Electronic Supplementary Material (ESI) for Chemical Science

Supplementary Information: Experimental Section

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

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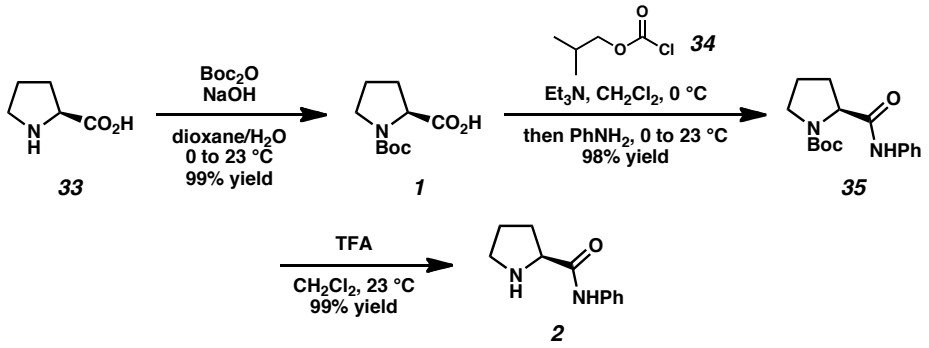
Materials and Methods. All reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, *N,N*-dimethylformamide, dichloromethane, hexanes, and toluene were purified by passing through activated alumina columns. Diisopropylamine was distilled over CaH_2. 2-Fluoropyridine 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.

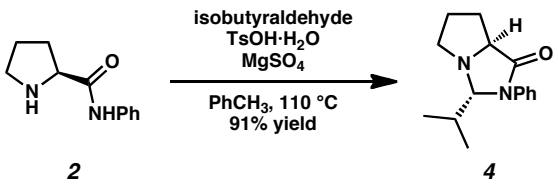
Experimental Section (from text).



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_2O (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_2SO_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.

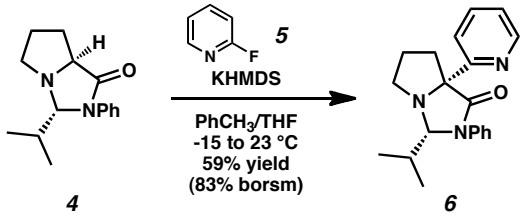
To a solution of (*S*)-*N*-Boc proline (2.50 g, 11.6 mmol) in CH_2Cl_2 (38.7 mL) at 0 ˚C was added isobutyl chloroformate (1.67 mL, 12.8 mmol) and triethylamine (1.80 mL, 12.8 mmol). After stirring for 20 minutes at 0 ˚C, aniline (1.16 mL, 12.8 mmol) was added, and the reaction was warmed to 23 ˚C and 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_2SO_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_2Cl_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_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until pH ~9. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_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.



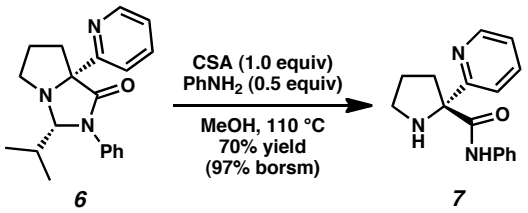
To a solution of amino amide **2** (1.50 g, 7.88 mmol) in $PhCH_3$ (26.3 mL) at 23 ˚C was added isobutyraldehyde (1.10 mL, 11.8 mmol), $TsOH{\cdot}H_2O$ (75.0 mg, 0.394 mmol), and $MgSO_4$ (1.40 g, 11.8 mmol). The suspension was heated to reflux and stirred overnight. Upon cooling to 23 ˚C, the solution 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_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2Cl_2); IR (film) 2963, 3053, 1683, 1504, 1411, 758, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{15}H_{20}N_2ONa]^+$: 267.1468, found 267.1468.



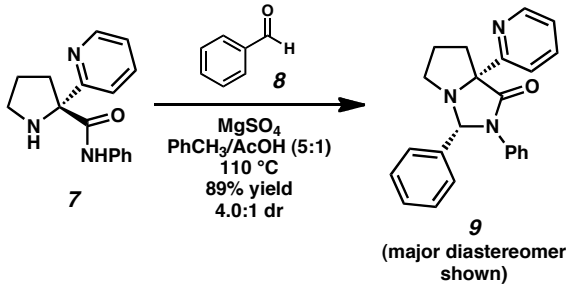
To a solution of aminal **4** (500 mg, 2.04 mmol), 2-fluoropyridine (176 μL, 2.04 mmol) in $PhCH_3$ (10.2 mL) at -15 ˚C was added KHMDS (408 mg, 2.04 mmol) in THF (4.10 mL) slowly over 1 h. Upon completion of addition, the reaction was allowed to warm to 23 ˚C and stirred overnight. The reaction was 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2Cl_2); IR (film) 2962, 1701, 1587, 1497, 1407, 752 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{20}H_{24}N_3O]^+$: 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), NH_2Ph (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. $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 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 borsm) R_f = 0.05 in 1:1 hexanes/EtOAc) as a beige solid.

Amide 7: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $(M+H)^+$ $[C_{16}H_{18}N_3O]^+$: 268.1444, found 268.1445.

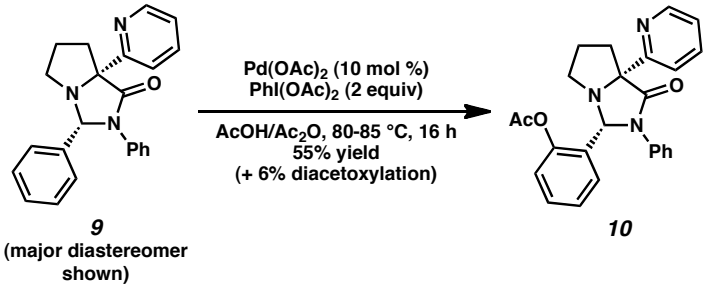


Representative procedure for the formation of *N,N*-aminals:

To amino amide **7** (234 mg, 0.875 mmol), benzaldehyde (115 μL, 1.14 mmol) and $MgSO_4$ (158 mg, 1.31 mmol) was added $PhCH_3$ (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 Na_2CO_3, and was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 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.

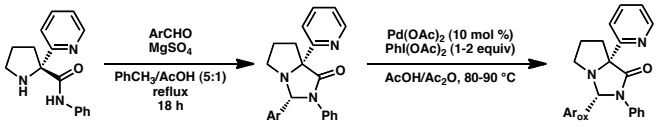
Aminal 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.53-7.48 (comp m, 4H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.20-7.15 (comp m, 5H), 7.10-7.04 (comp m,

2H), 5.68 (s, 1H), 3.48 (dt, J = 10.6, 6.4 Hz, 1H), 3.20 (dt, J = 10.6, 6.6 Hz, 1H), 2.70 (dt, J = 13.2, 7.6 Hz, 1H), 2.57 (ddd, J = 13.4, 7.4, 6.2 Hz, 1H), 2.04-1.91 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 161.1, 149.2, 139.74, 139.69, 137.2, 136.0, 128.8, 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 $(M+Na)^+$ $[C_{23}H_{21}N_3ONa]^+$: 378.1577, found 378.1574.

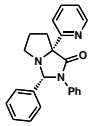
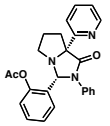
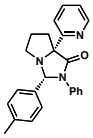
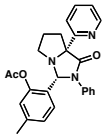
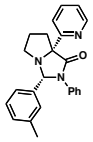
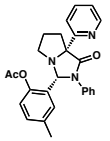
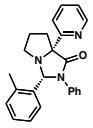
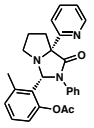
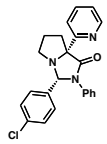
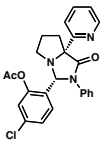
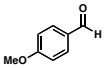
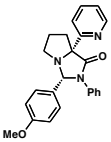
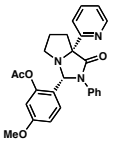
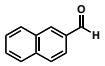
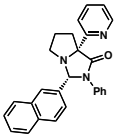
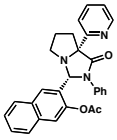


Representative procedure for the oxidation of amino amide 7-based aminals:
Pyridine **9** (84.7 mg, 0.238 mmol), $Pd(OAc)_2$ (5.3 mg, 0.0238 mmol), and $PhI(OAc)_2$ (115 mg, 0.357 mmol) were dissolved in AcOH (1.76 mL) and Ac_2O (1.76 mL) in a 2-dram vial. The vial was sealed with a Teflon cap and heated 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_2Cl_2 (10 mL) and water (10 mL) were added and the mixture was neutralized with Na_2CO_3 until pH ~9. The mixture was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac_2O. The crude residue was purified by flash chromatography (4:1 → 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, $CDCl_3$) δ 8.56 (ddd, J = 4.8, 1.7, 0.9 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 Hz, 1H), 6.78-6.77 (comp m, 2H), 5.94 (s, 1H), 3.57 (dt, J = 9.8, 5.7 Hz, 1H), 3.16 (ddd, J = 9.8, 7.8, 6.7 Hz, 1H), 2.75 (dt, J = 13.3, 7.9 Hz, 1H), 2.42 (s, 3H), 2.37 (td, J = 8.5, 4.7 Hz, 1H), 1.98-1.86 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $(M+H)^+$ $[C_{25}H_{24}N_3O_3]^+$: 414.1812, found 414.1814.

Table 1. Aminal formation and subsequent directed oxidation *(reproduced)*.



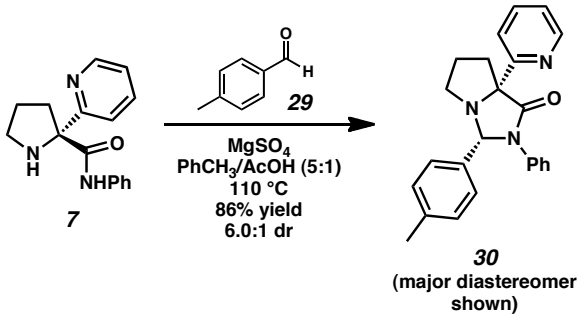
7 *11* *12*

entry	aldehyde	aminal	yield (%)[a]/ dr (syn/anti)[b]	oxidation product	yield (%)
1			89 4.0:1		55[c]
2			86 6.0:1		47[c]
3			76 5.8:1		72
4			87 1:1.5		85
5			67 3.8:1		39
6			78 5.8:1		39[c]
7			80 7.3:1		58

[a] Isolated yields. [b] Diastereomeric ratio measured by ^{1}H-NMR. [c] Diacetoxylation product also observed (Entry 1: 6%; Entry 2: 16%; Entry 6: 3%).

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.

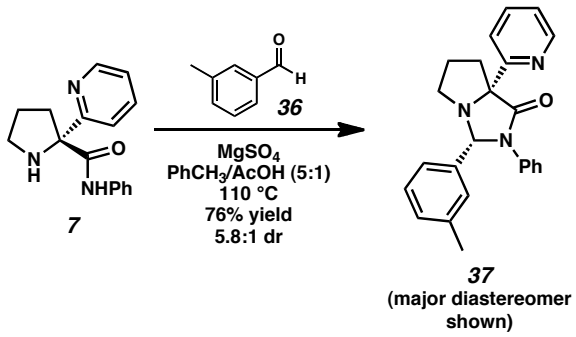


7 *30* (major diastereomer shown)

According to the general procedure, amino amide **7** (120 mg, 0.449 mmol), *p*-tolualdehyde (69.0 μL, 0.584 mmol), $MgSO_4$ (81.1 mg, 0.674 mmol), and $PhCH_3$/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, R_f = 0.53 in 40:1 EtOAc:MeOH eluent) as

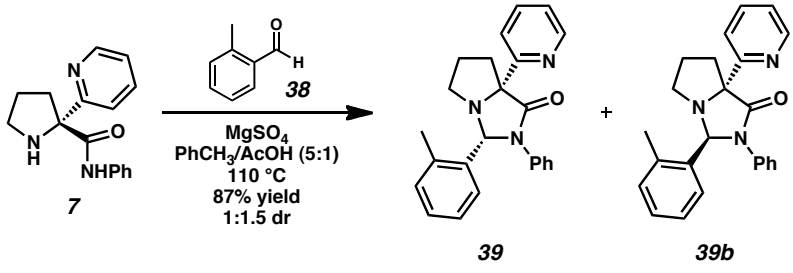
a beige solid. The major diastereomer could be further purified for characterization analysis.

Aminal 30: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $(M+H)^+$ $[C_{24}H_{24}N_3O]^+$: 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, 1300, 752, 692 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{23}N_3ONa]^+$: 392.1733, found 392.1732.

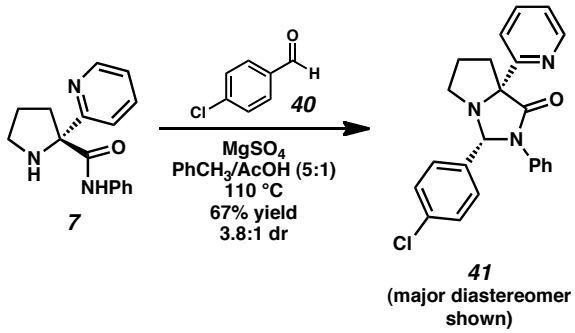


According to the general procedure, amino amide **7** (102 mg, 0.382 mmol), *o*-tolualdehyde (57.6 μL, 0.496 mmol), $MgSO_4$ (69.0 mg, 0.573 mmol), and $PhCH_3$/AcOH (5:1, 2.55 mL) were heated to 110 °C for 24 h. Aminals **39** and **39b** were isolated as a

1:1.5 mixture of inseparable diastereomers (123 mg, 87% yield, R_f = 0.58 in 40:1 EtOAc:MeOH eluent).

