Supporting Information for

Heterogeneously Catalyzed Selective Hydrogenation of Amides to Alcohols and Amines

Yinjun Xie[a,‡], Peng Hu[ab,‡], Tatyana Bendikov[c], and David Milstein[a,*]

[a] Department of Organic Chemistry, Weizmann Institute of Science, Rehovot, 76100, Israel
[b] School of Chemistry, Sun Yat-Sen University, Guangzhou, 510275, P. R. China
[c] Department of Chemical Research Support, Weizmann Institute of Science, Rehovot, 76100, Israel

*To whom correspondence should be addressed. Email: david.milstein@weizmann.ac.il

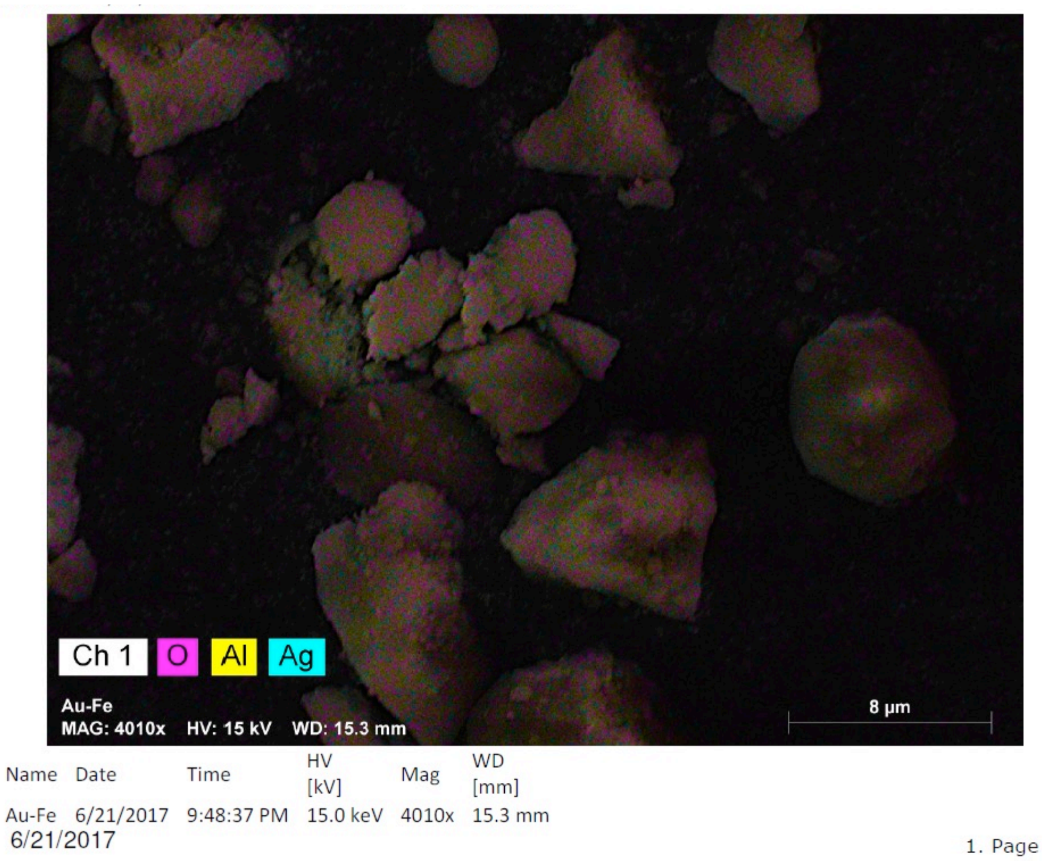
CONTENTS

1. General Information

All hydrogenation experiments were carried out under an atmosphere of purified nitrogen in a Vacuum Atmospheres glove box equipped with a MO 40-2 inert gas purifier or using standard Schlenk techniques. All solvents were reagent grade or better. All non-deuterated solvents were purified according to standard procedures under an argon atmosphere. Deuterated solvents were used as received. All solvents were degassed with N_2 and kept in the glove box. Most of the chemicals used in the catalytic reactions were purified according to standard procedures.[1] γ-Al_2O_3 (185 m^2/g) was purchased from Strem Chemicals. Silver nitrate was purchased form BDH Chemicals. Benzanilide, *N*-benzylbenzamide, benzamide, caprolactam, *neutral*-Al_2O_3, and *basic*- Al_2O_3 were purchased from Sigma-Aldrich. Acetanilide and *N*,*N*-Diethylbenzamide were purchased from Alfa Aesar. *N*-methylbenzamide was purchased from Acros. *N*-benzylhexanamide, *N*-benzylpentanamide, *N*-hexylbenzamide, *N*-cyclohexylbenzamide, *N*-(*p*-tolyl)benzamide, *N*-(4-fluorophenyl)benzamide, and *N*-(3-(diethylamino)propyl)benzamide were prepared by reported methods.[2] EDS was recorded at EDS Bruker XFlash/60mm, using Zeiss Ultra 55 Scanning Electron Microscope. ^1H, ^{13}C NMR spectra were recorded at 300, and 75 MHz, respectively, using a Bruker AMX-300 NMR spectrometer. Measurements were done at ambient temperature, as noted for each experiment. ^1H NMR chemical shifts are referenced to the residual hydrogen signals of the deuterated solvent, and the ^{13}C NMR chemical shifts are referenced to the ^{13}C signals of the deuterated solvent. GC analysis was performed on HP 6890 with Hp-5 column, flame ionization detector, and helium as carrier gas. GSMS analysis was performed on Agilent 7820A/5975C GCMS system with MS detector, and helium as carrier gas. X-Ray diffraction analysis was performed on sealed Cu-anode tube (line source) Rigaku ULTIMA III (2kW) theta-theta vertical diffractometer equipped with CBO. XPS measurements were carried out using a monochromatic Al Ka X-ray source ($h\nu = 1486.6$ eV) at 75W and detection pass energies ranging between 20 and 80 eV. Low-energy electron flood gun (eFG) was applied for charge neutralization. To define binding energies (BE) of different elements C 1s line at 284.8 eV[3,4] was taken as a reference. Curve fitting analysis was based on linear or Shirley background subtraction and application of Gaussian-Lorenzian line shapes.

