Supporting Information

Recyclable Silica-Supported Prolinamide Organocatalysts for Direct Asymmetric Aldol Reaction in Water

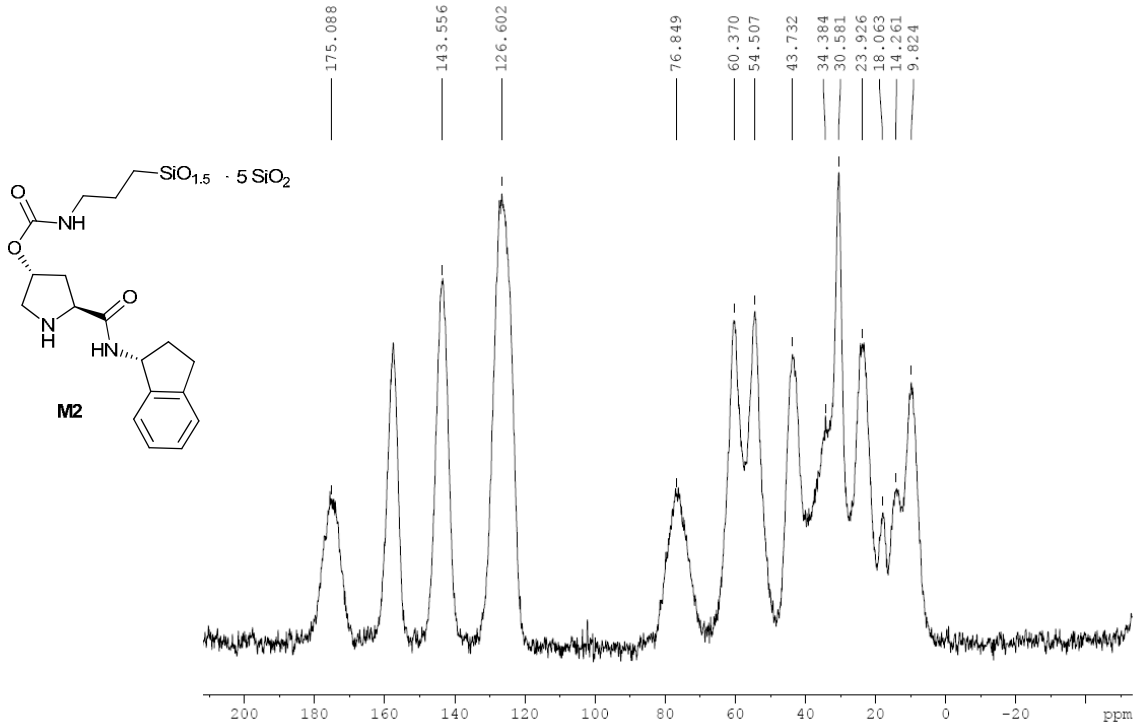
Amàlia Monge-Marcet,[a,b] Xavier Cattoën,[b] Diego A. Alonso,[c] Carmen Nájera,[c] Michel Wong Chi Man[b] and Roser Pleixats,*[a]

Contents

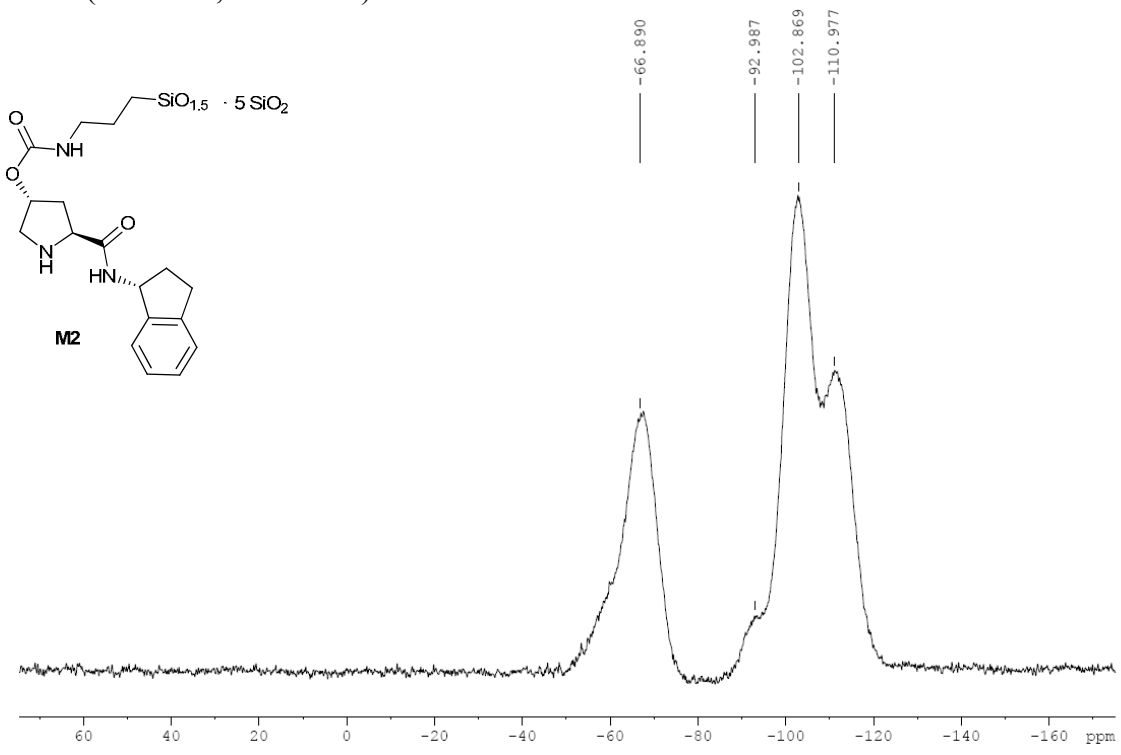
1 Characterization of supported organocatalysts M2 – M5

1.1 Hybrid silica material **M2**

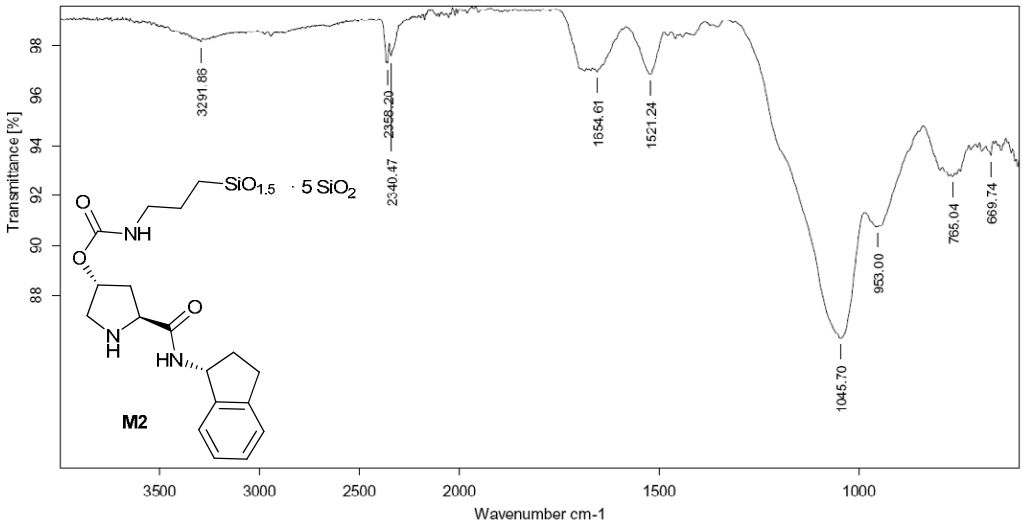
^{13}C NMR (CP-MAS, 100.6 MHz)



^{29}Si NMR (CP-MAS, 79.5 MHz)

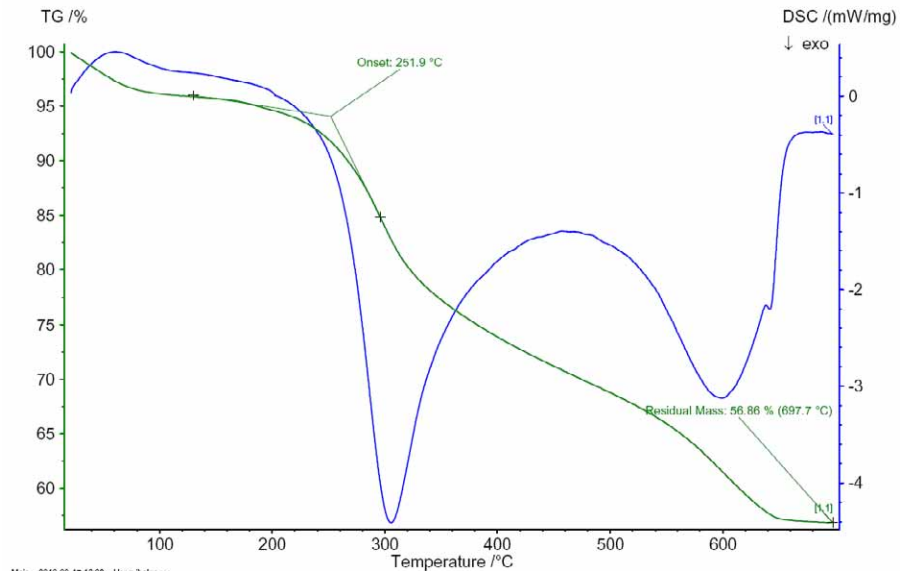


IR (ATR)

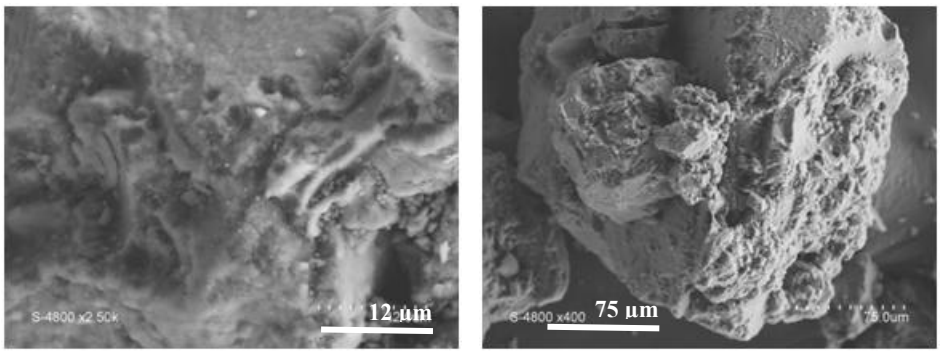


N_2 SORPTION MEASUREMENTS: below the detection limit of the instrument.

