Supporting information

Cyclic Allylic Carbonates as a Renewable platform for Protection Chemistry in Water

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Materials and methods

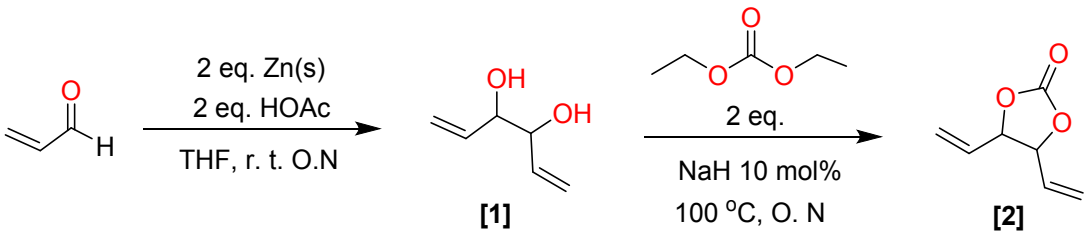
1.1 General

All reagents were purchased from commercial suppliers and used without additional purification unless otherwise noted. HPLC grade organic solvents and distilled water were used for all experiments.

1.2 NMR spectroscopy

1H NMR and 13C NMR spectra were recorded on a Bruker A scend spectrometer at 400 and 100 MHz, respectively, or a Bruker Avance spectrometer at 500 MHz. 1H NMR and 13C NMR spectra were internally calibrated with residual undeuterated solvent peaks (CHCl3: δ 7.26 for 1H NMR and δ 77. 16 for 13C NMR; DMSO-d6: δ 2.50 for 1H NMR and δ 39.52 for 13C NMR; CHD2OD: δ 3.31 for 1H NMR and δ 49.00 for 13C NMR; CHD2CN: δ 1.94 for 1H NMR). Chemical shifts (δ) are reported in ppm and peak multiplicity is designated as s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), and dt (doublet of triplets).

1.3 Synthesis of compounds

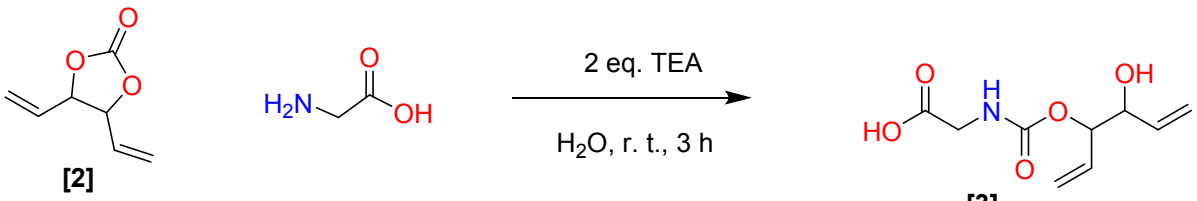


[1], 1,5-Hexadiene-3,4-diol, mixture of (±) and meso. The applied synthetic procedure was inspired by the reductive coupling developed by Hekmatshoar[1] and applied by Trost et al.[2] for the synthesis of 1,5-Hexadiene-3,4-diol, mixture of (±) and meso with some alterations. Acrolein (45 ml, 0.674 mol) was dissolved in 400 ml THF, followed by addition of acetic acid (50 ml, 0.841 mol). The solution was stirred for 5 minutes followed by rapid addition of granulated Zink(0) (50g, 0.765) ,the solution was left to stir over night (18 h). The crude reaction mixture was filtered the and the solute was concentrated followed by distillation to yield 33.1 g (88 %) of the desired product at a purity of 90 % as determined from ^{1}H NMR. The target compound was used without any further purification. ^{1}H (400 MHz, CDCl3): δ 5.94-5.84 (m, 2H), 5.42-5.24 (m, 4H), 4.25-4.00 (m,2H)

[2], Cis-1,2-divinylethylene carbonate and trans-1,2-divinylethylene carbonate (DVC). The synthesis of 1,2-divinylethylene carbonate was performed in accordance with the procedure developed by Braun with some alterations.[3] 1,5-Hexadien-3,4-diol (8 g, 70 mmol) was dissolved in diethyl carbonate (17 ml, 140 mmol) together with 10 mol% of NaH, 60% in a mineral oil dispersion (0.29 g, 7 mmol in a 50 ml round bottom flask and equipped with a reflux-condenser. The reaction mixture was left at 100 °C over-night followed by distillation yielding 9.1 g (79 %) of DVC at a purity 95 % as determined by ^{1}H NMR. ^{1}H (400 MHz, CDCl3): δ 5.81-5.70 (m, 2H), 5.47 (d,2H), 5.42 (d, 2H), 5.19-5.13 (m 2H).

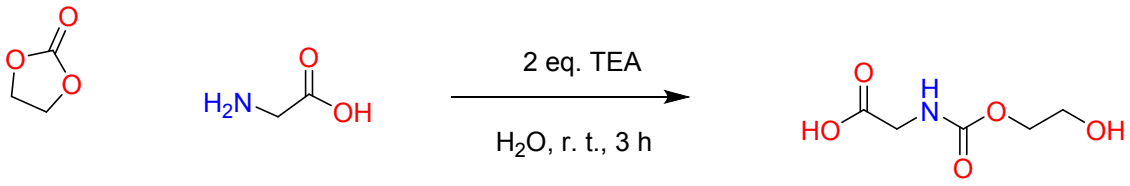
Ring opening of cyclic carbonates with amine nucleophiles in water

In a typical reaction; desired amount of glycine (210 mg, 2.8 mmol) was dissolved in 1 ml H_2O in a 5 ml vial equipped with a magnetic stirrer. After 5 minute TEA (0.2 ml, 1.4 mmol) was added to the solution and let to stir for 10 minutes. The stirring rate was increases and the desired carbonate (0.7 mmol) was added in one shot at ambient temperature. The reaction was let to proceed for 2h, followed by direct precipitation in 20 ml a THF:MeOH 3:1 mixture. The solute was collected and concentrated giving the desired carbamate as a TEA-adduct. In order to remove the TEA the product was passed through a silica-plug, EtOAc:AcOH 20:1, giving the carbamate



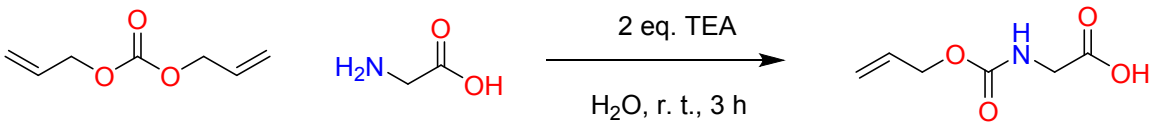
[2] **[3]**

[3], Cis and Trans (((4-hydroxyhexa-1,5-dien-3-yl)oxy)carbonyl)glycine (DVC-GLY) . Procedure according to above, TEA-adduct (0.63:1) 152 mg (yield 95% as a yellow oil), after silica-plug 100 mg (yield 81 % as a yellow oil) ^{1}H NMR. ^{1}H (400 MHz, D_2O): δ 5.97-5.85 (m, 2H), 5.40-5.29 (m, 4H), 5.17-5.11 (m, 1H), 5.39-5.31 (m, 1H), 3.93 (d, 2H). ^{13}C NMR (100 MHz, MeOD-d4): 172.4, 157.3, 136.8, 133.7, 132.4, 117.2, 117.1, 116.1, 78.2, 77.9, 74.1, 73.9, 42.0 HRMS (ESI): calculated for C9H13NO5Na: 238.0691; found 238.0686



[4]

[4], ((2-hydroxyethoxy)carbonyl)glycine Procedure according to above, TEA-adduct (0.40:1) 149 mg (yield 95 % as a transparent oil), after silica-plug 97 mg (yield 83 % as a transparent oil) after purification through the silica plug it was observed the formation of a side product constituting of the condensation reaction between the carboxylic acid and the primary alcohol ^{1}H (400 MHz, 1:1 D_2O:MeOD mixture): δ 4.12 (t, 2H), 3.82 (s, 2 H), 3.71 (t, 2 H), ^{13}C NMR (100 MHz, MeOD-d4): 173.7, 159.2, 67.7, 61.4, 43.1 HRMS (ESI): calculated for C5H9NO5Na: 186.0378; found 186.0375

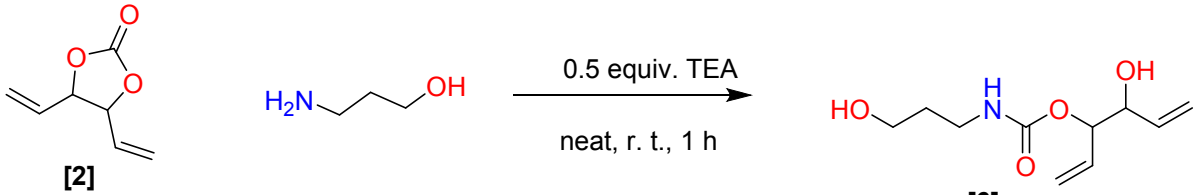


[5]

[5], ((allyloxy)carbonyl)glycine. Procedure according to above, TEA-adduct (0.40:1) 88 mg (yield 25 % as a transparent light-yellow oil). ^{1}H (400 MHz, MeOD-d4): δ 5.94 (ddt, 1H), 5.27 (m, 2 H), 4.56 (dd, 2 H), 3.19 (q, 2.4 H), 1.29 (t, 3.6 H), ^{13}C NMR (100 MHz, MeOD-d4): 175.9, 159.2, 133.7, 118.2, 66.8, 47.7, 44.0, 9.2.

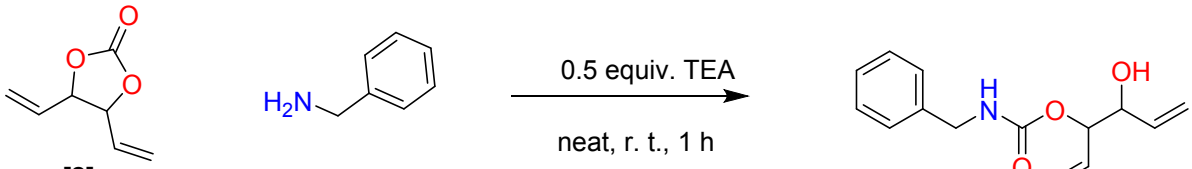
Ring opening of cyclic carbonates with amine nucleophiles under neat conditions

In a typical reaction, the desired amount of amine (2.8 mmol) was added in a 5 ml vial equipped with a magnetic stirrer followed by addition of TEA (0.2 ml, 1.4 mmol). The stirring rate was increases and the desired carbonate (1.4 mmol) was added in one shot at ambient temperature. The reaction was let to proceed for 1h. The reaction mixture was diluted in 40 ml of EtOAc and washed thrice with both brine and 1 M HCL. The organic layer was dried with Na_2SO_4 for 15 minutes and concentrated under vacuum to yield the desired compound.



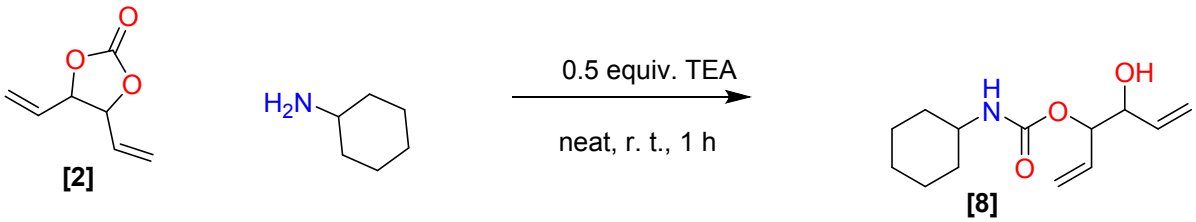
[2] **[6]**

[6] 4-hydroxyhexa-1,5-dien-3-yl (3-hydroxypropyl)carbamate. Procedure according to above 150 mg (yield 49 % as a transparent oil). ^{1}H (400 MHz, MeOD-d4): δ 5.88 (m, 2H), 5.25 (m, 4H), 5.07 (m, 1H), 4.14 (m, 1H), 3.59 (t, 2H), 3.19 (t, 2H), 1.71 (p, 2H), ^{13}C NMR (100 MHz, MeOD-d4): 158.6, 138.3, 138.2, 135.4, 135.1, 118,3, 118.1, 117.4, 117.3, 78.9, 78.7, 75.6, 75.1, 60.6, 39.0, 33.9.



[2] **[7]**

[7] 4-hydroxyhexa-1,5-dien-3-yl benzylcarbamate. Procedure according to above 220 mg (yield 62 % as a transparent oil). ^{1}H (400 MHz, MeOD-d4): δ 7.28 (m, 5H), 5.89 (m, 2H), 5.23 (m, 5H), 4.29 (s, 2H), 4.15 (m, 1H), ^{13}C NMR (100 MHz, MeOD-d4): 158.6, 140.8, 138.3, 135.4, 135.1, 129.7, 128.5, 128.4, 128.3, 118.4, 118.2, 117.5, 117.3, 79.1, 78.9, 75.6, 75.1, 45.7.

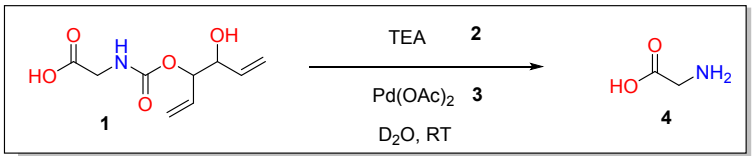


[2] [8]

[8] 4-hydroxyhexa-1,5-dien-3-yl cyclohexylcarbamate. Procedure according to above 210 mg (yield 61 % as a transparent yellow oil). ^{1}H (400 MHz, MeOD-d4): δ 5.87 (m, 2H), 5.25 (m, 5H), 4.13 (m, 1H), 3.36 (m, 1H), 1.78 (m, 4H), 1.62 (m, 1H), 1.26(m, 5H); ^{13}C NMR (100 MHz, MeOD-d4): 157.5, 138.1, 135.3, 134.9, 118.1, 117.9, 117.1, 117.0, 78.6, 78.3, 75.4, 74.9, 51.3, 34.1, 26.6, 26.2, 26.1.