2. Catalysts preparation

$AgNO_3$ (828 mg) and γ- Al_2O_3 (10.0 g) were added to deionized water (15 mL) at room temperature. The mixture was evaporated at room temperature in the dark (3 days), then dried at 80 °C for 12 h. The powder was heated to 600 °C in air at a rate of 57 °C/min and kept at 600 °C for 2 hours. The Ag/γ-Al_2O_3 was characterized by EDS (Energy-dispersive X-ray spectroscopy), XPS (X-ray photoelectron spectroscopy) and XRD (X-ray diffraction). The same procedure was used to prepare Ag/*neutral*-Al_2O_3, Ag/*basic*-Al_2O_3, Ag/SiO_2, and Ag/TiO_2.



Name	Date	Time	HV [kV]	Mag	WD [mm]
Au-Fe	6/21/2017	9:48:37 PM	15.0 keV	4010x	15.3 mm

6/21/2017

1. Page

Figure S-1. SEM picture of Ag/γ-Al_2O_3-5

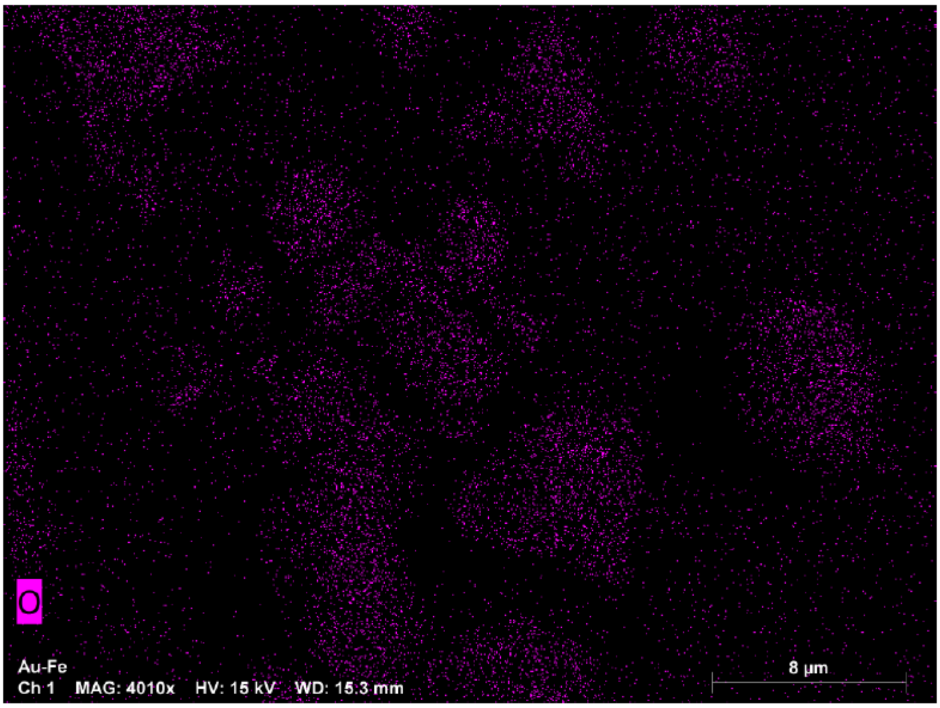


Figure S-2. Map of oxygen distribution measured by EDS

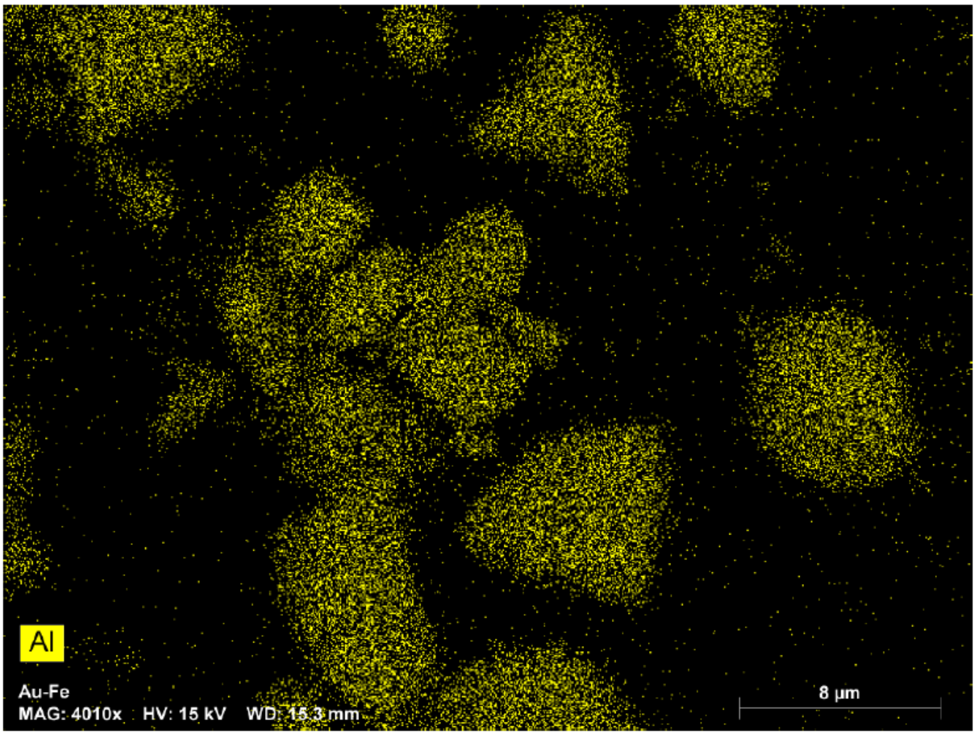


Figure S-3. Map of Aluminum distribution measured by EDS

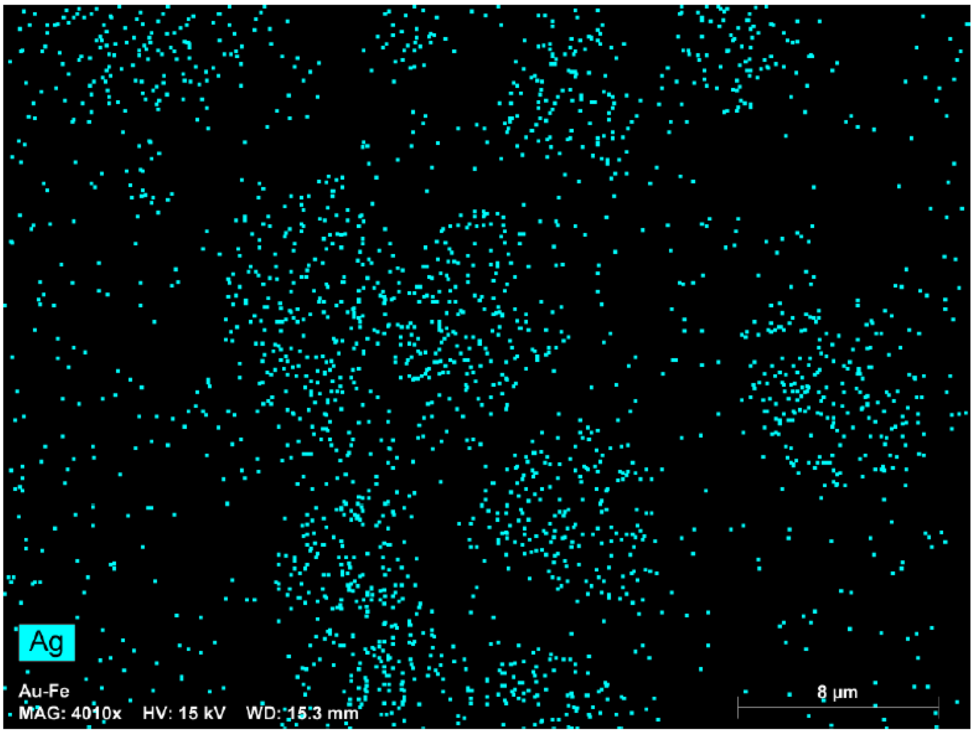
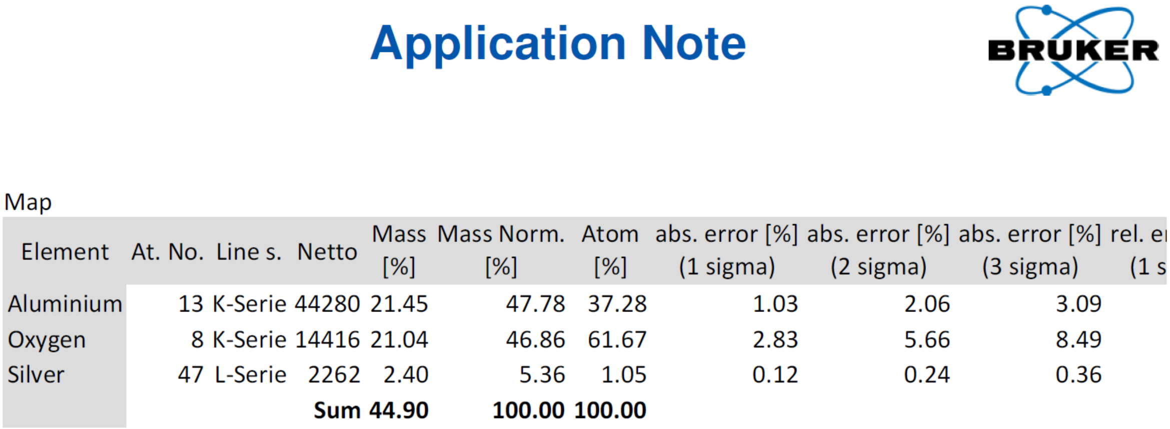


Figure S-4. Map of Silver distribution measured by EDS



Application Note

BRUKER

Map

Element	At. No.	Line s.	Netto	Mass [%]	Mass Norm. [%]	Atom [%]	abs. error [%] (1 sigma)	abs. error [%] (2 sigma)	abs. error [%] (3 sigma)	rel. e (1 s
Aluminium	13	K-Serie	44280	21.45	47.78	37.28	1.03	2.06	3.09	
Oxygen	8	K-Serie	14416	21.04	46.86	61.67	2.83	5.66	8.49	
Silver	47	L-Serie	2262	2.40	5.36	1.05	0.12	0.24	0.36	
			Sum	**44.90**	**100.00**	**100.00**				

