SUPPORTING INFORMATION.

One pot synthesis of cyclohexanone oxime from nitrobenzene with a bifunctional catalyst

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1. Experimental section

General

Reinforced glass reactors were dried in an oven at 175 ^{0}C before use and the ducts of the micro-reactor were cleaned with hexane. Reagents and solvents were obtained from commercial sources and were used without further purification otherwise indicated.

All the products obtained were characterized by GC-MS, ^{1}H- and ^{13}C-NMR, and DEPT. When available, the characterization given in the literature was used for comparison. Gas chromatographic analyses were performed in an instrument equipped with a 25 m capillary column of 5% phenylmethylsilicone. Dodecane was used as an external standard. GC-MS analyses were performed on a spectrometer equipped with the same column as the GC and operated under the same conditions. Column chromatography and TLC were performed over SiO_2. ^{1}H, ^{13}C and DEPT were recorded in a 300 MHz instrument using C_3OD_6 as solvent, containing TMS as internal standard. IR spectra of the compounds were recorded on a spectrophotometer as self-supported wafers or by impregnating the windows with a dichloromethane solution of the compound and leaving to evaporate before analysis.

Synthesis of the catalysts:

Supported catalysts were prepared[1] by the incipient wetness method on commercial charcoal (Norit GSX, steam activated, washed acid). The corresponding amount of each metal was dissolved in 1.6 ml of ethanol or water and added dropwise in 1 g of carbon black. Impregnated powders were left overnight in a muffle at 60 ˚C and then calcined under an atmosphere composed by 10% H_2 and 90% N_2 at 360 ˚C for 1 hour. [2]

Au/C and Au/Ce_2O_3 were prepared as previously reported.[3] Pd/C, Ru/C, Rh/C and all the homogeneous Lewis acids tested are commercially available. AuPd/C was commercially available or made following the impregnation procedure with sodium aurothiomalate.

Reaction procedures

Reaction was performed in reinforced glass reactors equipped with a temperature and pressure control.

*Typical reaction procedure for the synthesis of cyclohexanone oxime **2** in semi-continuous pressure from nitrobenzene **1**:*

Pd/C (5 wt%, 21.2 mg, 0.01 mmol of Pd) and Au/C (2 wt%, 25 mg, 0.005 mmol of Au) were placed into the reactor (2 ml capacity) equipped with a magnetic stirrer. Diethyl ether (0.5 ml), nitrobenzene **1** (21 μl, 0.2 mmol) and $NH_2OH{\cdot}HCl$ (67 mg, 1 mmol) were added, and after the micro-reactor was sealed, air was purged by flushing out four times with hydrogen and then pressurized with H_2 (~5 bar). The resulting mixture was magnetically stirred for 4 h in dynamic pressure. During the experiment, the hydrogen pressure was maintained constant by connecting the micro-reactor to a hydrogen dispenser (semi-continuous, dynamic pressure). The product composition was determined by means of gas chromatography, once the catalyst particles were removed from the solution by filtration. The products were identified by gas chromatography/mass spectrometry (GC-MS) and also by ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR). If desired, the reaction mixture is concentrated under reduced pressure and re-dissolved in dichloromethane in order to separate the oxime of the ammonium salts by filtering the solution trough a pad of celite and silica, and concentrating again under reduced pressure, to obtain 20.8 mg, 0.18 mmol (92% isolated yield) of oxime.

*Typical reaction procedure for the synthesis of cyclohexanone oxime **2** in static pressure from nitrobenzene **1**:*

Pd/C (5 wt%, 21.2 mg, 0.01 mmol of Pd) and Au/C (2 wt%, 50 mg, 0.005 mmol of Au) in diethyl ether (0.5 ml) were placed into the reactor (2 ml capacity) equipped with a magnetic stirrer. Diethyl ether (0.5 ml), nitrobenzene **1** (23 μl, 0.2 mmol) and $NH_2OH{\cdot}HCl$ (67 mg, 1 mmol) were added, and after the micro-reactor was sealed, air was purged by flushing out four times with hydrogen and then pressurized with 6 equivalents of H_2 (~10 bar). The resulting mixture was magnetically stirred overnight at 60 ºC. During the experiment, the hydrogen decreased as the reaction evolves. The product composition was determined by means of gas chromatography, once the catalyst particles were removed from the solution by filtration. The products were identified by gas chromatography/mass spectrometry (GC-MS) and also by ^{1}H and ^{13}C NMR.

*Typical reaction procedure for the synthesis of the secondary amines cyclohexylaniline **4** and dicyclohexylamine **5** from nitrobenzene **1**:*

Pd/C (5 wt%, 21.2 mg, 0.01 mmol of Pd) and hexane (0.5 ml) were placed into the reactor (2 ml capacity) equipped with a magnetic stirrer. Nitrobenzene **1** (21 µl, 0.2 mmol) was added, and after the micro-reactor was sealed, air was purged by flushing out four times with hydrogen and then pressurized with 6 equivalents of H_2 (~10 bar). The resulting mixture was magnetically stirred overnight in static pressure at 60 ºC. During the experiment, the hydrogen pressure was decreased as the reaction evolves. The product composition was determined by means of gas chromatography, once the catalyst particles were removed from the solution by filtration. The products were identified by gas chromatography/mass spectrometry (GC-MS) and also by ^{1}H and ^{13}C NMR.

