Supporting Information

Minimizing HCN in DIC/Oxyma mediated amide bond forming reactions

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1. General information

All HPLC analyses were carried out on an Agilent 1100 or a Waters Alliance instruments. LC-MS analyses in section 3 of this SI were performed on a tandem liquid chromatography mass spectrometry system consisting of an Agilent 1290, 1200 bar system with DAD, connected to an Agilent quadrupole time-of-flight (Q-TOF) mass spectrometer (Agilent, Santa Clara, CA, USA). The mass spectrometry system was operated in a positive mode using electron spray ionization (ESI), mass range 20-3200, mass accuracy at 0.02 u, resolution up to 20000 ppm. The following source settings were used: gas temp 300 ˚C, gas flow 8 l/min, nebulizer 30psig, sheath gas temperature 350 ˚C and sheat gas flow 7.5 l/min. Analytical separations were achieved using a Waters Acquity UPLC instrument. LC-MS analyses in sections 4 - 6 of this SI were performed on a Horizon high performance liquid chromatography system (Thermo, Waltham, Massachusetts, U.S) with variable wavelength detector connected to a Qexactive orbitrap mass spectrometry system (Thermo, Waltham, Massachusetts, U.S). The mass spectrometry system was operated in a positive mode using sheath ESI, mass range 50-750, mass accuracy 5ppm, resolution up to 140 000 ppm. The following source settings were used: sheath gas flow rate 35, aux gas flow rate 10, sweep gas flow rate 1, spray voltage (kV) 3.50, capillary temp. 250 °C, S-lens RF level 50,0 and Aux gas heater temp. 200 °C. NMR spectra were recorded on a 400 MHz (for section 8.2) and 500 MHz Bruker system. Spectral data were processed using TopSpin software. All the samples were placed in 3 mm tubes from Norell.

2. Details of the assessment of HCN formation during DIC/Oxyma mediated coupling of 2.0 equiv Fmoc-Ser(t-Bu)-OH with H-RMG resin in DMF

Fmoc-RMG AMS resin (0.43 mmol/g) was prepared as previously described.[1] For each Fmoc-Ser(*t*-Bu)-OH coupling experiment the requisite H-RMG AMS resin was prepared as follows: 2.33 g (1.0 mmol) of the Fmoc-RMG AMS resin was swollen in DMF, drained and shaken at rt for 1 h with 20 mL piperidine (pip)/DMF (20% v/v). The resulting H-RMG AMS resin was washed with DMF (6 x 20 mL), isopropanol (*i*-PrOH, 3 x 20 mL) and diethyl ether (2 x 20 mL) and dried to constant weight *in vacuo.* The dried H-RMG AMS resin was swollen in DMF and drained. The amount of residual DMF in the swollen and drained resin was determined to be ~5 mL. Next, in two reactions vessels, 766.9 mg (2.0 mmol, 1.0 equiv) of Fmoc-Ser(*t*-Bu)-OH) and 284.2 mg (2.0 mmol, 1.0 equiv) of Oxyma were dissolved in 20 mL DMF. To the first vessel, 313.2 μL DIC (2.0 mmol, 1.0 equiv) was added and to the second vessel, 939 μL DIC (6.0 mmol, 3.0 equiv) was added. The resulting reaction mixtures were allowed to stir at rt for 1 h and added to the washed and drained batches of H-RMG AMS resin prepared above. The resulting slurries of DIC/Oxyma mediated couplings of Fmoc-Ser(*t*-Bu)-OH with H-RMG AMS resins were shaken at rt (300 rpm) for 20 h. Conversions of these amidation reactions were followed by a qualitative (ninhydrin) color test.[2] During the course of Fmoc-Ser(*t*-Bu)-OH/DIC/Oxyma activations as well as the subsequent amidation reactions of the activated mixtures with H-RMG AMS resin 50 μL reaction aliquots were taken out and quenched with MeCN (1.0 mL). The samples thus obtained were analysed for the content of oxadiazole **3** (section 2.1 of this SI) based on which the conversions of Oxyma to HCN during these DIC/Oxyma mediated reactions were determined, see section 2.2 of this SI.

2.1 HPLC analysis of samples of Fmoc-Ser(*t*-Bu)-OH/DIC/Oxyma reaction mixtures containing oxadiazole 3 and determination of Oxyma to HCN conversions in these reactions

Experimental conditions: column: Waters XSelect CSH130 C18 2.5 μm 4.6x150mm; detection wavelength: 220 nm; column temperature: 30°C; injection volume: 2 μL; sampler temperature: 10°C; flow: 0.5 ml/min; mobile phase A: 0.1 % TFA in water, mobile phase B: 0.08 % TFA in 90% MeCN/10 %water. Gradient (Time(min), %B): 0, 0; 40, 100; 54, 100; 55, 0; 62, 0. Peak of oxadiazole **3** at ~17.4 min was integrated in all cases.

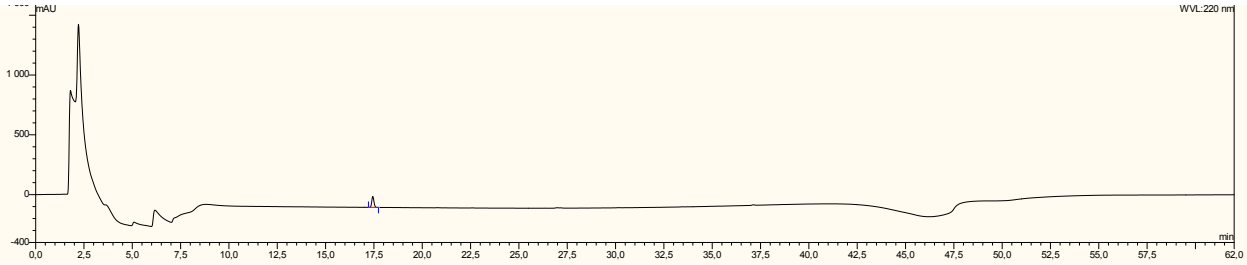

Figure S1. UV chromatogram overview of a 5 mg/mL reference sample of oxadiazole **3** in MeCN, 50 μL of which was diluted with MeCN (1.0 mL).

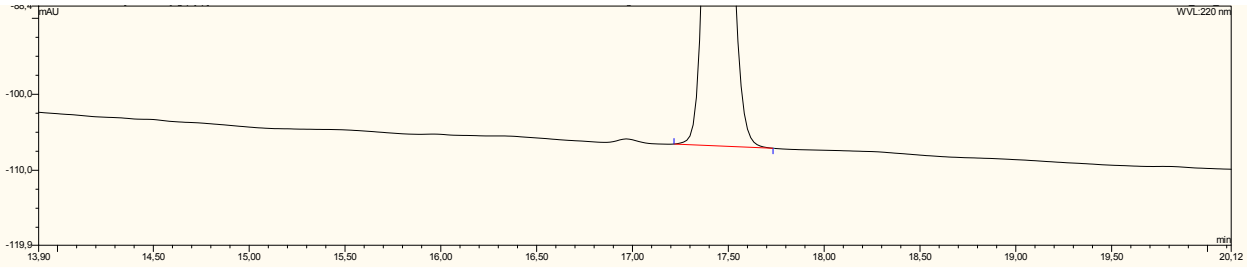

Figure S2. UV chromatogram zoom-in of a 5 mg/mL reference sample of oxadiazole **3** in MeCN, 50 μL of which was diluted with MeCN (1.0 mL).

Table S1. Area (mAu^{x}min) for the integrated peak of a 5 mg/mL reference sample of oxadiazole **3**, 50 μL of which was diluted with 0.5 % TFA/MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,433	11,8344	n.a.	BMB*	90,936	100,00	n.a.
Total:			**11,8344**	**0,0000**		**90,936**	**100,00**	

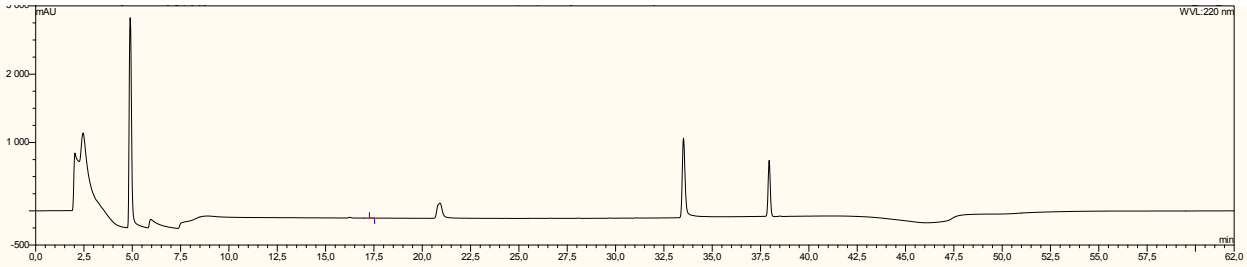

Figure S3. UV chromatogram overview of a reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) after 0.5 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

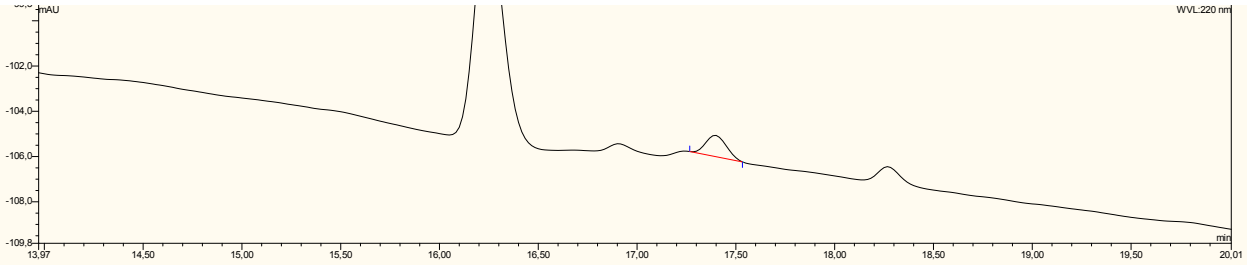

Figure S4. UV chromatogram zoom-in of a reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) after 0.5 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

Table S2. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) after 0.5 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,400	0,1139	n.a.	BMB*	0,941	100,00	n.a.
Total:			**0,1139**	**0,0000**		**0,941**	**100,00**	

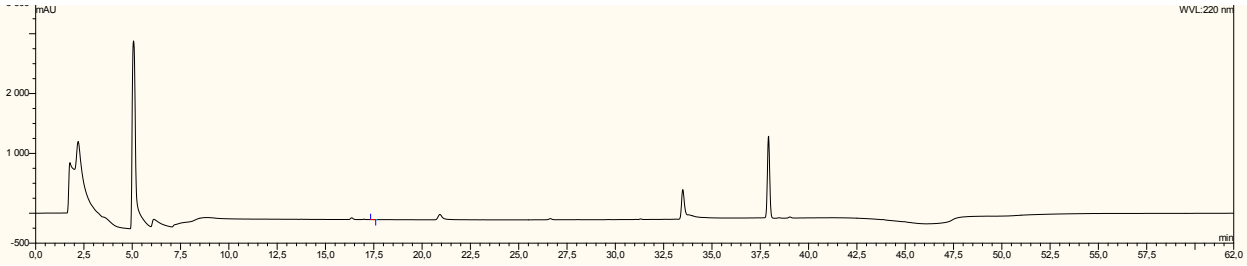

Figure S5. UV chromatogram overview of a reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) after 0.5 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

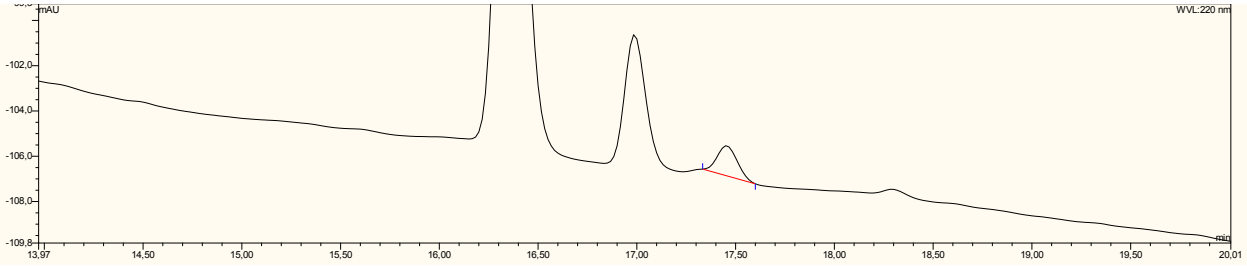

Figure S6. UV chromatogram zoom-in of a reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) after 0.5 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

Table S3. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) after 0.5 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,450	0,1570	n.a.	BMB*	1,320	100,00	n.a.
Total:			**0,1570**	**0,0000**		**1,320**	**100,00**	

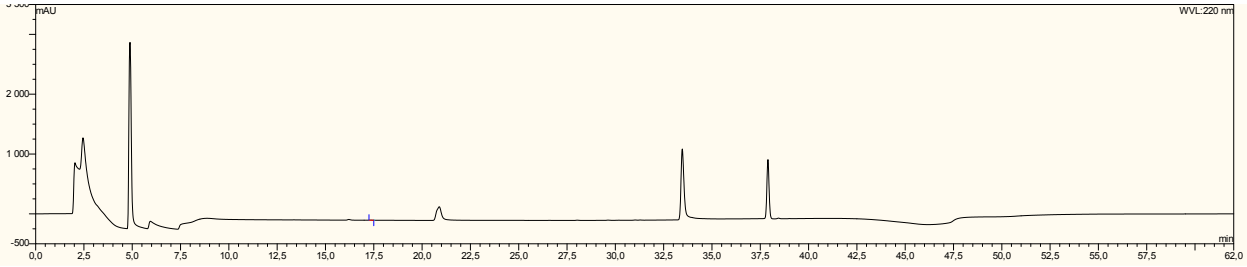

Figure S7. UV chromatogram overview of a reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) after 1.0 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

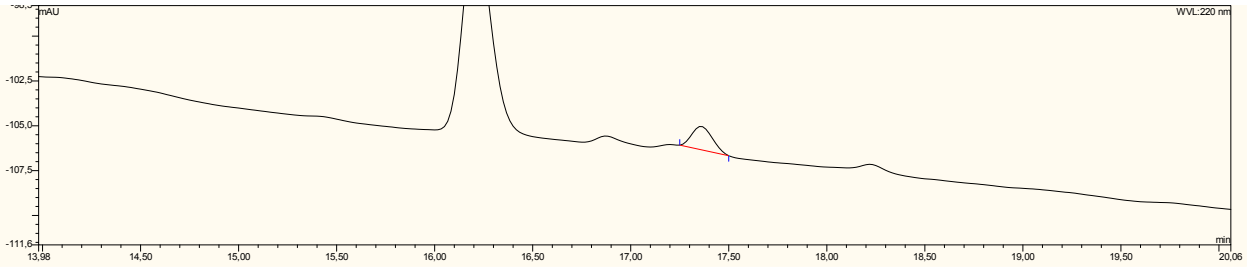

Figure S8. UV chromatogram zoom-in of a reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) after 1.0 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

Table S4. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) after 1.0 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,367	0,1586	n.a.	BMB*	1,303	100,00	n.a.
Total:			**0,1586**	**0,0000**		**1,303**	**100,00**	

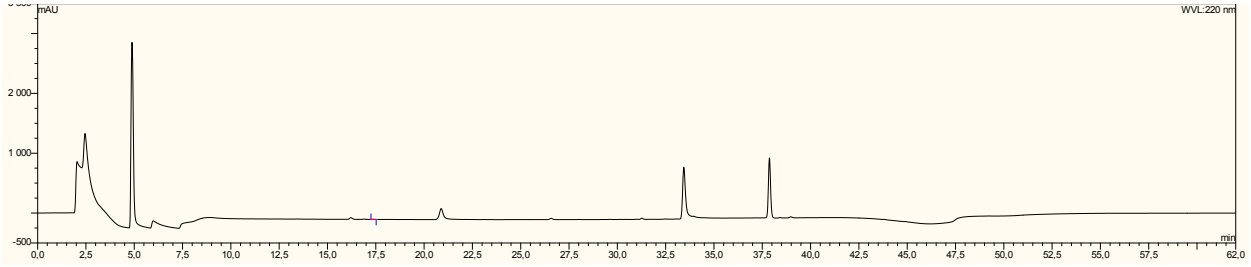

Figure S9. UV chromatogram overview of a reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) after 1.0 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

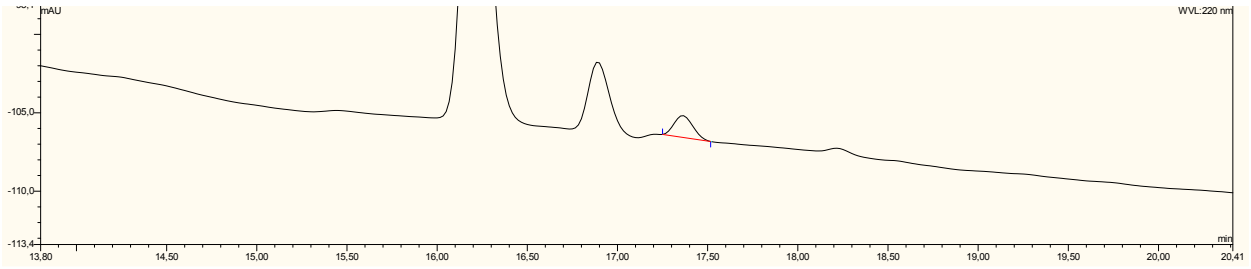

Figure S10. UV chromatogram zoom-in of a reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) after 1.0 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

Table S5. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) after 1.0 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,367	0,1677	n.a.	BMB*	1,389	100,00	n.a.
Total:			**0,1677**	**0,0000**		**1,389**	**100,00**	

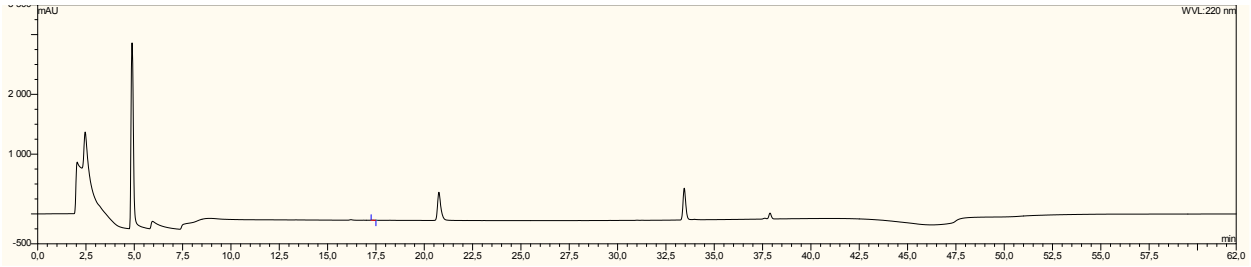

Figure S11. UV chromatogram overview of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 0.5 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

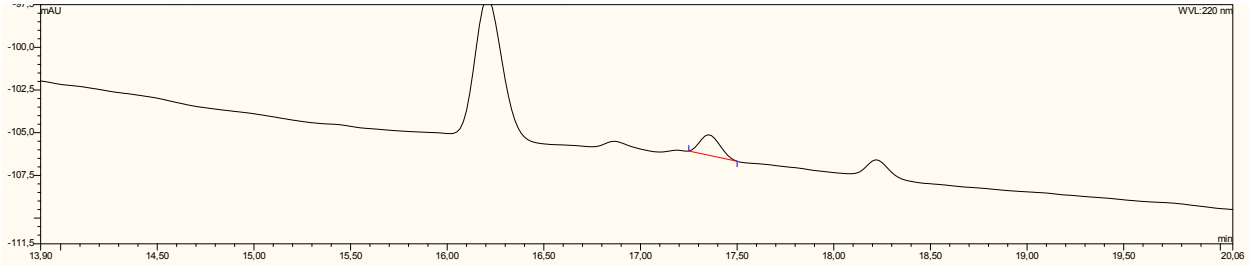

Figure S12. UV chromatogram zoom-in of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 0.5 h at rt, 50 μL of this mixture was diluted with MeCN (1.0 mL).

Table S6. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 0.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,350	0,1446	n.a.	BMB*	1,194	100,00	n.a.
Total:			**0,1446**	**0,0000**		**1,194**	**100,00**	

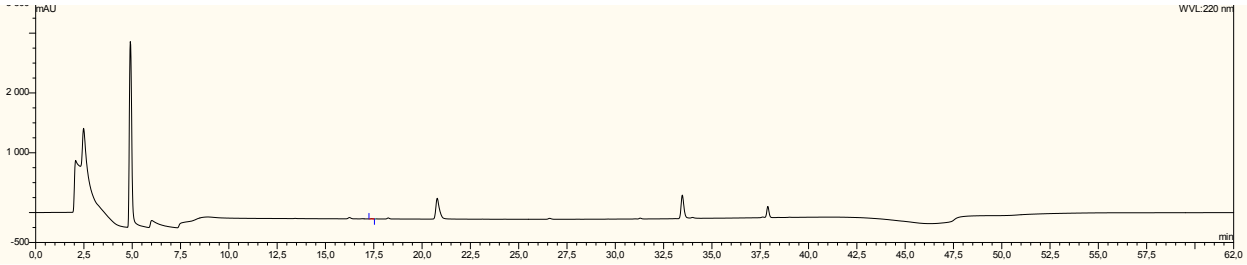

Figure S13. UV chromatogram overview of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 0.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

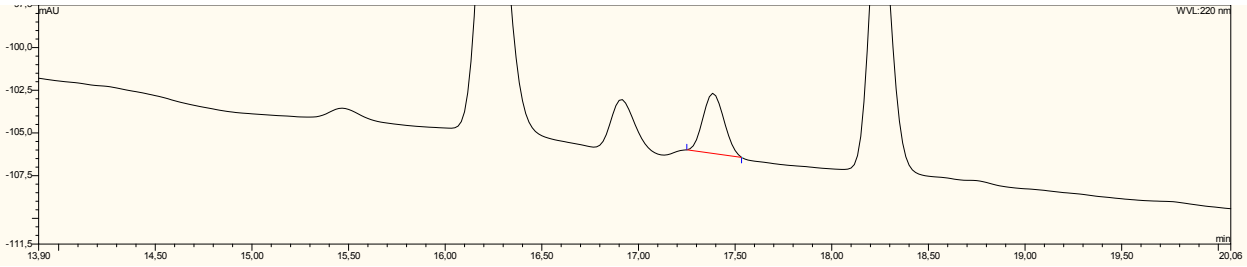

Figure S14. UV chromatogram zoom-in of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 0.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

Table S7. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 0.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,383	0,4439	n.a.	BMB*	3,520	100,00	n.a.
Total:			**0,4439**	**0,0000**		**3,520**	**100,00**	

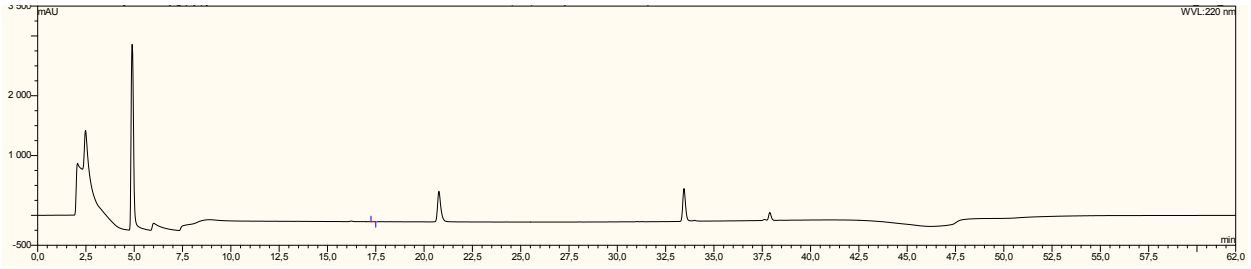

Figure S15. UV chromatogram overview of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 2.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

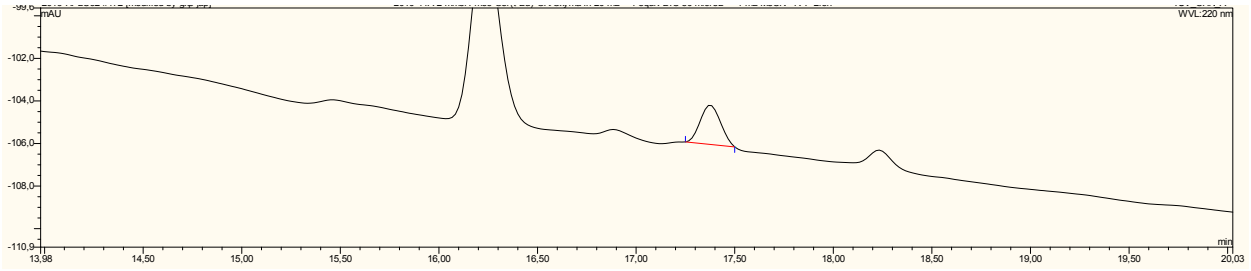

Figure S16. UV chromatogram zoom-in of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 2.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

Table S8. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 2.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,383	0,2202	n.a.	BMB*	1,828	100,00	n.a.
Total:			**0,2202**	**0,0000**		**1,828**	**100,00**	

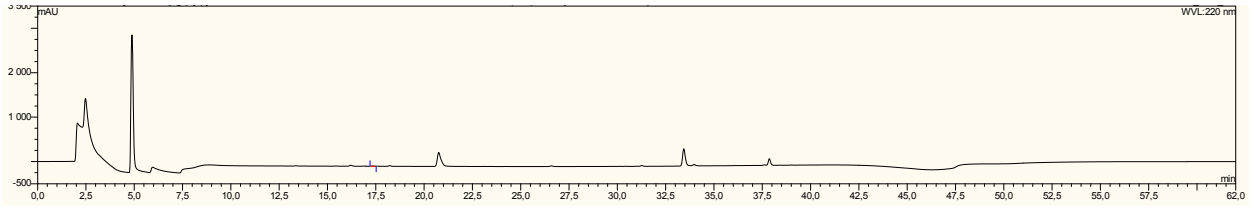

Figure S17. UV chromatogram overview of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 2.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

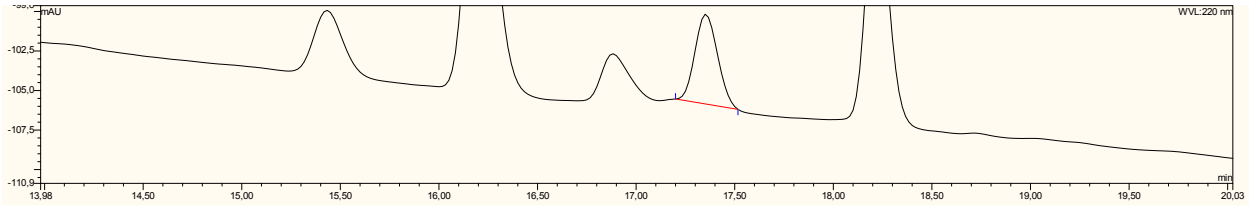

Figure S18. UV chromatogram zoom-in of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 2.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

Table S9. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 2.5 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,350	0,7537	n.a.	BMB*	5,671	100,00	n.a.
Total:			**0,7537**	**0,0000**		**5,671**	**100,00**	

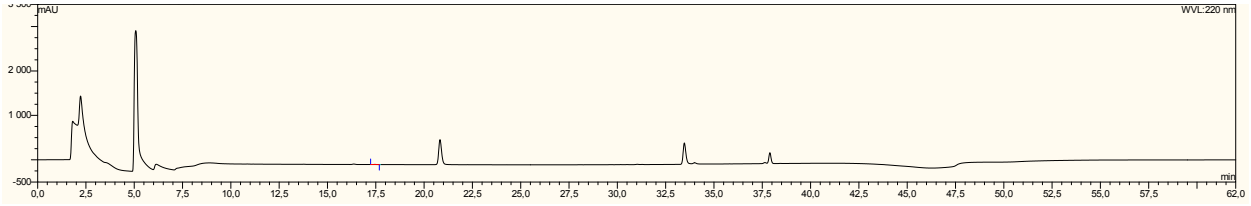

Figure S19. UV chromatogram overview of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 20 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

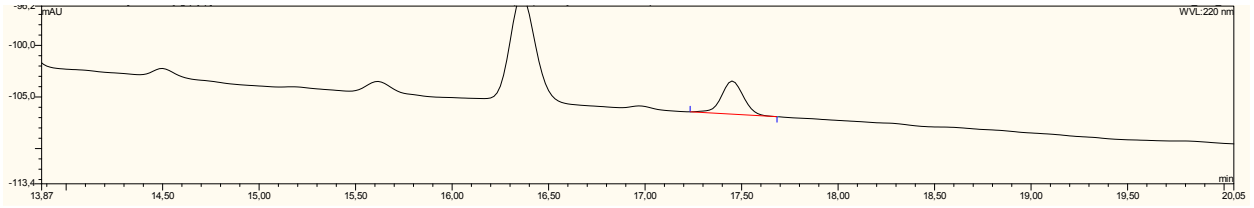

Figure S20. UV chromatogram zoom-in of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 20 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

Table S10. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1) with H-RMG AMS resin after 20 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,450	0,4261	n.a.	BMB*	3,216	100,00	n.a.
Total:			**0,4261**	**0,0000**		**3,216**	**100,00**	

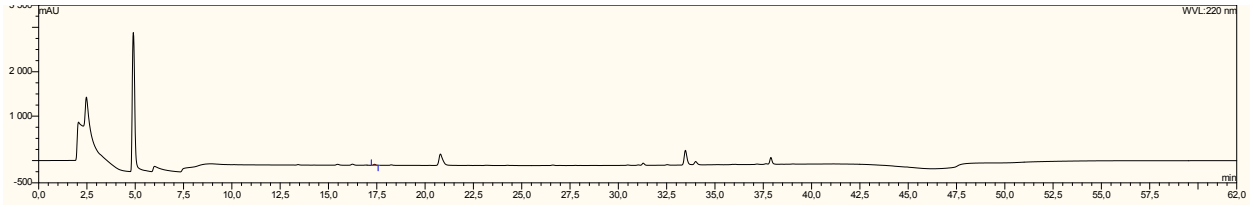

Figure S21. UV chromatogram overview of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 20 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

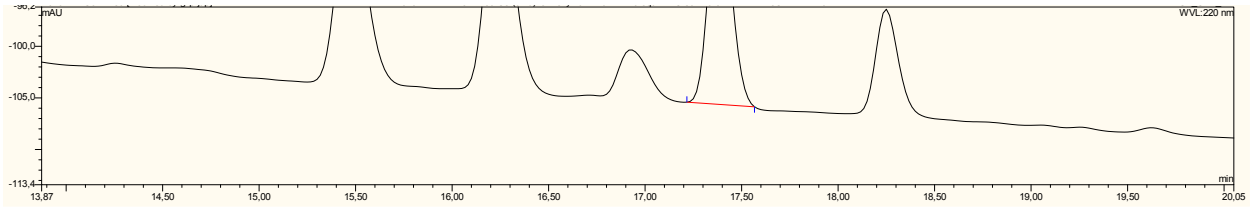

Figure S22. UV chromatogram zoom-in of a reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 20 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

Table S11. Area (mAu^{x}min) for the integrated peak of oxadiazole **3** from the reaction mixture supernate of 2 equiv Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) with H-RMG AMS resin after 20 h at rt, 50 μL of of this mixture was diluted with MeCN (1.0 mL).

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	Main peak	17,383	2,9014	n.a.	BMB*	21,621	100,00	n.a.
Total:			**2,9014**	**0,0000**		**21,621**	**100,00**	

2.2 Determination of Oxyma to HCN conversions and total amounts of HCN formed per mol of an amidation reaction based on HPLC analyses of samples of Fmoc-Ser(*t*-Bu)-OH/DIC/Oxyma reaction mixtures containing oxadiazole 3.

The marker of HCN formation oxadiazole **3** was prepared as previously described.[3]

Oxyma→HCN conversions and amounts of HCN formed mol^{-1} of the coupling reaction were determined as follows:

1) Integrated areas of oxadiazole **3** (mAu^{x}min) present in the samples of run A (Fmoc-Ser(*t*-Bu-OH/Oxyma/DIC (1:1:1) and run B (Fmoc-Ser(*t*-Bu-OH/Oxyma/DIC (1:1:3) were determined by HPLC analyses (see section 2.1 of this
SI) and are summarized in Table S12.

2) Based on the determined areas of oxadiazole **3** in all samples of Fmoc-Ser(*t*-Bu-OH/Oxyma/DIC concentrations of **3** (gL^{-1}) in all samples of Fmoc-Ser(*t*-Bu-OH/Oxyma/DIC were determined (Table S12).

3) Based on i) the known volumes of Fmoc-Ser(*t*-Bu-OH/Oxyma/DIC reaction mixtures (20 mL) and Fmoc-Ser(*t*-Bu-OH/Oxyma/DIC+H-RMG AMS resin slurries (25 mL), ii) the determined concentrations of **3** and iii) assuming that **3** and HCN are formed in 1:1 ration(see Fig. 1) the total amounts of HCN formed (μmol) thoroughout the course of Run A and Run B experiments were determined (Table S12).

4) Based on the amounts of HCN formed and known amounts of Oxyma employed in Run A and Run B experiments (2 mmol), the Oxyma→HCN conversions were determined (Table S12).

5) Based on the amounts of HCN formed and known scale of Run A and Run B experiments (1 mmol), the amounts of HCN formed mol^{-1} of the coupling reaction were determined in mmol and mg HCN, respectively (Table S12).

Table S12. A summary of i) areas (mAu^{x}min) for the integrated peak of oxadiazole **3** throughout run A (Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:1)) and run B (Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC (1:1:3) experiments; ii) concentrations of **3** throughout run A and Run B experiments; iii) Oxyma→HCN conversions throughout run A and Run B experiments; iv) amounts of HCN formed (mmol) mol^{-1} of the coupling experiment; v) amounts of HCN formed (mg) mol^{-1} of the coupling experiment.

Reaction time (h)	Run A: (mAuxmin) **3**	Run B: (mAuxmin) **3**	Run A: gL^{-1} **3**	Run B: gL^{-1} **3**	Run A: µmol **3**	Run B: µmol **3**	**Run A: %Oxyma->3**	**Run B: %Oxyma->3**	Run A: mmol HCN mol^{-1} AA coupling	Run B: mmol HCN mol^{-1} AA coupling	**Run A: mg HCN mol^{-1} AA coupling**	**Run B: mg HCN mol^{-1} AA coupling**
0,0 (preactivation)	0,00	0,00	0,00	0,00	0,00	0,00	**0,00**	**0,00**	0,00	0,00	**0,00**	**0,00**
0,5 (preactivation)	0,12	0,16	0,05	0,07	4,21	5,62	**0,21**	**0,28**	2,11	2,81	**56,96**	**75,95**
1,0 (preactivation)	0,16	0,17	0,07	0,07	5,62	5,97	**0,28**	**0,30**	2,81	2,99	**75,95**	**80,69**
0,5 (coupling)	0,18	0,55	0,08	0,23	7,90	24,15	**0,40**	**1,21**	3,95	12,07	**106,80**	**326,34**
2,5 (coupling)	0,28	0,94	0,12	0,40	12,29	41,27	**0,61**	**2,06**	6,15	20,63	**166,14**	**557,74**
20 (coupling)	0,54	3,62	0,23	1,53	23,71	158,93	**1,19**	**7,95**	11,85	79,46	**320,40**	**2147,90**

3. Details of the assessment of formation of linear and cyclic DIC/Oxyma adducts in the reaction of DIC with Oxyma with and without 10 mol% DITU in different solvents

The general protocol for the preparation of the requisite DIC/Oxyma solutions was as follows: 911 mg (6.4 mmol, 1.0 equiv) Oxyma was dissolved in a 10 x 10.0 mL of a given solvent (see below) at rt. To runs AT – ET (see below) 103 mg (0.64 mmol, 0.1 equiv) DITU was added and to all resulting solutions of runs A – E and AT – ET 1.0 mL DIC (7.8 mL, 1.2 equiv) was added. The resulting reaction mixtures were allowed to stand at rt for 17 days throughout which time 50 μL reaction aliquots were taken out, diluted with MeCN (1.0 mL) and analyzed by HPLC and LC-HRMS.

The ten experiments which were carried out:

1) Run A, DMF as solvent
2) Run B, NBP as solvent
3) Run C, NBP/EtOAc (1:1) as solvent
4) Run D, PC as solvent
5) Run E, PC/EtOAc (1:1) as solvent
6) Run AT, DMF as solvent, 10 mol% DITU
7) Run BT, NBP as solvent, 10 mol% DITU
8) Run CT, NBP/EtOAc (1:1) as solvent, 10 mol% DITU
9) Run DT, PC as solvent, 10 mol% DITU
10) Run ET, PC/EtOAc (1:1) as solvent, 10 mol% DITU

3.1 HPLC analysis of DIC/Oxyma solutions in different solvents with and without 10 mol% DITU

Experimental conditions as in section 2.1 of this SI. The presence of peaks of oxadiazole **3** at ~17.4 min, linear DIC/Oxyma adduct **2** at ~22.0 min and Oxyma at ~20.0 min was assessed in all cases.

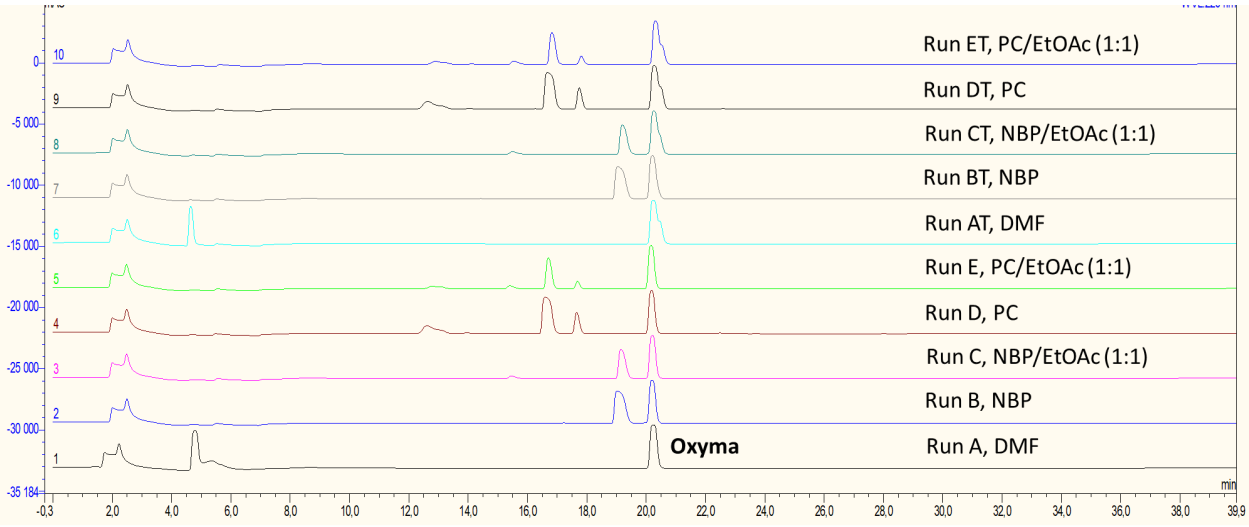

Figure S23. HPLC of Oxyma in five different solvents with and without 10 mol% DITU (t_0).

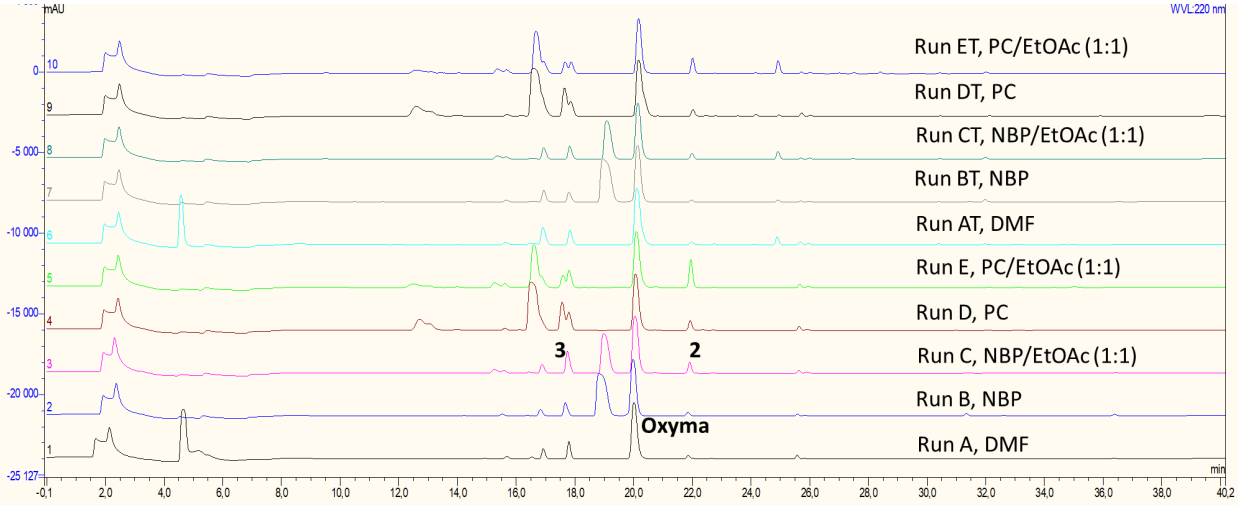

Figure S24. HPLC of Oxyma/DIC (1.0:1.2) mixtures with and without 10 mol% DITU in five different solvents after 5 hours at rt. Both linear (**2**) and cyclic (**3**) DIC/Oxyma adducts can be seen in all reaction mixtures in varying amounts. The presence of radical scavenger DITU in runs AT – ET did not prevent the formation of **2** and **3**.

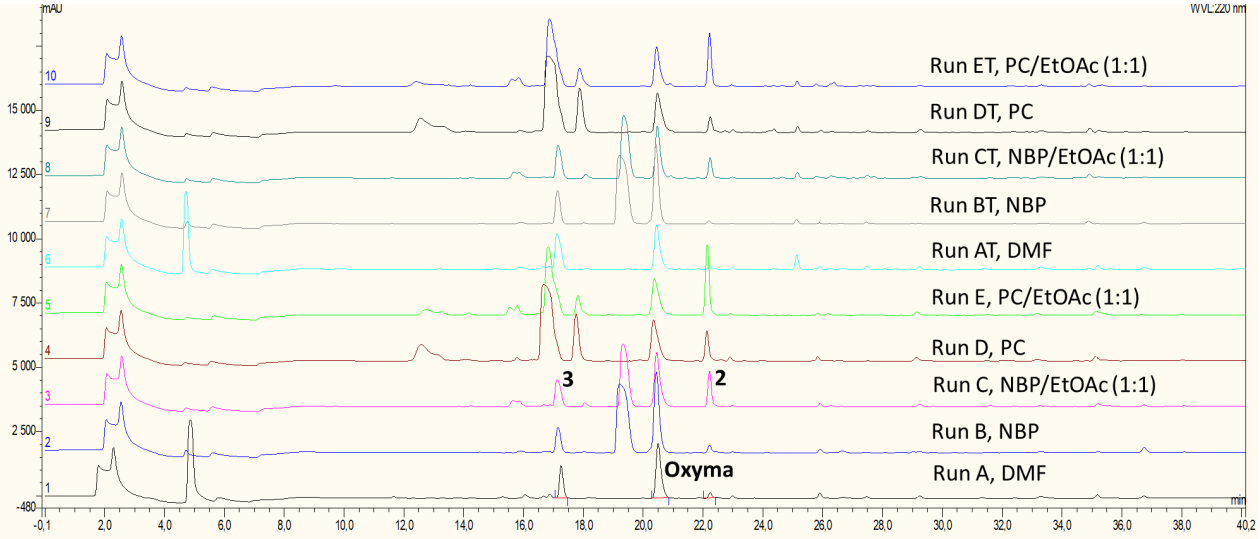

Figure S25. HPLC of Oxyma/DIC (1.0:1.2) mixtures with and without 10 mol% DITU in five different solvents after 4 days at rt. Both linear (**2**) and cyclic (**3**) DIC/Oxyma adducts can be seen in all reaction mixtures, in runs C – E and CT – ET the amount of the linear adduct **2** was significantly increased compared to A – B and AT – BT. The structures of **2** and **3** at this stage were confirmed by LC-HRMS, see section 3.2 of this SI.

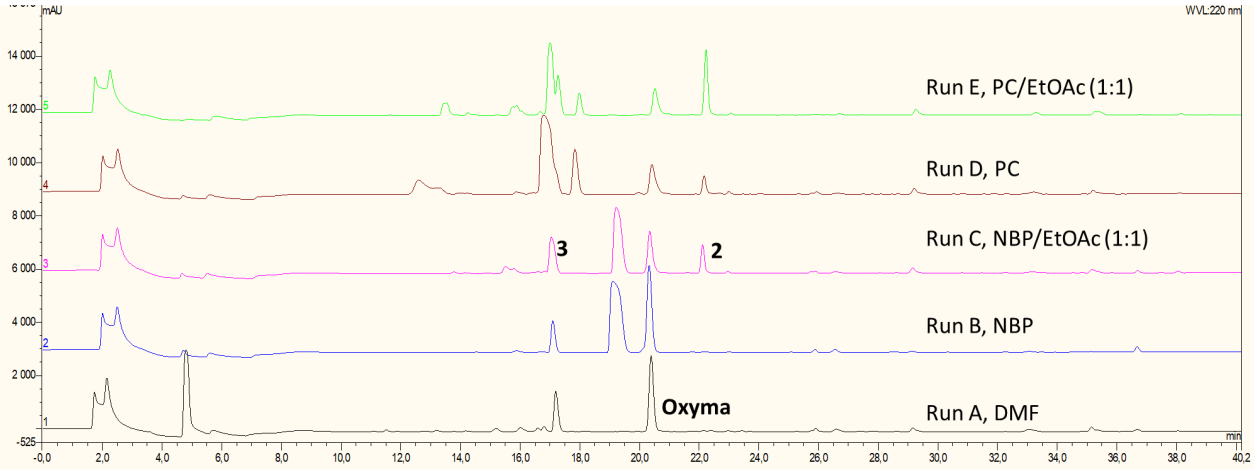

Figure S26. HPLC of Oxyma/DIC (1.0:1.2) mixtures in five different solvents after 17 days at rt. The linear DIC/Oxyma adduct **2** was still present to an appreciable extent in runs C – E while in runs A – B it was absent.

3.2 LC-HRMS analysis of DIC/Oxyma solutions in different solvents

Experimental conditions: column: Waters peptide CSH C18, 2.1x150mm, 1.7um, 130Å; column temperature: 30°C; injection volume: 1 µL; sampler temperature: 10°C; MS mode: positive 50-3200; DAD: 220 nm; data rate: 5Hz; detector cell: standard cell 1uL; flow: 0.2 ml/min; jet weaver: V380 mixer; mobile phase A: 0.1 % TFA in 90% water/MeCN, mobile phase B: 0.10 % TFA in 10% water/MeCN. Gradient (Time(min), %B): 0, 1; 1, 1; 30, 95; 32, 95; 32.1, 1; 42, 1. EIC (extracted ion chromatography)-MS analyses were carried out using a previously described methodology[4] in a following manner: upon performing the pertinent LC-HRMS selected extracted ion chromatograms (EICs) were obtained by inspecting the original chromatograms at appropriate m/z values, resulting in the EICs pertaining to the specific compounds investigated. To eliminate the risk that some of the peaks detected by EIC-MS were either other peptides and/or artefacts all peak assignments were a result of a two-step process:

1) an EIC-MS analysis was carried out searching for the most abundant mass of a given compound (z=+1) with the mass window of ±1 Da;

2) the mass spectra for the EIC-MS peaks thus obtained were inspected manually one by one and only the peaks for which the mass spectra were in full agreement with the expected mass spectrum of a given compound were included as the actual compounds. The peaks that were identified as hits in the initial screening round but subsequently did not fit with the expected mass spectrum were disregarded. The contents of peaks of oxadiazole **3** at ~11.0 min and linear DIC/Oxyma adduct **2** at ~15.5 min were assessed in all cases.

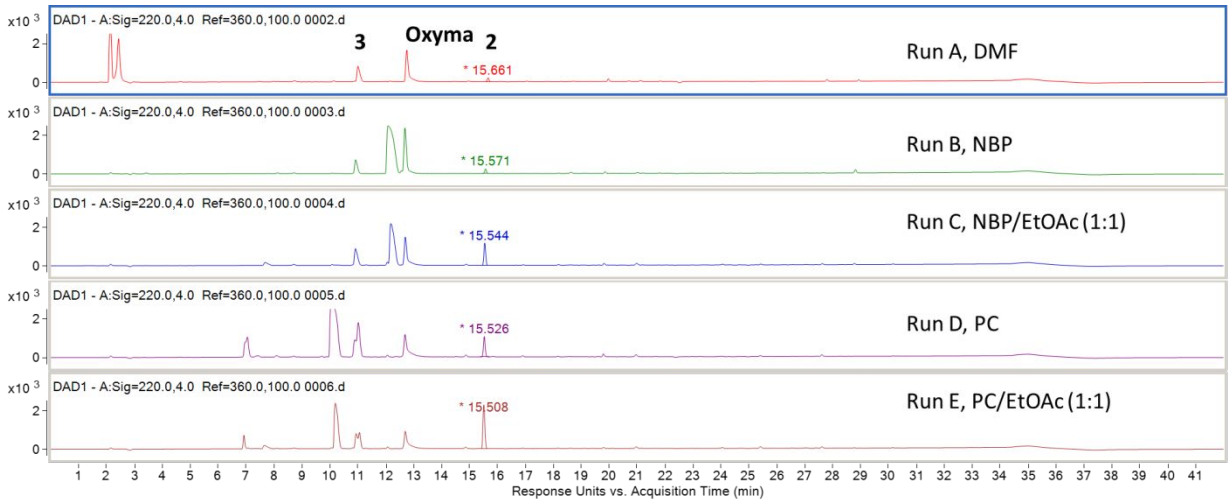

Figure S27. LC-HRMS (UV chromatogram overview) of Oxyma/DIC (1.0:1.2) mixtures in five different solvents after 4 days at rt.

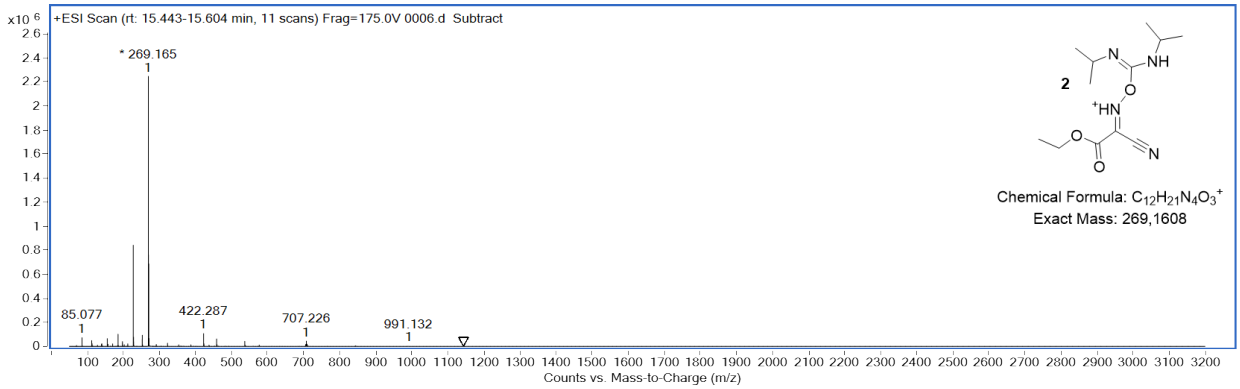

Figure S28. MS spectrum [M+H] of linear DIC/Oxyma adduct **2** detected in Oxyma/DIC (1.0:1.2) mixture in DMF after 4 days at rt.

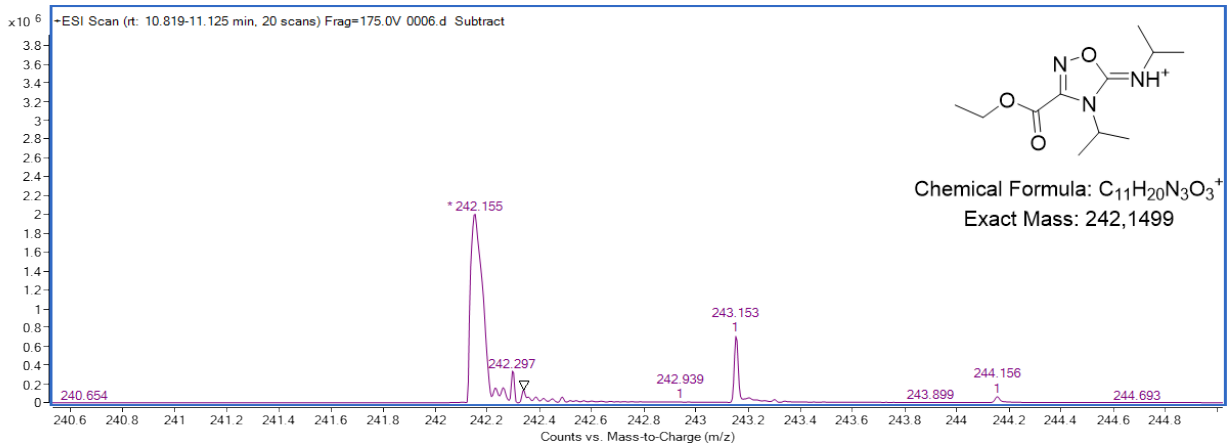

Figure S29. MS spectrum [M+H] of oxadiazole **3** detected in Oxyma/DIC (1.0:1.2) mixture in DMF after 4 days at rt.

Table S13. EIC-MS analysis of contents of linear DIC/Oxyma adduct **2** and oxadiazole **3** in Oxyma/DIC (1.0:1.2) mixtures in five different solvents after 4 days at rt (see Figure 2 for the corresponding chart).

Solvent	Quantification channel EIC	
	269.2 (**2**)	242.1 (**3**)
	Area (counts*min)	
DMF	14023022	71039476
NBP	13603308	66322408
NBP/EtOAc (1:1)	26735545	72034529
PC	25642669	69060166
PC/EtOAc (1:1)	34460762	57347695

4. Assessment of HCN formation during DIC/Oxyma mediated coupling of 2.0 equiv Fmoc-Ser(*t*-Bu)-OH with H-RMG resin in different solvents

8 x 1 mmol of dry H-RMG AMS resin was prepared as described in section 2 of this SI. The dried H-RMG AMS resins were swollen in solvents as specified for each reaction and drained. The amounts of residual solvent in the swollen and drained resins were determined to be ~5 mL. Next, in eight reactions vessels, 8 x 766.9 mg (2.0 mmol, 1.0 equiv) of Fmoc-Ser(*t*-Bu)-OH and 284.2 mg (2.0 mmol, 1.0 equiv) of Oxyma were dissolved in 20 mL of solvents as specified for each reaction. Next, the resulting Fmoc-Ser(*t*-Bu)-OH/Oxyma mixtures were added to the washed and drained batches of H-RMG AMS resins prepared above. To the resulting slurries of Fmoc-Ser(*t*-Bu)-OH/Oxyma with H-RMG AMS resins DIC was added in the following manner:

experiment R1, DMF, 313.2 μL DIC (2.0 mmol, 1.0 equiv)

experiment R2, DMF, 939 μL DIC (6.0 mmol, 3.0 equiv)

experiment R3, NBP, 313.2 μL DIC (2.0 mmol, 1.0 equiv)

experiment R4, NBP, 939 μL DIC (6.0 mmol, 3.0 equiv)

experiment R5, NBP/EtOAc (1:1), 313.2 μL DIC (2.0 mmol, 1.0 equiv)

experiment R6, NBP/EtOAc (1:1), 939 μL DIC (6.0 mmol, 3.0 equiv)

experiment R7, NBP/EtOAc (1:4), 313.2 μL DIC (2.0 mmol, 1.0 equiv)

experiment R8, NBP/EtOAc (1:4), 939 μL DIC (6.0 mmol, 3.0 equiv)

and the resulting reaction mixtures were shaken at rt (300 rpm) for 20 h. Conversions of the amidation reactions were followed by a qualitative (ninhydrin) color test.[2] Upon completion of all eight reactions (20 h), 50 μL reaction aliquots were taken out and quenched with 0.5 % TFA/MeCN (1.0 mL). The samples thus obtained were analysed by HPLC for the content of oxadiazole **3** using the method described in section 2 of this SI. As some of the solvents used in these experiments coeluted with **3** during the HPLC analyses using the experimental conditions reported in section 2 of this SI, an EIC MS for the detection of **3** was employed instead (see section 4.1 of this SI) based on which Oxyma to HCN conversions during these DIC/Oxyma mediated reactions were determined.

4.1 LC-HRMS analysis of Oxyma to HCN conversions during Fmoc-Ser(*t*-Bu)-OH + H-RMG AMS resin amidation reactions

Experimental conditions: column: Waters peptide CSH C18, 2.1x150mm, 1.7um, 130Å; column temperature: 30°C; injection volume: 0.4 µL; sampler temperature: 10°C; MS mode: Full scan; DAD: 220 nm; data rate: 5Hz; detector cell: standard cell 11µL; flow: 0.1 ml/min; jet weaver: V200 mixer; mobile phase A: 0.1 % TFA in water, mobile phase B: 0.10 % TFA in MeCN. Gradient (Time(min), %B): 0, 15; 40, 25; 48, 95; 54, 95; 55, 15; 62, 15. EIC (extracted ion chromatography) - MS analyses were carried out as previously described.[4] A methodology for determining %Oxyma→HCN conversions based on determining concentration of **3** was used, see section 2 of this SI.

Table S14. A summary of integrated EIC areas, concentrations of **3** (gL^{-1}), amounts of **3** formed and %Oxyma→HCN conversions after reaction time 20 h for experiments R1 – R8.

Solvent	Fmoc-Ser(t-Bu)-OH/Oxyma/DIC (1:1:**X**)	Rt (min), quantification channel EIC 242,15	Area (counts*min) quantification channel EIC	gL^{-1} **3**	µmol **3**	%Oxyma->HCN
DMF	1:1:**1**	16,936	3217592	0,14278	14,7933	0,7397
DMF	1:1:**3**	16,926	38447402	1,70608	176,7669	8,8383
NBP	1:1:**1**	16,868	1969508	0,08740	9,0551	0,4528
NBP	1:1:**3**	16,868	27756109	1,23166	127,6123	6,3806
NBP/EtOAc (1:1)	1:1:**1**	16,902	878422	0,03898	4,0387	0,2019
NBP/EtOAc (1:1)	1:1:**3**	16,872	49872540	2,21307	229,2955	11,4648
NBP/EtOAc (1:4)	1:1:**1**	16,901	370573	0,01644	1,7038	0,0852
NBP/EtOAc (1:4)	1:1:**3**	16,849	98067042	4,35167	450,8759	22,5438

Table S15. A summary of %Oxyma→HCN conversions after reaction time 20 h for experiments R1 – R8.

Fmoc-Ser(t-Bu)-OH/Oxyma/DIC (1:1:**X**)	Solvent			
	DMF	NBP	NBP/EtOAc (1:1)	NBP/EtOAc (1:4)
	Oxyma→HCN conversion (%)			
1:1:**1**	0,7397	0,4528	0,2019	0,0852
1:1:**3**	8,8383	6,3806	11,4648	22,5438

5. Assessment of HCN formation and amide bond formation kinetics during DIC/Oxyma mediated coupling of 1.3 equiv Fmoc-Ser(*t*-Bu)-OH with H-RMG resin in different solvents

Conversions of the amidation reactions were followed by determining the Fmoc content of the Fmoc-Ser(*t*-Bu)-RMG AMS resins as follows: resin aliquots (ca 50 – 100 mg) were taken out at specified times, washed thoroughly by DMF, *i*-PrOH and Et_2O and dried to constant weight in vacuo before determining the amidation conversions as described in section 5.1 of this SI. At specified times throughout the amidation reactions, 20 μL reaction aliquots were taken out and quenched with 0.5 % TFA/MeCN (1.0 mL). The samples thus obtained were analysed by LC-HRMS for the content of oxadiazole **3** using the method described in section 4 of this SI. EIC MS analyses for the detection of **3** were used (see section 5.2 of this SI) based on which Oxyma to HCN conversions were determined.

5.1 HPLC analysis of conversion during Fmoc-Ser(*t*-Bu)-OH + H-RMG AMS resin amidation reactions

Using the samples of Fmoc-Ser(*t*-Bu)-RMG AMS resins isolated as described in the section 5 of this SI. The Fmoc content determinations were carried out using a previously reported protocol[1] based on a literature method which utilizes the quantification of dibenzofulvene (DBF) liberated from the Fmoc containing resins by the action of the strong base 1,8-diazabicyclo[5.4. 0]undec-7-ene (DBU).[5] As a reference standard (100% conversion) we used a sample of a Fmoc-Ser(*t*-Bu)-RMG AMS resin for which full amidation conversion was attained. Following experimental conditions were used for all DBF quantifications: column: Phenomenex Kinetex C18 100Å 2.6µm 4.6x50mm; detection wavelength: 220 nm; column temperature: 45°C; injection volume: 1.0 µL; sampler temperature: 10°C; flow: 1.0 ml/min; mobile phase A: 0.1 % TFA in water, mobile phase B: 0.08 % TFA in 90% MeCN/10 %water. Gradient (Time(min), %B): 0, 1; 10, 100; 13, 100; 14, 100; 19, 1; 20, 1.

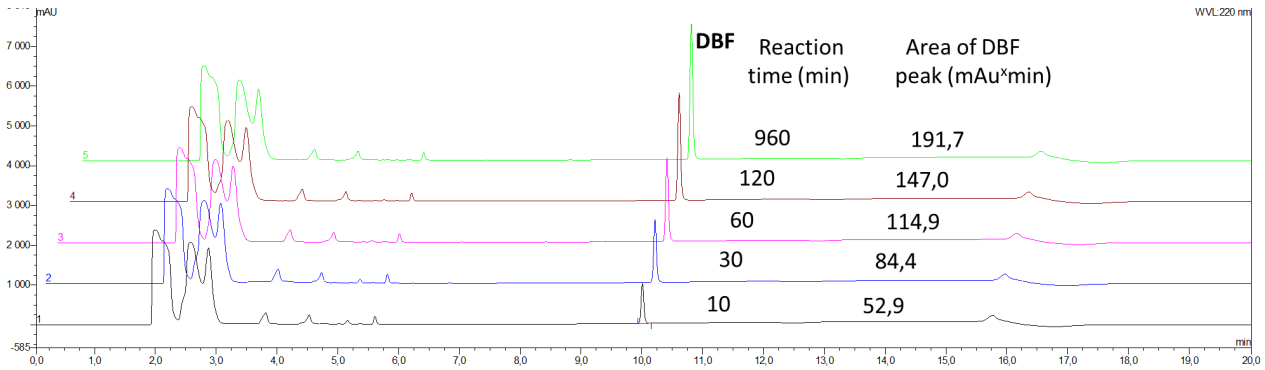

Figure S30. Integrated areas (mAuˣmin) of DBF peak from determinations of conversions of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/H-RMG-AMS resin amidation reactions in DMF.

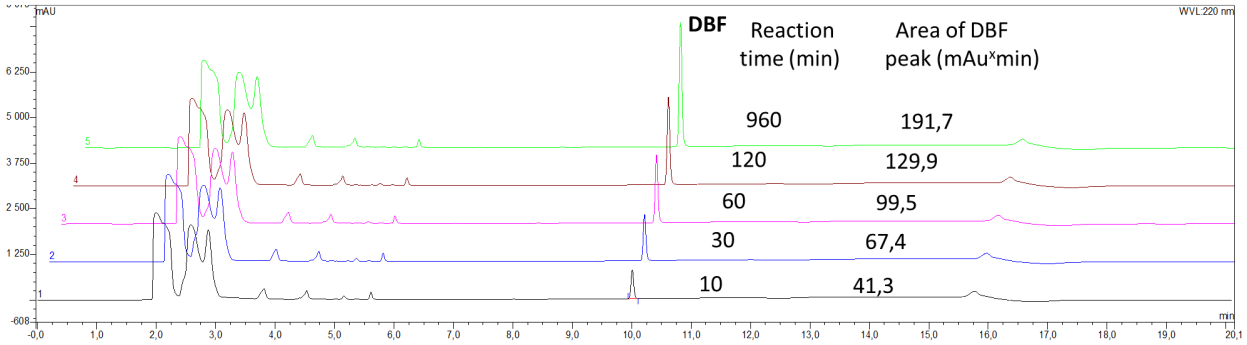

Figure S31. Integrated areas (mAuˣmin) of DBF peak from determinations of conversions of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/H-RMG-AMS resin amidation reactions in NBP.

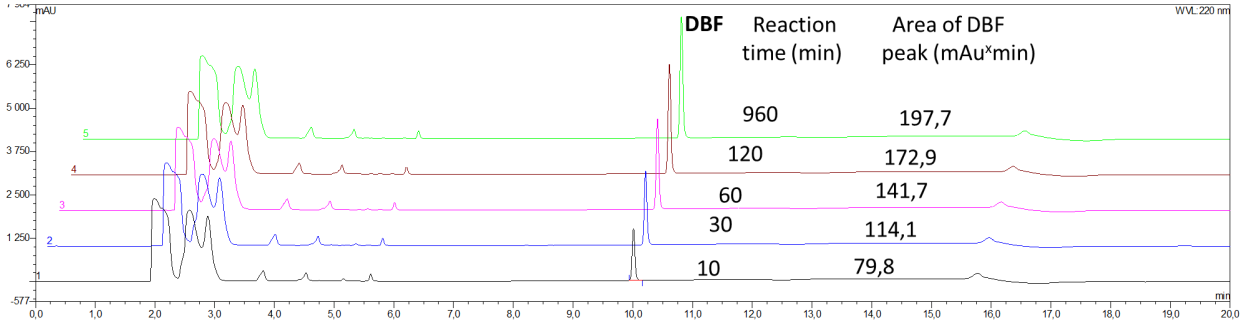

Figure S32. Integrated areas (mAu^{x}min) of DBF peak from determinations of conversions of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/H-RMG-AMS resin amidation reactions in NBP/EtOAc (1:1).

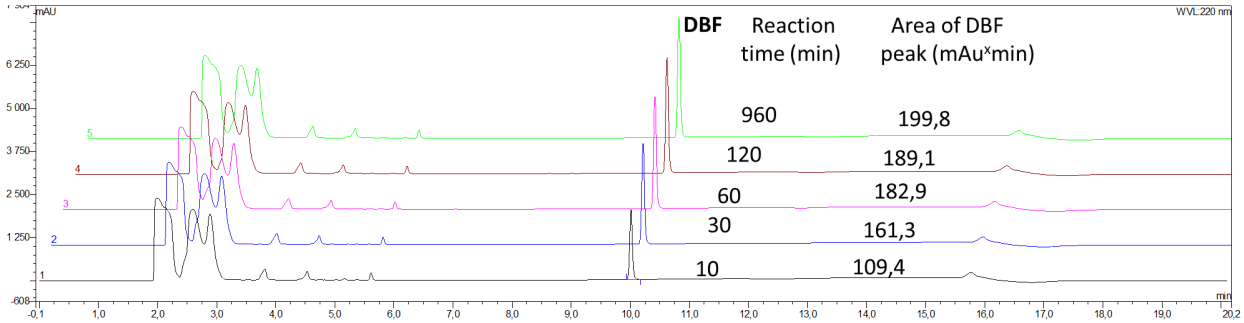

Figure S33. Integrated areas (mAu^{x}min) of DBF peak from determinations of conversions of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/H-RMG-AMS resin amidation reactions in NBP/EtOAc (1:4).

Table S16. A summary of integrated areas (mAu^{x}min) of DBF peak from determinations of conversions of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/H-RMG-AMS resin amidation reactions in DMF, NBP, NBP/EtOAc (1:1) and NBP/EtOAc (1:4).

Reaction time (min)	Solvent			
	DMF	NBP	NBP/EtOAc (1:1)	NBP/EtOAc (1:4)
	Integrated areas (mAu^{x}min) of DBF peak			
0	0,0	0,0	0,0	0,0
10	52,9	41,3	79,8	109,4
30	84,4	67,4	114,1	161,3
60	114,9	99,5	141,7	182,9
120	147,0	129,9	172,9	189,1
960	191,7	191,7	197,7	199,8

Table S17. A summary of conversions during Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/H-RMG-AMS resin amidation reactions in DMF, NBP, NBP/EtOAc (1:1) and NBP/EtOAc (1:4).

Reaction time (min)	Solvent			
	DMF	NBP	NBP/EtOAc (1:1)	NBP/EtOAc (1:4)
	Amidation conversion (%)			
0	0,0	0,0	0,0	0,0
10	26,5	20,7	39,9	54,7
30	42,2	33,7	57,1	80,7
60	57,5	49,8	70,9	91,5
120	73,5	65,0	86,5	94,6
960	95,9	95,9	98,9	99,9

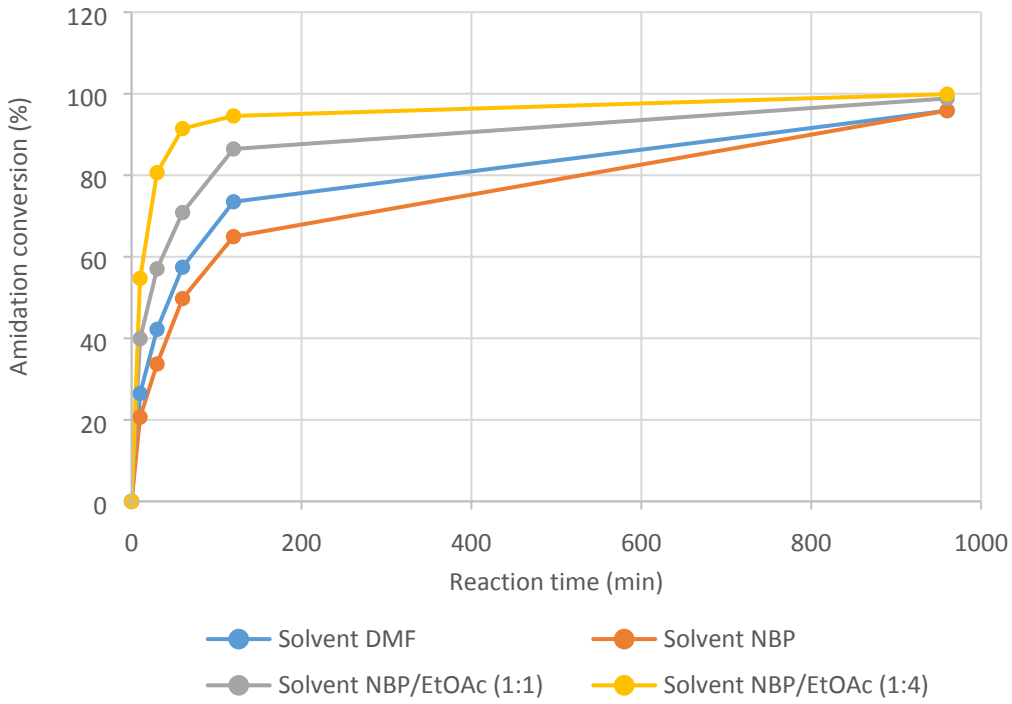

Figure S34. Schematic representation of conversions during Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/H-RMG-AMS resin amidation reactions in DMF, NBP, NBP/EtOAc (1:1) and NBP/EtOAc (1:4).

5.2 LC-HRMS analysis of Oxyma to HCN conversion during Fmoc-Ser(*t*-Bu)-OH + H-RMG AMS resin amidation reactions

Experimental conditions: column: Waters peptide CSH C18, 2.1x150mm, 1.7μm, 130Å; column temperature: 30°C; injection volume: 0.4 μL; sampler temperature: 10°C; MS mode: Full scan; DAD: 220 nm; data rate: 5Hz; detector cell: standard cell 11μL; flow: 0.1 ml/min; jet weaver: V200 mixer; mobile phase A: 0.1 % TFA in water, mobile phase B: 0.10 % TFA in MeCN. Gradient (Time(min), %B): 0, 15; 40, 25; 48, 95; 54, 95; 55, 15; 62, 15. EIC-MS analyses were carried out as previously described.[4] A methodology for determining %Oxyma→HCN conversions based on determining concentration of **3** was used, see section 2 of this SI.

Table S18. A summary of integrated EIC areas, **3** concentrations (gL^{-1}), amounts of **3** formed and %Oxyma→HCN conversions during experiments R1 – R4.

Solvent	Reaction time (min)	Rt (min), quantification channel EIC 242,15	Area (counts*min) quantification channel EIC 242,15	gL^{-1} **3**	μmol **3**	%Oxyma->HCN
DMF	10	17,280	13069	0,002780	0,2880	0,0222
NBP	10	17,274	6231	0,001326	0,1373	0,0106
NBP/EtOAc (1:1)	10	17,271	4758	0,001012	0,1049	0,0081
NBP/EtOAc (1:4)	10	17,299	5537	0,001178	0,1220	0,0094
DMF	30	17,259	19191	0,004082	0,4230	0,0325
NBP	30	17,249	10939	0,002327	0,2411	0,0185
NBP/EtOAc (1:1)	30	17,285	9465	0,002013	0,2086	0,0160
NBP/EtOAc (1:4)	30	17,287	8106	0,001724	0,1786	0,0137
DMF	60	17,282	41323	0,008790	0,9108	0,0701
NBP	60	17,269	19632	0,004176	0,4327	0,0333
NBP/EtOAc (1:1)	60	17,268	13710	0,002916	0,3022	0,0232
NBP/EtOAc (1:4)	60	17,248	12241	0,002604	0,2698	0,0208
DMF	120	17,266	89789	0,019100	1,9790	0,1522
NBP	120	17,254	45285	0,009633	0,9981	0,0768
NBP/EtOAc (1:1)	120	17,279	29201	0,006212	0,6436	0,0495
NBP/EtOAc (1:4)	120	17,345	17345	0,003690	0,3823	0,0294
DMF	960	17,323	577535	0,122855	12,7289	0,9791
NBP	960	17,293	255907	0,054437	5,6402	0,4339
NBP/EtOAc (1:1)	960	17,317	87195	0,018548	1,9218	0,1478
NBP/EtOAc (1:4)	960	17,349	37293	0,007933	0,8219	0,0632

Table S19. A summary of %Oxyma→HCN conversions during experiments R1 – R4.

