Supporting Information

Water Tolerant and Atom Economical Amide Bond Formation by Metal-Substituted Polyoxometalate Catalysts

Francisco de Azambuja and Tatjana N. Parac-Vogt*
Department of Chemistry, KU Leuven, 3001 Leuven, Belgium
*tatjana.vogt@kuleuven.be

Table of Contents:

General Remarks

Unless otherwise noted, reactions were performed without any precautions against air and moisture. Amide bond formation reactions were performed in 4 mL (1-dram) vials sealed with a rubber-lined screw cap. When anhydrous conditions were needed, the reactions were conducted under nitrogen atmosphere in 4 mL vials or round-bottom flasks that were sealed with rubber septa using oven-dried glassware and standard Schlenk techniques. High-quality laboratory-grade polypropylene and polyethylene syringes bearing stainless steel needles were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on Silica Gel 250 micron aluminum plates precoated with 230–400 mesh silica impregnated with a fluorescent indicator (250 nm), visualizing by quenching of fluorescence, iodine or phosphomolybdic acid solution (5% w/w in EtOH). Purifications by column chromatography (SiO_2) were conducted following Still's general procedure. ^{1}H NMR or GC Yields and isolated yields reported in the manuscript represent an average of at least two independent runs. Yields reported in the supporting information refer to a single experiment. Unless otherwise noted, reagents were purchased from commercial sources, and used as received. Anhydrous dimethylsulfoxide (DMSO) was purchased.

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 300 (300 and 75 MHz, respectively) or a Bruker Avance 400 (400 and 100 MHz, respectively) spectrometer. Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to proton resonance of residual solvent peak in the NMR solvent (D_2O: δ = 4.79 ppm, DMSO: δ = 2.50 ppm; $CDCl_3$: δ = 7.26 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak ($CDCl_3$: δ = 77.16 ppm). Phosphorous nuclear magnetic resonance (^{31}P NMR) spectra were recorded on a Bruker Avance 400 spectrometer (376 MHz, TD = 65536, D1 = 2). ^{31}P NMR chemical shifts (δ) are reported in ppm upfield from H_3PO_4 85% (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet), coupling constant in Hertz (Hz), integration.

Quantitative gas chromatography (GC) analyses were recorded on an Agilent Technologies 6890A GC-system with Flame Induced Detector (FID) and a CP-Sil 24 CB 30* column (0.32 mm × 30 m, film: 0.5 μm). The method used consisted of 90 ºC for 1 min, then 30 ºC/min to 275 ºC, and holding at 275 ºC for 2.5 min (injector: 275 °C; detector: 300 °C; constant flow 3.9 mL min^{-1}). Racemization of selected cyclic peptides (see below) was probed by optical rotation using a polarimeter or HPLC analysis (UV detector, enantiomeric ratio was calculated through integration of enantiomers corresponding signals, set by racemic samples).

Preparation of known compounds

$K_6P_2W_{18}O_{62}$,[1] $K_{10}[\alpha_2\text{-}P_2W_{17}O_{61}]$,[1] $K_9Li[\alpha_1\text{-}P_2W_{17}O_{61}]$,[1] $K_{(7\text{-}8)}[M(H_2O)(\alpha_2P_2W_{17}O_{61})]$ (M = Fe, Cu, Ni, Co),[2] $K_{15}H[Zr(\alpha_2\text{-}P_2W_{17}O_{61})_2]$,[3] $K_{16}[Hf(\alpha_2\text{-}P_2W_{17}O_{61})_2]$,[3] $K_{15}(NH_4)[M(\alpha_2\text{-}P_2W_{17}O_{61})_2]$ (M = Ce^{III}, Ce^{IV}),[4] were prepared according to previous literature reports. All compounds presented satisfactory analysis coherent with characterization data published previously. All catalyst were dried under high-vacuum for at least 2 hours before use.

General procedure for the preparation of $(Me_2NH_2)_{14}[M(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (M = Zr, Hf):[5] $HfCl_2O.8H_2O$ (0.22 g, 0.55 mmol) was dissolved in 30 mL of water. Next, solid $K_{10}[\alpha_2\text{-}P_2W_{17}O_{61}].22H_2O$ (2.48 g, 0.50 mmol) was added, and the mixture was stirred for 15 min. Using a HCl 1M solution, the pH was adjusted to 2.0, and the reaction was stirred for 30 min at 90 °C. To the colorless solution cooled to room temperature, Me_2NH_2Cl (6.0 g, 74 mmol) was added, and the reaction was stirred for 30 min at room temperature. The white precipitate was collected through vacuum filtration using a glass fritted funnel, washed with MeOH (2 x 20mL) and Et_2O (1 x 20mL), dried under air for 10 min and in high-vacuum for 2 h. ^{31}P NMR analysis confirmed the identity and purity of the product (yield 2.06g). ^{31}P NMR (HCl 0.1 M in H_2O:D_2O 9:1): δ –10.11, –13.73 for Hf complex; δ –9.95, –13.69 for Zr complex;

Perturbing the equilibrium between GlyGly (1a) and cyclo(GlyGly) (2a)

General Procedure A:

A 4 mL (1 dram) vial was charged with catalyst (5.0 µmol), glycylglycine (13.2 mg, 0.100 mmol), solvent (1.0 mL), and a magnetic stir bar. The reaction mixture was stirred for 24 h at 70 °C. Next, the reaction mixture was diluted with D_2O (1.0 mL), 0.100 mmol tBuOH was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. A 100 µL aliquot was transferred to a NMR tube, diluted with ~400 µL D_2O, and the ^1H NMR spectrum was recorded (64 scans, D1 = 5). Results are reported based on ^1H NMR yields.

Solvent effect:

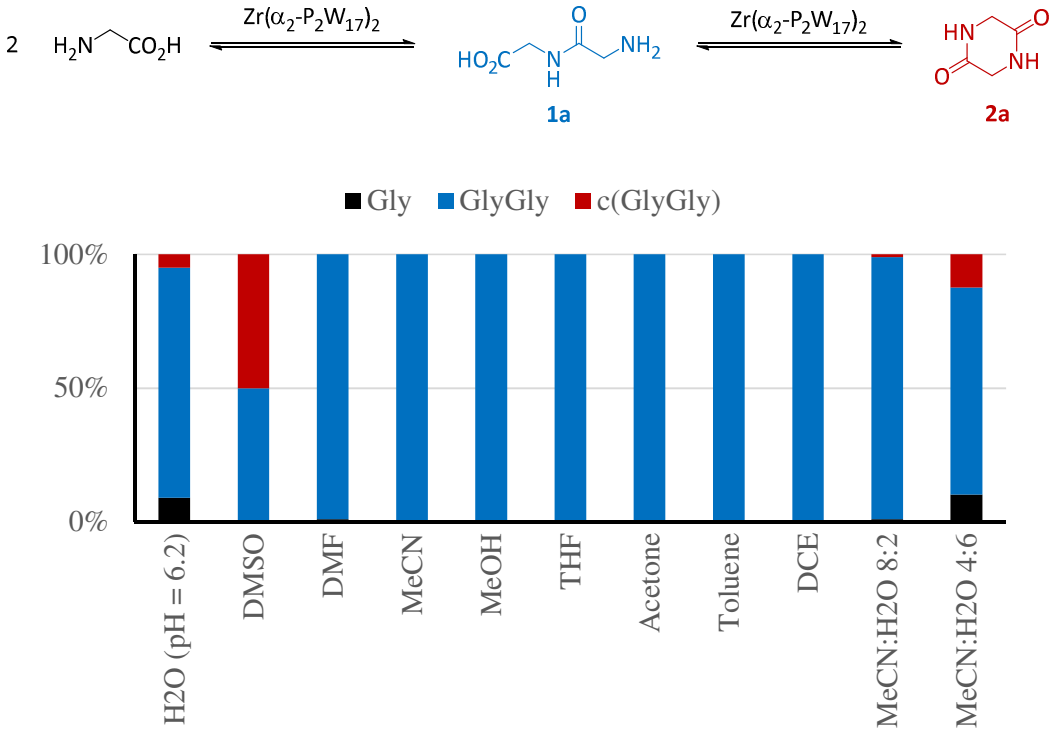
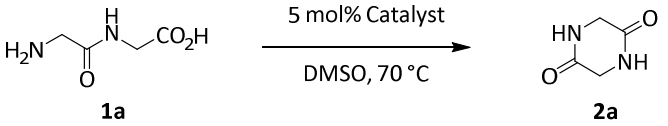


Figure S 1: Effect of the solvent on the equilibrium between GlyGly (**1a**) and cyclo(GlyGly) (**2a**) *Conditions:* 0.10 mmol **1a**, 5.0 mol% $K_{15}H[Zr(\alpha_2\text{-}P_2W_{17}O_{61})_2]$, solvent (1.00 mL), 70 °C, 24 h. $Zr(P_2W_{17})_2 = K_{15}H[Zr(\alpha_2\text{-}P_2W_{17}O_{61})_2]$

Catalyst structure:

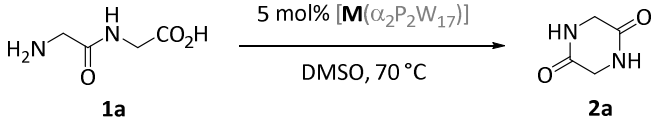
Table S 1: Catalytic activity of different Zr-POM complexes



1a **2a**

Entry	Catalyst	Yield **2a** (%)	Conversion **1a** (%)	Ratio Yield / Conv. (%)
1	$K_{15}H[Zr(\alpha_2\text{-}P_2W_{17}O_{61})_2]$	40	42	95
2	$(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$	100	100	100
3	$(Et_2NH_2)_{10}[Zr(PW_{11}O_{39})_2]$	28	32	87
4	$(Et_2NH_2)_8[Zr(PW_{11}O_{39})]_2$	38	36	100
5	$(Me_4N)_2[Zr(H_2O)_3W_5O_{18}]$	2	8	25
6	$TBA_5K[Zr(H_2O)_4(\alpha_1\text{-}P_2W_{17}O_{61})]$	3	14	21

Table S 2: Catalytic activity of different metal-Wells-Dawson POM complexes



1a **2a**

Entry	Catalyst	Yield **2a** (%)	Conversion **1a** (%)	Ratio Yield / Conv. (%)
1	$K_7[\mathbf{Fe}(H_2O)(\alpha_2P_2W_{17}O_{61})]$	0	7	0
2	$K_8[\mathbf{Co}(H_2O)(\alpha_2P_2W_{17}O_{61})]$	0	0	0
3	$K_8[\mathbf{Ni}(H_2O)(\alpha_2P_2W_{17}O_{61})]$	0	9	0
4	$K_8[\mathbf{Cu}(H_2O)(\alpha_2P_2W_{17}O_{61})]$	0	36	0
5	$K_{15}H[\mathbf{Zr}(\alpha_2\text{-}P_2W_{17}O_{61})_2]$	36	38	95
6	$K_{16}[\mathbf{Hf}(\alpha_2\text{-}P_2W_{17}O_{61})_2]$	75	100	75
7	$K_{15}(NH_4)[\mathbf{Ce^{IV}}(\alpha_2\text{-}P_2W_{17}O_{61})_2]$	0	31	0
8	$K_{15}(NH_4)[\mathbf{Ce^{III}}(\alpha_2\text{-}P_2W_{17}O_{61})_2]$	0	0	0

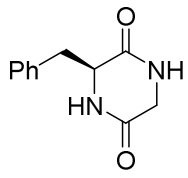
Experimental details and characterization of cyclic dipeptides

General Procedure B:

A 4 mL (1 dram) vial was charged with $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$[5] (48 mg, 5.0 µmol), dipeptide (0.100 mmol), DMSO (1.0 mL), and a magnetic stir bar. The reaction mixture was stirred for 24 h at 70 °C. Next, the reaction mixture was diluted with D_2O (1.0 mL), 0.100 mmol tBuOH was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. A 100 µL aliquot was transferred to a NMR tube, diluted with ~400 µL

D_2O, and the ^1H NMR spectrum was recorded (32 scans, D1 = 2). Results are reported based on ^1H NMR yields. For adducts c(GlyPhe) (**2b**) and c(GlyTrp) (**2c**), isolated yields are reported.

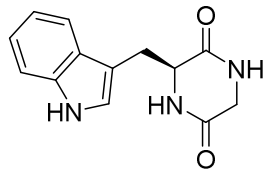
c(Gly–Phe) (2b)



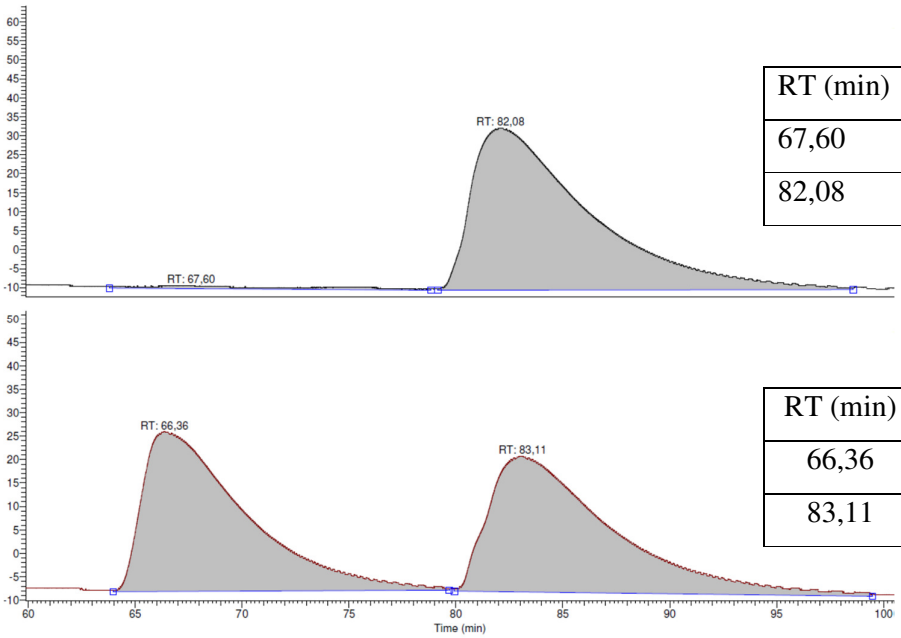
General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (0.24 g, 25 μmol), H-Gly-Phe-OH (110 mg, 0.500 mmol), and DMSO (5.00 mL). The reaction was stirred at 70 °C for 18 h. After cooling to the room temperature, H_2O (2 mL) was added, and after homogenization the reaction was allowed to stand overnight. The white solid crystallized overnight was collected by filtration, and washed with H_2O (10 mL). Next, the product was dissolved in methanol, concentrated under reduced pressure and dried under high vacuum to afford the title compound as a white solid (78 mg, 76%). A second crop of product was isolated from the mother liquor after a few days at room temperature (18 mg), totalizing 96 mg of product (94% yield). Spectroscopic data agreed with the previous report.[6]

$[\alpha]_D^{20} = +27.4$ (*c* 0.95, DMSO) {+ 26.6 (*c* 0.95, DMSO)}[7]

c(Gly–Trp) (2c)



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (0.24 g, 25 μmol), H-Gly-Trp-OH (110 mg, 0.500 mmol), and DMSO (5.00 mL). The reaction was stirred at 70 °C for 18 h. After cooling to the room temperature, H_2O (2 mL) was added, and after homogenization the reaction was allowed to stand overnight. The white solid crystallized overnight was collected by filtration, and washed with H_2O (10 mL). Next, the product was dissolved in methanol, concentrated under reduced pressure and dried under high vacuum to afford the title compound as a white solid (68 mg, 56%). A second crop of product was isolated from the mother liquor after a few days at room temperature (26 mg), totalizing 94 mg of product (77% yield). Spectroscopic data agreed with the previous report.[8] Racemic standard was prepared using the same protocol from (±)-H-Gly-Trp-OH (0.1 mmol scale).

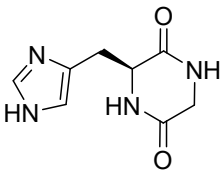


RT (min)	Area	%Area
67,60	299,962	1,82
82,08	16207,442	98,18

RT (min)	Area	%Area
66,36	11320,642	50,37
83,11	11156,513	49,63

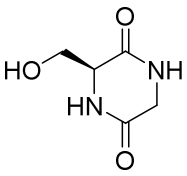
Figure S 2: HPLC of c(Gly–Trp) evidences no erosion of optical purity in the catalytic cyclization of H-Gly-Trp-OH. *Condition of analysis:* Daicel Chiralpak®IB column (4.6 mm x 250 mm) as stationary phase and Heptane:^{i}PrOH 90:10 mixture as mobile phase (1 mL min^{-1})

c(Gly–His) (2d)[9]



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (47 mg, 5.0 µmol), H-Gly-His-OH (21.2 mg, 0.100 mmol), and DMSO (1.00 mL). The reaction was stirred at 70 °C for 24 h. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 78% yield.

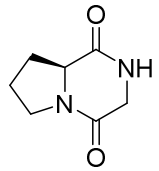
c(Gly–Ser) (2e)[10]



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (0.24 g, 25 µmol), H-Gly-Ser-OH (81 mg, 0.500 mmol), and DMSO (1.00 mL). The reaction was stirred at 70 °C for 24 h. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 87% yield.