*Typical reaction procedure for the synthesis of N-cyclohexylideneaniline **8**[4]:*

A mixture of cyclohexanone **9** (30 mmol, 3 ml) and aniline **3** (30 mmol, 2.7 ml) in dry toluene (30 ml) was warmed to 120 ºC in flask equipped with a Dean-Stark apparatus. Then *p*-toluenesulfonyl acid (0.3 mmol, 0.052 g) was added to the mixture and was keep at 120 ºC until complete disappearance of the starting materials (GC-MS monitoring). The mixture was allowed to reach room temperature, taken up in hexanes (20 ml), and filtered through Celite. The solvents were evaporated under reduced pressure. Purification was performed by Kugelrohr distillation under high vacuum.

*Typical reaction procedure for the study of metal-supported solids (Table S1) in the synthesis of cyclohexanone oxime **2** from nitrobenzene **1**:*

Pd/C (5 wt%, 21.2 mg, 0.01 mmol of Pd) and the corresponding metal (0.005 mmol of metal) in diethyl ether (0.5 ml) were placed into the reactor (2 ml capacity) equipped with a magnetic stirrer. Nitrobenzene **1** (23 µl, 0.2 mmol) and $NH_2OH{\cdot}HCl$ (67 mg, 1 mmol) were added, and after the micro-reactor was sealed, air was purged by flushing out four times with hydrogen and then pressurized with H_2 (~5 bar). The resulting mixture was magnetically stirred 4 h at 60 ºC. During the experiment, the hydrogen pressure was maintained constant by connecting the micro-reactor to a hydrogen dispenser. The product composition was determined by means of gas chromatography, once the catalyst particles were removed from the solution by filtration. The products were identified by gas chromatography/mass spectrometry (GC-MS) and also by ^1H and ^{13}C NMR.

Scaling-up of the reaction:

Scaling-up of the reaction was carried out in an autoclave engineer magnedrive III, with a temperature and pressure control. Pd/C (5 wt%, 5 mmol of Pd) and Au/C (2 wt%, 2.5 mmol of Au) were placed into the reactor (30 ml capacity) equipped with a stirrer. Diethyl ether (20 ml), nitrobenzene **1** (1.05 ml, 10 mmol) and $NH_2OH{\cdot}HCl$ (2 g, 29 mmol) were added, and after the reactor was sealed, air was purged by flushing out four times with hydrogen and then pressurized with H_2 (~5 bar). The resulting mixture was stirred for 1 h in dynamic pressure. During the experiment, the hydrogen pressure was maintained constant by connecting the reactor to a hydrogen dispenser (semi-continuous, dynamic pressure). The product composition was determined by means of gas chromatography, once the catalyst particles were removed from the solution by filtration. Then, the reaction mixture was concentrated under reduced pressure and re-dissolved in dichloromethane in order to separate the oxime of the ammonium salts by filtering the solution trough a pad of celite and silica, and concentrating again under reduced pressure, to obtain 949 mg, 8.4 mmol (84% isolated yield) of cyclohexanone oxime. The product was characterized by ^1H and ^{13}C NMR, and DEPT. Note that this reactor can lose about 10% of product due to the depressurization process.

2. References

[1] S.-Y. Huang, S.-M. Chang, C. –T. Yeh, *J. Phys. Chem B* **2005**, *110*, 234.

[2] M. T. Reetz, M. Maase, *Adv. Mat.* **1999**, *11*, 773.

[3] A. Abad, P. Concepción, A. Corma, H. García, *Angew. Chem. Int. Ed.* **2005**, *44*, 4066.

[4] J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.* **2009**, *131*, 4031.

3. Figures

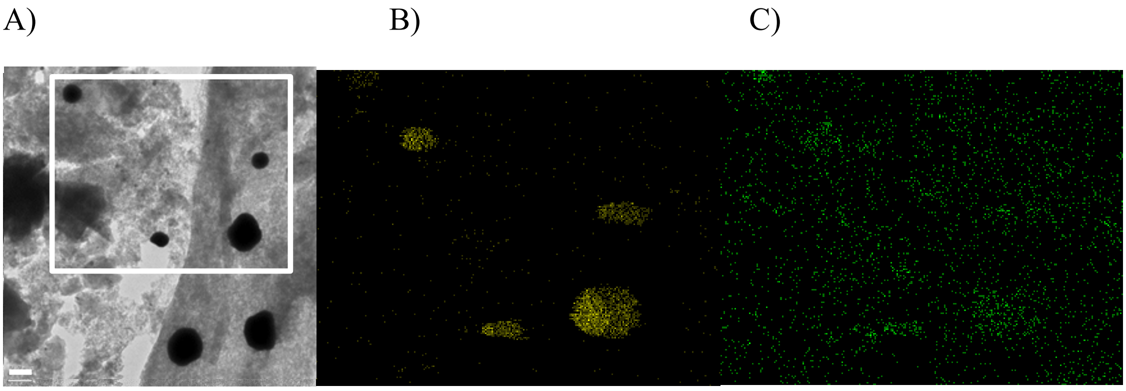
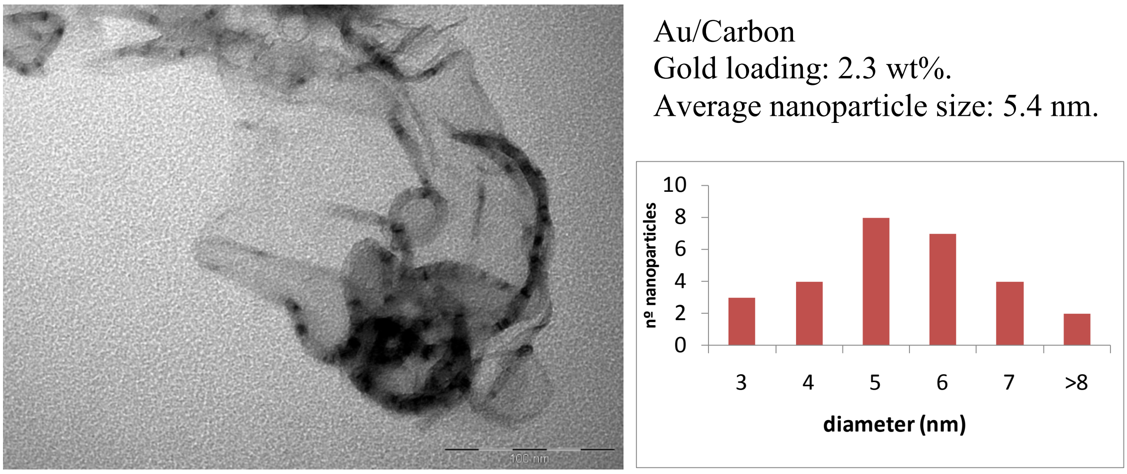


