Electronic supplementary information

The Au(Ⅲ)-catalyzed Coupling Reactions between Alcohols and N-heterocycles *via* C–H Bond Activation

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Contents

General considerations

All reagents and all solvents were obtained from commercial suppliers and used without further purification except as indicated below. For thin-layer chromatography (TLC), compounds were visualized by irradiation with UV light on GF 254 silica gel plates. And all experiments were carried out under air. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at Bruker ARX-300 MHz spectrometer with chemical shifts referenced to $SiMe_4$ as internal standard. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent resonance. Coupling constant (*J*) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = double, t = triplet, dd = double doublet, tt = triple triplet, q = quartet, m = multiplet, b = broad. HRMS were recorded on an Agilent 6210 TOF LC/MS equipped with electrospray ionization (ESI) probe operating in positive or negative ion mode.

Typical procedure:

$HAuCl_4 \cdot 4H_2O$ (0.025 mmol), TBHP (2.25 mmol) were placed in a dry sealable tube.

To this, dried alcohol (2.5 mL) and N-heterocycle (0.5 mmol) were added. The tube was sealed, and stirred for 24 hours at 120 ^{o}C. The reaction mixture was cooled to room temperature and flushed through a short column of silica gel with ethyl acetate. The solvent was removed under vacuum， and product was isolated by flash column chromatography.

Control experiment

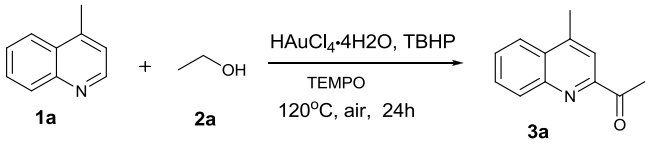
1. Reaction of isoquinoline with butyraldehyde:

$HAuCl_4 \cdot 4H_2O$ (0.025 mmol), TBHP (2.25 mmol) were placed in a dry sealable tube. To this, butyraldehyde (2.5 mL) and lepidine (0.5 mmol) (**1a**) were added. The tube was sealed, and stirred for 24 hours at 120 ^{o}C. The reaction mixture was cooled to room temperature and detected with MS, no alcohol intermediate was found, and the relative acylation product was found. Hence, it is ruled out the possibility of the peroxide oxidizing the alcohol to the the aldehyde in situ and the subsequent addition of the heterocycle to the aldehyde giving the intermediate. And it demonstrated that the reaction undergo the activation of the α sp^3 C–H of alcohols by a radical mechanism rather than the sp^2 C–H of aldehyde which was oxidized by the relative alcohol.

2. Reactions with 20 mol % HCl:

Dried ethanol (2.5 mL) and lepidine(0.5 mmol) (**1a**) were placed in a sealable tube. To this, 0.01 mol concentrated hydrochloric acid and TBHP (2.25 mmol) were added, and stirred for 24 hours at 120 ^{o}C. The reaction mixture was cooled to room temperature and flushed through a short column of silica gel with ethyl acetate. The solvent was removed under vacuum. Only 30% product (**3a**) was isolated by flash column chromatography. While with the gold catalyst the yield can be improved to 65%; thus the metal catalyst system was needed to the reaction and superior than the aicd (HCl).

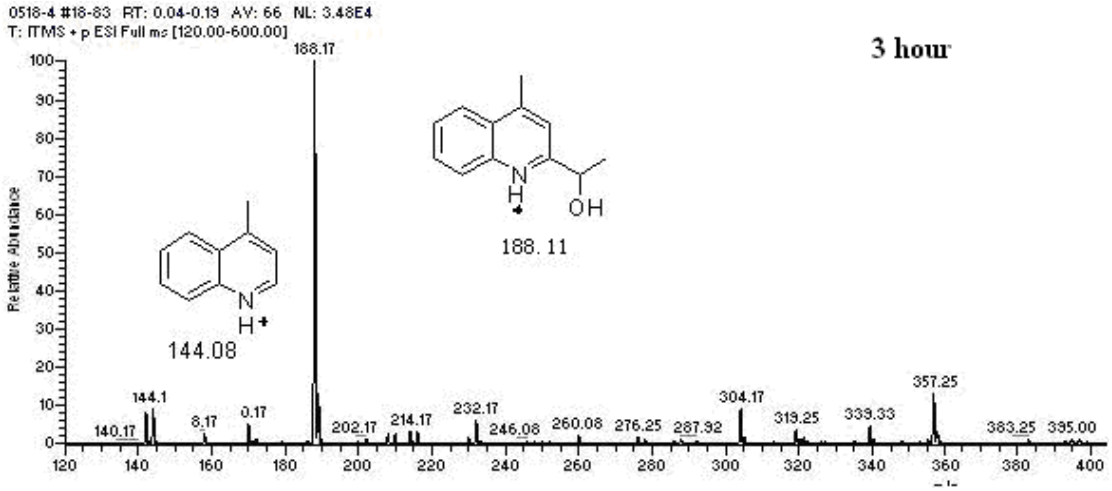
3. Effect of radical scavenger

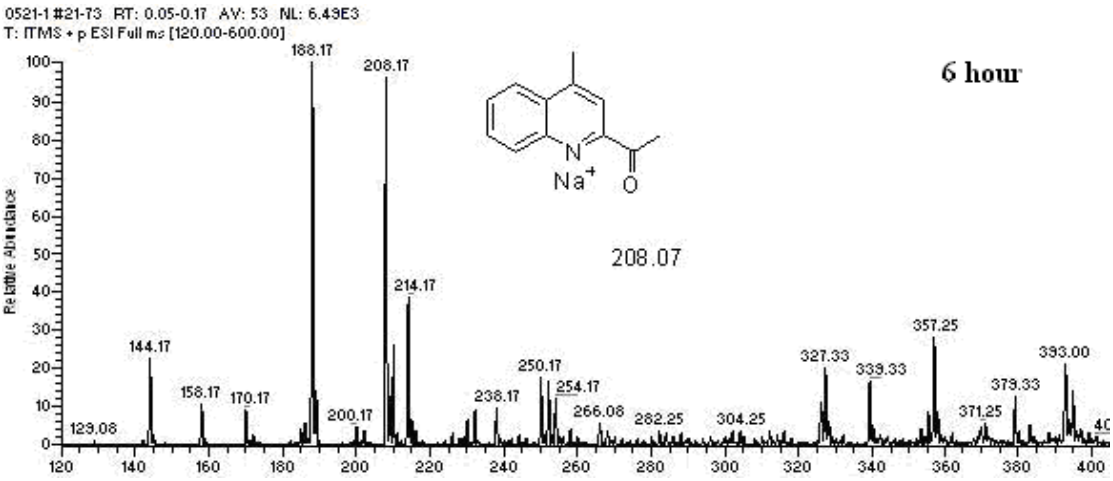


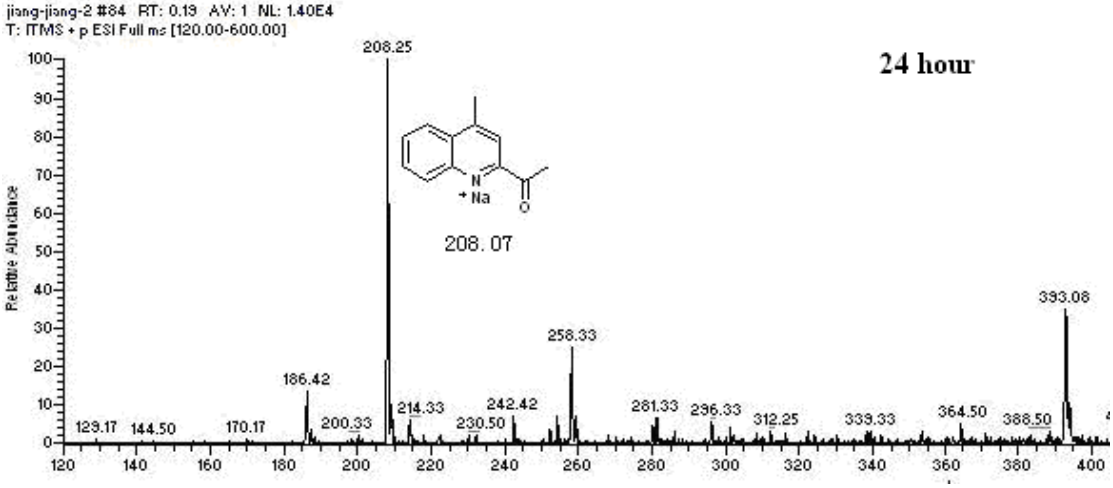
$HAuCl_4 \cdot 4H_2O$ (0.025 mmol), TBHP (2.25 mmol) were placed in a dry sealable tube. To this, dried ethanol (2.5 mL), lepidine (0.5 mmol) (**1a**) and TEMPO (4.5 equiv) were added. The tube was sealed, and stirred for 24 hours at 120 ^{o}C. The reaction mixture was cooled to room temperature and detected with MS, no alcohol intermediate or product (**3a**) were found. It indicated that the reaction may proceed through the activation of the α sp^3 C–H of alcohols by a radical mechanism.

4. The Spectrum of the MI

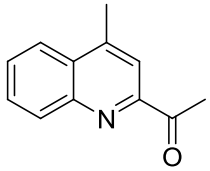
The Ms was detected 3 hours later, 6 hours later and 24 hours later respectively.



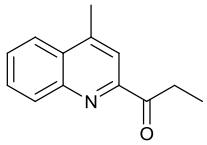




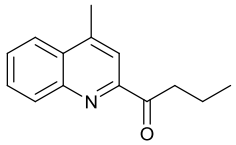
Characterization data for the direct acylation of N-heterocycles products



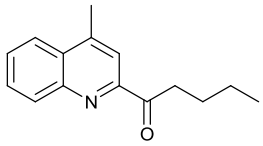
3a: White solid (71% yield); mp. 58-60 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.2 Hz, 1H), 8.02-7.89 (m, 1H), 7.79-7.58 (m, 1H), 2.84 (s, 1H), 2.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 152.9, 147.1, 145.3, 131.2, 129.7, 128.4, 123.84, 118.5, 25.6, 18.6; HRMS (ESI): calculated for $C_{12}H_{11}NONa$: 208.0738 $[M+Na]^+$; found: 208.0737



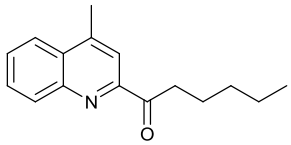
3b: White solid (47% yield); mp. 64-66 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.93 (s, 1H), 7.79-7.70 (m, 1H), 7.68-7.59 (m, 1H), 3.40 (q, *J* = 7.3 Hz, 2H), 2.73 (s, 3H), 1.26 (t, *J* = 7.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 152.8, 147.1, 145.3, 131.2, 129.6, 128.2, 123.9, 118.7, 30.9, 19.0, 8.2; HRMS (ESI): calculated for $C_{13}H_{13}NONa$: 222.0895 $[M+Na]^+$; found: 222.0884



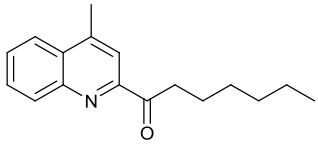
3c: White solid (45% yield); mp. 56-58 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.95 (s, 1H), 7.80-7.71 (m, 1H), 7.65 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.36 (t, *J* = 7.4 Hz, 2H), 2.74 (s, 3H), 1.90-1.73 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 152.9, 147.2, 145.4, 131.3, 129.7, 128.3, 123.9, 118.8, 39.4, 19.0, 17.8, 14.1; HRMS (ESI): calculated for $C_{14}H_{15}NONa$: 236.1051 $[M+Na]^+$; found: 236.1045



