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Amidation of Unactivated Ester Derivatives Mediated by Trifluoroethanol

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A catalytic amidation protocol mediated by 2,2,2-trifluoroethanol has been developed, facilitating the condensation of unactivated esters and amines, furnishing both secondary and tertiary amides. The complete scope and limitations of the method are described, along with modified conditions for challenging substrates such as acyclic secondary amines and chiral esters with retention of chiral integrity.

Introduction

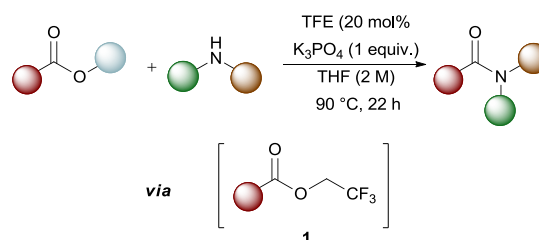
The amide functional group is extensively encountered within nature and medicinal chemistry, where it is commonly found in peptide bonds in proteins and small-molecule drugs, respectively.^{1,2} Approximately a quarter of registered drugs are found to contain an amide bond,³ thereby making amide bond formation one of the most frequently executed transformations within the pharmaceutical industry.^{4,5} However, established methods for the synthesis of amides from carboxylic acids have a number of drawbacks, particularly with regard to atom economy and sustainability, which ultimately limit their effective application.⁶ In recent years, several catalytic amidation methods have emerged seeking to improve the atom economy of this process, and thus minimising environmental impact.⁷⁻¹³

When considering the use of esters as coupling partners, stoichiometric approaches allowing the direct conversion of esters to amides have also been developed, overcoming the protracted reaction times and high temperatures associated with aminolysis.^{14,15} In recent years, catalytic approaches enabling the aminolysis of ester derivatives have been reported.¹⁶⁻²² However, despite the benefits of these catalytic approaches, a number of limitations hinder their application. In some cases only a limited substrate scope have been demonstrated with respect to the acylating species, whereas other approaches require the use of transition or rare earth metals, raising potential issues associated with both toxicity

and sustainability.

Within our own laboratories, a programme focused on catalytic amide bond formation has been developed in recent years,²³⁻²⁶ with a view to addressing some of the outstanding issues associated with this important transformation.

In a recent report, we aimed to determine if an exogenous alcohol-derived additive could be employed to facilitate an initial transesterification, forming an active ester intermediate (**1**, Scheme 1) *in situ*, and ultimately enabling the direct reaction of simple ester derivatives with amines.²⁷ Through a combination of reaction screening, where a range of additives, bases and solvents were evaluated, and the application of Design of Experiments (DoE) optimisation methods,²⁸ it was possible to develop a sustainable, inexpensive and unprotracted procedure for the synthesis of amides from unactivated ester derivatives and primary or cyclic secondary amines using a catalytic quantity (20 mol%) of 2,2,2-trifluoroethanol (TFE) as an additive (Scheme 1).



Scheme 1. TFE-mediated catalytic amidation procedure.

In the current study, we present the full scope and limitations of the complete process. We demonstrate the importance of the choice of base on the outcome of the reaction, as well as reporting further extension of the methodology in order to

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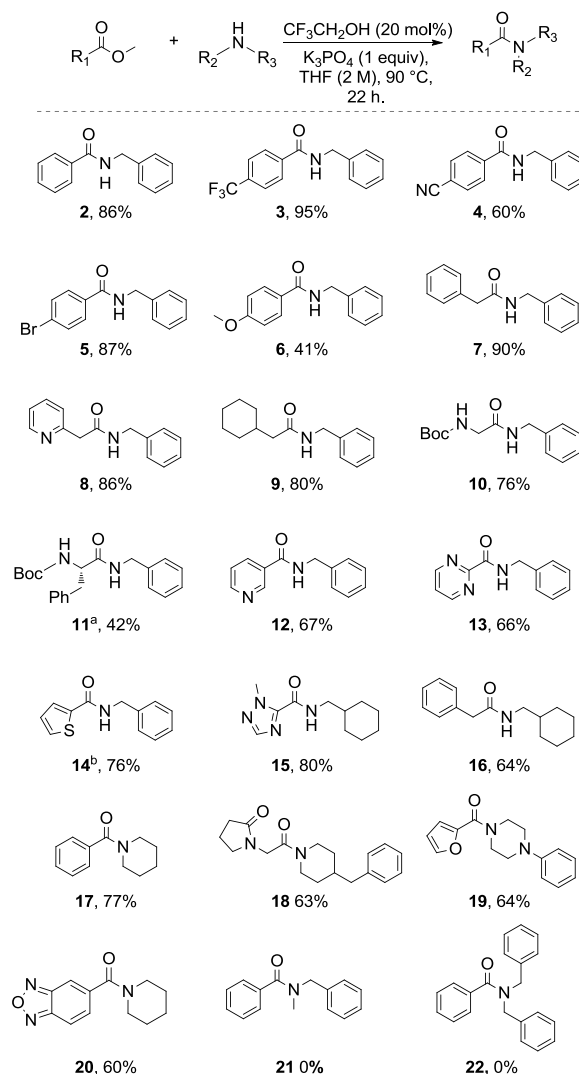
allow the incorporation of secondary acyclic amines, previously intractable in the progenitor process. In addition to this, we demonstrate an improved method for the preparation of amide substrates based on enantiopure starting materials with good retention of stereoconfiguration.

Results and Discussion

In our initial study, to investigate the general utility of the methodology, a range of ester and amine starting materials were assessed for their applicability in this reaction manifold (Scheme 2). In our preliminary communication, a broad range of amides were able to be prepared under the optimum conditions developed.²⁷ Several aryl esters, substituted with both electron-withdrawing and electron-donating groups were successfully coupled with benzylamine, furnishing the corresponding amides (**2-6**) in good to excellent yields. However, electron rich aryl esters (**6**) were noted to be comparatively less competent coupling partners.

Aliphatic esters were also tolerated (**7-11**), including two amino acid-derived substrates (**11** & **12**). However, significant erosion of enantiopurity was unfortunately observed when using an α -chiral ester, affording **11** (ee = 8% as determined by chiral HPLC), which represented a limitation of the first generation method at this stage. Esters containing heterocyclic motifs (**12-15**) were also found to be proficient coupling partners with pyridine- (**12**), pyrimidine- (**13**), and thiophene- (**14**) derived species furnishing good to excellent yields of the respective amide derivatives.

Variation of the amine coupling partner from benzylamine allowed further exemplification of the process. Aliphatic amines could be successfully applied alongside heterocyclic (**15**) and aliphatic (**16**) esters. The successful coupling of piperidine (**17**, **18**) and piperazine (**19**) derivatives extended the substrate scope, highlighting the applicability of the approach to cyclic secondary amines. In order to demonstrate the successful application of our methodology to a medically relevant compound, the experimental Ampakine Farampator (**20**), currently in Phase II trials for ADHD,²⁹ was prepared in a good yield of 60% in one step. Despite the general utility of the method with the exemplars shown above, tertiary amides prepared from acyclic secondary amines such as *N*-methylbenzylamine (**21**) and dibenzylamine (**22**) could not be prepared using this methodology, highlighting a second limitation of the initially developed method.



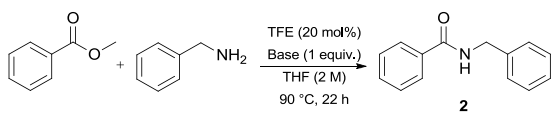
Scheme 2. Representative scope of first generation process reported previously.²⁷ Isolated yields shown. ^a 8% ee as determined by chiral HPLC. ^b Synthesised from the corresponding ethyl ester starting material.

In an effort to extend the utility of the process to accommodate previously problematic substrates such as acyclic secondary amines and chiral ester derivatives, we first sought to establish the role of pK_a of the conjugate acid associated with the base used. When developing our first generation process, it was noted that the pK_a values of both K_3PO_4 and TFE are extremely similar (12.3 and 12.5, respectively). In order to investigate whether this alignment of base and additive pK_a is a prerequisite for the reaction to proceed efficiently, a selection of bases, representing a broader range of pK_a values than initially studied, were screened using a model system (Table 1). Initial attempts focused on retaining the potassium counterion (Table 1, Entries 1-8). From this it could be noted that K_3PO_4 (Entry 6) was the optimal choice with a 78% conversion obtained, fully consistent with our

previous observations. Potassium *tert*-butoxide (Entry 8) also furnished the desired amide product but in a comparatively lower conversion of 47%. The phosphate species of the base was then retained and the role of the metal counterion was next examined. (Table 1, Entries 9-13). The use of Mg_3PO_4 (Entry 12) resulted in the only measurable conversion of 16%, with the other counterions proving unsuccessful for reaction progression. Cs_2CO_3 (Entry 14) also led to poor conversion, indicating that potassium was the preferred counterion.

A range of organic bases were then explored (Entries 15-19), with all but DBU (Entry 18, 61%) proceeding with either no or minimal conversion to the amide product. From consideration of this extended base study, it can be concluded that those bases with a pK_a in line with that of TFE (K_3PO_4 and DBU) perform considerably better in the reaction manifold than bases with a pK_a either greater or less than 12. The exception to this is $KOtBu$ which, although furnishes the amide in moderate yield, is still less effective than the original base of choice. Clearly, the choice of counterion is also important with other phosphate salts proving ineffective in the reaction. This observation may be attributable to the solubility of the TFE adduct in the reaction milieu.

Table 1. Further investigation into the nature of the base species.



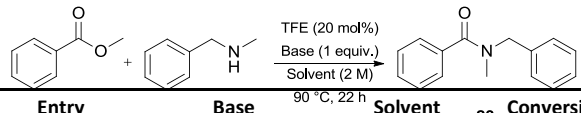
Entry	Base	pK_a	Conversion (%)
1	KTFA	0	1
2	KH_2PO_4	2	1
3	KOAc	6	1
4	K_2HPO_4	7	1
5	K_2CO_3	10	2
6	K_3PO_4	12	78
7	KOH	16	5
8	$KOtBu$	18	47
9	Ca_3PO_4	13	1
10	Cs_3PO_4	13	1
11	Li_3PO_4	13	0
12	Mg_3PO_4	13	16
13	Na_3PO_4	13	1
14	Cs_2CO_3	10	11
15	NMO	7	13
16	DABCO	9	4
17	Et_3N	11	1
18	DBU	12	61
19	BEMP	19	8

With further understanding into the choice of base used, attention then turned to addressing the limitations identified above. As discussed previously, the incompatibility of acyclic secondary amines with the previously optimised conditions to form tertiary amides represents a major gap in the scope of method. We proposed that altering the additive, base and solvent may overcome this problem. To this end, a model

system was again examined, and the effects of altering the additive, base and solvent analysed *via* HPLC, the results of which are presented in Table 2.

In the first instance, the model amidation was repeated using the conditions optimised for our progenitor process, resulting in only 1% conversion to the desired amide (Table 2, Entry 1). Moderate formation of the desired amide, however, was noted when using K_3PO_4 in conjunction with cyclopentylmethyl ether (CPME), 1,4-Dioxane and 2-MeTHF (Table 2, Entry 2-4). Consistent with the extended base screen discussed above, no other base was seen to promote the reaction. One exception to this is the use of $KOtBu$ (Table 2, Entries 5-7) where the desired amide could be formed in conversions of up to 96%. However, when the reaction was performed in the absence of the TFE additive, substantial direct aminolysis was observed (Table 2, Entry 7). This is consistent with earlier reports of using $KOtBu$ to promote amidation of ester derivatives, we believe that the $KOtBu$ is facilitating the reaction *via* radical-based process.^{31,32}

Table 2. Initial tertiary amide optimisation



Entry	Base	Solvent	Conversion (%)
1	K_3PO_4	THF	1
2	K_3PO_4	CPME	37
3	K_3PO_4	1,4-Dioxane	12
4	K_3PO_4	2-MeTHF	43
5	$KOtBu$	CPME	96
6	$KOtBu$	THF	56
7 ^a	$KOtBu$	CPME	58

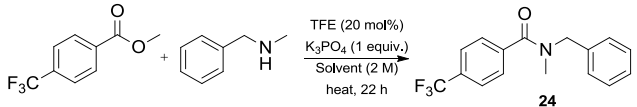
^aReaction performed in the absence of TFE.

With modest conversion to the desired amide observed, further optimisation was undertaken. At this point in the study, the ester species used in the model reaction was altered to methyl 4-(trifluoromethyl)benzoate, as the inherent electron-withdrawing characteristic of which was anticipated to make the desired amidation reaction more amenable. Despite examining a more activated substrate, the amidation reaction was still found to not proceed when run in THF (Table 3, Entry 1). Interestingly, altering the order of addition of the reaction, allowing a 30 minute window for formation of the active ester intermediate before addition of the amine, resulted in the desired amidation proceeding in 70% conversion (Table 3, Entry 2). This was then subsequently applied to the amidation of methyl benzoate where a significant increase in obtained conversion was again observed (Table 3, Entry 3). Based on these results, we reason that concomitant addition of the reactants result in a preferential formation of a quaternary ammonium salt between trifluoroethanol and the amine substrate, precluding

formation of the target amide due to sequestration of the TFE catalyst in the insoluble base matrix.

With the aim of further optimising this observed conversion, the temperature of the reaction was increased, with the solvent selected accordingly (Table 3, Entries 4-6). Pleasingly, this resulted in a 93% isolated yield of the desired amide when carrying out the reaction in dioxane (Table 3, Entry 5). Importantly, the corresponding control reactions resulted in no amide product (Table 3, Entries 7-9), confirming that the reaction does not proceed *via* direct aminolysis but instead requires formation of the TFE-derived active ester species.

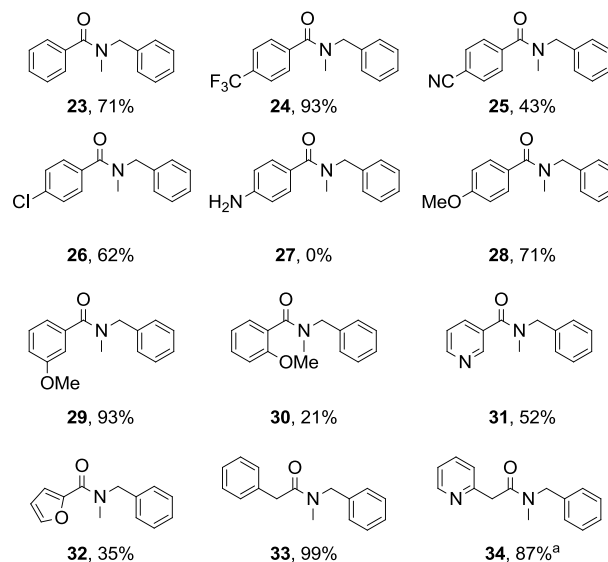
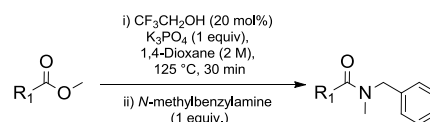
Table 3. Tertiary amide optimisation with increased temperature.



Entry	Solvent	Temperature (°C)	Conversion (%)
1	THF	90	0
2 ^a	THF	90	70
3 ^{a,b}	THF	90	62
4 ^a	CPME	125	77 ^c
5 ^a	1,4-Dioxane	125	93 ^c
6 ^a	2-MeTHF	100	72 ^c
7 ^{a,d}	1,4-Dioxane	125	0 ^c
8 ^{a,e}	1,4-Dioxane	125	0 ^c
9 ^{a,f}	1,4-Dioxane	125	0 ^c

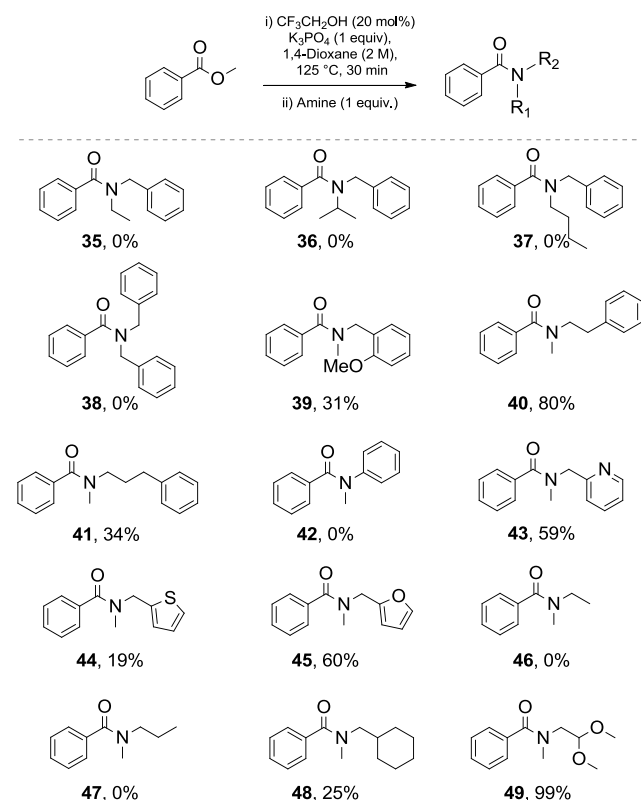
^a30 min preformation of active ester at reaction temperature. ^bMethyl benzoate used as ester substrate. ^cIsolated yield. ^dPerformed in the absence of K_3PO_4 . ^ePerformed in the absence of TFE. ^fPerformed in the absence of both K_3PO_4 and TFE.

With optimum conditions allowing the coupling of acyclic secondary amines now established, we first sought to investigate the scope of the ester component of the reaction (Scheme 3). Pleasingly, several aryl esters, containing both electron-withdrawing and electron-donating groups were successfully coupled with *N*-methylbenzylamine, furnishing the corresponding amides (**23-30**) in good to excellent yields. Exceptions to this include the coupling of methyl 4-aminobenzoate (**27**), and ring systems bearing *ortho* substitution (e.g. **30**). Heteroaryl esters were also tolerated within the reaction in moderate yields (**31** and **32**). Alkyl esters (**33** and **34**) furnished the corresponding amide products in excellent yields when evaluated using this second generation method.



Scheme 3. Investigating the scope of the ester component. ^aSynthesised from the corresponding ethyl ester starting material.

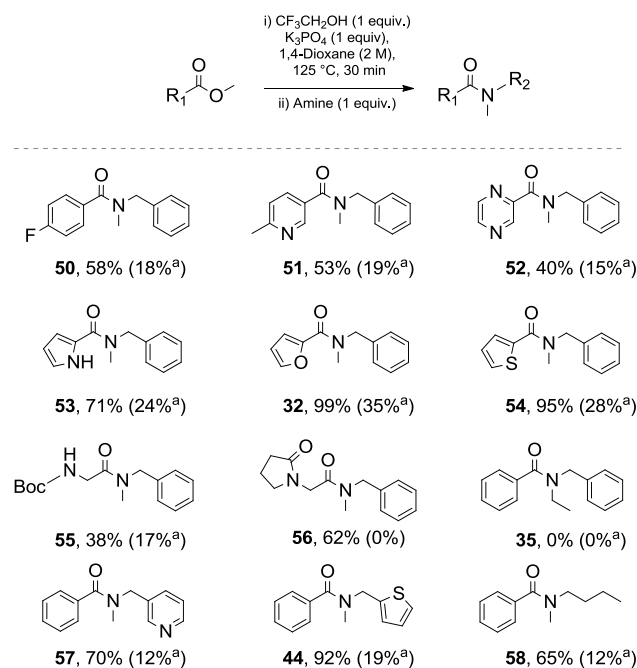
Having investigated the scope of the ester component in conjunction with a model acyclic secondary amine, attention was turned to variation of the amine coupling partner (Scheme 4). This was somewhat more limited in scope, as for example, it was found that increasing the size of the substituent from *N*-methylbenzylamine to the corresponding ethyl, isopropyl, butyl and dibenzyl- derivatives (**35-38**) was not tolerated, presumably due to steric hindrance. Returning to methylated derivatives, substitution on the aromatic ring in the form of an *o*-methoxy was tolerated in modest yield (**39**).



Scheme 4. Substrate scope of the acyclic secondary amine component

Pleasingly, homologation of the amine was tolerated in moderate to good yield (**40** and **41**). Unfortunately, aniline derivatives, such as **42**, were not competent substrates under these new conditions, which can be ascribed to their inherently lower nucleophilicity. A range of heteroaryl derived amines (**43–45**) were successful coupling partners with moderate to good yields of the corresponding amides obtained. By contrast, alkyl amines (**46**, **47** and **48**) were in general not compatible with the reaction manifold. In the case of amines such as **46** and **47** we propose this is attributable to the volatility of the amine starting material under the high temperature required for the reaction to proceed. However, as expected, the electron rich amine **49** was found to undergo amidation efficiently, forming the expected product in 99% yield.

Despite the success in developing reaction conditions that were suitable for a number of acyclic secondary amine substrates, from consideration of the substrate scope above, it can be noted that a number of exemplars could only be isolated in sub-optimal yields. In order to address this, we reasoned that increasing the quantity of the trifluoroethanol additive from a catalytic amount (20 mol%) to a full equivalent may lead to increased yields. Accordingly, a subset of the amide products previously examined were re-evaluated to investigate this proposal (Scheme 5).



Scheme 5. Application of stoichiometric TFE additive. a) yield obtained using 20 mol% TFE.

From the chosen subset, it was apparent that the use of a full equivalent of TFE does, indeed, in most cases increase the yield obtained. The *para* fluoro substrate (**50**) could be obtained in good yield of 58% compared to the previous 18%. A range of heteroaryl esters (**51–54**) demonstrate the same marked improvement, and in the case of the furan (**32**) and thiophene (**54**) derivatives, almost full conversion of the ester to the amide is obtained. For the glycine derived alkyl ester **55**, a more modest increase in yield to 38% is observed. Pleasingly, the pyrrolidinone derived ester **56**, which was not a competent substrate when using catalytic quantities of TFE, is now a viable with a good yield of 62%.

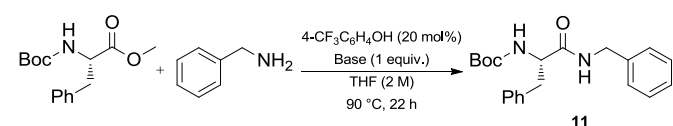
Unfortunately, the ethyl-derived amine **35** remained incompatible with these conditions, supporting our earlier observations that more sterically crowded secondary amines do not undergo the desired amidation. However, the pyridine derived amine **57** reflects the increased yields seen when varying the ester substrate, and affords the corresponding tertiary amide in 70%. In a similar fashion, the thiophene derived methylamine (**44**) also exhibits a significant improvement in yield, with 92% of the amide product isolated, compared to the previous 19%. Finally, an alkyl amine previously studied was re-evaluated using a full equivalent of TFE. Amide **58**, previously obtained in 12% yield, could now be isolated in a yield 65%.

Despite having compromised the catalytic nature of the reactions for these more demanding substrates, this stoichiometric approach compares favourably with other established methods of amide coupling, especially given the low cost of TFE³³ as an additive. Accordingly, application of stoichiometric quantities of TFE is a viable approach for

substrates that are not compatible with the catalytic reaction manifold.

Having successfully adapted the first generation method to enable the condensation of acyclic secondary amines, attention was turned to the remaining limitation of our progenitor process. As discussed above, the amidation of benzylamine and Boc-Phe-OMe to the corresponding amide (**11**) resulted essentially in complete epimerisation. Altering the additive used from trifluoroethanol to 4-(trifluoromethyl)phenol was found to minimise the extent of racemisation, affording the amide in a comparable yield of 38% with an ee of 65%. Encouraged by this, we conducted a more extensive screen of potential bases and additives in order to identify further enhancements in both the yield and corresponding enantiomeric excess of the amide product. Accordingly, the coupling of Boc-Phe-OMe with benzylamine mediated by 4-(trifluoromethyl)phenol was selected as the model reaction, with the effect of varying the base initially investigated (Table 4).

Table 4. Effect of varying the base on the yield and ee obtained.



Entry	Base	pK _a	Yield (%)	ee
1	KTFA	0	46	93
2	KH ₂ PO ₄	2	62	87
3	KOAc	6	55	92
4	NMO	7	36	92
5	K ₂ HPO ₄	7	48	92
6	DABCO	9	40	85
7	K ₂ CO ₃	10	46	75
8	Cs ₂ CO ₃	10	34	40
9	DBU	12	69	16

From consideration of the data in Table 4, a clear trend can be discerned between the strength of base and the extent of racemisation (Figure 2). The use of KTFA (Table 4, Entry 1), with a pK_a of 0, results in minimal racemisation, whereas, if a base with a pK_a of greater 10 is used (Table 4, Entries 7-9), high levels of racemisation are observed. Based on this, the base offering the best combination of isolated yield relative to product ee was deemed to be KOAc and, as such, was retained for use in the following additive screen (Table 5).

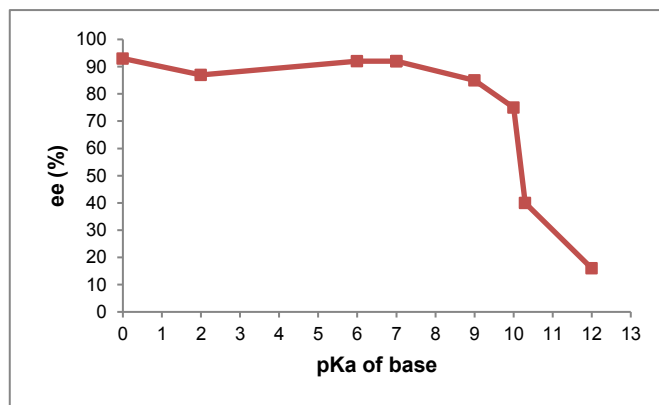
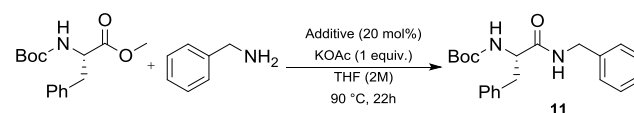


Figure 1. Effect of the pK_a of the base compared to the ee of the obtained product.

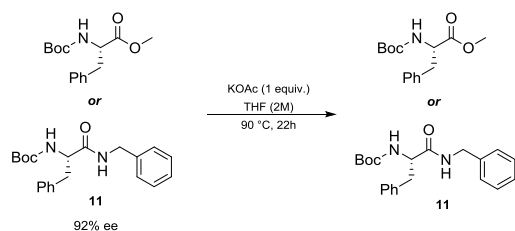
Table 5. Effect of varying the additive on the yield and ee obtained.



Entry	Additive	pK _a	Yield (%)	ee
1	Picoline n-oxide	-	28	87
2	HOCT	2	54	91
3	HOAt	3	32	89
4	HOBt	5	47	91
5	Oxyma	5	50	93
6	NHS	8	58	79
7	4-CF ₃ C ₆ H ₄ OH	9	55	92
8	HFIP	9	35	89
9	TFE	12	31	89

It can be noted from Table 5 that the nature of the additive has little effect on the ee obtained, with only N-hydroxysuccinimide (Table 5, Entry 6) leading to a product with an ee less than 87 % (Figure 3). The use of HOCT³⁴ (Table 5, Entry 2) and 4-(trifluoromethyl)phenol (Table 5, Entry 7) led to comparative yields and ee of the desired product, with 4-(trifluoromethyl)phenol selected as the optimum additive due to a marginally superior yield to ee balance.

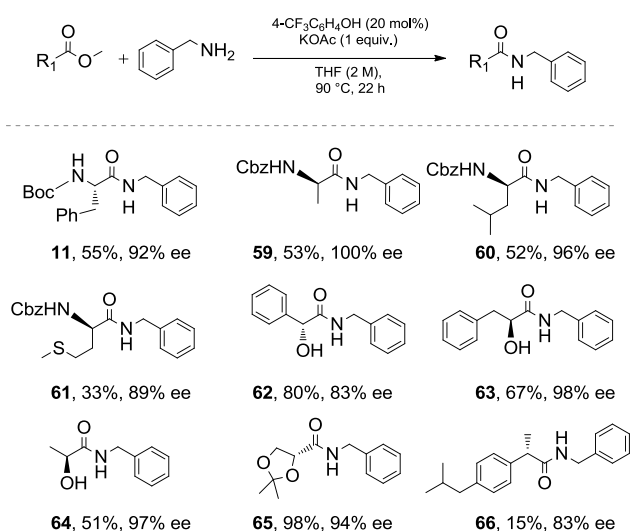
In order to elucidate at which point epimerisation occurred in the reaction, Boc-Phe-OMe and the corresponding amide product (**11**) were individually subjected to the reaction conditions in the absence of both 4-(trifluoromethyl)phenol and benzylamine (Table 6).

Table 6. Epimerisation Study

Entry	Substrate	Initial ee	ee upon reaction completion
1	Boc-Phe-OMe	100	100
2	11	92	92

As shown in Table 6, after being subjected to the reaction conditions, both Boc-Phe-OMe and **11** showed no degradation in enantiopurity. It can, therefore, be inferred that the observed level of racemisation in the reaction occurs at the point of nucleophilic attack of the amine to the activated ester species.

Having developed optimum conditions providing excellent levels of stereoretention, a range of α -chiral esters were prosecuted to validate the generality of the transformation (Scheme 6).

**Scheme 6.** Substrate scope of enantiopure esters.

Pleasingly, good to excellent levels of stereoretention were observed across the range of α -chiral esters subjected to the optimised conditions. Amino acid derived amides (**59-61**) were successfully synthesised in moderate yield. Incorporation of a hydroxyl group in the alpha position was also tolerated without significant deterioration in the observed enantiomeric excess, with the corresponding α -hydroxy amides obtained in moderate to good yields (**62-64**). A dioxolane containing ester was successfully coupled, furnishing the desired amide in excellent yield and stereoretention (**65**). Ibuprofen was also

successfully utilised as a substrate, however the corresponding amide was obtained in poor yield but with good retention of enantiopurity.

Conclusions

In summary, we have successfully developed a novel organocatalysed approach to amide bond formation, from readily available unactivated ester starting materials. From initial conditions allowing the coupling of primary and cyclic secondary amines, further tuning of reaction conditions allowed the process to be optimised for secondary amines which had previously proven intractable. A range of tertiary amides were then successfully synthesised, with the process tolerant to various functionalities. The original conditions were also successfully adapted *via* alteration of the additive and base from TFE/ K_3PO_4 to 4-(trifluoromethyl)phenol/KOAc, which successfully incorporated the application of alpha chiral esters to our amidation protocol. Corresponding chiral amides were synthesised accordingly with good to excellent retention of chiral integrity observed.

Experimental Section

General Methods. All reagents and solvents were used as obtained unless otherwise stated. Purification was carried out according to standard laboratory methods.³⁵ BEMP was purified by vacuum distillation from CaH_2 and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under nitrogen. Reactions were carried out under Schlenk conditions using oven-dried glassware, which was evacuated and purged with N_2 before use. Thin layer chromatography was carried out using aluminum-backed silica plates which were analysed under 254 nm UV light or developed using potassium permanganate solution. Flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel. 1H NMR spectra were recorded at 400 or 500 MHz, and ^{13}C NMR spectra were recorded at 101 or 126 MHz. Chemical shifts are reported in ppm, and coupling constants are reported in hertz with $CDCl_3$ referenced at 7.26 (1H) and 77.16 ppm (^{13}C), and DMSO referenced at 2.50 (1H) and 39.52 ppm (^{13}C). Variable temperature NMR experiments were performed at 400 MHz (1H) and 126 MHz (^{13}C) at 298 or 333K. Mass spectrometry data was generated using a TOF analyzer. Optical rotations were measured at 589 nm, with concentrations reported in grams per 100 mL. Conversions were determined by HPLC using caffeine as an internal standard. Chiral HPLC data was obtained on an Agilent 1260 Infinity HPLC using a Chiralpak IA column. The data for products 2 – 20 were reported in our earlier communication.²⁷

General Method for for Chiral Secondary Amide Substrate Scope

To an oven-dried, purged and sealed Schlenk tube containing 4-(trifluoromethyl)phenol (46 mg, 0.28 mmol, 0.2 equiv.), KOAc (139 mg, 1.42 mmol, 1 equiv.), ester (1.42 mmol, 1 equiv.) and THF (700 μL) was added benzylamine (155 μL , 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4 , and concentrated to a residue in vacuo which was purified by silica gel chromatography (MeOH/ CH_2Cl_2 or Acetone/Pet. Ether 40 – 60 °C).

General Method for Tertiary Amide Ester Substrate Scope

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (20 μ L, 0.28 mmol, 0.2 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and 1,4-Dioxane (700 μ L) was added ester (1.42 mmol, 1 equiv.) and the reaction heated at 125 $^{\circ}C$ for 30 min. *N*-methylbenzylamine (183 μ L, 1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at 125 $^{\circ}C$ for a further 22 h. Reaction was then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4 , and concentrated to a residue in vacuo which was purified by silica gel chromatography (MeOH/ CH_2Cl_2).

N-benzyl-*N*-methylbenzamide (23).³⁶ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (226 mg, 71%): ν_{max} (neat) 3060, 3029, 2921, 1629, 1398, 1264, 1068, 698 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 7.45 – 7.42 (m, 5H), 7.39 – 7.36 (m, 2H), 7.29 (t, $J = 7.2$ Hz, 3H), 4.60 (s, 2H), 2.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 172.4, 171.7, 137.2, 136.7, 136.4, 129.7, 128.9, 128.5, 128.3, 127.7, 127.1, 126.9, 55.3, 50.9, 37.1, 33.3 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{15}H_{16}NO$ 226.1226, found 226.1224.

N-benzyl-*N*-methyl-4-(trifluoromethyl)benzamide (24).³⁷ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (386 mg, 93%): ν_{max} (neat) 3066, 3032, 2926, 1634, 1407, 1325, 1167, 1109, 1072, 852, 700 cm^{-1} ; 1H NMR (500 MHz, 333 K, DMSO-*d*6): δ_H 7.79 (d, $J = 7.5$ Hz, 2H), 7.66 (d, $J = 7.7$ Hz, 2H), 7.39 – 7.28 (m, 5H), 4.69 – 4.44 (m, 2H), 2.85 (s, 3H); ^{13}C NMR (126 MHz, 333 K, DMSO-*d*6): δ_C 169.0, 140.3, 136.8, 129.5 (q, $^2J_{CF} = 32.0$ Hz), 128.4, 127.3, 127.0, 125.1 (q, $^3J_{CF} = 3.6$ Hz), 123.7 (q, $^1J_{CF} = 272.4$ Hz), 53.8, 49.8, 36.4, 32.5 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{16}H_{15}F_3NO$ 294.1100, found 294.1096.

N-benzyl-4-cyano-*N*-methylbenzamide (25).³⁸ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (153 mg, 43%): ν_{max} (neat) 3060, 3030, 2924, 2230, 1632, 1402, 1264, 1070, 850, 700 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 7.89 (d, $J = 7.9$ Hz, 2H), 7.62 (d, $J = 7.9$ Hz, 2H), 7.39 – 7.28 (m, 5H), 4.66 (s, 2H), 2.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 170.4, 169.7, 140.8, 140.7, 136.6, 136.0, 132.5, 129.2, 129.0, 128.4, 128.1, 127.9, 127.8, 127.6, 126.6, 118.2, 113.6, 55.1, 51.0, 36.9, 33.5 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{16}H_{15}N_2O$ 251.1179, found 251.1178.

N-benzyl-4-chloro-*N*-methylbenzamide (26).³⁷ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow solid (229 mg, 62%): ν_{max} (neat) 3055, 3030, 2913, 1632, 1409, 1087, 1074, 1016, 843, 739, 698 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 7.50 – 7.45 (m, 4H), 7.39 – 7.35 (m, 2H), 7.31 – 7.27 (m, 3H), 4.59 (s, 2H), 2.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 171.3, 170.7, 136.9, 136.5, 135.9, 134.7, 128.9, 128.7, 128.5, 128.4, 127.8, 126.7, 55.3, 51.1, 37.1, 33.5 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{15}H_{15}ClNO$ 260.0837, found 260.0831.

N-benzyl-4-methoxy-*N*-methylbenzamide (28).³⁹ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (258 mg, 71%): ν_{max} (neat) 2958, 2919, 2839, 1625, 1608, 1396, 1249, 1174, 1029, 841, 700 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 7.43 – 7.35 (m, 4H), 7.30 – 7.26 (m, 3H), 6.99 – 6.96 (m, 2H), 4.60 (s, 2H), 3.80 (s, 3H), 2.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 171.8, 160.8, 137.2, 129.1, 128.9, 128.4, 127.6, 126.9, 113.8, 55.4, 51.2, 37.3, 33.6 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1325.

N-benzyl-3-methoxy-*N*-methylbenzamide (29).³⁸ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (338 mg, 93%): ν_{max} (neat) 3062, 3029, 3004, 2935,

2835, 1630, 1580, 1398, 1269, 1042, 750, 698 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 7.39 – 7.27 (m, 6H), 7.01 – 6.95 (m, 3H), 4.58 (s, 2H), 3.76 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 159.7, 129.7, 128.9, 128.3, 127.7, 126.8, 119.2, 119.0, 115.9, 115.5, 112.6, 112.1, 55.4, 50.9, 37.1, 33.4 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1328.

N-benzyl-2-methoxy-*N*-methylbenzamide (30). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (78 mg, 21%): ν_{max} (neat) 3062, 3029, 3004, 2922, 2837, 1629, 1601, 1400, 1247, 1024, 754, 700 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 7.42 – 6.95 (m, 9H), 4.69 (s, 1H), 4.30 (s, 1H), 3.83 (s, 2H), 3.78 (s, 1H), 2.88 (s, 1H), 2.68 (s, 2H) (mixture of rotamers); ^{13}C NMR (101 MHz, 333 K, DMSO-*d*6): δ_C 168.2, 154.7, 137.1, 136.7, 129.9, 128.2, 127.4, 127.1, 127.0, 126.8, 126.7, 126.2, 120.5, 120.3, 111.4, 55.4, 55.2, 53.3, 49.1, 35.1, 31.6 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1330.

N-benzyl-*N*-methylnicotinamide (31). Purified by silica gel chromatography (2% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (166 mg, 52%): ν_{max} (neat) 3026, 2919, 1627, 1400, 1074, 1026, 734, 699 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 8.64 (d, $J = 5.4$ Hz, 2H), 7.86 (d, $J = 7.3$ Hz, 1H), 7.47 – 7.28 (m, 6H), 4.62 (s, 2H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 169.8, 169.1, 150.9, 148.1, 147.9, 136.7, 136.1, 135.1, 134.8, 132.2, 129.1, 129.0, 128.4, 127.9, 126.7, 123.5, 55.3, 51.1, 37.1, 33.7 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{14}H_{15}N_2O$ 227.1179, found 227.1173.

N-benzyl-*N*-methyl-2-phenylacetamide (33).³⁷ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (336 mg, 99%): ν_{max} (neat) 3062, 3029, 2921, 1640, 1400, 1109, 731, 698 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 7.31 – 7.20 (m, 10H), 4.62 (s, 1H), 4.53 (s, 1H), 3.77 (s, 2H), 2.94 (s, 2H), 2.82 (s, 1H) (mixture of rotamers); ^{13}C NMR (101 MHz, 333 K, DMSO-*d*6): δ_C 170.2, 137.5, 135.5, 128.7, 128.1, 127.9, 127.2, 126.7, 126.0, 52.6, 49.9, 34.8; HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{16}H_{18}NO$ 240.1383, found 240.1382.

N-benzyl-*N*-methyl-2-(pyridin-2-yl)acetamide (34). Purified by silica gel chromatography (2% MeOH/ CH_2Cl_2), affording the title compound as an orange oil (293 mg, 87%): ν_{max} (neat) 3060, 3029, 3008, 2924, 1642, 1435, 1400, 1111, 756, 733, 700 cm^{-1} ; 1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_H 8.49 (s, 1H), 7.73 (t, $J = 6.8$ Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 3H), 7.24 (d, $J = 7.0$ Hz, 3H), 4.69 (s, 1H), 4.54 (s, 1H), 3.94 (s, 1H), 3.91 (s, 1H), 2.99 (s, 2H), 2.82 (s, 1H) (mixture of rotamers); ^{13}C NMR (101 MHz, 333 K, DMSO-*d*6): δ_C 169.5, 156.0, 148.6, 136.0, 128.3, 128.1, 127.2, 126.9, 126.6, 126.4, 123.5, 121.4, 52.7, 49.9, 42.6, 35.0, 33.1 (mixture of rotamers); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{15}H_{17}N_2O$ 241.1335, found 241.1335.

General Method for Tertiary Amide Amine Substrate Scope

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (20 μ L, 0.28 mmol, 0.2 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and 1,4-Dioxane (700 μ L) was added methyl benzoate (178 μ L, 1.42 mmol, 1 equiv.) and the reaction heated at 125 $^{\circ}C$ for 30 min. Amine (1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at 125 $^{\circ}C$ for a further 22 h. Reaction was then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4 , and concentrated to a residue in vacuo which was purified by silica gel chromatography (MeOH/ CH_2Cl_2).

N-(2-methoxybenzyl)-*N*-methylbenzamide (39). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow solid (113 mg, 31%): ν_{max} (neat) 3017, 2924, 2842, 1629,

1241, 1024, 756, 728 cm^{-1} ; ^1H NMR (500 MHz, 333 K, DMSO-*d*6): δ_{H} 7.42 (s, 5H), 7.30 – 7.26 (m, 1H), 7.18 (s, 1H), 7.01 – 6.96 (m, 2H), 4.54 (s, 2H), 3.76 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.7, 171.7, 136.8, 136.6, 129.6, 129.3, 128.8, 128.4, 127.8, 127.0, 120.8, 120.7, 110.4, 55.5, 55.2, 50.7, 45.5, 37.5, 33.4 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$ 256.1332, found 256.1332.

N-methyl-*N*-phenethylbenzamide (40).⁴⁰ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (271 mg, 80%): ν_{max} (neat) 3060, 3027, 2928, 1629, 1400, 1070, 700 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.43 – 7.38 (m, 3H), 7.28 – 7.19 (m, 7H), 3.54 (s, 2H), 2.86 (s, 5H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.3, 171.4, 139.2, 138.0, 136.7, 129.5, 129.3, 129.0, 128.9, 128.7, 128.4, 127.0, 126.6, 53.1, 49.5, 38.4, 34.9, 33.6, 33.2 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{NO}$ 240.1383, found 240.1379.

N-methyl-*N*-(3-phenylpropyl)benzamide (41). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as an orange oil (121 mg, 34%): ν_{max} (neat) 3060, 3027, 2930, 2861, 1629, 1400, 1072, 700 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.42 – 7.37 (m, 3H), 7.35 – 7.33 (m, 2H), 7.27 – 7.23 (m, 2H), 7.18 – 7.14 (m, 2H), 3.35 (s, 2H), 2.92 (s, 3H), 2.54 (s, 4H), 1.87 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.1, 171.5, 141.8, 140.9, 136.8, 129.5, 128.6, 128.5, 128.2, 127.0, 126.7, 126.2, 51.0, 47.4, 37.6, 33.4, 32.9, 32.8, 29.9, 28.8 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{20}\text{NO}$ 254.1539, found 254.1533.

N-methyl-*N*-(pyridin-2-ylmethyl)benzamide (43).⁴¹ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (190 mg, 59%): ν_{max} (neat) 3058, 3010, 2926, 1629, 1398, 1072, 702 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 8.57 – 8.55 (m, 1H), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H), 7.44 (s, 5H), 7.31 – 7.28 (m, 2H), 4.66 (s, 2H), 2.95 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.7, 171.7, 157.3, 156.9, 150.0, 149.4, 137.0, 130.2, 129.8, 128.5, 127.2, 127.0, 122.6, 122.3, 121.0, 57.1, 53.1, 38.0, 33.8 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}$ 227.1179, found 227.1175.

N-(furan-2-ylmethyl)-*N*-methylbenzamide (45). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a brown oil (183 mg, 60%): ν_{max} (neat) 3116, 3060, 2922, 1630, 1400, 1068, 1014, 700 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.60 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.47 – 7.40 (m, 5H), 6.43 (dd, *J* = 3.2, 1.9 Hz), 6.35 (s, 1H), 4.54 (s, 2H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.2, 171.5, 150.9, 150.3, 142.8, 142.5, 136.2, 129.3, 128.5, 127.2, 110.5, 108.8, 108.6, 48.5, 43.8, 37.3, 33.0 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_2$ 216.1019, found 216.1016.

N-(cyclohexylmethyl)-*N*-methylbenzamide (48). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (83 mg, 25%): ν_{max} (neat) 2921, 2850, 1629, 1448, 1402, 1288, 1070, 700 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.44 – 7.40 (m, 3H), 7.35 – 7.32 (m, 2H), 3.23 (s, 2H), 2.90 (s, 3H), 1.70 – 1.55 (m, 7H), 1.22 – 1.17 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3): δ_{C} 172.5, 171.8, 167.7, 137.2, 137.1, 135.1, 131.4, 129.4, 129.2, 128.7, 128.5, 127.2, 127.0, 57.7, 53.7, 46.4, 38.5, 38.2, 36.5, 36.0, 33.3, 31.1, 30.9, 30.6, 26.6, 26.5, 26.4, 26.1, 26.0, 25.9 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{22}\text{NO}$ 232.1696, found 232.1693.

N-(2,2-dimethoxyethyl)-*N*-methylbenzamide (49). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (314 mg, 99%): ν_{max} (neat) 2935, 2835, 1632, 1400, 1126, 1072, 1027, 702 cm^{-1} ; ^1H NMR (500 MHz, 333 K,

DMSO-*d*6): δ_{H} 7.44 – 7.43 (m, 3H), 7.38 7.36 (m, 2H), 4.56 (s, 1H), 3.44 (s, 2H), 3.30 (s, 6H), 2.96 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ_{C} 172.6, 171.8, 136.5, 129.7, 128.5, 127.1, 103.5, 103.1, 54.8, 53.2, 50.0, 39.6, 34.5 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3$ 224.1281, Found 224.1281.

General Method for Tertiary Amide Substrate Scope Using a Full Equivalent of TFE

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (100 μL , 1.42 mmol, 1 equiv.), K_3PO_4 (301 mg, 1.42 mmol, 1 equiv.) and 1,4-Dioxane (700 μL) was added ester (1.42 mmol, 1 equiv.) and the reaction heated at 125 $^\circ\text{C}$ for 30 min. Amine (1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at 125 $^\circ\text{C}$ for a further 22 h. Reaction was then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4 , and concentrated to a residue in vacuo which was purified by silica gel chromatography (MeOH/ CH_2Cl_2).

N-benzyl-*N*-methylfuran-2-carboxamide (32).³⁷ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as an orange oil (304 mg, 99%): ν_{max} (neat) 3112, 3062, 3030, 2922, 1621, 1493, 1400, 1070, 746, 700 cm^{-1} ; ^1H NMR (500 MHz, 333 K, DMSO-*d*6): δ_{H} 7.80 (s, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.28 (dd, *J* = 10.1, 7.7 Hz, 3H), 7.00 (s, 1H), 6.60 (dd, *J* = 3.1, 1.6 Hz, 1H), 4.72 (s, 2H), 3.06 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3): δ_{C} 160.6, 148.1, 144.1, 137.0, 128.8, 128.3, 127.6, 127.1, 116.6, 111.4, 54.3, 52.0, 35.9, 34.4 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_2$ 216.1019, found 216.1015.

N-methyl-*N*-(thiophen-2-ylmethyl)benzamide (44). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (304 mg, 92%): ν_{max} (neat) 3062, 2924, 1629, 1398, 1068, 700 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.47 – 7.40 (m, 6H), 7.04 (s, 1H), 7.00 (dd, *J* = 5.1, 3.4 Hz, 1H) 4.74 (s, 2H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 174.1, 139.8, 136.2, 128.6, 127.1, 126.1, 125.7, 50.6, 45.9, 37.0, 32.9 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{NOS}$ 232.0791, found 232.0787.

N-benzyl-4-fluoro-*N*-methylbenzamide (50).³⁹ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (200 mg, 58%): ν_{max} (neat) 3064, 3029, 2922, 1630, 1604, 1400, 1225, 1068, 847, 700 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.53 – 7.49 (m, 2H), 7.39 – 7.35 (m, 2H), 7.31 – 7.22 (m, 5H), 4.60 (s, 2H), 2.87 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 170.7, 163.5 (d, $^1J_{\text{CF}}$ = 249.5 Hz), 137.0, 136.7, 132.4, 129.4, 129.0, 128.4, 127.8, 126.7, 115.6 (d, $^2J_{\text{CF}}$ = 21.8 Hz), 55.4, 51.1, 37.2, 33.6; HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{15}\text{FNO}$ 244.1132, found 244.1127.

N-benzyl-*N*,6-dimethylnicotinamide (51). Purified by silica gel chromatography (2% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (181 mg, 53%): ν_{max} (neat) 3030, 2922, 1629, 1599, 1402, 1074, 754, 700 cm^{-1} ; ^1H NMR (500 MHz, 333 K, DMSO-*d*6): δ_{H} 8.53 (s, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.29 (m, 4H), 4.62 (s, 2H), 2.90 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 170.1, 169.4, 160.1, 147.6, 147.3, 136.7, 136.2, 135.5, 135.2, 129.2, 129.0, 128.9, 128.3, 127.8, 126.6, 123.0, 55.3, 51.1, 37.1, 33.6, 24.5 (mixture of rotamers); HRMS (ESI) *m/z*: $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}$ 241.1335, found 241.1330.

N-benzyl-*N*-methylpyrazine-2-carboxamide (52). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (130 mg, 40%): ν_{max} (neat) 3058, 3025, 2924, 1632, 1085, 1019, 701 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 8.87 (d, *J* = 13.8 Hz, 1H), 8.72 (d, *J* = 9.9 Hz, 1H), 8.66 (d, *J* =

14.0 Hz, 1H), 7.37 – 7.26 (m, 5H), 4.73 (s, 1H), 4.60 (s, 1H), 2.96 (s, 1H), 2.93 (s, 2H) (mixture of rotamers); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 167.1, 166.8, 150.0, 149.9, 145.7, 145.6, 145.4, 142.7 (2), 136.5, 136.4, 128.9, 128.4, 128.0, 127.8, 127.5, 54.8, 51.6, 36.6, 33.8 (mixture of rotamers); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{12}\text{N}_3\text{O}$ 226.0986, found 226.0976.

N-benzyl-*N*-methyl-1*H*-pyrrole-2-carboxamide (53).⁴² Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as an orange solid (218 mg, 71%): ν_{max} (neat) 3231, 1589, 1400, 1134, 788, 730, 721, 691 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 11.31 (s, 1H), 7.38 – 7.26 (m, 5H), 6.90 (td, $J = 2.7, 1.4$ Hz, 1H), 6.48 (s, 1H), 6.11 (dt, $J = 3.6, 2.5$ Hz, 1H) 4.75 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 163.0, 137.3, 128.9, 127.5, 121.5, 112.8, 109.8, 52.5, 36.2 (mixture of rotamers); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}$ 215.1179, Found 215.1179.

N-benzyl-*N*-methylthiophene-2-carboxamide (54). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (313 mg, 95%): ν_{max} (neat) 3086, 3029, 2921, 1608, 1396, 1029, 700 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.74 (dd, $J = 5.0, 1.1$ Hz, 1H), 7.44 (d, $J = 3.0$ Hz, 1H), 7.41 – 7.36 (m, 2H), 7.31 – 7.27 (m, 3H), 7.10 (dd, $J = 5.0, 3.7$ Hz, 1H), 4.73 (s, 2H), 3.08 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 164.9, 137.9, 136.9, 129.2, 129.0, 127.7, 126.9, 53.5, 35.7; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{NOS}$ 232.0791, found 232.0786

tert-butyl (2-(benzyl(methyl)amino)-2-oxoethyl)carbamate (55).⁴³ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (152 mg, 38%): ν_{max} (neat) 3406, 2978, 2934, 1711, 1653, 1368, 1163, 1052, 702 cm^{-1} ; ^1H NMR (500 MHz, 333 K, DMSO-*d*6): δ_{H} 7.33 – 7.22 (m, 5H), 4.52 (s, 2H), 3.85 (d, $J = 4.9$ Hz, 2H), 3.68 (d, $J = 6.2$ Hz, 1H), 2.90 – 2.78 (m, 3H), 1.39 (s, 9H) (mixture of rotamers); ^{13}C NMR (126 MHz, 333 K, DMSO-*d*6): δ_{C} 170.5, 168.7, 155.4, 137.3, 128.4, 128.1, 127.3, 127.0, 126.7, 126.4, 78.0, 77.1, 51.2, 50.2, 41.6, 33.4, 27.9 (mixture of rotamers); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_3$ 279.1703, found 279.1696.

N-benzyl-*N*-methyl-2-(2-oxopyrrolidin-1-yl)acetamide (56). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow solid (216 mg, 62%): ν_{max} (neat) 2954, 2917, 2876, 1684, 1645, 754, 705 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.36 – 7.22 (m, 5H), 4.57 – 4.51 (m, 2H), 4.12 (s, 2H), 3.42 – 3.39 (m, 2H), 2.92 – 2.82 (m, 3H), 2.27 – 2.19 (m, 2H), 1.99 – 1.95 (m, 2H) (mixture of rotamers); ^{13}C NMR (101 MHz, 333 K, DMSO-*d*6): δ_{C} 174.0, 167.1, 128.4, 128.1, 127.3, 126.8, 126.4, 54.5, 51.5, 50.1, 47.0, 43.5, 33.6, 29.7, 17.3 (mixture of rotamers); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_2$ 247.1441, found 247.1445.

N-methyl-*N*-(pyridin-3-ylmethyl)benzamide (57). Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (225 mg, 70%): ν_{max} (neat) 3057, 3030, 2924, 1627, 1400, 1070, 1027, 787, 715, 702 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 8.51 (dd, $J = 4.7, 1.5$ Hz, 2H), 7.70 (s, 1H), 7.44 (s, 5H), 7.39 (dd, $J = 7.8, 4.8$ Hz, 1H), 4.64 (s, 2H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 171.9, 149.6, 149.2, 148.8, 136.2, 135.9, 134.6, 132.8, 130.0, 128.6, 127.1, 123.9, 52.9, 48.6, 37.2, 33.2 (mixture of rotamers); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}$ 227.1179, found 227.1176.

N-butyl-*N*-methylbenzamide (58).⁴⁴ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (176 mg, 65%): ν_{max} (neat) 2958, 2932, 2872, 1629, 1402, 1072, 702 cm^{-1} ; ^1H NMR (400 MHz, 333 K, DMSO-*d*6): δ_{H} 7.44 – 7.41 (m, 3H), 7.36 – 7.33 (m, 2H), 3.32 (s, 2H), 2.91 (s, 3H), 1.53 (m, 2H), 1.23 (s, 2H), 0.85 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.1, 171.4, 137.0, 129.4, 128.5, 127.0, 126.8, 51.2, 47.3, 37.6,

32.8, 30.5, 29.2, 20.2, 19.7, 14.0, 13.7 (mixture of rotamers); HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}$ 192.1383, found 192.1379.

General Method for for Chiral Secondary Amide Substrate Scope

To an oven-dried, purged and sealed Schlenk tube containing 4-(trifluoromethyl)phenol (46 mg, 0.28 mmol, 0.2 equiv.), KOAc (139 mg, 1.42 mmol, 1 equiv.), ester (1.42 mmol, 1 equiv.) and THF (700 μL) was added benzylamine (155 μL , 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na_2SO_4 , and concentrated to a residue in vacuo which was purified by silica gel chromatography (MeOH/ CH_2Cl_2 or Acetone/Pet. Ether 40 – 60 °C).

benzyl (R)-{(1-(benzylamino)-1-oxopropan-2-yl)carbamate (59).⁴⁵ Purified by silica gel chromatography (0.5% MeOH/ CH_2Cl_2), affording the title compound as a white solid (235 mg, 53%): ν_{max} (neat) 3284, 3060, 3034, 2978, 2932, 1684, 1644, 1526, 1258, 1228, 1048, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.37 – 7.22 (m, 10H), 6.55 (s, 1H), 5.43 (s, 1H), 5.08 – 5.01 (m, 2H), 4.46 – 4.36 (m, 2H), 4.29 – 4.26 (m, 1H), 1.42 – 1.37 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.3, 156.2, 138.0, 136.2, 128.9, 128.7, 128.4, 128.2, 127.8, 127.7, 67.2, 50.8, 43.7, 18.8; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3$ 313.1547, found 313.1545; ee = 100%; $[\alpha]_{\text{D}}^{20}$ -10.2 (c = 1.0, EtOH).

benzyl (S)-{(1-(benzylamino)-4-methyl-1-oxopentan-2-yl)carbamate (60).⁴⁶ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a white solid (262 mg, 52%): ν_{max} (neat) 3315, 3271, 3066, 2958, 2932, 1684, 1645, 1530, 1236, 1055, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.38 – 7.25 (m, 10H), 6.52 (s, 1H), 5.30 (d, $J = 7.7$ Hz, 1H), 5.13 – 5.05 (m, 2H), 4.49 – 4.38 (m, 2H), 4.25 – 4.24 (m, 1H), 1.75 – 1.65 (m, 2H), 1.58 – 1.54 (m, 1H), 0.99 – 0.94 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.2, 156.4, 138.0, 136.2, 128.9, 128.7, 128.4, 128.2, 127.8, 127.7, 67.2, 53.8, 43.7, 41.9, 41.6, 24.8, 23.1, 22.1; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_3$ 355.2016, found 355.2016; ee = 96%; $[\alpha]_{\text{D}}^{20}$ -16.0 (c = 1.2, EtOH), lit $[\alpha]_{\text{D}}^{22}$ -14.1 (c = 1.2, EtOH).

benzyl(S)-{(1-(benzylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (61).⁴⁷ Purified by silica gel chromatography (0.5% MeOH/ CH_2Cl_2), affording the title compound as a white solid (174 mg, 33%): ν_{max} (neat) 3280, 2915, 1690, 1642, 1534, 1256, 1238, 1050, 1029, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.37 – 7.23 (m, 10H), 6.52 (s, 1H), 5.54 (d, $J = 7.2$ Hz, 1H), 5.10 (d, $J = 11.6$ Hz, 2H), 4.49 – 4.35 (m, 3H), 2.61 – 2.45 (m, 2H), 2.15 – 1.95 (m, 6 H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 171.0, 137.9, 128.9, 128.7, 128.4, 128.3, 127.9, 127.8, 67.3, 54.1, 43.8, 31.7, 30.3, 15.3; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3\text{S}$ 373.1580, found 373.1580; ee = 89%; $[\alpha]_{\text{D}}^{20}$ 12.4 (c = 1.0, EtOH).

