SUPPORTING INFORMATION

Scalable Depolymerizing Transesterification and Amidation of (Poly)lactic Acid (PLA) Enabled by Resonant Acoustic Mixing (RAM)

Anton S. Makarov and Magnus Rueping*

KAUST Catalysis Center, King Abdullah University of Science and Technology (KAUST)
Thuwal, 23955-6900, Kingdom of Saudi Arabia

magnus.rueping@kaust.edu.sa

Table of contents

1. General Information

^{1}H NMR and ^{13}C NMR were recorded on Bruker DRX-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C NMR) spectrometer at ambient temperature; the chemical shifts (δ) were measured in ppm with respect to the solvent ($CDCl_3$,^{1}H: $\delta = 7.26$ ppm, ^{13}C: $\delta = 77.16$ ppm). Coupling constants (*J*) are given in Hertz. Splitting patterns of an apparent multiplets associated with an averaged coupling constants were designated as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sept (septet), m (multiplet), and br (broadened). Dibromomethane was used as an internal standard for quantitative NMR studies.

High resolution mass spectra were recorded on Bruker micro Time-of-Flight (TOF)-MS equipped with an ESI source.

GCMS data (EI-MS, 70 eV) were collected on Agilent 7890 gas chromatograph equipped with 5975C EI-MSD Triple-Axis Detector and HP5MS column. Quantitative GC data were obtained on Agilent 7890 gas chromatograph equipped with FID and HP5MS column at a flow rate 1.0 mL min^{-1}.

Size exclusion chromatography measurements were performed on Agilent 1260 HPLC, THF was used as eluent (1.0 mL min^{-1}) at 35°C with one guard column and two PLgel 5 μm mixed-C 7.5 × 300 mm columns, coupled with DRI detector (polystyrene as standards from 570 to 2,460,000 g mol^{-1})

All alcohols and amines were purchased from commercial suppliers and used as received. TBD used for optimization studies was purchased from Sigma Aldrich (catalog number 345571-5g).

A sample of virgin PLA was purchased from Sigma Aldrich (catalog number 38534-5g), Mw 65000, Đ 2.10 (Figure S1, *a*); Ultimaker^{TM} PLA 3D printing filament (Mw 205000, Đ 1.85) and Repurpose^{TM} PLA cups (Mw 179000, Đ 2.01) were used as model post-consumer PLA samples (Figure S1, *b,* and *c*).

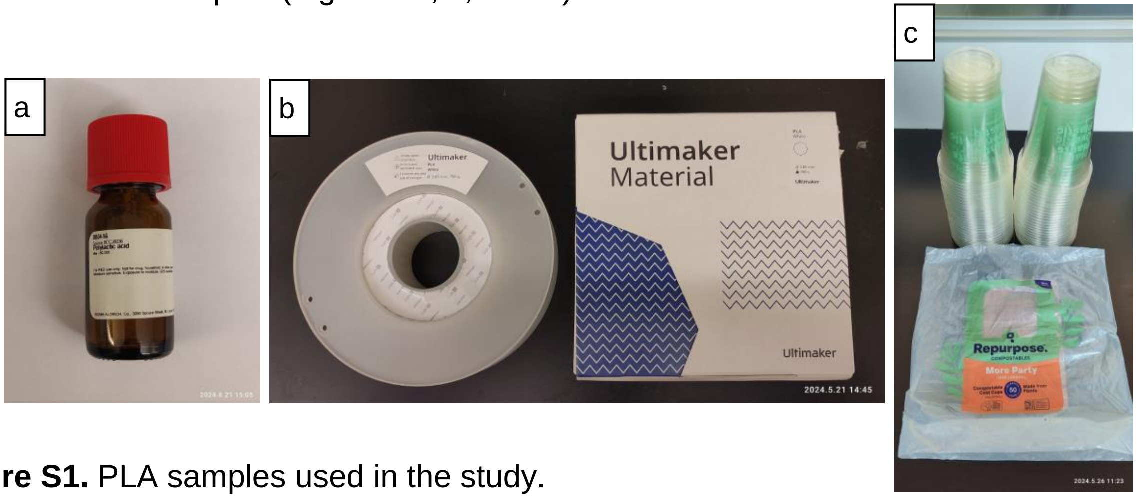


Figure S1. PLA samples used in the study.

All reactions were performed on LabRAM II$^{\text{TM}}$ mixer, Resodyn Acoustic Mixers (Figure S1, *a* and *b)*.[1] Reactions on 0.1 and 1 mmol scales were performed in standard 2 mL glass screw neck GC-vials equipped with closed top caps placed into 3D-printed polypropylene holder (Figure S2, *c*). Reactions on 10 mmol scale were performed in 3D-printed PTFE screw neck 5 mL vials (Figure S2, *d*) placed into 3D-printed polypropylene holder (Figure S3, *e*). Reactions on 100 mmol scale were performed in 3D-printed PTFE screw neck 100 mL (Figure S2, *f*) that were directly mounted into the LamRAM II. Reactions on 1 mol scale were performed in a 250 mL glass jar (Figure S2, *g*) that was directly mounted into the LabRAM II.

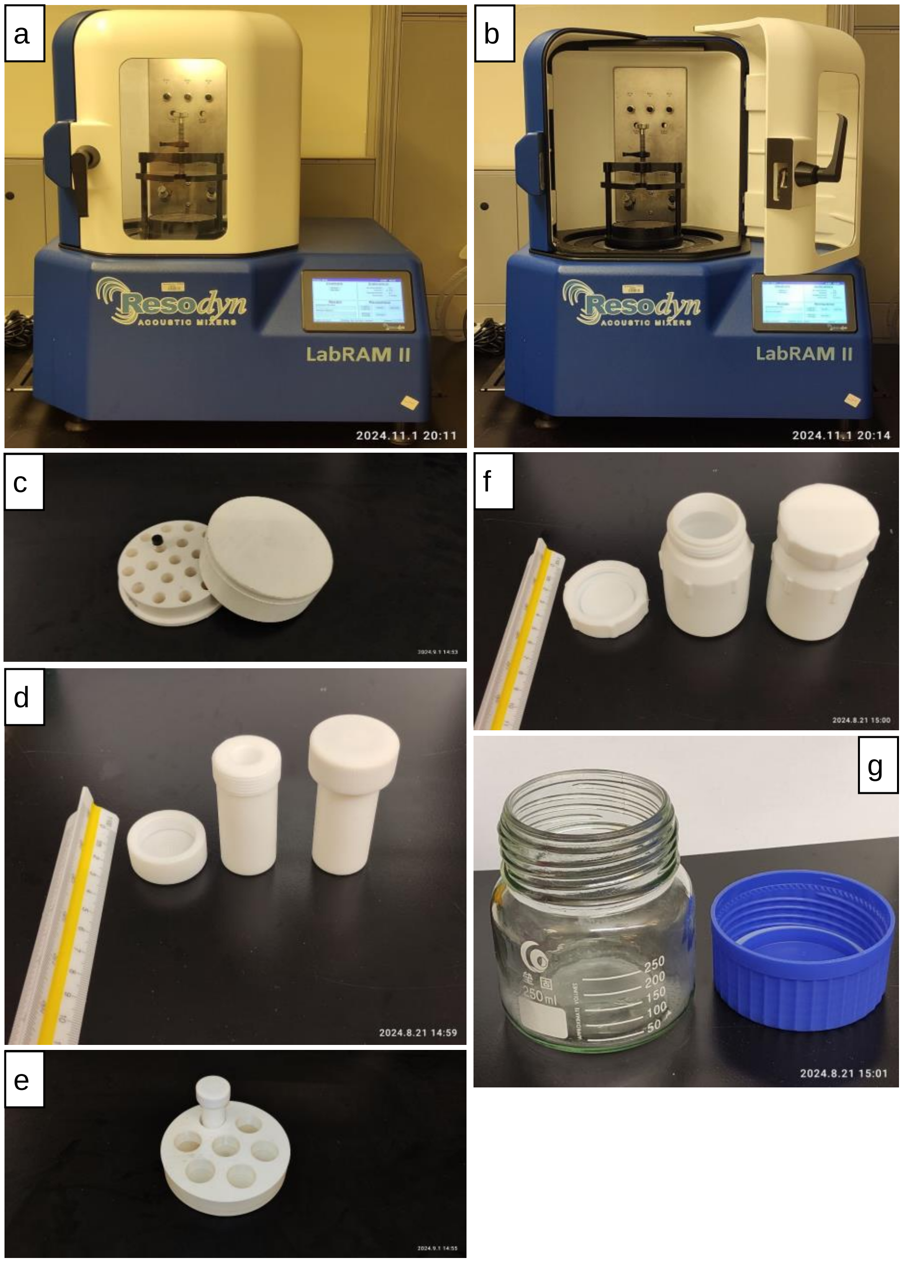
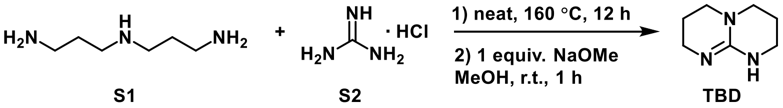


Figure S2. The LabRAM II mixer, reaction vessels and holders used in the study.

2. Synthesis of 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-*a*]pyrimidine (TBD)

For preparative experiments, TBD was synthesized adopting a protocol proposed by Usachev and Gridnev:[2]



A 100-mL round-bottom flask was charged with bis(3-aminopropyl) amine **S1** (12.4 g, 94 mmol), guanidine hydrochloride (9.05 g, 94 mmol) and a magnetic spin bar. *Note! Guanidine hydrochloride is hygroscopic. For higher yields of TBD, guanidine hydrochloride should be dry.* The flask was equipped with a condenser (temperature of the cooling liquid – 15 °C), placed into the oil bath preheated to 160 °C and stirred. After ca. 5 min of stirring, the ammonia began evolving. *Caution! Foam formation is possible. Active gas evolution takes approximately 1-2 hours. The reaction progress should be monitored, especially at the beginning of the reaction.* The reaction was stirred for 12 h, after which it was cooled to ambient temperature. *Note! The reaction mixture solidifies at ca. 80 °C. One might consider to take the spin bar out before cooling.* The solution of NaOMe in MeOH prepared from 2.7 g of Na and 50 mL of MeOH was slowly added to the reaction flask, and the reaction was stirred for 1 h. At the end of the reaction, all the initial solid had dissolved, and the reaction turned into white suspension. All the volatile contents were distilled on the rotary evaporator, and the residue was suspended in DCM (30 mL). The suspension was passed through silica gel (Schott tunnel, ca. 20 g of silica gel), washed with DCM (150 mL), the filtrate was concentrated and dried under vacuum overnight at ambient temperature to afford TBD as off-white solid, 12.4 g (89%). TBD could be further purified via sublimation (170 – 200 °C, $1 \cdot 10^{-1}$ mbar).

The spectral data were consistent with those reported in the literature and with those obtained for the authentic sample.

3. Synthesis of Ethyl Lactate

Analytical scales

Reactions on 0.1 mmol and 1.0 mmol scales were performed in standard 2 mL glass screw neck GC-vials equipped with closed top caps.

A typical experimental procedure for a 0.1 mmol scale reaction: a GC-vial is charged with virgin PLA (7.2 mg, 0.1 mmol based on the mass of a repeat unit), TBD and EtOH, the vial was placed into the holder, the holder was mounted into the LabRAM II, and the contents were agitated at a selected acceleration for a particular time. Upon completion, the contents of the vial were dissolved in 1 mL of DCM, 5 µL of dodecane (GC internal standard) was added, and the mixture was analyzed by GC-FID.

GC Calibration

A stock solution of ethyl lactate in THF (118 mg mL^{-1}) was dispensed in five 2 mL GC vials in the following manner: 10, 25, 50, 75, 100 µL, which reflected 10, 25, 50, 75, 100% theoretical yield of ethyl lactate in a model reaction on a 0.1 mmol scale. Dodecane (5 µL) was added to each vial, then the contents of all vials were diluted with DCM up to 1 mL and vigorously shaken. All vials were subjected to GC-FID for 3 times. The yield of ethyl lactate in % was plotted against $S_{analyte}/S_{internal\ standard}$*. The obtained trend line was described by the equation S1.*

$$\text{(S1)}\qquad \text{Yield of ethyl lactate, \%} = 98.531(S_{\text{analyte}}/S_{\text{internal standard}}) - 0.4073 \quad (R^2 = 0.9974)$$

A typical experimental procedure for a 1 mmol scale reaction: a GC-vial is charged with virgin PLA (72 mg, 1 mmol based on the mass of a repeat unit), TBD and EtOH, the vial was placed into the holder, the holder was mounted into the LabRAM II, and the contents were agitated at a selected acceleration for a particular time. Upon completion, the contents of the vial were dissolved in 1 mL of $CDCl_3$ and analyzed by ^1H NMR. TBD was used as an internal standard.

Figure S3 contains a picture of ^1H NMR spectrum after mixing 1 mmol PLA with 1.2 equiv. EtOH and 5 mol% TBD at 99 g for 6 h. Signals of TBD protons were integrated as follows: ^1H NMR (400 MHz, $CDCl_3$) δ = 3.21 (t, *J* = 5.9 Hz, 4H integrated as 0.2), 3.18 (t, *J* = 5.9 Hz, 4H integrated as 0.2), 1.89 (p, *J* = 5.9 Hz, 4 H integrated as 0.2) ppm. NMR yield of ethyl lactate is 94%.