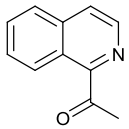
3d: Colorless oil (50% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.93 (s, 1H), 7.79-7.70 (m, 1H), 7.68-7.56 (m, 1H), 3.37 (t, *J* = 7.4 Hz, 2H), 2.72 (s, 3H), 1.84-1.69 (m, 2H), 1.54-1.35 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 152.9, 147.1, 145.3, 131.2, 129.6, 128.2, 123.9, 118.8, 37.2, 26.5, 22.7, 19.0, 14.2; HRMS (ESI): calculated for $C_{15}H_{17}NONa$: 250.1208 $[M+Na]^+$; found: 250.1202



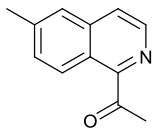
3e: Colorless oil (47% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.3, 1H), 7.94 (s, 1H), 7.80-7.71 (m, 1H), 7.69-7.58 (m, 1H), 3.36 (t, *J* = 7.5 Hz, 2H), 2.74 (s, 3H), 1.86-1.71 (m, 2H), 1.49-1.34 (m, 5H), 0.96-0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 152.9, 147.2, 145.3, 131.3, 129.7, 129.6, 128.3, 123.9, 118.8, 37.5, 31.7, 24.1, 22.7, 19.0, 14.1; HRMS (ESI): calculated for $C_{16}H_{19}NONa$: 264.1364 $[M+Na]^+$; found: 264.1360



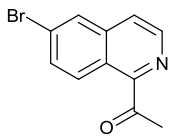
3f: White solid (42% yield); mp. 39-41 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.94 (s, 1H), 7.79-7.70 (m, 1H), 7.68-7.58 (m, 1H), 3.36 (t, *J* = 7.5 Hz, 2H), 2.73 (s, 3H), 1.84-1.71 (m, 2H), 1.49-1.28 (m, 7H), 0.90 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 152.9, 147.2, 145.3, 131.3, 129.7, 129.6, 128.2, 123.9, 118.8, 37.5, 31.8, 29.2, 24.3, 22.7, 19.0, 14.2; HRMS (ESI): calculated for $C_{17}H_{21}NONa$: 278.1521 $[M+Na]^+$; found: 278.1513



3g: White solid (79% yield); mp. 66-68 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98-8.92 (m, 1H), 8.57 (d, *J* = 5.5 Hz, 1H), 7.88-7.78 (m, 2H), 7.74-7.63 (m, 2H), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 152.9, 141.1, 137.1, 130.4, 129.2, 127.1, 126.9, 125.8, 124.8, 28.7; HRMS (ESI): calculated for $C_{11}H_9NONa$: 194.0582 $[M+Na]^+$; found: 194.0576

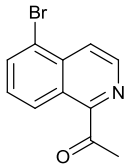


3h: White solid (45% yield); mp. 36-38 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (d, *J* = 8.8 Hz, 1H), 8.51 (d, *J* = 5.5 Hz, 1H), 7.69 (d, *J* = 5.5 Hz, 1H), 7.58 (s, 1H), 7.48 (d, *J* = 8.8, 1H), 2.84 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 152.5, 141.2, 140.8, 137.5, 131.6, 126.7, 125.9, 124.2, 28.6, 22.0; HRMS (ESI): calculated for $C_{12}H_{11}NONa$: 208.0738 $[M+Na]^+$; found: 208.0731

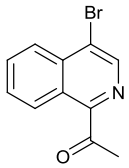


3i: White solid (60% yield); mp. 68-70 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (d, *J* = 9.2 Hz, 1H), 8.58 (d, *J* = 5.6 Hz, 1H), 7.99 (s, 1H), 7.74-7.67 (m, 2H), 2.84 (s, 2H);

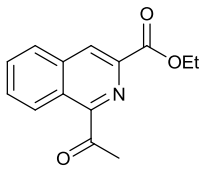
^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 152.7, 142.2, 138.2, 132.7, 129.1, 128.8, 125.4, 124.2, 123.6, 28.5; HRMS (ESI): calculated for $C_{11}H_9NONa$: 249.9868 $[M+H]^+$; found: 249.9857



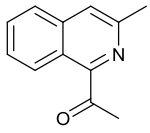
3j: White solid (65% yield); mp. 76-78 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, *J* = 8.7 Hz, 1H), 8.62 (d, *J* = 5.8 Hz, 1H), 8.15 (m, 5.1 Hz, 1H), 7.99-7.89 (m, 1H), 7.44 (m, 1H), 2.84(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 153.1, 142.4, 135.97, 134.2, 129.3, 126.8, 126.6, 123.4, 121.9, 28.8; HRMS: calculated for $C_{11}H_9NONa$: 249.9868 $[M+H]^+$; found: 249.9857



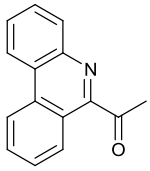
3k: White solid (53% yield); mp. 70-72 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.5 Hz, 1H), 8.73 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.83-7.63 (m, 2H), 2.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 151.8, 143.0, 135.7, 131.6, 130.0, 127.4, 126.9, 126.3, 124.1, 28.7; HRMS (ESI): calculated for $C_{11}H_9NONa$: 249.9868 $[M+H]^+$; found: 249.9857



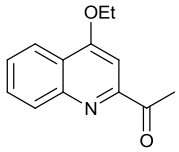
3l: White solid (73% yield); mp. 100-102 ^{o}C;^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00-8.90 (m, 1H), 8.65 (s, 1H), 8.01-7.94 (m, 1H), 7.81-7.72 (m, 2H), 4.51 (q, *J* = 7.1 Hz, 2H), 2.92 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 165.3, 153.0, 140.1, 137.1, 131.3, 131.1, 128.5, 127.4, 127.2, 126.9, 62.0, 28.7, 14.5; HRMS (ESI): calculated for $C_{14}H_{13}NO_3Na$: 266.0793 $[M+Na]^+$; found: 266.0789



3m: Colorless oil (70% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.69 -7.53 (m, 4H), 2.85 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 150.1, 137.9, 130.3, 128.2, 126.8, 126.5, 124.0, 122.8, 28.7, 24.1; HRMS (ESI): calculated for $C_{12}H_{11}NONa$: 208.0738 $[M+Na]^+$; found: 208.0731

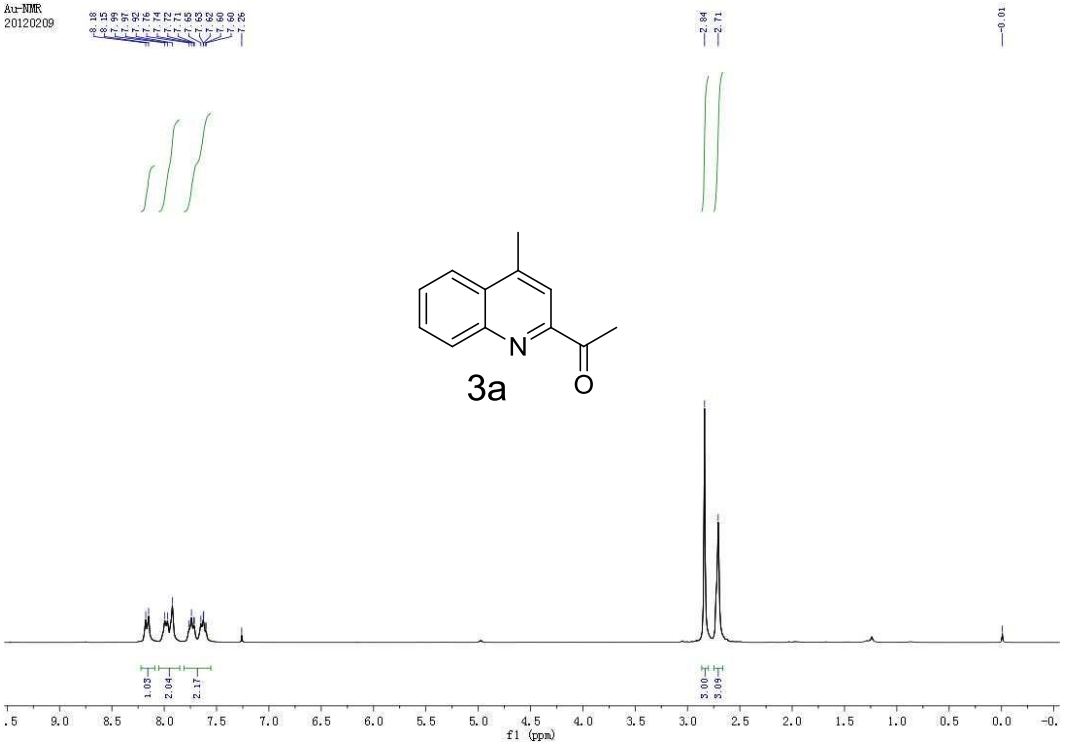


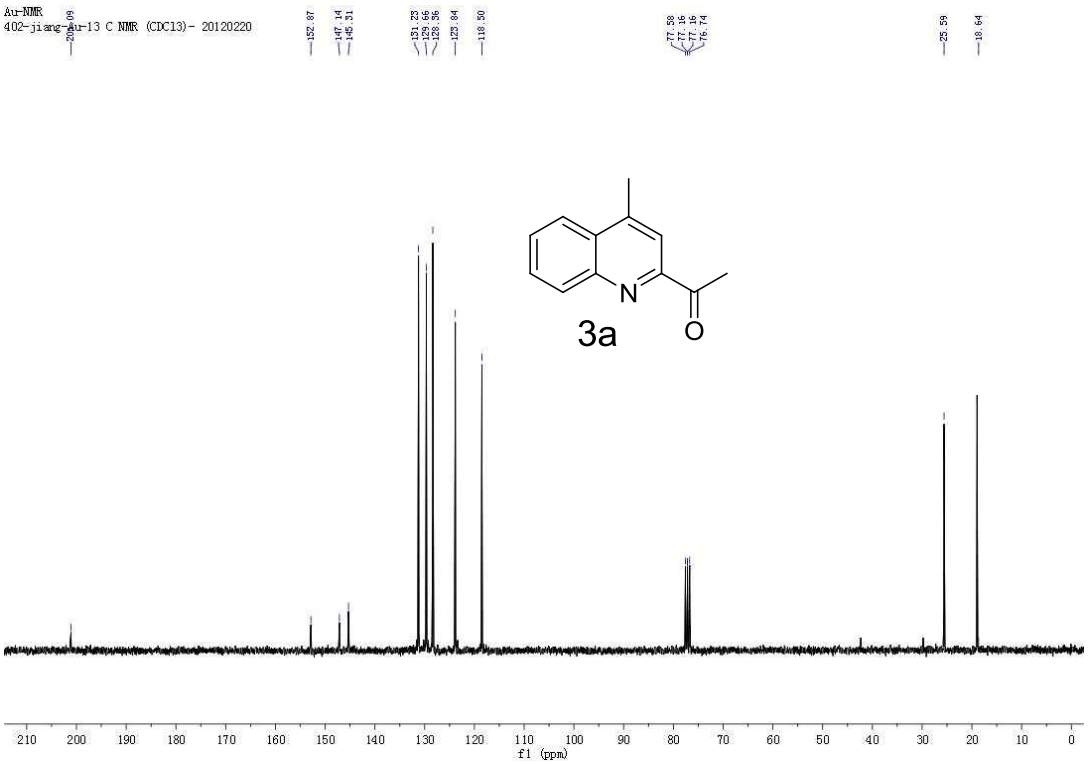
3n: White solid (76% yield); mp. 92-94 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, *J* = 8.4 Hz, 1H), 8.67-8.51 (m, 2H), 8.28-8.16 (m, 1H), 7.90-7.66 (m, 4H), 2.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 153.9, 142.6, 133.6, 131.1, 130.9, 129.0, 128.9, 128.2, 128.0, 125.4, 123.1, 122.2, 122.1, 28.7; HRMS (ESI): calculated for $C_{15}H_{11}NONa$: 244.0738 $[M+Na]^+$; found: 244.0733.

