Supporting Information

Visible-Light mediated heterogeneous C-H functionalization: Oxidative multi-component reactions using a recyclable titanium dioxide (TiO_2) catalyst

Carlos Vila and Magnus Rueping*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074, Aachen (Germany)

Magnus.Rueping@rwth-aachen.de

Table of Contents

General Methods 2

TEM and HR-TEM analysis of TiO_2 ** 3

General procedures for synthesis of compounds **3** 3

Characterization of Products **3** 4

We gratefully acknowledge Dr. T. E. Weirich and C. Herwartz for performing the TEM measurements.

General Methods. Unless otherwise noted, all commercially available compounds were used as received. TiO_2 was supplied by Sigma-Aldrich, product code: 718467. Analytical grade solvents used for reaction were dried and distilled prior to use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 aluminium plates with F-254 indicator, visualized by UV irradiation. Column chromatography was performed using MN silica gel (particle size 0.040-0.063 mm). ^{1}H-NMR and ^{13}C-NMR were recorded on a Mercury 300, Inova 400 or VNMRS-600 spectrometer in $CDCl_3$ or toluene-d_8 with residual proton signal of the deuterated solvents as the internal reference (δ_H = 7.26 ppm and δ_C = 77.00 ppm for $CDCl_3$) or TMS as internal reference. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), td (triplet of doublets), tt (triplet of triplets), ddd (doublet of doublet of doublets), m (multiplet), p (pentet), s (sextet); coupling constants (*J*) are in Hertz (Hz). ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra was conducted on GC-MS Shimadzu QP2010 (column: Equity®-5, length × I.D. 30 m × 0.25 mm, d_f 0.25 μm, lot # 28089-U, Supelco). HRMS were measured on a Finnigan MAT 95 or LTQ Orbitrap XL spectrometer. IR spectra were measured in a Perkin-Elmer ATR apparatus and are reported in terms of frequency of absorption (cm^{-1}).