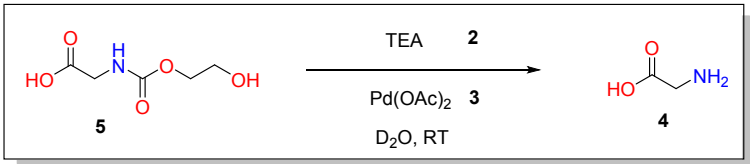
Deprotection of DVC-GLY with $Pd(OAc)_2$ with TEA in water

Table S1. Optimization of the deprotection conditions



1 4

Entry	1 (M)	1:2:3	Yield.4 [%]	$rate^{in.}$ (M*s^{-1})*10^6
[1]	0.16	[1.0]:**[0.6]**:[0.13]	<5[a] (17)[b]	0.7
[2]	0.16	[1.0]:**[0.9]**:[0.13]	<5 (25)	0.9
[3]	0.16	[1.0]:**[1.4]**:[0.13]	20 (92)	3.4
[4]	0.16	[1.0]:**[2.4]**:[0.13]	23 (>95)	5.4
[5]	0.16	[1.0]:**[5.4]**:[0.13]	23 (>95)	5.8
[6]	0.16	[1.0]:**[10.8]**:[0.13]	26 (>95)	6.2
[7]	0.16	[1.0]:[5.4]:**[0.03]**	<5 (38)	0.6
[8]	0.16	[1.0]:[5.4]:**[0.06]**	9 (72)	1.6
[9]	0.16	[1.0]:[5.4]:**[0.13]**	23 (>95)	5.8
[10]	0.16	[1.0]:[5.4]:**[0.22]**	72 (>95)	28
[11]	0.16	[1.0]:[5.4]:**[0.38]**	91[c] (>95)[d]	73

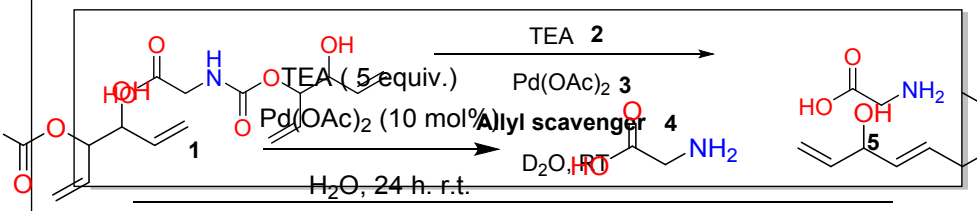


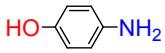
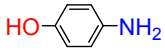
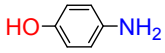
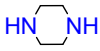
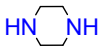
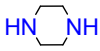
5 4

Entry	5 (M)	5:2:3	Yield.4 [%]	$rate^{in.}$ (M*s^{-1})*10^6
[12]	0.16	[1.0]:[5.4]:[0.13]	0[a] (0)[b]	no reaction

Reaction conditions; 1 equiv. of 1 with different amount of 2 and 3 at ambient temperature in D_2O.
[a] after 2h, [b] after 48 h, [c] after 1 h, [d] after 1.5 h

Table S2. Optimization of the deprotection conditions - allyl scavenger



Entry	1 (M)	Allyl scavenger. 4	1:2:3:4	Yield.5 [%]
[1]	0.16		[1.0]:[6.0]:[0.02]:[**1.0**]	2[a] (4)[b]
[2]	0.16		[1.0]:[6.0]:[0.02]:[**4.8**]	3 (5)
[3]	0.16		[1.0]:[6.0]:[0.02]:[**10.0**]	3 (6)
[4]	0.16		[1.0]:[6.0]:[0.02]:[**1.0**]	3 (5)
[5]	0.16		[1.0]:[6.0]:[0.02]:[**5.5**]	3 (5)
[6]	0.16		[1.0]:[6.0]:[0.02]:[**17.5**]	3 (6)
[7]	0.16		[1.0]:[6.0]:[0.02]:[**3.0**]	3 (15)
[8]	0.16		[1.0]:[6.0]:[0.02]:[**15.0**]	5 (19)
[9]	0.16		[1.0]:[6.0]:[0.02]:[**24.0**]	7 (24)

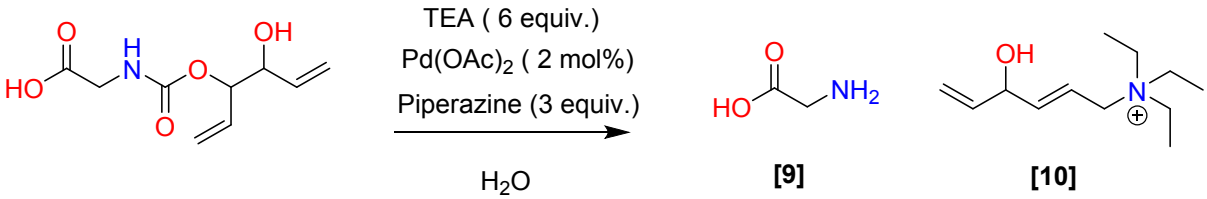
Reaction conditions; 1 equiv. of 1 with different amount of 2, 3 and 4 at ambient temperature in D_2O. [a] after 0.5 h [b] after 2h

In a typical **[4]** reaction; 1.6 desired (72 amount of mmol) (340 mg, 9 ml mmol) and $Pd(OAc)_2$ ml vial mg, 0.16 with a was dissolved in H_2O in a 20 After equipped TEA magnetic mmol) stirrer. to the 5 minutes (1.15 ml, 8 was added The reaction was mixture. reaction let to 24 h, proceed for followed by direct

precipitation in 100 ml a THF:MeOH 3:1 mixture.

The filtrate contained the contained compound **[5] (**off-white solid, 108mg, isolated yield 90%), the solute was concentrated, dissolved in the smallest amount of MeOH and diluted in 20 ml of DCM and left in the freezer for three days. The formed precipitate contained compound **[6]** (brown viscous oil, 127 mg, yield 40 %)

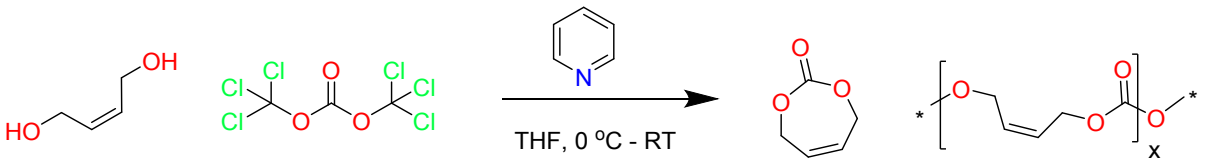
Deprotection of DVC-GLY with $Pd(OAc)_2$ with TEA in water with Piperazine



In a typical reaction; desired amount of **[4]** (34 mg, 0.16 mmol) and $Pd(OAc)_2$ (1.4 mg, 0.032 mmol) and Piperazine (41mg, 0.48 mmol) was dissolved in 0.85 ml H_2O in a 5 ml vial equipped with a magnetic stirrer. After 5 minutes TEA (0.14 ml, 1 mmol) was added to the reaction mixture. The reaction was let to proceed at the desired time and temperature, followed by direct analysis with NMR.

Ring-Closing evaluation

Seven-Membered Carbonate



Scheme S1. Ring-closing or oligomerization of (Z)-but-2-ene-1,4-diol with triphosgene.

The reaction was adapted from a procedure describe by K.S. Bisht et al. for the synthesis of a tartaric acid derived seven membered cyclic carbonate.[4,5]

Triphosgene (1 mmol, 0.297 g) was dissolved in dry THF (10 mL), the solution is added dropwise over 30 minutes to a mixture of (Z)-but-2-ene-1,4-diol (0.02 mol, 0.176 g) and pyridine (12 m mol, 0.949 g) dissolved in 20 mL in THF at 0 °C. After complete addition the solution was stirred in ambient temperature for 6 h. After reaction the precipitated pyridine hydrochloride was filtered off, and the filtrate was concentrated under reduced pressure at ambient temperature. The crude product was analyzed by both UHPLC and ^{1}H-NMR, see **figure S1** and **S2**.

UHPLC Data.

The analysis was performed on a 3 min run with C18 collum with 5-95 H_2O, MeCN gradient. The retention time for the oligomers was seen at around 0.45 min.

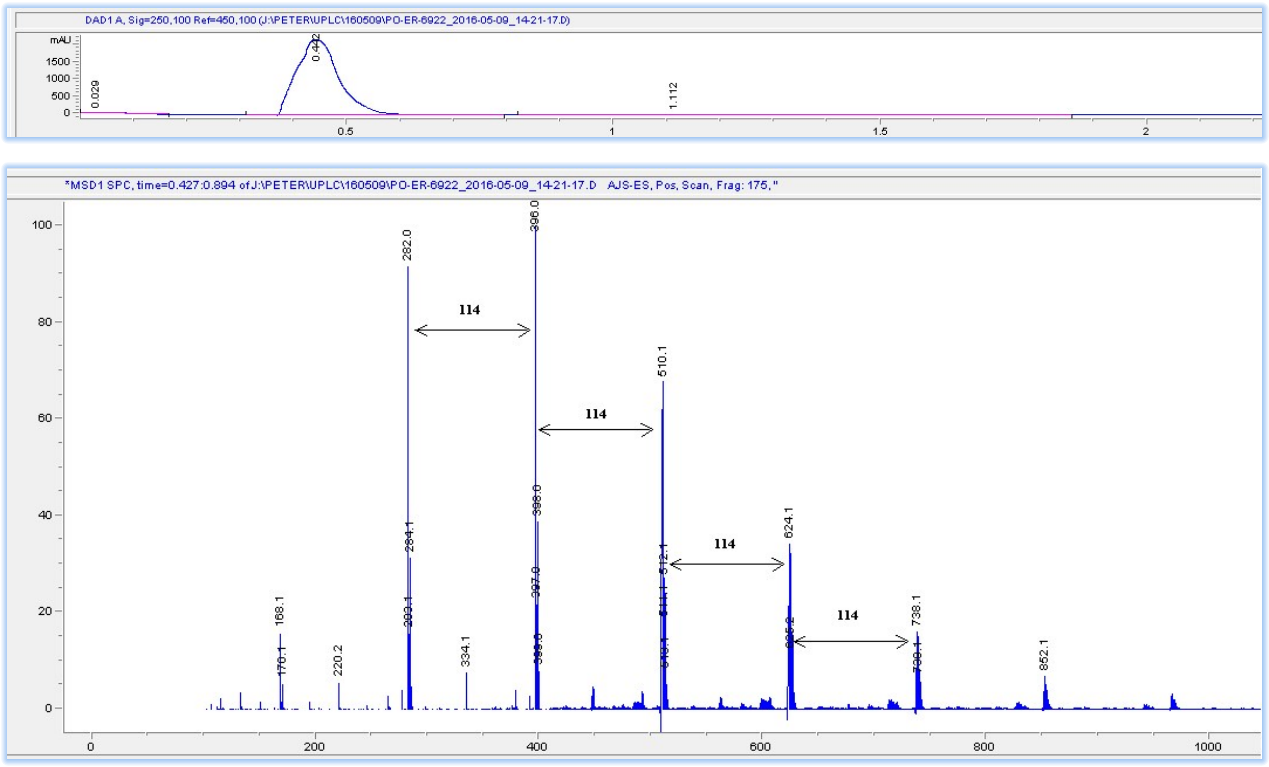


Figure S1. Show the UHPLC data of the crude mixture obtained from the attempted ring-closing reaction between (Z)-but-2-ene-1,4-diol and triphosgene. This shows a repeating unit mass of 114, which corresponds to depicted oligomeric structure in **Scheme 1**. Where

The UHPLC data reveals the repeating unit mass of 114, which corresponds to depicted repeating unit structure. It is also seen the isotopic pattern corresponding to chloride adduct. The oligomers range from 1-7 units.

