

LiCl-Mediated Preparation of Highly Functionalized Benzylic Zinc Chlorides

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Supporting Information

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General All reactions were carried out under an argon atmosphere in dried glassware. All starting materials which were purchased from commercial sources were used without further purification. Solvents were dried according to standard method by distillation over drying agents under nitrogen atmosphere as follows: DCM (CaH_2), toluene (Na), diethyl ether (Na/benzophenone). THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen before use. Yields refer to isolated yields of compounds estimated to be > 95% pure as determined by ^1H -NMR and capillary GC.

Preparation of the reagent $\text{CuCN}\cdot 2\text{LiCl}$ (1 M solution in THF).¹

$\text{CuCN}\cdot 2\text{LiCl}$ was prepared by drying CuCN (896 mg, 10.0 mmol) and LiCl (848 mg, 20.0 mmol) in a Schlenk-flask under vacuum for 5 h at 140 °C. After cooling to 25 °C, dry THF (10 mL) was added and stirring was continued until the salts were dissolved (24 h).

Preparation of the reagent ZnCl_2 (1 M solution in THF).

A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with ZnCl_2 (13.6 g, 100 mmol). The salt was heated to 140 °C under high vacuum for 4 h. After cooling to 25 °C, dry THF (100 mL) was added and stirring was continued until the salt was dissolved (4 h).

Preparation of the reagent $\text{TMPMgCl}\cdot\text{LiCl}$.

A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated $i\text{PrMgCl}\cdot\text{LiCl}^2$ (100 mL, 1.2 M in THF, 120 mmol). 2,2,6,6-Tetramethylpiperidine (TMPH, 19.8 g, 126 mmol) was added dropwise at 20 °C. The reaction mixture was stirred at 20 °C until gas evolution was completed (24–48 h).

TP1: Typical Procedure for the preparation of 1-[3-(chloromethyl)phenyl]-substituted ketones (2g-i).

ZnCl_2 solution (18.8 mL, 18.8 mmol, 1 M in THF) was added to the Grignard compound (18.0 mmol) at the required temperature. The solution was stirred for 30 min. $\text{CuCN}\cdot 2\text{LiCl}$ solution (19.5 mL, 19.5 mmol, 1 M in THF) was added and the reaction mixture was stirred for additional 30 min. 3-(Chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) was added dropwise and the solution was stirred for 2 h. The reaction mixture was quenched with 60 mL of a mixture of sat. aqueous NH_4Cl / NH_3 (25% in H_2O) = 2:1. The layers were separated and the organic layer was extracted with 60 mL of a mixture of sat. aqueous NH_4Cl / NH_3 (25% in

H₂O) = 2:1. The combined aqueous layers were extracted with Et₂O (3 x 250 mL). The combined organic extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by column chromatography afforded the expected ketones.

TP2: Typical Procedure for the preparation of the benzylic zinc reagents (1a-m).

A Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.5–2.0 equiv). The flask was heated with a heat gun (400 °C) for 10 min under high vacuum. After cooling to 25 °C, the flask was flushed with argon (3 times). Zinc dust³ (1.5–2.0 equiv) was added followed by THF. 1,2-Dibromethane was added (5 mol %) and the reaction mixture was heated until ebullition occurs. After cooling to 25 °C, trimethylsilyl chloride (1 mol %) was added and the mixture was heated again until ebullition occurs. The benzylic chloride (1.0 equiv) was added at the required temperature (usually 25 °C) as a solution in THF (usually 4 M). When capillary GC analysis of a hydrolyzed aliquot containing an internal standard showed a conversion of > 98%, the Schlenk-flask was centrifuged for 75 min at 2000 rpm or the reaction mixture was allowed to settle down for some hours. The yield of the resulting benzylic zinc chloride was determined by iodimetric titration.²

TP3: Typical Procedure for the reaction of benzylic zinc chlorides with aldehydes (preparation of secondary benzyl alcohols).

The aldehyde (1.0 equiv) was dissolved in THF at 0 °C and the benzylic zinc chloride solution (1.3 equiv) was added dropwise. The resulting solution was allowed to warm slowly to 25 °C and was stirred for the required time. Then, sat. aqueous NH₄Cl (20 mL) solution was added. The phases were separated and the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography afforded the expected alcohols.

TP4: Typical Procedure for the reaction of benzylic zinc chlorides with acid chlorides (preparation of substituted ketone derivatives).

To a CuCN·2LiCl solution (1.4 equiv) at –25 °C was added dropwise the desired benzylic zinc chloride solution (1.4 equiv). The resulting reaction mixture was stirred for 15 min at this temperature. Then, the solution was cooled to the required temperature and the acid chloride (1.0 equiv) was added dropwise. The reaction mixture was stirred overnight and allowed to warm to 25 °C. Then, a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 2:1 was added,

the layers were separated and the aqueous layer was extracted with Et₂O (3 x 100 mL). The combined organic extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography afforded the expected ketones.

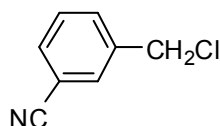
TP5: Typical Procedure for the reaction of benzylic zinc chlorides with unsaturated ketones (preparation of 3-benzylsubstituted cyclic ketones).

To a CuCN·2LiCl solution (1.25 equiv) at –25 °C was added dropwise the desired benzylic zinc chloride solution (1.25 equiv). The resulting reaction mixture was stirred for 15 min at this temperature. Then, the solution was cooled to the required temperature and a mixture of the unsaturated ketone (1.0 equiv), trimethylsilyl chloride (2.5 equiv) and THF was added dropwise. The reaction mixture was stirred overnight and allowed to reach 25 °C. Then, a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 2:1 was added. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 100 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography afforded the expected ketones.

Starting materials

Preparation of benzylic chlorides of type 2.

3-(Chloromethyl)benzonitrile (2f):



LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min). 3-(Bromomethyl)benzonitrile (9.8 g, 50.0 mmol) was added followed by THF (100 mL) at 0 °C. The reaction mixture was refluxed for 5 h. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over MgSO₄ followed by the evaporation of the solvents *in vacuo*. Again, LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min) and the crude product was added followed by THF (100 mL) at 0 °C. The reaction mixture was refluxed for 5 h. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over MgSO₄ followed by the evaporation of the solvents *in vacuo*. Once again, LiCl (6.36 g, 150 mmol) was dried (high vacuum, heat gun 400 °C, 10 min) and the crude product was added followed by THF (100 mL) at 0 °C. The resulting suspension was transferred into a separation funnel, washed with water (3 x 150 mL) and dried over MgSO₄ followed by the evaporation of the

solvents *in vacuo*. Purification by flash chromatography (short column, silica gel, pentane / Et₂O = 9:1) afforded the benzylic chloride **2f** (7.47 g, 99%) as a white solid.

mp (°C) = 73.3–74.5.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.70–7.65 (m, 1H), 7.65–7.57 (m, 2H), 7.52–7.43 (m, 1H), 4.58 (s, 2H).

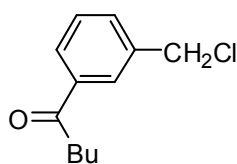
¹³C-NMR (300 MHz, CDCl₃): δ / ppm = 138.8, 132.8, 131.9, 131.9, 129.6, 118.2, 112.9, 44.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3060 (w), 2227 (m), 1584 (w), 1484 (m), 1445 (m), 1275 (m), 1240 (m), 1153 (m), 930 (w), 907 (m), 894 (w), 804 (s), 718 (m), 701 (vs), 679 (vs).

MS (EI, 70 eV): m/z (%) = 151 (100), 117 (17), 116 (83), 89 (45), 63 (11).

HRMS (C₈H₆ClN): calc.: 151.0189; found: 151.0183 (M⁺).

1-[3-(Chloromethyl)phenyl]pentan-1-one (**2g**):



According to **TP1** butylmagnesium chloride (12.2 mL, 18.0 mmol, 1.48 M in THF/toluene) was reacted with ZnCl₂ solution (18.8 mL, 18.8 mmol, 1 M in THF), CuCN·2LiCl solution (19.5 mL, 19.5 mmol, 1 M in THF) and 3-(chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) at -25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 2:1) afforded the benzylic chloride **2g** (2.89 g, 91%) as a colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.97–7.95 (m, 1H), 7.90 (dt, *J* = 7.7 Hz, *J* = 1.3 Hz, 1H), 7.60–7.56 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 4.62 (s, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 1.77–1.66 (m, 2H), 1.47–1.34 (m, 3H), 0.95 (t, *J* = 7.3 Hz, 3H).

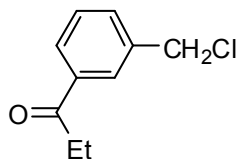
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 200.2, 138.3, 137.8, 133.1, 129.3, 128.3, 128.3, 45.9, 38.7, 26.6, 22.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2957 (m), 2931 (w), 2871 (w), 1717 (w), 1682 (s), 1443 (w), 1260 (m), 1233 (w), 1199 (w), 1179 (m), 1162 (m), 1109 (w), 1036 (w), 790 (w), 760 (w), 704 (vs), 654 (m).

MS (EI, 70 eV): m/z (%) = 210 (M⁺, 6), 175 (13), 170 (19), 168 (54), 155 (33), 154 (12), 153 (100), 125 (25), 89 (18).

HRMS (C₁₂H₁₅ClO): calc.: 210.0811; found: 210.0798 (M⁺).

1-[3-(Chloromethyl)phenyl]propan-1-one (2h):



According to **TP1** ethylmagnesium bromide (21.2 mL, 18.0 mmol, 0.85 M in *t*-BuOMe) was reacted with ZnCl₂ solution (18.8 mL, 18.8 mmol, 1 M in THF), CuCN·2LiCl solution (19.5 mL, 19.5 mmol, 1 M in THF) and 3-(chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) at -25 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 1:1) afforded the benzylic chloride **2h** (2.89 g, 94%) as a colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.98–7.95 (m, 1 H), 7.90 (dt, *J* = 7.7 Hz, *J* = 1.3 Hz, 1H), 7.60–7.56 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 4.62 (s, 2H), 3.00 (t, *J* = 7.3 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

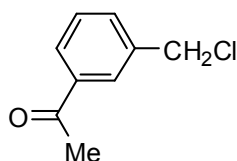
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 200.5, 138.3, 137.6, 133.1, 129.3, 128.2, 128.2, 45.9, 32.1, 8.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2978 (w), 1682 (s), 1604 (w), 1586 (w), 1444 (w), 1378 (w), 1350 (m), 1270 (w), 1242 (s), 1184 (m), 1164 (s), 974 (m), 786 (m), 704 (vs).

MS (EI, 70 eV): *m/z* (%) = 182 (M⁺, 7), 153 (100), 147 (14), 125 (27), 90 (14), 89 (19), 44 (16).

HRMS (C₁₀H₁₁ClO): calc.: 182.0498; found: 182.0472 (M⁺).

1-[3-(Chloromethyl)phenyl]propan-1-one (2i):



According to **TP1** methylmagnesium chloride (7.03 mL, 18.0 mmol, 2.56 M in THF) was reacted with ZnCl₂ solution (18.8 mL, 18.8 mmol, 1 M in THF), CuCN·2LiCl solution (19.5 mL, 19.5 mmol, 1 M in THF) and 3-(chloromethyl)benzoyl chloride (2.84 g, 15.0 mmol) at -10 °C. Purification by flash chromatography (silica gel, pentane / Et₂O = 3:1) afforded the benzylic chloride **2i** (2.46 g, 97%) as a colourless liquid.

¹H-NMR (600 MHz, C₆D₆): δ / ppm = 7.74–7.71 (m, 1H), 7.58 (dt, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H), 7.12–7.04 (m, 1H), 6.93 (t, *J* = 7.7 Hz, 1H), 4.02 (s, 1H), 2.06 (s, 1H).

^{13}C -NMR (150 MHz, C_6D_6): δ / ppm = 196.0, 138.2, 137.9, 132.8, 128.9, 128.4, 128.2, 45.5, 26.1.

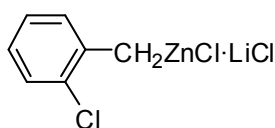
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1680 (vs), 1604 (m), 1586 (w), 1440 (m), 1428 (m), 1356 (s), 1280 (s), 1258 (s), 1192 (s), 1174 (m), 976 (w), 956 (w), 798 (m), 702 (vs), 688 (s).

MS (EI, 70 eV): m/z (%) = 168 (M^+ , 3), 164 (13), 153 (17), 149 (100), 121 (17), 65 (19), 43 (19).

HRMS ($\text{C}_9\text{H}_9\text{ClO}$): calc.: 168.0342; found: 168.0317 (M^+).

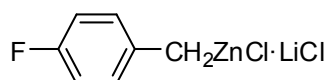
Preparation of benzyl zinc chlorides of type 1.

2-Chlorobenzylzinc chloride (**1a**):



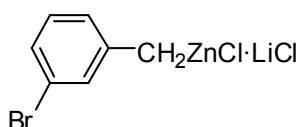
According to **TP2** 2-chlorobenzyl chloride (**2a**) (3.22 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: $\text{BrCH}_2\text{CH}_2\text{Br}$ (0.09 mL, 5 mol %), TMSCl (0.03 mL, 1 mol %)). The reaction mixture was stirred for 15 min at 0 °C followed by 1.75 h at 25 °C. After centrifugation iodometric titration² of **1a** indicates a yield of 99%.

4-Fluorobenzylzinc chloride (**1b**):



According to **TP2** 4-fluorobenzyl chloride (**2b**) (2.17 g, 15.0 mmol, in 4 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 3.5 mL THF (activation: $\text{BrCH}_2\text{CH}_2\text{Br}$ (0.07 mL, 5 mol %), TMSCl (0.02 mL, 1 mol %)). The reaction mixture was stirred for 24 h at 25 °C. After centrifugation iodometric titration² of **1b** indicates a yield of 87%.

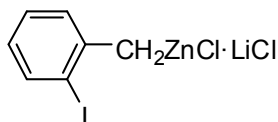
3-Bromobenzylzinc chloride (**1c**):



According to **TP2** 3-bromobenzyl chloride (**2c**) (4.11 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g,

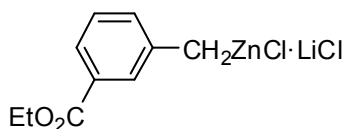
30.0 mmol) in 3.5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol %), TMSCl (0.03 mL, 1 mol %)). The reaction mixture was stirred for 4 h at 25 °C. After centrifugation iodometric titration² of **1c** indicates a yield of 95%.

2-Iodobenzylzinc chloride (**1d**):



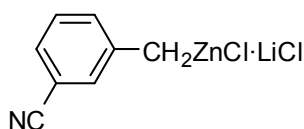
According to **TP2** 2-iodobenzyl chloride (**2d**) (5.05 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol %), TMSCl (0.03 mL, 1 mol %)). The reaction mixture was stirred for 20 min at 0 °C followed by 100 min at 25 °C. After centrifugation iodometric titration² of **1d** indicates a yield of 99%.

3-Ethoxycarbonylbenzylzinc chloride (**1e**):



According to **TP2** 3-ethoxycarbonylbenzyl chloride (**2e**) (3.97 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.70 g, 40.0 mmol) and zinc dust (2.62 g, 40.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol %), TMSCl (0.03 mL, 1 mol %)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation iodometric titration² of **1e** indicates a yield of 85%.

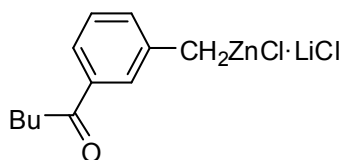
3-Cyanobenzylzinc chloride (**1f**):



According to **TP2** 3-cyanobenzyl chloride (**2f**) (3.03 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol %), TMSCl (0.03 mL,

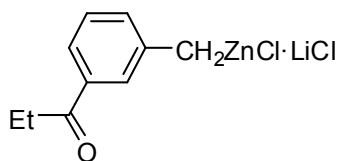
1 mol %)). The ice bath was removed and the reaction mixture was stirred for 3 h at 25 °C. After centrifugation iodometric titration² of **1f** indicates a yield of 93%.

3-Pentanoylbenzylzinc chloride (**1g**):



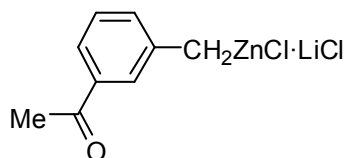
According to **TP2** 3-pentanoylbenzyl chloride (**2g**) (4.21 g, 20.0 mmol, in 5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol %), TMSCl (0.03 mL, 1 mol %)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation iodometric titration² of **1g** indicates a yield of 72%.

3-Propionylbenzylzinc chloride (**1h**):



According to **TP2** 3-propionylbenzyl chloride (**2h**) (2.01 g, 11.0 mmol, in 3.5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (0.70 g, 16.5 mmol) and zinc dust (1.08 g, 16.5 mmol) in 3 mL THF (activation: BrCH₂CH₂Br (0.05 mL, 5 mol %), TMSCl (0.01 mL, 1 mol %)). The reaction mixture was stirred for 3 h at 25 °C. After centrifugation iodometric titration² of **1h** indicates a yield of 72%.

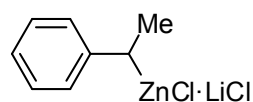
3-Acetylbenzylzinc chloride (**1i**):



According to **TP2** 3-acetylbenzyl chloride (**2il**) (1.85 g, 11.0 mmol, in 2.5 mL THF) was added dropwise at 25 °C to a suspension of LiCl (0.70 g, 16.5 mmol) and zinc dust (1.08 g, 16.5 mmol) in 3 mL THF (activation: BrCH₂CH₂Br (0.05 mL, 5 mol %), TMSCl (0.01 mL,

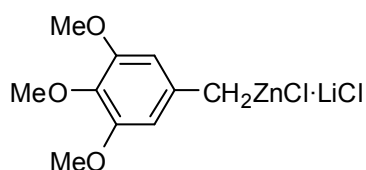
1 mol %)). The reaction mixture was stirred for 3.5 h at 25 °C. After centrifugation iodometric titration² of **1i** indicates a yield of 68%.

1-Phenylethylzinc chloride (**1j**):



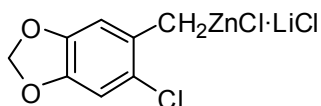
According to **TP2** 1-phenylethyl chloride (**2j**) (2.81 g, 20.0 mmol, in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol %), TMSCl (0.03 mL, 1 mol %)). The ice bath was removed and the reaction mixture was stirred for 11 h at 25 °C. After centrifugation iodometric titration² of **1j** indicates a yield of 85%.

3,4,5-Trimethoxybenzylzinc chloride (**1k**):



According to **TP2** 3,4,5-trimethoxybenzyl chloride (**2k**) (2.71 g, 12.5 mmol, solution in 3 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.06 g, 25.0 mmol) and zinc dust (1.64 g, 25.0 mmol) in 3.5 mL THF (activation: BrCH₂CH₂Br (0.05 mL, 5 mol %), TMSCl (0.02 mL, 1 mol %)). The ice bath was removed and the reaction mixture was stirred for 3 h at 25 °C. After centrifugation iodometric titration² of **1k** indicates a yield of 78%.

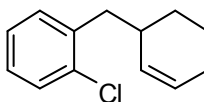
6-Chloro-1,3-benzodioxol-5-ylmethylzinc chloride (**1l**):



According to **TP2** 6-chloro-1,3-benzodioxol-5-ylmethyl chloride (**2l**) (4.10 g, 20.0 mmol, solution in 5 mL THF) was added dropwise at 0 °C to a suspension of LiCl (1.27 g, 30.0 mmol) and zinc dust (1.96 g, 30.0 mmol) in 5 mL THF (activation: BrCH₂CH₂Br (0.09 mL, 5 mol %), TMSCl (0.03 mL, 1 mol %)). The ice bath was removed and the reaction mixture was stirred for 1 h at 25 °C. After centrifugation iodometric titration² of **1l** indicates a yield of 93%.

Preparation of the products of type 4 and 5 (reaction of the benzylic zinc reagents with electrophiles).

1-Chloro-2-(cyclohex-2-en-1-ylmethyl)benzene (4a):



3-Bromocyclohexene (**3a**) (419 mg, 2.6 mmol) was added to 2-chlorobenzylzinc chloride (**1a**) (1.23 mL, 2.0 mmol, 1.62 M in THF) at 0 °C, followed by adding CuCN·2LiCl solution (2 drops). The solution was stirred for 1.5 h at 25 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution. The phases were separated and the aqueous layer was extracted with Et₂O (3 x 5 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane) afforded the cyclohexene **4a** (389 mg, 94%) as a colourless liquid.

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.33 (dd, J = 7.7 Hz, J = 1.3 Hz, 1H), 7.20–7.11 (m, 3H), 5.72–5.68 (m, 1H), 5.58–5.54 (m, 1H), 2.77–2.72 (m, 1H), 2.69–2.65 (m, 1H), 2.51–2.43 (m, 1H), 2.02–1.96 (m, 1H), 1.77–1.66 (m, 2H), 1.55–1.47 (m, 1H), 1.33–1.27 (m, 1H).

