Ritter Reactions in Continuous Flow Catalysed by a Solid-Supported Sulfonic Acid Catalyst

Lara J. Nolan,[a,b,c] Ailbhe A. Ryan,[a,b,c] Seán Dempsey,[a,b,c] Megan Smyth,[b] Thomas S. Moody,[b,c] Scott Wharry,[b] Karen Fahey,[c] Paul Dingwall,[a] David W. Rooney[a], Jillian M. Thompson,[*a] Mark J. Muldoon[*a] and Peter C. Knipe[*a]

a. School of Chemistry and Chemical Engineering, Queen's University Belfast, Belfast, BT9 5AG United Kingdom.
b. Arran Chemical Company, Athlone, Co. Roscommon, N37 DN24 Ireland.
c. Almac Group, Craigavon, BT63 5QD United Kingdom.

Supplementary Information

Contents

S1 General Experimental 3

S1.1 Solvents and Reagents 3

S1.2 Purification 3

S1.3 Solid-Supported Catalysts 4

S1.4 Reaction Monitoring 6

S1.5 Chromatography 6

S1.6 Spectroscopy 6

S1.7 Mass Spectrometry 6

S1.8 Residence Times 7

S2 Experimental procedures and General Characterization 8

S2.1 General Procedures 8

S2.1.1 General procedure 1: Batch amidation of 1-phenylethanol and PhCN using polymer acid resins 8

S2.1.2 General procedure 2: Milling of acid resin catalysts 8

S2.1.3 General procedure 3: Continuous flow experiments 8

S2.2 Catalyst Optimization Batch Studies 8

S2.2.1 Temperature Screen (catalyst beads) 8

S2.2.2 Solvent Screen (catalyst beads) 9

S2.2.3 Concentration Screen 10

S2.2.4 Side-product Analysis 11

S2.2.5 Effect of Additives 12

S2.3 Continuous Flow Studies 13

S2.3.1 Flow Reactor 13

S2.3.2 Flow Reactor Modification Studies for Diphenylmethanol Substrate 14

S3 Example GC Trace 16

S4 Characterization data 17

S5 References 20

S6 Spectroscopic Data 21

Experimental

S1 General Experimental

S1.1 Solvents and Reagents

All solvents and reagents were commercially sourced and used without further purification. Batch reactions were conducted in sealed microwave vials to prevent loss of material during heating. A magnetic stirrer bar was added, and reactions were heated and stirred using an oil bath and magnetic stirrer/hotplate.

S1.2 Purification

Flash column chromatography was carried out using Fluorochem 60 40-63 micron silica gel. Thin-layer chromatography was carried out using Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica, visualized under UV light (254 nm) or by staining with aqueous potassium permanganate solution, ninhydrin or ceric ammonium molybdate solutions.

S1.3 Solid-Supported Catalysts

The catalysts used in this study were as outlined in Table S1. Polymer-supported acid resins were titrated prior to use according to literature procedure.[1] This was conducted *via* an initial anion exchange using a saturated solution of NaCl, the reaction mixture was then filtered, and the filtrate was titrated against 0.05 M NaOH (Table 1.1).

Table S1 Description of resins as determined through titration with NaOH

Name	Description	Porosity	Mesh / Particle Size	Manufacturer/Supplier	Acid Conc. (mmol/g)[a]
Nafion™ NR50	Tetrafluoroethylene-based polymer sulfonic acid	Gel type[b]	7 – 9 mesh (3 mm x 4 mm	The Chemours Company	1.18
Polymer-supported p-toluene sulfonic acid (p-TSA_R)	polymer-bound *para*-toluenesulfonic acid	macroporous	30 – 60 mesh (250 – 600 µm)	Sigma Aldrich	4.65
Amberlyst™ 15 (dry)	Bead form crosslinked styrene-divinylbenzene sulfonic acid	macroporous	< 300 µm	DuPont	2.4
AmberLite™ HPR2900H	Bead form crosslinked styrene-divinylbenzene sulfonic acid	macroporous	575 ± 50 µm	DuPont	2.72
Trityl chloride	Bead form polystyrene crosslinked with divinylbenzene bearing trityl chloride groups.	Gel type	100 – 200 mesh (75 – 150 µm)	Novabiochem	1.1[c]

[a] Determined by titration with aqueous NaOH.

[b] The porosity of Nafion NR50 is very low in its dry state. However, it is known to swell in various organic and aqueous solvents leading to increased acidic site accessibility, see López, Dora E., James G. Goodwin, and David A. Bruce. "Transesterification of Triacetin with Methanol on Nafion® Acid Resins." *Journal of Catalysis* **2007**, *245*, 381-91. While this swelling has not been quantified for MeCN in the NR50 bead form, thin-film studies have reported MeCN to cause six times greater swelling of the resin than water, see Claire, Anna F., Peter Zacher, Danielle Lehto, Daysha Krahn, and Krysti L. Knoche Gupta. "Electrochemical Characterization of Recast Nafion® Film-Modified Electrodes in Acetonitrile with Various Electrolytes." *Electrochem* **2024**, *5*, 574-84.

[c] From datasheet https://www.sigmaaldrich.com/GB/en/specification-sheet/ALDRICH/93003, accessed 30/10/2025.

S1.4 Reaction Monitoring

Reactions were monitored by either GC-FID or ^{1}H NMR spectroscopy, as described in sections S1.5-S1.6 below. The method used for each substrate or series of experiments is indicated in the caption to schemes in the main paper.

S1.5 Chromatography

Flash column chromatography was carried out using Fluorochem silica gel 60 Å as stationary phase. Thin-layer chromatography was conducted using Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica.

Gas chromatography analysis was carried out using an Agilent 7820A series gas chromatograph. An Agilent 19091J-413HP-5 column (30.0 m x 320 µm x 0.25 µm nominal) was employed for all separations. Method conditions varied depending on substrate used. For all methods, the effluent was combusted in H_2/ Air flame and detected using FID (flame ionization detector). GC measured substrate conversions and product yields were determined based on relative response factors (RF) of substrates(s) and products with respect to internal standard dodecane as per the equations below. Reference standards were commercially sourced from Sigma Aldrich.

Equation 1:
$$RF = \frac{Area_{internal\ standard} \times Moles_{analyte}}{Area_{analyte} \times Moles_{internal\ standard}}$$

The quantity of a given analyte was then calculated according to the rearranged form of this equation:

Equation 2:
$$Moles_{analyte} = \frac{RF \times Moles_{internal\ standard} \times Area_{analyte}}{Area_{internal\ standard}}$$

S1.6 NMR *Spectroscopy*

^{1}H NMR spectra were attained using a Bruker (400 MHz) spectrometer running TopSpin™ software. All spectra were recorded at ambient temperatures. Mestranova software was used for processing and viewing NMR data. The ^{1}H NMR spectra are reported as follows: δ / ppm (multiplicity, coupling constant *J*/ Hz , number of protons). Multiplicity is abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet. Quantitative ^{1}H NMR was conducted using mesitylene as an internal standard. On analysis all measured integrals were exposed to linear correction. The corrected yield of product was determined using equation 3.

Equation 3:
$$Moles_{analyte} = \frac{Moles_{internal\ standard} \times Number\ of\ protons_{internal\ standard} \times Area_{analyte}}{Integral_{internal\ standard} \times Number\ of\ protons_{analyte}}$$

S1.7 Mass Spectrometry

High resolution mass spectra (HRMS) were recorded by Analytical Services and Environmental Projects (ASEP) at Queen's University Belfast on a Waters LCT Premier ToF mass spectrometer using the electrospray ionisation (ESI) technique.

S1.8 Residence Times

Residence times were calculated by submerging the desired quantity of catalyst required in the appropriate nitrile solvent and noting the displacement volume - this was then subtracted from the internal volume of the column itself to determine volume. Residence time was then determined as both flow rate and reactor volume were known.

S2 Experimental Procedures and Supplementary Optimization Data

S2.1 General Procedures

The following procedures were followed unless alternative conditions are specified in the text (e.g. variations in temperature, catalyst loading *etc.*).

S2.1.1 General procedure 1: Batch amidation of 1-phenylethanol and PhCN using polymer acid resins

To a microwave vial, 1-phenylethanol (1 mmol), dodecane (1 mmol), PhCN (5 mL) and polymer supported acid catalyst (10 mol%) was added. The microwave vial was sealed with a crimped cap. The reaction mixture was heated to 100 °C and stirred for 24 h. The reaction was monitored by sampling at regular time intervals. For samples, a 100 µL aliquot of reaction mixture was withdrawn and passed through a celite plug followed by addition of ethyl acetate (1.4 mL). The samples were monitored by GC-FID using the method of internal standard.

S2.1.2 General procedure 2: Milling of acid resin catalysts

1 g of polymer-bound acid was granularized in a commercial coffee grinder for 3 minutes. The acid resin was further pulverized using a Retsch PM100 Planetary Ball Mill (2 teflon balls, frequency: 30 Hz) for 3 h.

