

Copper-catalyzed one-pot oxidative amidation between methylenes and amines

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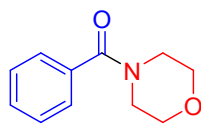
1. General details

Reaction solvents were obtained commercially, and used without further purification. Commercial reagents were used as received. Reaction were monitored by thin-layer chromatography (TLC) on 0.25mm precoated Merck Silica Gel 60 F254, visualizing with ultraviolet light. $^1\text{H}/^{13}\text{C}$ NMR spectra were recorded on 400/54 ascend purchased from Bruker Biospin AG, operating at 400/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. High-resolution mass spectra (HRMS) were obtained from Agilent 6520 LC-MS. Flash column chromatography was performed on Merck Silica Gel 60 (200-300mesh) using petroleum ether and ethyl acetate.

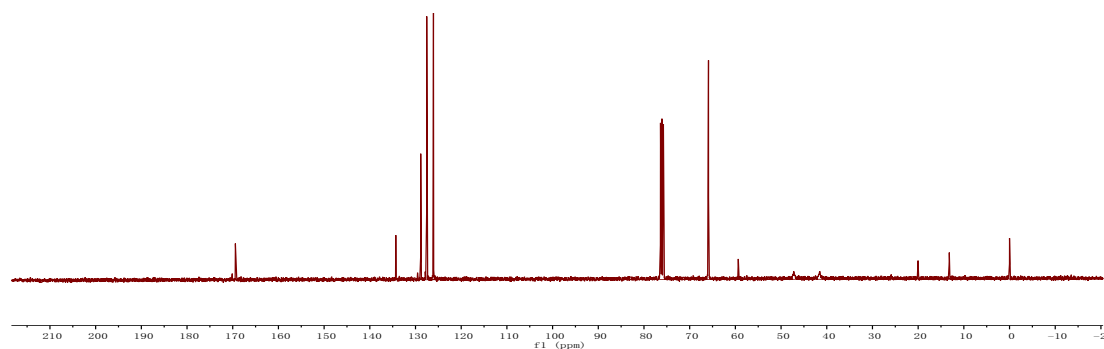
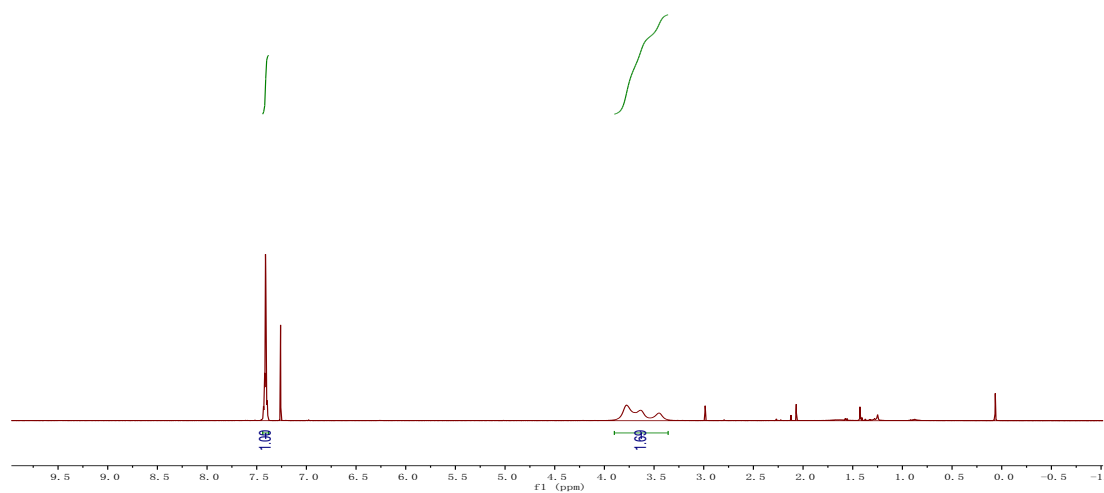
2. Experimental procedure

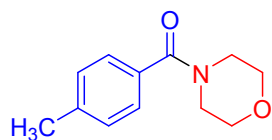
General procedure for synthesis of compound 3: 1.5mmol of amine (**1**) and 1.65mmol of NCS were dissolved in 10mL acetonitrile, stirring at room temperature for 3 h. Then methylene (**2**, 15.0mmol, 10.0 equiv.), $\text{Cu}(\text{OAc})_2$ (20 mol%), TBAI (20 mol%) and TBHP (70 wt% in water, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. The reaction mixture was quenched by NaHSO_3 solution and extracted with ethyl acetate, washed with NH_4Cl solution. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the amide product **3**.

3. NMR Spectra

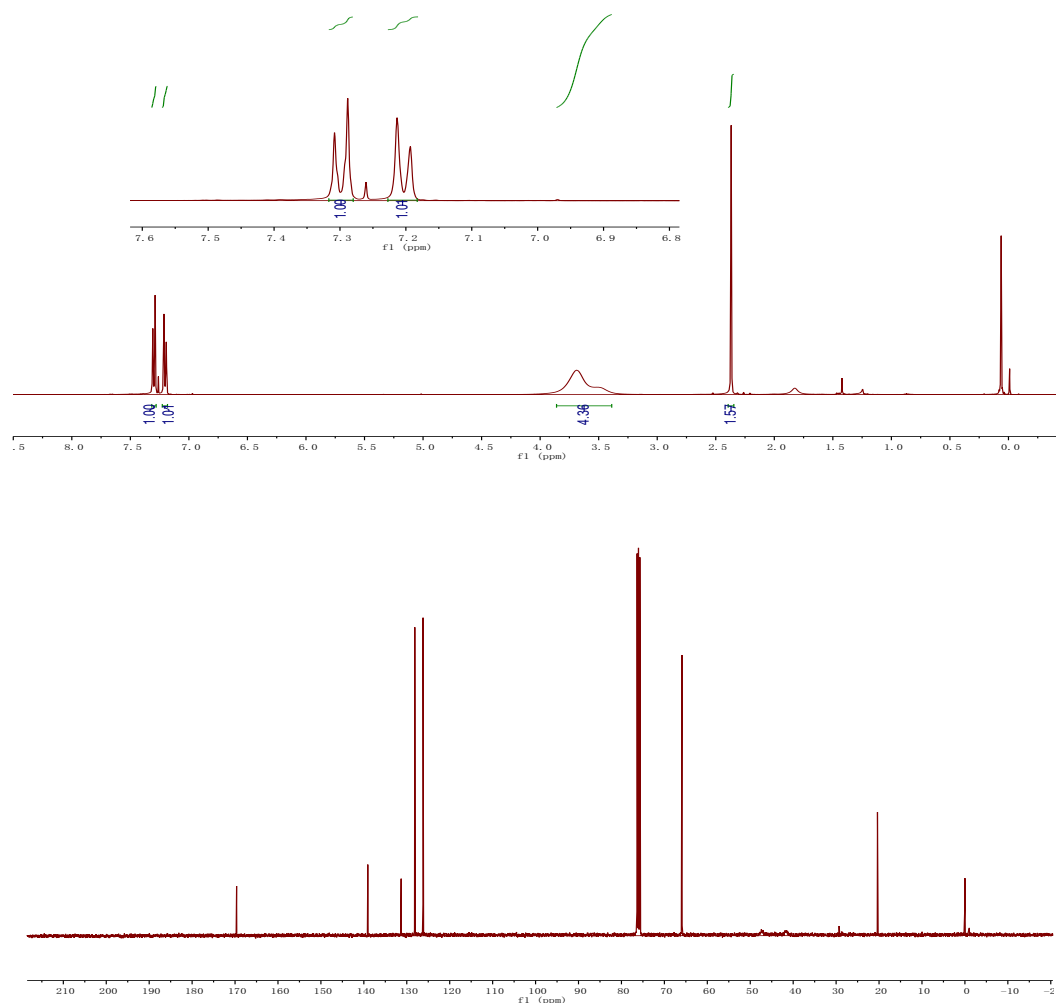


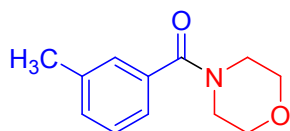
Benzoyl morpholine (3a). Morpholine (130mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (232mg, 81% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.44–7.38 (m, 5H), 3.90–3.36 (m, 8H); ¹³C NMR (101 MHz, CDCl₃) δ 170.1, 169.4, 134.3, 128.9, 127.5, 126.1, 65.9, 59.4, 20.0, 13.2; HRMS (ESI) *m/z* calcd for C₁₁H₁₃NO₂ [M+H]⁺ 192.1019, found 192.1040.



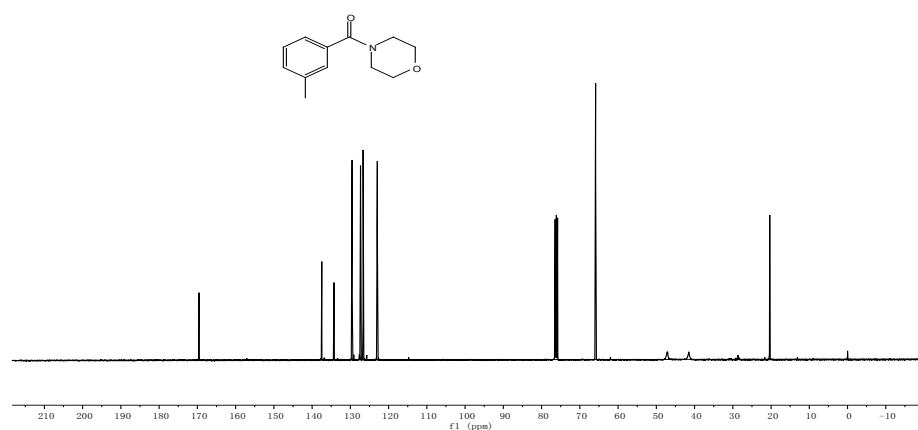
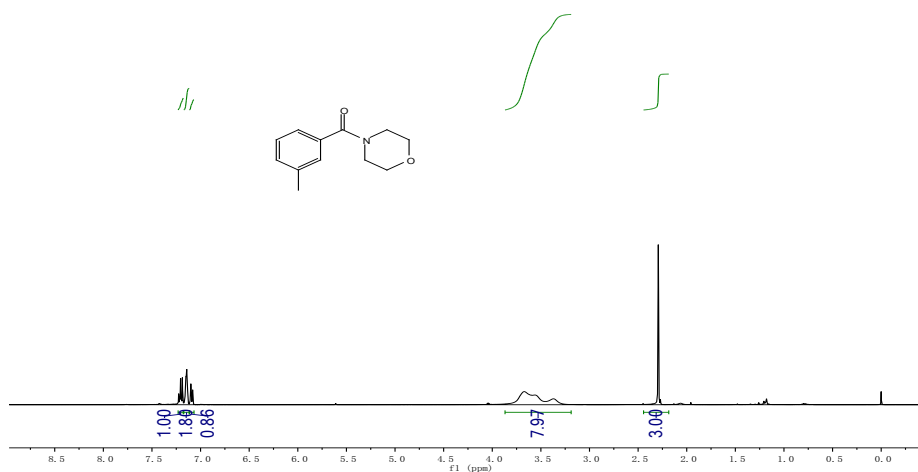


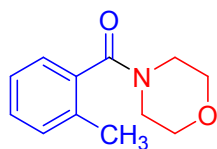
N-(4-Methylbenzoyl)morpholine (**3b**). Morpholine (130mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then *p*-xylene (1592mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as light yellow oil (264mg, 86% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, *J*=8.1 Hz, 2H), 7.20 (d, *J*=8.0 Hz, 2H), 3.69 (m, 8H), 2.37 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.6, 139.1, 131.3, 128.1, 126.2, 65.9, 29.3, 20.4; HRMS (ESI) *m/z* calcd for C₁₂H₁₅NO₂ [M+H]⁺ 206.1136, found 206.1147.



