

Synthesis of Azepines by a Gold-Catalyzed Intermolecular [4+3]-Annulation

Nathan D. Shapiro and F. Dean Toste*

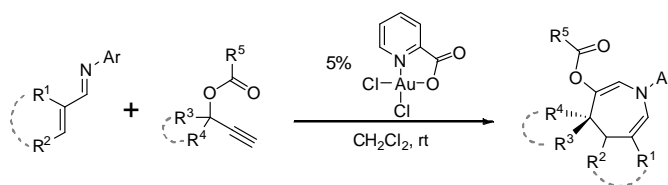
Department of Chemistry, University of California, Berkeley, California 94720

Supporting Information

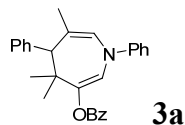
Table of Contents:

I.	General Information	S2
II.	Gold(III)-catalyzed [4+3] reaction	
	a. General Procedure	S2
	b. Characterization data	S2 - S8
III.	Synthesis of PicAuCl₂ (4)	S9
IV.	Mechanistic Experiments	
	a. Chirality transfer	S9
	b. Gold(III)-catalyzed oxidation of propargyl esters	S10 - S11
	c. Hammett Plots	S12
V.	NMR spectra	S13 - S73

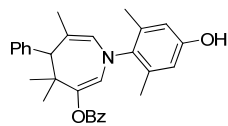
General Information. Unless otherwise noted, reagents were obtained commercially and used without further purification. Small scale reactions (< 3mL) were carried out in Fisher Scientific disposable scintillation vials. HPLC grade dichloromethane (CH₂Cl₂), ACS grade hexanes, and ACS grade ethyl acetate (EtOAc) were obtained from Fischer Scientific. TLC analysis of reaction mixtures was performed on Merck silica gel 60 F254 TLC plates using UV light and ceric ammonium molybdate stain to visualize the reaction components. Flash chromatography was carried out on ICN SiliTech 32-63 D 60 Å silica gel. ¹H and ¹³C NMR spectra were recorded with Bruker AV-300, AVB-400, AVQ-400, DRX-500, and AV-500 spectrometers and referenced to CDCl₃ unless otherwise noted. Mass spectral and analytical data were obtained via the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley. X-ray structure acquisition and analysis were performed by Dr. Frederick J. Hollander of the University of California, Berkeley College of Chemistry X-ray crystallographic facility.



General procedure for the gold(III)-catalyzed [4+3] reaction. To a one dram vial equipped with a magnetic stir bar, was sequentially added N-aryl imine (~0.3 mmol, 1 equiv), propargyl ester (1.3 equiv), CH₂Cl₂ (0.3 M) and PicAuCl₂ (0.05 equiv). The resulting mixture was stirred at room temperature and monitored periodically by TLC. Upon consumption of the imine (2 – 6 hrs), the reaction mixture was directly subjected to silica gel chromatography (hexanes/ethyl acetate/dichloromethane) to give the desired azepine products.

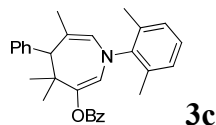


¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, 2H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 7.4 Hz), 7.41-7.24 (m, 11H), 7.09 (t, 1H, *J* = 7.2 Hz), 6.47 (s, 2H), 3.24 (s, 1H), 1.80 (s, 3H), 1.47 (s, 3H), 0.94 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 147.6, 143.8, 138.5, 133.3, 130.1, 130.0, 129.9, 129.4, 128.6, 127.9, 126.6, 124.1, 123.6, 120.9, 115.8, 62.5, 42.8, 30.1, 26.3, 25.7. HRMS (FAB) calc. for [C₂₈H₂₇NO₂]⁺ 409.2042, found 409.2041.

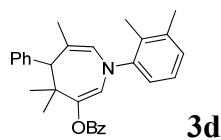


¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, 2H, *J* = 8.0 Hz), 7.53-7.48 (m, 3H), 7.39-7.32 (m, 4H), 7.26 (t, 1H, *J* = 7.3 Hz), 6.56 (s, 1H), 6.53 (s, 1H), 5.99 (s, 1H), 5.72 (s, 1H), 5.71 (bs, 1H), 3.25 (s, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 1.73 (s, 3H), 1.56 (s, 3H), 0.92 (s, 3H). ¹³C NMR (125 MHz,

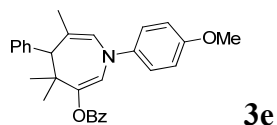
CDCl₃) δ 167.3, 154.7, 145.3, 140.1, 139.0, 137.3, 133.7, 133.3, 130.1, 130.0, 130.0, 128.6, 127.8, 126.3, 126.0, 125.4, 115.1, 115.1, 112.2, 63.5, 43.0, 31.3, 26.9, 25.5, 18.7, 18.7. HRMS (FAB) calc. for [C₃₀H₃₁NO₃]⁺ 453.2304, found 453.2306.