S2.1.3 General procedure 3: Continuous flow experiments

The reactor was heated to 120 °C and the appropriate nitrile was pumped through the reactor at a rate of 1 mL/min to condition the flow path. Following this, the substrate feed (0.2 M alcohol dissolved in nitrile) was pumped through the reactor at 1 mL/min for 5 min before reducing to a flow rate of 26 µL/min. The reaction mixture was allowed to pass over the catalyst bed, at a residence time of 1 h, for 3 reactor volumes prior to sampling to allow for steady-state to be achieved. Samples were collected at the outlet of the reactor at regular time intervals. Samples were collected over a 10 minute period and analyzed by GC-FID or ^{1}H NMR using dodecane or mesitylene, respectively, as an internal standard. Internal standards were added to the sample removed from the reaction mixture. For isolated yields, a volume of 4.68 mL of crude reaction material was collected and isolated by flash column chromatography (gradient elution, hexane: ethyl acetate, 5:1 → 1:1). For nitrile solvents of relatively low boiling point, the reaction mixture was concentrated under reduced pressure prior to purification to remove any residual nitrile starting material.

S2.2 Catalyst Optimization Batch Studies

S2.2.1 Temperature Screen (catalyst beads)

The active Bronsted acid catalysts determined in **Figure 2** were subsequently assessed over a range of temperatures (**Figure S1**). Minimal variation in reaction efficacy was observed on increasing reaction temperature from 80-120 °C for the sulfonic acid catalysts. By contrast, temperature proved to be a critical parameter in the case of Nafion™ NR50 with a clear positive correlation of product yield to temperature.

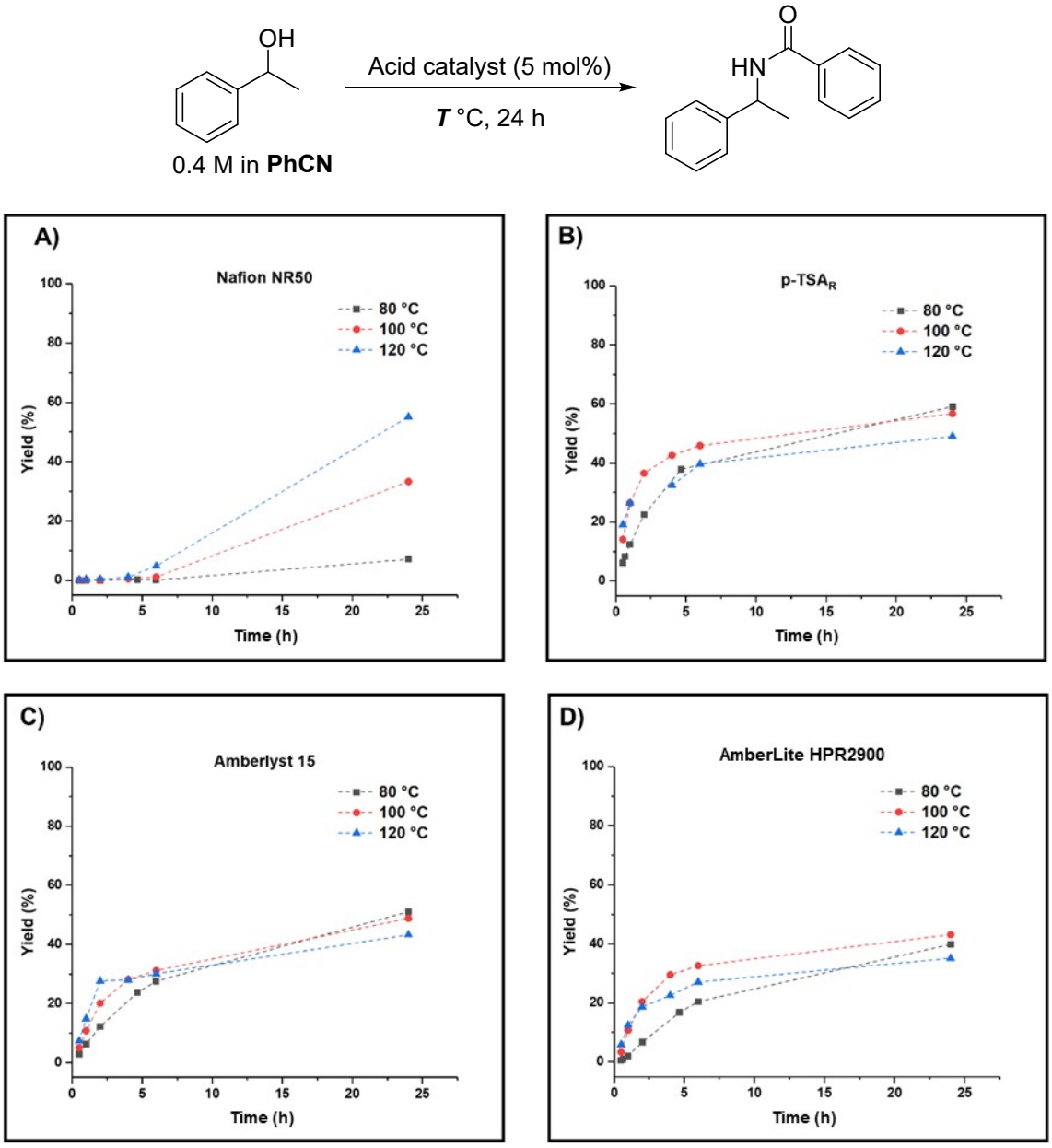


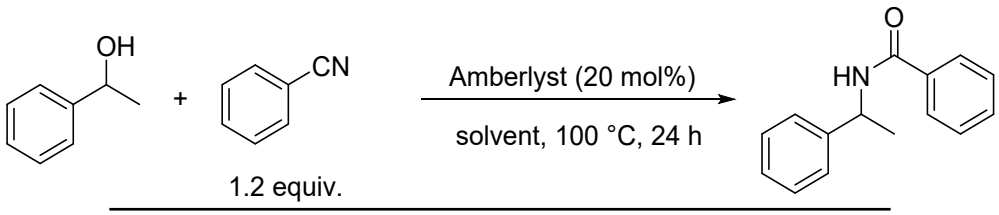
Figure S1. Time-course profiles depicting the effect of varying temperature for catalysts: A) Nafion™ NR50, B) Polymer-supported *p*-TSA$_R$, C) Amberlyst™ 15, D) AmberLite™ HPR2900. The yields reported were quantified using GC-FID with a dodecane internal standard**.**

S2.2.2 Solvent Screen (catalyst beads)

To expand the generality of this process, a series of polar protic, aprotic, aromatic, and aliphatic solvents were investigated to allow for incorporation of solid nitrile reagents. Due to the reactivity of alcohols toward the Ritter transformation, trifluoroethanol and methanol were selected as possible protic solvents due to the postulated instability of their carbocation counterpart disfavouring the Ritter transformation. Unfortunately, all solvents examined produced styrene as

the major product in lieu of the desired amide likely attributed to the significantly reduced stoichiometry of PhCN (**Table S1**).

Table S2. Solvent screen conducted for the Amberlyst™ 15 catalyzed reaction between 1-phenylethanol (0.2 M) and PhCN (1.2 equiv.) at 100 °C. [a] Reaction was conducted for 1-phenylethanol (0.2 M in PhCN). Yields reported are GC-FID yields.



Entry	Solvent	Yield (%)
1	Me-THF	0
2	MTBE	0
3	Toluene	0
4	Bu_2O	7
5	Heptane	0
6	Trifluoroethanol	0
7	THF	0
8	MeOH	0
9	EtOAc	7
10	PhCN (control)[a]	94

S2.2.3 Concentration Screen

The effect of increasing the concentration of 1-phenylethanol was examined with the Amberlyst™ 15 catalyst (**Figure S2**). At low concentrations of alcohol the amide **1a** was the major product, but as alcohol concentration increased the selectivity towards the product was decreased. At high concentrations, neither styrene **2** nor amide **1a** were the major products though conversion of

65% was observed. This suggested that the formation of the bis(1-phenylethyl) ether diastereoisomers *anti*-**3** and *syn*-**3** was in fact competing with product formation in the reaction. This was further confirmed by isolation of the diastereoisomers from the reaction mixture.

