Supporting Information

Zirconium Oxo Clusters as Discrete Molecular Catalysts for the Direct Amide Bond Formation

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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 PTFE-lined screw cap. Unless otherwise noted, reagents were purchased from commercial sources, and used as received.

Hydrogen nuclear magnetic resonance (^{1}H NMR) were recorded on a Bruker Avance 300 (300 MHz) or a Bruker Avance 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to resonance of residual solvent peak in the NMR solvent (^{1}H NMR: DMSO: δ = 2.50 ppm; $CDCl_3$: δ = 7.26 ppm). Fourier-transform infrared spectra (FTIR) were recorded on a Bruker Vertex 70 spectrometer and analysed with the Bruker OPUS software (version 7.5). The solid samples were measured directly, without sample preparation, using the attenuated total reflectance module (Platinum ATR).

Synthesis of Zr_{12}

$[Zr_6(OH)_4O_4(OAcr)_{12}]_2 \cdot 6$ AcrOH (OAcr = acrylate) (**Zr_{12}**) was prepared as previously reported:[1]

In a Schlenk tube under a nitrogen atmosphere, $Zr(O^nPr)_4$ (2.00 mL of a 70% wt% solution in *n*-propanol, 4.46 mmol) was mixed with acrylic acid （2.00 mL, 29.2 mmol). After homogenization for a few minutes, the mixture was kept still at room temperature. A white solid precipitated within 3 to 5 days, and it was collected by vacuum filtration. The compound was washed with 35 mL CH_2Cl_2, and dried under reduced pressure – first rotatory evaporator, and then under high-vacuum for 16 – 24 h ('overnight'). Yield: 0.44 g, 34% based on Zr). Analysis by infrared and ^{1}H NMR spectroscopies were consistent with those previously reported for similar compounds, confirming the identity of cluster obtained.[2] Despite extensive washing with CH_2Cl_2, usually 4 – 6 molecules of 'free' acrylic acid (presumably associated with the cluster through H bonding interactions)[1] were always observed by ^{1}H NMR.

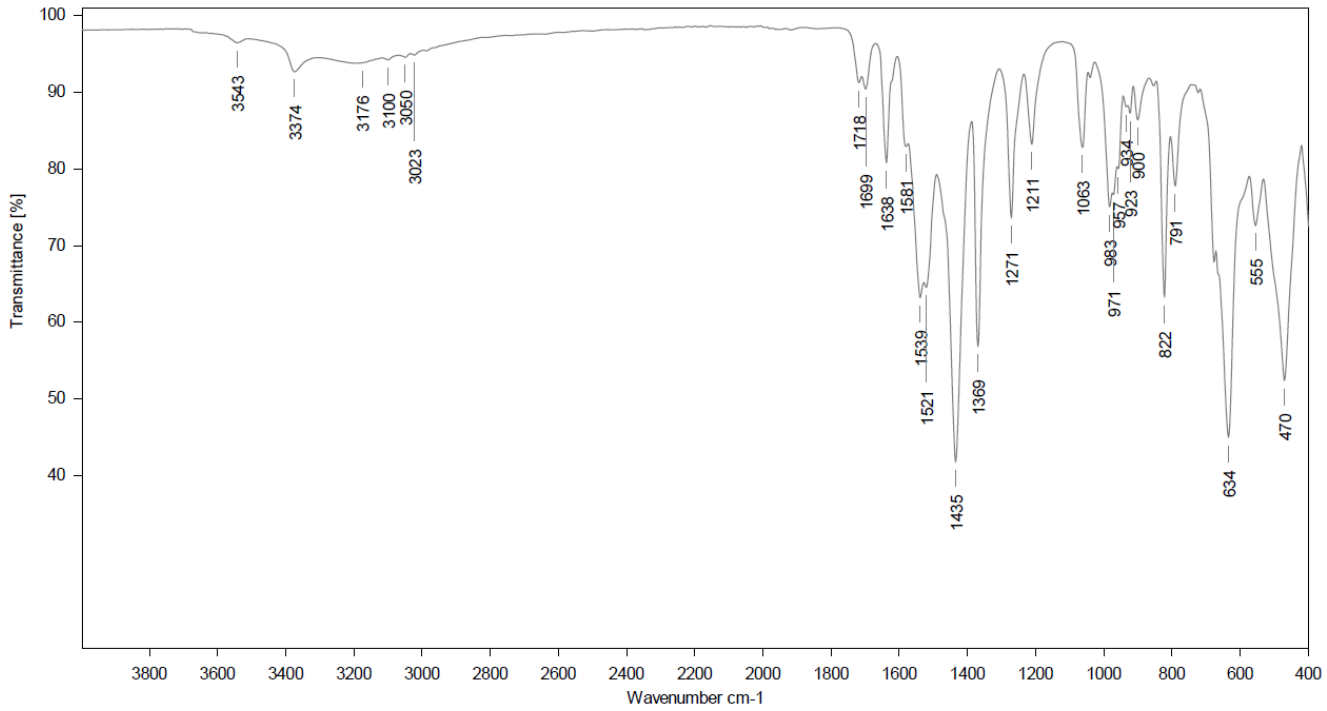


Figure S1. Infrared of **Zr_{12}** cluster as synthesized.

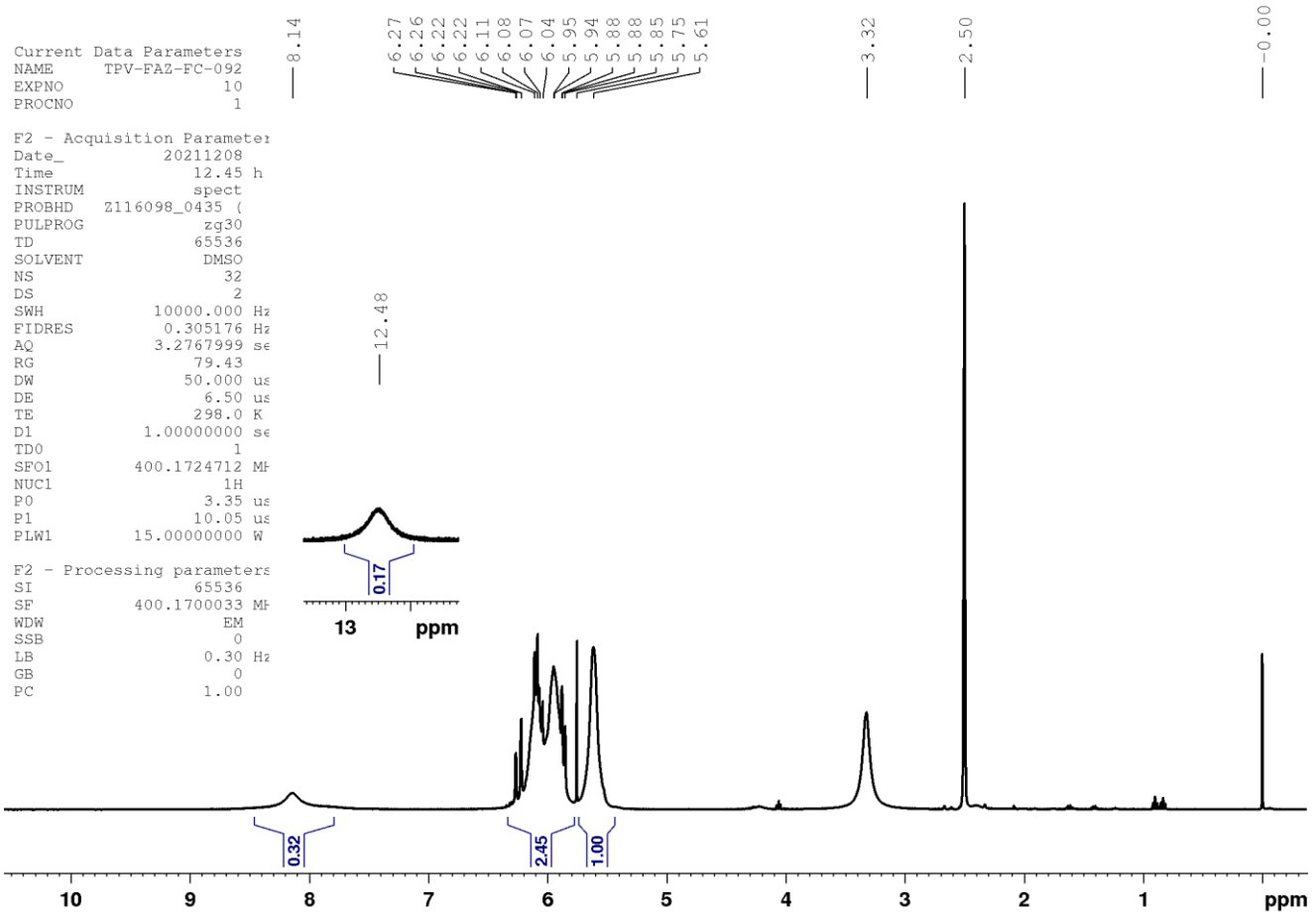


Figure S2. ^{1}H NMR of **Zr_{12}** cluster as synthesized.

Results and Discussion

Mechanistic study

NMR study

General Procedure A:

A 2-4 mL vial was charged with 450 µL DMSO-d_6, catalyst (7.50 µmol, 27.0 mg) and magnetic stirring bar. The mixture was stirred at 80 °C for around 10 minutes until homogenization has been observed. Then, different amounts of phenylacetic acid were added (see figure below), the solution was stirred for few minutes at 80°C until homogenization has been observed. An aliquot of ~450 was transferred to a NMR tube, and analyzed by ^{1}H NMR.