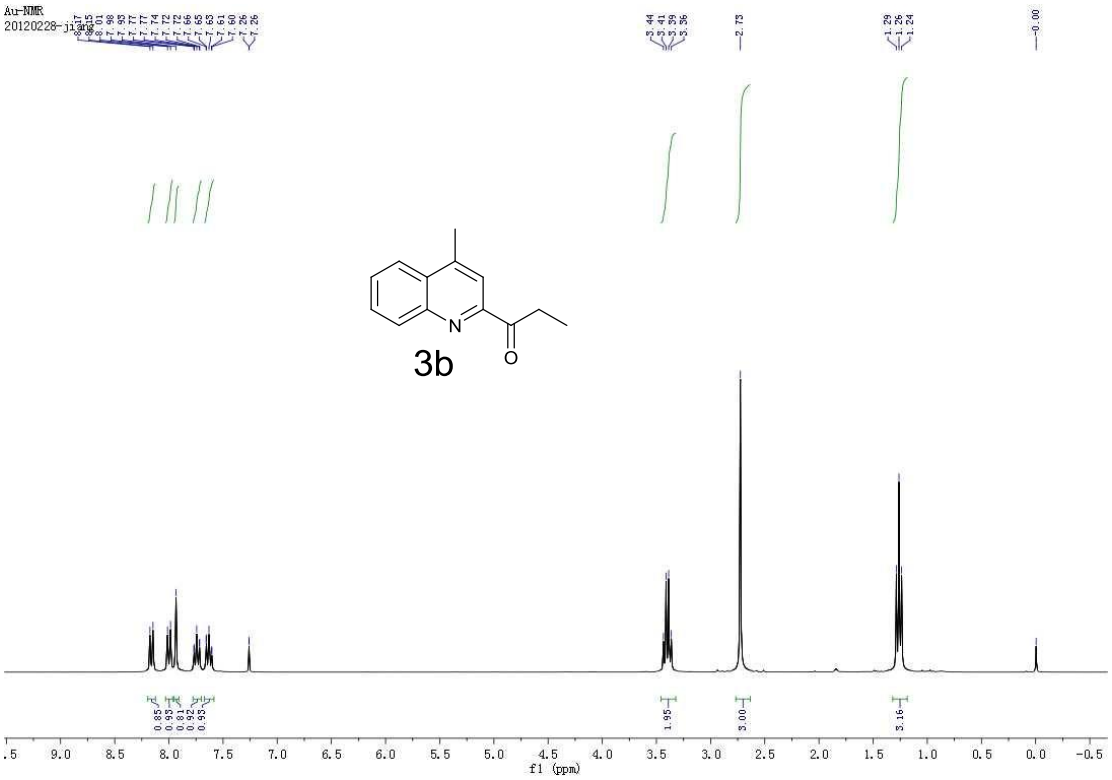


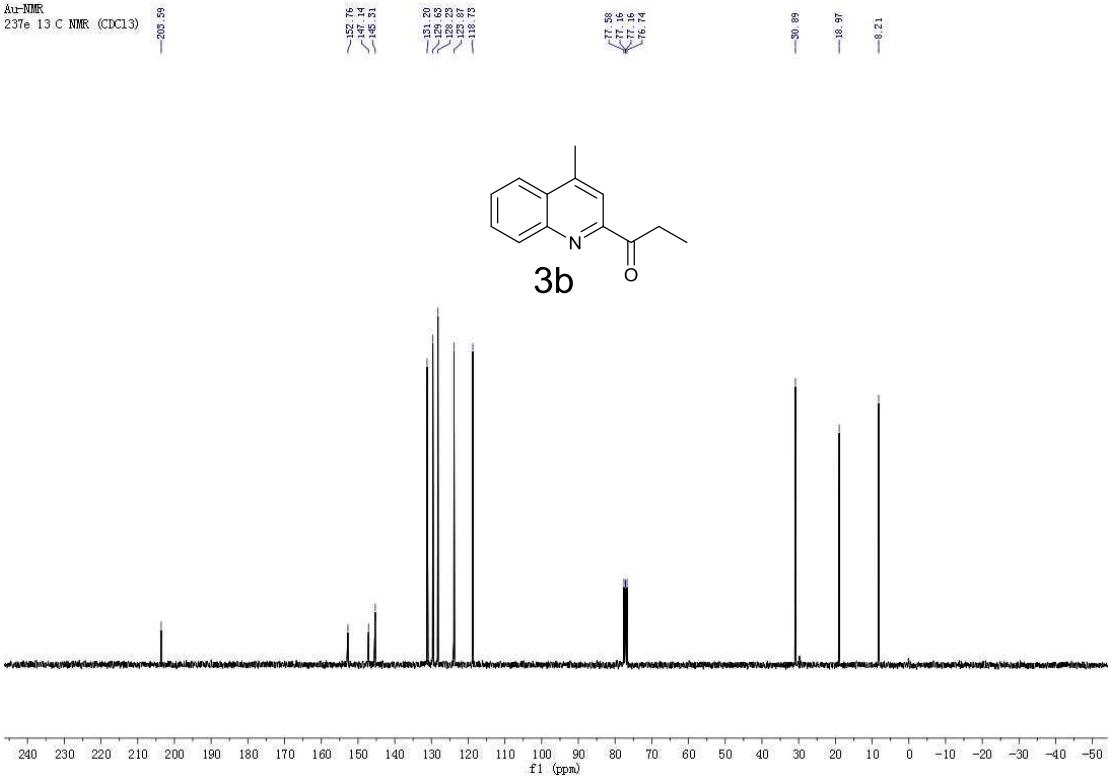
3o: White solid (38% yield); mp. 66-68 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 0.9 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4, 1.4 Hz, 1H), 7.62-7.51 (m, 1H), 7.45 (s, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 2.84 (s, 3H), 1.56 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 162.4, 154.7, 148.4, 130.2, 130.1, 127.5, 122.7, 122.107, 97.3, 64.6, 25.6, 14.6. HRMS (ESI): calculated for $C_{13}H_{13}NO_2Na$: 238.0838 $[M+H]^+$; found: 238.0840