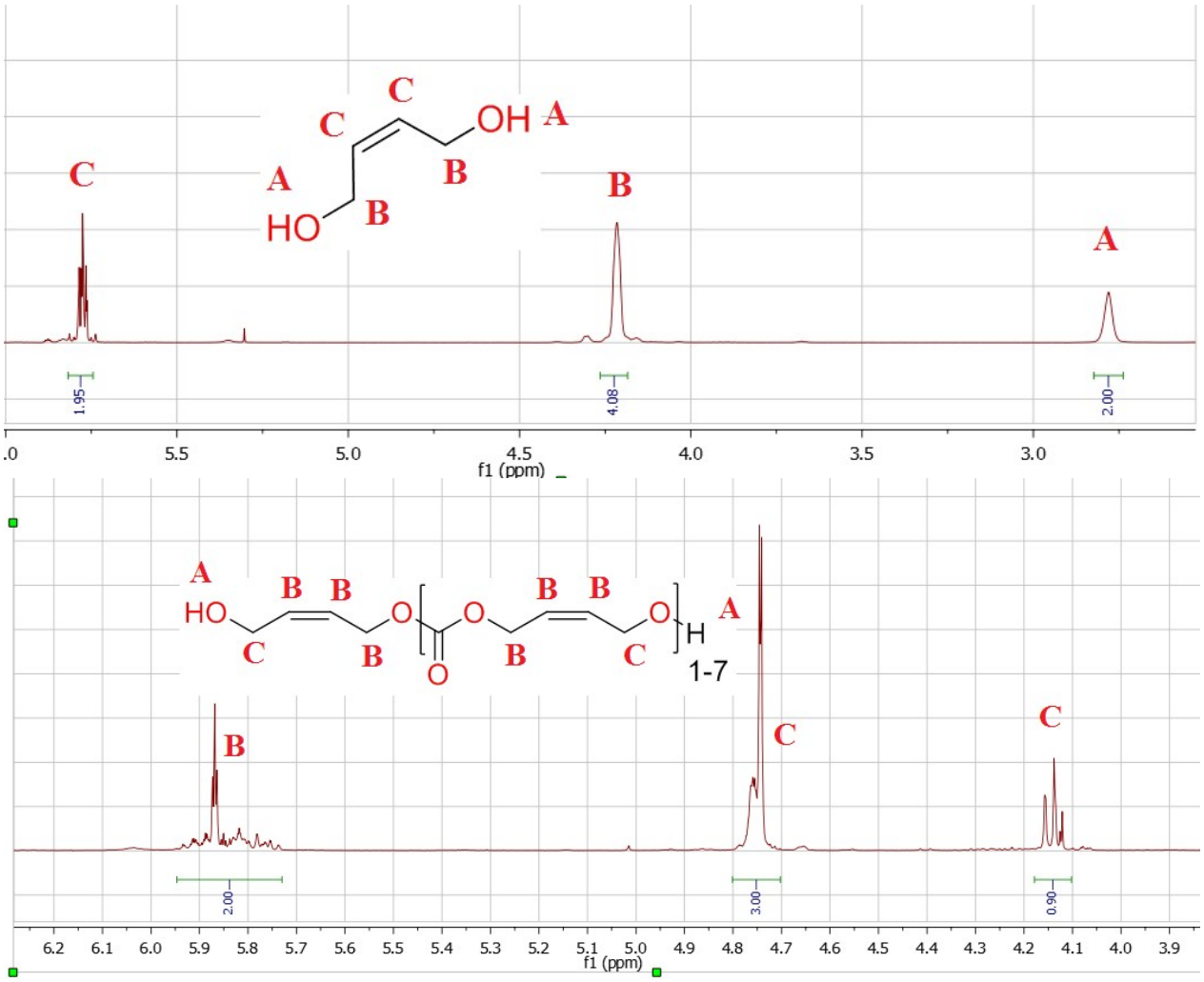
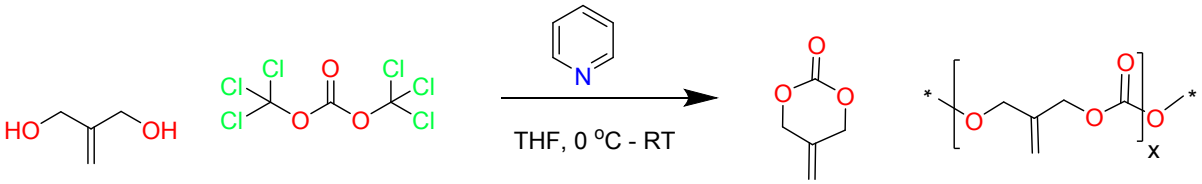


Figure S2. ^{1}H-NMR before and after reaction with triphosgen, displaying full formation of oligomeric species. The integration yields an average repeating unit close to 2, which is in good correspondence with the obtained mass data.

Six-Membered Carbonate



Scheme S2. Ring-closing or oligomerization of 2-methylenepropane-1,3-diol with triphosgene.

The ring closing reaction of 2-methylenepropane-1,3-diol with triphosgen was performed at the exact same reaction conditions as previous. The ^{1}H NMR was analyzed in accordance to Endo et al.[6]

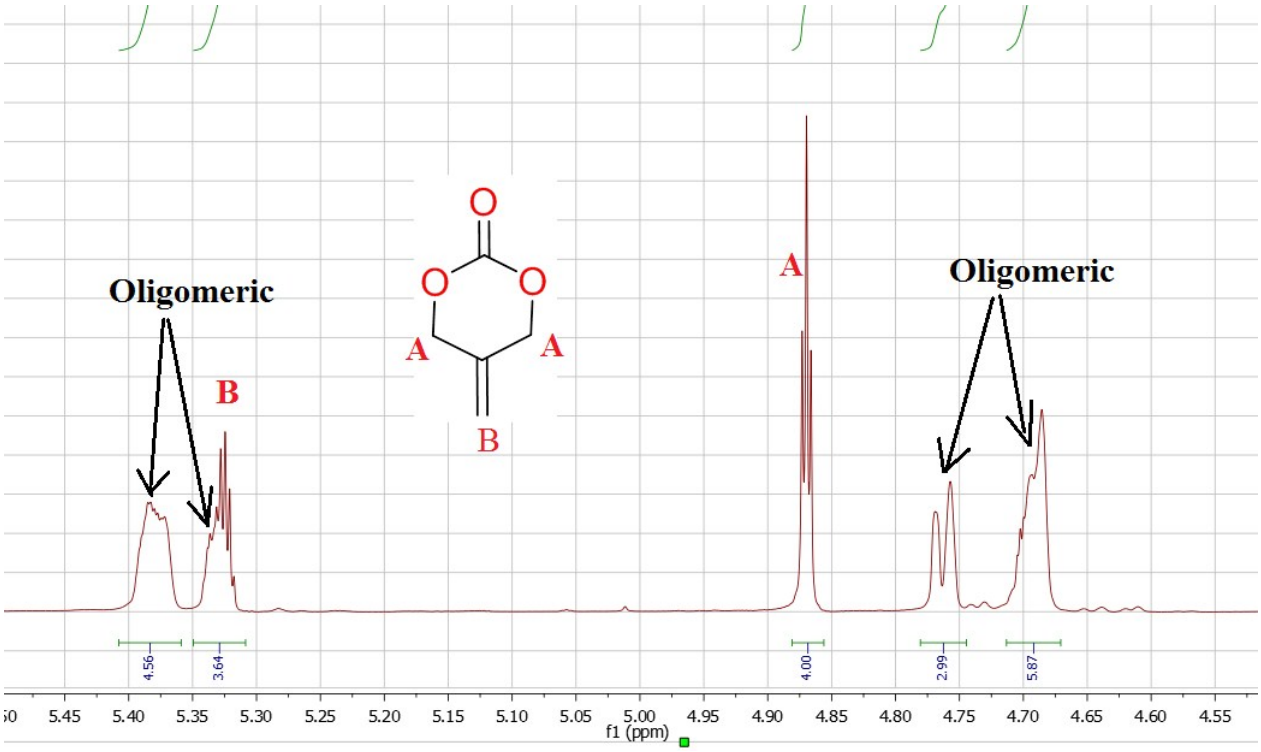
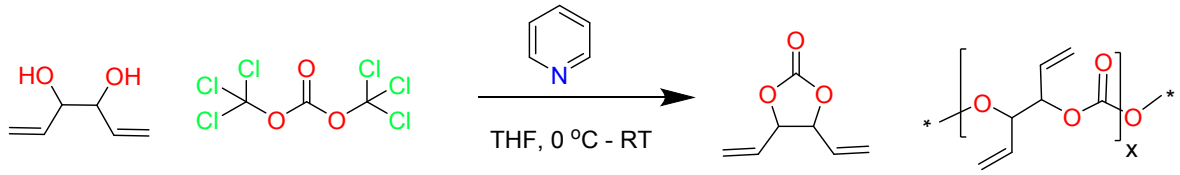


Figure S3. The crude ^{1}H NMR of the ring closing reaction of 2-methylenepropane-1,3-diol with triphoshgene. Giving the total conversion to cyclic as (4/(((4.56+(3.64-2))*2)+4)*100 = 24.4 %

Five-Membered Carbonate



Scheme S3. Ring-closing or oligomerization of 1,5-Hexadiene-3,4-diol, mixture of (±) and meso with triphosgene.

The ring closing reaction of 1,5-Hexadiene-3,4-diol, mixture of (±) and meso with triphosgen was performed at the exact same reaction conditions as previously. The ^{1}H NMR was analyzed in accordance to Trost et al.[2]

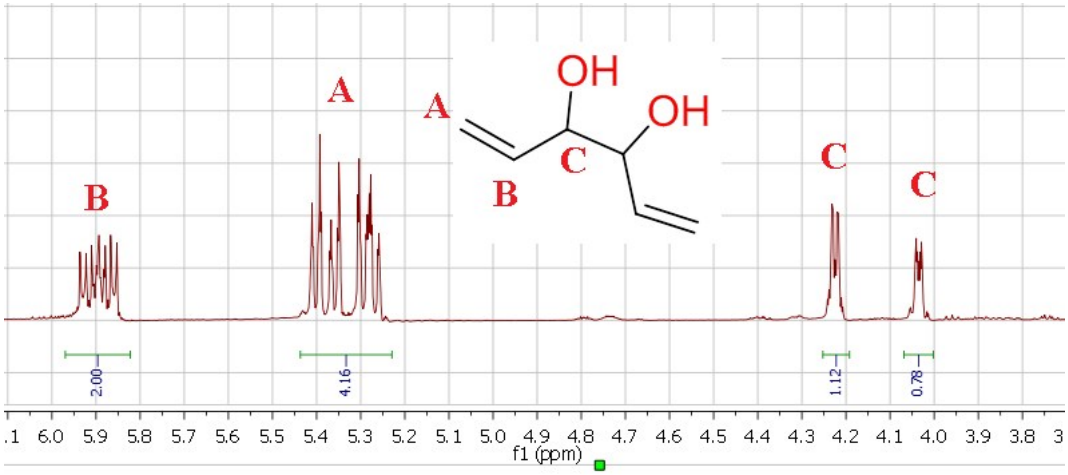


Figure S4. The crude ^{1}H NMR of the starting compound derived from reductive coupling of acrolein

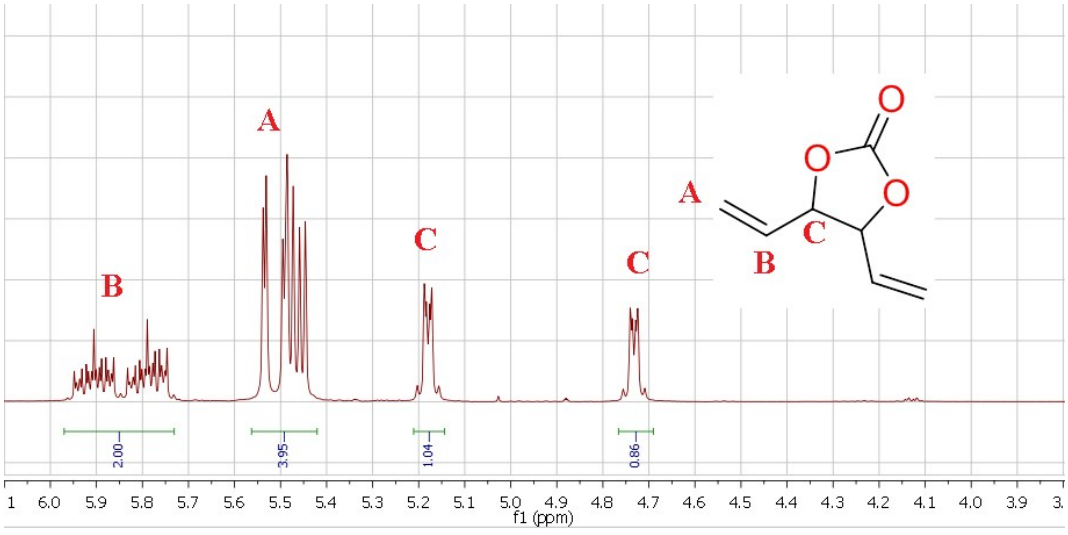
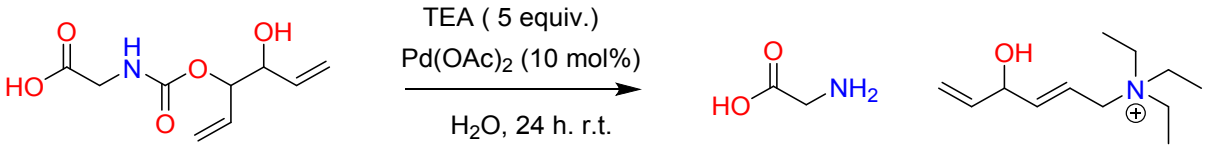


Figure S5. The crude ^{1}H NMR of the starting compound after ring closing conditions showing quantitate conversion to the desired cyclic carbonate.

Deprotection Kinetics



[4] **[5]** **[6]**

In a typical kinetic experiment; desired amount of **[4]** and $Pd(OAc)_2$ was dissolved in D_2O in a 5 ml vial equipped with a magnetic stirrer. After 5 minutes TEA was added to the reaction mixture. At specific time points, 50 μL was withdrawn and dissolved 0.5 ml D_2O containing 20 μL of AcOH. The AcOH was added in order to quench the reaction.