TEM and HR-TEM analysis of TiO_2

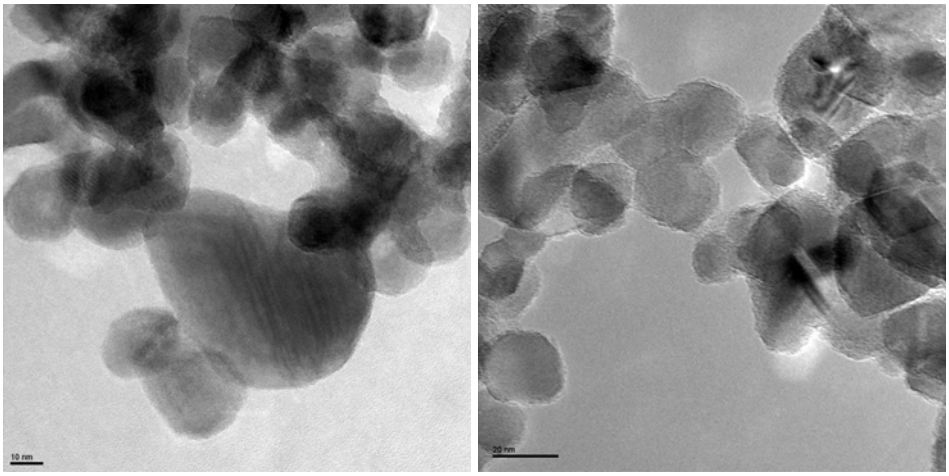


Figure 1: TEM-BF investigation of TiO2. (a) Before use (b) After use

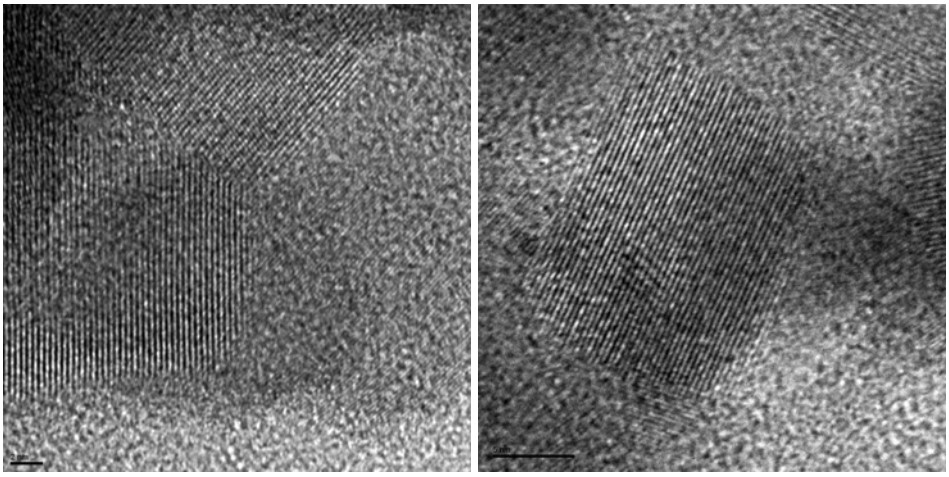


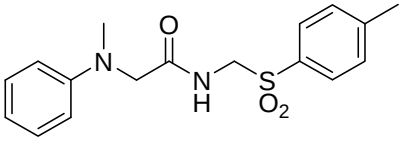
Figure 2: HR-TEM investigation of TiO2. (a) Before use (b) After use

General procedure for the synthesis of compounds 3

In a vial TiO_2 (12 mg, 0.15 mmol), amine **1** (0.3 mmol), isocyanide **2** (0.15 mmol) and H_2O (27 μL, 1.5 mmol) were dissolved in 1 mL of dioxane. The reaction mixture was stirred for 4 days under irradiation with an 11W lamp (distance app. 3 cm). After 4 days the solvent was removed under reduced pressure and the crude reaction mixture was directly charged on silica gel and purified by column chromatography (cyclohexane/EtOAc 8:2 to 6:4) to afford the corresponding product **3**.

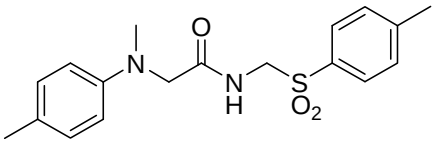
Characterization of products 3

2-(methyl(phenyl)amino)-*N*-(tosylmethyl)acetamide (3a)[1]



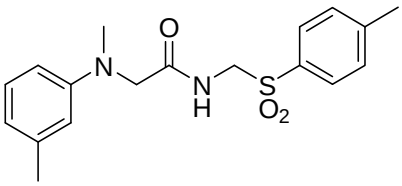
Synthesized according to the general procedure; m.p.: 112-115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 2H), 7.33-7.25 (m, 5H), 6.88 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 8.7 Hz, 2H), 4.66 (d, J = 6.9 Hz, 2H), 3.73 (s, 2H), 2.98 (s, 3H), 2.45 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 149.0, 145.5, 133.7, 129.9, 129.4, 128.8, 119.2, 113.4, 59.8, 58.5, 40.0, 21.8 ppm.

2-(methyl(p-tolyl)amino)-*N*-(tosylmethyl)acetamide (3b)[1]



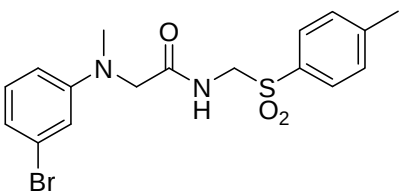
Synthesized according to the general procedure; m.p.: 130-133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.2 Hz, 2H), 7.40 (t, J = 6.7 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 4.66 (d, J = 6.9 Hz, 2H), 3.68 (s, 2H), 2.92 (s, 3H), 2.44 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 146.9, 145.5, 133.7, 129.9, 128.8, 128.7, 113.7, 59.8, 58.8, 40.3, 21.8, 20.3 ppm.

