Palladium-Catalyzed Intramolecular Nucleophilic Substitution at the Alkoxy carbonyl Group

Daniel Solé and Olga Serrano

Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

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**General Methods.** $^1$H- and $^{13}$C NMR spectra were recorded in CDCl$_3$ solution, using Me$_4$Si as internal standard. $^{31}$P NMR spectra were recorded in CDCl$_3$ with external H$_3$PO$_4$ as reference. Chemical shifts are reported in ppm downfield (δ) from Me$_4$Si. TLC was carried out on SiO$_2$ (silica gel 60 F$_{254}$, Merck), and the spots were located with UV light, iodoplitate reagent or 1% aqueous KMnO$_4$. Flash chromatography was carried out on SiO$_2$ (silica gel 60, SDS, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous MgSO$_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

**Experimental procedures and characterization data for the starting materials:**

**Methyl 3-[N-(2-iodo-4-methylphenyl)-N-methylamino]propionate (1a)**

A solution of $p$-toluidine (0.5 g, 4.67 mmol) and methyl acrylate (0.34 mL, 3.73 mmol) in acetic acid (0.25 mL) was stirred at 90°C in a sealed tube for 24 h. The reaction mixture was poured into cooled (ice) water, basified with Na$_2$CO$_3$, and extracted with Et$_2$O. The organic extracts were washed with saturated aqueous Na$_2$CO$_3$ solution, dried, and concentrated. The residue was dissolved in a CH$_2$Cl$_2$ (18 mL)-MeOH (9 mL) mixture, and CaCO$_3$ (0.53 g, 5.30 mmol) and BTMAICl$_2$ (1.57 g, 4.48 mmol) were added. The mixture was stirred at room temperature for 6 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to 4:1 hexanes-EtOAc) to give methyl 3-[N-(2-iodo-4-methylphenyl)amino]propionate (892 mg, 75%).

A mixture of methyl 3-[N-(2-iodo-4-methylphenyl)amino]propionate (892 mg, 2.80 mmol), K$_2$CO$_3$ (774 mg, 5.60 mmol), and iodomethane (1.42 mL, 22.4 mmol) in acetonitrile (5 mL) was stirred at 50°C in a sealed tube for 72 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH$_2$Cl$_2$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, CH$_2$Cl$_2$) to give methyl 3-[N-(2-iodo-4-methylphenyl)-N-methylamino]propionate$^3$ (1a, 694 mg, 74%).

**Methyl 3-[N-(2-bromo-4-methylphenyl)-N-methylamino]propionate (1b)**

A solution of 2-bromo-4-methylaniline (0.33 mL, 2.6 mmol) and methyl acrylate (0.7 mL, 7.8 mmol) in acetic acid (0.25 mL) was stirred at 90°C in a sealed tube for 24 h. The reaction mixture was poured into cooled (ice) water, basified with Na$_2$CO$_3$, and extracted with Et$_2$O.

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The organic extracts were washed with saturated aqueous Na₂CO₃ solution, dried, and concentrated. The residue was dissolved in acetonitrile (6 mL) and K₂CO₃ (0.72 g, 5.2 mmol) and iodomethane (0.6 mL, 9.6 mmol) were added. The mixture was stirred at 50°C in a sealed tube for 5 days. The solvent was removed in vacuo, and the residue was partitioned between water and CH₂Cl₂. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO₂ from hexanes to hexanes-EtOAc 4%) to give methyl 3-[N-(2-bromo-4-methylphenyl)-N-methylamino]propionate (1b, 0.3 g, 40%).

**1H NMR (CDCl₃, 300 MHz) δ 2.27 (s, 3H), 2.54 (t, J = 7.5 Hz, 2H), 2.73 (s, 3H), 3.32 (t, J = 7.5 Hz, 2H), 3.64 (s, 3H), 6.99 (d, J = 8.1 Hz, 1H), 7.05 (dd, J = 8.1 and 1.8 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H).**

**13C NMR (CDCl₃, 75.4 MHz) δ 20.3 (CH₃), 32.5 (CH₂), 41.7 (CH₃), 51.5 (CH₂), 51.6 (CH₂), 120.5 (C), 122.0 (CH), 128.6 (CH), 134.1 (CH), 134.6 (C), 147.7 (C), 172.6 (C).**

**Methyl 3-[N-(2-iodo-4-methoxyphenyl)-N-methylamino]propionate (4a)**

A solution of 2-iodo-4-methoxyaniline (0.5 g, 2 mmol) and methyl acrylate (0.54 mL, 6 mmol) in acetic acid (0.25 mL) was stirred at 90°C in a sealed tube for 24 h. The reaction mixture was poured into cooled (ice) water, basified with Na₂CO₃, and extracted with Et₂O. The organic extracts were washed with saturated aqueous Na₂CO₃ solution, dried, and concentrated. The residue was purified by flash chromatography (SiO₂ from hexanes to CH₂Cl₂) to give methyl 3-[N-(2-iodo-4-methoxyphenylamino]propionate (417 mg, 62%).

A mixture of methyl 3-[N-(2-iodo-4-methoxyphenyl)amino]propionate (417 mg, 1.24 mmol), K₂CO₃ (344 mg, 2.49 mmol), and iodomethane (0.62 mL, 9.95 mmol) in acetonitrile (6 mL) was stirred at 50°C in a sealed tube for 72 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH₂Cl₂. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO₂ from hexanes to 1:1 hexanes-EtOAc) to give methyl 3-[N-(2-iodo-4-methoxyphenyl)-N-methylamino]propionate (4a, 435 mg, quantitative).

**1H NMR (CDCl₃, 300 MHz) δ 2.49 (t, J = 7.5 Hz, 2H), 2.64 (s, 3H), 3.22 (t, J = 7.5 Hz, 2H), 3.66 (s, 3H), 3.76 (s, 3H), 6.88 (dd, J = 8.7 and 3 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 3 Hz, 1H).**

**13C NMR (CDCl₃, 75.4 MHz) δ 32.9 (CH₂), 43.4 (CH₃), 51.7 (CH₃), 52.5 (CH₂), 55.6 (CH₃), 100.8 (C), 115.0 (CH), 122.5 (CH), 124.4 (CH), 146.4 (C), 156.8 (C), 172.7 (C).**

**HRMS (ESI-TOF) calcd for C₁₂H₁₇INO₃: 350.0248 [M+H]+; found: 350.0233.**

**Methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)amino]propionate**

A solution of methyl p-aminobenzoate (1 g, 6.62 mmol) and methyl acrylate (0.66 mL, 7.28 mmol) in acetic acid (0.5 mL) was stirred at 90°C in a sealed tube for 24 h. The reaction mixture was poured into cooled (ice) water, basified with Na₂CO₃, and extracted with Et₂O. The organic extracts were washed with saturated aqueous Na₂CO₃ solution, dried, and
concentrated. The residue was dissolved in a CH₂Cl₂ (12 mL)-MeOH (6 mL) mixture, and CaCO₃ (793 mg, 7.92 mmol) and BTMAI Cl₂ (2.55 g, 7.31 mmol) were added. The mixture was stirred at room temperature for 24 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO₂, from hexanes to 3:1 hexanes-EtOAc) to give methyl 3-[N-(2-iodo-4-methoxy carbonylphenyl)amino]propionate (984 mg, 41%).

¹H NMR (CDCl₃, 300 MHz) δ 2.68 (t, J = 6.6 Hz, 2H), 3.57 (broad t, J = 6.6 Hz, 2H), 3.74 (s, 3H), 3.86 (s, 3H), 5.04 (broad, 1H), 6.53 (d, J = 8.7 Hz, 1H), 7.90 (dd, J = 8.7 and 2.1 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H). ¹³C NMR (CDCl₃, 75.4 MHz) δ 33.3 (CH₂), 39.2 (CH₂), 51.3 (CH₃), 51.9 (CH₃), 83.9 (C), 108.5 (CH), 120.0 (C), 131.4 (CH), 140.8 (CH), 149.9 (C), 165.7 (C), 172.0 (C).