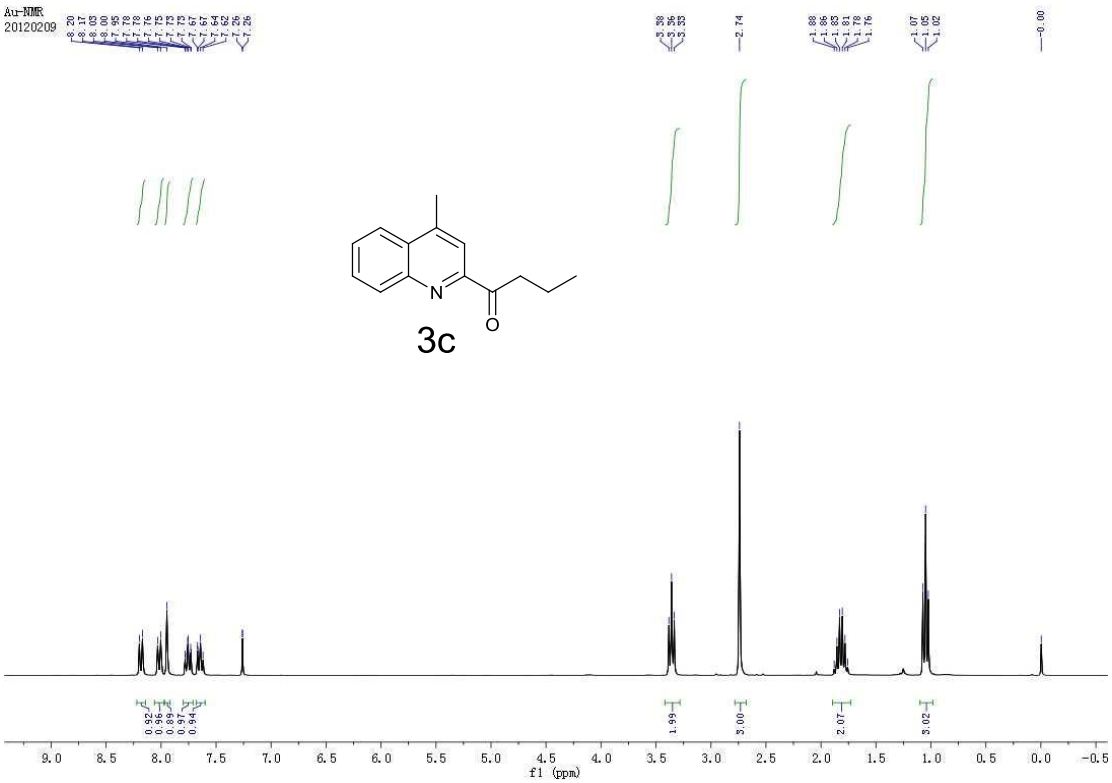
1H and 13C spectra of novel substrates

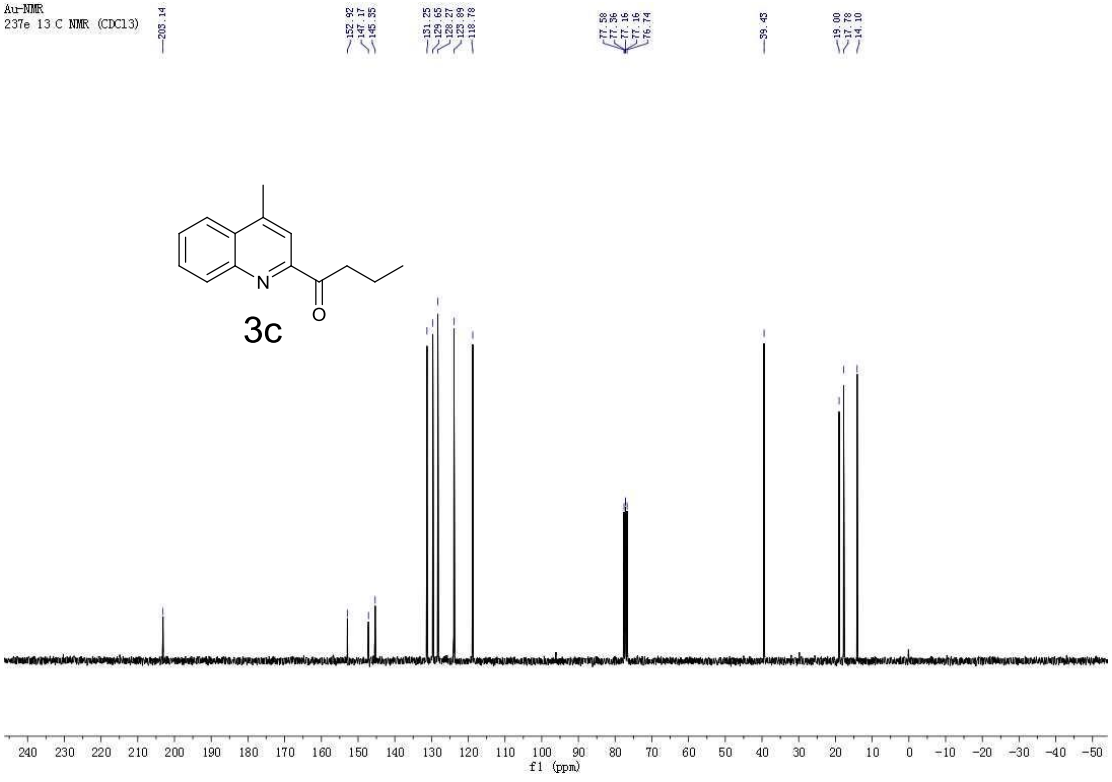


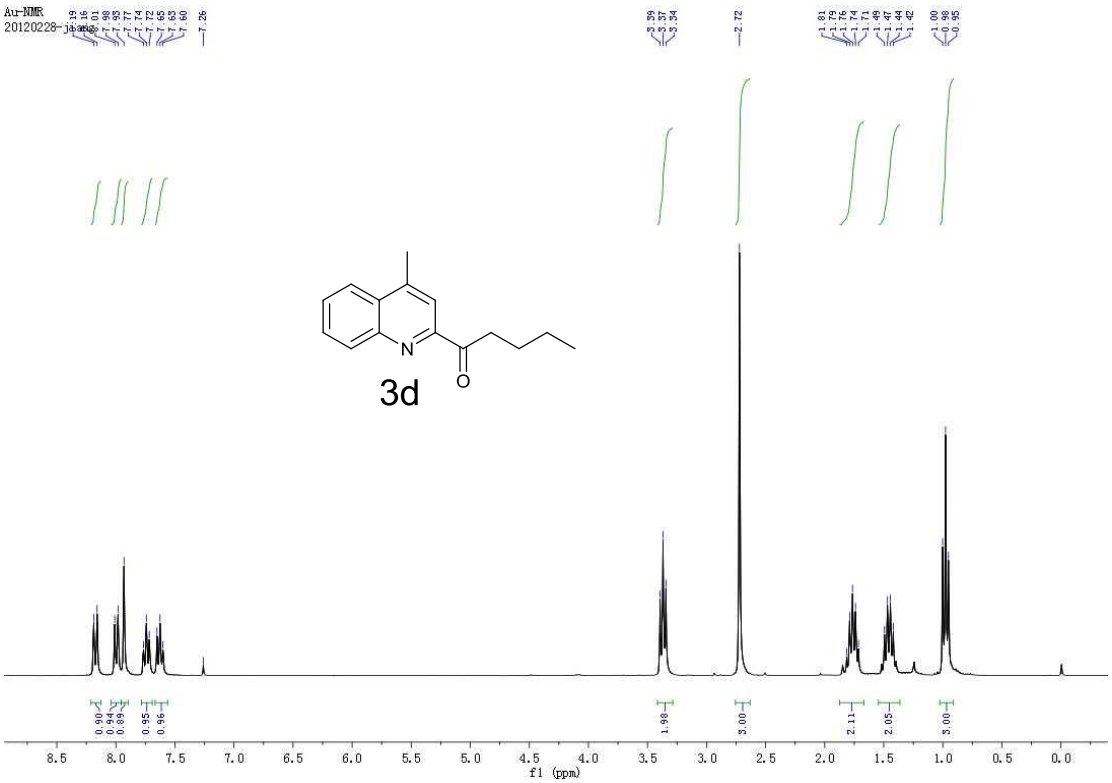


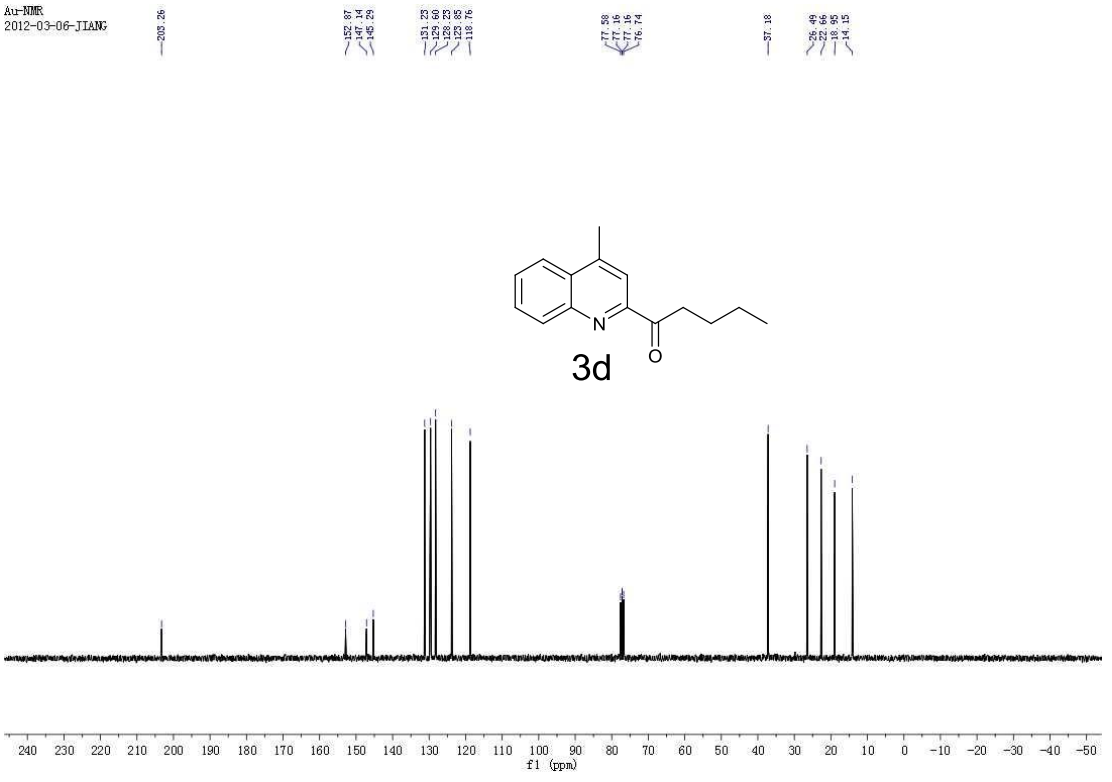


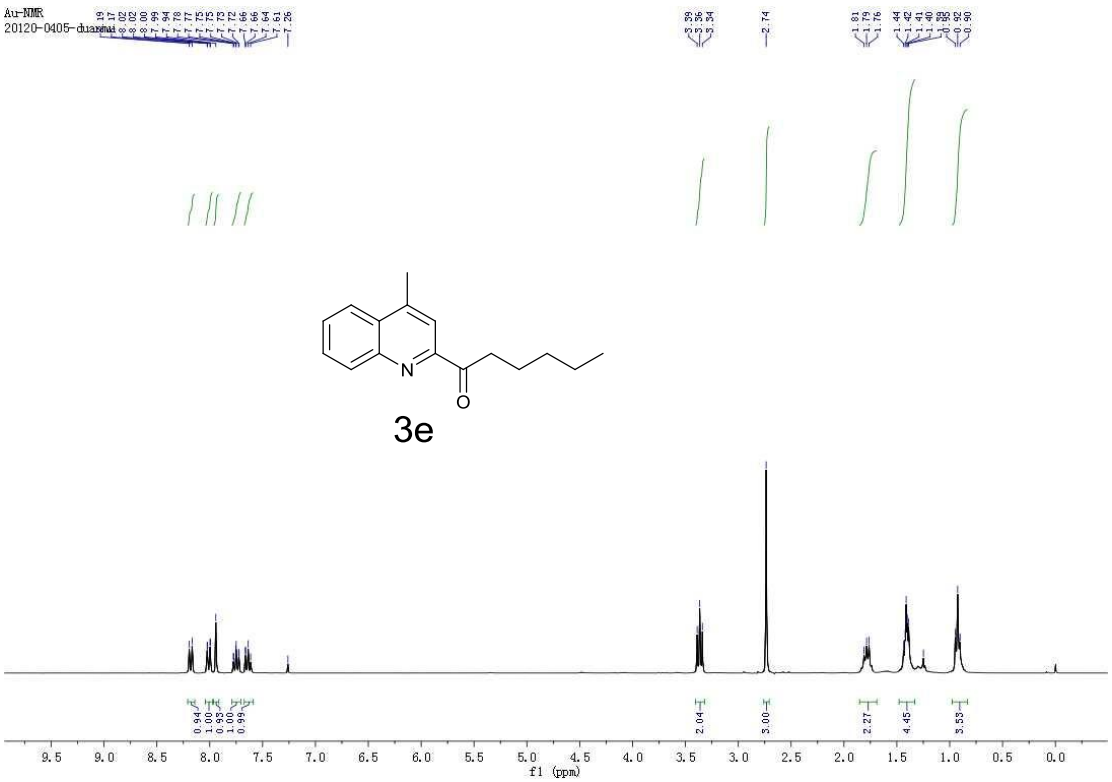



Au-NMR
20120209
3c
f1 (ppm)


Au-NMR
237e 13 C NMR (CDCl3)
3c
f1 (ppm)