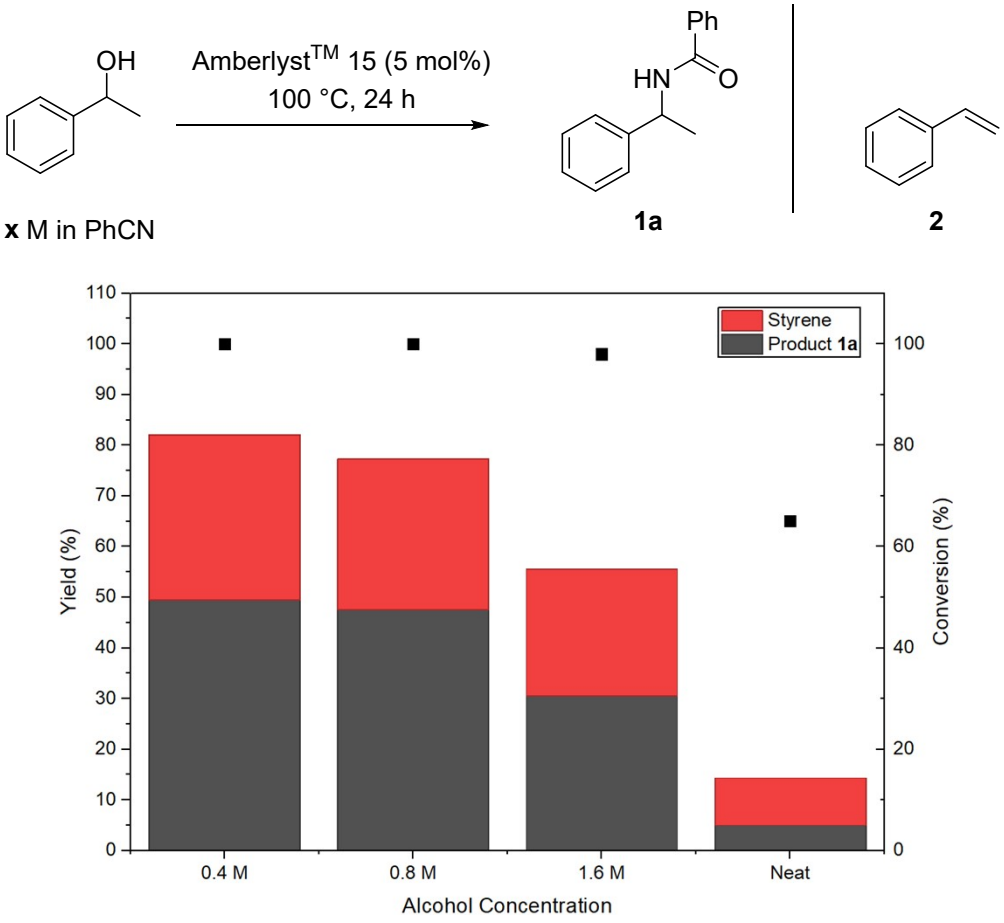
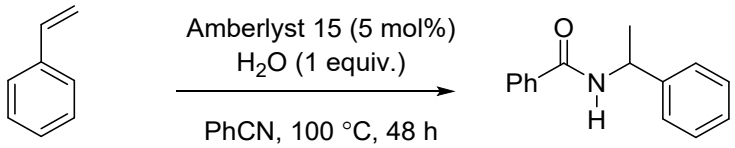


Figure S2. Time-course profiles for reactions with varying concentrations of 1-phenylethanol demonstrating the negative correlation between [1-phenylethanol] and yield of product **1a**. "Neat" refers to 1:1 stoichiometric equivalents of 1-phenylethanol and PhCN.

S2.2.4 Side-product Analysis

Styrene was identified by GC-FID as a side-product in the reaction using a commercially available styrene standard. Exposure of styrene to the reaction conditions was then examined. Water was added in stoichiometric amounts to allow conversion to the desired amide. As expected, styrene successfully reacted with the acid catalyst and PhCN to form product **1a** albeit at a reduced rate compared to the 1-phenylethanol (**Figure S3**).



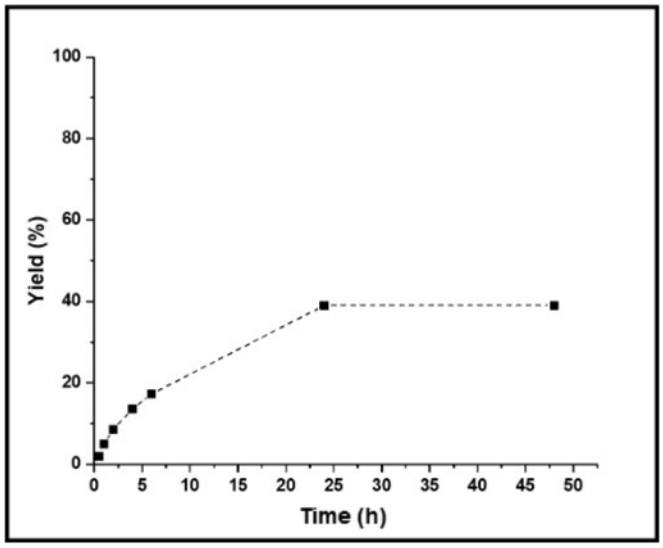
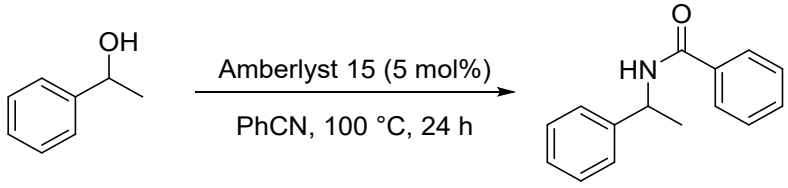


Figure S3. Graphical representation of the reactivity of styrene under the model reaction conditions. Yields plotted are GC-FID yields.

S2.2.5 Effect of Additives

The application of additives was investigated to prevent the formation of styrene and its resulting rate inhibition. Initially, aims to stabilize the carbocation in solution were investigated using external factors such as additives. As previously mentioned, polar protic compounds can be utilized to stabilize carbocations, however, protic compounds frequently contain the alcohol functionality rendering them incompatible as external additives. With this in mind, we studied the effect of using water and acetic acid as additives. It is well established in the literature that acetic acid reacts with styrene in the presence an acid to form acetates and similarly, the reaction of acetates with nitriles to form the corresponding amide is equally familiar. This introduces a plausible second benefit of utilizing acetic acid as a trapping agent to form a more reactive compound to the styrene intermediate thus reducing any rate inhibition. Sadly, no improvements were observed on addition of water and acetic acid (**Figure S4**). Notably, on application of 5 equivalents of water, complete suppression of product formation was observed, likely due to biasing the equilibrium towards the alcohol starting material rather than the carbocation intermediate.



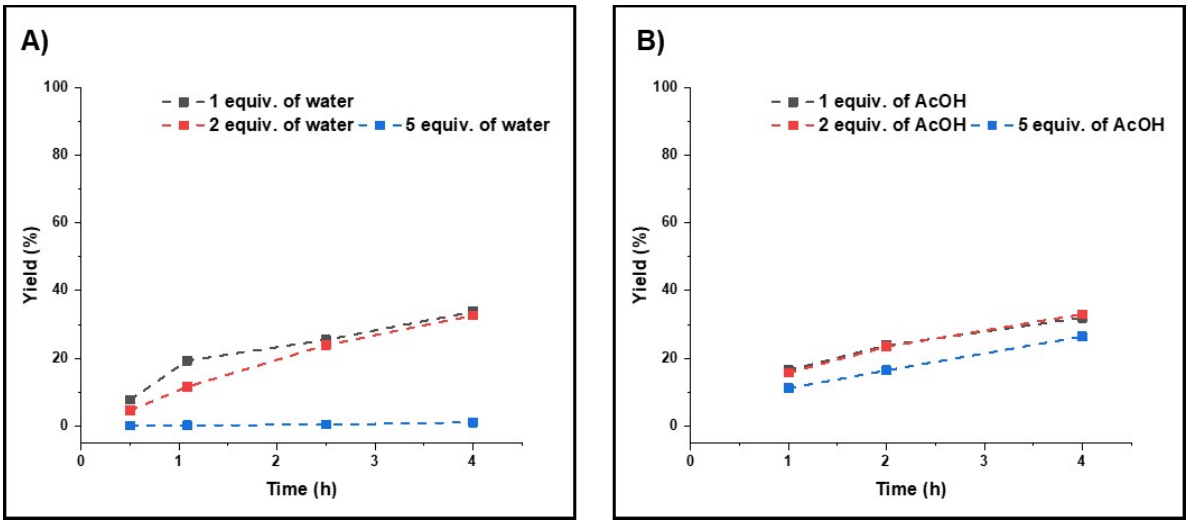


Figure S4. Reaction profiles for application polar protic additives in the reaction between 1phenylethanol and PhCN using Amberlyst 15 as the acid catalyst. Yields reported are GC/FID yields.

S2.3 Continuous Flow Studies

S2.3.1 Flow Reactor

All PTFE tubing and fittings (ferrules, T-mixer, union) were purchased from Kinesis. The Idex® back pressure regulator was purchased from Cole Palmer and peristaltic pump, model: Vapourtec SF-10, was purchased directly from Vapourtec. The packed bed reactor was made from an old Phenomenex HPLC column (150 x 4.6 mm ID), which was heated in a tubular Carbolite furnace.