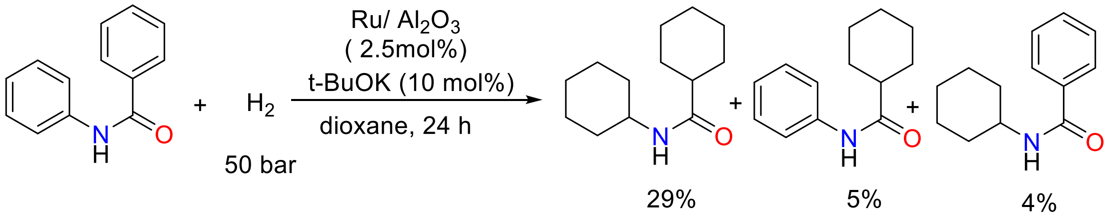
Table S-1. The rate of oxygen, aluminum, and silver measured by EDS

3. General procedure for hydrogenation of amides

In a glovebox, a 25 mL stainless steel autoclave lined with a Teflon tube containing a stir bar was charged with Ag/γ-Al_2O_3-5 (27 mg, 5 wt% Ag, 2.5 mol%), *t*-BuOK (5.6 mg, 10 mol%), amide (0.5 mmol), and 1,4-dioxane (2 mL). After purging with H_2 (10 atm × 2), the parallel autoclave was pressurized with H_2 (50 bar). The mixture was stirred at 150 ^{o}C for 48 hrs. After cooling to room temperature, the pressure was released carefully, and 1,3,5-mesitylene (60 mg, 0.5 mmol) was added to the reaction mixture as internal standard. After filtration, 100 μL of the clear solution was withdrawn and measured by ^{1}H NMR in $CDCl_3$ to determine the conversion and yields.

4. Optimization of the reaction conditions

Several catalysts were tested for the hydrogenation of benzanilide, including Pd/Al_2O_3, Ru/Al_2O_3, Cu/γ-Al_2O_3-5 and Ag/γ-Al_2O_3-5. When Ru/Al_2O_3 or Pd/Al_2O_3 was used as catalysts, benzyl alcohol and aniline were not detected by GCMS. The aromatic rings of benzanilide were hydrogenated, catalyzed by Ru/Al_2O_3 or Pd/Al_2O_3. When Cu/γ-Al_2O_3-5 was used as a catalyst, the conversion was 0%. With Ag/γ-Al_2O_3-5 as a catalyst, C-N bond cleavage products were observed.



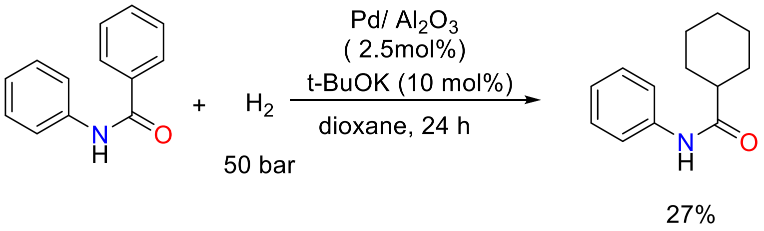
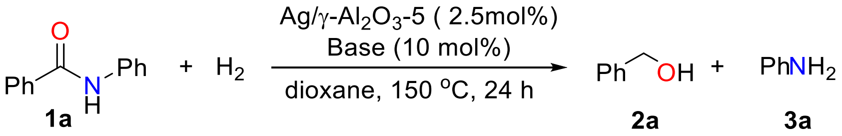


Table S-2. Screening of bases.

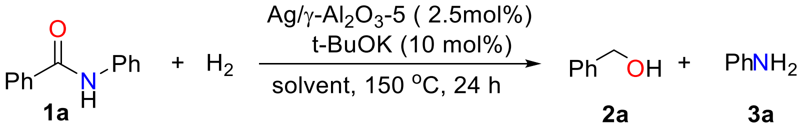


Entry	Base	Conv. (%)	Yield (%)	
			2a	**3a**
1	*t*-BuOK	75	73	74
2	KOEt	49	49	48
3	K_3PO_4	32	28	31
4	K_2CO_3	7.0	5.7	6.7
5	KOH	54	54	49
6	Cs_2CO_3	57	53	50
7	NaOEt	67	65	64
8	NaOMe	15	15	14

Reaction conditions: Ag/γ-Al_2O_3 (27 mg, 2.5 mol%), base (0.05 mmol), benzanilide (98.5 mg, 0.5 mmol), and 1,4-dioxane (2 mL) in an autoclave, H_2 (50 bar), oil bath 150 °C, for 24 hours. The conversions and yields were determined by ^{1}H NMR using 1,3,5-mesitylene as internal standard.

Based on the results presented in Table S-2, *t*-BuOK was selected as the best base for hydrogenation of benzanilide via C-N bond cleavage.

Table S-3. Screening of solvents.

