Electronic Supplementary Information: Direct NHC-Catalysed Redox Amidation Using CO_2 for Traceless Masking of Amine Nucleophiles

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General comments

Reagents obtained from commercial sources and used as received unless otherwise indicated. Reactions requiring anhydrous conditions were conducted in oven-dried glassware and under dried N_2 (Drierite®) or Ar atmosphere, using anhydrous solvents, with solvent and liquid reagent transfers performed under Ar atmosphere using purged needles and syringes. Specified solvents were dried by distillation Mg (DCM) or Na (PhMe, THF – benzophenone indicator) and stored under dried N_2 atmosphere. Commercially obtained anhydrous solvents were supplied by Sigma Aldrich (EtOH) or Merck (MeCN) as anhydrous or SeccoSolv® quality respectively and used as received.

Infrared spectra were recorded on a Perkin Elmer (Spectrum Express Version 1.03.00) spectrometer with automated background substraction. Reported absorption are strong (s) or medium (m) strength and given in wavenumbers (cm^{-1}).

^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 100 MHz. Chemical shifts (δ) are quoted in units of parts per million (ppm) downfield from tetramethylsilane and are referenced to a residual solvent peak: $CDCl_3$ (δ_H: 7.26, δ_C: 77.2), DMSO-d_6 (δ_H: 2.50, δ_C: 39.5), acetone-d_6 (δ_H: 2.05, δ_C: 206.3, 29.8).[1] Coupling constants (*J*) are quoted in units of Hertz (Hz). The following abbreviations are used to designate multiplicity within ^{1}H NMR analysis: s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, sext. = sextet, sept. = septet, non. = nonet, m = multiplet, br. = broad signal. Unless otherwise stated, NMR spectra were obtained at ambient temperature (293 – 299 K).

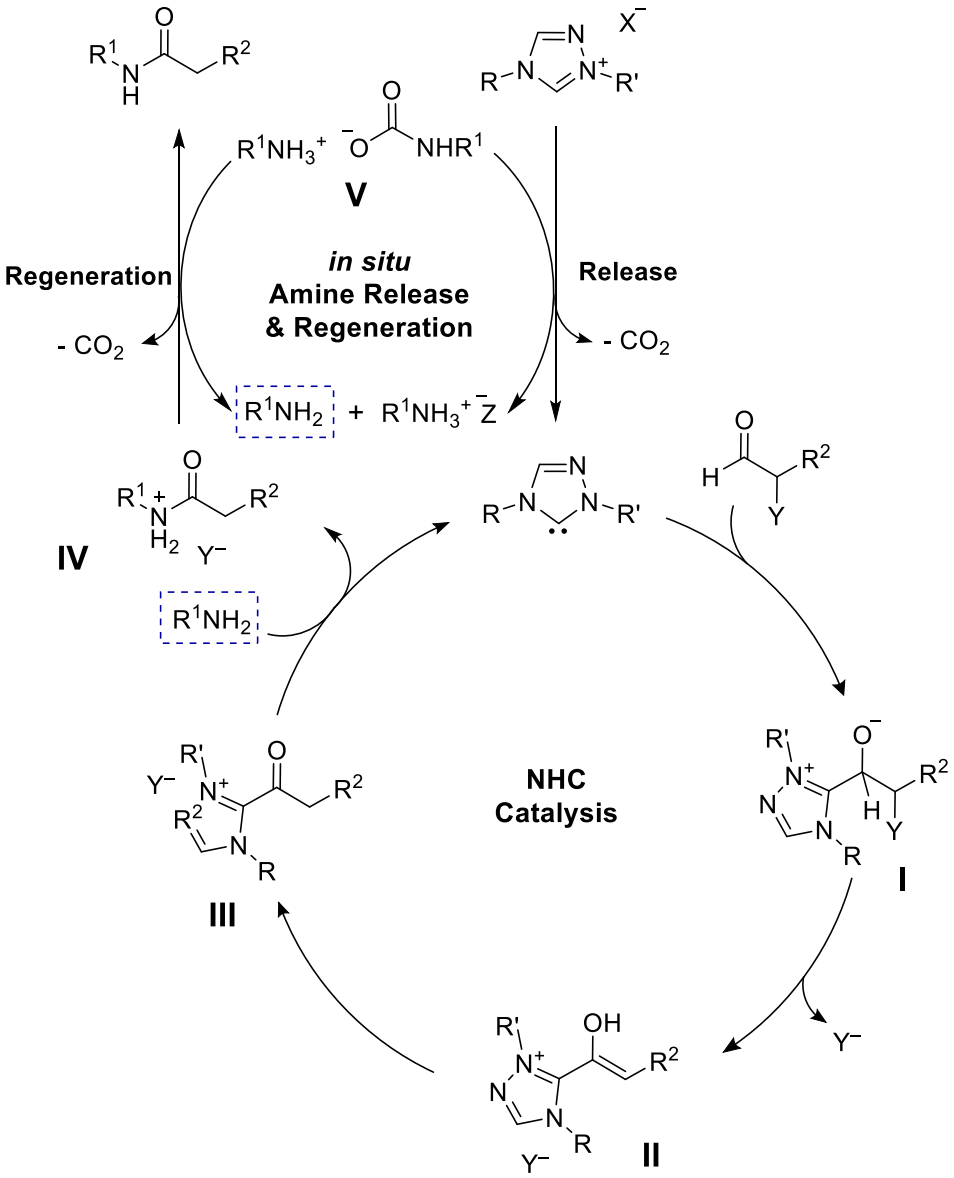
Low and high resolution mass spectrometry (CI, ESI) were recorded by the Imperial College London Department of Chemistry Mass Spectrometry Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer. Reported *m/z* values correspond to major ion peak, isotopic ion peaks are included where relevant.

All flash column chromatography was carried out on Merck silica gel 60, particle size 0.040–0.063 mm unless otherwise stated.

Thin layer chromatography (TLC) was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}), and visualised with ultraviolet light (254 nm). Visualisation using anisaldehyde, ethanolic H_2SO_4, ninhydrin, phosphomolybdic acid (PMA), potassium permanganate ($KMnO_4$) or vanillin stains was performed where deemed appropriate.

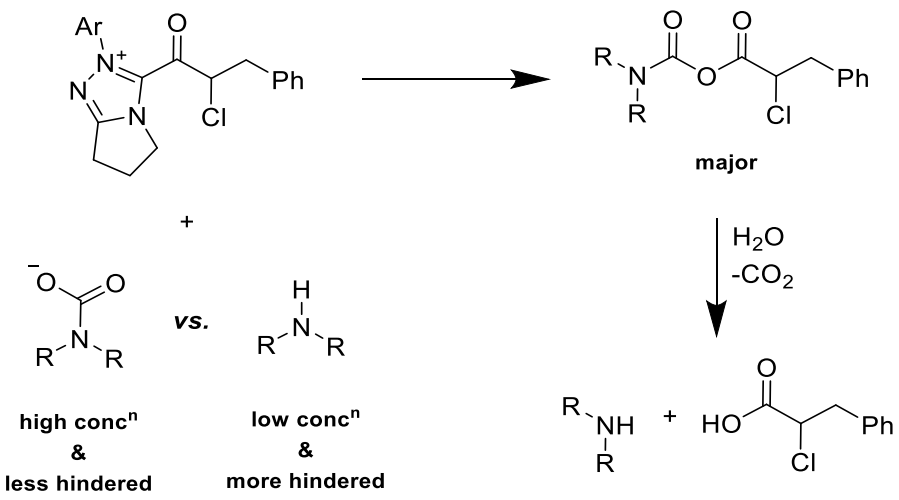
Intermediate compounds not featured in the main text have been assigned the lowercase Roman numerals **i**-**viii**.

Proposed catalytic cycles using alkylammonium alkylcarbamate salt pairs



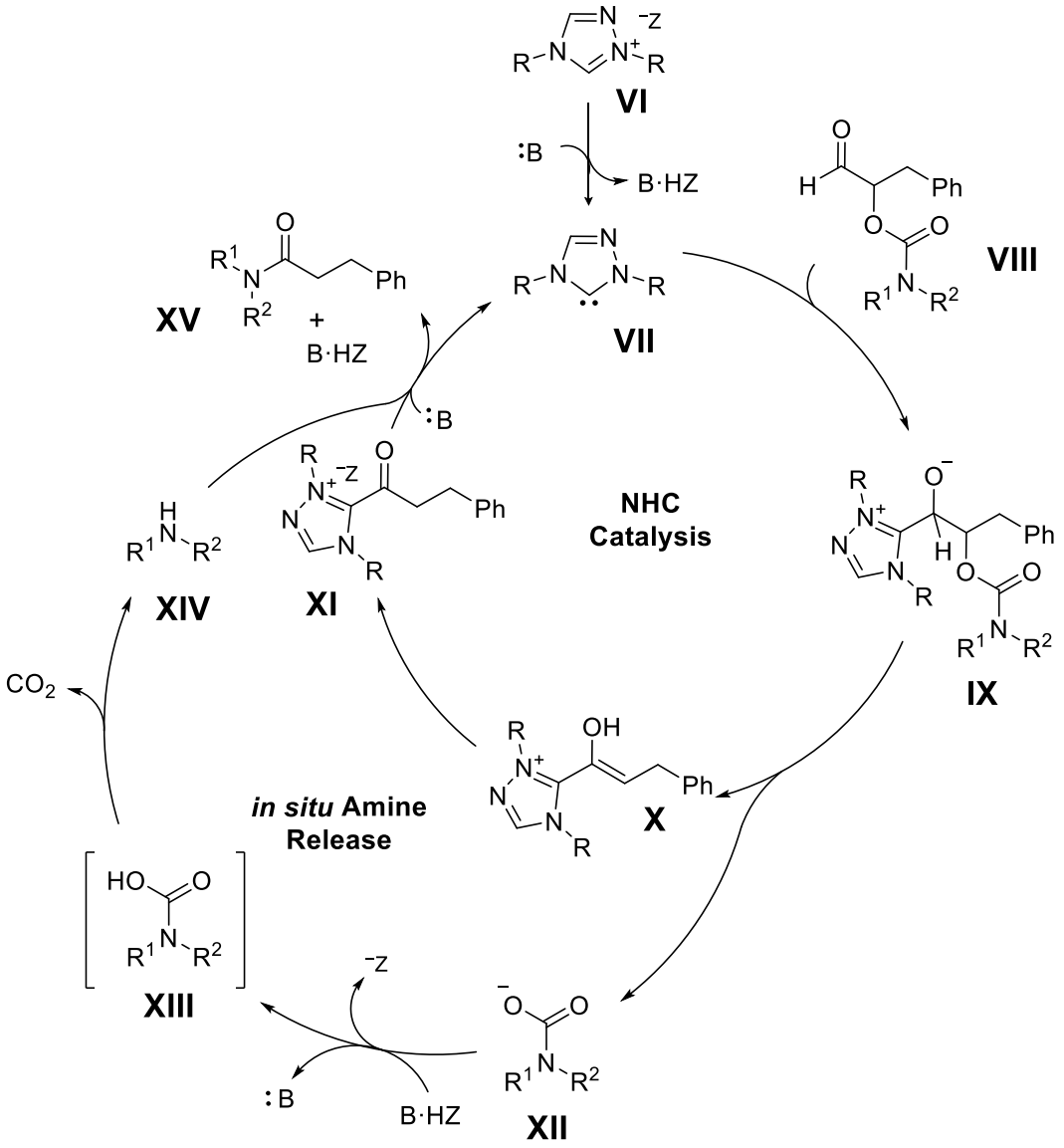
We propose that the reaction mechanism proceeds via initial deprotonation of the triazolium precatalyst by the carbamate anion of **V** to give the NHC species and a carbamic acid, which releases the amine upon decarboxylative degradation. The generated NHC, upon reaction with the aldehyde substrate, forms initial adduct **I** and undergoes redox-rearrangement to form acyl azolium **III**. Upon amidation, the NHC is released and the nascent product **IV** is deprotonated by another carbamate anion **V**, thus yielding the amide product and regenerating the free amine. Anion Z^- may be either of X^- or Y^-.

Carboxylic acid by-product formation



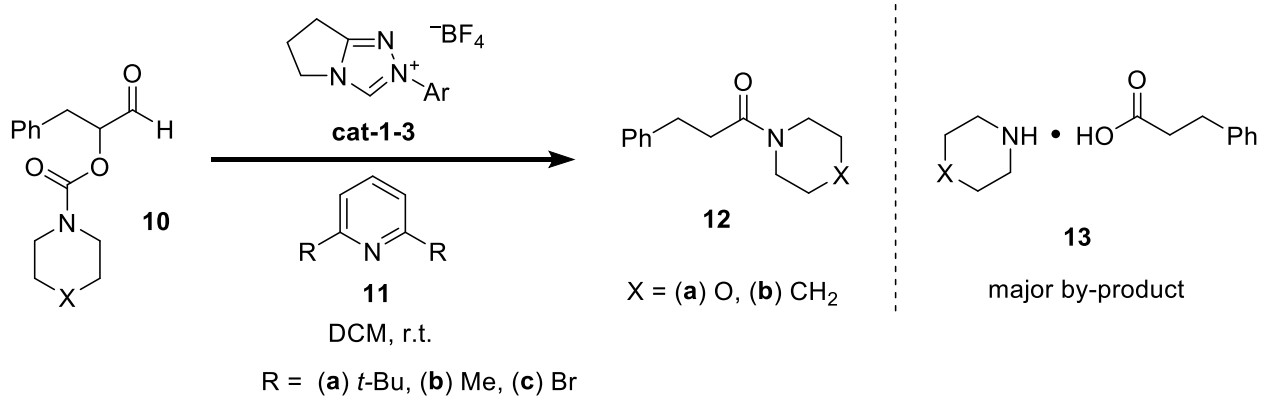
The main by-product observed in all cases utilizing bulky amines was the α-reduced carboxylic acid. Importantly however, the carboxylic acid was formed in larger amounts than should be expected under the rigorously anhydrous reaction conditions, even when considering the water generated through imine formation. Through careful monitoring, it was observed that there was reduced or no effervescence seen for less successful reactions involving bulky amines and, in general, the reactions proceeded much more slowly. Indeed, slower reactions took place over several hours, with aldehyde substrate still present after >12 h for the bulkiest examples. Rather than acyl azolium hydrolysis, the formation of the carboxylic acid side product in these examples was attributed to the sterically hindered amine nucleophiles being outcompeted by the carbamate anions, which are present in much greater concentration (especially at the start of the reaction). Ultimately, this would result in the formation of carboxylic–carbamic mixed anhydride. These byproducts would subsequently undergo hydrolytic decomposition, either through adventitious water generated from imine formation, or during work-up, to give the carboxylic acid and amine.

Proposed catalytic cycle using α-*O*-carbamoyl aldehyde substrates



Unlike the intermolecular variant, an additional base would be required for formation of the free NHC catalyst **VII** from triazolium precursor **VI** (and to act as a general proton shuttle during the reaction); however, since this base is regenerated at a later point in the catalytic cycle, it is only be needed in sub-stoichiometric quantities. The single stoichiometric byproduct would be one equivalent of CO_2. The NHC **VII** in combination with the aldehyde substrate **VIII**, would give initial adduct **IX**. At this stage, the leaving group should be displaced, resulting in carbamic anion **XII** and acyl azolium **XI**. Upon protonation, **XII** would be converted to carbamic acid **XIII** which would undergo spontaneous decarboxylation to release the amine nucleophile **XIV**. The amide product **XV** should be formed as the amine **XIV** is acylated by **XI** and at the same time the NHC **VII** is released to initiate the next catalytic cycle.

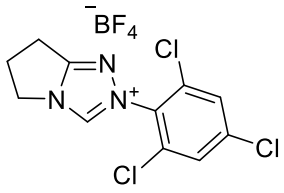
Screening conditions used for α-*O*-Carbamoyl aldehyde substrates



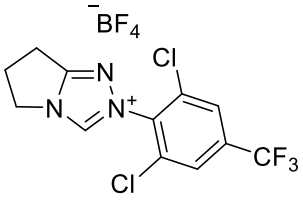
Entry	Substrate	Triazolium (n mol%)	Base (n mol%)	Conc. (M)	Ratio **12**:**13**[a]	Isolated yield of **12** (%)
1	**10a**	**Cat-1 (20 mol%)**	**11a (80 mol%)**	**0.1**	**7 : 1**	**nd**
2	**10a**	**Cat-1 (5 mol%)**	**11a (20 mol%)**	**0.1**	**7 : 1**	**57**[b]
3	**10a**	**Cat-1 (1 mol%)**	**11a (4 mol%)**	**0.1**	**3.5 : 1**	**nd**
4	**10a**	**Cat-1 (5 mol%)**	**11b (20 mol%)**	**0.1**	**3.5 : 1**	**52**[c]
5	**10a**	**Cat-1 (5 mol%)**	**11c (20 mol%)**	**0.1**	**5.7 : 1**	**55**[c]
6	**10a**	**Cat-1 (1 mol%)**	**11b (4 mol%)**	**0.5**	**1.7 : 1**	**nd**
7	**10a**	**Cat-2 (1 mol%)**	**11b (4 mol%)**	**0.5**	**1.6 : 1**	**nd**
8	**10a**	**Cat-3 (1 mol%)**	**11b (4 mol%)**	**0.5**	**1.4 : 1**	**nd**
9	**10a**	**Cat-3 (5 mol%)**	**11a (20 mol%**	**0.1**	**2 : 3**	**nd**
10	**10a**	**Cat-3 (1 mol%)**	**11a (4 mol%)**	**0.1**	**1 : 2**	**nd**
11	**10b**	**Cat-1 (5 mol%)**	**11a (20 mol%)**	**0.1**	**1 : 1.5**	**nd**
12	**10b**	**Cat-2 (5 mol%)**	**11c (20 mol%)**	**0.1**	**1 : 2**	**nd**

[a] ratio determined by ^{1}H NMR spectroscopy. [b] isolated yield after column chromatography (SiO_2). [c] isolated yield after acid/base extraction. nd = isolated yield not determined. See below for catalysts used – unfavoured catalysts **cat-4** – **cat-6** did not give desired redox rearrangement products.

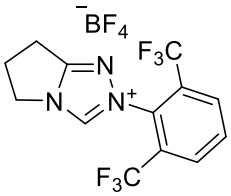
Favoured catalysts: electron poor, ortho-bulky *N*-aryl groups



cat-1

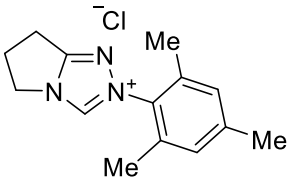


cat-2

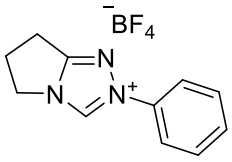


cat-3

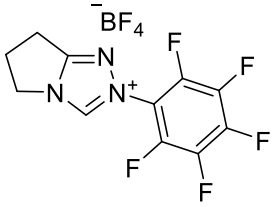
Unfavoured catalysts: electron rich or less ortho bulky *N*-aryl groups



cat-4

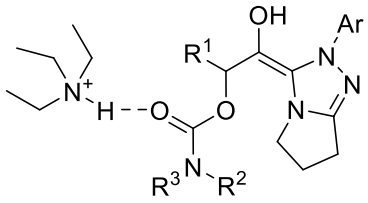


cat-5



cat-6

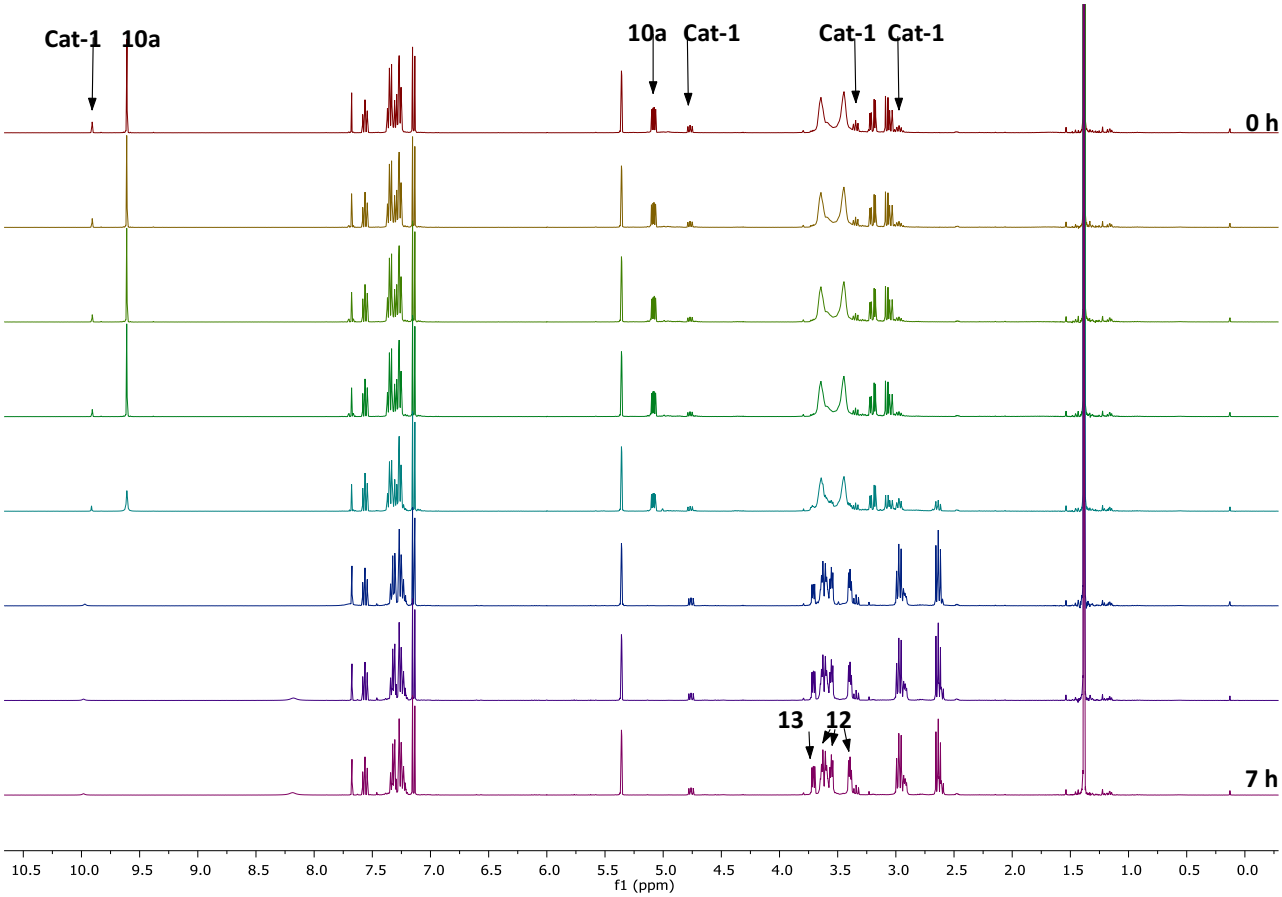
The reactivity of substrate **10a** was surveyed, using a range of sub-stoichiometric bases (<50 mol%) together with a triazolium precatalyst. Alongside **cat-1**, other precatalysts were screened including the most widely reported triazolium precatalysts **cat-4**, **cat-5** & **cat-6.** These latter three precatalysts were largely unproductive in this chemistry. It was also found that the use of strong bases such as NaH, DBU and DiPEA led to inseparable mixtures, mainly containing acyloin products, suggesting that the carbamoyl leaving group was not being effectively displaced and instead the Breslow intermediate was acting as a nucleophile towards a second equivalent of aldehyde substrate. The inability of the carbamate group to leave when strong bases were employed was hypothesized to arise from inefficient activation of this leaving group by hydrogen bonding to the conjugate acid of the base employed (see below): a similar observation was made previously in the lactam formation chemistry reported by Gravel (see Scheme 2 in main paper)



If valid, this hypothesis would mean a fine balance of the pK_{aH} of the base would be required in order for it to function both as an effective base for triazolium/amide deprotonation, but also as a proton shuttle to both facilitate cleavage of the α-carbamoyl C-O bond and protonation of the carbamate anion. To test this analysis it was necessary to vary the electronic nature of the *N*-aryl substituents and thereby the acidity of the C-2 carbenic carbon. Additionally it was envisaged that leaving group displacement would be aided by ortho-bulk on the *N*-aryl ring of the NHC. This led to the preparation of several triazolium precatalysts that contained electron-deficient, ortho-disubstituted *N*-aryl groups (**cat-2** & **cat-3**), which were surveyed alongside **cat-1**.

