Palladium-Catalyzed Intermolecular α -Arylation of *N*-Protected 2-piperidinones

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- Supporting Information -

General Considerations : Benzyl bromide, *p*-toluenesulfonyl chloride, butyllithium (2.5 M in hexanes), δ -valerolactame, lithium bis(trimethylsilyl)amide (1.0 M in THF), palladium dibenzylidene acetone, aryl halides (Aldrich) and Ligand **L**, 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (Strem, weighed under argon), were used without further purification. Zinc chloride was flame-dried, cooled at rt under argon atmosphere and sonicated in THF. THF was distilled over Na/benzophenone.

Reactions were performed in oven dried round flasks with magnetic stirring, under an argon atmosphere. Flash chromatography was carried out on Kieselgel 60 (230-400 mesh, Merck).

^1H and ^{13}C NMR spectra were respectively recorded on a Bruker AC 300 at 300 MHz and 75 MHz. Spectra were recorder in CDCl_3 as solvent, and chemical shifts (δ) were expressed in ppm relative to residual CHCl_3 at $\delta = 7.27$ for ^1H and to CDCl_3 at $\delta = 77.1$ for ^{13}C . ^1H NMR *J* values are given in Hz. Mass spectra were obtained by GC/MS with electron impact (EI) ionization by using a 5971 Hewlett Packard instrument at 70 eV : only selected ions are reported. IR spectra were recorded as neat films (NaCl cell) and KBr pellets for solids on a Perkin-Elmer 298. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris.

***N*-Tosyl-2-piperidinone **1**¹ :** To a stirred solution of *n*-BuLi (15.8 mL, 1.13 eq.) in THF (60 mL) at -78 °C was added a solution of δ -valerolactame (3.5 g, 1.0 eq.) in THF (40 mL) via cannula. After 20 min at -78 °C, a solution of *p*-toluenesulfonyl chloride (6.7 g, 1.0 eq) in THF (40 mL) was added and the solution was slowly warmed at rt and stirred overnight. The reaction was then quenched with aqueous NH_4Cl and extracted with Et_2O . The organic phase

(1) Padwa, A.; Eidell, C. K.; Ginn, J. D.; McClure, M. S. *J. Org. Chem.* **2002**, 67, 1595-1606.

was dried over MgSO_4 , filtered and concentrated under reduced pressure. The resulting white solid was purified by recrystallization from toluene to give 7.1 g (80 %) of **1**. mp : 148 °C. ^1H NMR (CDCl_3) δ : 7.89 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 3.90 (m, 2H), 2.41 (s, 3H), 2.40 (m, 2H), 1.93-1.85 (2H), 1.81-1.72 (2H). ^{13}C NMR (CDCl_3) δ : 170.5 (s), 145.0 (s), 136.4 (s), 129.6 (d), 129.0 (d), 47.2 (t), 34.4 (t), 23.6 (t), 21.9 (q), 20.7 (t). EI MS m/z (relative intensity) 189 (68), 160 (14), 155 (11), 146 (13), 133 (100), 120 (45), 108 (22), 98 (1), 91 (82), 82 (11), 77 (4), 65 (29), 55 (13), 51 (3). IR (cm^{-1}) : 2955, 1683, 1594, 1438, 1350, 1261, 1172, 972, 827.

***N*-Benzyl-2-piperidinone **4**²** : To a stirred solution of *n*-BuLi (18.4 mL, 1.13 eq.) in THF (130 mL) at -78 °C was added a solution of δ -valerolactame (4.1 g, 1.0 eq.) in THF (40 mL) via cannula. After 20 min at -78 °C, benzyl bromide (7.1 g, 1.0 eq) was added and the solution was slowly warmed at rt and stirred overnight. The reaction was then quenched with aqueous NH_4Cl and extracted with Et_2O . The organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure. The resulting oil was purified by distillation under reduced pressure (110 °C at 4.0×10^{-2} mbar) to give 7.7 g (97 %) of **4**. ^1H NMR (CDCl_3) δ : 7.26-7.12 (5H), 4.50 (s, 2H), 3.09 (m, 2H), 2.36 (m, 2H), 1.72-1.61 (4H). ^{13}C NMR (CDCl_3) δ : 169.7 (s), 137.3 (s), 128.5 (d), 128.0 (d), 127.2 (d), 50.0 (t), 47.2 (t), 32.4 (t), 23.1 (t), 21.3 (t). EI MS m/z (relative intensity) 189 (M^+ , 100), 160 (10), 146 (3), 132 (8), 118 (3), 112 (2), 106 (22), 98 (31), 91 (62), 85 (16), 77 (5), 70 (2), 65 (11), 55 (8), 51 (3). IR (cm^{-1}) : 2939, 1635, 1490, 1448, 1352, 1261, 1177.