2-(methyl(m-tolyl)amino)-*N*-(tosylmethyl)acetamide (3c)[1]



Synthesized according to the general procedure; m.p.: 119-121 °C. ^{11}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.2 Hz, 2H), 7.34-7.30 (m, 3H), 7.15 (t, J = 7.7 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.50 (s, 1H), 6.46 (dd, J = 8.2, 2.6 Hz, 1H), 4.66 (d, J = 6.9 Hz, 2H), 3.72 (s, 2H), 2.95 (s, 3H), 2.43 (s, 3H), 2.32 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 149.1, 145.4, 139.3, 133.8, 129.9, 129.3, 128.7, 120.2, 114.2, 110.6, 59.8, 58.5, 40.0, 21.8, 21.7 ppm.

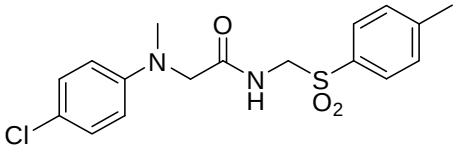
2-((3-bromophenyl)(methyl)amino)-*N*-(tosylmethyl)acetamide (3d)



Synthesized according to the general procedure; m.p.: 119-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 6.7 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.95 (ddd, J = 7.8, 1.6, 0.7 Hz, 1H), 6.78 (t, J = 2.2 Hz, 1H), 6.53 (dd, J = 8.4, 2.5 Hz, 1H), 4.65 (d, J = 6.9 Hz, 2H), 3.73 (s, 2H), 2.94

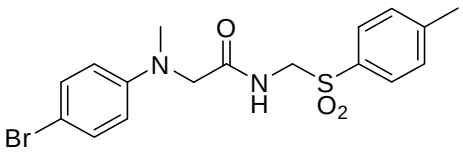
(s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 150.1, 145.6, 133.6, 130.6, 130.0, 128.7, 123.6, 121.8, 116.0, 111.8, 59.9, 57.8, 39.8, 21.8 ppm.

2-((4-chlorophenyl)(methyl)amino)-*N*-(tosylmethyl)acetamide (3e)



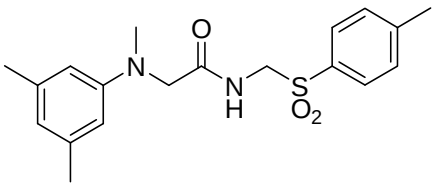
Synthesized according to the general procedure; m.p.: 157-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.20-7.16 (m, 3H), 6.54 (d, J = 9.1 Hz, 2H), 4.66 (d, J = 6.9 Hz, 2H), 3.71 (s, 2H), 2.94 (s, 3H), 2.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 147.5, 145.6, 133.7, 129.9, 129.2, 128.7, 124.1, 114.5, 59.8, 58.3, 40.2, 21.7 ppm.

2-((4-bromophenyl)(methyl)amino)-*N*-(tosylmethyl)acetamide (3f)[1]



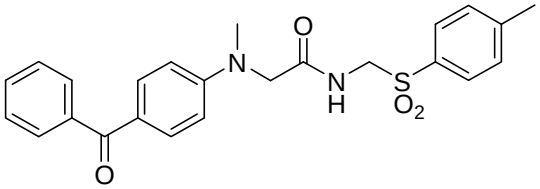
Synthesized according to the general procedure; m.p.: 144-146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.3 Hz, 2H), 7.32-7.30 (m, 4H), 6.48 (d, J = 9.1 Hz, 2H), 4.65 (d, J = 7.0 Hz, 2H), 3.71 (s, 2H), 2.94 (s, 3H), 2.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 147.9, 145.6, 133.6, 132.1, 129.9, 128.7, 114.9, 111.3, 59.8, 58.2, 40.1, 21.8 ppm.