Reaction time (min)	Solvent			
	DMF	NBP	NBP/EtOAc (1:1)	NBP/EtOAc (1:4)
	Oxyma→HCN conversion (%)			
0	0,0000	0,0000	0,0000	0,0000
10	0,0222	0,0106	0,0081	0,0094
30	0,0325	0,0185	0,0160	0,0137
60	0,0701	0,0333	0,0232	0,0208
120	0,1522	0,0768	0,0495	0,0294
960	0,9791	0,4339	0,1478	0,0632

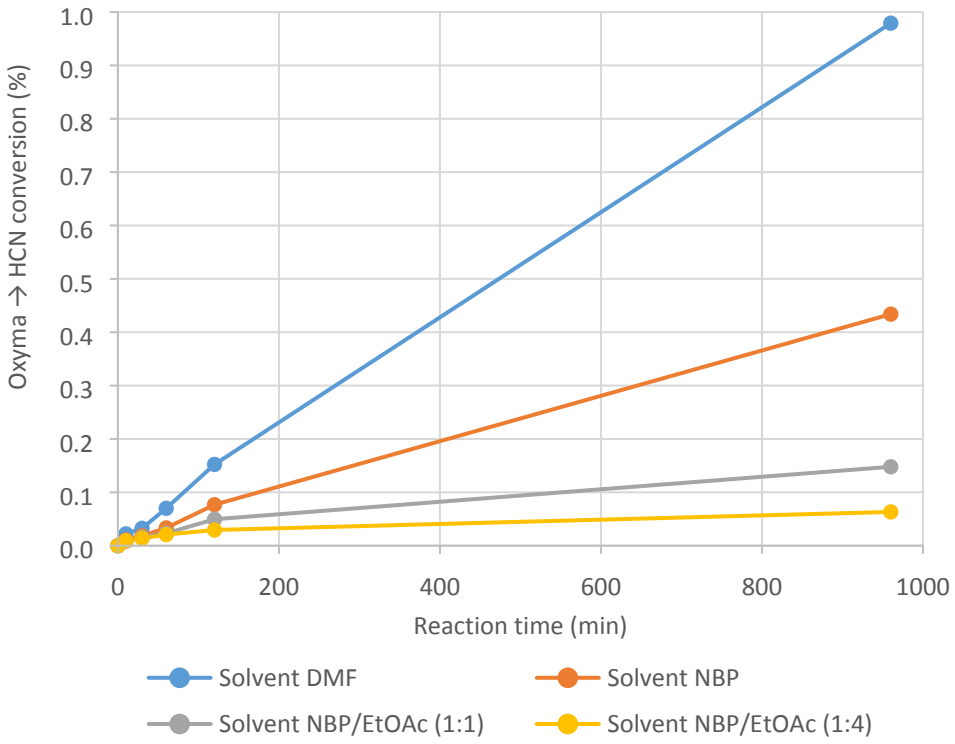

Figure S35. A schematic representation of %Oxyma→HCN conversions during experiments R1 – R4.

6. Assessment of HCN formation and amide bond formation kinetics during DIC/Oxyma mediated coupling of 1.0 equiv Fmoc-Ser(*t*-Bu)-OH with (S)-(-)-1-phenylethylamine in different solvents

For all four reactions 20 μL were taken out and quenched with 0.5 % TFA/MeCN (1.0 mL) at 0, 10, 30, 60, 120 and 960 min. Conversions of the amidation reactions at these timepoints were determined by HPLC (see section 6.1 of this SI) and the contents of oxadiazole **3** used for the calculations of conversion of Oxyma to HCN were determined by LC-HRMS (see section 6.2 of this SI).

6.1 HPLC analysis of conversions of the Fmoc-Ser(*t*-Bu)-OH + (S)-(-)-1-phenylethylamine amidation reactions

Experimental conditions used in the section 5.1 of this SI were employed. Following peaks were integrated: i) Fmoc-Ser(*t*-Bu)-OH (starting material), rt 9.0 min; ii) Fmoc-Ser(*t*-Bu)-S)-(-)-1-phenylethylamide (product of amidation reaction), rt 10.2 min.

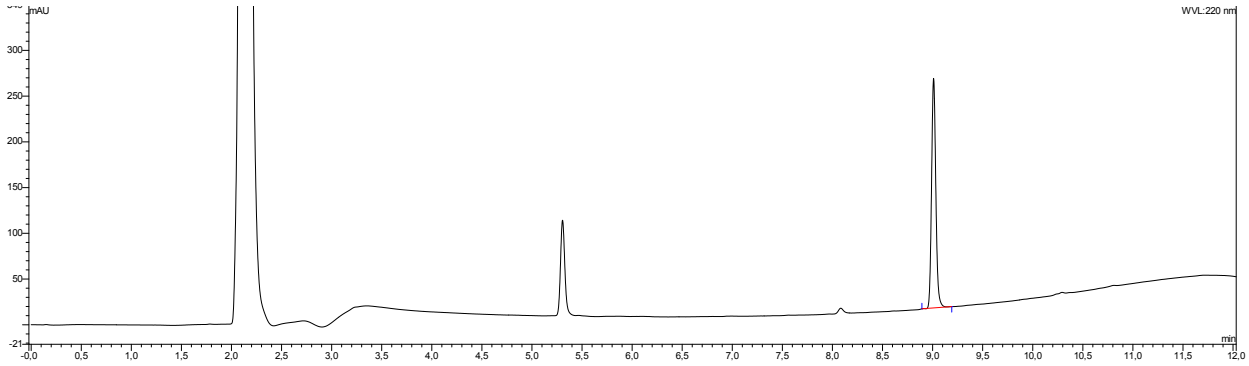

Figure S36. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=0 min (prior to DIC addition).

Table S20. Area% for the integrated peak.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	9,010	12,3148	n.a.	BMB*	250,950	100,00	n.a.
Total:			**12,3148**	**0,0000**		**250,950**	**100,00**	

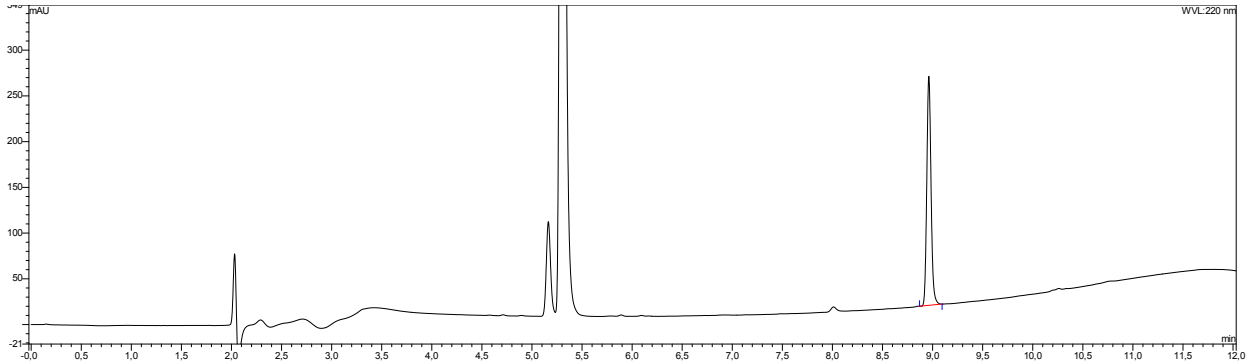

Figure S37. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP at t=0 min (prior to DIC addition).

Table S21. Area% for the integrated peak.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,962	12,3483	n.a.	BMB*	250,390	100,00	n.a.
Total:			**12,3483**	**0,0000**		**250,390**	**100,00**	

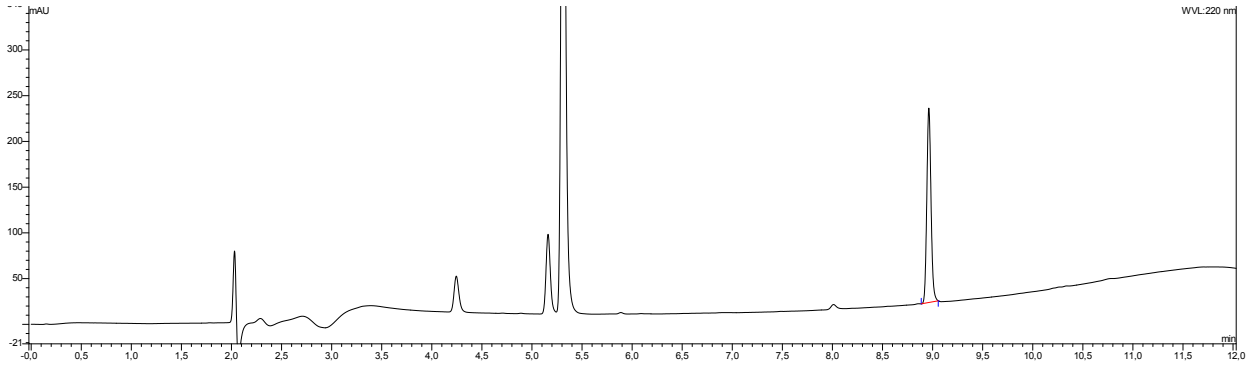

Figure S38. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:1) at t=0 min (prior to DIC addition).

Table S22. Area% for the integrated peak.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,962	10,3531	n.a.	BMB*	212,490	100,00	n.a.
Total:			**10,3531**	**0,0000**		**212,490**	**100,00**	

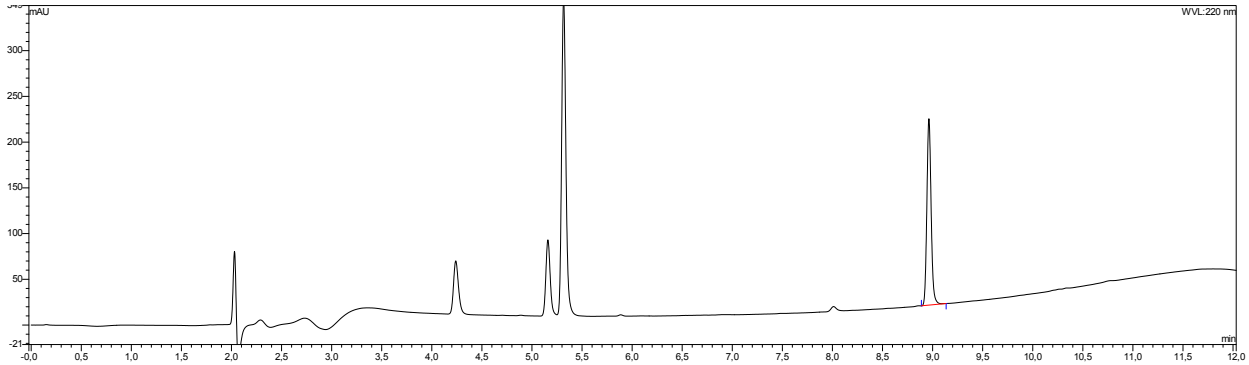

Figure S39. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=0 min (prior to DIC addition).

Table S23. Area% (mAu^{x}min) for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,963	10,0501	n.a.	BMB*	203,762	100,00	n.a.
Total:			**10,0501**	**0,0000**		**203,762**	**100,00**	

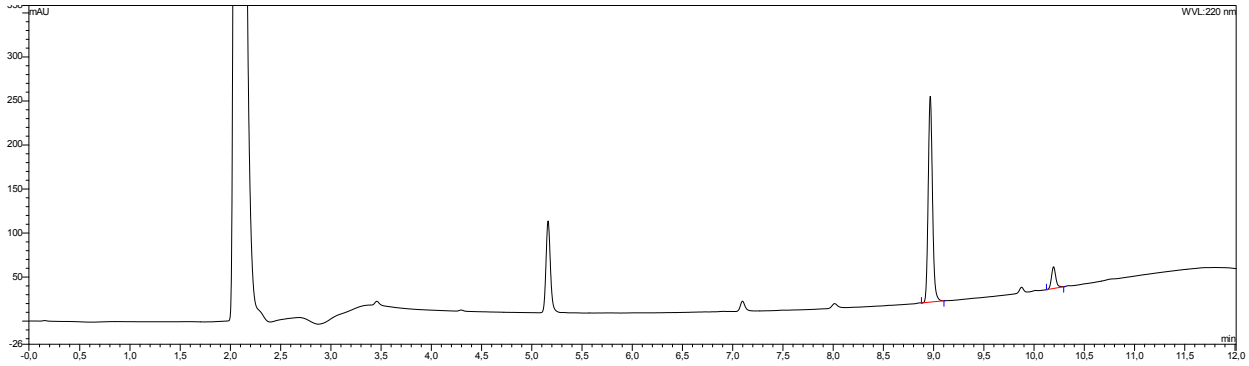

Figure S40. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=10 min.

Table S24. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	11,6847	n.a.	BMB*	235,327	90,91	16,11
2	n.a.	10,193	1,1687	n.a.	BMB*	24,343	9,09	n.a.
Total:			**12,8534**	**0,0000**		**259,671**	**100,00**	

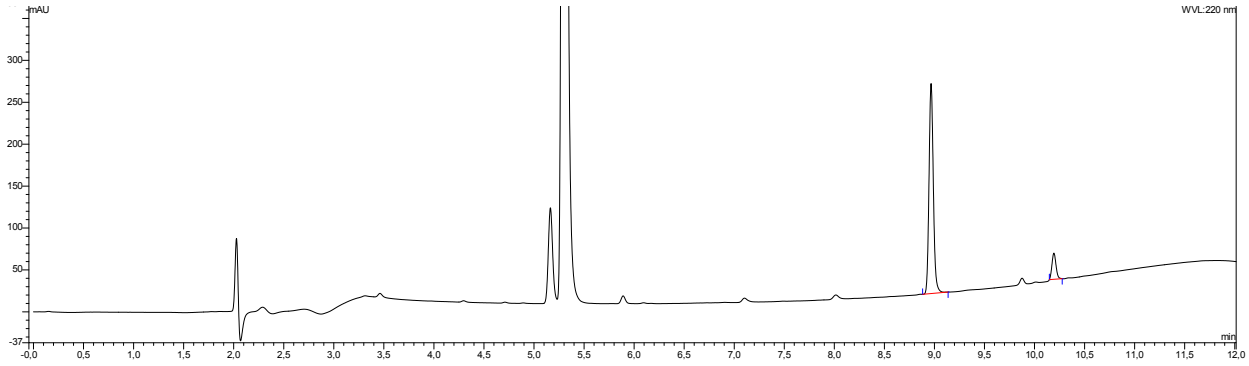

Figure S41. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP at t=10 min.

Table S25. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	12,5131	n.a.	BMB*	250,522	89,58	16,23
2	n.a.	10,193	1,4559	n.a.	BMB*	31,175	10,42	n.a.
Total:			**13,9691**	**0,0000**		**281,698**	**100,00**	

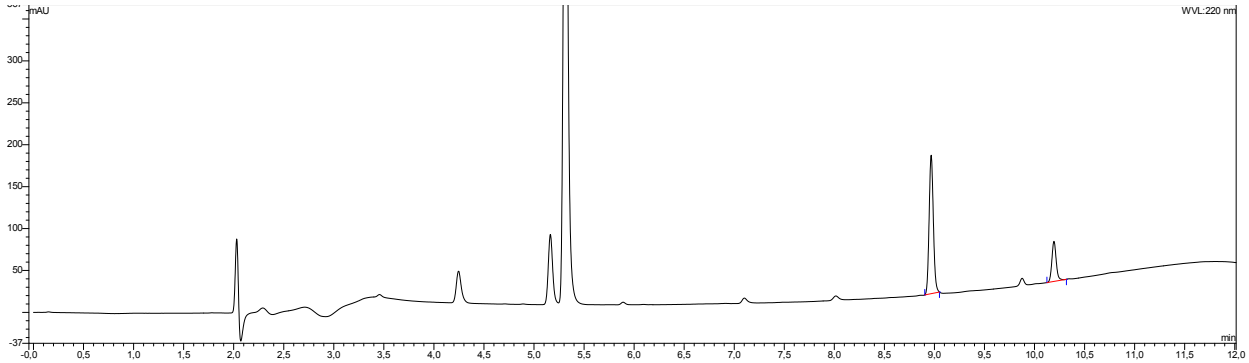

Figure S42. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:1) at t=10 min.

Table S26. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	8,0630	n.a.	BMB*	165,077	77,27	16,02
2	n.a.	10,193	2,3718	n.a.	BMB*	47,758	22,73	n.a.
Total:			**10,4348**	**0,0000**		**212,835**	**100,00**	

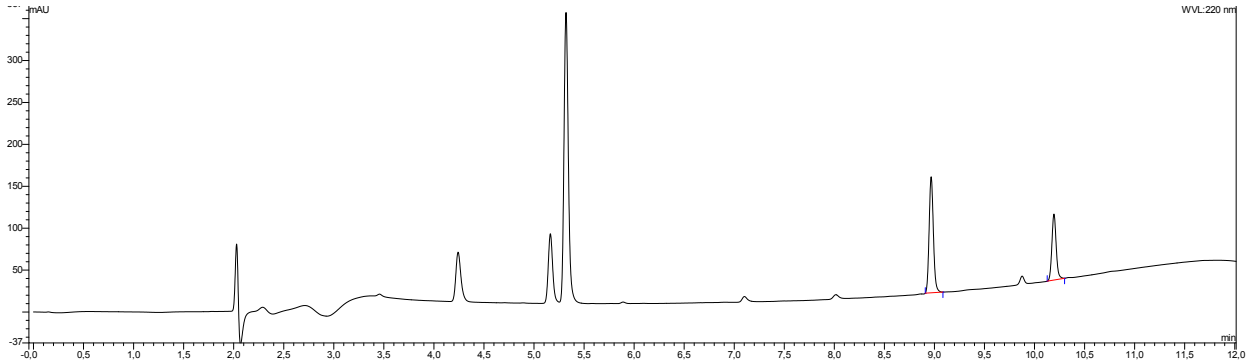

Figure S43. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=10 min.

Table S27. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	6,8166	n.a.	BMB*	138,442	63,56	16,02
2	n.a.	10,193	3,9082	n.a.	BMB*	78,659	36,44	n.a.
Total:			**10,7248**	**0,0000**		**217,101**	**100,00**	

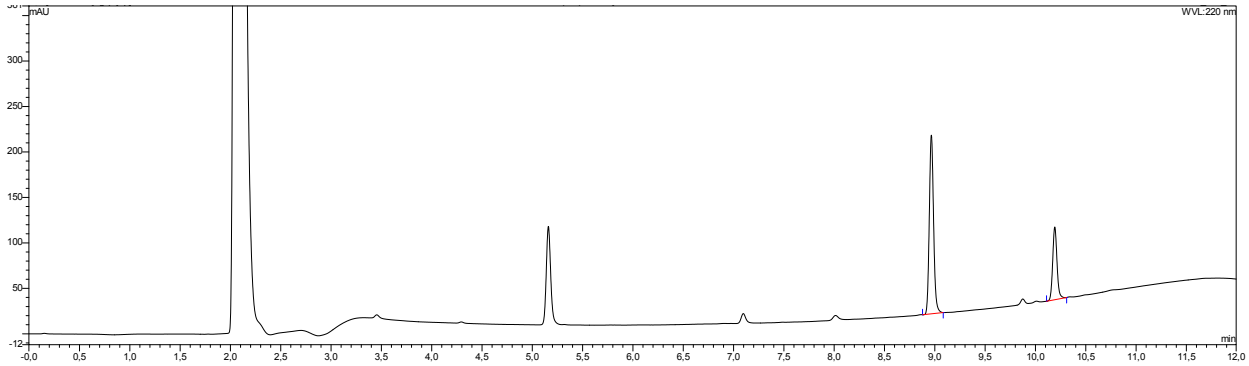

Figure S44. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=30 min.

Table S28. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,965	9,6487	n.a.	BMB*	196,445	70,99	16,17
2	n.a.	10,192	3,9437	n.a.	BMB*	79,987	29,01	n.a.
Total:			**13,5925**	**0,0000**		**276,432**	**100,00**	

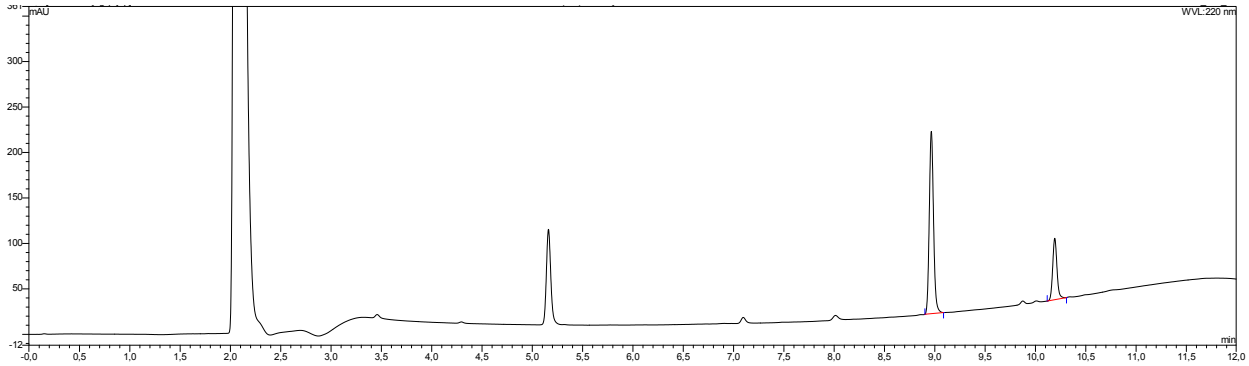

Figure S45. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP at t=30 min.

Table S29. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,965	9,7871	n.a.	BMB*	200,286	74,74	16,26
2	n.a.	10,192	3,3079	n.a.	BMB*	67,476	25,26	n.a.
Total:			**13,0950**	**0,0000**		**267,762**	**100,00**	

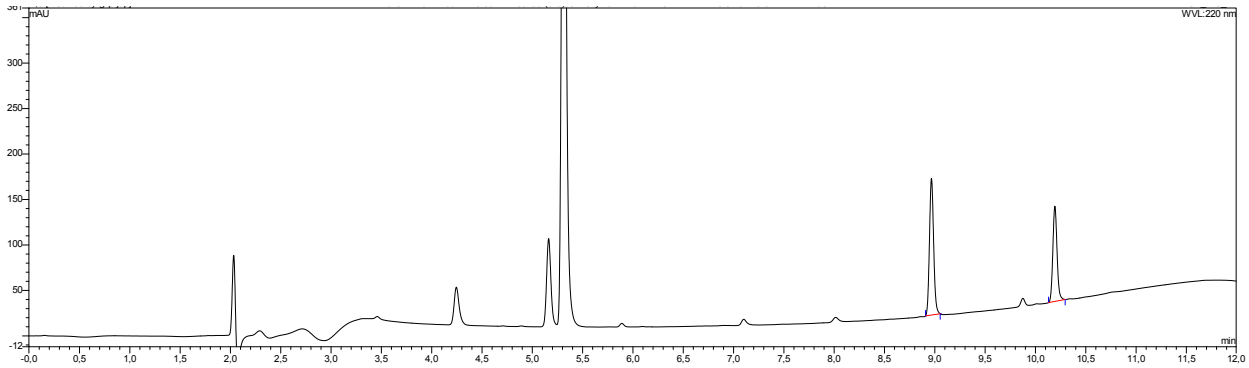

Figure S46. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:1) at t=30 min.

Table S30. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	7,1984	n.a.	BMB*	150,222	58,67	16,39
2	n.a.	10,193	5,0705	n.a.	BMB*	104,643	41,33	n.a.
Total:			**12,2689**	**0,0000**		**254,865**	**100,00**	

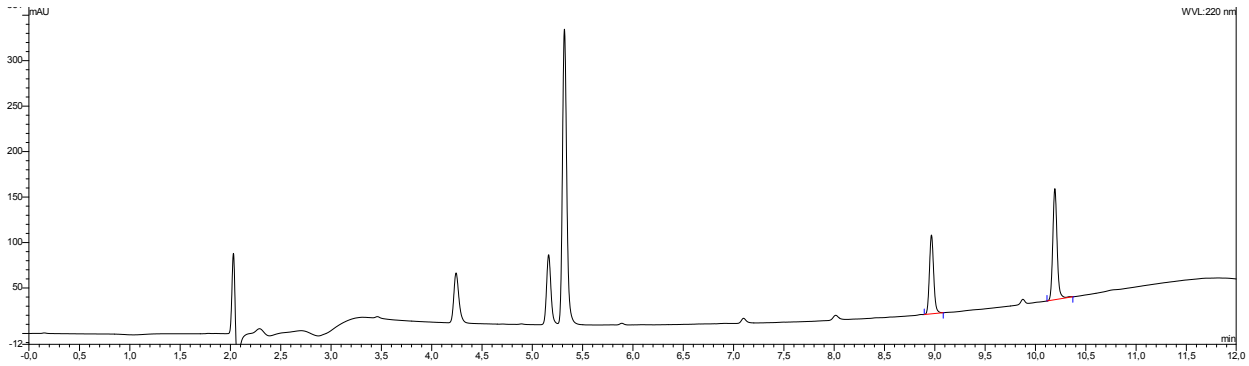

Figure S47. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=30 min.

Table S31. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	4,2138	n.a.	BMB*	86,671	41,03	16,26
2	n.a.	10,193	6,0550	n.a.	BMB*	122,114	58,97	n.a.
Total:			**10,2688**	**0,0000**		**208,785**	**100,00**	

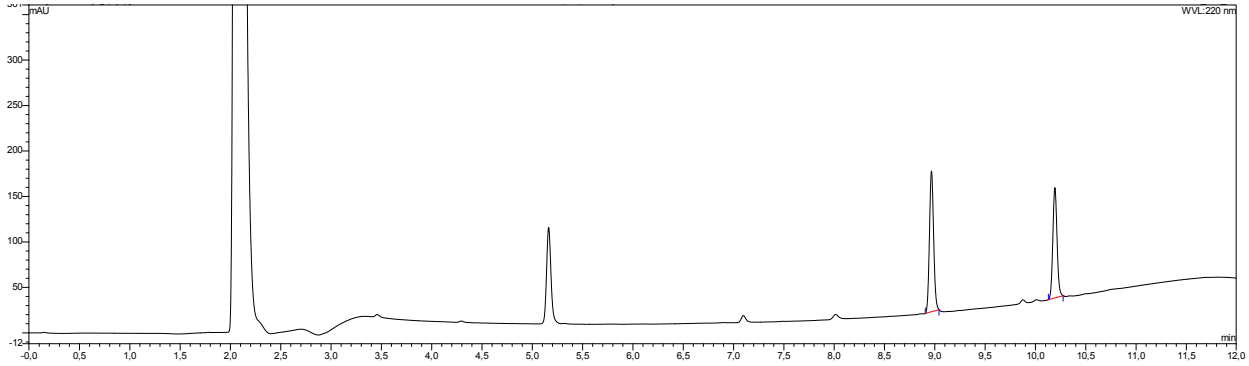

Figure S48. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=60 min.

Table S32. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	7,4052	n.a.	BMB*	154,573	55,83	16,26
2	n.a.	10,193	5,8587	n.a.	BMB*	121,264	44,17	n.a.
Total:			**13,2639**	**0,0000**		**275,837**	**100,00**	

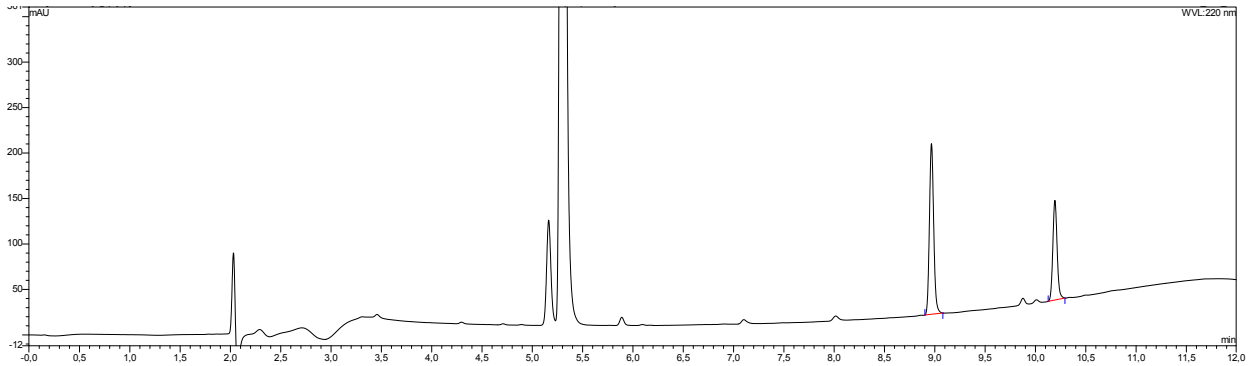

Figure S49. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP at t=60 min.

Table S33. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	9,2459	n.a.	BMB*	187,582	63,15	16,05
2	n.a.	10,193	5,3951	n.a.	BMB*	109,593	36,85	n.a.
Total:			**14,6410**	**0,0000**		**297,175**	**100,00**	

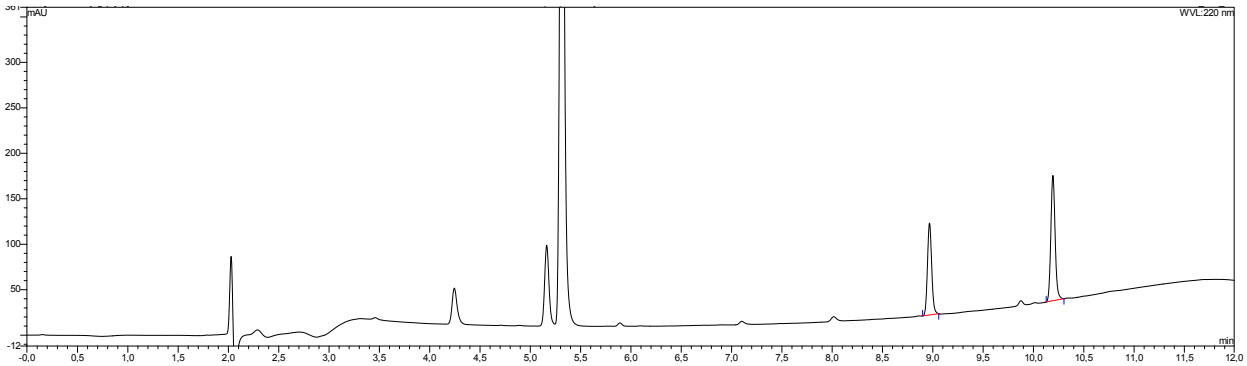

Figure S50. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:1) at t=60 min.

Table S34. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	4,9307	n.a.	BMB*	101,009	41,99	16,11
2	n.a.	10,193	6,8111	n.a.	BMB*	137,730	58,01	n.a.
Total:			**11,7418**	**0,0000**		**238,739**	**100,00**	

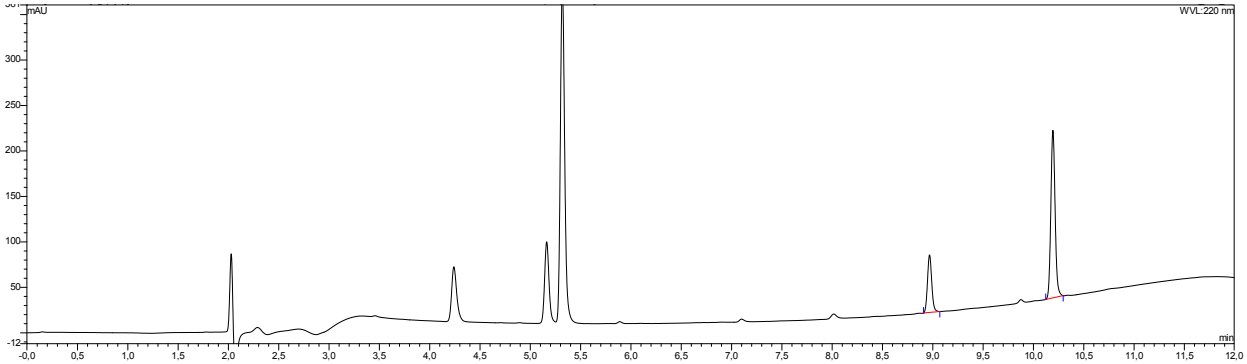

Figure S51. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=60 min.

Table S35. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	3,0762	n.a.	BMB*	63,186	25,33	16,14
2	n.a.	10,193	9,0704	n.a.	BMB*	184,199	74,67	n.a.
Total:			**12,1466**	**0,0000**		**247,385**	**100,00**	

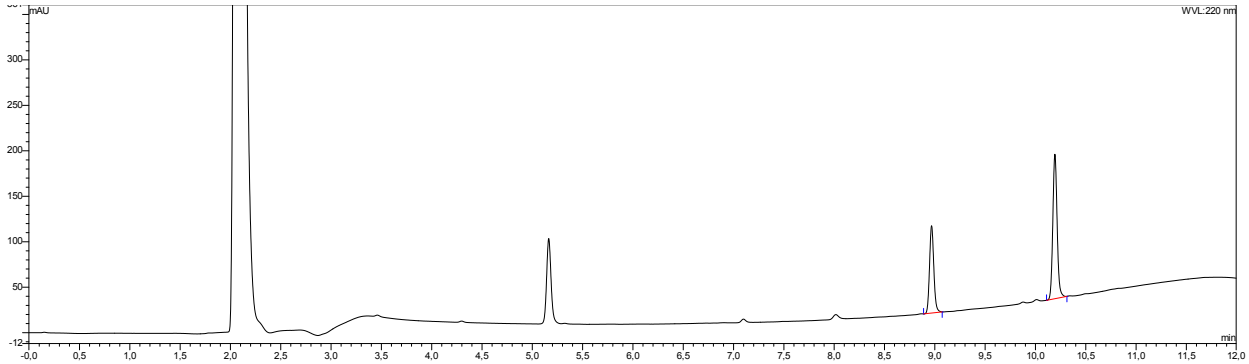

Figure S52. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=120 min.

Table S36. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,968	4,6978	n.a.	BMB*	95,872	37,36	16,09
2	n.a.	10,193	7,8753	n.a.	BMB*	158,831	62,64	n.a.
Total:			**12,5730**	**0,0000**		**254,703**	**100,00**	

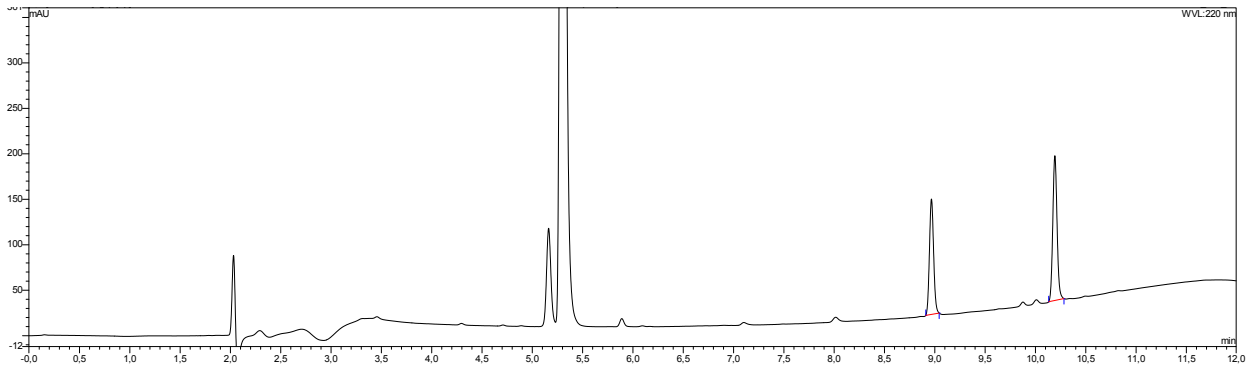

Figure S53. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP at t=120 min.

Table S37. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	6,0834	n.a.	BMB*	126,860	43,90	16,17
2	n.a.	10,193	7,7737	n.a.	BMB*	159,110	56,10	n.a.
Total:			**13,8571**	**0,0000**		**285,970**	**100,00**	

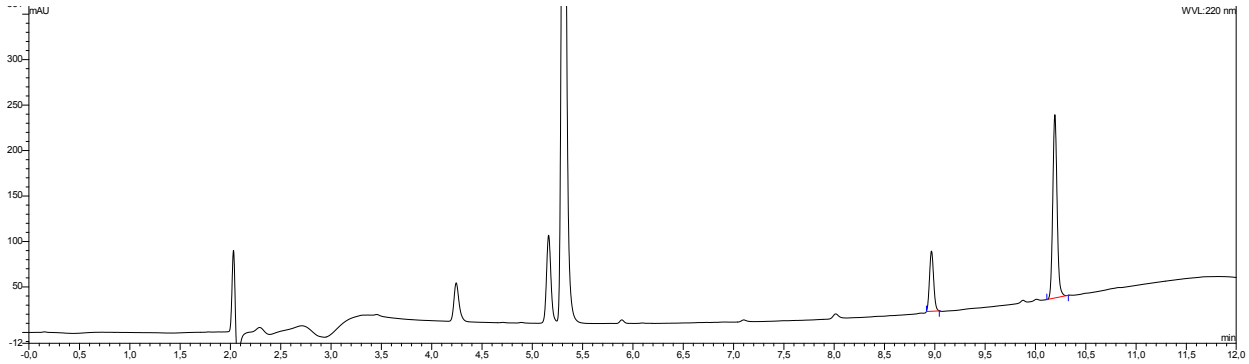

Figure S54. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:1) at t=120 min.

Table S38. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	3,1380	n.a.	BMB*	66,197	23,84	16,17
2	n.a.	10,193	10,0240	n.a.	BMB*	201,538	76,16	n.a.
Total:			**13,1620**	**0,0000**		**267,735**	**100,00**	

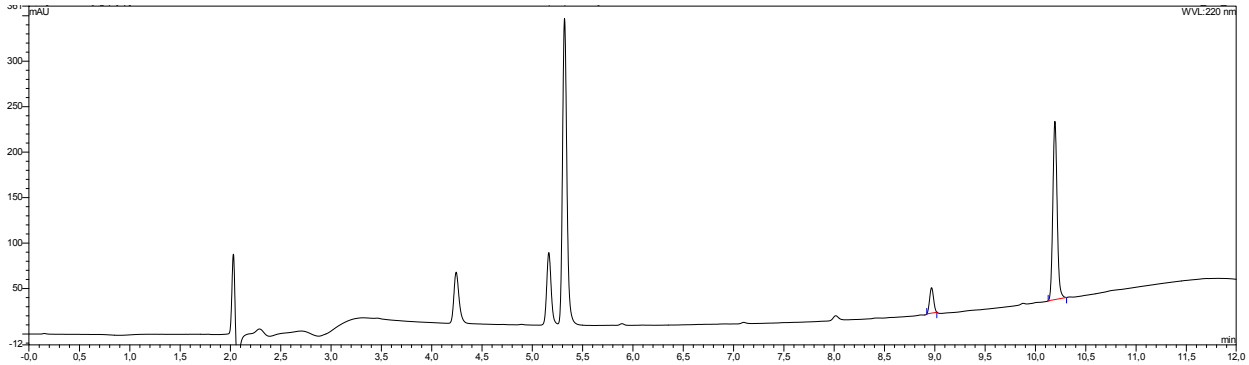

Figure S55. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=120 min.

Table S39. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	1,2687	n.a.	BMB*	27,944	11,52	16,26
2	n.a.	10,193	9,7475	n.a.	BMB*	195,935	88,48	n.a.
Total:			**11,0162**	**0,0000**		**223,879**	**100,00**	

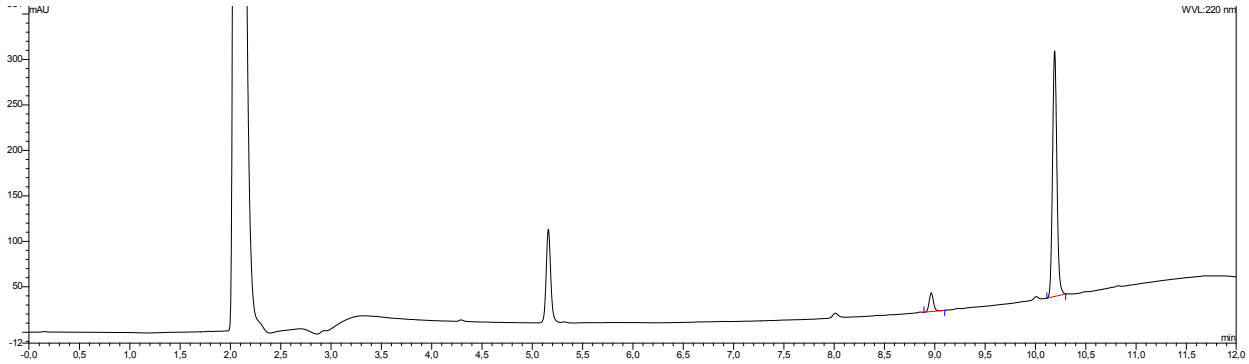

Figure S56. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=960 min.

Table S40. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,963	0,9936	n.a.	BMB*	20,490	6,84	15,94
2	n.a.	10,190	13,5421	n.a.	BMB*	270,108	93,16	n.a.
Total:			**14,5357**	**0,0000**		**290,598**	**100,00**	

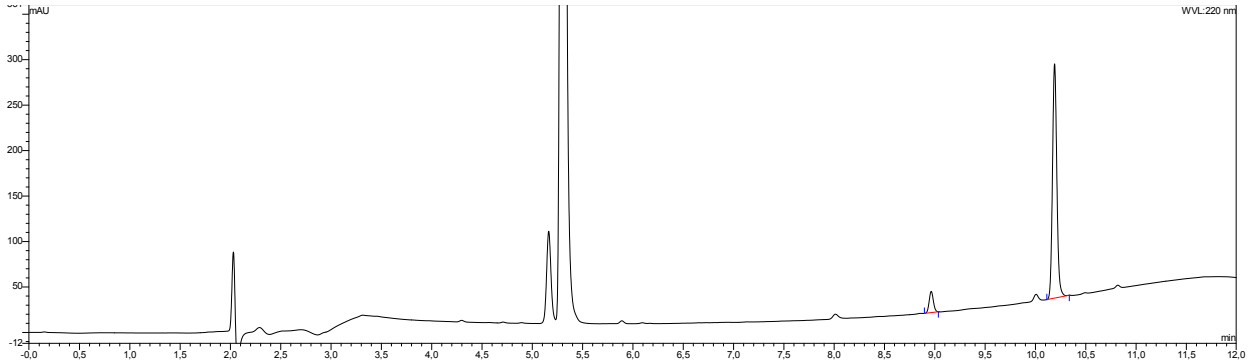

Figure S57. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP at t=960 min.

Table S41. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,963	1,1216	n.a.	BMB*	23,337	8,00	16,02
2	n.a.	10,190	12,9019	n.a.	BMB*	257,637	92,00	n.a.
Total:			**14,0235**	**0,0000**		**280,974**	**100,00**	

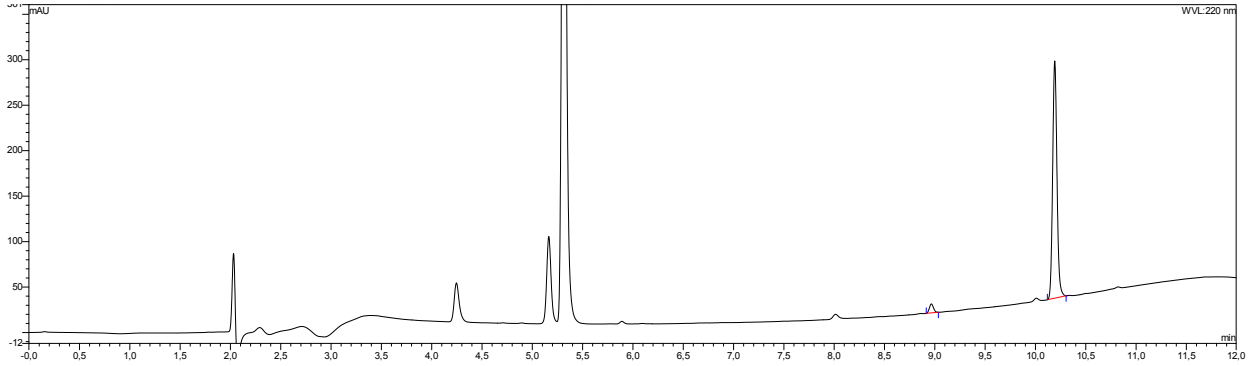

Figure S58. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:1) at t=960 min.

Table S42. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,965	0,4639	n.a.	BMB*	9,847	3,46	16,20
2	n.a.	10,192	12,9604	n.a.	BMB*	260,915	96,54	n.a.
Total:			**13,4243**	**0,0000**		**270,762**	**100,00**	

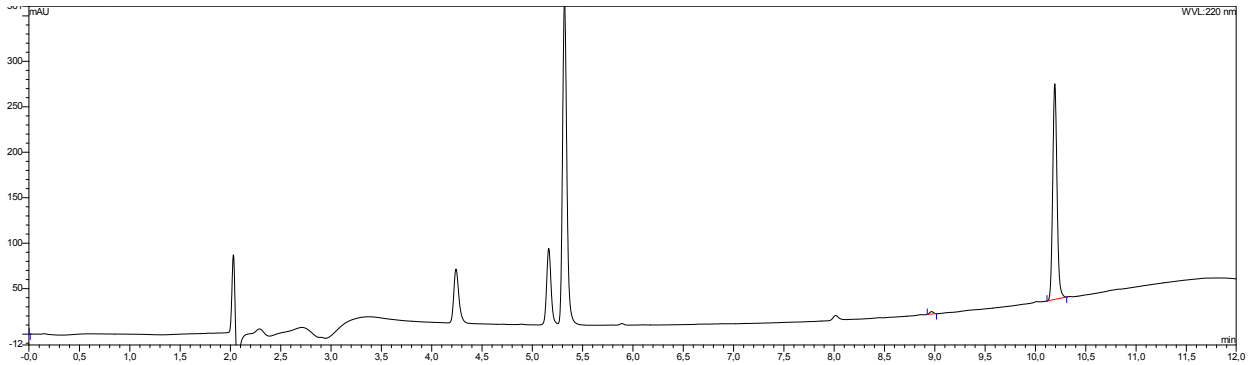

Figure S59. HPLC chromatogram of Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=960 min.

Table S43. Area% for the integrated peaks.

No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,967	0,1173	n.a.	BMB*	2,677	0,99	16,52
2	n.a.	10,192	11,7808	n.a.	BMB*	237,086	99,01	n.a.
Total:			**11,8980**	**0,0000**		**239,763**	**100,00**	

Table S44. A summary of conversions during Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reactions in DMF, NBP, NBP/EtOAc (1:1) and NBP/EtOAc (1:4).

Reaction time (min)	Solvent			
	DMF	NBP	NBP/EtOAc (1:1)	NBP/EtOAc (1:4)
	Amidation conversion (%)			
0	0,0	0,0	0,0	0,0
10	9,1	10,4	22,7	36,4
30	29,0	25,3	41,3	59,0
60	44,2	36,9	58,0	74,7
120	62,6	56,1	76,2	88,5
960	93,2	92,0	96,5	99,0

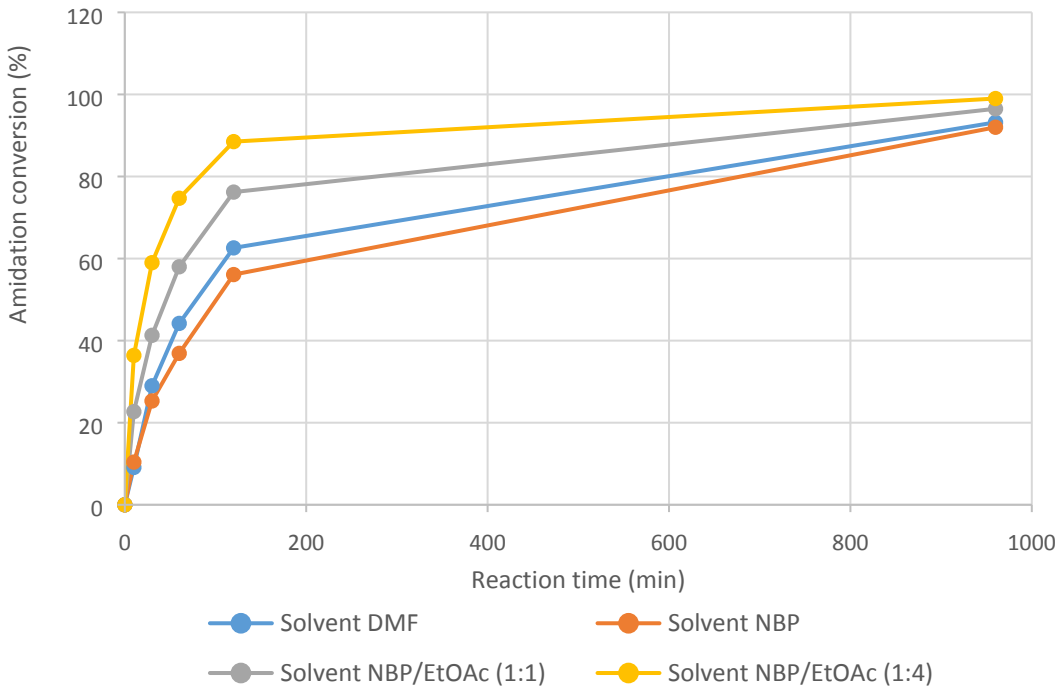

Figure S60. A schematic representation of conversions during Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reactions in DMF, NBP, NBP/EtOAc (1:1) and NBP/EtOAc (1:4).

6.2 LC-HRMS analysis of a product of Fmoc-Ser(*t*-Bu)-OH + (S)-(-)-1-phenylethylamine amidation reactions

Experimental conditions described in section 5.2 of this SI were employed. A sample of the crude product from the amidation in NBP/EtOAc (1:1) after 1 h was analyzed, and the structures of Fmoc-Ser(*t*-Bu)-OH and Fmoc-Ser(*t*-Bu)-(S)-(-)-1-phenylethylamide (product of amidation reaction) were confirmed, see MS spectra in Figures S63 and S64, respectively.

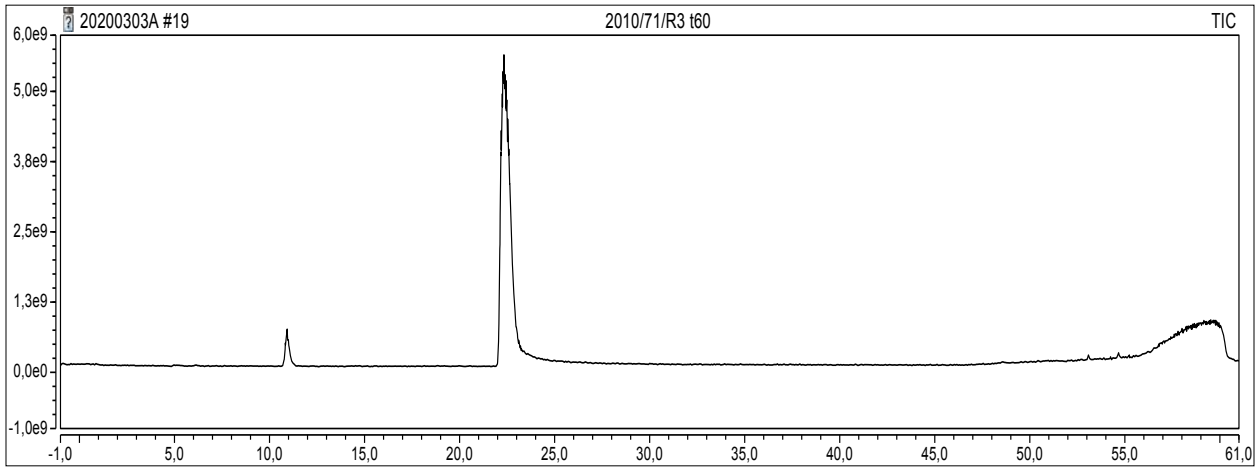

Figure S61. LC-HRMS, total ion count (TIC) overview of the crude product from the amidation in NBP/EtOAc (1:1) after 1 h, Fmoc-Ser(*t*-Bu)-OH (Rt 53.1 min) and Fmoc-Ser(*t*-Bu)-S)-(-)-1-phenylethylamide (Rt 54.7 min) are shown, for MS spectra of these compounds see Figures S63 and S64.

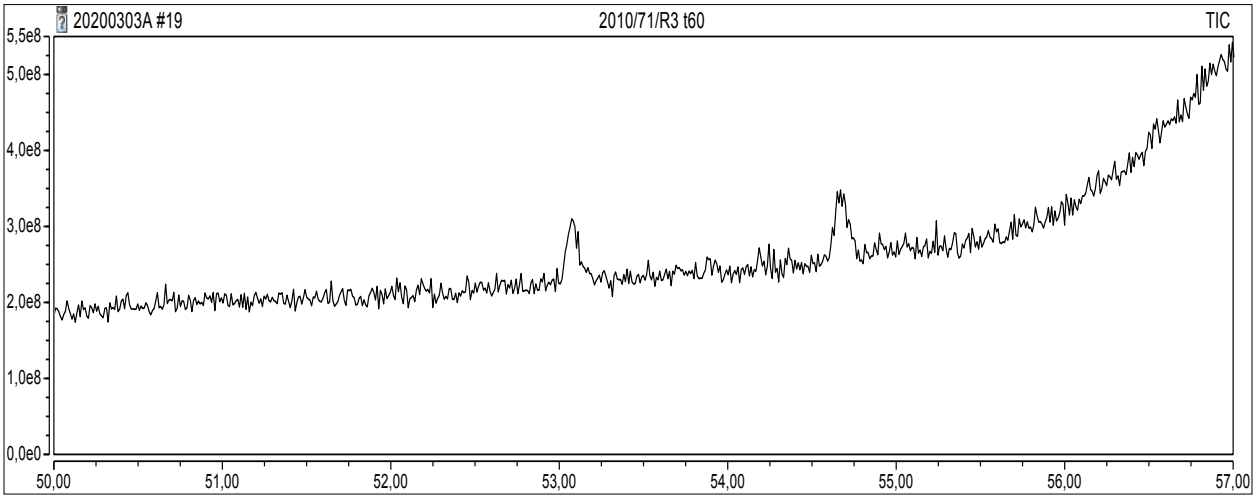

Figure S62. LC-HRMS, TIC zoom-in view of the crude product from the amidation in NBP/EtOAc (1:1) after 1 h, Fmoc-Ser(*t*-Bu)-OH (Rt 53.1 min) and Fmoc-Ser(*t*-Bu)-S)-(-)-1-phenylethylamide (Rt 54.7 min) are shown, for MS spectra of these compounds see Figures S63 and S64.

Table S45. EIC Area% for the integrated peaks in LC-HRMS (TIC) of the crude product from the amidation in NBP/EtOAc (1:1) after 1 h, Fmoc-Ser(*t*-Bu)-OH (Rt 53.1 min) and Fmoc-Ser(*t*-Bu)-(S)-(-)-1-phenylethylamide (Rt 54.7 min) are shown, for MS spectra of these compounds see Figures S63 and S64.

Peak Name	Retention Time (min)	Area (counts*min)	Area (%)
EIC 384,18	53,0736	1981521,4257	28,0
EIC 487,26	54,6695	5096596,5907	72,0
n.d.	n.d.	7078118,0163	100,0

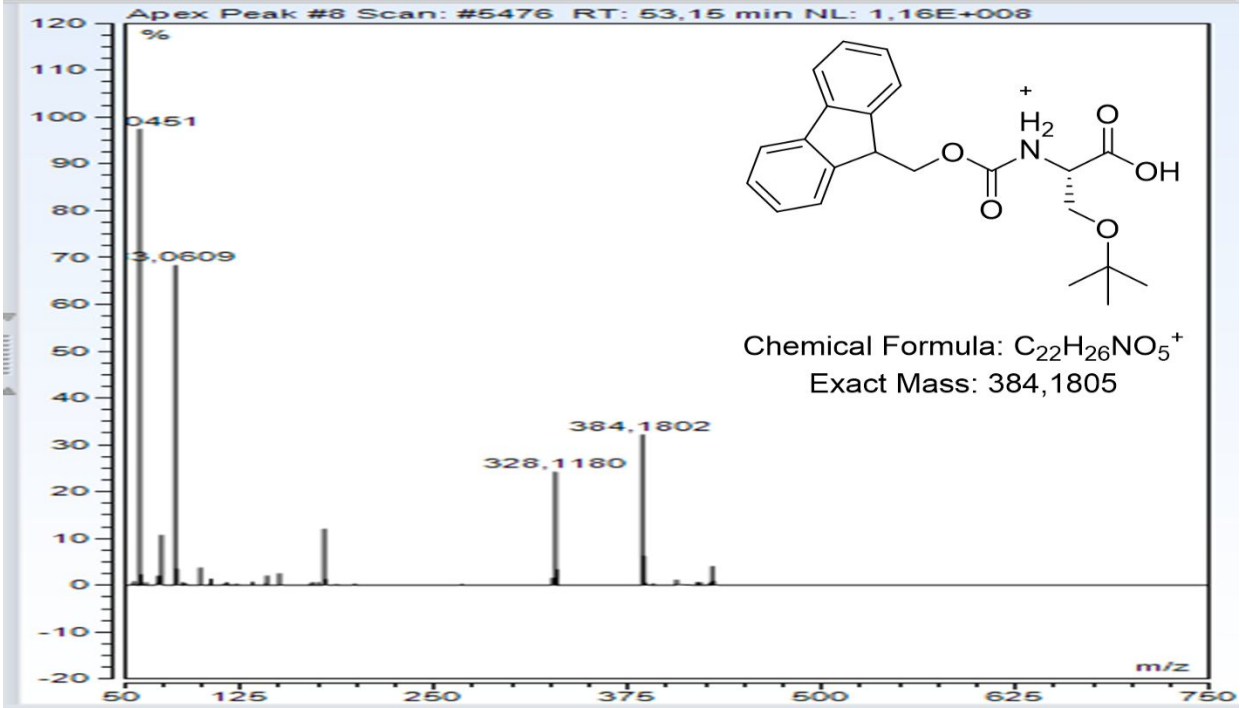

Figure S63. MS spectrum [M+H] of Fmoc-Ser(*t*-Bu)-OH detected in the crude product from the amidation in NBP/EtOAc (1:1) after 1 h.

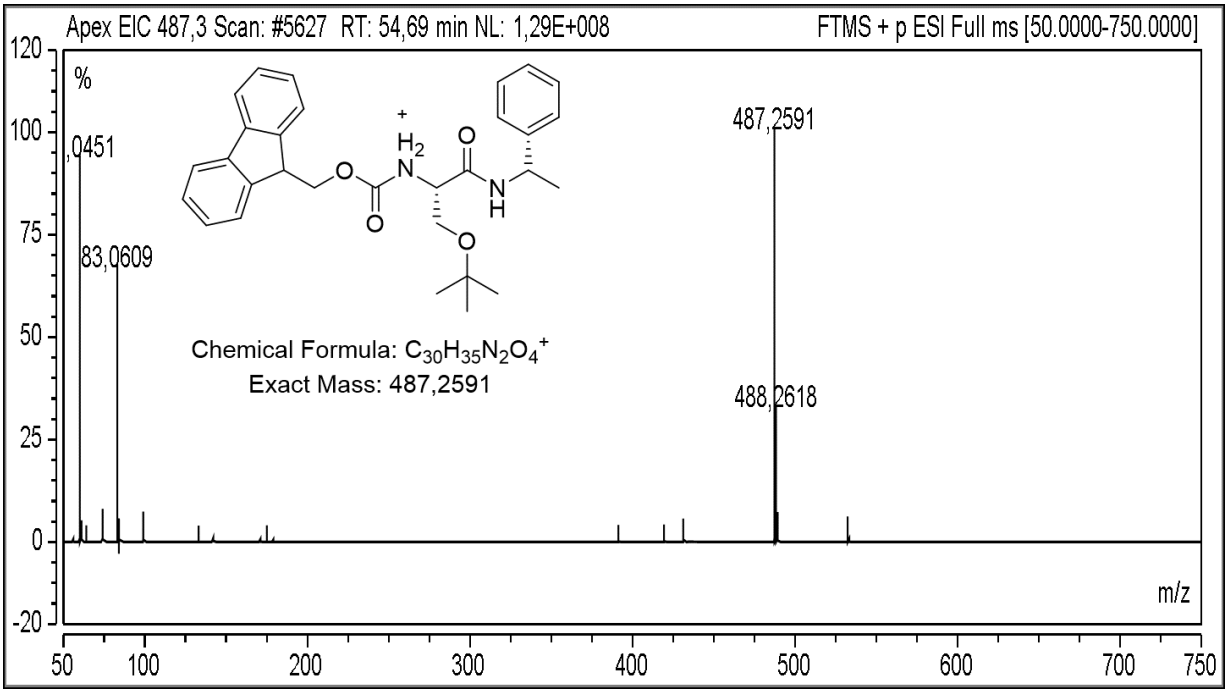

Figure S64. MS spectrum [M+H] of Fmoc-Ser(t-Bu)-S)-(-)-1-phenylethylamide detected in the crude product from the amidation in NBP/EtOAc (1:1) after 1 h.

6.3 LC-HRMS analysis of Oxyma to HCN conversion during Fmoc-Ser(*t*-Bu)-OH + (S)-(-)-1-phenylethylamine amidation reactions

Experimental conditions described in section 5.2 of this SI were employed. EIC-MS analyses were carried out as previously described.[4] A methodology for determining %Oxyma→HCN conversions based on determining concentration of **3** was used, see section 2 of this SI.

Table S46. A summary of integrated EIC areas, concentrations of **3** (gL^{-1}), amounts of **3** formed and %Oxyma→HCN conversions during experiments R1 – R4.

Solvent	Reaction time (min)	Rt (min), quantification channel EIC 242,15	Area (counts*min) quantification channel EIC 242,15	gL^{-1} **3**	µmol **3**	%Oxyma->HCN
DMF	10	17,309	1192	0,000253	0,0105	0,0021
NBP	10	17,274	2173	0,000462	0,0192	0,0038
NBP/EtOAc (1:1)	10	17,279	1755	0,000373	0,0155	0,0031
NBP/EtOAc (1:4)	10	17,269	1786	0,000380	0,0157	0,0031
DMF	30	17,315	10280	0,002187	0,0906	0,0181
NBP	30	17,279	5931	0,001262	0,0523	0,0105
NBP/EtOAc (1:1)	30	17,276	5981	0,001272	0,0527	0,0105
NBP/EtOAc (1:4)	30	17,284	4993	0,001062	0,0440	0,0088
DMF	60	17,285	22186	0,004719	0,1956	0,0391
NBP	60	17,281	12894	0,002743	0,1137	0,0227
NBP/EtOAc (1:1)	60	17,286	9641	0,002051	0,0850	0,0170
NBP/EtOAc (1:4)	60	17,311	9836	0,002092	0,0867	0,0173
DMF	120	17,381	60702	0,012913	0,5352	0,1070
NBP	120	17,309	33723	0,007174	0,2973	0,0595
NBP/EtOAc (1:1)	120	17,312	23836	0,005070	0,2101	0,0420
NBP/EtOAc (1:4)	120	17,303	14514	0,003087	0,1280	0,0256
DMF	960	17,310	538200	0,114487	4,7448	0,9490
NBP	960	17,310	268818	0,057184	2,3699	0,4740
NBP/EtOAc (1:1)	960	17,282	99983	0,021269	0,8815	0,1763
NBP/EtOAc (1:4)	960	17,296	42294	0,008997	0,3729	0,0746

Table S47. A summary of %Oxyma→HCN conversions during experiments R1 – R4.

Reaction time (min)	Solvent			
	DMF	NBP	NBP/EtOAc (1:1)	NBP/EtOAc (1:4)
	Oxyma→HCN conversion (%)			
0	0,0000	0,0000	0,0000	0,0000
10	0,0021	0,0038	0,0031	0,0031
30	0,0181	0,0105	0,0105	0,0088
60	0,0391	0,0227	0,0170	0,0173
120	0,1070	0,0595	0,0420	0,0256
960	0,9490	0,4740	0,1763	0,0746

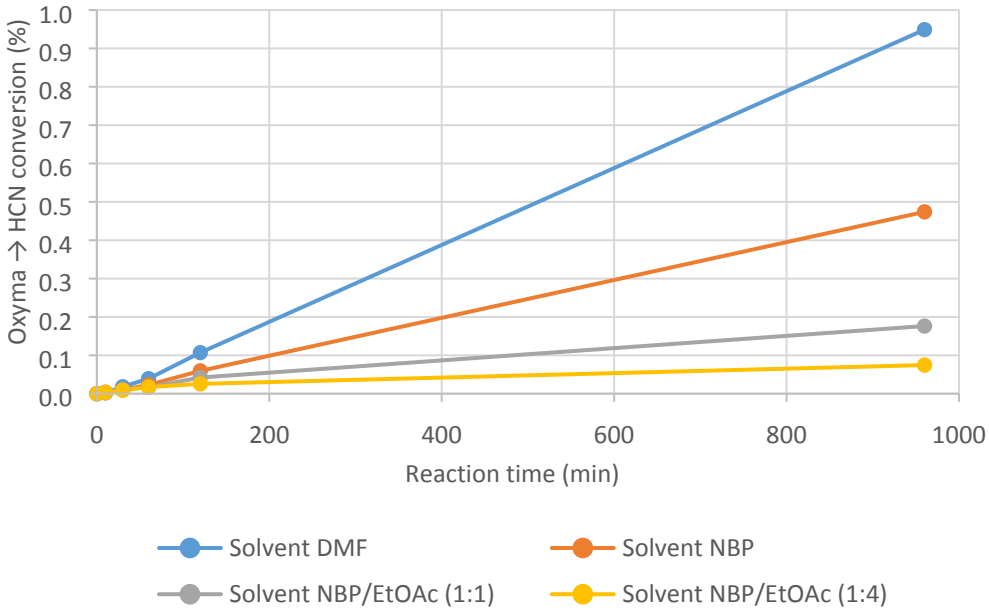

Figure S65. A schematic representation of %Oxyma→HCN conversions during experiments R1 – R4.

7. NMR analysis of HCN formation at different DIC/Oxyma concentrations

HCN is formed during the reaction between DIC and Oxyma. The goal of this section of the SI was to study this reaction to better understand and minimize the formation of HCN. Two different parameters were studied: first, the influence of the concentration and secondly, the addition of an HCN scavenger, DMTS.

7.1 Assessment of HCN formation in 0.3 M DMF-d_7 solution of Oxyma and DIC

General procedure for Oxyma and DIC reaction.

A solution was prepared by dissolving Oxyma (7.2 mg, 0.051 mmol, 1.0 equiv) and caffeine (2.1 mg, 0.011 mmol, 0.22 equiv) in 170 µL of DMF-d_7. The solution was mixed by using an ultrasound bath. DIC (8.0 µL, 0.051 mmol, 1.0 equiv) was added to the solution. The latter was transferred into a 3 mm NMR tube and transferred to the spectrometer for monitoring at 20°C. 1D ^{1}H NMR acquisition was done after 1 h, 5 h, 10 h and 16 h.

Method used to calculate the ratio of HCN vs oxadiazole 3.

1)The calibration was done on the signal of Hb at 4.70 ppm (Figure S66), which corresponds to 1 proton.

2) Singlet at 6.21 ppm, corresponding to Ha, was integrated and it gives the ratio between **3** and HCN (Figure S67).

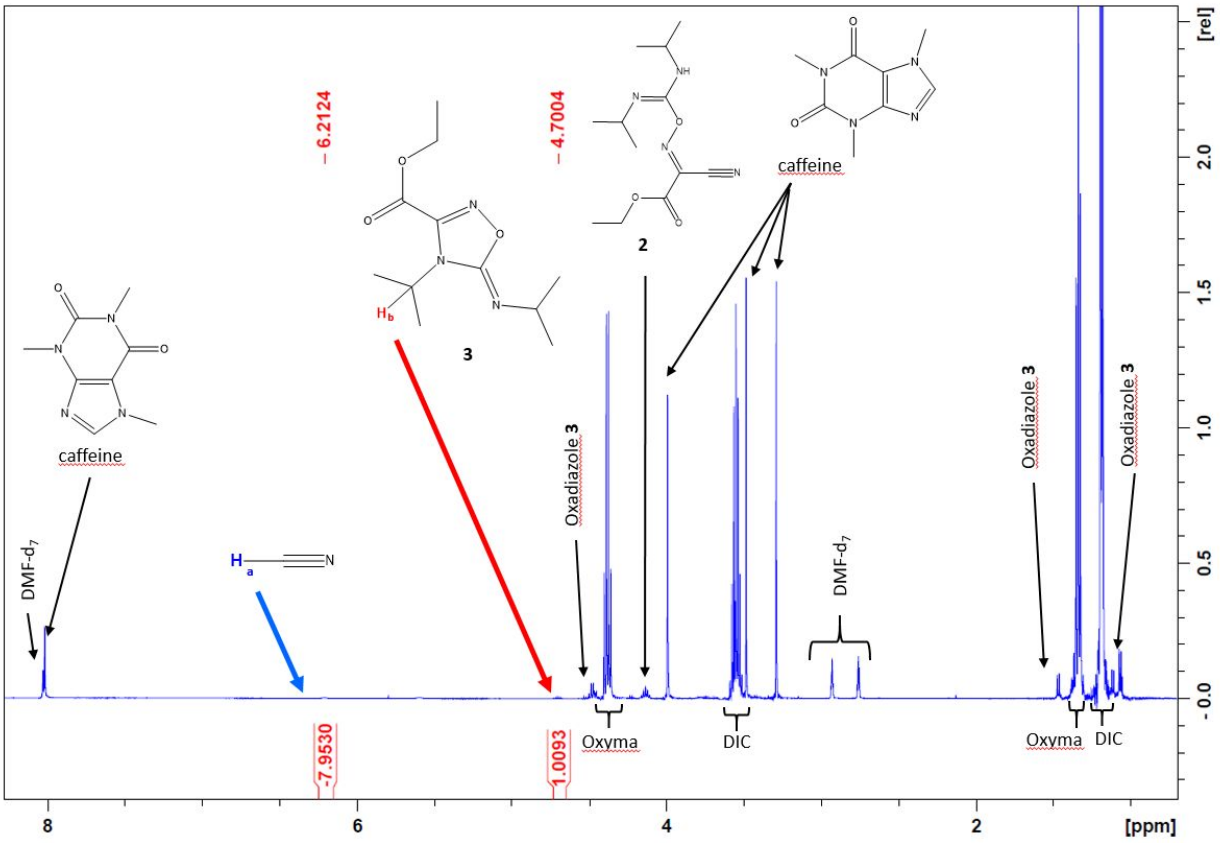

Figure S66. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.3M after 1 h in DMF-d_7 (full spectrum).