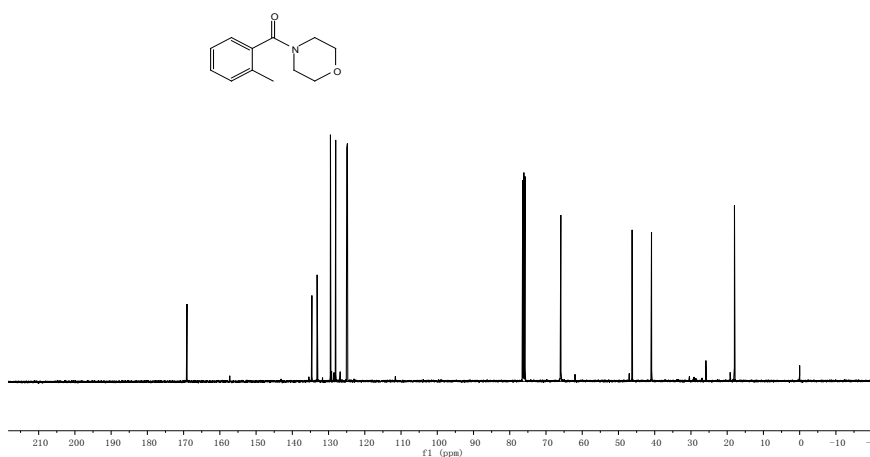
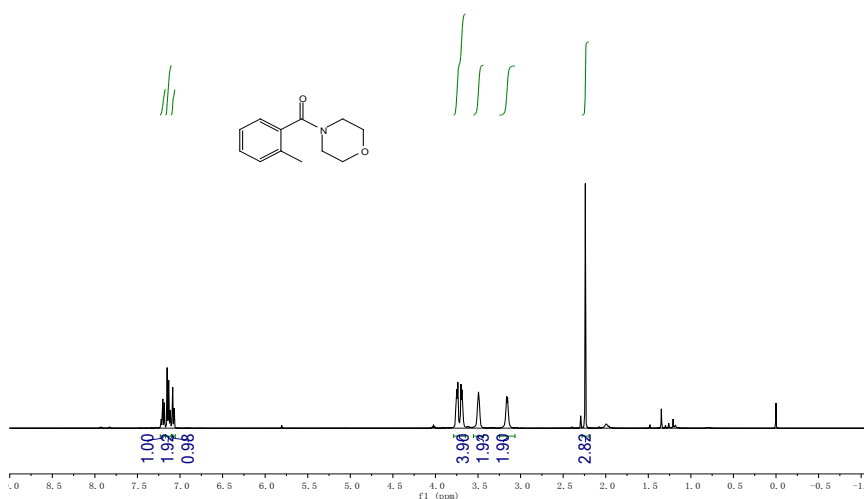


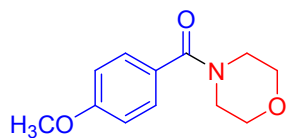
N-(3-Methylbenzoyl)morpholine (**3c**). Morpholine (130mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then *m*-xylene (1592mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as light yellow oil (249mg, 81% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.23–7.18 (m, 1H), 7.14 (dt, *J* = 10.8, 5.5 Hz, 2H), 7.09 (d, *J*=7.4 Hz, 1H), 3.87–3.19 (m, 8H), 2.28 (d, *J*=8.6 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.6, 137.5, 134.3, 129.5, 127.3, 126.7, 122.9, 65.9, 47.2, 41.4, 20.3.



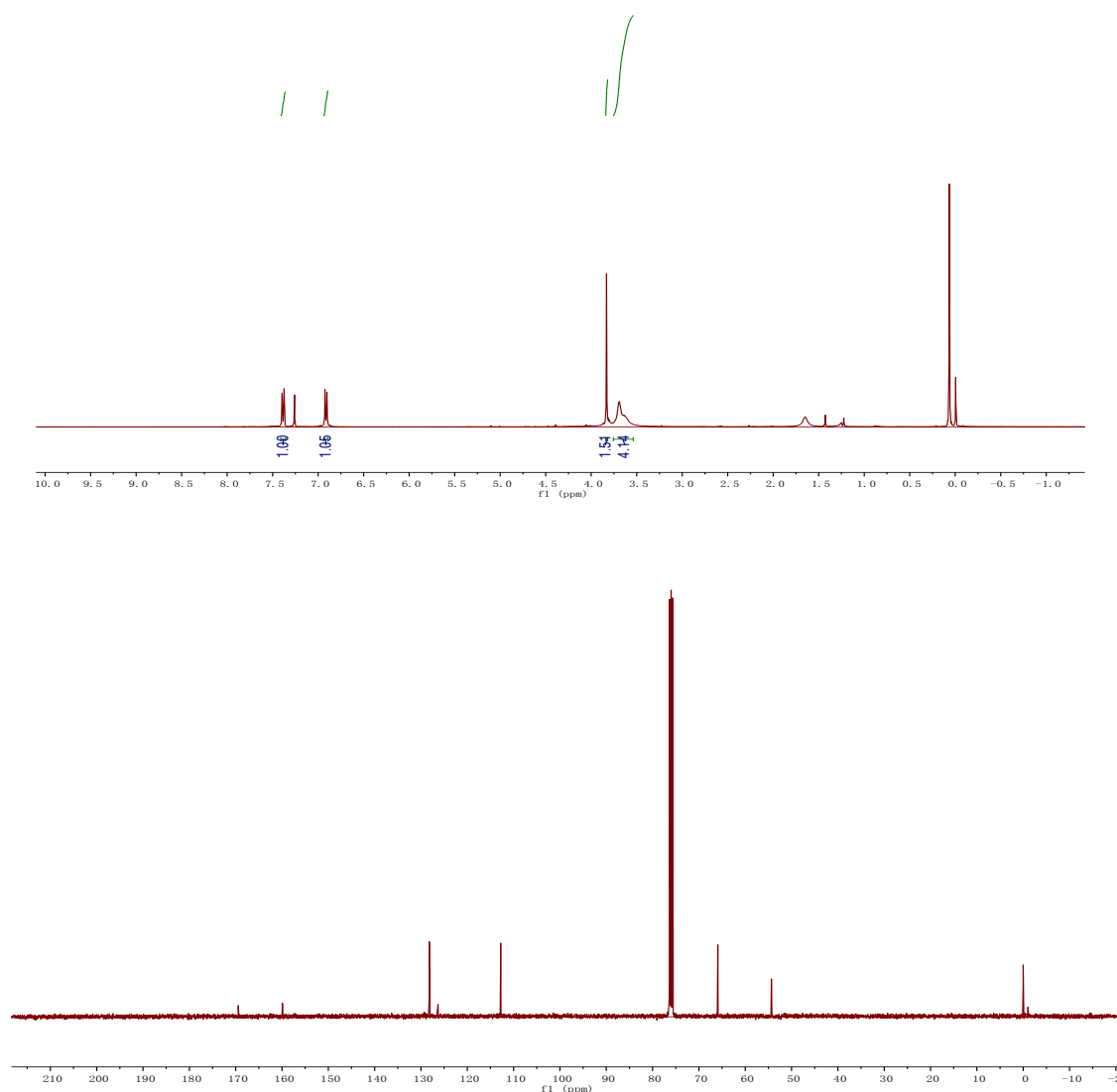


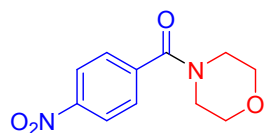
N-(2-Methylbenzoyl)morpholine (**3d**). Morpholine (130mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then *o*-xylene (1592mg, 15.0mmol, 10.0 equiv.), $\text{Cu}(\text{OAc})_2$ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as light yellow oil (249mg, 81% yield); ^1H NMR (400 MHz, CDCl_3) δ 7.23–7.17 (m, 1H), 7.17–7.10 (m, 2H), 7.08 (d, $J=7.2$ Hz, 1H), 3.79–3.65 (m, 4H), 3.49 (s, 2H), 3.16 (d, $J=4.5$ Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.1, 134.6, 133.2, 129.5, 128.0, 125.0, 124.8, 65.9, 46.2, 40.9, 25.9, 18.0.