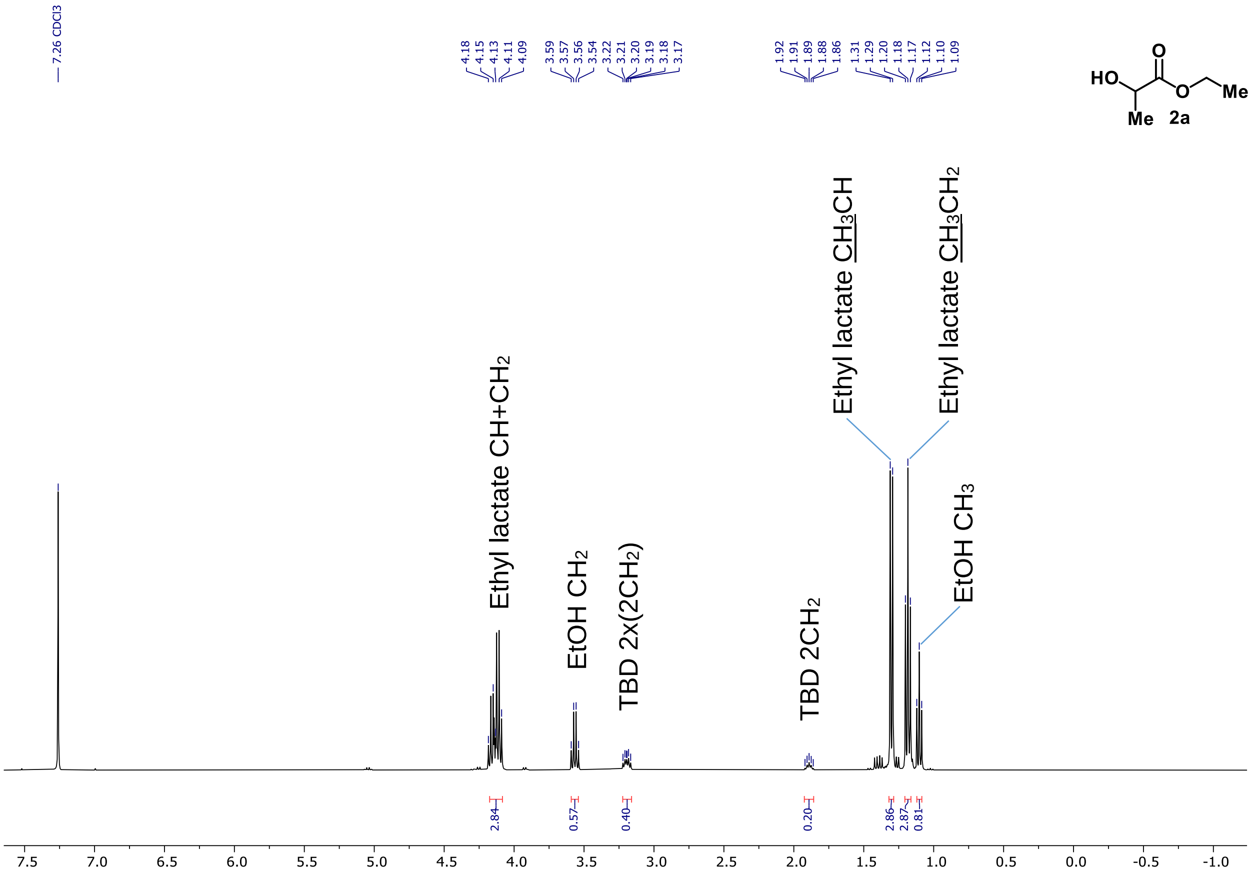


Figure S3. ^{1}H NMR spectrum of a reaction mixture after mixing 1 mmol PLA, 1.2 equiv. EtOH, 5 mol% TBD at 99 g for 6 h (400 MHz, $CDCl_3$).

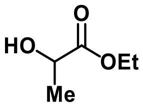
Preparative scales

10 mmol scale

5-mL PTFE vial (Figure 2, *b*) was charged with virgin PLA (720 mg, 10 mmol based on the mass of a repeat unit), TBD (69.6 mg, 0.5 mmol, 5 mol%) and EtOH (700 µL, 12 mmol, 1.2 equiv.). The vial was placed into a respective holder, the holder was mounted into LabRAM II, and the contents were mixed at 99 g for 3 h. Upon completion, the reaction mixture was quenched with acetic acid (29 µL, 0.5 mmol, 5 mol%) and transferred into 5-mL round-bottom flask. The excess of EtOH was removed on the rotary evaporator (55 °C, 100 mbar, 10 min). The residue was subjected to vacuum distillation using a Hickman distillation head with a known mass (Figure S4, *a*). The distillation head was weighted after distillation to calculate the isolated yield. The distillate was analyzed by ^{1}H NMR to evaluate the purity of the obtained sample. Ethyl lactate (**2a**) was isolated as a colorless liquid (1.07 g, 91%), which contained <5 mol% EtOH according to NMR data.

When cut PLA cups (Figure S4, *b*) were used instead of the virgin PLA, the yield of ethyl lactate (**2a**) was 1.06 g (90%) following the same procedure.

When cut 3D-printing filament made from PLA (Figure S4, *c*) was used instead of the virgin PLA, the yield of ethyl lactate (**2a**) was 1.06 g (90%) following the same procedure.



Ethyl 2-hydroxypropanoate (2a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 – 4.11 (m, 3 H), 3.28 (br s, 1H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 66.6, 61.4, 20.2, 14.0 ppm.

The spectral data were consistent with those reported in the literature.[3]

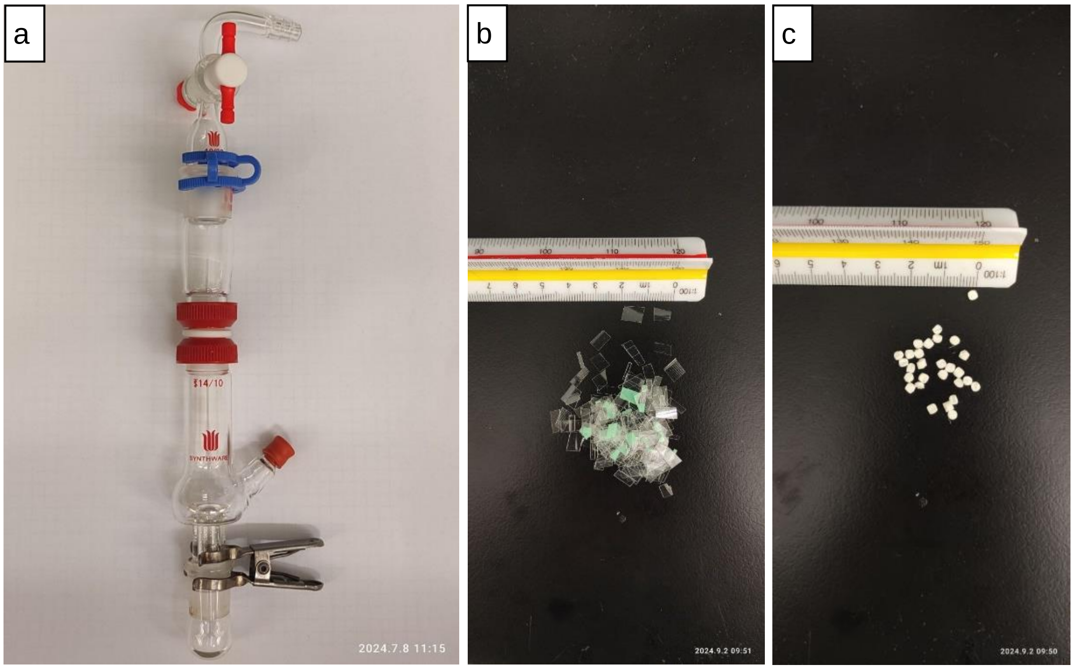


Figure S4. (a) Microdistillation apparatus equipped with a Hickman distillation head; (b) preprocessed PLA cups; (c) preprocessed 3D-printing filament made from PLA.

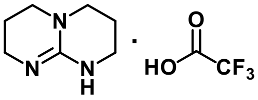
100 mmol scale

100-mL PTFE vial (Figure 2, *d*) was charged with either cut PLA cups or 3D-printing filament (7.2 g, 100 mmol based on the mass of a repeat unit), TBD (696 mg, 5 mmol, 5 mol%) and EtOH (7.0 mL, 120 mmol, 1.2 equiv.). The vial was mounted into LabRAM II, and the contents were mixed at 99 g for 3 h. Upon completion, the reaction mixture was quenched with acetic acid (290 µL, 5 mmol, 5 mol%) and transferred into 25-mL round-bottom flask. The excess of EtOH was removed on the rotary evaporator (55 °C, 100 mbar, 10 min). The residue was subjected to vacuum distillation using short-path distillation apparatuses (Figure S5, *a*). The contents were analyzed by ^{1}H NMR to evaluate the purity of the obtained sample. Ethyl lactate (**2a**) was isolated as a colorless liquid, which contained <5 mol% EtOH according to NMR data. Alternatively, the reaction mixture could be quenched with TFA (383 µL, 5 mmol, 5 mol%). After distillation of the major fraction, the residue was dried under vacuum (100 °C, $1 \cdot 10^{-1}$ mbar, 15 min) and suspended in Et_2O (10 mL). The solid was filtered, washed with Et_2O and dried. Thus obtained pale yellow solid was *TBD·TFA (**S3**), 1.13 g, 90%.*

Note! The same operation could be performed to obtain TBD·AcOH. However, TBD·AcOH is highly hygroscopic and, apparently, decomposes rather rapidly; therefore, it is seemed to be not practical to regenerate TBD through intermediate formation of TBD·AcOH.

PLA cups yielded 10.5 g (89%) of ethyl lactate (**2a**) (Figure S5, *b*).

3D-printing filament yielded 10.4 g (88%) of ethyl lactate (**2a**).



1,3,4,6,7,8-Hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidinium trifluoroacetate (S3)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (br s, 2H), 3.25 – 3.21 (m, 8H), 1.93 (p, *J* = 5.9 Hz, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163 (q, ^2J = 35 Hz), 151.4, 116.7 (q, ^1J = 294 Hz), 46.8, 37.8, 20.6 ppm.

^{19}F NMR (375 MHz, $CDCl_3$): δ = 75.68 ppm.

The spectral data were consistent with those reported in the literature.[4]

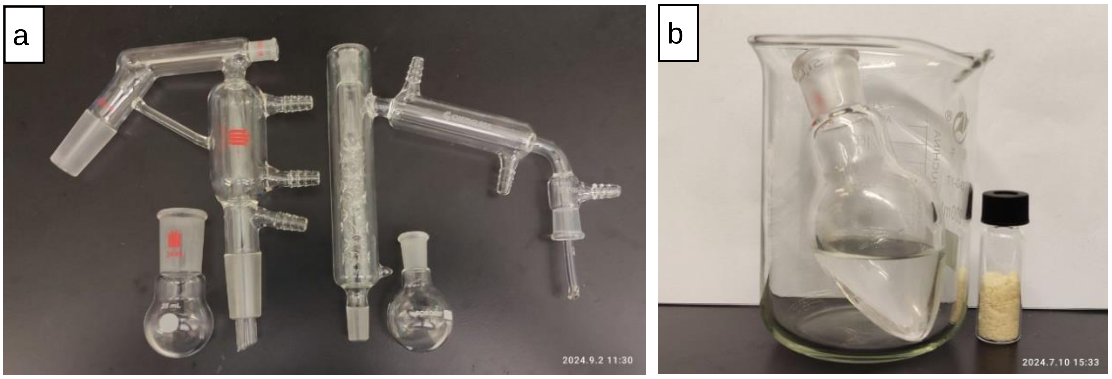


Figure S5. (a) Distillation equipment for large scale experiments; (b) samples of ethyl lactate obtained from PLA cups (in the conical flask) and TBD·TFA (in the vial) on a 10 mmol scale.

1 mol scale

250-mL glass jar (Figure 2, e) was charged with virgin cut PLA cups (72 g, 1 mol based on the mass of a repeat unit), TBD (6.96 g, 50 mmol, 5 mol%) and EtOH (70 mL, 1.2 mol, 1.2 equiv.). The vial was mounted into LabRAM II, and the contents were mixed at 99 g for 30 min. Upon completion, the reaction mixture was quenched with acetic acid (2.9 mL, 50 mmol, 5 mol%) and transferred into 250-mL round-bottom flask. The excess of EtOH was removed on the rotary evaporator (55 °C, 100 mbar, 10 min). The residue was subjected to vacuum distillation using short-path distillation apparatus (Figure S5, *a, on the left*). The content was analyzed by ^{1}H NMR to evaluate the purity of the obtained sample. Ethyl lactate (**2a**) was isolated as a colorless liquid, 107.4 g, 91% (Figure S6). Alternatively, the reaction mixture could be quenched with TFA (3.83 mL, 50 mmol, 5 mol%). After distillation of the major fraction, the residue was additionally dried under vacuum (100 °C, $1{\cdot}10^{-1}$ mbar, 15 min), upon which a minor fraction containing 5.3 g, 6% of dimer **3**, and suspended in Et_2O (50 mL). The solid was filtered, washed with Et_2O and dried. Thus obtained pale yellow solid was *TBD·TFA (**S1**), 11.3 g, 90%.*

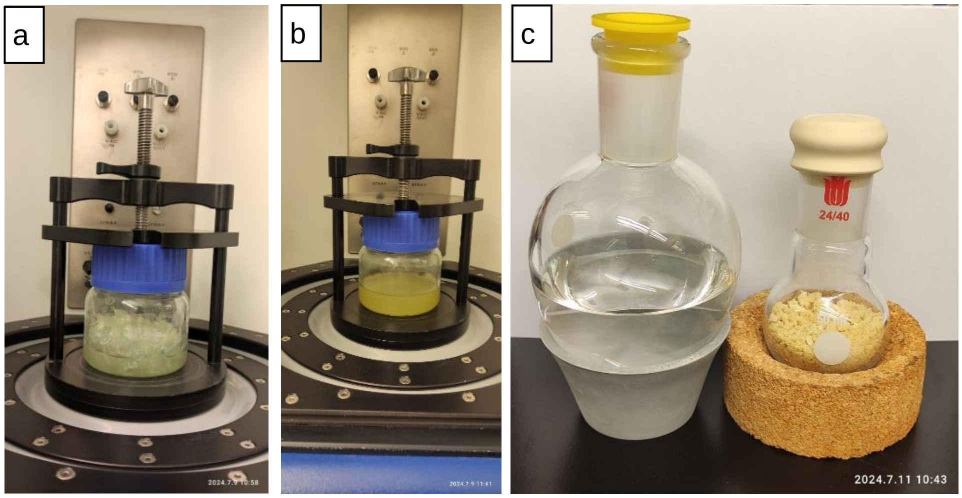
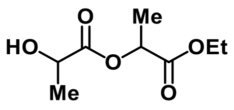


Figure S6. (a) Reaction mixture before mixing; (b) reaction mixture after mixing; (c) samples of ethyl lactate and TBD·TFA obtained from PLA cups on a 1 mol scale.

1-Ethoxy-1-oxopropan-2-yl 2-hydroxypropanoate (3)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 (q, *J* = 7.0 Hz, 1H), 4.51 (br s, 1H), 4.64 (q, *J* = 7.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1, 170.4, 69.4, 66.8, 61.7, 20.4, 16.9, 14.1 ppm.