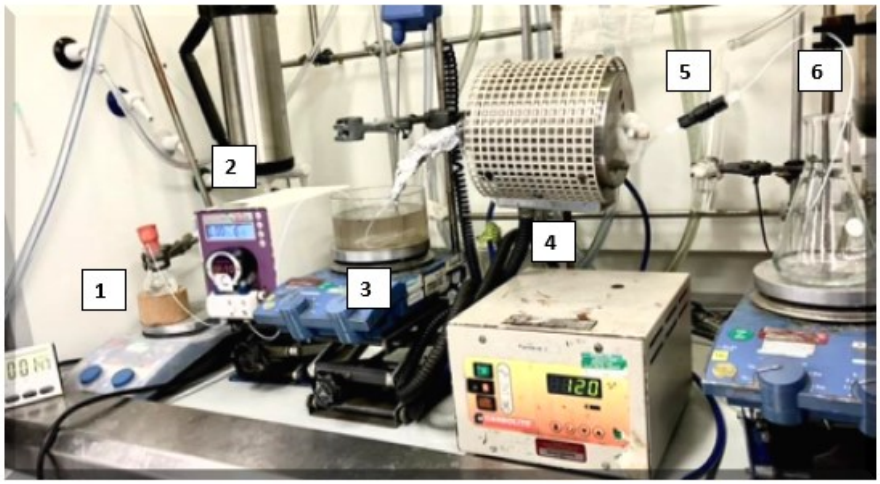


Figure S5. Apparatus for continuous flow experiments.

1. Feed solution containing alcohol and nitrile
2. Vapourtec peristaltic pump
3. Pre-heating loop
4. Carbolite heating furnace
5. Back pressure regulator

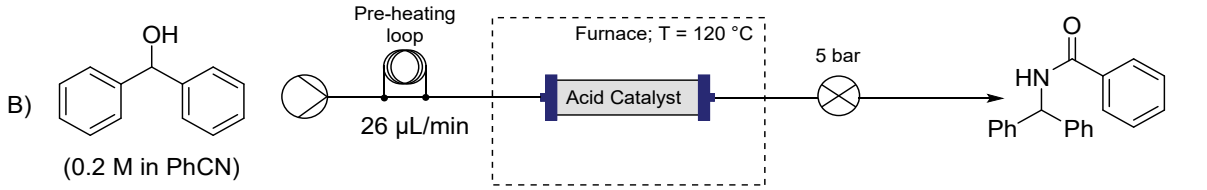
6. Collection flask

The continuous flow reactor design is depicted in **Figure S5**. 1.14 g of catalyst was packed into a stainless steel HPLC column (150 x 4.6 mm), with glass wool at either end of the column to keep the catalyst bed intact. The packed bed was contained and heated within a Carbolite furnace. A Vapourtec peristaltic pump was used to deliver the substrate feed to a pre-heating loop comprising of PTFE tubing (50 cm) immersed in an oil bath of the appropriate temperature prior to entering the packed bed reactor. A BPR was applied to the system to maintain a constant pressure of 5 bar. Reactor tubing (1/8'' O.D.), connections and fittings were PTFE.

S2.3.2 Flow Reactor Modification Studies for Diphenylmethanol Substrate

The application of diphenylmethanol as the alcohol substrate and PhCN as the nitrile reagent proved challenging with formation of a white precipitate, presumed to be the triphenylated amide, resulting in blockages within the flow reactor. To prevent the amide from crashing out of solution, the reaction was conducted at a range of concentrations (**Table**). However, in all cases the reactor blocked within 3 hours due to formation of the white precipitate

Table S3. Conditions: temperature; 120 °C, residence time; 1 h, flow rate: 26 µL/min.



Entry	[1-phenylethanol] (M)	Yield (%)
1	0.8	Reactor Foul
2	0.4	Reactor Foul
3	0.2	Reactor Foul

After observing that fouling initially occurred at the BPR, the reactor was first modified to feature the FBR in a vertical configuration such that the BPR could be removed from the system. This rationale was guided by the thought that the BPR was necessary to ensure the FBR was completely filled by the reaction mixture along the cross-section of the channel while held in a horizontal plane. If the reactor is held in a vertical plane, the same cross-sectional filling should be achieved as gravity acts against the direction of flow, removing the need for a BPR. Unfortunately, this provided no improvement with respect to reactor fouling, as precipitation of the amide product and eventual blockage of the reactor outlet was still observed, even when the reactor outlet was fully submerged in ethyl acetate in an attempt to dissolve the precipitate as it formed. Subsequent studies examined the incorporation of a co-solvent to enhance the solubility of the amide. Ethyl acetate was chosen as a co-solvent due to its compatibility with the reaction conditions, its miscibility with the nitrile solvent and its polarity. The reaction was conducted in a 2:1 ratio of PhCN: ethyl acetate. No reactor fouling was observed over a 5 hour- period achieving a yield of 80% yield at steady state without optimization of the solvent ratio. Due to the lack of

reactivity of diphenylmethanol towards competing pathways, the yield was lower than expected. In attempt to further improve this result, a second Vapourtec SF10 was employed to introduce a stream of ethyl acetate *via* a T-piece at the outlet of the FBR, in order to prevent the co-solvent from having any deleterious effect on reaction efficiency whilst enabling product solubility at the end of the reaction **(Figure S6C**). A quantitative yield was achieved under this set-up. However, the reactor blocked after approx. 3.5 h due to precipitation within the reactor. For challenging substrates which demonstrate low solubility within the reactor, a co-solvent such as ethyl acetate is recommended.

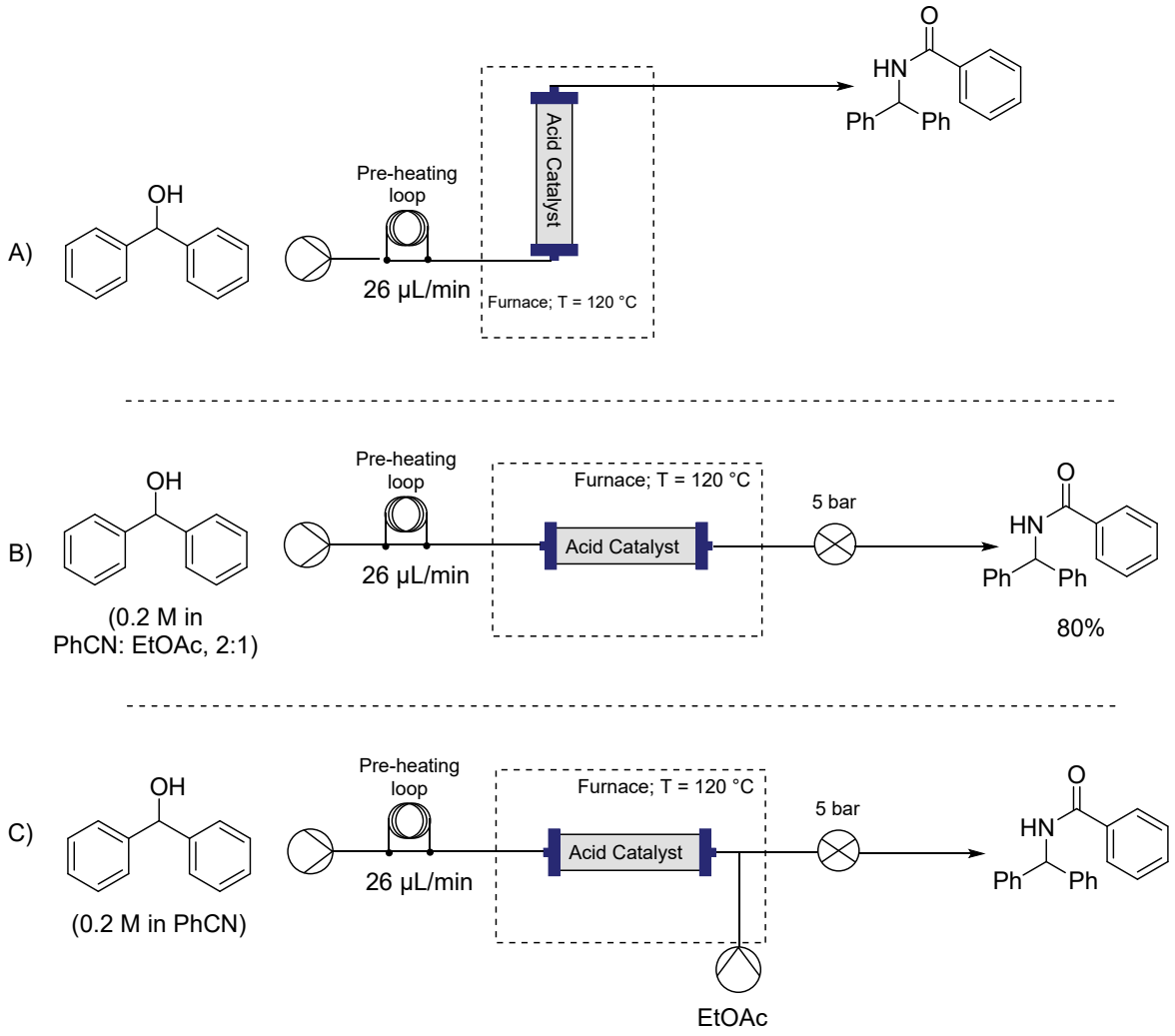
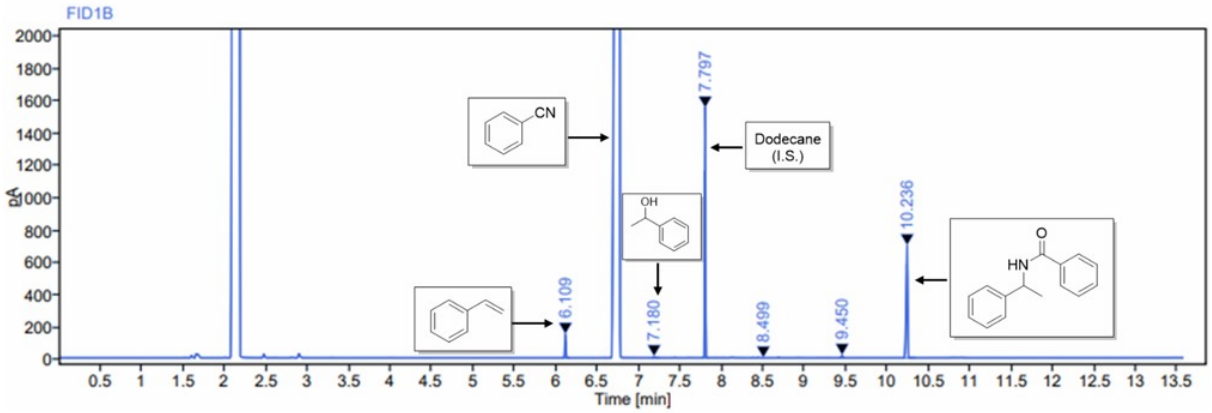