TGA

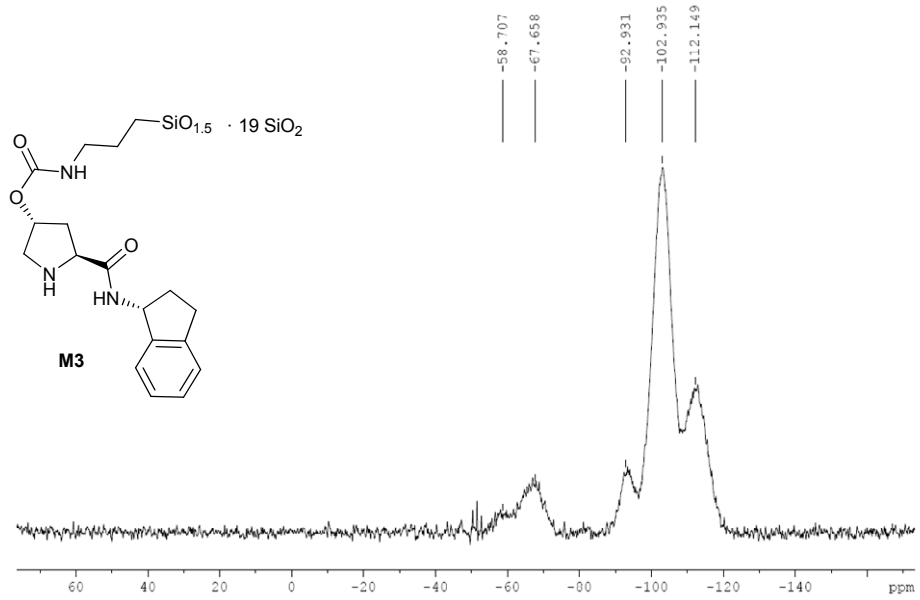


SEM

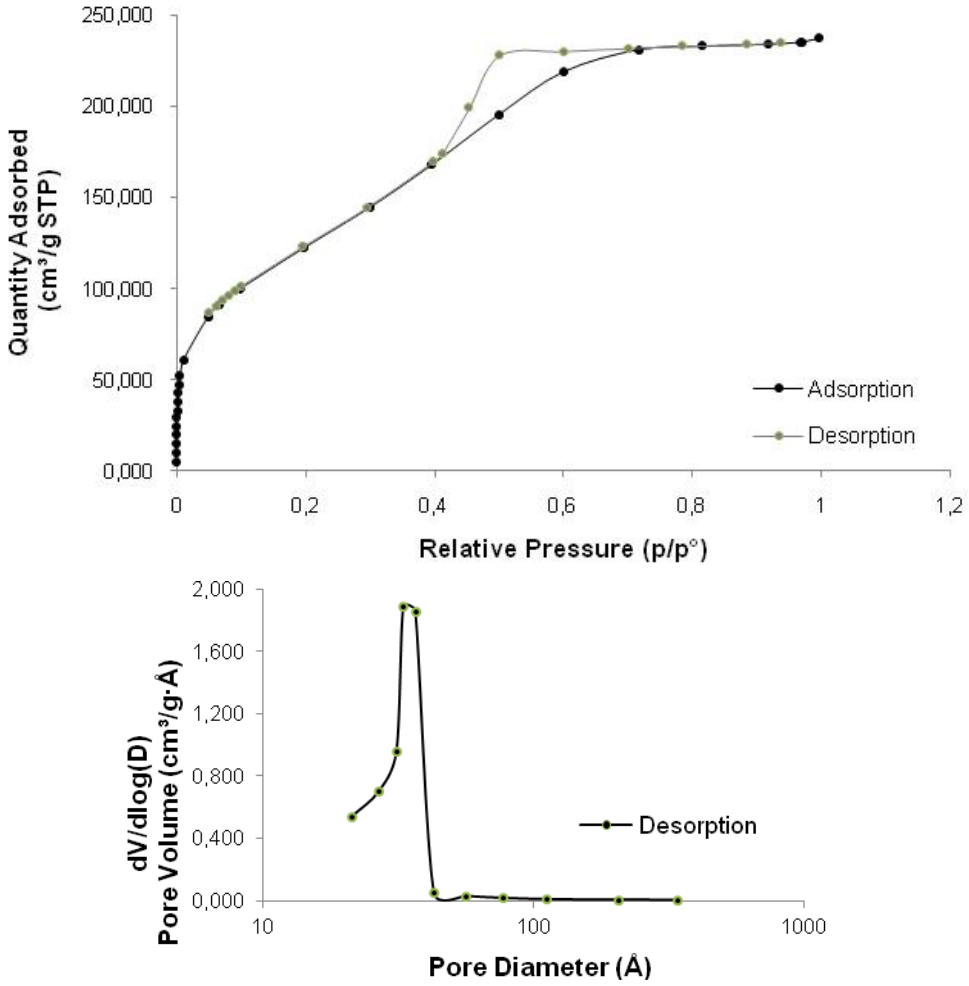


1.2 Hybrid silica material **M3**

^{29}Si NMR (CP-MAS, 79.5 MHz)



N_2 SORPTION MEASUREMENTS (BET)



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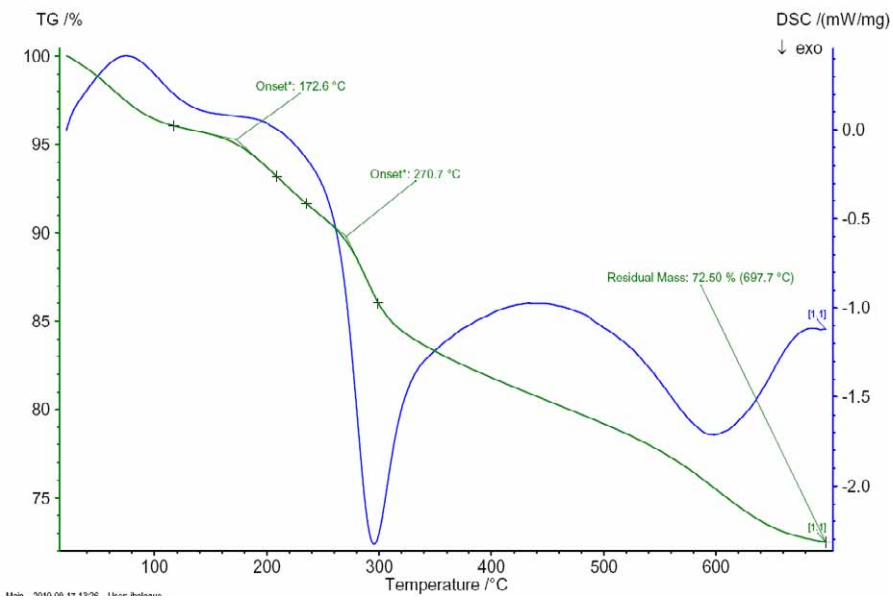

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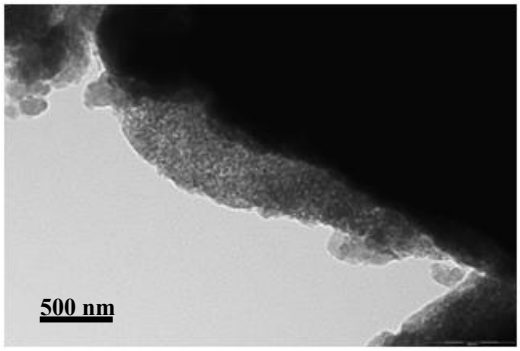

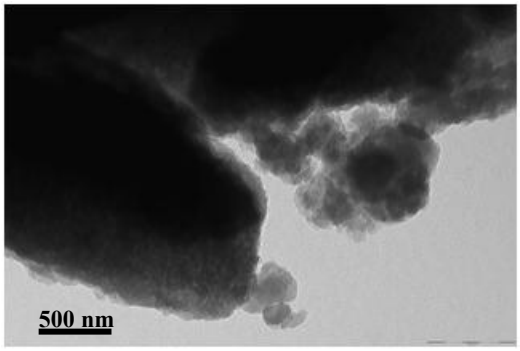

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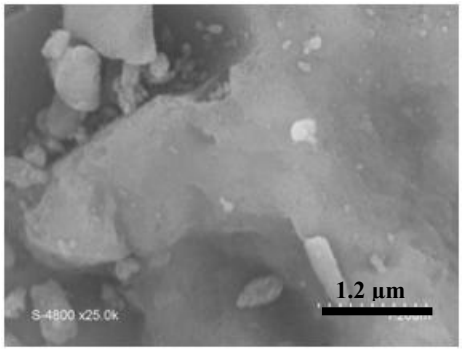
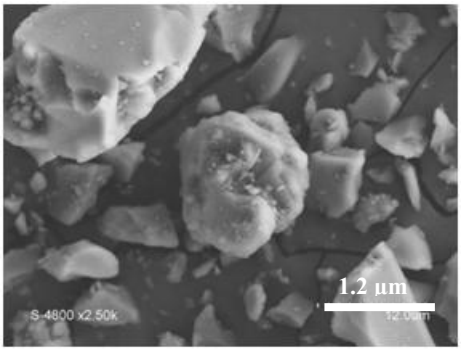
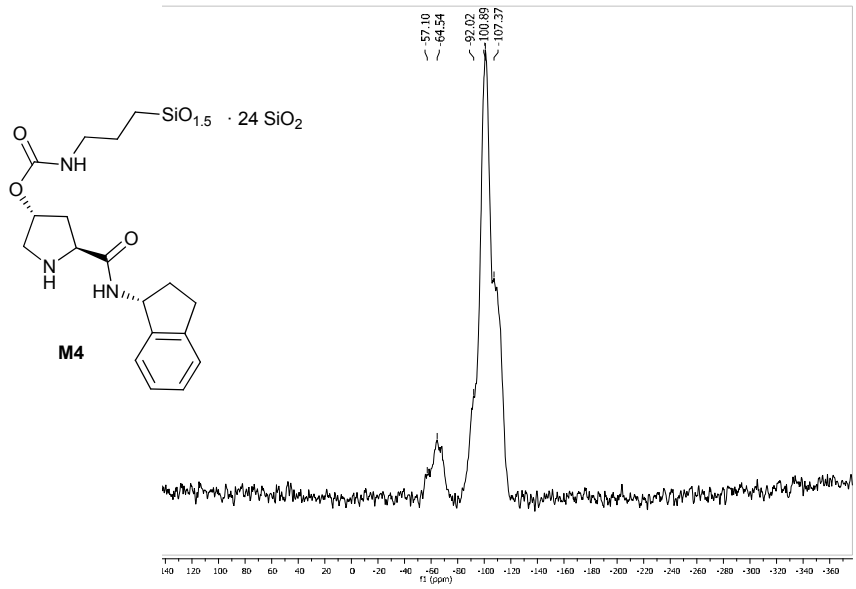




1.3 Hybrid silica material **M4**

^{29}Si NMR (CP-MAS, 79.5 MHz)



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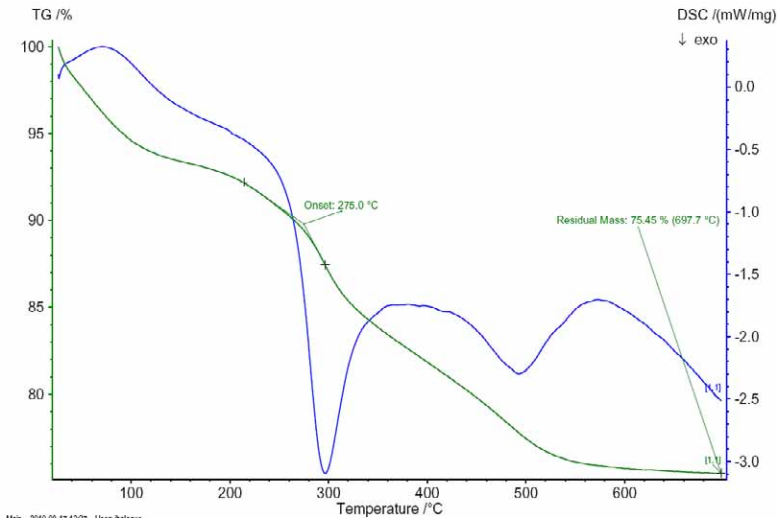
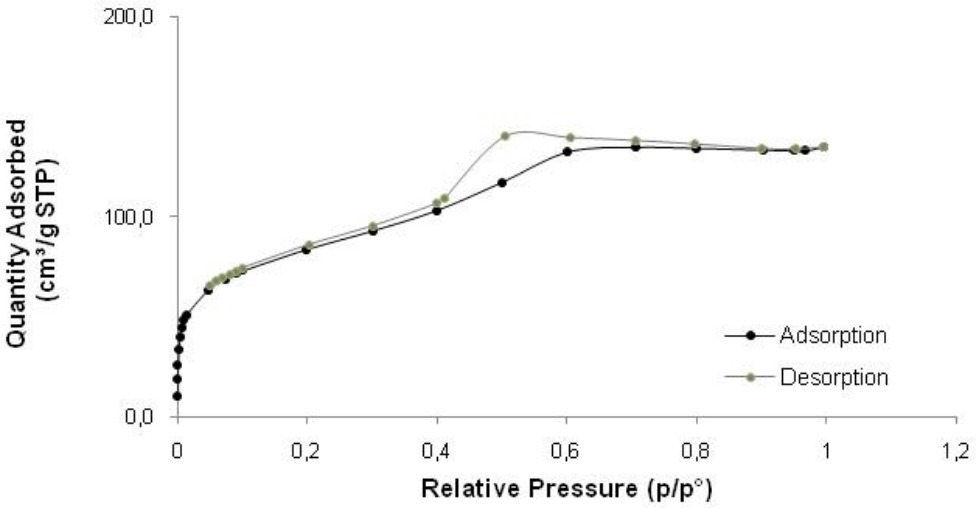
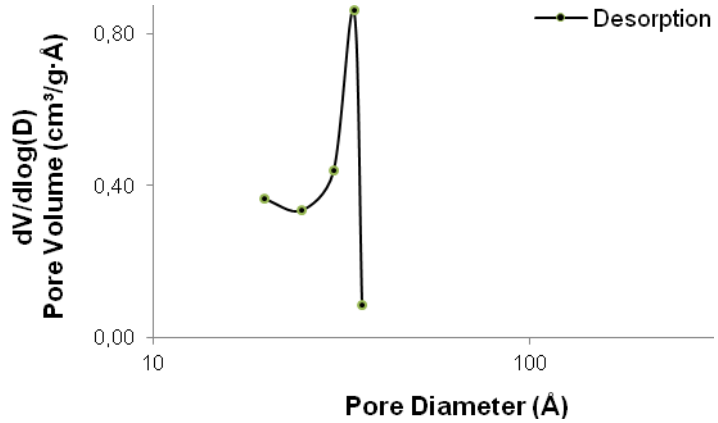


