Palladium-Catalyzed α -Arylation of Esters and Amides Under More Neutral Conditions

Takuo Hama, Xiaoxiang Liu, Darcy A. Culkin and John F. Hartwig*

Department of Chemistry, Yale University P.O. Box 208107, New Haven, CT 06520-8107

Supporting Information

General Methods. All reactions were performed in a nitrogen glovebox or with Schlenk techniques under N_2 . THF was distilled from sodium/benzophenone. Methylene chloride was distilled from calcium hydride. Anhydrous grade dioxane and DMF were purchased from Aldrich Chemical Co. and were used and stored in a nitrogen glovebox. All aryl halides, α -bromo esters, acid bromides, diethylamine (redistilled), and methyl trimethylsilyl ketene acetal were obtained from commercial suppliers and used without further purification. Zinc metal (granular, 20 mesh) was obtained from Mallinckrodt and activated according to literature procedure.¹ ZnF_2 and $P(t-Bu)_3$ were purchased from Strem. $Pd(dba)_2$ ² and pentaphenylferrocenyl di-*t*-butylphosphine (Q-phos)³ were prepared according to literature procedures. $\{P(t-Bu)_3\}PdBr_2$ was prepared by literature procedures⁴ or obtained from Johnson-Matthey. The silyl ketene acetal of *t*-butyl propionate⁵ and the trimethylsilyl ether derivative of the Evans auxiliary⁶ were prepared according to literature procedures. 1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker 400 or 500 MHz spectrometer, with shifts reported in parts per million downfield from tetramethylsilane and referenced to residual protiated (1H) or deuterated solvent (^{13}C). GC analyses were performed on a HP-6890 instrument using a DB-1301 narrow bore column for high temperature ramp applications (max. 120 °C /min). Elemental Analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ 07940.

General Procedure for the Preparation of α -Bromo Amides. Bromoacetyl bromide (0.05 mol) or 2-bromopropionyl bromide (0.05 mol) in methylene chloride (5 mL) was added dropwise via syringe to a stirred, cooled solution of diethylamine (0.1 mol) in methylene chloride (45 mL) at -10 °C. The reaction was stirred at -10 °C for 15 min and then warmed to room temperature over 1 h. The mixture was then filtered to remove the crystallized amine hydrobromide. The filtrate was poured into 50 mL of water and extracted with methylene chloride (1 x 30 mL) and chloroform (2 x 30 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated. The α -bromoamide was purified by Kugelrohr distillation.

2-Bromo-*N,N*-diethylacetamide.⁷ 1H NMR ($CDCl_3$) δ 1.14 (t, 7.2 Hz, 3H), 1.26 (t, 7.2 Hz, 3H), 3.39 (q, 7.2 Hz, 2H), 3.40 (q, 7.2 Hz, 2H), 3.85 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 12.27, 14.13, 26.27, 40.29, 42.71, 165.61.

2-Bromo-*N,N*-diethylpropionamide. 1H NMR ($CDCl_3$) δ 1.13 (t, 7.2 Hz, 3H), 1.24 (t, 7.2 Hz, 3H), 1.82 (d, 6.8 Hz, 3H), 3.26 (m, 2H), 3.53 (m, 2H), 4.53 (q, 6.8 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 12.28, 14.57, 21.74, 38.47, 40.74, 42.14, 168.28; Anal. Calc'd for $C_7H_{14}BrNO$: C, 40.40; H, 6.78; N, 6.73. Found: C, 40.21; H, 7.05; N, 6.74.

General Procedure for the Preparation of Reformatsky Reagents from α -Bromo Esters.^{8,9}

To activated 20-mesh zinc beads (7.68 g, 0.117 mol for reaction of the acetate; 11.2 g, 0.171 mol for reaction of the propionate) contained in a flask set in a water-ice bath was added under nitrogen *tert*-butyl bromoacetate (20.0 g, 0.102 mol) or *tert*-butyl 2-bromopropionate (16.0 g, 0.0767 mol) dissolved in 36 mL (for acetate) or 40 mL (for propionate) of THF. The reaction mixture was stirred for 6 h, while the cold bath was allowed to warm to room temperature. The resulting white solid was isolated by filtration and washed with cold THF in a drybox. The Reformatsky reagents were obtained as THF adducts. Acetic acid, *t*-butyl ester, zinc bromide complex (27.1 g, 80%): ¹H NMR (400 MHz, C₆D₆, TMS): δ 3.63-3.60 (4H, m), 2.26 (2H, s), 1.43 (9H, s), 1.32-1.29 (4H, m). ¹³C NMR (400 MHz, C₆D₆): δ 188.09, 82.61, 69.34, 29.16, 28.97, 25.80. Propanoic acid, *t*-butyl ester, zinc bromide complex (14.7 g, 55%):⁹ ¹H NMR (400 MHz, C₆D₆, TMS): δ 3.64-3.60 (4H, m), 2.63 (1H, s), 1.63 (3H, s), 1.44 (9H, s), 1.36-1.33 (4H, m). ¹³C NMR (400 MHz, C₆D₆): δ 187.34, 82.68, 69.14, 35.66, 29.03, 25.90, 12.76.

General Procedure for the Preparation of Reformatsky Reagents from α -Bromo Amides.

