Protecting group-free introduction of amino acids to polymers through the aza-Michael reaction

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Electronic Supporting Information

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Synthesis of ChAAILs (Choline Amino Acid Ionic Liquids)

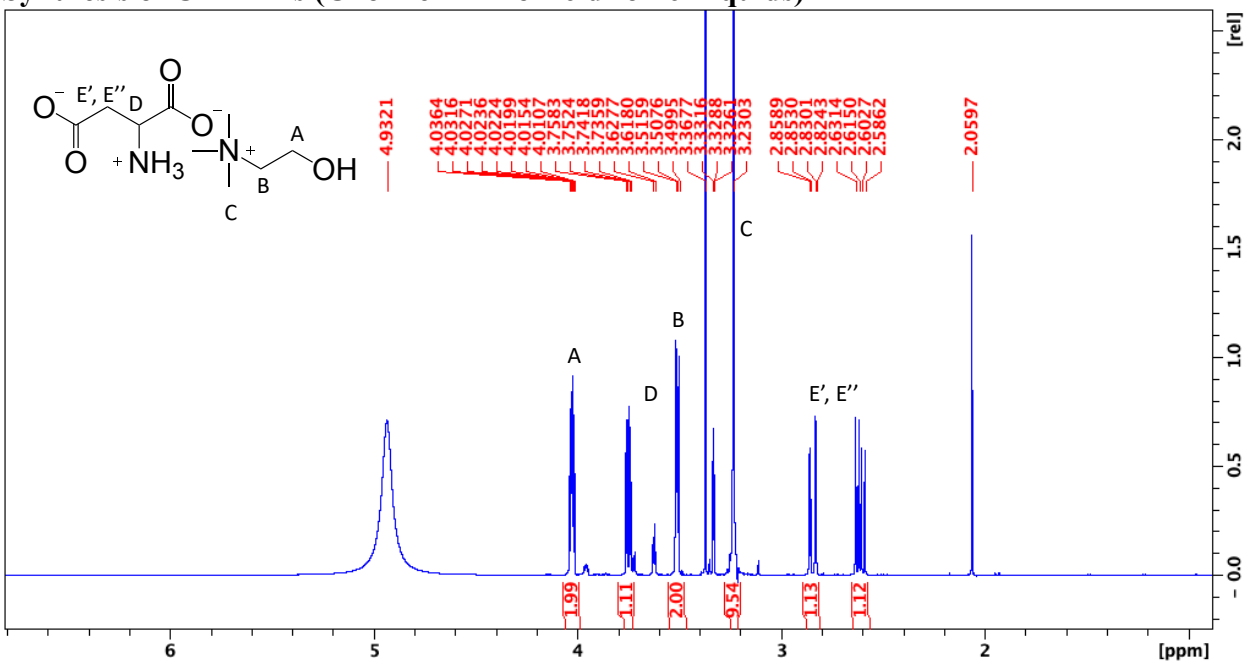


Figure S1. [1]H NMR of ChAspIL.

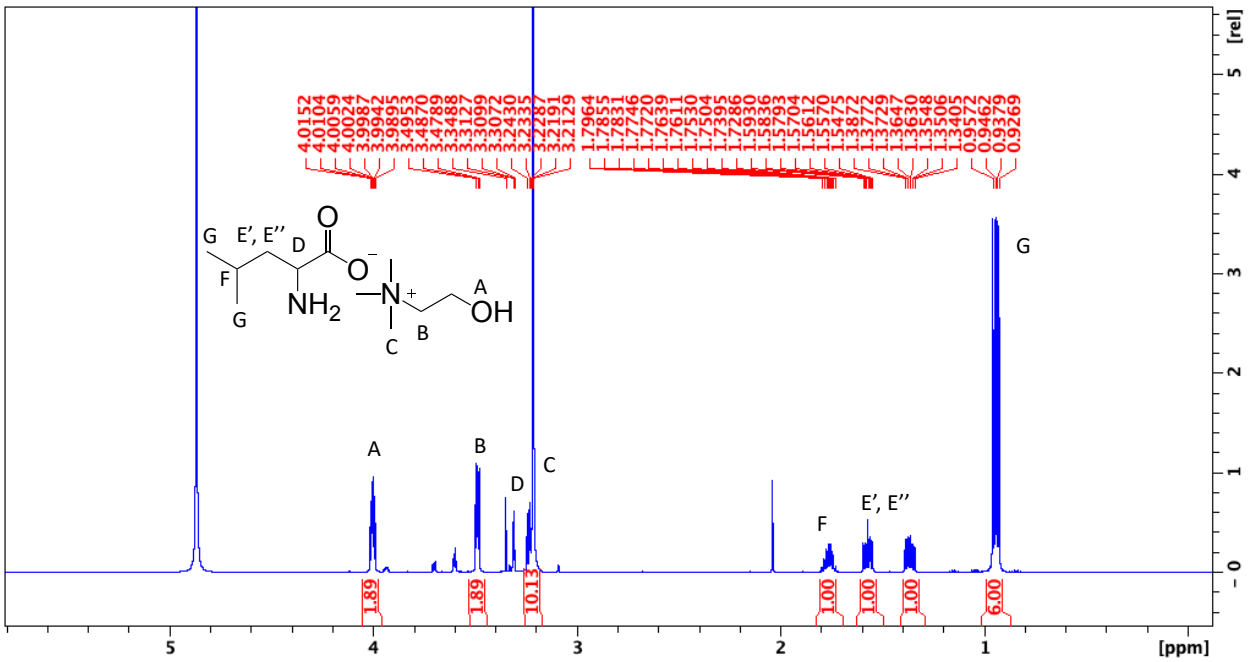


Figure S2. ^{1}H NMR of ChLeuIL.

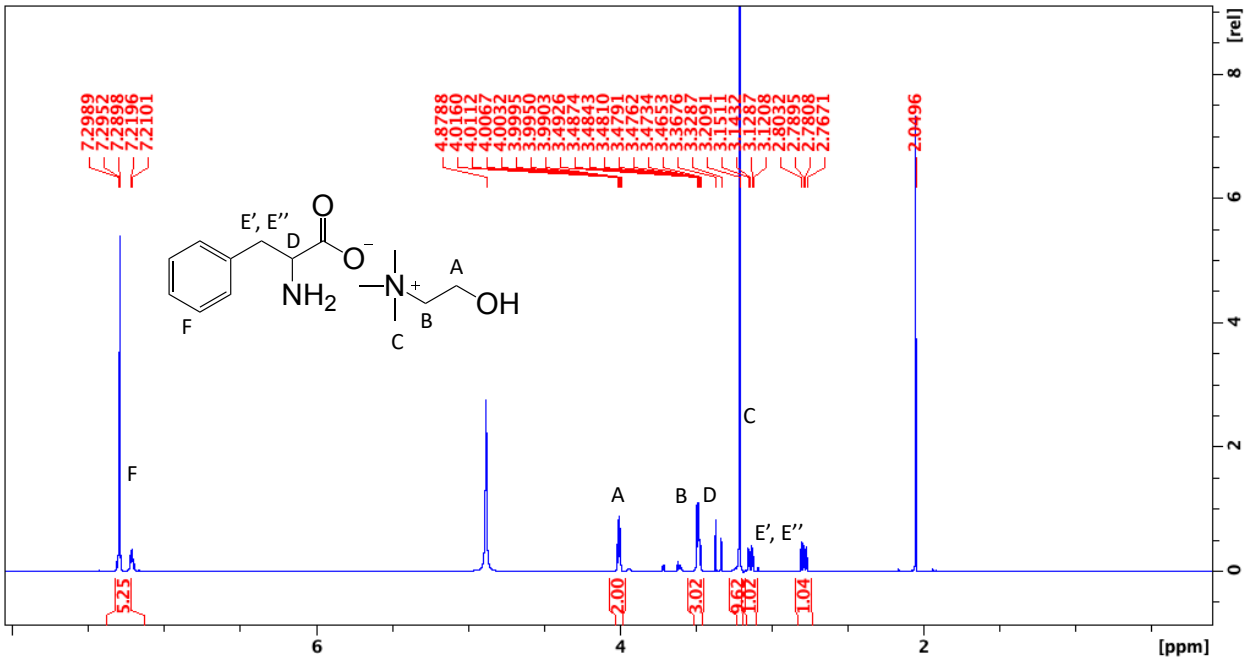


Figure S3. ^{1}H NMR of ChPheIL.

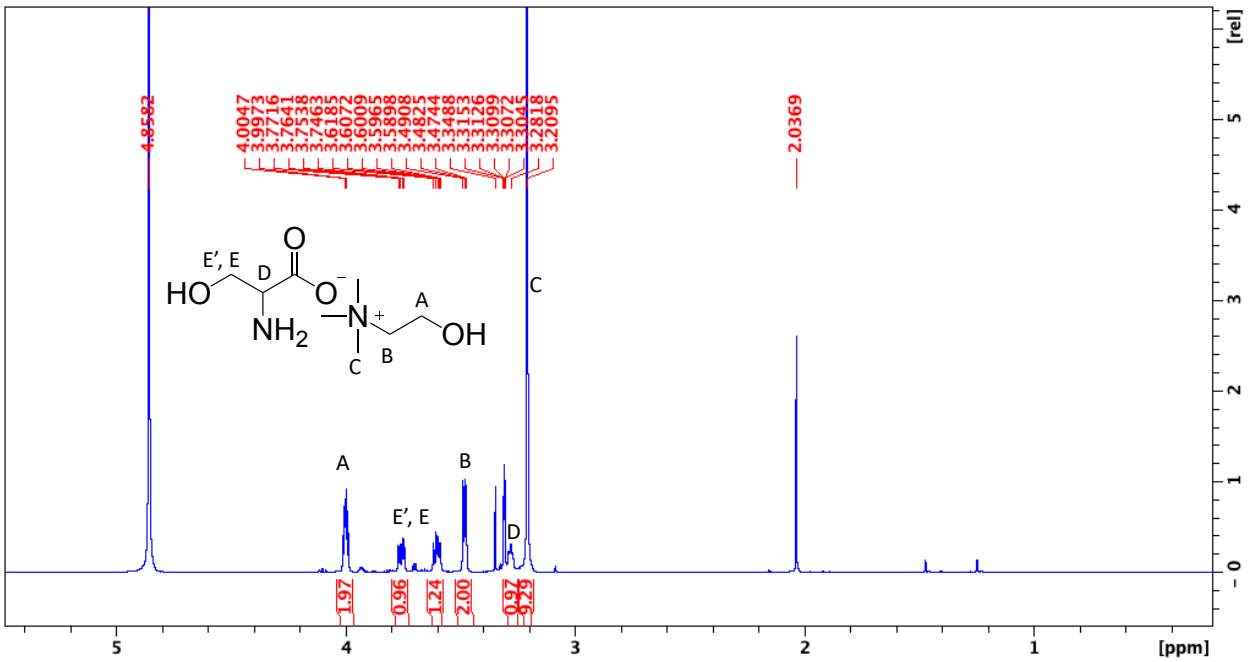


Figure S4. ^{1}H NMR of ChSerIL.

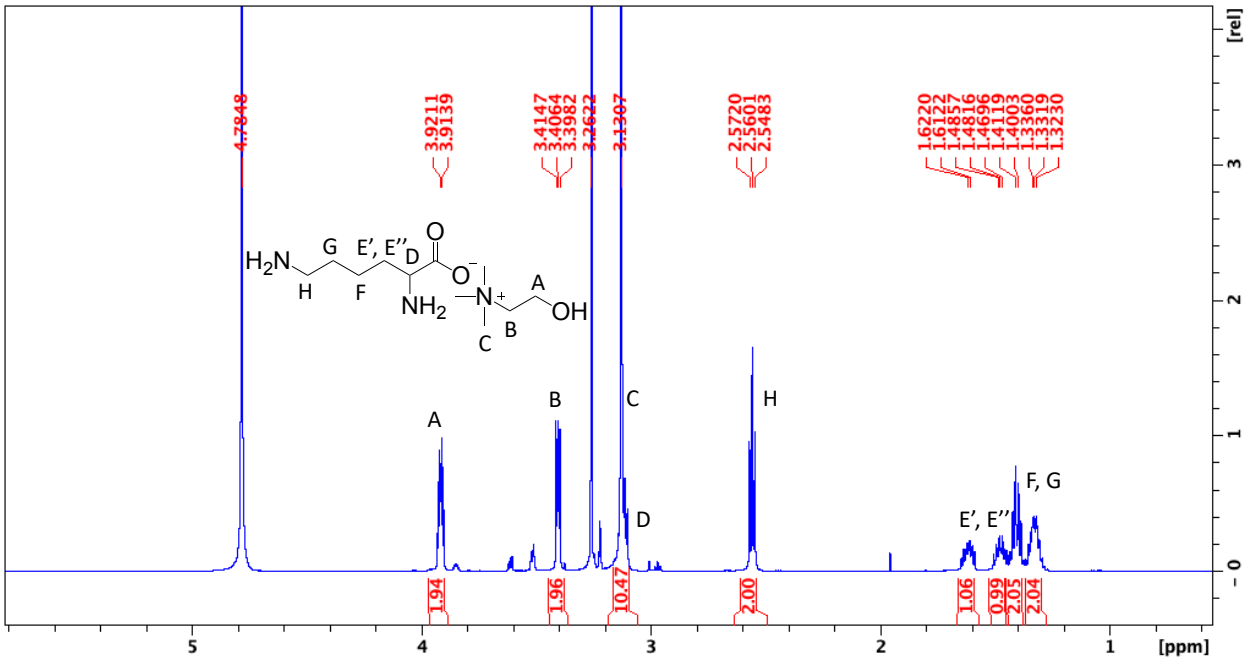


Figure S5. ^{1}H NMR of ChLysIL.

Table S1. Ionic liquid synthesis conditions

Amino acid	Mole AA (mmol)	Choline OH (mmol)	Temperature (°C)	Water (mL)	Reaction time (h)
Asp	15.1	13.6	50	40	72
Lys	13.7	12.4	50	40	72
Ser	19.1	17.2	50	40	72
Phe	12.1	10.9	50	40	72
Leu	15.3	13.8	50	40	72

ChAAIL and Acrylates Aqueous NMR Kinetic Studies

Table S2. Reaction summary of ChAAILs with simple acylates.

ChAAILs	Acrylate	Solvent	Reaction Time (min)	Total conversion*	Michael product*	Degradation product*
ChLysIL	EA	Water	30	100%	68%	32%
ChLysIL	HEA	Water	30	100%	40%	60%
ChLysIL	EA	Water	720	100%	17%	83%
ChLysIL	HEA	Water	720	100%	0%	100%
ChLysIL	EA	Neat	30	97%	86%	10%
ChLysIL	HEA	Neat	30	99%	59%	40%
ChLysIL	EA	Neat	1440	100%	89%	11%
ChLysIL	HEA	Neat	1440	99%	61%	39%
ChSerIL	EA	Water	30	70%	64%	6%
ChSerIL	HEA	Water	30	72%	57%	14%
ChSerIL	EA	Water	720	96%	51%	45%
ChSerIL	HEA	Water	720	91%	36%	54%
ChSerIL	EA	Neat	30	34%	31%	3%
ChSerIL	HEA	Neat	30	75%	56%	20%
ChSerIL	EA	Neat	1440	99%	87%	12%
ChSerIL	HEA	Neat	1440	97%	65%	33%
ChPheIL	EA	Water	30	64%	59%	4%
ChPheIL	HEA	Water	30	67%	58%	9%
ChPheIL	EA	Water	720	93%	45%	48%
ChPheIL	HEA	Water	720	83%	40%	44%
ChPheIL	EA	Neat	30	31%	23%	8%
ChPheIL	HEA	Neat	30	60%	55%	5%
ChPheIL	EA	Neat	1440	85%	71%	15%
ChPheIL	HEA	Neat	1440	83%	56%	27%
ChLeuIL	EA	Water	30	69%	64%	5%
ChLeuIL	HEA	Water	30	75%	62%	13%
ChLeuIL	EA	Water	720	98%	41%	57%
ChLeuIL	HEA	Water	720	86%	27%	59%
ChLeuIL	EA	Neat	30	48%	45%	3%
ChLeuIL	HEA	Neat	30	61%	51%	10%
ChLeuIL	EA	Neat	1440	100%	96%	4%
ChLeuIL	HEA	Neat	1440	94%	75%	20%
ChAspIL	EA	Water	30	0%	0%	0%
ChAspIL	HEA	Water	30	0%	0%	0%
ChAspIL	EA	Water	720	0%	0%	0%
ChAspIL	HEA	Water	720	0%	0%	0%

ChAspIL	EA	Neat	30	0%	0%	0%
ChAspIL	HEA	Neat	30	0%	0%	0%
ChAspIL	EA	Neat	1440	0%	0%	0%
ChAspIL	HEA	Neat	1440	0%	0%	0%

*Total conversion is defined by the % of acrylate reacted, Michael or degradation product conversion is determined by the ratio of the relative products of Michael product and degradation product by NMR out of the total conversion.

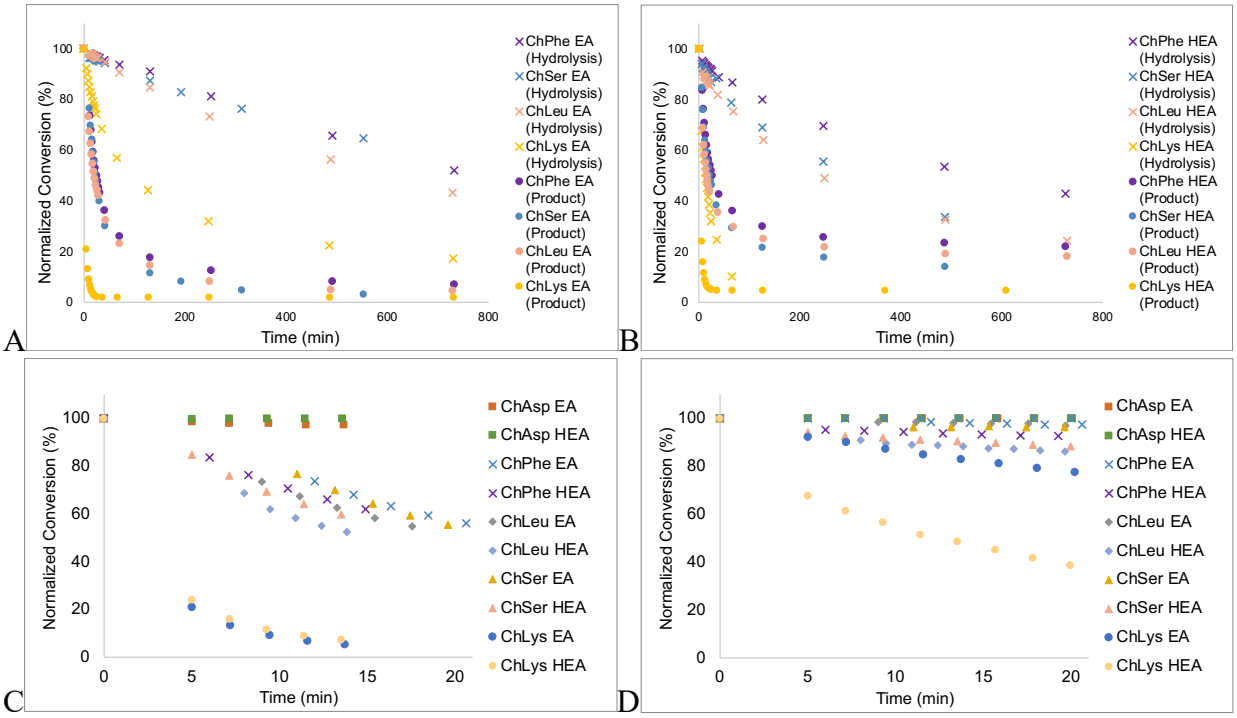


Figure S6. Kinetic monitoring showing data of the normalized conversion which was represented by the % consumption of acrylate proton signals by NMR A) ChAAILs with EA over 12 hours plotting Michael product conversion and hydrolysis product conversions. B) ChAAILs with HEA over 12 hours plotting Michael product conversion and hydrolysis product conversions. C) Kinetic monitoring of linear regions at 0-20 mins of Michael production conversion for ChAAILs with EA and HEA. Slopes of the best fit lines for each curve were used as initial rates of reactions. D) Kinetic monitoring of linear regions at 0-20 mins of hydrolysis production conversion for ChAAILs with EA and HEA. Slopes of the best fit lines for each curve were used as initial rates of reactions.