After additional screening against a series of amine bases of decreasing pK_{aH} (Et_3N, DABCO, cinchonidine derivatives), 2,6-disubstituted pyridines **11** emerged as the most promising class. Although the aldehyde was fully converted with the former bases, the major products of the reaction were hydrocinnamic acid and morpholine; giving "hydrolysis products" under anhydrous conditions (as seen in the intermolecular work). This would imply that there is a region of basicity that allows for the leaving group to be displaced, but in turn does not favour the subsequent decarboxylation step. Of the solvents screened, the reaction proceeded most rapidly in DCM (<6 h), compared to THF (<24 h) and MeCN (<48 h), as well as providing a much cleaner reaction profile.

Reaction of 10a with cat-1 (5 mol%) & 11a (20 mol%) in DCM-*d*$_2$ monitored at 1 h intervals.

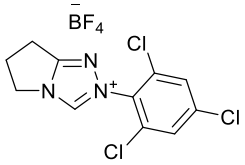


Given these observations, a more complete survey of the performance of catalysts **cat-1**, **cat-2** & **cat-3**, in the presence of several 2,6-disubstituted pyridine bases was carried out in DCM (see Table above). In general, it was found that the reaction proceeds cleanly to either the desired product **12** or the equivalent by-product **13** (see spectra). The combination of **cat-1** and base **11a** gave the best results for the conversion of substrate **10a** into amide **12a** and it was possible to lower the precatalyst loading from 20 mol% to 5 mol% (entries 1 & 2). Good selectivity was observed for the desired amide product **12a** over the side product **13a** (7:1), and the amide product was isolated in good yield (57% - entry 2). Lowering the loading of precatalyst **cat-1** further to 1 mol% led to a poorer **12**:**13** ratio (entry 3), even once the total reaction concentration was increased (entries 6 to 8). Increased by-product formation (**13**) was observed as the triazolium *N*-aryl substituent becomes more electron-deficient (**cat-2** and **cat-3**, entries 7-10). It is plausible that the acyl azolium intermediate XI derived from **cat-**

2/**3** is more activated, and therefore captured by carbamate anion **XII** more rapidly that protonation and decarboxylation of **XII**. Regardless of this decreased selectivity for the desired amide product, it should be still noted that **cat-2/3** are still much more active that than the electron-rich *N*-mesityl and *N*-phenyl precatalysts (**cat-4** & **cat-5** respectively). While productive reactivity was observed for an alternative substrate **10b** (entries 11 and 12) a poorer **12**:**13** ratio was observed. We believe this is due to a mismatch between the pK_{aH} of the amino (piperidine) leaving group and the optimised conditions for **10a**.

Experimental procedures

2-(2,4,6-Trichlorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (cat-1)[2]

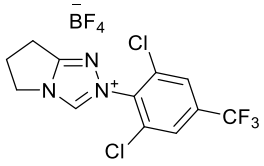


Procedure modified from literature preparation.[2] To 2-pyrrolidinone (2.5 mL, 33 mmol) in DCM (125 mL) was added triethyloxonium tetrafluoroborate 6.3 g, 33 mmol). The reaction mixture was stirred at r.t. for 16 h then 2,4,6-trichlorophenylhydrazine (7 g, 33 mmol) was added. The mixture was heated to 50 °C and stirred for a further 1 h during which time a white precipitate formed. The reaction mixture was returned to r.t. and the precipitate isolated by vacuum filtration. The white powder was suspended in a mixture of chlorobenzene (30 mL) and triethylorthoformate (120 ml, 710 mmol), $Et_2O{\cdot}HBF_4$ (1 mL, 7.1 mmol) was added, and the reaction heated to 120 °C for 12 h. Upon cooling an off-white precipitate formed which was isolated by vacuum filtration. The precipitate was recrystallised from EtOH to yield 6.5 g (32%) **cat-1** as a crystalline white solid.

N.B. It was found that the use of substoichiometric $Et_2O{\cdot}HBF_4$ was essential to ensure reproducible cyclisation to the triazolium.

^{1}H NMR (400MHz, acetone-d_6): δ_H 10.31 (s, 1H), 7.97 (s, 2H), 4.86–4.78 (m, 2H), 3.50–3.43 (m, 2H), 3.11–2.98 (m, 2H); HRMS (ESI) calcd. for $C_{11}H_9N_3{}^{35}Cl_3$ $[M+H]^+$: 287.9862; found *m/z*: 287.9857.

2-(2,6-dichloro-4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (cat-2)

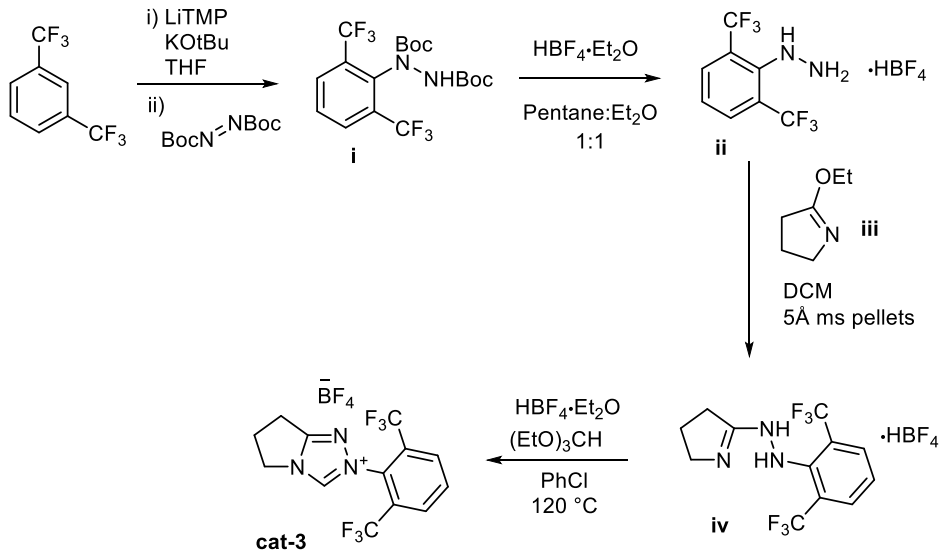


Preparation as for **cat-1** using (2,6-dichloro-4-(trifluoromethyl)phenyl)hydrazine (5 g, 20 mmol) with reagents scaled accordingly. Purification *via* soxhlet extraction (EtOH) to yield 1.4 g (17%) **cat-2** as a crystalline white solid.

IR (neat) 3086, 1599, 1315, 1133, 1055, 1029, 878, 826, 705 cm^{-1}; ^{1}H NMR (400MHz, acetone-d_6): δ_H 10.29 (s, 1H), 8.21 (d, *J* = 0.4 Hz, 2H), 4.81 (m, 3H), 3.46 (t, *J* = 7.8 Hz, 3H), 3.02 (quin., *J* = 7.6 Hz, 2H).); ^{13}C NMR (100MHz, acetone-d_6): δ_C 165.8, 144.0, 135.8, 135.7, 135.6 (q, *J* = 34.8

Hz), 127.5 (q, *J* = 3.8 Hz), 123.0 (q, *J* = 273.0 Hz), 49.5, 27.6, 22.6; HRMS (ESI) calcd. for $C_{12}H_9N_3F_3{}^{35}Cl_2$ $[M+H]^+$: 322.0126; found *m/z*: 322.0130.

Preparation of triazolium precatalyst cat-3.



a) (2,6-Bis(trifluoromethyl)phenyl)hydrazine hydrofluoroborate (ii)

Metalation procedure modified from literature preparation.[3] To a stirring solution of 2,2,6,6-tetramethylpiperidine (16.9 mL, 100 mmol) in THF (260 mL) at -78 °C was added *n*-BuLi (2.5 M soln. in hexanes, 40 mL, 100 mmol) dropwise. The reaction mixture was stirred at -78 °C for 1 h then potassium *tert*-butoxide (11.2 g, 100 mmol) was added. The reaction was stirred at -78 °C for a further 1 h during which time the solution became homogeneous and then 1,3-bis(trifluoromethyl)benzene (15.5 mL, 100 mmol) in THF (40 mL) was added dropwise. The mixture was stirred for a further 1 h at -78 °C and the solution turned dark purple. To the solution of metalated arene was added di-*tert*-butyl azodicarboxylate (23.0 g, 100 mmol) sequentially in 4 roughly equal portions. The reaction mixture was allowed to warm r.t. and stirred for 12 h. Saturated aqueous ammonium chloride solution (300 mL) and diethyl ether (500 mL) were added and phases separated. The organic phase was washed with H_2O (200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified *via* flash column chromatography (SiO_2, 100% DCM) to yield 19.8 g (45%) **i** as an off white solid.

i: ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.93 (m, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 6.48 (br. s, 1H), 1.50, 1.48 & 1.32 (3s, 18H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 153.8, 153.1, 137.9, 131.4 (q, *J* = 5.9 Hz), 130.4 (q, *J* = 31.5 Hz), 129.6, 129.3, 122.9 (q, *J* = 274.3 Hz), 83.3, 83.2, 81.9, 28.2, 28.1, 28.0, 27.8.

To a vigorously stirred solution of **i** (17.8 g, 40 mmol) in pentane:Et_2O (1:1, 900 mL) at r.t. was added $HBF_4.Et_2O$ (12.0 mL, 88 mmol). Congealed $HBF_4.Et_2O$ was scraped off the sides of the flask with a spatula. The reaction mixture was stirred rapidly at r.t. for 14 h in which time a

precipitate formed. The precipitate was isolated by vacuum filtration (washing with Et_2O) to yield 5.6 g (42%) **ii** as a pale yellow powder. *This hydrazine HBF_4 salt is hygroscopic but can be stored for weeks in a desiccator (P_2O_5).*

ii: ^{1}H NMR (400MHz, DMSO-d_6): δ_H 9.70 (s, 3H), 8.15 (d, *J* = 7.9 Hz, 2H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.32 (s, 1H); ^{13}C NMR (100MHz, DMSO-d_6): δ_C 139.1, 131.6 (q, *J* = 5.2 Hz), 129.6, 129.5 (q, *J* = 30.0 Hz), 123.0 (q, *J* = 273.5 Hz).

b) 5-Ethoxy-3,4-dihydro-2*H*-pyrrole (iii)[4]

Procedure modified from literature preparation.[5] To a stirred solution of 2-pyrrolidinone (3.5 mL, 47 mmol) in DCM (175 mL) was added triethyloxonium tetrafluoroborate (8.9 g, 47 mmol). The reaction mixture was stirred at r.t. for 16 h then saturated aqueous $NaHCO_3$ solution (200 mL) was added and the biphasic mixture was stirred rapidly at r.t. for 1 min. The layers were transferred to a separating funnel, separated and the organic layer was washed with $NaHCO_{3(sat.\ aq.)}$ (100 mL) and brine (100 mL) before being dried over $MgSO_4$ and concentrated via rotary evaporation (care must be taken as product is volatile) to yield 4.6 g **iii** as a colourless liquid. ~87% w/w purity with residual DCM determined by ^{1}H NMR spectrum integration - used directly in following reaction.

iii: ^{1}H NMR (400MHz, $CDCl_3$): δ_H 4.18 (q, *J* = 7.0 Hz, 2H), 3.64 (m, 2H), 2.44 (m, 2H), 2.00 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 173.2, 63.9, 55.3, 31.3, 23.2, 14.6.

c) 2-(2,6-Bis(trifluoromethyl)phenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (cat-3)

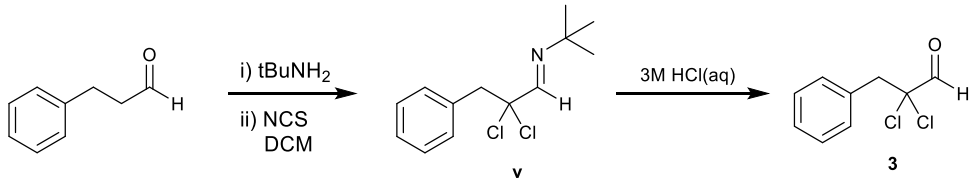
To a stirred solution of **iii** (1.6 g, 87% w/w in DCM, 12 mmol) in DCM (90 mL) with 5Å m.s. pellets was added **ii** (3.8 g, 11 mmol). The reaction mixture was stirred at r.t. for 12 h during which time a precipitate formed. The m.s. pellets were removed by filtering the reaction mixture through a paperless Büchner funnel. The precipitate was then isolated by vacuum filtration (washing with DCM) to yield 4.5 g **iv** as a pale grey powder.

This material was suspended in a mixture of chlorobenzene (10 mL) and triethylorthoformate (33 mL, 200 mmol), $Et_2O{\cdot}HBF_4$ (0.28 mL, 2.0 mmol) was added, and the reaction heated to 120 °C for 9 h with an air condenser open to the atmosphere ensuring any EtOH generated was efficiently removed from the system. Reaction was monitored by ^{1}H NMR until complete consumption of **iv** was observed. Upon cooling a grey precipitate formed which was isolated by vacuum filtration (washing with EtOH). The precipitate was purified *via* soxhlet extraction using EtOH to yield 1.45 g (35%) **cat-3** as a crystalline off-white solid.

cat-3: IR (neat) 3097, 1603, 1298, 1136, 1054, 1031, 968, 831, 676 cm^{-1}; ^{1}H NMR (400MHz, acetone-d_6): δ_H 10.39 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.30 (t, *J* = 7.9 Hz, 1H), 4.86 (t, *J* = 7.9 Hz, 2H), 3.48 (t, *J* = 7.8 Hz, 2H), 3.04 (quin., *J* = 7.6 Hz, 2H); ^{13}C NMR (100MHz, acetone-d_6): δ_C 165.0,

144.7, 135.3, 132.9 (q, *J* = 5.0 Hz), 131.2, 130.1 (q, *J* = 32.6 Hz), 122.9 (q, *J* = 274.0 Hz), 49.8, 27.6, 22.4; HRMS (ESI) calcd. for $C_{13}H_{10}N_3F_6$ $[M+H]^+$: 322.0779; found *m/z*: 322.0780.

Preparation of 2,2-Dichloro-3-phenylpropanal (3)[6]



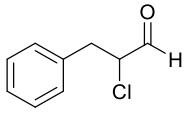
To hydrocinnamaldehyde (20 mL, 150 mmol) was added *t*-$BuNH_2$ (16 mL, 150 mmol) and the reaction mixture was stirred at r.t. for 5 min. $MgSO_4$ was added to form a slurry and the reaction was stirred for another 30 min - the heat generated was dissipated through the use of and external water bath at ambient temperature. The slurry was poured into DCM (500 mL) to aid removal of $MgSO_4$ by gravity filtration. The filtrate was transferred to a foil covered round-bottomed flask, *N*-chlorosuccinimide (60 g, 450 mmol) was added and the reaction mixture stirred rapidly for 12 h. The resulting suspension was filtered and the solids washed with DCM. The solvent of the filtrate was removed *in vacuo* and the resulting residue purified *via* flash column chromatography (1-5% Et_2O in pentane) to yield 22 g of the dichloroimine **v** as a white solid.

v: ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.72 (s, 1H), 7.43 (m, 2H), 7.34 (m, 3H), 3.76 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 155.2, 134.5, 131.9, 127.8, 127.4, 88.8, 57.5, 48.9, 29.2.[7]

N-(2,2-Dichloro-3-phenylpropylidene)-2-methylpropan-2-amine (22 g, 85 mmol) was treated with 3 M $HCl_{(aq)}$ (250 mL) and the reaction mixture was stirred at r.t. for 5 h. The aqueous reaction mixture was extracted with Et_2O (3x 250 mL) and the combined organics were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to yield the mono-hydrated (*gem*-diol) form of desired product as an off white solid. The solid was dissolved in PhMe (500 mL) and the water removed from the mono-hydrate adduct by azeotropic distillation using Dean–Stark apparatus. The organic solvent was removed *in vacuo* to yield 17 g (98%) **3** as a pale yellow oil. Distillation of this oil from NaH under reduced pressure (101-105 °C, 2 mbar) gave a recovery of 14 g (82%) **3** as a colourless oil.

3: IR (neat) 1741, 1497, 1456, 1224, 1079, 752, 697 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 9.35 (s, 1H), 7.37 (s, 5H), 3.62 (s, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 185.3, 132.6, 131.4, 128.3, 128.0, 87.3, 46.2.

2-Chloro-3-phenylpropanal (8)[8]



To hydrocinnamaldehyde (10 mL, 76 mmol) in DCM (150 mL) was added DL-proline (875 mg, 7.6 mmol) and *N*-chlorosuccinimide (10.7 g 80 mmol). The reaction mixture was stirred at r.t. for 12 h then the solids filtered off and the solvent removed *in vacuo* to yield 12.5 g (97%) **8** as a colourless oil (comprises ~10% wt. dichloroaldehyde **3**).

^{1}H NMR (400MHz, $CDCl_3$): δ_H 9.57 (d, *J* = 2.2 Hz, 1H), 7.39–7.23 (m, 5H), 4.41 (ddd, *J* = 8.1, 5.7, 2.2 Hz, 1H), 3.41 (dd, *J* = 14.4, 5.7 Hz, 1H), 3.11 (dd, *J* = 14.4, 8.1 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 194.4, 135.4, 129.4, 128.7, 127.4, 63.9, 38.3.

General procedure for the NHC-catalysed redox amidation of dichloroaldehyde 3:

Amines were purified *via* distillation from CaH_2 prior to use or following the relevant procedures outlined in *Purification of Laboratory Chemicals*.[9] The aldehyde **3** was used as purified in the above procedure.

(A) From commercially available amines.

$CO_{2(g)}$ was passed through a solution of amine (2.2 mmol, 2.2 eq.) in THF (5.0 mL) for 10 min with stirring. To this solution was added *N*-TCP triazolium **cat-1** (7.5 mg, 0.020 mmol, 2.0 mol%) followed by dichloroaldehyde **3** (200 mg, 1.0 mmol, 1.0 eq.) in THF (5.0 mL) dropwise at r.t. with stirring. Upon addition of the aldehyde reaction mixture solution turned yellow, accompanied by gas evolution. After 10 min a white precipitate formed and after a further 20 min the reaction mixture solution returned to colourless. The reaction mixture was stirred at r.t. for a further 15 min before SiO_2 (2.0 g) was added and the reaction evaporated *in vacuo* to dryness. The adsorbed compound on silica was dry loaded for purification *via* flash column chromatography (10-40% Et_2O in pentane) to yield the desired product.

(B) From commercially available alkylammonium alkylcarbamates.

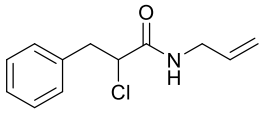
The preparative procedure used for amidation using isolated alkylammonium alkylcarbamates was the same as above but using 1.1 mmol alkylammonium alkylcarbamate (2.2 mol eq. amine) without the use of additional $CO_{2(g)}$.

General procedure for the NHC-catalysed redox amidation of chloroaldehyde 8:

(C) From commercially available amines.

$CO_{2(g)}$ was passed through a solution of amine (2.2 mmol) in THF (5 mL) for 10 min with stirring. To this solution was added *N*-TCP triazolium **cat-1** (7.5 mg, 0.02 mmol) followed by 2-chloro-3-phenylpropanal (**8**) (~90% purity 190 mg, 1.0 mmol) in THF (5 mL) dropwise at r.t. with stirring. The reaction mixture was stirred at r.t. for 45 min before SiO_2 (2 g) was added and the reaction evaporated *in vacuo* to dryness. The adsorbed compound on silica was dry loaded for purification *via* flash column chromatography (10-40% Et_2O in pentane) to yield the desired product.

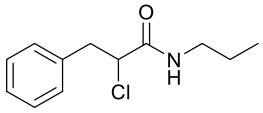
_N_-Allyl-2-chloro-3-phenylpropanamide (5a)



Using general procedure **A**: Yield **5a** 84% (187 mg) as a white solid.

IR (neat) 3254, 1665, 1644, 1553, 1509, 1261, 990, 927, 744, 693 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.33–7.24 (m, 5H), 6.57 (br. s, 1H), 5.74 (ddt, *J* = 16.5, 11.0, 5.6 Hz, 1H), 5.09 (m, 2H), 4.57 (dd, *J* = 7.8, 4.4 Hz, 1H), 3.87 (m, 2H), 3.46 (dd, *J* = 14.2, 4.4 Hz, 1H), 3.21 (dd, *J* = 14.2, 7.8 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 168.1, 136.2, 133.4, 129.8, 128.5, 127.3, 116.9, 61.6, 42.3, 41.4; HRMS (ESI) calcd. for $C_{12}H_{15}NO^{35}Cl$ $[M+H]^+$: 224.0842; found *m/z*: 224.0845.

