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A Novel 2,2-Bipyridine Ligand for Palladium-Catalyzed Regioselective Carbonylation

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Supporting Information

General. All NMR's were taken on either 300 or 400 MHz spectrometer in $CDCl_3$ unless noted and recorded in ppm. All starting amines were purchased and used as is. Melting points are not corrected.

Method A. Carbonylation Using $(PPh_3)_2PdCl_2$. To a 4 L autoclave were added sequentially 250 g (949 mmol) of 2,5-dibromo-3-methylpyridine, 21 g (30 mmol) of $(PPh_3)_2PdCl_2$, 1.1 eq. of amine, 154 mL (1.5 mol) of Et_3N, and 2 L of toluene. The autoclave was sealed, evacuated, purged with nitrogen, and charged with carbon monoxide to 80 psi. The reaction mixture was heated to 65 °C for the time listed in Table 1 of text with periodical refilling if necessary, and then cooled to r.t. The content in the autoclave was vented under vacuum and flushed with nitrogen, transferred to a 10 L flask with the aid of water and toluene. To the mixture were added 25 g of Darco and 25 g of Supercel. The contents were filtered through a pad of celite and washed with toluene. The filtrate was extracted with 2 X 1 L of toluene. The combined extract was washed with brine, and concentrated to 750 mL. The residual toluene was chased with 2-PrOH. The residue was recrystallized from hot *i*-PrOH and the precipitate was filtered, washed with 2-PrOH, and dried at 50 °C to give the amide. Alternatively, the crude product was chromatographed on silica gel to give the amide.

Method B using 2,2-Bipyridine as a Ligand. To a 4 L autoclave were added sequentially 250 g (949 mmol) of 2,5-dibromo-3-methylpyridine, 4.5 g (20 mmol) of $Pd(OAc)_2$, 3.4 g (22 mmol) of 2,2-bipyridine, 127 mL (1.1 mol) of aniline, 210 mL (1.4 mol) of 1,8-diazabicyclo[5,4,0]undec-7-ene, 2.5 L of toluene. The autoclave was sealed, evacuated, purged with nitrogen, and charged with carbon monoxide to 80 psi. The reaction mixture was heated to 65 °C for about 2 days with periodical refilling of CO if necessary, and then cooled to r.t. The content in the autoclave was vented under vacuum and flushed with nitrogen, transferred to a 10 L flask with the aid of water and toluene. To the

mixture were added 25 g of Darco and 25 g of Supercel. The contents were filtered through a pad of celite and washed with toluene. The filtrate was extracted with 2 X 1 L of toluene. The combined extract was washed with brine, and concentrated to 750 mL. The residual toluene was chased with *i*-PrOH. The residue was recrystallized from hot *i*-PrOH and the precipitate was filtered, washed with I-PrOH, and dried at 50 °C to give 220 g (76%) of the amide as a white solid. A 81% isolated yield was obtained at 14 Kg scale.

1. The product was isolated as an oil in 67% yield by column. ^{1}H NMR δ 8.37 (d, J = 2.1 Hz, 1H), 7.88 (bs, 1H), 7.71 (dt, J = 2.1 Hz, 1H), 2.70 (s, 3H), 1.45 (s, 9H). ^{13}C NMR δ 165.5, 147.6, 147.1, 143.9, 137.9, 123.4, 52.1, 30.0, 21.9. Anal. Calcd for $C_{11}H_{15}BrN_2O•1/4H_2O$: C, 47.93; H, 5.67; N, 10.16. Found: C, 48.08; H, 5.50; N, 9.83. IR (Neat) 3380, 2970, 1660 cm^{-1}.

2. This compound was obtained as a solid in 62% yield. Mp 40-41 °C. ^{1}H NMR δ 8.45 (d, J = 2.2 Hz, 1H), 7.71 (dt, J = 2.2, 0.7 Hz, 1 H), 3.65 (t, J = 6.8 Hz, 2 H), 3.26 (t, J = 6.8 Hz, 2 H), 2.35 (d, J = 0.7 Hz, 3 H), 1.96-1.87 (m, 4 H). ^{13}C NMR δ 167.1, 153.8, 148.2, 141.8, 133.7, 121.6, 49.0, 46.8, 27.3, 25.6, 19.1. Anal. Calcd for $C_{11}H_{13}BrN_2O•1/4\ H_2O$: C, 48.19; H, 5.15; N, 10.22. Found: C, 48.29; H, 5.18; N, 10.41. IR (Nujol) 2920, 1650 cm^{-1}.