N_2-SORPTION MEASUREMENTS (BET)





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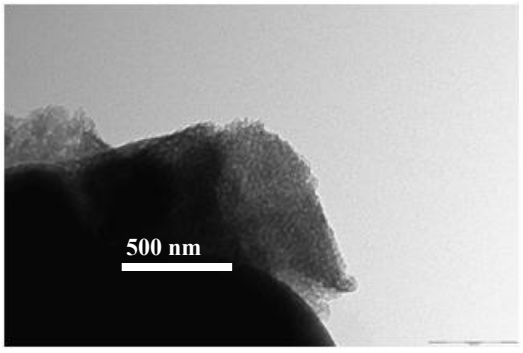
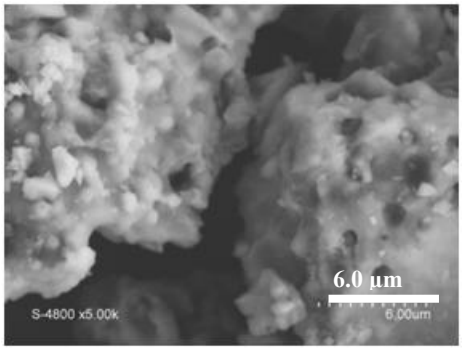
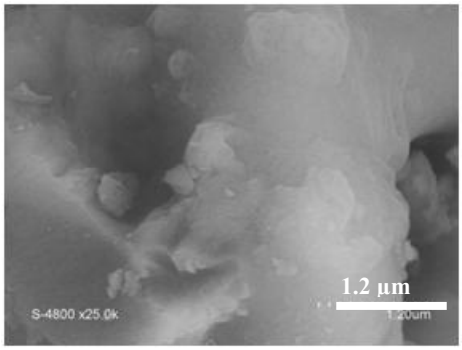
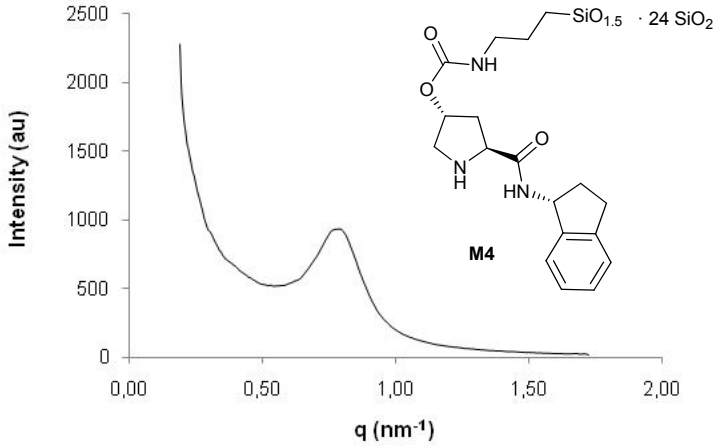


SEM



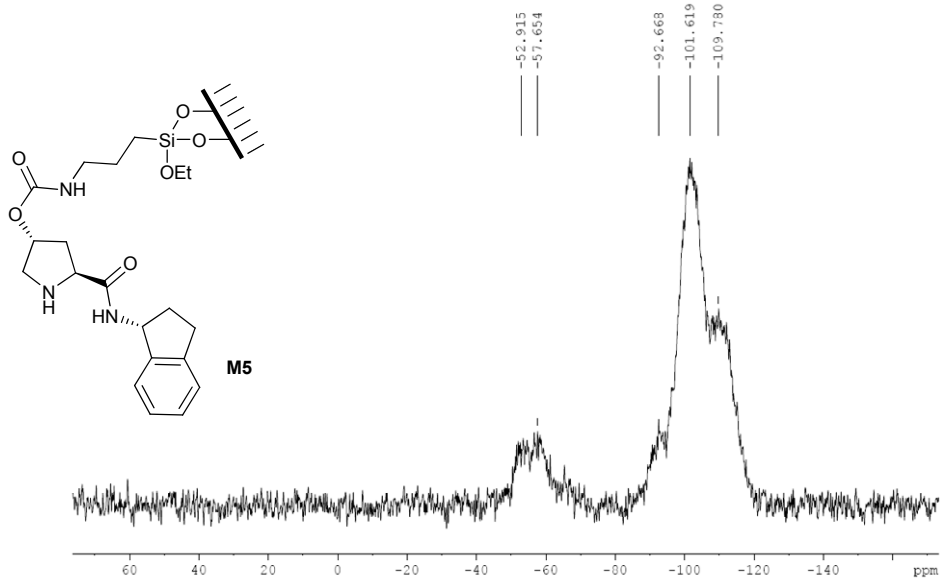


PXRD

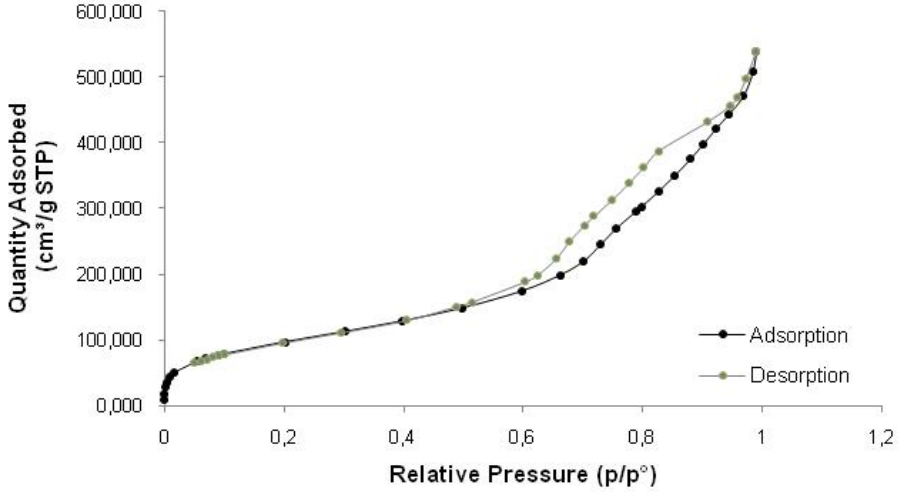


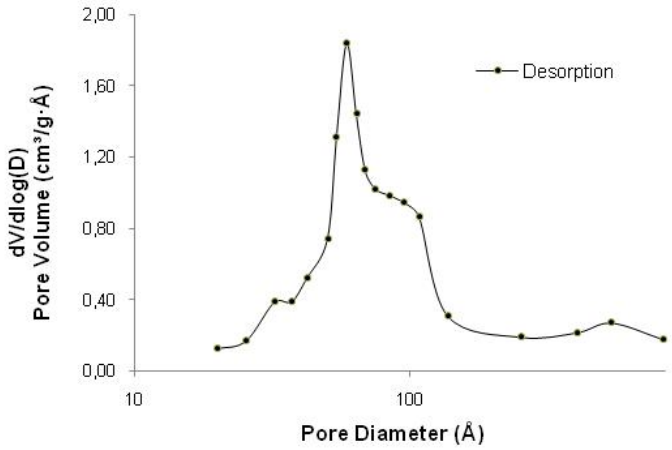
1.4 Hybrid silica material **M5**

^{29}Si NMR (CP-MAS, 79.5 MHz)

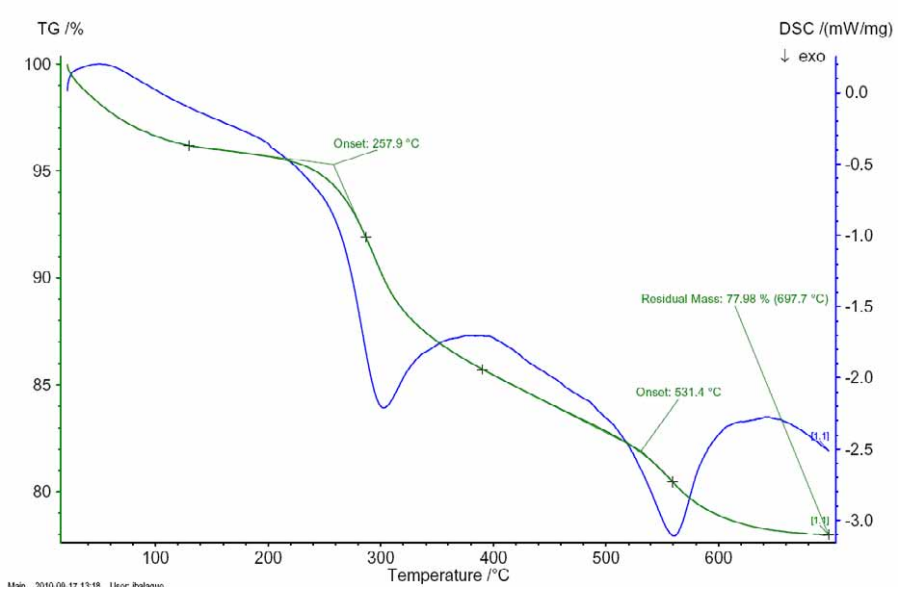


N_2-SORPTION MEASUREMENTS (BET)

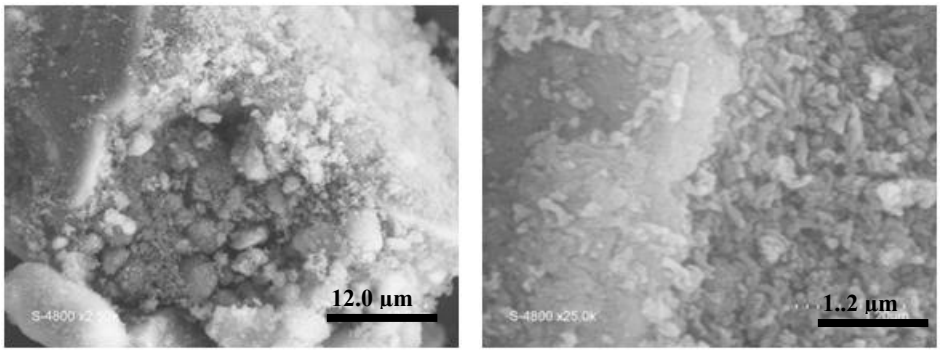



2,00
1,60
1,20
0,80
0,40
0,00
dV/dlog(D)
Pore Volume (cm³/g·Å)
Desorption
10
100
Pore Diameter (Å)

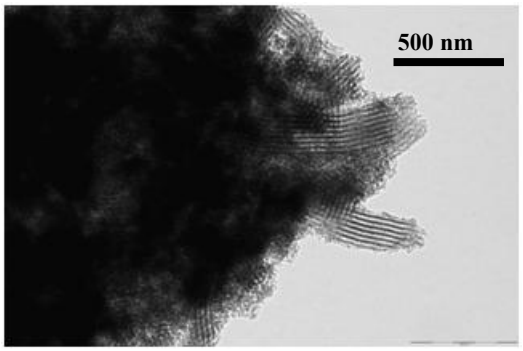
TGA


TG /%
DSC /(mW/mg)
↓ exo
100
95
90
85
80
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
Onset: 257.9 °C
Residual Mass: 77.98 % (697.7 °C)
Onset: 531.4 °C
100
200
300
400
500
600
Temperature /°C

SEM

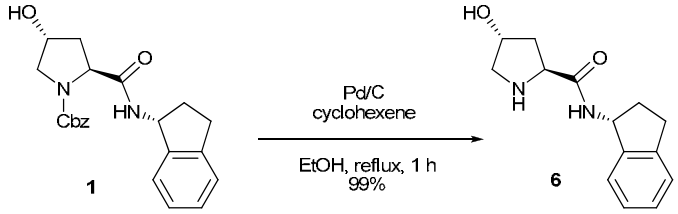

12.0 µm
1.2 µm

TEM



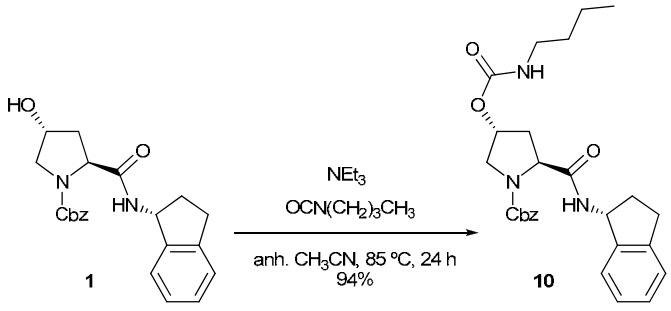
2 Preparation of non-silylated organocatalysts analogues