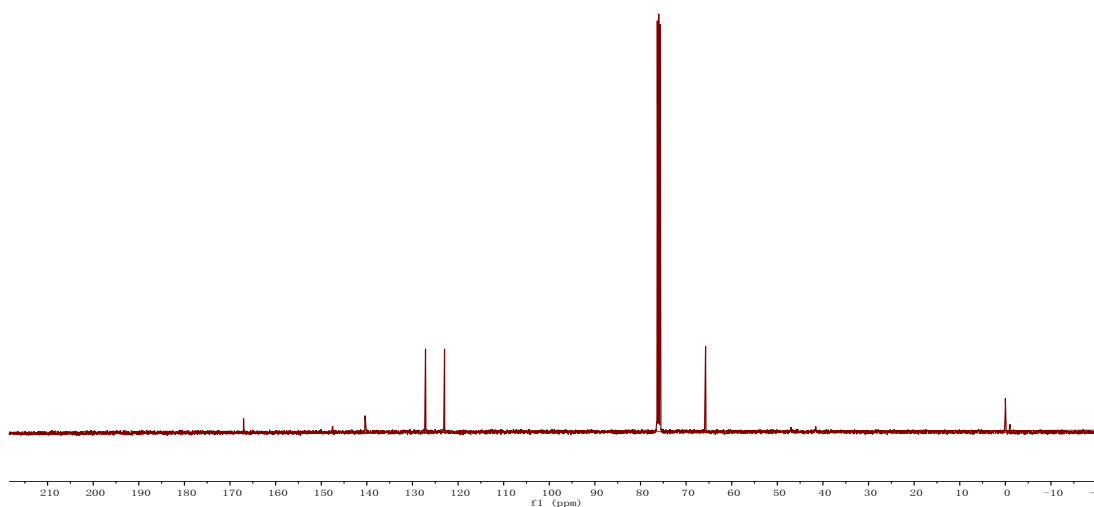
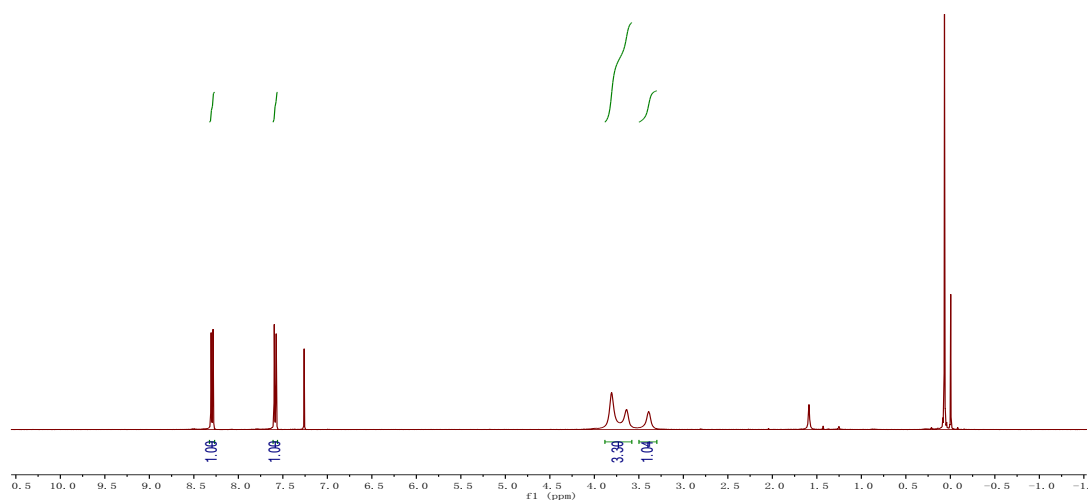


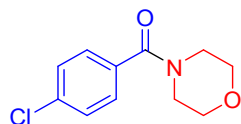
N-(4-Methoxybenzoyl)morpholine (**3e**). Morpholine (130mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then 4-methoxytoluene 1831mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 20h. And the product was obtained after purification as yellow oil (252mg, 76% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.36 (m, 2H), 6.94–6.89 (m, 2H), 3.84 (s, 3H), 3.76–3.54 (m, 8H); ¹³C NMR (101 MHz, CDCl₃) δ 169.4, 159.9, 128.2, 126.3, 112.8, 65.9, 54.4; HRMS (ESI) *m/z* calcd for C₁₂H₁₅NO₃ [M+H]⁺ 222.1085, found 222.1094.



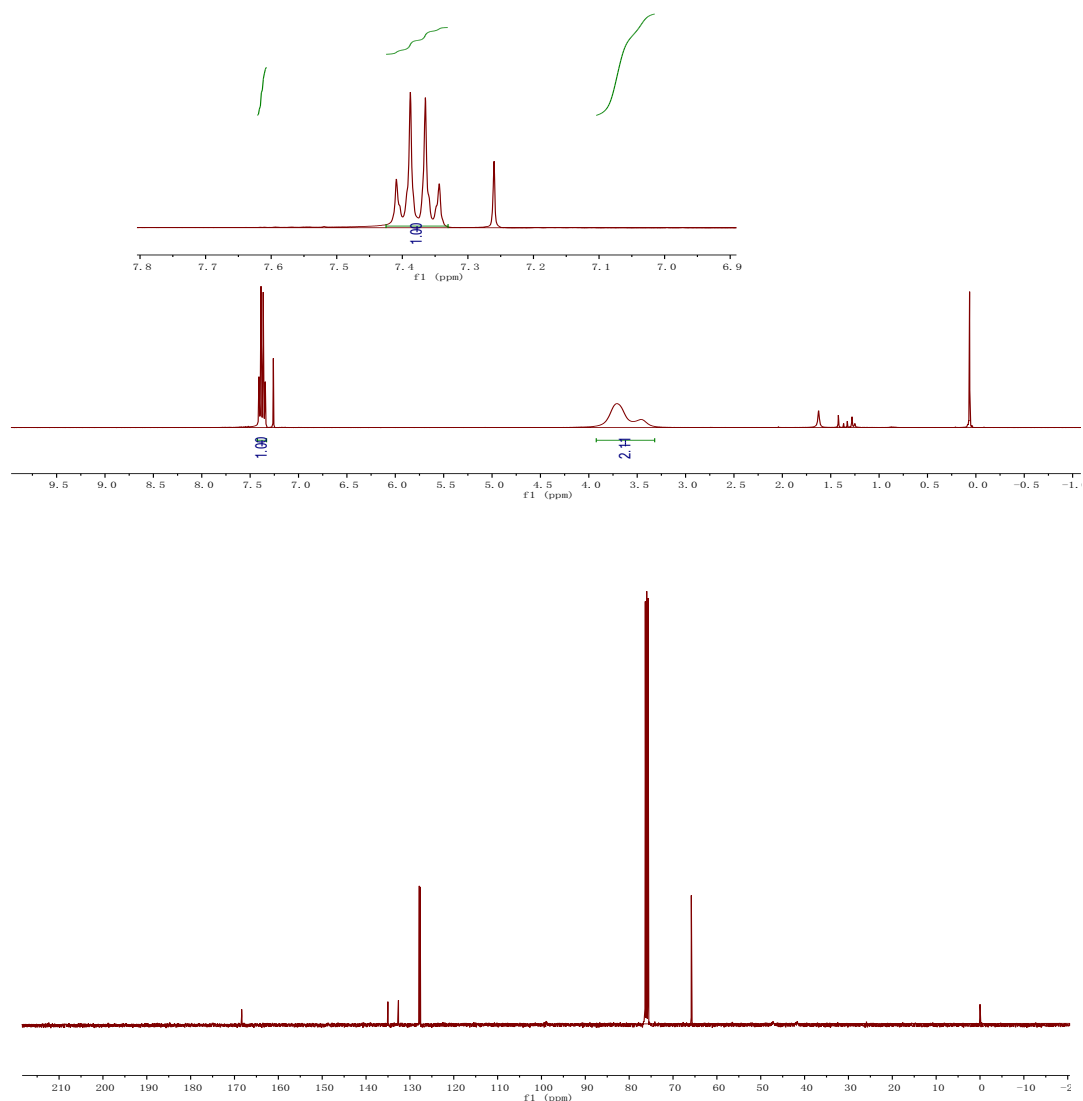


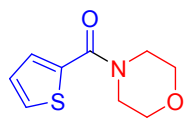
N-(4-Nitrobenzoyl)morpholine (**3f**). Morpholine (130mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then 4-nitrotoluene (2056mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as light yellow solid (304mg, 86% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.32–8.27 (m, 2H), 7.61–7.56 (m, 2H), 3.72 (d, *J* = 67.2 Hz, 6H), 3.39 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 167.0, 147.5, 140.4, 127.1, 123.0, 65.7; HRMS (ESI) *m/z* calcd for C₁₁H₁₁N₂O₄ [M+H]⁺ 237.0831, found 237.0857.





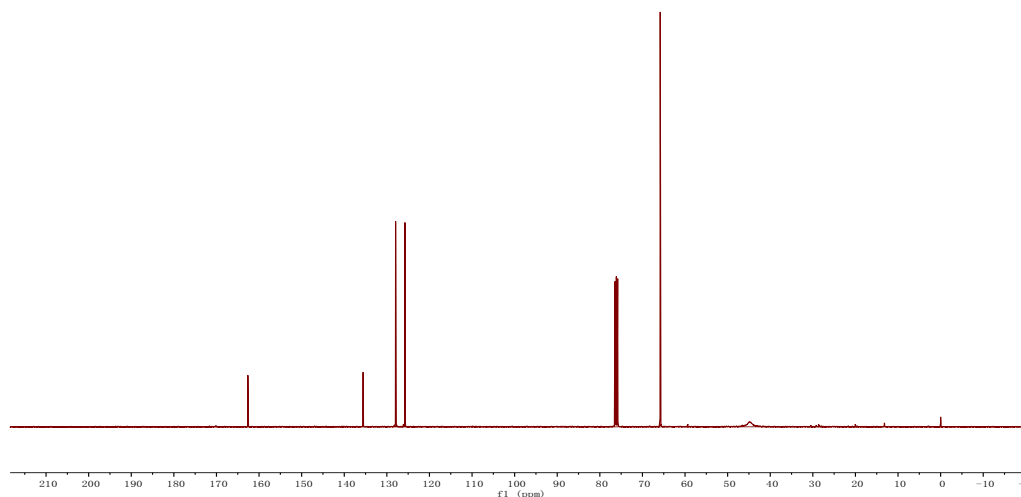
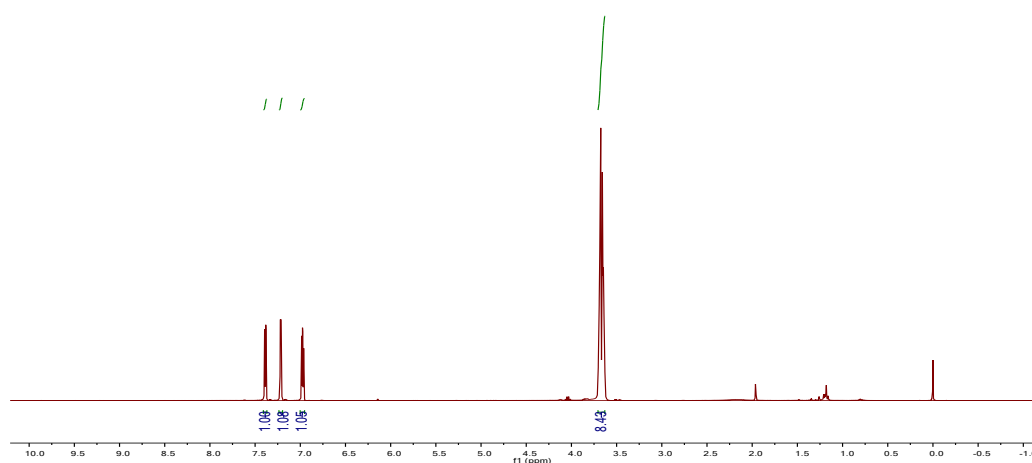
N-(4-Chlorobenzoyl)morpholine (**3g**). Morpholine (130mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then 4-chlorotoluene (1890mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 18h. And the product was obtained after purification as white solid (281mg, 83% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.38 (q, *J* = 8.5 Hz, 4H), 3.92–3.32 (m, 8H); ¹³C NMR (101 MHz, CDCl₃) δ 168.4, 135.0, 132.6, 127.9, 127.6, 99.9, 65.8; HRMS (ESI) *m/z* calcd for C₁₁H₁₂ClNO₂ [M+H]⁺ 226.6720, found 226.6724.

