ppm, d
Methyl 0.89 ppm, d
0.58 ppm, d

Acetate 1.93 ppm, s

22 (major): Aminal 4.54 ppm, d
Methyl 0.83 ppm, d

22 (minor): Aminal 4.78 ppm, d
Methyl 0.60 ppm, d

Acetate 2.06 ppm, s

23: Acetates 1.92 ppm, s
2.02 ppm, s

26: Aminal 4.59 ppm, d
Methyl 0.93 ppm, d
Further analysis of methyl functionalization

In addition to the X-ray crystal structure that confirmed the stereochemistry of ester 26 (and therefore acetate 22), a Mosher’s ester analysis was conducted. The findings were based on precedented studies done by Seebach and coworkers. The information from this study corroborated with the crystal structure of nitrobenzoate 26. Although a crystal structure based on acetate 19 was not obtained, the analogous Mosher’s ester analysis and structural similarities provide substantial evidence for similar stereoselective functionalization.

![Diagram of chemical reaction](image)

To a solution of alcohol 63 (45.0 mg, 0.128 mmol), (R)-(−)-MTPA (30.0 mg, 0.128 mmol), EDC (29.4 mg, 0.154 mmol), HOBT (6.0 mg, 0.0380 mmol) in CH₃CN (1.30 mL) at 23 °C was added Et₃N (19.0 µL, 0.134 mmol). The reaction was stirred 24 h at 23 °C. The solvent was removed, and the residue partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford ester 75a (30.5 mg, 42% yield, Rf = 0.52 in 1:1 hexanes/acetone) as a white solid. Ester 75a: ¹H NMR (400 MHz, CDCl₃) δ 8.55 (dd, J = 4.9, 0.9 Hz, 1H), 7.62 (td, J = 7.7, 1.8 Hz, 1H), 7.42-7.34 (comp m, 8H), 7.26-7.21 (comp m, 3H), 7.11 (ddd, J = 7.4, 5.0, 1.0 Hz, 1H), 4.40 (d, J = 4.7 Hz, 1H), 3.95 (dd, J = 10.8, 4.0 Hz, 1H), 3.86 (dd, J = 10.8, 7.5 Hz, 1H), 3.43 (d, J = 0.9 Hz, 3H), 3.39 (d, J = 13.2 Hz, 1H), 3.06 (d, J = 13.2 Hz, 1H), 3.05-3.01 (m, 1H), 2.77 (dt, J = 11.4, 5.7 Hz, 1H), 2.16-2.05 (comp m, 2H), 1.73-1.66 (comp m, 2H), 1.43-1.37 (m, 1H), 0.65 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 166.0, 157.9, 149.1, 149.0, 136.4, 136.0, 132.2, 129.6, 129.2, 128.3, 127.2, 126.8, 125.0, 124.9, 121.8, 83.7, 75.2, 67.3, 57.7, 55.2, 46.0, 37.9, 36.4, 24.7, 13.9; ¹⁹F NMR (300 MHz, CDCl₃) δ -72.081; [α]D²⁴ +67.6 (c 0.50, CH₂Cl₂); IR (film) 2967, 1749, 1704, 1592, 1169, 1024, 720, 698 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C₃₁H₃₃F₃N₃O₄]⁺: 568.2418, found 568.2420.
To alcohol 63 (70.6 mg, 0.201 mmol), (S)-(−)-MTPA (47.0 mg, 0.201 mmol), EDC (46.2 mg, 0.241 mmol), HOBt (27.7 mg, 0.0181 mmol) in CH₃CN (2.00 mL) at 23 °C was added Et₃N (29.6 µL, 0.211 mmol). The reaction was stirred 24 h at 23 °C. The solvent was removed, and the residue dissolved in water (10 mL) and EtOAc (10 mL). The organic layer was separated, then dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford ester 75b (74.5 mg, 65% yield, Rᵣ = 0.52 in 1:1 hexanes/acetone) as a white solid.

