

Supplementary Materials

Green Solvents for Eco-Friendly Synthesis of Dimethindene: A Forward-Looking Approach

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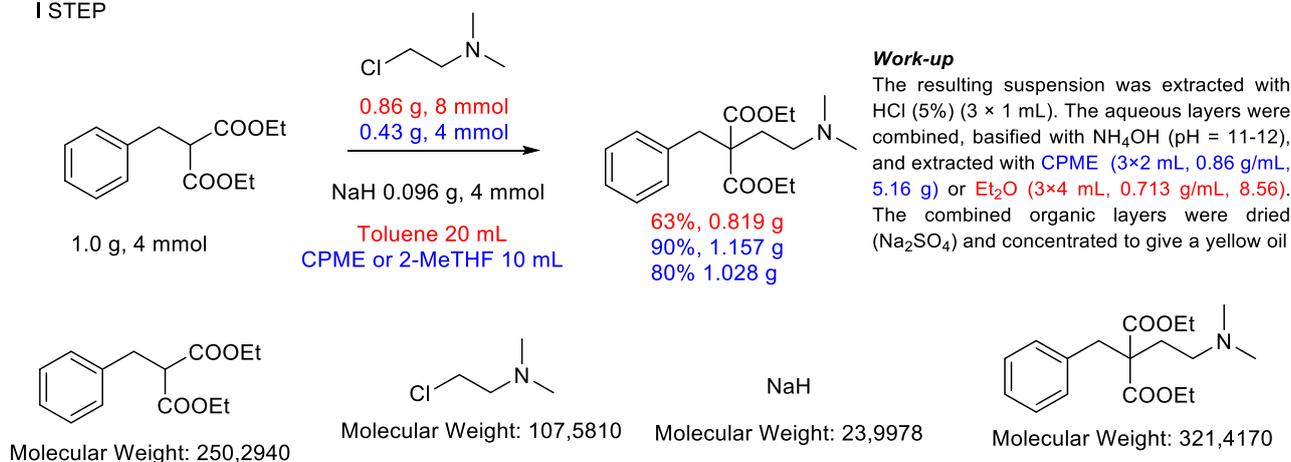
1. Typical metrics applied at Zero, First and Second Pass according to the CHEM21 Metrics Toolkit.¹

Metric	Acronym	Formula
Percentage yield	Y (%)	$\frac{\text{mol of product}}{\text{mol of limiting reactant}} \times 100$
Percentage conversion	Conv. (%)	$\frac{\text{final mass of limiting reactant (kg)}}{\text{initial mass of limiting reactant (kg)}} \times 100$
Percentage selectivity	Sel. (%)	$\frac{\% \text{ Yield}}{\% \text{ Conv.}} \times 100$
Reaction mass efficiency	RME	$\frac{\text{mass of product (kg)}}{\sum \text{mass reagents (kg)}} \times 100$
Atom economy	AE	$AE = \frac{\text{m. w product}}{\sum \text{m. w. reagents}} \times 100$
Effective mass yield	EM	$\frac{\text{mass of products (kg)}}{\text{mass of non benign reagents (kg)}} \times 100$
Optimum efficiency	OE	$\frac{\text{RME}}{\text{AE}} \times 100$
Mass intensity	MI	$\frac{\text{total mass used in a process step (kg)}}{\text{mass of product (kg)}}$
Process mass intensity	PMI	$\frac{\text{total mass in a process}}{\text{mass of product}}$
Renewables intensity	RI	$\frac{\text{mass of all renewably derivable materials used}}{\text{mass of product}}$
Renewables percentage	RP	$\frac{\text{RI}}{\text{PMI}} \times 100$
Detailed solvents	<i>Recommended, Problematic, Hazardous, Highly Hazardous</i>	
Energy	<ul style="list-style-type: none"> • 0–70 °C <i>Green Flag</i> • To 140 °C <i>Yellow Flag</i> • Reflux <i>Red Flag</i> 	
Workup	<ul style="list-style-type: none"> • <i>Green Flag</i>: quenching, filtration, centrifugation, crystallisation, • <i>Amber Flag</i>: solvent exchange, quenching into aqueous solvent. • <i>Red Flag</i>: chromatography, high temperature distillation 	

¹ C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton, J. H. Clark, *Green Chem.* **2015**, *17*, 3111.

2. Quantitative metrics of classical and eco-friendly approach for the synthesis of Dimethindene (6).

I STEP



Workup: Amber Flag (solvent exchange, quenching into aqueous solvent).

Detailed Solvent: Toluene and Et₂O: problematic and highly hazardous.

Detailed Solvent: CPME or 2-MeTHF: recommended

AE

M. W. reactants 250.3 + 107.6 + 24 = 381.9

AE = 321.4/381.9 % = 84.2%

RME

Classical Industrial Synthesis 0.819/1.956 % = 41.9%

Reaction in CPME 1.157/1.526 % = 75.8%

Reaction in 2-MeTHF 1.028/1.526 % = 67.4%

OE

Classical Industrial Synthesis 41.9/84.2 % = 49.8%

Reaction in CPME 75.8/84.2 % = 90.0%

Reaction in 2-MeTHF 67.4/84.2 % = 80.0%

EM

Classical Industrial Synthesis

Mass of non benign reagents 1.0 g + 0.86 g (2-chloro-*N,N*-dimethylethan-1-amine) + 0.096 (NaH) + 17.4 g (toluene) = 19.356

$$\text{EM} = 0.819/19.356 \% = 4.2\%$$

Reaction in CPME

Mass of non benign reagents 1.0 g + 0.43 g (2-chloro-*N,N*-dimethylethan-1-amine) + 0.096 (NaH) = 1.526 g

$$\text{EM} = 1.157/1.526 \% = 75.8\%$$

Reaction in 2-MeTHF

Mass of non benign reagents 1.0 g + 0.43 g (2-chloro-*N,N*-dimethylethan-1-amine) + 0.096 (NaH) = 1.526 g

$$\text{EM} = 1.028/1.526 \% = 67.4\%$$

MI

Classical Industrial Synthesis

Total amount of reactants: 1.0 g + 0.86 g + 0.096 g + 17.4 g (toluene) + [8.56 g (*Et*₂O) + 6.0 g (water)] = 19.36 g [33.92 g]

Amount of the final product: 0.819 g

$$\text{MI } 19.36/0.819 = 23.6$$

$$\text{MI}_{\text{WU}} 33.92/0.819 = 41.6$$

Reaction in CPME

Total amount of reactants: 1.0 g + 0.43 g + 0.096 g + 8.6 g (CPME) + [5.16 g (CPME) + 6.0 g (water)] = 10.13 g [21.29 g]

Amount of the final product: 1.157 g

$$\text{MI } 10.13/1.157 = 8.8$$

$$\text{MI}_{\text{WU}} 21.29/1.157 = 18.4$$

Reaction in 2-MeTHF

Total amount of reactants: 1.0 g + 0.43 g + 0.096 g + 8.6 g (2-MeTHF) + [5.16 g (2-MeTHF) + 6.0 g (water)] = 10.13 g [21.29 g]

Amount of the final product: 1.028 g

$$\text{MI } 10.13/1.028 = 9.9$$

$$\text{MI } 21.29/1.028 = 20.7$$

Ri and RP

Reaction in toluene

Renewable sources: 6.0 g (water)

$$\text{RI: } 6.0/0.819 = 7.3 \quad \text{RP: } 7.3/41.6 \% = 17.5\%$$

Reaction in CPME

Renewable sources: 6.0 g (water) + 13.76 g (CPME) = 19.76 g

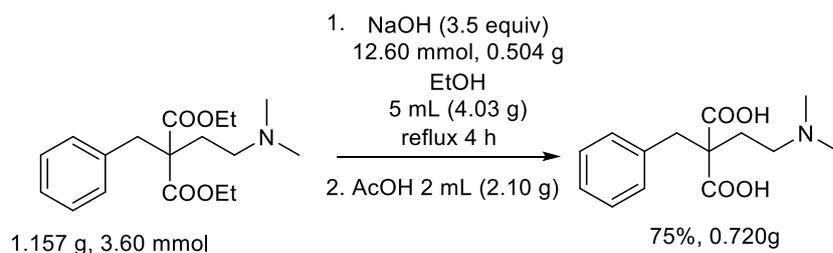
RI: 19.76 / 1.157 = **17.1** **RP:** 17.1 / 18.4 % = **92.9%**

Reaction in 2-MeTHF

Renewable sources: 6.0 g (water) + 13.76 (2-MeTHF) = 19.76 g

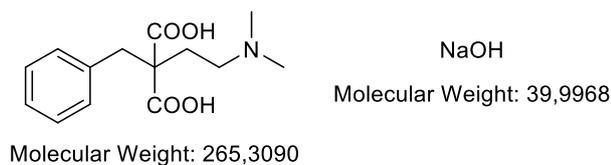
RI: 19.76 / 1.028 = **19.2** **RP:** 19.2 / 20.7 % = **92.8%**

II STEP



Work-up

The solid product was filtered, washed with cold water (2×3 mL) and ethanol (5 mL), and dried in a vacuum oven at 50 °C to give a white-yellow solid



Workup: Green Flag (filtration).

