Gold and silver-catalyzed reductive amination of aromatic carboxylic acids to benzylic amines

Gold and silver catalyzed reductive amination of aromatic carboxylic acids to benzylic amines

Robin Coeck,[a] Jittima Meeprasert,[b] Guanna Li,[c] Thomas Altantzis,[d] Sara Bals,[e] Evgeny A. Pidko,[b] and Dirk E. De Vos [a]

[a] *Centre for Membrane separations, Adsorption, Catalysis and Spectroscopy for sustainable solutions (cMACS), KU Leuven, Leuven, Belgium*

[b] *Inorganic Systems Engineering, Department of Chemical Engineering, Delft University of Technology, The Netherlands*

[c] *Biobased Chemistry and Technology, and [d]Laboratory of Organic Chemistry, Wageningen University & Research, The Netherlands*

[d] *Applied Electrochemistry & Catalysis, University of Antwerp, Belgium*

[e] *Electron Microscopy for Materials Science, University of Antwerp, Belgium*

The reductive amination of benzoic acid and its derivatives would be a green, efficient and cost effective addition to current synthesis methods for benzylamine. However, with current technology it is very difficult to keep the aromaticity intact when starting from benzoic acid, and salt wastes are often generated in the process. Here, we report the first (heterogeneous) catalytic system for such a reductive amination, requiring solely H_2 and NH_3 as the reactants. The Ag/TiO_2 or Au/TiO_2 catalysts can be used multiple times and are relatively cheap; only 0.025 mol% Au is required. The catalysts are bifunctional: the support catalyzes the dehydration of both the ammonium carboxylate to the amide and of the amide to the nitrile, while the sites at the metal-support interface promote the hydrogenation of the in situ generated nitrile. Yields of up to 92% benzylamine were obtained.

Introduction

Benzylamines are important chemical compounds with widespread applications in textile (i.e. dyes), military, agrochemical and pharmaceutical industries (Figure 2)[1-2]. Classically, benzylamines are made from toluene via one of three main pathways (Figure 1). The first method involves the chlorination of toluene to benzyl chloride which is then reacted with ammonia to form benzylamine.[2-3] This method is by far the least environment friendly: the reaction requires dangerous chlorine gas, forms many (ring-)chlorinated side products and salt waste is generated. Two halogen-free alternatives are the hydrogenation of benzonitrile and the reductive amination of benzaldehyde. Although both reduction reactions are highly efficient and can be performed with a wide variety of catalysts, there are some drawbacks related to the syntheses of both intermediates.[4-10] Benzonitrile is generally produced via ammoxidation of toluene at around 400°C.[11-12] Working under these conditions requires a significant energy input and one must be careful not to decompose or partially burn the reactants. Additionally, whereas ammoxidation processes are efficient for simple nitriles, more complex functionalized benzonitriles require hazardous cyanation reactions.[13-14] Alternatively, benzaldehyde is produced via oxidation of toluene. In contrast to ammoxidation, this oxidation reaction is performed under relatively mild conditions. However, with overoxidation as the main side reaction, a significant fraction of the substrate is lost to benzoic acid.[15-17]
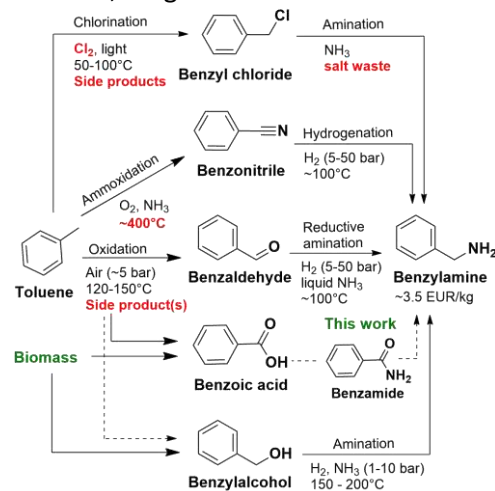

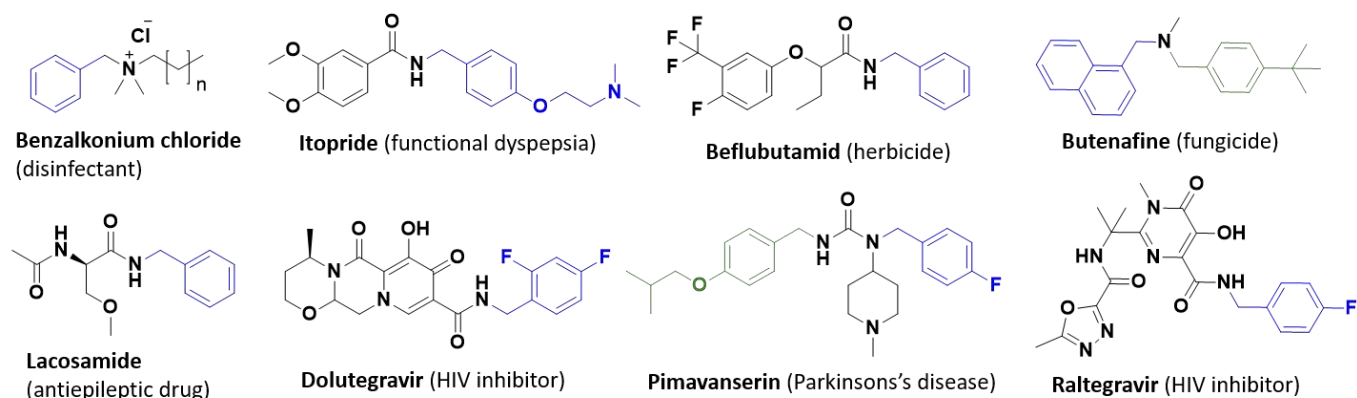**Figure 1** — Synthesis methods for benzylamine.

Figure 2 — Pharmaceutical compounds containing at least one benzylic amine.

In more recent years efforts have been made to synthesize benzylamine in an efficient manner from more green and renewable sources. Aside from a few exceptions[18-19], amination of benzyl alcohol has been the primarily investigated synthesis route.[20-26] In these reports, benzylamine yields typically range between 66 to 86%. Currently, benzyl alcohol is produced from benzyl chloride, via hydrolysis, and in small quantities during benzaldehyde synthesis.[27] However, biobased synthesis routes are available.[24,28] Nevertheless, a synthesis route starting from benzoic acid, and its derivatives (e.g. benzamide), would be a valuable addition to existing methods; benzoic acid is readily available and a lot cheaper than benzyl alcohol. Additionally, it can be synthesized from renewable sources.[29-30] The direct conversion of benzoic acid to benzylamine is a fairly unexplored domain. With current technology one has to either reduce benzoic acid to benzyl alcohol, followed by amination (i.e. a multi-step process)[31], or synthesize benzylamine via benzamide. As we recently showed, it is fairly easy to derivatise carboxylic acids to carboxamides.[32-33] However, the difficulty lies in reducing the carbonyl group and still keeping the aromatic ring intact. To achieve this goal, strong dehydrating agents, e.g. P_2O_5, can be added to in-situ generate a more easily reducible nitrile.[34] Alternatively, stoichiometric amounts of hydride reagents, e.g. $LiAlH_4$, silanes or boranes, are required for the selective reduction of the amide group.[35-41] Both approaches result in undesirable salt waste.

In this report we describe two heterogeneous highly efficient catalysts, i.e. Au/TiO_2 and Ag/TiO_2, for the one-pot catalytic conversion of benzoic acid (and its derivatives) to benzylamine. Reactions were performed in the green and benign cyclopentyl methyl ether (CPME) as solvent, with NH_3 and H_2 as the only and clean reactants. Yields of up to 92% benzylamine were observed. To our knowledge, this is the first report of an efficient (heterogeneous) reductive amination system for benzoic acid.

Results and discussion

Catalyst screening and evaluation

In previous research on the hydrogenation and reductive amination of aliphatic amides and carboxylic acids, it was shown that the catalytic reduction of these compounds is a green and sustainable method for the production of valuable amines.[32-33] However, aromatic rings do not remain stable in the presence of highly active hydrogenation catalysts based on noble metals like Ru, Rh, Pd and Pt (Figure S2). As a starting point for the current work, benzamide was selected as a substrate molecule, with Au and Ag as potential hydrogenation catalysts. Of these metals in particular, it is known that they can perform reductions, such as the hydrogenation of nitrobenzenes, while leaving the aromatic ring intact.[42-44] Therefore, several catalysts with different Ag and Au loadings were prepared on TiO_2, Nb_2O_5, HAP (hydroxyapatite) and ZrO_2. Commonly used supports such as fumed SiO_2 and carbon black were excluded since we were only interested in catalysts that could promote the dehydration of the ammonium carboxylate as well.[33] The commercially available AUROlite (Au/TiO_2) was also tested. This initial catalyst screening was performed at 200°C, with 6 bar NH_3, 50 bar H_2, 1 mol% Au or 5 mol% Ag, in CPME (Figure 3).
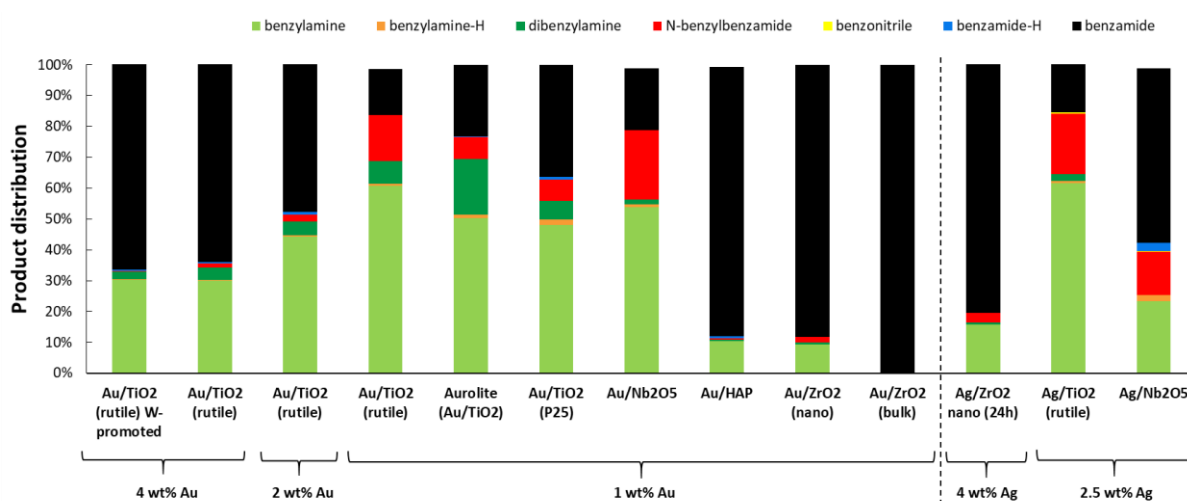