The spectral data were consistent with those reported in the literature.[5]

4. Regeneration of TBD and Subsequent Catalytic Activity Testing

25-mL round-bottom flask was charged with TBD·TFA (1.01 g, 4 mmol), methanol (4 mL) and a magnetic spin bar. The formed solution was treated with freshly prepared solution of sodium methoxide in methanol (2.0 M, 4 mL, 2 equiv.) at room temperature. The formed clear solution was stirred at the same temperature for 3 h and then concentrated. The white oily residue was suspended in DCM (4 mL) and the suspension was passed through a thin layer of silica put onto the cotton filter while washing with DCM (ca. 70 mL). The filtrate was concentrated to dryness and then dried further under vacuum ($1{\cdot}10^{-1}$ mbar) for 30 min to afford TBD base in the form of white waxy solid, 490 mg, 88%.

The NMR data of the obtained sample were consistent with those obtained from authentic and synthetic samples. The estimated NMR purity was 95% (Figure S7).

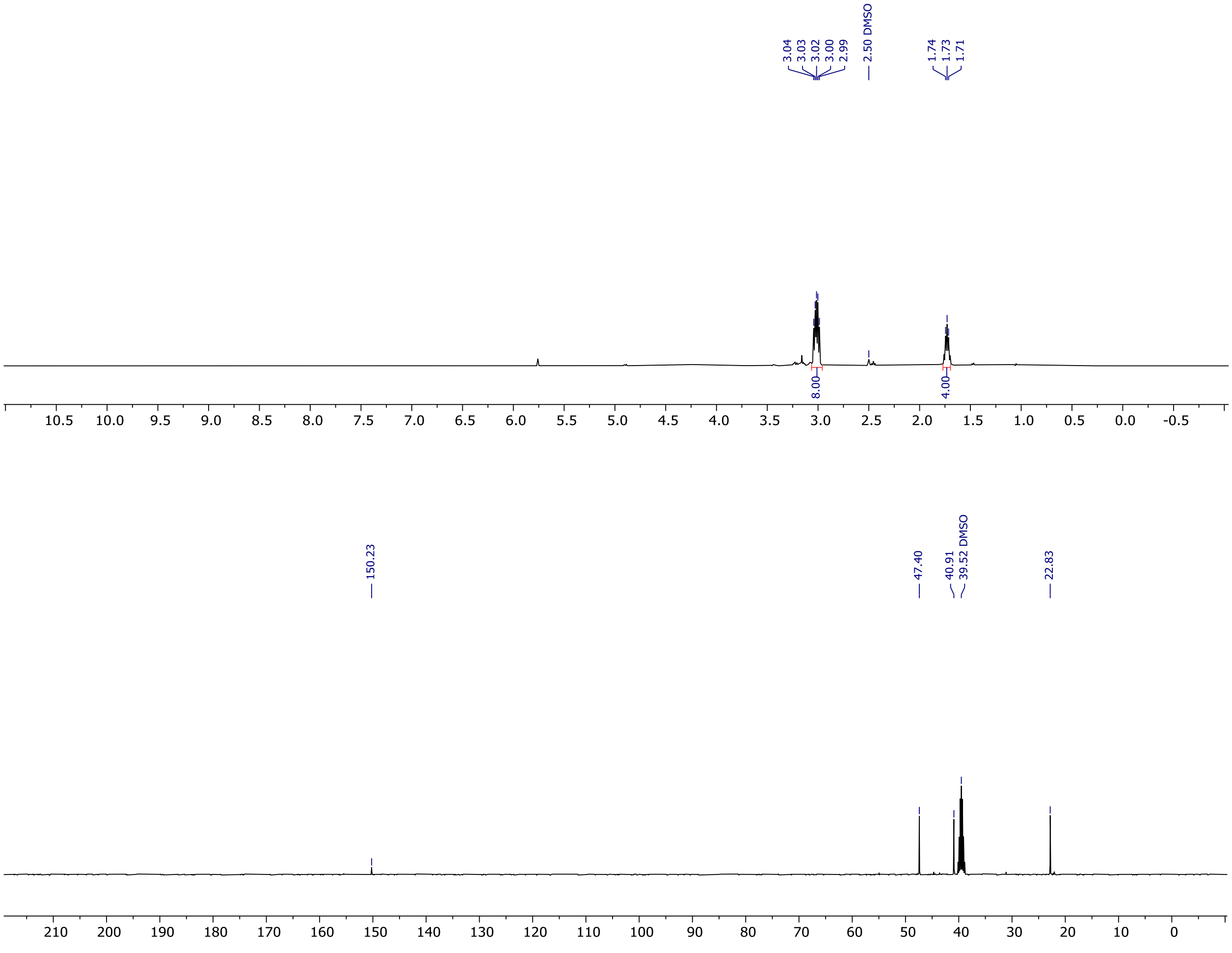


Figure S7. ^{1}H and ^{13}C NMR spectra of TBD obtained after regeneration (400 and 100 MHz respectively, DMSO-d_6).

5-mL PTFE vial (Figure 2, *b*) was charged with cut PLA cups (720 mg, 10 mmol based on the mass of a repeat unit), regenerated TBD (69.6 mg, 0.5 mmol, 5 mol%) and EtOH (700 µL, 12 mmol, 1.2 equiv.). The vial was placed into a respective holder, the holder was mounted into LabRAM II, and the contents were mixed at 99 g for 3 h. Upon completion, the reaction mixture was quenched with acetic acid (29 µL, 0.5 mmol, 5 mol%) and transferred into 5-mL round-bottom flask. The excess of EtOH was removed on the rotary evaporator (55 °C, 100 mbar, 10 min). The residue was subjected to vacuum distillation using a Hickman distillation head with a known mass (Figure S4, *a*). The distillation head was weighted after distillation to calculate the isolated yield. The distillate was analyzed by ^{1}H NMR to evaluate the purity of the obtained sample. Ethyl lactate (**2a**) was isolated as a colorless liquid (1.03 g, 89%).

5. Comparative Study of the Reaction Progress: RAM vs Conventional Stirring

For RAM experiments, nine 5-mL PTFE vials were charged with cut PLA cups (720 mg, 10 mmol based on the mass of a repeat unit), TBD (69.6 mg, 0.5 mmol, 5 mol%) and EtOH (700 µL, 12 mmol, 1.2 equiv.). The vials were placed into a respective holder, the holder was mounted into LabRAM II, and the contents were mixed at 99 g. Mixing was paused for 10 s every 20 min, and one of the vials was taken out for analysis. The contents of a given vial were quenched with acetic acid (29 µL, 0.5 mmol, 5 mol%), dissolved in $CDCl_3$ (2 mL) and analyzed by ^{1}H NMR.

For conventional stirring experiments, nine 5-mL PTFE vials were charged with cut PLA cups (720 mg, 10 mmol based on the mass of a repeat unit), TBD (69.6 mg, 0.5 mmol, 5 mol%), EtOH (700 µL, 12 mmol, 1.2 equiv.), and a spin bar (stick, 10 × 3 × 3 mm). The vials were placed into a water bath preheated to 35 °C and stirred (1500 rpm). The vials were periodically shaken to prevent the contents from sticking to the walls of the vials. Every 20 min, one of the vials was taken out for analysis. The contents of a given vial were quenched with acetic acid (29 µL, 0.5 mmol, 5 mol%), dissolved in $CDCl_3$ (2 mL) and analyzed by ^{1}H NMR.

Table S1. Analytical yields obtained during comparative study.

Time, min	Yield of ethyl lactate (RAM), %[a]	Yield of ethyl lactate (stirring), %[a]
20	17	14
40	33	20
60	46	24
80	59	28
10	67	32
120	76	35
140	84	38
160	89	41
180	95	45

[a] NMR yields, TBD was used as internal standard

6. Scope of Esters and Amides of Lactic Acid

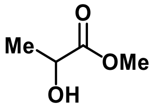
*General protocol for the synthesis of esters (**2b-f**) and amides (**4a-e**) of lactic acid*

5-mL PTFE vial (Figure 2, *b*) was charged with cut PLA cups (720 mg, 10 mmol based on the mass of a repeat unit), TBD (69.6 mg, 0.5 mmol, 5 mol%) and the respective alcohol or amine (12 mmol, 1.2 equiv.). The vial was placed into a holder, the holder was mounted into LabRAM II, and the contents were mixed at 99 g for 3 h. Upon completion, the reaction mixture was quenched with acetic acid (29 μL, 0.5 mmol, 5 mol%) and transferred into 5-mL round-bottom flask. The residue was subjected to vacuum distillation using a Hickman distillation head with a known mass (Figure S4, *a*). The distillation head was weighted after distillation to calculate the isolated yield. The distillate was analyzed by ^{1}H NMR to evaluate the purity of the obtained sample.

Note 1. Excess amine component could be nearly quantitatively removed by rotovaping the reaction mixture prior to distillation due to the large difference in boiling points between the amines and the respective amides.

Note 2. One might consider distilling an excess alcohol component to a Hickman distillation head without applying vacuum for better separation.

Note 3. If necessary, the Hickman distillation head can be cooled by wrapping it with a piece of fabric soaked in water.



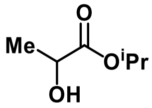
Methyl 2-hydroxypropanoate (2b)

Compound **2b** was obtained as a colorless liquid, 977 mg (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 (q, *J* = 6.9 Hz, 1H), 3.68 (s, 3H), 3.39 (br s, 1 H), 1.32 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 66.7, 52.4, 20.2 ppm.

The spectral data were consistent with those reported in the literature.[6]



Isopropyl 2-hydroxypropanoate (2c)

Compound **2c** was obtained as a colorless liquid, 1081 mg (82%).

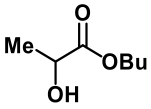
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 (hept, *J* = 6.2 Hz, 1H), 4.02 (q. *J* = 6.9 Hz, 1H), 3.58 (br s, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.04 (dd, *J* = 6.2 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 68.6, 66.5, 21.3 (2C), 19.9 ppm.

The spectral data were consistent with those reported in the literature.[6]

Butyl 2-hydroxypropanoate (2d)

Compound **2d** was obtained as a colorless liquid, 1210 mg (83%).



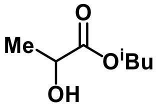
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (q, *J* = 6.9 Hz, 1H), 4.20 – 4.13 (m, 2H), 4.05 (br s, 1H), 1.66 – 1.59 (m, 2H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.39 – 1.32 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 66.9, 65.7, 30.6, 20.4, 19.1, 13.7 ppm.

The spectral data were consistent with those reported in the literature.[6]

Isobutyl 2-hydroxypropanoate (2e)

Compound **2e** was obtained as a colorless liquid, 1183 mg (81%).



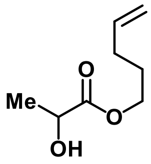
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (q, *J* = 6.9 Hz, 1H), 4.01 – 3.89 (m, apparent ABdq, 2H), 2.96 (br s, 1H), 2.02 – 1.88 (m, 1H), 1.41 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 71.7, 66.8, 27.8, 20.6, 19.1, 19.0 ppm.

The spectral data were consistent with those reported in the literature.[6]

Pent-4-en-1-yl 2-hydroxypropanoate (2f)

Compound **2f** was obtained as a colorless liquid, 1326 mg (84%).



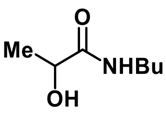
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 – 5.70 (m, 1H), 5.02 – 4.94 (m, 2H), 4.23 (q, *J* = 6.9 Hz, 1H), 4.19 – 4.09 (m, 2H), 3.10 (br s, 1H), 2.11 – 2.06 (m, 2H), 1.76 – 1.69 (m, 2H), 1.37 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 137.2, 115.5, 66.8, 65.0, 29.9, 27.7, 20.4 ppm.

HRMS (ESI-TOF) *m/z* calcd for $C_8H_{14}NaO_3$ $[M + Na]^+$ 181.0835, found 181.0829.

N-Butyl-2-hydroxypropanamide (4a)

Compound **4a** was obtained as a colorless liquid, 1262 mg (87%).

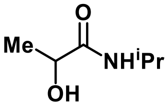


^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (br s, 1H), 4.45 (br s, 1H), 4.13 (q, *J* = 6.8 Hz, 1H), 3.20 (q, *J* = 7.2 Hz, 2H), 1.48 – 1.43 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.34 – 1.28 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 68.1, 38.8, 31.5, 21.0, 20.0, 13.7 ppm.

The spectral data were consistent with those reported in the literature.[7]

2-Hydroxy-*N*-isopropylpropanamide (4b)



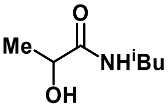
Compound **4b** was obtained as a colorless liquid, 1035 mg (79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (br s, 1H), 4.77 (br s, 1H), 4.09 (q, *J* = 6.8 Hz, 1H), 4.00 – 3.92 (m, 1H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 68.1, 41.0, 22.6 (2C), 22.1 ppm.

The spectral data were consistent with those reported in the literature.[8]

2-Hydroxy-*N*-isobutylpropanamide (4c)



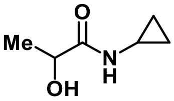
Compound **4c** was obtained as a colorless liquid, 1245 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (br s, 1H), 4.19 (q, *J* = 6.8 Hz, 1H), 3.11 – 3.01 (m, 2H), 1.81 – 1.71 (m, 1H), 1.39 (d, *J* = 6.8 Hz, 3H), 0.89 (d *J* = 6.6 Hz, 6H) ppm. A resonance for a proton of the OH group has not been detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 68.5, 46.5, 28.6, 21.5, 20.2, 20.1 ppm.

HRMS (ESI-TOF) *m/z* calcd for $C_7H_{15}NO_2$ $[M + H]^+$ 146.1176, found 146.1170

N-Cyclopropyl-2-hydroxypropanamide (4d)



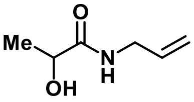
Compound **4d** was obtained as a colorless liquid, 1098 mg (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (br s, 1H), 4.43 (br s, 1H), 4.14 (q, *J* = 6.9 Hz, 1H), 2.69 – 2.63 (m, 1H), 1.34 (d, *J* = 6.9 Hz, 3H), 0.76 – 0.72 (m, 2H), 0.50 – 0.46 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 67.9, 22.0, 20.8, 6.1 (2C) ppm.

The spectral data were consistent with those reported in the literature.[9]

N-Allyl-2-hydroxypropanamide (4e)



Compound **2b** was obtained as a colorless liquid, 1172 mg (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ =7.11 (br s, 1H), 5.76 (ddt, *J* = 17.2, 10.3, 5.5 Hz, 1H), 5.16 – 5.06 (m, 2H), 4.89 (br s, 1H), 4.15 (q, *J* = 6.8 Hz, 1H), 3.82 – 3.78 (m, 2H), 1.33 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ =175.5, 133.7, 116.4, 68.2, 41.4, 21.1 ppm.