Reformatsky reagents were formed by the addition of the corresponding amide in THF (5 mL) to a suspension of 2 equiv of activated zinc in THF (30 mL) under nitrogen at 0 °C. The reaction was allowed to warm to room temperature. After 3 h at room temperature, the resulting white solid Reformatsky reagent was filtered, dried under vacuum, and used without further purification.

BrZnCH₂C(O)NEt₂·THF.¹⁰ ¹H NMR (C₆D₆) δ 0.85 (br t, 6.8 Hz, 3H), 0.98 (br t, 6.8 Hz, 3H), 1.38 (m, 4H), 2.21 (br s, 2H), 3.13 (br s, 4H), 3.61 (m, 4H); ¹³C{¹H} NMR (C₆D₆) δ 13.51, 13.59, 25.62, 41.30, 44.07, 44.22, 68.34, 182.38.

BrZnCHCH₃C(O)NEt₂·THF. ¹H NMR (C₆D₆) δ 0.86 (br s, 3H), 1.09 (br s, 3H), 1.39 (m, 4H), 1.82 (br s, 3H), 2.78 (br s, 4H), 3.59 (m, 4H), 3.75 (br s, 1H); ¹³C{¹H} NMR (C₆D₆) δ 13.69, 14.23, 25.70, 29.49, 41.56, 42.52, 43.21, 68.03, 183.94.

General Procedure for the Arylation of the Reformatsky Reagents of Esters. In a drybox, Pd(dba)₂ (5.00 μ mol), P(C₅H₄FeC₅Ph₅)(*t*-Bu)₂ (5.00 μ mol), and aryl halide (0.500 mmol) in 2.0 mL of THF were added to the Reformatsky reagent (0.550 mmol) in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was then stirred at room temperature or 70 °C for 4-24 h. The reaction mixture was then adsorbed onto silica gel and purified by flash column chromatography on silica gel, eluting with 20% ethyl acetate in hexanes. These conditions were used to isolate all reaction products, unless otherwise stated.

General Procedure for the Arylation of the Reformatsky Reagents of Esters with Bromophenols. In a drybox, aryl halide (0.500 mmol) in 1.0 mL of THF was added to KH (0.525 mmol). Gas evolution occurred immediately. The reaction mixture was stirred for 10 min at room temperature. Then, the suspension of potassium bromophenoxide was added to {P(*t*-Bu)₃}[PdBr]₂ (2.50 μ mol) in 1.0 mL of THF. The resulting suspension was added to the Reformatsky reagent (0.550 mmol) in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was then stirred

at room temperature for 4 h. The reaction mixture was adsorbed onto silica gel and purified by flash column chromatography on silica gel, eluting with 20% ethyl acetate in hexanes.

General Procedure for the Arylation of the Reformatsky Reagents of Esters with Bromoanilines. In a drybox, aryl halide (0.500 mmol) in 1.0 mL of THF was added to KH (0.525 mmol). Gas evolution occurred immediately. The reaction mixture was stirred for 30 min at room temperature. Then, the suspension of potassium bromoanilide was added to $\{P(t\text{-Bu})_3\}PdBr_2$ (2.50 μ mol) in 1.0 mL of THF. The resulting suspension was added to the Reformatsky reagent (0.550 mmol) in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was then stirred at room temperature for 12-24 h. The reaction mixture was diluted with Et_2O (30 mL). The resulting solution was washed with 0.1 N HCl (7 mL), with saturated $NaHCO_3$ (20 mL), and then with H_2O (20 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was then purified by flash column chromatography on silica gel, eluting with 20% ethyl acetate in hexanes.

General Procedure for the Preparation of α -Aryl Amides. In the drybox, a solution of $Pd(dba)_2$ (11.5 mg, 0.0200 mmol) and Q-phos (14.3 mg, 0.0200 mmol) in 6 mL of dioxane was added to a round-bottom flask containing a stirred solution of the zinc enolate of the α -bromo amide (1.20 mmol) in dioxane (10 mL). Aryl halide (1.00 mmol) was added, and the flask was sealed with a rubber septum and removed from the drybox. The reaction mixture was stirred at room temperature and monitored by GC analysis. Upon consumption of the aryl halide, the reaction mixture was poured into 40 mL of saturated aqueous NH_4Cl and extracted with ether (3 x 30 mL). The combined ether extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel.

4-(1-*tert*-Butoxycarbonyl)ethyl)benzoic acid methyl ester. (Table 1, Entry 1, 2) Purified by chromatography on silica gel (hexane/ethyl acetate = 90/10). 1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.00 (2H, d, $J=8.4$ Hz), 7.36 (2H, d, $J=8.0$ Hz), 3.91 (3H, s), 3.67 (1H, q, $J=7.2$ Hz), 1.46 (3H, d, $J=7.2$ Hz), 1.38 (9H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 173.29, 167.17, 146.56, 130.02, 129.00, 127.71, 81.08, 52.27, 46.76, 28.10, 18.48. Anal. Calc'd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.96; H, 7.63.

4-Diethylcarbamoylmethylbenzoic acid ethyl ester. (Table 1, Entry 3) Purified by chromatography on silica gel (hexane/ethyl acetate = 75/25). 1H NMR ($CDCl_3$) δ 1.11 (t, 7.2 Hz, 3H), 1.13 (t, 7.2 Hz, 3H), 1.39 (t, 7.2 Hz, 3H), 3.29 (q, 7.2 Hz, 2H), 3.40 (q, 7.2 Hz, 2H), 3.75 (s, 2H), 4.37 (q, 7.2 Hz, 2H), 7.34 (d, 8.4 Hz, 2H), 8.00 (d, 8.4 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 12.74, 14.10, 14.18, 40.03, 40.62, 42.21, 60.72, 128.62, 128.78, 129.67, 140.58, 166.28, 169.15; Anal. Calc'd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.20; H, 8.16; N, 5.37.