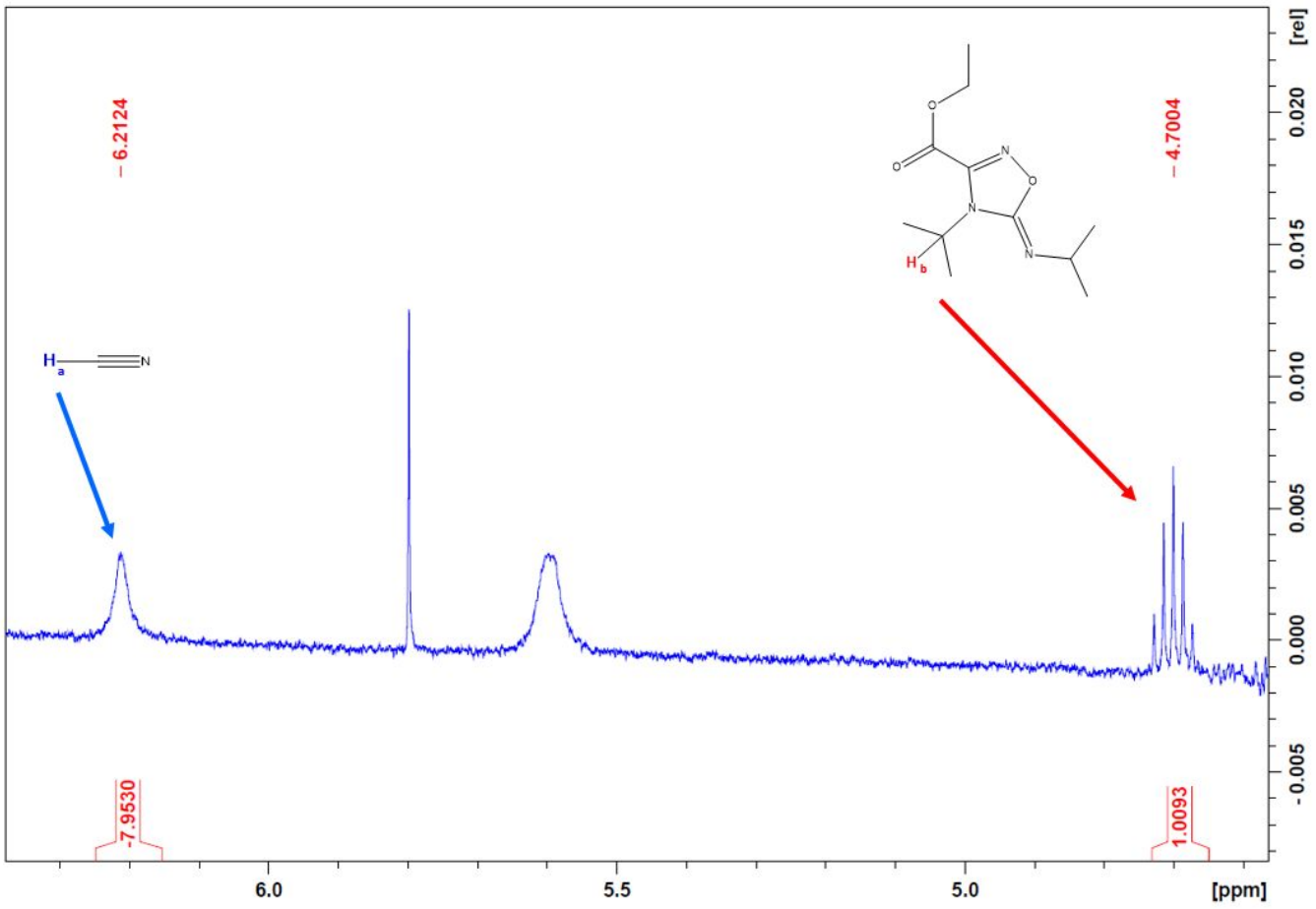

Figure S67. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.3M after 1 h in DMF-d_7 (zoom-in).

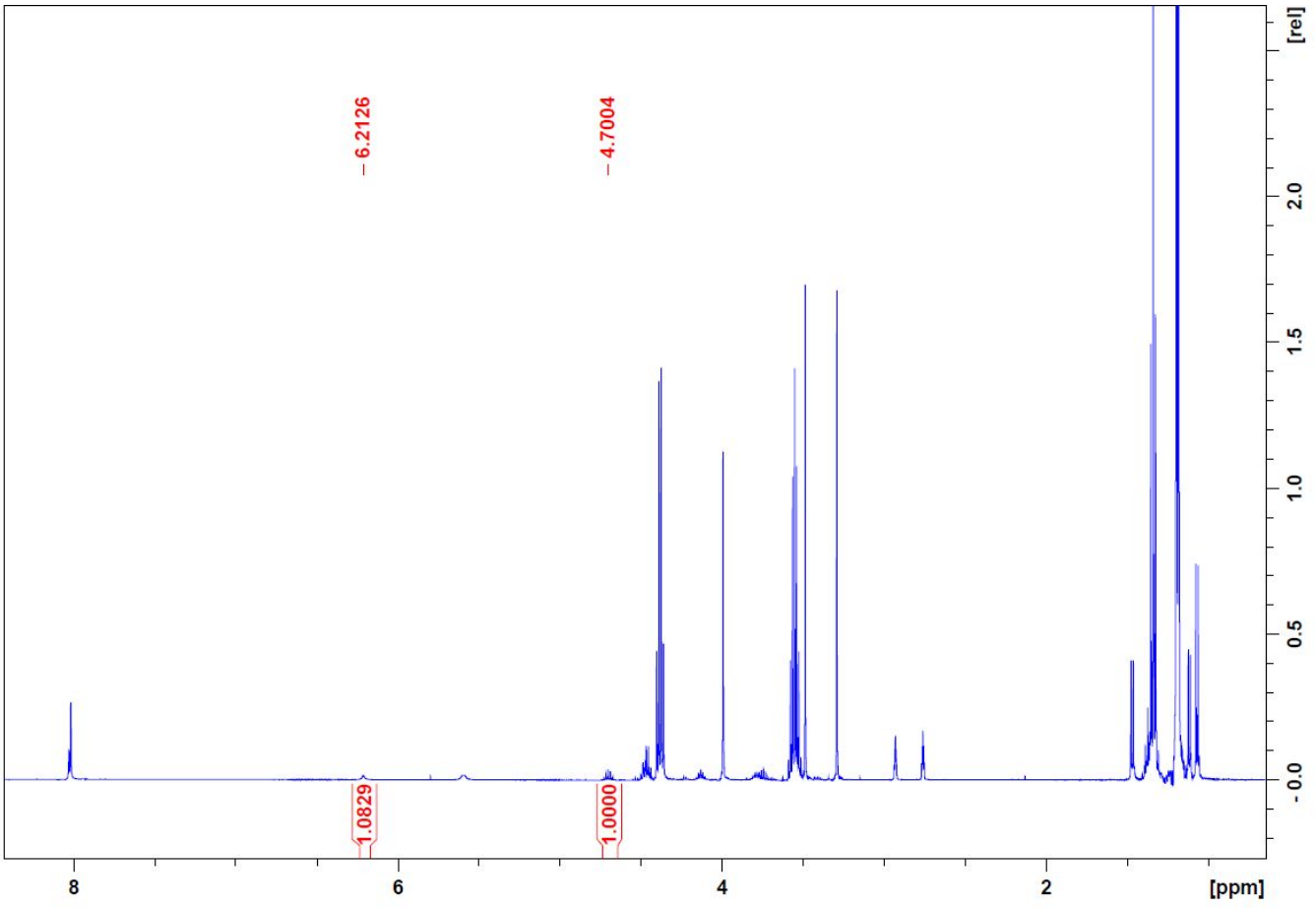

Figure S68. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.3M after 5 h in DMF-d_7 (full spectrum).

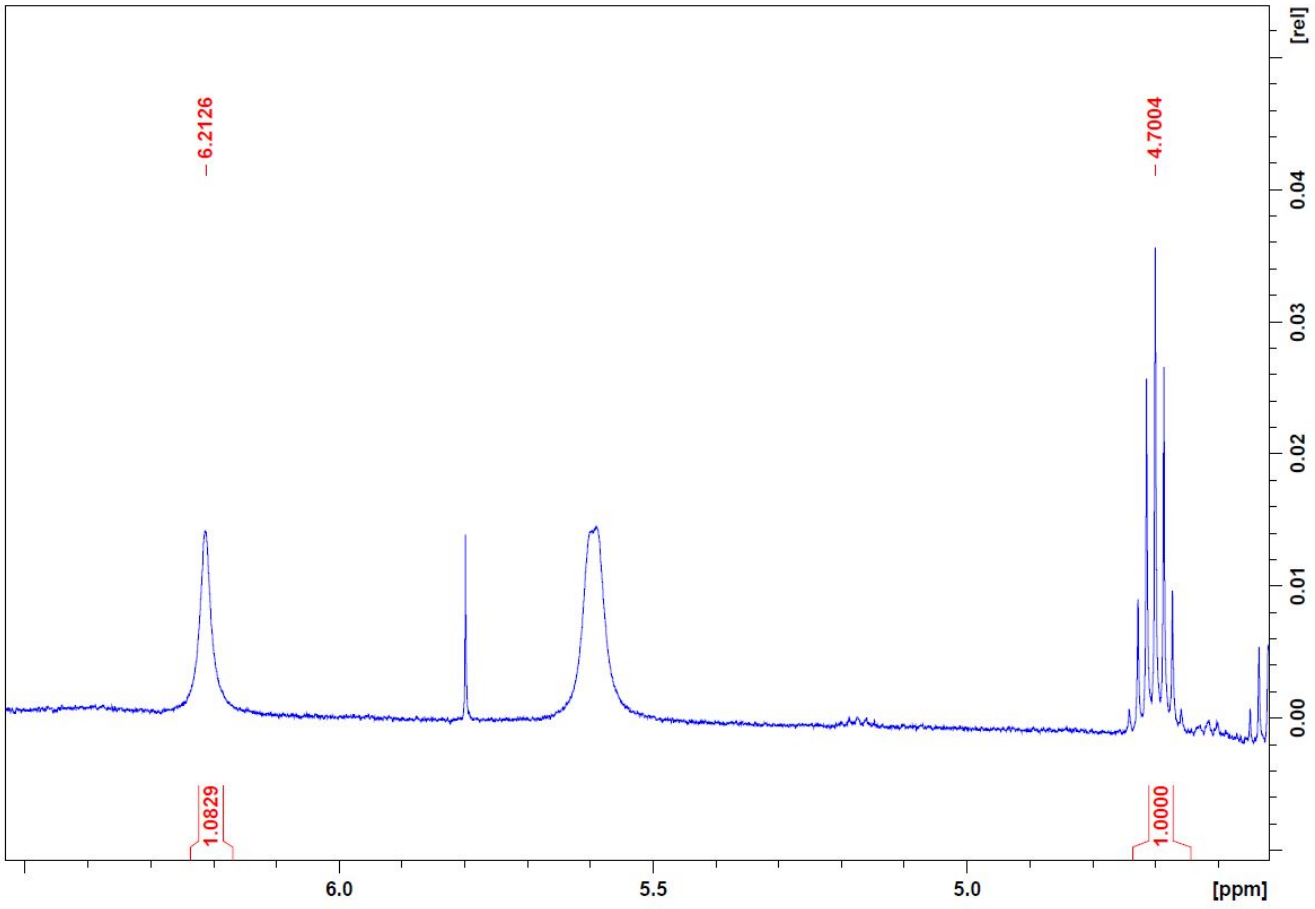

Figure S69. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.3M after 5 h in DMF-d_7 (zoom-in).

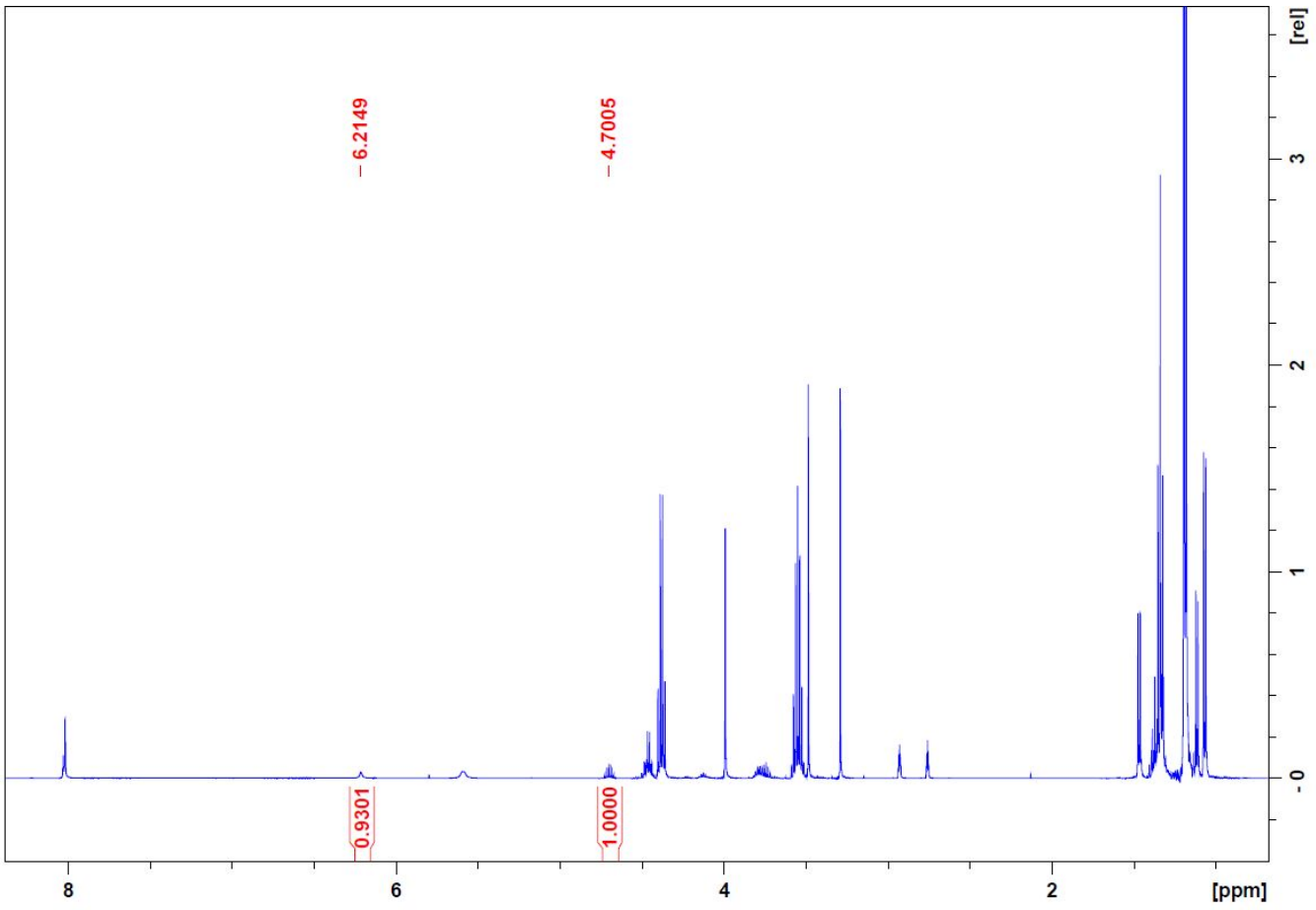

Figure S70. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.3M after 10 h in DMF-d_7 (full spectrum).

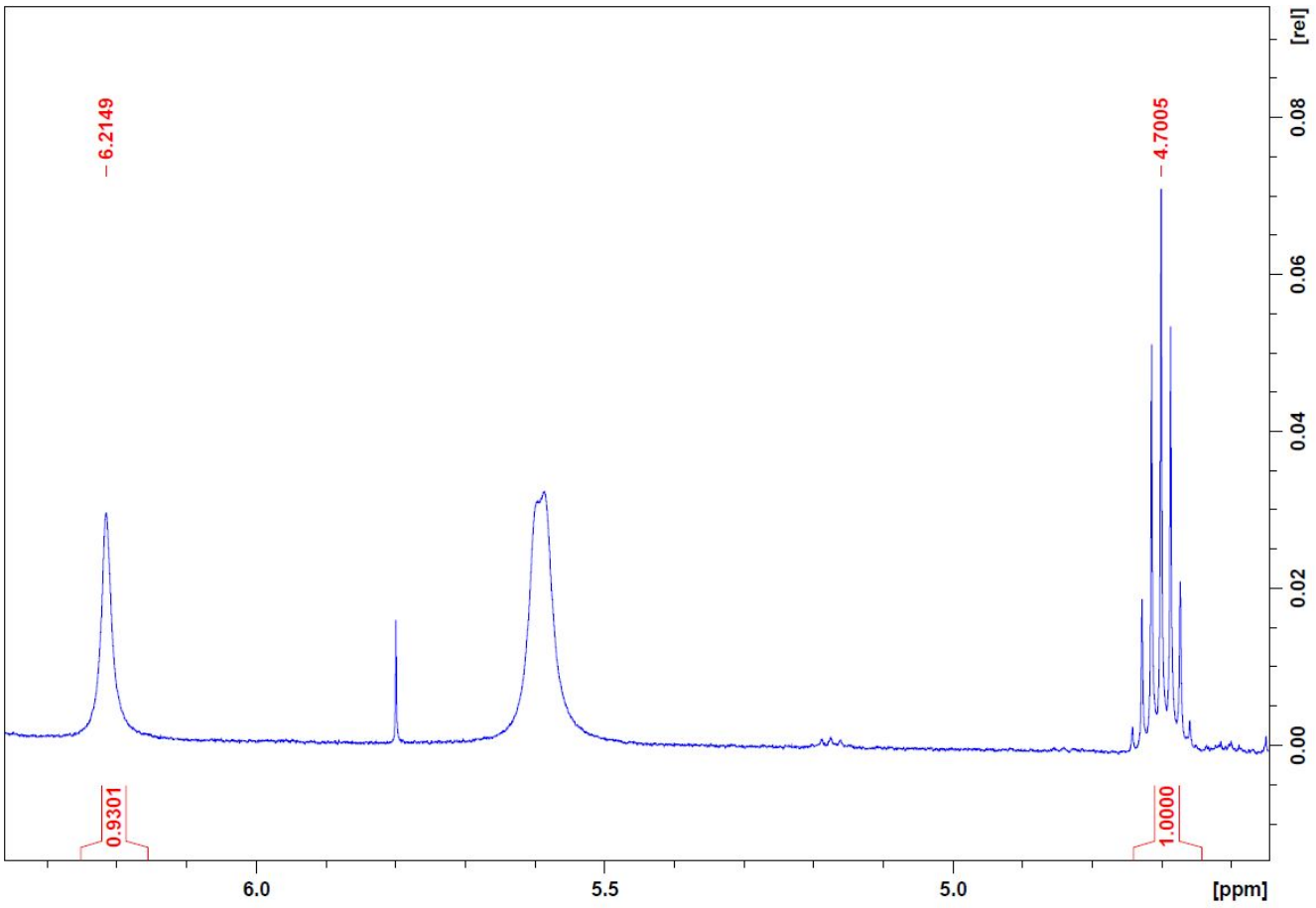

Figure S71. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.3M after 10 h in DMF-d_7 (zoom-in).

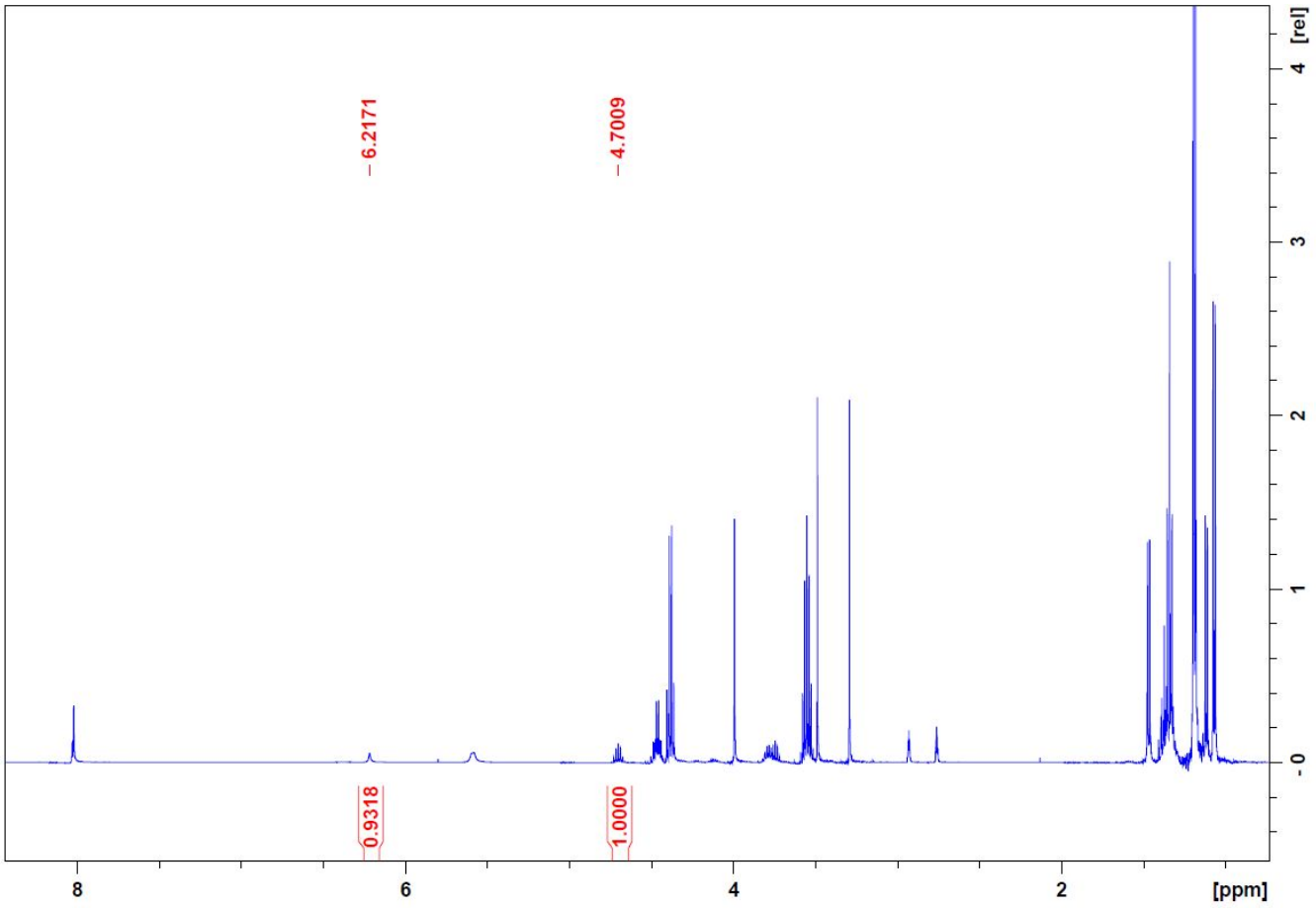

Figure S72. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.3M after 16 h in DMF-d_7 (full spectrum).

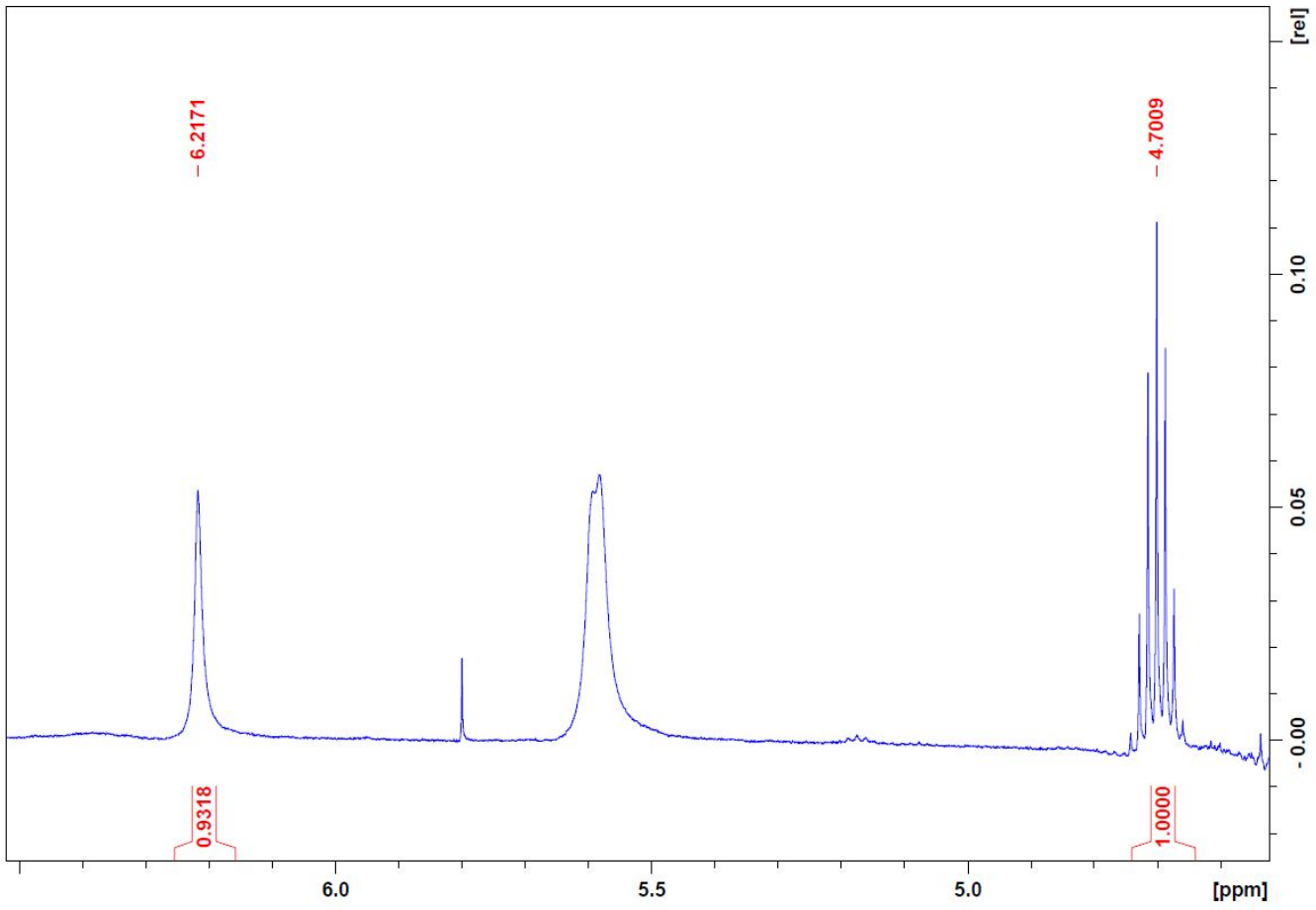

Figure S73. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.3M after 16 h in DMF-d_7 (zoom-in).

7.2 Assessment of HCN formation in 0.4 M DMF-d_7 solution of Oxyma and DIC

The general procedure for the reactions of DIC and Oxyma in DMF-d_7 as described in the section 7.1 of this SI was followed. The following amounts of starting materials were used: Oxyma (9.7 mg, 0.068 mmol, 1.0 equiv), caffeine (2.5 mg, 0.013 mmol, 0.19 equiv), DIC (10.7 µL, 0.068 mmol, 1.0 equiv).

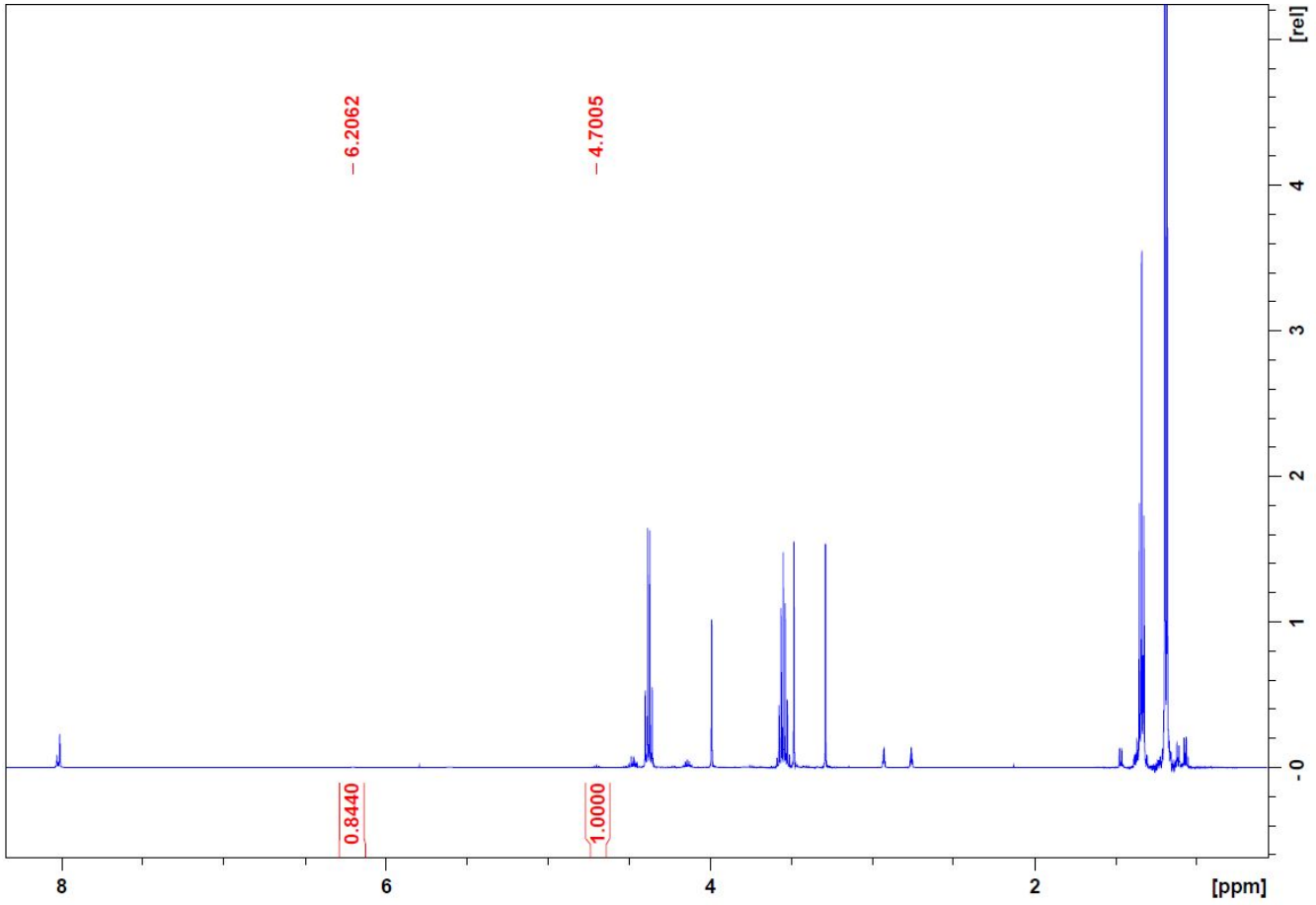

Figure S74. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.4M after 1h in DMF-d_7 (full spectrum).

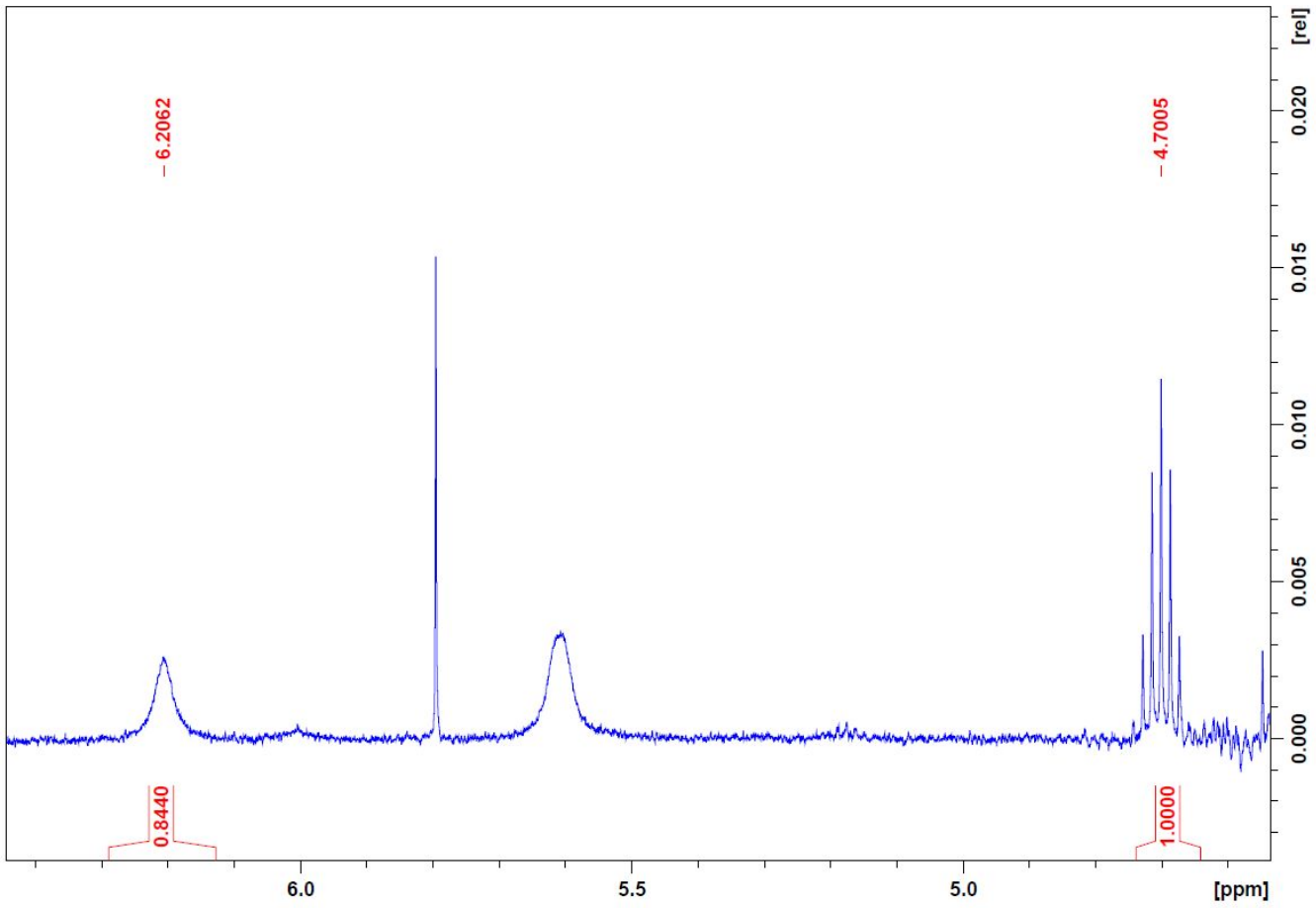

Figure S75. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.4M after 1h in DMF-d_7 (zoom-in).

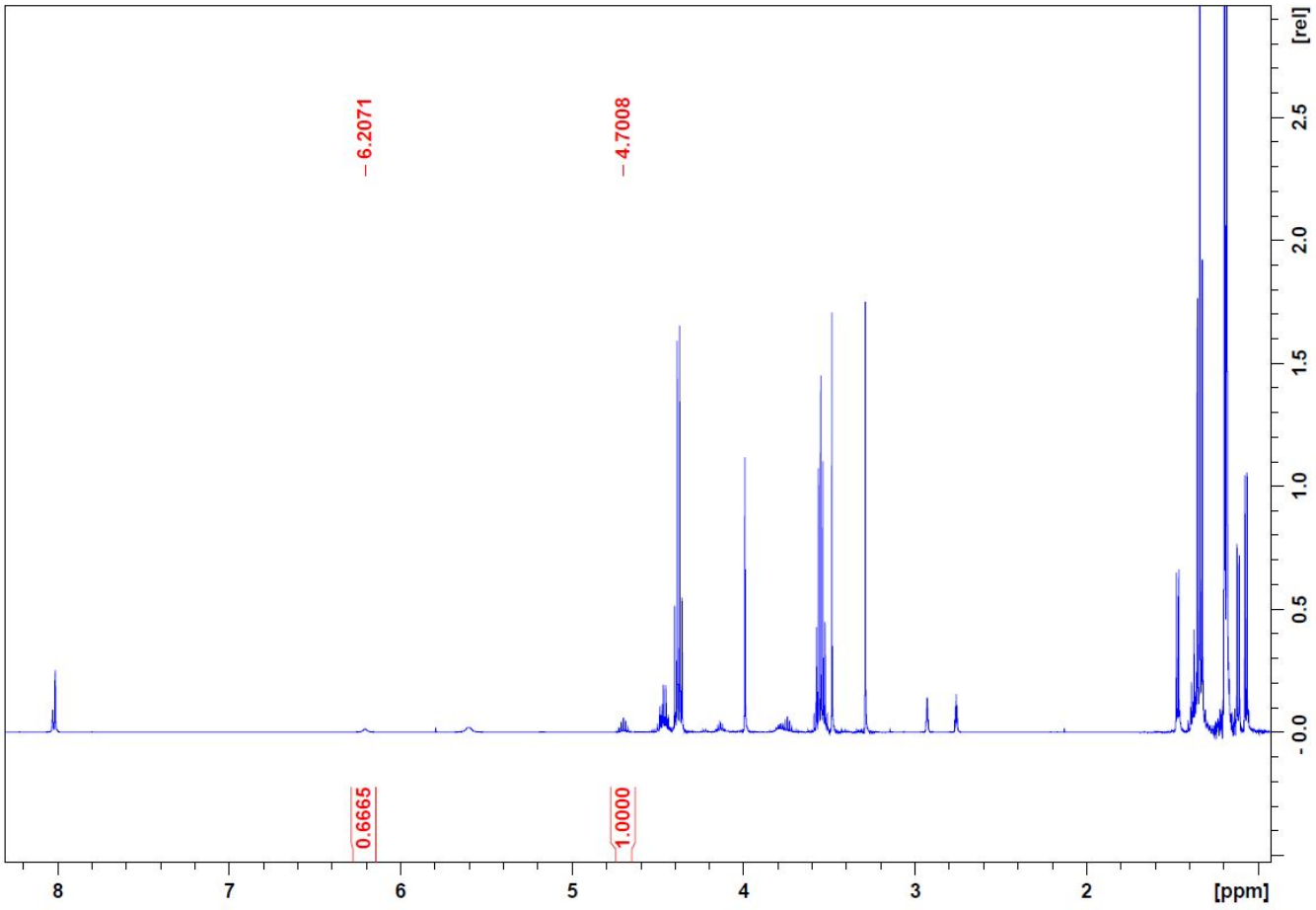

Figure S76. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.4M after 5 h in DMF-d_7 (full spectrum).

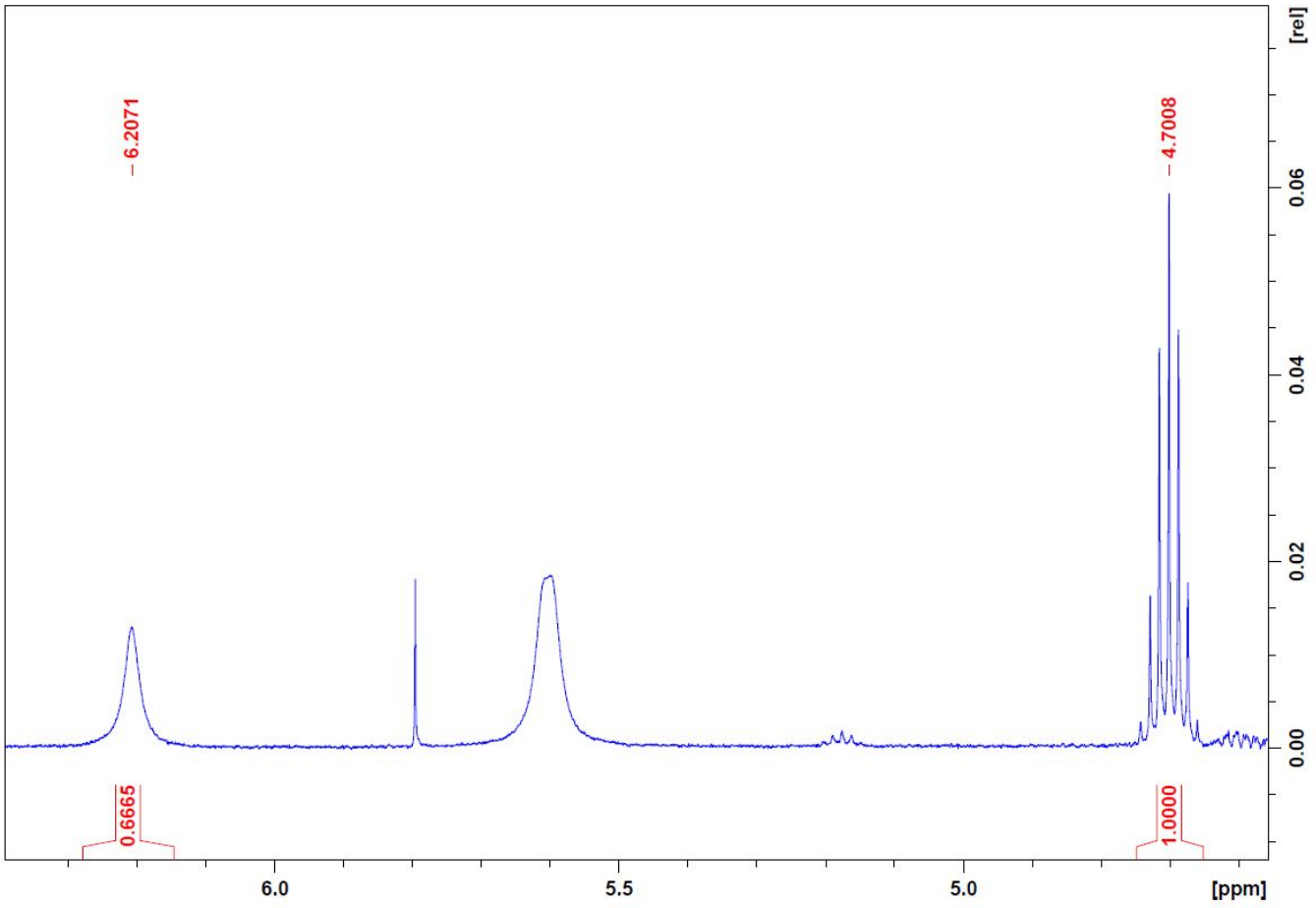

Figure S77. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.4M after 5 h in DMF-d_7 (zoom-in).

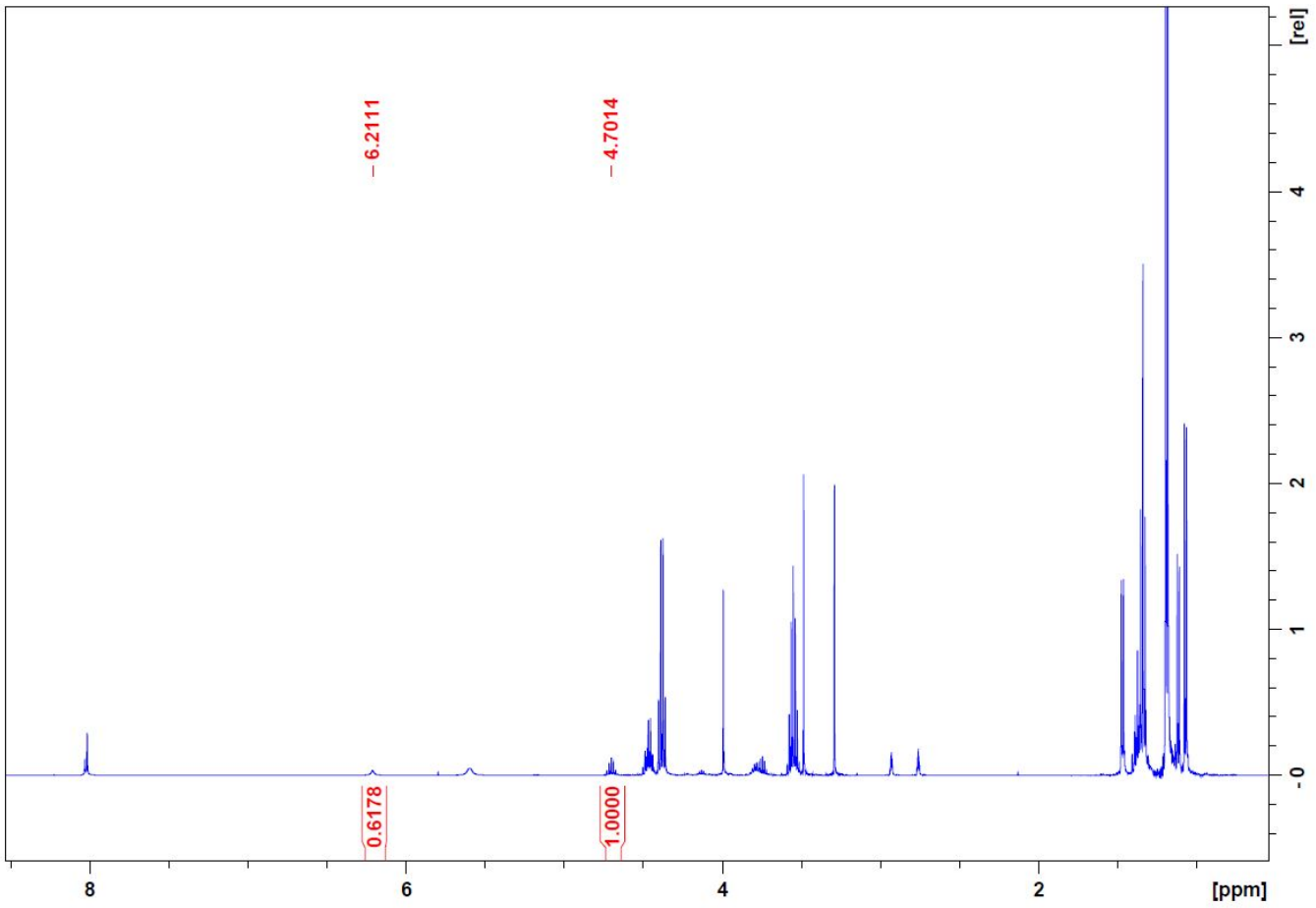

Figure S78. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.4M after 10 h in DMF-d_7 (full spectrum).

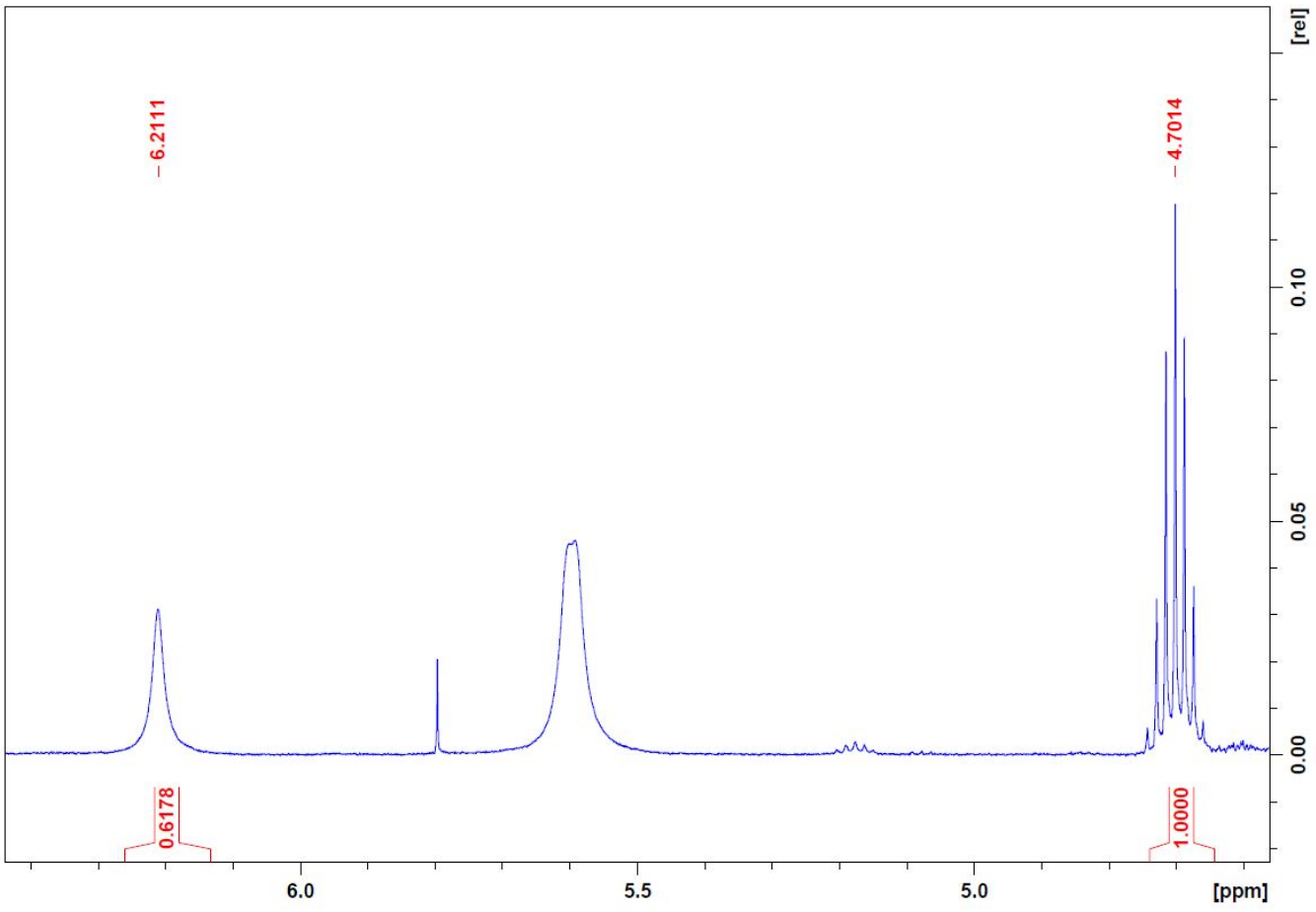

Figure S79. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.4M after 10 h in DMF-d_7 (zoom-in).

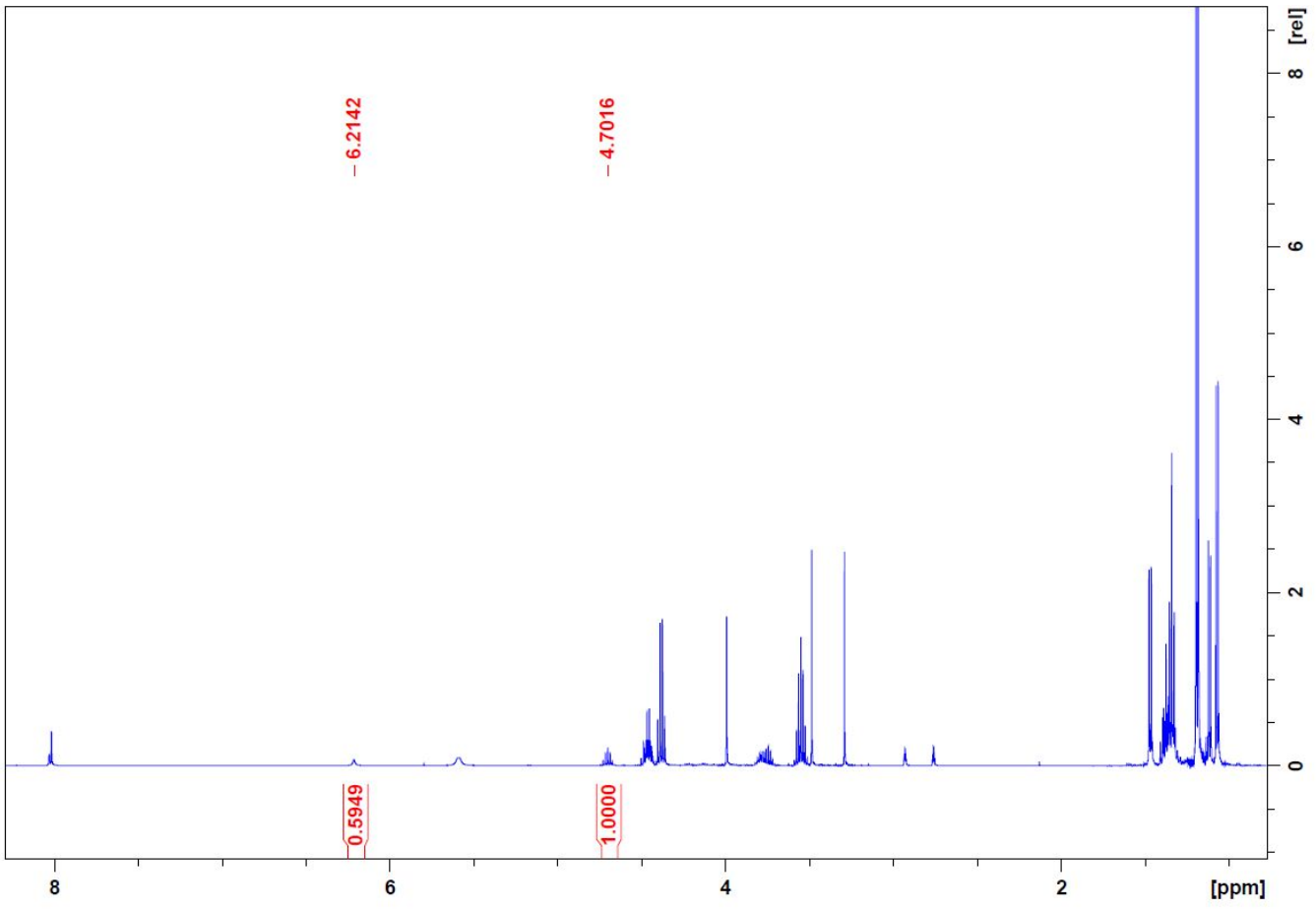

Figure S80. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.4M after 16 h in DMF-d_7 (full spectrum).

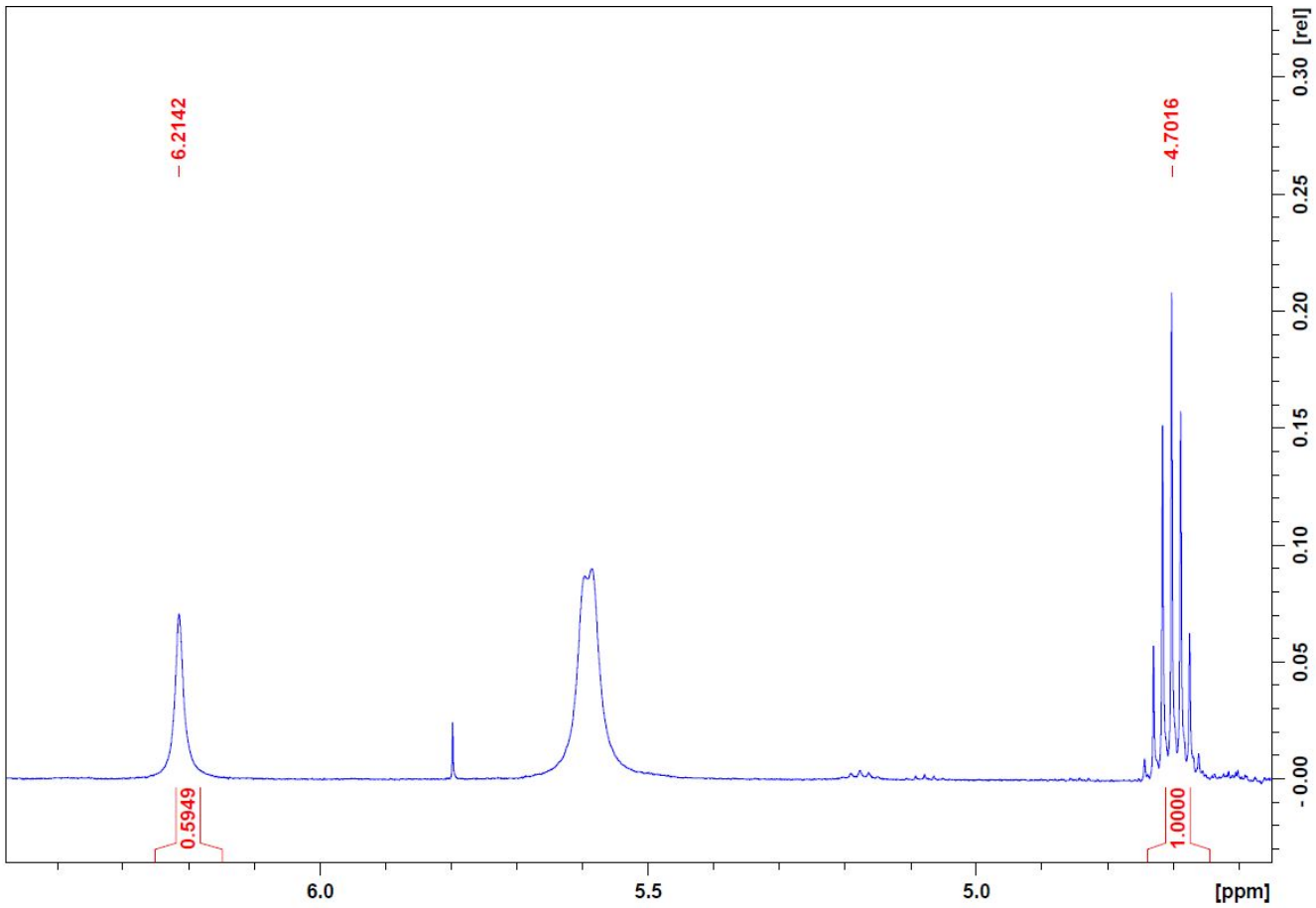

Figure S81. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.4M after 16 h in DMF-d_7 (zoom-in).

7.3 Assessment of HCN formation in 0.5 M DMF-d_7 solution of Oxyma and DIC

The general procedure for the reactions of DIC and Oxyma in DMF-d_7 as described in the section 7.1 of this SI was followed. The following amounts of starting materials were used: Oxyma (12.5 mg, 0.088 mmol, 1.03 equiv), caffeine (2.1 mg, 0.011 mmol, 0.13 equiv), DIC (13.3 µL, 0.085 mmol, 1.00 equiv).

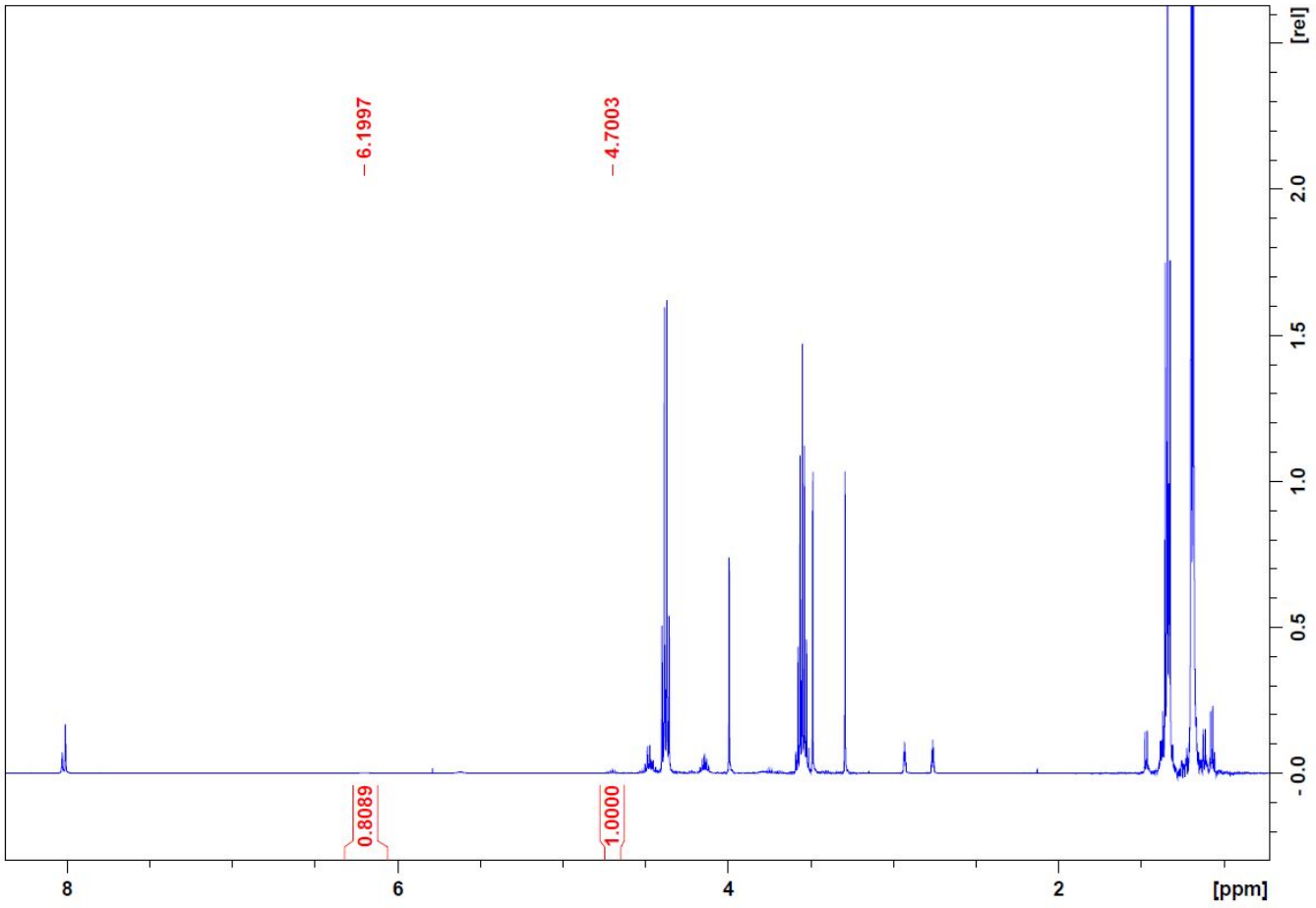

Figure S82. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.5M after 1 h in DMF-d_7 (full spectrum).

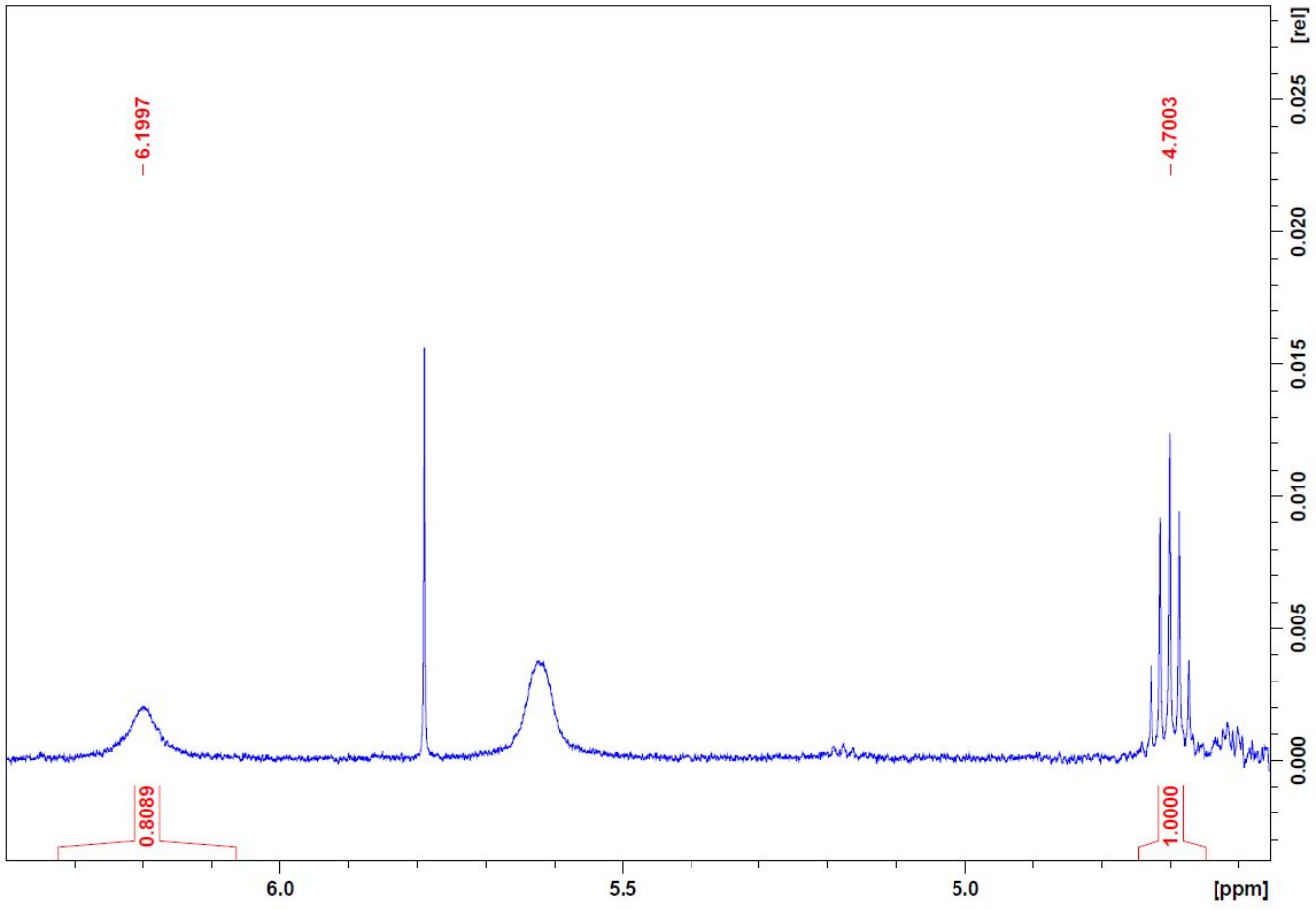

Figure S83. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.5M after 1 h in DMF-d_7 (zoom-in).

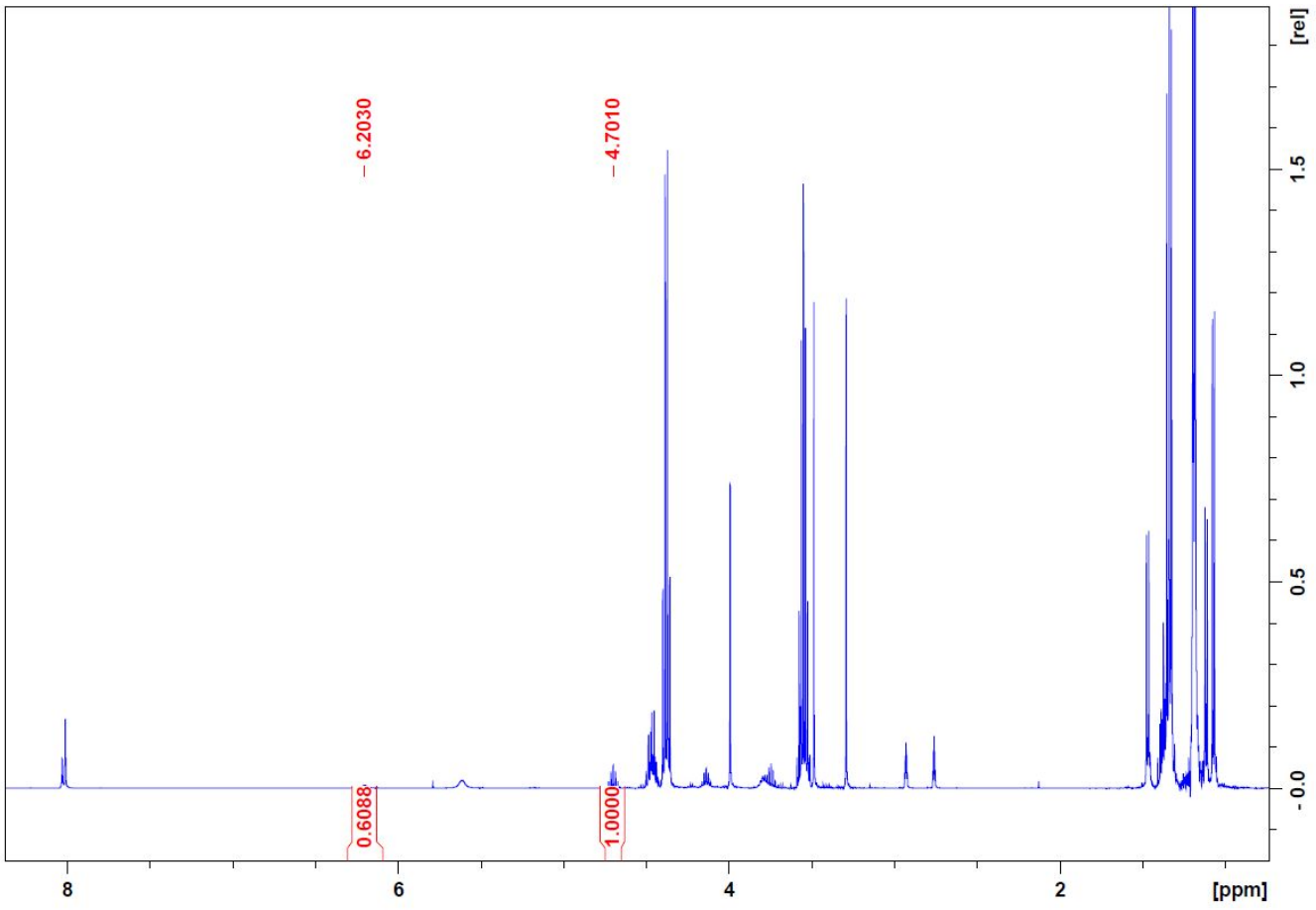

Figure S84. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.5M after 5 h in DMF-d_7 (full spectrum).

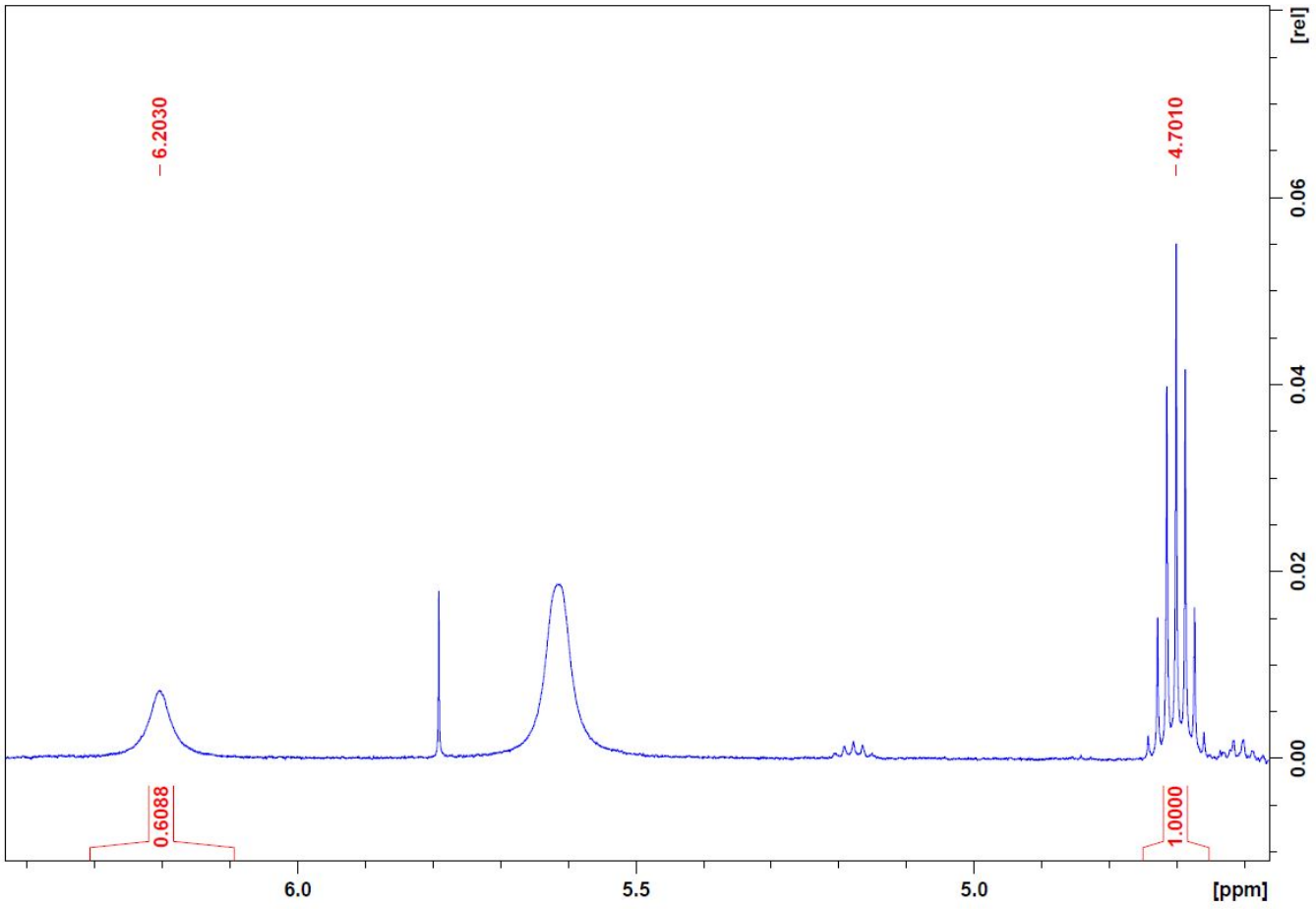

Figure S85. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.5M after 5 h in DMF-d_7 (zoom-in).

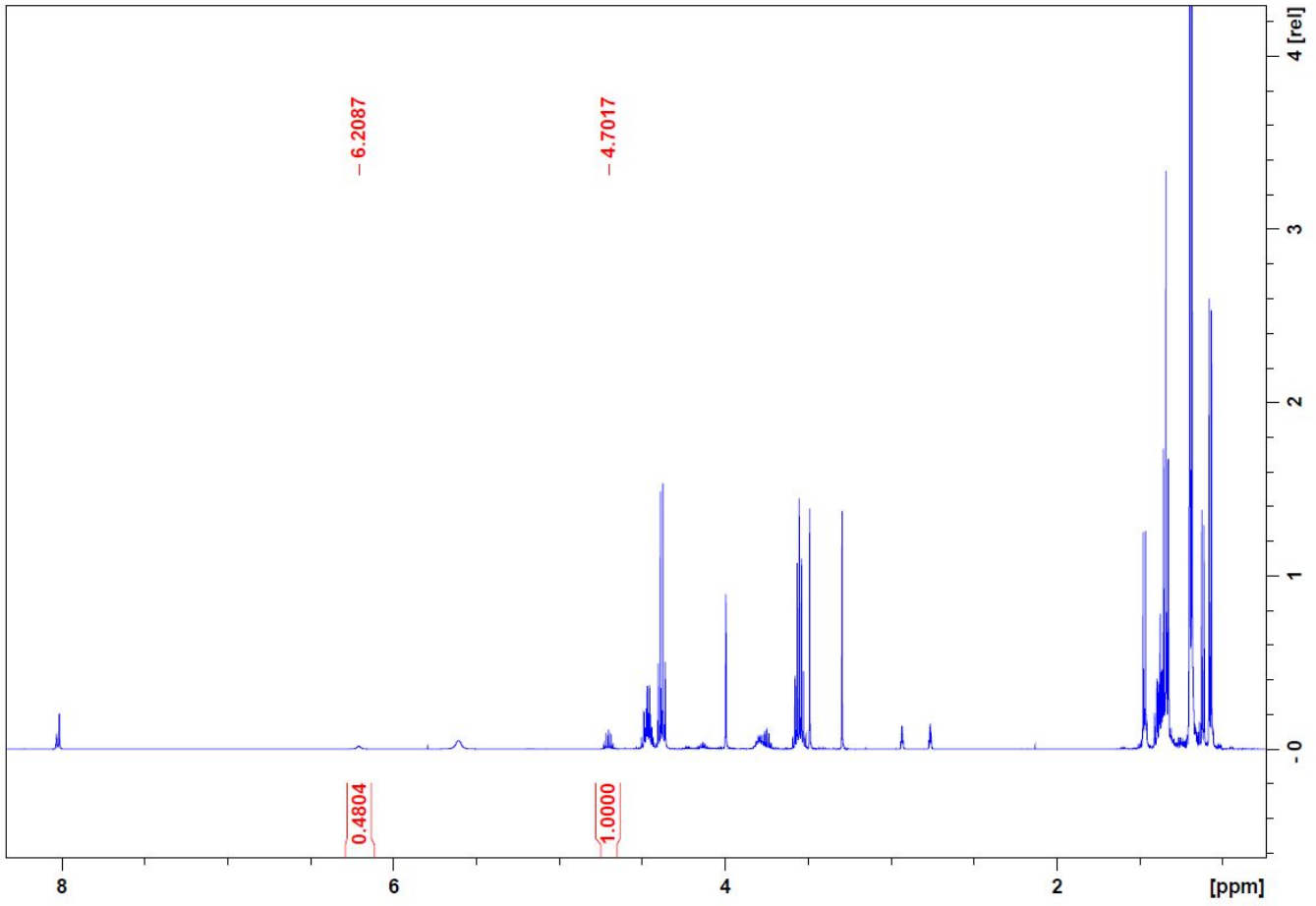

Figure S86. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.5M after 10 h in DMF-d_7 (full spectrum).

