

Selective Hydrogenation of Nitriles to Primary Amines Catalyzed by a Polysilane/SiO₂-Supported Palladium Catalyst under Continuous-Flow Conditions

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Hydrogenation of nitriles to primary amines with heterogeneous catalysts under liquid-phase continuous-flow conditions is described. Newly developed polysilane/SiO₂-supported Pd was found to be an effective catalyst and various nitriles were converted into primary amine salts in almost quantitative yields under mild reaction conditions. Interestingly, a complex mixture was obtained under batch conditions. Lifetime experiments showed that this catalyst remained active for more than 300 h ($TON \geq 10000$) without loss of selectivity and no metal leaching from the catalyst occurred. By using this continuous-flow hydrogenation, synthesis of venlafaxine, an antidepressant drug, has been accomplished.

Amines are important compounds in society as well as in industry. Particularly, primary amines are often seen in bioactive compounds and are used as synthetic intermediates of natural products and active pharmaceutical ingredients (APIs).^[1] Recent development of transition-metal catalysis with primary amines such as C–N coupling reactions^[2a,b] and hydroaminations^[2c] has expanded the range of potential applications for the synthesis of complex molecules.^[3] Among several synthetic methods of primary amines,^[4–7] the catalytic hydrogenation of nitriles is one of the most attractive approaches from the viewpoint of both green chemistry and the availability of starting materials. However, the reaction generally suffers from limited substrate scope and low selectivity. A serious issue is the formation of side products such as secondary and tertiary amines.^[8] Whereas homogeneous catalysts based on precious metals such as Ir, Rh, and Ru with complex ligands have often been employed,^[9] quite recently Beller et al. and Milstein et al.

independently developed abundant and less toxic Fe, Co, and Mn catalysts for the selective hydrogenation of nitriles to primary amines.^[10] On the other hand, heterogeneous catalysts have advantages over homogeneous catalysts in terms of the separation of catalysts and products as well as the recovery and reuse of catalysts. However, heterogeneous Co, Ni, and Rh for hydrogenation of nitriles have been employed as catalysts under harsh conditions and with limited substrate scope.^[11] Relatively mild conditions were achieved with Pd catalysts; however, there is still much room for improvement with respect to both yield and selectivity.^[12]

Although, with the exception of gaseous reactions,^[13] most previous methods with homogeneous and heterogeneous catalysts have been conducted in batch systems, continuous-flow systems have several advantages over batch systems in terms of environmental compatibility, efficiency, and safety.^[14,15] High productivity and saving of energy and space can be attained by using flow systems, and it is possible to adjust the quantity of production by controlling the rate of introduction of starting materials (“just-in-time” production). Furthermore, the separation of catalysts from products is not required when columns packed with suitable heterogeneous catalysts are used. However, compared with batch methods, synthesis by using flow methods is generally more challenging. In particular, continuous-flow reactions with heterogeneous catalysts are difficult, despite of the advantages noted above. Here, we describe hydrogenation of nitriles to primary amines with heterogeneous catalysts under liquid-phase continuous-flow conditions.

At the outset, poly(dimethylsilane)-supported Pd catalysts^[16] with different second supports (DMPSi-Pd/support) such as Al₂O₃ and SiO₂ were prepared. The prepared heterogeneous catalysts were then employed for the hydrogenation of decanenitrile (**1a**), which was chosen as a model substrate for this investigation. A solution of **1a** in 1-propanol/H₂O co-solvent was flowed through a plastic tube by using a peristaltic pump and then passed through a glass tube packed with a DMPSi-Pd/support catalyst heated in an aluminum heating block with a stream of H₂ gas, the pressure of which was regulated by using a mass-flow controller. The resulting solution was collected, evaporated, and analyzed with ¹H NMR spectroscopy.

Under these conditions, a range of reaction parameters such as catalyst, temperature, concentration, flow rate, and additive were investigated (Table 1). Hydrogenation of **1a** with DMPSi-Pd/Al₂O₃ catalyst under 150 kPa(G) H₂ pressure resulted in 19% conversion, yielding less than 16% of the primary amine along with small amounts of the secondary and the tertiary amines (Table 1, entry 1). To our delight, the addition of HCl^[17] im-

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Table 1. Optimization of Flow Hydrogenation of decanenitrile (1a).