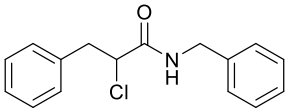
2-Chloro-3-phenyl-_N_-propylpropanamide (5b)



Using general procedure **A**: Yield **5b** 70% (158 mg) as a white solid.

IR (neat) 3280, 1655, 1560, 1456, 1216, 979, 747, 695 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.31–7.24 (m, 5H), 6.48 (br. s, 1H), 4.55 (dd, *J* = 7.7, 4.4 Hz, 1H), 3.45 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.22–3.18 (m, 3H), 1.49 (sext., *J* = 7.0 Hz, 2H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 168.1, 136.3, 129.8, 128.4, 127.2, 61.8, 41.7, 41.4, 22.6, 11.3; HRMS (ESI) calcd. for $C_{12}H_{17}NO^{35}Cl$ $[M+H]^+$: 226.0999; found *m/z*: 226.0991.

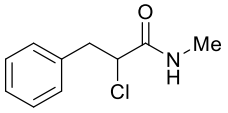
_N_-Benzyl-2-chloro-3-phenylpropanamide (5c)[6]



Using general procedure **A**: Yield **5c** 48% (130 mg) as a white solid.

IR (neat) 3277, 1681, 1662, 1553, 1493, 1454, 745, 694 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.29–7.24 (m, 8H), 7.16 (m, 2H), 6.70 (br. s, 1H), 4.62 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.43 (dd, *J* = 14.8, 5.8 Hz, 1H), 4.40 (dd, *J* = 14.9, 5.6 Hz, 1H), 3.47 (dd, *J* = 14.3, 4.5 Hz, 1H), 3.26 (dd, *J* = 14.1, 7.5 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 168.1, 137.4, 136.2, 129.9, 128.9, 128.5, 127.8, 127.3, 61.7, 44.1, 41.4; HRMS (ESI) calcd. for $C_{16}H_{17}NO^{35}Cl$ $[M+H]^+$: 274.0999; found *m/z*: 274.1001.

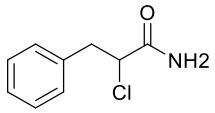
2-Chloro-_N_-methyl-3-phenylpropanamide (5d)[10]



Using general procedure **A**: Yield **5d** 74% (146 mg) as a white solid.

IR (neat) 3255, 3090, 1652, 1571, 1454, 1215, 747, 697, 680 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.36–7.22 (m, 5H), 6.50 (br. s, 1H), 4.57 (dd, *J* = 7.9, 4.2 Hz, 1H), 3.48 (dd, *J* = 14.2, 4.3 Hz, 1H), 3.22 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.84 (d, *J* = 4.9 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 168.9, 136.4, 129.8, 128.5, 127.3, 61.8, 41.5, 26.7; HRMS (ESI) calcd. for $C_{10}H_{13}NO^{35}Cl$ $[M+H]^+$: 198.0686; found *m/z*: 198.0695.

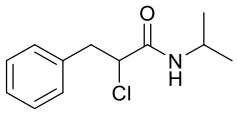
2-Chloro-3-phenylpropanamide (5e)[11]



Using general procedure **B**: Yield **5e** 73% (136 mg) as a white solid.

IR (neat) 3391, 3187, 1651, 1606, 1498, 1453, 1432, 1260, 744, 694 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.35–7.26 (m, 5H), 6.39 (br. s, 1H), 5.83 (br. s, 1H), 4.53 (dd, *J* = 8.1, 4.4 Hz, 1H), 3.48 (dd, *J* = 14.3, 4.4 Hz, 1H), 3.20 (dd, *J* = 14.2, 8.2 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 171.0, 136.2, 129.8, 128.6, 127.4, 61.0, 41.4; HRMS (ESI) calcd. for $C_9H_{11}NO^{35}Cl$ $[M+H]^+$: 184.0529; found *m/z*: 184.0532.

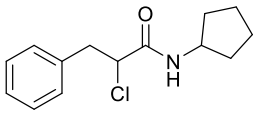
2-chloro-*N*-isopropyl-3-phenylpropanamide (5f)



Using general procedure **A**: Yield **5f** 13% (30 mg) as a white solid.

IR (neat) 3247, 1671, 1644, 1560, 1494, 1455, 1216, 745, 695 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.34–7.23 (m, 5H), 6.19 (br. s, 1H), 4.52 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.04 (dsept., *J* = 7.9, 6.6 Hz, 1H), 3.42 (dd, *J* = 14.3, 4.4 Hz, 1H), 3.22 (dd, *J* = 14.2, 7.6 Hz, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 167.2, 136.3, 129.9, 128.4, 127.3, 61.7, 42.1, 41.4, 22.6, 22.5; HRMS (ESI) calcd. for $C_{12}H_{17}NO^{35}Cl$ $[M+H]^+$: 226.0999; found *m/z*: 226.0993.

2-chloro-*N*-cyclopentyl-3-phenylpropanamide (5h)

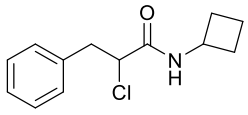


Using general procedure **A**: Yield **5h** 33% (83 mg) as a white solid.

IR (neat) 3256, 2955, 1649, 1561, 1497, 1452, 1227, 947, 703, 679 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.30–7.23 (m, 5H), 6.30 (br. d, *J* = 7.8 Hz, 1H), 4.53 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.16 (m, 1H), 3.42 (dd, *J* = 14.2, 4.4 Hz, 1H), 3.22 (dd, *J* = 14.3, 7.5 Hz, 1H), 1.93 (m, 2H), 1.56 (m, 4H),

1.33–1.22 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 167.6, 136.3, 129.9, 128.4, 127.3, 61.7, 51.7, 41.4, 32.9, 23.8; HRMS (ESI) calcd. for $C_{14}H_{19}NO^{35}Cl$ $[M+H]^+$: 252.1155; found *m/z*: 252.1155.

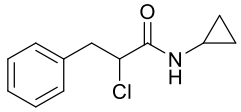
2-chloro-*N*-cyclobutyl-3-phenylpropanamide (5i)



Using general procedure **A**: Yield **5i** 48% (114 mg) as a white solid.

IR (neat) 3252, 1681, 1647, 1557, 1492, 1455, 1308, 742, 697 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.33–7.22 (m, 5H), 6.48 (br. s, 1H), 4.50 (dd, *J* = 7.7, 4.2 Hz, 1H), 4.35 (m, 1H), 3.43 (dd, *J* = 14.3, 4.3 Hz, 1H), 3.20 (dd, *J* = 14.2, 7.7 Hz, 1H), 2.30 (m, 2H), 1.87 – 1.67 (m, 4H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 167.2, 136.3, 129.9, 128.5, 127.3, 61.6, 45.2, 41.5, 31.0, 30.9, 15.2; HRMS (ESI) calcd. for $C_{13}H_{17}NO^{35}Cl$ $[M+H]^+$: 238.0999; found *m/z*: 238.0999.

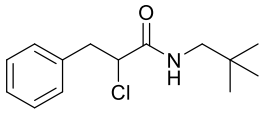
2-chloro-*N*-cyclopropyl-3-phenylpropanamide (5j)



Using general procedure **A**: Yield **5j** 54% (120 mg) as a white solid.

IR (neat) 3253, 1687, 1655, 1556, 1493, 1456, 1361, 742, 697 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.31–7.23 (m, 5H), 6.43 (s, 1H), 4.52 (dd, *J* = 7.5, 4.4 Hz, 1H), 3.43 (dd, *J* = 14.3, 4.3 Hz, 1H), 3.21 (dd, *J* = 14.3, 7.6 Hz, 1H), 2.69 (m, 1H), 0.76 (m, 2H), 0.45 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 169.6, 136.2, 129.9, 128.5, 127.4, 61.5, 41.4, 23.0, 6.6, 6.5; HRMS (ESI) calcd. for $C_{12}H_{15}NO^{35}Cl$ $[M+H]^+$: 224.0842; found *m/z*: 224.0848.

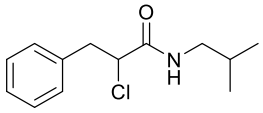
2-chloro-*N*-neopentyl-3-phenylpropanamide (5l)



Using general procedure **A**: Yield **5l** 44% (112 mg) as a white solid.

IR (neat) 3275, 2959, 1674, 1661, 1572, 1474, 1466, 1205, 747, 698 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.34–7.24 (m, 5H), 6.50 (s, 1H), 4.59 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.49 (dd, *J* = 14.3, 4.2 Hz, 1H), 3.19 (dd, *J* = 14.3, 8.1 Hz, 1H), 3.09 (dd, *J* = 13.3, 6.3 Hz, 1H), 3.03 (dd, *J* = 13.3, 6.3 Hz, 1H), 0.87 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 168.2, 136.5, 129.9, 128.5, 127.3, 62.3, 51.2, 41.6, 32.0, 27.2; HRMS (ESI) calcd. for $C_{14}H_{21}NO^{35}Cl$ $[M+H]^+$: 254.1312; found *m/z*: 254.1312.

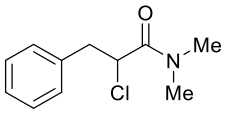
2-chloro-N-isobutyl-3-phenylpropanamide (5m)



Using general procedure **A**: Yield **5m** 61% (144 mg) as a white solid.

IR (neat) 3278, 2930, 1651, 1559, 744, 695 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.34–7.24 (m, 5H), 6.48 (br. s, 1H), 4.57 (dd, *J* = 7.8, 4.4 Hz, 1H), 3.46 (dd, *J* = 14.4, 4.3 Hz, 1H), 3.21 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.07 (m, 2H), 1.73 (non., *J* = 6.8 Hz, 1H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 168.1, 136.3, 129.9, 128.5, 127.3, 62.0, 47.4, 41.5, 28.4, 20.1; HRMS (ESI) calcd. for $C_{13}H_{19}NO^{35}Cl$ $[M+H]^+$: 240.1155; found *m/z*: 240.1146.

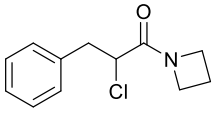
2-Chloro-*N*,*N*-dimethyl-3-phenylpropanamide (5p)[12]



Using general procedure **B**: Yield **5p** 10% (21 mg) as a pale yellow oil.

IR (neat) 1650, 1495, 1454, 1400, 1136, 746, 699 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.32–7.22 (m, 5H), 4.62 (dd, *J* = 7.3, 7.2 Hz, 1H), 3.47 (dd, *J* = 13.9, 7.5 Hz, 1H), 3.16 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.96 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 168.3, 137.1, 129.7, 128.6, 127.2, 54.4, 49.0, 37.3, 36.3; HRMS (ESI) calcd. for $C_{11}H_{15}NO^{35}Cl$ $[M+H]^+$: 212.0842; found *m/z*: 212.0848.

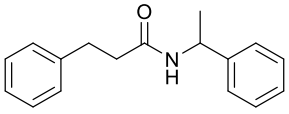
1-(Azetidin-1-yl)-2-chloro-3-phenylpropan-1-one (5q)



Using general procedure **A**: Yield **5q** 69% (154 mg) as a colourless oil.

IR (neat) 1654, 1498, 1454, 1437, 745, 698 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.34–7.24 (m, 5H), 4.26 (dd, *J* = 8.2, 6.5 Hz, 1H), 4.14 (td, *J* = 8.7, 6.1 Hz, 1H), 4.05 (td, *J* = 9.7, 6.1 Hz, 1H), 3.96 (td, *J* = 9.7, 6.2 Hz, 1H), 3.75 (td, *J* = 8.7, 5.9 Hz, 1H), 3.39 (dd, *J* = 13.8, 8.2 Hz, 1H), 3.13 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.20 (m, 1H), 2.10 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 167.7, 136.7, 129.7, 128.7, 127.4, 53.9, 50.6, 48.5, 40.8, 15.4; HRMS (ESI) calcd. for $C_{12}H_{15}NO^{35}Cl$ $[M+H]^+$: 224.0842; found *m/z*: 224.0840.

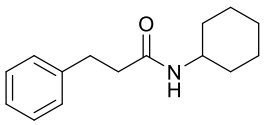
3-phenyl-*N*-(1-phenylethyl)propanamide (9a)[13]



Using general procedure **C**: Yield **9a** 40% (102 mg) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.40–7.13 (m, 10H), 5.61 (br. d, *J* = 7.7 Hz, 1H), 5.12 (dq, *J* = 7.2, 7.2 Hz, 1H), 2.99 (t, *J* = 7.5 Hz, 2H), 2.50 (m, 2H), 1.43 (d, *J* = 6.8 Hz, 3H).

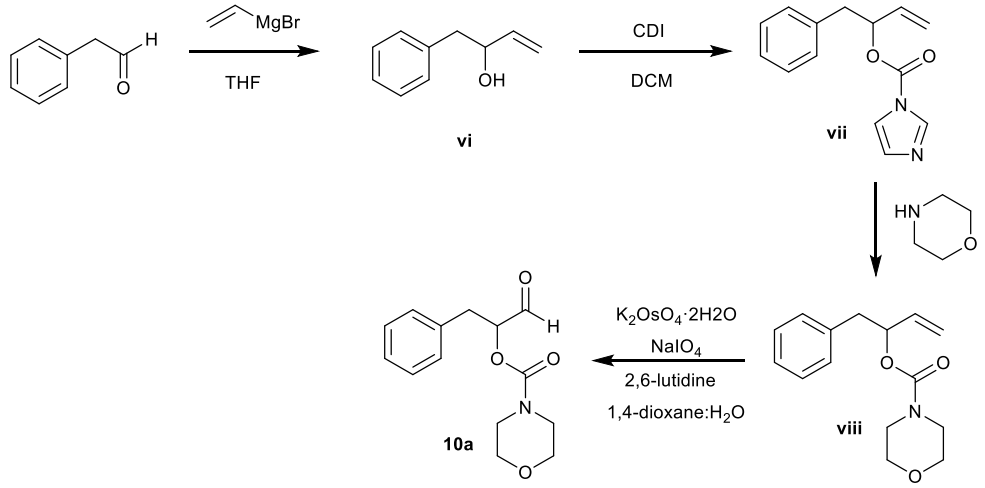
_N_-Cyclohexyl-3-phenylpropanamide (9b)[14]



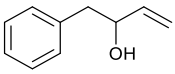
Using general procedure **C**: Yield **9b** 22% (51 mg) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.35–7.17 (m, 5H), 5.17 (br. d, *J* = 5.1 Hz, 1H), 3.75 (m, 1H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 1.85 (m, 2H), 1.71–1.57 (m, 3H), 1.42–1.29 (m, 2H), 1.19–1.09 (m, 1H), 1.08–0.97 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 171.0, 140.9, 128.5, 128.4, 126.2, 48.0, 38.8, 33.1, 31.9, 25.5, 24.8.

Preparation of α -*O*-Carbamoyl aldehyde substrate 10a.



1-Phenylbut-3-en-2-ol (vi)[15]

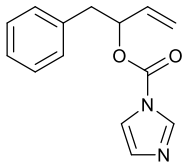


Reaction performed in a 3 L Morton flask. To a vigourously stirred solution of vinylmagnesium bromide (0.7 M in THF, 1.6 L, 1.1 mol) at 0 °C was added phenylacetaldehyde (117 mL, 1.0 mol) in THF (100 mL) dropwise. The reaction mixture was warmed to r.t. and stirred for 6 h then returned to 0 °C and quenched with sat. $NH_4Cl_{(aq)}$ (500 mL). The biphasic mixture was transferred to a 5 L separatory funnel and water (1.0 L) was added. The layers were separated and the aqueous layer extracted with Et_2O (3x 500 mL). The combined organics were dried over $MgSO_4$ and the solvent removed portionwise (1.0 L) *in vacuo* to give a pale yellow oil. The oil was redissolved in Et_2O (500 mL) and 40% $NaHSO_{3(aq)}$ (250 mL) was

added. The biphasic mixture was stirred for 4 h during which time a white precipitate formed (bisulfite adduct of phenylacetaldehyde). The solid was removed by vacuum filtration and the solvent from the filtrate removed *in vacuo* to give **vi** as a pale yellow oil (120 g). The product was further purified by distillation under reduced pressure (108–110 °C, 20 mbar) to yield 105 g (63%) **vi** as a colourless oil.

IR (neat) 3368, 1645, 1603, 1455, 1117, 1077, 1030, 991, 697 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.36 (m, 2H), 7.28 (m, 3H), 5.98 (ddd, *J* = 16.7, 10.5, 5.8 Hz, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.3 Hz, 1H), 4.39 (m, 1H), 2.92 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.83 (dd, *J* = 13.6, 8.0 Hz, 1H), 1.65 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 140.1, 137.7, 129.6, 128.5, 126.6, 115.0, 73.7, 43.8; HRMS (CI) calcd. for $C_{10}H_{16}NO$ $[M+NH_4]^+$: 166.1232; found *m/z*: 166.1236.

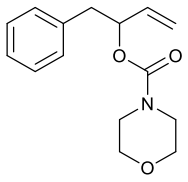
1-Phenylbut-3-en-2-yl 1*H*-imidazole-1-carboxylate (vii)



To allylic alcohol **vi** (6.0 g, 6.7 mmol) in DCM (120 mL) was added 1,1'-carbonyldiimidazole (10.0 g, 60.7 mmol) and the reaction mixture was stirred at r.t. for 12 h. The reaction mixture was diluted with DCM (100 mL), partitioned with water (100 mL) washed with further portions of water (2x 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, then the solvent was removed *in vacuo* to yield 9.6 g (98%) **vii** as a pale yellow oil.

IR (neat) 1754, 1648, 1604, 1526, 1471, 1387, 1278, 1237, 1171, 999, 699 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 8.11 (s, 1H), 7.40 (m, 1H), 7.35–7.20 (m, 5H), 7.07 (m, 1H), 5.93 (ddd, *J* = 17.1, 10.5, 6.7 Hz, 1H), 5.63 (app. q, *J* = 6.7 Hz, 1H), 5.38 (d, *J* = 17.5 Hz, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 3.11 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 147.9, 137.0, 135.7, 134.2, 130.6, 129.5, 128.6, 127.1, 119.1, 117.0, 79.8, 40.7; MS (CI) *m/z* 243 $[M+H]^+$.

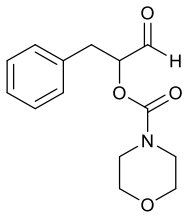
1-Phenylbut-3-en-2-yl morpholine-4-carboxylate (viii)



To 1-phenylbut-3-en-2-yl 1*H*-imidazole-1-carboxylate (**vii**) (2.4 g, 10 mmol) was added morpholine (0.87 mL, 10 mmol) and the reaction mixture was heated to 80 °C for 3 h with stirring. The reaction mixture was cooled to r.t. and purified directly *via* flash column chromatography (SiO_2, 100% DCM) to yield 2.2 g **viii** (85%) as a colourless oil.

IR (neat) 1697, 1647, 1604, 1497, 1456, 1420, 1237, 1114, 700 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 7.36–7.17 (m, 5H), 5.86 (ddd, *J* = 16.9, 10.5, 6.0 Hz, 1H), 5.44 (m, 1H), 5.23 (d, *J* = 16.7 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 1H), 3.63 (m, 4H), 3.45 (m, 4H), 2.98 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 154.6, 137.0, 136.4, 129.6, 128.2, 126.5, 116.5, 76.1, 66.6, 44.1, 41.1; HRMS (ESI) calcd. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1443; found *m/z*: 262.1449.

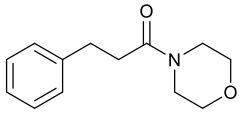
1-Oxo-3-phenylpropan-2-yl morpholine-4-carboxylate (10a)



To 1-phenylbut-3-en-2-yl morpholine-4-carboxylate (**viii**) (1.8 g, 6.9 mmol) in 1,4-dioxane:H_2O (3:1, 160 mL) was added 2,6-lutidine (3.2 mL, 27.5 mmol), $K_2OsO_4 \cdot 2H_2O$ (25 mg, 0.07 mmol) and $NaIO_4$ (3.7 g, 17.2 mmol). The reaction mixture was stirred at r.t. for 3 days then partitioned with DCM (100 mL) and water (100 mL). The layers were separated and the aqueous phase extracted with DCM (3x 100mL). The combined organic phases were washed sequentially with 1 M $HCl_{(aq)}$ (100 mL), 1 M $NaOH_{(aq)}$ (100 mL), water (100 mL) and brine (100 mL). The organic layer was then dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield 1.1 g (61%) **10** as a pale yellow oil.

IR (neat) 1736, 1698, 1429, 1241, 1113, 701 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ_H 9.61 (s, 1H), 7.33–7.19 (m, 5H), 5.12 (dd, *J* = 8.6, 4.7 Hz, 1H), 3.77–3.52 (m, 4H), 3.45 (br. s, 4H), 3.18 (dd, *J* = 14.3, 4.8 Hz, 1H), 3.04 (dd, *J* = 14.4, 8.6 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 198.9, 154.5, 135.8, 129.5, 128.7, 127.2, 79.7, 66.6, 66.5, 44.6, 44.2, 35.5; HRMS (ESI) calcd. for $C_{14}H_{18}NO_4$ $[M+H]^+$: 264.1236; found *m/z*: 264.1237.

