Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

Enantioselective α-Amination of 1,3-Dicarbonyl Compounds in Batch and Flow with Immobilized Thiourea Organocatalysts

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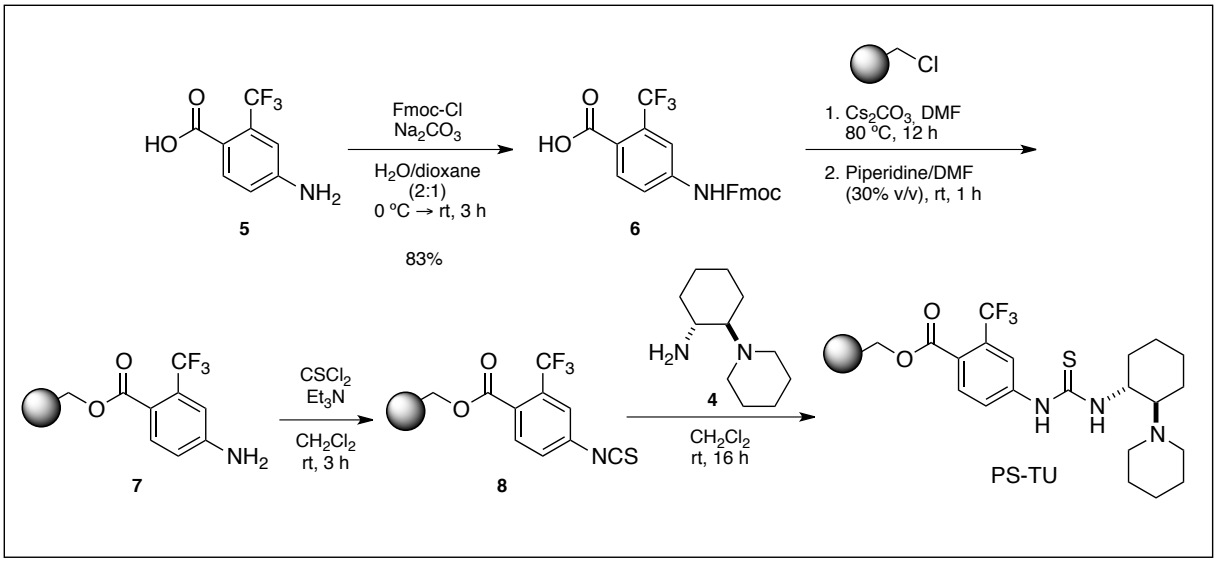
1. General Information

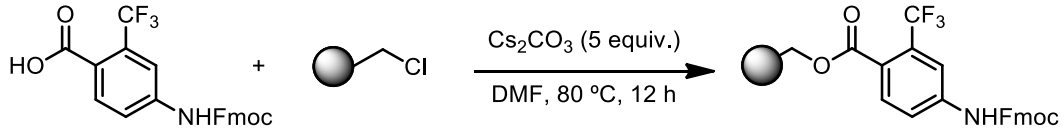
All temperatures given for reaction conditions were externally measured. Organocatalytic reactions were performed without any precaution to exclude air but dry solvents were always used. Merrifield resin (1% DVB, *f* = 0.53 mmol Cl g^{-1} resin) was obtained from Novabiochem. Commercial materials were used as received with the following exceptions: all solvents were taken from Solvent Purification System [1] prior to use. All flash chromatographies were carried out using 60 mesh silica gel and dry-packed columns.[2] The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H or at 100 MHz and 125 MHz for ^{13}C, respectively. TMS or $(CD_3)_2SO$ (2.50 ppm) was used as internal standard for ^{1}H NMR and $CDCl_3$ (77.16 ppm) or $(CD_3)_2SO$ (39.52 ppm) for ^{13}C NMR. Chemical shifts are reported in ppm. FT-IR measurements were carried out on a FTIR spectrometer equipped with a DTGS detector, KBr beamsplitter at 4 cm^{-1} resolution. Elemental analyses were performed on a CHNS 932 micro-analyzer. The experiments under microwave irradiation were carried out in a CEM Discover microwave reactor. High performance liquid chromatography (HPLC) was performed by using commercial Chiralpak columns and guard columns. Racemic standard products were prepared using triethylamine or DABCO (20 mol%) as catalyst in order to establish HPLC conditions. Compound **4** was synthesized according to a reported procedure.[3] The degree of functionalization of a resin can be calculated from the results of elemental analysis with the formulas: $f_N = (0.714/n_N)\%N$, where n_N is the number of nitrogen atoms in the functional unit and %N is the percent of nitrogen provided by the elemental analysis.[4]

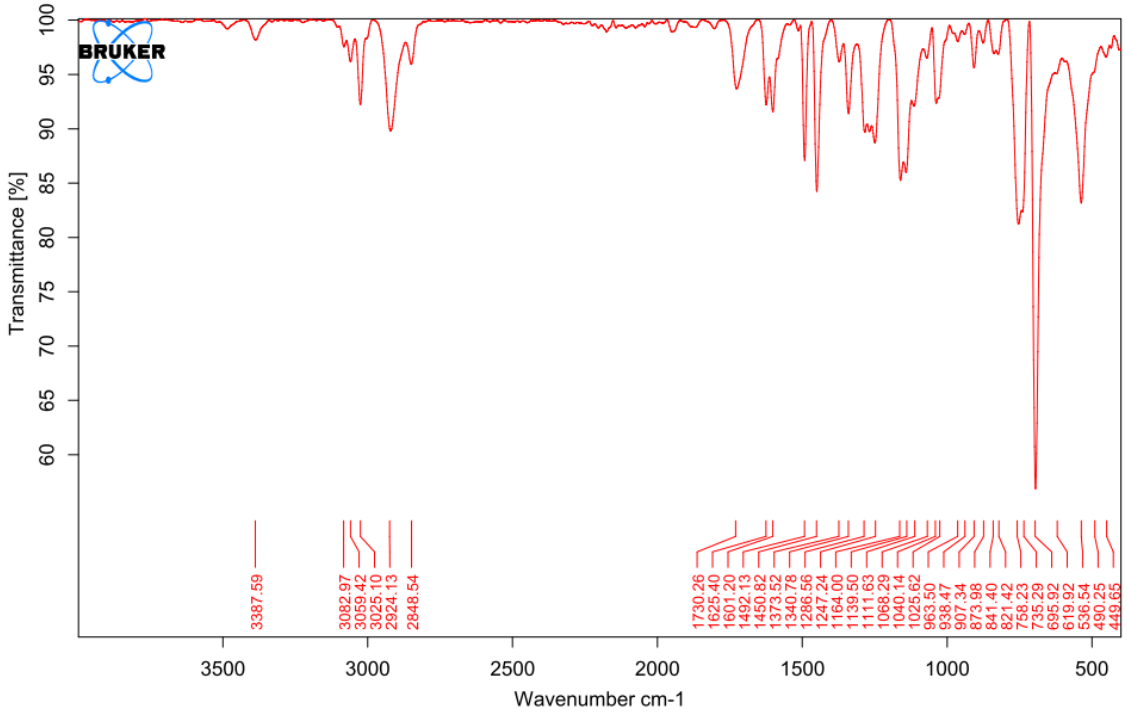
[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518-1520.
[2] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.
[3] Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.*, **2010**, *49*, 153-156.
[4] A. Bastero, D. Font and M. A. Pericàs, *J. Org. Chem.* **2007**, *72*, 2460-2468.

2. IR Spectra of Resins in the Synthesis of the PS-Thiourea Catalyst (PS-TU)

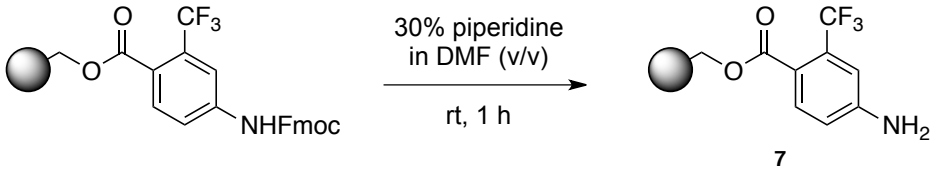


PS-NHFmoc resin





PS-NH_2 resin (7)



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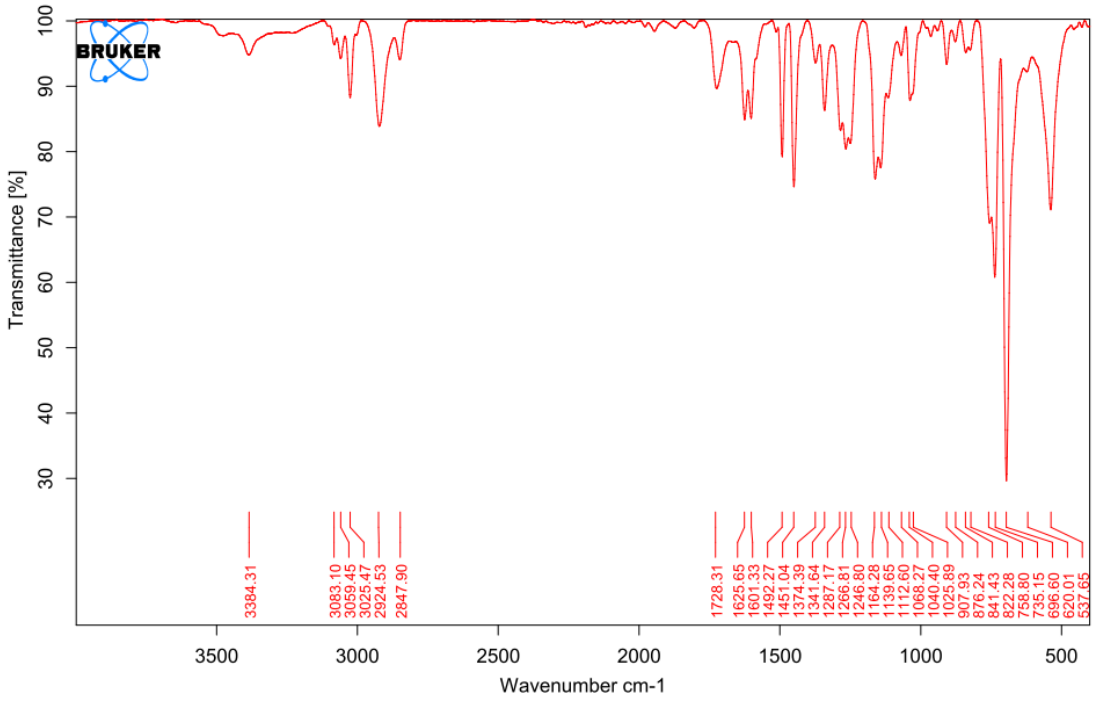
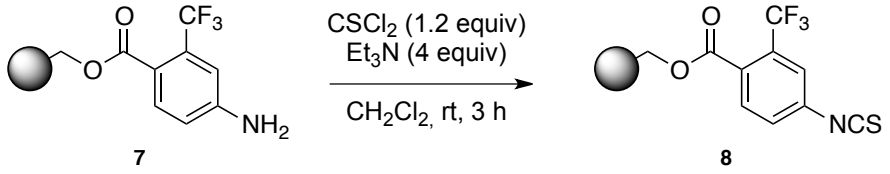


Polystyrene-supported 4-isothiocyanato-2-(trifluoromethyl)benzoate (8)