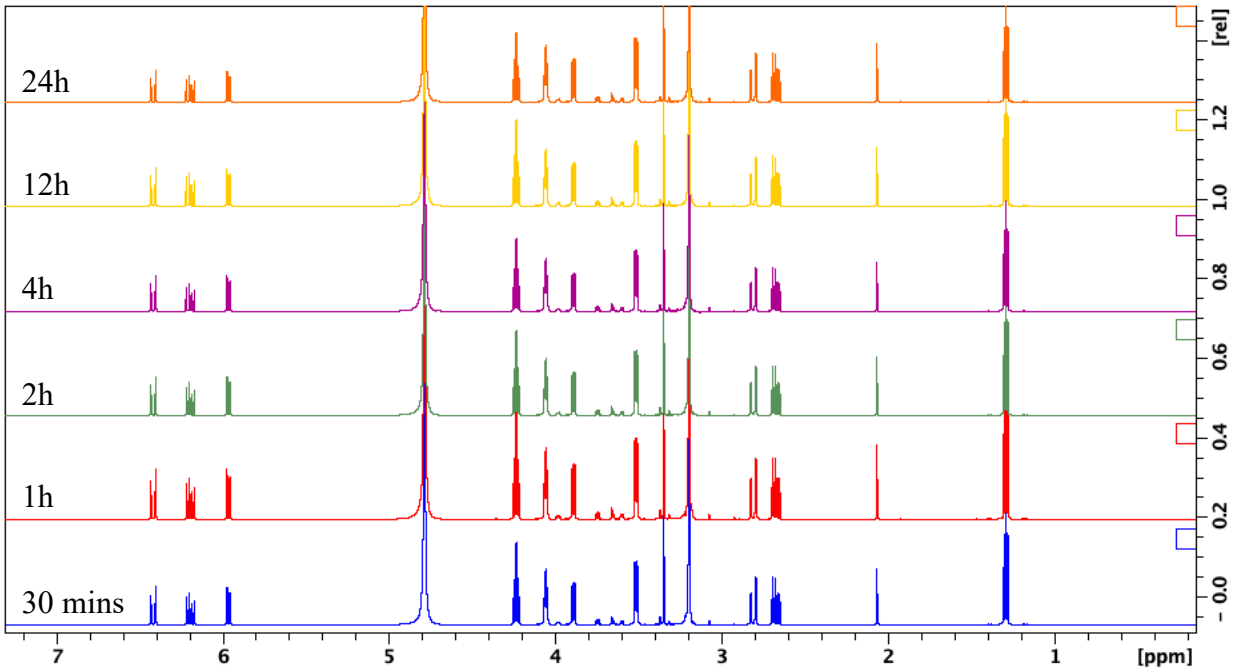


Figure S7. ^{1}H NMR stacked plots of reaction monitoring of ChAspIL and EA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

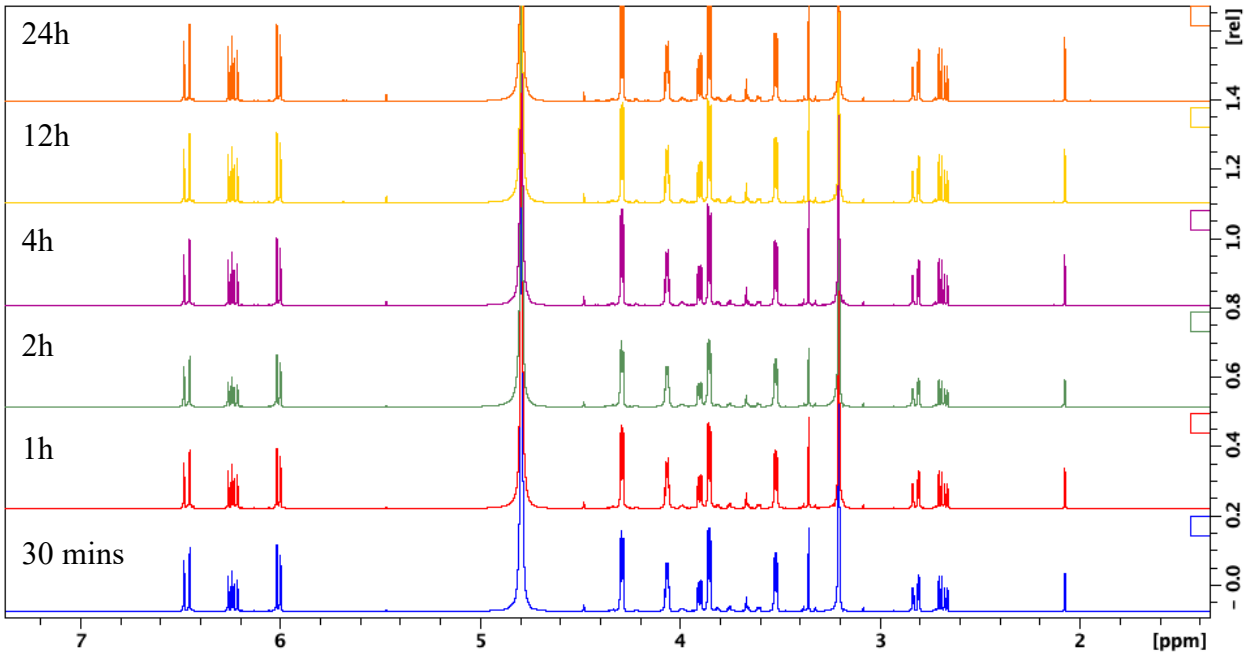


Figure S8. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL and HEA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

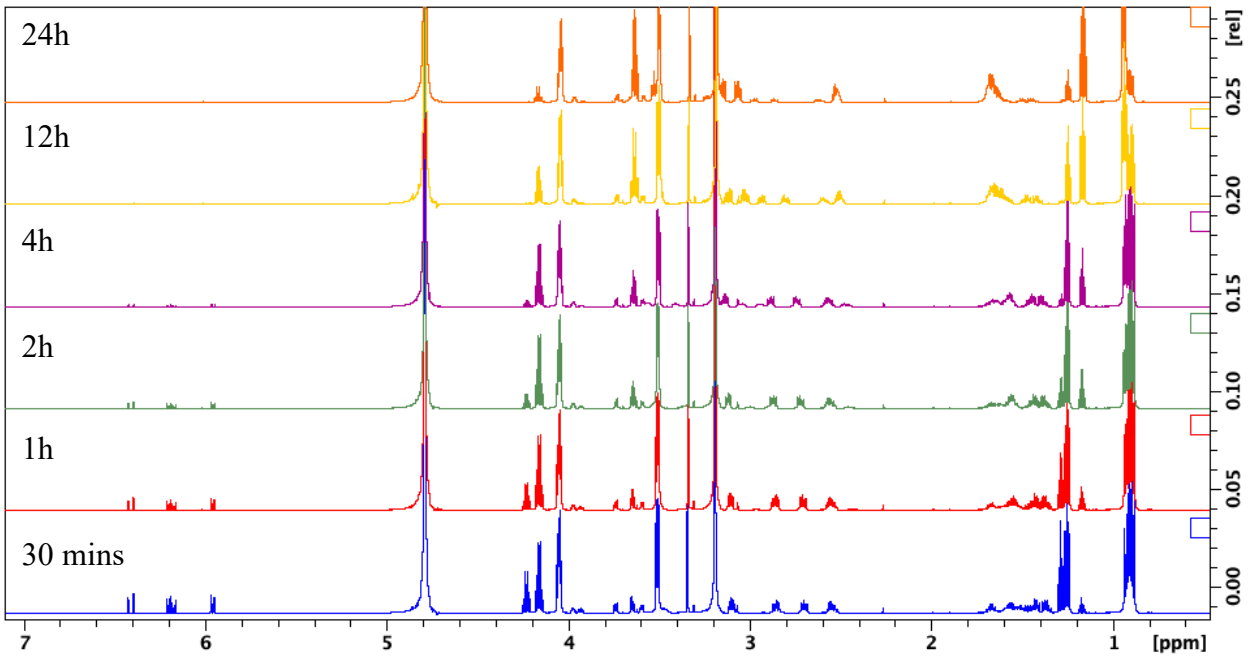


Figure S9. ^{1}H NMR stacked plots for reaction monitoring of ChLeuIL and EA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

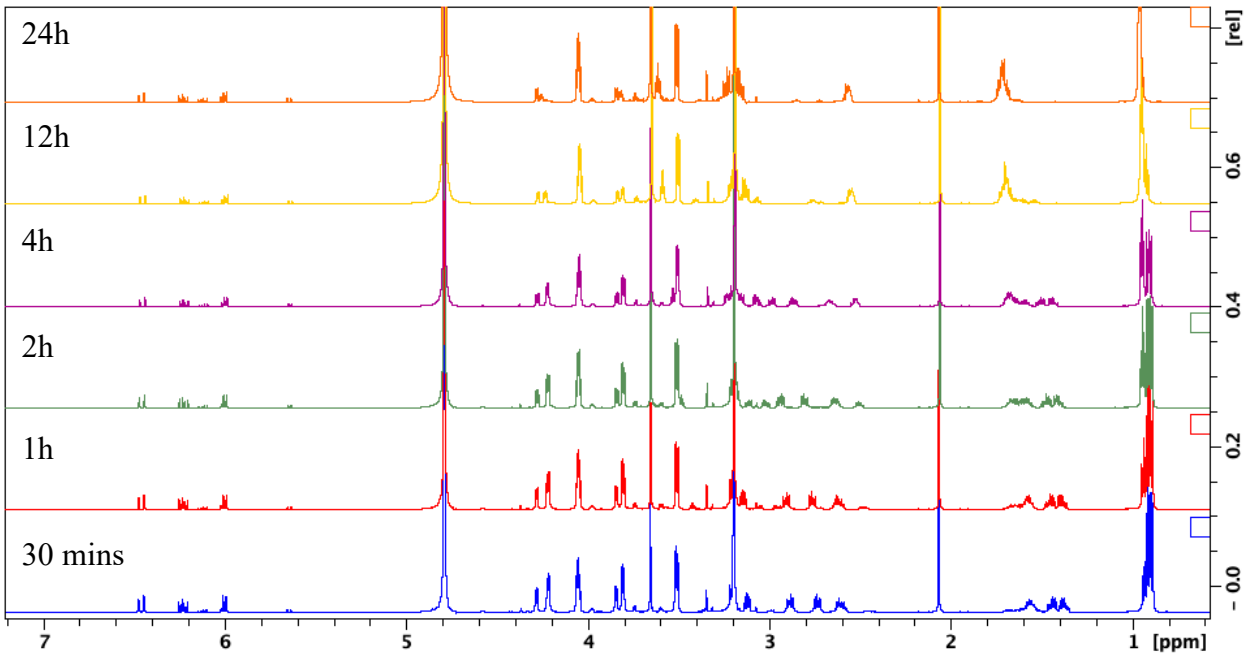


Figure S10. ^{1}H NMR stacked plots for reaction monitoring of ChLeuIL and HEA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

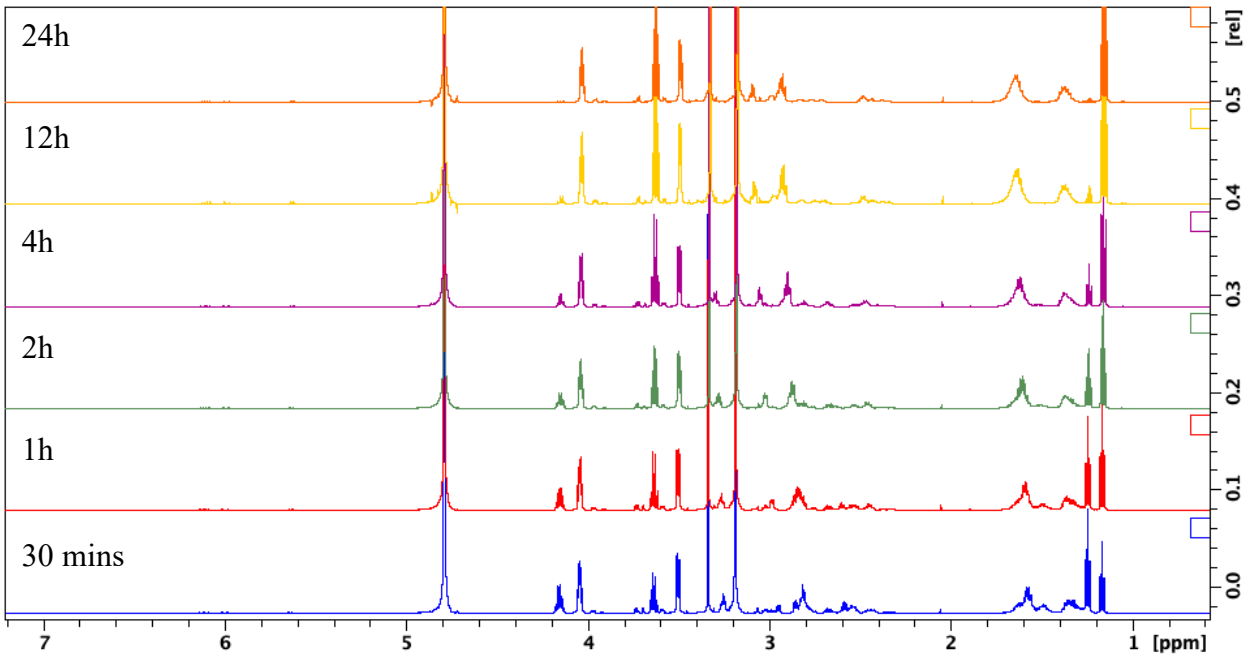


Figure S11. ^{1}H NMR stacked plots for reaction monitoring of ChLysIL and EA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

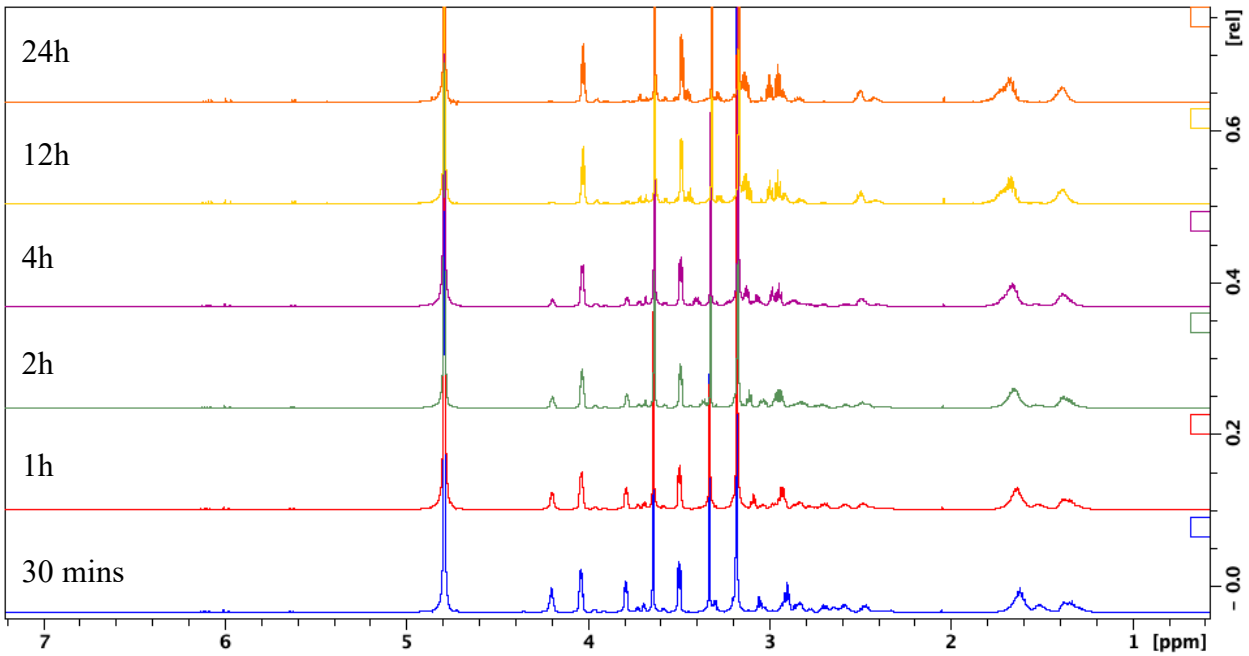


Figure S12. ^{1}H NMR stacked plots for reaction monitoring of ChLysIL and HEA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

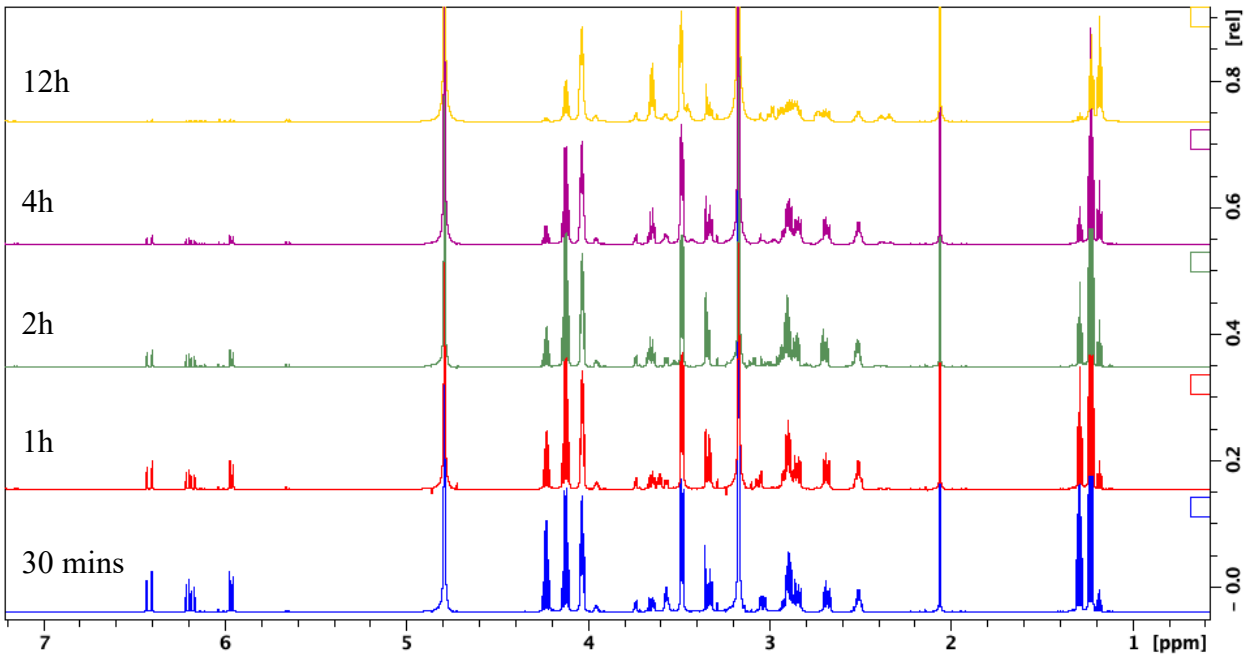


Figure S13. ^{1}H NMR stacked plots for reaction monitoring of ChPheIL and EA in D_2O, at 30min, 1h, 2h, 4h, 12h from bottom to top.