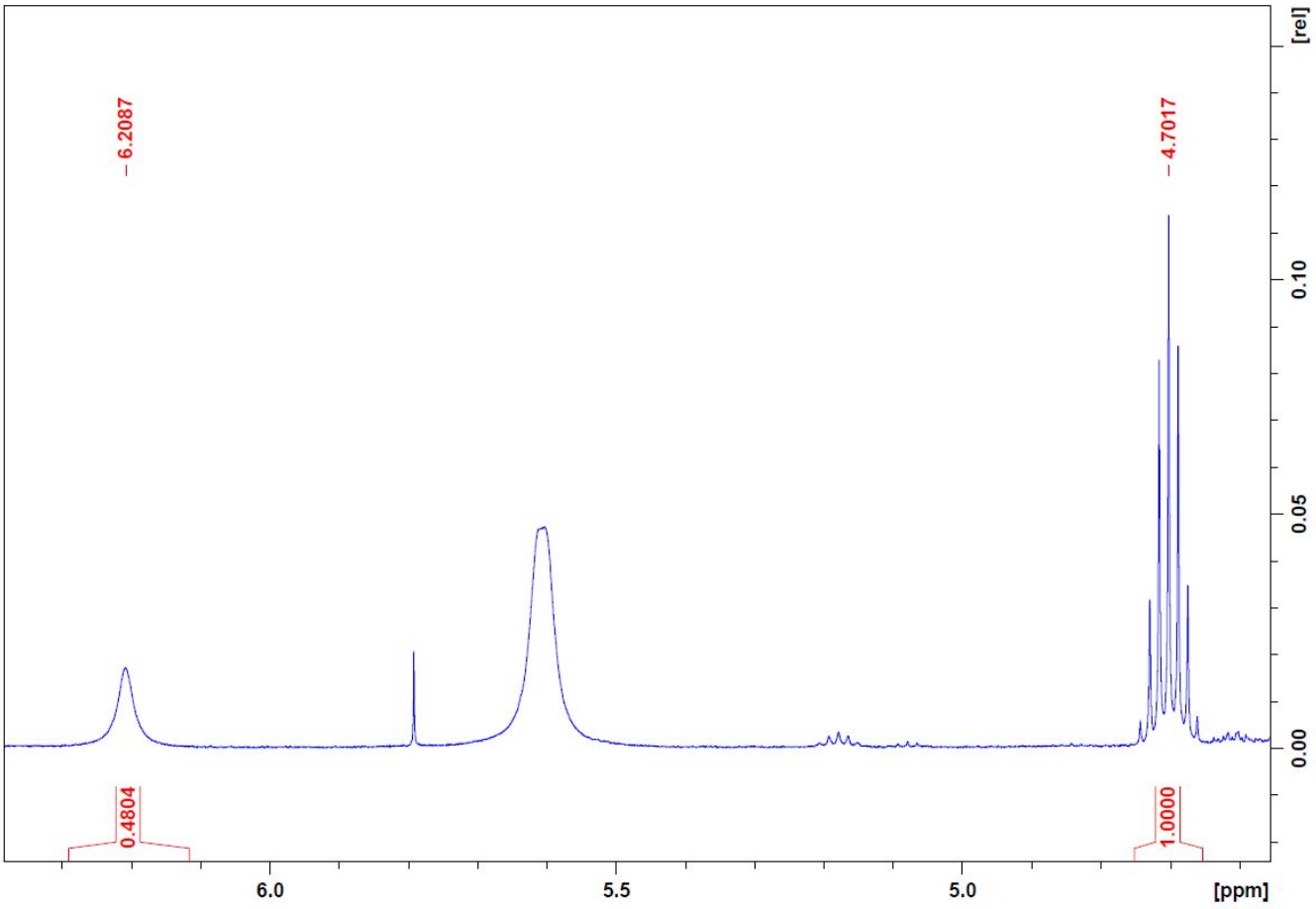

Figure S87. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.5M after 10 h in DMF-d_7 (zoom-in).

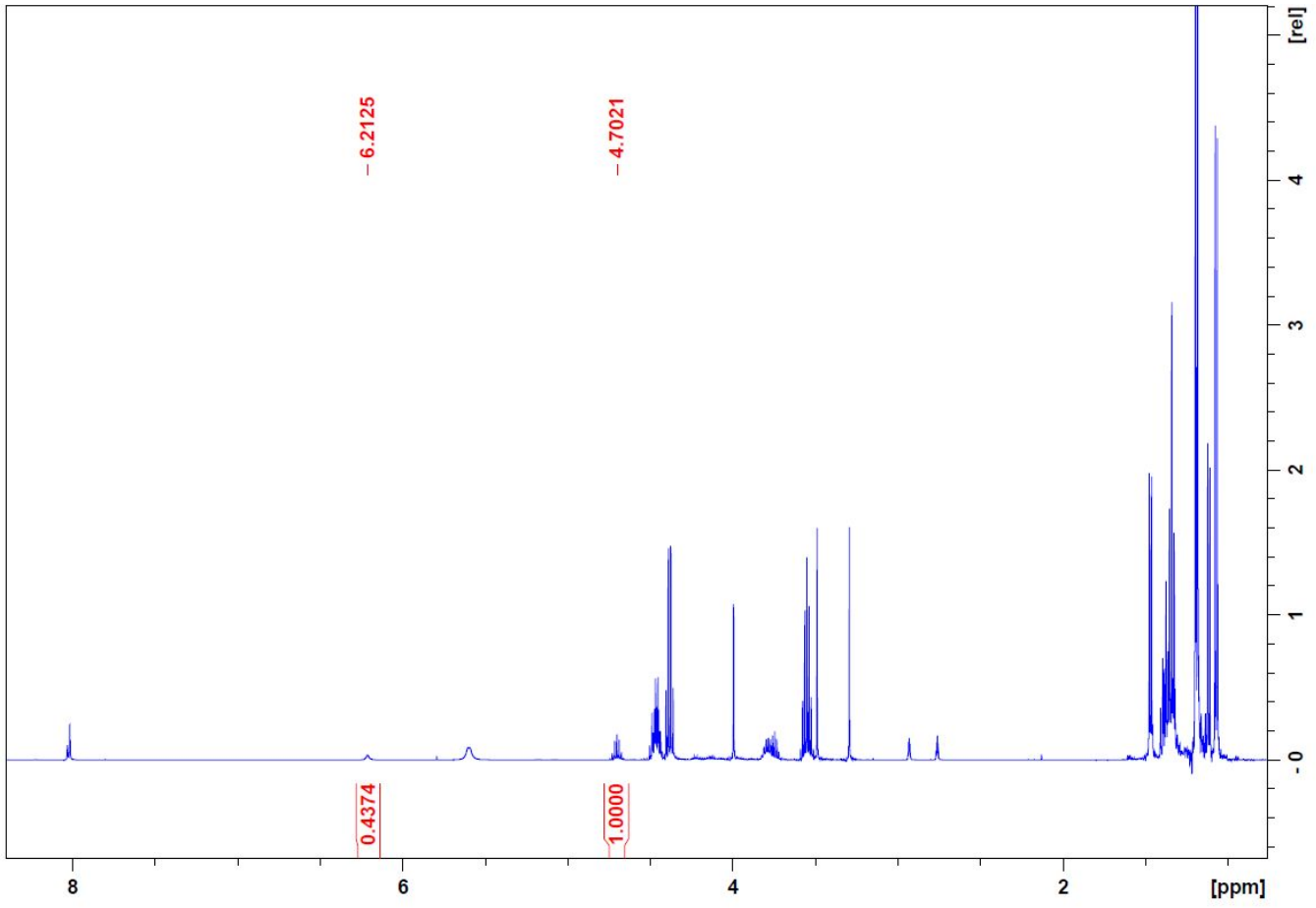

Figure S88. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.5M after 16 h in DMF-d_7 (full spectrum).

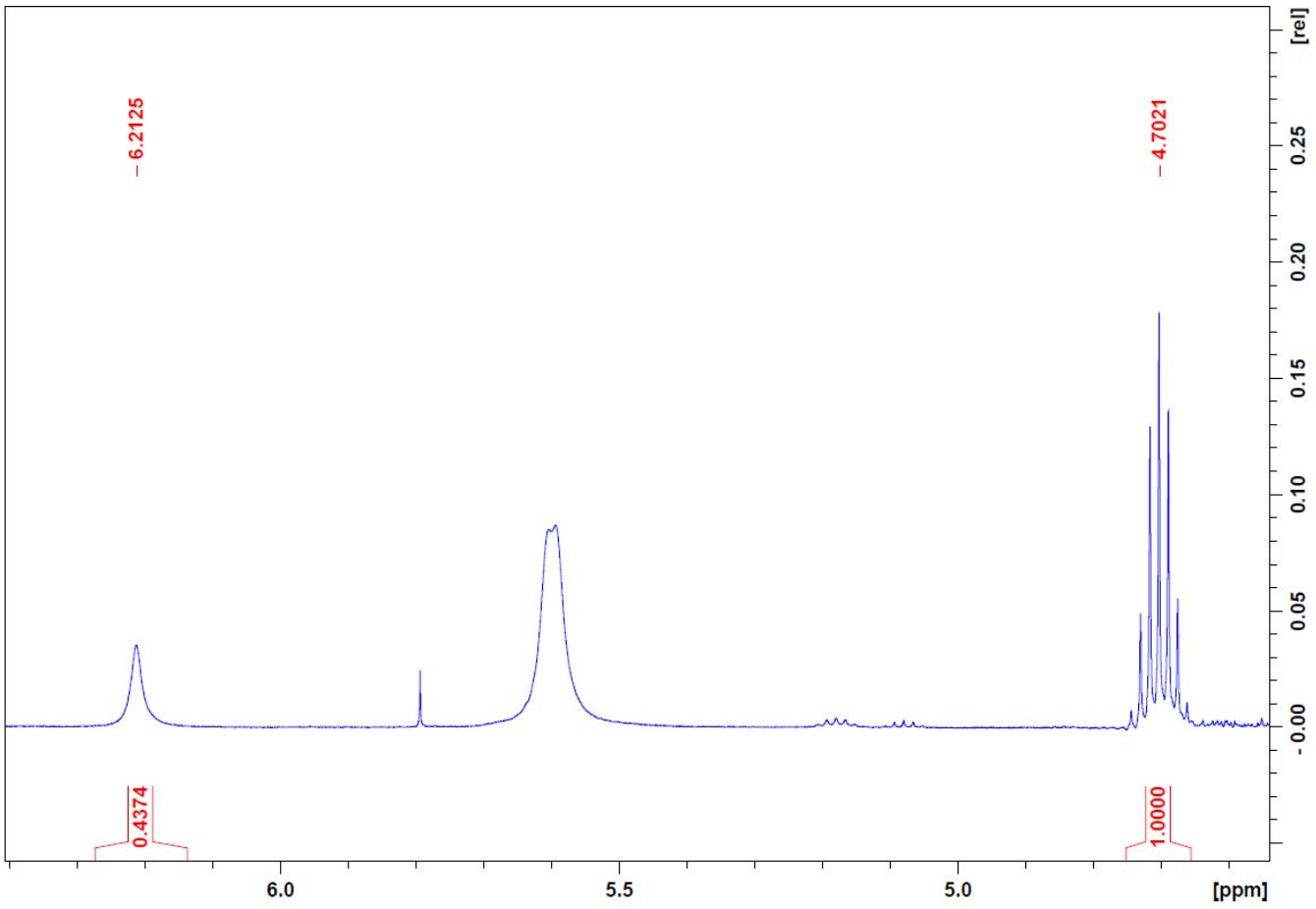

Figure S89. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction at 0.5M after 16 h in DMF-d_7 (zoom-in).

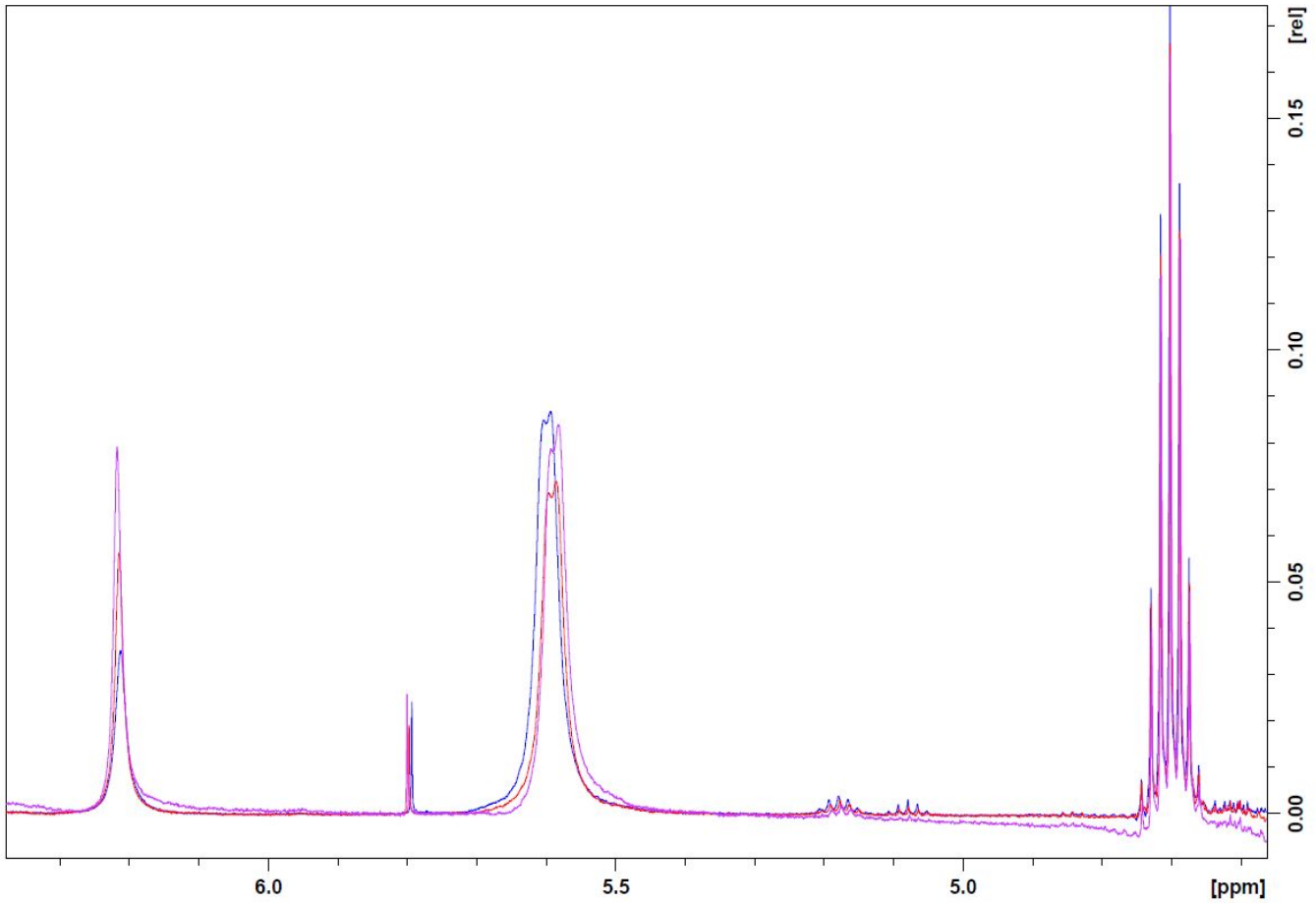

Figure S90. Overlay of 1D ^{1}H NMR spectra of DIC/Oxyma reaction at 0.5M (in blue), 0.4M (in red) and 0.3M (in purple) after 16 h in DMF-d_7 (zoom-in).

7.4 Assessment of HCN formation in 0.37M DMF-d_7 solution of Oxyma and DIC with 5 equiv DMTS

General Procedure for Oxyma and DIC reaction using DMTS

A solution was prepared by dissolving Oxyma (12.0 mg, 0.084 mmol, 1 equiv) and caffeine (2.3 mg, 0.012 mmol, 0.14 equiv) in 170 µL of DMF-d_7. The solution was mixed by using an ultrasound bath. DMTS (44.0 µL, 0.425 mmol, 5 equiv) and DIC (13.3 µL, 0.085 mmol, 1 equiv) were added to the solution. DMTS is carried out prior to addition of DIC. The latter was transferred into a 3mm NMR tube and transferred to the spectrometer for monitoring at 20°C. 1D ^{1}H NMR acquisition was done after 1 h, 5 h, 10 h and 16 h.

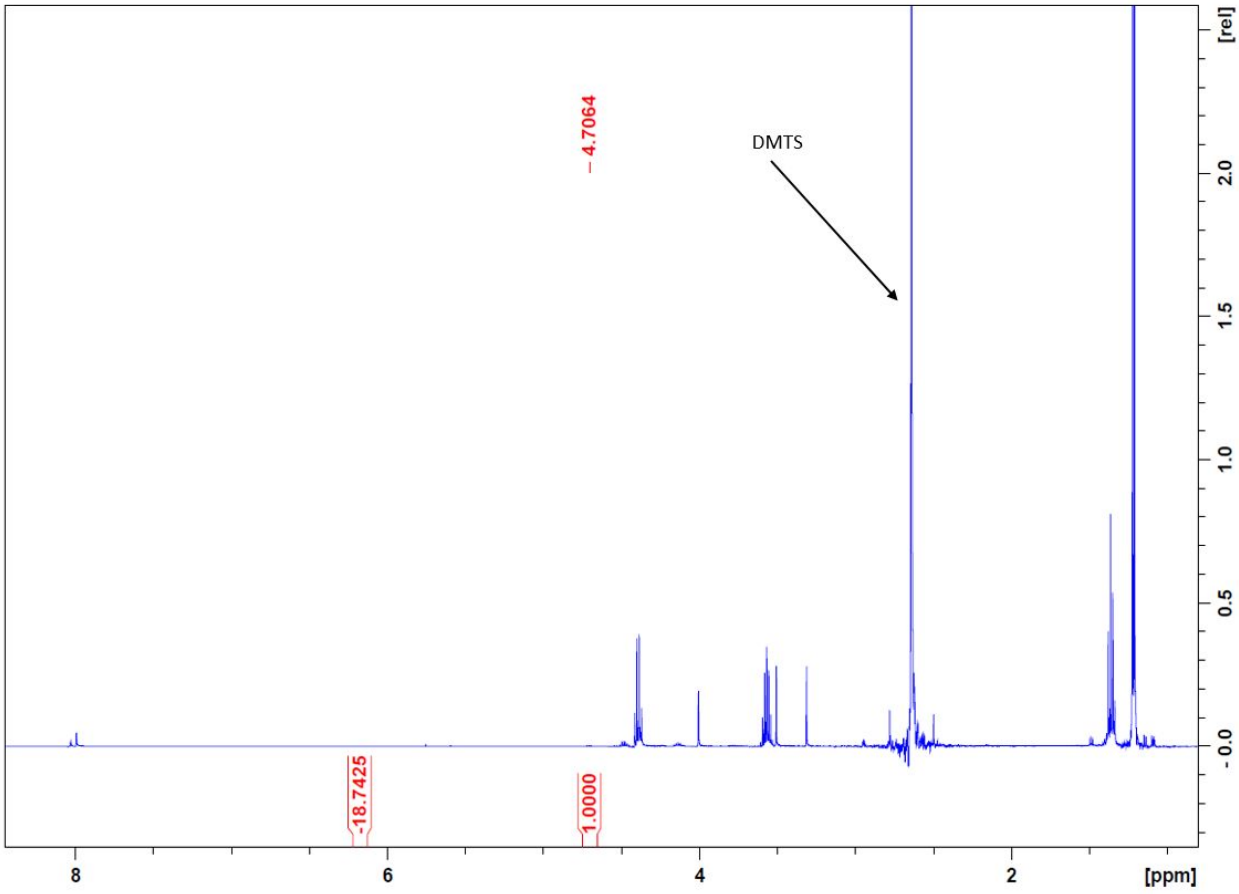

Figure S91. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 1h in DMF-d_7 (full spectrum).

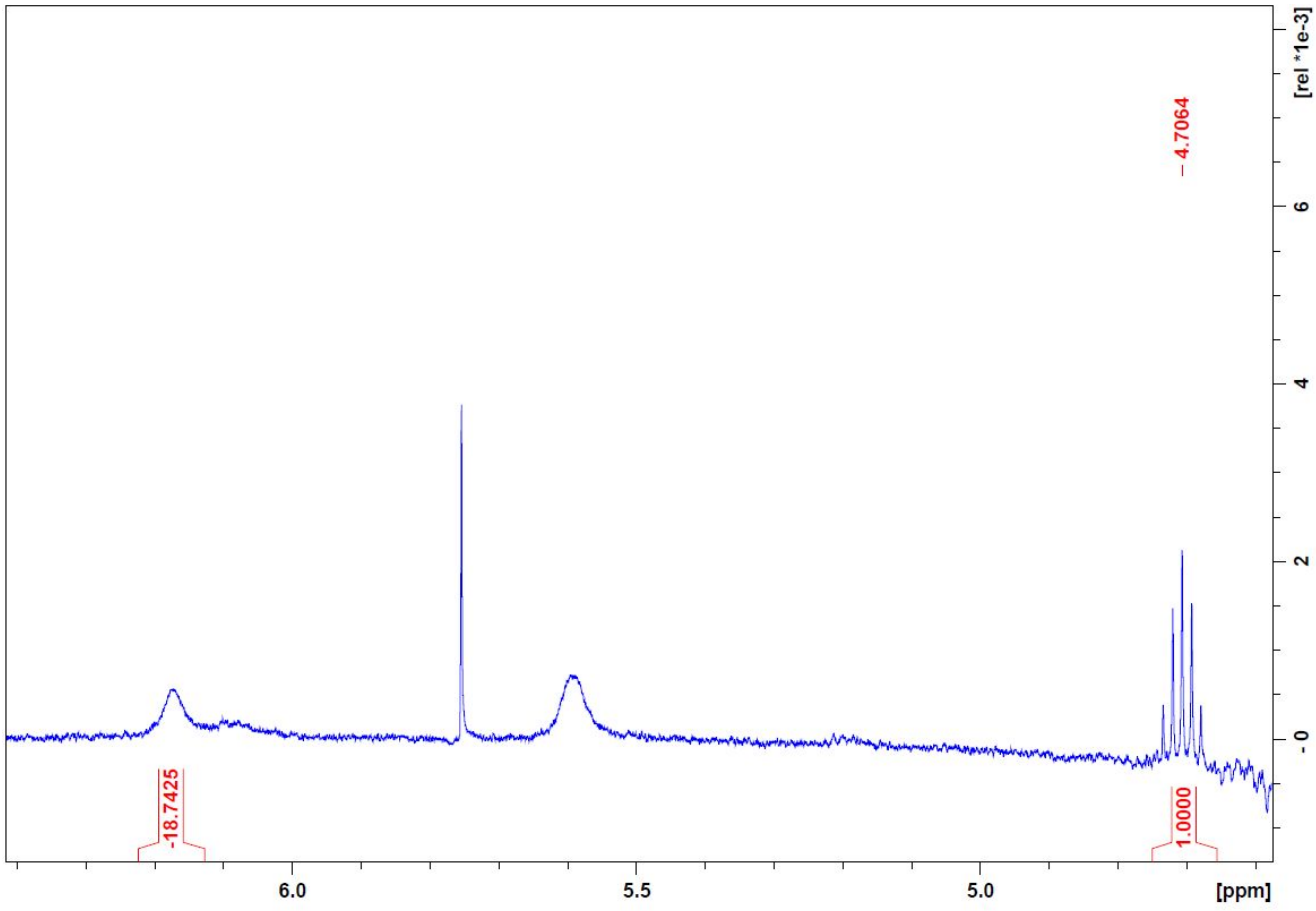

Figure S92. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 1 h in DMF-d_7 (zoom-in).

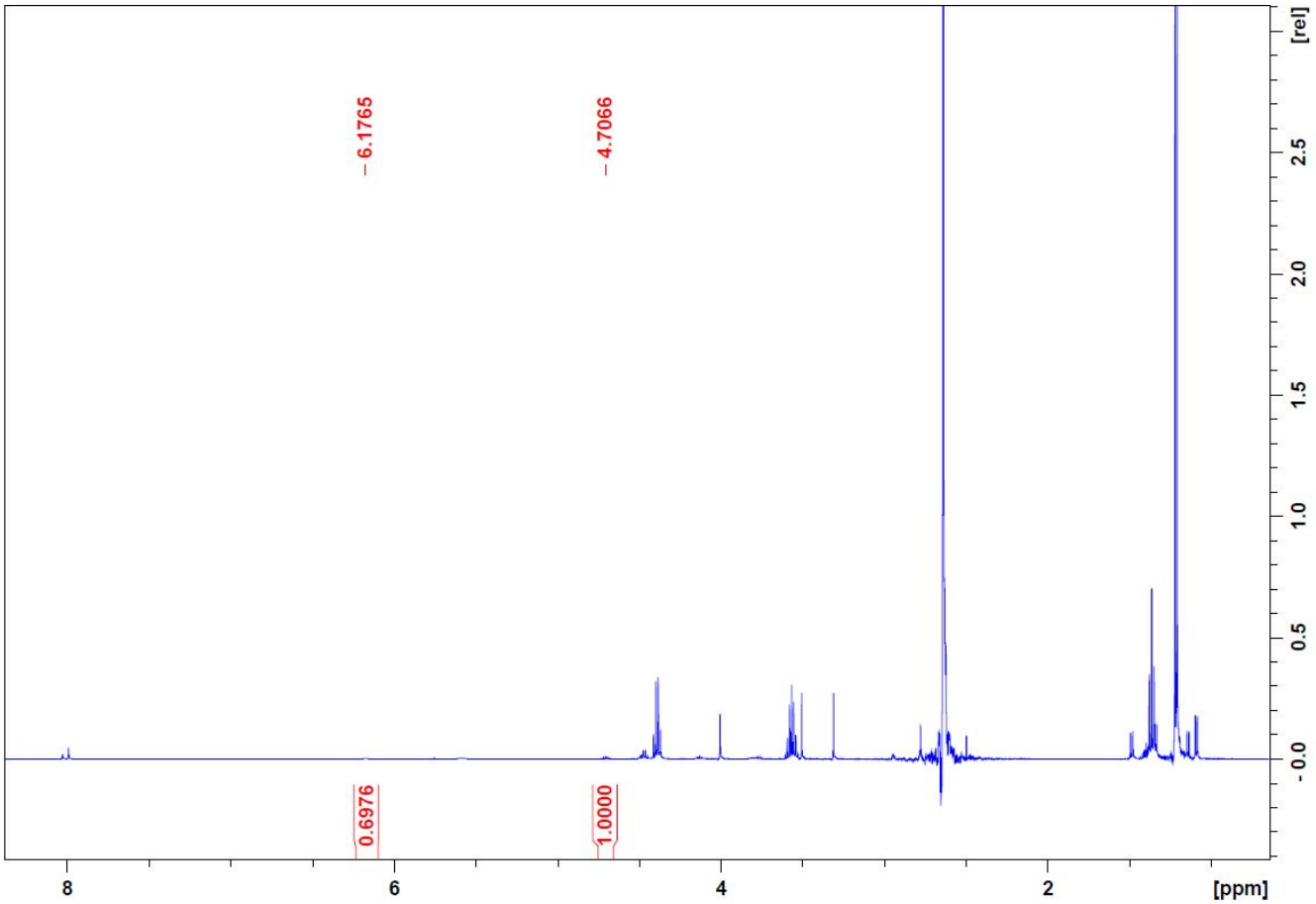

Figure S93. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 5 h in DMF-d_7 (full spectrum).

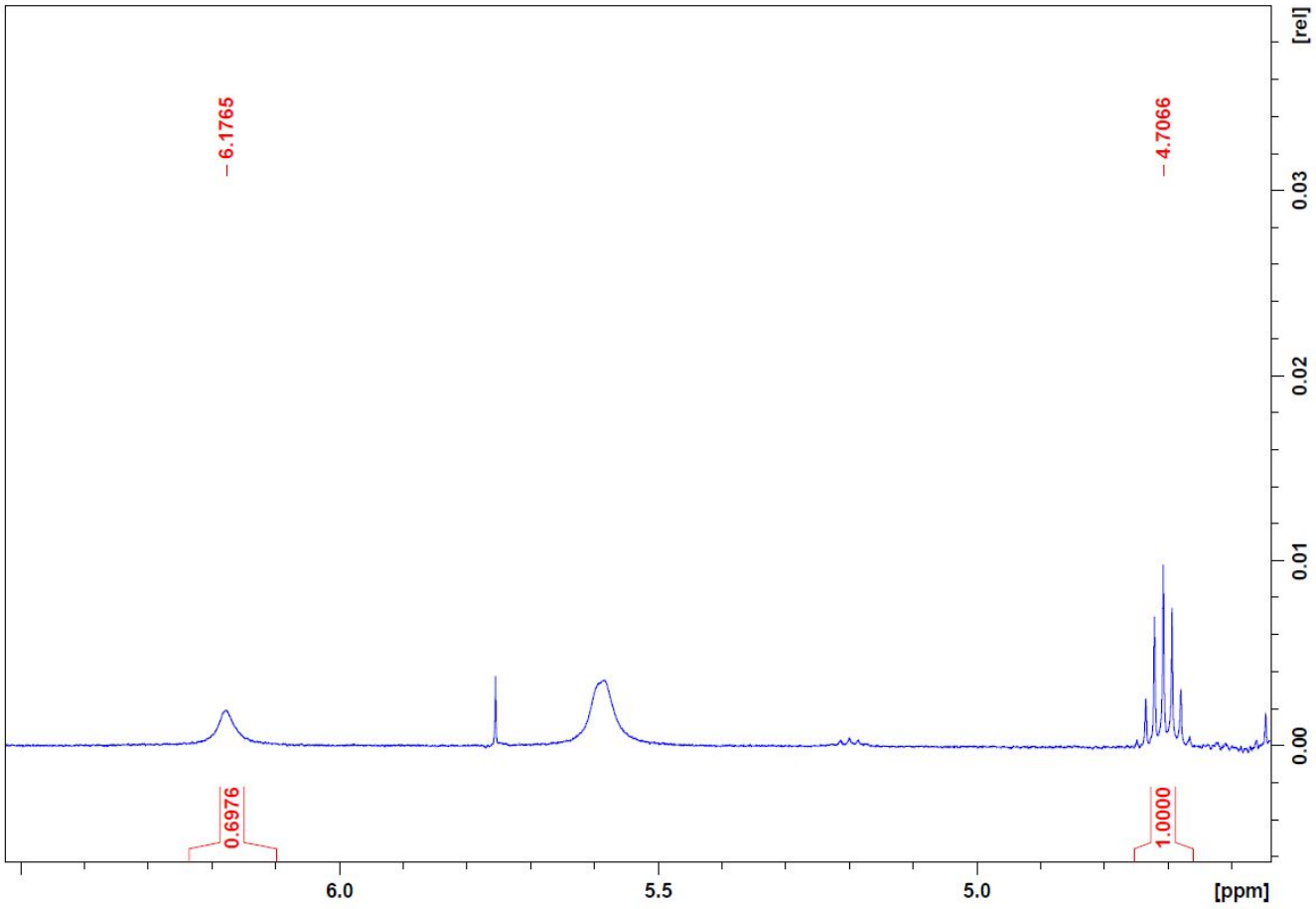

Figure S94. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 5 h in DMF-d_7 (zoom-in).

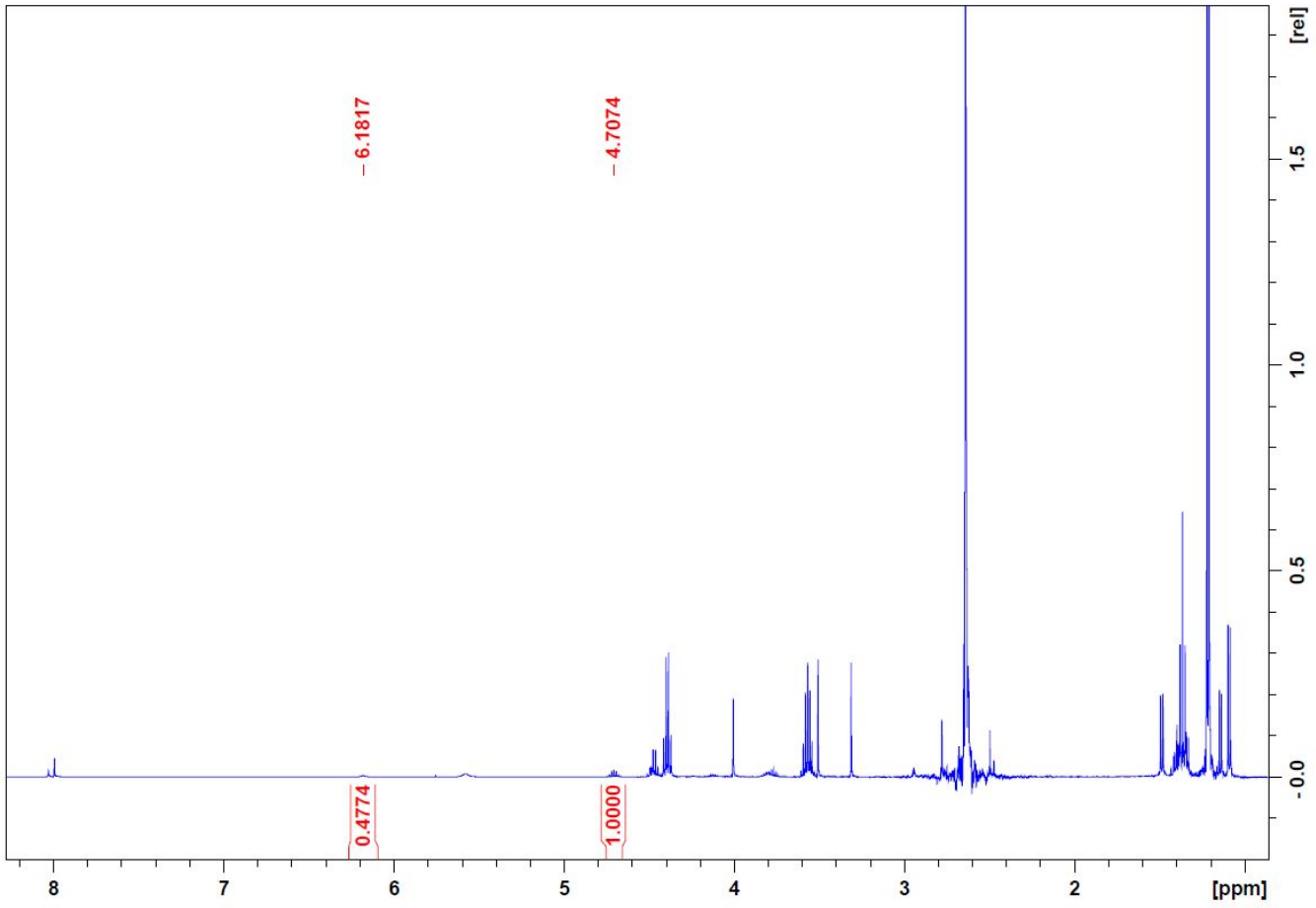

Figure S95. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 10 h in DMF-d_7 (full spectrum).

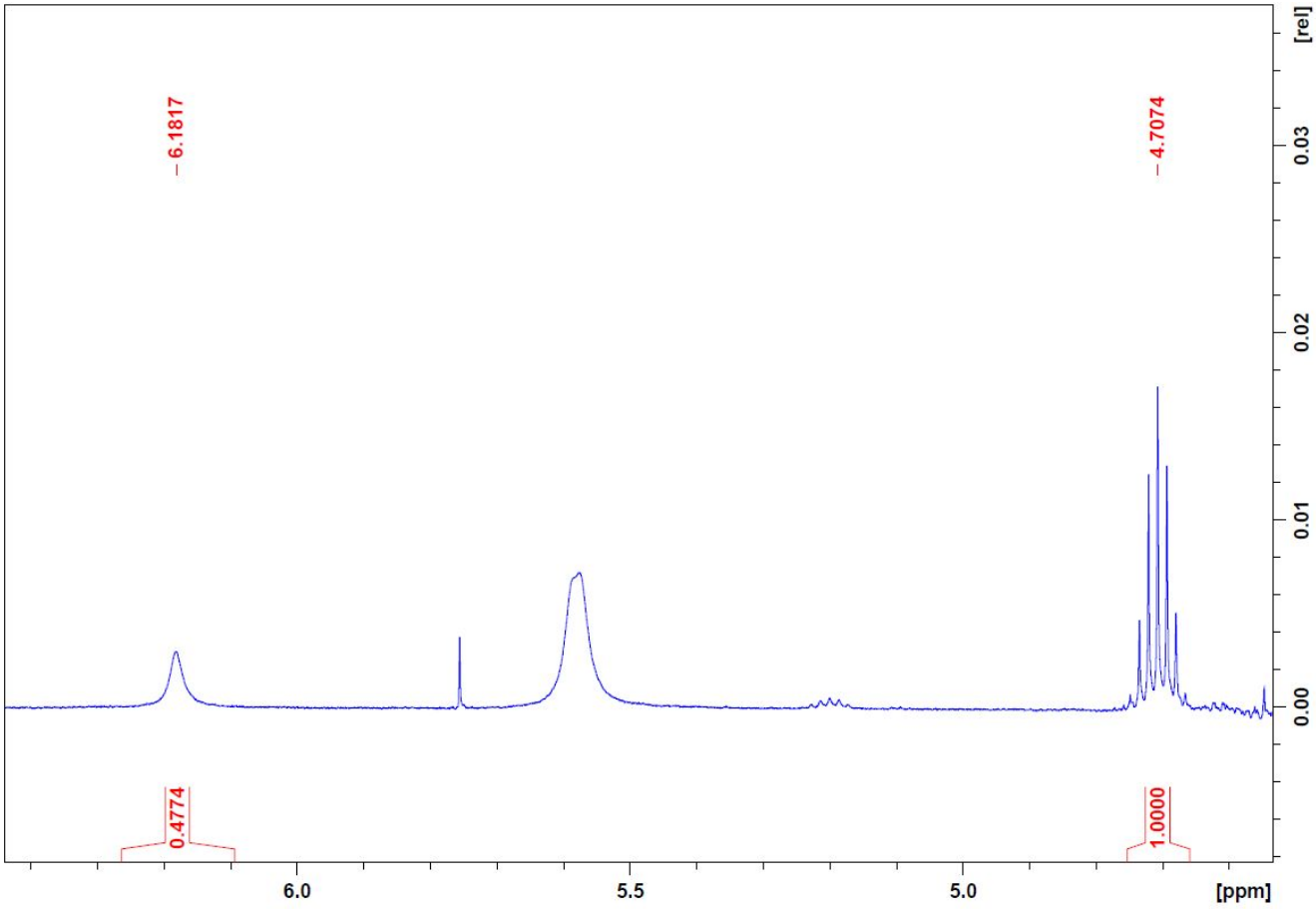

Figure S96. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 10 h in DMF-d_7 (zoom-in).

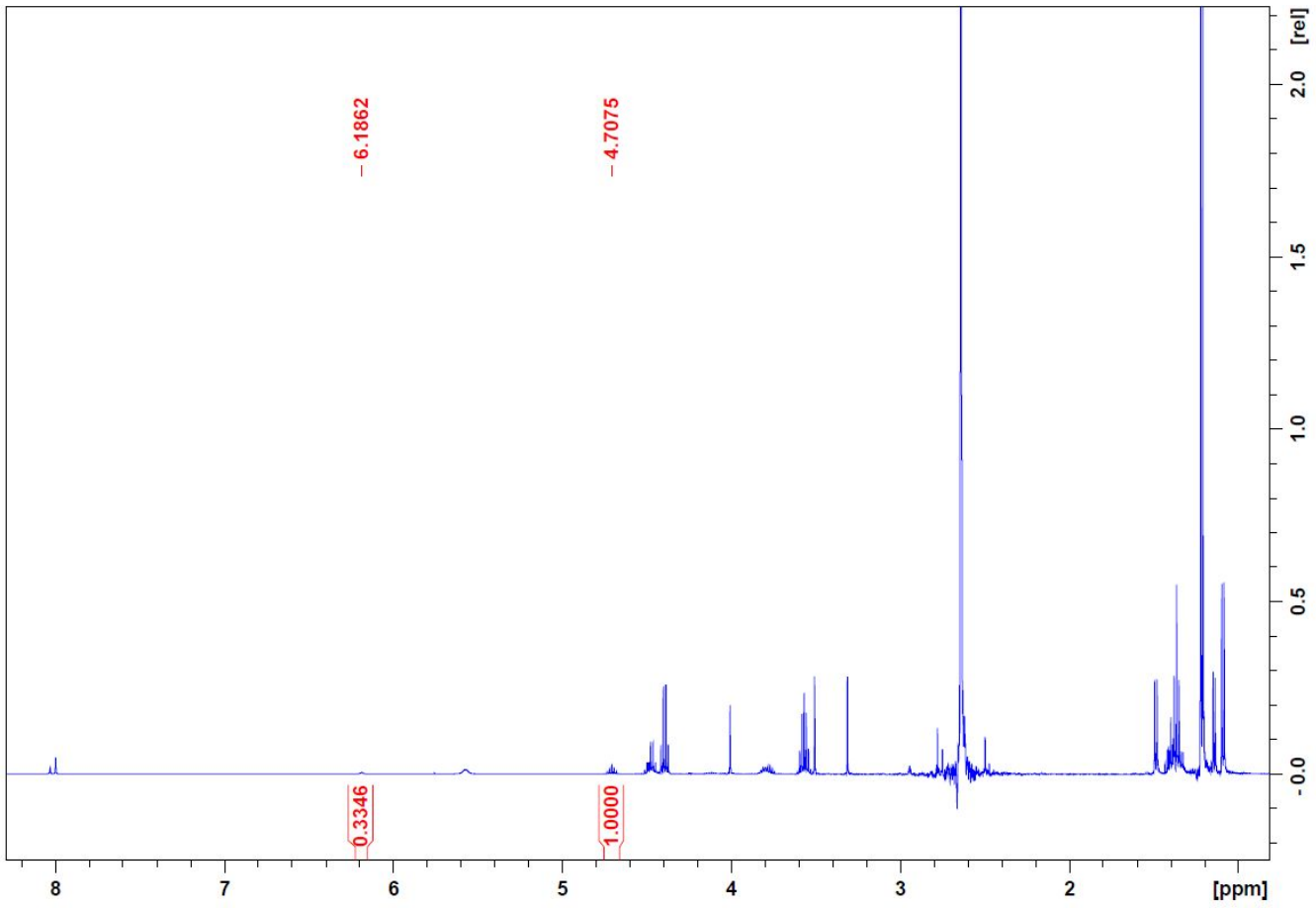

Figure S97. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 16 h in DMF-d_7 (full spectrum).

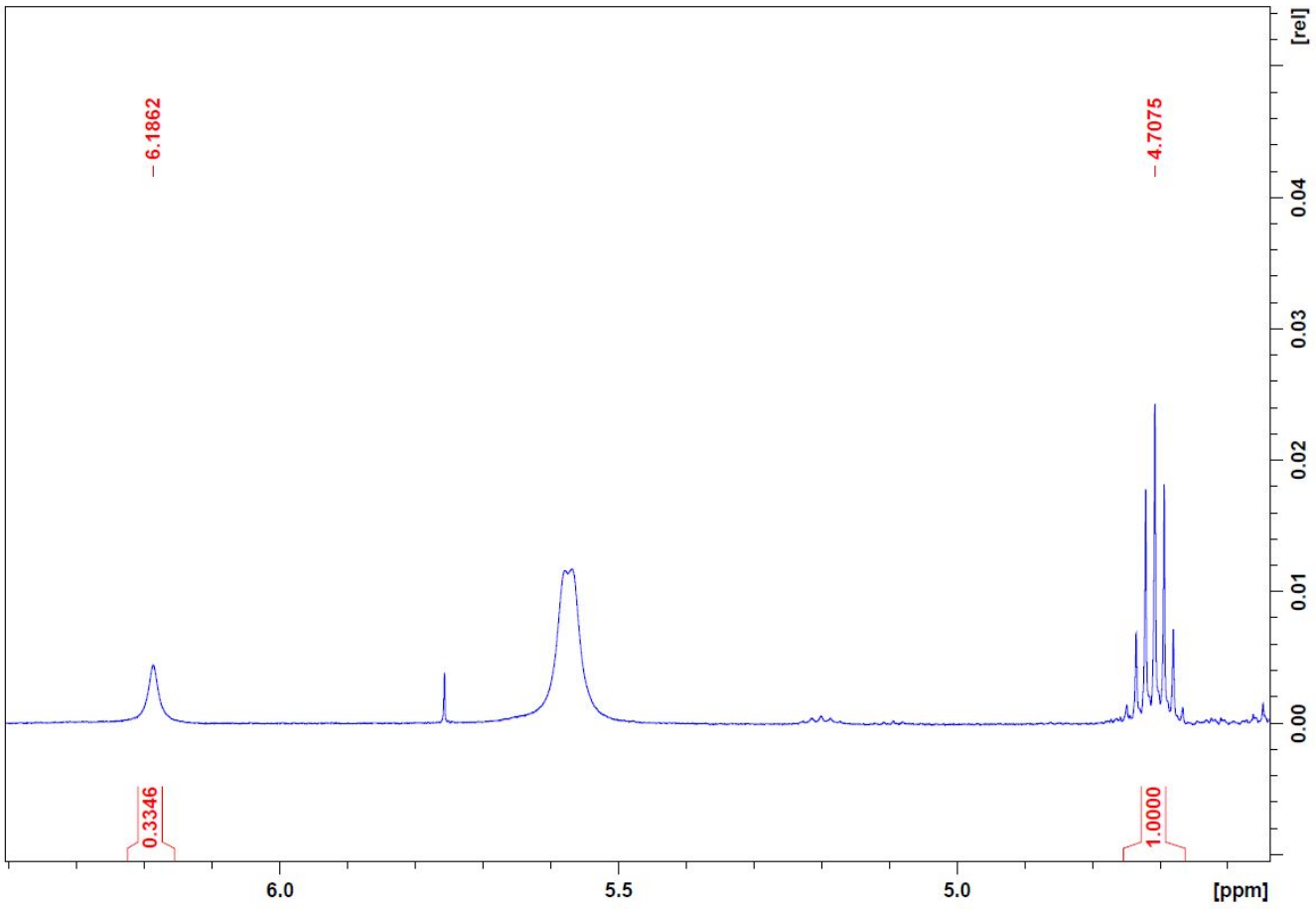

Figure S98. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 16 h in DMF-d_7 (zoom-in).

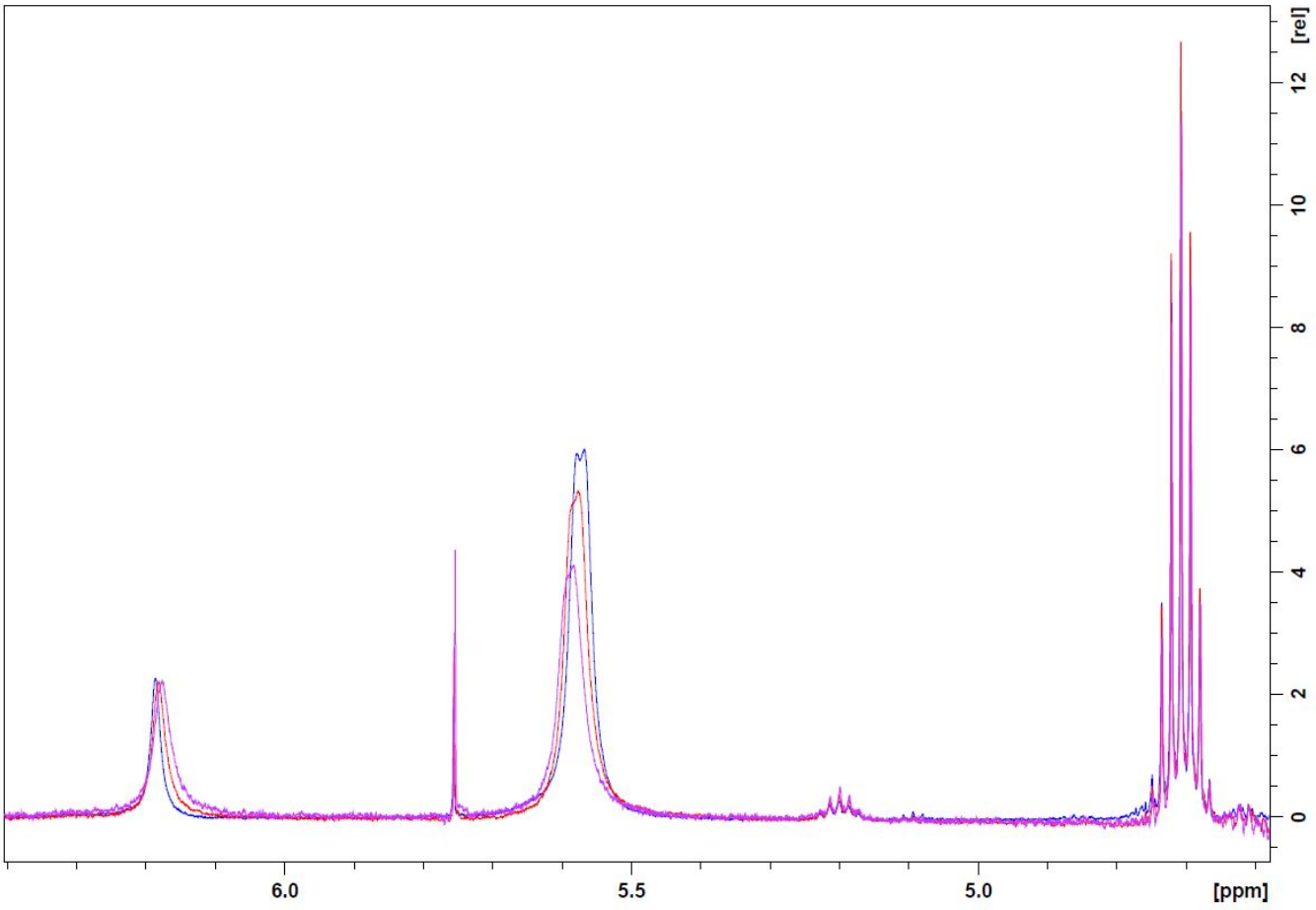

Figure S99. Overlap of 1D ^{1}H NMR spectra of DIC/Oxyma reaction with 5 equiv DMTS at 0.37M after 5 h (in purple), 10 h (in red) and 16 h (in blue) in DMF-d_7 (zoom-in).

7.5 Assessment of HCN formation in 0.32M DMF-d_7 solution of Oxyma and DIC with 10 equiv DMTS

The general procedure for the reactions of DIC and Oxyma using DMTS in DMF-d_7 as described in the section 7.4 of this SI was followed. The following amounts of starting materials were used: Oxyma (12.4 mg, 0.087 mmol, 1.03 equiv), caffeine (1.9 mg, 0.010 mmol, 0.12 equiv), DMTS (89.6 µL, 0.85 mmol, 10 equiv), DIC (13.3 µL, 0.085 mmol, 1.0 equiv).

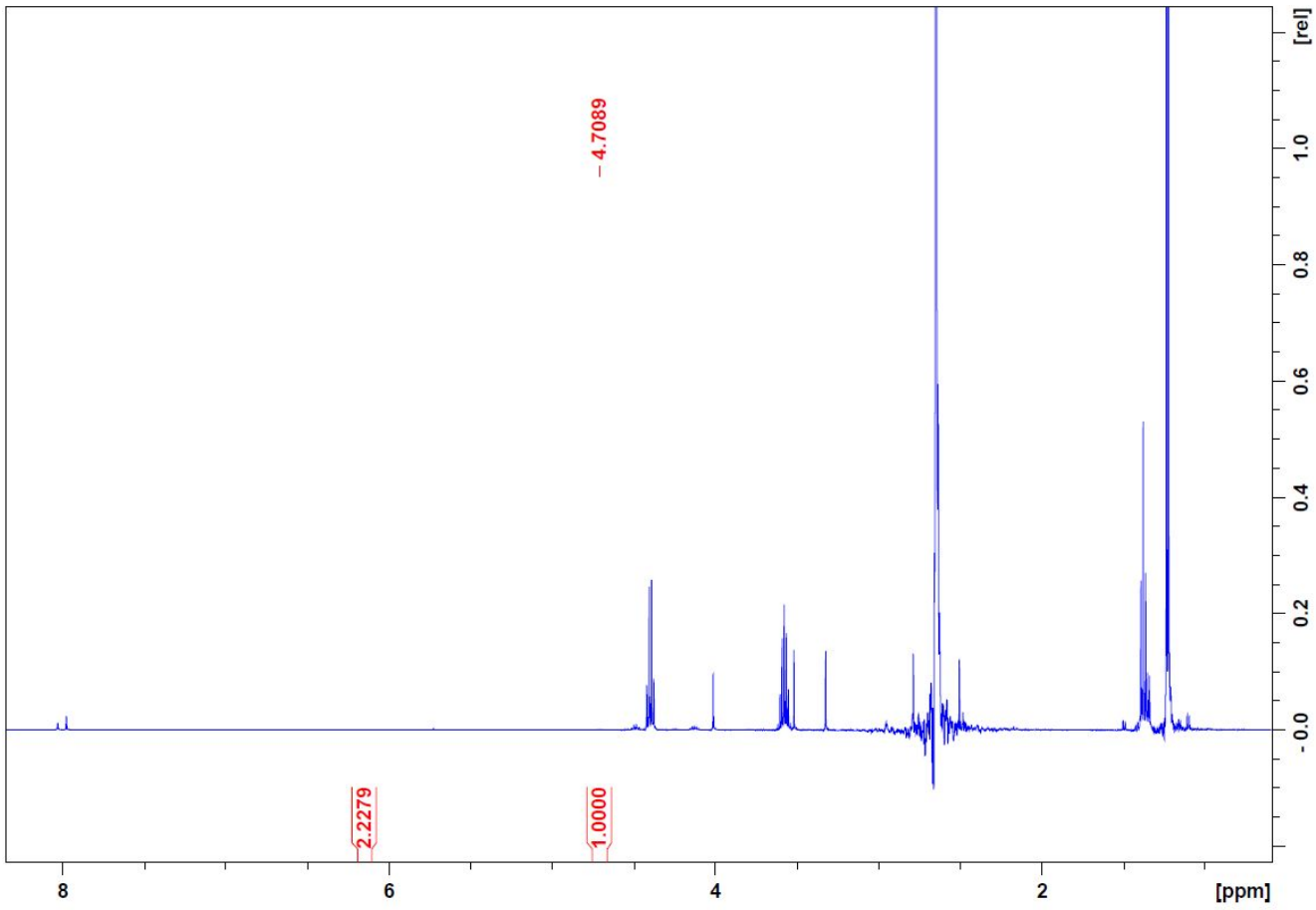

Figure S100. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 1 h in DMF-d_7 (full spectrum).

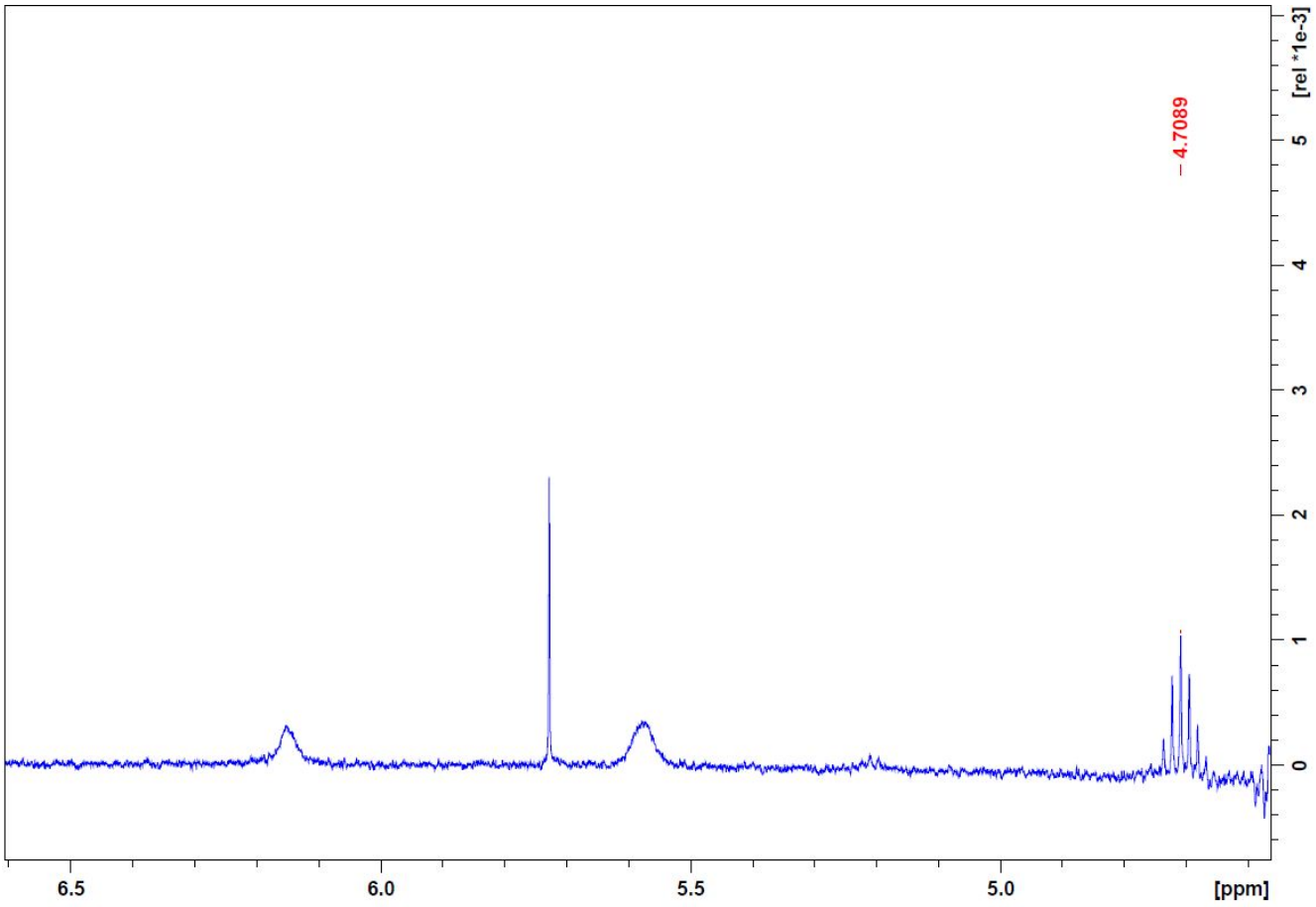

Figure S101. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 1 h in DMF-d_7 (zoom-in).

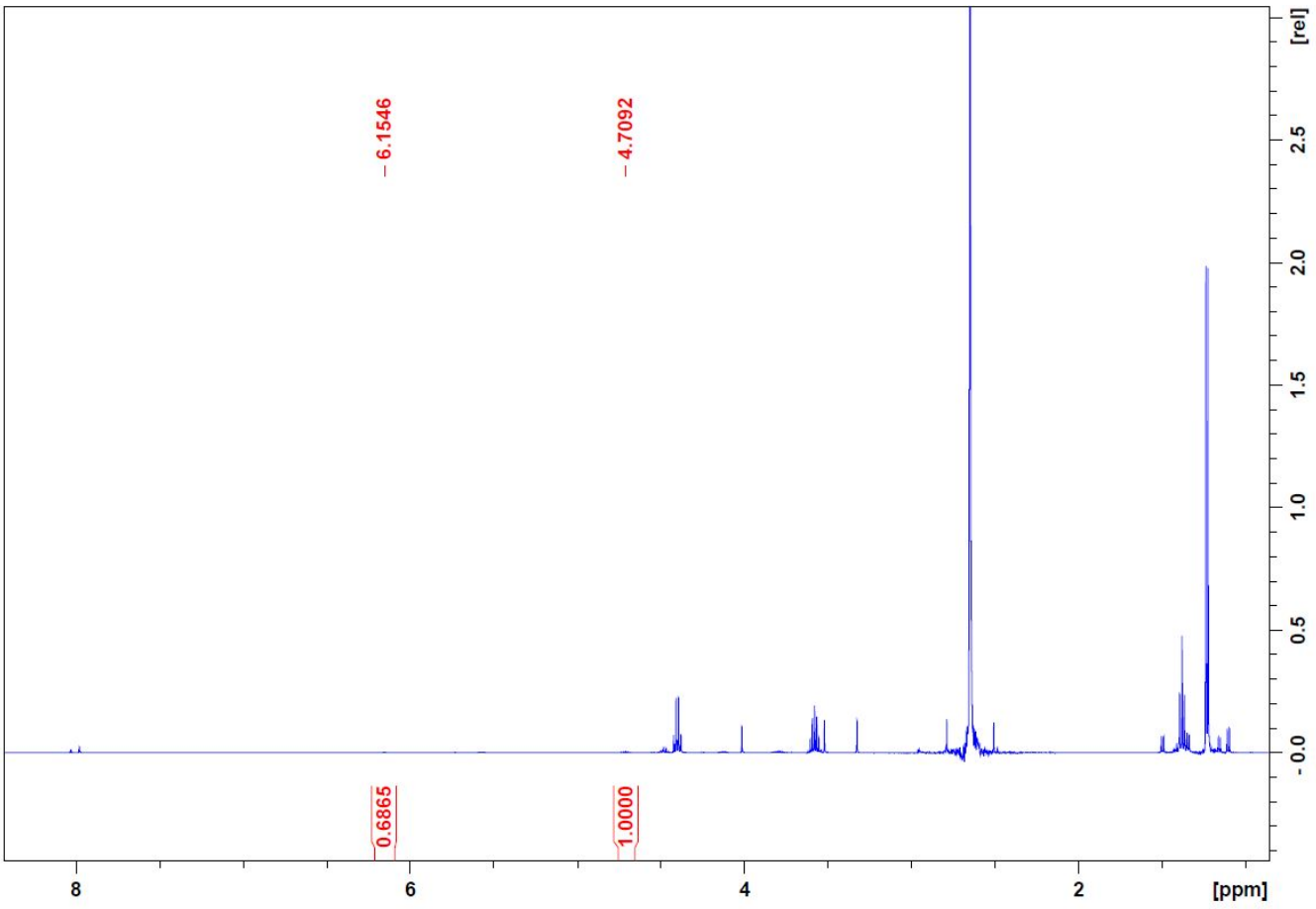

Figure S102. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 5 h in DMF-d_7 (full spectrum).

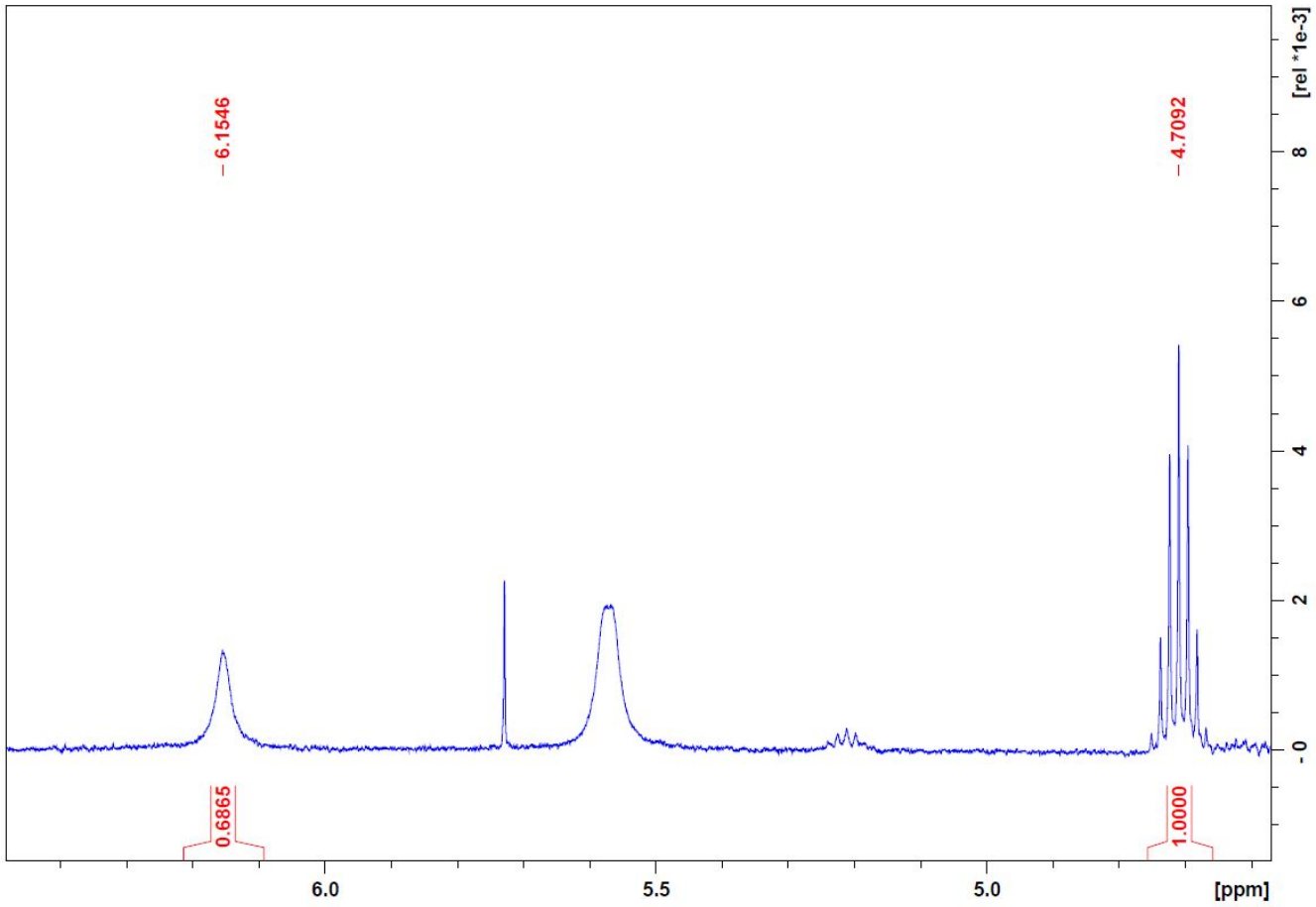

Figure S103. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 5 h in DMF-d_7 (zoom-in).

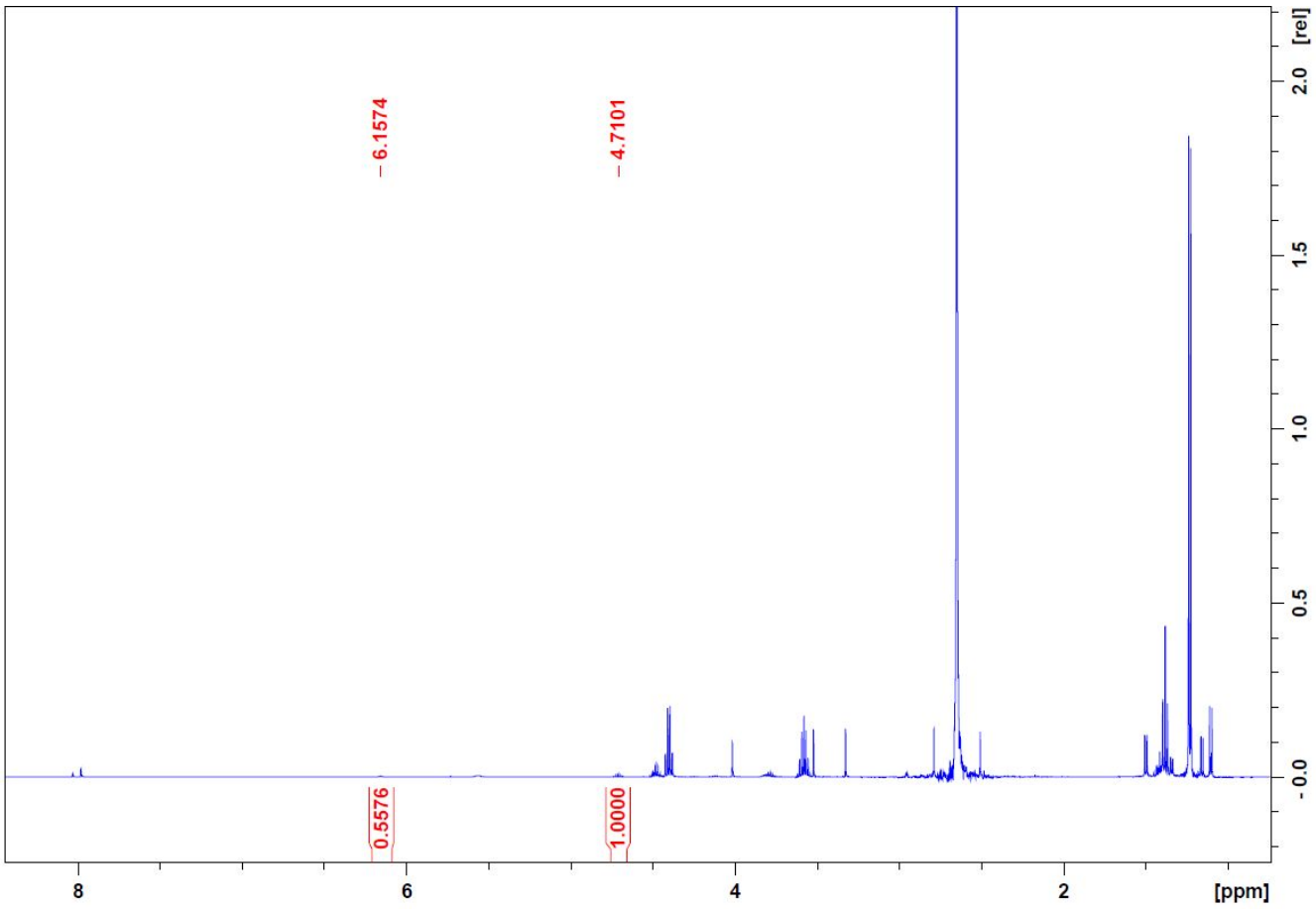

Figure S104. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 10 h in DMF-d_7 (full spectrum).