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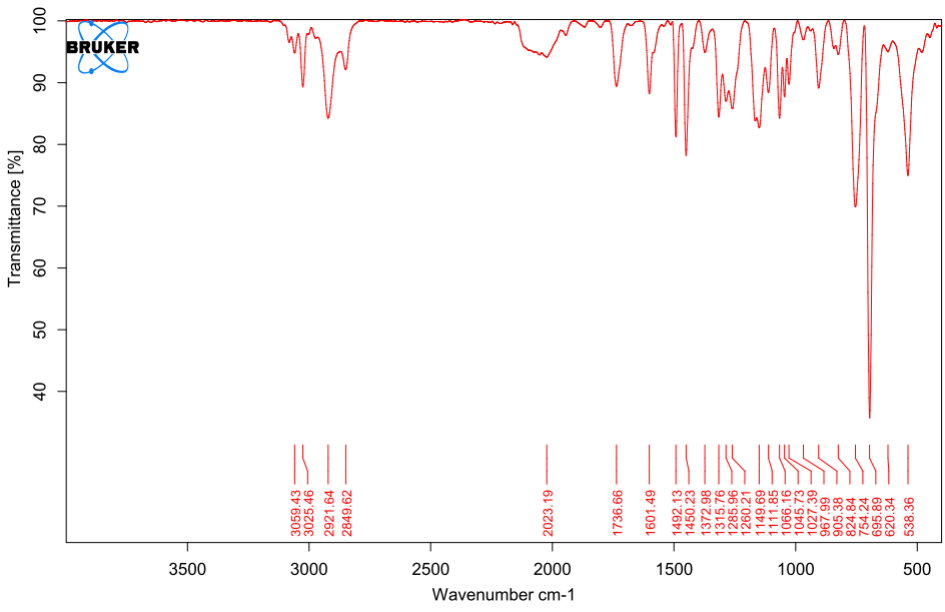
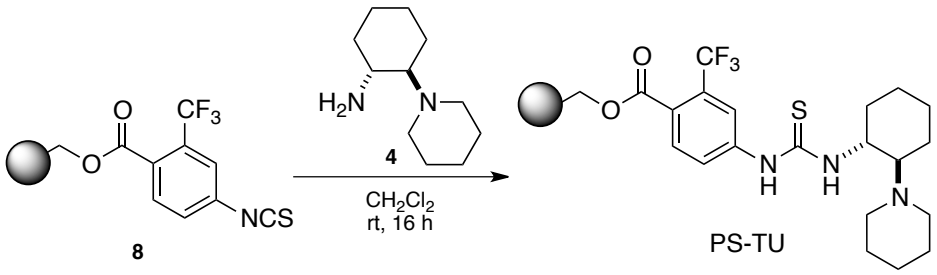
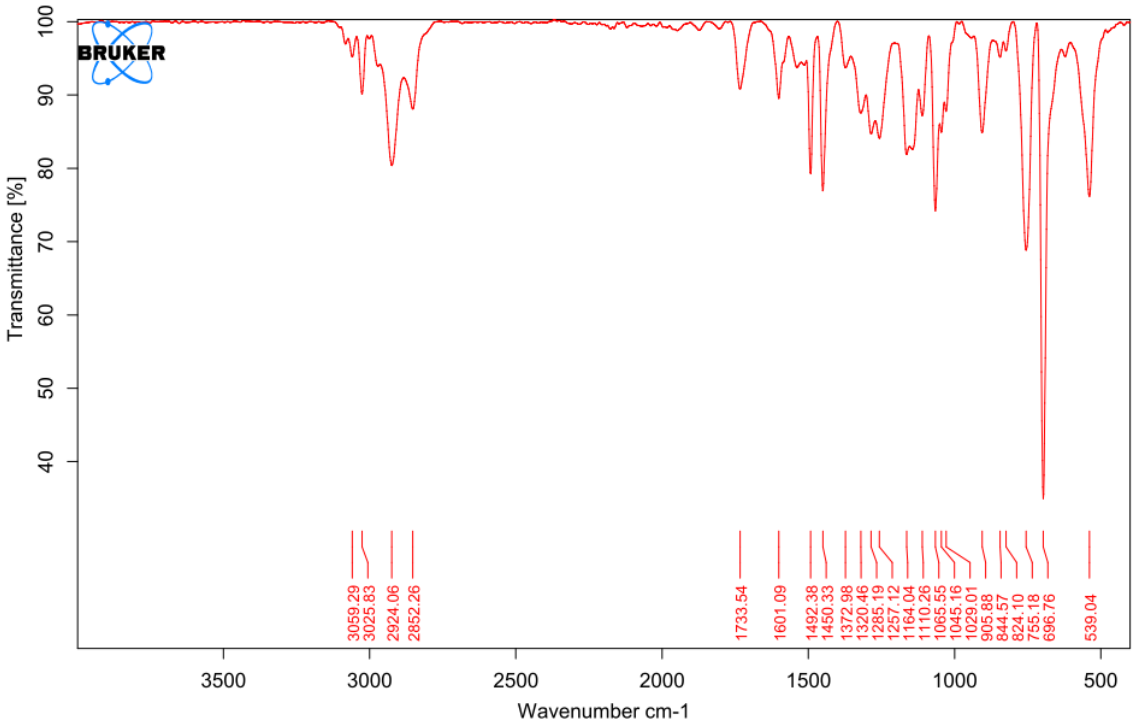


PS-TU Catalyst





3. Description of the experimental set-up for the continuous-flow amination catalyzed by PS-TU

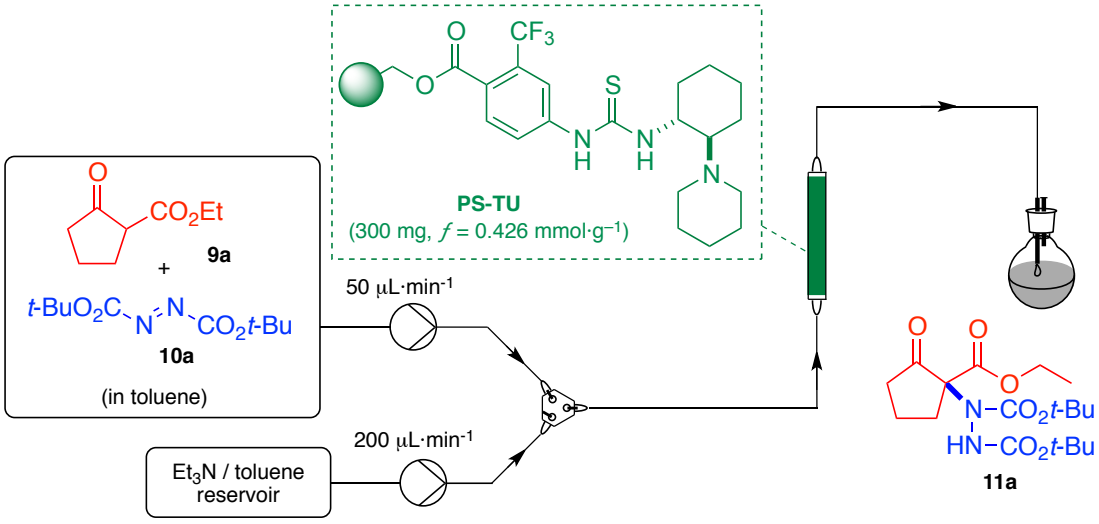


Figure S1. Continuous flow setup for the reaction of di-*tert*-butyl azodicarboxylate and ethyl 2-oxocyclopentanecarboxylate.

For the continuous flow experiments, the instrumental setup shown in **Figure S1** was used. The packed bed reactor consisted of a vertical mounted and fritted low-pressure Omnifit glass chromatography column (10 mm bore size and up to maximal 70 mm of adjustable bed height) loaded with the polymer-supported thiourea resin **PS-TU** (300 mg, f = 0.426 mmol·g^{-1}). The reactor inlet was connected to a three-way connector that allowed switching between two channels, connected to an Asia120® flow chemistry system developed by Syrris. At the start, toluene was flushed for 30 min at 200 µL·min^{-1} flow rate to swell the resin. After that, the solvent channel was switched to a solution of di-*tert*-butyl azodicarboxylate (1.52 g, 6.59 mmol, 1 equiv.) and ethyl 2-oxocyclopentanecarboxylate (1.46 mL, 9.89 mmol, 1.50 equiv.) in toluene (22 mL) (no reaction occurs in the absence of catalyst), which was pumped through the reactor at 50 µL·min^{-1} flow rate. The reactor outlet was connected to a receiving flask, where the product was collected. The other inlet channel was connected to a flask containing a triethylamine (700 µL) in toluene (25 mL) reservoir to clean the system (every 2 h, this solution was pumped through the reactor for 20 min at 200 µL·min^{-1} flow rate to restore catalytic activity and discarded without being collected). The formed product at any moment was characterized by ^{1}H NMR (conversion) and HPLC (enantiomeric excess) measurements of periodically collected samples. After 7.5

h of flowing the reactants, the flow process was stopped and the catalytic resin was washed with toluene for 30 min. Then, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (cyclohexane-ethyl acetate, 95:5 to 90:10) to afford the final product as a thick colorless oil with 71% isolated yield (1.81 g, 4.68 mmol). Productivity: 4.88 mmol·mmol$_{cat}^{-1}$·h^{-1}; TON: 37 (from pure isolated product).

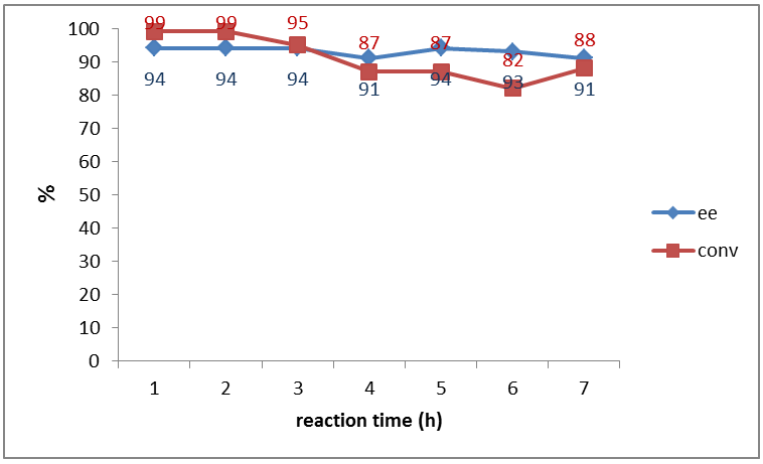


Figure S2. Data recorded for the continuous flow experiment over time.