(R)-N-benzyl-2-hydroxy-2-phenylacetamide (62).⁴⁸ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a white solid (273 mg, 80%): ν_{max} (neat) 3406, 3285, 3183, 1647, 1539, 1455, 1068, 758, 707 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.39 – 7.24 (m, 8H), 7.17 (d, $J = 7.4$ Hz, 2H), 6.67 (s, 1H), 5.02 – 5.01 (m, 1H), 4.44 – 4.34 (m, 2H), 3.89 – 3.86 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ_{C} 172.2, 139.6, 137.8, 128.9, 128.8, 128.8, 127.7,

126.9, 74.3, 43.5; HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{15}H_{16}NO_2$ 242.1176, found 242.1174; ee = 83%; $[\alpha]_D^{20}$ -26.6 ($c = 0.23$, MeOH), lit $[\alpha]_D^{20}$ -5.6 ($c = 0.23$, MeOH).

(*S*)-*N*-benzyl-2-hydroxy-3-phenylpropanamide (63).⁴⁹ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a white solid (241 mg, 67%): v_{max} (neat) 3366, 2919, 1629, 1534, 1091, 1074, 702 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ_H 7.34 – 7.23 (m, 8H), 7.19 (d, $J = 6.8$ Hz, 2H), 6.82 (br. s, 1H), 4.49 – 4.33 (m, 3H), 3.25 (dd, $J = 13.9$, 4.1 Hz, 1H), 2.94 (dd, $J = 13.9$, 8.2 Hz, 1H), 2.70 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 172.6, 138.0, 136.9, 129.7, 128.9, 128.8, 127.9, 127.7, 127.2, 73.0, 43.2, 41.0; HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1333; ee = 98%; $[\alpha]_D^{20}$ -55.7 ($c = 3.4$, EtOAc), lit $[\alpha]_D^{20}$ -44.4 ($c = 3.4$, EtOAc)

(*S*)-*N*-benzyl-2-hydroxypropanamide (64).⁵⁰ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow oil (129 mg, 51%); v_{max} (neat) 3310, 1644, 1532, 1273, 1122, 698 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ_H 7.34 – 7.24 (m, 5H), 7.04 (s, 1H), 4.42 (d, $J = 5.9$ Hz, 2H), 4.24 (qd, $J = 6.8$, 4.8 Hz, 1H), 3.53 (d, $J = 4.7$ Hz, 1H), 1.42 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 174.9, 138.0, 128.8, 127.8, 127.7, 115.7, 68.5, 43.2, 21.4; HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{10}H_{14}NO_2$ 180.1019, found 180.1015; ee = 97%; $[\alpha]_D^{20}$ -4.2 ($c = 0.25$, $CHCl_3$), lit $[\alpha]_D^{26}$ -21.5 ($c = 0.25$, $CHCl_3$)

(*R*)-*N*-benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide (65). Purified by silica gel chromatography (15% acetone/Pet. ether 40 – 60 °C), affording the title compound as an off-white solid (329 mg, 98%): v_{max} (neat) 3332, 2988, 2932, 1649, 1537, 1221, 1029, 839, 735, 702 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ_H 7.36 – 7.32 (m, 2H), 7.30 – 7.26 (m, 3H), 6.89 (br. s, 1H), 4.54 (dd, $J = 7.6$, 5.3 Hz, 1H), 4.48 (d, $J = 6.0$ Hz, 2H), 4.31 (dd, $J = 8.7$, 7.6 Hz, 1H), 4.15 (dd, $J = 8.8$, 5.3 Hz, 1H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 171.2, 137.9, 128.9, 127.7, 127.7, 111.1, 75.21, 67.9, 43.1, 26.3, 25.1; HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{13}H_{18}NO_3$ 236.1281, found 236.1280; ee = 94%; $[\alpha]_D^{20}$ +16.0 ($c = 1.0$, EtOH).

(*S*)-*N*-benzyl-2-(4-isobutylphenyl)propanamide (66).⁵¹ Purified by silica gel chromatography (1% MeOH/ CH_2Cl_2), affording the title compound as a yellow solid (61 mg, 15%): v_{max} (neat) 3299, 3030, 2950, 2921, 2867, 1640, 1537, 1454, 1230, 737, 696 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ_H 7.27 – 7.19 (m, 5H), 7.14 – 7.10 (m, 4H), 6.61 (s, 1H), 4.39 (d, $J = 5.8$ Hz, 2H), 3.58 (q, $J = 7.2$ Hz, 1H), 2.45 (d, $J = 7.2$ Hz, 2H), 1.91 – 1.78 (m, 1H), 1.55 (d, $J = 7.2$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C 174.5, 141.0, 138.6, 138.5, 129.8, 128.7, 127.5, 127.5, 47.0, 45.1, 43.7, 30.3, 22.5, 18.6; HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{20}H_{26}NO$ 296.2009, found 296.2005; ee = 83%; $[\alpha]_D^{20}$ +3.0 ($c = 0.88$, DCM), lit $[\alpha]_D^{25}$ +7.2 ($c = 0.88$, DCM).

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Amidation of Unactivated Ester Derivatives Mediated by Trifluoroethanol

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1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.¹

1.1 Purification of Solvents

- i) Anhydrous THF and toluene were obtained from a PureSolv SPS-400-5 solvent purification system.
- ii) Acetonitrile, 1,2-Dichloroethane, isopropanol and 2-MeTHF were purified by fractional distillation under vacuum from CaH₂; n-butanol was purified by stirring over 4 Å molecular sieves; CPME was purified by vacuum distillation from sodium metal; 1,4-Dioxane was purified by vacuum distillation from LiAlH₄; Dimethyl carbonate was purified by fractional distillation under vacuum from 4 Å molecular sieves; DMF was purified by fractional distillation under vacuum from MgSO₄.
- iii) Purified solvents were transferred to and stored in septum-sealed oven-dried flasks over previously activated 4 Å molecular sieves and purged with and stored under nitrogen.

1.2 Purification of Starting Materials

- i) Methyl benzoate, benzylamine and *N*-methylbenzylamine used for optimisation reactions, were purified by vacuum distillation from KOH; trifluoroethanol, used as an additive, was purified by fractional distillation from Na₂SO₄.
- ii) BEMP was purified by vacuum distillation from CaH₂; Ca₃(PO₄)₂, Cs₂CO₃, Cs₃PO₄, K₂CO₃, KH₂PO₄, K₂HPO₄, K₃PO₄, Li₃PO₄, Mg₃(PO₄)₂ and Na₃PO₄ were stored in a vacuum oven at 60 °C; DABCO was recrystallised from MeOH/diethyl ether (1:1); DBU was purified by fractional distillation under vacuum; Et₃N was purified by fractional distillation under vacuum over CaH₂. Potassium acetate was stored in a desiccator over P₂O₅; KOAc, KOH and KTFA were stored in a desiccator over P₂O₅; KOtBu was purified by sublimation.
- iii) Dichloromethane, ethyl acetate, methanol, and petroleum ether 40–60 °C for purification purposes were used as obtained from suppliers without further purification.

1.3 Experimental Details

- i) All reactions were carried out using oven-dried glassware, which was evacuated and purged with N₂ before use.
- ii) Amidation reactions were performed using 25 mL Schlenk reaction vessels.
- iii) Purging refers to a vacuum/nitrogen-refilling procedure.
- iv) Room temperature was generally ca. 20 °C.
- v) Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.
- vi) Amidation reactions at elevated temperatures were carried out using a STEM heating block.
- vii) Reactions requiring the use of Radleys tubes with elevated temperatures were performed in a carousel resting on a temperature-regulated hotplate/stirrer.

1.4 Purification of Products

- i) Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate solution.
- ii) Flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel.

1.5 Analysis of Products

- i) Fourier Transformed Infra-Red (FTIR) spectra were obtained using an A2 Technologies ATR 32 machine.
- ii) ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX 500 spectrometer at 500 and 126MHz, respectively or on a Bruker AV3 400 at 400 and 101 MHz, respectively, or on a Bruker AVANCE 400 spectrometer at 400 and 101 MHz respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with CDCl_3 referenced at 7.26 (^1H) and 77.16 ppm (^{13}C), and DMSO referenced at 2.50 (^1H) and 39.52 ppm (^{13}C).
- iii) Variable temperature NMR experiments were obtained using a Bruker AVANCE 400 spectrometer at 400 and 100 MHz respectively, or a Bruker DRX 500 spectrometer at 500 and 126MHz, respectively at 333 K.
- iv) High-resolution mass spectra were obtained on a Thermofisher LTQ Orbitrap XL instrument at the EPSRC National Mass Spectrometry Service Centre (NMSSC), Swansea.
- v) Reverse phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column.
- vi) Chiral HPLC data was obtained on an Agilent 1260 Infinity HPLC using a Chiralpak IA column.
- vii) Optical rotations were measured at 589 nm using a Perkin Elmer 341 Polarimeter

1.6 HPLC Methods

- i) For *N*-Benzylbenzylamide **2**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 80% MeCN/ H_2O over 5 minutes at a flow rate of 2 mL/min, with methyl benzoate, 2,2,2-trifluoroethyl benzoate intermediate, *N*-benzylbenzamide product **2**, and iodobenzene internal standard eluting at 2.0, 2.5, 1.9 and 2.9 minutes, respectively

Time (min)	Concentration of MeCN (%)
0	5
1	55
3.9	60
4.1	80
4.3	5
5	5

For *N*-benzyl-*N*-methylbenzamide **23**: Reversed phase HPLC analysis was performed using a gradient method, eluting with 5 – 60% MeCN/ H_2O over 8 minutes at a flow rate of 2 mL/min, with methyl benzoate, *N*-methylbenzylamine, *N*-benzyl-*N*-methylbenzamide product **23**, and caffeine internal standard eluting at 4.7, 1.0, 5.1 and 2.0, respectively.

Time (min)	Concentration of MeCN (%)
0	5
5.5	60
5.8	5
8	5

- ii) For *N*-Benzylbenzylamide **2**: For reactions using an internal standard, prior HPLC calibration was carried out using samples containing varying molarities of product and iodobenzene, allowing calculation of the response factor by substituting values into the following equation:

$$\text{Response Factor} = \frac{\left(\frac{\text{Area}}{\text{Molarity}}\right)_{\text{Product}}}{\left(\frac{\text{Area}}{\text{Molarity}}\right)_{\text{Standard}}}$$

Screening reactions were carried out using a known molarity of iodobenzene internal standard as indicated in the relevant general experimental procedures.

Unknown molarities of product were calculated by rearranging the above equation, using the average value for the response factor as determined during calibration.

Conversion to product was calculated as a percentage of the theoretical molarity for the reaction.

For *N*-benzyl-*N*-methylbenzamide **23**: Conversion factor established by running 3 samples with a ratio of 0.25:1 caffeine:analyte, with the average conversion factor calculated by substituting values for each sample into the following equation:

$$\text{Conversion factor} = \frac{\text{Peak Area Analyte}}{\text{Peak Area Caffeine}}$$

For standard sampling of reaction mixtures, the ratio of Caffeine:Analyte is 0.25:1. Therefore, when calculating the % conversion:

$$\frac{\text{Peak Area Analyte}}{\text{Peak Area Caffeine} \times 4} = X$$

$$\frac{X}{\text{Average Conversion Factor}} = \% \text{ Conversion}$$

- iii) For *N*-Benzylbenzylamide **2**: Samples for HPLC analysis were prepared by diluting a 10 μL aliquot from the reaction mixture to 1 mL with MeCN.

For *N*-benzyl-*N*-methylbenzamide **23**: Samples for HPLC analysis were prepared through the addition of 7 mL of a 0.05 M caffeine standard to the completed reaction mixture. The resulting solution was then stirred before the removal of a 200 μL aliquot. The

aliquot was diluted to 1 mL with MeOH, a 200 μ L aliquot of the diluted solution was then further diluted with 800 μ L MeOH and then filtered for HPLC analysis against established conversion factors.

iv) For compounds **11**, **63**, **64**, **65**, **66** and **72**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 20 minutes with a flow rate of 1 mL/min.

For compound **59**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 5% IPA/hexanes over 1 hour with a flow rate of 1 mL/min.

For compounds **60** and **61**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 1 hour with a flow rate of 1 mL/min.

For compound **62**: Chiral HPLC was performed using an isocratic method, using a Chiralpak IA column, eluting with 10% IPA/hexanes over 40 min with a flow rate of 1 mL/min.

For compounds **69**, **70** and **71**: Chiral HPLC was performed using an isocratic method, using a ChiralpakIA column, eluting with 5% IPA/hexanes over 40 min with a flow rate of 1 mL/min.

The major and minor enantiomers were found to elute as follows:

Product	Major enantiomer retention time (min)	Minor enantiomer retention time (min)
11	8.44	11.78
59	38.34	N/A
60	11.16	17.24
61	24.78	51.32
62	15.34	24.06
63	11.91	10.12
64	9.38	8.87
65	8.79	10.31
66	9.13	16.91
69	34.01	N/A
70	18.17	N/A
71	50.66	N/A
72	9.37	N/A

2. General Experimental Procedures

2.1 General Procedure A for Investigating the Nature of the Base Species

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (20 μ L, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.) and THF (700 μ L) was added methyl benzoate (178 μ L, 1.42 mmol, 1 equiv.) and benzylamine (155 μ L, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to iodobenzene (1.4 M), which was used as an internal standard.

Entry	Base	pKa	Conversion (%)
1	KTFA	0	1
2	KH ₂ PO ₄	2	1
3	KOAc	6	1
4	K ₂ HPO ₄	7	1
5	K ₂ CO ₃	10	2
6	K ₃ PO ₄	12	78
7	KOH	16	5
8	KOtBu	18	47
9	Ca ₃ PO ₄	13	1
10	Cs ₃ PO ₄	13	1
11	Li ₃ PO ₄	13	0
12	Mg ₃ PO ₄	13	16
13	Na ₃ PO ₄	13	1
14	Cs ₂ CO ₃	10	11
15	NMO	7	13
16	DABCO	9	4
17	Et ₃ N	11	1
18	DBU	12	61
19	BEMP	19	8

2.2 General Procedure B for Optimisation of the TFE Mediated Tertiary Amide Formation: Additive Screen

To an oven-dried, purged and sealed Schlenk tube containing additive (0.28 mmol, 0.2 equiv.), K₃PO₄ (301 mg, 1.42 mmol, 1 equiv.) and THF (700 μ L) was added methyl benzoate (178 μ L, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μ L, 1.42 mmol, 1 equiv.) was added and the reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05M caffeine solution.

Entry	Additive	Conversion (%)
1	4-CF ₃ C ₆ H ₄ OH	1
2	HFIP	0

3	HOAt	0
4	HOBt	0
5	HOAt	0
6	N-hydroxysuccinimide	0
7	Oxyma	0
8	2-Picoline <i>N</i> -oxide	0
9	TFE	1

2.3 General Procedure C for Optimisation of the TFE Mediated Tertiary Amide Formation: Base and Solvent Screen

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (20 μ L, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.) and solvent (700 μ L) was added methyl benzoate (178 μ L, 1.42 mmol, 1 equiv.) and *N*-methylbenzylamine (183 μ L, 1.42 mmol, 1 equiv.) was added and the reaction mixture was heated at 90 °C for 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05M caffeine solution.

Entry	Base	Solvent	Conversion (%)
1	DABCO	n-butanol	0
2	K ₃ PO ₄	n-butanol	3
3	DBU	n-butanol	2
4	KOtBu	n-butanol	22
5	DABCO	CPME	0
6	K ₃ PO ₄	CPME	37
7	DBU	CPME	4
8	KOtBu	CPME	96
9	DABCO	DCE	0
10	K ₃ PO ₄	DCE	0
11	DBU	DCE	0
12	KOtBu	DCE	0
13	DABCO	1,4-Dioxane	0
14	K ₃ PO ₄	1,4-Dioxane	12
15	DBU	1,4-Dioxane	3
16	KOtBu	1,4-Dioxane	37
17	DABCO	DMC	0
18	K ₃ PO ₄	DMC	0
19	DBU	DMC	0
20	KOtBu	DMC	0
21	DABCO	DMF	0
22	K ₃ PO ₄	DMF	8
23	DBU	DMF	3
24	KOtBu	DMF	21
25	DABCO	IPA	0
26	K ₃ PO ₄	IPA	9
27	DBU	IPA	2
28	KOtBu	IPA	0
29	DABCO	2-MeTHF	1

30	K ₃ PO ₄	2-MeTHF	43
31	DBU	2-MeTHF	5
32	KOtBu	2-MeTHF	2
33	DABCO	MeCN	0
34	K ₃ PO ₄	MeCN	0
35	DBU	MeCN	4
36	KOtBu	MeCN	32
37	DABCO	THF	2
38	K ₃ PO ₄	THF	1
39	DBU	THF	8
40	KOtBu	THF	56

2.4 General Procedure D for Optimisation of the TFE Mediated Tertiary Amide Formation: Elevated Temperature Screen

To an oven-dried, purged and sealed Schlenk tube containing trifluoroethanol (20 μ L, 0.28 mmol, 0.2 equiv.), K₃PO₄ (301 mg, 1.42 mmol, 1 equiv.) and solvent (700 μ L) was added methyl 4-(trifluoromethyl)benzoate (229 μ L, 1.42 mmol, 1 equiv.) and the reaction heated at the desired temperature for 30 min. *N*-methylbenzylamine (183 μ L, 1.42 mmol, 1 equiv.) was then added and the reaction mixture was heated at the desired temperature for a further 22 h. The reaction mixture was sampled at the end of the required reaction time and the conversion was determined by HPLC with reference to a 0.05M caffeine solution.

Entry	Solvent	Temperature ($^{\circ}$ C)	Conversion (%)
1	THF	90	0
2 ^a	THF	90	70
3 ^{a,b}	THF	90	62
4 ^a	CPME	125	77 ^c
5 ^a	1,4-dioxane	125	93 ^c
6 ^a	2-MeTHF	100	72 ^c
7 ^{a,d}	1,4-dioxane	125	0 ^c
8 ^{a,e}	1,4-dioxane	125	0 ^c
9 ^{a,f}	1,4-dioxane	125	0 ^c

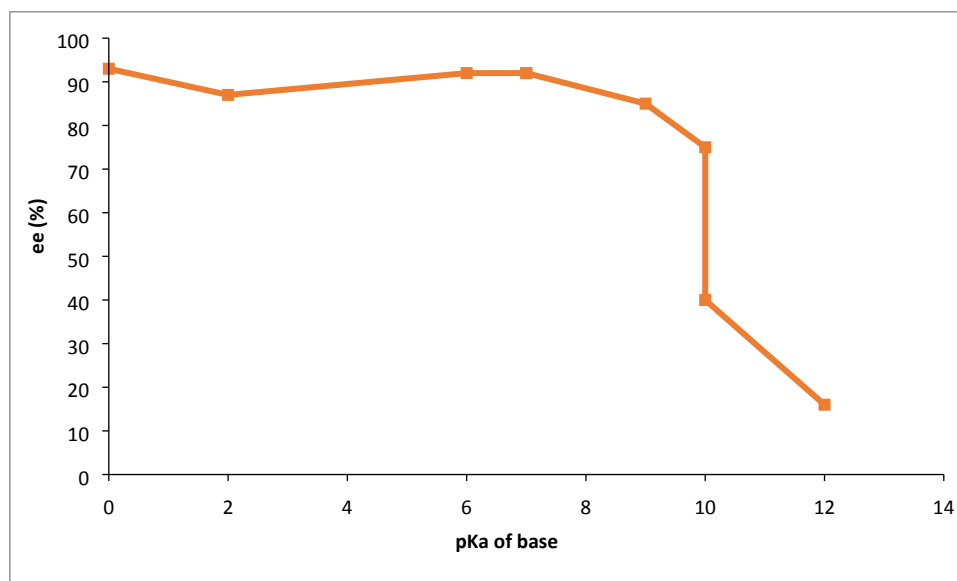
^aPreformation of the active ester intermediate for 30 min at reaction temperature. ^bMethyl benzoate used as ester substrate. ^cIsolated Yield. ^dPerformed in the absence of K₃PO₄. ^ePerformed in the absence of TFE. ^fPerformed in the absence of both K₃PO₄ and TFE.

2.5 General Procedure E for Chiral Secondary Amide Base Screen

To an oven-dried, purged and sealed Schlenk tube containing 4-(trifluoromethyl)phenol (46 mg, 0.28 mmol, 0.2 equiv.), base (1.42 mmol, 1 equiv.), Boc-L-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) and THF (700 μ L) was added benzylamine (155 μ L, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 $^{\circ}$ C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na₂SO₄, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (1% MeOH/CH₂Cl₂).

Entry	Base	Base pKa	Yield (%)	ee (%)
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1	KTFA	0	46	93
2	KH ₂ PO ₄	2	62	87
3	KOAc	6	55	92
4	NMO	7	36	92
5	K ₂ HPO ₄	7	48	92
6	DABCO	9	40	85
7	K ₂ CO ₃	10	46	75
8	Cs ₂ CO ₃	10	34	40
9	DBU	12	69	16



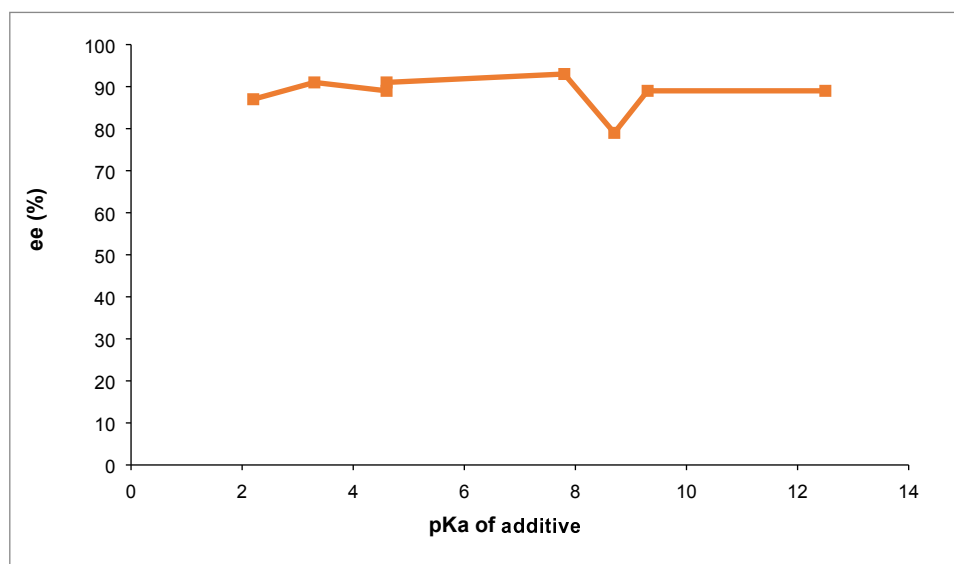
2.6 General Procedure F for Chiral Secondary Amide Additive Screen

To an oven-dried, purged and sealed Schlenk tube containing additive (0.28 mmol, 0.2 equiv.), KOAc (139 mg, 1.42 mmol, 1 equiv.), Boc-L-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) and THF (700 μ L) was added benzylamine (155 μ L, 1.42 mmol, 1 equiv.). The reaction mixture was heated at 90 $^{\circ}$ C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na₂SO₄, and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (1% MeOH/CH₂Cl₂).

Entry	Additive	Additive pKa	Yield (%)	ee (%)
1	Picoline n-oxide	-	28	87
2	HOt	2.2	54	91
3	HOAt	3.3	32	89
4	HOBt	4.6	47	91
5	Oxyma	4.6	50	93
6	NHS	7.8	58	79
7	4-CF ₃ C ₆ H ₄ OH	8.7	55	92
8	HFIP	9.3	35	89
9	TFE	12.5	31	89

10 ^a	4-CF ₃ C ₆ H ₄ OH	8.7	44	92
11	No additive	-	17	89
12 ^a	No additive	-	28	88

^aPerformed in the absence of KOAc



2.8 General Procedure G for Investigating the Point of Racemisation in the Chiral Secondary Amide Methodology.

To an oven-dried, purged and sealed Schlenk tube containing KOAc (1 equiv.), Boc-L-phenylalanine methyl ester (397 mg, 1.42 mmol, 1 equiv.) **or** amide **11** (150 mg, 0.43 mmol, 1 equiv.) was added THF (700/210 μ L respectively). The reaction mixture was heated at 90 °C for 22 h then diluted with EtOAc (10 mL), washed with brine (3 x 10 mL), dried over Na₂SO₄, and concentrated to a residue *in vacuo*. The ee of the resulting products was then determined by HPLC.

Entry	Substrate	Initial ee (%)	ee upon reaction completion (%)
1	Boc-Phe-OMe	100	100
2	11	92	92

2.7 General Procedure H for Synthesis of Secondary Amine Starting Materials

To a round-bottomed flask containing a solution of amine (1 equiv.) in DCM (10 mL) at 0 °C was added Et₃N (2 equiv.) and a solution of di-*tert*-butyl dicarbonate (1.2 equiv.) in DCM (5 mL). Reaction warmed to room temperature and stirred for 16 h, at which point it was washed sequentially with 2M HCl (10 mL), 5% NaHCO₃ (aq) (10 mL) and water (10 mL). Organics dried over Na₂SO₄ and

concentrated to a residue *in vacuo*, to which was added THF (10 mL) and NaH (1.1 equiv.) reaction stirred until effervescence had ceased, at which point methyl iodide (1.2 equiv.) was added and the reaction heated at 45 °C for 72 hours. THF removed *in vacuo*, the resulting crude product dissolved in EtOAc (10 mL), washed with water (3 x 10 mL), dried over Na₂SO₄ and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (5% EtOAc/Pet. ether 40–60 °C).

To a solution of the resulting *N*-methylated Boc-protected amine in DCM (10 mL) was added TFA (10 mL). Reaction stirred at room temperature for 16 h, at which point the reaction mixture was concentrated to a residue *in vacuo*. Resulting crude product dissolved in EtOAc (10 mL) and washed with 2M NaOH (aq) until pH ≥ 9. Organics extracted with EtOAc (3 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo* to afford the desired *N*-methyl amine.

2.8 General Procedure I for Synthesis of Chiral Ester Starting Materials *via* Esterification

To an oven-dried, purged Radleys tube containing carboxylic acid (1 equiv.) was added MeOH (20 mL), and the solution cooled to 0 °C. SOCl₂ (1.2 equiv.) added dropwise and the reaction refluxed for 16 h. Reaction mixture washed with saturated NaHCO₃ (aq) until pH ≥ 8, extracted with DCM (3 x 20 mL), dried over Na₂SO₄ and concentrated to a residue *in vacuo*. Resulting crude product was purified by silica gel chromatography (EtOAc/Pet. ether 40–60 °C).

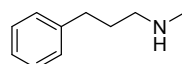
2.9 General Procedure J for Synthesis of Chiral Ester Starting Materials *via* Cbz Protection

To a round-bottomed flask was added ester hydrochloride salt (1 equiv.), *N*-(benzyloxycarbonyloxy)succinimide (1.1 equiv.), NaHCO₃ (2.5 equiv.), THF (7 mL) and water (7 mL). Reaction stirred for 16 h at room temperature, at which point the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). Organics dried over Na₂SO₄ and concentrated to a residue *in vacuo* which was purified by silica gel chromatography (EtOAc/pet. ether 40–60 °C).

3. Characterisation Data

3.1 Characterisation Data for Synthesised Starting Materials

N-methyl-3-phenylpropan-1-amine (67).²



Synthesised according to General Experimental Procedure H using 3.7 mmol of 3-phenylpropan-1-amine, affording the title compound as a pale yellow liquid (372 mg, 67%).

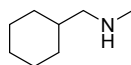
ν_{\max} (neat): 3027, 2932, 2857, 2794, 1673, 1455, 1033, 748, 700 cm⁻¹

¹H NMR (500 MHz, DMSO-*d*₆): δ 7.27, (t, *J* = 7.5 Hz, 2H), 7.17 (dd, *J* = 16.9, 7.5 Hz, 3H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.45 (t, *J* = 7.0 Hz), 1.68 (p, *J* = 7.8 Hz, 5H)

¹³C NMR (126 MHz, DMSO-*d*₆): δ 142.2, 128.2, 128.2, 125.6, 50.9, 36.1, 32.9, 31.0

HRMS m/z : $[M+H]^+$ Calcd for $C_{10}H_{16}N$ 150.1277, Found 150.1275

1-cyclohexyl-*N*-methylmethanamine (68).³



Synthesised according to General Experimental Procedure H using 8.8 mmol of cyclohexylmethanamine, affording the title compound as a pale yellow liquid (404 mg, 36%).

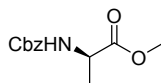
ν_{\max} (neat): 2919, 2850, 2788, 1448, 1126, 1150, 742 cm^{-1}

1H NMR (500 MHz, $CDCl_3$): δ 2.41 (d, J = 9.2 Hz, 4H), 1.74 – 1.64 (m, 5H), 1.49 – 1.42 (m, 2H), 1.28 – 1.10 (m, 3H), 0.95 – 0.87 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 54.3, 44.4, 35.5, 34.4, 33.2, 29.7, 29.7, 25.6, 25.6, 25.0, 25.0

HRMS m/z : $[M+H]^+$ Calcd for $C_8H_{18}N$ 128.1434, Found 128.1429

Methyl ((benzyloxy)carbonyl)-*D*-alaninate (69).⁴



Synthesised according to General Experimental Procedure J, using 3.58 mmol of methyl *D*-alaninate hydrochloride, and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (581 mg, 68%).

ν_{\max} (neat): 3336, 3036, 2993, 2958, 1753, 1684, 1526, 1215, 1174, 1076, 754, 702 cm^{-1}

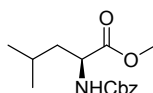
1H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 5H), 5.31 (s, 1H), 5.11 (m, 2H), 4.40 (p, J = 7.2 Hz, 1H), 3.75 (s, 3H), 1.42 (d, J = 7.2 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6, 155.7, 136.4, 128.6, 128.3, 128.2, 67.0, 52.5, 49.7, 18.8

HRMS m/z : $[M+H]^+$ Calcd for $C_{12}H_{16}NO_4$ 238.1074, Found 238.1076

ee = 100%

Methyl ((benzyloxy)carbonyl)-*L*-leucinate (70).⁵



Synthesised according to General Experimental Procedure J, using 2.75 mmol of methyl *L*-leucinate hydrochloride, and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a colourless oil (683 mg, 89%).

ν_{\max} (neat): 3339, 2956, 1699, 1526, 1262, 1208, 1171, 1046, 739, 700 cm^{-1}

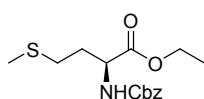
^1H NMR (500 MHz, CDCl_3): δ 7.36 – 7.30 (m, 5H), 5.12 (m, 3H), 4.4 (dd, J = 13.8, 8.8 Hz, 1H), 3.74 (s, 3H), 1.74 – 1.61 (m, 2H), 1.55 – 1.49 (m, 1H), 0.94 (m, 6H)

^{13}C NMR (126 MHz, CDCl_3): δ 173.8, 156.1, 136.4, 128.7, 128.3, 128.3, 67.1, 52.6, 52.4, 24.9, 23.0, 22.0

HRMS m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_4$ 280.1543, Found 280.1541

ee = 100%

ethyl ((benzyloxy)carbonyl)-*L*-methioninate (71).⁶



Synthesised according to General Experimental Procedure J, using 2.81 mmol of methyl *L*-methioninate hydrochloride, and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (629 mg, 72%).

ν_{\max} (neat): 3326, 2980, 2917, 1705, 1521, 1210, 1046, 1029, 700 cm^{-1}

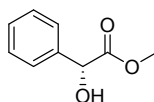
^1H NMR (500 MHz, CDCl_3): δ 7.36 – 7.29 (m, 5H), 5.42 (s, 1H), 5.11 (s, 2H), 4.48 (dd, J = 12.7, 7.6 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.58 – 2.47 (m, 2H), 2.20 – 2.09 (m, 4H), 1.96 (td, J = 14.4, 7.5 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H)

^{13}C NMR (126 MHz, CDCl_3): δ 172.1, 156.0, 136.3, 128.7, 128.3, 128.3, 67.2, 61.8, 53.4, 32.2, 30.0, 15.6, 14.3

HRMS m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_4\text{S}$ 312.1264, Found 312.1261

ee = 100%

Methyl (*R*)-2-hydroxy-2-phenylacetate (72).⁷



Synthesised according to General Experimental Procedure I, using 4.93 (mmol) of (*R*)-2-hydroxy-2-phenylacetic acid, and purified by flash column chromatography (20% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a colourless oil (643 mg, 80%).

ν_{\max} (neat): 3434, 1738, 1206, 1191, 1068, 977, 739, 696 cm^{-1}

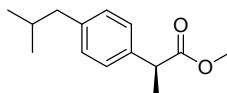
^1H NMR (400 MHz, CDCl_3): δ 7.43 – 7.31 (m, 5H), 5.18 (d, J = 5.3 Hz, 1H), 3.76 (d, J = 1.7 Hz, 3H), 3.49 – 3.43 (m, 1H)

^{13}C NMR (101 MHz, CDCl_3): δ 174.3, 138.4, 128.8, 128.7, 126.7, 73.0, 53.2

HRMS m/z : $[M+H]^+$ Calcd for $C_9H_{11}O_3$ 167.0703, Found 167.0701

ee = 100%

Methyl (S)-2-(4-isobutylphenyl)propanoate (73).⁸



Synthesised according to General Experimental Procedure I, using 3.64 mmol of (S)-2-(4-isobutylphenyl)propanoic acid, and purified by flash column chromatography (10% EtOAc/Pet. ether 40 – 60 °C) to afford the title compound as a pale yellow oil (583 mg, 73%).

ν_{\max} (neat): 2954, 2870, 1738, 1206, 1163, 1066 cm^{-1}

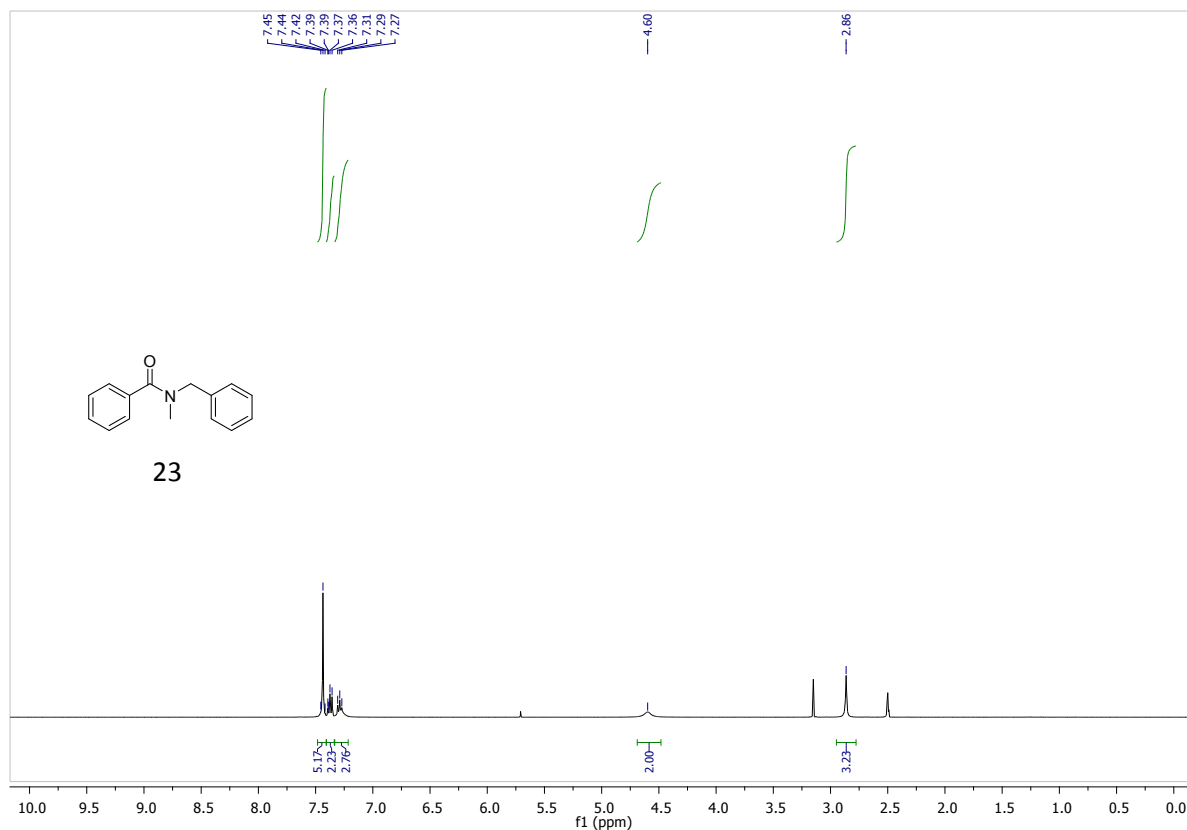
1H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.18 (m, 2H), 7.11 – 7.09 (m, 2H), 3.70 (q, J = 7.2 Hz, 1H), 3.66 (s, 3H), 2.45 (d, J = 7.2 Hz, 2H), 1.92 – 1.76 (m, 1H), 1.49 (d, J = 7.2 Hz, 3H), 0.90 (d, J = 6.6 Hz, 6H)

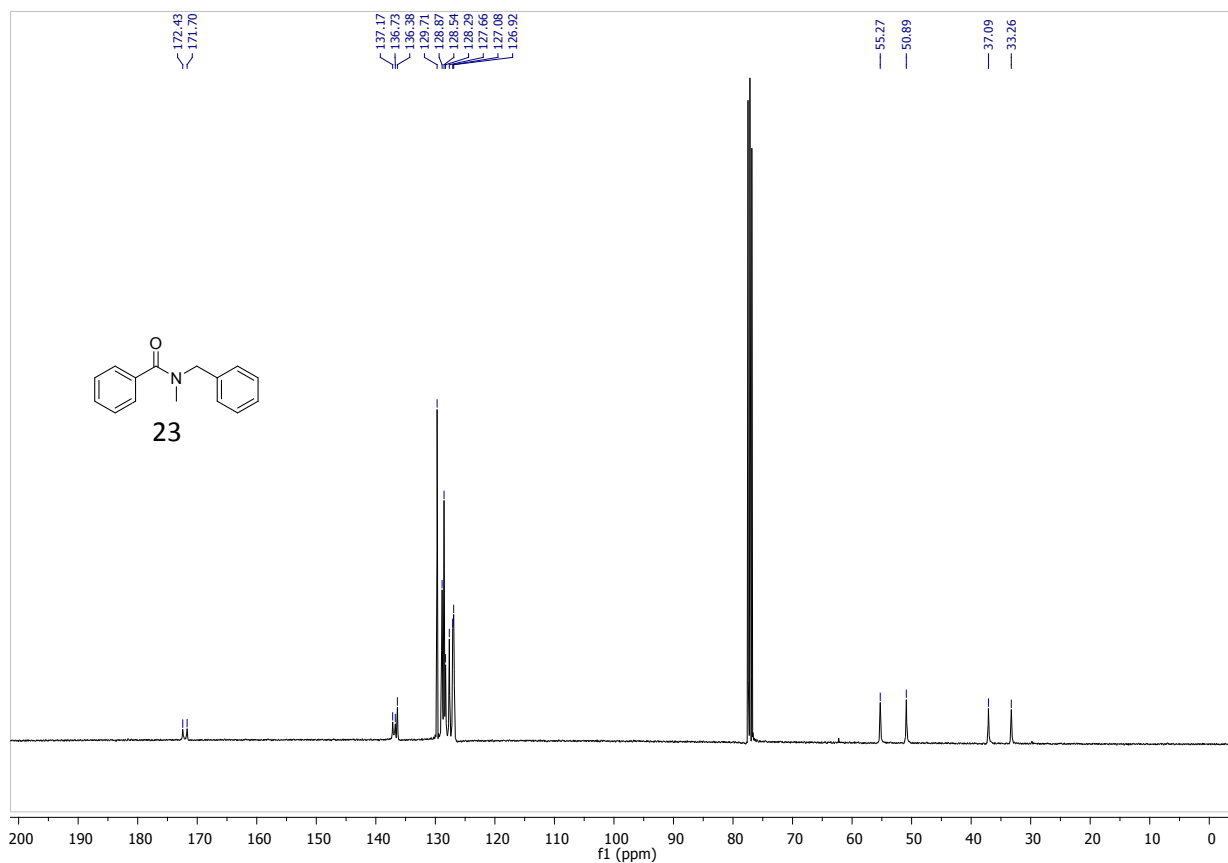
^{13}C NMR (101 MHz, $CDCl_3$): δ 175.4, 140.7, 137.9, 129.5, 127.3, 52.1, 45.2, 30.3, 22.5, 18.8

HRMS m/z : $[M+H]^+$ Calcd for $C_{14}H_{21}O_2$ 221.1536, Found 221.15

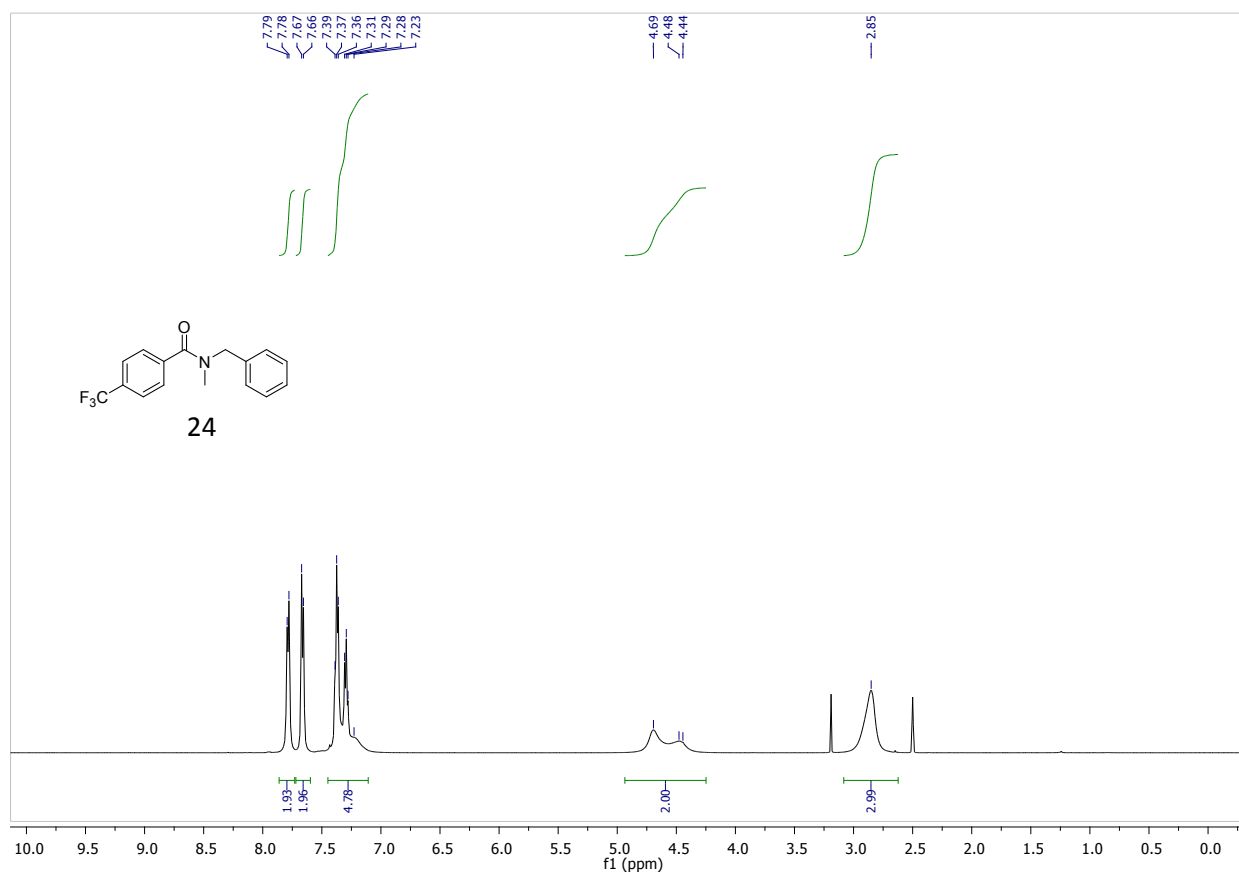
4. 1H and ^{13}C Spectra for Exemplified Compounds

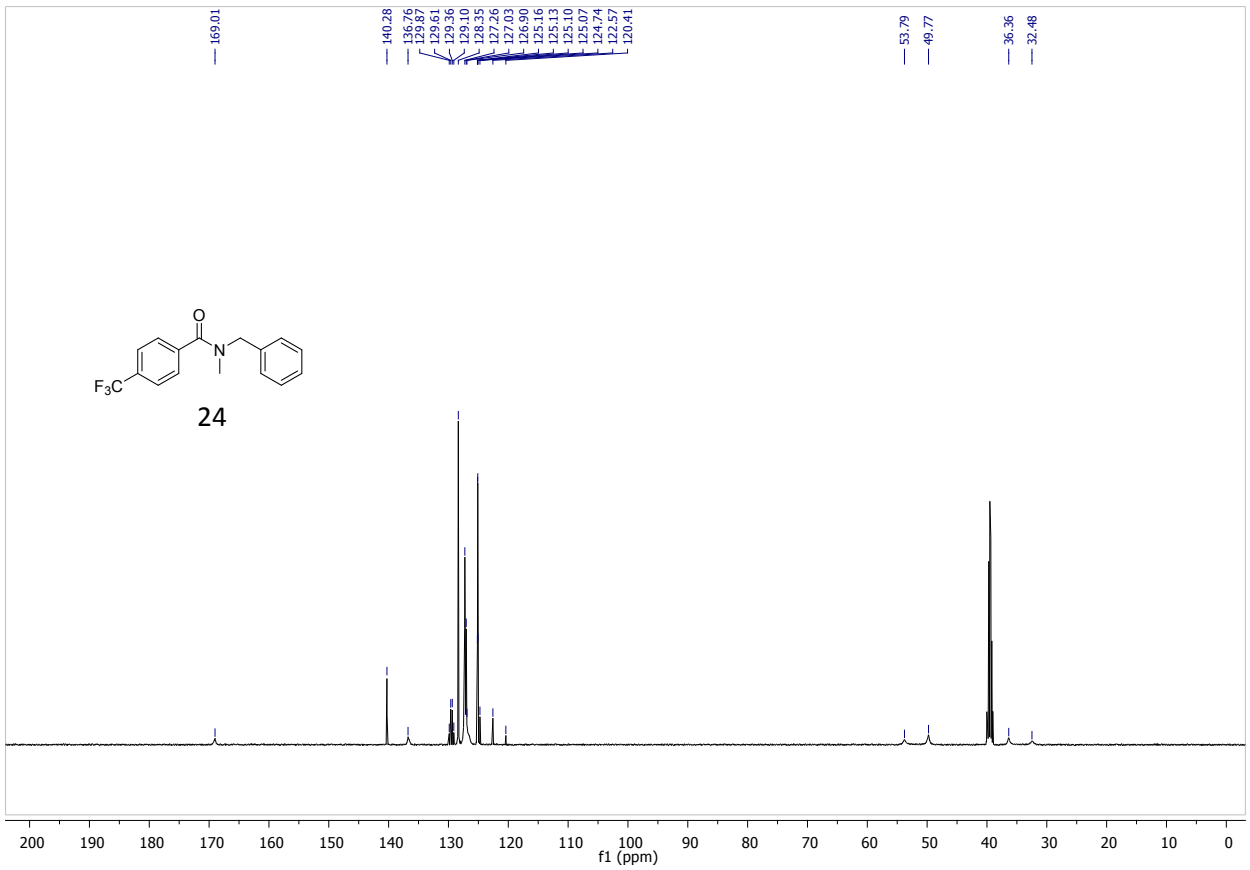
N-benzyl-*N*-methylbenzamide (23).



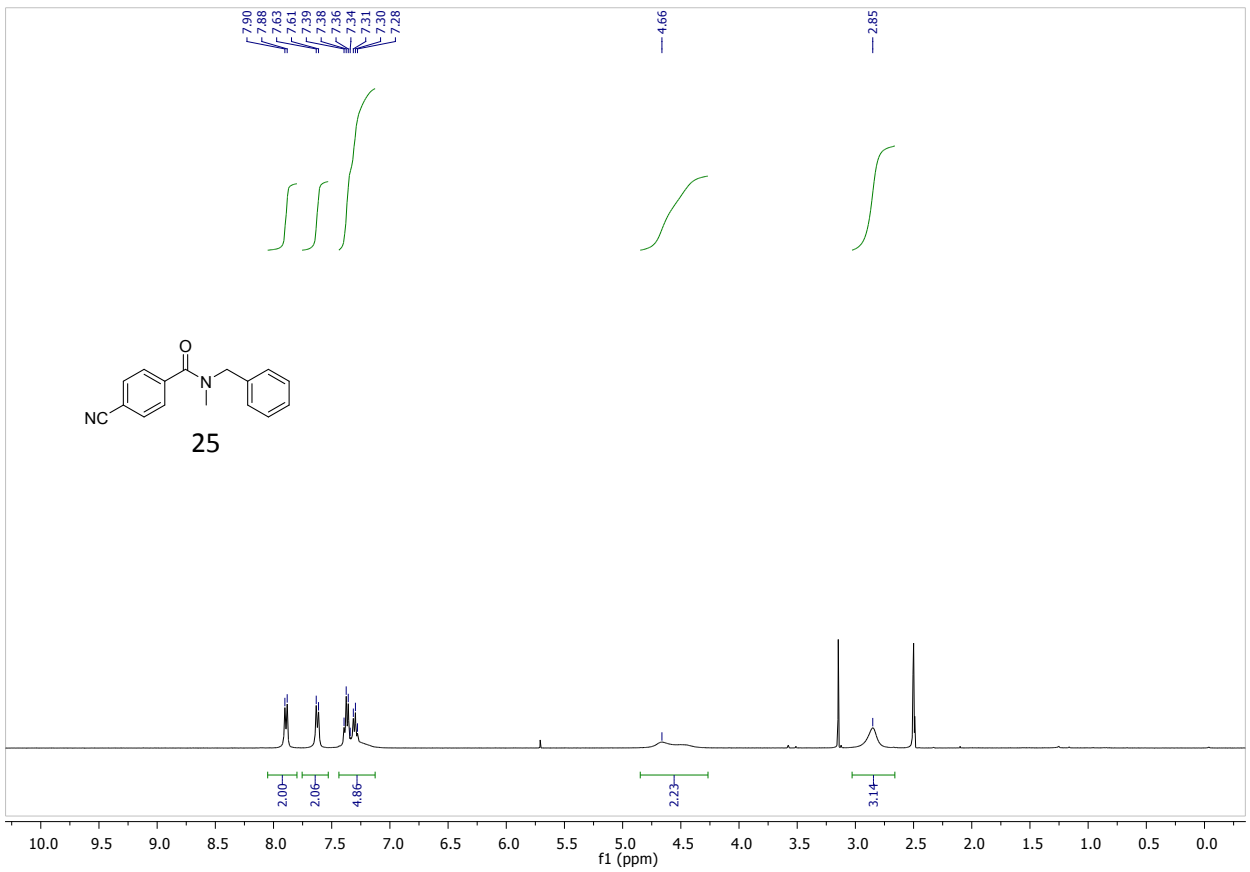


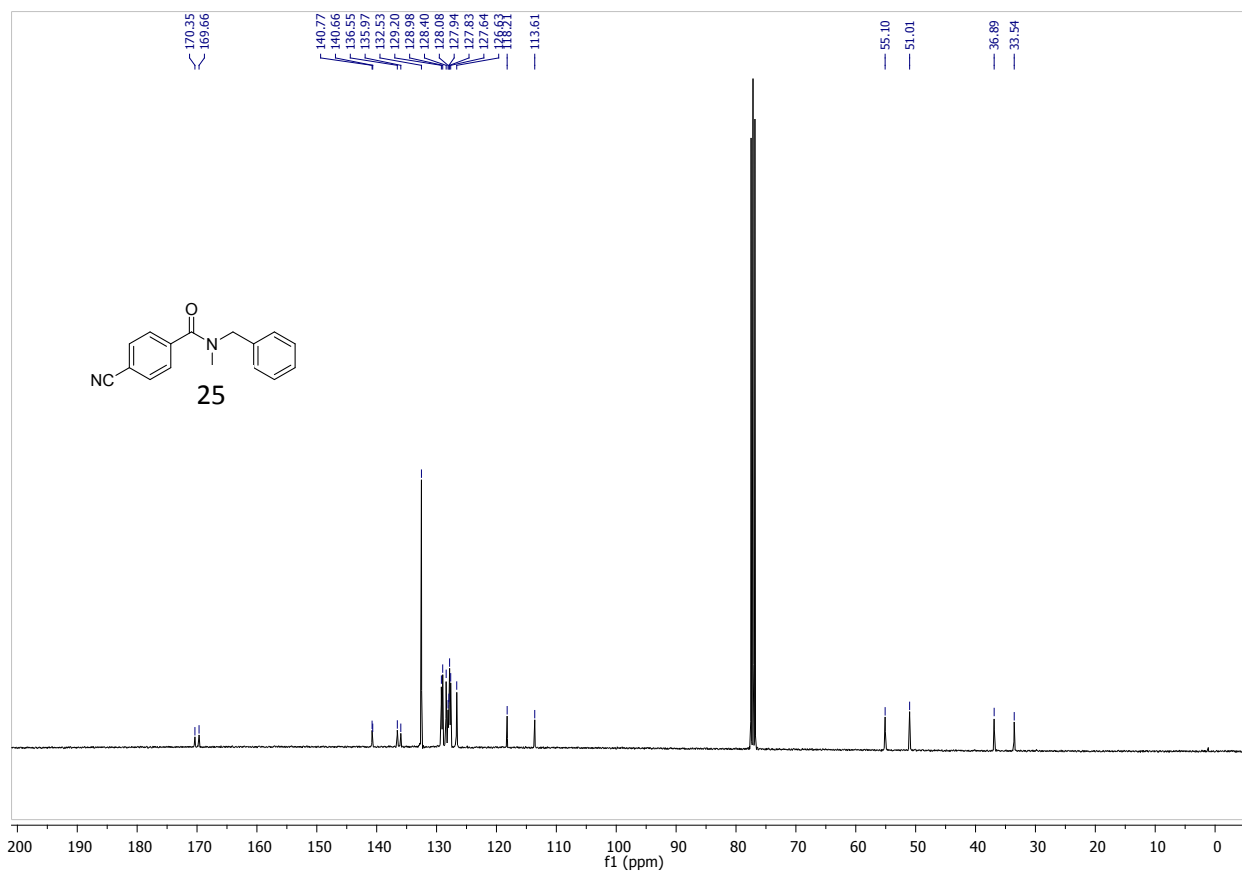
***N*-benzyl-*N*-methyl-4-(trifluoromethyl)benzamide (24)**