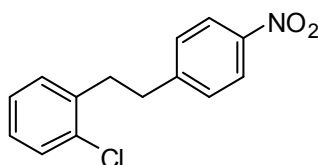
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 138.5, 134.3, 131.4, 131.0, 129.5, 127.5, 127.3, 126.4, 40.0, 35.4, 28.8, 25.4, 21.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3017 (m), 2922 (s), 2857 (m), 2834 (m), 1473 (s), 1446 (m), 1439 (m), 1052 (m), 1032 (m), 746 (vs), 718 (m), 683 (m), 665 (m).

MS (EI, 70 eV): m/z (%) = 208 (M⁺, 9), 206 (31), 125 (22), 82 (12), 81 (24), 80 (100), 79 (24).

HRMS (C₁₃H₁₅Cl): calc.: 206.0862; found: 206.0840 (M⁺).

1-Chloro-2-[2-(4-nitrophenyl)ethyl]benzene (4b):



To a solution of 4-nitrobenzyl bromide (**3b**) (594 mg, 2.75 mmol) in 2.7 mL THF at 0 °C was added successively 2-chlorobenzylzinc chloride (**1a**) (2.17 mL, 3.3 mmol, 1.62 M in THF) and CuCN·2LiCl solution (2 drops). The mixture was stirred for 3 h at 0 °C. The reaction mixture was quenched with sat. aqueous NH₄Cl solution. The phases were separated and the

aqueous layer was extracted with Et₂O (5 x 5 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the diarylethane **4b** (643 mg, 89%) as a white solid.

mp (°C) = 66.9–67.9 °C.

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 8.14–8.11(m, 2H), 7.38–7.34 (m, 1H), 7.32–7.29 (m, 2H), 7.18–7.13 (m, 2H), 7.09–7.06 (m, 1H), 3.07–3.00 (m, 2H).

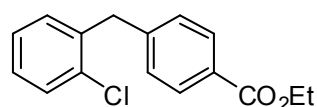
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 149.3, 138.2, 134.1, 130.7, 129.9, 129.6, 128.1, 127.1, 123.9, 36.0, 35.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2932 (w), 2854 (w), 1596 (m), 1509 (s), 1470 (m), 1457 (m), 1444 (m), 1334 (m), 1313 (m), 1256 (m), 1107 (m), 1049 (m), 1036 (m), 829 (s), 750 (vs), 698 (s).

MS (EI, 70 eV): m/z (%) = 263 (11), 261 (M⁺, 29), 127 (33), 125 (100), 89 (13).

HRMS (C₁₄H₁₂ClNO₂): calc.: 261.0557; found: 261.0560 (M⁺).

Ethyl 4-(2-chlorobenzyl)benzoate (**4c**):



To a solution of ethyl 4-iodobenzoate (**3c**) (690 mg, 2.5 mmol) in 2.5 mL THF at 25 °C was added successively 2-chlorobenzylzinc chloride (**1a**) (1.96 mL, 3.0 mmol, 1.53 M in THF) and Pd(PPh₃)₄ (69 mg, 2 mol %). The resulting reaction mixture was heated to 60 °C for 5 h. After cooling to 25 °C, the reaction mixture was diluted with Et₂O (5 mL) and quenched with sat. aqueous NH₄Cl solution. The phases were separated and the aqueous layer was extracted with Et₂O (5 x 5 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 9:1) afforded the diarylmethane **4c** (667 mg, 97%) as a pale yellow liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.06–8.01 (m, 3H), 7.46–7.42 (m, 1H), 7.34–7.28 (m, 2H), 7.27–7.18 (m, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.21 (s, 2H), 1.44 (t, *J* = 7.2 Hz, 3H).

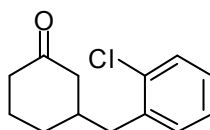
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 166.8, 145.0, 138.0, 134.5, 131.3, 130.0, 129.9, 129.1, 128.9, 128.2, 127.2, 61.1, 39.5, 14.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2980 (w), 1712 (vs), 1610 (m), 1473 (w), 1443 (m), 1415 (m), 1366 (w), 1271 (vs), 1177 (m), 1103 (s), 1050 (m), 1039 (m), 1020 (m), 747 (s).

MS (EI, 70 eV): m/z (%) = 276 (23), 275 (15), 274 (M⁺, 77), 248 (109, 246 (30), 239 (13), 232 (38), 231 (17), 230 (100), 211 (21), 203 (12), 201 (32), 167 (20), 166 (399), 165 (67).

HRMS (C₁₆H₁₅ClO₂): calc.: 274.0671; found: 274.0748 (M⁺).

3-(2-Chlorobenzyl)cyclohexanone (4d):



According to **TP5** a mixture of cyclohex-2-en-1-one (**3d**) (480 mg, 5.0 mmol) and TMSCl (1.6 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.3 mL, 6.3 mmol) and 2-chlorobenzylzinc chloride (**1a**) (3.83 mL, 6.25 mmol, 1.63 M in THF) at −40 °C. The reaction mixture was allowed to reach 25 °C overnight and was quenched with a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 4:1) afforded the ketone **4d** (1.03 g, 93%) as a colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.33–7.27 (m, 1H), 7.18–7.05 (m, 3H), 2.81–2.62 (m, 2H), 2.38–1.94 (m, 6H), 1.89–1.78 (m, 1H), 1.66–1.48 (m, 1H), 1.47–1.32 (m, 1H).

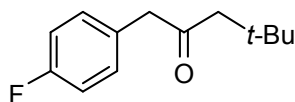
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 211.4, 137.5, 134.4, 131.5, 129.9, 128.0, 126.9, 47.9, 41.6, 40.6, 39.6, 31.2, 25.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{−1} = 2936 (w), 2864 (w), 1708 (vs), 1476 (m), 1444 (m), 1348 (w), 1312 (w), 1224 (m), 1128 (w), 1052 (m), 1036 (m), 748 (vs), 680 (s), 596 (w).

MS (EI, 70 eV): m/z (%) = 222 (M⁺, 3), 187 (39), 186 (23), 164 (18), 142 (19), 130 (10), 129 (24), 127 (11), 125 (28), 115 (16), 97 (87), 91 (29), 89 (14), 69 (100), 55 (46), 44 (15), 41 (58).

HRMS (C₁₃H₁₅ClO): calc.: 222.0811; found: 222.0800 (M⁺).

1-(4-Fluorophenyl)-3,3-dimethylbutan-2-one (4e):



According to **TP4** 3,3-dimethylbutyryl chloride (**3e**) (377 mg, 2.8 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.92 mL, 3.9 mmol) and 4-fluorobenzylzinc chloride (**1b**) (2.69 mL, 3.9 mmol, 1.46 M in THF) at −40 °C. The reaction mixture was allowed to reach 25 °C overnight and was quenched with a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 4:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the ketone **4e** (555 mg, 95%) as a pale yellow liquid.

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.15–7.10 (m, 2H), 7.02–6.97 (m, 2H), 3.36 (s, 1H), 2.35 (s, 1H), 1.00 (s, 9H).

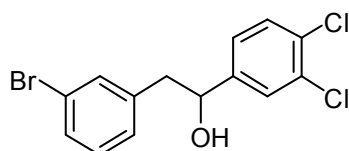
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 207.8, 162.9, 161.3, 131.2, 131.2, 130.1, 130.1, 115.7, 115.6, 54.4, 51.2, 31.3, 29.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2956 (m), 1712 (s), 1508 (vs), 1364 (m), 1352 (m), 1220 (vs), 1160 (m), 1084 (m), 1064 (m), 824 (m), 780 (m), 524 (m).

MS (EI, 70 eV): m/z (%) = 208 (3), 109 (53), 99 (60), 71 (17), 57 (100), 43 (13), 42 (16).

HRMS (C₁₃H₁₇FO): calc.: 208.1263; found: 208.1261 (M⁺).

2-(3-Bromophenyl)-1-(3,4-dichlorophenyl)ethanol (**4f**):



According to **TP3** 3-bromobenzylzinc chloride (**1c**) (1.72 mL, 2.7 mmol, 1.56 M in THF) was reacted with 3,4-dichlorobenzaldehyde (**3f**) (361 mg, 2.1 mmol, in 1.5 mL THF). After 17 h the reaction mixture was quenched with sat. aqueous NH₄Cl solution. Purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the alcohol **4f** (699 mg, 98%) as a white solid.

mp (°C) = 64.2–65.4.

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.43 (d, *J* = 2.0 Hz, 1H), 7.41–7.34 (m, 3H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.12 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 4.81 (dd, *J* = 8.4 Hz, *J* = 4.6 Hz, 1H), 2.96–2.85 (m, 2H), 2.09 (s, 1H).

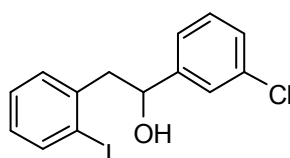
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 143.6, 139.6, 132.6, 132.4, 131.5, 130.4, 130.1, 130.0, 128.1, 127.8, 125.1, 122.6, 73.8, 45.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3288 (m), 1564 (m), 1470 (s), 1424 (m), 1202 (m), 1128 (m), 1070 (s), 1046 (s), 1026 (s), 998 (s), 884 (s), 782 (vs), 668 (vs).

MS (ESI): m/z (%) = 328 (3), 175 (100), 111 (40), 91 (20), 75 (10).

HRMS (C₁₅H₁₂BrCl₂O₃): calc.: 388.9352; found: 388.9360 (M⁺ + formiate).

1-(3-Chlorophenyl)-2-(2-iodophenyl)ethanol (**4g**):



According to **TP3** 2-iodobenzylzinc chloride (**1d**) (1.28 mL, 2.0 mmol, 1.53 M in THF) was reacted with 3-chlorobenzaldehyde (**3g**) (211 mg, 1.5 mmol, in 1.5 mL THF). After 5 h the reaction mixture was quenched with sat. aqueous NH_4Cl solution. Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1 to 7:3) afforded the alcohol **4g** (470 mg, 87%) as a pale yellow solid.

mp ($^\circ\text{C}$) = 67.6–69.5.

$^1\text{H-NMR}$ (600 MHz, CDCl_3): δ / ppm = 7.86 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.45 (m, 1H), 7.30–7.24 (m, 3H), 7.18 (dd, J = 7.5 Hz, J = 1.8 Hz, 1H), 5.01–4.97 (m, 1H), 3.17–3.13 (m, 1H), 3.08–3.03 (m, 1H), 1.92 (d, J = 3.3 Hz, 1H).

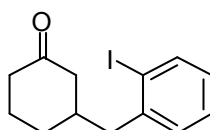
$^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ / ppm = 145.7, 140.4, 139.7, 134.4, 131.3, 129.7, 128.7, 128.3, 127.8, 125.9, 123.9, 100.9, 72.8, 50.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3322 (w), 3252 (w), 1596 (w), 1575 (w), 1468 (m), 1435 (m), 1198 (m), 1055 (s), 1015 (s), 884 (m), 783 (s), 746 (s), 725 (s), 695 (vs).

MS (EI, 70 eV): m/z (%) = 358 (M^+ , 1), 218 (100), 142 (8), 141 (27), 77 (13).

HRMS ($\text{C}_{14}\text{H}_{12}\text{ClIO}$): calc.: 357.9621; found: 357.9629 (M^+).

3-(2-Iodobenzyl)cyclohexanone (**4h**):



According to **TP5** a mixture of cyclohex-2-en-1-one (**3d**) (480 mg, 5.0 mmol) and TMSCl (1.6 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of $\text{CuCN}\cdot 2\text{LiCl}$ (6.3 mL, 6.3 mmol) and 2-iodobenzylzinc chloride (**1d**) (4.81 mL, 6.25 mmol, 1.30 M in THF) at $-40\text{ }^\circ\text{C}$. The reaction mixture was allowed to reach $25\text{ }^\circ\text{C}$ overnight and was quenched with a mixture of sat. aqueous NH_4Cl / NH_3 (25% in H_2O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the ketone **4d** (1.13 g, 72%) as a colourless liquid.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ / ppm = 7.80 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.28–7.22 (m, 1H), 7.13–7.09 (m, 1H), 6.91–6.85 (m, 1H), 2.82–2.64 (m, 2H), 2.43–1.98 (m, 6H), 1.95–1.83 (m, 1H), 1.70–1.53 (m, 1H), 1.53–1.37 (m, 1H).

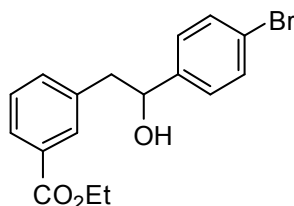
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ / ppm = 211.3, 142.2, 139.7, 130.4, 128.1 (overlap), 101.0, 47.6, 47.2, 41.4, 39.5, 30.9, 25.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2933 (m), 2863 (m), 1706 (vs), 1466 (m), 1446 (m), 1224 (m), 1008 (s), 744 (s), 646 (m).

MS (EI, 70 eV): m/z (%) = 314 (M^+ , 9), 217 (818), 188 (13), 187 (100), 1269 (15), 115 (16), 97 (66), 91 (22), 89 (12), 69 (72), 55 (34), 41 (33).

HRMS ($\text{C}_{13}\text{H}_{15}\text{IO}$): calc.: 314.0168; found: 314.0166 (M^+).

Ethyl 3-[2-(4-bromophenyl)-2-hydroxyethyl]benzoate (4i):



According to **TP3** 3-ethoxycarbonylbenzylzinc chloride (**1e**) (4.1 mL, 5.4 mmol, 1.3 M in THF) was reacted with 4-bromobenzaldehyde (**3h**) (775 mg, 4.2 mmol, in 3 mL THF). After 4.5 h the reaction mixture was quenched with sat. aqueous NH_4Cl solution. Purification by flash chromatography (silica gel, pentane / Et_2O = 7:3) afforded the alcohol **4i** (1.33 g, 91%) as a white solid.

mp ($^{\circ}\text{C}$) = 64.5–65.8.

$^1\text{H-NMR}$ (600 MHz, CDCl_3): δ / ppm = 7.92–7.90 (m, 1H), 7.86–7.85 (m, 1H), 7.47–7.44 (m, 2H), 7.37–7.30 (m, 2H), 7.22–7.19 (m, 2H), 4.91–4.87 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.04–3.01 (m, 2H), 1.97 (d, J = 3.1 Hz, 1H), 1.39 (t, J = 7.2 Hz, 3H).

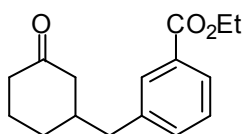
$^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ / ppm = 166.5, 142.5, 137.9, 134.1, 131.5, 130.7, 130.4, 128.5, 127.9, 127.6, 121.5, 74.6, 61.0, 45.6, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3466 (w), 1704 (s), 1682 (s), 1484 (m), 1446 (m), 1400 (m), 1366 (m), 1278 (s), 1200 (s), 1108 (s), 1066 (s), 1024 (s), 1004 (s), 746 (vs), 698 (s).

MS (EI, 70 eV): m/z (%) = 348 (M^+ , <1), 164 (100), 136 (29), 135 (13), 118 (10), 92 (10), 91 (16), 90 (11), 78 (10), 77 (20).

HRMS ($\text{C}_{17}\text{H}_{17}\text{BrO}_3$): calc.: 348.0361; found: 348.0372 (M^+).

Ethyl 3-[(3-oxocyclohexyl)methyl]benzoate (4j):



According to **TP5** a mixture of cyclohex-2-en-1-one (**3d**) (480 mg, 5.0 mmol) and TMSCl (1.6 mL, 12.5 mmol) in 2 mL THF was added dropwise to a mixture of CuCN·2LiCl (6.3 mL, 6.3 mmol) and 3-ethoxycarbonylbenzylzinc chloride (**1e**) (4.46 mL, 6.25 mmol, 1.40 M in THF) at −40 °C. The reaction mixture was allowed to reach 25 °C overnight and was quenched with a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 2:1 (20 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 5:1 to 1:1) afforded the ketone **4j** (1.26 g, 97%) as a colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.82–7.78 (m, 1H), 7.74–7.72 (m, 1H), 7.28–7.24 (m, 1H), 7.24–7.21 (m, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.63–2.53 (m, 2H), 2.28–2.21 (m, 2H), 2.20–2.13 (m, 1H), 2.01–1.89 (m, 3H), 1.79–1.73 (m, 1H), 1.57–1.47 (m, 1H), 1.33–1.25 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H).

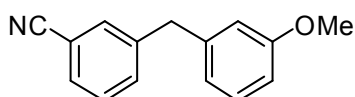
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 211.2, 166.7, 140.0, 133.7, 130.8, 130.2, 128.6, 127.7, 61.1, 47.8, 42.9, 41.5, 40.9, 31.0, 25.2, 14.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{−1} = 2936 (w), 1708 (vs), 1444 (m), 1368 (w), 1276 (vs), 1196 (s), 1108 (s), 1024 (m), 864 (w), 748 (s), 700 (m), 672 (w).

MS (EI, 70 eV): *m/z* (%) = 260 (M⁺, 30), 215 (36), 214 (79), 164 (26), 129 (39), 121 (83), 115 (20), 97 (80), 91 (33), 69 (100), 55 (46), 41 (50).

HRMS (C₁₆H₂₀O₃): calc.: 260.1412; found: 260.1386 (M⁺).

3-(3-Methoxybenzyl)benzonitrile (**4k**):



To a solution of 3-iodoanisole (585 mg, 2.5 mmol) in 2.0 mL THF at 25 °C was added successively 3-cyanobenzylzinc chloride (**1f**) (2.03 mL, 3.0 mmol, 1.48 M in THF) and Pd(PPh₃)₄ (139 mg, 5 mol %). The resulting reaction mixture was heated to 60 °C for 5 h. After cooling to 25 °C, the reaction mixture was diluted with Et₂O (5 mL) and quenched with sat. aqueous NH₄Cl solution. The phases were separated and the aqueous layer was extracted with Et₂O (5 x 5 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 9:1) afforded the diarylmethane **4k** (492 mg, 88%) as a colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.51–7.34 (m, 4H), 7.26–7.20 (m, 1H), 6.81–6.67 (m, 3H), 3.97 (s, 2H), 3.78 (s, 3H).

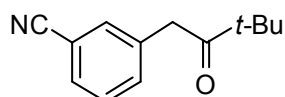
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 160.2, 142.7, 141.2, 133.6, 132.6, 130.2, 130.0, 129.5, 121.5, 119.2, 115.2, 112.8, 112.0, 55.4, 41.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2937 (w), 2228 (s), 1596 (s), 1582 (s), 1488 (s), 1453 (m), 1435 (m), 1257 (vs), 1151 (m), 1048 (s), 779 (m), 741 (m), 686 (s).

MS (EI, 70 eV): m/z (%) = 224 (15), 223 (M⁺, 100), 222 (812), 208 (13), 190 (10).

HRMS (C₁₅H₁₃NO): calc.: 223.0997; found: 223.0988 (M⁺).

3-(3,3-Dimethyl-2-oxobutyl)benzonitrile (**4l**):



According to **TP4** 2,3-dimethylpropionyl chloride (**3j**) (225 mg, 1.87 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.6 mL, 2.6 mmol) and 3-cyanobenzylzinc chloride (**1f**) (1.9 mL, 2.6 mmol, 1.37 M in THF) at -60 °C. The reaction mixture was allowed to reach -20 °C overnight and was quenched with a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 6:1) afforded the ketone **4l** (292 mg, 78%) as a white solid.

mp (°C) = 38.5–39.7.

¹H-NMR (600 MHz, C₆D₆): δ / ppm = 7.03–7.01 (m, 1H), 6.98–6.95 (m, 2H), 6.74 (t, *J* = 7.8 Hz, 1H), 3.13 (s, 2H), 0.89 (s, 9H).

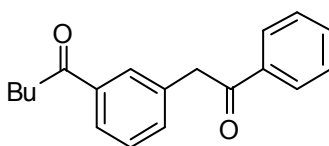
¹³C-NMR (150 MHz, C₆D₆): δ / ppm = 209.7, 136.7, 134.0, 133.2, 130.2, 128.8, 118.9, 112.9, 44.3, 42.2, 26.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2956 (m), 2226 (m), 1700 (s), 1482 (m), 1364 (m), 1330 (s), 1058 (vs), 1020 (s), 808 (m), 770 (vs), 684 (vs).

MS (EI, 70 eV): m/z (%) = 201 (M⁺, <1), 117 (28), 116 (22), 85 (22), 57 (100), 41 (30).

HRMS (C₁₃H₁₅NO): calc.: 201.1154; found: 201.1131 (M⁺).