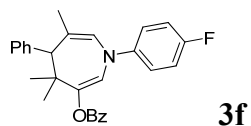
¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, 2H, *J* = 7.2 Hz), 7.51-7.48 (m, 3H), 7.38-7.31 (m, 4H), 7.28-7.25 (m, 1H), 7.10 (s, 3H), 5.98 (s, 1H), 5.74 (s, 1H), 3.25 (s, 1H), 2.47 (s, 3H), 2.40 (s, 3H), 1.74 (s, 3H), 1.56 (s, 3H), 0.91 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 166.9, 162.6, 146.8, 145.4, 137.7, 136.0, 130.3, 130.2, 130.1, 129.0, 129.0, 128.6, 127.9, 127.7, 126.5, 125.5, 124.9, 112.5, 63.6, 43.2, 31.4, 27.0, 25.6, 18.8. HRMS (FAB) calc. for [C₃₀H₃₁NO₂]⁺ 437.2355, found 437.2362.



¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, 2H, *J* = 8.0 Hz), 7.49 (t, 1H, *J* = 7.6 Hz), 7.47 (d, 2H, *J* = 8.0 Hz), 7.38-7.32 (m, 4H), 7.26 (t, 1H, *J* = 7.2 Hz), 7.19 (d, 1H, *J* = 7.6 Hz), 7.11 (t, 1H, *J* = 7.2 Hz), 7.06 (d, 1H, *J* = 7.2 Hz), 6.13 (s, 1H), 5.96 (s, 1H), 3.25 (s, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 1.76 (s, 3H), 1.56 (s, 3H), 0.94 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 148.1, 144.9, 138.7, 134.2, 133.6, 133.1, 130.2, 130.0, 130.0, 128.5, 128.3, 127.9, 126.5, 126.4, 126.3, 125.6, 125.3, 112.5, 63.2, 43.0, 30.9, 26.7, 25.5, 20.8, 14.8. HRMS (FAB) calc. for [C₃₀H₃₁NO₂]⁺ 437.2355, found 437.2346.

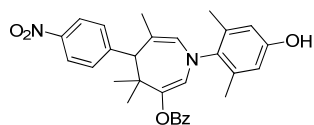


¹H NMR (500 MHz, CDCl₃) δ 7.92 (d, 2H, *J* = 7.5 Hz), 7.52 (t, 1H, *J* = 7.5 Hz), 7.41-7.36 (m, 4H), 7.32 (t, 2H, *J* = 7.5 Hz), 7.26 (t, 1H, *J* = 7.5 Hz), 7.21 (d, 2H, *J* = 9.0 Hz), 6.88 (d, 2H, *J* = 9.0 Hz), 6.38 (s, 1H), 6.34 (s, 1H), 3.81 (s, 3H), 3.24 (s, 1H), 1.80 (s, 3H), 1.48 (s, 3H), 0.94 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 166.6, 156.4, 144.2, 141.8, 136.8, 133.2, 130.1, 129.9, 128.5, 127.9, 126.5, 125.0, 124.1, 123.2, 114.6, 114.5, 62.7, 55.8, 42.9, 30.5, 26.4, 25.7. HRMS (FAB) calc. for [C₂₉H₂₉NO₃]⁺ 439.2147, found 439.2144.



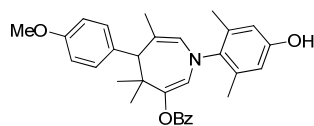
¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, 2H, *J* = 7.5 Hz), 7.53 (t, 1H, *J* = 7.0 Hz), 7.40-7.35 (m, 4H), 7.31 (t, 2H, *J* = 7.5 Hz), 7.27-7.20 (m, 3H), 7.03 (t, 2H, *J* = 8.5 Hz), 6.38 (s, 1H), 6.36 (s,

1H), 3.23 (s, 1H), 1.79 (s, 3H), 1.46 (s, 3H), 0.94 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 166.5, 159.5 (d, *J* = 241 Hz), 144.1 (d, *J* = 4 Hz), 143.8, 138.1, 133.3, 130.1, 129.9, 129.9, 128.6, 127.9, 126.6, 124.4, 123.7, 122.9 (d, *J* = 8 Hz), 116.0 (d, *J* = 23 Hz), 115.6, 62.5, 42.9, 30.2, 26.3, 25.7. HRMS (FAB) calc. for [C₂₈H₂₆NO₂F]⁺ 427.1948, found 427.1954.



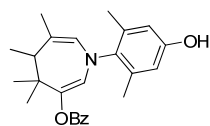
6a

¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, 2H, *J* = 8.8 Hz), 7.92 (d, 2H, *J* = 7.6 Hz), 7.67 (d, 2H, *J* = 8.8 Hz), 7.53 (t, 1H, *J* = 7.6 Hz), 7.38 (t, 2H, *J* = 7.6 Hz), 6.57 (s, 1H), 6.55 (s, 1H), 6.02 (s, 1H), 5.77 (s, 1H), 5.77 (bs, 1H), 3.40 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.72 (s, 3H), 1.58 (s, 3H), 0.92 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 154.9, 153.1, 146.7, 139.8, 138.7, 137.0, 133.5, 133.0, 130.6, 130.0, 129.7, 128.7, 127.0, 125.8, 123.1, 115.3, 115.2, 110.8, 63.3, 43.1, 31.4, 26.7, 25.3, 18.7, 18.6. HRMS (FAB) calc. for [C₃₀H₃₀N₂O₅]⁺ 498.2155, found 498.2156