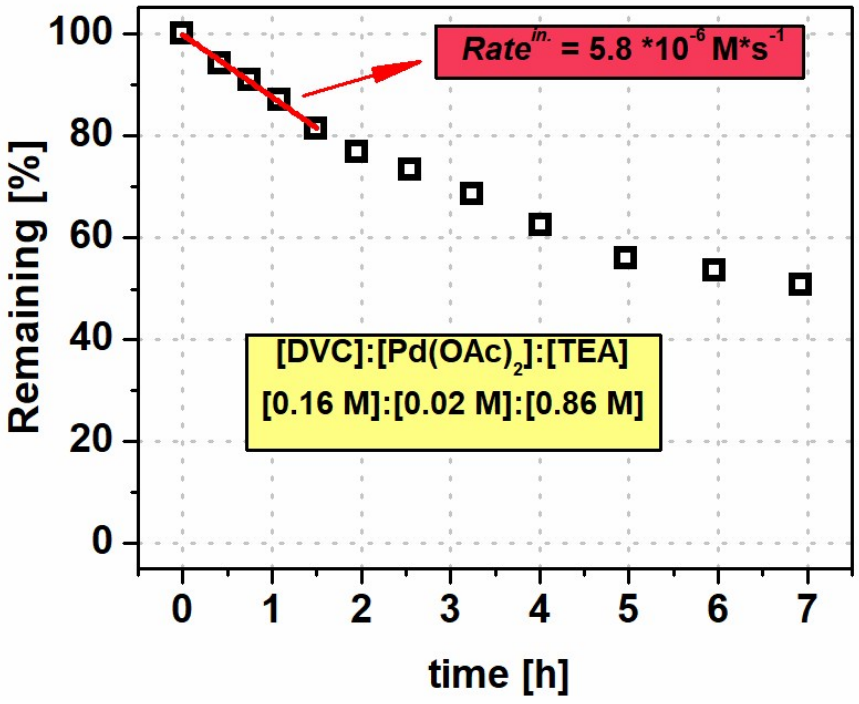


Figure S6. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.02M $Pd(OAc)_2$ and 0.86M TEA at ambient temperature.

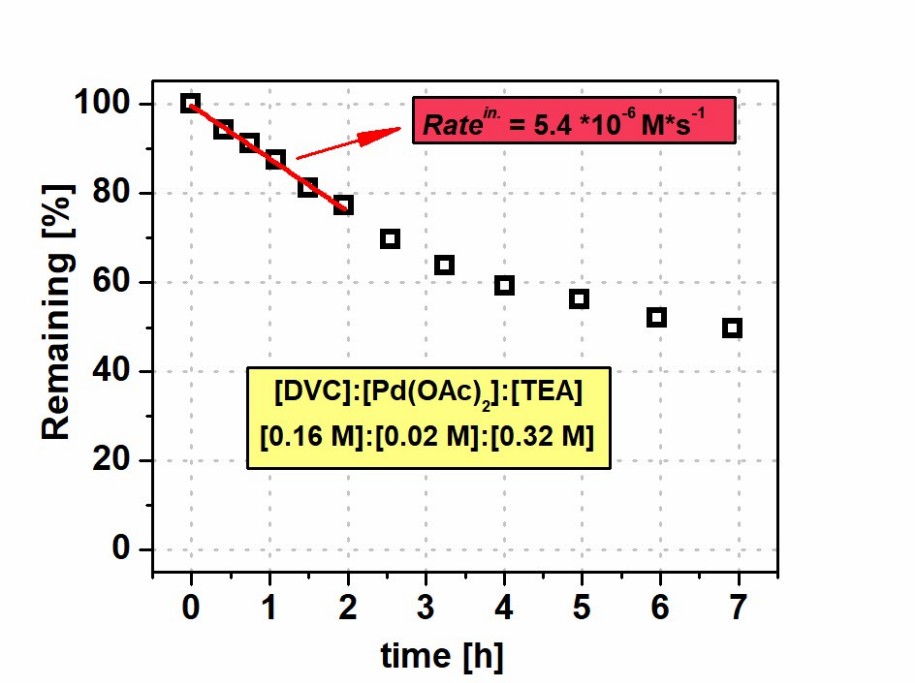


Figure S7. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.02M $Pd(OAc)_2$ and 0.32M TEA at ambient temperature.

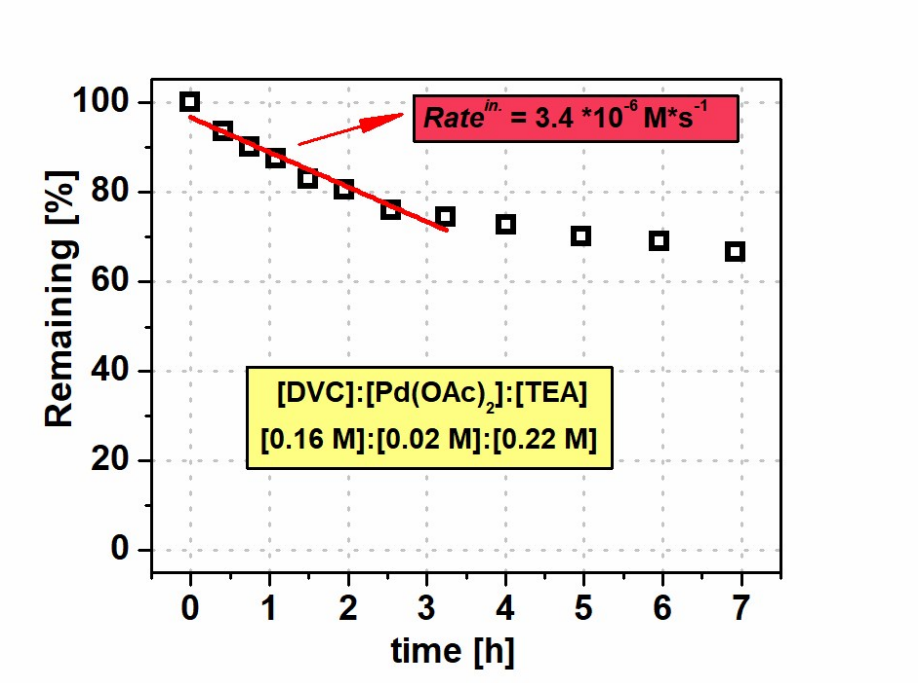


Figure S8. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.02M $Pd(OAc)_2$ and 0.22M TEA at ambient temperature.

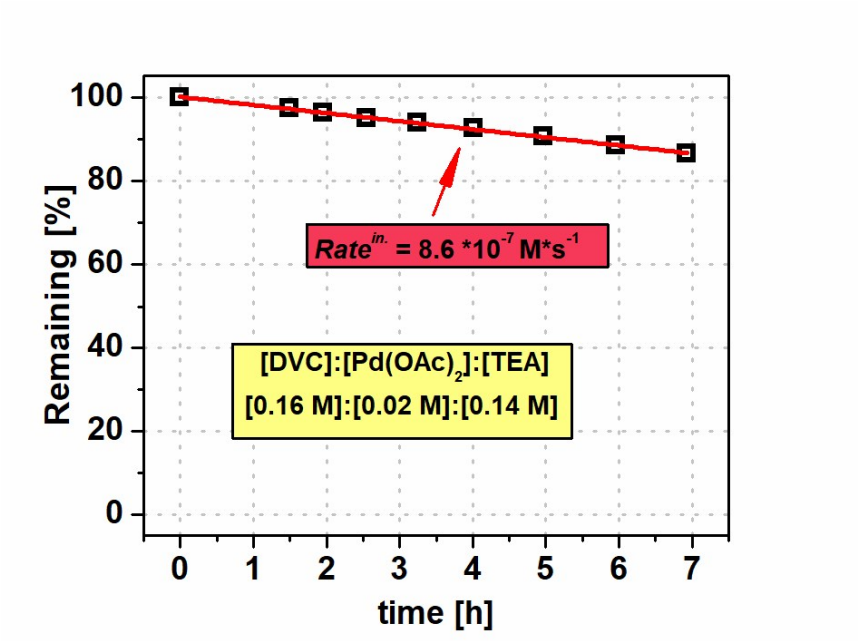


Figure S9. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.02M $Pd(OAc)_2$ and 0.14M TEA at ambient temperature.

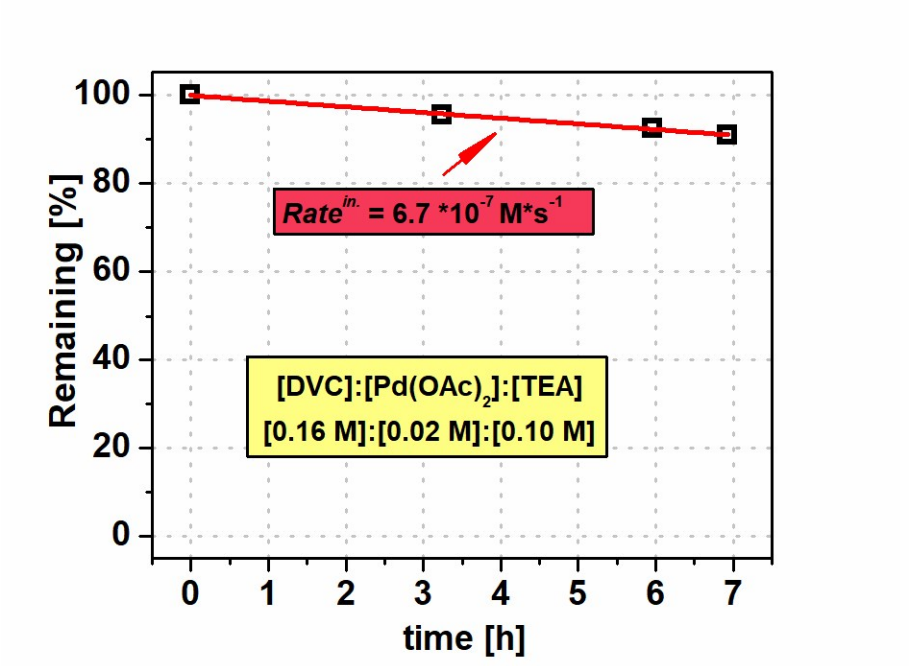


Figure S10. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.02M $Pd(OAc)_2$ and 0.10M TEA at ambient temperature.

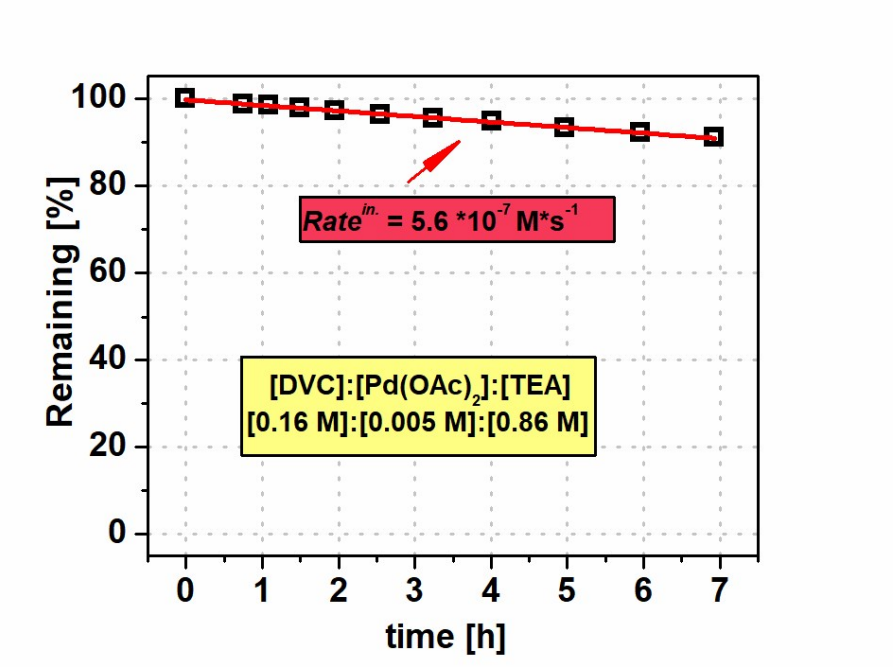


Figure S11. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.005M $Pd(OAc)_2$ and 0.86M TEA at ambient temperature.

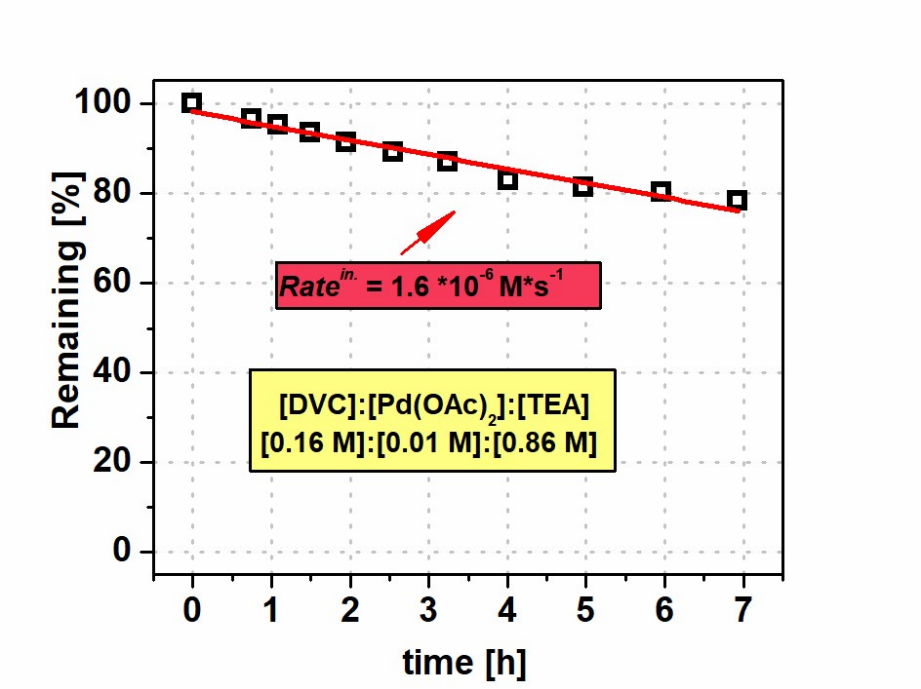


Figure S12. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.01M $Pd(OAc)_2$ and 0.86M TEA at ambient temperature.