4-(1-Diethylcarbamoyl)ethyl)benzoic acid ethyl ester. (Table 1, Entry 4) Purified by chromatography on silica gel (hexane/ethyl acetate = 85/15). 1H NMR ($CDCl_3$) δ 1.00 (t, 7.2 Hz, 3H), 1.09 (t, 7.2 Hz, 3H), 1.39 (t, 7.2 Hz, 3H), 1.46 (d, 7.2 Hz, 3H), 3.13 (m, 1H), 3.28 (m, 2H), 3.52 (m, 1H), 3.89 (q, 6.8 Hz, 1H), 4.37 (q, 7.2 Hz, 2H), 7.36 (d, 8.4 Hz, 2H), 8.00 (d, 8.4 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 12.65, 14.14, 14.23, 20.66, 40.20, 41.50, 42.97, 60.79, 127.18,

128.87, 129.98, 147.45, 166.28, 171.88; Anal. Calc'd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 68.98; H, 8.41; N, 5.14.

(4-Benzoylphenyl)acetic acid *tert*-butyl ester. (Table 1, Entry 5) Purified by chromatography on silica gel (hexane/ethyl acetate = 90/10). 1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.79 (4H, t of t, $J = 7$ Hz, 2 Hz), 7.58 (1H, t of t, $J = 7.4$ Hz, 1.6 Hz), 7.47 (2H, t of t, $J = 8.4$ Hz, 2 Hz), 7.39 (2H, d, $J = 8.4$ Hz), 3.62 (2H, s), 1.46 (9H, s). ^{13}C NMR (400 MHz, $CDCl_3$): δ 196.52, 170.32, 139.61, 137.77, 136.27, 132.51, 130.49, 130.14, 129.36, 128.40, 81.44, 42.72, 28.16. Anal. Calc'd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.21; H, 6.70.

2-(4-Benzoylphenyl)propionic acid *tert*-butyl ester. (Table 1, Entry 6) Purified by chromatography on silica gel (hexane/ethyl acetate = 95/5). 1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.79 (4H, t of t, $J = 8.8$ Hz, 2 Hz), 7.59 (1H, t of t, $J = 7.4$ Hz, 1.6 Hz), 7.49 (2H, t, $J = 7.6$ Hz), 7.41 (2H, d, $J = 8.0$ Hz), 3.70 (1H, q, $J = 7.2$ Hz), 1.49 (3H, d, $J = 6.8$ Hz), 1.44 (9H, s). ^{13}C NMR (400 MHz, $CDCl_3$): δ 196.61, 173.33, 146.30, 137.86, 136.35, 132.56, 130.63, 130.20, 128.47, 127.64, 81.16, 46.75, 28.13, 18.64. Anal. Calc'd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.10; H, 7.05.

(4-Propionylphenyl)acetic acid *tert*-butyl ester. (Table 1, Entry 7) Purified by chromatography on silica gel (hexane/ethyl acetate = 90/10). 1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.93 (2H, d, $J = 8.4$ Hz), 7.36 (2H, d, $J = 8.4$ Hz), 3.59 (2H, s), 3.00 (2H, q, $J = 7.2$ Hz), 1.44 (9H, s), 1.22 (3H, t, $J = 7.4$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 200.67, 170.35, 140.04, 135.76, 129.65, 128.40, 81.47, 42.78, 31.96, 28.19, 8.45. Anal. Calc'd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.60; H, 8.05.

(4-Nitrophenyl)acetic acid *tert*-butyl ester.¹¹ (Table 1, Entry 8) Purified by standard conditions. 1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.18 (2H, d, $J = 4.2$ Hz), 7.45 (2H, d, $J = 4.2$ Hz), 3.64 (2H, s), 1.44 (9H, s). ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.57, 147.21, 142.29, 130.38, 123.81, 81.90, 42.52, 28.15.

(2-Nitrophenyl)acetic acid *tert*-butyl ester.¹² (Table 1, Entry 9) Purified by chromatography on silica gel (hexane/dichloromethane = 75/25). 1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.09 (1H, dd, $J = 8.2$ Hz, 1.4 Hz), 7.58 (1H, t of d, $J = 7.4$ Hz, 1.6 Hz), 7.45 (1H, t of d, $J = 7.8$ Hz, 1.6 Hz), 7.34 (1H, dd, $J = 7.6$ Hz, 1.2 Hz), 3.94 (2H, s), 1.44 (9H, s). ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.33, 149.01, 133.63, 133.49, 130.55, 128.53, 125.33, 81.95, 41.18, 28.12.