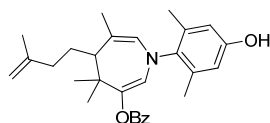
6b

¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, 2H, *J* = 7.5 Hz), 7.52 (t, 1H, *J* = 7.5 Hz), 7.41 (d, 2H, *J* = 8.5 Hz), 7.38 (t, 2H, *J* = 8.0 Hz), 6.89 (d, 2H, *J* = 8.5 Hz), 6.55 (s, 1H), 6.53 (s, 1H), 5.97 (s, 1H), 5.69 (s, 1H), 5.68 (bs, 1H), 3.84 (s, 3H), 3.19 (s, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 1.73 (s, 3H), 1.54 (s, 3H), 0.91 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 167.3, 158.2, 154.7, 139.0, 140.1, 139.0, 137.6, 137.3, 133.7, 133.3, 130.8, 130.1, 128.6, 125.8, 125.4, 115.1, 115.1, 113.2, 112.6, 62.6, 55.4, 43.1, 31.2, 26.9, 25.5, 18.7, 18.7. HRMS (FAB) calc. for [C₃₁H₃₃NO₄]⁺ 483.2410, found 483.2421.



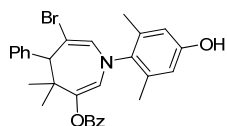
8

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, 2H, *J* = 8.0 Hz), 7.57 (t, 1H, *J* = 7.4 Hz), 7.45 (t, 2H, *J* = 8.0 Hz), 6.50 (s, 2H), 6.15 (bs, 1H), 5.77 (s, 1H), 5.52 (s, 1H), 2.23 (s, 3H), 2.16 (s, 3H), 2.13 (q, 1H, *J* = 7.0 Hz), 1.81 (s, 3H), 1.38 (s, 3H), 1.28 (d, 3H, *J* = 7.0 Hz), 1.15 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.9, 154.7, 140.0, 138.3, 138.1, 133.3, 132.1, 130.3, 130.1, 128.6, 125.6, 125.1, 117.6, 115.0, 114.8, 50.2, 43.2, 31.5, 26.7, 25.1, 18.3, 18.2, 17.3. HRMS (FAB) calc. for [C₂₅H₂₉NO₃]⁺ 391.2147, found 391.2153.



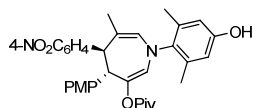
10

^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, 2H, $J = 7.4$ Hz), 7.56 (t, 1H, $J = 7.4$ Hz), 7.42 (t, 2H, $J = 7.4$ Hz), 6.50 (d, 1H, $J = 3.0$ Hz), 6.48 (d, 1H, $J = 3.0$ Hz), 5.72 (s, 1H), 5.62 (s, 1H), 5.51 (bs, 1H), 4.75 (s, 1H), 4.74 (s, 1H), 2.32-2.26 (m, 1H), 2.26 (s, 3H), 2.16 (s, 3H), 2.12-2.02 (m, 2H), 1.99 (app t, 2H, $J = 7.8$ Hz), 1.83 (s, 3H), 1.77 (s, 3H), 1.36 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.7, 154.5, 146.8, 140.2, 138.3, 138.1, 133.3, 132.1, 130.4, 130.1, 128.6, 126.4, 124.9, 117.0, 115.1, 114.7, 109.9, 55.8, 43.4, 36.4, 31.9, 29.9, 27.0, 26.9, 23.0, 18.4, 18.2. HRMS (FAB) calc. for $[\text{C}_{29}\text{H}_{35}\text{NO}_3]^+$ 445.2617, found 445.2619.



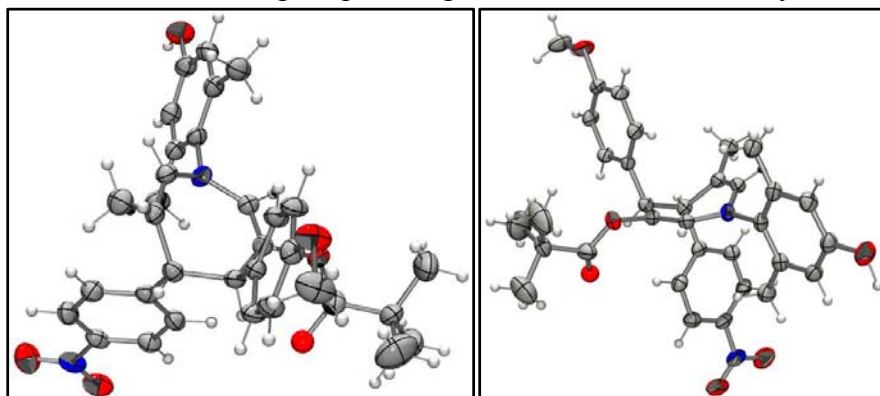
12

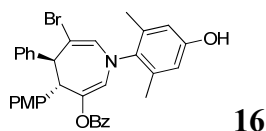
^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, 2H, $J = 7.6$ Hz), 7.53 (t, 1H, $J = 7.4$ Hz), 7.47 (d, 2H, $J = 7.0$ Hz), 7.41-7.35 (m, 4H), 7.32 (t, 1H, $J = 7.0$ Hz), 6.56 (s, 1H), 6.53 (s, 1H), 6.40 (s, 1H), 6.01 (s, 1H), 5.60 (bs, 1H), 3.84 (s, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 1.68 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 155.1, 143.2, 139.0, 138.8, 137.1, 135.5, 133.6, 131.4, 130.1, 129.8, 129.5, 128.7, 128.2, 127.1, 125.2, 115.3, 100.1, 67.6, 44.2, 30.7, 26.6, 18.7, 18.6. HRMS (FAB) calc. for $[\text{C}_{29}\text{H}_{28}\text{NO}_3\text{BrNa}]^+$ 540.1150, found 540.1147.