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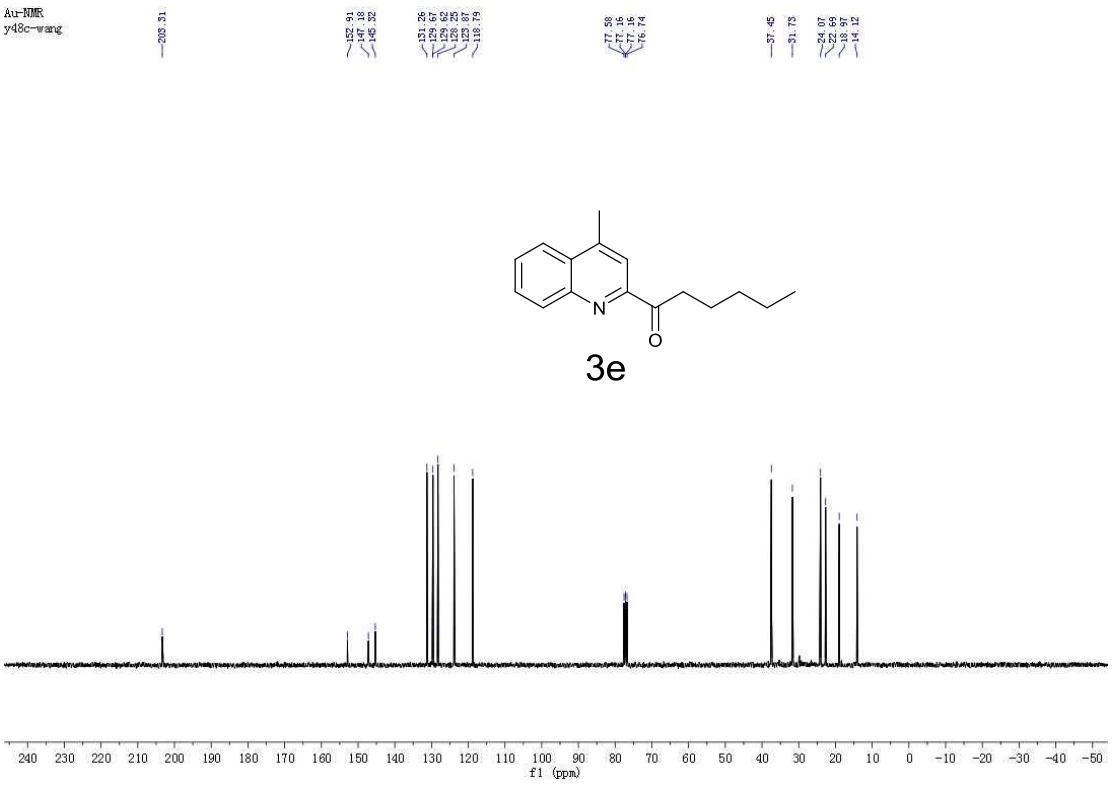
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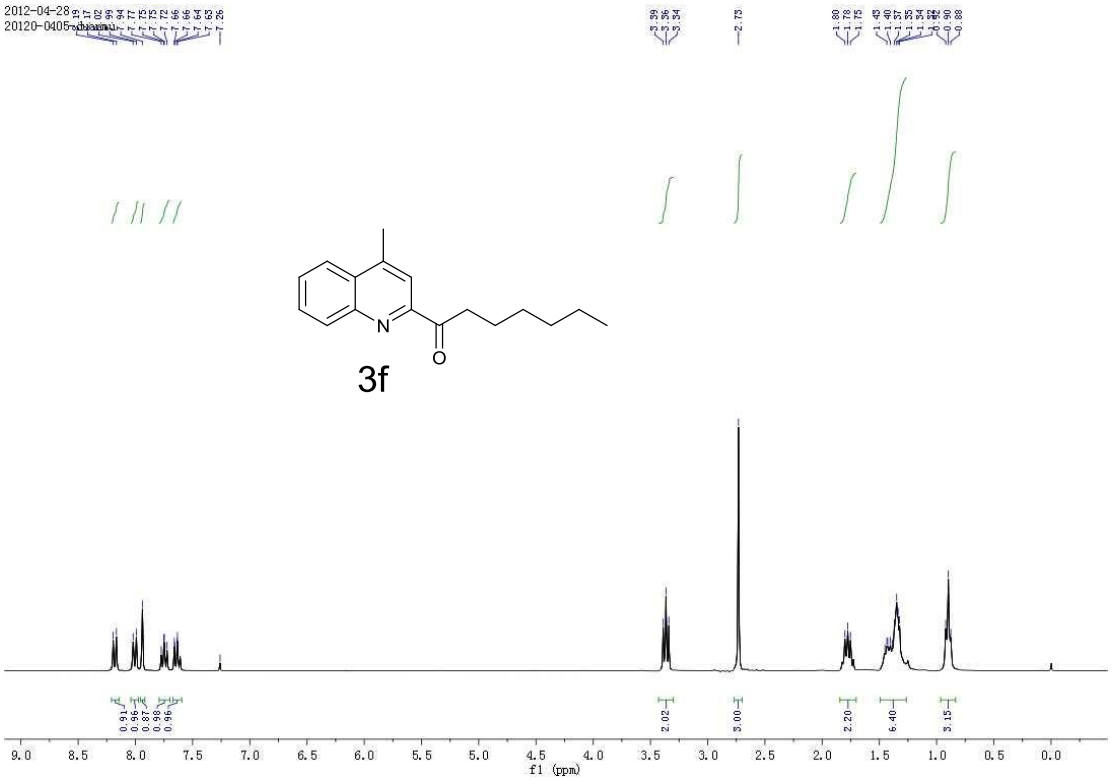
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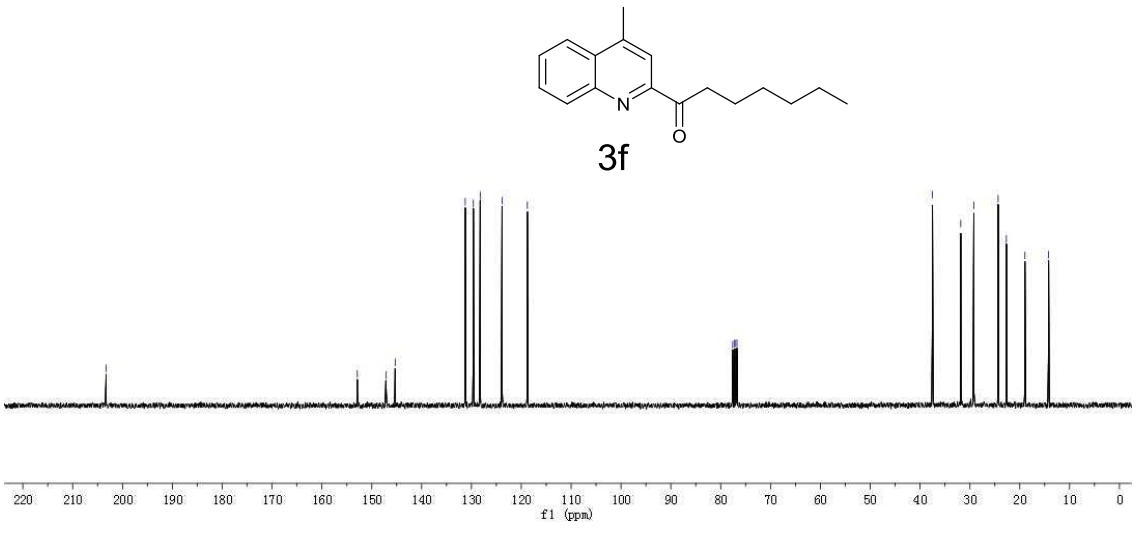