The spectral data were consistent with those reported in the literature.[10]

7. Process Mass Intensity Assessment

Green chemistry metrics evaluate the efficiency and environmental impact of chemical processes by encouraging reduced solvent use and minimizing reagent and waste loads.[11] To demonstrate the sustainability of our method compared to the representative example of a liquid-phase reaction, we calculated the green metric Process Mass Intensity (PMI). PMI measures the total mass (in kilograms) of raw materials required (input) to produce 1 kilogram of product (output). When comparing two processes, the one with the lower PMI reflects greater environmental benefits and efficiency, identifying it as the greener option. PMI is calculated according to equation S2.

$$\text{PMI} = \frac{\text{Total mass used in the process (kg)}}{\text{Mass of products (kg)}} \qquad \text{(S2)}$$

As an example of conventional liquid-phase synthesis of alkyl lactates, we have chosen the protocol towards methyl lactate published by Enthaler *at al.*[12]

"Used PLA-cups were washed with water and dried in air. PLA cups (1a, NatureWorks, ~17 exemplars) (20.0 g, 277.5 mmol based on the repeating unit, for simplification we insinuate that the PLA-product is composed of 100% of PLA), methanol (250 g, 7802.7 mol, 28.1 equiv. based on the repeating unit of 1), and catalytic amounts of $Zn(OAc)_2$ (1.0 mol%, 509.2 mg, 2.78 mmol based on the repeating unit of 1) were placed with a stirring bar in flask (500 mL), which was connected to a reflux condenser. The mixture was heated at reflux conditions (oil bath temperature: 90 °C) for 24 hours. The reaction mixture was filtered over a paper filter to remove $Zn(OAc)_2$. Afterwards the receiving flask was attached to a rotary evaporator and the methanol was removed in vacuum. The residue was dissolved in ethyl acetate (100 mL) and the mixture was washed with water (3x 100 mL) and brine (1x 100 mL). The organic layer was dried over Na_2SO_4. Afterwards the solvent was removed to obtain a clear liquid (m = 25.7 g, n = 24.7 mmol, 89%)."

In order to obtain 0.0257 kg of methyl lactate, Enthaler's protocol requires 0.02 kg PLA, 0.25 kg MeOH, 0.000509 kg $Zn(OAc)_2$; **PMI = 10.5**.

In order to obtain 0.000978 kg of methyl lactate, our protocol requires 0.00072 kg PLA, 0.0000485 kg MeOH, 0.0000696 kg TBD, 0.00003 kg AcOH. **PMI = 1.3**

For the large-scale synthesis of ethyl lactate by our protocol, **PMI = 1.3** as well according to the following calculations: in order to obtain 0.1074 kg of ethyl lactate, the protocol requires 0.072 kg PLA, 0.05523 kg EtOH, 0.00696 kg TBD, 0.003045 kg AcOH. Therefore, it is reasonable to propose that, in the case of methyl lactate, if large-scale synthesis is performed, one could expect a PMI value very close to 1.3. It should be stressed out that the auxiliary resources spent during the work-up procedure (organic solvents for extraction, drying agents etc.) or resources spend to maintain reaction conditions (such as water to cool the condenser) are not taken into consideration when calculating PMI.

8. References

1. Resodyn Acoustic Mixers website contains important information about LabRAM II including basic working principles, potential applications and references the patents that describe technical features, https://resodynmixers.com.

2. S. Usachev and A. Gridnev, *Synth. Commun.,* 2011, **41**, 3683.

3. J. J. Monteith and S. A. L. Rousseaux, *Org. Lett.*, 2021, **23**, 9485.

4. S. M. Baghbanian and M. Farhang, *J. Mol. Liq.*, 2013, **183**, 45.

5. D. Bykowski, A. Grala and P. Sobota, *Tetrahedron Lett.*, 2014, **55**, 5286.

6. R. Petrus, D. Bykowski and P. Sobota, *ACS Catal.*, 2016, **6**, 5222.

7. A. Westerbeek, W. Szymański, H. J. Wijma, S. J. Marrink, B. L. Feringa and D. B. Janssen, *Adv. Synth. Catal.*, 2011, **353**, 93.

8. A. Solladie-Cavallo and M. Bencheqroun, *J. Org. Chem.*, 2002, **57**, 5831.

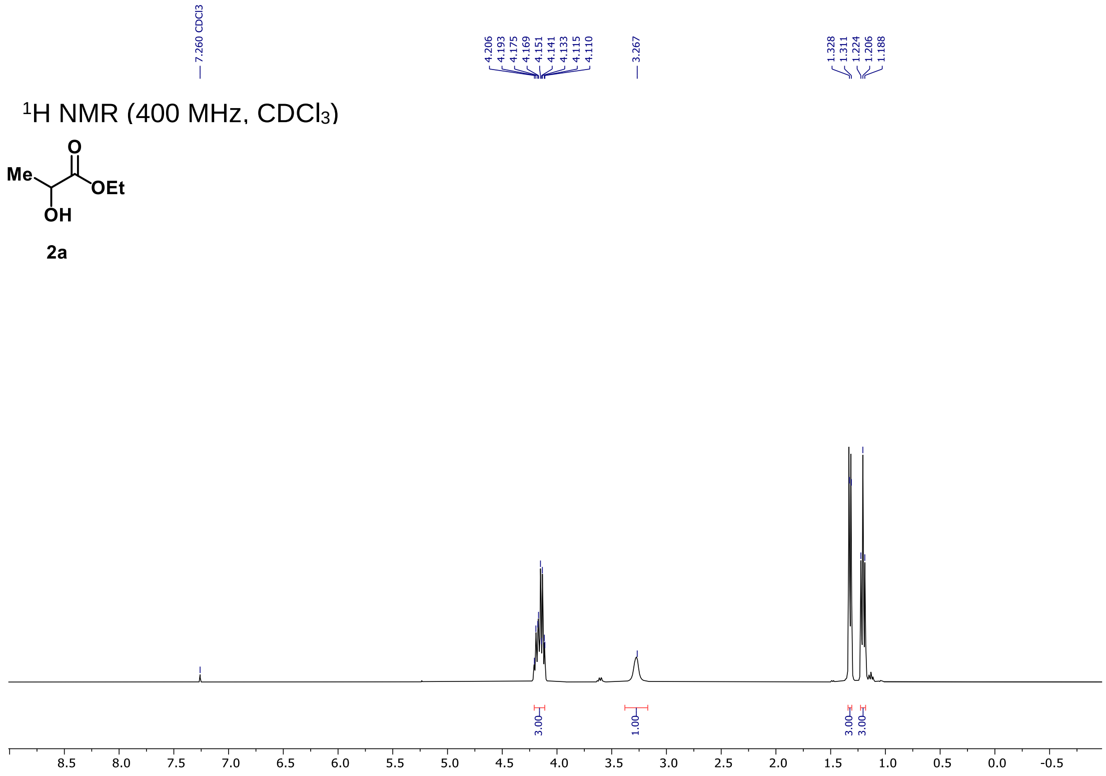
9. D. Grayson, F. Lewis and M. Eichler, *Synlett*, **2009**, 1923.

10. R. Tanifuji, K. Koketsu, M. Takakura, R. Asano, A. Minami, H. Oikawa and H. Oguri, *J. Am. Chem. Soc.*, 2018, **140**, 10705.

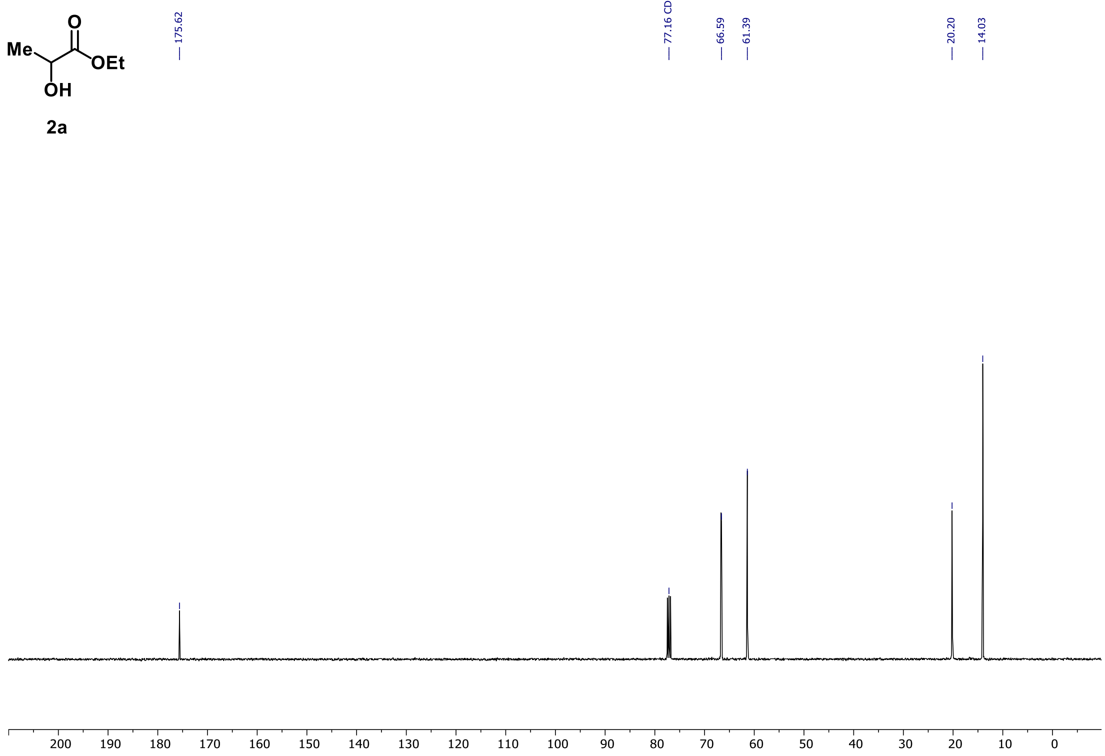
11. N. Fantozzi, J.-N. Volle, A. Porcheddu, D. Virieux, F. García, E. Colacino, *Chem. Soc. Rev.,* 2023*,* **52**, 6680.

12. E. Cheung, C. Alberti, S. Enthaler, *ChemistryOpen*, 2020, **9**, 1224.

9. Copies of NMR Spectra

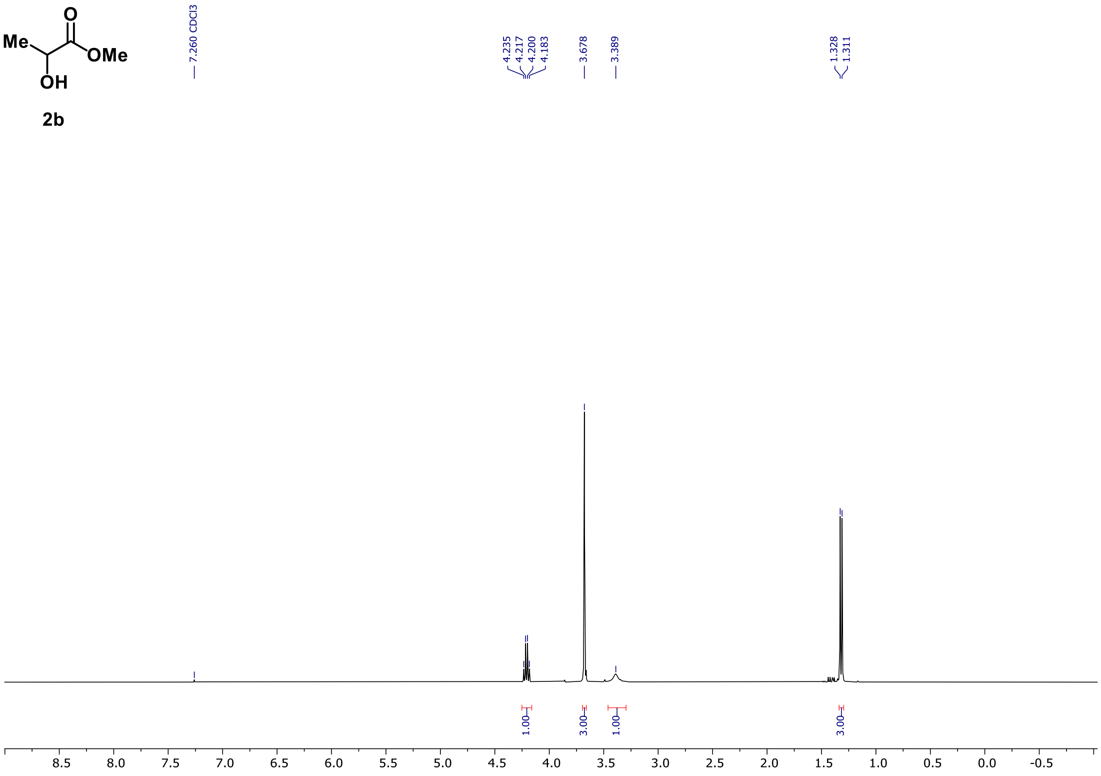

^1H NMR (400 MHz, $CDCl_3$)

2a


^{13}C NMR (100 MHz, $CDCl_3$)

2a

^{1}H NMR (400 MHz, CDCl$_3$)