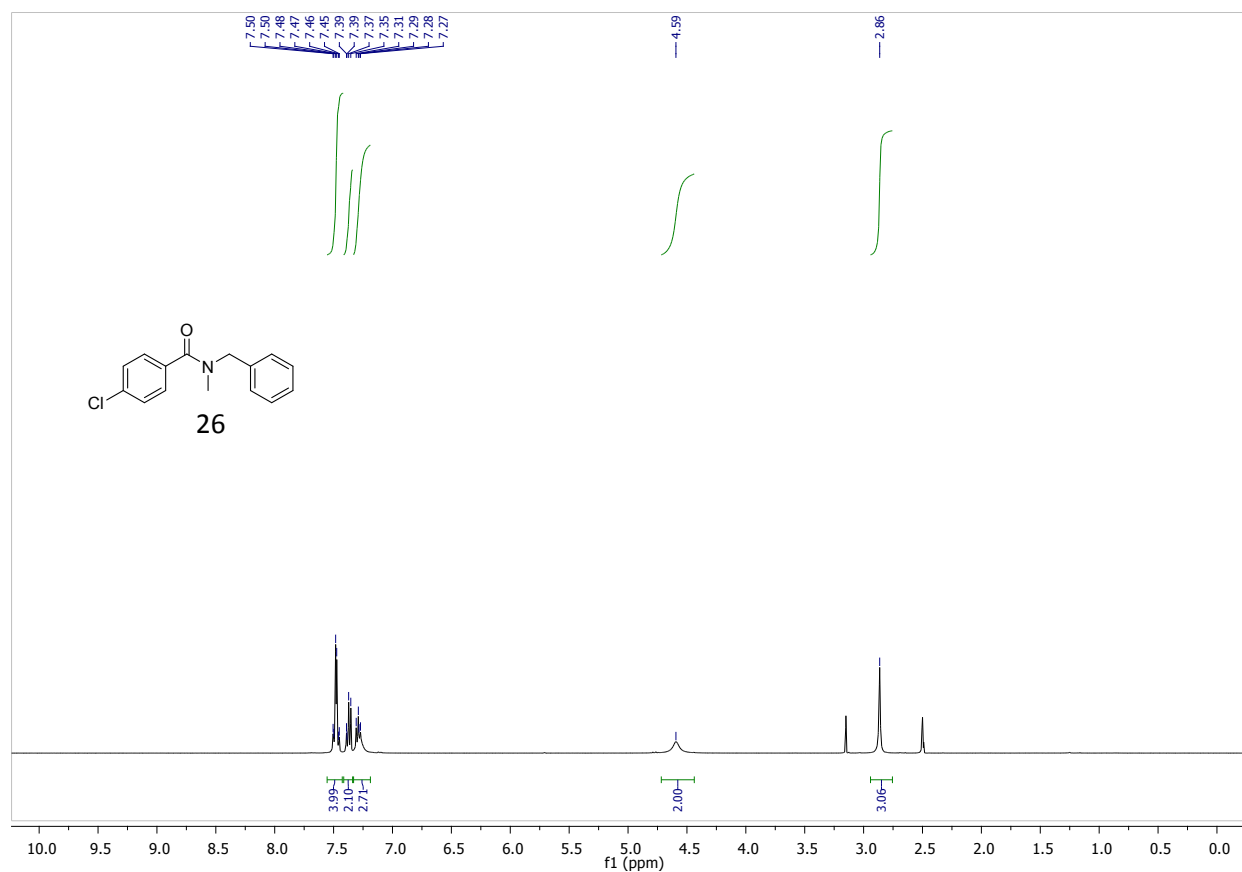


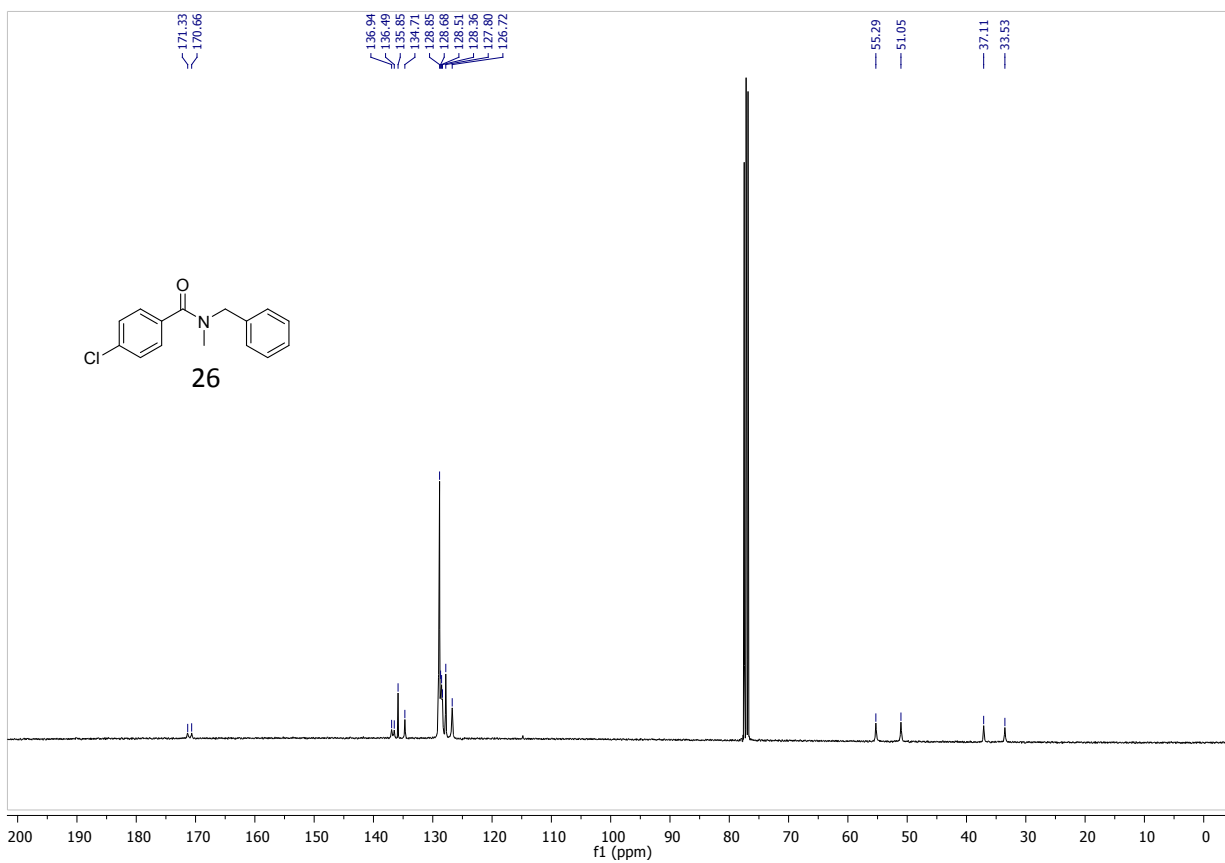
N-benzyl-4-cyano-N-methylbenzamide (25)



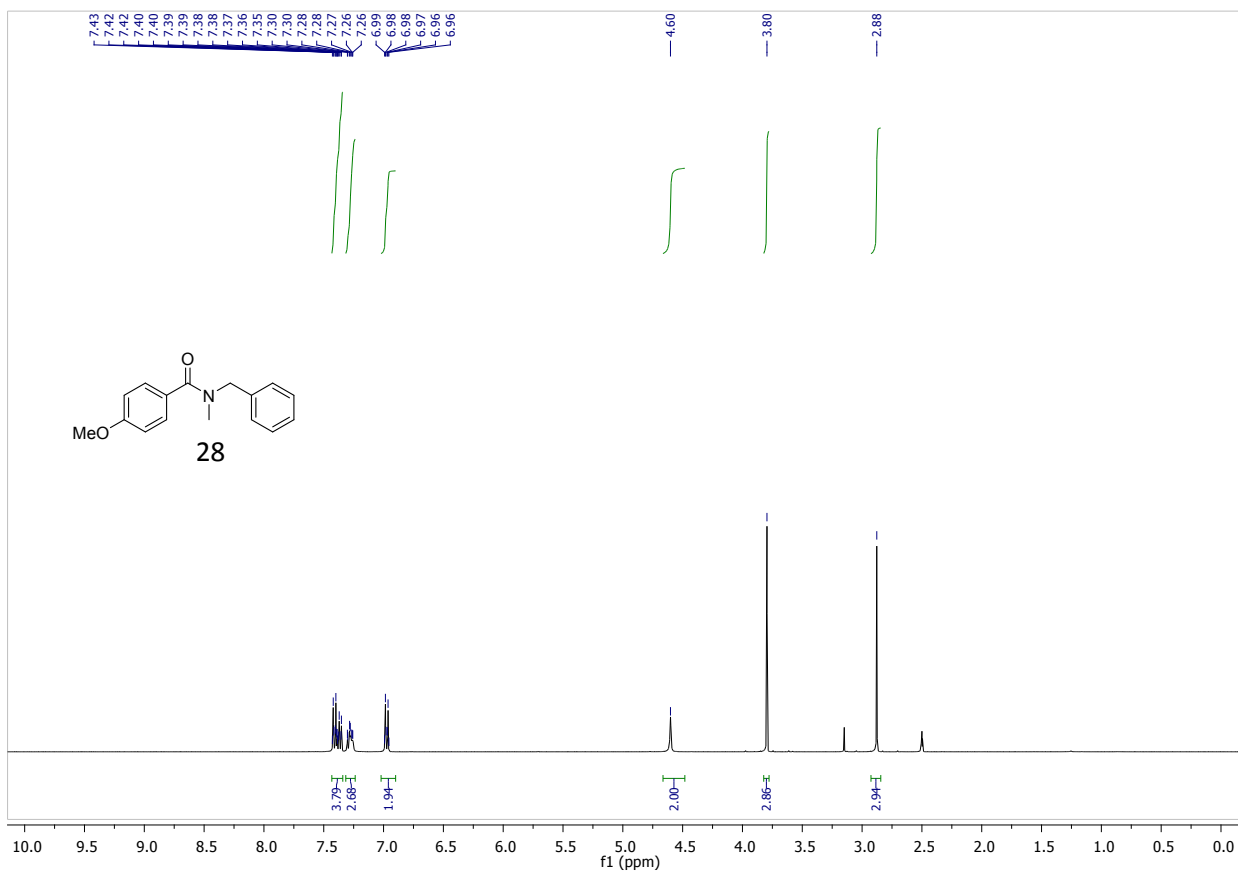


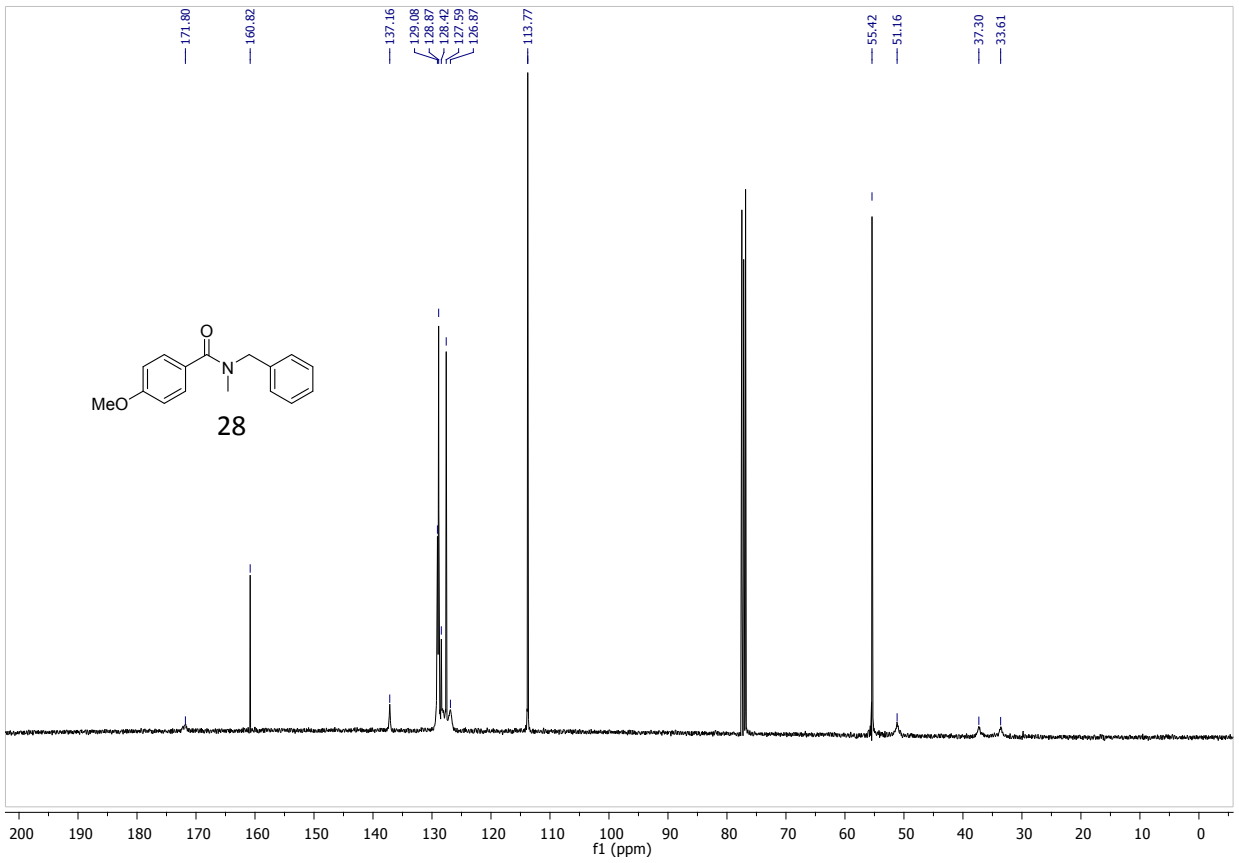
N-benzyl-4-chloro-N-methylbenzamide (26)



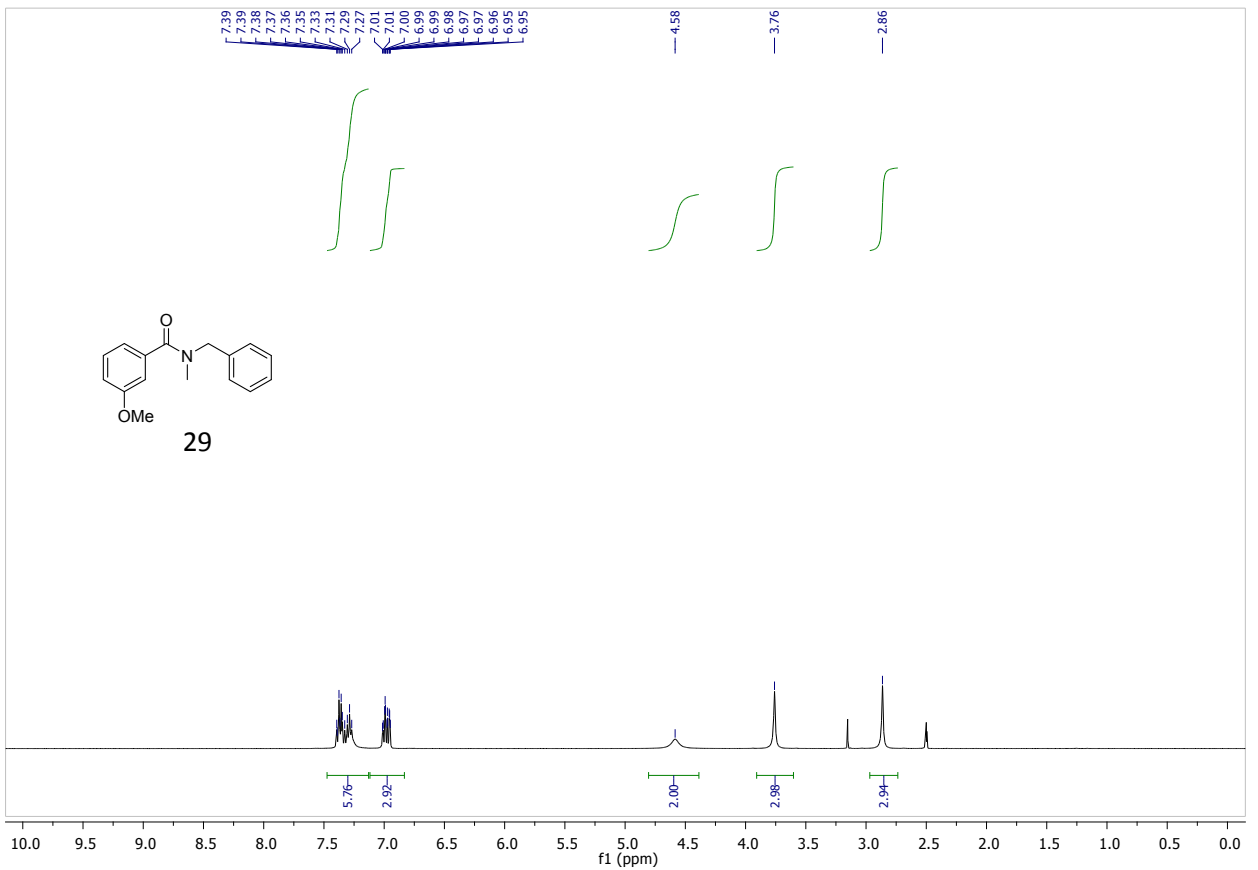


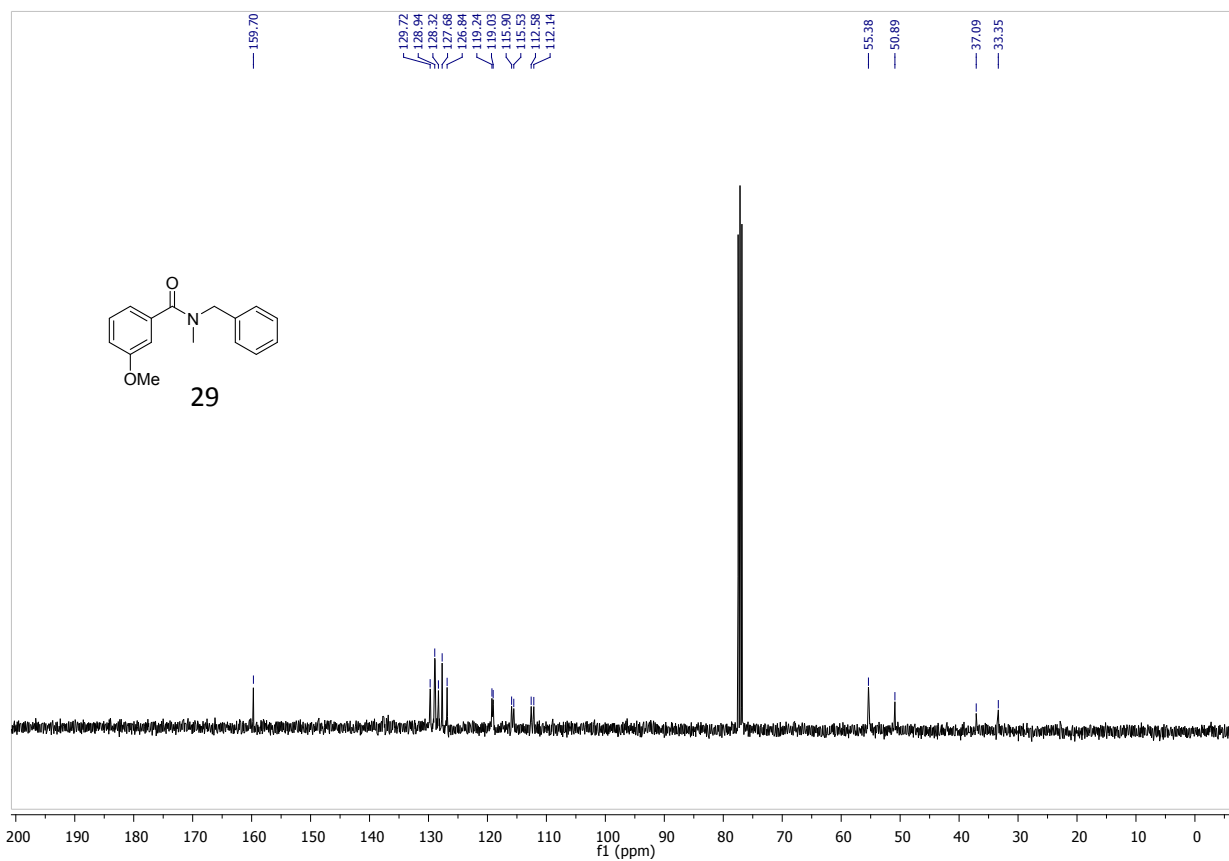
N-benzyl-4-methoxy-N-methylbenzamide (28)



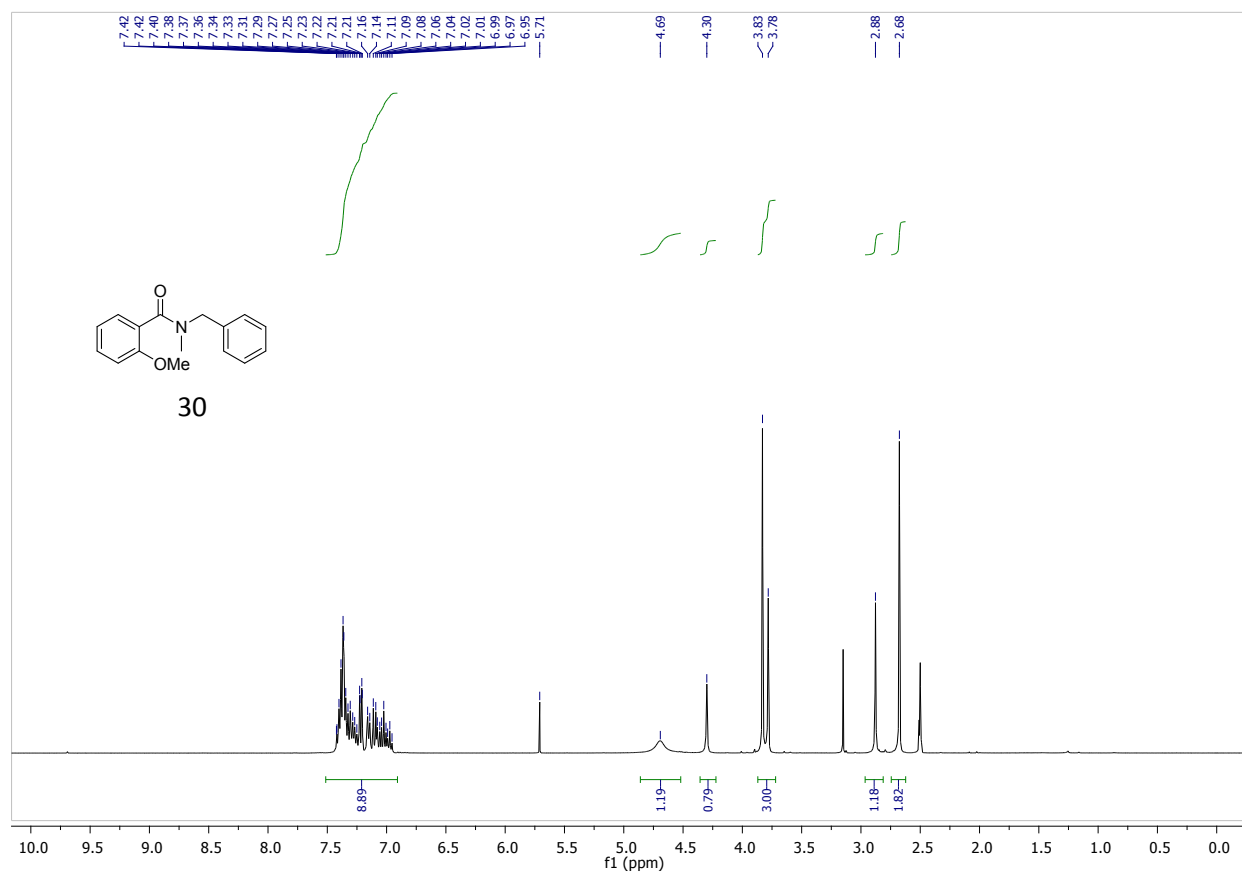


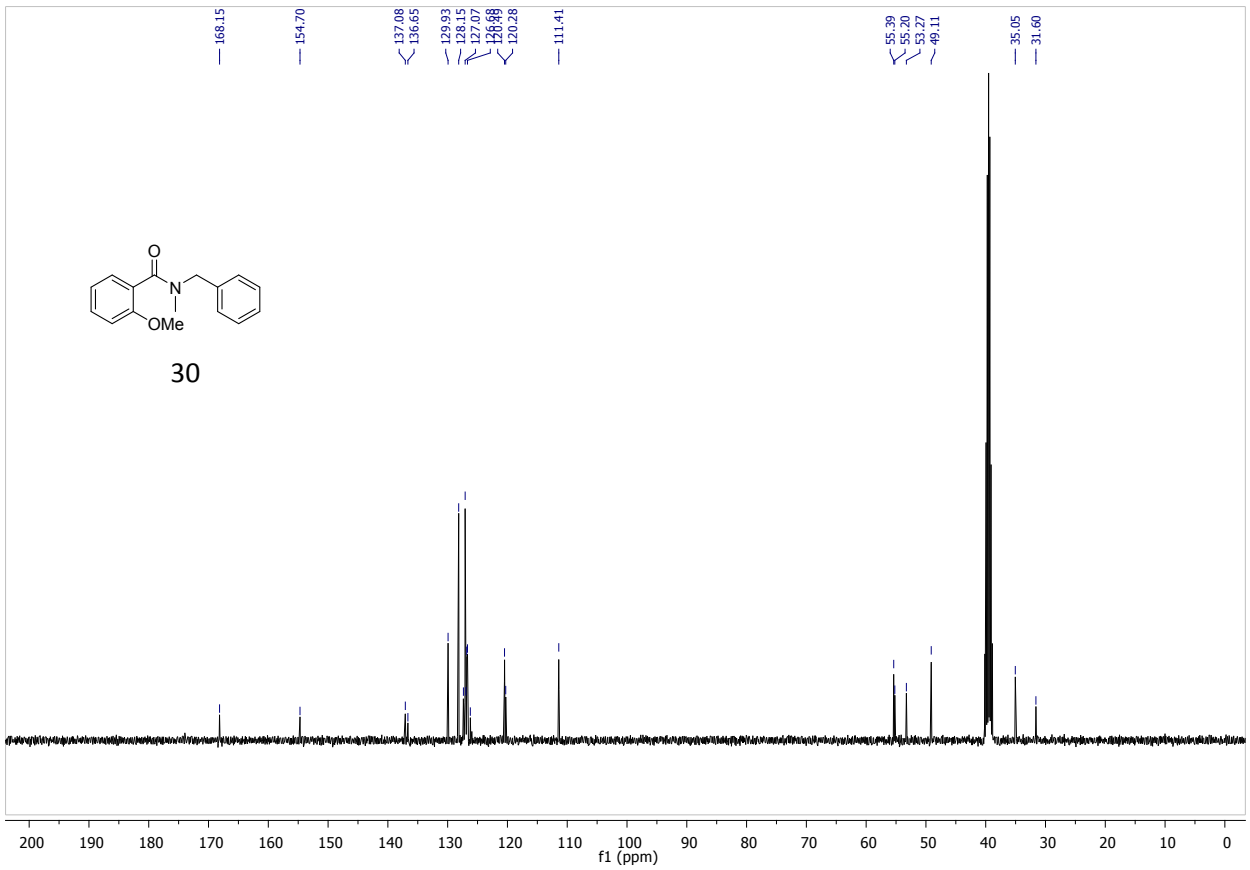
***N*-benzyl-3-methoxy-*N*-methylbenzamide (29)**



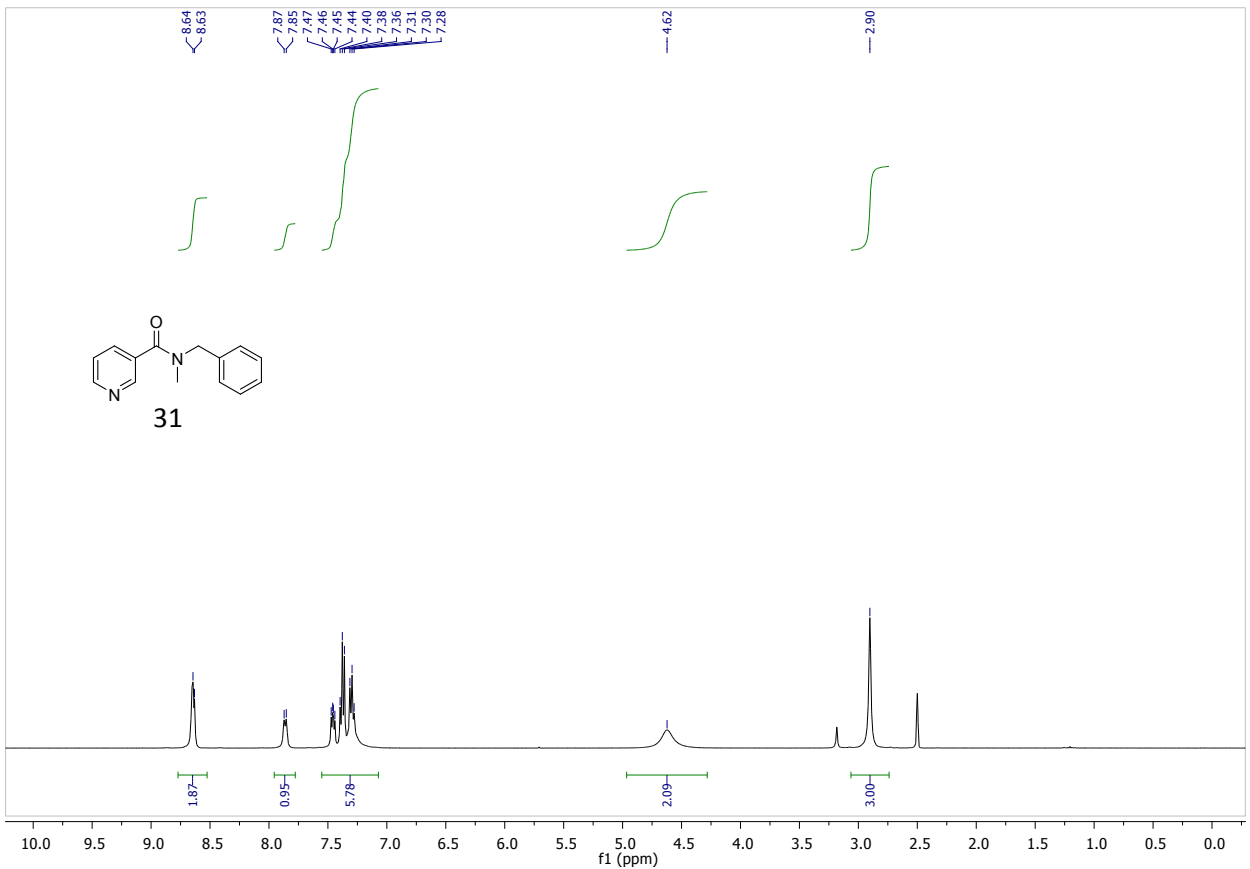


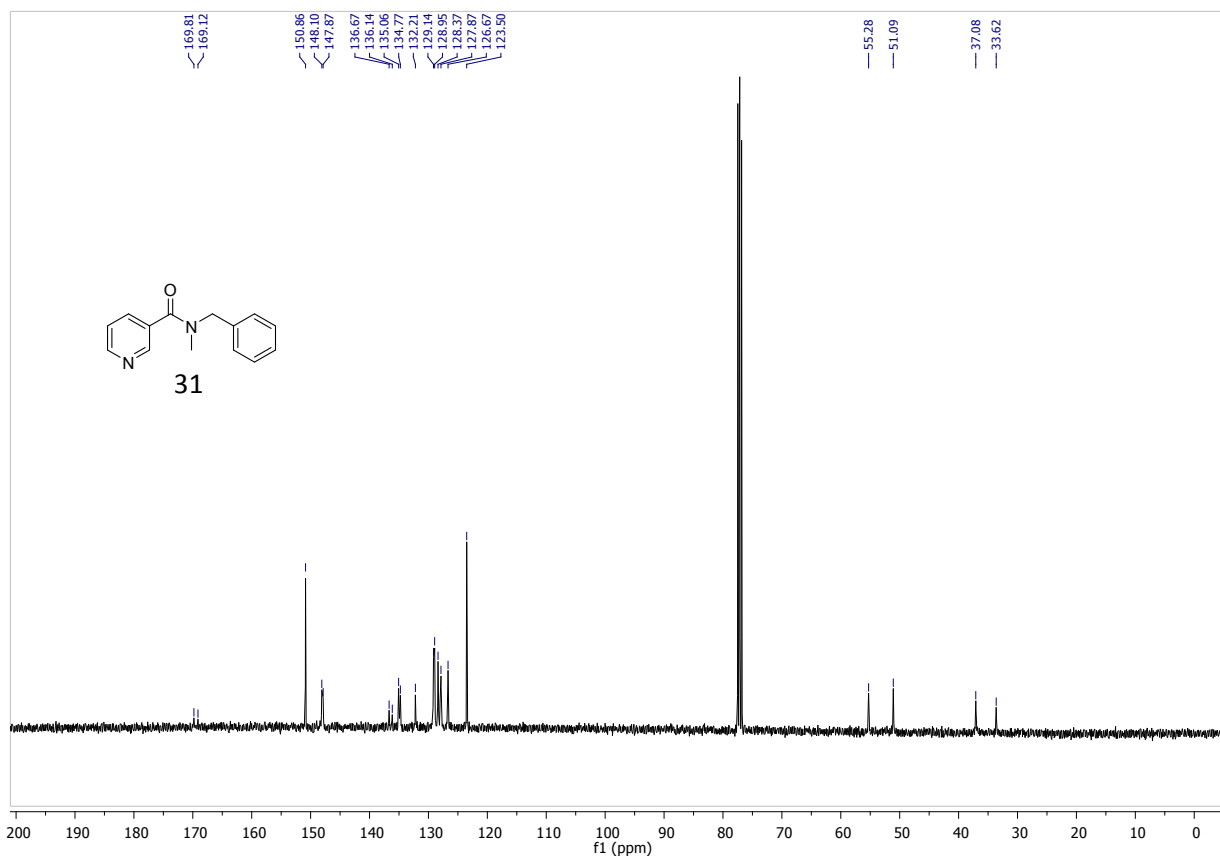
N-benzyl-2-methoxy-N-methylbenzamide (30)



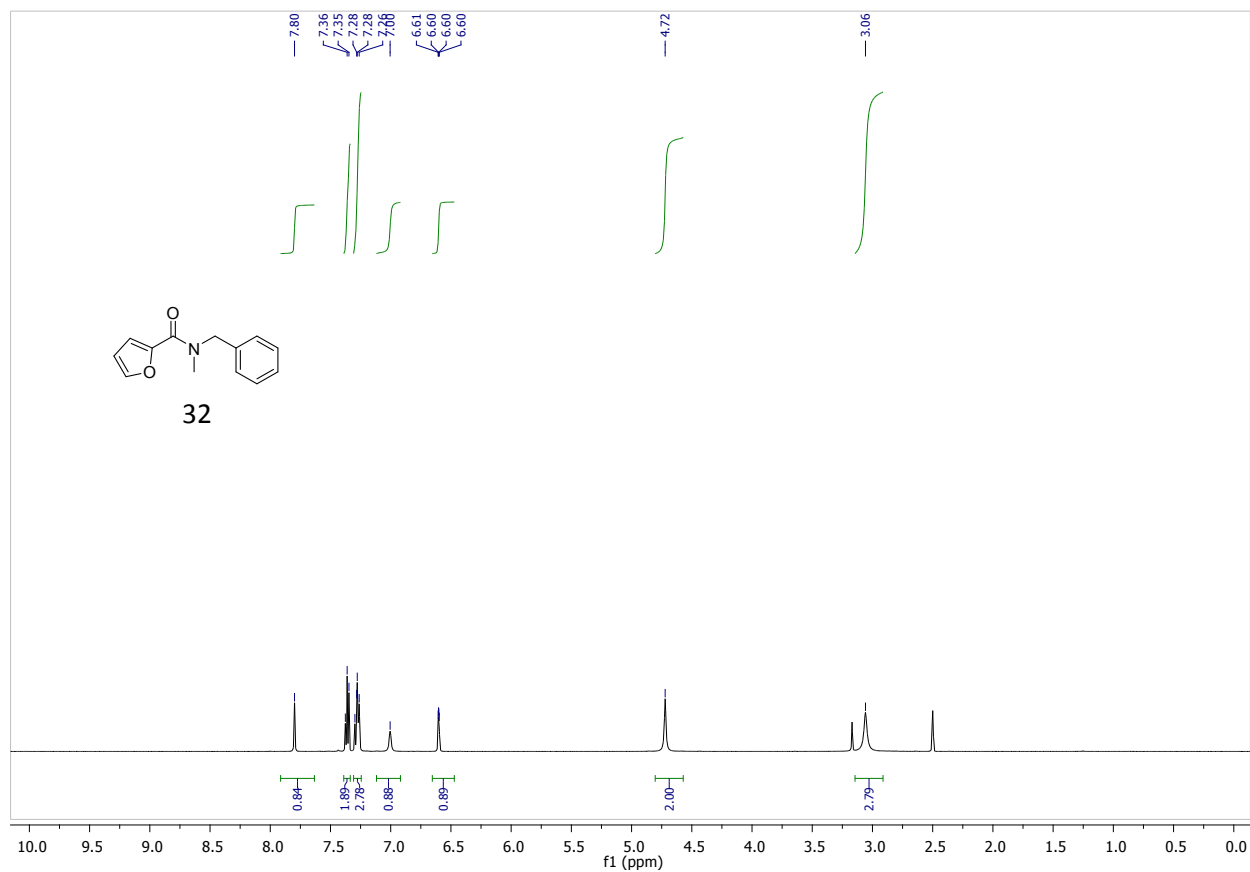


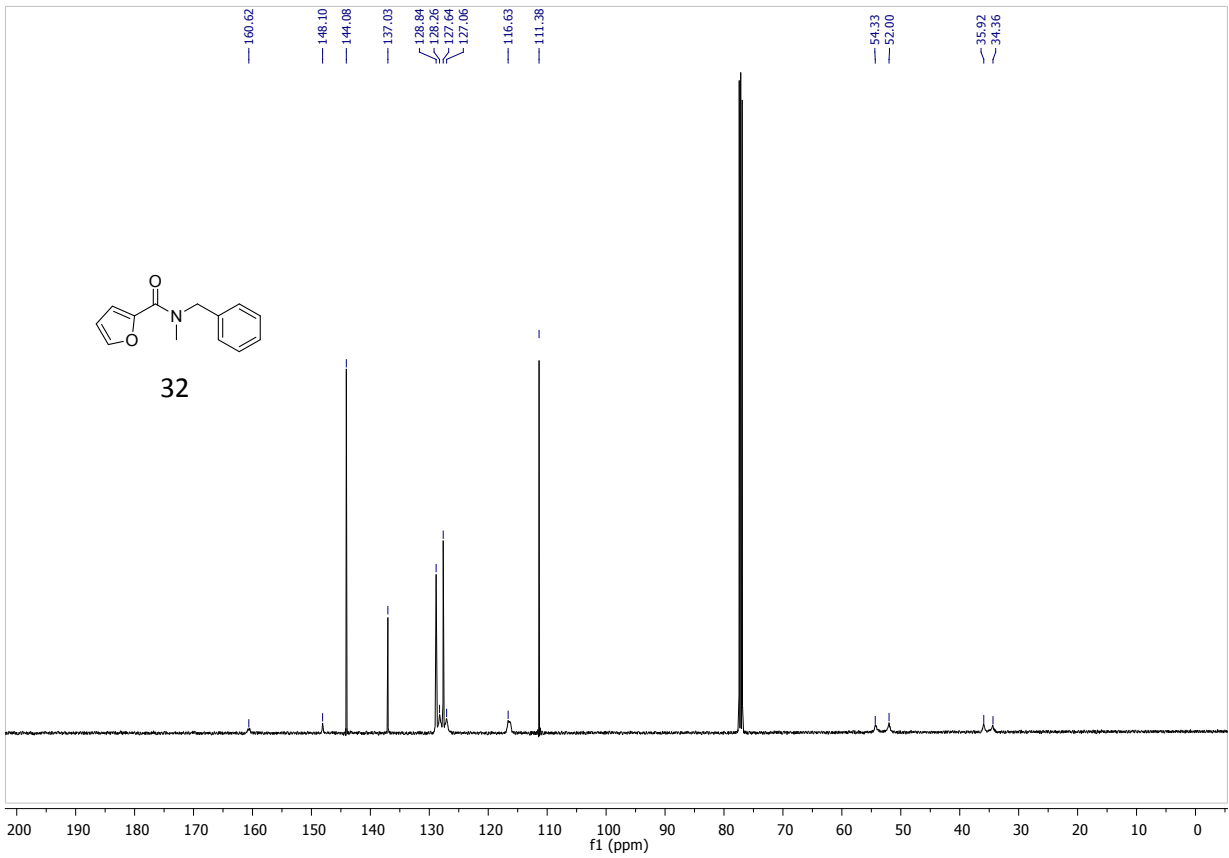
***N*-benzyl-*N*-methylnicotinamide (31)**



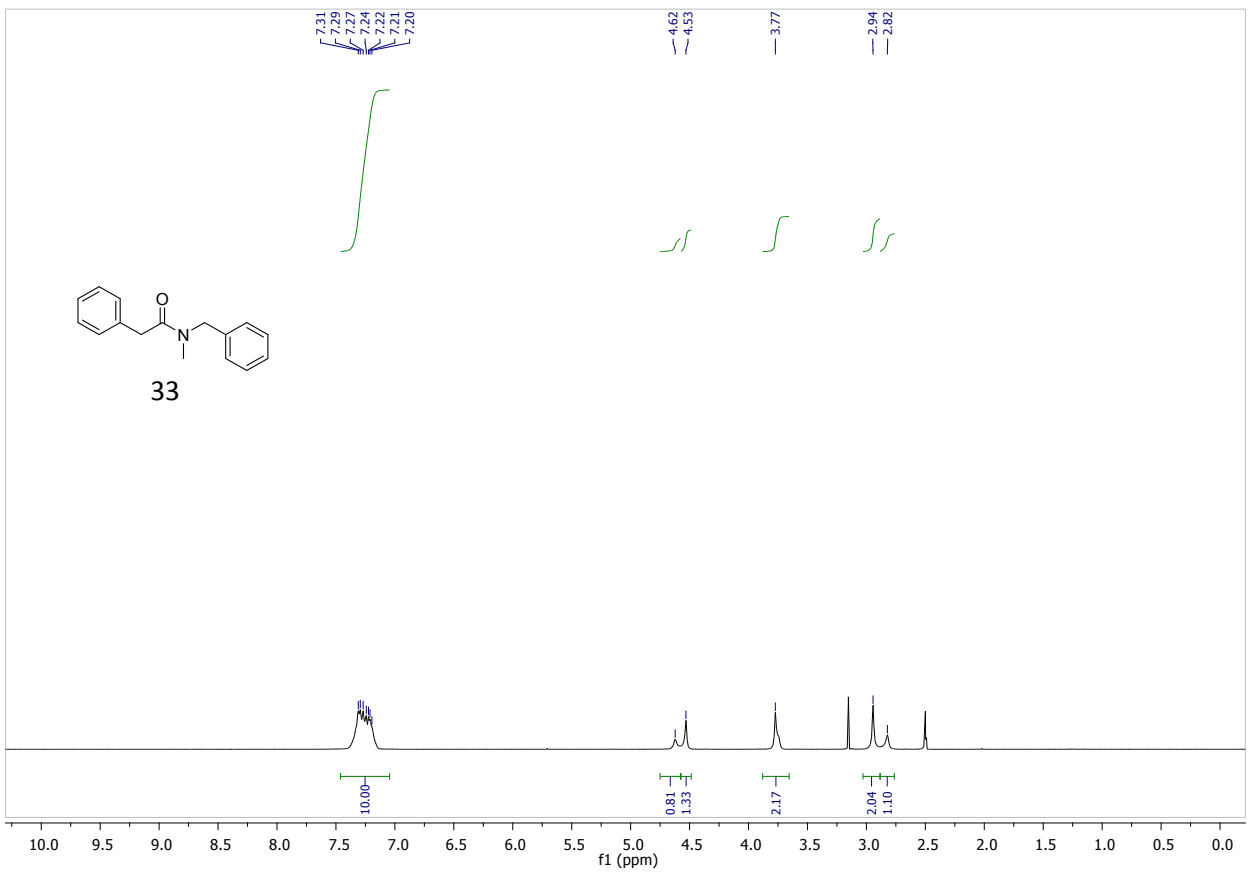


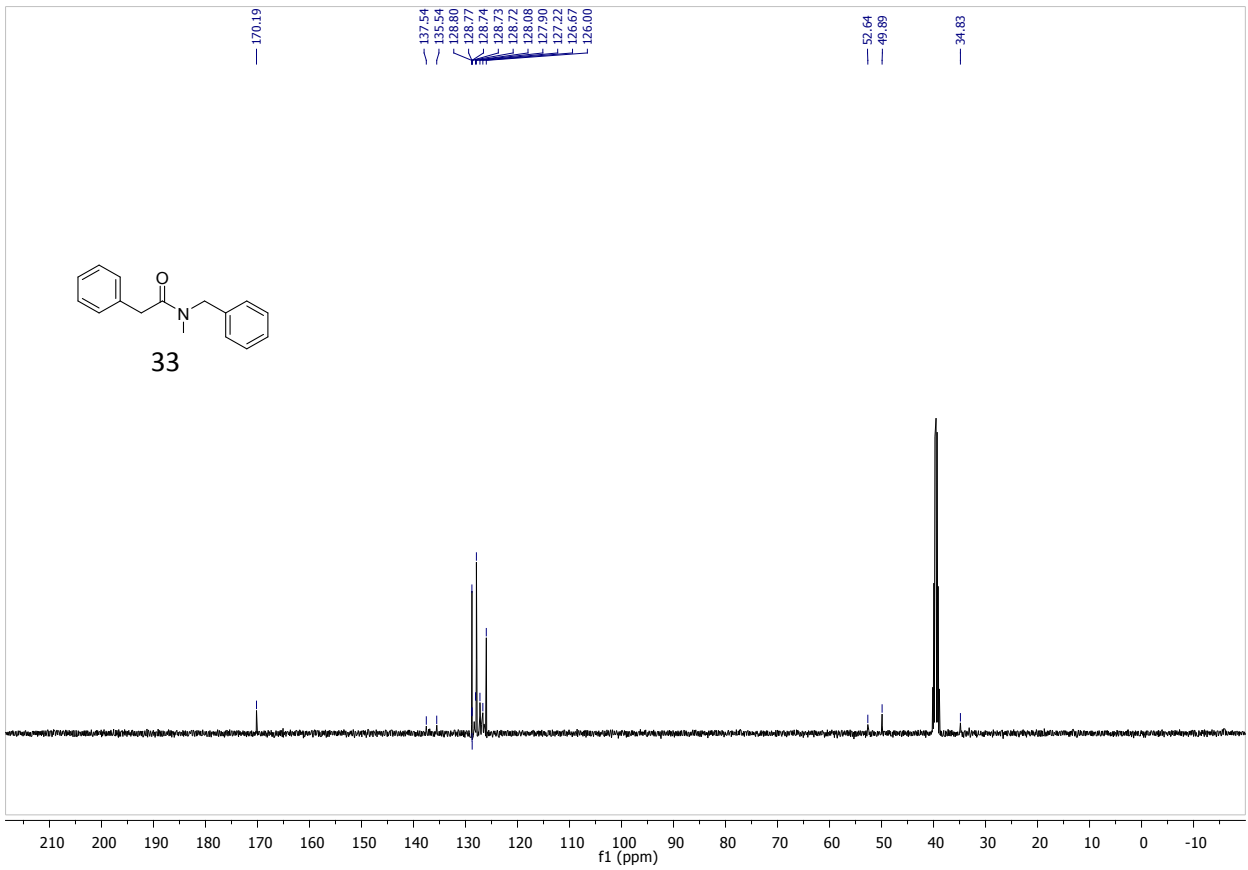
N-benzyl-N-methylfuran-2-carboxamide (32)



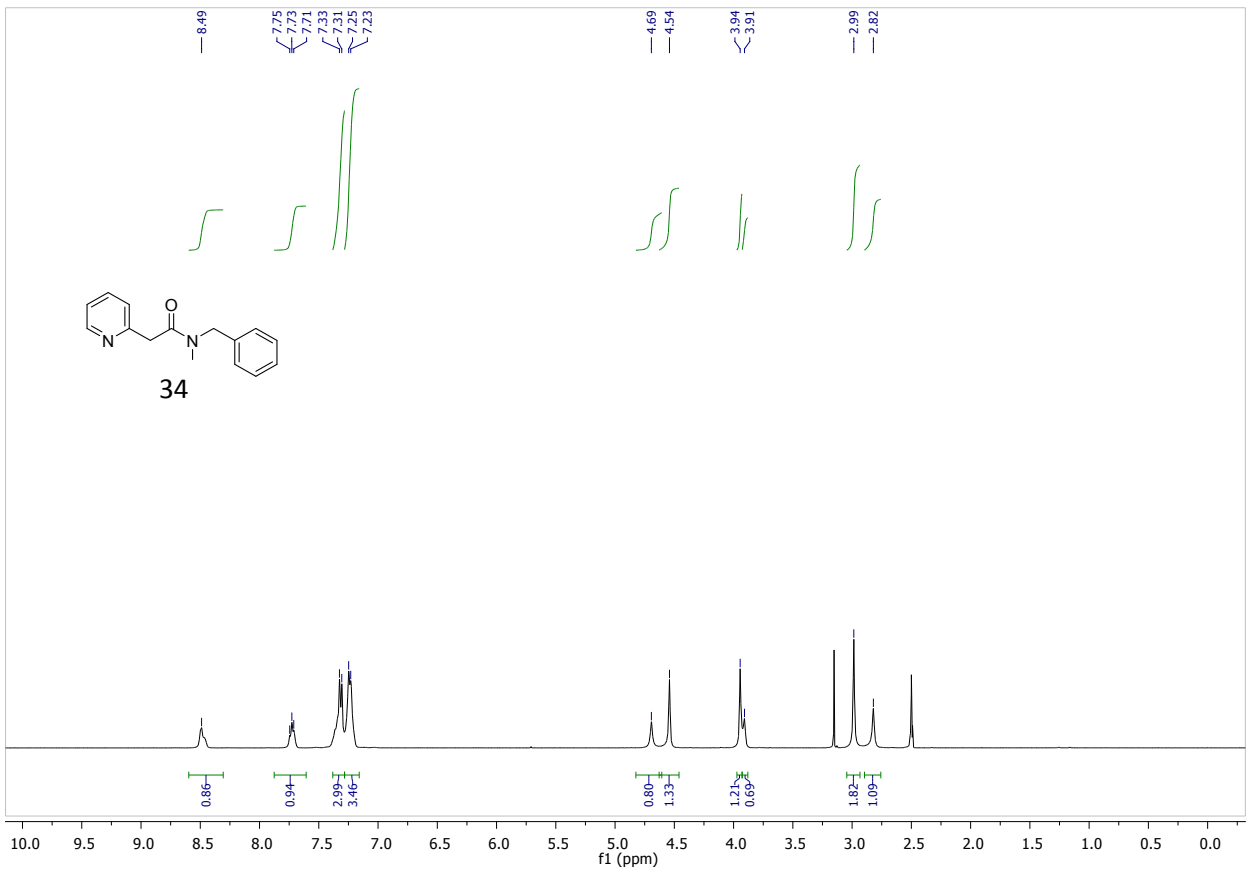


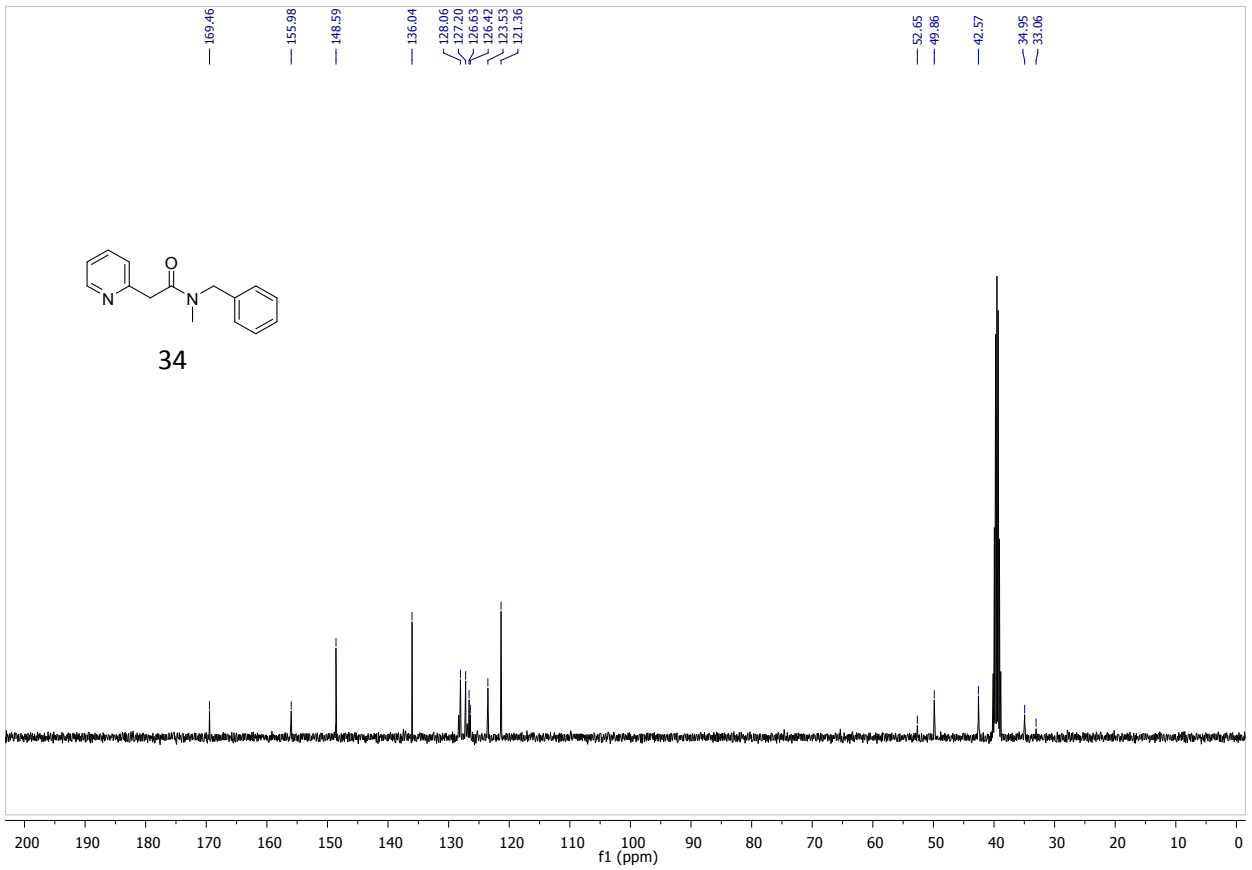
***N*-benzyl-*N*-methyl-2-phenylacetamide (33)**



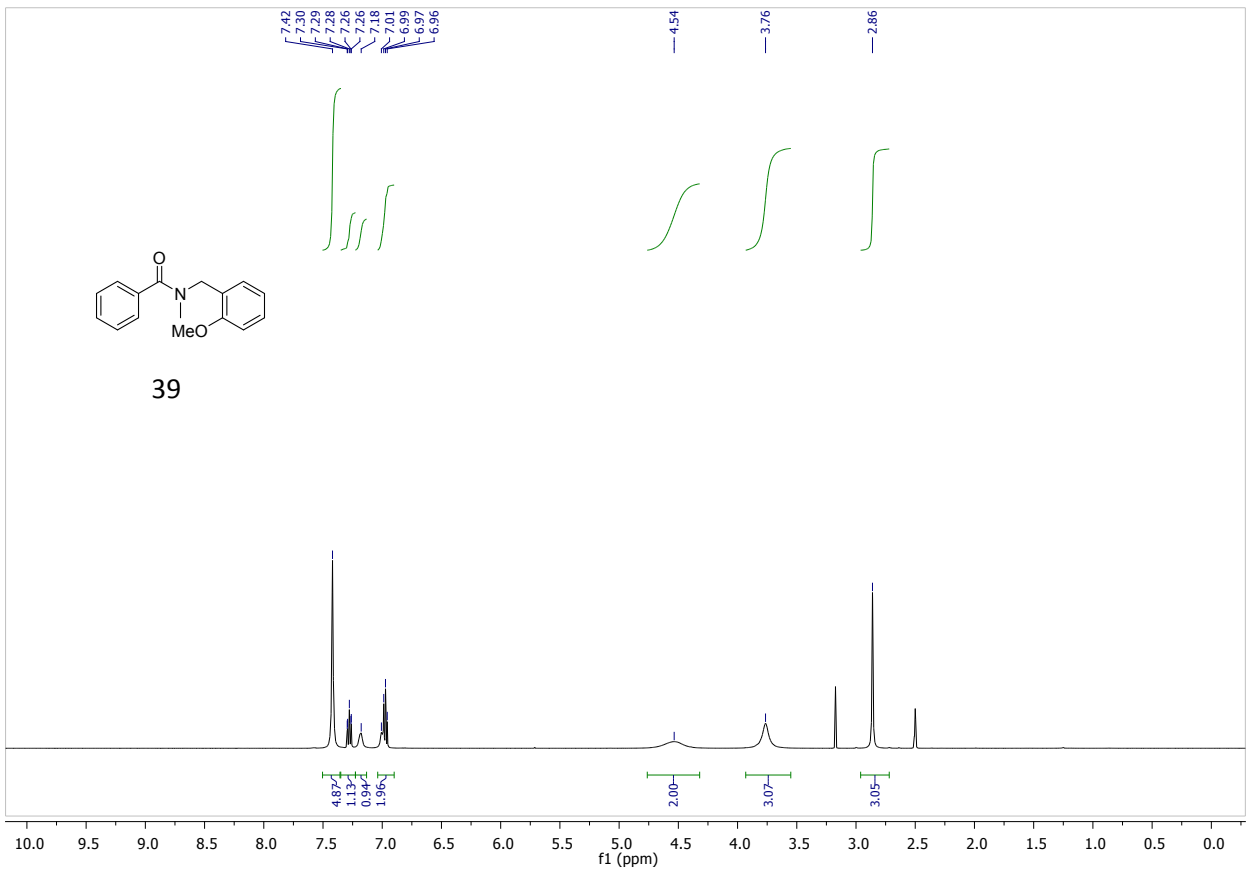


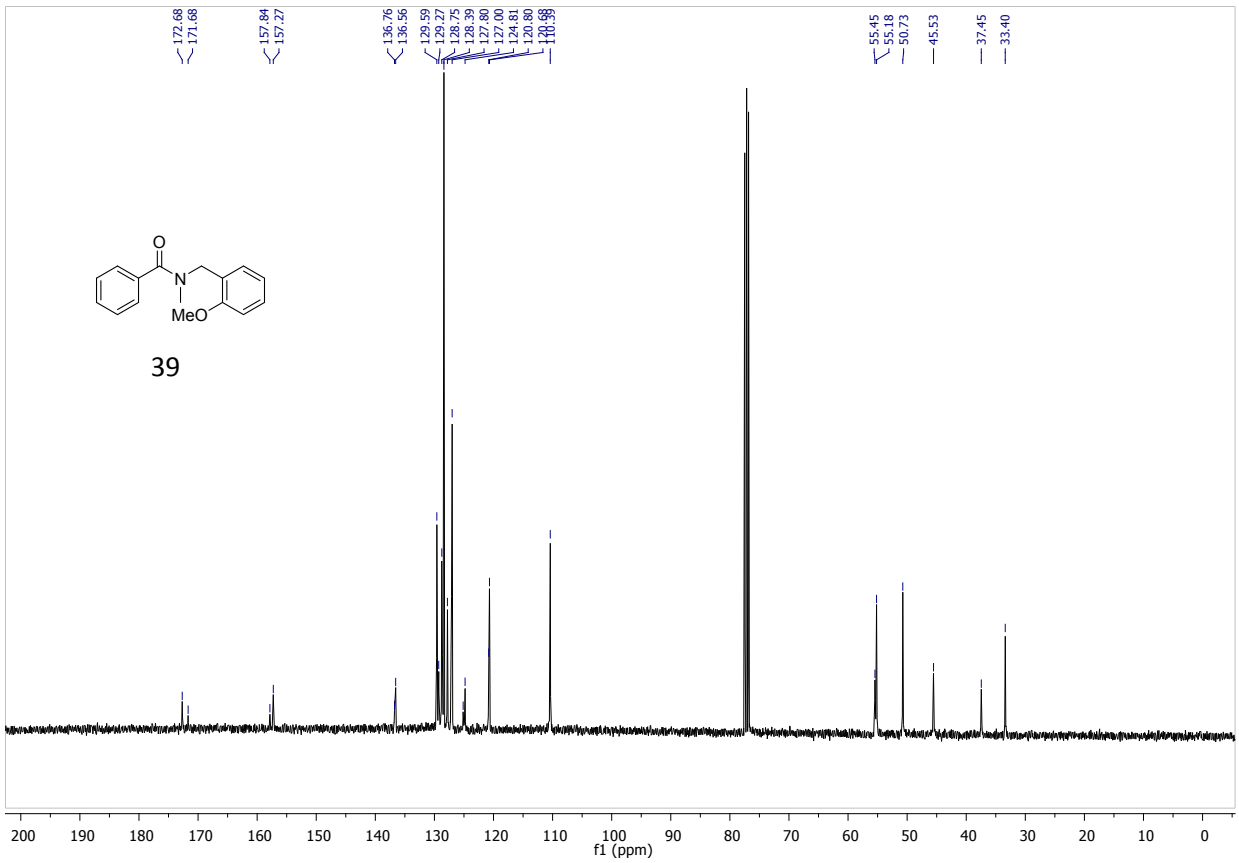
N-benzyl-N-methyl-2-(pyridin-2-yl)acetamide (34)