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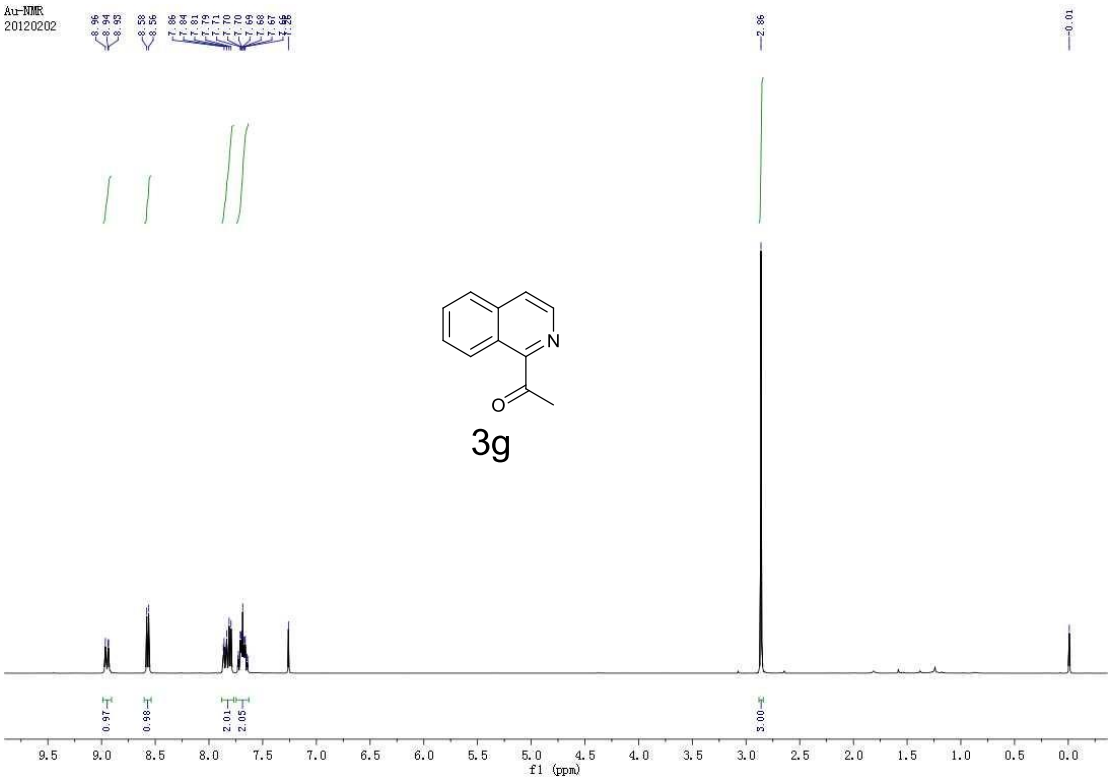
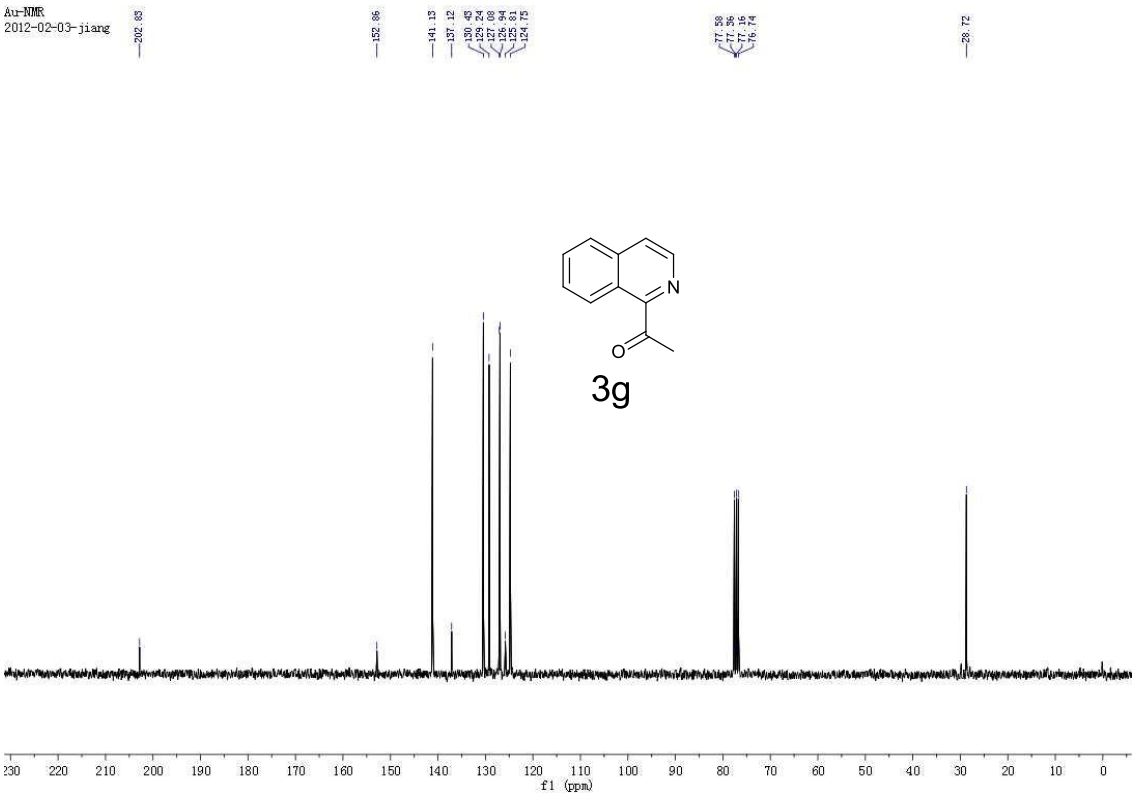
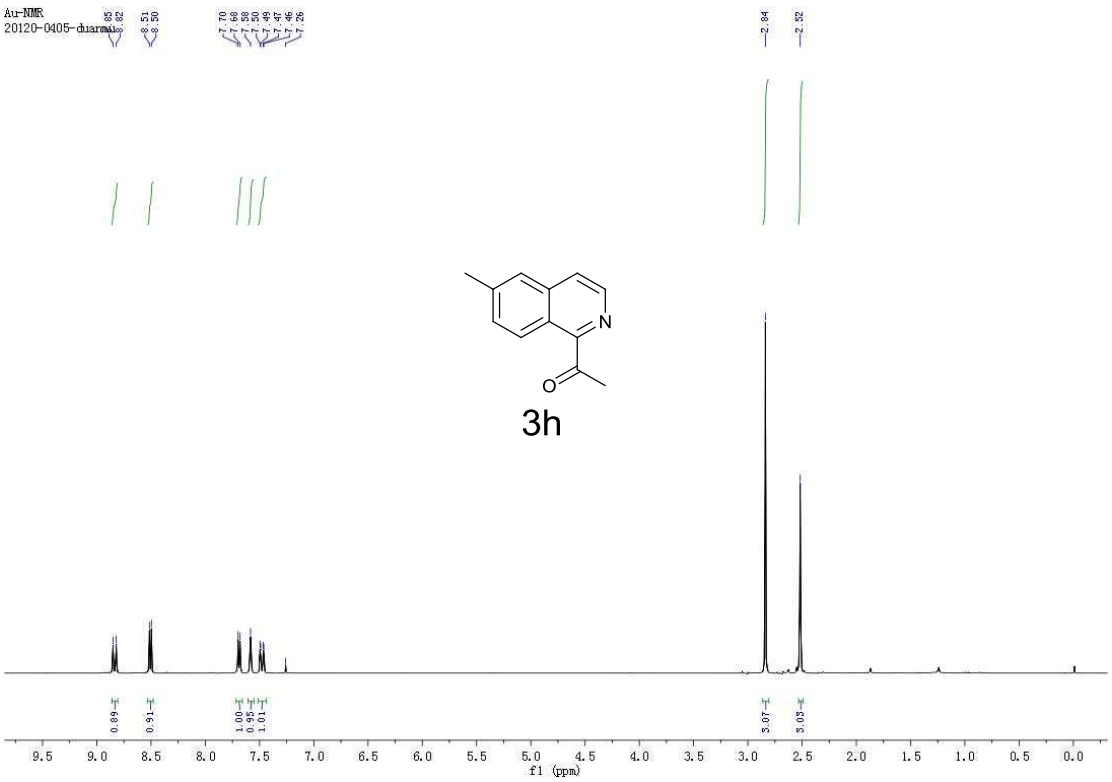
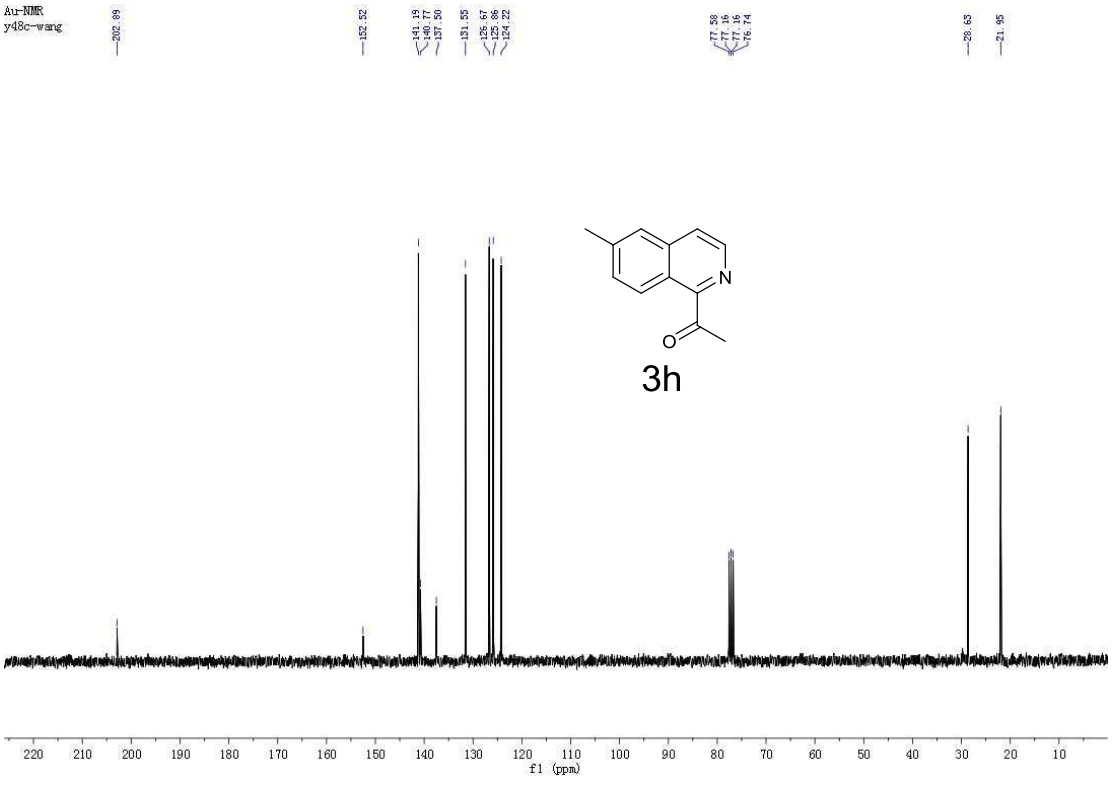
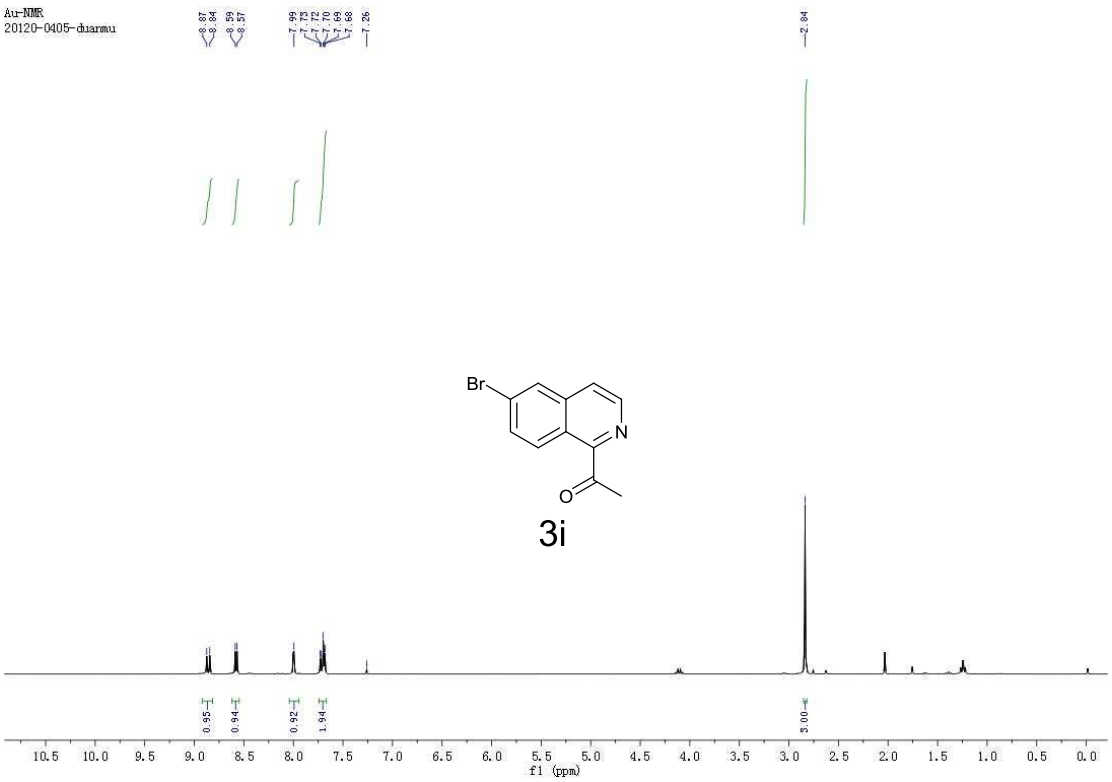
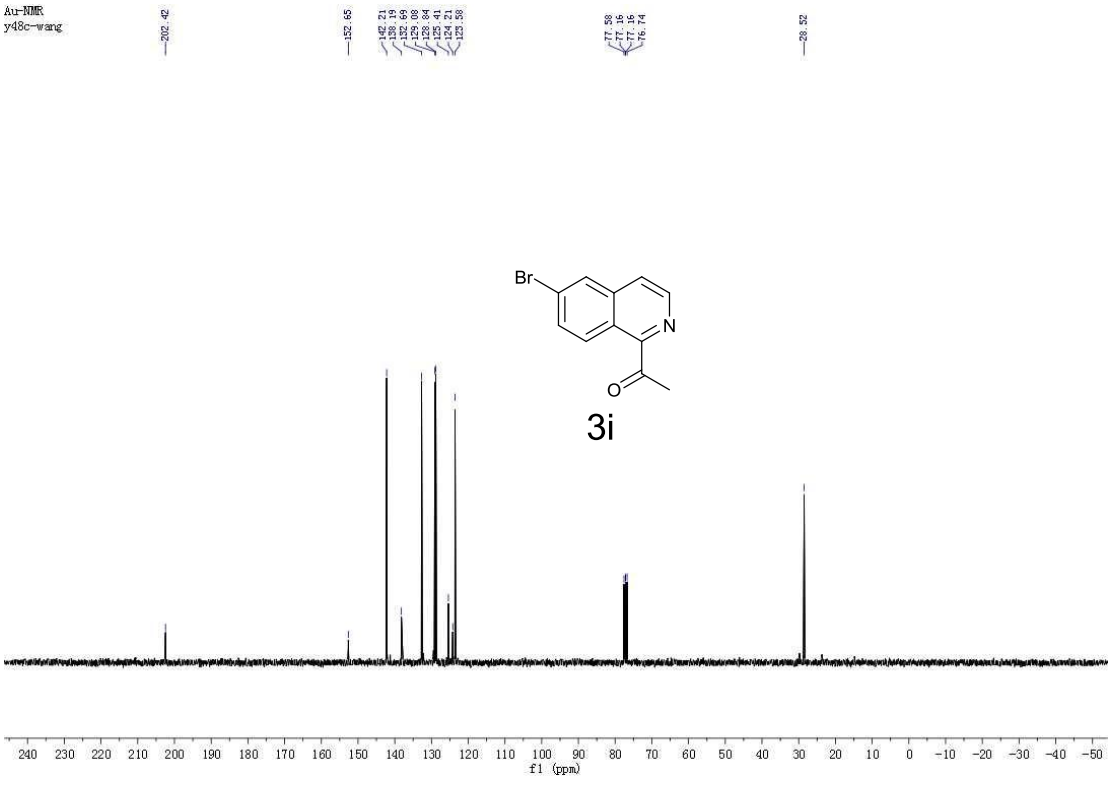