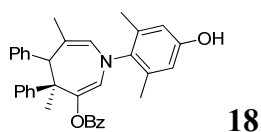
14

A single isomer was detected by ^1H NMR. ^1H NMR (500 MHz, CDCl_3) δ 8.20 (d, 2H, $J = 8.3$ Hz), 7.78 (d, 2H, $J = 8.3$ Hz), 7.39 (d, 2H, $J = 8.5$ Hz), 6.88 (d, 2H, $J = 8.5$ Hz), 6.54 (s, 1H), 6.47 (s, 1H), 5.98 (s, 1H), 5.84 (s, 1H), 5.40 (bs, 1H), 4.12 (d, 1H, $J = 3.0$ Hz), 3.82 (d, 1H, $J = 3.0$ Hz), 3.82 (s, 3H), 2.30 (s, 3H), 1.99 (s, 3H), 1.62 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 178.4, 158.4, 154.7, 152.3, 146.5, 139.6, 137.9, 137.8, 136.4, 130.2, 129.3, 129.2, 128.4, 127.7, 123.6, 115.4, 115.0, 113.8, 113.1, 55.4, 54.7, 52.7, 38.9, 27.2, 25.7, 18.6, 18.4. HRMS (FAB) calc. for $[\text{C}_{33}\text{H}_{36}\text{N}_2\text{O}_6]^+$ 556.2573, found 556.2558. X-ray quality crystals were grown from ethanol. Views showing azepine ring and *trans* stereochemistry:

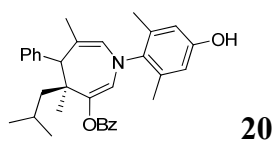




A single isomer was detected by ^1H NMR. ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, 2H, $J = 7.6$ Hz), 7.66 (d, 2H, $J = 7.6$ Hz), 7.54-7.48 (m, 3H), 7.43 (t, 2H, $J = 7.6$ Hz), 7.38-7.29 (m, 3H), 6.94 (d, 2H, $J = 8.4$ Hz), 6.50 (s, 2H), 6.48 (s, 1H), 6.20 (s, 1H), 5.28 (bs, 1H), 4.50 (d, 1H, $J = 2.8$ Hz), 4.25 (d, 1H, $J = 2.8$ Hz), 3.84 (s, 3H), 2.23 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 158.5, 154.9, 143.3, 138.9, 137.9, 137.8, 135.7, 134.0, 133.4, 131.3, 130.0, 129.9, 129.2, 128.6, 128.5, 128.3, 127.2, 127.0, 115.3, 115.2, 114.0, 99.7, 59.4, 55.5, 54.8, 18.5. HRMS (FAB) calc. for $[\text{C}_{34}\text{H}_{30}\text{NO}_4\text{Br}]^+$ 595.1358, found 595.1357.

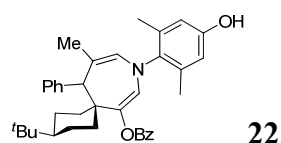


Obtained as an inseparable 3.3:1 mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) Major diastereomer: δ 7.60 (d, 2H, $J = 8.0$ Hz), 7.41-7.03 (m, 13H), 6.59 (s, 2H), 6.21 (s, 1H), 5.81 (s, 1H), 5.60 (bs, 1H), 3.49 (s, 1H), 2.47 (s, 3H), 2.44 (s, 3H), 1.96 (s, 3H), 1.68 (s, 3H). Minor diastereomer: δ 7.92 (d, 2H, $J = 8.0$ Hz), 7.75 (d, 2H, $J = 7.6$ Hz), 7.71 (d, 2H, $J = 7.6$ Hz), 7.50 (t, 1H, $J = 7.2$ Hz), 7.41-7.03 (m, 8H), 6.50 (s, 2H), 6.40 (s, 1H), 5.60 (bs, 1H), 5.51 (s, 1H), 3.98 (s, 1H), 2.28 (s, 3H), 2.03 (s, 3H), 1.58 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 155.0, 149.7, 144.4, 143.9, 143.4, 140.2, 139.9, 139.0, 138.3, 137.6, 137.2, 133.4, 133.1, 131.1, 130.8, 130.7, 130.0, 129.8, 129.2, 128.6, 128.3, 128.2, 128.0, 127.5, 127.4, 127.3, 127.0, 126.7, 126.6, 126.4, 126.0, 125.9, 116.1, 115.3, 115.1, 113.6, 63.9, 61.5, 52.2, 52.0, 29.0, 28.7, 25.3, 24.8, 19.0, 18.6, 18.4, 15.4. HRMS (FAB) calc. for $[\text{C}_{35}\text{H}_{33}\text{NO}_3]^+$ 515.2460, found 515.2463.