Figure S1. A) High Resolution Transmission Electron Microscopy (HR-TEM) of AuPd/C. B) Mapping of Au on AuPd/C. C) Mapping of Pd on AuPd/C. White bar represents 200 nm and the square the mapped area.



Au/Carbon
Gold loading: 2.3 wt%.
Average nanoparticle size: 5.4 nm.

Figure S2. Representative Transmission Electron Microscopy (TEM) image and Particle Size Distribution of Au/C.

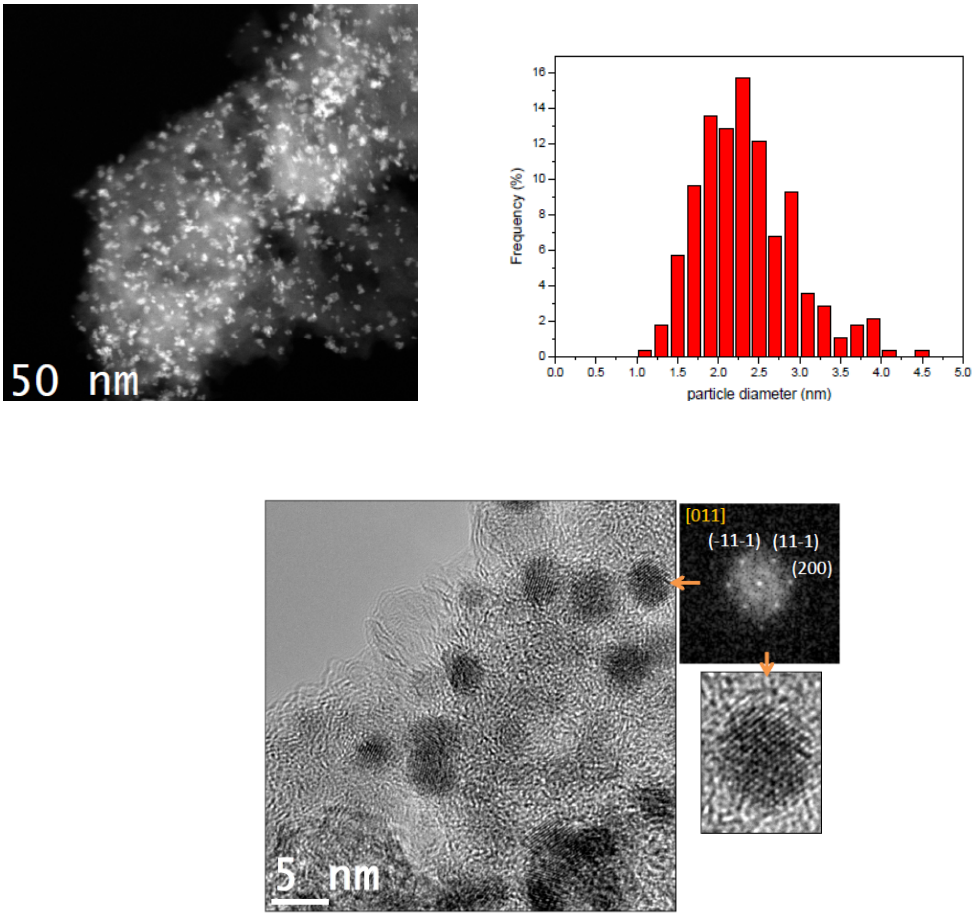


Figure S3. Electron Microscopy study of the Pd/C catalyst. *Top*: (left) representative High Angle Annular Dark Field Scanning Transmission Electron Microscopy (HAADF-STEM) image; (right) Particle Size Distribution obtained from the whole collection of HAADF-STEM images. Average Pd particle diameter: 2.3 nm. *Bottom*: Representative HRTEM image showing the presence of f.c.c Pd nanoparticles. The case of a [011] oriented particle is illustrated by the image and digital diffractogram shown at the right.