Methyl 3-[N-(2-iodo-4-methoxy carbonylphenyl)-N-methylamino]propionate (4b)
A mixture of methyl 3-[N-(2-iodo-4-methoxy carbonylphenyl)amino]propionate (984 mg, 2.71 mmol), K₂CO₃ (750 mg, 5.42 mmol), and iodomethane (1.7 mL, 27.1 mmol) in acetonitrile (6 mL) was stirred at 90°C in a sealed tube for 72 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH₂Cl₂. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO₂, CH₂Cl₂) to give methyl 3-[N-(2-iodo-4-methoxy carbonylphenyl)-N-methylamino]propionate (4b, 645 mg, 63%) and methyl 3-[N-(2-iodo-4-methoxy carbonylphenyl)amino]propionate (266 mg, 27%).

¹H NMR (CDCl₃, 300 MHz) δ 2.61 (t, J = 7.5 Hz, 2H), 2.79 (s, 3H), 3.41 (t, J = 7.5 Hz, 2H), 3.66 (s, 3H), 3.89 (s, 3H), 7.05 (d, J = 8.4 Hz, 1H), 7.97 (dd, J = 8.4 and 2.1 Hz, 1H), 8.50 (d, J = 2.1 Hz, 1H). ¹³C NMR (CDCl₃, 75.4 MHz) δ 32.7 (CH₂), 41.8 (CH₃), 51.5 (CH₂), 51.8 (CH₃), 52.1 (CH₃), 96.1 (C), 120.9 (CH), 126.4 (C), 130.4 (CH), 141.8 (CH), 157.7 (C), 165.4 (C), 172.3 (C). HRMS (ESI-TOF) calcd for C₁₃H₁₇INO₄: 378.0196 [M+H]+; found: 378.0198.

Benzyl 3-[N-(4-methylphenyl)amino]propionate
A solution of p-toluidine (0.5 g, 4.67 mmol) and benzyl acrylate (758 mg, 4.67 mmol) in acetic acid (0.25 mL) was stirred at 90°C in a sealed tube for 24 h. The reaction mixture was poured into cooled (ice) water, basified with Na₂CO₃, and extracted with Et₂O. The organic extracts were washed with saturated aqueous Na₂CO₃ solution, dried, and concentrated. The residue was purified by flash chromatography (SiO₂, from hexanes to hexanes-EtOAc 6%) to give benzyl 3-[N-(4-methylphenyl)amino]propionate (635 mg, 51%).

¹H NMR (CDCl₃, 300 MHz) δ 2.23 (s, 3H), 2.64 (t, J = 6.3 Hz, 2H), 3.44 (t, J = 6.3 Hz, 2H), 3.84 (broad, 1H), 5.13 (s, 2H), 6.52 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 7.30-7.42 (m, 5H). ¹³C NMR (CDCl₃, 75.4 MHz) δ 20.3 (CH₃), 33.9 (CH₂), 39.8 (CH₂), 66.3 (CH₂), 113.2
Benzyl 3-\[N-(2-iodo-4-methylphenyl)amino\]propionate

To a solution of benzyl 3-\[N-(4-methylphenyl)amino\]propionate (635 mg, 2.36 mmol) in a CH$_2$Cl$_2$ (12 mL)-MeOH (6 mL) mixture were added CaCO$_3$ (307 mg, 3.07 mmol) and BTMAICl$_2$ (904 mg, 2.60 mmol). The mixture was stirred at room temperature for 6 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to 85:15 hexanes-EtOAc) to give benzyl 3-\[N-(2-iodo-4-methylphenyl)amino\]propionate (870 mg, 93%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.20 (s, 3H), 2.69 (t, $J$ = 6.6 Hz, 2H), 3.49 (q, $J$ = 6.6 Hz, 2H), 4.33 (broad t, $J$ = 6.6 Hz, 1H), 5.16 (s, 2H), 6.50 (d, $J$ = 8.1 Hz, 1H), 7.01 (dd, $J$ = 8.1 and 1.5 Hz, 1H), 7.30-7.40 (m, 5H), 7.50 (d, $J$ = 1.5 Hz, 1H).

$^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 19.8 (CH$_3$), 34.0 (CH$_2$), 40.0 (CH$_2$), 66.6 (CH$_2$), 85.8 (C), 110.6 (CH), 128.3 (2 CH), 128.5 (C), 128.6 (CH), 130.0 (CH), 135.7 (C), 139.4 (CH), 144.5 (C), 171.8 (C).

HRMS (ESI-TOF) calcd for C$_{18}$H$_{21}$INO$_2$: 410.0612 [M+H]$^+$; found: 410.0600.

Benzyl 3-\[N-(2-iodo-4-methylphenyl)-N-methylamino\]propionate (4c)

A mixture of benzyl 3-\[N-(2-iodo-4-methylphenyl)amino\]propionate (870 mg, 2.2 mmol), K$_2$CO$_3$ (608 mg, 4.4 mmol), and iodomethane (1.1 mL, 17.6 mmol) in acetonitrile (7 mL) was stirred at 50°C in a sealed tube for 72 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH$_2$Cl$_2$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to 85:15 hexanes-EtOAc) to give benzyl 3-\[N-(2-iodo-4-methylphenyl)-N-methylamino\]propionate (4c, 825 mg, 92%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.26 (s, 3H), 2.56 (t, $J$ = 7.5 Hz, 2H), 2.67 (s, 3H), 3.29 (t, $J$ = 7.5 Hz, 2H), 5.10 (s, 2H), 6.98 (d, $J$ = 8.1 Hz, 1H), 7.10 (dd, $J$ = 8.1 and 1.5 Hz, 1H), 7.30-7.38 (m, 5H), 7.67 (d, $J$ = 1.5 Hz, 1H).

$^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 20.2 (CH$_3$), 33.1 (CH$_2$), 43.0 (CH$_3$), 52.1 (CH$_2$), 66.3 (CH$_2$), 99.8 (C), 121.9 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 129.7 (CH), 135.8 (C), 135.9 (C), 140.2 (CH), 150.8 (C), 172.0 (C). HRMS (ESI-TOF) calcd for C$_{18}$H$_{21}$NO$_2$: 410.0612 [M+H]$^+$; found: 410.0600.

Methyl 2-methyl-3-\[N-(4-methylphenyl)amino\]propionate

A solution of p-toluidine (1 g, 9.34 mmol) and methyl methacrylate (1.1 mL, 10.3 mmol) in acetic acid (0.5 mL) was stirred at 90°C in a sealed tube for 24 h. The reaction mixture was poured into cooled (ice) water, basified with Na$_2$CO$_3$, and extracted with Et$_2$O. The organic extracts were washed with saturated aqueous Na$_2$CO$_3$ solution, dried, and concentrated. The
residue was purified by flash chromatography (SiO\(_2\), from hexanes to 1:1 hexanes-EtOAc) to give methyl 2-methyl-3-[N-(4-methylphenyl)amino]propionate (332 mg, 17%).

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.22 (d, \(J = 6.9\) Hz, 3H), 2.23 (s, 3H), 2.80 (m, 1H), 3.19 (dd, \(J = 13.2\) and 7.8 Hz, 1H), 3.69 (s, 3H), 3.82 (broad, 1H), 6.53 (d, \(J = 8.1\) Hz, 2H), 6.98 (d, \(J = 8.1\) Hz, 2H).

\(^1\)C NMR (CDCl\(_3\), 75.4 MHz) \(\delta\) 15.0 (CH\(_3\)), 20.3 (CH\(_3\)), 39.2 (CH), 47.3 (CH\(_2\)), 51.7 (CH\(_3\)), 113.1 (CH), 126.7 (C), 129.7 (CH), 145.4 (C), 175.8 (C).

### Methyl 3-[N-(2-iodo-4-methylphenyl)amino]-2-methylpropionate

To a solution of methyl 2-methyl-3-[N-(4-methylphenyl)amino]propionate (332 mg, 1.60 mmol) in a CH\(_2\)Cl\(_2\) (10 mL)-MeOH (5 mL) mixture were added CaCO\(_3\) (208 mg, 2.08 mmol) and BTMAICl\(_2\) (613 mg, 1.76 mmol). The mixture was stirred at room temperature for 6 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried and concentrated. The residue was purified by flash chromatography (SiO\(_2\), CH\(_2\)Cl\(_2\)) to give methyl 3-[N-(2-iodo-4-methylphenyl)amino]-2-methylpropionate (410 mg, 77%).