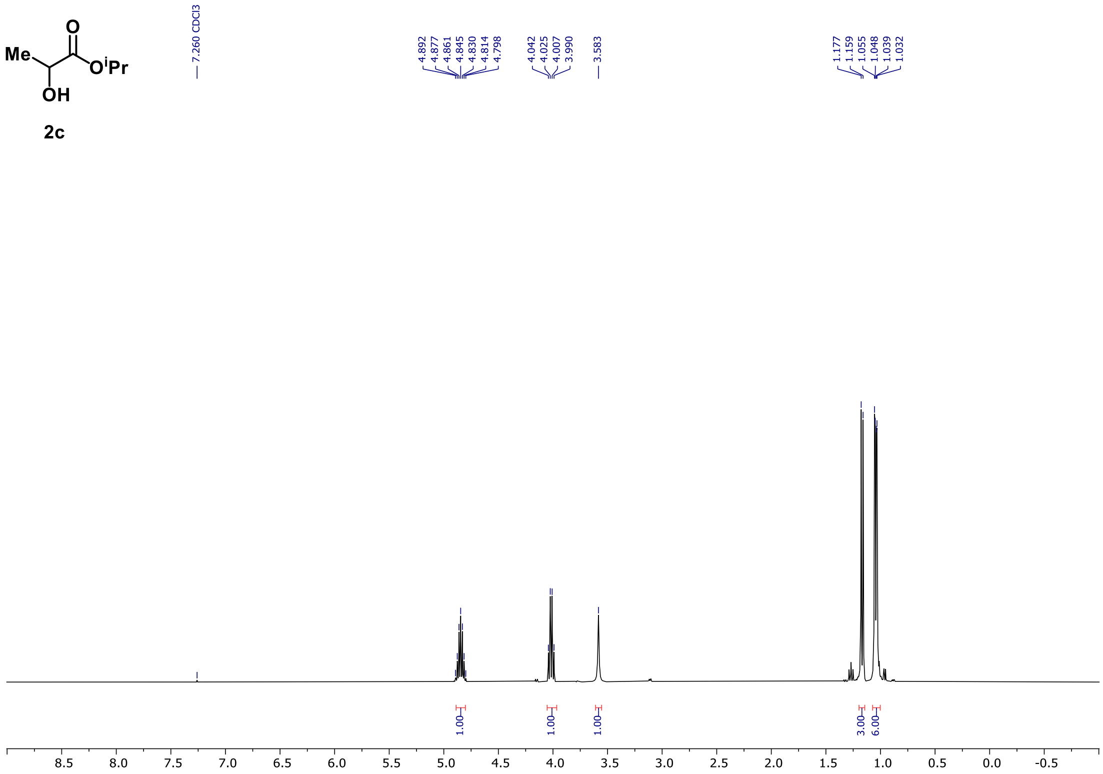


2b

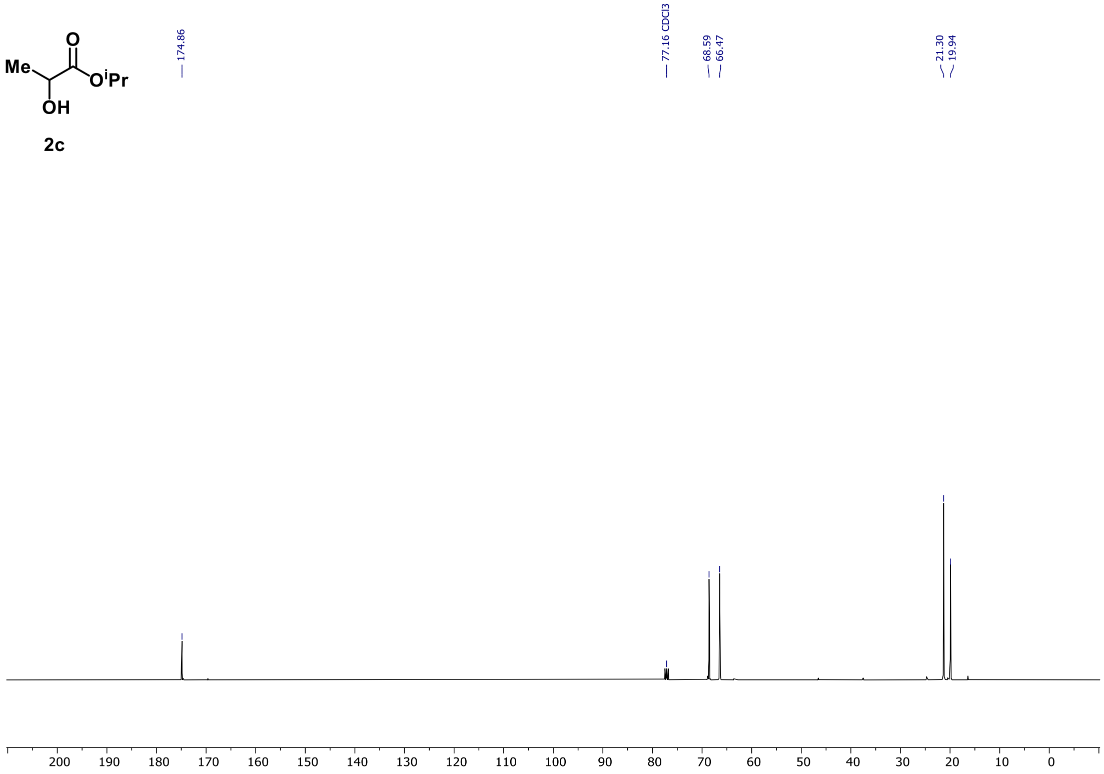
^{13}C NMR (100 MHz, CDCl$_3$)

2b

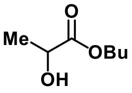
^{1}H NMR (400 MHz, CDCl$_3$)


2c

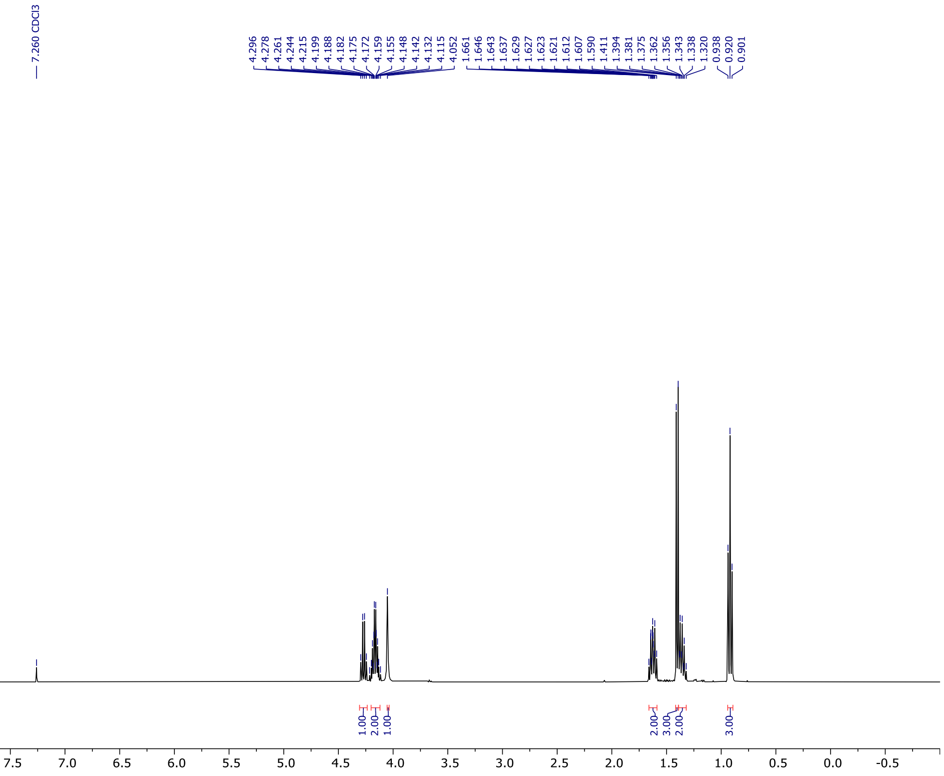
^{13}C NMR (100 MHz, CDCl$_3$)


2c

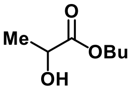
^{1}H NMR (400 MHz, CDCl$_3$)



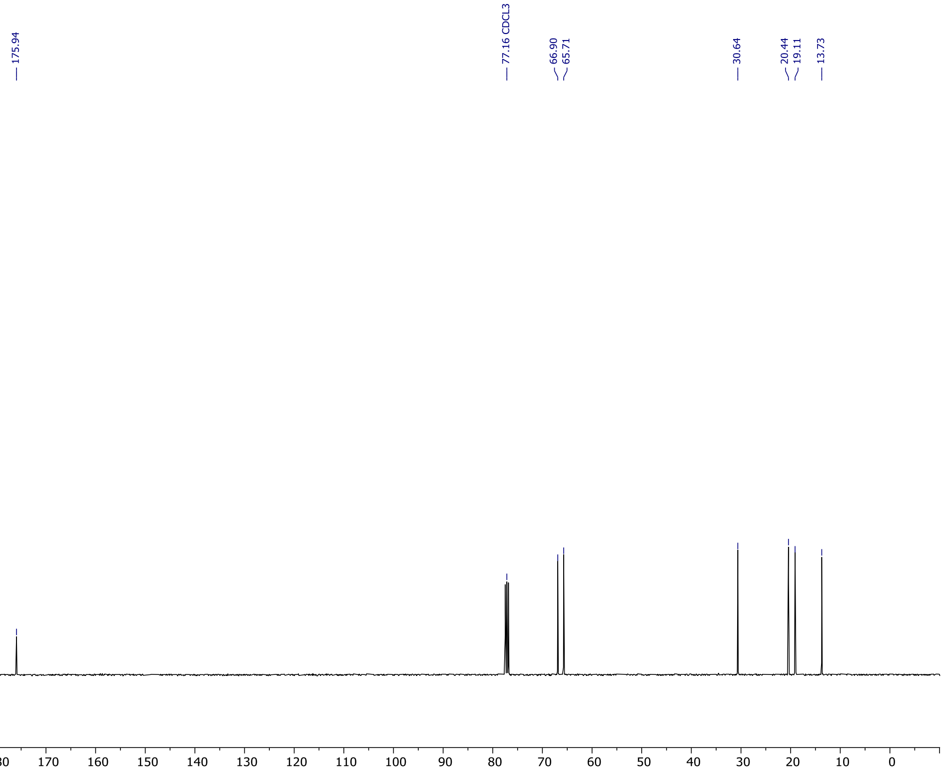
2d



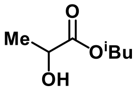
^{13}C NMR (100 MHz, CDCl$_3$)



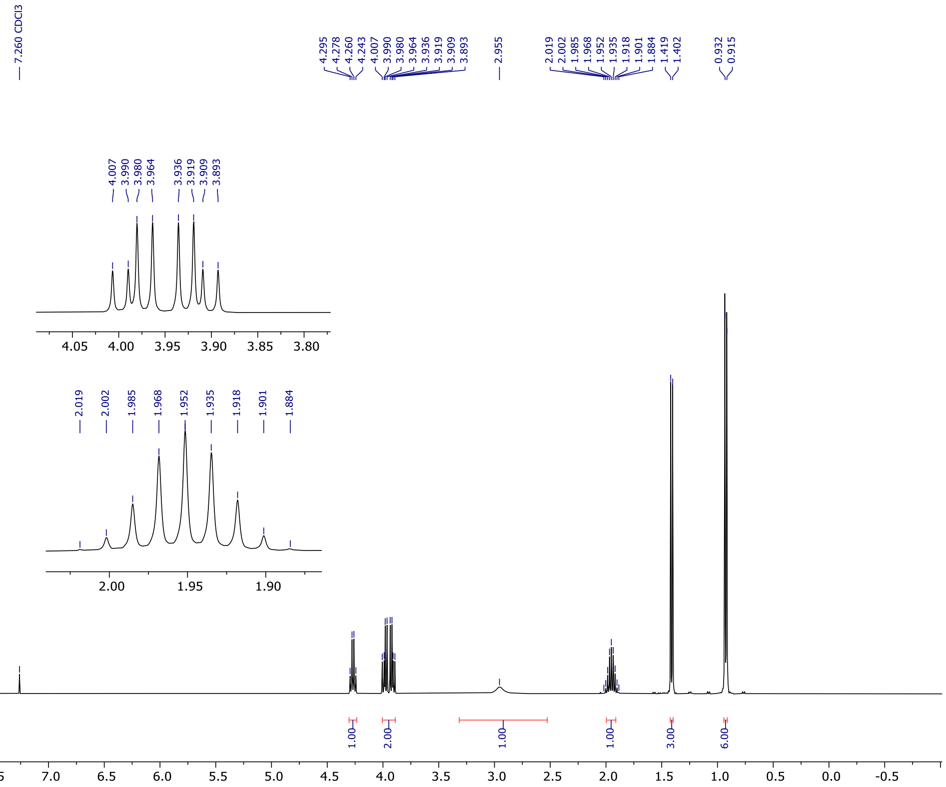
2d



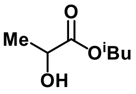
^{1}H NMR (400 MHz, CDCl$_3$)