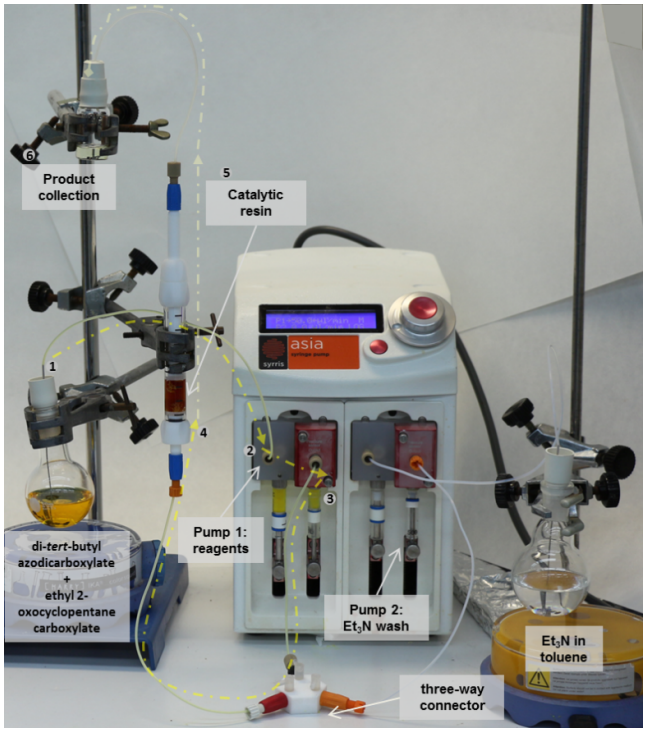
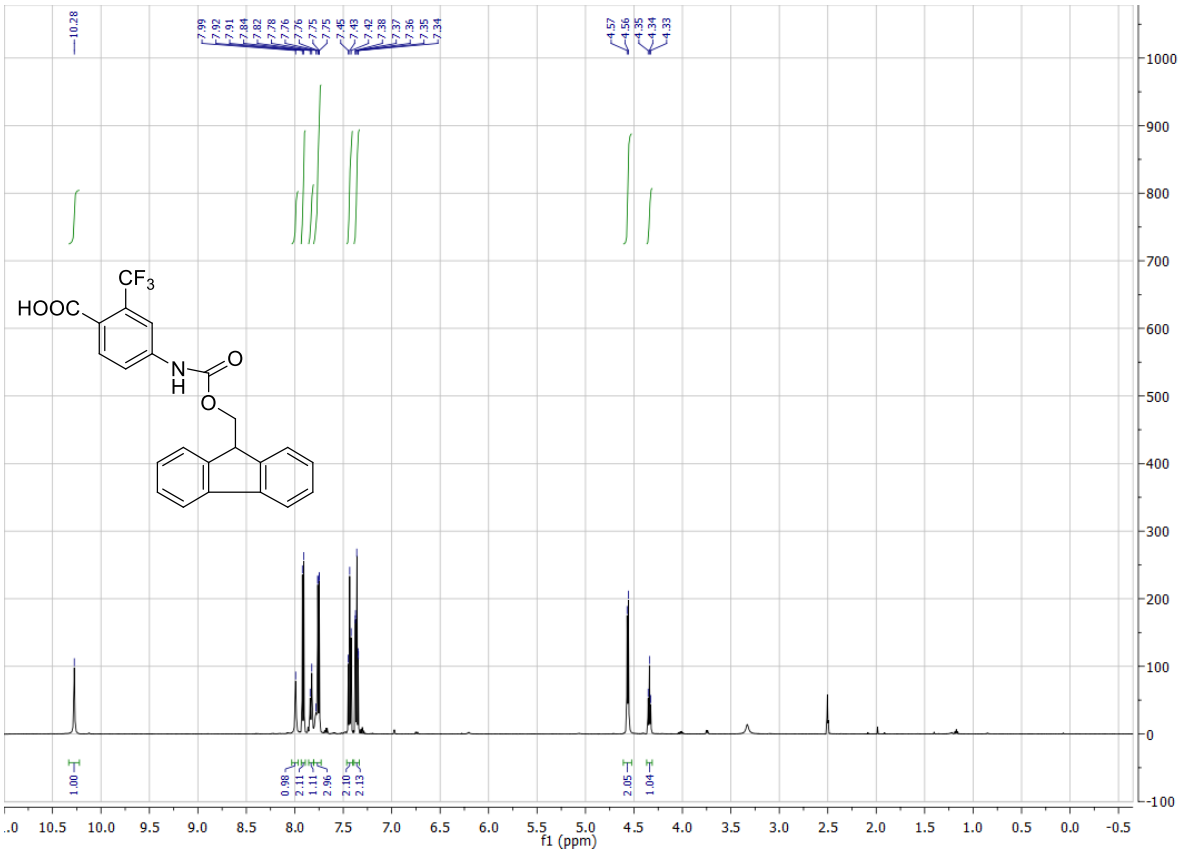
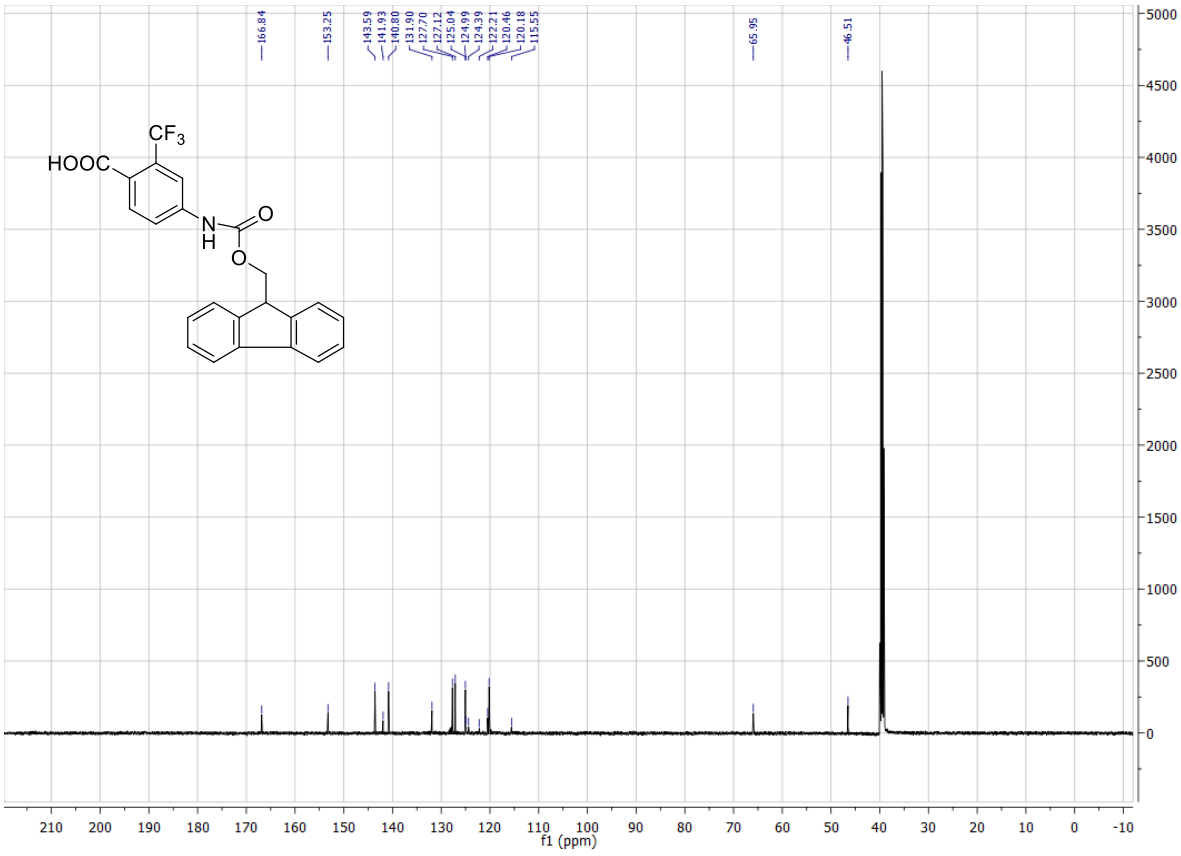


Figure S3. Continuous flow apparatus during the flow reaction.

