Catalytic Asymmetric Prins Cyclizations: Cation Generation and Trapping with (BINAP)Pt-dications.

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Supporting Information

General Methods. Methyl glyoxylate was prepared according to literature procedure¹ and freshly distilled from P₂O₅ prior to use. Ethyl glyoxylate was purchased from Lancaster and freshly distilled prior to use by the method of Evans.² Isopropyl glyoxylate and *tert*-butyl glyoxylate were prepared according to a literature procedure¹ and purified/cracked by the following method: 5 g glyoxylate was refluxed in 75 mL benzene in the presence of 2 mg pyridinium tosylate for 1 h. Benzene/water azeotrope and excess benzene were distilled off at a bath temperature of 95 °C. Then the bath temperature was raised to 115° C for 1 h. Distillation at reduced pressure yielded a mixture of glyoxylate and benzene the proportions of which can be measured by ¹H NMR (generally 50-70% glyoxylate). Substituted 2-allyl phenols (**1**, **6**, **8**, **10**, **12**)³ and (cod)PtCl₂⁴ were prepared according to literature procedures. (*R*)-tol-BINAP was purchased from Strem and used as received. Toluene and CH₂Cl₂ were passed through a column of alumina, and freeze-pump-thaw degassed prior to use. All other chemicals were purchased from Aldrich and used as received. All Prins cyclization reactions were performed under N₂ using standard Schlenk techniques. NMR chemical shifts are reported in ppm and referenced to residual solvent peaks (¹H and ¹³C) or to an external standard (85% H₃PO₄, ³¹P) (CFCl₃, ¹⁹F). SFC was performed on a Berger Mini-Gram. GC was performed on an HP 6890. Elemental analysis preformed by Robertson Microlit Laboratories, Inc. (Madison, NJ).

Scheme 1. Net reactions and structures referred to in procedures and characterizations.

5 (R)-[(tol-BINAP)Pt(NCC₆F₅)₂][SbF₆]₂. To a stirring solution of 275.8 mg (0.737 mmol) of (cod)PtCl₂ in 20 mL of CH₂Cl₂ was added dropwise 500.0 mg (0.737 mmol) of (R)-tol-BINAP in 20 mL CH₂Cl₂. After 30 min of stirring the solvent was removed in *vacuo* and the yellow solid precipitated from CH₂Cl₂/hexanes to yield 602 mg (86% yield) of (R)-(tol-BINAP)PtCl₂ as a white powder. (R)-(tol-BINAP)PtCl₂ (560 mg, 0.593 mmol) and 448.3 mg (1.30 mmol) of AgSbF₆ were then taken up in 50 mL CH₂Cl₂ under N₂ in a flask protected from light. Pentafluorobenzonitrile (747 μ L, 5.93 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was opened to the atmosphere and filter through a 0.45 μ m PTFE filter and the solvent removed in *vacuo*. The oily residue was then precipitated from CH₂Cl₂/hexanes to yield 925 mg (90% yield) of white powder. ³¹P NMR (162 MHz, CD₂Cl₂) δ -0.4 (s, $J_{\text{P-Pt}}$ = 3719 Hz). ¹⁹F NMR (376 MHz, CD₂Cl₂) δ -127.2 (2F), -135.6 (1F), -157.0 (2F). ¹H NMR (400 MHz, CD₂Cl₂) δ 7.76 (m, 7H), 7.70 (d, J = 8.4 Hz, 4H), 7.56 (m, 5H), 7.46 (d, J = 7.6 Hz, 5H), 7.25 (t, J = 8.0 Hz, 3H), 6.75 (d, J = 8.8 Hz, 4H), 2.40 (s, 6H), 2.01 (s, 6H). ¹³C{¹H, ³¹P} NMR (76 MHz, CD₂Cl₂) δ 144.6, 143.6, 139.7, 135.3, 134.9, 134.8, 129.9, 130.3, 130.1, 128.5, 127.3, 122.0, 120.6, 114.5, 112.1, 21.4, 21.3. Anal. Calcd. for C₆₂H₄₀F₂₂N₂P₂Sb₂: C, 43.01; H, 2.33, N 1.62. Found: C, 43.05, H, 2.45, N, 1.77.