Figure 3 — Catalyst evaluation for the hydrogenation of benzamide. Reaction conditions: benzamide (2 mmol), 200°C, 6 bar NH_3, 50 bar H_2, 1 mol% Au or 5 mol% Ag, undecane (40 µL), CPME (20 mL), 5 h. (Product names ending with "–H" have at least one aromatic ring that is hydrogenated toward a cyclohexyl moiety)

From this catalyst screening, several observations can be made. Firstly, virtually all Au and Ag catalysts have at least some hydrogenation activity with very little overhydrogenation of the aromatic ring (below 5%). Beside the formation of the desired product (up to 65%), significant amounts of dibenzylamine and *N*-benzylbenzamide are formed as well. Secondly, whereas Ru catalysts can be modified with WO_x to improve their amide hydrogenation activity, this strategy does not seem effective for Au.[32-33] Lastly and most importantly, the catalyst support seems to play a very important role in the overall conversion. Especially catalysts with low metal loadings and sufficient Lewis acid sites on the support are very active, e.g. TiO_2 and Nb_2O_5.[45-49] Catalysts with supports that are only mildly Lewis acidic to even basic, e.g. ZrO_2 and HAP (hydroxyapatite), performed poorly. This observation comes to no surprise, since it is generally known that Lewis acid sites help to adsorb the amide to the catalytic surface.[32-33,41,50-57] The quantity of catalyst support plays a remarkably prominent role in the final product yield. A reference reaction with only catalyst support reveals that an intermediate product, i.e. benzonitrile, is formed (Figure S3). This dehydration reaction from amide to nitrile is significantly faster on a TiO_2 (rutile) surface in comparison with the employed ZrO_2. The importance of a sufficient quantity of support becomes clear when comparing the results for Au/TiO_2 (rutile) with a 1, 2 and 4 wt% Au loading (Figure 3). For all three reactions an equal amount of gold (thus a different amount of support) was added; there is a clear increase in product yield when the metal loading is decreased, i.e. when the amount of support is increased. Since differences in Au nanoparticle (NP) size and dispersion between these catalysts were minor, these results suggest that the reaction proceeds via two

consecutive reactions: starting molecule **A** (the amide) is converted to molecule **B** (nitrile intermediate) at the catalyst support, and **B** is converted to **C** (amine product) at the gold surface. To further test this hypothesis, experiments were performed with a fixed weight of catalyst, rather than with the same amount of Au or Ag (Figure S 4). Even with four times less gold present, a 1 wt% Au catalyst (Au/TiO$_2$) still performed slightly better than the 4 wt% Au catalyst, proving that at least for the 1-4 wt% Au/TiO$_2$ catalysts, the amount of Au is largely sufficient; rather the amount of support determines the rate of the slowest step in the sequence, viz. the dehydration of the amide. For the Ag/TiO$_2$ catalyst however, this did not seem to be the case. Replacing a 2.5 wt% Ag catalyst with a 1 wt% Ag catalyst (same catalyst weight) resulted in a clear drop in product yield. Thus, for the Ag catalyst, the hydrogenation on the metal surface seems to be significantly slower. Au/TiO$_2$ (rutile, 1 wt% Au) and Ag/TiO$_2$ (rutile, 2.5 wt% Ag) were selected as the best catalysts. At first glance, it appears that Au/Nb$_2$O$_5$ (1 wt% Au) is an excellent catalyst as well. However, reactions performed with a longer reaction time revealed that this material easily catalyzed the overhydrogenation of the aromatic ring (Figure S 5). Note also that Ag/Nb$_2$O$_5$ performed rather poorly. This is likely also the result of a different catalyst preparation: in contrast to the Au catalysts, the Ag catalyst requires activation at 600°C (calcination). At temperatures above 400°C, Nb$_2$O$_5$ is known to start losing its active sites.[58]

Optimization of the reaction conditions

Reaction conditions were optimized for both Ag/TiO$_2$ (2.5 wt% Ag) and Au/TiO$_2$ (1 wt% Au; Table 1). The favourable influence of the NH$_3$ pressure on the selectivity for benzylamine is expected: high concentrations of NH$_3$ decrease the formation of secondary amine and secondary amides where, in both cases, an extra NH$_3$ molecule is generated (entries 1-3, 10-12). Interestingly, more NH$_3$ also increases the reaction rate itself, although this effect is more pronounced with Ag than with Au. Specifically for the Au catalyst, NH$_3$ has an additional positive effect on the selectivity by hindering the overhydrogenation of the aromatic ring (14% of the initial substrate was overreduced after a reaction with only 2 bar NH$_3$). It is suggested that NH$_3$ is competitive for the adsorption sites on which an aromatic ring can adsorb (they are both Lewis bases). An excess of NH$_3$ will therefore dominate these adsorption sites, thus keeping the aromatic rings relatively safe from overhydrogenation. For the Ag catalyst only traces of overreduced product were detected under the same reaction conditions. This decreased hydrogenation activity, in comparison with the Au catalyst, was also very noticeable when varying the H$_2$ pressure (entries 3-6, 12-20). For Ag/TiO$_2$ there is a clear drop in product yield and reaction rate with decreasing H$_2$ pressure (entries 3-6). The amount of residual benzonitrile increases as well. For Au/TiO$_2$ however, there is nearly no decrease in product yield nor reaction rate with decreasing H$_2$ pressure (entries 12-20). Only when reducing the H$_2$ pressure from 10 to 5 bar, there is a clear drop. This again illustrates that for the Au catalyst, not the hydrogenation but the dehydration of the amide is determining the overall rate. For Au/TiO$_2$ a H$_2$ pressure of 30 bar was selected as the optimum. At this point, there is more than enough H$_2$ for a smooth reaction, but not as much as would result in an overreduction of the aromatic ring (entries 18-20). Next the reaction temperature was varied (entries 3, 8-9, 13, 21-22). Reducing the reaction temperature resulted in a clear drop in product conversion. Not only the endothermic dehydration of the amide is hindered, but the hydrogenation as well; indeed an increasing amount of benzonitrile is present after reaction at lower reaction temperature. Finally, the solvent tolerance was determined (entries 13, 23-30). In general the reaction can be performed in any ether or hydrocarbon solvent, resulting in similar conversions. However, the selectivity for benzylamine differs strongly. This is mainly the influence of the amount of dissolved NH$_3$. Condensation reactions, like secondary amine and amide formation, are prevented in solvents that dissolve more NH$_3$ (at 6 bar NH$_3$, Figure S 6 & S 7). Therefore a higher benzylamine yield can be expected. Nevertheless, one should not add an excessive amount of NH$_3$. A clear drop in reaction rate is observed for a reaction in dioxane where the reaction mixture consists for approximately 33 wt% of NH$_3$ (at 6 bar NH$_3$). Although low quantities of benzonitrile were detected, no hydrogenation products were observed when performing this reaction in an alcohol solvent (entry 30). It is advisable to perform the reaction in either CPME or anisole, as both solvents are recommended in green solvent guides.[59-60] CPME has the advantage to ensure an energy-efficient product isolation,

because of its low heat of evaporation. Anisole, however, ensures a slightly higher benzylamine yield: it dissolves more NH_3 at 6 bar, and more favorably suppresses the competing reduction of the aromatic ring.

Table 1 — Variation of the reaction conditions for the hydrogenation of benzamide with Ag and Au catalysts.[a]

#	Metal	P_{H_2} [bar]	P_{NH_3} [bar]	T [°C]	t [h]	Solvent	Conversion [%]	Selectivity [%]					
								BAm[b]	DiBAm[c]	BAm-H[d]	N-BBenz[e]	Bnit[f]	others
1	Ag	50	2	200	5	CPME[g]	61	42	10	2	42	1	4
2	Ag	50	4	200	5	CPME	79	50	7	1	40	1	1
3	**Ag**	**50**	**6**	**200**	**5**	**CPME**	**84**	**73**	**3**	**1**	**23**	**1**	**<1**
4	Ag	25	6	200	5	CPME	77	56	3	2	33	2	3
5	Ag	10	6	200	5	CPME	60	57	4	<1	28	8	3
6	Ag	5	6	200	5	CPME	36	41	4	<1	21	34	<1
7	**Ag**	**50**	**6**	**200**	**16**	**CPME**	**> 99**	**92**	**4**	**4**	**<1**	**<1**	**<1**
8	Ag	50	6	185	5	CPME	26	65	2	<1	12	18	2
9	Ag	50	6	170	5	CPME	9	37	<1	<1	<1	62	1
10	Au	50	2	200	5	CPME	79	26	11	8	41	1	14
11	Au	50	4	200	5	CPME	86	45	10	5	32	<1	7
12	Au	50	6	200	5	CPME	82	69	9	2	19	<1	2
13	**Au**	**30**	**6**	**200**	**5**	**CPME**	**83**	**70**	**7**	**1**	**21**	**1**	**<1**
14	Au	20	6	200	5	CPME	79	62	7	<1	26	3	2
15	Au	15	6	200	5	CPME	70	61	7	<1	27	4	<1
16	Au	10	6	200	5	CPME	80	58	6	1	31	1	2
17	Au	5	6	200	5	CPME	49	64	5	<1	24	5	3
18	Au	50	6	200	16	CPME	> 99	78	12	6	<1	1	4
19	**Au**	**30**	**6**	**200**	**16**	**CPME**	**97**	**77**	**15**	**1**	**6**	**<1**	**2**
20	Au	15	6	200	16	CPME	97	73	11	2	10	<1	4
21	Au	30	6	185	5	CPME	36	60	7	<1	12	21	1
22	Au	30	6	170	5	CPME	20	42	4	<1	3	49	1
23	Au	30	6	200	5	MeCyclohex.[h]	71	47	46	1	4	1	1
24	Au	30	6	200	5	Toluene	90	58	15	<1	24	2	<1
25	Au	30	6	200	5	TAME[i]	81	55	13	<1	23	7	3
26	Au	30	6	200	5	MeTHF[j]	80	80	5	<1	13	2	1
27	Au	30	6	200	5	DME[k]	72	86	3	<1	7	6	<1
28	Au	30	6	200	5	Anisole	84	74	5	<1	21	1	<1
29	Au	30	6	200	5	Dioxane	45	72	<1	<1	4	26	<1
30	Au	30	6	200	5	TAA[l]	No hydrogenation products						

[a] Reaction conditions: Au/TiO$_2$ (1mol%) or Ag/TiO$_2$ (5 mol%), benzamide (2 mmol) in solvent (20 mL), undecane standard (40 µL) with NH$_3$ and H$_2$. [b]Benzylamine. [c]Dibenzylamine. [d]Benzylamine-H (i.e. aminomethylcyclohexane). [e]N-benzylbenzamide. [f]Benzonitrile. [g]Cyclopentyl methyl ether. [h]Methylcyclohexane. [i]tert-Amyl methyl ether. [j]2-Methyltetrahydrofuran. [k]1,2-Dimethoxyethane. [l]tert-Amyl alcohol.