2-((3,5-dimethylphenyl)(methyl)amino)-*N*-(tosylmethyl)acetamide (3g)



Synthesized according to the general procedure; m.p.: 117-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.7 Hz, 2H), 7.32-7.29 (m, 3H), 6.53 (br s, 1H), 6.31 (s, 2H), 4.66 (d, J = 6.9 Hz, 2H), 3.72 (s, 2H), 2.93 (s, 3H), 2.43 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 149.1, 145.4, 139.2, 133.9, 129.9, 128.7, 121.2, 111.4, 59.9, 58.5, 40.0, 21.7 ppm.

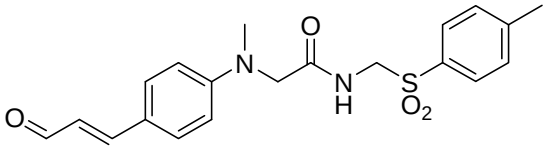
2-((4-benzoylphenyl)(methyl)amino)-*N*-(tosylmethyl)acetamide (3h)



Synthesized according to the general procedure; m.p.: 188-191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 9.0 Hz, 2H), 7.74-7.70 (m, 4H), 7.56 (tt, J = 7.4, 1.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 6.7 Hz, 1H), 6.64 (d, J = 9.1 Hz, 2H), 4.69 (d, J = 6.8 Hz, 2H), 3.90 (s, 2H), 3.10 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1,

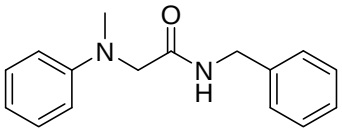
169.1, 151.9, 145.7, 138.5, 133.6, 132.6, 131.7, 130.0, 129.5, 128.7, 128.1, 127.5, 111.7, 59.8, 57.2, 39.8, 21.7 ppm; IR (KBr): ν = 3280, 1974, 1676, 1598, 1532, 1376, 1309, 1209, 1141, 1085, 934, 826, 734, 696 cm^{-1}; MS-EI: *m/z* (%) 436 (4), 224 (47), 119 (21), 105 (36), 92 (59), 91 (81), 77 (68), 65 (100), 51 (30). HRMS (ESI) calculated for $C_{24}H_{24}O_4N_2SNa$ [M+Na] 459.13490 found 459.13486.

(*E*)-2-(methyl(4-(3-oxoprop-1-enyl)phenyl)amino)-*N*-(tosylmethyl)acetamide (3i)



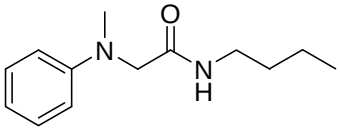
Synthesized according to the general procedure; oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (d, J = 7.81 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.9 Hz, 2H), 7.37-7.31 (m, 3H), 6.64 (d, J = 8.9 Hz, 2H), 6.54 (dd, J = 15.7, 7.8 Hz, 1H), 4.68 (d, J = 6.8 Hz, 2H), 3.87 (s, 2H), 3.07 (s, 3H), 2.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 169.3, 152.9, 150.9, 145.6, 133.8, 130.4, 129.9, 128.7, 125.3, 124.3, 112.8, 60.0, 57.3, 39.8, 21.8 ppm; IR (KBr): ν = 3288, 2925, 1667, 1590, 1519, 1375, 1315, 1122, 809, 724 cm^{-1}; MS-EI: *m/z* (%) 386 (8), 278 (26), 174 (75), 161 (22), 156 (87), 139 (66), 92 (51), 91 (100), 77 (13), 65 (36). HRMS (ESI) calculated for $C_{20}H_{23}O_4N_2S$ [M+H] 387.13730 found 387.13680.