1-[3-(2-Oxo-2-phenylethyl)phenyl]pentan-1-one (**4m**):



According to **TP4** benzoyl chloride (**3k**) (278 mg, 1.98 mmol) was added dropwise to a mixture of CuCN·2LiCl (2.6 mL, 3.9 mmol) and 3-pentanoylbenzylzinc chloride (**1g**) (2.3 mL, 2.6 mmol, 1.15 M in THF) at -20 °C. The reaction mixture was stirred overnight at

this temperature followed by quenching with a mixture of sat. aqueous NH_4Cl / NH_3 (25% in H_2O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the ketone **4m** (470 mg, 85%) as a white solid.

mp ($^\circ\text{C}$) = 33.3–36.0.

^1H -NMR (600 MHz, CDCl_3): δ / ppm = 8.03–8.00 (m, 2H), 7.86–7.83 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.40 (m, 4H), 4.35 (s, 2 H), 2.94 (t, J = 7.4 Hz, 2H), 1.73–1.67 (m, 2H), 1.43–1.35 (m, 2 H), 0.94 (t, J = 7.4 Hz, 3H).

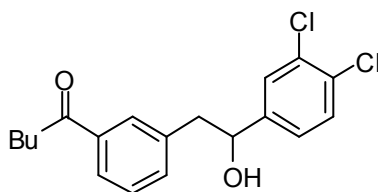
^{13}C -NMR (150 MHz, CDCl_3): δ / ppm = 200.4, 197.0, 137.4, 136.4, 135.0, 134.1, 133.4, 129.2, 128.8, 128.7, 128.5, 126.7, 45.1, 38.4, 26.4, 22.4, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2932 (w), 1678 (vs), 1594 (m), 1580 (m), 1446 (m), 1328 (m), 1266 (m), 1206 (s), 1164 (m), 994 (m), 974 (m), 748 (s), 692 (vs).

MS (EI, 70 eV): m/z (%) = 280 (M^+ , 6), 223 (6), 105 (100), 77 (17).

HRMS ($\text{C}_{19}\text{H}_{20}\text{O}_2$): calc.: 280.1463; found: 280.1439 (M^+).

1-{3-[2-(3,4-dichlorophenyl)-2-hydroxyethyl]phenyl}pentan-1-one (**4n**):



According to **TP3** 3-pentanoylbenzylzinc chloride (**1g**) (2.4 mL, 2.6 mmol, 1.08 M in THF) was reacted with 3,4-dichlorobenzaldehyde (**3f**) (350 mg, 2.0 mmol, in 1.5 mL THF). After 5.5 h the reaction mixture was quenched with sat. aqueous NH_4Cl solution. Purification by flash chromatography (silica gel, pentane / Et_2O = 2:1) afforded the alcohol **4n** (665 mg, 95%) as a white solid.

mp ($^\circ\text{C}$) = 46.8–47.8.

^1H -NMR (300 MHz, CDCl_3): δ / ppm = 7.84–7.80 (m, 1H), 7.75–7.72 (m, 1H), 7.45–7.30 (m, 4 H), 7.16–7.11 (m, 1H), 4.92–4.85 (m, 1H), 3.04–3.00 (m, 2H), 2.01 (t, J = 7.4 Hz, 2H), 2.11–1.93 (s, 1H), 1.76–1.62 (m, 2H), 1.47–1.32 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H).

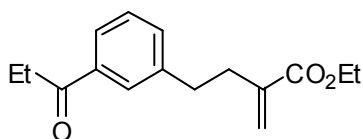
^{13}C -NMR (75 MHz, CDCl_3): δ / ppm = 200.5, 143.8, 137.8, 137.4, 134.1, 132.6, 131.5, 130.4, 129.0, 128.8, 127.9, 126.7, 125.2, 73.9, 45.7, 38.4, 26.5, 22.5, 13.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3434 (w), 2871 (w), 2930 (m), 1583 (m), 2956 (m), 1379 (m), 885 (m), 1179 (m), 656 (m), 730 (m), 1163 (m), 1261 (m), 787 (m), 1042 (s), 1057 (s), 1466 (s), 675 (s), 820 (s), 1673 (s), 692 (s), 1028 (vs).

MS (EI, 70 eV): m/z (%) = 350 (M^+ , <1), 293 (7), 177 (15), 176 (100), 175 (14), 119 (8).

HRMS (C₁₉H₂₀Cl₂O₂): calc.: 350.0840; found: 350.0839 (M⁺).

Ethyl 2-[2-(3-propionylphenyl)ethyl]acrylate (4o**):**



To a solution of ethyl 2-bromomethylacrylate (**3l**) (560 mg, 2.90 mmol) in 1.5 mL THF at -60 °C was added 3-propionylbenzylzinc chloride (**1h**) (2.80 mL, 3.48 mmol, 1.25 M in THF) followed by adding CuCN·2LiCl solution (2 drops). The reaction mixture was stirred at -60 °C for 30 min, followed by stirring at 0 °C for additional 30 min. Then, the reaction mixture was quenched by adding sat. aqueous NH₄Cl solution. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 95:5) afforded the acrylate **4o** (694 mg, 92%) as a pale yellow liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.80–7.74 (m, 2H), 7.39–7.34 (m, 2H), 6.16–6.14 (m, 1H), 5.48 (q, *J* = 1.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.98 (q, *J* = 7.1 Hz, 2H), 2.89–2.80 (m, 2H), 2.66–2.59 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H).

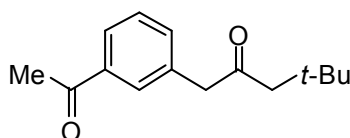
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 200.9, 167.0, 141.9, 139.8, 137.1, 133.1, 128.5, 128.0, 125.8, 125.4, 60.7, 34.8, 33.8, 31.8, 14.2, 8.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2978 (w), 2938 (w), 1712 (vs), 1684 (vs), 1300 (m), 1240 (s), 1184 (vs), 1164 (s), 1132 (s), 1028 (m), 944 (m), 782 (s), 694 (s).

MS (EI, 70 eV): *m/z* (%) = 260 (M⁺, 23), 232 (16), 231 (100), 214 (11), 213 (11), 185 (16), 147 (28), 129 (14), 128 (12), 118 (10), 91 (12), 90 (19), 57 (15).

HRMS (C₁₆H₂₀O₃): calc.: 260.1412; found: 260.1419 (M⁺).

1-(3-Acetylphenyl)-4,4-dimethylpentan-2-one (4p**):**



According to **TP4** 3,3-dimethylbutyryl chloride (**3e**) (192 mg, 1.44 mmol) was added dropwise to a mixture of CuCN·2LiCl (1.88 mL, 1.88 mmol) and 3-acetylbenzylzinc chloride (**1i**) (1.68 mL, 1.88 mmol, 1.12 M in THF) at -60 °C. The reaction mixture was stirred at

–20 °C overnight and quenched with a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 5:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 7:3) afforded the ketone **4p** (248 mg, 74%) as a pale yellow liquid.

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.85–7.82 (m, 1H), 7.75–7.74 (m, 1H), 7.43–7.40 (m, 1H), 7.38–7.36 (m, 1H), 3.73 (s, 2H), 2.58 (s, 3H), 2.37 (s, 2H), 1.00 (s, 9H).

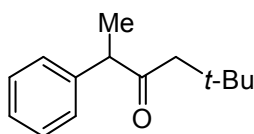
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 207.1, 197.9, 137.4, 134.7, 134.2, 129.2, 128.8, 127.0, 54.4, 51.5, 31.1, 29.6, 26.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{–1} = 2868 (w), 920 (w), 1602 (w), 1584 (w), 2953 (m), 1439 (m), 790 (m), 1063 (m), 1083 (m), 1189 (m), 1713 (m), 1356 (s), 693 (s), 1269 (s), 1681 (vs).

MS (EI, 70 eV): m/z (%) = 232 (M⁺, 3), 134 (18), 133 (50), 99 (100), 90 (15), 71 (17), 57 (72), 43 (27).

HRMS (C₁₅H₂₀O₂): calc.: 232.1463; found: 232.1447 (M⁺).

5,5-Dimethyl-2-phenylhexan-3-one (**4q**):



According to **TP4** 3,3-dimethylbutyryl chloride (**3e**) (382 mg, 2.84 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.90 mL, 3.90 mmol) and 1-phenylethylzinc chloride (**1j**) (2.73 mL, 3.90 mmol, 1.43 M in THF) at –60 °C. The reaction mixture was allowed to reach 25 °C overnight and was quenched with a mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 9:1 (25 mL). Purification by flash chromatography (silica gel, pentane / Et₂O = 95:5) afforded the ketone **4q** (556 mg, 96%) as a colourless liquid.

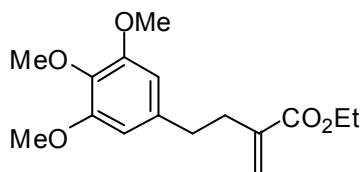
¹H-NMR (600 MHz, CDCl₃): δ / ppm = 7.39–7.35 (m, 2H), 7.32–7.28 (m, 1H), 7.26–7.23 (m, 2H), 3.76 (q, *J* = 6.9 Hz, 1H), 2.37 (d, *J* = 15.3 Hz, 1H), 2.23 (d, *J* = 15.5 Hz, 1H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 9H).

¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 210.3, 140.5, 128.8, 128.0, 127.0, 54.4, 53.2, 30.9, 29.6, 17.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{–1} = 2952 (m), 2868 (w), 1712 (s), 1492 (w), 1452 (m), 1364 (m), 1068 (w), 1044 (w), 1028 (w), 1016 (w), 912 (w), 756 (m), 700 (vs), 548 (m), 520 (w).

MS (EI, 70 eV): m/z (%) = 204 (M⁺, 3), 105 (63), 99 (74), 83 (14), 79 (11), 71 (29), 69 (13), 57 (100), 55 (13), 43 (23).

HRMS (C₁₄H₂₀O): calc.: 204.1514; found: 204.1525 (M⁺).

Ethyl 2-[2-(3,4,5-trimethoxyphenyl)ethyl]acrylate (4r):

To a solution of ethyl 2-bromomethylacrylate (**3l**) (579 mg, 3.00 mmol) in 1.5 mL THF at $-60\text{ }^{\circ}\text{C}$ was added 3,4,5-trimethoxybenzylzinc chloride (**1k**) (7.40 mL, 3.75 mmol, 0.51 M in THF) followed by adding CuCN·2LiCl solution (3 drops). The reaction mixture was stirred at $-60\text{ }^{\circ}\text{C}$ for 30 min, followed by stirring at $0\text{ }^{\circ}\text{C}$ for additional 30 min. Then, the reaction mixture was quenched by adding sat. aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined extracts were dried over MgSO_4 . Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 7:1) afforded the acrylate **4o** (867 mg, 98%) as colourless liquid.

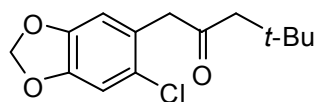
$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ / ppm = 6.36 (s, 2H), 6.11 (s, 1H), 5.48 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.79 (s, 6H), 3.77, (s, 3H), 2.73–2.63 (m, 2H), 2.62–2.51 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ / ppm = 167.3, 153.3, 140.3, 137.5, 136.4, 125.3, 105.6, 61.0, 60.8, 56.2, 35.6, 34.2, 14.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2936 (w), 2840 (w), 1712 (m), 1588 (m), 1508 (m), 1456 (m), 1420 (m), 1332 (m), 1236 (s), 1184 (s), 1120 (vs), 1008 (m), 944 (m), 820 (m).

MS (EI, 70 eV): m/z (%) = 294 (31), 182 (20), 181 (100), 148 (7), 121 (9).

HRMS ($\text{C}_{16}\text{H}_{22}\text{O}_5$): calc.: 294.1467; found: 294.1457 (M^+).

1-(6-Chloro-1,3-benzodioxol-5-yl)-4,4-dimethylpentan-2-one (4s):

According to **TP4** 2,3-dimethylpropionyl chloride (**3j**) (377 mg, 2.80 mmol) was added dropwise to a mixture of CuCN·2LiCl (3.92 mL, 3.92 mmol) and 6-chloro-1,3-benzodioxol-5-ylmethylzinc chloride (**1l**) (2.80 mL, 3.92 mmol, 1.40 M in THF) at $-60\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to reach $25\text{ }^{\circ}\text{C}$ overnight and was quenched with a mixture of sat. aqueous NH_4Cl / NH_3 (25% in H_2O) = 5:1 (25 mL). Purification by flash chromatography

(silica gel, pentane / Et₂O = 95:5) afforded the ketone **4s** (703 mg, 93%) as a pale yellow liquid.

¹H-NMR (600 MHz, CDCl₃): δ / ppm = 6.84 (s, 1H), 6.63 (s, 1H), 5.95 (s, 2H), 3.70 (s, 2H), 2.38 (s, 2H), 1.02 (s, 9H).

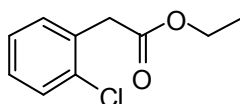
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 206.5, 147.4, 146.7, 126.0, 125.7, 110.9, 109.8, 101.7, 54.3, 49.2, 31.0, 29.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2952 (m), 2904 (w), 1716 (m), 1504 (s), 1480 (vs), 1364 (m), 1248 (s), 1232 (s), 1120 (s), 1036 (vs), 984 (m), 932 (s), 840 (s), 724 (w), 684 (w).

MS (EI, 70 eV): m/z (%) = 268 (77), 171 (76), 169 (50), 110 (23), 99 (100), 71 (65), 57 (43), 41 (33).

HRMS (C₁₄H₁₇ClO₃): calc.: 268.0866; found: 268.0855 (M⁺).

Ethyl (2-chlorophenyl)acetate (**5**):



Reaction 1 using ethyl chloroformate:

To 2-chlorobenzylzinc chloride (**1a**) (2.62 mL, 4.00 mmol, 1.5 M in THF) at -30 °C was added THF (0.5 mL) followed by Pd(PPh₃)₄ (116 mg, 5 mol %). The reaction mixture was stirred for 5 min. Then, ethyl chloroformate (227 mg, 2.09 mmol) was added dropwise. Stirring was continued for 10 min at -30 °C followed by 6.25 h at 25 °C. The reaction mixture was quenched by adding mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 4:1 (15 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the phenylacetic acid ester **5** (336 mg, 81%) as colourless liquid.

Reaction 2 using ethyl cyanoformate:

To 2-chlorobenzyl zinc chloride (**1a**) (0.67 mL, 1.00 mmol, 1.5 M in THF) at -30 °C was added dropwise TMSCH₂Li (1.00 mL, 1.00 mmol, 1 M in pentane). The reaction mixture was stirred for 30 min. CuCN·2LiCl solution (1.00 mL, 1.00 mmol, 1 M in THF) was added dropwise and the mixture was stirred for additional 30 min. Ethyl cyanoformate (150 mg, 1.5 mmol) was added dropwise. Stirring was continued for 10 min at -30 °C followed by 6 h at 0 °C. The reaction mixture was quenched by adding mixture of sat. aqueous NH₄Cl / NH₃ (25% in H₂O) = 2:1 (15 mL). The layers were separated and the aqueous layer

was extracted with DCM (3 x 50 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 98:2) afforded the phenylacetic acid ester **5** (152 mg, 77%) as colourless liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.42–7.34 (m, 1H), 7.32–7.17 (m, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 170.5, 134.5, 132.5, 131.4, 129.4, 128.6, 126.8, 61.0, 39.2, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2981 (w), 1367 (m), 1335 (m), 1122 (m), 1475 (m), 1445 (m), 1246 (m), 1053 (s), 681 (s), 1216 (s), 1028 (s), 741 (vs), 1156 (vs), 1731 (vs).

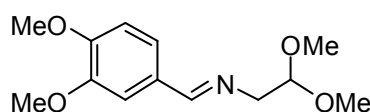
MS (EI, 70 eV): *m/z* (%) = 198 (M⁺, 4), 163 (100), 135 (23), 127 (78), 125 (35), 89 (21).

HRMS (C₁₀H₁₁ClO₂): calc.: 198.0448; found: 198.0462 (M⁺).

Preparation of papaverine.

Starting materials.^{4,5}

N-[(1*E*)-(3,4-Dimethoxyphenyl)methylene]-2,2-dimethoxyethanamine (**9**):



To a solution of 3,4-dimethoxybenzaldehyde (8.31 g, 50.0 mmol) in 150 mL toluene was added aminoacetaldehyde dimethylacetal (8.24 mL, 76 mmol). The reaction mixture was refluxed for 6 h and the water was removed by using Dean–Stark apparatus. After cooling to 25 °C, the solvent was removed *in vacuo*. The yellow oil was dissolved in DCM (50 mL) and washed with water (4 x 50 mL), then dried over Na₂SO₄. Evaporation of the solvents *in vacuo* gives the crude product **9** (12.8 g, 100%) as a pale yellow solid, which was used without further purification.

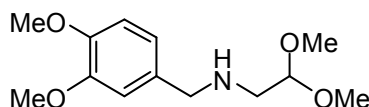
mp (°C) = 54.7–56.3.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.18–8.17 (m, 1H), 7.41 (d, *J* = 1.9 Hz, 1H), 7.14 (dd, *J* = 8.1 Hz, *J* = 1.9 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.65 (t, *J* = 5.4 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.73 (dd, *J* = 5.4 Hz, *J* = 1.3 Hz, 2H), 3.40 (s, 6H).

¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 163.0, 151.4, 149.2, 129.3, 123.3, 110.3, 108.8, 103.9, 63.4, 55.9, 55.9, 54.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2832 (w), 1600 (m), 1583 (s), 1641 (s), 1422 (s), 1512 (s), 1158 (s), 868 (s), 752 (s), 809 (s), 1137 (vs), 1238 (vs), 959 (vs), 1015 (vs), 1263 (vs).

(3,4-Dimethoxybenzyl)(2,2-dimethoxyethyl)amine (10):



To a solution of *N*-[(1*E*)-(3,4-dimethoxyphenyl)methylene]-2,2-dimethoxyethanamine (**9**) (12.8 g, 50.0 mmol) in ethanol (50 mL) was added sodium borohydride (3.78 g, 100 mmol) and the reaction mixture was stirred for 60 h at 25 °C. Then, water (150 mL) was added carefully. The layers were separated and the aqueous phase was extracted with DCM (3 x 300 mL). The combined extracts were washed with water (3 x 300 mL), brine (1 x 300 mL) and then dried over Na₂SO₄. Evaporation of the solvents *in vacuo* gives the crude product **10** (11.0 g, 86%) as a pale yellow liquid which was used without further purification.

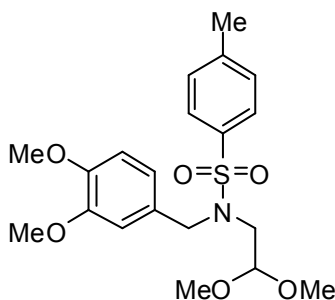
¹H-NMR (300 MHz, CDCl₃): δ / ppm = 6.88–6.85 (m, 1H), 6.84–6.76 (m, 2H), 4.46 (t, *J* = 5.5 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (s, 2H), 3.34 (s, 6H), 2.72 (d, *J* = 5.8 Hz, 2H).

¹³C-NMR (75Hz, CDCl₃): δ / ppm = 148.8, 147.9, 132.6, 120.1, 111.2, 110.9, 103.7, 55.7, 55.7, 53.7, 53.5, 50.3.

MS (EI, 70 eV): *m/z* (%) = 255, M⁺, 2), 180 (5), 151 (100), 107 (3), 75 (14).

HRMS (C₁₃H₂₁NO₄): calc.: 255.1464; found: 255.1471(M⁺).

***N*-(3,4-dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (11):**



Pyridine (3.40 mL, 42.0 mmol) was added dropwise at 0 °C to a solution of 3,4-dimethoxybenzyl(2,2-dimethoxyethyl)amine (**10**) (7.66 g, 30.0 mmol) in DCM (60 mL). Tosyl chloride (7.43 g, 39.0 mmol) was added and the reaction mixture was allowed to warm to 25 °C overnight and then poured on sat. aqueous NaHCO₃ solution. The layers were separated and the aqueous phase was extracted with DCM (3 x 100 mL), then dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 1:2) afforded the sulphonamide **11** (12.2 g, 99%) as a pale yellow liquid.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.74–7.68 (m, 2H), 7.30–7.24 (m, 2H), 6.73–6.71 (m, 2H), 6.66–6.64 (m, 1H), 4.38 (s, 2H), 4.33 (t, *J* = 5.4 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.23 (s, 6H), 3.18 (d, *J* = 5.4 Hz, 2H), 2.39 (s, 3H).

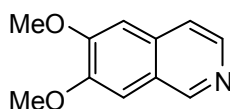
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 149.0, 148.5, 143.1, 137.7, 129.5, 128.4, 127.1, 121.0, 111.3, 110.7, 110.7, 103.8, 55.8, 55.6, 54.5, 52.2, 48.3, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2935 (w), 2834 (w), 1595 (w), 1514 (s), 1438 (m), 1337 (s), 1255 (s), 1236 (s), 1155 (vs), 1066 (s), 1026 (vs), 997 (s), 911 (s), 813 (s), 760 (s), 706 (m), 658 (vs).