Reaction using H-Ser-Gly-OH (16 mg, 0.100 mmol) was done following the same procedure. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 82% yield.

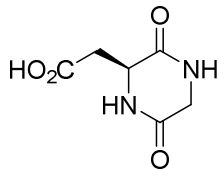
c(Gly–Pro) (2f)[11]



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (47 mg, 5.0 μmol), H-Gly-Pro-OH (17.2 mg, 0.100 mmol), and DMSO (1.00 mL). The reaction was stirred at 70 °C for 24 h. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 79% yield.

Reaction using H-Pro-Gly-OH (17.2 mg, 0.100 mmol) was done following the same procedure. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 78% yield.

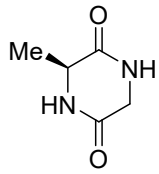
c(Gly–Asp) (2g)[12]



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (47 mg, 5.0 μmol), H-Gly-Asp-OH (19.0 mg, 0.100 mmol), and DMSO (1.00 mL). The reaction was stirred at 70 °C for 24 h. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 85% yield.

Reaction using H-Asp-Gly-OH (19.0 mg, 0.100 mmol) was done following the same procedure. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 35% yield.

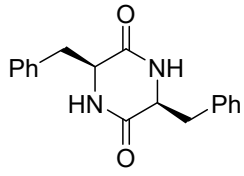
c(Gly–Ala) (2h)[13]



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (47 mg, 5.0 μmol), H-Gly-Ala-OH (15.0 mg, 0.100 mmol), and DMSO (1.00 mL). The reaction was stirred at 70 °C for 24 h. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 91% yield.

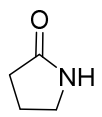
Reaction using H-Ala-Gly-OH (15.0 mg, 0.100 mmol) was done following the same procedure. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in 86% yield.

c(Phe–Phe) (2i)[7, 14]



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (47 mg, 5.0 μmol), H-Phe-Phe-OH (15.0 mg, 0.100 mmol), and DMSO (1.00 mL). The reaction was stirred at 70 °C for 24 h. Analysis by ^{1}H NMR in DMSO-d_6 with ^{t}BuOH as internal standard showed the product formation in 38% yield. Spectroscopic data agreed with the previous report.

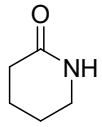
Pyrrolidin-2-one (2j)[15]



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (47 mg, 5.0 μmol), 4-aminobutanoic acid (10.3 mg, 0.100 mmol), and DMSO (1.00 mL). The

reaction was stirred at 70 °C for 24 h. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in >99% yield.

Piperidin-2-one (2k)[15]



General procedure B was followed using $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (47 mg, 5.0 µmol), 5-aminopentanoic acid (11.7 mg, 0.100 mmol), and DMSO (1.00 mL). The reaction was stirred at 70 °C for 24 h. Analysis by ^{1}H NMR with ^{t}BuOH as internal standard showed the product formation in >99% yield.

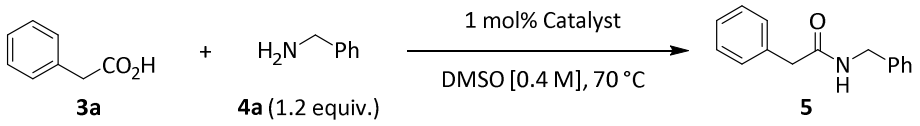
Intermolecular amide bond formation

Reaction optimization:

General Procedure C:

A 4 mL (1 dram) vial was charged with catalyst (0.31 – 5.0 µmol of metal-POM complex), phenylacetic acid (68.0 mg, 0.500 mmol), benzylamine (64 mg, 0.60 mmol), solvent (0.15 – 5.0 mL) and a magnetic stir bar. The reaction mixture was stirred overnight (18 – 24 h) at 30 – 70 °C. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (~3 mL), 25 µL of dodecane was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot was analyzed by GC-FID, and the yield was determined based on a standard curve. Results are reported based on GC yields.

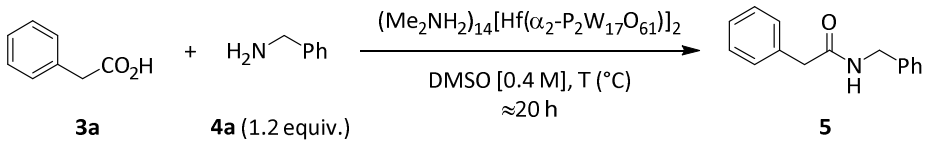
Table S 3: Catalytic activity of different Zr(IV)-/Hf(IV)-POM complexes



3a **4a** (1.2 equiv.) **5**

Entry	Catalyst	Yield **5** (%)	Conversion **3a** (%)
1	$K_{15}H[Zr(\alpha_2\text{-}P_2W_{17}O_{61})_2]$	14	78
2	$K_{16}[Hf(\alpha_2\text{-}P_2W_{17}O_{61})_2]$	19	84
3	$(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$	29	82
4	$(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$	47	85
5	$(Et_2NH_2)_{10}[Zr(PW_{11}O_{39})_2]$	10	80
6	$(Et_2NH_2)_8[Zr(PW_{11}O_{39})]_2$	16	78
7	$TBA_5K[Zr(H_2O)_4(\alpha_1\text{-}P_2W_{17}O_{61})]$	8	86

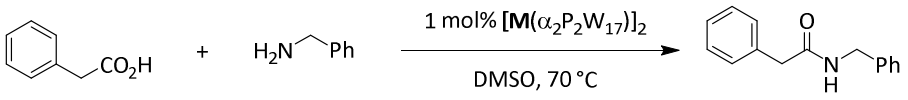
Table S 4: Effect of the solvent in the formation of product **5**



3a **4a** (1.2 equiv.) **5**

Entry	Solvent	Yield **5** (%)
1	DMSO	47
2	THF	11
3	MeCN	10
4	Toluene	1

Table S 5: Effect of the reaction concentration in the formation of product **5**

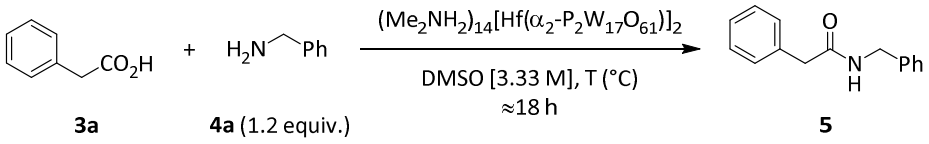


3a **4a** (1.2 equiv.) **5**

Entry	**M**	Concentration of **3a** (mol L^{-1})	Yield **5** (%)	Conversion **3a** (%)
1	Hf	0.10	12	100
2	Hf	0.20	20	82
3	Hf	0.42	41	90
4	Hf	0.83	70	100
5	Hf	1.67	88	100
6	Hf	3.33	99	100
7	Zr	0.42	29	82
8	Zr	1.67	82	100
9	Zr	3.33	82	100

[a] $[M(\alpha_2P_2W_{17})]_2 = (Me_2NH_2)_{14}[M(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$

Table S 6: Effect of the temperature in the formation of product **5**

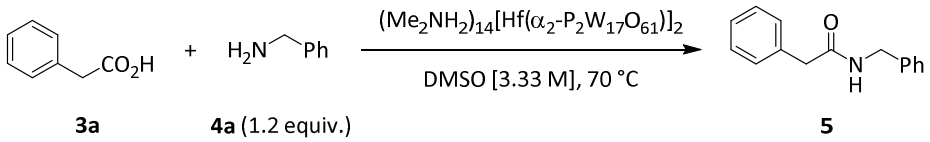


3a **4a** (1.2 equiv.) **5**

Entry	T (°C)	Yield **5** (%)
1	30	14
2[a]	30	37
3	50	46
4	70	>99

[a] 72 h

Table S 7: Effect of the catalyst loading in the formation of product **5**



3a **4a** (1.2 equiv.) **5**

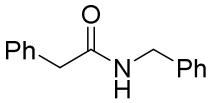
Entry	Catalyst loading (mol%)	Yield **5** (%)
1	1.00	>99
2	0.50	98
3	0.25	98
4	0.12	34

Experimental details and characterization of amide compounds

General Procedure D:

A 4 mL (1 dram) vial was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid (68.0 mg, 0.500 mmol), amine (0.60 – 1.00 mmol), DMSO (0.15 mL) and a magnetic stir bar. The reaction mixture was stirred for 18–24 h at 70 – 90 °C. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (~50 mL), and washed with HCl 1M (15 mL), $NaHCO_{3(sat)}$ (15 mL), H_2O (3 x 15 mL) and $NaCl_{(sat)}$ (15 mL). Next, the organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the desired amide product in high purity (≥ 90%). When necessary, further purification was performed through recrystallization, filtration in SiO_2 (EtOAc:Et_3N 200:1) or flash column chromatography.

_N_-benzyl-2-phenylacetamide (5)



General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid (68.0 mg, 0.500 mmol), benzylamine (64 mg, 0.60 mmol), DMSO (0.15 mL). The reaction was stirred at 70 °C for 21 h. Work up afforded the title compound as a white solid (110 mg, 98%). Further purification by recrystallization in EtOAc/hexanes afforded 80 mg (71%) of the product. Spectroscopic data agreed with the previous report.[16]

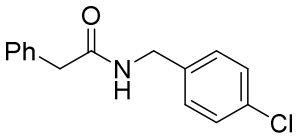
Gram-scale reaction: A 100 mL round-bottom flask was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (2.0 g, 0.21 mmol), phenylacetic acid (5.60 g, 41.2 mmol), DMSO (12.5 mL) and a magnetic stir bar. The reaction mixture was stirred at 70 °C until a clear solution was obtained. Next, the reaction was removed from oil bath, and benzylamine (5.29 g, 49.5 mmol) was immediately added dropwise. The reaction mixture was stirred for 24 h at 70 °C. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (~500 mL), and washed with HCl 1M (100 mL), $NaHCO_{3(sat)}$ (100 mL), H_2O (3 x 100 mL) and $NaCl_{(sat)}$ (100 mL). Next, the organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford 8.37 g (90%) of the desired amide product as a white solid.

Table S 8: Product Mass Intensity calculation for the gram-scale experiment[17]

Component	Mass (g)
Reaction	
Catalyst	2.00
Acid **3a**	5.60
Amine **4a**	5.29
DMSO	13.75
Work-up	
DCM	663
HCl 1M	100
$NaHCO_{3\ (sat)}$	100
H_2O	300
$NaCl_{\ (sat)}$	100
$MgSO_4$	15

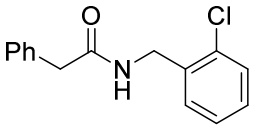
Total – reaction	26.64 g
Total – work-up	1278 g
Total (Reaction + Work-up)	1304.64 g
Product yield	8.37 g
PMI (*reaction only*)	**3.2**
PMI (*reaction + work-up*)	**155.9**

***N*-[(4-chlorophenyl)methyl]-2-phenylacetamide (6)**



General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 μmol), phenylacetic acid (68.0 mg, 0.500 mmol), 4-chlorobenzylamine (0.11 g, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 70 °C for 21 h. Work up afforded the title compound as a white solid (90 mg, 69%). Further purification by recrystallization in EtOAc/hexanes afforded 75 mg (58%) of the product. Spectroscopic data agreed with the previous report.[18]

***N*-[(2-chlorophenyl)methyl]-2-phenylacetamide (7)**



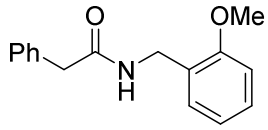
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 μmol), phenylacetic acid (68.0 mg, 0.500 mmol), 2-chlorobenzylamine (0.11 g, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 23 h. Work up afforded the title compound as a white solid (120 mg, 92%). Further purification by recrystallization in EtOAc/hexanes afforded 92 mg (71%) of the product.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.18 (m, 9H), 5.85 (bs, 1H), 4.48 (d, *J* = 6.1 Hz, 2H), 3.60 (s, 2H).

^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 171.0, 135.6, 134.8, 133.6, 130.0, 129.6 (2C),129.2, 129.0, 127.6, 127.2, 43.9, 41.8.

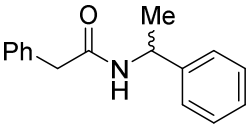
MS: *ESI-MS* – *m/z* calcd for $C_{15}H_{14}ClNO$ $[M+Na]^+$ 282.1 (100), 284.1 (32), found 282.3 (100) and 284.2 (32). *GC-MS* (EI, 70eV): 224.4 (100), 127.3 (12), 125.3 (34)

***N*-[(2-methoxyphenyl)methyl]-2-phenylacetamide (8)**



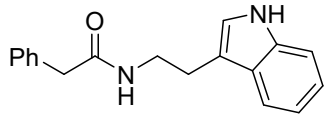
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid (68.0 mg, 0.500 mmol), 2-methoxybenzylamine (0.11 g, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 21 h. Work up afforded the title compound as a light yellow solid (123 mg, 96%). Further purification by recrystallization in EtOAc/hexanes afforded 76 mg (59%) of the product. Spectroscopic data agreed with the previous report.[19]

(±)-2-Phenyl-*N*-(1-phenylethyl)acetamide (9)



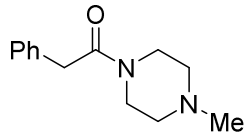
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid (68.0 mg, 0.500 mmol), α-methylbenzylamine (0.12 g, 1.0 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 23 h. Work up afforded the title compound as an off-white solid (114 mg, 95%). Purification by filtration in SiO_2 using EtOAc:Et_3N 200:1 afforded the title compound as an off-white solid (106 mg, 88%). Spectroscopic data agreed with the previous report.[16]

***N*-(2-(1H-Indol-3-yl)ethyl)-2-phenylacetamide (10)**



General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid (68.0 mg, 0.500 mmol), tryptamine (0.12 g, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 21 h. Work up afforded the title compound as a brown solid (113 mg, 81%). Further purification by recrystallization in EtOAc/hexanes afforded 98 mg (70%) of the product. Spectroscopic data agreed with the previous report.[19]

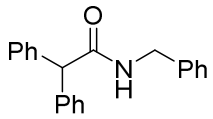
***N*-Methyl-*N′*-phenylacetylpiperazine (11)**



General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid (68.0 mg, 0.500 mmol), 1-methylpiperazine (0.12 g, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 21 h. For this product, special work up was performed: the reaction mixture was diluted with CH_2Cl_2 (~50 mL), and extracted with HCl 1M (15 mL). After the phases were separated, the pH of the aqueous layer was adjusted to 8 – 9 using $NaHCO_3$ 10% w/w. The basified aqueous phase was washed with CH_2Cl_2 (3 x 25 mL). After the phases were separated, the organic phase was

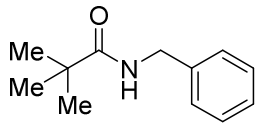
washed with H_2O (3 x 15 mL) and $NaCl_{(sat)}$ (15 mL). Next, the organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the desired amide product as a yellow oil (82 mg, 75%). Spectroscopic data agreed with the previous report.[19]

N-benzyl-2,2-diphenylacetamide (12)



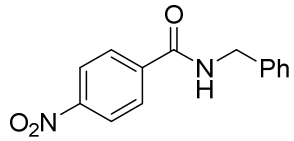
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), diphenylacetic acid (106 mg, 0.500 mmol), benzylamine (80 mg, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 24 h. Work up afforded the title compound as a white solid (66 mg, 44%). Spectroscopic data agreed with the previous report.[20]

***N*-benzyl-2,2-dimethylpropanamide (13)**



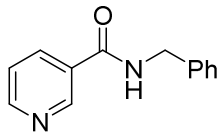
General procedure D was followed using $((Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), pivalic acid (51.0 mg, 0.500 mmol), benzylamine (80 mg, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 70 °C for 24 h. Work up afforded the title compound as an off-white solid (76 mg, 79%). Spectroscopic data agreed with the previous report.[21]

***N*-benzyl-4-nitrobenzamide (14)**



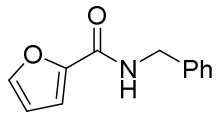
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), 4-nitrobenzoic acid (68.0 mg, 0.500 mmol), benzylamine (0.11 g, 1.0 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 24 h. Work up and purification by filtration in SiO_2 using EtOAc:Et_3N 200:1 afforded the title compound as a light yellow solid (122 mg, 95%). Spectroscopic data agreed with the previous report.[18]

***N*-benzylpyridine-3-carboxamide (15)**



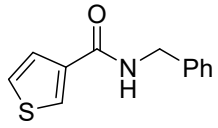
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), nicotinic acid (62.0 mg, 0.500 mmol), benzylamine (80 mg, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 24 h. Work up afforded the title compound as a white solid (106 mg, >99%). Spectroscopic data agreed with the previous report.[22]

_N_-benzylfuran-2-carboxamide (16)



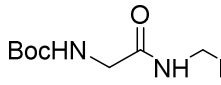
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), 2-furoic acid (56.0 mg, 0.500 mmol), benzylamine (80 mg, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 24 h. Work up afforded the title compound as a light yellow solid (79 mg, 78%). Spectroscopic data agreed with the previous report.[23]