3. This compound was obtained as a solid in 70 % yield. Mp 98-99 °C. ^{1}H NMR δ 8.48 (d, 1.8 Hz, 1 H), 7.72 (d, J = 1.8 Hz, 1 H), 7.25 (dd, J = 8.7, 7.1 Hz, 2 H), 6.91-6.89 (m, 3 H), 3.95 (t, J = 5.2 Hz, 2 H), 3.38 (t, J = 5.0 Hz, 2 H), 3.26 (t, J = 5.2 Hz, 2 H), 3.10 (t, J = 5.0 Hz, 2 H), 2.34 (s, 3 H). 13C NMR δ 166.4, 151.8, 150.8, 147.5, 140.8, 133.0, 129.2, 129.0, 120.6, 116.8, 49.9, 49.5, 48.5, 41.5, 17.7. Anal. Calcd for $C_{17}H_{18}BrN_3O$: C, 56.68; H, 5.04; N, 11.66. Found: C, 56.66; H, 5.37; N, 11.25. IR (Nujol) 2920, 1640, 1600 cm^{-1}.

4. This product was obtained as a solid in 69% yield. Mp 101-102 °C. ^{1}H NMR δ 8.47 (dd, J = 1.4, 0.7 Hz, 1 H), 7.72 (dt, J = 1.4, 0.7 Hz, 1 H), 3.82 (t, J = 5.0 Hz, 2 H), 3.24 (t, J = 5.0 Hz, 2 H), 2.49 (t, J = 5.0 Hz, 2 H), 2.34-2.32 (m, 2 H), 2.33 (d, J = 0.7 Hz, 3 H), 2.31 (s, 3 H). ^{13}C NMR δ 167.3, 153.0, 148.5, 141.8, 133.8, 121.5, 55.4, 55.8, 47.7, 47.2, 42.7, 19.0. Anal. for

$C_{12}H_{16}BrN_3O$•1/4: C, 46.92; H, 5.58; N, 13.68. Found: C, 47.15; H, 5.41; N, 13.35. IR (Nujol) 3430 2920, 1645, 1570 cm^{-1}.

5. This compound was isolated as a solid in 64% yield. Mp 91-92 °C. ^1H NMR δ 8.44, (d, J = 2.2 Hz, 1 H), 7.70 (d, J = 2.4 Hz, 1 H), 3.79-3.73 (m, 4 H), 3.59 (t, J = 4.9 Hz, 2 H), 3.22 (t, J = 4.9 Hz, 2 H), 2.31 (s, 3 H). ^{13}C NMR δ 166.5, 151.5, 147.4, 141.0, 133.1, 120.7, 66.8, 66.7, 47.0, 41.9, 17.6. Anal. Calcd for $C_{11}H_{13}BrN_2O_2$: C, 46.34; H, 4.60; N, 9.82. Found: C, 46.32; H, 4.82; N, 9.70. IR (Nujol) 2920, 1590 cm^{-1}.

6. This compound was obtained as an oil in 59% isolated yield. ^1H NMR δ 8.45 (d J = 2.1 Hz, 1 H), 7.71 (d, J = 2.1 Hz, 1 H), 3.77 (t, J = 5.5 Hz, 2 H), 3.67 (d, J = 5.4 Hz, 2 H), 3.41 (bs, 4 H), 3.73 (s, 3 H), 3.21 (s, 3 H), 2.32 (s, 3 H). ^{13}C NMR δ 168.5, 152.6, 146.9, 140.7, 133.3, 120.3, 70.6, 70.4, 58.8, 58.7, 41.0, 45.4, 17.5. Anal. Calcd for $C_{13}H_{19}BrN_2O_3Br$: C, 47.14; H, 5.78; N, 8.46. Found: C, 46.81; H, 6.09; N, 8.33. IR (neat) 2920, 1630 cm^{-1}.

7. This compound was obtained as an oil in 72 % yield and exists in two stable rotamers on NMR time scale in a 1:1 ratio. ^1H NMR δ 8.41 (d, J = 1.8 Hz, 1/2 H), 8.38 (d, J = 2.1 Hz, 1/2 H), 7.67 (bs, 1 H), 3.68 (t, J = 6.9 Hz, 1 H), 3.21 (t, J = 6.9 Hz, 1 H), 3.06 (t, J = 7.4 Hz, 1 H), 3.06 (s, 1/2 CH_3), 2.81 (s, 1/2 CH_3), 2.68 (t, J = 6.9 Hz, 1 H), 2.40 (t, J = 6.9 Hz, 1 H), 2.36 (s, 3 H), 2.28 (s, 1/2 CH_3), 2.26 (s, 1/2 CH_3), 2.00 (s, 3 H), 1.36 (t, J = 7.4 Hz, 2 H). ^{13}C NMR δ 167.9, 167.6, 152.0, 151.9, 147.0, 146.4, 140.5, 140.4, 133.3, 132.2, 120.1, 120.0, 56.5, 55.3, 48.0, 45.8, 45.0, 44.8, 43.9, 36.2, 32.7.17.4, 17.1, 8.4. Anal. Calcd for $C_{12}H1_8BrN_3O$•1/2H_2O: C, 46.61; H, 6.19; N, 13.59. Found: C, 46.79; H, 6.10; N, 13.75.