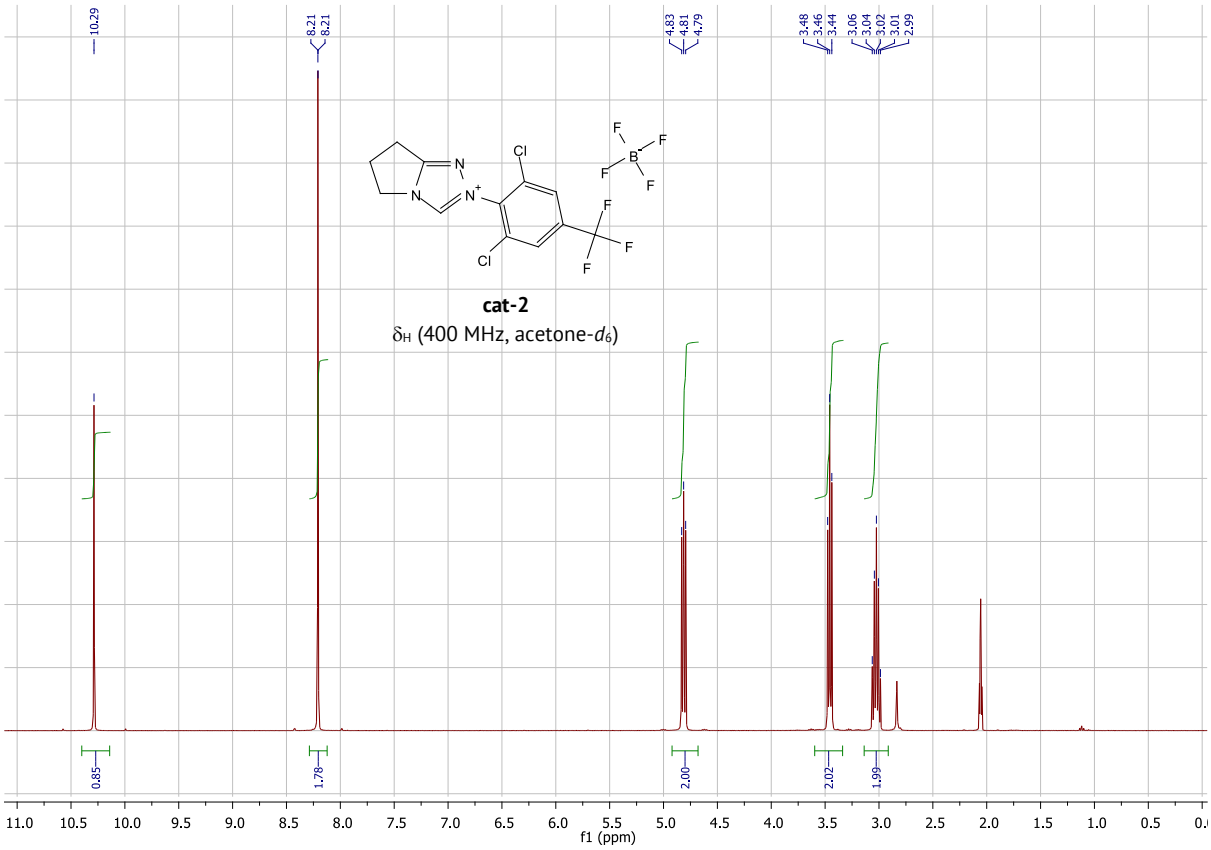
1-Morpholino-3-phenylpropan-1-one (12a)[16]



To 1-oxo-3-phenylpropan-2-yl morpholine-4-carboxylate (**10a**) (260 mg, 1.0 mmol) in DCM (10 mL) was added 2,6-di-*tert*-butylpyridine (**11a**) (45 µL, 0.20 mmol), followed by **cat-1** (19 mg, 0.05 mmol). The reaction mixture was stirred at r.t. for 12 h then diluted with DCM (10 mL) and washed with 1 M $HCl_{(aq)}$ (2x 10 mL). The layers were separated and the aqueous phase extracted with DCM (2x 10mL). The combined organic phases were washed sequentially with 10% $K_2CO_{3(aq)}$ (10 mL) and brine (10 mL). The organic layer was then dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting residue was purified *via*

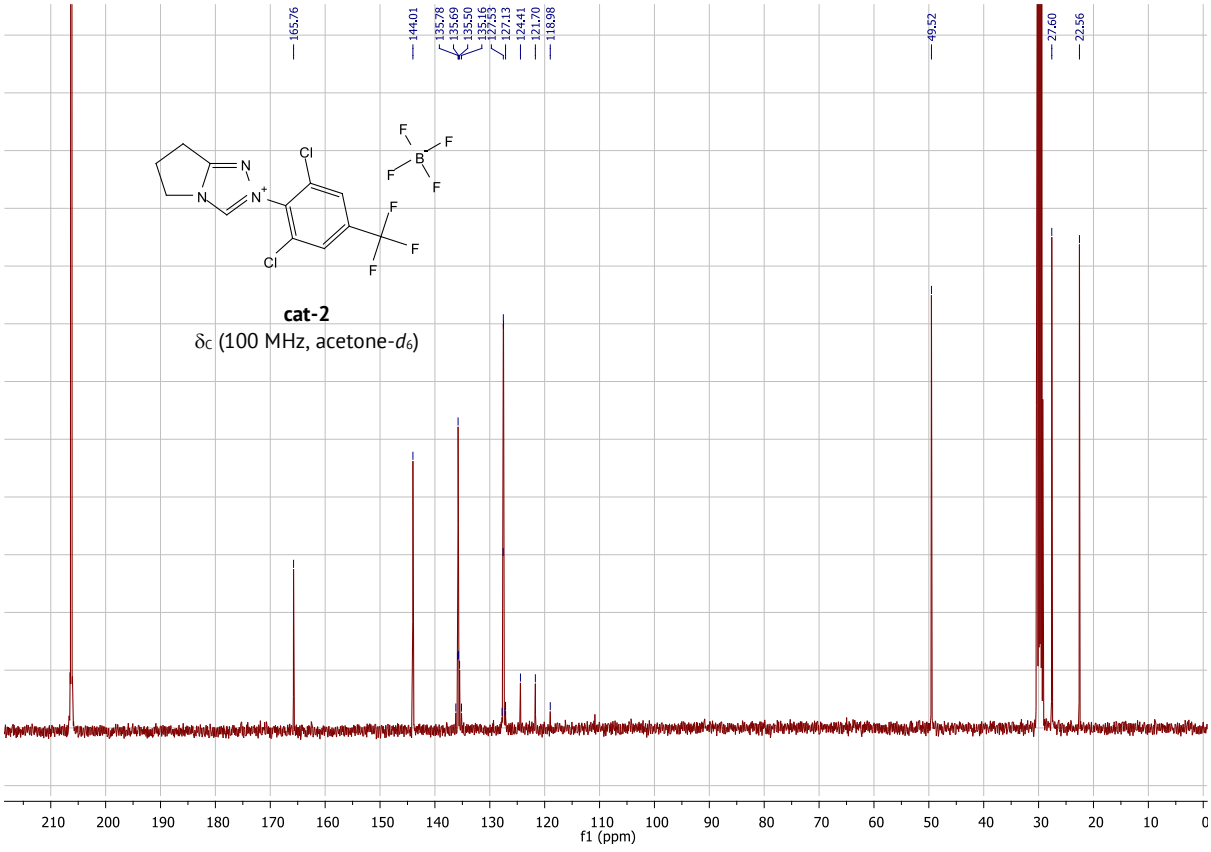
flash column chromatography (SiO_2, 50-100% Et_2O in pentane) to yield 125 mg (57%) **12a** as a colourless oil.

IR (neat) 2856, 1637, 1431, 1226, 1112, 1024, 751, 700 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ_H 7.32–7.26 (m, 2H), 7.24–7.18 (m, 3H), 3.62 (br. s, 4H), 3.51 (m, 2H), 3.35 (m, 2H), 2.98 (m, 2H), 2.61 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ_C 171.0, 141.2, 128.7, 128.6, 126.5, 67.0, 66.7, 46.1, 42.1, 35.0, 31.7; HRMS (ESI) calcd. for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1338; found *m/z*: 220.1340.



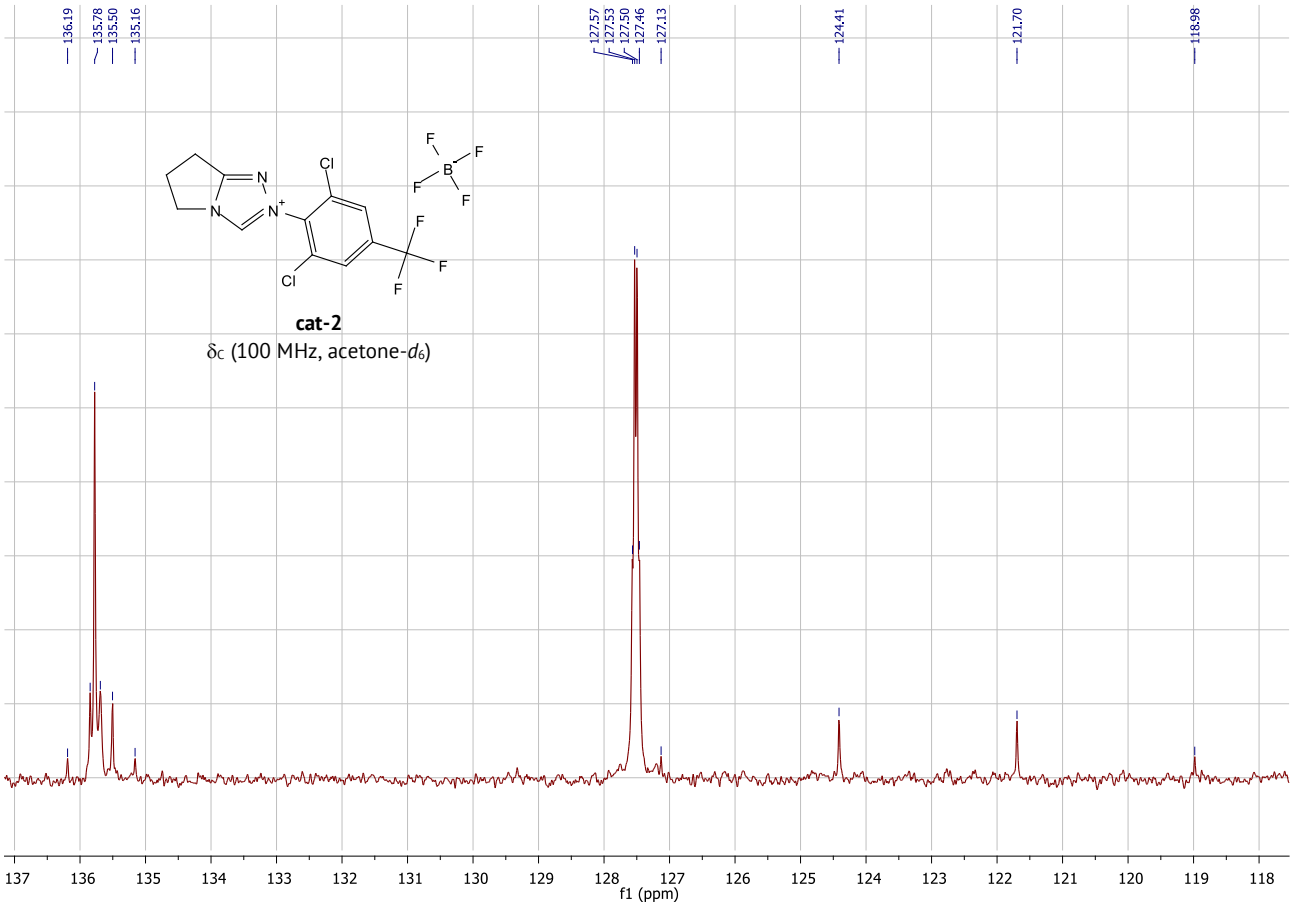
cat-2

δ_H (400 MHz, acetone-d_6)



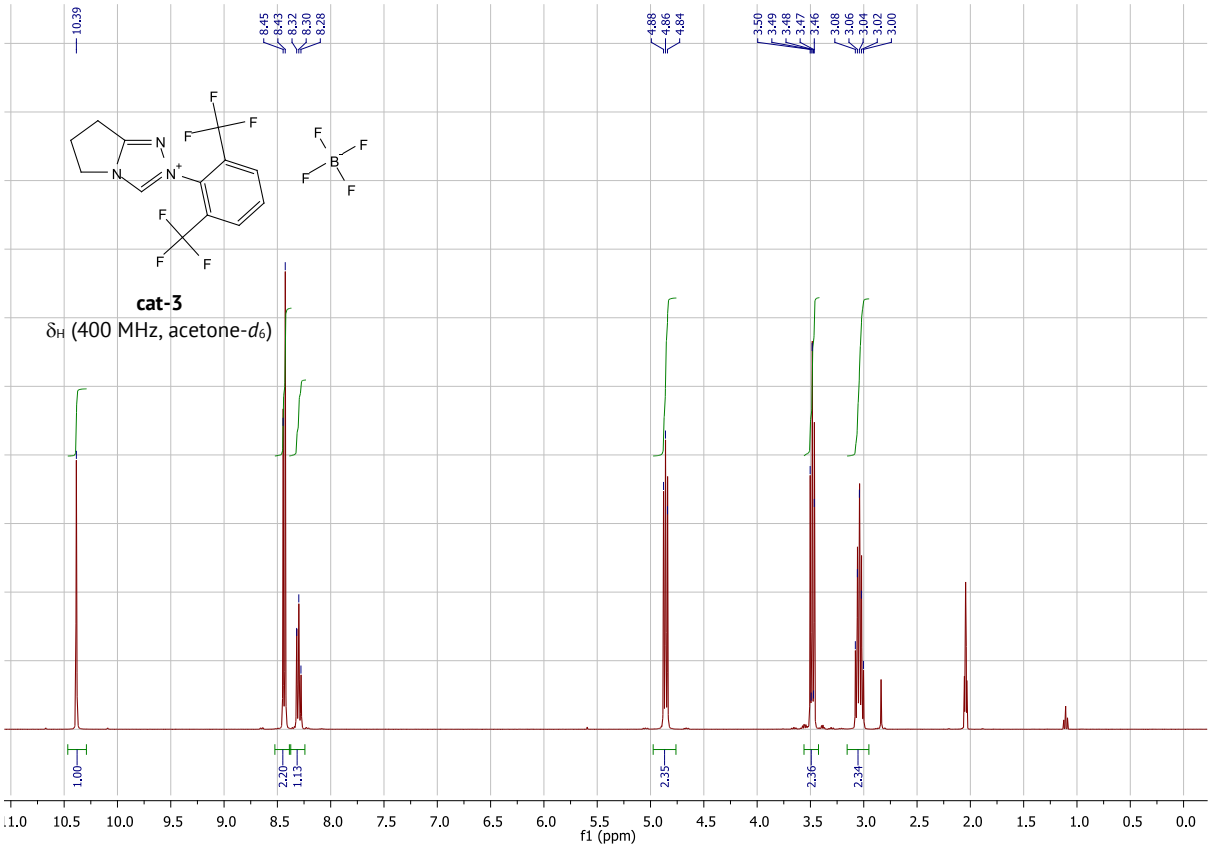
cat-2

δ_C (100 MHz, acetone-d_6)



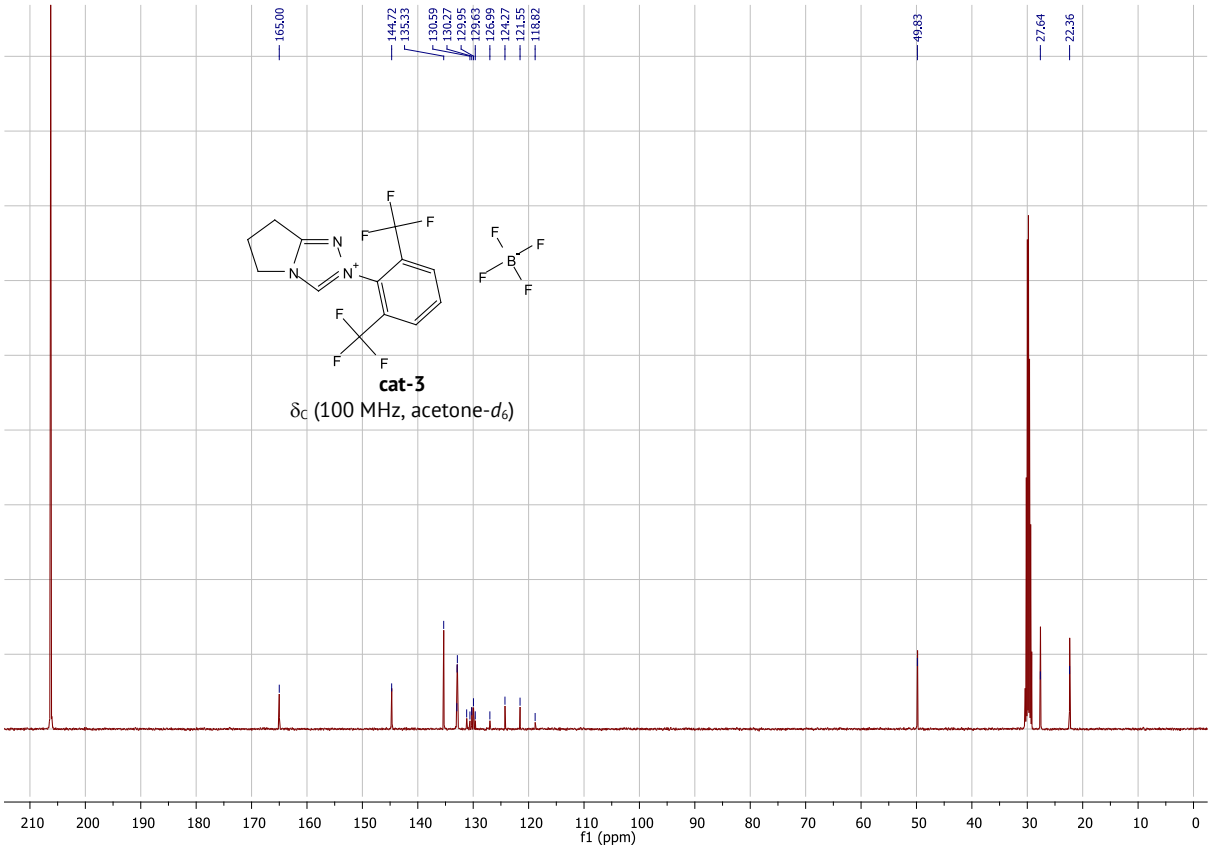
cat-2

δ_C (100 MHz, acetone-d_6)



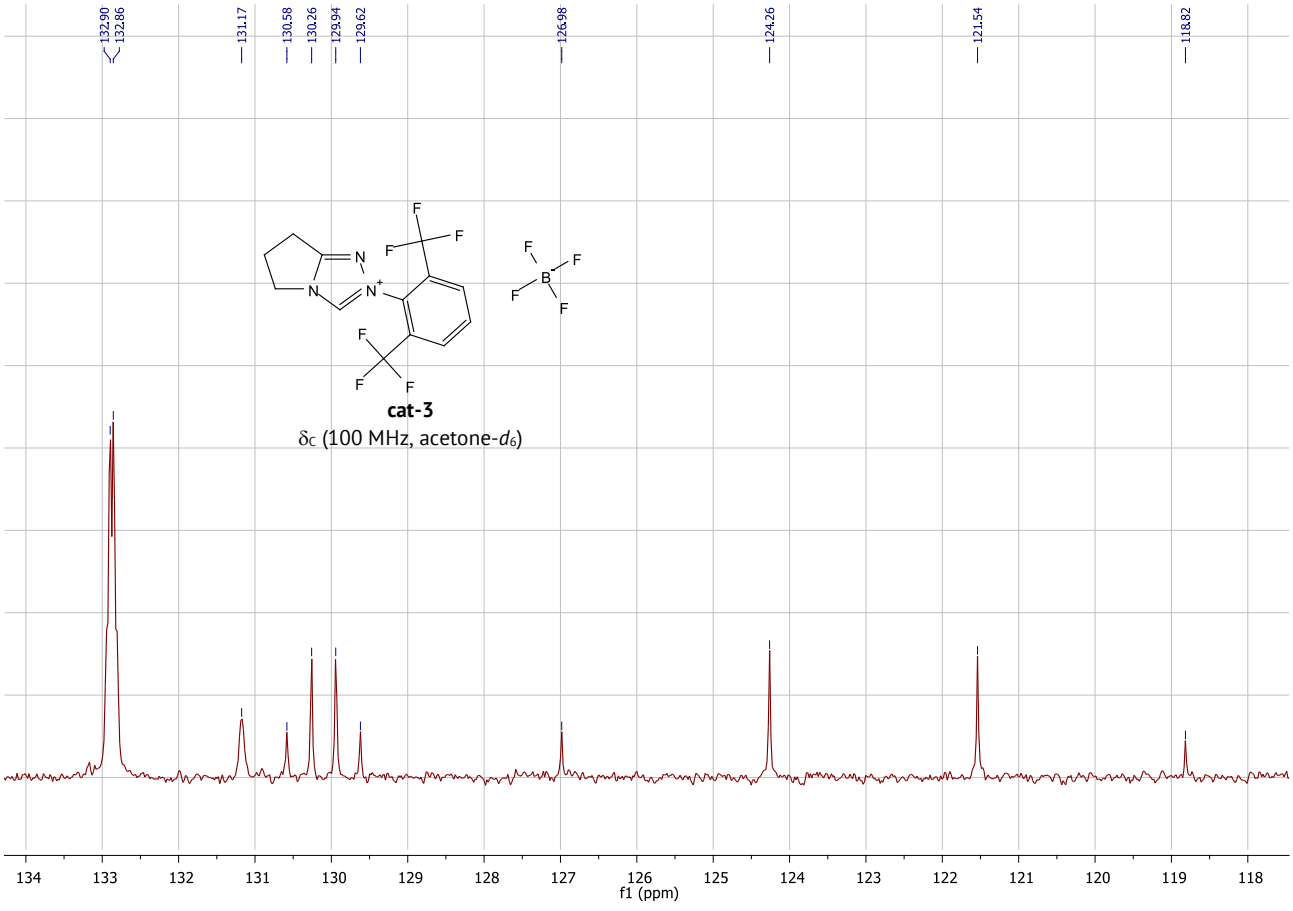
cat-3

δ_H (400 MHz, acetone-d_6)