Reaction Procedure for α -Arylation of *N*-Protected-2-Piperidinones : To a stirred solution (or suspension) of the *N*-protected 2-piperidinone (1.1 mmol, 2.2 equiv) in THF (2 mL) at -20 °C was added a solution of LiHMDS (1.0 mL, 2.0 equiv). After 20 min at -20 °C, a solution of ZnCl_2 (0.150 g, 1.1 mmol, 2.2 equiv) in THF (1 mL) was added. After another 20 min at -20 °C, the solution of zinc enolate was cannulated into a solution of 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl **L** (0.015 g, 37.5 μmol , 7.5 mol%), $\text{Pd}(\text{dba})_2$ (0.014 g, 25.0 μmol , 5.0 mol%) and aryl bromide (0.5 mmol, 1.0 equiv) in THF (1 mL). The solution was then heated in an oil bath at 65 °C for 8 h, cooled to rt, quenched with aqueous NH_4Cl and extracted with Et_2O . The organic phase was dried over

(2) Nakagawa, M.; Torisawa, Y.; Hosaka, T.; Tanaba, K.; Tavet, F.; Aikawa, M.; Hino, T. *Heterocycles* **1993**, 35, 1157-1170.

MgSO₄, filtered and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel using 80/20 cyclohexane/ethyl acetate, unless otherwise stated.

N*-Tosyl-3-phenyl-2-piperidinone **2* : After chromatography, **2** (152 mg, 92 %) was isolated as an oil. ¹H NMR (CDCl₃) δ : 7.93 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.26-7.20 (3H), 7.07-7.02 (2H), 4.06 (m, 2H), 3.63 (dd, *J* = 9.2, 6.2 Hz, 1H), 2.42 (s, 3H), 2.22-1.86 (4H). ¹³C NMR (CDCl₃) δ : 171.7 (s), 145.0 (s), 139.5 (s), 136.4 (s), 129.6 (d), 129.1 (d), 128.9 (d), 128.4 (d), 127.4 (d), 50.8 (d), 47.3 (t), 29.7 (t), 22.2 (t), 22.0 (q). CI⁺ (CH₄) MS *m/z* (relative intensity) : 330 (M+H⁺, 100), 204 (12), 176 (67), 175 (14), 174 (48), 157 (18), 154 (15), 133 (14), 125 (23). IR (cm⁻¹): 2950, 1690, 1595, 1452, 1353, 1282, 1169, 1088, 1008. HRMS (CI⁺, CH₄) : Calcd for C₁₈H₂₀NO₃S (M + H⁺) : 330.1164. Found : 330.1171.

N*-Tosyl-3-(2-methylphenyl)-2-piperidinone **3* : After chromatography, **3** (70 mg, 41 %) was isolated as an oil. ¹H NMR (CDCl₃) δ : 7.94 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.13-7.04 (3H), 6.89 (d, *J* = 7.0 Hz, 1H), 4.21 (m, 1H), 3.95 (m, 1H), 3.77 (m, 1H), 2.43 (s, 3H), 2.16-2.10 (2H), 2.12 (s, 3H), 2.01-1.81 (2H). ¹³C NMR (CDCl₃) δ : 171.5 (s), 144.8 (s), 138.4 (s), 136.2 (s), 135.6 (s), 130.9 (d), 129.3 (d), 128.9 (d), 128.6 (d), 127.3 (d), 126.3 (d), 48.5 (d), 47.3 (t), 28.9 (t), 22.6 (t), 21.7 (q), 19.6 (q). EI MS *m/z* (relative intensity) 344 (M⁺, 1), 343 (M⁺, 5), 280 (21), 279 (100), 188 (13), 172 (8), 146 (10), 145 (75), 131 (8), 130 (16), 129 (8), 120 (16), 119 (30), 117 (21), 115 (13), 105 (25), 91 (33), 65 (8). IR (cm⁻¹) : 2952, 1690, 1456, 1350, 1281, 1168, 1089, 1006, 814. HRMS (CI⁺, CH₄) : Calcd for C₁₉H₂₂NO₃S (M + H⁺) : 344.1320. Found : 344.1322.