***N,N*-Diethyl-2-(4-nitrophenyl)propionamide.** (Table 1, Entry 10) Purified by chromatography on silica gel (hexane/ethyl acetate = 80/20). 1H NMR ($CDCl_3$) δ 1.07 (t, 7.2 Hz, 3H), 1.12 (t, 7.2 Hz, 3H), 1.49 (d, 3H, 7.2 Hz), 3.15-3.34 (m, 3H), 3.50 (m, 1H), 3.97 (q, 7.2 Hz, 1H), 7.49 (d, 8.8 Hz, 2H), 8.19 (d, 8.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) 12.73, 14.41, 20.59, 40.47, 41.74, 42.60, 123.92, 128.25, 146.78, 149.72, 171.41; Anal. Calc'd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.32; H, 7.27; N, 11.12.

(2-Cyanophenyl)acetic acid *tert*-butyl ester. (Table 1, Entry 11, 12) Purified by chromatography on silica gel (hexane/ethyl acetate = 90/10). 1H NMR (400 MHz, $CDCl_3$, TMS):

δ 7.66 (1H, dd, $J=7.6$ Hz, 1.2 Hz), 7.56 (1H, t of d, $J=7.7$ Hz, 1.2 Hz), 7.38 (2H, m), 3.80 (2H, s), 1.46 (9H, s). ^{13}C NMR (500 MHz, CDCl_3): δ 169.10, 138.64, 132.91, 132.88, 130.71, 127.68, 117.79, 113.64, 82.03, 41.09, 28.12. Anal. Calc'd for $\text{C}_{13}\text{H}_{15}\text{NO}_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.72; H, 7.15; N, 6.41.

2-(2-Cyanophenyl)propionic acid *tert*-butyl ester. (Table 1, Entry 13) Purified by chromatography on silica gel (hexane/ethyl acetate = 90/10). ^1H NMR (400 MHz, CDCl_3 , TMS): δ 7.65 (1H, dd, $J=7.6$ Hz, 1.2 Hz), 7.57 (1H, t of d, $J=7.7$ Hz, 1.6 Hz), 7.46 (1H, dd, $J=7.6$ Hz, 1 Hz), 7.35 (1H, t of d, $J=7.7$ Hz, 1.2 Hz), 4.11 (1H, q, $J=7.2$ Hz), 1.51 (3H, d, $J=7.2$ Hz), 1.41 (9H, s). ^{13}C NMR (500 MHz, CDCl_3): δ 172.30, 145.15, 133.16, 133.11, 127.59, 127.52, 117.93, 112.92, 81.66, 44.67, 28.08, 18.24. Anal. Calc'd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.68; H, 7.29; N, 5.94.

(4-Cyanophenyl)-*N,N*-diethylacetamide. (Table 1, Entry 14) Purified by chromatography on silica gel (hexane/ethyl acetate = 60/40). ^1H NMR (CDCl_3) 1.14 (t, 7.2 Hz, 3H), 1.17 (t, 7.2 Hz, 3H), 3.33 (q, 7.2 Hz, 2H), 3.41 (q, 7.2 Hz, 2H), 3.74 (s, 2H), 7.38 (d, 8.0 Hz, 2H), 7.62 (d, 8.0 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ 12.90, 14.33, 40.37, 42.34, 110.60, 118.82, 129.84, 132.23, 141.02, 168.60; Anal. Calc'd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.07; H, 7.23; N, 12.69.

(4-Hydroxyphenyl)acetic acid *tert*-butyl ester.¹³ (Table 1, Entry 15) Purified by standard conditions. ^1H NMR (400 MHz, CDCl_3 , TMS): δ 7.08 (2H, d, $J=8.4$ Hz), 6.70 (2H, d, $J=8.0$ Hz), 5.90 (1H, s), 3.46 (2H, s), 1.45 (9H, s). ^{13}C NMR (400 MHz, CDCl_3): δ 172.39, 154.98, 130.53, 126.45, 115.67, 81.38, 41.93, 28.23.

2-(4-Hydroxyphenyl)propionic acid *tert*-butyl ester. (Table 1, Entry 16) Purified by standard conditions. ^1H NMR (500 MHz, CDCl_3 , TMS): δ 7.12 (2H, d, $J=8.0$ Hz), 6.74 (2H, d, $J=7.5$ Hz), 6.13 (1H, s), 3.56 (1H, q, $J=7.0$ Hz), 1.43 (3H, d, $J=7$ Hz), 1.40 (9H, s). ^{13}C NMR (500 MHz, CDCl_3): δ 175.14, 155.01, 132.90, 128.70, 115.60, 81.05, 45.90, 28.14, 18.55. Anal. Calc'd for $\text{C}_{13}\text{H}_{18}\text{O}_3$: C, 70.24; H, 8.16. Found: C, 69.99; H, 8.10.

(2-Hydroxyphenyl)acetic acid *tert*-butyl ester.¹⁴ (Table 1, Entry 17) Purified by standard conditions. ^1H NMR (400 MHz, CDCl_3 , TMS): δ 8.05 (1H, s), 7.19 (1H, t of d, $J=7.6$ Hz, 1.4 Hz), 7.08 (1H, dd, $J=7.2$ Hz, 1 Hz), 6.96 (1H, dd, $J=8.0$ Hz, 1.2 Hz), 6.87 (1H, t of d, $J=7.4$ Hz, 1.2 Hz), 3.60 (2H, s), 1.47 (9H, s). ^{13}C NMR (400 MHz, CDCl_3): δ 173.89, 155.67, 131.17, 129.28, 121.22, 120.89, 118.07, 83.19, 39.94, 28.14.