N-benzylthiophene-3-carboxamide (17)



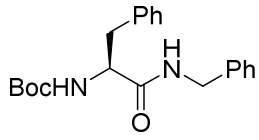
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), 3-thiophenecarboxylic acid (64.0 mg, 0.500 mmol), benzylamine (80 mg, 0.75 mmol), DMSO (0.15 mL). The reaction was stirred at 90 °C for 24 h. Work up afforded the title compound as a yellow solid (98 mg, 90%). Spectroscopic data agreed with the previous report.[24]

***tert*-Butyl (2-(benzylamino)-2-oxoethyl)carbamate (18)**



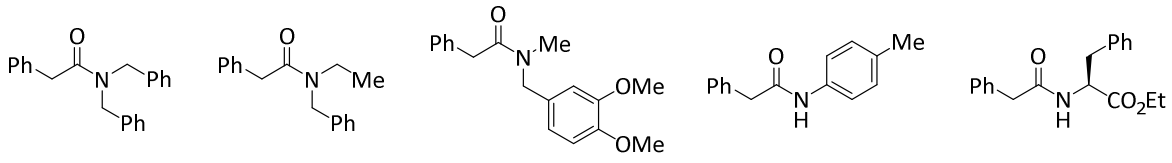
General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), *N*-(*tert*-Butoxycarbonyl)glycine (88.0 mg, 0.500 mmol), benzylamine (64 mg, 0.60 mmol), DMSO (0.15 mL). The reaction was stirred at 70 °C for 24 h. Work up and purification by column chromatography (0–5% MeOH in CH_2Cl_2) afforded the title compound as a yellowish oil (119 mg, 90%). Spectroscopic data agreed with the previous report.[25]

***tert*-butyl N-[(1S)-1-(benzylcarbamoyl)-2-phenylethyl]carbamate (19)**



General procedure D was followed using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), *N*-(*tert*-Butoxycarbonyl)-L-phenylalanine (133 mg, 0.500 mmol), benzylamine (64 mg, 0.60 mmol), DMSO (0.15 mL). The reaction was stirred at 70 °C for 24 h. Work up afforded the title compound as a light yellow solid (153 mg, 86%). Spectroscopic data agreed with the previous report.[26]

Products that were observed in low yields (typically < 5%) using standard reaction conditions



< 30%
(^{1}H NMR, @90 °C)

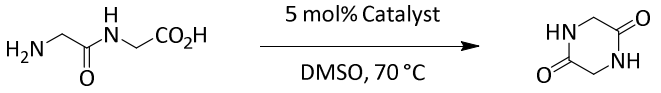
Mechanism investigation

Control experiments

General Procedure E:

A 4 mL (1 dram) vial was charged with catalyst (5.0 μmol for POM, 10 μmol for Zr salts), glycylglycine (13.2 mg, 0.100 mmol), DMSO (1.0 mL), and a magnetic stir bar. The reaction mixture was stirred for 24 h at 70 °C. Next, the reaction mixture was diluted with D_2O (1.0 mL), 0.100 mmol tBuOH was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. A 100 μL aliquot was transferred to a NMR tube, diluted with ~400 μL D_2O, and the ^1H NMR spectrum was recorded (64 scans, D1 = 5). Results are reported based on ^1H NMR yields.

Table S 9: Control experiments for GlyGly (**1a**) cyclization



1a **2a**

Entry	Catalyst	Yield **1a** (%)	Conversion **2a** (%)	Ratio Yield / Conv. (%)
1	---	0	0	0
2	$K_7(P_2W_{17}O_{61})$	0	13	0
3	Li_2WO_4 or Na_2WO_4	0	10	0
4	$ZrCl_4$	32	34	94
5	$Zr(SO_4)_2$	32	47	68

General Procedure F:

A 4 mL (1 dram) vial was charged with catalyst (5.0 µmol for POM complexes, 10 µmol for Zr salts, 35 µmol for boric acid), phenylacetic acid (68.0 mg, 0.500 mmol), benzylamine (64 mg, 0.60 mmol), DMSO (0.15 – 1.2 mL) and a magnetic stir bar. The reaction mixture was stirred overnight (~18 h) at 70 °C. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (~3 mL), 25 µL of dodecane was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot was analyzed by GC-FID, and the yield was determined based on a standard curve. Results are reported based on GC yields.

Table S 10: Control experiments and comparison to Zr(IV)-/Hf(IV)-POM catalyzed intermolecular amide coupling reactions

3a **4a** (1.2 equiv.) **5**

Entry	Catalyst	Concentration (mol L^{-1})	Yield **5** (%)
1	---	0.4	3
2	$ZrCl_4$ (2 mol%)	0.4	34
3	$(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$	0.4	29
4	$(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$	0.4	47
5	---	3.33	16
6[a]	---	3.33	34
7[b]	---	3.33	58
8	$K_7(P_2W_{17}O_{61})$	3.33	5
9	$ZrCl_4 + K_7(P_2W_{17}O_{61})$	3.33	34
10	$Zr(OH)_4 + K_7(P_2W_{17}O_{61})$	3.33	10
11	$ZrCl_4$ (2 mol%)	3.33	27
12	$Zr(OH)_4$ (2 mol%)	3.33	7
13	$Zr(O^iPr)_4$ (2 mol%)	3.33	33
15	$Zr(acac)_4$ (2 mol%)	3.33	22
16	$(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$	3.33	82
17	$(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$	3.33	99
18	$B(OH)_3$	3.33	8
19	3,4,5-trifluorophenylboronic acid	3.33	11

[a] 90 °C, 20 h; [b] 90 °C, 45 h.

Behavior of the metal-POM catalyst in solution

Speciation of [Zr(IV)-/Hf(IV)-(α_2-$P_2W_{17}O_{61}$)]$_2$ in DMSO by ^{31}P NMR

The behavior of $(Me_2NH_2)_{14}[M(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (M = Zr, Hf) catalyst in DMSO was investigated by ^{31}P NMR. We studied solutions with different concentrations of catalyst, as well the effect of successive additions of water and/or substrates in this behavior.

General Procedure G:

A 2-4 mL vial was charged with $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (see table below), DMSO-*d*$_6$ (see table below) and a magnetic stir bar. The mixture was stirred for few minutes at 70 °C until homogenization has been observed. Next, the solution was transferred to a NMR tube, and analyzed by ^{31}P NMR (an external H_3PO_4 85% reference was used).

Table S 11: Quantity of Zr-POM and solvent used in the solutions studied by ^{31}P NMR

Entry	Zr-POM (mg)	DMSO-*d*$_6$ (mL)	Concentration (mol L^{-1})
1	97	0.60	0.017
2	47	0.60	0.008
3	47	1.00	0.005
4	24	1.20	0.002
5	10	1.05	0.001

A) The dissolution of $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ in DMSO shows the presence of two species. These species are in equilibrium to each other as evidence by changing the concentration of the solution.

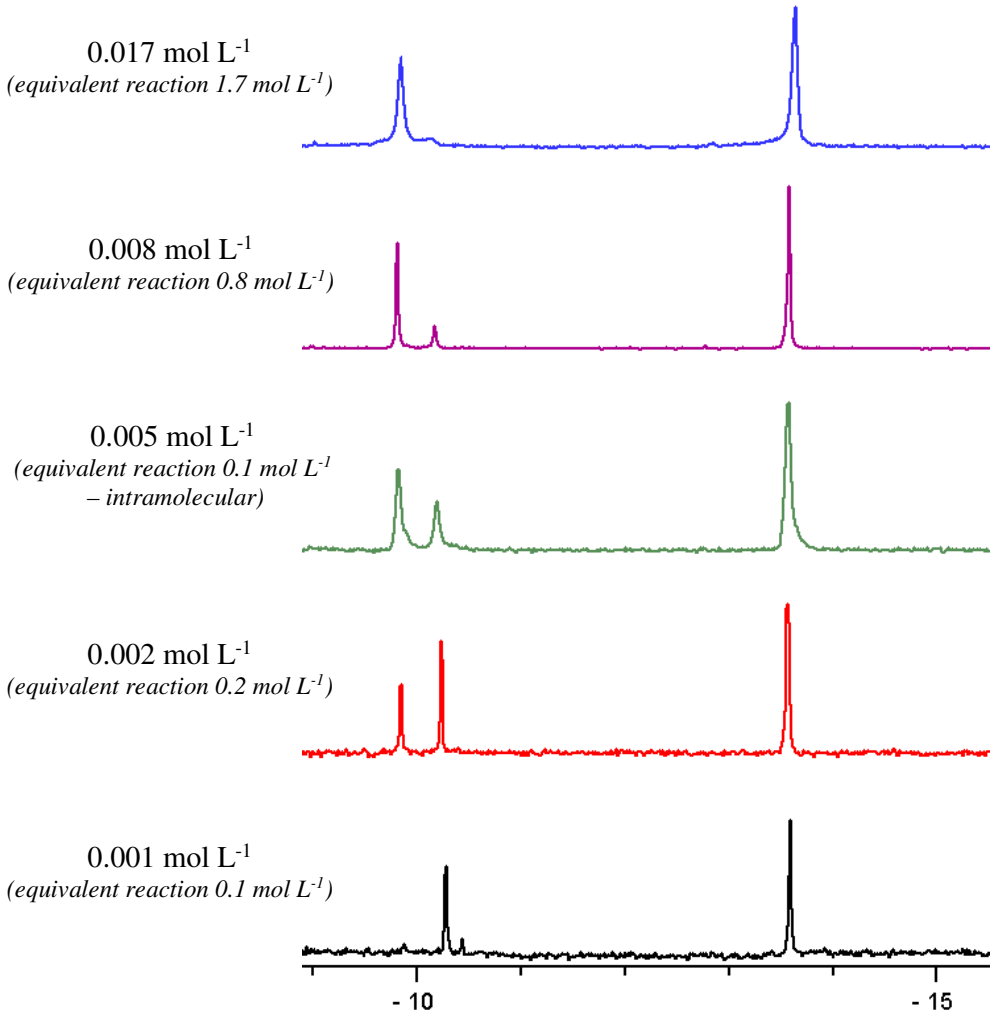


Figure S 3: Dissolution of $(Me_2NH_2)_{14}[Zr(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ in DMSO shows the presence of two species in equilibrium. Equivalent reaction = equivalent to reaction with concentration of the limiting substrate at the given concentration.

B) Following the General Procedure G, the same behavior is observed for the $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ when it was dissolved in DMSO,

Table S 12: Quantity of Hf-POM and solvent used in the solutions studied by ^{31}P NMR

Entry	Hf-POM (mg)	DMSO-d_6 (mL)	Concentration (mol L^{-1})
1	194	0.60	0.03
2	48	1.20	0.004
3	14	0.60	0.002

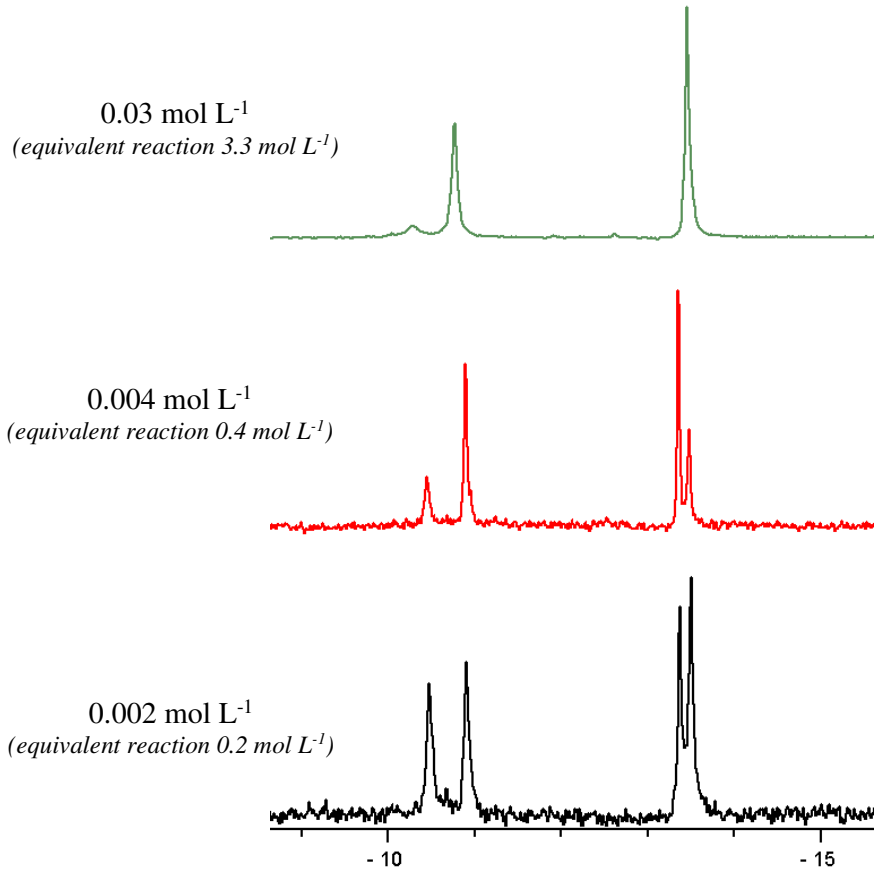


Figure S 4: Dissolution of $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ in DMSO shows the presence of two species in equilibrium. Equivalent reaction = equivalent to reaction with concentration of the limiting substrate at the given concentration.

C) The equilibrium involving the $[Hf(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ catalyst in DMSO is perturbed by the substrates as evidenced by ^{31}P NMR. To check influence of the substrates on $[Hf(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ catalyst speciation, a solution of catalyst was treated with phenylacetic acid and/or benzylamine. Of note, the

stoichiometric relationship of the reaction was kept constant to stay as close as possible to the reaction conditions. The addition of more than 1.20 mmol of benzylamine caused the jellification of the sample preventing its analysis by ^{31}P NMR.

General Procedure H:

A 2 mL vial was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (194 mg, 20 µmol), DMSO-d_6 (0.60 mL), and a magnetic stir bar. The mixture was stirred for few minutes at 70 °C until homogenization has been observed. Next, phenylacetic acid (0.27 g, 2.0 mmol) or benzylamine (0.26 g, 2.4 mmol) were added, and the solution was kept stirring for 10 minutes at 70 °C. Next, the solution was transferred to a NMR tube, and analyzed by ^{31}P NMR (an external H_3PO_4 85% reference was used). Next, to the tube containing phenylacetic acid, an aliquot of benzlamine (64 mg, 0.60 mmol) was added. The tube was homogenized and analyzed by ^{31}P NMR again under the same conditions. Next, a second portion of benzylamine (64 mg, 0.60 mmol) was added. The tube was homogenized and analyzed by ^{31}P NMR again under the same conditions.

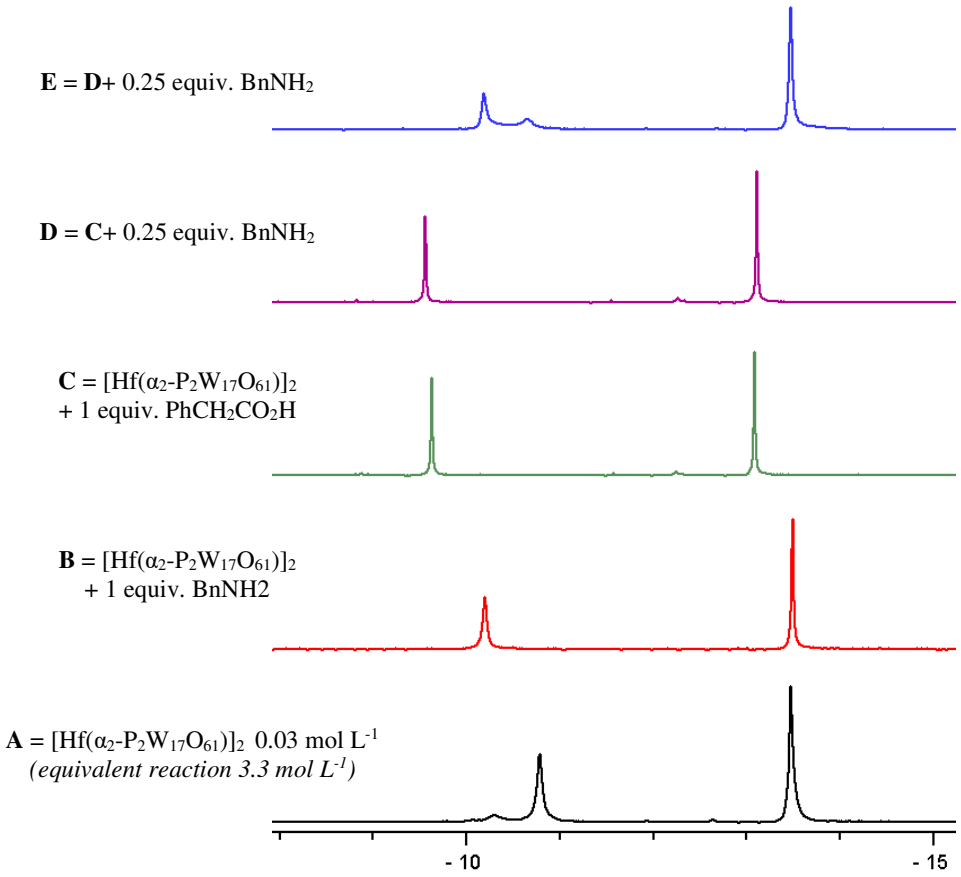


Figure S 5: Phenylacetic acid and benzylamine substrates perturb the equilibrium between $[Hf(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ species formed in DMSO solution (0.03 mol L^{-1}). Equivalent reaction = equivalent to reaction with concentration of the limiting substrate at the given concentration.