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.24 (d, \(J = 7.2\) Hz, 3H), 2.20 (s, 3H), 2.83 (m, 1H), 3.24 (dd, \(J = 13.2\) and 6 Hz, 1H), 3.43 (dd, \(J = 13.2\) and 7.8 Hz, 1H), 3.72 (s, 3H), 4.40 (broad, 1H), 6.49 (d, \(J = 8.1\) Hz, 1H), 7.01 (dd, \(J = 8.1\) and 2.1 Hz, 1H), 7.49 (d, \(J = 2.1\) Hz, 1H).

\(^1\)C NMR (CDCl\(_3\), 75.4 MHz) \(\delta\) 15.0 (CH\(_3\)), 19.8 (CH\(_3\)), 38.9 (CH), 47.4 (CH\(_2\)), 51.9 (CH\(_3\)), 85.7 (C), 110.6 (CH), 128.4 (C), 130.0 (CH), 139.4 (CH), 144.5 (C), 175.4 (C).

### Methyl 3-[N-(2-iodo-4-methylphenyl)-N-methylamino]-2-methylpropionate (7)

A mixture of methyl 3-[N-(2-iodo-4-methylphenyl)amino]-2-methylpropionate (410 mg, 1.23 mmol), K\(_2\)CO\(_3\) (340 mg, 2.46 mmol), and iodomethane (0.6 mL, 9.84 mmol) in acetonitrile (5 mL) was stirred at 50°C in a sealed tube for 72 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH\(_2\)Cl\(_2\). The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO\(_2\), CH\(_2\)Cl\(_2\)) to give methyl 3-[N-(2-iodo-4-methylphenyl)-N-methylamino]-2-methylpropionate (7, 400 mg, 94%).

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.18 (d, \(J = 6.9\) Hz, 3H), 2.26 (s, 3H), 2.64 (s, 3H), 2.65 (m, 1H), 2.97 (dd, \(J = 12.6\) and 6.6 Hz, 1H), 3.28 (dd, \(J = 12.6\) and 8.1 Hz, 1H), 3.67 (s, 3H), 6.99 (d, \(J = 8.1\) Hz, 1H), 7.11 (dd, \(J = 8.1\) and 1.8 Hz, 1H), 7.67 (d, \(J = 1.8\) Hz, 1H).

\(^1\)C NMR (CDCl\(_3\), 75.4 MHz) \(\delta\) 15.5 (CH\(_3\)), 20.2 (CH\(_3\)), 38.5 (CH), 44.3 (CH\(_3\)), 51.8 (CH\(_3\)), 59.0 (CH\(_2\)), 99.8 (C), 122.0 (CH), 129.8 (CH), 135.8 (C), 140.2 (CH), 151.2 (C), 176.1 (C).

HRMS (ESI-TOF) calcd for C\(_{13}\)H\(_{19}\)INO\(_2\): 348.0455 [M+H]\(^+\); found: 348.0453.
Methyl 2,2-dimethyl-3-[N-(4-methylphenyl)amino]propionate

Following the previously described protocol for the preparation of closely related products, a solution of SDS (625 mg, 2.16 mmol) in water (29 mL) were successfully added p-toluidine (580 mg, 5.41 mmol), formaldehyde (37 wt. % in water, 0.45 mL), 1-methoxy-1-trimethylsiloxy-2-methylpropene (3.3 mL, 14.3 mmol), and 48% aqueous HBF₄ solution (0.1 mL, 0.55 mmol) at 0°C. After being stirred at the same temperature for 30 min, Dowex 1-X8 (100-200 mesh, Cl⁻ form) and water were added to quench the reaction, and the reaction mixture was further stirred for 10 min. The mixture was extracted with CH₂Cl₂ and the combined organic extracts were washed with brine, dried, and concentrated to give methyl 2,2-dimethyl-3-[N-(4-methylphenyl)amino]propionate (1.20 g, quantitative), which was used in the next step without purification.

¹H NMR (CDCl₃, 300 MHz) δ 1.26 (s, 6H), 2.22 (s, 3H), 3.21 (s, 2H), 3.67 (s, 3H), 3.80 (broad, 1H), 6.55 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H). ¹³C NMR (CDCl₃, 75.4 MHz) δ 20.3 (CH₃), 23.5 (CH₃), 43.7 (C), 52.0 (CH₃), 53.2 (CH₂), 113.1 (CH), 126.5 (C), 129.6 (CH), 146.2 (C), 177.5 (C).

Methyl 3-[N-(2-iodo-4-methylphenyl)-N-methylamino]-2,2-dimethylpropionate (10a)

To a solution of methyl 2,2-dimethyl-3-[N-(4-methylphenyl)amino]propionate (1.20 g, 5.41 mmol) in a CH₂Cl₂ (23 mL)-MeOH (10 mL) mixture were added CaCO₃ (720 mg, 7.2 mmol) and BTMAICl₂ (1.88 g, 5.41 mmol). The mixture was stirred at room temperature for 6 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried, and concentrated to give methyl 3-[N-(2-iodo-4-methylphenyl)amino]-2,2-dimethylpropionate (1.64 g, 87%), which was used in the next step without purification.

A mixture of methyl 3-[N-(2-iodo-4-methylphenyl)amino]-2,2-dimethylpropionate (1.53 g, 4.40 mmol), K₂CO₃ (1.22 g, 8.80 mmol), and iodomethane (2.2 mL, 35.3 mmol) in acetonitrile (15 mL) was stirred at 50°C in a sealed tube for 72 h. Iodomethane (2.2 mL, 35.3 mmol) was added and the mixture was stirred at 50°C in a sealed tube for an additional 72 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH₂Cl₂. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO₂, from hexanes to 8:2 hexanes-EtOAc) to give methyl 3-[N-(2-iodo-4-methylphenyl)-N-methylamino]-2,2-dimethylpropionate (10a, 1.10 g, 69%).

¹H NMR (CDCl₃, 300 MHz) δ 1.18 (s, 6H), 2.25 (s, 3H), 2.64 (s, 3H), 3.24 (s, 2H), 3.56 (s, 3H), 7.05-7.13 (m, 2H), 7.66 (m, 1H). ¹³C NMR (CDCl₃, 75.4 MHz) δ 20.2 (CH₃), 23.9 (CH₃), 44.6 (C), 46.8 (CH₃), 51.6 (CH₃), 65.1 (CH₂), 100.5 (C), 123.7 (CH), 129.9 (CH), 135.6 (C), 146.2 (C).

Methyl 3-[N-(2-iodo-4-methoxyphenyl)amino]-2,2-dimethylpropionate

To a solution of SDS (115 mg, 0.40 mmol) in water (5 mL) were successfully added 2-iodo-4-methoxyaniline (250 mg, 1 mmol), formaldehyde (37 wt. % in water, 80 µL), 1-methoxy-1-trimethylsiloxy-2-methylpropene (0.6 mL, 3 mmol), and 48% aqueous HBF$_4$ solution (18 µL, 0.1 mmol) at 0°C. After being stirred overnight at room temperature, Dowex 1-X8 (100-200 mesh, Cl$^-$ form) and water were added to quench the reaction, and the reaction mixture was further stirred for 10 min. The mixture was extracted with CH$_2$Cl$_2$ and the combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$, CH$_2$Cl$_2$) to give methyl 3-[N-(2-iodo-4-methoxyphenyl)amino]-2,2-dimethylpropionate (192 mg, 53%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.30 (s, 6H), 3.20 (s, 2H), 3.70 (s, 3H), 3.72 (s, 3H), 4.13 (broad, 1H), 6.55 (d, $J = 8.7$ Hz, 1H), 6.82 (dd, $J = 8.7$ and 3 Hz, 1H), 7.26 (d, $J = 3$ Hz, 1H).

$^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 23.6 (CH$_3$), 43.5 (C), 52.1 (CH$_3$), 53.9 (CH$_2$), 56.0 (CH$_3$), 85.8 (C), 111.6 (CH), 115.6 (CH), 124.4 (CH), 142.2 (C), 151.8 (C), 177.1 (C).

Methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)-N-methylamino]-2,2-dimethylpropionate (10b)

A mixture of methyl 3-[N-(2-iodo-4-methoxyphenyl)amino]-2,2-dimethylpropionate (192 mg, 0.53 mmol), K$_2$CO$_3$ (146 mg, 1.1 mmol), and iodomethane (0.26 mL, 4.2 mmol) in acetonitrile (5 mL) was stirred at 50°C in a sealed tube for 72 h. Iodomethane (0.26 mL, 4.2 mmol) was added and the mixture was stirred at 50°C in a sealed tube for an additional 72 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH$_2$Cl$_2$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to hexanes-EtOAc 2%) to give methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)-N-methylamino]-2,2-dimethylpropionate (10b, 140 mg, 70%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.18 (s, 6H), 2.61 (s, 3H), 3.20 (s, 2H), 3.55 (s, 3H), 3.75 (s, 3H), 6.87 (dd, $J = 8.7$ and 3 Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 1H), 7.36 (d, $J = 3$ Hz, 1H).

$^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 24.0 (CH$_3$), 44.5 (C), 47.0 (CH$_3$), 51.7 (CH$_3$), 55.6 (CH$_3$), 65.6 (CH$_2$), 101.2 (C), 115.2 (CH), 124.1 (CH), 124.4 (CH), 148.8 (C), 156.5 (C), 177.7 (C). HRMS (ESI-TOF) calcd for C$_{14}$H$_{21}$NO$_3$: 378.0561 [M+H]$^+$; found: 378.0553.

Methyl 3-[N-(4-methoxycarbonylphenyl)amino]-2,2-dimethylpropionate

To a solution of SDS (575 mg, 2 mmol) in water (25 mL) were successfully added methyl 4-aminobenzoate (750 mg, 4.96 mmol), formaldehyde (37 wt. % in water, 0.4 mL), 1-methoxy-1-trimethylsiloxy-2-methylpropene (3 mL, 15 mmol), and 48% aqueous HBF$_4$ solution (90 µL,
0.5 mmol) at 0°C. After being stirred at room temperature for 4 h, Dowex 1-X 8 (100-200 mesh, Cl⁻ form) and water were added to quench the reaction, and the reaction mixture was further stirred for 10 min. The mixture was extracted with CH₂Cl₂ and the combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO₂, from hexanes to hexanes-EtOAc 7:3) to give methyl 3-[N-(4-methoxycarbonylphenyl)amino]-2,2-dimethylpropionate (507 mg, 39%).

1H NMR (CDCl₃, 300 MHz) δ 1.26 (s, 6H), 3.29 (s, 2H), 3.67 (s, 3H), 3.83 (s, 3H), 4.53 (broad, 1H), 6.57 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H). 13C NMR (CDCl₃, 75.4 MHz) δ 23.4 (CH₃), 43.7 (C), 51.4 (CH₃), 51.5 (CH₂), 52.0 (CH₃), 111.4 (CH), 118.2 (C), 131.4 (CH), 152.1 (C), 167.1 (C), 177.1 (C).

Methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)amino]-2,2-dimethylpropionate

To a solution of methyl 3-[N-(4-methoxycarbonylphenyl)amino]-2,2-dimethylpropionate (507 mg, 1.9 mmol) in a CH₂Cl₂ (12 mL)-MeOH (5 mL) mixture were added CaCO₃ (250 mg, 2.5 mmol) and BTMAICl₂ (0.8 g, 2.3 mmol). After stirring at room temperature for 24 h, CaCO₃ (250 mg, 2.5 mmol) and BTMAICl₂ (0.4 g, 1.15 mmol) were added. The mixture was stirred at room temperature for 6 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO₂, CH₂Cl₂) to give methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)amino]-2,2-dimethylpropionate (582 mg, 78%).

1H NMR (CDCl₃, 300 MHz) δ 1.31 (s, 6H), 3.32 (s, 2H), 3.72 (s, 3H), 3.85 (s, 3H), 5.15 (broad, 1H), 6.54 (d, J = 8.4 Hz, 1H), 7.87 (dd, J = 8.4 and 1.8 Hz, 1H), 8.33 (d, J = 1.8 Hz, 1H). 13C NMR (CDCl₃, 75.4 MHz) δ 23.5 (CH₃), 43.5 (C), 51.7 (CH₃), 52.1 (CH₂), 52.3 (CH₃), 84.0 (C), 108.8 (CH), 119.7 (C), 131.4 (CH), 140.8 (CH), 150.6 (C), 165.9 (C), 176.8 (C).

Methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)-N-methylamino]-2,2-dimethylpropionate (10c)

A mixture of methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)amino]-2,2-dimethylpropionate (563 mg, 1.44 mmol), K₂CO₃ (400 mg, 2.89 mmol), and iodomethane (0.9 mL, 14.5 mmol) in acetonitrile (10 mL) was stirred at 80°C in a sealed tube for 72 h. Iodomethane (0.9 mL, 14.5 mmol) was added and the mixture was stirred at 80°C in a sealed tube for an additional 72 h. The solvent was removed in vacuo, and the residue was partitioned between water and CH₂Cl₂. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO₂, from hexanes to hexanes-EtOAc 8%) to give methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)-N-methylamino]-2,2-dimethylpropionate (10c, 345 mg, 59%) and
methyl 3-[N-(2-iodo-4-methoxycarbonylphenyl)amino]-2,2-dimethylpropionate (225 mg, 40%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.18 (s, 6H), 2.78 (s, 3H), 3.38 (s, 2H), 3.55 (s, 3H), 3.88 (s, 3H), 7.18 (d, $J = 8.4$ Hz, 1H), 7.95 (dd, $J = 8.4$ and 2.1 Hz, 1H), 8.49 (d, $J = 2.1$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 23.8 (CH$_3$), 44.7 (C), 46.1 (CH$_3$), 51.7 (CH$_3$), 52.8 (CH$_3$), 64.0 (CH$_2$), 97.5 (C), 122.8 (CH), 126.4 (C), 130.4 (CH), 141.7 (CH), 159.6 (C), 165.4 (C), 177.3 (C). HRMS (ESI-TOF) calcd for C$_{15}$H$_{21}$INO$_4$: 406.0510 [M+H]$^+$; found: 406.0496.

Methyl 2-methyl-3-[N-(4-methylphenyl)amino]-2-phenylpropionate

To a solution of SDS (185 mg, 0.64 mmol) in water (8 mL) were successfully added p-toluidine (170 mg, 1.59 mmol), formaldehyde (37 wt. % in water, 0.13 mL), 1-methoxy-1-trimethylsiloxo-2-phenylpropene (1.5 g, 6.35 mmol), and 48% aqueous HBF$_4$ solution (30 µL, 0.17 mmol) at 0°C. After being stirred at the same temperature for 5 h, Dowex 1-X8 (100-200 mesh, Cl$^-$ form) and water were added to quench the reaction, and the reaction mixture was further stirred for 10 min. The mixture was extracted with CH$_2$Cl$_2$ and the combined organic extracts were washed with brine and concentrated. The residue was dissolved in Et$_2$O and extracted with 2N HCl. The aqueous layer was alkalinized with Na$_2$CO$_3$ and extracted with CH$_2$Cl$_2$. The organic extracts were dried and concentrated to give methyl 2-methyl-3-[N-(4-methylphenyl)amino]-2-phenylpropionate (250 mg, 55%), which was used in the next step without purification.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.68 (s, 3H), 2.21 (s, 3H), 3.45 (d, $J = 12.6$ Hz, 1H), 3.68 (s, 3H), 3.72 (d, $J = 12.6$ Hz, 1H), 6.50 (d, $J = 8.4$ Hz, 2H), 6.94 (d, $J = 8.4$ Hz, 2H), 7.24-7.40 (m, 5H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 20.3 (CH$_3$), 21.5 (CH$_3$), 51.9 (C), 52.3 (CH$_3$), 52.6 (CH$_2$), 113.1 (CH), 126.1 (CH), 126.6 (C), 127.2 (CH), 128.6 (CH), 129.6 (CH), 141.3 (C), 146.1 (C), 179.9 (C).