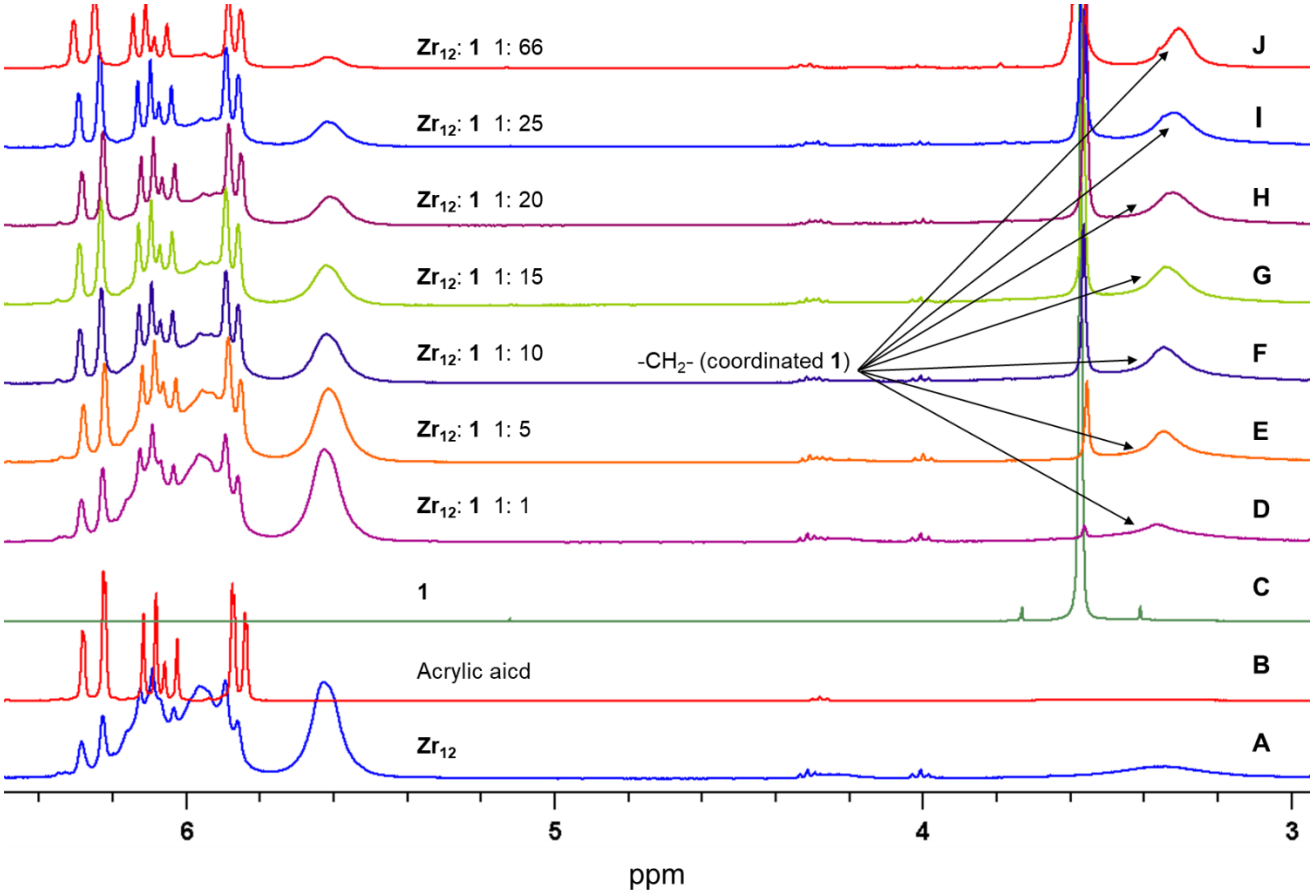


Figure S3. ^{1}H NMR of phenylacetic acid **1** and **Zr_{12}** cluster mixtures. **Zr_{12}** at equivalent concentration to the standard reaction condition (A). Acrylic acid (B). **1** (C). Solution (A) plus 1 equiv. (D), 5 equiv. (E), 10 equiv. (F), 15 equiv. (G), 20 equiv. (H), 25 equiv. (I), 66 equiv. (J) of **1**.

General Procedure B:

A 2-4 mL vial was charged with 450 µL DMSO-d_6. In a second vail, acrylic acid (750 µmol, 52 µL) was dissolved in 948 µL DMSO-d_6. Then, 10 µL of this acrylic acid solution (7.50 µmol) was added to the first vial. The solution was stirred at 80 °C for around 10 minutes until homogenization has been observed. Then, different amounts of **2** were added (see figure below), the mixture was stirred at 80°C for few minutes until homogenization was observed. An aliquot of ~ 500 µL was transferred to a NMR tube, and analyzed by ^{1}H NMR.

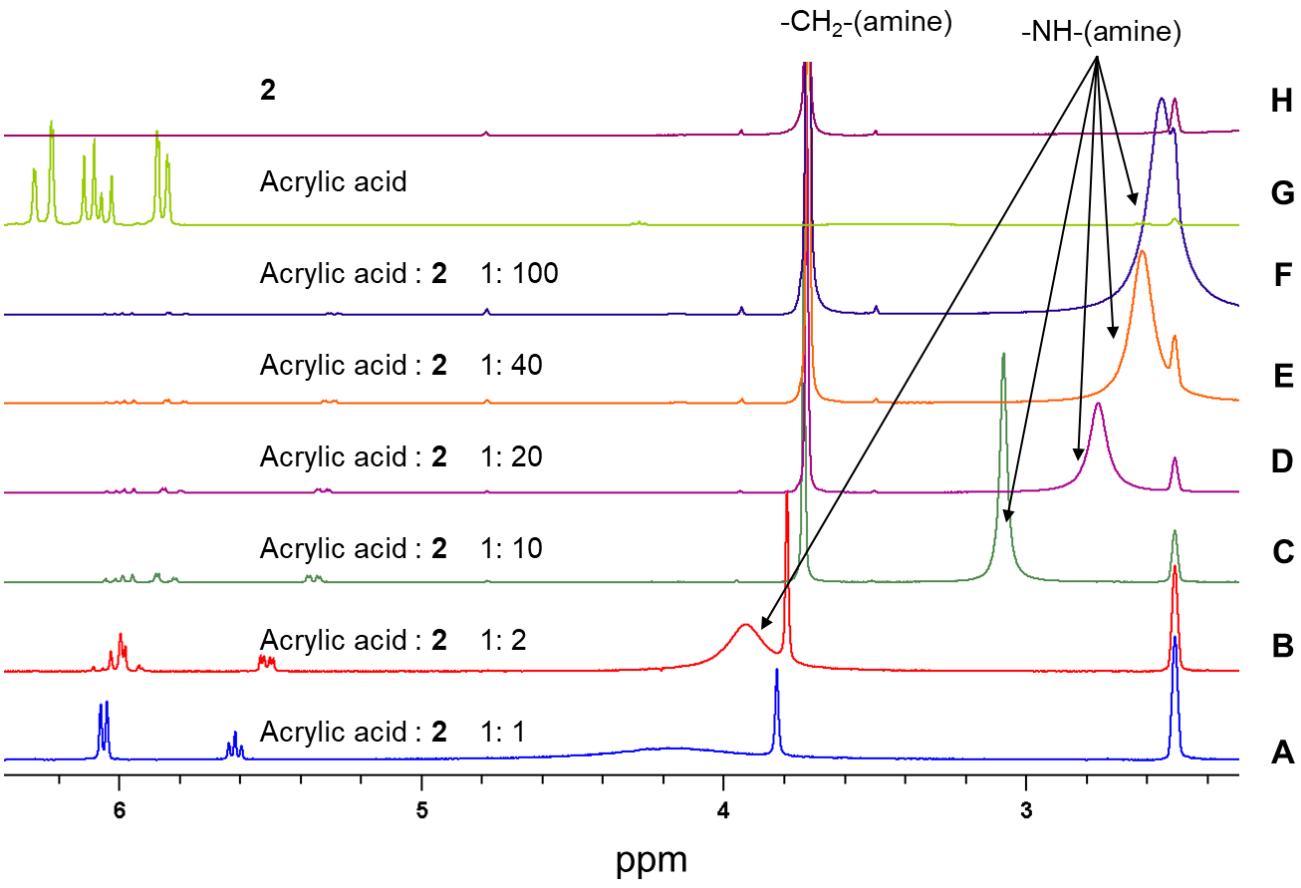


Figure S4. ^{1}H NMR of acrylic acid and **2** mixture. Acrylic acid (0.0075 mmol) plus 1 equiv. (A), 2 equiv. (B), 10 equiv. (C), 20 equiv. (D), 40 equiv. (E), 100 equiv. (F) of **2**. Acrylic acid (G). Pure **2** (H).

The addition of benzylamine resulted in NH_2 migration from 1.84 ppm to 4.17 ppm and benzylic CH_2 migration from 3.72 ppm to 3.83 ppm. Increasing amount of amine shifted the benzylic CH_2 signal back 3.72 ppm, similar to the pure amine.

General procedure C:

A 2-4 mL vial was charged with 450 µL DMSO-d_6, **Zr_{12}** (7.50 µmol, 27.0 mg) and magnetic stirring bar. The mixture was stirred at 80 °C for around 10 minutes until homogenization has been observed. Then, different amounts of benzylamine were added (see figure below), the solution was homogenized. An aliquot of ~ 500 µL was transferred to a NMR tube, and analyzed by ^{1}H NMR.