2.1 Preparation of compound **6**



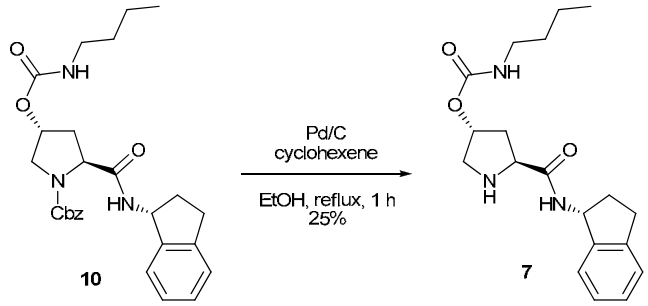
(2*S*,4*R*)-*N*-[(*R*)-2,3-dihydro-1*H*-inden-1-yl]-4-hydroxypyrrolidine-2-carboxamide, 6. *N*-Cbz-protected prolinamide derivative **1** (0.400 g, 1.05 mmol) and cyclohexene (0.60 mL, 0.814 g/cm^3, 5.91 mmol) were dissolved in EtOH (50 mL). Then Pd/C 10% (0.273 g, 0.26 mmol) was added and the mixture stirred at reflux under inert atmosphere. When TLC showed that all starting material was consumed (about 1 h), the reaction was cooled to room temperature and filtered through Celite®. The filtrates were concentrated under vacuum and recrystallized from AcOEt/MeOH to afford **6** as a white solid (0.256 g, 99%). Mp 128 - 129 ºC; $[\alpha]_D$ + 53.1 º (*c* 0.37 in EtOH); IR ν_{max} (ATR)/cm^{-1} 3333 (OH), 3294 (NH), 3248 (NH), 3022 (Csp^2-H), 2926, 2895 and 2871 (Csp^3-H), 1630 (C=O); δ_H (400 MHz, DMSO-d$_6$) 8.11 (1H, d, *J* 8.4, CON*H*), 7.25 - 7.10 (4H, m, H$_{Ar}$), 5.24 (1H, m, CONHC*H*), 4.65 (1H, br, O*H*), 4.18 (1H, s, C*H*OH), 3.73 (1H, t, *J* 8.0, NHC*H*CO), 2.94 - 2.83 (1H, m, NHC*H*H), 2.81 - 2.77 (2H, m, NHCH*H* and NHCHCH$_2$C*H*H), 2.70 (1H, m, NHCHCH$_2$CH*H*), 2.36 (1H, m, NHCHC*H*H), 1.90 (1H, m, CH(OH)C*H*HCH), 1.82 - 1.74 (1H, m, NHCHCH*H* and CH(OH)CH*H*CH); δ_C (100 MHz, DMSO-d$_6$,) 174.2, 144.1, 142.8, 127.3, 126.4, 124.5, 123.4, 71.3, 59.3, 55.1, 53.1, 32.9, 29.6. ESI-HRMS calc. for $C_{14}H_{18}N_2O_2$+Na$^+$: 269.1260; found: 269.1263.

2.2 Preparation of compound **7**



(2*S*,4*R*)-benzyl-4-(butylcarbamoyloxy)-2-[(*R*)-2,3-dihydro-1*H*-inden-1-ylcarbamoyl]-pyrrolidine-1-carboxylate, 10. Some dry DMF (*ca.* 2 mL) was added dropwise to a stirred

suspension of prolinamide derivative **1** (0.515 g, 1.35 mmol) in dry CH_3CN (8 mL) at 70 ºC under an inert atmosphere, until a homogeneous solution was obtained. Then *n*-butylisocyanate (0.30 mL, 0.88 g/cm^3, 2.66 mmol) and NEt_3 (0.25 mL, 0.726 g/cm^3, 1.79 mmol) were added and the mixture was stirred at 85ºC under argon for 48 h. After this time, the volatiles were removed under vacuum and the excess of isocyanate was distilled off. The residue was dissolved in the minimum amount of dry THF. Upon addition of dry Et_2O compound **10** precipitated and it was filtered to afford a white solid (0.607 g, 94%). Mp 150 - 151 ºC; $[\alpha]_D$ + 39.2 º (*c* 0.63 in EtOH); IR ν_{max} (ATR)/cm^{-1} 3288 (NH), 2931 and 2860 (Csp^3-H), 1688 (C=O), 1648 (C=O); δ_H (400 MHz, DMSO-d_6, rotamers mixture, aprox. 50/50) 8.41 (1H, m, CON*H*), 7.39 - 6.90 (10H, m, H_{Ar} and OCON*H*), 5.35 (1H, m, NHC*H*), 5.09 (3H, m, PhCH_2 and C*H*OCON), 4.30 (1H, m, Cbz-NC*H*CO), 3.62 (1H, m, Cbz-NC*H*H), 3.55 (1H, m, Cbz-NCH*H*), 2.98 - 2.80 (3H, m, OCONHCH_2 and NHCHC*H*H), 2.78 - 2.63 (1H, m, NHCHCH*H*), 2.36 - 2.32 (2H, m, NHCHCH$_2$C*H*H and Cbz-NCHC*H*H), 2.12 (1H, m, Cbz-NCHCH*H*), 1.76 (1H, m, NHCHCH$_2$CH*H*), 1.36 (2H, m, CH_2CH$_2$CH$_3$), 1.25 (2H, m, CH$_2$CH_2CH$_3$), 0.85 (3H, t, *J* 7.2, CH_3); δ_C (100 MHz, DMSO-d_6, rotamers mixture, aprox. 50/50) 171.2, 171.0, 155.5, 153.9, 153.8, 144.0, 143.6, 142.8, 142.7, 136.8, 136.7, 128.4, 128.3, 127.8, 127.6, 127.5, 127.3, 127.1, 126.3, 126.2, 124.6, 124.3, 124.1, 123.9, 72.4, 71.6, 66.0, 58.6, 58.0, 53.6, 53.0, 52.6, 45.6, 37.2, 36.0, 32.7, 31.4, 29.7, 19.3, 13.6.



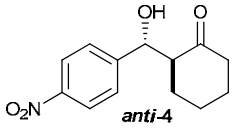
(3*R*,5*S*)-5-[(*R*)-2,3-dihydro-1*H*-inden-1-ylcarbamoyl]pyrrolidin-3-yl butylcarbamate, 7. Compound **10** (0.415 g, 0.865 mmol) and cyclohexene (0.40 mL, 0.814 g/cm^3, 3.94 mmol) were dissolved in EtOH (15 mL). Then Pd/C 10% (0.110 g, 0.103 mmol) was added and the mixture stirred at reflux under inert atmosphere. When TLC showed that all starting material was consumed (about 1 h), the reaction was cooled to room temperature and filtered through Celite®. The filtrates were concentrated under vacuum and the residue was recrystallized from AcOEt/CH_2Cl_2 to afford pure **7** as a white solid (0.057 g, 19 %). Mp 152 - 153 ºC: $[\alpha]_D$ + 55.3 º (. 0.55 in EtOH); IR ν_{max} (ATR)/cm^{-1} 3297 (broad, NH), 2953, 2928 and 2868 (Csp^3-H), 1698 (C=O), 1652 (C=O); δ_H (500 MHz, DMSO-d_6) 8.17 (1H, d, *J* 8.5, CON*H*), 7.23 (1H, t, *J* 7.0, H_{Ar}), 7.19 (2H, m, H_{Ar}), 7.13 (1H, d, *J* 7.0, H_{Ar}), 7.07 (1H, m, OCON*H*), 5.25 (1H, m, CHCONHC*H*), 4.99 (1H, br, NHCH$_2$C*H*O), 3.70 (1H, m, NHC*H*CONH), 3.02 (1H, dd, *J* 12.2 *J* 4.8, NHC*H*H), 2.94 (2H, m, OCONHCH_2), 2.89 (1H, dd, *J* 9.0 *J* 2.5, NHCHCH$_2$C*H*H), 2.83 - 2.76 (2H, m, NHCHCH$_2$CH*H* and NHCH*H*), 2.36 (1H, m, NHCHC*H*H), 2.04 (1H, dd, *J* = 12.2 *J* 8.0, NHCH(CO)C*H*H), 1.93 (1H, m, NHCH(CO)CH*H*), 1.82 (1H, m, NHCHCH*H*), 1.37 (2H, m, CH_2CH$_2$CH$_3$), 1.25 (2H, m, CH$_2$CH_2CH$_3$), 0.85 (3H, t, *J* 7.2, CH_3); δ_C (62.5 MHz, DMSO-d_6) 174.3, 156.9, 144.9, 143.8, 128.3, 127.4, 125.4, 124.5, 76.3, 60.4, 54.2, 53.7, 38.3, 33.8, 32.5, 30.6, 20.4, 14.5; ESI-HRMS calc. for $C_{19}H_{27}N_3O_3$+H$^+$: 346.2125; found: 346.2125.

3 Catalytic tests with homogeneous organocatalysts 6 and 7

In a vial, cyclohexanone (110 µL, 0.947 g/mL, 1.07 mmol), *milliQ* water (106 µL, 0.5 mL/mmol aldehyde) and **6** or **7** (0.021 mmol) were stirred together for 20 min at 22ºC. After this time, *p*-nitrobenzaldehyde (32.8 mg, 0.215 mmol) was added and the mixture was stirred at 22ºC for the

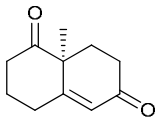
time indicated on Table 2 (when TLC showed that all starting aldehyde was consumed). Then the crude mixture was diluted with AcOEt (2 mL) and anhydrous Na_2SO_4 was added. The organic layer was then filtered and concentrated under vacuum to give a yellowish solid. From this crude mixture, conversion, *anti:syn* ratio and *ee* were determined.

4 Spectroscopic data of compounds 4 and 9



anti-4

Compound 4. The diastereomeric ratio, as determined by ^{1}H NMR analysis of the crude mixture, was found to favour the *anti* isomer (see Table 2, *anti:syn* from 72:28 to 87:13). δ_H (250 MHz, $CDCl_3$) 8.22 ($2H_{anti}$, $2H_{syn}$, d, *J* 8.6), 7.49 ($2H_{anti}$, $2H_{syn}$, d, *J* 8.6), 5.49 ($1H_{syn}$, br), 4.90 ($1H_{anti}$, d, *J* 8.3), 4.08 ($1H_{anti}$, br), 2.64-2.30 ($2H_{anti}$, $2H_{syn}$, m), 2.19-2.04 ($1H_{anti}$, $1H_{syn}$, m), 1.80-1.18 ($6H_{anti}$, $6H_{syn}$, m). The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak AD-H column, flow 1 mL/min, 254 nm, *n*-hexane/*i*-PrOH 80:20, *anti* isomer: t_{maj} 17.30 min, t_{min} 13.52 min; *syn* isomer: t_{maj} 12.45 min, t_{min} 11.78 min). Compound **4** has been previously described and its spectral and analytical data were consistent with literature values.[1]



9

Compound 9. δ_H (250 MHz, $CDCl_3$) 5.87 (1H, d, *J* 1.8), 2.73-2.69 (2H, m), 2.54-2.45 (4H, m), 2.20-2.12 (3H, m), 1.79-1.63 (1H, m,), 1.47 (3H, m). The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralpak IC column, flow 1 mL/min, 254 nm, *n*-hexane/*i*-PrOH 80:20, t(*R*): 32.90 min, t(*S*): 37.08 min). Compound **9** has been previously described and its spectral and analytical data were consistent with literature values. [1]