Methyl 3-[N-(2-iodo-4-methylphenyl)amino]-2-methyl-2-phenylpropionate

To a solution of methyl 2-methyl-3-[N-(4-methylphenyl)amino]-2-phenylpropionate (250 mg, 0.88 mmol) in a CH$_2$Cl$_2$ (12 mL)-MeOH (5 mL) mixture were added CaCO$_3$ (114 mg, 1.14 mmol) and BTMAI$\text{Cl}_2$ (334 mg, 0.96 mmol). The mixture was stirred at room temperature for 6 h and then filtered. The solution was concentrated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to hexanes-EtOAc 8%) to give methyl 3-[N-(2-iodo-4-methylphenyl)amino]-2-methyl-2-phenylpropionate (257 mg, 71%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.70 (s, 3H), 2.17 (s, 3H), 3.50 (dd, $J = 12.6$ and 5.1 Hz, 1H), 3.71 (m, 1H), 3.72 (s, 3H), 4.18 (broad t, $J = 6$ Hz, 1H), 6.47 (d, $J = 8.4$ Hz, 1H), 6.96 (dd, $J =
8.4 and 1.8 Hz, 1H), 7.24-7.40 (m, 5H), 7.45 (d, J = 1.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) δ 19.7 (CH$_3$), 21.4 (CH$_3$), 51.7 (C), 52.4 (CH$_3$), 52.6 (CH$_2$), 85.9 (C), 110.8 (CH), 126.2 (CH), 127.4 (CH), 128.1 (C), 128.7 (CH), 129.8 (CH), 139.2 (CH), 140.9 (C), 145.2 (C), 175.7 (C).

**Methyl 3-[[N-(2-iodo-4-methylphenyl)-N-methylamino]-2-methyl-2-phenylpropionate (10d)]**

A mixture of methyl 3-[[N-(2-iodo-4-methylphenyl)amino]-2-methyl-2-phenylpropionate (257 mg, 0.63 mmol), K$_2$CO$_3$ (174 mg, 1.26 mmol), and iodomethane (0.4 mL, 6.3 mmol) in acetonitrile (5 mL) was stirred at 90°C in a sealed tube for 72 h. The solvent was removed *in vacuo*, and the residue was partitioned between water and CH$_2$Cl$_2$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, from CH$_2$Cl$_2$ to CH$_2$Cl$_2$-MeOH 2%) to give methyl 3-[[N-(2-iodo-4-methylphenyl)-N-methylamino]-2-methyl-2-phenylpropionate (10d, 268 mg, quantitative).

$^1$H NMR (CDCl$_3$, 300 MHz) δ 1.66 (s, 3H), 2.25 (s, 3H), 2.52 (s, 3H), 3.42 (d, J = 13.8 Hz, 1H), 3.60 (s, 3H), 3.88 (d, J = 13.8 Hz, 1H), 7.08 (m, 2H), 7.20-7.38 (m, 5H), 7.65 (s, 1H).

$^{13}$C NMR (CDCl$_3$, 75.4 MHz) δ 20.2 (CH$_3$), 21.6 (CH$_3$), 47.2 (CH$_3$), 52.0 (CH$_3$), 52.6 (C), 65.1 (CH$_2$), 100.7 (C), 124.1 (CH), 126.2 (CH), 126.9 (CH), 128.3 (CH), 130.0 (CH), 136.6 (C), 140.0 (CH), 142.2 (C), 153.6 (C), 175.7 (C). HRMS (ESI-TOF) calcd for C$_{19}$H$_{23}$INO$_2$: 424.0768 [M+H]$^+$; found: 424.0752.

**Methyl 3-[N-(2-iodo-5-methylphenyl)amino]-2,2-dimethylpropionate**

To a solution of SDS (390 mg, 1.36 mmol) in water (18 mL) were successfully added 2-iodo-5-methylaniline (790 mg, 3.39 mmol), formaldehyde (37 wt. % in water, 0.28 mL), 1-methoxy-1-trimethylsiloxy-2-methylpropene (2 mL, 10 mmol), and 48% aqueous HBF$_4$ solution (62 µL, 0.34 mmol) at 0°C. After being stirred at room temperature for 24 h, Dowex 1-X 8 (100-200 mesh, Cl$^-$ form) and water were added to quench the reaction, and the reaction mixture was further stirred for 10 min. The mixture was extracted with CH$_2$Cl$_2$ and the combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to hexanes-EtOAc 4%) to give methyl 3-[N-(2-iodo-5-methylphenyl)amino]-2,2-dimethylpropionate (198 mg, 17%).

$^1$H NMR (CDCl$_3$, 300 MHz) δ 1.31 (s, 6H), 2.26 (s, 3H), 3.25 (s, 2H), 3.71 (s, 3H), 6.28 (dd, J = 7.8 and 2.1 Hz, 1H), 6.41 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100.5 MHz) δ 21.4 (CH$_3$), 23.6 (CH$_3$), 43.4 (C), 52.1 (CH$_3$), 52.8 (CH$_2$), 81.9 (C), 111.6 (CH), 119.8 (CH), 138.6 (CH), 139.4 (C), 147.1 (C), 177.1 (C).
**Methyl 3-[N-(2-iodo-5-methylphenyl)-N-methylamino]-2,2-dimethylpropionate (12a)**

A mixture of methyl 3-[N-(2-iodo-5-methylphenyl)amino]-2,2-dimethylpropionate (198 mg, 0.57 mmol), K$_2$CO$_3$ (158 mg, 1.14 mmol), and iodomethane (0.7 mL, 11.3 mmol) in acetonitrile (5 mL) was stirred at 90°C in a sealed tube for 68 h. The solvent was removed *in vacuo*, and the residue was partitioned between water and CH$_2$Cl$_2$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to hexanes-EtOAc 2%) to give methyl 3-[N-(2-iodo-5-methylphenyl)-N-methylamino]-2,2-dimethylpropionate (12a, 140 mg, 68%).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.19 (s, 6H), 2.28 (s, 3H), 2.66 (s, 3H), 3.26 (s, 2H), 3.56 (s, 3H), 6.61 (dd, $J = 8$ and 1.6 Hz, 1H), 7.00 (d, $J = 1.6$ Hz, 1H), 7.67 (d, $J = 8$ Hz, 1H).

$^{13}$C NMR (CDCl$_3$, 100.5 MHz) $\delta$ 21.0 (CH$_3$), 23.9 (CH$_3$), 44.6 (CH$_3$), 46.6 (CH$_3$), 51.6 (CH$_3$), 64.9 (CH$_2$), 96.2 (C), 125.1 (CH), 126.8 (CH), 139.2 (C), 139.4 (CH), 155.5 (C), 177.8 (C). HRMS (ESI-TOF) calcd for C$_{14}$H$_{21}$INO$_2$: 362.0611 [M+H]$^+$; found: 362.0612.

**Methyl 3-[N-(5-chloro-2-iodophenyl)-N-methylamino]-2,2-dimethylpropionate (12b)**

Sodium (235 mg, 10.2 mmol) was slowly added to MeOH (10 mL). Once the evolution of hydrogen had ceased, 5-chloro-2-iodoaniline (515 mg, 2.03 mmol) was added and the resulting solution was poured onto a suspension of paraformaldehyde (85 mg, 2.83 mmol) in MeOH (5 mL). The resulting mixture was stirred at room temperature for 5 h and then hydrolyzed with cool water and extracted with Et$_2$O. The organic extracts were washed with water, dried, and concentrated in vacuo, taking care that the temperature remained below 25 °C. A 1:1 mixture of 5-chloro-2-iodoaniline and N-(methoxymethyl)-5-chloro-2-iodoaniline was obtained. This mixture was dissolved in dichloromethane (5 mL) and the solution was cooled to -78°C. A solution of BF$_3$·Et$_2$O (0.3 mL, 2.4 mmol) in dichloromethane (3 mL) was added dropwise, the resulting mixture was stirred at -78°C for 5 min and then a solution of 1-methoxy-1-trimethylsiloxy-2-methylpropene (0.25 mL, 1.25 mmol) in dichloromethane (3 mL) was added. After 4 h at -78°C, the reaction mixture was allowed to reach room temperature, poured into brine, and extracted with dichloromethane. The organic extracts were dried and concentrated to give a 1:5 mixture of 5-chloro-2-iodoaniline and methyl 3-[N-(5-chloro-2-iodophenyl)amino]-2,2-dimethylpropionate. The mixture was dissolved in CH$_3$CN (5 mL) and K$_2$CO$_3$ (0.25 g, 1.8 mmol) and iodomethane (0.56 mL, 9 mmol) were added. After 72 h at 90 °C in a sealed tube, iodomethane (1.5 mL, 24 mmol) was added, and heating was maintained for 24 h. The solvent was removed in vacuo and the residue was partitioned.