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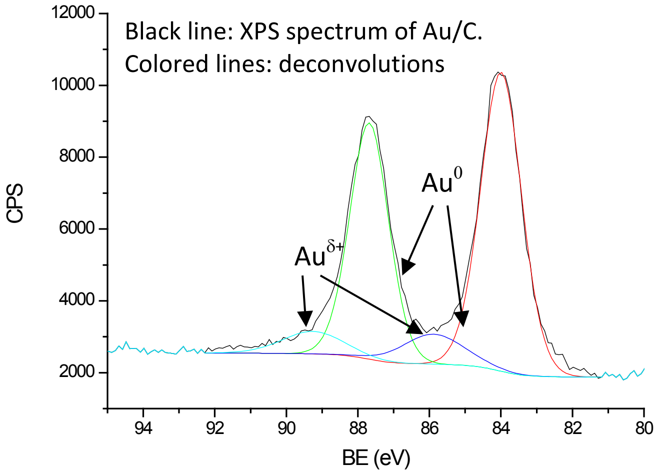


Figure S4. X-Ray Photoelectron Spectroscopy (XPS) spectrum of Au/C. The reduction treatment is as follows: Hydrogenation of gold chloride dissolved in acetonitrile and impregnated on carbon, at 300 ºC under a flow of 100 ml per min of N_2:H_2 (10:1) gas. The estimated percentage of cationic gold is approximately 10%.

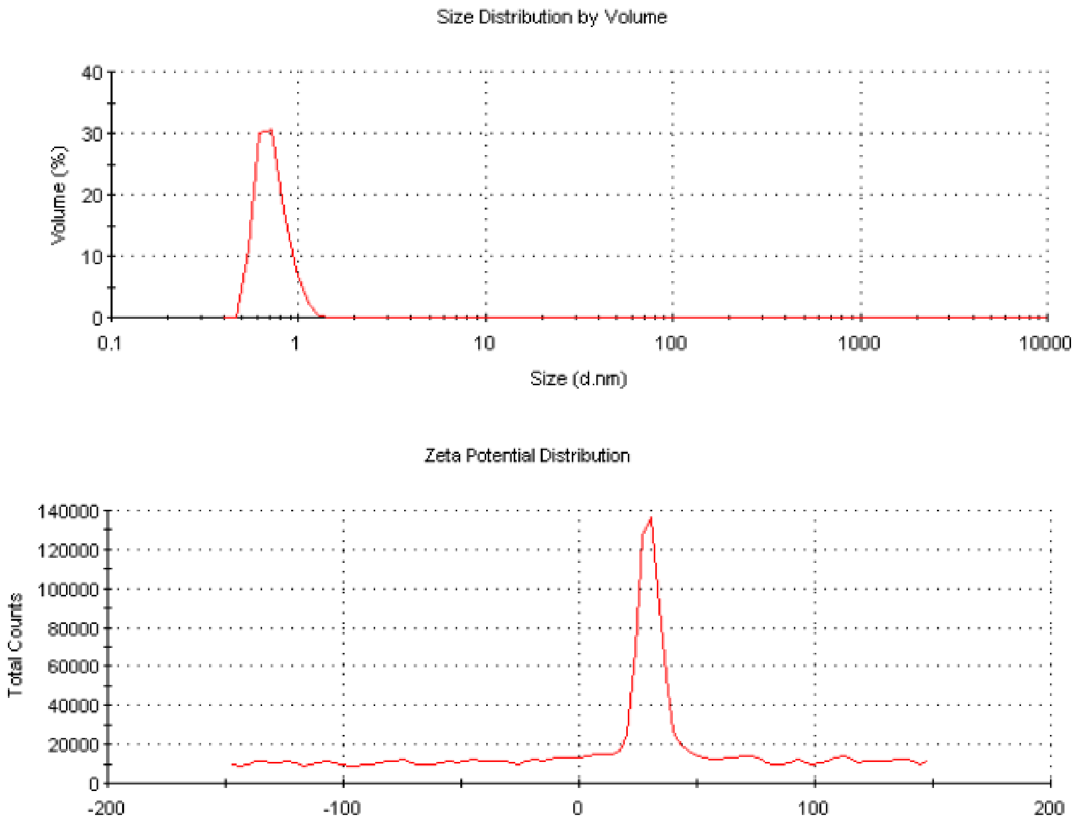


Figure S5. Size (top) and Zeta potential (bottom) distribution of the filtrates of the Au/C and Pd/C-catalyzed formation of cyclohexanone oxime **2** from nitrobenzene **1**.