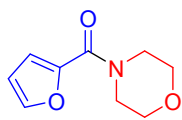




4-Morpholinyl-2-thienylmethanone (3h). Morpholine (130mg, 1.5mmol, 1

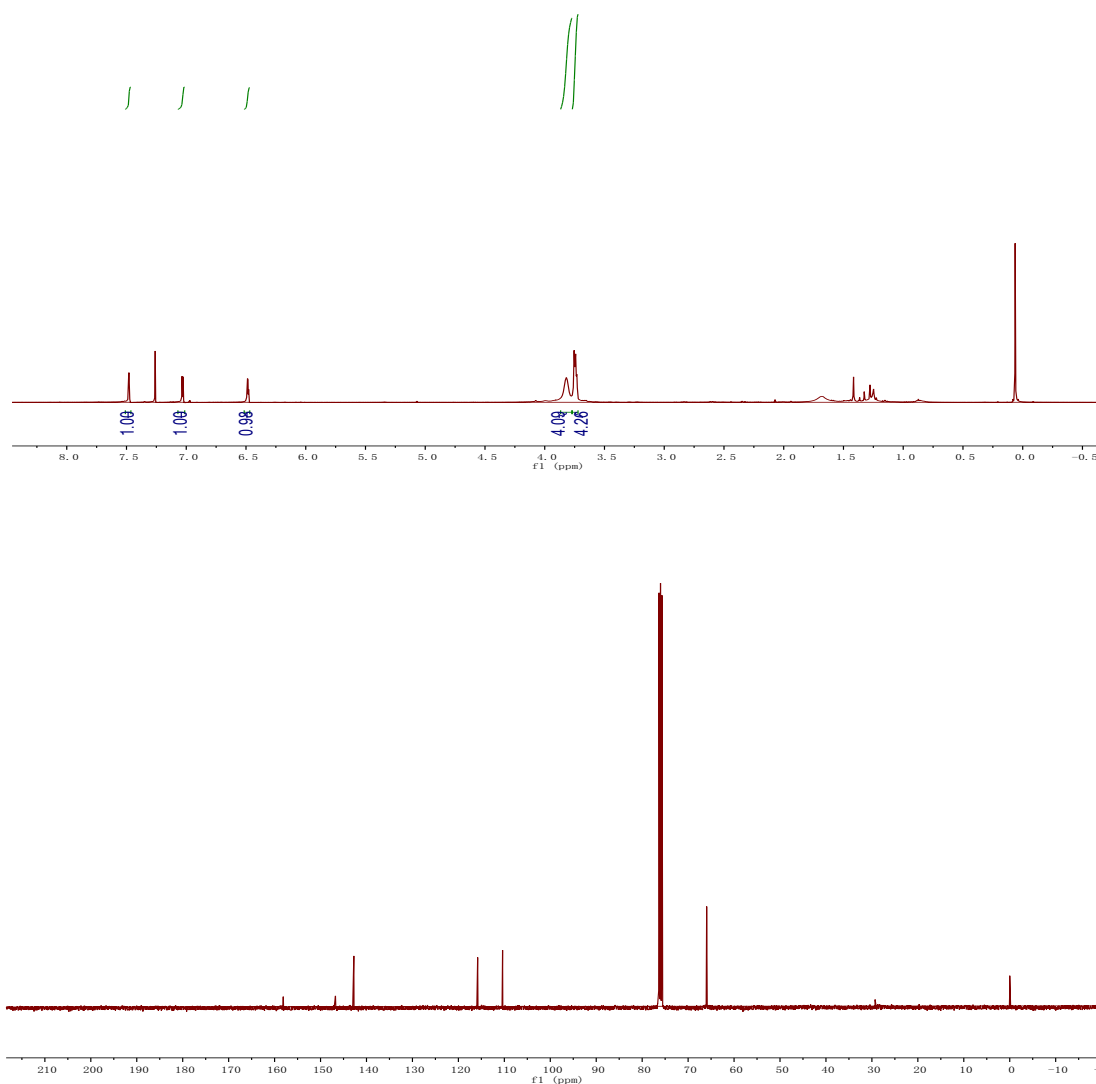
equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then 2-methylthiophene (1473mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as light yellow oil (230mg, 78% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.39 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.22 (dd, *J* = 3.6, 1.0 Hz, 1H), 6.97 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.71–3.63 (m, 8H); ¹³C NMR (101 MHz, CDCl₃) δ 162.63, 135.57, 127.9, 127.8, 125.7, 65.8, 59.4, 20.0, 13.2; HRMS (ESI) *m/z* calcd for C₉H₁₁NO₂S [M+H]⁺ 198.0544, found 198.0568.

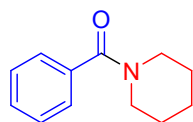




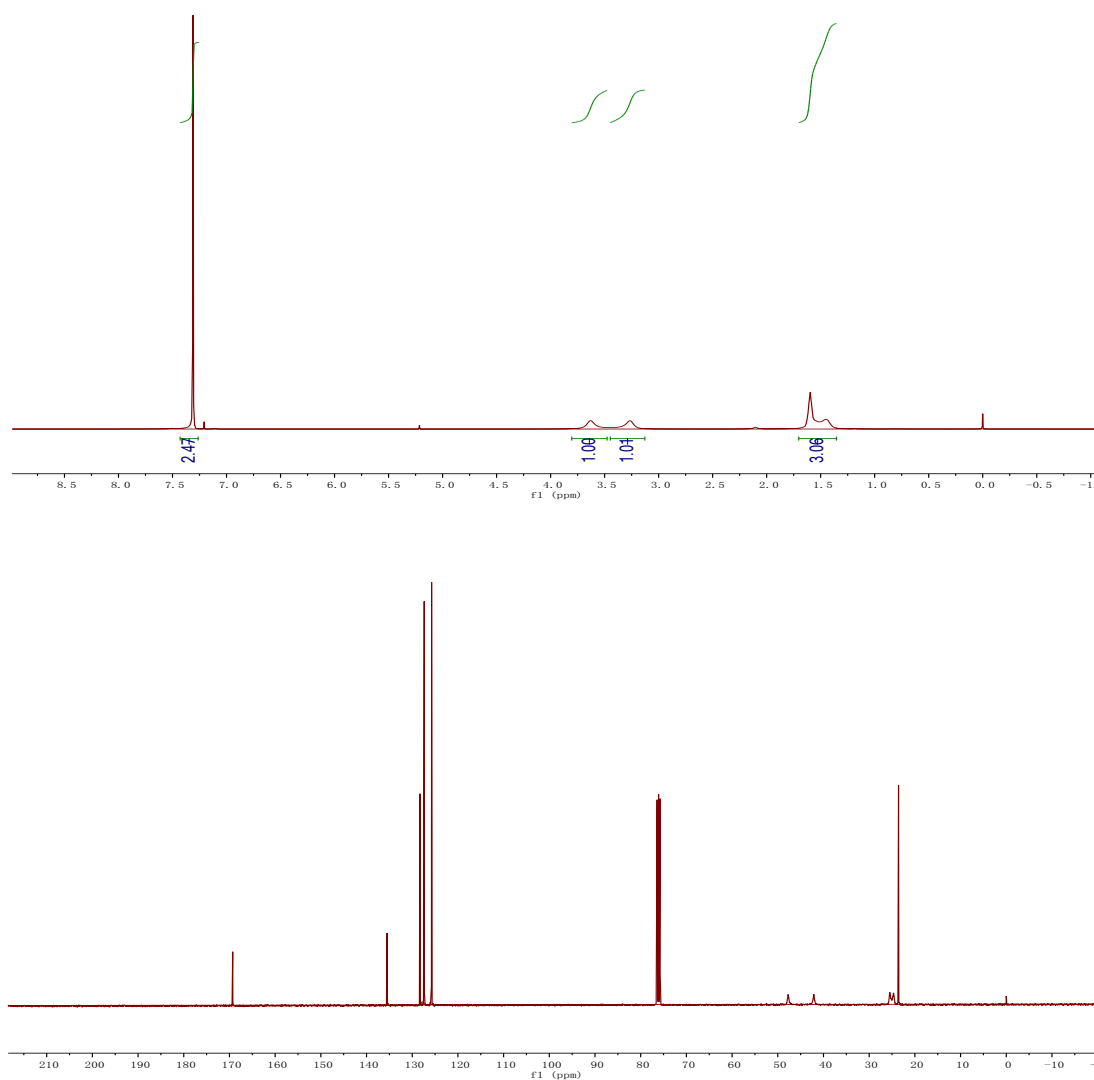
2-Furanyl-4-morpholinylmethanone (3i). Morpholine (130mg, 1.5mmol, 1

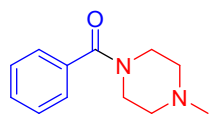
equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then 2-methylfuran (1231mg, 15.0mmol, 10.0 equiv.), $\text{Cu}(\text{OAc})_2$ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 20h. And the product was obtained after purification as yellow oil (210mg, 82% yield); ^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, J = 1.7, 0.8 Hz, 1H), 7.03 (dd, J = 3.5, 0.7 Hz, 1H), 6.49 (dd, J = 3.5, 1.8 Hz, 1H), 3.82 (s, 4H), 3.77–3.72 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.1, 146.8, 142.8, 115.8, 110.4, 65.9, 29.3; HRMS (ESI) m/z calcd for $\text{C}_9\text{H}_{11}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 182.0772, found 182.0783.