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between dichloromethane and water. The organic extracts were dried and concentrated. Chromatography (from hexanes to hexanes-ETAOAc 1%) yielded 12b (107 mg, 14%).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.19 (s, 6H), 2.68 (s, 3H), 3.26 (s, 2H), 3.57 (s, 3H), 6.79 (dd, $J$ = 8.4 and 2 Hz, 1H), 7.15 (d, $J$ = 2 Hz, 1H), 7.73 (d, $J$ = 8.4 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100.5 MHz) $\delta$ 23.9 (CH$_3$), 44.6 (C), 46.5 (CH$_3$), 51.7 (CH$_3$), 64.6 (CH$_2$), 97.2 (C), 124.7 (CH), 125.8 (CH), 134.8 (C), 140.5 (CH), 156.8 (C), 177.5 (C).

Methyl 3-[N-(2-iodophenyl)-N-(methoxycarbonyl)amino]propionate (14a)
A solution of 2-iodoaniline (1 g, 4.56 mmol) and methyl acrylate (1.24 mL, 13.7 mmol) in acetic acid (0.5 mL) was stirred at 90°C in a sealed tube for 24 h. The reaction mixture was poured into cooled (ice) water, basified with Na$_2$CO$_3$, and extracted with Et$_2$O. The organic extracts were washed with saturated aqueous Na$_2$CO$_3$ solution, dried, and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to 3:7 hexanes-CH$_2$Cl$_2$) to give methyl 3-[N-(2-iodophenyl)amino]propionate (245 mg, 18%).

A mixture of methyl 3-[N-(2-iodophenyl)amino]propionate (245 mg, 0.80 mmol) and K$_2$CO$_3$ (221 mg, 1.60 mmol) in methyl chloroformate (5 mL) was stirred at 60°C for 12 h. The mixture was poured into water and extracted with CH$_2$Cl$_2$. The organic extracts were dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, from hexanes to 7:3 hexanes-CH$_2$Cl$_2$) to give methyl 3-[N-(2-iodophenyl)-N-(methoxycarbonyl)amino]propionate (14a, 269 mg, 93%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.69 (t, $J$ = 7.5 Hz, 2H), 3.63 (s, 3H), 3.65 (s, 3H), 3.66 (m, 1H), 4.13 (dt, $J$ = 13.8 and 7.5 Hz, 1H), 7.03 (ddd, $J$ = 7.8, 7.2, and 1.5 Hz, 1H), 7.20 (d, $J$ = 7.5 Hz, 1H), 7.37 (ddd, $J$ = 7.8, 7.5, and 1.5 Hz, 1H), 7.89 (d, $J$ = 7.2 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 33.0 (CH$_2$), 46.1 (CH$_2$), 51.6 (CH$_3$), 53.1 (CH$_3$), 100.2 (C), 129.2 (CH), 129.5 (CH), 139.7 (CH), 143.6 (C), 155.2 (C), 171.7 (C). HRMS (ESI-TOF) calcd for C$_{12}$H$_{15}$INO$_4$: 364.0040 [M+H]$^+$; found: 364.0031.

Methyl 3-[N-(2-iodophenyl)-N-(p-toluenesulfonyl)amino]propionate (14b)
A solution of methyl 3-[N-(2-iodophenyl)amino]propionate (348 mg, 1.14 mmol) and p-toluenesulfonyl chloride (2.17 g, 11.4 mmol) in pyridine (12 mL) was stirred at reflux for 24 h. The mixture was poured into water and extracted with Et$_2$O. The organic extracts were washed with 1N hydrochloric acid and 10% aqueous KOH solution, dried and concentrated. The residue was purified by flash chromatography (SiO$_2$, from CH$_2$Cl$_2$ to CH$_2$Cl$_2$-MeOH 5%) to give methyl 3-[N-(2-iodophenyl)-N-(p-toluenesulfonyl)amino]propionate (14b, 407 mg, 78%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.45 (s, 3H), 2.66 (m, 2H), 3.59 (s, 3H), 3.70 (ddd, $J$ = 14.1, 9.3, and 6 Hz, 1H), 3.98 (ddd, $J$ = 14.1, 9.6, and 6.3 Hz, 1H), 6.96 (dd, $J$ = 7.8 and 1.5 Hz,
1H), 7.04 (dd, J = 7.8, 7.5, and 1.5 Hz, 1H), 7.26-7.32 (m, 3H), 7.65 (d, J = 8.4 Hz, 2H), 7.92 (dd, J = 7.8 and 1.5 Hz, 1H). 13C NMR (CDCl3, 75.4 MHz) δ 21.5 (CH3), 33.4 (CH2), 47.4 (CH2), 51.6 (CH3), 102.9 (C), 128.0 (CH), 128.8 (CH), 129.5 (CH), 130.0 (CH), 130.2 (CH), 135.6 (C), 140.4 (CH), 141.2 (C), 143.8 (C), 171.1 (C). HRMS (ESI-TOF) calcd for C17H19NO4S: 460.0074 [M+H]+; found: 460.0056.

Representative procedure for the Pd-catalyzed nucleophilic attack at the alkoxy carbonyl group:
A mixture of methyl 3-[(N-(2-iodo-4-methylphenyl)-N-methylamino)propionate (1a, 75 mg, 0.23 mmol), K3PO4 (143 mg, 0.68 mmol), Et3N (0.32 mL, 2.25 mmol), and Pd(PPh3)4 (52 mg, 0.045 mmol) in toluene (6 mL) was stirred at 110°C in a sealed tube for 72 h. The reaction mixture was poured into water and extracted with Et2O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO2, from hexanes to hexanes-EtOAc 8%) to give 1,6-dimethyl-2,3-dihydro-1H-quinolin-4-one (2, 27 mg, 65%) and methyl 3-[N-methyl-N-(4-methylphenyl)amino]propionate (3, 14 mg, 30%).

1,6-Dimethyl-2,3-dihydro-1H-quinolin-4-one (2)
1H NMR (CDCl3, 300 MHz) δ 2.25 (s, 3H), 2.72 (t, J = 6.9 Hz, 2H), 2.96 (s, 3H), 3.42 (t, J = 6.9 Hz, 2H), 6.65 (d, J = 8.7 Hz, 1H), 7.23 (dd, J = 8.7 and 2.1 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H). 13C NMR (CDCl3, 75.4 MHz) δ 20.1 (CH3), 38.5 (CH2), 39.5 (CH3), 51.7 (CH2), 113.4 (CH), 119.8 (C), 126.4 (C), 127.7 (CH), 136.5 (CH), 151.0 (C), 193.9 (C). Anal. Calcd for C11H13NO: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.70; H, 7.53; N, 8.01. HRMS (ESI-TOF) calcd for C11H14NO: 176.1069 [M+H]+; found: 176.1069.

Methyl 3-[N-methyl-N-(4-methylphenyl)amino]propionate (3)
1H NMR (CDCl3, 300 MHz) δ 2.25 (s, 3H), 2.56 (t, J = 7.5 Hz, 2H), 2.90 (s, 3H), 3.64 (t, J = 7.5 Hz, 2H), 3.67 (s, 3H), 6.67 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H). 13C NMR (CDCl3, 75.4 MHz) δ 20.2 (CH3), 31.4 (CH2), 38.4 (CH3), 49.0 (CH2), 51.7 (CH3), 113.0 (CH), 126.2 (C), 129.7 (CH), 146.6 (C), 172.8 (C).