Unraveling the reaction network

After optimization of the reaction conditions, a time profile was made for the Ag and Au catalysts (Figure 4). The reaction proceeds very similarly on both catalysts. The first products are benzonitrile and benzylamine, with benzonitrile as the intermediate as discussed earlier. Soon after, two additional products are formed: dibenzylamine and *N*-benzylbenzamide. Both are consecutive condensation products of benzylamine. While dibenzylamine is a dead-end product under the conditions of this catalytic reaction, *N*-benzylbenzamide is not. It can be converted into benzylamine. An additional experiment starting from *N*-benzylbenzamide showed that the secondary amide bond can be broken again by ammonolysis, yielding 15% benzamide and 47% benzylamine after a reaction time of 2 h (Figure S 8). This observation is surprising since silver catalysts have been reported to catalyze the hydrogenolytic C-N cleavage of secondary amines resulting in primary amines and alcohols.[41] In none of our experiments was benzyl alcohol detected, nor is the catalyst capable of aminating benzyl alcohol to benzylamine (Figure S 8). This experiment also confirmed that *N*-benzylbenzamide is not hydrogenated directly towards dibenzylamine either. For Ag/TiO$_2$ an excellent yield of 92% benzylamine was obtained after a reaction time of 16 h (full conversion). It is advisable to stop the reaction in time to prevent overreduction and secondary amine

formation. The Au catalyst yielded 80% benzylamine after a reaction time of 24 h, with 18% dibenzylamine as the main side product (full conversion). The global reaction scheme is shown in Figure 5.
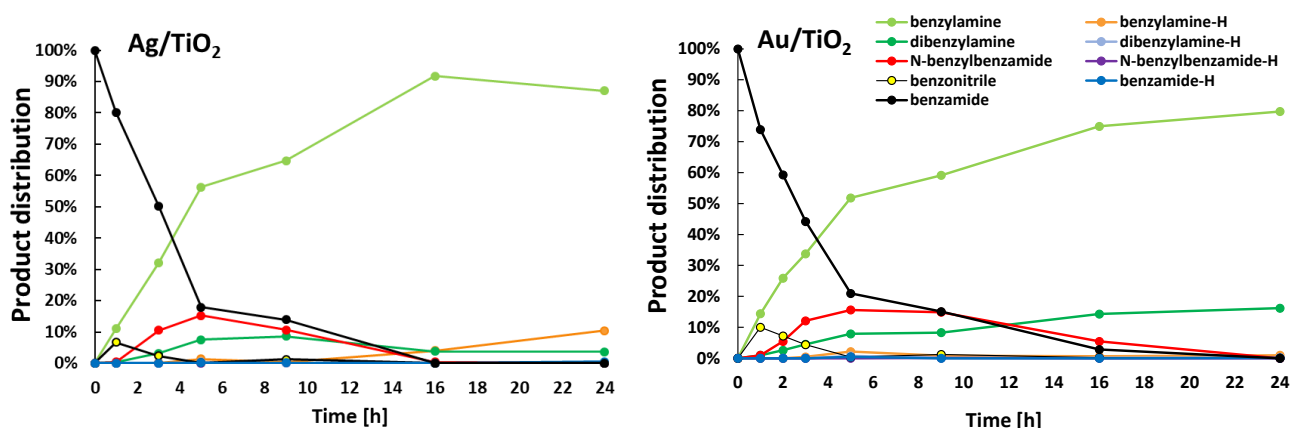

Figure 4 — Time profiles for the hydrogenation of benzamide with Ag/TiO$_2$ (left) and Au/TiO$_2$ (right). Reaction conditions: benzamide (2 mmol), 200°C, 6 bar NH$_3$, 30 bar H$_2$ (Au) or 50 bar H$_2$ (Ag), 1 mol% Au (1 wt% Au catalyst) or 5 mol% Ag (2.5 wt% Ag catalyst), undecane (internal standard, 40 μL), CPME (20 mL). (Product names ending with "–H" have at least one aromatic ring that is hydrogenated toward a cyclohexyl moiety).
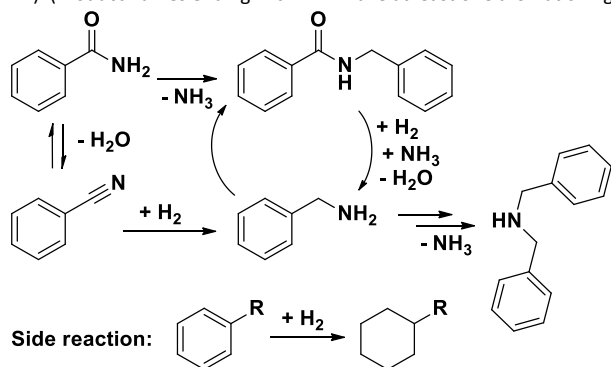
Figure 5 — Reaction scheme for the hydrogenation of benzamide to benzylamine.

DFT calculations

To understand in more detail the mechanism of the selective nitrile hydrogenation on the Au/TiO$_2$ catalyst, we next turned to periodic density functional theory (DFT) calculations using Au$_{13}$/TiO$_2$ as a model catalyst. The detailed description of the computational models and results is summarized in the supporting information, while the key findings are presented in Figure 6. The reaction mechanism for the catalytic reaction is schematically presented in Figure 6a. DFT calculations reveal the synergistic role of the Lewis acid and base sites of the titania support and the metallic Au nanoparticle to establish a low-energy reaction path for the heterolytic cleavage of H$_2$ and subsequent selective hydrogenation of the polar nitrile moiety. The DFT calculations reveal that the Lewis acidic 5-fold coordinated Ti surface sites (Ti^{5c}) preferentially adsorb and activate the benzonitrile substrate (Figure S 16 – S 17), while the Au-O^{2c} Lewis acid-base pair at the Au/TiO$_2$ interface promotes the H$_2$ dissociation. Heterolytic H$_2$ cleavage over the Au-O^{2c} pair site is exothermic (ΔE = 0.29 eV) and has a small activation energy (E_a = 0.29 eV); it produces a couple of proton (H$^+$) and hydride (H$^-$) which can serve for the selective hydrogenation of benzonitrile. Previous studies of H$_2$ dissociation on bare rutile TiO$_2$ (110)[64] and Au/TiO$_2$ (110)[65-66] found that the heterolytic dissociation is favoured in comparison with the homolytic H$_2$ activation. Therefore, here only the former mechanism is considered. Our calculations confirmed that the H$_2$ dissociation at the Ti^{5c}-O^{2c} pair site on the support is both thermodynamically and kinetically less favourable than at the interface Au-O^{2c} site (Figure S 18). The hydrogenation of benzonitrile (PhCN) to benzylamine (PhCH$_2$NH$_2$) proceeds in four consecutive hydride and proton transfer reaction steps (Figure 6c). Our results indicate the H$_2$ activation to be the most energy-demanding reaction step. The end-on coordination of benzonitrile to the Lewis acidic Ti^{5c} site polarizes and activates the CN moiety facilitating thus the hydride transfer step. Indeed, once the H$^{\delta+}$...H$^{\delta-}$ pair is generated at the interface site, the subsequent benzonitrile hydrogenation is

energetically favourable and proceeds with very small activation barriers of 0.10 eV and 0.26 eV for the hydride and proton transfer steps, respectively. Further reduction of the benzylimine intermediate (PhCHNH) to benzylamine (PhCH$_2$NH$_2$) is barrierless. However, the desorption of the PhCH$_2$NH$_2$ product and the regeneration of the Lewis acidic Ti site are quite endothermic by 2.25 eV. By accounting for the translational and rotational entropy gains due to the product desorption at 200 °C, we estimate the Gibbs free energy for this final step to be only 1.11 eV, which is comparable to the overall free energy barriers estimated for the H$_2$ activation steps (Figure S 20). These DFT results indicate that the synergetic action of the multisite environment at the Au-TiO$_2$ interface is the key for the selective nitrile hydrogenation.
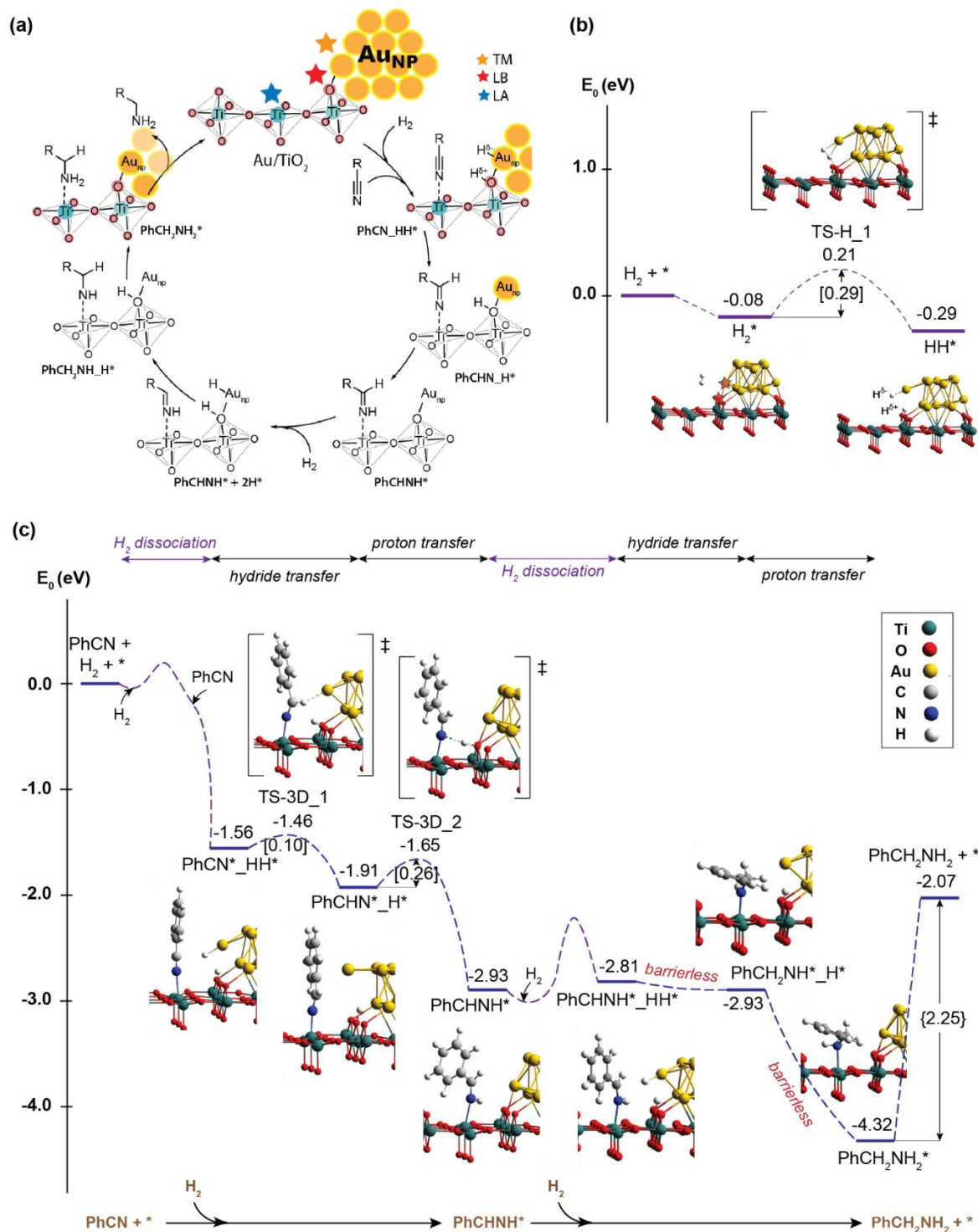
Figure 6 — (a) The mechanism of benzonitrile hydrogenation at the Au/TiO$_2$ interface and the respective DFT-computed reaction energy diagrams for (b) the heterolytic H$_2$ activation at the bare interface site and (c) the catalytic reduction of benzonitrile to benzylamine on the Au$_{13}$/TiO$_2$ model catalyst surface.