Figure S6. Schematic representation of the flow regime for the acid catalysed conversion of diphenylmethanol and PhCN to *N*-(diphenylmethyl)benzamide. Reactions were conducted at 0.2 M concentration following the model flow regime, depicted in (fig. from paper), with modification on; A) Without BPR, using a vertical FBR, B) Use of ethyl acetate as a co-solvent, C) Application of a second pump to introduce a feed of EtOAc after the reaction FBR to aid with solubility.

S3 Example GC Trace



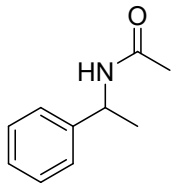
S4 Characterization data

A mixture of *syn*-**3** and *anti*-**3** was prepared according to **general procedure 1** with $pTSA_R$ catalyst but in the absence of any nitrile. The reaction mixture was filtered to remove acid catalyst, concentrated *in vacuo*. ^{1}H NMR analysis of the crude mixture revealed a 2.4:1:1.1:1.3 ratio of 1-phenylethanol:styrene:**3**:**3**[*]. The crude mixture was purified by flash column chromatography (silica gel, ethyl acetate:hexane 1:20) to afford the mixture of diastereomers of **3** in a 1.6:1 ratio and 29% combined yield.

(±)

^{1}H NMR (400 MHz, $CDCl_3$): *major diastereomer* 7.26-7.08 (10H, m), 4.43 (2H, q, *J* 6.4) 1.36 (6H, d, *J* 6.2), *minor diastereomer* 7.26-7.08 (10H, m), 4.14 (2H, q, *J* 6.5), 1.28 (6H, d, *J* 6.5). These data are in agreement with literature values.[2]

***N*-(1-Phenylethyl)acetamide (1b)** was prepared according to **general procedure 3** employing alcohol substrate 1-phenylethanol and nitrile reagent acetonitrile to afford the desired amide as a white solid (107 mg, 70%).

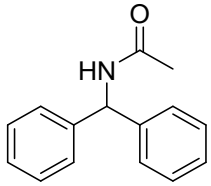


^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H\ (ppm)$ = 7.34-7.26 (m, 4H), 5.73 (br s, NH), 5.17 (quintet, *J*= 7.2 Hz , 1H), 1.98 (s, 3H), 1.50 (d, *J* = 6.9 Hz, 3H). ^{13}C {^{1}H} NMR: δ 169.0, 143.2, 128.7, 127.4, 126.2, 48.8, 23.5, 21.7. HRMS (ESI+) found 164.1076; C10H13NOH, [M+H]+ requires 164.1075.

These data are in agreement with literature values.[3]

***N*-Benzydrylacetamide (1c)** was prepared according to **general procedure 3** employing alcohol substrate diphenylmethanol and nitrile reagent acetonitrile to afford the desired amide as a white solid (158 mg, 75%).

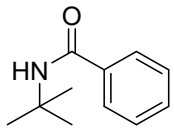
[*] The diastereomers of **3** were not unambiguously distinguished from one another.



^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H\,(ppm)$ = 7.28-7.15 (m, 10H), 6.20 (d, *J* = 8.0 Hz, 1H), 5.95 (brs, NH), 2.00 (s, 3H). ^{13}C {^{1}H} NMR: δ 169.07, 141.51 128.7, 127.5, 127.4, 57.0, 23.4. HRMS (ESI+) found 226.1225; C15H15NOH, [M+H]+ requires 226.1232.

These data are in agreement with literature values.[4]

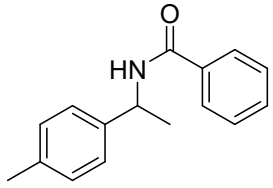
***N-tert*-Butylbenzamide (1d)** was prepared according to **general procedure 3** employing alcohol substrate *tert*-butanol and nitrile reagent PhCN to afford the desired amide as a white powder (125 mg, 75%).



^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H\,(ppm)$ = 7.73-7.71 (m, 2H), 7.47-7.26 (m, 3H), 5.95 (br s, NH), 1.48 (s, 9H). HRMS (ESI+) found 178.1194; C11H15NOH, [M+H]+ requires 178.1232.

These data are in agreement with literature values.[3]

***N*-(1-p-tolylethyl)Benzamide** (**1e**) was prepared according to **general procedure 3** employing alcohol substrate 1-(p-tolyl)ethanol and nitrile reagent PhCN to afford the desired amide as a white solid (135 mg, 60%).

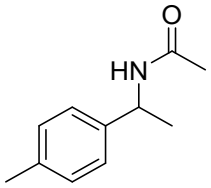


^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H\,(ppm)$ = 7.77-7.75 (m, 2H), 7.50-7.46 (m, 1H), 7.42-7.3 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8 Hz, 2H), 6.35 (br d, *J* = 5.2 Hz, 1H), 5.31 (quintet , *J* = 7.1

Hz, 1H), 2.34 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H). ^{13}C {^{1}H} NMR: δ 166.6, 140.2, 137.2, 134.7, 131.4, 129.4, 128.6, 126.9, 126.2, 49.0, 21.7, 21.1. HRMS (ESI+) found 240.1395; C16H17NOH, [M+H]+ requires 240.1388.

These data are in agreement with literature values.[5]

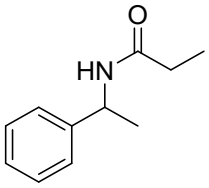
***N*-(1-*p*-Tolylethyl)acetamide (1f)** was prepared according to **general procedure 3** employing alcohol substrate 1-(p-tolyl)ethanol and nitrile reagent acetonitrile to afford the desired amide as a white solid (93.8 mg, 57%).



^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H\,(ppm)$ = 7.20 (d, *J* 8.0 Hz, 2H), 7.13 (d, *J* 7.8 Hz, 2H), 6.09 (br d, *J* 5.5 Hz, NH), 5.07 (quintet,*J* = 7.2 Hz, 1H), 2.32 (s, 3H), 1.94 (3H, s), 1.45 (d, *J* = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR: δ 169.2, 140.3, 137.0, 129.3, 126.2, 48.5, 23.4, 21.8, 21.1. HRMS (ESI+) found 178.1228; C11H15NOH, [M+H]+ requires 178.1232.

These data are in agreement with literature values.[3]

***N*-(1-Phenylethyl)propionamide (1h)** was prepared according to general **procedure 3** employing alcohol substrate 1-phenylethanol and nitrile reagent propionitrile to afford the desired amide as a white solid (126 mg, 76%).



^{1}H NMR (400 MHz, $CDCl_3$): $\delta_H\,(ppm)$ = 7.34–7.22 (m, 5H), 6.11 (br s, NH), 5.13 (quintet, *J* = 7.2 Hz , 1H), 2.20-2.15 (m, 2H), 1.45 (d, *J* = 6.9 Hz, 3H), 1.10 (t, *J* = 7.6 Hz, 3H). HRMS (ESI+) found 200.0966; C11H15NOH, [M+Na]+ requires 200.1051.