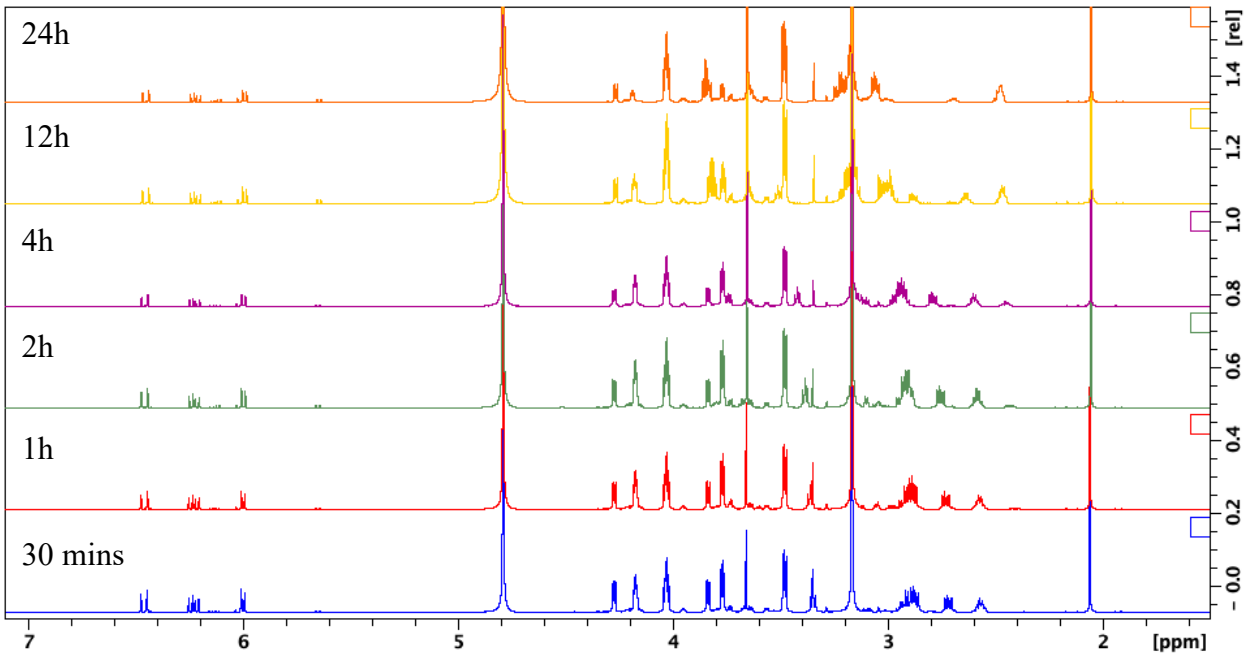


Figure S14. ^{1}H NMR stacked plots for reaction monitoring of ChPheIL and HEA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

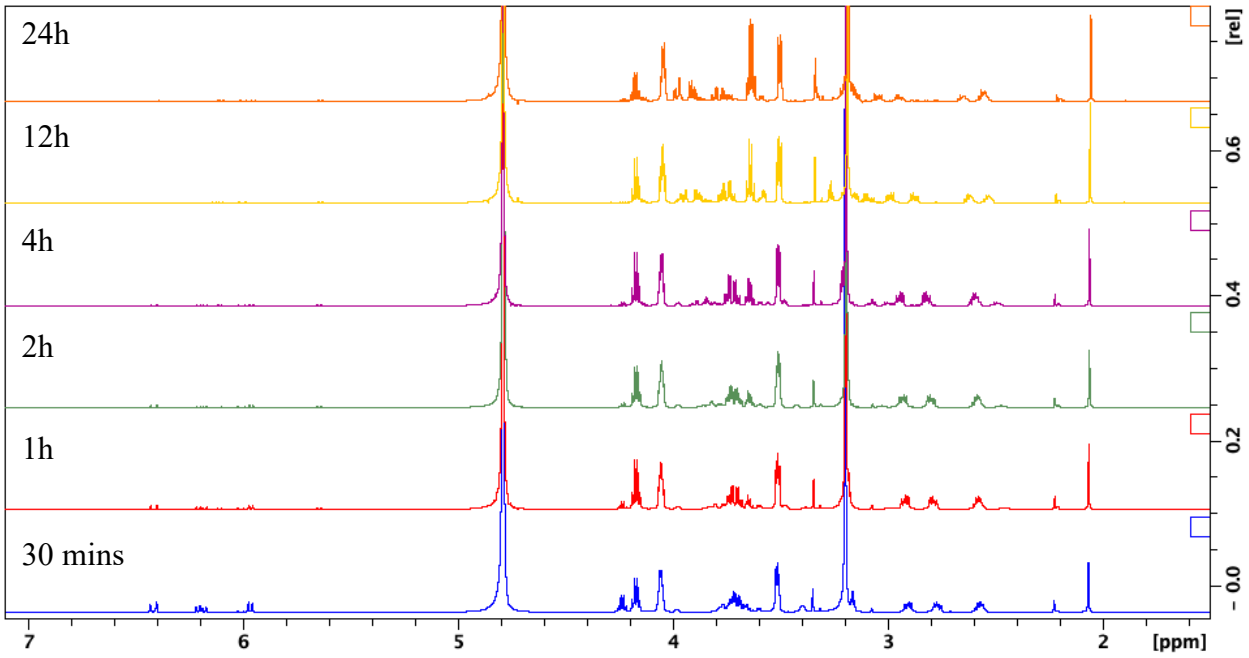


Figure S15. ^{1}H NMR stacked plots for reaction monitoring of ChSerIL and EA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

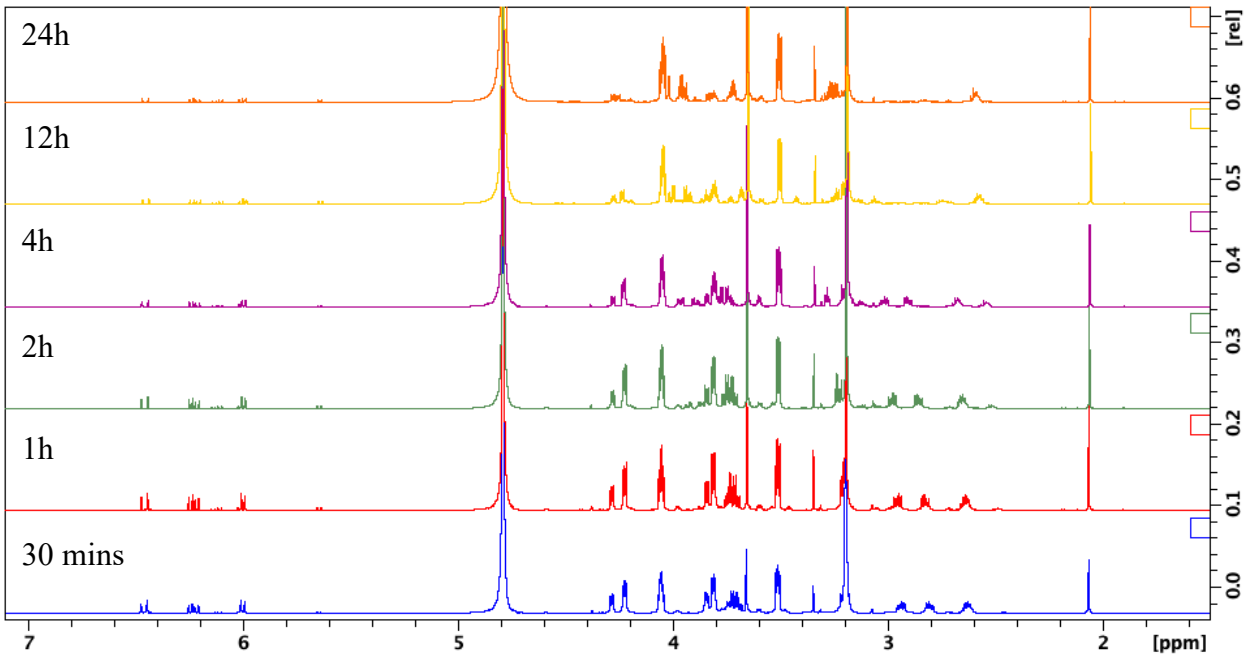


Figure S16. ^{1}H NMR stacked plots for reaction monitoring of ChSerIL and HEA in D_2O, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top.

ChAAIL and Acrylate Solvent Free Reactions

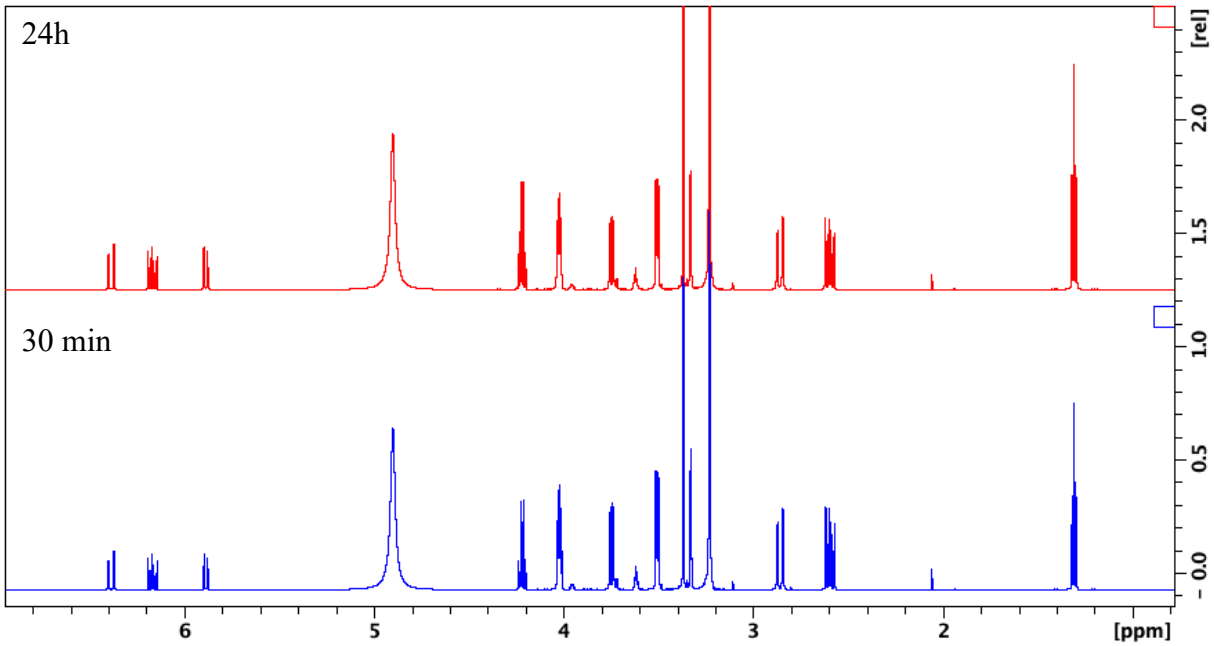


Figure S17. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL and EA neat, at 30min and 24h from bottom to top.

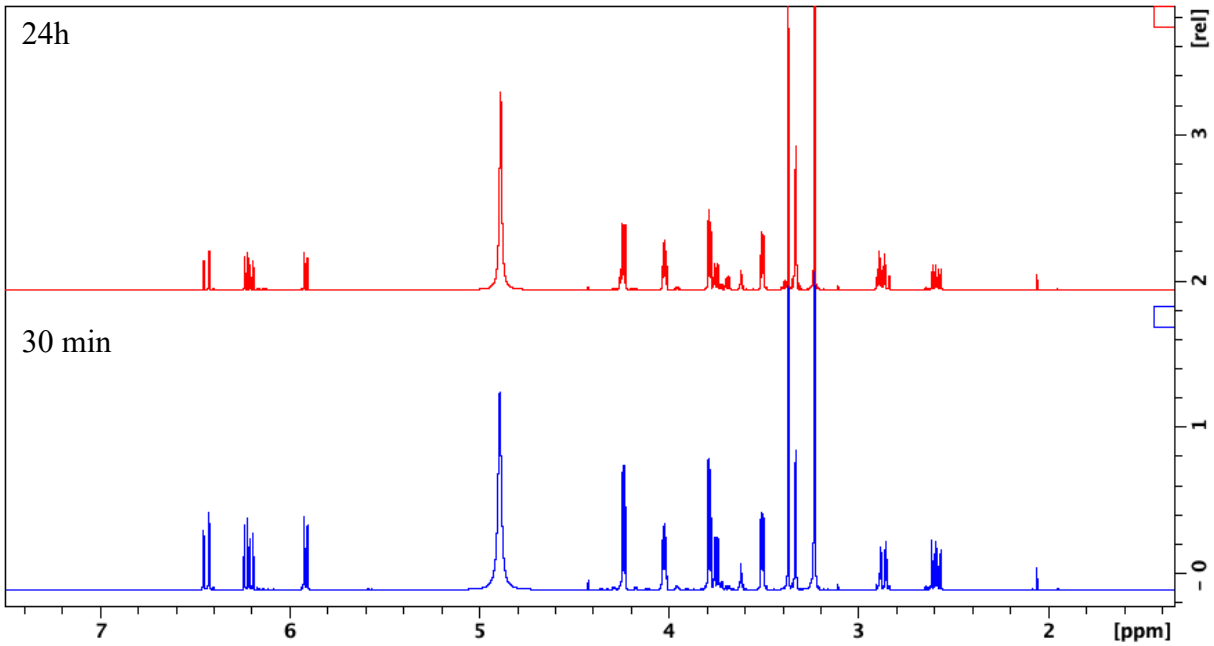


Figure S18. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL and HEA neat, at 30min and 24h from bottom to top.

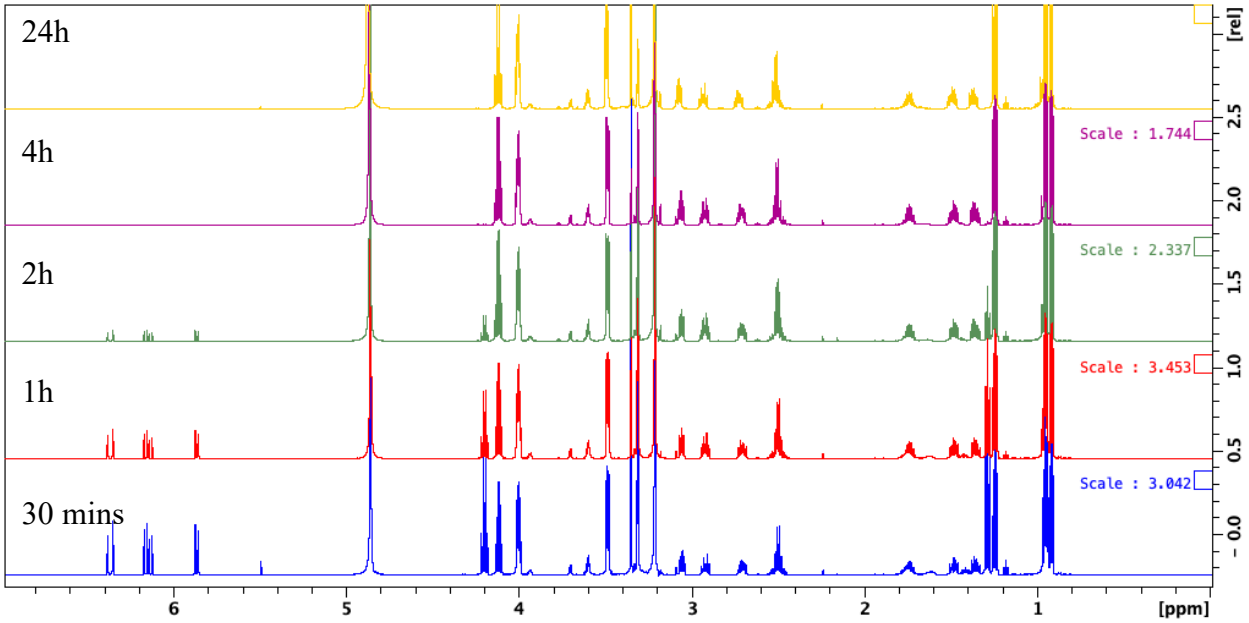


Figure S19. ^{1}H NMR stacked plots for reaction monitoring of ChLeuIL and EA neat, at 30min, 1h, 2h, 4h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

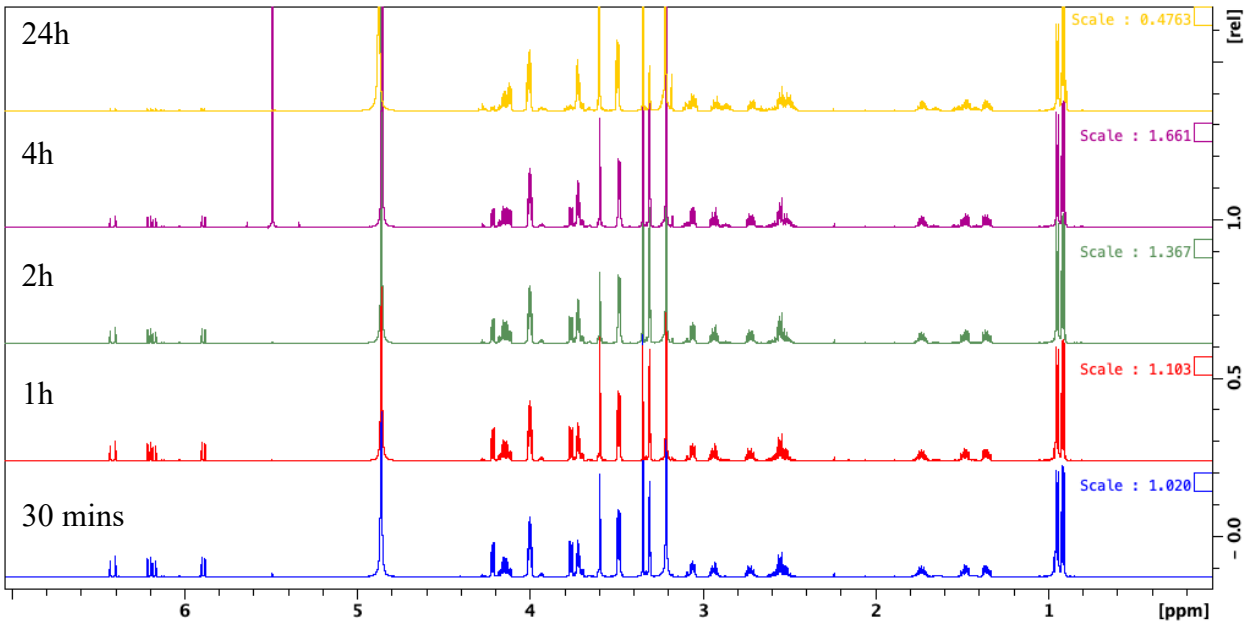


Figure S20 ^{1}H NMR stacked plots for reaction monitoring of ChLeuIL and HEA neat, at 30min, 1h, 2h, 4h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

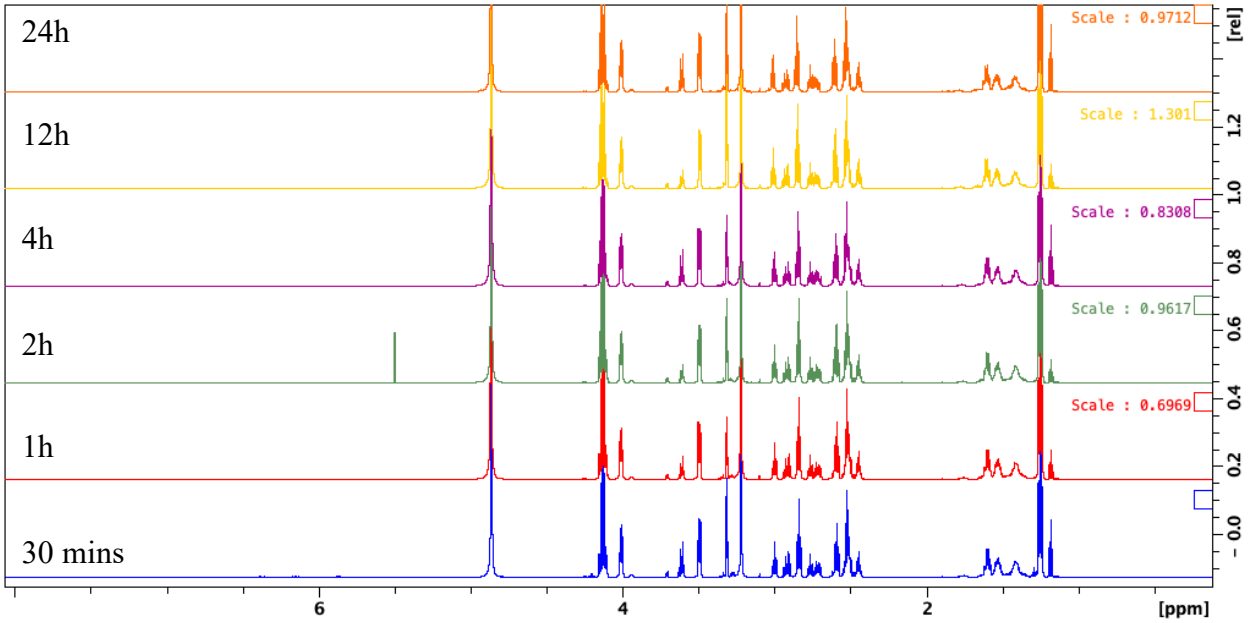


Figure S21. ^{1}H NMR stacked plots for reaction monitoring of ChLysIL and EA neat, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