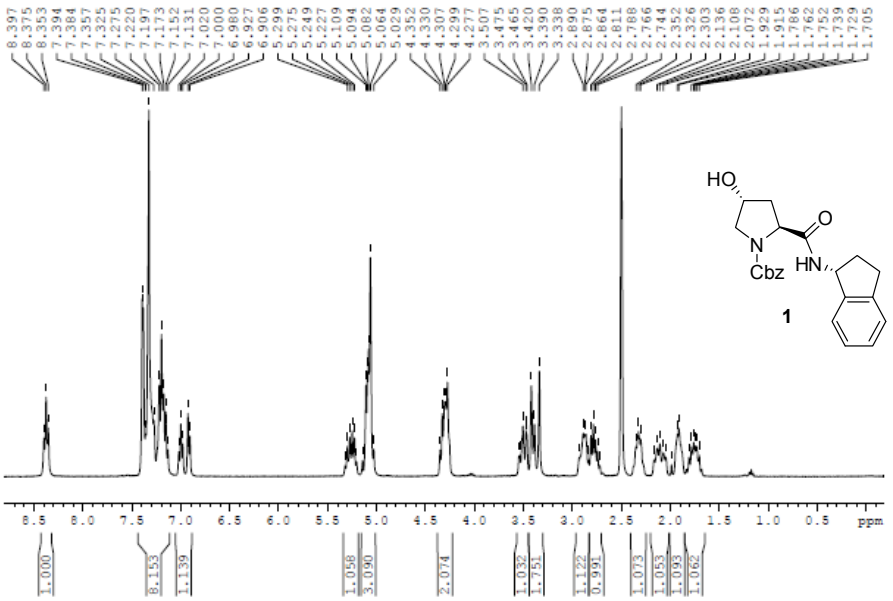
5 References

1. D. Almaşi, D. A. Alonso, C. Nájera, *Adv. Synth. Catal*., **2008**, *350*, 2467.

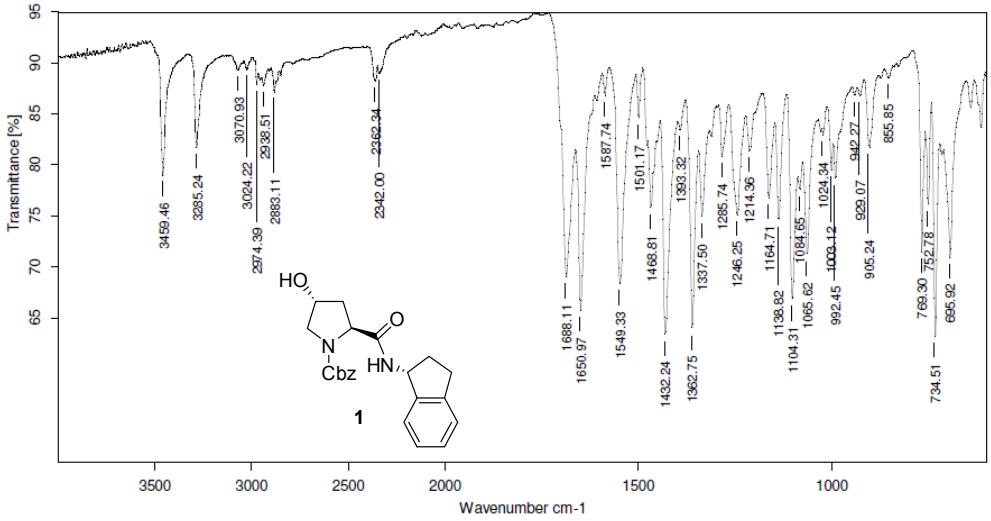
6 NMR and IR spectra of compounds 1-3, 6, 7 and 10

Compound **1**

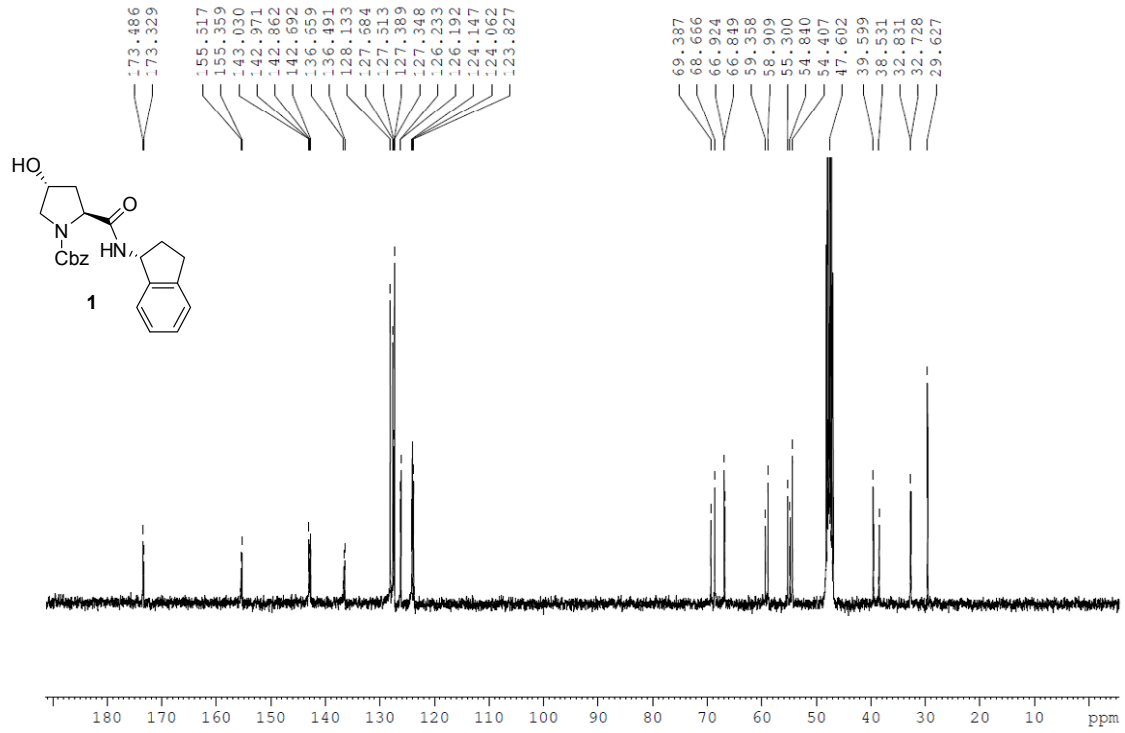
^{1}H NMR (DMSO-d$_6$, 400 MHz)



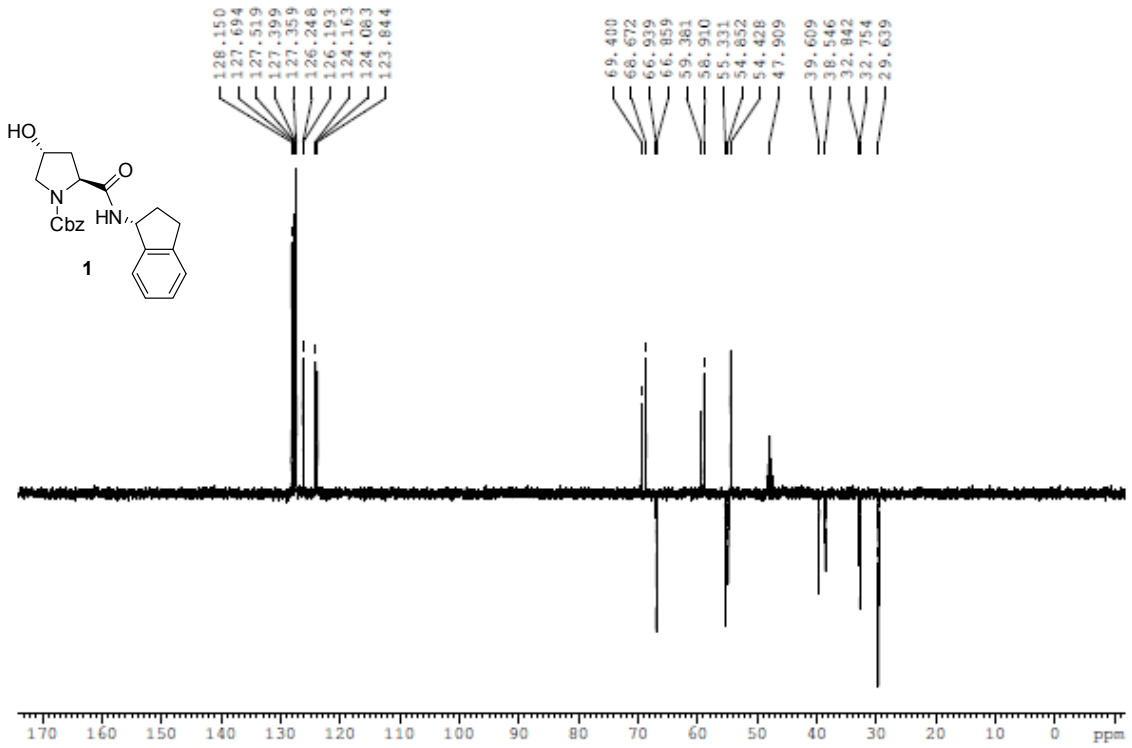
IR (ATR)



^{13}C-NMR (DMSO-d$_6$, 100 MHz)

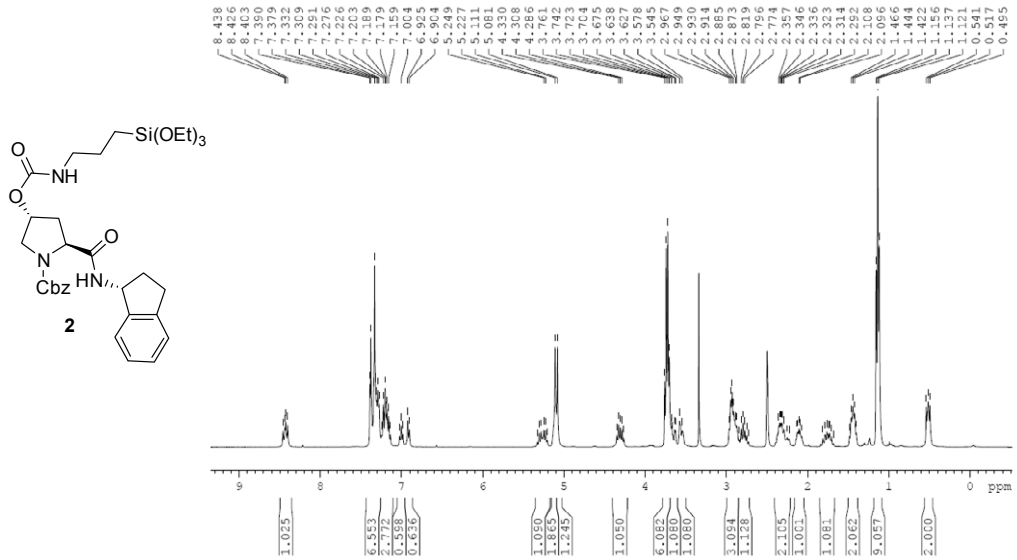


DEPT ^{13}C NMR (DMSO-d$_6$, 100 MHz)

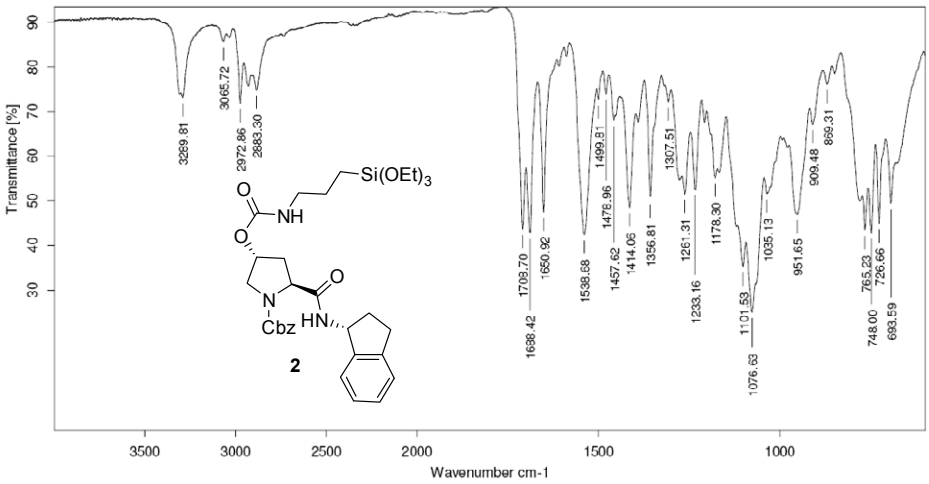


Compound **2**

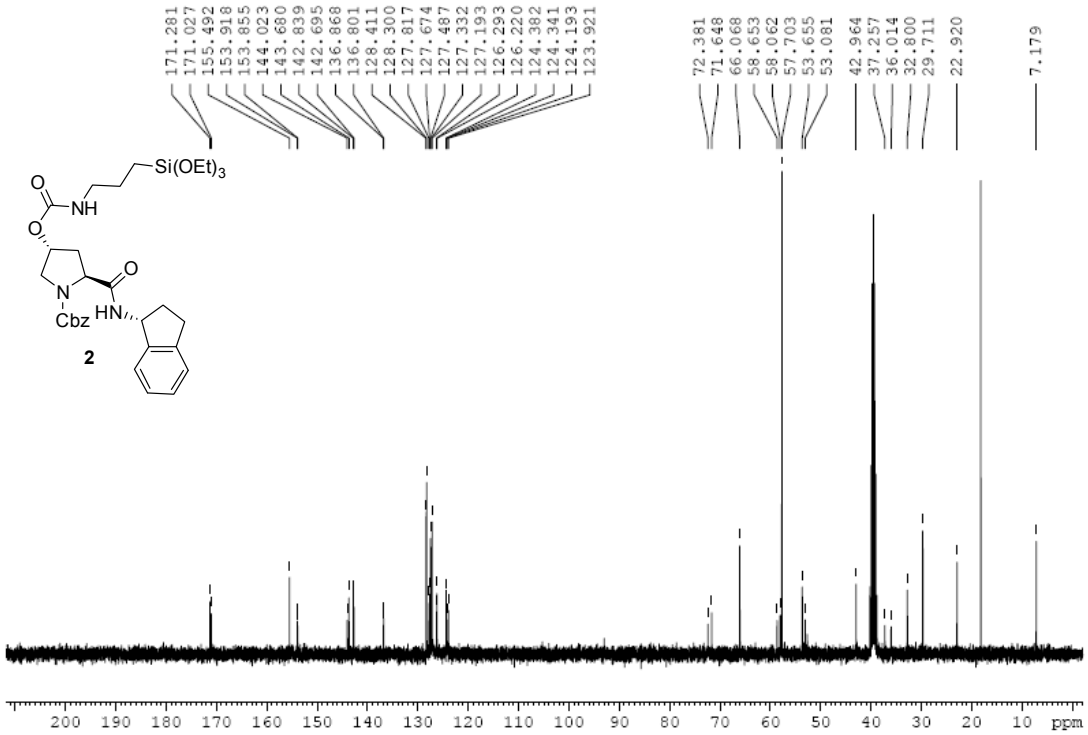
^{1}H-NMR (DMSO-d$_6$, 360 MHz)