***N*-Benzyl-3-phenyl-2-piperidinone **5**³** : After chromatography, **5** (130 mg, 98 %) was isolated as an oil. ¹H NMR (CDCl₃) δ : 7.29-7.22 (7H), 7.19-7.14 (3H), 4.65 (d, *J* = 14.5 Hz, 1H), 4.57 (d, *J* = 14.5 Hz, 1H), 3.68 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.26 (m, 2H), 2.10 (m, 1H), 1.97-1.62 (3H). ¹³C NMR (CDCl₃) δ : 170.5 (s), 141.7 (s), 137.4 (s), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.4 (d), 126.6 (d), 50.4 (t), 48.7 (d), 47.4 (t), 30.4 (t), 20.9 (t). EI MS *m/z* (relative intensity) 265 (M⁺, 100), 174 (27), 148 (6), 132 (11), 131 (78), 117 (6), 116 (6), 115 (6), 104 (11), 92 (6), 91 (71), 77 (5), 65 (7), 51 (2). IR (cm⁻¹) : 2940, 1640, 1488, 1450, 1349, 1250, 1190. HRMS (EI) Calcd for C₁₈H₁₉NO: 265.1467. Found : 265.1462.

(3) Grunewald, G. L.; Brouillette, W. J. *J. Org. Chem.* **1978**, *43*, 1839-1841.

***N*-Benzyl-3-(4-methylphenyl)-2-piperidinone 6** : After chromatography, **6** (73 mg, 52 %) was isolated as an oil. ^1H NMR (CDCl_3) δ : 7.37-7.29 (5H), 7.17-7.11 (4H), 4.73 (d, J = 14.5 Hz, 1H), 4.63 (d, J = 14.5 Hz, 1H), 3.71 (dd, J = 8.1, 6.3 Hz, 1H), 3.32 (m, 2H), 2.34 (s, 3H), 2.15 (m, 1H), 2.03-1.70 (3H). ^{13}C NMR (CDCl_3) δ : 171.1 (s), 139.0 (s), 137.8 (s), 136.3 (s), 129.4 (d), 128.8 (d), 128.6 (d), 128.4 (d), 127.6 (d), 50.8 (t), 48.6 (d), 47.8 (t), 30.7 (t), 27.2 (t), 21.3 (q). EI MS m/z (relative intensity) 279 (M^+ , 100), 188 (21), 145 (67), 130 (10), 119 (17), 118 (12), 117 (17), 105 (19), 91 (48). IR (cm^{-1}) : 2940, 1680, 1490, 1450, 1350, 1192. HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}$: 279.1623. Found : 279.1626.

***N*-Benzyl-3-(2-methylphenyl)-2-piperidinone 7** : After chromatography, **7** (64 mg, 46 %) was isolated as an oil. ^1H NMR (CDCl_3) δ : 7.39-7.29 (5H), 7.19-7.14 (3H), 7.09 (m, 1H), 4.75 (d, J = 14.5 Hz, 1H), 4.66 (d, J = 14.5 Hz, 1H), 3.93 (dd, J = 7.7, 6.6 Hz, 1H), 3.36 (m, 2H), 2.36 (s, 3H), 2.12 (m, 1H), 1.96-1.75 (3H). ^{13}C NMR (CDCl_3) δ : 171.2 (s), 140.7 (s), 137.7 (s), 136.1 (s), 130.9 (d), 128.9 (d), 128.7 (d), 128.4 (d), 127.7 (d), 126.9 (d), 126.3 (d), 50.9 (t), 47.9 (t), 46.3 (d), 29.6 (t), 21.6 (t), 19.8 (q). EI MS m/z (relative intensity) 279 (M^+ , 100), 264 (7), 188 (14), 174 (36), 145 (37), 130 (9), 119 (12), 117 (17), 115 (9), 105 (18), 91 (51). IR (cm^{-1}) : 2940, 1635, 1490, 1452, 1350, 1198. HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}$: 279.1623. Found : 279.1626.