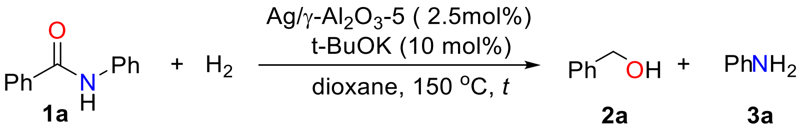


Entry	Solvent	Conv. (%)	Yield (%)	
			2a	**3a**
1	1,4-dioxane	75	73	74
2	THF	70	67	70
3	*n*-heptane	49	42	44
4	toluene	20	17	20

Reaction conditions: Ag/γ-Al_2O_3 (27 mg, 2.5 mol%), *t*-BuOK (5.6 mg, 0.05 mmol), benzanilide (98.5 mg, 0.5 mmol), and solvent (2 mL) in an autoclave, H_2 (50 bar), oil bath 150 °C, for 24 hours. The conversions and yields were determined by ^1H NMR using 1,3,5-mesitylene as internal standard.

Based on the results presented in Table S-3, 1,4-dioxane was selected as the best solvent for hydrogenation of benzanilide via C-N bond cleavage.

Table S-4. Screening of H_2 pressure and reaction time.

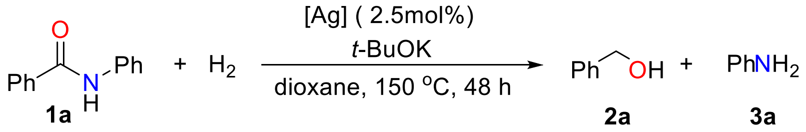


Entry	H_2 (bar)	*t* (hours)	Conv. (%)	Yield (%)	
				2a	**3a**
1	50	24	75	73	74
2	50	48	>99	96	94
3	30	48	94	93	94
4	10	48	56	56	55

Reaction conditions: Ag/γ-Al_2O_3 (27 mg, 2.5 mol%), *t*-BuOK (5.6 mg, 0.05 mmol), benzanilide (98.5 mg, 0.5 mmol), and 1,4-dioxane (2 mL) in an autoclave, H_2, oil bath 150 °C, for 48 hours. The conversions and yields were determined by ^1H NMR using 1,3,5-mesitylene as internal standard.

Based on the results presented in Table S-4, hydrogenation of benzanilide at 50 bar of H_2 for 48 hours gives the best conversion and yield.

Table S-5. Screening of base amount and catalysts (different supports).

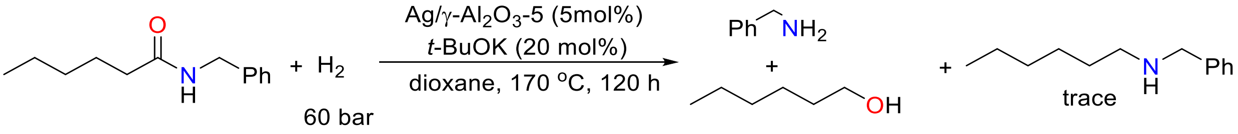


Entry	Catalyst	*t*-BuOK	Conv. (%)[a]	Yield (%)[a]	
				2a	**3a**
1	Ag/γ-Al_2O_3	10 mol%	>99	96	94
2	Ag/γ-Al_2O_3	5 mol%	78	78	76
3	Ag/*neutral*-Al_2O_3	5 mol%	30	30	27
4	Ag/*basic*-Al_2O_3	5 mol%	76	75	73
5	Ag/SiO_2	10 mol%	0	0	0
6	Ag/TiO_2	10 mol%	17	17	16
7[b]	$Ru_3(CO)_{12}$/$Mo(CO)_6$	10 mol%	0	0	0
8[c]	$Rh_6(CO)_{16}$/$Mo(CO)_6$	10 mol%	0	0	0

Reaction conditions: [Ag] (27 mg, 2.5 mol%), *t*-BuOK, benzanilide (98.5 mg, 0.5 mmol), and 1,4-dioxane (2 mL) in an autoclave, H_2, oil bath 150 °C, for 48 hours. [a]The conversions and yields were determined by ^1H NMR using 1,3,5-mesitylene as internal standard. [b] $Ru_3(CO)_{12}$ (1.8 mg, [Ru] 1.7 mol%), $Mo(CO)_6$ (1.0 mg, 0.85 mol%). [c] $Rh_6(CO)_{16}$ (1.5 mg, [Rh] 1.7 mol%), $Mo(CO)_6$ (1.0 mg, 0.85 mol%).

Based on the results presented in Table S-5, reaction with Ag/γ-Al_2O_3 (2.5 mol%), *t*-BuOK (10 mol%), in 1,4-dioxane, under H_2 (50 bar), at 150 °C, for 48 hours gives the best conversion and yields.

Hydrogenation of *N*-benzylhexanamide: Besides benzylamine and 1-hexylalcohol as products, a trace amount of *N*-benzylhexan-1-amine, the C-O cleavage product, was observed by GCMS, as shown in Figure S-6.



```
File        :C:\msdchem\1\data\XIE\XY-20170525-1.D
Operator    : xie
Acquired    : 25 May 2017  17:05     using AcqMethod XIE-DIOXANE.M
Instrument  :    MSD1
Sample Name: xy-x170520-1
Misc Info   :
Vial Number: 1
```