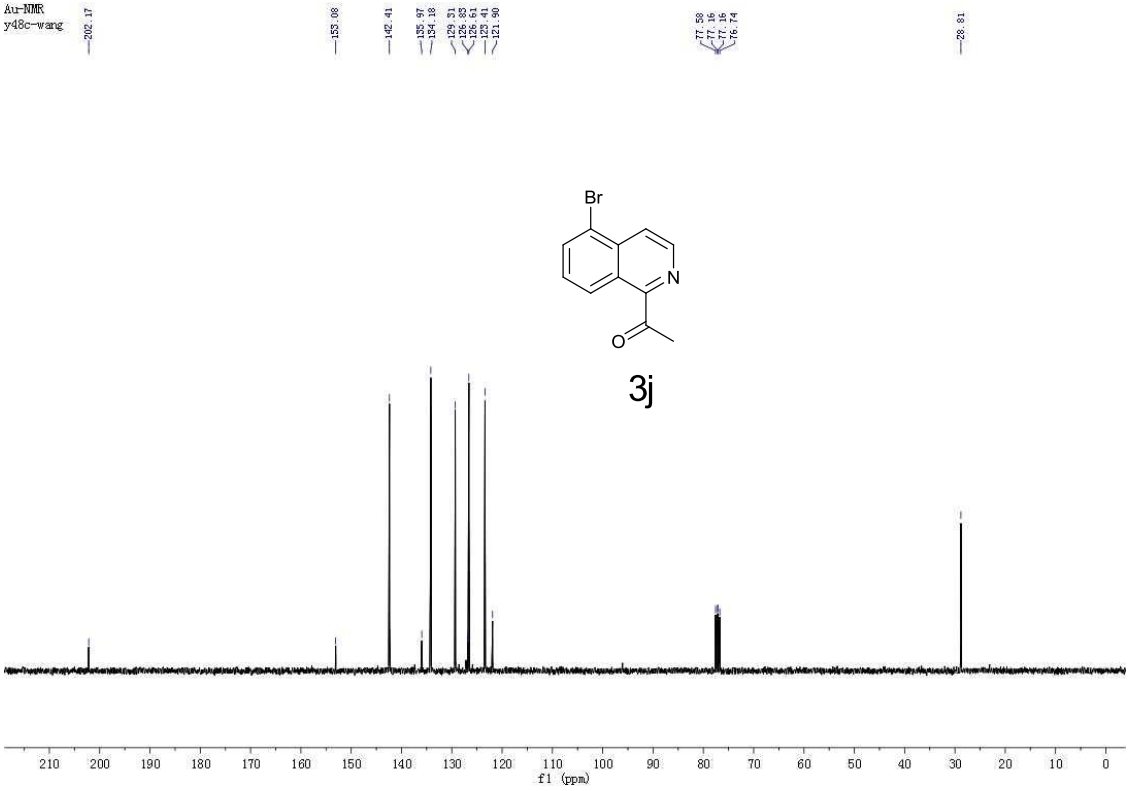


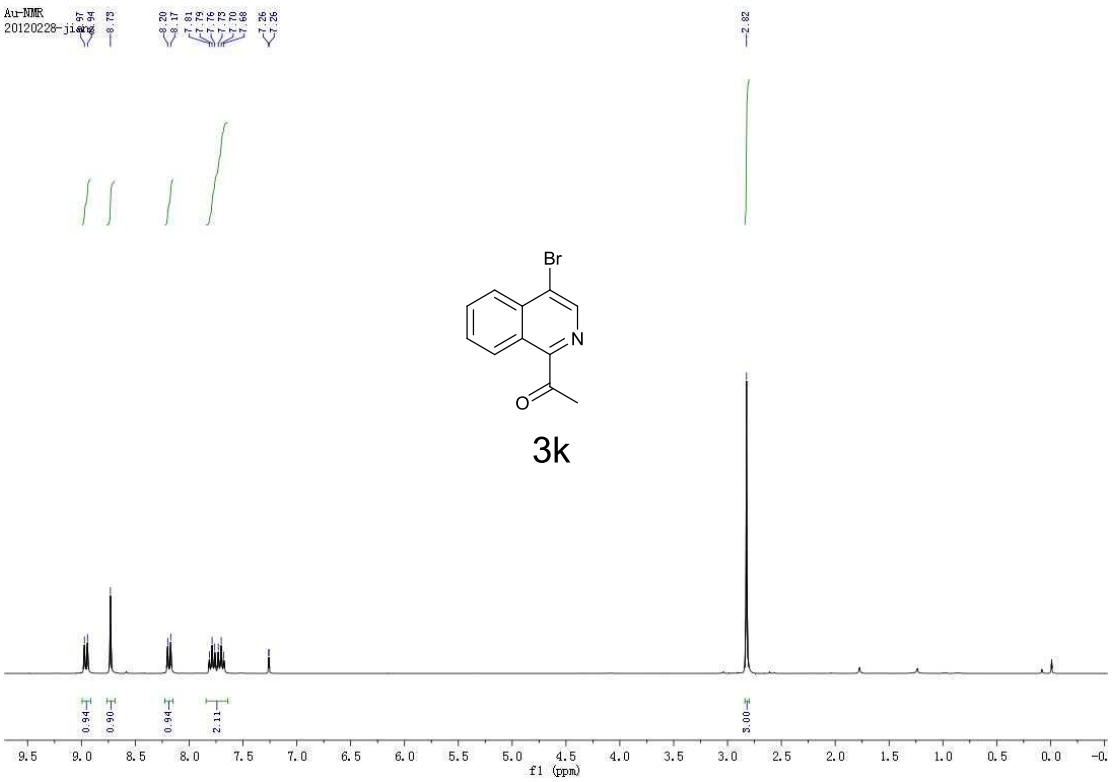


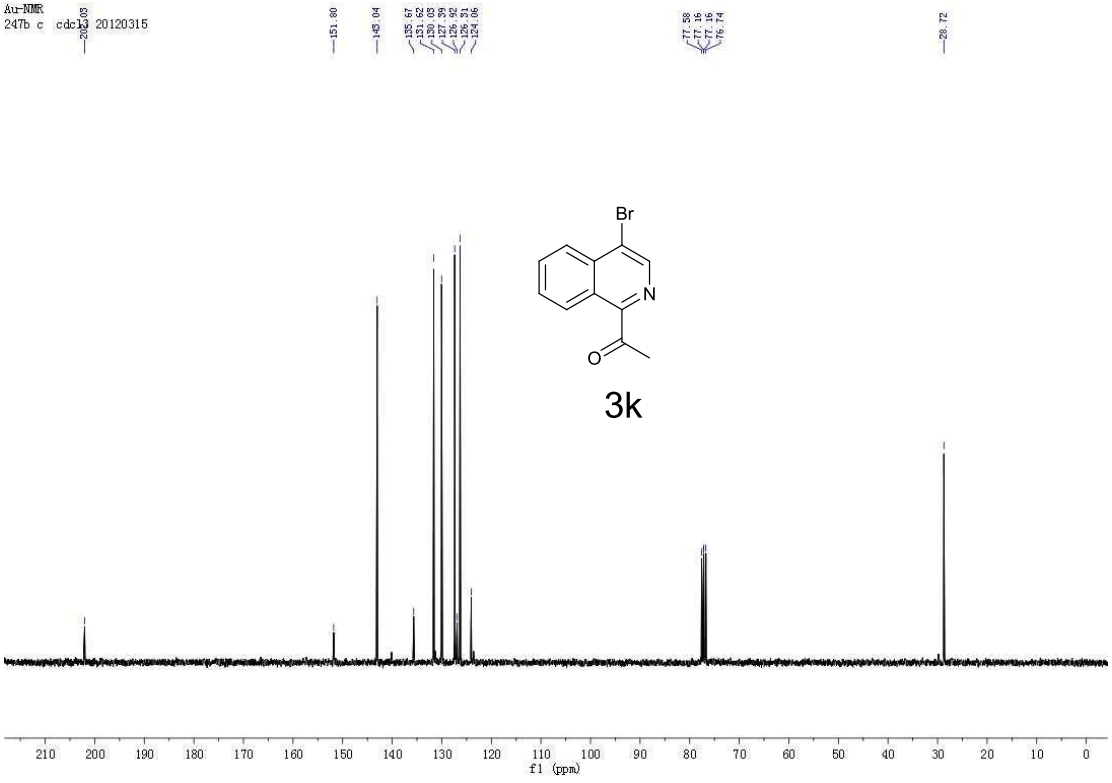


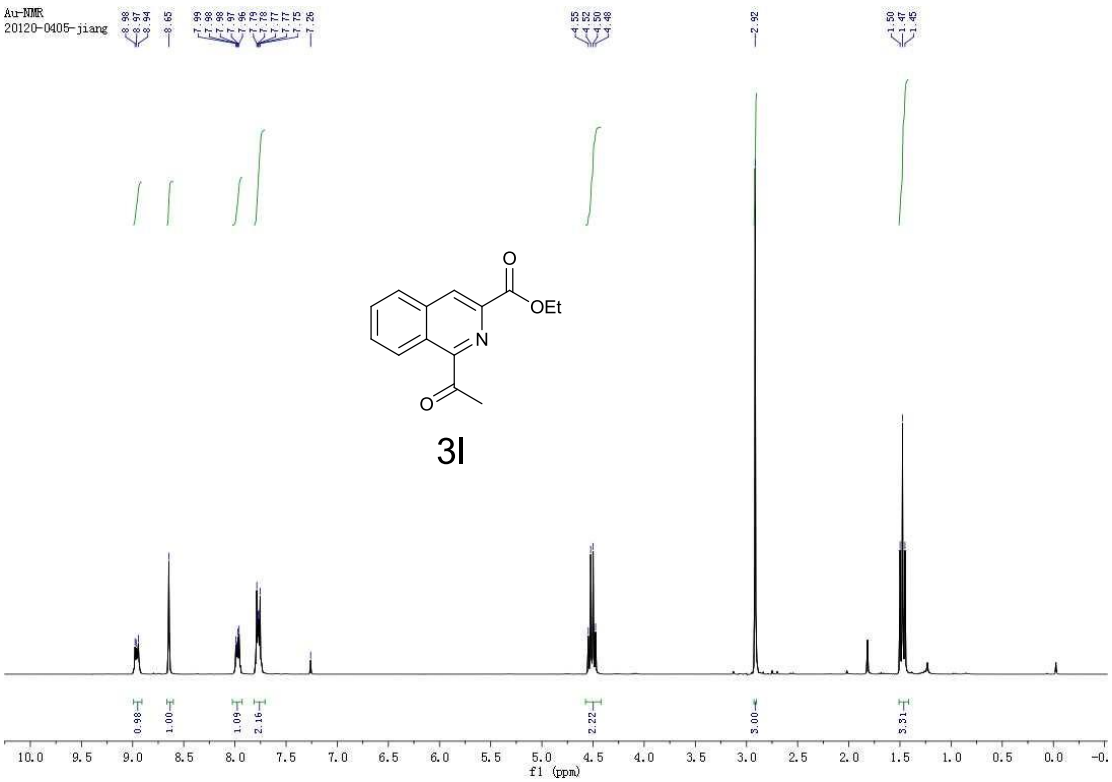


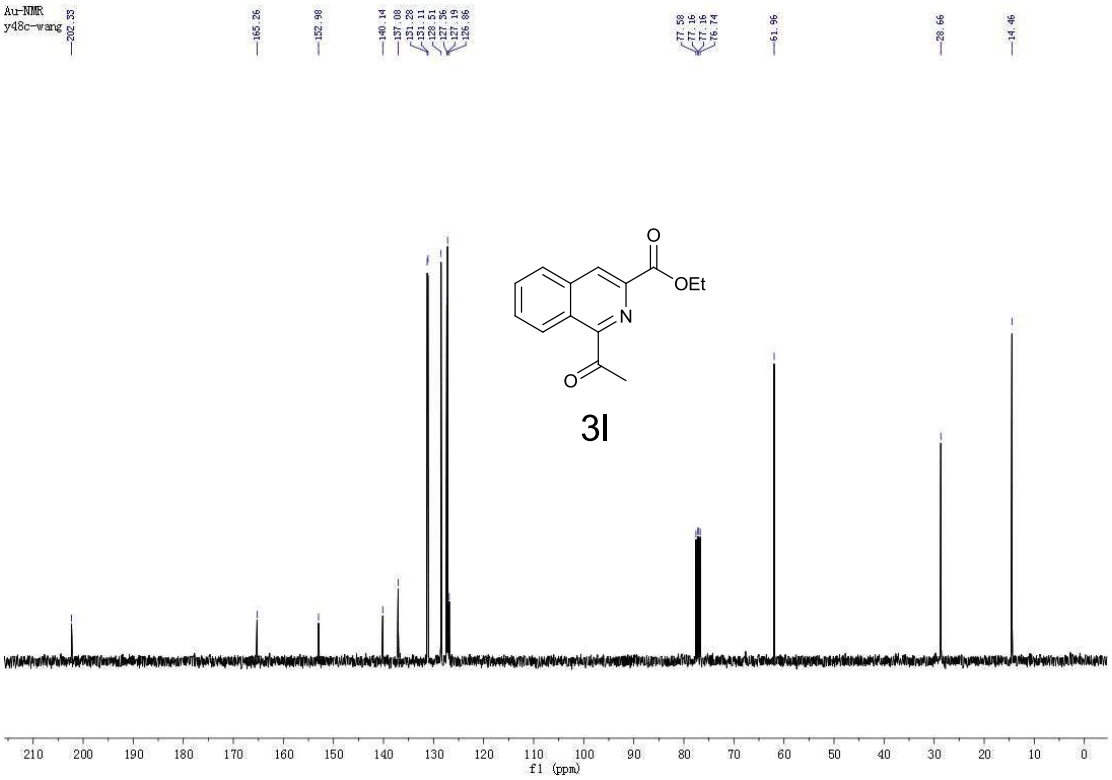


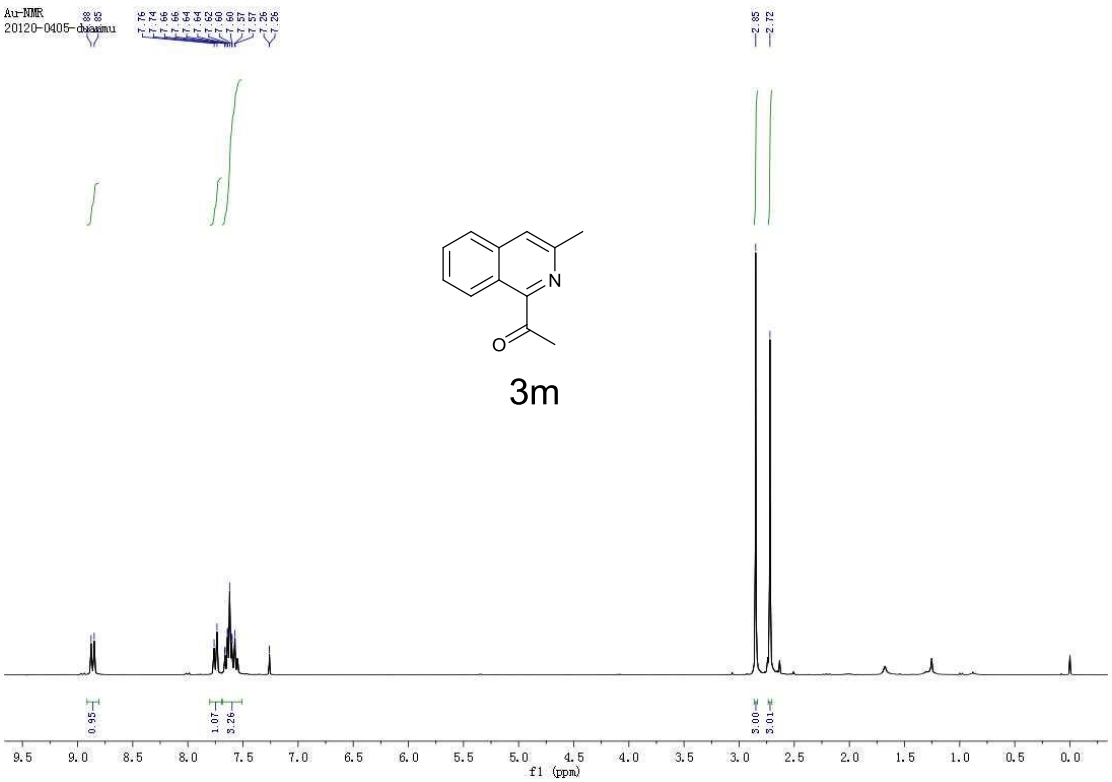