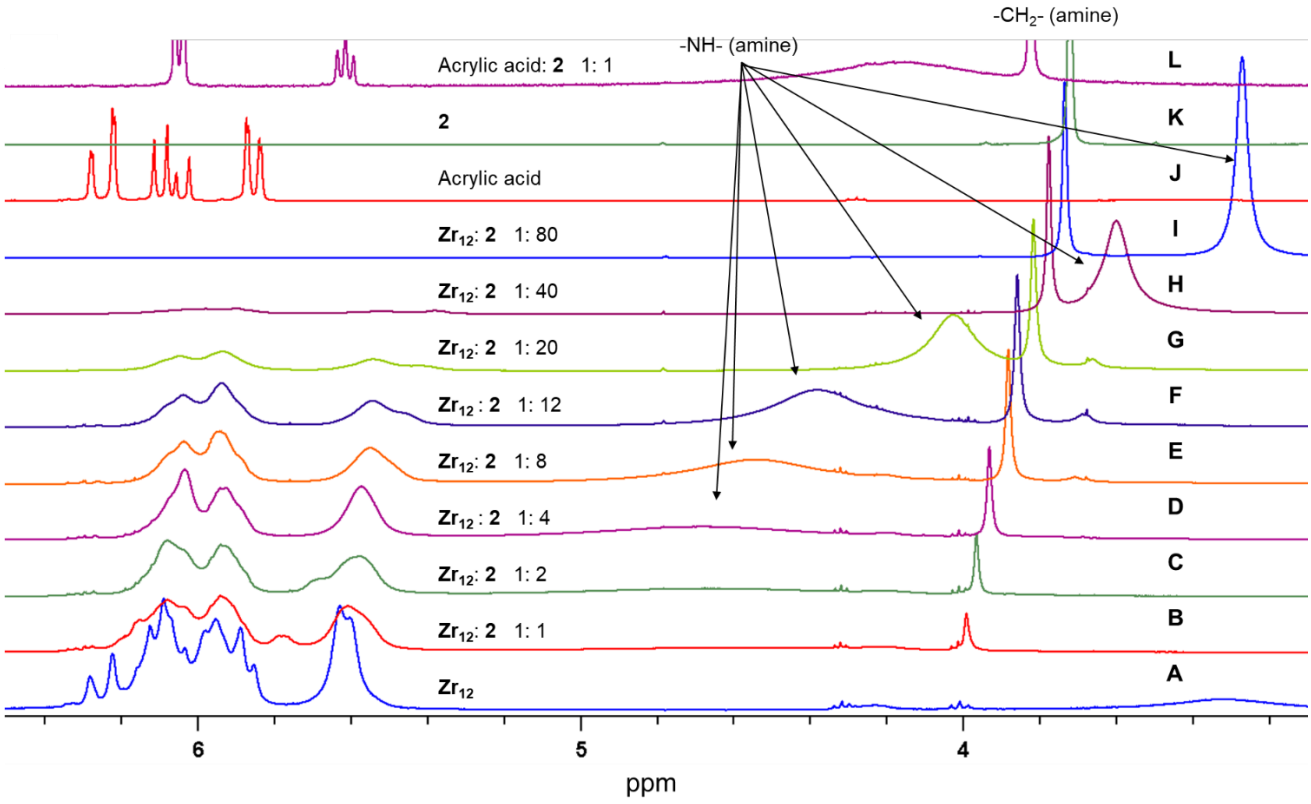


Figure S5. ^{1}H NMR of benzylamine **2** and **Zr_{12}** cluster when **2** was slowly added to the solution of **Zr_{12}** cluster. **Zr_{12}** at equivalent concentration to the standard reaction condition (A). Solution (A) plus 1 equiv. (B), 2 equiv. (C), 4 equiv. (D), 8 equiv. (E), 12 equiv. (F), 20 equiv. (G), 40 equiv. (H), 80 equiv. (I) of **2**. Acrylic acid (J). **2** (K). Mixture of acrylic acid and **2** with a ratio of 1:1 (L).

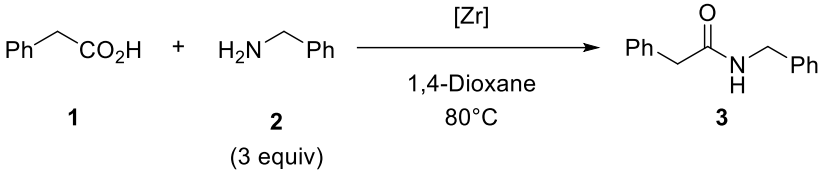
Control experiments

General Procedure D:

A 4 mL (1 dram) vial was charged with catalyst (2.5 – 30 µmol of Zr), phenylacetic acid (68.0 mg, 0.500 mmol), benzylamine (161 mg, 1.5 mmol), solvent (0.15 mL) and a magnetic stir bar. The reaction mixture was stirred 26 h at 80 °C. After cooling to room temperature, reaction yield was determined ^{1}H NMR. For ^{1}H NMR, the reaction mixture was diluted with $CDCl_3$ (1 mL), 3,5-bistrifluoromethyl-bromobenzene (1.0 equiv.) was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. Next, 50 µL of the crude mixture was transferred to a 1.5 mL centrifuge tube and diluted with 450 µL of $CDCl_3$. The final solution was centrifuged. The supernatant

(~500 µL) was transferred to an NMR tube and ^{1}H NMR was recorded. Results are reported based on ^{1}H NMR yields.

Table S1. Catalytic activity of different Zr-salts.



1 **2** (3 equiv) **3**

Entry	[Zr]	mol%	Yield of **3** (%)
1	Zr_{12}	0.5	94 (98)[a]
2	$ZrOCl_2 \cdot 8H_2O$	6	16
3	$Zr(OH)_4$	6	14
4	ZrO_2	6	13
5	$ZrCl_4$	6	17
6[a]	$Zr(O^nPr)_4$	6	98

Conditions: **1** (0.500 mmol), **2** (1.5 mmol), 0.5 mol% **Zr_{12}**, 1,4-dioxane (0.15 mL), 80 °C, 26 h. ^{1}H NMR yields. [a] 48 h.

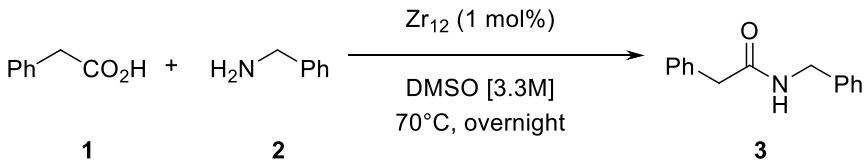
To probe for a potential disassembly of the cluster in up to 12 mononuclear zirconium complexes, we compared the catalytic activity of **Zr_{12}** with an equimolar amount of different zirconium salts (Table S9). Under the same conditions, several zirconium salts provided **3** in < 20% yield, indicating that conventional mono- and binuclear Zr complexes as previously proposed were not the catalytic active species in this case (entries 2-5).[3, 4] In contrast, $Zr(O^nPr)_4$ surprisingly catalyzed product **3** formation with a comparable efficiency to the **Zr_{12}** (entries 1 and 6). In this case, we hypothesized that a ZrOC might be forming *in situ*, similarly to previously suggested for titanium[5] and cerium[6] catalyzed reactions, since $Zr(O^nPr)_4$ is a common precursor for the synthesis of ZrOC, including the **Zr_{12}**.[7] However, more experiments beyond the scope of this work are needed to clarify this point. Overall, these results support **Zr_{12}** as the real catalytic species in the amide bond formation presented here, since both the stability of the hexazirconium oxo core unit, and the non-interconversion between a hexa and dodecazirconium oxo clusters have also been demonstrated previously.[2, 8]

Reaction optimization

General procedure E:

A 4 mL (1 dram) vial was charged with 0.5 – 2.5 µmol of **Zr_{12}** catalyst, phenylacetic acid (68.0 – 272 mg, 0.50 – 2.0 mmol), benzylamine (54.0 – 214 mg, 0.5-2.0 mmol), solvent (0.15 – 1.20 mL) and a magnetic stir bar. The reaction mixture was stirred overnight (16 – 24 h) at 60 – 110 °C. After cooling to room temperature, reaction yield was determined ^{1}H NMR. For ^{1}H NMR, the reaction mixture was diluted with $CDCl_3$ (1 mL), 3,5-bistrifluoromethyl-bromobenzene (1.0 equiv.) was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. Next, 50 µL of the crude mixture were transferred to a 1.5 mL centrifuge tube and diluted with 450 µL of $CDCl_3$. The final solution was centrifuged. The supernatant (~500 µL) was transferred to an NMR tube, and ^{1}H NMR was recorded. Results are reported based on ^{1}H NMR yields.

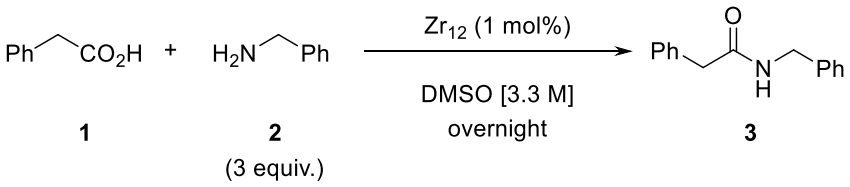
Table S2. Effect of the amount of benzylamine in the formation of product **3** in DMSO.



1 **2** **3**

Entry	**2** (equiv.)	Yield of **3** (%)
1	1	16
2	1.2	20
3	2	48
4	3	67
5	4	78

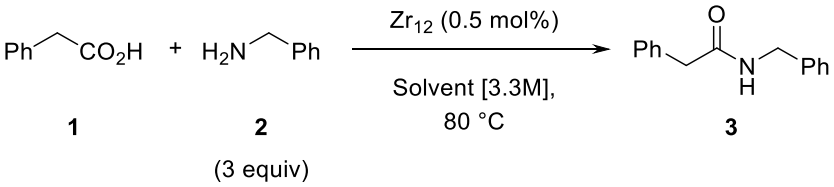
Table S3. Effect of temperature in the formation of product **3** in DMSO.



1 **2** (3 equiv.) **3**

Entry	T (°C)	Yield of **3** (%)
1	60	57
2	70	67
3	80	81
4	90	89
5	100	92
6	110	96

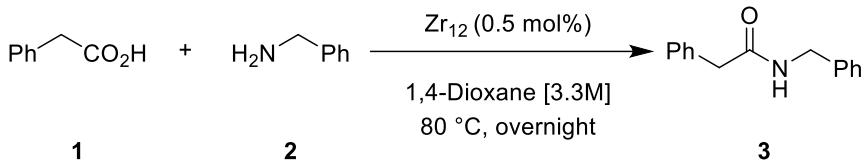
Table S4. Effect of solvent on the formation of product **3**.