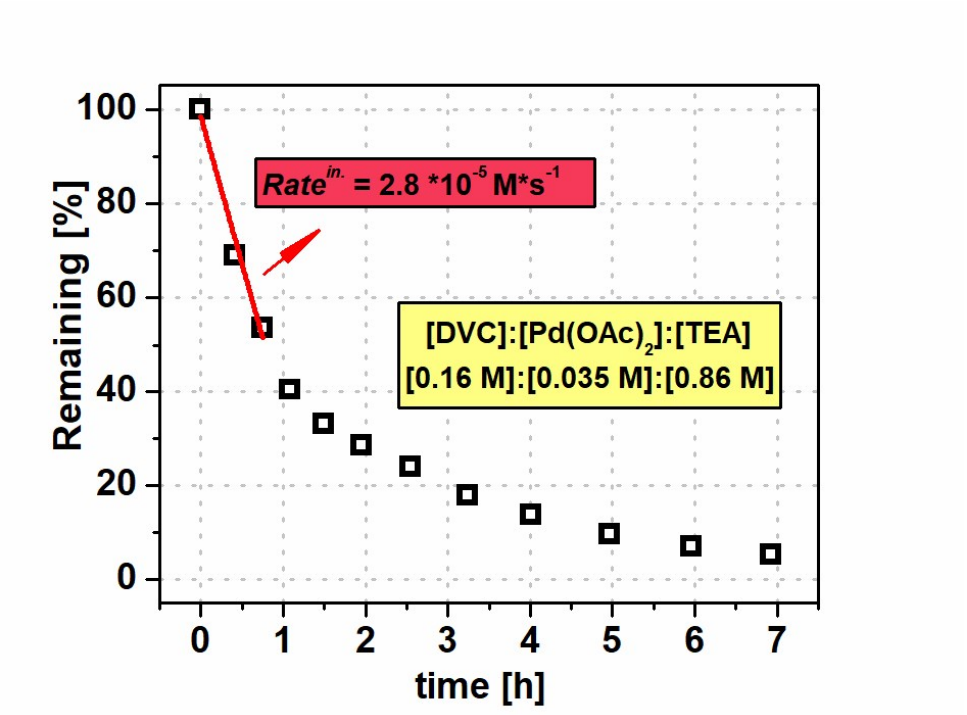


Figure S13. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.035M $Pd(OAc)_2$ and 0.86M TEA at ambient temperature.

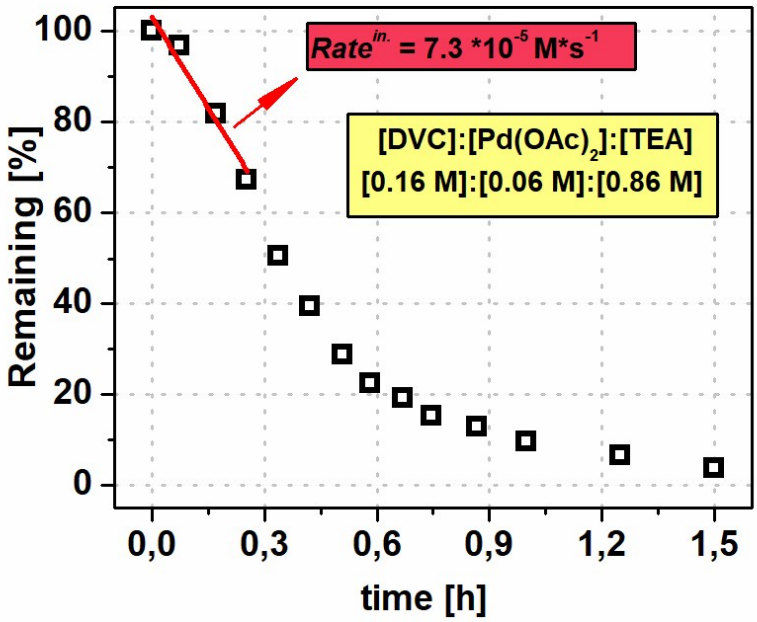


Figure S14. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.06M $Pd(OAc)_2$ and 0.86M TEA at ambient temperature.

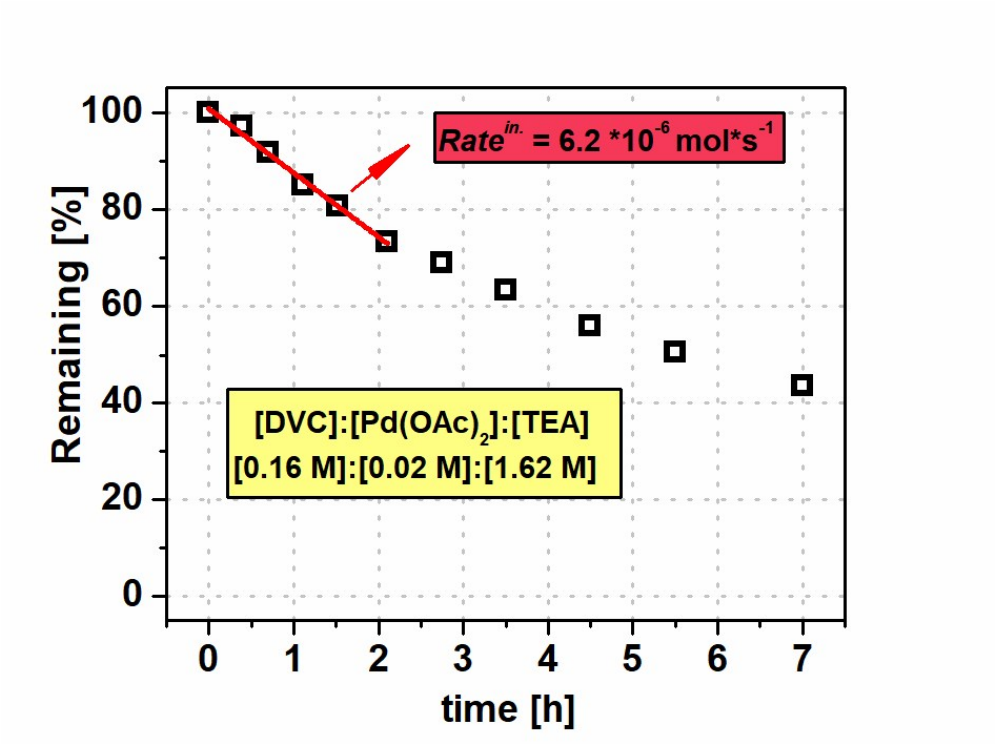


Figure S15. Kinetic evaluation of the deprotection behavior at 0.16M concentration of **[4]** with 0.02M $Pd(OAc)_2$ and 1.62M TEA at ambient temperature.

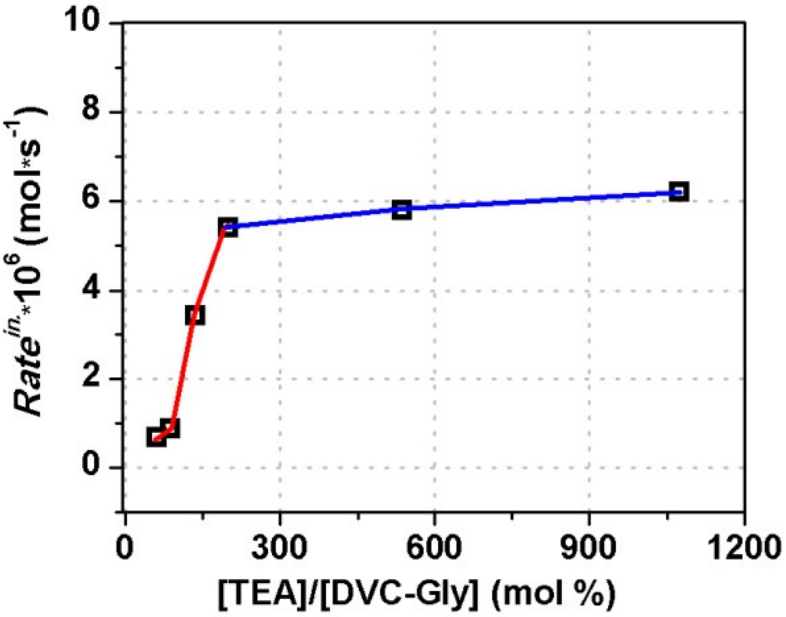


Figure S16. Initial rate of deprotection as a function of the molar ratio of TEA. The red line show second order dependence whereas the blue line close to zero order dependence in TEA

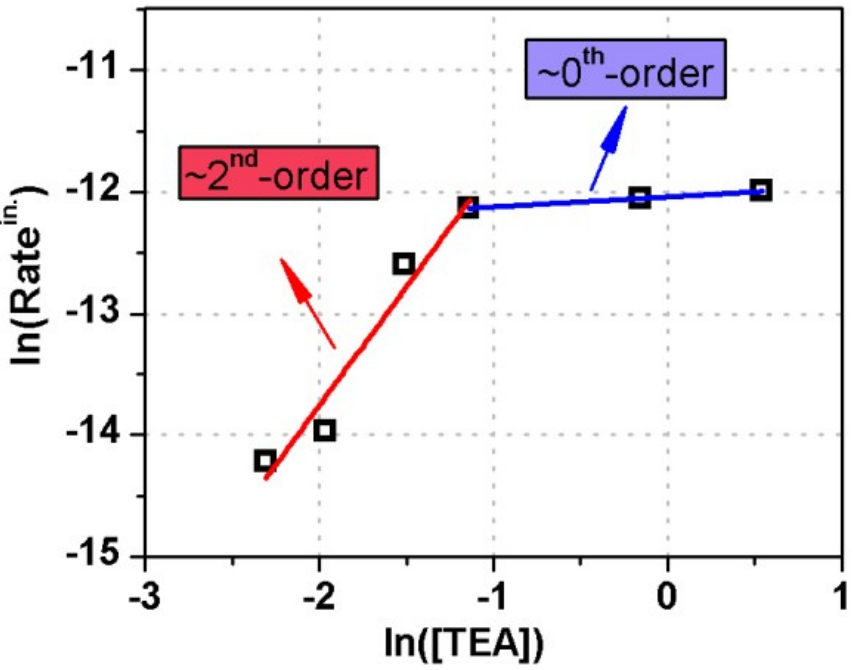
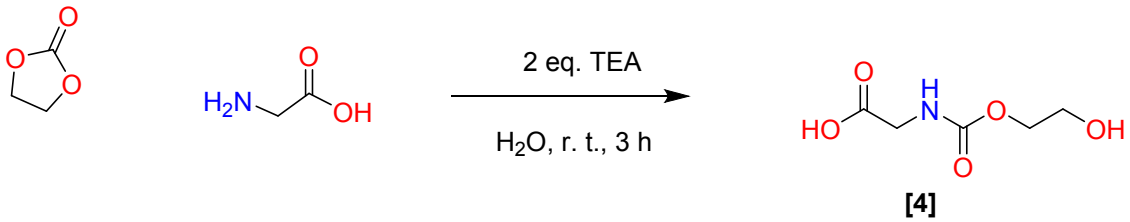


Figure S17. The logarithm of Initial rate as a function of the logarithm of the concentration of TEA. The red line show second order dependence whereas the blue line close to zero order dependence in TEA

NMR data on compounds



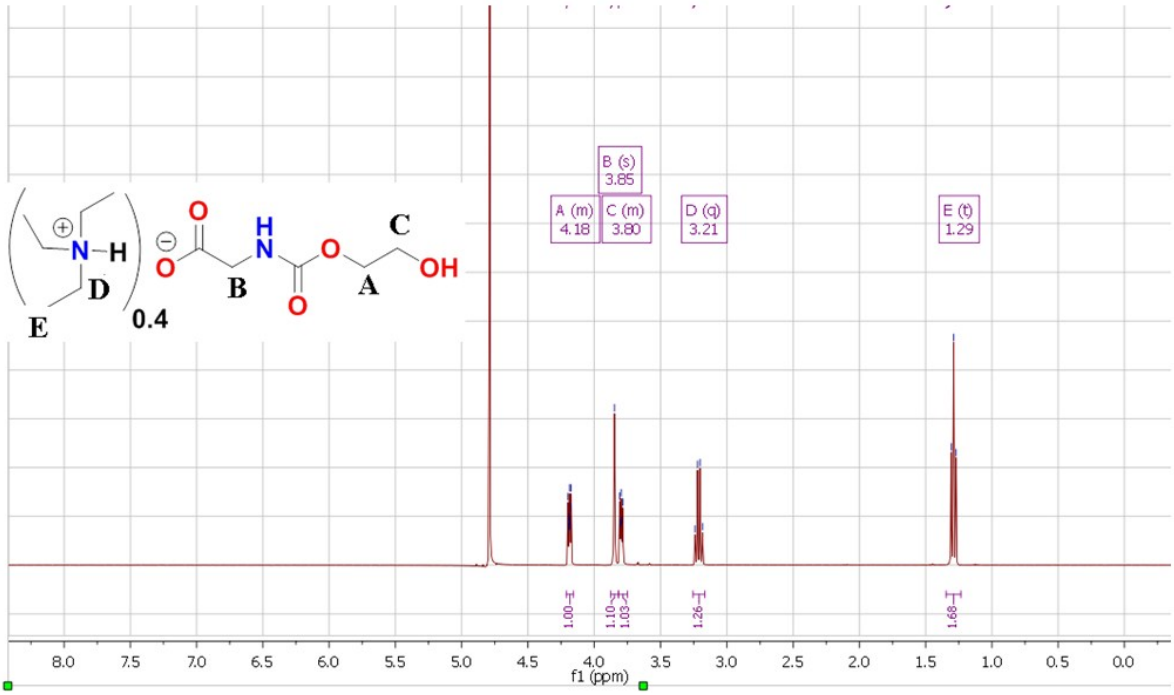
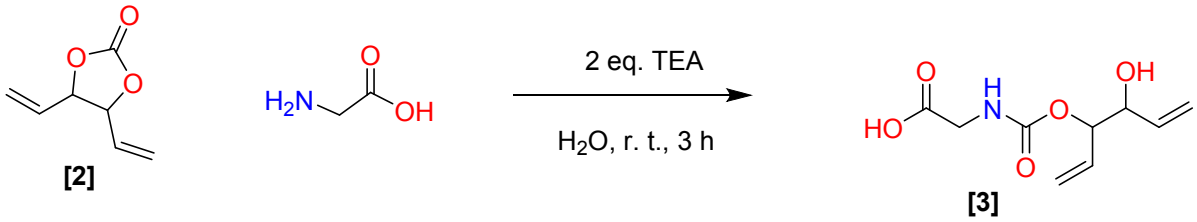