(4-Aminophenyl)acetic acid *tert*-butyl ester.¹⁵ (Table 1, Entry 18) Purified by standard conditions. ^1H NMR (400 MHz, CDCl_3 , TMS): δ 7.05 (2H, d, $J=8.0$ Hz), 6.65 (2H, d, $J=8.4$ Hz), 3.42 (2H, s, br), 3.40 (2H, s), 1.43 (9H, s). ^{13}C NMR (400 MHz, CDCl_3): δ 171.77, 145.17, 130.22, 124.94, 115.48, 80.71, 41.95, 28.42.

2-(4-Aminophenyl)propionic acid *tert*-butyl ester. (Table 1, Entry 19, 20) Purified by standard conditions. ^1H NMR (400 MHz, CDCl_3 , TMS): δ 7.08 (2H, d, $J=8.4$ Hz), 6.64 (2H, d, $J=8.0$ Hz), 3.49 (3H, q, $J=7.0$ Hz and broad NH peak overlapped), 1.39 (3H, d, $J=7$ Hz), 1.38 (9H, s). ^{13}C NMR (400 MHz, CDCl_3): δ 174.58, 145.22, 131.44, 128.42, 115.39, 80.36, 45.75,

28.14, 18.72. Anal. Calc'd for $C_{13}H_{15}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.36; H, 8.91; N, 6.20.

Pyridin-4-yl-acetic acid *tert*-butyl ester.¹⁶ (Table 1, Entry 21) Purified by standard conditions. 1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.56 (2H, d, $J=6.0$ Hz), 7.21 (2H, d, $J=6.0$ Hz), 3.53 (2H, s), 1.45 (9H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 169.49, 150.09, 143.67, 124.69, 81.82, 42.20, 28.19.

Pyridin-3-yl-acetic acid *tert*-butyl ester.¹⁷ (Table 1, Entry 22) Purified by standard conditions. 1H NMR (400 MHz, $CDCl_3$, TMS): δ 8.52 (2H, s, br), 7.27 (1H, d of d, $J=5.2, 2.4$ Hz), 3.54 (2H, s), 1.44 (9H, s). ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.10, 150.47, 148.46, 136.91, 130.58, 123.52, 81.60, 39.94, 28.16.

Pyridin-3-yl-propionic acid *tert*-butyl ester. (Table 1, Entry 23) Purified by chromatography on silica gel (hexane/ethylacetate = 70/30). 1H NMR (500 MHz, $CDCl_3$, TMS): δ 8.54 (1H, d, $J=2.0$ Hz), 8.50 (1H, d of d, $J=4.5, 1.5$ Hz), 7.65 (1H, d of t, $J=8.0, 1.5$ Hz), 7.25 (1H, m), 3.63 (1H, q, $J=7.0$ Hz), 1.48 (3H, d, $J=7.0$ Hz), 1.40 (9H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 173.16, 149.51, 148.57, 136.81, 134.88, 123.63, 81.31, 44.27, 28.11, 18.52. Anal. Calc'd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.38; H, 8.42; N, 6.67.

2-(4-*tert*-Butylphenyl)-*N,N*-diethylacetamide. (Table 1, Entry 24) Purified by chromatography on silica gel (hexane/ethyl acetate = 65/35). 1H NMR ($CDCl_3$) δ 1.11 (t, 7.2 Hz, 3H), 1.14 (t, 7.2 Hz, 3H), 1.31 (s, 9H), 3.32 (q, 7.2 Hz, 2H), 3.40 (q, 7.2 Hz, 2H), 3.67 (s, 2H), 7.19 (d, 8.0 Hz, 2H), 7.34 (d, 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 12.90, 14.14, 31.27, 34.31, 40.09, 40.20, 42.29, 125.39, 128.25, 132.34, 149.32, 170.21; Anal. Calc'd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.42; H, 10.16; N, 5.45.

2-(4-*tert*-Butylphenyl)-*N,N*-diethylpropionamide. (Table 1, Entry 25) Purified by chromatography on silica gel (hexane/ethyl acetate = 80/20). 1H NMR ($CDCl_3$) δ 1.00 (t, 7.2 Hz, 3H), 1.10 (t, 7.2 Hz, 3H), 1.30 (s, 9H), 1.45 (d, 6.8 Hz, 3H), 3.11 (m, 1H), 3.26 (m, 1H), 3.33 (m, 1H), 3.48 (m, 1H), 3.81 (q, 6.8 Hz, 1H), 7.20 (d, 8.4 Hz, 2H), 7.31 (d, 8.4 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 12.86, 14.19, 20.85, 31.32, 34.35, 40.24, 41.63, 42.43, 125.54, 126.81, 139.20, 149.33, 172.95; Anal. Calc'd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 78.17; H, 10.39; N, 5.29.

***N,N*-Diethyl-2-(4-methoxyphenyl)acetamide.** (Table 1, Entry 26) Purified by chromatography on silica gel (hexane/ethyl acetate = 55/45). 1H NMR ($CDCl_3$) δ 1.10 (t, 7.2 Hz, 3H), 1.13 (t, 7.2 Hz, 3H), 3.30 (q, 7.2 Hz, 2H), 3.39 (q, 7.2 Hz, 2H), 3.64 (s, 2H), 3.80 (s, 3H), 6.86 (d, 8.8 Hz, 2H), 7.18 (d, 8.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 12.81, 14.11, 39.83, 39.96, 42.15, 55.10, 113.85, 127.38, 129.53, 158.17, 170.27; Anal. Calc'd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.31; H, 8.90; N, 6.28.