1 **2** (3 equiv) **3**

Entry	Solvent	Yield of **3** (%)
1	Dimethyl sulfoxide	70
2	1,4-Dioxane	94
3	Acetonitrile	87
4	Acetone	31
5	Toluene	88
6	Ethanol	75
7	Diethyl ether	85
8	Tetrahydrofuran	83

Table S5. Effect of the amount of benzylamine in the formation of product **3** in 1,4-Dioxane.

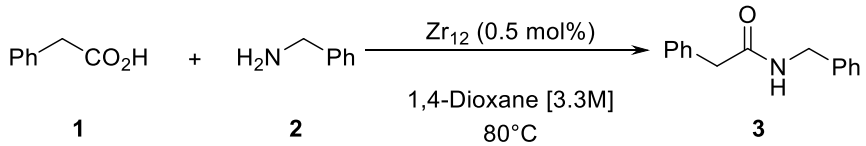


1 **2** **3**

Entry	**2** (equiv.)	Yield of **3** (%)
1	1.2	51
2	1.5	60
3	2	78
4[a]	2	95
5[a,b]	2	24
6	3	94
7	4	98

[a] 48 h. [b] No **Zr_{12}**.

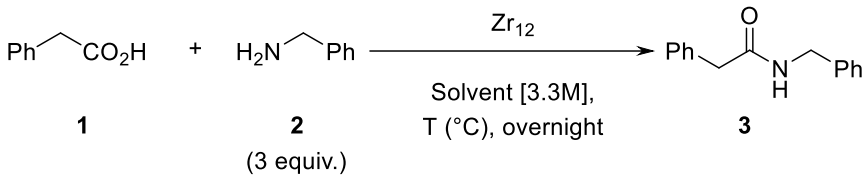
Table S6. Effect of the amount of phenylacetic acid in the formation of product **3** in 1,4-Dioxane.



1 **2** **3**

Entry	**1** (equiv.)	Yield of **3**(%)
1	0.8	51
2	1	42
3	1.2	32
4	1.6	29
5	2.5	25
6	3.3	20

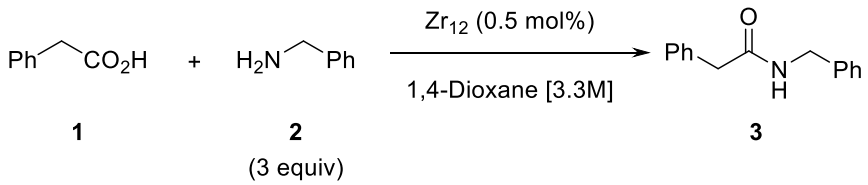
Table S7. Effect of catalyst loading on the yield of product **3**.



1 **2** (3 equiv.) **3**

		Yield of **3** (%)	
Entry	Cat (mol%)	DMSO, 90 °C	1,4-Dioxane, 80 °C
1	0.1	57	68
2	0.5	87	94
3	1	89	90
4	2	74	84
5	5	37	44

Table S8. Effect of temperature in the formation of product **3** in 1,4-dioxane.

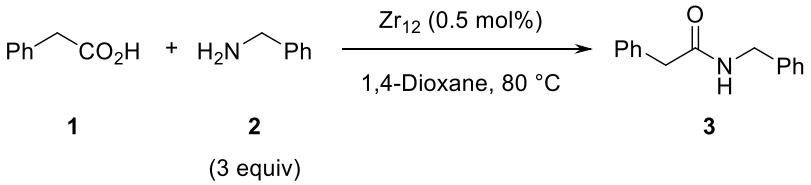


1 **2** (3 equiv) **3**

Entry	T (°C)	Cat (mol%)	Yield of **3** (%)
1	50	Zr_{12} (0.5)	38
2[a]	50	Zr_{12} (0.5)	99
3	50	---	0
4	60	Zr_{12} (0.5)	62
5	60	---	0
6	80	Zr_{12} (0.5)	94
7	80	---	9

[a] 0.1 g molecular sieves 4Å, 96 h .

Table S9. Effect of concentration in the formation of product of **3** in 1,4-dioxane.



1 **2** (3 equiv) **3**

Conc. (mol L^{-1})	0.42	0.83	1.67	3.33
Yield **3** (%)	64	81	86	94

Comparison Zr_{12} vs $ZrCl_4$

General procedure F:

A 4 mL (1 dram) vial was charged with catalyst (2.5 – 60 µmol of Zr source), phenylacetic acid (68.0 – 163 mg, 0.50 – 1.20 mmol), benzylamine (64.0 – 161 mg, 0.60 – 1.5 mmol), 1,4-dioxane (0.15 – 2.50 mL) and a magnetic stirring bar. The reaction mixture was stirred 24 h at 70 – 80 °C. After cooling to room temperature, reaction yield was determined by ^{1}H NMR. For ^{1}H NMR, the reaction mixture was diluted with $CDCl_3$ (1 mL), 3,5-bistrifluoromethyl-bromobenzene (1.0 equiv.) was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. Next, 50 µL of the crude mixture was transferred to a 1.5 mL centrifuge tube and diluted with 450 µL of $CDCl_3$. The final solution was centrifuged. The supernatant (~500 µL) was transferred to an NMR tube, and ^{1}H NMR was recorded. Results are reported based on ^{1}H NMR yields.

Zr_{12} recyclability

Catalyst recovery:

A 10 mL vial was charged with **Zr_{12}** (87 mg, 25 µmol), phenylacetic acid (680 mg, 5.00 mmol), benzylamine (1.61 g, 15 mmol), 1,4-dioxane (1.50 mL) and a magnetic stirring bar. The reaction mixture was stirred 24 h at 80 °C. After cooling to room temperature, the reaction was transferred to a 250 mL round-bottom flask, and volatiles were evaporated under reduced pressure, affording a white solid. This solid was washed with MeOH (3 x 15 mL), and the undissolved material was recovered through centrifugation. This solid was suspended in CH_2Cl_2, transferred to a 25 mL round-bottom flask, and the solvent was removed under reduced pressure. The solid was dried in high vacuum for 10 minutes, and used without further purification in the next experiments. The methanol fraction was evaporated, redissolved in CH_2Cl_2 (100 mL), and subsequently washed with HCl 1M (3 x 20 mL), $NaHCO_{3(sat)}$ (25 mL), and NaCl(sat) (25 mL). The organic phase was dried with $MgSO_4$, and removal of volatiles under reduced pressure afforded 1.07 g of amide **3** (95% yield).

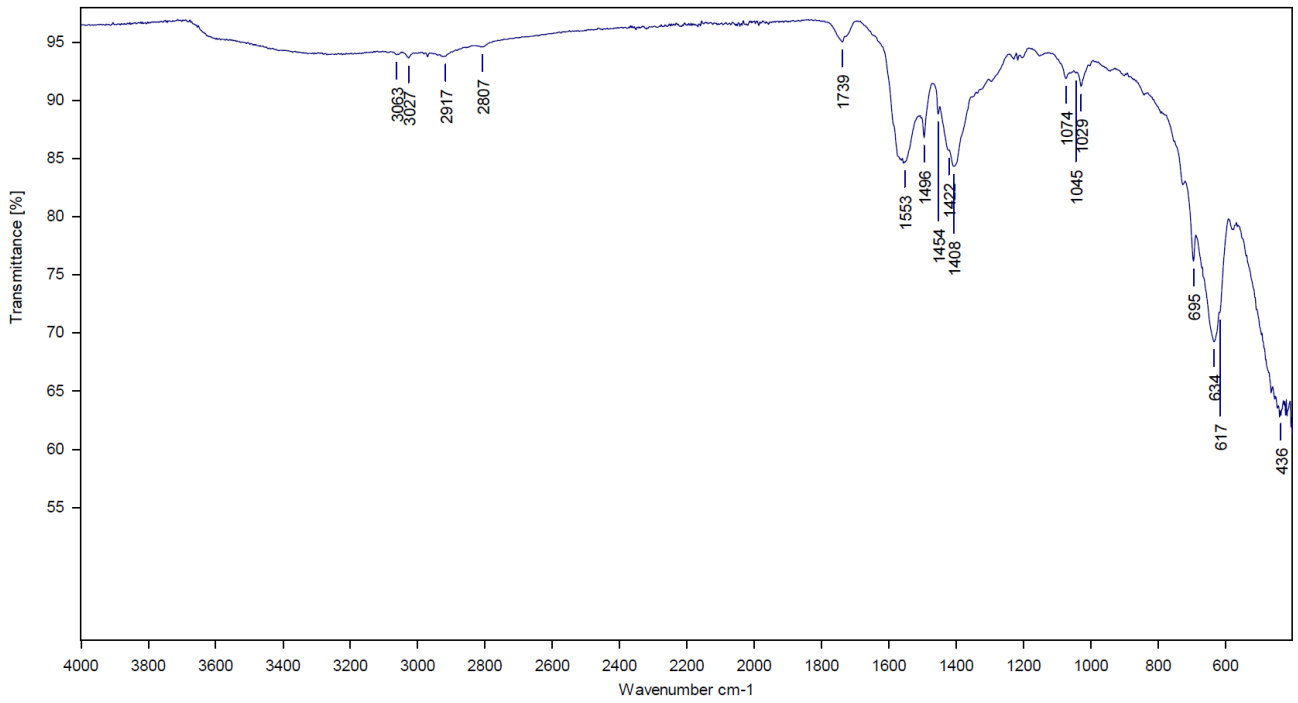


Figure S6. Infrared of **Zr_{12}** cluster as recovered from the reaction.