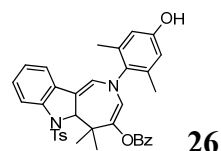


Obtained as an inseparable 1.4:1 mixture of diastereomers. ^1H NMR (400 MHz, CDCl_3) Major diastereomer: δ 7.99-7.90 (m, 2H), 7.59-7.22 (m, 8H), 6.58 (s, 1H), 6.54 (s, 1H), 6.17 (bs, 1H), 6.12 (s, 1H), 5.70 (s, 1H), 3.35 (s, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.04 (app sept, 1H, $J = 6.0$ Hz), 1.97-1.92 (m, 1H), 1.76 (s, 3H), 1.11 (d, 3H, $J = 6.4$ Hz), 1.08 (d, 3H, $J = 6.4$ Hz), 0.96 (s, 3H). Minor diastereomer: δ 7.99-7.90 (m, 2H), 7.59-7.22 (m, 8H), 6.56 (s, 1H), 6.53 (s, 1H), 6.17 (bs, 1H), 5.99 (s, 1H), 5.70 (s, 1H), 3.53 (s, 1H), 2.33 (s, 3H), 2.26 (s, 3H), 1.87-1.79 (m, 1H), 1.78 (s, 3H), 1.33-1.27 (m, 1H), 1.22-1.77 (m, 1H), 0.81 (d, 3H, $J = 6.4$ Hz), 0.80 (d, 3H, $J = 6.4$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 166.7, 154.9, 145.0, 144.9, 140.2, 140.0, 138.7, 138.3, 137.6, 137.3, 134.8, 133.4, 133.3, 132.8, 130.5, 130.3, 130.2, 130.1, 130.0, 128.6, 128.2, 128.0, 127.9, 127.8, 126.3, 126.2, 126.0, 126.0, 125.8, 115.2, 115.1, 112.5, 112.3, 62.0, 60.6,

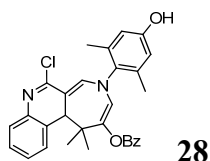
53.4, 46.7, 46.3, 45.6, 27.3, 26.1, 25.9, 25.8, 25.5, 25.4, 25.1, 25.0, 23.9, 23.6, 18.8, 18.8, 18.7, 18.6 . HRMS (FAB) calc. for $[C_{33}H_{37}NO_3]^+$ 495.2773, found 495.2768.



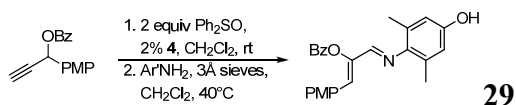
Prepared by slight modification the general procedure. Imine (1 eq), propargyl ester (2 eq) and PicAuCl₂ (10 mol %) were stirred in dichloroethane (0.3M) at 60°C overnight. NMR analysis of the crude reaction mixture indicated a 2.5:1 ratio of diastereomers. Chromatography (10% → 20% EtOAc in hexanes) provided the diastereomeric mixture as a pale yellow foam (68 mg, 58% yield). ¹H NMR (500 MHz, CDCl₃) Major diastereomer: δ 7.82 (d, 2H, *J* = 8.0 Hz), 7.59-7.26 (m, 8H), 6.58 (s, 2H), 6.19 (s, 1H), 5.96 (bs, 1H), 5.79 (s, 1H), 3.26 (s, 1H), 2.67 (app d, 1H, *J* = 11.5 Hz), 2.36 (s, 3H), 2.34 (s, 3H), 1.89-0.98 (m, 8H), 1.69 (s, 3H), 0.77 (s, 9H). Minor diastereomer: δ 7.93 (d, 2H, *J* = 7.5 Hz), 7.59-7.26 (m, 8H), 6.54 (s, 2H), 6.02 (s, 1H), 5.96 (bs, 1H), 5.77 (s, 1H), 3.99 (s, 1H), 2.42 (app d, 1H, *J* = 11.0 Hz), 2.33 (s, 3H), 2.32 (s, 3H), 1.89-0.98 (m, 8H), 1.79 (s, 3H), 0.92 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 165.9, 154.8, 144.8, 144.4, 139.9, 139.9, 139.0, 138.8, 137.2, 137.1, 135.9, 133.4, 133.1, 130.6, 130.2, 130.2, 130.1, 130.0, 129.8, 128.6, 128.6, 127.9, 127.6, 126.8, 126.7, 126.4, 126.3, 126.2, 125.8, 115.2, 115.1, 110.8, 110.5, 65.2, 51.8, 48.0, 47.4, 46.3, 45.3, 38.1, 37.4, 36.3, 32.6, 32.5, 30.5, 27.7, 25.5, 25.4, 25.0, 23.8, 23.4, 21.6, 18.8, 18.8. HRMS (FAB) calc. for $[C_{37}H_{43}NO_3]^+$ 549.3243, found 549.3227.