Detailed Solvent: EtOH, water: recommended

AE

M. W. reactants 321.4 + 40 = 361.4

AE = 265.3/361.4 % = 73.4%

RME

0.72/1.66 % = 43.4%

OE

43.44/73.4 % = 59.1 %

EM

0.72 g/ (1.16 g + 0.504 g + 2.10 g = 3.76) % = 19.1%

MI

Total amount of reactants: 1.16 g + 0.504 g + 4.03 g + 2.10 g + [4.03 g (EtOH) + 6.0 g (water)] = 7.79 g [17.82 g]

Amount of the final product: 0.72 g

$$MI = 7.79 / 0.72 = 10.82$$

$$MI_{WU} = 17.82 / 0.72 \text{ g} = 24.75$$

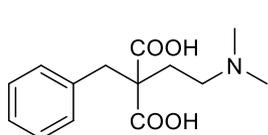
RI and RP II STEP

Renewable sources: 8.06 g (EtOH) + 2.1 g (AcOH) + 6.0 g (water) = 16.16 g

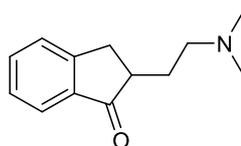
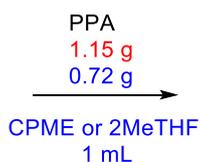
$$RI: 16.16 / 0.72 = 22.4$$

$$RP: 22.4 / 24.75 \% = 90.6\%$$

III STEP



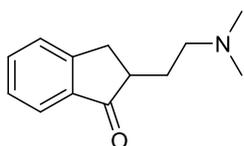
0.72 g, 2.71 mmol



VOCs: 20%, 0.11 g
CPME: 50%, 0.28 g
2-MeTHF: 55%, 0.303 g

Work-up

The reaction was quenched with cold water (1 mL) and basified with K_2CO_3 (2 M). The mixture was extracted with CPME (3×1 mL, 2.58 g), or Et_2O (3×2 mL, 4.28 g) washed with water (5 mL), dried (Na_2SO_4), and evaporated to give a yellow oil in yield



Molecular Weight: 203,2850

Workup: Amber Flag (solvent exchange, quenching into aqueous solvent).

Detailed Solvent: CPME or 2-MeTHF: recommended

AE

$$203.3 / (265.3 + 100) \% = 55.7\%$$

RME

Classical Industrial Synthesis

Amount of the final product: 0.11 g

Total amount of reactants: $0.72 \text{ g} + 1.15 \text{ g} = 1.87 \text{ g}$

RME: $0.11/1.87 \% = 5.9\%$

Reaction in CPME

Amount of the final product: 0.28 g

Total amount of reactants: $0.72 \text{ g} + 0.72 \text{ g} = 1.44 \text{ g}$

RME = $0.28/1.44 \% = 19.4\%$

Reaction in 2-MeTHF

Amount of the final product: 0.303 g

Total amount of reactants: $0.72 \text{ g} + 0.72 \text{ g} = 1.44 \text{ g}$

RME = $0.303/1.44 \% = 21.0\%$

OE

Classical Industrial Synthesis $9.6/55.7 \% = 17.2\%$

Reaction in CPME $19.4/55.7 \% = 34.8\%$

Reaction in 2-MeTHF $21.0/55.7 \% = 37.7\%$

EM

Classical Industrial Synthesis

Amount of the final product: 0.11 g

Total mass of non benign reagents: $0.72 \text{ g} + 1.15 \text{ g} + 4.28 \text{ g (Et}_2\text{O)} = 6.15 \text{ g}$

EM = $0.11 / 6.15 \% = 1.8\%$

Reaction in CPME

Amount of the final product: 0.28 g

Total mass of non benign reagents: $0.72 \text{ g} + 0.72 \text{ g} = 1.44 \text{ g}$

EM: $0.28/1.44 = 19.4\%$

Reaction in 2-MeTHF

Amount of the final product: 0.303 g

Total mass of non benign reagents: $0.72 \text{ g} + 0.72 \text{ g} = 1.44 \text{ g}$

EM: $0.303/1.44 = 21.0\%$

MI

Classical Industrial Synthesis

Total amount of reactants: $0.72 \text{ g} + 1.15 \text{ g} + [4.28 \text{ g (Et}_2\text{O)} + 6 \text{ g (water)}] = 1.87 \text{ g [12.15 g]}$

Amount of the final product: 0.11 g

MI: $1.87/0.11 = 17.0$

MI_{WU}: $12.15/0.11 = 110.4$

Reaction in CPME

Total amount of reactants: $0.72 \text{ g} + 0.72 \text{ g} + 0.86 \text{ g (CPME)} + [2.58 \text{ g (CPME)} + 6 \text{ g (water)}] = 2.30 \text{ g [10.88 g]}$

Amount of the final product: 0.28 g

MI: $2.3/0.28 = 8.2$

MI_{WU}: $10.88/0.28 = 38.8$

Reaction in 2-MeTHF

Total amount of reactants: $0.72 \text{ g} + 0.72 \text{ g} + 0.86 \text{ g (2-MeTHF)} + [2.58 \text{ g (2-MeTHF)} + 6 \text{ g (water)}] = 2.30 \text{ g [10.88 g]}$

Amount of the final product: 0.303 g

MI: $2.3/0.303 = 7.6$

MI_{WU}: $10.88/0.303 = 35.9$

RI and RP

Reaction in toluene Renewable sources: 6.0 g (water)

RI: $6.0/0.11 = 54.5$ **RP:** $54.5/110.4\% = 49.4\%$

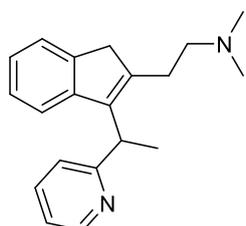
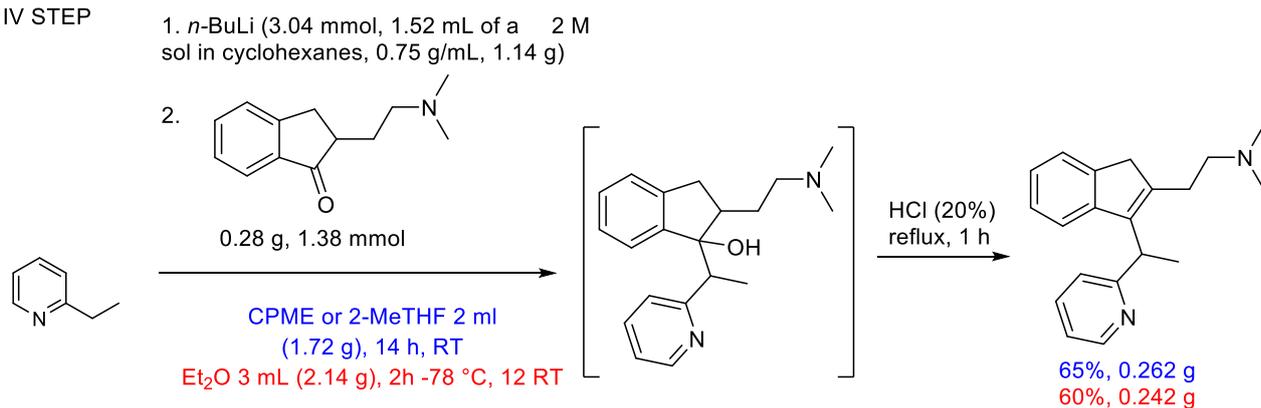
Reaction in CPME Renewable sources: $6.0 \text{ g (water)} + 3.44 \text{ g (CPME)} = 9.44 \text{ g}$

RI: $9.44/0.28 = 33.7$ **RP:** $33.7/38.8\% = 86.9\%$

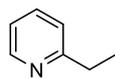
Reaction in 2-MeTHF Renewable sources: $6.0 \text{ g (water)} + 3.44 \text{ g (2-MeTHF)} = 9.44 \text{ g}$

RI: $9.44/0.303 = 31.2$ **RP:** $31.2/35.9\% = 87.0\%$

IV STEP



Molecular Weight: 292,4260



Molecular Weight: 107,1560

Work-up

The reaction was quenched with cold water, washed with saturated NaHCO₃ (2x2 mL) and extracted with HCl (20%) (2x2 mL). The water layer was refluxed for 1 h, cooled to RT, basified with NH₄OH sol. and extracted with CPME (3x1 mL) or Et₂O (3x1 mL). The organic phase was dried over anhydrous Na₂SO₄. Evaporation of the solvent under reduced pressure afforded the crude that was purified by flash-chromatography on silica gel

Workup: Amber Flag (solvent exchange, quenching into aqueous solvent) / Red Flag (chromatography).

Detailed Solvent: Et₂O: problematic.