Kinetic dependence on the concentration of substrates

General Procedure I:

A 4 mL (1 dram) vial was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid (see table below), benzylamine (see table below), DMSO (0.15 mL) and a magnetic stir bar. The reaction mixture was stirred at 70 °C. At 5-20 minutes intervals, a 10 µL aliquot was taken, immediately quenched with CH_2Cl_2 and analyzed by GC-FID. Using the data from GC-FID analysis, kinetic plots (product vs. reaction time) were obtained based on a standard curve. All data was processed using Microsoft Excel®.

Table S 13: Amounts of phenylacetic acid and benzylamine used in the reaction to study the kinetic dependence on the concentration of substrates

Reaction	Phenylacetic acid **3a** (mmol)	Benzylamine **4a** (mmol)
1	1.00	0.60
2	0.50	0.60
3	0.50	1.20

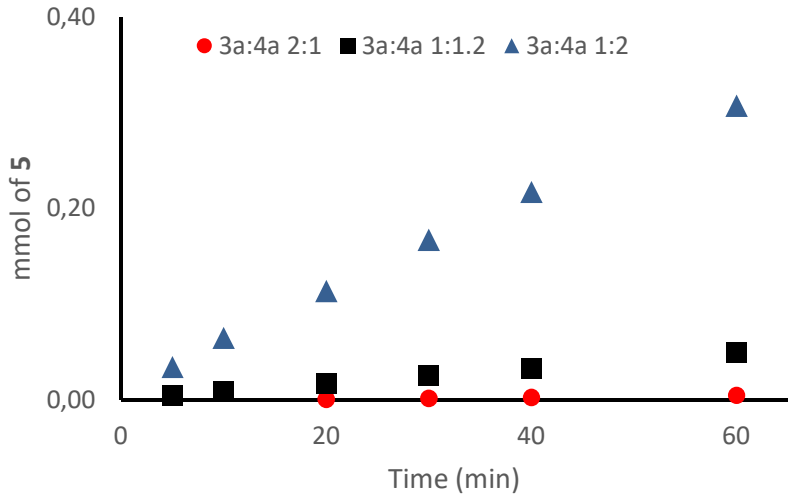


Figure S 6: Kinetic plot varying the initial concentration of substrates

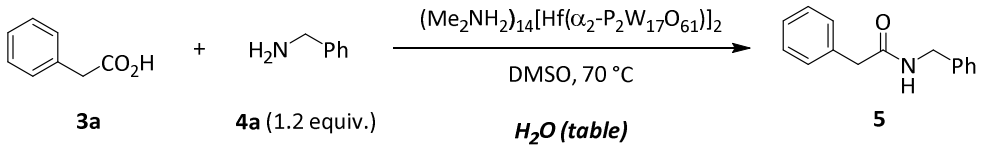
Tolerance to water

Effect of water on reaction yield

General Procedure J:

A 4 mL (1 dram) vial was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (see table below), phenylacetic acid (68.0 mg, 0.500 mmol), anhydrous DMSO (see table below), benzylamine (64 mg, 0.60 mmol), water (see table below) and a magnetic stir bar. The reaction mixture was stirred overnight (~20 h) at 70 °C. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (~3 mL), 25 µL of dodecane was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot was analyzed by GC-FID, and the yield was determined based on a standard curve. Results are reported based on GC yields.

Table S 14: Amount of water and DMSO used on the experiments to probe the effect of water on the yield of **5**



3a **4a** (1.2 equiv.) ***H_2O (table)*** **5**

Entry	Water (µL)	DMSO (µL)	Catalyst (µmol)	Yield (%)
1	0	150	5.0	>99
2	10	150	5.0	94
3	20	150	5.0	90
4	25	150	5.0	69
5	30	150	5.0	71
6	75	150	5.0	46
7	30	120	5.0	76
8	75	75	5.0	16
9	75	150	10.0	40
10	75	150	2.50	31
11	37	75	2.50	39
12	75	300	10.0	47
13	30	150	10.0	63

Effect of water on initial reaction rate

General Procedure K:

An oven-dried 4 mL (1 dram) vial was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid (68.0 mg, 0.500 mmol) and a magnetic stir bar. Next, the vial was evacuated and backfilled with N_2 (3x). After atmosphere exchange, anhydrous DMSO (0.15 mL) was added and the reaction mixture was stirred at 70 °C for a few minutes until homogenization. Next, water (0 – 30 µL) was added, followed by benzylamine (64 mg, 0.60 mmol). The reaction mixture was stirred overnight at 70 °C. At 5-20 minutes intervals, a 10 µL aliquot was taken, immediately quenched with a few drops of CH_2Cl_2, and analyzed by GC-FID. Using the data from GC-FID analysis, kinetic plots (product vs. reaction time) were obtained based on a standard curve. All data was processed using Microsoft Excel®.

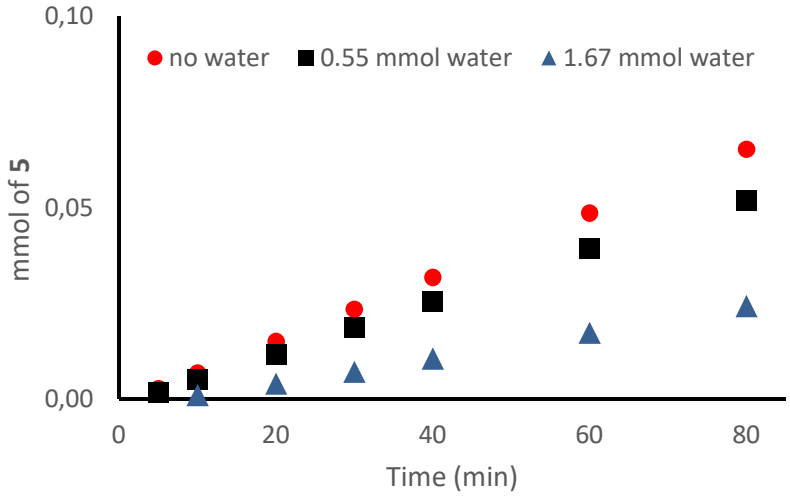


Figure S 7: Initial rate of reaction in the presence of different amounts of water (external addition)

Effect of water on the speciation of [Hf(IV)-(α_2-$P_2W_{17}O_{61}$)]$_2$ in DMSO by ^{31}P NMR

A) The behavior of $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ catalyst in DMSO is perturbed by the addition of water. To a 0.03 mol L^{-1} solution of catalyst, increasing amounts of water were added.

General Procedure L:

A 4 mL (1 dram) vial was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (194 mg, 20 µmol), DMSO-d_6 (0.60 mL) and a magnetic stir bar. The mixture was stirred for few minutes at 70 °C until homogenization has been observed. Next, the solution was transferred to a NMR tube, and analyzed by ^{31}P NMR (an external H_3PO_4 85% reference was used). Next, a aliquot of water was added (see table below), the tube was homogenized and analyzed by ^{31}P NMR again under the same conditions.

Table S 15: Additions of water to Hf-POM solution in DMSO studied by ^{31}P NMR

Addition (µL)	Volume added (µL)	Total water added (µL)
1	10	10
2	10	20
3	20	40
4	40	80
5	40	120
6	180	300

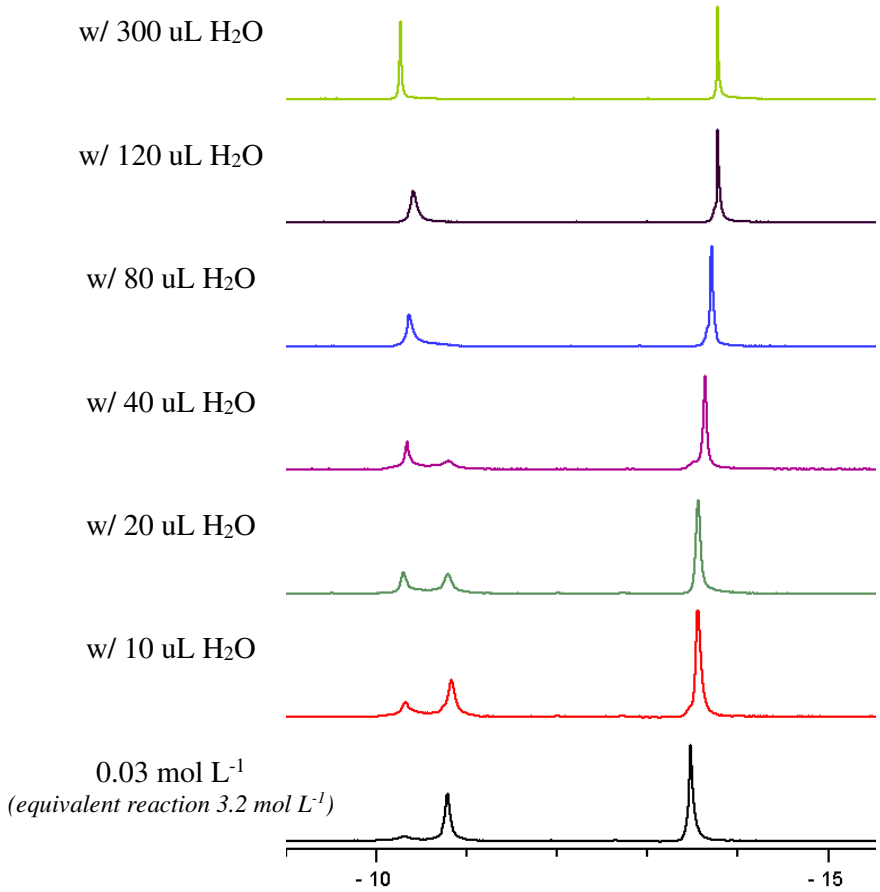


Figure S 8: Water perturbs the equilibrium between $[Hf(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ species formed in DMSO solution (0.03 mol L^{-1}). Equivalent reaction = equivalent to reaction with concentration of the limiting substrate at the given concentration.

B) The equilibrium perturbation due to the water does not happen in the presence of the substrates.

General Procedure M:

A 2 mL vial was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (194 mg, 20 µmol), DMSO-*d*$_6$ (0.60 mL), water (40 µL), phenylacetic acid (0.27 g, 2.0 mmol) and a magnetic stir bar. The mixture was stirred for few minutes at 70 °C until homogenization has been observed. Next, the solution was transferred to a NMR tube, and analyzed by ^{31}P NMR (an external H_3PO_4 85% reference was used). Next, benzylamine (64 mg, 0.6 mmol) was added, the tube was homogenized and analyzed by ^{31}P NMR again under the same conditions. The same was done for two more additions of water (40 µL). The addition of more than 0.25 equiv. of benzylamine caused the jellified of the sample preventing its analysis by ^{31}P NMR.

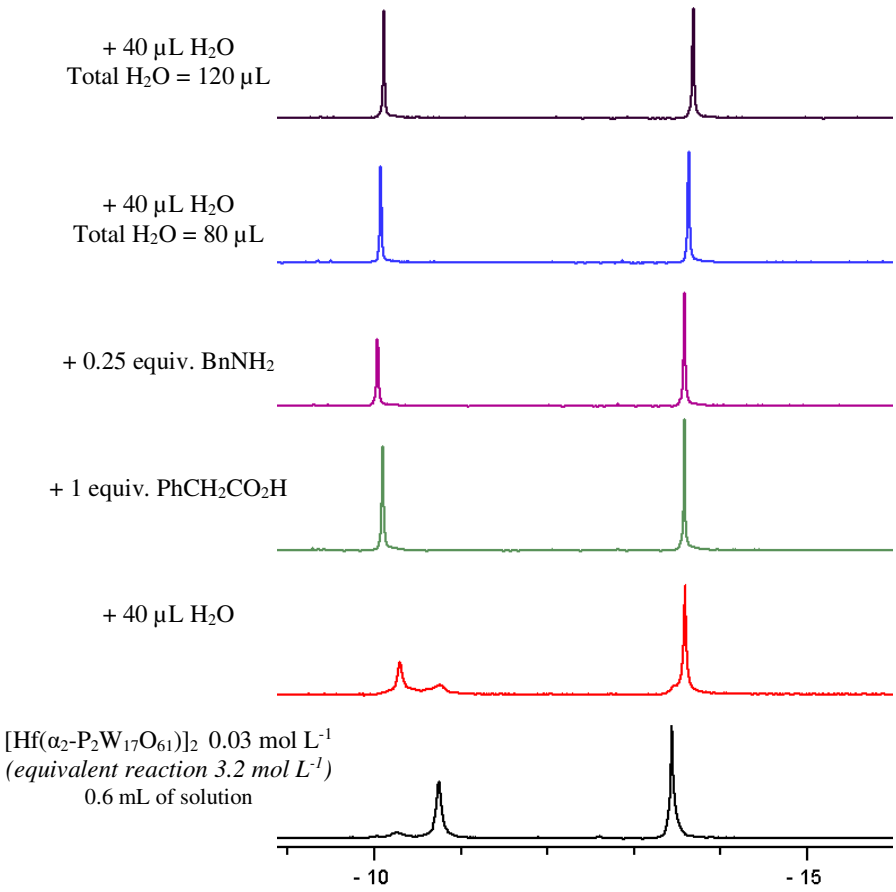
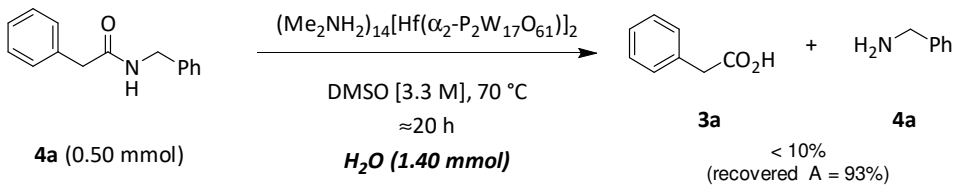


Figure S 9: The perturbation in the $[Hf(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ species equilibrium in DMSO solution caused by water does not happen in the presence of the substrates

Stability of the product under the reaction conditions in the presence of water

A 4 mL (1 dram) vial was charged with $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), amide product **5** (112 mg, 0.500 mmol), DMSO (0.15 mL), and water (25 µL, 1.4 mmol) and a magnetic stir bar. The reaction mixture was stirred overnight (~20 h) at 70 °C. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (~3 mL), 25 µL of dodecane was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. An aliquot was analyzed by GC-FID, and the yield was determined based on a standard curve. Results are reported based on GC yields.