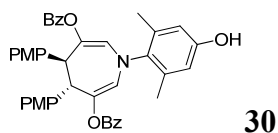
Prepared by slight modification the general procedure. Imine (1 eq), propargyl ester (2 eq) and PicAuCl₂ (10 mol %) were stirred in dichloroethane (0.3M) at 60°C overnight. Chromatography provided the desired compound as a yellow powder. ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, 2H, *J* = 7.2 Hz), 7.67 (d, 1H, *J* = 8.0 Hz), 7.59 (t, 1H, *J* = 7.4 Hz), 7.46 (t, 2H, *J* = 7.6 Hz), 7.36 (d, 2H, *J* = 8.0 Hz), 7.11 (td, 1H, *J* = 7.2, 1.6 Hz), 7.05 (d, 2H, *J* = 8.0 Hz), 7.02-6.95 (m, 2H), 6.55 (s, 1H), 6.53 (s, 1H), 6.22 (s, 1H), 5.87 (s, 1H), 5.40 (bs, 1H), 4.77 (s, 1H), 2.30 (s, 3H), 2.27 (s, 3H), 2.03 (s, 3H), 1.62 (s, 3H), 1.00 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 155.3, 143.9, 142.2, 138.4, 138.0, 137.3, 134.5, 133.8, 133.6, 133.4, 130.2, 129.8, 129.3, 128.7, 128.0, 126.5, 125.9, 125.9, 122.7, 119.7, 118.0, 115.4, 115.0, 114.9, 71.2, 48.1, 24.5, 23.4, 21.7, 18.1, 17.8 . HRMS (FAB) calc. for $[C_{36}H_{34}N_2O_5S]^+$ 606.2188, found 606.2195.



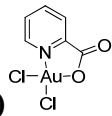
^1H NMR (500 MHz, CDCl_3) δ 8.08 (d, 2H, $J = 8.0$ Hz), 7.60 (t, 1H, $J = 7.3$ Hz), 7.47 (t, 2H, $J = 7.5$ Hz), 7.41 (d, 1H, $J = 8.0$ Hz), 7.31 (s, 1H), 7.30 (t, 1H, $J = 7.5$ Hz), 7.25 (d, 2H, $J = 8.0$ Hz), 7.18 (t, 1H, $J = 7.3$ Hz), 6.66 (s, 1H), 6.61 (s, 1H), 6.01 (s, 1H), 3.93 (s, 1H), 2.33 (s, 3H), 2.22 (s, 3H), 1.19 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.5, 155.1, 144.5, 144.1, 133.8, 132.0, 130.2, 129.5, 128.8, 128.5, 127.4, 126.0, 125.7, 125.6, 115.9, 115.3, 49.9, 48.5, 26.3, 24.5, 18.1, 18.0, 14.4. HRMS (FAB) calc. for $[\text{C}_{30}\text{H}_{27}\text{N}_2\text{O}_3\text{Cl}]^+$ 498.1710, found 498.1712.



To a one dram vial equipped with a magnetic stir bar, was added propargyl ester (233mg, 0.875 mmol, 1 equiv), diphenylsulfoxide (353mg, 1.75 mmol, 2 equiv) and CH_2Cl_2 (2.9 mL). The mixture was cooled to 10°C and PicAuCl_2 (6.8 mg, 0.017 mmol, 2 mol %) was added. The cooling bath was subsequently removed and the mixture was stirred for 1 hour at which point TLC analysis indicated consumption of the propargyl ester. 3\AA molecular sieves (250 mg) and 4-hydroxy-2,6-dimethylaniline (132 mg, 0.962 mmol, 1.1 equiv) were added and the solution was stirred at 40°C overnight. After cooling to room temperature, the mixture was subjected twice to silica gel chromatography (first with 1% triethylamine in 10% \rightarrow 50% EtOAc in hexanes, and then with 20 \rightarrow 35% EtOAc in hexanes) to yield the desired imine as a yellow solid (204 mg, 58% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.25 (d, 2H, $J = 7.5$ Hz), 7.82 (s, 1H), 7.64-7.60 (m, 3H), 7.50 (t, 2H, $J = 7.5$ Hz), 7.86 (d, 2H, $J = 8.0$ Hz), 6.67 (s, 1H), 6.43 (s, 2H), 5.25 (bs, 1H), 3.80 (s, 3H), 2.04 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.4, 160.6, 157.4, 152.2, 144.2, 143.8, 133.7, 131.6, 130.6, 129.6, 129.5, 129.2, 128.8, 125.9, 114.9, 114.5, 55.5, 18.7, 14.4.