Detailed Solvent: CPME or 2-MeTHF: recommended

Energy: Red Flag, -78 °C

Energy: Green Flag, 0 °C

AE

$$292.4 / (203.3 + 107.2 + 64.1) \% = 78.1\%$$

RME

Classical Industrial Synthesis

Amount of the final product: 0.242 g

Total amount of reactants: 0.326 g + 1.14 g + 0.28 g = 1.75 g

RME: 0.242/1.75 % = 13.8 %

Reaction in CPME

Amount of the final product: 0.26 g

Total amount of reactants: $0.326 \text{ g} + 1.14 \text{ g} + 0.28 \text{ g} = 1.75 \text{ g}$

RME = $0.262/1.75 \text{ \%} = 15.0\%$

Reaction in 2-MeTHF

Amount of the final product: 0.262 g

Total amount of reactants: $0.326 \text{ g} + 1.14 \text{ g} + 0.28 \text{ g} = 1.75 \text{ g}$

RME = $0.262/1.75 \text{ \%} = 15.0\%$

OE

Classical Industrial Synthesis $13.8/78.1 \text{ \%} = 17.7 \text{ \%}$

Reaction in CPME $15/78.1 \text{ \%} = 19.2 \text{ \%}$

Reaction in 2-MeTHF $15/78.1 \text{ \%} = 19.2 \text{ \%}$

EM

Classical Industrial Synthesis

Amount of the final product: 0.24 g

Total mass of non benign reagents: $0.326 \text{ g} + 1.14 \text{ g} + 0.28 \text{ g} + 2.14 \text{ g (Et}_2\text{O)} + 2.14 \text{ g (Et}_2\text{O)} = 6.03 \text{ g}$

EM = $0.24 / 6.03 \text{ \%} = 4.0 \text{ \%}$

Reaction in CPME

Amount of the final product: 0.26 g

Total mass of non benign reagents: $0.326 \text{ g} + 1.14 \text{ g} + 0.28 \text{ g} = 1.75 \text{ g}$

EM: $0.26/1.75 = 14.9 \text{ \%}$

Reaction in 2-MeTHF

Amount of the final product: 0.26 g

Total mass of non benign reagents: $0.326 \text{ g} + 1.14 \text{ g} + 0.28 \text{ g} = 1.75 \text{ g}$

EM: $0.26/1.75 = 14.9 \text{ \%}$

MI

Classical Industrial Synthesis

Total amount of reactants: $0.326 \text{ g} + 1.14 \text{ g} + 0.28 \text{ g} + 2.14 \text{ g (Et}_2\text{O)} + [2.14 \text{ g (Et}_2\text{O)} + 8.0 \text{ g (water)}] = 3.89 \text{ g}$
[14.03 g]

Amount of the final product: 0.24 g

MI: $3.89/0.24 = 16.2$

$$MI_{WU} = 14.03/0.24 = 58.5$$

Reaction in CPME

Total amount of reactants: 0.326 g + 1.14 g + 0.28 g + 1.72 g (CPME) + [2.58 g (CPME) + 8.0 g (water)] = 3.46 g [14.04 g]

Amount of the final product: 0.26 g

$$MI: 3.46/0.26 = 13.3$$

$$MI_{WU} = 14.04/0.26 = 54.0$$

Reaction in 2-MeTHF

Total amount of reactants: 0.326 g + 1.14 g + 0.28 g + 1.72 g (2-MeTHF) + [2.58 g (2-MeTHF) + 8.0 g (water)] = 3.46 g [14.04 g]

Amount of the final product: 0.26 g

$$MI: 3.46/0.26 = 13.3$$

$$MI_{WU} = 14.04/0.26 = 54.0$$

RI and RP IV STEP

Reaction in toluene Renewable sources: 8.0 g (water)

$$RI: 8.0/0.242 = 33.1 \quad RP: 33.1/58.5\% = 56.6\%$$

Reaction in CPME Renewable sources: 8.0 g (water) + 4.30 (CPME) = 12.30 g

$$RI: 12.3/0.262 = 46.9 \quad RP: 46.9/54.0\% = 86.9\%$$

Reaction in 2-MeTHF Renewable sources: 8.0 g (water) + 4.30 (2-MeTHF) = 12.30 g

$$RI: 12.3/0.262 = 46.9 \quad RP: 46.9/54.0\% = 86.9\%$$

Process for Dimethindene Synthesis

$$AE 292.4/[(250.3 + 107.6 + 24.0) + 40.0 + 100 + (107.2 + 64.1)]\% = 42.2\%$$

RME

Classical Industrial Synthesis 0.242/ (1.956 + 1.66 + 1.87 + 1.75 = 7.236) % = 3.3 %

Reaction in CPME 0.262/ (1.526 + 1.66 + 1.44 + 1.75 = 6.376) % = 4.1 %

Reaction in 2-MeTHF 0.246/ (1.526 + 1.66 + 1.44 + 1.75) % = 3.9 %

OE

Classical Industrial Synthesis $3.3/42.2 \% = 7.8 \%$

Reaction in CPME $4.1/42.2 \% = 9.3 \%$

Reaction in 2-MeTHF $3.9/42.2 \% = 8.8 \%$

PMI

Classical Industrial Synthesis

Total amount of reactants: $19.4 + 7.79 + 1.87 + 3.89 = 32.95$

Amount of the final product: 0.242 g

PMI $32.95/0.242 = 136.2$

Reaction in CPME

Total amount of reactants: $10.13 + 7.79 + 2.3 + 3.46 = 23.68$

Amount of the final product: 0.262 g

PMI $23.68/0.262 = 90.4$

Reaction in 2-MeTHF

Total amount of reactants: $10.13 + 7.79 + 2.3 + 3.46 = 23.68$

Amount of the final product: 0.252 g

PMI $23.68/0.252 = 94.0$

PMI_{wu}

Classical Industrial Synthesis

Total amount of reactants: $33.92 + 17.82 + 12.15 + 14.03 = 77.92$

Amount of the final product: 0.242 g

PMI $77.92/0.242 = 322.0$

Reaction in CPME

Total amount of reactants: $21.39 + 17.82 + 10.88 + 14.04 = 64.03$

Amount of the final product: 0.262 g

PMI $64.03/0.262 = 244.4$

Reaction in 2-MeTHF

Total amount of reactants: $21.39 + 17.82 + 10.88 + 14.04 = 64.03$

Amount of the final product: 0.252 g

PMI $64.03/0.252 = 254.1$

EM

Classical Industrial Synthesis

Total mass of non benign reagents: $19.36 \text{ g} + 3.76 \text{ g} + 6.15 \text{ g} + 6.03 \text{ g} = 35.30 \text{ g}$

Amount of the final product: 0.242 g

EM $0.242/35.30 \% = 0.7\%$

Reaction in CPME

Total mass of non benign reagents: $1.526 \text{ g} + 3.76 \text{ g} + 1.44 \text{ g} + 1.75 \text{ g} = 8.32$

Amount of the final product: 0.262 g

EM $0.262/8.32 \% = 3.1\%$

Reaction in 2-MeTHF

Total mass of non benign reagents: $1.526 \text{ g} + 3.76 \text{ g} + 1.44 \text{ g} + 1.75 \text{ g} = 8.32$

Amount of the final product: 0.246 g

EM $0.246/8.32 \% = 3.0\%$

RI and RP

Classical Industrial Synthesis

RI: $(6.0 + 16.16 + 6.0 + 8.0) \text{ g} / 0.242 \text{ g} = 149.4$

RP $149.4/322.0 = 46.4\%$

Reaction in 2-MeTHF

RI $(19.76 + 16.16 + 9.44 + 12.3)/0.252 = 228.8$

RP $228.8 / 254.1 \% = 90.0\%$

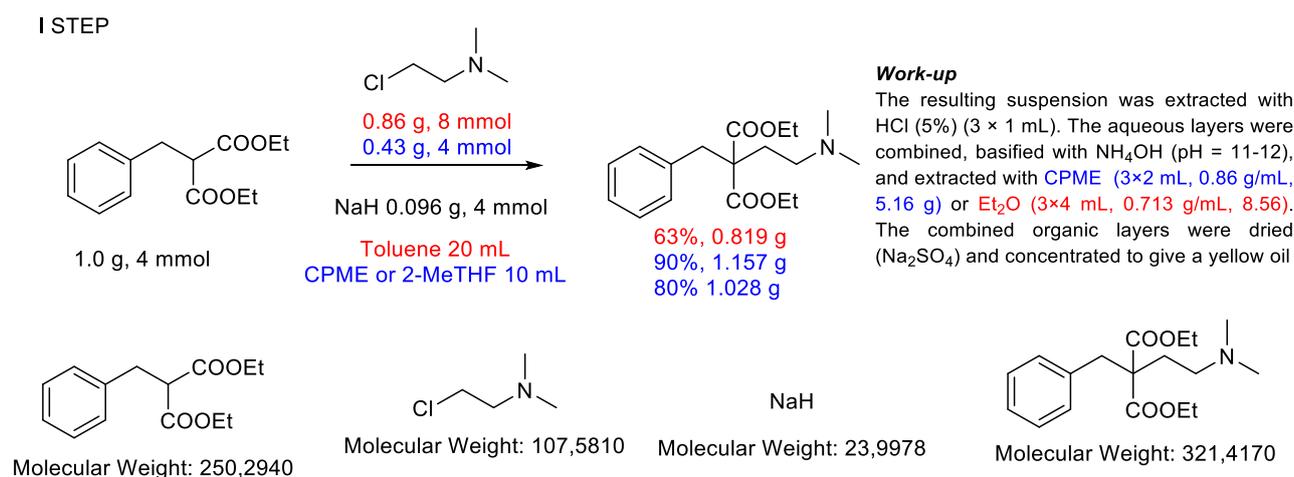
Reaction in CPME

RI $(19.76 + 16.16 + 9.44 + 12.3)/0.262 = 220.1$

RP $220.1 / 244.4 \% = 90.1\%$

3. E-factor calculation for the synthesis of Dimethindene (6).

According to its original definition (*Green Chem.* **2007**, *9*, 1273), the Sheldon E-factor value (total mass of waste/mass of product) takes into account only the mass of waste generated in a process, and its calculation is performed by simply dividing the sum of the molecular weight of all substances produced by molecular weight of the desired products, with reference to the stoichiometric equation. We have followed this general equation in our own calculation.



