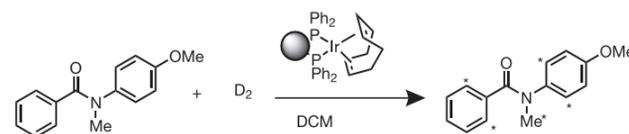


reaction. Deuterium labelled materials play a key role in drug discovery for studying drug metabolism. Deuterated compounds are ideal for stable isotopically labeled internal standards for LC-MS/MS techniques, but due to the high cost of deuterium gas, and the associated safety issues, their use is not widely supported. In the application from Habraken et al. the first use of Ir(I)-catalyzed C-H deuteration in a continuous flow manner is detailed with

a comparative study using batch, continuous stirred tank reactor (CSTR), and two types of prepacked reactors (microreactor and H-Cube Pro™) [4.].



Entry	Reactor type	Gas flow rate (mL/min)	Liquid flow rate (mL/min)	Conversion (%)	M + 1 (%)	M + 2 (%)	M + 3 (%)
1 ¹	CSTR	0.02	0.08	12	8.1	3.6	-
2 ¹	CSTR	0.02	0.025	16	9.8	4.8	-
3 ¹	CSTR	0.08	0.085	2.8	2.8	-	-
4 ¹	Microreactor	0.04	0.01	54	4.9	16.2	12.1
5 ²	H-Cube Pro™	40 bar	0.3	56	14.3	38.4	2.8
6 ^{2,3}	H-Cube Pro™	40 bar	0.3	64	14	43.4	4.5

Table 3: Reaction parameters and results of deuteration reaction; 1: 1 mg/mL SM, 10 mg catalyst, RT, yields and conversion (determined by LC-MS) are the average of 3 independent points; 2: 1 mg/mL SM, 100 mg catalyst, RT, yields and conversion (determined by LC-MS) are the average of 5 independent points; 3: the liquid stream is the one exiting entry 5 which is redirected over the catalyst bed.

As it can be observed from Table 3, the CSTR with its 0.7 mL mixing chamber and deuterium feeding through a mass flow controller, could result only in a maximum 16% conversion with a maximum deuterium incorporation of M +2. With the use of prepacked microreactor 54% conversion was achieved, and the product mixture contained deuterium incorporation up to M +7 (not displayed in Table 3). Using the H-Cube Pro reactor there was no need for a mass flow controller and deuterium tank, because the deuterium was produced from deuterated water, and the reaction pressure could be set to 40 bar. In this way 64% conversion was achieved as a maximum.

REFERENCES

- Verho, O.; Gustafson, K. P. J.; Nagendiran, A.; Tai, C.; Backvall, J.; *ChemCatChem*; **2014**; 6; 3153 – 3159

- Clavel, G.; Molinari, V.; Kraupner, A.; Giordano, C.; *Chem. Eur. J.*; **2014**; 20 (29); 9018-9023
- Molinari, V.; Giordano, C.; Antonietti, M.; Esposito, D.; *J. Am. Chem. Soc.*; **2014**; 136; 1758–1761
- Habraken, E. R. M.; Haspeslagh, P.; Vliegen, M.; Noel, T.; *Journal of Flow Chemistry*; **2015**; 5 (1); 2-5

CONCLUSION

The above examples demonstrate the usefulness of flow chemistry in the testing of different nanoparticles in various hydrogenation reactions and for H-D exchange reaction. The combination of using nanoparticles and flow chemistry further increases the sustainability of the processes and makes the involvement of expensive catalysts and reagents or dangerous methods unnecessary.

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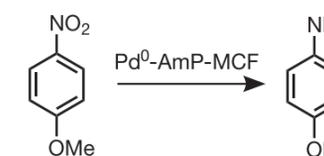
Synthesis of nanoparticles and their efficient use in the H-Cube® and H-Cube Pro™ flow reactors for reductions and H-D exchange reactions

In this application note we demonstrate the results of newly developed Pd, Ni nanocomposites, and immobilized Ir complex catalysts for a wide range of chemical applications.