Catalyst re-use:

A 4 mL (1 dram) vial was charged with the solid recovered in the previous experiment (8.7 mg, ≈2.5 µmol), phenylacetic acid (68.0 mg, 0.500 mmol), 1,4-dioxane (0.15 mL) and a magnetic stir bar. Depending on the experiment, benzylamine (161 mg, 1.50 mmol) was added immediately after 1,4-dioxane, or only after stirring the reaction at 80 ℃ for 15 minutes. The reaction mixture was stirred at 80 °C for 24 h. After cooling to room temperature, reaction yield was determined ^{1}H NMR. For ^{1}H NMR, the reaction mixture was diluted with $CDCl_3$ (1 mL), 3,5-bistrifluoromethyl-bromobenzene (1 equiv.) was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. Next, 100 µL of the crude mixture was transferred to a 1.5 mL centrifuge tube and diluted with 500 µL of $CDCl_3$. The final solution was centrifuged. The supernatant (~500 µL) was transferred to an NMR tube, and ^{1}H NMR was recorded. Results are reported based on ^{1}H NMR yields.

Treatment of recovered solid with an excess of acrylic acid:

A 4 mL (1 dram) vial was charged with the solid recovered in the previous experiment (30 mg, ≈8.5 µmol), 1,4-dioxane (1.00 mL) and a magnetic stir bar. Next, acrylic acid (77 µL, 1.12 mmol) was added, and the suspension was stirred overnight at 80 ℃. After cooling to room temperature, the solid was recovered by centrifugation, suspended in CH_2Cl_2, transferred to a 25 mL round-bottom flask and dried under reduced pressure to afford 27 mg of a white solid, whose infrared analysis confirmed to be the **Zr_{12}** cluster.

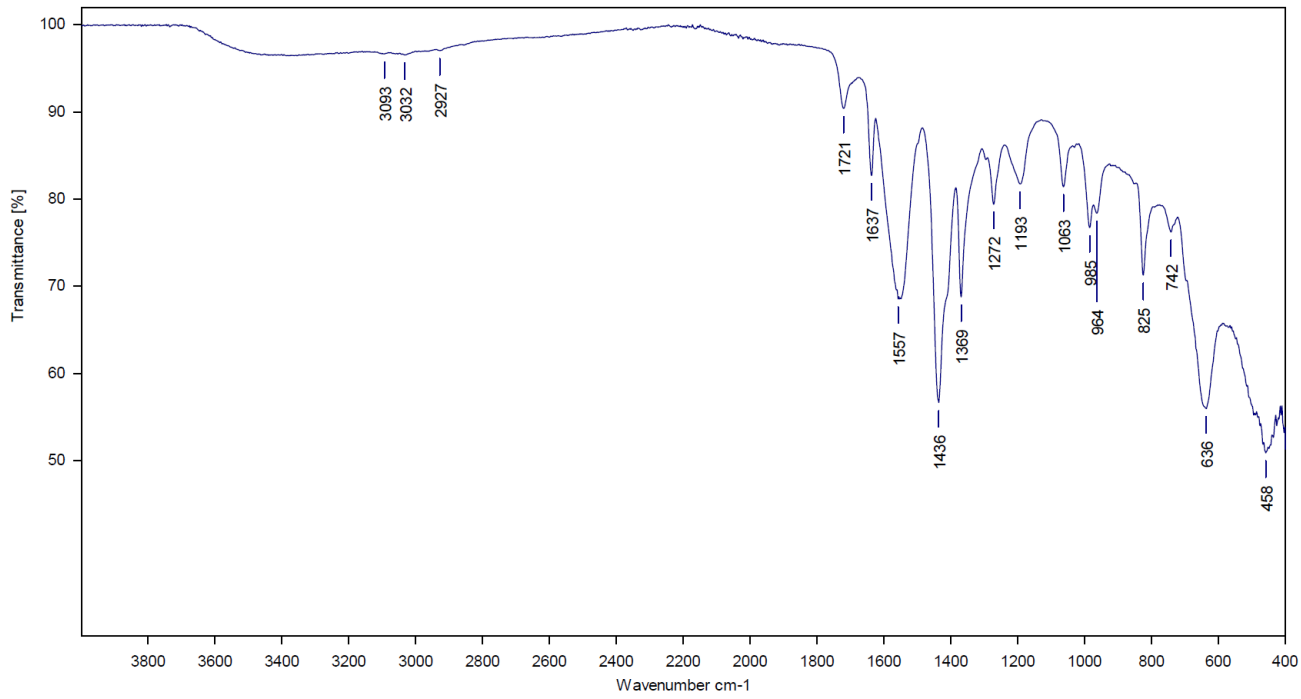


Figure S7. Infrared of recovered **Zr_{12}** cluster after treating it with an excess of acrylic acid.

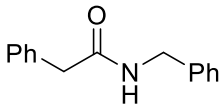
Experimental details of products in Table 3

General Procedure G:

A 4 mL (1 dram) vial was charged with **Zr_{12}** cluster (8.7 – 35 mg, 2.5 – 10 µmol), phenylacetic acid (68.0 mg, 0.500 mmol), benzylamine (161 mg, 1.50 mmol), solvent (0.15 mL) and a magnetic stir bar. The reaction mixture was stirred overnight (24 – 26 h) at 80 – 120 °C. After cooling to room temperature, reaction yield was determined ^{1}H NMR. For ^{1}H NMR, the reaction mixture was diluted with $CDCl_3$ (1 mL), 3,5-bistrifluoromethyl-bromobenzene (1 equiv.) was added as an internal standard, and the reaction mixture was stirred at room temperature for 10 minutes to ensure thorough mixing. Next, 50 µL of the crude mixture was transferred to a 1.5 mL centrifuge tube and diluted with 450 µL of $CDCl_3$. The final solution was centrifuged. The supernatant (~500 µL) was transferred to an NMR tube, and ^{1}H NMR was recorded. Results are reported based on ^{1}H NMR yields.

For the isolated yields reported, reactions were isolated and purified as follows: 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 (3×15 mL) and $NaCl_{(sat)}$ (15 mL). Next, the organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography in silica gel using mixtures of pentane/ethyl acetate (70:30 – 30:70 v/v).

***N*-benzyl-2-phenylacetamide (3)**

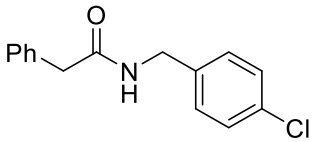


General procedure G was followed using **Zr_{12}** cluster (2.5 µmol, 9.0 mg), phenylacetic acid (68.0 mg, 0.500 mmol), benzylamine (161 mg, 1.50 mmol), 1,4-Dioxane (0.15 mL) and a magnetic stir bar. The reaction was stirred at 80 °C for 20 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 94% yield.[9]

Gram-scale reaction – 20 mmol: A 100 mL round-bottom flask was charged with **Zr_{12}** (0.36 g, 0.03 mmol), phenylacetic acid (2.80 g, 20.6 mmol), 1,4-Dioxane (6.2 mL) and a magnetic stir bar. Next, benzylamine (6.61 g, 61.8 mmol) was added dropwise. The reaction mixture was stirred for 24 h at 80 °C. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (~250 mL), and washed with HCl 1M (50 x 2 mL), $NaHCO_3$(sat) (50 x 2 mL), H_2O (150 x 2 mL) and NaCl(sat) (50 x 2 mL). Next, the organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford 4.23 g (91%) of the desired amide product as a white solid.

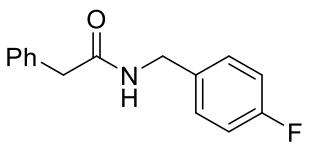
Gram-scale reaction – 50 mmol: A 100 mL round-bottom flask equipped with a reflux condenser was charged with **Zr_{12}** (0.87 g, 0.25 mmol), phenylacetic acid (6.80 g, 50.0 mmol), 1,4-Dioxane (15 mL) and a magnetic stir bar. Next, benzylamine (16.07 g, 150.0 mmol) was added dropwise. The reaction mixture was stirred for 28 h at 80 °C. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (~250 mL), and washed with HCl 1M (150 x 2 mL), $NaHCO_3$(sat) (150 mL), H_2O (100 x 3 mL) and NaCl(sat) (50 x 2 mL). Next, the organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford 9.34 g (83%) of the desired amide product as a white solid.

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



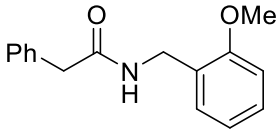
General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), phenylacetic acid (68.0 mg, 0.500 mmol), 4-chlorobenzylamine (0.21 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard showed the product formation in 97% yield. Purification by column chromatography (EtOAc/pentane 50:50 v/v) afforded 117 mg (90%) of the product. Spectroscopic data agreed with the previous report.[10]

***N*-[(4-florophenyl)methyl]-2-phenylacetamide (7)**



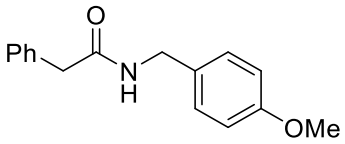
General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), phenylacetic acid (68.0 mg, 0.500 mmol), 4-florobenzylamine (0.19 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 71% yield.[11]

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



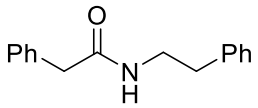
General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), phenylacetic acid (68.0 mg, 0.500 mmol), 2-methoxybenzylamine (0.21 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard showed the product formation in 88% yield. An identical reaction conducted using only 2.5 µmol **Zr_{12}** cluster at 90 °C for 22 h showed the product formation in 88% yield. Purification by column chromatography (EtOAc/pentane 70:30 v/v) afforded 112 mg (87%) of the product. Spectroscopic data agreed with the previous report.[12]

***N*-[(4-methoxyphenyl)methyl]-2-phenylacetamide (9)**



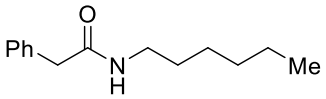
General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), phenylacetic acid (68.0 mg, 0.500 mmol), 4-methoxybenzylamine (0.21 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene, and comparison with previous spectral description, as internal standard showed the product formation in 99% yield.[13]

***N*-Phenethyl-2-phenylacetamide (10)**



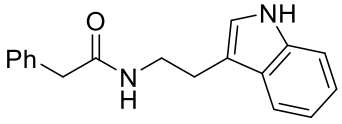
General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), phenylacetic acid (68.0 mg, 0.500 mmol), 2-Phenethylamine (0.18 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 95 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 91% yield.[14]