General Procedure of Prins Cyclizations of 1, 6, 8, 10, 12 with glyoxylates. To a stirring suspension of **5** (69.4 mg, 0.040 mmol) in 2 mL toluene was added 1.2 mmol **2**. After 30 min of stirring the now homogeneous solution is transferred via syringe into another flask under N₂ containing 0.40 mmol substrate (**1**, **6**, **8**, **10**, or **12**) and 40 μ L of a 0.05M solution of 2,6-ditertbutyl-4-methyl pyridine (0.002 mmol) in CH₂Cl₂. In the case of **12** the 2,6-ditertbutyl-4-methyl pyridine is replaced with 4 μ L of a 0.05 M solution of HOTf (0.0002 mmol) in CH₂Cl₂. This solution is stirred overnight. The solvent is removed in *vacuo* and the residue purified by flash chromatography on silica gel.

Repeated chromatography is sometimes necessary to separate diastereomers. Unless otherwise noted, yields are reported for mixtures of diastereomers and NMR data is for diastereo-pure materials.

3b. 90 mg, 85% yield. Anal. Calcd. for C₁₅H₂₀O₄: C, 68.16; H, 7.36. Found: C, 68.16; H, 7.73. **3₁b.** Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 8.1 min (major); t_R 7.5 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO₂/MeOH 97/3, 1.5 mL/min] as 78% *ee*. $[\alpha]^{25}_D = -20.91$ (*c* 0.35, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.07 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 6.8 Hz, 1H), 6.81 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 4.49 (dd, J = 4.8, 1.6 Hz, 1H), 4.25 (m, 2H), 2.26 (m, 2H), 2.92 (m, 2H), 2.28 (m, 2H), 1.54 (s, 3H), 1.29 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.9, 153.3, 129.4, 127.3, 121.2, 119.9, 117.2, 69.7, 62.4, 44.0, 27.6, 21.8, 22.6, 14.6. **3₂b.** Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 12.1 min (major); t_R 11.3 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO₂/MeOH 97/3, 1.5 mL/min] as 44% *ee*. $[\alpha]^{25}_D = +16.62$ (*c* 0.60, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.05 (m, 2H), 6.81 (dt J = 7.2, 1.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.20 (m, 3H), 2.94 (dd, J = 16.4, 11.2 Hz, 1H), 2.84 (d, J = 6.0 Hz, 1H), 2.70 (dd, J = 16.4, 5.2 Hz, 1H), 2.35 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.30 (t, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 174.7, 153.2, 129.2, 127.4, 120.9, 120.0, 117.0, 72.3, 62.0, 44.7, 27.8, 26.6, 22.2, 14.0.

3d. 89 mg, 76% yield. Anal. Calcd. for C₁₇H₂₄O₄: C, 69.84; H, 8.27. Found: C, 70.08; H, 7.98. **3₁d.** Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 7.6 min (major); t_R 6.7 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO₂/MeOH 98.5:1.5, 1.5 mL/min] as 96% *ee*. $[\alpha]^{25}_D = -30.7$ (*c* 0.50, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.07 (t, J = 8.7 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.81