4. NMR Spectra

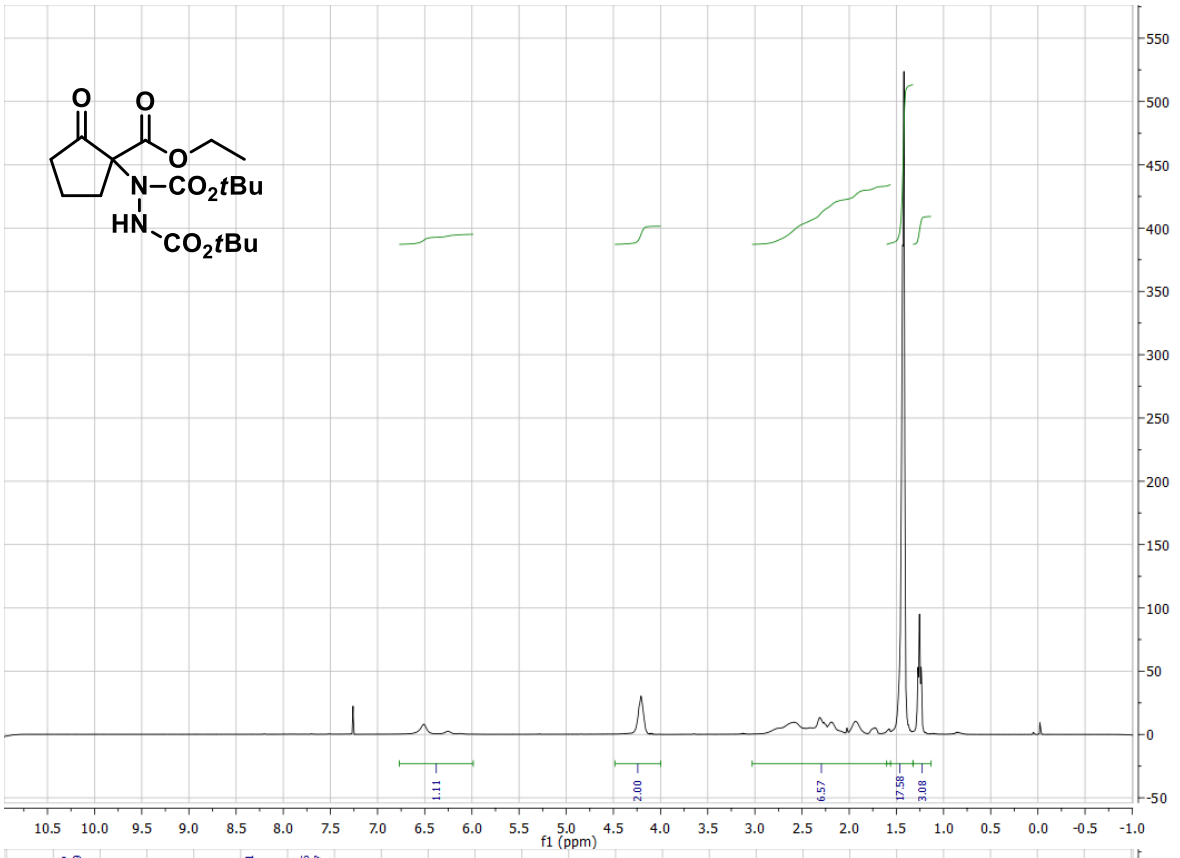
Carboxylic acid 6

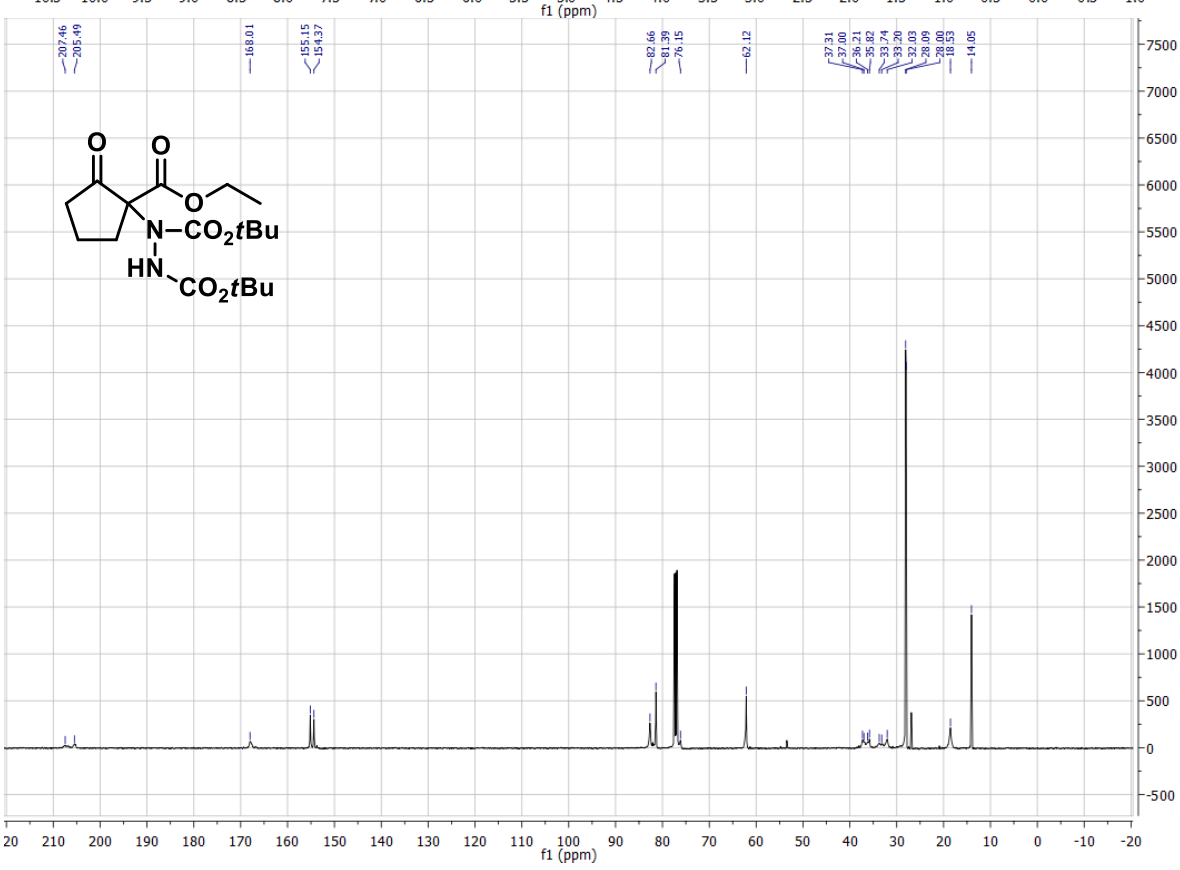




α-Amination products

11a





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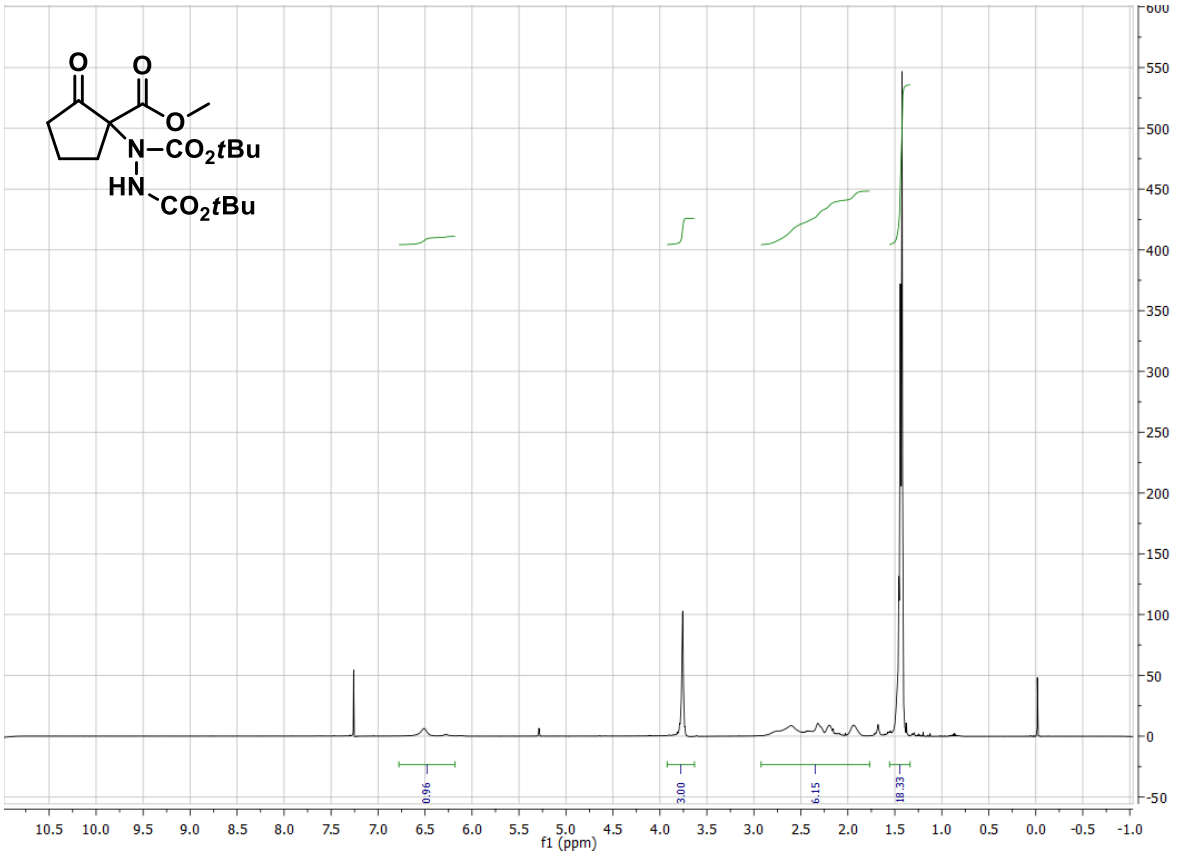
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O
O
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HN
CO2tBu
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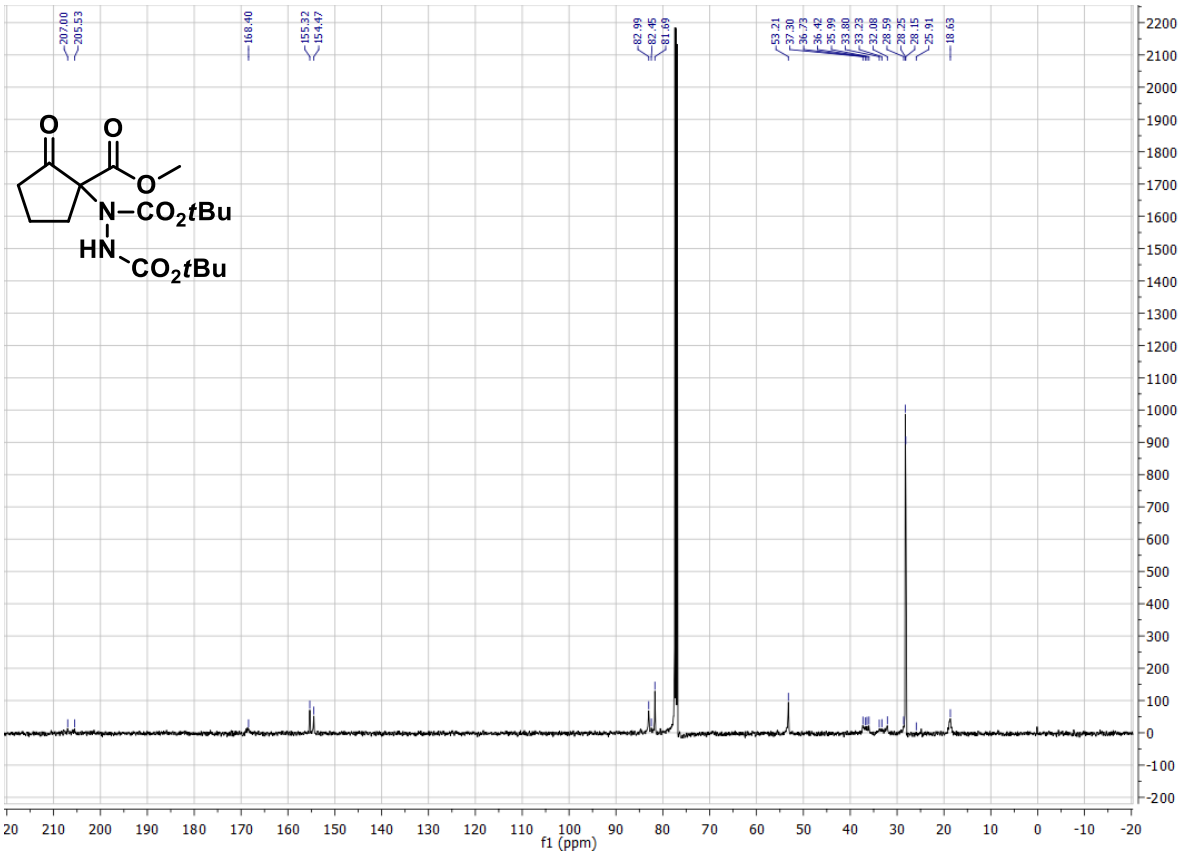
3.00
6.15
18.33
f1 (ppm)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168.40
155.32
154.47
82.99
82.45
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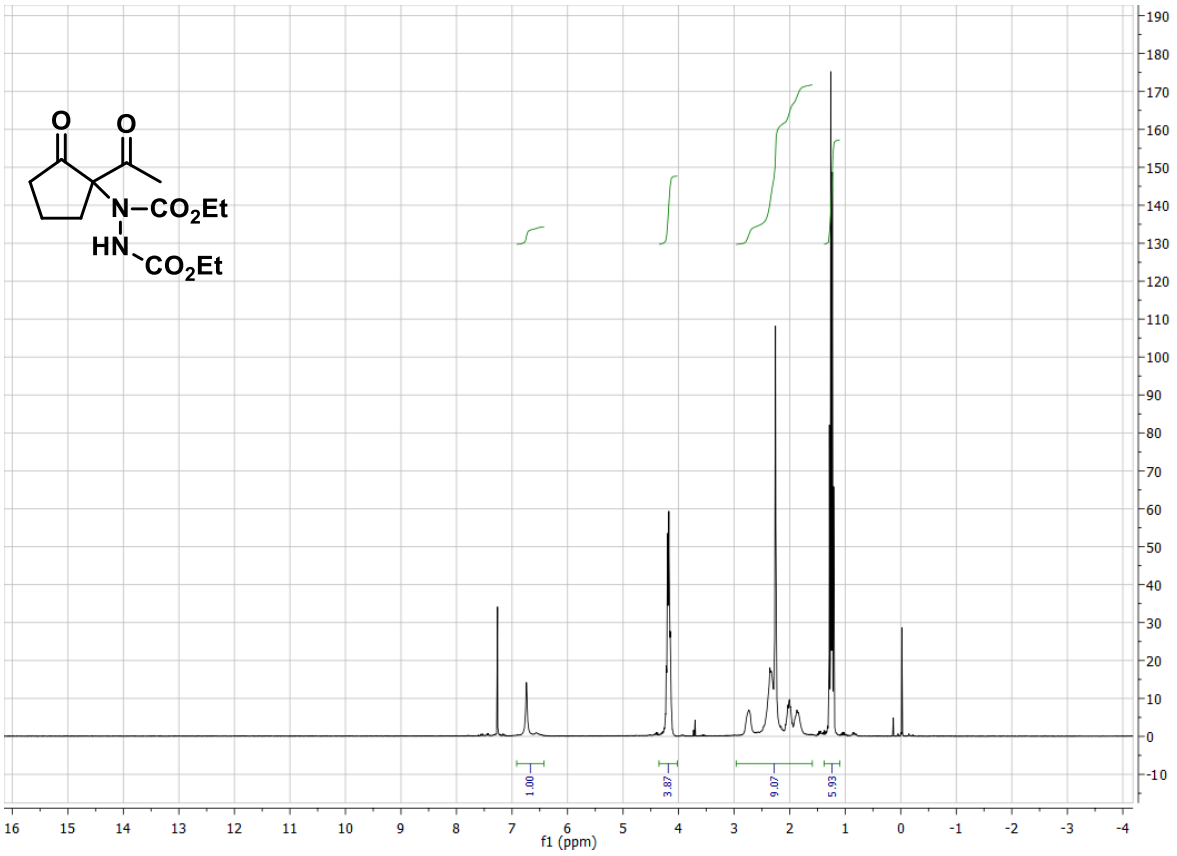
37.30
36.73
36.42
35.99
33.80
33.23
32.08
28.59
28.25
28.15
25.91
18.63
O
O
O
N–CO2tBu
HN
CO2tBu
f1 (ppm)

