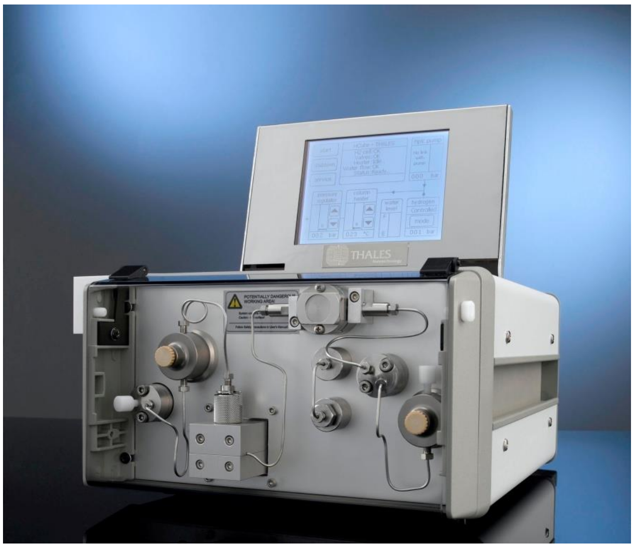
Simple flow deuterodehalogenation using polymer-based activated carbon (PBSAC) supported palladium catalysts in CatCart®



Introduction

Deuterium-labelling is a widely used method in the fields of biomedical, chemical and pharmaceutical industry.[1] The FDA recently approved the first deuterated API, and nowadays several molecules with deuterated moieties are under clinical testing in order to treat Alzheimer's, cystic fibrosis, Freidreich's ataxia, and psoriasis. The kinetic isotope effect enhances pharmacokinetic properties of deuterium-labelled molecules, which might lead to high therapeutic values.[2]

Continuous-flow deuteration has been demonstrated in the H-Cube® before, however the possibility to use it in a green chemical solvent is practically unexplored.[3]

In this application note we report the excellent work of Orsy et al. who developed a simple method, which is directly transferrable to deuterodehalogenation transformations using the H-Cube® flow reactor. Reactions were performed in a green chemical solvent (propylene carbonate) by applying a novel polymer-based spherical activated carbon (PBSAC) supported palladium loaded catalyst cartridges (**CatCarts®**).[4]

Instrumentation

H-Cube® has a built-in electrolytic H_2 generator providing hydrogen gas up to 100 bar using only water as the gas source. H-Cube Pro™, the upgraded version of H-Cube® enables more precise control of p and T and widens the temperature range and H_2 flow rate (see the table below).

Properties	**H-Cube®**	**H-Cube Pro™**
H_2 amount	"no H_2", "controlled" and "full H_2" modes are available	can be set between 0-100% independently from the gas pressure
	up to 30 mL/min H_2 (NTP)*	up to 60 mL/min H_2 (NTP)*
Pressure setting increments	10 bar	1 bar
Temperature range (°C)	rt - 100	10 - 150
Software	graphical user interface to control the instrument	graphical user interface; Simplex for optimization; timer function for automation

NTP = NORMAL TEMPERATURE AND PRESSURE

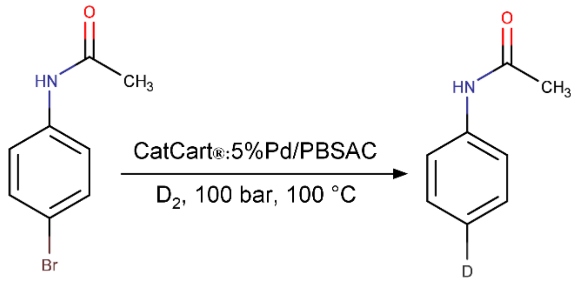
Experimental

How to turn any type of H-Cube reactor to a D-Cube?

Water needs to be totally removed from the reservoir tank. After purging the reactor system with a small amount (30 ml D_2O), the reservoir can be filled up with deuterated water.

In the authors work, D_2 activation was provided by a **CatCart®** catalyst cartridge loaded with three kinds of supported Pd catalysts. Within the **CatCarts®** range there are 100s of different catalysts available and designed to tolerate 100 bar pressure and 150°C. Cartridges can also be filled manually via a **CatCart®** packer with catalysts that are either homemade or not available in our catalogue

In order to optimize the deuterodehalogenation conditions, 4-bromoacetanilide (4-BAN) was selected as a model compound (Scheme 1.).



Scheme 1.: Deuterodehalogenation of 4-bromoacetanilide with *in situ* generated D_2 reacted over a novel 5% Pd/PBSAC catalyst loaded **CatCart®**.

In a general procedure the solvent (EtOAc or PC) and starting material was homogenized in an ultrasound bath for 5 minutes before being pumped through the H-Cube® reactor. In all experiments, a 1 mL min^{-1} flow rate was applied. After collection, the product (100 mg) was diluted with water and freeze-dried. Deuterium incorporation efficiency was analyzed by ^{1}H-NMR.