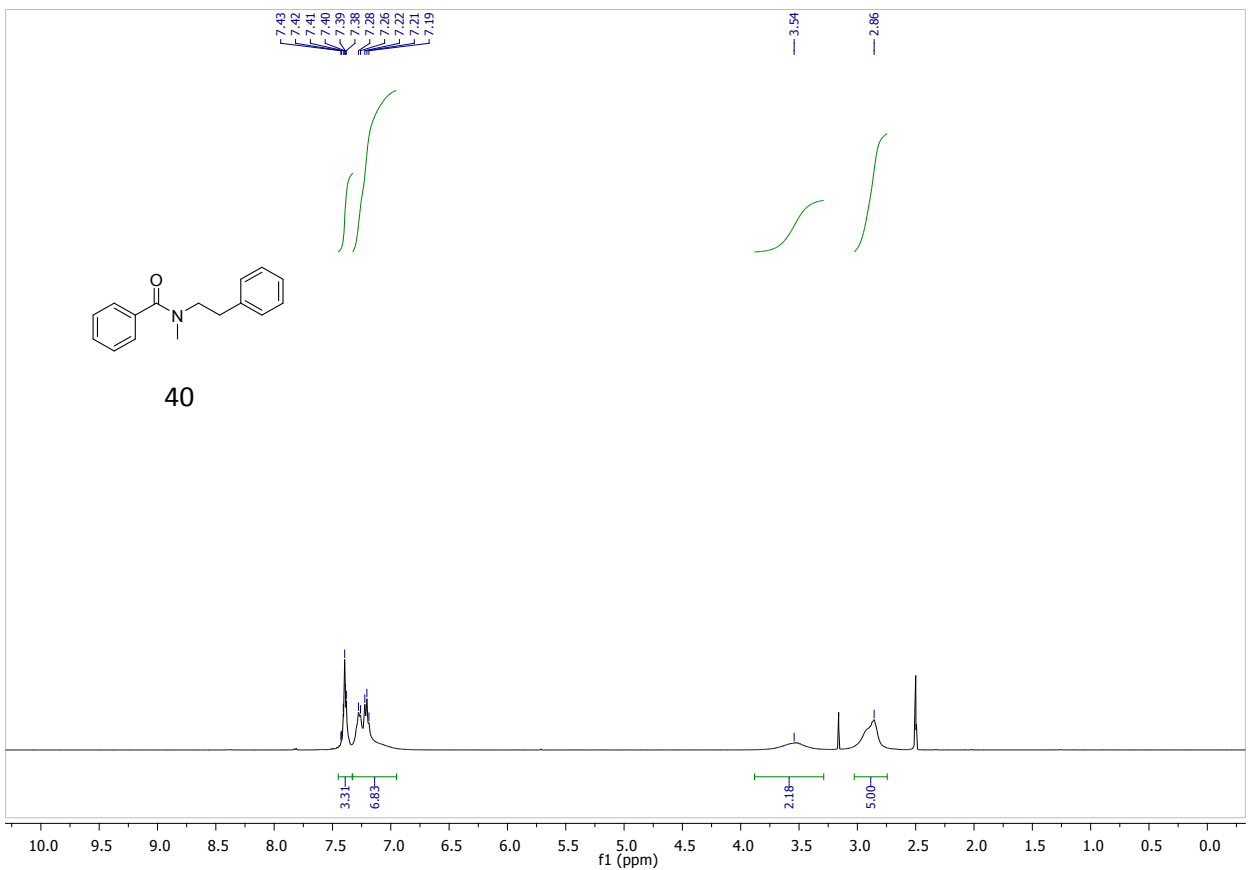


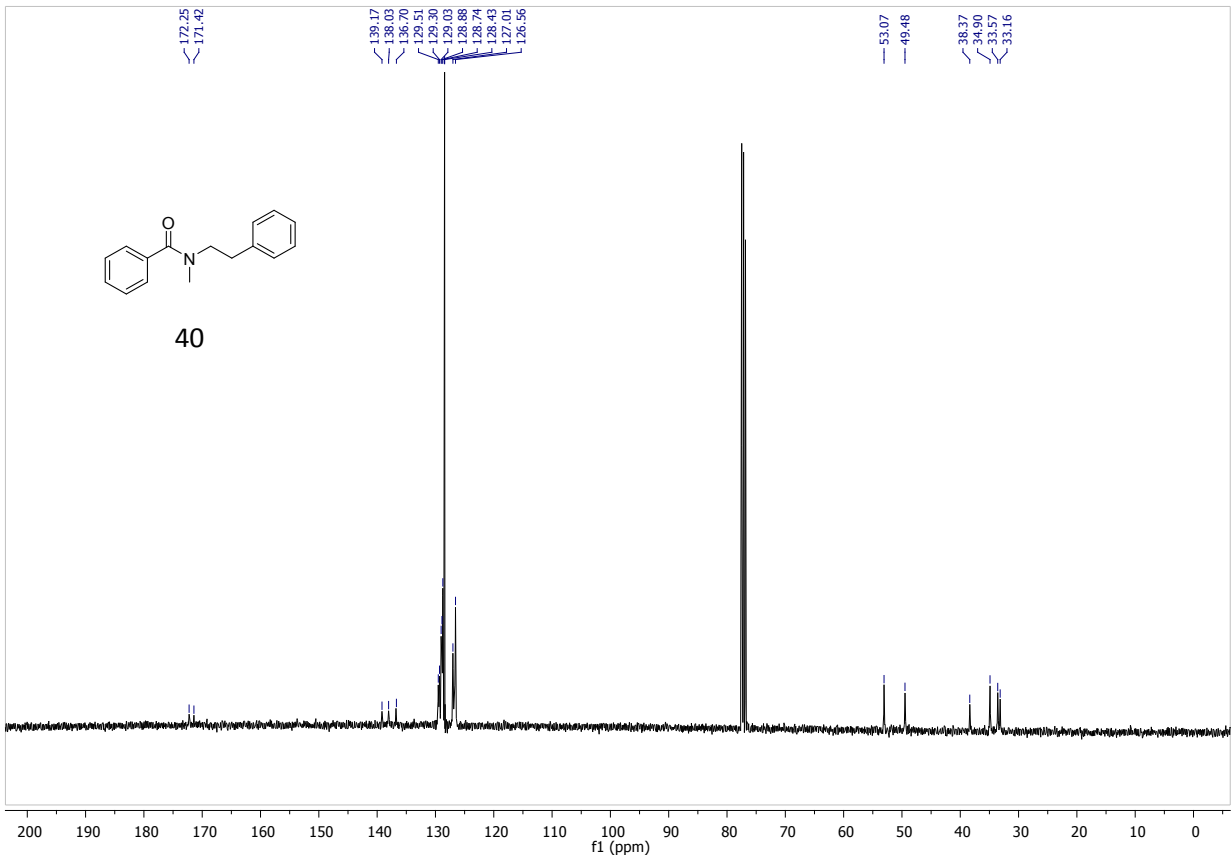
***N*-(2-methoxybenzyl)-*N*-methylbenzamide (39)**



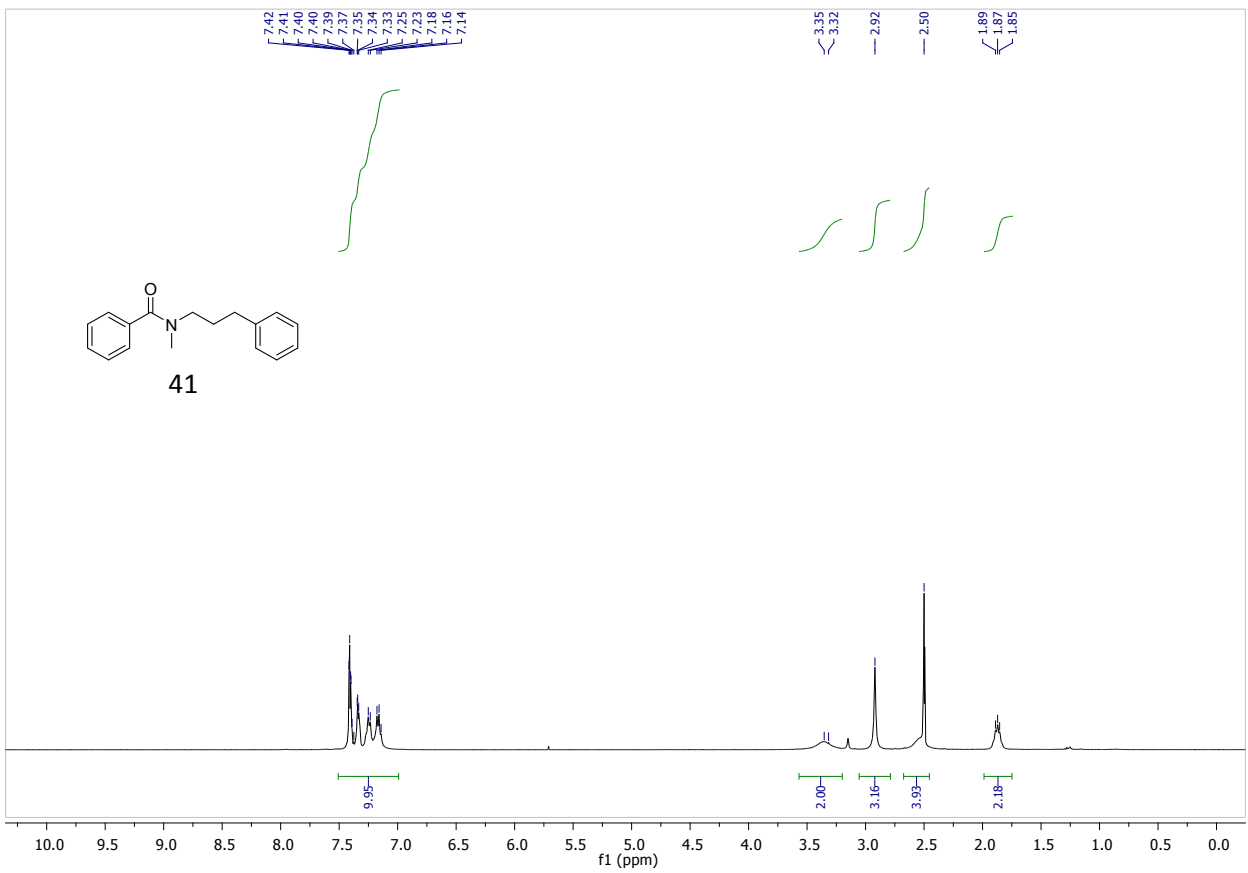


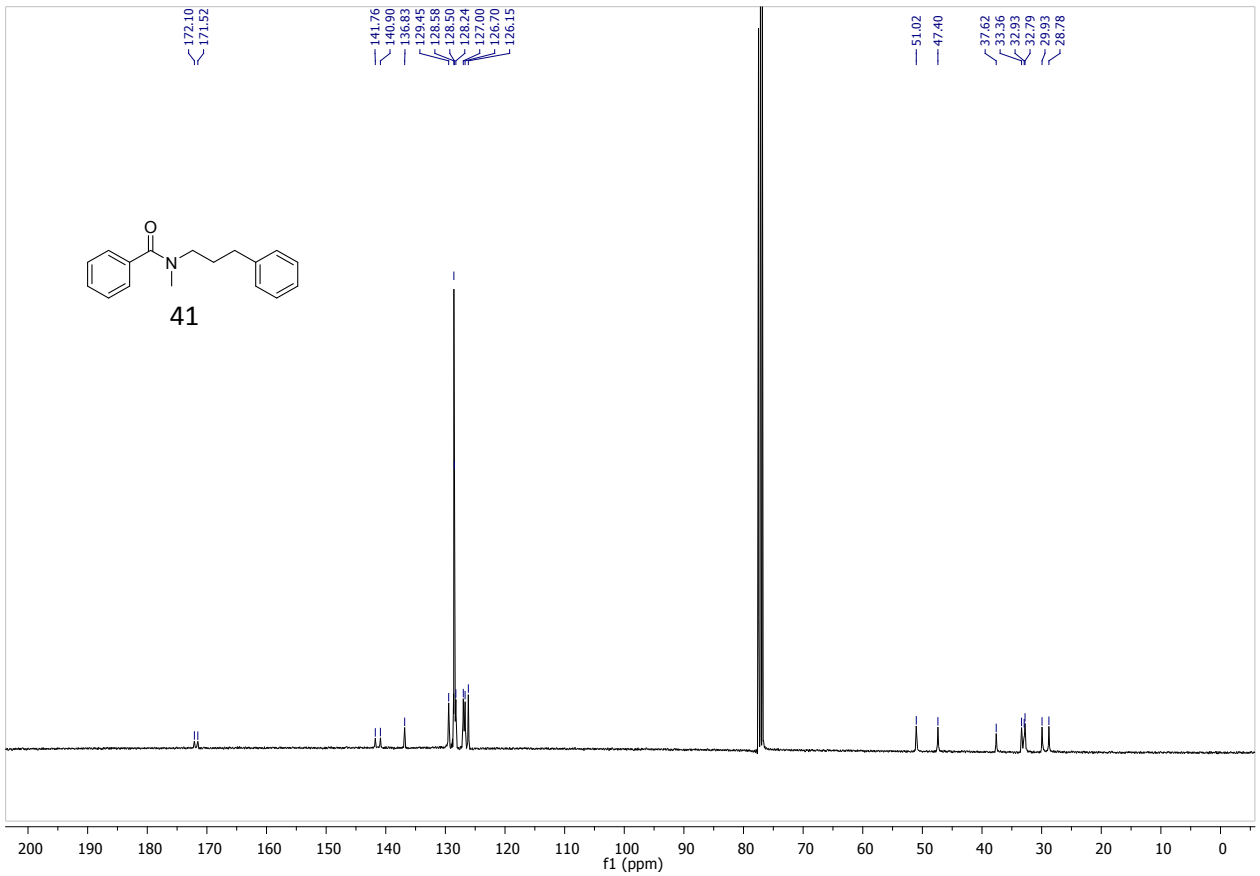
***N*-methyl-*N*-phenethylbenzamide (40)**



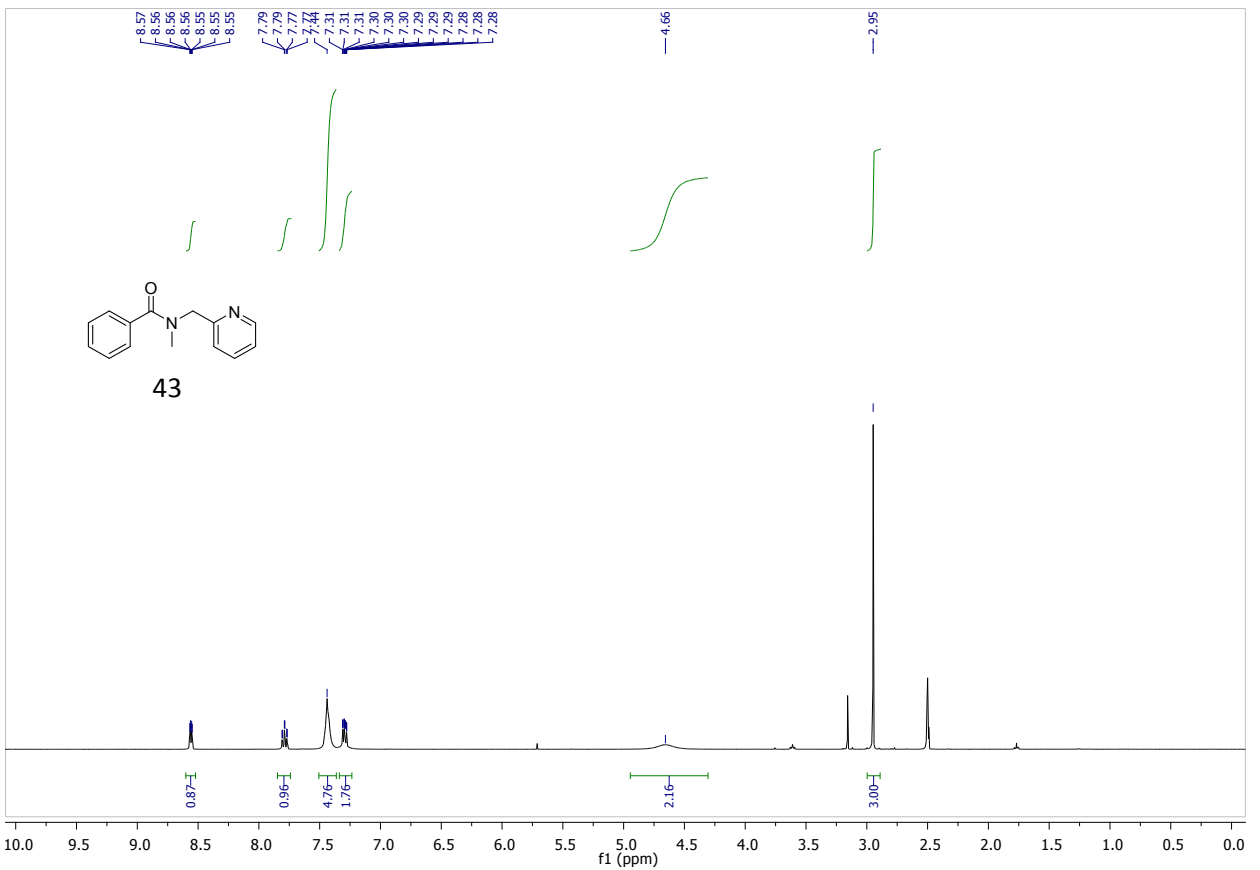


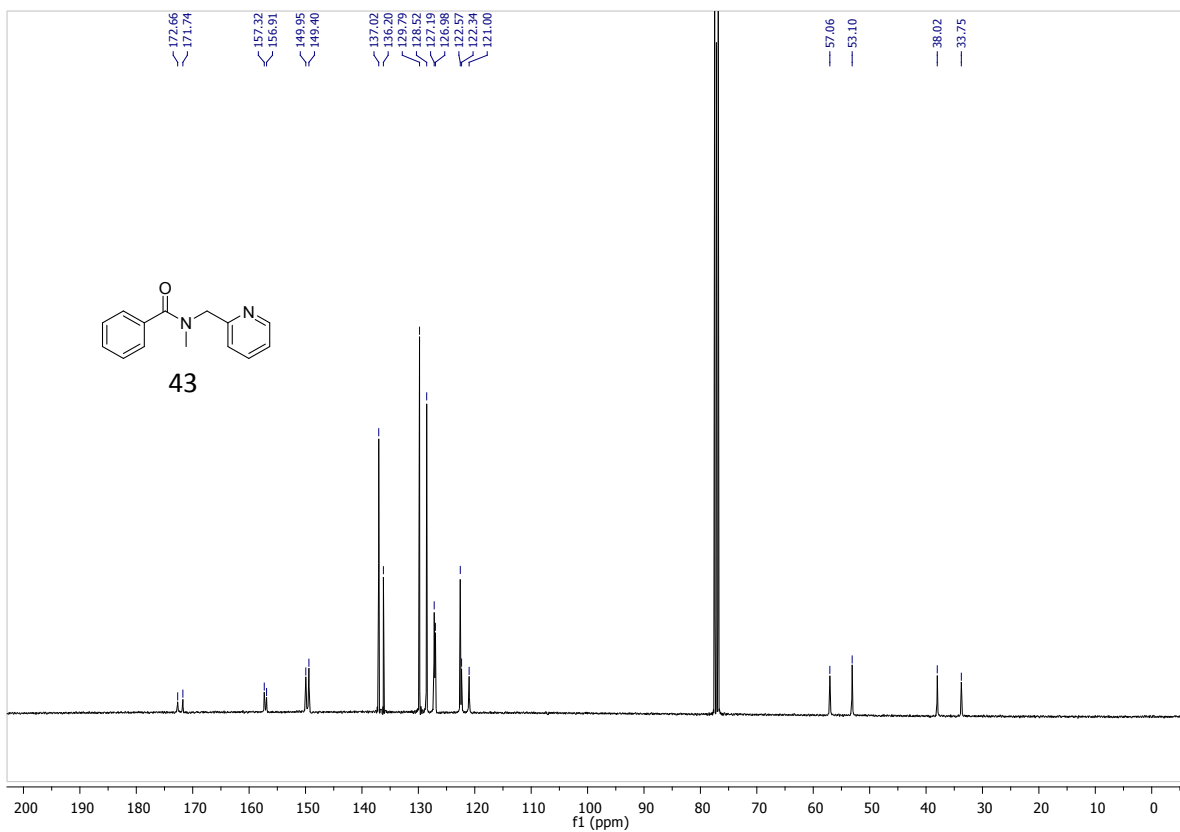
***N*-methyl-*N*-(3-phenylpropyl)benzamide (41)**



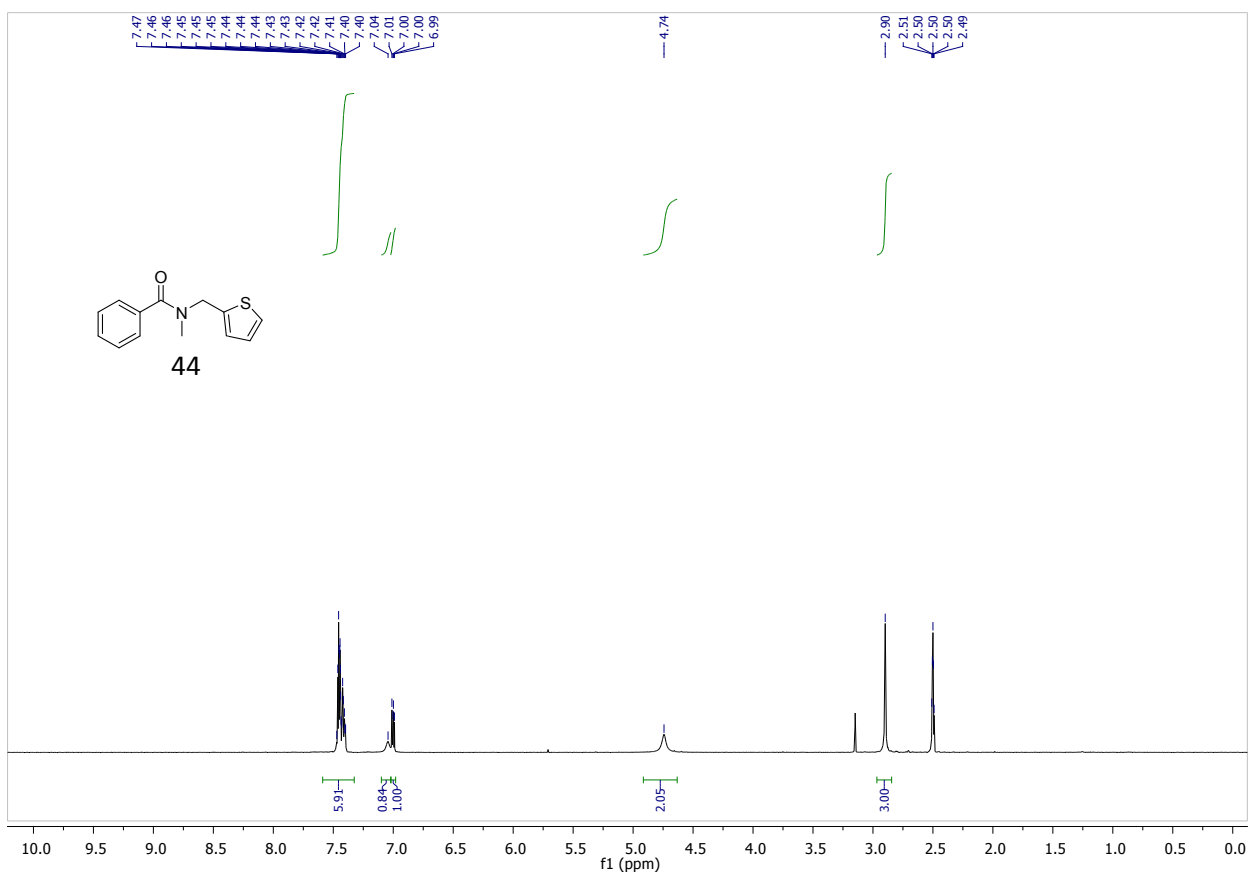


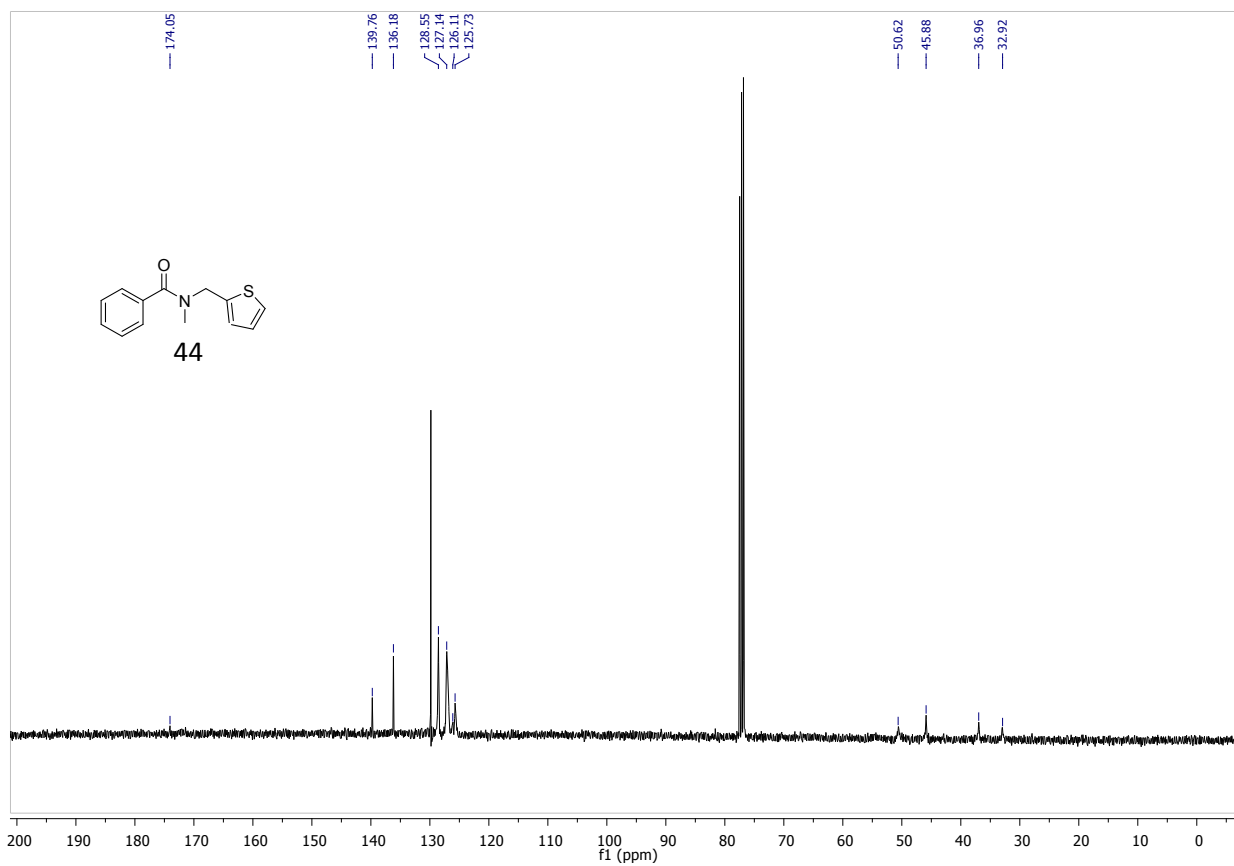
N-methyl-N-(pyridin-2-ylmethyl)benzamide (43)



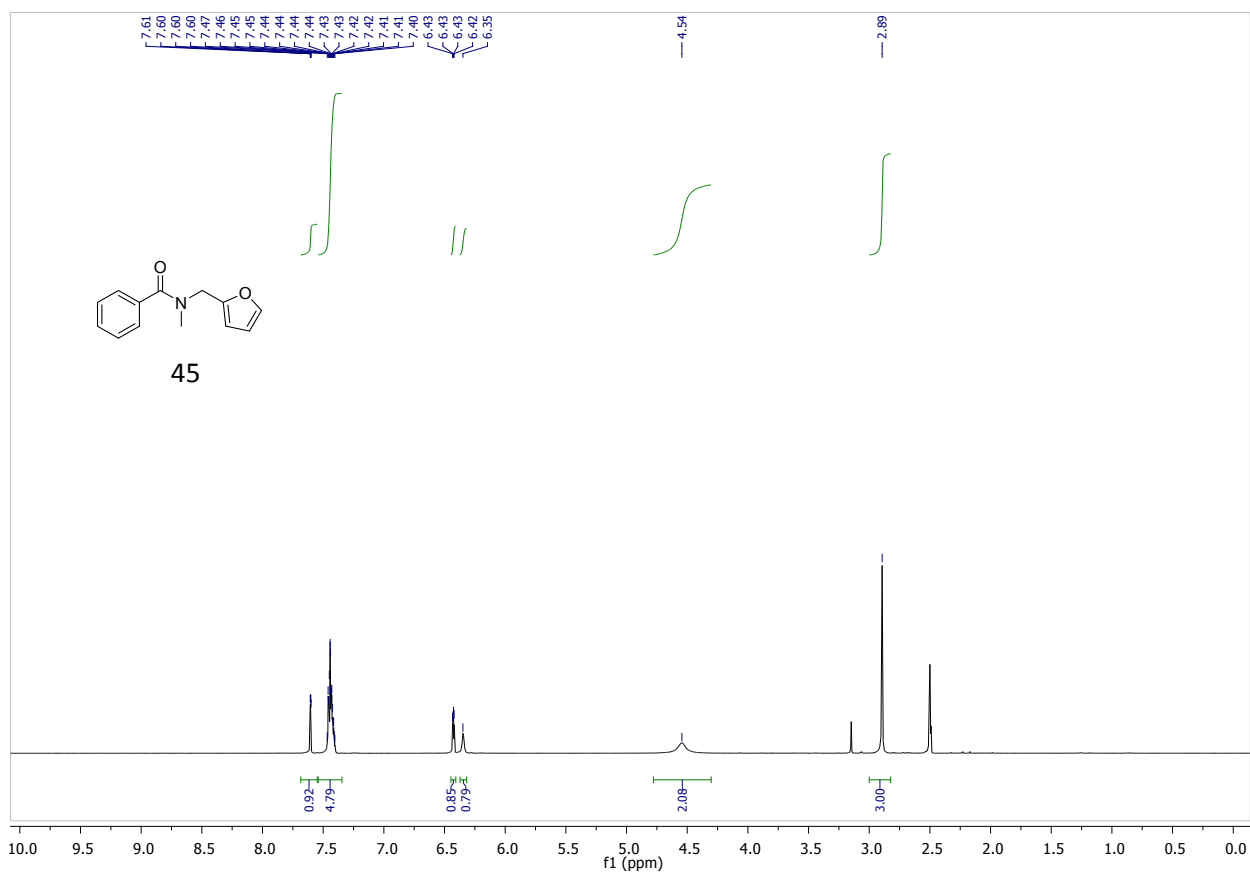


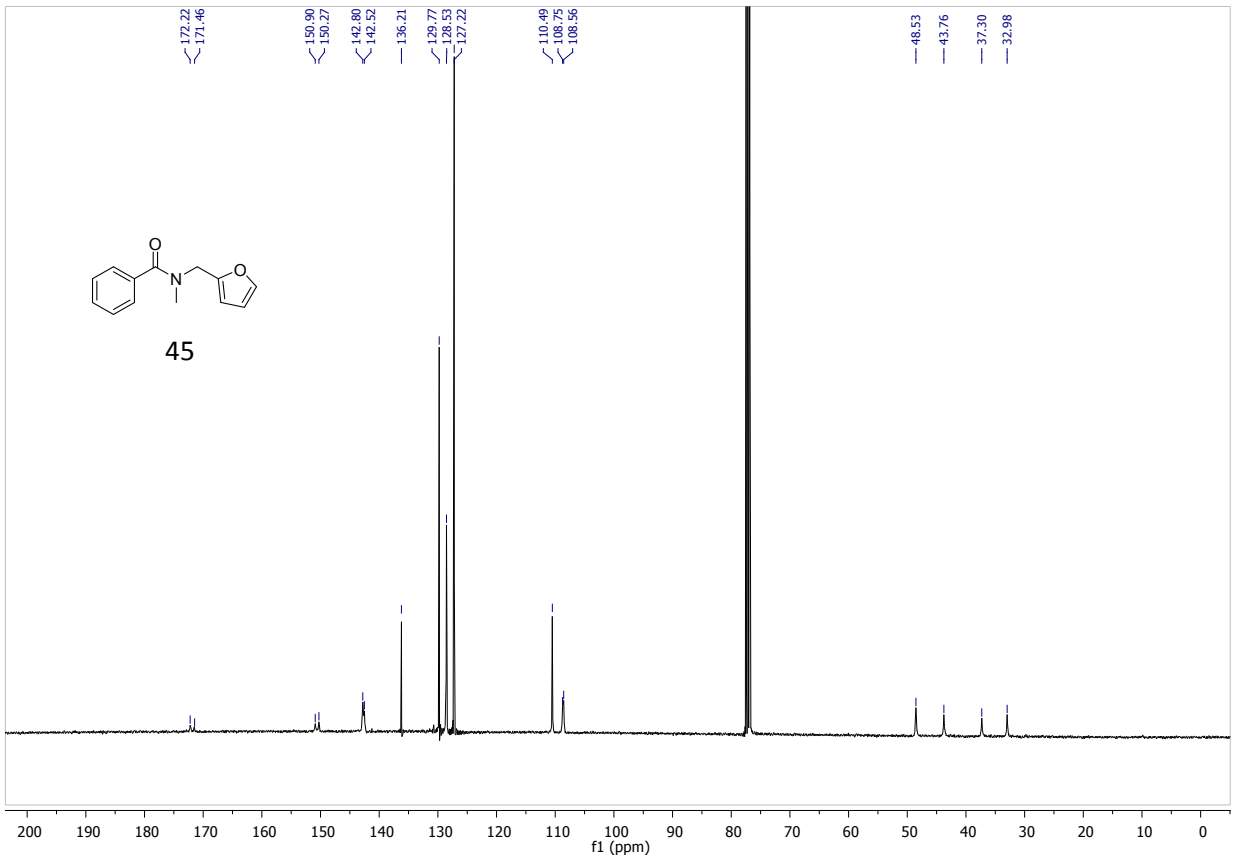
N-methyl-N-(thiophen-2-ylmethyl)benzamide (44)



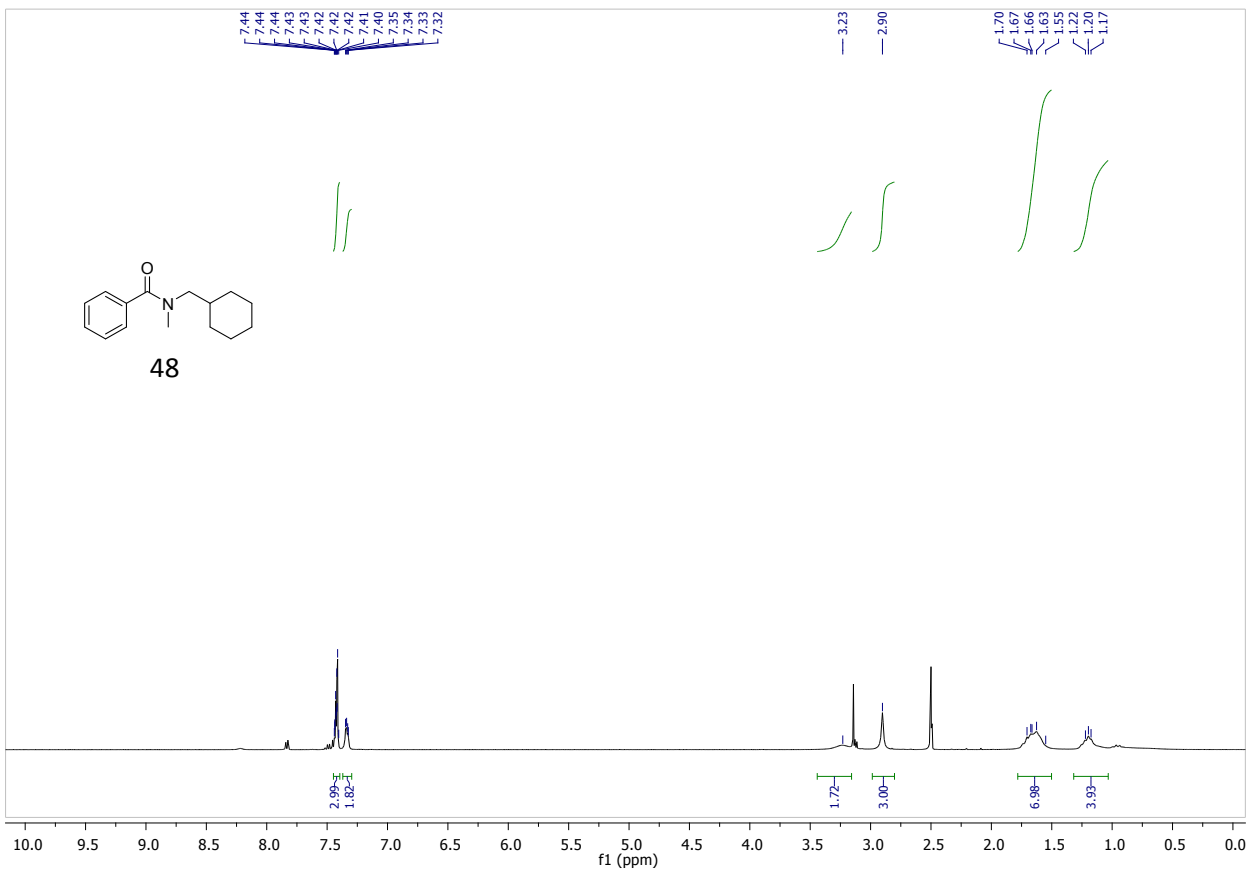


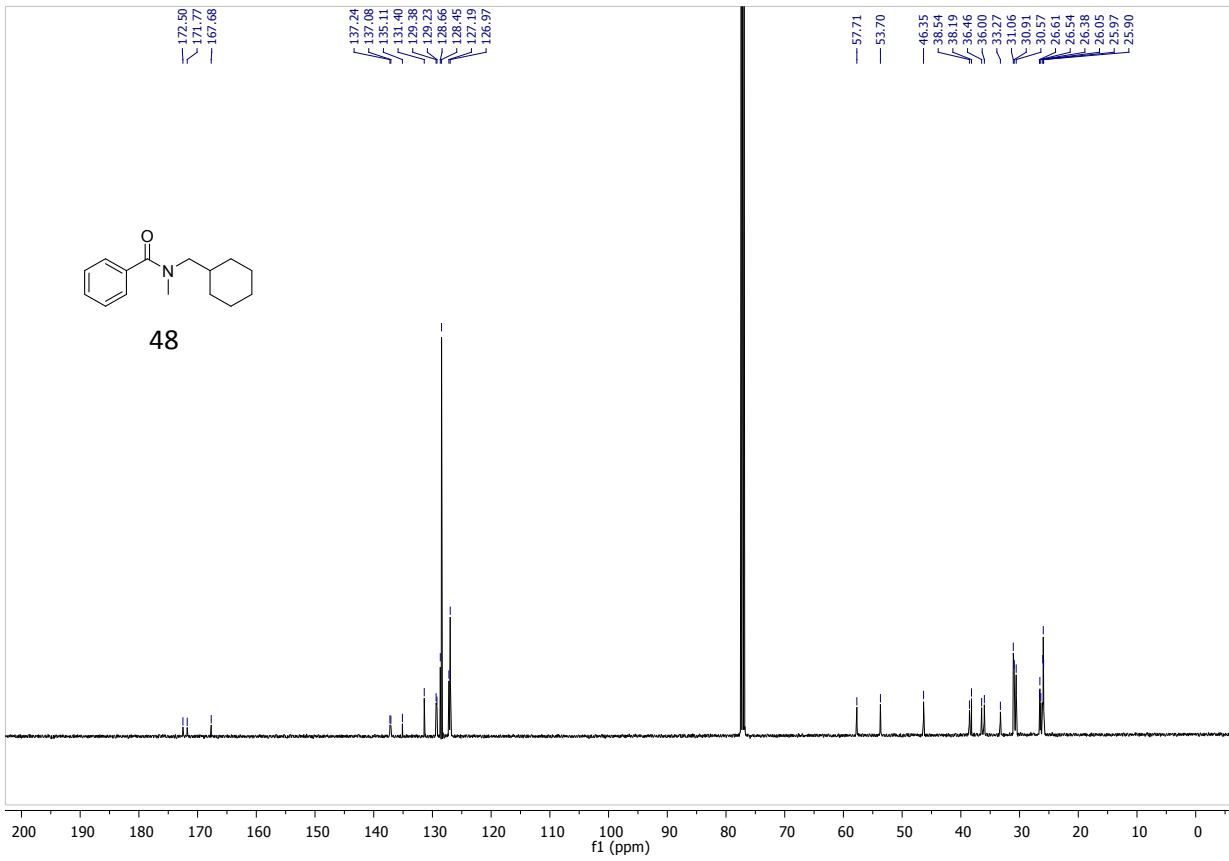
***N*-(furan-2-ylmethyl)-*N*-methylbenzamide (45)**



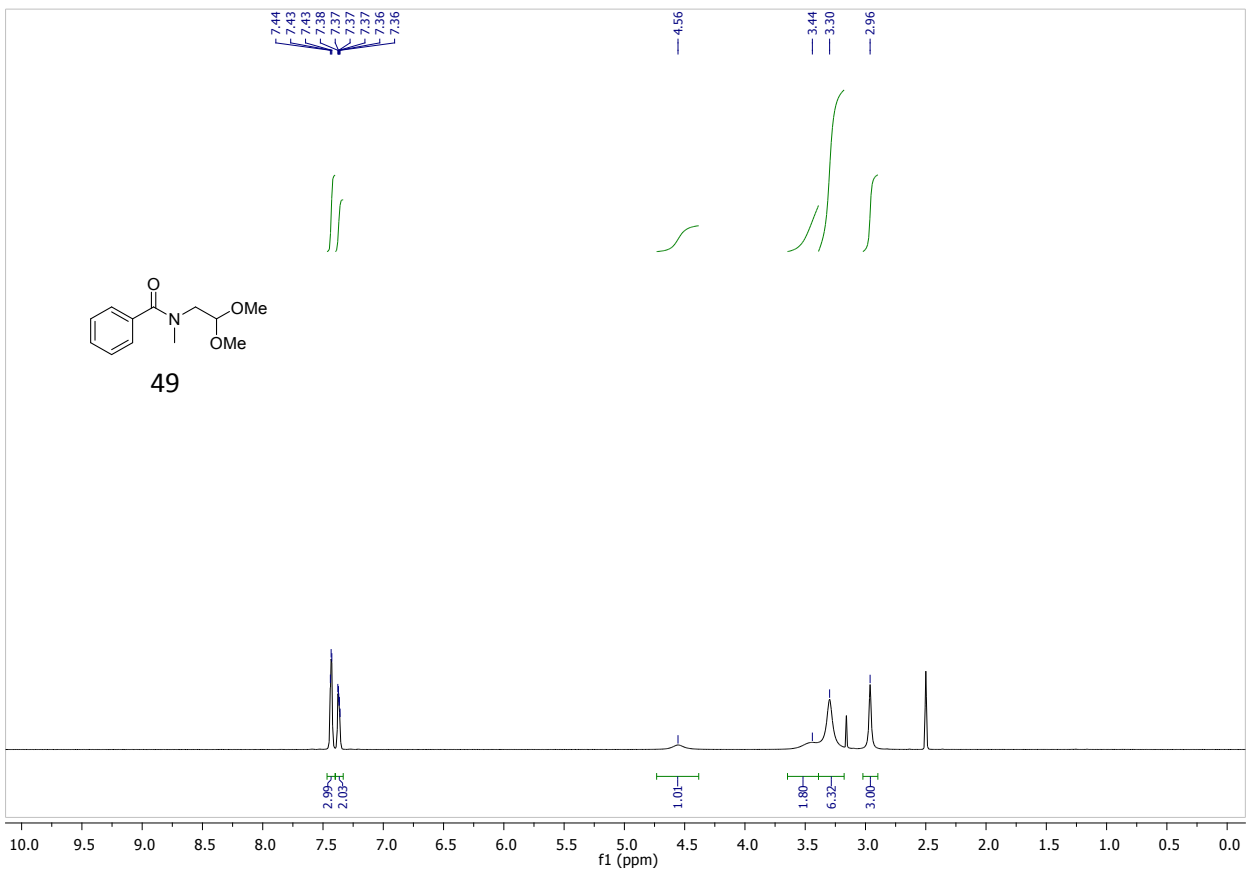


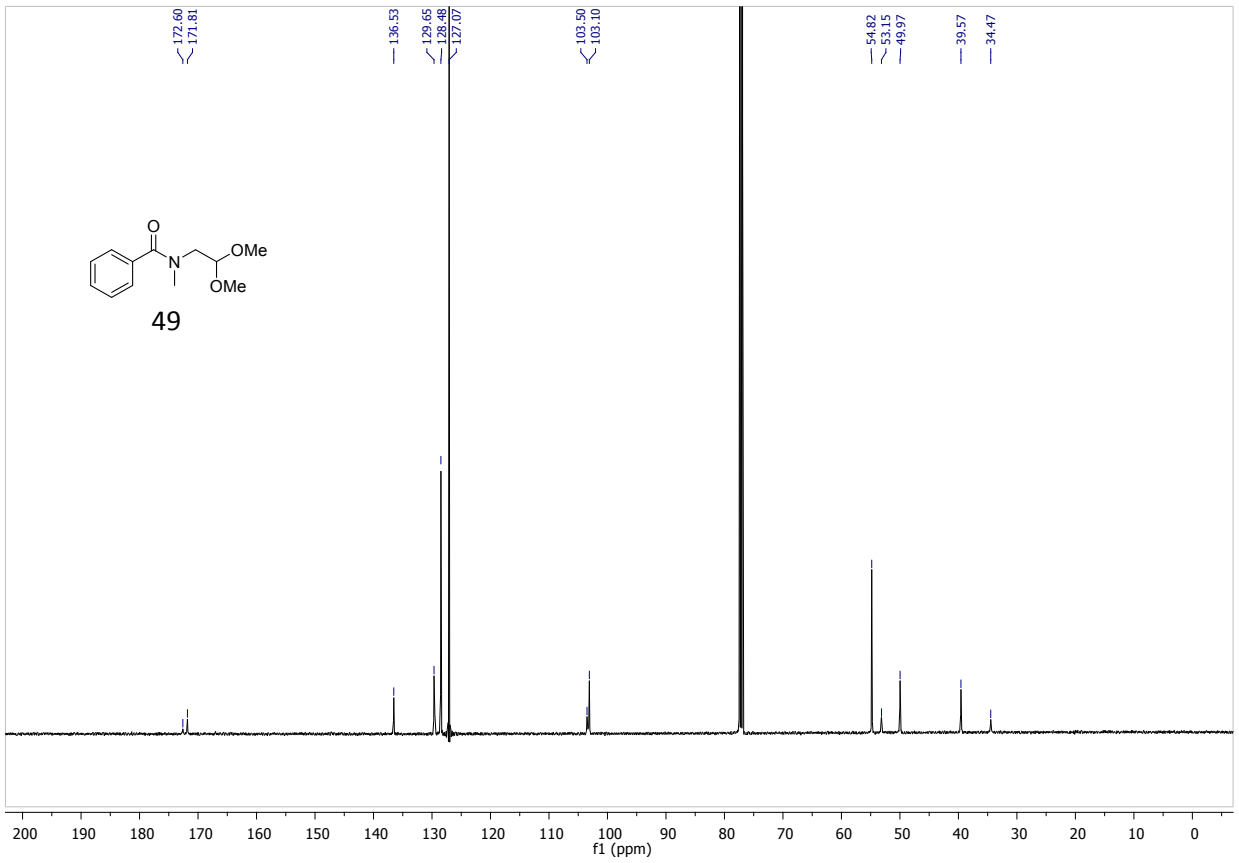
***N*-(cyclohexylmethyl)-*N*-methylbenzamide (48)**



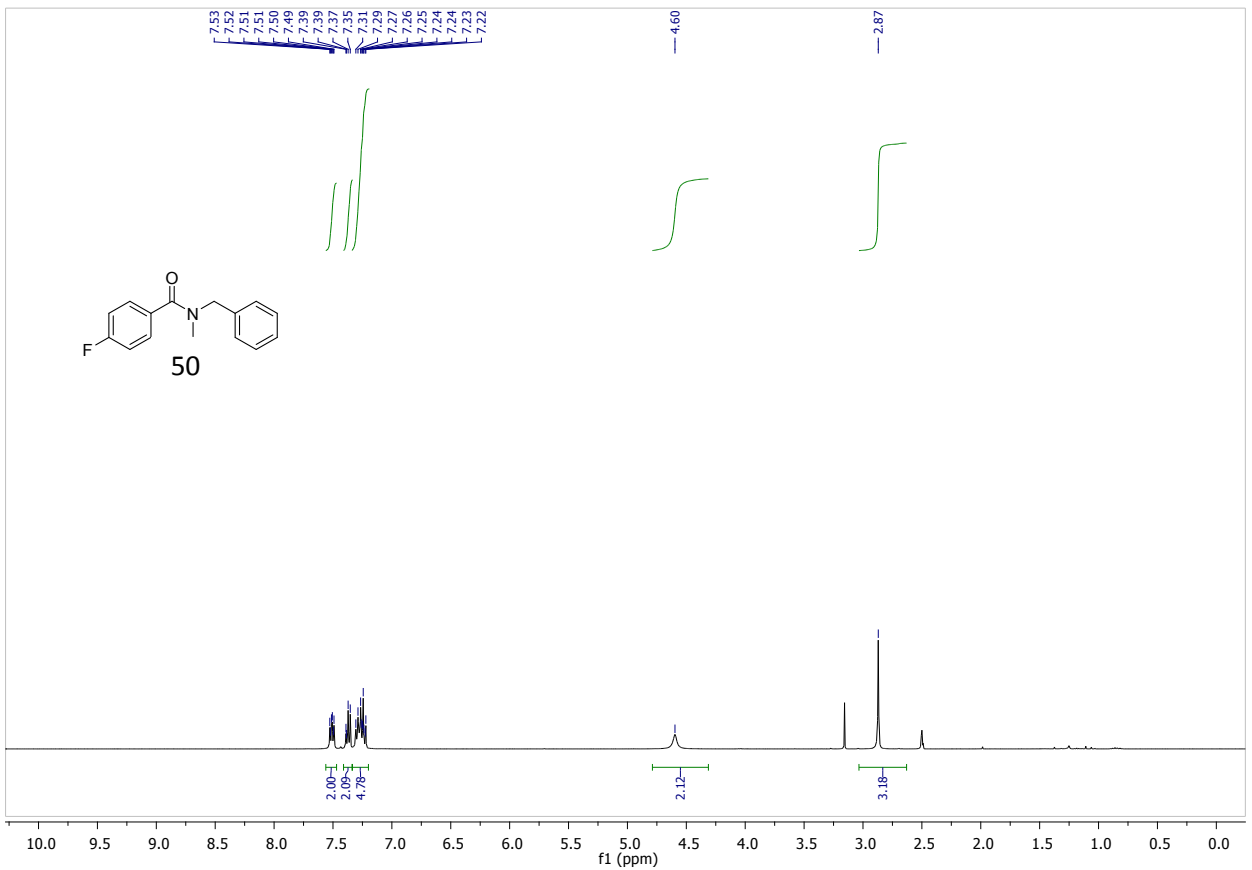


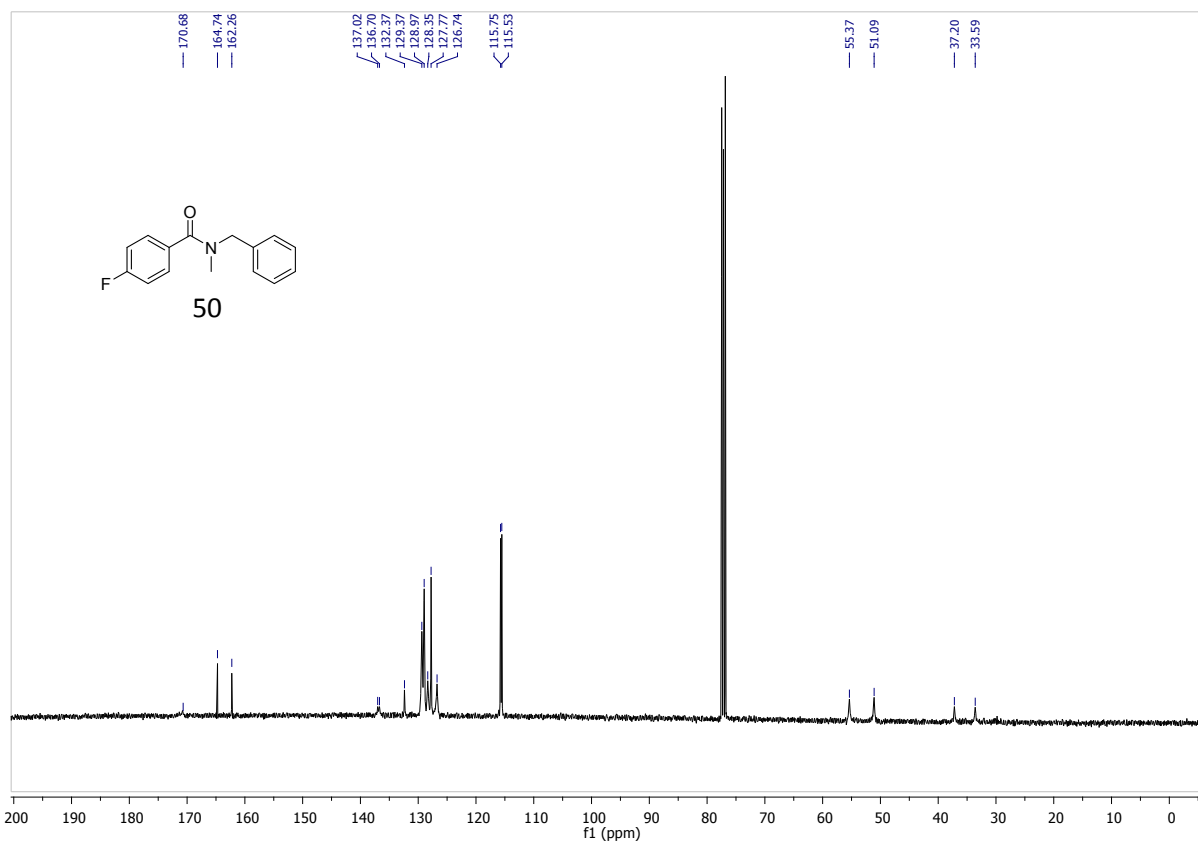
***N*-(2,2-dimethoxyethyl)-*N*-methylbenzamide (49)**