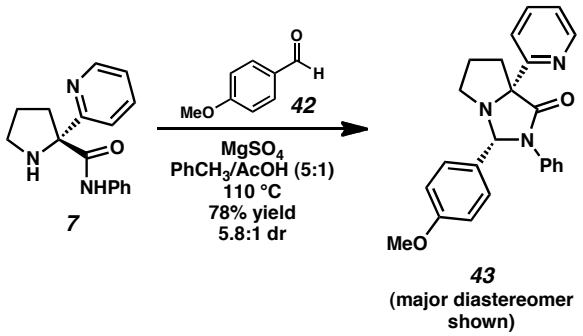
Aminal 39 (syn): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.1, 0.8 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.31-6.94 (comp m, 8H), 6.73-6.64 (comp m, 2H), 5.91 (s, 1H), 3.67 (dt, *J* = 9.6, 5.2 Hz, 1H), 3.18 (td, *J* = 8.8, 6.9 Hz, 1H), 2.87-2.73 (m, 1H), 2.57 (s, 3H), 2.35 (ddd, *J* = 13.2, 7.9, 5.3 Hz, 1H), 2.01-1.90 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $(M+Na)^+$ $[C_{24}H_{23}N_3O_3Na]^+$: 392.1733, found 392.1735.

Aminal 39b (anti): ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $(M+Na)^+$ $[C_{24}H_{23}N_3ONa]^+$: 392.1733, found 392.1730.



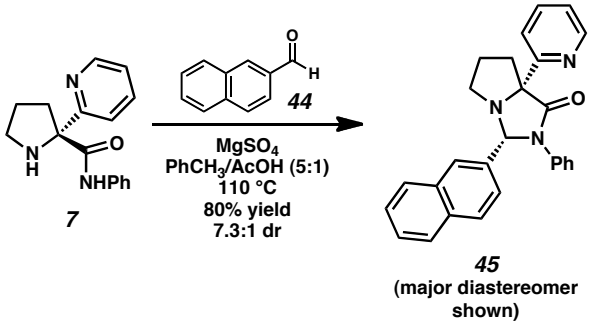
According to the general procedure, amino amide **7** (106 mg, 0.397 mmol), *p*-chlorobenzaldehyde (72.4 mg, 0.515 mmol), $MgSO_4$ (71.7 mg, 0.596 mmol), and $PhCH_3$/AcOH (5:1, 2.65 mL) were heated to 110 °C for 24 h. Aminal **41** was isolated as a 3.8:1 mixture of diastereomers (104 mg, 67% yield, 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $(M+H)^+$ $[C_{23}H_{21}N_3OCl]^+$: 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 $(M+H)^+$ $[C_{24}H_{24}N_3O_2]^+$: 386.1863, found 386.1849.



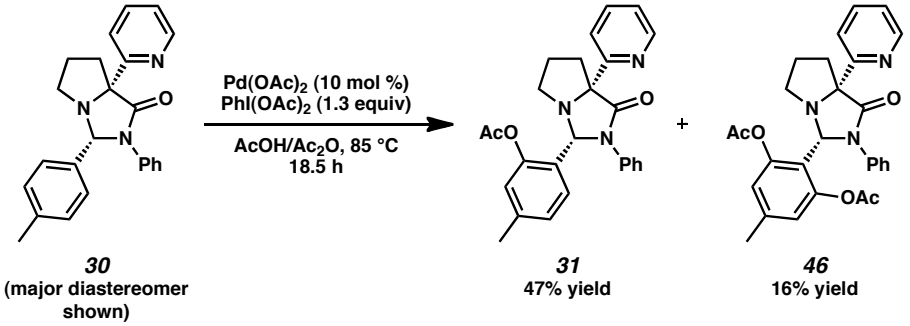
According to the general procedure, amino amide **7** (101 mg, 0.378 mmol), 2-naphthaldehyde (76.7 mg, 0.491 mmol), $MgSO_4$ (68.2 mg, 0.567 mmol), and $PhCH_3$/AcOH (5:1, 2.52 mL) were heated to 110 °C for 24 h. Aminal **45** was isolated as a 7.3:1 mixture of diastereomers (123 mg, 80% yield, R_f = 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), 7.76-7.73 (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

(film) 2967, 1707, 1597, 1499, 1380, 1317, 749 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+Na)^+$ $[C_{27}H_{23}N_3ONa]^+$: 428.1733, found 428.1729.

Pd-Catalyzed Oxidations

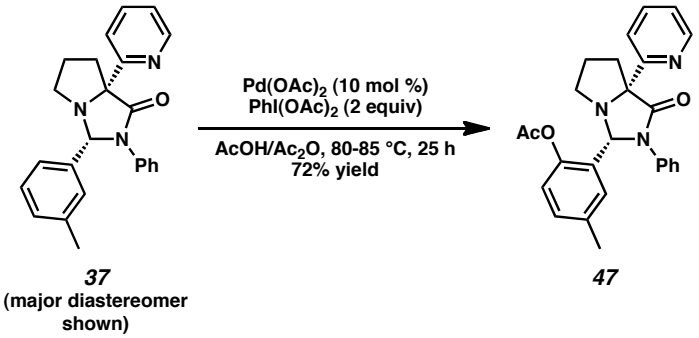
The palladium-catalyzed oxidations of the synthesized aminals were performed via the same procedure as the oxidation of aminal **9**. All reactions were conducted using the diastereomeric mixtures of aminals as the starting material. In all cases, the product was isolated as a single diastereomer, which 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 $AcOH/Ac_2O$ (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).

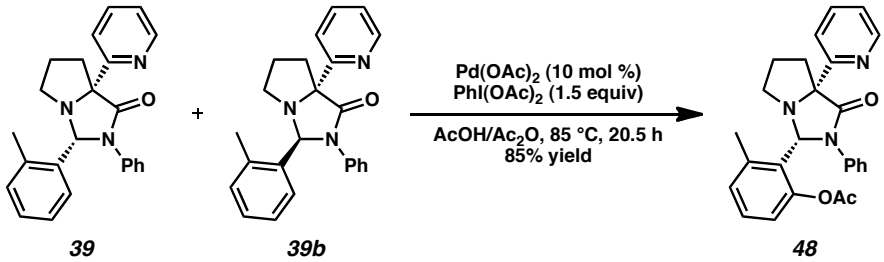
Acetate 31: ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.58-7.55 (comp m, 2H), 7.38-7.30 (comp m, 3H), 7.28-7.23 (m, 1H), 7.08-7.00 (comp m, 2H), 6.90 (d, *J* = 0.6 Hz, 1H), 6.68-6.60 (comp m, 2H), 5.89 (s, 1H), 3.53 (dt, *J* = 9.9, 5.8 Hz, 1H), 3.15 (dt, *J* = 9.9, 7.1 Hz, 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, $CDCl_3$) δ 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, 733, 692 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+Na)^+$ $[C_{26}H_{25}N_3O_3Na]^+$: 450.1788, found 450.1796.

Diacetate 46: ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $(M+Na)^+$ $[C_{28}H_{27}N_3O_5Na]^+$: 508.1843, found 508.1852.



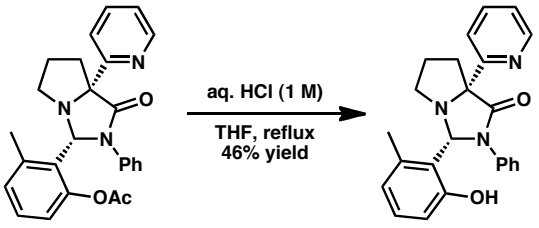
According to the general procedure, pyridine **37** (124 mg, 0.336 mmol), $Pd(OAc)_2$ (7.5 mg, 0.0336 mmol), $PhI(OAc)_2$ (162 mg, 0.504 mmol), and $AcOH/Ac_2O$ (1:1, 3.36 mL) were stirred at 80 °C for 15.5 h. $PhI(OAc)_2$ (54.1 mg, 0.168 mmol) was added, and the reaction stirred at 85 °C for an additional 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, $CDCl_3$) δ 8.57 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.60-7.57 (comp m, 2H), 7.36-7.24 (comp m, 4H), 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, $CDCl_3$) δ 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, 121.7, 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 $(M+H)^+$ $[C_{26}H_{26}N_3O_3]^+$: 428.1969, found 428.1974.



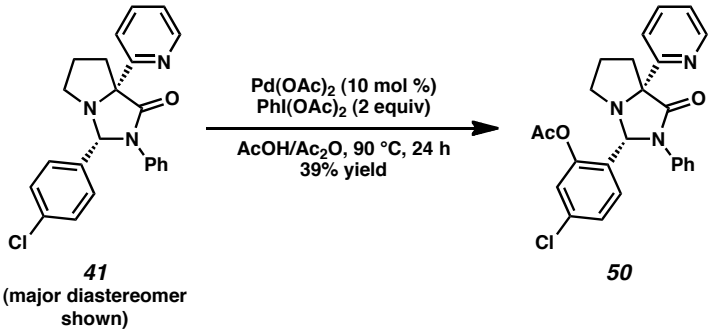
According to the general procedure, pyridines **39** and **39b** (123 mg, 0.333 mmol), $Pd(OAc)_2$ (7.5 mg, 0.0333 mmol), $PhI(OAc)_2$ (107 mg, 0.333 mmol) and $AcOH/Ac_2O$ (1:1, 3.33 mL) were stirred at 85 °C for 10 h. $PhI(OAc)_2$ (53.6 mg, 0.167 mmol) was added, and the reaction stirred an additional 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 $(M+Na)^+$ $[C_{26}H_{25}N_3O_3Na]^+$: 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_2CO_3 until pH ~9. The mixture was then extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_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_f = 0.28 in 1:1 hexanes/acetone) as a light yellow oil.

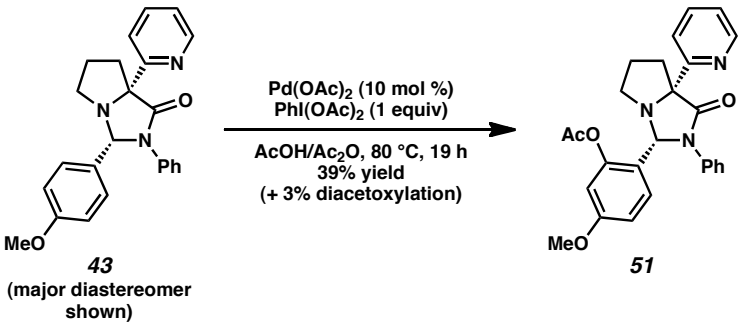
Phenol 49: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (br s, 1H), 8.67 (dt, *J* = 4.8, 1.4 Hz, 1H), 7.77-7.75 (comp m, 2H), 7.29-7.24 (m, 1H), 7.23-7.19 (comp m, 3H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.95-6.90 (comp m, 2H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 3.18 (dt, *J* = 12.5, 8.0 Hz, 1H), 3.08 (ddd, *J* = 12.4, 7.8, 4.4 Hz, 1H), 2.73-2.65 (comp m, 2H), 2.23-2.16 (m, 1H), 1.99-1.91 (m, 1H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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; IR (film) 3061, 2959, 1709, 1586, 1471, 1397, 1123, 749, 702 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{24}H_{23}N_3O_2Na]^+$: 408.1682, found 408.1690.



According to the general procedure, pyridine **41** (104 mg, 0.267 mmol), $Pd(OAc)_2$ (6.0 mg, 0.0267 mmol), $PhI(OAc)_2$ (172 mg, 0.534 mmol) and $AcOH/Ac_2O$ (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_f = 0.48 in 1:1 hexanes/acetone).

Acetate 50: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.56-7.53 (comp m, 2H), 7.44-7.37 (comp m, 2H), 7.30-7.24 (comp m, 2H), 7.13 (d, *J* = 1.8 Hz, 2H), 7.04 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 1H), 3.56 (dt, *J* = 9.8, 5.8 Hz, 1H), 3.14 (dt, *J* = 9.7, 7.2 Hz, 1H), 2.75 (dt, *J* = 13.3, 7.8 Hz, 1H), 2.42 (s, 3H), 2.36 (ddd, *J* = 13.2, 7.5, 5.7 Hz, 1H), 2.02-1.90 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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,

38.1 25.2, 21.0; IR (film) 2959, 1769, 1701, 1598, 1376, 1193, 754, 692 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+Na)^+$ $[C_{25}H_{22}N_3O_3ClNa]^+$: 470.1242, found 470.1247.



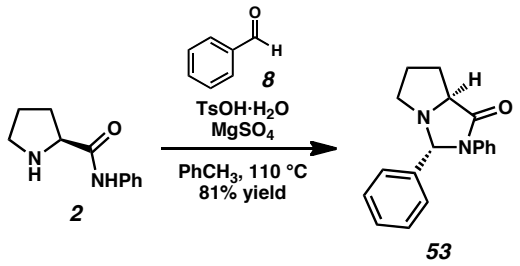
According to the general procedure, pyridine **43** (135 mg, 0.350 mmol), $Pd(OAc)_2$ (7.9 mg, 0.0350 mmol), $PhI(OAc)_2$ (113 mg, 0.350 mmol) and $AcOH/Ac_2O$ (1:1, 3.50 mL) were stirred at 80 °C for 19 h. Acetate **51** was isolated as a beige solid (83.9 mg, 39% yield (45% borsm), R_f = 0.40 in 1:1 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: ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $(M+Na)^+$ $[C_{26}H_{25}N_3O_4Na]^+$: 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 $AcOH/Ac_2O$ (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).