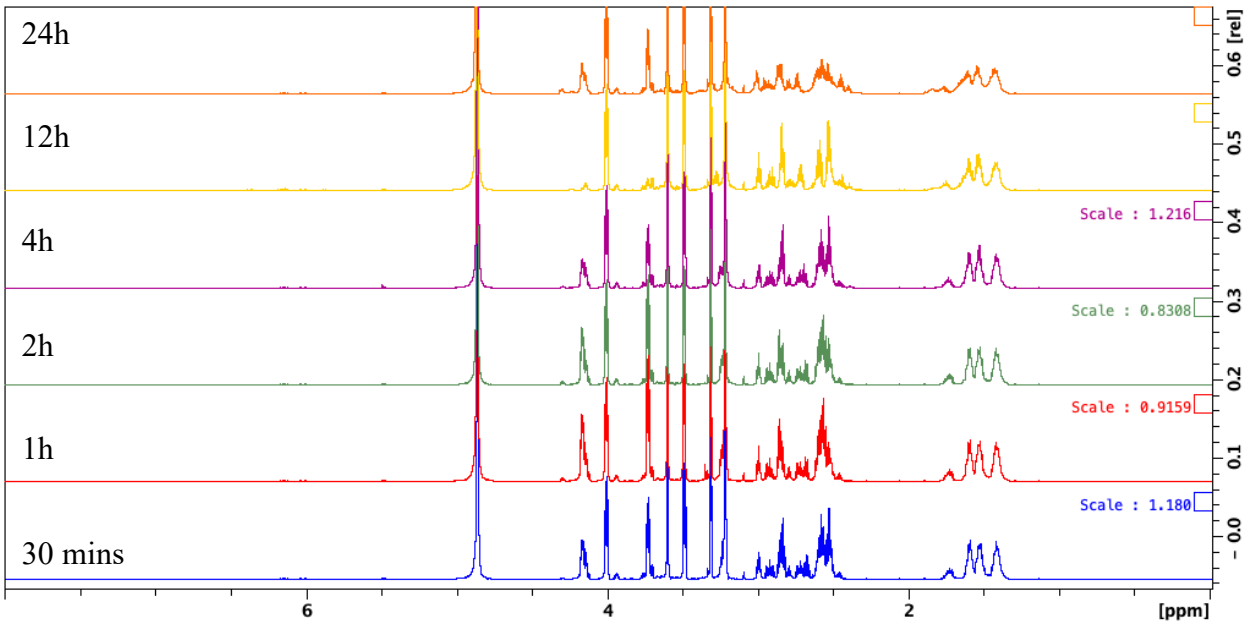


Figure S22. ^{1}H NMR stacked plots for reaction monitoring of ChLysIL and HEA neat, at 30min, 1h, 2h, 4h, 12h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

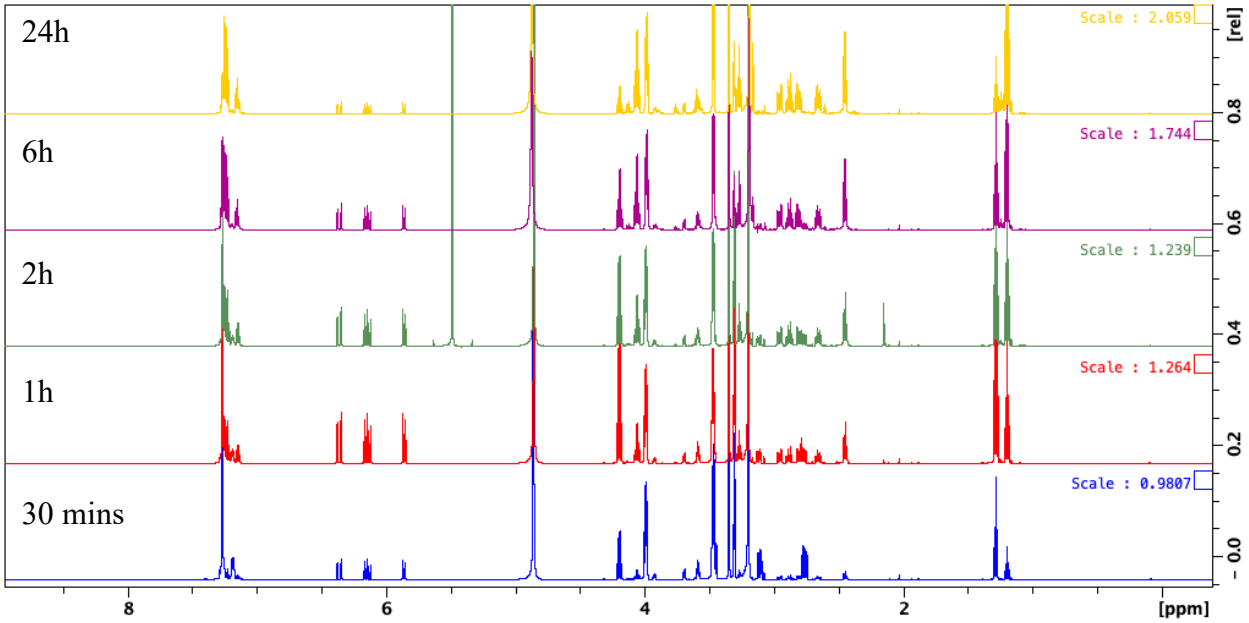


Figure S23. ^{1}H NMR stacked plots for reaction monitoring of ChPheIL and EA neat, at 30min, 1h, 2h, 6h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points. It is noted that the mixture was inhomogeneous and liquid sample was not able to be collected uniformly at different time points.

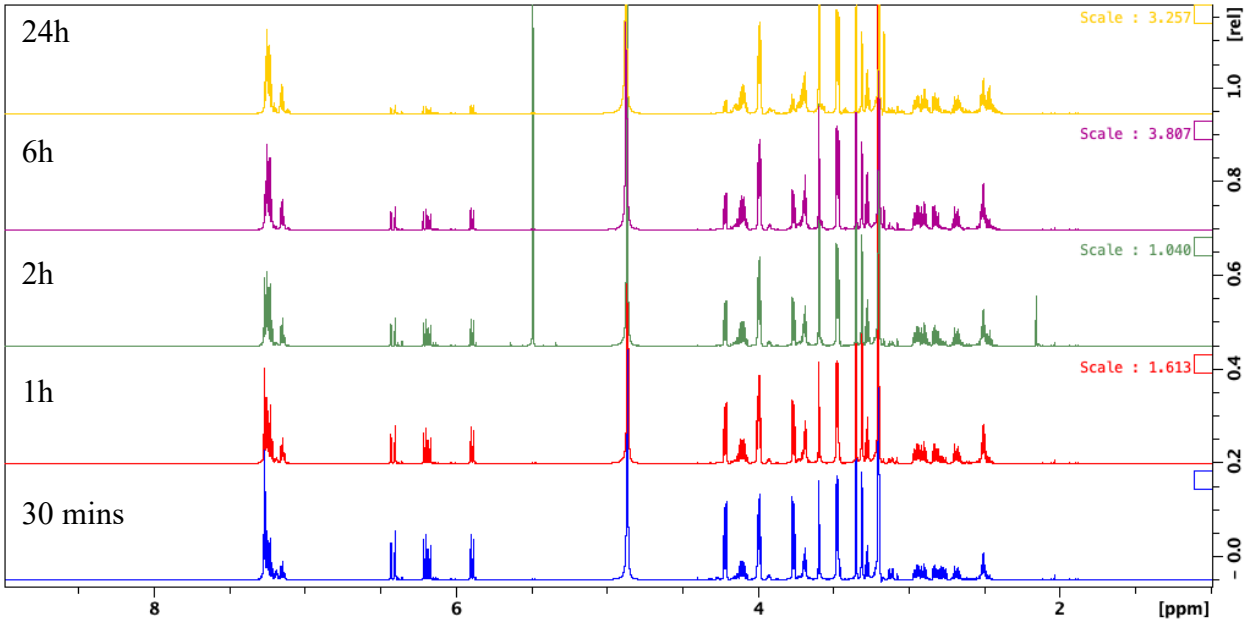


Figure S24. ^{1}H NMR stacked plots for reaction monitoring of ChPheIL and HEA neat, at 30min, 1h, 2h, 6h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

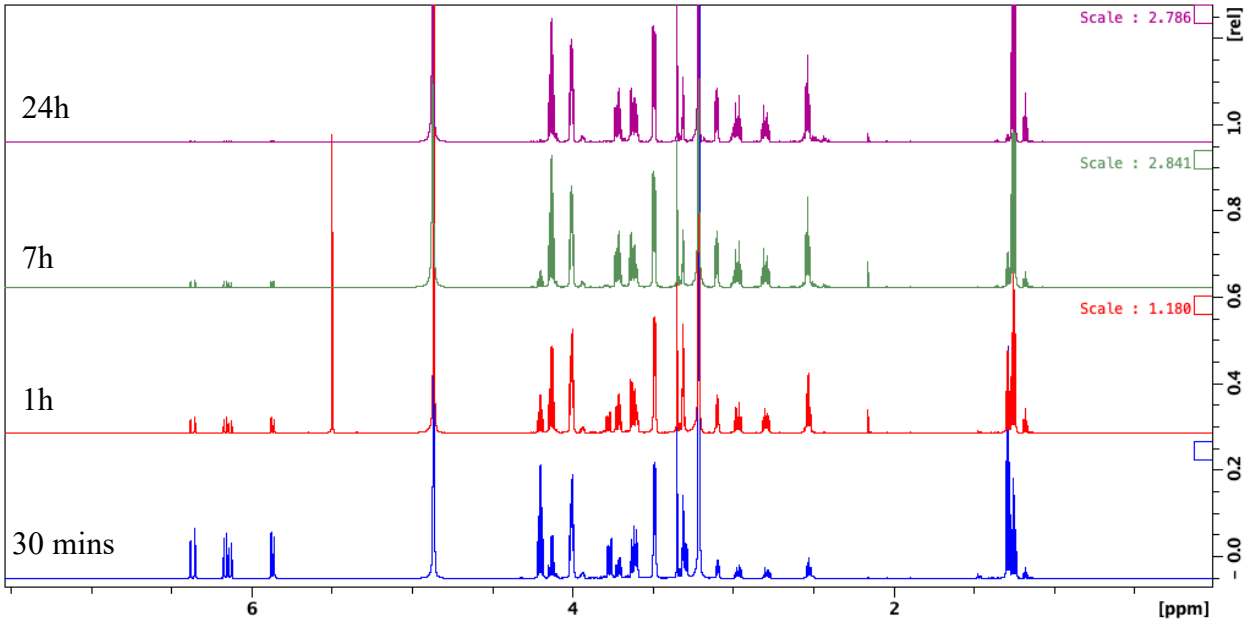


Figure S25. ^{1}H NMR stacked plots for reaction monitoring of ChSerIL and EA neat, at 30min, 1h, 7h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

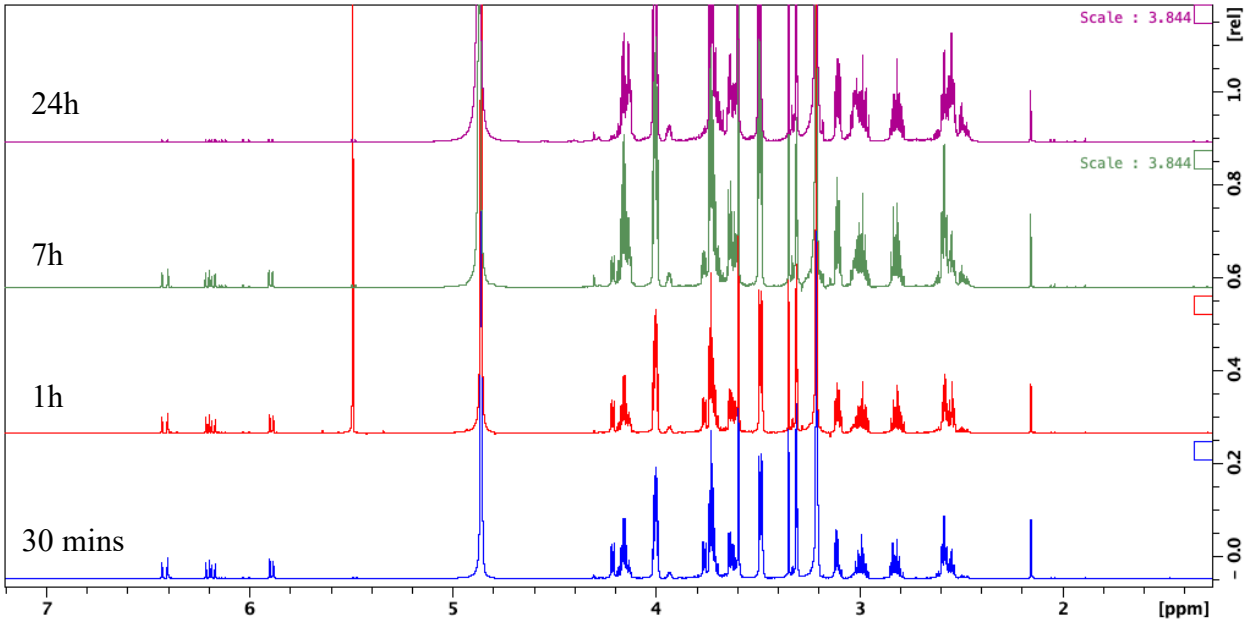


Figure S26. ^{1}H NMR stacked plots for reaction monitoring of ChSerIL and HEA neat, at 30min, 1h, 7h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

Experimental for reaction of ChSerIL with HEA under dry nitrogen

~2 g of ChSerIL was placed in a 25 mL round bottom flask and dried under reduced pressure at 60 degrees for 1 hour using rotary evaporator. 0.3 g (1.35 mmol) of the dried ChSerIL was then placed in a 15 mL glass vial (preheated at 80 °C overnight) equipped with stir bar and septum. 141 uL of HEA was then added to the vial and stirred for 24 hours under dried nitrogen. ^{1}H NMR was taken at end of reaction.

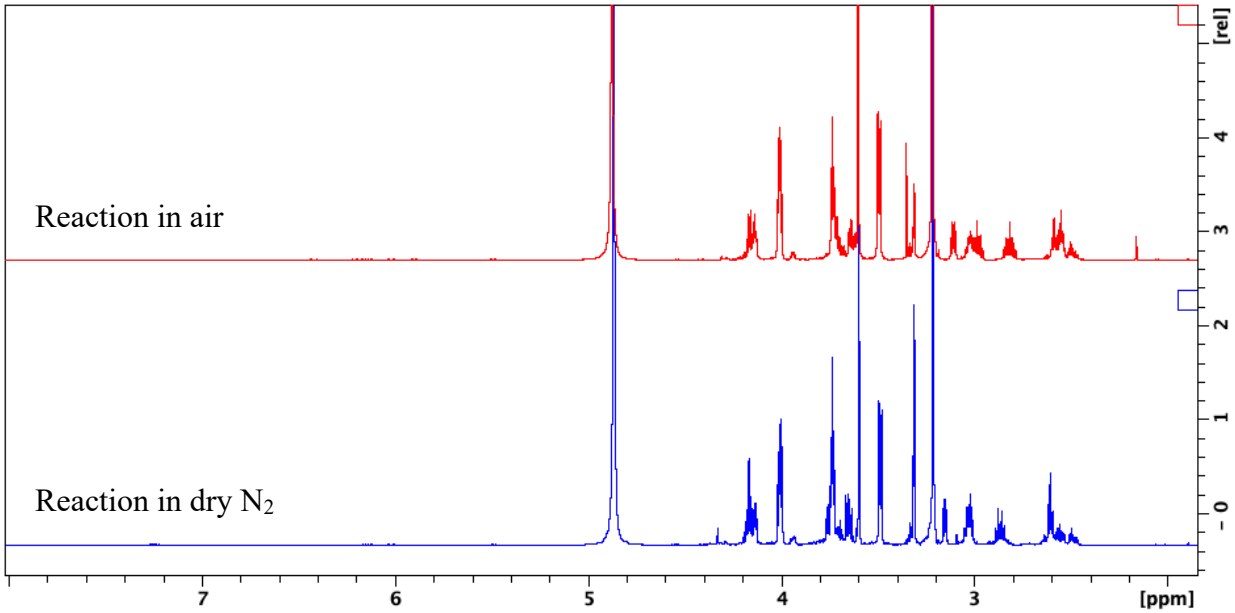


Figure S27. ^{1}H NMR comparison of the reaction of ChSerIL with HEA under dry nitrogen vs atmospheric air. The 24 hours conversion rate comparison of the two reactions were nearly identical, however under air, the hydrolysis product was 1.6 times higher compared to the outcome under nitrogen; employing dry conditions can reduce hydrolysis product.

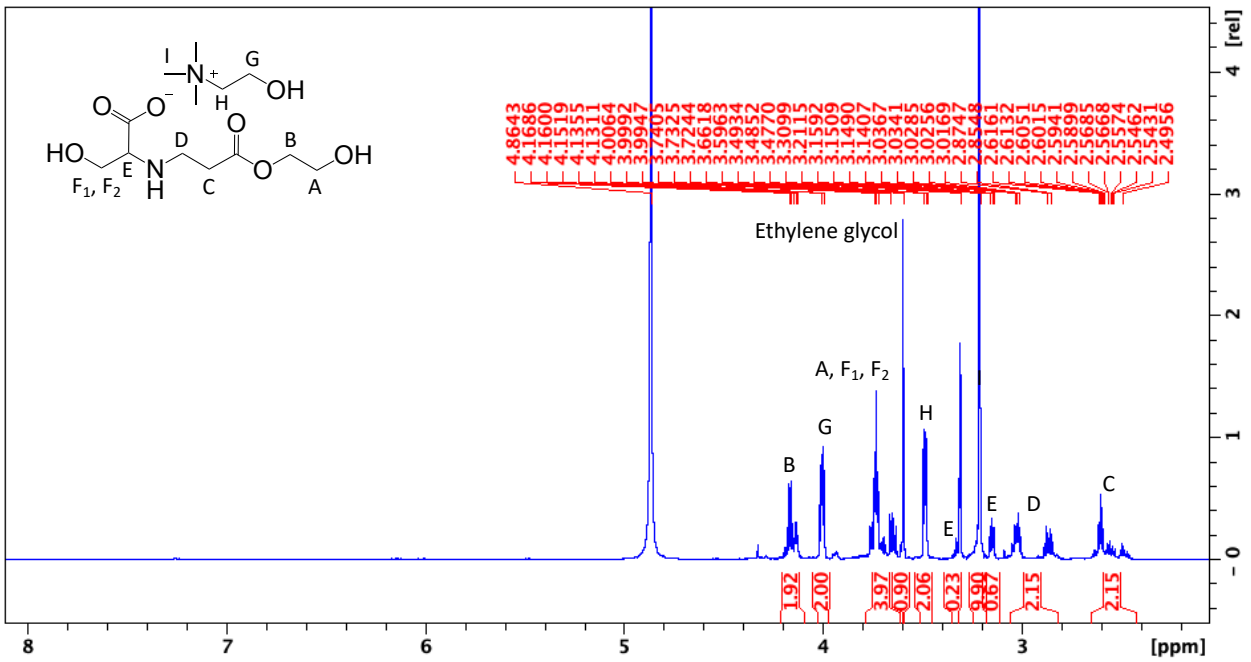


Figure S28. Assigned ^{1}H NMR of ChSerIL and HEA reaction product after 24h.

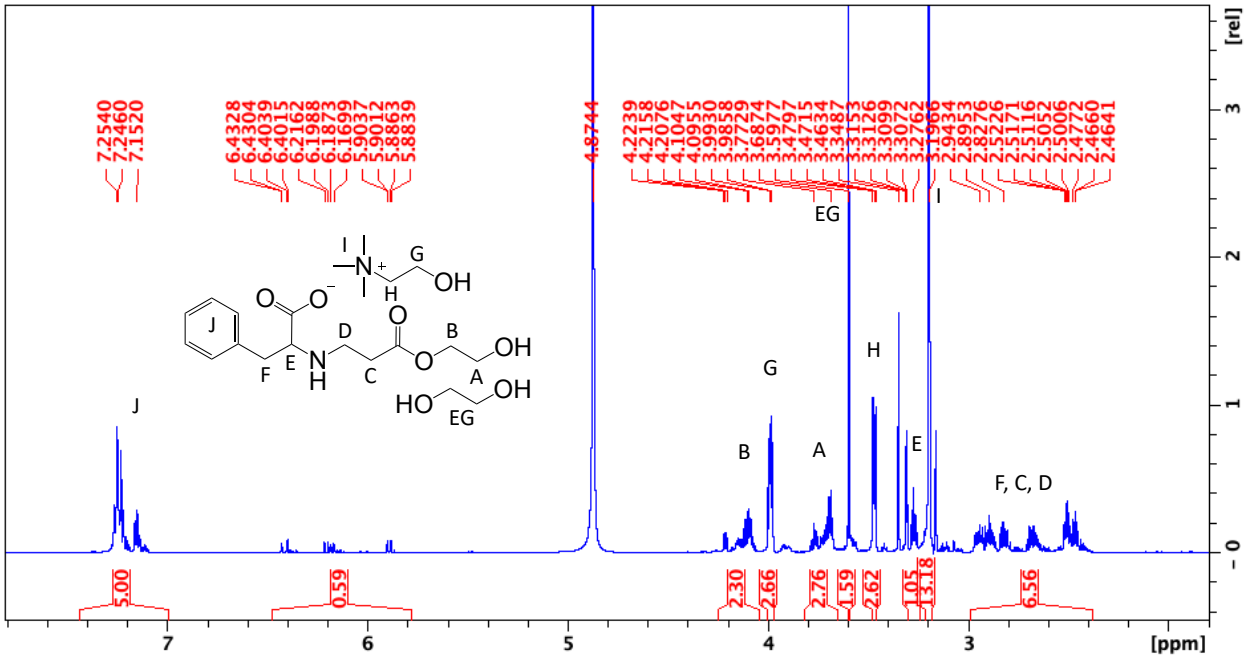


Figure S29 Assigned ^{1}H NMR of ChPheIL and HEA reaction product after 24 hours.