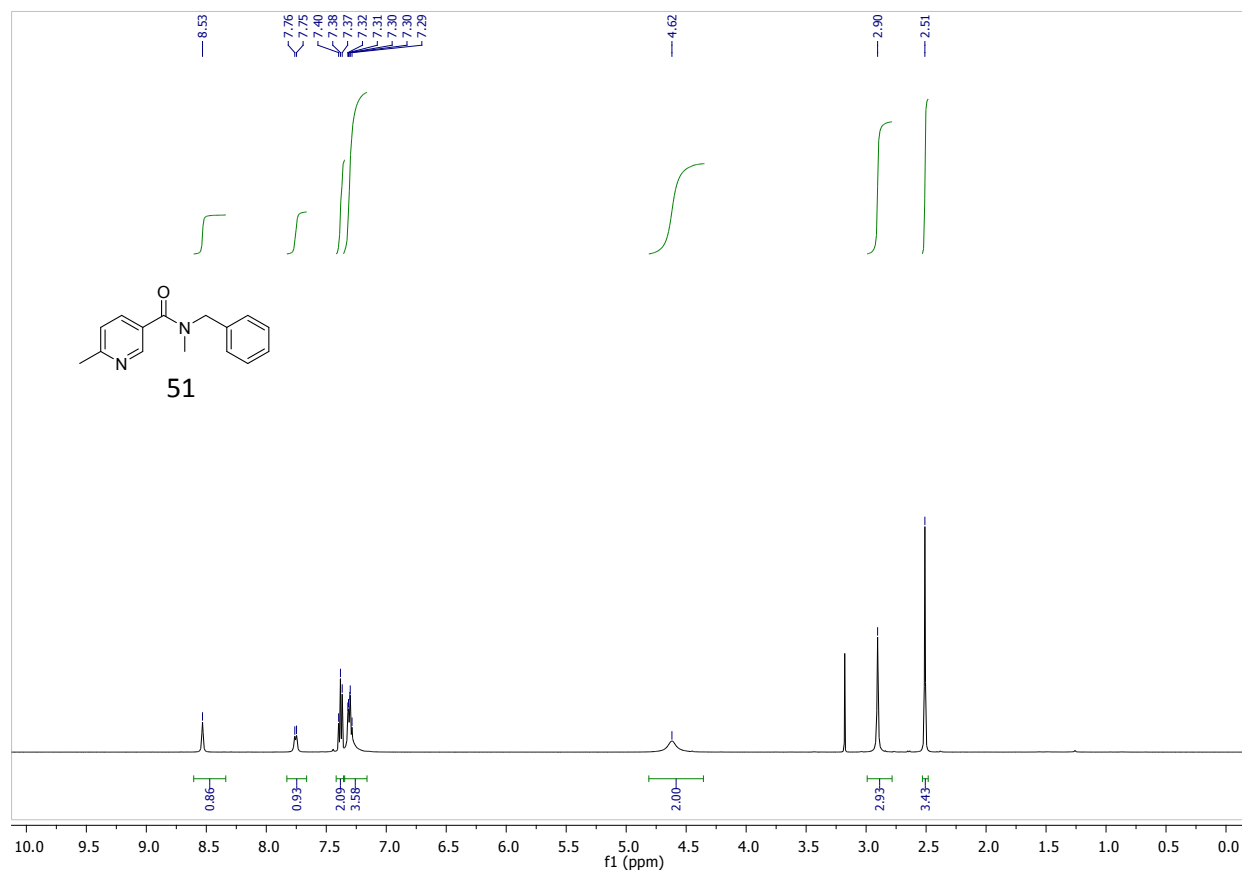


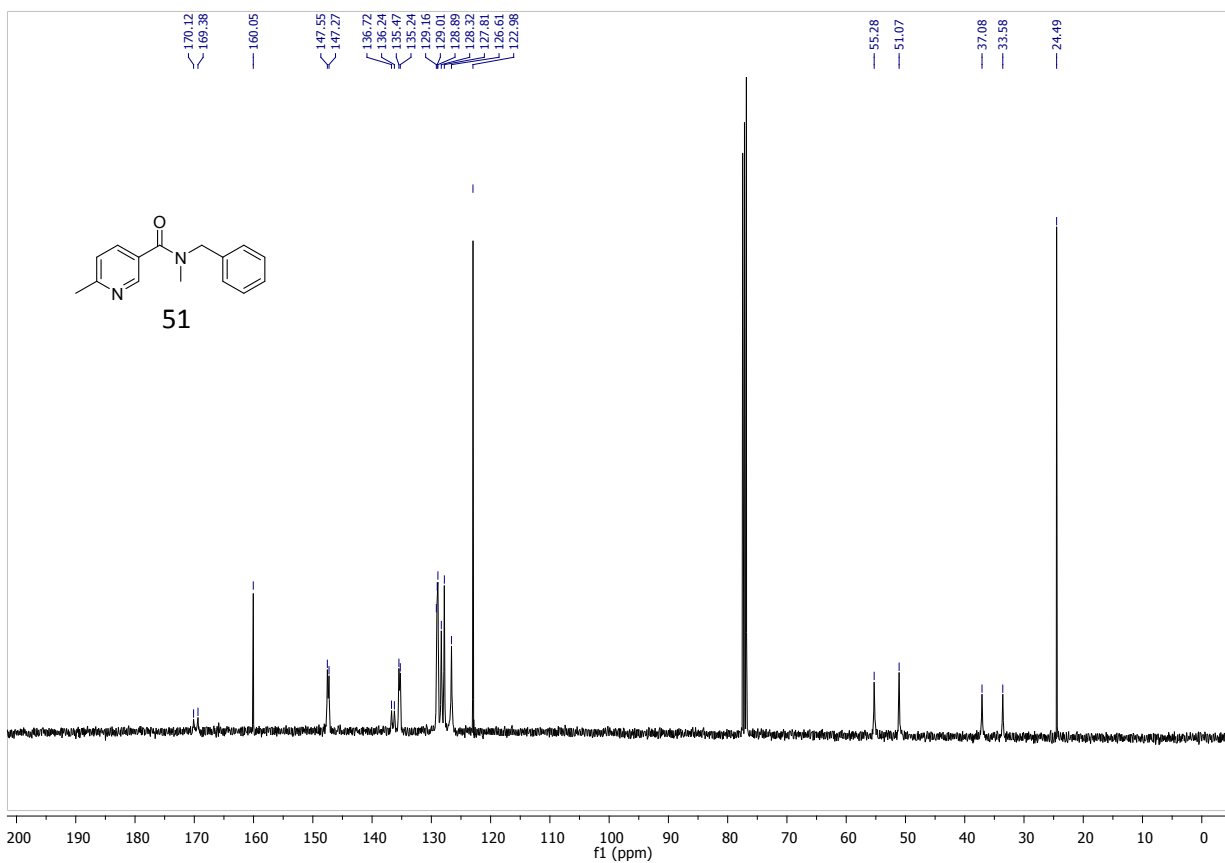
N-benzyl-4-fluoro-N-methylbenzamide (50)



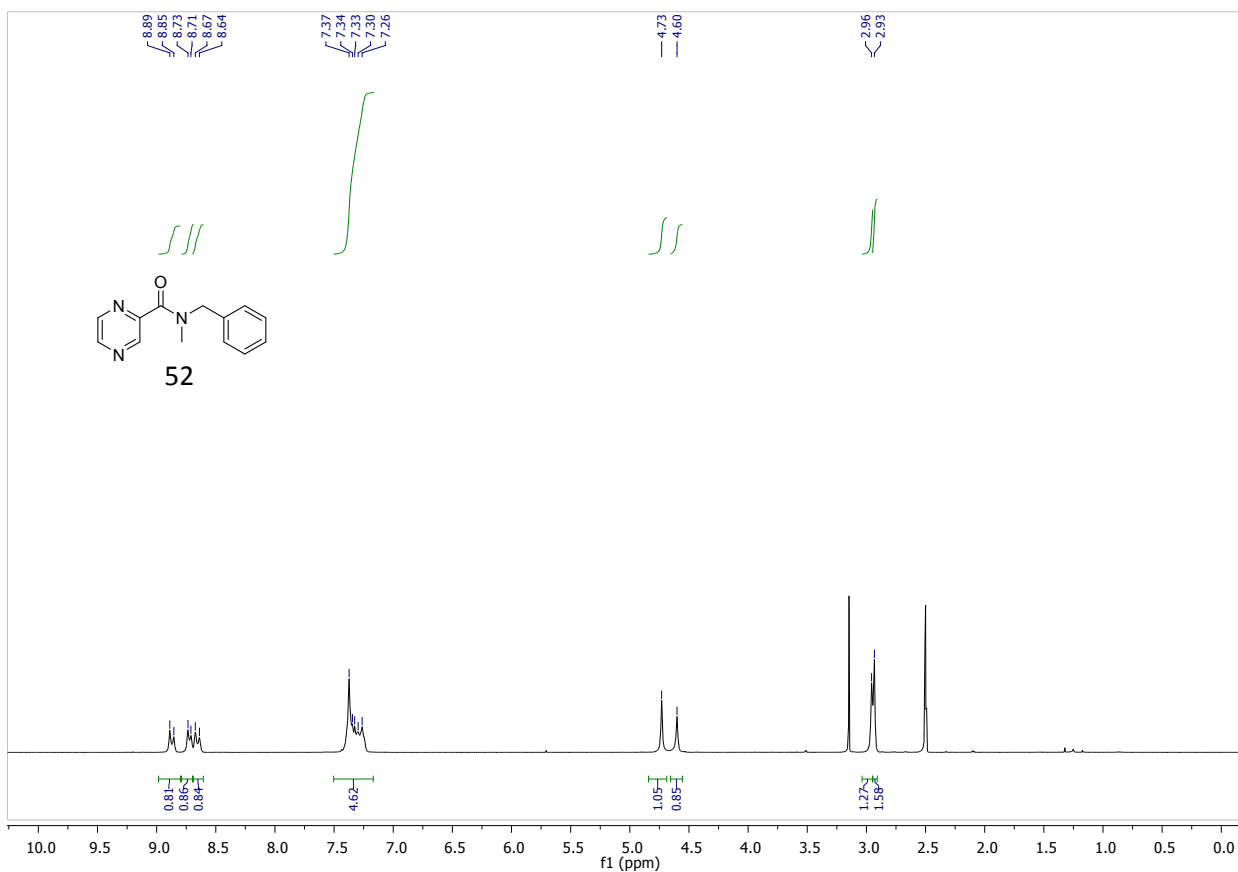


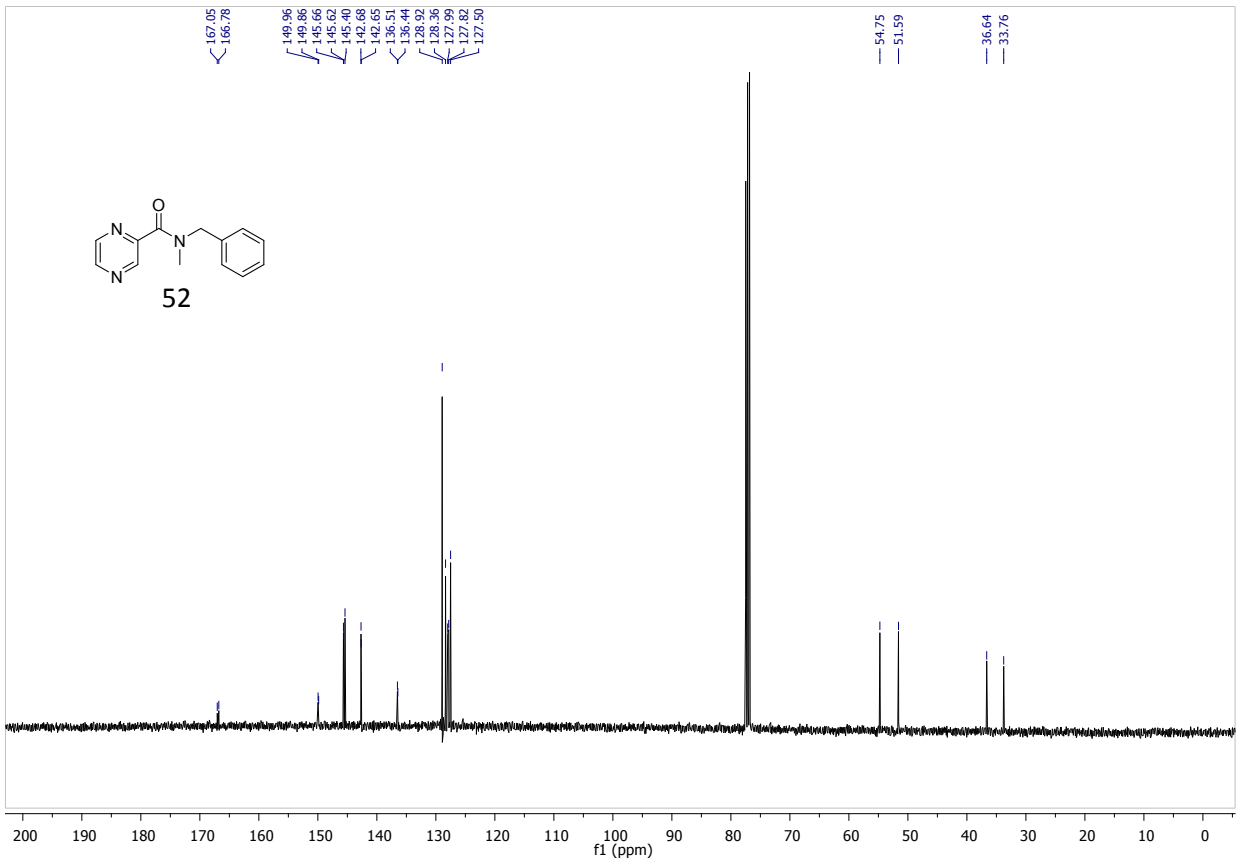
N-benzyl-N,6-dimethylnicotinamide (51)



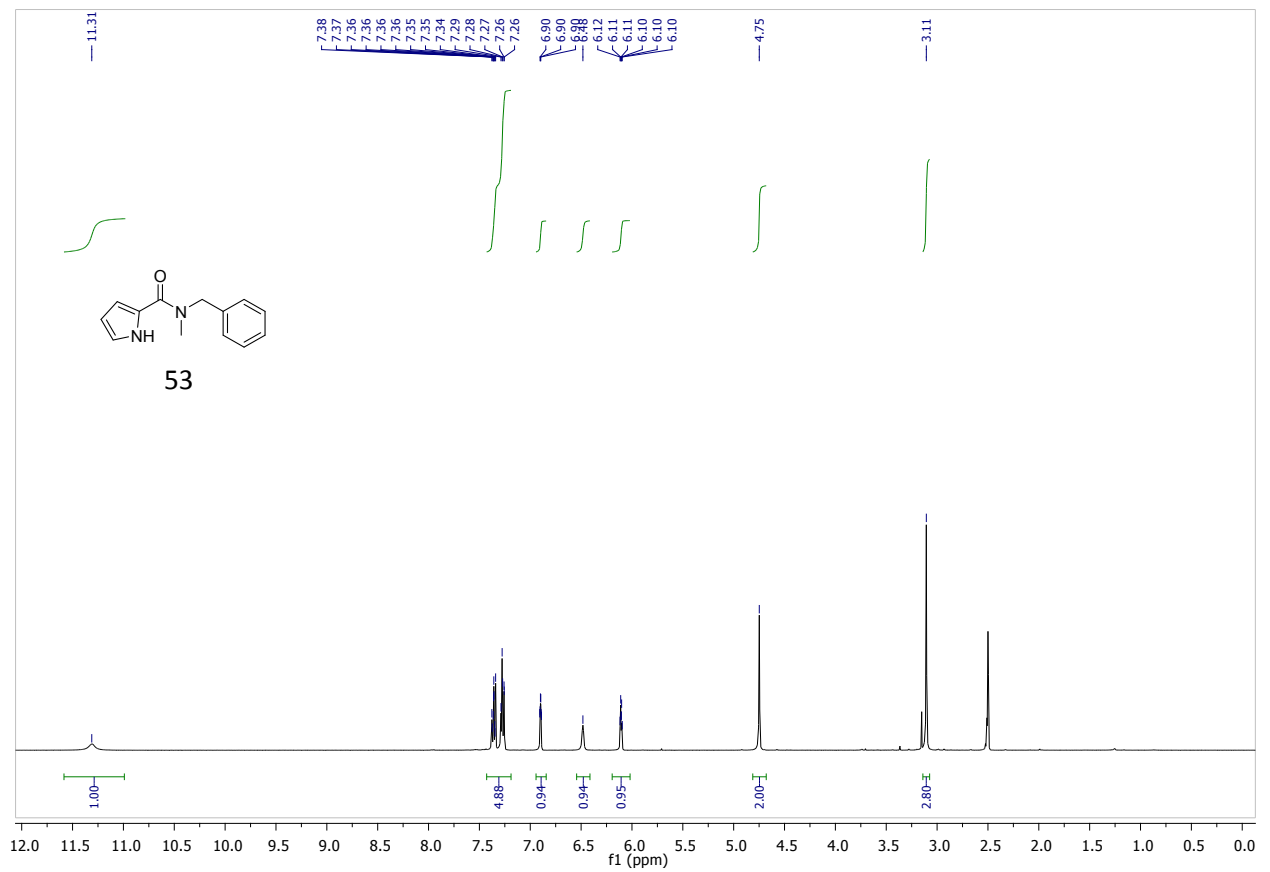


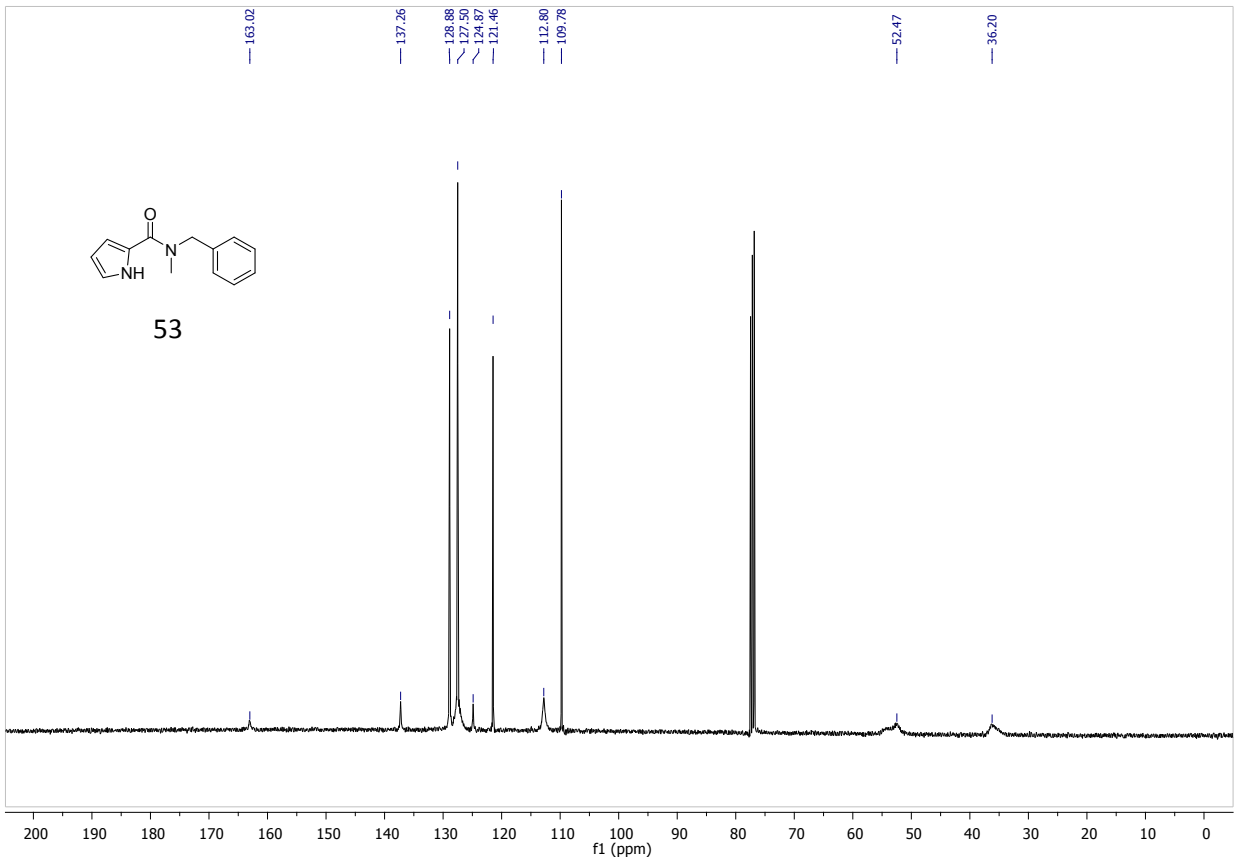
N-benzyl-N-methylpyrazine-2-carboxamide (52)



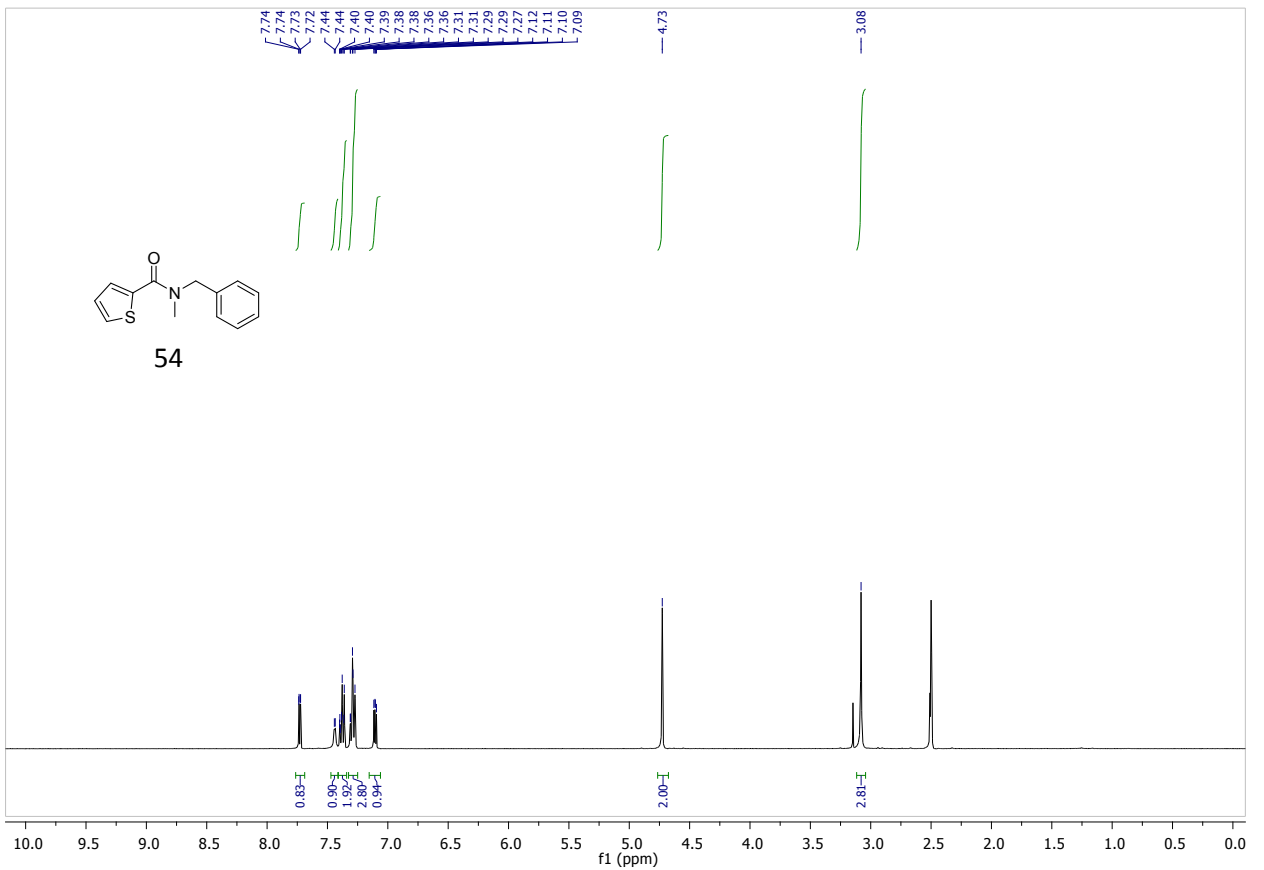


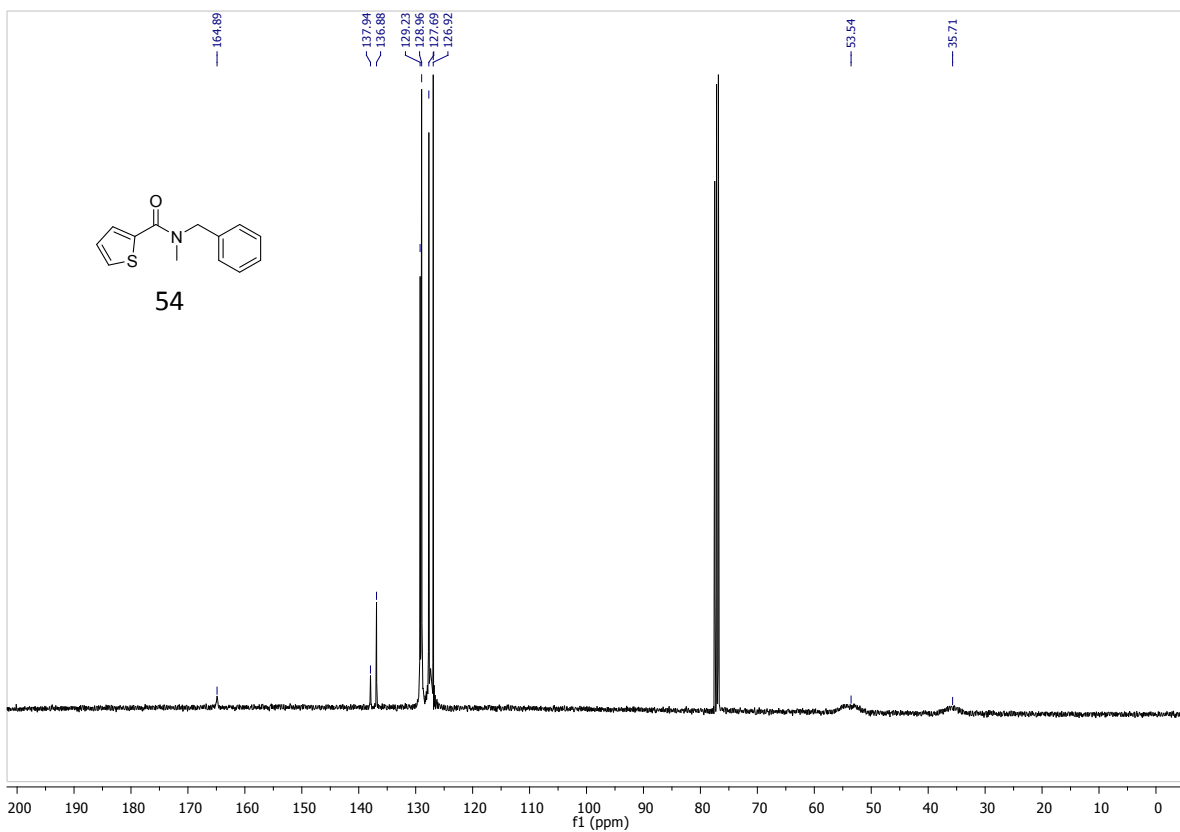
***N*-benzyl-*N*-methyl-1H-pyrrole-2-carboxamide (53)**



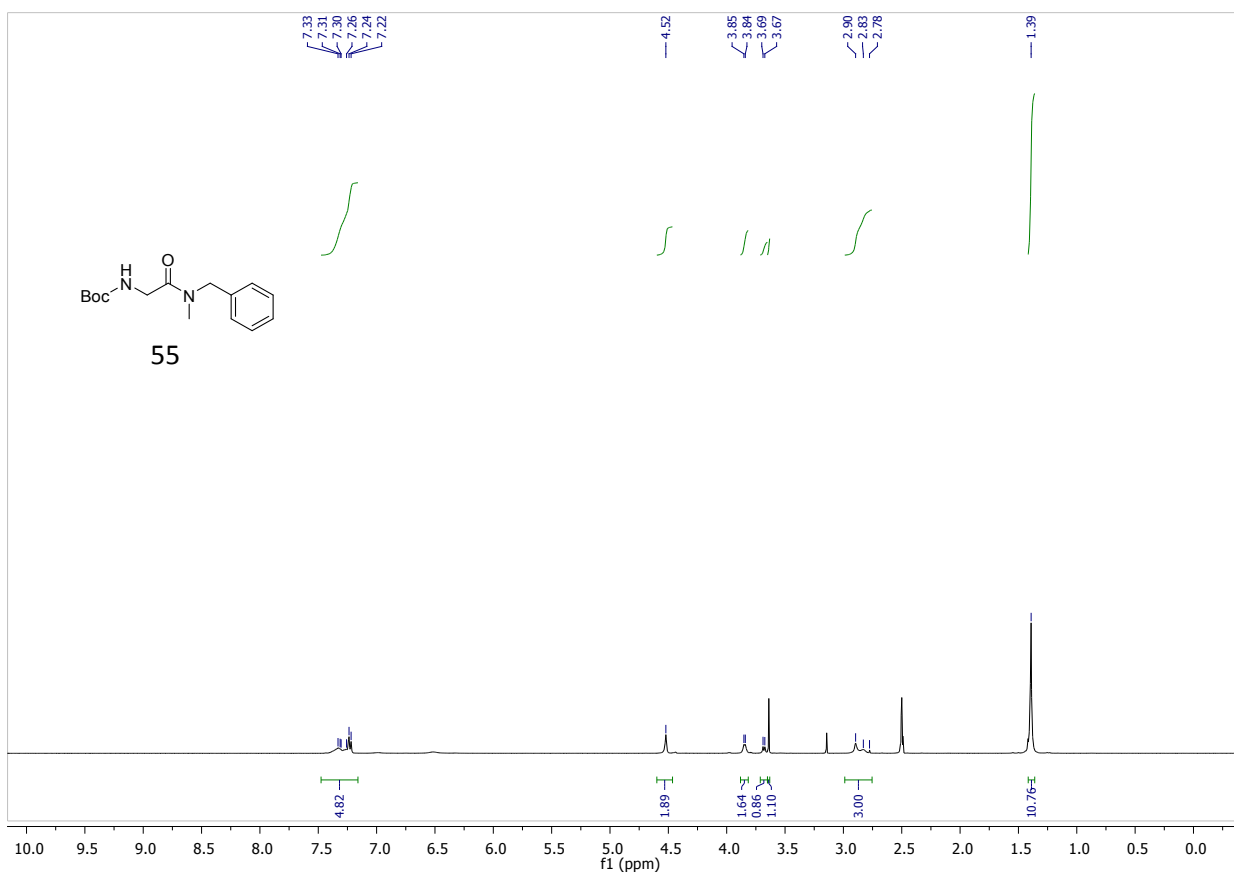


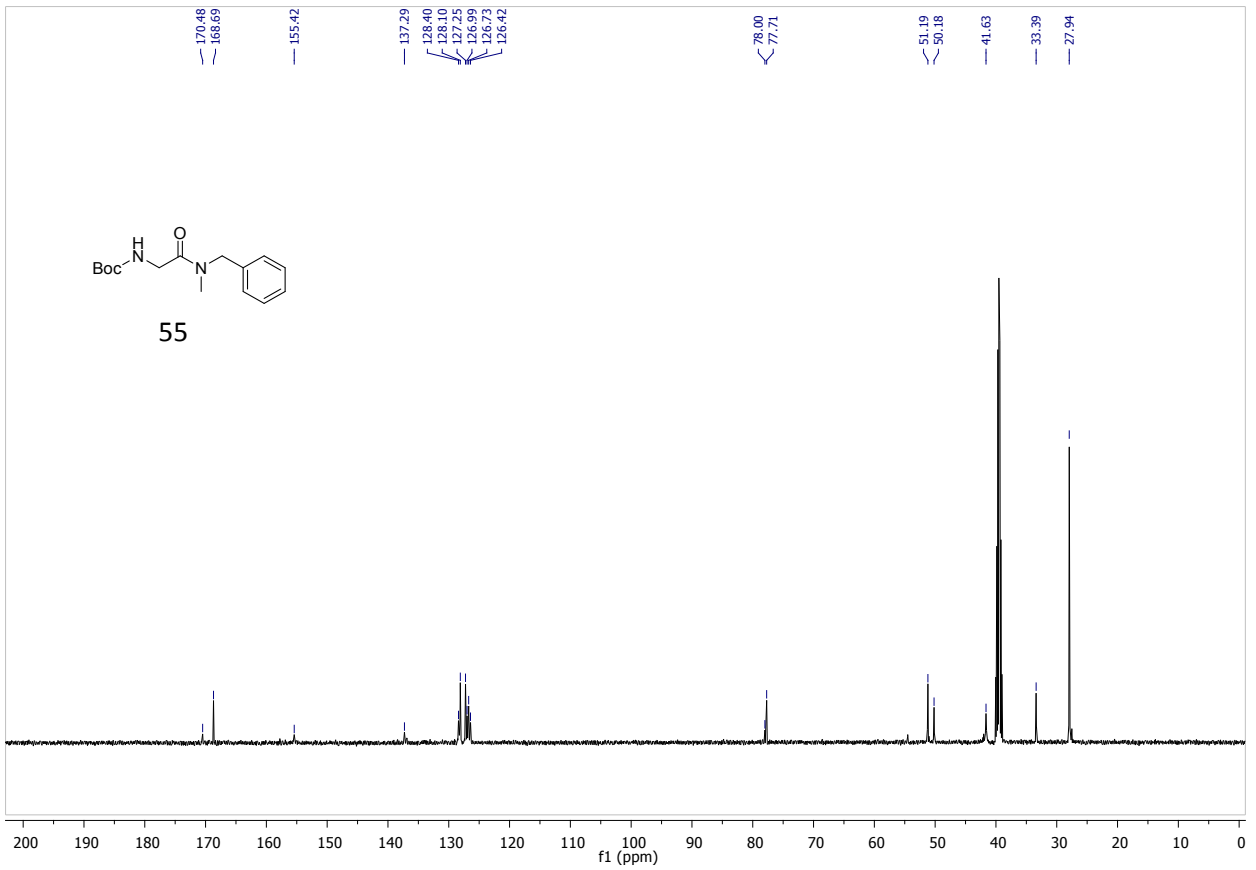
N-benzyl-N-methylthiophene-2-carboxamide (54)



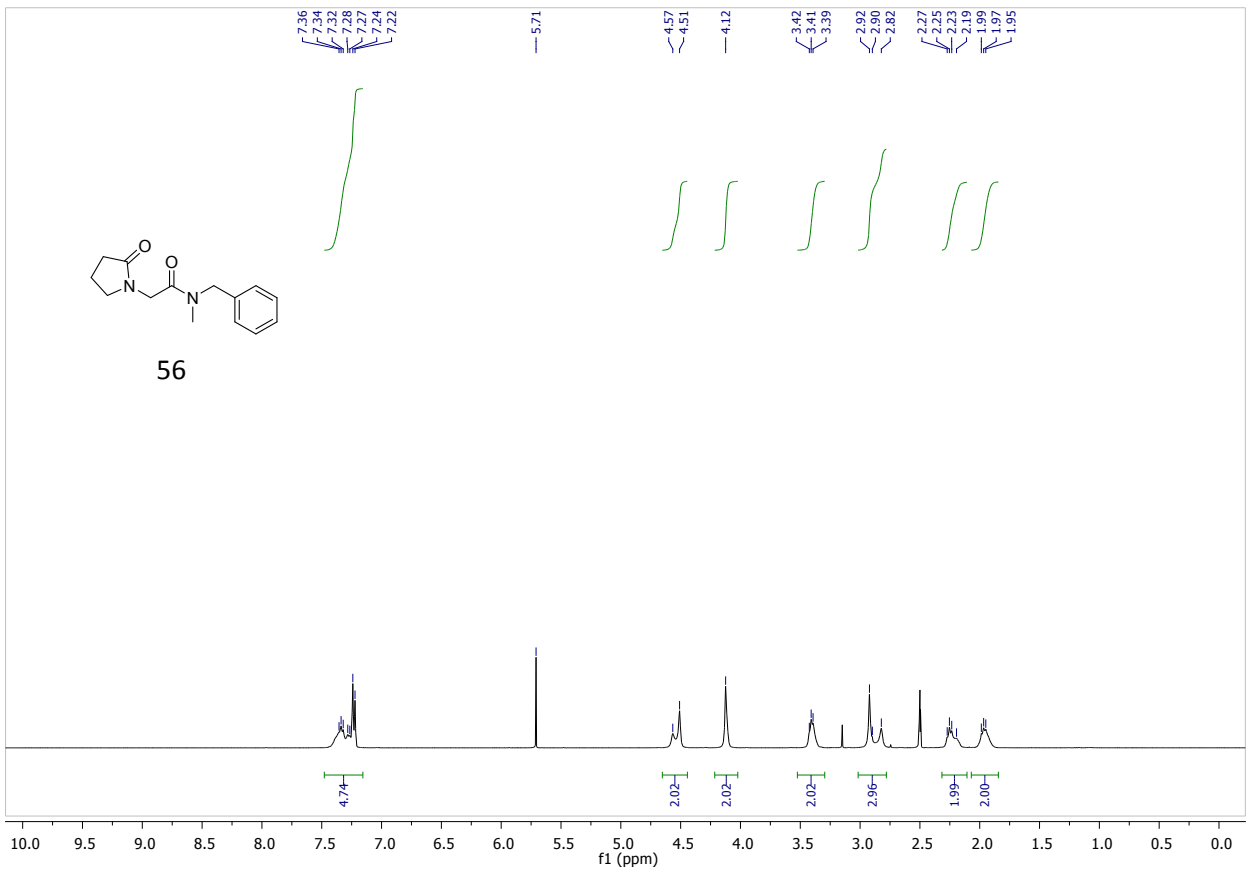


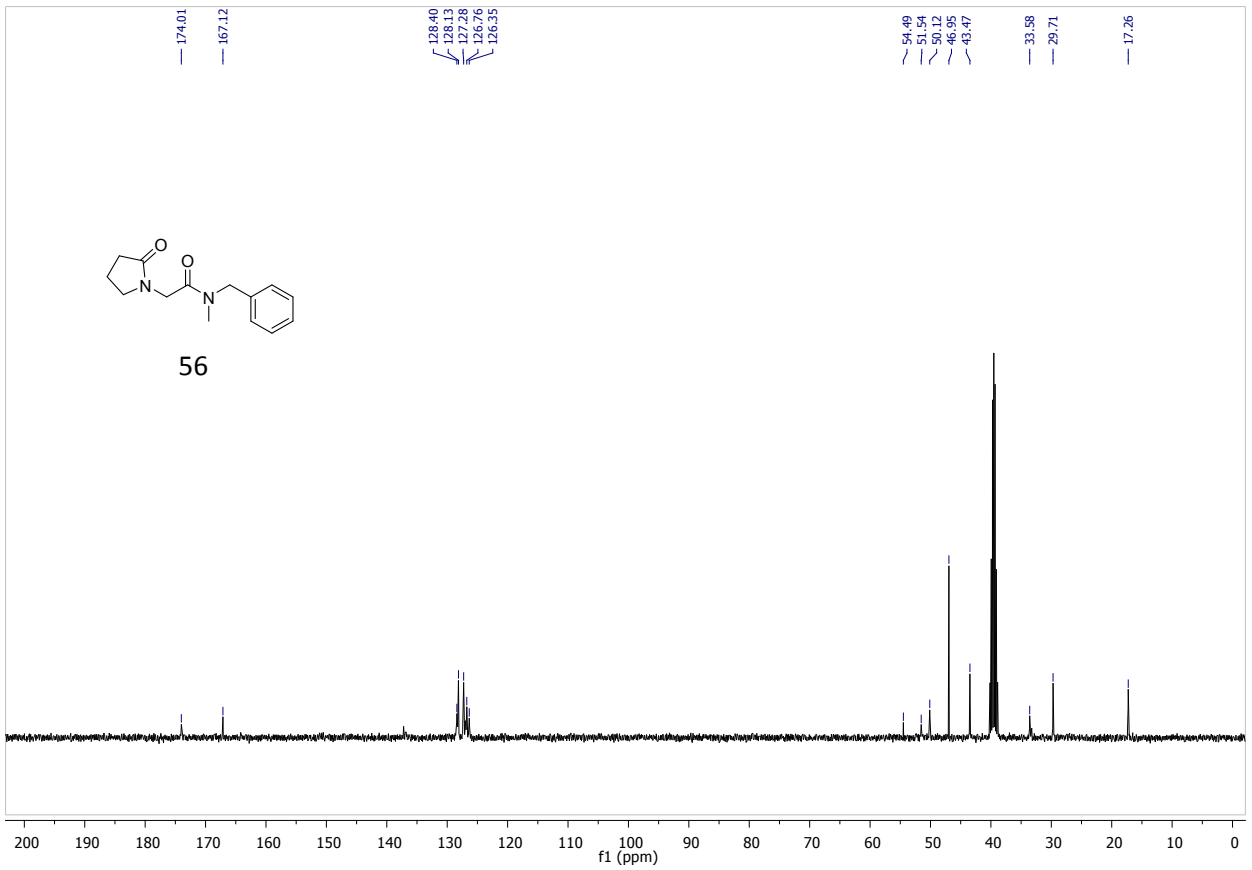
tert-butyl (2-(benzyl(methyl)amino)-2-oxoethyl)carbamate (55)



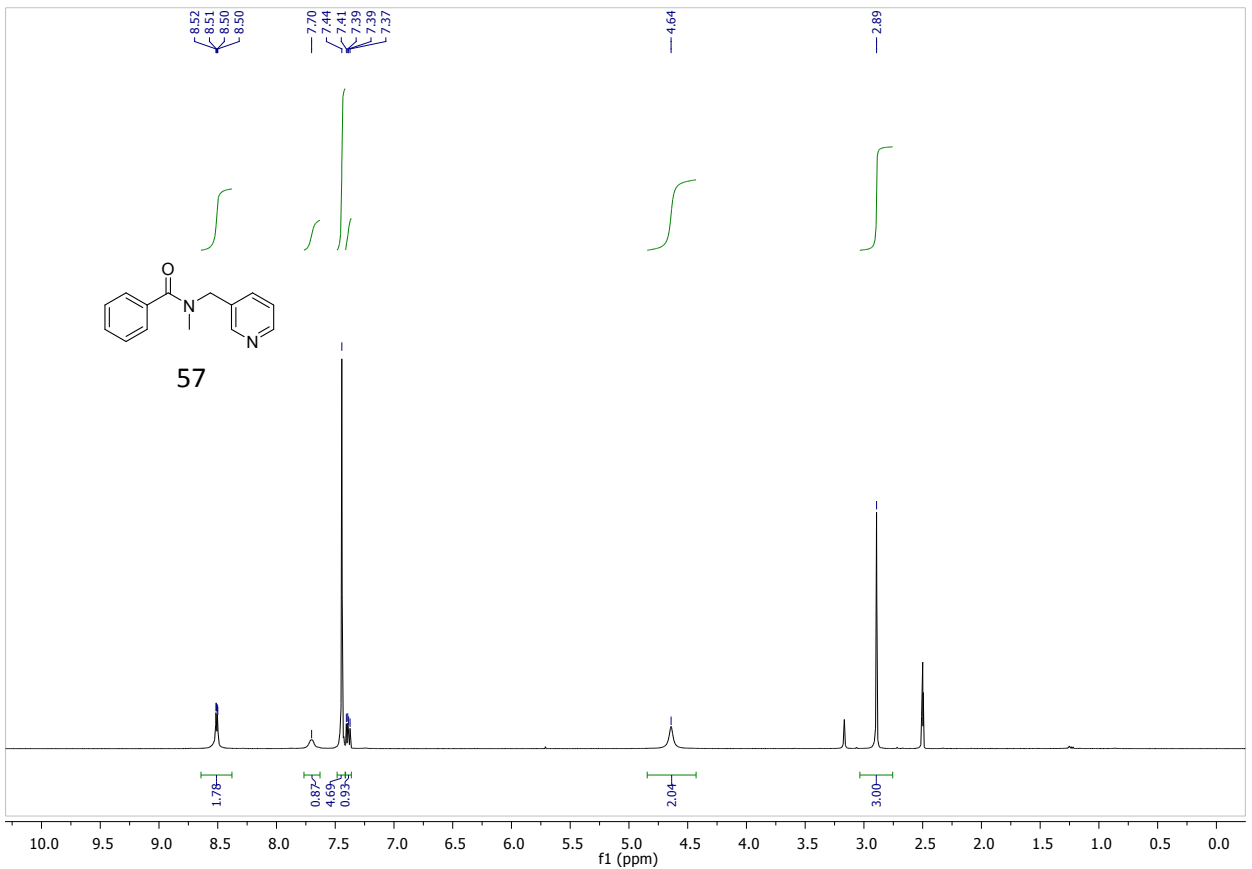


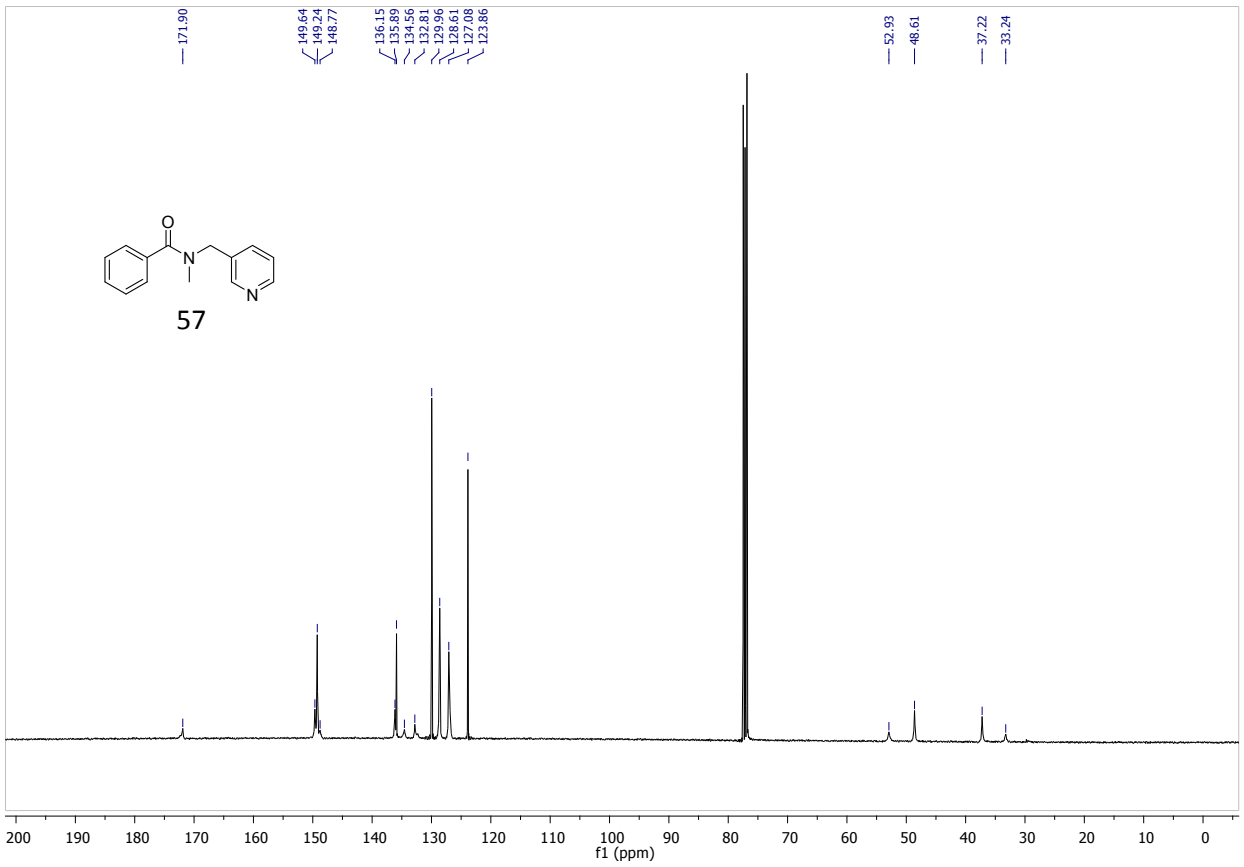
***N*-benzyl-*N*-methyl-2-(2-oxopyrrolidin-1-yl)acetamide (56)**



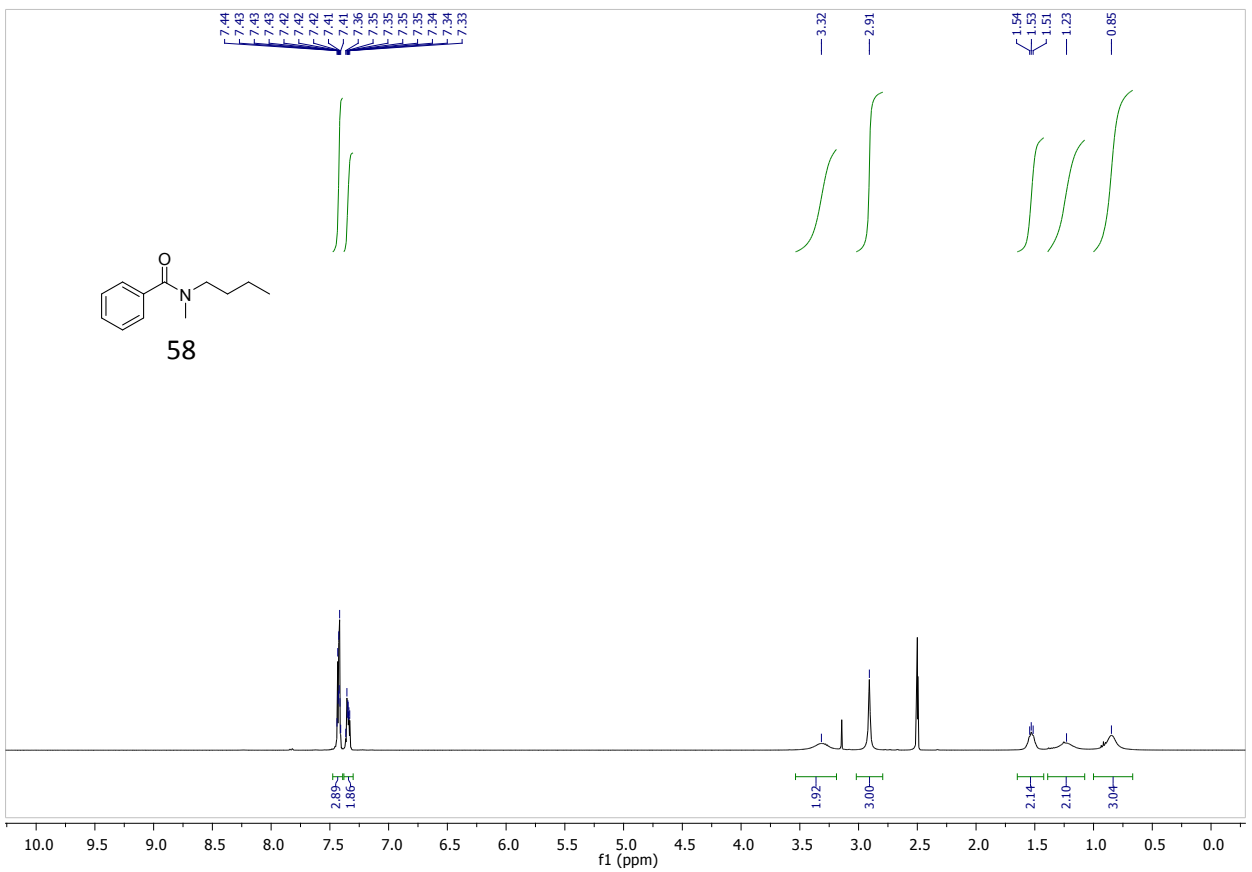


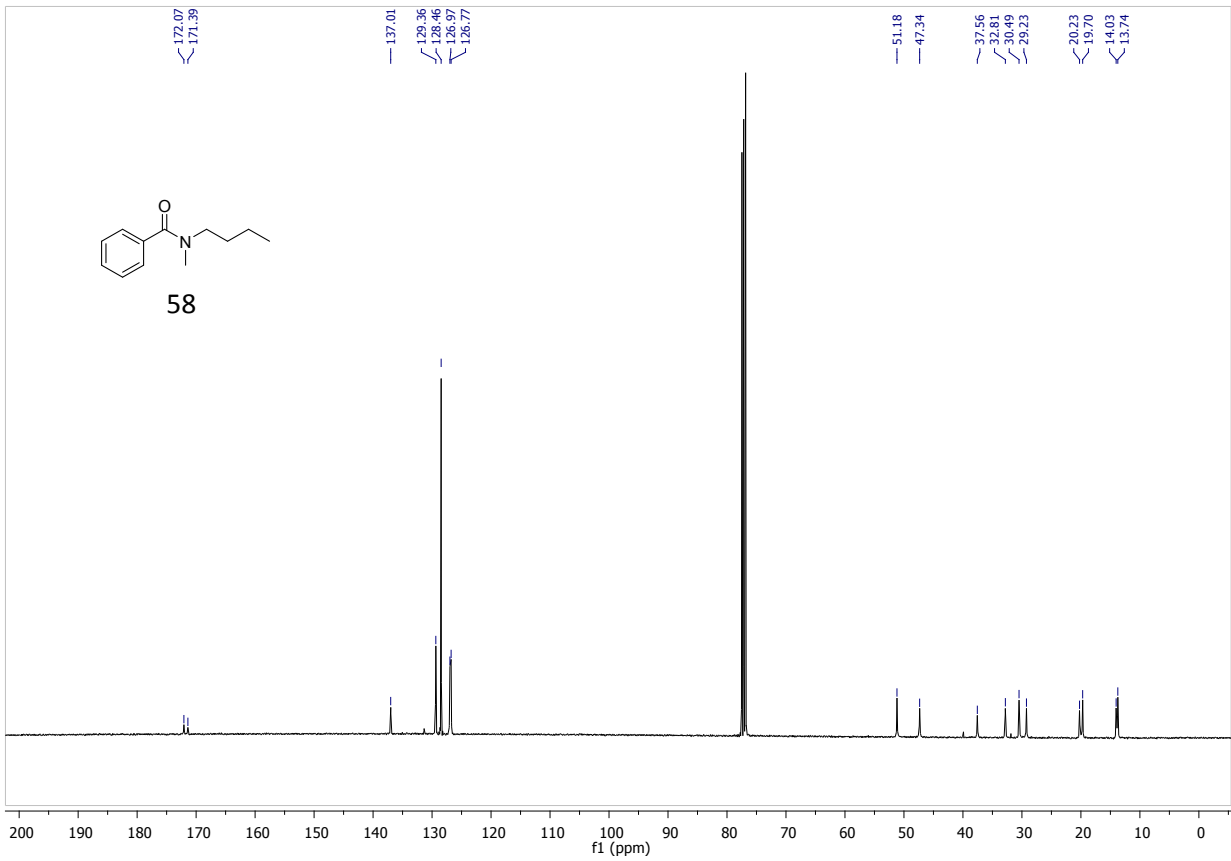
***N*-methyl-*N*-(pyridin-3-ylmethyl)benzamide (57)**