Reducing the Au loading of the catalyst

Gold is a very valuable and expensive metal. For this reason it is highly recommended to work with as little gold as possible. Initial experiments suggested that with a 1 wt% Au catalyst on TiO_2 support, the Au does not limit the product formation, but rather the TiO_2 support effecting the dehydration of the amide does (Figure 3, 7 & S 4). Therefore, the Au loading was further decreased and hydrogenation experiments were performed with the same weight of catalyst (Figure 8). From these experiments, two main conclusions arise. Firstly, down to a 0.01 wt% Au loading of the catalyst, the benzamide conversion remains constant. Below this critical point, the activity of the catalyst dropped drastically with decreasing Au loading. Secondly, the selectivity for dibenzylamine decreases with decreasing gold loading. This results in an increase in benzylamine selectivity and yield. As less gold is present, there are fewer active sites that catalyze secondary amine formation (requiring metal catalysis).[32-33,61] The Au/TiO_2 catalyst with a 0.025wt% Au metal loading was selected as the optimal catalyst. This catalyst displays both a good activity and selectivity for the desired product. A hydrogenation experiment with benzamide and this 0.025wt% Au catalyst for 16h, with only 0.025mol% Au, resulted in a yield of 92% benzylamine (Figure S 5). This is identical to the result initially obtained for Ag/TiO_2 (2.5 wt% Ag). Both catalysts are therefore very suitable and relatively cheap hydrogenation catalysts; gold is 70 times more expensive than silver, but 110 times less (metal) weight is required (0.025 mol% Au versus 5 mol% Ag).
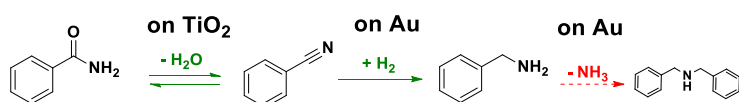
Figure 7 — Simplified reaction scheme for the hydrogenation of benzamide to benzylamine.
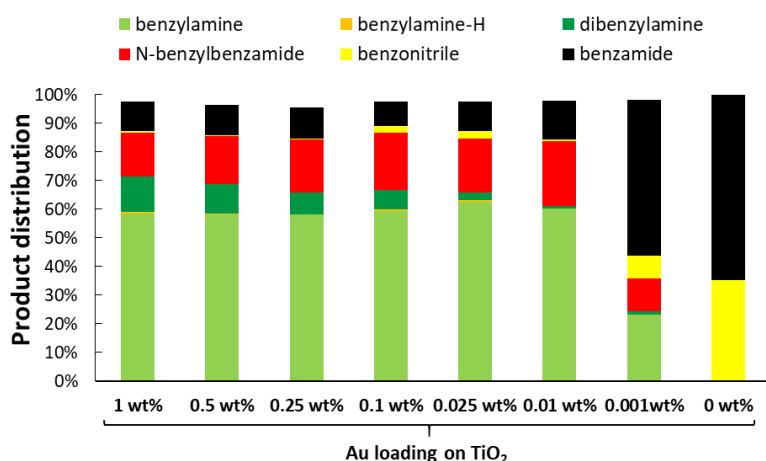
Figure 8 — Variation of the gold loading on a TiO_2 support during the hydrogenation of benzamide. Reaction conditions: benzamide (2 mmol), 200°C, 6 bar NH_3, 30 bar H_2, 0.60 g Au catalyst, undecane (internal standard, 40 µL), CPME (20 mL), 5 h. (Product names ending with "–H" have at least one aromatic ring that is hydrogenated toward a cyclohexyl moiety).

Increasing the volumetric productivity and the influence of water

To make this catalytic system more interesting for application, it may be useful to work in as concentrated conditions as possible. For this reason the concentration of substrate was increased, while the ratio of substrate to catalyst was kept constant (Figure 9). Two main observations could be made. Firstly, although the substrate to catalyst ratio is constant, we see a clear drop in conversion with increasing substrate concentration. This is caused by the hindering effect of extra water which is formed during the reaction (Figure **Figure** 10). Indeed, water accumulation will influence the dehydration equilibrium. More water pushes the equilibrium to the amide, making the reverse reaction (i.e. the hydration of the nitrile) more pronounced. Certainly with catalysts for which the hydrogenation was already limiting, this hindering effect is very noticeable, e.g. for the 2.5 wt% Ag catalyst (Figure 9). Additionally, water also adsorbs to the catalyst.[33] This appears to slow down hydrogenation; observable amounts of benzonitrile were formed with even 3 equivalents of water (Figure 10). We typically find such benzonitrile

accumulation at the very beginning of a reaction (Figure 4). This hindering effect is not surprising since alcohols (i.e. hydroxyl-bearing solvents) have a similar effect (Table 1, entry 30). Secondly, by increasing the substrate concentration, the ratio of substrate to NH_3 increases. This has clear implications for the product selectivity. With relatively less NH_3 present, condensation reactions occur more frequently. Therefore, more dibenzylamine and *N*-benzylbenzamide are formed; for instance, with a 1 wt% Au catalyst at nearly full conversion a yield of 47% benzylamine and 47% dibenzylamine was obtained based on initial benzamide (Figure 9). Industrially, controlled amounts of liquid NH_3 can be added to the reactor to mitigate this selectivity issue. In general, it is definitely possible to work with more concentrated reaction mixtures. However, it is advisable to work in the presence of as little water as possible to improve the catalyst's activity. Increasing the metal loading also improves the overall reaction rate by increasing the hydrogenation rate; this is shown by comparing reactions with 1 wt% Au catalyst with those using 2.5 wt% Ag catalyst). These observations were taken into account when conducting experiments with benzoic acid instead of benzamide (Table 2).
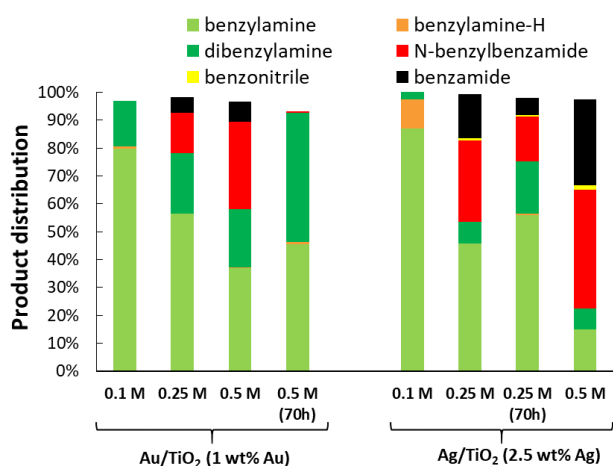
Figure 9 — Hydrogenation of benzamide in more concentrated reaction mixtures. Reaction conditions: benzamide, 200°C, 6 bar NH_3, 30 bar H_2 (Au) or 50 bar H_2 (Ag), 1 mol% Au (1 wt% Au catalyst) or 5 mol% Ag (2.5 wt% Ag catalyst), undecane (internal standard, 40 µL), CPME (20 mL), 24 h. (Product names ending with "–H" have at least one aromatic ring that is hydrogenated toward a cyclohexyl moiety).
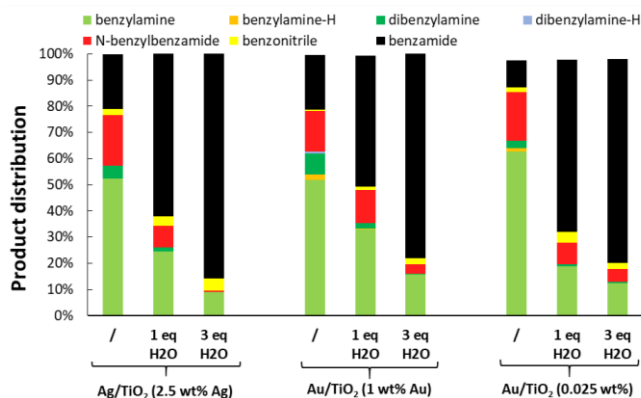

Figure 10 — The influence of water on the hydrogenation of benzamide with Au and Ag catalysts. Reaction conditions: benzamide (2 mmol), 200°C, 6 bar NH_3, 30 bar H_2 (Au) or 50 bar H_2 (Ag), 0.40 g Au catalyst (1 wt% or 0.025 wt%) or 5 mol% Ag (2.5 wt% Ag catalyst), undecane (40 µL), CPME (20 mL), variable amount of water expressed in equivalent in comparison with the amount of substrate, 5 h. (Product names ending with "–H" have at least one aromatic ring that is hydrogenated toward a cyclohexyl moiety).