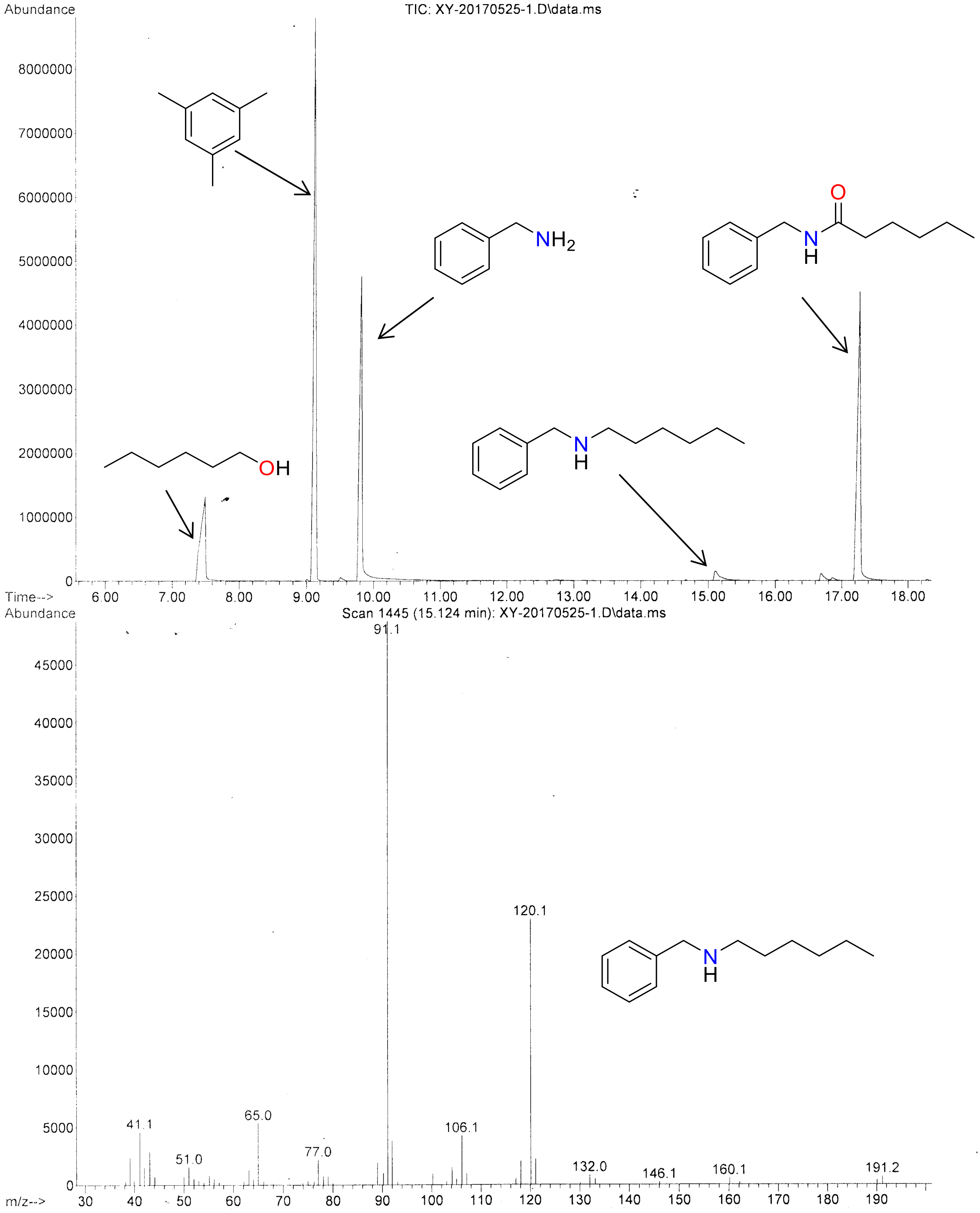


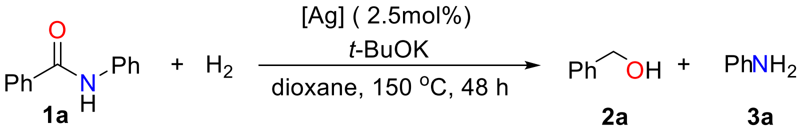
Figure S-5. **GCMS spectra of the hydrogenation reaction of *N*-benzylhexanamide**

5. Recycling of the catalyst

General procedure for catalyst recycling: The catalyst was recovered by filtration, washed with dichloromethane, and then dried under vacuum at room temperature for 12 hours.

Catalyst reactivation: After recovery by filtration, the catalyst was washed with methanol and water, dried at 80 °C, and then calcined at 600 °C for 10 minutes.

Table S-6. Results of recycling and reactivation experiments.



	Conversion (%)[a]	Yield of BnOH (%)[a]	Yield of aniline (%)[a]
New catalyst	99	96	94
1st recycling	99	96	95
2nd recycling	75	73	75
3rd recycling	56	51	52
4th recycling[b]	99	96	96
5th recycling	93	90	91
6th recycling[b]	94	94	93

Reaction conditions: Ag/γ-Al_2O_3 (27 mg, 2.5 mol%), *t*-BuOK (5.6 mg, 0.05 mmol), benzanilide (98.5 mg, 0.5 mmol), and 1,4-dioxane (2 mL) in an autoclave, H_2 (50 bar), oil bath 150 °C, for 48 hours. [a] The conversions and yields were determined by ^1H NMR, using 1,3,5-mesitylene as internal standard. [b] Catalyst was calcined at 600 °C for 10 minutes before using.