6-Methoxy-1-methyl-2,3-dihydro-1H-quinolin-4-one (5a)
1H NMR (CDCl3, 300 MHz) δ 2.73 (t, J = 7.2 Hz, 2H), 2.94 (s, 3H), 3.39 (t, J = 7.2 Hz, 2H), 3.79 (s, 3H), 6.71 (d, J = 9 Hz, 1H), 7.07 (dd, J = 9 and 3 Hz, 1H), 7.41 (d, J = 3 Hz, 1H). 13C NMR (CDCl3, 75.4 MHz) δ 38.5 (CH2), 39.7 (CH3), 51.9 (CH2), 55.7 (CH3), 108.9 (CH), 115.0 (CH), 120.0 (C), 124.9 (CH), 148.3 (C), 151.6 (C), 193.6 (C). Anal. Calcd for C11H13NO2: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.83; H, 6.93; N, 7.13.
Methyl 3-[N-(4-methoxyphenyl)-N-methylamino]propionate (6a)

$^1$H NMR (CDCl$_3$, 300 MHz) δ 2.54 (t, $J = 7.2$ Hz, 2H), 2.86 (s, 3H), 3.59 (t, $J = 7.2$ Hz, 2H), 3.66 (s, 3H), 3.76 (s, 3H), 6.72-6.86 (m, 4H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) δ 31.4 (CH$_2$), 38.9 (CH$_3$), 49.9 (CH$_2$), 51.7 (CH$_3$), 55.7 (CH$_3$), 114.8 (CH), 115.1 (CH), 143.4 (C), 152.1 (C), 172.8 (C). HRMS (ESI-TOF) calcd for C$_{12}$H$_{18}$NO$_3$: 224.1281 [M+H]$^+$; found: 224.1283.

Methyl 1-methyl-4-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate (5b)

$^1$H NMR (CDCl$_3$, 300 MHz) δ 2.77 (t, $J = 7.2$ Hz, 2H), 3.09 (s, 3H), 3.58 (t, $J = 7.2$ Hz, 2H), 3.87 (s, 3H), 6.71 (d, $J = 9$ Hz, 1H), 8.04 (dd, $J = 9$ and 2.4 Hz, 1H), 8.57 (d, $J = 2.4$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) δ 37.7 (CH$_2$), 39.3 (CH$_3$), 50.9 (CH$_2$), 51.8 (CH$_3$), 112.8 (CH), 118.4 (C), 118.7 (C), 130.5 (CH), 136.1 (CH), 154.7 (C), 166.7 (C), 192.6 (C). Anal. Calcd for C$_{12}$H$_{13}$NO$_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.97; H, 6.10; N, 5.85.

Methyl 3-[N-(4-methoxycarbonylphenyl)-N-methylamino]propionate (6b)

$^1$H NMR (CDCl$_3$, 300 MHz) δ 2.61 (t, $J = 7.2$ Hz, 2H), 3.03 (s, 3H), 3.68 (s, 3H), 3.74 (t, $J = 7.2$ Hz, 2H), 3.86 (s, 3H), 6.66 (d, $J = 9$ Hz, 2H), 7.90 (d, $J = 9$ Hz, 2H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) δ 31.6 (CH$_2$), 38.3 (CH$_3$), 48.0 (CH$_2$), 51.5 (CH$_3$), 51.8 (CH$_3$), 110.7 (CH), 117.4 (C), 131.3 (CH), 151.6 (C), 167.2 (C), 172.1 (C). HRMS (ESI-TOF) calcd for C$_{13}$H$_{18}$NO$_4$: 252.1230 [M+H]$^+$; found: 252.1226.

Benzyl 3-[N-methyl-N-(4-methylphenyl)amino]propionate (6c)

$^1$H NMR (CDCl$_3$, 300 MHz) δ 2.24 (s, 3H), 2.60 (t, $J = 7.2$ Hz, 2H), 2.87 (s, 3H), 3.65 (t, $J = 7.2$ Hz, 2H), 5.10 (s, 2H), 6.66 (d, $J = 8.4$ Hz, 2H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.30-7.38 (m, 5H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) δ 20.2 (CH$_3$), 31.7 (CH$_2$), 38.3 (CH$_3$), 49.0 (CH$_2$), 66.4 (CH$_2$), 113.1 (CH), 126.2 (C), 128.2 (CH), 128.5 (CH), 129.7 (CH), 135.8 (C), 146.6 (C), 172.2 (C). HRMS (ESI-TOF) calcd for C$_{18}$H$_{22}$NO$_2$: 284.1645 [M+H]$^+$; found: 284.1639.

1,3,6-Trimethyl-2,3-dihydro-1H-quinolin-4-one (8)

$^1$H NMR (CDCl$_3$, 300 MHz) δ 1.21 (d, $J = 7.2$ Hz, 3H), 2.26 (s, 3H), 2.60 (t, $J = 7.2$ Hz, 2H), 2.87 (s, 3H), 3.65 (t, $J = 7.2$ Hz, 2H), 5.10 (s, 2H), 6.66 (d, $J = 8.4$ Hz, 2H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.30-7.38 (m, 5H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) δ 20.2 (CH$_3$), 31.7 (CH$_2$), 38.3 (CH$_3$), 49.0 (CH$_2$), 66.4 (CH$_2$), 113.1 (CH), 126.2 (C), 128.2 (CH), 128.5 (CH), 129.7 (CH), 135.8 (C), 146.6 (C), 172.2 (C). HRMS (ESI-TOF) calcd for C$_{18}$H$_{22}$NO$_2$: 284.1645 [M+H]$^+$; found: 284.1639.
Methyl 2-methyl-3-[N-methyl-N-(4-methylphenyl)amino]propionate (9)

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.16 (d, $J = 7.2$ Hz, 3H), 2.24 (s, 3H), 2.90 (m, 1H), 2.91 (s, 3H), 3.27 (d, $J = 14.7$ and 6.6 Hz, 1H), 3.62 (s, 3H), 3.64 (d, $J = 14.7$ and 7.8 Hz, 1H), 6.63 (d, $J = 8.4$ Hz, 2H), 7.03 (d, $J = 8.4$ Hz, 2H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 15.1 (CH$_3$), 20.2 (CH$_3$), 38.3 (CH), 51.7 (CH$_3$), 56.7 (CH$_2$), 112.5 (CH), 125.8 (C), 129.6 (CH), 146.9 (C), 176.1 (C).

1,3,3,6-Tetramethyl-2,3-dihydro-1H-quinolin-4-one (11a)

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.16 (s, 6H), 2.26 (s, 3H), 2.99 (s, 3H), 3.13 (s, 2H), 6.64 (d, $J = 8.7$ Hz, 1H), 7.23 (dd, $J = 8.7$ and 2.4 Hz, 1H), 7.73 (dd, $J = 2.4$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 20.1 (CH$_3$), 22.0 (CH$_3$), 39.3 (CH$_3$), 41.8 (C), 63.5 (CH$_2$), 112.9 (CH), 117.9 (C), 126.1 (C), 128.3 (CH), 136.1 (CH), 149.9 (C), 198.8 (C). Anal. Calcd for C$_{13}$H$_{17}$NO: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.63; H, 8.48; N, 6.81.

6-Methoxy-1,3,3-trimethyl-2,3-dihydro-1H-quinolin-4-one (11b)

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.17 (s, 6H), 2.98 (s, 3H), 3.11 (s, 2H), 3.79 (s, 3H), 6.70 (d, $J = 9$ Hz, 1H), 7.07 (dd, $J = 9$ and 2.7 Hz, 1H), 7.43 (d, $J = 2.7$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 22.0 (CH$_3$), 39.6 (CH$_3$), 41.9 (C), 55.7 (CH$_3$), 63.8 (CH$_2$), 109.5 (CH), 114.6 (CH), 118.1 (C), 124.5 (CH), 147.2 (C), 151.5 (C), 198.6 (C). Anal. Calcd for C$_{13}$H$_{17}$NO$_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.75; H, 7.96; N, 6.17.

Methyl 1,3,3-trimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate (11c)

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.15 (s, 6H), 3.10 (s, 3H), 3.26 (s, 2H), 3.85 (s, 3H), 6.69 (d, $J = 9$ Hz, 1H), 8.00 (dd, $J = 9$ and 2.1 Hz, 1H), 8.57 (d, $J = 2.1$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 21.9 (CH$_3$), 39.2 (CH$_3$), 41.4 (C), 51.7 (CH$_3$), 62.7 (CH$_2$), 112.3 (CH), 117.0 (C), 118.4 (C), 131.2 (CH), 135.6 (CH), 153.6 (C), 166.7 (C), 197.5 (C). Anal. Calcd for C$_{14}$H$_{17}$NO$_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.88; H, 6.86; N, 5.48.