**Ester 75b:** ¹H NMR (400 MHz, CDCl₃) δ 8.56 (dd, J = 4.9, 0.9 Hz, 1H), 7.62 (td, J = 7.7, 1.8 Hz, 1H), 7.43-7.32 (comp m, 8H), 7.26-7.21 (comp m, 3H), 7.12 (dd, J = 7.4, 5.0, 0.9 Hz, 1H), 4.41 (d, J = 4.9 Hz, 1H), 4.03 (dd, J = 10.8, 7.4 Hz, 1H), 3.82 (dd, J = 10.8, 3.8 Hz, 1H), 3.43 (d, J = 0.8 Hz, 3H), 3.39 (d, J = 13.2 Hz, 1H), 3.07 (d, J = 13.2 Hz, 1H), 2.97 (dt, J = 11.3, 7.0 Hz, 1H), 2.71 (dt, J = 11.3, 5.7 Hz, 1H), 2.17-2.06 (comp m, 2H), 1.71-1.61 (comp m, 2H), 1.48-1.39 (m, 1H), 0.65 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 166.1, 157.9, 149.1, 136.5, 136.0, 132.2, 129.6, 129.2, 128.3, 127.22, 127.21, 126.7, 124.9, 121.8, 83.6, 75.1, 67.5, 57.6, 55.2, 46.0, 38.0, 36.2, 24.7, 13.9; ¹⁹F NMR (300 MHz, CDCl₃) δ -72.079; [α]D²⁴ +37.5 (c 0.57, CH₂Cl₂); IR (film) 3063, 2967, 2881, 1749, 1703, 1592, 1170, 735 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C₃₁H₃₃F₃N₃O₄]⁺: 568.2418, found 568.2421.
To a solution of acetate 19 (127 mg, 0.335 mmol) in MeOH (3.30 mL) was added K₂CO₃ (92.5 mg, 0.669 mmol) at 23 °C, and the resulting mixture was stirred for 24 h. The reaction was partitioned between water (10 mL) and EtOAc (10 mL), and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo to afford alcohol 76 (113 mg, 99% yield, Rᵣ = 0.34 in 1:1 hexanes/acetone) as a white solid. The alcohol was sufficiently pure to be taken on to the next step.

**Alcohol 76:** ¹H NMR (400 MHz, CDCl₃) δ 8.57 (d, J = 4.9 Hz, 1H), 7.78-7.73 (comp m, 2H), 7.39 (t, J = 7.9 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 7.27-7.22 (comp m, 2H), 4.72 (d, J = 3.5 Hz, 1H), 3.60 (dd, J = 12.1, 1.1 Hz, 2H), 3.44 (dt, J = 11.1, 6.7 Hz, 1H), 3.33 (dd, J = 12.1, 5.8 Hz, 1H), 3.09 (dt, J = 11.3, 5.8 Hz, 1H), 2.56 (dt, J = 13.2, 6.9 Hz, 1H), 2.33 (dt, J = 13.2, 6.7 Hz, 1H), 1.91 (app. quintet, J = 6.7 Hz, 2H), 1.82-1.78 (m, 1H), 1.04 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.9, 160.8, 148.2, 137.1, 136.3, 129.2, 126.7, 124.9, 122.8, 121.8, 86.4, 78.2, 61.6, 58.1, 38.8, 37.6, 25.4, 13.9; [α]ᴰ +23.3 (c 0.18, CH₂Cl₂); IR (film) 3333, 2964, 1701, 1591, 1407, 751 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+H)⁺ [C₂₀H₂₄N₃O₃]⁺: 338.1863, found 338.1871.

To a solution of alcohol 76 (48.7 mg, 0.144 mmol), (+)-MTPA (33.8 mg, 0.144 mmol), EDC (33.2 mg, 0.173 mmol), HOBT (6.6 mg, 0.0432 mmol) in CH₃CN (1.40 mL) at 23 °C was added Et₃N (21.3 μL, 0.152 mmol). The reaction was stirred overnight at 23 °C. The solvent was removed, and the residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford ester 77a (27.0 mg, 34% yield, Rᵣ = 0.52 in 1:1 hexanes/acetone) as a white solid.