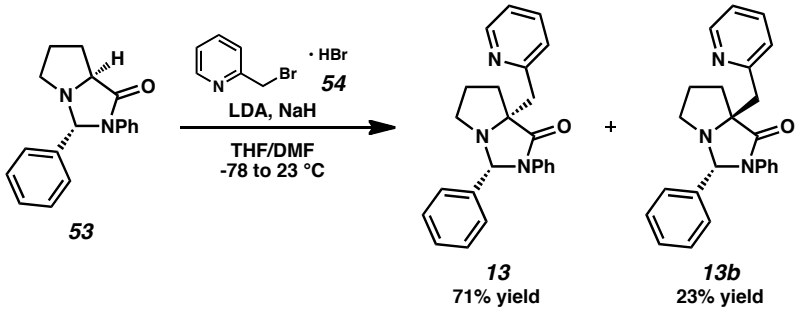
Acetate 52: ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.72-7.69 (comp m, 3H), 7.58 (s, 1H), 7.42-7.37 (m, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.29-7.24 (comp m, 3H), 7.18 (s, 1H), 7.15 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.08-7.02 (comp m, 2H), 6.78 (ddd, *J*

= 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, $CDCl_3$) δ 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 $(M+H)^+$ $[C_{29}H_{26}N_3O_3]^+$: 464.1969, found 464.1969.



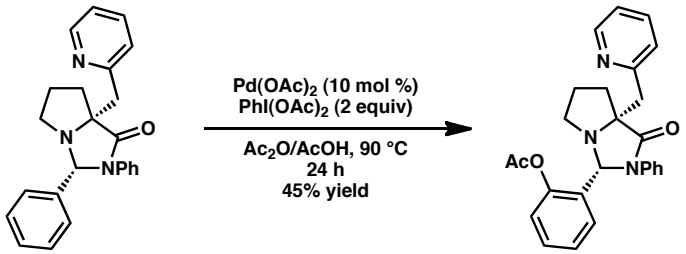
To a solution of amino amide **2** (1.50 g, 7.90 mmol) in $PhCH_3$ (26.3 mL) at 23 ˚C was added benzaldehyde (1.00 mL, 10.2 mmol), $TsOH{\cdot}H_2O$ (75.0 mg, 0.395 mmol), and $MgSO_4$ (1.40 g, 11.8 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried over Na_2SO_4 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, R_f = 0.24 in 1:1 hexanes/EtOAc) as a light brown solid.

Aminal 53: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ +8.9 (*c* 0.28, CH_2Cl_2); IR (film) 2969, 3032, 1699, 1598, 1498, 1384, 757 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+H$^+$) $[C_{18}H_{19}N_2O]^+$: 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 H_2O (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 Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford

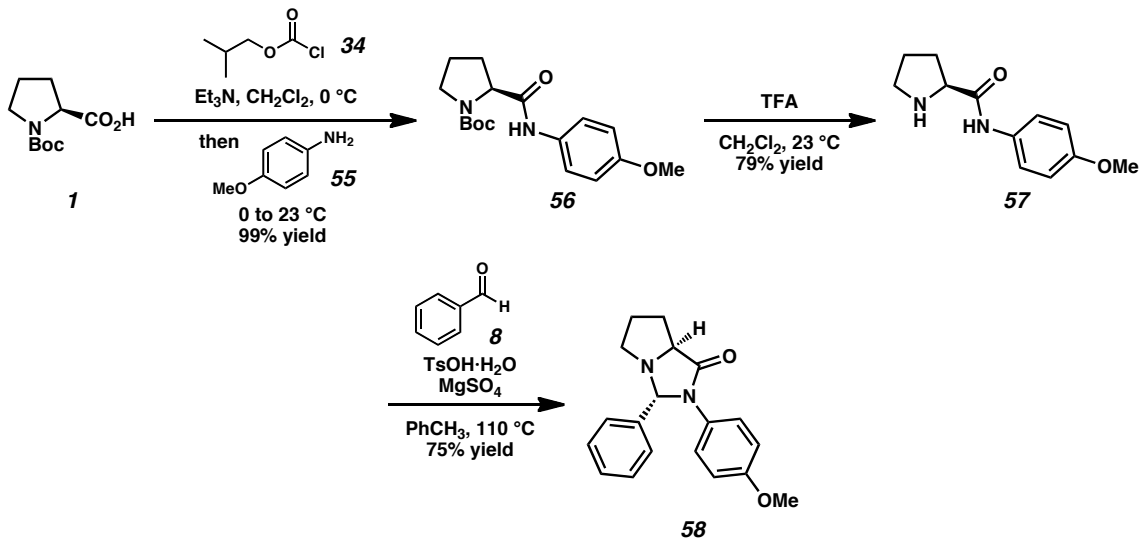
pyridine **13** (1.38 g, 71% yield, R_f = 0.46 in 40:1 EtOAc/MeOH) as a beige solid and pyridine **13b** (458 mg, 23% yield, R_f = 0.21 in 40:1 EtOAc/MeOH) as a light beige solid.
Pyridine 13: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 3.6 Hz, 1H), 7.53 (app. t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.9 Hz, 2H), 7.18-7.13 (comp m, 4H), 7.07 (t, *J* = 8.1 Hz, 2H), 6.89-6.88 (comp m, 2H), 5.44 (s, 1H), 3.20 (ABq, *J* = 13.1 Hz, Δν = 80.5 Hz, 2H), 3.18-3.14 (m, 1H), 2.99 (dt, *J* = 11.2, 5.7 Hz, 1 H), 2.33-2.26 (m, 1H), 2.23-2.16 (m, 1H), 1.83-1.76 (m, 1H), 1.63-1.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 157.8, 148.6, 140.1, 137.0, 135.8, 128.7, 128.3, 128.2, 127.0, 125.4, 125.3, 122.5, 121.5, 83.1, 75.1, 55.8, 45.2, 35.5, 24.6; $[\alpha]_D^{24}$ +131.2 (*c* 0.25, CH_2Cl_2); IR (film) 3052, 2968, 1702, 1592, 1499, 1391, 747, 702 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+Na)^+$ $[C_{24}H_{23}N_3ONa]^+$: 392.1733, found 392.1732.
Pyridine 13b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.0 Hz, 1H), 7.50 (td, *J* = 7.7, 1.7 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20-7.15 (comp m, 6H), 7.11-7.09 (comp m, 2H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 5.34 (s, 1H), 3.48 (d, *J* = 13.1 Hz, 1H), 3.12 (d, *J* = 13.1 Hz, 1H), 2.57-2.50 (m, 1H), 2.45-2.36 (comp m, 2H), 2.10 (dt, *J* = 12.7, 6.1 Hz, 1H), 1.66-1.60 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 157.6, 149.1, 137.5, 136.1, 134.3, 128.5, 128.42, 128.40, 128.2, 124.9, 124.6, 122.1, 121.7, 78.5, 75.0, 51.2, 46.2, 35.8, 24.5; $[\alpha]_D^{24}$ +27.9 (*c* 0.76, CH_2Cl_2); IR (film) 2967, 1707, 1591, 1377, 1301, 746, 703 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{24}N_3O]^+$: 370.1914, found 370.1917.



13 ***14***

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_2O (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, $CDCl_3$) δ 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, 1 H), 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, $CDCl_3$) δ 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; $[\alpha]_D^{24}$ +86.0 (*c* 0.40, CH_2Cl_2); IR (film) 3062, 2966, 1767,

1702, 1497, 1385, 1199 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for ($M+H^+$) $[C_{26}H_{26}N_3O_3]^+$: 428.1969, found 428.1976.

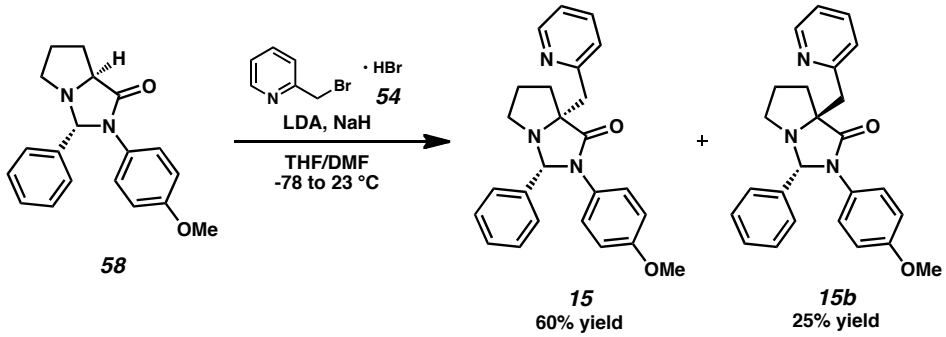


To a solution of (*S*)-*N*-Boc proline (0.500 g, 2.32 mmol) in CH_2Cl_2 (11.6 mL) at 0 ˚C was added isobutyl chloroformate (0.334 mL, 2.56 mmol) and Et_3N (0.359 mL, 2.56 mmol). After stirring for 20 minutes at 0 ˚C, *p*-anisidine (315 mg, 2.56 mmol) was added, and the reaction was allowed to warm to 23 ˚C and stirred overnight. The reaction mixture was washed sequentially with aq. $KHSO_4$ (1 M, 15 mL), sat. aq. $NaHCO_3$ (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4 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, R_f = 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 CH_2Cl_2 (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 CH_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until pH ~9-10. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford amino amide **57**[3] (2.03 g, 79% yield, R_f = 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 $PhCH_3$ (5.70 mL) at 23 ˚C was added benzaldehyde (0.150 mL, 1.48 mmol), $TsOH \cdot H_2O$ (11.0 mg, 0.0578 mmol), and $MgSO_4$ (205 mg, 1.70 mmol). The suspension was heated to reflux overnight. 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_2SO_4 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 R_f = 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_2Cl_2); IR (film) 2966, 1513, 1248, 1031, 831, 700 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{19}H_{21}N_2O_2]^+$: 309.1598, found 309.1595.

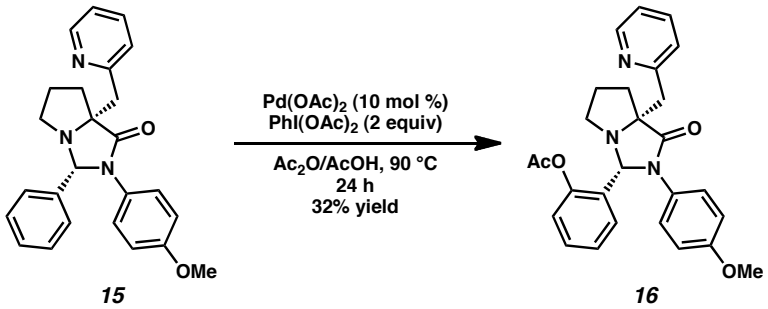


To a solution of freshly distilled diisopropylamine (484 μL, 3.45 mmol) in THF (4.10 mL) at -78 ˚C was added *n*-BuLi (1.32 mL, 2.5 M in hexanes, 3.31 mmol). The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **58** (1.02 g, 3.31 mmol) in THF (7.00 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 ˚C. 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 ˚C was added 2-(bromomethyl)pyridine hydrobromide (697 mg, 2.76 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 H_2O (30 mL) at 23 ˚C, 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_2SO_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 (dd, *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_2Cl_2); IR (film) 2958, 1700, 1589, 1513, 1249, 749, 702 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{25}H_{26}N_3O_2]^+$: 400.2020, found 400.2024.

Pyridine 15b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *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,

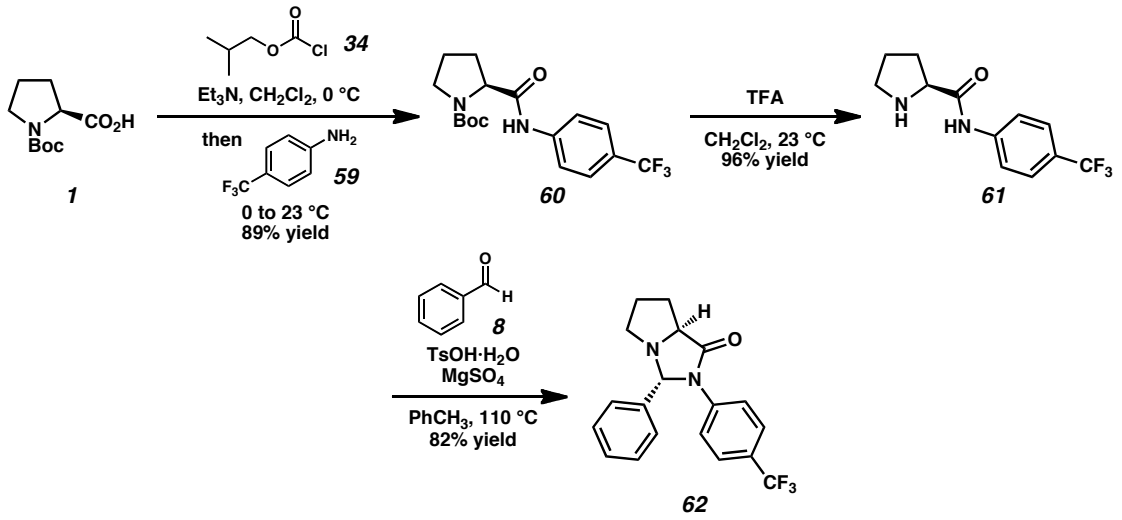
2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 177.4, 157.6, 156.7, 136.1, 134.4, 128.54, 128.47, 128.2, 124.7, 123.7, 121.7, 113.8, 78.8, 75.1, 55.3, 51.1, 46.2, 35.9, 24.6; $[\alpha]_D^{24}$ +4.0 (*c* 0.45, CH_2Cl_2); IR (film) 2961, 1703, 1512, 1248, 1032, 830, 702 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+H)^+$ $[C_{25}H_{26}N_3O_2]^+$: 400.2020, found 400.2016.