IR (ATR)

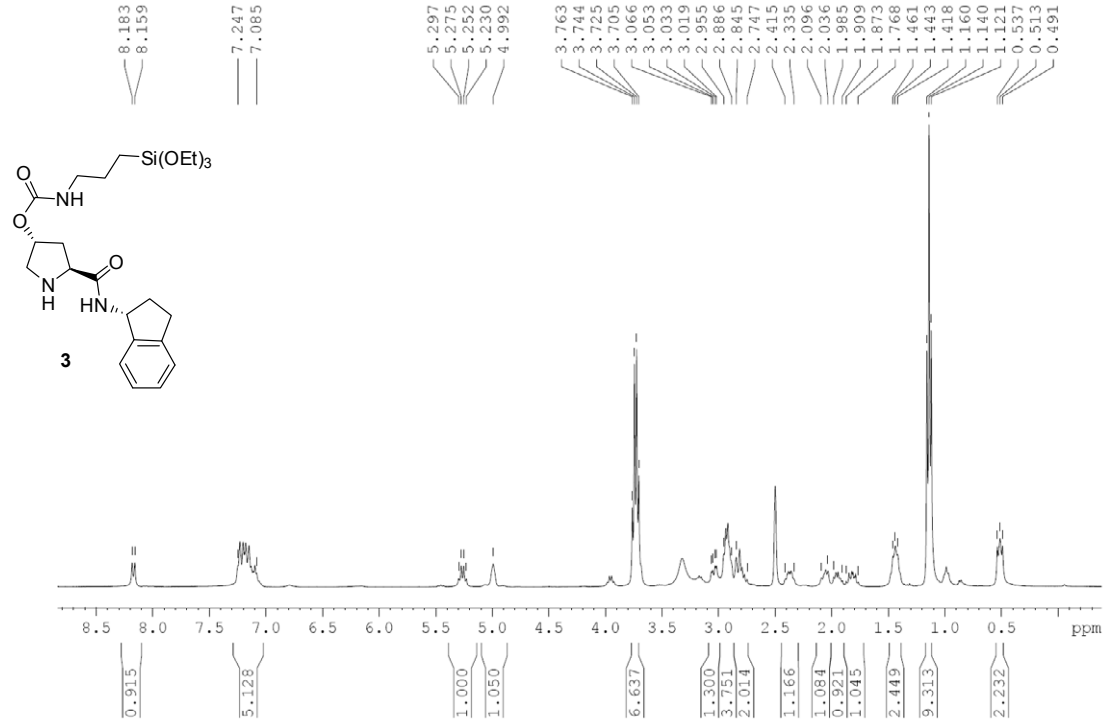


^{13}C-NMR (DMSO-d_6, 100 MHz)

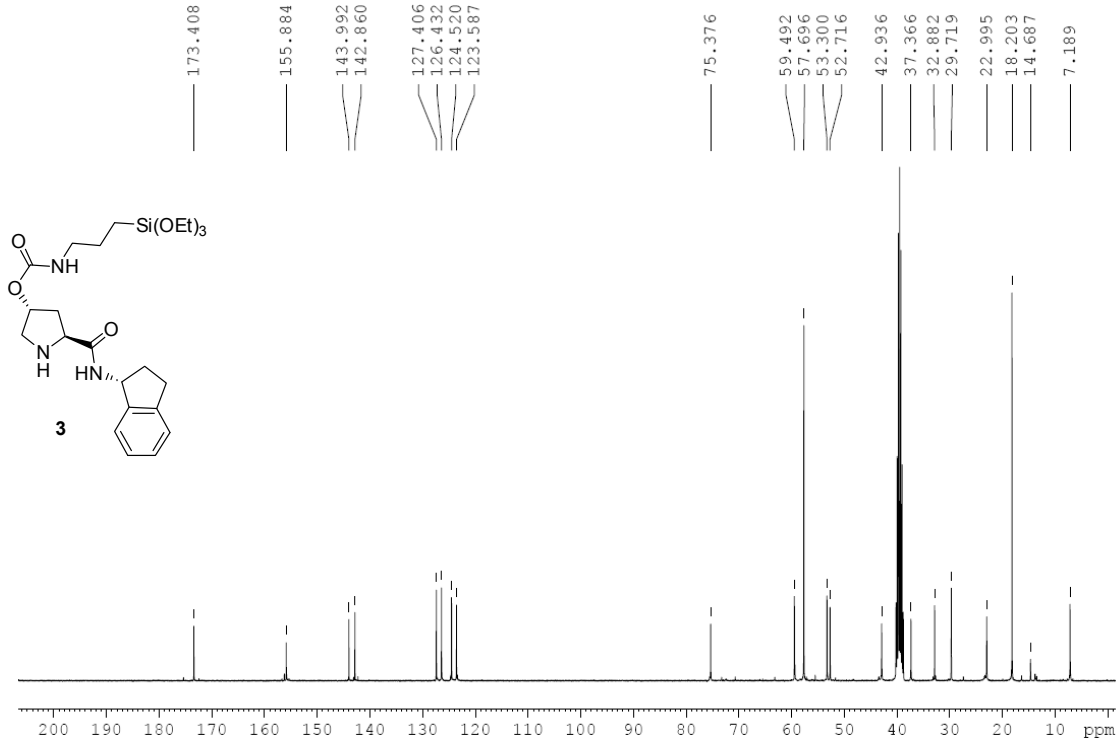


Compound **3**

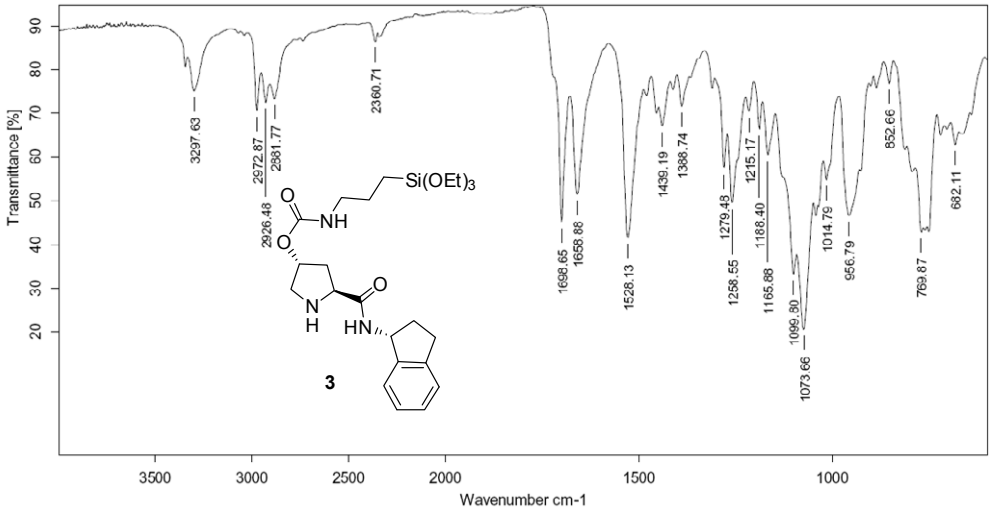
^{1}H-NMR (DMSO-d_6, 360 MHz)



^{13}C-NMR (DMSO-d_6, 90 MHz)

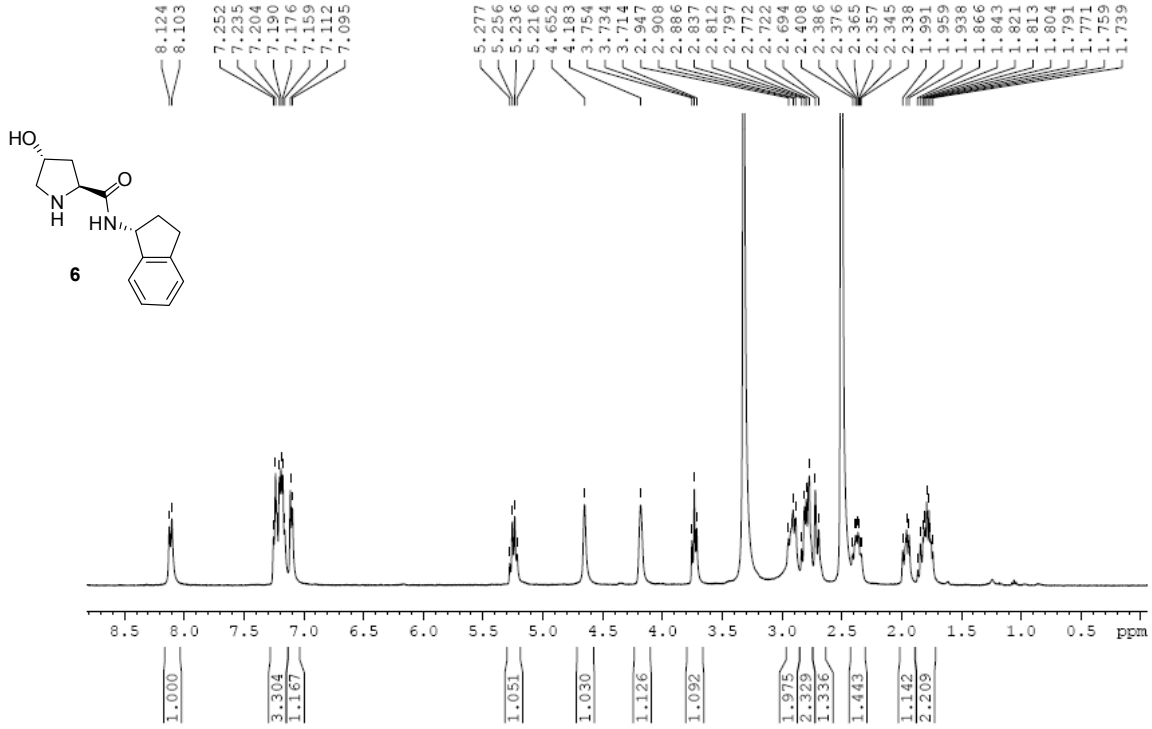


IR (ATR)