4a (0.50 mmol)

Recycling of catalyst

For probing the recycle of the catalyst, the coupling between phenylacetic acid and benzylamine substrates was performed according to General procedure D using $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ (48 mg, 5.0 µmol), phenylacetic acid **3a** (68.0 mg, 0.500 mmol), benzylamine **4a** (64 mg, 0.60 mmol), DMSO (0.15 mL). The reaction was stirred at 70 °C for 21 – 24 h. After the reaction yield was determined by GC-FID analysis, the reaction mixture was transferred to a 15 mL centrifuge tube. After centrifugation (3 min, 5000 rpm), the supernatant was removed, and the solid was washed with MeOH (2 x 6 mL) and Et_2O (1 x 6 mL). The recovered solid was left to dry under air for a minimum of 24 h. This recovered solid was used again as catalyst in a new reaction, which was done using the exactly same procedure. The ^{31}P NMR analysis of the recovered catalysts was done using a 0.1 mol L^{-1} HCl solution in H_2O:D_2O 9:1.[5]

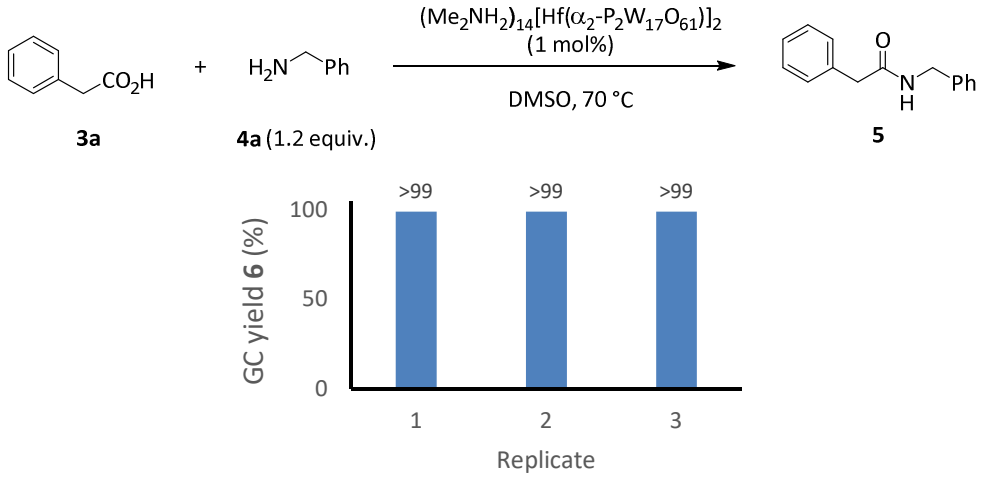


Figure S 10: Yield of product **6** for each replicate using the same catalyst

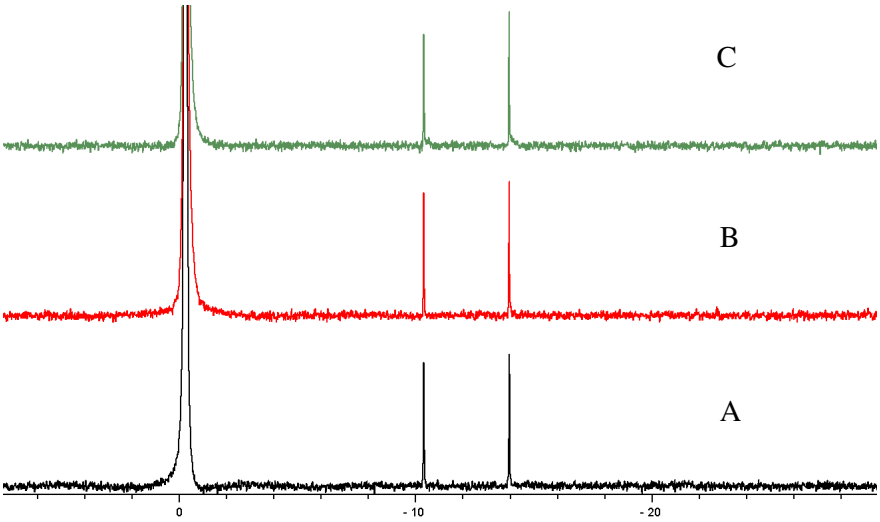


Figure S 11: ^{31}P NMR analysis of $(Me_2NH_2)_{14}[Hf(\mu\text{-}O)(H_2O)(\alpha_2\text{-}P_2W_{17}O_{61})]_2$ catalyst (A) freshly synthesized, (B) after one reaction , and (C) after 3 reactions confirms its structural stability.

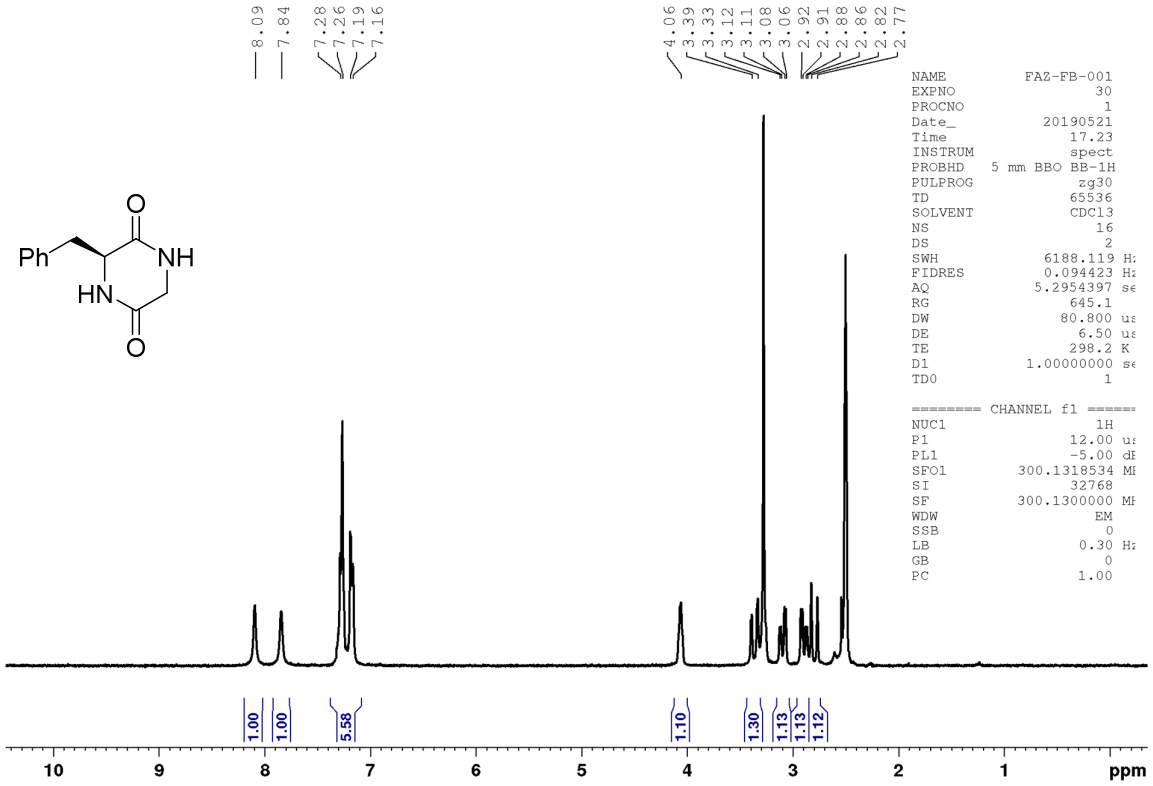
References

1. Klemperer, W. G., Introduction to Early Transition Metal Polyoxoanions. In *Inorg. Synth.*, Ginsberg, A. P., Ed. 1990; Vol. Vol. 27, pp 71-132.
2. Lyon, D. K.; Miller, W. K.; Novet, T.; Domaille, P. J.; Evitt, E.; Johnson, D. C.; Finke, R. G., Highly Oxidation Resistant Inorganic-Porphyrin Analog Polyoxometalate Oxidation Catalysts. 1. The Synthesis and Characterization of Aqueous-Soluble Potassium Salts of α_2-$P_2W_{17}O_{61}(Mn^{+}.OH_2)_{(n-10)}$ and Organic Solvent Soluble Tetra-*n*-butylammonium salts of α_2-$P_2W_{17}O_{61}(Mn+.Br)_{(n-11)}$ (M = Mn^{3+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}). *J. Am. Chem. Soc.* **1991,** *113*, 7209-7221.
3. Kato, C. N.; Shinohara, A.; Hayashi, K.; Nomiya, K., Syntheses and X-ray Crystal Structures of Zirconium(IV) and Hafnium(IV) Complexes Containing Monovacant Wells−Dawson and Keggin Polyoxotungstates. *Inorg. Chem.* **2006,** *45*, 8108-8119.
4. Iijima, J.; Naruke, H., Synthesis and Structural Characterization of $[Ce^{IV}(\alpha_2\text{-}P_2W_{17}O_{61})_2]^{16-}$ in the solid state and in aqueous solution. *J. Mol. Struct.* **2013,** *1040*, 33-38.
5. Saku, Y.; Sakai, Y.; Nomiya, K., Relation Among the 2:2-, 1:1- and 1:2-type Complexes of Hafnium(IV)/Zirconium(IV) with Mono-Lacunary α_2-Dawson Polyoxometalate Ligands: Synthesis and Structure of the 2:2-Type Complexes $[\{\alpha_2\text{-}P_2W_{17}O_{61}M(\mu\text{-}OH)(H_2O)\}_2]^{14-}$ (M=Hf, Zr). *Inorg. Chim. Acta* **2010,** *363*, 967-974.
6. Kleinsmann, A. J.; Nachtsheim, B. J., Phenylalanine-containing Cyclic Dipeptides – the Lowest Molecular Weight Hydrogelators Based on Unmodified Proteinogenic Amino Acids. *Chem. Commun.* **2013,** *49*, 7818-7820.
7. Pérez-Picaso, L.; Escalante, J.; Olivo, H. F.; Rios, M. Y., Efficient Microwave Assisted Syntheses of 2,5-Diketopiperazines in Aqueous Media. *Molecules* **2009,** *14*, 2836-2849.
8. Mendive-Tapia, L.; Albornoz-Grados, A.; Bertran, A.; Albericio, F.; Lavilla, R., Oxidative Couplings on Tryptophan-based Diketopiperazines Leading to Fused and Bridged Chemotypes. *Chem. Commun.* **2017,** *53*, 2740-2743.
9. Arena, G.; Impellizzeri, G.; Maccarrone, G.; Pappalardo, G.; Sciotto, D.; Rizzarelli, E., Thermodynamic and ^{1}H NMR Study of Proton Complex Formation of Histidine-containing Cyclodipeptides in Aqueous Solution. *J. Chem. Soc., Perkin Trans. 2* **1992**, 371-376.
10. Sun, D.; Sun, L.; Luo, M.; Gou, Z., One-pot Preparation of 3-Hydroxymethyl 2,5-Diketopiperazine for Total Synthesis of Pepticinnamin E. *Asian J. Chem.* **2011,** *23*, 5169-5170.
11. a) Furtado, N. A. J. C.; Pupo, M. T.; Carvalho, I.; Campo, V. L.; Duarte, M. C. T.; Bastos, J. K., Diketopiperazines Produced by an Aspergillus Fumigatus Brazilian Strain. *J. Braz. Chem. Soc.* **2005,** *16*, 1448-1453; b) Campbell, J.; Lin, Q.; Geske, G. D.; Blackwell, H. E., New and Unexpected Insights into the Modulation of LuxR-Type Quorum Sensing by Cyclic Dipeptides. *ACS Chem. Biol.* **2009,** *4*, 1051-1059.
12. a) Ly, H. G. T.; Absillis, G.; Parac-Vogt, T. N., Influence of the Amino Acid Side Chain on Peptide Bond Hydrolysis Catalyzed by a Dimeric Zr(IV)-Substituted Keggin Type Polyoxometalate. *New J. Chem.* **2016,** *40*, 976-984; b) Jamin, N.; Baron, D.; Lumbroso-Bader, N., Nuclear Magnetic Resonance Study of Ln^{3+} Complexes with Aspartate and Glutamate Residues. Thermodynamic and Structural Analysis. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1-8.
13. Coursindel, T.; Restouin, A.; Dewynter, G.; Martinez, J.; Collette, Y.; Parrot, I., Stereoselective Ring Contraction of 2,5-Diketopiperazines: An Innovative Approach to the Synthesis of Promising Bioactive 5-Membered Scaffolds. *Bioorg. Chem.* **2010,** *38*, 210-217.
14. Selvakumar, S.; Sivasankaran, D.; Singh, V. K., Enantioselective Henry reaction catalyzed by C2-symmetric chiral diamine–copper(II) complex. *Org. Biomol. Chem.* **2009,** *7*, 3156-3162.
15. Kiely-Collins, H. J.; Sechi, I.; Brennan, P. E.; McLaughlin, M. G., Mild, Calcium Catalysed Beckmann Rearrangements. *Chem. Commun.* **2018,** *54*, 654-657.
16. Lundberg, H.; Tinnis, F.; Adolfsson, H., Direct Amide Coupling of Non-activated Carboxylic Acids and Amines Catalysed by Zirconium(IV) Chloride. *Chem. Eur. J.* **2012,** *18*, 3822-3826.

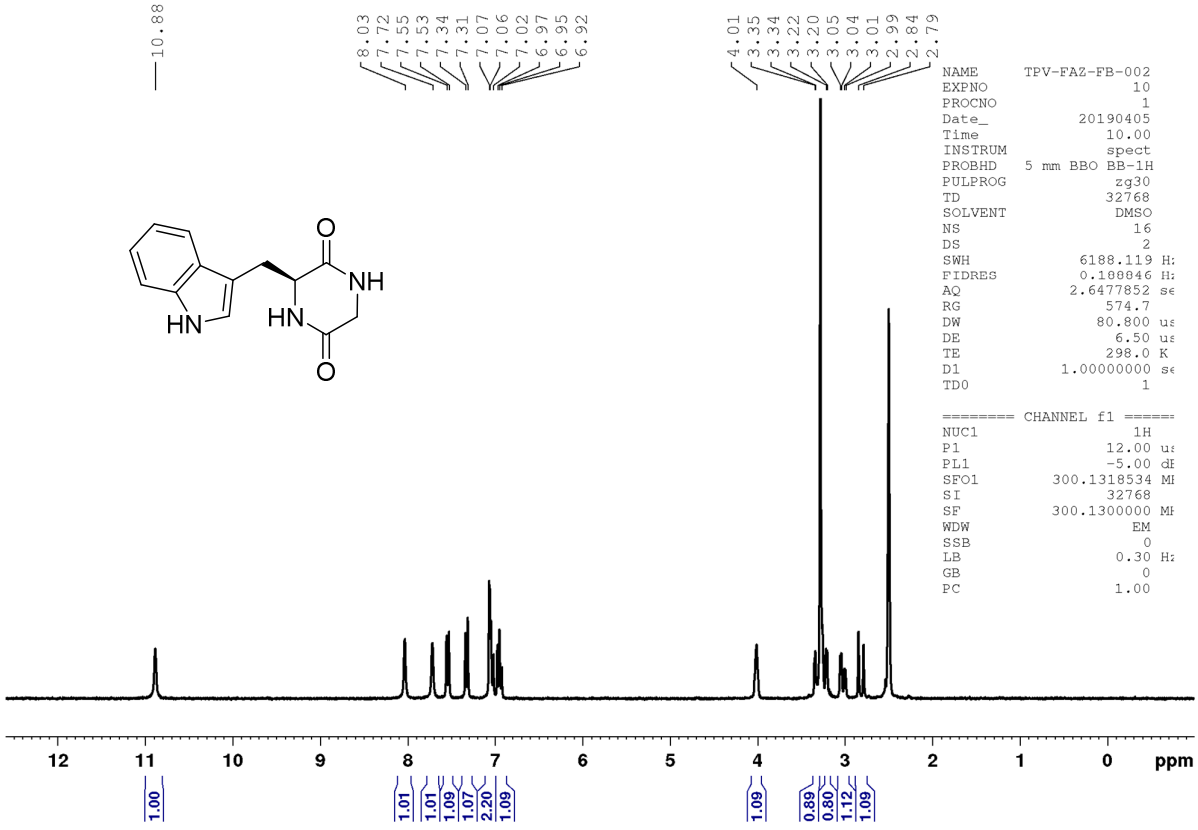
17. Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B., Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes. *Org. Proc. Res. Dev.* **2011,** *15*, 912-917.
18. Lundberg, H.; Adolfsson, H., Hafnium-Catalyzed Direct Amide Formation at Room Temperature. *ACS Catal.* **2015,** *5*, 3271-3277.
19. Lanigan, R. M.; Starkov, P.; Sheppard, T. D., Direct Synthesis of Amides from Carboxylic Acids and Amines Using B(OCH2CF3)3. *J. Org. Chem.* **2013,** *78*, 4512-4523.
20. Maki, T.; Ishihara, K.; Yamamoto, H., 4,5,6,7-Tetrachlorobenzo[d][1,3,2]dioxaborol- 2-ol as an Effective Catalyst for the Amide Condensation of Sterically Demanding Carboxylic Acids. *Org. Lett.* **2006,** *8*, 1431-1434.
21. Hardee, D. J.; Kovalchuke, L.; Lambert, T. H., Nucleophilic Acyl Substitution via Aromatic Cation Activation of Carboxylic Acids: Rapid Generation of Acid Chlorides under Mild Conditions. *J. Am. Chem. Soc.* **2010,** *132*, 5002-5003.
22. Cui, X.; Zhang, Y.; Shi, F.; Deng, Y., Organic Ligand-Free Alkylation of Amines, Carboxamides, Sulfonamides, and Ketones by Using Alcohols Catalyzed by Heterogeneous Ag/Mo Oxides. *Chem. Eur. J.* **2011,** *17*, 1021-1028.
23. Chen, C.; Zhang, Y.; Hong, S. H., N-Heterocyclic Carbene Based Ruthenium-Catalyzed Direct Amide Synthesis from Alcohols and Secondary Amines: Involvement of Esters. *J. Org. Chem.* **2011,** *76*, 10005-10010.
24. Ren, W.; Yamane, M., Palladium-Catalyzed Carbamoylation of Aryl Halides by Tungsten Carbonyl Amine Complex. *J. Org. Chem.* **2009,** *74*, 8332-8335.
25. Sanz Sharley, D. D.; Williams, J. M. J., Acetic Acid as a Catalyst for the N-Acylation of Amines Using Esters as the Acyl Source. *Chem. Commun.* **2017,** *53*, 2020-2023.
26. Dineen, T. A.; Zajac, M. A.; Myers, A. G., Efficient Transamidation of Primary Carboxamides by in Situ Activation with N,N-Dialkylformamide Dimethyl Acetals. *J. Am. Chem. Soc.* **2006,** *128*, 16406-16409.