***N*-benzyl-2-(methyl(phenyl)amino)acetamide (3j)[1]**



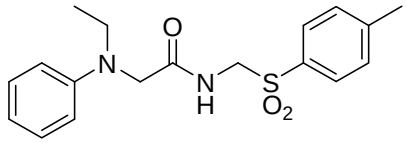
Synthesized according to the general procedure; m.p.: 95-97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.18 (m, 7H), 6.96 (br s, 1H), 6.82 (t, J = 7.3 Hz, 1H), 6.72 (d, J = 8.6 Hz, 2H), 4.47 (d, J = 6.0 Hz, 2H), 3.90 (s, 2H), 2.98 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 149.2, 137.9, 129.4, 128.6, 127.4, 118.8, 113.2, 58.9, 43.1, 39.9 ppm.

***N*-butyl-2-(methyl(phenyl)amino)acetamide (3k)**



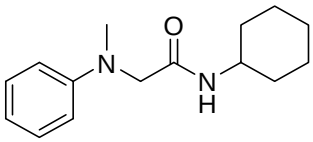
Synthesized according to the general procedure; oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (dd, J = 8.8, 7.3 Hz, 2H), 6.82 (t, J = 7.3 Hz, 1H), 6.71 (dd, J = 8.8, 0.9 Hz, 2H), 6.56 (br s, 1H), 3.83 (s, 2H), 3.26 (q, J = 7.0 Hz, 2H), 2.98 (s, 3H), 1.43 (p, J = 7.1 Hz, 2H), 1.31-1.21 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 149.3, 129.3, 118.6, 113.1, 58.9, 39.7, 38.9, 31.5, 19.9, 13.7 ppm.

2-(ethyl(phenyl)amino)-*N*-(tosylmethyl)acetamide (3l)



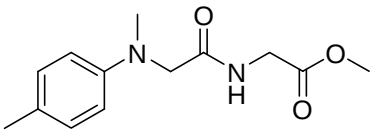
Synthesized according the general procedure; m.p.: 112-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.3 Hz, 2H), 7.30-7.23 (m, 5H), 6.87-6.82 (m, 1H), 6.64 (dd, J = 8.80, 0.90 Hz, 2H), 4.64 (d, J = 6.9 Hz, 2H), 3.72 (s, 2H), 3.39 (q, J = 7.0 Hz, 2H), 2.43 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 147.3, 145.5, 133.8, 129.9, 129.5, 128.7, 119.0, 113.7, 59.8, 55.4, 46.5, 21.7, 11.5 ppm.

***N*-cyclohexyl-2-(methyl(phenyl)amino)acetamide (3m)**



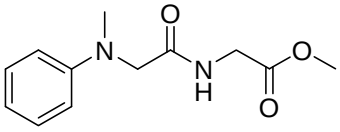
Synthesized according to the general procedure; m.p.: 92-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (dd, J = 8.9, 7.3 Hz, 2H), 6.82 (t, J = 7.3 Hz, 1H), 6.71 (d, J = 7.9 Hz, 2H), 6.42 (d, J = 6.3 Hz, 1H), 3.85-3.75 (m, 3H), 2.97 (s, 3H), 1.86-1.82 (m, 2H), 1.65-1.53 (m, 3H), 1.38-1.28 (m, 2H), 1.13-1.01 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 149.4, 129.3, 118.8, 113.2, 59.1, 47.8, 39.7, 33.0, 25.4, 24.7 ppm.

Methyl 2-(2-(methyl(p-tolyl)amino)acetamido)acetate (3n)



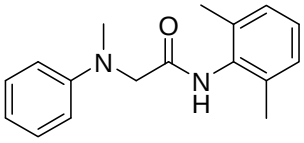
Synthesized according to the general procedure; oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (br s, 1H), 7.08 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.5 Hz, 2H), 4.06 (d, J = 5.8 Hz, 2H), 3.85 (s, 2H), 3.73 (s, 3H), 3.00 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.0, 147.3, 129.8, 128.2, 113.7, 59.0, 52.3, 40.8, 40.0, 20.2 ppm; IR (KBr): ν = 3329, 2922, 1748, 1663, 1513, 1363, 1202, 1120, 990, 943, 807, 698 cm^{-1}; MS-EI: *m/z* (%) 250 (M^+, 20), 134 (100), 91 (10). HRMS (ESI) calculated for $C_{13}H_{19}O_3N_2$ [M+H] 251.13902 found 251.13797.