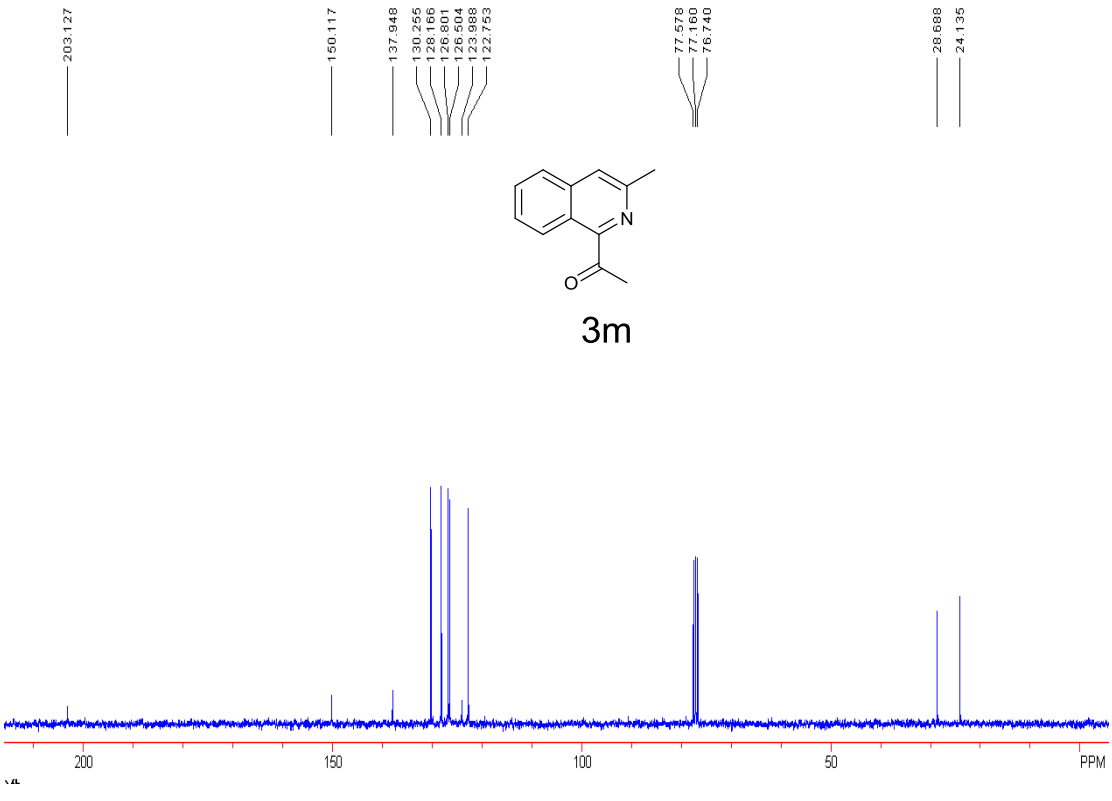








3m



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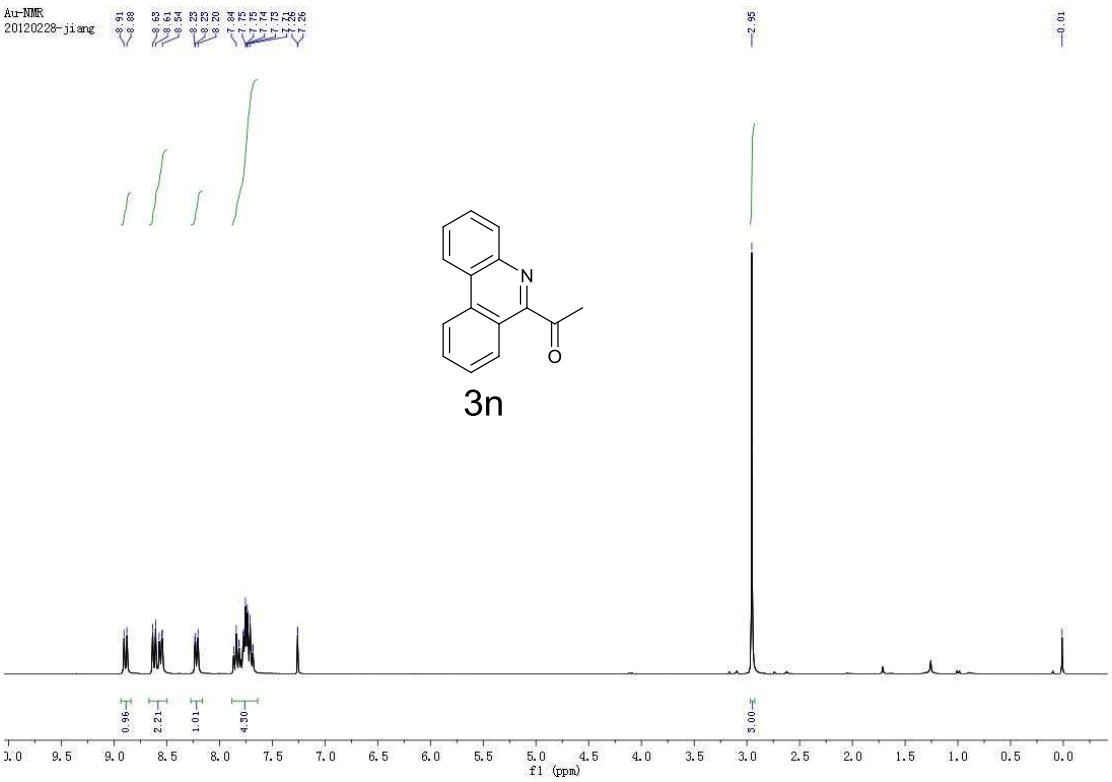

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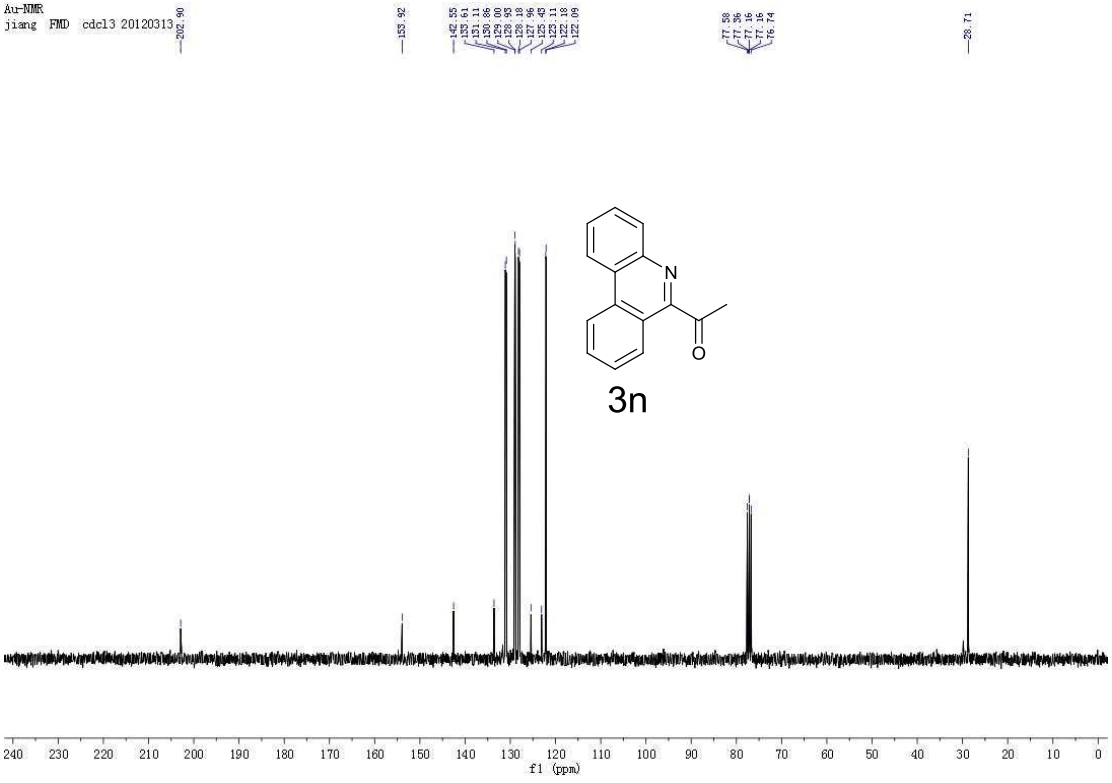

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