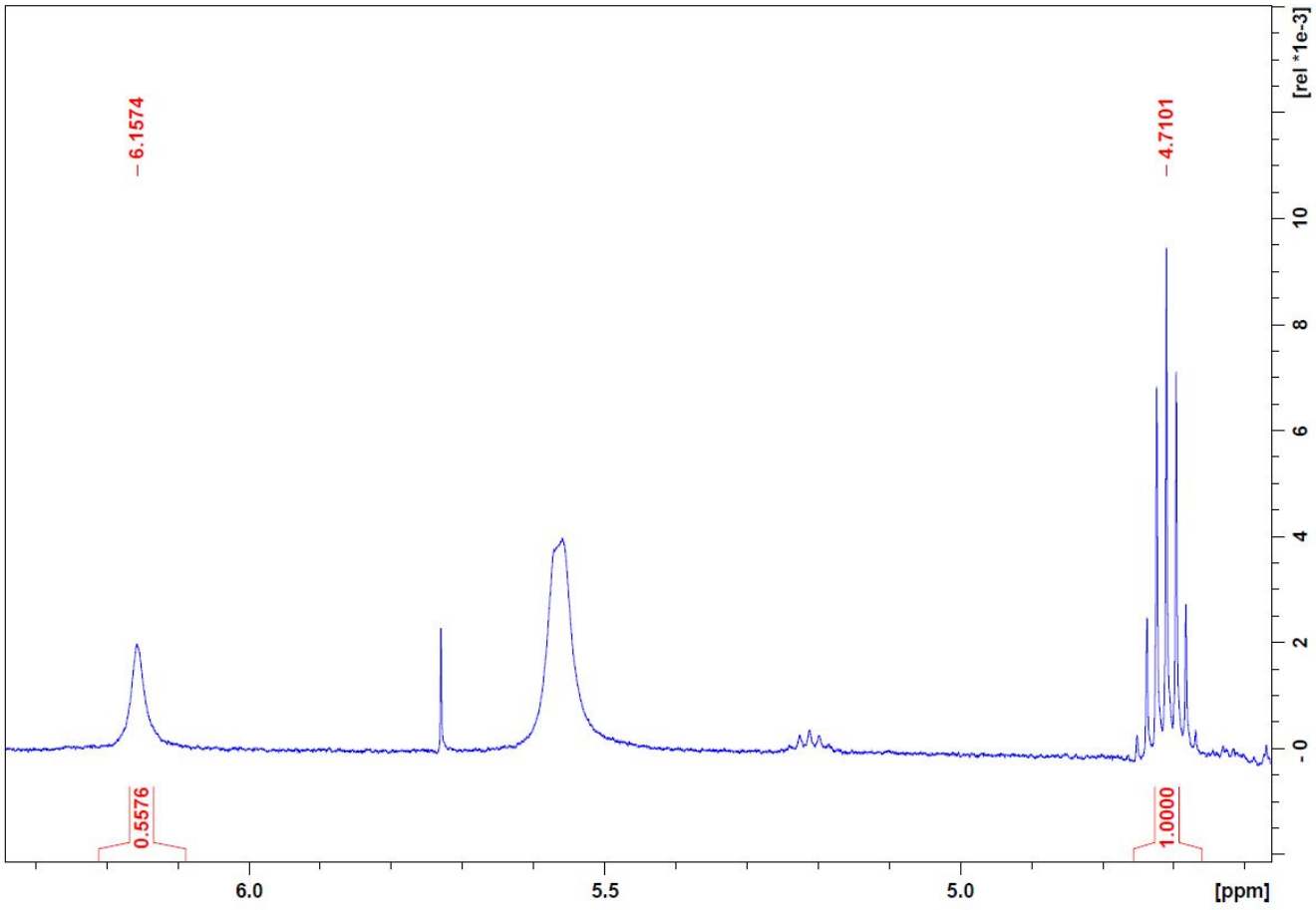

Figure S105. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 10 h in DMF-d_7 (zoom-in).

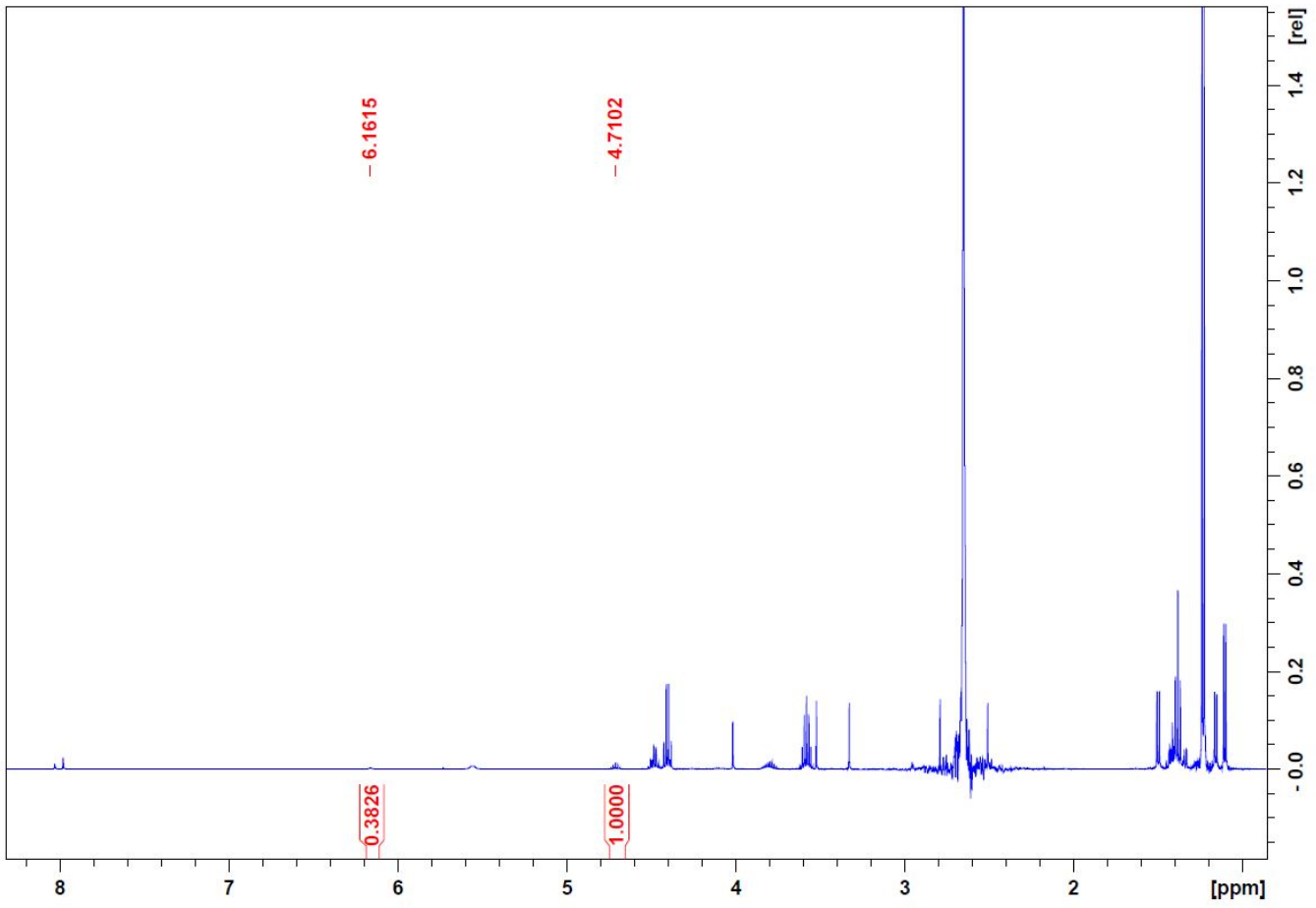

Figure S106. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 16 h in DMF-d_7 (full spectrum).

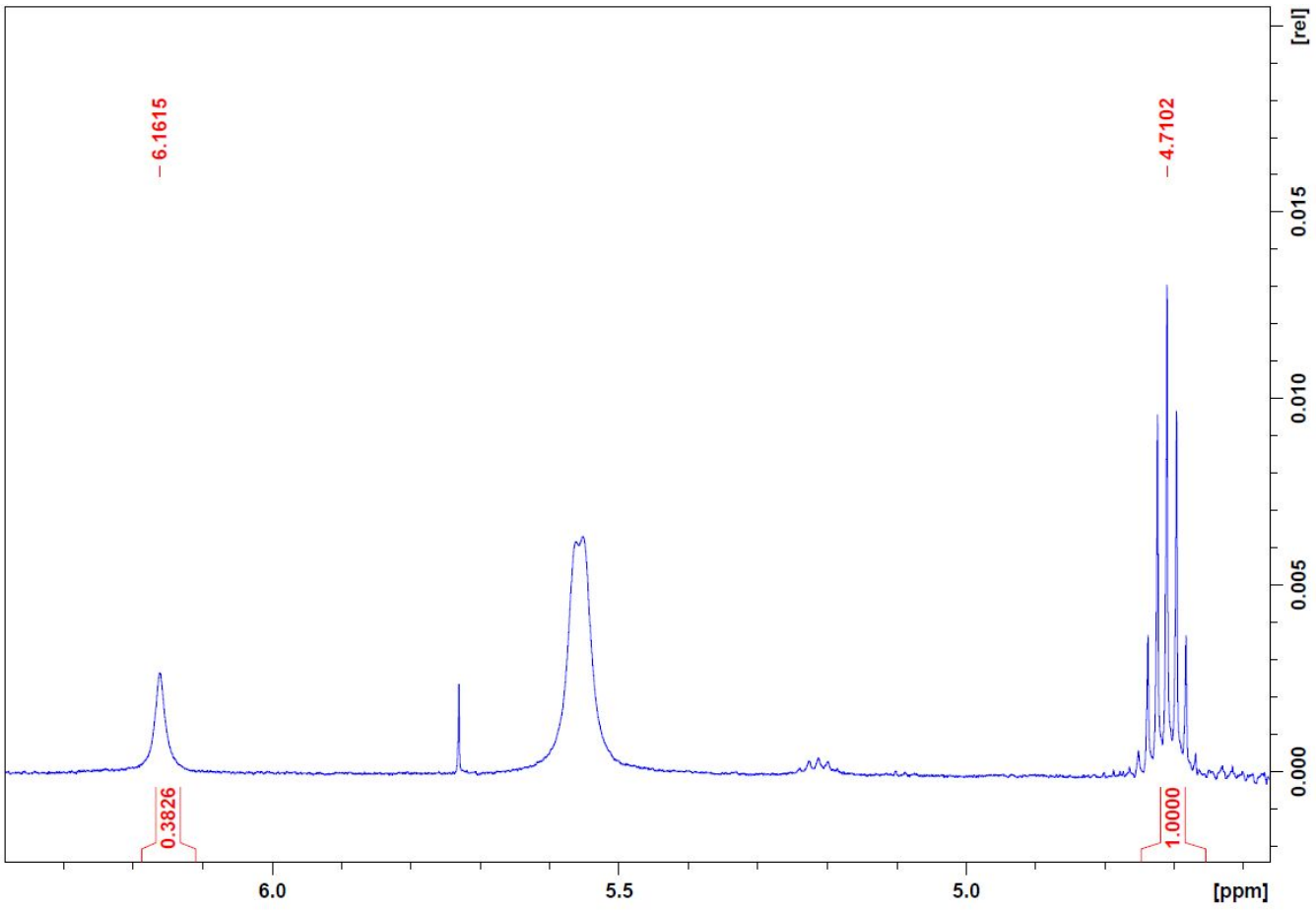

Figure S107. 1D ^{1}H NMR spectrum of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 16 h in DMF-d_7 (zoom-in).

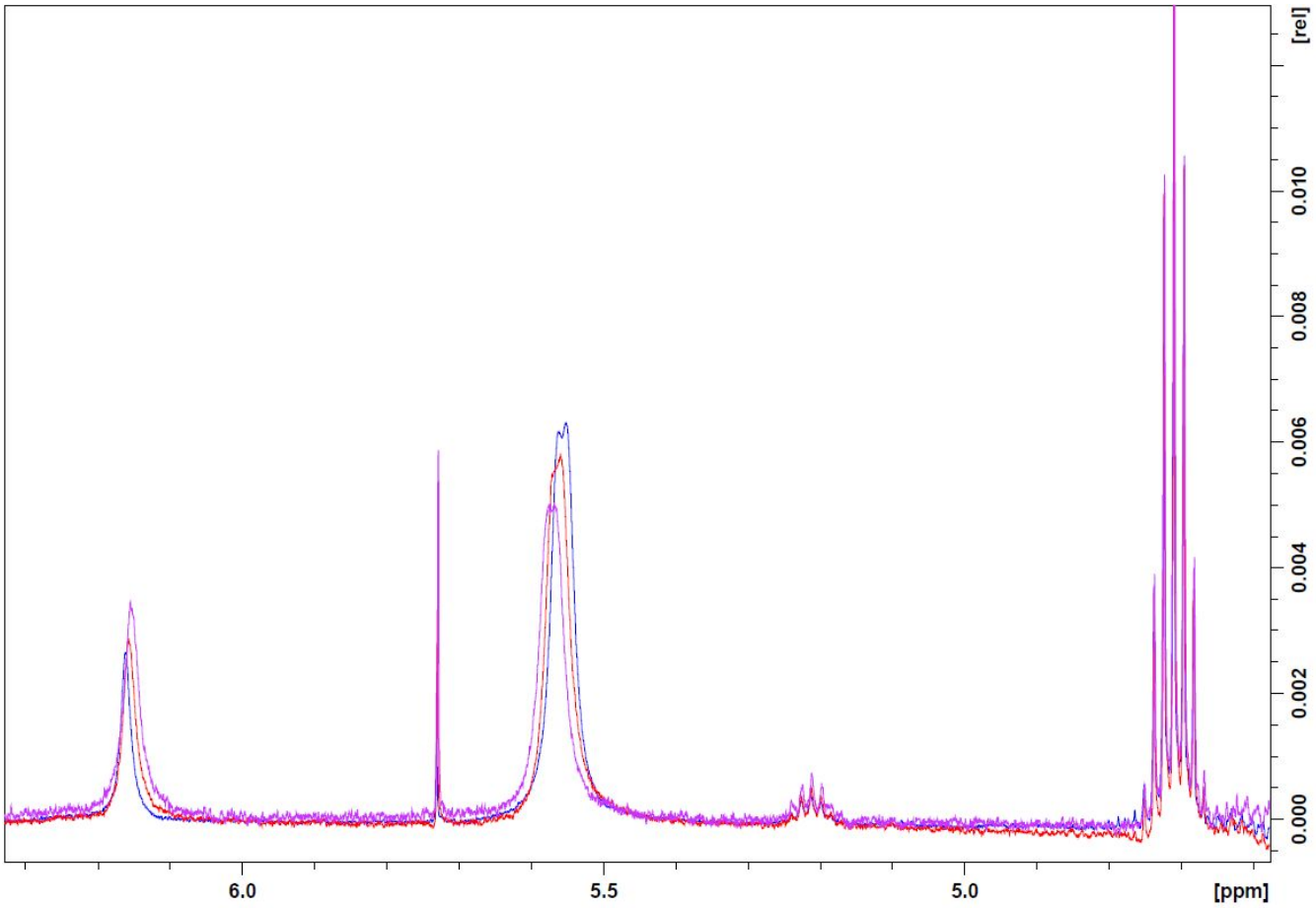

Figure S108. Overlay of 1D ^{1}H NMR spectra of DIC/Oxyma reaction with 10 equiv DMTS at 0.32M after 5 h (in purple), 10 h (in red) and 16 h (in blue) in DMF-d_7 (zoom-in).

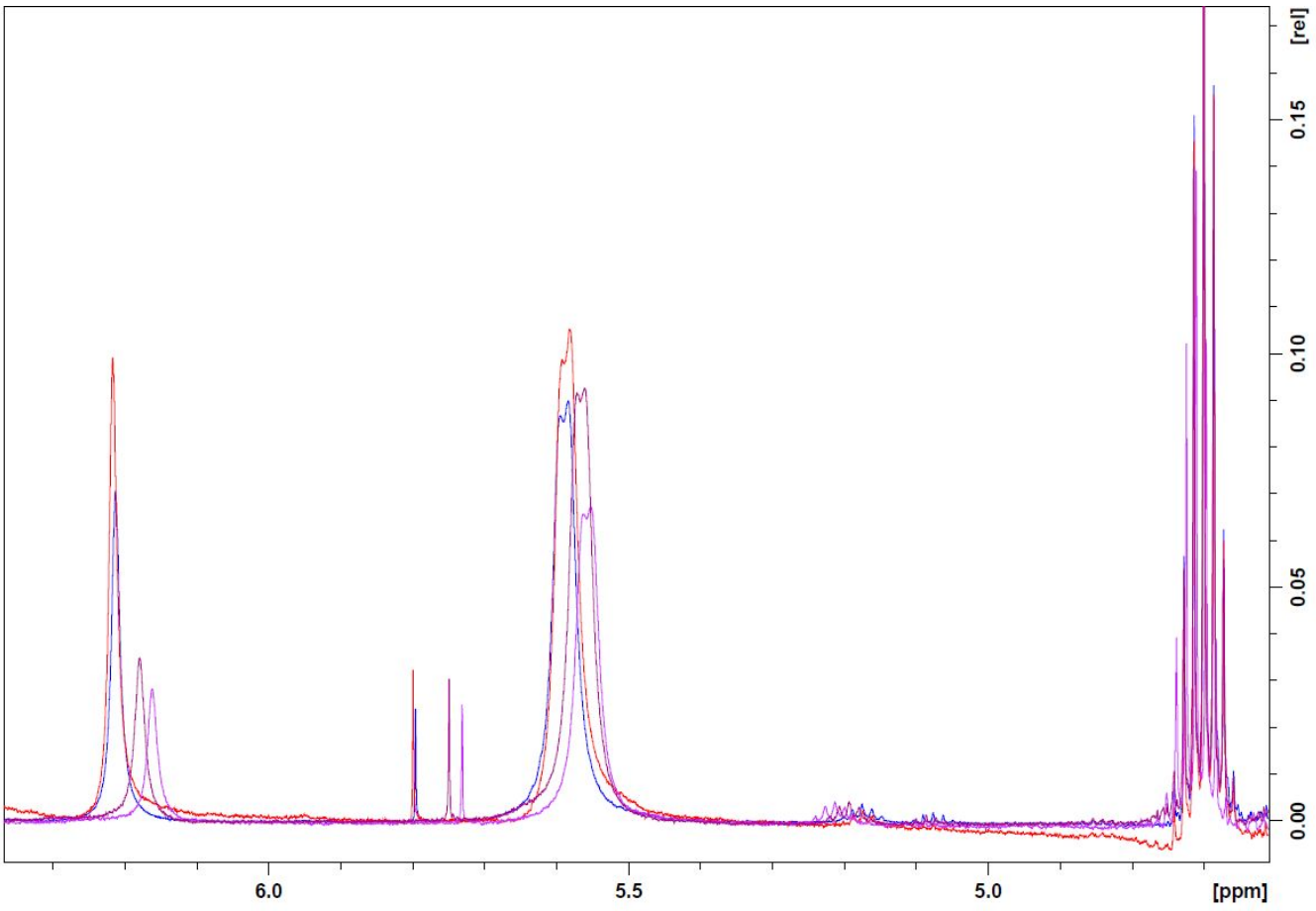

Figure S109. Overlay of 1D ^{1}H NMR spectra of DIC/Oxyma reaction after 16 h at 0.3M (in red), 0.4M (in blue), at 0.32M with 10 equiv of DMTS (in purple) and at 0.37M with 5 equiv of DMTS (in brown) in DMF-d_7 (zoom-in).

7.6 Summary of HCN formation during Oxyma/DIC reaction at different concentrations in DMF-d_7 with and without DMTS

This section summarize the results in sections 7.1 – 7.6.

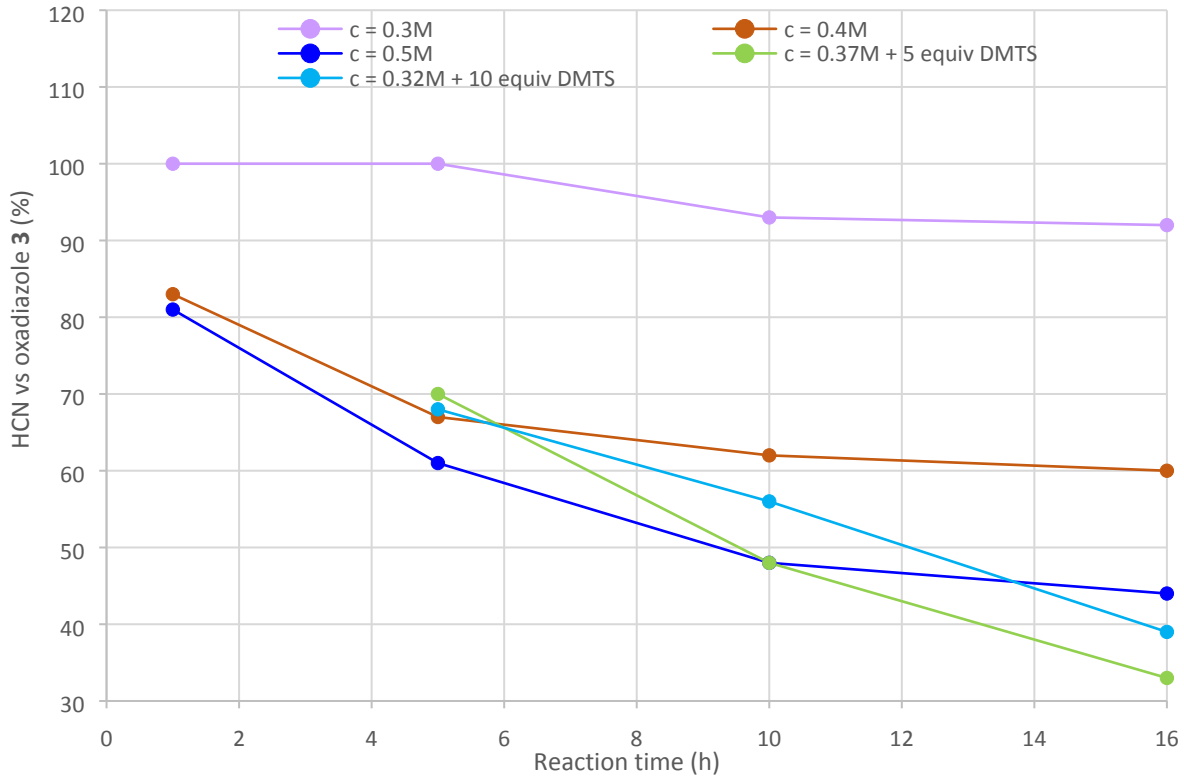

Figure S110. ^{1}H NMR assessment of the presence of HCN in DMF-d_7 solutions of DIC/Oxyma (1:1) with 0, 5, 10 equiv DMTS at different concentrations at rt.

Conclusion of the experiments summarized in Fig. S110: i) keeping the concentration low appears to be a good way to keep HCN formed in the solution and avoid the release in the gas phase; ii) of an HCN scavenger (DMTS) decreases significantly the amount of HCN in the solution. The use of this scavenger during DIC/Oxyma mediated amide bond formations is detailed in the ensuing sections of this SI.

8. NMR analysis of different constituents of DIC/Oxyma mediated amide bond formations

8.1 Starting materials

In this section, NMR analyses are reported for the starting materials used in the DIC/Oxyma mediated amidation of Fmoc-Gly-OH and (S)-(-)-1-phenylethylamine, with and without DMTS (sections 8.1.1 – 8.1.2). The purpose of this investigation was to determine whether any of these materials reacts with DMTS to an appreciable extent and thereby could affect the course of the amidations in the presence of DMTS.

8.1.1 Starting materials without addition of DMTS

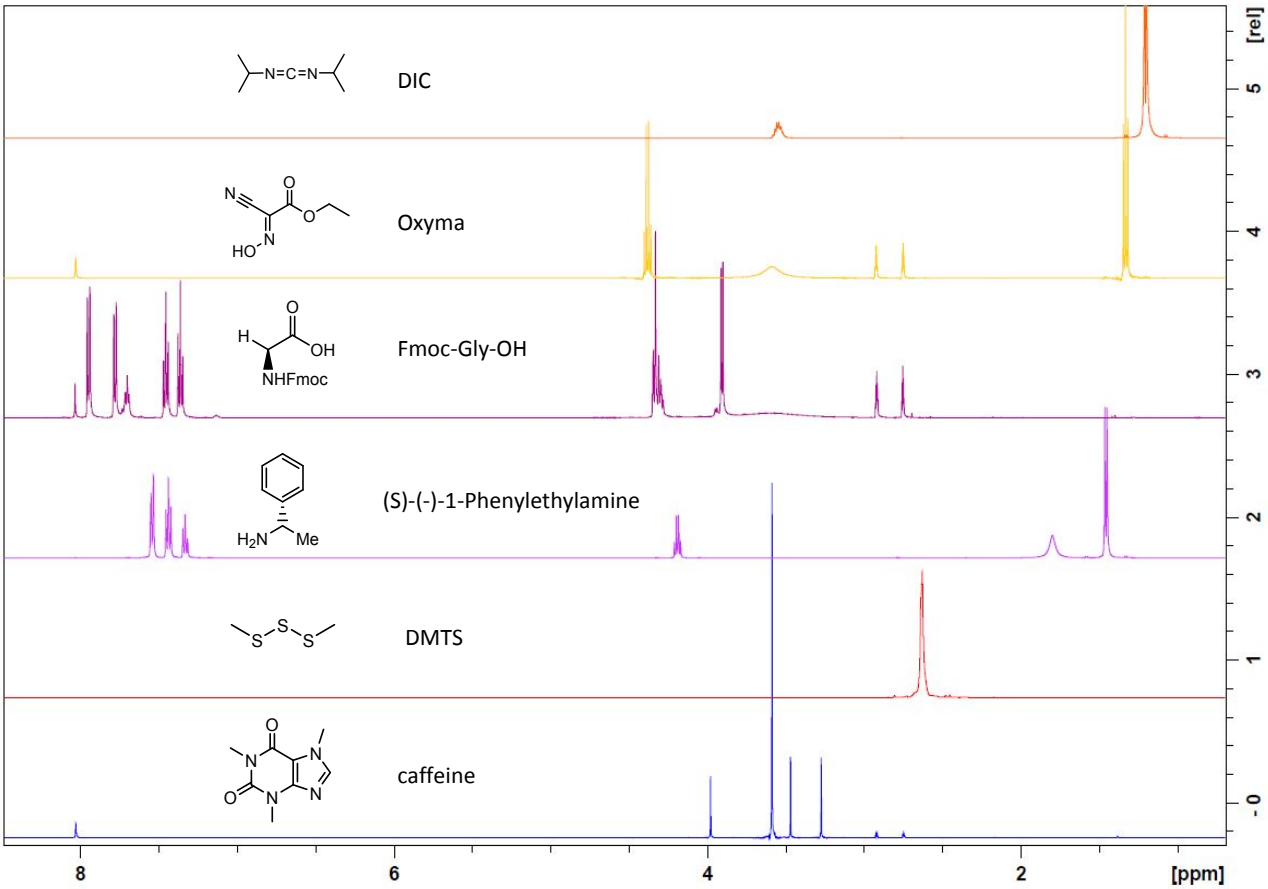

Figure S111. Overlay of 1D ^{1}H NMR spectra of starting materials and internal standard in DMF-d_7.

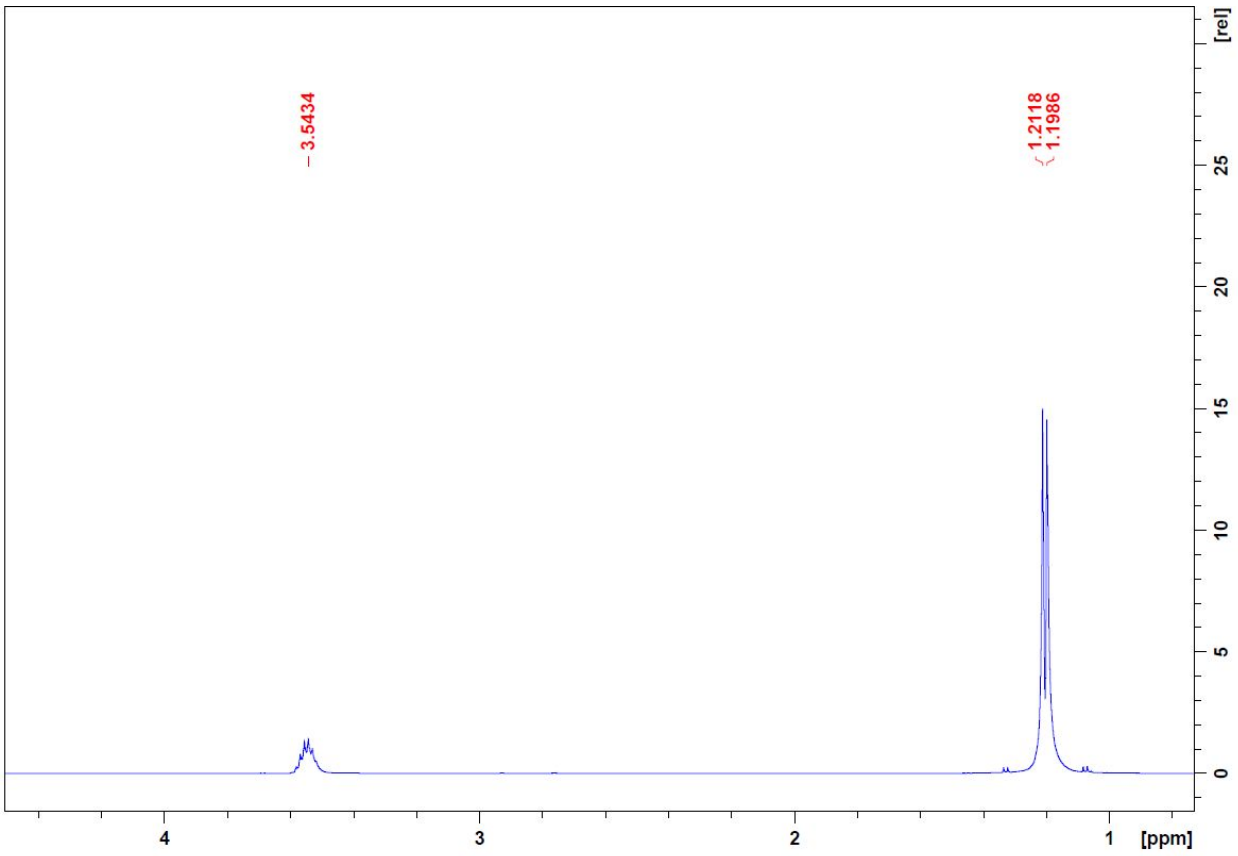

Figure S112. 1D ^{1}H NMR spectrum of DIC in DMF-d_7.

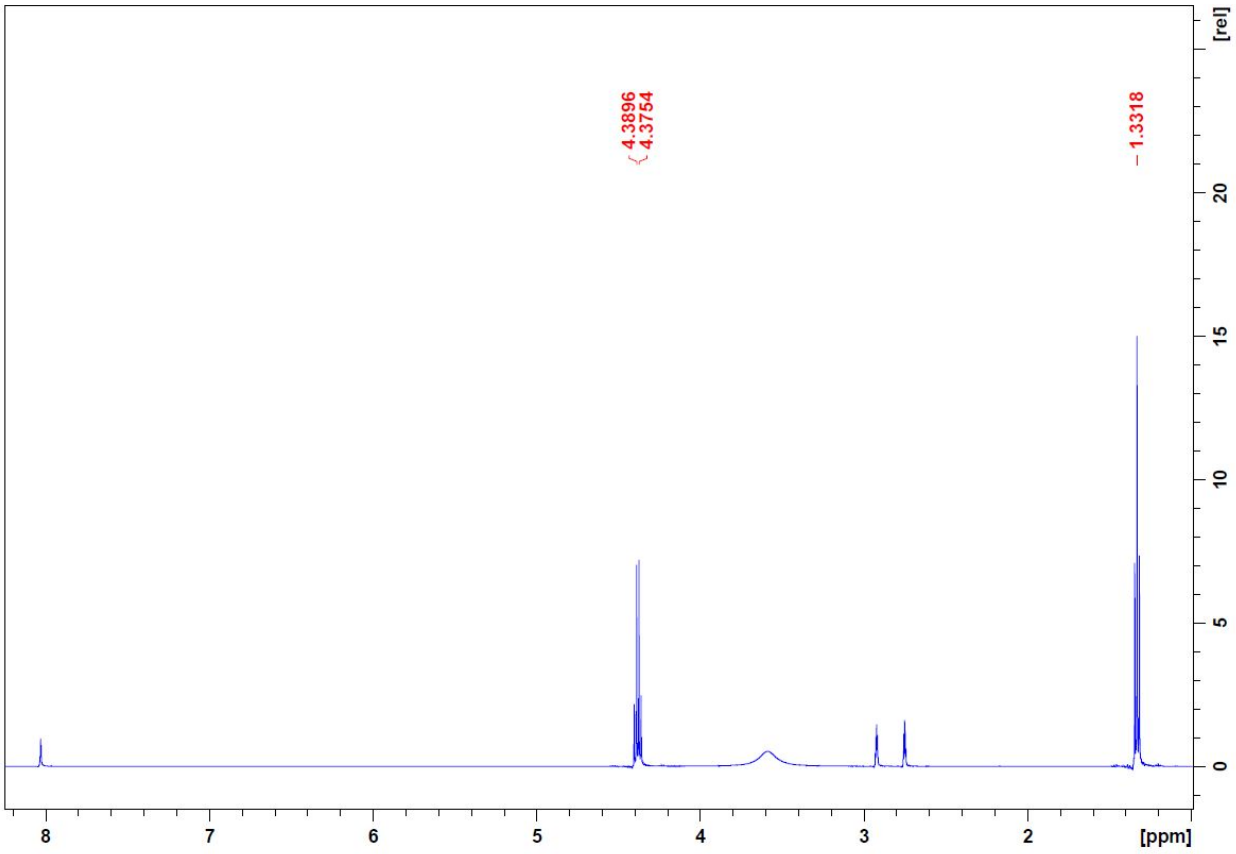

Figure S113. 1D ^{1}H NMR spectrum of Oxyma in DMF-d_7.

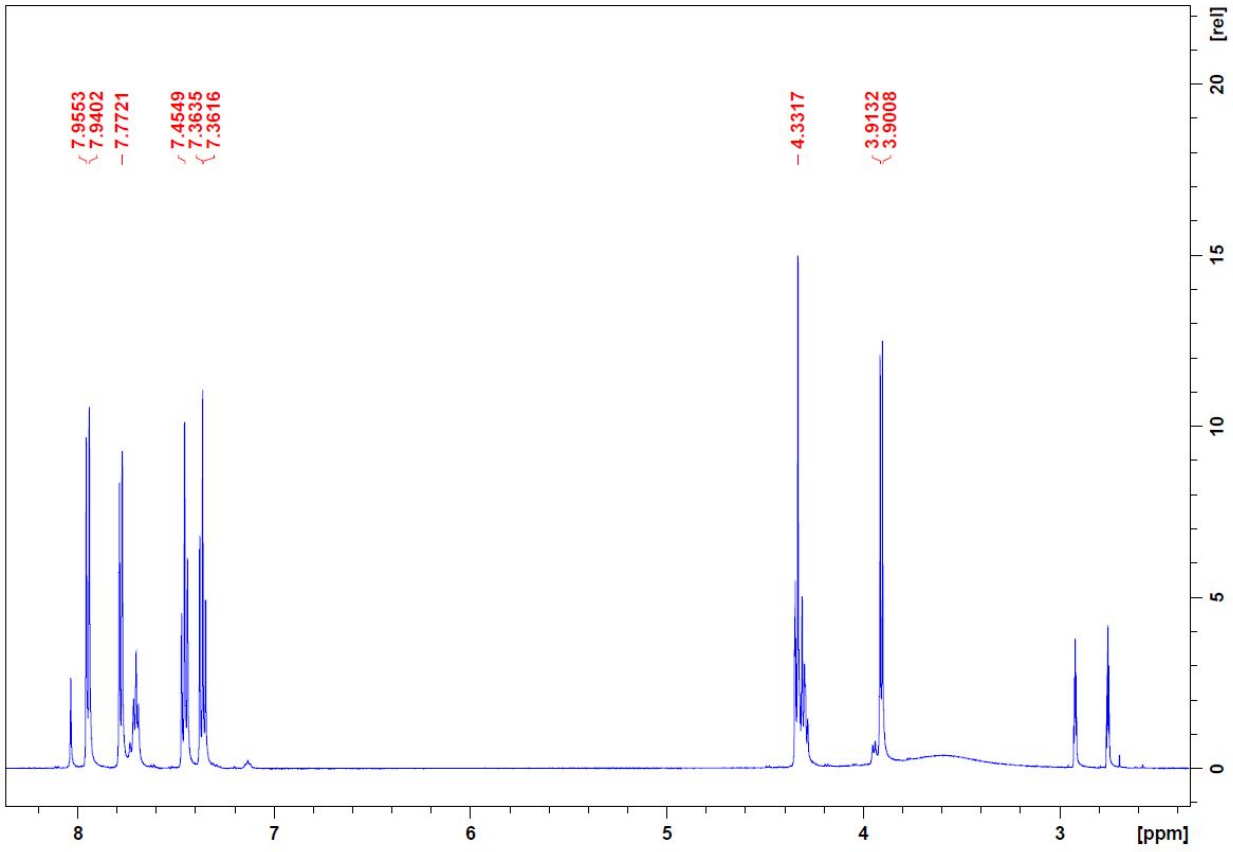

Figure S114. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH in DMF-d_7.

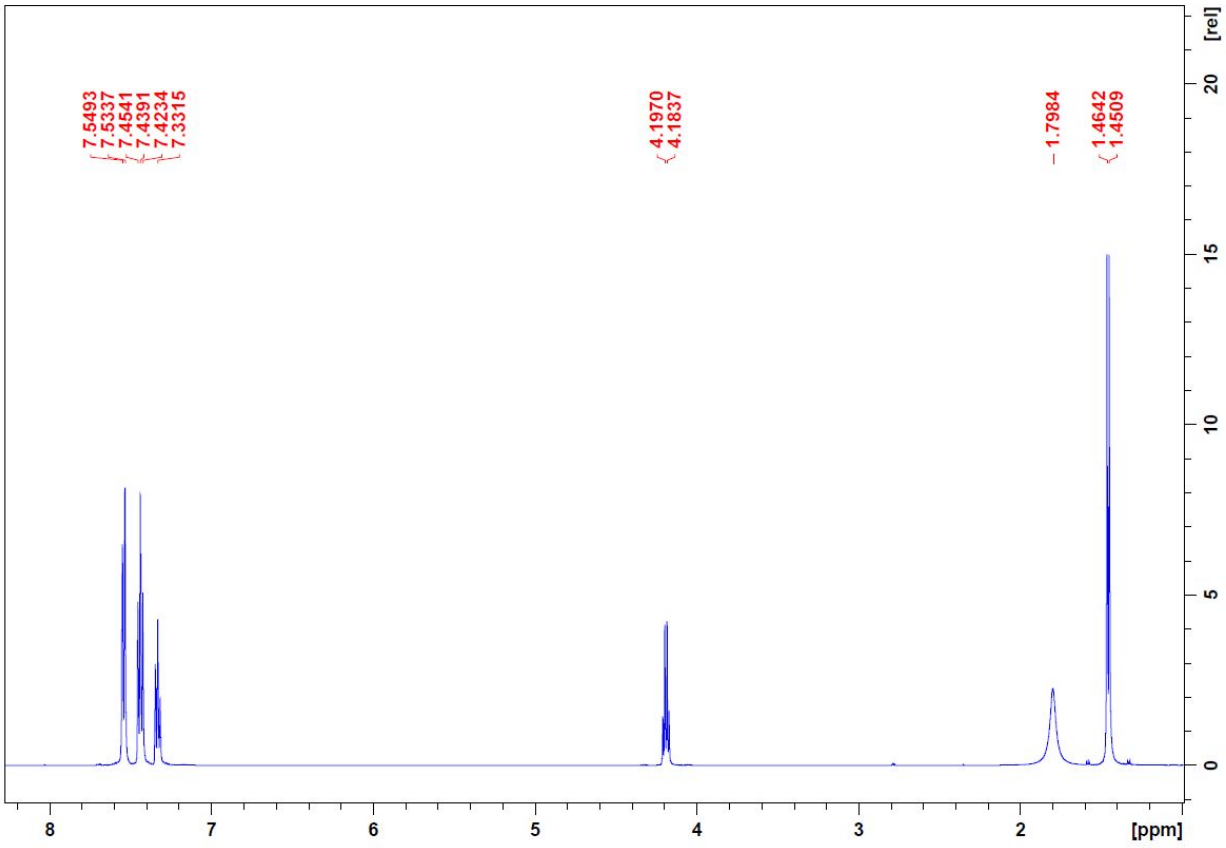

Figure S115. 1D ^{1}H NMR spectrum of (S)-(-)-1-phenylethylamine in DMF-d_7.

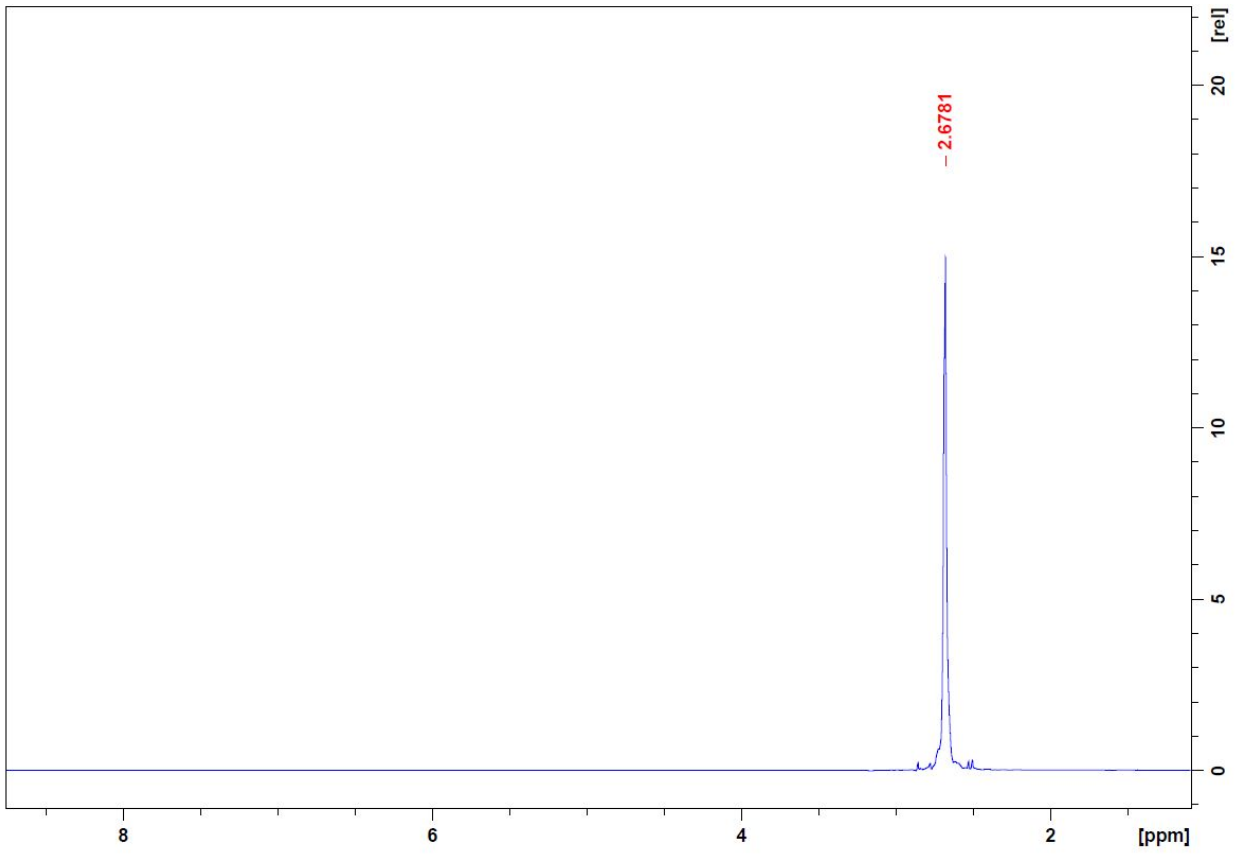

Figure S116. 1D ^{1}H NMR spectrum of DMTS in DMF-d_7.

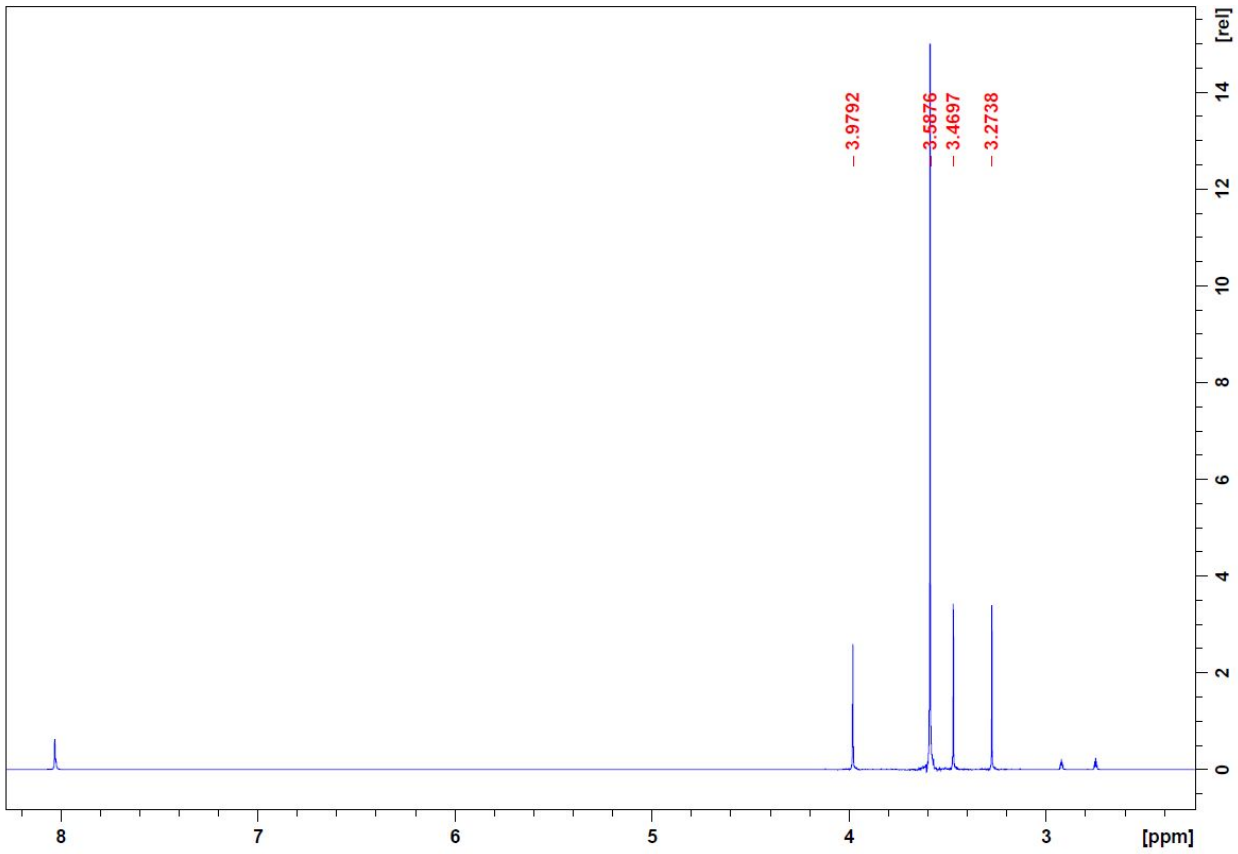

Figure S117. 1D ^{1}H NMR spectrum of caffeine in DMF-d_7.

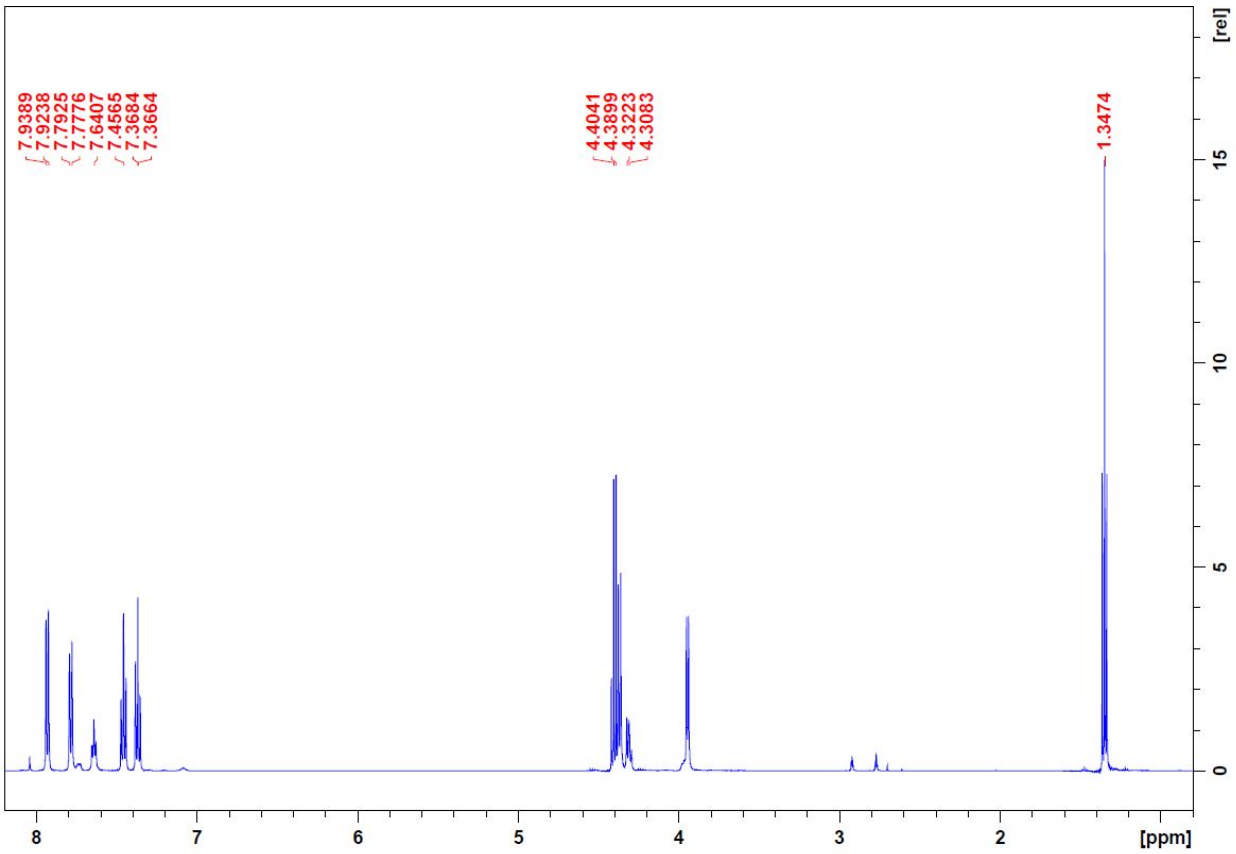

Figure S118. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH with Oxyma in DMF-d_7.

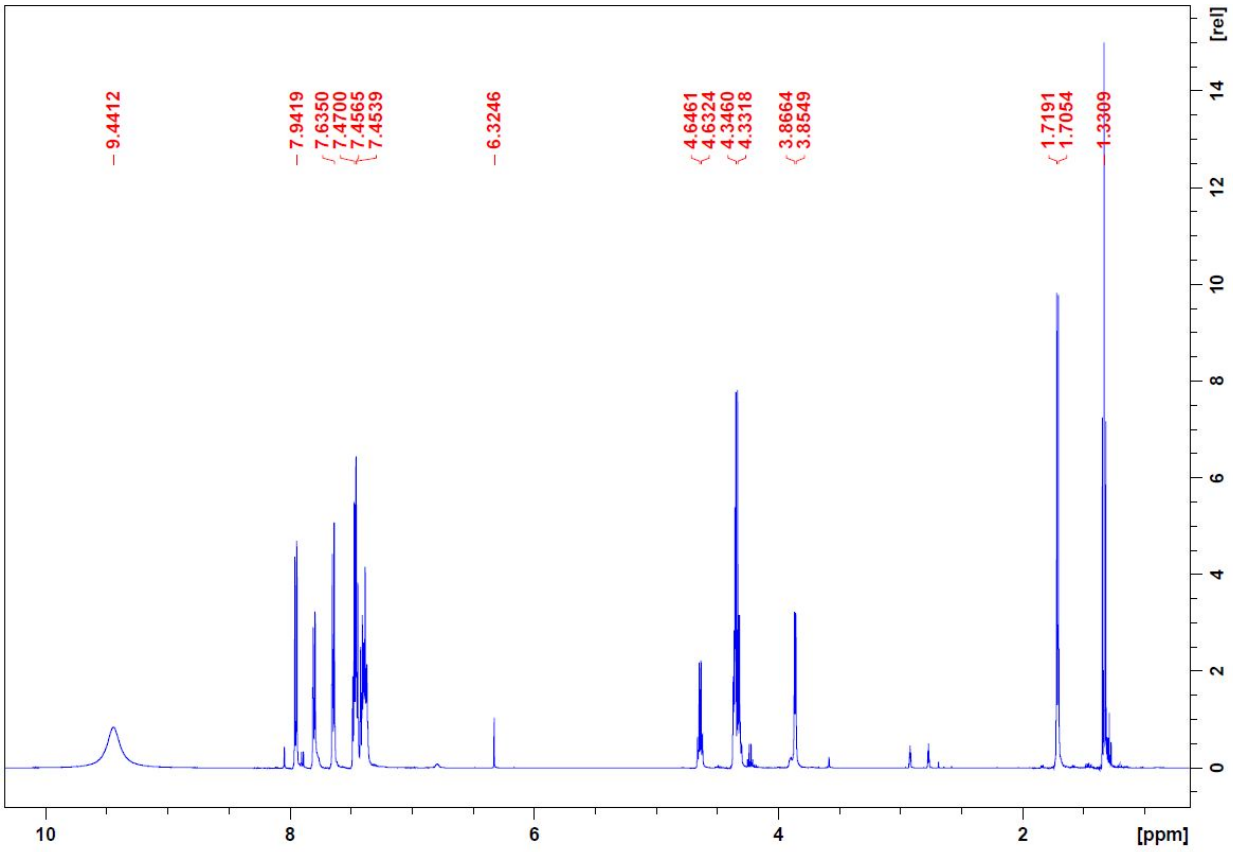

Figure S119. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH with Oxyma and (S)-(-)-1-phenylethylamine in DMF-d_7.

8.1.2 Starting materials with addition of DMTS

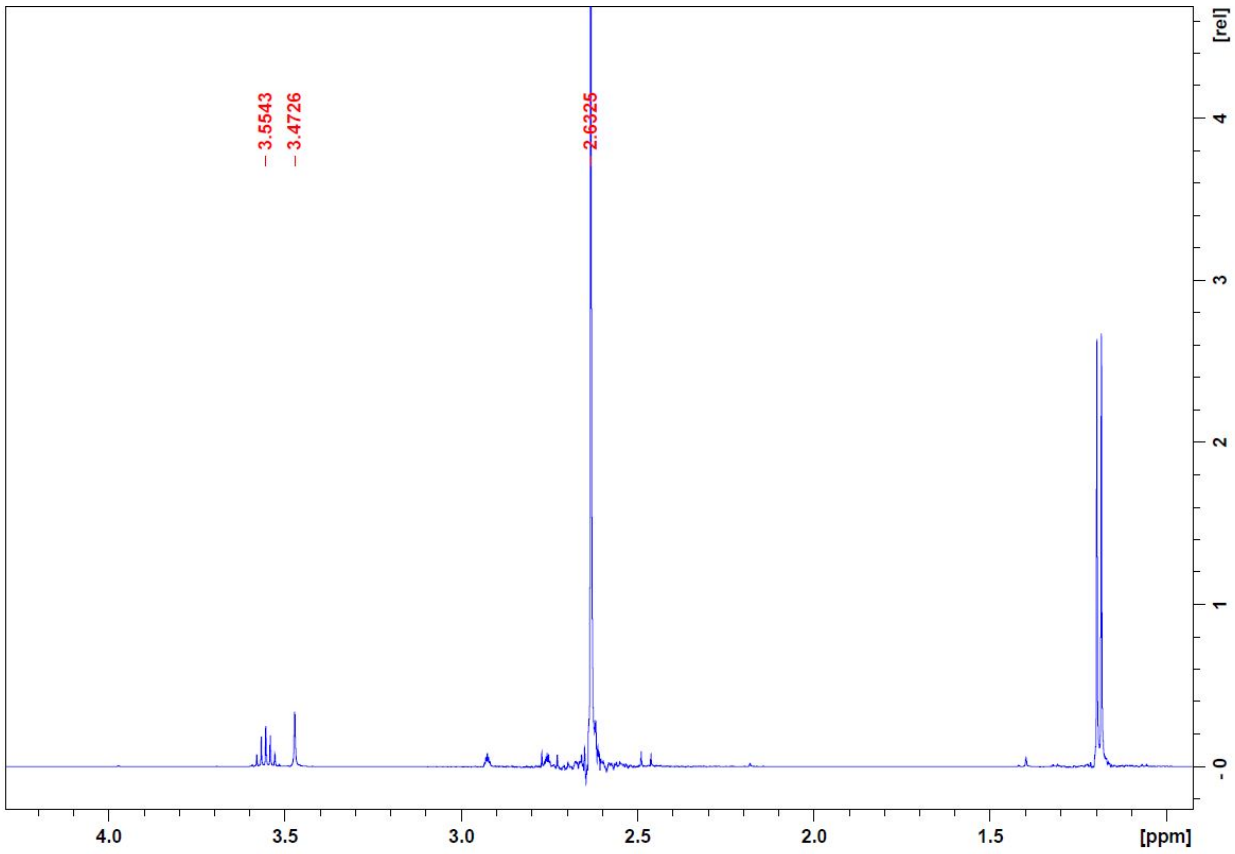

Figure S120. 1D ^{1}H NMR spectrum of DIC with 5 equiv DMTS in DMF-d_7.

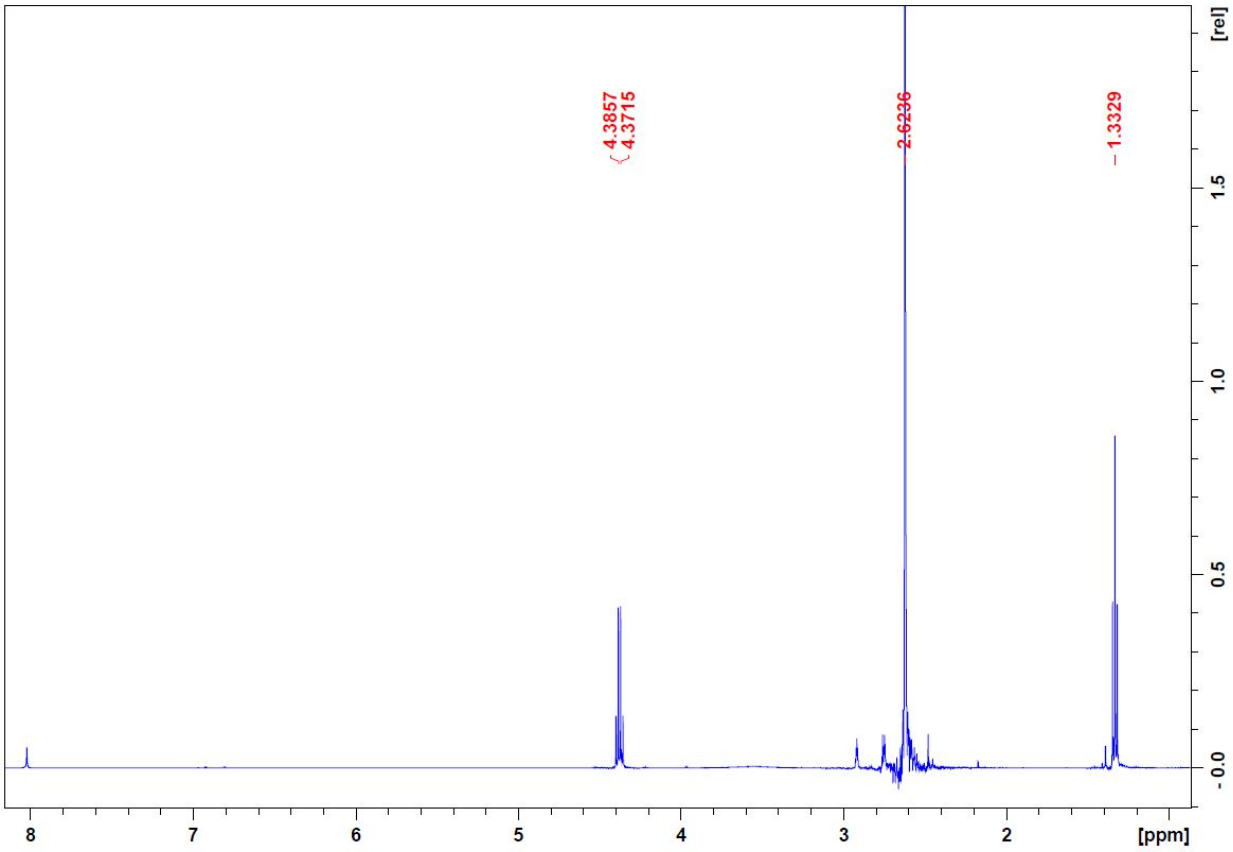

Figure S121. 1D ^{1}H NMR spectrum of Oxyma with 5 equiv DMTS in DMF-d_7.

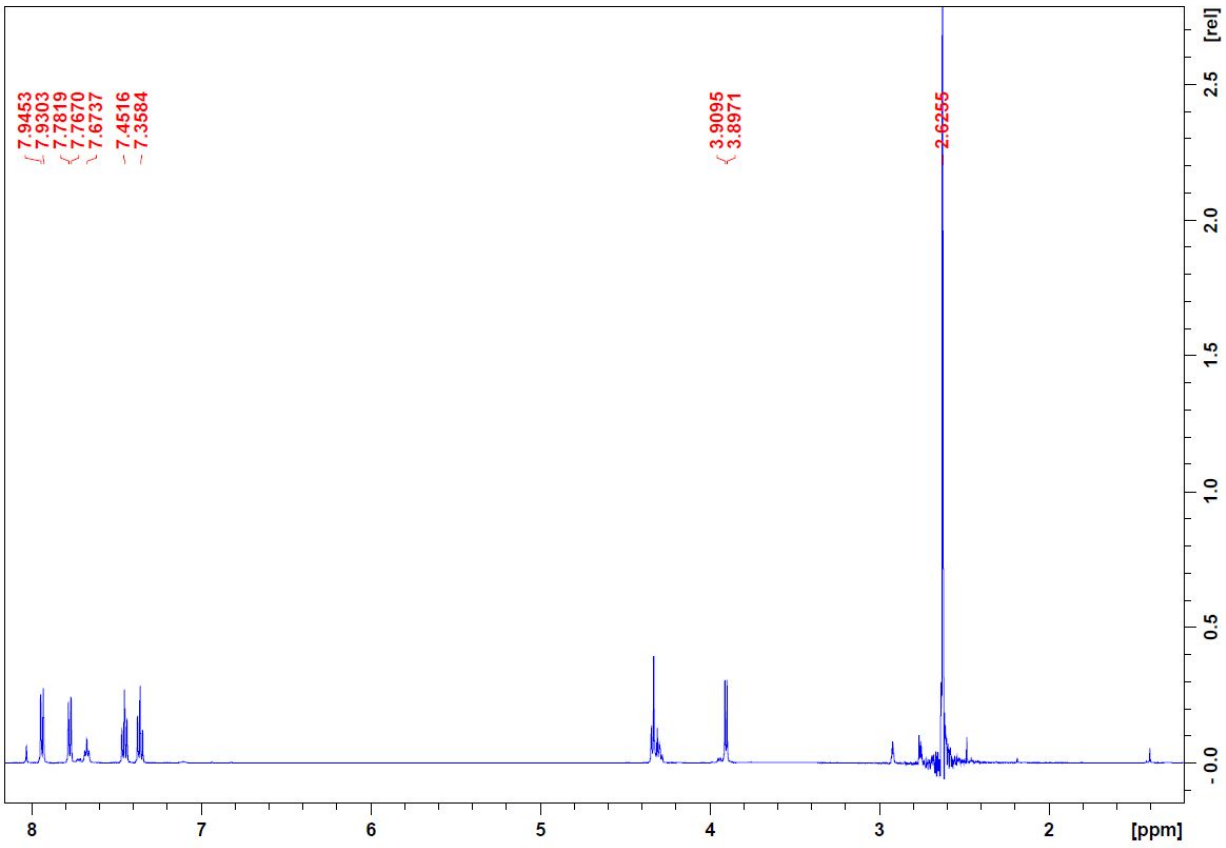

Figure S122. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH with 5 equiv DMTS in DMF-d_7.

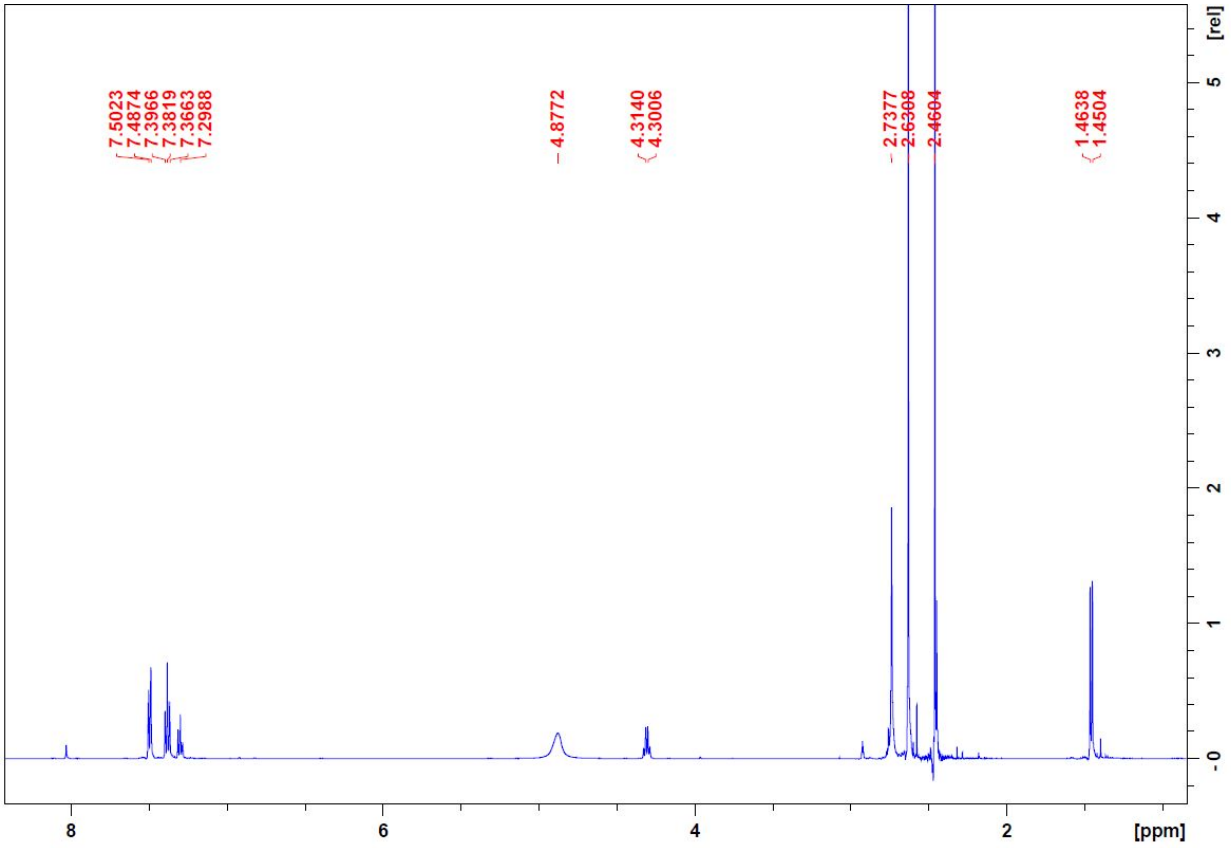

Figure S123. 1D ^{1}H NMR spectrum of (S)-(-)-1-phenylethylamine with 5 equiv DMTS in DMF-d_7.

8.2 Products

Considering that NMR was used to assess the DIC/Oxyma mediated reactions herein, ^{1}H NMR spectra of the different products was required.

All NMR spectra in section 8.2 of this SI were recorded on a 400 MHz Brucker instrument.

Sample of **2**[3] was obtained as follows:

Oxyma (142.1 mg, 1 mmol, 1 equiv) was dissolved in 2 mL MeCN. DIC (156.6 μL, 1 mmol, 1 equiv) was added to the solution. The resulting mixture was stirred for 16 h at rt and concentrated under vacuum. The residue was purified by normal phase chromatography using silica gel as stationary phase employing Cyclohexane/EtOAc (10:1) → EtOAc to elute the product. 8.9 mg of a colorless oil was obtained.

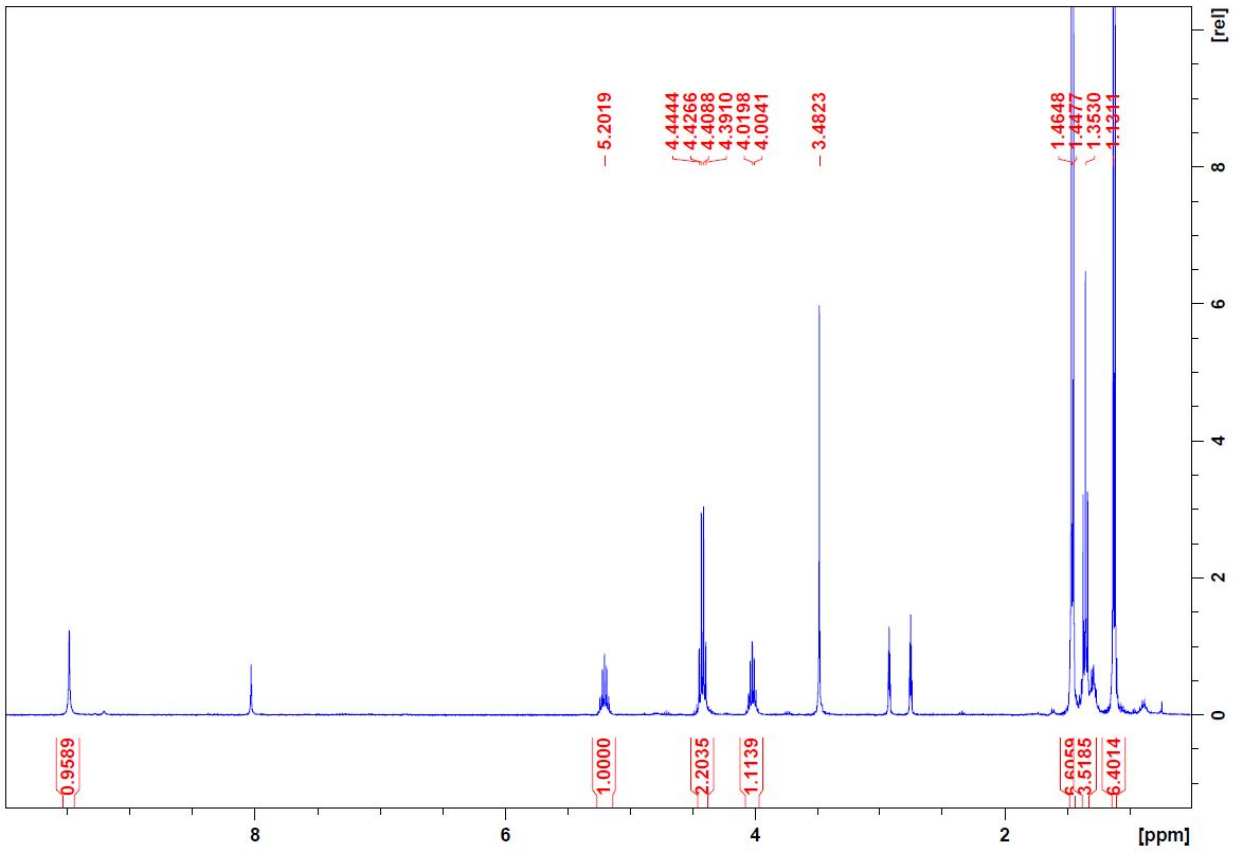

Figure S124. 1D ^{1}H NMR spectrum of **2** in DMF-d_7.

The ^{1}H NMR spectra of **2** and **3** were in keeping with those described by Mc Farland et al.[3]

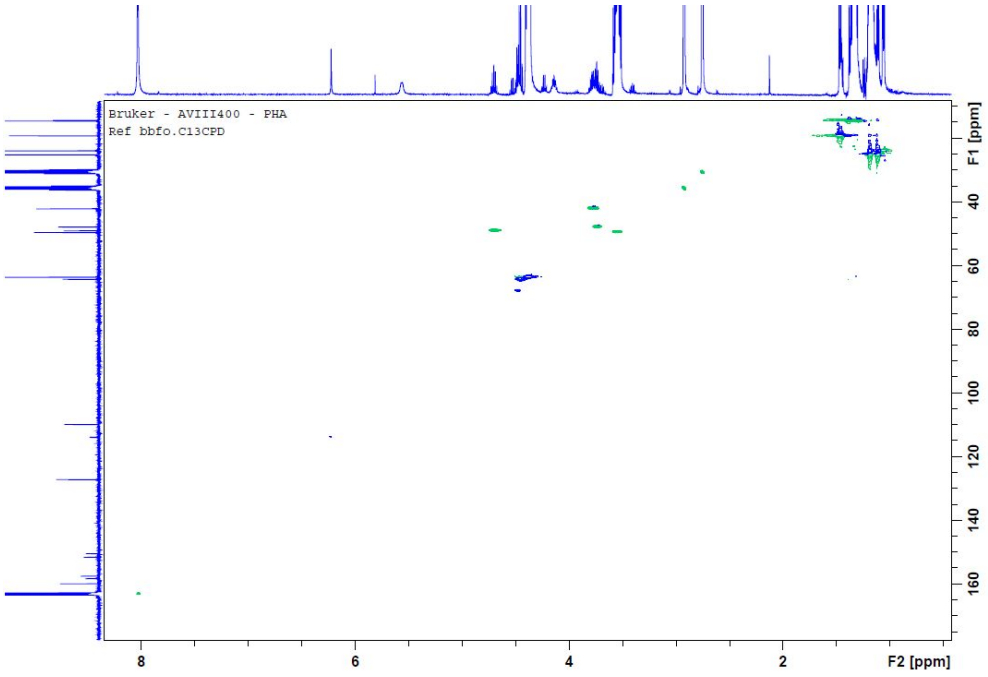

Figure S125. 2D HSQC NMR spectrum of DIC/Oxyma reaction in DMF-d_7: evidence of HCN presence in the solution, a correlation of H and C resonances in ^{1}H and ^{13}C was observed.