Figure S18 ^{1}H NMR on compound **[4]**



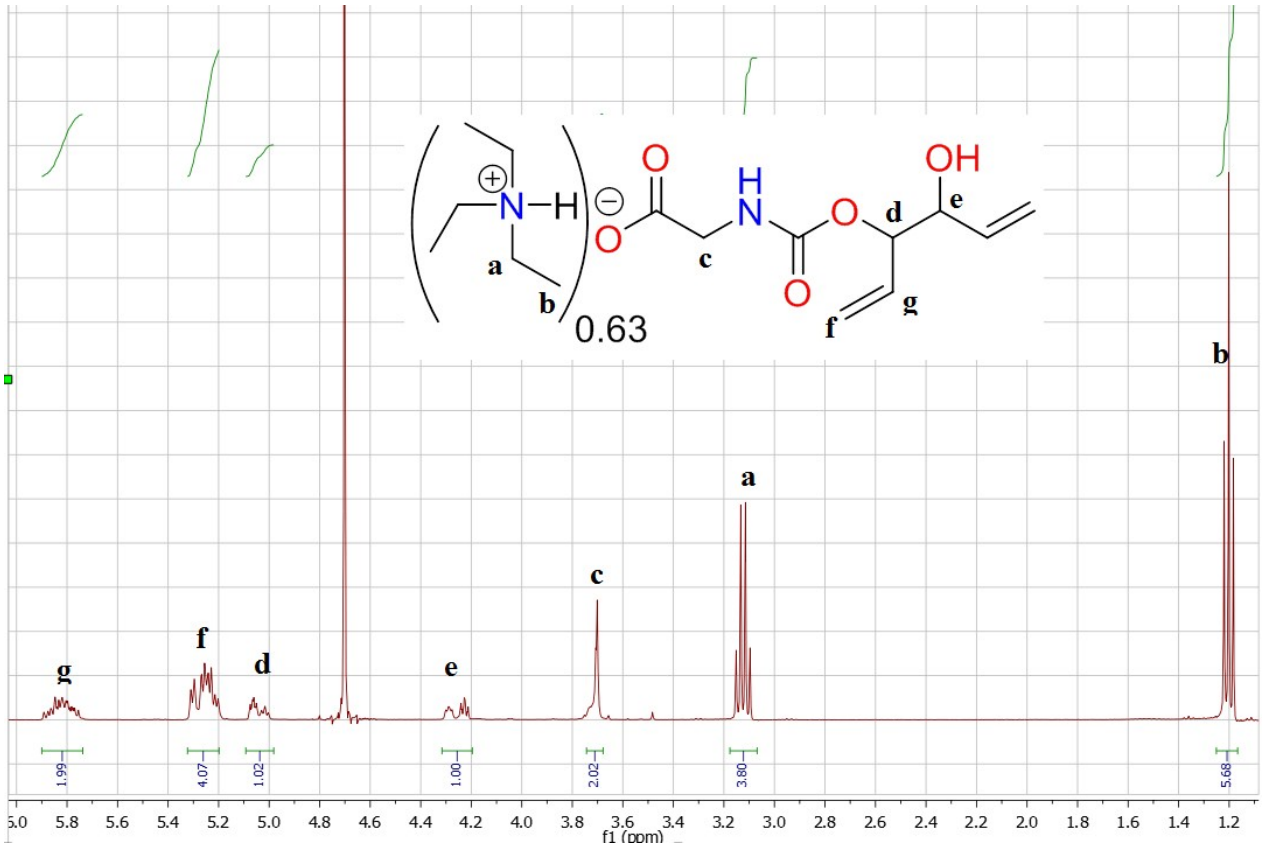
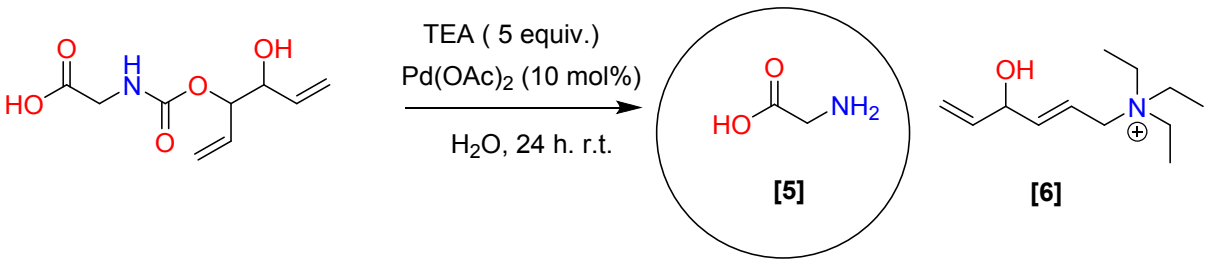


Figure S19 ^{1}H NMR on compound **[3]**



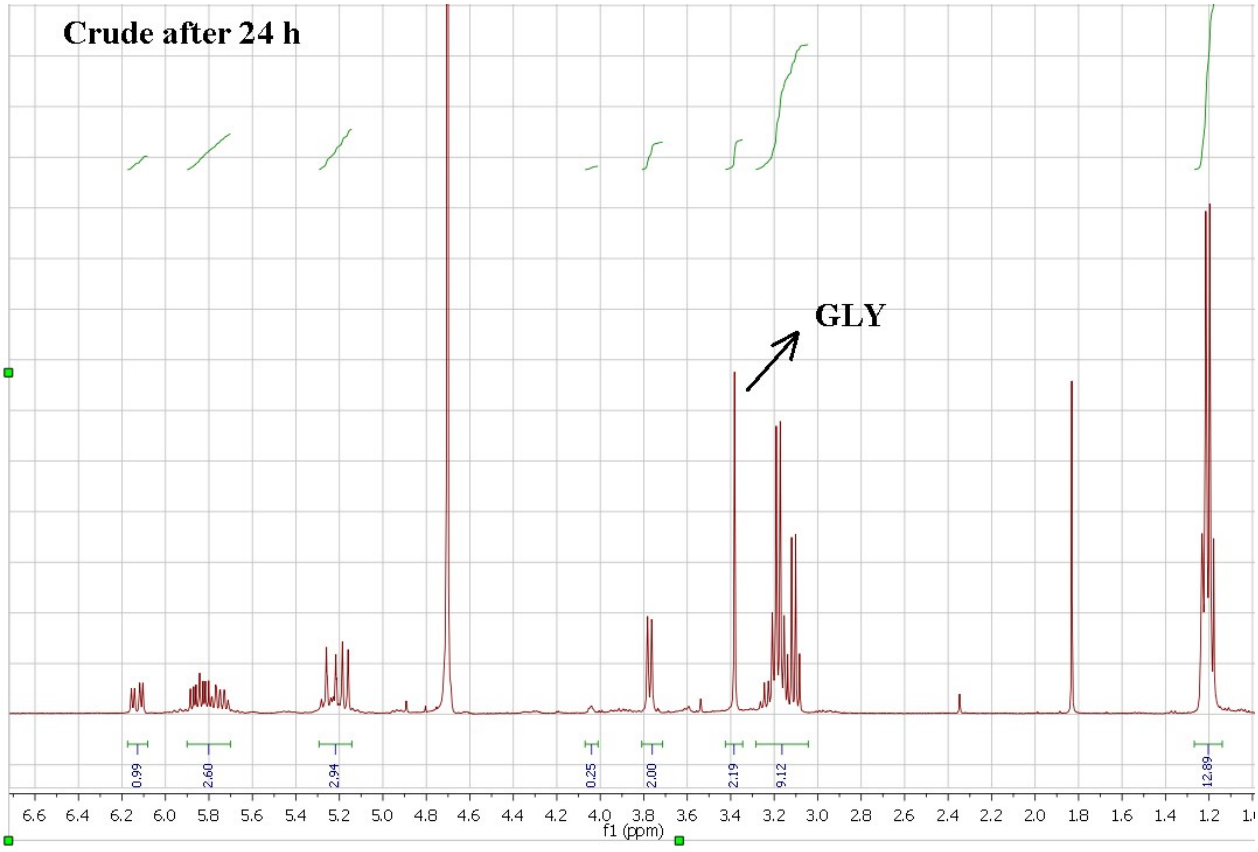


Figure S20 Crude ^{1}H NMR on the deprotection after 24 h, showing the appearance of a singlet related free glycine.

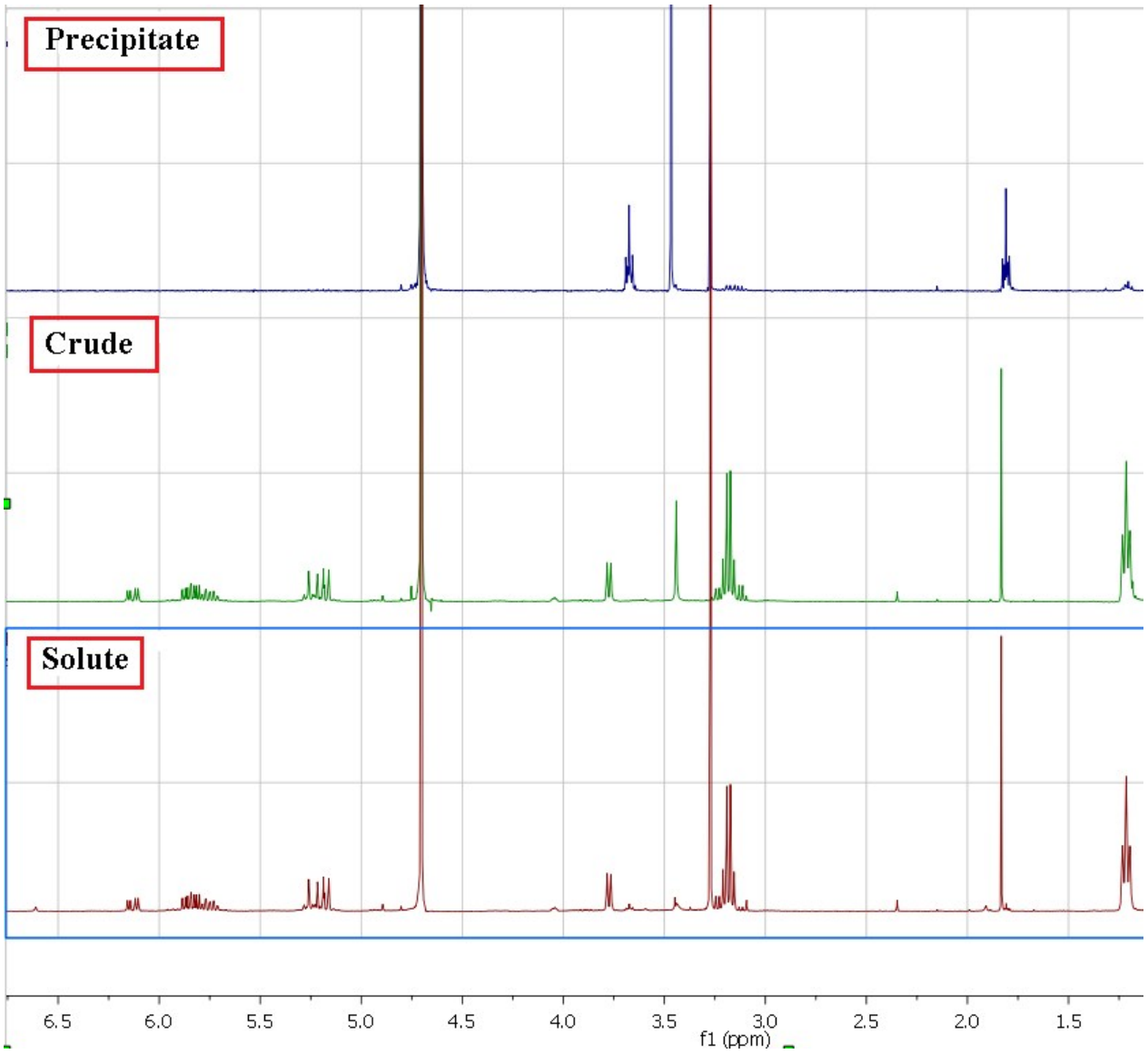


Figure S21 Overlaid sequence of ^{1}H NMR on showing removal of pure glycine form the reaction mixture.