***N,N*-Diethyl-2-(3-methoxy-phenyl)propionamide.** (Table 1, Entry 27) Purified by chromatography on silica gel (hexane/ethyl acetate = 75/25). 1H NMR ($CDCl_3$) δ 1.01 (t, 7.2 Hz, 3H), 1.10 (t, 7.2 Hz, 3H), 1.44 (d, 7.2 Hz, 3H), 3.11 (m, 1H), 3.23 (m, 1H), 3.34 (m, 1H), 3.52 (m, 1H), 3.79 (s, 3H), 3.80 (q, 7.2 Hz, 1H), 6.78 (m, 1H), 6.85 (m, 2H), 7.23 (t, 8.0 Hz, 1H);

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ 12.73, 14.14, 20.84, 40.20, 41.52, 43.80, 55.12, 112.07, 112.59, 119.61, 129.65, 144.00, 159.82, 172.45; Anal. Calc'd for $\text{C}_{14}\text{H}_{21}\text{NO}_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.31; H, 9.13; N, 5.77.

***N,N*-Diethyl-2-(4-trifluoromethylphenyl)acetamide.** (Table 1, Entry 28) Purified by chromatography on silica gel (hexane/ethyl acetate = 80/20). ^1H NMR (CDCl_3) δ 1.14 (t, 7.2 Hz, 3H), 1.16 (t, 7.2 Hz, 3H), 3.32 (q, 7.2 Hz, 2H), 3.41 (q, 7.2 Hz, 2H), 3.75 (s, 2H), 7.39 (d, 8.0 Hz, 2H), 7.58 (d, 8.0 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ 12.87, 14.26, 40.26, 40.28, 42.32, 124.15 (q, 272.3 Hz), 125.40 (q, 3.9 Hz), 128.95 (q, 32.4 Hz), 129.22, 139.57 (q, $J < 2$ Hz), 169.09; Anal. Calc'd for $\text{C}_{13}\text{H}_{16}\text{F}_3\text{NO}$: C, 60.22; H, 6.22; N, 5.40. Found: C, 60.49; H, 6.21; N, 5.44.

***N,N*-Diethyl-2-(4-trifluoromethylphenyl)propionamide.** (Table 1, Entry 29) Purified by chromatography on silica gel (hexane/ethyl acetate = 85/25). ^1H NMR (CDCl_3) δ 1.04 (t, 7.2 Hz, 3H), 1.10 (t, 7.2 Hz, 3H), 1.46 (d, 6.8 Hz, 3H), 3.15 (m, 1H), 3.30 (m, 2H), 3.51 (m, 1H), 3.91 (q, 6.8 Hz, 1H), 7.42 (d, 8.0 Hz, 2H), 7.58 (d, 8.0 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3) δ 12.68, 14.23, 20.67, 40.31, 41.61, 42.64, 124.07 (q, 272.0 Hz), 125.59 (q, 3.7 Hz), 127.61, 128.88 (q, 32.2 Hz), 146.31, 171.88; Anal. Calc'd for $\text{C}_{14}\text{H}_{18}\text{F}_3\text{N}$: C, 61.53; H, 6.64; N, 5.13. Found: C, 61.81; H, 6.71; N, 5.17.

Representative Procedure for the Arylation of Silyl Ketene Acetals.

***tert*-Butyl (3-cyanophenyl)propionate.** (Table 2, entry 1) To a screw-capped vial containing P^tBu_3 (0.500 M solution in toluene, 40 μL , 0.020 mmol), $\text{Pd}(\text{dba})_2$ (5.8 mg, 0.010 mmol), ZnF_2 (52.0 mg, 0.500 mmol) and 3-cyanophenyl bromide (182.0 mg, 1.00 mmol) was added *tert*-butyl trimethylsilyl methyl ketene acetal (301.0 mg, 1.49 mmol) followed by DMF (4.0 mL). The vial was sealed with a cap containing a PTFE septum and removed from the dry box. The heterogeneous reaction mixture was stirred at 80 $^\circ\text{C}$ for 12 h. The crude reaction was then allowed to cool to room temperature and was diluted with Et_2O (50 mL). The resulting solution was washed with H_2O (5 X 20 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated at reduced pressure. The residue was then purified by chromatography on silica gel eluting with 1-2% EtOAc in Hexane gradient to provide the title compound (154 mg) in 67% yield. ^1H NMR (CDCl_3): δ 7.60 (1H, s), 7.55-7.57 (2H, m), 7.44 (1H, t, $J = 7.8$ Hz), 3.66 (1H, q, $J = 7.2$ Hz), 1.48 (3H, d, $J = 7.2$ Hz), 1.41 (9H, s). ^{13}C NMR (CDCl_3): δ 173.09, 142.88, 132.49, 131.65, 131.08, 129.69, 119.19, 112.98, 81.65, 46.49, 28.03, 18.71. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.59; H, 7.46; N, 6.21.

***tert*-Butyl (4-methoxycarbonylphenyl)propionate.** (Table 2, Entry 2)

^1H NMR (CDCl_3): δ 8.00 (2H, d, $J = 8.3$ Hz), 7.37 (2H, d, $J = 8.3$ Hz), 3.92 (3H, s), 3.68 (1H, q, $J = 7.1$ Hz), 1.47 (3H, d, $J = 7.1$ Hz), 1.39 (9H, s). ^{13}C NMR (CDCl_3): δ 173.48, 167.35, 146.76, 130.21, 129.20, 127.91, 81.25, 52.44, 46.94, 28.28, 18.67. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4$: C, 68.16; H, 7.63. Found: C, 68.07; H, 7.88.