Reaction in toluene

Total amount of reactants: 1.0 g + 0.86 g + 0.096 g + 17.4 g (toluene) + 8.56 g (Et₂O) = 27.92 g

Amount of the final product: 0.819 g

Amount of waste: 27.92 g – 0.819 g = 27.10 g

E-factor = amount of waste/amount of product = 27.10/0.819 g = **33.1**

Reaction in CPME

Total amount of reactants: 1.0 g + 0.43 g + 0.096 g + 8.6 g (CPME) + 5.16 g (CPME) = 15.29 g

Amount of the final product: 1.157 g

Amount of waste: 15.29 g – 1.157 g = 14.133 g

E-factor = amount of waste/amount of product = 14.13/1.157 g = **12.2**

Reaction in 2-MeTHF

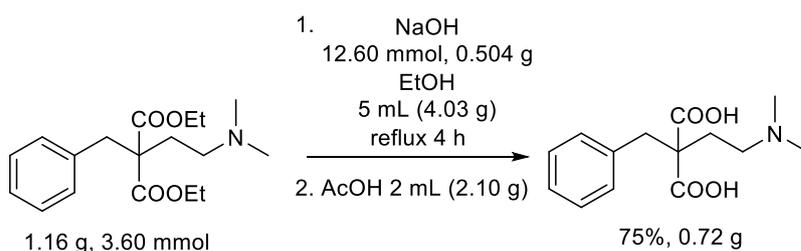
Total amount of reactants: 1.0g + 0.43g + 0.096g + 8.6 g (2-MeTHF) + 5.16 g (2-MeTHF) = 15.29 g

Amount of the final product: 1.028 g

Amount of waste: 15.29 g – 1.028 g = 14.262 g

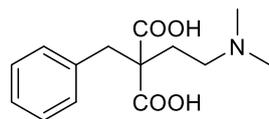
E-factor = amount of waste/amount of product = 14.262/1.028 g = **13.8**

II STEP



Work-up

The solid product was filtered, washed with cold water (2×3 mL) and ethanol (5 mL), and dried in a vacuum oven at 50 °C to give a white-yellow solid



Molecular Weight: 265,3090

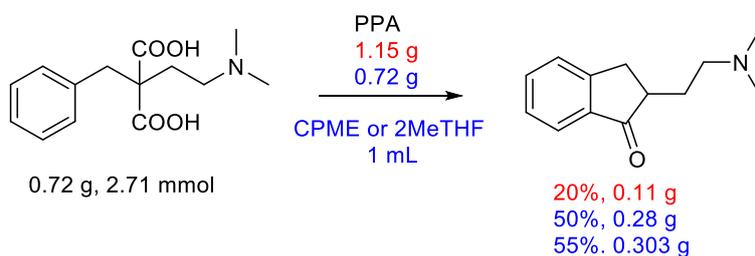
Total amount of reactants: 1.16 g + 0.504 g + 4.03 g + 2.10 g = 7.79 g

Amount of the final product: 0.72 g

Amount of waste: 7.79 g – 0.72 g = 7.07 g

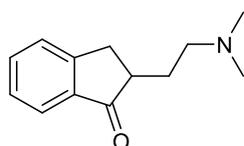
E-factor = amount of waste/amount of product = 7.07/0.72 g = **9.8**

III STEP



Work-up

The reaction was quenched with cold water (1 mL) and basified with K₂CO₃ (2 M). The mixture was extracted with CPME (3×1 mL, 2.58 g), or Et₂O (3×2 mL, 4.28 g) washed with water (5 mL), dried (Na₂SO₄), and evaporated to give a yellow oil in yield



Molecular Weight: 203,2850

Classical Industrial Synthesis

Total amount of reactants: 0.72 g + 1.15 g + 4.28 g (Et₂O) = 6.15 g

Amount of the final product: 0.11 g

Amount of waste: 6.15 g – 0.11 g = 6.04 g

E-factor = amount of waste/amount of product = 6.04/0.11 g = **54.9**

Reaction in CPME

Total amount of reactants: 0.72 g + 0.72 g + 0.86 g (CPME) + 2.58 g (CPME) = 4.88 g

Amount of the final product: 0.28 g

Amount of waste: $4.88 \text{ g} - 0.28 \text{ g} = 4.60 \text{ g}$

E-factor = amount of waste/amount of product = $4.60/0.28 \text{ g} = 16.4$

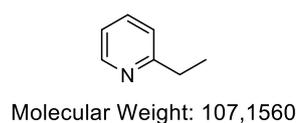
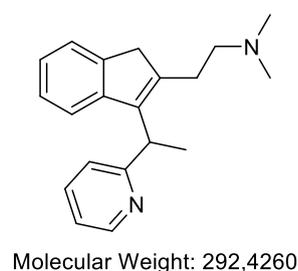
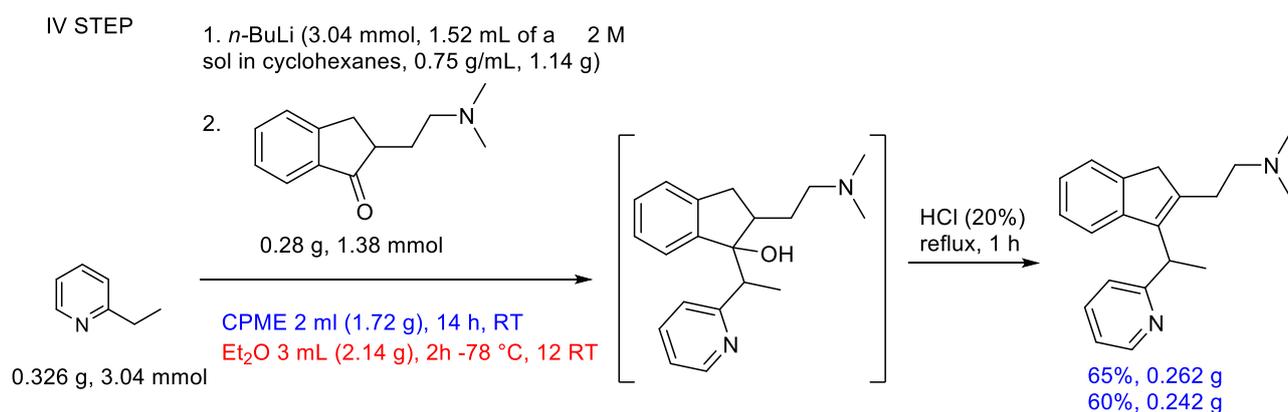
Reaction in 2-MeTHF

Total amount of reactants: $0.72 \text{ g} + 0.72 \text{ g} + 0.86 \text{ g (2-MeTHF)} + 2.58 \text{ g (2-MeTHF)} = 4.88 \text{ g}$

Amount of the final product: (55%) 0.303 g

Amount of waste: $4.88 \text{ g} - 0.303 \text{ g} = 4.577 \text{ g}$

E-factor = amount of waste/amount of product = $4.577/0.303 \text{ g} = 15.1$



Work-up

The reaction was quenched with cold water (2 mL), washed with saturated NaHCO₃ (2x2 mL) and extracted with HCl (20%) (2x2 mL). The water layer was refluxed for 1 h, cooled to RT, basified with NH₄OH sol. and extracted with CPME (3x1 mL) or Et₂O (3x1 mL). The organic phase was dried over anhydrous Na₂SO₄. Evaporation of the solvent under reduced pressure afforded the crude that was purified by flash-chromatography on silica gel

Classical Industrial Synthesis

Total amount of reactants: $0.326 \text{ g} + 1.14 \text{ g} + 0.28 \text{ g} + 2.14 \text{ g (Et}_2\text{O)} + 2.14 \text{ g (Et}_2\text{O)} = 6.03 \text{ g}$

Amount of the final product: 0.24 g

Amount of waste: $6.03 \text{ g} - 0.24 \text{ g} = 5.79 \text{ g}$

E-factor = amount of waste/amount of product = $5.79/0.24 \text{ g} = 24.1$

Reaction in CPME

Total amount of reactants: $0.326 \text{ g} + 1.14 \text{ g} + 0.28 \text{ g} + 1.72 \text{ g (CPME)} + 2.58 \text{ g (CPME)} = 6.04 \text{ g}$