Entry	Pd [mmol]	2nd support	Temp. [°C]	Time [h]	Conv. [%] ^[a]	Yield [%] ^[a]
1 ^[b]	0.045	Al ₂ O ₃	60	3	19	< 16
2	0.045	Al ₂ O ₃	60	3	76	73 ^[h]
3	0.045	SiO ₂	60	3 (18)	23 (23)	23 (23)
4	0.045	C	60	3 (18)	80 (33)	80 (33)
5	0.18	Al ₂ O ₃	80	3 (18)	82 (84)	68 (70) ^[i]
6	0.18	SiO ₂	80	3 (18)	89 (89)	89 (89)
7	0.18	C	80	3 (18)	85 (56)	79 (49)
8 ^[c]	0.18	SiO ₂	80	3	86	86
9 ^[d]	0.18	SiO ₂	80	3	95	85
10 ^[e]	0.18	SiO ₂	80	3	92	81
11	0.18	SiO ₂	90	3	95	95
12 ^[f]	0.36	SiO ₂	70–60	3	99	98
13 ^[g]	2.5 mol%	SiO ₂	90	3	ND	complex

[a] Determined by using ¹H NMR analysis; numbers in parenthesis are the results after 18 h. [b] Without HCl. [c] H₂ pressure = 250 kPa(G). [d] Concentration = 0.1 M. [e] Flow rate = 0.05 mL min⁻¹. [f] Connecting a second identical catalyst column after the first column; reaction temperature for first column: 70 °C, second column: 60 °C. [g] Reaction was performed under batch conditions; ND = not determined. [h] Side product, 1-decanol was obtained in 3% yield. [i] 1-Decanol was obtained in 12 (11)% yield.

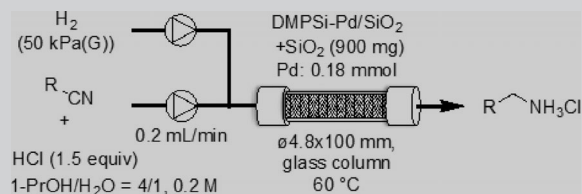
proved both the conversion and the selectivity (entry 2). Considering that amine salts are more stable than free amines and are easily purified by recrystallization, we prepared amine salts instead of free amines in this investigation. To improve the selectivity, alternative second supports were investigated. By using SiO₂ as the second support, the primary amine salt was obtained in 23% yield without any side products formation (entry 3). The catalyst activity was not lost during 15 h further reaction. On the other hand, the use of commercially available Pd/C led to excellent reactivity and selectivity for the first 3 h; however, after 18 h, the reactivity dropped significantly (entry 4). For a more detailed comparison of these catalysts with higher conversion, the loading of Pd was increased to 0.18 mmol and the reaction temperature was increased to 80 °C. Under these conditions, DMPSi-Pd/Al₂O₃ gave a slightly improved conversion; however, a significant amount of an alcohol was produced and almost the same result was obtained after 18 h (entry 5). However, by using DMPSi-Pd/SiO₂ as the catalyst, the conversion improved dramatically without any formation of side products (entry 6). Pd/C also gave a good conversion for the first 3 h; however, a non-negligible amount of a secondary amine was produced and, moreover, the catalyst activity was significantly diminished after 18 h (entry 7). We decided to use DMPSi-Pd/SiO₂ as an optimal catalyst and other reaction conditions were examined. Increasing the H₂ pressure did not improve the conversion (entry 8). Decreasing the concentration and the flow rate improved the conversion to 95 and 92%, respectively. However, 10% of the secondary amine

was obtained as a side product in both cases (entries 9 and 10). On the other hand, increasing the reaction temperature to 90 °C improved the conversion to 95% without any side product formation (entry 11). Alternatively, connecting a second identical catalyst column after the first column enabled the desired product to be afforded in 98% yield even at 60 and 70 °C (entry 12). Interestingly, performing the reaction under batch conditions gave a complex mixture (entry 13). Although direct comparison between the result in a batch system and that in a flow system is difficult, the flow condition is the key to achieving high conversion and selectivity.

With optimized reaction conditions in hand, the substrate scope of the reaction with respect to nitriles was investigated. The reaction was performed for 18 h, and analyzed at 3, 6, and 18 h stages after the flow started. First, aromatic nitriles were tested. Generally, aromatic nitriles are more easily reduced to primary amines, which allowed the reaction temperature to be decreased to 60 °C and the pressure of H₂ to 50 kPa(G). Furthermore, the flow rate could be increased to 0.2 mL min⁻¹, which could produce more than 40 mmol of the product for 18 h continuous-flow reaction. By using benzonitrile or *m*- or *p*-Me substituted benzonitrile derivatives as substrates, the products were obtained in almost quantitative yields (Table 2, entries 1–3). A sterically demanding *o*-Me substituent derivative required higher H₂ pressure to achieve a quantitative yield (entry 4). Higher pressure of H₂ was also required for electron-donating *p*-OMe and OH-substituted derivatives (entries 5 and 6). On the other hand, electron-poor aromatic substrates produced benzylic alcohols as side products. However, changing the solvent system to an anhydrous system completely suppressed the formation of side products (entries 7–9). Heteroaromatic nitriles also gave corresponding amines in excellent yields (entries 10 and 11). Interestingly, when DMPSi-Pd/Al₂O₃ was used as a catalyst, hydrogenation of the pyridine ring also took place to give a complex mixture. Furthermore, a dinitrile could be reduced to the corresponding diamine in an almost quantitative yield (entry 12). It should be noted that, in all cases, almost pure compounds were obtained in excellent yields through simple evaporation of the solvent, and the yields were stable for at least 18 h under continuous-flow conditions.