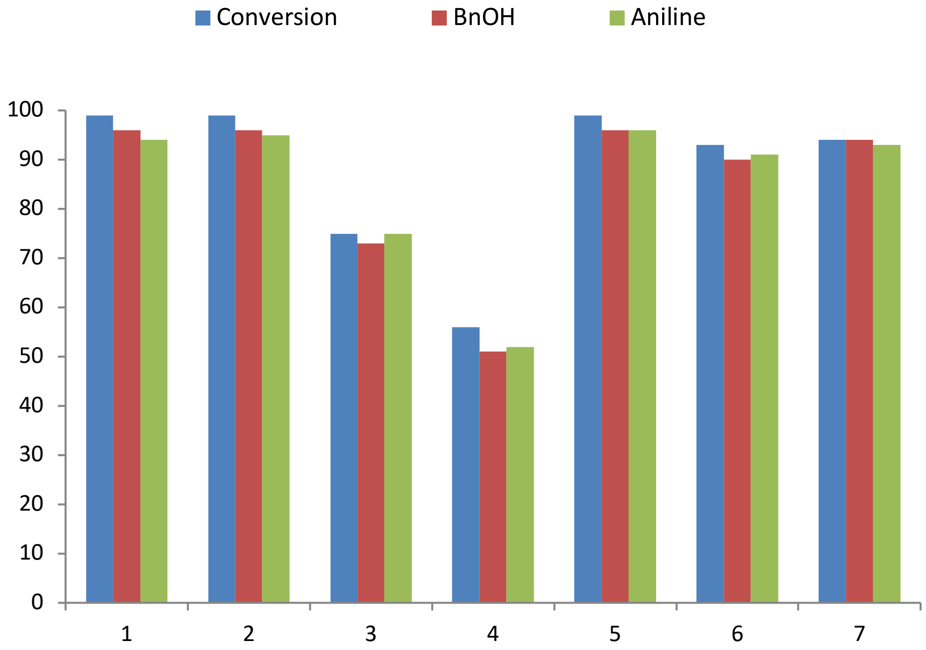


Figure S-6, Recycling of Ag/γ-Al$_2$O$_3$ catalyst.

As shown in Table S-6 and Figure S-6, Ag/γ-Al$_2$O$_3$ shows very good stability.

XRD and XPS analysis of the catalyst

The electronic and structural changes of γ-Al$_2$O$_3$, Ag/γ-Al$_2$O$_3$, recovered Ag/γ-Al$_2$O$_3$ after 3 times recycling, and calcined recovered Ag/γ-Al$_2$O$_3$ was studied by XRD and XPS.

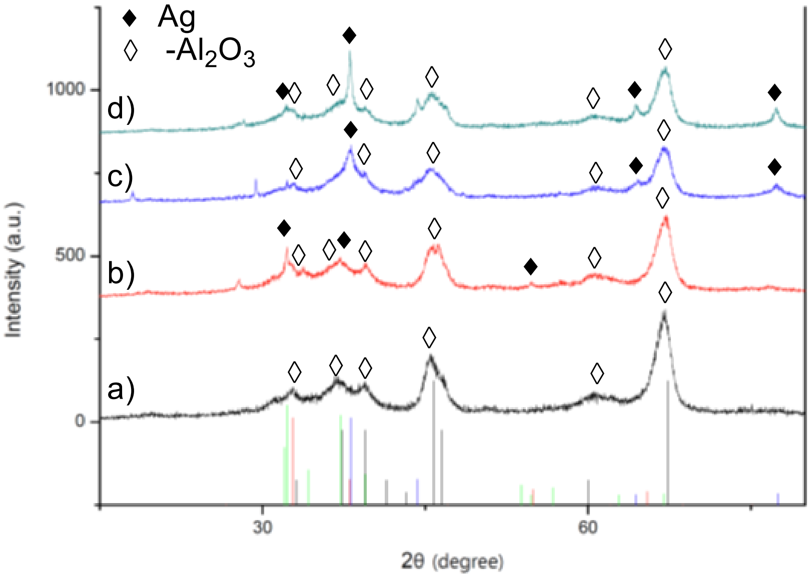


Figure S-7. XRD pattern of the support and catalysts. a) γ-Al$_2$O$_3$; b) Ag/γ-Al$_2$O$_3$; c) Recovered Ag/γ-Al$_2$O$_3$; d) Calcined Ag/γ-Al$_2$O$_3$

The XRD pattern is shown in Figure S-7. In all samples the γ-Al$_2$O$_3$ phase was detected, which means that the addition of silver, and the reaction system did not change the structure of the support. In samples **b**, only Ag(I) species (at 2θ of 32.8, 38.0, and 54.9) was observed, but in sample **c** and **d,** metallic Ag(0) phase was also observed (at 2θ of 38.1, 44.3, 64.4 and 77.5). This result suggested that Ag(I) species could be reduced by H_2.