Amount of the final product: 0.26 g

Amount of waste: $6.04 \text{ g} - 0.26 \text{ g} = 5.78 \text{ g}$

E-factor = amount of waste/amount of product = 5.78/0.26 g = **22.1**

Reaction in 2-MeTHF

Total amount of reactants: 0.326 g + 1.14 g + 0.28g + 1.72g (2-MeTHF) + 2.58g (2-MeTHF) = 6.04 g

Amount of the final product: 0.26 g

Amount of waste: 6.04 g – 0.26 g = 5.78 g

E-factor = amount of waste/amount of product = 5.78/0.26 g = **22.1**

E factor for the whole process

Classical Industrial Synthesis

Total amount of reactants: 1.0 g + 0.86 g + 0.096 g + 17.4 g (toluene) + 8.56 g (Et₂O) + 0.504 g + 4.03 g + 2.10 g + 1.15 g + 4.28 g (Et₂O) + 0.326 g + 1.14 g + 2.14 g (Et₂O) + 2.14 g (Et₂O) = 45.73

Amount of the final product: 0.24 g

Amount of waste: 45.73 g – 0.24 g = 45.49 g

E-factor = amount of waste/amount of product = 45.49/0.242 g = **188.0**

Reaction in CPME

Total amount of reactants: 1.0 g + 0.43 g + 0.096 g + 8.6 g (CPME) + 5.16 g (CPME) + 0.504 g + 4.03 g + 2.10 g + 0.72 g + 0.86 g (CPME) + 2.58 g (CPME) 0.326 g + 1.14 g + 0.28 + 4.30 (CPME) = 32.13 g

Amount of the final product: 0.26 g

Amount of waste: 32.13 g – 0.26 g = 31.87 g

E-factor = amount of waste/amount of product = 31.87/0.262 g = **121.6**

Reaction in 2-MeTHF

Total amount of reactants: 1.0 g + 0.43 g + 0.096 g + 8.6 g (2-MeTHF) + 5.16 g (2-MeTHF) + 0.504 g + 4.03 g + 2.10 g + 0.72 g + 0.86 g (2-MeTHF) + 2.58 g (2-MeTHF) 0.326 g + 1.14 g + 0.28 + 4.30 (2-MeTHF) = 32.13 g

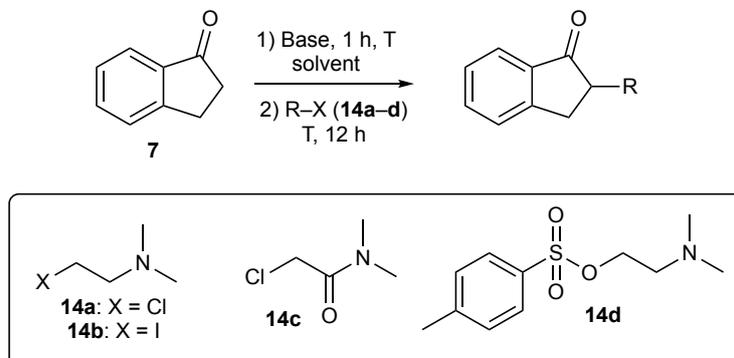
Amount of the final product: 0.25 g

Amount of waste: 32.13 g – 0.252 g = 31.88 g

E-factor = amount of waste/amount of product = 31.88/0.252 g = **126.5**

4. Experimental Procedures. α -Functionalization of indanone.

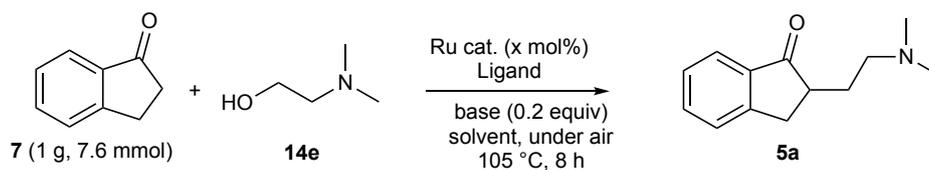
4.1. Table S1. Treatment of 1-indanone (**7**) with different bases and reaction with electrophiles (Scheme 3, a–c, main text).



Entry	RX (equiv)	Solvent	Base (equiv)	T (1) °C	T (2) °C	NMR yield%
1	14a (1)	THF	LDA (2)	-78	-78	NR ^[a]
2	14b (1)	THF	LDA (2)	-78	-78	NR
3	14a (1)	THF	LDA (2)	-78	RT	NR
4	14a (1)	THF	KHMDS (2)	-78	RT	NR
5	14c (1)	THF	LDA (2)	-78	-78	30 ^[b]
6	14c (2)	THF	LDA (2)	-78	0	20
7	14a (1.2)	toluene	NaHMDS (2)	-20	0	NR ^[a]
8	14c (2)	CPME	LDA (2)	0	0	20
9	14c (1.2)	CPME	LDA (2)	0	0	20
10	14c (1)	CPME	LDA (2)	0	0	30
11	14c (1)	ChCl/Gly ^[c]	LDA (2)	RT	RT	NR
12	14c (1)	ChCl/urea ^[c]	LDA (2)	RT	RT	NR
13	14c (1)	CPME- ChCl/urea ^[d]	LDA (2)	0	RT	NR
14	14c (1)	CPME	NaH (1)	RT	RT	20 ^[e]
15	14d (1.2)	toluene	NaH (1.5)	-20	0	NR
16	14d (1.2)	THF	NaH (2)	-78	RT	NR
17	14d (1.2)	THF	LDA (2)	0	0	NR
18	14d (1.2)	CPME	NaH (1.5)	0	0	NR

Reaction conditions: to a solution of 1-indanone (**7**) (1 mmol) in the proper solvent, the base was added under an Argon atmosphere at T (1). After stirring at T (1) for 1 h, the electrophile was added, and after 12 h stirring at T (2), the reaction was quenched with water. [a] Quenching with MeI: 80% yield. [b] Yield of isolated compound after column chromatography on silica gel. [c] Choline chloride (ChCl)/ glycerol (Gly) (1:2 mol mol⁻¹); ChCl /urea (1:2 mol mol⁻¹). [d] The solution of indanone **7** and LDA in CPME was added to a solution of amide **14c** in DES. [e] The product of bis-addition also formed. RT = room temperature, 25 °C. ¹H NMR yield calculated using dibromomethane as an internal standard. NR = no reaction.

4.2. Table S2. Ru-catalyzed hydrogen-borrowing C–C bond formation: reaction between 1-indanone (**7**) and 2-(dimethylamino)ethan-1-ol (**14e**) (Scheme 3,d, main text).

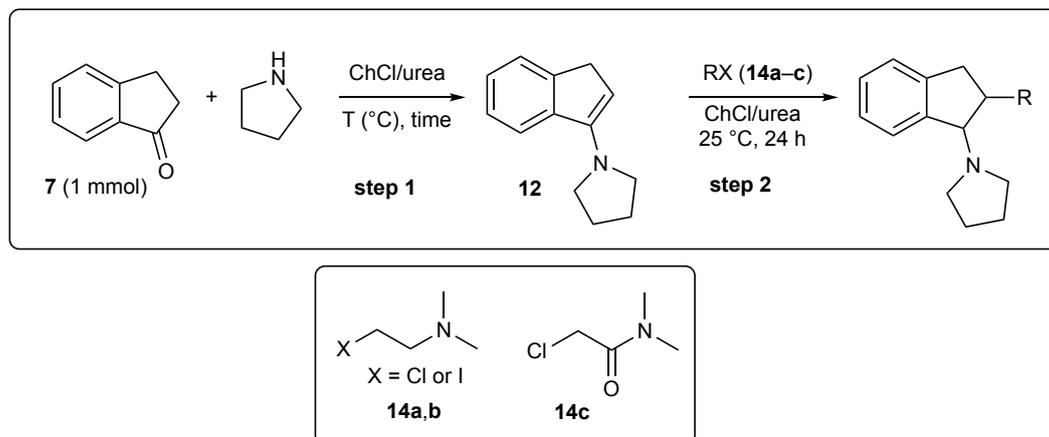


Ru cat.: dichloro(*p*-cymene)ruthenium (II) dimer
Ligand: (oxydi-2,1-phenylene)bis(diphenylphosphine)

Entry	14e (equiv)	Ru cat. mol%	Solvent	Base	Yield % (5a)
1	2	0.5	toluene	NaOH	NR
2	2	0.5	toluene	CsCO ₃	NR
3	7	0.5	toluene	CsCO ₃	NR
4	14	0.5	— ^[a]	CsCO ₃	NR
5	14	5	— ^[a]	CsCO ₃	NR

Reaction conditions: to a solution of **7** (7.6 mmol) and **14e** in toluene (entries 1–3), the catalyst, the ligand and the base were added under air, and the reaction mixture was heated to 105 °C. After 8 h stirring at this temperature, the mixture was cooled to 25 °C. Then, after the addition of diisopropyl ether (5 mL), the mixture was filtered on silica gel. [a] Neat conditions. NR = no reaction.