15 *16*

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 (3.50 mL) and Ac_2O (3.50 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_2CO_3 until pH ~9. The mixture was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (17:3 → 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2Cl_2); IR (film) 2959, 1766, 1513, 1249, 1199, 832 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+H)^+$ $[C_{27}H_{28}N_3O_4]^+$: 458.2074, found 458.2080.



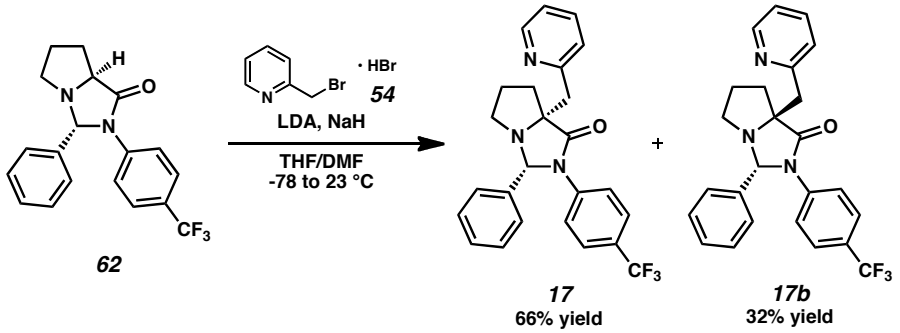
To a solution of (*S*)-*N*-Boc proline (2.50 g, 11.6 mmol) in CH_2Cl_2 (33.2 mL) at 0 ˚C was added isobutyl chloroformate (1.67 mL, 12.8 mmol) and Et_3N (1.80 mL, 12.8 mmol). After stirring for 20 minutes at 0 ˚C, *p*-trifluoromethylaniline (1.59 mL, 12.8 mmol) was added and the reaction was warmed to 23 ˚C and stirred overnight. The reaction was washed sequentially with aq. $KHSO_4$ (1 M, 50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_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 **60**[4] (4.44 g, 89% yield, R_f = 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 CH_2Cl_2 (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 CH_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until pH ~9. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford amino amide **61**[5] (2.57 g, 96% yield, R_f = 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 $PhCH_3$ (18.3 mL) at 23 ˚C was added benzaldehyde (0.482 mL, 4.80 mmol), $TsOH{\cdot}H_2O$ (34.9 mg, 0.184 mmol), and $MgSO_4$ (663 mg, 5.50 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 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, R_f = 0.45 in 1:1 hexanes/EtOAc) as a light yellow solid.

Aminal 62: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 140.8, 138.6, 129.2,

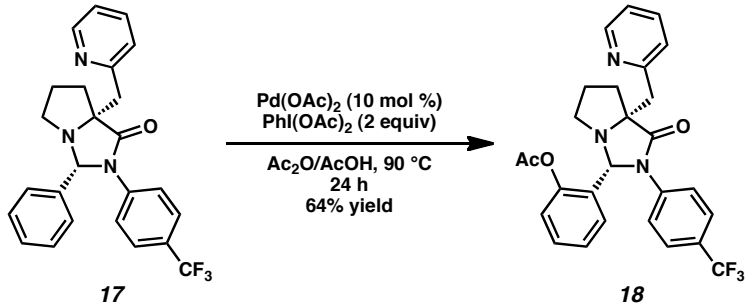
128.8, 126.1 (q, J = 3.8 Hz), 125.8, 120.0, 83.1, 64.2, 56.0, 27.4, 24.8; $[\alpha]_D^{24}$ +6.1 (*c* 0.49, CH_2Cl_2); IR (film) 3034, 2971, 1711, 1615, 1522, 1380, 1327, 1124 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+H)^+$ $[C_{19}H_{19}F_3N_2O]^+$: 347.1366, found 347.1365.



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 H_2O (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 Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine **17** (1.04 g, 66% yield, R_f = 0.58 in 40:1 EtOAc/MeOH) as a beige solid and pyridine **17b** (498 mg, 32% yield, R_f = 0.19 in 40:1 EtOAc/MeOH) as a light beige solid.

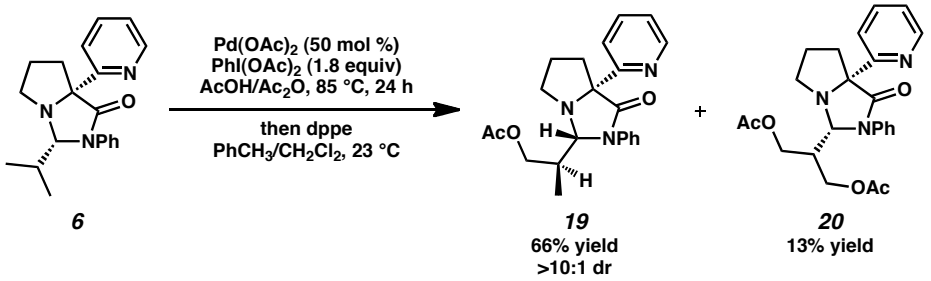
Pyridine 17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, J = 4.9, 0.8 Hz, 1H), 7.55-7.47 (comp m, 5H), 7.22-7.19 (comp m, 3H), 7.17-7.14 (m, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.88 (dd, J = 7.6, 1.8 Hz, 2H), 5.49 (s, 1H), 3.19 (ABq, J = 13.2 Hz, Δν = 69.6 Hz, 2H), 3.21 (dt, J = 11.1, 6.8 Hz, 1H), 3.00 (dt, 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ +63.2 (*c* 0.31, CH_2Cl_2); IR (film) 3063, 2967, 1710, 1614, 1326, 1122 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+Na)^+$ $[C_{25}H_{22}F_3N_3ONa]^+$: 460.1607, found 460.1614.

Pyridine 17b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, J = 4.9, 0.9 Hz, 1H), 7.52 (td, J = 7.7, 1.8 Hz, 1 H), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ +11.6 (*c* 0.59, CH_2Cl_2); IR (film) 2967, 1713, 1614, 1324, 1166, 1119, 844, 703 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+H)^+$ $[C_{25}H_{23}F_3N_3O]^+$: 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_2O (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_2CO_3 until pH ~9. The aqueous mixture was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic phases were dried over Na_2SO_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 (d, *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* = 10.2, 6.1 Hz, 1H), 3.08 (ABq, *J* = 13.2 Hz, Δν =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_2Cl_2); IR (film) 2968, 1768, 1712, 1379, 1326, 1199, 843, 736 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{27}H_{25}F_3N_3O_3]^+$ 496.1843, found 496.1843.



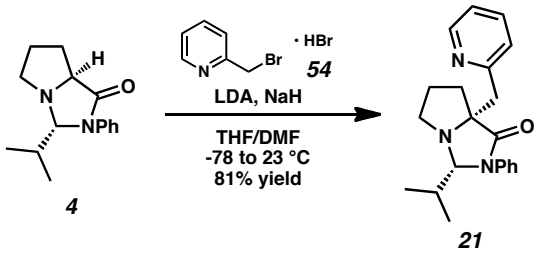
Pyridine **6** (200 mg, 0.622 mmol), $Pd(OAc)_2$ (69.8 mg, 0.311 mmol), and $PhI(OAc)_2$ (351 mg, 1.10 mmol) were dissolved in AcOH (3.10 mL) and Ac_2O (3.10 mL) in a round-bottomed flask. The flask was capped and heated to 85 ˚C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 15 mL). The residue

was treated with 1,2-bis(diphenylphosphino)ethane (249 mg, 0.622 mmol) in $PhCH_3/CH_2Cl_2$ (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/acetone eluent) to afford acetate **19** (>10:1 dr, 156 mg, 66% yield, R_f = 0.45 in 1:1 hexanes/acetone) as a light yellow oil and diacetate **20** (36.0 mg, 13% yield, R_f = 0.43 in 1:1 hexanes/acetone) as a light yellow oil.

Acetate 19: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ +20.7 (*c* 2.05, CH_2Cl_2); IR (film) 3061, 2967, 1735, 1701, 1497, 1408, 1237 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+H)^+$ $[C_{22}H_{26}N_3O_3]^+$: 380.1969, found 380.1970.

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

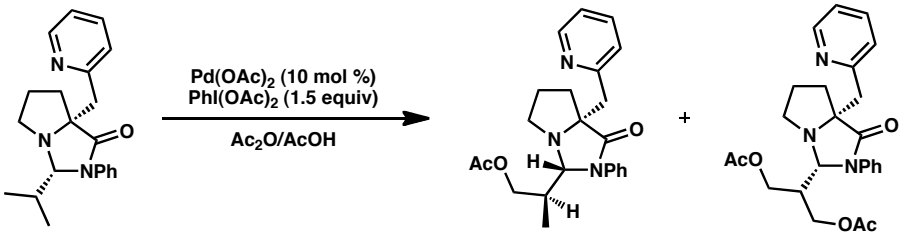
Diacetate 20: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.5 Hz, 1H), 7.75-7.67 (comp m, 2H), 7.47-7.39 (comp m, 4H), 7.23-7.19 (comp m, 2H), 5.02 (d, *J* = 3.9 Hz, 1H), 4.12 (dd, *J* = 11.3, 7.3 Hz, 1H), 4.04 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.95 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.85 (dd, *J* = 11.3, 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ +26.6 (*c* 0.50, CH_2Cl_2); IR (film), 2961, 1738, 1703, 1588, 1226, 1039, 753, 697 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{28}N_3O_5]^+$: 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 H_2O (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 Na_2SO_4 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, R_f = 0.74 in 40:1 EtOAc/MeOH) as a beige solid.

Pyridine 21: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ +85.0 (*c* 0.38, CH_2Cl_2); IR (film) 2969, 2870, 1676, 1600, 1524, 1443, 755 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{21}H_{25}N_3ONa]^+$: 358.1890, found 358.1894.



temp, time	yield *22*	dr	yield *23*
55 °C, 24 h	43%	10 : 1	13%
70 °C, 13 h	48%	5.7 : 1	19%

(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 Ac_2O (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 Na_2CO_3 until pH ~9. The aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac_2O. The crude residue was purified by flash chromatography (3:1 → 1:1 hexanes/acetone eluent) to afford acetate **22** (25.1 mg, 43% yield, 10:1 dr, R_f = 0.48 in 1:1 hexanes/acetone) as a light yellow amorphous solid and diacetate **23** (8.7 mg, 13% yield, R_f = 0.35 in 1:1 hexanes/acetone) as a light yellow amorphous solid.

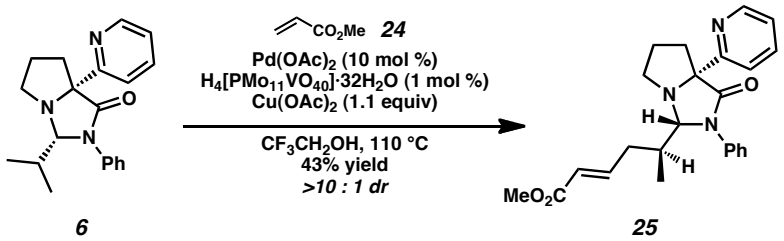
(At 70 °C) Pyridine **21** (50.0 mg, 0.149 mmol), $Pd(OAc)_2$ (3.3 mg, 0.0149 mmol), and $PhI(OAc)_2$ (72.0 mg, 0.224 mmol) were dissolved in AcOH (0.750 mL) and Ac_2O (0.750 mL) in a round-bottomed flask. The flask was capped and heated to 70 ˚C for 13 h. Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac_2O. 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, R_f = 0.48 in 1:1 hexanes/acetone) as a light yellow amorphous solid and diacetate **23** (12.9 mg, 19% yield, R_f = 0.35 in 1:1 hexanes/acetone) as a light yellow amorphous solid.

Acetate 22: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, Δν = 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, $CDCl_3$) δ 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; $[\alpha]_D^{24}$ +70.4 (*c* 0.50, CH_2Cl_2); IR (film) 3061, 2967, 2881, 1736, 1699, 1594, 1499, 1236, 754 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{23}H_{27}N_3O_3]^+$: 394.2125, found 394.2126.