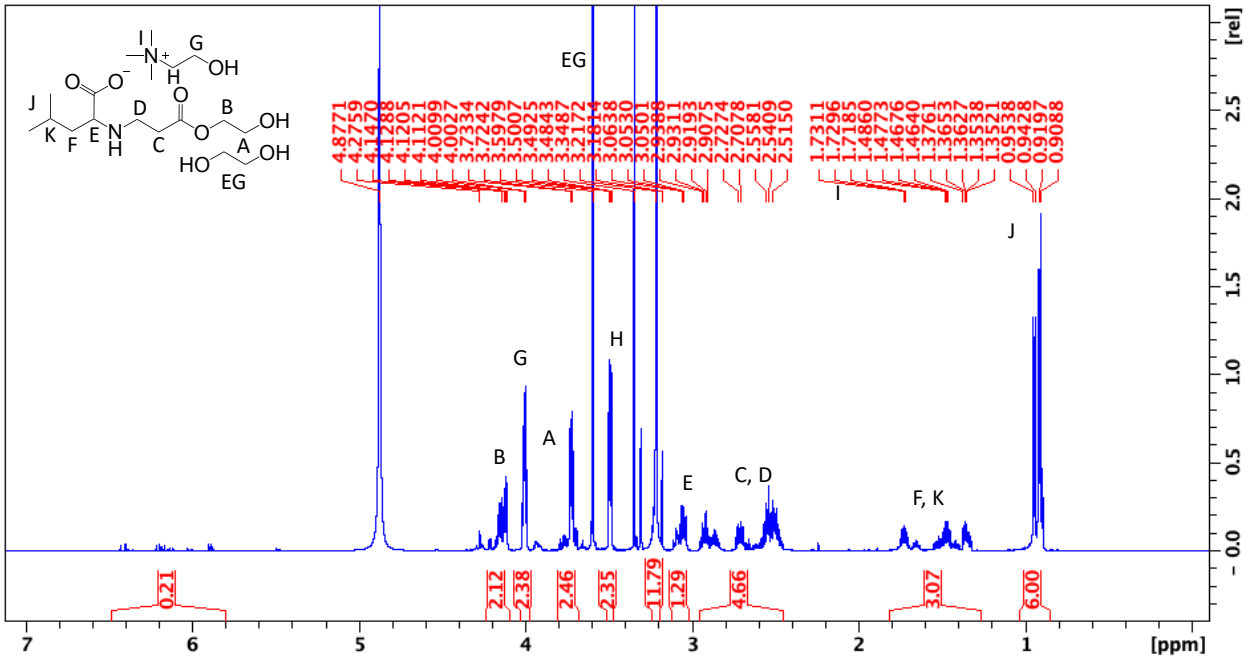


Figure S30 Assigned ^{1}H NMR of ChLeuIL and HEA reaction product after 24h.

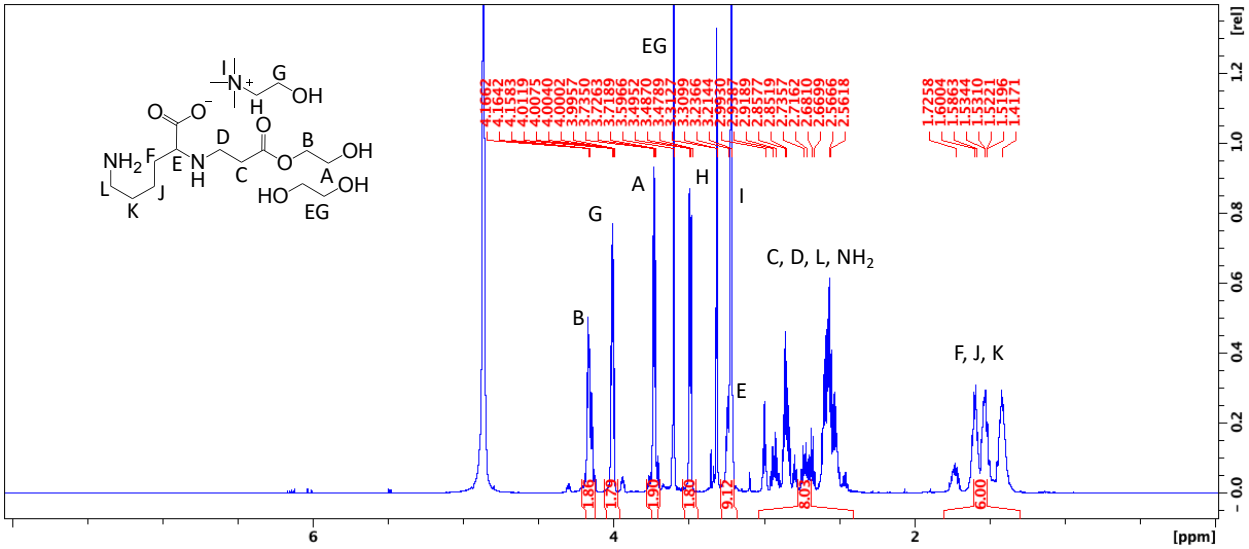


Figure S31 Assigned ^{1}H NMR of ChLysIL and HEA reaction product after 24h.

Reaction Quenching and Effect of Base on aza-Michael Reactivity

Table S3 Effect of base on aza-Michael reaction

ChAAILs	Acrylate	ChOH mole eq	24 h Conversion before ChOH	reaction time after ChOH	Conversion after ChOH
ChAspIL	EA	1	0%	30 min	94%
ChAspIL	EA	1	0%	24 h	100%
ChAspIL	EA	0.01	0%	30 min	24%
ChAspIL	EA	0.01	0%	24 h	81%
ChAspIL	HEA	1	0%	30 min	81%
ChAspIL	HEA	1	0%	24 h	100%
ChAspIL	HEA	0.01	0%	30 min	45%
ChAspIL	HEA	0.01	0%	24 h	69%

Table S4 Effect of Acid quenching on aza-Michael reaction

ChAAILs	Acrylate	AcOH mole eq	2 h Conversion before ChOH	reaction time after AcOH (h)	Conversion after AcOH
ChPheIL	EA	1	71%	24	0%
ChPheIL	HEA	1	50%	24	0%

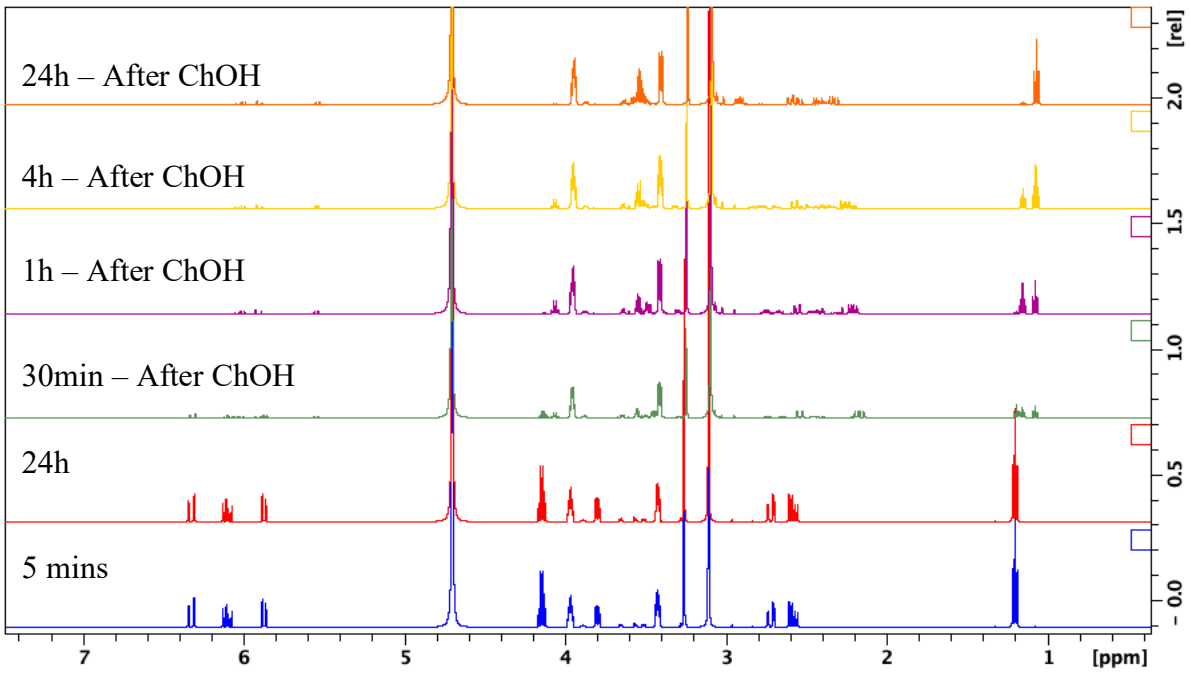


Figure S32. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL with EA, before and after 1 eq ChOH added after 24 hours. From bottom to top first two spectra represent 5 mins and 24 h after reaction before ChOH is added. 1eq ChOH added at 24 hours timepoint, then the top four spectra representing reaction monitored at 30 min, 1h, 4h, and 24h after the addition of ChOH.

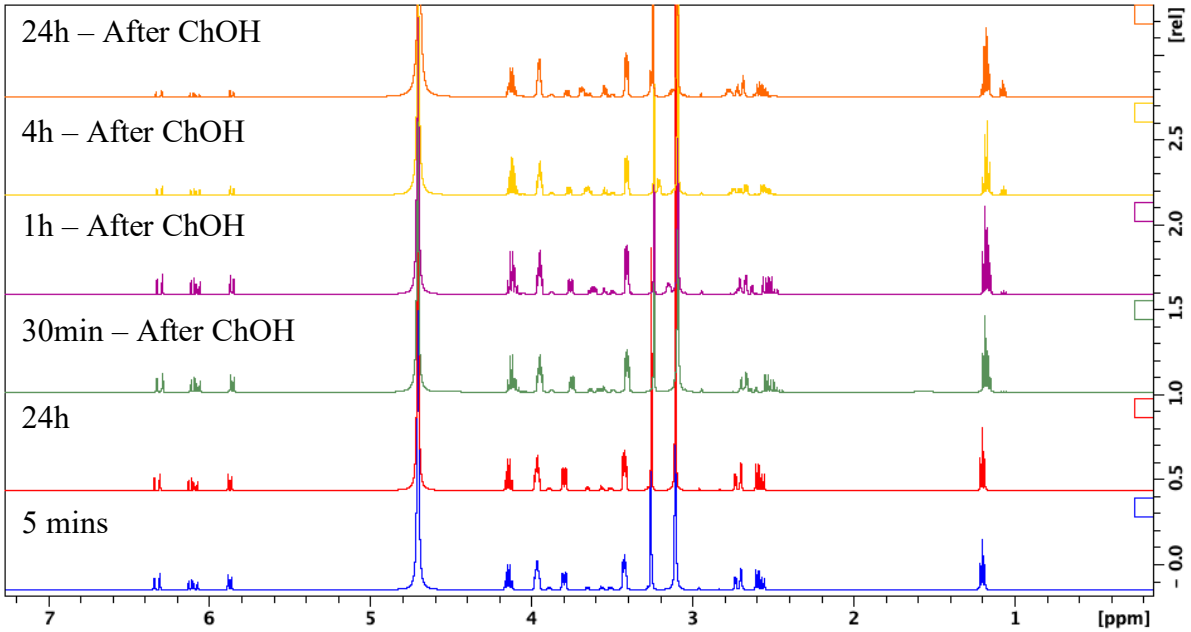


Figure S33. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL with EA, before and after 0.01 eq ChOH added after 24 hours. From bottom to top first two spectra represent 5 mins and 24 h after reaction before ChOH is added. 1eq ChOH added at 24 hours timepoint, then the top four spectra representing reaction monitored at 30 min, 1h, 4h, and 24h after the addition of ChOH.

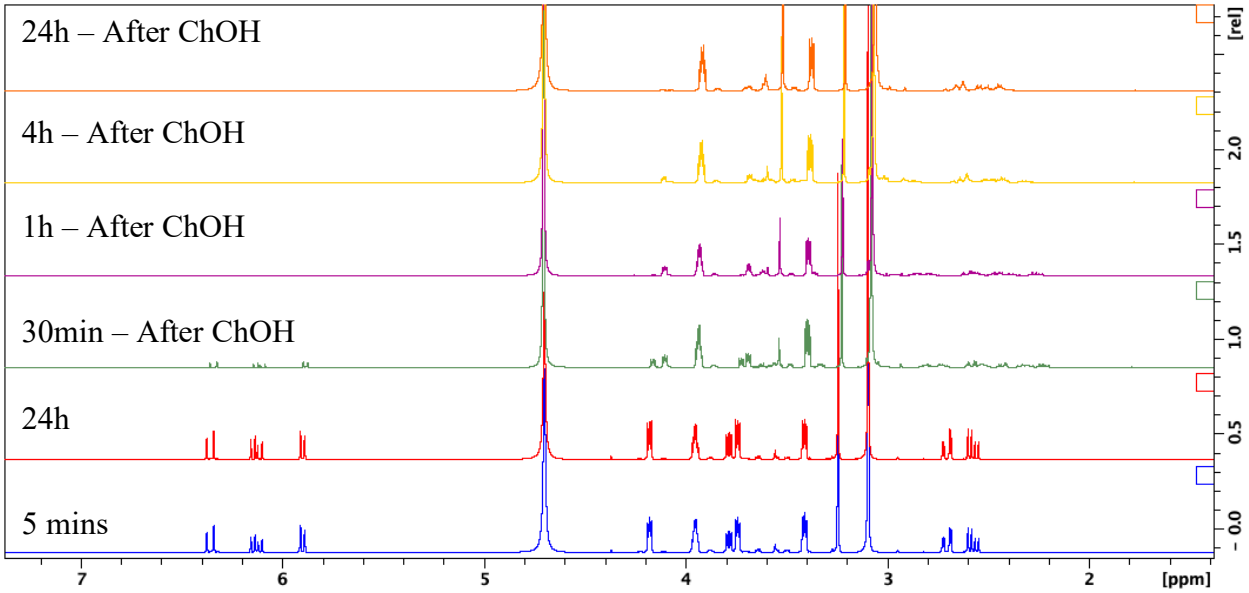


Figure S34. ^{1}H NMR stacking for reaction monitoring of ChAspIL with HEA, before and after 1 eq ChOH added after 24 hours. From bottom to top first two spectra represent 5 mins and 24 h after reaction before ChOH is added. 1eq ChOH added at 24 hours timepoint, then the top four spectra representing reaction monitored at 30 min, 1h, 4h, and 24h after the addition of ChOH.

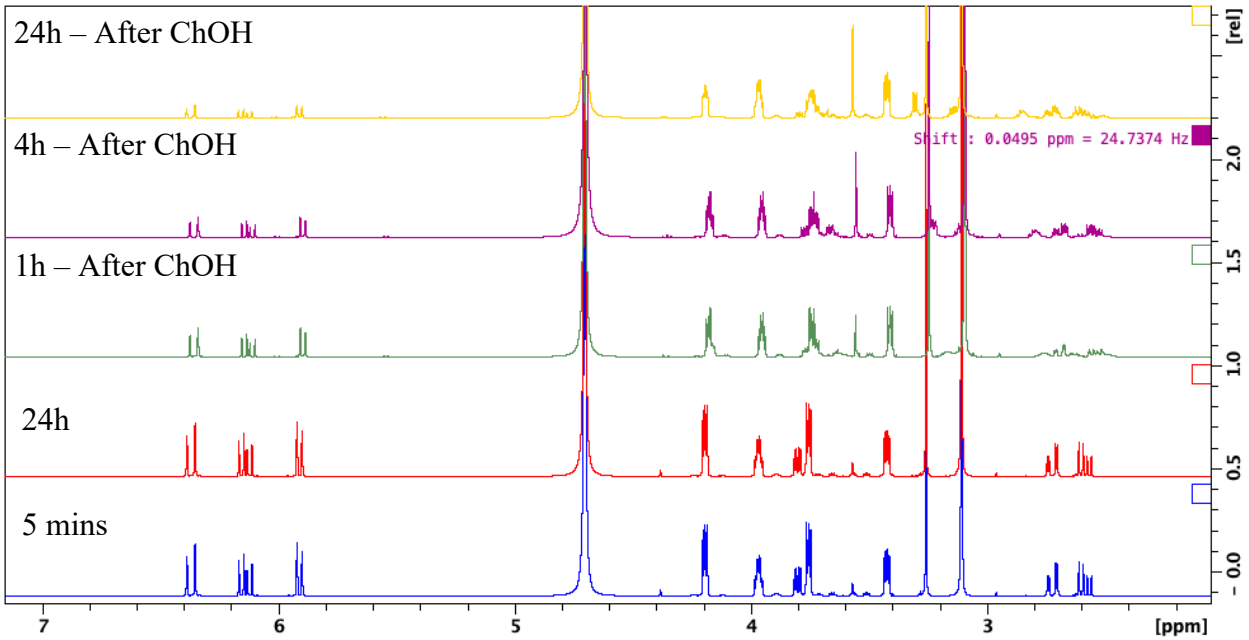


Figure S35. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL with HEA, before and after 0.01 eq ChOH added after 24 hours. From bottom to top first two spectra represent 5 mins and 24 h after reaction before ChOH is added. 1eq ChOH added at 24 hours timepoint, then the top three spectra representing reaction monitored at 1h, 4h, and 24h after the addition of ChOH.

24h – After AcOH

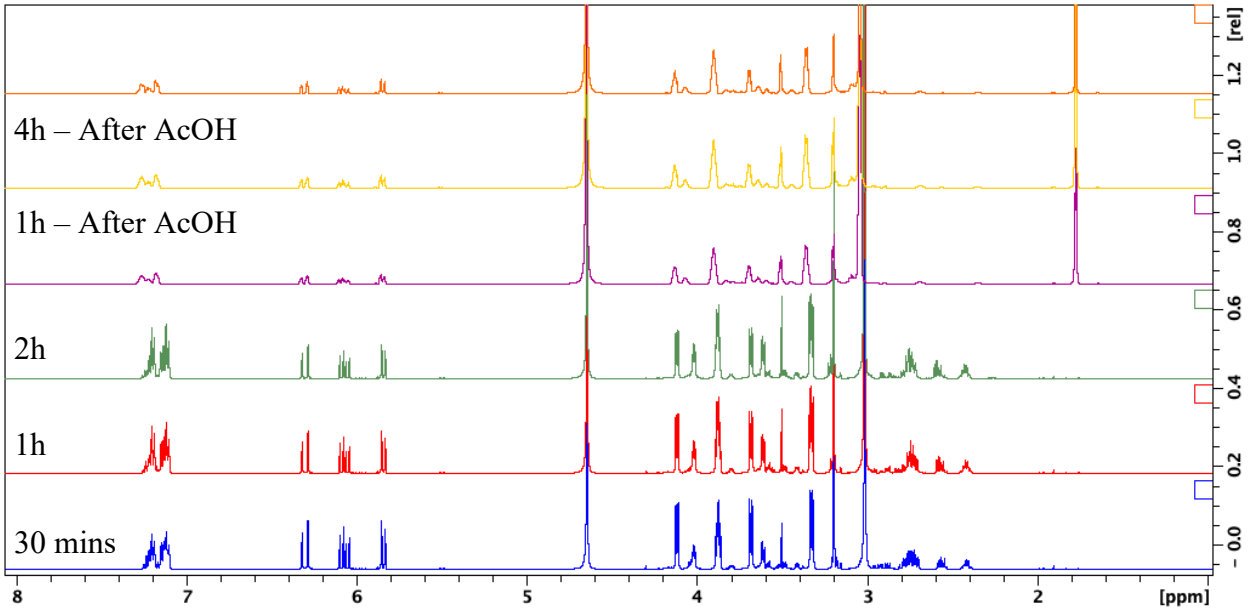


Figure S36. ^{1}H NMR stacked plots for reaction monitoring of ChPheIL with HEA. From bottom to top, it is shown the reaction was let reacted and monitored at 30 min, 1h and 2h (bottom three), the reaction mixture was then quenched with 1 eq AcOH and precipitate formed was then removed before the reaction was monitored at 1h, 4h, and 24h after reaction work up (top three).