HCN. ^{1}H NMR (400 MHz, DMF-d_7): 6.21 ppm. ^{13}C NMR (400 MHz, DMF-d_7): 113.97 ppm.

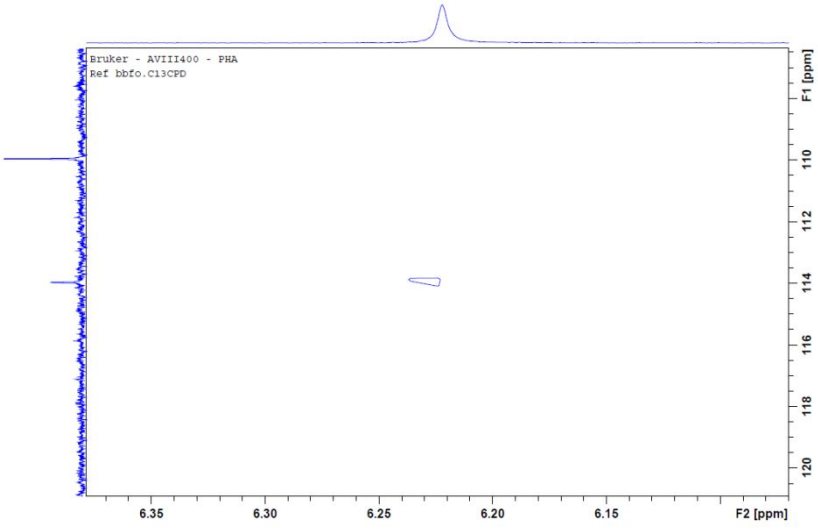

Figure S126. 2D HSQC NMR spectrum of DIC/Oxyma reaction in DMF-d_7 (zoom-in).

8.3 Reaction of Fmoc-Gly-OH, Oxyma and DIC in DMF-d_7 with and without DMTS

In this section, NMR assessment of HCN formation during the reaction of Fmoc-Gly-OH, Oxyma and DIC in DMF-d_7 with and without DMTS is delineated. The results pertaining to the reaction of Fmoc-Gly-OH, Oxyma and DIC without DMTS are described in section 8.3.1 and the results related to this reaction performed in the presence of DMTS are summarized in section 8.3.2. A summary of the results of both experiments is detailed in section 8.3.3.

8.3.1 Assessment of HCN formation during activation of Fmoc-Gly-OH using Oxyma/DIC in 0.1 M DMF-d_7

General Procedure for Fmoc-Gly-OH/Oxyma/DIC (1:1:1) reaction.

A stock solution was prepared by dissolving Oxyma (10.0 mg, 0.070 mmol, 1.03 equiv), Fmoc-Gly-OH (20.1 mg, 0.068 mmol, 1.00 equiv) and caffeine (8.2 mg, 0.042 mmol, 0.62 equiv) in 680 µL of DMF-d_7 and the solution was mixed by using an ultrasound bath until all starting materials were dissolved after which DIC (10.65 µL, 0.068 mmol, 1 equiv) was added to the stock solution. 2 x 170 µL (25% v/v of the solution i.e. ~ 0.017 mmol based on Fmoc-Gly-OH) of this stock solution was taken out and transferred to a separate reaction vessel. To this vessel, 5 equiv of DMTS (8.96 µL, 0.085 mmol, 5 equiv) was added and the resulting mixture was transferred to a 3 mm NMR tube. Resulting Fmoc-Gly-OH/Oxyma/DIC DMF-d_7 mixtures with and without DMTS were analysed by ^{1}H NMR at 1 h, 5 h, 10 h and 16 h and the contents of HCN at these time points were determined.

Protocol for the determination of HCN content.

1) Caffeine (2.05 mg, 0.0105 mmol, 0.155 equiv) present in each NMR tube was the reference standard, the singlet at 3.47 ppm (Figure S117) corresponds to 3 protons (CH_3).

2) The integration of the singlet at 6.23 ppm, which corresponds to the HCN proton, would be 1 if the amount of substance was 0.0105 mmol.

3) The integration of peaks in 1) and 2) enabled us to determine the amount of HCN formed from which the concentration of HCN was calculated.

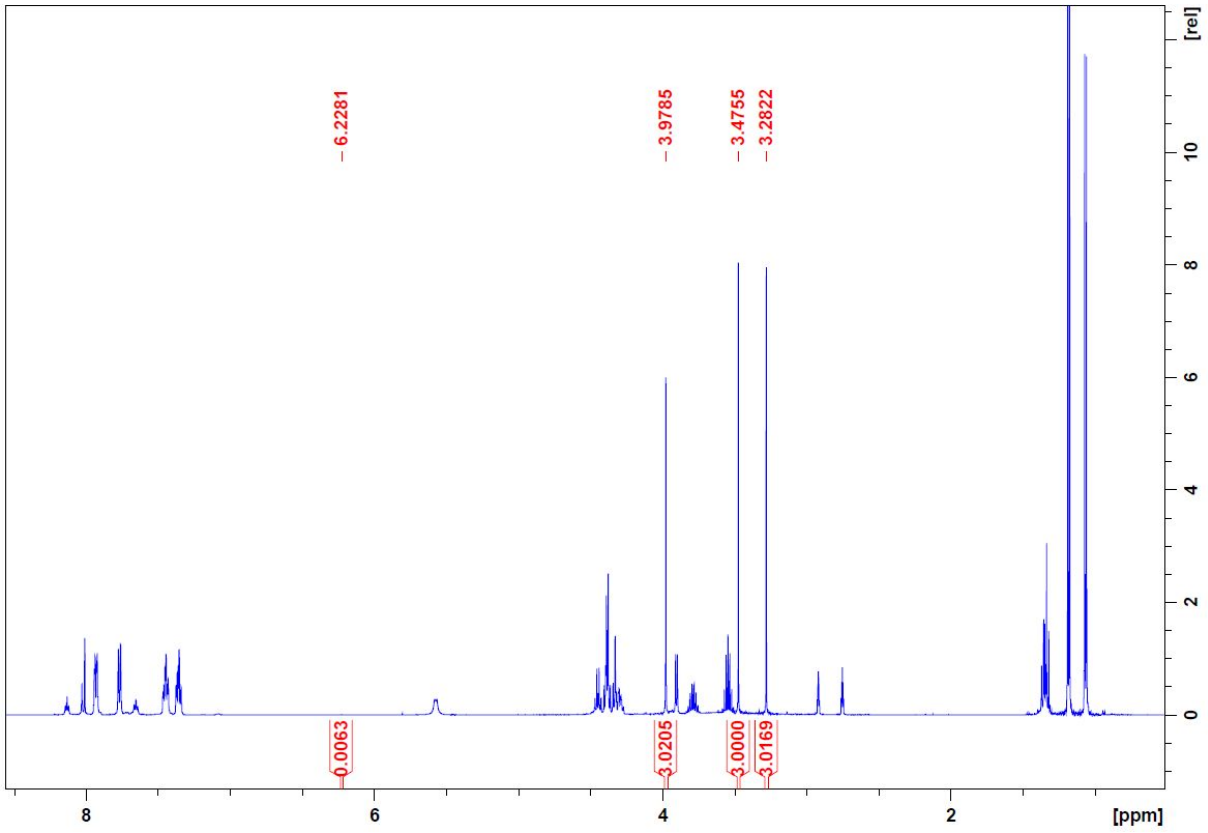

Figure S127. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction at 0.1M after 1 h in DMF-d_7 (full spectrum).

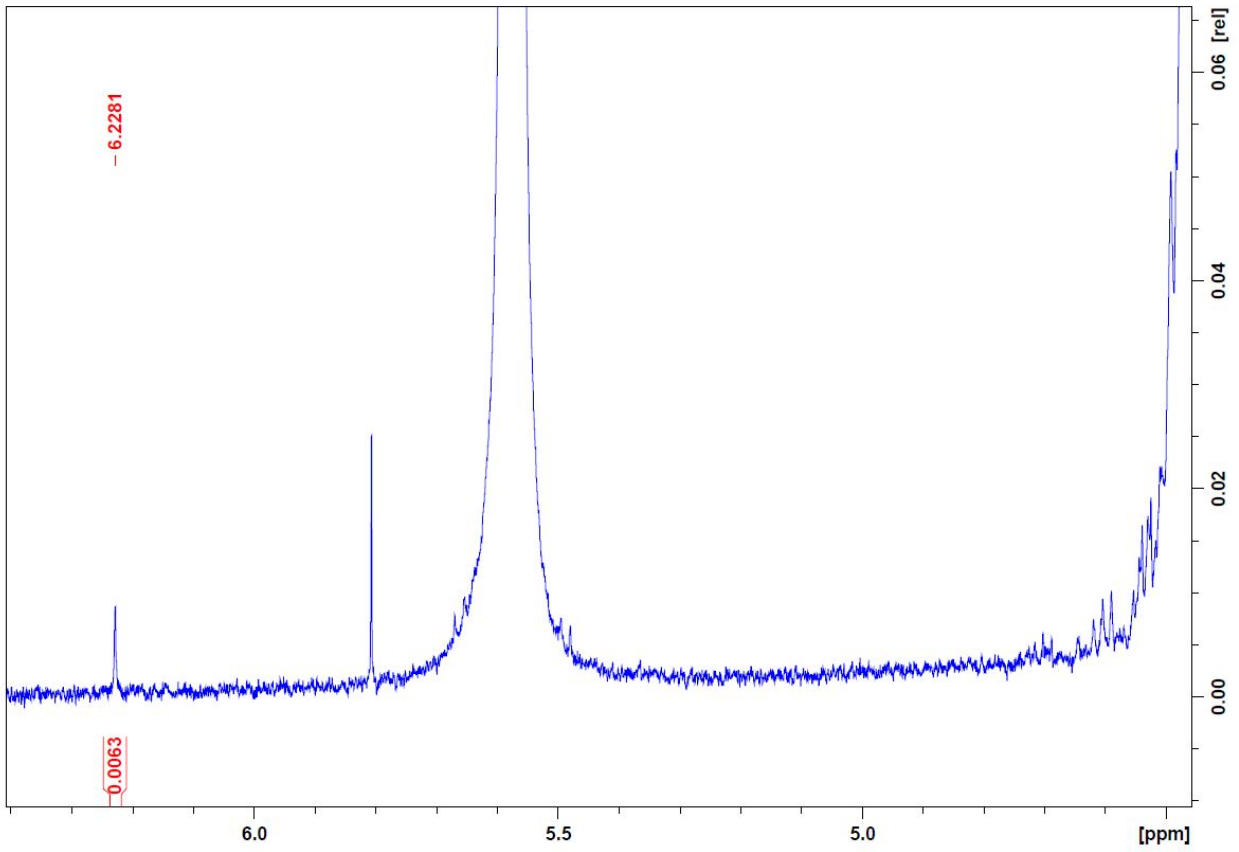

Figure S128. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction at 0.1M after 1 h in DMF-d_7 (zoom-in).

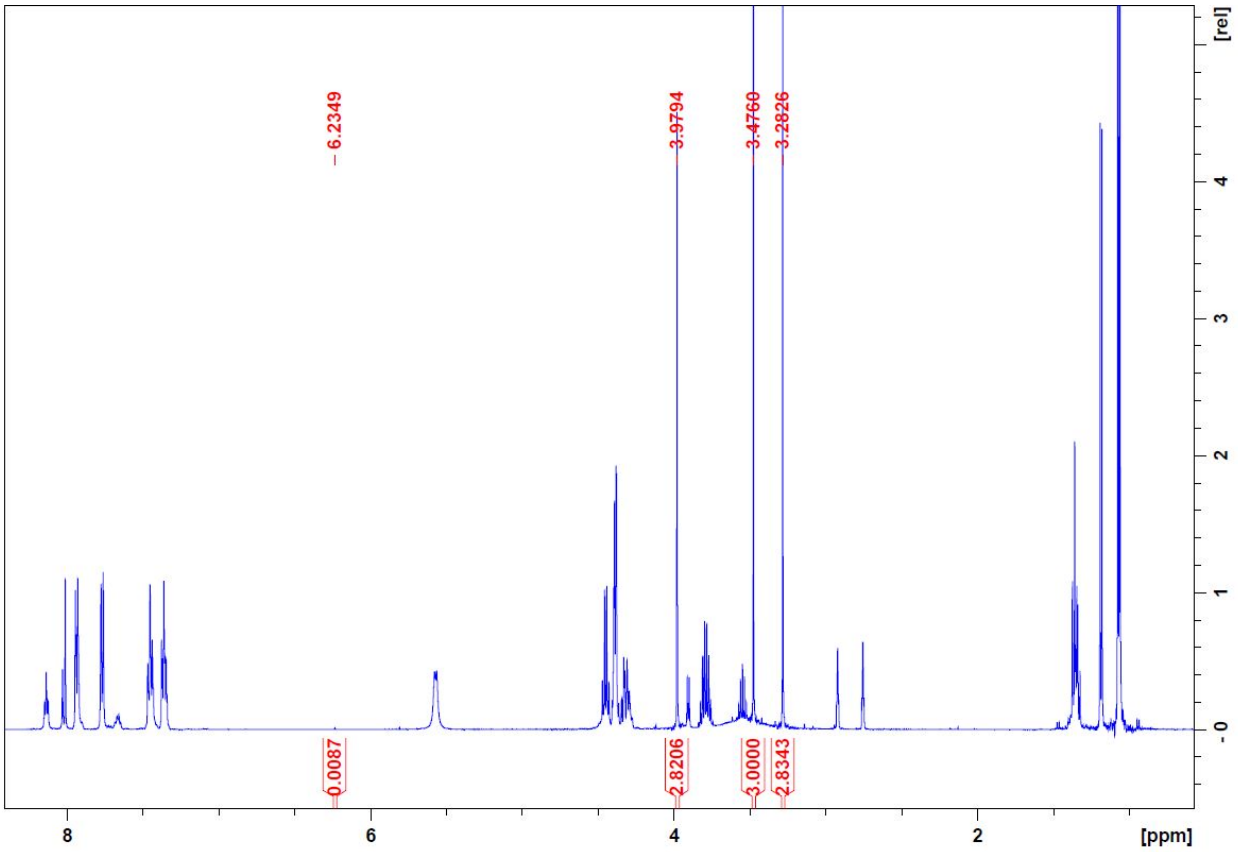

Figure S129. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction at 0.1M after 5 h in DMF-d_7 (full spectrum).

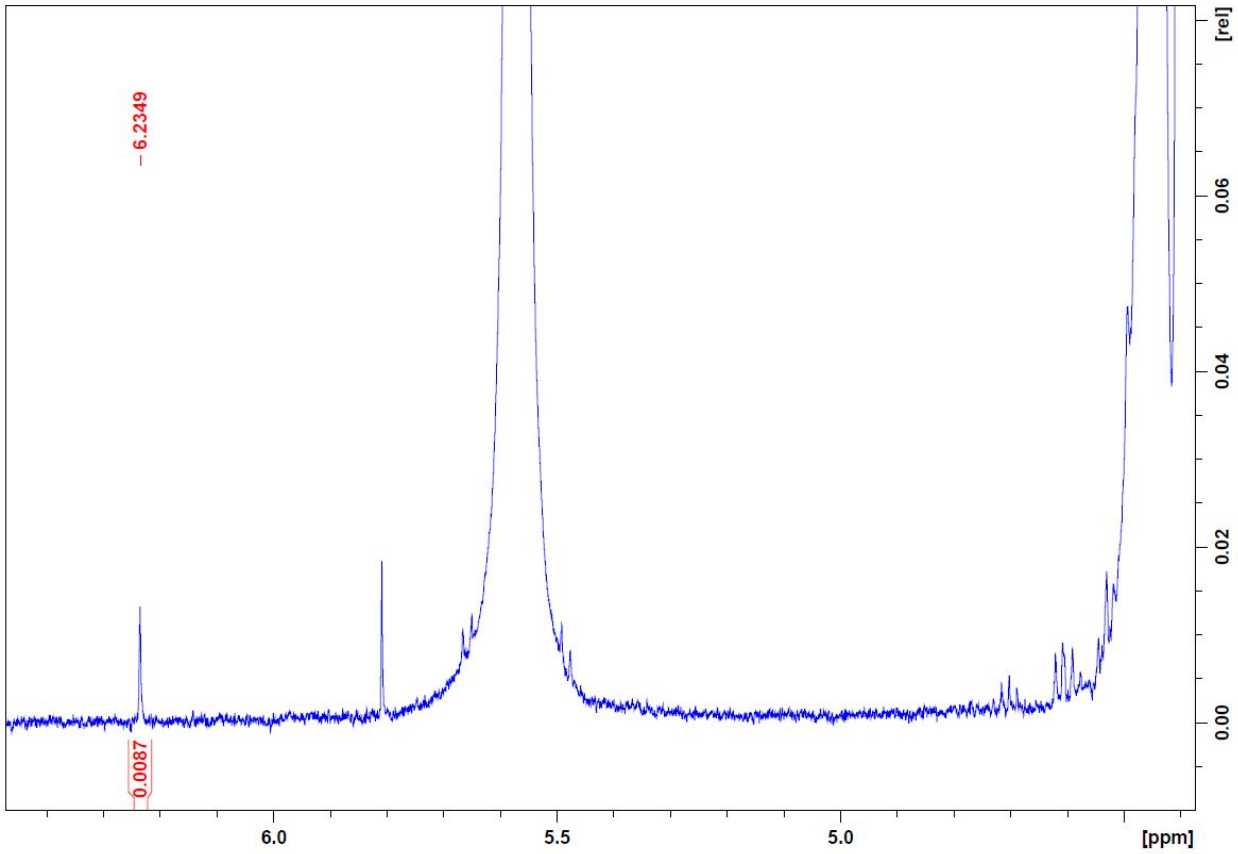

Figure S130. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction at 0.1M after 5 h in DMF-d_7 (zoom-in).

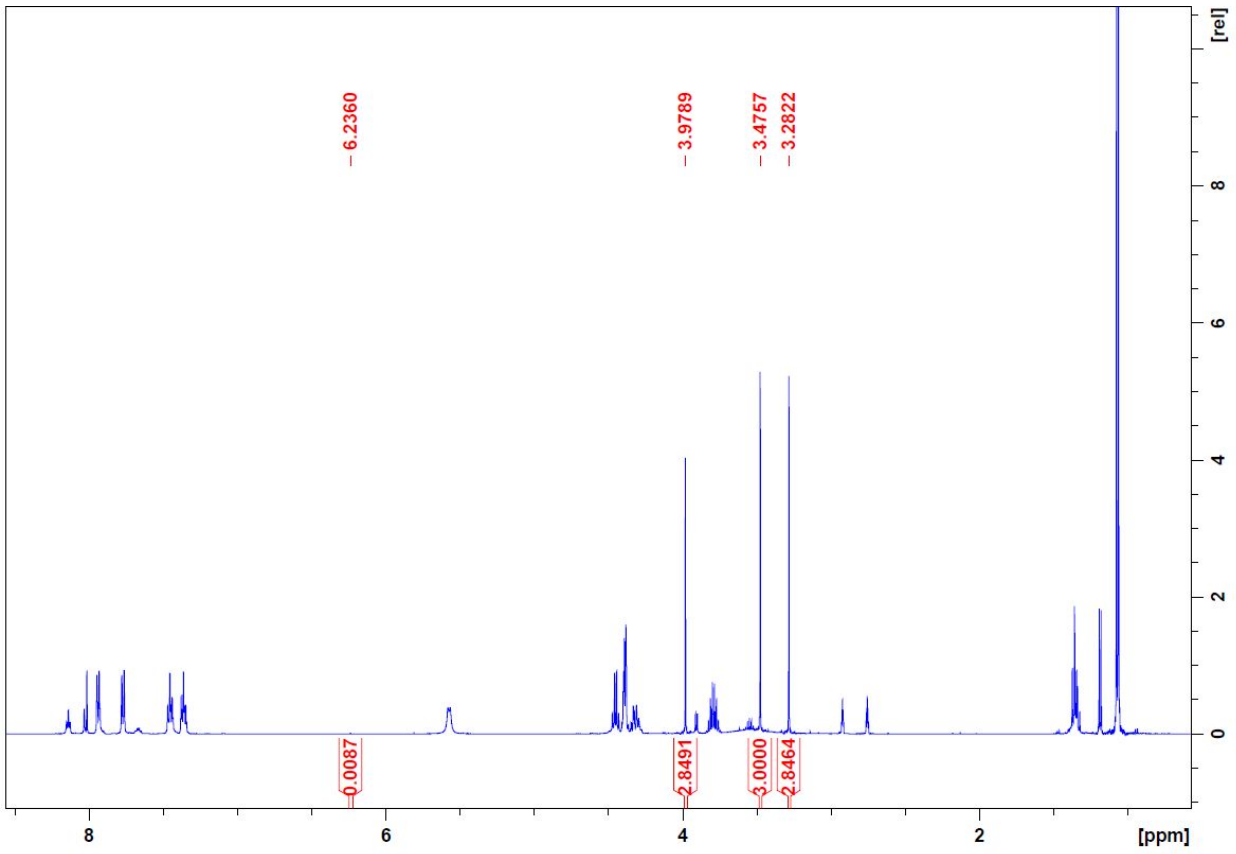

Figure S131. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction at 0.1M after 10 h in DMF-d_7 (full spectrum).

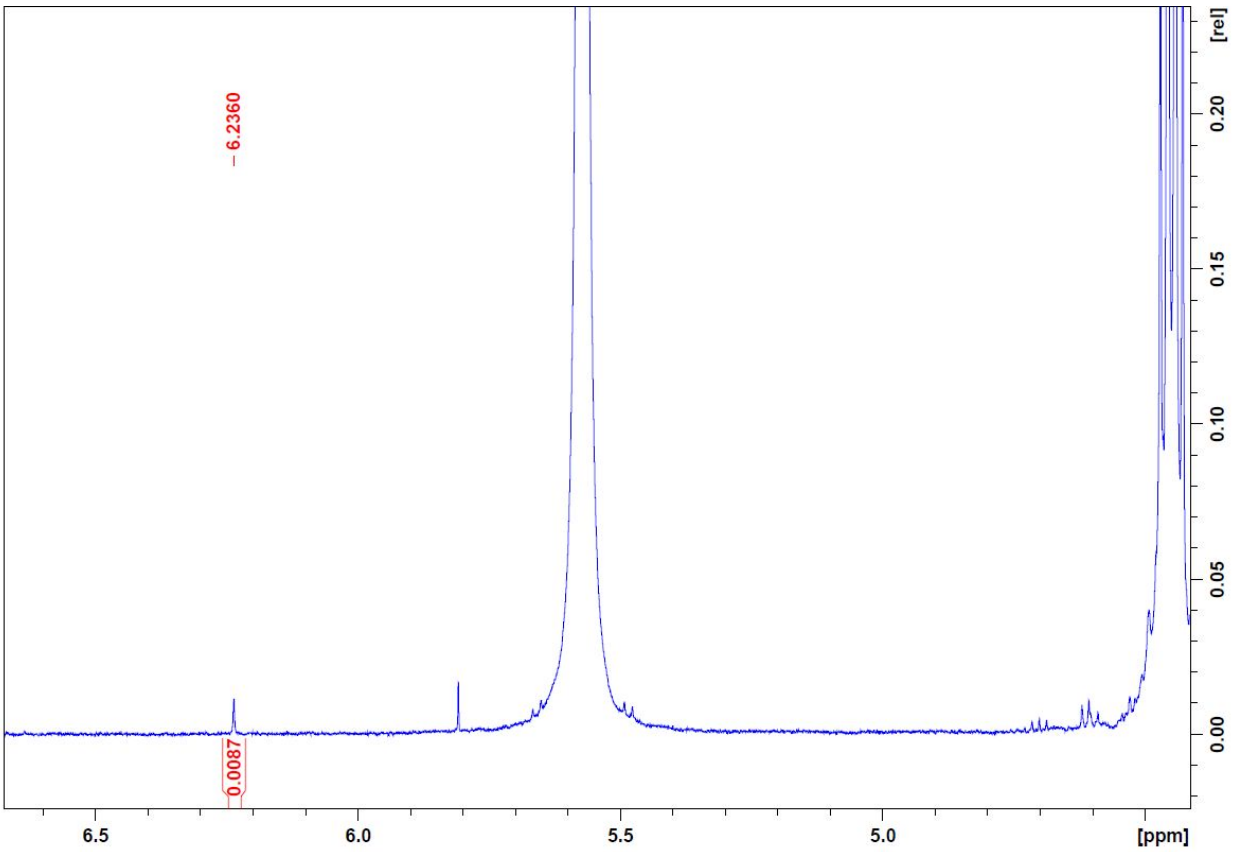

Figure S132. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction at 0.1M after 10 h in DMF-d_7 (zoom-in).

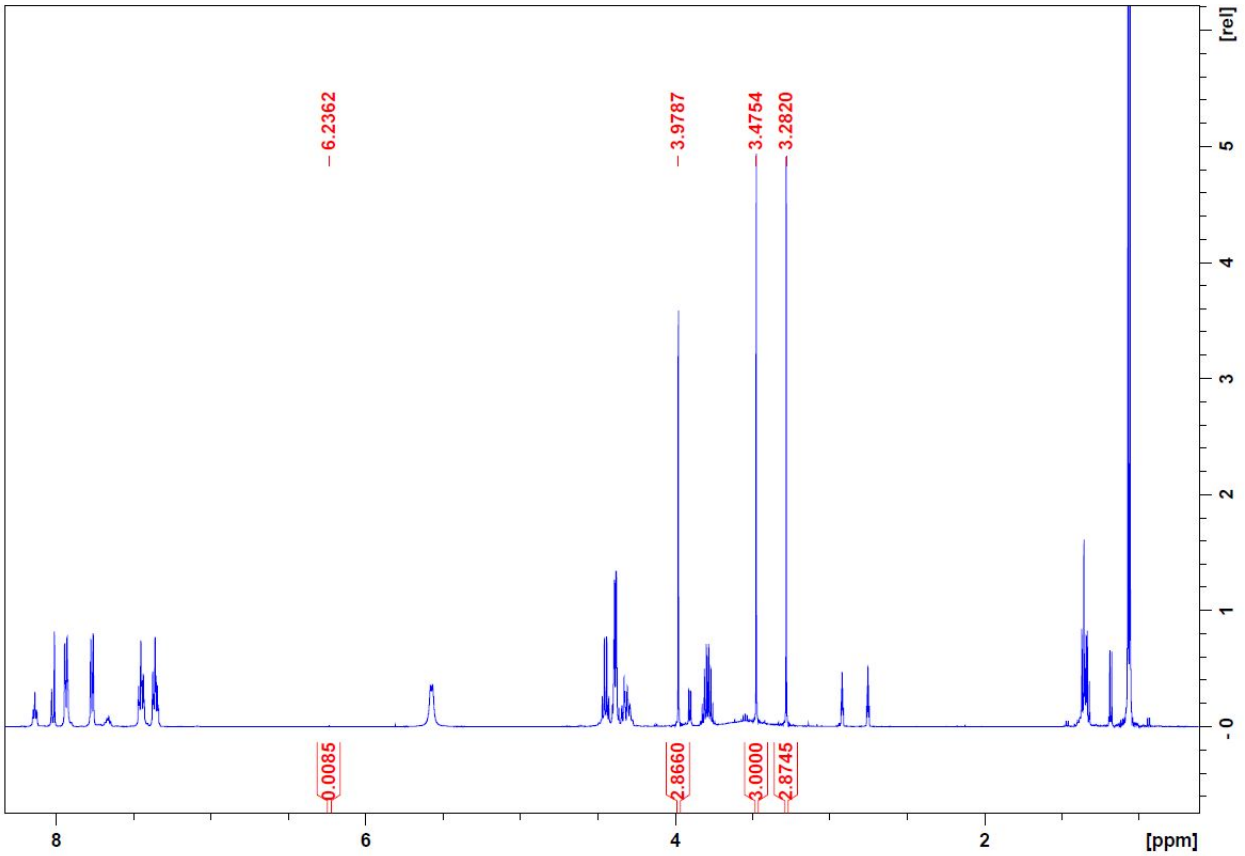

Figure S133. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction at 0.1M after 16 h in DMF-d_7 (full spectrum).

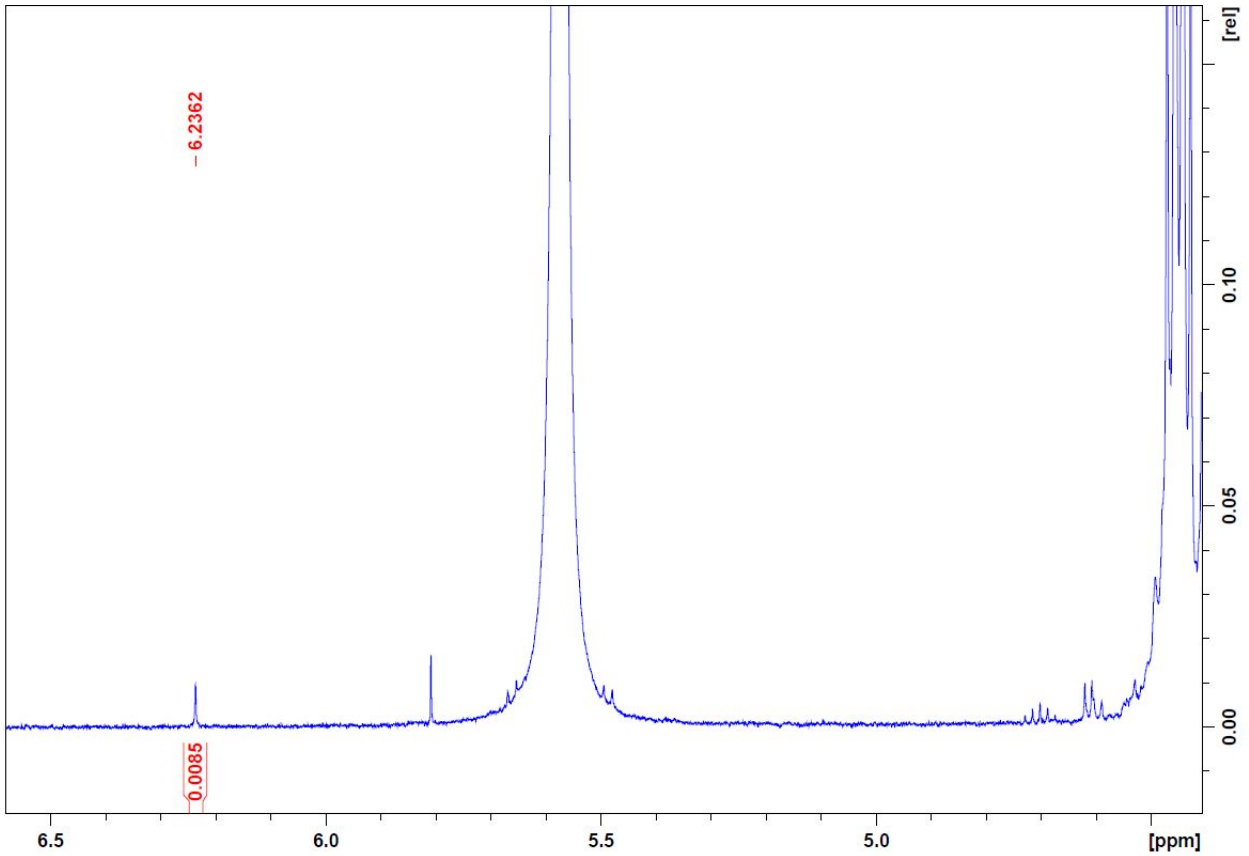

Figure S134. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction at 0.1M after 16 h in DMF-d_7 (zoom-in).

8.3.2 Assessment of HCN formation during activation of Fmoc-Gly-OH using Oxyma/DIC with 5 equiv DMTS in 0.1 M DMF-d_7

The general procedure for the reactions of Fmoc-Gly-OH activation in DMF-d_7 as described in the section 8.3.1 of this SI was followed.

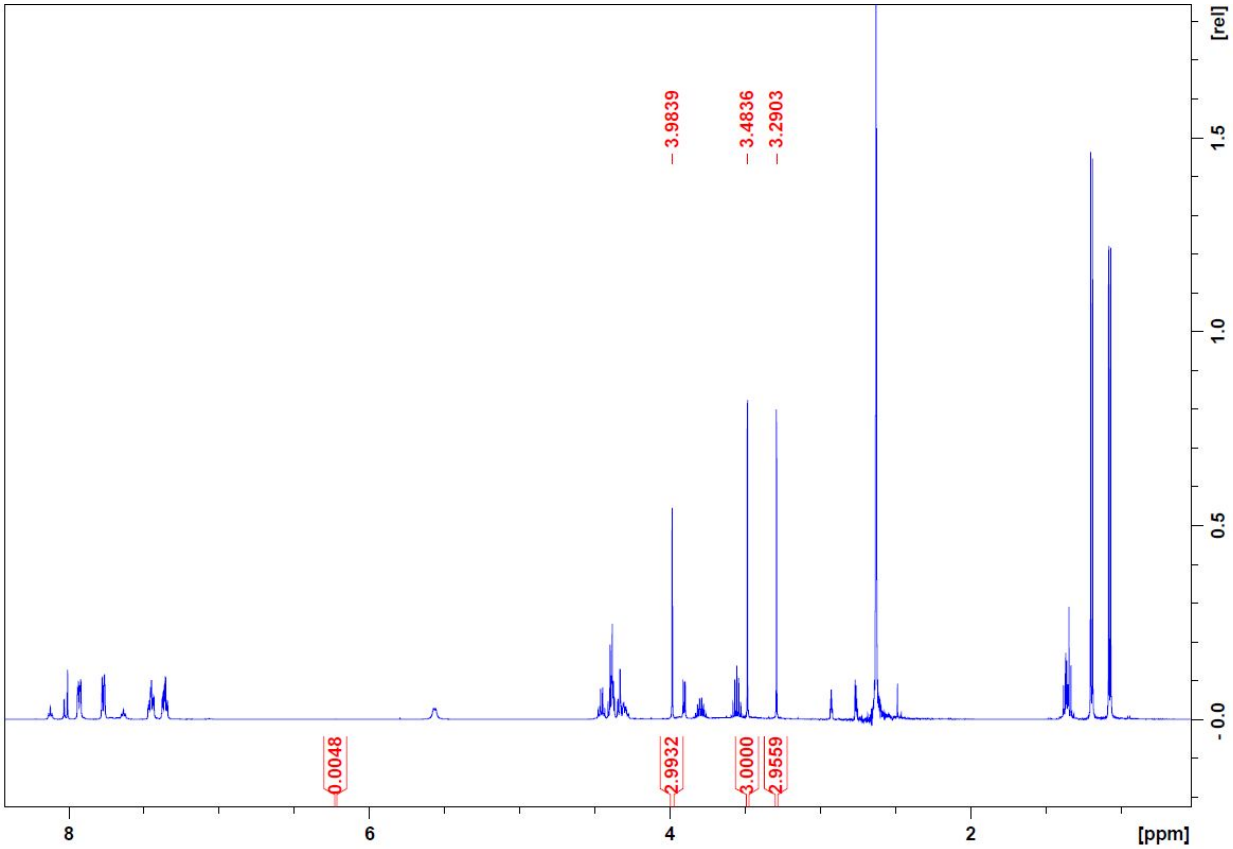

Figure S135. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction with 5 equiv DMTS at 0.1M after 1 h in DMF-d_7 (full spectrum).

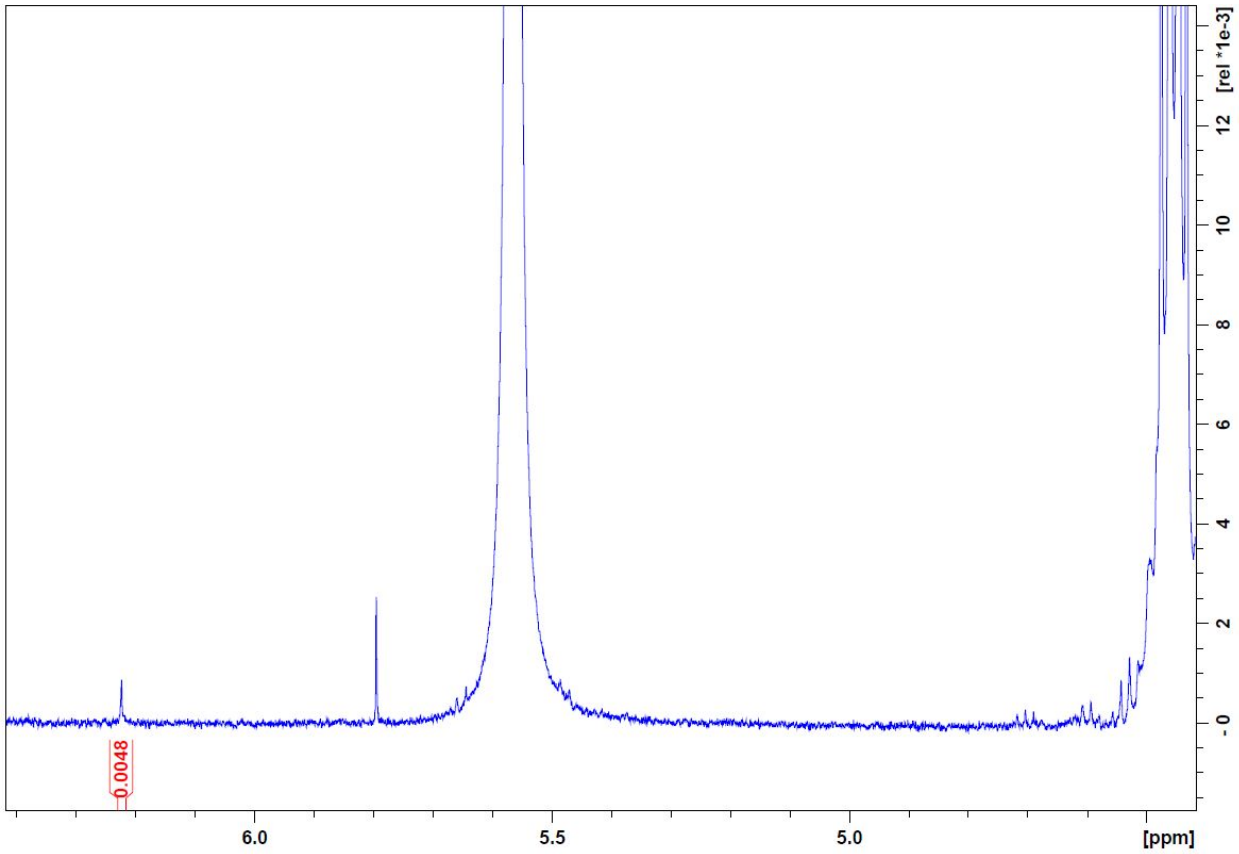

Figure S136. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction with 5 equiv DMTS at 0.1M after 1 h in DMF-d_7 (zoom-in).

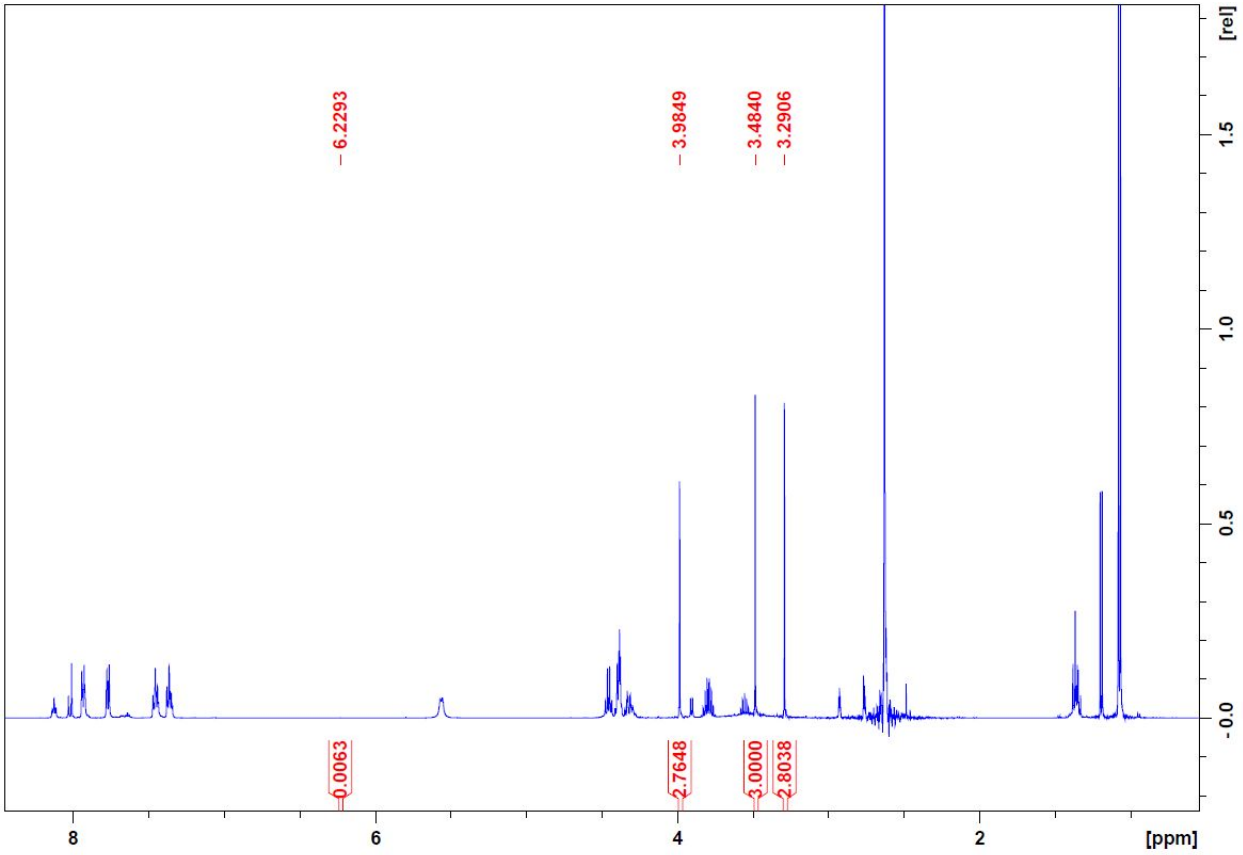

Figure S137. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction with 5 equiv DMTS at 0.1M after 5 h in DMF-d_7 (full spectrum).

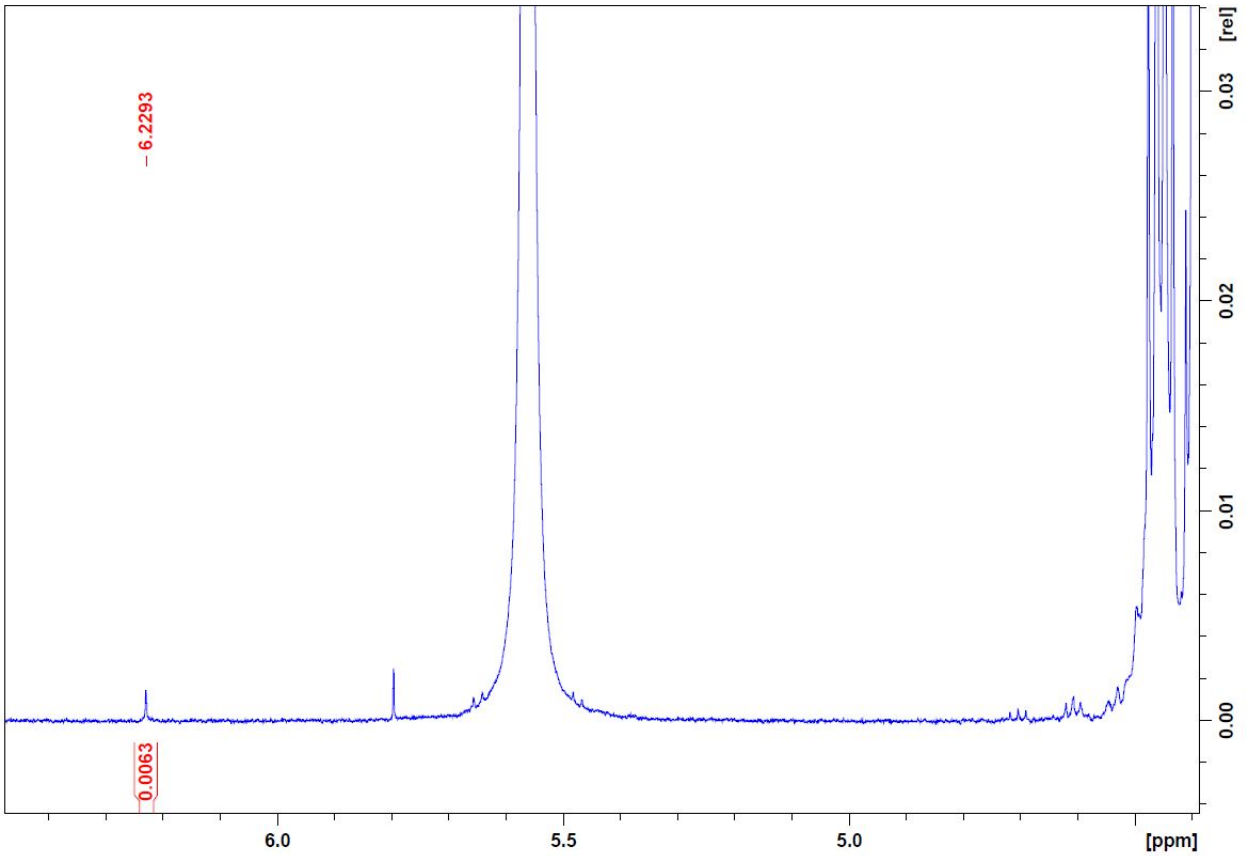

Figure S138. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction with 5 equiv DMTS at 0.1M after 5 h in DMF-d_7 (zoom-in).

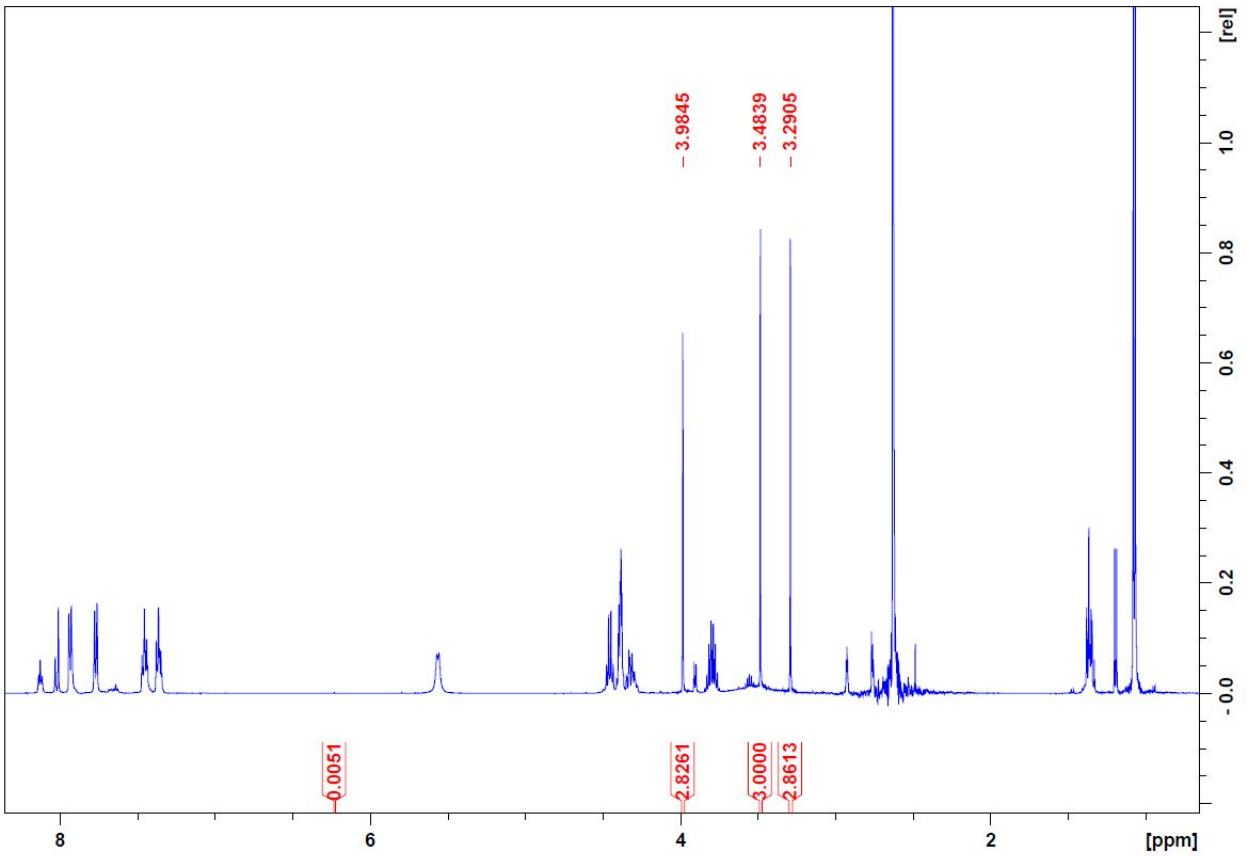

Figure S139. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction with 5 equiv DMTS at 0.1M after 10 h in DMF-d_7 (full spectrum).

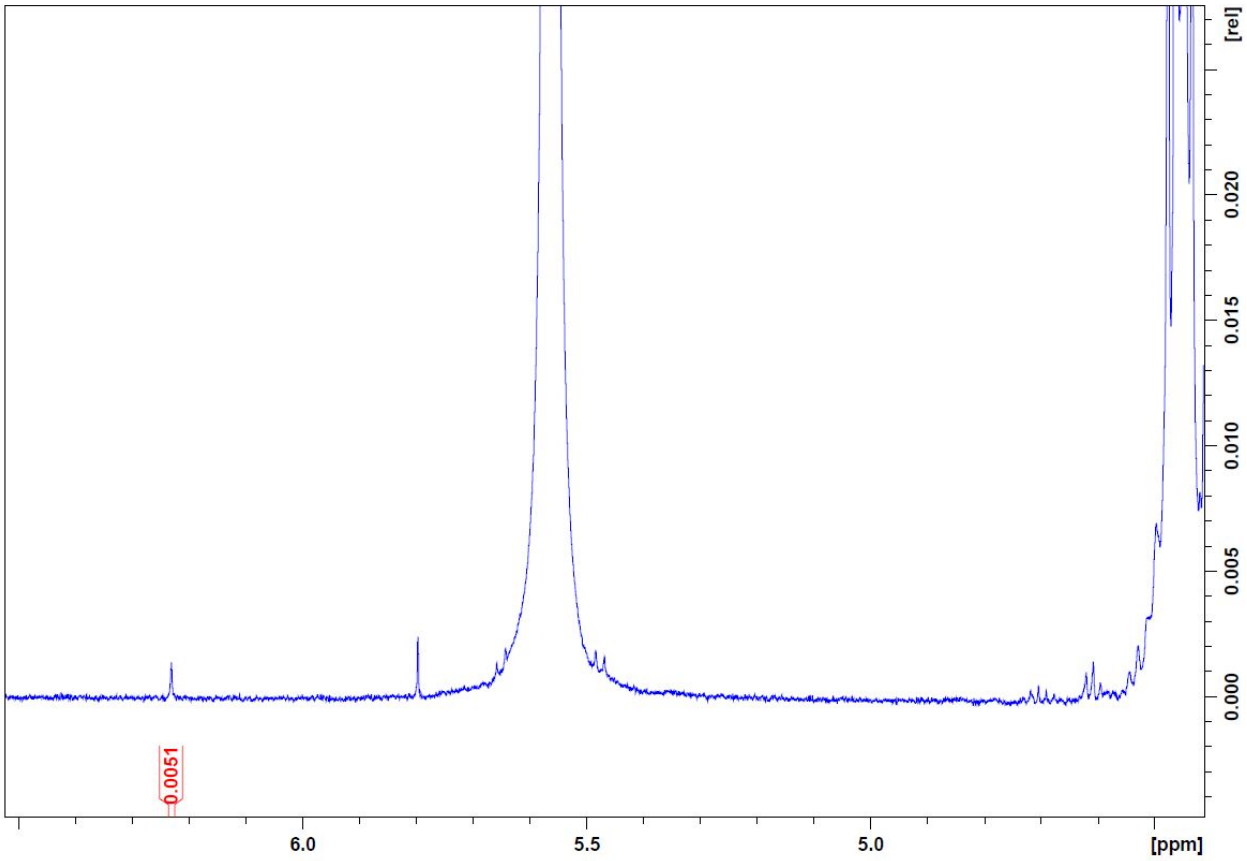

Figure S140. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction with 5 equiv DMTS at 0.1M after 10 h in DMF-d_7 (zoom-in).

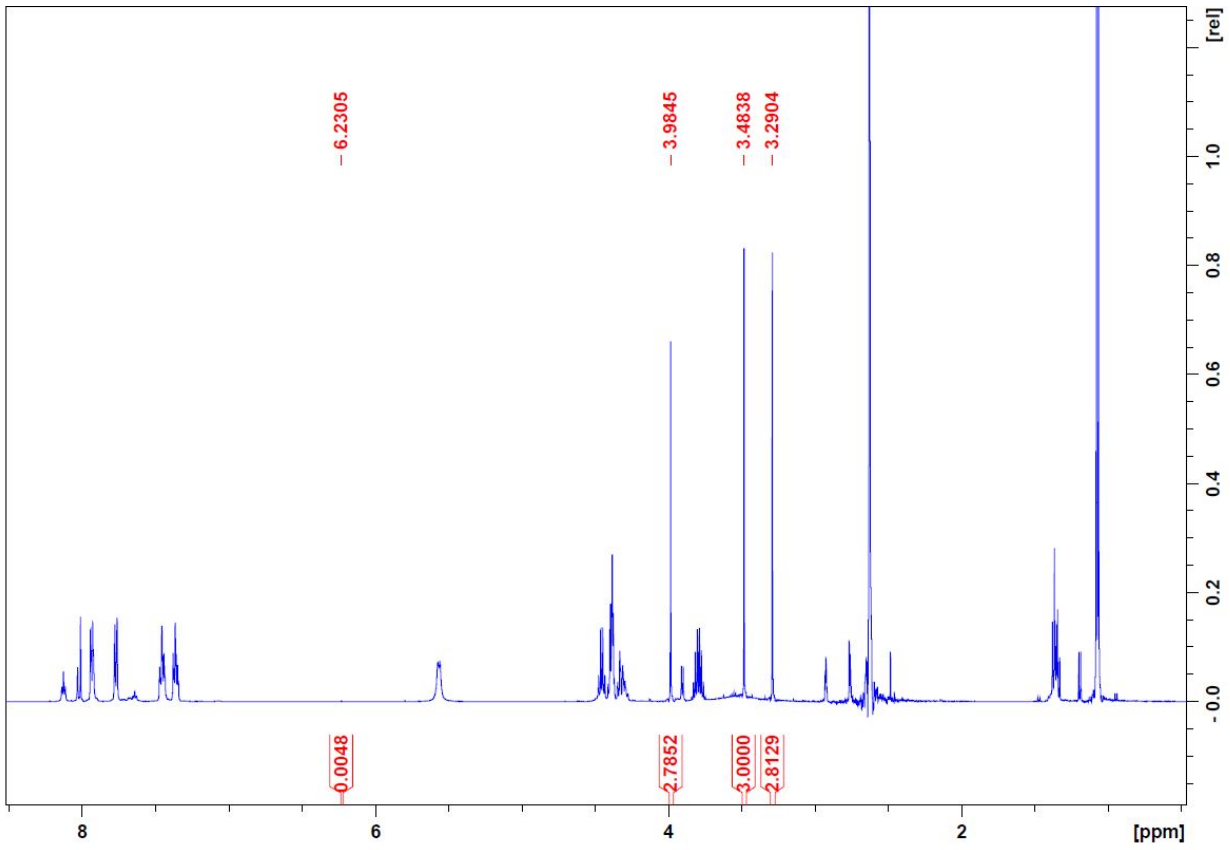

Figure S141. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction with 5 equiv DMTS at 0.1M after 16 h in DMF-d_7 (full spectrum).

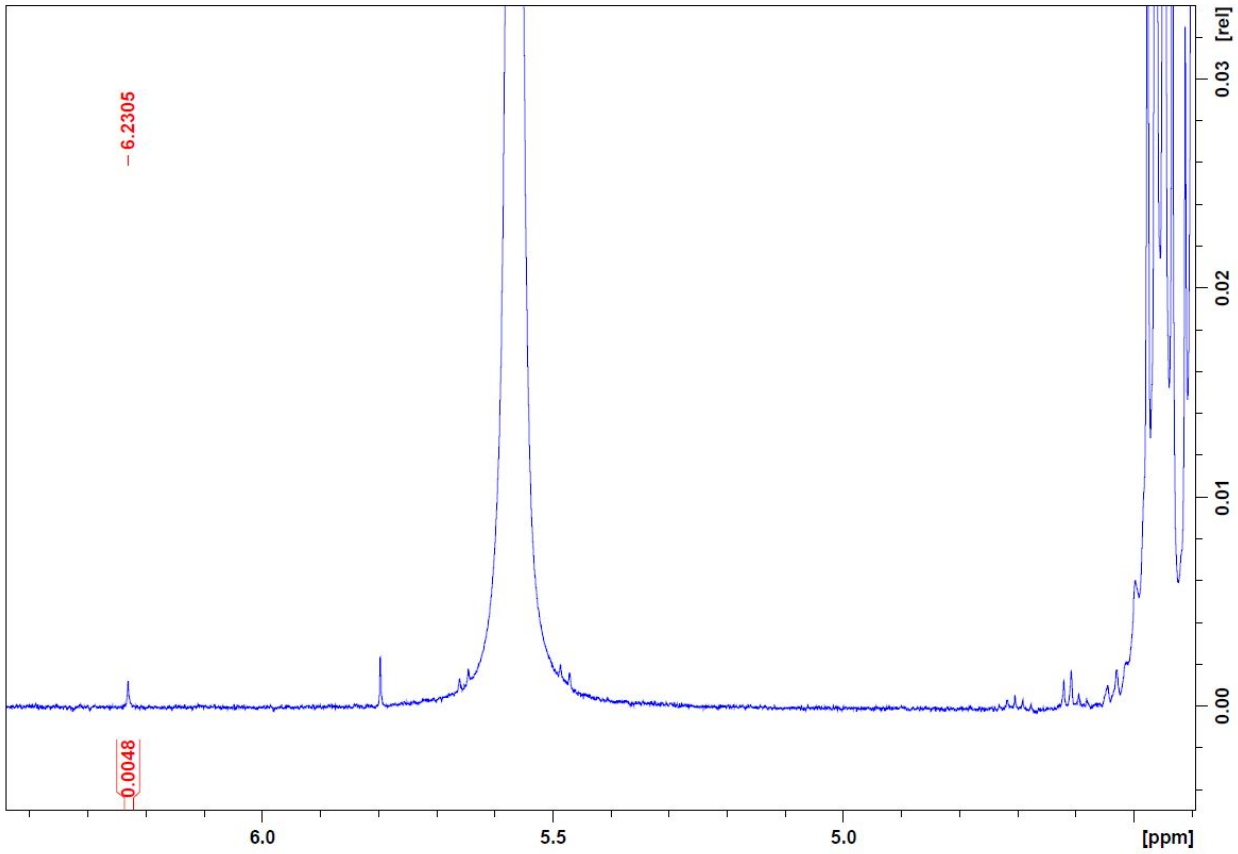

Figure S142. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction with 5 equiv DMTS at 0.1M after 16 h in DMF-d_7 (zoom-in).

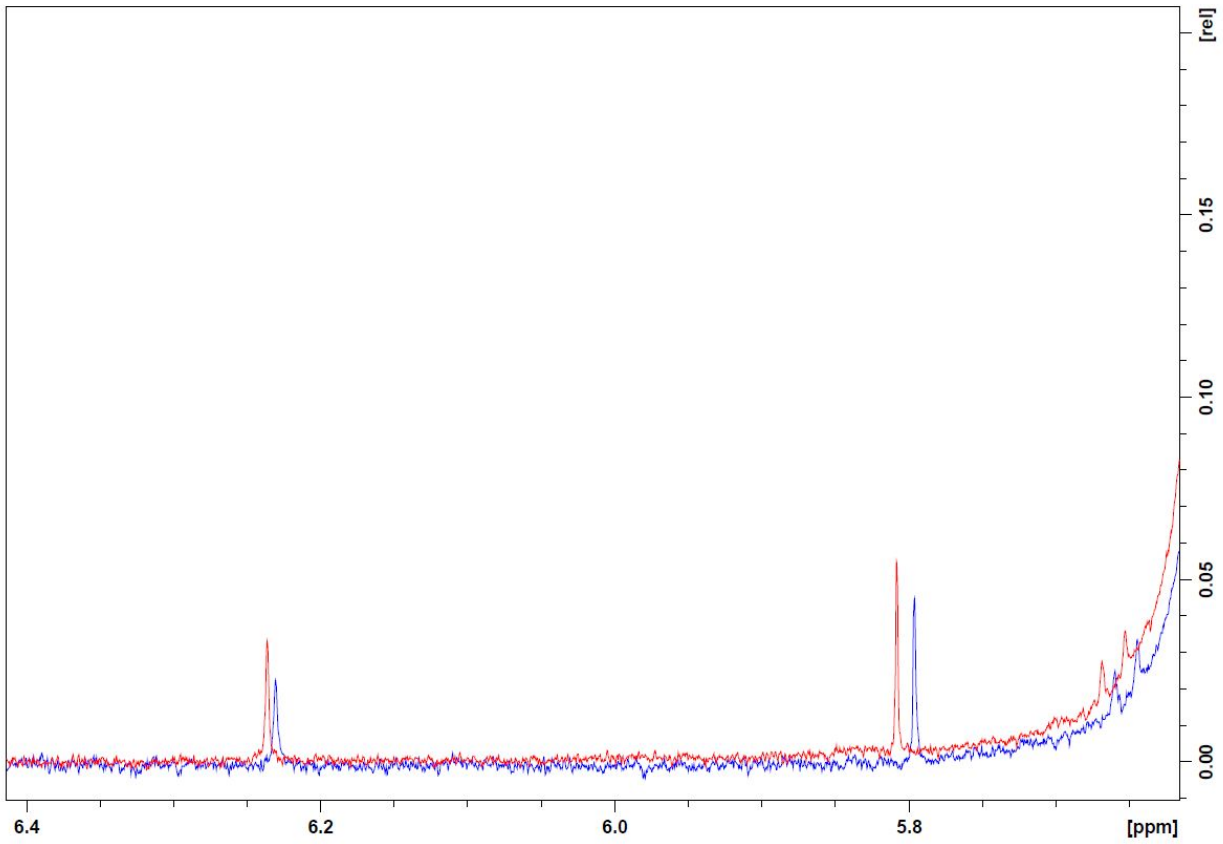

Figure S143. Overlap of 1D ^{1}H NMR spectra of Fmoc-Gly-OH/DIC/Oxyma (1:1:1) reaction without DMTS (in red) and with 5 equiv DMTS (in blue) after 16 h in DMF-d_7 (zoom-in).

8.3.3 Summary of HCN formation during activation of Fmoc-Gly-OH using Oxyma/DIC in 0.1 M DMF-d_7

This section summarize the results in sections 8.3.1 and 8.3.2.

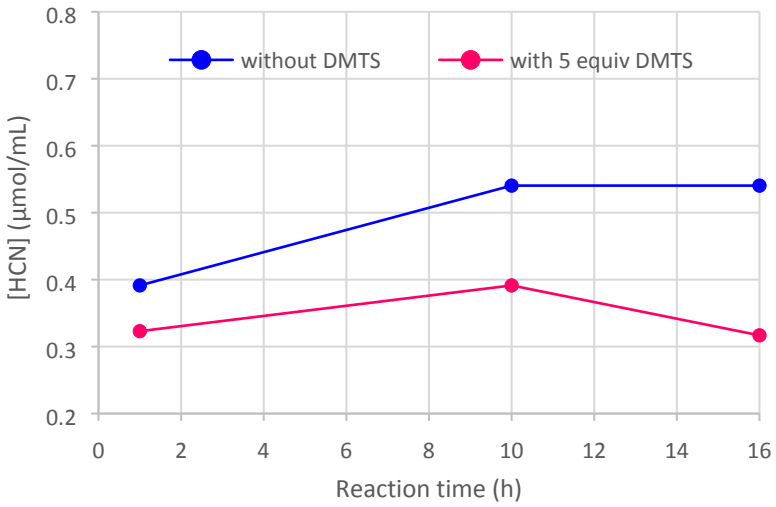

Figure S144. HCN concentration over time at rt in DMF-d_7 with and without 5 equiv DMTS. The concentration was calculated according to the method described in section 8.3.1.

Conclusion of the experiments summarized in Fig. S144: HCN concentration was lowered by using 5 equiv of DMTS during activation of Fmoc-Gly-OH with Oxyma/DIC. As the key step of peptide synthesis is not the activation of the AA but rather the amide bond formation itself, the impact of using DMTS as HCN scavenger during DIC/Oxyma mediated amide bond formation is described in the ensuing section of this SI.

9. NMR analysis of HCN formation during amide bond formations mediated by DIC/Oxyma with and without DMTS

The impact of using DMTS as HCN scavenger in the reaction of DIC with Oxyma and during Fmoc-Gly-OH activation by DIC/Oxyma was described in sections 7 and 8 of this SI, respectively. The aim of this section was to assess the amide bond formation using DMTS as an HCN scavenger. First, amidation reaction without DMTS was evaluated over time by ^{1}H NMR after which the same amide bond formation in the presence of 5 and 10 equiv of DMTS was evaluated.

9.1 Assessment of HCN formation during amide bond formation in 0.1 M DMF-d_7

General Procedure for amide bond formation.

A stock solution was prepared by dissolving Oxyma (10.1 mg, 0.071 mmol, 1.04 equiv), Fmoc-Gly-OH (20.3 mg, 0.068 mmol, 1 equiv) and caffeine (8.0 mg, 0.042 mmol, 0.62 equiv) in 680 µL of DMF-d_7. The solution was mixed by using an ultrasound bath. (S)-(-)-1-phenylethylamine (8.77 µL, 0.068 mmol, 1.0 equiv) and DIC (10.65 µL, 0.068 mmol, 1.0 equiv) were added to the stock solution. (S)-(-)-1-phenylethylamine addition was carried out prior to addition of DIC. 170 µL (25% v/v of the solution i.e. ~ 0.017 mmol based on Fmoc-Gly-OH) of this stock solution was taken out and 0, 5, 10 equiv of DMTS were added to the 170 µL solution. The latter was transferred into a 3 mm NMR tube and transferred to the spectrometer for monitoring at 20°C. 1D ^{1}H NMR acquisition was done after 1 h, 5 h, 10 h and 16 h.

The method used for the determination of HCN concentration is described in section 8.3 of this SI.

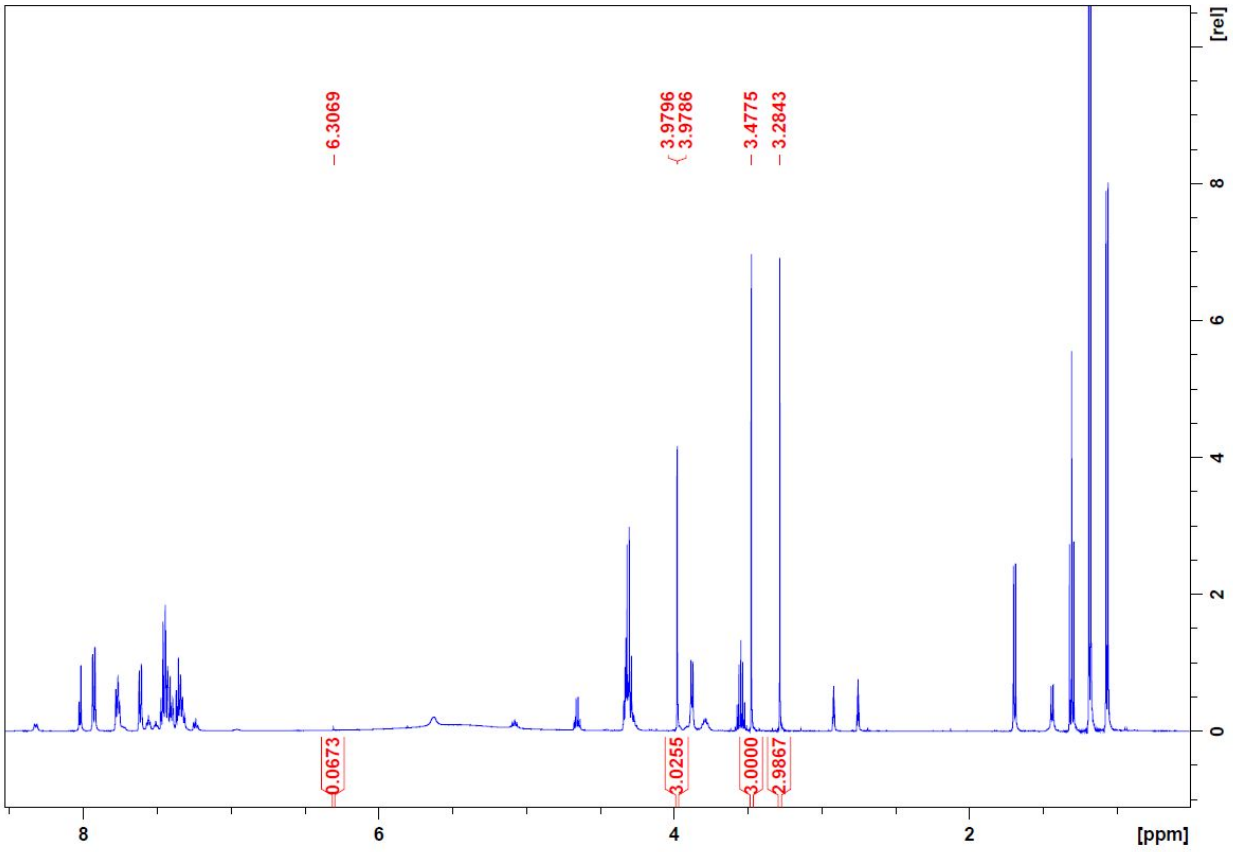

Figure S145. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 1 h in DMF-d_7 (full spectrum).

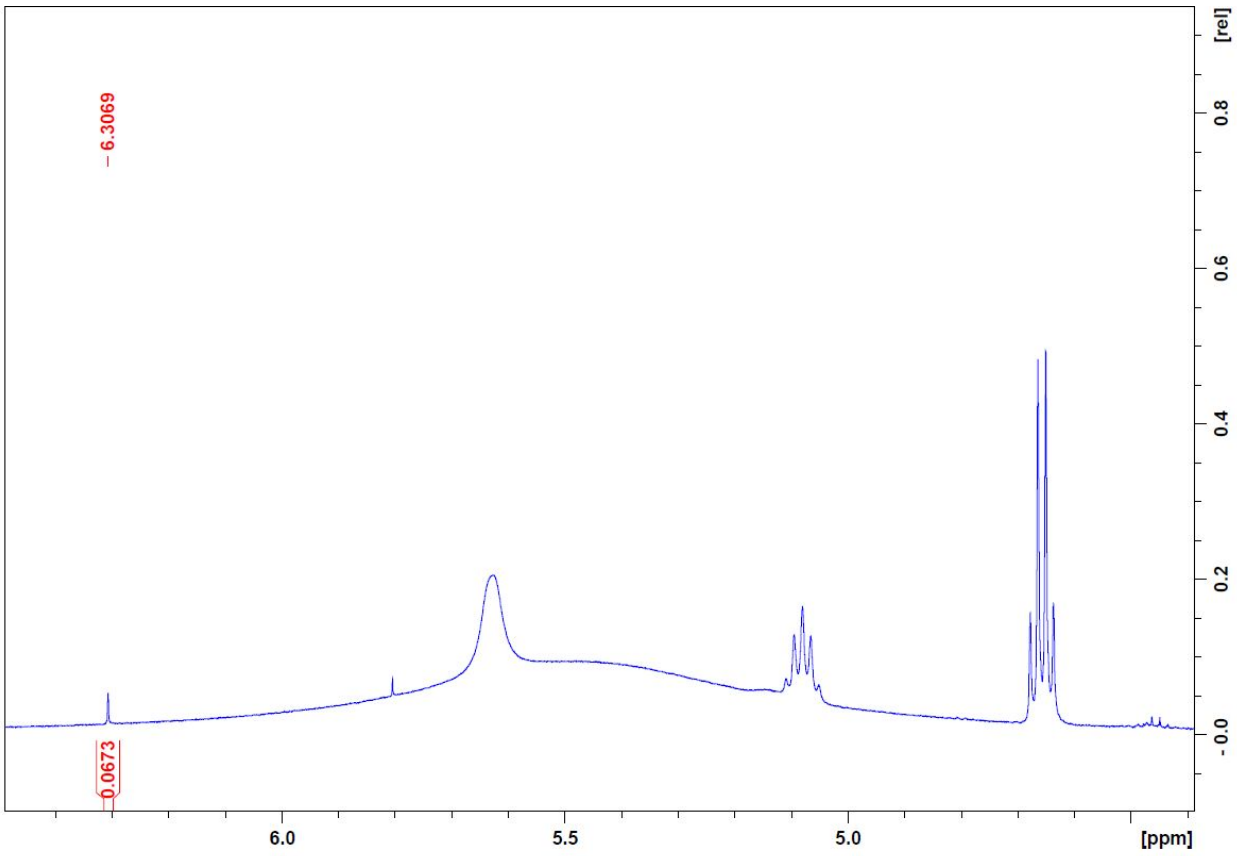

Figure S146. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 1 h in DMF-d_7 (zoom-in).