NMR Spectra

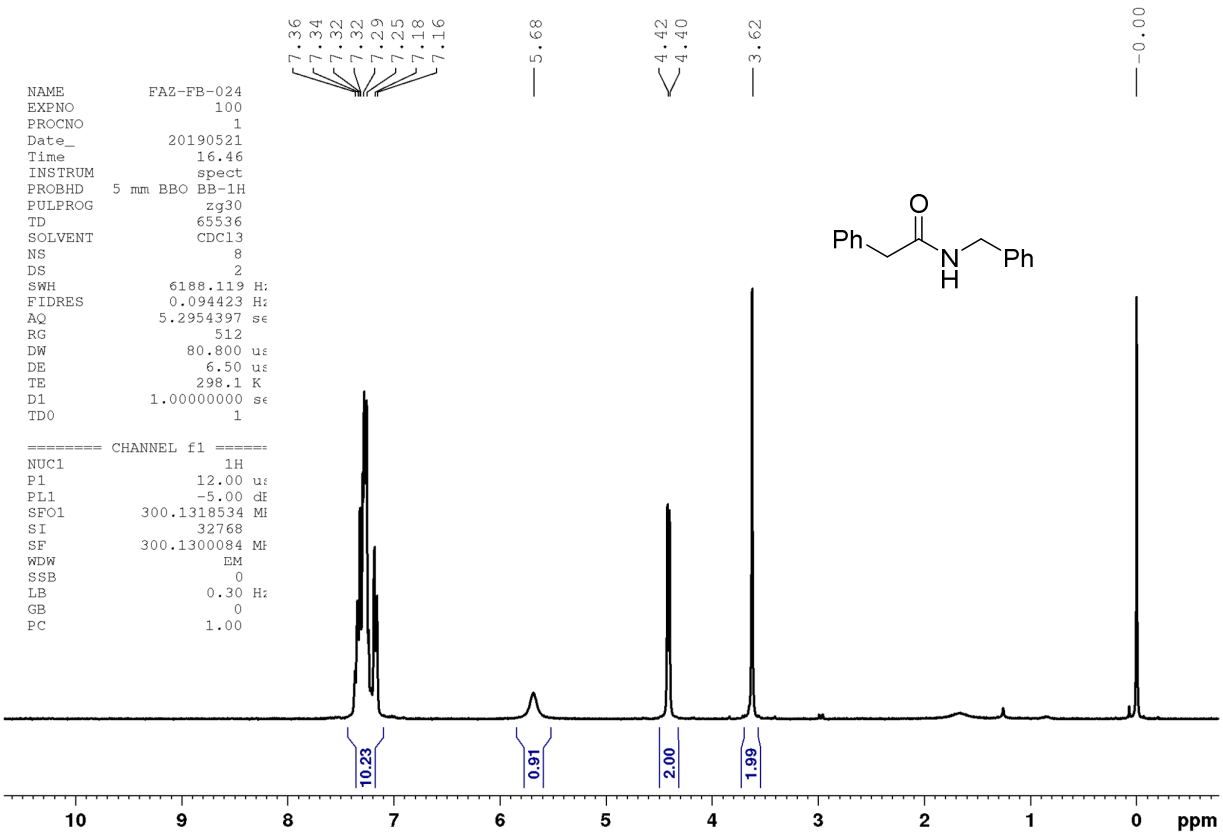
c(Gly–Phe) (2b)



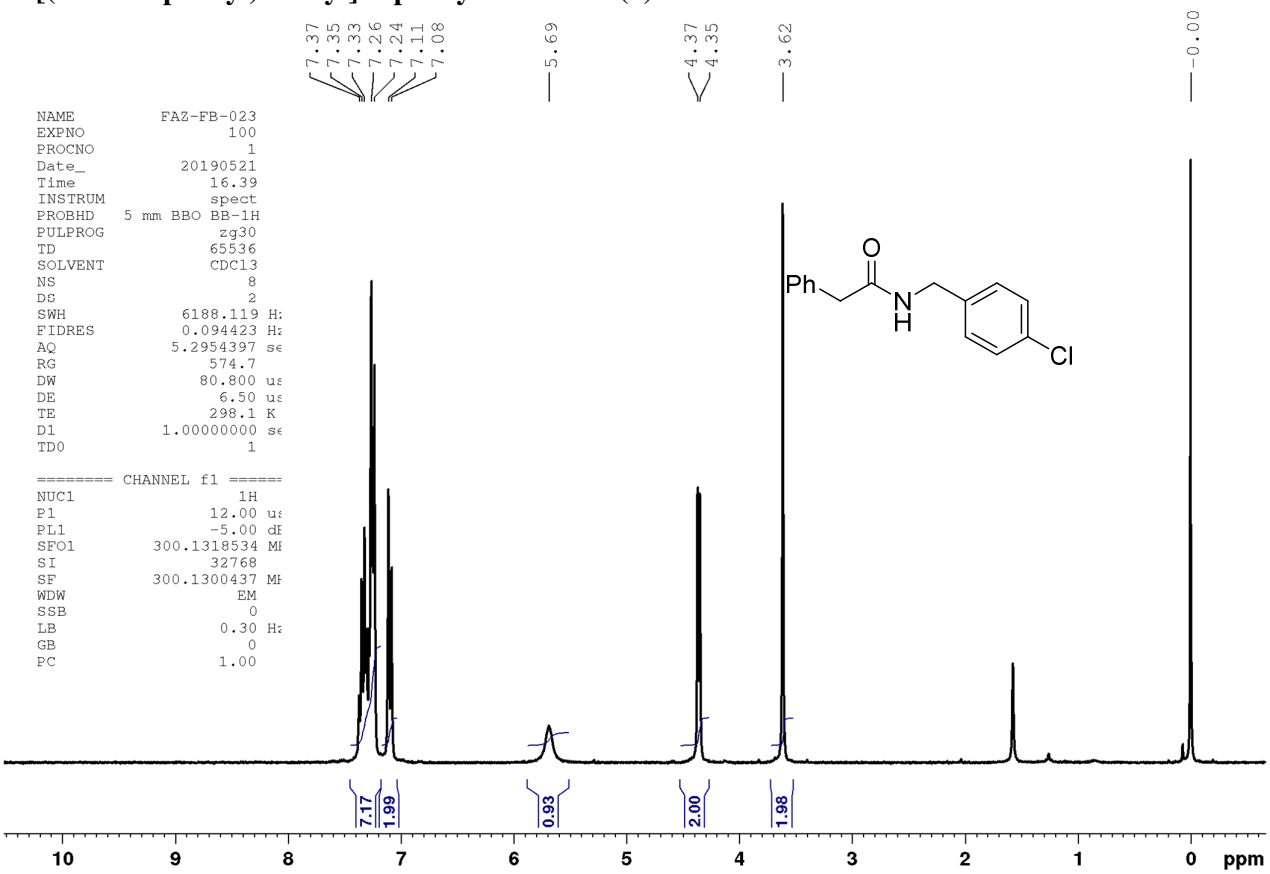
c(Gly–Trp) (2c)



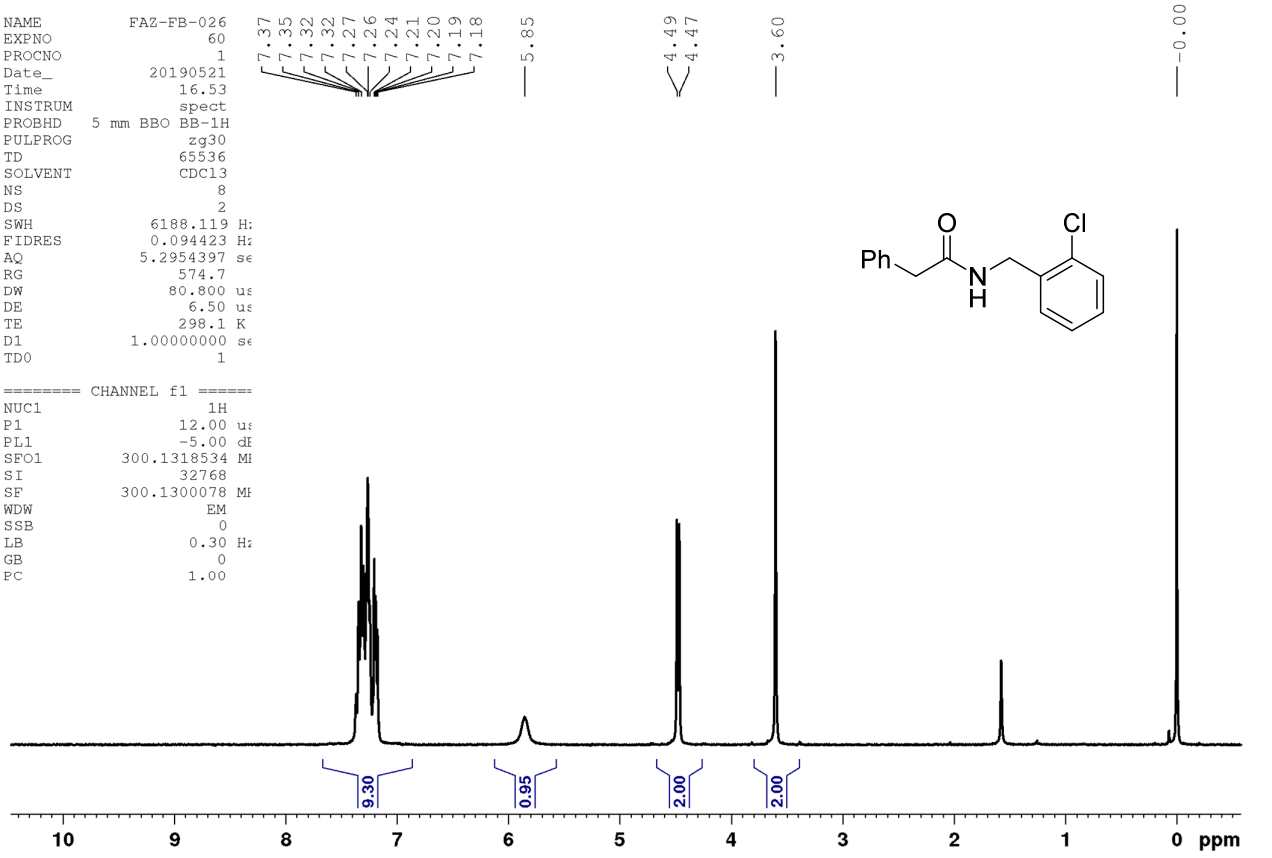
N-benzyl-2-phenylacetamide (5)

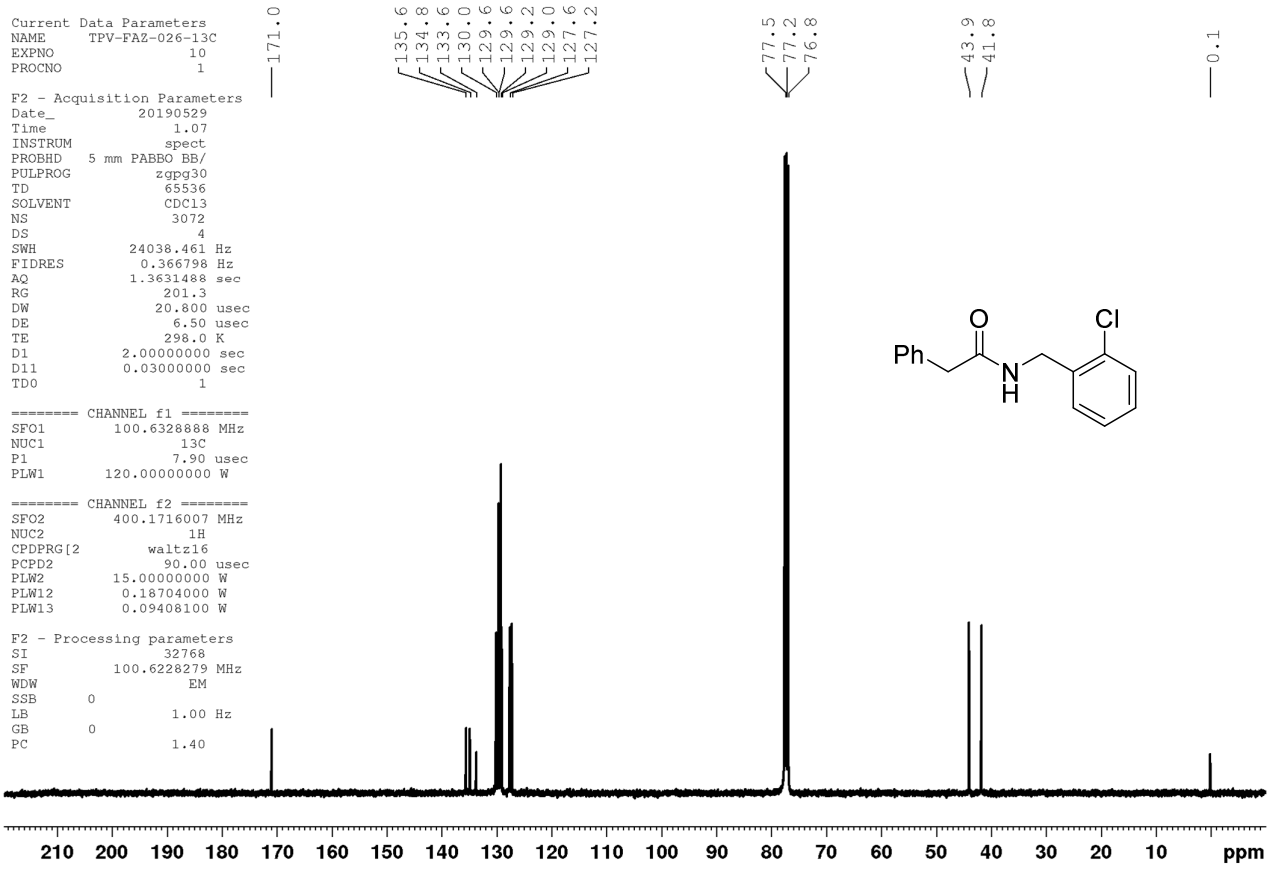


N-[(4-chlorophenyl)methyl]-2-phenylacetamide (6)

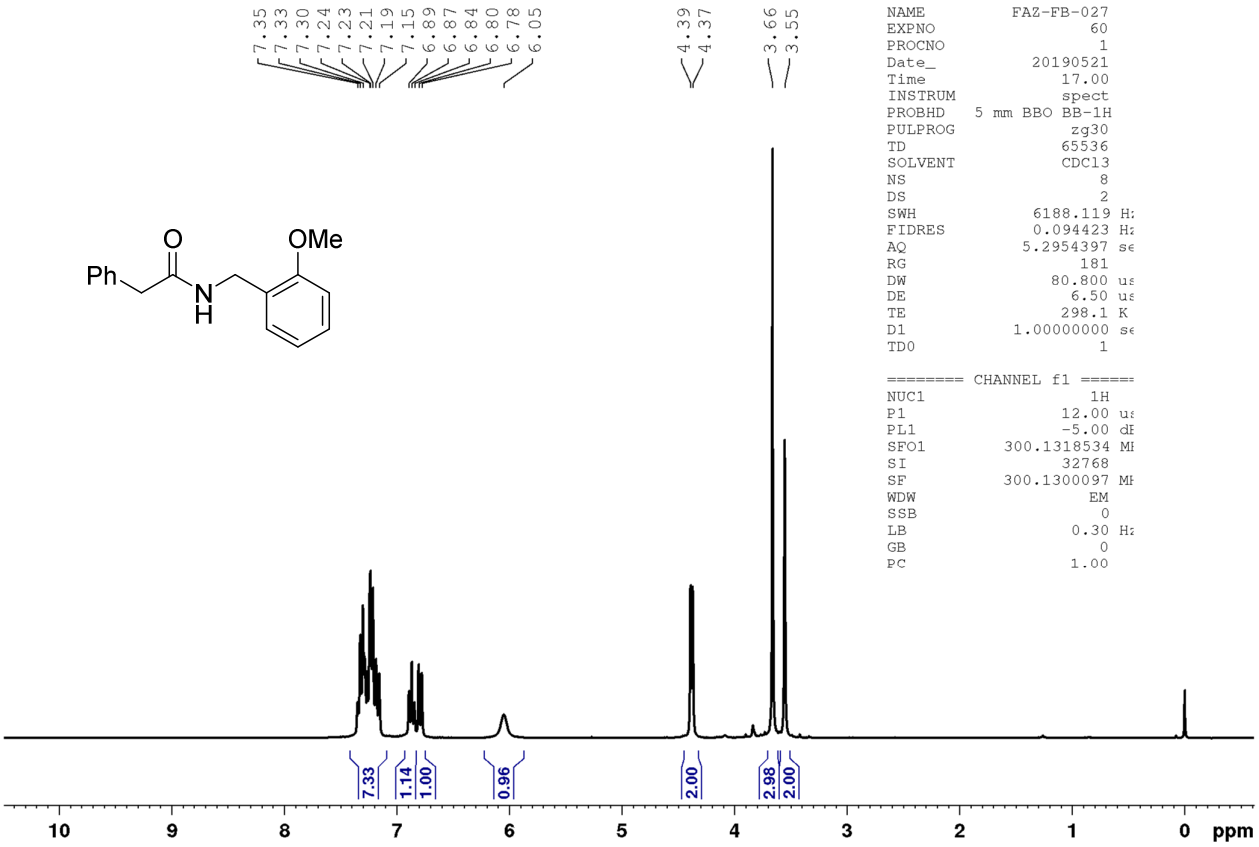


N-[(2-chlorophenyl)methyl]-2-phenylacetamide (7)