Pd NANOPARTICLES FOR NITRO REDUCTION

Verho et al. [1.] detailed how palladium nanoparticles supported on amino-functionalized mesocellular foam can be used under mild conditions for the selective hydrogenation of aromatic and heterocyclic nitro compounds to amines, which are intermediates for the production of various dyes, pharmaceuticals, pigments, and polymers. The catalyst (Pd⁰-AmP-MCF) was tested for both batch and continuous methods. In the batch reference 1.60 mmol starting material (*p*-nitroanisole) was treated with atmospheric pressure hydrogen in the presence of 0.5 mol% catalyst in 2 mL EtOAc at room temperature. After 1 hr of reaction time the corresponding amine could be collected in >99% yield. Using the H-Cube® continuous flow reactor, 70 mg of this metal nanoparticle was filled into the catalyst cartridge (CatCart®), and the mixture of starting material and *in-situ* generated high pressure hydrogen was reacted inside the CatCart® at atmospheric pressure. 2.50 g *p*-nitroanisole in EtOAc was continuously pumped through the catalyst bed at 1.5 mL/min and 40 °C reaction temperature resulting in 0.90 g (95% yield) final product after 110 min with <1 ppm Pd content. The experiments showed that the Pd nanoparticle, which is a green alternative to the bulk metal catalyst, is active both under batch and flow conditions.



NICKEL NITRIDE NANOPARTICLES FOR REDUCTIONS

At the Max-Planck-Institute for Colloids and Interfaces there is an extensive research towards different metal-nitride nanoparticles. One of their publications is about nickel nitride [2.], which was mainly investigated for lithium batteries. There are different approaches for the synthesis of these nitrides. One of them is the „urea glass route”, which is a simple, scalable and versatile method: the first step is the formation of metal-urea gel followed by thermal decomposition under inert atmosphere. The used urea also forms the carbonaceous matrix (size: around 25 nm), which directs the formation of nanoparticles and prevents their aggregation. Depending on the used temperature, the reaction can result in a NiN@carbon hybrid composite at 350 °C, and Ni@C at a higher temperature.

The produced catalysts were then filled into CatCarts® and used in the H-Cube Pro™ system for nitro group, double bond, and nitrile group reductions. Results of the experiments are summarized in Table 1 using 4.33 mmol Ni₃N ~630 mg, or ~305 mg Ni, and 0.05 M starting material in EtOH. Both nanocomposites show high activity at low temperatures for the different functional groups.

It is notable that while they represent similar activity for nitro reduction, the Ni₃N nanocomposite was not able to reduce cyclohexene.

However an interesting phenomenon occurred for the highly temperature sensitive nitrile reduction, when the use of Ni₃N catalyst allowed the production of dibenzylimine.

	Catalyst	Flow rate (mL/min)	p (bar)	T (°C)	Conversion (%)	Product
Nitrobenzene	Ni	0.5	25	50	>99	aniline
	Ni ₃ N	0.5	25	75	>99	
<i>p</i> -nitroacetophenone	Ni	0.3	25	75	>99	4-aminoacetophenone
	Ni ₃ N	0.3	25	75	>99	
Cyclohexene	Ni	0.3	12	25	>99	Cyclohexane
	Ni ₃ N	0.5	12	75	>10	
Benzonitrile	Ni	0.5	25	55	>99	>99% dibenzylamine
	Ni ₃ N	0.3	25	75	>99	22% benzylamine, 69% dibenzylimine, 8% dibenzylamine
	Ni ₃ N	0.5	25	135	>99	88% benzylamine, 9% dibenzylimine, 4% dibenzylamine

Table 1: Reaction parameters and results of hydrogenation using Ni and Ni₃N nanocomposites

TITANIUM NITRIDE – NICKEL NANOCOMPOSITE FOR THE HYDROGENOLYSIS OF ARYL ETHERS

As described by Molinari et al., titanium nitride was also synthesized similarly to the nickel nitride, and the TiN was used as support to enhance the catalytic activity of Ni [3.]. TiN is a biocompatible material with thermal stability and acid resistance. TiN nanoparticles were synthesized via the previously described urea route. Calcination was

performed at 750 °C. Addition of Ni was performed by impregnation of TiN with Ni acetate tetrahydrate in EtOH, followed by calcination. The TiN-Ni nanocomposite is composed of spherical intergrown core-shell nanoparticles of ~10 nm in diameter. The produced catalysts (TiN and TiN-Ni) were then tested for the hydrogenolysis of aryl ethers, together with control experiments using Ni. The selected compounds are the most common aryl ethers found in lignin.