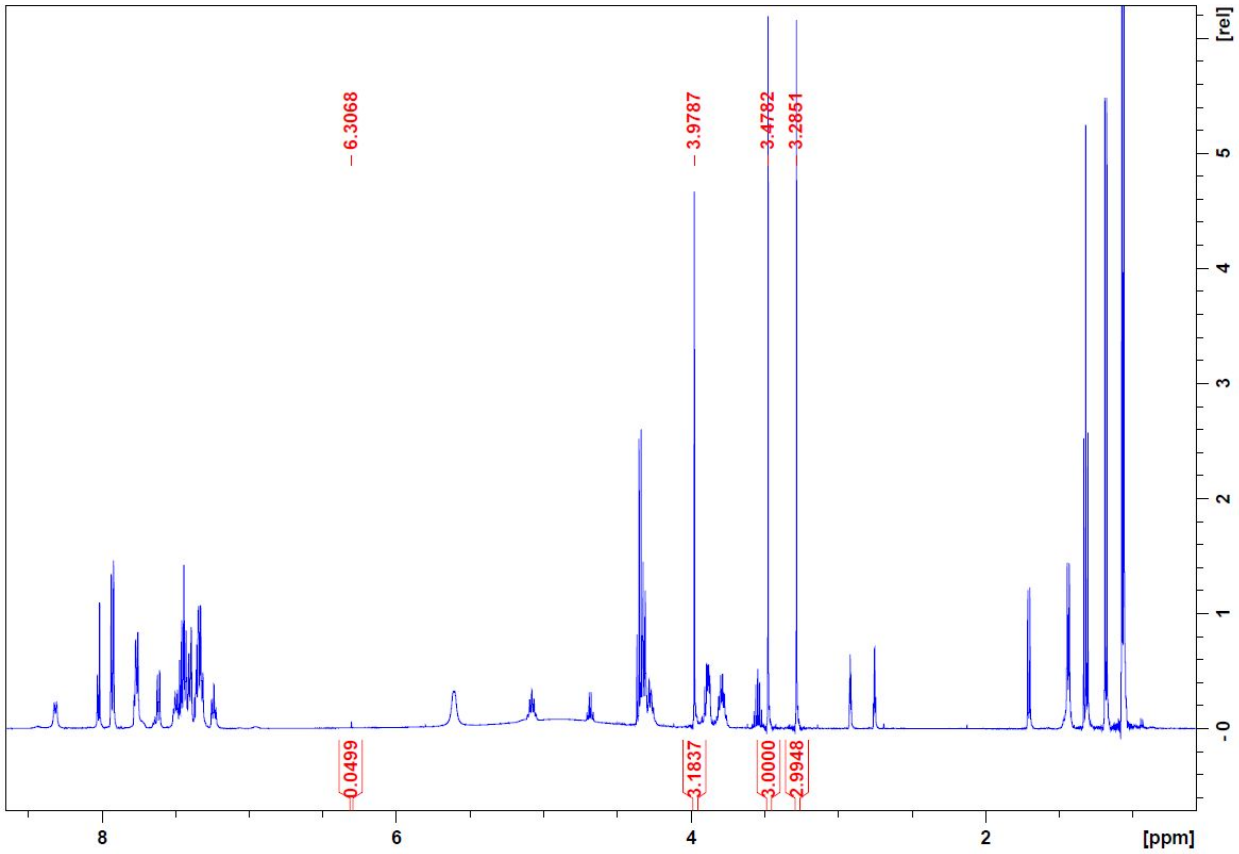

Figure S147. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 5 h in DMF-d_7 (full spectrum).

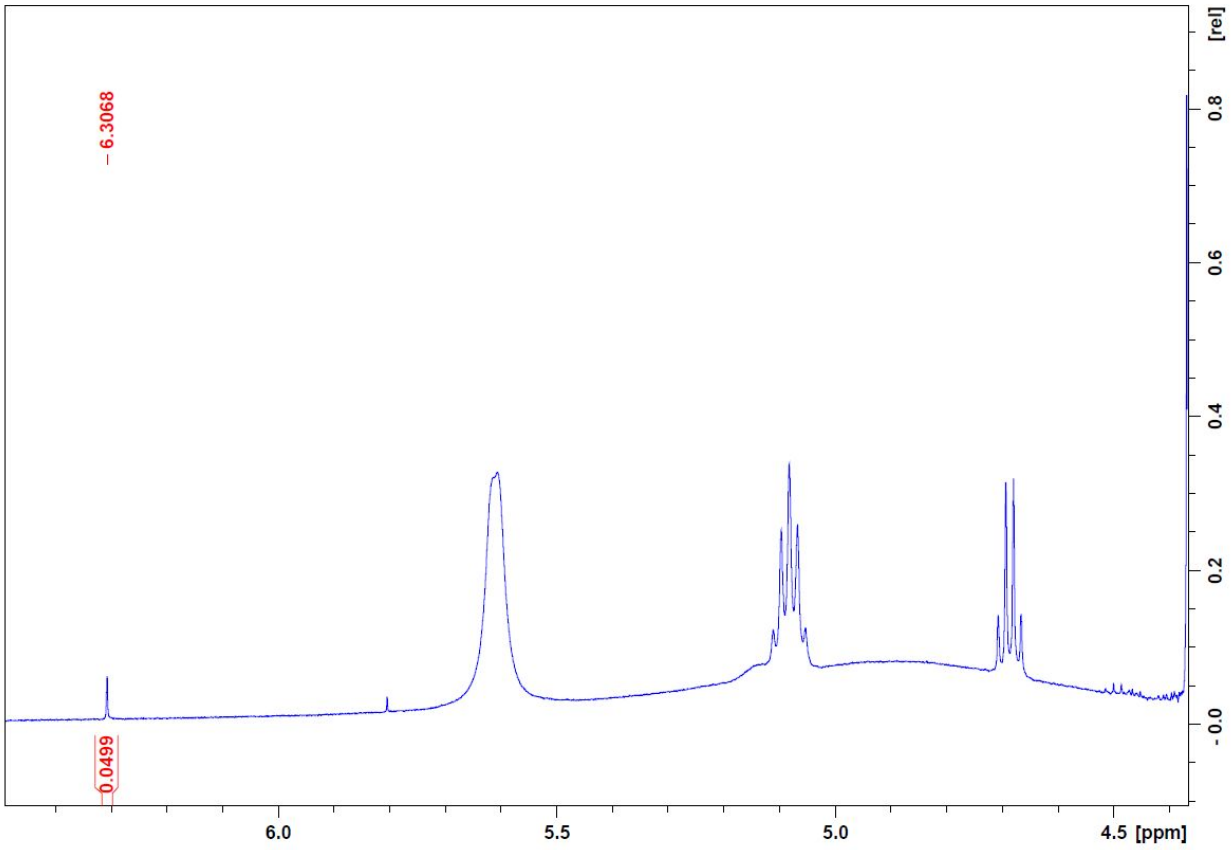

Figure S148. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 5 h in DMF-d_7 (zoom-in).

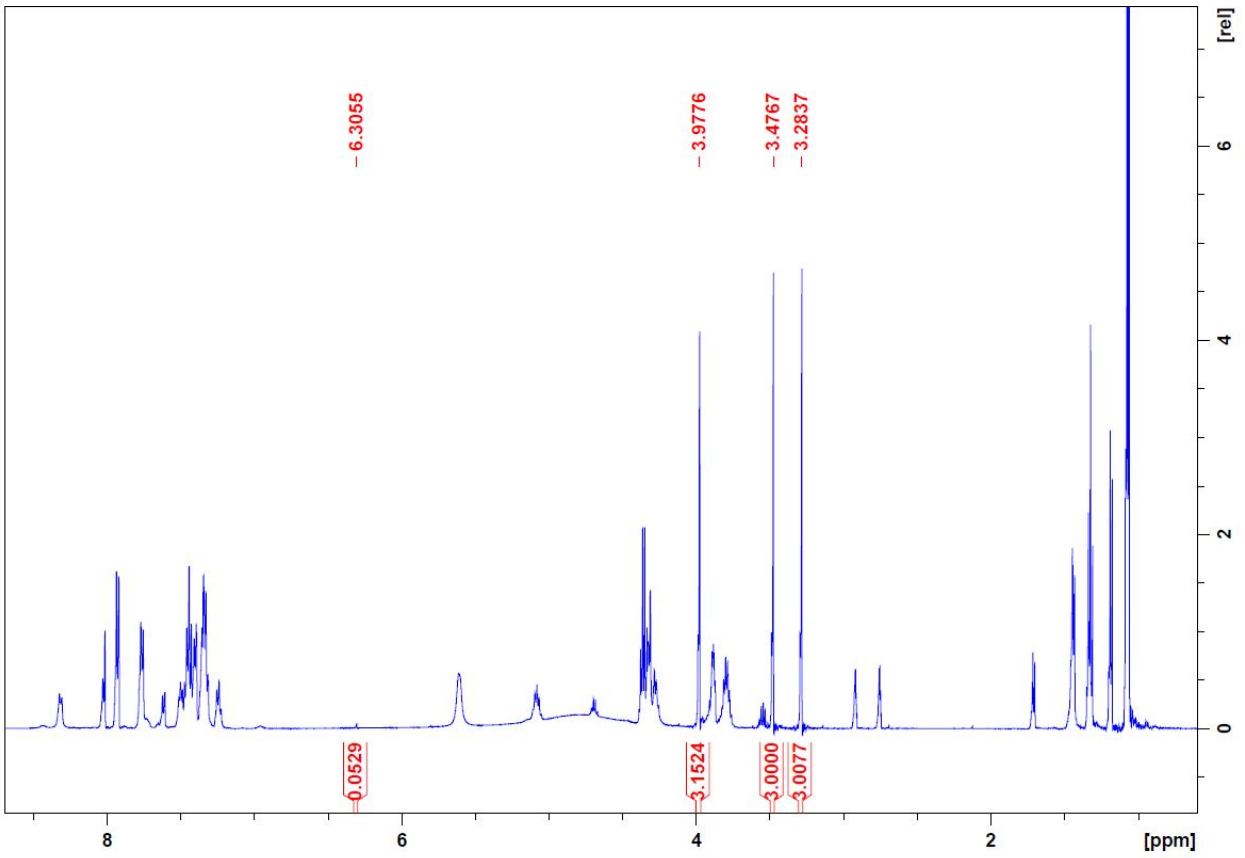

Figure S149. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 10 h in DMF-d_7 (full spectrum).

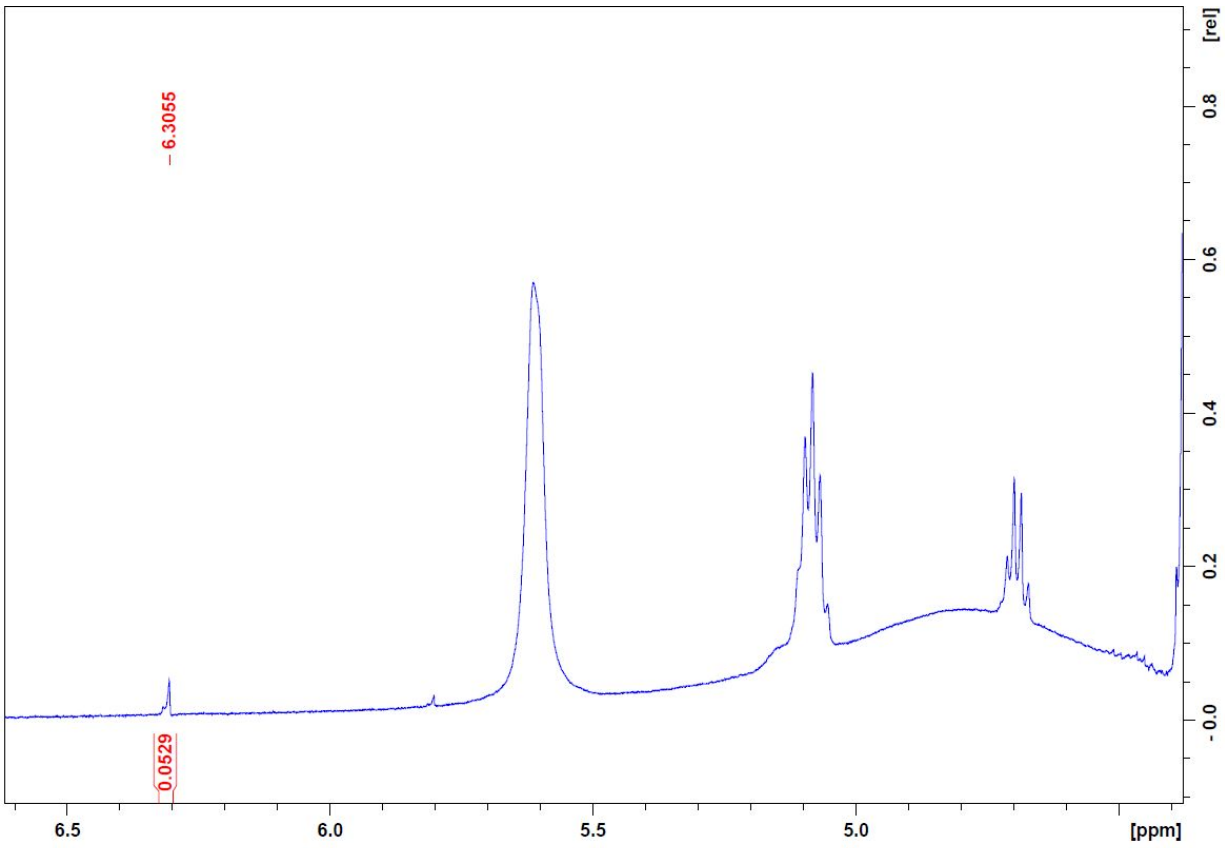

Figure S150. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 10 h in DMF-d_7 (zoom-in).

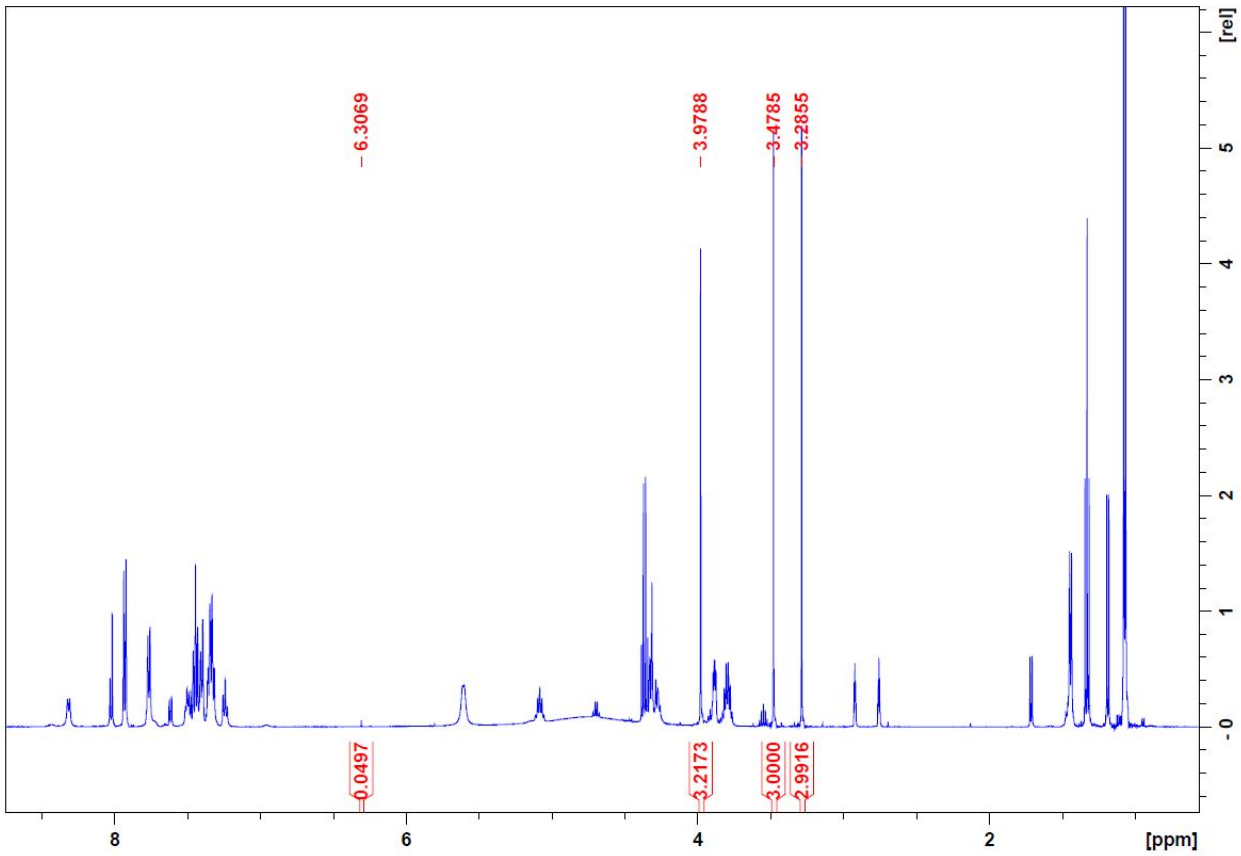

Figure S151. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 16 h in DMF-d_7 (full spectrum).

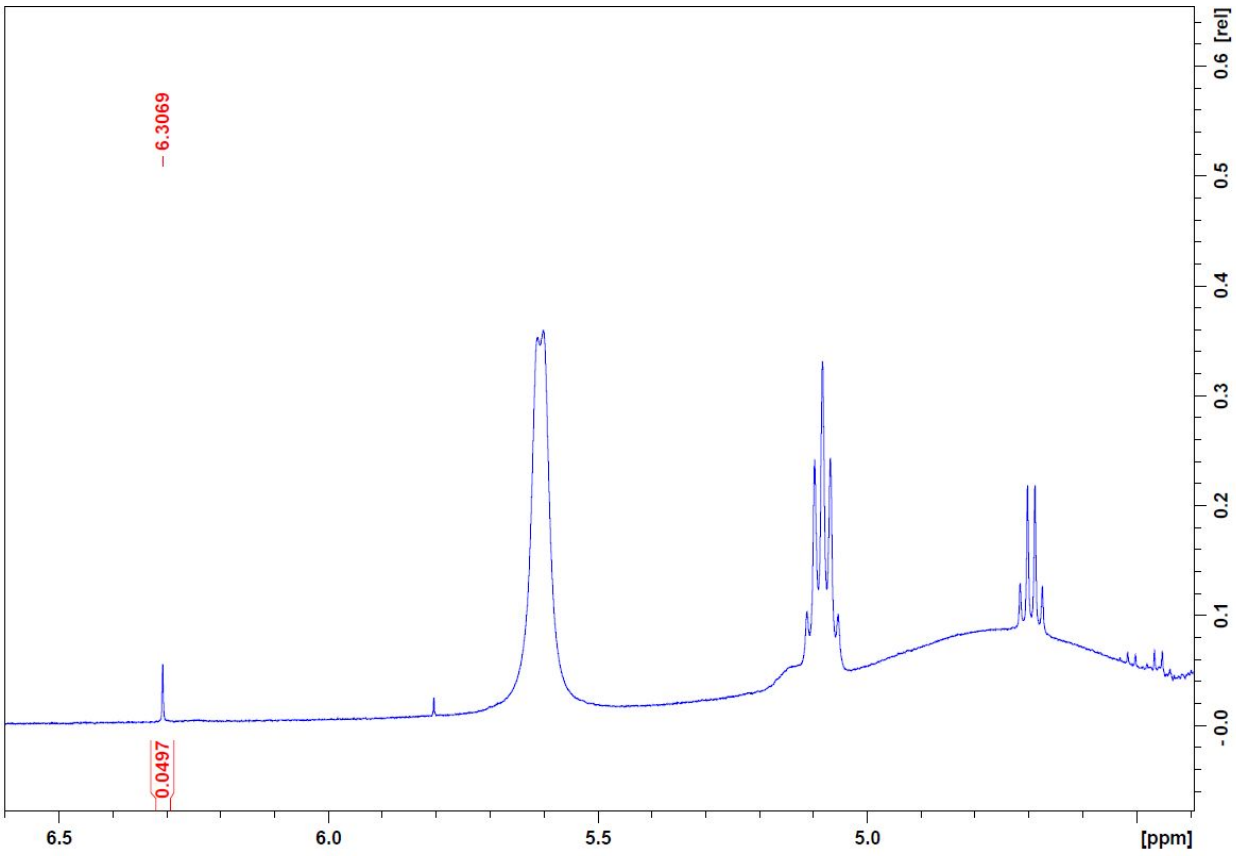

Figure S152. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 16 h in DMF-d_7 (zoom-in).

9.2 Assessment of HCN formation during amide bond formation with 5 equiv DMTS in 0.1 M DMF-d_7

The general procedure for the amide bond formation in DMF-d_7 as described in the section 9.1 of this SI was followed. The following amount of DMTS was used: (8.96 μL, 0.085 mmol, 5 equiv).

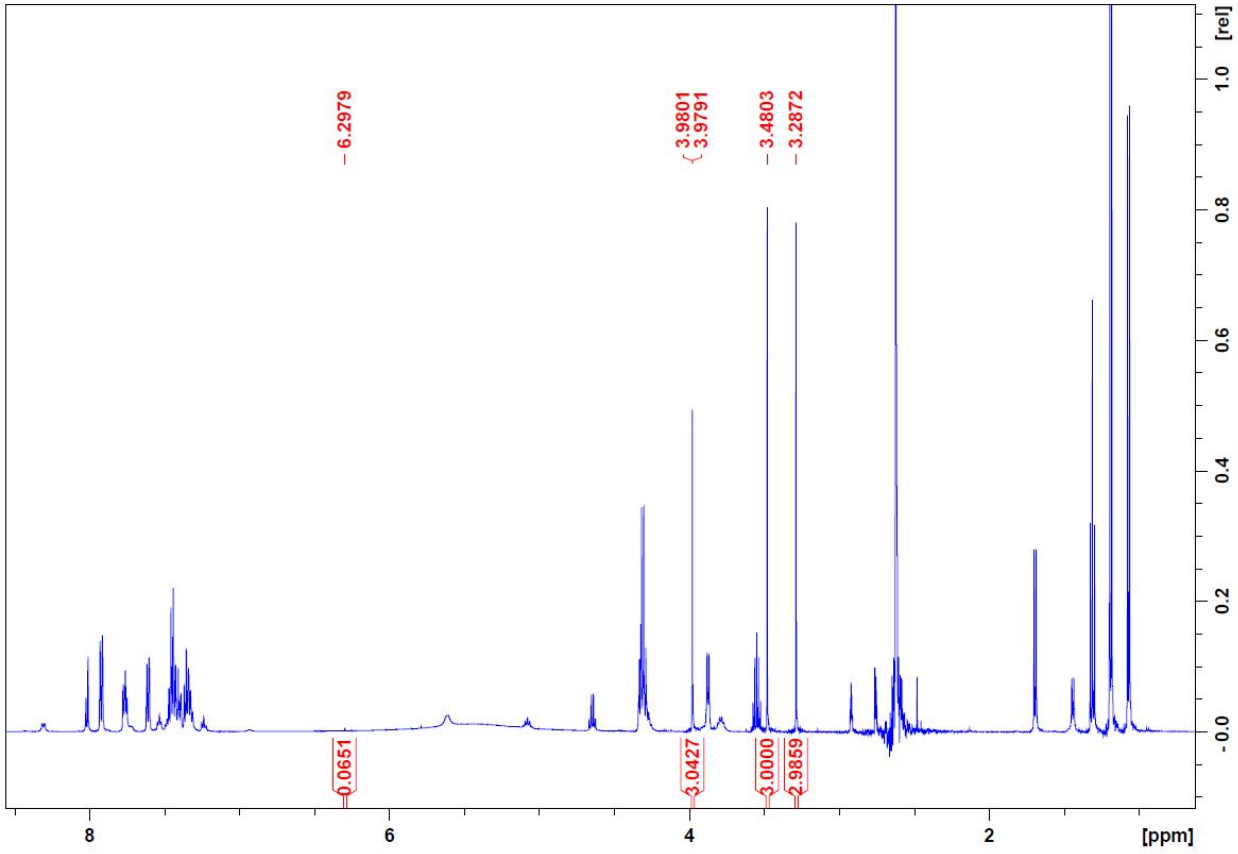

Figure S153. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 5 equiv DMTS at 0.1M after 1 h in DMF-d_7 (full spectrum).

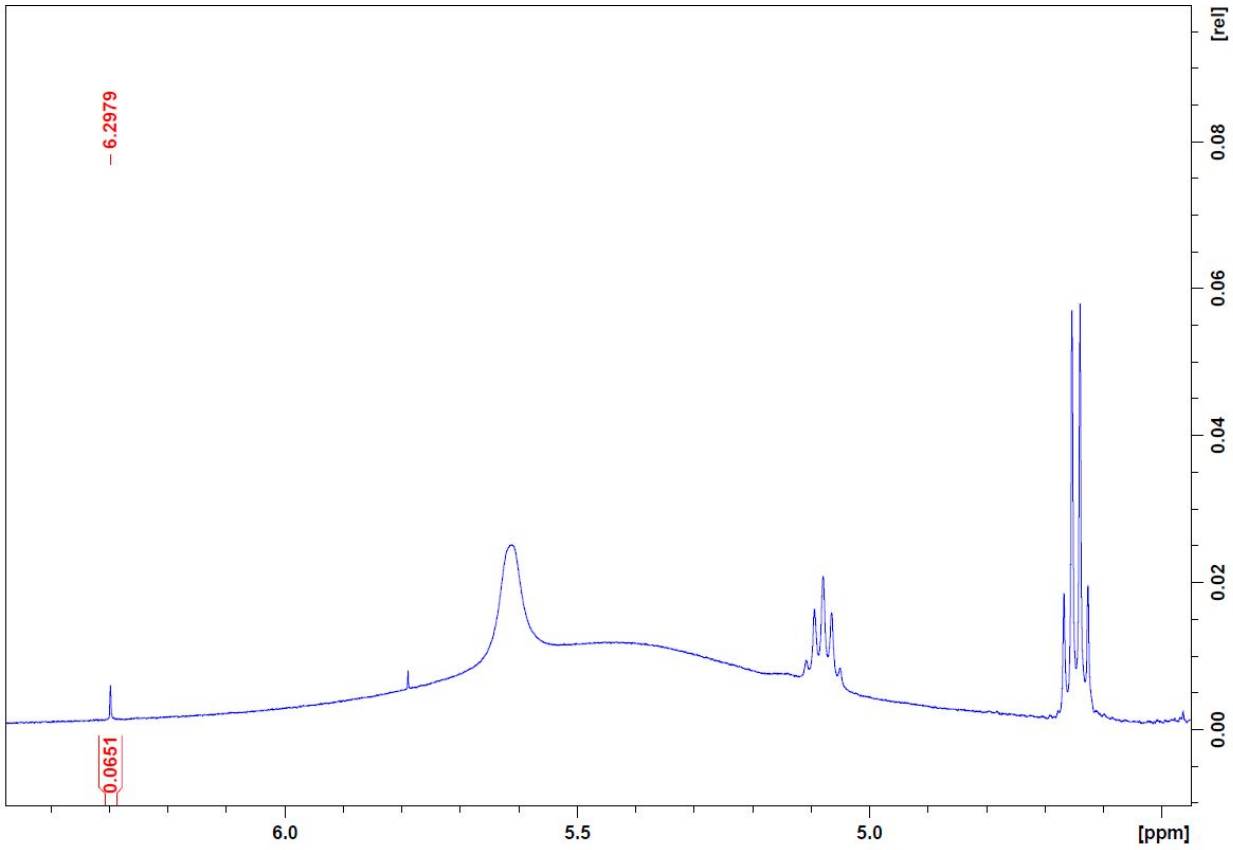

Figure S154. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 5 equiv DMTS at 0.1M after 1 h in DMF-d_7 (zoom-in).

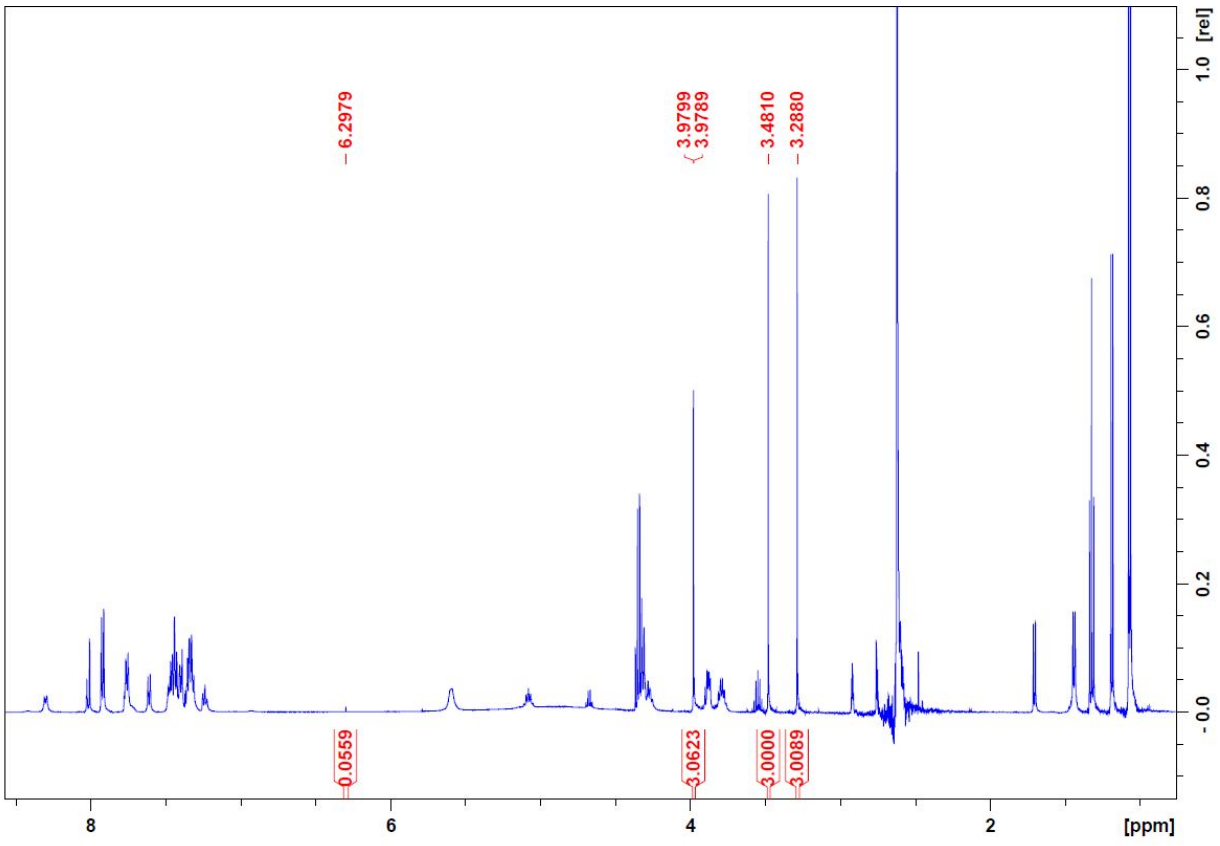

Figure S155. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 5 equiv DMTS at 0.1M after 5 h in DMF-d_7 (full spectrum).

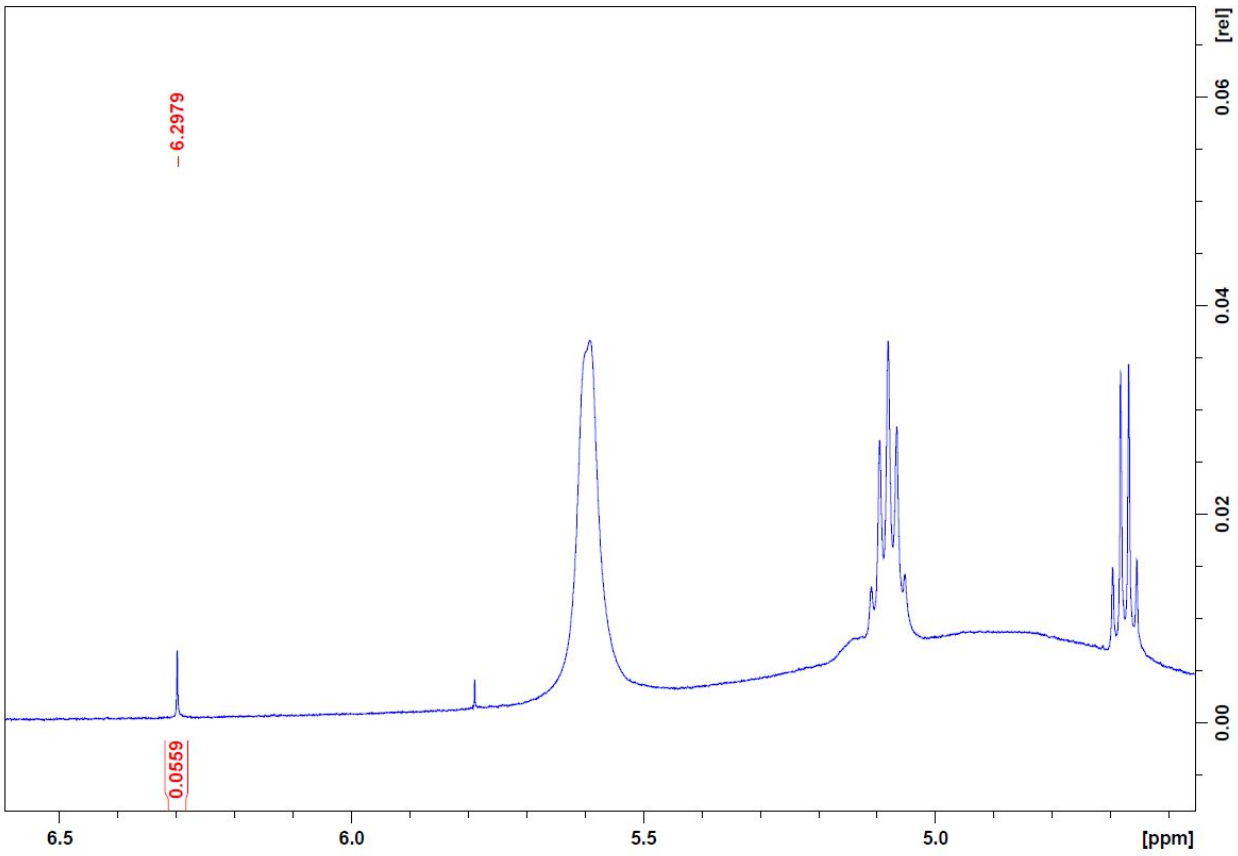

Figure S156. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 5 equiv DMTS at 0.1M after 5 h in DMF-d_7 (zoom-in).

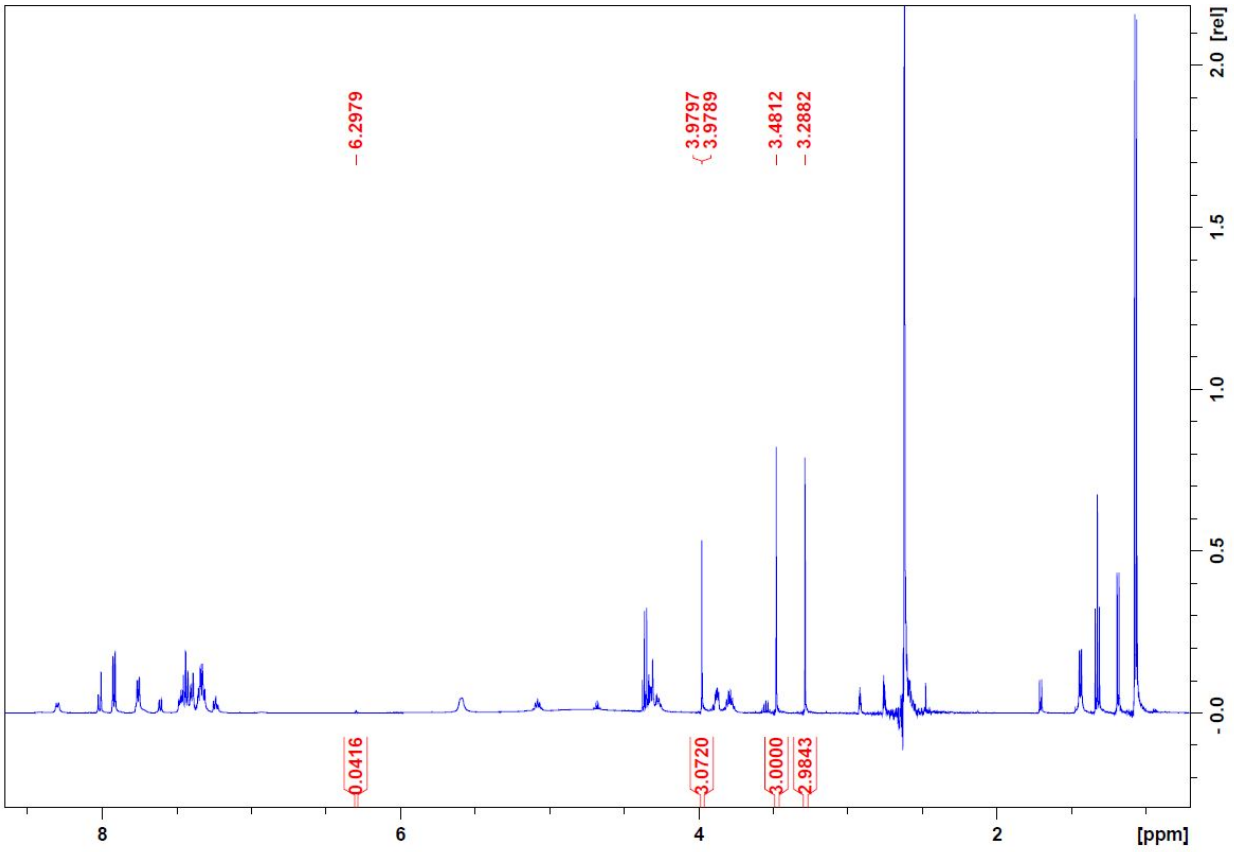

Figure S157. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 5 equiv DMTS at 0.1M after 10 h in DMF-d_7 (full spectrum).

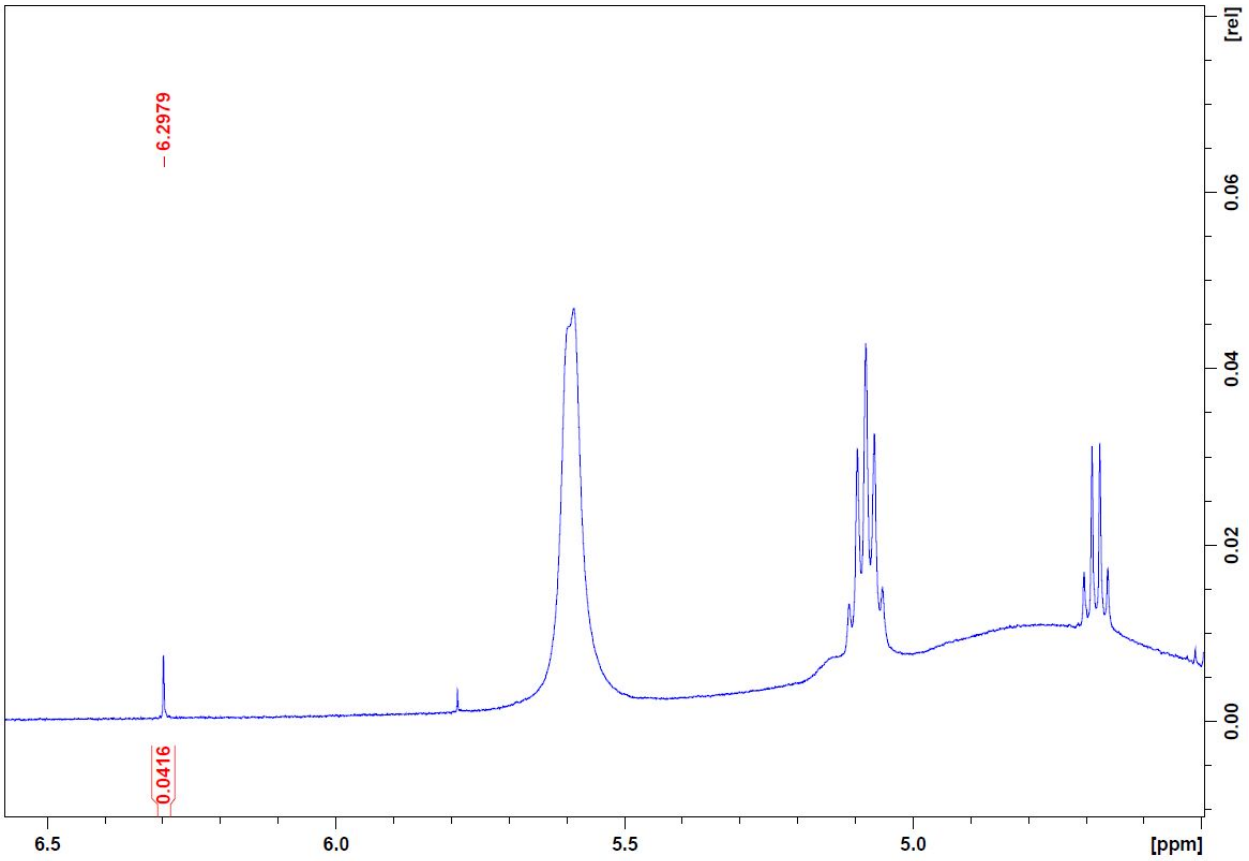

Figure S158. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 5 equiv DMTS at 0.1M after 10 h in DMF-d_7 (zoom-in).

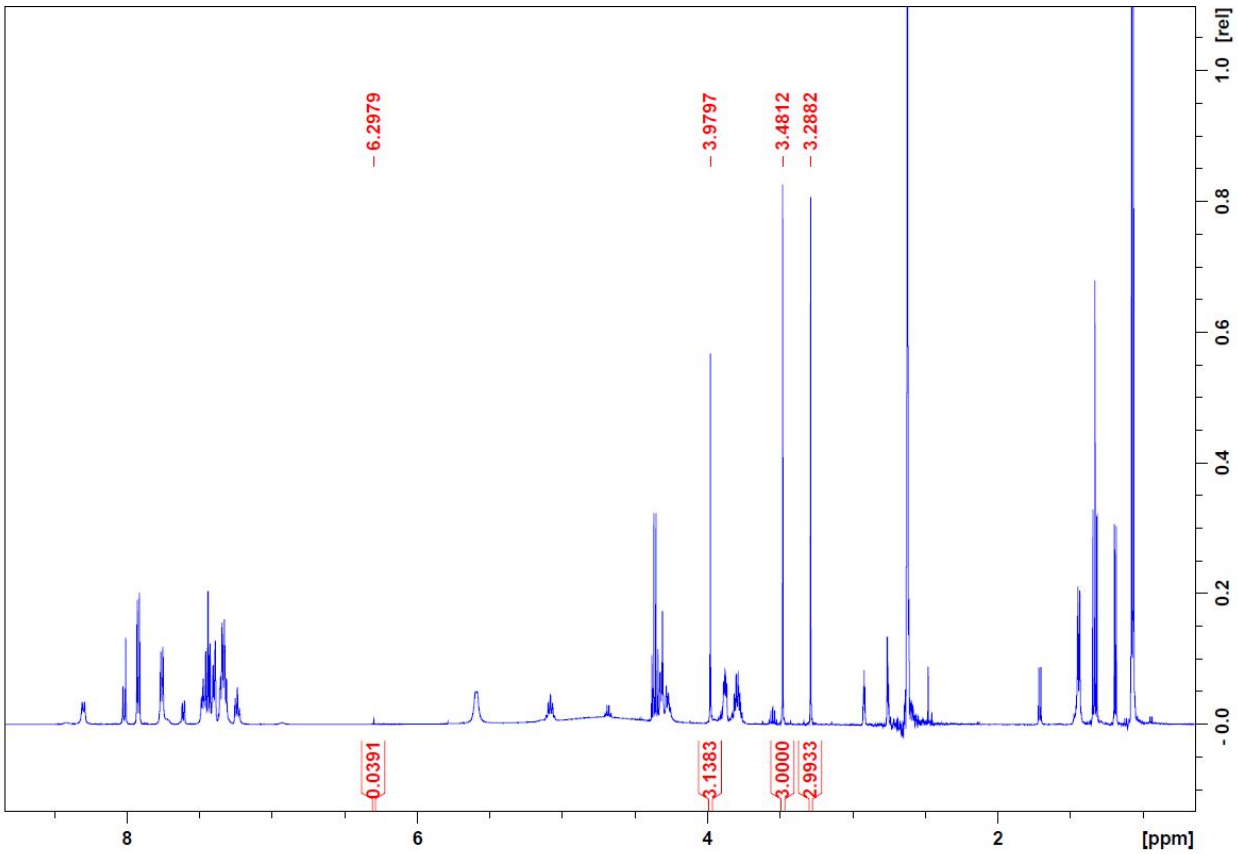

Figure S159. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 5 equiv DMTS at 0.1M after 16 h in DMF-d_7 (full spectrum).

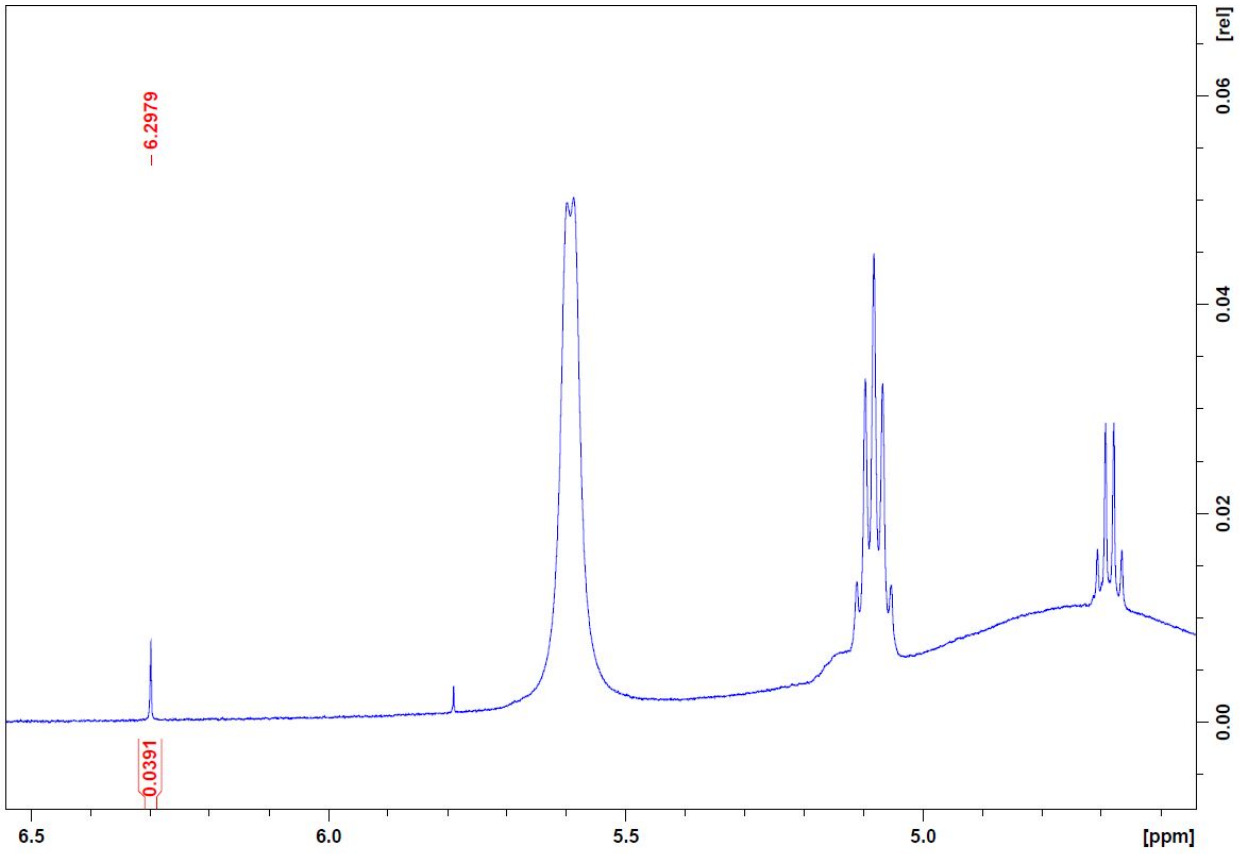

Figure S160. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 5 equiv DMTS at 0.1M after 16 h in DMF-d_7 (zoom-in).

9.3 Assessment of HCN formation during amide bond formation with 10 equiv DMTS in 0.1 M DMF-d_7

The general procedure for the amide bond formation in DMF-d7 as described in the section 9.1 of this SI was followed. The following amount of DMTS was used: (17.92 μL, 0.17 mmol, 10 equiv).

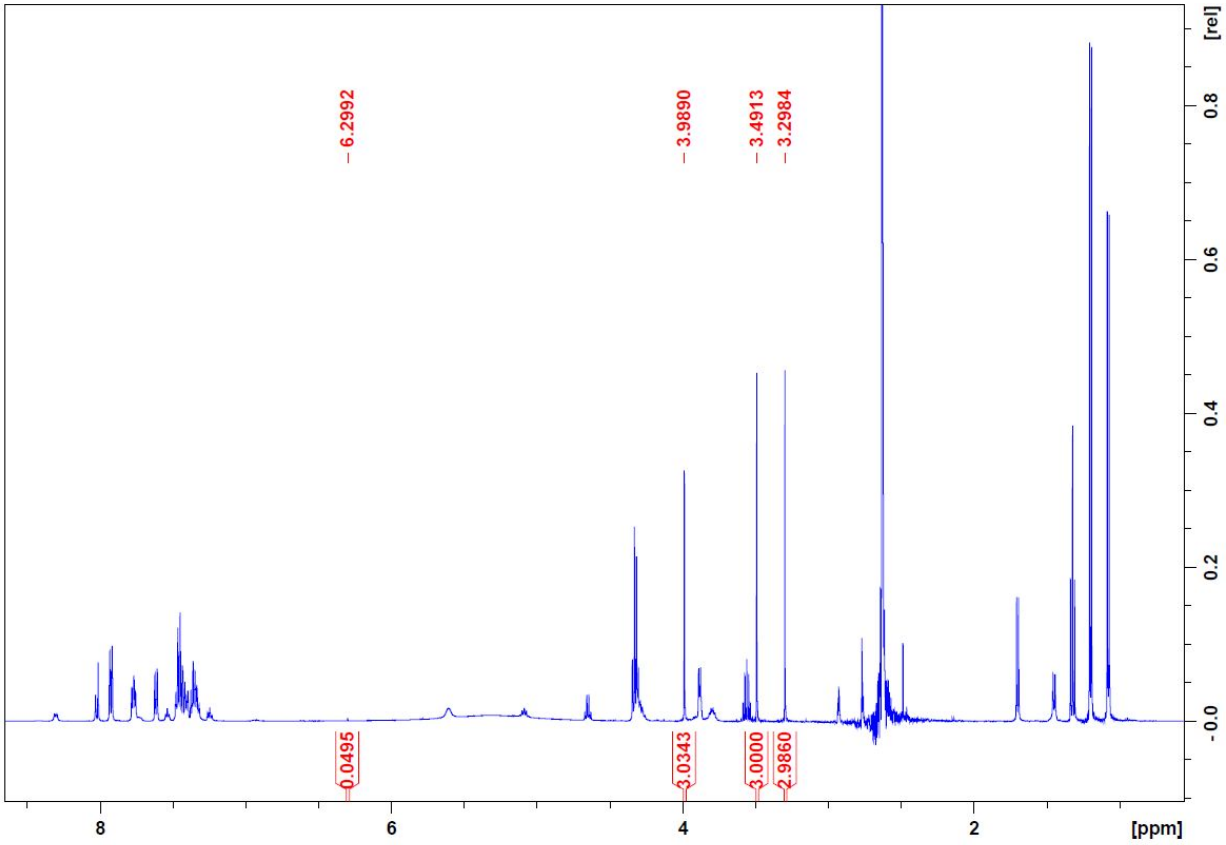

Figure S161. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 10 equiv DMTS at 0.1M after 1 h in DMF-d_7 (full spectrum).

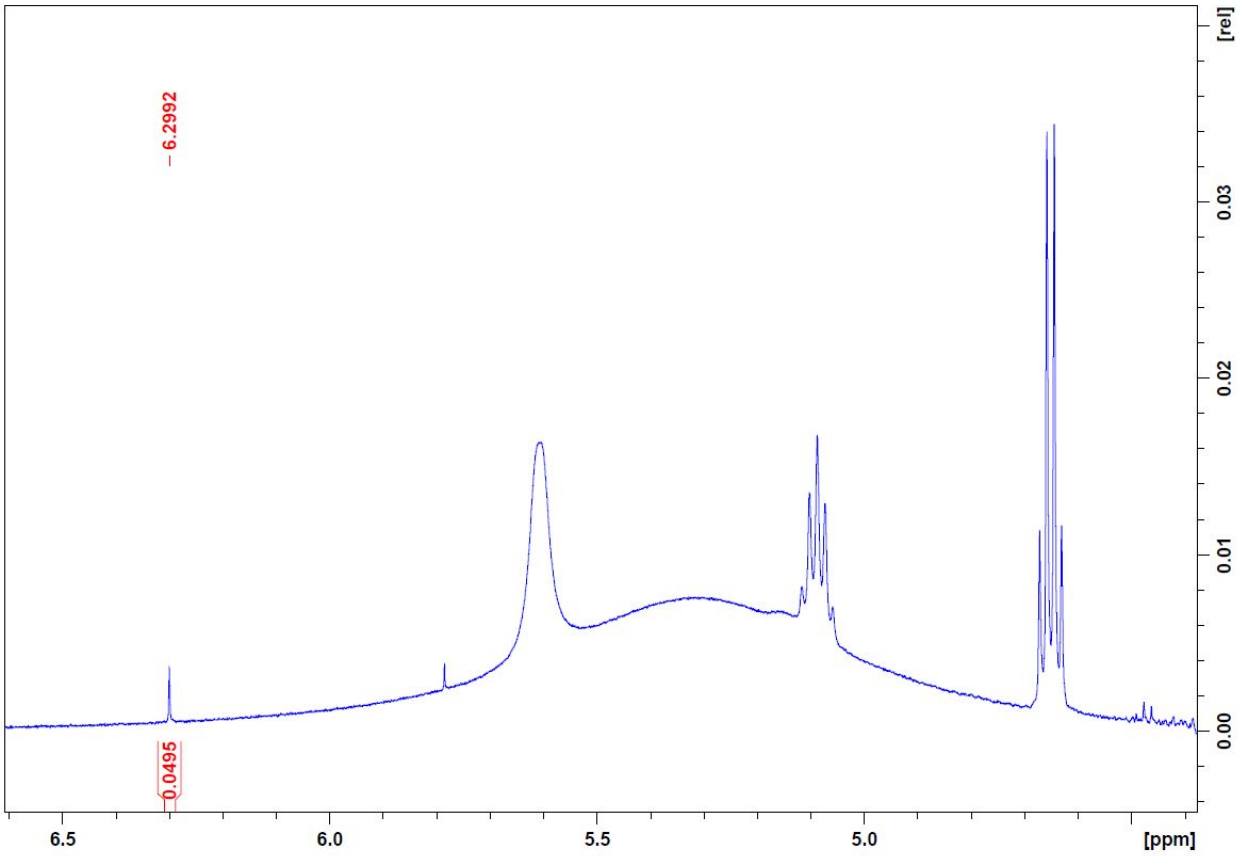

Figure S162. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 10 equiv DMTS at 0.1M after 1 h in DMF-d_7 (zoom-in).

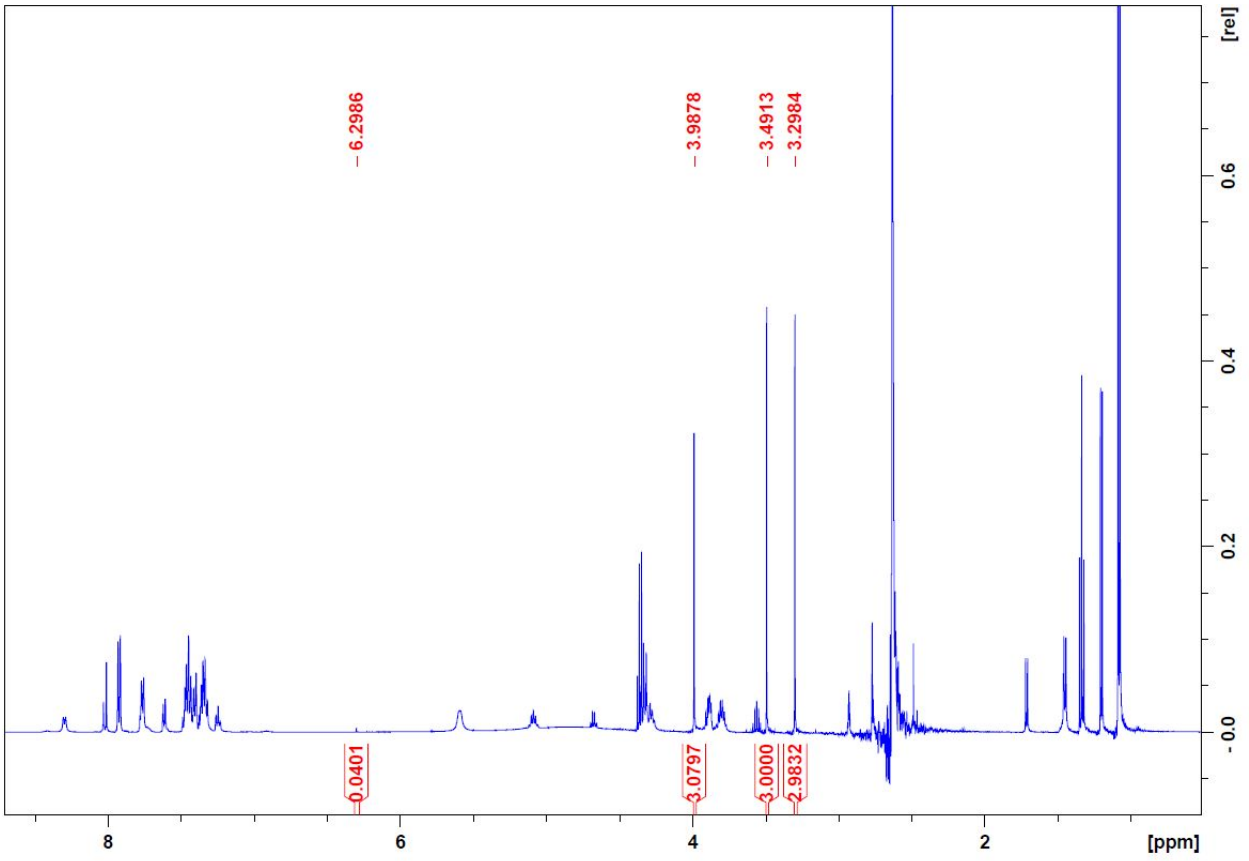

Figure S163. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 10 equiv DMTS at 0.1M after 5 h in DMF-d_7 (full spectrum).

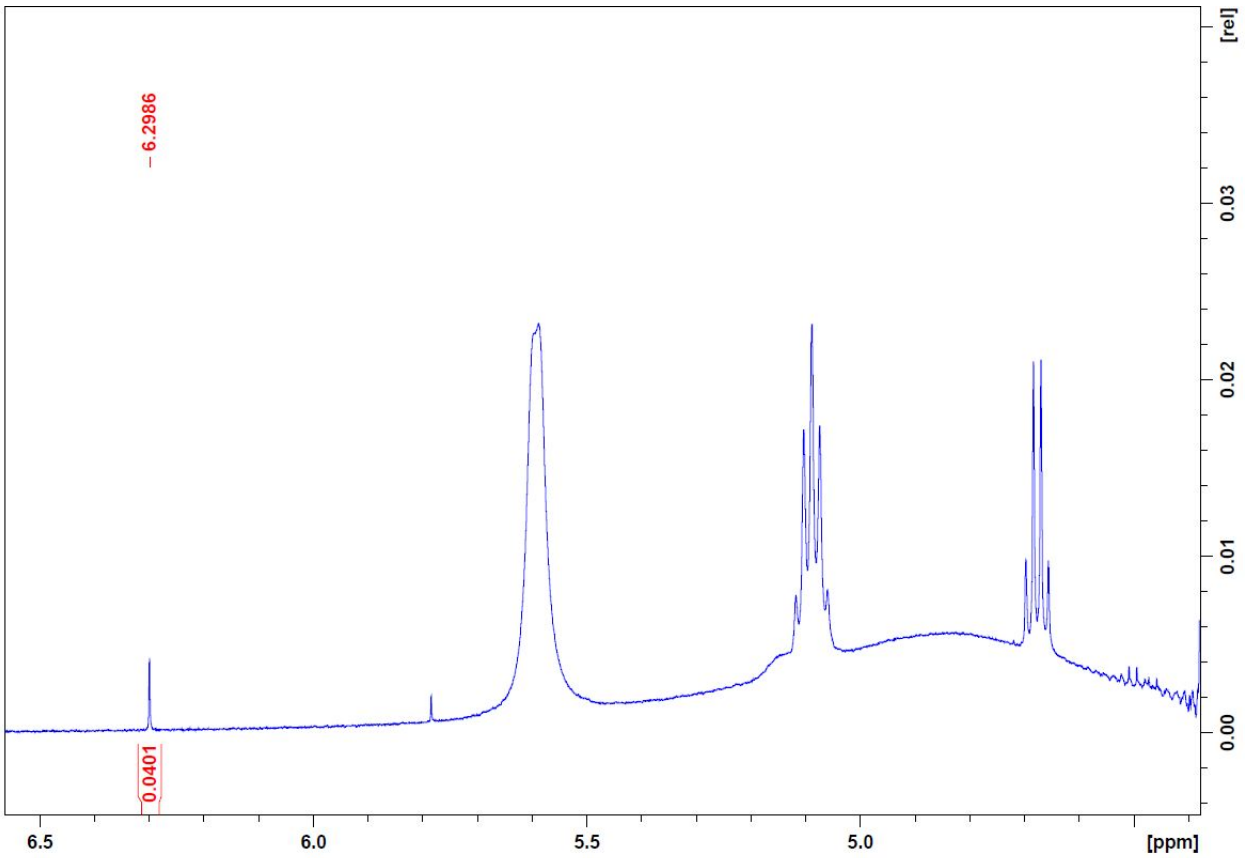

Figure S164. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 10 equiv DMTS at 0.1M after 5 h in DMF-d_7 (zoom-in).

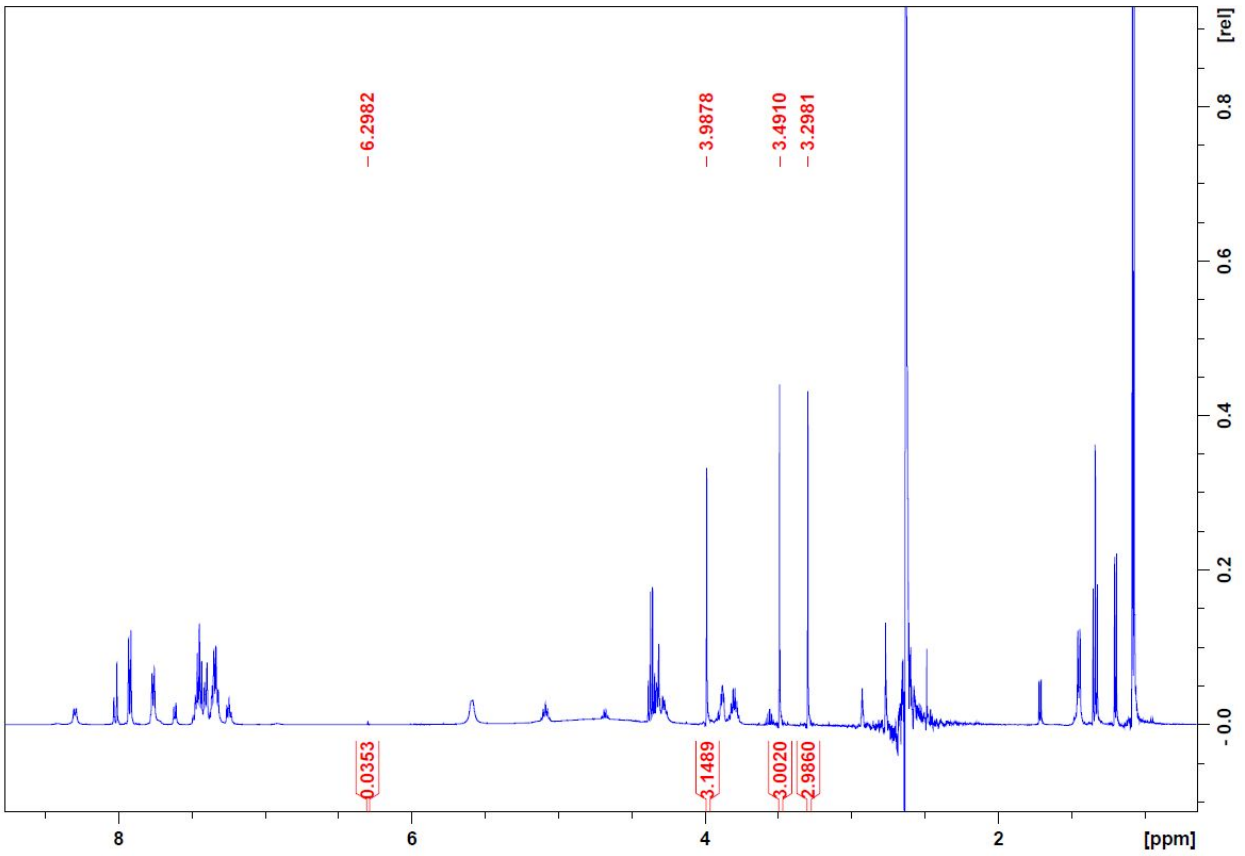

Figure S165. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 10 equiv DMTS at 0.1M after 10 h in DMF-d_7 (full spectrum).

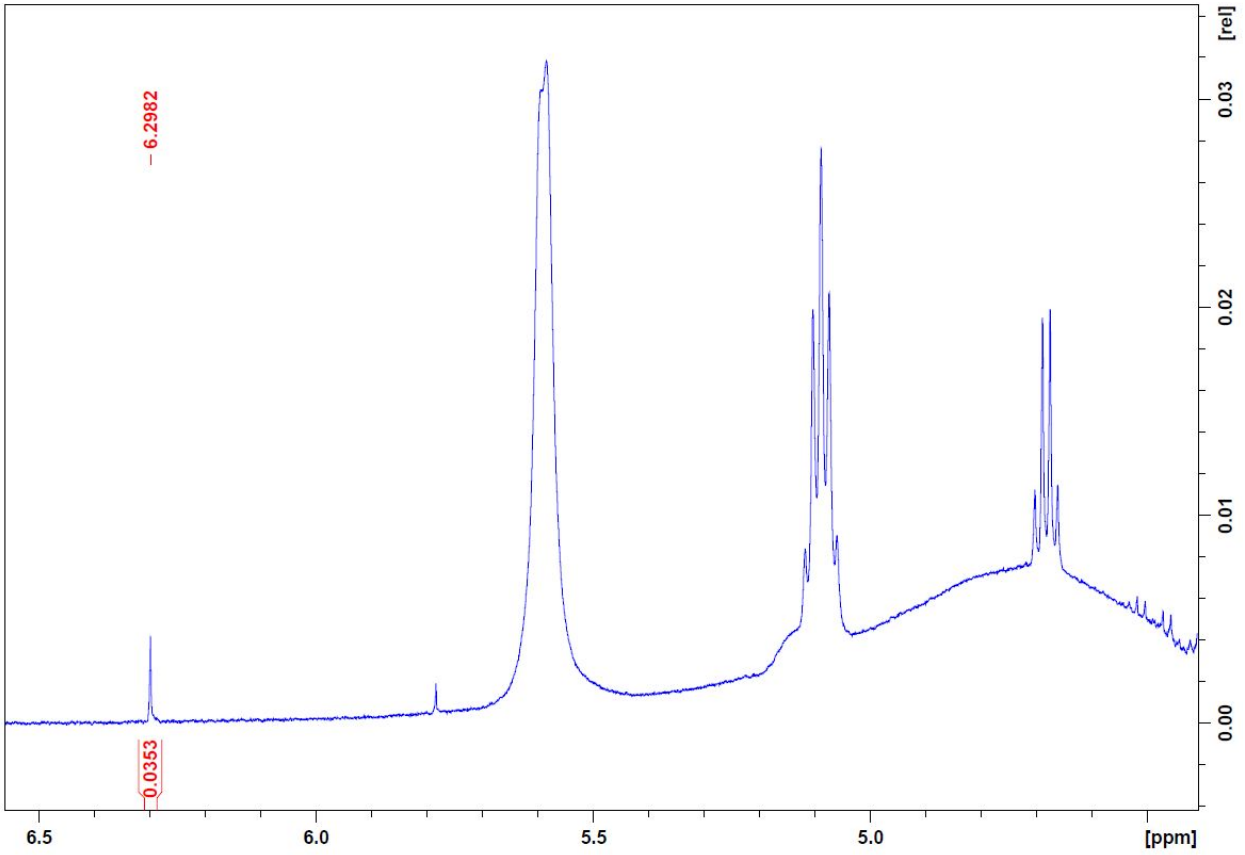

Figure S166. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 10 equiv DMTS at 0.1M after 10 h in DMF-d_7 (zoom-in).

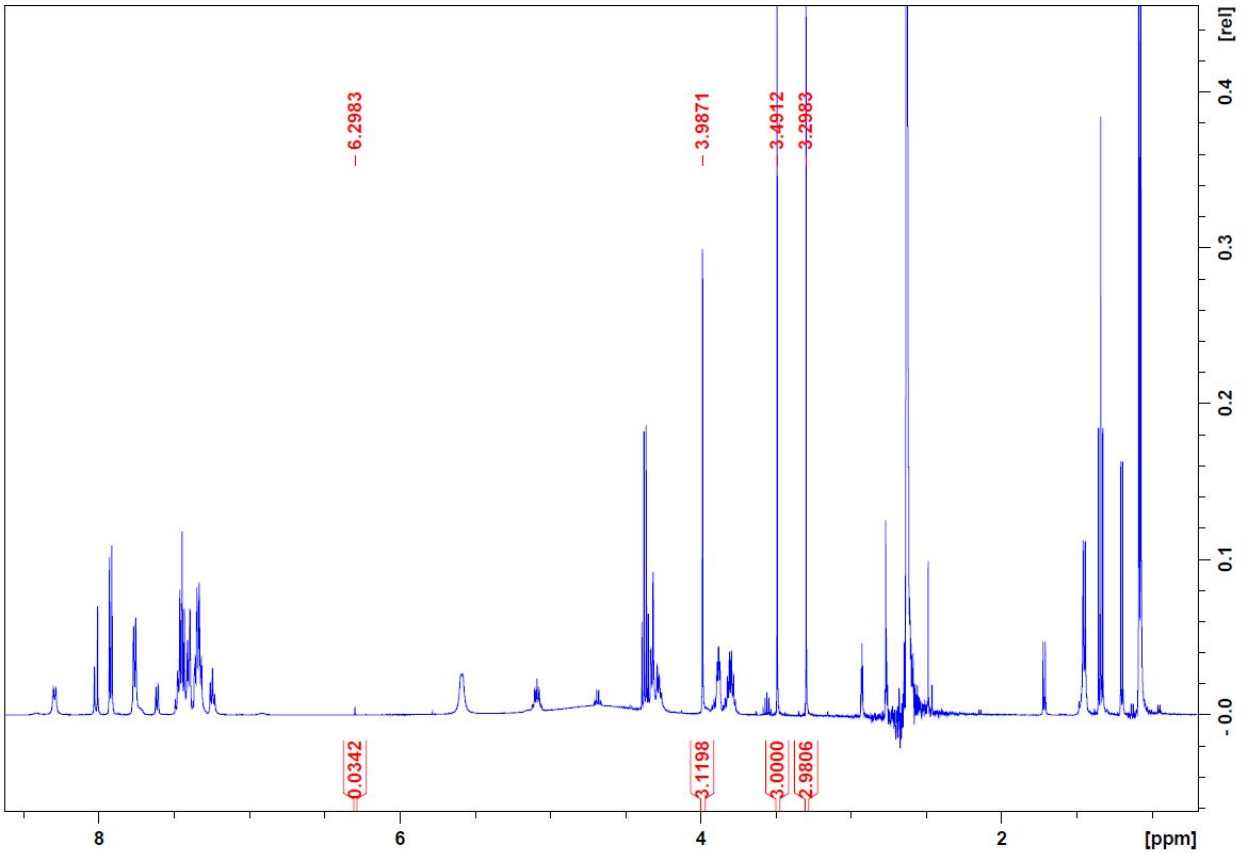

Figure S167. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 10 equiv DMTS at 0.1M after 16 h in DMF-d_7 (full spectrum).