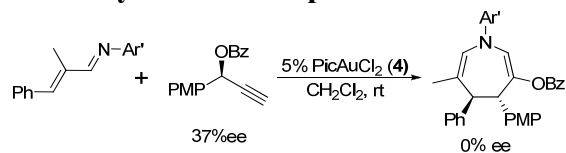
Obtained as an inseparable 20:1 mixture of diastereomers. ^1H NMR (500 MHz, CDCl_3) Major diastereomer: δ 7.88 (d, 4H, $J = 8.0$ Hz), 7.57 (d, 4H, $J = 8.5$ Hz), 7.50 (t, 2H, $J = 7.5$ Hz), 7.35 (t, 4H, $J = 7.5$ Hz), 6.94 (d, 4H, $J = 8.5$ Hz), 6.52 (s, 2H), 6.26 (s, 2H), 5.70 (bs, 1H), 4.16 (s, 2H), 3.81 (s, 6H), 2.35 (s, 6H). Additionally, the following peaks were assigned to the minor diastereomer: 8.11 (d, 4H, $J = 7.5$ Hz), 7.80 (d, 4H, $J = 7.5$ Hz), 6.67 (m, 6H), 6.18 (s, 2H), 4.52 (s, 2H), 3.72 (s, 6H), 2.44 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.1, 158.4, 138.1, 136.1, 133.3, 131.1, 130.4, 130.1, 130.0, 129.6, 128.7, 128.5, 127.1, 115.2, 113.8, 55.4, 53.4, 18.6. HRMS (FAB) calc. for $[\text{C}_{42}\text{H}_{37}\text{NO}_7]^+$ 667.2570, found 667.2568.



Synthesis of PicAuCl₂ (4)

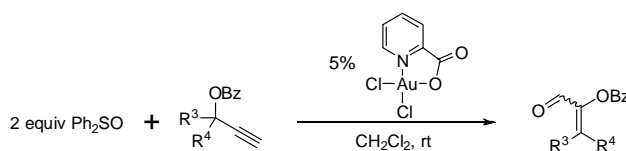
Prepared according to Dar *et. al.*¹ As such, 2-picolinic acid (175mg, 1.42 mmol) in water (14 mL) was added slowly to a stirred solution of sodium tetrachloroaurate (III) hydrate (283mg, 0.71 mmol) in 14 mL of water. After 3 hours, the resulting solution was filtered through celite. The yellow precipitate rinsed with water (15 mL) and eluted with acetone. Concentration *in vacuo* provided the desired dichloro(pyridine-2-carboxylato)gold(III) complex (PicAuCl₂, **4**) as a yellow powder (190mg, 68% yield). ¹H NMR (400 MHz, acetone-d₆) δ 9.31 (d, 1H, *J* = 6.0 Hz), 8.69 (t, 1H, *J* = 7.6 Hz), 8.26 (app t, 1H, *J* = 6.8 Hz), 8.20 (d, 1H, *J* = 7.6 Hz).

Chirality Transfer Experiment

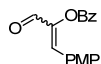


Subjecting enantioenriched propargyl ester **15** (37% ee) to the standard reaction conditions produced racemic azepine product.

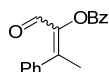
¹ Dar, A.; Moss, K.; Cottrill, S. M.; Parish, R. V.; McAuliffe, C. A.; Pritchard, R. G.; Beagley, B.; Sandbank, J. *J. Chem. Soc. Dalton Trans.* **1992**, 1907.



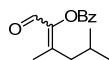
General procedure for the gold(III)-catalyzed oxidation of propargyl esters. To a one dram vial equipped with a magnetic stir bar, was sequentially added propargyl ester (1 equiv), diphenylsulfoxide (2 equiv), CH_2Cl_2 (0.3M) and PicAuCl_2 (5 mol %). The resulting mixture was stirred at room temperature and monitored periodically by TLC. Upon consumption of the propargyl ester (15-30 min), an aliquot was removed from the reaction mixture for $^1\text{H-NMR}$ analysis of the resulting diastereomeric ratio. The reaction mixture was subsequently subjected to silica gel chromatography to give the desired aldehydes.



NMR analysis of the crude reaction mixture indicated a 12:1 *Z:E* ratio. Chromatography (2% \rightarrow 20% EtOAc in Hexanes) provided the minor *E* diastereomer as a clear oil (38.1 mg, 7% yield). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.82 (s, 1H), 8.16 (d, 2H, $J = 7.5$ Hz), 7.63 (t, 1H, $J = 7.5$ Hz), 7.52-7.48 (m, 3H), 7.42 (d, 2H, $J = 8.5$ Hz), 6.97 (d, 2H, $J = 8.5$ Hz), 3.87 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CD_2Cl_2) δ 184.3, 165.0, 161.7, 145.8, 137.8, 134.2, 132.3, 130.8, 129.1, 129.0, 123.9, 114.8, 55.9. The major *Z* diastereomer was isolated as a mixture with diphenylsulfoxide, further silica gel chromatography (1% EtOAc in benzene) provided the major *Z* as a clear oil (350 mg, 66% yield). $^1\text{H NMR}$ (500 MHz, CD_2Cl_2) δ 9.47 (s, 1H), 8.23 (d, 2H, $J = 7.5$ Hz), 7.69-7.66 (m, 3H), 7.54 (t, 1H, $J = 7.5$ Hz), 7.08 (s, 1H), 6.90 (d, 2H, $J = 8.5$ Hz), 3.82 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CD_2Cl_2) δ 185.5, 163.6, 162.0, 144.8, 137.2, 134.2, 132.7, 130.7, 129.0, 128.8, 124.6, 114.8, 55.6. HRMS (EI) calc. for $[\text{C}_{17}\text{H}_{14}\text{O}_4]^+$ 282.0892, found 282.0889.

