SUPPORTING INFORMATION.

A bifunctional palladium/acid catalyst directs the synthesis of cyclohexylanilines and dicyclohexylamines from nitrobenzenes

Paula Rubio-Marqués,^a Antonio Leyva-Pérez^a* and Avelino Corma.^a*

^a Instituto de Tecnología Química. Universidad Politécnica de Valencia-Consejo Superior de Investigaciones Científicas. Avda. de los Naranjos s/n, 46022, Valencia, Spain.

*Corresponding authors: anleyva@itq.upv.es, acorma@itq.upv.es. Phone: +34963877800; Fax: +34963877809.

TABLE OF CONTENTS:

- Experimental section:

0	General	S2
0	Reaction procedures	S2
0	Synthesis of the catalysts	S5
Refer	rences	
Figur	res S1-S5	S6
Table	es S1-S4	S11

1. Experimental section

General

Reinforced glass reactors were dried in an oven at 175 ^oC before use and the ducts of the microrreactor 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 gas chromatography/mass spectrometry (GC-MS), ¹H- and ¹³C-Nuclear Magnetic Resonance (NMR), and Distortionless Enhancement by Polarization Transfer (DEPT). When available, the characterization provided in the literature was used for comparison. Gas chromatography (GC) 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 rising the same conditions. Column chromatography and Thin Layer Chromatography (TLC) were performed over SiO₂. ¹H, ¹³C and DEPT were recorded in a 300 MHz instrument using C₃OD₆ as solvent, containing TMS as internal standard. Infrared (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.

Reaction procedures

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

Typical reaction procedure for the synthesis of cyclohexylaniline **5** from nitrobenzene **2**:

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 **2** (21 μ L, 0.2 mmol) and methanesulfonic acid (10 μ L, 0.15 mmol) were added, and after the micro-reactor was sealed, air was purged by flushing four times with hydrogen and then pressurized with 6 equivalents of H₂ (~10 bar). The resulting mixture was magnetically stirred overnight at room temperature, the hydrogen pressure decreased as the reaction evolved. Once the catalyst particles were removed from the solution by filtration, the product composition was determined by GC. The products were identified by GC-MS and also by ¹H NMR and ¹³C NMR.

Typical reaction procedure for the synthesis of dicyclohexylamine 6 from nitrobenzene 2:

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 **2** (21 μ L, 0.2 mmol) and methanesulfonic acid (10 μ L, 0.15 mmol) were added, and after the micro-reactor was sealed, air was purged by flushing four times with hydrogen and then pressurized with 6 equivalents of H₂ (~10 bar). The resulting mixture was magnetically stirred overnight at room temperature, the hydrogen pressure decreased as the reaction evolved. Once the catalyst particles were removed from the solution by filtration, the product composition was determined by GC. The products were identified by GC-MS and also by ¹H NMR and ¹³C NMR.

Typical reaction procedure for the scope (Table 1):

Pd/C (5 wt%, 21.2 mg, 0.01 mmol of Pd) and hexane (1 mL) were placed into the reactor (2 mL capacity) equipped with a magnetic stirrer. Nitroderivatives (0.2 mmol-1 mmol) and the corresponding acid (10 μ L, 0.15 mmol) were added, and after the microreactor was sealed, air was purged by flushing four times with hydrogen and then pressurized with 6 equivalents. The resulting mixture was magnetically stirred overnight at room temperature, the hydrogen pressure decreased as the reaction evolved. Once the catalyst particles were removed from the solution by filtration, the product composition was determined by GC. The products were identified by GC-MS and also with ¹H NMR and ¹³C NMR.

Typical reaction procedure for the acid screening (Table S1):

Pd/C (5 mol%, 0.01 mmol of Pd) and hexane (1 mL) were placed into the reactor (2 mL capacity) equipped with a magnetic stirrer. Nitrobenzene **2** (23 μ L, 0.2 mmol) and the corresponding acid (0.15 mmol) were added, and after the microreactor was sealed, air was purged by flushing four times with hydrogen and then pressurized with 6 equivalents. The resulting mixture was magnetically stirred overnight at room temperature, the hydrogen pressure decreased as the reaction evolved. Once the catalyst

particles were removed from the solution by filtration, the product composition was determined by GC. The products were identified by GC-MS and also with ¹H NMR and ¹³C NMR.

Typical reaction procedure for the scaling up of the process (Table S2):

Pd/C (5 mol%) catalyst (5 mol%) and hexane (5 mL) were placed into the reactor (25 mL or 250 mL capacity) equipped with a magnetic stirrer. Nitrobenzene **2** (115 μ L, 1 mmol or 1.15 mL, 10 mmol) and triflic acid (0.75 eq.) were added, and after the microreactor was sealed, air was purged by flushing four times with hydrogen and then pressurized with 6 equivalents. The resulting mixture was magnetically stirred overnight at room temperature, the hydrogen pressure decreased as the reaction evolved. Once the catalyst particles were removed from the solution by filtration, the product composition was determined by GC. The products were identified by GC-MS and also with ¹H NMR and ¹³C NMR.