***N*-Benzyl-3-(4-methoxyphenyl)-2-piperidinone 9** : After chromatography (30 % ethyl acetate in cyclohexane), **9** (114 mg, 77 %) was isolated as an oil. ^1H NMR (CDCl_3) δ : 7.37-7.29 (5H), 7.16 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.72 (d, J = 14.5 Hz, 1H), 4.63 (d, J = 14.5 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, J = 8.4, 6.0 Hz, 1H), 3.32 (m, 2H), 2.15 (m, 1H), 2.03-1.70 (3H). ^{13}C NMR (CDCl_3) δ : 171.1 (s), 158.5 (s), 137.7 (s), 134.1 (s), 129.4 (d), 128.8 (d), 128.5 (d), 127.6 (d), 55.5 (q), 50.7 (t), 48.1 (d), 47.7 (t), 30.7 (t), 21.3 (t). EI MS m/z (relative intensity) 295 (M^+ , 100), 204 (19), 187 (12), 161 (52), 160 (29), 159 (59), 147 (11), 135 (14), 134 (22), 121 (20), 91 (69). IR (cm^{-1}) : 2938, 1638, 1510, 1451, 1245, 1180, 1035. HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: 295.1572. Found : 295.1570.

***N*-Benzyl-3-(3-methoxyphenyl)-2-piperidinone 10** : After chromatography (30 % ethyl acetate in cyclohexane), **10** (74 mg, 50 %) was isolated as an oil. ^1H NMR (CDCl_3) δ : 7.36-7.22 (6H), 6.84-6.77 (3H), 4.76 (d, J = 14.5 Hz, 1H), 4.59 (d, J = 14.5 Hz, 1H), 3.78 (s, 3H), 3.73 (dd, J = 7.5, 6.0 Hz, 1H), 3.33 (m, 2H), 2.16 (m, 1H), 2.03-1.70 (3H). ^{13}C NMR (CDCl_3)

δ : 170.8 (s), 159.9 (s), 143.6 (s), 137.8 (s), 129.7 (d), 128.9 (d), 128.6 (d), 127.7 (d), 120.9 (d), 114.5 (d), 112.3 (d), 55.4 (q), 50.8 (t), 49.0 (d), 47.8 (t), 30.7 (t), 21.2 (t). EI MS m/z (relative intensity) 295 (M^+ , 100), 204 (25), 176 (7), 161 (57), 148 (7), 134 (13), 135 (15), 121 (13), 91 (64), 65 (8). IR (cm^{-1}) : 2940, 1638, 1490, 1452, 1260. HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: 295.1572. Found : 295.1575.

***N*-Benzyl-3-(2,4-dimethoxyphenyl)-2-piperidinone 11** : After chromatography (30 % ethyl acetate in cyclohexane), **11** (137 mg, 84 %) was isolated as an oil. ^1H NMR (CDCl_3) δ : 7.36-7.28 (5H), 7.03 (d, J = 8.1 Hz, 1H), 6.47 (d, J = 2.6 Hz, 1H), 6.44 (dd, J = 8.1, 2.6 Hz, 1H), 4.94 (d, J = 14.3 Hz, 1H), 4.41 (d, J = 14.3 Hz, 1H), 3.79 (s, 3H), 3.78 (m, 1H), 3.73 (s, 3H), 3.36 (m, 1H), 3.27 (m, 1H), 2.05-1.95 (2H), 1.90-1.74 (2H). ^{13}C NMR (CDCl_3) δ : 171.6 (s), 160.0 (s), 157.9 (s), 138.1 (s), 130.6 (d), 128.7 (d), 127.5 (d), 123.5 (s), 104.4 (d), 99.3 (d), 55.6 (q), 55.5 (q), 51.0 (t), 48.0 (t), 45.0 (d), 29.4 (t), 22.5 (t). EI MS m/z (relative intensity) 325 (M^+ , 98), 191 (19), 190 (17), 189 (15), 187 (37), 177 (19), 160 (19), 159 (100), 158 (20), 151 (21), 149 (13), 121 (19), 91 (57). IR (cm^{-1}) : 2936, 1638, 1508, 1450, 1295, 1212, 1155, 1030. HRMS (EI) Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_3$: 325.1678. Found : 325.1683.

N-Tostyl-3-(2-methylphenyl)-2-piperidinone