Catalyst characterization and recycling test

To characterize the catalyst and check the catalysts' stability, high angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) imaging was performed along with energy dispersive X-ray spectroscopy (EDS) elemental mapping and a recycling test (Figure 11 - 13, Table S 1, Figure S 9 – S 13). Overall, the Au catalysts were found to be very catalytically stable, with the catalysts having an average Au nanoparticle (NP) size ranging from 6 nm to 10 nm (0.025 wt% and 1 wt% Au catalyst respectively), with the NPs well dispersed over the catalyst support (Table S 1). After using them once, the mean Au NP size increased very slightly. This stability is also noticeable in the recycling test (Figure 11 – 12). The activity of both the 0.025 wt% and 1 wt% Au catalyst is retained over multiple runs. Characterization of Au/ZrO_2 (1 wt% Au) again illustrated the importance of the catalyst support. While the catalyst has a higher number of surface Au atoms, with an average Au NP size of 6 nm vs 9 nm for 1 wt% Au on TiO_2, it still performed very poorly due to a low amide dehydration rate (Figure 3).

The Ag/TiO_2 catalyst is clearly less stable than the Au catalysts. After using Ag/TiO_2 only once, the average Ag NP size increased drastically from 2.5 nm to 9 nm (Table S 1). Agglomerates with a size even larger than 100 nm were detected (Figure S 12). This decreased stability was also noticeable when performing the recycling test. A clear drop in catalytic activity was observed between the first and second run (Figure 113). Afterwards, however, the catalytic activity remained stable. Thus, although the average Ag NP size increased, the catalyst can be reused several times as well.
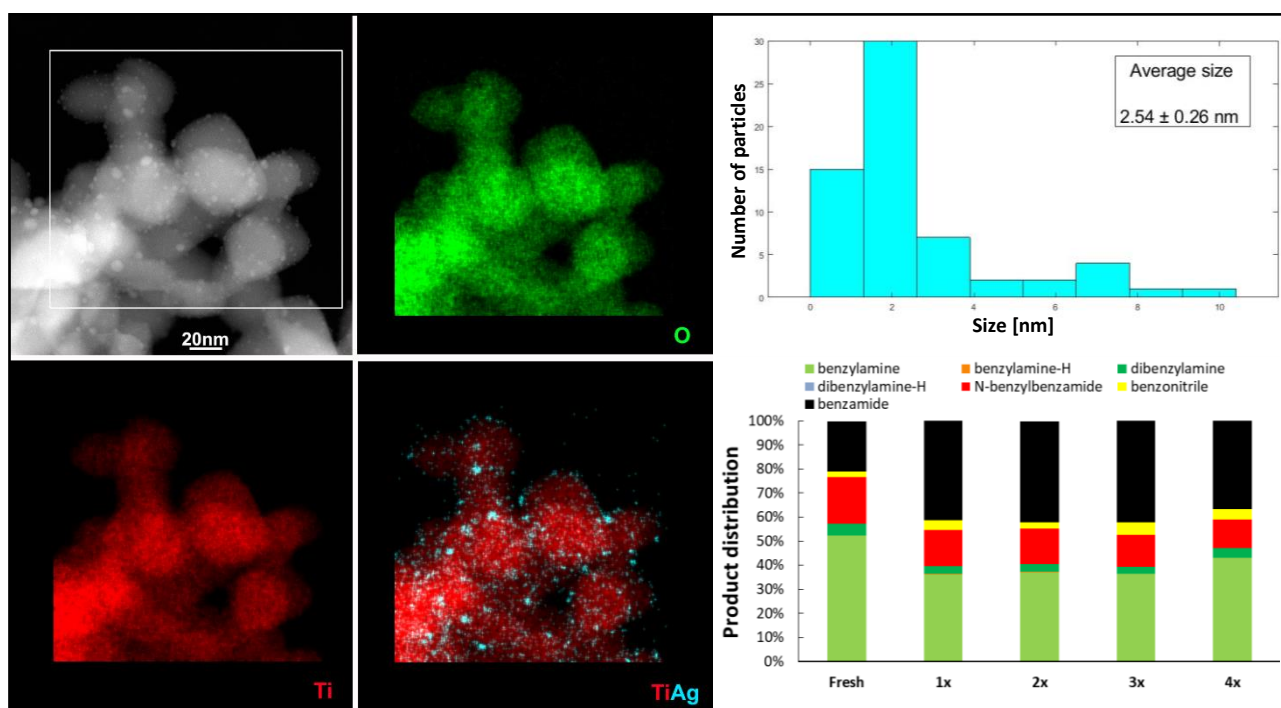
Figure 11 — HAADF-STEM imaging and EDS elemental mapping of Ag/TiO_2 (2.5 wt%, fresh) catalyst. Left: HAADF-STEM overview image of the investigated sample, together with the corresponding EDS elemental maps of Ti, O and Ag. Top right: Size distribution of the supported Ag nanoparticles (NPs) based on 62 NPs. Bottom right: Recycling test of the investigated Ag catalyst. Reaction conditions: benzamide (2 mmol), 200°C, 6 bar NH_3, 50 bar H_2, 5 mol% Ag, undecane (40 µL), CPME (20 mL), 5 h. (Product names ending with "–H" have at least one aromatic ring that is hydrogenated toward a cyclohexyl moiety).
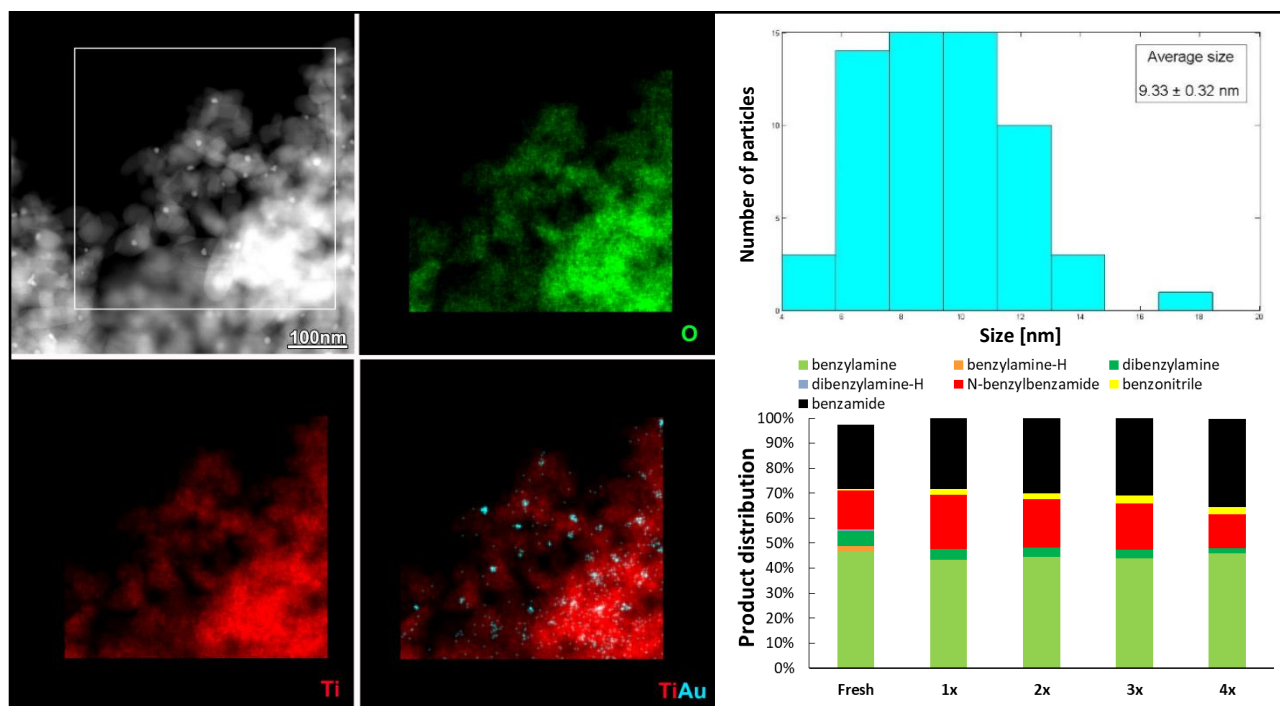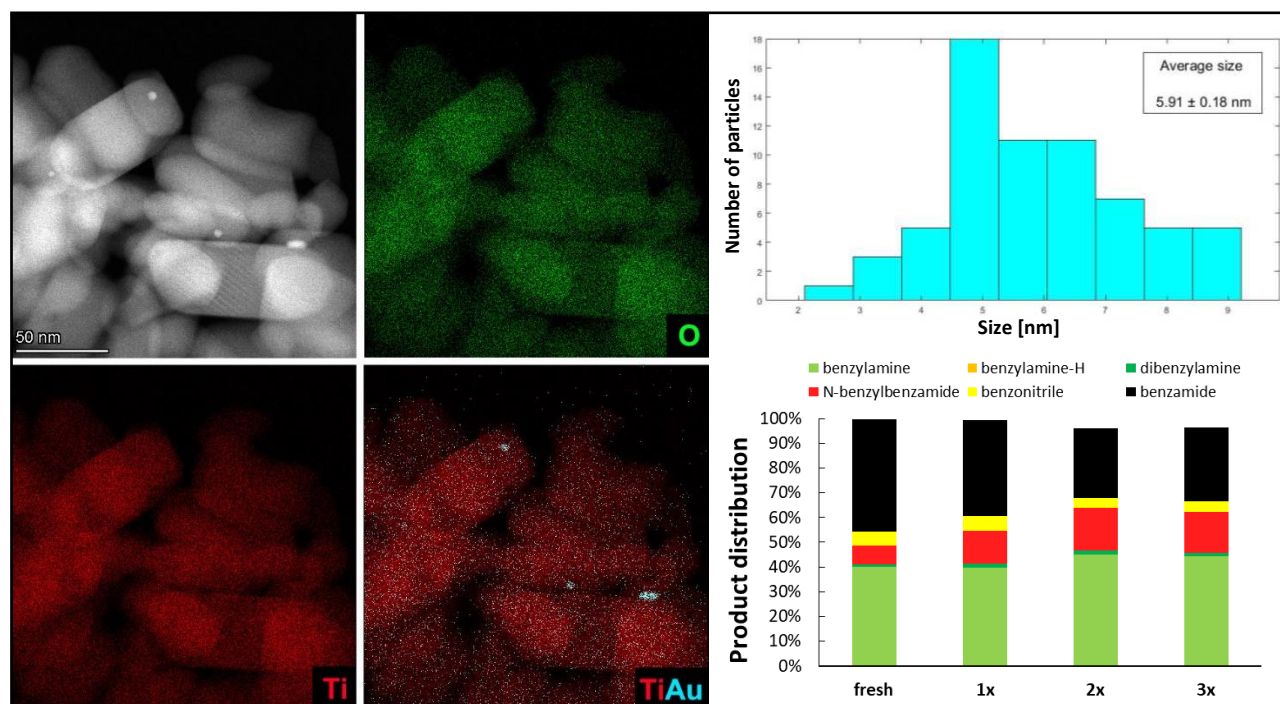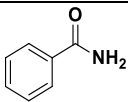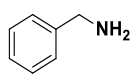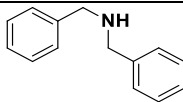
Figure 12 — HAADF-STEM imaging and EDS elemental mapping of Au/TiO$_2$ (1 wt%, fresh) catalyst. Left: HAADF-STEM overview image of the investigated sample, together with the corresponding EDS elemental maps of Ti, O and Au. Top right: Size distribution of the supported Au nanoparticles (NPs) based on 61 NPs. Bottom right: Recycling test of the investigated Au catalyst. Reaction conditions: benzamide (2 mmol), 200°C, 6 bar NH$_3$, 30 bar H$_2$, 1 mol% Au, undecane (40 µL), CPME (20 mL), 5 h. (Product names ending with "–H" have at least one aromatic ring that is hydrogenated toward a cyclohexyl moiety).
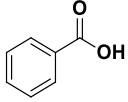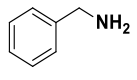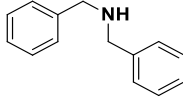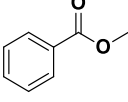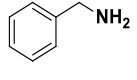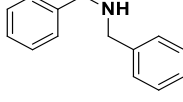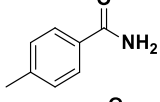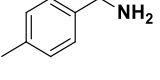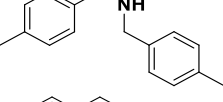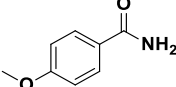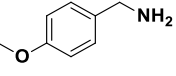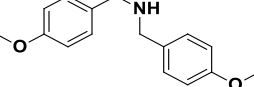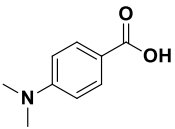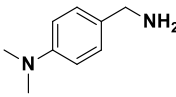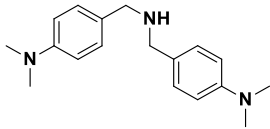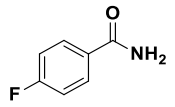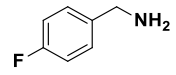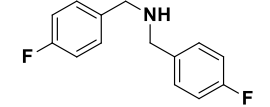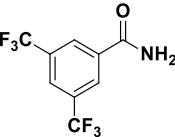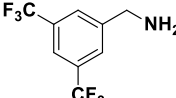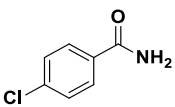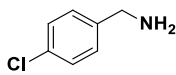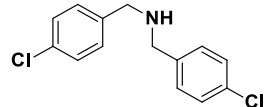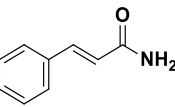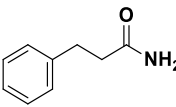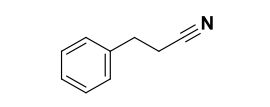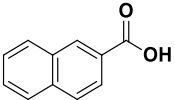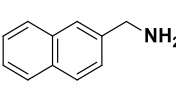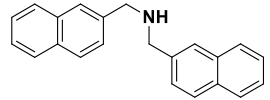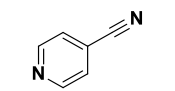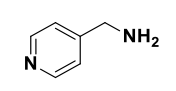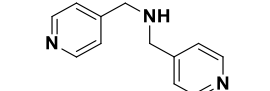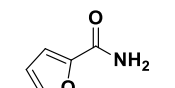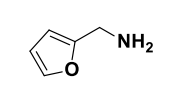
Figure 13 — HAADF-STEM imaging and EDS elemental mapping of Au/TiO$_2$ (0.025 wt%, fresh) catalyst. Left: HAADF-STEM overview image of the investigated sample, together with the corresponding EDS elemental maps of Ti, O and Au. Top right: Size distribution of the supported Au nanoparticles (NPs) based on 66 NPs. Bottom right: Recycling test of the investigated Au catalyst. Reaction conditions: benzamide (2 mmol), 200°C, 6 bar NH$_3$, 30 bar H$_2$, 0.025 mol% Au, undecane (40 µL), CPME (20 mL), 5 h. (Product names ending with "–H" have at least one aromatic ring that is hydrogenated toward a cyclohexyl moiety).