All catalytic reactions were performed using H-Cube Pro™. Starting with a control experiment of hydrogenation of nitrobenzene with Ni, TiN and TiN-Ni (500 °C), TiN did not show any catalyst activity in a temperature range of 25-100 °C. Ni particles exhibited a moderate activity at

100 °C, while 100% conversion was achieved with the TiN-Ni nanocomposite, even at 25°C. Finally different aryl ethers were hydrogenated, as shown in Table 2, indicating a significant activity increase for the TiN-Ni catalyst for all the three compounds.

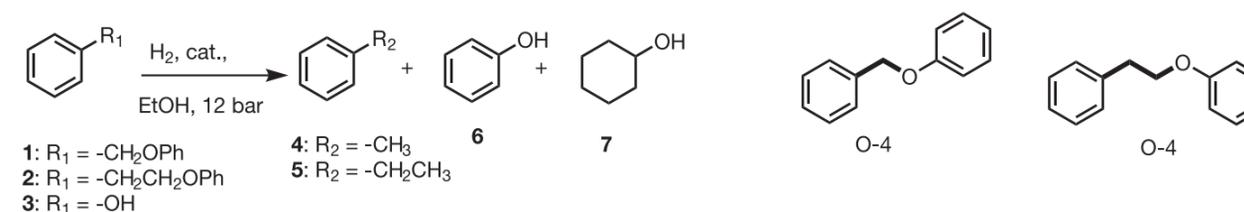


Figure 2: Hydrogenolysis of ethyl ethers

Entry	Catalyst	Substrate	T (°C)	Conversion (%)	Selectivity (%)				Product (mmol h ⁻¹ g _{cat} ⁻¹)
					4	5	6	7	
1 ^a	Ni ₃ N	1	125	18	51	-	49	-	0.225
2 ^a	TiN-Ni	1	125	>99	54	-	46	-	1.013
3 ^a	Ni	2	150	0	-	-	-	-	-
4 ^a	TiN-Ni	2	150	>99	-	54	-	46	0.608
5 ^a	TiN-Ni	3	150	55	-	-	-	100	0.620

Table 2: Reaction parameters and results of ethyl ether hydrogenolysis. a: 0.05 M, 0.5 mL/min; b: 0.3 mL/min. Selectivity and conversion were determined by GC-MS

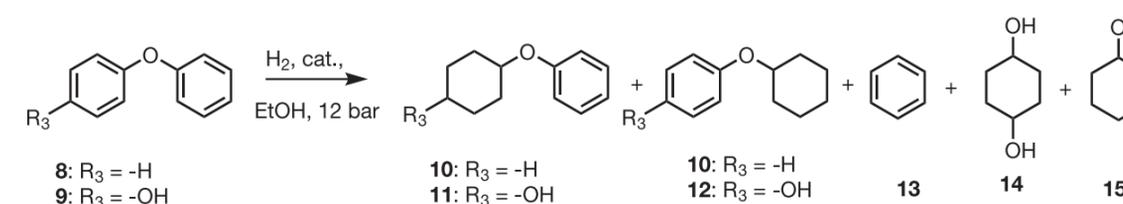


Figure 3: Hydrogenolysis of diphenylether, and hydroxy-diphenyl ether

Furthermore, the research was extended to the above displayed 4-O-5 bond, which is one of the strongest ether bonds in lignin. Its hydrogenolysis was modeled using diphenyl ether. The hydrogenolysis was carried out with Ni, TiN and TiN-Ni at 150 °C. Neither Ni nor TiN were capable of efficiently performing the reaction, while TiN-Ni showed 99% and 65% for the diphenyl ether and its hydroxyl derivative respectively when applying a 0.3 mL/min flow rate to the 0.025 M substrates. During the hydrogenation of diphenylether 46% of **13** and 49% of **15** were formed, whereas the presence of the

-OH group changed the product distribution to 49% of **13**, 25% of **14**, and only 4% of **15**. Qualitative evaluation confirmed that the catalyst remained active even for a ~40 hr reaction time.

H-D EXCHANGE WITH IRIIDIUM COMPLEX

The members of the H-Cube Series generate hydrogen via electrolysis of water. Consequently, when heavy water is filled into the reactor the corresponding deuterium gas is generated and introduced into the reaction zone at high pressure resulting in deuterated compounds after the