11cEt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5.93
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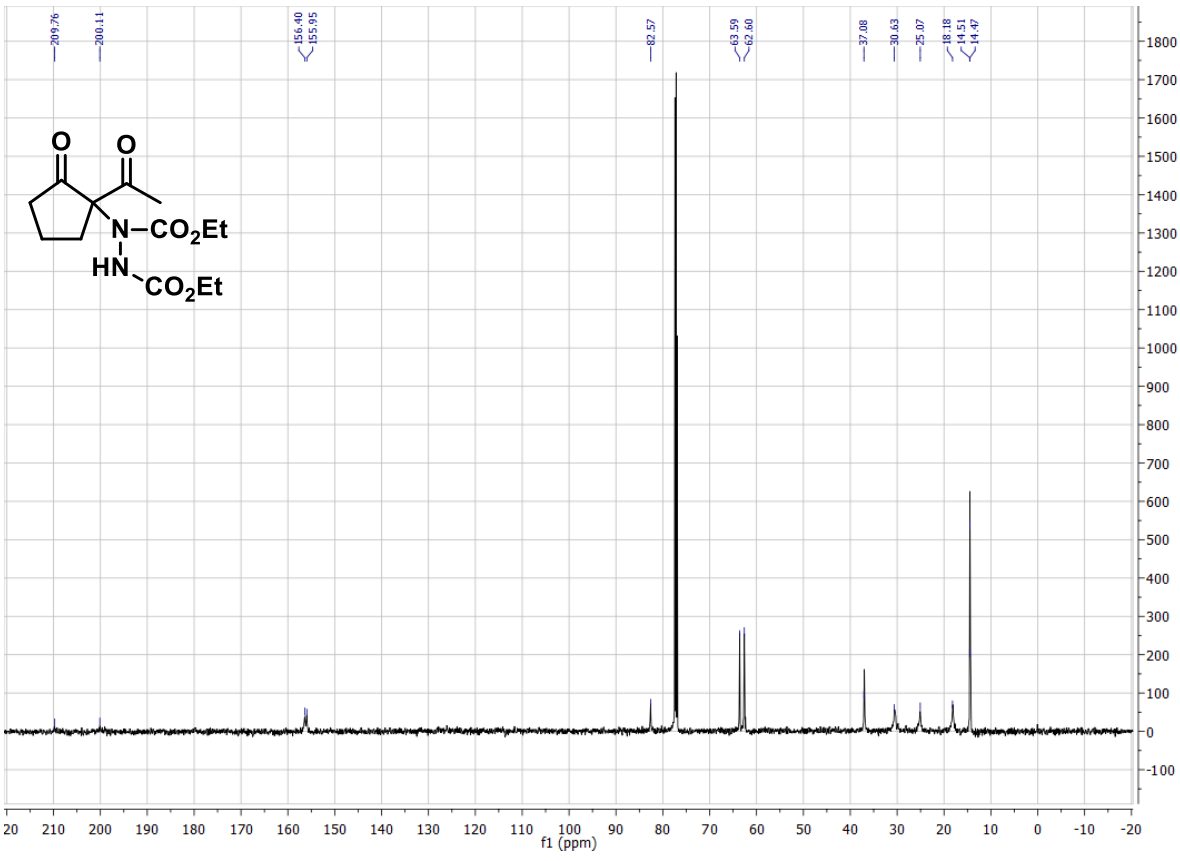
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156.40
155.95
82.57
63.59
62.60
37.08
30.63
25.07
18.18
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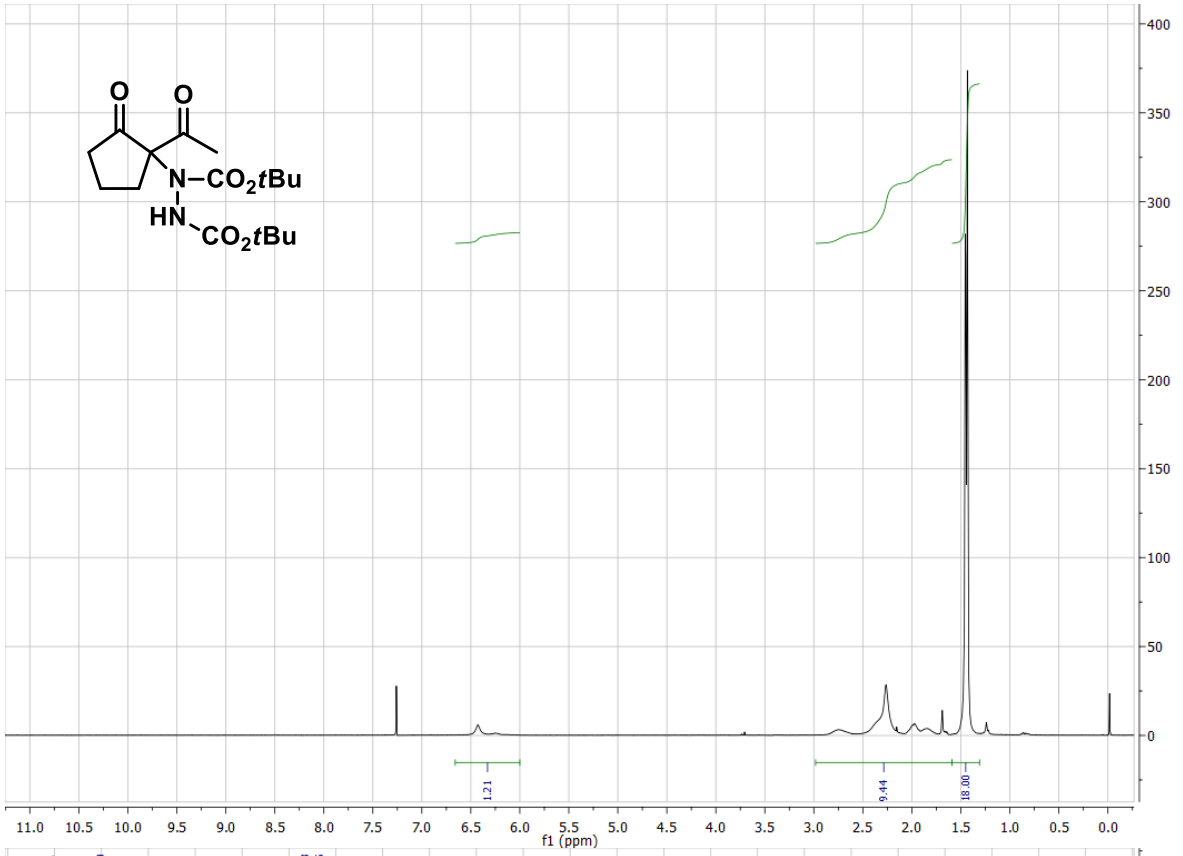
O
N–CO2Et
HN
CO2Et
f1 (ppm)

11c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HN
CO2tBu
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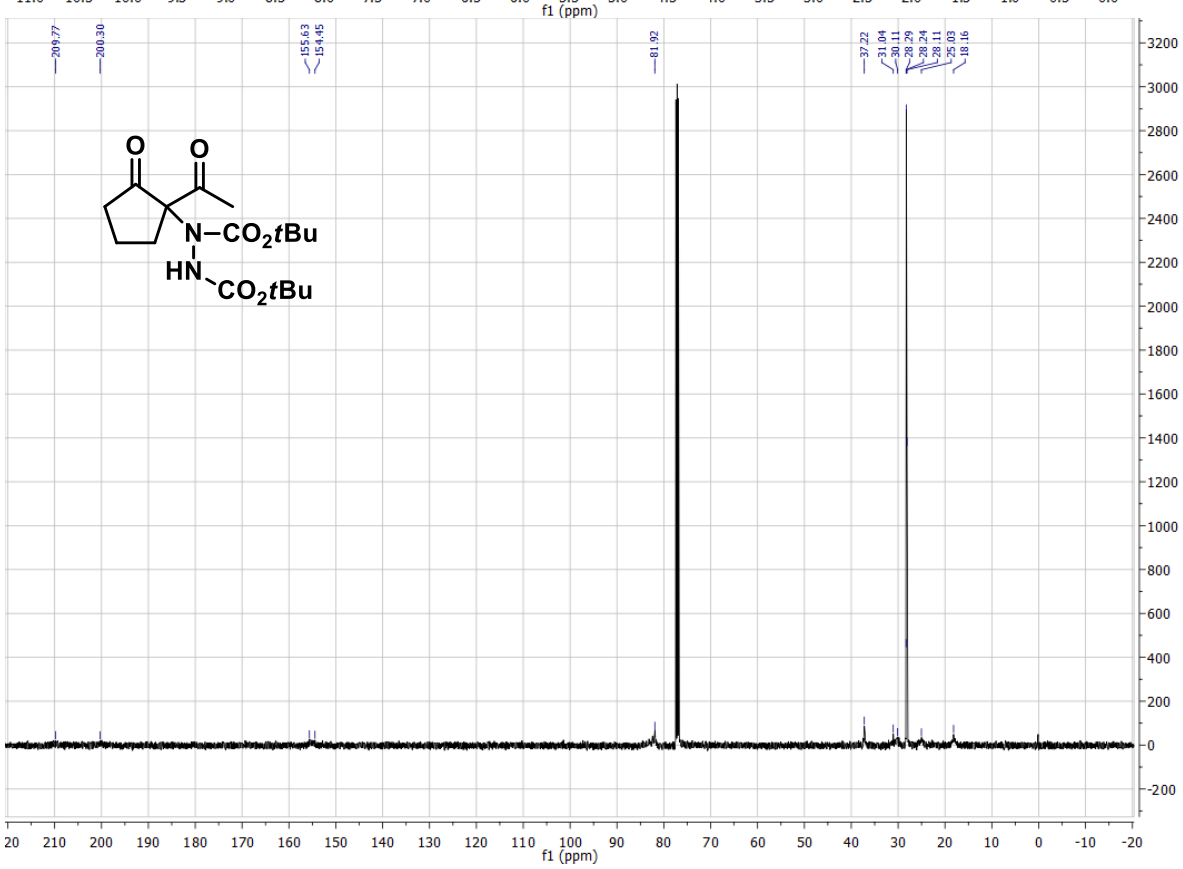
18.00
f1 (ppm)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37.22
31.04
30.11
28.29
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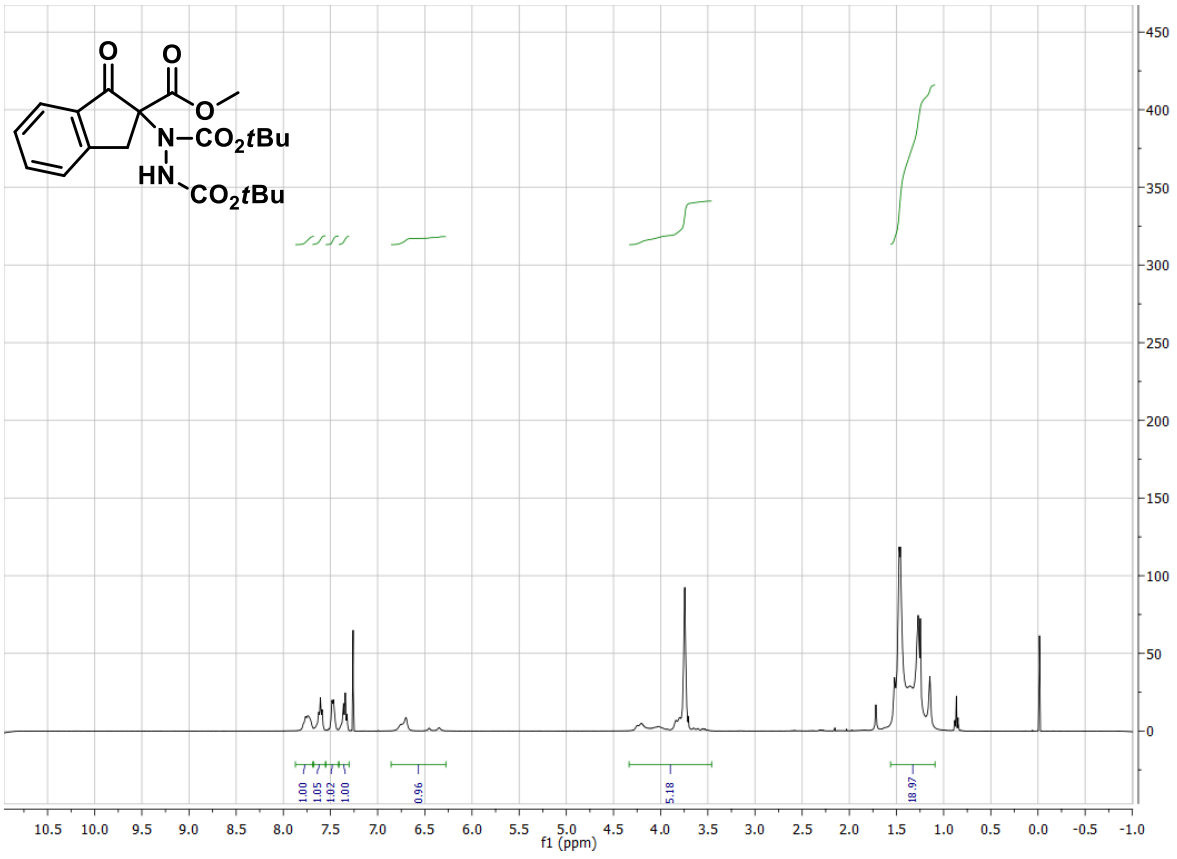
28.11
25.03
18.16
O
O
N–CO2tBu
HN
CO2tBu
f1 (ppm)