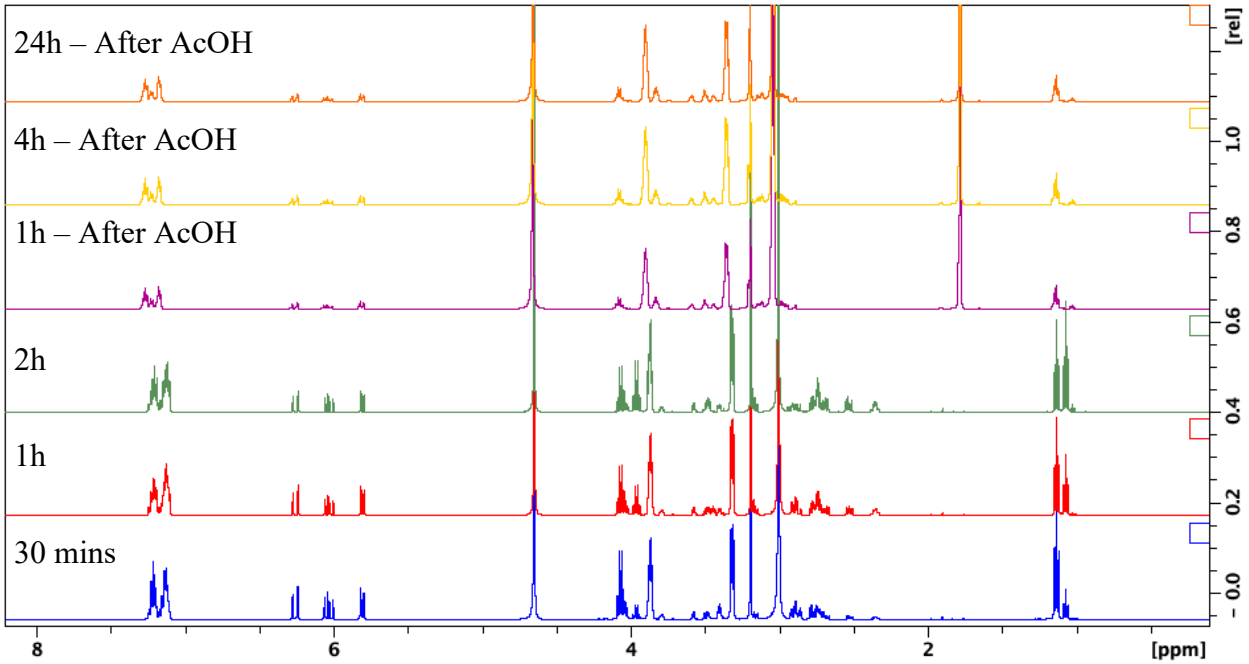


Figure S37. ^{1}H NMR stacked plots for reaction monitoring of ChPheIL with EA. From bottom to top, it is shown the reaction was let reacted and monitored at 30 min, 1h and 2h (bottom three), the reaction mixture was then quenched with 1 eq AcOH and precipitate formed was then removed before the reaction was monitored at 1h, 4h, and 24h after reaction work up (top three).

ChAAIL Reactivity with PEG

Table S5. Reaction summary of ChAAILs with polymer acrylates.

	PEG	Conversion (%) at		Silicones	Conversion at	
		1 hour	24 hours		1 hour	24 hours
ChLeuIL	**PEGACR**	82		**Di10**	34	89
				HODi9	74	88
ChLysIL	**PEGACR**	97	99	**Di10**	26	99
	OHGlyACR	99	99	**HODi9**	88	99
ChPheIL	**PEGACR**	57	61	**Di10**	1	48
	OHGlyACR	24	83	**HODi9**	60	80
ChSerIL	**PEGACR**	23	75	**Di10**	5	26
	OHGlyACR	72	98	**HODi9**	67	88
ChAspIL				**Di10**	0	0
				HODi9	0	0

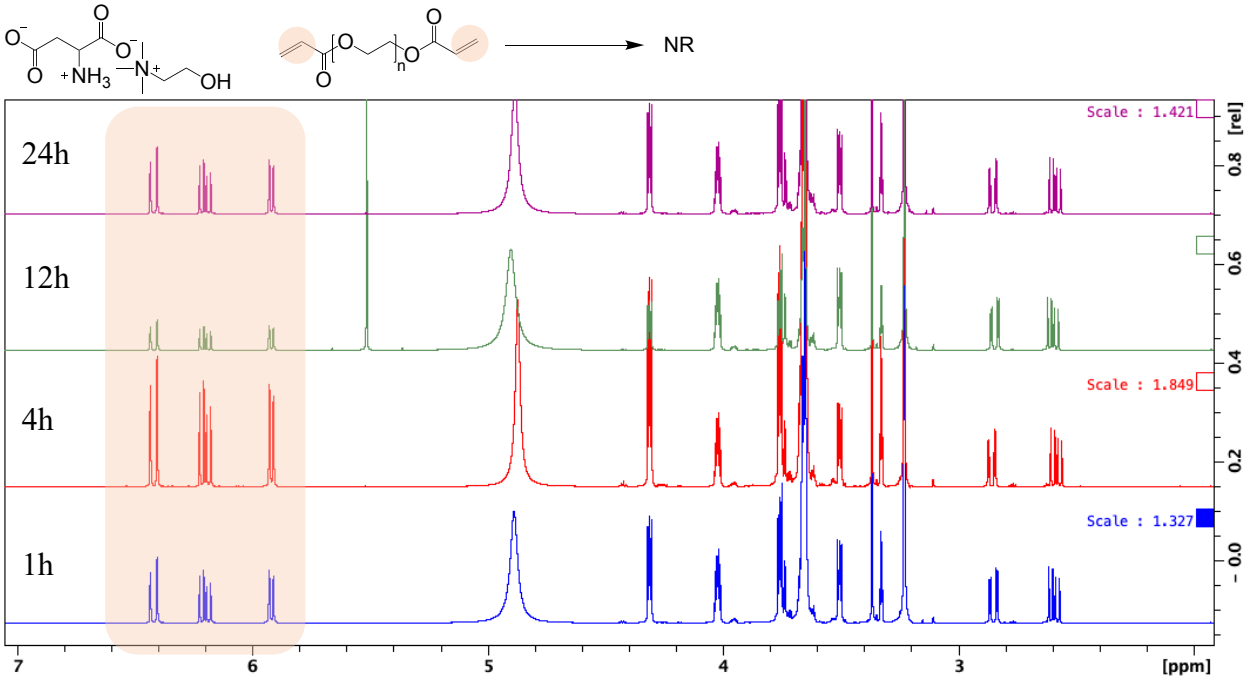


Figure S38. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL with **PEGACR**, from bottom to top, reaction at 1h, 4h, 12h, 24h. The spectral window is scaled to the choline peak at ~4 ppm for better relative comparison between different time points. The mixture was inhomogeneous, therefore different aliquot had variations of amsount of acrylates.

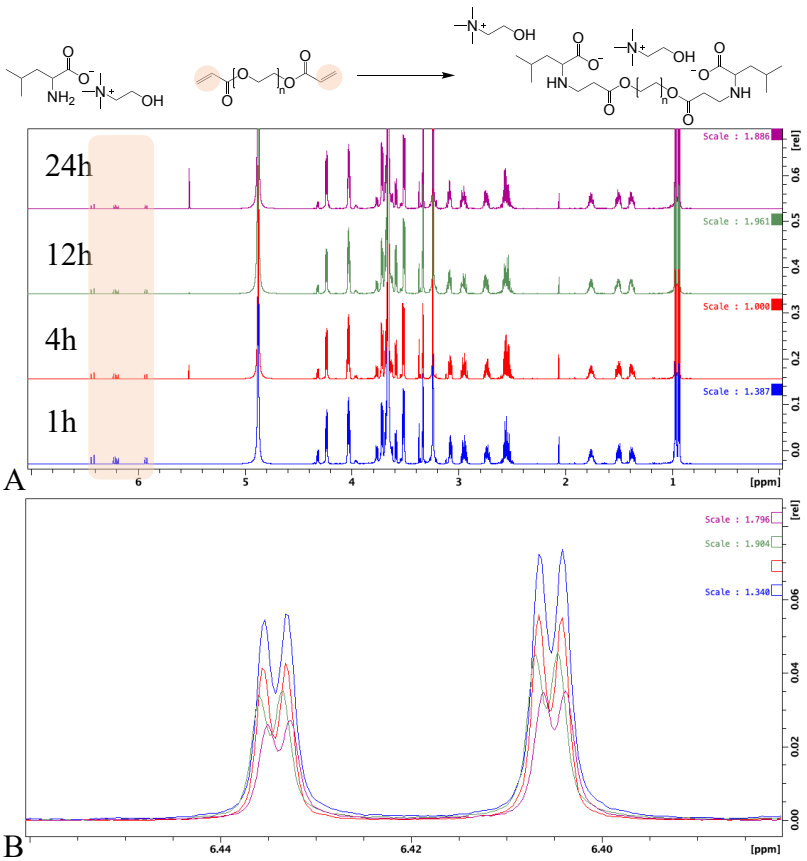
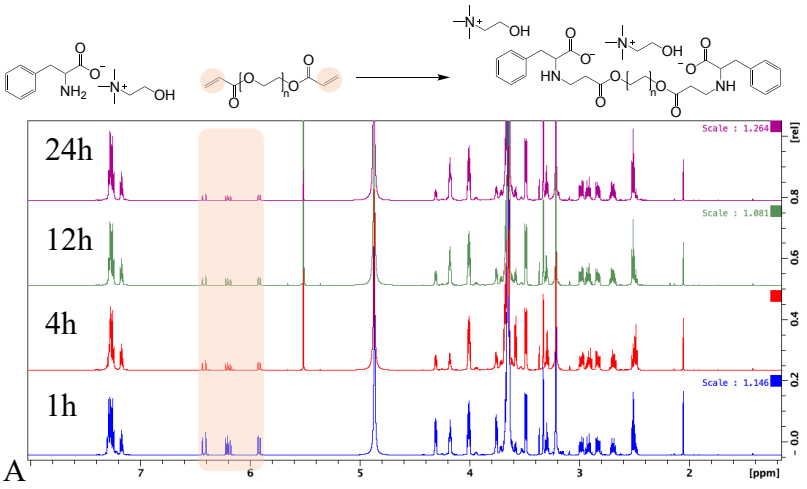
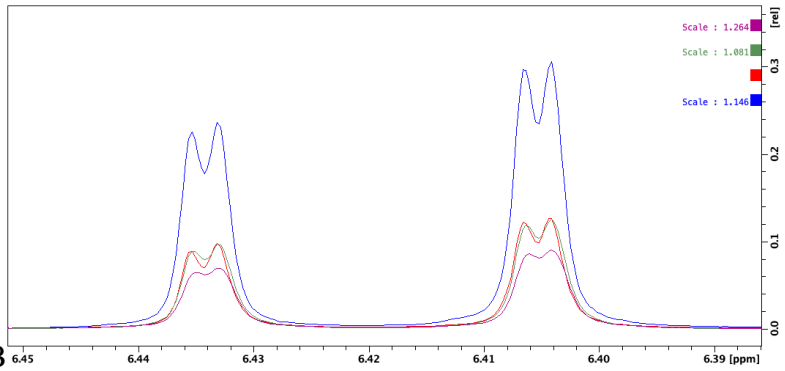


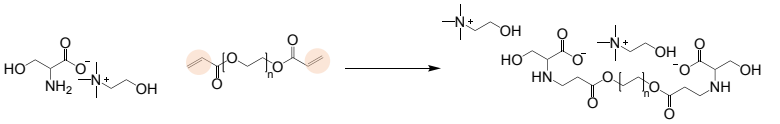
Figure S39. A) ^{1}H NMR stacked plots for reaction monitoring of for ChLeuIL with **PEGACR**, from bottom to top, reaction at 1h, 4h, 12h, 24h. B) Zoom-in image of the acrylate depletion trend over time around 6.38 – 6.46 ppm. The spectral window is scaled to the Choline peak at ~4 ppm for better relative comparison between different time points.

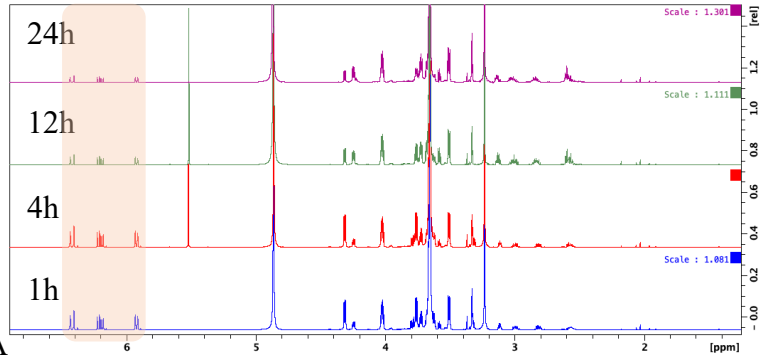




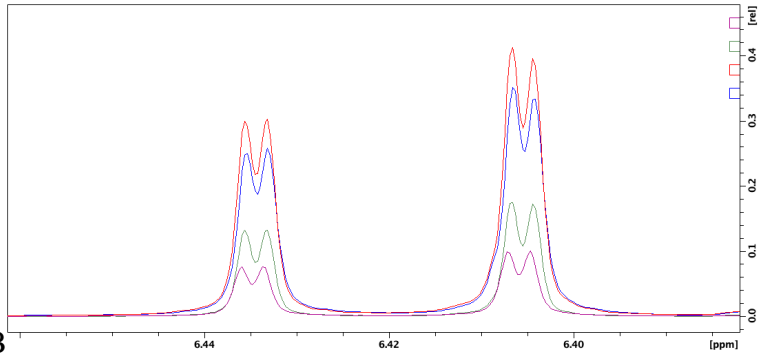
B

Figure S40. A) ^{1}H NMR stacked plots for reaction monitoring of ChPheIL with **PEGACR**, from bottom to top, reaction at 1h, 4h, 12h, 24h. B) Zoom-in image of acrylate depletion trend over time around 6.38 – 6.46 ppm. The spectral window is scaled to the Choline peak at ~4 ppm for better relative comparison between different time points.





A



B

Figure S41. A) ^{1}H NMR stacked plots for reaction monitoring of ChSerIL with **PEGACR**, from bottom to top, reaction at 1h, 4h, 12h, 24h. B) Zoom-in image of acrylate depletion trend over time around 6.38 – 6.46 ppm. The spectral window is scaled to the Choline peak at ~4 ppm for better relative comparison between different time points.

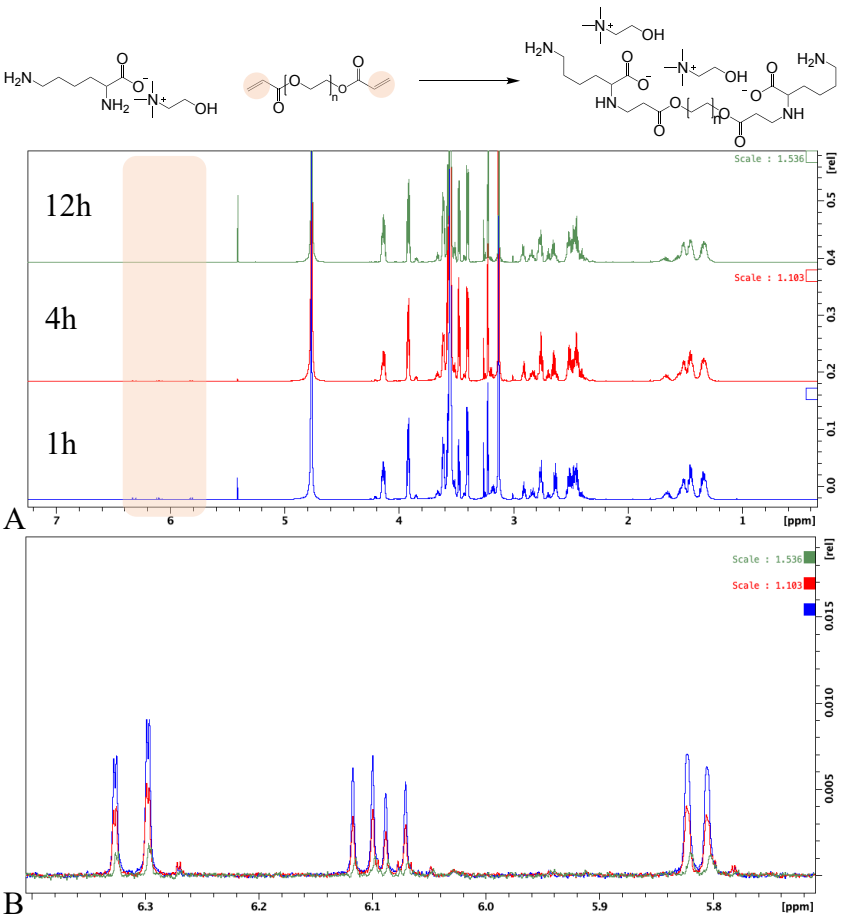


Figure S42. A) ^{1}H NMR stacked plots for reaction monitoring of ChLysIL with **PEGACR**, from bottom to top, reaction at 1h, 4h, 12h. B) Zoom-in image of acrylate depletion trend over time around 5.7 – 6.4 ppm. The spectral window is scaled to the Choline peak at ~4 ppm for better relative comparison between different time points.

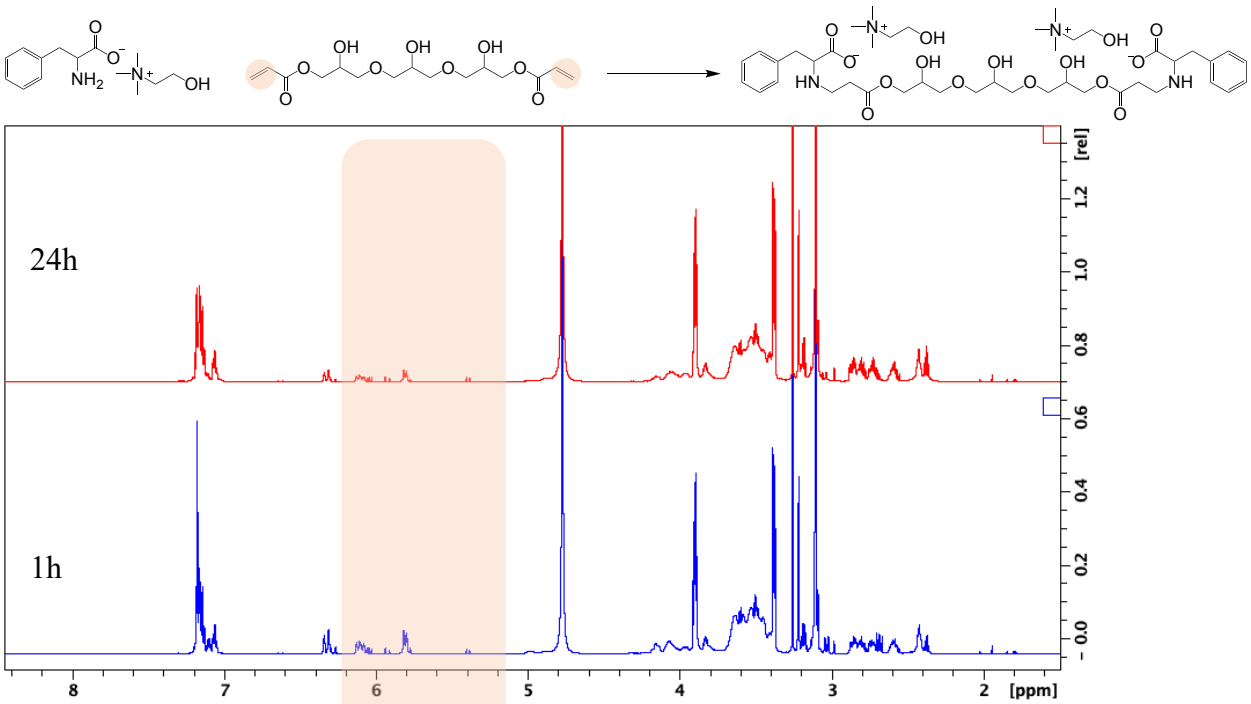


Figure S43. ^{1}H NMR stacked plots for reaction monitoring of ChPheIL with **OHGlyACR** at 1h and 24 hours.