8. This product was obtained as a solid in 64% yield. Mp 72-73 °C. ^1H NMR δ 8.37 (d, J = 1.5 Hz, 1 H), 7.85, (d, J = 6.9 Hz, 1 H), 7.69 (d, J = 1.5 Hz, 1 H), 3.88-3.84 (m, 1 H), 2.69 (s, 3 H), 1.97-1.94 (m, 2 H), 1.75-1.70 (m, 2 H), 1.62-1.58 (m, 1 H), 1.43-1.33 (m, 2 H), 1.30-1.17 (m, 2 H). ^{13}C NMR d 164.2, 146.3, 145.9, 142.8, 137.2, 122.4, 48.0, 33.0, 25.5, 24.8, 20.4. Anal. for $C_{13}H_{17}BrN_2O$: C, 52.54; H, 5.77; N, 9.43. Found: C, 53.02; 5.87; N, 9.25. IR (Nujol) 3400, 2920, 1680, 1640 cm^{-1}.

9. This product was obtained as a solid in 50% isolated yield and has two rotamers in a 73:27 ratio. Mp 94-95 °C. Major rotamer: ^{1}H NMR δ 8.51 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1 H), 7.78 (dt, J = 2.2, 0.3 Hz, 1 H), 7.28-7.21 (m, 2 H), 7.09 (t, J = 7.4 Hz, 1 H), 3.90 (t, J = 8.4 Hz, 2 H), 3.90 (t, 8.4 Hz, 2 H), 2.41 (d, J = 0.3 Hz, 3 H). Minor rotamer: 8.55 (s, 1 H), 7.82 (s, 1 H), 7.23 (d, J = 7.5 Hz, 1 H), 6.93 (t, J = 7.5 Hz, 1 H), 6.83 (t, J = 7.9 Hz, 1 H), 5.50 (d, J = 7.9 Hz, 1 H), 4.32 (t, J = 8.4 Hz, 2 H), 3.18 (t, J = 8.4 Hz, 2 H), 2.32 (s, 3 H). Anal for $C_{15}H_{13}BrN_2O•1/2H_2O$: C, 55.23; H, 4.33; N, 8.59. Found: C, 55.02; H, 4.05; N, 8.47.

10. This product was obtained as a solid in 59% yield. Mp 102-103 °C. ^{1}H NMR δ 9.90 (bs, 1 H), 8.49 (d, J = 1.5 Hz, 1 H), 7.80 (d, J = 1.5 Hz, 1 H), 7.64 (d, J = 8.9 Hz, 2 H), 7.62-7.32 (m, 5 H), 6.98 (d, J = 8.9 Hz, 2 H), 5.08 (s, 2 H), 2.80 (s, 3 H). ^{13}C NMR δ 162.5, 155.4, 146.3, 145.3, 143.2, 137.7, 136.9, 131.2, 128.5, 127.9, 127.4, 122.9, 121.2, 115.1, 70.2, 20.6. Anal. Calcd for $C_{20}H_{17}BrN_2O_2$: C, 60.47; H, 4.31; N, 7.05. Found: C, 60.49; H, 4.48; N, 7.03. IR (Nujol) 3360, 2940, 1680 cm^{-1}.

11. This product was obtained as a solid in 57% yield. Mp 128-129 °C. ^{1}H NMR δ 9.90 (s, 1 H), 8.48 (d, J = 1.8 Hz, 1 H), 7.79 (d, J = 1.8 Hz, 1 H), 7.62 (dd, J = 7.0, 2.2 Hz, 2 H), 6.90 (dd, J = 7.0, 2.2 Hz, 2 H), 3.81 (s, 3 H), 2.79 (s, 3 H). ^{13}C NMR δ 163.6, 157.2, 147.3, 147.2, 146.4, 144.3, 138.8, 132.0, 124.0, 122.3, 115.2, 56.7, 22.0. Anal. for $C_{14}H_{13}BrN_2O_2•1/4H_2O$: 51.03; H, 4.18; N, 8.60. Found: C, 51.45; H, 4.29; N, 8.53. IR (Nujol) 3380, 2920, 1680 cm^{-1}.