(t, $J = 8.4$ Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 4.35 (dd, $J = 4.8, 2.0$ Hz, 1H), 2.91 (m, 2H), 2.25 (m, 2H), 1.54 (s, 3H), 1.47 (s, 9H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 153.3, 129.5, 127.2, 121.4, 119.9, 117.2, 83.3, 70.0, 44.1, 28.0, 27.7, 21.5. **3₂d**. Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 13.5 min (major); t_R 12.6 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5:1.5, 1.5 mL/min] as 94% *ee*. $[\alpha]^{25} = +14.84$ (c 0.38, MeOH). ^1H NMR (400 MHz, CDCl_3) δ 7.07 (t, $J = 7.2$ Hz, 1H), 7.03 (d, $J = 8.0$ Hz, 1H), 6.82 (t, $J = 8.4$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 4.01 (t, $J = 4.0$ Hz, 1H), 2.96 (dd, $J = 16.8, 12.0$ Hz, 1H), 2.88 (d, $J = 5.2$ Hz, 1H), 2.70 (dd, $J = 16.8, 5.6$ Hz, 1H), 2.32 (ddd, $J = 11.6, 5.2, 3.6$ Hz, 1H), 1.47 (s, 9H), 1.42 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 173.9, 153.3, 129.2, 127.4, 121.2, 120.0, 117.0, 83.4, 72.8, 44.6, 28.0, 27.9, 27.1, 22.3.

7b. 71 mg, 60% yield. Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_5$: C, 65.28; H, 7.45. Found: C, 65.45; H, 7.63. **7₁b**. Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 9.7 min (major); t_R 10.4 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 97/3, 1.5 mL/min] as 76% *ee*. $[\alpha]^{25} = -32.5$ (c 0.50, MeOH). ^1H NMR (400 MHz, CDCl_3) δ 6.67 (m, 2H), 6.57 (d, $J = 2.8$ Hz, 1H), 4.47 (dd, $J = 4.8, 1.6$ Hz, 1H), 4.26 (m, 1H), 3.72 (s, 3H), 2.89 (m, 2H), 2.26 (m, 2H), 1.52 (s, 3H), 1.29 (s, 3H), 1.28 (t, $J = 6.4$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.9, 153.1, 147.2, 121.8, 117.7, 113.9, 113.5, 76.6, 69.7, 62.4, 55.7, 44.0, 27.6, 22.2, 21.5, 14.2. **7₂b**. Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 14.5 min (major); t_R 18.6 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 97/3, 1.5 mL/min] as 44% *ee*. $[\alpha]^{25} = +18.6$ (c 0.45, MeOH). ^1H NMR (400 MHz, CDCl_3) δ 6.67 (m, 2H), 6.57 (s, 1H), 4.20 (m, 3H), 3.72 (s, 3H), 2.92 (dd, $J = 16.8, 11.6$ Hz, 1H), 2.83 (d, $J = 5.6$ Hz, 1H), 2.35 (m, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.28 (t, $J = 4.6$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.7, 153.1, 147.1, 121.5, 117.6, 113.6, 113.5, 76.4, 72.3, 62.0, 55.7, 44.6, 27.7, 27.0, 22.2, 14.0.

9d 94 mg, 72% yield. Anal. Calcd. for $\text{C}_{17}\text{H}_{23}\text{ClO}_4$: C, 62.48; H, 7.09. Found: C, 62.76; H, 7.10. **9₁d**. Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 8.4 min (major); t_R 7.9 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5/1.5, 1.5 mL/min] as 92% *ee*. $[\alpha]^{25} = -44.7$ (c 0.60, MeOH). ^1H NMR (400 MHz, CDCl_3) δ 7.01 (m, 2H), 6.69 (d, $J = 8.0$ Hz, 1H), 4.33 (dd, $J = 4.4, 1.6$ Hz), 2.95 (d, $J = 4.8$ Hz, 1H), 2.87 (dd, $J = 18.0, 14.0$ Hz, 1H), 2.21 (m, 1H), 1.52 (s, 3H), 1.48 (s, 9H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 151.9, 129.0, 127.3, 124.6, 123.0, 118.5, 83.5, 69.5, 43.8, 28.0, 27.9, 27.5, 21.5. **9₂d**. Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 13.3 min (major); t_R 14.0 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5:1.5, 1.5 mL/min] as 88% *ee*. $[\alpha]^{25} = +19.1$ (c 0.20, MeOH). ^1H NMR (400 MHz, CDCl_3) δ 7.02 (m, 2H), 6.80 (d, $J = 6.8$ Hz, 1H), 4.06 (d, $J = 3.6$ Hz), 2.92 (m, 2H), 2.67 (dd, $J = 16.8, 5.6$ Hz), 2.29 (m, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 151.9, 128.7, 127.4, 124.6, 122.8, 118.4, 83.9, 72.6, 44.2, 28.3, 27.9, 27.0, 22.3.