Methyl (4-methoxycarbonylphenyl)isobutyrate.¹⁸ (Table 2, Entry 3)

^1H NMR (CDCl_3): δ 8.01 (2H, d, J = 8.4 Hz), 7.42 (2H, d, J = 8.4 Hz), 3.93 (3H, s), 3.68 (3H, s), 1.62 (6H, s). ^{13}C NMR (CDCl_3): δ 177.02, 167.18, 150.16, 130.12, 128.99, 126.16, 52.74, 52.47, 47.19, 26.79.

***tert*-Butyl (4-acetylphenyl)propionate.** (Table 2, Entry 4)

^1H NMR (CDCl_3): δ 7.93 (2H, d, J = 8.3 Hz), 7.40 (2H, d, J = 8.3 Hz), 3.68 (1H, q, J = 7.1 Hz), 2.60 (3H, s), 1.48 (3H, d, J = 7.2 Hz), 1.40 (9H, s). ^{13}C NMR (CDCl_3): δ 198.16, 173.42, 146.98, 136.27, 129.01, 128.10, 81.32, 46.93, 28.30, 26.99, 18.70. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3$: C, 72.55; H, 8.12. Found: C, 72.31; H, 8.15.

Methyl (4-acetylphenyl)isobutyrate. (Table 2, Entry 5)

^1H NMR (CDCl_3): δ 7.93 (2H, d, J = 8.5 Hz), 7.43 (2H, d, J = 8.5 Hz), 3.67 (3H, s), 2.60 (3H, s), 1.61 (6H, s). ^{13}C NMR (CDCl_3): δ 198.01, 176.98, 150.39, 136.04, 128.92, 126.37, 52.77, 47.24, 26.98, 26.79. Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: C, 70.89; H, 7.32. Found: C, 70.66; H, 7.60.

Methyl (4-benzoylphenyl)isobutyrate.¹⁹ (Table 2, Entry 6)

^1H NMR (CDCl_3): δ 7.79-7.84 (4H, m), 7.61 (1H, t, J = 7.4 Hz), 7.45-7.52 (4H, m), 3.70 (3H, s), 1.65 (6H, s). ^{13}C NMR (CDCl_3): δ 196.67, 177.10, 149.74, 137.98, 136.38, 132.84, 130.73, 130.44, 128.70, 126.12, 52.84, 47.25, 26.86.

***tert*-Butyl (2-cyanophenyl)propionate.** (Table 2, Entry 7)

^1H NMR (CDCl_3): δ 7.66 (1H, dd, J = 7.8 and 1.0 Hz), 7.58 (1H, dt, J = 7.6 and 1.2 Hz), 7.47 (1H, d, J = 7.9 Hz), 7.36 (1H, dt, J = 7.6 and 1.0 Hz), 4.11 (1H, q, J = 7.2 Hz), 1.52 (3H, d, J = 7.2 Hz), 1.42 (9H, s). ^{13}C NMR (CDCl_3): δ 172.52, 145.33, 133.99, 133.32, 127.78, 127.74, 118.16, 113.09, 81.86, 44.84, 28.27, 18.45. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.43; H, 7.21; N, 6.24.

Methyl (4-methoxyphenyl)isobutyrate.¹⁹ (Table 2, Entry 8) ^1H NMR (CDCl_3): δ 7.29 (2H, d, J = 8.8 Hz), 6.88 (2H, d, J = 8.9 Hz), 3.82 (3H, s), 3.67 (3H, s), 1.59 (6H, s). ^{13}C NMR (CDCl_3): δ 177.90, 158.63, 137.16, 127.15, 114.11, 55.65, 52.63, 46.16, 27.05.

Methyl (4-nitrophenyl)isobutyrate.²⁰ (Table 2, Entry 9)

^1H NMR (CDCl_3): δ 8.20 (2H, d, J = 9.0 Hz), 7.52 (2H, d, J = 9.0 Hz), 3.70 (3H, s), 1.64 (6H, s). ^{13}C NMR (CDCl_3): δ 176.44, 152.35, 147.08, 127.25, 124.01, 52.97, 47.34, 26.79.

***tert*-Butyl (4-nitrophenyl)propionate.** (Table 2, Entry 10)

^1H NMR (CDCl_3): δ 8.19 (2H, d, J = 8.7 Hz), 7.47 (2H, d, J = 8.7 Hz), 3.74 (1H, q, J = 7.2 Hz), 1.50 (3H, d, J = 7.2 Hz), 1.40 (9H, s). ^{13}C NMR (CDCl_3): δ 172.81, 148.90, 147.39, 128.84, 124.13, 81.75, 46.83, 28.26, 18.71. Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.32; H, 6.98; N, 5.74.

Methyl (4-trifluoromethylphenyl)isobutyrate.¹⁹ (Table 2, Entry 11)

^1H NMR (CDCl_3): δ 7.61 (2H, d, J = 8.3 Hz), 7.47 (2H, d, J = 8.4 Hz), 3.69 (3H, s), 1.62 (6H, s). ^{13}C NMR (CDCl_3): δ 176.96, 149.03, 129.38 (q, J = 32.7 Hz), 126.55, 125.76 (q, J = 3.5 Hz), 124.55 (q, J = 271.9 Hz), 52.77, 47.06, 26.78.