12. This product was obtained as a solid in 55% yield following method A and in 82% yield following method B. Mp 94-95 °C. 1H NMR δ 10.0 (s, 1 H), 8.49 (d, J = 2.0 Hz, 1 H), 7.79 (d, J = 2.0, 1 H), 7.72 (d, J = 7.5 Hz, 2 H), 7.37 (dd, J = 7.5, 7.4 Hz, 2 H), 7.13 (t, J = 7.4 Hz, 1 H), 2.79 (s, 3 H). ^{13}C NMR δ 162.8, 146.3, 145.2, 143.3, 137.9, 137.7, 128.9, 124.2, 123.1, 119.6, 20.7. Anal. for $C_{13}H_{11}BrN_2O$: C, 53.63; H, 3.81; N, 9.62. Found: C, 53.50; H, 3.79; N, 9.51. IR (Nujol) 3380, 2920, 1680 cm^{-1}. **12A** (bisamide) Mp 184-186 °C. ^{1}H NMR (DMSO-d_6) δ 10.63 (s 1 H), 10.5 (s, 1 H), 8.99 (d, 1.6 Hz, 1 H), 8.29 (d, J = 1.6 Hz, 1 H), 7.82 (d, J = 7.5 Hz, 2 H), 7.77 (d, J = 7.7 Hz, 2 H), 7.36 (dd, J = 7.7, 7.5 Hz, 4 H), 7.13 (dd, J = 7.7, 7.5 Hz, 2 H), 2.62 (s, 3 H). ^{13}C NMR

(DMSO-d_6) δ 165.6, 164.8, 153.1, 146.5, 140.7, 140.1, 140.0, 134.5, 133.2, 130.2, 125.7, 125.4, 121.9, 121.5, 20.8. Anal. Calcd for $C_{20}H_{17}N_3O_2 \cdot 1/4H_2O$: C, 71.52; H, 5.25; N, 12.51. Found: C, 71.25; H, 5.17; N, 12.17. IR (Nujol) 3320, 3290, 2920, 1650, 1650, 1600 cm^{-1}.

13. This product was obtained as a solid in 40% yield following method A and in 72% isolated yield following method B. Mp 125-126 °C. ^1H NMR δ 10.02 (bs, 1 H), 8.46 (d, J = 2.2 Hz, 1 H), 7.78 (d, J = 2.2 Hz, 1 H), 7.65 (d, J = 8.9 Hz, 2 H), 7.0 (d, J = 8.9 Hz, 2 H), 2.76 (s, 3 H). ^{13}C NMR δ 163.7, 147.4, 147.3, 145.8, 144.4, 139.0, 137.4, 130.0, 124.4, 121.8, 22.0. Anal for $C_{13}H_{10}BrClN_2O$: C, 47.93; H, 3.10; N, 8.60. Found: C, 48.11; H, 3.38; N, 8.58. IR (Nujol) 3380, 2920, 1690 cm^{-1}.

14. This product was obtained as a solid in 24% isolated yield. Mp 161-162 °C. ^1H NMR δ 9.97 (s, 1 H), 8.47 (d, J = 2.0 Hz, 1 H), 7.79 (d, J = 2.0 Hz, 1H), 7.68-7.65 (m, 2 H), 7.07-7.02 (m, 2 H), 2.77 (s, 3 H). ^{13}C NMR δ 162.8, 159.2, (d, J = 243.3 Hz), 146.4, 145.1, 143.4, 138.0, 133.8 (d, J = 2.8 Hz), 123.2, 121.3 (d, J = 8.0 Hz), 115.6 (d, J = 22.2 Hz), 20.6. Anal for $C_{13}H_{10}BrFN_2O$: C, 50.51; H, 3.26; N, 9.06. Found: C, 50.29; H, 3.50; N, 8.88. IR (Nujol) 3380, 2920, 1690 cm^{-1}.

15. This product was isolated as a solid in 30% isolated yield following method A and in 66% HPLC yield following method B. Two rotamers were observed with a 90:10 ratio. Mp 58-59 °C. Major rotamer: ^1H NMR δ 8.25 (s, 1 H), 7.49 (s, 1 H), 7.17 (d, J = 7.7 Hz, 2 H), 7.12 (t, J = 7.7 Hz, 1 H), 7.05 (d, J = 7.7 Hz, 2 H), 3.51 (s, 3 H), 2.27 (s, 3 H). ^{13}C NMR δ 168.9, 153.7, 148.0, 143.7, 141.2, 133.3, 130.0, 128.1, 127.5, 121.0, 38.2, 19.0. Anal for $C_{14}H_{13}BrN_2O$: C, 55.10; H, 4.29; N, 9.18. Found: 55.40; H, 4.55; N, 9.12. IR (Nujol) 1650 cm^{-1}.