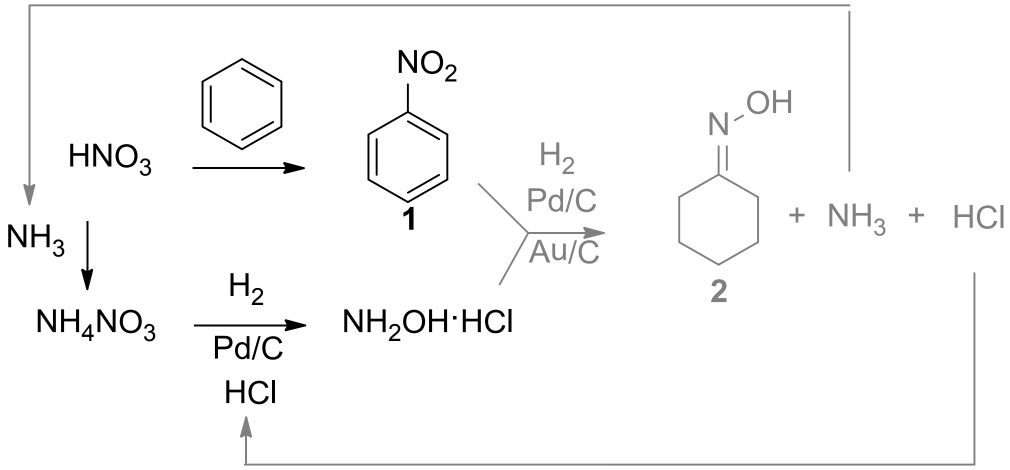
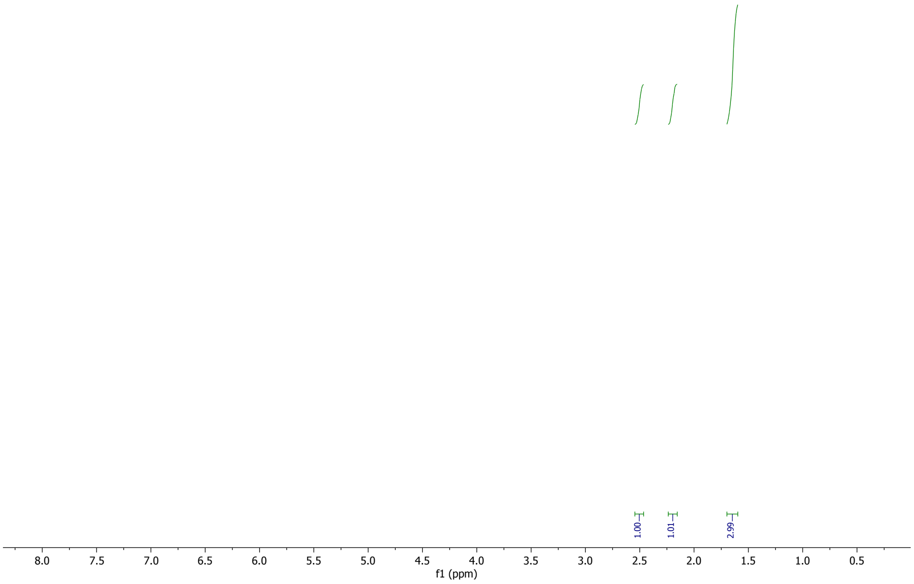
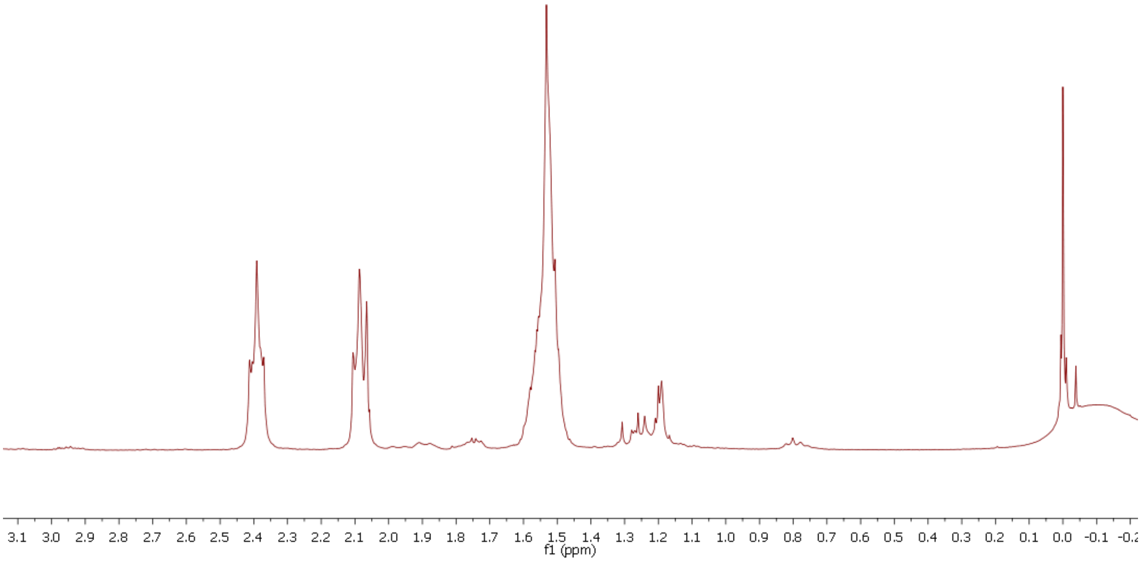
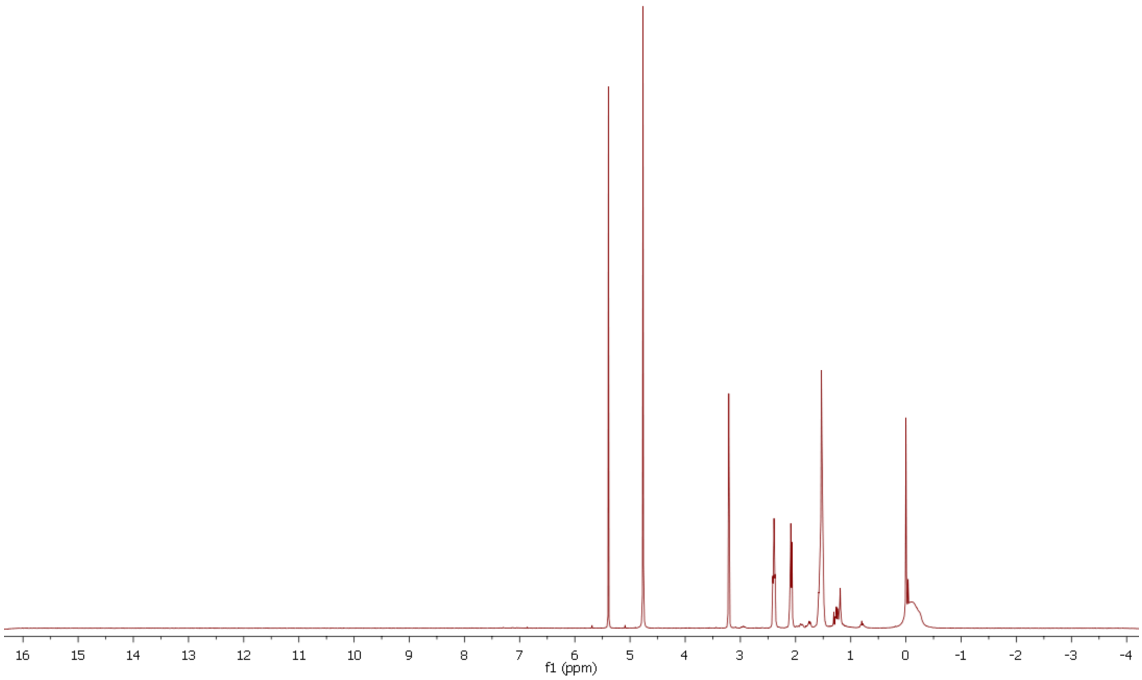
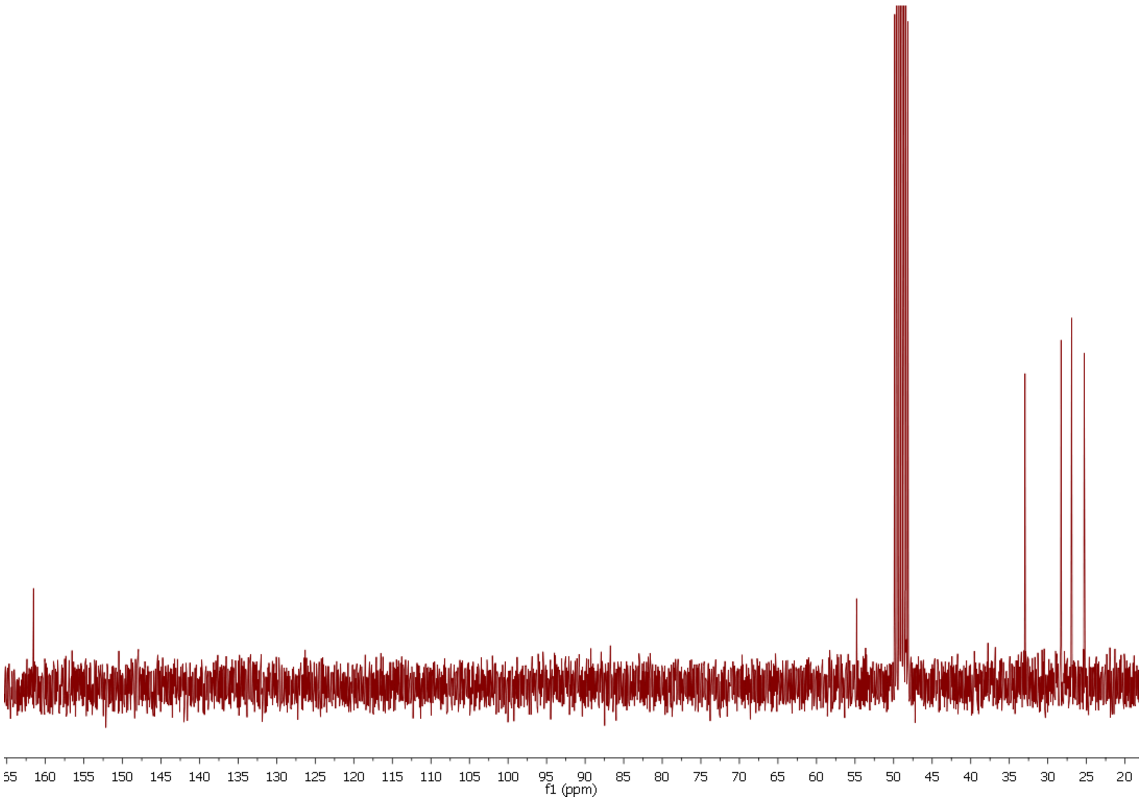