11d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O
O
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HN
CO2tBu
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1.02
1.00
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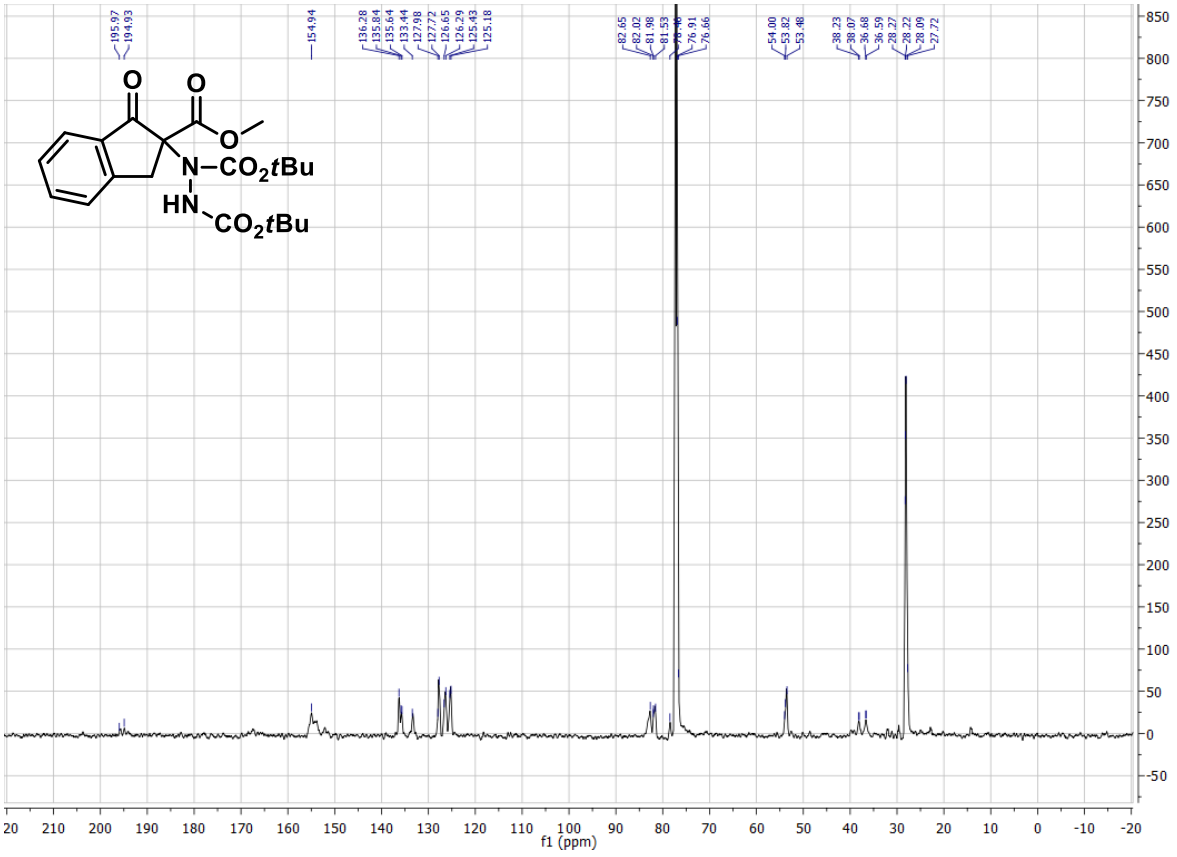
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127.72
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126.29
125.43
125.18
82.65
82.02
81.98
81.53
76.91
76.66
54.00
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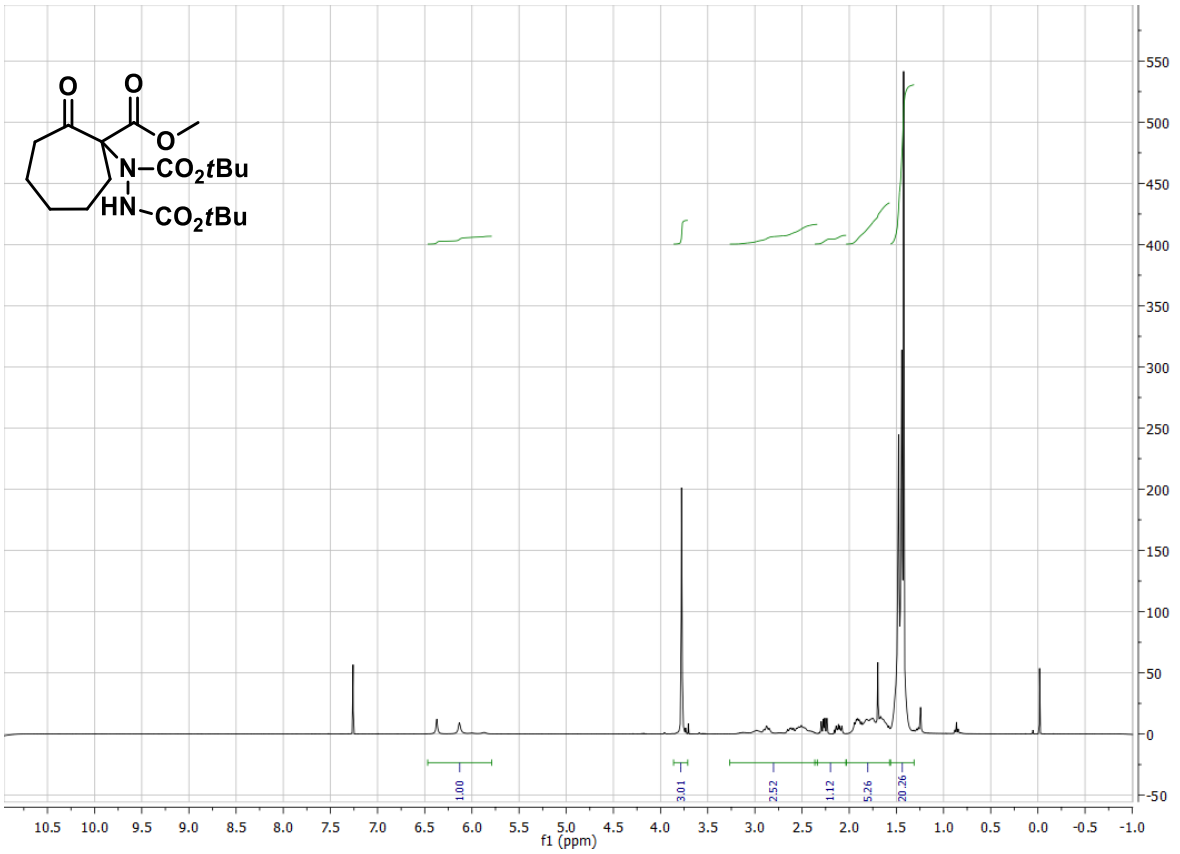
28.23
28.07
26.68
26.59
28.22
28.00
27.72
f1 (ppm)

11e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O
O
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HN–CO2tBu
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2.52
1.12
5.26
20.26
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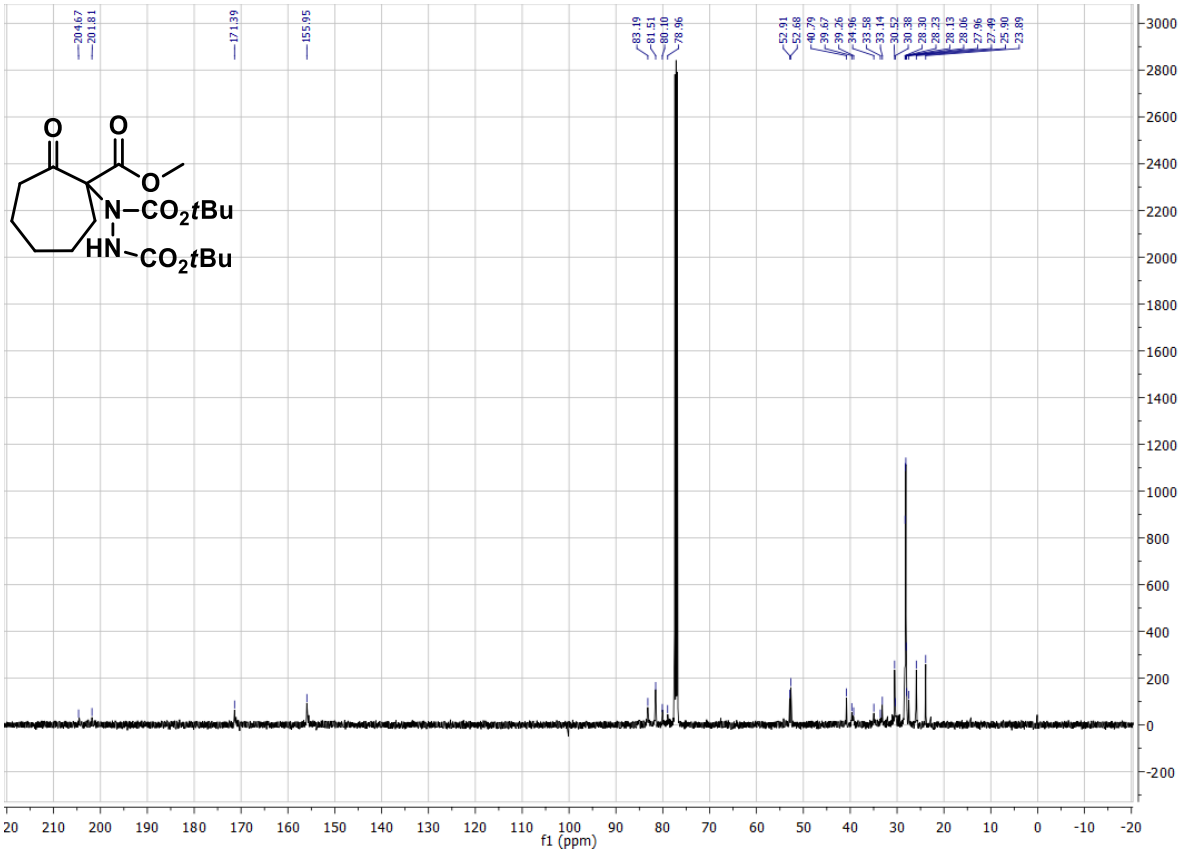
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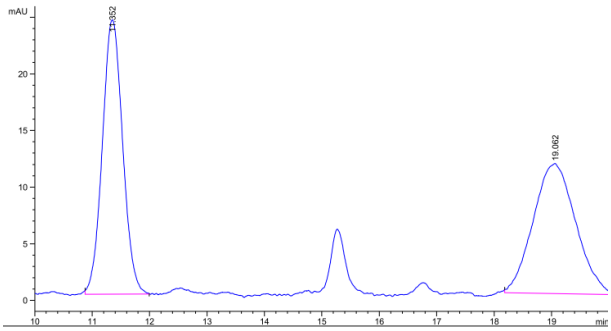
34.96
33.58
33.14
30.52
30.38
28.30
28.23
28.13
28.06
27.96
27.49
25.90
23.89
O
O
O
N–CO2tBu
HN–CO2tBu
f1 (ppm)

5. HPLC Traces

11a



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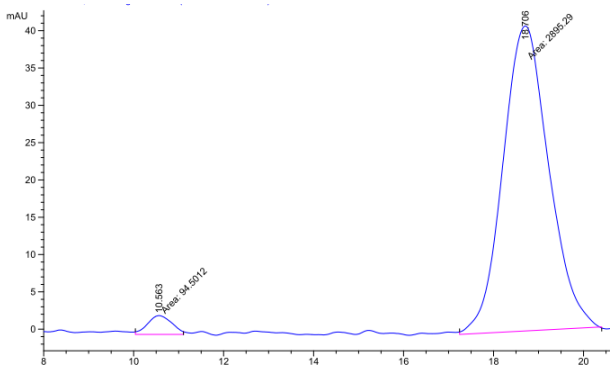