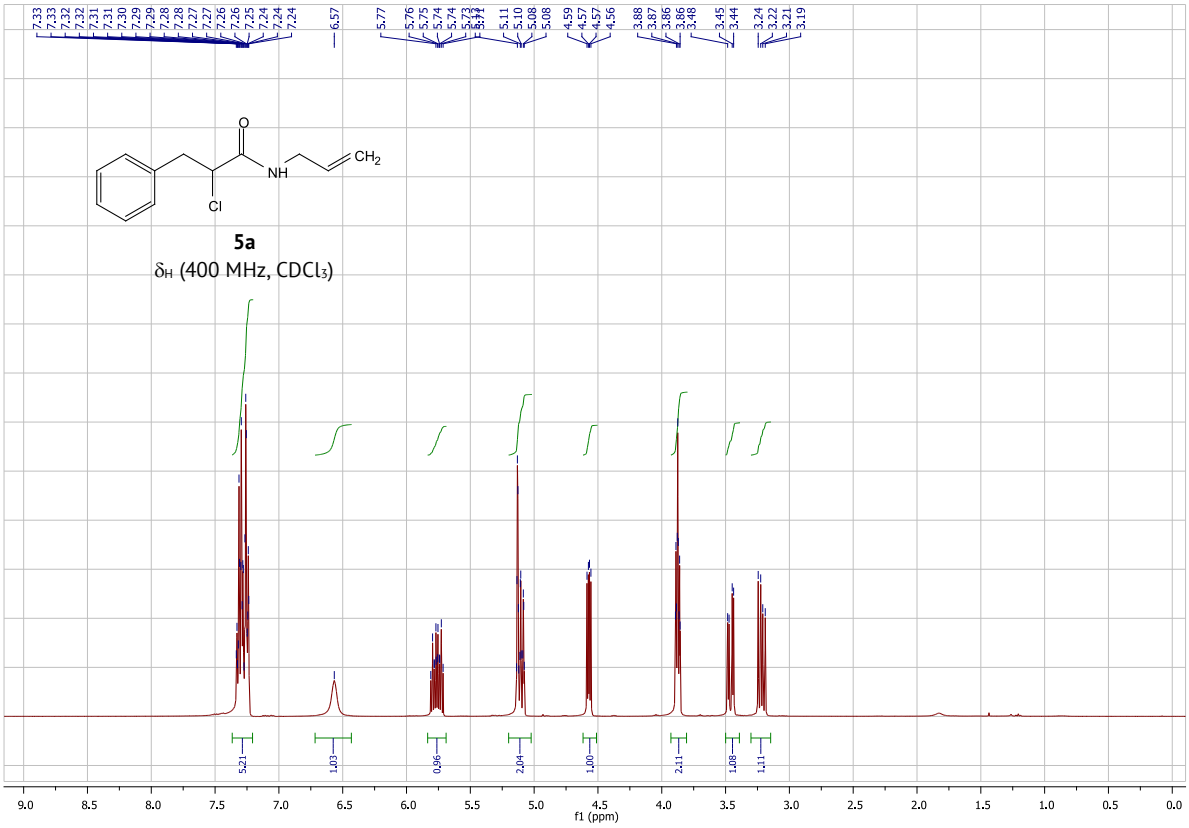
cat-3

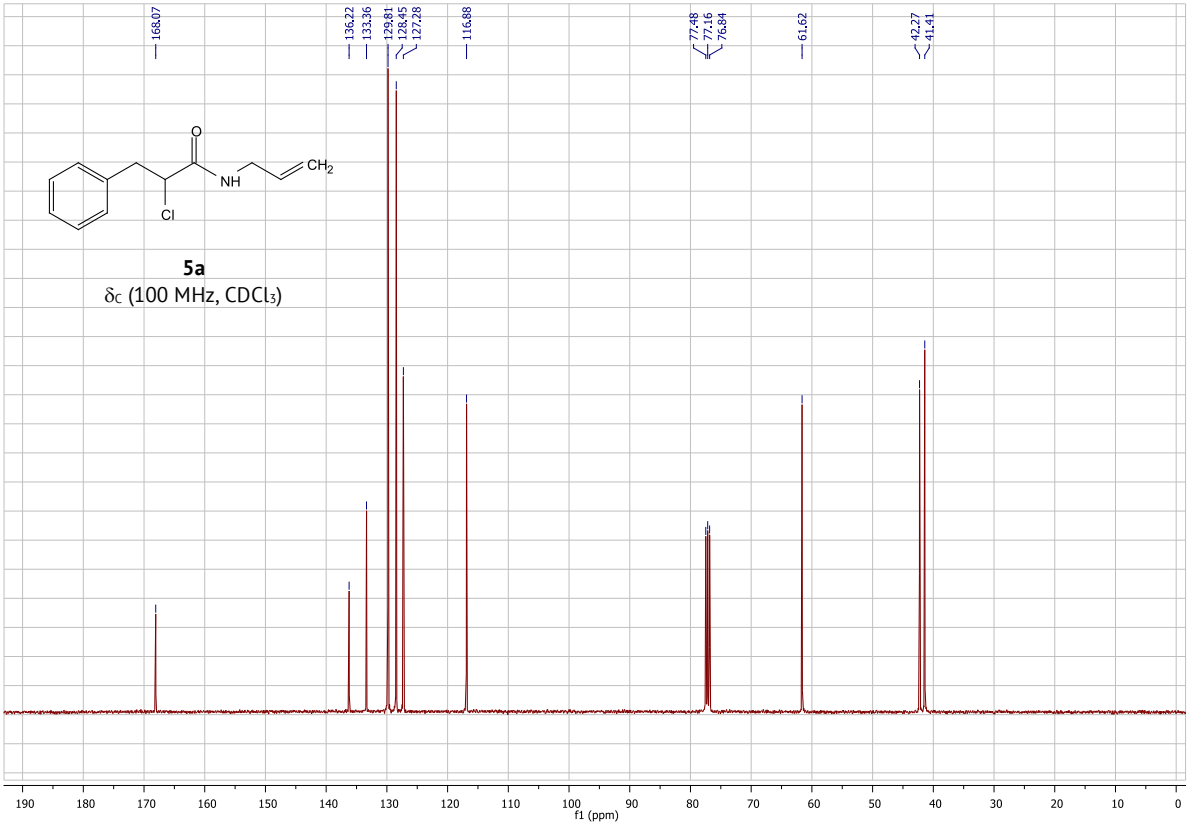
δ_C (100 MHz, acetone-d_6)

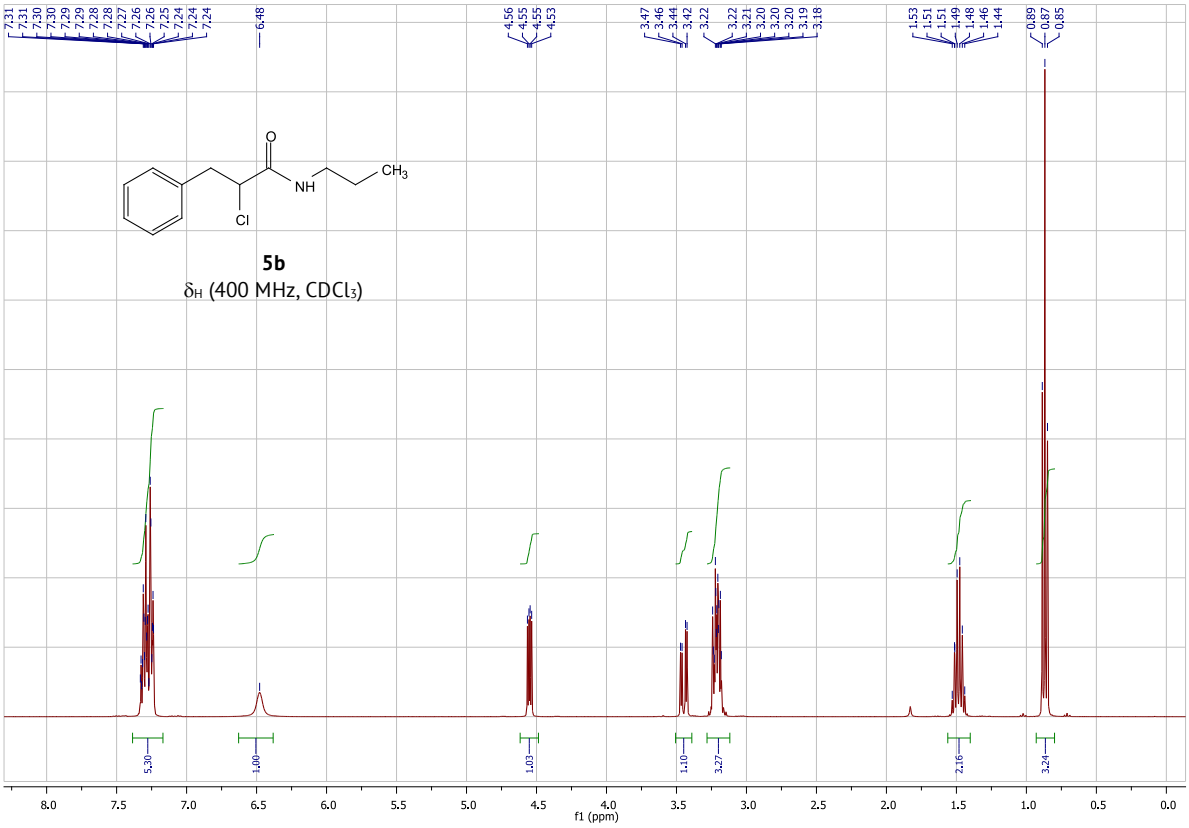


cat-3

δ_C (100 MHz, acetone-d_6)

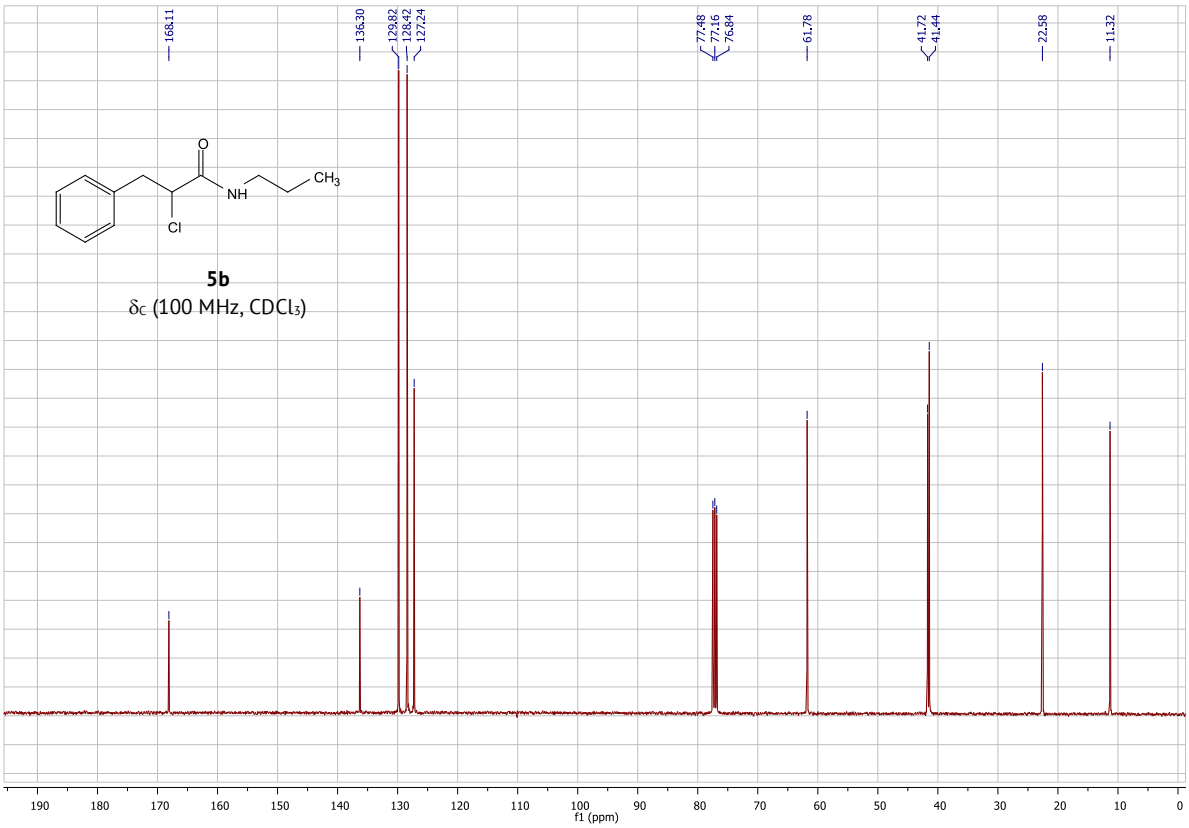

O
NH
CH2
Cl
5a
δH (400 MHz, CDCl3)
f1 (ppm)


O
NH
CH2
Cl
5a
δC (100 MHz, CDCl3)
f1 (ppm)



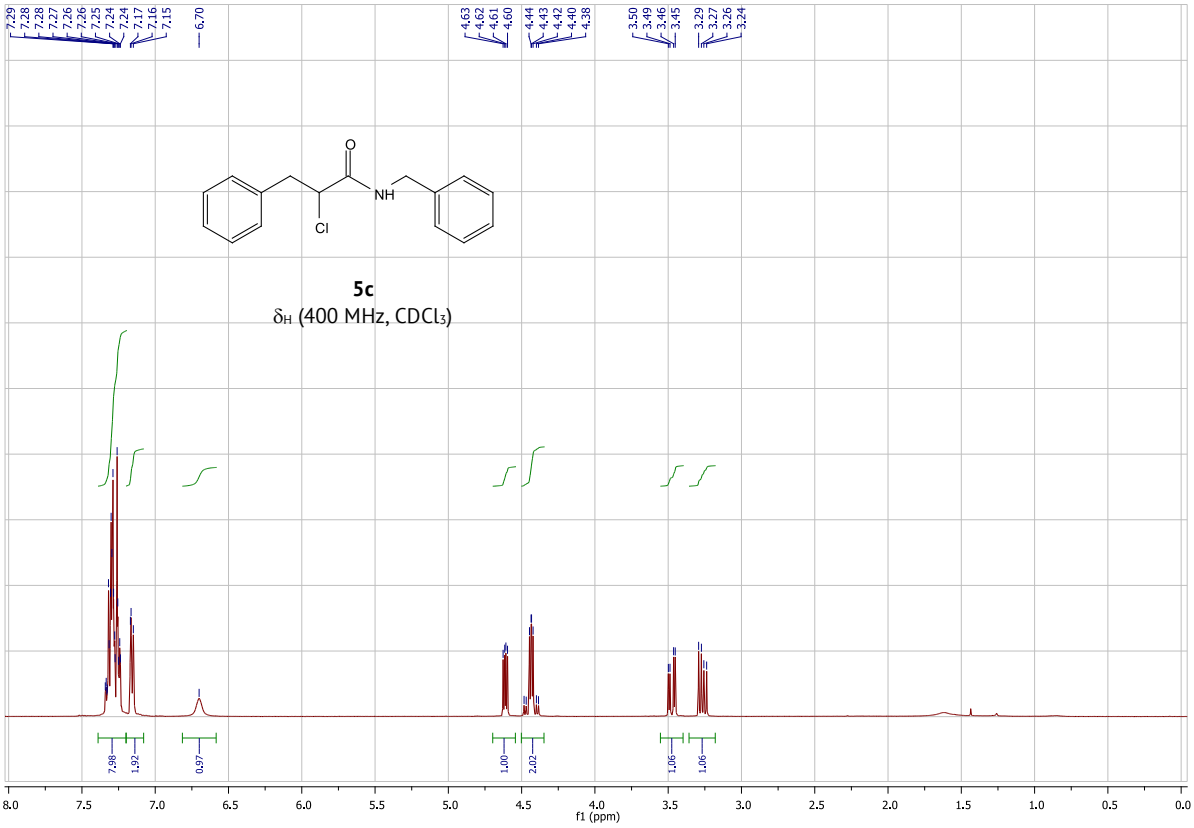
5b

δ_H (400 MHz, $CDCl_3$)



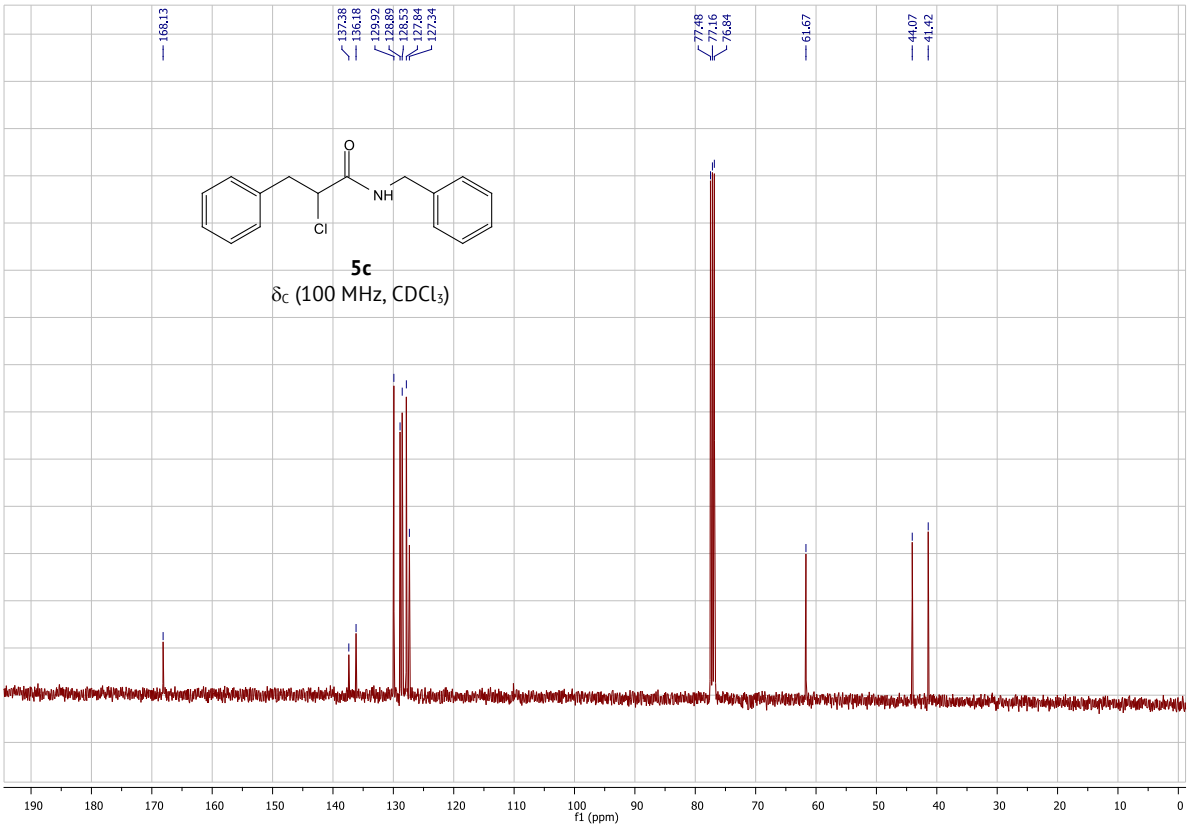
5b

δ_C (100 MHz, $CDCl_3$)



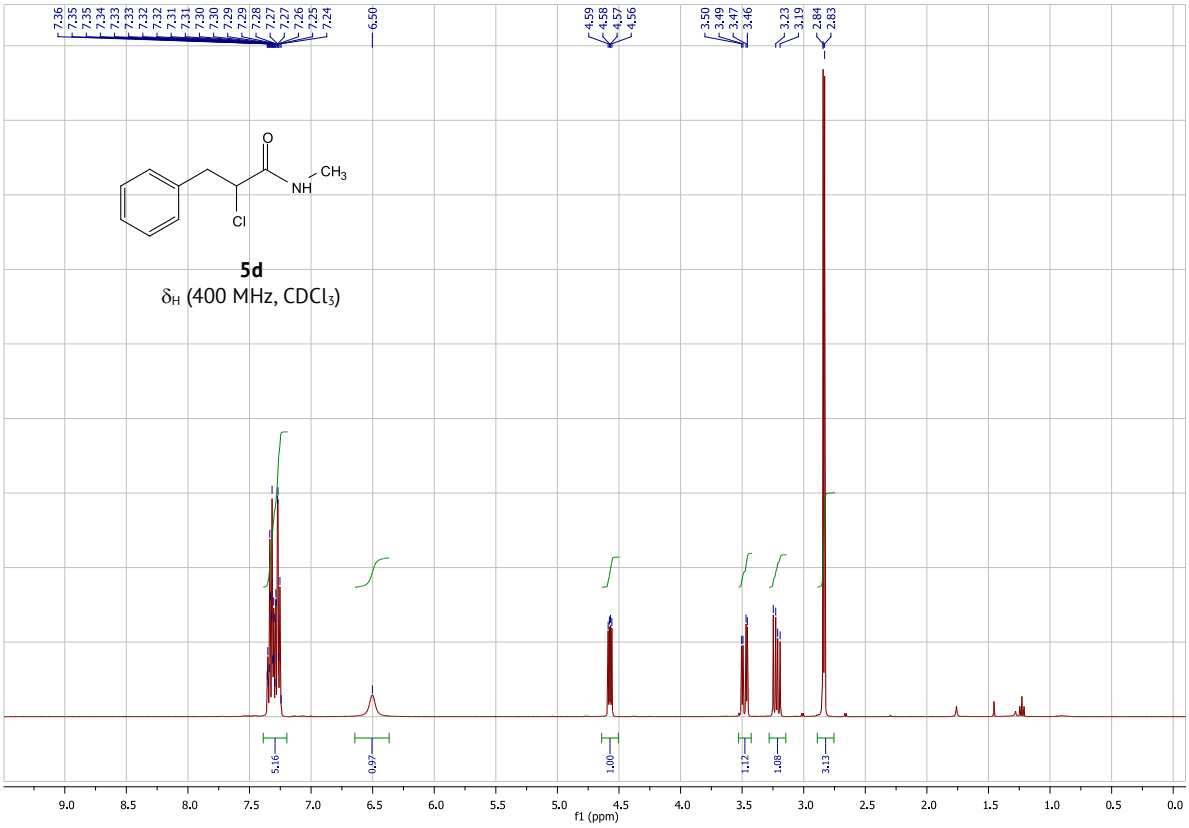
5c

δ_H (400 MHz, $CDCl_3$)



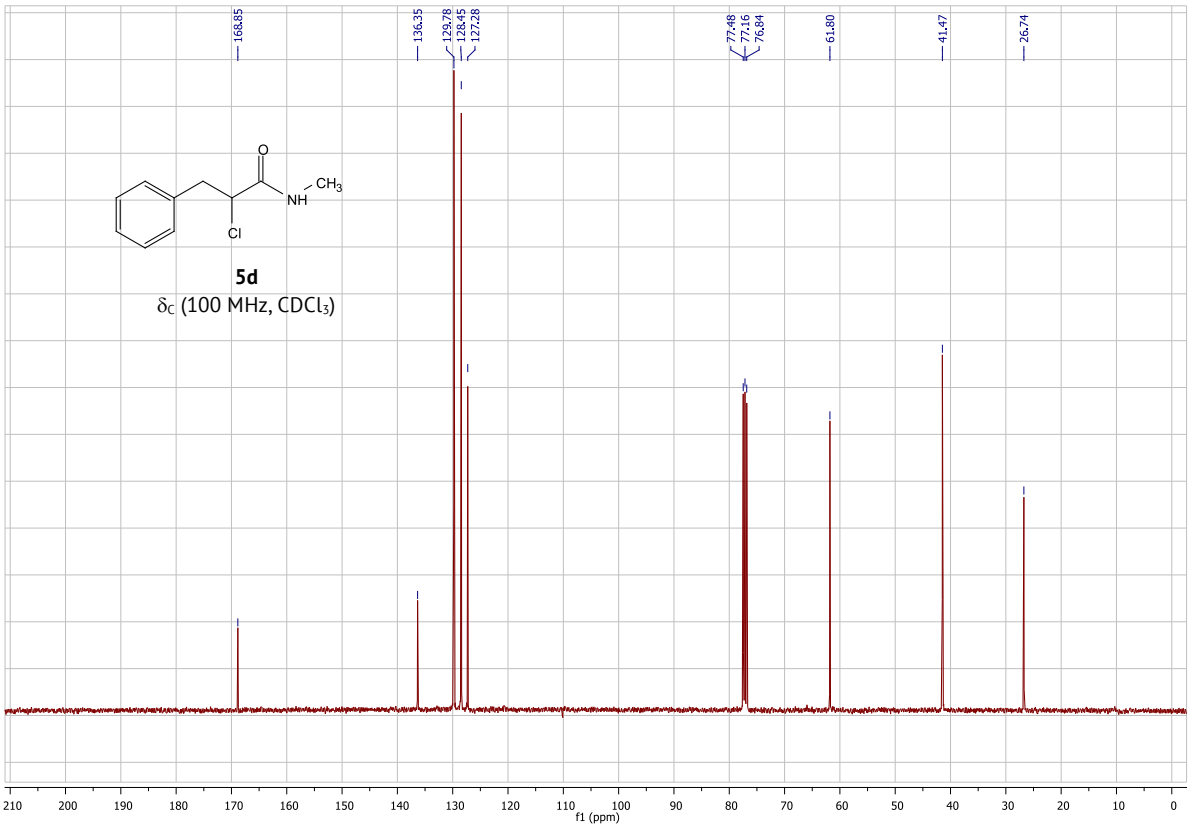
5c

δ_C (100 MHz, $CDCl_3$)