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

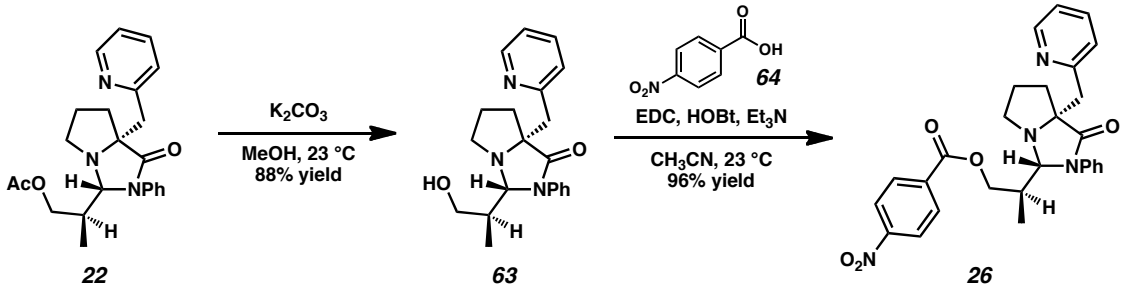
Diacetate 23: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.1 Hz, 1H), 7.62 (td, *J* = 7.6, 1.5 Hz, 1H), 7.43-7.35 (comp m, 5H), 7.23-7.21 (m, 1H), 7.15 (dd, *J* = 6.8, 5.4 Hz, 1H), 4.78 (d, *J* = 3.6 Hz, 1H), 3.94 (dd, *J* = 13.6, 6.1 Hz, 4H), 3.23 (ABq, *J* = 13.2 Hz, Δν = 33.8 Hz, 2H), 2.93-2.84 (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, $CDCl_3$) δ 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; $[\alpha]_D^{24}$ +72.8 (*c* 0.43, CH_2Cl_2); IR (film) 2965, 1739, 1702, 1593, 1409, 1226 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{25}H_{29}N_3O_5Na]^+$: 474.1999, 474.1997.



6 *25*

A 2-dram vial was charged with pyridine **6** (31.9 mg, 0.0992 mmol), $H_4[PMo_{11}VO_{40}]\cdot 32H_2O$ (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_3CH_2OH, 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, R_f = 0.10 in 1:1 hexanes/EtOAc) as a pale yellow oil.

Alkene 25: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 172.1, 166.8, 162.2, 149.6, 148.0, 136.4, 136.3, 129.3, 126.6, 124.4, 124.3, 122.1, 120.7, 86.0, 77.8, 59.3, 51.4, 38.9, 36.3, 32.9, 25.7, 15.9; IR (film) 2960, 1714, 1587, 1496, 1405, 1273, 1173 cm^{-1}; HMRS (ESI^{+}) *m/z* calc'd for $(M+H)^{+}$ $[C_{24}H_{28}N_3O_3]^{+}$: 406.2125, found 406.2129.



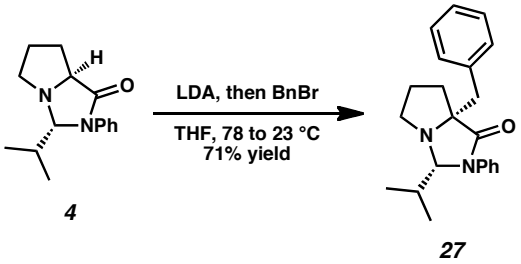
22 *63* *26*

To a solution of acetate **22** (118 mg, 0.300 mmol) in MeOH (3.00 mL) at 23 °C was added K_2CO_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_2SO_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, $CDCl_3$) δ 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, Δν = 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, $CDCl_3$) δ 174.3, 156.8, 149.0, 136.2, 129.2, 126.7, 125.2, 124.9, 123.7, 121.7, 86.5, 74.4, 62.0, 57.7, 45.1, 37.7, 34.3, 24.6, 14.1; $[\alpha]_D^{24}$ +54.0 (*c* 0.45, CH_2Cl_2); IR (film) 3332, 2961, 1696, 1594, 1476, 753, 698 cm^{-1}; HRMS (ESI^{+}) *m/z* calc'd for $(M+H)^{+}$ $[C_{21}H_{26}N_3O_2]^{+}$: 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_3CN (2.50 mL) at 23 °C was added Et_3N (38.0 μL, 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_2O (15 mL) and EtOAc (15 mL). The organic layer was dried over Na_2SO_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_2Cl_2 and hexanes.

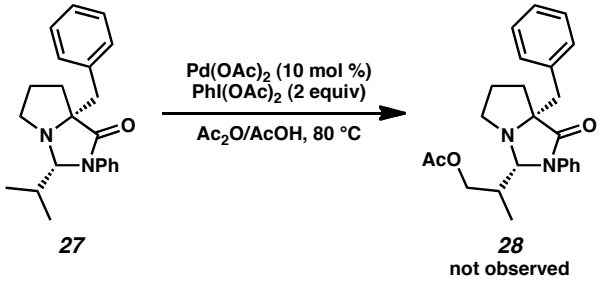
Ester 26: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 5.0, 0.9 Hz, 1H), 8.31-8.21 (comp m, 2H), 8.07-7.99 (comp m, 2H), 7.72 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.39-7.29 (comp m, 4H), 7.25-7.20 (comp m, 2H), 4.59 (d, *J* = 3.4 Hz, 1H), 3.99 (dd, *J* = 10.9, 4.9 Hz, 1H), 3.93 (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, 2H), 0.93 (d, *J* = 7.0 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, 44.9, 36.4, 35.9, 24.7, 14.3; $[\alpha]_D^{24}$ +61.0 (*c* 1.14, CH_2Cl_2); IR (film) 2968, 1723, 1721, 1527, 1276, 1103, 720 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{28}H_{29}N_4O_5]^+$: 500.2132, found 500.2137; mp 110-116 °C.



4 *27*

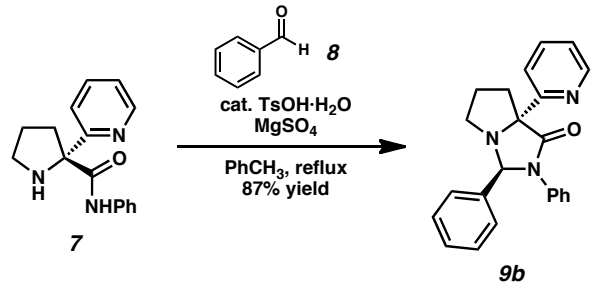
To a solution of freshly distilled diisopropylamine (167 μL, 1.19 mmol) in THF (5.00 mL) at -78 ˚C was added *n*-BuLi (0.460 mL, 2.5 M in hexanes, 1.15 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **4** (200 mg, 0.818 mmol) in THF (3.20 mL) was added, 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_2SO_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; $[\alpha]_D^{24}$ +63.7 (*c* 0.16, CH_2Cl_2); IR (film) 3029, 2964, 1700, 1498, 1409, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{22}H_{27}N_2O]^+$: 335.2118, found 335.2120.



27 ***28*** not observed

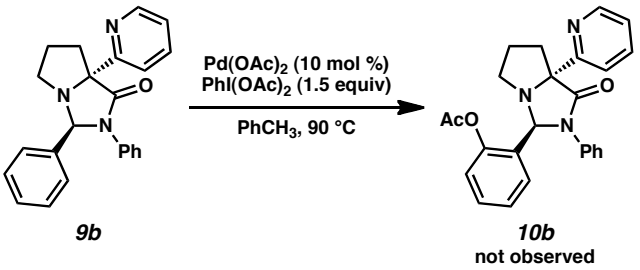
Aminal **27** (20.0 mg, 0.0598 mmol), $Pd(OAc)_2$ (1.3 mg, 5.98 μmol), and $PhI(OAc)_2$ (28.9 mg, 0.0897 mmol) were dissolved in $AcOH/Ac_2O$ (1:1, 0.600 mL) in a scintillation vial. The vial was heated to 80 °C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (2 x 10 mL). Water (10 mL) was added to the residue, and the mixture was neutralized with solid Na_2CO_3 until pH ~9. The mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. Only starting material was observed by ^1H NMR.



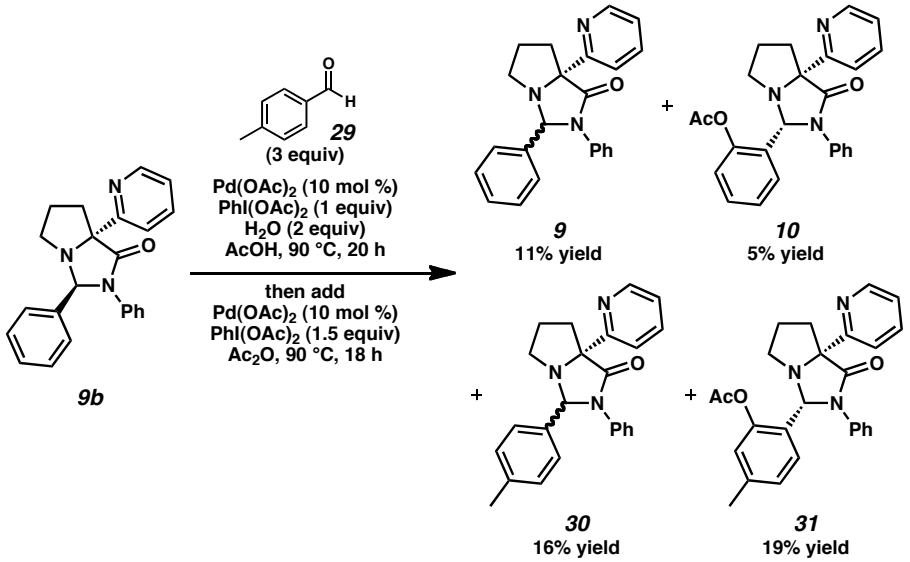
7 ***9b***

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), $TsOH·H_2O$ (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_2SO_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_2Cl_2/MeOH) as a beige solid.

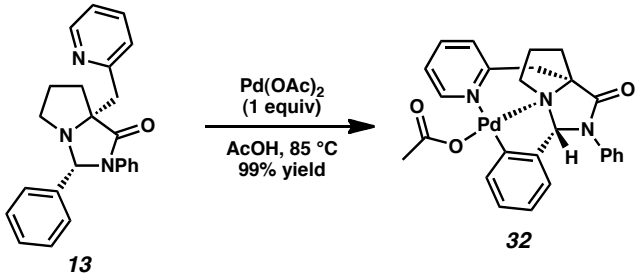
Aminal 9b: ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.70-7.60 (comp m, 2H), 7.33-7.27 (comp m, 7 H), 7.23-7.17 (comp m, 3H), 7.06-7.02 (m, 1H), 6.47 (s, 1H), 2.85-2.77 (comp m, 2H), 2.57-2.53 (m, 1H), 2.50-2.44 (m, 1H), 1.92-1.81 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $(M+Na)^+$ $[C_{23}H_{21}N_3ONa]^+$: 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 ^1H 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_2O (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_2O (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_2CO_3 and water (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over Na_2SO_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).



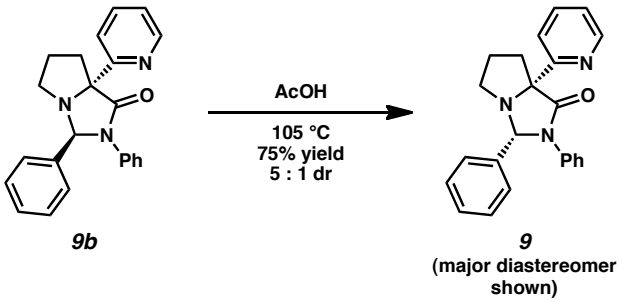
13 ***32***

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_2Cl_2 and hexanes.

Palladacycle 32: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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

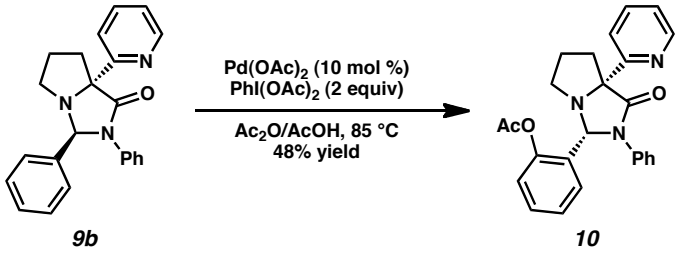
*Isomerization of anti diastereomer **9b***



9b ***9*** (major diastereomer shown)

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 CH_2Cl_2 (10 mL) and H_2O (10 mL). The mixture was treated with solid Na_2CO_3 until pH 9. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 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.

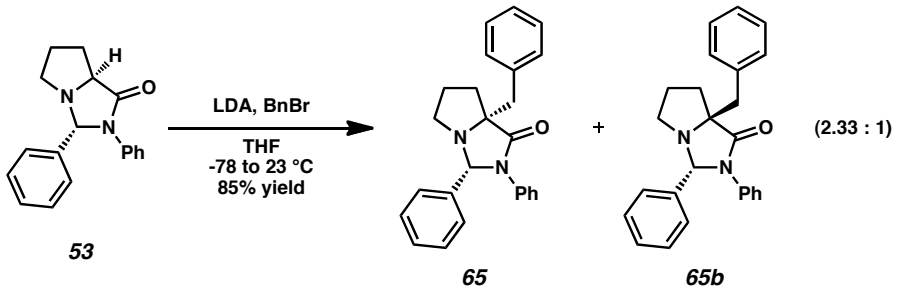
*Acetoxylation of anti diastereomer **9b***



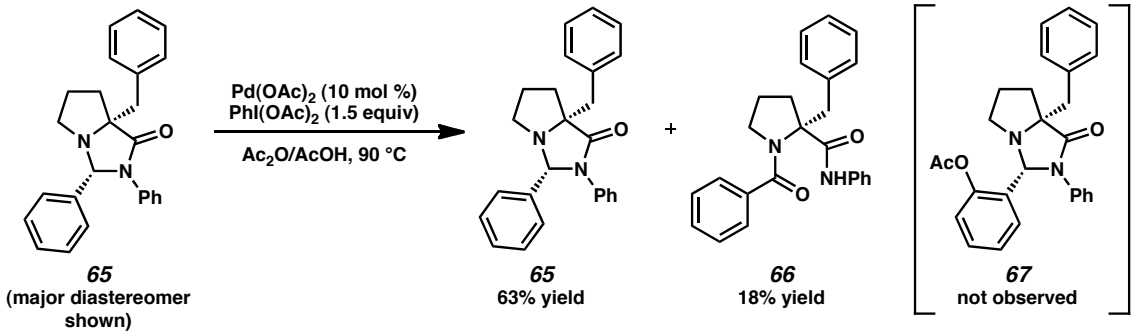
9b ***10***

Pyridine **9b** (100 mg, 0.281 mmol), $Pd(OAc)_2$ (6.3 mg, 0.0281 mmol), and $PhI(OAc)_2$ (90.5 mg, 0.281 mmol) were dissolved in AcOH (1.76 mL) and Ac_2O (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 $PhI(OAc)_2$ (90.5 mg, 0.281 mmol) was added. The reaction was heated at 85 °C for an additional 12 h. Upon cooling, CH_2Cl_2 (10 mL) and water (10 mL) were added and the mixture was neutralized with Na_2CO_3 until pH ~9. The mixture was extracted with CH_2Cl_2 (2 x 15 mL). The combined organics were dried over Na_2SO_4 and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac_2O. The crude residue was purified by flash chromatography (4:1 → 7:3 hexanes/acetone eluent) to afford acetate **10** (55.2 mg, 48% yield, R_f = 0.45 in 1:1 hexanes/acetone) as a beige solid.