**Ester 77a:** ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, J = 4.3 Hz, 1H), 7.74-7.65 (comp m, 2H), 7.47-7.30 (comp m, 9H), 7.26-7.16 (comp m, 2H), 4.70 (d, J = 5.3 Hz, 1H), 4.19-4.11 (comp m, 2H), 3.52-3.44 (m, 1H), 3.44 (s, 3H), 2.96 (dt, J = 10.5, 6.5 Hz, 1H), 2.59-2.52 (m, 1H), 2.44-2.37 (m, 1H), 2.03-1.94 (comp m, 2H), 1.92-1.82 (m, 1H), 0.79 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 166.1, 161.84, 161.82, 149.4, 136.9, 136.5, 132.1, 129.6, 129.2, 128.4, 127.3, 126.5, 124.4, 122.2, 120.7, 83.4, 77.9, 68.1, 58.5, 55.3, 55.2, 38.4, 25.6, 13.8; ¹⁹F NMR (300 MHz, CDCl₃) δ -72.18; [α]ᴰ +42.7 (c 0.41, CH₂Cl₂); IR (film) 2968, 1748, 1705, 1588, 1169, 1122, 696 cm⁻¹; HRMS (ESI⁺) m/z calc’d for (M+Na)⁺ [C₃₀H₃₀F₃N₃O₃Na]⁺: 576.2081, found 576.2069.
To a solution of alcohol 76 (53.2 mg, 0.158 mmol), (-)-MTPA (36.9 mg, 0.158 mmol), EDC (36.3 mg, 0.189 mmol), HOBt (7.2 mg, 0.0473 mmol) in CH$_3$CN (1.60 mL) at 23 °C was added Et$_3$N (23.3 µL, 0.166 mmol). The reaction was stirred overnight at 23 °C. The solvent was removed by rotary evaporation, and the residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford ester 77b (33.7 mg, 39% yield, R$_f$ = 0.52 in 1:1 hexanes/acetone) as a white solid.

**Ester 77b:** $^1$H NMR (400 MHz, CDCl$_3$) δ 8.68 (d, J = 4.5 Hz, 1H), 7.75-7.66 (comp m, 2H), 7.43-7.29 (comp m, 9H), 7.26-7.15 (comp m, 2H), 4.70 (d, J = 5.4 Hz, 1H), 4.28 (dd, J = 10.8, 6.8 Hz, 1H), 4.02 (dd, J = 10.8, 4.1 Hz, 1H), 3.46-3.41 (m, 1H), 2.93 (dt, J = 10.5, 6.5 Hz, 1H), 2.56-2.51 (m, 1H), 2.43-2.36 (m, 1H), 2.03-1.93 (comp m, 2H), 1.91-1.82 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.5, 166.2, 161.9, 149.3, 136.9, 136.6, 132.2, 129.6, 129.2, 128.4, 127.2, 126.5, 124.7, 124.4, 122.3, 121.9, 120.7, 83.2, 77.6, 68.1, 58.4, 55.3, 38.4, 38.3, 25.6, 13.9; $^{19}$F NMR (300 MHz, CDCl$_3$) δ -72.16; [α]$_D^{24}$ +1.2 (c 0.40, CH$_2$Cl$_2$); IR (film) 2969, 1749, 1708, 1588, 1273, 1169, 1023 cm$^{-1}$; HRMS (ESI$^+$) m/z calc’d for (M+Na)$^+$ [C$_{30}$H$_{36}$F$_3$N$_3$O$_4$Na]$^+$: 576.2081, found 576.2080.
8 Although the yield was below 50%, the reaction could be advanced to further conversion by addition of HOBT. An optical rotation of the starting material alcohol was
taken before the reaction and after reisolation, and the value and sign were consistent. These results confirm that there was no resolution occurring from this coupling process.