Substrate scope

Finally, the substrate scope was explored (Table 2 & Table S 2). As indicated before, the most attractive option is to perform this reaction starting from benzoic acid. The reaction was performed in fed-batch mode, via an analogous protocol as described in our previous paper: first the amide was formed after a reaction with NH_3.[33] Secondly, H_2 was added and the hydrogenation took place. Although this reaction, resulting in more water formation, required a longer reaction time and slightly higher gold loading, the transformation of benzoic acid to benzylamine could be performed successfully. A yield of 91% benzylamine was obtained, which is an analogous result as when the reaction is performed using benzamide (entries 1-2). Esters of benzoic acid, e.g. methyl benzoate, are also possible reactants (entry 3). Again, the inhibitory effect of an -OH group is clearly noticeable, with methanol being released in the ammonolysis. Despite a ten-fold excess of Au in comparison with a reaction with benzamide, 26% amide remained after reaction (15% benzamide and 11% N-benzylbenzamide). Next, the influence of substituents on the aromatic ring was investigated. Simple substituents such as methyl groups hardly seem to influence the reaction (entry 4). The same can be said for methoxy and dimethylamino groups (entry 5 - 6). These groups remain stable during the reaction, although such mesomerically donating groups appear to promote secondary amine formation. Fluorine groups form no problem either. Although these electron withdrawing groups make the aromatic ring less reactive, the reaction could be performed successfully with both –CF₃ and –F substituents on the aromatic ring (entries 7-8). Reactions with other halogens on the aromatic ring were less successful. Although a significant amount of 4-chlorobenzylamine is formed after a reaction with 4-chlorobenzamide, tiny amounts of dechlorination products were observed as well (2%, entry 9 & Table S2). Since Au is very sensitive to halogen-induced sintering at elevated temperatures[62-63], this is not beneficial for the catalyst stability and will quickly halt the hydrogenation activity of the catalyst; after increasing the reaction time (not shown in table), significant amounts of 4-chlorobenzonitrile still remain. The –Br and –I groups are not stable at all. The same holds for double carbon-carbon bounds outside a ring structure (entry 10). A reaction with cinnamamide resulted in the formation of 3-phenylpropanamide and 3-phenylpropanenitrile. This led to the conclusion that although nitrile formation occurs, the carbonyl group must be located directly on the ring in order to be susceptible to reduction to the amine. If this is not the case, no hydrogenation of the formed nitrile will take place. Not only different substituents but also different types of aromatic rings were studied (entries 11 - 13). The reaction was successful with polycyclic aromatic compounds such as 2-naphthoic acid (entry 11). However, such polycyclic aromatic compounds seem to be more prone to overreduction of the aromatic ring and defunctionalization (Table S 2). The hydrogenation of compounds with N-heterocycles also posed no problem (entry 12). For compounds such as 2-furamide however, i.e. with an oxygen in the ring, the hydrogenation occurred extremely slowly (entry 13).

Table 2 — Substrate scope for the synthesis of aromatic amines with Au catalyst.

	Catalyst	tᵃ [h]	Substrate	Xᵇ [%]	Main product	Sᶜ [%]	Side product	Sᶜ [%]
1	0.025 wt% Au 0.025 mol% Au	16	benzamide	97	benzylamine	95	N-benzylbenzylamine	3
2ᵈ	0.1 wt% Au 0.35 mol% Au	70	benzoic acid	99	benzylamine	91	N-benzylbenzylamine	4
3	0.25 wt% Au 0.25 mol% Au	16	methyl benzoate	74	benzylamine	75	N-benzylbenzylamine	10
4	0.025 wt% Au 0.038 mol% Au	16	4-methylbenzamide	> 99	4-methylbenzylamine	89	di(4-methylbenzyl)amine	10
5	0.025 wt% Au 0.038 mol% Au	16	4-methoxybenzamide	93	4-methoxybenzylamine	73	di(4-methoxybenzyl)amine	26

Entry	Catalyst	Time[a]	Substrate	Conv.[b]	Product	Sel.[c]	By-product	
6[d]	0.1 wt% Au / 0.3 mol% Au	72	(4-dimethylamino benzoic acid)	97	(4-dimethylamino benzylamine)	82	(secondary amine)	15
7	0.025 wt% Au / 0.038 mol% Au	16	(4-fluorobenzamide)	74	(4-fluorobenzylamine)	89	(secondary amine)	11
8	0.025 wt% Au / 0.05 mol% Au	16	(3,5-bis(trifluoromethyl)benzamide)	40	(3,5-bis(trifluoromethyl)benzylamine)	99	/	/
9	0.025 wt% Au / 0.05 mol% Au	16	(4-chlorobenzamide)	31	(4-chlorobenzylamine)	63	(secondary amine)	7
10[d]	0.025 wt% Au / 0.038 mol% Au	16	(cinnamamide)	>99	(3-phenylpropanamide)	65	(3-phenylpropanenitrile)	31
11	0.1 wt% Au / 0.3 mol% Au	72	(2-naphthoic acid)	>99	(2-naphthalenemethanamine)	33	(secondary amine)	12
12	0.025 wt% Au / 0.038 mol% Au	5	(4-cyanopyridine)	68	(4-pyridylmethanamine)	93	(secondary amine)	5
13	0.025 wt% Au / 0.038 mol% Au	16	(furan-2-carboxamide)	10	(furfurylamine)	97	/	/

[a]Reaction time. [b]Conversion, with both primary and secondary amide counted as leftover reagent. [c]Selectivity. Reaction conditions: Substrate (2 mmol), 200°C, 6 bar NH$_3$, 30 bar H$_2$, Au catalyst on TiO$_2$ support, undecane (40 μL), CPME (20 mL). [d] Reactions with carboxylic acids were performed fed batch where first a dehydration of the carboxylic acid to the amide was performed for several hours under solely NH$_3$. Then, the reactor is pressurized with H$_2$ for the giving reaction time.