11. 46.8 mg, 42% yield as an inseparable mixture of diastereomers. Enantiomeric excesses determined by GC: t_R 58.6 min (diastereomer 1, major); t_R 59.9 min (diastereomer 1, minor); t_R 62.2 min (diastereomer 2, major); t_R 64.7 min (diastereomer 2, minor) [SupelCo, β -dex 120(30M x 0.25mm), H_2 , 145°C, 20 psi] as 53% and 88% *ee*, respectively. ^1H NMR (400 MHz, CDCl_3) δ 7.10 (m, 2H), 6.81 (m, 1H), 6.72 (t, $J = 8.0$ Hz, 1H), 4.26 (m, 1H), 3.38 (d, $J = 15.6, 0.5$ Hz), 3.31 (d, $J = 16.0$ Hz, 0.5H), 3.10 (d, $J = 6.0$ Hz, 0.5H), 3.08 (d, $J = 4.4$ Hz, 0.5H), 2.97 (d, $J = 16.0$ Hz, 0.5H), 2.95 (d, $J = 16.0$ Hz, 0.5H), 2.33 (m, 1H), 1.99 (m, 1H), 1.50 (s, 1.5H), 1.49 (s, 1.5H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 174.0, 158.4, 158.3, 128.0, 127.9, 127.1, 125.1, 120.2, 120.2, 116.8, 87.9, 87.8, 68.4, 44.5, 44.4, 42.4, 41.4, 28.1, 28.0, 27.0, 26.2. Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_4$: C, 69.04; H, 7.97. Found: C, 68.76; H, 7.88.

13. 20 mg, 81% yield. Anal. Calcd. for C₂₂H₂₆O₅: C, 71.33 H, 7.07. Found: C, 70.97, H, 7.42. **13₁.** Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 31 min (minor); t_R 39 min (major) [Chiracel AD-H (0.46 cm x 25 cm) CO₂/MeOH 97/3, 1 mL/min] as 97% *ee*. [α]_D²⁵ = -11.9 (*c* 1.1, MeOH). ¹H NMR (400MHz, CDCl₃) δ 7.43 (d, *J* = 8.4 Hz, 2H), δ 7.11 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.88 (m, 2H), 4.90 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 3.75 (dd, *J* = 4.4, 2.4 Hz, 1H), 3.10 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.87 (d, *J* = 4.4 Hz, 1H), 2.42 (m, 2H), 1.45 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 173.6, 159.7, 154.9, 131.0, 129.7, 128.7, 127.3, 121.5, 120.5, 116.8, 114.1, 83.2, 79.4, 69.4, 55.4, 41.6, 28.0. **13₂** Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 48 min (major); t_R 62 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO₂/MeOH 98.5/1.5, 1.5 mL/min] as 92% *ee*. [α]_D²⁵ = +10.7 (*c* 0.9, MeOH). ¹H NMR (400MHz, CDCl₃) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.09 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.82 (m, 2H), 5.08 (d, *J* = 9.2 Hz, 1H), 3.90 (dd, *J* = 6.8 Hz, 3.6 Hz, 1H), 3.00 (d, *J* = 4.0 Hz, 1H), 2.96 (dd, *J* = 16.0, 4.8 Hz, 1H), 2.77 (dd, *J* = 16.0, 4.8 Hz, 1H), 2.61 (m, 1H), 1.45 (s, 9H). ¹³C NMR (100MHz, CDCl₃) δ 172.8, 159.7, 154.7, 131.3, 129.4, 128.8, 127.5, 121.2, 120.4, 116.6, 113.8, 83.6, 78.6, 1.3, 55.3, 42.6, 28.1.