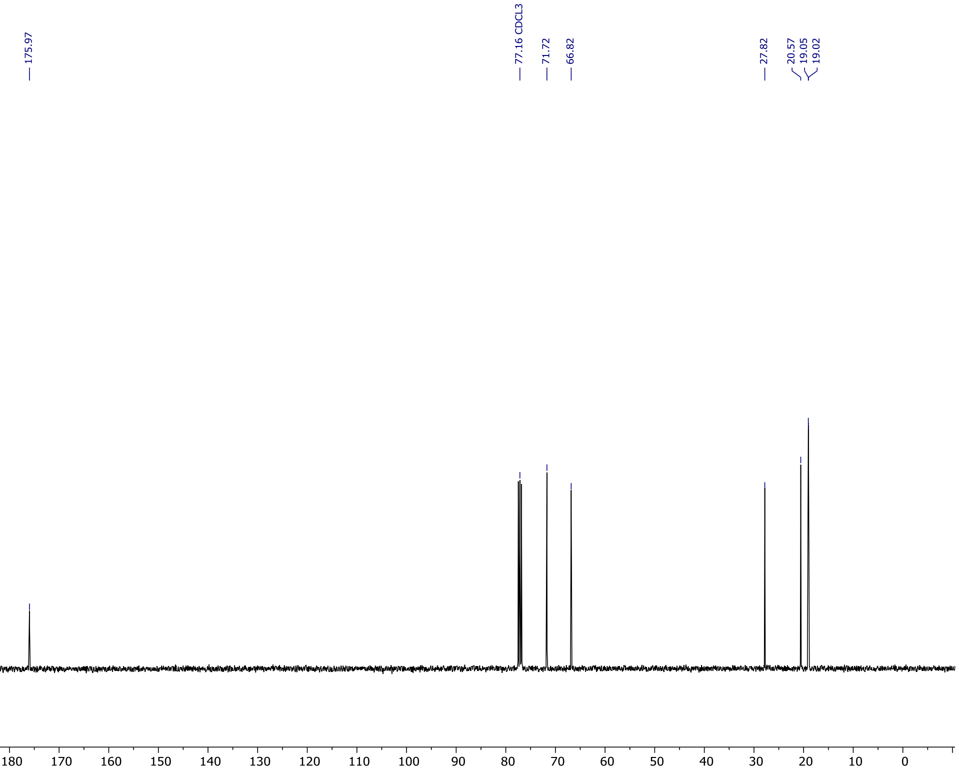
2e



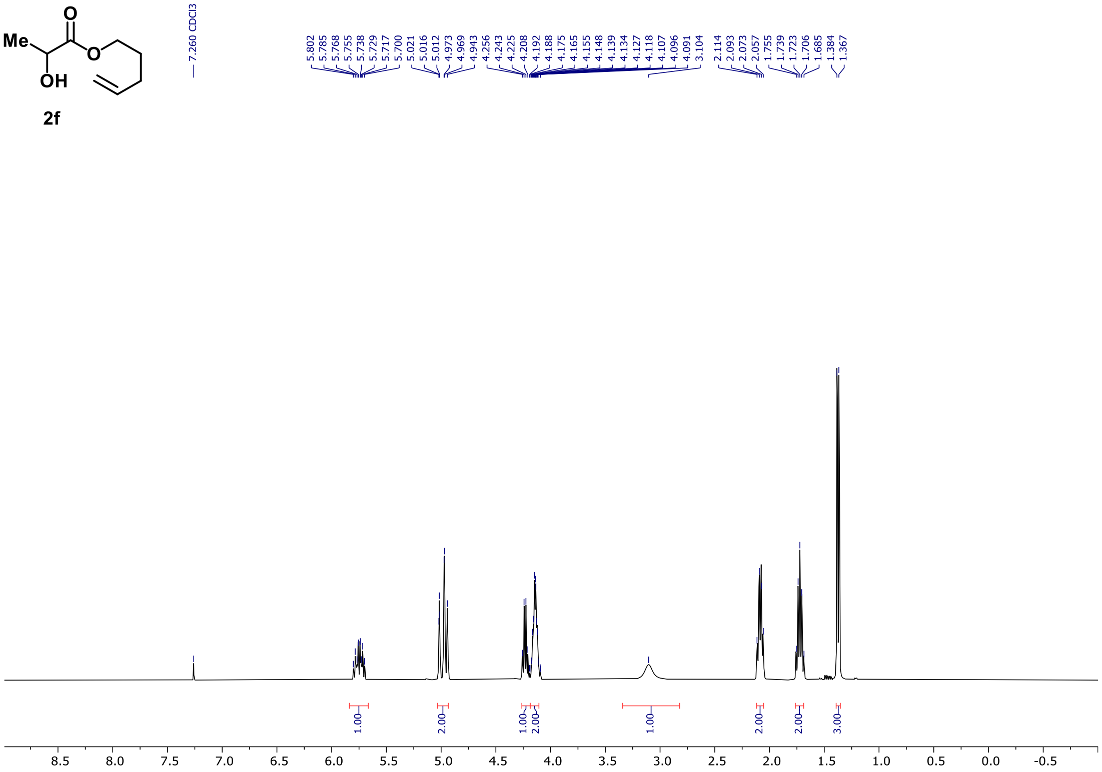
^{13}C NMR (100 MHz, CDCl$_3$)



2e

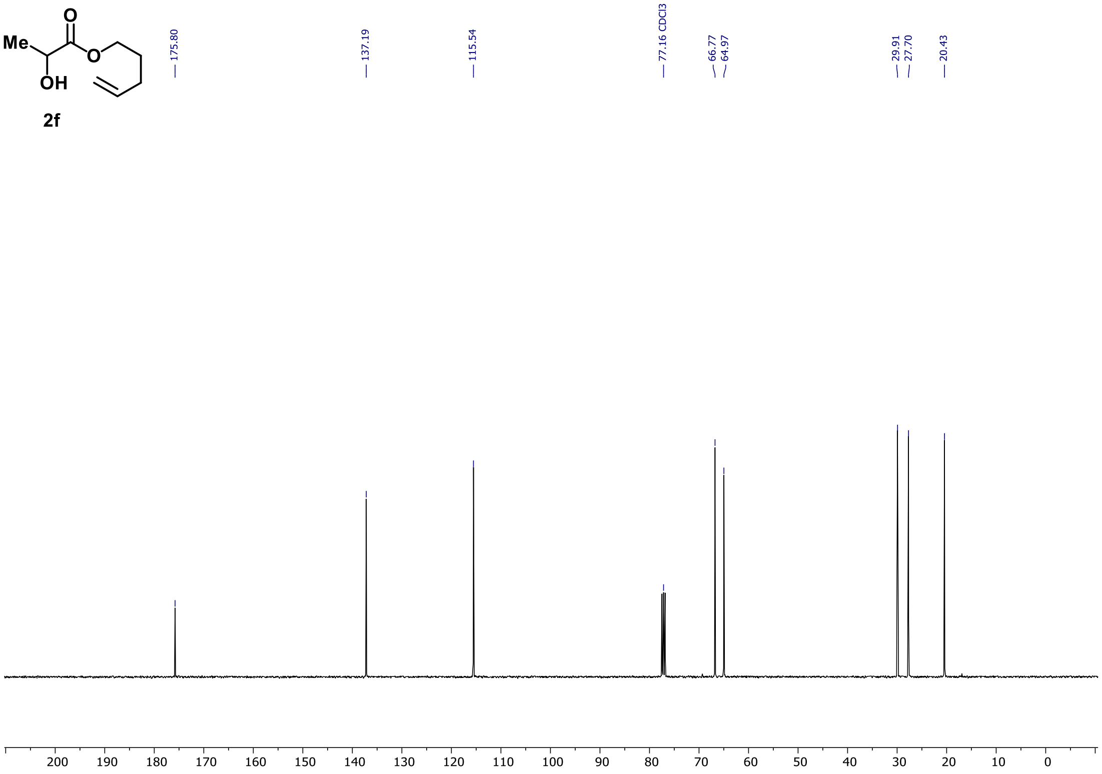


^{1}H NMR (400 MHz, CDCl$_3$)



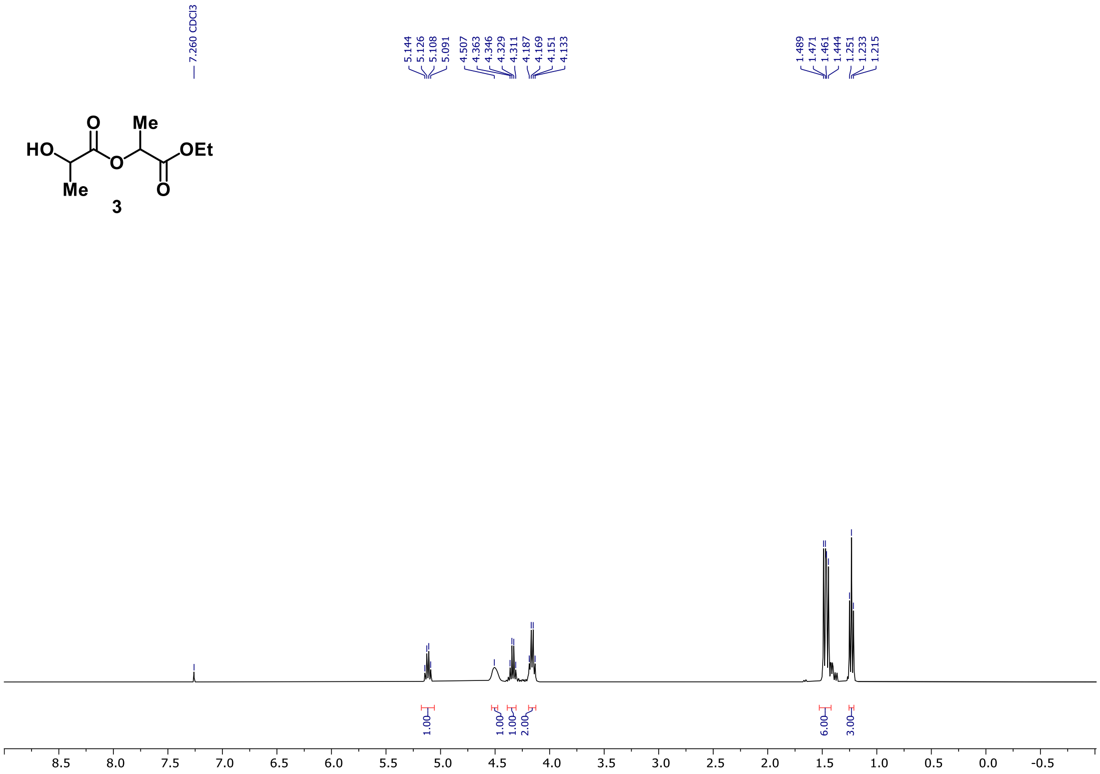
2f

^{13}C NMR (100 MHz, CDCl$_3$)

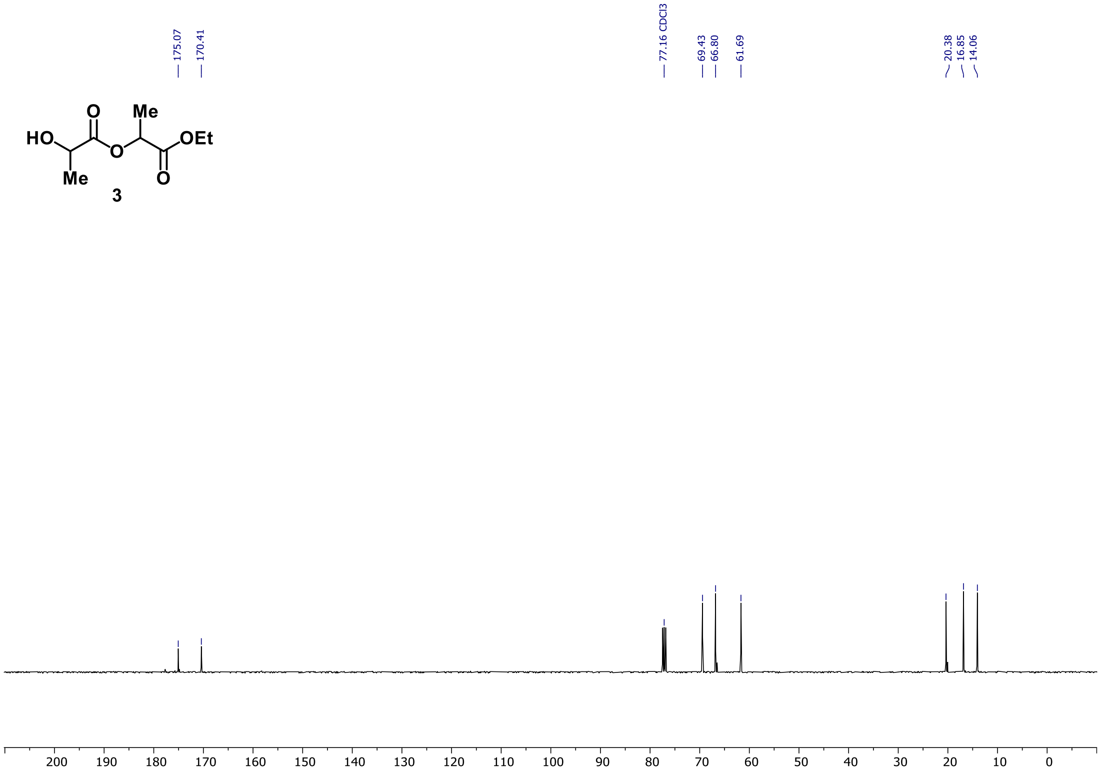


2f

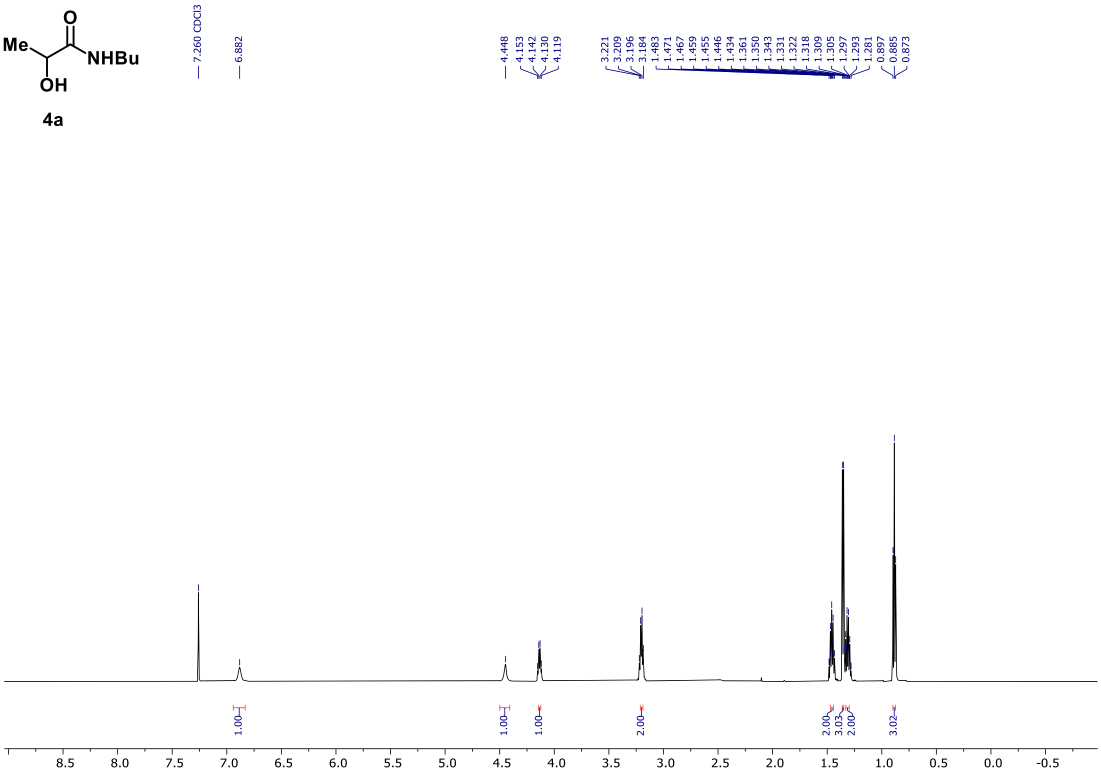
^{1}H NMR (400 MHz, $CDCl_3$)