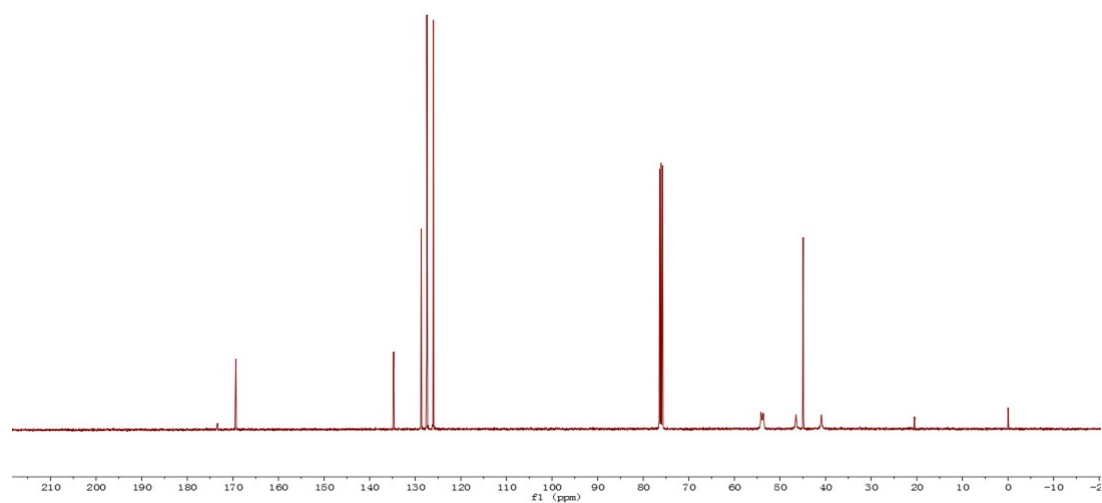
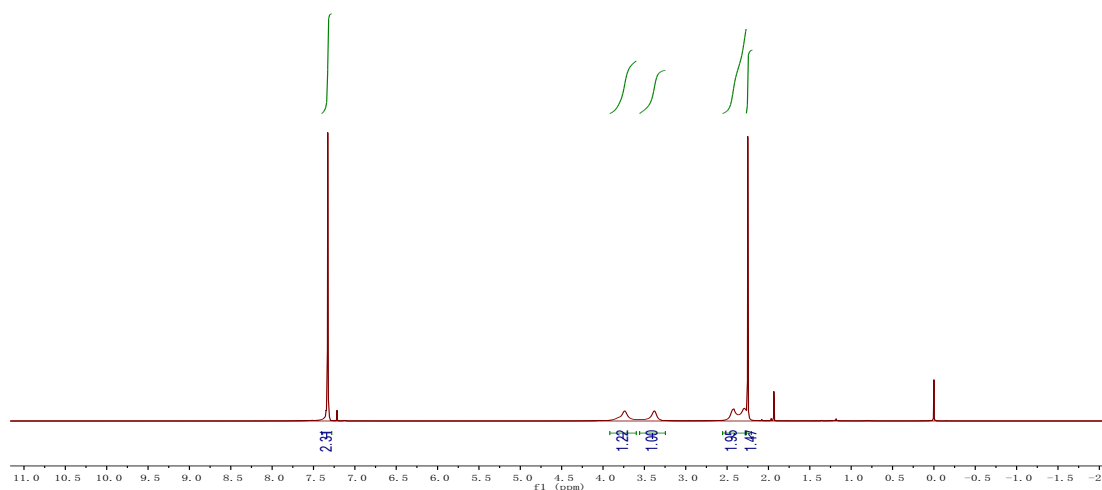


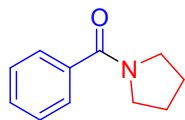
Benzoylpiperidine (3j). Piperidine (128mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as colourless oil (246mg, 87% yield); ¹H NMR(400 MHz, CDCl₃) δ 7.31(s, 5H), 3.63 (s, 2H), 3.27 (s, 2H), 1.70–1.35 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 169.3, 135.5, 128.3, 127.4, 125.8, 47.8, 42.1, 25.4, 24.6, 23.6; HRMS (ESI) m/z calcd for C₁₂H₁₅NO [M+H]⁺ 190.1187, found 190.1192.



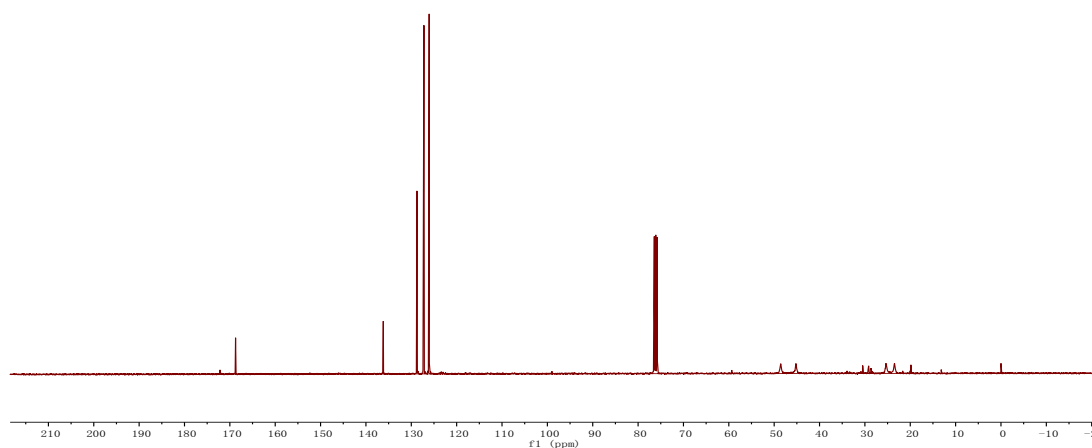
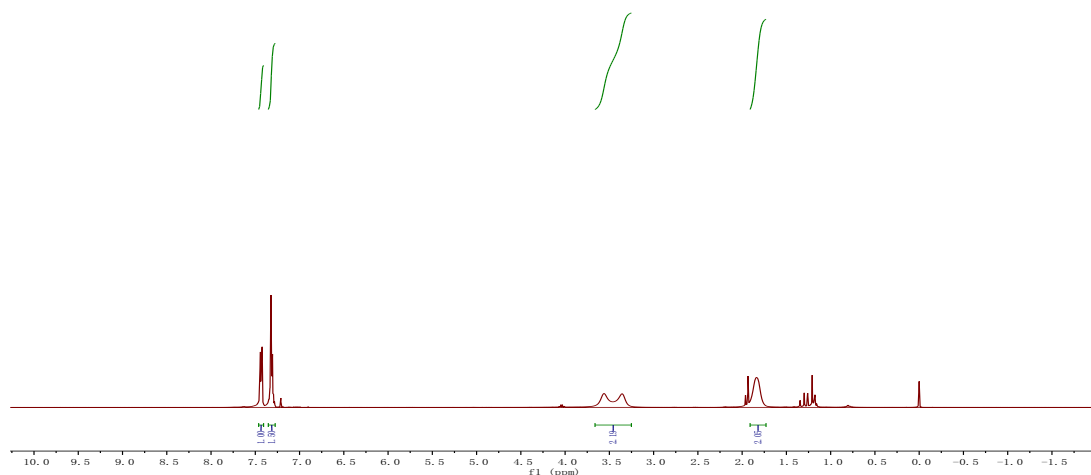


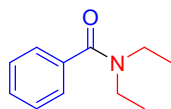
1-Benzoyl-4-methylpiperazine (3k). 1-Methylpiperazine (150mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (5mg, 1.5mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as yellow oil (242mg, 79% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.28 (m, 5H), 3.74 (s, 2H), 3.34 (s, 2H), 2.55–2.27 (m, 4H), 2.25 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 173.4, 169.3, 134.7, 128.7, 127.5, 126.0, 54.2, 53.6, 46.5, 44.9, 40.9, 20.5; HRMS (ESI) *m/z* calcd for C₁₂H₁₆N₂O [M+H]⁺ 205.1296, found 205.1305.



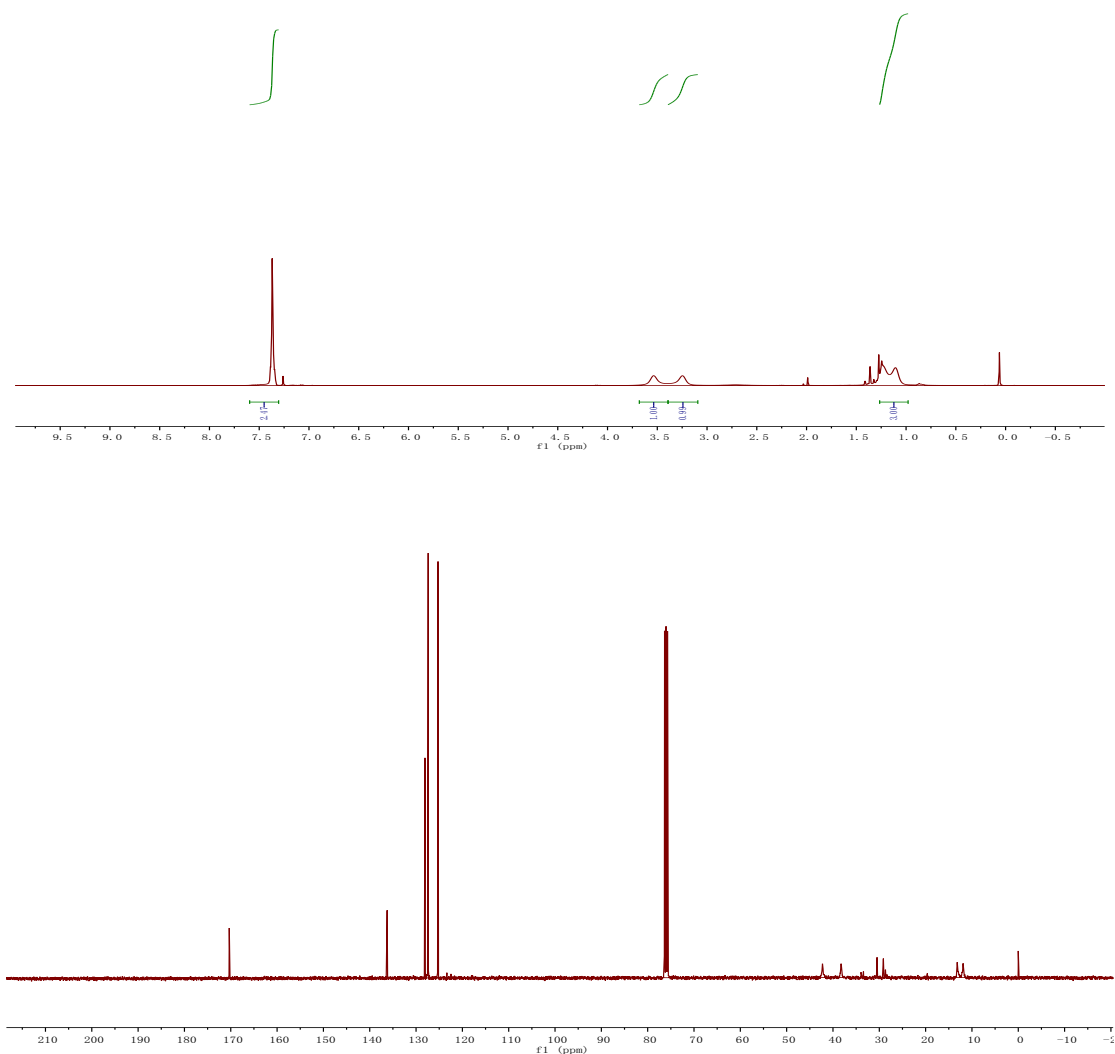


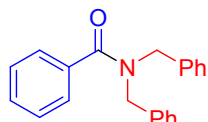
Benzoylpyrrolidine (31). Pyrrolidin (106mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as colourless oil (231mg, 88% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.43 (dt, *J* = 8.5, 3.7 Hz, 2H), 7.35–7.28 (m, 3H), 3.46 (d, *J* = 81.7 Hz, 4H), 1.84 (s, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 168.7, 136.2, 128.8, 127.2, 126.0, 48.6, 45.2, 25.4, 23.5; HRMS (ESI) *m/z* calcd for C₁₁H₁₃NO [M+H]⁺ 176.1031, found 176.1045.