MS (EI, 70 eV): *m/z* (%) = 409 (M⁺, <1), 254 (5), 151 (28), 91 (4), 75 (100).

HRMS (C₂₀H₂₇NO₆S): calc.: 409.1559; found: 409.1546 (M⁺).

6,7-Dimethoxyisoquinoline (7):



To a solution of *N*-(3,4-dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (**11**) (12.1 g, 29.5 mmol) in dioxane (280 mL) was added 6N HCl (22 mL). The reaction mixture was refluxed for 22 h. After cooling to 25 °C, the solution was poured on water. The layers were separated and the aqueous phase was extracted with Et₂O (2 x 250 mL), DCM (3 x 250 mL). The combined aqueous phases were treated with NaOH (10%) solution until pH > 9. The aqueous phase was extracted with Et₂O (2 x 250 mL), DCM (3 x 250 mL) and the combined extracts were dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, EtOAc) afforded the isoquinoline **7** (4.78 g, 86%) as a white solid.

mp (°C) = 93.3–95.4.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.98 (s, 1H), 8.33 (d, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 5.83 Hz, 1H), 7.11 (s, 1H), 6.98 (s, 1H), 3.95 (s, 3H).

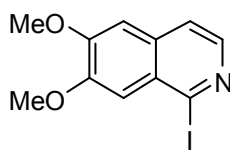
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 152.8, 150.1, 149.8, 141.8, 132.3, 124.6, 119.0, 105.1, 104.4, 55.9, 55.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3015 (w), 2836 (w), 1573 (m), 1502 (s), 1477 (s), 1459 (m), 1433 (m), 1412 (s), 1335 (s), 1248 (vs), 1206 (s), 1138 (vs), 1001 (s), 923 (s), 852 (vs), 755 (s), 632 (s).

MS (EI, 70 eV): *m/z* (%) = 189 (M⁺, 100), 174 (11), 146 (24), 117 (8), 103 (6), 91 (6).

HRMS (C₁₁H₁₁NO₂): calc.: 189.0790; found: 189.0788 (M⁺).

1-Iodo-6,7-dimethoxyisoquinoline (**8**):



To a solution of 6,7-dimethoxyisoquinoline (**7**) (946 mg, 5.00 mmol) in THF (5 mL) was added TMPMgCl·LiCl (5.13 mL, 6.00 mmol, 1.17 M in THF) at 25 °C. The reaction mixture was stirred for 4 h. Iodine (1.52 g, 6.00 mmol) was dissolved in THF (3 mL) in a second flask at –40 °C. To this solution, the magnesium compound was added dropwise. The solution was stirred 10 min at –40 °C, then 10 min at 0 °C. The reaction mixture was quenched by adding a mixture of sat. aqueous NH₄Cl solution and sat. aqueous Na₂S₂O₃ solution, then sat. aqueous NaHCO₃ until pH>7. The layers were separated and the aqueous phase was extracted with DCM (3 x 100 mL), then dried over MgSO₄. Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et₂O = 1:4) afforded the isoquinoline **8** (1.14 g, 73%) as a pale yellow solid.

mp (°C) = 140.0–141.1 (decomposition).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 8.06 (d, *J* = 5.6 Hz, 1H), 7.37 (d, *J* = 5.1 Hz, 1H), 7.29 (s, 1H), 6.59 (s, 1H), 4.03 (s, 3H), 4.00 (s, 3H).

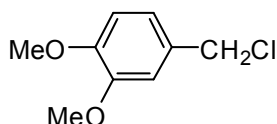
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 153.3, 151.3, 141.8, 132.4, 127.9, 124.6, 120.0, 111.0, 105.0, 56.3, 56.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{–1} = 2936 (w), 1504 (s), 1473 (s), 1458 (s), 1431 (s), 1392 (s), 1296 (s), 1251 (s), 1226 (s), 1140 (vs), 1006 (s), 929 (s), 858 (vs), 774 (s), 671 (s).

MS (EI, 70 eV): *m/z* (%) = 314 (M⁺, 539), 189 (12), 188 (100), 145 (3), 94 (6).

HRMS (C₁₁H₁₀INO₂): calc.: 314.9751; found: 314.9756 (M⁺).

4-(Chloromethyl)-1,2-dimethoxybenzene (**2m**):



To a solution of LiCl (6.87 g, 60.0 mmol, dried for 10 min under high vacuum at 400 °C using a heat gun) in THF (50 mL) was added 3,4-dimethoxybenzylic alcohol (3.30 g, 20.0 mmol) at 0 °C. Then, NEt₃ (5.60 mL, 40.0 mmol) was added dropwise, followed by mesyl chloride (2.33 mL, 30.0 mmol). The reaction mixture was allowed to reach 25 °C overnight. Then, DCM (300 mL) was added and the solution was washed with water (3 x 250 mL). The combined extracts were dried over MgSO₄. Evaporation of the solvents *in*

vacuo and purification by flash chromatography (silica gel, pentane / Et₂O = 4:1) afforded the benzylic chloride **2m** (2.56 g, 69%) as a white solid.

mp (°C) = 54.8–56.0.

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 6.94–6.88 (m, 1H), 6.89 (s, 1H), 6.83–6.77 (m, 1H), 4.54 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H).

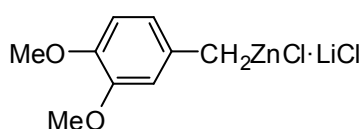
¹³C-NMR (150 MHz, CDCl₃): δ / ppm = 149.1, 149.0, 129.9, 121.0, 111.6, 110.9, 55.8, 55.8, 46.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3010 (w), 2935 (w), 2838 (w), 1593 (m), 1514 (s), 1463 (s), 1450 (m), 1437 (m), 1259 (s), 1232 (vs), 1154 (vs), 1139 (vs), 1036 (s), 1022 (vs), 848 (s), 815 (s), 685 (vs).

MS (EI, 70 eV): *m/z* (%) = 186 (M⁺, 17), 151 (100), 107 (9), 91 (3), 77 (4).

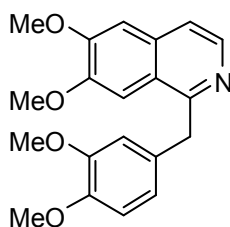
HRMS (C₉H₁₁ClO₂): calc.: 186.0448; found: 186.0434 (M⁺).

3,4,-Dimethoxybenzyl zinc chloride (**1m**):



According to **TP2** 3,4-dimethoxybenzyl chloride (**2m**) (933 mg, 5.00 mmol, in 2 mL THF) was added dropwise at 0 °C to a suspension of LiCl (848 mg, 20.0 mmol) and zinc dust (1.31 g, 20.0 mmol) in 2 mL THF (activation: BrCH₂CH₂Br (0.02 mL, 5 mol %), TMSCl (3 drops, 1 mol %)). The reaction mixture was stirred for 2 h at 0 °C followed by stirring for 2.5 h at 25 °C. After centrifugation iodometric titration² of **1m** indicates a yield of 72%.

Papaverine (**6**):



To a solution of 1-iodo-6,7-dimethoxyisoquinoline (**8**) (315 mg, 1.00 mmol) in THF (3 mL) was added S-Phos (20.5 mg, 0.05 mmol, 5 mol %), Pd(OAc)₂ (5.61 mg, 0.03 mmol, 2.5 mol %). Then, 3,4,-dimethoxybenzylzinc chloride (**1m**) (2.0 mL, 1.40 mmol, 0.70 M in THF) was added dropwise. The reaction mixture was stirred for 1.25 h at 25 °C, then

quenched by adding a mixture of sat. aqueous NH_4Cl / NH_3 (25% in H_2O) = 5:1. The layers were separated and the aqueous layer was extracted with DCM (5 x 50 mL). The combined extracts were dried over MgSO_4 . Evaporation of the solvents *in vacuo* and purification by flash chromatography (silica gel, pentane / Et_2O = 1:4, 2% NEt_3 , 2% EtOH) afforded papaverine **6** (229 mg, 68%) as pale yellow solid.

mp ($^\circ\text{C}$) = 144.2–145.8.

^1H -NMR (300 MHz, CDCl_3): δ / ppm = 8.35 (d, J = 6.0 Hz, 1H), 7.46 (d, J = 5.7 Hz, 1H), 7.37 (s, 1H), 7.06 (s, 1H), 6.83–6.80 (m, 2H), 6.75 (d, J = 8.1 Hz, 1H), 4.58 (s, 2H), 4.00 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H).

^{13}C -NMR (150 MHz, CDCl_3): δ / ppm = 157.7, 152.3, 149.7, 149.0, 147.4, 140.9, 133.4, 132.2, 122.8, 120.4, 118.6, 111.8, 111.1, 105.2, 104.1, 55.9, 55.8, 55.8, 55.7, 42.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2956 (w), 2939 (w), 2835 (w), 1504 (vs), 1478 (s), 1463 (s), 1454 (m), 1434 (s), 1414 (s), 1257 (vs), 1232 (vs), 1202 (s), 1157 (s), 1153 (s), 1147 (s), 1139 (vs), 1075 (m), 1045 (m), 1028 (vs), 986 (s), 875 (s), 867 (m), 860 (s), 843 (s), 822 (s), 805 (m), 785 (s), 768 (m), 736 (m), 732 (m), 661 (s), 645 (m).

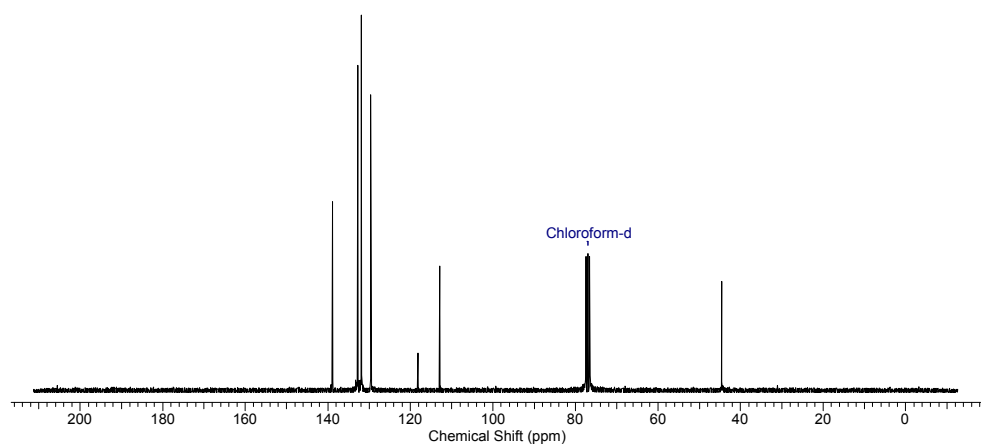
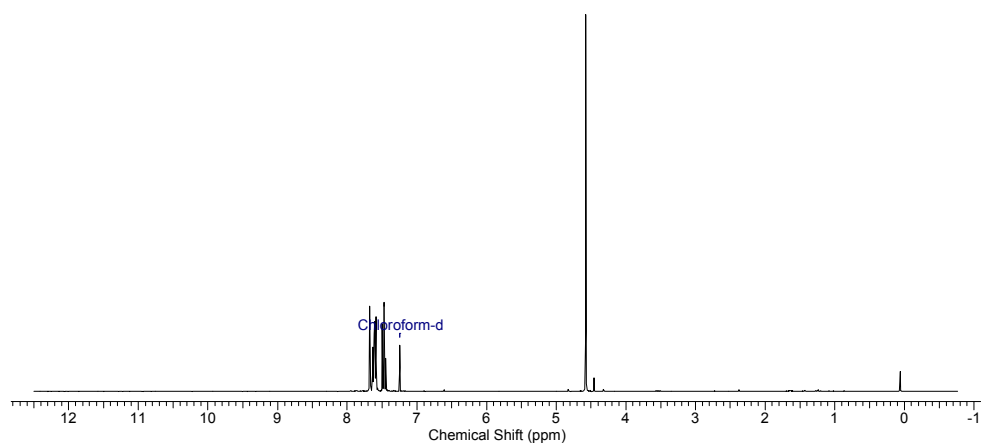
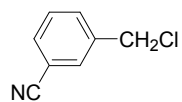
MS (EI, 70 eV): m/z (%) = 339 (M^+ , 55), 324 (75), 308 (20), 154 (13).

HRMS ($\text{C}_{20}\text{H}_{21}\text{NO}_4$): calc.: 339.1471; found: 339.1455 (M^+).

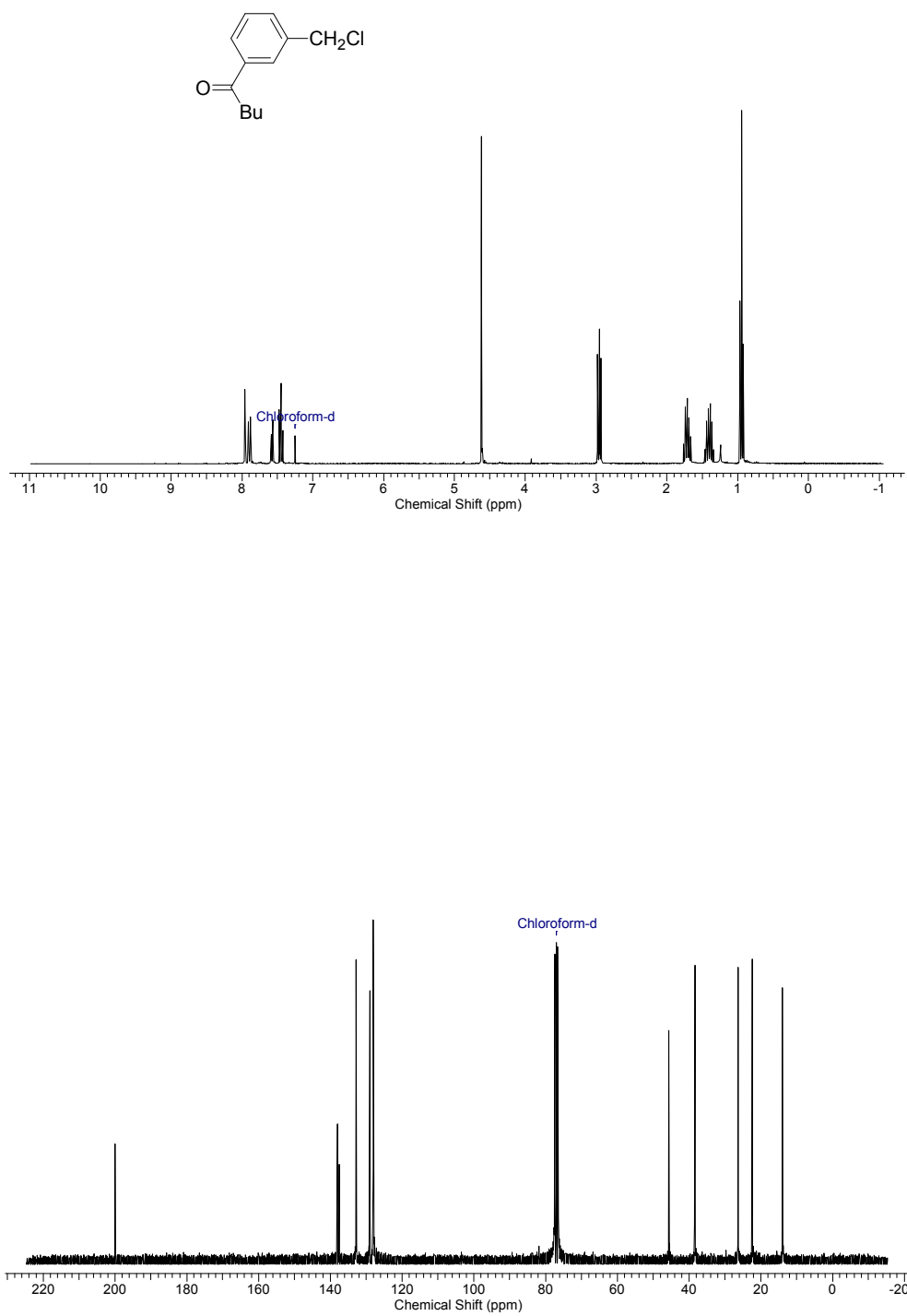
References:

- 1) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
- 2) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.
- 3) Zinc dust, commercial available by Aldrich; <10 micron.
- 4) Product **9** and **10** were prepared according to (a) Arnold, N. J.; Arnold, R.; Beer, D.; Bhalay, G.; Collingwood, S. P.; Craig, S.; Devereux, N.; Dodds, M.; Dunstan, A. R.; Fairhurst, R. A.; Farr, D.; Fullerton, J. D.; Glen, A.; Gomez, S.; Haberthuer, S.; Hatto, J. D. I.; Howes, C.; Jones, D.; Keller, T. H.; Leuenberger, B.; Moser, H. E.; Muller, I.; Naef, R.; Nicklin, P. A.; Sandham, D. A.; Turner, K. L.; Tweed, M. F.; Watson, S. J.; Zurini, M. *Bioorg. & Medicinal Chem. Lett.* **2007**, *17*, 2376; (b) Ioanaviciu, A.; Antony, S.; Pommier, Y.; Staker, B. L.; Stewart, L.; Cushman, M. *J. Med. Chem.* **2005**, *48*, 4803.
- 5) Product **7** was prepared according to: Boger, D. L.; Brotherton, C. E.; Kelley, M. D. *Tetrahedron* **1981**, *37*, 5181.

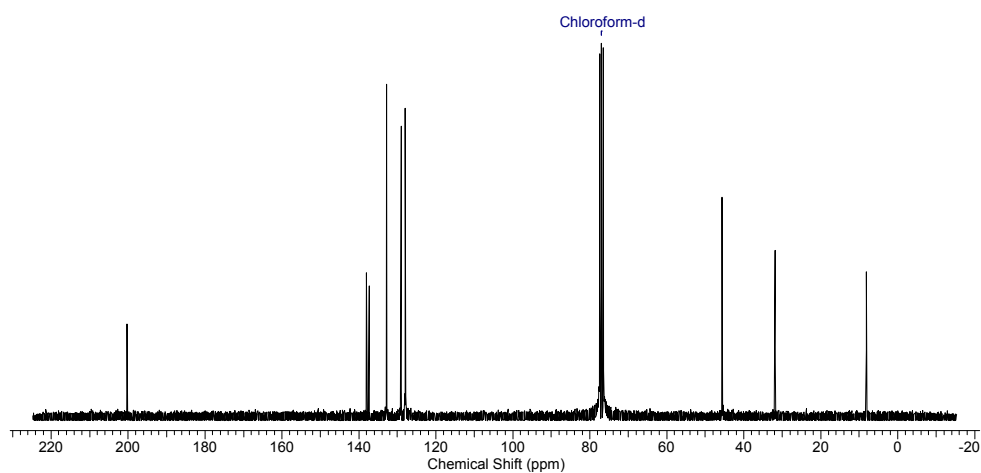
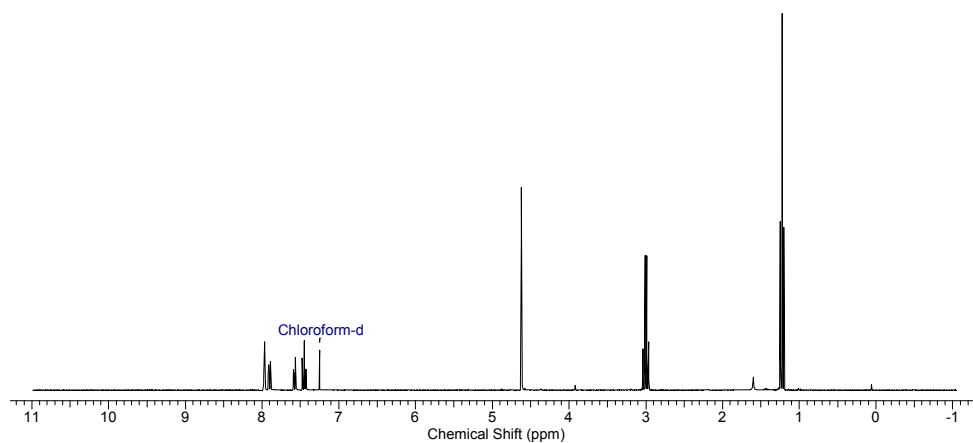
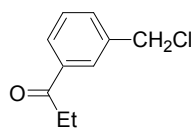
NMR-SPECTRA
3-(Chloromethyl)benzonitrile (2f)