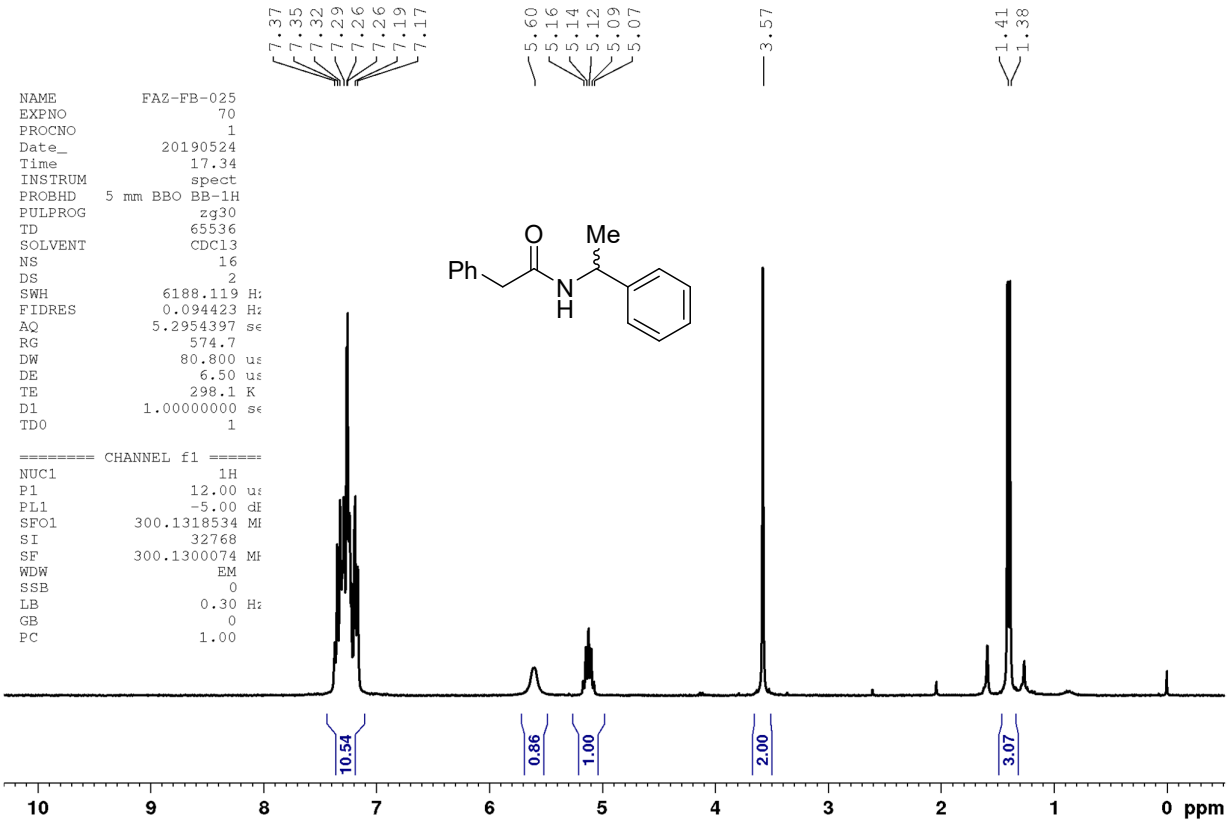




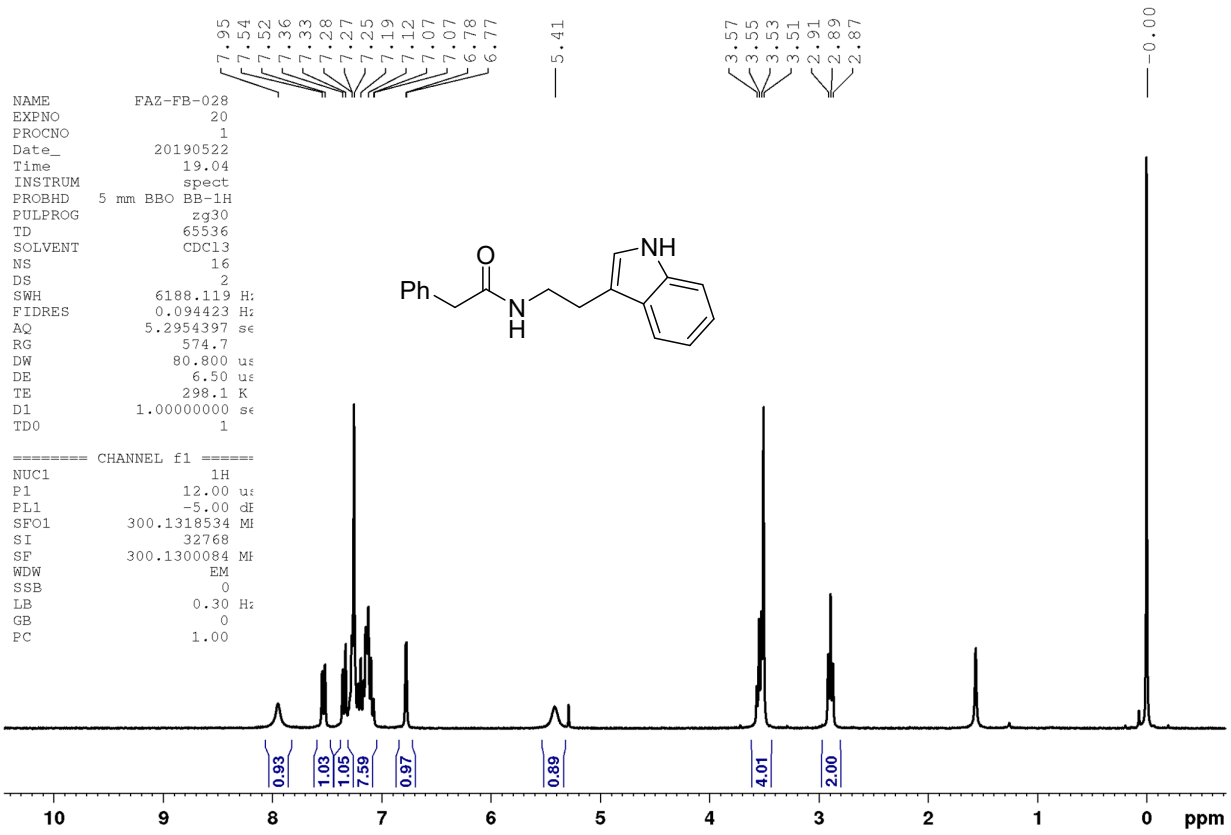
_N_-[(2-methoxyphenyl)methyl]-2-phenylacetamide (8)



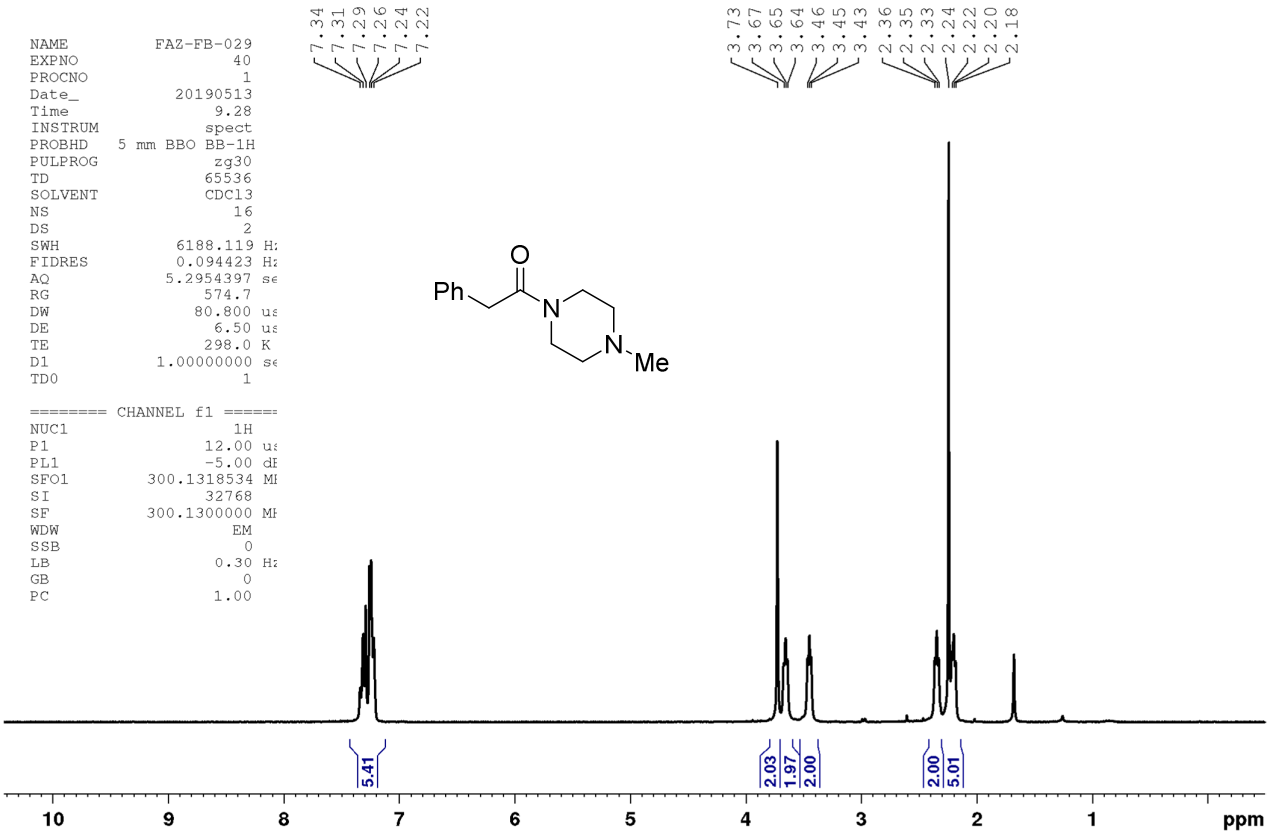
(±)-2-Phenyl-_N_-(1-phenylethyl)acetamide (9)



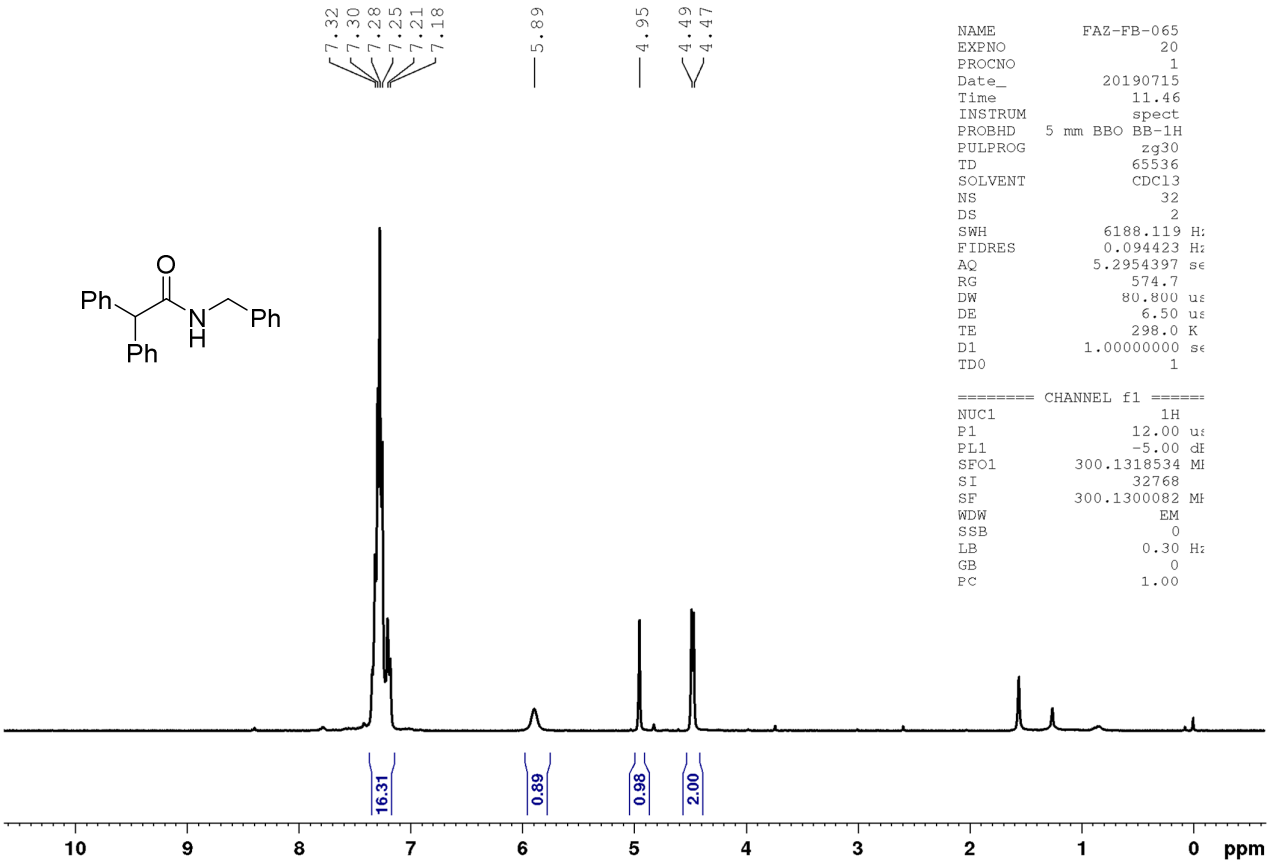
N-(2-(1H-Indol-3-yl)ethyl)-2-phenylacetamide (10)



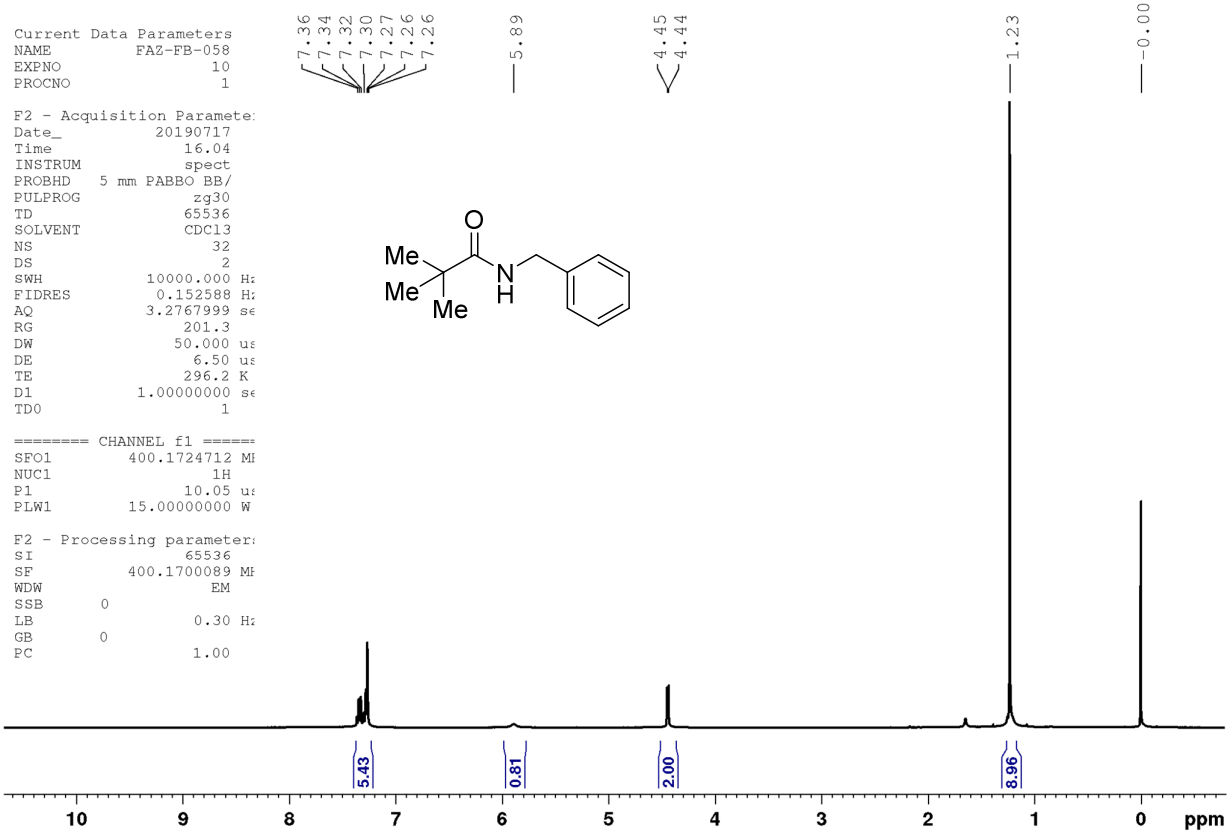
N-Methyl-*N′*-phenylacetylpiperazine (11)