Conclusion

In conclusion, both Ag/TiO$_2$ and Au/TiO$_2$ are excellent catalysts for the catalytic transformation of benzoic acid (and derivatives) to benzylamine: yields of up to 92% benzylamine were obtained with H$_2$ and NH$_3$ as the only reagents. Additionally, these silver and gold catalyst are reusable and relatively cheap. In case of Au/TiO$_2$ only 0.025 mol% Au is required. Mechanistic analysis by periodic DFT calculations indicates that the synergistic action of the multisite reaction environment at the metal-support interface plays a crucial role in the heterolytic cleavage of H$_2$ and selective polarization and reduction of the CN moiety. We also demonstrated that this reaction can be performed in any ether or hydrocarbon solvent, however we recommend CPME or anisole to establish a green catalytic process. Reactions could be performed with highly concentrated reaction mixtures, although adjustments had to be made (e.g. longer reaction time) to drive the reaction to completion. This is caused by the hindering effect of water. Finally, an extensive substrate scope investigation was performed. The catalyst seemed to be suitable for a significant variety of substrates, resulting in good yields and selectivities for the corresponding primary amine. To our knowledge, this is the first report of a (heterogeneous) reductive amination system for benzoic acids, yielding benzylamines selectively.

Author information

Corresponding Author
E-mail: dirk.devos@kuleuven.be.

ORCID
Robin Coeck: 0000-0002-0630-3753.
Dirk De Vos: 0000-0003-0490-9652.
Sara Bals: 0000-0002-4249-8017.
Thomas Altantzis: 0000-0002-4940-7931.
Jittima Meeprasert: 0000-0002-9947-2600
Guanna Li: 0000-0003-3031-8119
Evgeny Pidko: 0000-0001-9242-9901

Conflicts of interest
There are no conflicts to declare.

Acknowledgements

References

(1)   Nair, U. R.; Sivabalan, R.; Gore, G. M.; Geetha, M.; Asthana, S. N.; Singh, H. Hexanitrohexaazaisowurtzitane (CL-20) and CL-20-Based Formulations (Review). *Combust. Explos. Shock Waves* **2005**, *41* (2), 121–132.

(2)   Heuer, L. Benzylamine. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2006; pp 3–6.

(3)   Xungang, G.; Guoqing, L.; Shaosuo, L.; Yinghui, L.; Xuefeng, L.; Gang, W.; Song, X.; Yunbing, Z. Method for synthesizing benzyl chloride. Patent CN109721466A, 2019.

(4)   Dai, C.; Li, Y.; Ning, C.; Zhang, W.; Wang, X.; Zhang, C. The Influence of Alumina Phases on the Performance of Pd/Al$_2$O$_3$ Catalyst in Selective Hydrogenation of Benzonitrile to Benzylamine. *Appl. Catal. A Gen.* **2017**, *545* (May), 97–103.

(5)   Cao, Y.; Zhang, H.; Dong, J.; Ma, Y.; Sun, H.; Niu, L.; Lan, X.; Cao, L.; Bai, G. A Stable Nickel-Based Catalyst Derived from Layered Double Hydroxide for Selective Hydrogenation of Benzonitrile. *Mol. Catal.* **2019**, *475* (May), 110452.

(6)   De Bellefon, C.; Fouilloux, P. Homogeneous and Heterogeneous Hydrogenation of Nitriles in a Liquid Phase: Chemical, Mechanistic, and Catalytic Aspects. *Catal. Rev.* **1994**, *36* (3), 459–506.

(7)   López-De Jesús, Y. M.; Johnson, C. E.; Monnier, J. R.; Williams, C. T. Selective Hydrogenation of Benzonitrile by Alumina-Supported Ir-Pd Catalysts. *Top. Catal.* **2010**, *53* (15–18), 1132–1137.

(8)   Liu, X.; Wang, Y.; Jin, S.; Li, X.; Zhang, Z. High Performance of Nitrogen-Doped Carbon-Supported Cobalt Catalyst for the Mild and Selective Synthesis of Primary Amines. *Arab. J. Chem.* **2020**, *13* (4), 4916–4925.

(9)   Gomez, S.; Peters, J. A.; Van der Waal, J. C.; Zhou, W.; Maschmeyer, T. Preparation of Benzylamine by Highly Selective Reductive Amination of Benzaldehyde over Ru on an Acidic Activated Carbon Support as the Catalyst. *Catal. Letters* **2002**, *84* (1–2), 1–5.

(10)   Heinen, A. W.; Peters, J. A.; Van Bekkum, H. The Reductive Amination of Benzaldehyde over Pd/C Catalysts: Mechanism and Effect of Carbon Modifications on the Selectivity. *European J. Org. Chem.* **2000**, No. 13, 2501–2506.

(11)   Goto, Y.; Shimizu, K.; Kon, K.; Toyao, T.; Murayama, T.; Ueda, W. NH$_3$-Efficient Ammoxidation of Toluene by Hydrothermally Synthesized Layered Tungsten-Vanadium Complex Metal Oxides. *J. Catal.* **2016**, *344*, 346–353.

(12)   Murugesan, K.; Senthamarai, T.; Sohail, M.; Sharif, M.; Kalevaru, N. V.; Jagadeesh, R. V. Stable and Reusable Nanoscale Fe$_2$O$_3$-Catalyzed Aerobic Oxidation Process for the Selective Synthesis of Nitriles and Primary Amides. *Green Chem.* **2018**, *20* (1), 266–273.

(13)   Anbarasan, P.; Schareina, T.; Beller, M. Recent Developments and Perspectives in Palladium-Catalyzed Cyanation of Aryl Halides: Synthesis of Benzonitriles. *Chem. Soc. Rev.* **2011**, *40* (10), 5049.

(14)   Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. Progress in the Palladium-Catalyzed Cyanation of Aryl Chlorides. *Chem. - A Eur. J.* **2003**, *9* (8), 1828–1836.

(15)   Lv, J.; Shen, Y.; Peng, L.; Guo, X.; Ding, W. Exclusively Selective Oxidation of Toluene to Benzaldehyde on Ceria Nanocubes by Molecular Oxygen. *Chem. Commun.* **2010**, *46* (32), 5909–5911.

(16)   Navio, J. A.; Garcia Gómez, M.; Pradera Adrian, M. A.; Fuentes Mota, J. Partial or Complete Heterogeneous Photocatalytic Oxidation of Neat Toluene and 4-Picoline in Liquid Organic Oxygenated Dispersions Containing Pure or Iron-Doped Titania Photocatalysts. *J. Mol. Catal. A Chem.* **1996**, *104* (3), 329–339.

(17)   Satrio, J. A. B.; Doraiswamy, L. K. Production of Benzaldehyde: A Case Study in a Possible Industrial Application of Phase-Transfer Catalysis. *Chem. Eng. J.* **2001**, *82* (1–3), 43–56.

(18)   Edinger, C.; Waldvogel, S. R. Electrochemical Deoxygenation of Aromatic Amides and Sulfoxides. *European J. Org. Chem.* **2014**, *2014* (24), 5144–5148.

(19)   Zhou, Y.; Wu, S.; Mao, J.; Li, Z. Bioproduction of Benzylamine from Renewable Feedstocks via a Nine-Step Artificial Enzyme Cascade and Engineered Metabolic Pathways. *ChemSusChem* **2018**, *11* (13), 2221–2228.

(20)   Li, M.; Pischetola, C.; Cárdenas-Lizana, F.; Keane, M. A. Production of Benzylamine by Tandem Dehydrogenation/Amination/Reduction over Cu and Au Catalysts. *Appl. Catal. A Gen.* **2020**, *590*, 117368.

(21)   Fujita, K. I.; Furukawa, S.; Morishima, N.; Shimizu, M.; Yamaguchi, R. N-Alkylation of Aqueous Ammonia with Alcohols Leading to Primary Amines Catalyzed by Water-Soluble N-Heterocyclic Carbene Complexes of Iridium. *ChemCatChem* **2018**, *10* (9), 1993–1997.

(22)   Gunanathan, C.; Milstein, D. Selective Synthesis of Primary Amines Directly from Alcohols and Ammonia. *Angew. Chemie* **2008**, *120* (45), 8789–8792.

(23)   Imm, S.; Bähn, S.; Zhang, M.; Neubert, L.; Neumann, H.; Klasovsky, F.; Pfeffer, J.; Haas, T.; Beller, M. Improved Ruthenium-Catalyzed Amination of Alcohols with Ammonia: Synthesis of Diamines and Amino Esters. *Angew. Chemie - Int. Ed.* **2011**, *50* (33), 7599–7603.

(24)   Liu, Y.; Afanasenko, A.; Elangovan, S.; Sun, Z.; Barta, K. Primary Benzylamines by Efficient N-Alkylation of Benzyl Alcohols Using Commercial Ni Catalysts and Easy-to-Handle Ammonia Sources. *ACS Sustain. Chem. Eng.* **2019**, *7* (13), 11267–11274.

(25)   Shimizu, K. I.; Kon, K.; Onodera, W.; Yamazaki, H.; Kondo, J. N. Heterogeneous Ni Catalyst for Direct Synthesis of Primary Amines from Alcohols and Ammonia. *ACS Catal.* **2013**, *3* (1), 112–117.

(26)   Shimizu, K. I.; Kanno, S.; Kon, K.; Hakim Siddiki, S. M. A.; Tanaka, H.; Sakata, Y. N-Alkylation of Ammonia and Amines with Alcohols Catalyzed by Ni-Loaded CaSiO$_3$. *Catal. Today* **2014**, *232*, 134–138.

(27)   Brühne, F.; Wright, E. Benzyl Alcohol. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2000, p 4.

(28)   Pugh, S.; McKenna, R.; Halloum, I.; Nielsen, D. R. Engineering Escherichia Coli for Renewable Benzyl Alcohol Production. *Metab. Eng. Commun.* **2015**, *2* (45), 39–45.

(29)   Arceo, E.; Ellman, J. A.; Bergman, R. G. A Direct, Biomass-Based Synthesis of Benzoic Acid: Formic Acid-Mediated Deoxygenation of the Glucose-Derived Materials Quinic Acid and Shikimic Acid. *ChemSusChem* **2010**, *3* (7), 811–813.