4.3 Table S3. α -Functionalization of 1-indanone (**7**) via enamine **12** (Scheme 3,e, main text).



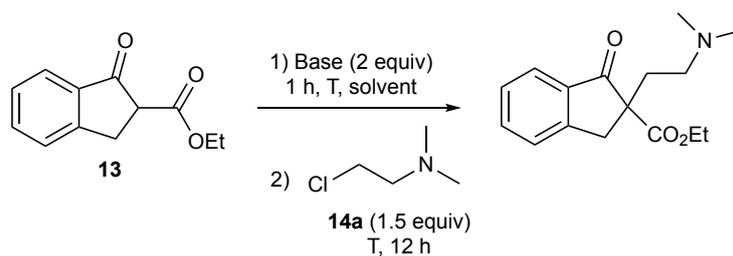
Entry	12 (equiv)	T (°C) (1st step)	Time (h)	NMR yield% (12)
1	2	50	24	NR
2	2	RT	24	80
3	4	RT	2	93

¹H NMR yield calculated using dibromomethane as an internal standard. NR = no reaction.

By reacting 1-indanone (**7**) with pyrrolidine (2 equiv), at 50 °C in ChCl/urea for 24 h, no reaction took place (entry 1, Table 4.3). The temperature was lowered to room temperature (RT, 25 °C), and the reaction was monitored via GC for 24 h: adduct **12** was isolated in 80% yield (entry 2, Table 4.3). After adding pyrrolidine (4 equiv) at RT, the desired adduct **12** was isolated in 93% yield after 2 h (entry 3, Table 4.3).

The reaction between 1-indanone (**7**) and pyrrolidine, to give enamine **12**, was run at RT in ChCl/urea, and monitored by GC. After 2 h, amine **14a** or **14b**, or amide **14c** (2 equiv each), was added to the reaction mixture, which was additionally stirred for 24 h: no reaction took place.

4.4. Table S4. Reaction between 2-chloro-*N,N*-dimethylethan-1-amine (**14a**) and β -ketoester **13** (Scheme 3,f, main text).

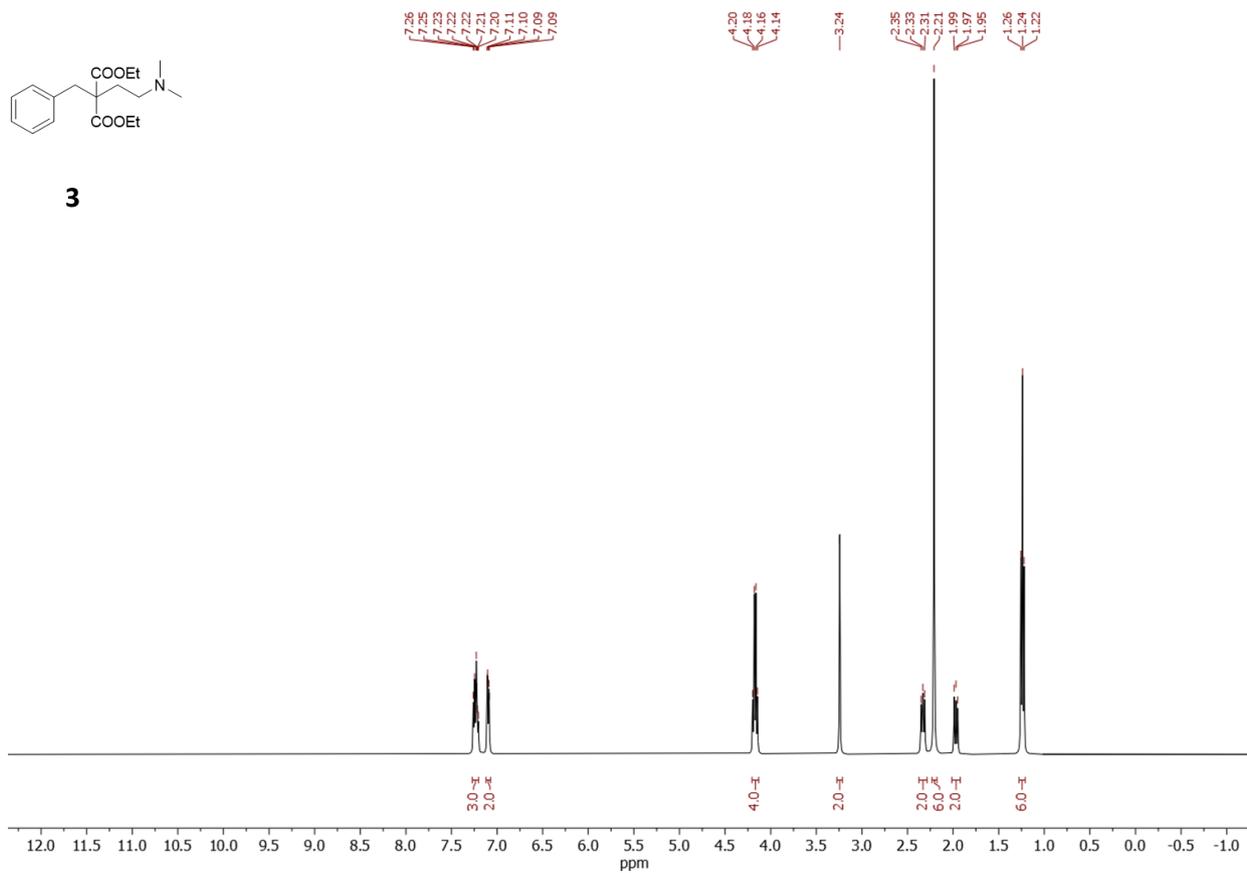


Entry	Solvent	Base	T (1) °C	T (2) °C	Yield %
1	THF	LDA	-78	-78	NR
2	THF	LDA	0	RT	NR
3	THF	KHMDS	-20	RT	NR
4	THF	NaHMDS	-20	RT	NR
5	THF	NaH	-20	RT	NR
6	toluene	NaH	-20	RT	NR
7	CPME	NaH	-20	RT	NR
8	CPME-ChCl/urea ^[a]	NaH	0	RT	NR
9	CPME-ChCl/urea ^[a]	LDA	0	RT	NR

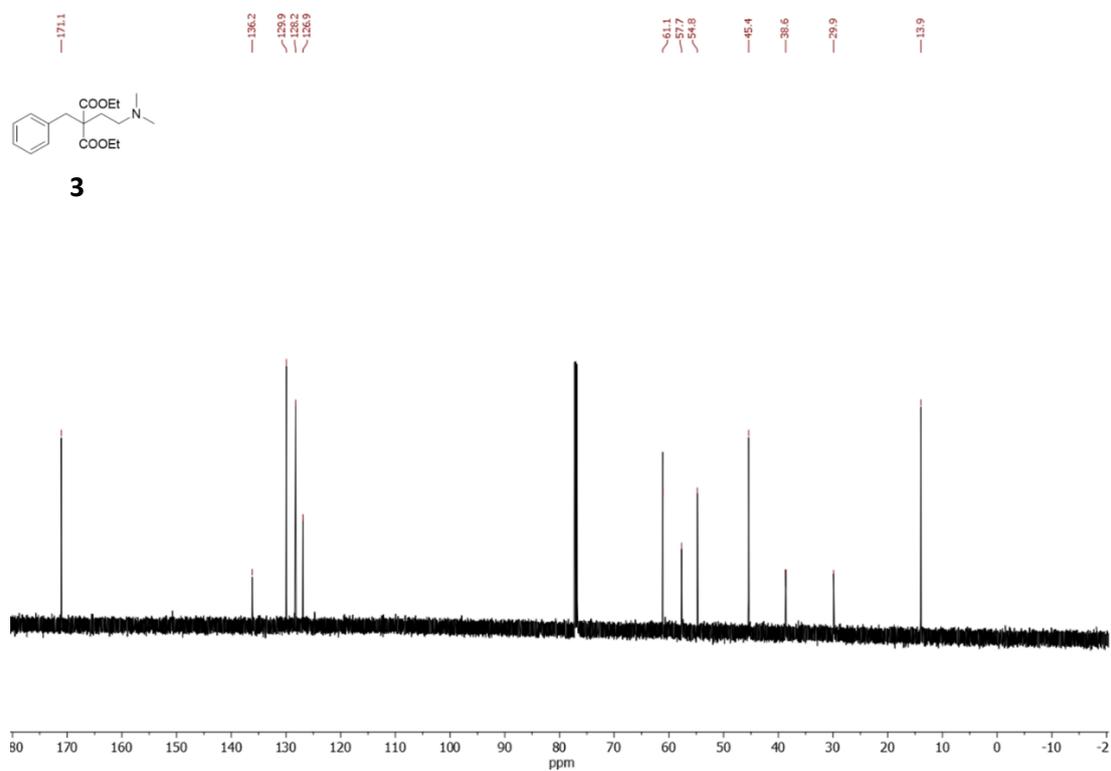
Reaction conditions: to a solution of **13** in the proper solvent, the base was added under an Argon atmosphere at T (1). After stirring at T (1) for 1 h, **14a** was added, and the reaction was finally quenched with water after 12 h stirring at T (2). [a] ChCl/urea (1:2 mol mol⁻¹); the solution of ketoester **13** and base in CPME were added to a solution of amine **14a** in DES. NR = no reaction.