Typical reaction procedure for the reuse of the catalyst (Table S3):

Pd/C (5 mol%) catalyst (5 mol%) and hexane (50 mL) were placed into the reactor (250 mL capacity) equipped with a magnetic stirrer. Nitrobenzene **2** (1150 μ L, 10 mmol) and methanesulfonic acid (0.75 eq.) were added, and after the microreactor was sealed, air was purged by flushing four times with hydrogen and then pressurized with 6 equivalents. The resulting mixture was magnetically stirred overnight at room temperature. During the experiment, the pressure was falling down as the hydrogen was consumed. After completion, the solid catalyst was recovered by filtration, washed, dried, weighed and reused in a next run after re-calculating the amounts of reagents. Once the catalyst particles were removed from the solution by filtration, the product composition was determined by GC. The products were identified by GC-MS and also with ¹H NMR and ¹³C NMR.

Influence of a solid acid in the reaction (Table S4).

The corresponding catalyst (5 mol%) and hexane (1 mL) were placed into the reactor (2 mL capacity) equipped with a magnetic stirrer. Nitrobenzene **2** (23 μ L, 0.2 mmol) and the corresponding acid (0.15 mmol) were added, and after the microreactor was sealed, air was purged by flushing four times with hydrogen and then pressurized with 6 equivalents. The resulting mixture was magnetically stirred overnight at room temperature, the hydrogen pressure decreased as the reaction evolved. Once the catalyst

particles were removed from the solution by filtration, the product composition was determined by GC. The products were identified by GC-MS and also with ¹H NMR and ¹³C NMR.

Synthesis of the catalysts:

Pd/C (a) and (c) (Figure 5) are commercially available. Pd/C (b) was prepared¹ by the incipient wetness method on commercial charcoal (Norit GSX, steam activated, washed acid). The corresponding amount palladium acetyl acetonate was dissolved in 1.6 mL of ethanol or water and added dropwise in 1 g of carbon black. The impregnated powder was left overnight in a muffle at 60 °C and then calcined under an atmosphere composed by 10% H₂ and 90% N₂ at 360 °C for 1 hour.²

2. References

- 1. S.-Y. Huang, S.-M. Chang and C.-T. Yeh, J. Phys. Chem B, 2005, **110**, 234-239.
- 2. M. T. Reetz and M. Maase, *Adv. Mat.*, 1999, **11**, 773-777.

3. Figures



Fig. S1. 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.



Fig. S2. Electron Microscopy study of the Pd/C (b) 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: **3.2 nm**. *Bottom*: Representative HRTEM images 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 left.



Fig. S3. Electron Microscopy study of the Pd/C (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: 32.5 nm.



Fig. S4. Plot-time yield before and after filtration for the cascade-catalyzed reaction by Pd/C under H_2 atmosphere at r.t. Lines are a guide to the eyes.



Fig. S5. RMN spectrum of the crude of the cyclohexylaniline formation reaction in deuterated chloroform.

4. Tables

Table S1. Results for the hydrogenation-amine coupling-hydrogenation cascade of nitrobenzene 2 in the presence of Pd/C, under H_2 atmosphere and with different acids as additives.

2	.NO ₂ solid (<u>(5 m</u> H ₂ (6 eq.), hexane, r.	catalyst nol%), acid (1 eq.), t.,overnight	3	∕NH₂	+ (H 5
Run	Catalyst	Acid	pKa	3	5	8	Selectivi
				(%)	(%)	(%)	ty to 5
							(%)
1 ^a	Pd/-C	AcOH	4.76	11	84	5	94
2 ^a	Pd/C	CH_3SO_3H	-2.6	2	84	14	86
3ª	Pd/C	<i>p</i> -TsOH	-2.8	38	61	1	98
4 ^a	Pd/C	HCI	-8.0	51	48	1	98
5 ^{a, b}	Pd/C	ZSM-5	-	-	1	-	-
6 ^c	-	CH₃SO₃H	-2.6	-	-	-	-
7 ^d	-	CH₃SO₃H	-2.6	1	-	2	-
8 ^c	-	ZSM-5	-	-	-	-	-

GC yields. ^a 100% Conversion ^b 99% Cyclohexylamine **4**. ^c No conversion of nitrobenzene **2**. ^d 60 °C, 3 % conversion of nitrobenzene **2**.

Table S2. Scale-up of the process.

$\begin{array}{c c} & NO_2 & Pd/C \\ & \underbrace{(5 mol\%),}_{H_2 (6 eq.)} \\ 2 & CH_3SO_3H (0.8 eq.), \\ & hexane, r.t., overnight \end{array} + \begin{array}{c} NH_2 \\ H_2 & H_3 \\ H_2 & H_3 \\ H$								
Initial amount of 2 (mg)	Scaling	3 (%)	5 (%)	8 (%)				
125	x5	4	93	3				
1250	x50	7	88	5				

GC yields. 100% Conversion in all cases.





At 1.25 gram-scale. GC yields. 100% Conversion in all cases.

Table S4. Influence of	f a solid	acid in	the react	tion
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2 N	IO ₂ Pd/C (5 mol? H ₂ (6 eq.), CH ₃ S hexane, r.t., c	%) O₃H (1 eq.), overnight	NH ₂ +	5 H +	0 8
Run	Acid	3 (%)	5 (%)	8 (%)	
1 ^[a]	none	61	23	5	
2	CH₃SO₃H	2	92	4	
3 ^[b]	Amberlyst A15	77	27	-	

GC yields. [a] 1% of cyclohexylamine 4. [b] 4% of dicyclohexylamine 6.