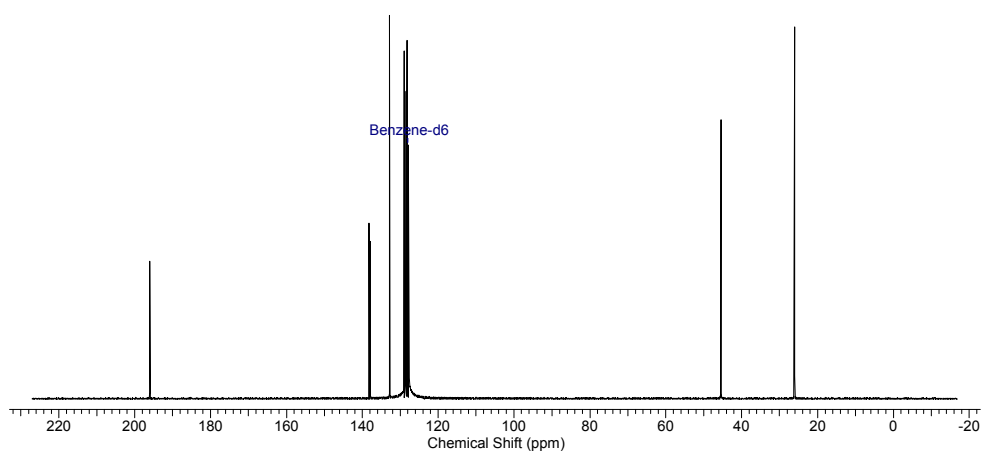
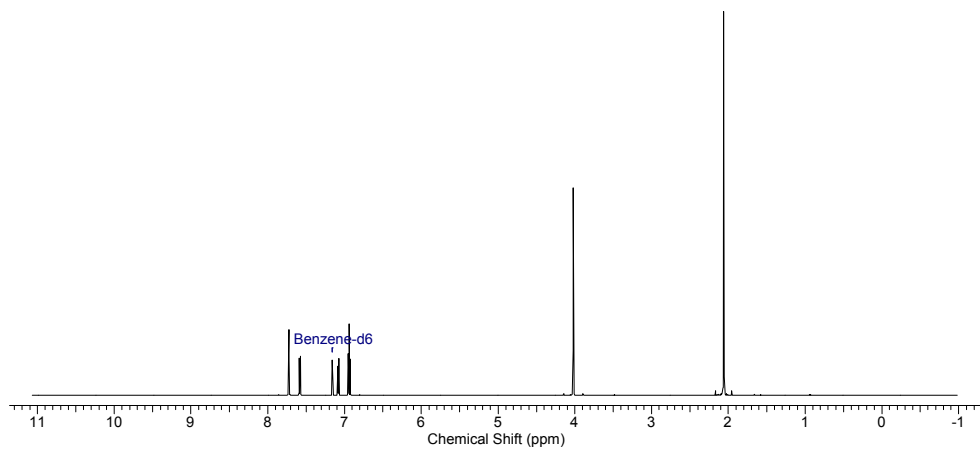
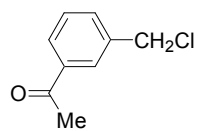
1-[3-(Chloromethyl)phenyl]pentan-1-one (2g)



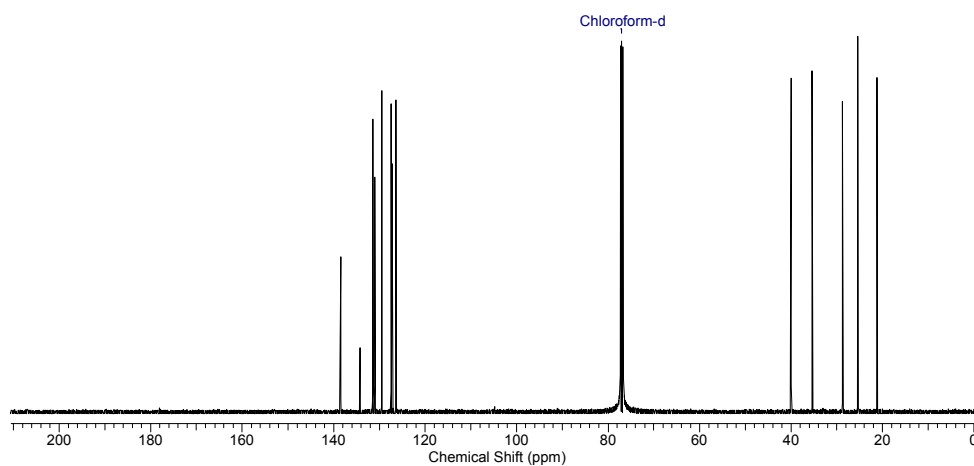
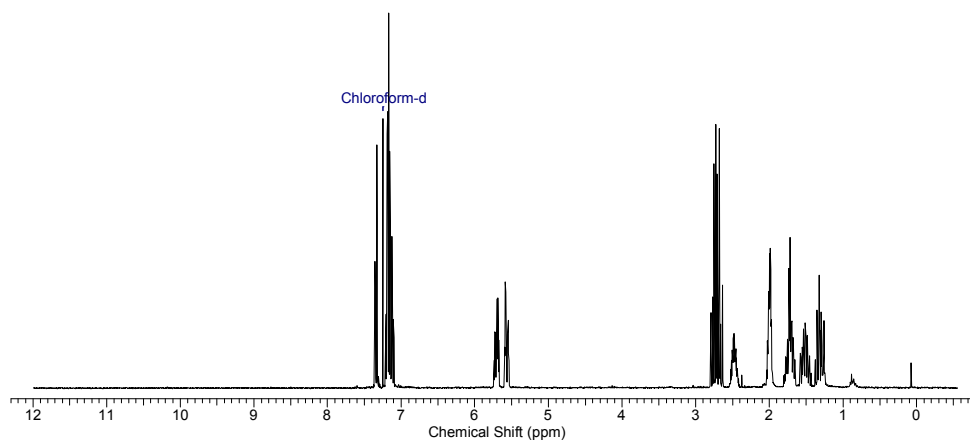
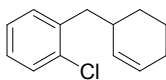
1-[3-(Chloromethyl)phenyl]propan-1-one (2h)



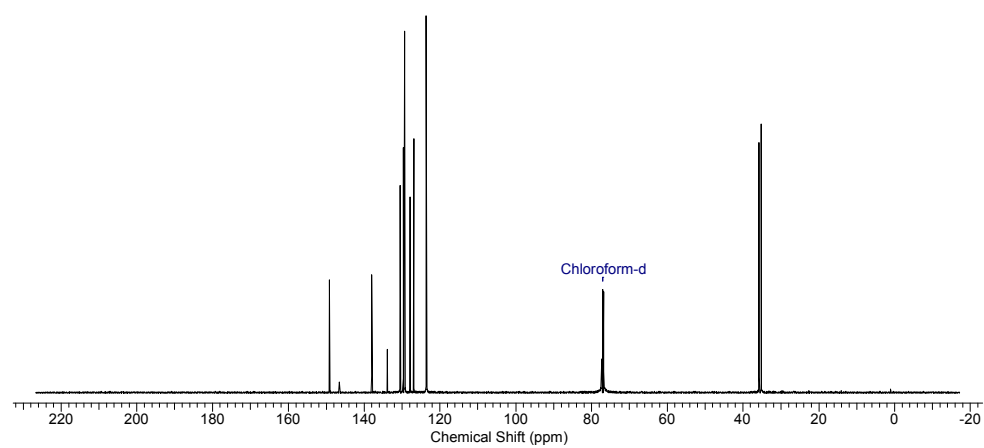
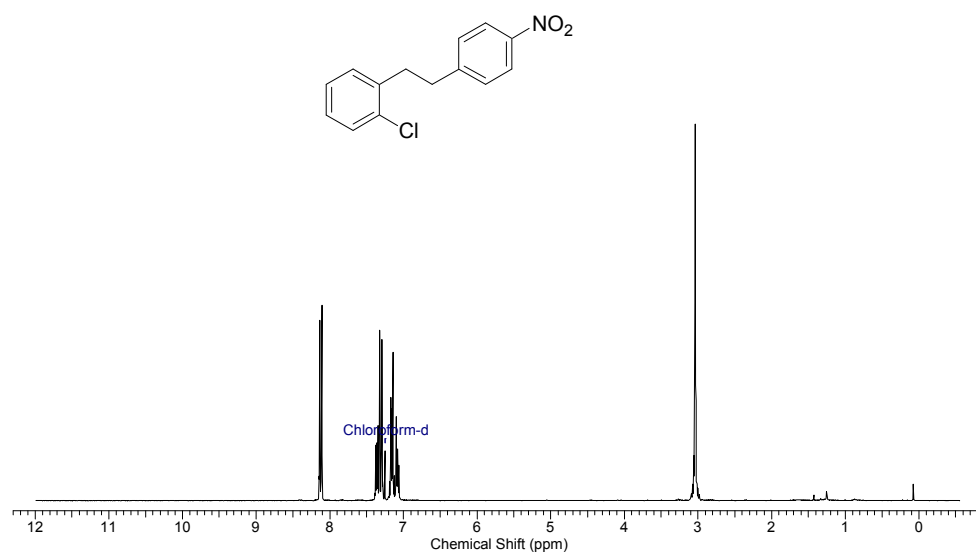
1-[3-(Chloromethyl)phenyl]propan-1-one (2i)



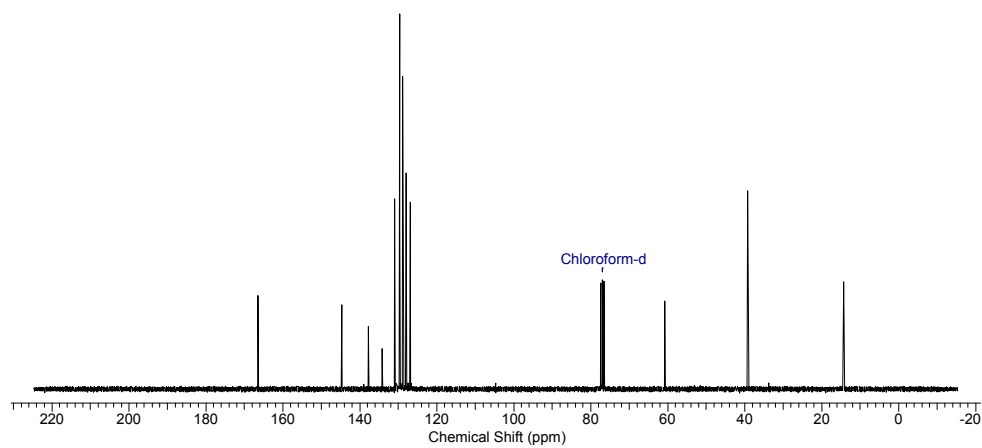
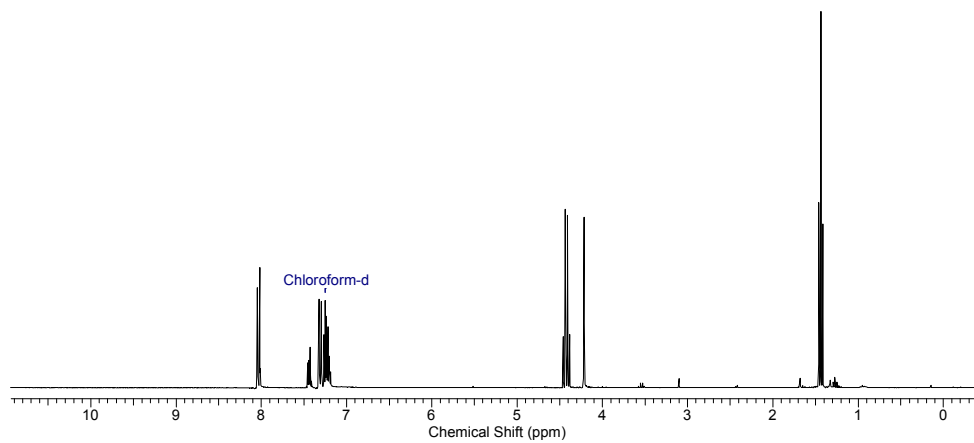
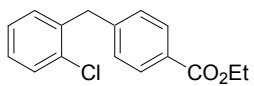
1-Chloro-2-(cyclohex-2-en-1-ylmethyl)benzene (4a)



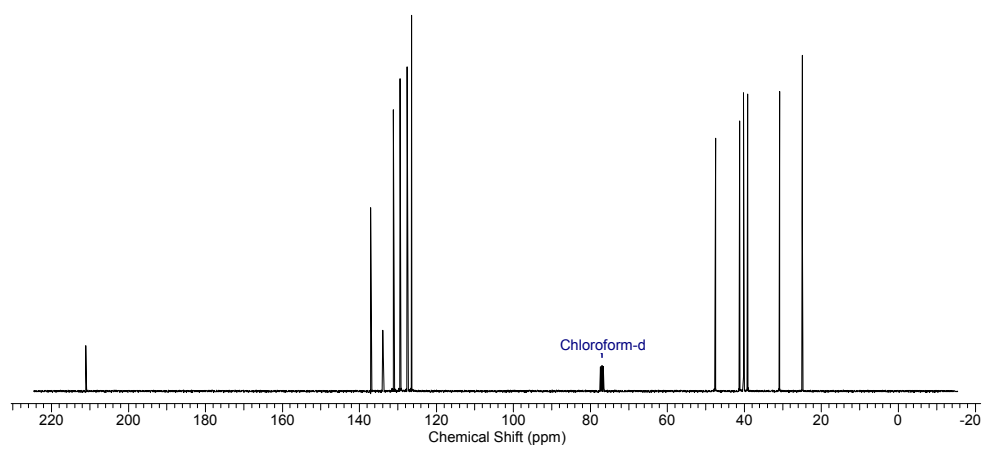
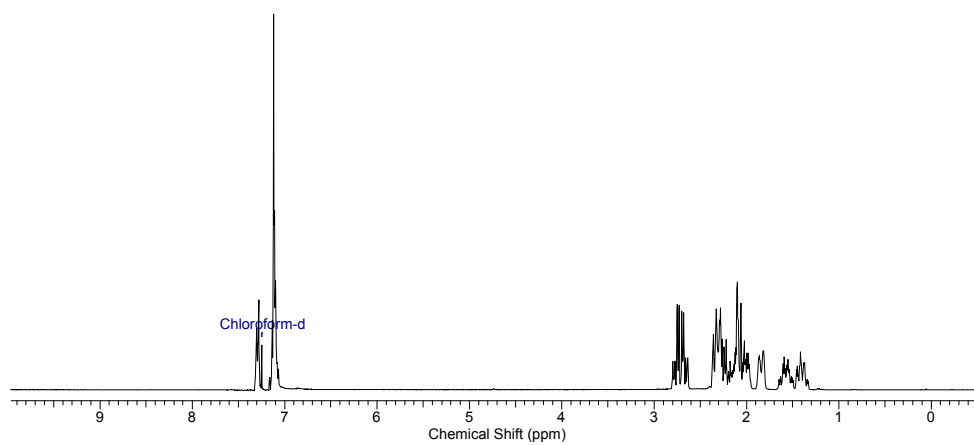
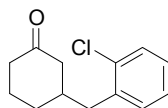
1-Chloro-2-[2-(4-nitrophenyl)ethyl]benzene (4b)



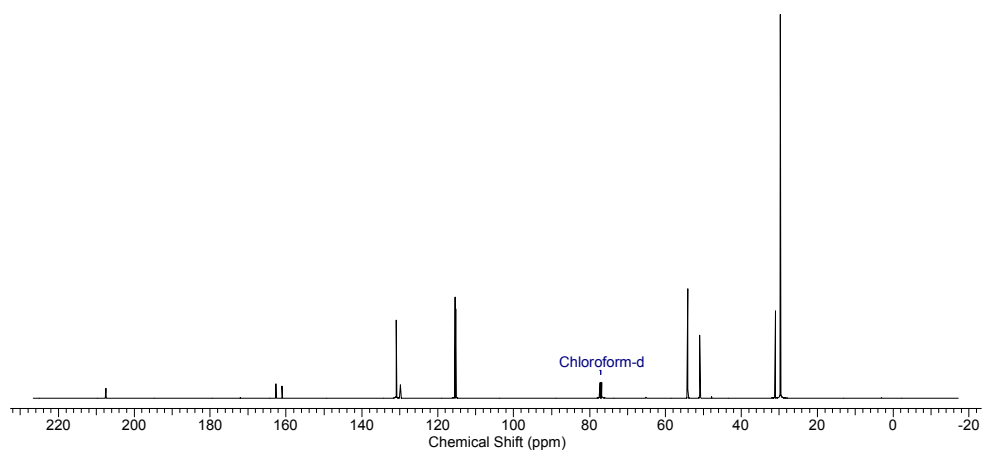
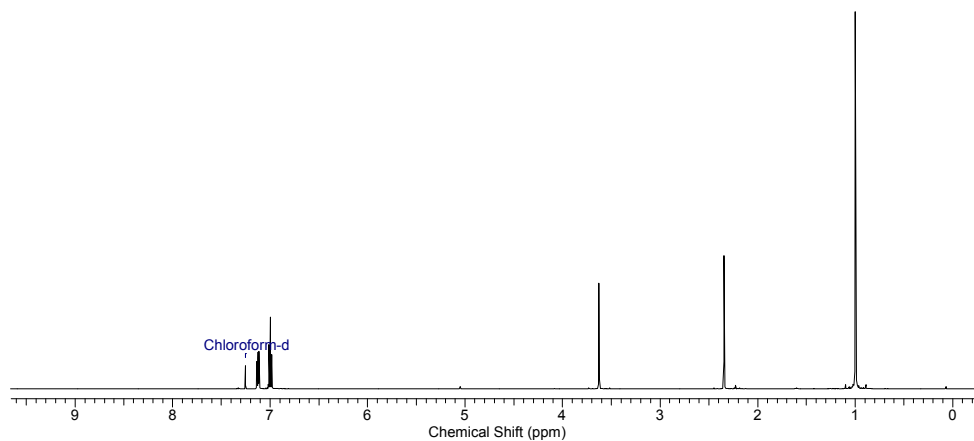
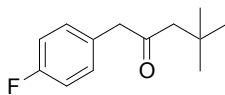
Ethyl 4-(2-chlorobenzyl)benzoate (4c)



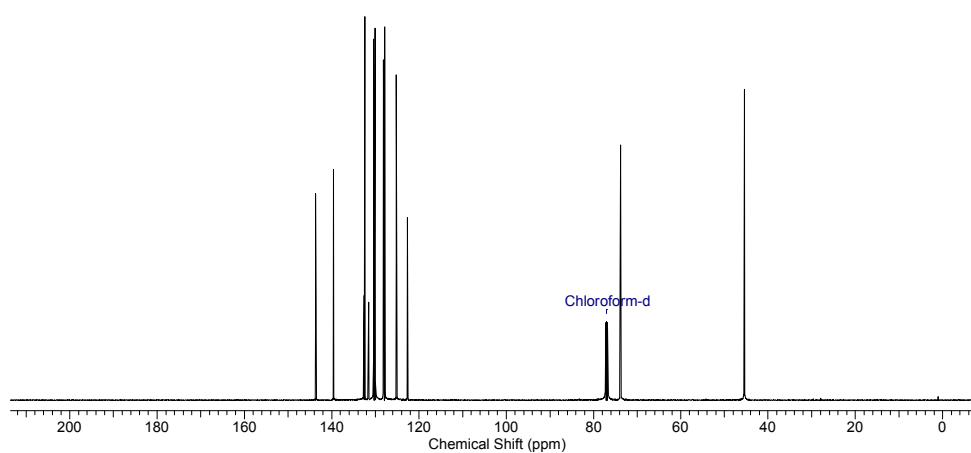
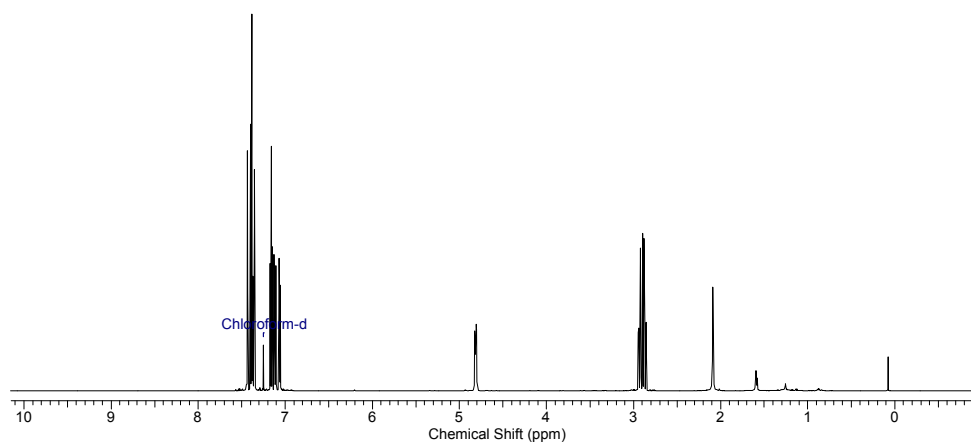
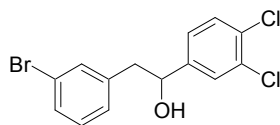
3-(2-Chlorobenzyl)cyclohexanone (4d)