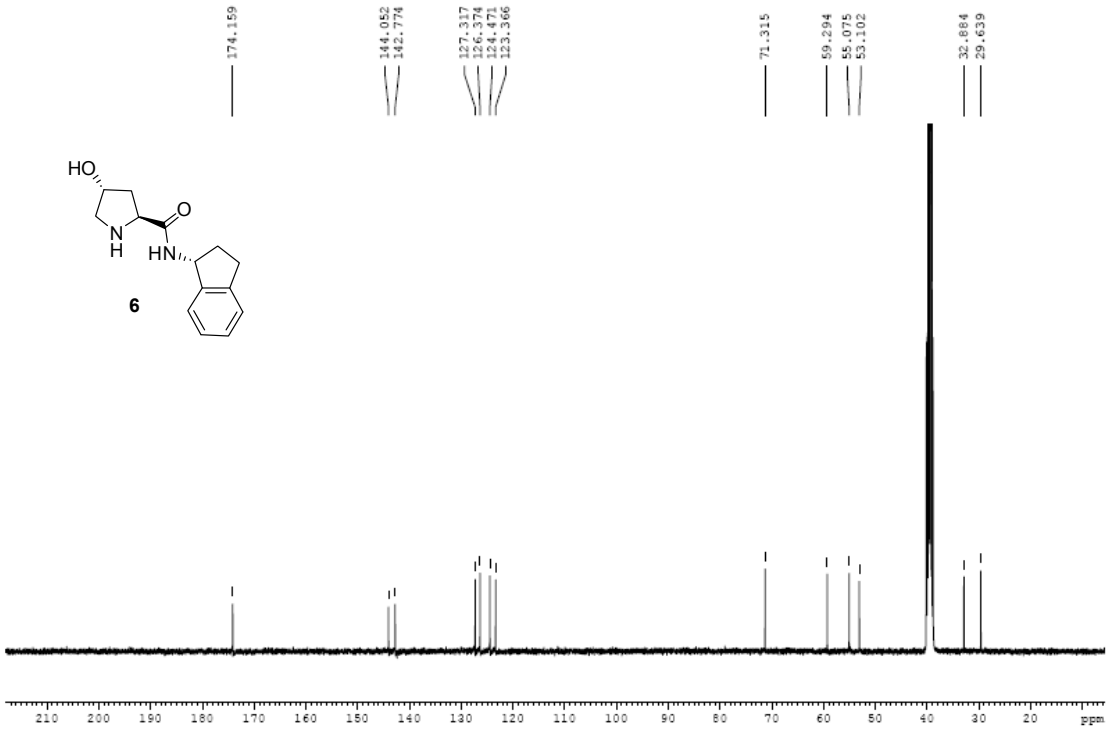


Compound **6**

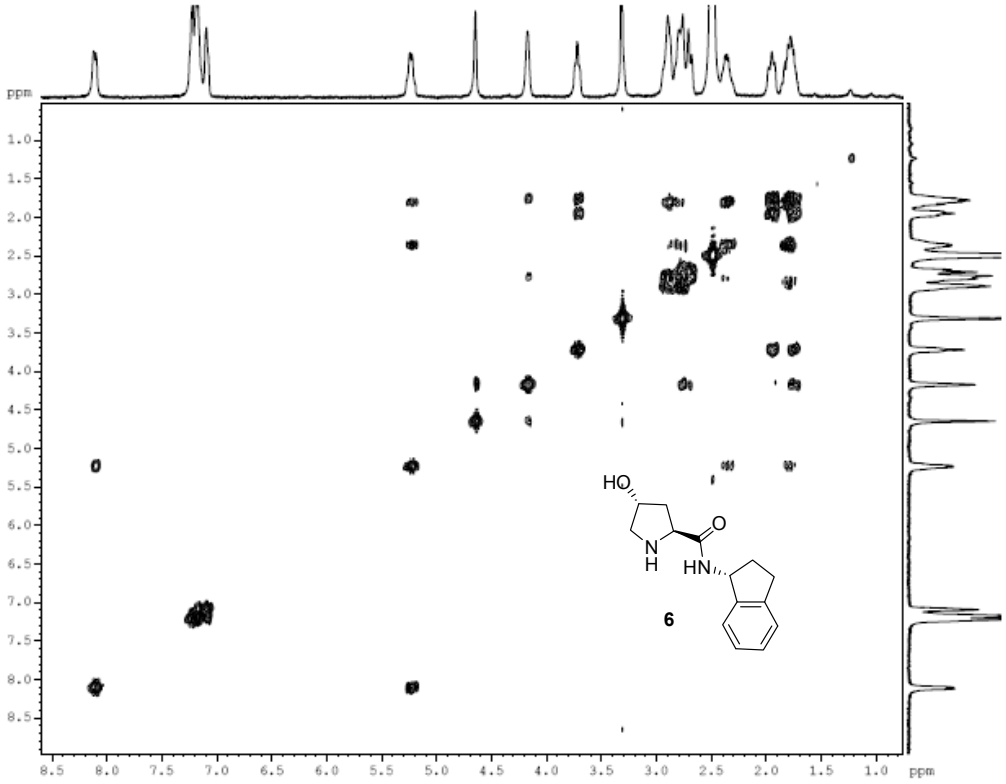
^{1}H-NMR (DMSO-d$_6$, 400 MHz)



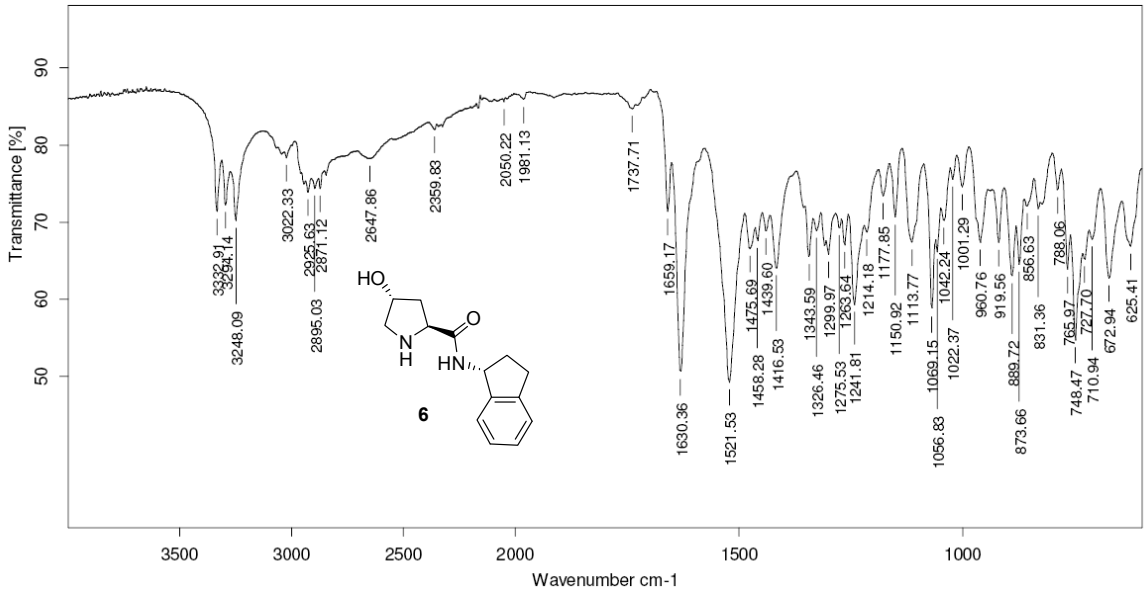
^{13}C-NMR (DMSO-d$_6$, 100 MHz)



^{1}H-^{1}H COSY (DMSO-d_6, 400 MHz)

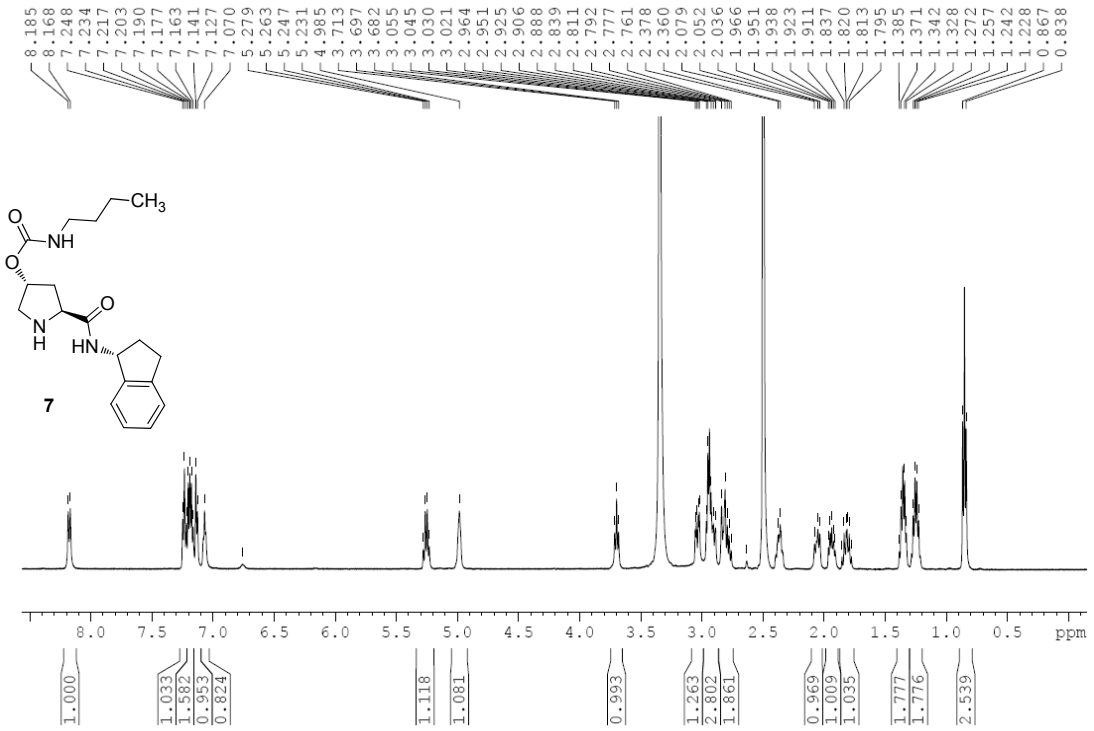


IR (ATR)