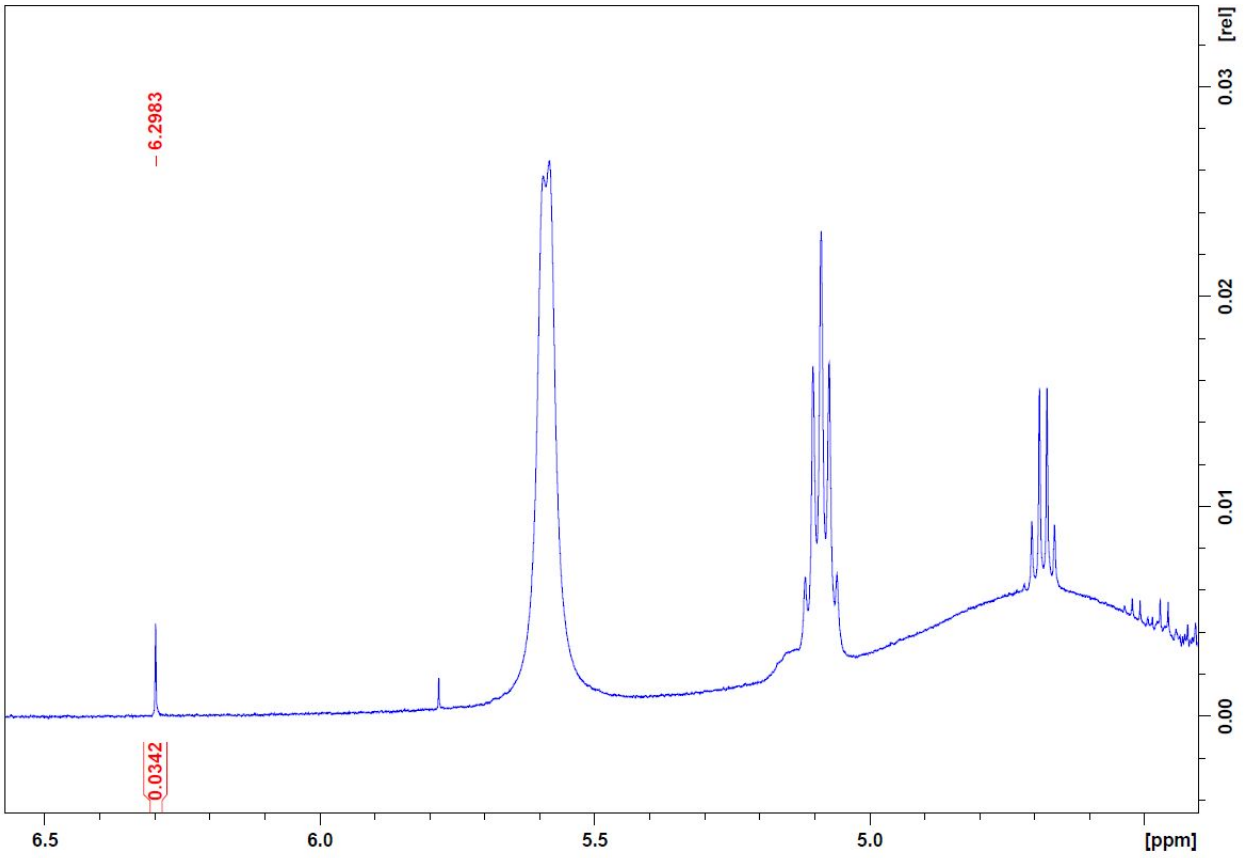

Figure S168. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction with 10 equiv DMTS at 0.1M after 16 h in DMF-d_7 (zoom-in).

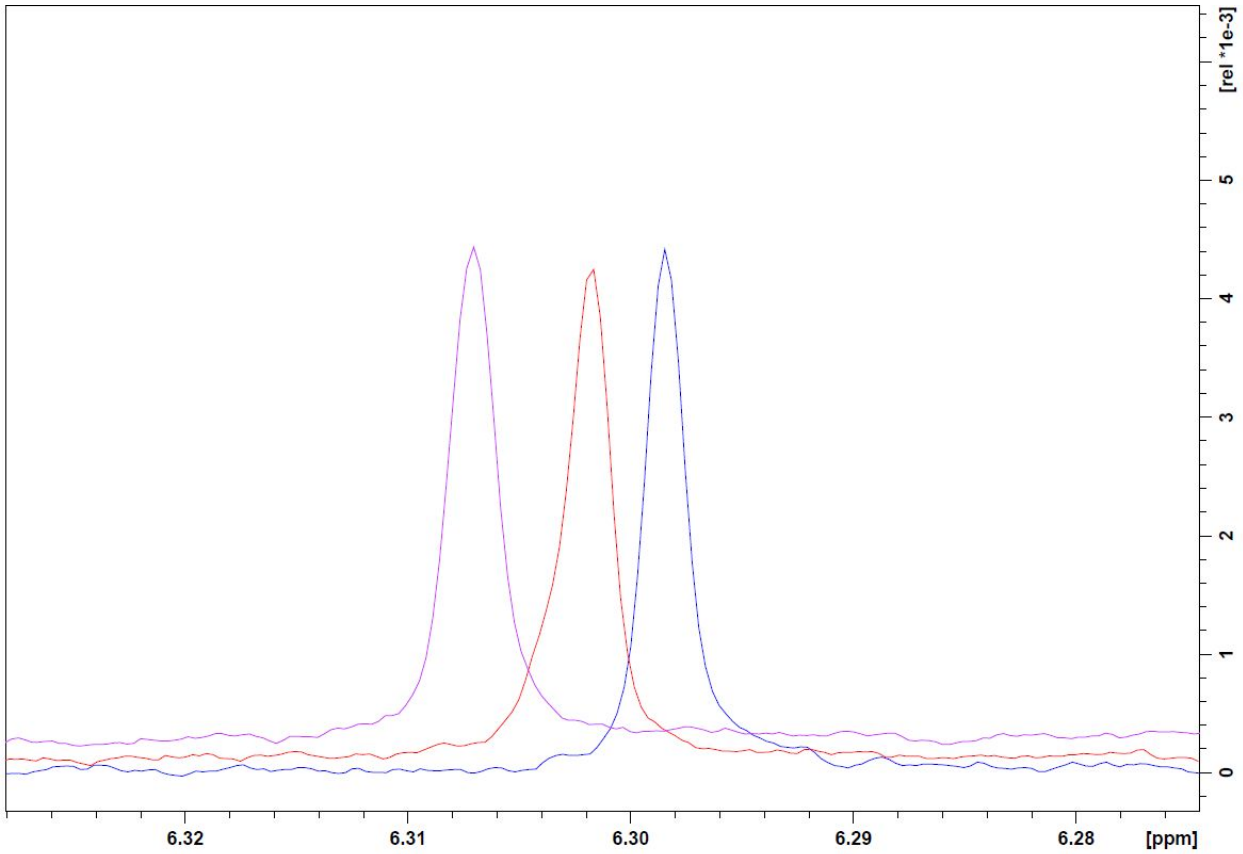

Figure S169. Overlap of ^{1}H NMR spectra of amide bond formation at 0.1M (in purple), with 5 equiv DMTS (in red) and with 10 equiv DMTS (in blue) after 16 h in DMF-d_7 (zoom-in).

9.4 Determination of amidation conversion based on ^{1}H NMR spectra of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction mixtures with and without DMTS containing caffeine as internal standard

General method to calculate the amidation conversion.

1) One well defined (without any overlap) signal of a starting material had to be chosen to follow the amount of this starting material over time. The well defined septuplet at 3.55 ppm corresponding to DIC was deemed as a signal suitable for use in amide bond formation conversion calculations (Figure S170).

2) The amount of DIC was calculated using the internal standard (caffeine) which does not react with the constituent of the amide bond forming reaction and has three well defined singlets at 3.28, 3.48 and 3.98 ppm respectively corresponding to its three methyl groups.

3) The calibration was done on the septuplet at 3.55 ppm corresponding to DIC, which corresponds to two protons. We considered that 1 equiv of DIC was in the solution at this time point.

4) Once the calibration was completed, we carried out the integration for the caffeine at 3.28, 3.48 and 3.98 ppm, corresponding to three protons. Comparing the integrated peak ares for 3) and 4) respectively allowed us to determine the area of the DIC peak at the outset of the amide bond forming reaction.

5) The conversion throughout all amide bond forming reactions studied was calculated integrating the peak of the DIC vs the peak of the caffeine reference at a given timepoint.

This method was used to calculate the conversion of the amide bond forming reactions shown in Fig. 5.

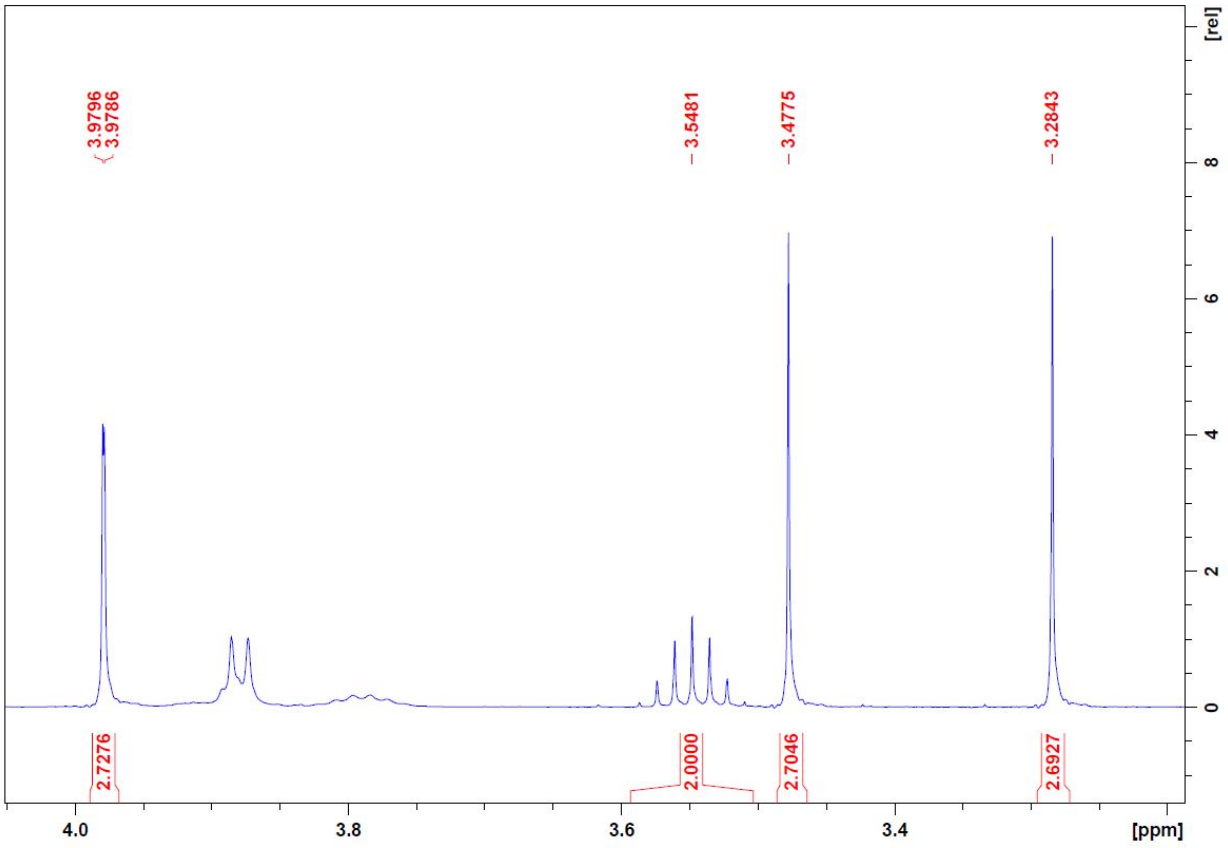

Figure S170. 1D ^{1}H NMR spectrum of Fmoc-Gly-OH/DIC/Oxyma/(S)-(-)-1-phenylethylamine (1:1:1:1) reaction at 0.1M after 1 h in DMF-d_7 (zoom-in).

The results of this section are summarized in Fig. 5.

Specifically, DMTS exhibited good properties in terms of minimizing HCN concentration, both with 5 equiv as well as 10 equiv. The lowering of HCN concentration proceeded faster and more efficiently by using 10 equiv of DMTS. No significant additional peaks were observed by using DMTS, i.e the HCN scavenger does not seem to interfere with the amide bond forming reaction by means of side product formation.

10. Assessment of amide bond formation kinetics during DIC/Oxyma mediated coupling of 1.0 equiv Fmoc-Ser(*t*-Bu)-OH with (S)-(-)-1-phenylethylamine with and without 10 equiv DMTS in DMF and NBP/EtOAc (1:4)

The aim of this section of the SI was to show that DMTS does not interfere with the amidation using different solvents, for which DMF and NBP/EtOAc (1:4) were evaluated.

The general procedure for the assessment of the kinetics of amide bond formation during DIC/Oxyma mediated couplings of Fmoc-Ser(t-Bu)-OH with (S)-(-)-1-phenylethylamine in DMF and NBP/EtOAc (1:4) as described in the section 6 of this SI was followed. In this section, the impact of using 10 equiv DMTS on the kinetics of the amide bond formation is described. Specifically, in section 10.2 an experiment carried out in DMF in the presence of 10 equiv DMTS is described and in section 10.4, an experiment carried out in NBP/EtOAc (1:4) in the presence of 10 equiv DMTS is described. In both cases, DMTS addition was carried out prior to addition of DIC. For all four experiments 10 μL of aliquots of reaction mixtures were taken out and quenched with 0.5 % TFA/MeCN (1.0 mL) at 0, 10, 30, 60, 120 and 960 min. The conversions of the amidation reactions were then determined by HPLC using the following analytical system: column: Waters XBridge C18 100Å 3.5 μm 4.6x50mm; column temperature: 25°C; injection volume: 12 μL; sampler temperature: 4°C; detection wavelength: 273 nm, flow: 1.0 ml/min; mobile phase A: 0.1 % TFA in water, mobile phase B: 0.1 % TFA in MeCN. Gradient (Time(min), %B): 0, 10; 15, 100; 20, 10; 25,10. Following peaks were integrated: i) Fmoc-Ser(*t*-Bu)-OH (starting material), rt 11.8 min; ii) Fmoc-Ser(*t*-Bu)- (S)-(-)-1-phenylethylamide (product of amidation reaction), rt 13.7 min.

10.1 Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF

Following amounts of starting materials were used: Fmoc-Ser(*t*-Bu)-OH (95.6 mg, 0.25 mmol, 1.0 equiv), Oxyma (35.4 mg, 0.25 mmol, 1.0 equiv), (S)-(-)-1-phenylethylamine (32.2 μL, 0.25 mmol, 1.0 equiv), DIC (39.1 μL, 0.25 mmol, 1.0 equiv) in 5 mL DMF.

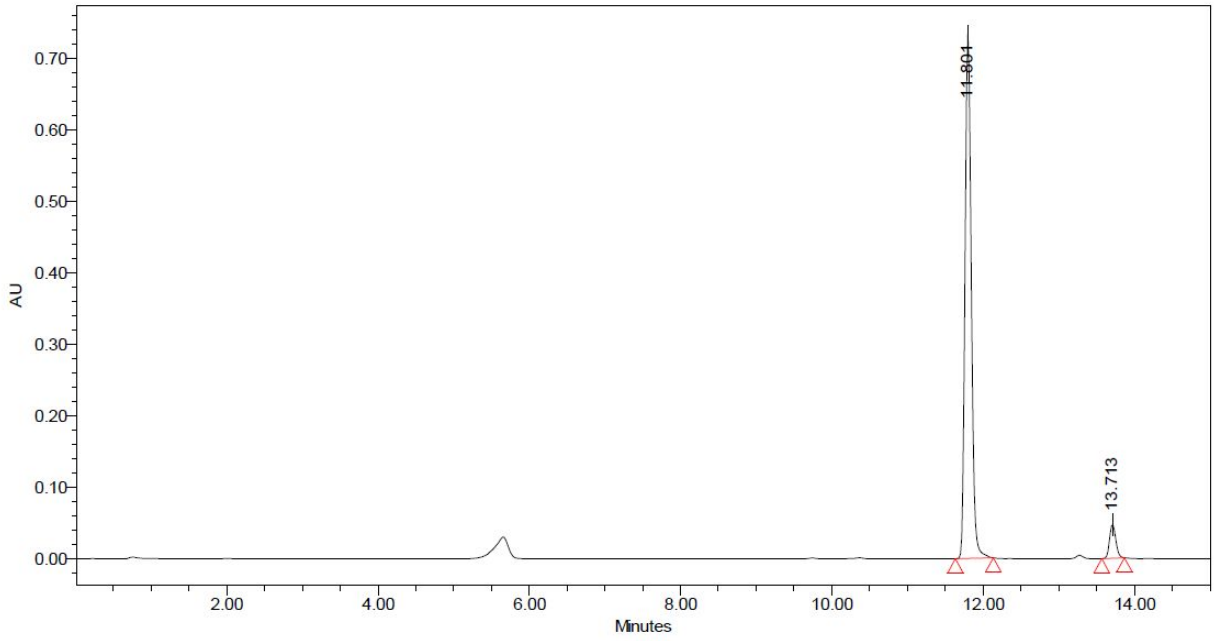

Figure S171. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=10 min.

Table S48. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.801	730370	4178091	93.93
2	13.713	46942	269876	6.07
Sum			4447967.0	

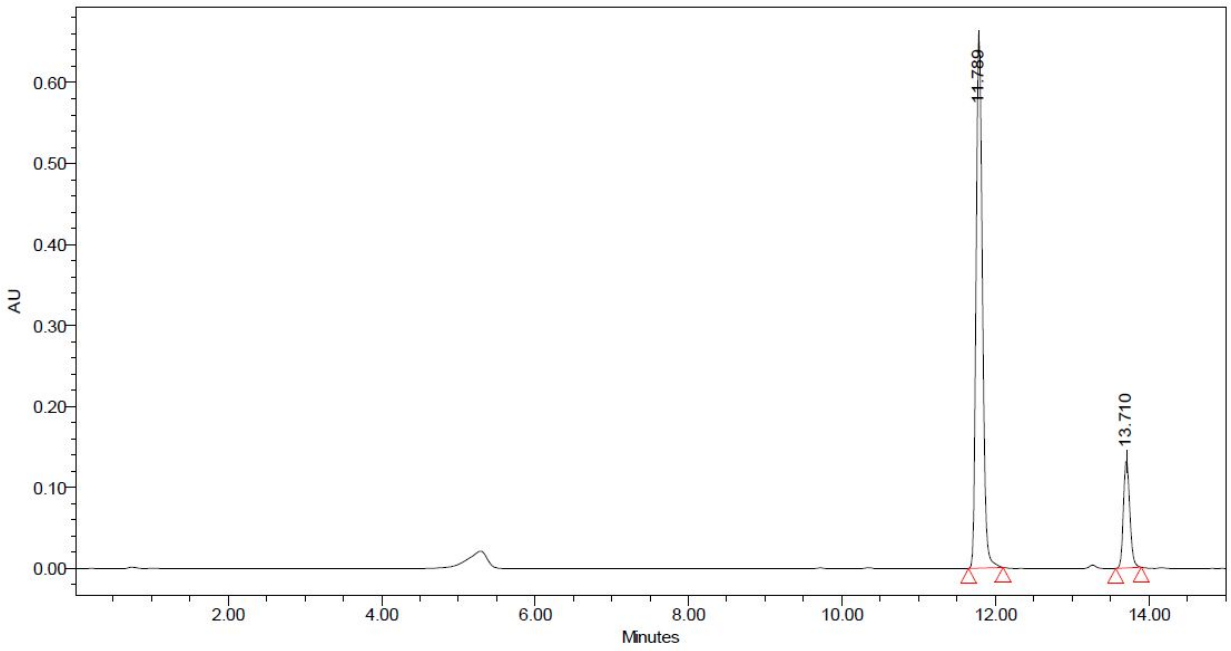

Figure S172. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=30 min.

Table S49. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.789	658758	3751181	83.13
2	13.710	132088	761246	16.87
Sum			4512427.1	

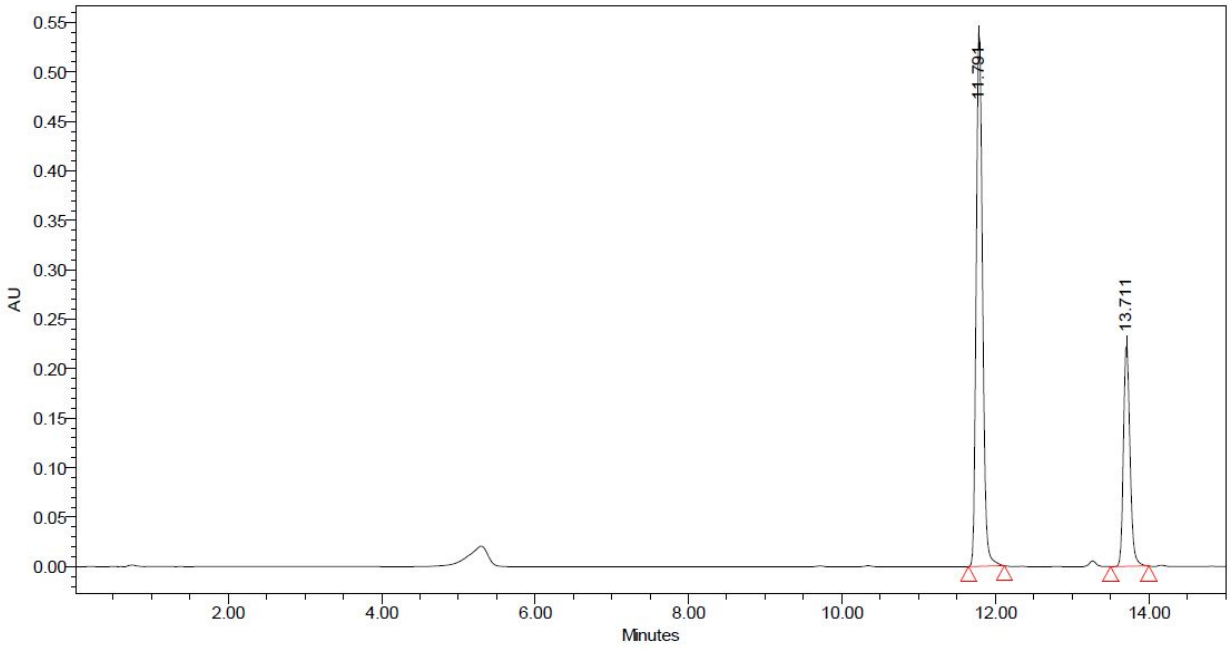

Figure S173. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=60 min.

Table S50. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.791	542126	3079930	70.01
2	13.711	223576	1319498	29.99
Sum			4399428.0	

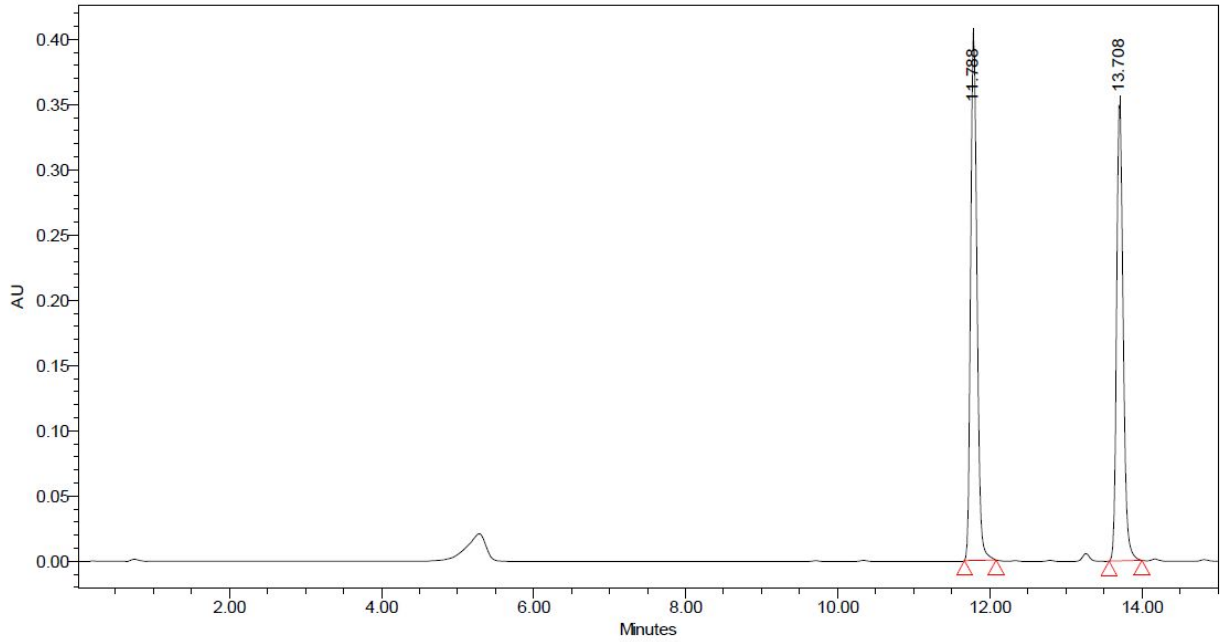

Figure S174. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=120 min.

Table S51. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.788	403677	2325455	52.54
2	13.708	351999	2100488	47.46
Sum			4425942.6	

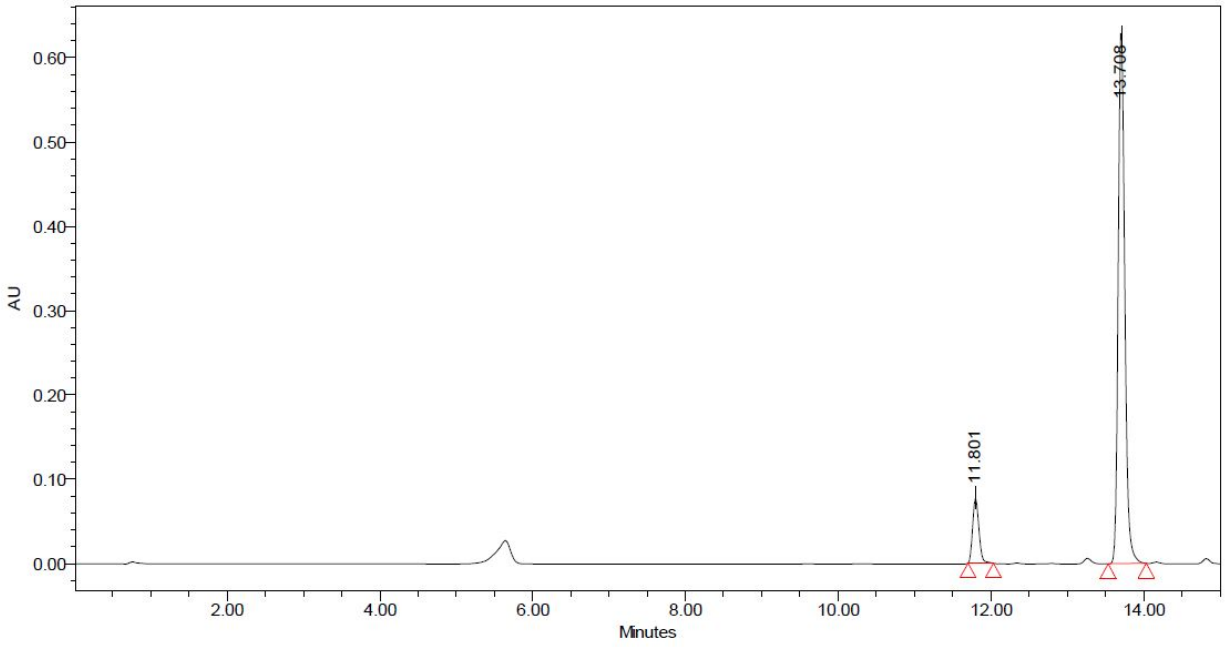

Figure S175. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in DMF at t=960 min.

Table S52. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.801	76905	431896	10.27
2	13.708	633240	3775326	89.73
Sum			4207222.0	

10.2 Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in DMF

The following amounts of starting materials were used: Fmoc-Ser(*t*-Bu)-OH (95.5 mg, 0.25 mmol, 1.0 equiv), Oxyma (35.4 mg, 0.25 mmol, 1.0 equiv), (S)-(-)-1-phenylethylamine (32.2 μL, 0.25 mmol, 1.0 equiv), DMTS (263.5 μL, 2.5 mmol, 10 equiv), DIC (39.1 μL, 0.25 mmol, 1.0 equiv) in 5 mL DMF.

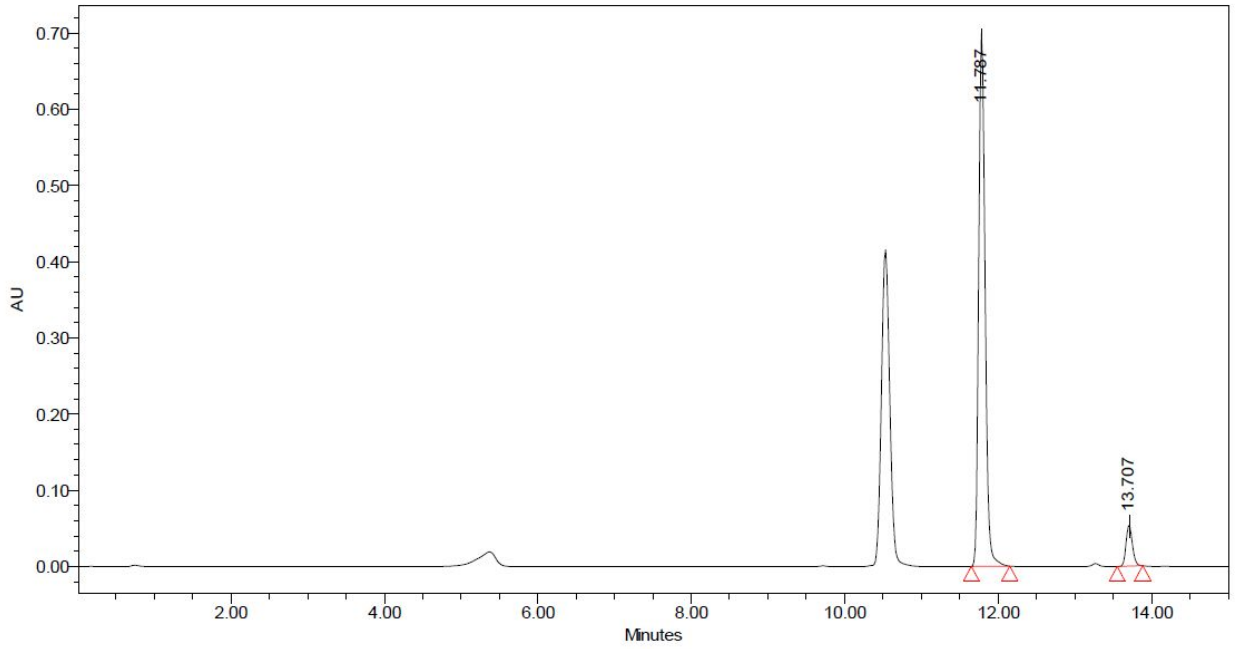

Figure S176. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in DMF at t=10 min.

Table S53. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.787	696418	4036771	92.92
2	13.707	53079	307573	7.08
Sum			4344343.4	

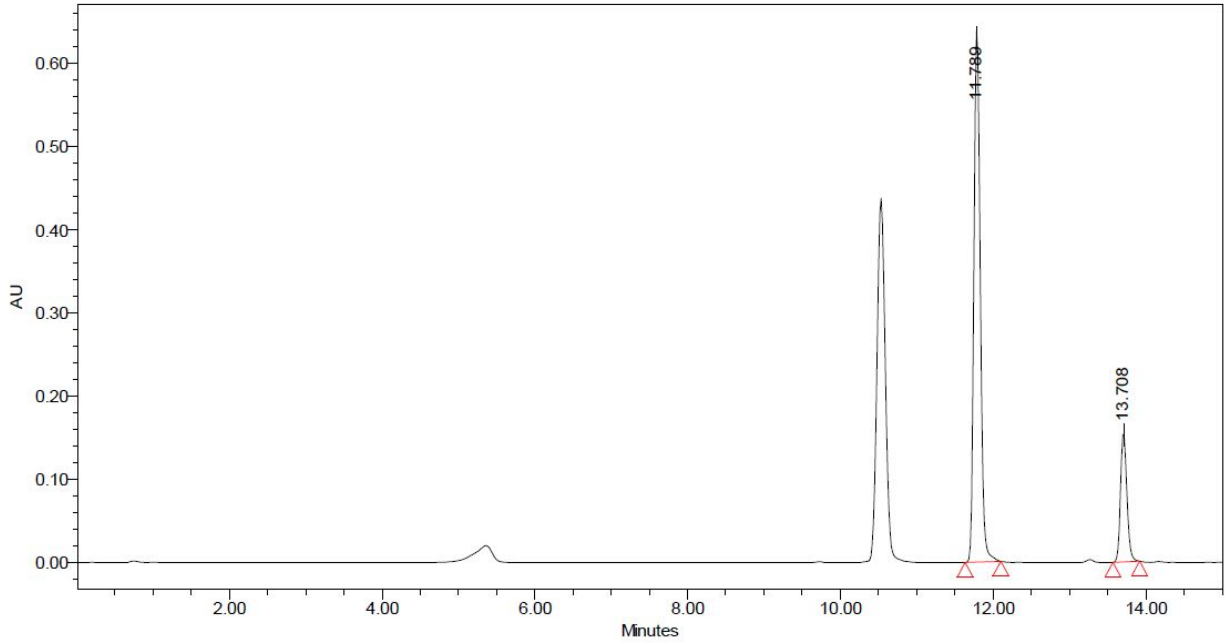

Figure S177. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in DMF at t=30 min.

Table S54. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.789	637978	3683668	80.44
2	13.708	154044	895850	19.56
Sum			4579518.0	

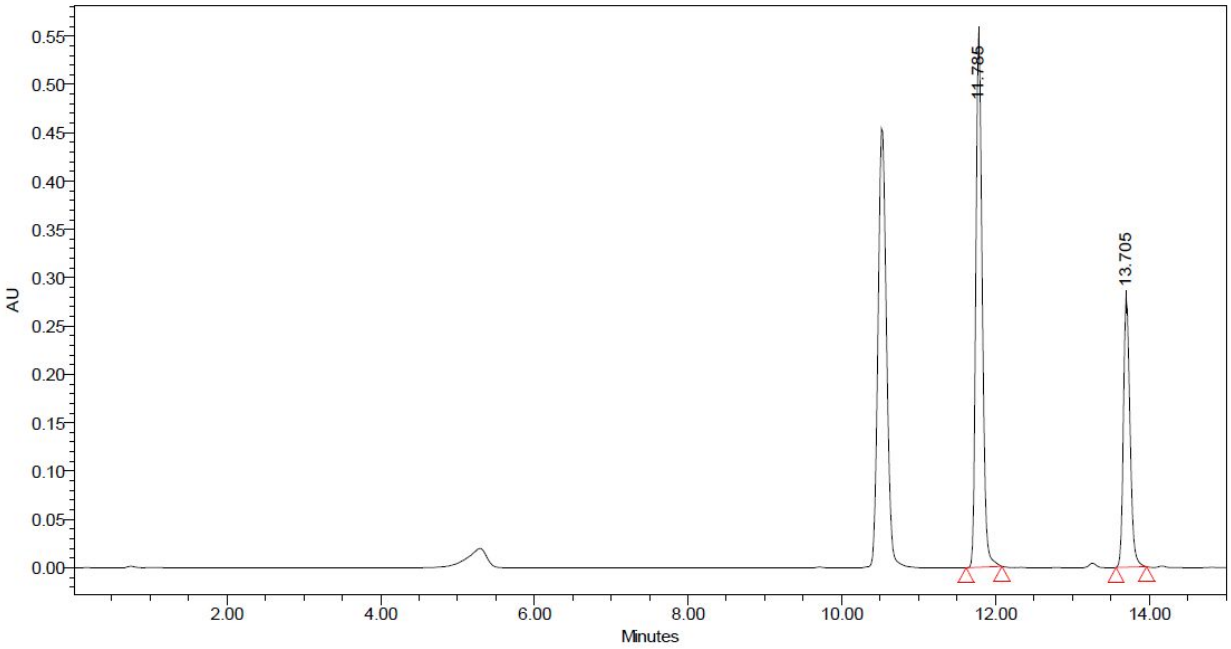

Figure S178. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in DMF at t=60 min.

Table S55. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.785	547927	3168506	65.65
2	13.705	278064	1657638	34.35
Sum			4826144.3	

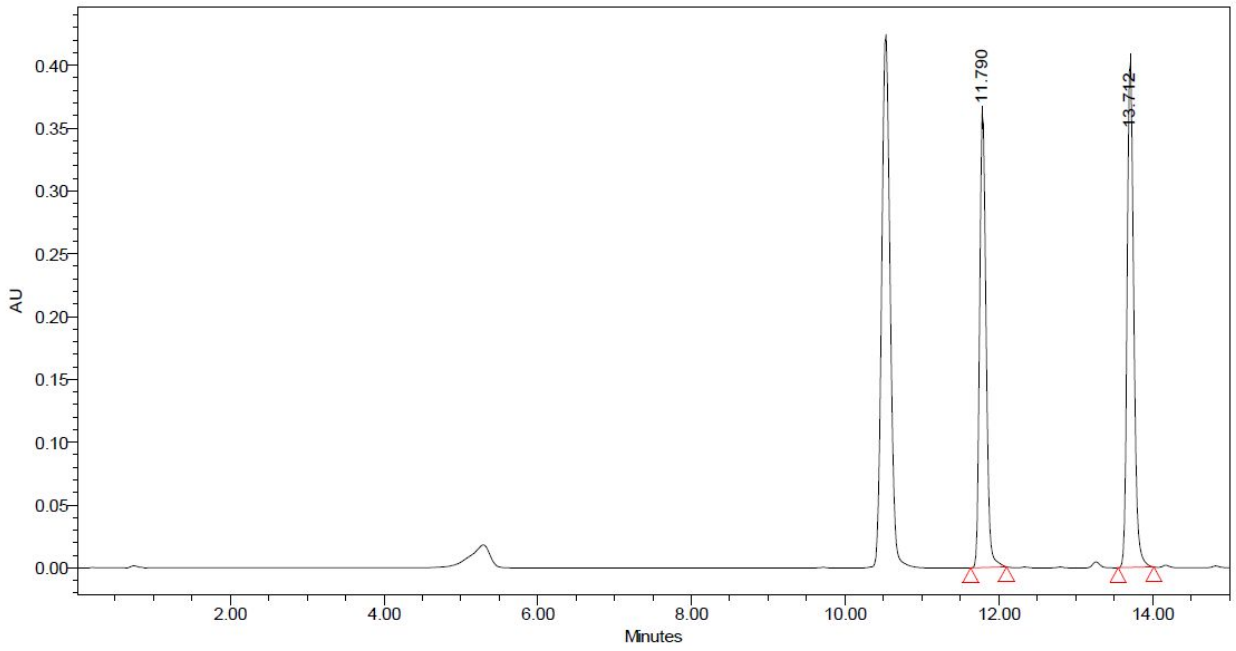

Figure S179. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in DMF at t=120 min.

Table S56. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.790	362895	2096326	46.56
2	13.712	402521	2405872	53.44
Sum			4502197.7	

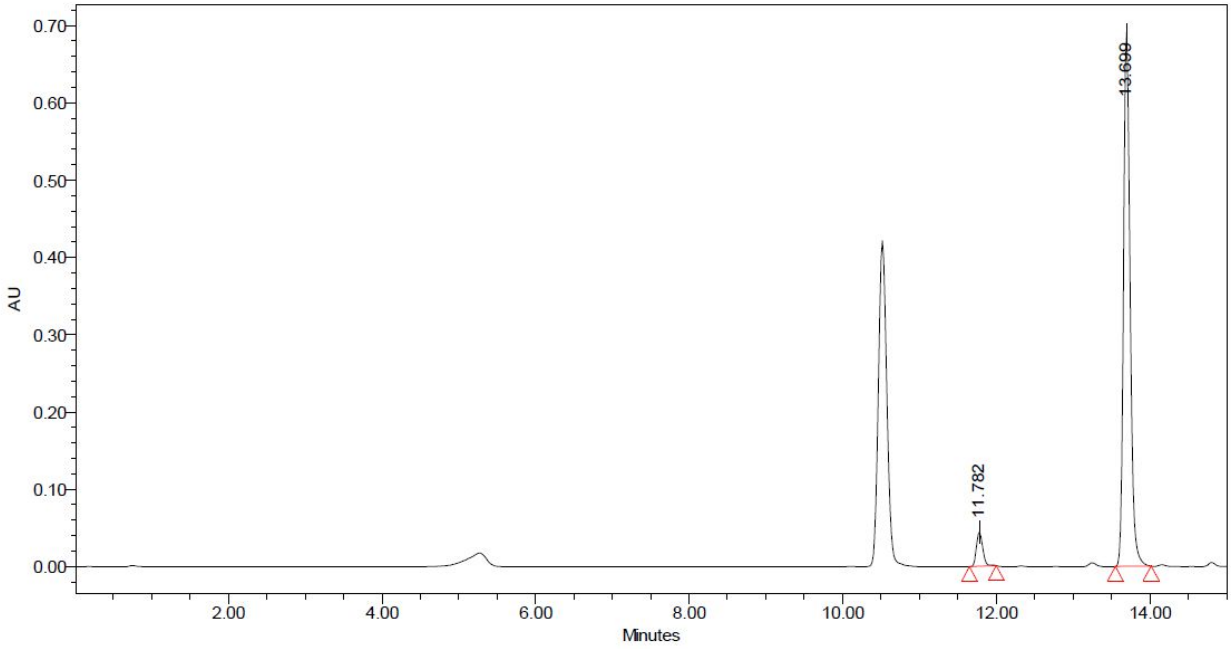

Figure S180. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in DMF at t=960 min.

Table S57. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.782	43785	252376	5.75
2	13.699	686673	4135052	94.25
Sum			4387428.4	

10.3 Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4)

The following amounts of starting materials were used: Fmoc-Ser(*t*-Bu)-OH (95.5 mg, 0.25 mmol, 1.0 equiv), Oxyma (35.1 mg, 0.25 mmol, 1.0 equiv), (S)-(-)-1-phenylethylamine (32.2 μL, 0.25 mmol, 1.0 equiv), DIC (39.1 μL, 0.25 mmol, 1.0 equiv) in 5 mL NBP/EtOAc (1:4).

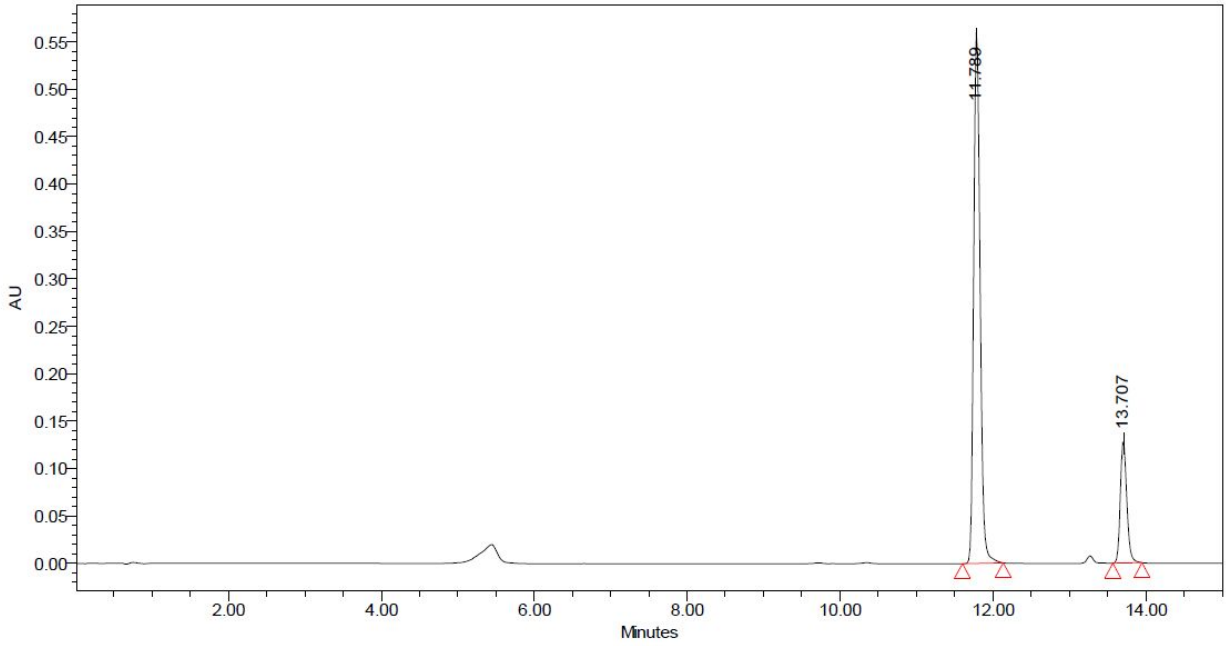

Figure S181. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=10 min.

Table S58. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.789	560175	3234886	81.14
2	13.707	127593	751970	18.86
Sum			3986855.9	

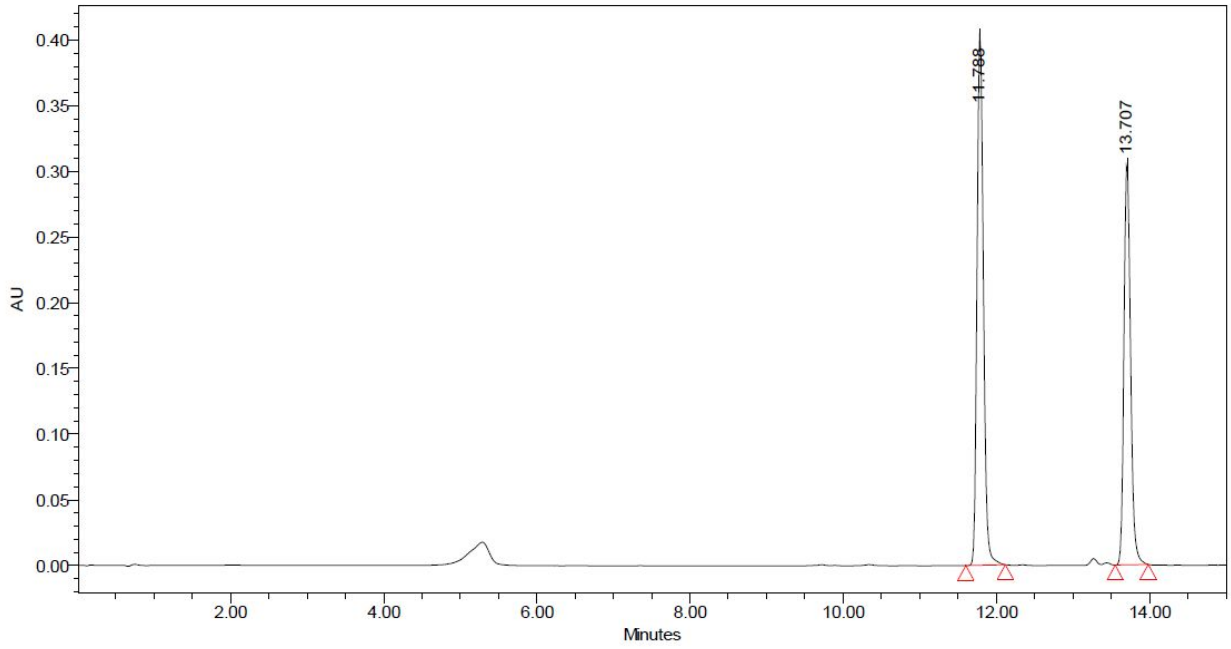

Figure S182. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=30 min.

Table S59. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.788	404595	2327562	56.02
2	13.707	305532	1827204	43.98
Sum			4154765.8	

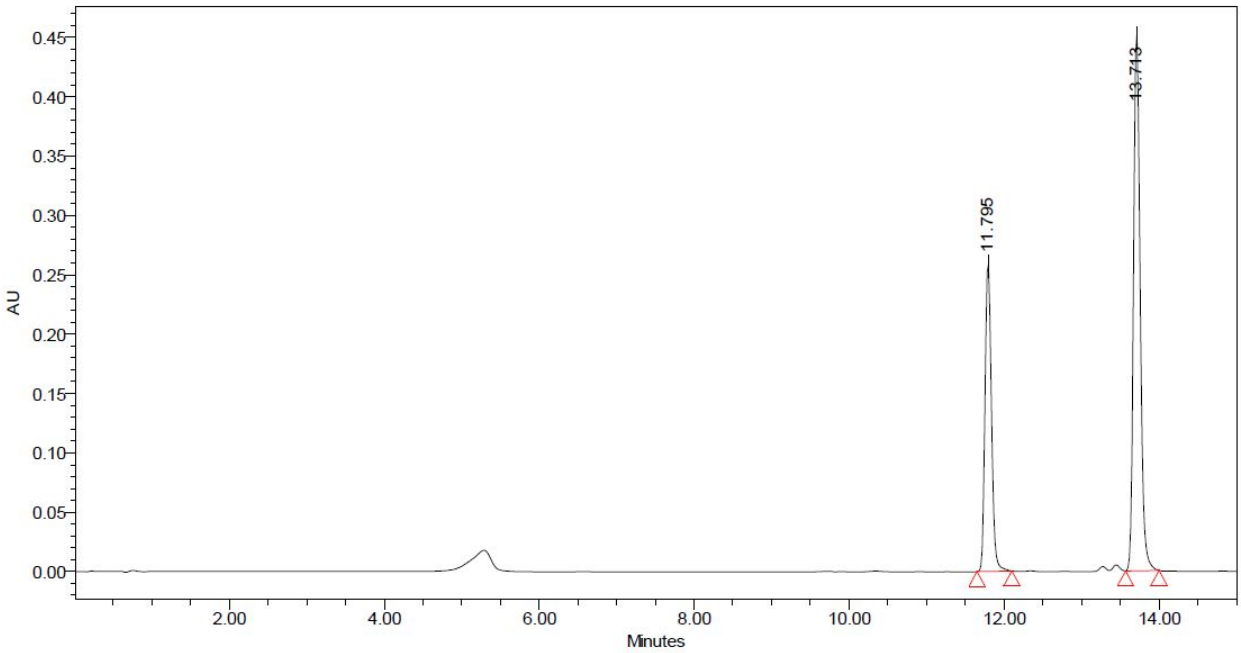

Figure S183. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=60 min.

Table S60. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.795	258492	1484410	35.58
2	13.713	450966	2687963	64.42
Sum			4172373.5	

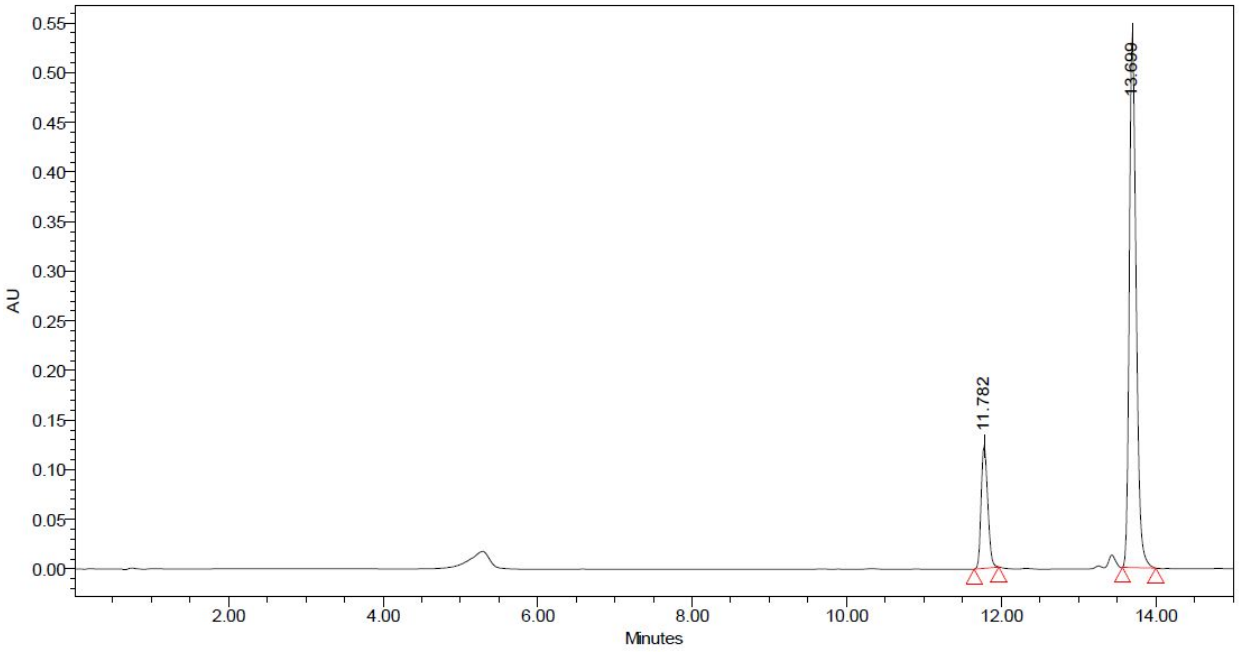

Figure S184. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=120 min.

Table S61. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.782	122951	722478	17.86
2	13.699	535258	3322753	82.14
Sum			4045231.1	

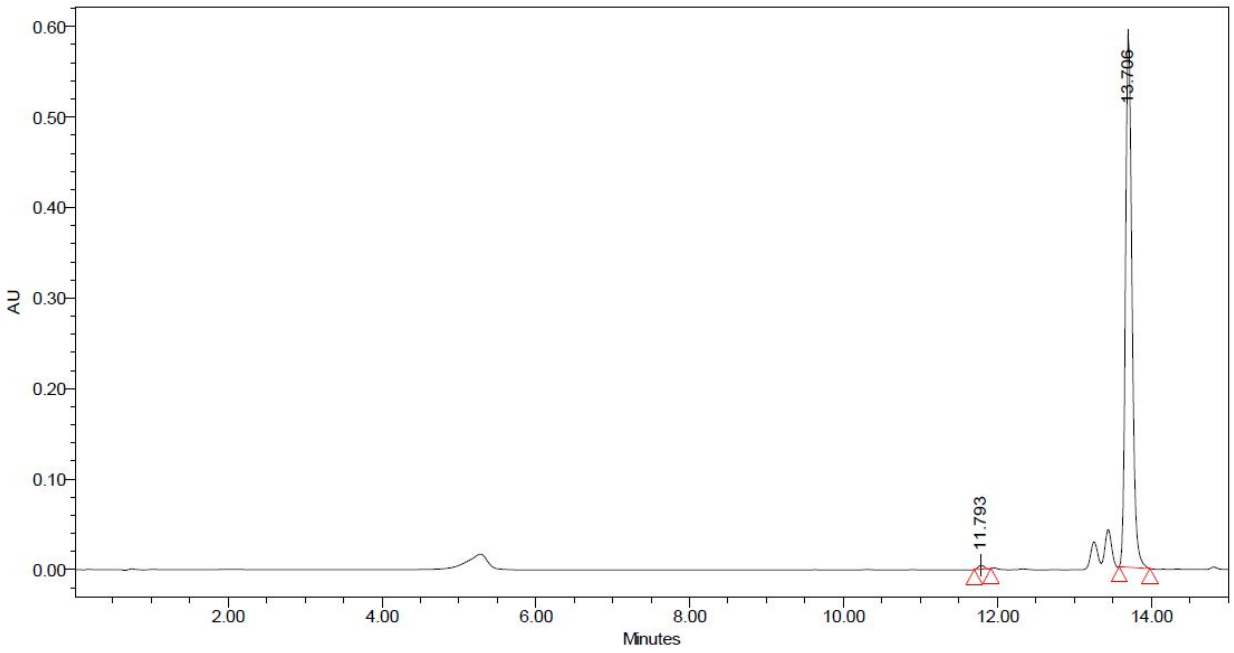

Figure S185. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction in NBP/EtOAc (1:4) at t=960 min.

Table S62. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.793	4304	22750	0.65
2	13.706	588928	3457374	99.35
Sum			3480124.5	

10.4 Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in NBP/EtOAc (1:4)

The following amounts of starting materials were used: Fmoc-Ser(*t*-Bu)-OH (95.8 mg, 0.25 mmol, 1.0 equiv), Oxyma (35.2 mg, 0.25 mmol, 1.0 equiv), (S)-(-)-1-phenylethylamine (32.2 μL, 0.25 mmol, 1.0 equiv), DMTS (263.5 μL, 2.5 mmol, 10 equiv), DIC (39.1 μL, 0.25 mmol, 1.0 equiv) in 5 mL NBP/EtOAc (1:4).

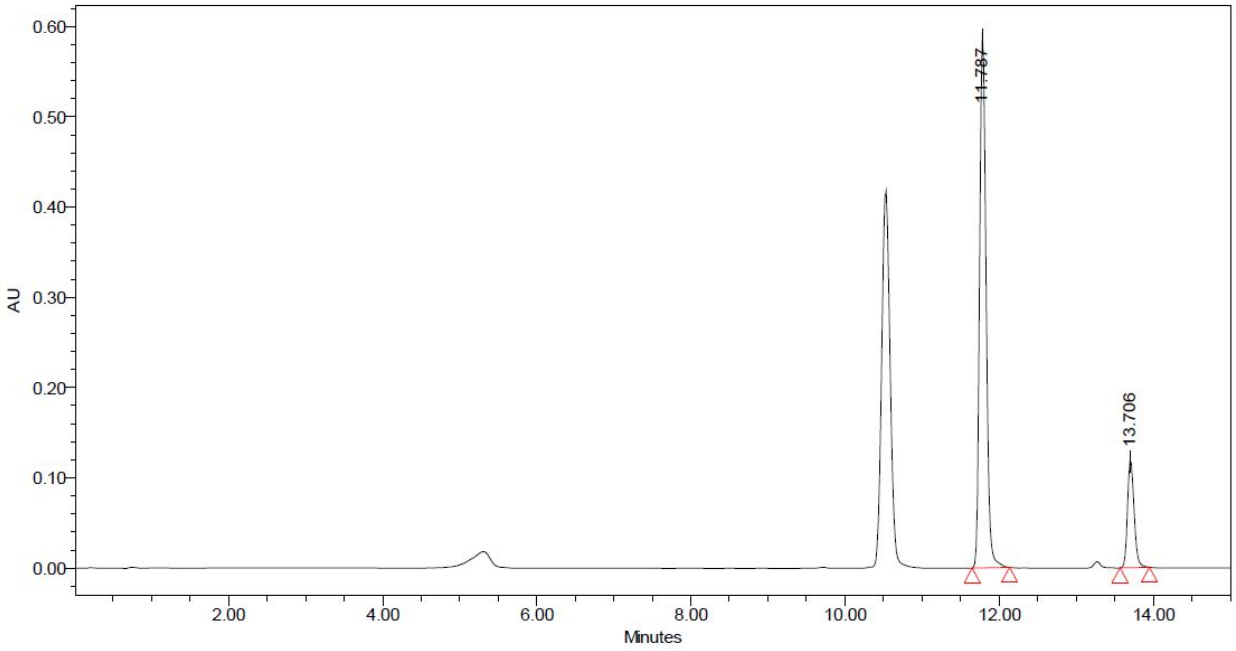

Figure S186. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in NBP/EtOAc (1:4) at t=10 min.

Table S63. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.787	590375	3436636	82.96
2	13.706	119033	705902	17.04
Sum			4142538.1	

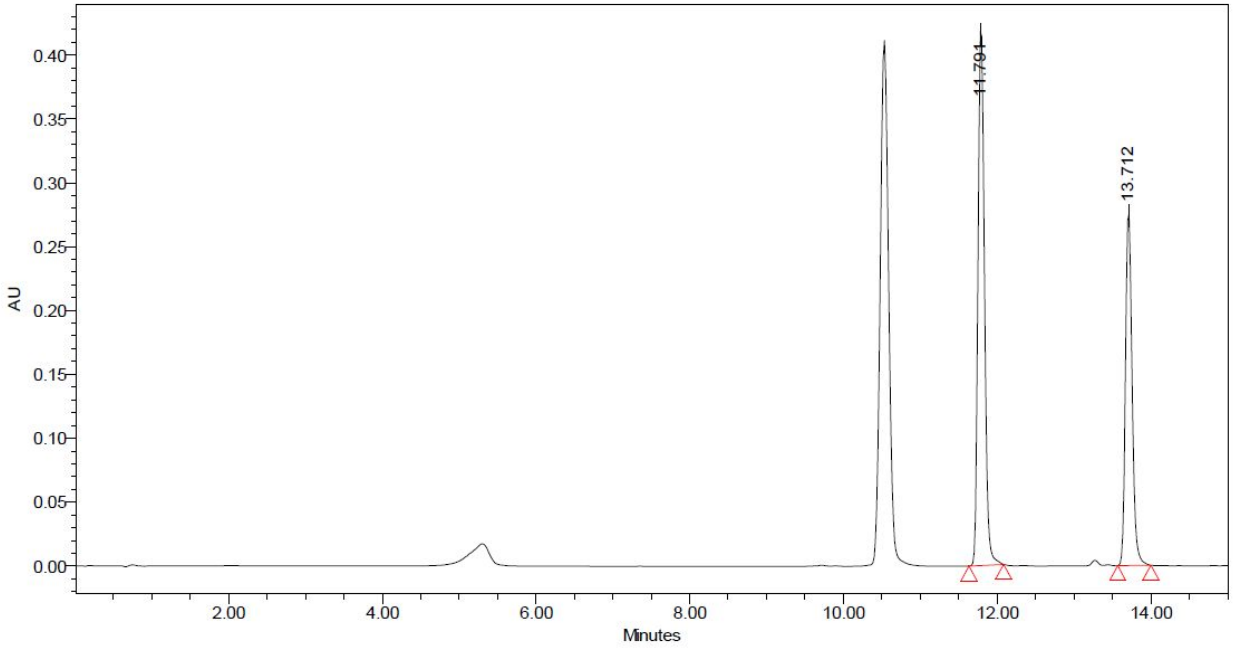

Figure S187. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in NBP/EtOAc (1:4) at t=30 min.

Table S64. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.791	421528	2445923	59.69
2	13.712	275439	1651494	40.31
Sum			4097416.9	

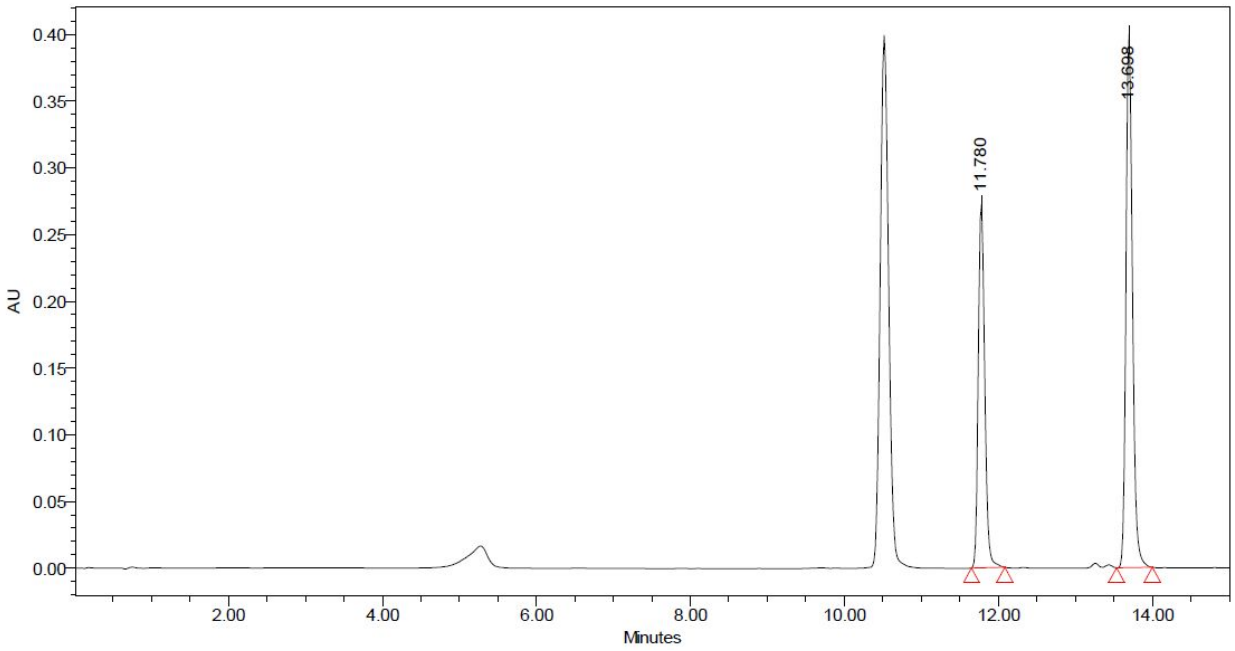

Figure S188. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in NBP/EtOAc (1:4) at t=60 min.

Table S65. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.780	271592	1578353	40.07
2	13.698	397067	2360712	59.93
Sum			3939064.6	

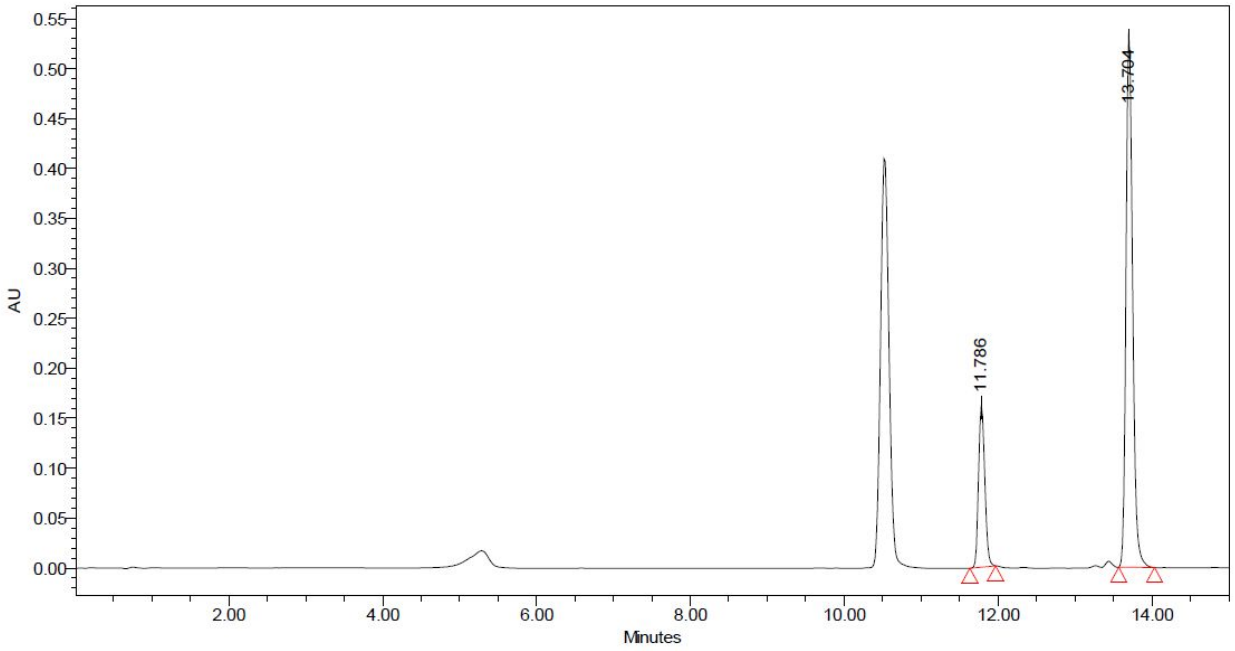

Figure S189. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in NBP/EtOAc (1:4) at t=120 min.

Table S66. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.786	160973	905647	22.09
2	13.704	532832	3194348	77.91
Sum			4099995.5	

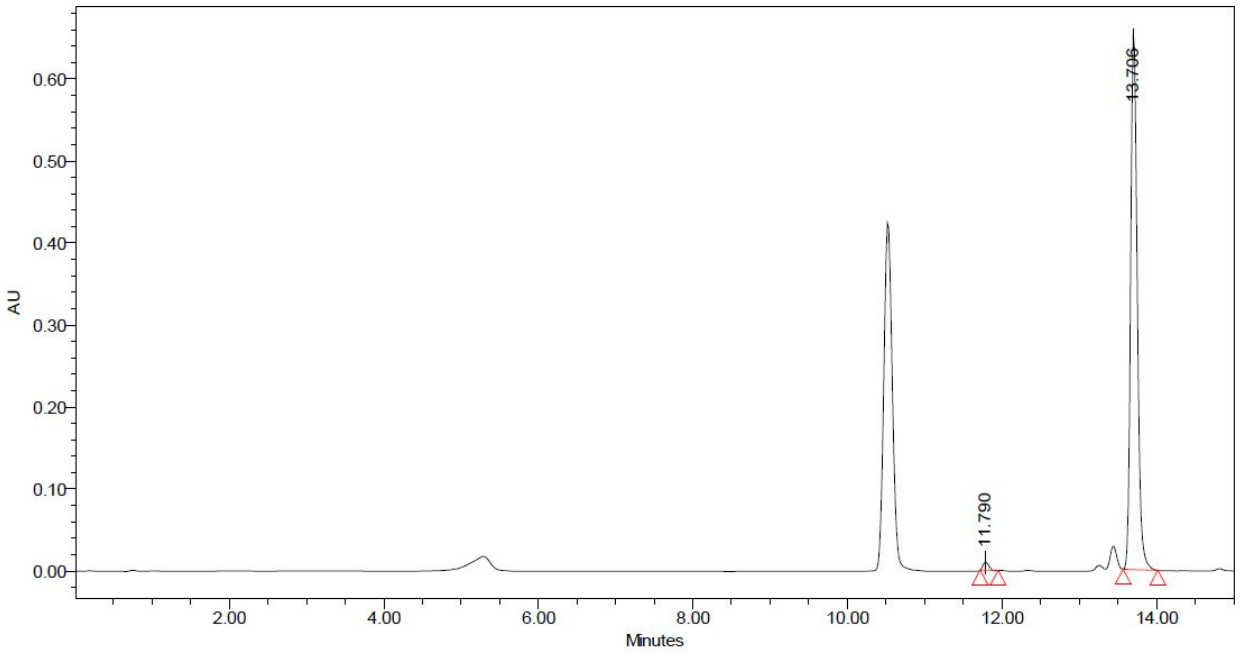

Figure S190. HPLC chromatogram of the Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reaction with 10 equiv DMTS in NBP/EtOAc (1:4) at t=960 min.

Table S67. Area% for integrated peaks.

	RT	Height	Area	% Area
1	11.790	9682	50440	1.28
2	13.706	654833	3900331	98.72
Sum			3950770.8	

10.5 Summary of HPLC conversions for amide bond formation kinetics during DIC/Oxyma mediated coupling of Fmoc-Ser(*t*-Bu)-OH with (S)-(-)-1-phenylethylamine with and without 10 equiv DMTS in DMF and NBP/EtOAc (1:4)

Table S68. A summary of conversions during Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reactions with and without 10 equiv DMTS in DMF and NBP/EtOAc (1:4).

Solvent	DMTS	Time (min)					
		0	10	30	60	120	960
		HPLC % conversion					
DMF	**No**	0.0	6.1	16.9	30.0	47.5	89.7
DMF	**Yes**	0.0	7.1	19.6	34.4	53.4	94.3
NBP/EtOAc (1:4)	**No**	0.0	18.9	44.0	64.4	82.1	99.3
NBP/EtOAc (1:4)	**Yes**	0.0	17.0	40.3	59.9	77.9	98.7

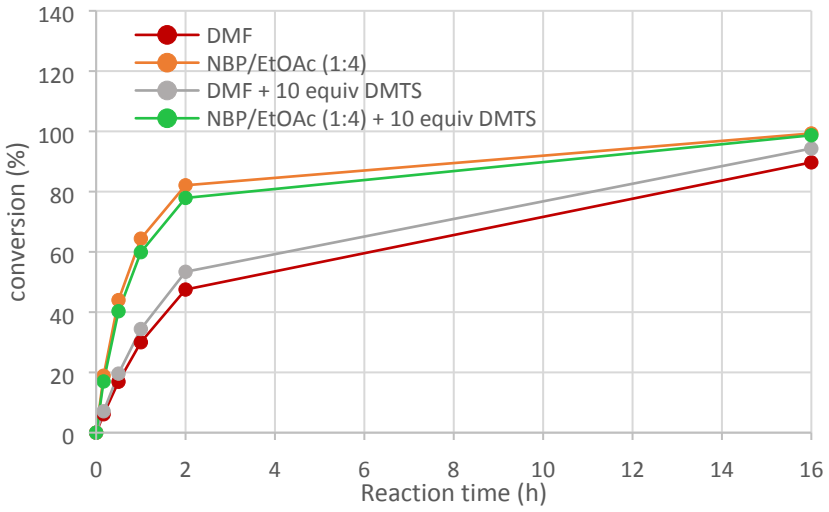

Figure S191. A schematic representation of conversions during Fmoc-Ser(*t*-Bu)-OH/Oxyma/DIC/(S)-(-)-1-phenylethylamine amidation reactions with and without 10 equiv DMTS in DMF and in NBP/EtOAc (1:4).

Conclusions of the experiments summarized in Fig. S191: The presence of DMTS did not have an appreciable impact on the conversion of amide bond forming reaction in neither of the two solvents. Irrespective of whether DMF or NBP/EtOAc (1:4) was used as a solvent no appreciable side reactions were observed as a consequence of addition of DMTS to the DIC/Oxyma mediated amide bond forming reactions.

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