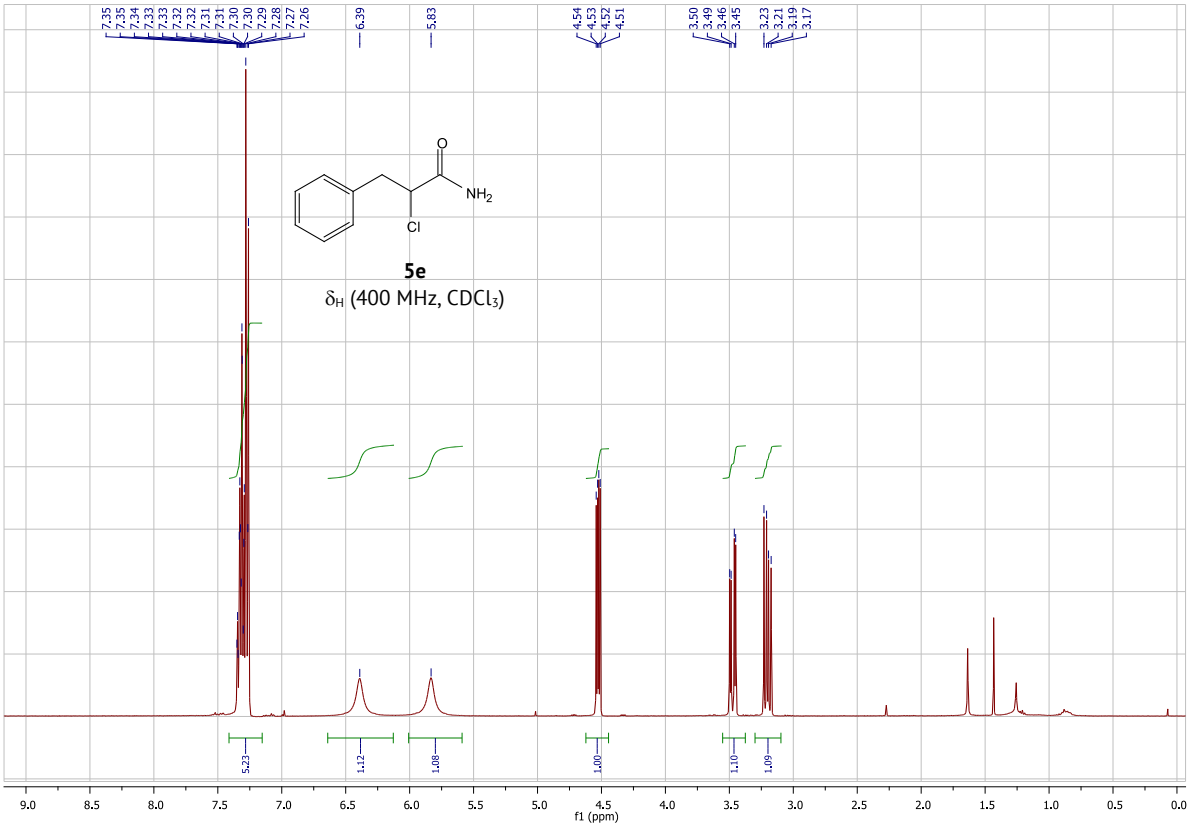
5d

δ_H (400 MHz, $CDCl_3$)



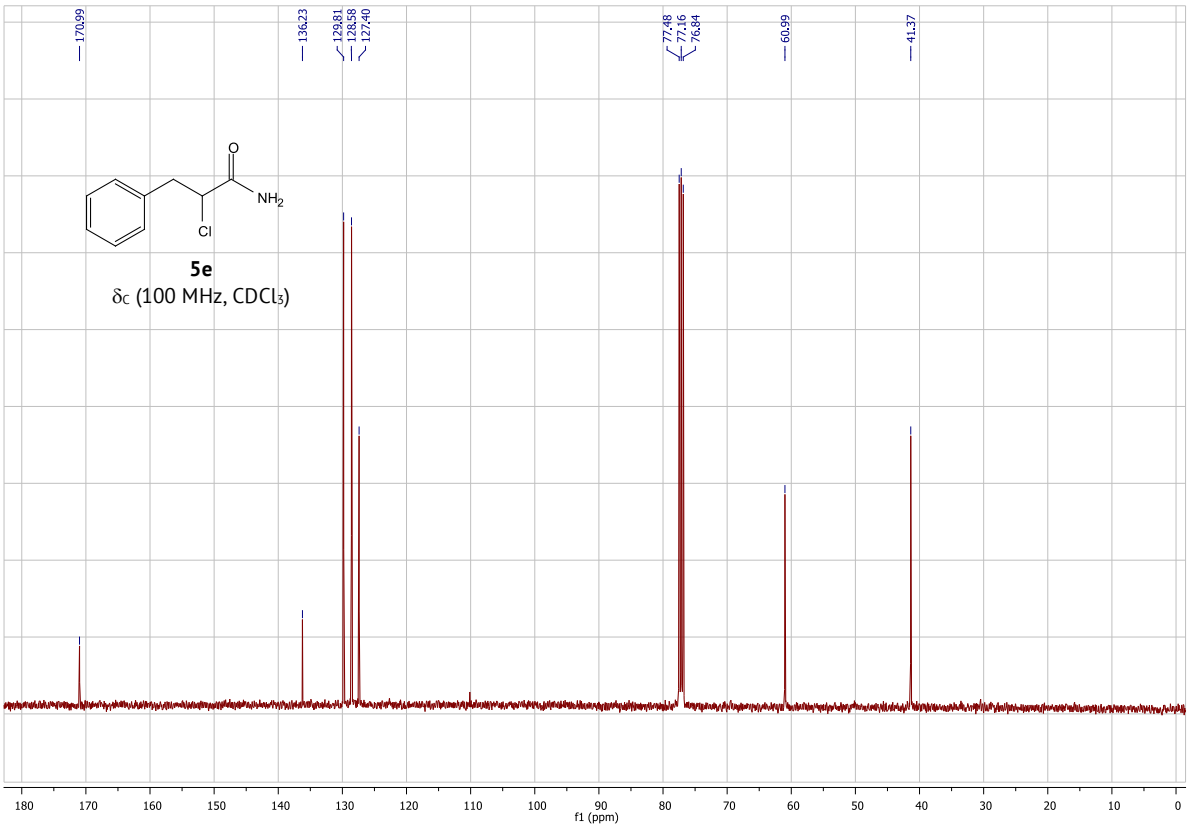
5d

δ_C (100 MHz, $CDCl_3$)



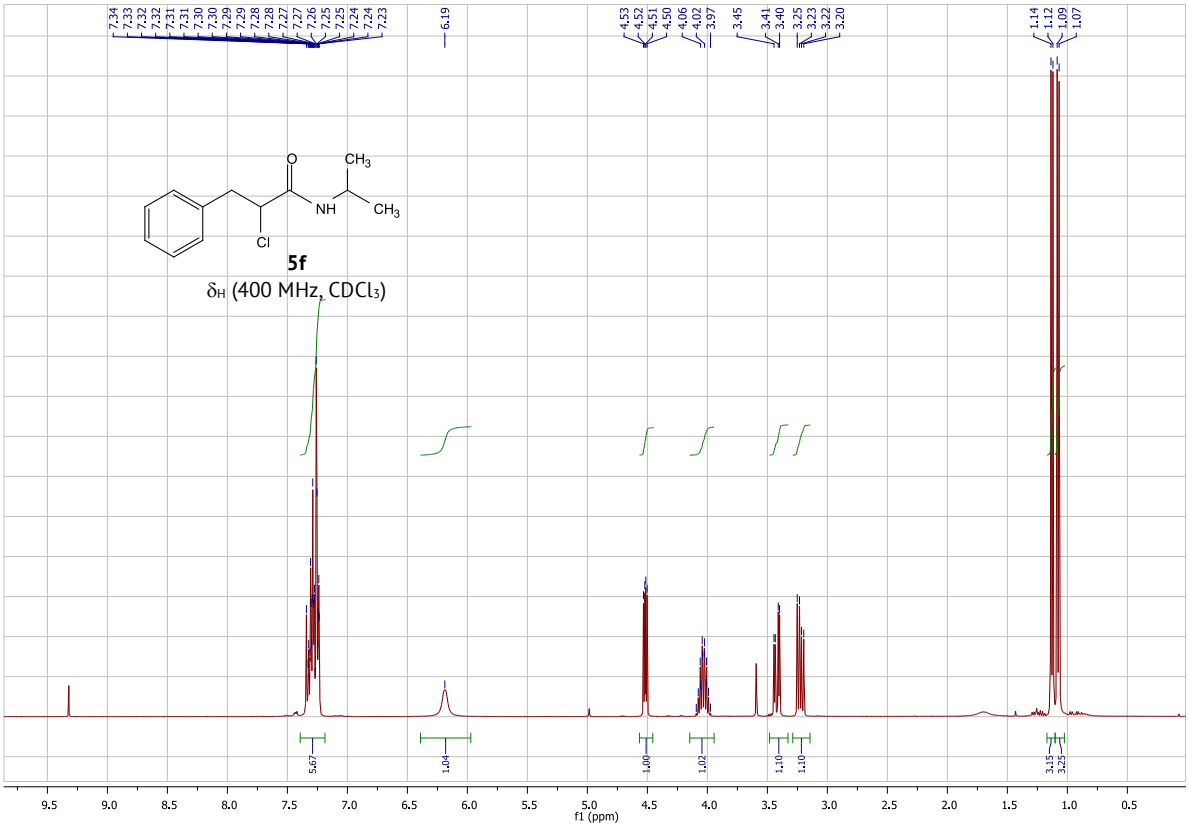
5e

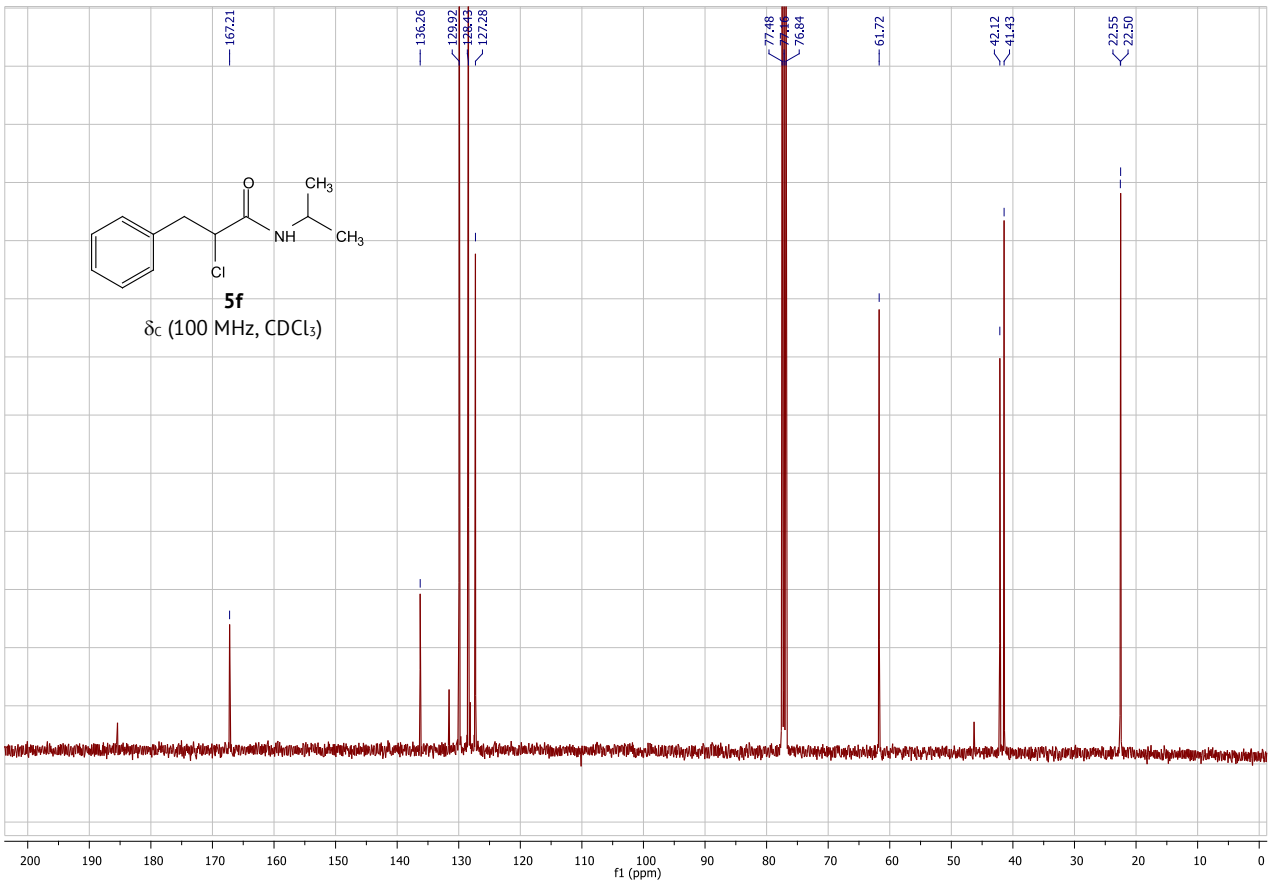
δ_H (400 MHz, $CDCl_3$)

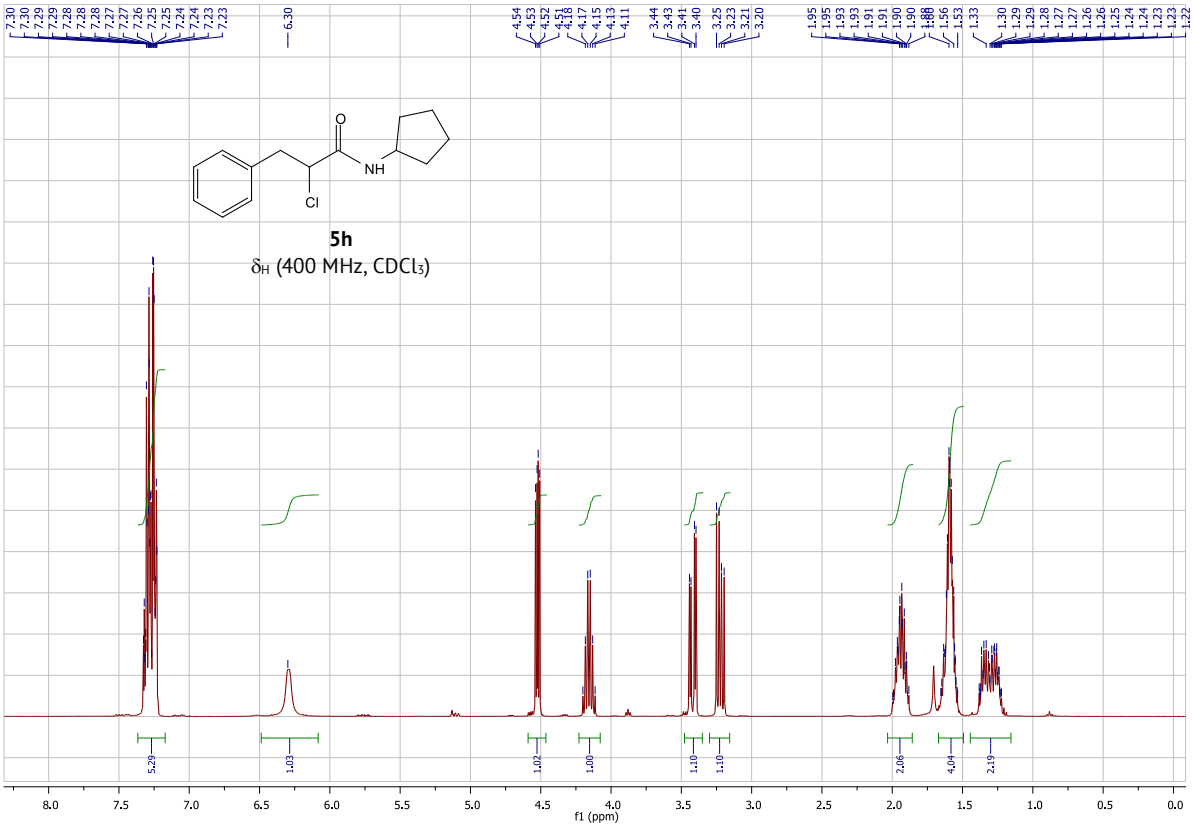


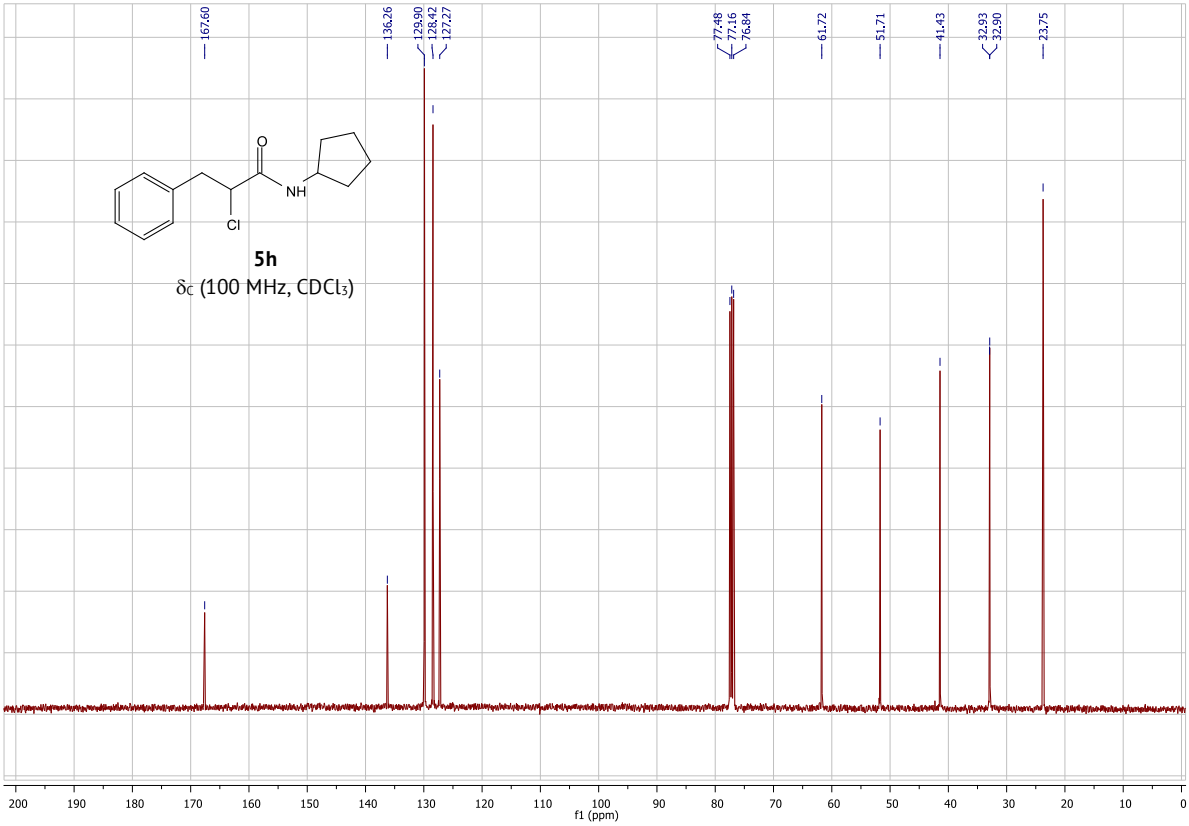
5e

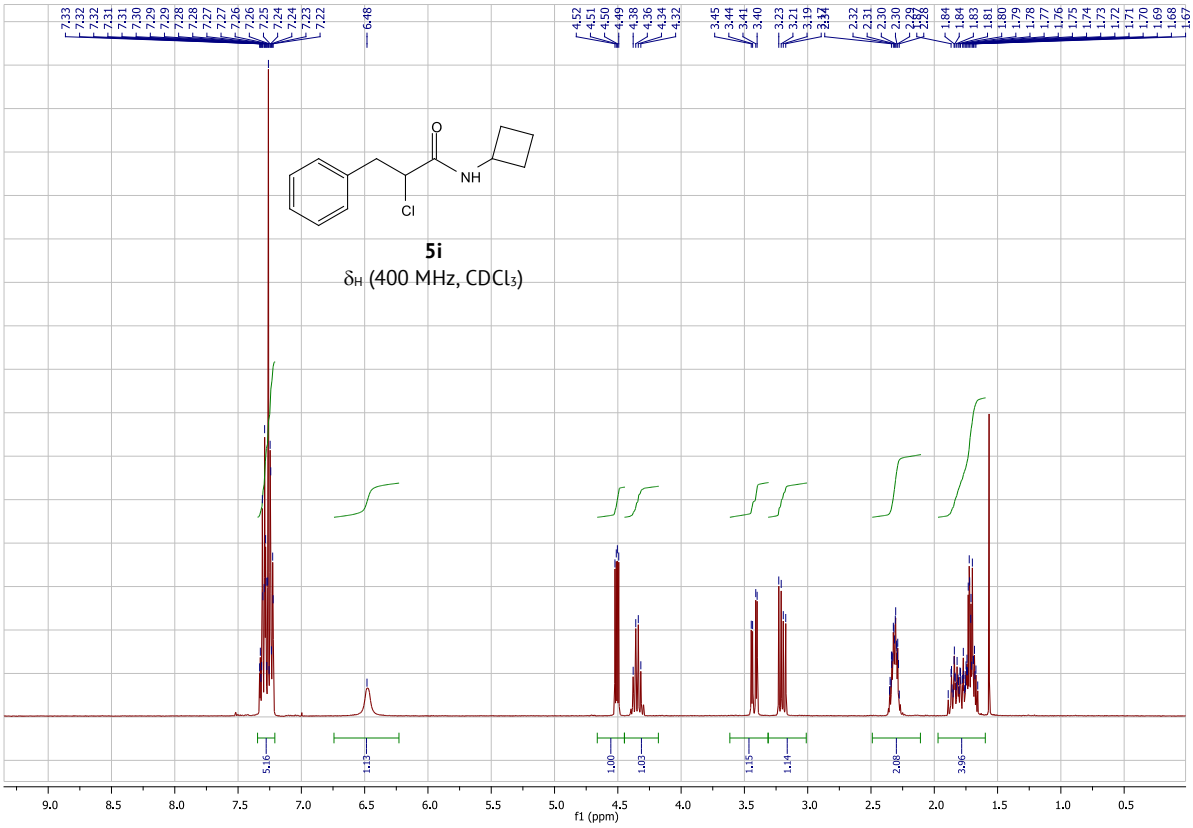
δ_C (100 MHz, $CDCl_3$)