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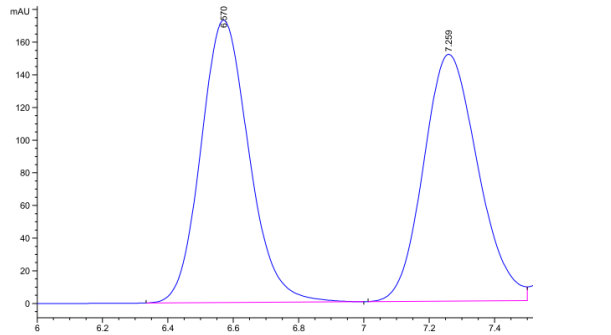

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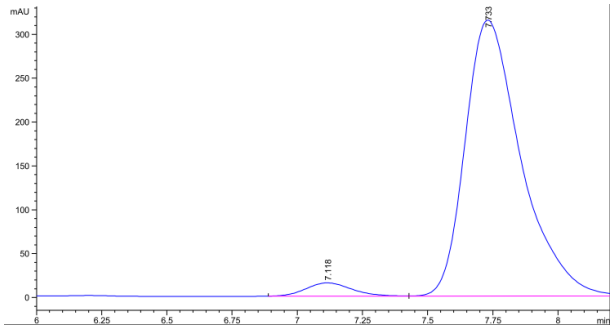

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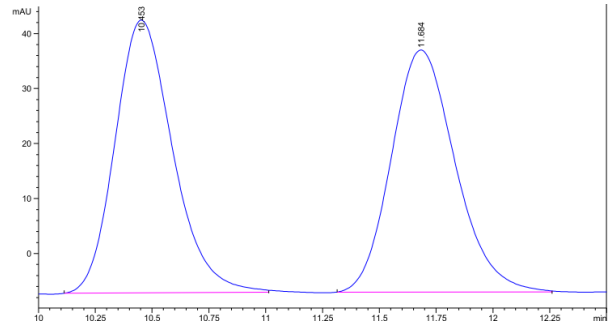
11cEt



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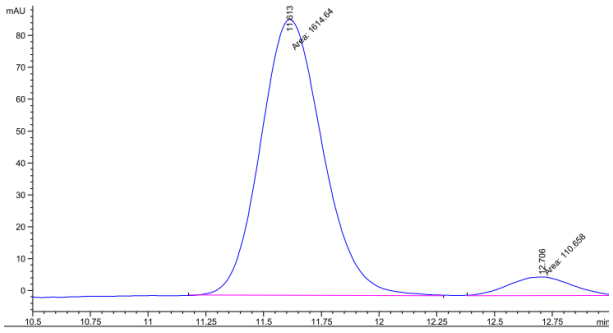

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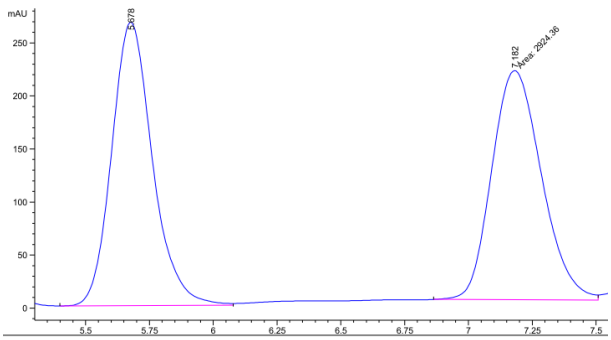
11c



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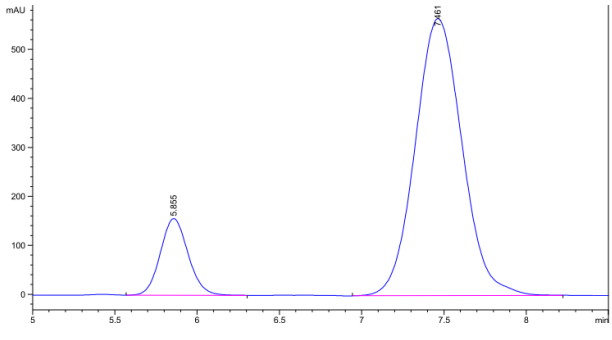

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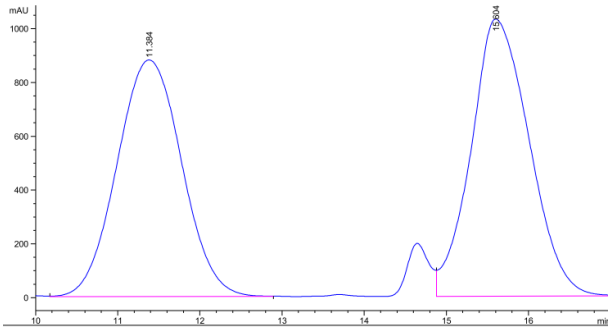

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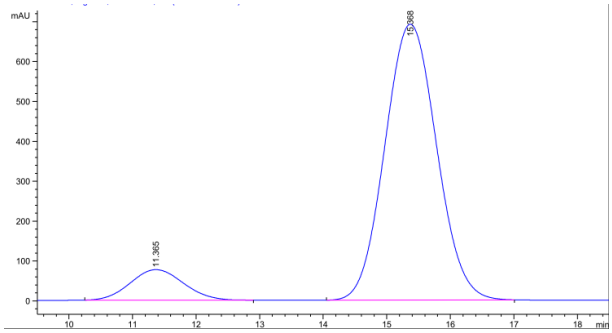

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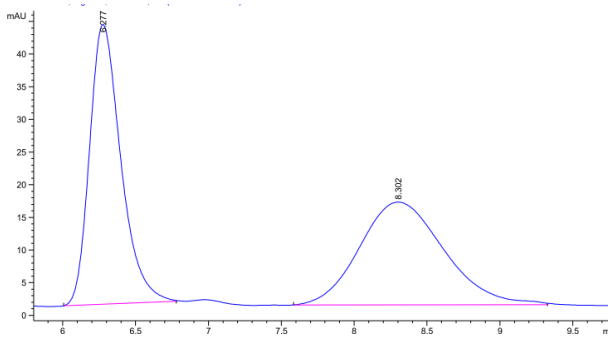
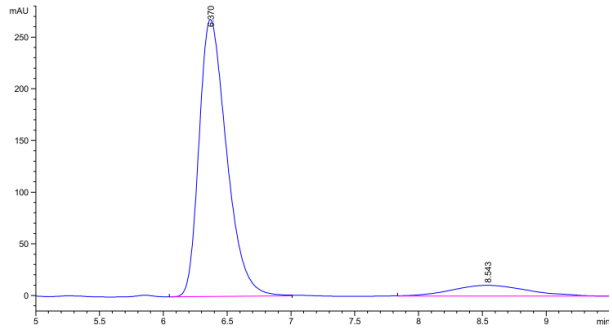
2	15.368	BB	0.8843	3.91491e4	691.74908	89.7293

11e

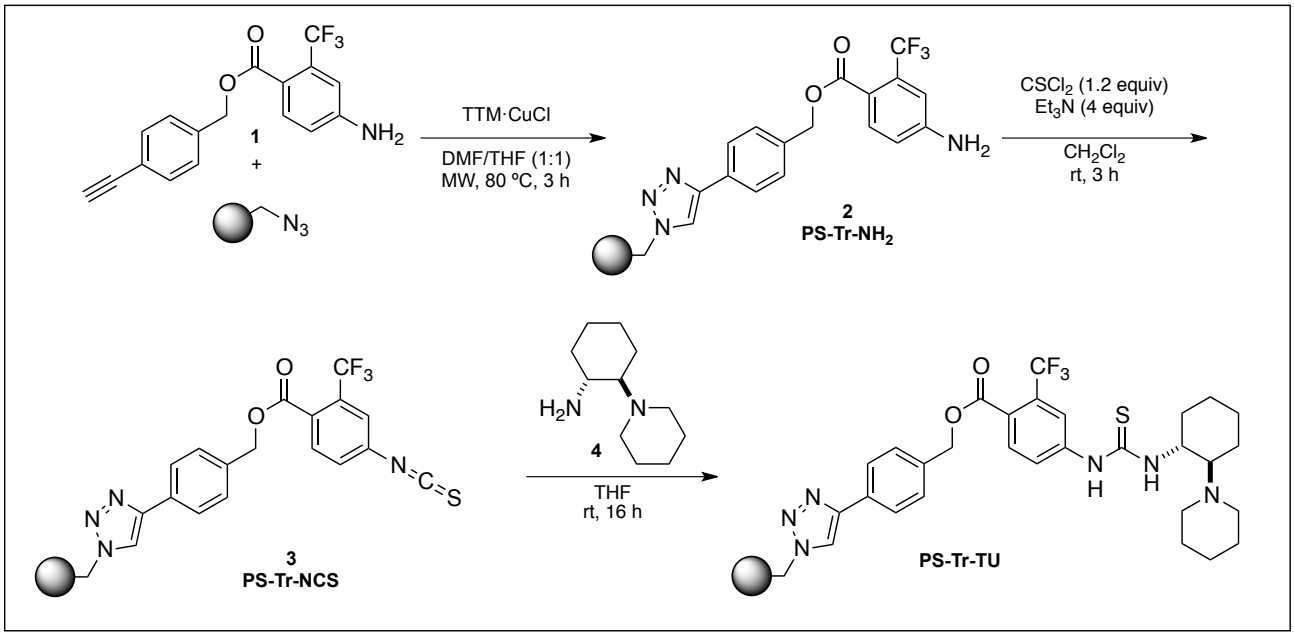


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.277	BB	0.2281	639.11914	42.81872	50.2765
2	8.302	BB	0.6050	632.09021	15.72526	49.7235

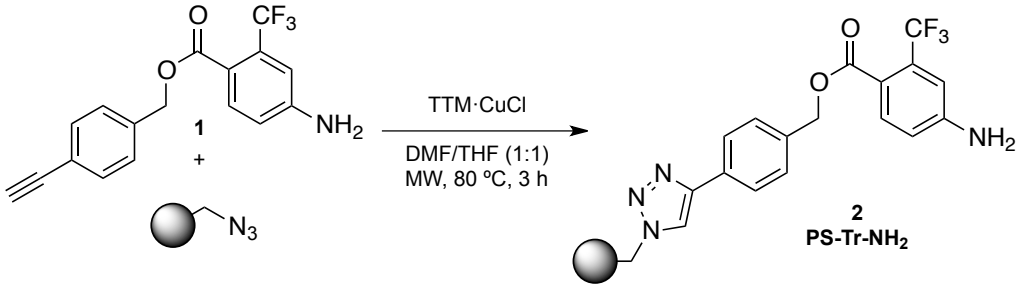


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.370	VB	0.2308	4015.44702	268.02518	90.2243
2	8.543	BB	0.6270	435.06824	10.42213	9.7757

6. Synthesis of the PS-thiourea catalyst involving a triazole linker (PS-Tr-TU)



PS-Tr-NH_2 (2)

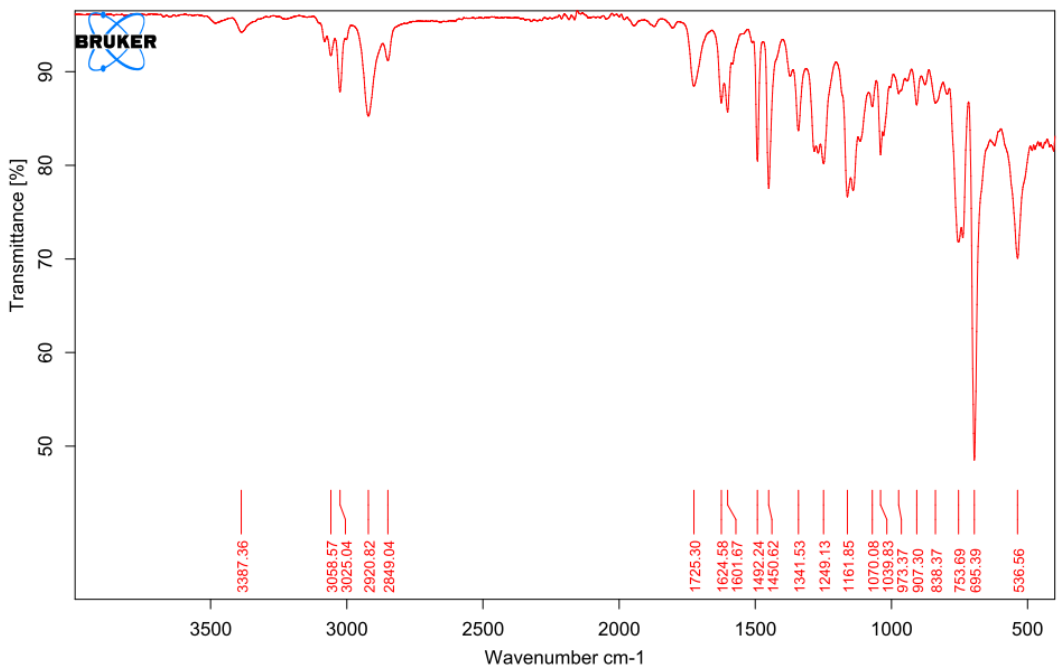


Azidomethylpolystyrene resin (0.60 g, f = 0.521 mmol g^{-1}) was swollen for 10 min in 6 mL of dimethylformamide–tetrahydrofuran (1:1) inside a microwave vial. Then 4-ethynylbenzyl 4-amino-2-(trifluoromethyl)benzoate[5] (0.40 mmol, 0.22 g) was added. Afterwards, TTM·CuCl[6] (8 mol%) was added to the microwave tube and the reaction mixture was heated at 80 ºC, 200 W for 3 h. The reaction was followed by IR spectroscopy, and after it was completed, the resin was filtered and washed with dimethylformamide (200 mL), water (200 mL), THF (200 mL), methanol (200 mL), and again THF (200 mL). The resin was dried overnight in vacuo at 40 ºC.