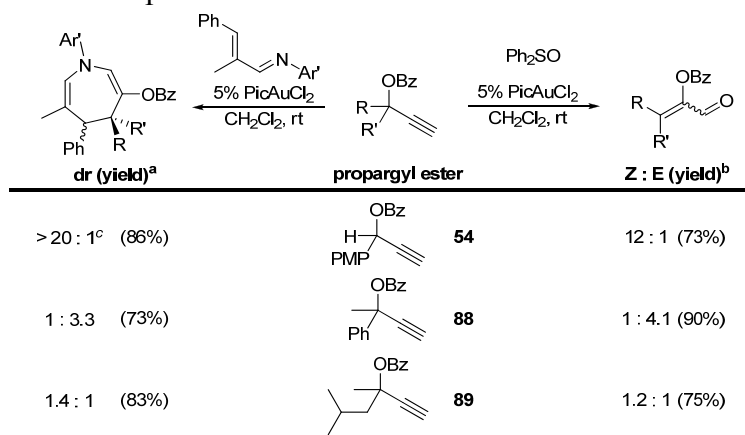


NMR analysis of the crude reaction mixture indicated a 4.1:1 *E:Z* ratio. Chromatography (2% \rightarrow 10% EtOAc in hexanes) provided first the major *E* diastereomer as a clear oil (37.5 mg, 72% yield). $^1\text{H NMR}$ (500 MHz, CD_2Cl_2) δ 9.39 (s, 1H), 8.18 (d, 2H, $J = 7.5$ Hz), 7.68 (t, 1H, $J = 7.5$ Hz), 7.55 (t, 2H, $J = 7.5$ Hz), 7.50-7.45 (m, 5H), 2.29 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CD_2Cl_2) δ 184.5, 164.4, 150.2, 144.8, 137.0, 134.3, 130.7, 129.9, 129.6, 129.4, 129.2, 129.1, 20.5. Followed by the major *Z* diastereomer as a clear oil (9.5 mg, 18% yield). $^1\text{H NMR}$ (500 MHz, CD_2Cl_2) δ 10.09 (s, 1H), 7.94 (d, 2H, $J = 7.5$ Hz), 7.58 (t, 1H, $J = 7.5$ Hz), 7.45-7.39 (m, 4H), 7.37-7.29 (m, 3H), 2.61 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CD_2Cl_2) δ 183.4, 165.0, 146.4, 142.6, 138.5, 134.1, 130.5, 129.5, 129.3, 129.1, 128.9, 127.7, 18.3. HRMS (EI) calc. for $[\text{C}_{17}\text{H}_{14}\text{O}_3]^+$ 266.0943, found 266.0943.



NMR analysis of the crude reaction mixture indicated a 1.2:1 *Z:E* ratio. Chromatography (2% → 10% EtOAc in Hexanes) provided first the minor *E* diastereomer as a clear oil (17.4 mg, 35% yield). ¹H NMR (500 MHz, CD₂Cl₂) δ 9.89 (s, 1H), 8.12 (d, 2H, *J* = 7.5 Hz), 7.65 (t, 1H, *J* = 7.5 Hz), 7.51 (t, 2H, *J* = 7.5 Hz), 2.56 (d, 2H, *J* = 7.5 Hz), 1.98 (nonet, 1H, *J* = 6.8 Hz), 1.92 (s, 3H), 1.03 (d, 6H, *J* = 6.5 Hz). ¹³C NMR (125 MHz, CD₂Cl₂) δ 182.0, 164.5, 150.3, 144.6, 134.1, 130.6, 129.6, 129.1, 40.9, 28.0, 22.6, 18.5. Followed by the major *Z* diastereomer as a clear oil (19.7 mg, 40% yield). ¹H NMR (500 MHz, CD₂Cl₂) δ 9.92 (s, 1H), 8.11 (d, 2H, *J* = 7.5 Hz), 7.65 (t, 1H, *J* = 7.5 Hz), 7.51 (t, 2H, *J* = 7.5 Hz), 2.27 (s, 3H), 2.18 (d, 2H, *J* = 7.5 Hz), 1.94 (nonet, 1H, *J* = 6.5 Hz), 0.93 (d, 6H, *J* = 6.5 Hz). ¹³C NMR (125 MHz, CD₂Cl₂) δ 182.6, 164.6, 149.5, 143.8, 134.1, 130.5, 129.6, 129.2, 43.1, 27.4, 22.9, 16.7. HRMS (EI) calc. for [C₁₅H₁₈O₃]⁺ 246.1256, found 246.1258.

Comparison of observed diastereoselectivities:



^a. Conditions: 1.3 equiv. propargyl ester, 5% **4**, CH₂Cl₂, rt. ^b. Conditions: 2 equiv. Ph₂SO, 5% **4**, CH₂Cl₂, rt. ^c. Only the *trans* diastereomer was observed. Ar' = 4-HO-2,6-Me₂-C₆H₂

Hammett Plots

A solution of 3 equiv. R=H imine, 3 equiv. R = X imine, 1 equiv. of propargyl ester, and 0.3 equiv. internal standard (1,3,5-trinitrobenzene) were dissolved in d₂-DCM (0.1 M in propargyl ester). An initial ¹H-NMR spectrum was acquired followed by addition of 0.1 equiv. PicAuCl₂. The reaction was monitored periodically by NMR. Upon completion, relative rates were obtained from NMR integrations of the products in the crude reaction mixture.