5. ^1H and ^{13}C NMR spectra

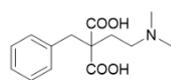
^1H NMR, 600 MHz, CDCl_3



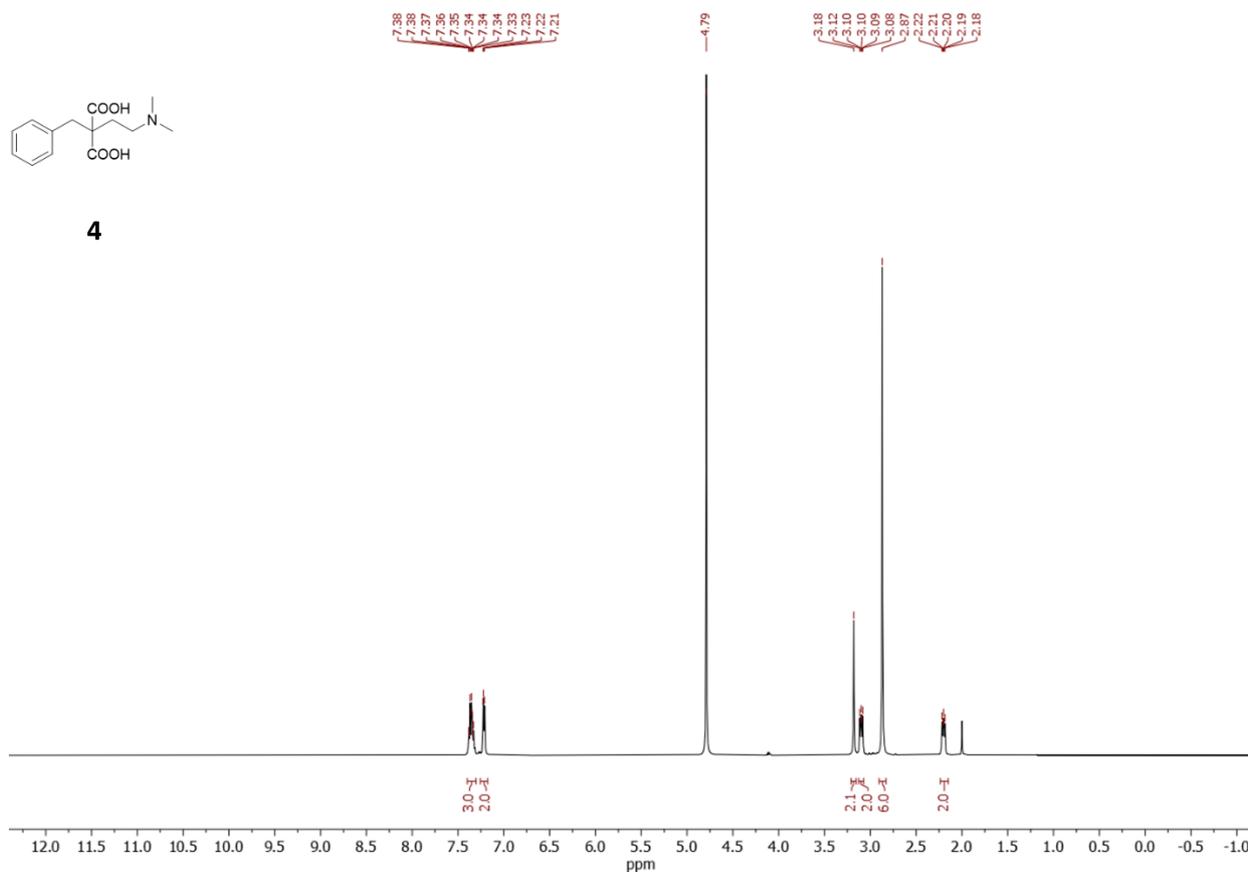
^{13}C NMR, 150 MHz, CDCl_3



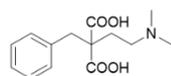
^1H NMR, 600 MHz, D_2O



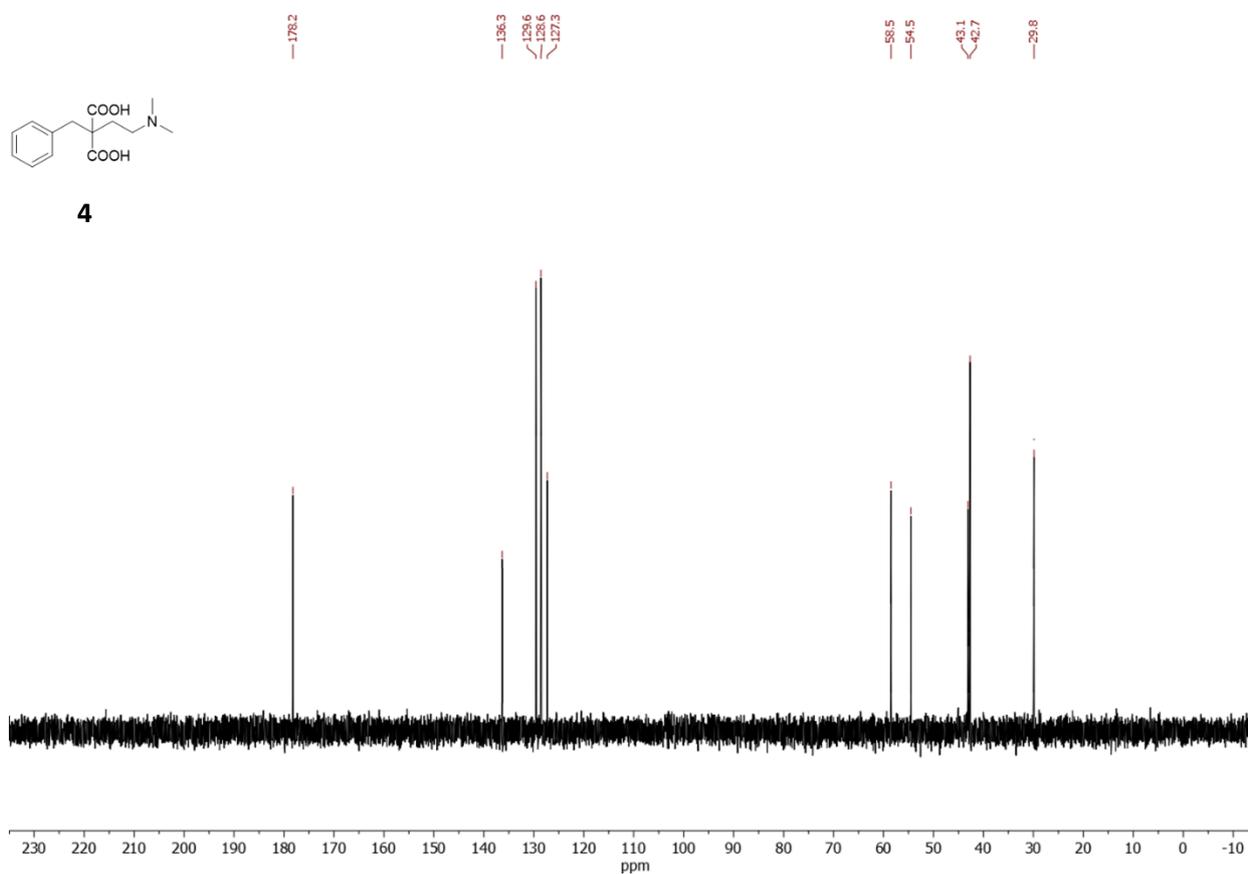