***N*-hexyl-2-phenylacetamide (11)**



General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), phenylacetic acid (68.0 mg, 0.500 mmol), n-hexylamine (0.15 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 68% yield.[15]

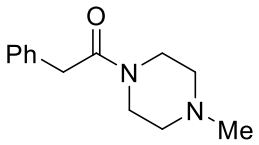
***N*-(2-(1H-Indol-3-yl)ethyl)-2-phenylacetamide (12)**



General procedure G was followed using **Zr_{12}** cluster (10.0 µmol, 34.8 mg), phenylacetic acid (68.0 mg, 0.500 mmol), tryptamine (0.24 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 95 °C for 24 h. Analysis

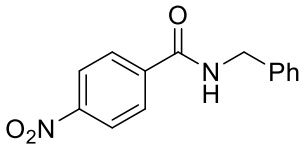
by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 75% yield.[12]

N-Methyl-N′-phenylacetylpiperazine (13)



General procedure G was followed using **Zr_{12}** cluster (10.0 µmol, 34.8 mg), phenylacetic acid (68.0 mg, 0.500 mmol), 1- methylpiperazine (0.15 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 95 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 48% yield.[12]

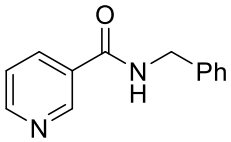
***N*-benzyl-4-nitrobenzamide (14)**



General procedure G was followed using **Zr_{12}** cluster (10.0 µmol, 34.8 mg), 4-nitrobenzoic acid (84.0 mg, 0.500 mmol), benzylamine (0.16 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 95 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard showed the product formation in 50% yield. An identical reaction conducted using only 2.5 µmol **Zr_{12}** cluster at 101 °C for 24 h showed the product formation in 39% yield. Purification by column chromatography (EtOAc/pentane 30:70 v/v) afforded 49 mg (38%) of the product. Spectroscopic data agreed with the previous report.[9]

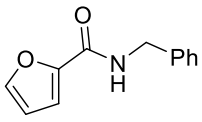
Reaction conducted at 120 °C was done, and analyzed following the same procedure. Analysis by ^{1}H NMR showed the product formation in 86% yield.

***N*-benzylnicotinamide (15)**



General procedure G was followed using **Zr_{12}** cluster (10.0 µmol, 34.8 mg), 4-nicotinic acid (62.0 mg, 0.500 mmol), benzylamine (0.16 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 95 °C for 28 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 45% yield.[16]

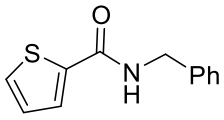
***N*-benzylfuran-2-carboxamide (16)**



General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), 2-furoic acid (56.0 mg, 0.500 mmol), benzylamine (0.16 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard showed the product formation in 76% yield. An identical reaction conducted using only 2.5 µmol **Zr_{12}** cluster at 80 °C for 23 h showed the product formation in 65% yield.

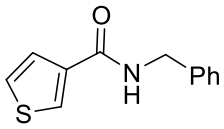
Purification by column chromatography (EtOAc/pentane 30:70 v/v) afforded 67 mg (67%) of the product. Spectroscopic data agreed with the previous report.[17]

N-benzylthiophene-2-carboxamide (17)



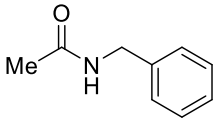
General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), 2-thiophenecarboxylic acid (64.0 mg, 0.500 mmol), benzylamine (0.16 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 95 °C for 28 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard showed the product formation in 57% yield.[16]

N-benzylthiophene-3-carboxamide (18)



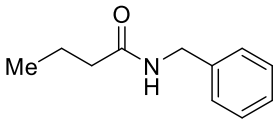
General procedure G was followed using **Zr_{12}** cluster (5.0 µmol, 17.4 mg), 3-thiophenecarboxylic acid (64.0 mg, 0.500 mmol), benzylamine (0.16 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 95 °C for 28 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard showed the product formation in 50% yield. Purification by chromatography (EtOAc/pentane 30:70 v/v) afforded 61 mg (55%) of the product. Spectroscopic data agreed with the previous report.[18]

N-benzylacetamide (19)



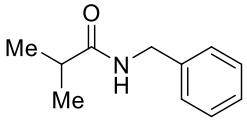
General procedure G was followed using **Zr_{12}** cluster (2.5 µmol, 9.0 mg), acetic acid (30 mg, 0.500 mmol), benzylamine (0.16 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 67% yield.[19]

N-benzylbutyramide (20)



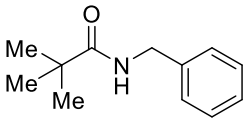
General procedure G was followed using **Zr_{12}** cluster (2.5 µmol, 9.0 mg), butyric acid (44 mg, 0.500 mmol), benzylamine (0.16 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 57% yield.[20]

_N_-benzylisobutyramide (21)



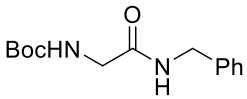
General procedure G was followed using **Zr_{12}** cluster (2.5 µmol, 9.0 mg), iso butyric acid (44 mg, 0.500 mmol), benzylamine (0.16 g, 1.50 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 24 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 53% yield.[21]

_N_-benzyl-2,2-dimethylpropanamide (22)



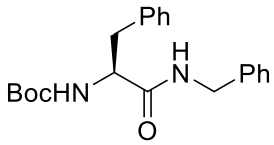
General procedure G was followed using **Zr_{12}** cluster (2.5 µmol, 9.0 mg), pivalic acid (51 mg, 0.500 mmol), benzylamine (0.16 g, 1.5 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 26 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 15% yield.[21]

***tert*-Butyl (2-(benzylamino)-2-oxoethyl)carbamate (23)**



General procedure G was followed using **Zr_{12}** cluster (2.5 µmol, 9.0 mg), N-(tert-Butoxycarbonyl)glycine (88 mg, 0.500 mmol), benzylamine (0.16 g, 1.5 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 26 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 90% yield.[22]

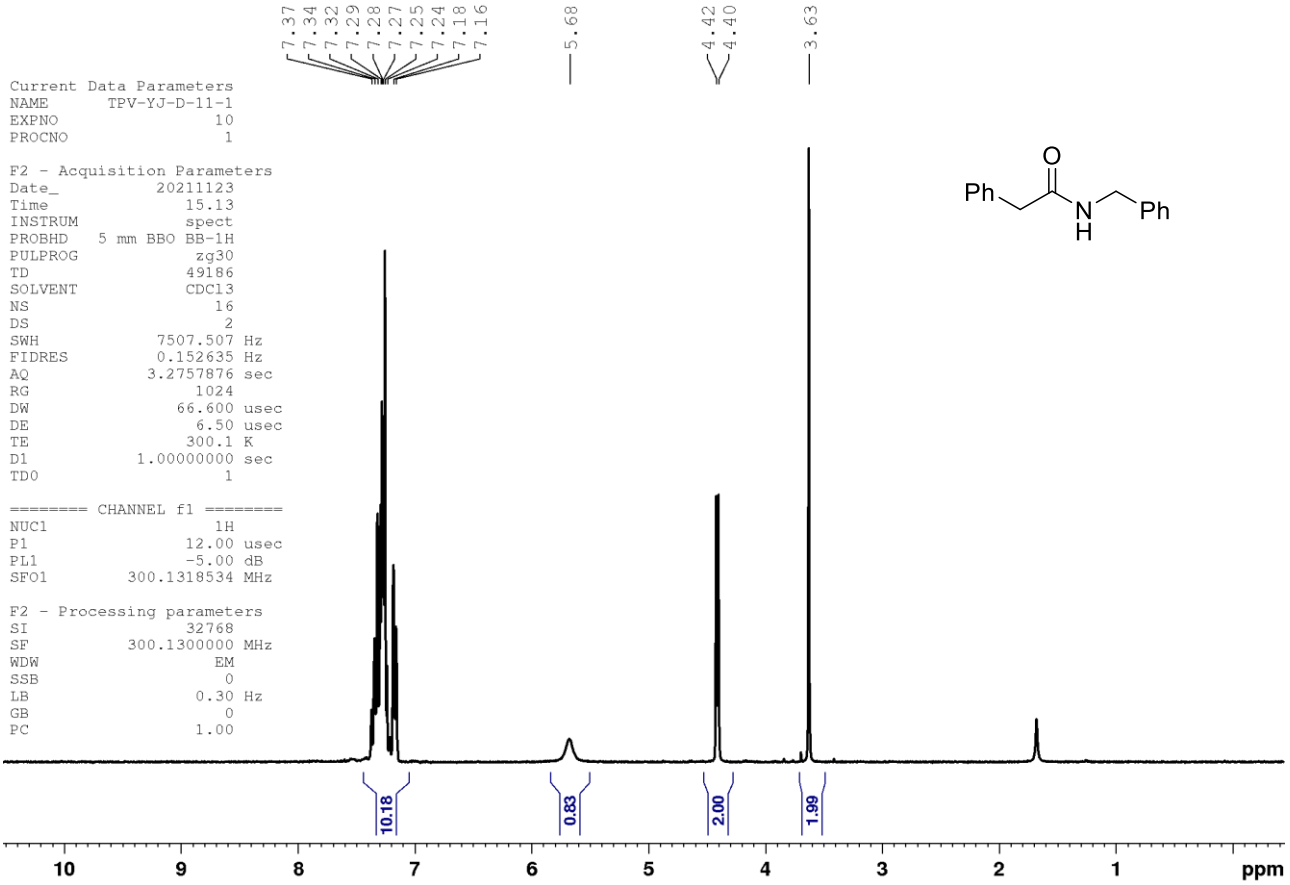
***tert*-butyl N-[(1S)-1-(benzylcarbamoyl)-2-phenylethyl]carbamate (24)**