1,3,6-Trimethyl-3-phenyl-2,3-dihydro-1H-quinolin-4-one (11d)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.46 (s, 3H), 2.23 (s, 3H), 2.99 (s, 3H), 3.44 (d, $J = 12.8$ Hz, 1H), 3.73 (d, $J = 12.8$ Hz, 1H), 6.54 (d, $J = 8.4$ Hz, 1H), 7.15-7.31 (m, 6H), 7.79 (s, 1H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 20.1 (CH$_3$), 23.2 (CH$_3$), 39.1 (CH$_3$), 49.7 (C), 61.9 (CH$_2$), 113.0 (CH), 118.9 (C), 126.2 (C), 126.3 (CH), 126.9 (CH), 128.3 (CH), 128.5 (CH), 136.3 (CH), 140.9 (C), 149.7 (C), 196.5 (C). Anal. Calcd for C$_{18}$H$_{19}$NO: C, 81.47; H, 7.22; N, 5.28. Found: C, 79.86; H, 7.20; N, 5.13.
1,3,3,7-Tetramethyl-2,3-dihydro-1H-quinolin-4-one (13a)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.15 (s, 6H), 2.33 (s, 3H), 3.01 (s, 3H), 3.15 (s, 2H), 6.50 (s, 1H), 6.57 (d, $J$ = 8 Hz, 1H), 7.82 (d, $J$ = 8 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 22.0 (CH$_3$), 23.3 (CH$_3$), 39.2 (CH$_3$), 41.6 (C), 63.5 (CH$_2$), 112.9 (CH), 116.0 (C), 118.5 (CH), 128.8 (CH), 145.9 (C), 151.7 (C), 198.4 (C). Calcd for C$_{13}$H$_{17}$NO: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.63; H, 8.48; N, 6.81.

7-Chloro-1,3,3-trimethyl-2,3-dihydro-1H-quinolin-4-one (13b)

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.16 (s, 6H), 3.02 (s, 3H), 3.19 (s, 2H), 6.69 (s, 1H), 6.70 (dd, $J$ = 7.8 and 1.8 Hz, 1H), 7.84 (d, $J$ = 7.8 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 21.9 (CH$_3$), 39.2 (CH$_3$), 41.6 (C), 63.2 (CH$_2$), 112.5 (CH), 116.5 (C), 117.5 (CH), 130.3 (CH), 141.4 (C), 152.0 (C), 197.7 (C). Calcd for C$_{12}$H$_{14}$ClNO: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.59; H, 6.20; N, 6.71.

Methyl 3-[N-(methoxycarbonyl)-N-phenylamino]propionate (15a)

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.61 (t, $J$ = 7.5 Hz, 2H), 3.60 (s, 3H), 3.68 (s, 3H), 3.98 (t, $J$ = 7.5 Hz, 2H), 7.15-7.40 (m, 5H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 33.2 (CH$_2$), 46.5 (CH$_2$), 51.6 (CH$_3$), 52.9 (CH$_3$), 126.9 (CH), 127.3 (CH), 129.1 (CH), 141.3 (C), 155.8 (C), 171.7 (C). HRMS (ESI-TOF) calcd for C$_{12}$H$_{15}$NO$_4$Na: 260.0893 [M+Na]$^+$; found: 260.0885.

Methyl 3-[N-phenyl-N-(p-toluenesulfonyl)amino]propionate (15b)

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.43 (s, 3H), 2.56 (t, $J$ = 7.5 Hz, 2H), 3.60 (s, 3H), 3.84 (t, $J$ = 7.5 Hz, 2H), 7.04 (m, 2H), 7.23-7.33 (m, 5H), 7.47 (d, $J$ = 8.7 Hz, 2H). $^{13}$C NMR (CDCl$_3$, 75.4 MHz) $\delta$ 21.6 (CH$_3$), 34.0 (CH$_2$), 46.8 (CH$_2$), 51.7 (CH$_3$), 127.7 (CH), 128.1 (CH), 128.9 (CH), 129.1 (CH), 129.4 (CH), 135.1 (C), 139.0 (C), 143.5 (C), 171.3 (C). HRMS (ESI-TOF) calcd for C$_{17}$H$_{20}$NO$_4$S: 334.1108 [M+H]$^+$; found: 334.1110.

Palladium complex 16

To a solution of methyl 3-[N-(2-iodo-4-methylphenyl)-N-methylamino]propionate (1a, 40 mg, 0.12 mmol) in benzene (10 mL) were added Pd$_2$(dba)$_3$ (77 mg, 0.084 mmol) and PPh$_3$ (44 mg, 0.168 mmol). The reddish reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was purified by “flash” chromatography (SiO$_2$). Elution with hexane/EtOAc (75:25) afforded pure azapalladacycle 16 as an orange foam (115 mg, 73%).

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$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.88 (s, 3H), 2.84 (m, 1H), 3.16 (d, $J = 3$ Hz, 3H), 3.28-3.68 (m, 3H), 3.55 (s, 3H), 5.54 (s, 1H), 6.71 (d, $J = 7.8$ Hz, 1H), 6.82 (d, $J = 7.8$ Hz, 1H), 7.30-7.50 (m, 9H), 7.65-7.75 (m, 6H). $^{13}$C NMR (CDCl$_3$, 100.5 MHz) $\delta$ 21.8 (CH$_3$), 34.0 (CH$_2$), 51.3 (CH$_3$), 51.6 (CH$_3$), 54.9 (CH$_2$), 118.9 (CH), 125.8 (d, $J = 10.1$ Hz, C), 126.1 (CH), 128.2 (d, $J = 11.6$ Hz, CH), 129.0 (d, $J = 7.7$ Hz, CH), 130.8 (d, $J = 2.3$ Hz, CH), 131.6 (d, $J = 52.7$ Hz, C), 135.0 (d, $J = 12.4$ Hz, CH), 158.6 (d, $J = 3.9$ Hz, C), 171.5 (C). One C was not observed.

$^{31}$P NMR (CDCl$_3$, 121.5 MHz) $\delta$ 40.6. HRMS (ESI-TOF) calcd for C$_{30}$H$_{32}$INO$_2$PPd: 702.0245 [M+H]$^+$; found: 702.0234.
**UNITAT DE RNM O ALT CAMP**
SERVEI CIENTIFIC-TECNIC
UNIVERSITAT DE BARCELONA

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**H5 / 29pul / GemiN-300**
cdcl3 / Temp: Ambient / W reg: G33999-221165959712
User: san / Mostr: replhe204620
Memo: DANIL Dole _AB._20
Date:12/11/95 / SST automatic

***************

**Pulse Sequence: 29pul**
Solvent: cdcl3
Ambient temperature
Sample #10, user san
File: 1001
GEMINI-300 *zaps*

Relax. delay 1.000 sec
Pulse 45.0 degree
Acq. time 0.686 sec
Width 4000./ Hz
18 repetitions

**Observe: 300.045 MHz**
**Record: 10000000 Hz**

**INDEX** | **FREQUENCY** | **PPM** | **HEIGHT**
--- | --- | --- | ---
1 | 2305.046 | 7.847 | 8.8 |
2 | 2305.561 | 7.844 | 11.1 |
3 | 2306.086 | 7.840 | 11.2 |
4 | 2306.610 | 7.837 | 10.6 |
5 | 2178.087 | 7.281 | 13.7 |
6 | 2180.032 | 7.180 | 8.1 |
7 | 2180.444 | 7.080 | 22.0 |
8 | 2092.028 | 8.974 | 14.4 |
9 | 1007.105 | 3.456 | 151.3 |
10 | 980.240 | 3.287 | 15.8 |
11 | 878.014 | 3.283 | 25.7 |
12 | 871.035 | 3.033 | 16.8 |
13 | 801.637 | 2.871 | 128.0 |
14 | 763.051 | 2.543 | 20.0 |
15 | 755.432 | 2.518 | 26.6 |
16 | 746.359 | 2.494 | 16.8 |
17 | 677.775 | 2.255 | 81.8 |

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**Diagram**

- **Me**
- **N**
- **O-Me**
- **1a**

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**SI9**
Me\[\text{Br}\]Me

\[\text{N}\]

\[\text{O}\]

OMe

1b
MeO-\text{Py}-\text{OMe}

\text{6a}