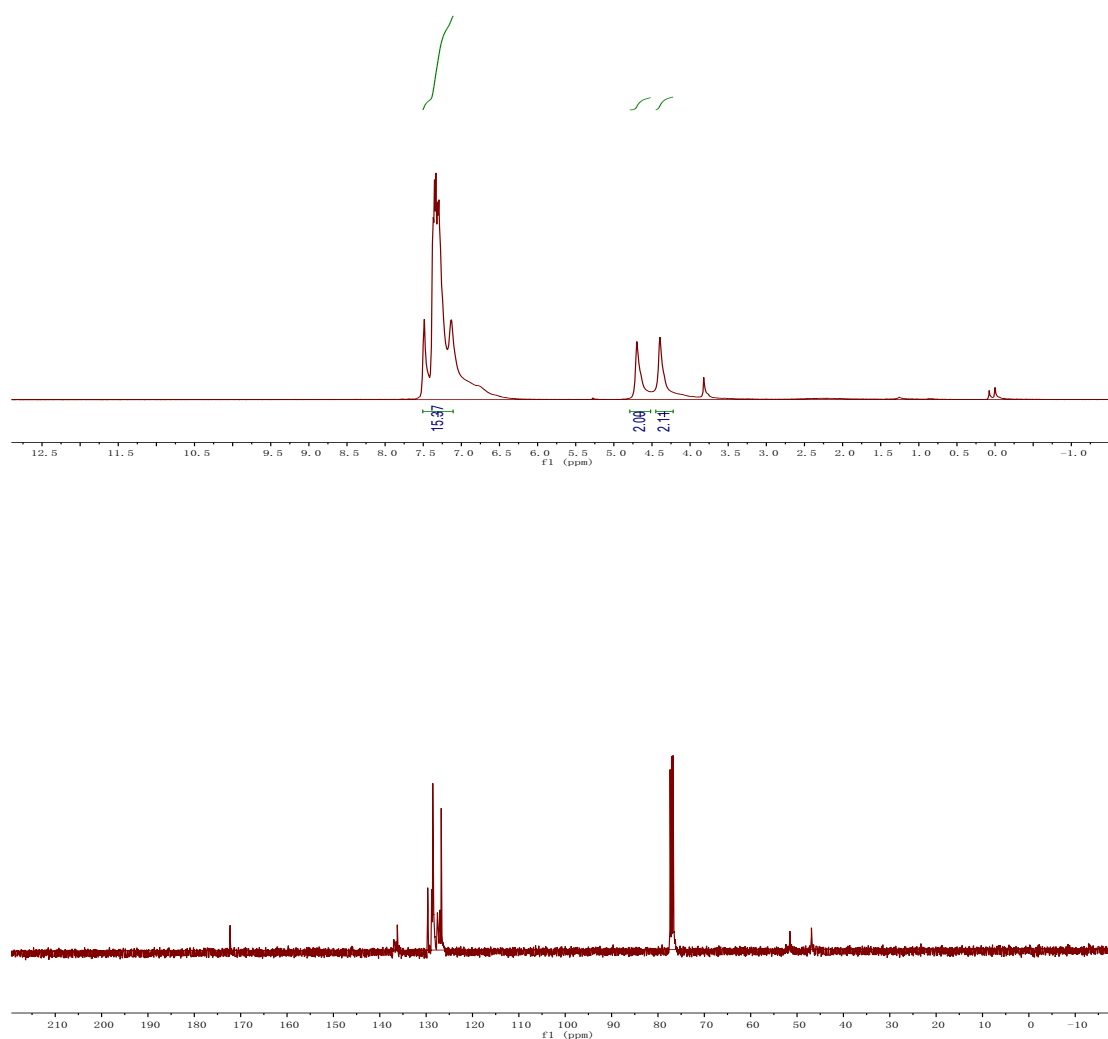
N,N-Diethylbenzamide (3m). Diethylamine (110mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as colourless oil (175mg, 66% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.60–7.30 (m, 5H), 3.54 (s, 2H), 3.25 (s, 2H), 1.27–0.98 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 170.3, 136.2, 128.1, 127.4, 125.3, 42.3, 38.2, 30.5, 29.1, 13.2, 11.9; HRMS (ESI) *m/z* calcd for C₁₁H₁₅NO [M+H]⁺ 178.1187, found 178.1183.

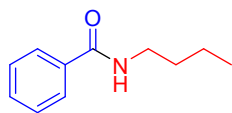




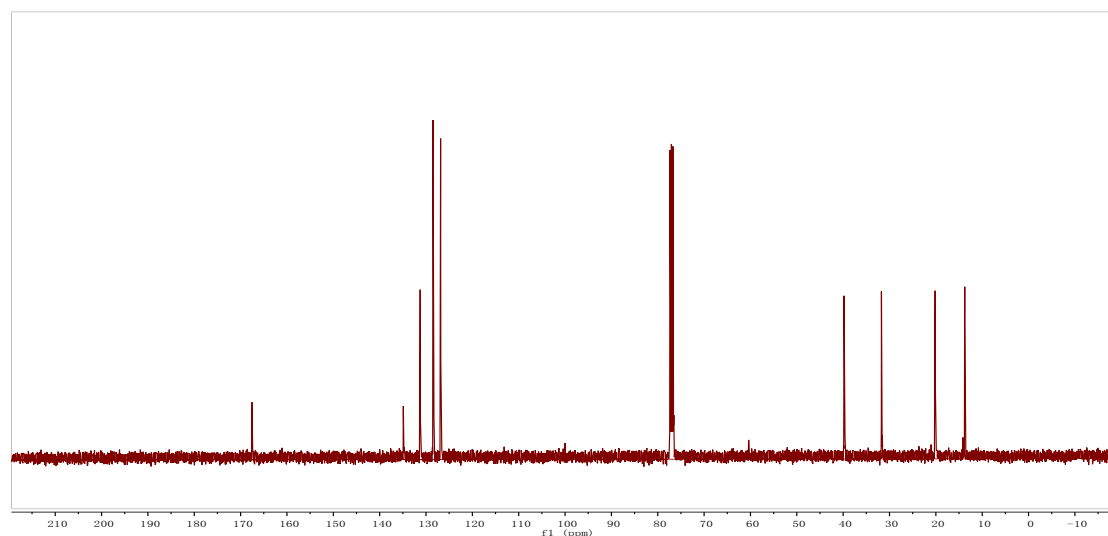
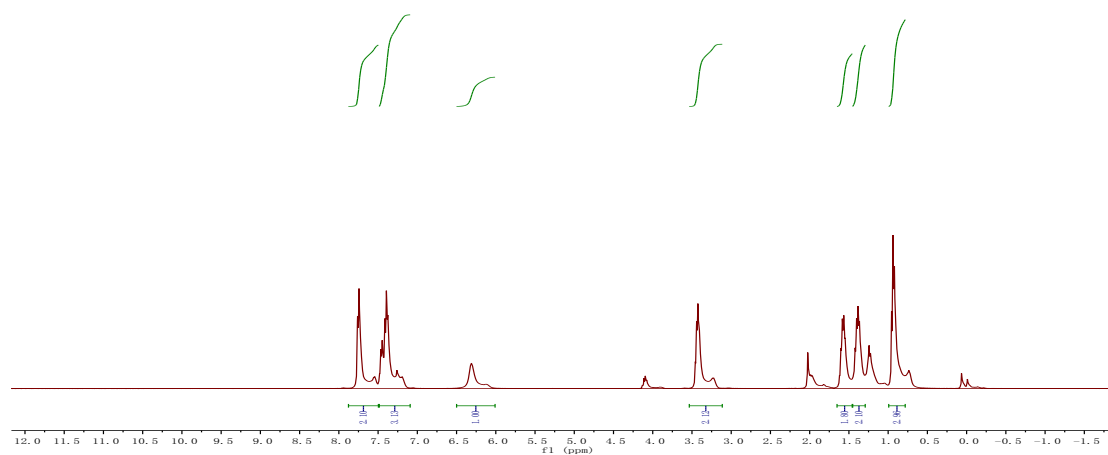
N,N-Dibenzylbenzamide (**3n**). Dibenzylamine (296mg, 1.5mmol, 1 equiv.) was

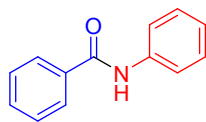
treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (401mg, 89% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.51–7.11 (m, 15H), 4.70 (s, 2H), 4.40 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 172.3, 137.0, 136.4, 136.2, 129.7, 128.8, 128.6, 128.4, 127.6, 127.0, 126.7, 51.6, 46.9; HRMS (ESI) *m/z* calcd for C₂₁H₁₉NO [M+H]⁺ 302.1500, found 302.1509.