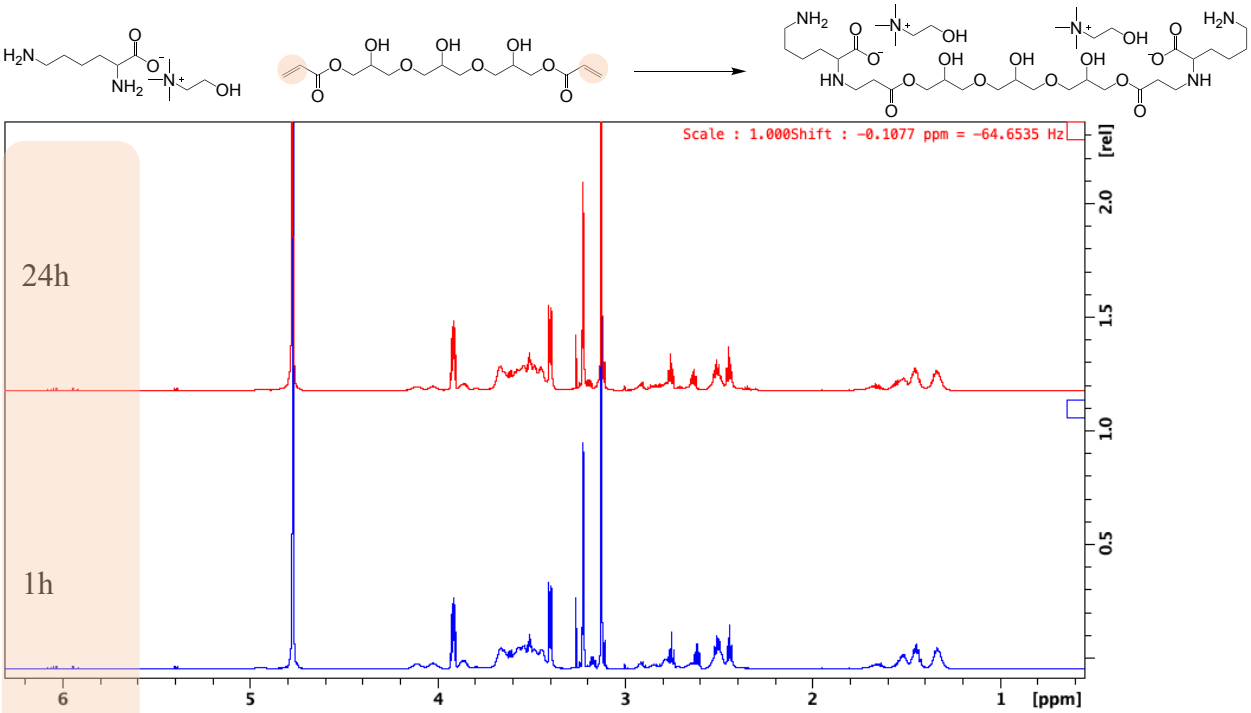


Figure S44. ^{1}H NMR stacked plots for reaction monitoring of ChLysIL with **OHGlyACR** at 1h and 24 hours.

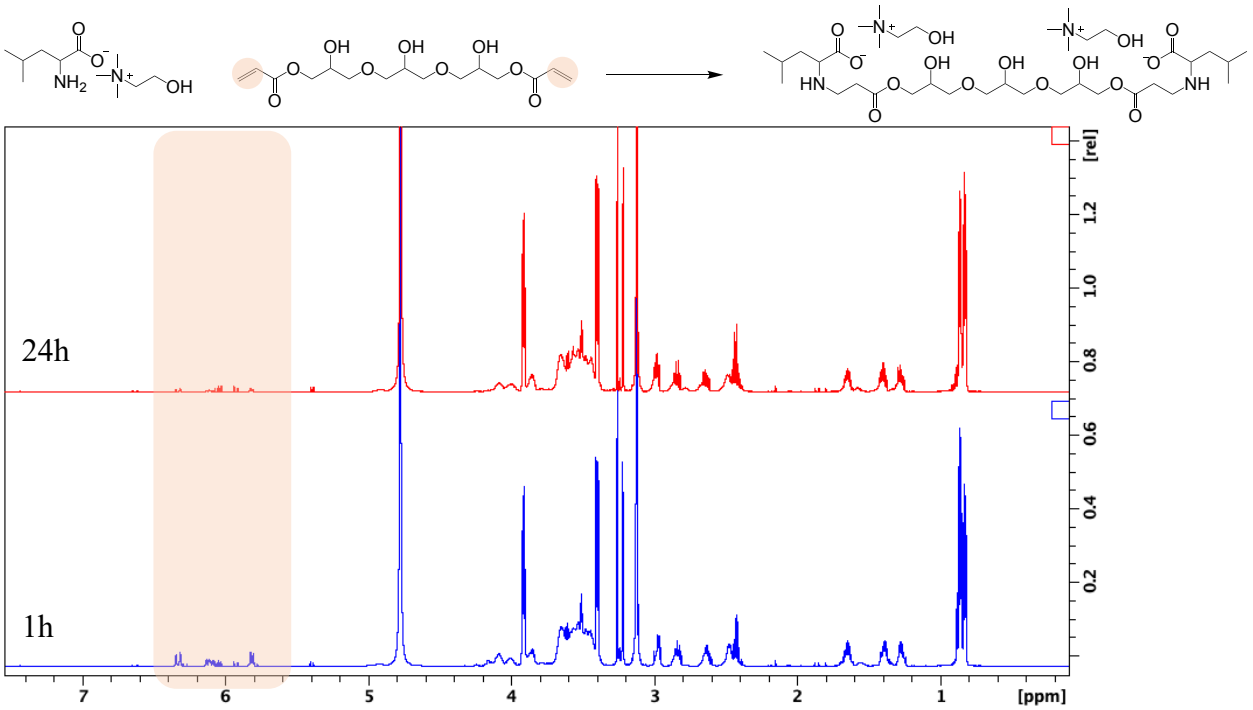


Figure S45. ^{1}H NMR stacked plots for reaction monitoring of ChLeuIL with **OHGlyACR** at 1h and 24 hours.

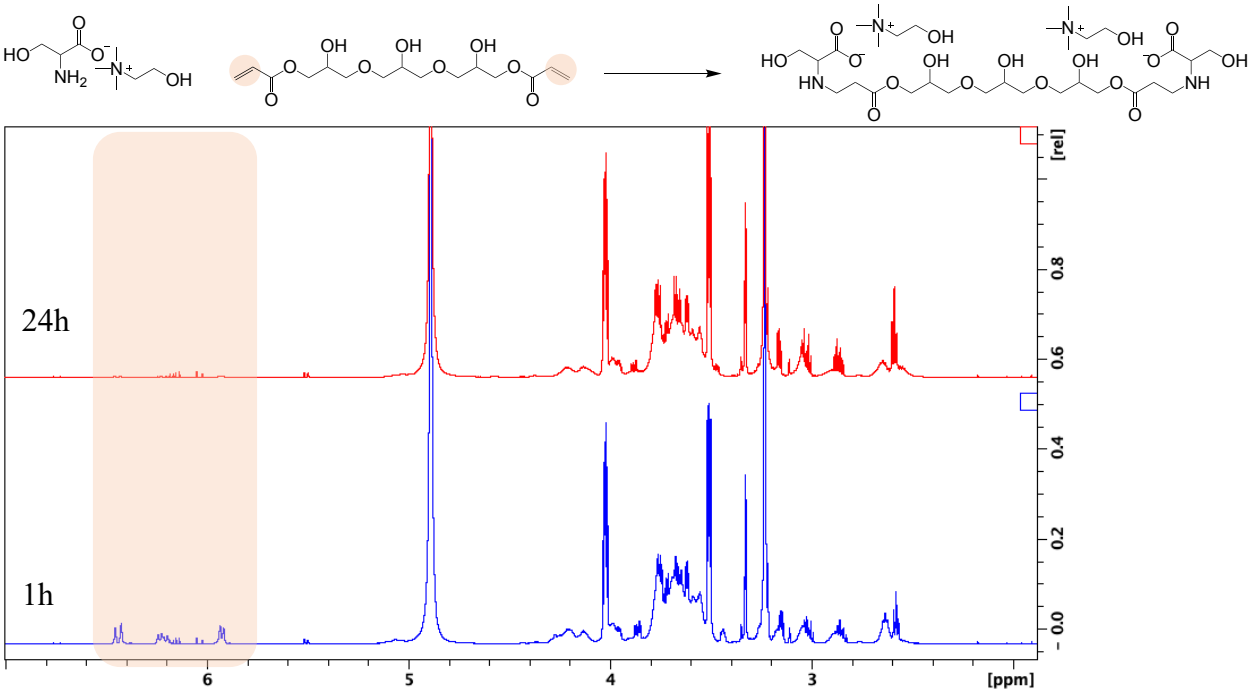


Figure S46. ^{1}H NMR stacked plots for reaction monitoring of ChSerIL with **OHGlyACR** at 1h and 24 hours.

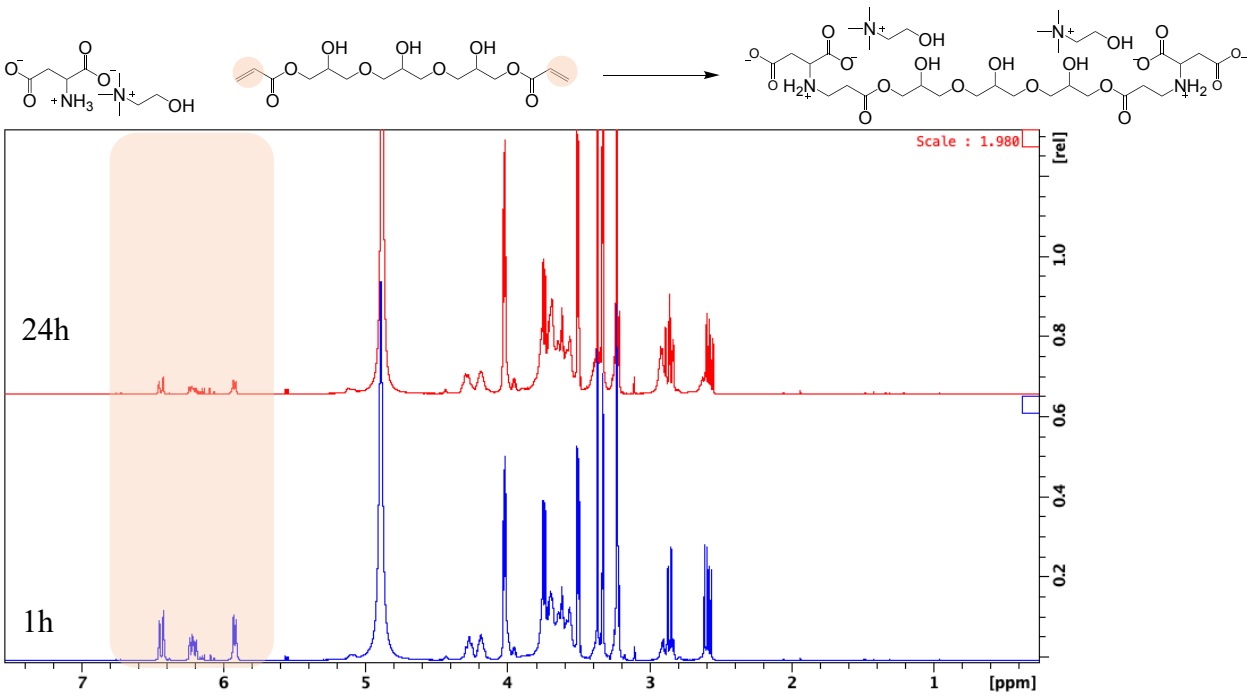
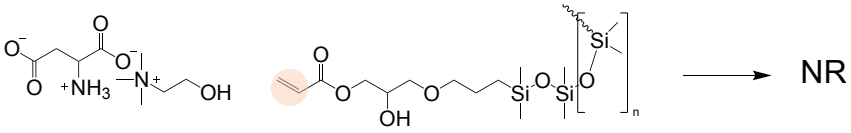


Figure S47. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL with **OHGlyACR** at 1h and 24 hours.

ChAAIL Reactivity with Silicones



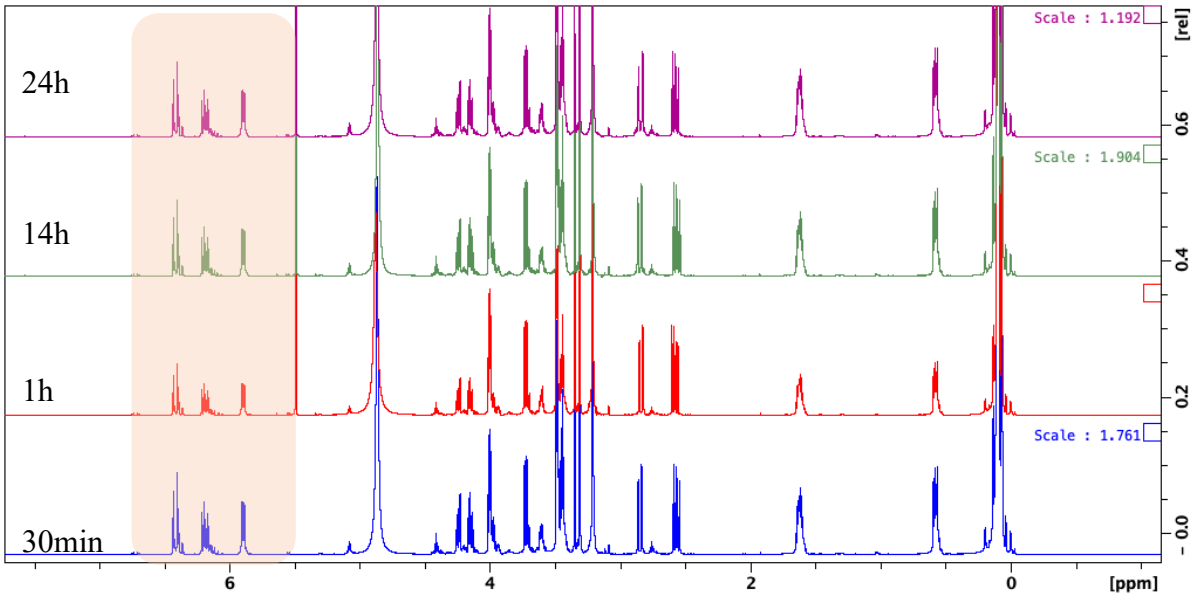


Figure S48. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL and **HODi9** neat, at 30min, 1h, 14h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

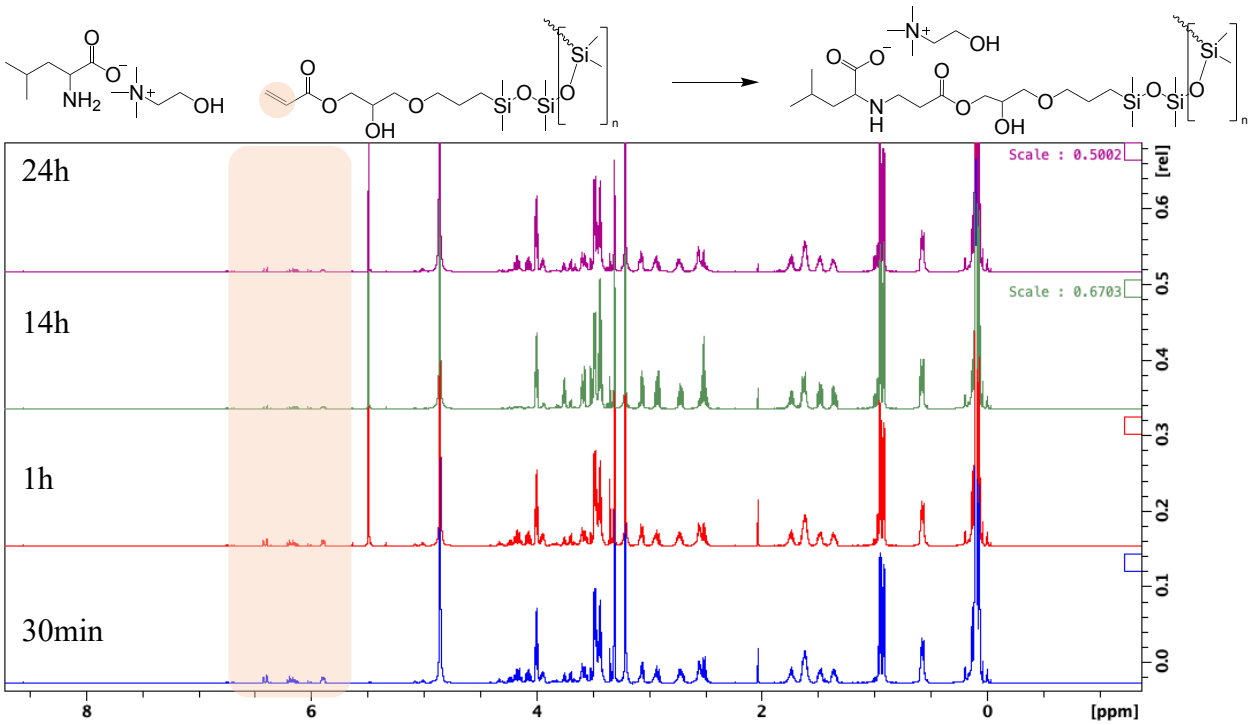


Figure S49. ^{1}H NMR stacked plots for reaction monitoring of ChLeuIL and **HODi9** neat, at 30min, 1h, 14h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~3.5 ppm for better relative comparison between different time points.

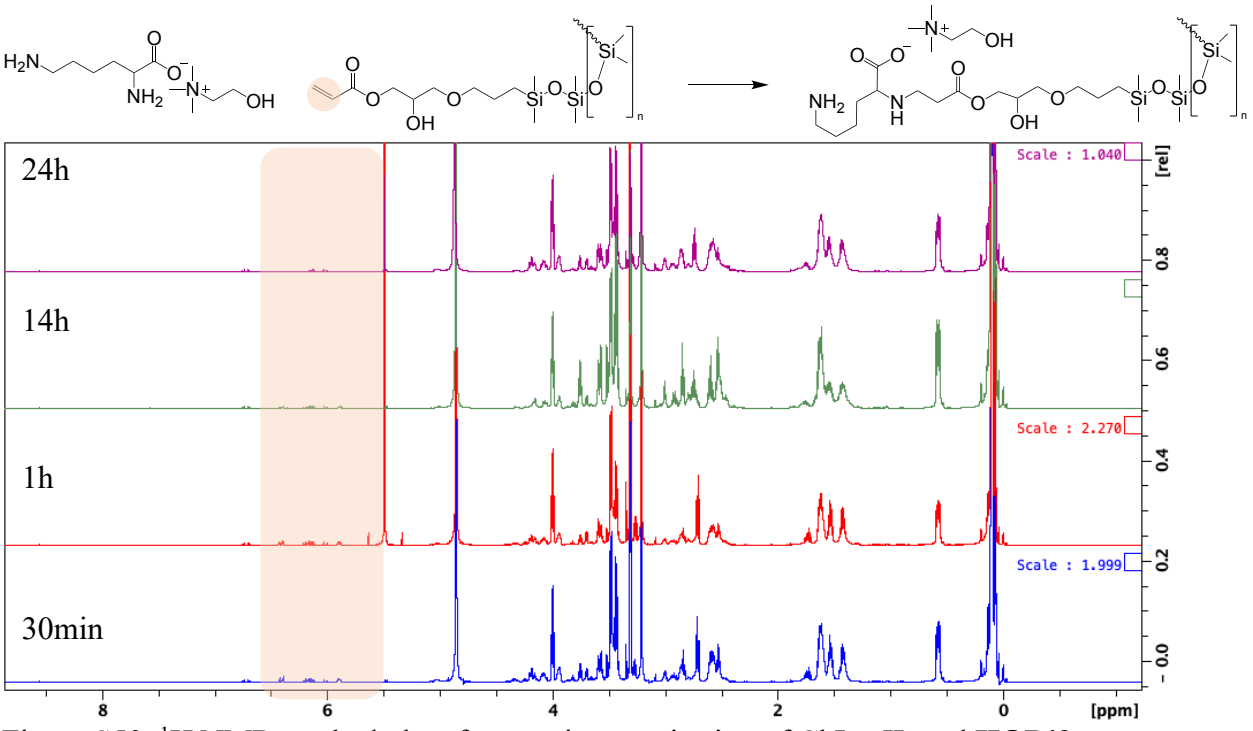


Figure S50. ^{1}H NMR stacked plots for reaction monitoring of ChLysIL and **HODi9** neat, at 30min, 1h, 14h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~4ppm for better relative comparison between different time points.