15. 114mg, 84% yield. Enantiomeric excess determined by SFC (220 nm, 35° C): t_R 32.6 min (major); t_R 27.9 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO₂/MeOH 96/4, 1 mL/min] as 68% *ee*. [α]_D²⁵ = -32.7 (*c* 0.65, MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.42 (m, 2H), 7.36 (m, 3H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 2H), 5.11 (d, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 3.2 Hz, 1H), 3.96 (m, 1H), 3.79 (m, 1H), 3.03 (dd, *J* = 16.4, 11.2 Hz, 1H), 2.92 (m, 2H), 2.75 (m, 1H), 1.24 (t, 5.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 154.7, 139.0, 129.4, 128.6, 128.3, 127.9, 127.5, 121.4, 120.5, 116.6, 78.7, 71.4, 61.9, 42.0, 28.4, 13.9. Anal. Calcd. for C₁₉H₂₀O₄: C, 73.06; H, 6.45 Found: C, 72.92; H, 6.27.

Determination of Stereochemistry for **3a-d**, **7b**, **9d**::

To assign the relative stereochemistry of products **3a-d**, **7b**, and **9d**, we carefully analyzed the stereoisomers of **3a** and then assigned the remainder by analogy. To begin, the structures of the lowest energy conformers/rotomers were computed using Monte-Carlo methods (AM1, MacSpartan 04). These structure(s) were then used to predict nOes. (Figure S1). They were then compared with experimental nOes for each isolated diastereomer of **3b** and **3d**, and assigned on the basis of the key differentiating nOes shown in Figure S1. The relative stereochemistry of the **3a,c-d**, **7b**, and **9d** were assigned by analogy. Supporting a “by analogy” assignment, were relative chromatographic retention times of the diastereomers (SFC, GC, and tlc), characteristic upfield shift of the faster eluting isomer’s carbinol hydrogen resonance (¹H NMR), and the sign of the optical rotation (Table S1). The faster eluting diastereomer was arbitrarily given the subscript ₁ while the slower was given the subscript ₂. These data, in combination with Mosher’s ester analysis⁵ to determine the absolute stereochemistry of the carbinol center, allowed the assignment of diastereomer #₁ as having the *S* configuration at the ring junction (C3) and the *S* configuration at the carbinol center (C2); diastereomer #₂ was assigned the (3*R*,2*S*) stereochemistry.

Figure S1 Key nOes predicted and observed for **3a-d**, **7b**, and **9**. Diastereomer #₁ (left) and diastereomer #₂ (right).

Table S1.

	δ carbinol # ₁	Rotation # ₁	δ carbinol # ₂	Rotation # ₂
3a	4.51	-	4.23	+
3b	4.35	-	4.22	+
3c	4.43	-	4.15	+
3d	4.35	-	4.07	+
7b	4.48	-	4.20	+
9d	4.33	-	4.05	+

Determination of stereochemistry for **13** and **15**.

To assign the relative stereochemistry of products **13** and **15**, we carefully analyzed the stereoisomers of **15**. The relative stereochemistry between the ring stereocenters 3 and 4 was determined to be *trans* by the H-H coupling observed in the ¹H NMR (see characterization data) for all products of this type. The structures of the lowest energy conformers/rotomers were computed using Monte-Carlo methods (AM1, MacSpartan 04). These structure(s) were then used to predict nOes. (Figure S2). They were then compared with experimental nOes for each isolated diastereomer of **13** and **15**, and assigned on the basis of the key differentiating nOes shown in Figure S2. These data, in combination with Mosher's ester analysis⁵ to determine the absolute stereochemistry of the carbinol center, allowed the assignment of **13**₁ as (4*R*,3*S*,2*S*), **13**₂ as (4*S*,3*R*,2*S*) and **15** as (4*R*,3*S*,2*R*).

Figure S2: Key nOes predicted and observed for **13** and **15**. Diastereomer #₁ (left) and diastereomer #₂ (right).

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