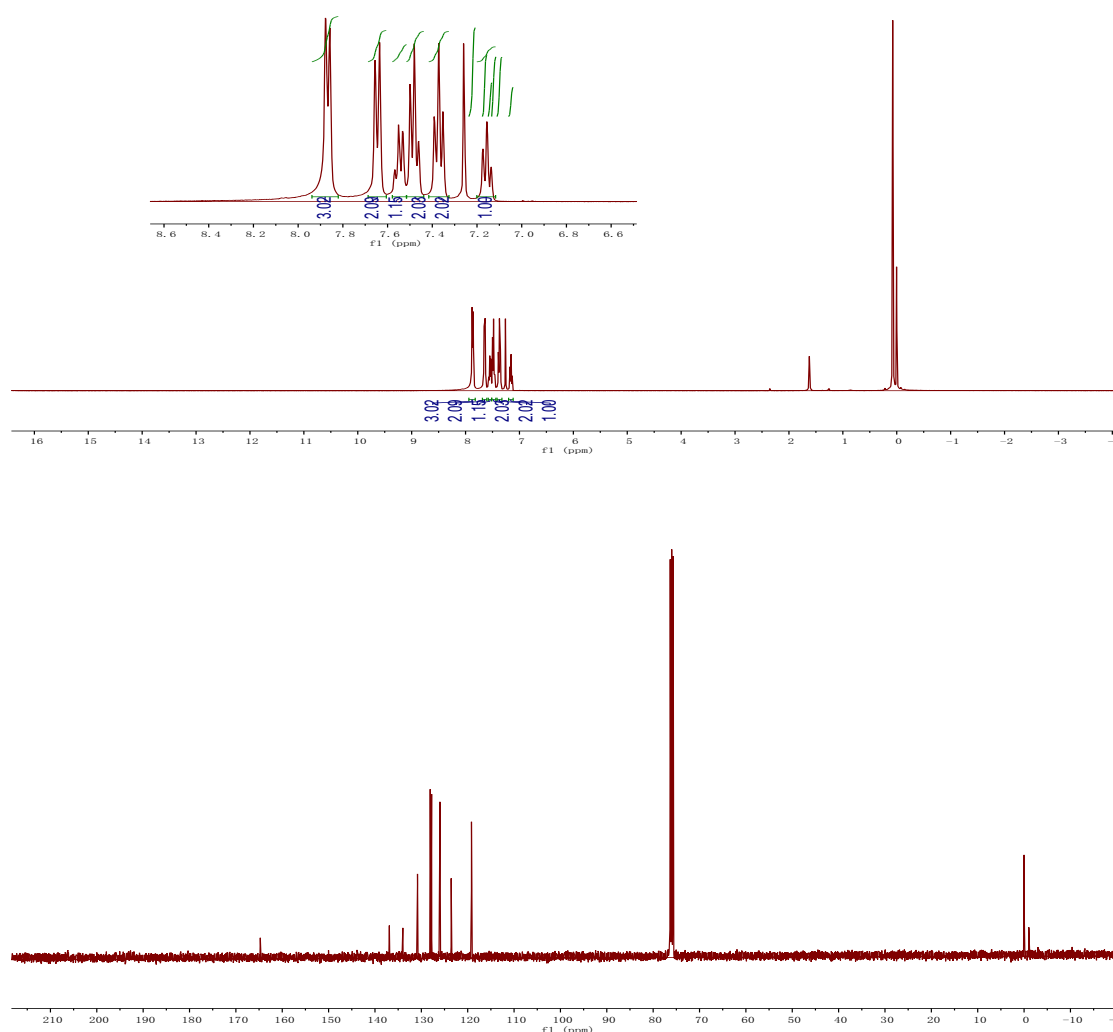


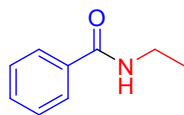
***N*-Butylbenzamide (3o).** Butylamine (110mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (210mg, 79% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 93.1, 13.0 Hz, 2H), 7.48–7.09 (m, 3H), 6.22 (d, *J* = 75.4 Hz, 1H), 3.53–3.11 (m, 2H), 1.58 (dt, *J* = 14.0, 7.0 Hz, 2H), 1.39 (dd, *J* = 14.5, 7.2 Hz, 2H), 0.94 (dd, *J* = 9.2, 5.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 167.6, 134.9, 131.2, 128.5, 126.8, 39.8, 31.7, 20.2, 13.8; HRMS (ESI) *m/z* calcd for C₁₁H₁₅NO [M+H]⁺ 178.1187, found 178.1189.





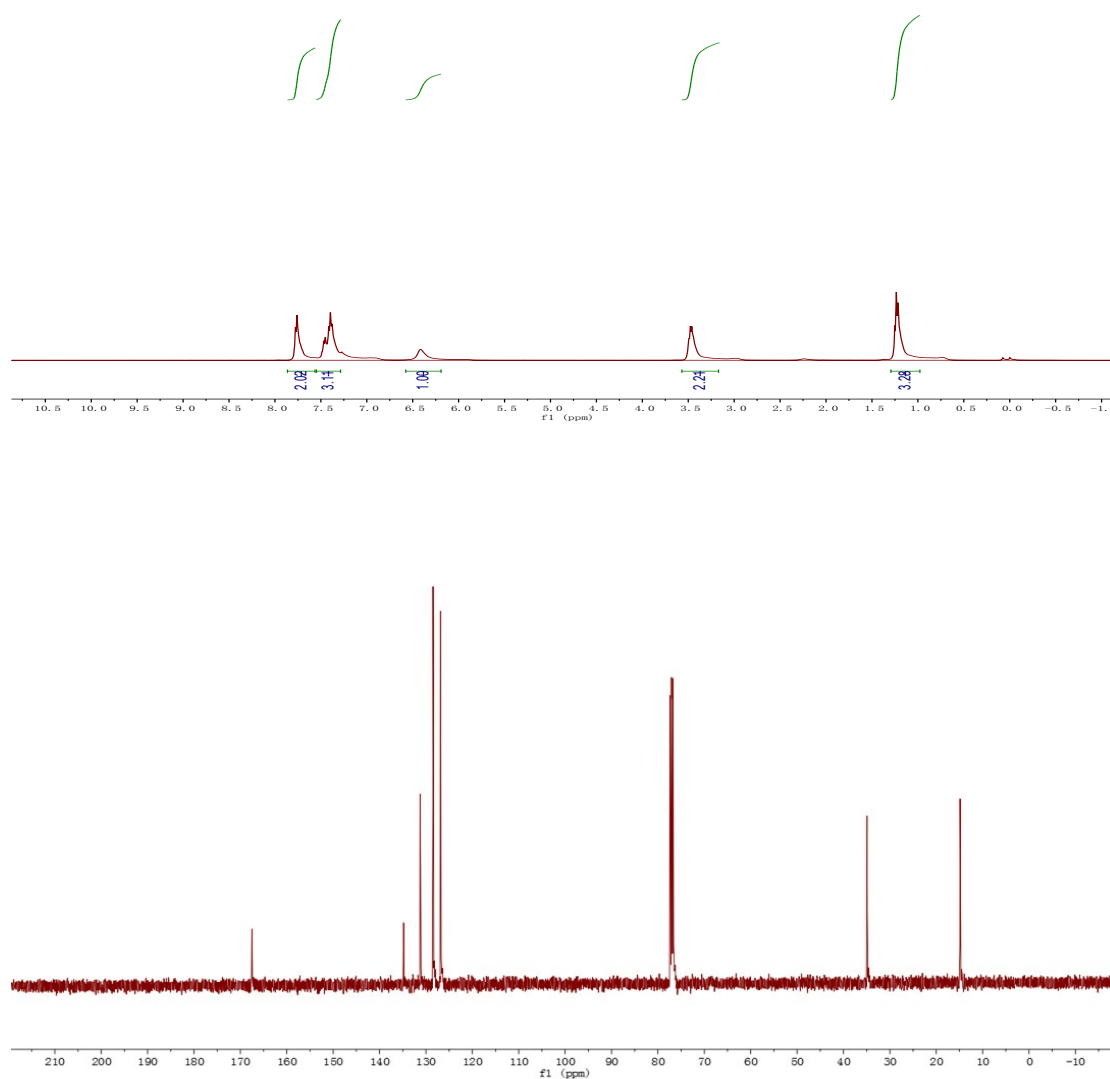
N-Phenylbenzamide (3p). Aniline (140mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (229mg, 78% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 7.9 Hz, 3H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.58–7.52 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 164.7, 136.9, 134.0, 130.8, 128.1, 127.8, 126.0, 123.6, 119.2; HRMS (ESI) *m/z* calcd for C₁₃H₁₁NO [M+H]⁺ 198.0874, found 198.0886.

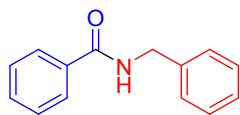




N-Ethylbenzamide (**3q**). Ethylamine (68mg, 1.5mmol, 1 equiv.) was treated with

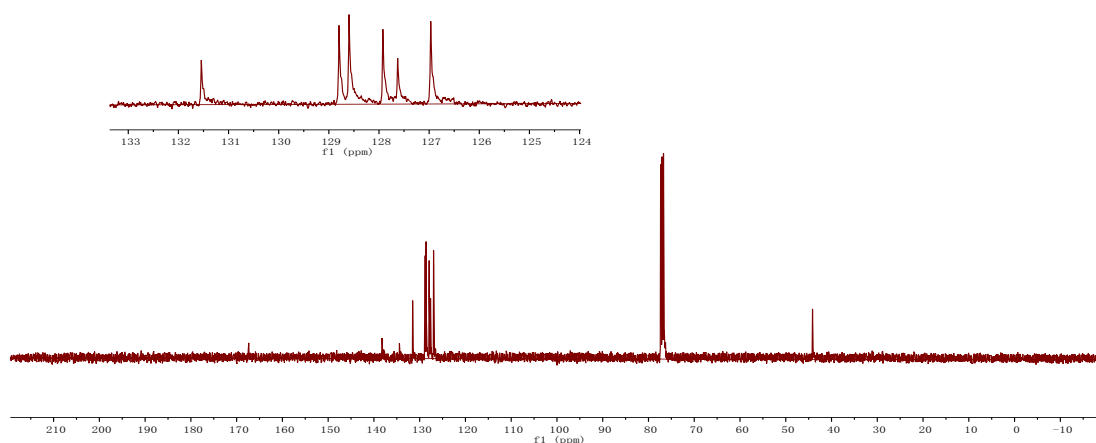
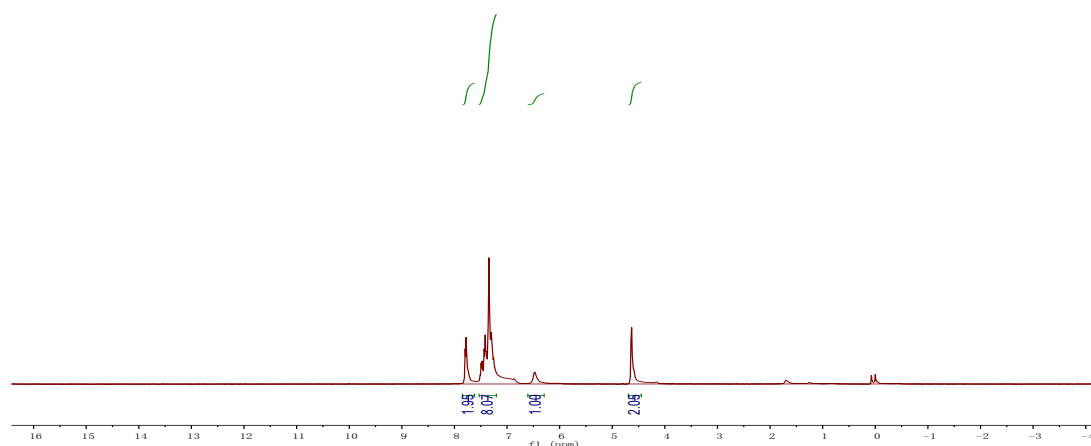
N-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (170mg, 76% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 7.1 Hz, 2H), 7.55–7.29 (m, 3H), 6.41 (s, 1H), 3.57–3.17 (m, 2H), 1.29–0.98 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 167.5, 134.8, 131.3, 128.5, 126.9, 34.9, 14.9; HRMS (ESI) *m/z* calcd for C₉H₁₁NO [M+H]⁺ 150.0874, found 150.0887.