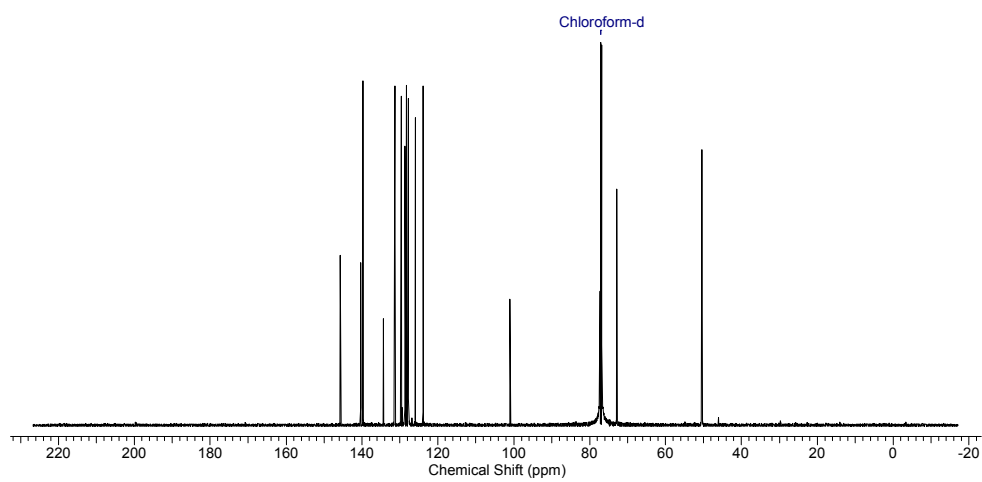
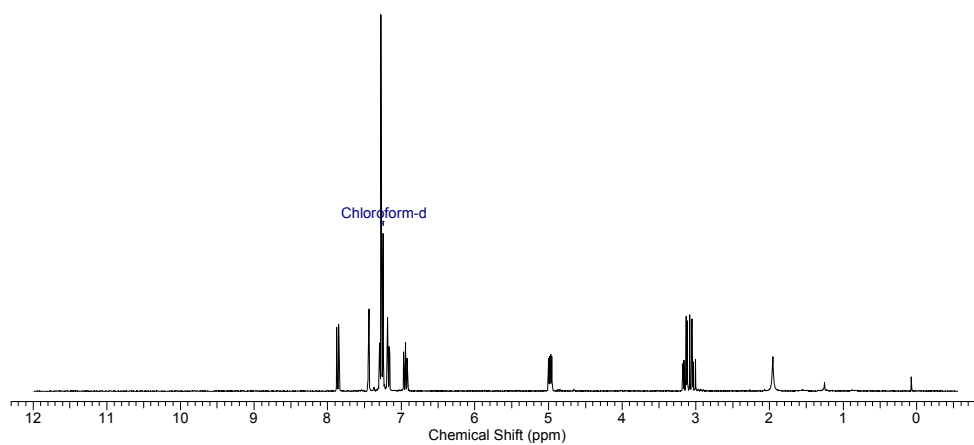
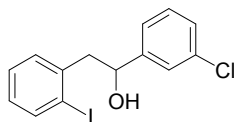
1-(4-Fluorophenyl)-3,3-dimethylbutan-2-one (4e)



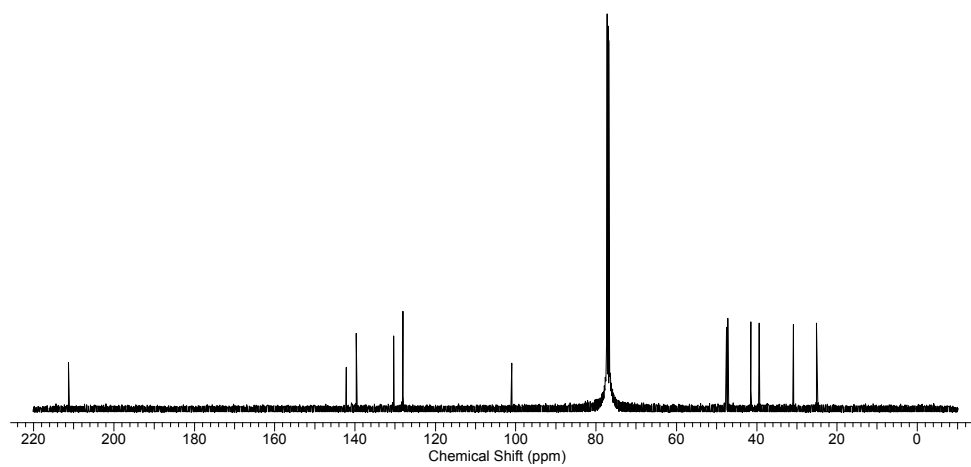
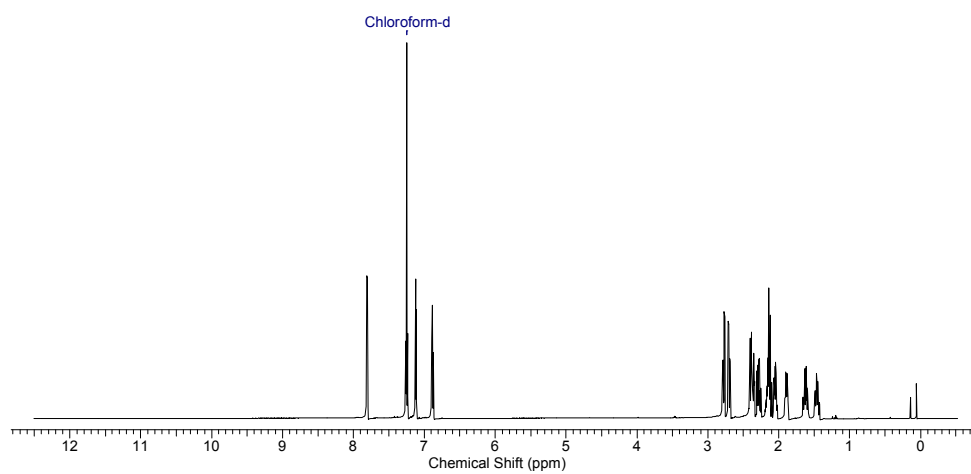
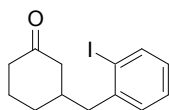
2-(3-Bromophenyl)-1-(3,4-dichlorophenyl)ethanol (4f)



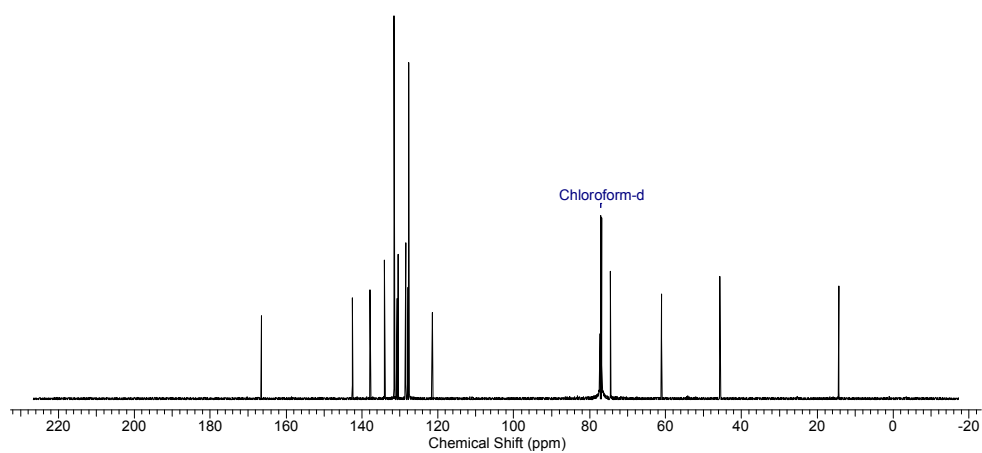
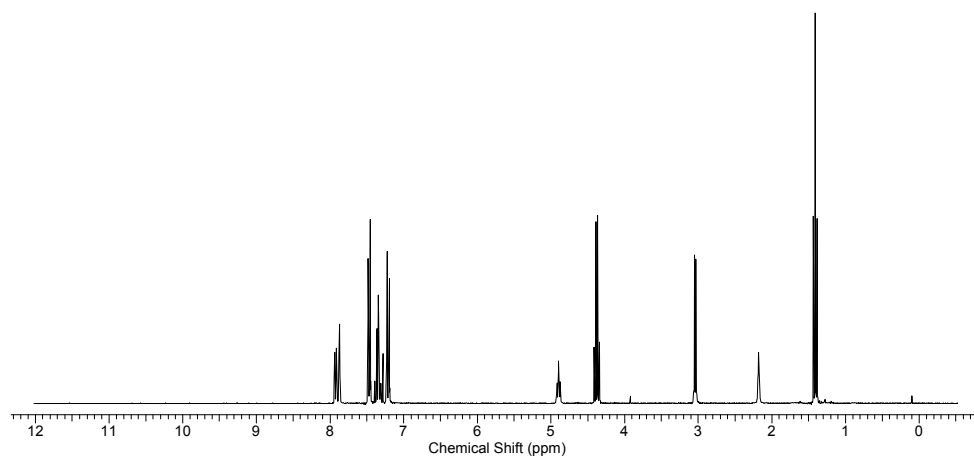
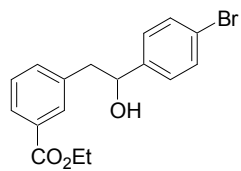
1-(3-Chlorophenyl)-2-(2-iodophenyl)ethanol (4g)



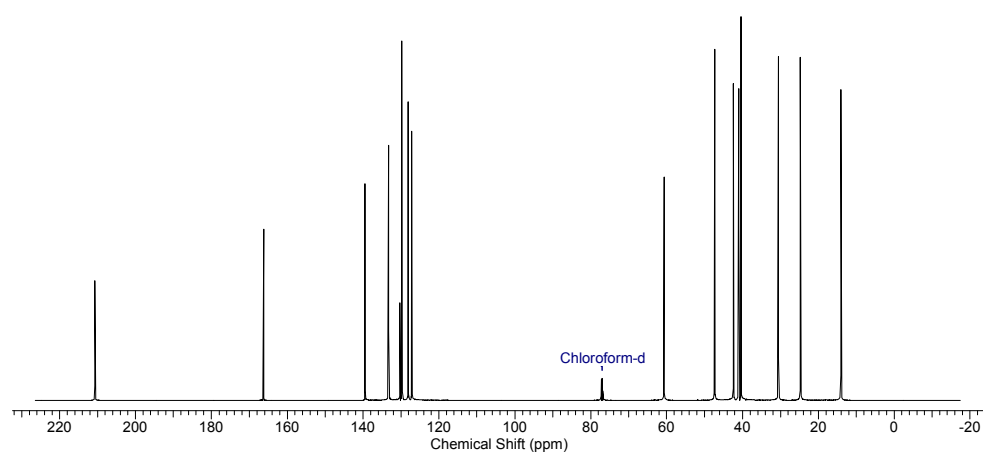
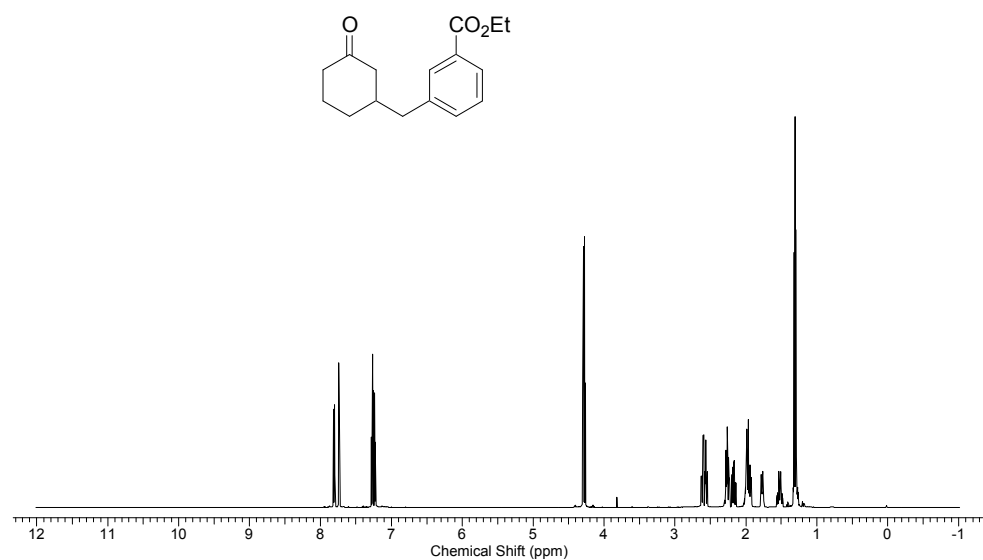
3-(2-Iodobenzyl)cyclohexanone (4h)



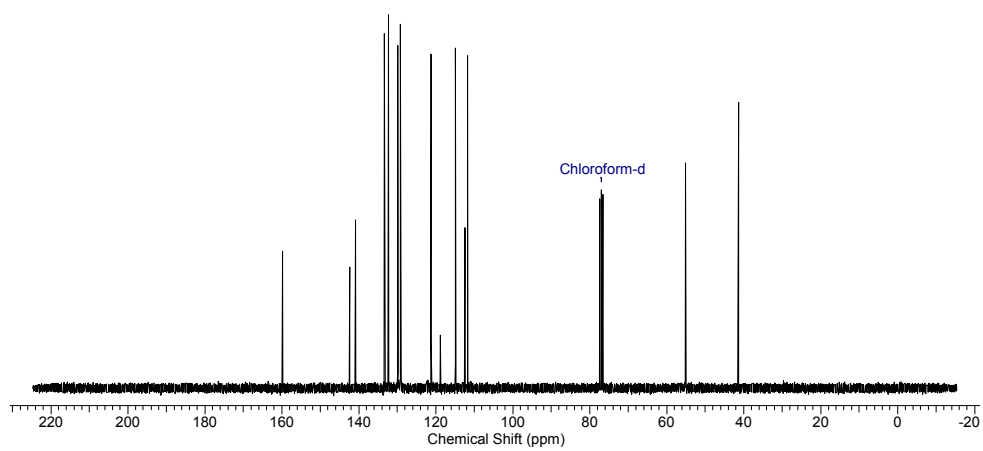
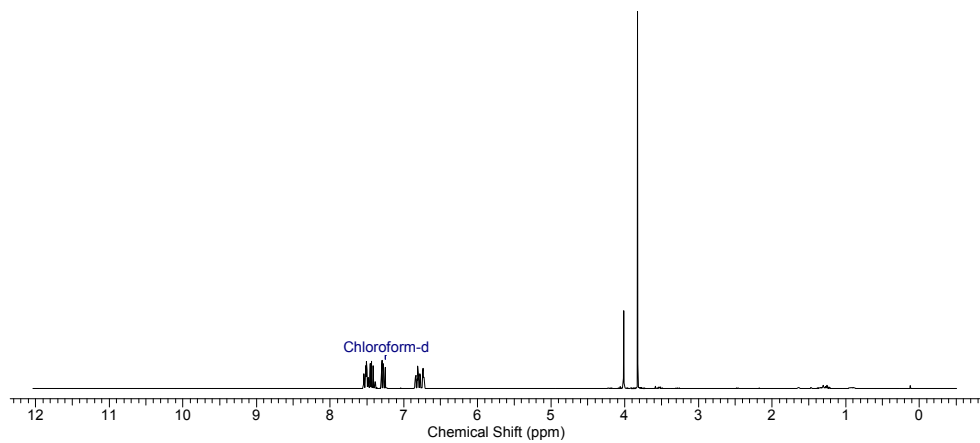
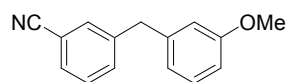
Ethyl 3-[2-(4-bromophenyl)-2-hydroxyethyl]benzoate (4i)



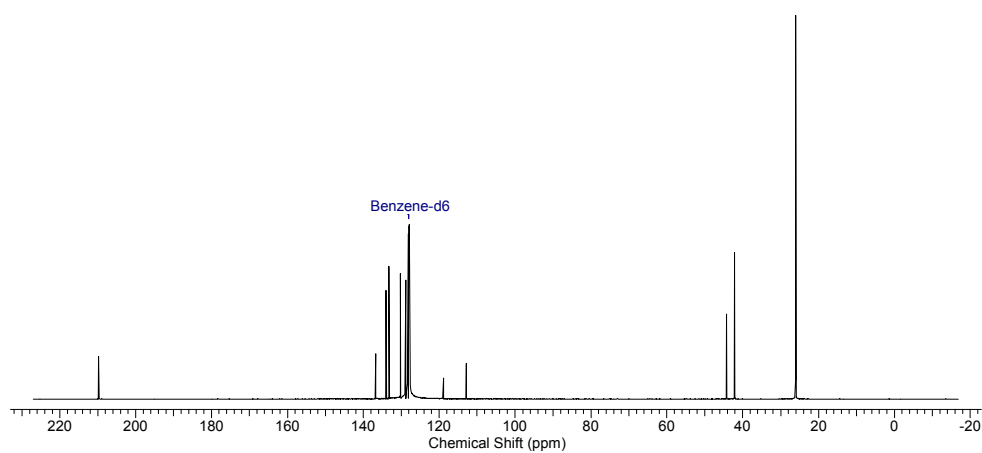
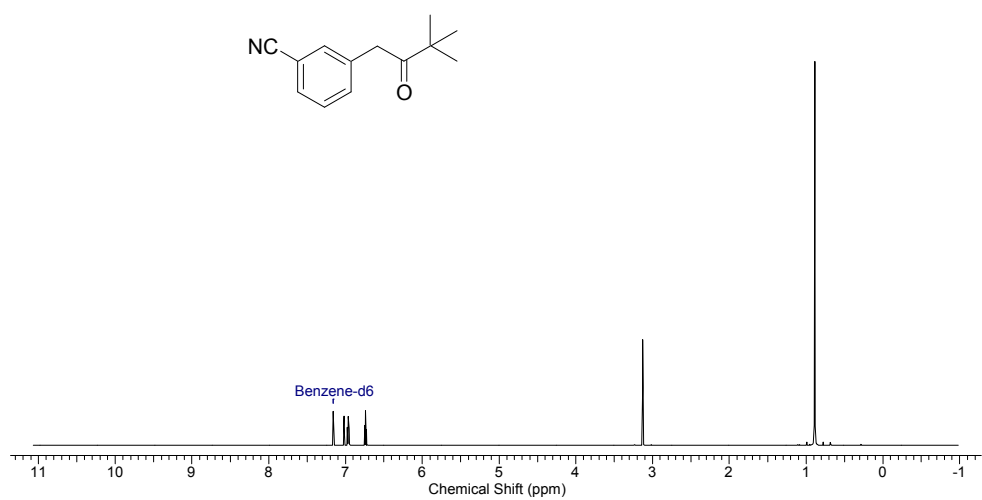
Ethyl 3-[(3-oxocyclohexyl)methyl]benzoate (4j)



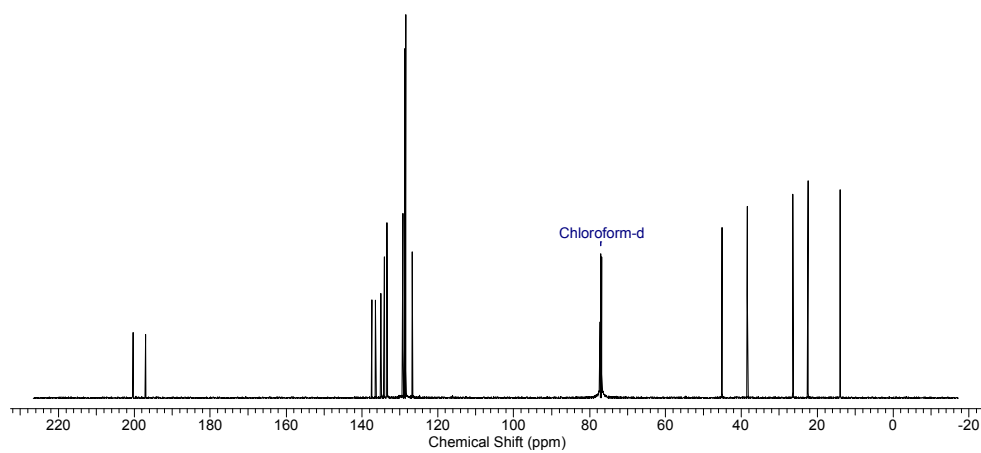
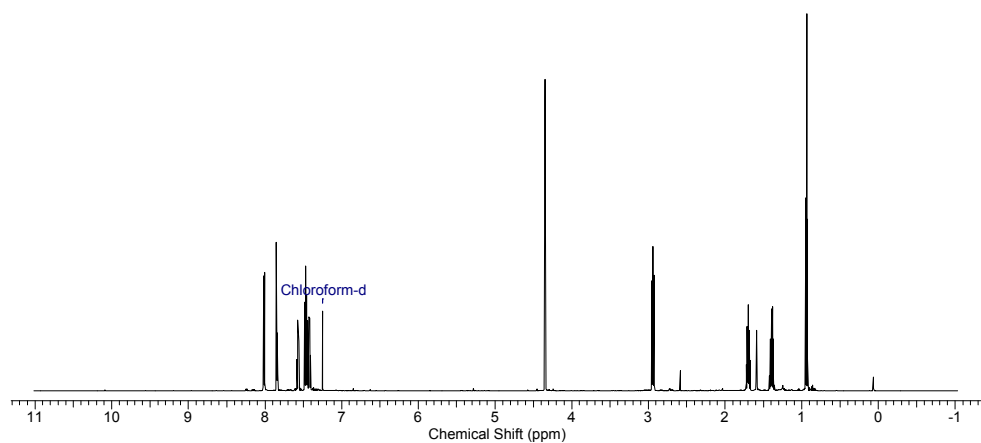
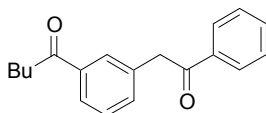
3-(3-Methoxybenzyl)benzonitrile (4k)