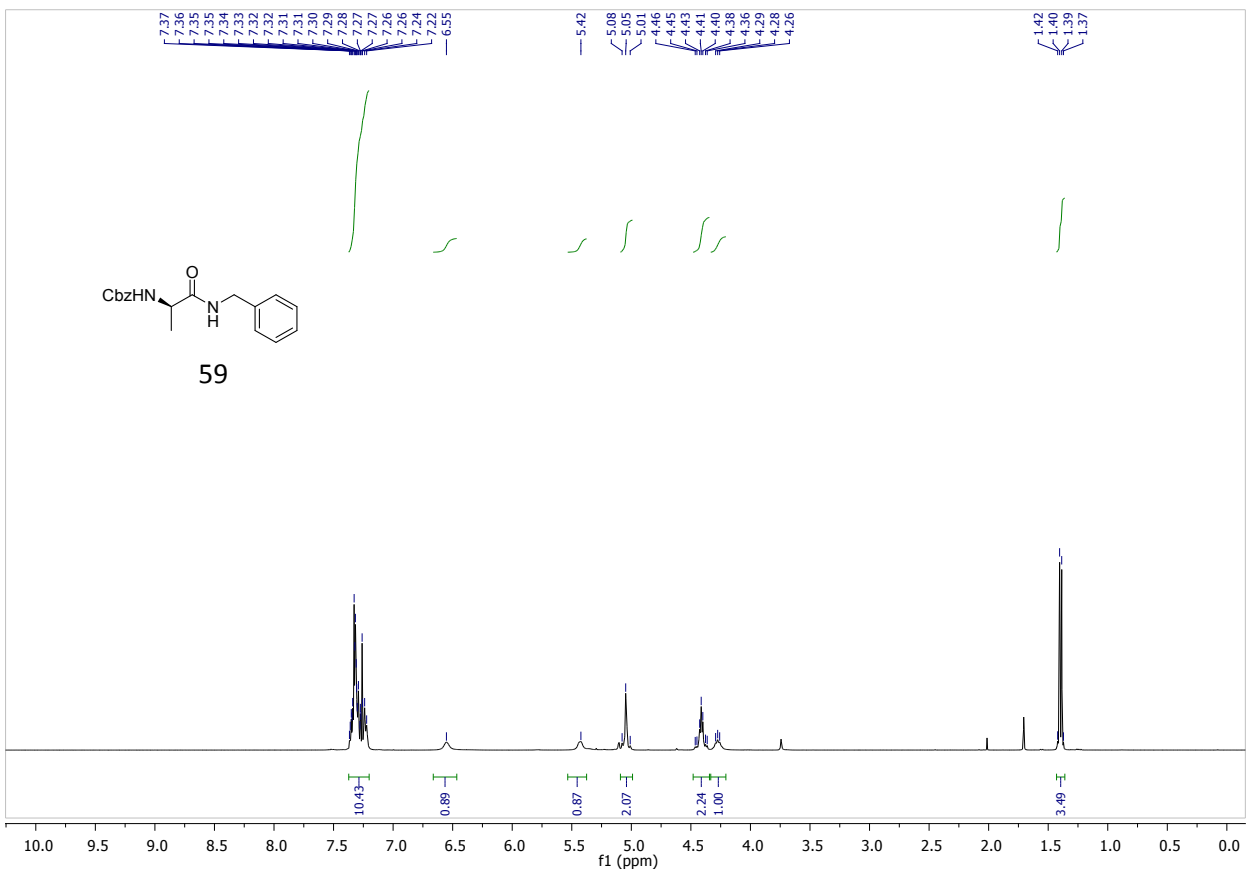


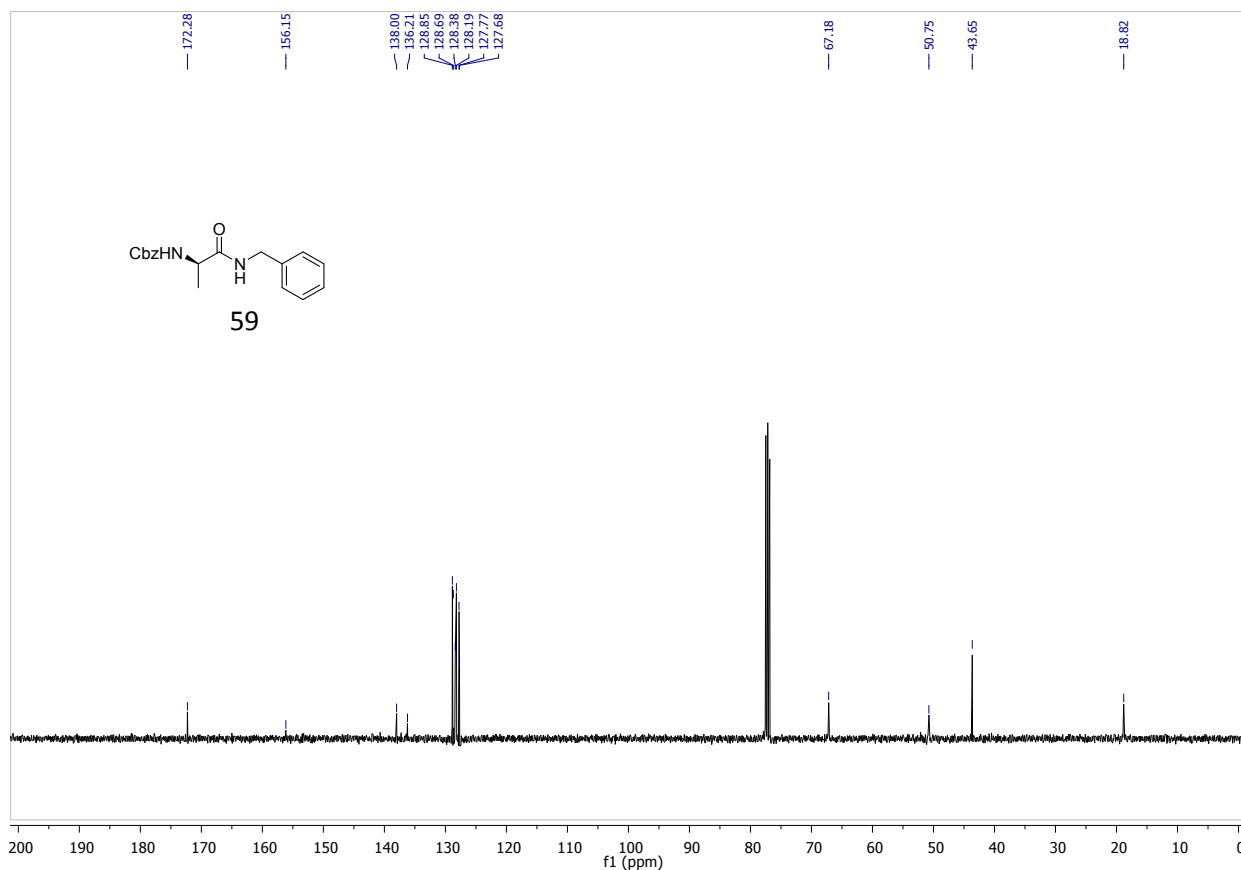
N-butyl-N-methylbenzamide (58)



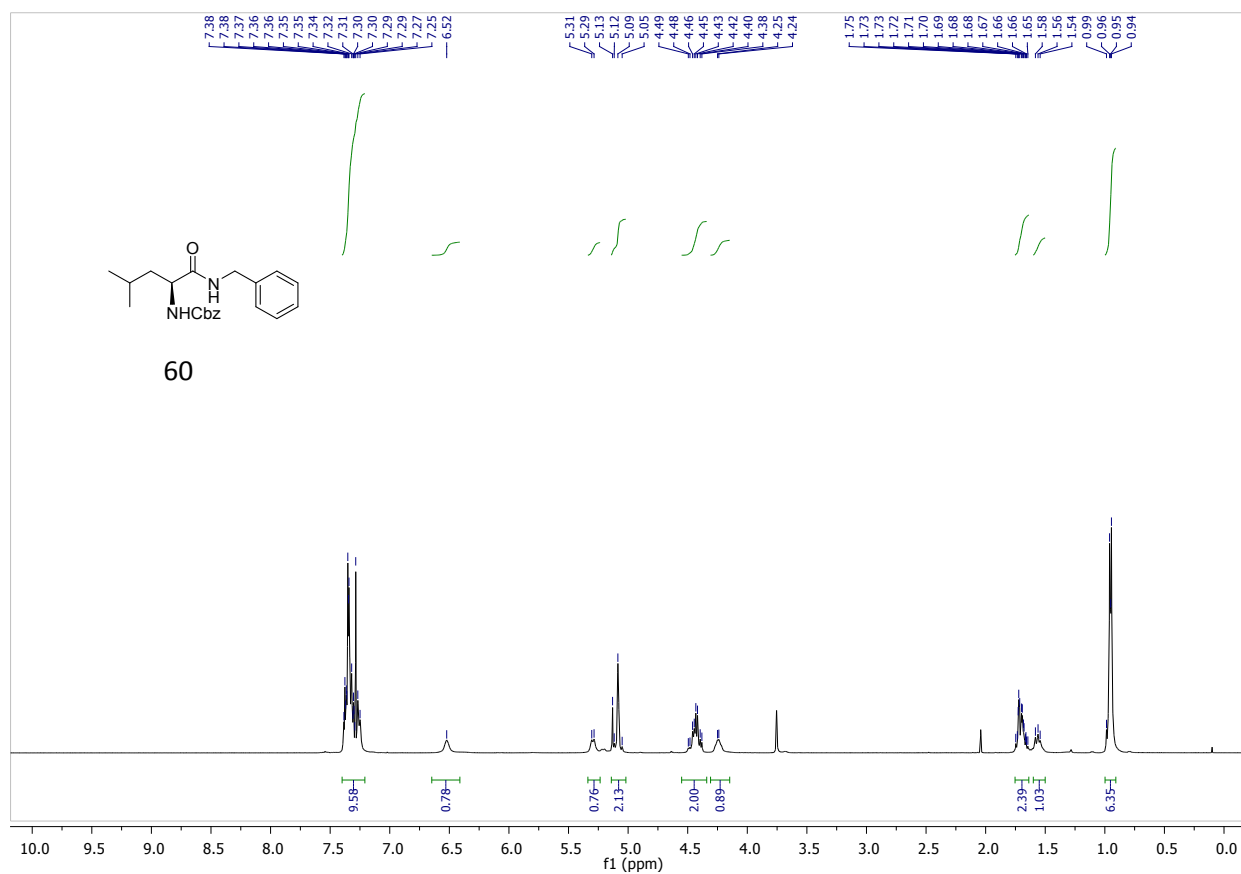


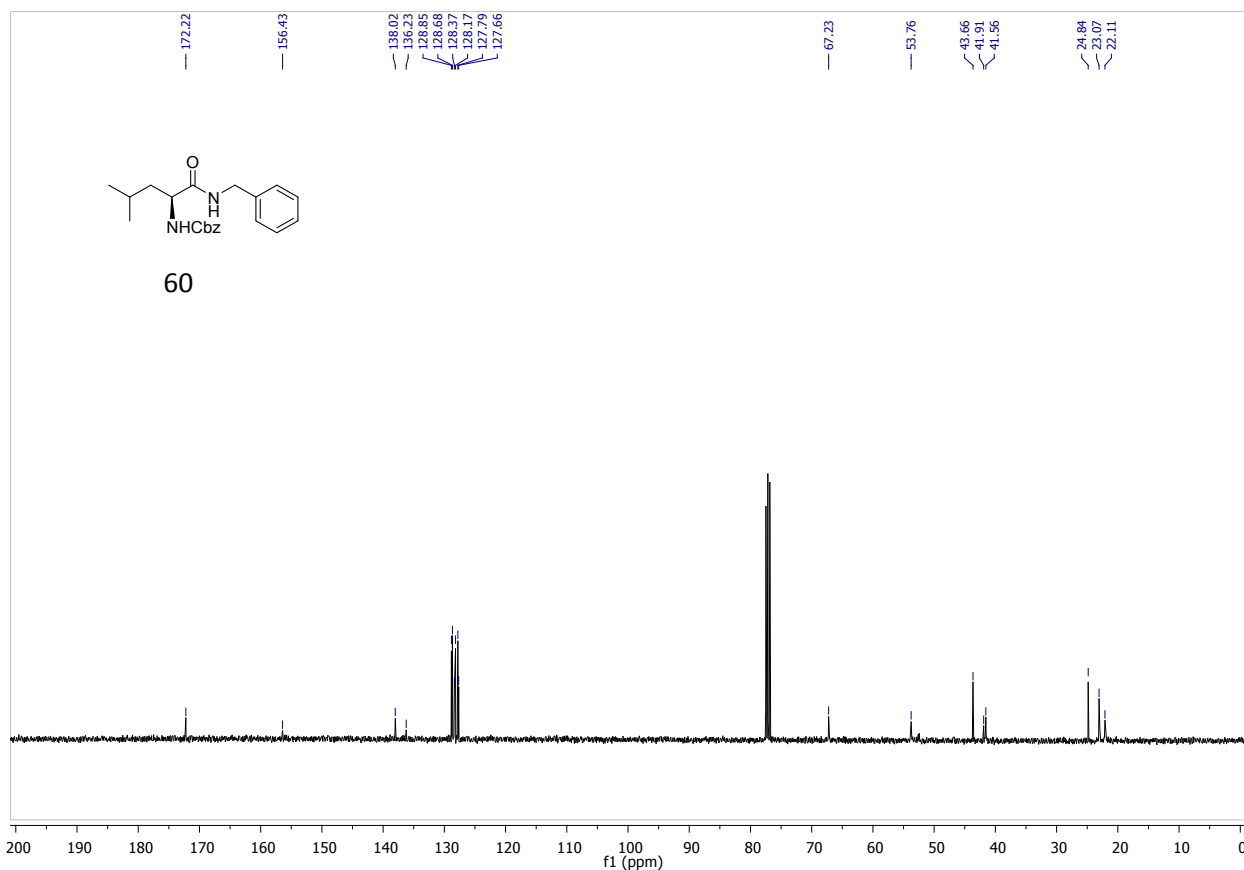
benzyl (*R*)-(1-(benzylamino)-1-oxopropan-2-yl)carbamate (59)



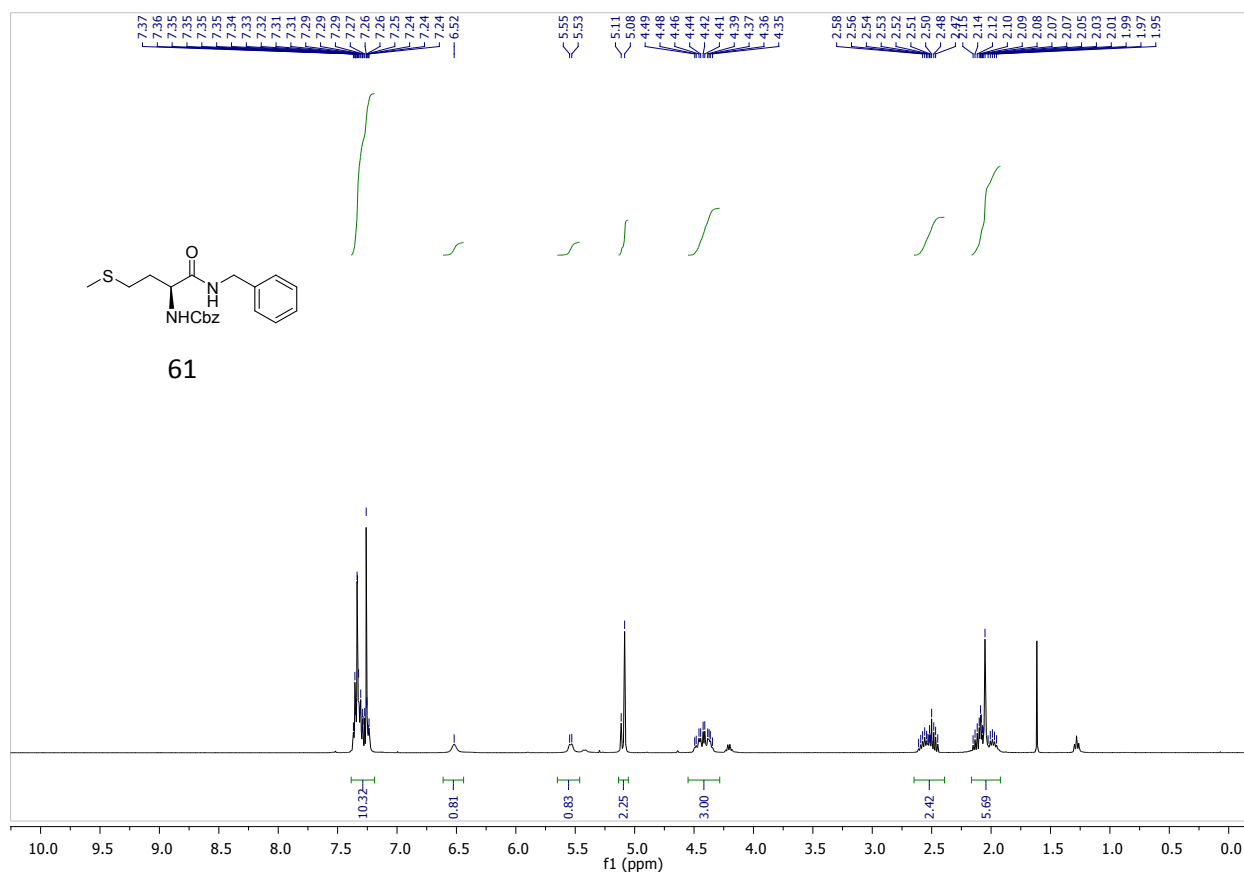


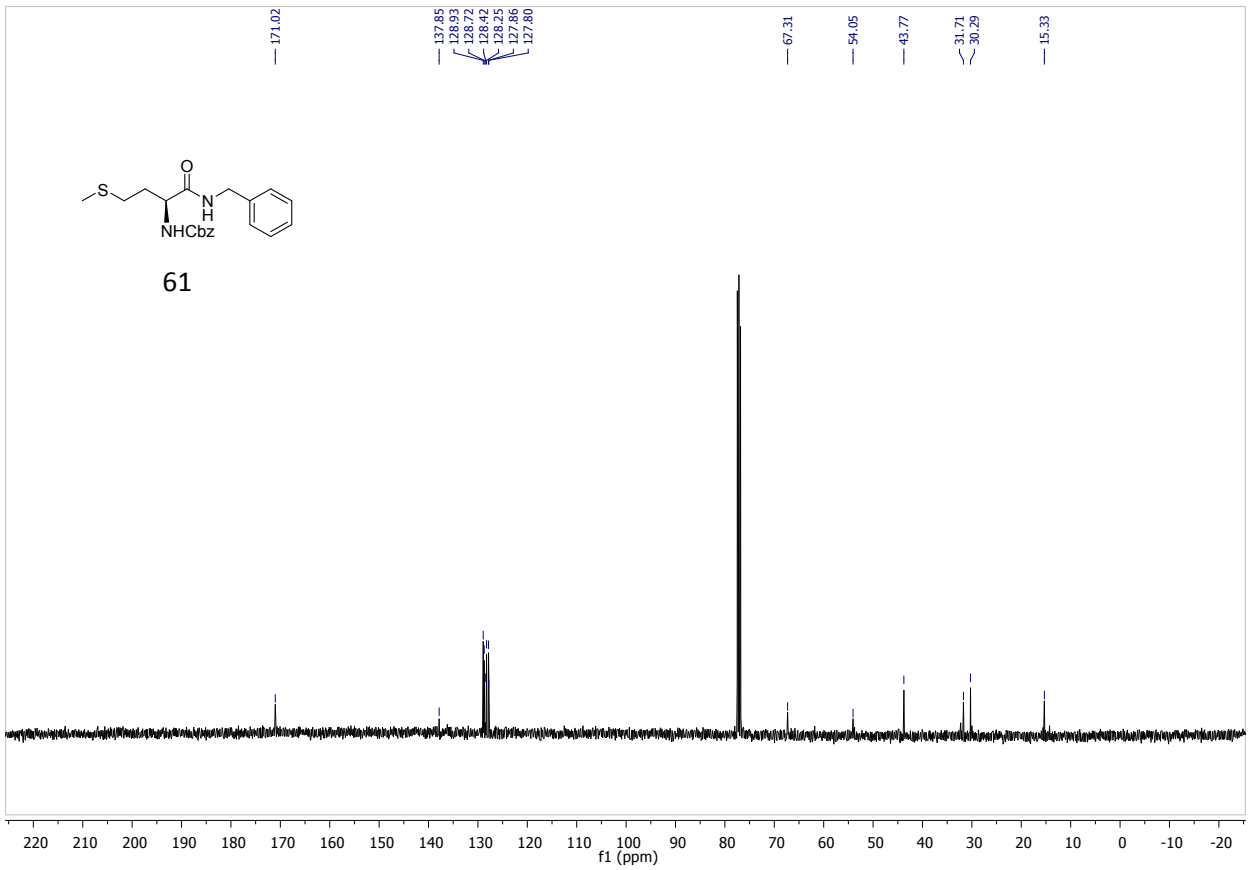
benzyl (S)-(1-(benzylamino)-4-methyl-1-oxopentan-2-yl)carbamate (60)



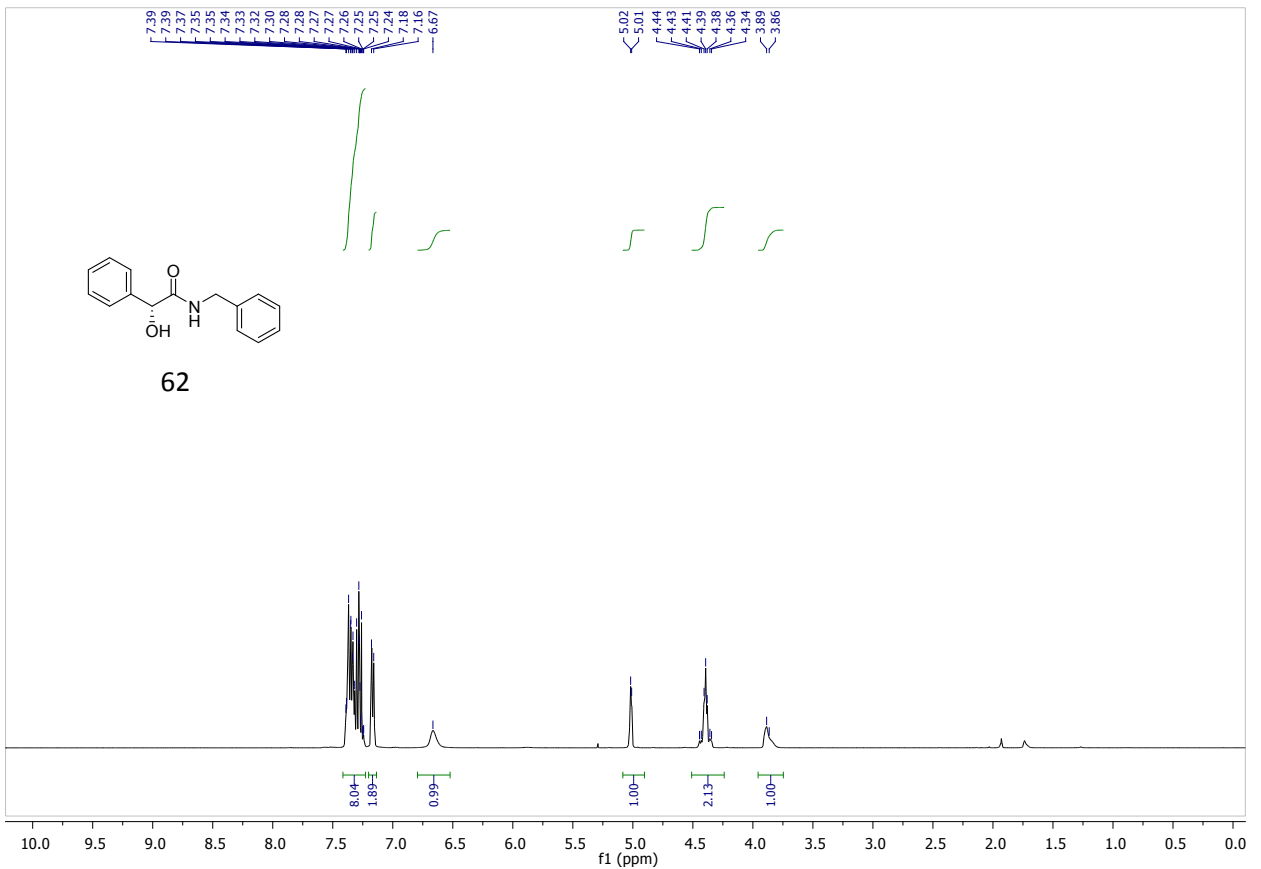


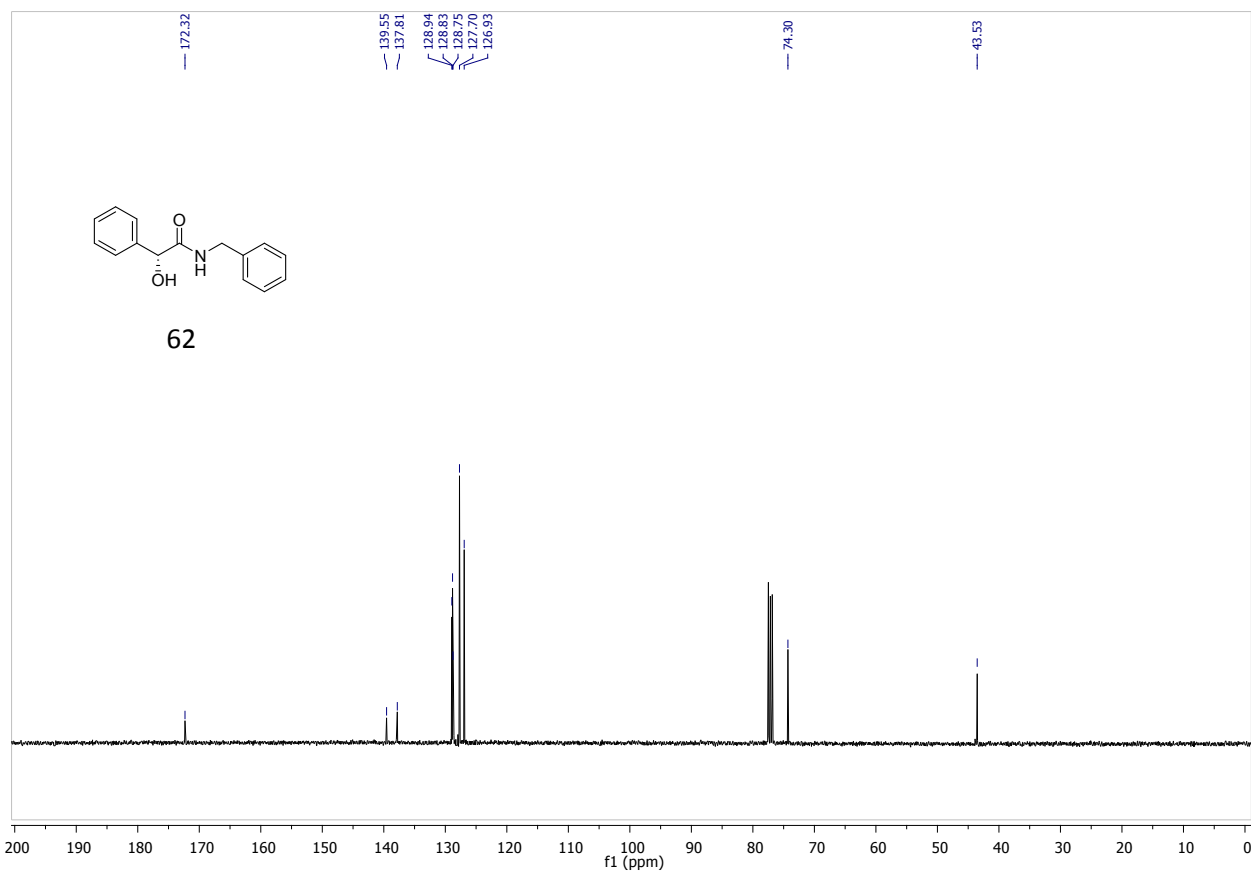
benzyl (S)-(1-(benzylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (61)



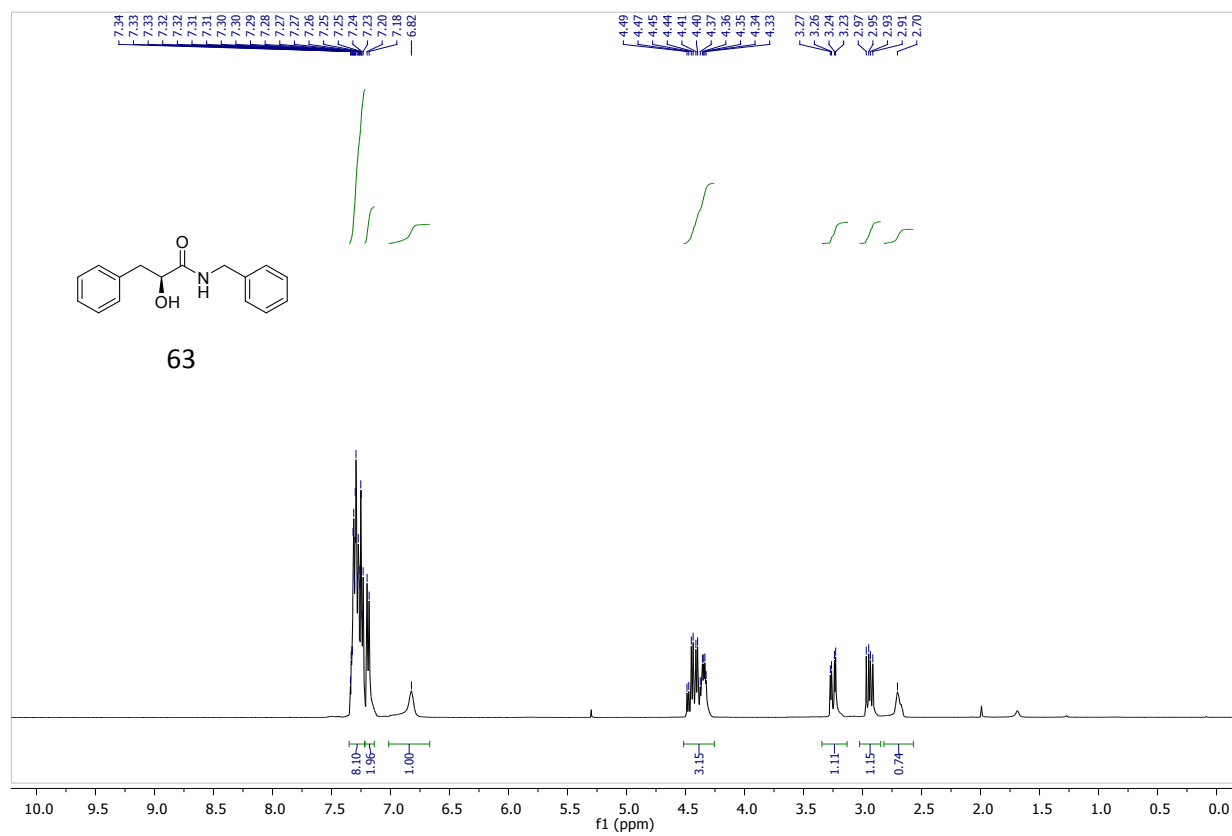


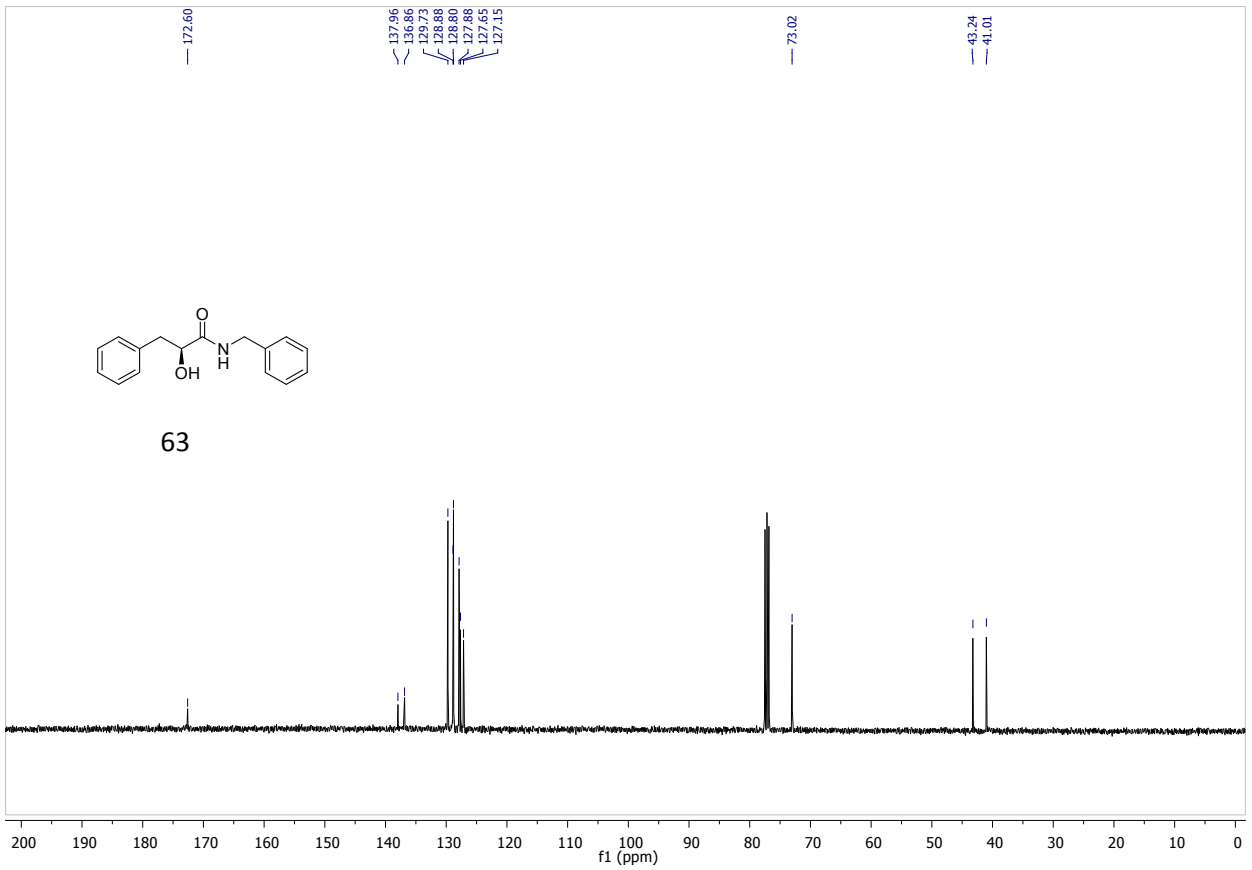
(R)-N-benzyl-2-hydroxy-2-phenylacetamide (62)



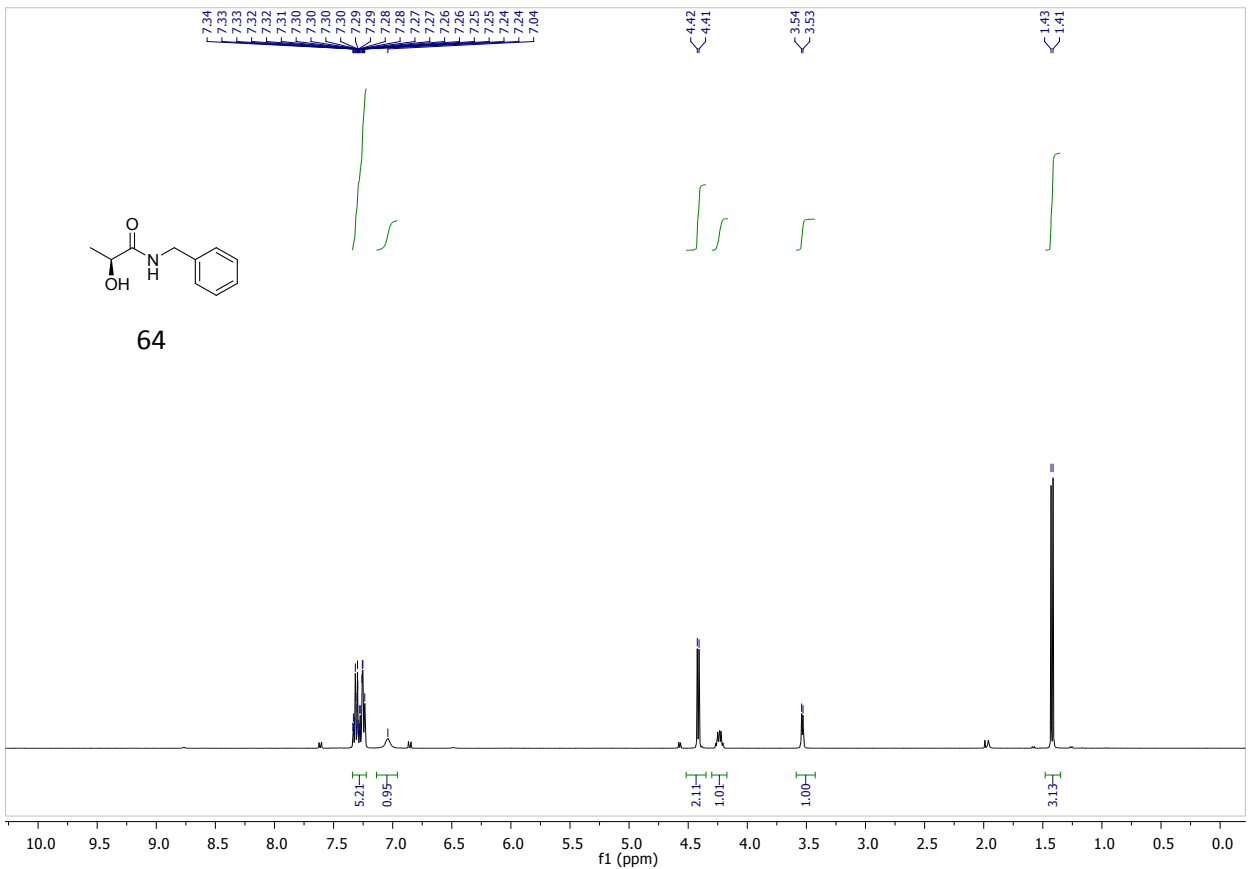


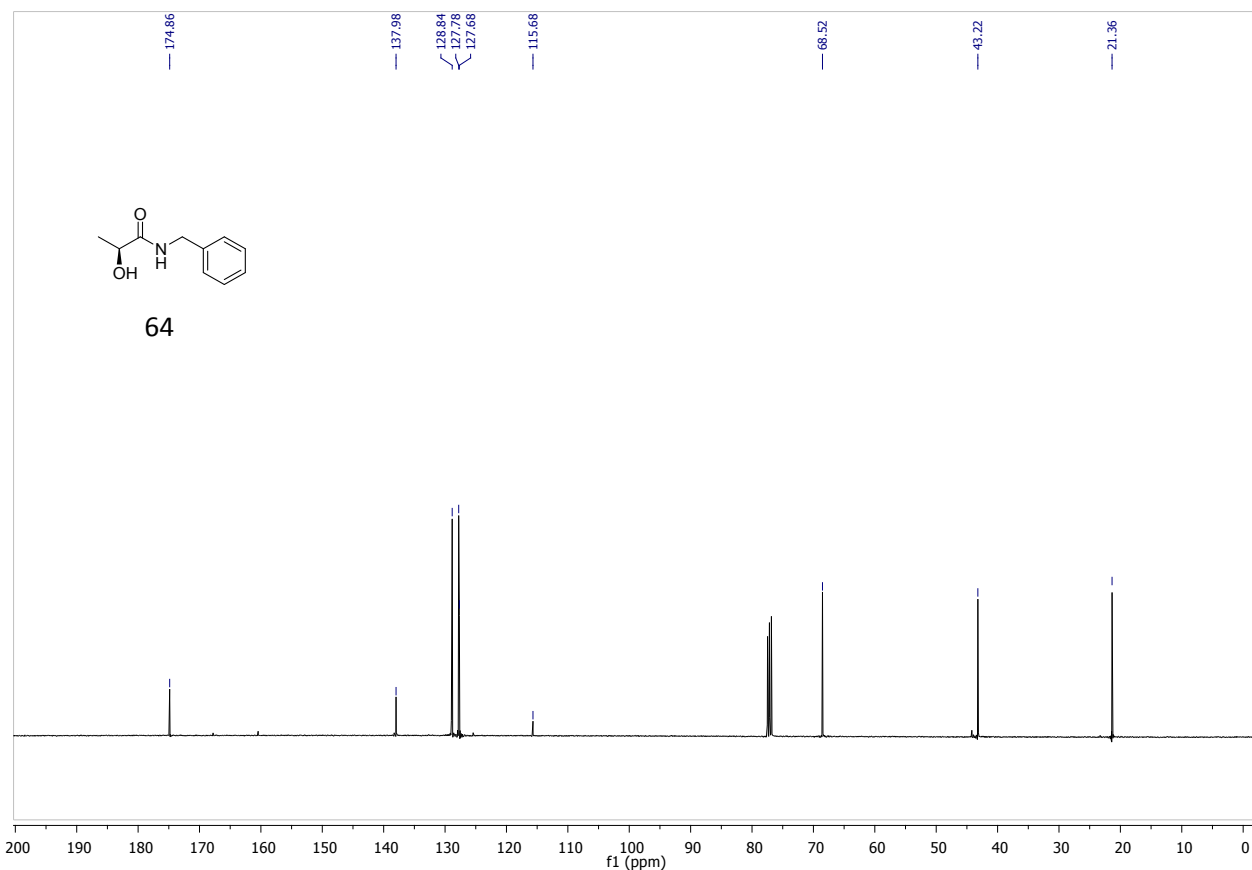
(S)-N-benzyl-2-hydroxy-3-phenylpropanamide (63)



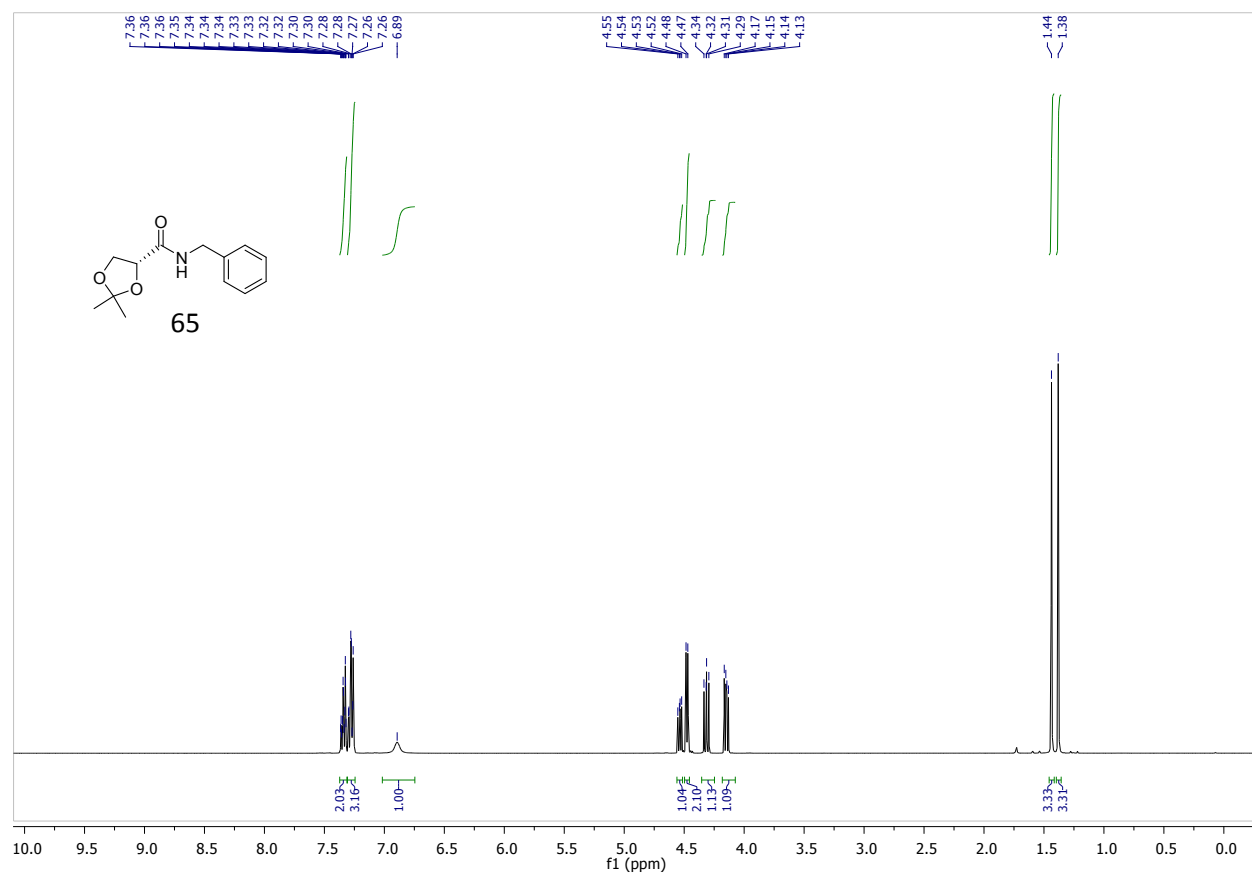


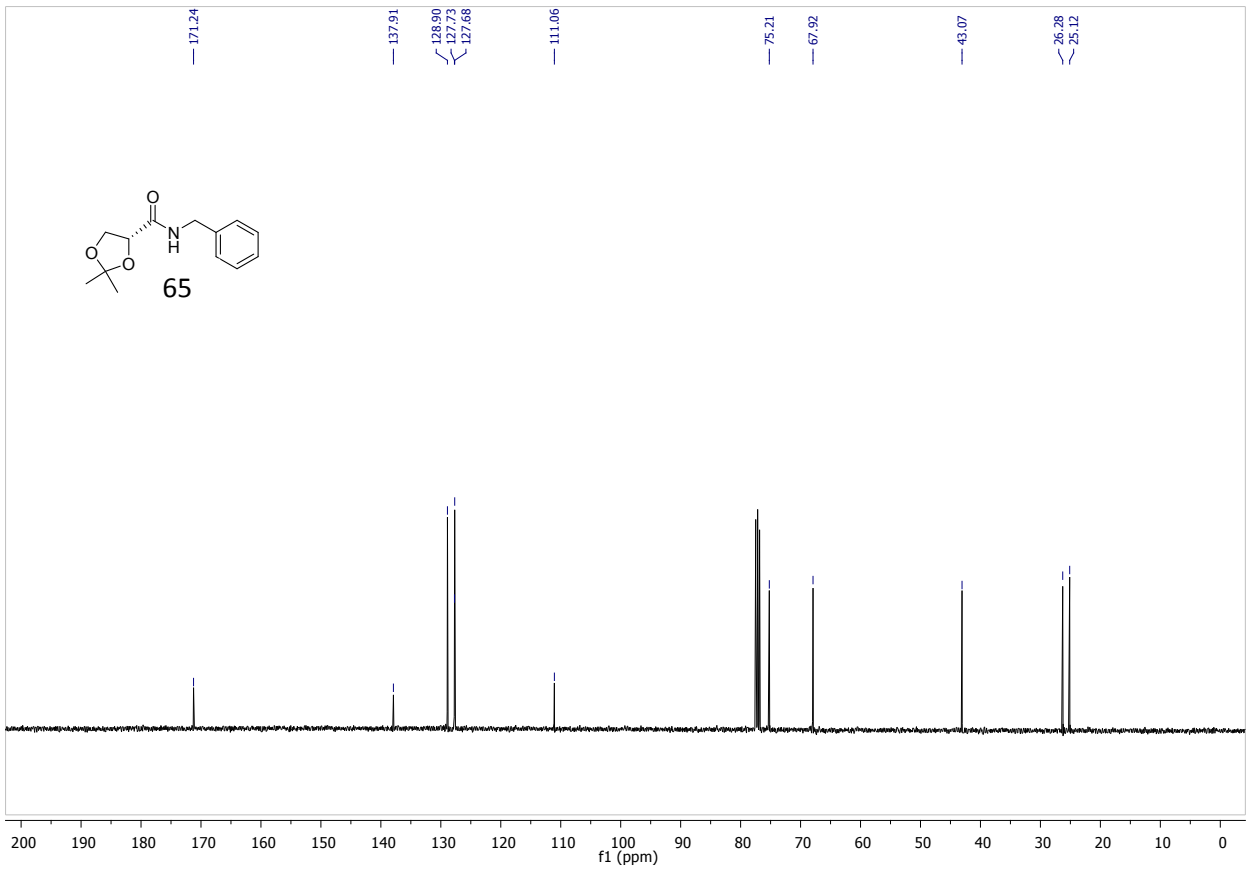
(S)-N-benzyl-2-hydroxypropanamide (64)



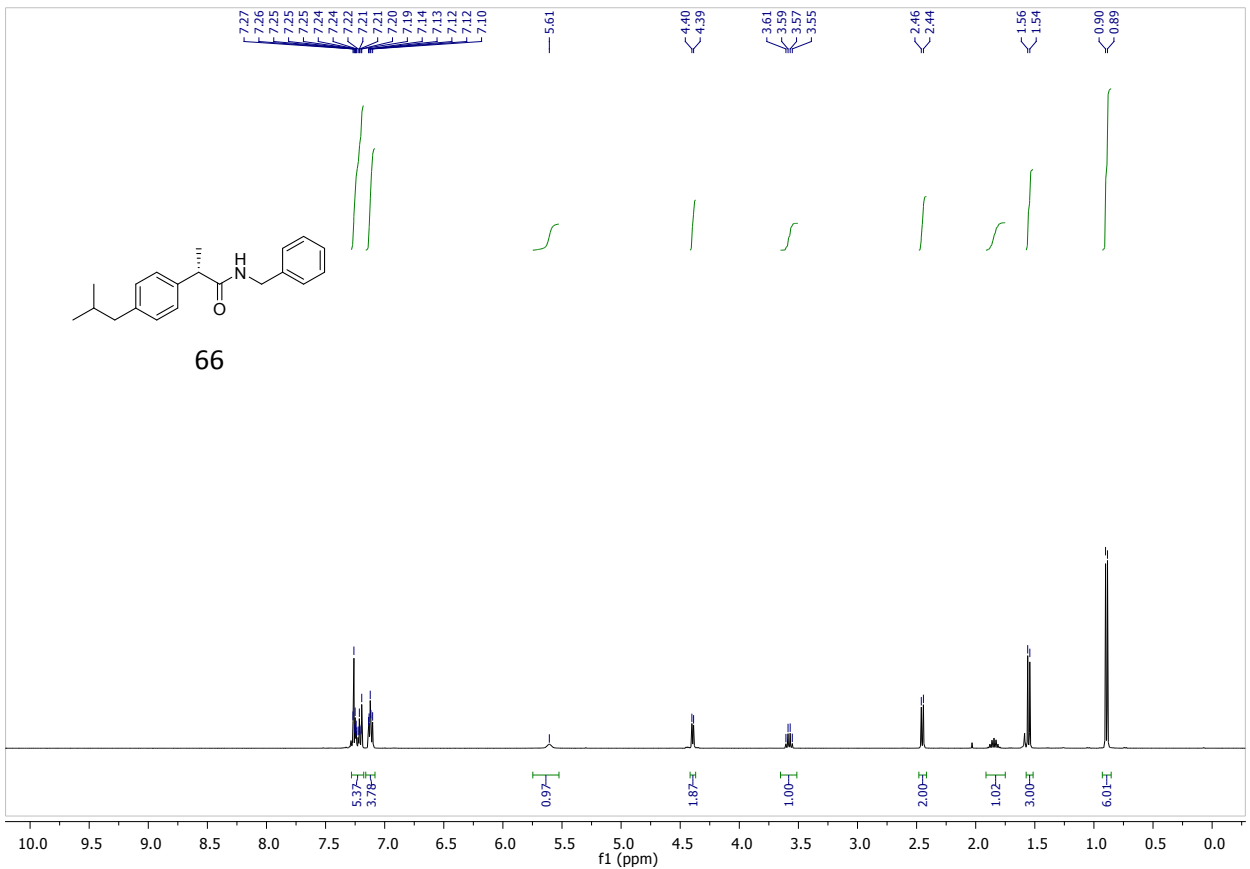


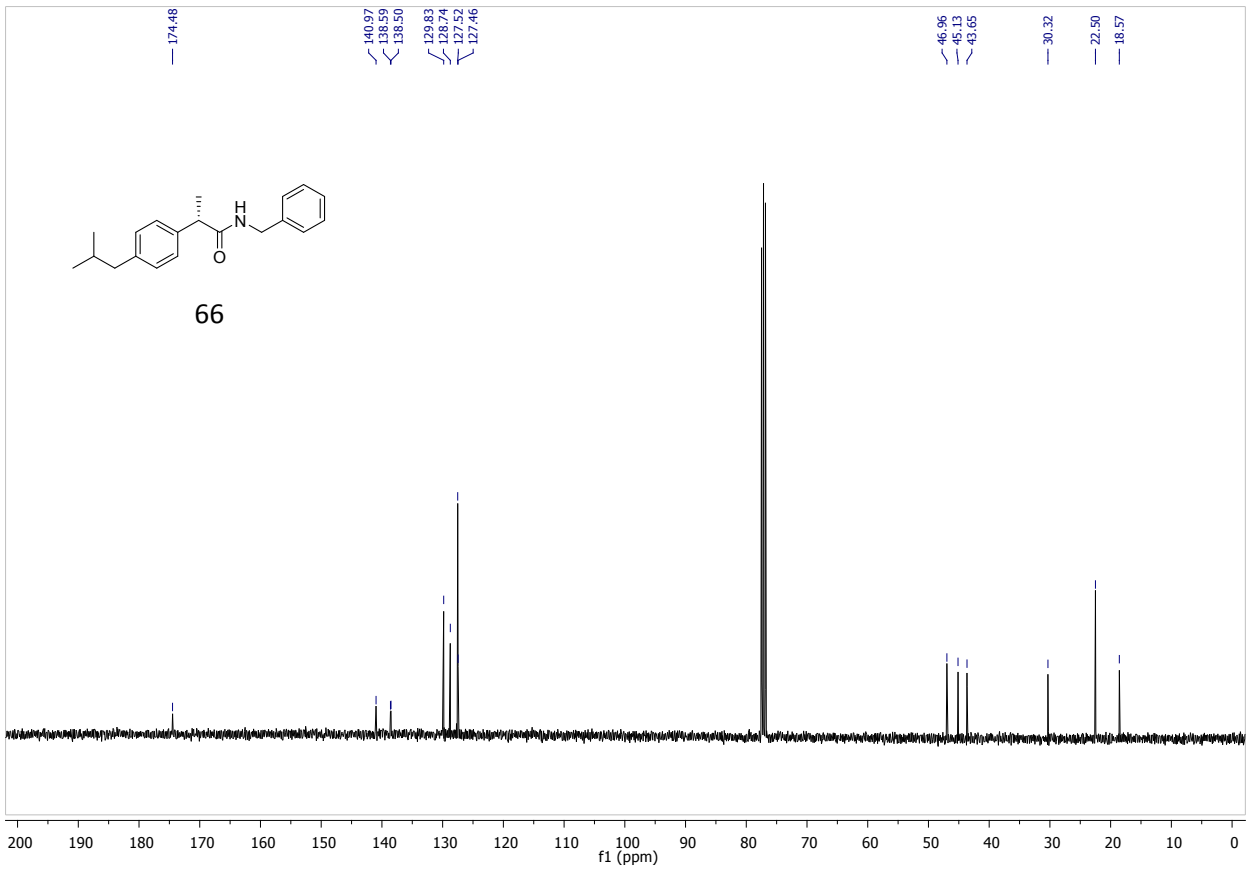
(R)-N-benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide (65)



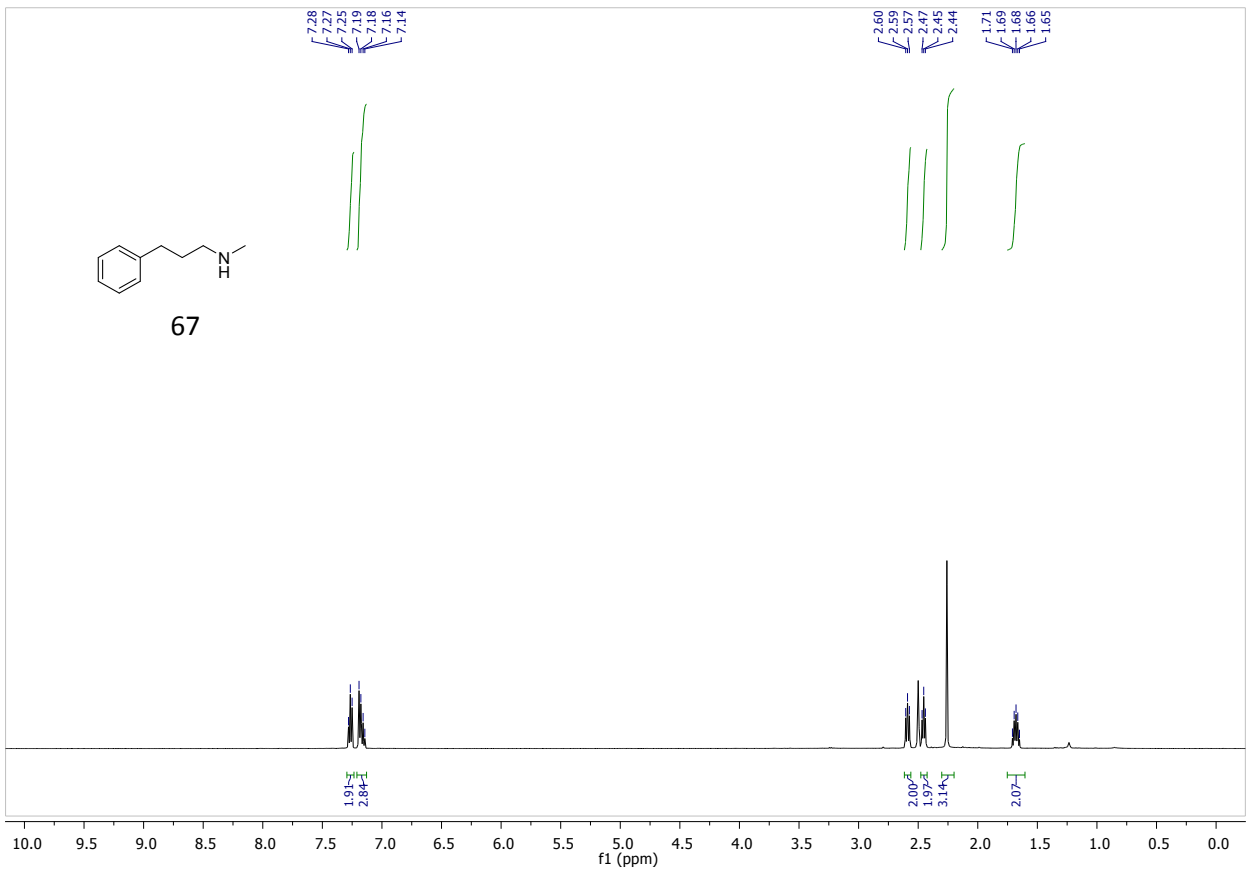


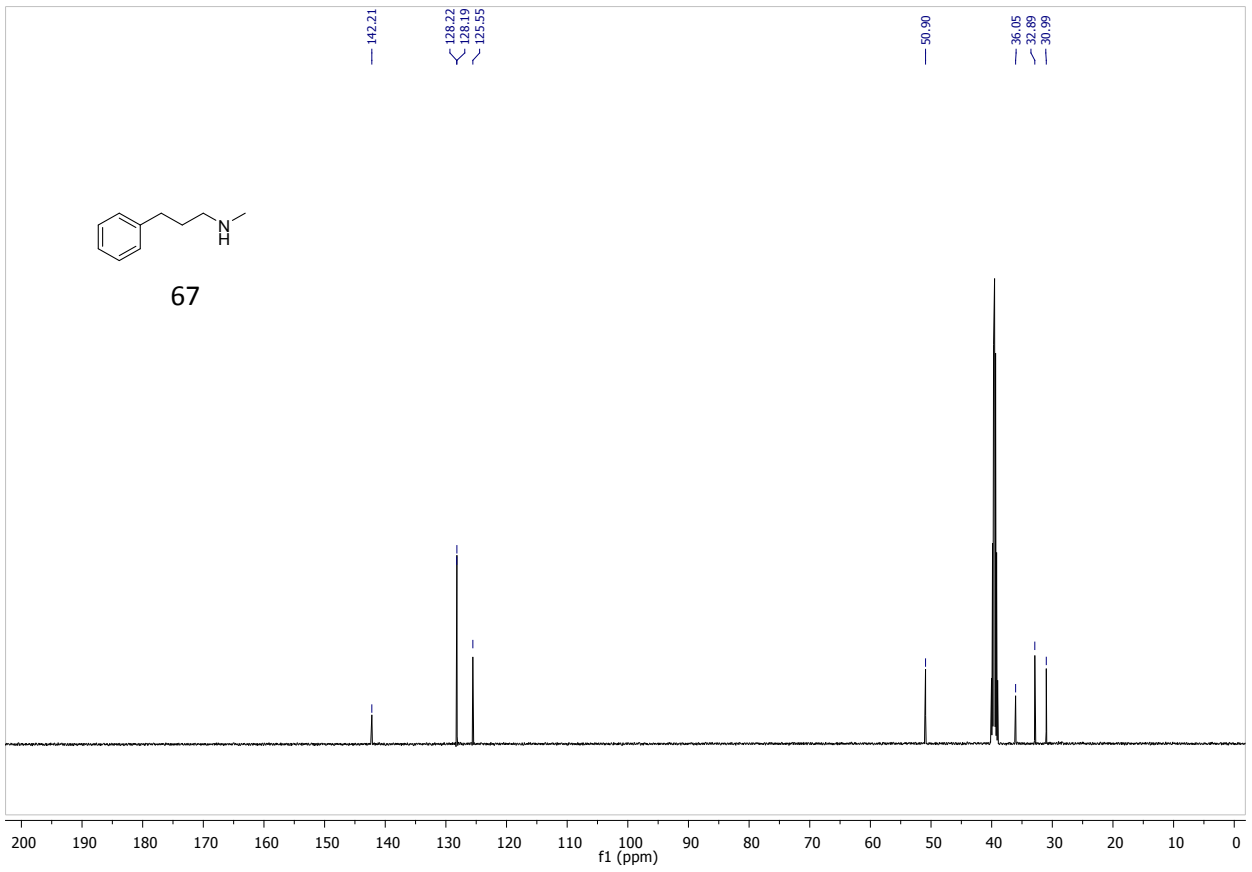
(S)-N-benzyl-2-(4-isobutylphenyl)propanamide (66)