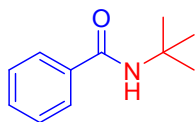




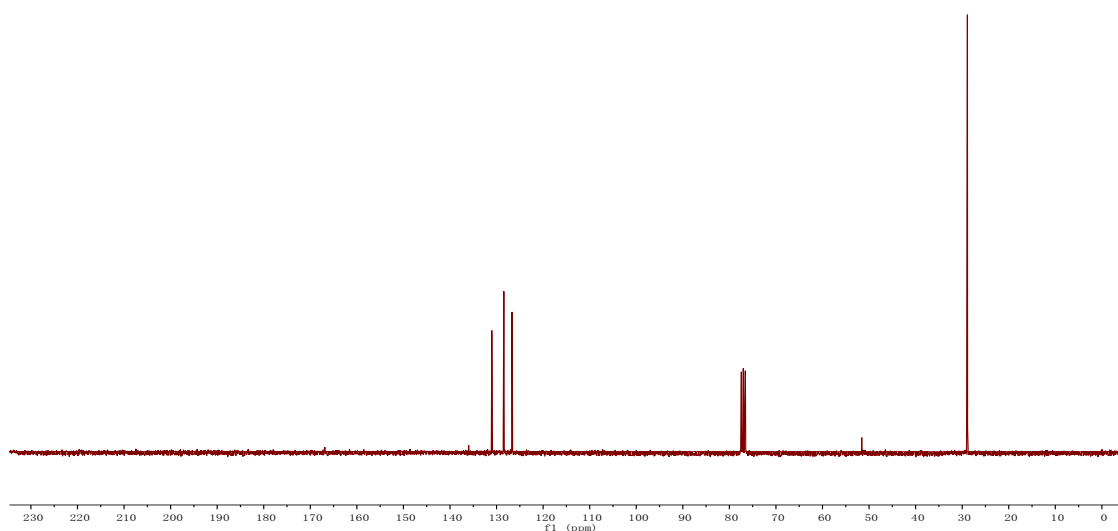
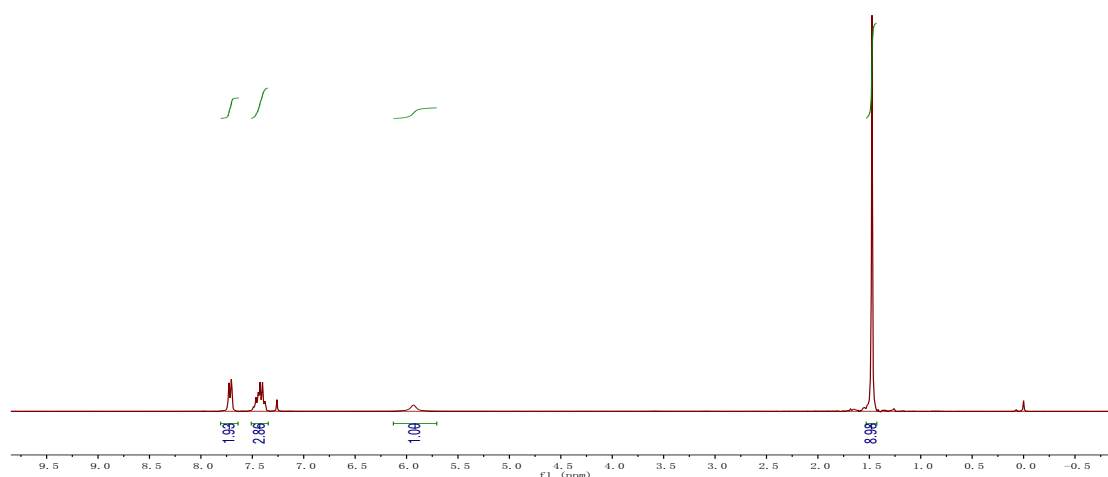
N-Benzylbenzamide (**3r**). Benzylamine (160mg, 1.5mmol, 1 equiv.) was

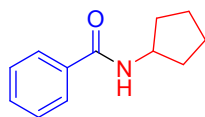
treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (266mg, 84% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.53–7.20 (m, 8H), 6.48 (s, 1H), 4.64 (d, *J* = 5.5 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 167.4, 138.2, 134.4, 131.5, 128.8, 128.6, 127.9, 127.6, 127.0, 44.2; HRMS (ESI) *m/z* calcd for C₁₄H₁₃NO [M+H]⁺ 212.1031, found 212.1084.





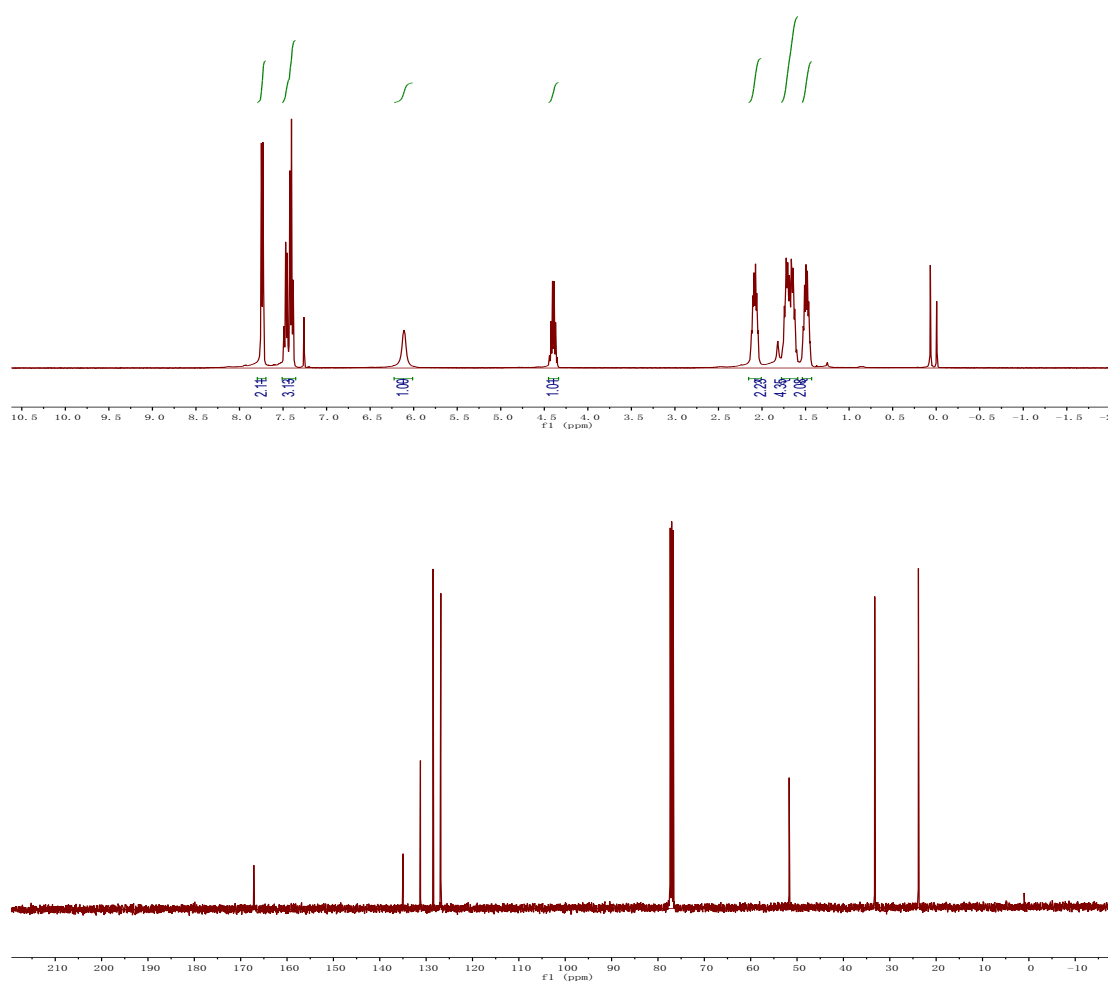
N-tert-butylbenzamide (**3q**). Tert-Butylamine (110mg, 1.5mmol, 1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (170mg, 64% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, *J* = 7.0 Hz, 2H), 7.51 – 7.35 (m, 3H), 5.93 (s, 1H), 1.47 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.87, 135.99, 131.02, 128.44, 126.67, 51.57, 28.88 ; HRMS (ESI) *m/z* calcd for C₁₁H₁₅NO [M+H]⁺178.1226, found 178.1228.

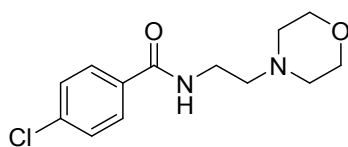




N-Cyclopentylbenzamide (**3t**). Cyclopentylamine (128mg, 1.5mmol, 1 equiv.)

was treated with *N*-chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then toluene (1381mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (232mg, 82% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.80–7.70 (m, 2H), 7.51–7.35 (m, 3H), 6.11 (s, 1H), 4.45–4.34 (m, 1H), 2.08 (td, *J* = 11.4, 6.1 Hz, 2H), 1.78–1.59 (m, 4H), 1.49 (td, *J* = 12.5, 6.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 167.2, 135.0, 131.2, 128.5, 126.8, 51.7, 33.2, 23.8; HRMS (ESI) *m/z* calcd for C₁₂H₁₅NO [M+H]⁺ 190.1187, found 190.1192.





4-Chloro-N-(2-morpholinoethyl)benzamide (**2**). 4-(2-

Aminoethyl)morpholine (195mg, 1.5mmol, 1 equiv.) was treated with *N*- chlorosuccinimide (NCS) (220mg, 1.65mmol, 1.1 equiv.) in 10mL acetonitrile at room temperature for 3h, and then 4-Chlorotoluene (1899mg, 15.0mmol, 10.0 equiv.), Cu(OAc)₂ (54mg, 0.3mmol, 20 mol%), TBAI (111mg, 0.3mmol, 20 mol%) and TBHP (70 wt% in water, 1544mg, 12.0mmol, 8.0 equiv.) were added to the reaction mixture, stirring at 80°C for 24h. And the product was obtained after purification as white solid (277mg, 69% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.72 (s, 1H), 3.79 – 3.68 (m, 4H), 3.54 (dd, *J* = 11.1, 5.6 Hz, 2H), 2.60 (t, *J* = 6.0 Hz, 2H), 2.55 – 2.45 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 166.28, 137.63, 133.02, 128.82, 128.32, 56.82, 53.34, 36.10; HRMS (ESI) *m/z* calcd for C₁₃H₁₇N₂O₂Cl [M+H]⁺ 269.1051, found 269.1044.