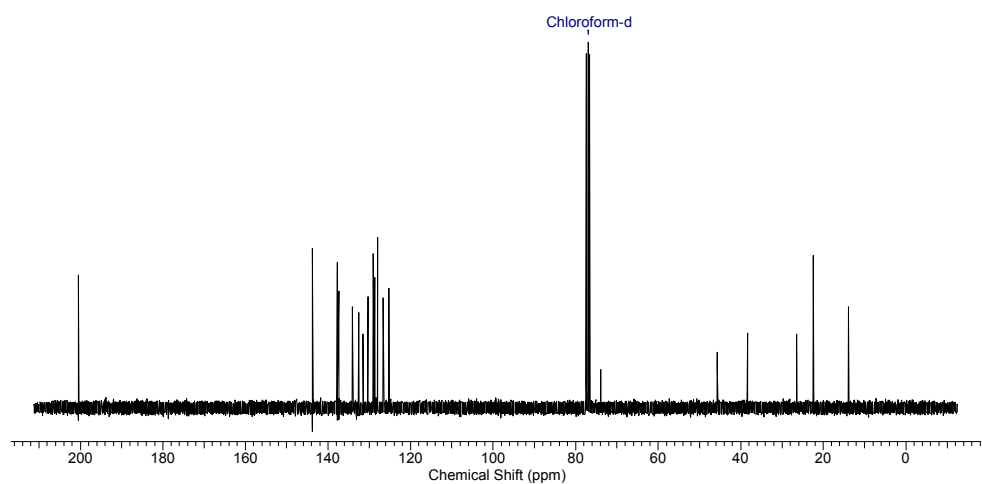
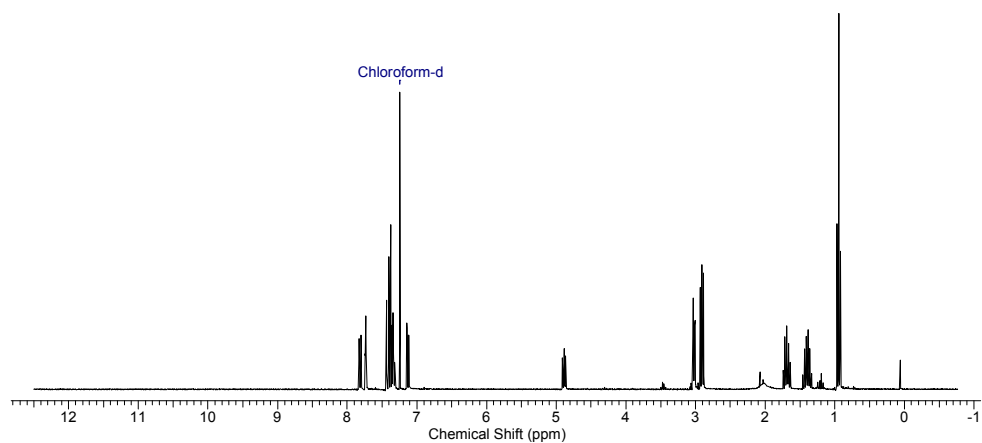
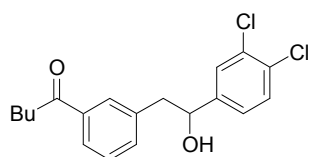
3-(3,3-Dimethyl-2-oxobutyl)benzonitrile (4l)



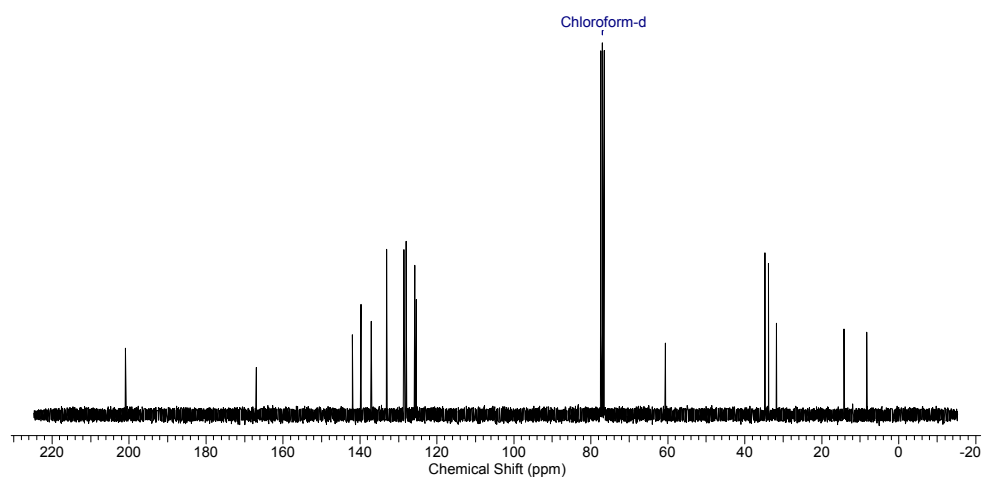
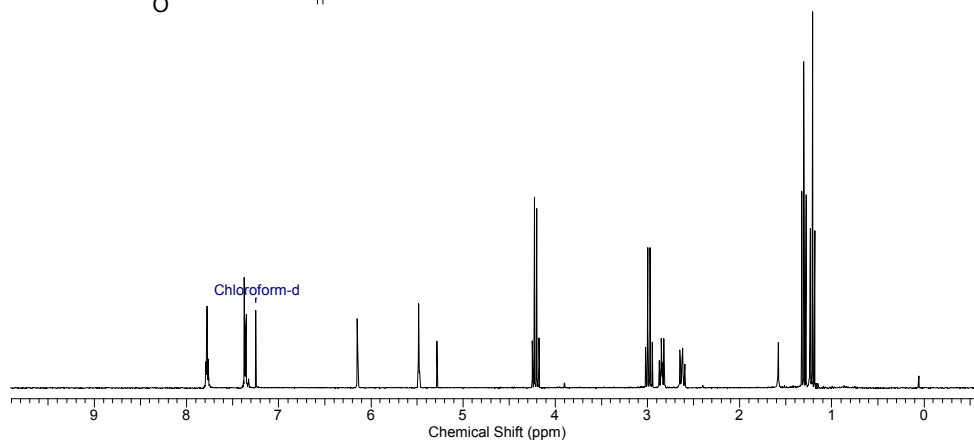
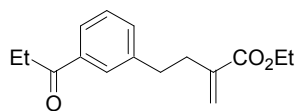
1-[3-(2-Oxo-2-phenylethyl)phenyl]pentan-1-one (4m)



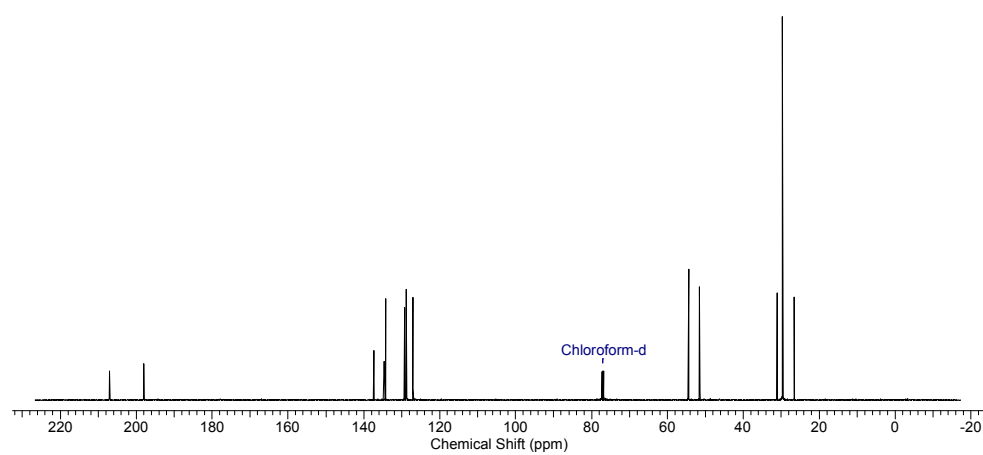
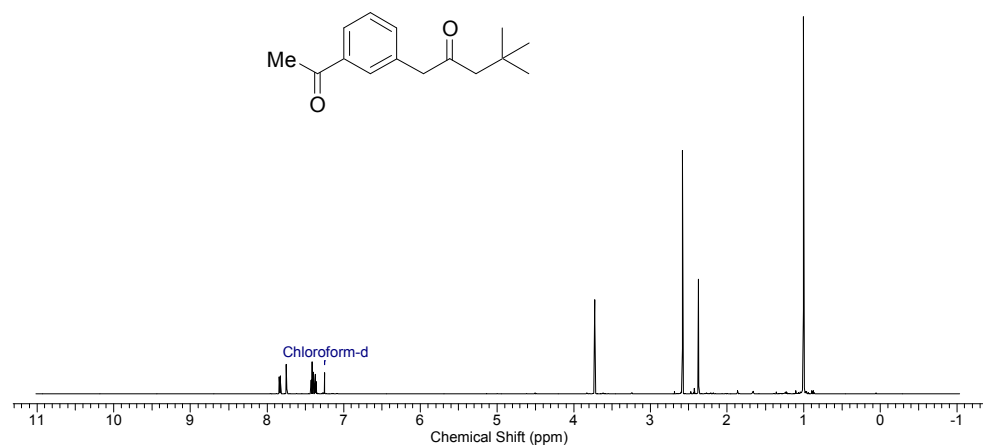
1-{3-[2-(3,4-dichlorophenyl)-2-hydroxyethyl]phenyl}pentan-1-one (4n)



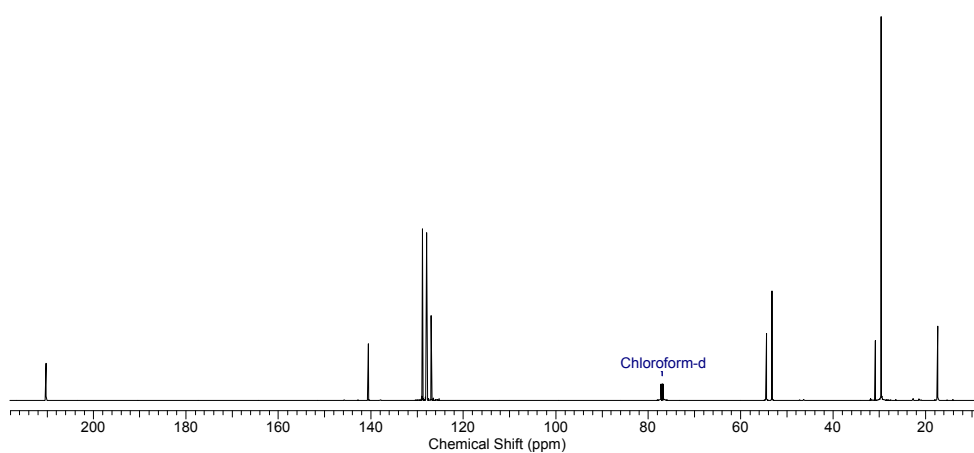
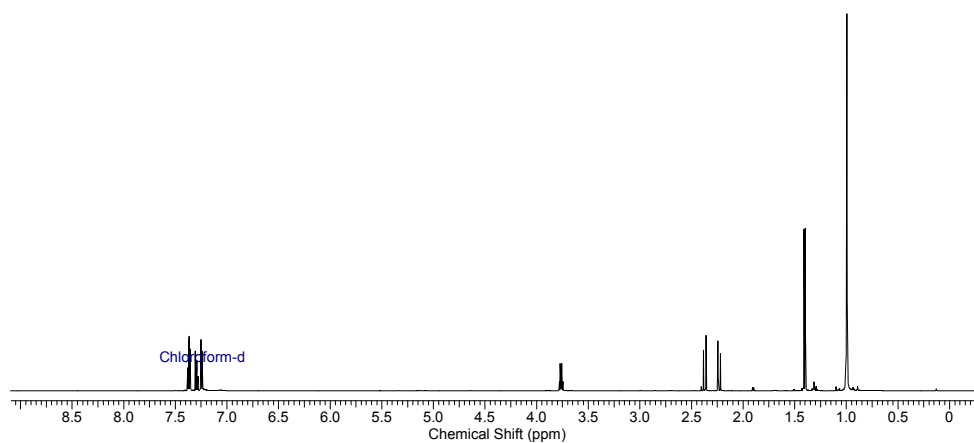
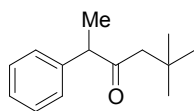
Ethyl 2-[2-(3-propionylphenyl)ethyl]acrylate (4o)



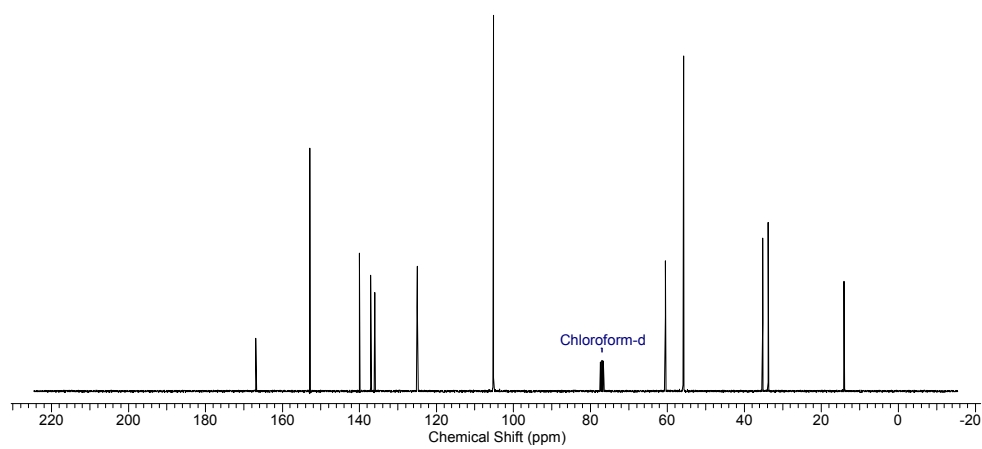
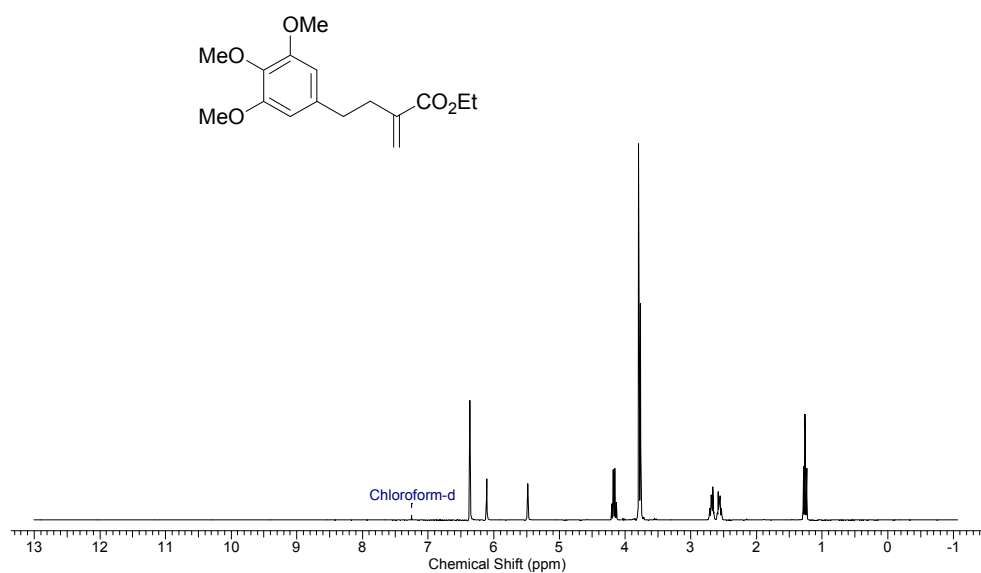
1-(3-Acetylphenyl)-4,4-dimethylpentan-2-one (4p)



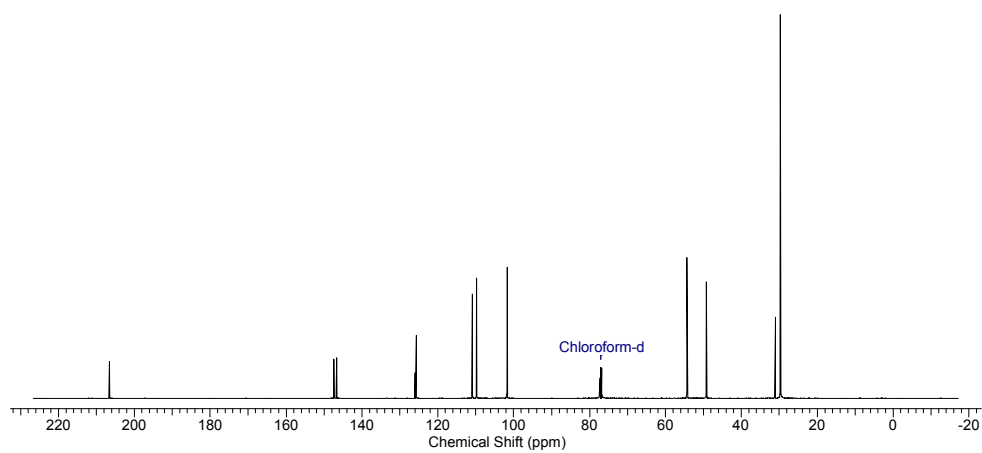
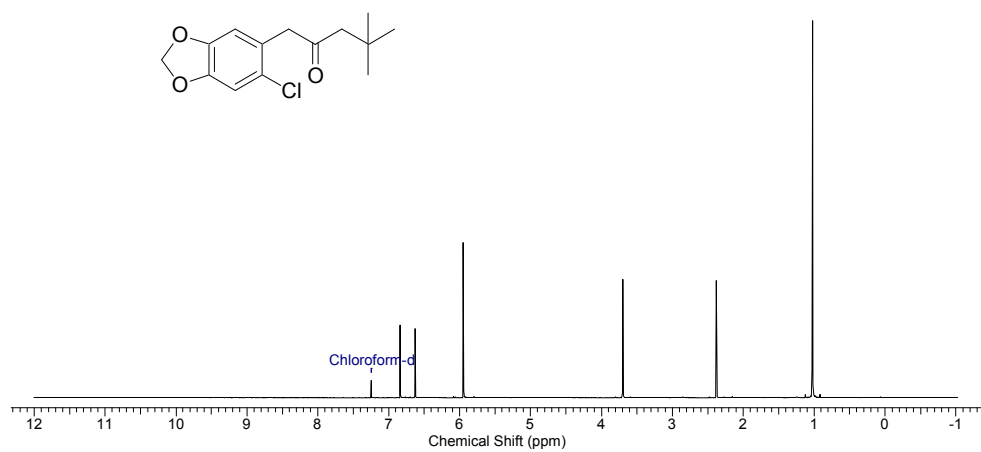
5,5-Dimethyl-2-phenylhexan-3-one (4q)