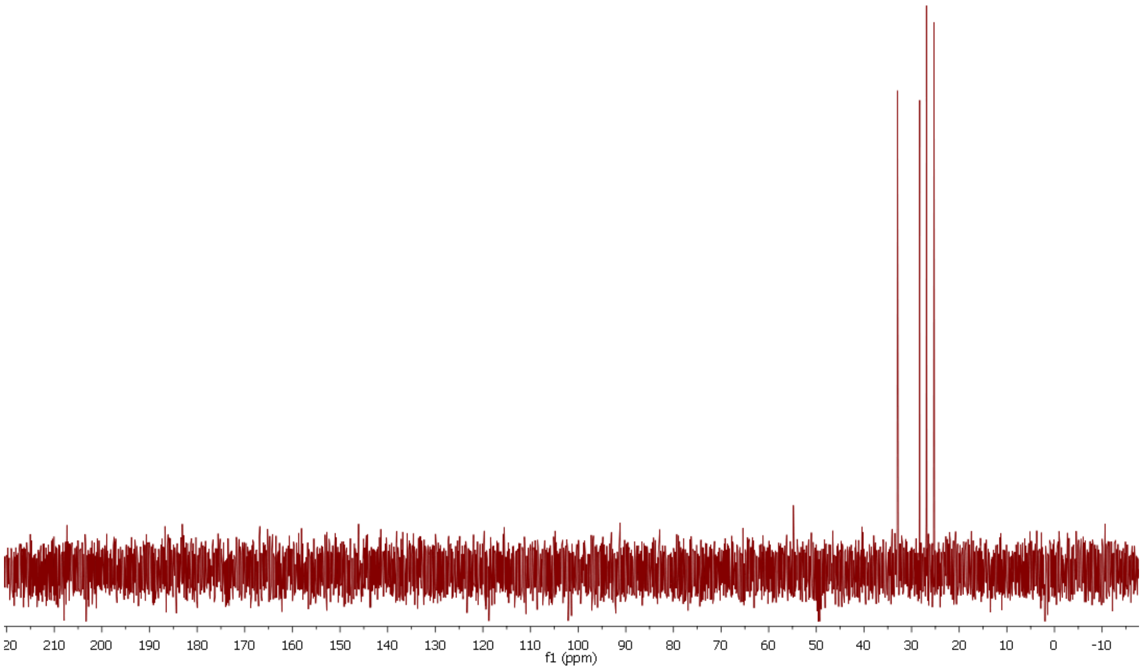
Figure S6. Overall route based on current industrial processes for the synthesis of cyclohexanone oxime **2** from nitrobenzene **1**.