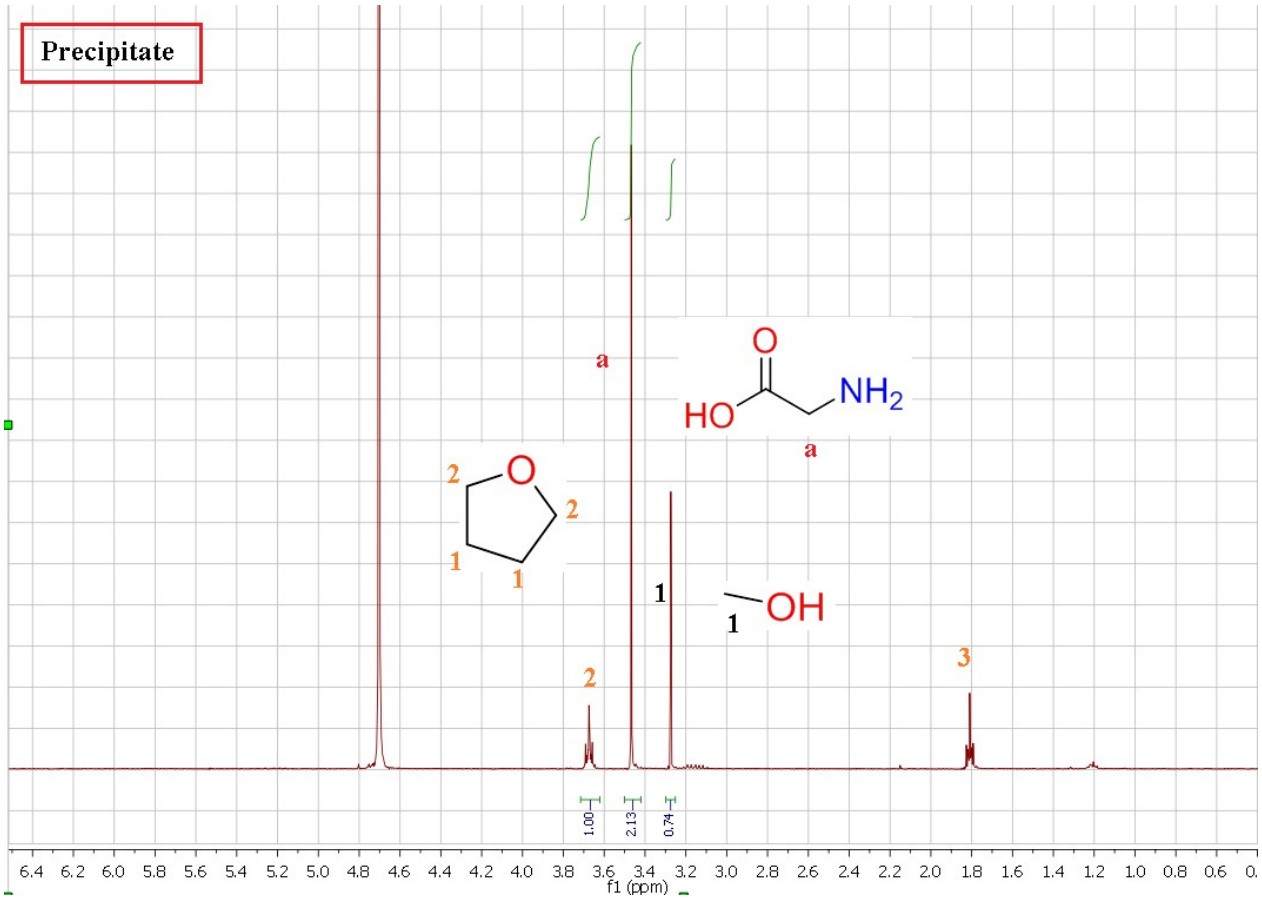
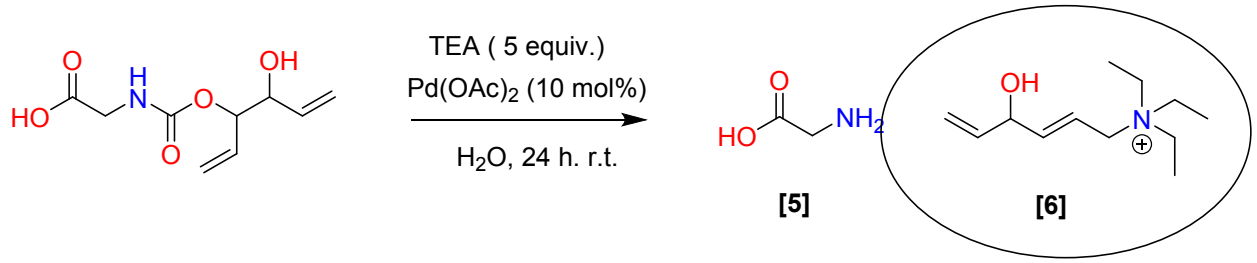


Figure S22. Full spectra of the ^{1}H NMR precipitate retained for an THF:MEOH 3:1 mixture,, showing removal of glycine form the reaction mixture.

Structure elucidation of the side product



Due to the envisioned structure of the side products its isolation was attempted in the mildest possible manner. The solute was concentrated, followed by resolvation in DCM and left in the freezer for 4 days. This yielded a precipitate containing a purer sample of the formed side product.

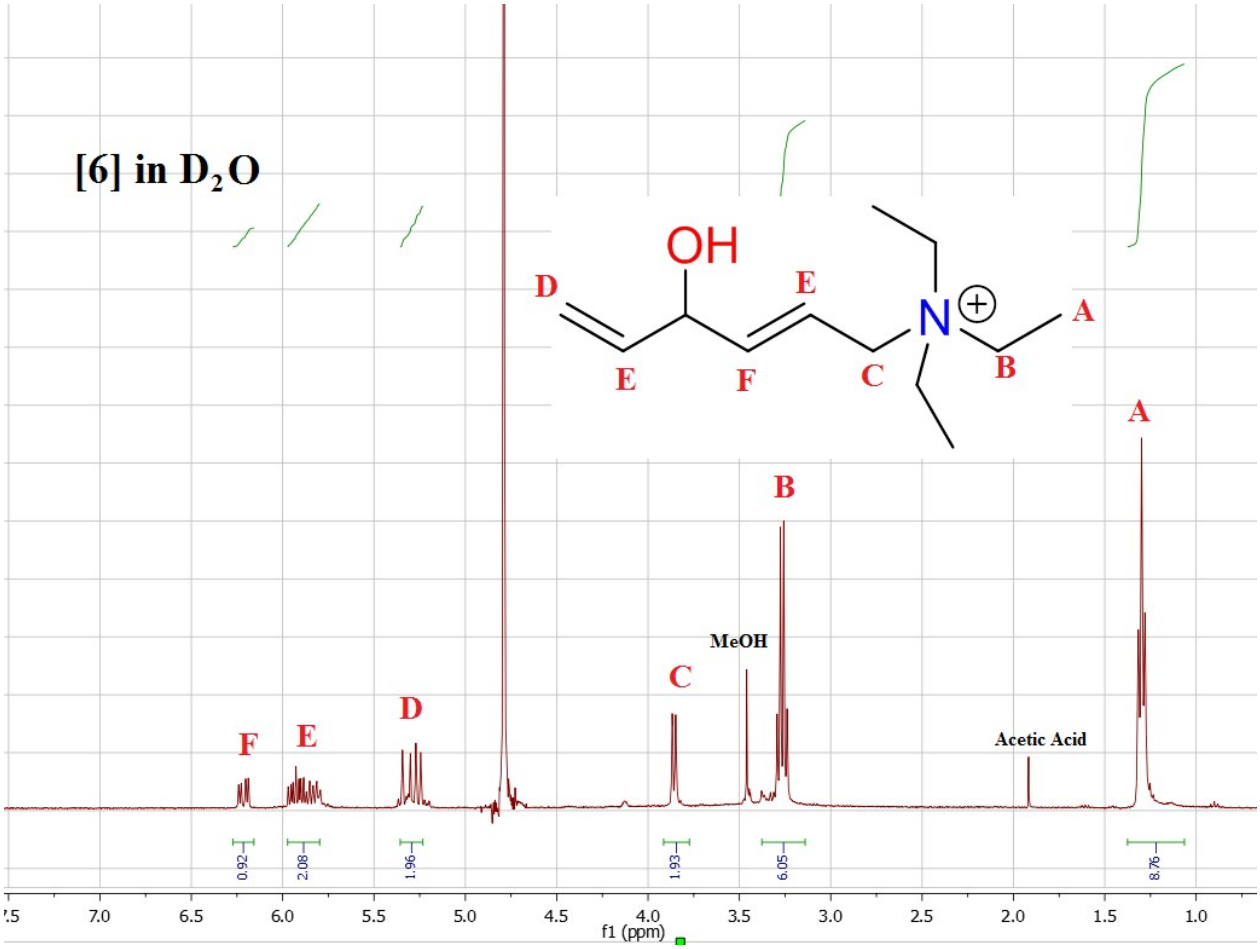


Figure S23. Product obtained from the precipitation in DCM analyzed in deuterated D_2O