Next, more demanding aliphatic nitriles were employed as substrates by connecting two catalyst columns. As described in the optimization section, two connected columns heated at 70 and 60 °C, respectively, were used for aliphatic substrates. At first, primary nitriles were reduced to the corresponding amines in excellent yields (Table 2, entries 1 and 2). More sterically demanding secondary and tertiary nitriles also gave the desired amines in excellent yields (entries 3 and 4). The low reaction temperature means that acetonitrile (b.p. 82 °C) could be employed in this reaction to afford an almost quantitative yield (entry 5). Furthermore, an ester group is tolerant under the conditions, giving the amino ester in EtOH/dioxane (entry 6). Finally, by using DMPSi-Pd/Al₂O₃, adiponitrile was converted into 1,6-hexamethylene diamine, which is an industrially important process (entry 7).

Table 2.



Entry	R	Yield [%]	Entry	R	Yield [%]
Substrate scope (1): aromatic nitriles					
1	C ₆ H ₅ (2b)	quant.	7 ^[a]	<i>p</i> -CF ₃ C ₆ H ₄ (2h)	quant.
2	<i>m</i> -MeC ₆ H ₄ (2c)	99–quant.	8 ^[a]	<i>p</i> -FC ₆ H ₄ (2i)	quant.
3	<i>p</i> -MeC ₆ H ₄ (2d)	99–quant.	9 ^[a,b]	1-Naph (2j)	97–98
4 ^[c]	<i>o</i> -MeC ₆ H ₄ (2e)	quant.	10 ^[a]	2-Py (2k)	99
5 ^[c]	<i>p</i> -OMeC ₆ H ₄ (2f)	99	11 ^[a]	3-Py (2l)	99–quant.
6 ^[c]	<i>p</i> -OHC ₆ H ₄ (2g)	97–98	12	<i>m</i> -CNC ₆ H ₄ (2m)	99
Substrate scope (2): aliphatic nitriles					
1	ⁿ C ₉ H ₁₉ (2a)	98	5	Me (2q)	99–quant.
2	Me ₂ CHCH ₂ (2n)	98–99	6	EtO ₂ CCH ₂ (2r)	97
3	ⁱ Pr (2o)	98	7	CN(CH ₂) ₄ (2s)	97
4	^t Bu (2p)	quant.			
Substrate scope (3): benzyl cyanides					
1	PhCH ₂ (2t)	99–quant.	3	3,4-(OMe) ₂ C ₆ H ₃ CH ₂ (2v)	quant.
2	4-OMeC ₆ H ₄ CH ₂ (2u)	quant.	4	4-FC ₆ H ₄ CH ₂ (2w)	quant.

[a] MeOH/dioxane = 9:1 as solvent. [b] 0.1 M concentration and 0.4 mL min⁻¹ flow rate. [c] 150 KPa(G). [d] EtOH/dioxane = 9:1 as solvent. [e] Using DMPSi-Pd/Al₂O₃ as catalyst.

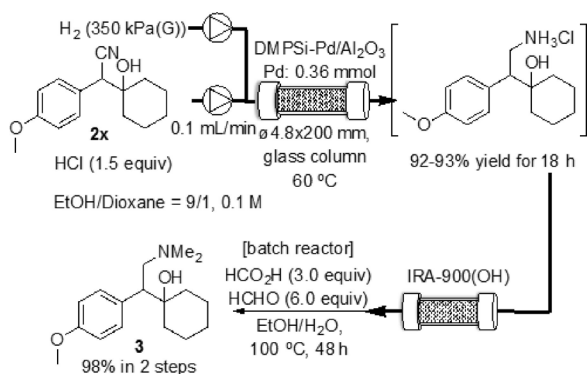
Hydrogenation of benzyl cyanides provided compounds of the phenethylamine family, which is known to have biological activity. Notably, the hydrogenation of benzyl cyanide (**2t**) took place even at 50 °C to afford the desired product in excellent yield (Table 2, entry 1). Other benzyl cyanides with either electron-donating or electron-withdrawing substituents on the phenyl ring were also converted into the corresponding primary amine salts in quantitative yields under the same conditions (entries 2–4). Interestingly, benzyl cyanides could be hydrogenated under milder reaction conditions than decanenitrile (**1a**). The result may indicate that reactivity of CN parts does not affect the overall conversion or yield of the reduction. To confirm this point, hydrogenation of isovaleronitrile was performed under optimized conditions for benzyl cyanides. As a result, the desired product was obtained in almost quantitative yield. Considering that the reactivity of the CN part did not affect the yield and that increasing H₂ pressure did not improve the conversion, the rate-limiting step of this catalysis might be the adsorption of a nitrile or the desorption of an amine. Given that long alkyl chain amines are known to be good stabilizers for Pd nanoparticles, the desorption of an amine may be the rate-determining step. Addition of HCl may enhance the desorption of an amine to make an amine salt, which results in a higher conversion.