(30)   Pfennig, T.; Carraher, J. M.; Chemburkar, A.; Johnson, R. L.; Anderson, A. T.; Tessonnier, J.-P.; Neurock, M.; Shanks, B. H. A New Selective Route towards Benzoic Acid and Derivatives from Biomass-Derived Coumalic Acid. *Green Chem.* **2017**, *19* (20), 4879–4888.

(31)   Perret, N.; Wang, X.; Delgado, J. J.; Blanco, G.; Chen, X.; Olmos, C. M.; Bernal, S.; Keane, M. A. Selective Hydrogenation of Benzoic Acid over Au Supported on CeO_2 and $Ce_{0.62}Zr_{0.38}O_2$: Formation of Benzyl Alcohol. *J. Catal.* **2014**, *317*, 114–125.

(32)   Coeck, R.; Berden, S.; De Vos, D. E. Sustainable Hydrogenation of Aliphatic Acyclic Primary Amides to Primary Amines with Recyclable Heterogeneous Ruthenium–Tungsten Catalysts. *Green Chem.* **2019**, *21* (19), 5326–5335.

(33)   Coeck, R.; De Vos, D. E. One-Pot Reductive Amination of Carboxylic Acids: A Sustainable Method for Primary Amine Synthesis. *Green Chem.* **2020**, *22* (15), 5105–5114.

(34)   Jiye, B.; Shaohui, C.; Xinhua, C.; Yilong, G.; Lin, K.; Na, L.; Jun, M.; Hailong, S.; Yanyu, W.; Yuexing, X.; Aiwu, Y. Manufacturing method of nitrile and corresponding amine thereof, Patent CN104557357A, 2015.

(35)   Kenji, Y. Method for producing amine through reduction of amide, Patent WO2020129749, 2020.

(36)   Itagaki, S.; Sunaba, H.; Kamata, K.; Yamaguchi, K.; Mizuno, N. Hydrosilylation of Various Multiple Bonds by a Simple Combined Catalyst of a Tungstate Monomer and Rhodium Acetate. *Chem. Lett.* **2013**, *42* (9).

(37)   Zhang, T.; Zhang, Y.; Zhang, W.; Luo, M. A Convenient and General Reduction of Amides to Amines with Low-Valent Titanium. *Adv. Synth. Catal.* **2013**, *355* (14–15), 2775–2780.

(38)   Giannis, A.; Sandhoff, K. $LiBH_4(NaBH_4)/Me_3SiCl$, an Unusually Strong and Versatile Reducing Agent. *Angew. Chemie Int. Ed. English* **1989**, *28* (2), 218–220.

(39)   Yang, C.; Pittman, C. U. Reductions of Organic Functional Groups Using $NaBH_4$ or $NaBH_4/LiCl$ in Diglyme at 125 to 162 °C. *Synth. Commun.* **1998**, *28* (11), 2027–2041.

(40)   Zhao, Y.; Zhang, S.; Yamamoto, Y.; Bao, M.; Jin, T.; Terada, M. Heterogeneous Catalytic Reduction of Tertiary Amides with Hydrosilanes Using Unsupported Nanoporous Gold Catalyst. *Adv. Synth. Catal.* **2019**, *361* (20), 4817–4824.

(41)   Xie, Y.; Hu, P.; Bendikov, T.; Milstein, D. Heterogeneously Catalyzed Selective Hydrogenation of Amides to Alcohols and Amines. *Catal. Sci. Technol.* **2018**, *8* (11), 2784–2788.

(42)   Chen, Y.; Wang, C.; Liu, H.; Qiu, J.; Bao, X. Ag/SiO_2: A Novel Catalyst with High Activity and Selectivity for Hydrogenation of Chloronitrobenzenes. *Chem. Commun.* **2005**, *8* (42), 5298.

(43)   Ai, L.; Jiang, J. Catalytic Reduction of 4-Nitrophenol by Silver Nanoparticles Stabilized on Environmentally Benign Macroscopic Biopolymer Hydrogel. *Bioresour. Technol.* **2013**, *132* (42), 374–377.

(44)   Qin, L.; Zeng, G.; Lai, C.; Huang, D.; Zhang, C.; Cheng, M.; Yi, H.; Liu, X.; Zhou, C.; Xiong, W.; Huang, F.; Cao, W. Synthetic Strategies and Application of Gold-Based Nanocatalysts for Nitroaromatics Reduction. *Sci. Total Environ.* **2019**, *652* (42), 93–116.

(45)   Murayama, T.; Chen, J.; Hirata, J.; Matsumoto, K.; Ueda, W. Hydrothermal Synthesis of Octahedra-Based Layered Niobium Oxide and Its Catalytic Activity as a Solid Acid. *Catal. Sci. Technol.* **2014**, *4* (12), 4250–4257.

(46)   Bensitel, M.; Saur, O.; Lavalley, J. C.; Mabilon, G. Acidity of Zirconium Oxide and Sulfated ZrO_2 Samples. *Mater. Chem. Phys.* **1987**, *17* (3), 249–258.

(47)   Nakajima, K.; Hirata, J.; Kim, M.; Gupta, N. K.; Murayama, T.; Yoshida, A.; Hiyoshi, N.; Fukuoka, A.; Ueda, W. Facile Formation of Lactic Acid from a Triose Sugar in Water over Niobium Oxide with a Deformed Orthorhombic Phase. *ACS Catal.* **2018**, *8* (1), 283–290.

(48)   Ferretto, L.; Glisenti, A. Surface Acidity and Basicity of a Rutile Powder. *Chem. Mater.* **2003**, *15* (5), 1181–1188.

(49)   Komanoya, T.; Nakajima, K.; Kitano, M.; Hara, M. Synergistic Catalysis by Lewis Acid and Base Sites on ZrO_2 for Meerwein–Ponndorf–Verley Reduction. *J. Phys. Chem. C* **2015**, *119* (47), 26540–26546.

(50)   Tamura, M.; Ishikawa, S.; Betchaku, M.; Nakagawa, Y.; Tomishige, K. Selective Hydrogenation of Amides to Alcohols in Water Solvent over a Heterogeneous CeO_2-Supported Ru Catalyst. *Chem. Commun.* **2018**, *54* (54), 7503–7506.

(51)   Shimizu, K.; Onodera, W.; Touchy, A. S.; Siddiki, S. M. A. H.; Toyao, T.; Kon, K. Lewis Acid-Promoted Heterogeneous Platinum Catalysts for Hydrogenation of Amides to Amines. *ChemistrySelect* **2016**, *1* (4), 736–740.

(52)   Hirosawa, C.; Wakasa, N.; Fuchikami, T. Hydrogenation of Amides by the Use of Bimetallic Catalysts Consisting of Group 8 to 10, and Group 6 or 7 Metals. *Tetrahedron Lett.* **1996**, *37* (37), 6749–6752.

(53)   Mitsudome, T.; Miyagawa, K.; Maeno, Z.; Mizugaki, T.; Jitsukawa, K.; Yamasaki, J.; Kitagawa, Y.; Kaneda, K. Mild Hydrogenation of Amides to Amines over a Platinum-Vanadium Bimetallic Catalyst. *Angew. Chemie Int. Ed.* **2017**, *56* (32), 9381–9385.

(54)   Smith, A. M.; Whyman, R. Review of Methods for the Catalytic Hydrogenation of Carboxamides. *Chem. Rev.* **2014**, *114* (10), 5477–5510.

(55)   Beamson, G.; Papworth, A. J.; Philipps, C.; Smith, A. M.; Whyman, R. Selective Hydrogenation of Amides Using Bimetallic Ru/Re and Rh/Re Catalysts. *J. Catal.* **2011**, *278* (2), 228–238.

(56)   Beamson, G.; Papworth, A. J.; Philipps, C.; Smith, A. M.; Whyman, R. Selective Hydrogenation of Amides Using Rh/Mo Catalysts. *J. Catal.* **2010**, *269* (1), 93–102.

(57)   Beamson, G.; Papworth, A. J.; Philipps, C.; Smith, A. M.; Whyman, R. Selective Hydrogenation of Amides Using Ruthenium/ Molybdenum Catalysts. *Adv. Synth. Catal.* **2010**, *352* (5), 869–883.

(58)   Murayama, T.; Chen, J.; Hirata, J.; Matsumoto, K.; Ueda, W. Hydrothermal Synthesis of Octahedra-Based Layered Niobium Oxide and Its Catalytic Activity as a Solid Acid. *Catal. Sci. Technol.* **2014**, *4* (12), 4250–4257.

(59)   Prat, D.; Hayler, J.; Wells, A. A Survey of Solvent Selection Guides. *Green Chem.* **2014**, *16* (10), 4546–4551.

(60)   de Gonzalo, G.; Alcántara, A. R.; Domínguez de María, P. Cyclopentyl Methyl Ether (CPME): A Versatile Eco-Friendly Solvent for Applications in Biotechnology and Biorefineries. *ChemSusChem* **2019**, *12* (10), 2083–2097.

(61)   Lu, S.; Wang, J.; Cao, X.; Li, X.; Gu, H. Selective Synthesis of Secondary Amines from Nitriles Using Pt Nanowires as a Catalyst. *Chem. Commun.* **2014**, *50* (26), 3512–3515.

(62)   Cárdenas-Lizana, F.; Keane, M. A. The Development of Gold Catalysts for Use in Hydrogenation Reactions. *J. Mater. Sci.* **2013**, *48* (2), 543–564.

(63)   Oros-Ruiz, S.; Zanella, R.; López, R.; Hernández-Gordillo, A.; Gómez, R. Photocatalytic Hydrogen Production by Water/Methanol Decomposition Using Au/TiO_2 Prepared by Deposition–Precipitation with Urea. *J. Hazard. Mater.* **2013**, *263* (2), 2–10.

(64)   Hu, G.; Wu, Z., Jiang, D. First Principles Insight into H_2 Activation and Hydride Species on TiO_2 Surfaces. *J. Phys. Chem. C.* **2018**, 122, 20323-20328

(65)   Yang, B.; Cao, X.-M.; Gong, X.-Q.; Hu, P. A density functional theory study of hydrogen dissociation and diffusion at the perimeter sites of Au/TiO_2. *Phys. Chem. Chem. Phys.* **2012**, 14, 3741-3745.

(66)   Sun, K.; Kohyama, M.; Tanaka, S.; Takeda, S. A Study on the Mechanism for H_2 Dissociation on Au/TiO_2 Catalysts. . *J. Phys. Chem. C.* **2014**, 118, 1611-1617.