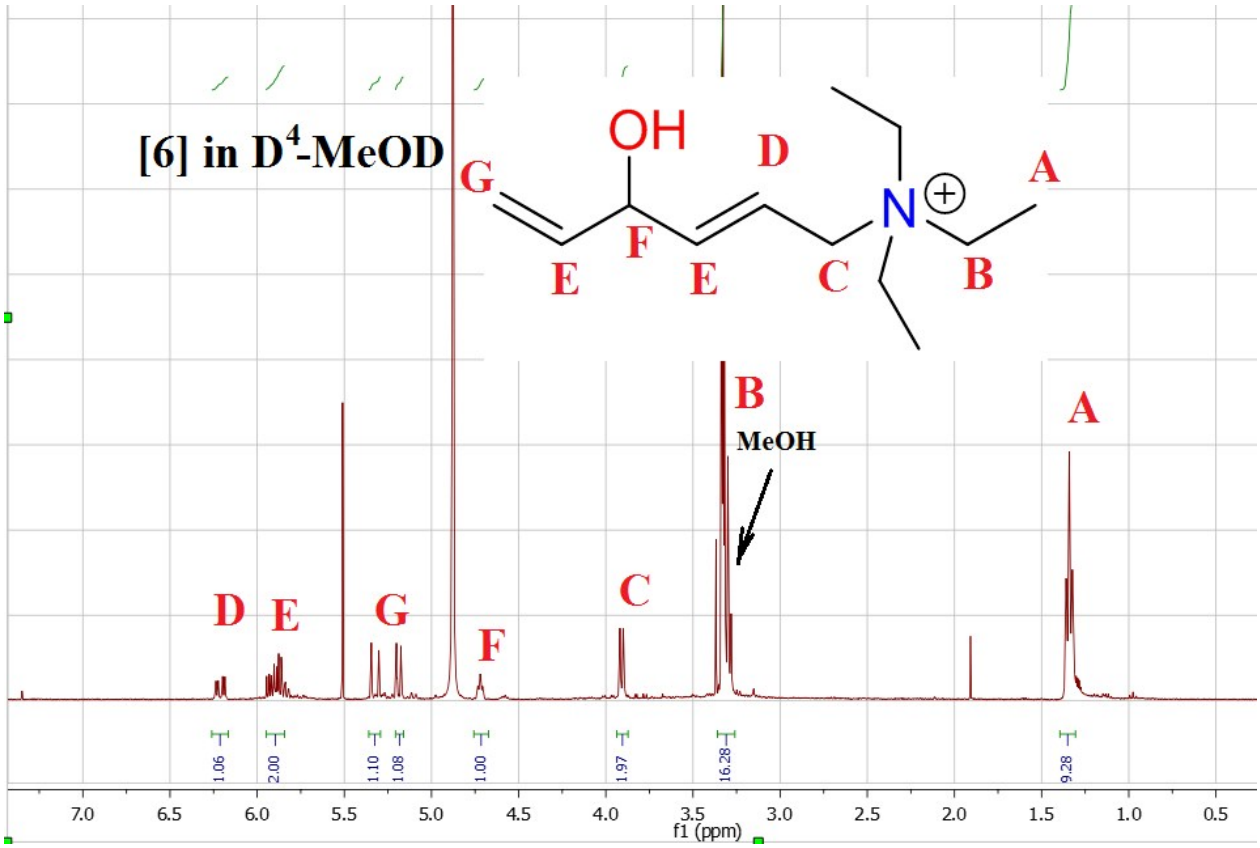


Figure S24. Obtained from the precipitation in DCM analyzed in deuterated MeOD

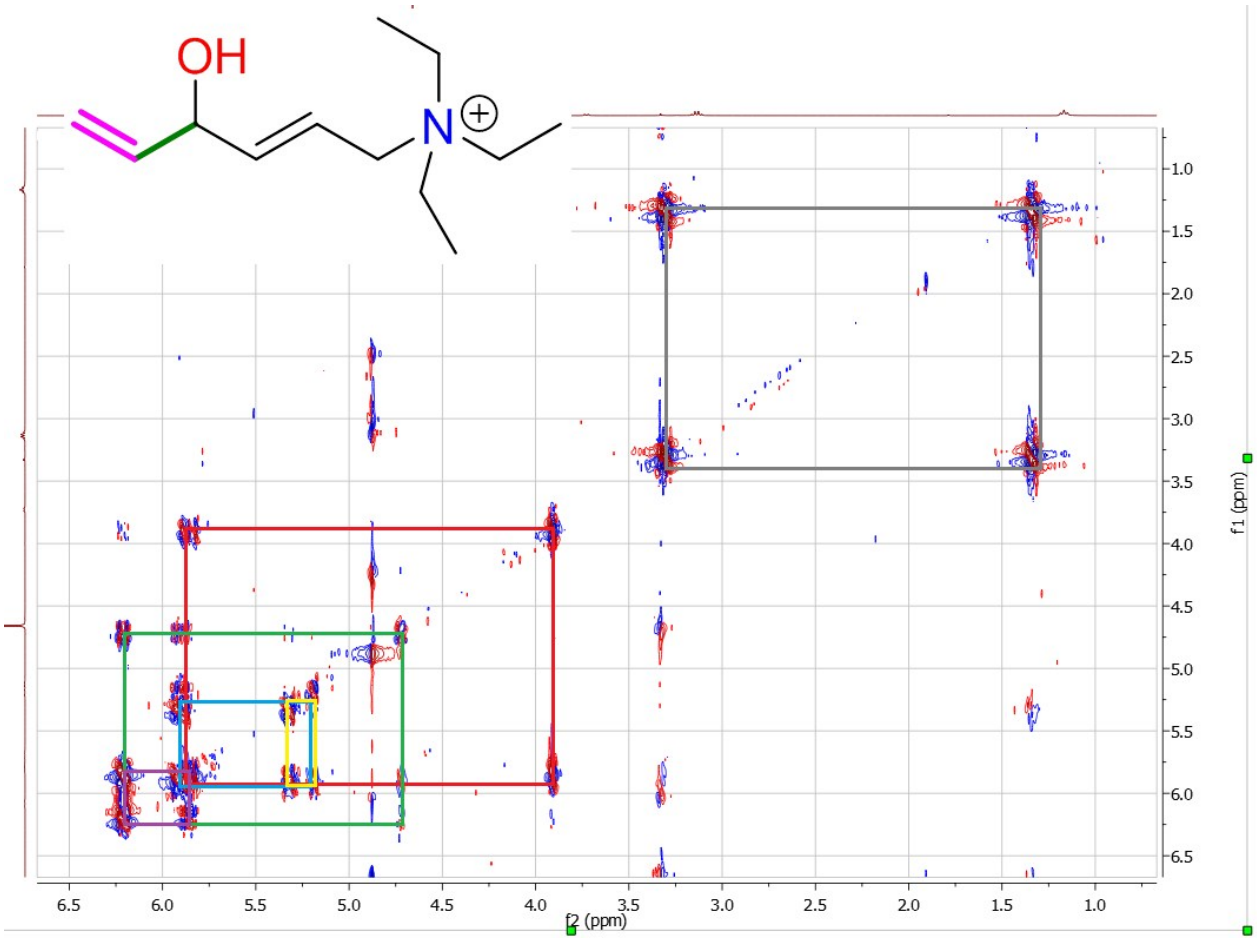
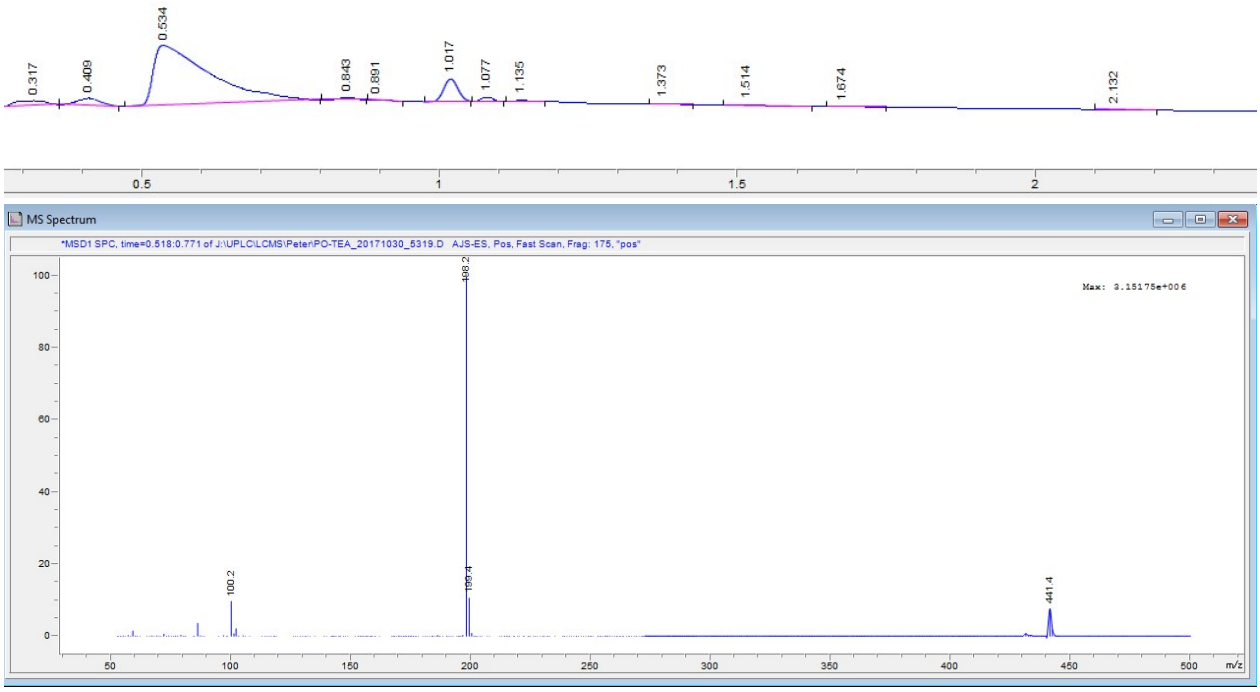
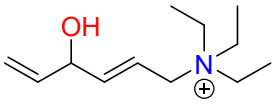


Figure S25. ^{1}H-^{1}H COSY on the deprotection side-product





m/z: 198.19 (100.0%), 199.19 (13.0%)

Figure S26. UHPLC on the deprotection side-product

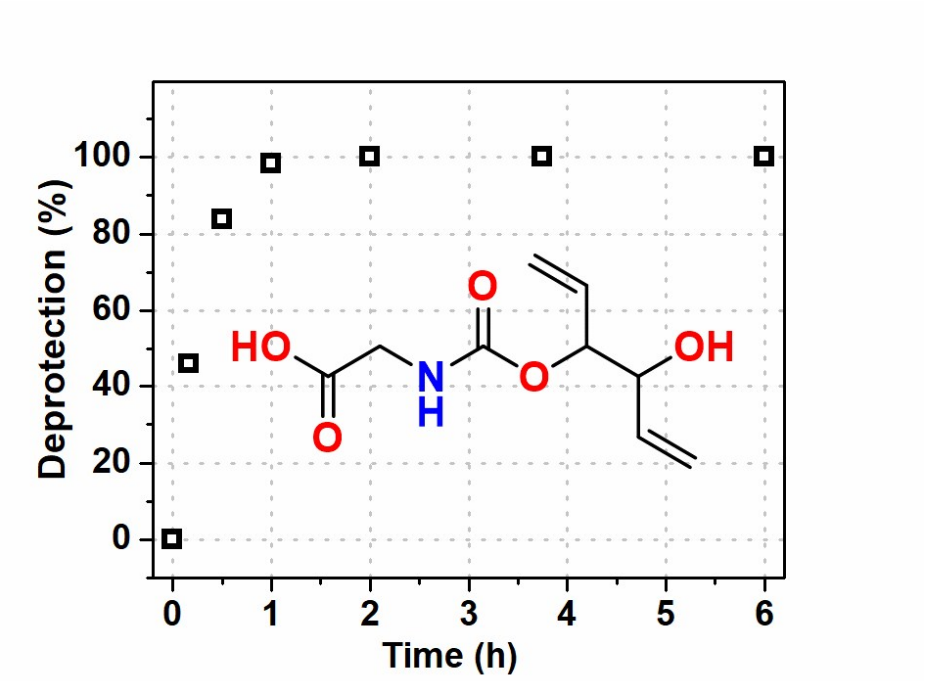


Figure S27. Deprotection was performed in 0.16 M concentration of substrate in D_2O with 2 mol % of Pd(OAc)2 and 6 equiv. of TEA, and 3 equiv. of piperazine at 75 °C.

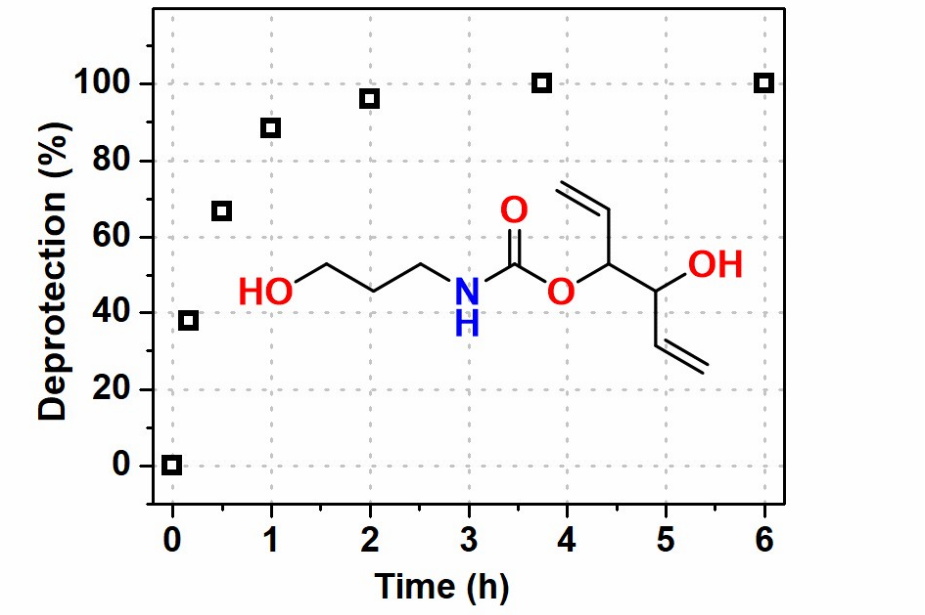


Figure S28. Deprotection was performed in 0.16 M concentration of substrate in D_2O with 2 mol % of Pd(OAc)2 and 6 equiv. of TEA, and 3 equiv. of piperazine at 75 °C.

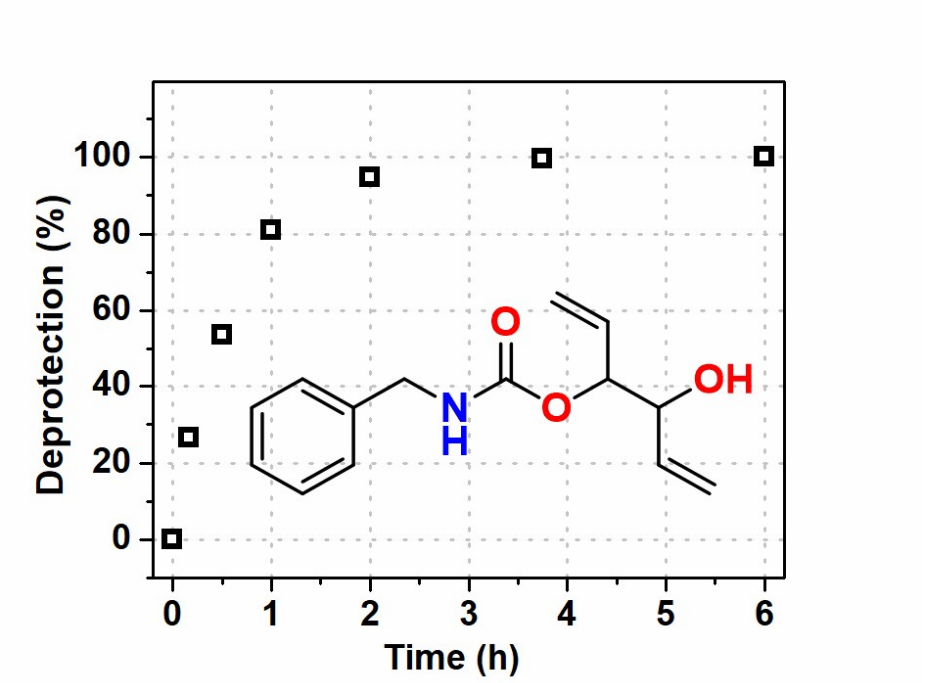


Figure S29. Deprotection was performed in 0.16 M concentration of substrate in D_2O with 2 mol % of Pd(OAc)2 and 6 equiv. of TEA, and 3 equiv. of piperazine at 75 °C.

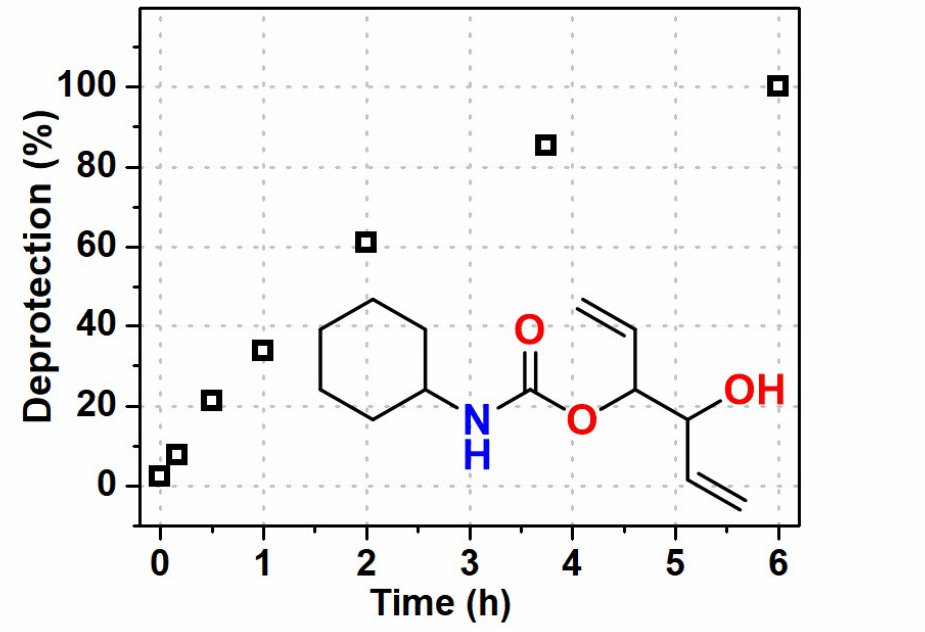


Figure S30. Deprotection was performed in 0.16 M concentration of substrate in D_2O with 2 mol % of Pd(OAc)2 and 6 equiv. of TEA, and 3 equiv. of piperazine at 75 °C.

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