These data are in agreement with literature values.[4]

S5 References

1. P. A. Son, S. Nishimura and K. Ebitani, *React. Kinet. Mech. Catal.*, 2012, **106**, 185–192.

2. Q. Xu, H. Xie, P. Chen, L. Yu, J. Chem and X. Hu, *Green Chem* 2015, **17**, 2774

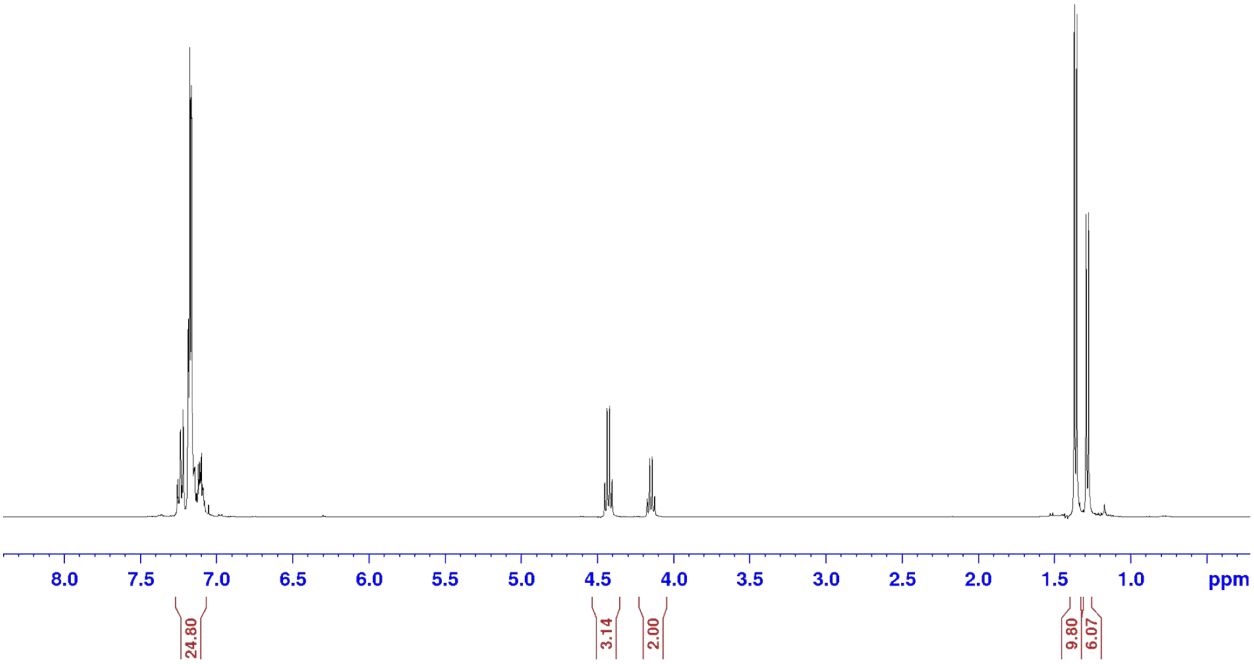
3 S. Nandy, A. K. Das and S. Bhar, *Synth. Commun.*, 2020, **50**, 3326–3336.

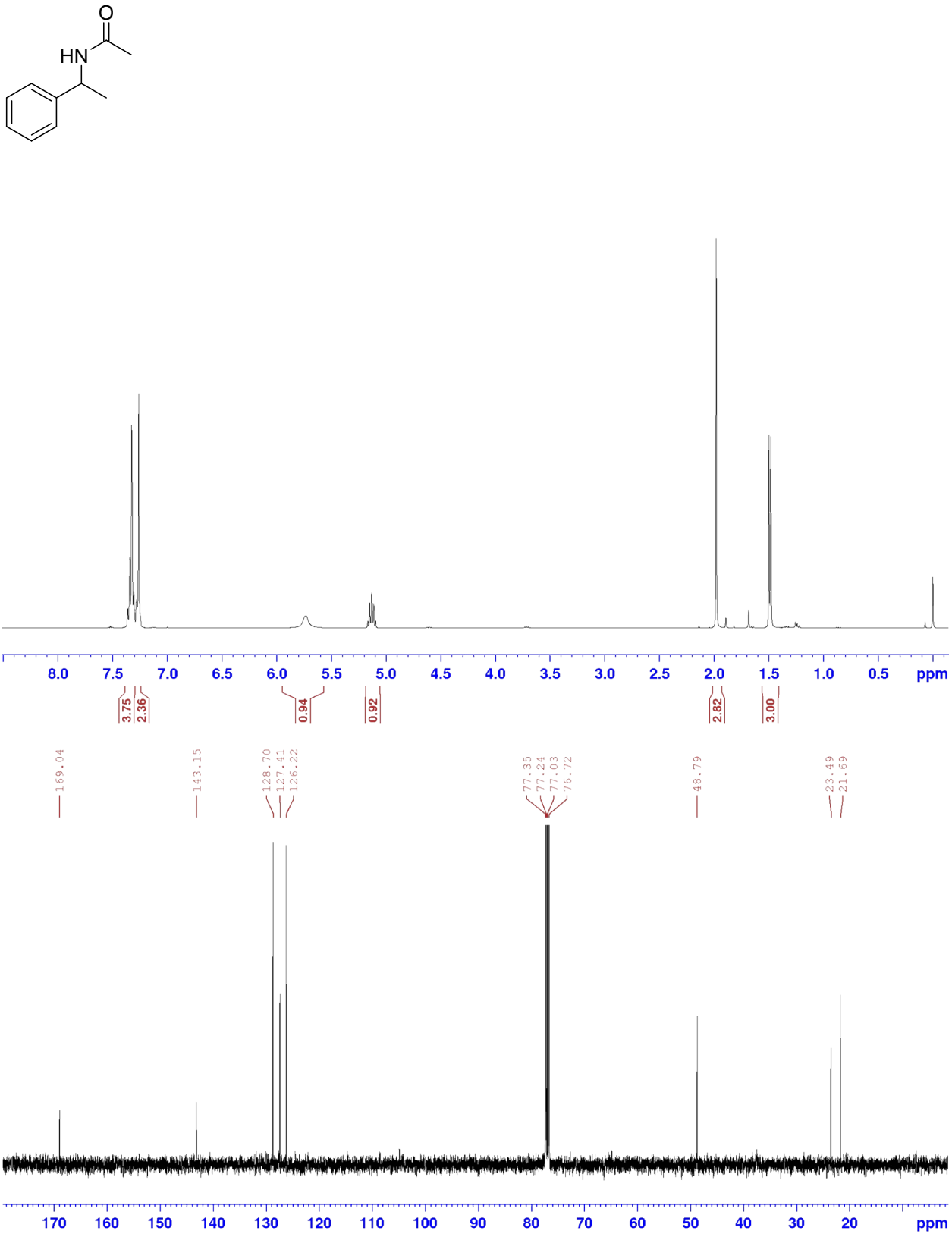
4 S. H. Doan, M. A. Hussein and T. V. Nguyen, *Chem. Commun.*, 2021, **57**, 8901–8904.

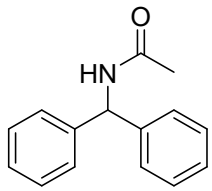
5 H. Qian and R. A. Widenhoefer, *Org. Lett.*, 2005, **7**, 2635–2638.