CatCarts® (length: 30 mm, internal diameter: 4 mm) were filled with 100 mg catalyst using the **CatCart® packer,** which enables the users to pack their own catalyst and reagents into cartridges and screen them for rapid reaction optimization..

Risk assessment and hazards

The H-Cube family of flow reactors enhances laboratory safety with pyrophoric catalysts contained in sealed cartridges and hydrogen generated *in situ* from water. Therefore, the need for hydrogen cylinders and catalyst filtering is eliminated. The reaction line is made from stainless steel (0.5 mm internal diameter, SS 316L). The hydrogenation process takes place solely inside the cartridge. The reaction zone is less than 0.3 mL (void volume of 30×4 mm **CatCart®**). The extremely low volume complies with NFPA 45, Annex C part C.5.3 paragraphs (5 and 6). (NFPA – National Fire Protection Association – 45: Standard on Fire Protection for Laboratories Using Chemicals).

Results and discussion

The authors performed optimization reactions to find the optimum p and T range and catalyst for efficient deuterodehalogenation. Table 1. summarizes the examined parameters and results of the screening.

In the first part of the optimization experiments, reactions were performed in EtOAc having 1 mg mL^{-1} concentration of 4-BAN. In the case of the 5% Pd/$BaSO_4$ catalyst, the first detectable conversion occurred at 25°C and 100 bar. Elevating the pressure to 100 bar the conversion increased to 4%. At 100 C and 100bar, 13% conversion was observed with 0% of deuterated product. Keeping these reaction conditions, 5% Pd/C catalyst was tested. In this case, conversion increased to 48% and the product was obtained with an 81% deuterium content. Novel 5% Pd/PBSAC showed the best results with an 87% conversion and a 92% deuterium incorporation.

Solvent	**Catalyst.** (5% Pd)	**T** (°C)	**p** (bar)	**Conc.** (mg mL^{-1})	**D** (%)	**Conv.** (%)
EtOAc	$BaSO_4$	25	50	1	n.d.	0
EtOAc	$BaSO_4$	25	100	1	n.d.	4
EtOAc	$BaSO_4$	100	100	1	n.d.	13
EtOAc	$BaSO_4$	100	100	1	81	48
EtOAc	PBSAC	100	100	1	92	87
PC	PBSAC	100	100	1	96	99
PC	PBSAC	100	100	3	96	99
PC	PBSAC	100	100	4	97	94

Table 1.: Optimization of deuterodehalogenation reaction parameters.

Recently propylene carbonate was ranked as the greenest solvent in GSKs' solvent selection guide,[5] and the experiments were continued in this media. As it can be seen, concentration could be elevated to 3 mg mL^{-1} with a 99% conversion and a 96% deuterium incorporation efficiency.

The robustness of the 5% Pd/PBSAC catalyst from an activity point of view was also investigated. Figure 1. shows that the activity did not decrease significantly in the first 5 cycles and the amount of incorporated deuterium remained at 95-96% in the product.

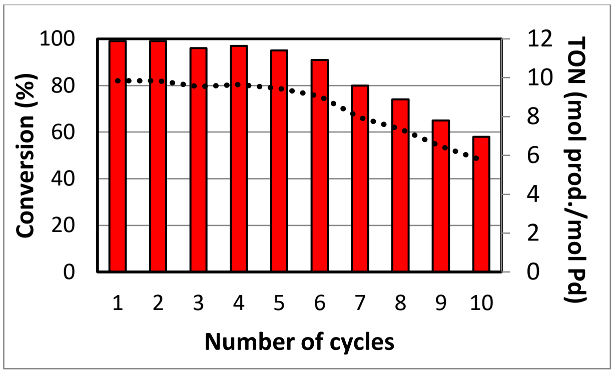


Figure 1.: Robustness of the continuous-flow deuterodehalogenation of 4-BAN. The reaction was repeated 10 times on the same catalyst bed. The dashed line shows the TON value for each cycle.

Scope and limitations

Deuterodehalogenation reactions could be run effectively in the case of bromine- and chlorine substituted haloarenes using H-Cube® with D_2O. However, fluorine-substituted compounds do not show any deuterium exchange, moreover iodine substituted molecules could poison the catalyst.

Conclusion

Applicability of **CatCart®** for Pd-catalyzed continuous flow deuterodehalogenation were demonstrated by Orsy and coworkers. The green propylene carbonate solvent enabled a 3 fold increase in the substrate concentration. The novel, in-house packed (by **CatCart® packer**) PBSAC support allowed a 95% deuterium incorporation under harsh conditions in the cases of bromine- and chlorine substituted haloarenes. This method has opened the door for preparation of versatile deuterated model compounds and API candidates.

References

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