1.00
1.01
2.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
f1 (ppm)

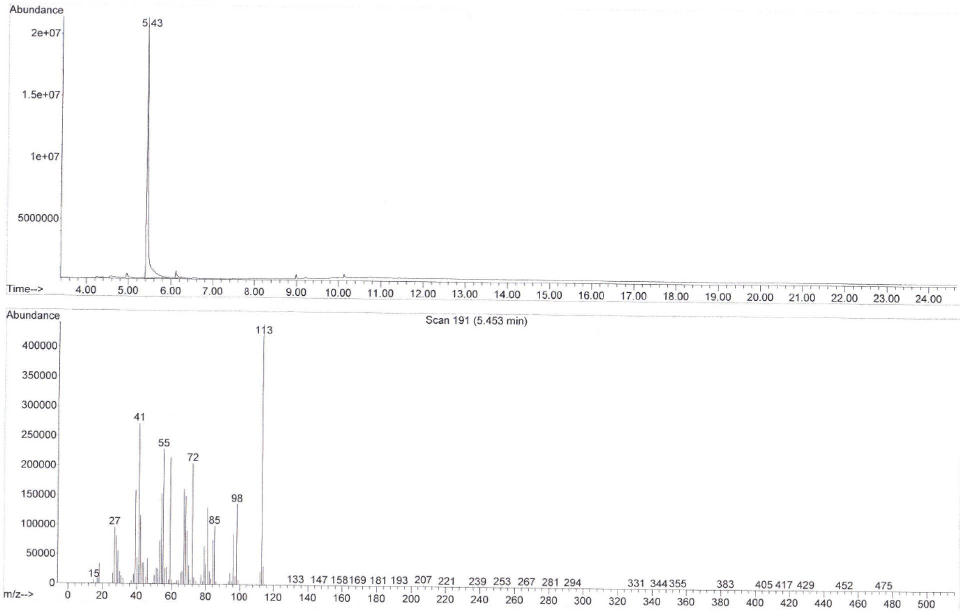

16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

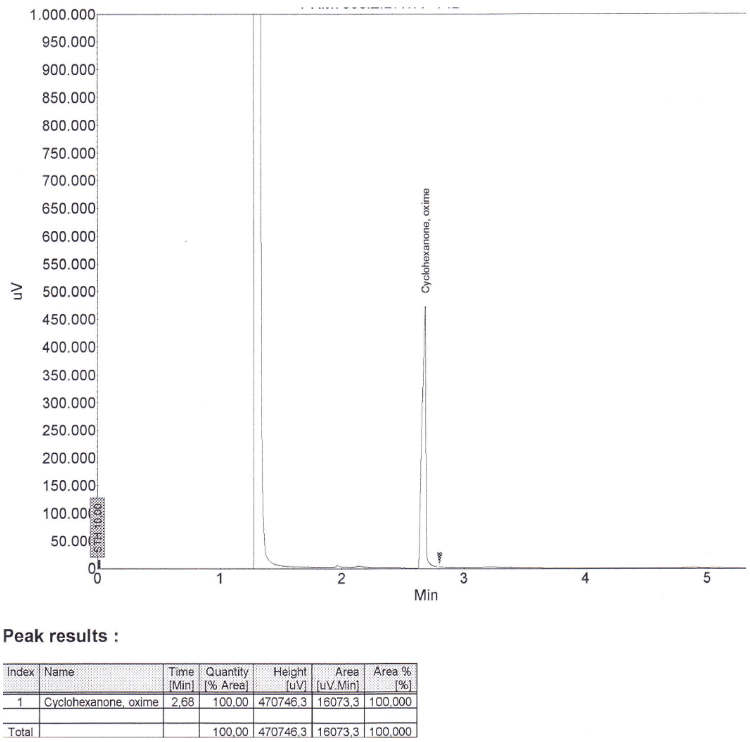

55
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
f1 (ppm)



^{1}H NMR (δ, ppm; *J*, Hz): 2.50 (CH$_2$, m), 7.56-7.42.20 (CH$_2$, m), 1.65 (CH$_2$, m). ^{13}C NMR (δ, ppm; J, Hz): 161.25 (C=NOH), 32.76(CH$_2$), 28.18(CH$_2$), 26.71(CH$_2$), 25.41(CH$_2$).

Figure S7. A) ^{1}H NMR spectra of the product of the reaction without treatment. B) ^{1}H NMR spectra of the reaction filtered with dichlorometane in celite C) ^{1}H NMR spectra of the reaction filtered with dichlorometane in celite D) ^{13}C NMR spectra E) DEPT spectra. Spectra in a Bruker of 300 MHz in deuterated methanol.