Methyl 2-(2-(methyl(phenyl)amino)acetamido)acetate (3o)



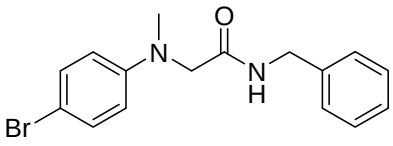
Synthesized according to the general procedure; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (dd, J = 8.6, 7.1 Hz 2H), 7.04 (br s, 1H), 6.83 (t, J = 7.3 Hz, 1H), 6.76 (dd, J = 8.7, 0.8 Hz, 2H), 4.05 (d, J = 5.8 Hz, 2H), 3.89 (s, 2H), 3.71 (s, 3H), 3.02 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.0, 149.3, 129.3, 118.8, 113.3, 58.7, 52.3, 40.8, 39.7 ppm.

_N_-(2,6-dimethylphenyl)-2-(methyl(phenyl)amino)acetamide (3p)[1]



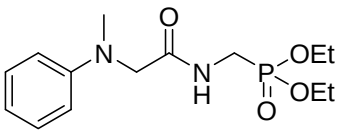
Synthesized according to the general procedure; m.p.: 96-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (br s, 1H), 7.30 (dd, J = 8.6, 7.5 Hz, 2H), 7.10-7.02 (m, 3H), 6.88-6.84 (m, 3H), 4.04 (s, 2H), 3.13 (s, 3H), 2.16 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 149.0, 135.2, 133.1, 129.5, 128.2, 127.4, 119.0, 113.3, 58.9, 40.0, 18.5 ppm.

_N_-benzyl-2-((4-bromophenyl)(methyl)amino)acetamide (3q)



Synthesized according to the general procedure; m.p.: 102-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.24 (m, 5H), 7.17 (dd, J = 8.1, 1.7 Hz, 2H), 6.76 (br s, 1H), 6.57 (d, J = 9.1 Hz, 2H), 4.46 (d, J = 6.0 Hz, 2H), 3.87 (s, 2H), 2.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 148.2, 137.8, 132.0, 128.7, 127.6, 127.5, 114.8, 110.9, 58.9, 43.2, 40.1 ppm; IR (KBr): ν = 3286, 2926, 1649, 1591, 1493, 1363, 1213, 1119, 806, 749, 692 cm^{-1}; MS-EI: *m/z* (%) 334 (M+2, 14), 332 (M$^+$, 16), 200 (80), 198 (100), 185 (14), 91 (21). HRMS (ESI) calculated for $C_{16}H_{18}ON_2Br$ [M+H] 333.05970 found 333.05902.

Diethyl (2-(methyl(phenyl)amino)acetamido)methylphosphonate (3r)



Synthesized according to the general procedure; oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.21 (m, 2H), 6.88-6.86 (m, 1H), 6.81 (tt, J = 7.4, 1.0 Hz, 1H), 6.70 (dd, J = 8.7, 0.8 Hz, 2H), 4.08-4.01 (m, 4H), 3.87 (d, J = 1.3 Hz, 2H), 3.70 (dd, J = 12.0, 6.1 Hz, 2H), 2.99 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (d, J_{C-P} = 4.6 Hz), 149.1, 129.3, 118.8, 113.3, 62.5 (d, J_{C-P} = 6.4 Hz), 58.7, 39.9, 34.4 (d, J_{C-P} = 156.5 Hz), 16.3 (d, J_{C-P} = 6.0 Hz).

References:

(1) Ye, X.; Xie, C.; Huang, R.; Liu, J. *Synlett.* **2012**, *23*, 409.