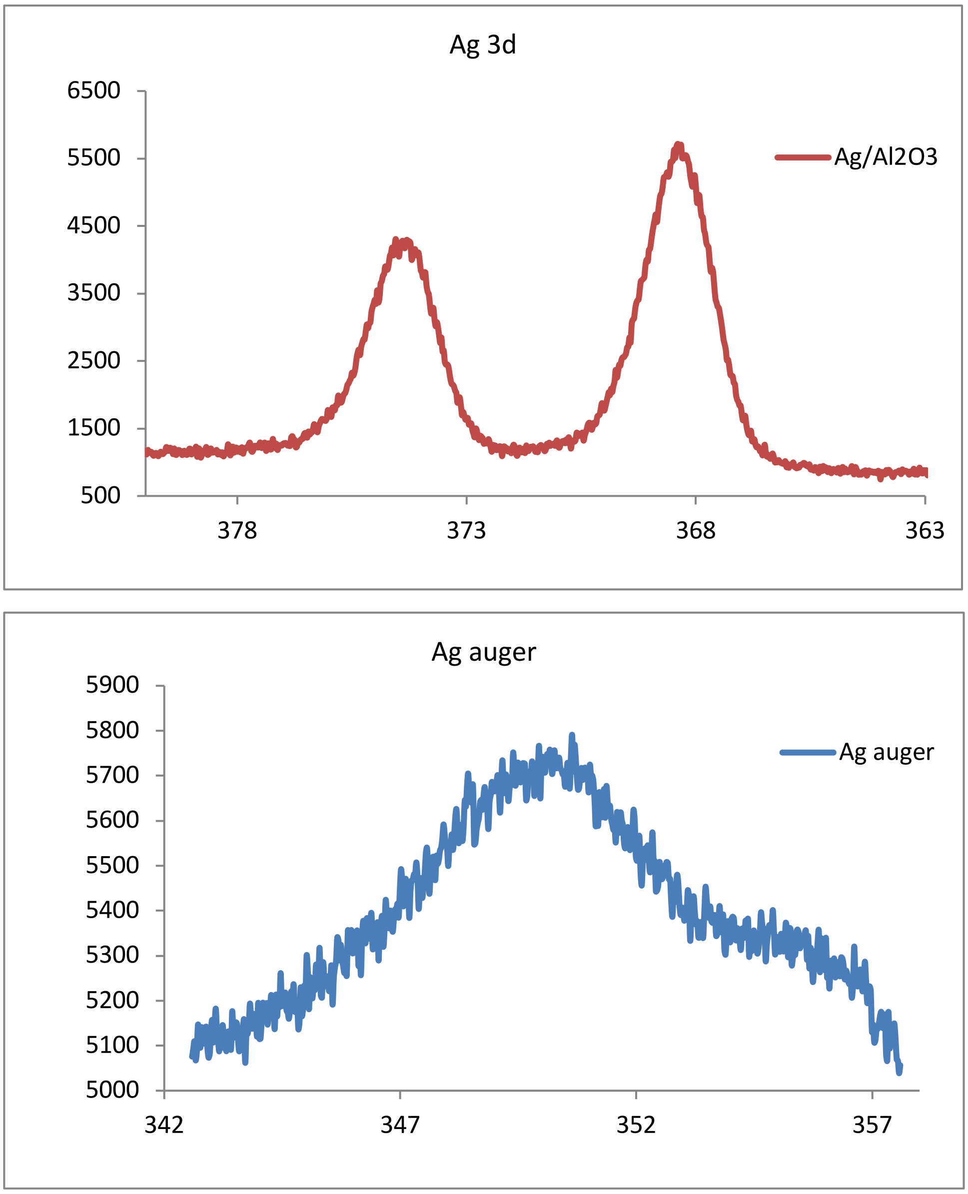


Figure S-8. High resolution XPS spectra of a) Ag 3d region; b) Ag MVV auger region for freshly prepared Ag/γ-Al_2O_3

Characteristic Ag 3d doublet with the position of Ag $3d_{5/2}$ peak maximum at approximately 368.4 eV shown in Figure S-8a. This, first, proves presence of silver on the top surface of the Al_2O_3 particles; second, the position of the peak may fit to Ag(I) or Ag(0) oxidation states of silver.[3,4] Since the characteristic for Ag(0) satellite plasmon peaks are not observed in the Ag 3d spectra, Ag(0) oxidation state can be excluded. In addition, position of Ag MVV auger line at 350.6 eV indicates Ag(I) oxidation state. From the mentioned above and taking into consideration surface sensitivity of the XPS technique (10-15 nm), we assume that Ag is present on the top surface of the catalyst and has Ag(I) oxidation state.

Presence of Ag on the top surface was also detected by XPS for the additional two samples: catalysts after recycling 3 times (Sample 2, Table S-7); and Sample 3 – the same as Sample 2, with further calcination at 600 °C.

As shown in Table S-7, atomic concentration ratio of Ag and Al_2O_3 particles on the top surface of catalyst decreased from 1.80 % (for the freshly prepared catalyst) to 0.89 % (after recycling 3 times), Samples 1 and 2, respectively. This decrease in the Ag concentration on the top surface may explain partial catalyst deactivation. After calcination at 600 °C for 10 minutes, the Ag/Al_2O_3 ratio increases to 1.27 % (Sample 3, Table S-6), revealing reactivation of the catalyst.

Table S-7, Ag/Al_2O_3 atomic concentrations ratio on the catalysts top surface

Sample	Catalyst	Ag/Al_2O_3 Ratio (%)
1	Ag/γ-Al_2O_3 freshly prepared	1.80
2	Ag/γ-Al_2O_3 after recycling 3 times	0.89
3	Ag/γ-Al_2O_3 after recycling 3 times, then calcination	1.27

6. References

1. W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals* (Pergamon Press, Oxford, 1988, 3rd ed.).
2. W. R. Bowman, A. J. Fletcher, J. M. Pedersen, P. J. Lovell, M. R. J. Elsegood, E. H. Lopez, V. Mckee, G. B. S. Potts, *Tetrahedron* 2007, **63**, 191.
3. J. F. Moulder, W. F. Stickle, P. E. Sobol, K. D. Bomben, "Handbook of X-ray Photoelectron Spectroscopy", Perkin-Elmer Corporation; 1992.
4. A. V. Naumkin, A. Kraut-Vass, S. W. Gaarenstroom, C. J. Powell, *NIST X-ray Photoelectron Spectroscopy Database*, Version 4.1, 2012.