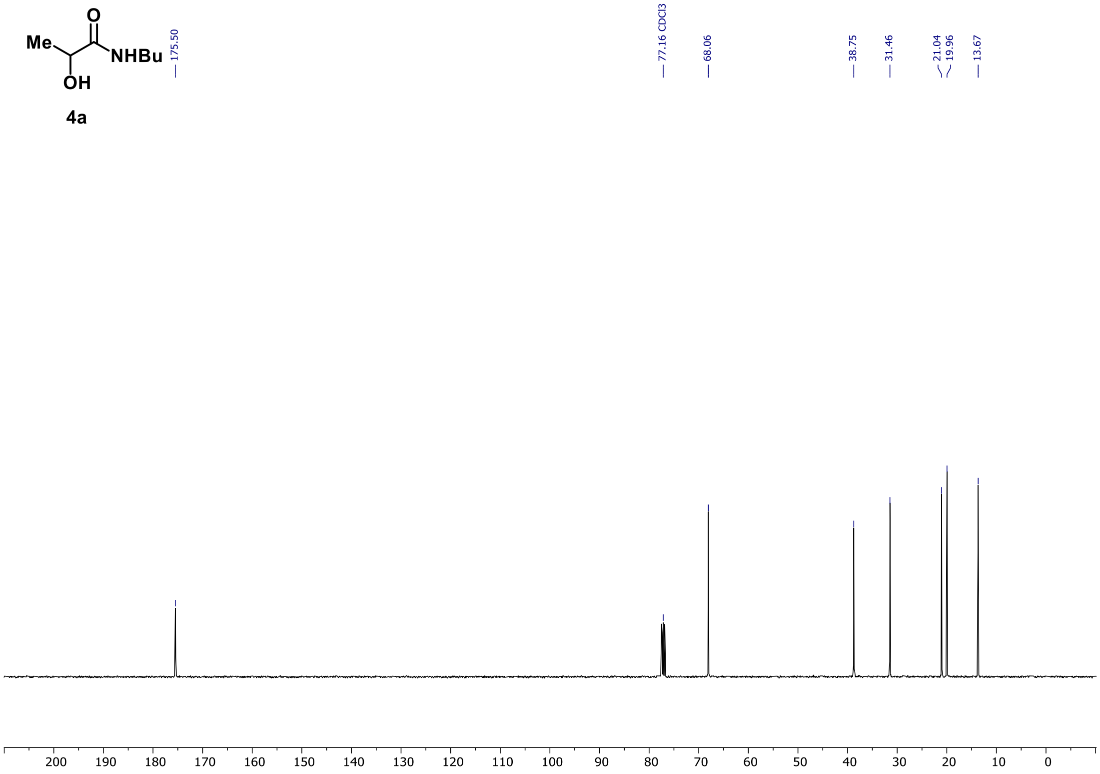
^{13}C NMR (100 MHz, $CDCl_3$)



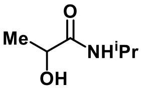
^{1}H NMR (400 MHz, CDCl$_3$)



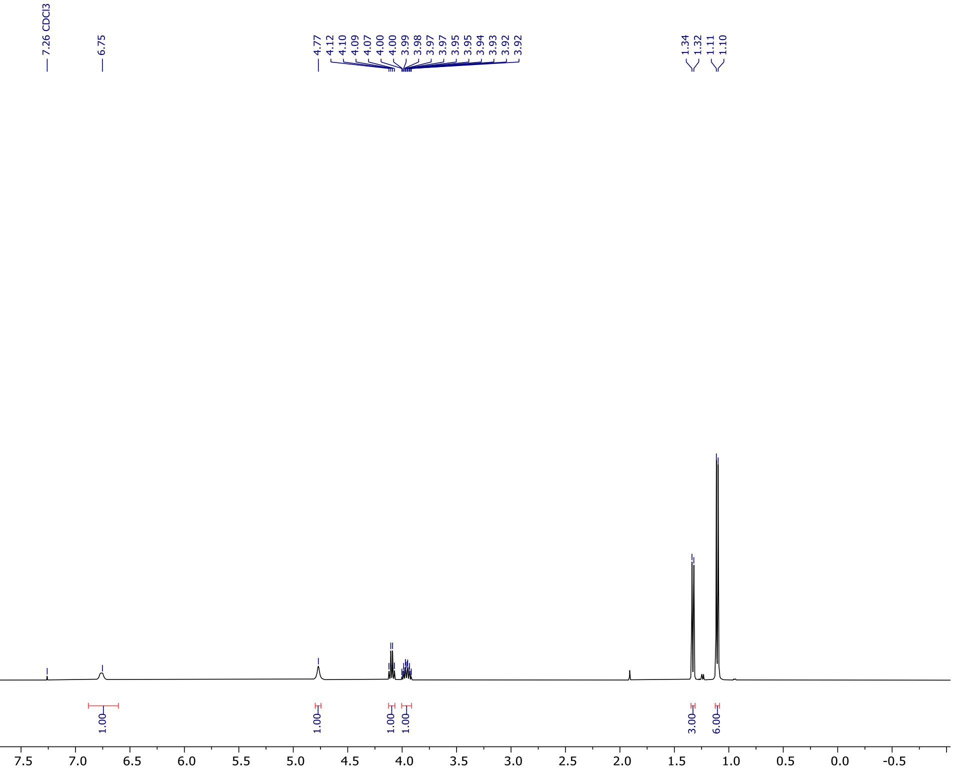
^{13}C NMR (100 MHz, CDCl$_3$)



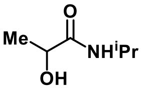
^{1}H NMR (400 MHz, $CDCl_3$)



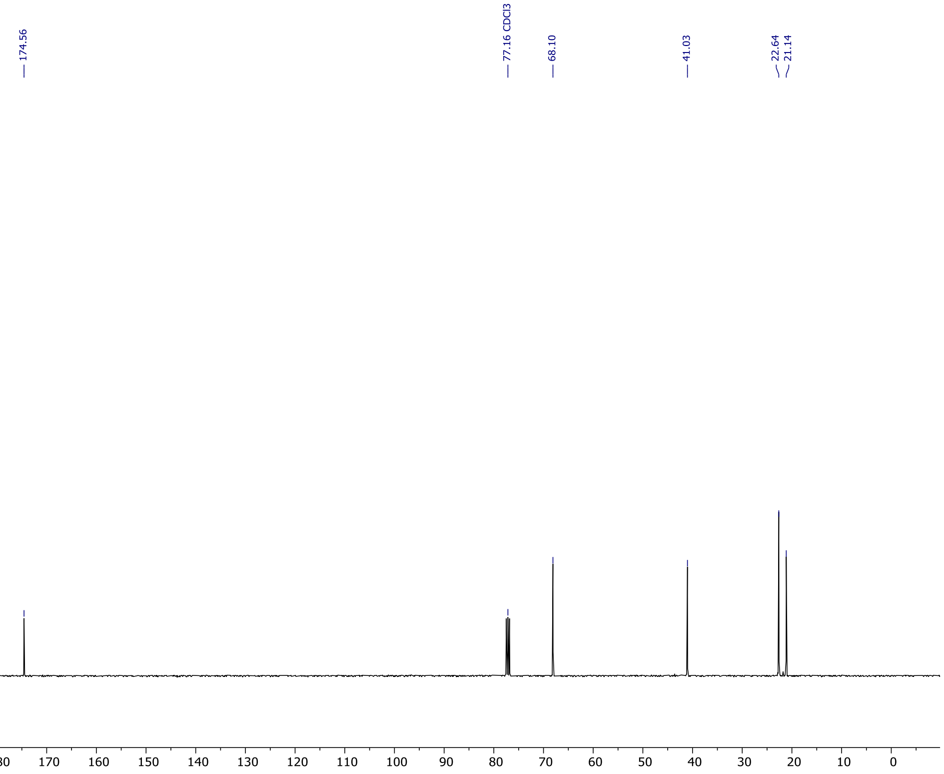
4b



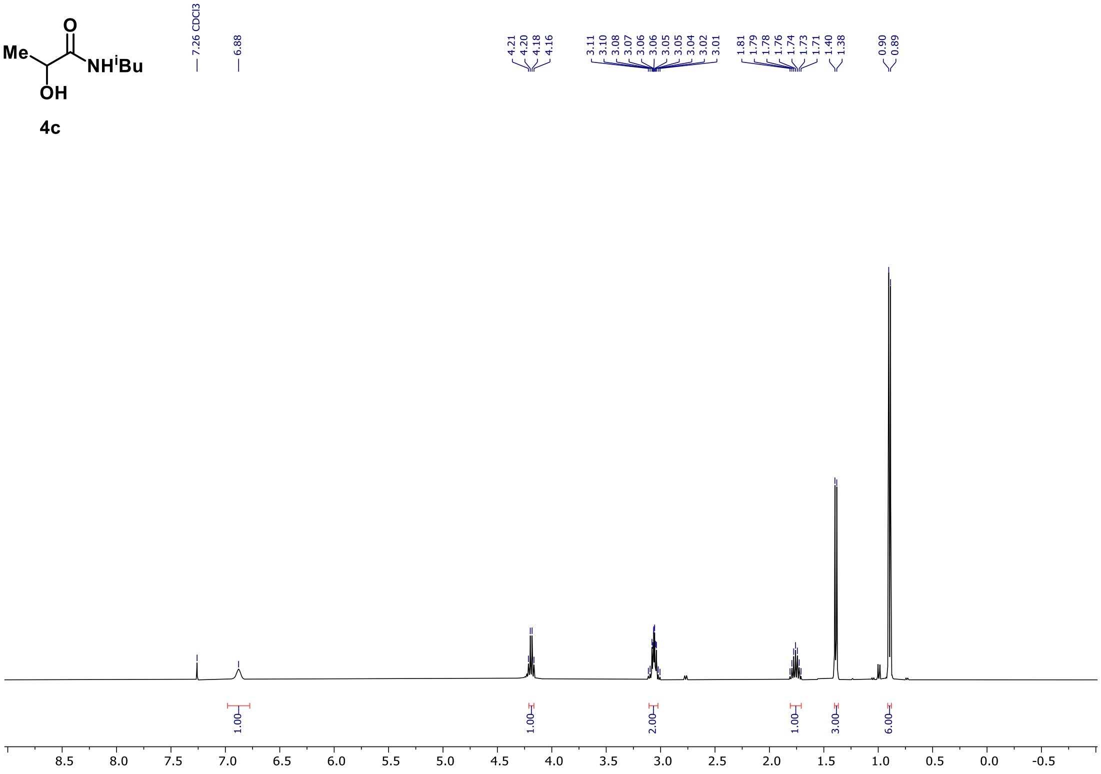
^{13}C NMR (100 MHz, $CDCl_3$)



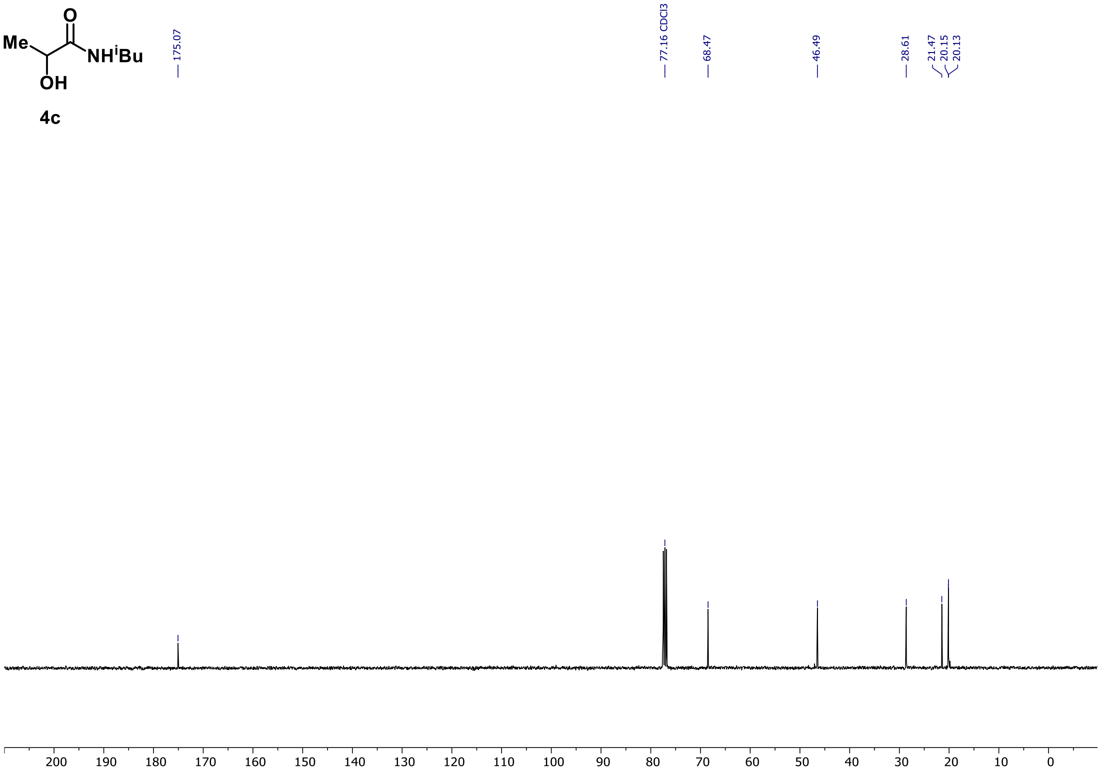
4b



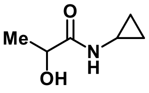
^{1}H NMR (400 MHz, $CDCl_3$)



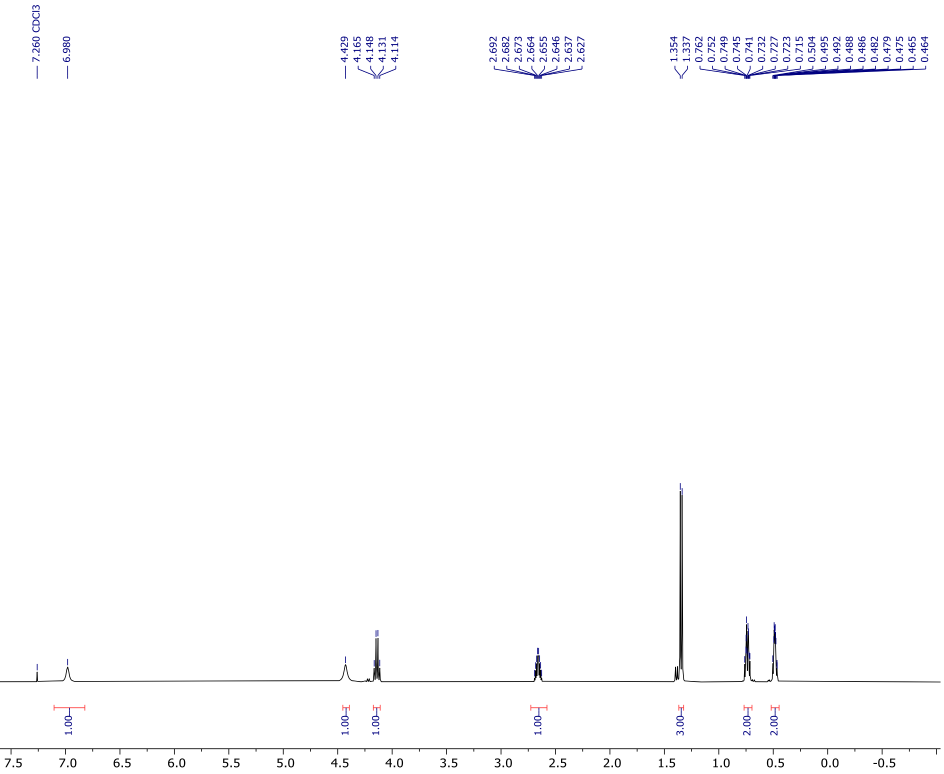
^{13}C NMR (100 MHz, $CDCl_3$)