7.34 7.33 7.32 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.27 7.26 7.25 7.25 7.24 7.24 7.23
6.19
4.53 4.52 4.51 4.50 4.06 4.02 3.97 3.45 3.41 3.40 3.25 3.23 3.22 3.20
1.14 1.12 1.09 1.07
O
CH3
NH
CH3
Cl
5f
δH (400 MHz, CDCl3)
5.67 1.04 1.00 1.02 1.10 1.10 3.15 3.25
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


167.21
136.26
129.92
128.43
127.28
77.48
77.16
76.84
61.72
42.12
41.43
22.55
22.50
O
CH3
NH
CH3
Cl
5f
δC (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

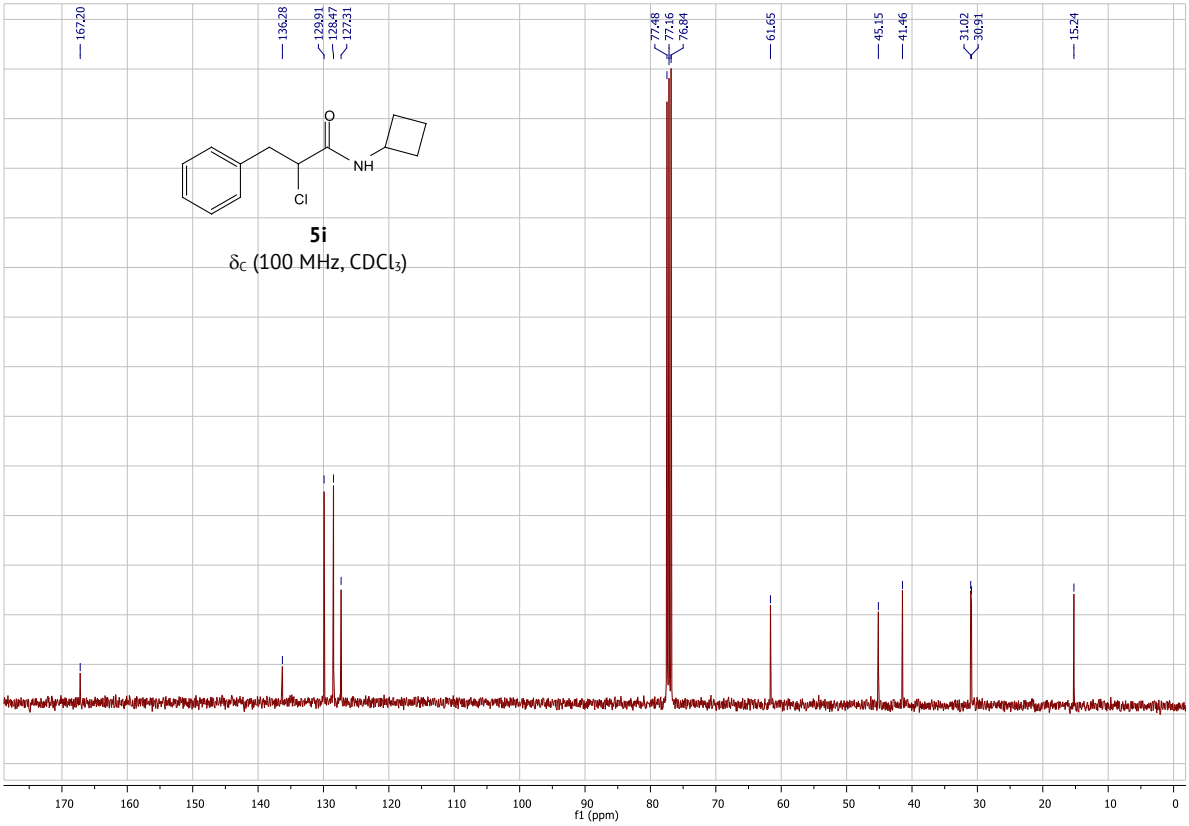

O
NH
Cl
5h
δH (400 MHz, CDCl3)
f1 (ppm)


O
NH
Cl
5h
δC (100 MHz, CDCl3)
f1 (ppm)



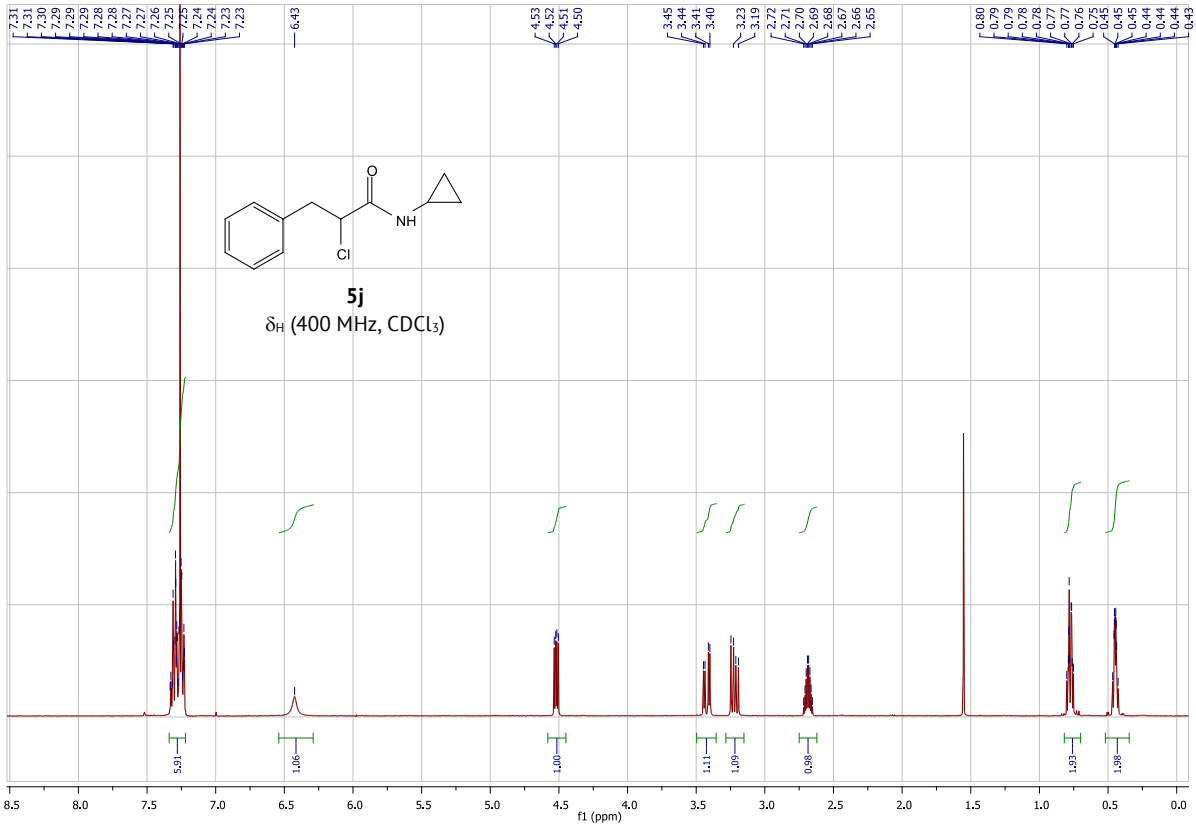
5i

δ_H (400 MHz, $CDCl_3$)



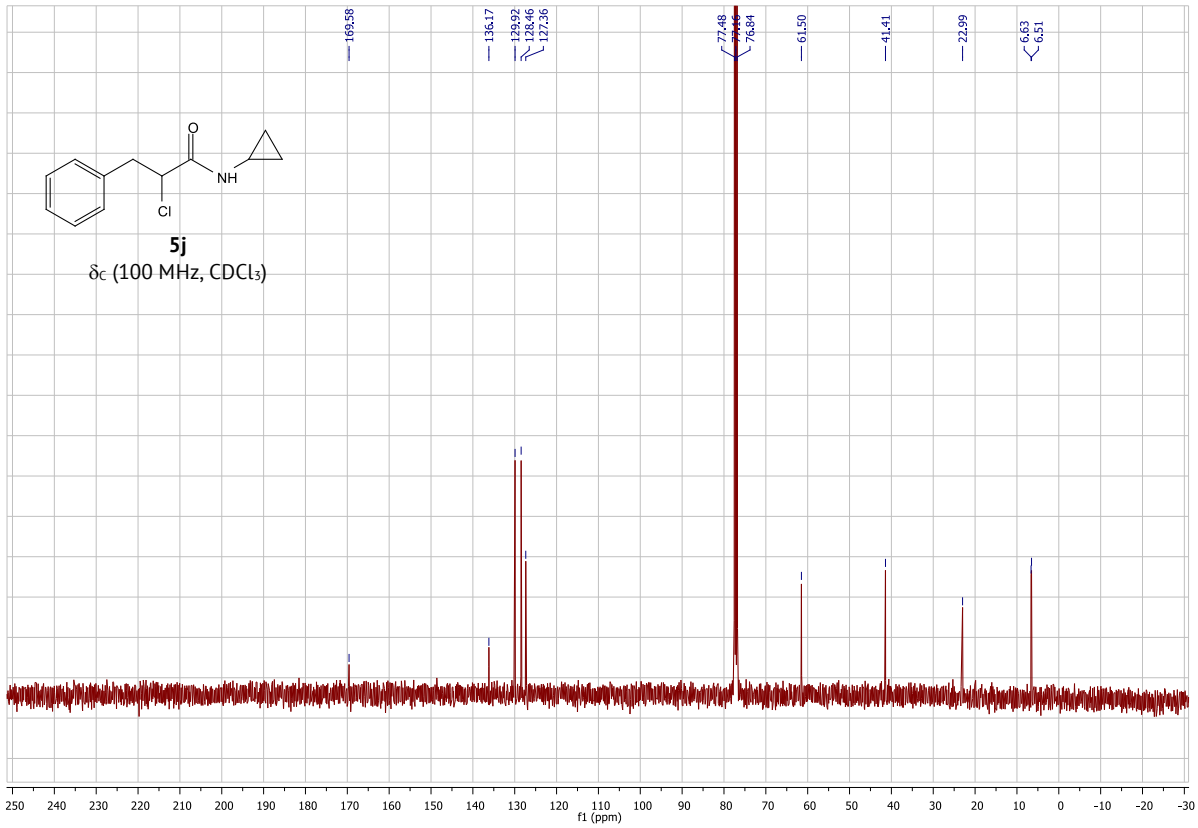
5i

δ_C (100 MHz, $CDCl_3$)



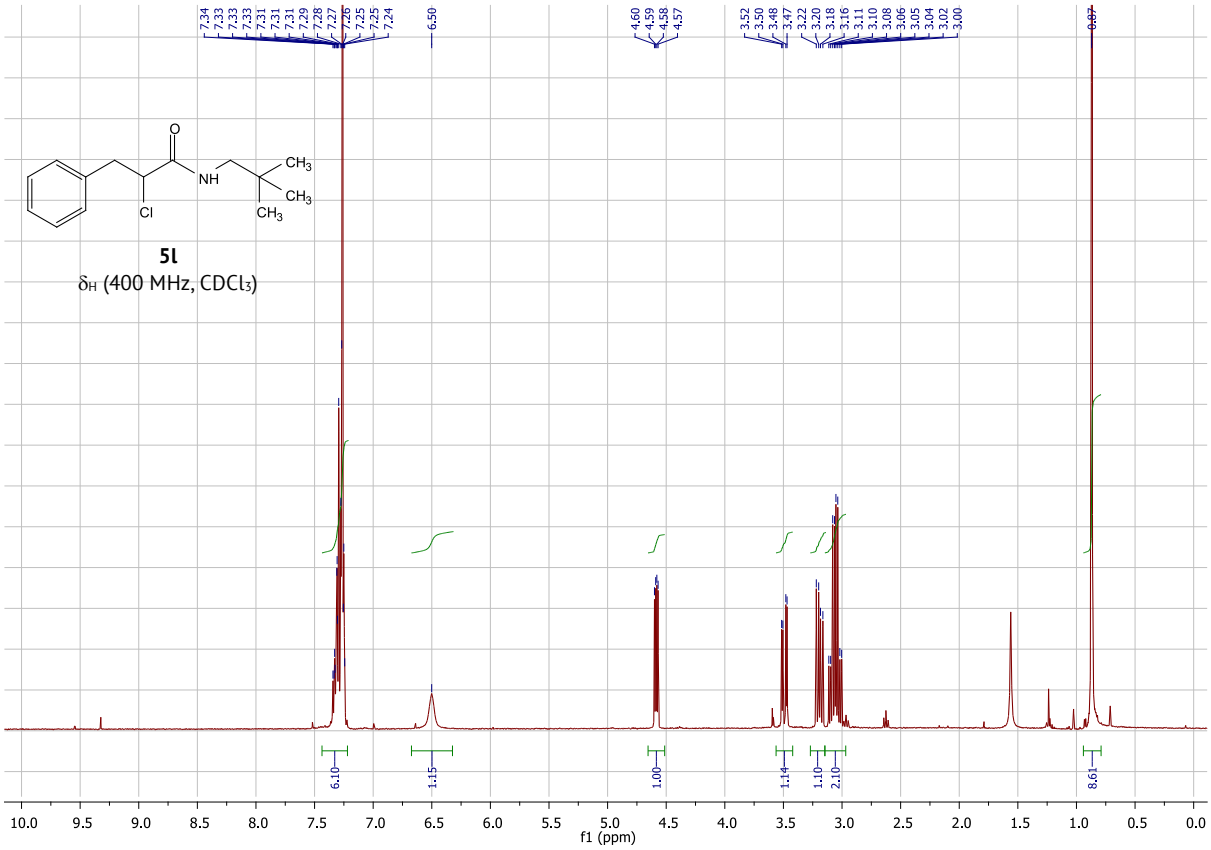
5j

δ_H (400 MHz, $CDCl_3$)



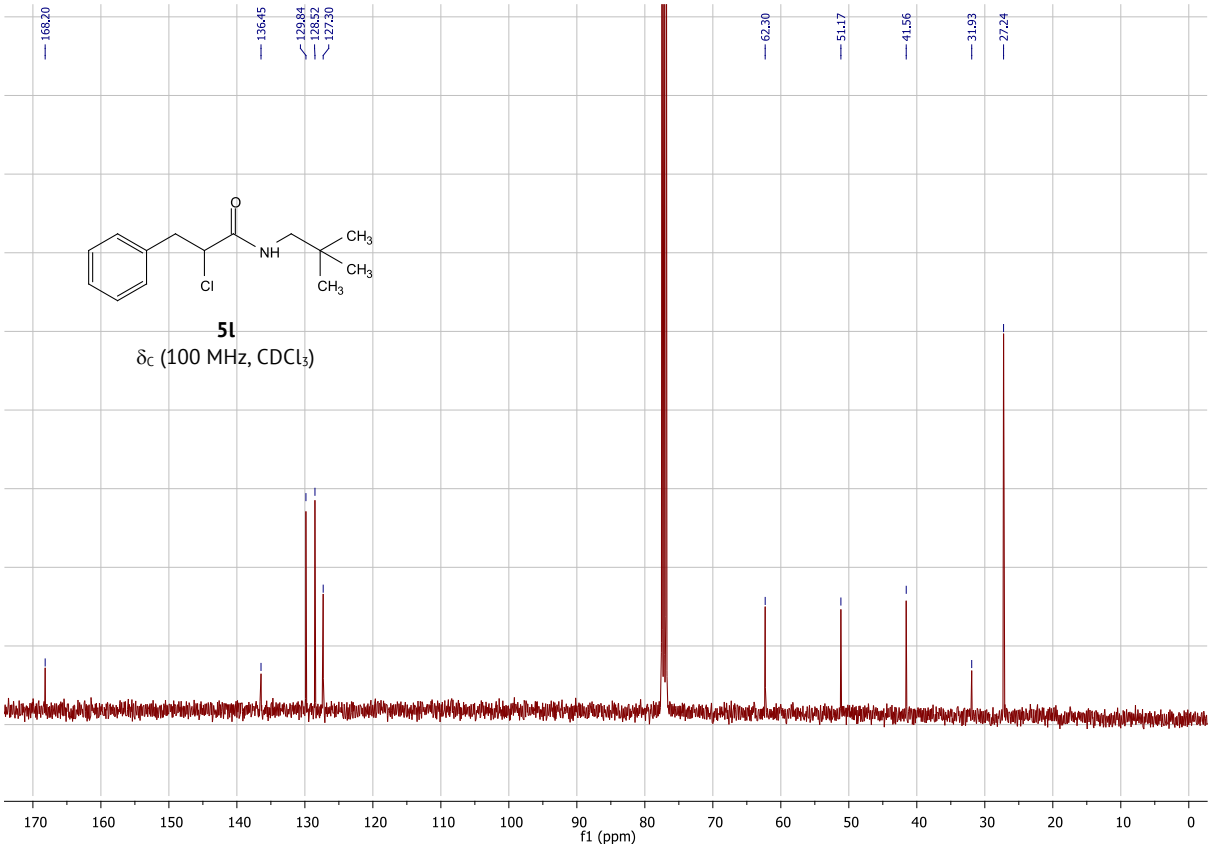
5j

δ_C (100 MHz, $CDCl_3$)



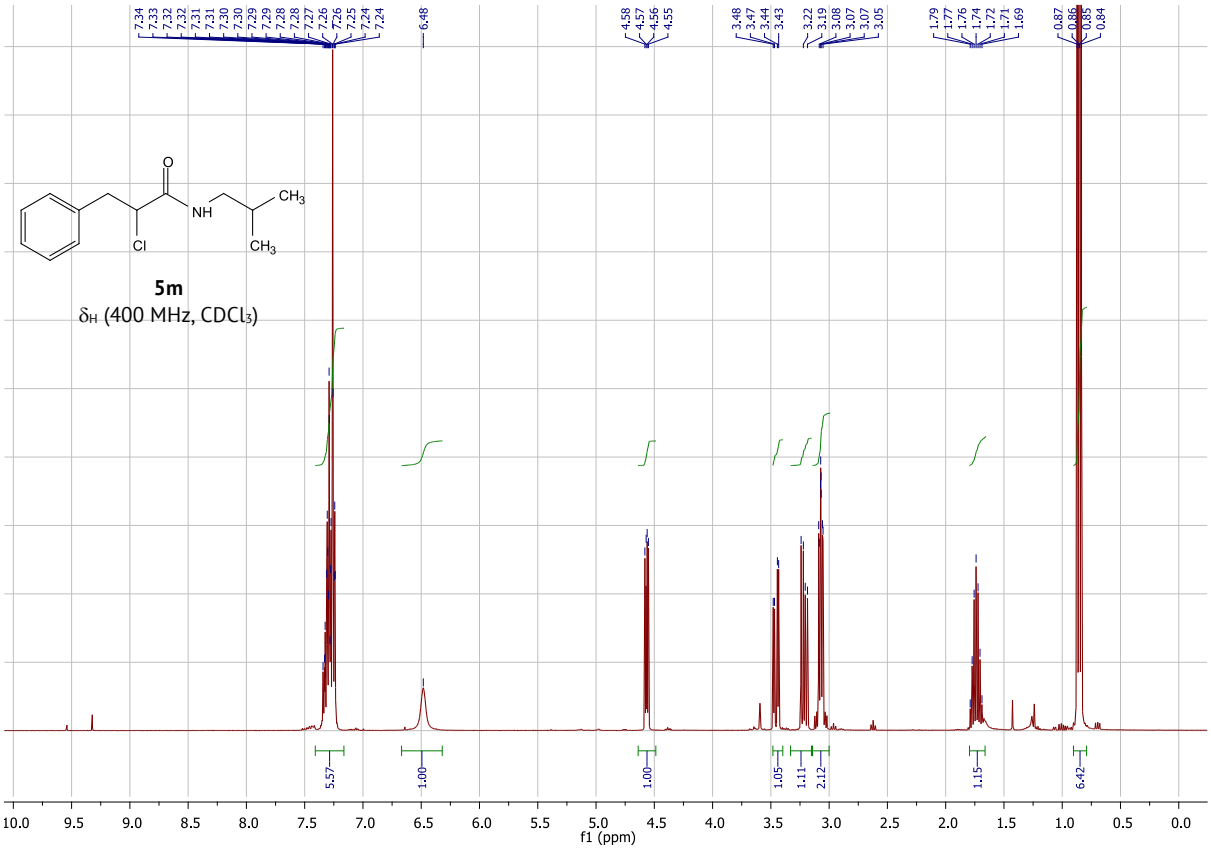
5l

δ_H (400 MHz, $CDCl_3$)