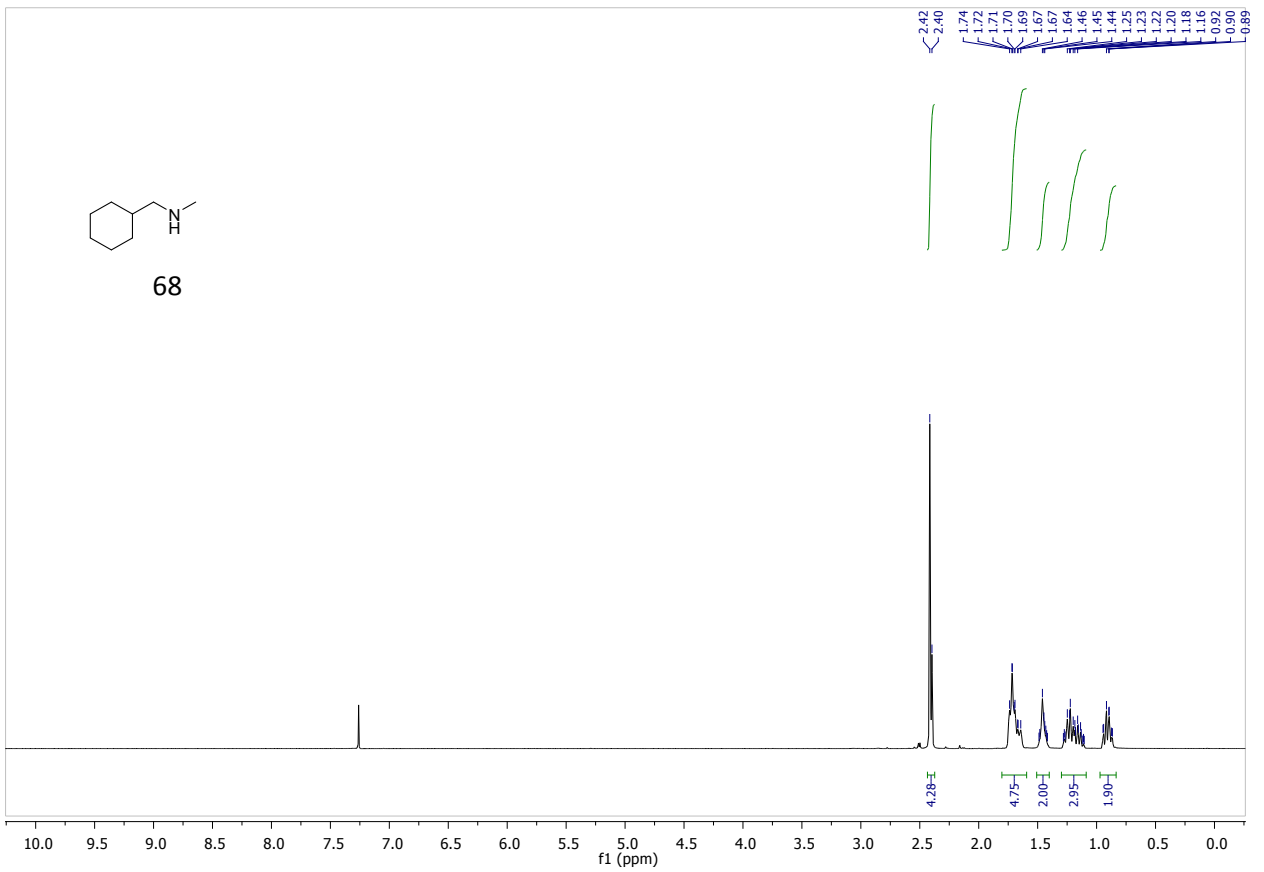


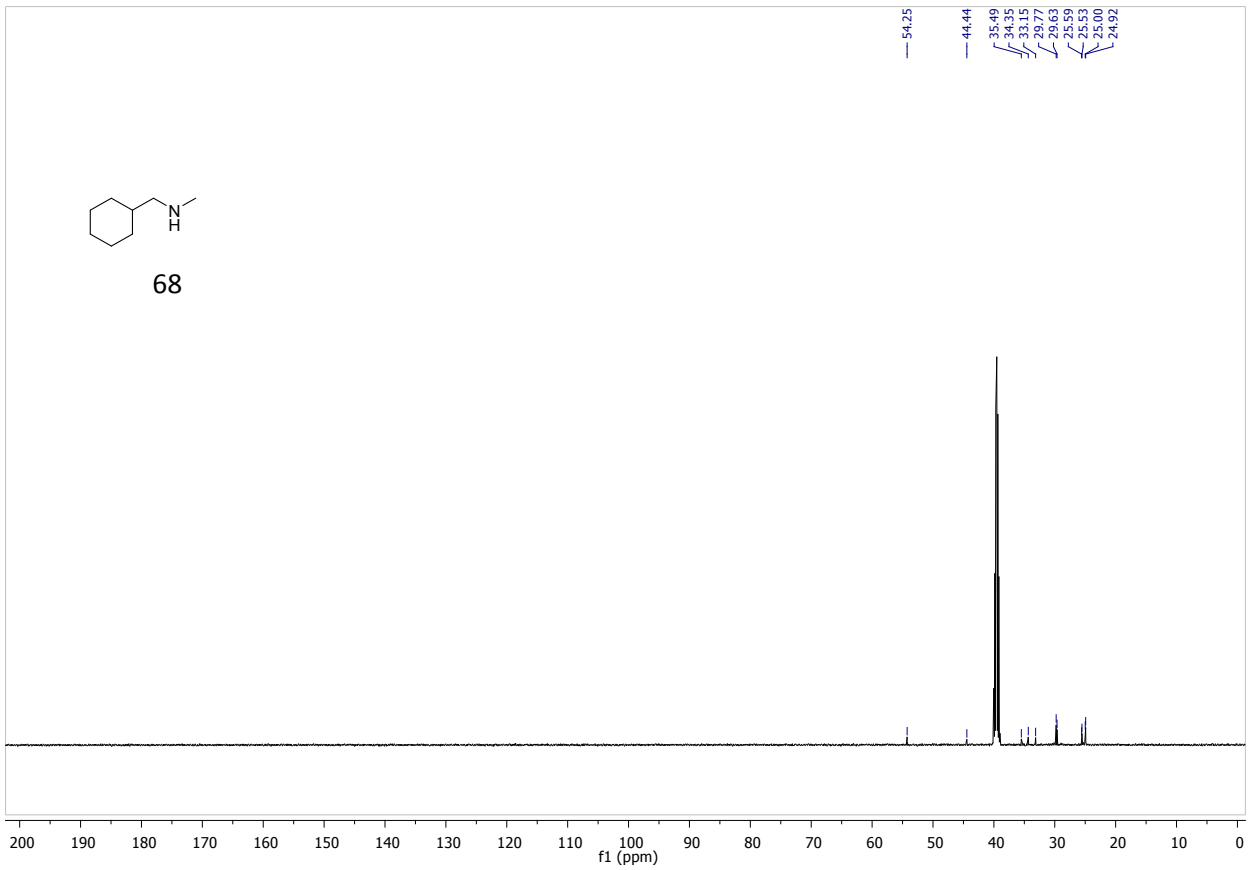
N-methyl-3-phenylpropan-1-amine (67)



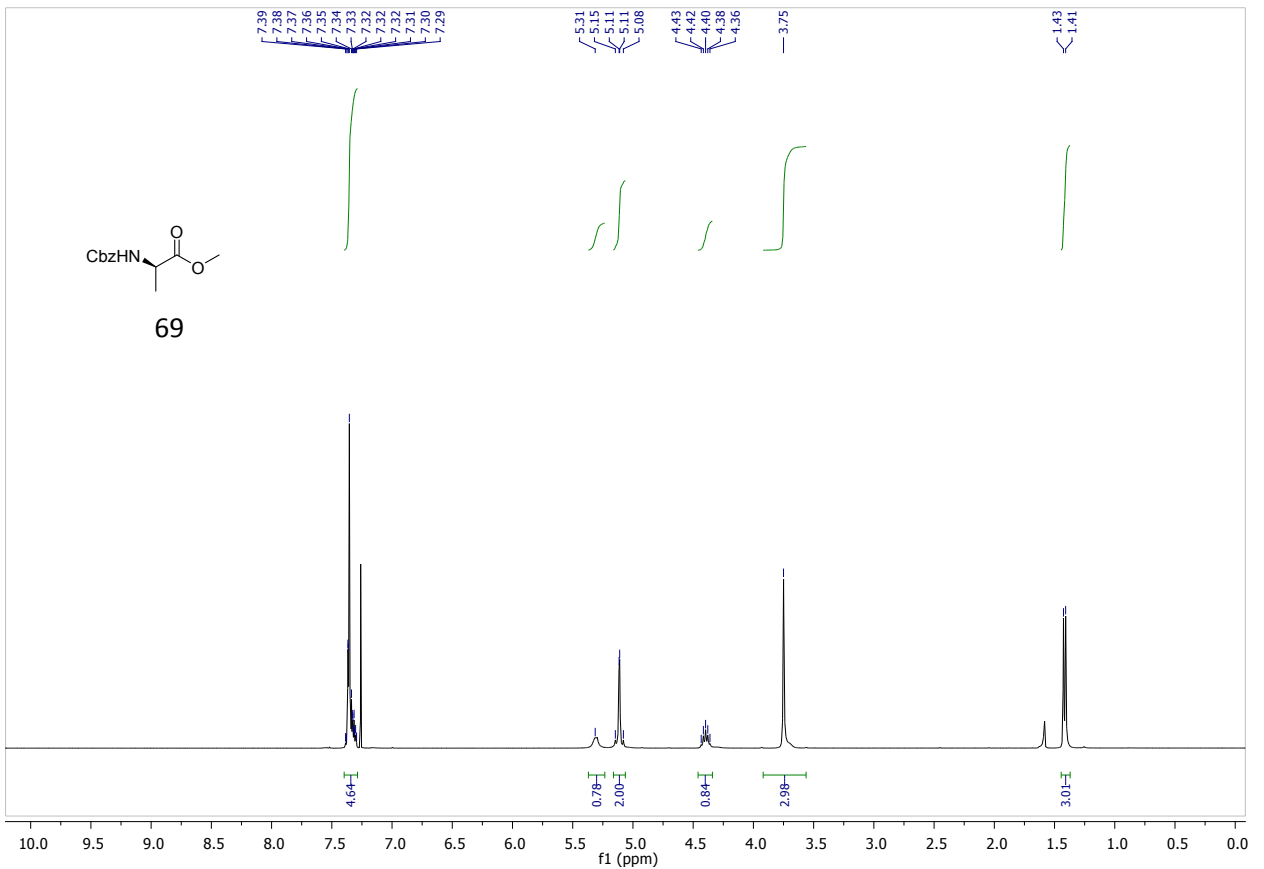


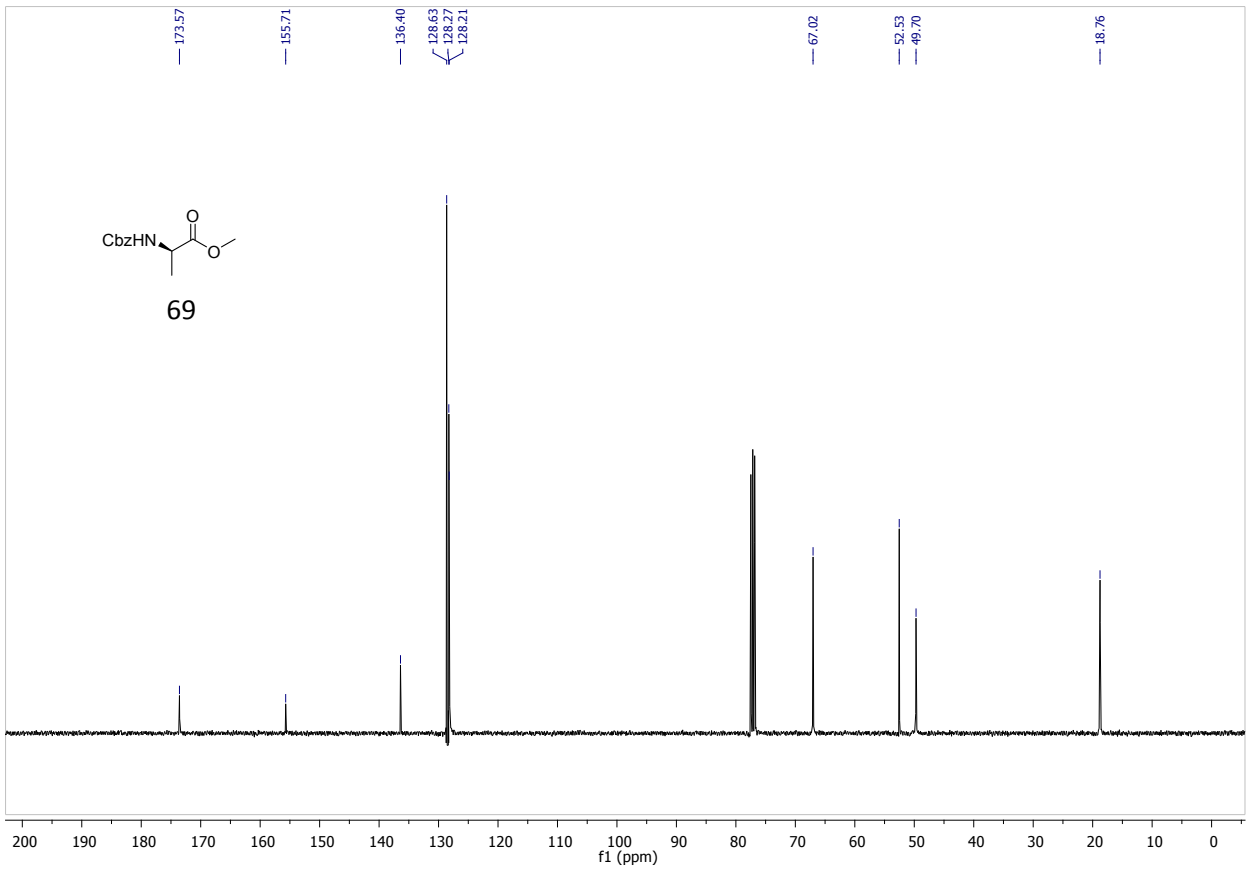
1-cyclohexyl-N-methylmethanamine (68)



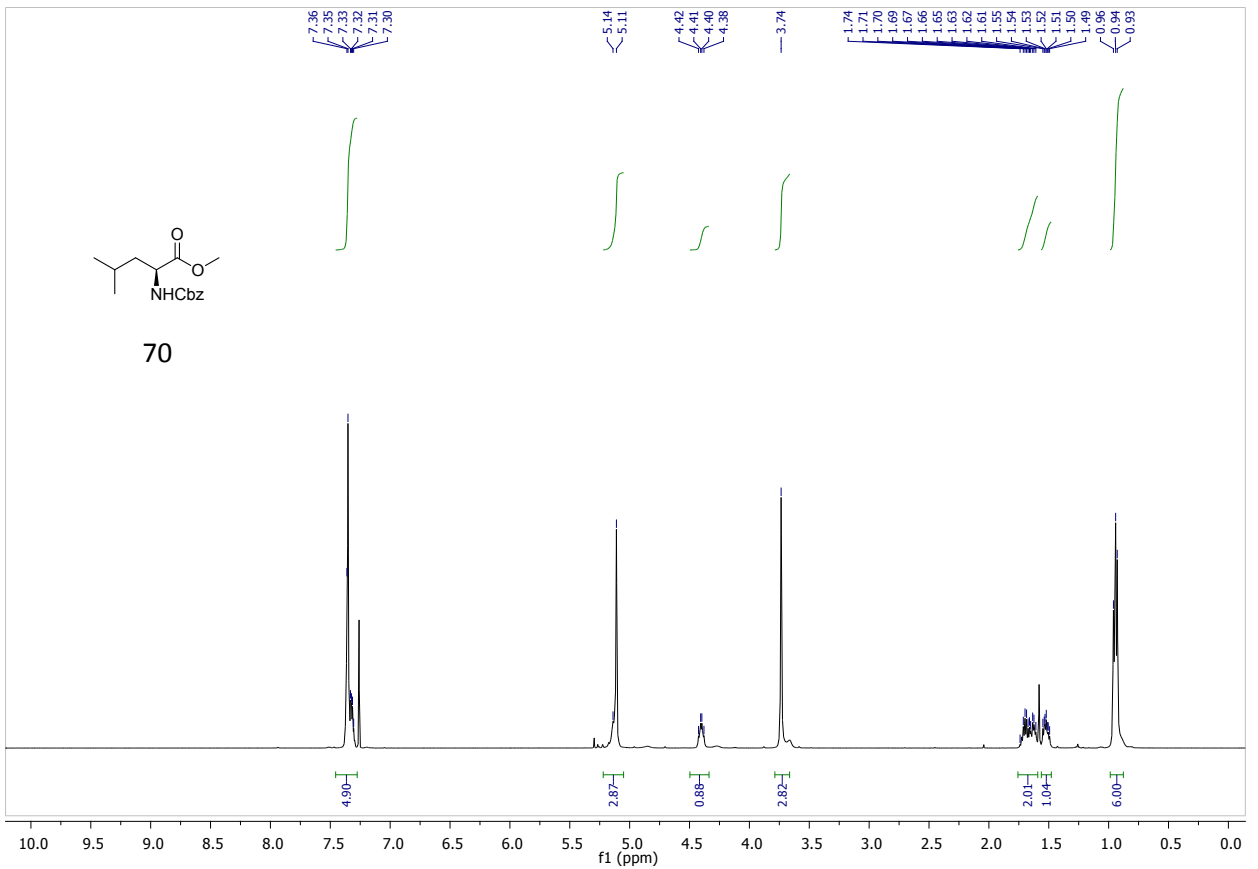


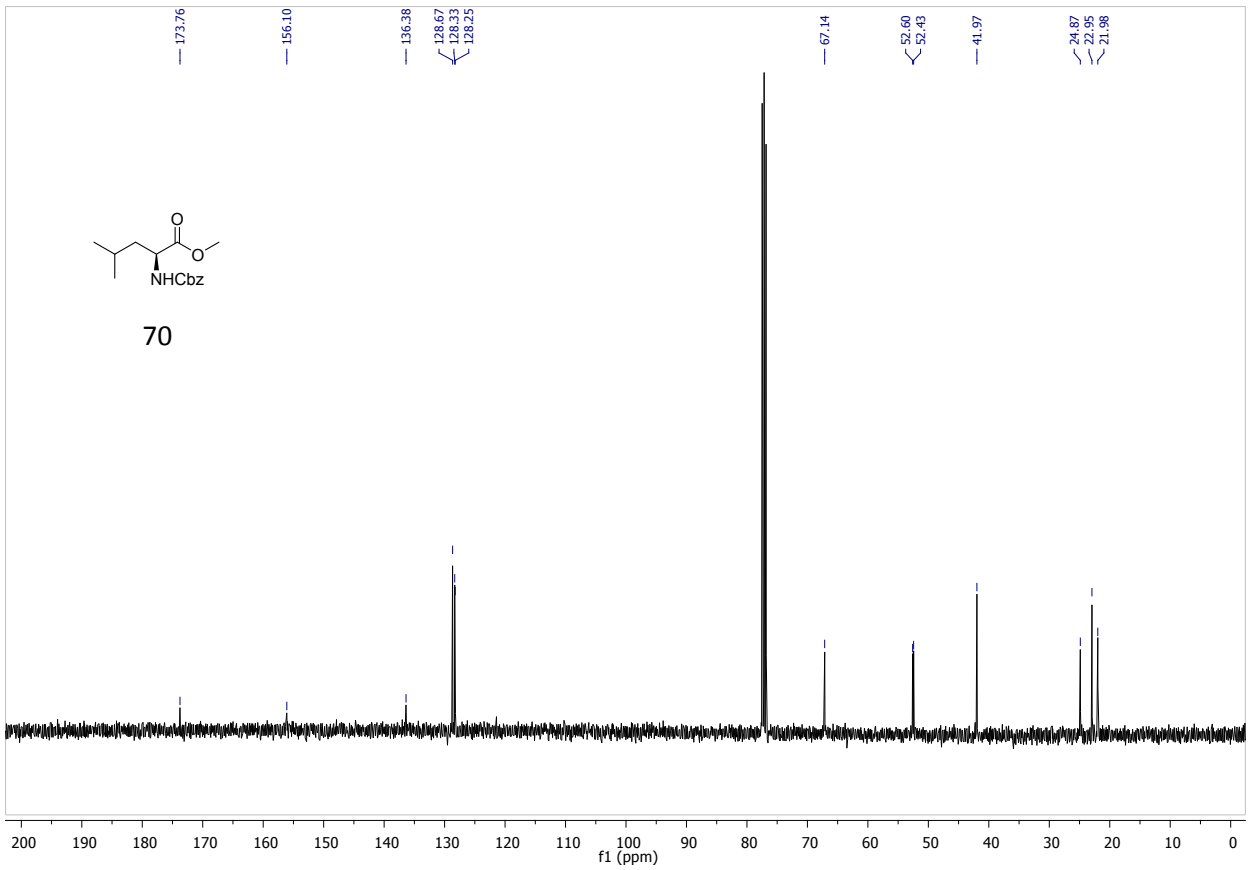
Methyl ((benzyloxy)carbonyl)-D-alaninate (69)



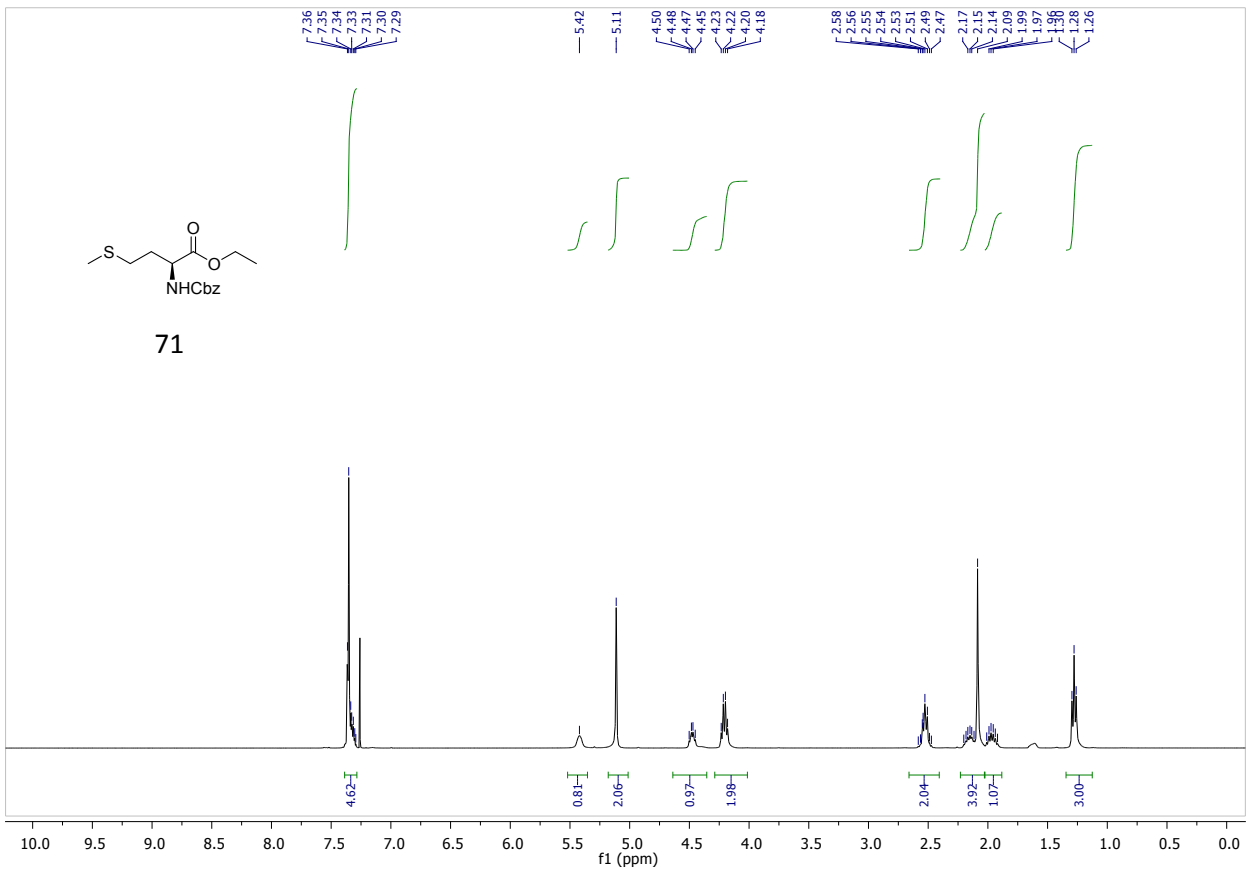


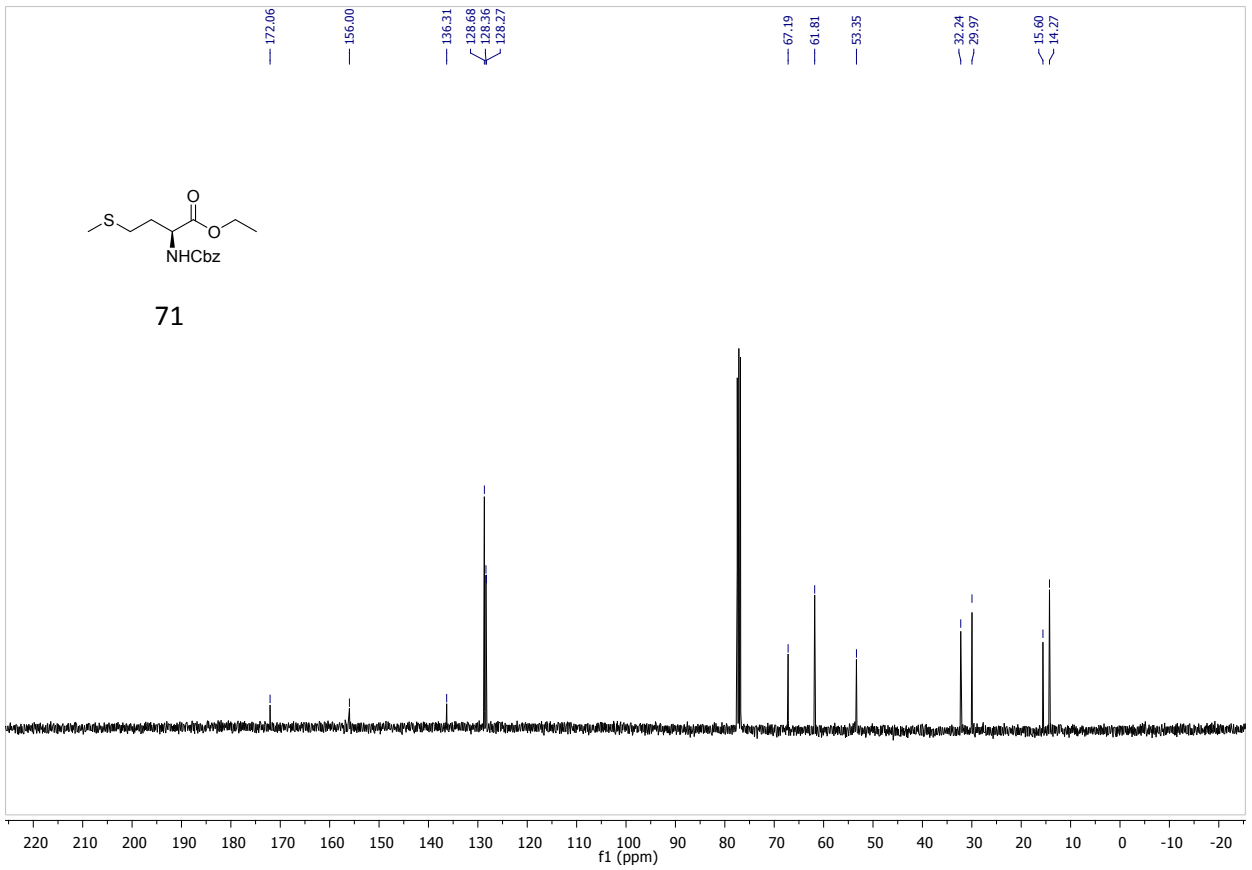
Methyl ((benzyloxy)carbonyl)-L-leucinate (70)



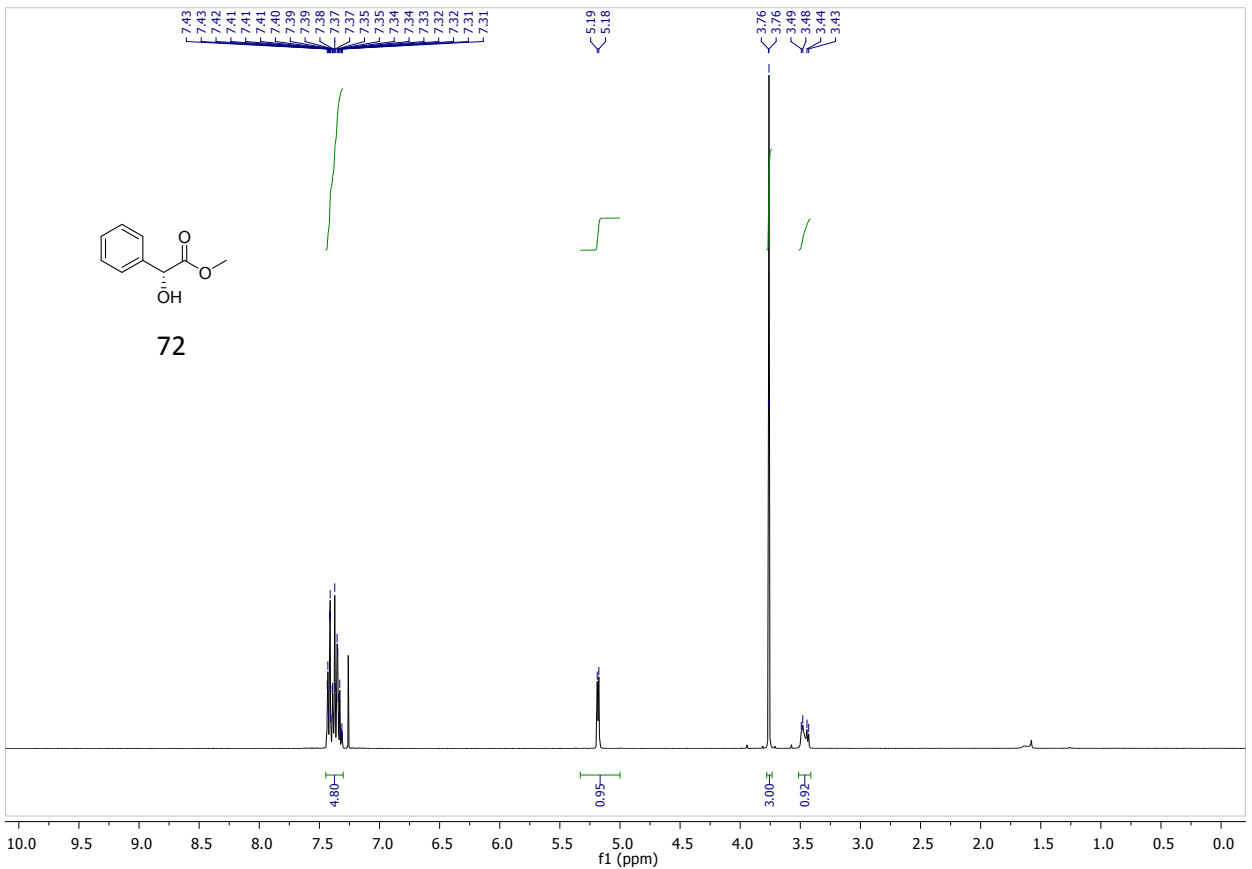


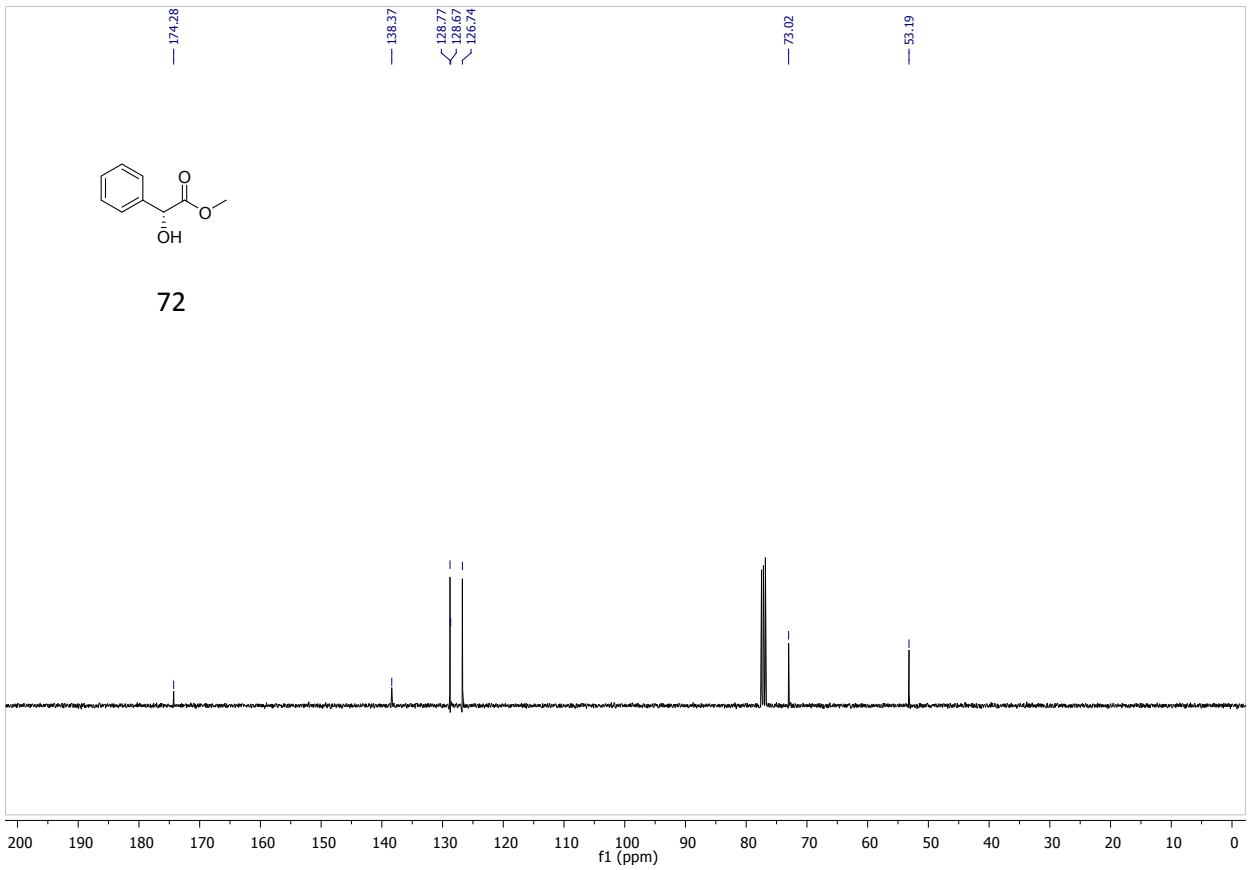
ethyl ((benzyloxy)carbonyl)-L-methioninate (71)



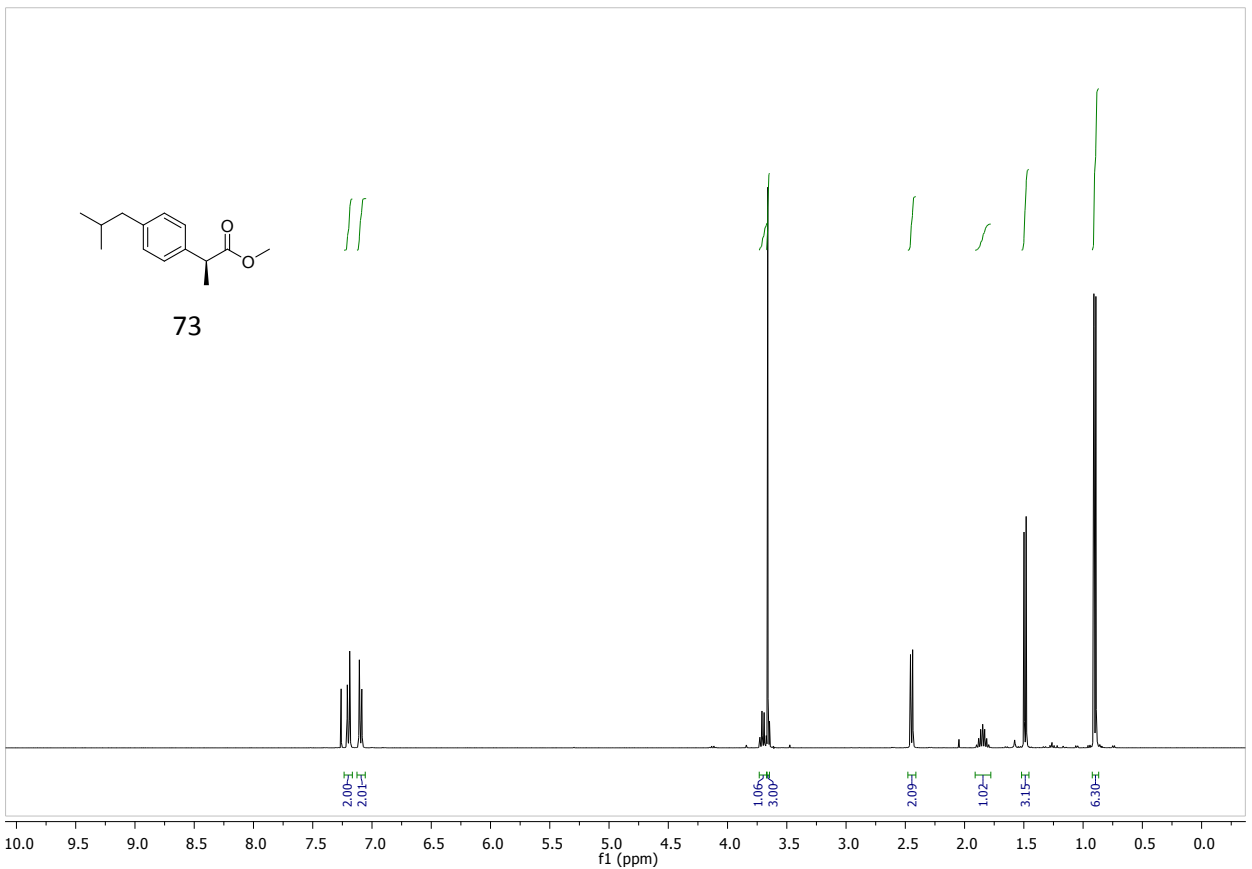


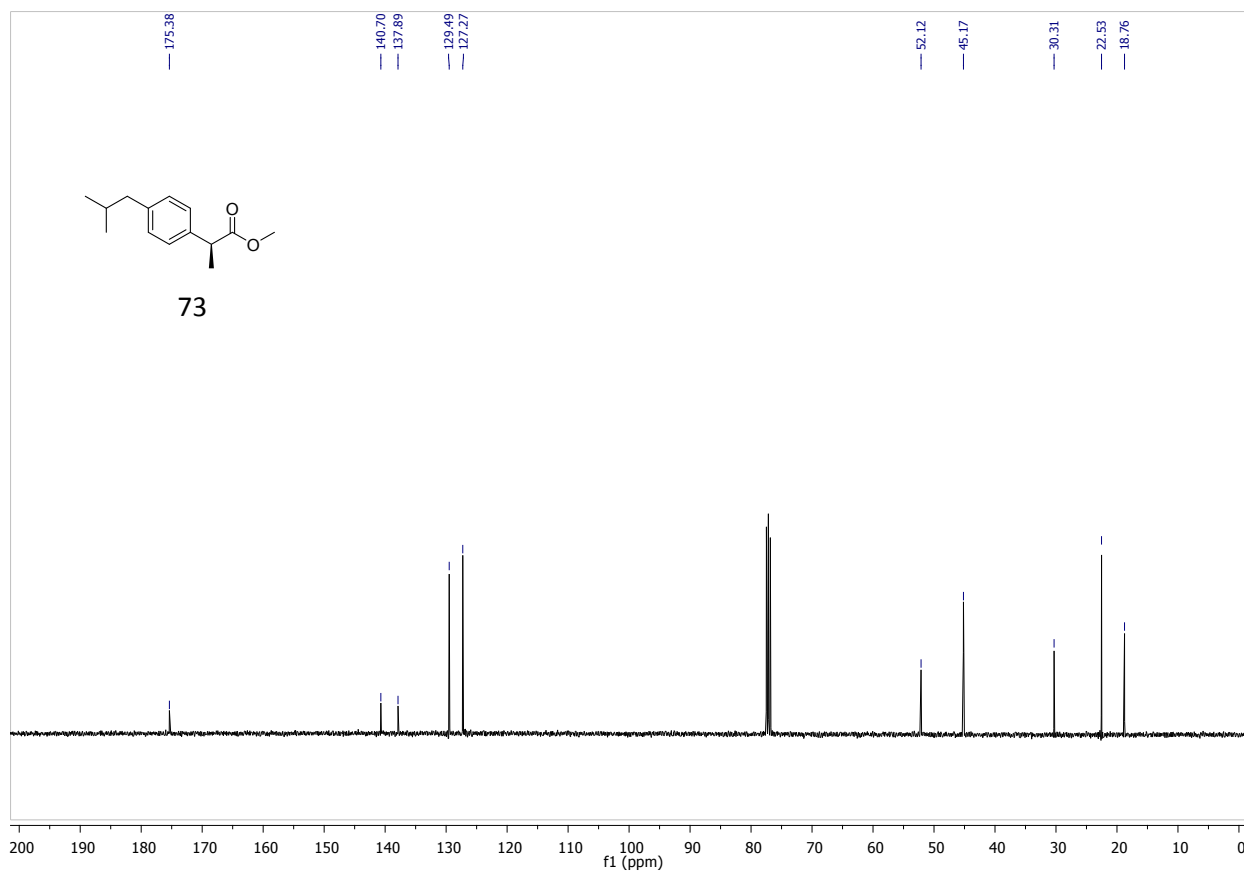
Methyl (R)-2-hydroxy-2-phenylacetate (72)





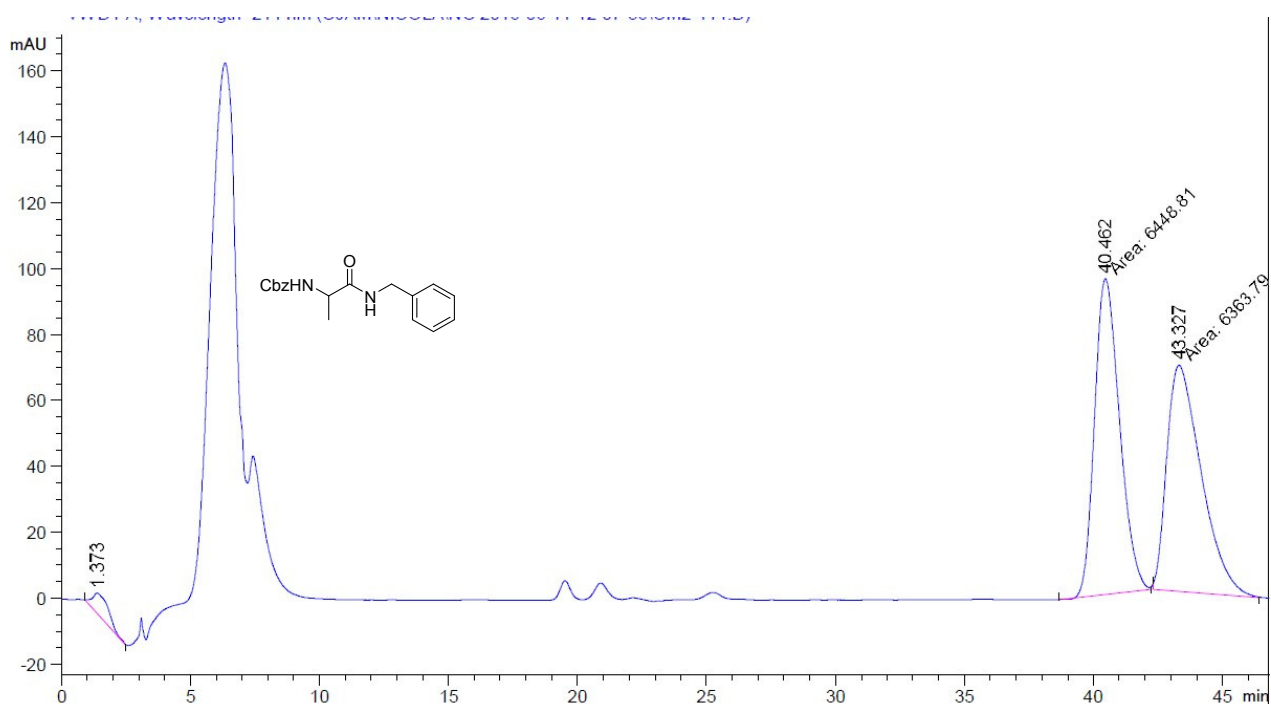
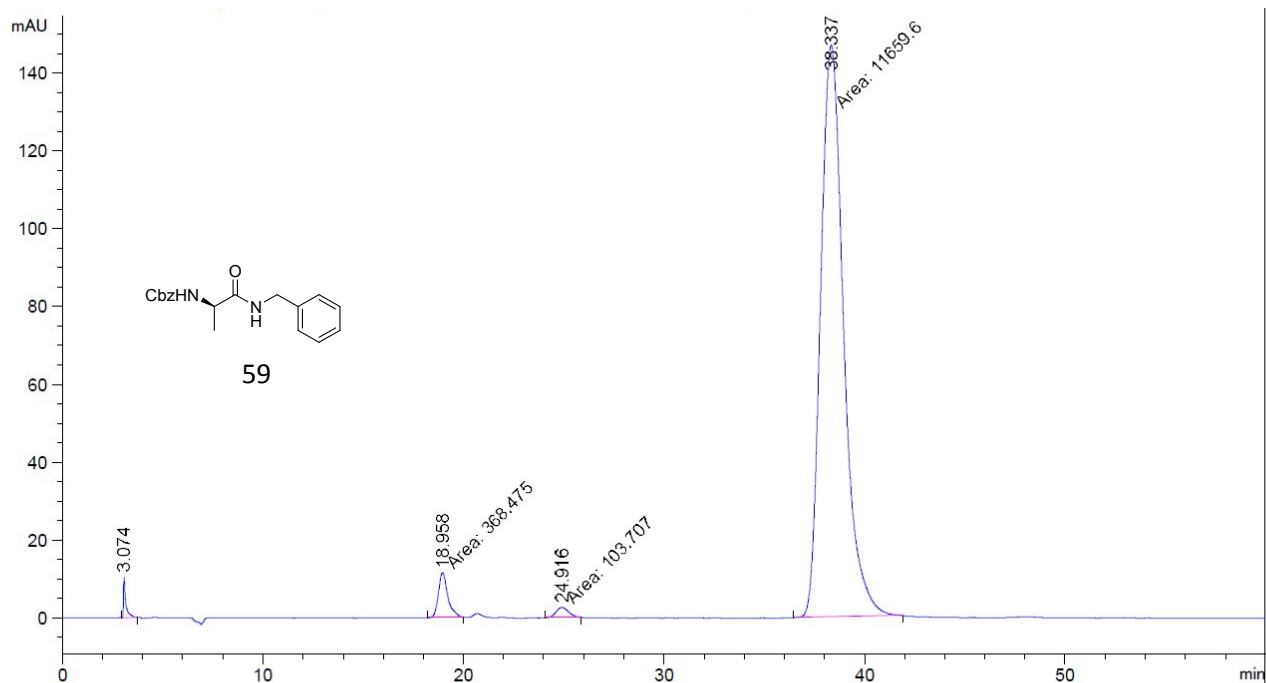
Methyl (S)-2-(4-isobutylphenyl)propanoate (73).



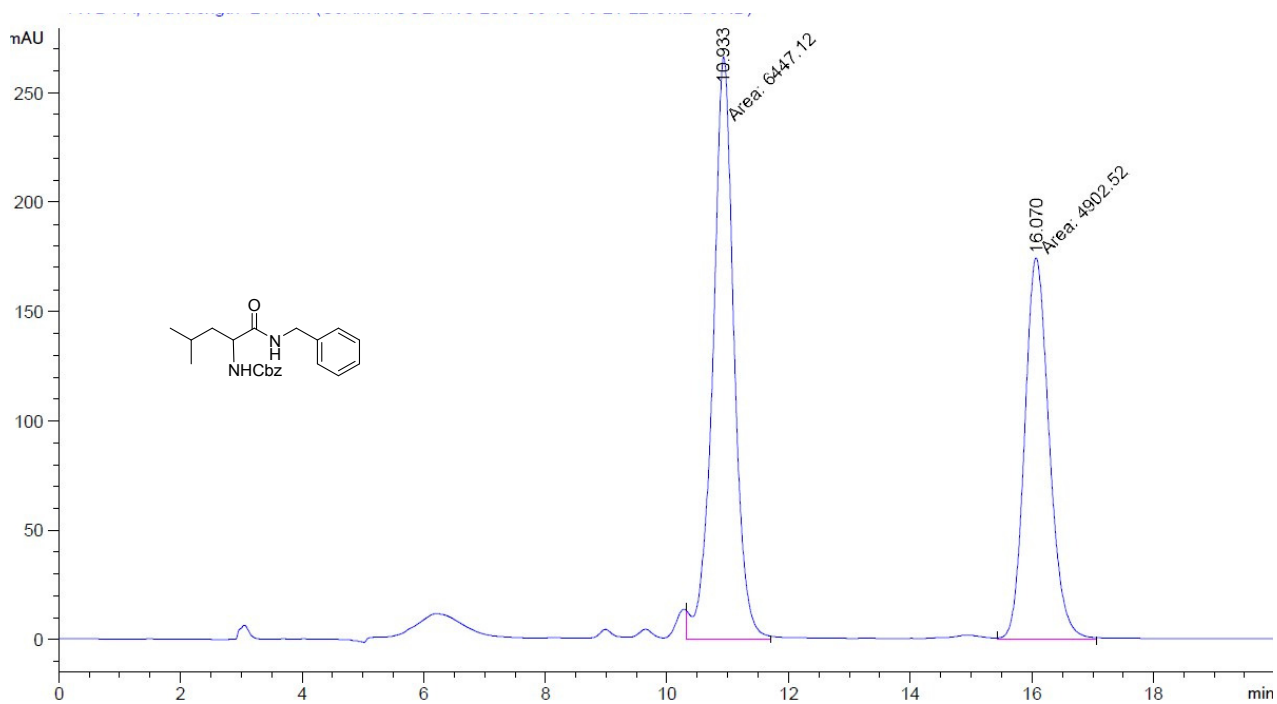
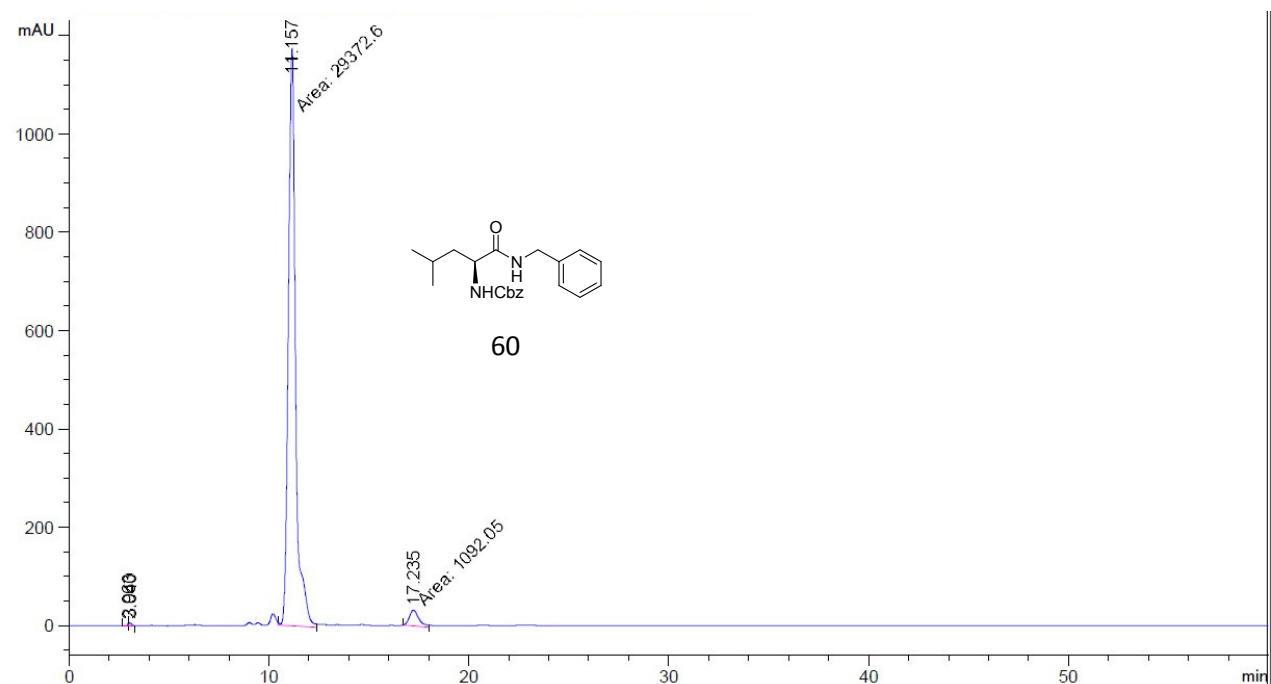


5. Chiral HPLC Spectra

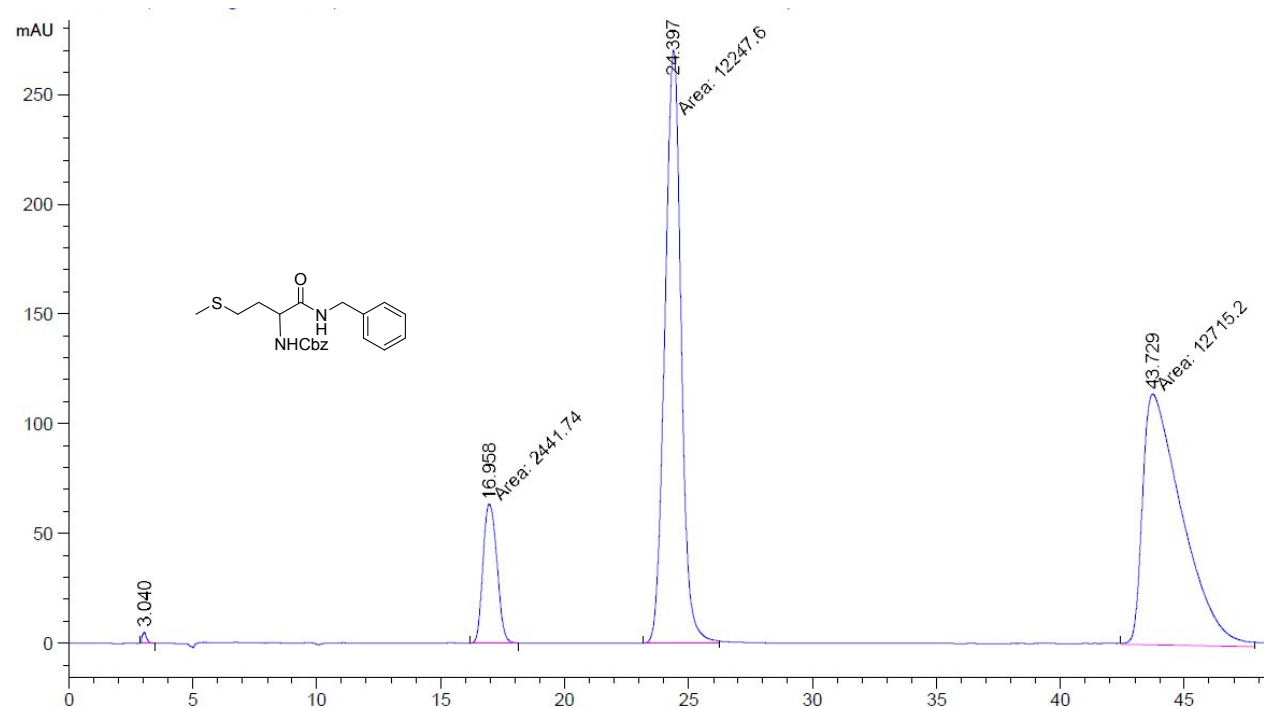
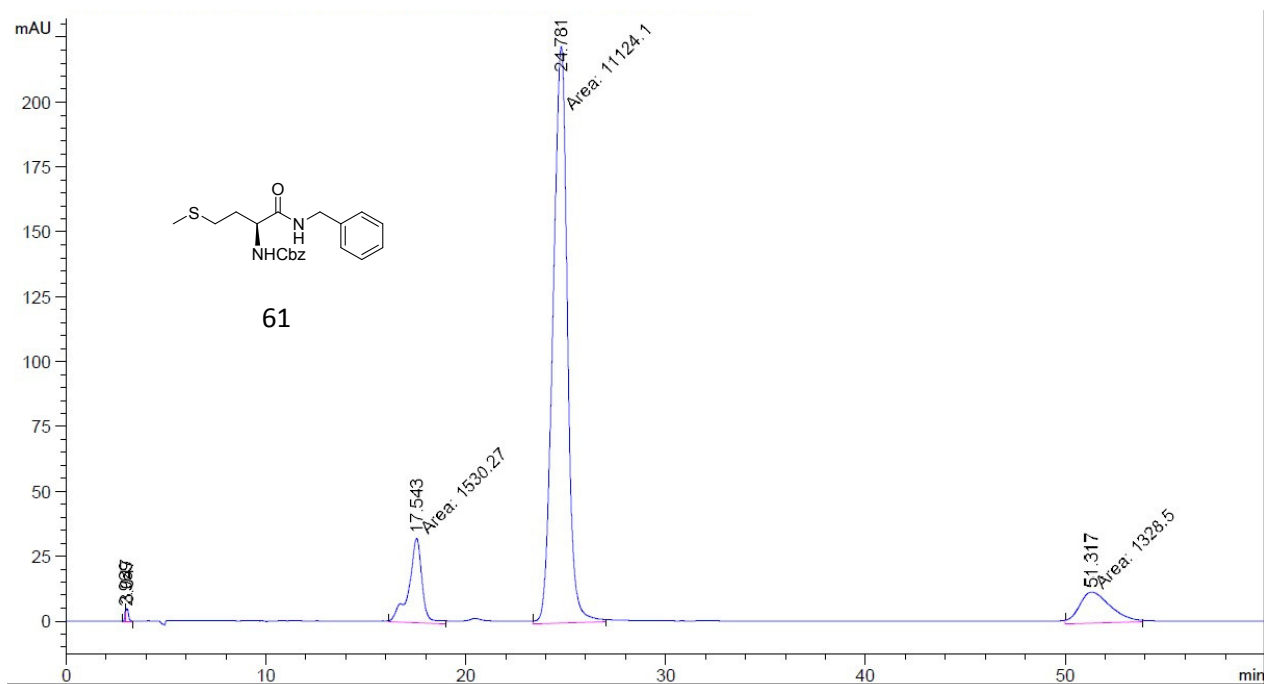
benzyl (*R*)-(1-(benzylamino)-1-oxopropan-2-yl)carbamate (**59**).