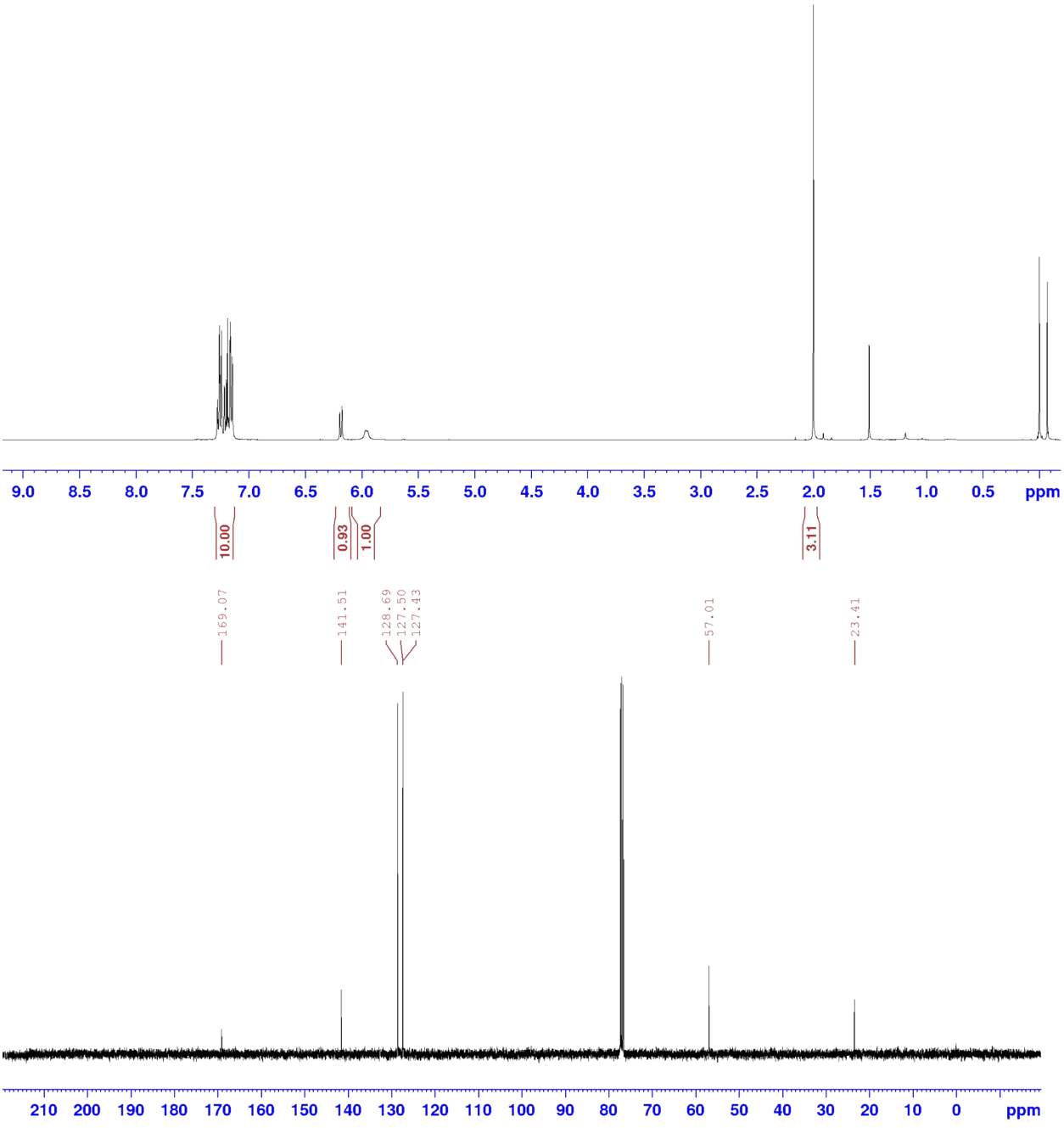
S6 Spectroscopic Data

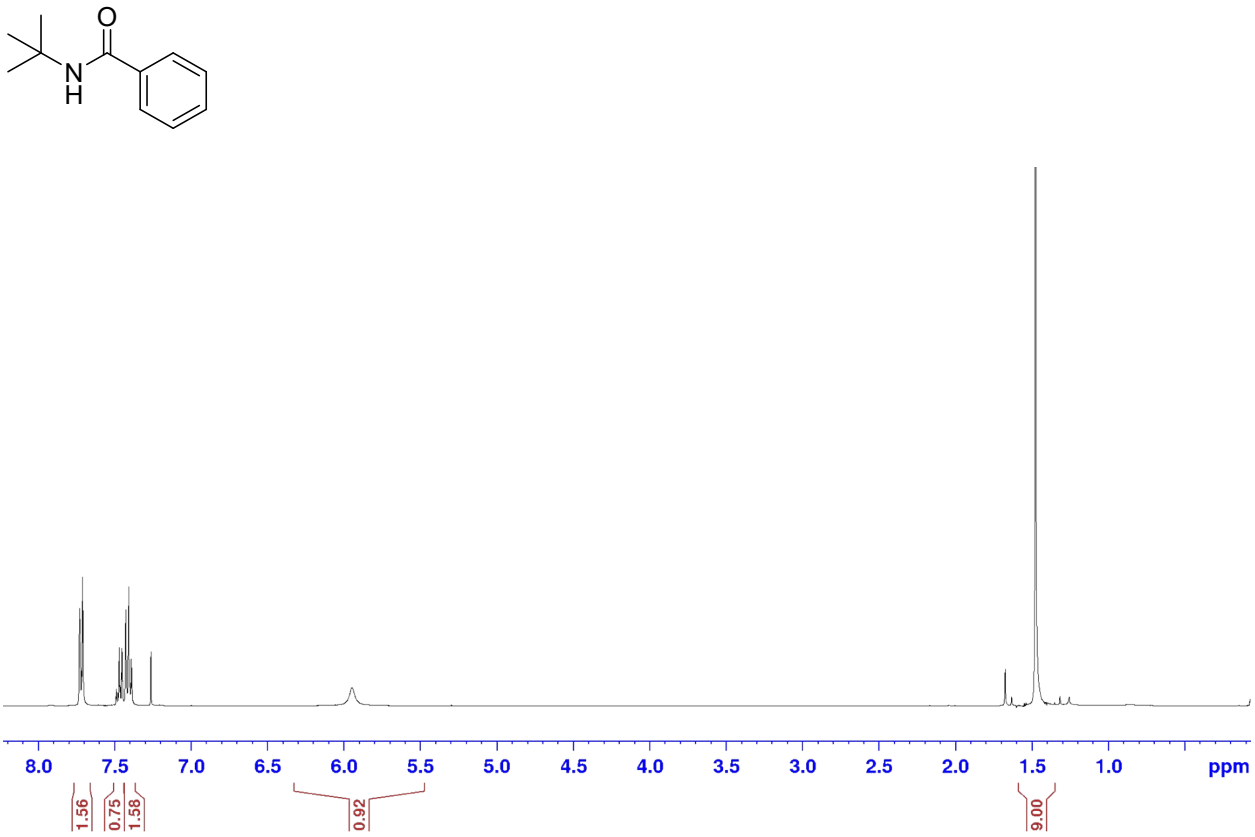
(±)