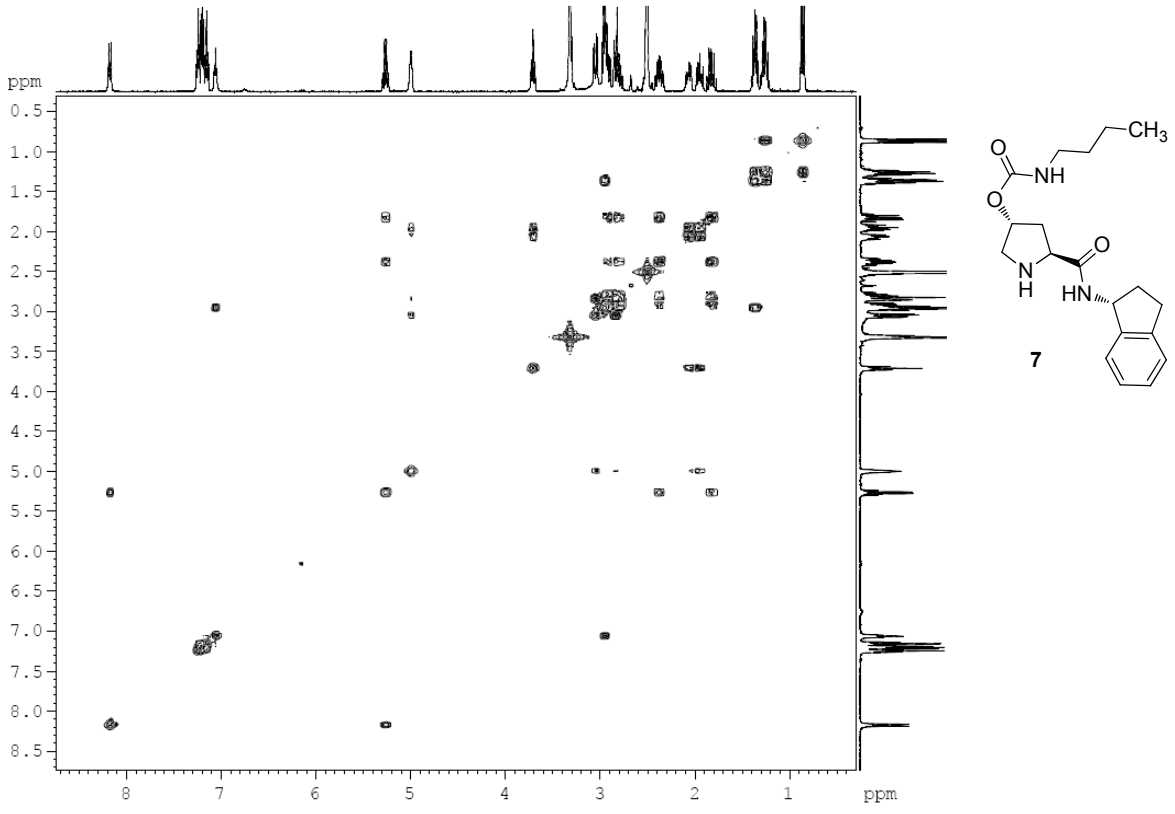


Compound **7**

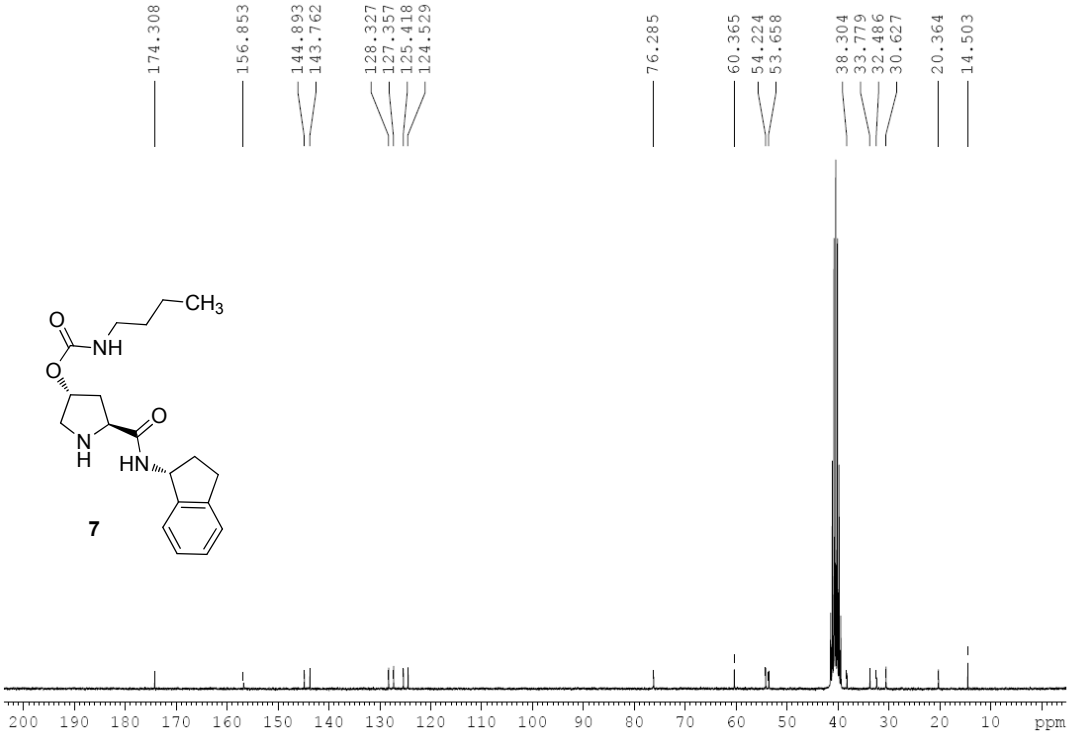
^{1}H-NMR (DMSO-d$_6$, 500 MHz)



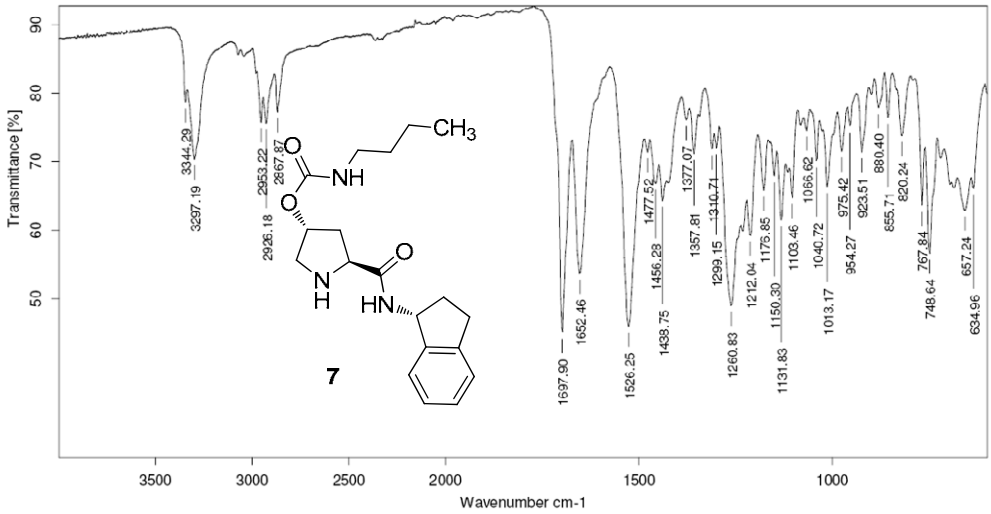
^{1}H-^{1}H COSY (DMSO-d$_6$, 400 MHz)



^{13}C-NMR (DMSO-d_6, 62.5 MHz)

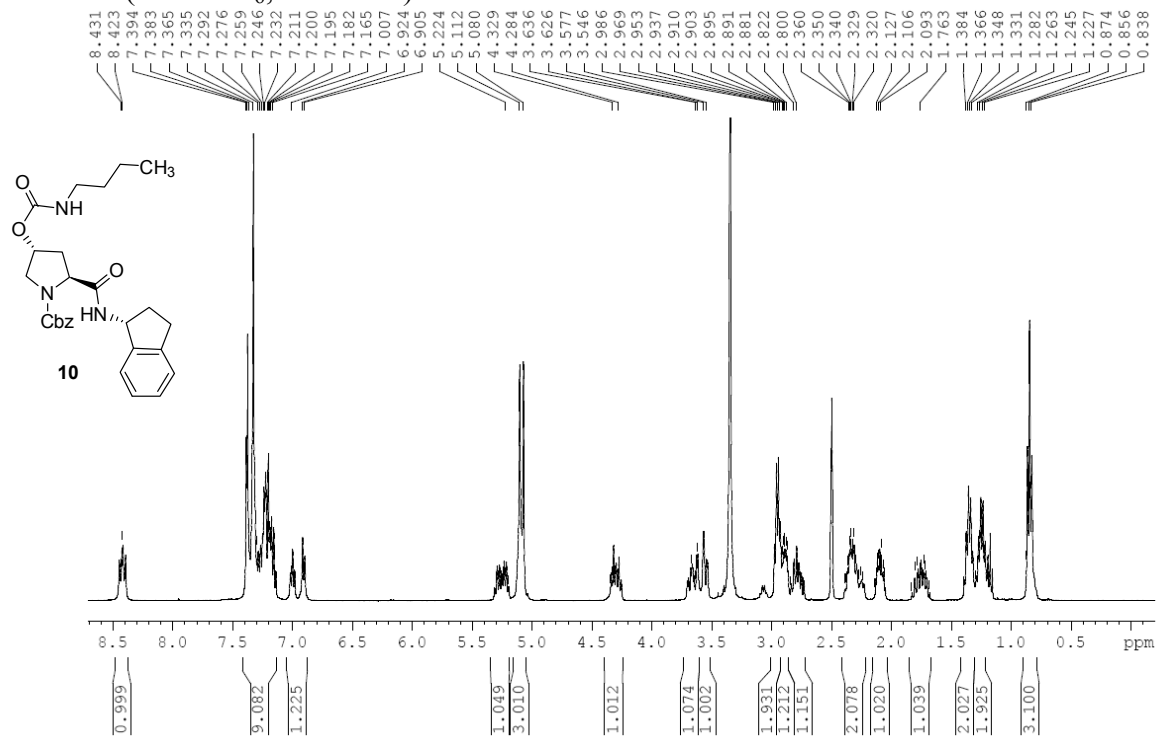


IR (ATR)

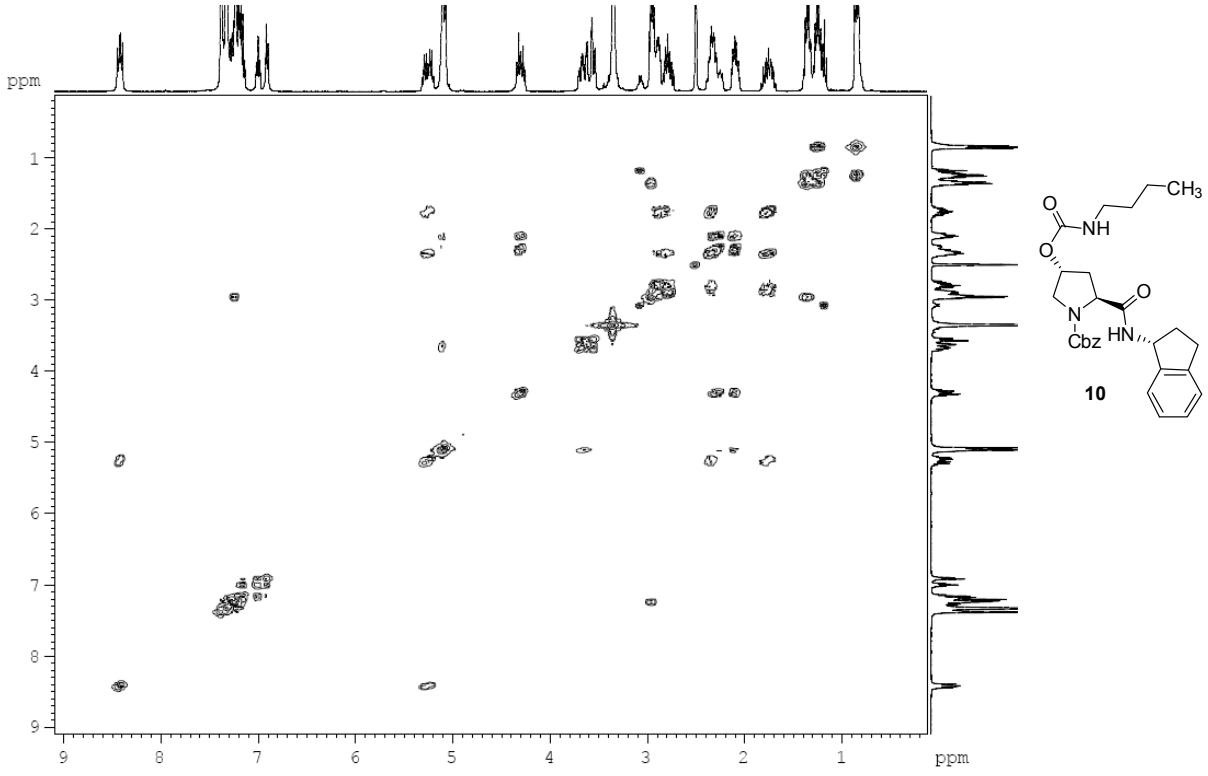


Compound **10**

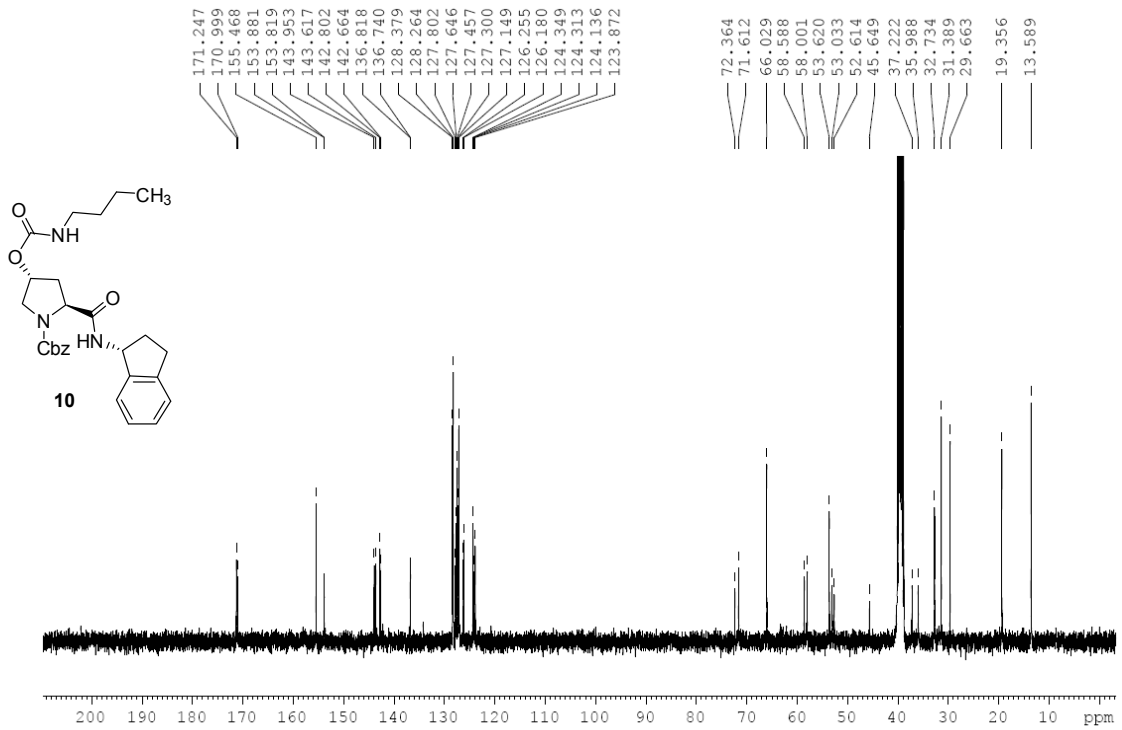
^{1}H-NMR (DMSO-d$_6$, 400 MHz)



^{1}H-^{1}H COSY (DMSO-d$_6$, 400 MHz)



^{13}C-NMR (DMSO-d_6, 100 MHz)



IR (ATR)