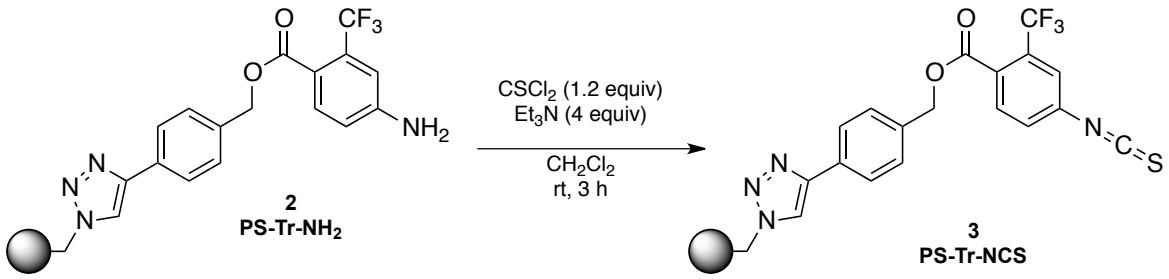
Elemental analysis: (%) = N 2.56, C 85.43, H 7.43, f = 0.457 mmol·g^{-1}.

IR (ATR): ν = 3387, 3025, 2921, 1725, 1625, 1492, 1450, 1342, 1249, 1162 cm^{-1}.

[5] P. Kasaplar, P. Riente, C. Hartmann, M. A. Pericàs, *Adv. Synth. Catal.* **2012,** *354*, 2905-2910.
[6] S. Özçubukçu, E. Ozkal, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2009** *11*, 4680-4683.



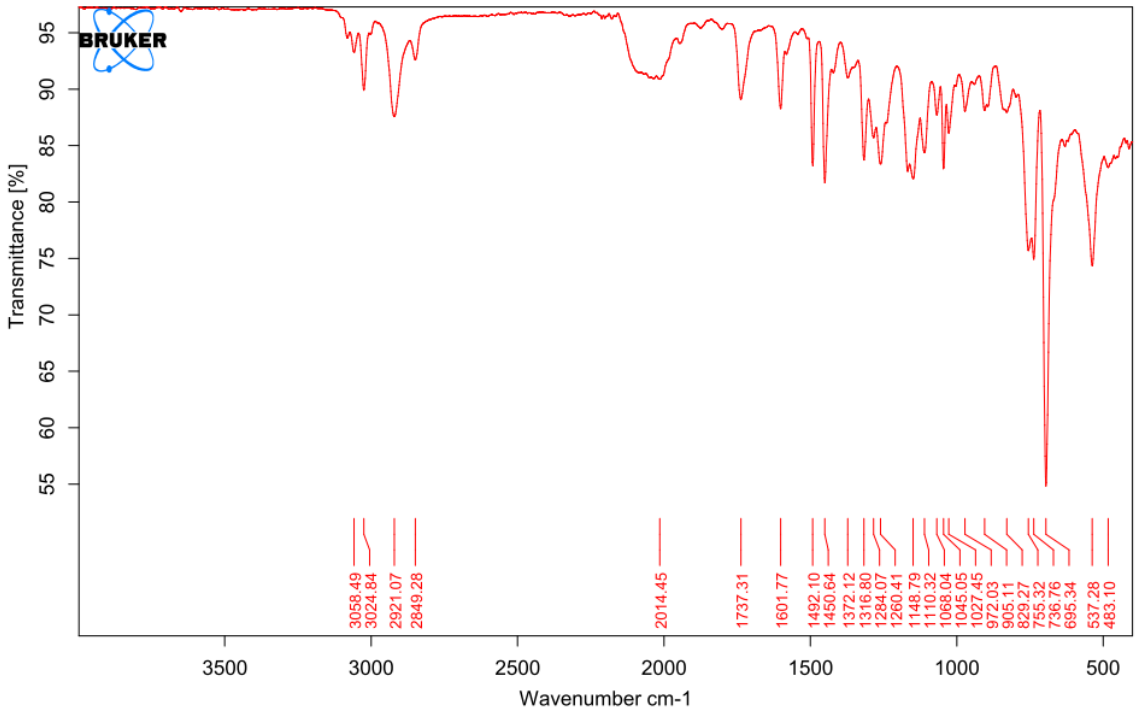
PS-Tr-NCS (3)



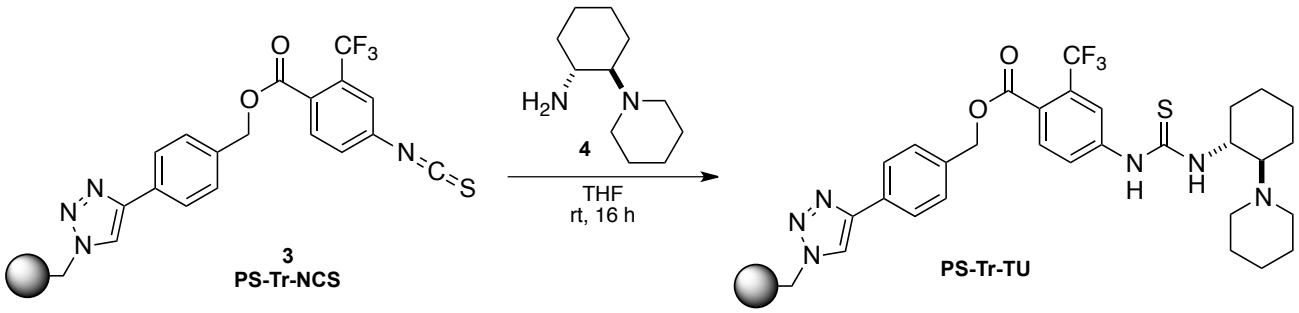
PS-Tr-NH$_2$ (650 mg, 0.336 mmol, 1 equiv.) was swollen for 30 min in dichloromethane (13 mL); then, triethylamine (181 µL, 1.30 mmol, d = 0.726 g/mL, 4.00 equiv.) and thiophosgene (31 µL, 0.41 mmol, 1.2 equiv.) were added dropwise at rt. After 5 h, the dark brown reaction mixture was filtered and the resin was washed with dichloromethane (30 mL), THF (30 mL), dichloromethane (30 mL), THF (30 mL), dichloromethane (30 mL), and finally, the dark brown resin **3** was vacuum dried for 30 min and used directly in the next step.

Elemental analysis: (%) = N 2.45, C 84.35, H 6.90, S 1.32; f = 0.437 mmol·g^{-1}.

IR (ATR): ν = 3025, 2921, 2014, 1737, 1601, 1492, 1450, 1372, 1284, 1148 cm^{-1}.

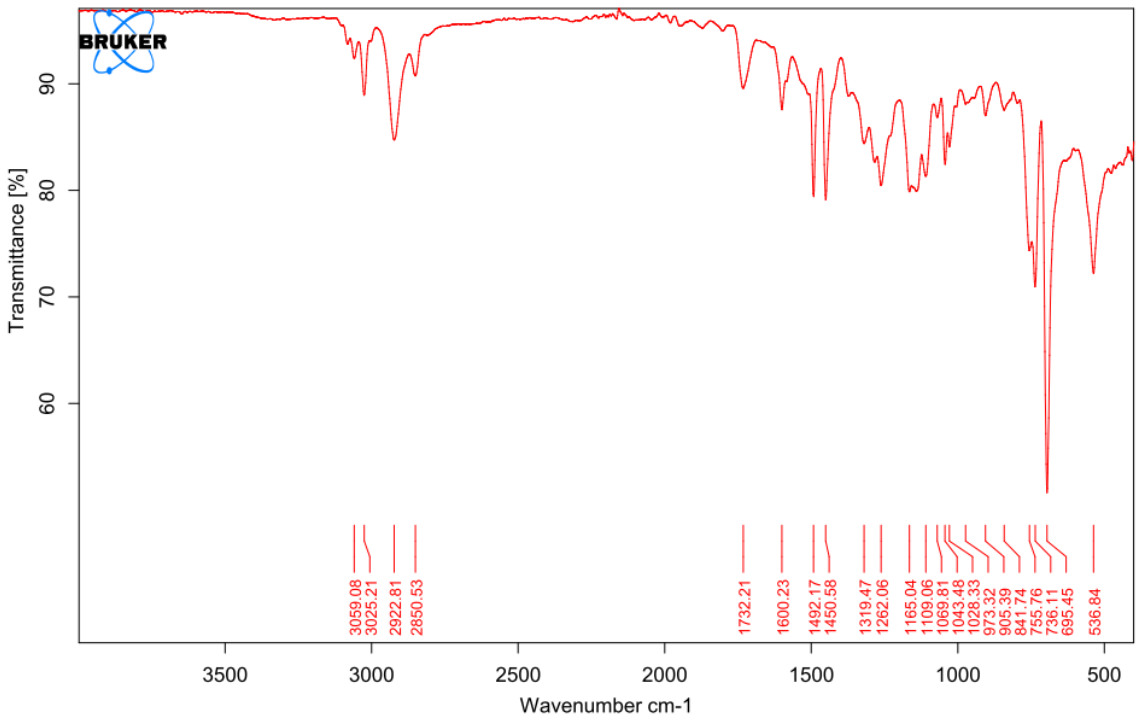


PS-Tr-TU



PS-Tr-NCS 3 (600 mg, 0.30 mmol, 1 equiv.) was swollen for 30 min in THF (3 mL) and (*1R,2R*)-2-(piperidin-1-yl)cyclohexanamine **4** (55 mg, 0.30 mmol, 1 equiv.) in tetrahydrofuran (5 mL) was added to this suspension at rt. After shaking for 48 h, the dark brown reaction mixture was filtered and the resin was washed with dichloromethane (30 mL), THF (30 mL), dichloromethane (30 mL), THF (30 mL), dichloromethane (30 mL), and finally, the dark brown resin **PS-TrTU** was dried under vacuum at 35 ºC for 12 h. Elemental analysis: (%) = N 3.22, C 83.31, H 7.28, S 1.26 f = 0.383 mmol·g^{-1}.

IR (ATR): ν = 3025, 2923, 1737, 1600, 1492, 1450, 1262, 1165 cm^{-1}.


BRUKER
Transmittance [%]
90
80
70
60
3059.08
3025.21
2922.81
2850.53
1732.21
1600.23
1492.17
1450.58
1319.47
1262.06
1165.04
1109.06
1069.81
1043.48
1028.33
973.32
905.39
841.74
755.76
736.11
695.45
536.84
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1