4



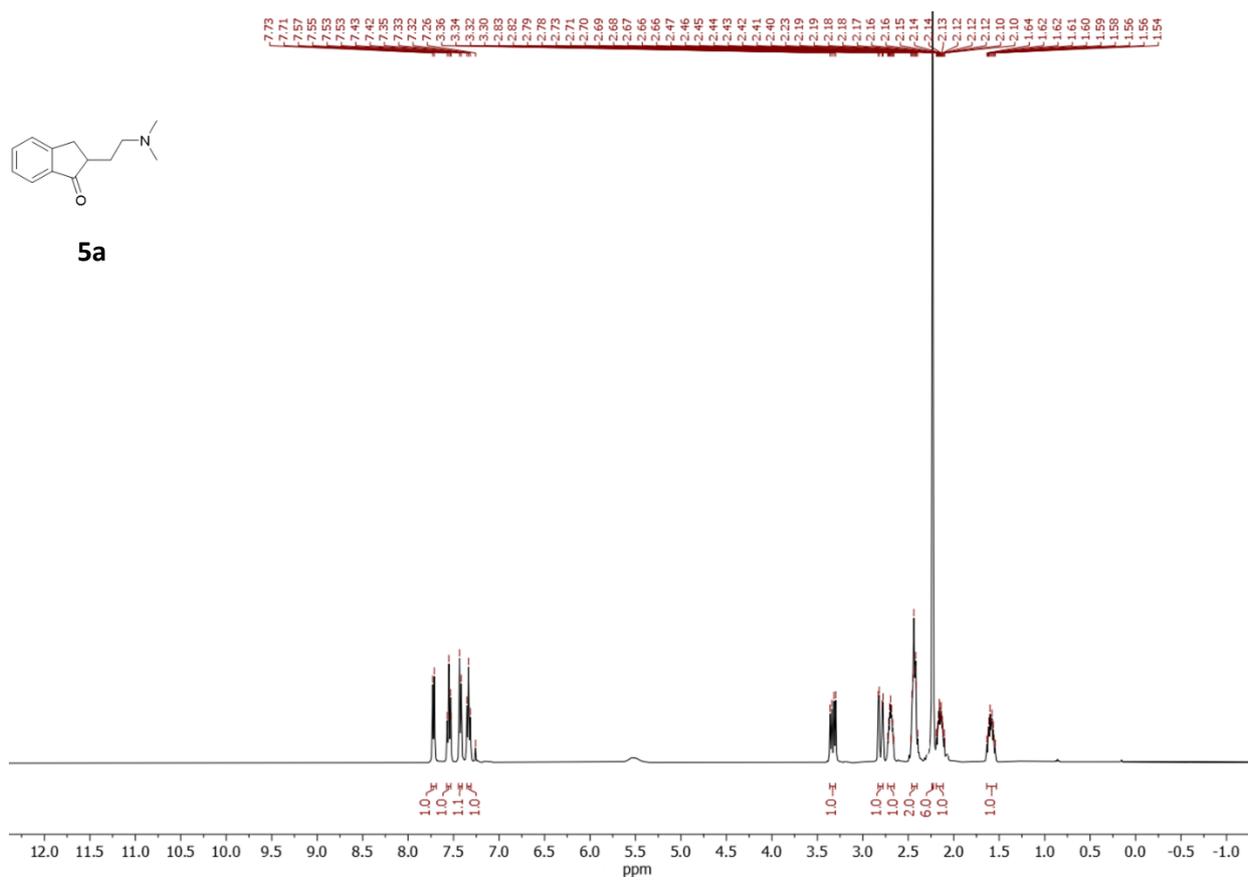
^{13}C NMR, 150 MHz, D_2O



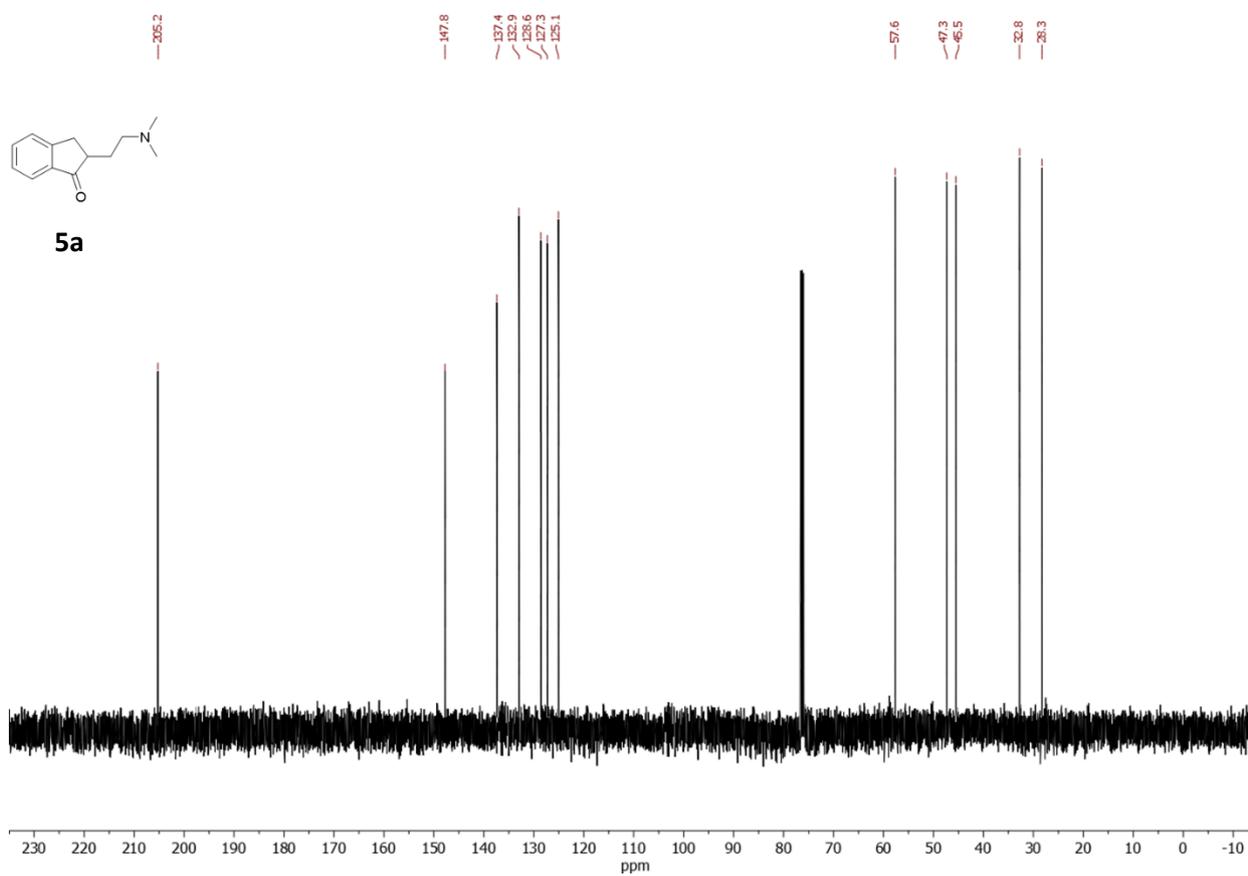
4



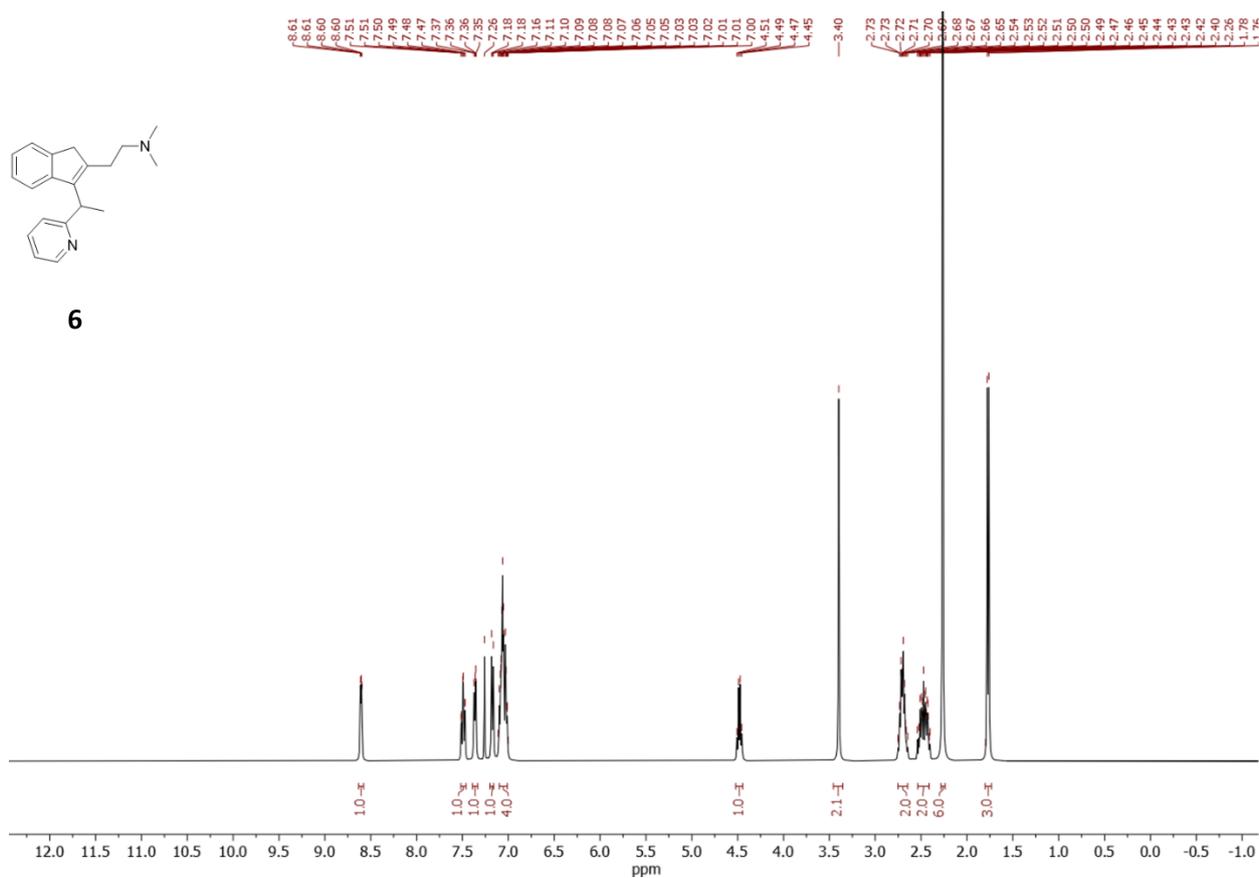
^1H NMR, 600 MHz, CDCl_3



^{13}C NMR, 150 MHz, CDCl_3



^1H NMR, 600 MHz, CDCl_3



^{13}C NMR, 150 MHz, CDCl_3