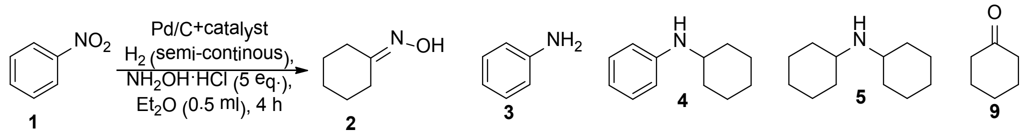
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [uV]	Area [uV.Min]	Area % [%]
1	Cyclohexanone, oxime	2,68	100,00	470746,3	16073,3	100,000
Total			100,00	470746,3	16073,3	100,000

Figure S8. A) GC-MS spectra of the product of the reaction without treatment. B) GC spectra of the reaction of the product of reaction without treatment.

4. Tables

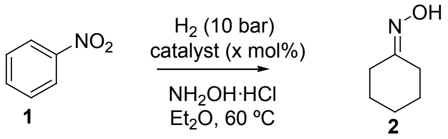
Table S1. Study of metal-supported solids as catalysts in the formation of cyclohexanone oxime **2** from nitrobenzene **1**.



Run	Catalyst (2.5 mol%)	**2** (%)	**3** (%)	**4** (%)	**5** (%)	**9** (%)
1	None	48	20	6	10	16
2	Au/C	97	-	-	-	-
3	$FeCl_3$	-	-	22	78	-
4	Ru/C	-	46	54	-	-
5[a]	Rh/C	5	90	1	1	-
6	$Sc(OTf)_3$	7	93	-	-	
7	$CoCl_2$	37	2	-	21	40
8	$CeCl_3$	85	-	-	-	15
9[a]	$NiCl_2$	9	51	3	2	15
10[a]	$AlCl_3$	19	-	25	26	14
11	$CuCl_2$	44	55	-	-	1
12	VCl_3	22	77	-	-	1
13	$ZnCl_4$	18	65	-	-	17
14[a]	$RuCl_3$	-	10	7	60	5
15[a]	$PtCl_2$	54	6	24	-	-
16	CeO_2	75	-	-	-	20
17	$ZrCl_4$	-	100	-	-	-

GC yields. 100% Conversion in all cases. [a] Complete balance with cyclohexylamine **6**.

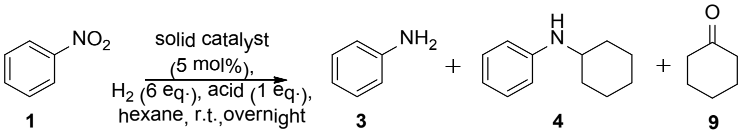
Table S2. Study of metal loadings in the formation of cyclohexanone oxime **2** from nitrobenzene **1**.



Run	**Load Pd (mol %)**	**Load Au (mol %)**	**Time (h)**	**Yield of 2 (%)**
1	0.5	0.25	4.5	18
2	0.5	0.25	50	31
3	1	0.5	4.5	29
4	1	0.5	8.0	56
5	1	0.5	20	>97
6	2	1.0	5.5	>97
7	3	1.5	4.5	>97

GC yields.

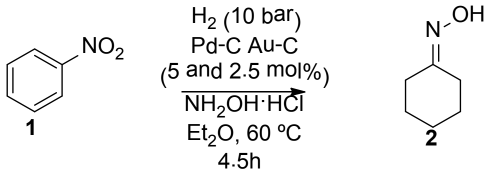
Table S3. Study of Bronted acids in the formation of cyclohexanone **9** from nitrobenzene **1**.



Run	Acid	pK$_a$	**3** (%)	**4** (%)	**9** (%)
1[a]	AcOH	4.76	11	84	5
2[a]	*p*-TsOH	-2.8	38	61	1
3[a]	H_2SO_4	-4.0	42	55	3
4[a,b]	HCl	-8.0	51	48	1

GC yields. [a] 100% Conversion [b] 99% Cyclohexylamine **6**.

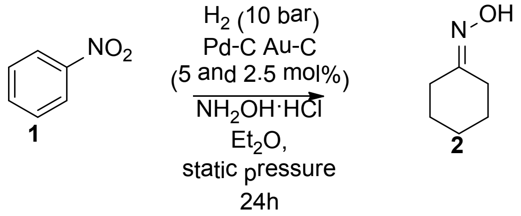
Table S4. Study of solvent amount in the formation of cyclohexanone oxime **2** from nitrobenzene **1**.



Run	**Solvent (mL)**	**Yield of 2 (%)**
1	1	72
2	0.5	97

GC yields.

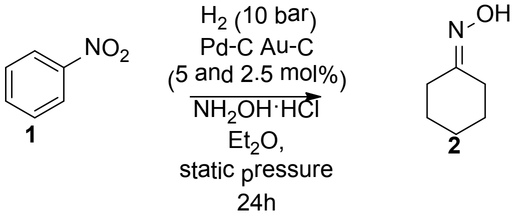
Table S5. Reaction at room temperature in the formation of cyclohexanone oxime **2** from nitrobenzene **1**.



Run	**Temperature (ºC)**	**Yield of 2 (%)**
1	rt	2

GC yields.

Table S6. Reusability of the catalyst in the formation of cyclohexanone oxime **2** from nitrobenzene **1**.



Reuse	**Time (h)**	**Yield of 2 (%)**
0	4.5	97
1	4.5	67
2	4.5	5
3	24	18

GC yields.