*Control experiment with benzaldehyde analog of aminal **27***

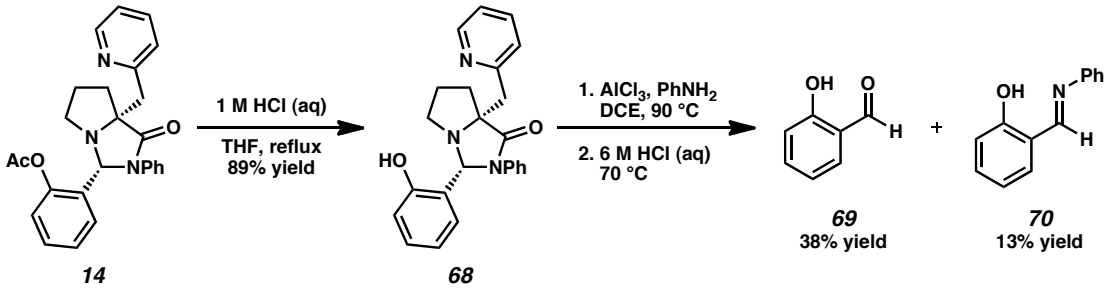


To a solution of freshly distilled diisopropylamine (146 μL, 1.04 mmol) in THF (4.00 mL) at -78 ˚C was added *n*-BuLi (0.400 mL, 2.5 M in hexanes, 1.01 mmol). The solution was stirred for 10 min at -78 ˚C, at which time aminal **53** (250 mg, 0.720 mmol) in THF (3.20 mL) was added, and the resulting 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 Na_2SO_4, 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, R_f = 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/Ac_2O (0.678 mL) was added $Pd(OAc)_2$ (1.5 mg, 6.78 μmol) and $PhI(OAc)_2$ (32.8 mg, 0.102 mmol), and the mixture was heated to 90 °C for 22 h. The reaction was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The mixture was treated with Na_2CO_3 until pH 9. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 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

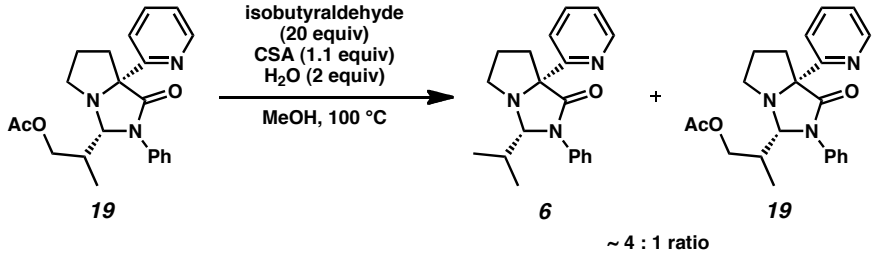


Acetate **14** (122 mg, 0.284 mmol) was dissolved in aq. HCl (1 M, 2.80 mL) and THF (5.70 mL), and the resulting solution was heated to reflux overnight. Upon cooling the reaction was quenched with solid Na_2CO_3 until pH ~9-10. The mixture was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, 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 H_2O, 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 Na_2SO_4, filtered and concentrated to afford phenol **68** (98.0 mg, 89% yield, R_f = 0.42 in 1:1 acetone:hexanes) as a beige solid.

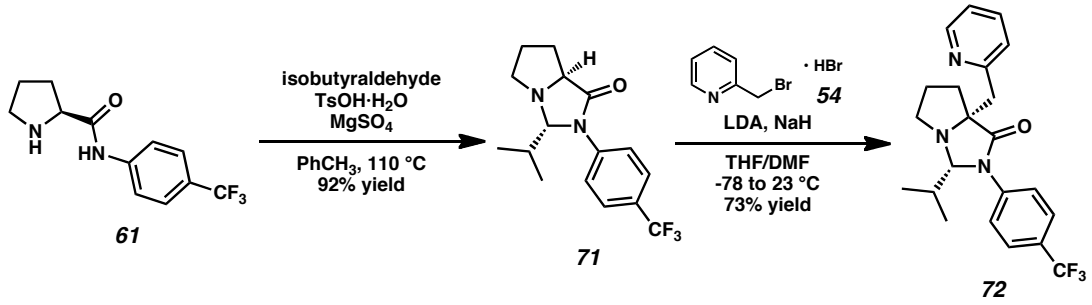
Phenol 68: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.29-7.25 (m, 1H), 7.23-7.20 (comp m, 3H), 7.17-7.10 (comp m, 2H), 7.06-7.04 (comp m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.65 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.57 (td, *J* = 7.4, 1.0 Hz, 1H), 5.34 (s, 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ -1.2 (*c* 0.46, CH_2Cl_2); IR (film) 3061, 2965, 1699, 1597, 1499, 1399, 755 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{24}N_3O_2]^+$: 386.1863, found 386.1865.

To a solution of phenol **68** (76.0 mg, 0.198 mmol) and $AlCl_3$ (66.9 mg, 0.502 mmol) in DCE (1.30 mL) at 23 °C was added $PhNH_2$ (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 Na_2SO_4 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 Na_2SO_4 and concentrated to afford a mixture of salicylaldehyde (9.3 mg, 38% yield) and imine **70**[6] (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 H_2O (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. $NaHCO_3$ (10 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. ^{1}H NMR showed an approximately 4:1 ratio of aminals **6** and **19**.



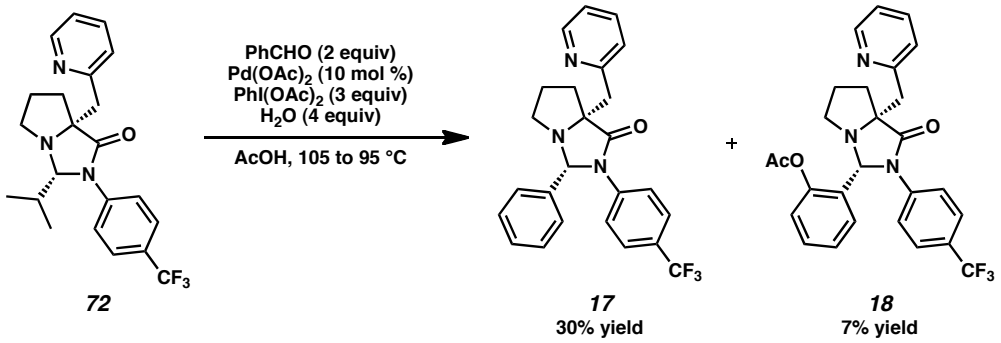
To a solution of amino amide **61** (1.00 g, 3.87 mmol) in $PhCH_3$ (19.4 mL) at 23 ˚C was added isobutyraldehyde (0.530 mL, 5.81 mmol), $TsOH{\cdot}H_2O$ (37.0 mg, 0.194 mmol), and $MgSO_4$ (0.700 g, 5.81 mmol). The mixture was heated to reflux overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (20 mL), and the resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified via flash chromatography (4:1 hexanes/EtOAc eluent) to give aminal **71** (1.12 g, 92% yield, R_f = 0.49 in 1:1 hexanes/EtOAc) as a light yellow oil.

Aminal 71: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ -2.2 (*c* 0.98, CH_2Cl_2); IR (film) 2967, 1704, 1614, 1328, 1122, 1068, 843 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{16}H_{20}N_2OF_3]^+$: 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 H_2O (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 35 mL), dried over Na_2SO_4 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, R_f = 0.21 in 1:1 hexanes/EtOAc) as a light yellow solid.

Pyridine 72: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, Δν = 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, $CDCl_3$) δ 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, CH_2Cl_2); IR (film) 2966, 1704, 1614, 1325, 1124, 845, 748 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{22}H_{25}N_3OF_3Na]^+$: 426.1764, found 426.1766.



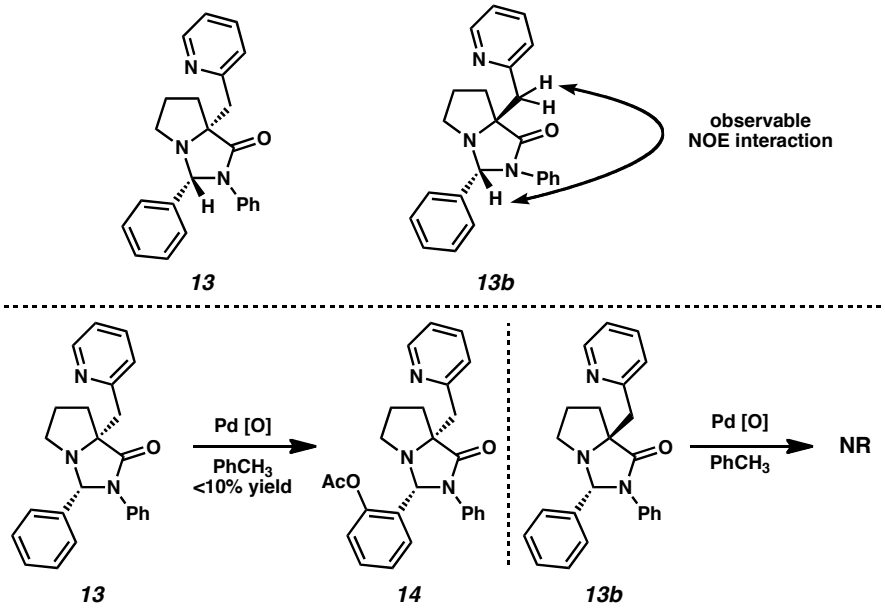
Pyridine **72** (100 mg, 0.248 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0124 mmol), $PhI(OAc)_2$ (80.0 mg, 0.248 mmol), PhCHO (50.0 μL, 0.496 mmol), and H_2O (18.0 μL, 0.992 mmol) were dissolved in AcOH (2.50 mL) in a scintillation vial. The vial was capped and heated to 105 °C for 10 h. The reaction was cooled 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 Na_2CO_3 and water (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 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

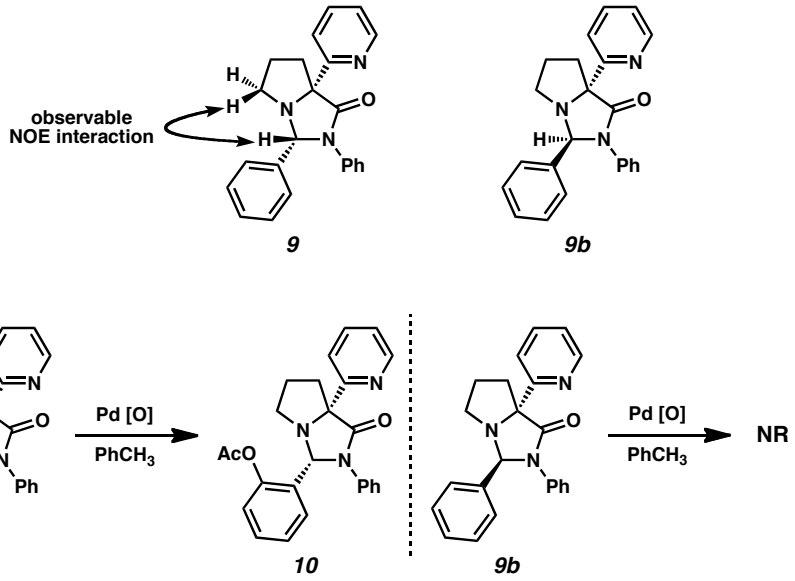
Diastereomeric analysis of aminals

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%).

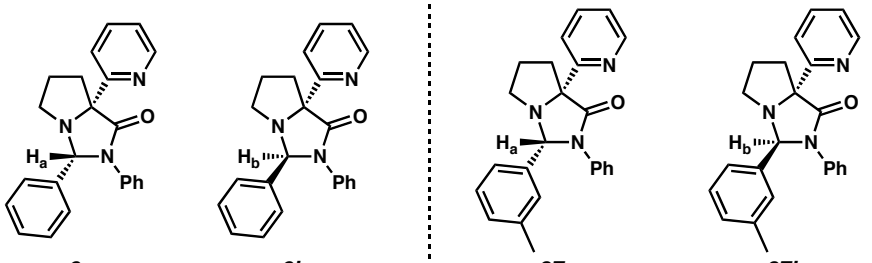


NOE studies on analogous diastereomeric compounds **9** and **9b** revealed a key interaction between the aminal proton and a pyrrolidine proton, indicating that 9 was the syn diastereomer. The same reaction analysis was also performed, and corroborated this assignment. Based on the NOE studies and the decisive role of the pyridyl group on the oxidation, aminal **9** was assigned as syn, and **9b** was assigned anti.