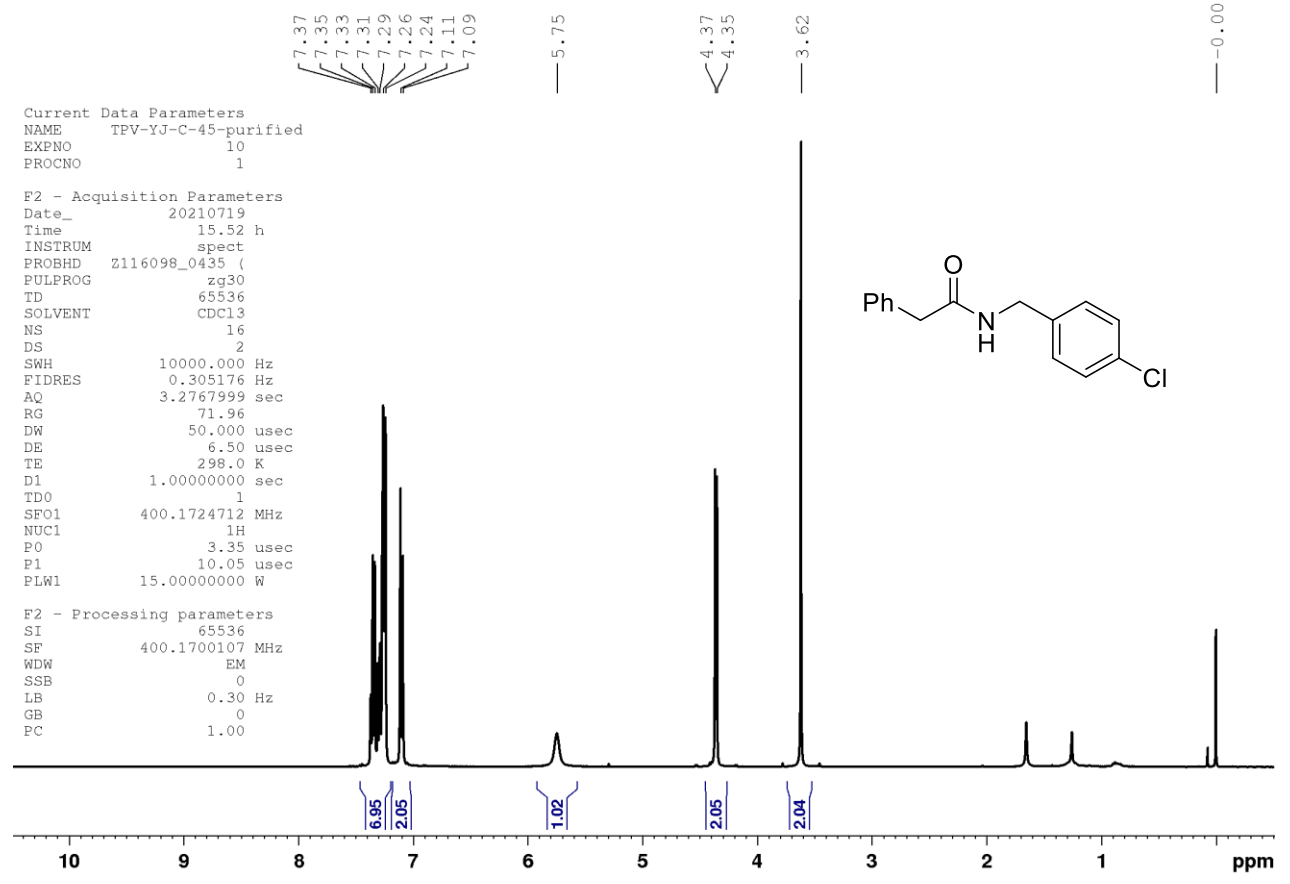
General procedure G was followed using Zr_{12} cluster (2.5 µmol, 9.0 mg), N-(tert-Butoxycarbonyl)-L-phenylalanine (133 mg, 0.500 mmol), benzylamine (0.16 g, 1.5 mmol), 1,4-Dioxane (0.15 mL). The reaction was stirred at 80 °C for 26 h. Analysis by ^{1}H NMR with 3,5-bistrifluoromethyl-bromobenzene as internal standard, and comparison with previous spectral description, showed the product formation in 31% yield.[23]

NMR spectra

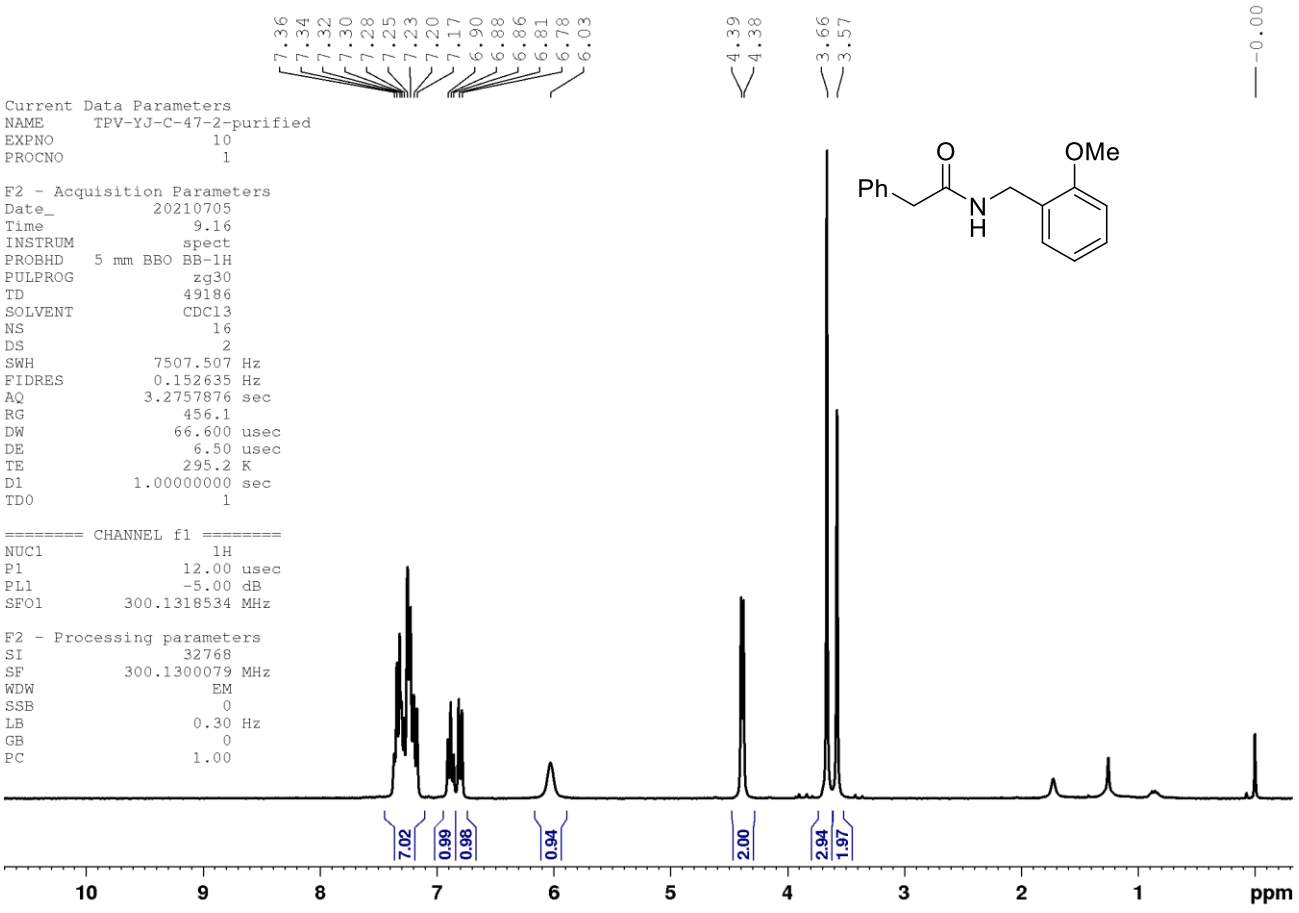
N-benzyl-2-phenylacetamide (3)