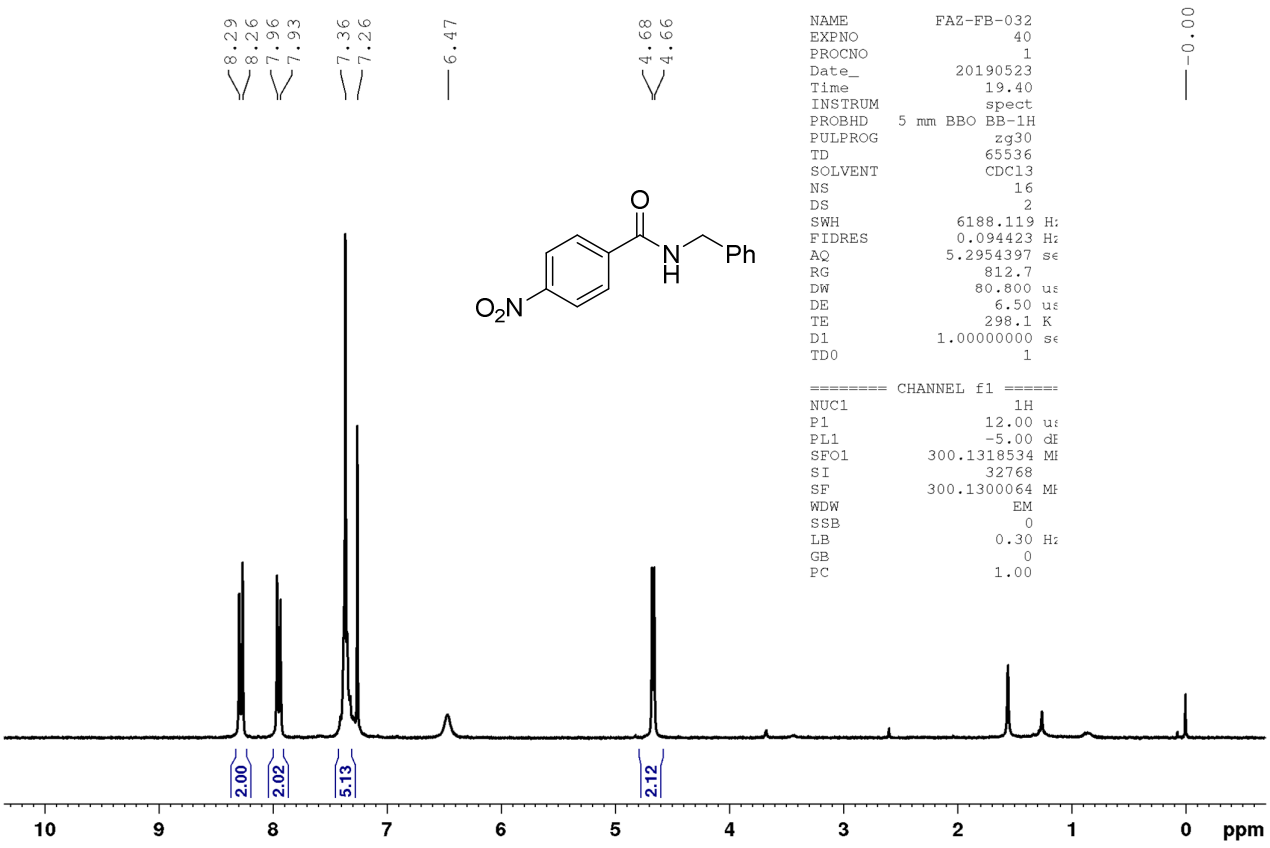
N-benzyl-2,2-diphenylacetamide (12)



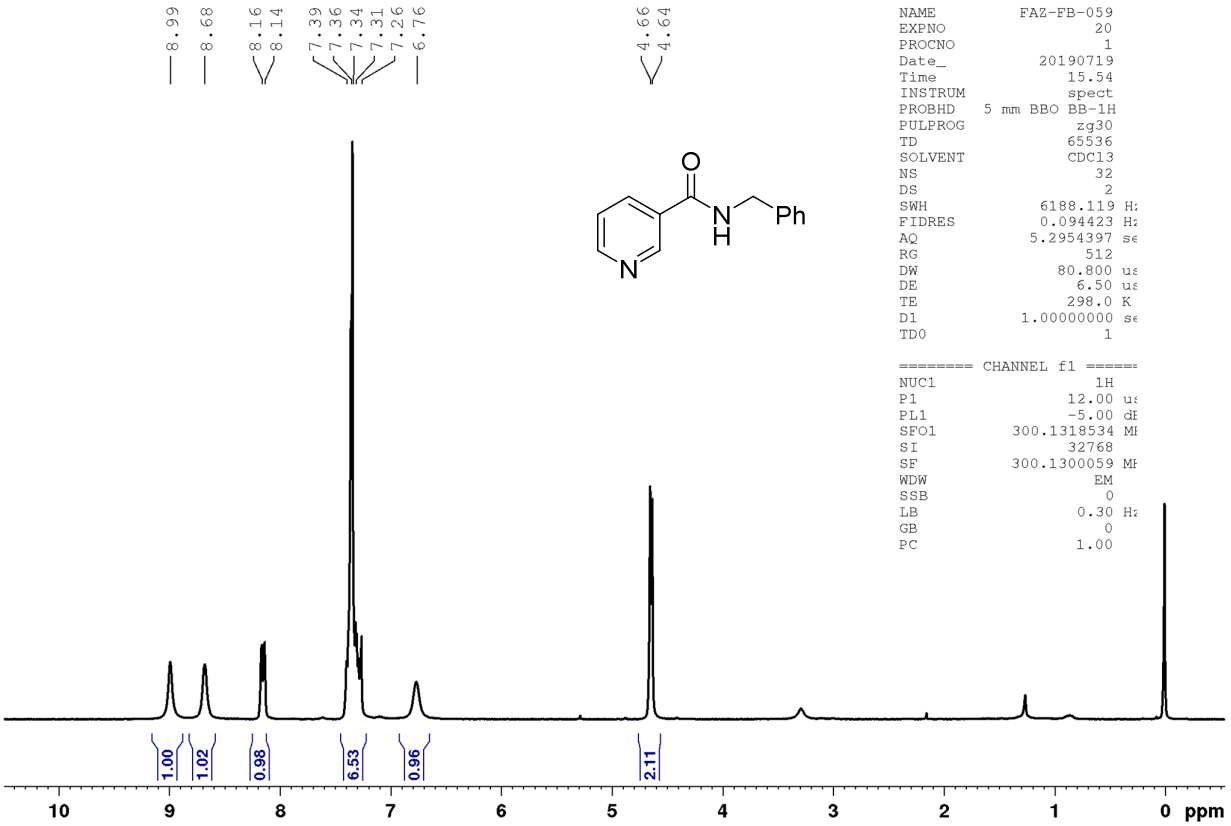
***N*-benzyl-2,2-dimethylpropanamide (13)**



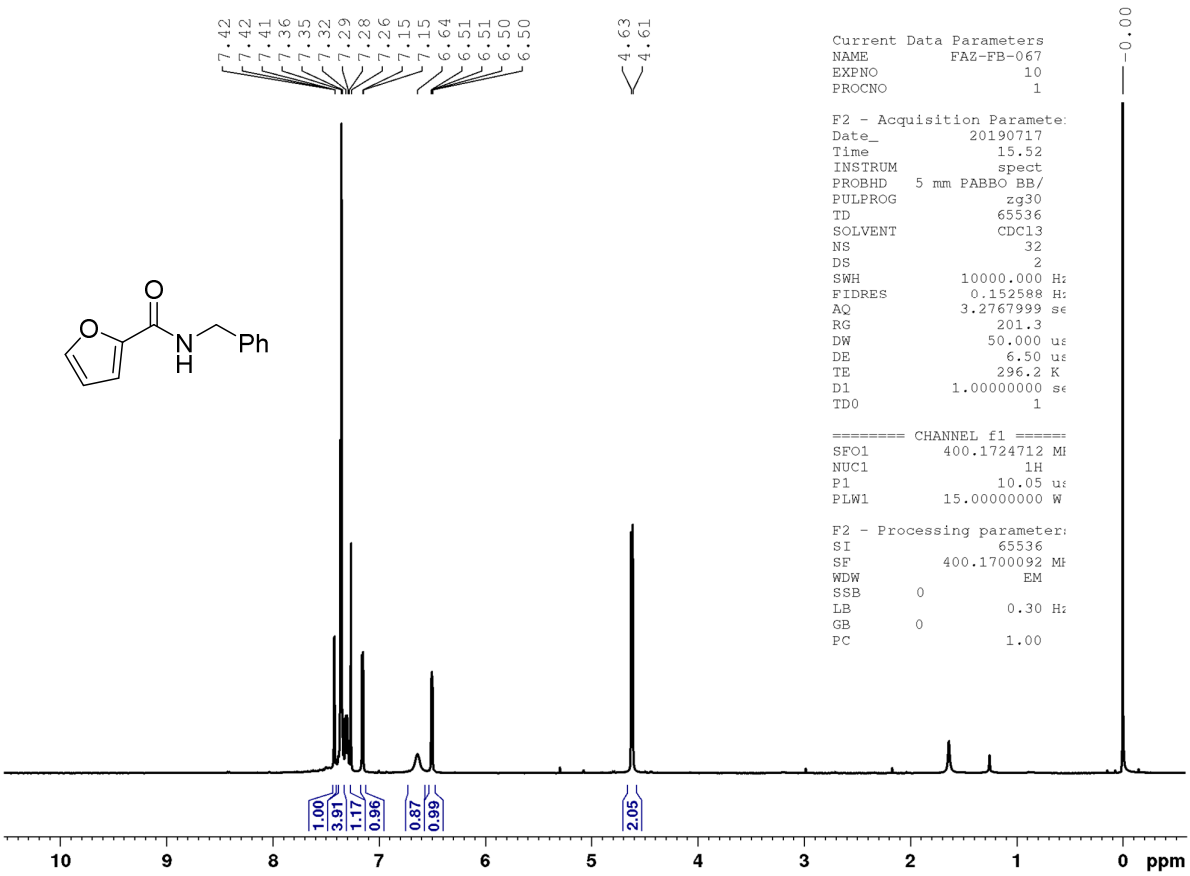
_N_-benzyl-4-nitrobenzamide (14)



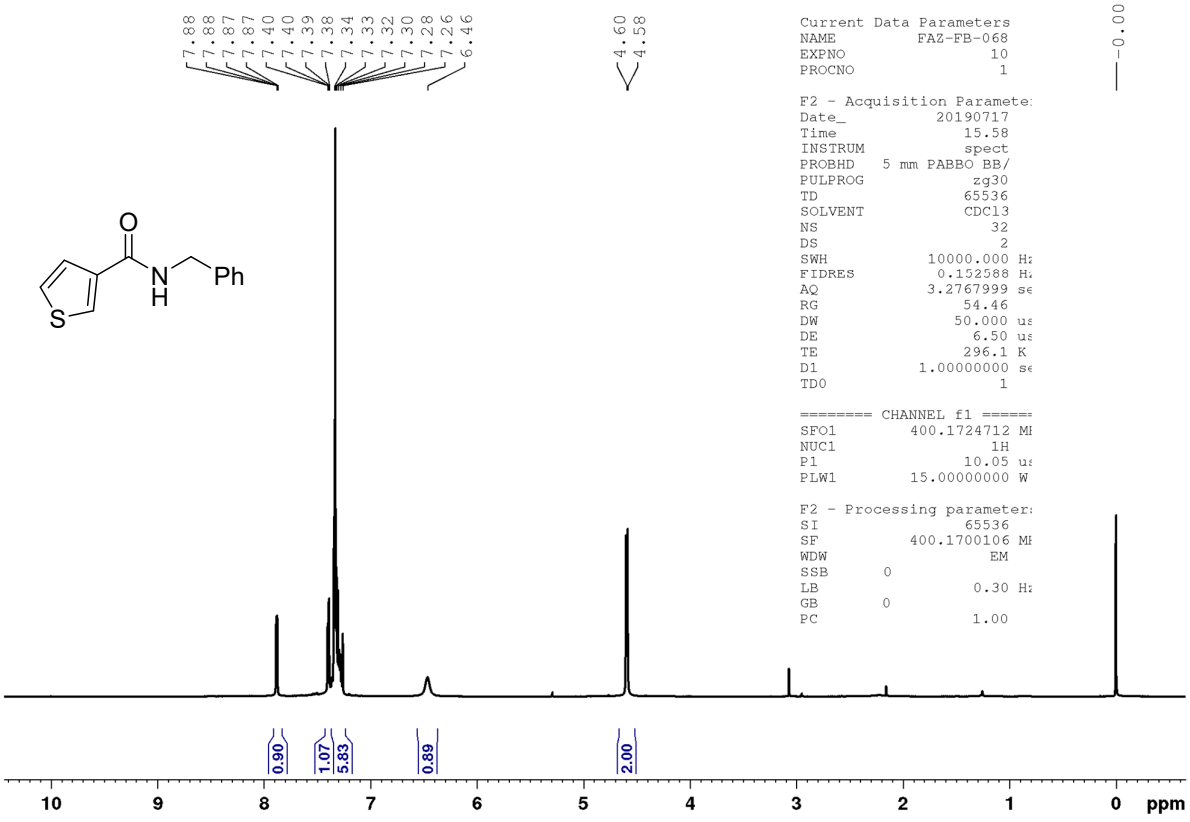
_N_-benzylpyridine-3-carboxamide (15)



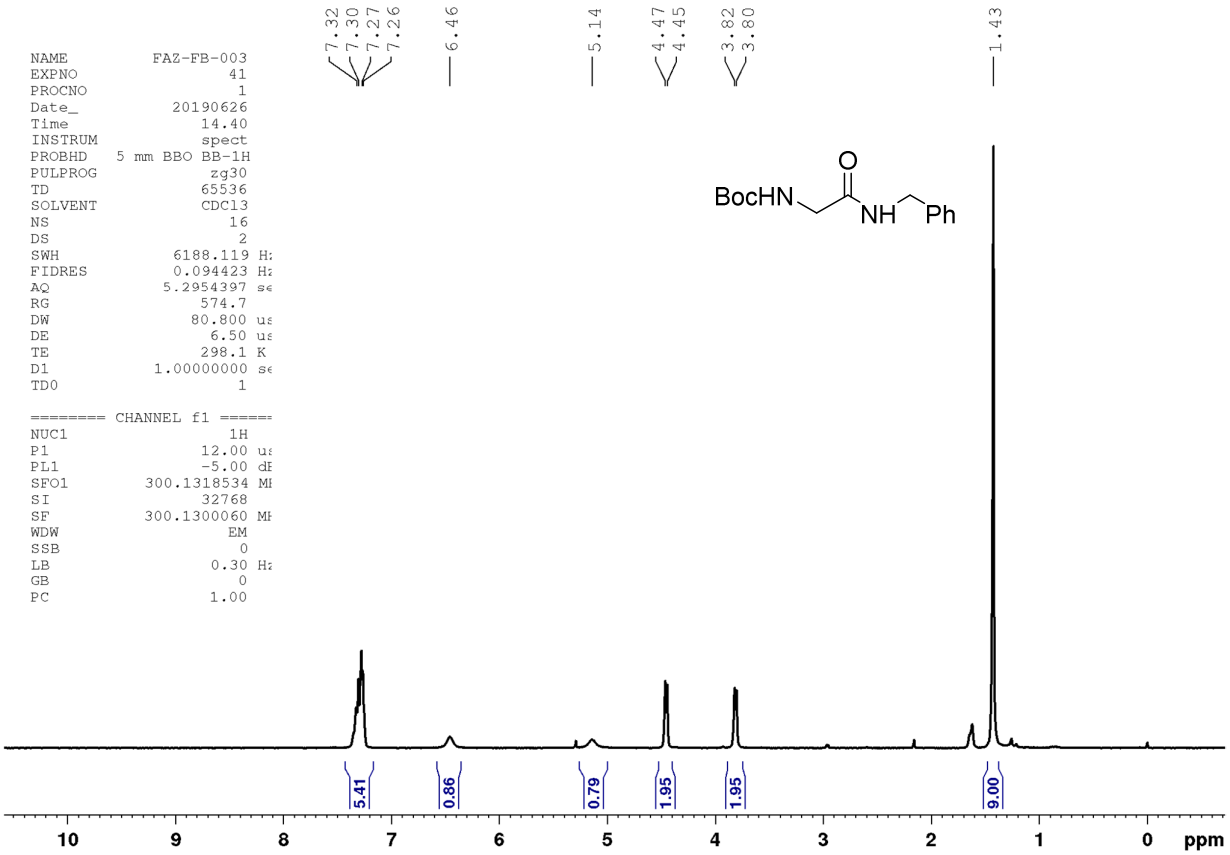
N-benzylfuran-2-carboxamide (16)



N-benzylthiophene-3-carboxamide (17)



tert-Butyl (2-(benzylamino)-2-oxoethyl)carbamate (18)



***tert*-Butyl N-[(1S)-1-(benzylcarbamoyl)-2-phenylethyl]carbamate (19)**