9 *9b* *10* *9b*

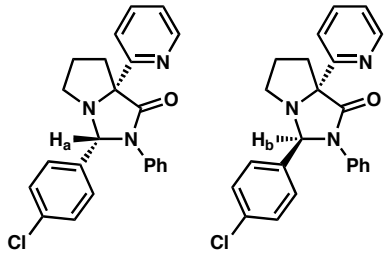
NMR data of the aminal protons in **9** and **9b** allowed for analogous assignments of other diastereomeric mixtures in aromatic aldehyde-based aminals. Some illustrative examples are below.



9 *9b* *37* *37b*

Proton	^{1}H NMR δ
H_a	5.68 ppm
H_b	6.47 ppm

Proton	^{1}H NMR δ
H_a	5.63 ppm
H_b	6.42 ppm

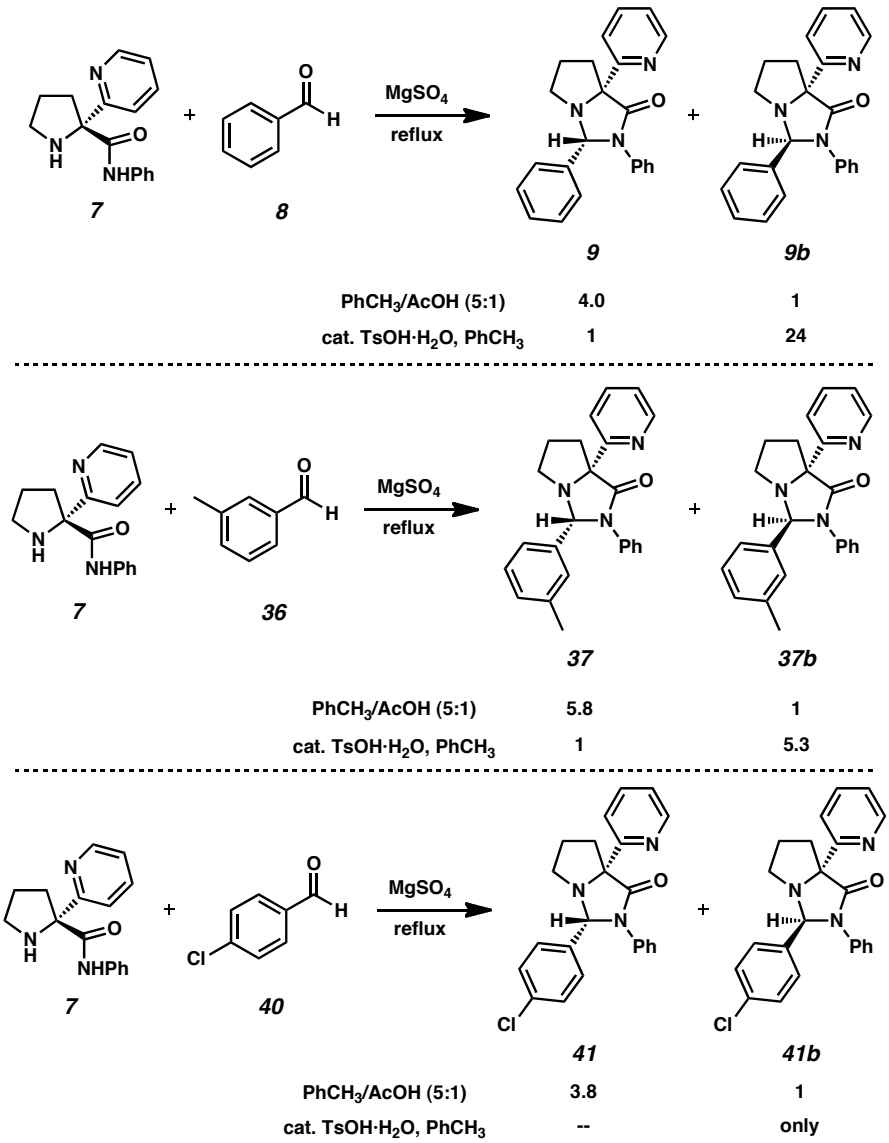


41 *41b*

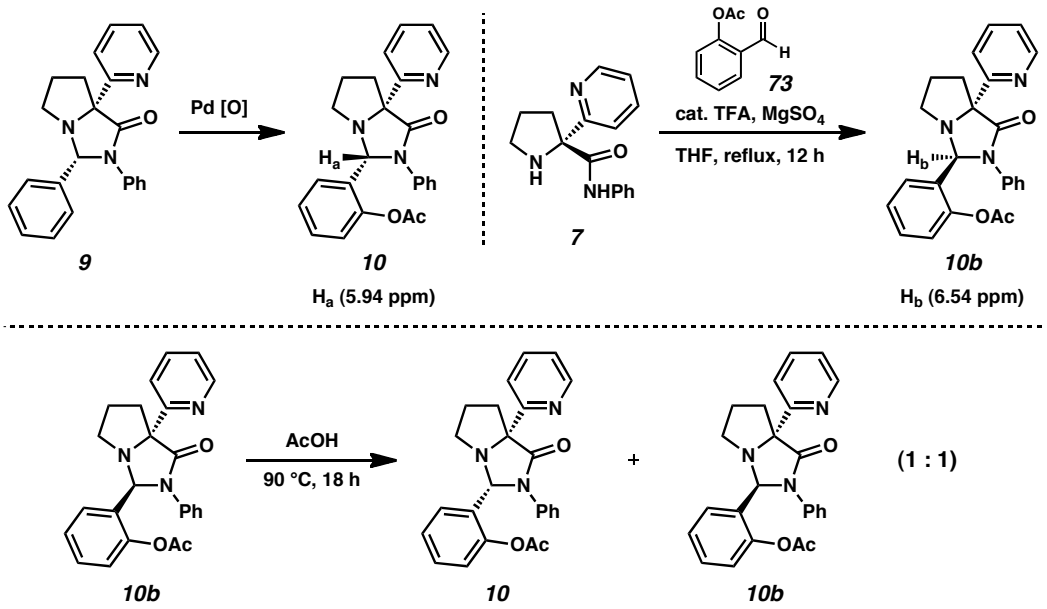
Proton	^{1}H NMR δ
H_a	5.65 ppm
H_b	6.45 ppm

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

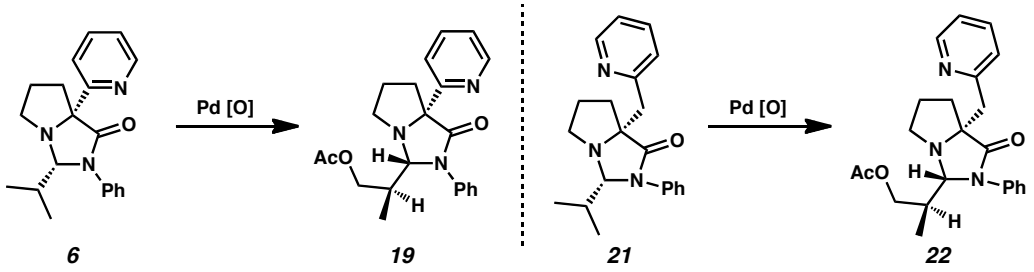
condensation utilizing $TsOH \cdot H_2O$ in $PhCH_3$ gave the anti diastereomer as the major product.



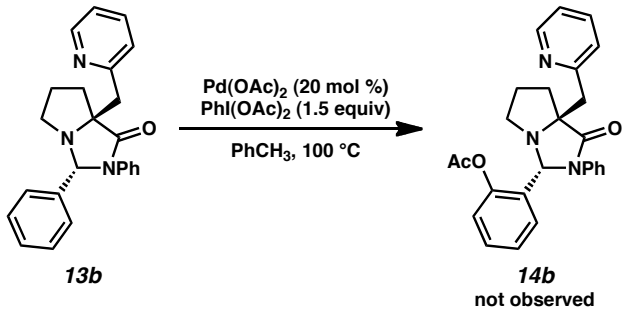
The acetoxylated arene products warrant further discussion. In each case, only one diastereomer is observed. This has been assigned as the syn product based on the following analysis. The aminal proton of **10**, the oxidation product, is at 5.94 ppm, more similar to the chemical shift of the syn diastereomers of the aminal precursors. Furthermore, amino amide **7** was condensed with *O*-acetylsalicylaldehyde (**73**) 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.



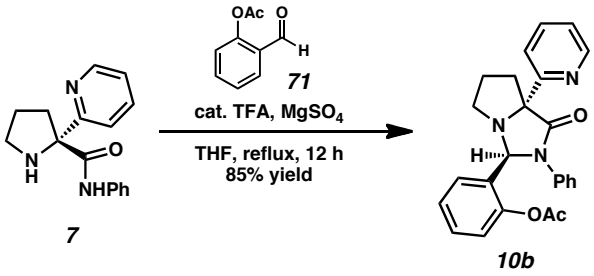
For all aminals based on isobutyraldehyde and subsequently functionalized species, only one diastereomer was observed by NMR. The reactivity of compounds **6** and **21** in the Pd-catalyzed transformations is consistent with the reactivity observed in the aromatic systems. The X-ray crystal structure 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

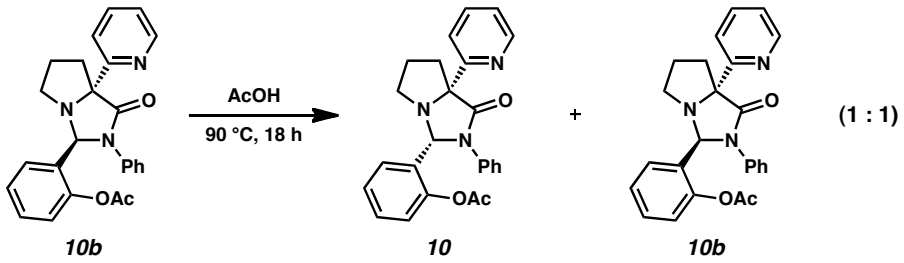


Pyridine **13b** (10.0 mg, 0.0271 mmol), $Pd(OAc)_2$ (1.2 mg, 5.41 μmol), and $PhI(OAc)_2$ (13.1 mg, 0.0406 mmol) were dissolved in $PhCH_3$ (0.300 mL) in a scintillation vial. The vial was sealed and heated to 100 °C for 24 h. Upon cooling, the solvent was removed by rotary evaporation. Starting material, 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_2SO_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.

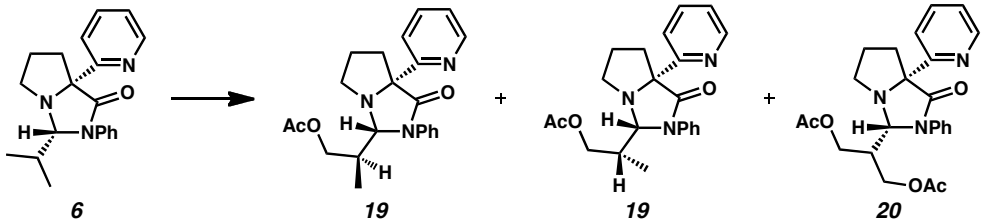
Acetate 10b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 4.1, 0.8 Hz, 1H), 7.69-7.62 (comp m, 2H), 7.33-7.17 (comp m, 6H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.07-7.02 (comp m, 3H), 6.54 (s, 1H), 2.83 (dt, *J* = 13.5, 8.9 Hz, 1H), 2.74 (td, *J* = 9.5, 6.7 Hz, 1H), 2.59-2.55 (m, 1H), 2.42 (ddd, *J* = 12.9, 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 $(M+Na)^+$ $[C_{25}H_{23}N_3O_3Na]^+$: 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 ^{1}H NMR diagnostic signals for diastereomeric analysis