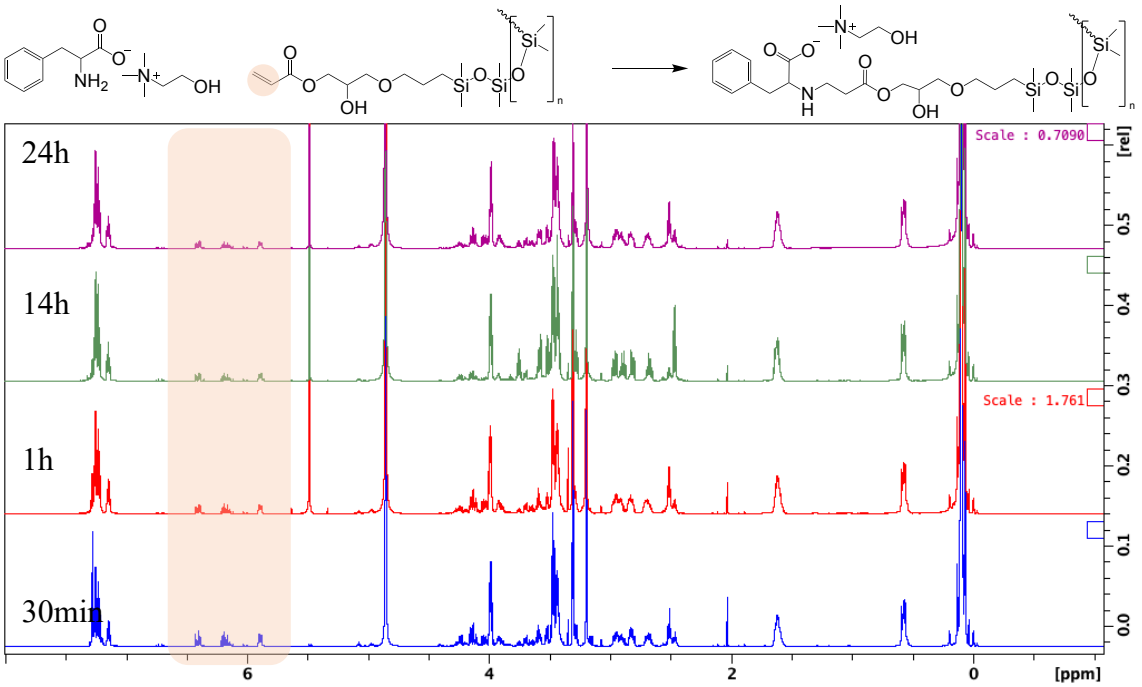


Figure S51. ^{1}H NMR stacking for reaction monitoring of ChPheIL and **HODi9** neat, at 30min, 1h, 14h, 24h from bottom to top. The spectral window is scaled to the height of choline peak at ~4 ppm for better relative comparison between different time points.

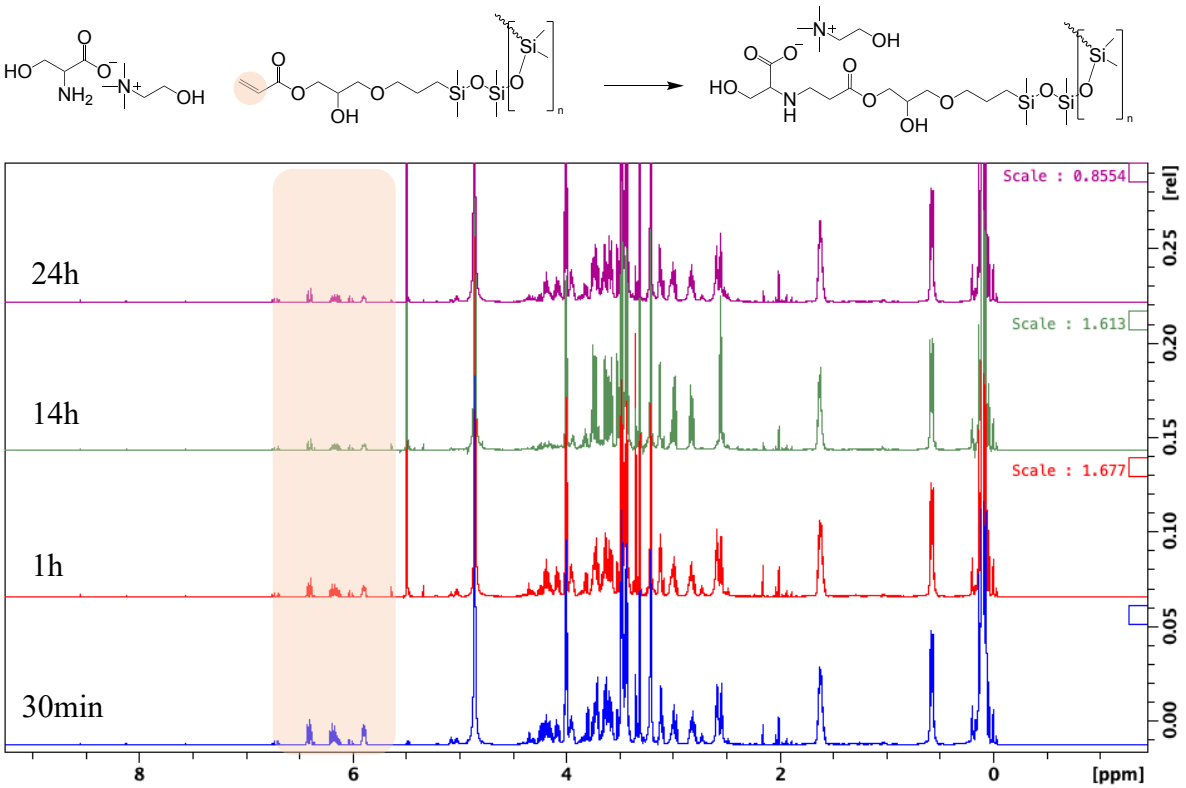


Figure S52. ^{1}H NMR stacked plots for reaction monitoring of ChSerIL and **HODi9** neat, at 30min, 1h, 14h, 24h from bottom to top. The spectral window is scaled to the ethylene peak at ~0.5 ppm for better relative comparison between different time points.

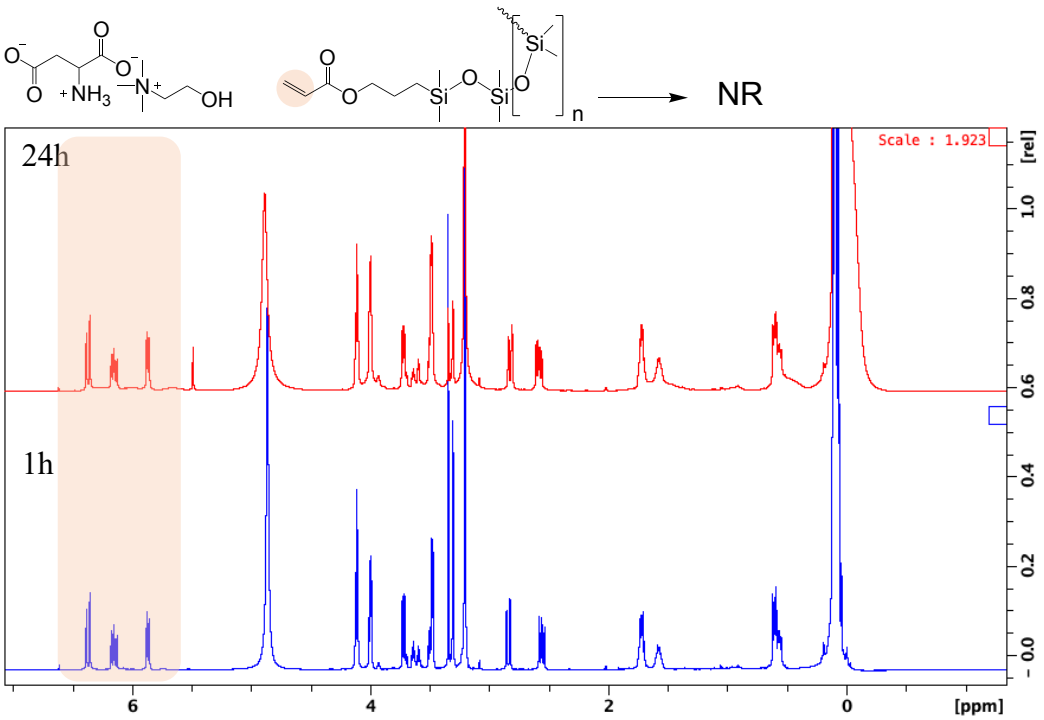


Figure S53. ^{1}H NMR stacked plots for reaction monitoring of ChAspIL and **Di10** neat, at 1h, and 24h from bottom to top.

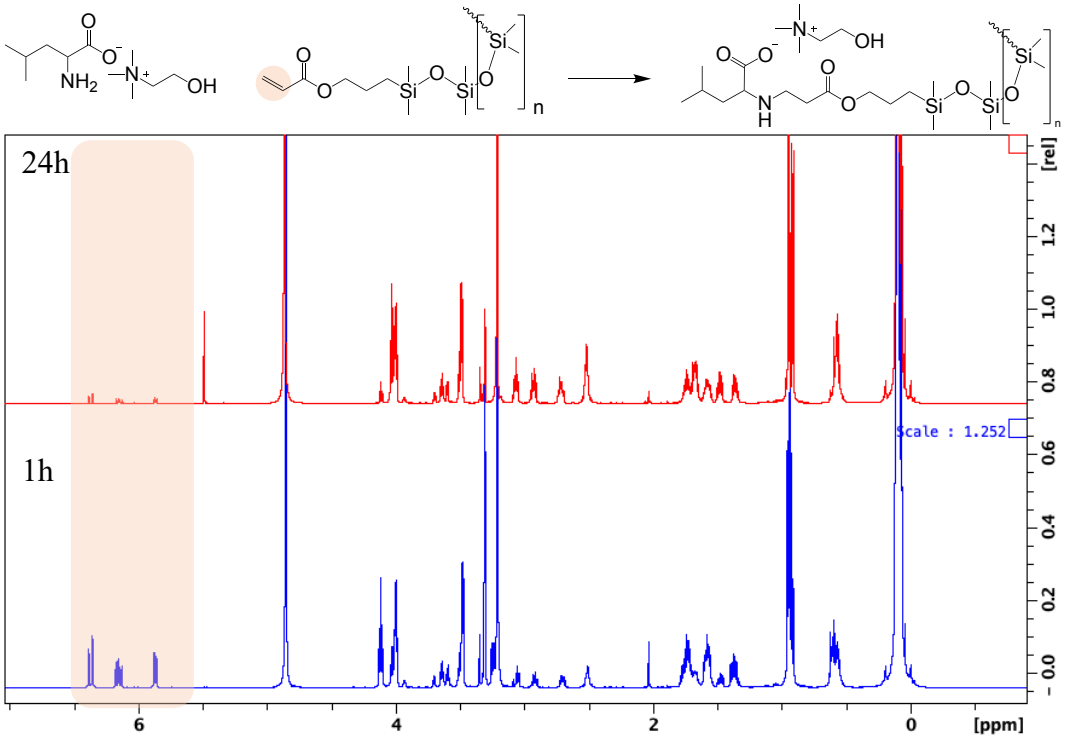


Figure S54. ^{1}H NMR stacked plots for reaction monitoring of ChLeuIL and **Di10** neat at 1h and 24h from bottom to top.

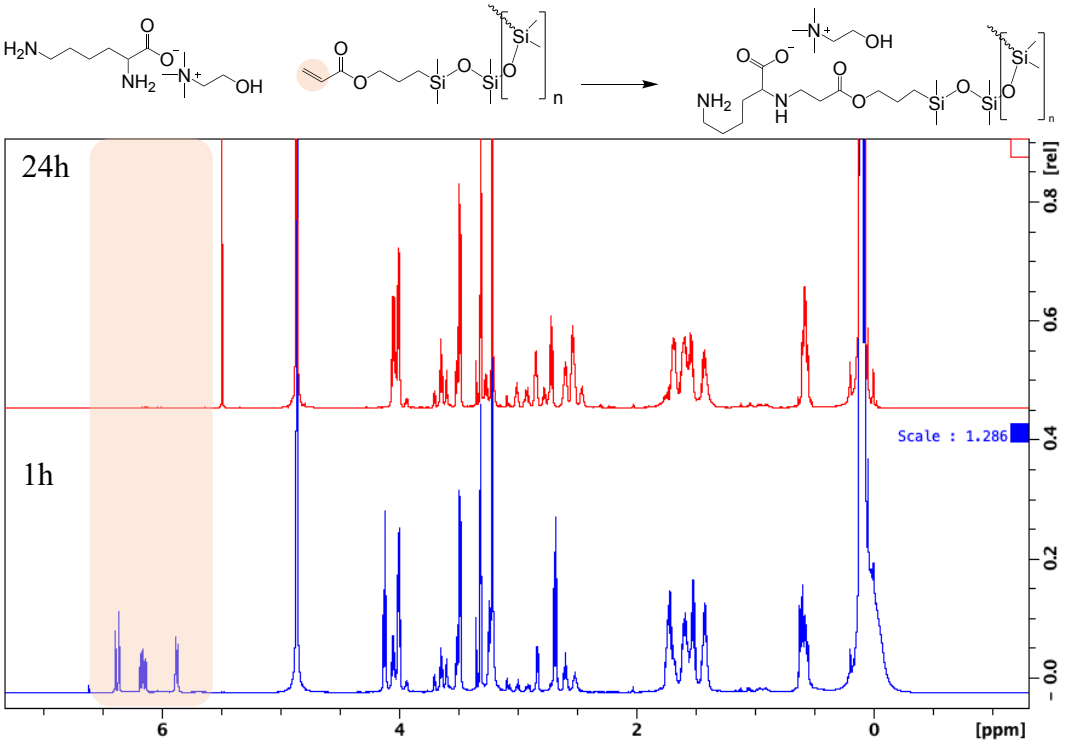


Figure S55. ^{1}H NMR stacked plots for reaction monitoring of ChLysIL and **Di10** neat at 1h and 24h from bottom to top.

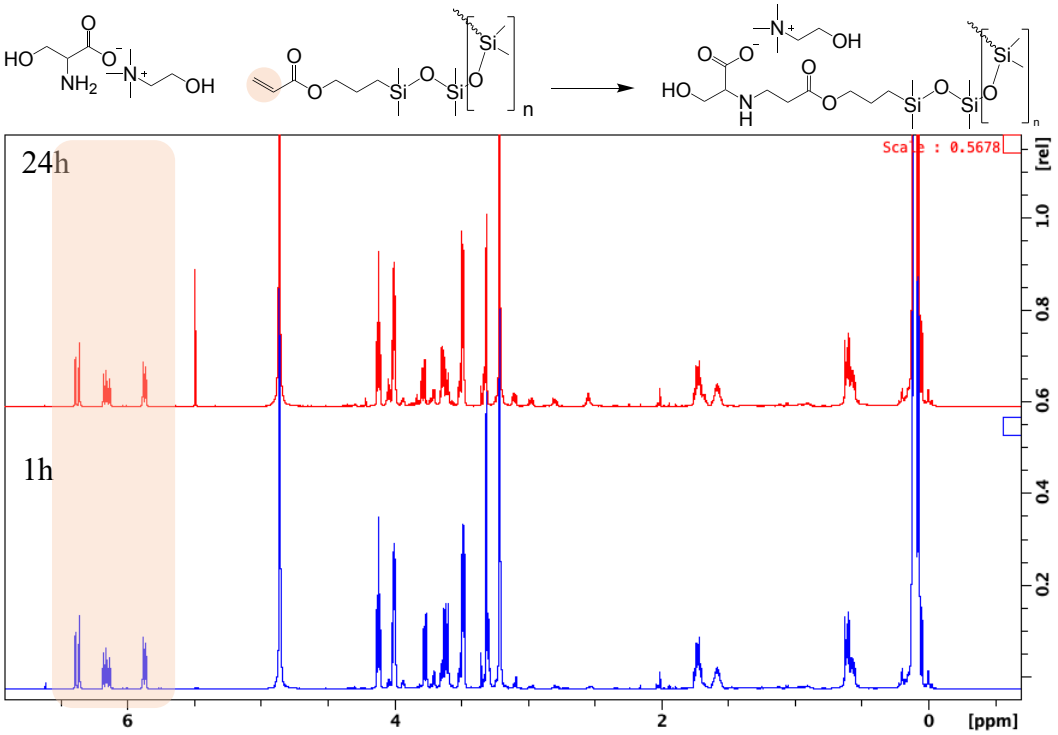


Figure S56. ^{1}H NMR stacked plots for reaction monitoring of ChSerIL and **Di10** at 1h and 24h from bottom to top.

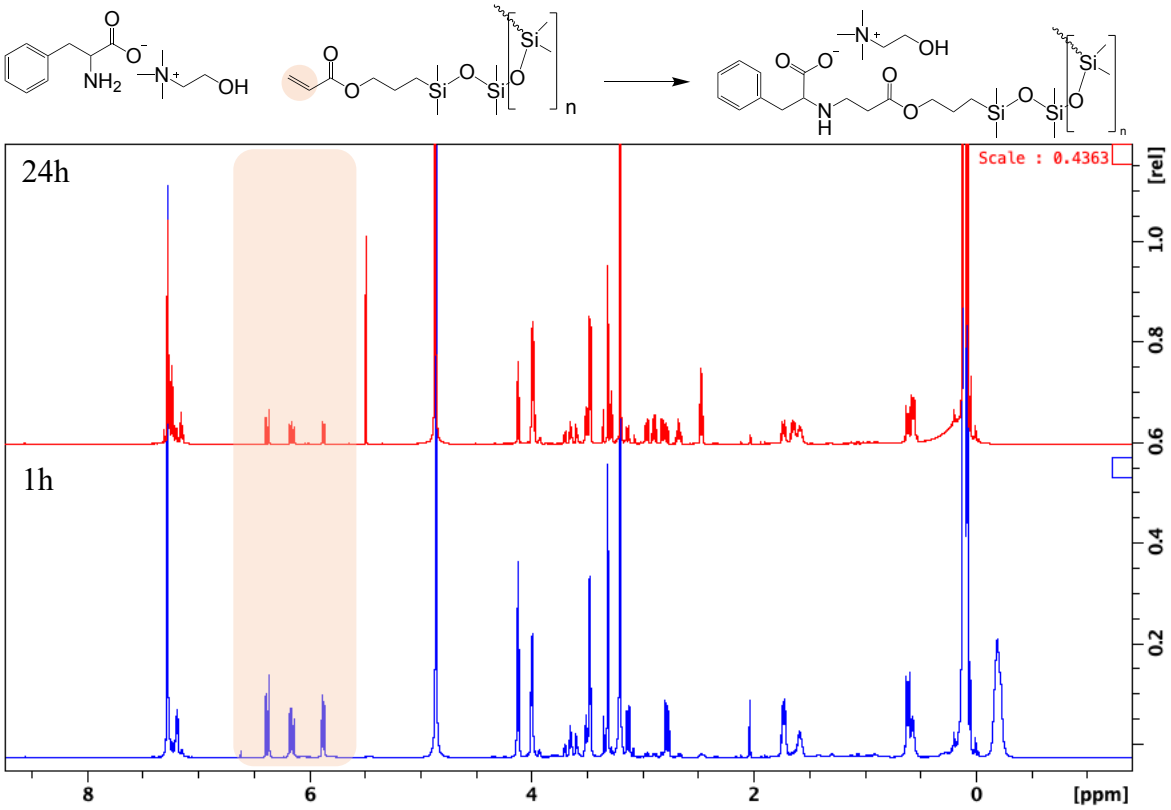


Figure S57. ^{1}H NMR stacked plots for reaction monitoring of ChPheIL and **Di10** neat at 1h and 24h from bottom to top.