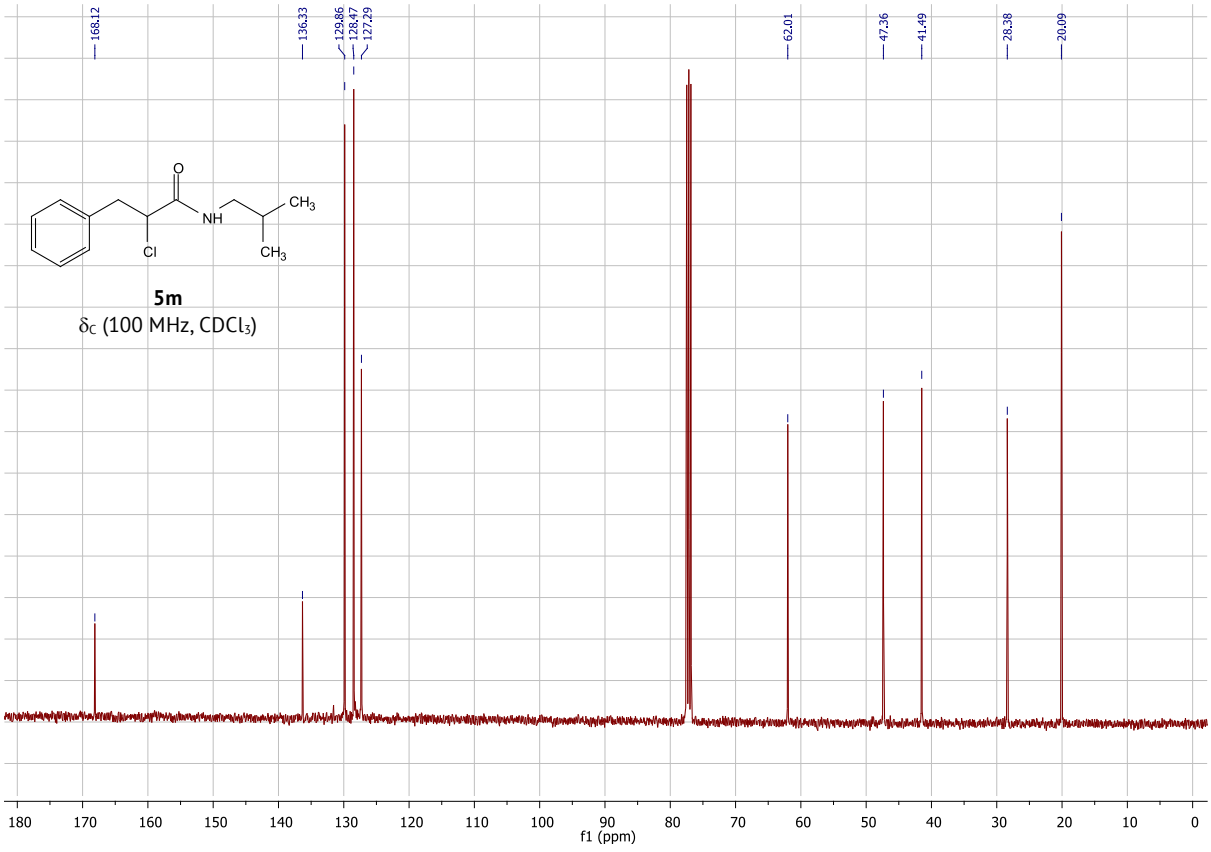
5l

δ_C (100 MHz, $CDCl_3$)



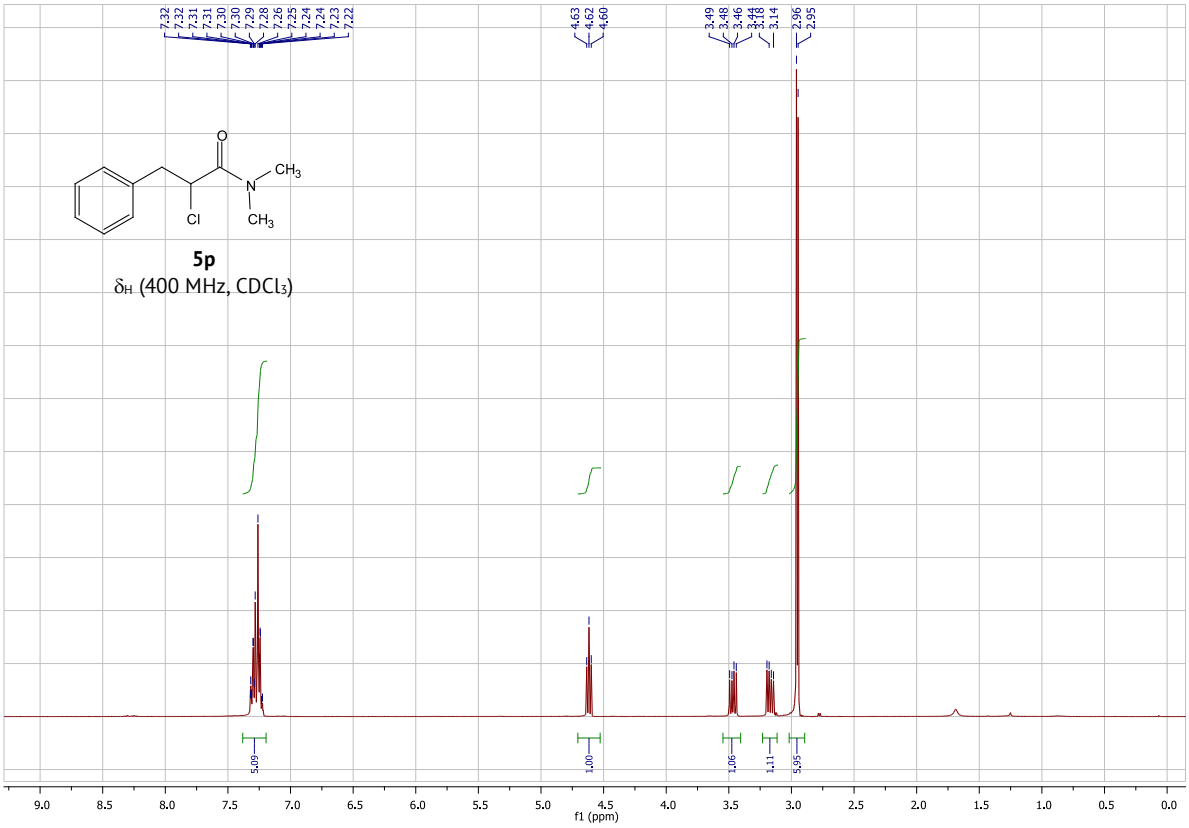
5m

δ_H (400 MHz, $CDCl_3$)



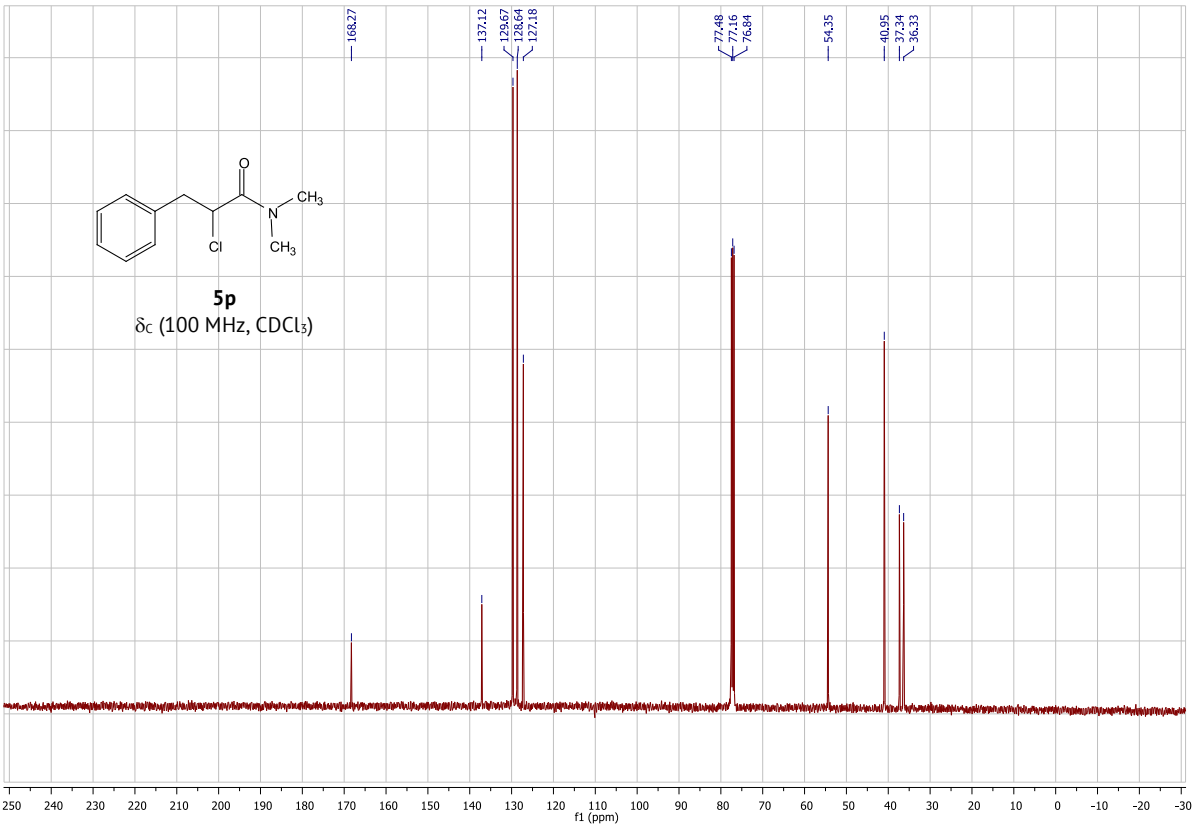
5m

δ_C (100 MHz, $CDCl_3$)



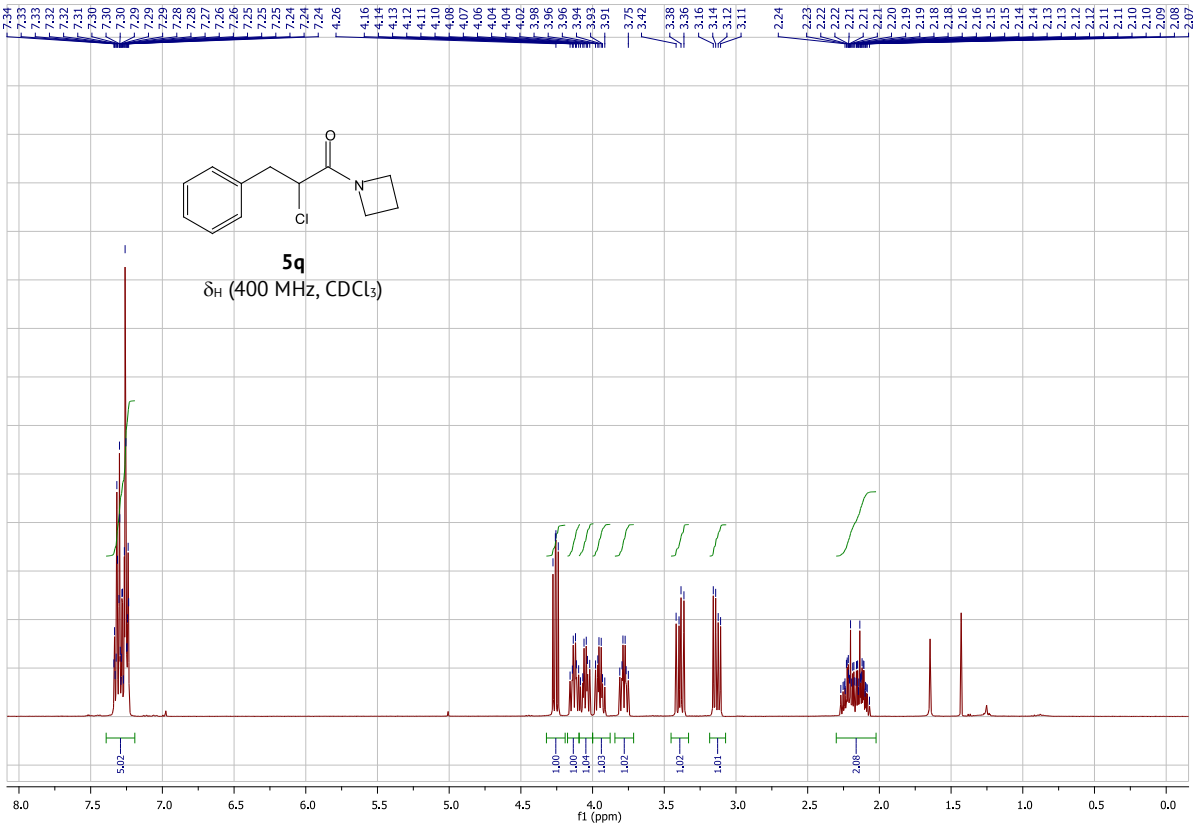
5p

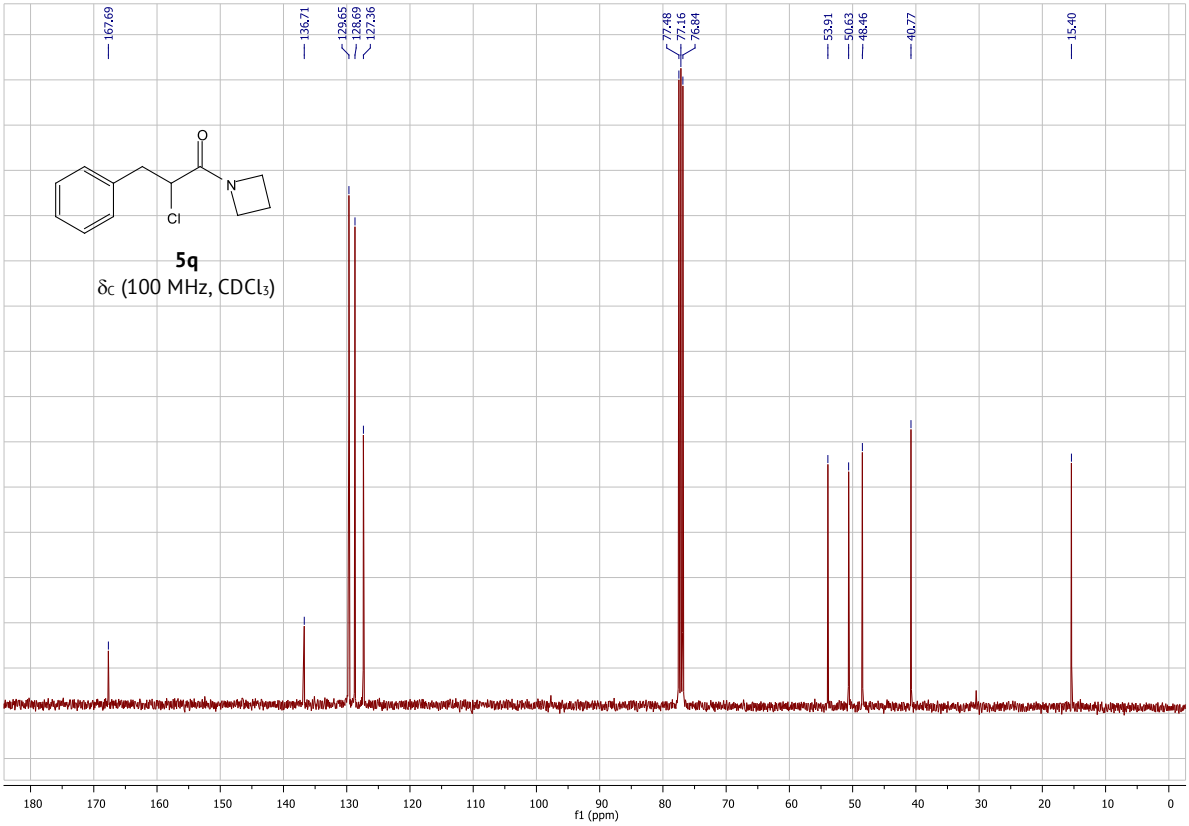
δ_H (400 MHz, $CDCl_3$)

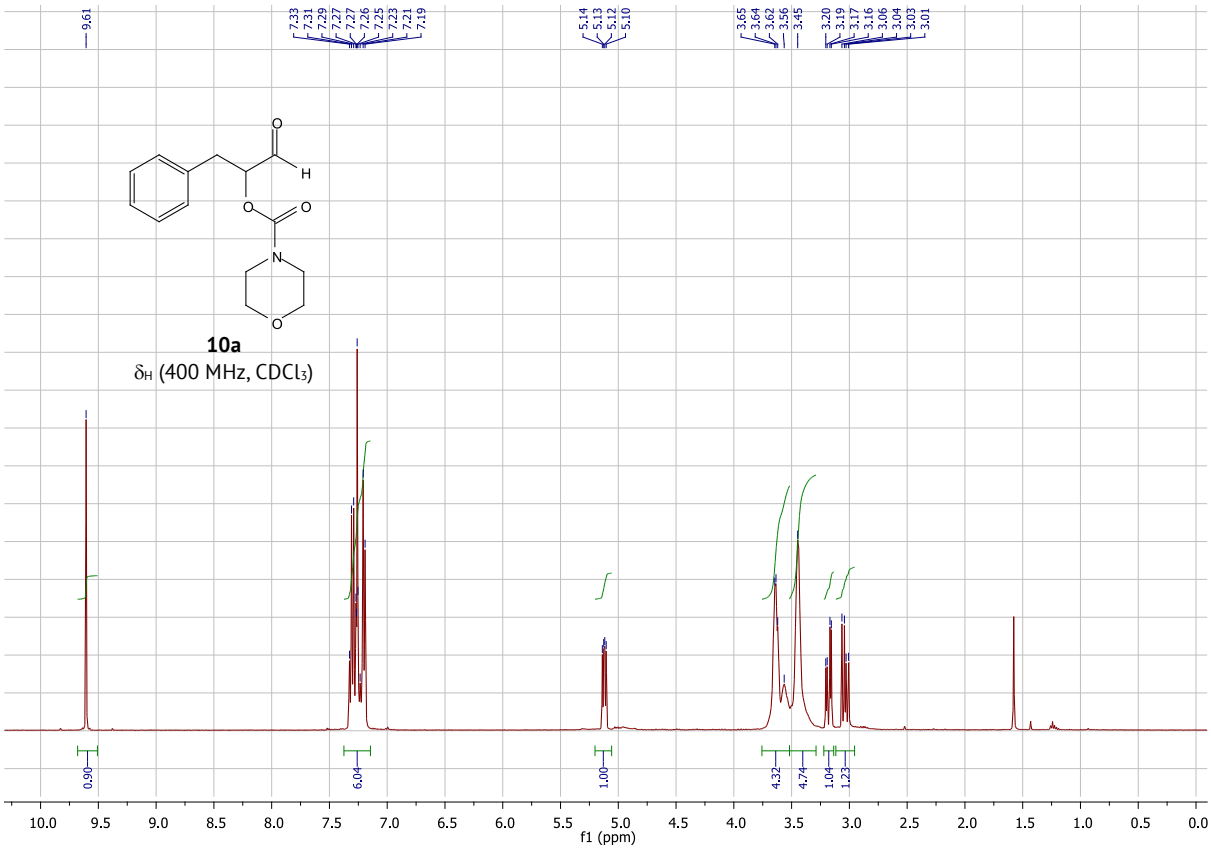


5p

δ_C (100 MHz, $CDCl_3$)

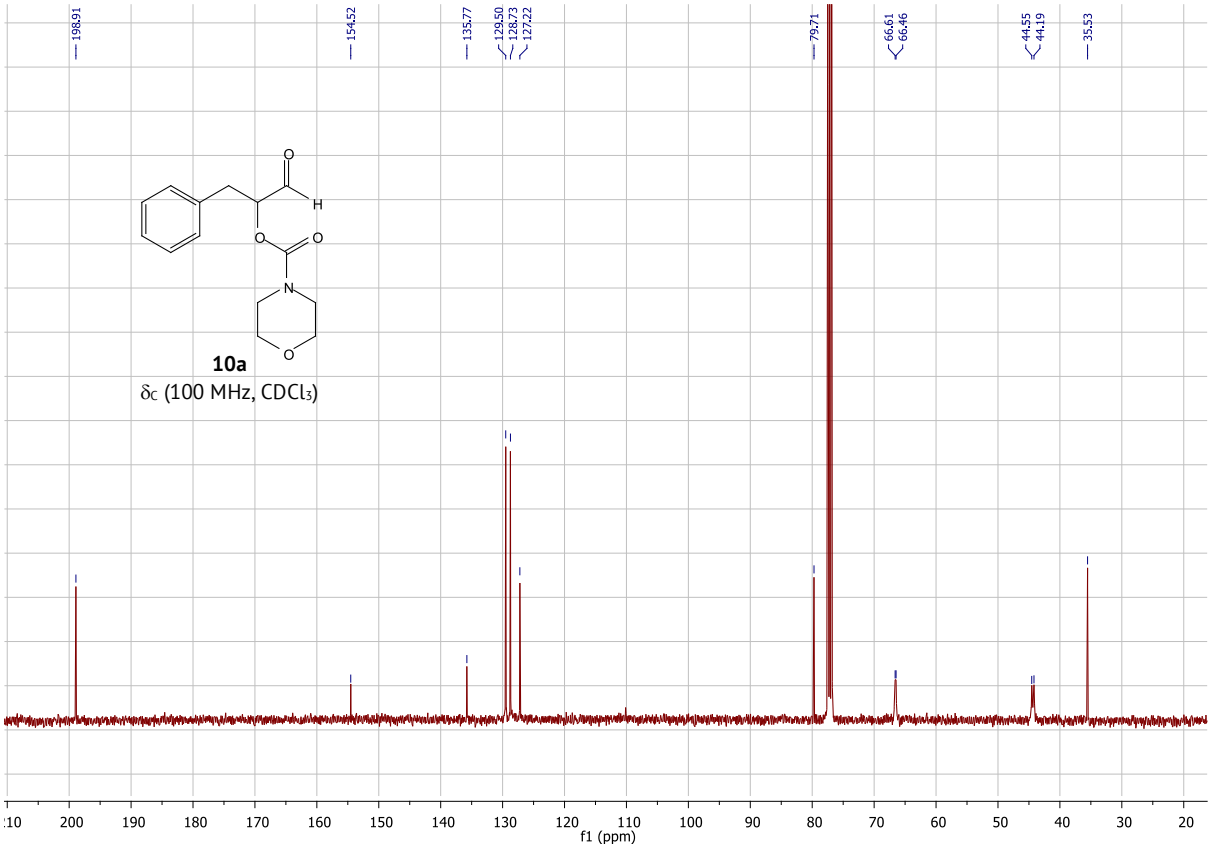

O
N
Cl
5q
δH (400 MHz, CDCl3)
f1 (ppm)


167.69
136.71
129.65
128.69
127.36
77.48
77.16
76.84
53.91
50.63
48.46
40.77
15.40
O
N
Cl
5q
δC (100 MHz, CDCl3)
f1 (ppm)



10a

δ_H (400 MHz, $CDCl_3$)



10a

δ_C (100 MHz, $CDCl_3$)

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