ISOPROPYL SUBSTRATES

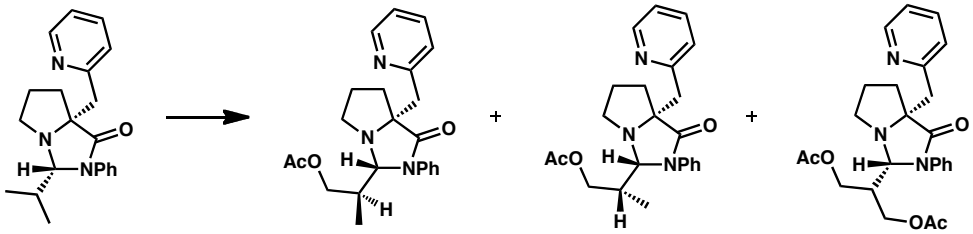


6
4.64 ppm

19
(major)
4.77 ppm

19
(minor)
4.97 ppm

20
5.02 ppm



21
4.47 ppm

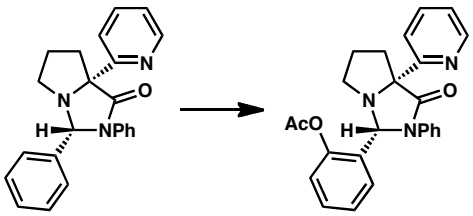
22
(major)
4.54 ppm

22
(minor)
4.78 ppm

23
4.78 ppm

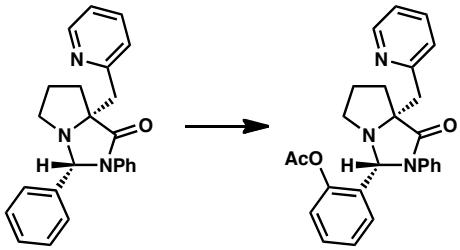
PHENYL SUBSTRATES

SYN DIASTEREOMERS



9
5.68 ppm

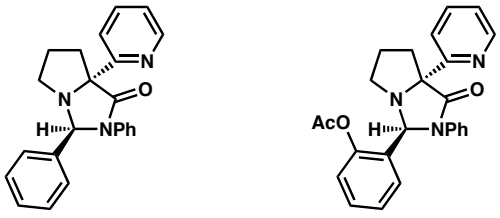
10
5.94 ppm



13
5.44 ppm

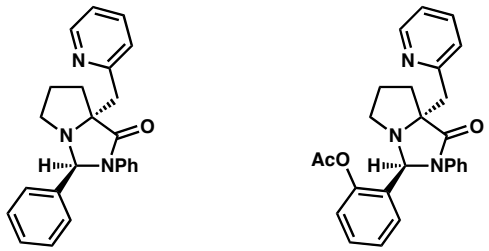
14
5.80 ppm

ANTI DIASTEREOMERS



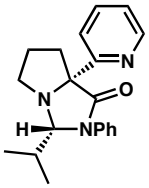
9b
6.47 ppm

10b
(independently synthesized)
6.54 ppm



13b
5.34 ppm
does not functionalize

14b
not synthesized

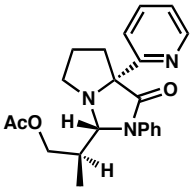


6

Aminal 4.64 ppm, d

Methyls 0.93 ppm, d

0.55 ppm, d

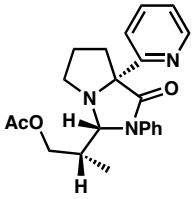


19
(major)

Aminal 4.77 ppm, d

Methyl 0.92 ppm, d

Acetate 1.82 ppm, s

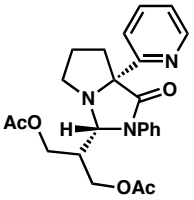


19
(minor)

Aminal 4.97 ppm, d

Methyl 0.51 ppm, d

Acetate 2.06 ppm, s

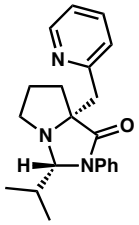


20

Aminal 5.02 ppm, d

Acetates 1.82 ppm, s

2.03 ppm, s

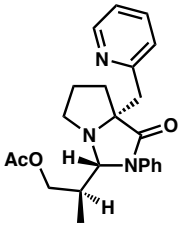


21

Aminal 4.47 ppm, d

Methyls 0.89 ppm, d

0.58 ppm, d

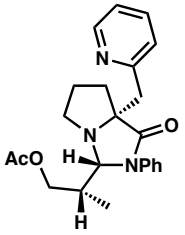


22
(major)

Aminal 4.54 ppm, d

Methyl 0.83 ppm, d

Acetate 1.93 ppm, s

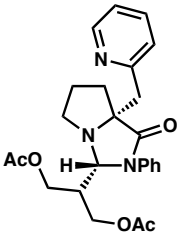


22
(minor)

Aminal 4.78 ppm, d

Methyl 0.60 ppm, d

Acetate 2.06 ppm, s

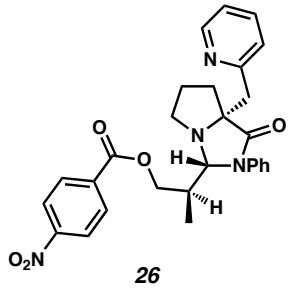


23

Aminal 4.78 ppm, d

Acetates 1.92 ppm, s

2.02 ppm, s



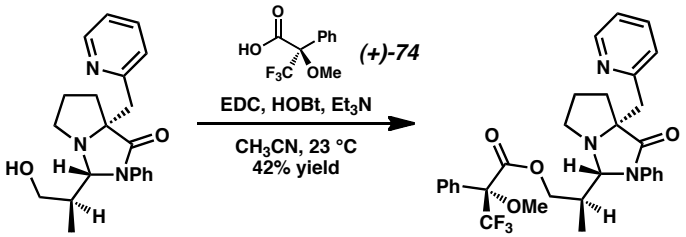
26

Aminal 4.59 ppm, d

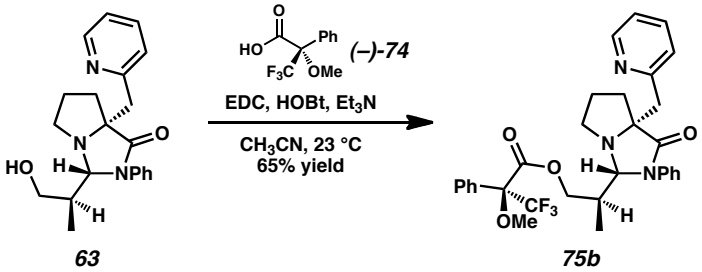
Methyl 0.93 ppm, d

Further analysis of methyl functionalization

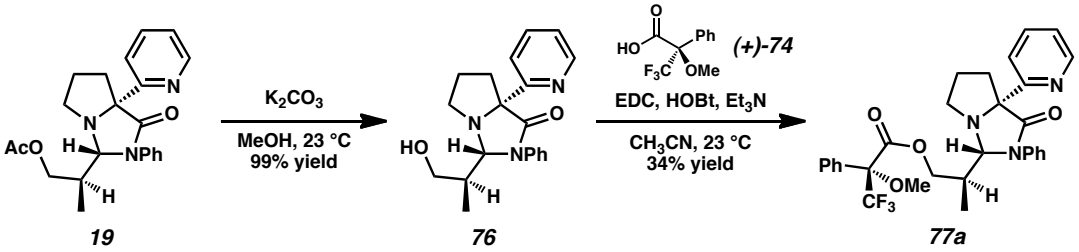
In addition to the X-ray crystal structure that confirmed the stereochemistry of ester **26** (and therefore acetate **22**), a Mosher's ester analysis was conducted. The findings were based on precedented studies done by Seebach and coworkers.[7] The information from this study corroborated with the 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.



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 CH_3CN (1.30 mL) at 23 ˚C was added Et_3N (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 Na_2SO_4 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, R_f = 0.52 in 1:1 hexanes/acetone) as a white solid.[8]
Ester 75a: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; ^{19}F NMR (300 MHz, $CDCl_3$) δ -72.081; $[\alpha]_D^{24}$ +67.6 (*c* 0.50, CH_2Cl_2); IR (film) 2967, 1749, 1704, 1592, 1169, 1024, 720, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{31}H_{33}F_3N_3O_4]^+$: 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 CH_3CN (2.00 mL) at 23 ˚C was added Et_3N (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 Na_2SO_4, 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, R_f = 0.52 in 1:1 hexanes/acetone) as a white solid.
Ester 75b: ^{1}H NMR (400 MHz, $CDCl_3$) 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 (ddd, *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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; ^{19}F NMR (300 MHz, $CDCl_3$) δ -72.079; $[\alpha]_D^{24}$ +37.5 (*c* 0.57, CH_2Cl_2); IR (film) 3063, 2967, 2881, 1749, 1703, 1592, 1170, 735 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{31}H_{33}F_3N_3O_4]^+$: 568.2418, found 568.2421.

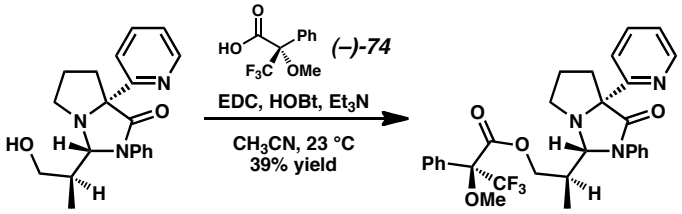


To a solution of acetate **19** (127 mg, 0.335 mmol) in MeOH (3.30 mL) was added K_2CO_3 (92.5 mg, 0.669 mmol) at 23 ˚C, and the resulting mixture was stirred 24 h. The reaction was partitioned between water (10 mL) and EtOAc (10 mL), and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to afford alcohol **76** (113 mg, 99% yield, R_f = 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: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; $[\alpha]_D^{24}$ +23.3 (*c* 0.18, CH_2Cl_2); IR (film) 3333, 2964, 1701, 1591, 1407, 751 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{20}H_{24}N_3O_2]^+$: 338.1863, found 138.1871.

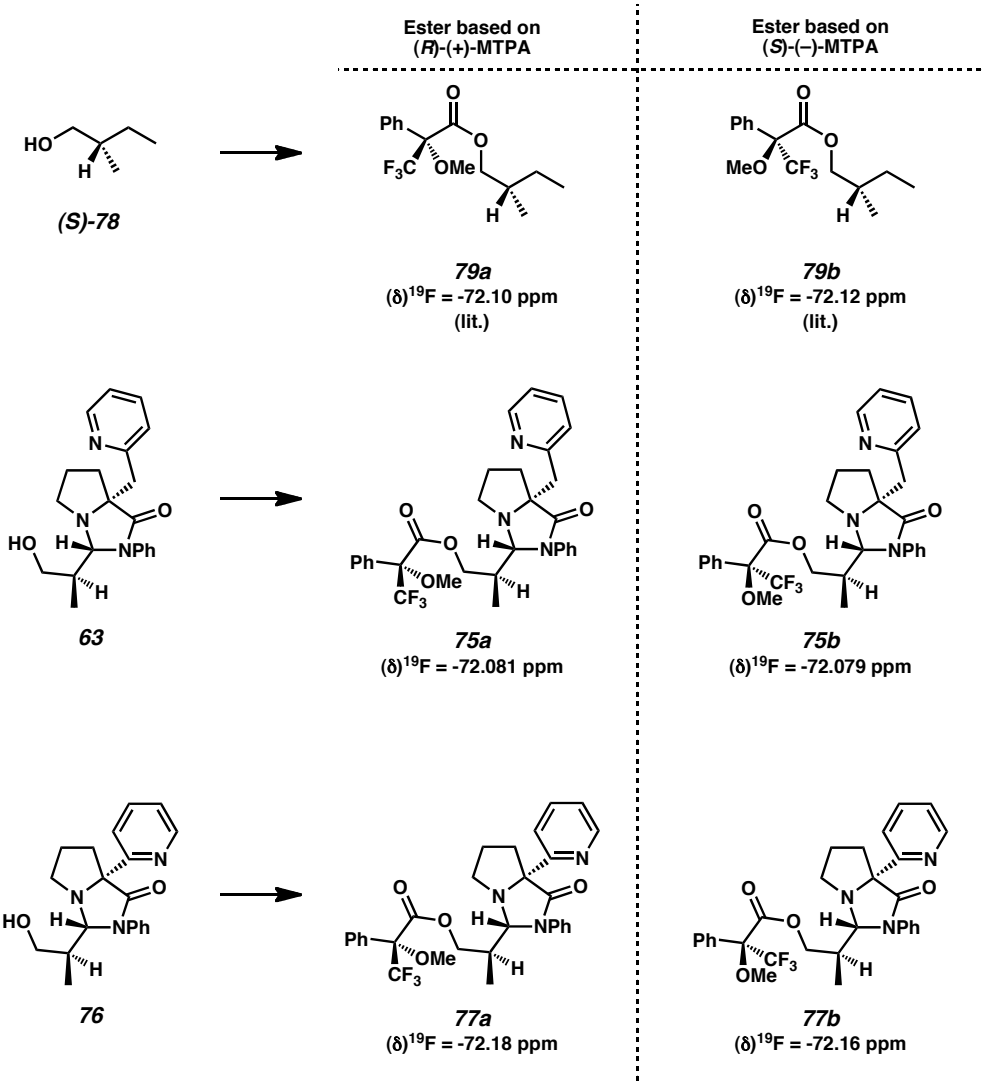
To a solution of alcohol **76** (48.7 mg, 0.144 mmol), (+)-MTPA (33.8 mg, 0.144 mmol), EDC (33.2 mg, 0.173 mmol), HOBt (6.6 mg, 0.0432 mmol) in CH_3CN (1.40 mL) at 23 ˚C was added Et_3N (21.3 μL, 0.152 mmol). The reaction was stirred overnight at 23 ˚C. The solvent was removed, and the residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was dried over Na_2SO_4 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, R_f = 0.52 in 1:1 hexanes/acetone) as a white solid.[8]

Ester 77a: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; ^{19}F NMR (300 MHz, $CDCl_3$) δ -72.18; $[\alpha]_D^{24}$ +42.7 (*c* 0.41, CH_2Cl_2); IR (film) 2968, 1748, 1705, 1588, 1169, 1122, 696 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{30}H_{30}F_3N_3O_4Na]^+$: 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_3CN (1.60 mL) at 23 ˚C was added Et_3N (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_2SO_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.[8]

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), 3.43 (d, *J* = 0.7 Hz, 3H), 2.93 (dt, *J* = 10.5, 6.5 Hz, 1H), 2.58-2.51 (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; $[\alpha]_D^{24}$ +1.2 (*c* 0.40, CH_2Cl_2); IR (film) 2969, 1749, 1708, 1588, 1273, 1169, 1023 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{30}H_{30}F_3N_3O_4Na]^+$: 576.2081, found 576.2080.



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[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.