Methyl phenylisobutyrate.¹⁹ (Table 2, Entry 12)

¹H NMR (CDCl₃): δ 7.27-7.38 (5H, m), 3.69 (3H, s), 1.62 (6H, s). ¹³C NMR (CDCl₃): δ 177.72, 145.08, 128.85, 127.15, 126.02, 52.64, 46.94, 26.98.

Experimental Procedure for the Evaluation of Epimerization During the α-Arylation:

To a screw-capped vial containing P^tBu₃ (0.500 M solution in toluene, 20 μL, 0.010 mmol), Pd(dba)₂ (2.9 mg, 0.0050 mmol), ZnF₂ (5.2 mg, 0.050 mmol) and phenylbromide (15.7 mg, 0.100 mmol) was added the trimethylsilyl ether derivative of the Evans chiral auxiliary (37.0 mg, 0.144 mmol) and compound **1** (> 90% de),²¹ followed by DMF (1.0 mL). The vial was sealed with a cap containing a PTFE septum and removed from the dry box. The heterogeneous reaction mixture was stirred at 80 °C for 12 h. The crude reaction was then allowed to cool to room temperature and was diluted with Et₂O (5.0 mL). The resulting solution was washed with H₂O (5 x 2.0 mL). The organic phase was then dried over Na₂SO₄, filtered, and concentrated at reduced pressure. The residue was then analyzed by ¹H NMR spectroscopy. Only one set of signals was observed for the possible diastereomeric mixture of compound **1** and its (2')epimer.²¹ From integration of the ¹H NMR signals, the diastereomeric ratio of the isopropyl derivative formed from the α-arylation was 88:12. The same reaction on a 1.00 mmol scale in the absence of the added α-aryl imide provided the major diastereomer in 67% yield after purification by flash chromatography eluting with 2% EtOAc in hexanes.

(4S, 2'S)-4-isopropyl-3-(2'-phenyl-propanoyl)oxazolidin-2-one:²¹ ¹H NMR (CDCl₃): δ 7.27 (2H, d, *J* = 7.4 Hz), 7.22 (2H, t, *J* = 7.3 Hz), 7.15 (1H, t, *J* = 7.3 Hz), 5.06 (1H, q, *J* = 7.0 Hz), 4.25-4.28 (1H, m), 4.00-4.07 (2H, m), 2.33-2.37 (1H, m), 1.43 (3H, d, *J* = 7.0 Hz), 0.84 (3H, d, *J* = 6.6 Hz), 0.82 (3H, d, *J* = 6.1 Hz). ¹³C NMR (CDCl₃): δ 175.04, 153.99, 140.72, 128.98, 128.56, 127.59, 63.50, 59.43, 43.45, 28.94, 20.09, 18.42, 15.11.

References:

- (1) Vaughan, W. R.; Bernstein, S. C.; Lorber, M. E. *J. Org. Chem.* **1965**, *30*, 1790.
- (2) Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253.
- (3) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718.
- (4) Dura-Villa, V.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J. *J. Organomet. Chem.* **2000**, *600*, 198.
- (5) Hoffman, R.; Kim, H. O. *J. Org. Chem.* **1988**, *53*, 3855.
- (6) Fuentes, L. M.; Shinkai, I.; Salzmänn, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675.
- (7) Loeber, C.; Wieser, C.; Matt, D.; Cian, A. D.; Fischer, J.; Toupet, L. *Bull. Soc. Chim. Fr.* **1995**, *132*, 166.
- (8) Orsini, F.; Pelizzoni, F.; Ricca, G. *Tetrahedron Lett.* **1982**, *23*, 3945.
- (9) Orsini, F.; Pelizzoni, F.; Ricca, G. *Tetrahedron* **1984**, *40*, 2781.
- (10) Poller, R. C.; Silver, D. *J. Organomet. Chem.* **1978**, *157*, 247.
- (11) Makosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494.
- (12) Mudryk, B.; Makosza, M. *Synthesis* **1988**, *12*, 1007.
- (13) Bhawal, B. M.; Khanapure, S. P.; Biehl, E. R. *Synthesis* **1991**, *2*, 112.

- (14) Nussbaumer, P.; Bilban, M. *J. Org. Chem.* **2000**, *65*, 7660.
- (15) Dowell, R. I.; Springer, C. J.; Davies, D. H.; Hadley, E. M.; Burke, P. J.; Boyle, F. T.; Melton, R. G.; Connors, T. A.; Blakey, D. C.; Mauger, A. B. *J. Med. Chem.* **1996**, *39*, 1100.
- (16) Sammes, M. P.; Lee, C. M.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, *9*, 2476.
- (17) van Leeuwen, M.; McKillop, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, *20*, 2433.
- (18) Jackson, W. R.; Rae, I. D.; Wong, M. G. *Aust. J. Chem.* **1986**, *39*, 303.
- (19) Jorgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557.
- (20) RajanBabu, T. V.; Chenard, B. L.; Petti, M. A. *J. Org. Chem.* **1986**, *51*, 1704.
- (21) Fukuzawa, S.; Chino, Y.; Yokoyama, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1645.