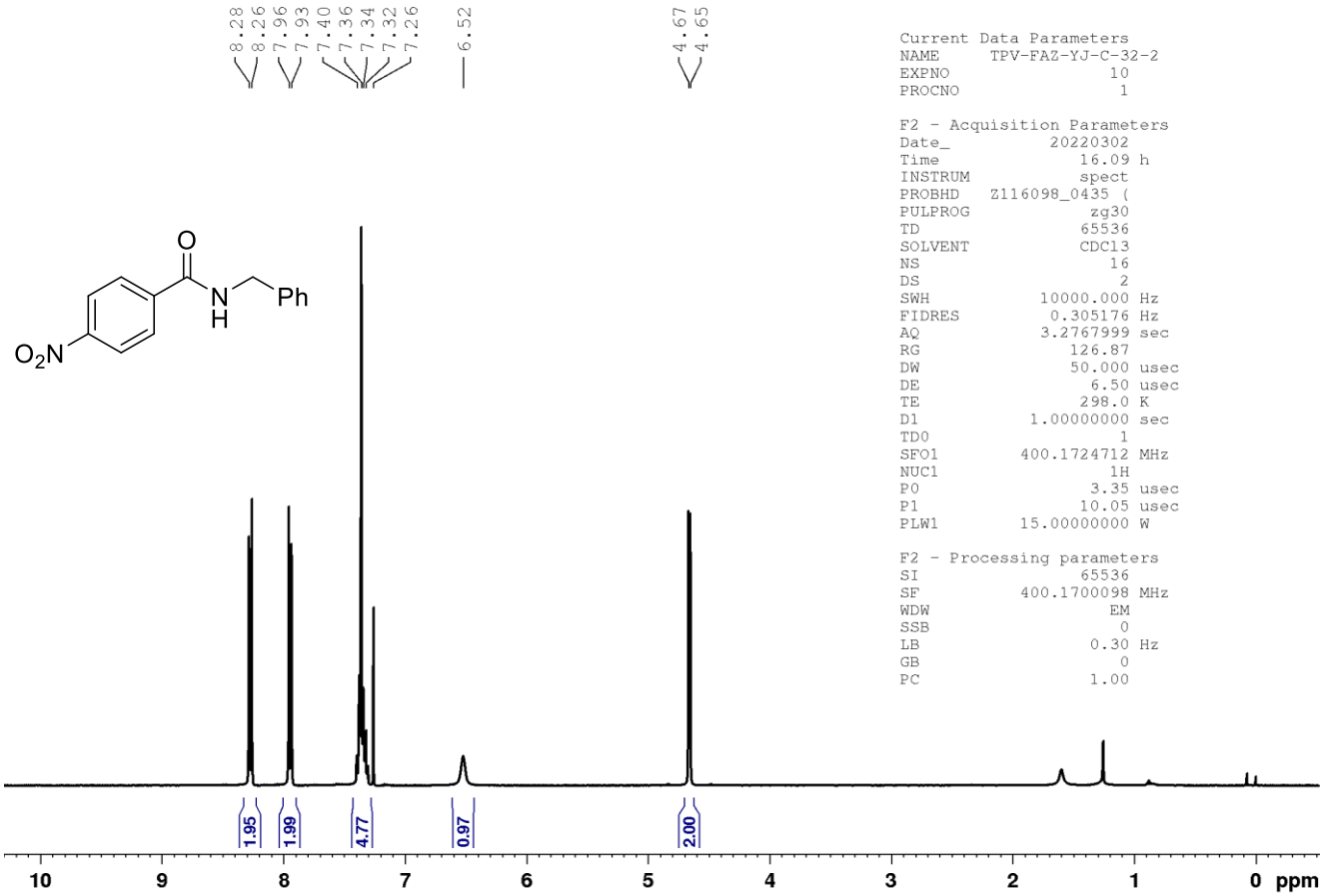
N-[(4-chlorophenyl)methyl]-2-phenylacetamide (6)



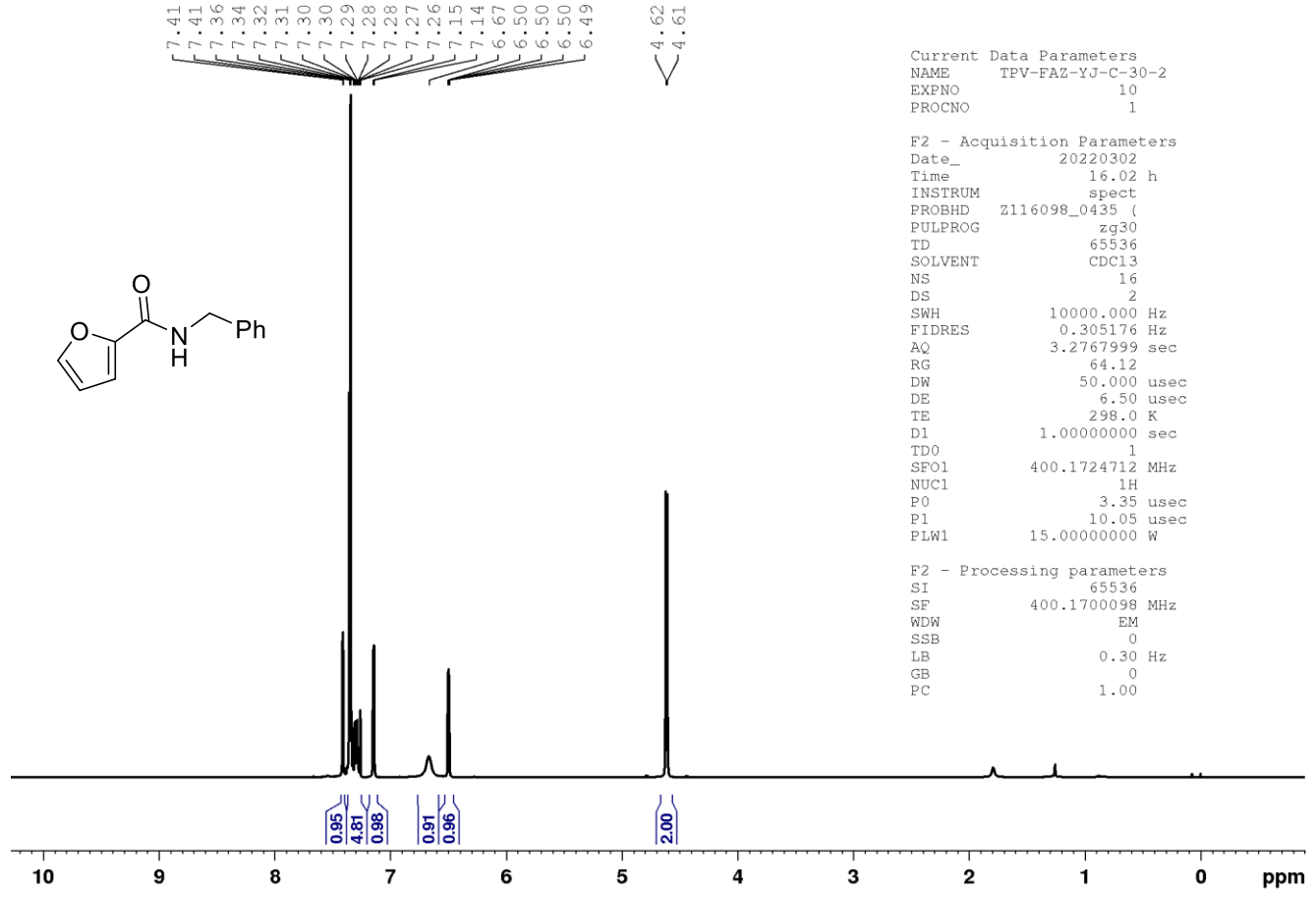
N-[(2-methoxyphenyl)methyl]-2-phenylacetamide (8)



N-benzyl-4-nitrobenzamide (14)



N-benzylfuran-2-carboxamide (16)

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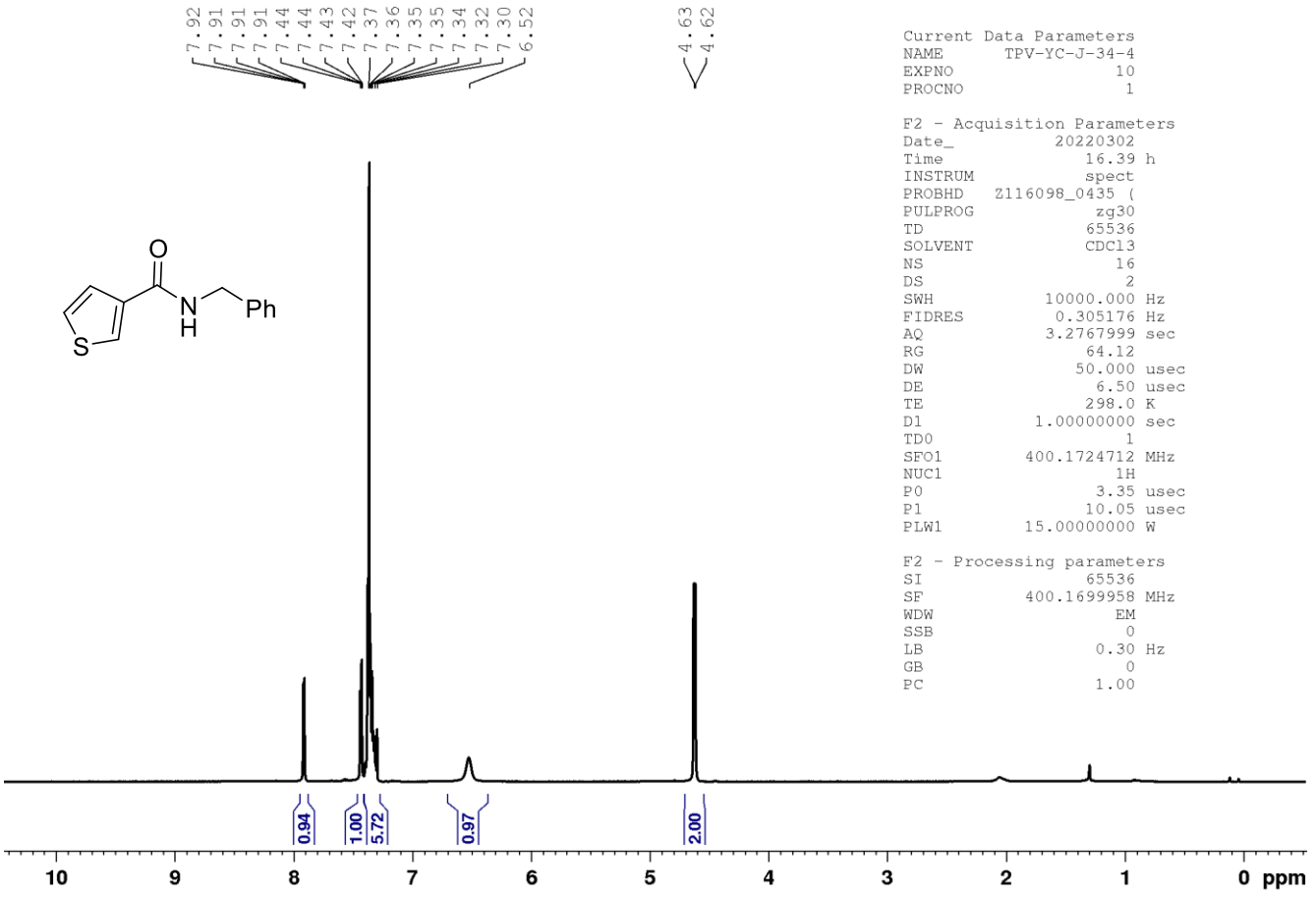
N-benzylthiophene-3-carboxamide (18)

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