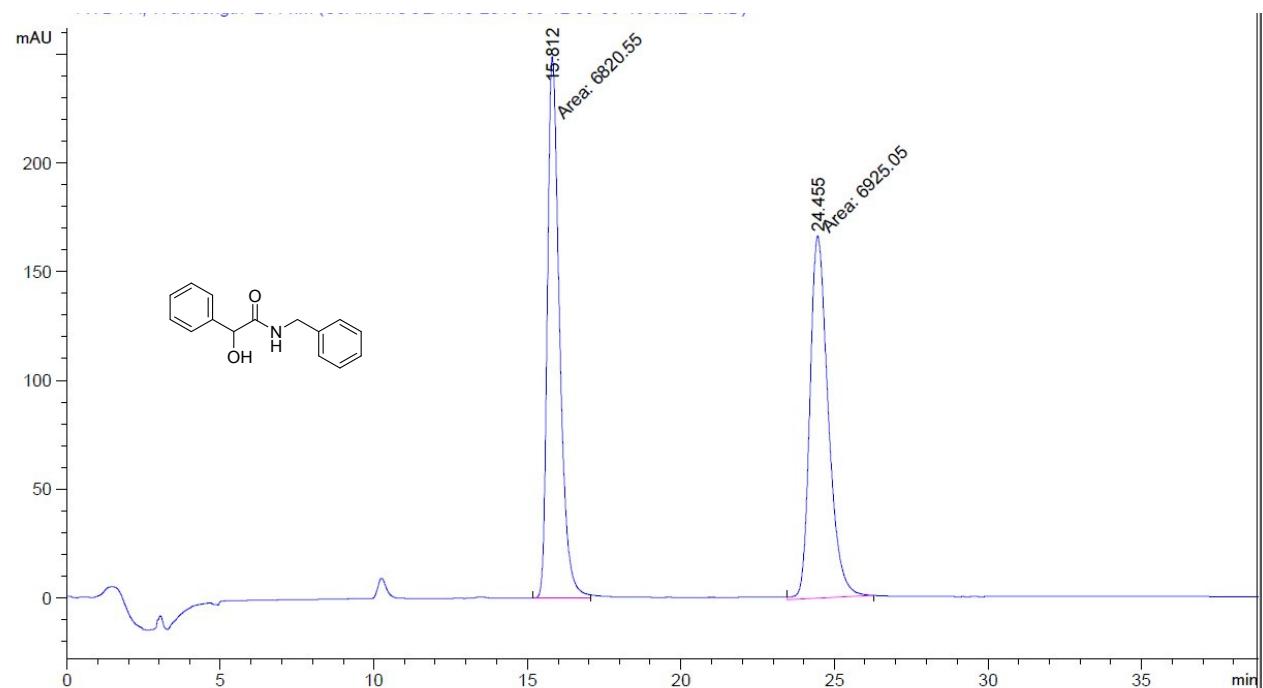
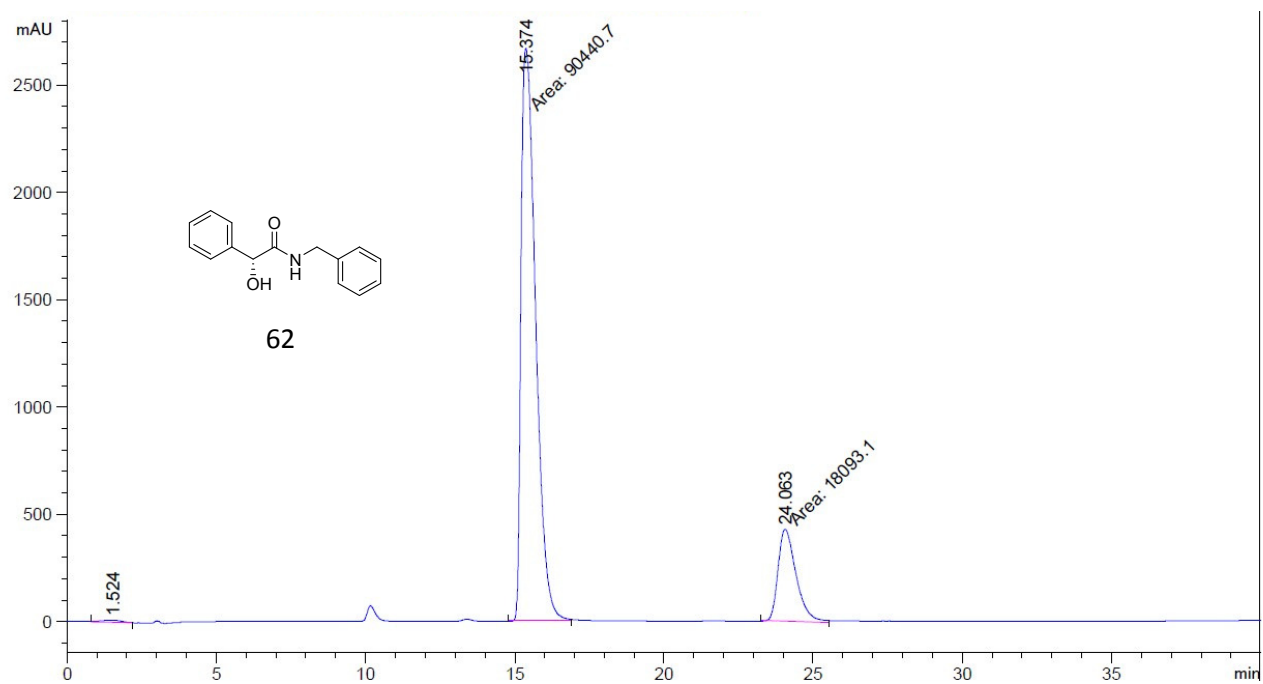
benzyl (S)-1-(benzylamino)-4-methyl-1-oxopentan-2-yl)carbamate (60).



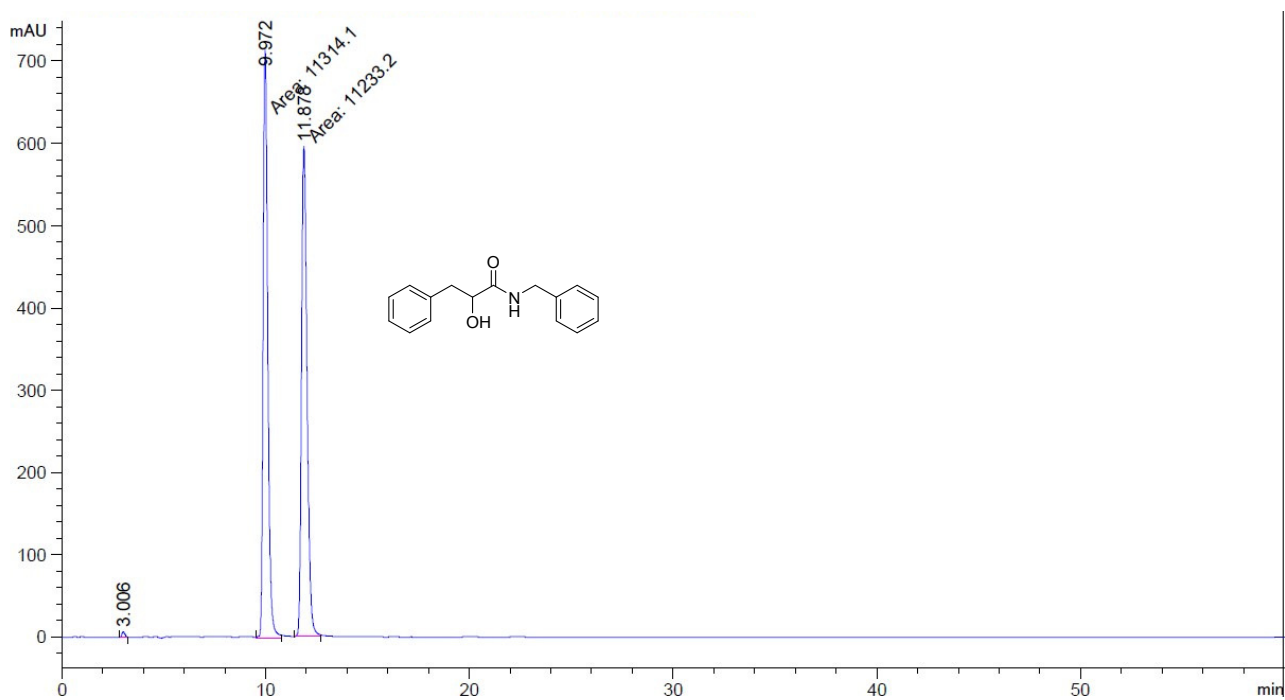
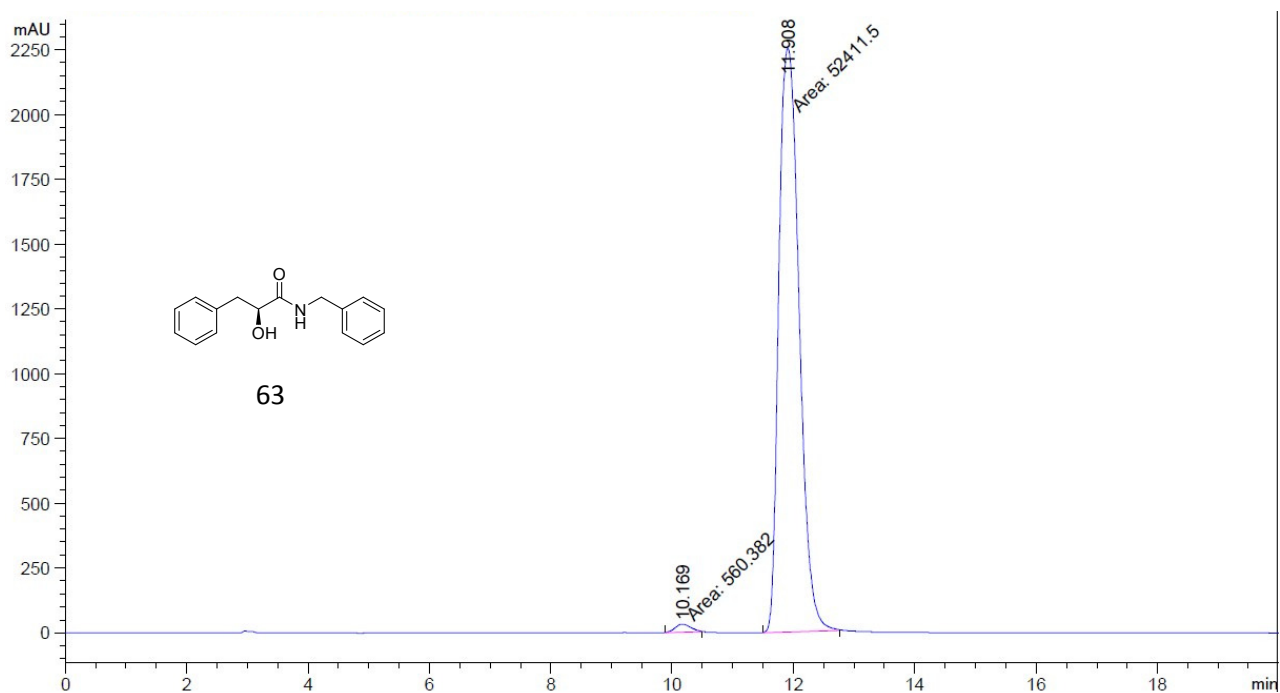
benzyl (S)-(1-(benzylamino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (61).



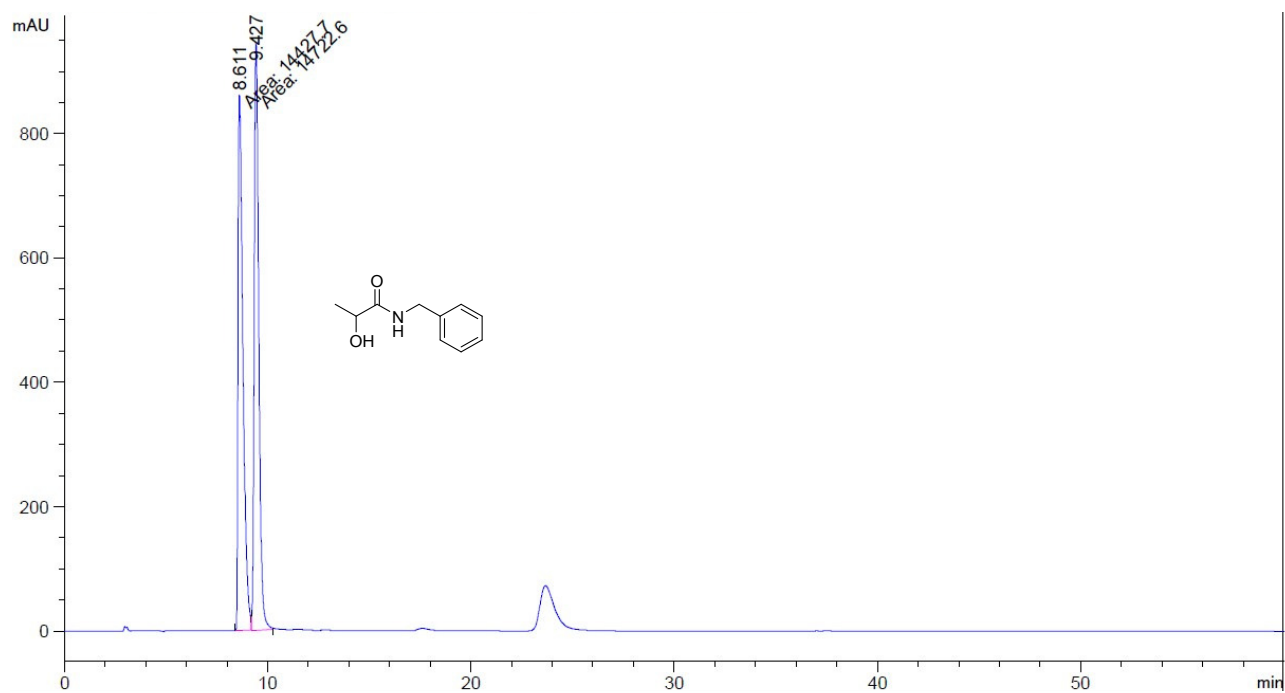
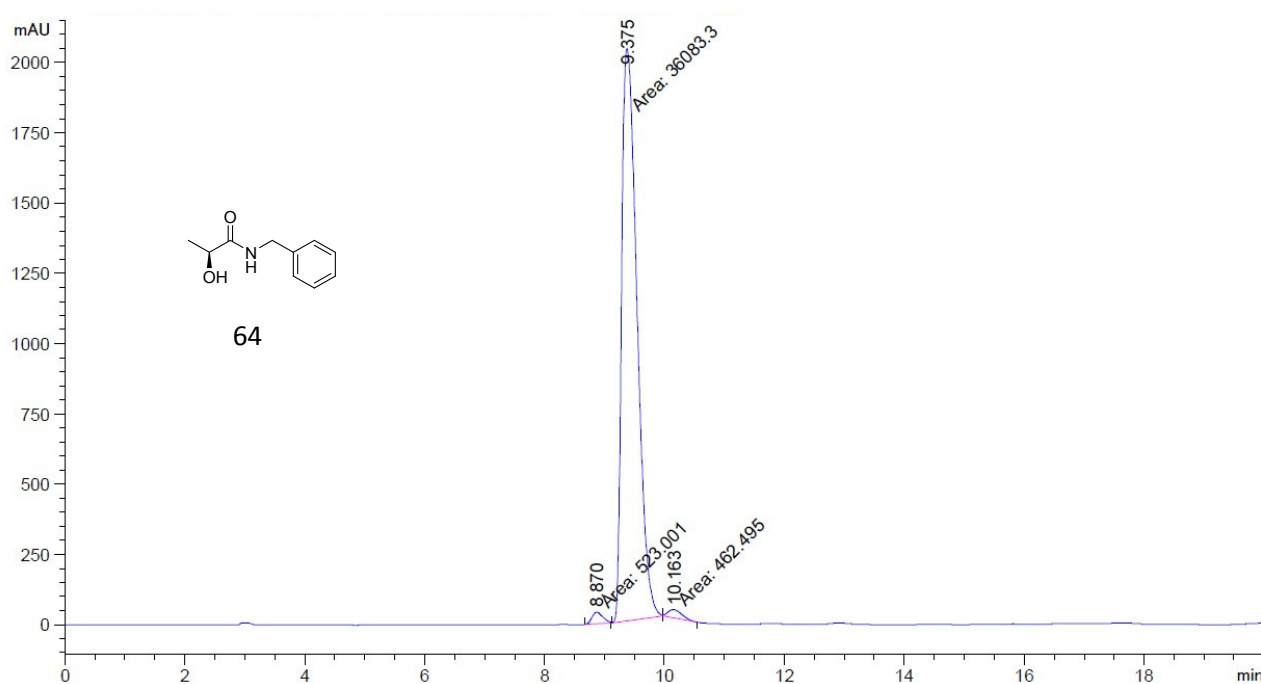
(R)-N-benzyl-2-hydroxy-2-phenylacetamide (62).



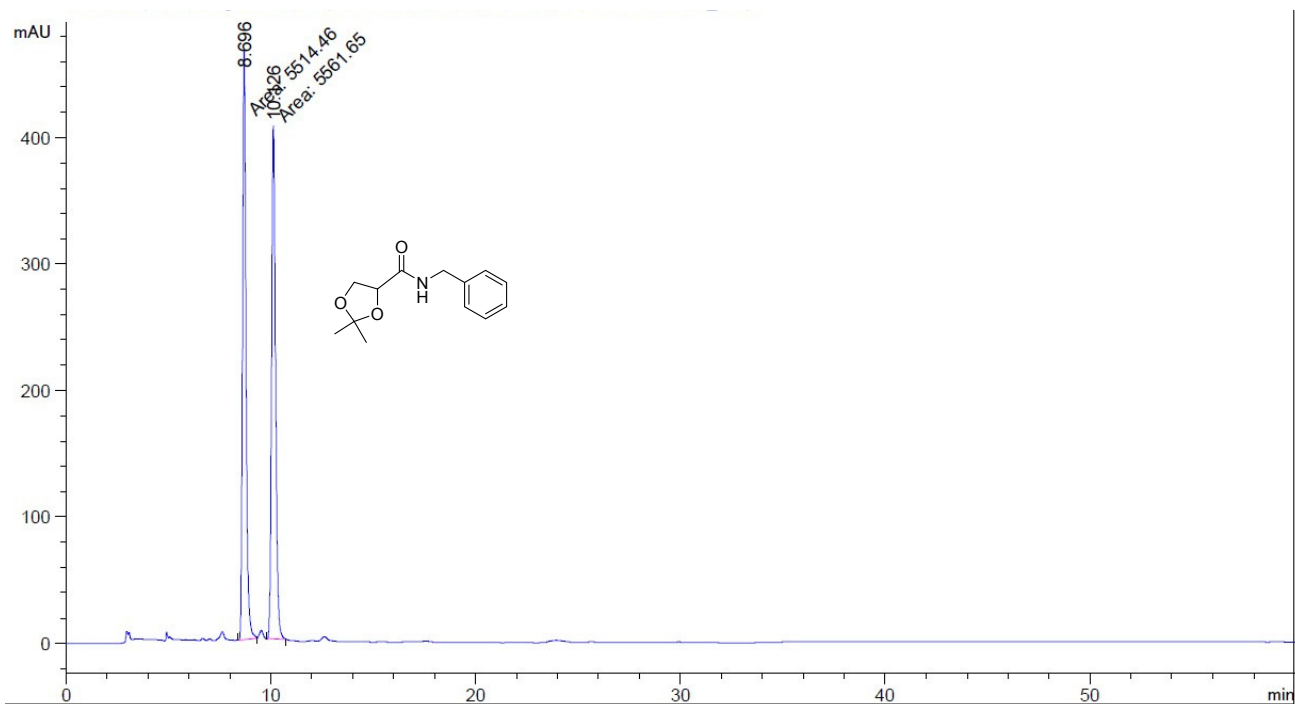
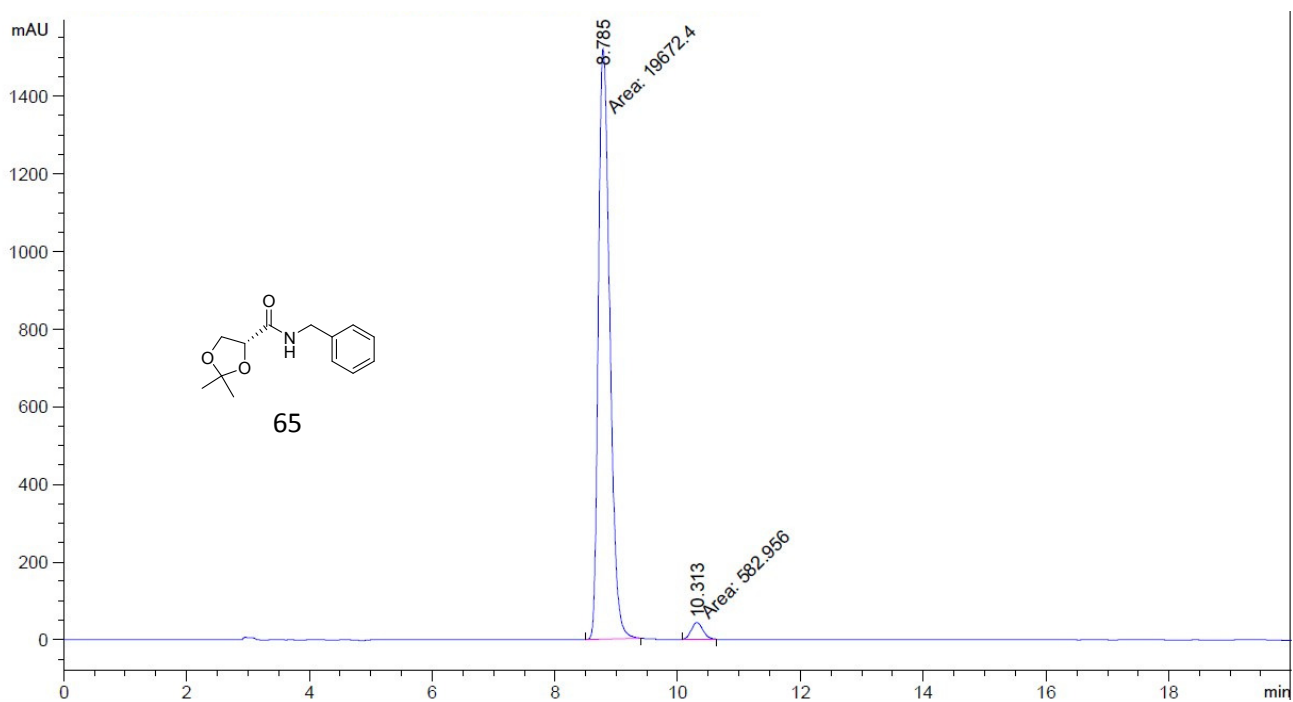
(S)-N-benzyl-2-hydroxy-3-phenylpropanamide (63).



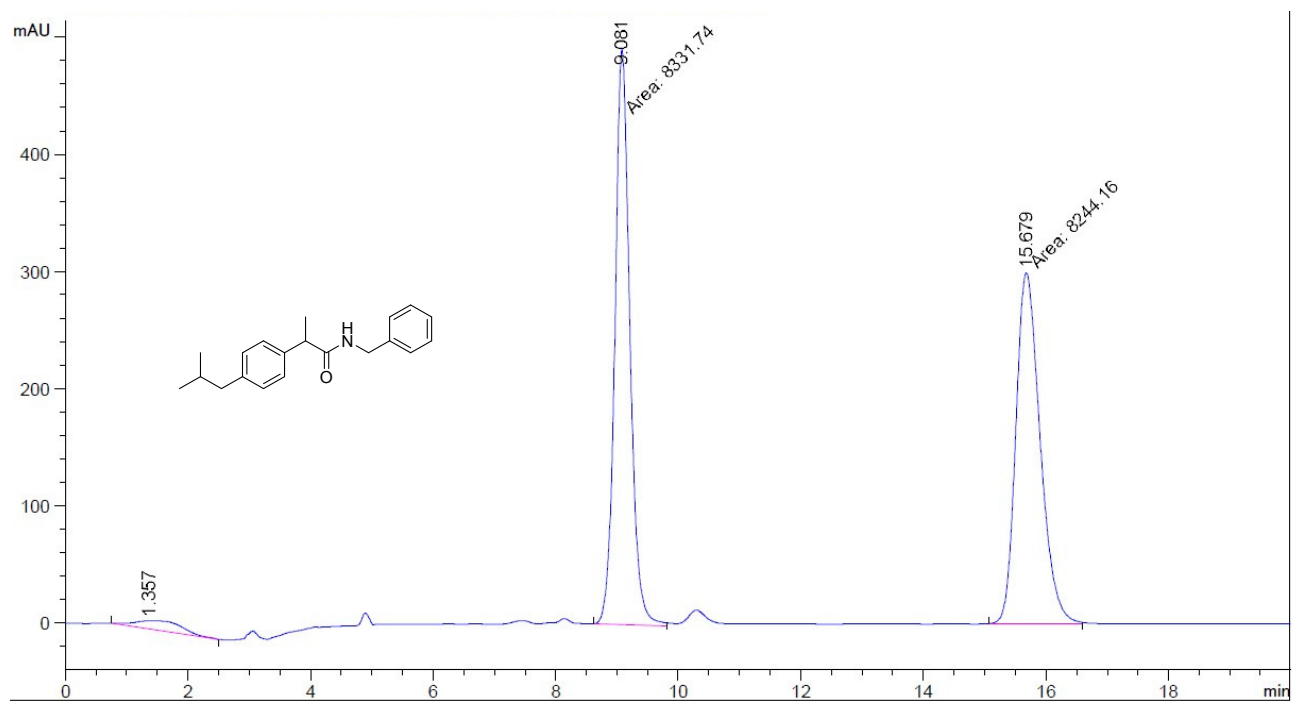
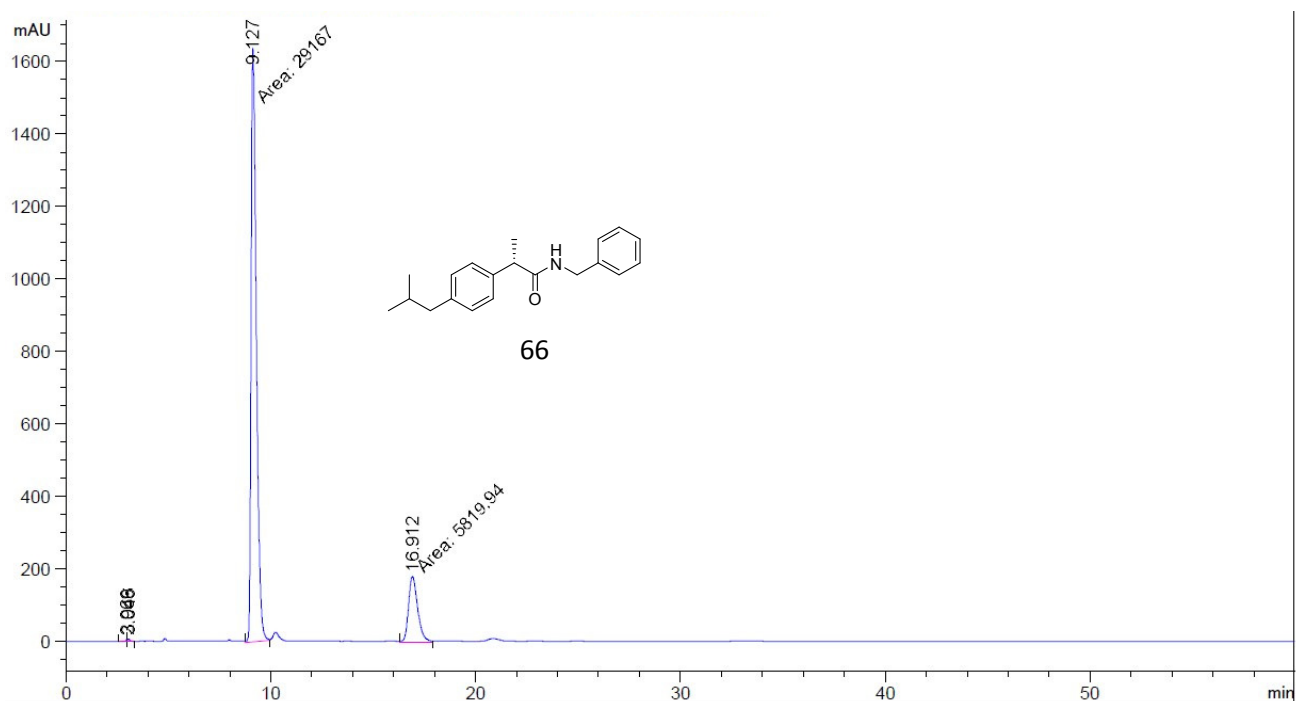
(S)-N-benzyl-2-hydroxypropanamide (64).



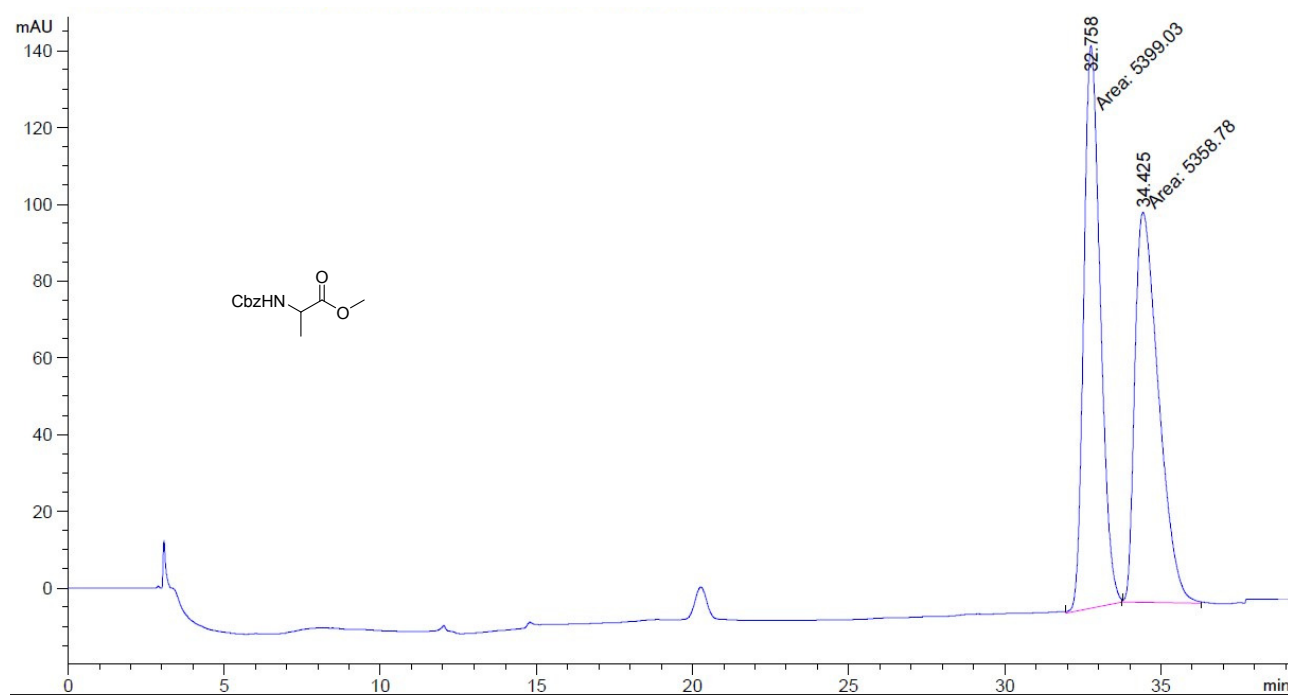
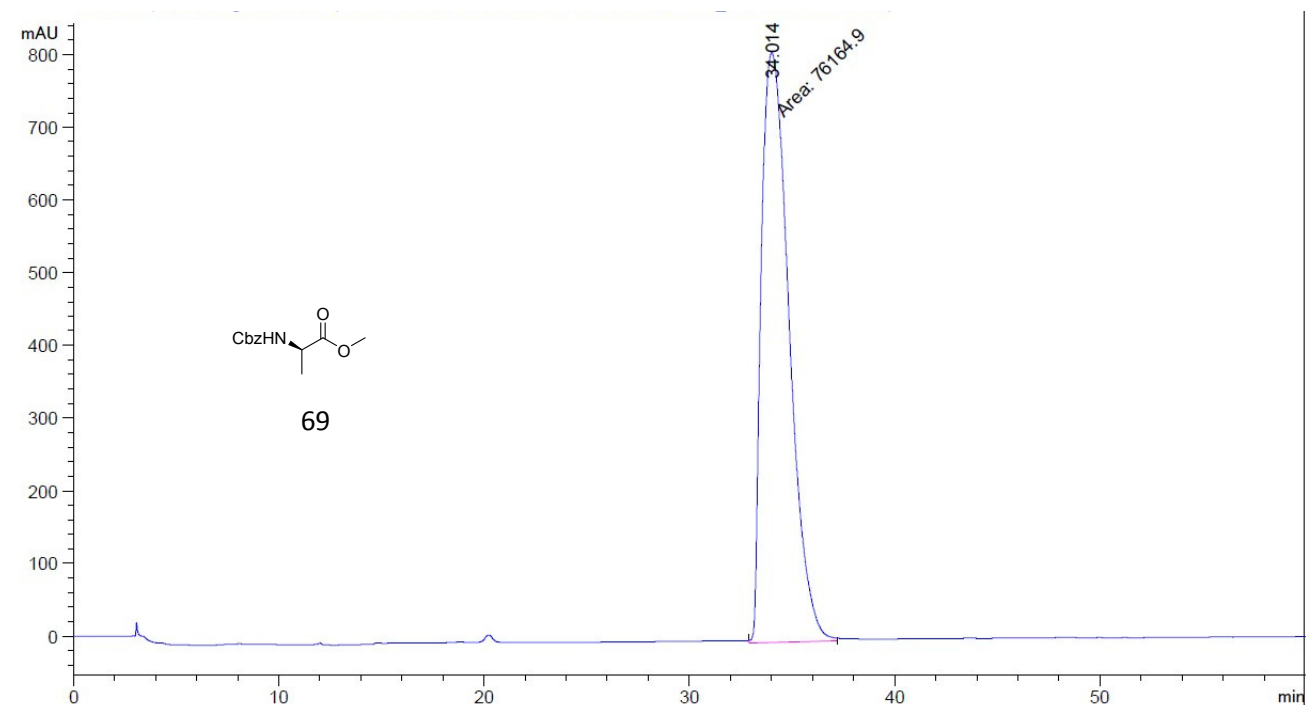
(R)-N-benzyl-2,2-dimethyl-1,3-dioxolane-4-carboxamide (65).



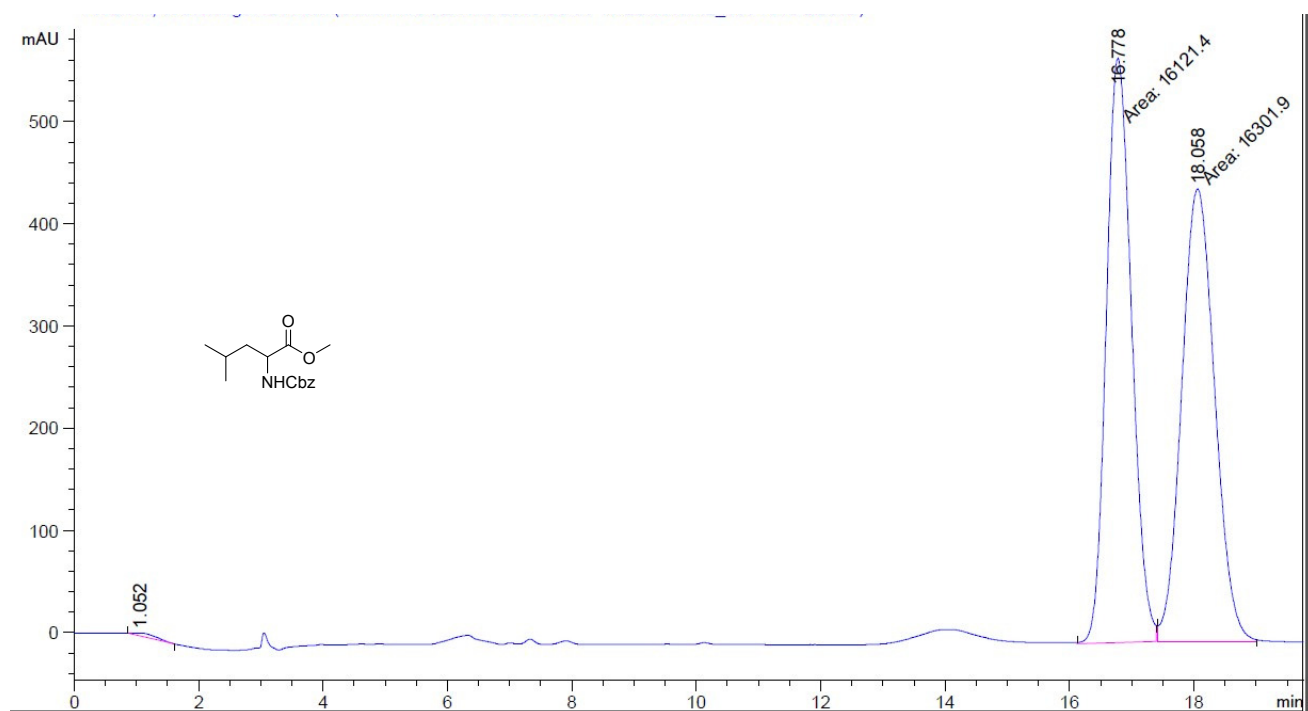
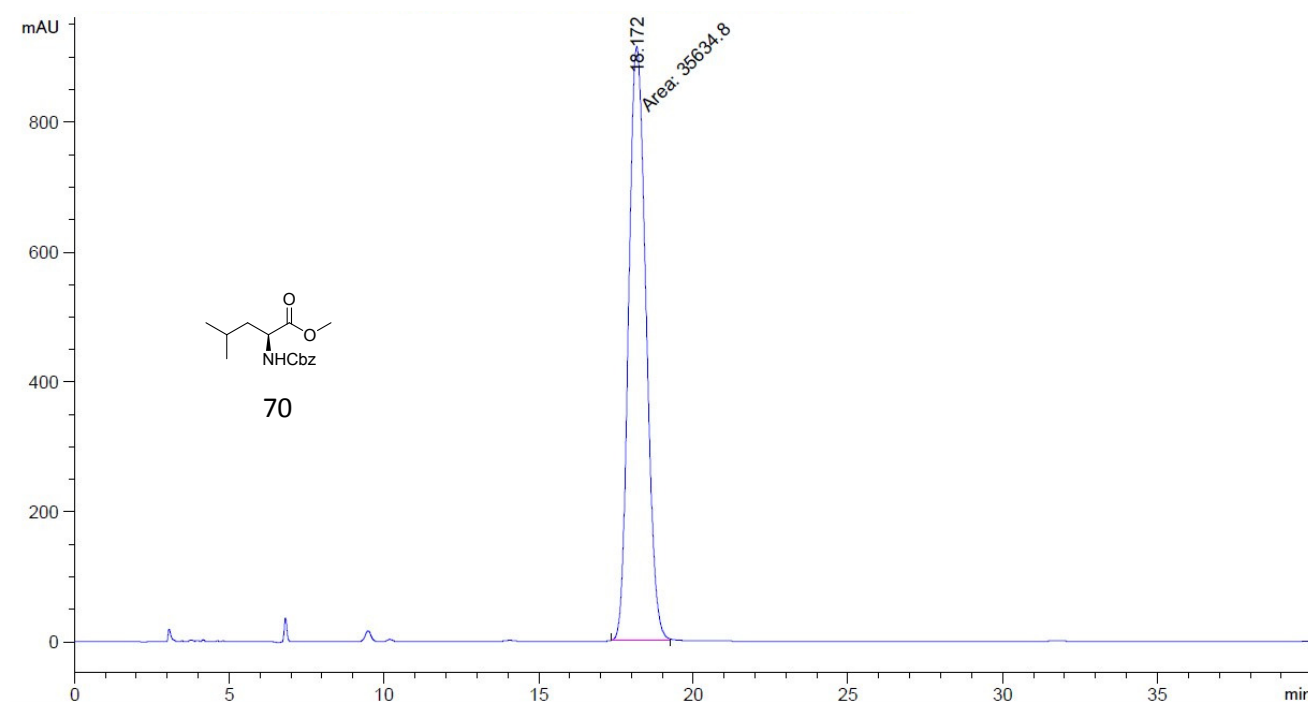
(S)-N-benzyl-2-(4-isobutylphenyl)propanamide (66).



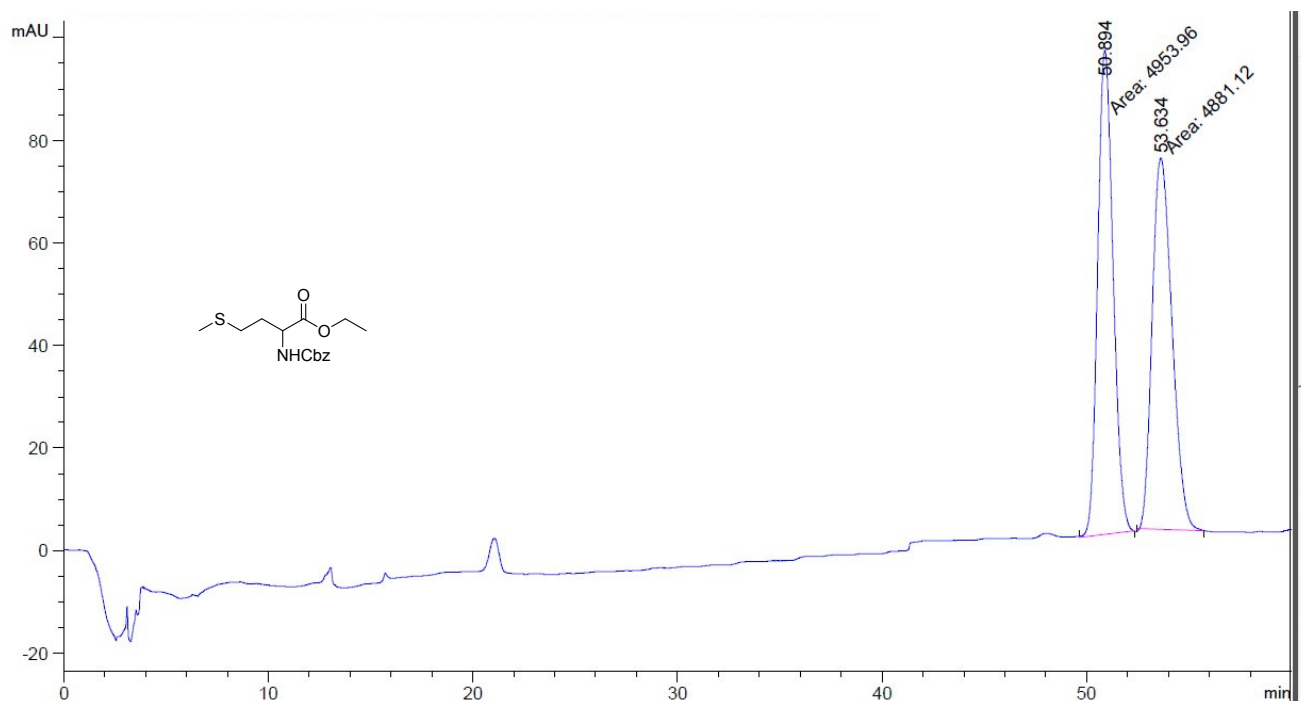
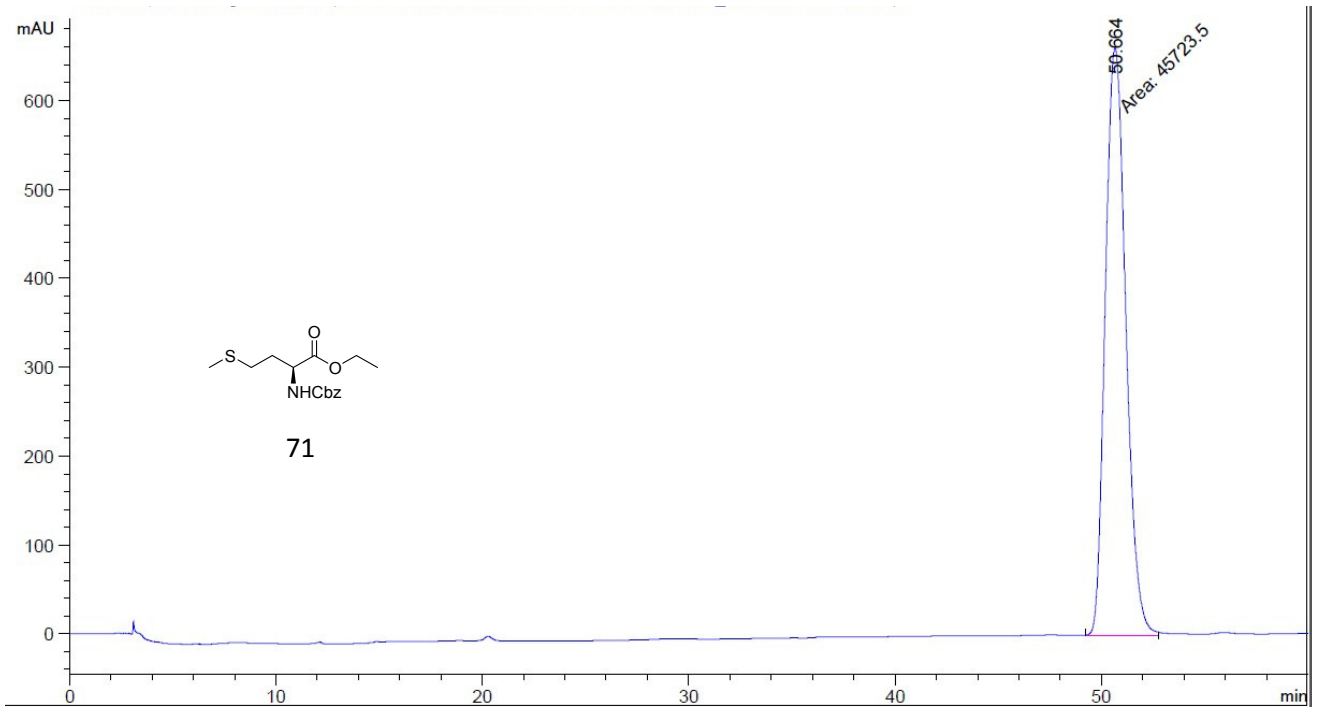
Methyl ((benzyloxy)carbonyl)-D-alaninate (69).



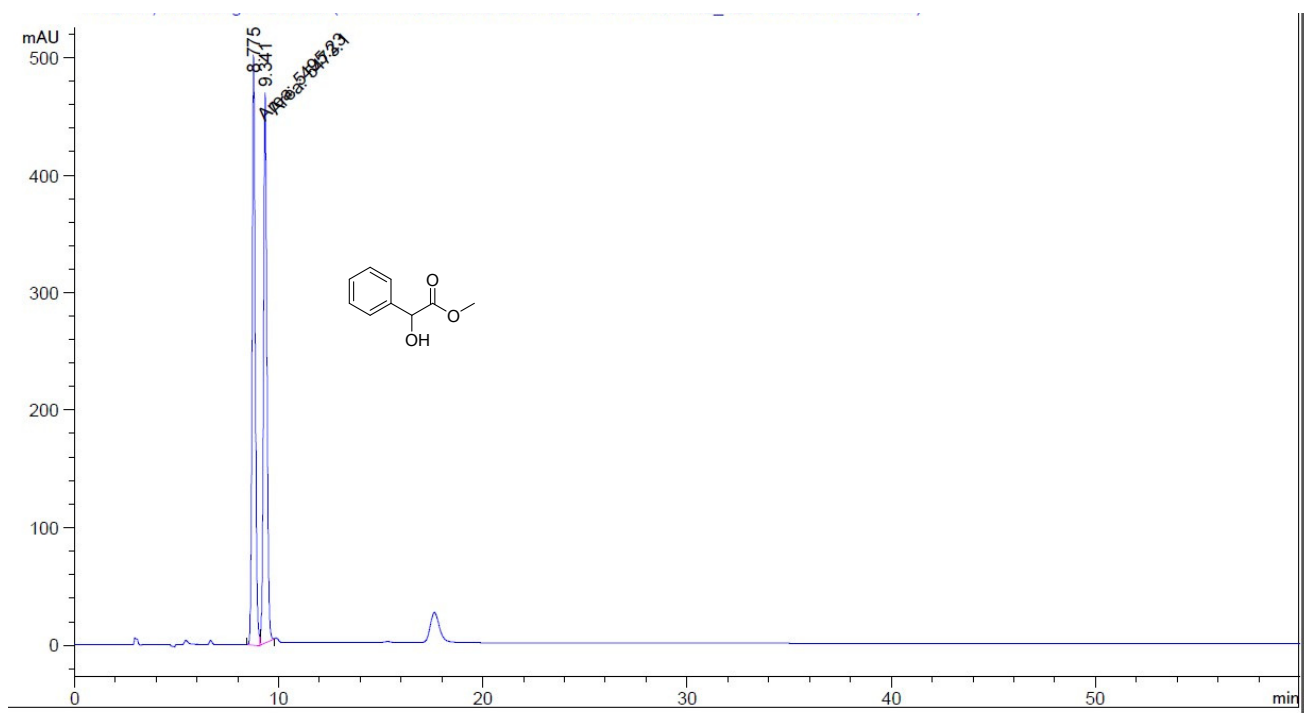
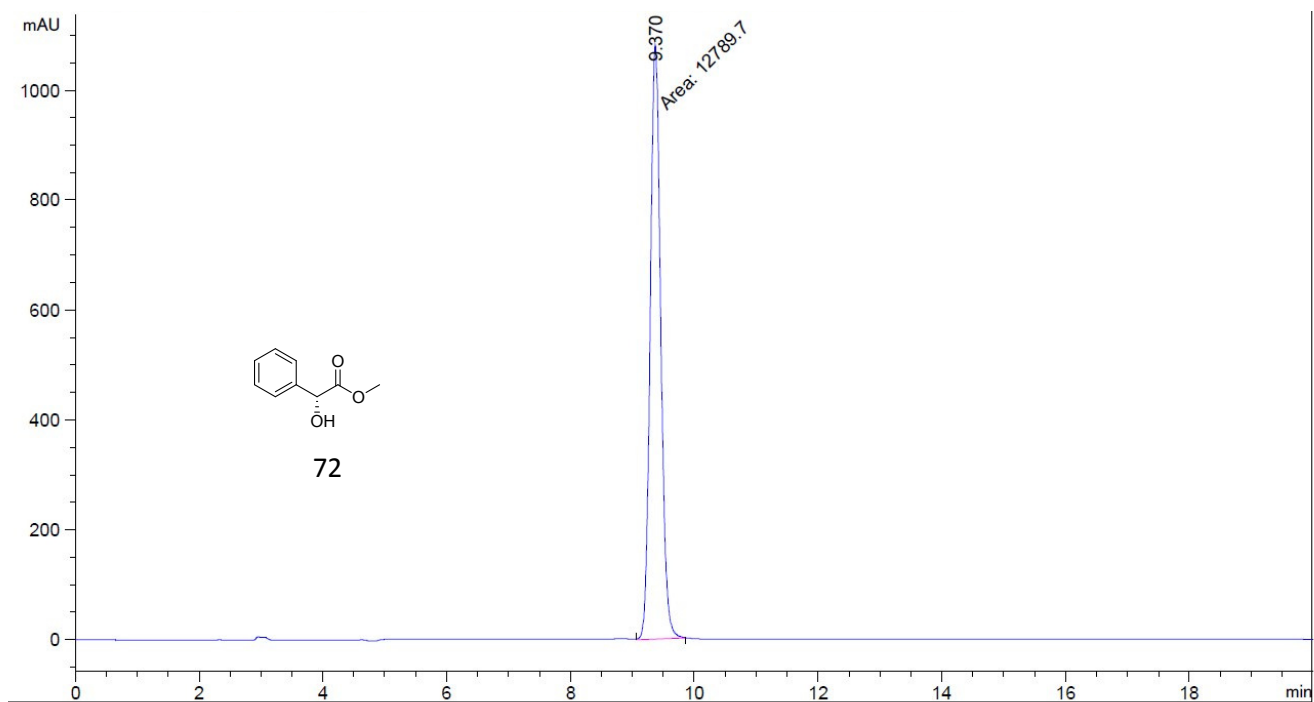
Methyl ((benzyloxy)carbonyl)-L-leucinate (70).



ethyl ((benzyloxy)carbonyl)-L-methioninate (71).



Methyl (*R*)-2-hydroxy-2-phenylacetate (72).



6. References

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