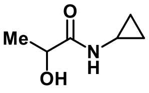
^{1}H NMR (400 MHz, CDCl$_3$)



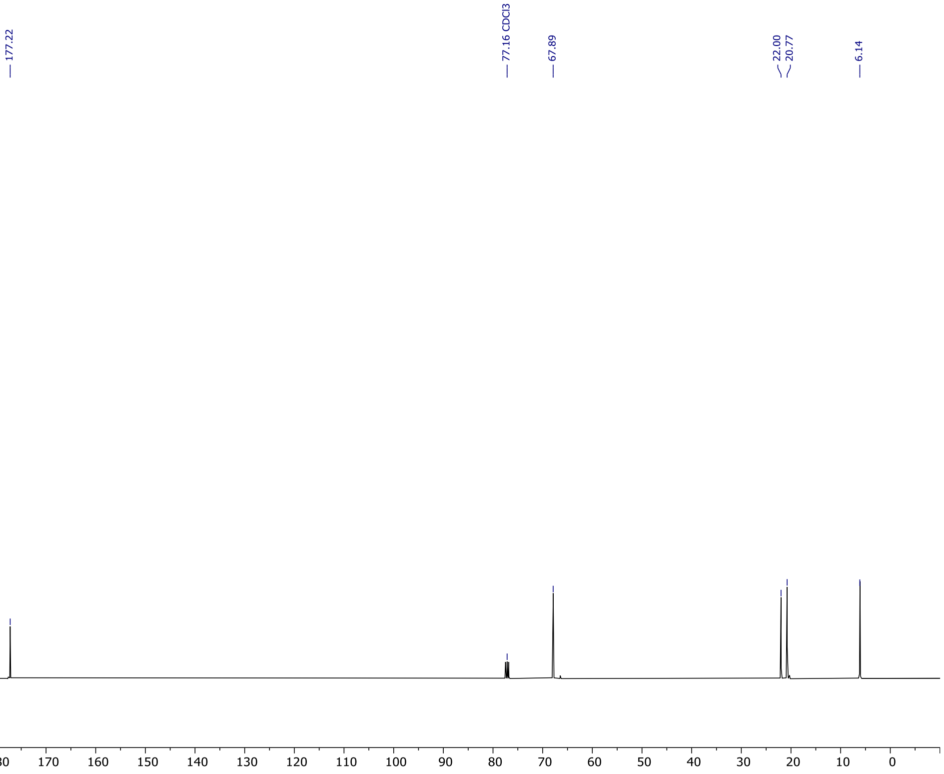
4d



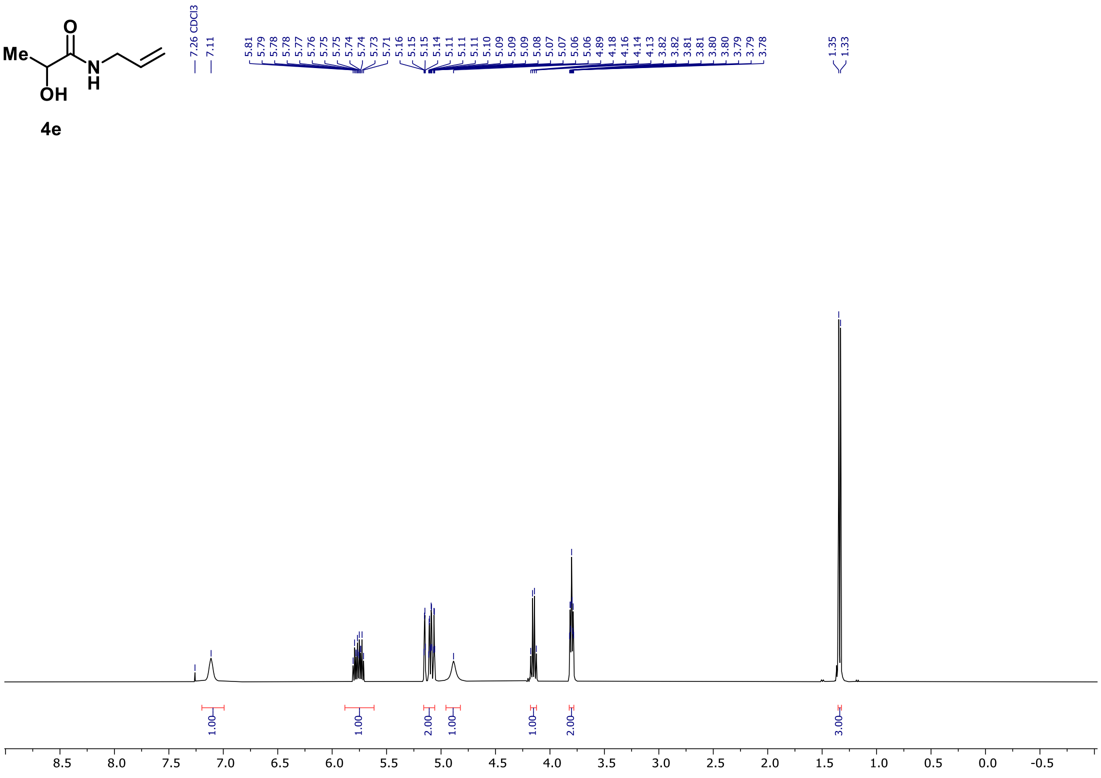
^{13}C NMR (100 MHz, CDCl$_3$)



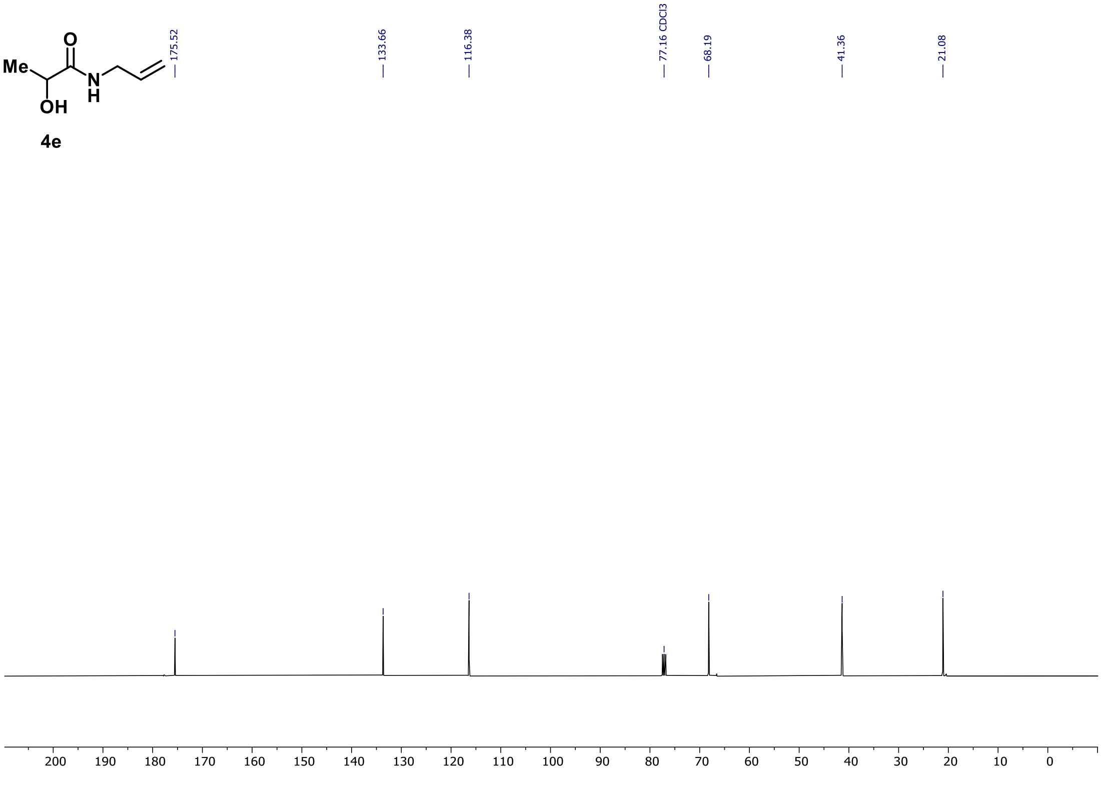
4d



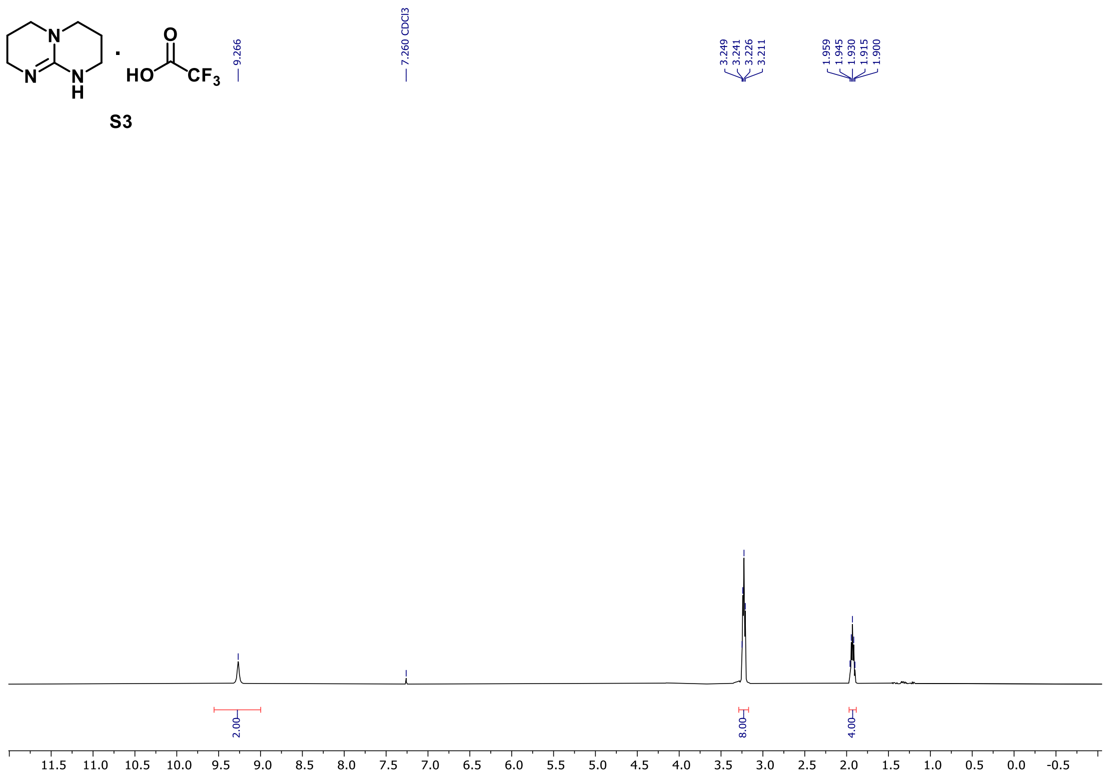
^{1}H NMR (400 MHz, $CDCl_3$)


4e

^{13}C NMR (100 MHz, $CDCl_3$)

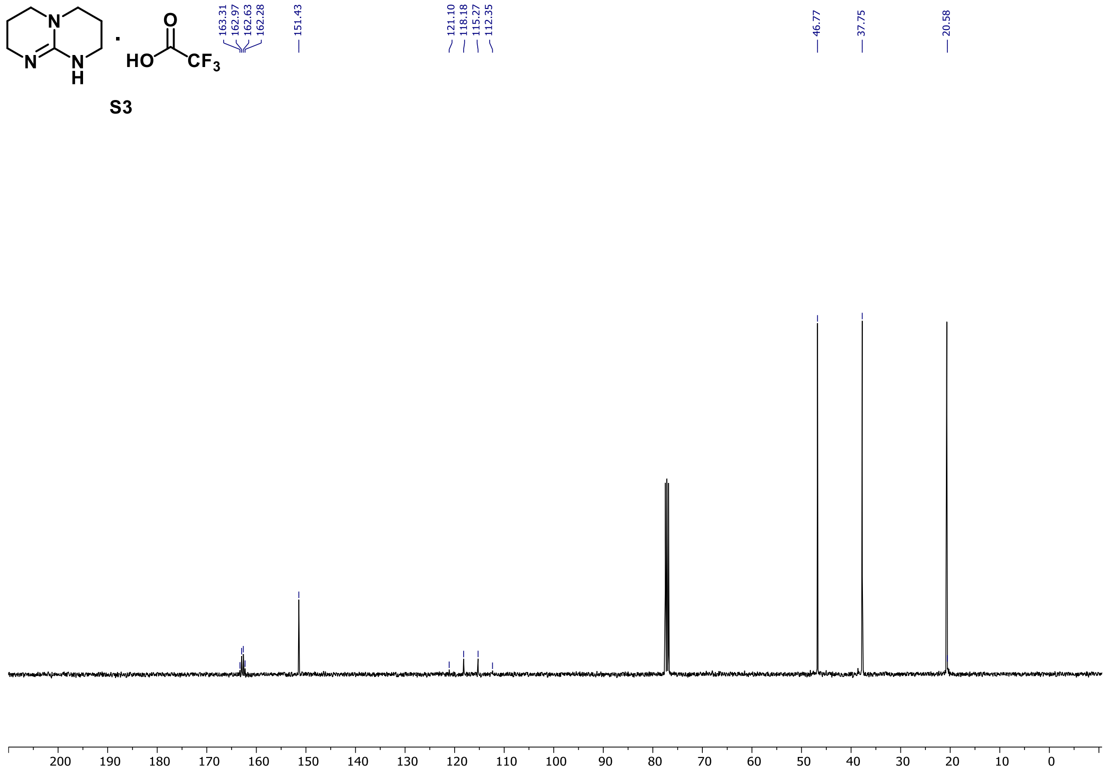

4e

^{1}H NMR (400 MHz, CDCl$_3$)



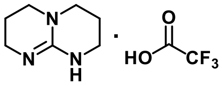
S3

^{13}C NMR (100 MHz, CDCl$_3$)



S3

^{19}F NMR (375 MHz, CDCl$_3$)



S3