Investigations on lifetime and leaching of this catalyst were conducted for 300 h with 0.5 M concentration using benzonitrile as the substrate. The yield was determined every 12 h and the contamination of Pd in the product was determined every 24 h through inductively coupled plasma (ICP) analysis. As

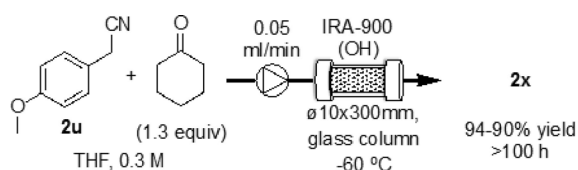
a result, the product was obtained in quantitative yield for 300 h (1.80 mol, TON = 10078) and the yield remained stable during the whole reaction time. Furthermore, the ICP analysis showed the amount of Pd contaminated in the product was under the detection limit (less than 7.44 × 10⁻² μg per 1 g of the product). The leaching of Si was also measured by using the same method, and the amount of Si in 1 g of the product was determined to be 1.99 μg. The catalyst after the reaction proceeded for 300 h was analyzed by using scanning transmission electron microscopy (STEM), and the obtained image shows that some parts of the Pd particles aggregated to form > 50 nm particles, whereas the remaining parts maintained an average particle size of 7.0 nm.

Finally, to demonstrate the utility of this continuous-flow reaction, the synthesis of venlafaxine (**3**) was undertaken (Scheme 1). Venlafaxine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor class. The key step for the synthesis is hydrogenation of nitrile **2x**.^[18] DMPSi-Pd/Al₂O₃ was found to be a suitable catalyst for this reaction, giving the desired compound in 92–93% yield after 18 h. Subsequent neutralization and dimethylation led to the formation of **3** in excellent yield.

It was also found that nitrile **2x** was readily prepared from commercially available benzyl nitrile **2u** and cyclohexanone by using ion-exchange resin IRA-900 (OH) as the catalyst under continuous-flow conditions (Scheme 2). Development of multi-step continuous-flow synthesis of venlafaxine (**3**) from commercially available materials is ongoing in our laboratories.



Scheme 1. Synthesis of Venlafaxine (3).



Scheme 2. Continuous-flow Aldol Reaction.

In conclusion, hydrogenation of nitriles to primary amine salts has been developed under continuous-flow conditions. Newly developed DMPSi-Pd/SiO₂ was found to be the best catalyst. Control experiments suggested that polysilane might play a key role in maintaining the catalyst activity and that SiO₂ contributed to the improved selectivity. Under the optimized reaction conditions, a range of aromatic, heteroaromatic, and aliphatic nitriles were converted into primary amine salts in almost quantitative yields under mild reaction conditions. Lifetime experiments showed that this catalyst remained active for more than 300 h ($TON \geq 10000$) without loss of selectivity, and almost no metal leaching from the catalyst occurred. Finally, the synthesis of venlafaxine, an antidepressant drug, has been accomplished by using the continuous-flow conditions. We anticipate that the present method could be applied to continuous synthesis of many pharmaceuticals, agrochemicals, and other fine chemicals. Further investigations to clarify the catalyst structure as well as to achieve a multistep continuous-flow synthesis of venlafaxine are ongoing.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: continuous flow · fine chemical synthesis · heterogeneous catalysis · hydrogenation · nitriles

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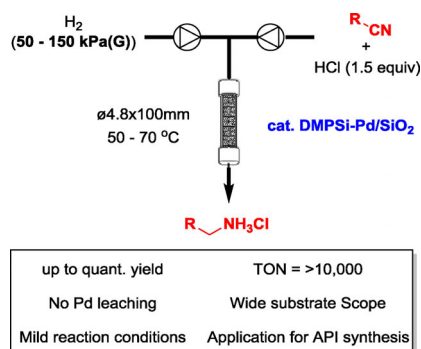
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 **Selective Hydrogenation of Nitriles to Primary Amines Catalyzed by a Polysilane/SiO₂-Supported Palladium Catalyst under Continuous-Flow Conditions**



Primary aim: Continuous flow hydrogenation of nitriles to primary amines over heterogeneous Pd catalyst is described. A newly developed DMPSi-Pd/SiO₂ catalyst demonstrates high activity and selectivity, broad substrate scope, and long lifetime without any Pd leaching.