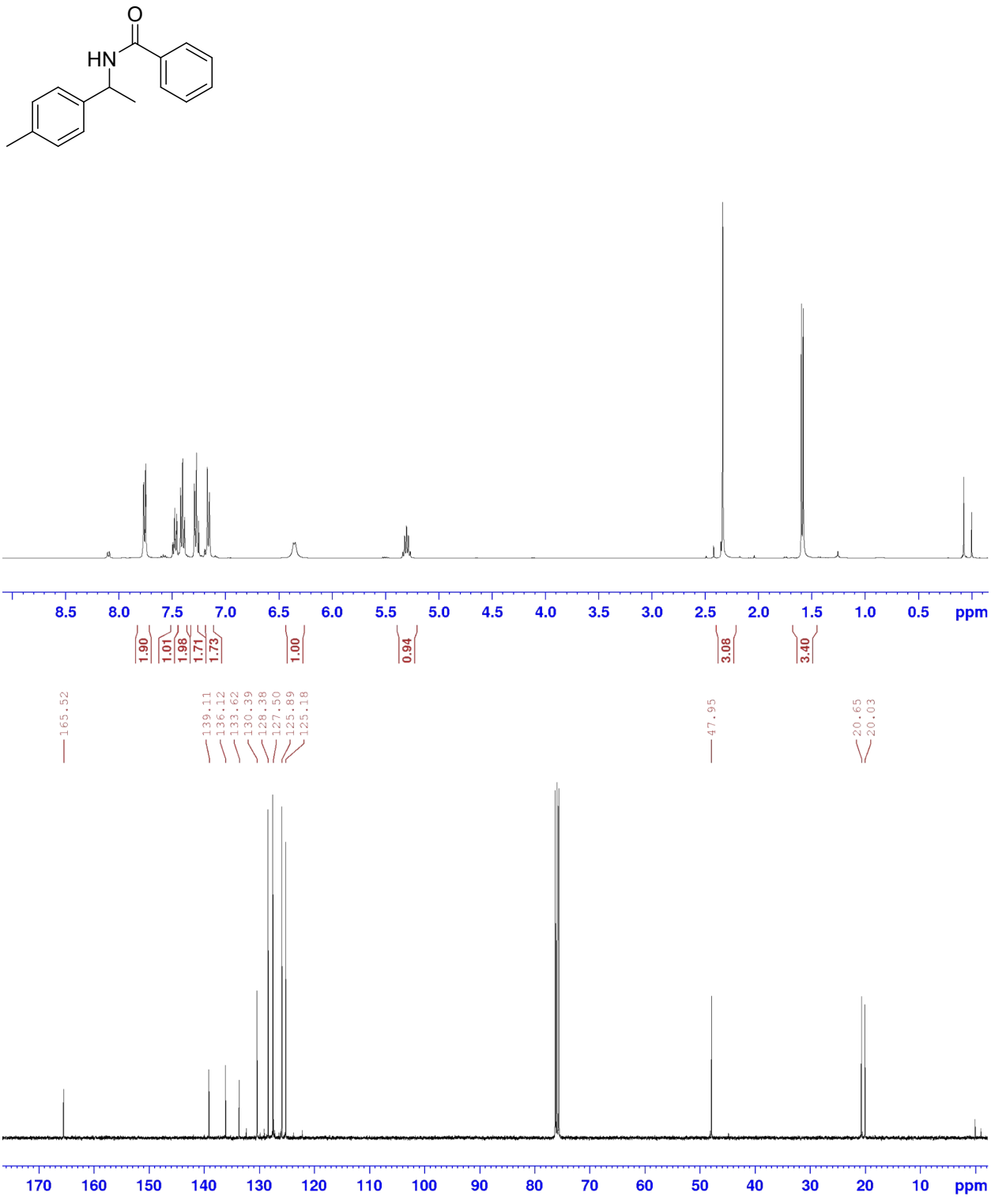


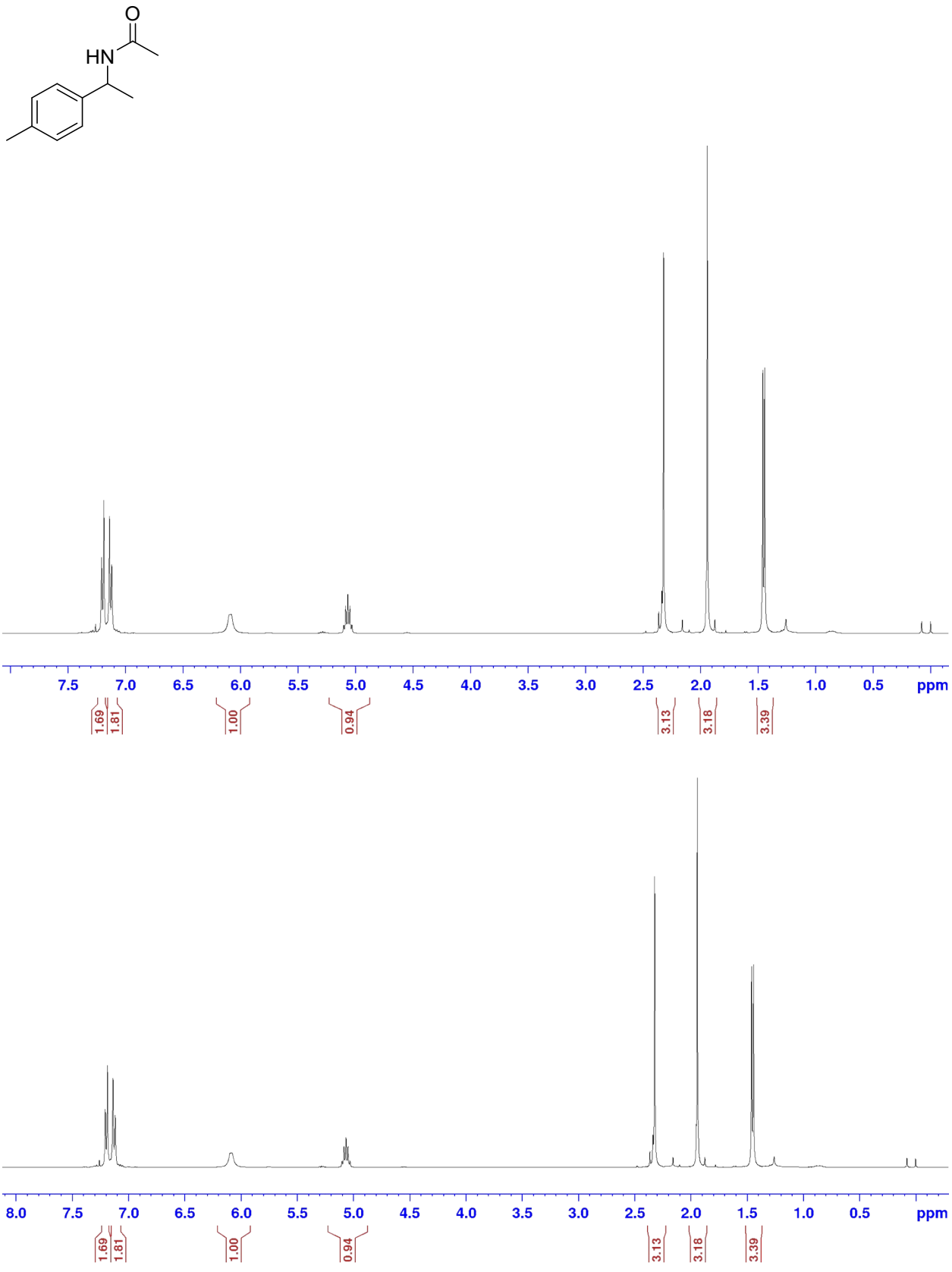

O
HN
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.75
2.36
0.94
0.92
2.82
3.00
169.04
143.15
128.70
127.41
126.22
77.35
77.24
77.03
76.72
48.79
23.49
21.69
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

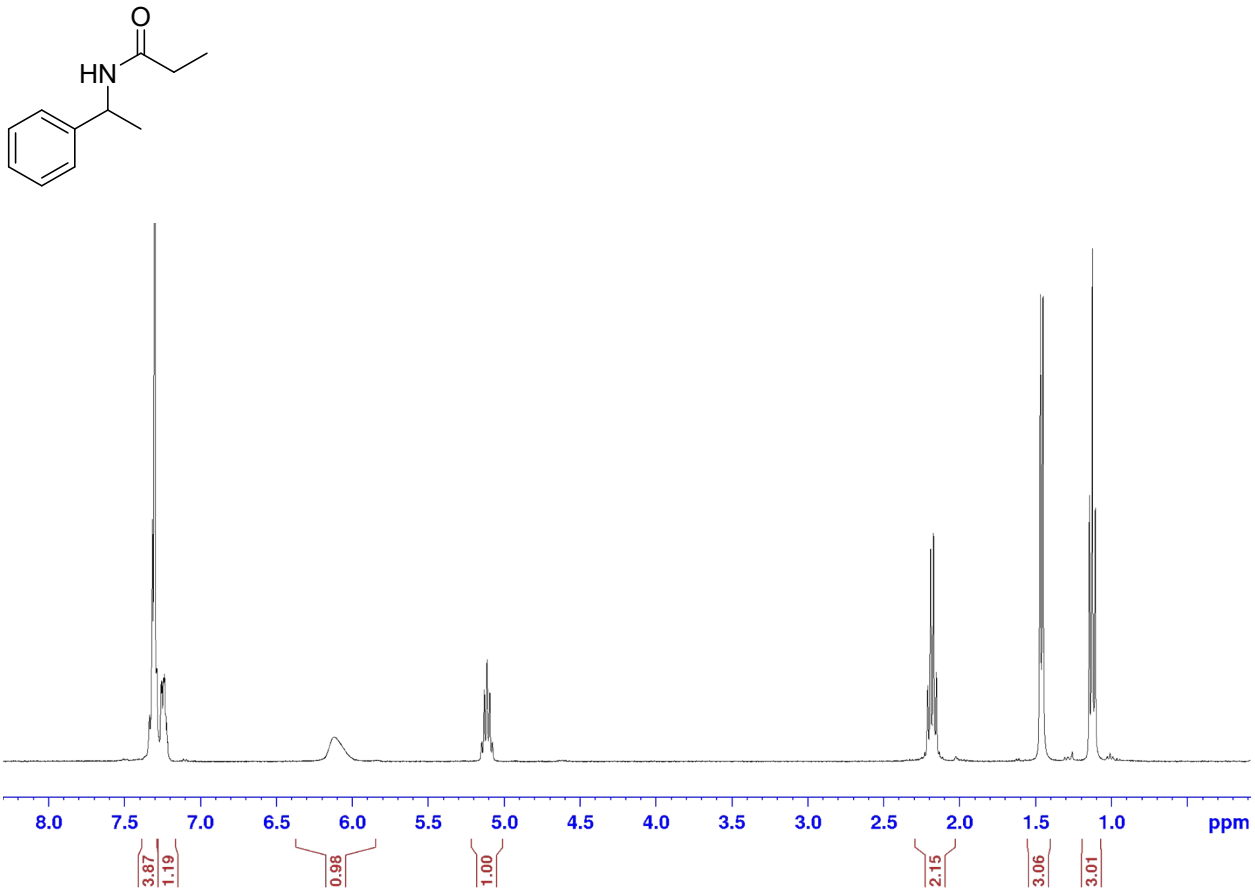

O
HN


9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
10.00
0.93
1.00
3.11
169.07
141.51
128.69
127.50
127.43
57.01
23.41
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


O
N
H
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.56
0.75
1.58
0.92
9.00


O
HN
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.90 1.01 1.98 1.71 1.73 1.00 0.94 3.08 3.40
165.52 139.11 136.12 133.62 130.39 128.38 127.50 125.89 125.18 47.95 20.65 20.03
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
HN
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.69
1.81
1.00
0.94
3.13
3.18
3.39
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.69
1.81
1.00
0.94
3.13
3.18
3.39


O
HN
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
3.87
1.19
0.98
1.00
2.15
3.06
3.01