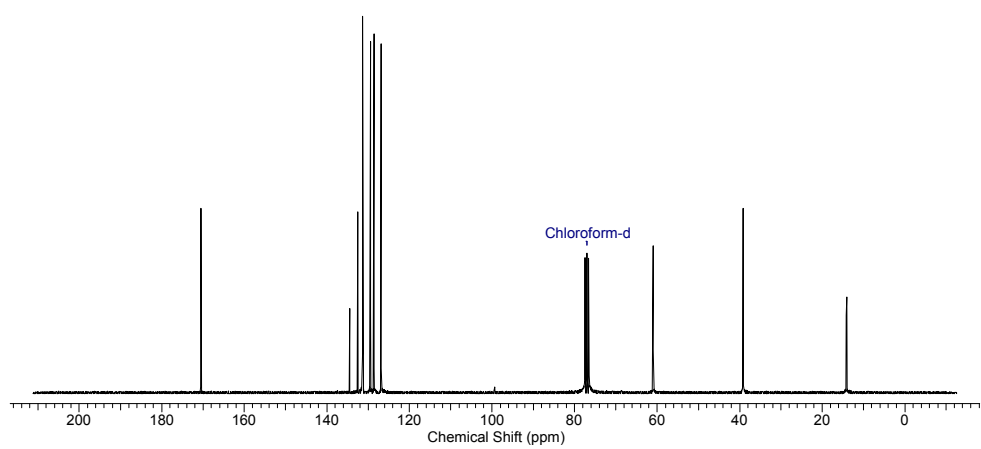
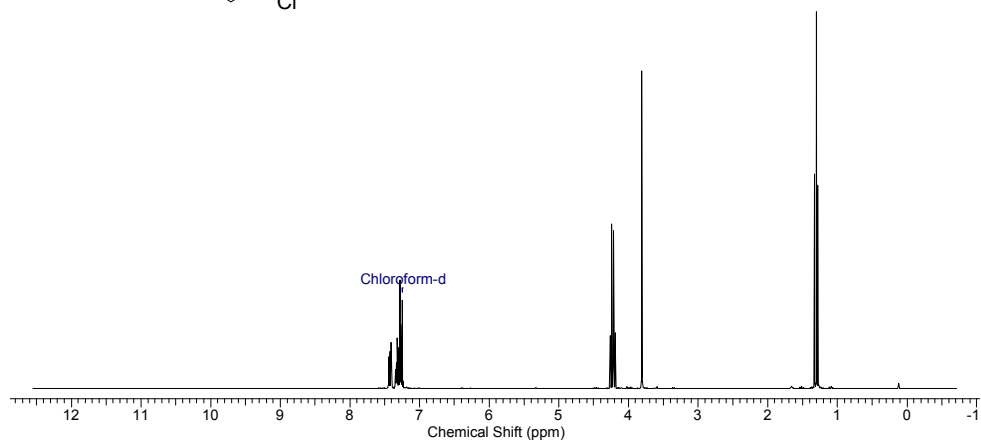
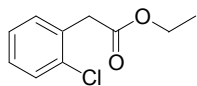
Ethyl 2-[2-(3,4,5-trimethoxyphenyl)ethyl]acrylate (4r)



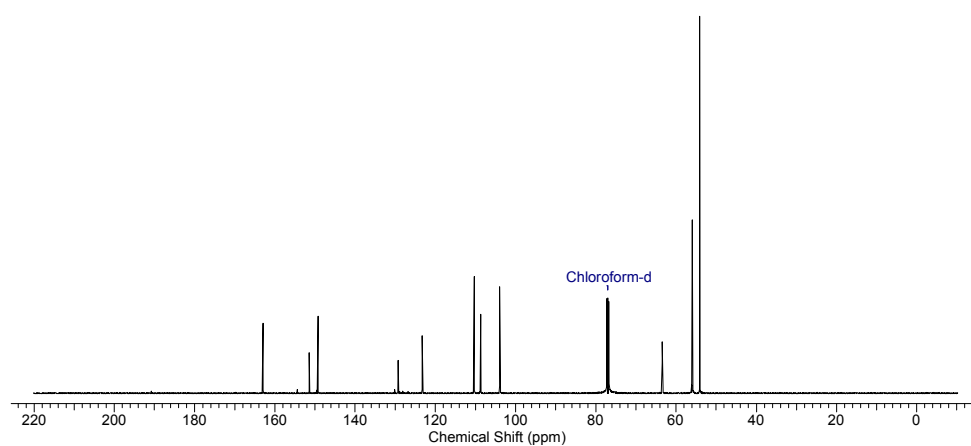
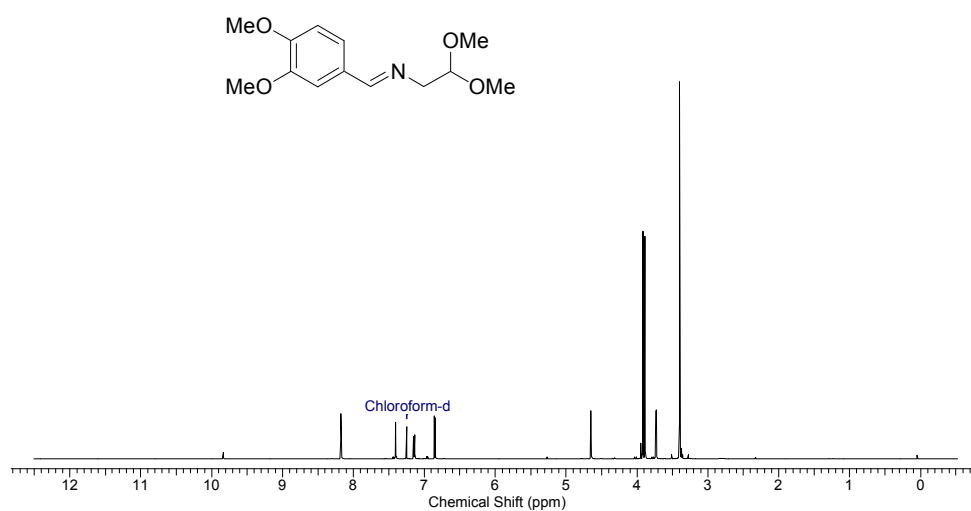
1-(6-Chloro-1,3-benzodioxol-5-yl)-4,4-dimethylpentan-2-one (4s)



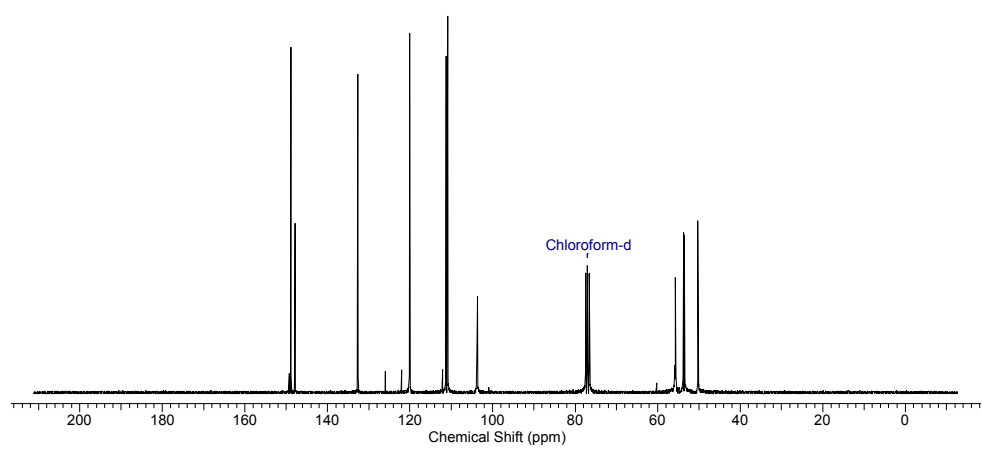
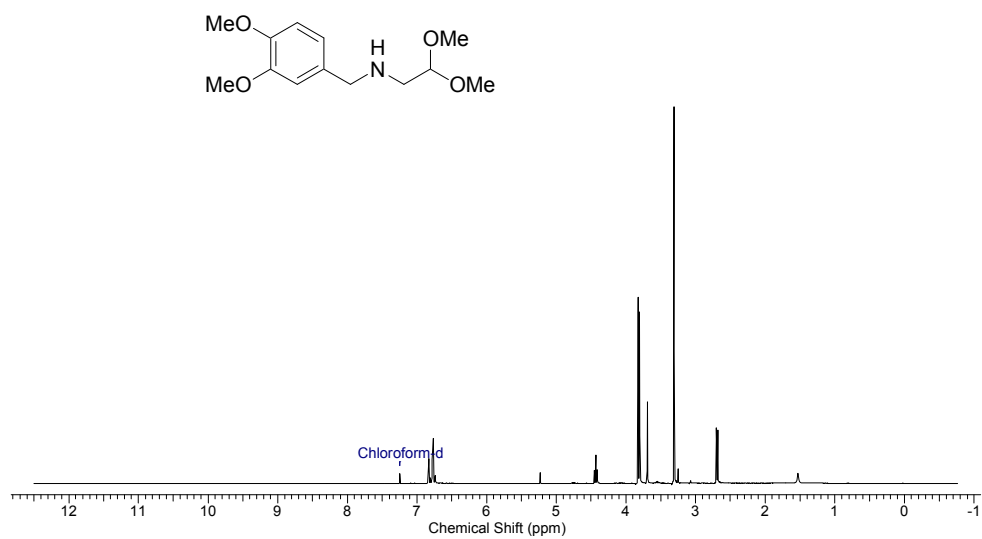
Ethyl (2-chlorophenyl)acetate (5)



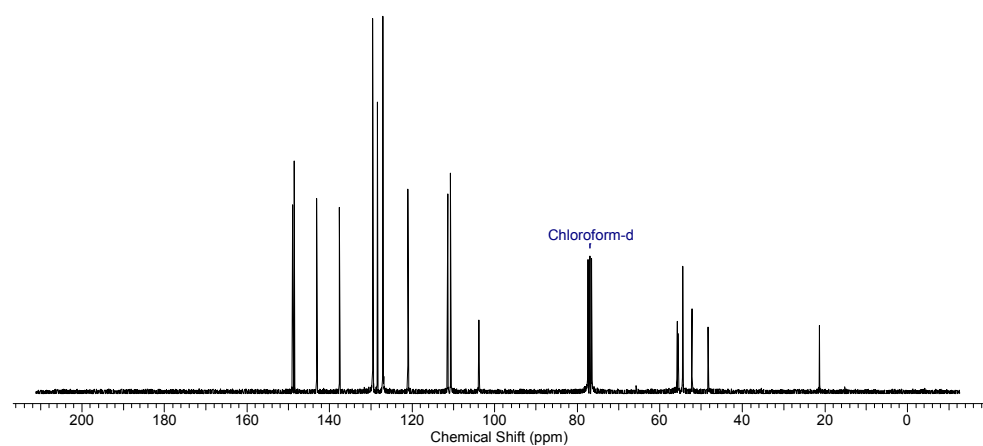
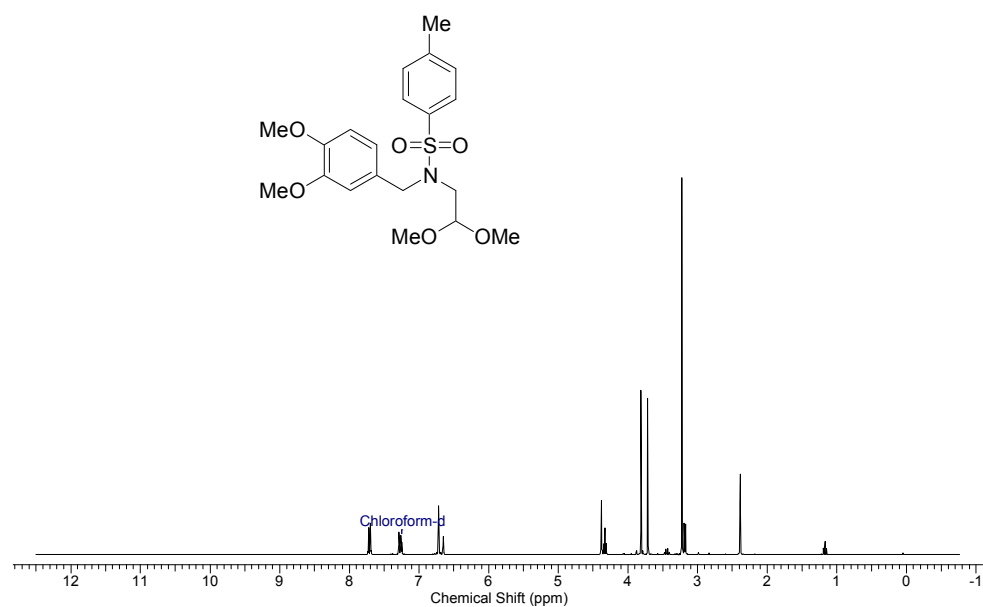
***N*-[(1*E*)-(3,4-dimethoxyphenyl)methylene]-2,2-dimethoxyethanamine (9)**



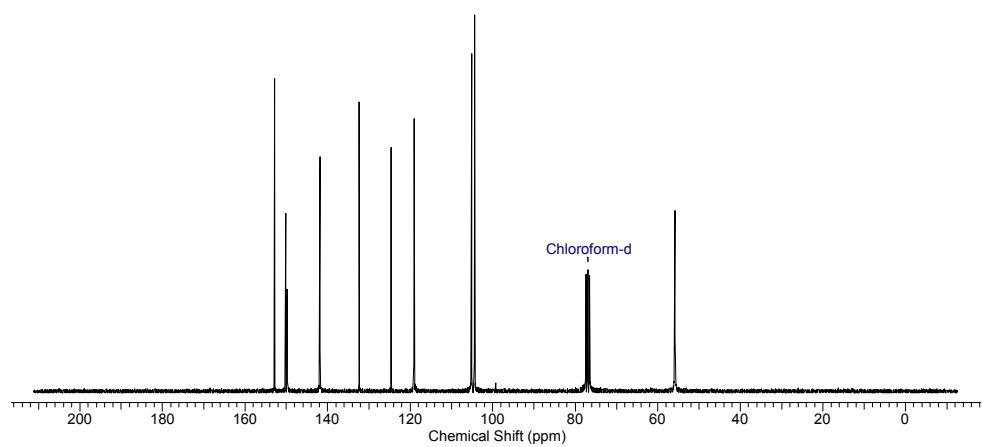
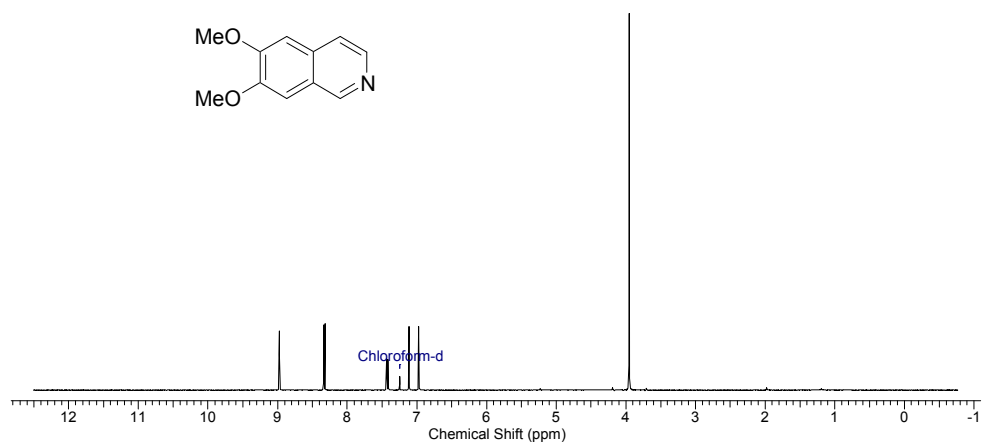
(3,4-Dimethoxybenzyl)(2,2-dimethoxyethyl)amine (10)



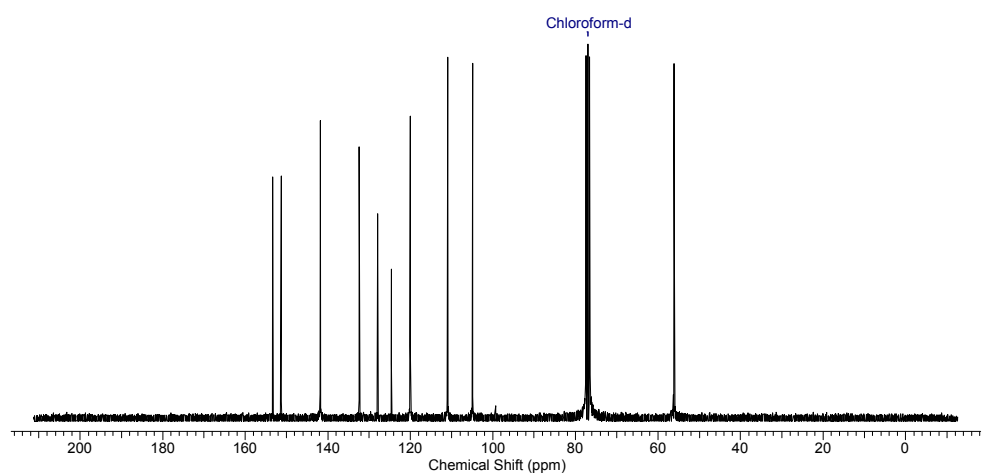
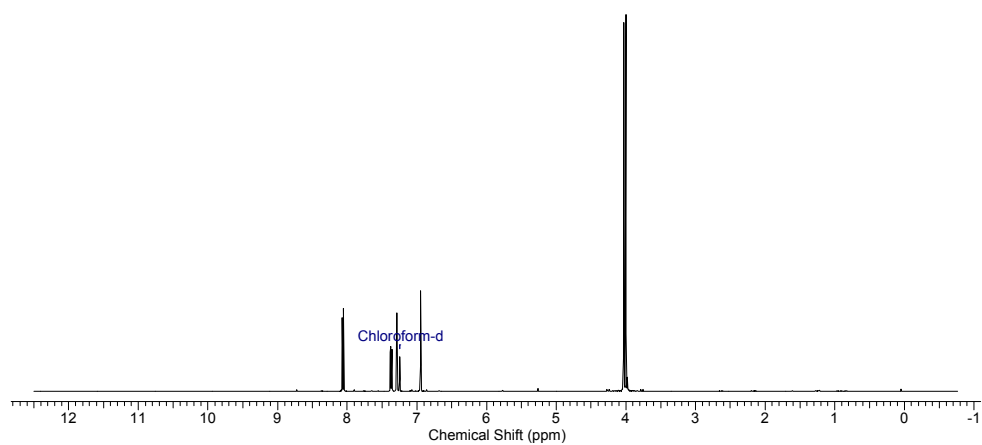
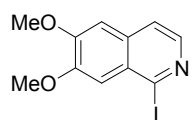
***N*-(3,4-dimethoxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (11)**



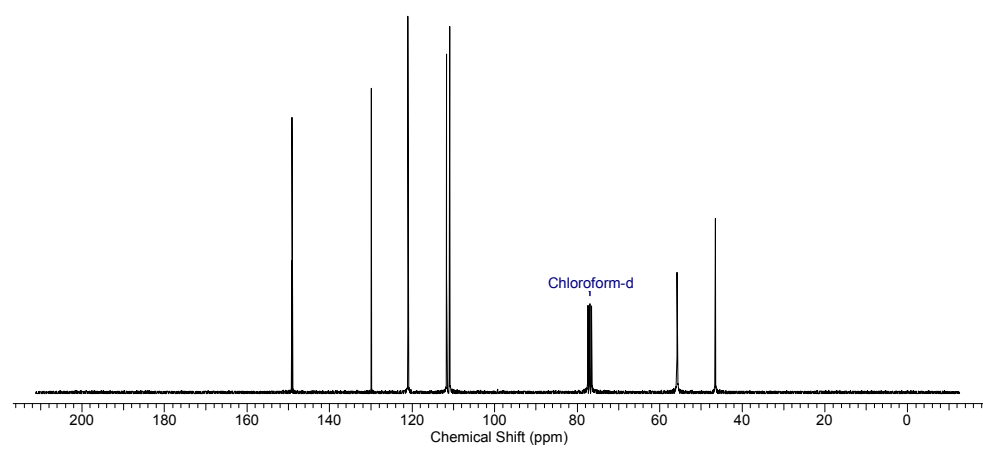
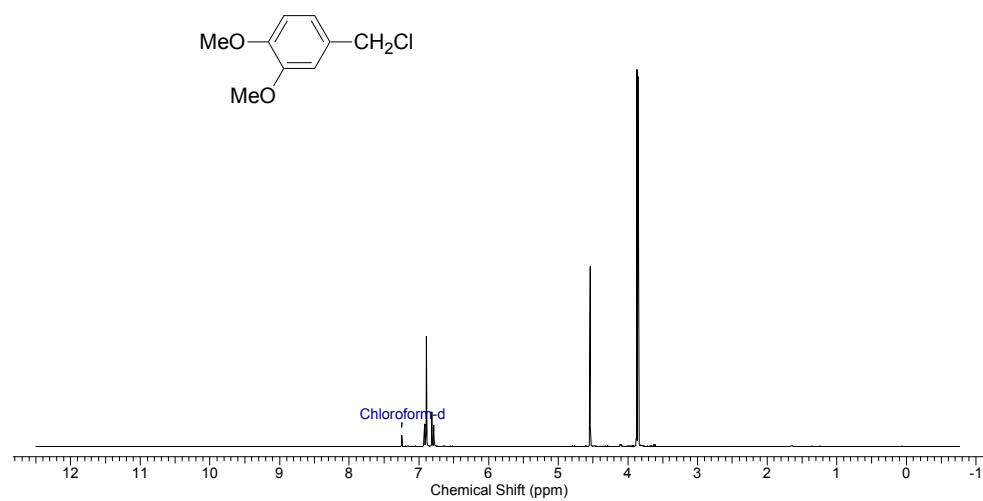
6,7-Dimethoxyisoquinoline (7)



1-Iodo-6,7-dimethoxyisoquinoline (8) 474



4-(Chloromethyl)-1,2-dimethoxybenzene (2m)



Papaverine (6)

